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Chicago, IL



AMERICAN COLLEGE
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ACR/ARHP PATIENT PERSPECTIVES

SUNDAY, OCTOBER 21, 2018

ACR/ARHP Combined Session

12:00 - 2:00 PM

(#PP01–PP13) Patient Perspectives Poster Session

Profiling of B-Cell Related Factors and Its Decoy Receptors in Rheumatoid Arthritis: Potential Clues for Patient Stratification

Javier Rodríguez-Carrio^{1,2}, Mercedes Alperi-López³, Patricia López¹, Francisco Javier Ballina-García⁴ and Ana Suárez¹,
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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: B-cell over-activation plays a key role in the pathogenesis of rheumatoid arthritis (RA), thus being recognized as a therapeutic target. However, the activation of the B-cell compartment is under the control of a complex network of mediators, including ligands and receptors, expressed as membrane (m) and soluble (s) forms. The main aim of this study was to gain insight into the associations of B-cell related factors and its decoy receptors in RA, focusing on its clinical relevance.

Methods: serum levels of sBLyS, sAPRIL, sBCMA, sTACI, sBLyS-R (BR3), IFN α , MIP1 α , TNF α , IL-10, IFN γ and GM-CSF levels were measured by immunoassays in 104 RA patients (EULAR/ACR 2010 criteria) and 33 healthy controls (HC). The gene expression of IFI44, IFI44L, IFI6 and MX1 was measured in peripheral blood and averaged into an IFN score. The membrane BLyS (mBLyS) expression was assessed on B cells, monocytes (M ϕ), myeloid (mDC) dendritic cells and neutrophils (N ϕ) by flow cytometry in blood samples. A group of biological-naïve RA patients was prospectively followed for 3 months upon TNF α -blockade.

Results: RA patients exhibited increased sAPRIL ($p<0.001$) and sBCMA levels ($p=0.002$) than HC. sBLyS was higher in patients with very early RA (VERA, recruited at onset) compared to those with long-standing disease ($p=0.051$) and HC ($p=0.024$). No differences in sTACI and sBLyS-R were observed ($p=0.462$ and $p=0.507$). The sBLyS/sBLyS-R ratio was increased in VERA patients compared to HC and patients with established disease, where a positive correlation with DAS28 was noted ($r=0.298$, $p=0.008$). Moreover, increased sBLyS/sBLyS-R ratio at onset was associated with poor clinical response after 6 and 12 months (both $p<0.050$) in VERA patients. IFN score was negatively associated with sBLyS ($r=-0.463$, $p=0.031$) in VERA, whereas it was positively associated with sBLyS-R ($r=0.271$, $p=0.029$) and sTACI ($r=0.210$, $p=0.050$) in patients with established disease. mBLyS expression was increased on B cells, M ϕ , mDC (all $p<0.001$) and N ϕ ($p=0.014$) in RA, without differences by disease duration. An unsupervised cluster analysis based on sBLyS, sAPRIL, sBCMA, sTACI and sBLyS-R identified 2 clusters (I and II), cluster II being hallmarked by increased sAPRIL and sBCMA levels. Cluster II was overrepresented in RA compared to HC (32/104 vs 3/33, $p=0.015$). Cluster II RA patients showed increased prevalence of RF ($p=0.008$) and ACPA ($p=0.008$) positivity and were more likely treated with anti-TNF α agents ($p=0.020$) compared to their cluster I counterparts. Moreover, higher IFN α ($p=0.035$), TNF α ($p<0.001$), GM-CSF ($p<0.001$), IL-37 ($p=0.015$) levels and IFN score ($p=0.015$) were found in cluster II. Finally, increasing sBLyS ($p=0.043$) and sBCMA levels ($p=0.019$) were associated with poor clinical outcome upon TNF α -blockade.

Conclusion: Altered serum levels of B-cell factors are found in RA, with important differences between the very early and established stages. sAPRIL and sBCMA identify a subset of patients with a more severe disease, probably linked to a B-cell over-activation, and inadequate response to TNF α -blockade. A less efficient negative feedback from their decoy receptors may underlie these associations.

Disclosure: J. Rodríguez-Carrio, None; M. Alperi-López, None; P. López, None; F. J. Ballina-García, None; A. Suárez, None.

The Influence of Abatacept on Human B Cell Functions

Ming-Han Chen¹, Yen-Po Tsao², Chuen-Miin Leu³ and Chang Youh Tsai³, ¹Division of Allergy- Immunology- Rheumatology, Department of Medicine, Division of Allergy- Immunology- Rheumatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ²Division of Allergy- Immunology- Rheumatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ³National Yang-Ming University, Taipei, Taiwan

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Cytotoxic T lymphocyte antigen-4 (CTLA-4) competes with CD28 for binding the CD80/CD86 on antigen presenting cells to inhibit further activation of T cells. Abatacept, a CTLA-4 fusion protein, has been used for rheumatoid arthritis (RA) treatment worldwide. The aim of this study was to test whether CTLA-4 regulates human B cell functions.

Methods: The influence of abatacept on B cell functions in both *in vitro* and *in vivo* conditions was assayed. Blood was taken from 30 patients with RA before and after abatacept treatment. RA disease activity was measured using the Disease Activity Score 28 using ESR (DAS28-ESR). Serum level of rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (ACPA), and anti-tetanus toxoid antibodies was measured by ELISA. The expression of CD80/CD86 on B cells was detected using immunofluorescent staining. Purified human B cells from healthy donors were treated by T-independent (TI) and T-dependent (TD) stimulation in the presence of abatacept and cell proliferation, cytokine production, plasma cell differentiation, and antibody production were measured.

Results: RA patients showed significant clinical improvement after 6 months of abatacept treatment and a decrease in mean DAS28-ESR score was found. Abatacept transiently reduced the level of CD80/CD86 on peripheral blood memory B cells. A decrease in serum RF level was observed in our RA patients during the 6 months of abatacept treatment. However, the serum level of ACPA and anti-tetanus toxoid antibodies were not influenced. In the *in vitro* assays, we observed that the CD80 and CD86 induced by T-independent (TI) but not T-dependent (TD) stimulation was significantly downregulated by abatacept at both the mRNA level and protein level. TI-induced TNF- α and IL-6 production by B cells was also reduced by abatacept. Neither TI nor TD-stimulated B cell proliferation was reduced by abatacept in ³H-thymidine incorporation assay. Finally, abatacept inhibited Daudi-B cell induced allogeneic T cell proliferation, indicating a significant blockade of T-B interaction by abatacept.

Conclusion: Abatacept may decrease RF level by blocking the interaction of CD28 with CD80/CD86, therefore preventing B cells from T cells' help for differentiation into plasma cells. Our results also demonstrate that abatacept may provoke a negative reverse signal to B cells to further regulate B cells activation.

Disclosure: M. H. Chen, None; Y. P. Tsao, None; C. M. Leu, None; C. Y. Tsai, None.

Abstract Number: 3

Interferon-Alpha Disrupts DNA-Specific B Cell Tolerance in 3H9 Mice

Dario Ferri¹, Yuriy Baglaenko², Ariana Karanxha¹, Kieran Manion¹, Carolina Grajales¹ and Joan E. Wither¹, ¹Genetics and Development, Krembil Research Institute, University Health Network, Toronto, ON, Canada, ²Department of Biomedical Informatics, Brigham Women's Hospital, Harvard Medical School, Boston, MA

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: A central mediator of Systemic Lupus Erythematosus (SLE) pathogenesis is interferon-alpha (IFN α), which is elevated in the serum of SLE patients. IFN α has been shown to enhance B cell signaling and promote survival. It also plays a major role in the induction of B cell activating factor (BAFF). While past studies have explored the effects BAFF on B cell tolerance, little work has focused on how IFN α itself directly affects this process. We hypothesize that elevated levels of IFN α directly contribute to the breach of B cell tolerance in SLE. To address this question, we have obtained an adenoviral vector encoding mouse IFN α (mDEF201), which we are using to induce sustained elevation of serum IFN α in a mouse model of B cell tolerance (3H9).

Methods: 6-8 week old 3H9 transgenic mice, which contain a knock-in Ig heavy chain derived from a DNA-specific hybridoma, were injected IV with 10⁷ PFU of Ad-mIFN α (mDEF201) or Ad-dI70-3 (empty vector). At 2 weeks post-treatment immune cell populations in the spleen and bone marrow were examined by flow cytometry, and anti-DNA antibody production was measured by ELISA. Serum levels of IFN α and BAFF were quantified by ELISA and IFN-induced gene expression was assessed by qRT-PCR.

Results: Mice administered with mDEF201 showed elevation of serum IFN α from 48h to 2 weeks post infection. At 2 weeks post infection, the mRNA expression of several IFN-inducible genes, but not BAFF, was also elevated in infected mice. There was only a 0.5 fold increase in BAFF expression at the protein level. mDEF201 infection resulted in a marked increase in the level of anti-ss/dsDNA IgM^a autoantibodies (OD450 PBS=0.32, Ad-di70-3=0.29, mDEF201=1.46 for ssDNA, and PBS=0.13, Ad-di70-3=0.10, mDEF201=0.56 for dsDNA, $p<0.0001$) signifying a potential breach of B cell tolerance. Consistent with this idea, mDEF201 infected mice displayed altered B cell activation and homeostasis, with a significant increase in the frequency of CD86⁺ B cells as well as total number of mature B cells. mDEF201 infection also resulted in increased frequency of plasmablasts, CD138⁺ plasma cells and IgM^a/IgG2^a germinal center (GC) B cells. Despite the increase in IgG2^a GC B cells, anti-ss/dsDNA IgG2^a antibodies were not increased with elevated IFN α at 2 weeks post infection. To assess the effect of IFN α on B cell anergy we examined the Ig λ 1⁺ population, a well characterized dsDNA-specific anergic B cell population in 3H9 mice. Ig λ 1⁺ B cells also displayed increased activation (CD86⁺) and entry into germinal centers; however, anti-ss/dsDNA Ig λ 1⁺ levels were not increased. Infection with mDEF201 resulted in a mild increase in T cell activation (CD69⁺); although, no difference was seen in the total number of T follicular helper cells.

Conclusion: Taken together, these data suggest that IFN α may be a major contributing factor in breaches of B cell tolerance in SLE not only through the induction of BAFF, but also through direct effects on autoreactive B cells. Elevation of IFN α may promote the activation and differentiation of autoreactive B cells towards an antibody producing state; however, in the absence of other immune defects, some peripheral tolerance mechanisms seem to remain partially intact preventing a whole-cell breach of tolerance.

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Abstract Number: 4

Anti-Jo1 Positive Myositis Patients Display a Characteristic IgG Fc-Glycan Profile Which Is Further Enhanced in Anti-Jo1 Autoantibodies

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: IgG Fc-glycans affect IgG function and are altered in autoimmune diseases and autoantibodies. Anti-histidyl tRNA synthetase autoantibodies (anti-Jo1) are frequent in myositis associated with interstitial lung disease (ILD). We tested if total IgG Fc-glycans from Jo1⁺ versus Jo1⁻ myositis patients and anti-Jo1-IgG showed characteristic differences, and if particular Fc-glycan features could be associated with specific clinical manifestations.

Methods: Total IgG was isolated by affinity purification from serum of 44 myositis patients (19 Jo1⁺ and 25 Jo1⁻) and 24 age/sex matched healthy controls (HC). Anti-Jo1-IgG was further purified from eleven patients using a recombinant Jo1-coupled affinity column. A shotgun proteomics approach was used to profile serum-derived IgG-Fc-glycans and IgG-chain distributions. Uni- and multivariate statistics were used to find characteristics and correlate data with clinical information.

Results: A high abundance of agalactosylated IgG₁ Fc-glycans was observed in myositis patients compared to HC. Using intra-individual normalization of the main agalactosylated glycan (FA2) of IgG₁ vs FA2-IgG₂, myositis and HC were distinguished with an area under the curve (AUC) of 79±6%. For Jo1⁺ the AUCs went up to 88±6%. Bisected and afucosylated Fc-glycans were significantly lower in Jo1⁺ compared to Jo1⁻ patients. Anti-Jo1 IgG contained even lower abundance of bisected, afucosylated and galactosylated forms compared to matched total IgG. ASS and ILD diagnosis correlated with the Jo1⁺ characteristic Fc-glycan features via multivariate analysis.

Conclusion: The anti-Jo1⁺ patient IgG Fc-glycan profile contains phenotype specific features which may underlie the pathogenic role of Jo1 autoantibodies.

Disclosure: C. Fernandes-Cerqueira, None; N. Renard, None; A. Notarnicola, None; E. Wigren, None; S. Graslund, None; R. Zubarev, None; I. E. Lundberg, Bristol-Myers Squibb, 2, AstraZeneca, 2, AstraZeneca, 5, UCB, Inc., 5, Corbus Pharmaceuticals, 5, Novartis, 1, Roche, 1; S. L. Lundström, None.

Abstract Number: 5

Short Chain Fatty Acid Acetate Induces Regulatory B Cells in Mice and Humans, Which Can Protect Against Arthritis

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SESSION INFORMATION

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Background/Purpose: Autoimmunity and more broadly non-communicable diseases develop with the imbalance between anti- and pro-inflammatory immune cell subsets, leading to an uncontrolled and damaging inflammation. Evidences have shown that short chain fatty acids promote anti-inflammatory regulatory T cell protecting from type 1 diabetes, colitis and allergies in mice. In the present study, we investigated the benefits of short chain fatty acid acetate extend to other immune cells involved in tolerance, the regulatory B cells (Breg).

Methods: For this purpose, we assessed the effect of acetate on Breg *in vitro* and *in vivo* through oral supplementation or intraperitoneal injections. The functions of acetate-induced Bregs were assessed i) *in vitro* using co-culture with naïve T cells to assess Th17 differentiation ii) *in vivo* with adoptive transfer of acetate-stimulated B cells in a model of collagen antibody-induced arthritis (CAIA). In addition, the effect of acetate was also evaluated on B cells from human samples.

Results: We showed that both *in vivo* and *in vitro* acetate promoted Breg differentiation from B1a cells but not from B2 cells in mice. Acetate-induced Breg cells could protect from collagen antibody-induced arthritis development when adoptively transferred. These effects were neither through specific G-protein receptor activation nor HDAC inhibition but by inducing metabolic changes particularly in B1a cells by fueling TCA cycle. Similarly, we found that acetate also promotes human Breg cells through metabolic changes.

Conclusion: This work suggest that acetate might be a promising therapeutic approach to restore Breg population in autoimmune diseases such as Rheumatoid Arthritis in which they are defective.

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Abstract Number: 6

Ro52/Trim21 Influences Follicular B Cell Homeostasis and Immunoglobulin Production

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SESSION INFORMATION

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Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

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

Background/Purpose: Systemic rheumatic diseases are characterized by abnormal B cell activation with autoantibody production and hypergammaglobulinemia. The autoantigen Ro52/SSA, also denoted TRIM21, is a major autoantigen in Sjögren's syndrome and systemic lupus erythematosus. Interestingly, Trim21-deficient mice develop systemic autoimmunity with B cell-related features such as autoantibodies, hypergammaglobulinemia and glomerulonephritis following tissue injury. The mechanisms by which Trim21 deficiency leads to enhanced B cell activation and antibody production are not well understood, and to further elucidate the role of Trim21 in systemic autoimmunity we investigated the B cell phenotype of Trim21^{-/-} mice.

Methods: Littermate C57BL/6J Trim21^{+/+} and Trim21^{-/-} mice were immunized with antigens eliciting thymus-dependent or thymus-independent B cell responses: nitrophenol-coupled ovalbumin (NP-OVA), lipopolysaccharide (NP-LPS) and ficoll (NP-ficoll). Anti-NP-IgM and IgG antibody titers were measured by ELISA, and B cell subpopulations were assessed by flow cytometry. CD19⁺ splenic cells from naïve mice were sorted and stimulated with anti-IgM antibodies, and proliferation was estimated by H³-thymidine incorporation and Ki67 expression. CD19⁺CD21⁺CD23^{high} follicular B cells were isolated from naïve mice and subjected to RNA extraction and microarray analysis.

Results: Higher specific IgG and IgM antibody titers were detected in Trim21^{-/-} mice compared to wild-type littermates upon immunization with NP-OVA and NP-ficoll. Consistent with these observations, NP-OVA-immunized Trim21^{-/-} mice had higher frequencies of splenic follicular (CD19⁺CD21⁺CD23^{high}) cells and bone marrow plasma (CD19⁺CD138⁺) cells. B cell receptor-specific stimulation of naïve splenic B cells *in vitro* resulted in significantly higher proliferation of Trim21^{-/-} cells. We also observed that splenic follicular B cells were more frequent already in naïve Trim21^{-/-} mice. Transcriptome analysis of these cells revealed differential regulation of genes associated with B cell differentiation, proliferation and metabolism.

Conclusion: Our findings reveal a link between the rheumatic autoantigen Ro52/Trim21 and increased antibody production associated with expansion of follicular B cells, suggesting a potential role for this autoantigen in the pathogenesis of systemic autoimmunity.

Disclosure: M. Ivanchenko, None; S. Brauner, None; G. E. Thorlacius, None; A. Ambrosi, None; M. Wahren-Herlenius, None.

Abstract Number: 7

RNA Sequencing Detection of Gene Dysregulation in B Cells Sorted from Salivary Gland Tissue and from Peripheral Blood Reveals New Pathways Involved in Primary Sjögren's Syndrome Pathophysiology

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SESSION INFORMATION

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Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

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

Background/Purpose: Primary Sjögren's syndrome (pSS) is a chronic auto-immune disorder characterized by lymphocytic infiltrates and destruction of the salivary glands. Chronic B cell activation, the secretion of autoantibodies and the critical role of BAFF have been demonstrated. However, mechanisms leading to B cells dysregulation remain partially understood. The objective of this study was to establish transcriptomic maps of the B cells sorted from the salivary glands and from blood in pSS patients and controls.

Methods: Patients had pSS according to 2016 EULAR/ACR criteria and controls had sicca symptoms without any antibodies and with normal salivary gland biopsy. B cells were sorted from salivary gland biopsies and from blood. Total RNASeq profiling was performed using MiSeq (Illumina). Statistical analysis (DESeq2) identified differentially expressed genes between pSS and controls in B cells sorted from salivary glands (9 pSS patients and 4 controls), from blood (16 pSS patients and 7 controls); and between B cells sorted from salivary glands and blood in the same patients (4 pSS patients). Functional enrichment analysis was performed using Ingenuity Pathway Analysis software.

Results: The pSS vs controls comparison in B cells sorted from salivary glands identified up-regulated genes involved in activation of B cells including CD48, CD22 and CD40. TLR10, which is involved in innate immunity was also up-regulated in pSS. The analysis of the non-coding expressed RNAs showed an up-regulation of Mir155 which is essential for B cell differentiation and antibody production (**Table 1A**).

In blood B cells, TLR7 and the downstream signaling molecule IRF7 were up-regulated in pSS. Additionally, IL-6 which is involved in B cells growth was up-regulated (**Table 1B**). Enrichment analysis highlighted EIF2 signaling pathway, interferon (IFN) signaling pathway and role of JAK in IFN signaling (**Table 2**).

The paired comparison between B cells from salivary glands and from blood identified up-regulated genes including CD138, a plasma cell marker, IL-6, TLR5 and IFN induced genes (**Table 1C**). As non-coding RNA, Mir155 was also up-regulated.

The confirmation by qPCR method of these results is ongoing.

Conclusion: This study allowed to explore the mechanisms that support B cell activation in pSS focusing on tissue resident and circulating cells. Our data confirmed the B cell activation and differentiation through several markers including CD40, CD22, CD48, CD138 and highlighted the role of innate immunity with the TLRs and key pathways including IFN and JAK signaling. Precise understanding of these dysregulation should offer development of new targeted therapeutic perspectives for patients.

Table 1A, 1B and 1C: Selection of genes differentially expressed between pSS and controls in B cells sorted from salivary gland biopsy (**1A**), blood (**1B**) and between salivary glands and blood B cells from the same pSS patients (**1C**)

	Gene Symbol	log2 fold-change	p-value
1A	Salivary B cells (pSS vs controls)		
	CD48	2.59	0.009
	CD22	2.29	0.048
	CD40	2.64	0.017
	TLR10	5.67	0.002
	Mir155HG	4.94	0.002
1B	Blood B cells (pSS vs controls)		
	TLR7	1.40	0.008
	IRF7	0.76	0.041
	IL-6	1.54	0.006
1C	Salivary vs blood B cells in pSS		
	CD138	6.92	9.63e-05
	IL-6	3.05	0.004
	TLR5	8.86	8.26e-06
	Mir155	3.10	0.011

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Abstract Number: 8

Repertoire Studies in Rheumatoid Arthritis Reveal B-Cell Distortions and Baseline Shifts in Unmutated IgG

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: The immunological hallmark of rheumatoid arthritis (RA) is autoreactivity to citrullinated proteins and rheumatoid factor activity. Hence, the adaptive immune system and B cells are postulated to be central in RA pathogenesis, yet possible underlying B cell baseline autoreactivity defects have not been studied. Here, we use next generation sequencing (NGS) to study overall B cell repertoire shifts in RA patients compared to healthy individuals, as well as in ACPA specific B-cell populations.

Methods: Peripheral blood B cell receptor (BCR) repertoires were investigated in 13 seropositive RA patients and six age-matched healthy blood donors using PCR multiplex amplicon libraries with a molecular barcode strategy and the Illumina MiSeq platform to generate full variable region coverage. Citrullinated vimentin (Cit-Vim, aa 59-74) and citrullinated fibrinogen (Cit-Fib, aa a566-580) positive B cells were sorted using antigen-tetramers based on a scaffold with grafted RA peptides into the sunflower trypsin inhibitor-1, SFTI-1. Sequences were filtered using pRESTO, annotated by IMGT and Change-O. Filtering of 14×10^6 transcript reads generated 587 000 unique antibody V-regions. Genomic DNA was used to analyze recombination frequency in out-of-frame (OOF) sequences. Analysis of variable gene frequency was performed by Chi-square with Yates correction.

Results: Several significant shifts in the RA B cell repertoire could be observed. RA-derived circulating B cells had increased class-switching to IgG3 and IgG4 but lower IgA. Strikingly, there was a significantly higher frequency of VH with low somatic hypermutation (SHM) level in RA-derived B cells (<5 mutations, $p < 0.0001$ 14.7% vs 8.7). This was seen in all sequences, IgM and class-switched, but especially prominent in IgG1 rearrangements (9.6% vs 18.8% low mutation, $p < 0.0001$ OR=2.2 CI:2.0-2.35). Yet, IgG1 displayed evidence of stronger antigen selection pressure as compared to controls (5.5% vs 3.7%, $p < 0.0001$ OR=1.5 CI: 1.3-1.7) suggesting that an increased IgG1 class-switching of unmutated BCR may initiate further B cells selection. Recombination of VH4 sequences were higher in RA and there was a general RA VH4 bias that was enriched in Cit-Vim and Cit-Fib positive cells, although class-switched Cit-Fib had a VH1, VH3 profile. Furthermore, VH N-linked glycosylation sites accumulated with SHM and were increased in RA (IgG > 15 mutations, $p < 0.0001$, 17.2% vs 13.8%), primarily driven by IgG1, and further elevated in Cit-Vim and Cit-Fib populations (19.3%, 32.2%). BCR carrying the autoreactivity-associated VH4-34 gene with a germline-encoded N-glyc site were also enriched in RA and tetramer-sorted populations, especially in IgMs.

Conclusion: We found significant distortions in the B cell populations in seropositive RA compared to controls, especially within IgG1. Many findings were further enriched in the citrulline specific B cells suggesting correlation with ACPA autoreactivity. Overall, the differences may partly be explained by a strong ongoing B cell response but could also reflect baseline shifts and elevated natural autoreactivity as an underlying mechanism in the RA pathogenesis.

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Abstract Number: 9

Integration of Cytokine Profiles with Distinct B-Cell Functions Reveals a Specific Micro-Environmental Framework in Autoimmune Diseases

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SESSION INFORMATION

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Background/Purpose: The functional duality of B cells is central to balance immune homeostasis by regulating or promoting the immune response. However, the mechanisms by which the cytokine environment is involved in B-cell fate decisions leading to distinct B-cell functions are largely unknown.

Methods: We designed an *in vitro* approach to understand how extracellular components participate in human B-cell functional plasticity, and how this network might be involved in autoimmune diseases. Two activated T cell subsets ($CD4^+CD45RA^+$ (T_{RA}) and $CD4^+CD45RO^+$ (T_{RO}) T cells) were used to expose a common pool of B cells to distinct microenvironments. We showed that the same B-cell population could experience two possible opposite evolutions, to either helper or suppressor functions, in a flexible manner. These cells were thus referred to as effector B cells (Eff B) or suppressor B cells (Supp B). We analyzed the nature of those distinct bystander signals to assess the different functional cytokine clusters linked to phenotypic changes in B cells and explored the influence of those cytokine patterns in 179 Patients with systemic autoimmune diseases (SADs) and 48 healthy volunteers included in the PRECISESADS project [RA (n=44), SLE (n=45), systemic sclerosis (n=46), and Sjogren's syndrome (SjS, n=44)].

Results: We showed that distinct cytokine modules were involved in the modulation of B-cell functions. The identification of functional cytokine modules showed that the suppressive function of B cells was associated with Th2-related cytokines (IL-13, IL-5, IL-9 and IL-10) while the effector module, headed by IL-6 and CXCL10, also included CXCL1 and IL-8. Finally, we observed a common last cluster of cytokines that we considered to be a master modulator group able to control each cytokine network. This module included TNF- α , IFN- γ , IL-2 and IL-21. The key players of the effector module consisting of IL-6 and CXCL10 were over-represented in the four SADs, underlining a common key pathogenic cytokine network. We then wanted to address whether the analysis of the two different clusters of patients could be linked to biological activities and/or clinical manifestations. The measure of anti-nuclear antigen autoAb in patients delimited a more autoreactive pattern in the disconnected SLE patients cluster, demonstrating a significant increase in anti-DNA Ab and anti-SSA-52KD Ab. We, next confirmed a selective increase in systemic autoreactivity in disconnected SjS patients cluster with the upregulation of anti-SSB Ab and the increase of rheumatoid factors in disconnected RA patients. Finally, we underlined a major increase of extra-glandular clinical manifestations in the disconnected SjS patients group depicting a strong systemic activity of the disease. We also observed in SLE patients that the appearance of clinical symptoms of nephritic disorders during the course of the disease was significantly higher in the disconnected cluster.

Conclusion: Our experimental and translational approach identified subgroups of SADs patients, particularly distinguished by an effector B-cell signature.

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Disclosure: Q. Simon, EFPIA, 2; A. Grasseau, EFPIA, 2; B. Rouvière, EFPIA, 2; L. Le Pottier, EFPIA, 2; D. Cornec, None; M. O. Borghi, EFPIA, 2; R. Aguilar Quesada, EFPIA, 2; Y. Renaudineau, EFPIA, 2; M. Alarcón-Riquelme, Sanofi, Bayer, UCB, Eli Lilly and Servier, 2; J. O. Pers, EFPIA, 2; S. Hillion, EFPIA, 2.

Abstract Number: 10

Fibroblast like Synoviocytes (FLS) Are Capable of Inducing Phenotypical Changes Including Class Switch Recombination (CSR) in Naive B Cells, but Additional Factors Are Required to Trigger Immunoglobulin Secretion

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Background/Purpose: Rheumatoid Arthritis (RA) is a disease characterized by chronic inflammation of the synovial tissue in joints. It is driven by highly activated B cells. Synovial cells, primarily Fibroblast like synoviocytes (FLS) play an important role in activating these B cells. It was previously shown, that FLS upregulate CD40L under pro-inflammatory conditions (other abstract). In order to investigate the interactions responsible for B cell activation, a co-culture model was established with RAFLS and SF from Osteoarthritis (OA) patients.

Methods: IgD+ B cells were isolated from human peripheral blood by MACS and co-cultured w/o SFs in medium only, in the presence of CpG, IFN-gamma, TNF-alpha or both, respectively. B cell subpopulations, survival and proliferation were determined by FACS. IgG and IgM were measured by ELISA. Images of co-cultures were produced by immunocytochemistry.

Results: B cell survival is increased in co-culture after 6 days without additional stimulation (RAFLS: +20.65% +/-1.27%; OAFLS: +14.53% +/- 5.54% compared to B cell control) Proliferation of B cells is already increased after 3 hours of co-culture without additional stimulation (RASf: +13.48% +/- 2.16%; OASF: +13.02% +/- 1.16% compared to B cell control). Without additional stimulation IgD+ B cells are reduced in FLS co-culture after 6 days (RAFLS: -26.2% +/- 12.8%; OAFLS: -23.1 +/- 5.5% compared to B cell control). With IFN-gamma, the reduction of IgD+ B cells is even more pronounced (RAFLS: -44.6% +/- 4.7%; OAFLS: -33.6% +/- 9.2% compared to B cell control). The proportion of CD138+ B cells is increased after 6 days in co-culture (RAFLS: from 0.37% to 14.8% +/- 0.9%; OAFLS: from 0.37% to 15% +/- 2.9%) IgM could only be measured in considerable amounts in the supernatant after stimulation with CpG and exclusively in the co-cultures (RAFLS: from: 6.7 ng/mL +/- 0.95 ng/mL to 517.5 ng/mL +/- 228.4 ng/mL; OAFLS: from: 5.9 ng/mL +/-

0.3 ng/mL to 189.6 ng/ml \pm 204.4 ng/ml) IgG could not be detected in the supernatant above baseline levels. However, immunofluorescence staining showed IgG positive B cells in the co-cultures.

Conclusion: FLS are capable of inducing CSR in naïve B cells, probably through CD40L upregulated under pro-inflammatory conditions (shown in other abstract), but they do not supply enough stimulation to drive the B cells to immunoglobulin secretion. TLR stimuli (or hypothetically BCR stimuli) are required for Ig release.

Disclosure: D. Bleck, None; T. Lowin, None; M. Schneider, None; G. Pongratz, None.

Abstract Number: 11

PAD4-Independent Interaction of ACPA with Nuclear Antigens in Apoptotic Cells and Neutrophil Extracellular Traps (NETs) Defines a Subset of Autoantibodies

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) associated anti-citrullinated protein autoantibodies (ACPA) bind a wide range of citrullinated proteins with high cross-reactivity. Recent findings suggest that certain, but not all, ACPA may have pathogenic properties. Citrullination occurs during physiological processes such as apoptosis, neutrophil extracellular trap (NET) formation and histone modifications, yet little is known about the interaction of ACPA with these antigens. Since uncleared apoptotic cells and NET products have been postulated to be central sources of autoantigen and immunostimulation in autoimmune disease, we sought to determine the anti-nuclear and anti-neutrophil ACPA reactivity.

Methods: We screened a total of 11 recombinant single B-cell isolated RA monoclonal human ACPA-IgG, derived from different cellular origin and compartments, for binding to full-length citrullinated nuclear antigens including histones and hnRNPs by ELISA. All ACPA mAbs have previously been confirmed anti-CCP2 reactive, with specific and extensive cit-peptide reactivity demonstrated by ELISA and antigen-arrays. ACPA apoptotic cell binding was determined by flow cytometry and immunoprecipitation. Immunofluorescence was utilized for primary human neutrophil and the Ecom-G murine neutrophil systems. ACPA binding to Ecom-G cells was also evaluated with flow cytometry. Anti-nuclear antibody reactivity (ANA) was evaluated with standard HEp-2 tests. CRISPR-Cas9 technology was used to generate peptidylarginine deiminase type 4 (PAD4) KO neutrophils and chlor-amidine (Cl-A) was used as pharmacological inhibition of PAD enzymes.

Results: We could observe that a subset of three monoclonal ACPA (37CEPT2C04, 37CEPT1G09, 1325:01B09) had high ANA reactivity and high binding to apoptotic cells. This did to some extent correlate with ELISA reactivity patterns to full-length citrullinated histones, but less so to citrullinated hnRNPs. Indeed, immunoprecipitations from apoptotic cell lysates revealed citrullinated histones as primary targets. One of the ACPA (1325:01B09) had a high capacity to induce IL-8 release from human peripheral mononuclear cells in plate-bound immune complexes with citrullinated histones. Importantly, all the anti-nuclear ACPA mAbs bound strongly to activated murine and human neutrophils and NETs. However, we also found two mAbs (1325:01C03 and BVCA1) in a second NET-reactive ACPA subset with contrasting perinuclear neutrophil binding and cross-reactivity patterns more towards the cytoplasmic antigens vimentin and alpha-enolase. Notably, CRISPR-Cas9 KO studies and pharmacological PAD inhibition showed that the cytoplasmic NET binding was fully dependent on PAD4 while the nuclear and histone mediated NET-reactivity was independent of PAD4.

Conclusion: When investigating monoclonal ACPA, we identified distinct subsets based on binding to neutrophils and NETs with either a nuclear pattern or a cytoplasmic perinuclear pattern. Importantly, only the cytoplasmic anti-neutrophil ACPA binding was PAD4 dependent. This may have important functional impact and provide insights in RA pathogenesis.

Disclosure: G. Wigerblad, None; K. A. Lloyd, None; P. Sahlström, None; K. Chemin, None; J. Steen, None; P. J. Titcombe, None; D. Zhou, None; R. Stalesen, None; B. Marklein, None; E. Ossipova, None; J. Rönnelid, None; L. Piccoli, None; A. Lanzavecchia, None; D. L. Mueller, None; K. Skriner, None; L. Klareskog, None; F. Wermeling, None; V. Malmström, None; C. Grönwall, None.

Abstract Number: 12

Protein Phosphatase 2A, a Serine/Threonine Phosphatase, Is Essential for Optimal B Cell Function

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Protein phosphatase 2A (PP2A) is a serine/threonine phosphatase ubiquitously expressed in eukaryotic cells. PP2A levels and activity are increased in T cells from patients with systemic lupus erythematosus and account for certain aspects of their aberrant function. We asked whether PP2A is similarly involved in the control of B cell function in lupus.

Methods: To understand the contribution of PP2A to B cell function, we generated a Cd19^{Cre}Ppp2r1a^{flox/flox} (*flox/flox*) mouse which lacks functional PP2A specifically in B cells along with Cd19^{Cre}Ppp2r1a^{WT/WT} (*control*) mice. B cells were isolated from lupus-prone *Mrl.lpr*, *SLE1.2.3* and *B6.lpr* mice to study the activity and protein levels of PP2A. Flow cytometry was performed in peripheral blood mononuclear cells of 15 patients with systemic lupus erythematosus and age, sex and race-matched healthy controls to measure the level of catalytic subunit of PP2A.

Results: We found that *in vitro* activated B cells by CpG, anti-IgM and anti-CD40 display increased PP2A activity. *Flox/flox* mice displayed decreased spontaneous germinal center B cells and decreased serum immunoglobulin levels compared to control mice. Immunization of *flox/flox* mice with sheep red blood cells resulted in decreased germinal center formation and immunization with T-dependent and T-independent antigens resulted in impaired antigen specific immunoglobulin production. *In vitro* stimulation of *flox/flox* B cells with anti-CD40/IL-4 and CpG/IL-4 similarly resulted in decreased immunoglobulin production. B cells from lupus-prone mice showed increased levels of PP2A and PP2A activity. B cells from patients with systemic lupus erythematosus expressed increased levels of PP2A.

Conclusion: Our results demonstrate that PP2A is required for optimal B cell function and contributes to increased B cell activity in systemic autoimmunity.

Disclosure: E. Meidan, None; H. Li, None; C. Ioannidis, None; W. Pan, None; N. Rodriguez Rodriguez, None; J. Crispin, None; S. Apostolidis, None; J. Manis, None; A. Sharabi, None; M. G. Tsokos, None; G. C. Tsokos, Janssen Research & Development, LLC, 2.

Abstract Number: 13

Shared Genetic Origins Among Anti-Proteinase 3 and Anti-Glomerular Basement Membrane Double-Positive Human Autoantibodies

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Patients with ANCA vasculitis and anti-glomerular basement membrane (GBM) nephritis (Goodpasture's Disease) develop pathogenic autoantibodies (autoAb) that destroy the microvasculature in lungs and kidneys. A substantial subset of patients develops double-positive (DP) ANCA+ anti-GBM+ autoAb and a clinical overlap syndrome. A recent analysis of a large patient cohort suggests that clinical relapse is particularly likely in the surviving DP patients with anti-PR3 ANCA. Little is known about the sequence and structure of autoAb of either specificity or about the relationship between ANCA and anti-GBM autoAb in DP patients. To gain insight into the origins of human anti-PR3 DP autoAb, we took advantage of the HuHSC-NSG model in which conditioned immunodeficient NOD-scid-gamma (NSG) mice are injected with human hematopoietic stem cells (HSC) to reconstitute a human immune system *in vivo*.

Methods: We measured binding to purified native human PR3 in two panels of HuHSC-NSG-derived human antibodies: 1) Six clonally unrelated human anti-GBM monoclonal antibodies (mAb) previously generated from collagen-immunized HuHSC-NSG mice and selected for binding to the non-collagenous domain-1 of the alpha3 chain of collagen IV, the antigen targeted by pathogenic anti-GBM autoAb; and, 2) Serum from a cohort of HuHSC-NSG mice (n=29) 4-6 months post engraftment and 1-3 months post aspiration of vehicle (saline) or crystalline silica, the environmental exposure most compellingly linked to human autoimmunity including ANCA vasculitis. Results using ELISA are reported as mean sample OD after subtraction of mean OD on diluent-coated plates.

Results: Two human anti-GBM mAb bound to PR3 (ODs = 0.618 and 0.455; positive control ANCA+ patients' plasma IgG diluted 1:50 mean OD = 1.376). PR3 binding did not reflect broad polyreactivity, as neither mAb bound to MPO or Hep-2 cells. Low level anti-PR3 activity (mean OD = 0.084, diluted 1:50) was detected among human antibodies in the blood of a subset of silica-exposed HuHSC-NSG subjects derived from the same HSC unit.

Conclusion: Detection of both anti-GBM and anti-PR3 specificities in individual human mAb confirms that a single immunoglobulin can bind both autoantigens and that anti-GBM and anti-PR3 autoAb can share genetic origins. Prior sequence analysis of the human mAb revealed uncommon motifs that favor autoreactivity and are typically selected against in the immune repertoire. Our findings in humanized immune system mice suggest that genetics of the HSC donor and permissive environmental exposures may facilitate their expression. Sequence analysis of single-positive anti-PR3 and patients' pathogenic autoAb will provide further insight into their genetic relationship and immune regulation, as well as potential novel targets for therapy.

Disclosure: J. R. Ord, None; A. G. Clark, None; M. H. Foster, None.

Abstract Number: 14

Individual RA-Derived Monoclonal Anti-Citrullinated Protein Autoantibodies (ACPA) Have Extensive Citrulline Multi-Reactivity Demonstrated By a Large-Scale Protein Array Platform

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: The presence of serum IgG anti-citrullinated protein autoantibodies (ACPA) in rheumatoid arthritis (RA), is associated with more aggressive disease progression. Although ACPA have been suggested to be important in the pathogenesis, the mechanisms and pathogenic targets are still poorly described. ACPA multi-reactivity to synthetically citrullinated peptides have been reported, yet how this corresponds to ACPA full-length protein targeting have not previously been explored. Here we used a novel protein array approach to investigate the citrulline reactivity broadness of three single-cell derived ACPA monoclonal antibodies (mAbs) compared to polyclonal IgG anti-CCP2.

Methods: The macroarray platform (hEXselect, Engine) consists of 20 776 *E.coli* on-array expressed protein fragments from 6 909 genes with between 1-37 fragments for each gene. All originating from human fetal brain cDNA, cloned into an IPTG inducible vector with N-terminal RGS-His6-Tag as expression control. The array was enzymatically citrullinated with rabbit PAD. Duplicated spotting and alkaline phosphatase conjugated anti-human IgG (Fc) with AttoPhos substrate enabled reliable spectral fluorescent intensity detection that were scored from 0-3 using a grid based analyzing software. Binding of two recombinant ACPA mAbs derived from RA synovial plasma cells (1325:01B09 and 1325:04C03) and one mAb derived from tetramer sorted blood memory cells (37CEPT2C04) were evaluated. The technology was validated with ELISA and Western blot using individually expressed selected protein fragments.

Results: Purified polyclonal IgG anti-CCP2 from ACPA+ RA patients contained, as expected, reactivity to a range of citrullinated full-length proteins and protein fragments (674 total hits, 154 with visual scoring 3). However, interestingly, the individually analyzed monoclonal ACPA also displayed reactivity to a large number of citrullinated targets. While some shared targets were identified, also unique mAb-specific antibody targets were detected. The ACPA mAb 1325:01B09 reacted to in total 1790 citrullinated protein fragments (1328 mAb-unique; 190 with visual scoring 3), 1325:04C03 reacted to 408 (115 mAb-unique; 42 with visual scoring 3), and 37CEPT2C04 reacted to 792 (487 mAb-unique; 118 with visual scoring 3). Reactivity to native unmodified proteins were limited (53, 19, or 22 hits, respectively). Among the identified proteins were known targets e.g. Cit-vimentin, Cit-hnRNPs, and Cit-histones, as well as less studied RA autoimmunity targets e.g. Cit-40S ribosomal proteins.

Conclusion: All investigated monoclonal ACPA were multi-reactive to citrullinated protein targets to a much larger extent than previously described and bound hundreds of full-length proteins and protein fragments. Nevertheless, ACPA mAbs demonstrate individual distinct binding patterns. Further studies on how ACPA bind to proteins in cells during physiological citrullination and the clinical relevance of ACPA multi-reactivity will be of importance.

Disclosure: P. Sahlström, None; J. Steen, None; M. Jennings, None; P. J. Titcombe, None; U. Nonhoff, Engine GmbH, 3; R. Stalesen, None; B. Marklein, None; D. L. Mueller, None; Z. Konthur, Engine GmbH, 3; K. Lundberg, None; A. I. Catrina, None; L. Klareskog, None; V. Malmström, None; K. Skriver, None; C. Grönwall, None.

Abstract Number: 15

Abnormal ZAP-70 Expression in B Cells: New Potential Role in Tolerance Breakdown

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Abnormal expression of the tyrosine kinase ZAP-70 by tumoral B cells in chronic lymphocytic leukemia (CLL) is associated with B cell receptor (BCR) hypersignalling and autoimmune cytopenia (AIC), mostly induced by polyclonal IgG from non-tumoral B cells. We previously shown that ZAP-70 is also expressed by residual non tumoral B cells in CLL and associated with AIC occurrence. We therefore hypothesized that ZAP-70 expression in non tumoral B cells could generally predispose to tolerance breakdown.

Methods: Ig heavy and light chain were amplified from FACS-sorted non tumoral mature switched ZAP-70⁺ B cells of CLL patients with AIC, for production of recombinant antibodies (rAb). Reactivity of these rAb was tested in ELISA and on HEp-2 cells. A knock in *Zap-70⁺/Mb1-Cre⁺* mouse model (KI ZAP) was generated to conditionally express ZAP-70 in B cells since proB stage, to study functional consequences of ZAP-70 expression in B cells *in vivo*. *Zap-70⁺/Mb1-Cre⁻* mice were used as controls (CTRL).

Results: Among the 13 rAb produced to date from 5 different patients, 2 (15,5%) have an antinuclear autoreactivity and two others (15,5%) were polyreactive (DNA, lipopolysaccharide, insulin), compared respectively to 6% and 4,3% of control B cells. Compared to CTRL, microarrays revealed that KI ZAP mice were significantly enriched in circulating IgG and IgM autoantibodies against various antigens (mainly nuclear). These mice had reduced apoptosis rates of proB, preB and immatures B cells, enrichment in marginal zone (p=0.01) and reduction in B1a B cells (p=0.008). In the other part, KI ZAP mice had persistent hypogammaglobulinemia since 16 weeks-old (p=0.003 for IgG and p=0.03 for IgM), together with a reduction in matures naive, matures switched as well as in germinal center B cells (p=0.001, p=0.002 and p<0.001 respectively) and a trend was observed for plasma cells (p=0.07). After immunization by ovalbumin + Freund's adjuvant, a reduced production of specific IgG and IgM was observed (p=0.01 and p=0.03 respectively). KI ZAP B cells shown increased spontaneous activation and proliferation levels holding after BCR stimulation, as well as an increased intracellular calcic flow. Preliminary data suggested a reduced SYK phosphorylation after BCR stimulation in KI ZAP B cells compared to CTRL.

Conclusion: We report for the first time that non tumoral ZAP-70⁺ B cells could be enriching in autoreactive cells *in vitro* and that ZAP-70 expression in B cells is associated *in vivo* with medullar selective advantage, enrichment in circulating autoreactive Ig and potential autoreactive B cells (marginal zone) with reduced immunoregulatory B cells (B1a). This expression is also associated with partial block in B cells peripheral development, but with a conversely early increased activation and proliferation status. ZAP-70 could interfere early with SYK leading to an altered BCR signaling responsible for defect in normal B maturation promoting emergence of autoreactive B cells. Mechanistic role of ZAP-70 in BCR signaling has to be further analyzed but our data open new opportunities involving ZAP-70 in the understanding of B cell development and physiopathology of tolerance breakdown.

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Abstract Number: 16

Comprehensive Antibody Profiling Using High Density Peptide Arrays Reveals Novel Citrullinated Protein Targets in Rheumatoid Arthritis Serum Samples

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Autoantibodies against citrullinated proteins are found in 64-89% of rheumatoid arthritis (RA) patients, with a specificity of 88-99%. While citrullinated vimentin, fibrin and histone have been implicated as targets of autoantibody reactivity, new targets, such as Tenascin-C, continue to be uncovered. To this end, we performed an unbiased epitope-level characterization of autoantibodies from RA serum samples using a high density peptide microarray.

Methods: Our high-density peptide array, comprised of over 4.6M peptides, contains the entire annotated human proteome from the UNIPROT database. The 20,188 unique proteins were represented as overlapping 16-mer peptides. In addition to native peptide sequences, sequences containing arginine residues were replaced with citrulline and lysine residues were replaced with homo-citrulline to provide a comprehensive screen against all possible epitopes. We analyzed IgG antibodies for 27 serum samples (9 control, 9 RA DMARDS responders and 9 RA DMARDS non-responders).

Results: Autoantibody reactivity was seen ubiquitously in all RA serum samples, with citrullinated peptides being the most prevalent over homocitrullinated and native peptide sequences. Hierarchical clustering revealed strong autoantibody reactivity against citrullinated peptides in almost all (8/9) RA DMARDS non-responder and 4/9 RA DMARDS responder samples. Within this group of RA samples with high reactivity, identical immunodominant epitopes were observed in 959

proteins. Within the 959 proteins, which included previously known targets such as vimentin, fibrin and type II collagen, over half have not been previously associated with RA. These include proteins such as PATE4 and NENF.

Conclusion: Using high-density peptide arrays, antibody reactivity was observed against citrullinated proteins that have not been previously associated with RA. These protein targets may further contribute to our understanding of the role of autoantibodies in RA pathophysiology.

Disclosure: K. Lo, Roche, 3,Roche, 1; H. Li, Roche, 3; E. Sullivan, Roche, 3; J. Patel, Roche, 3,Roche, 1.

Abstract Number: 17

Kappa-Deleting Recombination Excision Circles (KREC) in B Cells and Serum B Cell Activating Factor (BAFF): Possible Aids in Predicting Juvenile Dermatomyositis Response to Rituximab

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SESSION INFORMATION

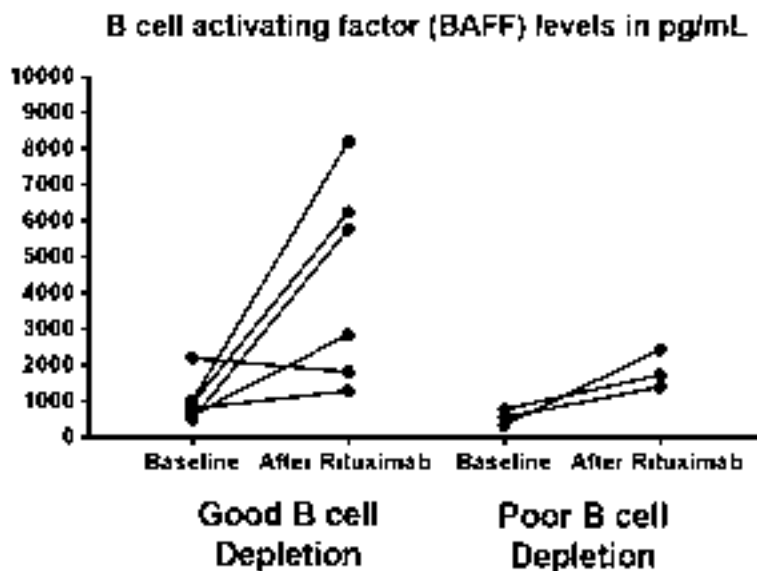
Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Rituximab is used for the treatment of juvenile dermatomyositis (JDM) with variable success. Some of this variability is presumed to be related to the effectiveness of tissue B cell depletion. Forming new B cells requires B cell receptor recombination and the formation of KREC. The KREC does not replicate with B cell divisions. The recombination site on chromosomal DNA is known as the joining code (JC). The ratio of JC: KREC determined by qRT-PCR estimates the number of B cell divisions that have occurred in a B cell population. BAFF is a cytokine produced by activated macrophages and dendritic cell to promote B cell survival and proliferation. We hypothesized that Rituximab treated JDM who have near complete tissue B cell depletion will have a low JC to KRECs ratio and increased soluble BAFF level, which is associated with a more effective response to Rituximab.



Gender	Race	HLA	Medication	Age at 1st Ritux	No of Ritux doses	Disease Manifestations	Oligoclonal B cell expansion	B cell depletion	Response	Relapse
1	F	W	Ro ind, p155/140+	CYC, IVIG, MTX, MMF, steroid	12.3 yr	5	S only	Yes	Yes	Yes
2	M	W	p155/140+	CYC, IVIG, MTX, MMF, steroid	12.4 yr	2	S only	Yes	Yes	Yes
3	M	W	U1RNP+, MDA5+, Ro	MTX, MMF, HCQ, steroid	12.4 yr	1	S only	Yes	Yes	No
4	F	H	p155/140+	CYC, IVIG, MTX, MMF, HCQ, steroid	17 yr	1	S+Mu	Yes	No	n/a
5	F	W	P155/140+	CYC, IVIG, MTX, MMF, HCQ, steroid	11 yr	1	S only	Yes	Yes	No
6	M	B	MJ+	CYC, MMF, HCQ, steroid	14.7 yr	2	Mu only	Yes	No	Yes
7	F	W	P155/140+	CYC, IVIG, MTX, MMF, HCQ, steroid	11 yr	1	S+ Mu	No	Yes	n/a
8	F	H	p155/140+	CYC, IVIG, MTX, MMF, HCQ, steroid	11.2 yr	3	S+ Mu	No	No	n/a
9	F	W	P155/140+	CYC, IVIG, MTX, MMF, HCQ, steroid	15.9 yr	4	S only	No	Yes	n/a

F = Female, M = Male, W = White, H = Hispanic, B = Black, yr = years, m = months, S = Skin, Mu = Muscle, Cyc = Cyclosporine, MMF = mycophenolate mofetil (cellcept), IVIG = Intravenous Immunoglobulin, MTX = methotrexate, HCQ = hydroxychloroquine, Ritux=Rituximab

Methods: This is an IRB approved, retrospective pilot study conducted at Lurie Children's Hospital. We included 9 JDM patients (mean age 12.5 ± 2.2 years). Their demographics are presented in Table 1. We measured JC and KREC qRT-PCR from serial PBMC stored (-80°C) in the CureJM Center Repository. BAFF level was measured using Mesoscale® technology. We defined oligoclonal B cell expansion as a JC:KRECs ratio of 8 or more before Rituximab therapy. A JC:KREC ratio of 2.5 or less on the first detectable sample post-Rituximab was considered as an evidence of good B cell depletion. A good response to therapy was defined as improvement of the Disease Activity Score (DAS) by at least 2 points on two consecutive visits. This study is supported by a grant from CARRA.

Results: 6 out of 9 JDM had evidence of oligoclonal B cell expansion prior to Rituximab use. Of those 6 subjects, 4 had good B cell depletion and responded well to Rituximab therapy. On the other hand, 1 out of 2 subjects with poor B cells depletion had a lack of response to Rituximab. All JDM without oligoclonal B cell expansion had a poor response to Rituximab therapy (Table 1). Although serum BAFF level increased in almost all subjects after Rituximab therapy, subjects with poor B cell depletion appeared to have only a minor increase (Fig 1).

Conclusion: Children with JDM who demonstrate oligoclonal B cell expansion prior to the use of Rituximab have a more favorable outcome. If this finding is confirmed, KREC PCR may serve as a selection criterion for Rituximab therapy. BAFF levels increase after Rituximab therapy, which may contribute to disease flare and may provide a therapeutic target. Limitations of this pilot study include the low numbers of subjects, which requires validation in additional cohorts.

Disclosure: A. khojah, None; V. Hans, None; W. Marin, None; G. A. Morgan, None; L. M. Pachman, None.

Abstract Number: 18

Cytoplasmic FOXO1 Identifies Novel Disease-Activity Associated B Cell Subsets in SLE

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SESSION INFORMATION

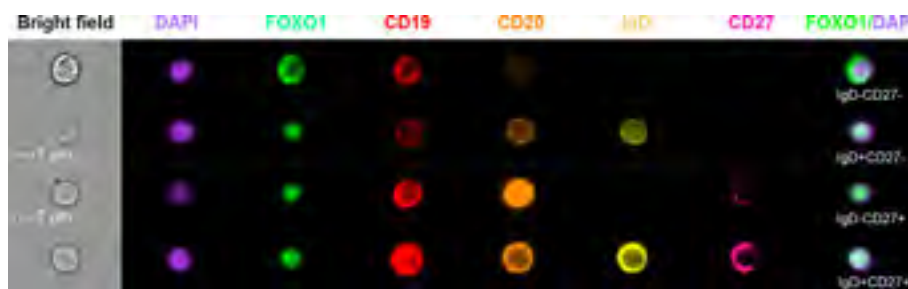
Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: A key integrator of external stimuli in lymphocytes, Forkhead box protein O1 (FOXO1) is a highly attractive factor to study in SLE because it is central to B cell activation/maturation and integration of metabolic and inflammatory stimuli. When active, it remains in the nucleus, but upon Akt phosphorylation downstream of T or B Cell Receptor signaling, FOXO1 is inactivated and shuttles to the cytoplasm, linking FOXO1 localization to function. In SLE, both T and B cells are hyperactive, and respond more quickly and strongly to antigen, producing a disproportionate



inflammatory response. Thus, we hypothesized that SLE lymphocytes would have altered FOXO1 localization, reflecting altered lymphocyte activation.

Methods: To address this hypothesis, we first developed a method of examining dynamic native FOXO1 localization in human peripheral lymphocyte subsets using imaging flow cytometry (IFC). IFC combines the quantitative power of flow cytometry with the qualitative images of microscopy and can be performed with many fewer cells than are needed for the more traditional methods. We demonstrated that we can visualize native FOXO1 and detect significant kinetic differences in localization within user-defined subsets of primary peripheral human T and B cells. We then used IFC to compare FOXO1 localization in SLE and healthy donor lymphocytes.

Results: Most T and B cell subsets demonstrated nuclear FOXO1 localization in both healthy controls and individuals with SLE. However, FOXO1 was significantly more cytoplasmic in SLE in atypical memory IgD-CD27- B cells (see representative figure below). Cytoplasmic-predominant FOXO1 (CytoFox) B cells were significantly increased in SLE patients as compared to healthy controls, and the levels of CytoFox B cells correlated positively with SLE disease activity. The highest abundance of CytoFox B cells was observed in African American females with SLEDAI ≥ 6 and elevated anti-dsDNA Antibodies or lupus nephritis. The phenotype of CytoFox B cells in SLE included relatively low CD20 expression and high granularity/side scatter.

Conclusion: We report, here, on dramatic cytoplasmic localization of FOXO1 in IgD-CD27-(atypical memory) B cells. So-called “Double Negative” (DN) B cells have previously been shown to be increased in SLE and enriched in autoreactive clones. As FOXO1 phosphorylation downstream of B cell receptor-dependent signaling is required for nuclear exclusion, CytoFox B cells likely represent a high state of B cell activation with excess signaling and/or loss of phosphatase activity. We hypothesize that CytoFox B cells in lupus represent a novel biomarker for the expansion of pathologic, autoreactive B cells which may provide new insights into the pathophysiology of SLE.

Disclosure: M. Hritzo, None; A. Golding, None.

Abstract Number: 19

Citrulline-Multispecific B Cell Receptor Clades in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Anti-citrullinated protein antibodies (ACPA) have proven highly useful as biomarkers in rheumatoid arthritis (RA) and appear to be important to disease pathogenesis. Nevertheless, the relationship between progressive B cell receptor (*IGH*, *IGK*, and *IGL*) gene somatic hypermutation (SHM) and citrullinated protein antigen specificity in RA B cells remains only poorly understood. In this investigation, we aimed to characterize citrullinated peptide reactivity as a function of heavy and light chain SHM events using a panel of citrullinated autoantigen-specific RA B cells.

Methods: Three subjects from the University of Minnesota ACPA⁺ RA cohort gave consent for the study of peripheral blood B cell receptor antigen specificity. Citrullinated filaggrin peptide (CFC1) and citrullinated a-enolase peptide (CEP-1) tetramer-bound B cells were subjected to flow cytometric cell sorting and single-cell *IGH*, *IGK*, and *IGL* gene sequencing. BCR genes demonstrating related V-(D)-J region gene usage and conserved junction structures were compared using the PHYLP/DNApars algorithm and B cell lineage relationships (clades) were characterized. BCR gene sequences were also expressed as recombinant monoclonal antibodies (mAbs) for direct evaluation of citrullinated antigen binding by ELISA.

Results: Paired heavy and light chain *Ig* gene sequences were obtained at a single time point from subjects RA14 (n = 9) and RA62 (n = 10). Additionally, 86 paired nucleotide sequences were obtained from subject RA37 at three separate time points. Parsimonious clustering of related immunoglobulin gene nucleotide sequences revealed that 52 of these 105 B cells (50%) arose within 9 unique clades as a consequence of clonal expansion and progressive SHM. The frequency of clade membership by citrullinated peptide tetramer-bound B cells in each subject varied from 44% to 89% ($\chi^2 = 7.0$, P-value = 0.030). The distribution of clade membership by CEP-1 tetramer-bound B cells in subject RA37 also varied significantly across time ($\chi^2 = 25.9$, P-value = 0.011). In ELISA, 9 of 20 recombinant human mAbs (45%) generated from a sample of these BCR sequences proved capable of binding to at least one citrullinated antigen, and all 9 of these citrullinated peptide-binding mAbs derived from a highly mutated clade-associated B cell. Citrulline-dependent cross-reactivity (*citrulline multispecificity*) extending beyond the citrullinated peptides used for B cell capture was observed in all clade-derived mAbs tested.

Conclusion: Our findings suggest that the acquisition of broad ACPA specificity in RA arises from a restricted repertoire of continuously evolving citrulline-multispecific B cell clades.

Disclosure: P. J. Titcombe, None; N. Sippl, None; M. Hansson, None; L. Israelsson, None; K. Amara, None; T. B. Niewold, EMD Serono, 2; L. Klareskog, None; V. Malmström, None; D. L. Mueller, None.

Abstract Number: 20

Expression and Functions of the Transcription Factors Ikaros and Aiolos in Sjogren's Syndrome and Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Polymorphisms of the transcription factors Ikaros (IKZF1) and Aiolos (IKZF3), which are essential for the maturation, differentiation and survival of B cells, have been linked to systemic autoimmunity. The Cereblon modulator CC-220, known to induce the degradation of Ikaros and Aiolos, is being explored as a therapeutic option in Systemic Lupus Erythematosus (SLE). The involvement of IKZF1 and 3 in other autoimmune diseases is poorly known, and their effects on B cell activation and differentiation in the context of autoimmunity have been only partially described. Aim of this study was to evaluate the expression of IKZF1 and IKZF3 in the salivary glands (SGs) of patients with Sjogren's syndrome (SS) and the effects of CC-220 on the TLR7-mediated activation and plasmablast differentiation of B cells isolated from patients with Sjogren and SLE.

Methods: SG biopsies of patients with SS (n=29) and sicca controls (n=11) were analysed by immunohistochemistry for IKZF1 and IKZF3 expression using a semi-quantitative (SQ) score (0-3, based on number of positive cells) to quantify expression. Sequential sections were stained for B and T cells, and patients were classified into Ectopic Lymphoid Structures (ELS) positive and negative. CD19⁺ B cells were isolated from the peripheral blood of patients with SLE (n=16) and Sjogren's (n=4), triggered with TLR7 ligand Resiquimod +/- IFN α , with or without CC-220 (1, 10, 100 nM). After 5 days, cells were analysed by FACS, IgG and IgM measured by ELISA and ANA by immunofluorescence. In parallel experiments, SLE B cells (n=7) were differentiated into plasmablasts in vitro by stimulation with IL-2, IL-10, IL-15, CD40L & Resiquimod for 5 days and analysed as above.

Results: Ikaros expression was significantly higher in the SGs of SS patients vs sicca controls ($p < 0.05$), while aiolos was expressed at similar levels. SS patients with ectopic lymphoid structure (ELS) had significantly higher scores than ELS negative for both IKZF1 ($p = 0.041$) and IKZF3 ($p = 0.016$). CC-220 significantly inhibited the TLR7 and IFN α -mediated production of IgM and IgG from B cells from SLE and Sjogren's patients, in a dose dependent manner, inhibited the production of anti-nuclear antibodies, and significantly reduced the number of CD27⁺ memory B cells. CC-220 significantly inhibited in vitro differentiation of plasmablasts (CD19⁺CD20⁻CD27^{hi}CD38^{hi}) from SLE B cells, while leaving IgD⁺ naive B cells unaffected.

Conclusion: This study shows that Ikaros and Aiolos expression in the salivary glands of patients with Sjogren's syndrome is associated with the presence of ectopic lymphoid structures. CC-220, a cereblon modulator which induces IKZF1/3 degradation, reduced B cell activation and autoantibody production triggered by TLR-7 and IFN- α , and inhibited the differentiation of SLE B cells into plasmablasts. Our work further confirms the relevance of Ikaros and Aiolos in SLE, and suggests that they might be useful therapeutic targets in B cell driven systemic autoimmune diseases, such as Sjogren's.

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Abstract Number: 21

Elevated EPSTI1 Promote B Cells Hyperactivation through NF-Kb Signaling in Patients with Sjögren's Syndrome

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Sjogren's syndrome (SS) is a common systemic autoimmune disease characterized with aberrant B cells activation. B cells play a key role in the pathogenesis of SS, however, the abnormal B cell activation in SS is partially understood.

Methods: We performed whole transcriptome sequencing of B cells from 3 SS patients and 3 matched Healthy controls (HC). We then confirmed the differential gene expressions in 40 SS patients and 40 HC by quantitative PCR and Western-blot. We further transfected with siRNA targeting candidate genes into B cells and stimulated B cells with anti-IgM or CpG to measure the proliferation potential and immunoglobulins secretion. We also explored TLR9 signaling to identify the potential molecular mechanism of B cell hyperactivation in SS.

Results: We identified 51 up-regulated and 22 down-regulated differentially expression genes in B cells from SS patients. We confirmed the RNA and protein level of EPSTI1(Epithelial Stromal Interaction 1) in B cells from 40 SS patients was significantly higher than those from 40 HCs. Comparing with control B cells, EPSTI1-siencing B cells stimulated with CpG (but not anti-IgM) were proliferated less and produced lower level of IgG. We observed the level of p-p65, but not pJNK and (p38MAPK), were decreased in EPSTI1-siencing B cells stimulated with CpG. Consistently, we also found the level of p-p65 was significantly higher in B cells from SS patients than those from HC. Finally, the level of I κ Ba, a key regulator of p65, was significantly up-regulated in EPSTI1-siencing B cells and B cells from HC.

Conclusion: Elevated EPSTI1 expression in B cells from SS patients promoted TLR9 signaling activation and contributed to the abnormal B cells activation. Mechanistically, EPSTI1 stimulated the phosphorylation of p65, which was likely through the interaction and degradation of I κ Ba.

Disclosure: J. L. Sun, None; Z. L. Chen, None; C. F. Lian, None; T. H. Shao, None; H. Z. Zhang, None; H. Chen, None; F. C. Zhang, None.

Monoclonal Anti-Citrullinated Protein Antibodies Generated from RA-Derived B Cells Recognize Amino Acid Motifs Rather Than Specific Proteins

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) associated anti-citrullinated protein autoantibodies (ACPA) develop before RA diagnosis, at which point a wide range of citrullinated proteins have been shown to be targeted based on different peptide assays. Intriguingly, ACPAs have been found to be multi-reactive even on monoclonal level. We set out to study the breadth of that multireactivity and try to determine what the antibodies recognize, as recent findings suggest that certain, but not all, ACPA may have pathogenic properties.

Methods: We screened 6 different monoclonal ACPAs, originating from 3 different patients, 4 were derived from synovial fluid plasma cells and 2 were derived from peptide-tetramer captured B cells from peripheral blood. All ACPA mAbs have confirmed anti-CCP2 reactivity and have demonstrated multi-citrulline-peptide reactivity by ELISA. A custom-made peptide array (NimbleGen, Roche) was designed with 16aa peptides derived from 1610 extracellular matrix- or RA associated- proteins. Peptides containing either an arginine or lysine were synthesized in pairs with a modified version containing either a citrulline or a homocitrulline in the respective position. Altogether >53,000 citrullinated peptides, >49,000 carbamylated peptides and >70,000 native peptides were included. Monoclonal antibodies were run on the array at a concentration of 1ug/ml, while serum and synovial fluid were diluted 1/100.

Results: The monoclonal ACPAs consistently displayed low reactivity (<0.06%) to unmodified peptides, while all 6 reacted to 1,000s (3.4-9.4%) of the citrullinated peptides. Intriguingly, 3 out of the 6 ACPAs also reacted with the carbamylated peptides to a similar broad extent (2.2-4.5% of the peptides). Based on the sequences from the positive peptides we could create LOGOs of the preferred amino acids. Intriguingly, two dominating aa-patterns were identified and only minor contributions from the flanking sequences were observed.

Serum and synovial fluid (SF) from the same patient as the synovial plasma cell-derived ACPAs were also assessed at both the time point of the cell draw and a 10-year follow-up. The SF samples displayed a robust citrulline-reactivity with only 10% divergence between the two samples taken 10 years apart. In contrast, the homocitrulline reactivity was significantly altered between the two time points as approximately 50% of the signals were lost at follow-up in both SF and peripheral blood.

Conclusion: An ACPA serum response is a hallmark of seropositive RA and develops early, often before clinical symptoms. Our study of monoclonal ACPAs generated from established RA implicates that a truly broad citrulline-reactivity is found also on individual immunoglobulin level and may be the result of multiple antigen encounters which have selected for very focused citrulline-recognition with only modest contribution from flanking amino acids. This citrulline autoimmunity appears robust with minimal changes over time, while that was less true for the homocitrulline response.

Disclosure: J. Steen, None; P. J. Titcombe, None; B. Forsström, None; C. Grönwall, None; A. I. Catrina, Glaxo Smith Kline PLC, 2; D. Lightwood, Daniel Lightwood, 3; P. Nilsson, None; L. Klareskog, None; V. Malmström, None.

Treatment with Immune Checkpoint Inhibitors and the Development of Autoantibodies

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: The field of autoimmunity may benefit from the knowledge gained by studying immune checkpoint inhibitors (ICIs). These agents have shown enormous efficacy in oncology by (re)activating T-cells to assault cancer cells, but come at the cost of immune-related adverse events (irAEs). Since ICI's mode of action is not antigen-specific, we hypothesized that tolerance may be broken not only to tumor antigens but also to autoantigens, leading to the formation of autoantibodies. Therefore, we investigated whether patient treated with ICIs develop autoantibodies, and whether this trait is associated irAEs and ICI efficacy.

Methods: In pre- and post-treatment sera of 133 ipilimumab (anti-CTLA4)-treated melanoma patients, we determined 23 common clinical autoantibodies associated with autoimmune diseases (Figure 1). The association between autoantibody development and irAEs (under ipilimumab or subsequent anti-PD-1 therapy), best overall response, and overall survival was investigated.

Results: Autoantibodies developed in 19.2% (19/99) of pre-treatment autoantibody-negative patients ($p < 0.0001$; Figure 1). A non-significant association was observed between development of any autoantibodies and any irAEs: 5/19 (26.3%) patients that developed any autoantibodies had irAEs, versus 46/80 (57.5%) patients that did not develop autoantibodies (OR: 2.92 [95% CI: 0.85 to 10.01]). Predominantly anti-TPO (4.8%, 6/125) and anti-TG antibodies (6.0%, 8/132) developed ($p = 0.03$ and $p = 0.008$, respectively). Patients with anti-thyroid antibodies after ipilimumab had significantly more thyroid dysfunction under subsequent anti-PD-1 therapy: 7/11 (63.6%) patients with anti-thyroid antibodies after ipilimumab developed thyroid dysfunction under anti-PD-1, versus 7/49 (14.3%) patients without antibodies (OR: 9.96 [95% CI: 1.94 to 51.1]). For most other autoantibodies, including RA-associated antibodies, post-treatment positivity increased only marginally and was not associated with occurrence of irAEs in the organ system related to the autoantibody specificity. Becoming autoantibody positive showed a trend towards better overall survival (HR for all-cause death: 0.66 [95% CI: 0.34 to 1.26]; Figure 2) and therapy response (OR: 2.64 [95% CI: 0.85 to 8.16]).

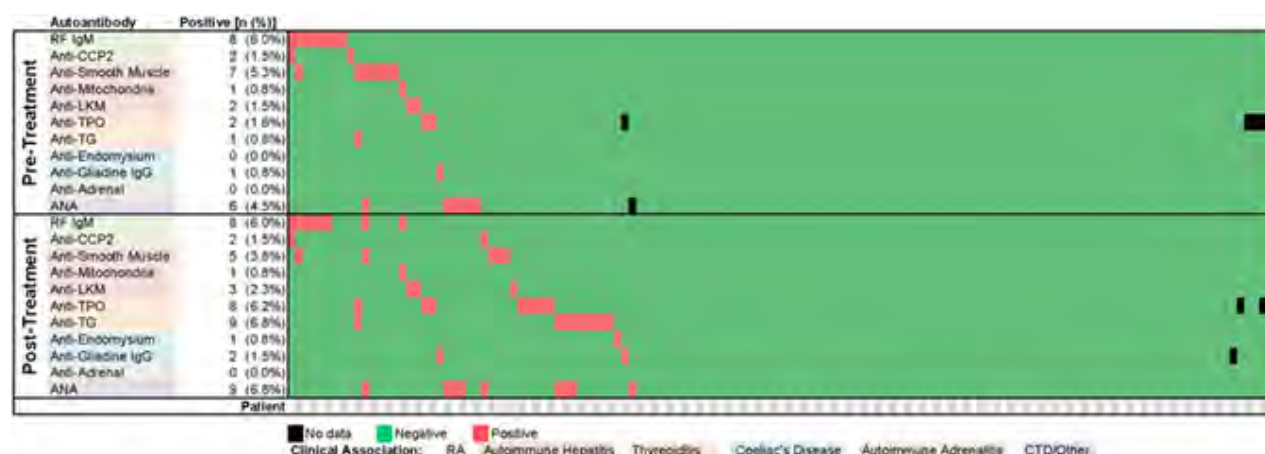


Figure 1. Heatmap of antibody positivity pre- and post-ipilimumab treatment. Not shown: all patients were anti-ENA negative at baseline, while at follow-up, two patients became anti-ENA positive, specifically anti-SSA positive.

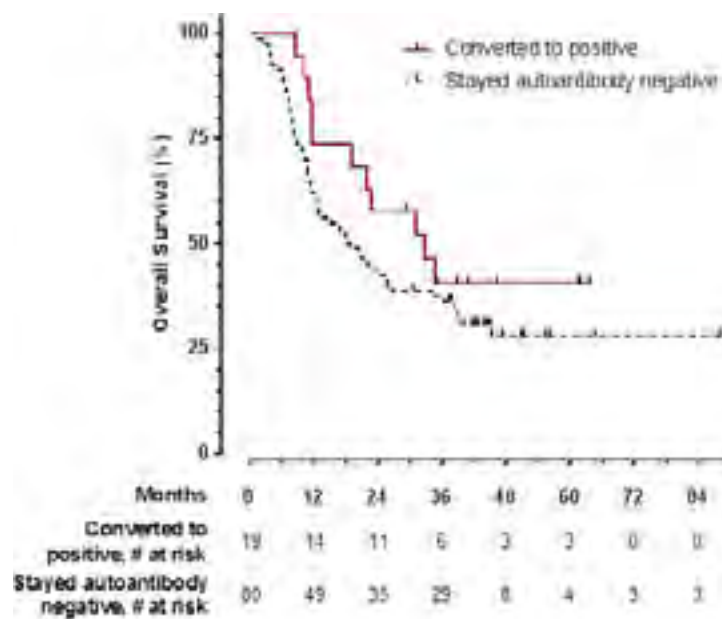


Figure 2: Overall survival for baseline autoantibody negative patients that developed any autoantibodies ("Converted to positive") compared to those that did not develop any autoantibodies ("Stayed autoantibody negative"). Numbers below the graph indicate the number of patients at risk within each group.

Conclusion: Breaking of humoral tolerance as measured by development of autoantibodies is relatively common under treatment with ipilimumab and holds promise as a marker of ICI toxicity and efficacy. The nature of the autoantigens towards which tolerance is broken is not reflected in the phenotype of the irAEs.

Disclosure: E. de Moel, None; E. Rozeman, None; E. Kapiteijn, None; E. Verdegaal, None; A. Grummels, None; J. A. Bakker, None; T. W. J. Huizinga, BMS, 2,EU, 2,Arthritis Foundation, 2,IMI, 2,LUMC, 3,Abblynx, 5,Merck & Co., 5,UCB, Inc., 5,BMS, 5,Biotest AG, 5,Janssen, 5,Pfizer, Inc., 5,Novartis, 5,Roche, 5,Sanofi-Aventis, 5,Abbott, 5,Consulting Bioscience, 5,Galapagos, 5,Nycomed, 5,Boehringer, 5,Takeda, 5,Zydus, 5,Epirus, 5,Eli Lilly and Co., 5; J. Haanen, None; R. E. M. Toes, None; D. van der Woude, None.

Abstract Number: 24

Rituximab Induces an Early Re-Assessment of the Immune and Vascular Systems in Patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: While the role of Rituximab (RTX) in controlling the clinical manifestations of Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) has been documented, the mechanisms underlying the interplay between B-cell depletion and pro-inflammatory status leading to clinical response remain unknown. This translational multicenter study explored changes in serologic variables following B-lymphocyte depletion by *in vivo* Rituximab (RTX) treatment in Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA) patients and investigated RTX *in vitro* effects on the activity of other immune cells and on the vascular endothelium.

Methods: Sixteen SLE patients and 16 RA patients treated with RTX were enrolled. Changes in circulating inflammatory mediators, oxidative stress markers, and NETosis-derived products were evaluated at baseline and after 3 months. Serum miRNomes were identified using next-generation sequencing miRNA assay, and RTX-induced changes were delineated. Purified lymphocytes from RA and SLE patients were treated *in vitro* with RTX for 24h and B-cell depletion and inflammatory profile were evaluated by flow cytometry and RT-PCR respectively. Serum from RA and SLE patients at baseline and after RTX therapy were further added to HUVECs, monocytes, and neutrophils purified from healthy donors and activity profiles were evaluated.

Results: *In vivo* treatment of SLE and RA patients with RTX caused a significant decrease of disease activity along with a prominent alteration in circulating biomolecules related to inflammation, oxidative stress and NETosis. Reversion in altered expression of miRNAs regulating those molecules was also noticed. The *in vitro* treatment of SLE and RA purified lymphocytes with RTX significantly decreased the percentage of B lymphocytes, and was also effective in reducing the levels of a cytokine panel integrated by IL-1 β , IL-6, IFN- γ and TNF- α . Likewise, the treatment of HUVECs, monocytes and neutrophils -isolated from healthy donors- with serum of SLE and RA patients after 3 months of RTX therapy, prevented the overexpression of pro-thrombotic and pro-inflammatory markers induced by the serum of those patients before RTX therapy, and avoided the induction of NETosis in neutrophils.

Conclusion: 1. The role of B cells in autoimmunity is not confined to the production of auto-antibodies, also playing important roles in shaping the outcome of pathological immune responses. 2. RTX induced an early re-assessment of the pro-inflammatory status in RA and SLE patients, involving a re-establishment of the homeostatic equilibrium in the immune system and the vascular wall, thus paving the way to more tailored therapeutic approaches.

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Abstract Number: 25

Circulating CD24^{hi}CD38^{hi} Regulatory B-Cells Influence Th17-Cell Responses in Patients with Granulomatosis with Polyangiitis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: To investigate whether there is a direct relation between expanded proportions of Th17-effector memory (Th_{EM}17) cells and diminished proportions of regulatory B-cells (Bregs) in peripheral blood of granulomatosis with polyangiitis (GPA) patients.

Methods: Frequencies of both Bregs and Th_{EM}17-cells were determined by FACS in blood samples from 42 GPA-patients in remission and 18 matched healthy controls (HCs). Breg frequency was defined as the percentage of CD24^{hi}CD38^{hi} cells within the CD19⁺ population. Th_{EM}17-cell frequency was defined as the percentage of CCR6⁺CXCR3⁺CCR4⁺ cells within the CD3⁺CD4⁺CD45RO⁺CCR7⁺ population. In addition, CD3⁺CD4⁺ Th-cells were sorted from 9 GPA-patients and co-cultured with either total B-cells or with a Breg-depleted cell fraction. Cultured cells were stimulated with Staphylococcus Enterotoxin B (SEB) and CpG-oligodeoxynucleotides (CpG-ODN). Frequencies of Th17- (IL-17⁺) and Th1-cells (IFN γ ⁺) were determined at baseline and day 5 upon restimulation with PMA and Ca²⁺ ionophore.

Results: In remission GPA-patients, the Breg frequency was lower ($p < 0.05$), whereas the Th_{EM}17-cell frequency was increased ($p < 0.001$) compared to HCs. In remission GPA-patients the circulating Breg frequency correlated negatively with circulating Th_{EM}17-cell frequency ($r = -0.371$; $p = 0.007$). The co-culture experiments revealed a significant increase in the frequency of IL-17⁺ Th-cells in Breg-depleted samples (median:3%; range:1-7.5%) compared to undepleted samples ($p = 0.002$; undepleted samples median:2.1%; range:0.9-6.4%), whereas a trend towards a decrease in the frequency of IFN γ ⁺ Th-cells in Breg-depleted cultures was observed ($p = 0.08$; undepleted median:11.8%; range:2.8-21% vs. Breg-depleted median:12.2%; range:2.6-17.6%).

Conclusion: Bregs modulate Th_{EM}17 responses in AAV-patients. Future studies should elaborate on clinical and therapeutic implications of the Breg-Th17 interaction in GPA patients.

Disclosure: A. von Borstel, None; L. L. Lintermans, None; P. Heeringa, None; A. Rutgers, None; C. A. Stegeman, None; J. S. F. Sanders, None; W. H. Abdulahad, None.

Abstract Number: 26

Hints for Catecholamine-Driven Autocrine Mechanisms to Regulate Regulatory B Cells

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease affecting 1% of the worldwide population and characterized by synovial hypertrophy and chronic joint inflammation. In recent work, it has been shown that release of catecholamines by the sympathetic nervous system (SNS) modulates development and course of arthritis. In this context, we were able to show that catecholamines increase the production of the anti-inflammatory cytokine IL-10, which can ameliorate joint inflammation. In the current study, we investigated whether regulatory B cells have enzymes for catecholamine biosynthesis and adrenergic receptors to determine if autocrine mechanisms could contribute to controlling regulatory B cell function.

Methods: In *in vitro* experiments on IgM/CpG-activated murine primary B cells, the basics for the mechanism(s) of increased regulatory B cell function and its targeted influence were investigated. Tyrosine hydroxylase (TH) as well as the expression of adrenergic receptors were analyzed in naïve (0h) or IgM/CpG activated B cells after 24h and 48h by FACS, Western Blot and qRT-PCR. For analysis of IL-10 production released IL-10 from inactivated and activated B cells were quantified in supernatant of B cell cultures by ELISA or directly in B cells by intracellular FACS staining.

Results: Here, we demonstrated that tyrosine hydroxylase (TH), the rate limiting enzyme of catecholamine biosynthesis are strongly expressed by splenic mouse B cells after activation with the BCR/TLR9 stimulus IgM/CpG. Analysis of B cells by FACS showed a raised expression of tyrosine hydroxylase with duration of IgM/CpG activation (0h vs. 24h, $n = 12$, $p^{***} < 0.0001$; 0h vs. 48h, $n = 12$, $p^{***} < 0.0001$; 24h vs. 48h, $n = 12$, $p^{**} = 0.0091$). A sign that catecholamines are not only provided by the sympathetic nervous system, but also produced by B cells. Furthermore, qRT-PCR and FACS showed that all adrenergic receptors (ADR) determined (ADR α 1a, ADR α 1b, ADR α 2b, ADR β 1 and ADR β 2) are expressed on the surface of IgM/CpG-activated B cells ($n = 12$). The number of TH⁺ cells, as determined by FACS correlates with the expression of ADR α 1a ($r = 0.575$, $p = 0.2$, $n = 6$), ADR α 2b ($r = 0.582$, $p = 0.046$, $n = 12$), and ADR β 2 ($r = 0.742$, $p = 0.006$, $n = 12$) ADR β 1 ($r = 0.575$, $p = 0.2$, $n = 6$). After activation with IgM/CpG B cells produce IL-10 as determined by ELISA ($n = 6$, $p^{***} < 0.0001$) and FACS ($n = 5$, $p^{***} < 0.0001$) and the production can be increased by addition of isoproterenol, a ADR-

beta agonist (n=12, p**=0,006), an effect that was blocked by nadolol (n=12, p*=0,0293). FACS analysis showed that IL-10 was mainly produced by TH+ B cells (n=6, p***<0,0001; TH+:23%, IL-10+:1,68% TH+IL-10+:2,13%; 99,3% of IL-10+ cells are TH+).

Conclusion: In conclusion, our data suggest that IgM/CpG-induced expression of TH in murine, primary B cells is associated with an increase in IL-10 mediated by stimulation of betaAR adrenergic receptors. This might point to an autocrine mechanism to control regulatory B cells, which could be exploited for therapeutic purposes in RA.

Disclosure: N. Honke, None; T. Lowin, None; B. Opgenoorth, None; M. Schneider, None; G. Pongratz, None; K. Krebber, None.

Abstract Number: 27

Top-Down Proteomics Coupled with Antibody Sequencing from Single B Cells Reveals a Monoclonal Anti-Sm Clone Present in the Serum of an SLE Patient over Three Years

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Proteomics is becoming an increasingly powerful tool to study autoantibodies. Current bottom-up approaches are yielding a plethora of knowledge about public clonotypes and clonal turnover. However, reports using top-down proteomics are scarce and the advantages of not using digestions to increase the complexity of already complex mixtures are enormous. *De novo* top-down sequencing approaches, however, are extremely difficult. To overcome these limitations, we have coupled antibody sequencing from single B cells with targeted top-down MS for analysis and quantification of antibodies in autoimmune patient serum.

Methods: Fully human recombinant monoclonal antibodies were generated from single B cells. Antibody secreting cells (ASCs), sorted 7 days after vaccination of an SLE patient, have specificities to the vaccine antigen, but SLE patients also have persistent ASCs with auto-specificities which we have detected using this methodology. After identifying monoclonal specificities of interest, we then applied top-down proteomics to search for this antibody clone of known heavy and light chain sequences in longitudinal serum samples from the same donor. The detected ion intensities of known masses were used for quantitation. This allows us to directly link the presence of a specific antibody-producing B cell with a specific monoclonal antibody in the polyclonal serum antibody pool.

Results: An anti-Sm monoclonal was characterized from an SLE donor with high (>mg/ml) levels of anti-Sm. This particular antibody was isolated from an ASC following vaccination with the influenza vaccine. Although this antibody does not bind to influenza virus, it binds to both SmB' (1.5 nM affinity) and SmD (2.6 nM affinity). The serum of the donor was also carefully analyzed over a three-year period and this patient's antibody response to Sm affinity matured, increasing in overall affinity in each year. In order to determine whether this antibody was present in the serum during these three years we purified IgG from the donor's serum using protein A, and applied the polyclonal IgG to an Ultra High-pressure Liquid Chromatography-High Resolution Mass Spectrometry system for top-down proteomics analysis. We determined that the antibody is present in the serum in the year the ASC was isolated, as well as the years before and after.

Conclusion: Our results demonstrate the ability of top-down proteomics, coupled with single cell sequencing of monoclonal antibodies, to perform targeted analysis of specific serum autoantibody clones over time. In this particular SLE patient, we characterized an anti-Sm monoclonal antibody from a single B cell and determined that this antibody is present in the serum over a period of at least three years. Although clonal turnover may produce new predominant clones over a period of months, this technique shows that particular antibody clones are still present for extended periods of time (years). Overall, using single cell sequencing to enable "targeted" top-down proteomics, is a potent method for analyzing single monoclonal antibody specificities in the serum.

Disclosure: Z. Wang, None; J. Muther, None; J. A. James, None; S. Wu, None; K. Smith, None.

The Rho Kinase Family Member, ROCK2, Promotes Germinal Center Responses and Is Required for Optimal Humoral Immunity

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Rho GTPases, such as RhoA, are emerging as important regulators of lymphocyte biology owing to their ability to be rapidly activated downstream of a broad range of signals. Two of the major effectors of RhoA signaling are the Rho Kinases (ROCKs), ROCK1 and ROCK2, a pair of serine-threonine kinases that have been previously implicated in the control of cell adhesion, migration, proliferation/survival, and gene expression. Despite the fundamental reliance of T and B cells on these processes, the precise involvement of the ROCKs in lymphocyte biology is yet to be elucidated. Our laboratory previously identified a role for ROCK2 in the differentiation of T_H17 cells through the phosphorylation of IRF4. This ROCK2-pIRF4 pathway drives the production of key effector cytokines, such as IL-21, and is deregulated in several autoimmune models. While previous studies have focused on the role of ROCK2 in the T cell compartment, ROCK2 is expressed in other immune cell types, including B cells, leading us to hypothesize that ROCK2 may play a broad role in immunoregulation and T-B collaborations.

Methods: To assess the role of B-cell ROCK2 in T cell-dependent responses, WT mice or mice with B cell-specific deletion of ROCK2 were immunized with a T-dependent antigen and differentiation of germinal center (GC) B cells and plasmablasts/plasma cells (PB/PCs) was monitored by FACS. The molecular mechanisms employed by ROCK2 to promote B cell differentiation was further examined by FACS-sorting B cell populations from spleens of immunized mice followed by qPCR and immunoblot analyses. Total and antigen-specific antibody responses were assessed by ELISA.

Results: We found that ROCK2 is activated in GC B cells and in PB/PCs following immunization and that ROCK2 activity is also induced *in vitro* upon stimulation with T-cell derived signals such as aCD40 and IL-21. Mice with B cell-specific deletion of ROCK2 exhibited no abnormalities in their mature B cell compartments at baseline, yet showed marked decreases in total and antigen-specific antibody titers in response to immunization with a TD antigen. These decreased humoral responses corresponded with diminished germinal center formation and maintenance following antigen challenge. Residual germinal centers in ROCK2-deficient mice revealed skewed frequencies of GC subpopulations, reduced proliferation, and attenuated class switching to IgG1.

Conclusion: Our study demonstrates that ROCK2 is activated in B cells following immunization with a TD antigen and is required for optimal GC maintenance and function. These findings thus uncover a previously unknown B cell-intrinsic role for ROCK2 in promoting humoral responses and further support the notion that targeting ROCK2 activity may provide therapeutic benefit for the treatment of diseases marked by aberrant B cell responses.

Disclosure: E. Ricker, None; C. Ye, None; D. Flores-Castro, None; S. Gupta, None; M. Manni, None; Y. Chinenov, None; T. Pannellini, None; J. K. Liao, None; A. B. Pernis, None.

CD70-Mediated CD27 Downregulation Contributed to Regulatory B10 Cell Impairment in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Impaired function of regulatory B10 cells has been shown in autoimmune diseases. However, the underlying mechanism is still obscure. In the present study, we investigated the potential contribution of CD70-CD27 interaction to B10 cell impairment in rheumatoid arthritis.

Methods: A total of 120 RA patients and 73 healthy controls were enrolled in our study. CD19⁺CD24^{hi}CD27⁺ regulatory B10 cells and CD19⁺IL-10⁺ B cells in PBMCs were assessed by flow cytometry. CD70, CD27, IL-10, TNF- α , IL-1 β , IL-6, IFN- γ and IL-17 was evaluated by qPCR. PBMCs from healthy controls were pretreated with or without anti-CD70 antibody before anti-CD3 plus anti-CD28 antibodies treatment. Soluble CD27 and IL-10 in sera and supernatants was detected by ELISA. CD70 expression on CD4⁺ T and CD19⁺ B cells were assessed by flow cytometry in RA and healthy controls.

Results: The frequencies of CD19⁺CD24^{hi}CD27⁺ regulatory B10 cells were decreased and their IL-10-producing competency was impaired in patients with RA. The impairment of CD19⁺CD24^{hi}CD27⁺ B10 cells was partially attributed to the decreased expression of CD27 induced by upregulated CD70 on CD19⁺ B cells and CD4⁺ T cells. The frequencies of CD19⁺CD24^{hi}CD27⁺ regulatory B10 cells could be restored after blocking CD70-CD27 interaction by anti-CD70 antibody. Furthermore, CD70-CD27 interaction significantly elevated the IL-10 expression accompanied and compensated for the number decreasing of CD19⁺CD24^{hi}CD27⁺ B cells.

Conclusion: CD70-CD27 interaction may play a critical role in the numerical and functional impairment of regulatory B10 cells, thus contributing to RA pathogenesis.

Disclosure: L. Shi, None; F. Hu, None; R. Mu, None; Z. G. Li, None.

Abstract Number: 30

CD21^{lo} Cells Are Increased in Patients with Systemic Sclerosis and May be Associated with Interstitial Lung Disease

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Systemic sclerosis (SSc) is a severe systemic disease characterized by fibrosis of the skin and visceral organs. While the exact pathogenesis of SSc is incompletely understood, there is increasing evidence that B cells and autoantibodies may play a role. Several autoimmune-prone B cell subsets have been previously described in other autoimmune conditions including subsets with low CD21 expression (CD21^{lo}), high expression of CD19 (CD19^{hi}), high expression of CD24 and CD38 (CD24^{hi}CD38^{hi}), and high expression of IgD with low expression of IgM (B_{ND} cells). We describe preliminary investigations to the presence of these subsets in SSc.

Methods: Cryopreserved peripheral blood mononuclear cells (PBMCs) were stored as part of the MYSTIC cohort (VUMC IRB141415). Detailed clinical phenotyping was performed at the time of patient enrollment. PBMCs were thawed and subjected to fluorescence flow cytometry to investigate B cell phenotypes in patients with SSc (n=11) versus healthy controls (n=5). Data was analyzed with biaxial gating and the multi-dimensional unsupervised analysis tool viSNE, which displays single cells on a 2D 'map' based on their phenotypic similarity to each other in high dimensional space. Cell frequencies were compared using Mann-Whitney tests.

Results: Biaxial gating revealed that SSc patients had a significantly higher proportion of CD21^{lo} cells relative to healthy controls (Figure 1). There was no difference in the frequency of CD19^{hi}, B_{ND}, or CD24^{hi}CD38^{hi} cells. Subgroup analysis revealed patients with SSc associated ILD (SSc-ILD) had a higher frequency of CD21^{lo} cells relative to patients without

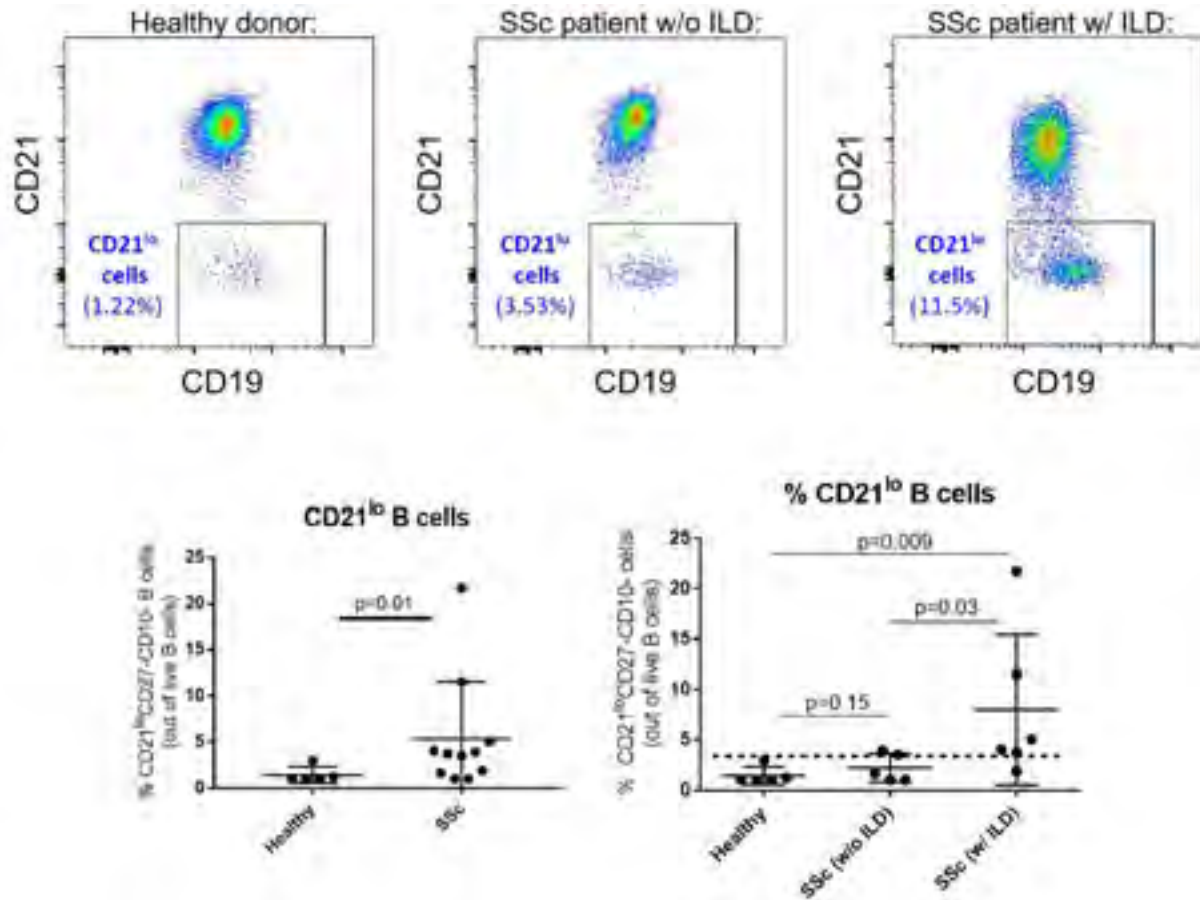


Figure 1. Biaxial gating of CD21^{lo} cells in SSc patients and healthy controls

ILD (mean frequency 7.99% vs. 2.23%, $p=0.03$). Further analysis of the data—using viSNE—confirmed that CD21^{lo} B cells were increased in SSc-ILD patients compared to SSc without ILD ($p=0.03$) (Island 1, Figure 2). viSNE analysis also revealed a population of CD24+IgM- memory B cells (Island 2) that were underrepresented in SSc patients without ILD ($p=0.03$).

Conclusion: Preliminary studies indicate that certain populations of B cells may be associated with SSc-ILD compared to SSc patients without ILD and healthy controls. These findings need to be validated in the larger MYSTIC cohort.

Disclosure: E. Wilfong, None; K. Vowell, None; L. Crofford, None; P. Kendall, None.

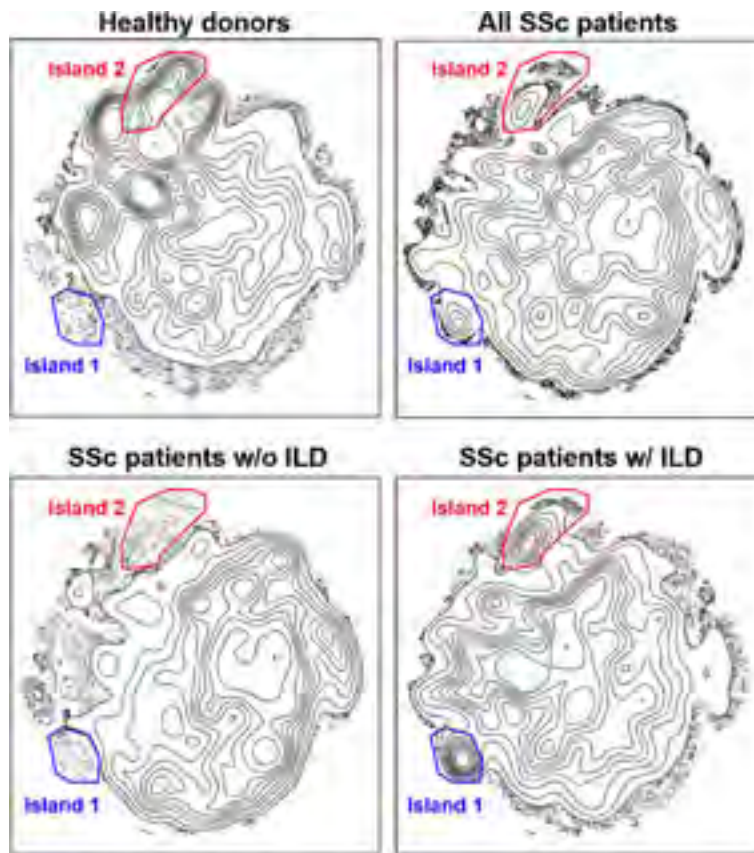


Figure 2. tSNE analysis for concatenated FCS files for healthy donors and systemic sclerosis patients.

Abstract Number: 31

Dendritic Cell-Specific Transmembrane Protein (DC-STAMP) Regulates Inflammation and Joint Damage in the TNF-Tg Mouse Model

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Pathologic bone resorption in rheumatoid arthritis (RA) is mediated by multinucleated osteoclasts (OC) at the bone-pannus junction. OC differentiation (OCgenesis) is dependent on a number of signals that promote cell fusion, formation of specific organelles and the development of a ruffled border. Dendritic Cell-Specific Transmembrane Protein (DC-STAMP), is upregulated in monocytes at early stages of OCgenesis and is required for cell-cell fusion. DC-STAMP^{-/-} mice develop mild osteopetrosis, due to the presence of mononuclear OC with limited capacity to resorb bone. The role of DC-STAMP in the induction of joint inflammation and pathologic bone resorption has not been examined. Therefore, we determine whether the absence of DC-STAMP ameliorates joint inflammation and bone damage in the TNF transgenic murine arthritis model.

Methods: Four experimental groups of 7-month old C57BL/6, DC-STAMP^{-/-}, TNF-Tg and DC-STAMP^{-/-} x TNF-Tg mice were generated. The presence of arthritis was determined by visual examination along with recording of grip strength, and ankle width. We analyzed the impact of DCSTAMP deficiency on bone architecture with mCT-scan analysis. The extent of tibial bone resorption was determined by the area occupied by OC in bone sections. Serum cytokines were quantitated by

multiplex assay and the accumulation of inflammatory cells in bone sections was quantitated by immunofluorescence microscopy.

Results: DC-STAMP^{-/-} x TNF-Tg mice had a 2.5-fold decrease in ankle thickness from week 28 to 49 of age, compared to age-matched TNF-Tg mice ($p < 0.0001$), and was comparable to that of C57BL/6 and DC-STAMP^{-/-} mice. Notably, DC-STAMP^{-/-} x TNF Tg mice had a significantly smaller TRAP⁺ area in the tibia, compared to the TRAP⁺ area in the tibia of TNF-Tg mice (1.05 ± 0.1 vs 17.3 ± 0.6 , $p = 0.0001$). Consistent with the reduction in OC in the tibia, we found a four-fold reduction in bone resorption by OCs in DCSTAMP^{-/-} x TNF-Tg mice, compared to TNF-Tg mice (0.053 ± 0.05 vs 0.21 ± 0.005 , $p = 0.002$). Accumulation of inflammatory cells in the synovia and systemic levels of proinflammatory molecules were markedly reduced in DC-STAMP^{-/-} x TNF-Tg mice (IL- α : 80 pg/ml, 3-fold decrease, $p = 0.001$; TNF- α : 20 pg/ml, 30-fold decrease, $p = 0.04$ and MCP1: 56 pg/ml, 3-fold decrease, $p = 0.04$). In contrast, macrophage infiltration was abundant in the synovial tissue from TNF-Tg mice and correlated with the significantly higher levels of MCP1 (170 pg/ml), a chemokine that attracts macrophages into inflamed tissues.

Conclusion: In addition to the well-known role of DC-STAMP in cell-cell fusion, we found that it is required for progressive development of synovitis and joint damage in the setting of TNF mediated arthritis. Apparently, DC-STAMP modulates synovitis and joint damage through regulation of signaling events that promote differentiation and activation of monocytes and possibly other immune cells.

Disclosure: M. D. L. L. Garcia-Hernandez, None; J. Rangel-Moreno, None; A. Paine, None; B. D. Korman, None; N. Huertas, None; C. T. Ritchlin, AbbVie, Amgen, UCB, 2, AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer Inc, 5.

Abstract Number: 32

T Cell-Intrinsic Nod2 Protects Against Th17-Mediated Autoimmune Arthritis in SKG Mice

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Nucleotide-binding oligomerization domain-containing protein 2 (Nod2) is an innate immune receptor known primarily for its role in host protection against bacterial infections. Intriguingly, Nod2 also appears to have a role outside of infection, as a single point mutation in this molecule leads to 100% incidence of arthritis in Blau Syndrome. Although the contribution of autoreactive CD4⁺ T cells to autoimmune arthritis is appreciated, the molecules that regulate their development and propagation remain unknown. Here we sought to elucidate the role of Nod2 in the generation of autoreactive CD4⁺ T cells using SKG mice, which are genetically predisposed to arthritis.

Methods: SKG and Nod2^{-/-}SKG mice housed under specific pathogen-free conditions were i.p. injected with zymosan (1.5 mg) at 6-8 wk age, clinically monitored for arthritis and analyzed histologically for joint pathology. CD4⁺ T cells from ankle-draining lymph nodes of naïve or zymosan treated mice were stimulated *in vitro* with PMA/io and production of pro-inflammatory cytokines was quantified by ICS and flow cytometry. IL-17 concentration in synovial fluid was determined by ELISA. The role of IL-17 in disease was assessed by *in vivo* neutralization with anti-IL-17A monoclonal antibody. T regulatory (Treg) cell (CD4⁺CD25⁺Foxp3⁺) frequency and ability to suppress T effector (CD4⁺CD25⁻) cell proliferation was determined by Treg suppression assays and flow cytometry. For adoptive T cell transfers, splenic CD4⁺T cells (4×10^6) purified from naïve mice by magnetic positive selection were injected i.v. into lymphopenic Nude (*nu/nu*) recipients who were injected 24h later with zymosan. Experiments were performed three independent times ($n = 5-6$ mice/genotype) and data were analyzed using non-parametric statistics.

Results: Nod2^{-/-} SKG mice developed markedly worse arthritis following zymosan injection that coincided with increased numbers of pro-inflammatory Th17 (CD4⁺IL-17⁺) cells in the ankle-draining lymph nodes and elevated IL-17 protein levels in joint synovial fluid. The increase in Th17 cell frequency was likely not due to compromised Treg responses as the frequency and suppressive capacity of Tregs was not affected by Nod2 deletion. Neutralization of IL-17A *in vivo*

attenuated arthritis in Nod2^{-/-} SKG mice suggesting Nod2 is a negative regulator of IL-17. Importantly, CD4⁺ T cells from naïve Nod2^{-/-}SKG mice had a fundamental capacity to produce more IL-17 and had enhanced ability to passively transfer arthritis to T cell-deplete nude recipients.

Conclusion: These data uncover a previously unappreciated role for T cell-intrinsic Nod2 as an endogenous negative regulator of the Th17 response and the arthritogenicity of CD4⁺ T cells on a single cell level. Understanding how Nod2 participates in immune tolerance mechanisms could illuminate protective mechanisms in arthritis that may be exploited for the future development of novel treatments.

Disclosure: R. Napier, None; E. Lee, None; E. Vance, None; P. Snow, None; C. Dawson, None; K. Samson, None; A. Moran, None; M. Davey, None; S. Sakaguchi, None; H. Rosenzweig, None.

Abstract Number: 33

Card9 Is a Critical Regulator of Autoimmune Arthritis in SKG Mice

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Caspase recruitment domain-containing protein 9 (Card9) is a C-type lectin receptor known for its function in protection against fungal infection and association with human diseases including ankylosing spondylitis and inflammatory bowel disease. Recently, polymorphisms in Card9 were linked to the pathogenesis of a prevalent type of autoimmune arthritis, Rheumatoid arthritis (RA). Here we sought to investigate the role of Card9 in the pathogenesis of arthritis using the genetically susceptible strain of mice (SKG) that develop a T cell-mediated arthritis in response to microbial triggers. Understanding how Card9 affects the pathogenesis of T cell-mediated arthritis will contribute to our understanding of the etiology of RA and development of future therapeutics.

Methods: SKG and Card9^{-/-}SKG mice housed under specific pathogen-free conditions were intraperitoneally injected with zymosan (1.5 mg) at 6-8 wk age, clinically monitored for arthritis, and analyzed histologically for joint pathology. CD4⁺ T cells from ankle-draining (popliteal) lymph nodes were stimulated *in vitro* with PMA/ionomycin and production of pro-inflammatory cytokines was quantified by intracellular cytokine staining and flow cytometry. For adoptive T cell transfers, splenic CD4⁺ T cells (4x10⁶) purified from naïve mice by magnetic positive selection were intravenously injected into lymphopenic nude (*nu/nu*) recipients who were injected 24h later with zymosan. Three independent experiments were performed (n=5-6 mice/genotype), and data analyzed using non-parametric statistics.

Results: To investigate the role of Card9 in arthritis we created Card9-deficient SKG (Card9^{-/-} SKG) mice. In stark contrast to SKG mice that develop chronic arthritis following zymosan injection, Card9^{-/-}SKG mice developed no detectable arthritis. Further examination of the popliteal lymph nodes showed reduced numbers of CD4⁺, CD8⁺, and CD4⁺CD8⁺T cells and decreased total numbers of pro-inflammatory CD4⁺ T effector cells including; Th17, Th1, and Th22. Although Card9^{-/-}SKG had reduced T cell responses and no arthritis there was still a substantial induction in Th17, Th22, and Th1 responses relative to naïve SKG and Card9^{-/-}SKG mice. Furthermore, Card9-deficiency did not affect the arthritogenic capacity of SKG T cells as adoptive transfer of CD4⁺ T cells from naïve Card9^{-/-}SKG or naïve SKG mice into T cell-deplete nude recipients resulted in equal levels of arthritis. These data indicate that Card9 expression is required for the development of arthritis in SKG mice but not for the induction of a pro-inflammatory T effector response.

Conclusion: These findings identify Card9 as an essential mediator of arthritis induced by environmental microbial β -glucans (zymosan) in SKG mice and imply that Card9 positively regulates the magnitude of pathogenic T cell responses and ankle/joint inflammation in SKG mice. Understanding the immunological mechanism by which Card9 controls arthritis will contribute to our understanding of how the environment influences development of autoimmunity in genetically predisposed individuals.

Disclosure: R. Napier, None; E. Lee, None; E. Vance, None; K. Samson, None; P. Snow, None; S. Sakaguchi, None; H. Rosenzweig, None.

Microbiome-Driven Aberration of Hematopoietic Stem Cell Development Facilitates Immune Deregulation on the Onset of Collagen-Induced Arthritis in Mice

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SESSION INFORMATION

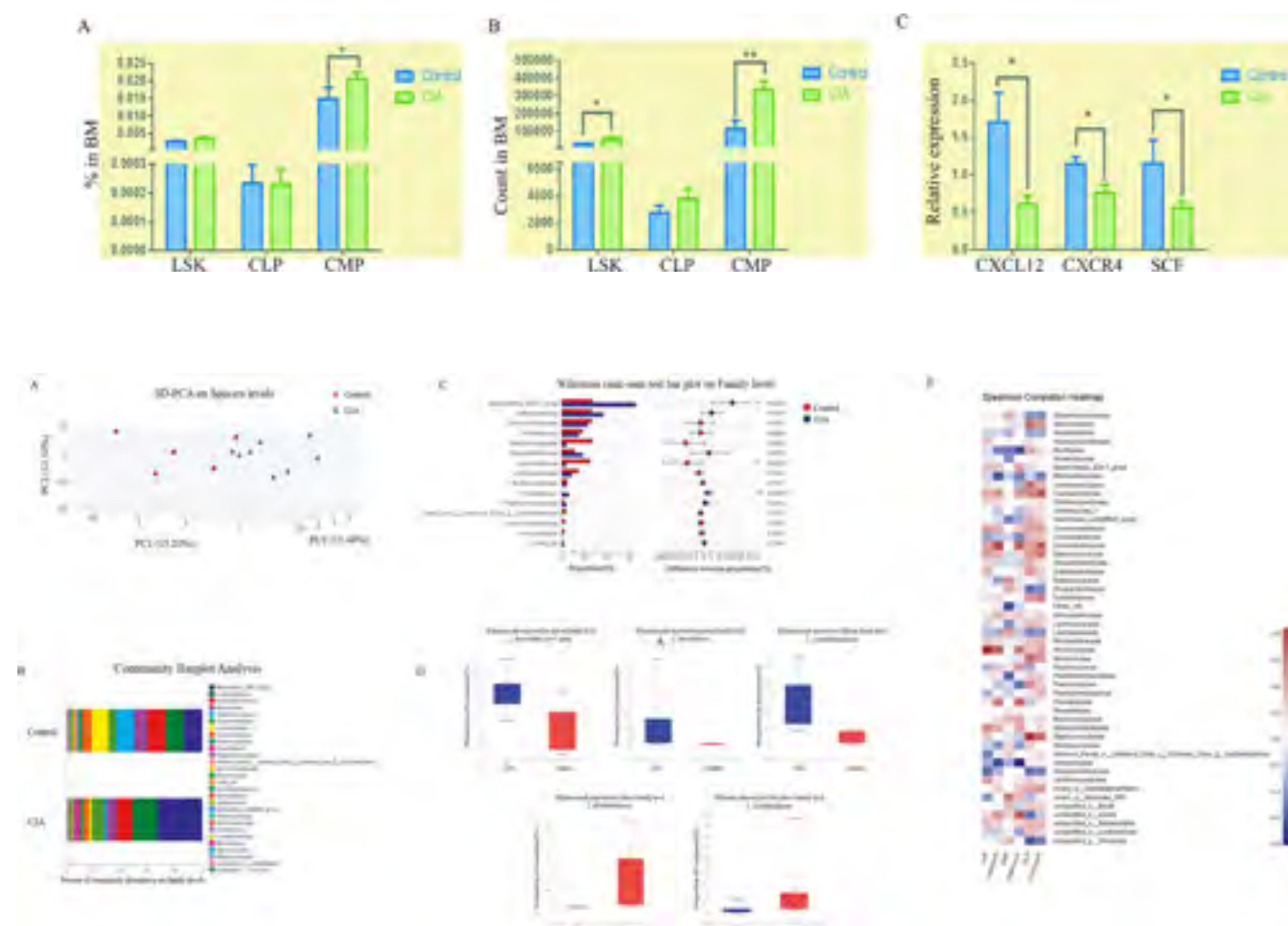
Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Increasing studies indicate that immune deregulation occurs prior to symptom in Rheumatoid arthritis (RA). Hematopoietic stem cell (HSC) gives rise to multipotent progenitors differentiating to lymphoid and myeloid immune cells. The turbulence of HSC development, precisely regulated by bone niche markers, may be the radical factor causing immune deregulation during RA progression. Gut microbiome (GM) is reported to implicate into RA and specific bacteria are known to influence immune cells and HSC⁺'s development. However, whether GM alteration is causation or consequence of RA is still unclear. In this study, we test whether GM affects RA development via regulating HSC⁺'s development in BM at the early stage of arthritis.



Methods: Collagen induced arthritis (CIA) in mice was applied in this study. HSC, common lymphoid progenitor (CLP) and common myeloid progenitor (CMP) in bone marrow were stained with Lineage, Sca-1, c-kit and CD127 cell surface markers and detected by flow cytometry on day 14 after the first immunization. Total numbers of stem cells and progenitors were monitored using beads. Stools were collected and the composition of the intestinal bacterial flora was detected by 16S rRNA sequencing. RT-PCR analysis was used to detect the genes expression of bone niche marker including CXCL12, CXCL4 and SCF.

Results: The percentages of hematopoietic stem cell (LSK, Lin⁻Sca-1⁺c-Kit⁺) and CLP was not altered in CIA mice, whereas the total number of LSK was significantly increased compared with control mice. In contrast, the frequency and number of CMP were significantly enhanced in CIA mice (Fig 1A and B). The gene expressions of SCF, CXCL12 and CXCR4 in CIA mice were significantly lower than that of control. Additionally, the gut microbial communities in cecum of CIA mice was remarkably altered at the species and family level (Fig 2A and B). Analyses of the microbiota at the family level indicated an increase of *Bacteroidales*, *Prevotellaceae*, *Corynebacteriaceae* and a decrease of *Lactobacillaceae* and *Bifidobacteriaceae*(Fig 2C-D). Interestingly, *Prevotellaceae* was positively correlated with both LSK and CMP count. *Corynebacteriaceae* also showed highly positive correlation with LSK, CMP and CLP count. In contrast, *Bifidobacteriaceae* was negatively correlated with LSK count. No significant correlation was found between *Bacteroidales*/*Lactobacillaceae* and HSC and progenitors (Fig 2E).

Conclusion: The increase of HSC count and its differentiation toward CMP occurs in bone marrow at the early stage of CIA mice, which is closely associated with GM alteration.

Disclosure: P. Yang, None; L. Su, None; Y. Li, None; Y. Liu, None; Y. Luo, None.

Abstract Number: 35

Arthritis and Atherosclerosis in KRN Ag7 Mice Involve Distinct Inflammatory Cell Populations and Are Independent of CCR2

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) is an inflammatory disease of the joints associated with cardiovascular disease, which accounts for 40% of RA mortality. Macrophages are implicated in pathology of both RA and atherosclerosis, however it remains unknown if shared immune mechanisms are involved at both sites of disease. To investigate this, KRN Ag⁷ mice which develop spontaneous arthritis and atherosclerosis were used to monitor changes in the cellular composition of the synovium and aorta during development of disease. To further characterize the role of monocyte and macrophage populations, CCR2^{-/-} mice, which have reduced Ly6c^{hi} monocytes and impaired macrophage recruitment, were crossed with KRN Ag⁷ mice to create KRN Ag⁷ CCR2^{-/-}.

Methods: KRN Ag⁷, C57Bl/6, and KRN Ag⁷ CCR2^{-/-} mice were bred in house and euthanized at desired timepoints from 1 - 24 months. Ankles and aortas were collected and single cell suspensions were prepared. Cell suspensions were stained with an antibody cocktail designed to identify monocyte and macrophage populations which were analyzed by flow cytometry. Statistical analysis was carried out in Flowjo v9 and Prism7. Statistical significance was defined at $P \leq 0.05$.

Results: KRN Ag⁷ mice developed arthropathy from birth. Flow cytometric analysis of synovial immune cell populations in KRN Ag⁷ mice from 1-24months identified two phases of disease. From 1-3 months, an inflammatory phenotype is characterized by significant increases in monocytes, eosinophils, and neutrophils and a decrease in dendritic cells, compared to C57Bl/6. During an erosive phase from 6-24months levels of these populations trended towards C57Bl/6 levels, but remained significantly different. Macrophage populations MHCII⁻CX3CR1⁺ and MHCII⁺CX3CR1⁻ were associated with the inflammation phase and were significantly increased and decreased respectively compared to C57Bl/6. KRN Ag⁷ CCR2^{-/-} mice developed comparable arthropathy to KRN Ag⁷ mice from birth, although levels of total CD11b⁺ cells, neutrophils and monocytes were all significantly lower in KRN Ag⁷ CCR2^{-/-} synovium than in KRN Ag⁷. Composition of the macrophage compartment of KRN Ag⁷ and KRN Ag⁷ CCR2^{-/-} mice displayed similar trends including an increased and decreased proportions of MHCII⁻CX3CR1⁺ and MHCII⁺CX3CR1⁻ macrophages. Cell populations isolated from the

aorta of KRN Ag⁷ CCR2^{-/-} mice displayed a striking inflammatory phenotype from 1 month, comprising more total CD11b⁺ cells, neutrophils, and decreased dendritic cells than both KRN Ag⁷ and C57Bl/6 controls. KRN Ag⁷ CCR2^{-/-} aorta also had a significant increase in monocytes, although levels of macrophages were comparable to those of C57Bl/6 controls. All trends were maintained at 3 months.

Conclusion: These findings suggest CCR2 is not essential for the development of inflammatory arthritis in KRN Ag⁷ mice, but does affect cell burden. Surprisingly, aorta tissue from KRN Ag⁷ CCR2^{-/-} mice developed a more striking inflammatory phenotype than KRN Ag⁷. Taken together these findings indicate distinct inflammatory mechanisms are involved in arthritis and concomitant atherosclerosis, and neither process is dependent on CCR2.

Disclosure: A. B. Montgomery, None; C. M. Cuda, None; S. Dominguez, None; M. Mayr, None; D. R. Winter, None; H. Perlman, None.

Abstract Number: 36

The Pleiotropic Effects of TAM Signaling on Inflammatory Arthritis in Mice Using Kbxn Serum Transfer Induced Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

Session Type: ACR Poster Session A

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

Background/Purpose: TAM receptors are a small family of receptor tyrosine kinases comprising Tyro-3, Axl and Mer, which are activated by GAS6 and Protein-S. TAM signaling is involved in phagocytosis, apoptosis, efferocytosis, and leukocyte stabilization and adhesion, and thus has been implicated in inflammatory disease. In fact, our findings from a previous study show apoptosis of neutrophils in the murine joint during inflammatory arthritis induces polarization of synovial macrophages, a key effector cell in arthritis. These data strongly suggest TAM signaling is involved in inflammatory arthritis in mice. However, TAM signaling can also induce immunoregulatory effects via inhibition of TLR signaling and blockade of the cytokine cascade. To that end, we used a number of genetic mouse models lacking TAM receptors Tyro3, Axl and Mer, or GAS6 to investigate the disparate functionalities of TAM signaling in inflammation using the KBxN model of inflammatory arthritis.

Methods: Female GAS6^{-/-}, Tyro-3^{-/-}, Mer^{-/-}Axl^{-/-} and C57Bl/6 mice were bred in house until 8-10 weeks of age. Serum transfer induced arthritis was induced in mice using intravenous administration of KBxN sera at a dose of 85µl/20g. Inflammatory arthritis was monitored and scored for severity from day 0-21 or until all mice had 0 clinical score of disease. Clinical score was measured by scoring each distal joint from 0-3 based on inflammation, and summed to give a maximum clinical score of 12 per mouse. Mean clinical scores of N=4 mice in each treatment group were compared using GraphPad Prism. Differences were considered significant if $P \leq 0.05$.

Results: Tyro-3^{-/-} mice developed less severe inflammatory arthritis than C57Bl/6 controls. Mean clinical score in Tyro-3^{-/-} was less than that of C57Bl/6 controls from day 7 until day 14 although this did not reach statistical significance. Both groups had resolved all inflammation by day 21. Mer^{-/-}Axl^{-/-} mice also had reduced mean clinical score compared to C57Bl/6 controls which was statistically significant from day 11-23 ($P < 0.05$). Inflammation in the Mer^{-/-}Axl^{-/-} group resolved more quickly at day 21 vs day 25. Conversely, the Gas6^{-/-} group had increased disease compared to control mice from day 2 until day 11, which became statistically significant at peak disease on day 7 ($P < 0.05$).

Conclusion: These findings demonstrate the pro-inflammatory effects of Tyro-3, Mer and Axl. In these models Tyro3 deletion inhibited early stage disease, whereas MerAxl deletion resulted in faster disease resolution, thus indicating these receptors induce different downstream effects. Meanwhile, loss of GAS6 in these studies resulted in significantly increased inflammatory arthritis, suggesting GAS6 induces an anti-inflammatory or modulatory effect. Previous studies have shown TAM signaling causes both pro-inflammatory effects and induces a negative feedback loop to reduce inflammation via blockade of TLR signaling. The findings presented here indicate that TAM receptors Tyro-3, Mer and Axl have direct pro-inflammatory functions, whilst specific ligation of GAS6 is required to activate the anti-inflammatory negative feedback process.

Disclosure: A. B. Montgomery, None; S. Dominguez, None; M. Mayr, None; H. Perlman, None.

Discovery of DWP213388, a Potent ITK and BTK Dual Target Inhibitor with Excellent Efficacy, As a Treatment for Autoimmune Diseases

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SESSION INFORMATION

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Background/Purpose: Interleukin-2-inducible T-cell Kinase (ITK) and Bruton's tyrosine kinase (BTK) are critical for B cells and T cells activation, and dysregulation of this process has been known to cause various immune-related diseases. Overexpression or hyperactivation of ITK/BTK has been shown to cause various autoimmune diseases. Existing BTK inhibitors has low clinical efficacy, which creates huge demands for treatment with higher efficacy. Thus, ITK and BTK dual target inhibitors may have synergistic therapeutic efficacy for the treatment of autoimmune diseases, including rheumatoid arthritis (RA). Therefore, we developed a novel ITK and BTK dual target inhibitor (DWP213388), which demonstrates higher pharmacological efficacy than existing selective BTK inhibitor.

Methods: Inhibition of ITK and BTK enzyme activity and selectivity against Cys-family kinase group were evaluated by biochemical assay. Target occupancy in human T and B cells (Jurkat/Ramos) was measured by quantifying unbound ITK or BTK in ELISA-based assay using biotinylated-DWP213388, which binds to free active site of target following DWP213388 pre-incubation. Cellular assays for TCR or BCR stimulation-dependent activation and cytokine secretion were determined in human peripheral blood mononuclear cells (hPBMC). The efficacy of DWP213388 was investigated in collagen-induced arthritis (CIA) models in mouse and rat, in comparison with selective BTK inhibitor. To measure BTK occupancy, mouse spleen was extracted 2 hours and 24 hours after oral administration of DWP213388.

Results: We developed a novel, potent dual target inhibitor, DWP213388, with ITK IC₅₀ value of 1.4 nM and BTK IC₅₀ value of 0.7 nM. More importantly, this compound is highly selective against ITK and BTK, yet has low affinity toward EGFR. DWP213388 potently occupied both of its targets at low concentration (ITK EC₅₀ value of 4.3 nM and BTK IC₅₀ value of 2.2 nM), which shows successful inhibition of TCR/BCR-dependent CD69 expression in T cells (54.4% inhibition at 100 nM) and B cells (58.2% inhibition at 10 nM). Unlike other selective BTK inhibitors, DWP213388 has an inhibitory effect on IL-17 production by Th17 (IC₅₀=29.1 nM). In mouse CIA model, treatment of DWP213388 improved arthritis in a dose-dependent manner, and the inhibitory effect was more potent than selective BTK inhibitor. In addition, histological damages in ankle and knee were markedly improved in mouse CIA model. The ED₅₀ value of DWP213388 is 0.38 mg/kg in mouse CIA model. Oral administration of DWP213388 at 1 mg/kg dose showed BTK occupancy in mouse splenocytes at 2 and 24 hours as 86% and 55%, respectively. BTK occupancy in mouse splenocytes shows strong correlation with the efficacy in mouse CIA model.

Conclusion: We developed a novel, highly potent, and selective covalent inhibitor of ITK and BTK, DWP213388. We demonstrated that DWP213388 has potent in vitro and in vivo pharmacological activities compared to existing selective BTK inhibitor without affecting EGFR. These results suggest that DWP213388 may serve as a next generation therapeutic agent for autoimmune diseases, including RA.

Disclosure: J. H. Jung, Daewoong pharmaceutical, 3; D. Eom, Daewoong pharmaceutical, 3; S. U. Jeon, Daewoong pharmaceutical, 3; Y. D. Shin, Daewoong pharmaceutical, 3; W. Kim, Daewoong pharmaceutical, 3; J. Jung, Daewoong pharmaceutical, 3; Q. Li, Daewoong pharmaceutical, 3; H. Hyun, Daewoong pharmaceutical, 3; J. S. Park, Daewoong pharmaceutical, 3.

Pre-Clinical Clonally-Expanded aggrecan⁸⁹⁻¹⁰³-Specific CD4⁺ T Cells Are a Target for Autoimmune Arthritis Prevention

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SESSION INFORMATION

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Session Type: ACR Poster Session A

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Background/Purpose: In the pre-clinical rheumatoid arthritis (RA) prodrome, autoantibodies and transient symptoms may develop. Pre-clinical autoantibody development suggests concomitant expansion of autoantigen-specific CD4⁺ follicular helper T cells (T_{FH}). A biased T cell receptor (TCR) repertoire in the joints of recent-onset RA patients suggests clonal expansion in early RA. Antigen-specific CD4⁺ T cells were clonally expanded at onset of murine collagen-induced arthritis. To model the pathogenetic role played by autoantigen-specific CD4⁺ T cells before and after autoantibody development, we longitudinally assessed the frequency, phenotype and clonotypic composition of the dominant aggrecan⁸⁹⁻¹⁰³ epitope-specific CD4⁺ T cell repertoire in proteoglycan-induced arthritis (PGIA). We aimed to elucidate how and when autoantigen-specific CD4⁺ T cells contribute to arthritis progression.

Methods: PGIA was induced in BALB/cAnNCrI and BALB/c FoxP3-GFP mice by intraperitoneal injection (prime and two booster injections) of recombinant G1 epitope of human proteoglycan (rhG1-PG) emulsified in DDA adjuvant. MHC class II (I-A^d)-aggrecan⁸⁹⁻¹⁰³ tetramers and single-cell multiplex-nested PCR-TCR sequencing was used to study splenic aggrecan⁸⁹⁻¹⁰³-specific CD4⁺ T cells before and after onset of PGIA. Quantitative and phenotypic analysis of aggrecan⁸⁹⁻¹⁰³-specific CD4⁺ T cells was assessed by flow cytometry, based on the expression of CD44, CD62L, FoxP3, CXCR5 and PD1 and index sorting in TCR sequencing experiments. ELISA measured anti-human PG-specific antibodies.

Results: Splenic aggrecan⁸⁹⁻¹⁰³-specific CD4⁺ T cells expanded in the prodrome before the detection of autoantibodies or persistent disease activity. Aggrecan⁸⁹⁻¹⁰³-specific CD4⁺ T cells shifted from naïve to activated effector memory (T_{EM}) and T_{FH}, associated with a loss of aggrecan⁸⁹⁻¹⁰³-specific FoxP3⁺ Treg. CD4⁺ TCR β-chain variable genes (TRBV)13-1⁺, 13-2⁺ and 2⁺ aggrecan⁸⁹⁻¹⁰³-specific T_{EM} and T_{FH} cells clonally expanded in the prodromal period during transient joint inflammation. After clonotype depletion with anti-TRBV13 mAb, disease onset was delayed, autoantibody titres reduced and arthritis attenuated. Three public TRBV13⁺ clonotypes were shared between mice and between different BALB/c strains. All public clonotypes had conserved amino acid residues arising from convergent recombination, supporting selection of TCR for antigen recognition.

Conclusion: Antigen-specific public clonotypes expand during the prodromal period, prior to development of autoantibodies. Therefore longitudinal antigen-specific TCR repertoire analysis prior to high titre autoantibody development may identify expanding autoreactive CD4⁺ T cell clones in individuals at risk of RA.

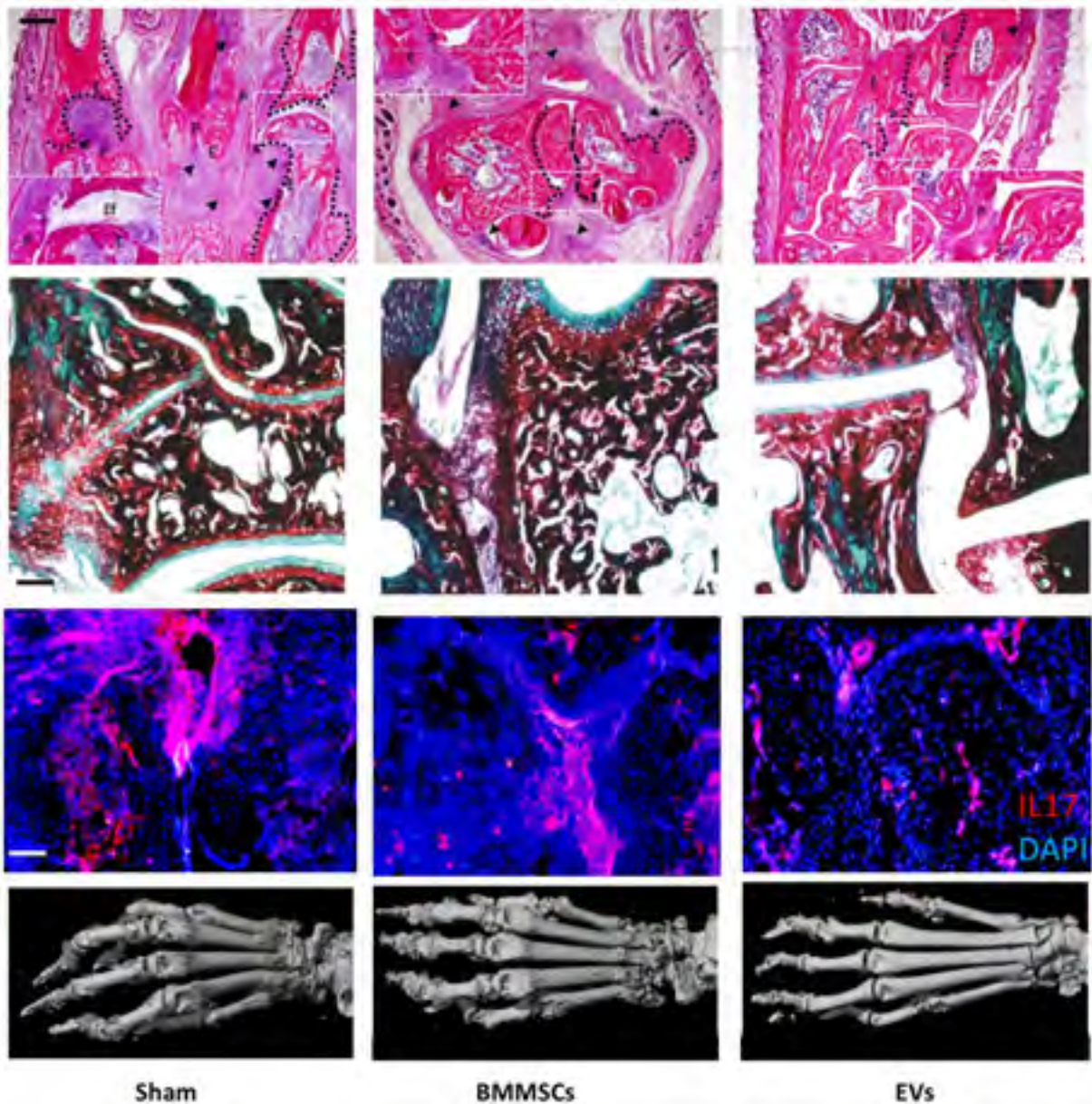
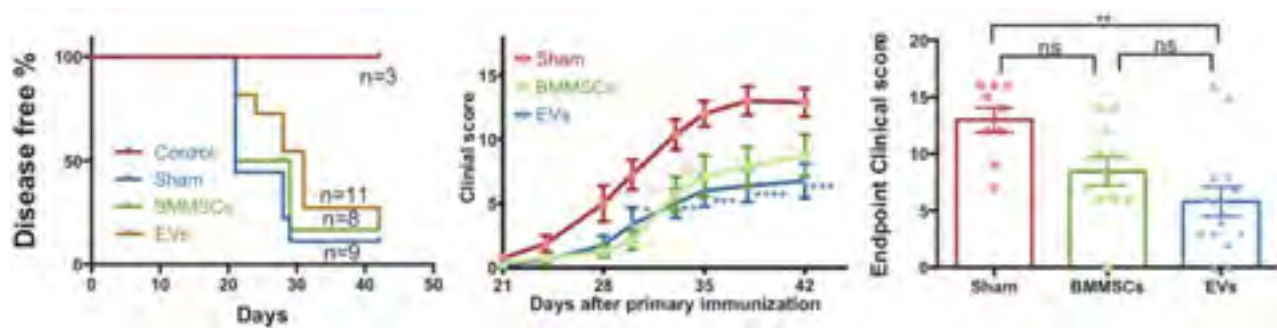
Disclosure: P. Wehr, None; H. Nel, None; S. C. Law, None; D. Jansen, None; N. La Gruta, None; H. Reid, None; J. Rossjohn, None; R. Thomas, None.

Allogeneic Mesenchymal Stem Cells Derived Extracellular Vesicles As a Superior Immunosuppressant in Murine Arthritis Therapy

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The authors declare no conflict of interest.

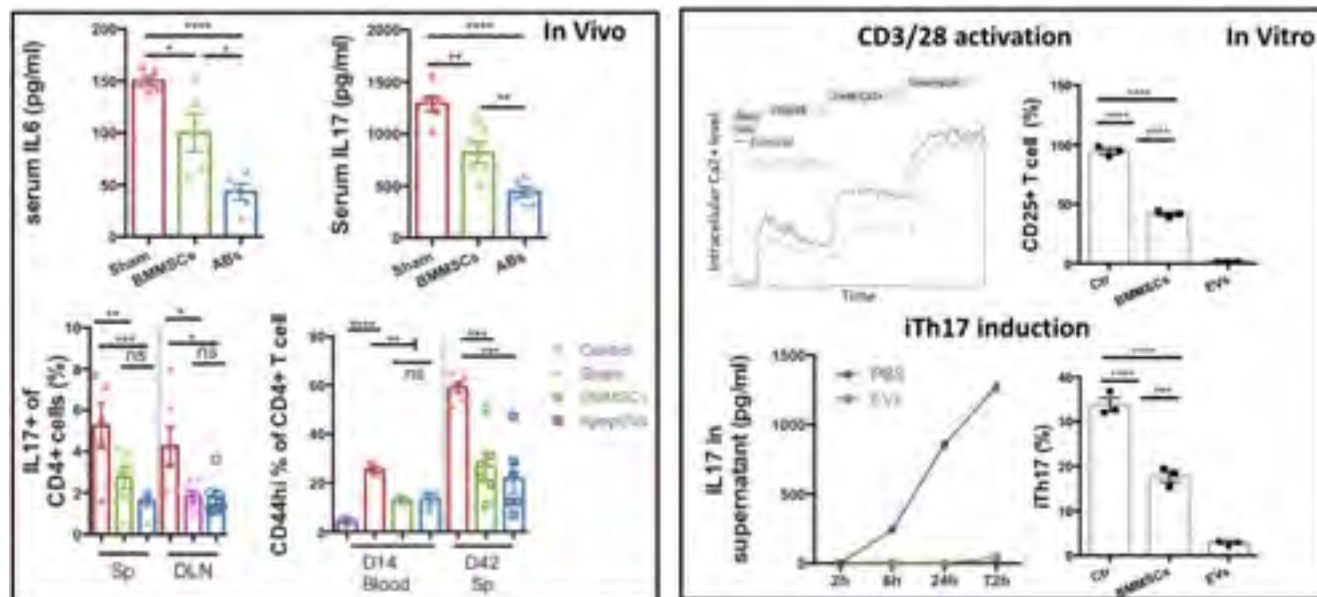
SESSION INFORMATION

Session Date: Sunday, October 21, 2018



Session Title: Rheumatoid Arthritis – Animal Models Poster
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Mesenchymal stemcells (MSCs) are creating promising new options for autoimmune disorders. MSCs utilize multiple mechanisms to modulate immune cells, and extracellular vesicles (EVs) have recently been



recognized as important intercellular mediators, in this study we tested whether EVs derived from allogeneic MSCs would have therapeutic potential in comparison with their parent cells in murine collagen-induced arthritis model.

Methods: At the time of primary immunization with type II collagen, DBA/1 mice were systemically infused with PBS (sham), EVs derived from 1×10^6 allogeneic BMMSCs, and 1×10^6 allogeneic bone marrow MSCs (BMMSCs) as control. Therapeutic efficacy was determined by arthritis activity, joint histology, and CT imaging. Serum cytokine level, as well as T cell phenotypes in blood, spleen and draining lymph nodes were analyzed. Naïve CD4⁺ T cells were isolated and co-cultured with BMMSCs or EVs to assess activation and differentiation.

Results: EVs outperformed BMMSCs in three aspects: clinically, EVs treated mice had delayed onset and milder arthritis score; histologically, with decreased joint inflammation, pannus formation, collagen disruption, IL-17+ cells infiltration, as well as CT visual score; and immunologically, with lower serum IL-6 and IL-17, as well as decreased Th17 and activated CD4⁺ T cells in the circulation and lymphoid organs. When co-cultured in vitro and compared with BMMSCs, EVs decreased Ca²⁺ release upon CD3/28 stimulation and greatly suppressed naïve T cells activation, and suppressed Th17 differentiation.

Conclusion: Collectively, these data demonstrated the outstanding therapeutic efficacy of EVs derived from allogeneic MSCs, and provided a new strategy for stem cell-based immunotherapy.

Disclosure: R. Wang, None; Y. Liu, None; S. Shi, None.

Abstract Number: 40

IFN Regulatory Factor 3 but Not IFN Regulatory Factor 7 Contributes to Bone Erosion in Collagen Induced Arthritis

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Session Title: Rheumatoid Arthritis – Animal Models Poster

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

Background/Purpose: Type I interferons and their mRNA signatures have become prominent in biomarkers of autoimmune and autoinflammatory disease activity. Two master regulators of type I interferon have emerged: interferon

regulatory factor (IRF) 3 and 7. These transcription factors are differentially expressed in immune cells. Prior studies using the K/BxN serum transfer model demonstrated that the *Irf7*^{-/-} mice had increased swelling and the *Irf3*^{-/-} mice had reduced swelling compared to their C57BL/6 WT counterparts. Here we used the collagen induced arthritis (CIA) model to examine the roles of IRF3 and IRF7 in developing arthritis in a model dependent on the adaptive immune system.

Methods: *Irf7*^{-/-} and *Irf3*^{-/-} mice were backcrossed on to the DBA/1J background. To induce arthritis we gave an initial immunization sc with 100mg bovine type II collagen (bCII) in complete Freund's adjuvant with 5mg/mL mycobacterial extract (Chondrex) and then a boost on day 21 with bCII in IFA. In confirmatory experiments bCII was injected in CFA with 2mg/ml M. Tb extract and then to synchronize arthritis 5mg of lipopolysaccharide was injected on day 28. Hind paws prepared for histology or microCT on Day 35 or 40. Sera tested by ELISA for IL-6 and anti-mouse collagen antibodies. Synovial tissues were frozen and mRNA harvested and qPCR performed.

Results: In the CIA model, DBA.Irf7 mice had greater ankle swelling ($P<0.0001$; $F(2, 2095) = 27.51$), than DBA.Irf3 and WT mice, and DBA.Irf3 mice had with lower clinical scores ($P<0.0001$; $F(2, 1302) = 35.85$). There was no difference anti-mouse collagen type II (mCII) antibody levels or serum IL-6 between the groups. Strikingly there was minimal inflammation, bone erosion and cartilage damage in the DBA.Irf3 compared to the other groups ($P=0.036$; $F(2, 27) = 3.978$). In a second protocol adapted to increase arthritis severity using an injection of LPS on day 28. Using this protocol DBA.Irf3 ($p<0.0001$; $F(1, 962) = 24.33$) and DBA.Irf7 ($P<0.001$, $F(1, 731) = 99.74$) mice had decreased joint scores compared to WT DBA mice. DBA.Irf3 and DBA.Irf7 mice had the same levels of anti-mCII antibodies as WT. In the DBA.Irf3 male mice there was no significant difference in the cortical bone fraction (% BA/TA; 68.05 ± 2.56 vs. 70.05 ± 0.30 , $p>0.05$) compared to WT, but there was a significantly lower trabecular bone volume fraction than WT as assessed by microCT (% BV/TV; 15.72 ± 1.24 vs. 29.82 ± 1.37 ; $p<0.05$). Joint extracts were prepared and gene expression was determined by qPCR. Interferon β and associated transcripts (*Cxcl10*, *Ccl5*) were reduced in the synovial tissues DBA.Irf3, but not the DBA.Irf7 mice ($p < 0.05$). *Mmp3*, *Mmp9*, *Mmp13*, *Rank* and *Opg* mRNA were increased in the DBA.Irf3 mice and Cathepsin K mRNA was decreased. There was no significant difference in RANKL.

Conclusion: IRF7 deficiency had an impact on swelling but minimal impact on histologic bone damage in the CIA model. In contrast IRF3 deficiency was markedly protective of bone erosion and was associated with a decline in IFN β and cathepsin K mRNA.

Disclosure: S. Sweeney, Eli Lilly and Co., 3; D. L. Boyle, None; Y. Fujita, None; A. Bui, None; G. S. Firestein, None; M. Corr, None.

Abstract Number: 41

TAS5315, a Novel Bruton's Tyrosine Kinase Inhibitor, Improves Bone Strength in Mouse Model for Rheumatoid Arthritis

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Background/Purpose: The erosions of bone and cartilage are a cardinal feature of rheumatoid arthritis (RA) and associated with disease severity and poor functional outcome. Although several anti-inflammatory drugs for treatment of RA improve symptoms of articular inflammation and bone erosion, unfortunately they do not have a powerful potency against repair of existing bone erosion. Bruton's tyrosine kinase (BTK), which is expressed in immune cells and mature osteoclasts, is reported to be a key molecule in inflammatory response and bone resorption. Thus, targeting BTK may be efficacious against not only inflammation but also bone erosion through direct regulation of activation of effector cells such as B cells, macrophages and osteoclasts in RA.

Previously, we evaluated the effect of TAS5315, a novel BTK inhibitor, on bone damage in an established mouse collagen-induced arthritis (CIA) by micro-CT analysis, and revealed that TAS5315 improves bone erosion in a mouse CIA.

However, it remained uncertain whether TAS5315 improves the bone quality.

In this study, we assessed mechanical bone strength of the tibia in a mouse CIA for the purpose of examining whether TAS5315 improves bone quality as well as bone erosion.

Methods: Kinase selectivity of TAS5315 was assessed by available kinase assay panels. The BioMAP Diversity PLUS panels were used to determine the profile of TAS5315 in primary human cell systems. The effects of TAS5315 on osteoclasts were

assessed by examining phosphorylation of BTK, osteoclast *differentiation and bone resorptions*. TAS5315 were orally administrated once a day for 14 or 21 consecutive days in an established mouse CIA model. Bone mineral density (BMD) and bone erosion were assessed using micro-CT analysis. The mechanical strength of the tibia was evaluated by a three-point bending test of the tibial diaphysis and a compression test of proximal metaphysis using a material-testing machine.

Results: TAS5315 selectively inhibited the enzyme activity of BTK and had less off target inhibition against other kinases. In BioMAP Systems, TAS5315 decreased the production of IgG and the expression of cytokines (TNF α , IL-8, IL-17A, IL-6, IL-17F and IL-2) and increased the expression of IL-10. TAS5315 also inhibited RANKL and M-CFS-induced phosphorylation of BTK, and bone resorbing activity in osteoclasts.

In an established mouse CIA model, TAS5315 significantly ameliorated paw swelling and pathological features at a dose of 0.1 mg/kg. TAS5315 also showed repair of BMD by time-dependent micro-CT analysis. The mechanical strength tests of tibia were performed in an established mouse CIA model. Whereas the mechanical strength of tibia was decreased in CIA model mice compared to normal mice, TAS5315 led to recovery of the decreased parameters of mechanical strength of tibia.

These data suggests that TAS5315 indicated more potent efficacy on joint damage as well as inflammation, and improved bone quality as well as bone erosion in mouse model for RA through direct inhibitory effects against osteoclasts function.

Conclusion: Our study demonstrates that TAS5315 would be an ideal RA therapeutic agent that could improve bone destruction as well as inflammation.

Disclosure: R. Kaneko, None; F. Hosoi, None; S. Iguchi, None; H. Hayashi, None; Y. Yoshiga, None; Y. Nakachi, None; D. Akasaka, None; K. Tanaka, None; T. Utsugi, None; E. Sasaki, None; Y. Iwasawa, None.

Abstract Number: 42

Modulation of Autoimmune Arthritis By Protein Tyrosine Phosphatase SHP-1

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

Session Type: ACR Poster Session A

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

Background/Purpose: The protein tyrosine phosphatase termed Src homology region 2 domain-containing phosphatase-1 (SHP-1) is known to exert negative regulatory effects on immune cell signaling. Mice with mutations in the Shp1 gene display inflammatory skin disease and autoimmune features, but no arthritis.

The objective of this study is to explore the role of SHP-1 in arthritis using cartilage proteoglycan (PG)-induced arthritis (PGIA), an autoimmune model of rheumatoid arthritis (RA). We generated Shp1 transgenic (Shp1-Tg) mice overexpressing this phosphatase to study the impact of SHP-1 overexpression on arthritis susceptibility and adaptive immune responses.

Methods: Wild-type (WT) and Shp1-Tg mice were immunized with cartilage PG in adjuvant, and arthritis symptoms were monitored. Tyrosine phosphatase activity, T-cell and B-cell proliferation and activation in response to polyclonal stimulation as well as global protein tyrosine phosphorylation (pTyr) levels were measured in spleen cells from WT and Shp1-Tg mice using cell proliferation and enzyme activity assays, flow cytometry, and Western blot. Statistical analysis was carried out employing GraphPad Prism 7.

Results: Interestingly, while all of the WT mice developed arthritis after PG immunization, none of the Shp1-Tg mice developed disease (n=13-16 mice per genotype). Shp1-Tg spleen cells showed 7-fold higher tyrosine phosphatase activity than WT cells. In response to polyclonal stimulation, T and B cells from Shp1-Tg mice proliferated less well and expressed significantly lower levels of activation markers than those from WT mice. Global pTyr levels were also lower in T and B cells from Shp1-Tg mice than in cells from WT animals.

Conclusion: Resistance to autoimmune arthritis in Shp1-Tg mice is likely due to impaired T- and B-cell responses to PG immunization. Reduced T- and B-cell activation and resistance to arthritis in the presence of SHP-1 overexpression seem to result from the impairment of tyrosine phosphorylation (deactivation) of key T-cell and B-cell signaling proteins, due to the overwhelming tyrosine phosphatase activity of the enzyme in Shp1-Tg mice. Our study is the first to investigate the role of SHP-1 in autoimmune arthritis. Further experiments with the animal model may identify a therapeutic target for the treatment of human autoimmune arthritis such as RA.

Abstract Number: 43

Novel Anti-Malarial Drug Derivative Inhibited Anti-Citrullinated Protein/Peptide Antibodies and Rheumatoid Factors Production in Dnaseii/Ifnr Double Knock out Mice

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

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Background/Purpose: Rheumatoid Arthritis (RA) is a highly prevalent autoimmune disease affecting ~1% of the world population and can lead to permanent joint damage and severe disability. Although current biologics improve disease, they do not cure or even lead to long-term remission. DNase II is an enzyme that degrades endosomal DNA. When DNaseII^{-/-} mice are crossed to mice that lack the Type 1 Interferon Receptor (IFNAR) to create double knockouts (DKO), the DKO develop a rheumatoid arthritis (RA)-like disease including ACPA antibodies in the serum. The arthritis is dependent on activation of the cGAS-STING pathway, likely caused by leakage of DNA from the endosome into the cytosol. Since we synthesized a novel antimalarial like drug (X6) that was effective in the inhibition of cGAS in mice in vivo, we tested the effects of X6 on arthritis and serology in the DNaseII/IFNAR DKO mouse model of RA.

Methods: DNaseII DKO mice were treated orally with either Splenda alone or X6 in Splenda at 25mg/kg/day (n=6) from 2 to 6 months of age. Anti-Citrullinated Protein/Peptide Antibodies (ACPA) were quantified with ELISA kit (IMMUNOSCAN CCPlus kit from Euro Diagnostica), except that Alkaline Phosphatase-conjugated goat antibody against mouse immunoglobulin (IgM) was used as the detection antibody. RF IgG/IgM and total IgG/IgM were quantified by in house ELISAs. Swelling of the forelimb and hindlimb joints was inspected manually and scored blindly. Cytokines in the synovial tissues were quantified by qPCR.

Results: ACPA is a highly specific and sensitive serologic biomarker of RA. There was increased IgM-ACPA expression in IFNAR^{-/-}/DNaseII^{-/-} (DKO) mice compared to IFNAR^{-/-}/DNaseII^{+/+} (WT) and IFNAR^{-/-}/DNaseII^{+/-} (Het) mice (Fig. 1A). X6 treatment statistically significantly reduced IgM-ACPA compared to untreated controls (p<0.01, Fig. 1A). X6 treatment reduced IgM-RF although these values did not reach statistical significance. Total IgM and IgG were significantly elevated in DKO mice compared to DNaseII WT and Het mice (Fig. 1B and 1C). X6 treatment statistically significantly decreased total IgM (p<0.01, Fig. 1B) and total IgG (p<0.01, Fig. 1C) compared to untreated controls. Tumor Necrosis Factor (TNF)

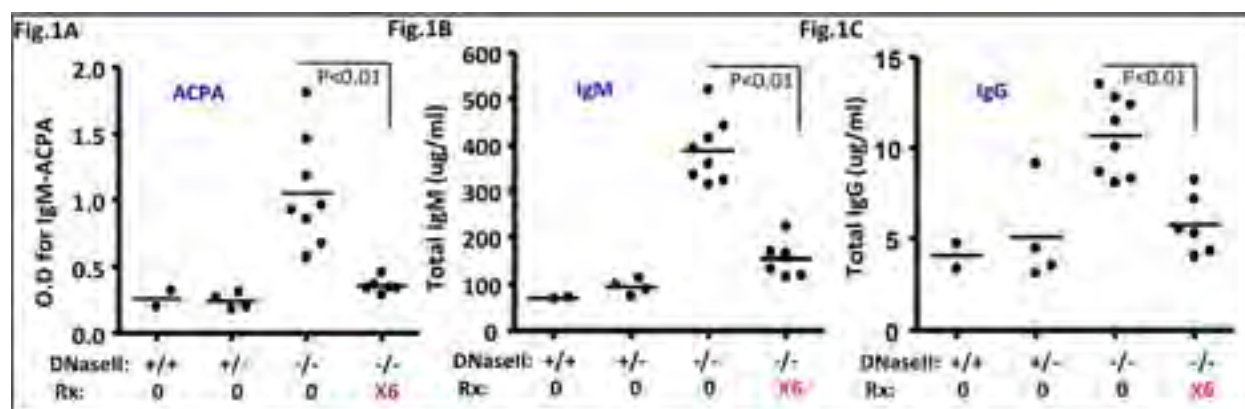


Figure 1. Drug X6 treatment decreased the IgM-ACPA(1A), total IgM(1B) and total IgG(1C) production in the serum of DNaseII/IFNAR DKO mice

is the key cytokine implicated in the pathogenesis of arthritis in DKO mice. X6 treatment reduced mRNA expression of TNF although reduction did not reach statistical significance. Clinically, X6 treatment did not significantly reduce the arthritis score and joint thickness.

Conclusion: Our studies demonstrate that X6 was highly effective in reducing the elevated arthritis-relevant serology that includes ACPA and total immunoglobulins. While clinical arthritis did not change significantly at 25 mg/kg/day, higher drug doses may be beneficial. Differential impact of X6 on the cGAS-STING versus the TLR pathways may also be relevant for future exploration.

Disclosure: J. An, None; B. Madarampalli, None; X. Sun, None; L. Tanaka, None; E. H. Noss, None; J. Woodward, None; T. Sasaki, None; K. B. Elkon, None.

Abstract Number: 44

Histone Deacetylase 1 (HDAC1): A Novel Therapeutic Target in Patients with Rheumatoid Arthritis

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Background/Purpose: Despite enormous efforts to develop new therapeutic strategies for treatment of rheumatoid arthritis (RA), the large number of non responding patients to currently available drugs underlies the unmet need to identify new therapeutic targets. Certain CD4⁺T cell subsets, especially Th17 cells, have been shown to be major drivers of inflammation in patients with RA. The expression of their key transcription factors is controlled by histone modifications which includes acetylation of *lysine residues* mediated by histone deacetylases (HDAC). Indeed, pan HDAC inhibitors have been shown to be a potential therapeutic strategy. However, major side effects limited the clinical use and underline the need of more specific HDAC inhibitors. We therefore addressed the individual role of HDAC1 on the development of collagen-induced arthritis model (CIA).

Methods: Mice with a T cell specific deletion of HDAC1 (HDAC1 cKO) were generated by using the CD4Cre/LoxP system. Collagen induced arthritis (CIA) was induced at week 8. Animals were scored for paw swelling and grip strength. After 10 weeks, mice were sacrificed and paraffin sections of the affected joints were analysed for histomorphologic signs of inflammation, cartilage and bone destruction. Anti-CII antibody levels were determined by ELISA. Serum samples were analysed for various cytokines by multiplex assays. CCR6 expression in CD4 T cells was analysed by flow cytometry.

Results: To address potential effects of HDAC1 in the pathogenesis of RA, CIA was induced in *HDAC1cKO* mice and *WT* mice. Surprisingly *HDAC1cKO* mice were completely protected from the development of arthritis. In line with the clinical data, histological analysis revealed no signs of inflammation, no bone erosion and no osteoclasts in the joints of *HDAC1cKO* mice. Anti-CII antibodies, including total IgG and IgG2c were detected in *HDAC1cKO* and *WT* mice. Surprisingly, IL-17 was significantly decreased in the serum of *HDAC1 cKO* mice as compared to *WT* mice, suggesting a role of HDAC1 in the development of Th17 cells. To see whether HDAC1 is involved in the regulation of the chemokine receptor 6 (CCR6), the main marker of Th17 cells, we compared the upregulation of CCR6 in CD4⁺ T cells from *WT* and *HDAC1cKO* mice. Indeed, CCR6 could not be upregulated in CD4⁺ T cells from *HDAC1cKO* mice upon IL-6 *in vitro*. These data support the role of HDAC1 in the regulation of CCR6, an important chemokine receptor, which is necessary for the migration of pathogenic Th17 cells and therefore for the development of arthritis.

Conclusion: Our data show the importance of HDAC1 as a key immune regulator in the pathogenesis of T cell driven collagen induced arthritis. Therefore, it might be considered as an interesting novel therapeutic target in RA.

Disclosure: L. Goschl, None; V. Saferding, None; J. Bäcklund, None; C. Scheinecker, None; J. S. Smolen, Abbvie, Astra-Zeneca - to Institution, 2, Abbvie, Chugai, Gilead, ILTOO, Janssen, Lilly, MSD, Novartis-Sandoz, Pfizer, Samsung, Sanofi, 5, Abbvie, Celgene, Chugai, Janssen, Lilly, MSD, Pfizer, Samsung, Sandoz, UCB, 9; G. Steiner, Thermo Fisher Scientific, 2, 5; W. Ellmeier, None; M. Bonelli, None.

Abstract Number: 45

CKD-506, First-in-Class Histone Deacetylase (HDAC) 6 Inhibitor, Ameliorates Rheumatoid Arthritis through Regulation of Inflammation and T Cell Function

Jieun Shin¹, Nina Ha¹, Daekwon Bae¹, Dong-Hyeon Suh¹, Ji-yeon Baek¹, Jae Hyun Jun¹, Yong Jae Lee¹, Changsik Lee¹, Sei-Hwan Kim¹, Young Il Choi¹, Keun Ho Ryu¹, Yu Jin Jang², Sehui Shon², Yeong Wook Song³, Gi Soo Youn⁴ and Jinseu Park⁴, ¹Research Institute of Chong Kun Dang Pharmaceutical Corporation, Yongin, Korea, Republic of (South), ²Department of Molecular Medicine and Biopharmaceutical Sciences, Seoul National University, Seoul, Korea, Republic of (South), ³Seoul National University College of Medicine, Seoul, Korea, Republic of (South), ⁴Department of Biomedical Science, Hallym University, Chuncheon, Korea, Republic of (South)

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Background/Purpose: Broad-spectrum histone deacetylase inhibitors are well known for immunomodulatory functions. However, due to their toxicity, HDAC subtype specific inhibition has been proposed as therapeutic strategy for treatment of autoimmune diseases. Herein, we introduce CKD-506, a potent and selective HDAC6 inhibitor, as an immunomodulatory agent for treatment of rheumatoid arthritis.

Methods: The selectivity and potency of CKD-506 were determined by enzyme assay. Adjuvant- (AIA) induced arthritis animal model was used to evaluate its *in vivo* efficacy. Peripheral blood mononuclear cells (PBMCs) and fibroblast-like synoviocytes (FLS) from rheumatoid arthritis (RA) patients were used for *ex vivo* studies. Macrophage cells with HDAC6 overexpression were used for mechanism studies.

Results: CKD-506 showed potent and selective inhibitory activity on HDAC6 with an IC₅₀ of 5 nM in enzyme assay and induced tubulin acetylation in human PBMCs and rat lymphocytes. In AIA model, CKD-506 strongly inhibited arthritis score as well as serum anti-CCP level. Interestingly, CKD-506 exhibited strong synergistic efficacy with MTX in rat AIA model. In *ex vivo* study with RA patients' samples, CKD-506 inhibited secretion of inflammatory cytokines and chemokines such as TNFα and CXCL10 but induced IL-10 secretion. Moreover, the induced regulatory T cells of RA patients, which had been differentiated in the presence of CKD-506, significantly inhibited the proliferation of effector T cells. In mechanism studies, HDAC6 overexpression induced the expression of various inflammation mediators such as cytokines, chemokines and adhesion molecules from macrophages but CKD-506 inhibited HDAC6-mediated inflammatory responses of macrophage in a dose dependent manner. CKD-506 with MTX exhibited better anti-inflammatory effect on macrophages with HDAC6 overexpression.

Conclusion: CKD-506 exhibited strong efficacy in *ex vivo* studies with RA patients' samples as well as *in vivo* rat AIA model. CKD-506 is a first-in-class HDAC6 inhibitor for treatment of rheumatoid arthritis. (Current status: in preparation of Phase IIa for moderate to severe RA patients in EU).

Disclosure: J. Shin, None; N. Ha, None; D. Bae, None; D. H. Suh, None; J. Y. Baek, None; J. H. Jun, None; Y. J. Lee, None; C. Lee, None; S. H. Kim, None; Y. I. Choi, None; K. H. Ryu, None; Y. J. Jang, None; S. Shon, None; Y. W. Song, None; G. S. Youn, None; J. Park, None.

Organic Dust Inhalants Shift Immune Responses and Extracellular Matrix Balance between Synovium and Lung in the Collagen-Induced Arthritis Mouse Model

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SESSION INFORMATION

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Background/Purpose: Emerging evidence suggests that the lungs may be an initiating site of autoimmunity leading to RA with organic inhalant exposures such as those from cigarette smoking acting as a trigger. To study the impact of organic inhalant exposures in RA pathogenesis, we previously developed a novel mouse model by exposing mice with collagen induced arthritis to repeated organic dust extract (ODE). Our objective in the present study was to evaluate autoantibody responses and tissue expression of extracellular matrix proteins (ECM) that have been implicated in RA pathogenesis and that may be involved in articular and lung responses in this model.

Methods: Male DBA/1J mice were injected with chicken collagen type II with Freund's complete adjuvant (CIA) or saline on day 1 and 21. ODE or saline was instilled by intranasal inhalation daily for 5 weeks. Groups are identified as: 1) Saline, 2) ODE, 3) CIA, and 4) ODE + CIA. Anti-citrullinated protein antibody (ACPA) and IgG antibody to malondialdehyde-acetaldehyde (MAA) were measured in serum. Synovial and lung tissues were collected and stained for the presence of MAA, collagen II, fibronectin and vimentin. Confocal microscopy was used to assess tissue expression of ECM and MAA. Coloc 2 plugin (ImageJ) was used to quantify correlations between the tissue expression of ECM and MAA.

Results: Serum ACPA concentrations were significantly increased ($p < 0.05$) in mice treated with ODE + CIA compared to all other treatment groups. Anti-MAA levels were increased in the ODE exposed mice compared to Saline or CIA ($p < 0.0001$) and decreased with the addition of ODE + CIA ($p < 0.02$). ECM and MAA expression mean pixel density in lung and joint tissues are shown in the Table 1. Paralleling enhanced arthritis and attenuated lung disease previously reported in ODE + CIA, differential colocalization of MAA with both collagen II and vimentin was observed in both synovium and lung ($p < 0.001$) in ODE + CIA (Figure 1). In contrast, fibronectin + MAA colocalization was similarly predominate in the lung in all groups.

Conclusion: Increased ACPA and decreased anti-MAA levels in the ODE + CIA treated group suggests a shift in the immune response with dual exposures. Likewise, ECM protein expression was markedly altered between synovium and lung in the combined ODE + CIA model. Our study importantly characterizes alterations in immune responses and ECM proteins that may explain the compartmentalized response of increase in inflammatory arthritis with the simultaneous attenuation of pulmonary disease previously observed in CIA mice exposed to ODE.

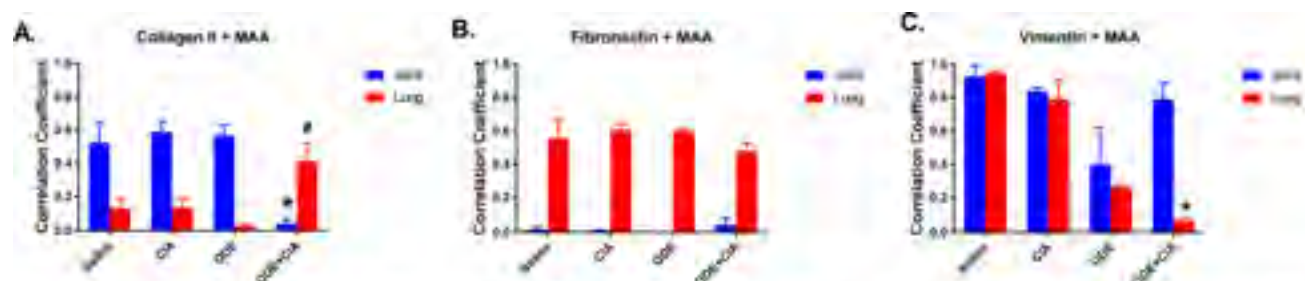


Figure 1. Correlation coefficients between Extracellular matrix proteins and MAA in saline, CIA, ODE, and ODE + CIA treated mice (A) Collagen II + MAA antibody (B) Fibronectin + MAA antibody (C) Vimentin + MAA antibody. Collagen + MAA significantly decreased in lung tissue for all groups (* $p < 0.001$), significantly increased in the lung for all groups (# $p < 0.001$). Vimentin + MAA significantly decreased in the lung for all groups (* $p < 0.001$).

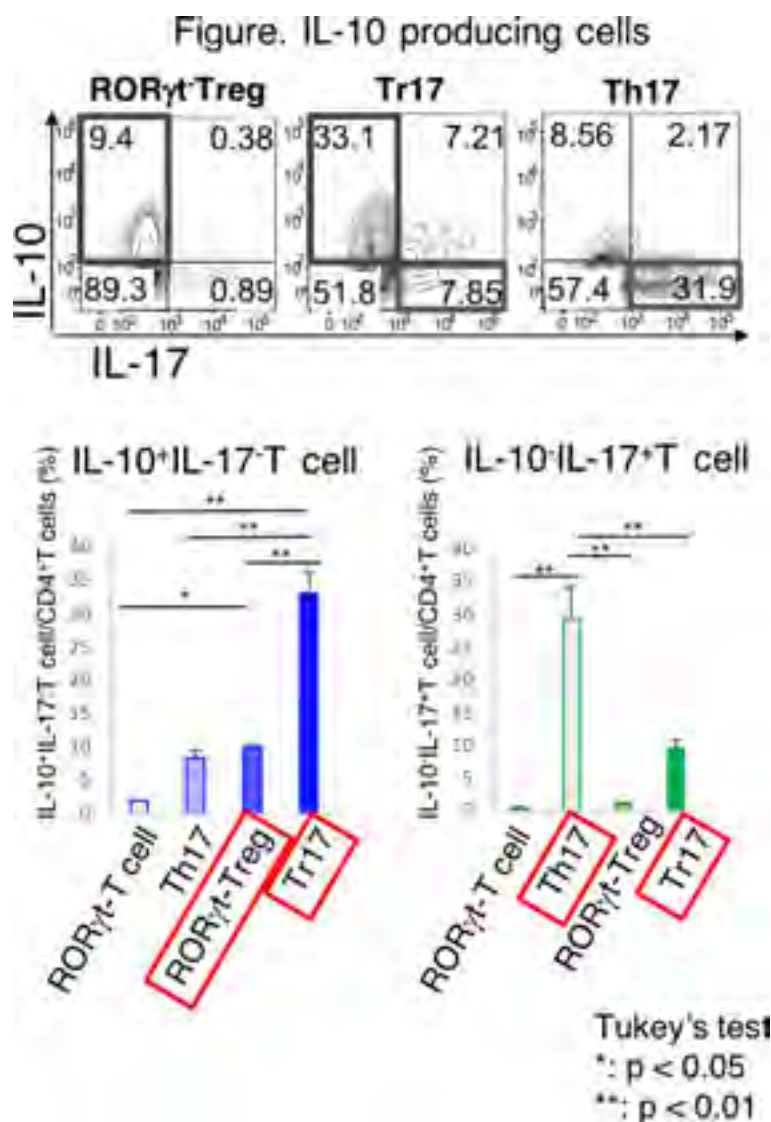
	Joint Tissue Mean Pixel Density				Lung Tissue Mean Pixel Density			
	Saline	CIA	ODE	ODE + CIA	Saline	CIA	ODE	ODE + CIA
MAA	1.39 ± 0.25	16.3* ± 1.85	33.25*# ± 1.48	20.2* ± 4.5	8.4 ± 0.4	17.7 ± 1.6	28.62* ± 6.0	21.1* ± 4.9
Collagen II (CII)	5.50 ± 1.32	4.45 ± 1.23	5.54 ± 1.46	59.3* ± 15.7	2.56 ± 0.42	59.6* ± 17.7	0.48 ± 0.03	0.19 ± 0.044
Fibronectin	3.6 ± 0.9	12.8 ± 1.50	35.8*# ± 8.9	24.9* ± 2.4	0.02 ± 0.004	0.04 ± 0.006	1.91*# ± 0.31	2.80*# ± 0.736
Vimentin	15.9 ± 3.46	46.5*# ± 5.03	2.8\$ ± 0.92	49.1*# ± 7.0	35.4 ± 16.9	68.7\$ ± 9.2	0.47* ± 0.19	4.0* ± 1.0
Significance	Increased (*p<0.05) compared to saline MAA increase (#p<0.05) compared to CIA CII increase (*p<0.01) compared to all groups Fibronectin increase (*p<0.05) compared to saline Vimentin increase (#p<0.04) compared to CIA Vimentin Increase (\$p<0.04) compared to ODE				MAA increase (*p<0.01) compared to saline CII increase (*p<0.01) compared to all groups Fibronectin increase (*p<0.05) compared to saline Vimentin Decreased (*p<0.01) compared to saline Vimentin Decreased (\$p<0.05) compared to CIA			
	Note: All values shown are 10 ⁵ units				Note: All values shown are 10 ⁵ units			

Disclosure: M. J. Duryee, None; J. Poole, None; A. Nelson, None; K. Janike, None; L. W. Klassen, None; J. R. O'Dell, Medac, 5; B. R. England, None; T. R. Mikuls, BMS, Ironwood, Horizon, 2, Pfizer, Inc., 5; G. M. Thiele, None.

Abstract Number: 47

Analysis of the Role of ROR γ t+Foxp3+ T Regulatory 17 (Tr17) Cells in Murine Autoimmune Arthritis Model

Kotona Furuyama¹, Yuya Kondo¹, Masaru Shimizu², Iizuka Akira¹, Masahiro Yokosawa¹, Seiji Segawa¹, Hiroto Tsuboi¹, Isao Matsumoto¹ and Takayuki Sumida¹, ¹Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, ²Internal Medicine, Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan



SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

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Background/Purpose: ROR γ ⁺Foxp3⁺ regulatory T (Treg) cells, designated as Tr17 is one of the new subset of Treg cells, having the potential to regulate the development of experimental autoimmune encephalomyelitis (EAE) through a specific repression of Th17 mediated inflammation. The function of Tr17 remain unclear in the development of other autoimmune diseases such as collagen induced arthritis (CIA). To clarify the role of ROR γ ⁺Foxp3⁺ Tr17 in the development CIA.

Methods: 1) Lymphocytes in draining lymph node were harvested from C57BL/6 mice on 10 days after immunization of type II collagen (CII) emulsified with complete Freund's adjuvant. The expression of ROR γ t in Foxp3⁺Treg cells was analyzed by flow cytometry and compared them with lymphocytes of non-immunized mice. 2) At 10 days after CII immunization, C-chemokine receptor type 6 (CCR6), CD25, cytotoxic T-lymphocyte antigen 4 (CTLA-4), and Glucocorticoid-induced TNF-receptor (GITR) expression on Tr17, ROR γ t Treg cells, and ROR γ ⁺ T cells (Th17) in lymph node were analyzed by flow cytometry. 3) Lymphocytes in draining lymph node were harvested from Foxp3^{IREs-gfp} reporter mice on 10 days after first CII immunization. CD4⁺GFP⁺ Treg and CD4⁺GFP⁺ T cells were isolated and stimulated with PMA and Ionomycin *in vitro*. The expression of IL-10 and IL-17 in ROR γ ⁺GFP⁺ Tr17 cells was analyzed by flow cytometry and compared with that in ROR γ t GFP⁺ cells or ROR γ ⁺GFP⁺ cells. 4) After the induction of CIA, lymphocytes in inflamed ankle joints and draining lymph node were harvested from Foxp3^{IREs-gfp} reporter mice. The expression of CCR6, CD25, and CTLA-4 were analyzed in ROR γ ⁺GFP⁺ cells, ROR γ t GFP⁺ cells or ROR γ ⁺GFP⁺ cells by flow cytometry.

Results: 1) ROR γ ⁺Foxp3⁺ Tr17 cells in draining lymph nodes were significantly increased in CII-immunized mice compared with non-immunized mice. 2) CCR6 and CD25 expression was elevated on Tr17 cells compared with ROR γ t Treg cells and Th17 cells and CTLA-4 and GITR expression was also up-regulated on Tr17 cells compared with ROR γ t Treg cells. 3) IL-10 producing cells were increased in Tr17 cells compared with ROR γ t Treg cells (33.2 \pm 2.95, $p < 0.001$). On the other hand, IL-17 producing cells were decreased in Tr17 cells in spite of the high expression of ROR γ t compared with ROR γ ⁺Th17 cells (9.57 \pm 1.25, $p = 0.002$) (Figure). 4) CCR6⁺Treg cells were increased in inflamed ankle joints compared with draining lymph node after the induction of CIA. CD25 expression was elevated on joint infiltrating CCR6⁺Treg cells compared with CCR6⁺ Treg cells. There was no difference of CTLA-4 expression between CCR6⁺ and CCR6⁺Treg cells in inflamed joints.

Conclusion: Tr17 cells were increased in the course of CIA and might preferentially infiltrate into inflamed joints. Moreover, Tr17 cells had the potential to regulate the development of CIA through the high expression of suppressive molecules such as IL-10 and CTLA-4 in inflamed joints.

Disclosure: K. Furuyama, None; Y. Kondo, None; M. Shimizu, None; I. Akira, None; M. Yokosawa, None; S. Segawa, None; H. Tsuboi, None; I. Matsumoto, None; T. Sumida, None.

Abstract Number: 48

In Vivo Demonstration of Tmtnf Reverse Signaling: Significance in the Therapeutic Response to Anti-TNF Agents during Murine Arthritis

Numa Simons¹, Andrey Kruglov², Yannick Degboe³, Arnaud Constantin³, Sergei Nedospasov⁴, Alain Cantagrel⁵, Jean-Luc Davignon⁶ and Benjamin Rauwel⁶, ¹Rheumatology, Purpan Hospital, Toulouse III University, Toulouse, France, ²German Rheumatism Research Centre, Berlin, Germany, ³Department of Rheumatology, Purpan Hospital, Toulouse III University, Toulouse, France, ⁴Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, Russian Federation, ⁵Center of Rheumatology of CHU, Toulouse, France, ⁶CPTP, INSERM UMR 1043, Toulouse, France

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

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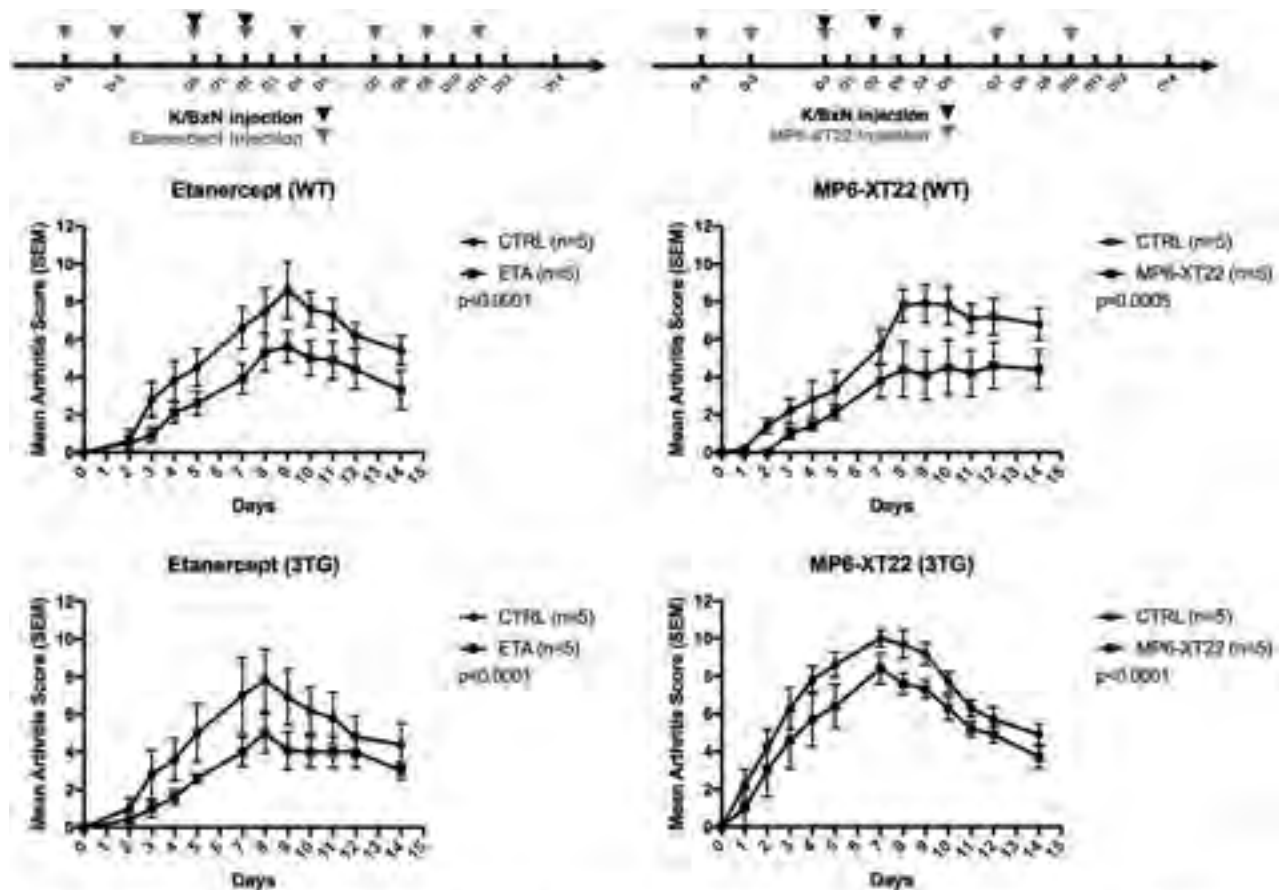


Figure 1: Evolution of K/BxN serum arthritis-induced clinical scores in WT (n=10) and 3TG (n=10) mice over time. K/BxN serum was injected I.P. on days 0 and 2. Etanercept (ETA) or MP6-XT22 were injected (10 mg/kg) I.P. on days -5, -3, then every 2 or 3 days.

Background/Purpose: Anti-TNF agents are widely used in rheumatoid arthritis (RA). Their effect on inflammation results from the neutralization of soluble TNF (sTNF), but also supposedly from the induction of reverse signaling through their binding to membrane TNF (tmTNF). Despite possible clinical relevance, reverse signaling has been described only *in vitro* but has not been proven *in vivo*.

Methods: Triple transgenic mouse model (3TG), KO for TNFR1 / TNFR2 and KI for tmTNF, thus secreting no sTNF was developed. To analyze reverse signaling, mice were injected either with etanercept (ETA), an anti-mouse TNF antibody (MP6-XT22, rat IgG1) or an anti-human IL17 antibody (secukinumab, SEC) as a control. Daily clinical evaluation of K/BxN serum induced-arthritis was performed in 3TG as well as WT mice. Polarization of bone marrow-derived macrophages (BMDM) from non-arthritic WT and 3TG mice under the action of anti-TNF *in vitro* was evaluated by RT-qPCR and flow cytometry.

Results: *In vivo*, the administration of anti-TNF (ETA or MP6-XT22) decreased arthritic scores in WT mice ($p=0.005$) as well as in 3TG mice ($p<0.001$), unlike SEC which had no effect, proving that anti-TNF binding of tmTNF decreased arthritis (fig. 1). *In vitro* effect of anti-TNF on BMDM from WT as well as 3TG mice induced a decrease in the expression of genes specific of inflammatory macrophages, and an increase in the expression of genes specific of alternative macrophages. This suggested a switch in macrophage polarization as a probable mechanism for modulation of inflammation during K/BxN serum-induced arthritis.

Conclusion: Our work provides *in vivo* evidence for the involvement of reverse signaling in the anti-TNF-mediated modulation of arthritis. Reverse signaling is expected to result in the modulation of macrophage polarization from an inflammatory to an alternative functional phenotype in arthritic mice. Our data prompt us to consider new interpretation of the effects of anti-TNF in the treatment of RA.

Disclosure: N. Simons, Société Française de rhumatologie, 2; A. Kruglov, None; Y. Degboe, MSD Avenir, 2; A. Constantin, MSD Avenir, 2; S. Nedospasov, None; A. Cantagrel, MSD Avenir, 2; J. L. Davignon, MSD Avenir, 2; B. Rauwel, MSD Avenir, 2.

Tofacitinib Facilitates the Expansion of Myeloid-Derived Suppressor Cells and Ameliorates Interstitial Lung Disease in SKG Mice

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Background/Purpose: SKG mice, which are rheumatoid arthritis (RA) model, develop not only arthritis but interstitial lung disease (ILD) resembling RA-ILD. Myeloid-derived suppressor cells (MDSCs) are heterogeneous immature myeloid cells with suppressive functions. We previously reported that tofacitinib, which is JAK inhibitor, facilitates the expansion of MDSCs and ameliorates arthritis in SKG mice. The purpose of this study is to elucidate the effect of tofacitinib on ILD in SKG mice.

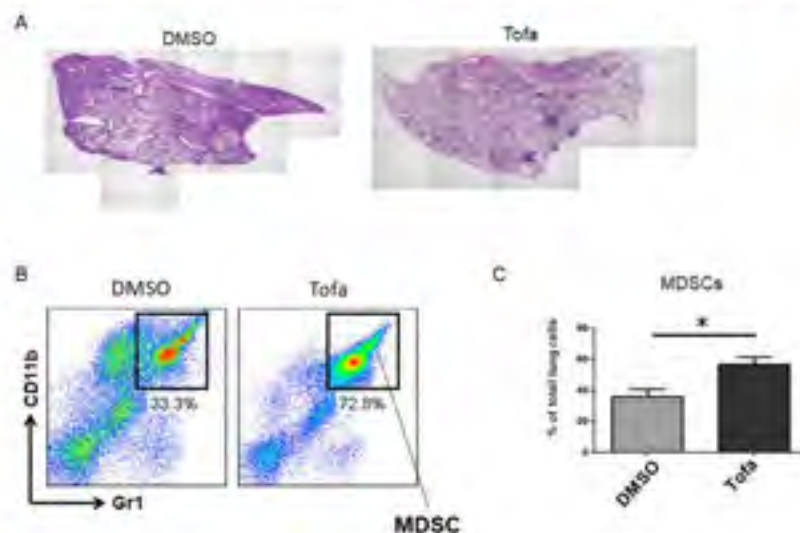
Methods: SKG mice were induced ILD by Zymosan A (ZyA) injection. Four weeks after the ZyA-injection, tofacitinib (20 mg/kg) or DMSO was intraperitoneally injected three times per week for eight weeks. We evaluated lung infiltrating cells by flow cytometry, and severity of ILD by HE staining. DC generation, T-cell proliferation and Th17 cell differentiation assays were performed in vitro.

Results: Tofacitinib significantly suppressed the progression of ILD compared to control. Flow cytometry revealed that tofacitinib significantly increased MDSCs and suppressed Th17 cells, group 1 innate lymphoid cells (ILC1s), and GM-CSF⁺ILCs in vivo. Tofacitinib suppressed the Th17 cell differentiation and increased MDSCs expansion in vitro. MDSCs expanded in the inflamed lungs also suppressed T cell proliferation and Th17 cell differentiation ex vivo.

Discussion: To our knowledge, this is the first report to show that tofacitinib is effective for RA-ILD model. Tofacitinib not only directly but also indirectly suppress the pathogenic lymphocytes by facilitating the expansion of MDSCs. These results indicate a potential therapeutic effect of tofacitinib for RA-ILD.

Conclusion: Tofacitinib facilitates the expansion of MDSCs and suppresses Th17 cells, which in turn suppress the progression of ILD in SKG mice.

Figure: Tofacitinib suppressed the progression of ILD and facilitated the expansion of MDSCs in the lung



Disclosure: S. Sendo, None; J. Saegusa, None; Y. Ichise, None; H. Yamada, None; I. Naka, None; Y. Ueda, None; T. Okano, None; A. Morinobu, None.

Abstract Number: 50

Intra-Articularly Delivering Lentivirus-Based CRISPR Interference Targeting Long Non-Coding RNA H19 in Synovial Fibroblasts Ameliorates Experimental Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

Session Type: ACR Poster Session A

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Background/Purpose: Aberrantly higher expression of long non-coding RNAs (lncRNAs) in synovial fibroblasts (SFs) plays pathogenic roles in rheumatoid joint. Studying the effects on knocking down lncRNAs expression in arthritis models would contribute to the development of lncRNAs-related therapeutics in rheumatoid arthritis (RA). We examined whether intra-articularly (i.a.) delivering the lentivirus (LV)-based CRISPR interference (CRISPRi) targeting H19, an oncofetal lncRNA involved in tumor metastasis, in SFs can ameliorate experimental arthritis.

Methods: H19 expression levels were examined by quantitative real-time PCR (qRT-PCR) in mononuclear cells (MNCs) from RA before and after receiving a TNF blockade therapy and osteoarthritis (OA) patients. Synovial tissues were from arthritis patients and an experimental model, collagen-induced arthritis (CIA). SFs were purified from patients, and normal human SFs were obtained commercially. Single guide RNA oligonucleotides that directing Cas9 to target sites were designed according to available algorithms. A 1.9 kb stuffer was removed from LV plasmid pAll-dCAS9-KRAB.pPuro for cloning, and created single guide RNA vectors were transiently transfected into 293T cells to obtain recombinant LV vectors. SFs were transduced with LVCRISPRi-H19 under polybrene, followed by selection with puromycin incubation to produce stable H19-silenced transfectants. Cell lysates were subjected to immunoblot with anti-EZH2, anti-pGSK-3 β (a Wnt signaling) and anti-Snail. Cell invasion was assayed by Transwells with membrane coated with Matrigel. Supernatant IL-6 was quantified by ELISA. Arthritis indexes and histological scores were evaluated in CIA joints receiving LVCRISPRi-H19 or LVCRISPRi-GFP (negative control) injection, and synovial H19 expression was examined by qRT-PCR.

Results: Synovial tissues, SFs and MNCs from RA had higher H19 expression as compared with OA patients. RA MNCs had lower H19 expression after a TNF blockade injection. H19 and EZH2 levels were up-regulated in normal SFs in the presence of TNF in vitro. Lower EZH2, pGSK-3 β and Snail expression was found in H19-silenced SF transfectants. LVCRISPRi-H19-injected CIA joints with lower synovial H19 expression had reduced arthritis indexes and histological scores.

Conclusion: Our results demonstrate that a TNF-mediated lncRNA pathway with H19-EZH2-Wnt signaling-Snail axis might exist in RASFs, and i.a. delivering CRISPRi targeting lncRNA H19 in SFs could ameliorates experimental arthritis.

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Genetic Ablation of Inducible Nitric Oxide Synthase in TNF Transgenic Mice with Inflammatory-Erosive Arthritis Prevents Lymph Node Expansion and Decreases Synovial Infiltrates

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SESSION INFORMATION

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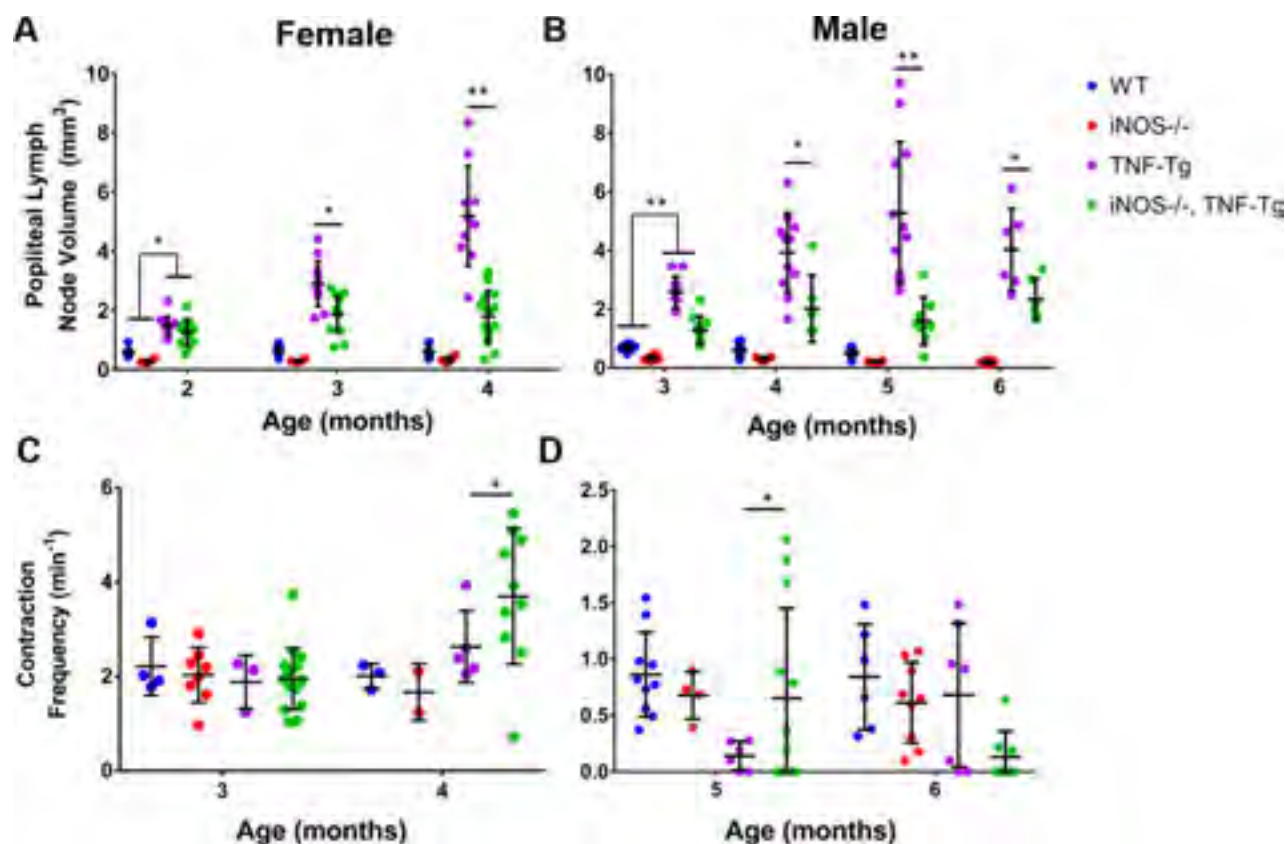
Session Title: Rheumatoid Arthritis – Animal Models Poster

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Background/Purpose: Recent studies in the TNF-Tg mouse model of rheumatoid arthritis (RA) demonstrated a critical role of lymphatic vessel (LV) function in joint homeostasis and arthritis progression, as loss of LV contractions promotes synovitis and erosions due to decrease drainage of joint inflammation. The joint draining lymph nodes (LN) were also found to be a biomarker of arthritic progression, as they expand in volume during the onset of arthritis. It is also known that macrophages and lymphatic endothelial cells express inducible nitric oxide synthase (iNOS), which disrupts LV contractions and transport of immune cells to the draining LNs. Lastly, pharmacological inhibition of iNOS transiently recovers LV contractions in TNF-Tg mice, and maintains flow in the LVs and LNs, which correlates with reduced synovitis and bone damage in inflamed joints. Therefore, we hypothesized that global genetic ablation of iNOS prevents expansion of draining LN, maintains LV contractions, and ameliorates synovitis in TNF-Tgmice.

Methods: Male and female $iNOS^{-/-}$ x TNF-Tg mice and control littermates ($iNOS^{-/-}$, TNF-Tg, and WT; n=4-12 per group) were examine for LN volume, LV contraction frequency and synovitis. Since stark sexual dimorphism exists in TNF-Tg mice, female LN volume and LV contraction frequency were measured at 2, 3 and 4 months of age via 3D ultrasound;



while male LN volume was determined at 3, 4, 5 and 6 months. Knees were harvested for histology after the last ultrasound.

Results: No differences were seen in LN volume at the earliest time points in both sexes between TNF-Tg and iNOS^{-/-} x TNF-Tg (Figure A, Female 2mo: 1.6 ± 0.4 vs 1.4 ± 0.5 mm³; B, Male 3mo: 2.5 ± 0.6 vs 1.2 ± 0.6 mm³), however these were all significantly increase from their sex-aged matched WT and iNOS^{-/-} counterparts (WT and iNOS pooled data, Female 2mo: 0.6 ± 0.2 mm³, $p < 0.05$; Male 3mo: 0.6 ± 0.2 mm³, $p < 0.05$). Importantly, both female and male iNOS^{-/-} x TNF-Tg LNs were significantly decreased at 4 and 5 months of age compared to their TNF-Tg littermates, respectively (Female 4mo: 6.3 ± 1.9 vs 1.9 ± 0.9 , $p < 0.05$; Male 5mo: 5.3 ± 2.4 vs 1.6 ± 0.8 mm³, $p < 0.05$). LV contraction frequency was also increased at these timepoints for iNOS^{-/-} x TNF-Tg compared to TNF-Tg (Figure C, Female 4mo: 3.2 ± 1.4 vs 2.5 ± 1 contractions/min, $p < 0.05$; D, Male 5mo: 0.6 ± 0.7 vs 0.1 ± 0.1 contractions/min, $p < 0.05$). Lastly, female iNOS^{-/-} x TNF-Tg contain significantly fewer cells within their synovium compared to TNF-Tg counterparts ($1.3 \times 10^4 \pm 5.2 \times 10^3$ vs $2.6 \times 10^4 \pm 5.2 \times 10^3$).

Conclusion: These data indicate an iNOS independent phase of LN expansion precedes an iNOS dependent phase, and that pharmacological inhibition of iNOS may ameliorate RA progression by preventing the full expansion of the LN while increasing LV function, which would increase inflammatory cells egress from the synovium.

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Abstract Number: 52

Interferon-Alpha Protects Against Pain and Joint Damages in Experimental Arthritis and Is Associated with Expansion of Highly Suppressive Regulatory T Lymphocytes in Protected Mice and in Tocilizumab-Treated Rheumatoid Arthritis Patients

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Background/Purpose: Type I interferons (IFN-I) can be both anti- and pro-inflammatory. Among them, IFN- α inhibits normal Th17 differentiation, whereas it is pathogenic in lupus. The role of IFN-I is controversial in rheumatoid arthritis (RA) and experimental models. An IFN-I signature has been reported in RA patients, the significance of which is unclear. In mice, IFN-I enhance or inhibit arthritis development according to IFN subtype, arthritis model and kinetics. We aimed to evaluate the therapeutic effect of IFN- α in collagen-induced arthritis (CIA) and its relation with regulatory T lymphocytes (Treg) in RA patients, where Treg are functionally deficient.

Methods: CIA was induced by 2 immunizations with collagen/CFA. Disease development was studied in conditional transgenic mice over-expressing mouse IFN- α 1 and non-transgenic littermates after cessation of doxycycline administration (Tet-off system). Arthritis was followed by clinical evaluation. Inflammation/bone destruction were estimated by histology. Pain was followed by Von Frey tests. Plasma cytokines/anti-collagen antibodies were measured by Luminex/ELISA. Leukocytes sub-populations and Th polarization were analyzed by flow cytometry. Osteoclasts were prepared from the bone marrow (BM) after culture with M-CSF/RANKL. CD4⁺CD25⁺ Treg and CD4⁺CD25⁻ effector T cells (Teff) were purified by magnetic sorting. ATPase activity was determined in vitro. Treg inhibition of Teff activation was measured by flow cytometry/ELISA. The in vivo therapeutic capacity of purified Treg was estimated by adoptive transfer. Blood Treg (CD4⁺FoxP3⁺CD25⁺CD127^{low}) and suppressive phenotype (CD39 expression) were analyzed by flow cytometry in RA patients before and 3 months after anti-IL-6-receptor therapy. Plasma IFN- α concentrations were measured by digital ELISA.

Results: IFN- α 1 induction by doxycycline cessation before the first or even between both immunizations resulted in CIA protection/lower pain in transgenic mice. Anti-collagen antibody and IL-6 productions were lower in IFN- α 1⁺ mice.

Protected mice show decreased polarization to Th17 and increased polarization to Th2 and IFN- γ -positive Th1/NK cells. CIA protection in IFN- α 1-overexpressing mice was associated with lower osteoclastogenesis and osteoclast activity, altered BM-B cells, increased BM-CD86⁺ neutrophils, and particularly expansion of Treg with higher CD39/CTLA-4 expression, higher ATPase activity and higher suppressive capacity on Teff. Importantly, adoptive transfer of these Treg purified from CIA-IFN- α 1⁺ mice impaired CIA development in recipients in comparison to Treg purified from CIA-IFN- α 1⁻ mice. In RA patients, therapy blocking IL-6 signalling was associated with increased IFN- α plasma concentrations and in vivo expansion of Treg after 3 months, with increased CD39 expression. Most importantly, blood IFN- α and Treg frequencies were correlated in these patients. Thus, results in CIA mimic thus these obtained in RA patients.

Conclusion: IFN- α 1 protects against inflammatory arthritis, even in mice already seropositive, clarifying its role and showing its potent modulatory or therapeutic effect. In RA patients, IFN- α might serve as a biomarker in response to treatment.

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Abstract Number: 53

Cyclin-Dependent Kinase 4/6 Inhibitor: A Promising Development Candidate Targeting Synovial Hypertrophy for Rheumatoid Arthritis Treatment

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Session Title: Rheumatoid Arthritis – Animal Models Poster

Session Type: ACR Poster Session A

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

Background/Purpose: The pathogenesis of rheumatoid arthritis (RA) is characterized by the infiltration of immune cells into the synovial tissues and the hypertrophy of synovial fibroblasts, resulting in the destruction of bone and joint. Given the pathogenesis, the ideal therapeutic strategy for RA is to target both immune cells/pro-inflammatory cytokines and synovial fibroblasts. However, there is no drug targeting the latter, whereas anti-immune cell/cytokine drugs such as methotrexate, biologics and JAK inhibitors are the mainstay in the current treatment of RA. To date we found Compound X, a highly selective and potent inhibitor against cyclin-dependent kinase (CDK) 4/6, which is a key regulator of cell cycle. Compound X inhibits the proliferation and matrix metalloproteinase 3 (MMP-3) secretion in synovial fibroblasts from RA patients, and the progression of arthritis in adjuvant-induced arthritic rats. To determine the potential of CDK4/6 inhibitor targeting the hypertrophy of synovial fibroblasts, as development candidate for RA treatment, we examined the efficacy of Compound X using preclinical animal models.

Methods: To examine the effects of Compound X on arthritis, collagen-induced arthritis (CIA) was used. To induce arthritis, DBA/1 mice were administered twice with intradermal injection of type II collagen at the tail root on Day0 and 3. Compound X was orally administered twice daily for 19 days. To examine the effect of Compound X on arthritis after the activation of immune system, anti-type II collagen antibody-induced arthritis (CAIA) model was used. DBA/1 mice were intraperitoneally injected with anti-type II collagen antibody on Day0 and LPS on Day3. Compound X was orally administered twice daily for 18 days. Arthritic score over time, serum MMP-3 level and bone destruction were examined in CIA and CAIA mice. In addition, MMP-3 expression in the joint and anti-type II collagen IgG level were examined in CIA mice.

Results: CIA mice developed the arthritis and showed gradual increase in arthritic score. Compound X significantly suppressed the progression of arthritis in a dose-dependent manner. Serum MMP-3 level in CIA mice was increased compared with Intact animals, which is consistent with MMP-3 expression in the joint. Compound X suppressed serum MMP-3 level and tissue expression. CIA mice with Compound X had lower incidence of bone destruction than CIA mice. Compound X did not reduce type II collagen IgG level, suggesting that Compound X has no impact on the immune system. Consistent with this, Compound X also suppressed the progression of arthritis in CAIA mice without immunization. Bone erosion score was reduced by Compound X, and correlated to arthritic score.

Conclusion: Compound X suppressed RA-related events such as the progression of the arthritis, increased serum MMP-3 and bone destruction. These results suggest that CDK4/6 inhibitor can be the first-in-class drug which targets the hypertrophy of synovial fibroblasts.

Disclosure: S. Tsujimoto, TEIJIN PHARMA LIMITED, 3; K. Horie, TEIJIN PHARMA LIMITED, 3; T. Mashiko, TEIJIN PHARMA LIMITED, 3; J. Nomura, TEIJIN PHARMA LIMITED, 3; T. Kobayashi, TEIJIN PHARMA LIMITED, 3.

Abstract Number: 54

In a Macaque Model of RA By Immunization with Citrullinated Peptides, the Valine in the 11 Position of the DRB1 Molecule Has Greater Impacts on T-Cell Response to Citrullinated Peptides Than the 70-74 Position in the Shared Epitope

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Session Title: Rheumatoid Arthritis – Animal Models Poster

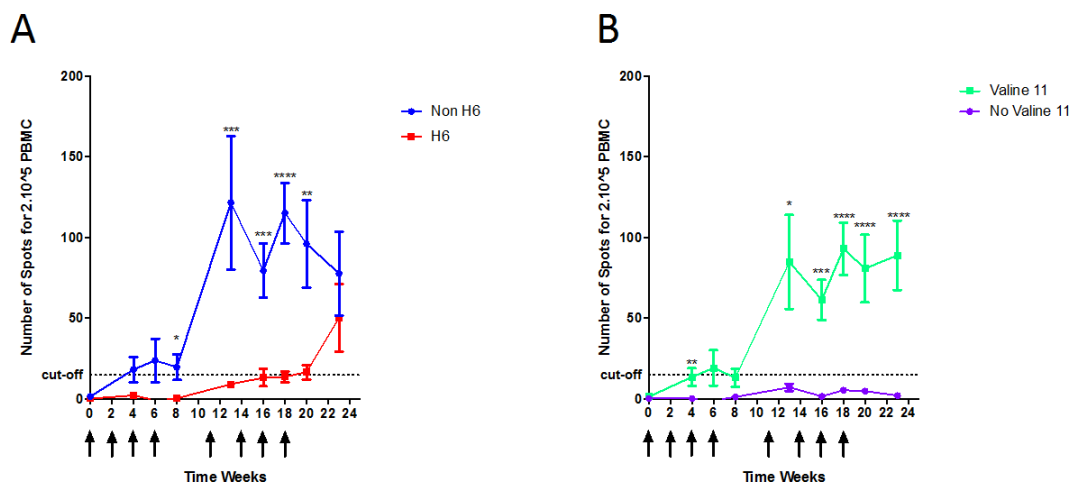
Session Type: ACR Poster Session A

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

Background/Purpose: Among genetic risk factors of RA, HLA class II molecules confers the highest risk of ACPA positive RA. The shared epitope (SE) hypothesis that initially involved positions 70 to 74 on the HLA molecule has been recently challenged by the influence of other positions such as the valine 11 position. The presence of the SE is thought to influence presentation of citrullinated peptides (Cit-P) by antigen presenting cells to T cells. Study of T-cell response in patients with various HLADRB1 haplotype is challenging. Rodent models lack the expression of the equivalent of the DRB1 molecule and transgenic mice for the SE have led to controversial results. Certain macaques express DRB1 molecules in a similar fashion compared to humans. They are thus a great tool to analyze the effect of the HLA molecule on T cell response to Cit-P. In these macaques, we previously demonstrated that immunization with Cit-P and an intra-articular boost are able to induce aspecific T-cell anti-Cit-P response independent of the SE epitope and amonoarthritis (Bitoun et al. Frontiers Immunol 2017).

Methods: We selected two macaque haplotypes to have the greatest difference in the risk induced by the HLADRB1. The H6 haplotype has a similar sequence to the human RA risk-conferring HLADRB1*01:01 and displays QRRAA in the 70 to 74 positions and a F in the 11 position. The H3 haplotype is the closest to RA protective haplotypes HLA-DRB1 04:02 and 13:01 and expresses DRRAS (70-74 positions) but a V in position 11. Two groups of six animals were immunized with four Cit-P: vimentin (59–71) and (66–78), fibrinogen α (79–91) and aggrecan (89–103). These peptides were selected based on their ability to induce an anti-citrullinated T-cell response in RA patients carrying the SE. T-cell response was assessed using Interferon γ ELISPOT. Timepoints were compared using Mann Whitney tests.

Results: After a prime and 7 boosts, we obtained a detectable anti-citrullinated T cell response in only 7 out of twelve animals. The analysis dividing animals according to the presence of the SE motif (H6 in macaques) show a significantly



diminished T-cell response in H6 macaques (FigureA). This was contradictory with the common description of higher T cell response in patients carrying the SE. When we reanalyzed the data based on the presence or not of a V in position 11, we found that this valine in position 11 was strongly associated with the presence of a T-cell response against citrullinated peptides, whatever the 70-74 sequence was (Figure B).

Conclusion: As recently described in humans for association to RA and anti-CCP positivity, T-cell response to Cit-P in macaques is more influenced by the presence of a valine at position 11 in the HLA-DRB1 than with the presence of the QRRAA 70-74 SE. The respective influence of the V in position 11 and the 70-74 QRRAA sequence should be studied regarding a better binding and presentation of Cit-P.

Disclosure: S. Bitoun, None; P. Roques, None; R. Le Grand, None; X. Mariette, None.

Abstract Number: 55

Adipose Derived Stem Cell Suppressed Synovial Inflammation and Repaired Cartilage Destruction in Rheumatoid Arthritis Model Mice

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Session Title: Rheumatoid Arthritis – Animal Models Poster

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Background/Purpose: Adipose derived stem cell (ADSC) is one of the stem cells produced by adipose tissue which can be collected easily and in large quantities. It has been reported the anti-inflammatory effect of ADSC in some disease models. However, the effect of ADSC for synovitis such as rheumatoid arthritis (RA) is unknown. The aim of this study is to investigate the effects of ADSC for intra-articular synovitis and cartilage degeneration in SKG/Jcl mice in vivo and the effects of ADSC for synovial fibroblast in vitro.

Methods: SKG/Jcl mice which developed auto-immune arthritis by adjuvant stimulation were used as RA animal model. In vivo, the intra-articular injections of ADSC or PBS were performed to the bilateral knee of SKG mice with arthritis. The knee joint was histologically assessed with synovitis score and Mankin score at week 2 after ADSC injection. In vitro, the anti-inflammatory effect of ADSC for stimulated human synovial fibroblast was analyzed by real-time RT-PCR.

Results: In vivo, the synovitis score and Mankin score were significantly lower in ADSC group (synovitis score 2.0 ± 0.7 vs 6.0 ± 1.6 , $p < 0.01$ and Mankin score 2.2 ± 0.8 vs 4.9 ± 0.8 , $p < 0.01$) (Figure 1). Surprisingly, the cartilage degeneration was repaired in ADSC group (Figure 2). As a comparison, glucocorticoid injection suppressed the synovial inflammation but cartilage degeneration was not improved (Figure 2). In vitro, the expression of tumor necrosis factor-stimulated gene-6 (TSG-6), the anti-inflammatory cytokine, was significantly higher in ADSC than in synovial cell ($p < 0.01$). The inflammatory cytokine levels in stimulated synovial cell were significantly decreased by ADSC treatment ($p < 0.01$).

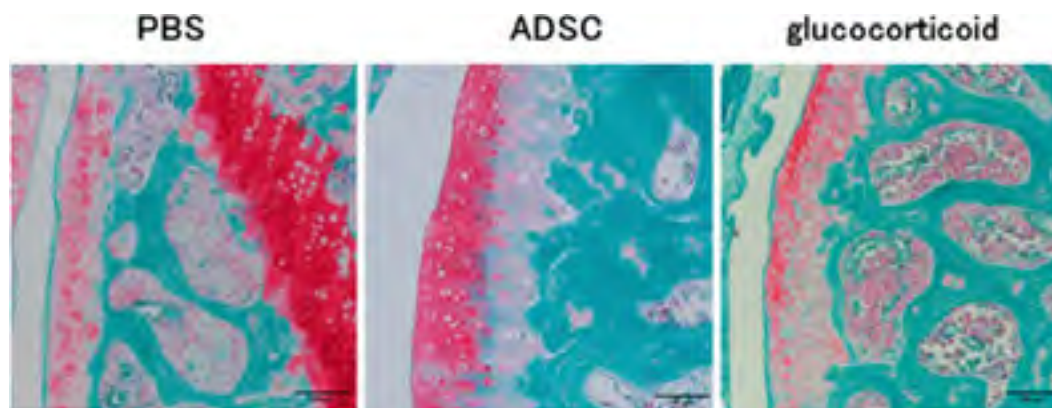


Figure 1. The anti-inflammatory effects of intra-articular ADSC injection.

The H-E stain of knee joint in SKG/Jcl mice (a) and PBS treated SKG/Jcl mice after induction of synovitis (b). The synovial proliferation was suppressed in ADSC treated SKG/Jcl mice after induction of synovitis (c). The Safranin-O stain in SKG/Jcl mice without synovitis (d), PBS treated SKG/Jcl mice (e) and ADSC treated SKG/Jcl mice (f) after induction of synovitis. The cartilage staining was reduced in SKG/Jcl mice with inflammatory synovitis (yellow arrows).

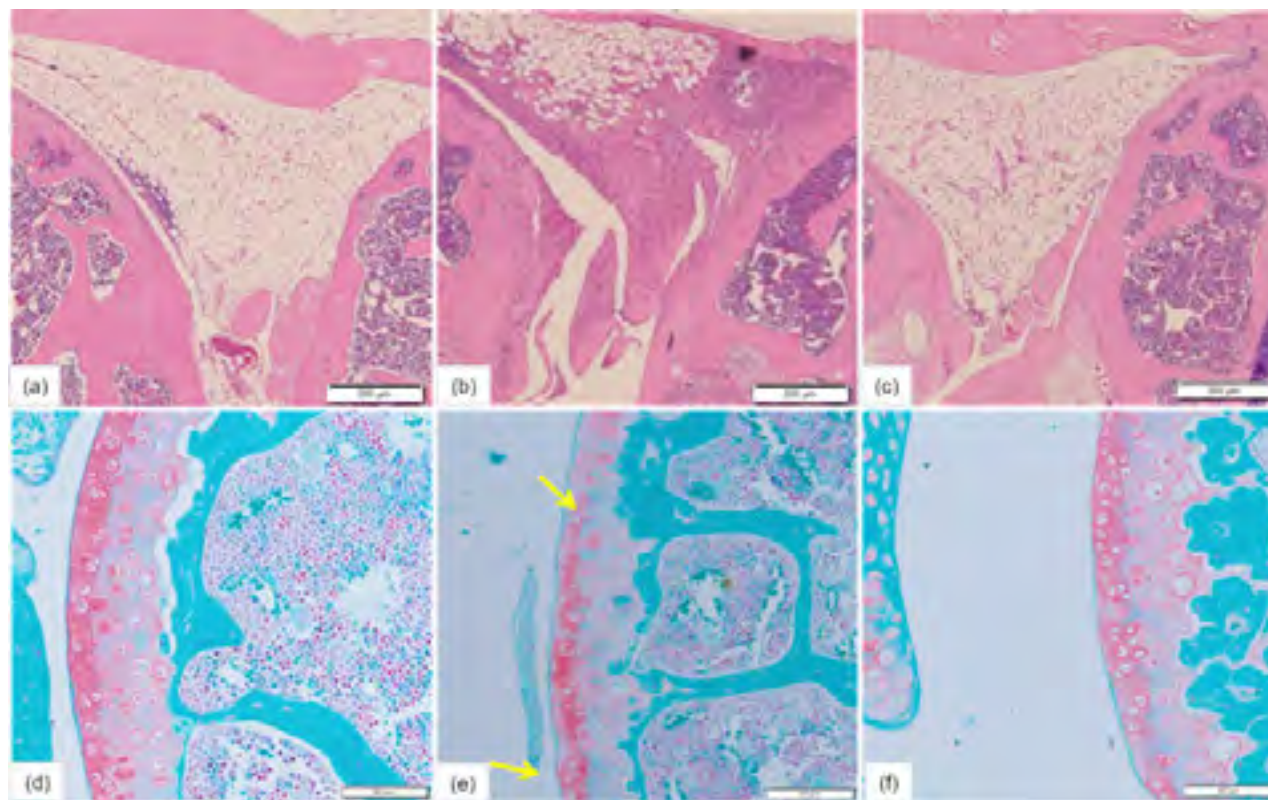


Figure 2. Cartilage repair in ADSC group

Conclusion: This is the first report to show the anti-inflammatory effect of ADSC for synovitis in RA animal model. ADSC can be collected with a minimally invasive technique more easily than other mesenchymal stem cells. ADSC might have potential to be one of the RA treatment and repair cartilage degeneration.

Disclosure: T. Okano, None; K. Inui, None; H. Ueyama, None; K. Orita, None; T. Koike, None; H. Nakamura, None.

Abstract Number: 56

Comparison of Metabolic Changes in Osteoarthritis and Rheumatoid Arthritis Mouse Models

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Background/Purpose: Adipocytokines are bioactive factors produced mainly by adipose tissue. They not only regulate energy homeostasis, but also influence immune responses. Osteoarthritis (OA) is one of the most common degenerative joint diseases whereas rheumatoid arthritis (RA) is a chronic autoimmune joint disease. Therefore, an obesity model (High-fat diet, HFD) was combined with a model for OA (DMM, destabilization of the medial meniscus) or a model for RA (collagen induced arthritis, CIA) to evaluate the role of the adipokines adiponectin, leptin and visfatin in these settings. This work evaluates the influence of different adipokines and obesity on OA compared to RA regarding systemic vs. local effects at different time points.

Methods: The OA model was performed in C57Bl/6 mice fed with HFD or ND (normal diet) prior to OA induction. The RA model was performed in DBA/1Rj mice fed with the same diets. Mice were sacrificed and analyzed 4, 6 and 8 weeks (OA model) or 4, 5.5 and 7 weeks (RA model) after induction of RA/OA. For systemic analysis, sera were evaluated for the adipokines adiponectin, leptin and visfatin and inflammatory markers. Diet induced systemic changes were analyzed using a fatty liver score and evaluation of crown-like structures (CLS) in adipose tissue. Histological scoring for OA and a clinical score for RA was performed. Immunohistochemical stainings of OA joints were performed to evaluate local adipokines and the producing cell types.

Results: All three models in the respective combinations were successful, represented by histological destruction of the joints and increased fatty liver score (C57Bl/6) or bodyweight (DBA/1Rj). The number of CLS were significantly higher comparing HFD (0.2 ± 0.1553 , $n=7$) with ND (5.219 ± 0.9831 , $n=8$) in C57Bl/6 mice and fatty-liver score was significantly higher in HFD compared to ND in C57Bl/6 but not in DBA/1Rj. Leptin was significantly induced by HFD in both mouse strains, this effect could be annulled by leptin reducing effects of the CIA model. DMM reduced systemic leptin but with much weaker effect. HFD, DMM or the combination of both did not show significant effects on serum levels of adiponectin, visfatin or IL-6. However, in DBA/1Rj mice CRP was significantly induced by CIA. Local adipokine distribution in the joints after DMM surgery was independent from systemic metabolism parameters.

Conclusion: Our data show that similar to observations in humans, OA is deteriorated by HFD which correlates mainly with the bodyweight. This phenomenon was not visible in our RA model. CIA and DMM both decreased systemic leptin, which was much more effective in CIA suggesting an inflammation-dependent mechanism. Interestingly, in OA the local adipokine expression was independent from systemic adipokine levels.

Disclosure: M. L. Hülser, None; H. M. Sauermilch, None; C. Schreyäck, None; Y. Luo, None; A. Bozec, None; G. Schett, None; U. Müller-Ladner, None; E. Neumann, None.

Abstract Number: 57

Repository Corticotropin Injection (H.P. Acthar® Gel) Inhibits Bone Degradation in Rat Adjuvant-Induced Arthritis Model

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Background/Purpose: Repository corticotropin injection (RCI: H.P. Acthar® gel) contains a purified porcine pituitary ACTH-analogue, and is an FDA-approved treatment for short-term adjunctive therapy of acute episode or exacerbation in rheumatic disorders. It has been suggested that ACTH modulates the immune response via binding to melanocortin receptors (MC1R to MC5R). These receptors are expressed on a number of cells including immune cells and bone cells, and have been shown to modulate several immuneresponses. This study was designed to investigate the effects of RCI treatment compared to prednisolone with regard to arthritis disease attenuation and boneprotection.

Methods: Ratadjuvant-induced arthritis (AIA) model was used to determine efficacy in the subacute inflammation setting. Disease was induced by an injection of alipoidal amine in Freund's complete adjuvant (FCA) on day 0. The AIA rats were treated with either vehicle, prednisolone (5 mg/kg) or RCI (40, 160, 400 IU/kg) every other day by subcutaneous injection beginning on the day of disease induction and continuing for 15 days (8 total doses). Disease progression was monitored on days 7-14 by measuring both paw diameter and body weight. Inflammation and bone damage were evaluated histologically at the end of the study.

Results: Treatment with RCI showed significant and dose responsive inhibition of disease induction as determined by evaluation of ankle diameter (area under the curve (AUC) inhibition of 44%, 74%, 94% for 40 IU/kg, 160 IU/kg and 400

IU/kg, respectively) whereas prednisolone reduced swelling by 33%. Microscopic examination of the ankle joints showed that RCI significantly inhibited total histopathology sum score by 64% and 85% at 160 IU/kg and 400 IU/kg, respectively, while treatment with prednisolone resulted in 33% inhibition, which was not significantly different from the controls. Furthermore, RCI inhibited inflammation-related bone resorption and reduced the number of osteoclasts in the inflamed joint. Interestingly, prednisolone significantly reduced the number of osteoclasts but did not show a significant benefit on joint damage as evaluated by bone resorption and cartilage damage.

Conclusion: RCI treatment significantly inhibited the development of disease in rat AIA, whereas prednisolone treatment alone only showed a minor benefit. Furthermore, there was a significant reduction in the number of osteoclasts following RCI treatment. These findings support the use of RCI for treatment of rheumatoid arthritis and suggest a potential bone sparing effect.

Histopathology Scoring

Treatment	Inflammation	Pannus	Cartilage Damage	Bone Resorption	Periosteal Bone Formation	Osteoclast Numbers
Disease	5.56 ± 0.11	0.97 ± 0.16	0.97 ± 0.16	4.81 ± 0.09	1.03 ± 0.24	14.04 ± 0.95
RCI 40 IU/kg	4.13 ± 0.38	0.66 ± 0.08	0.66 ± 0.08	2.50 ± 0.52*	0.69 ± 0.22	6.75 ± 0.84*
RCI 160 IU/kg	2.56 ± 0.24*	0.34 ± 0.08*	0.44 ± 0.06*	1.22 ± 0.29*	0.19 ± 0.06*	2.82 ± 0.58*
RCI 400 IU/kg	1.41 ± 0.13*	0.03 ± 0.03*	0.06 ± 0.04*	0.44 ± 0.26*	0 ± 0*	0.70 ± 0.34*
Prednisolone	4.06 ± 0.32	0.59 ± 0.08	0.59 ± 0.08	3.28 ± 0.23	0.38 ± 0.05*	8.67 ± 0.93*

Severity Score = 0-7, Mean ± SE

Osteoclast Count (in 5 different joint areas of potential disease related bone resorption)

* p<0.01 Dunn's multiple comparisons test

Disclosure: D. Wright, Mallinckrodt Pharmaceuticals, 1, 3; B. Zweifel, Mallinckrodt Pharmaceuticals, 3; S. Settle, Mallinckrodt Pharmaceuticals, 1, 3; R. Fitch, Mallinckrodt Pharmaceuticals, 1, 3.

Abstract Number: 58

Inhibition of Lipid Phosphatase SHIP1 Expands Myeloid-Derived Suppressor Cells and Attenuates Rheumatoid Arthritis in Mice

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

Session Type: ACR Poster Session A

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

Background/Purpose: The SH2-containing inositol-5'-phosphatase-1 (SHIP1) controls PI3K initiated signaling by limiting membrane recruitment and activation of AKT. SHIP1 knockout in mice leads to an increase of myeloid-derived suppressor cells (MDSCs) as well as the regulatory T-cells (T_{reg}), both are important autoimmune regulators. MDSCs are blood cells of myeloid origin that are able to suppress T cell responses. A recent study suggests that MDSCs play a critical role in the regulation of collagen-induced arthritis (CIA) in mice, where the MDSCs suppress disease progression by inhibiting the immune response of CD4⁺ T cells. Although, an increased MDSCs seems to have suppressive effect on RA progression, the exact role of SHIP1 in the differentiation/expansion of MDSCs in RA remains unknown. Therefore, the objective of this project is to determine the role of SHIP1 in initiation and progression of RA. Our long-term goal is to develop novel strategies for the treatment of inflammatory arthritis diseases.

Methods: A specific SHIP1 inhibitor 3a-aminocholestane (3AC)-injected DBA mice were compared to vehicle-injected mice during Collagen-induced Arthritis (CIA) development. The development and severity of arthritis was assed using scoring system, histological analysis and X-ray imaging. We examined the effect of 3AC on the population of MDSCs and T cells obtained from peripheral blood, spleen, and bone marrow during CIA development through flow cytometry analysis.

Results: We found a delay of CIA onset and significant decrease in the progression of disease, compared with vehicle-injected mice. However, we also found that early suppressive effect on incidence and severity of CIA by 3AC disappeared around day 65. Additionally, there was significant reduction in 3AC-induced expansion of MDSC from day 43 to 63, while the number of T cells in peripheral blood of 3AC-treated mice was recovered to control levels. Histologic examinations of

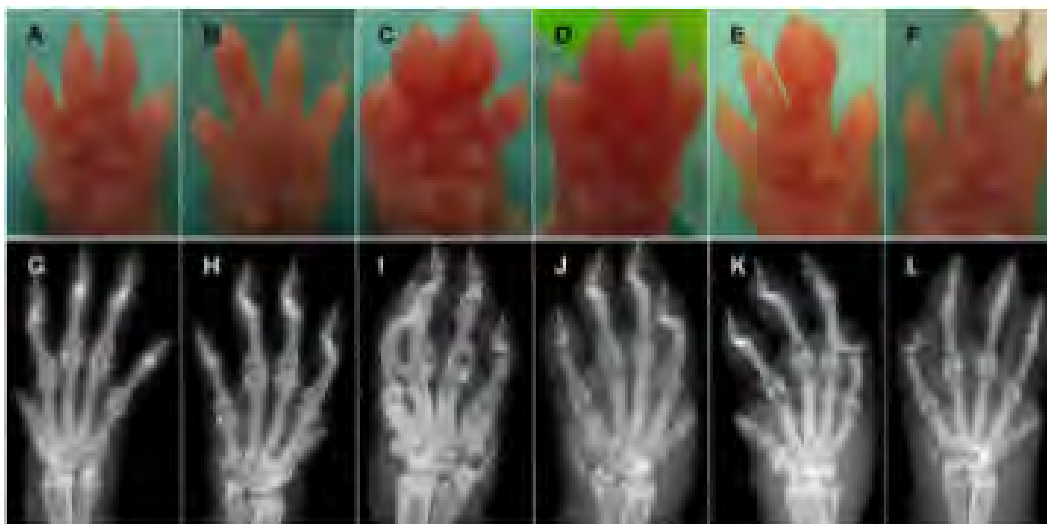


Figure 1. X-ray analysis to examine the erosion and destruction of bone. Untreated (A and B), vehicle-injected (C and D), and 3AC injected (E and F) mice at day 45. Equivalent X-ray images at day 70 (G-L). Triplicate experiments.

the joints from the CIA mice treated with 3AC showed no evidence of erosive arthritis, whereas the joints from mice treated with vehicle showed markedly erosive changes (Figure 1).

Conclusion: Our results suggest that SHIP1 inhibitor maintains the immunoregulatory microenvironment through an increase of regulatory myeloid (MDSCs) and T-cells (Treg). Further, pre-treatment of 3AC inhibits early onset of arthritis, and although this effect was limited and disappeared at later stage of the disease. SHIP1 inhibition was able to protect mice from severe bone destruction which it could be observed at late stage CIA.

Disclosure: E. Y. So, None; C. Sun, None; P. M. Dubielecka, None; A. M. Reginato, None; O. D. Liang, None.

Abstract Number: 59

Elucidating the Expression and Role of Heparan Sulfate Proteoglycan Editing Sulfatases in Human Rheumatoid Arthritis Synovium and a Rat Adjuvant-Induced Arthritis Model

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Syndecans are cell-surface heparan sulfate proteoglycans (HSPGs) that modulate the receptor/ligand binding of chemokines, cytokines, and growth factors in order to facilitate cellular signaling. Two extracellular sulfatase enzymes, namely Sulf-1 and Sulf-2, cleave 6-O-sulfates to dynamically edit the sulfation pattern of syndecans and other membrane-bound HSPGs in response to the microenvironment. However, the role of syndecans and sulfatases in inflammatory condition such as rheumatoid arthritis (RA) remains poorly understood.

Methods: Sulf-1, Sulf-2, and syndecans expression were evaluated in de-identified synovial tissues (ST) and isolated synovial fibroblasts (SFs) from RA and non-diseased (NL) donors under the IRB approved protocol, and in the rat adjuvant-induced arthritis (AIA) model of RA. Effect of TNF- α or IL-1 β on the expression of Sulf-1, Sulf-2, and

syndecans in RASFs was determined. The effect of OKN-007, a known Sulf-2 inhibitor, on TNF- α -induced IL-6 and IL-8 production in RASFs was determined using an ELISA assay. The role of nuclear factor- κ B (NF- κ B) and mitogen-activated protein kinases (MAPKs) in TNF- α -induced Sulf-1 and Sulf-2 expression was evaluated using known chemical inhibitors. Statistical value of $p < 0.05$ was considered significant.

Results: Human RASTs showed an increased expression of Sulf-1 and Sulf-2 protein compared to the NLSTs, which also correlated with a selective increase in syndecan-2 expression in RASTs ($p < 0.05$; $n = 5$). Furthermore, Sulf-1 and Sulf-2 expression in the joints of AIA rats showed a concerted increase with the disease severity, where their expression increased around day 8 (onset of arthritis) and peaked around day 18 (established arthritis) in AIA, and concomitantly correlated with a robust expression in syndecan-2 ($p < 0.01$ for day 18; $n = 5$). Stimulation of RASFs with TNF- α (0.1-20 ng/mL) or IL-1 β (0.1-10 ng/mL) showed a dose-dependent increase in Sulf-1 and Sulf-2 expression that increased to >2 -fold when compared to the non-stimulated samples. Evaluation of the signaling pathways using chemical inhibitors showed that among the inhibitors tested, the inhibitor of TAK1 (5Z-7-oxozeanone) and NF- κ B (PDTC) were most effective in inhibiting TNF- α -induced Sulf-1 and Sulf-2 expression. Furthermore, pretreatment of RASFs with Sulf-2 inhibitor (OKN-007; 40-200 μ M) reduced TNF- α -induced IL-6 and IL-8 production by $\sim 50\%$ and $\sim 20\%$, respectively, suggesting its anti-inflammatory potential in RA. However, we did not observe a significant reduction in TNF- α -induced MAPKs (ERK, JNK, or p38) by OKN-007, suggesting that TNF- α induces Sulf-1 and Sulf-2 expression in RASF potentially via TAK1-NF- κ B pathway.

Conclusion: Our preliminary findings suggest that the Sulf-1 and Sulf-2 expression is increased in RASTs and in rat AIA, and may potentially play an important role in modulating cytokine signaling. Understanding their role in HSPG processing may help elucidate the pathology of aggressive RASFs and may direct our studies towards targeted drug design for treatment of RA.

Disclosure: R. J. Siegel, None; S. A. Agere, None; A. K. Singh, None; S. Ahmed, None.

Abstract Number: 60

Combined Inhibition of Mechanistic Target of Rapamycin and Glutamine Metabolism Inhibits CD4 T Cell Proliferation and Th17 Differentiation, Facilitates the Expansion of Myeloid-Derived Suppressor Cells, and Synergistically Ameliorates Arthritis in SKG Mice

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

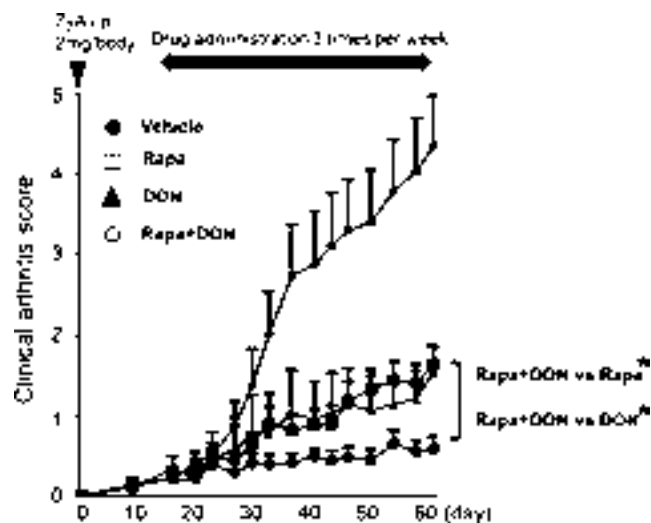
Session Type: ACR Poster Session A

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

Background/Purpose: The mechanistic target of rapamycin (mTOR) pathway and glutamine metabolism are activated cooperatively in the differentiation and the activation of inflammatory immune cells such as effector lymphocytes and M1 macrophages. Myeloid-derived suppressor cells (MDSCs) are an immature myeloid cell population with immunosuppressive ability. The promotion of the expansion and immunosuppressive ability of MDSCs by mTOR inhibition has been reported. The aim of this study is to elucidate the effect of combined inhibition of mTOR and glutamine metabolism on immune cells and therapeutic effect in a mouse model of rheumatoid arthritis.

Methods: The proliferation of CD4⁺ T cells treated with four patterns of drugs; 1) DMSO (control), 2) rapamycin (Rapa), 3) 6-Diazo-5-oxo-L-norleucine (DON; a glutamine antagonist), or 4) the combination of rapamycin and DON (Rapa+DON), were assessed by CFSE-dilution assay. The differentiation of CD4⁺ T cells and bone marrow cells from untreated Balb/c mice were analyzed by flow cytometry. Immunosuppressive ability of *in vitro* generated-MDSCs were assessed by co-culture with CFSE-labeled CD4⁺ T cells. The four patterns of drugs were administered intraperitoneally to arthritic SKG mice and splenocytes were analyzed by flow cytometry.

Results: Rapamycin and DON synergistically inhibited the CD4⁺ T cell proliferation and both of them inhibited the Th17 cell differentiation *in vitro*. DON significantly suppressed the differentiation of dendritic cells and macrophages, and increased the proportions of MDSCs *in vitro*. Most of *in vitro* generated-MDSCs treated with rapamycin or DON were Ly6G⁺ granulocytic (G)-MDSCs. On the other hand, *in vitro*-generated G-MDSCs treated with rapamycin suppressed the proliferation of CD4⁺ T cells more strongly than G-MDSCs treated without rapamycin. The combination of rapamycin and



DON synergistically suppressed arthritis in SKG mice *in vivo* (see Figure). The number of CD4⁺ T cells in splenocytes was the most suppressed in the combination therapy group and the proportions of Th17 cells were suppressed in rapamycin, DON, or the combination therapy groups.

Conclusion: The combination of rapamycin and DON synergistically ameliorated arthritis in SKG mice possibly through suppressing CD4⁺ T cell proliferation and Th17 differentiation.

Disclosure: Y. Ueda, None; J. Saegusa, None; T. Okano, None; S. Sendo, None; H. Yamada, None; K. Akashi, None; A. Onishi, None; A. Morinobu, None.

Abstract Number: 61

A Human ACPA Monoclonal Antibody Is Preferably Localized at Inflammatory Gingival Tissue and Activates Osteoclastogenesis in *Porphyromonas Gingivalis* Infected SKG Mouse

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Periodontal disease (PD) is the chronic inflammatory disease caused by the infection of periodontal pathogenic bacteria, *Porphyromonas gingivalis* (Pg). Pg infection is known as a major pathogenic factor of some systemic diseases including rheumatoid arthritis (RA). Our group established b-galcan (laminarin, LA) induced RA model mouse with Pg infection (Pg-RA mouse) by using SKG mouse. Pg-RA mouse showed severe arthritis and joint destruction like human RA compared with RA mouse. The cause of exacerbation of joint destruction by Pg infection was the activation of osteoclastogenesis (OCD) in Pg-RA mouse with the elevation of ACPA, IL-6, and MMP-3 in serum (Clin Exp Immunol. 2016 Nov; 186 (2):177-189.). Immune complex (IC) is also important in the activation of OCD. However, the involvement of IC derived from citrullinated protein (CP) in the progression of OCD is unclear. It is also unclear that the involvement of Pg pathogenic factors even if there are some enzymes possessed by Pg such as peptidyl arginine diamidase (PAD) and gingipain. In this study, the involvement of Pg which is a major source of endogenous CP in bacteria in the synthesis of IC in the periodontal tissue and joint tissue was determined. The localization and effect of ACPA in the progression of RA in model mouse were also analyzed by using a ACPA monoclonal antibody generated from RA patients B cell (CCP1-Ab).

Methods: In order to induce periodontal bone loss in SKG mouse, Pg was diluted into 2% *carboxyl methyl cellulose* (CMC, 10f8 CFU/50 ml) and also infected into mouse oral cavity twice a week for 2 weeks with the placement of 5-0 silk thread around the maxillary second molar. As a control, CMC was only applied into oral cavity. At the same time for induction of RA, the single i.p. injection of LA was performed. In order to measure the amount of CP and ACPA, mouse was received adaptive transferred CCP-Ab1 (Arthritis Rheumatol. 2015 May; 67(8):2020-31.). Then, the tissue homogenates of periodontal tissue, joint tissue, spleen and serum were determined by ELISA. The immune fluorescence microscopic analysis was also performed to determine the localization of ACPA and IC in periodontal tissue. In order to determine the effect of ACPA in the activation of OCD, bone marrow mononuclear cell (BMC) was cultured with sRANKL and M-CSF in the presence or absence of CCP-Ab1 and analyzed by TRAP staining and by CellInsight CX-5 HCS Platform for quantitative analysis of osteoclast. mRNA expression of OCD related genes in BMC was determined by quantitative RT-PCR.

Results and Conclusion: The distributions of ACPA in periodontal tissue, joint tissue, and spleen were observed in Pg infected periodontitis mouse by ELISA. IC was also generated in Pg infected periodontitis mouse compared with healthy mouse. The adaptive transfer of CCP1-Ab resulted in the elevation of AS compared with the that of control IgG. OCD was activated in the presence of CCP1-Ab compared with control antibody. mRNA expression of OCD related gene (*traf6*, *nfatc1*, *Oscar*, *dc-stamp*, *mmp-9*, and *catK*) in BMC was induced by CCP1-Ab. The possibility of the involvement of IC from ACPA and CP generated by Pg in periodontal tissue for the progression of bone resorption was observed in Pg-RA mouse.

Disclosure: K. Ouhara, None; T. Ozawa, None; S. Munnaga, None; T. Kuranobu, None; Y. Hamamoto, None; T. Kawai, None; E. Sugiyama, None; H. Kurihara, None.

Abstract Number: 62

CCR6+CD4+ T Cells Drive IL-23R Signaling-Dependent Progression of Antigen-Induced Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

Session Type: ACR Poster Session A

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

Background/Purpose: The IL-23/IL-17A immune pathway is important for the progression of T cell-mediated arthritis. However, it is not known where IL-23R⁺ T cells locate during the different stages of arthritis and which IL-23R⁺ T cells drive joint inflammation. We aimed to identify IL-23R⁺ T cells in the secondary lymphoid organs during the development and progression of antigen-induced arthritis (AIA). Furthermore, we studied which IL-23R⁺ T cells drive full-blown AIA.

Methods: To induce AIA, IL-23R^{+/+} (WT), heterozygous IL-23R^{+/-GFP}, and IL-23R^{GFP/GFP} (IL-23RKO) mice were immunized with methylated bovine serum albumin (mBSA) in Complete Freund's Adjuvant. After 7 days mice were injected in the knee joints with mBSA. Mice were macroscopically scored at different time points and knees were used for histological analysis of the joints. The spleen, inguinal and popliteal lymph nodes (LN) were collected and analyzed for the expression of GFP⁺/IL-23R⁺ T cells. To study which T cells drive AIA, CCR6⁺CD4⁺ T cells and $\gamma\delta$ T cells from CFA/mBSA immunized WT mice were adoptively transferred into IL-23RKO recipient mice prior to AIA induction and disease severity was assessed at the peak of AIA.

Results: AIA disease progression was mainly driven by the IL-23R pathway since IL-23RKO mice had significantly lower arthritis scores and less bone damage. Furthermore, the fraction and total CD4⁺ and TCR $\gamma\delta$ ⁺ cell counts were lower in IL-23RKO joints at day 4 of AIA. *In vitro*, cells of IL-23RKO mice produced less IL-17A. Heterozygous IL-23R reporter mice had similar disease scores to WT mice, indicating that half of the receptor expression is sufficient to drive disease. Flow cytometric analysis of GFP/IL-23R in T cells of naïve and arthritic IL-23R reporter mice revealed that a fraction of CCR6⁺CD4⁺ T cells and $\gamma\delta$ T cells, but not CD8⁺ T cells, expressed IL-23R in the lymphoid tissues. Already one day after arthritis induction, the fraction IL-23R⁺ CCR6⁺CD4⁺ T cells was increased in the draining LNs from the joints. The fraction of these IL-23R⁺ T cells decreased gradually during the progression of disease, possibly due to their migration towards the synovium. Adoptively transferred CCR6⁺CD4⁺ T cells, but not $\gamma\delta$ T cells, were able

Conclusion: The IL-23R signaling pathway is essential for full-blown AIA. CCR6⁺CD4⁺ T cells and $\gamma\delta$ T cells, but not CD8⁺ T cells, express IL-23R during naïve and inflammatory conditions. Interestingly, adoptive transfer of CCR6⁺CD4⁺ T cells but not $\gamma\delta$ T cells, can rescue arthritis in IL-23R deficient mice.

Disclosure: W. Razawy, None; N. Salioska, None; P. Asmawidjaja, None; A. Otten-Mus, None; N. Kops, None; M. Oukka, None; V. Kuchroo, None; E. Lubberts, None.

Abstract Number: 63

TNF- α Blockade Incompletely Reverses Inflammatory Pulmonary Pathology in the TNF-Transgenic Mouse Model of Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Interstitial lung disease (ILD) is a significant contributor to rheumatoid arthritis (RA) mortality, yet its pathogenesis remains enigmatic. One hypothesis is that initial inflammatory RA-ILD pathology occurs secondary to systemic inflammation, prior to transitioning to irreversible fibrotic lung disease. This idea is supported by the TNF-transgenic (TNF-Tg) mouse model of RA, which manifests a purely inflammatory pulmonary pathology of interstitial infiltrate, perivascular inflammation, vascular occlusion, and follicle formation. While anti-TNF agents are largely effective for arthritis, some reports have found them to be ineffective, and possibly detrimental, to patients with RA-ILD. Here, we tested the hypothesis that pre-fibrotic inflammatory ILD is reversible by treating established ILD in TNF-Tg mice.

Methods: TNF-Tg mice underwent in vivo micro-computed tomography (μ CT) to establish baseline ILD. Once they achieved a minimum lung tissue volume of 400 mm³, mice (n=6) were randomized to 6-weeks of treatment with anti-TNF or Placebo (10 mg/kg/wk i.p.). Body weight, grip strength, and knee ultrasound were measured bi-weekly. Terminal outcomes included lung μ CT, histology, and flow cytometry.

Results: Anti-TNF treated mice recovered their body weight, grip strength and had resolution of their arthritis. Further, they demonstrated a dramatic yet incomplete amelioration of lung pathology. Total lung tissue volume was significantly reduced vs. placebo (302.25 \pm 38.40 mm³ vs. 471.53 \pm 27.13 mm³; p<0.0001) (Fig. 1). Histologic analysis corroborated this finding, with marked decreases in interstitial infiltrate, perivascular inflammation, and vascular occlusion in anti-TNF treated lungs. In contrast, prominent follicle-like structures remained (Fig. 2A-C). Flow cytometry identified a novel CD11b^{int}/CD11c⁻ population, which declined with a concomitant increase in a CD11b^{hi}/CD11c^{hi} cDC2-like population in placebo treated lungs, and reverted to WT in the anti-TNF treated lungs (Fig. 2D-F).

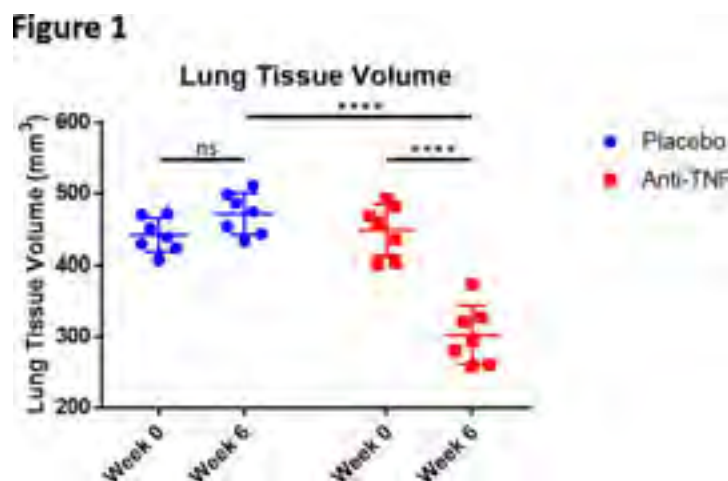
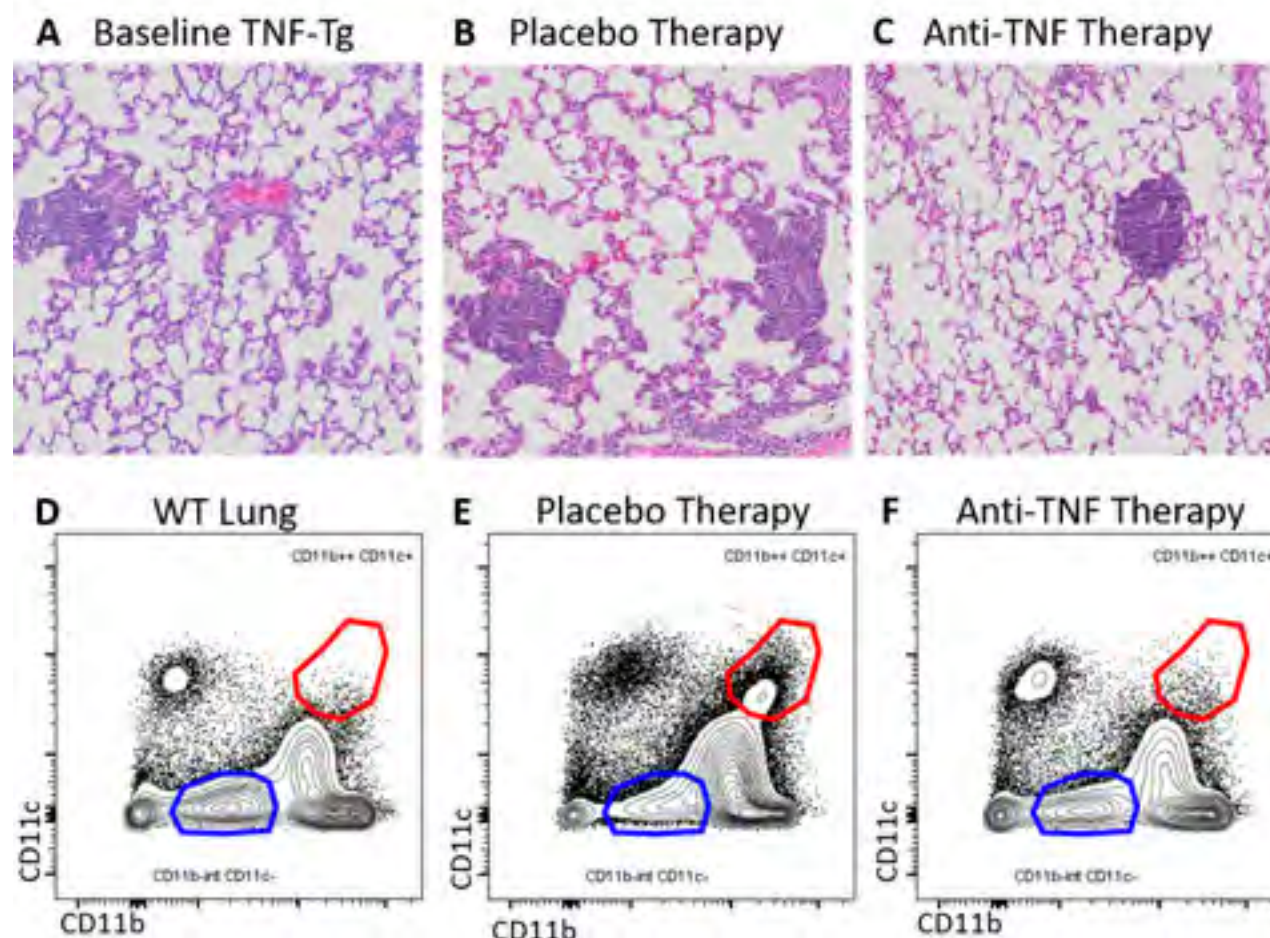


Figure 2



Conclusion: Our results demonstrate that a purely inflammatory RA-ILD is largely resolved with anti-TNF therapy, supporting the hypothesis that the inflammatory phase of ILD is potentially reversible. Interestingly, the follicle-like structures in the pulmonary tissue were not cleared by anti-TNF therapy, and a novel cell population was identified in TNF-Tg mice lungs that was no longer present after anti-TNF therapy. Further research is needed to investigate the role of the follicle-like structures and to characterize this novel cell population.

Disclosure: E. Wu, None; R. Bell, None; E. Schwarz, None; H. Rahimi, None.

Abstract Number: 64

Dietary Magnesium Modulates the Intestinal Microbiome and T Cell Subsets

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Several studies have demonstrated that Magnesium (Mg) has a key role in the immune responses. Our previous studies showed that a short-term low Mg diet was significantly protective in mice with Collagen-Induced Arthritis (CIA) arthritis decreasing disease severity and preserving normal joints' architecture without any erosive changes. Spleen from these mice had reduced levels of Th17 cells and increased numbers of CD4+FoxP3+ Treg cells. Given the strong relationship between Tregs, Th17 cell and the gut microbiota we examined the effect of different Mg diets on the intestinal microbiota of arthritic mice.

Methods: Mice were placed either on a low (50 ppm), regular (500 ppm) or high Mg diet (2800 ppm) 22 days before the induction of CIA, and discontinued three days after the induction. The diets were then converted into a regular Mg diet that was continued until the end of the arthritis experiment. Fecal samples were collected before starting the Mg diets (day 0), after 22 days of diet and at the end of the arthritis scoring period (day 56); Fecal genomic DNA was extracted and expression of the commensal bacteria *Bacteroides fragilis* (BFR), *Bifidobacterium* (Bfd), clostridium cluster IV (sg-Clep), *Clostridium coccoides* group (g-Ccoc), *Clostridium Perfringens* (Closp), *Lactobacillus* (Lact) and Segmented filamentous bacteria (SFB) determined by qPCR by amplifying 16S rRNA genes and normalizing for Eubacteria. Splenocytes were used for flow cytometry quantification of Th17 and CD4+FoxP3+ Tregs.

Results: There were no significant group differences in the baseline levels of microbiota before starting the diets. At the end of the arthritis experiment (day 56) the low and high Mg diet groups had significantly lower levels of SFB ($p=0.04$ and $p=0.05$, respectively; unpaired t-test; $n=5/\text{group}$), compared with the regular Mg diet (500ppm) group. These results correlated with decreased numbers of Th17 cells in low Mg treated mice. The low Mg diet group also had significantly increased levels of BFR ($p=0.05$; unpaired t-test, $n=5/\text{group}$) and increased numbers of CD4+FoxP3+ Treg cells. BFR has been shown to promote differentiation and increased suppressive activity of CD4+FoxP3+ Treg cells.

Conclusion: This study describes for the first time that alterations in dietary Mg may affect the status of the gut microbiome and those changes correlate with numbers of Tregs and Th17 cells. These results suggest that changes in dietary Mg may affect arthritis by inducing changes in the microbiome and in pathogenic and protective T cell subsets.

Disclosure: T. Laragione, None; C. Harris, None; P. S. Gulko, None.

Abstract Number: 65

Bacteria-Derived Indole Drives Autoimmune Arthritis By Altering B Cell Glycosylation of Autoantibodies

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Ongoing studies in rheumatoid arthritis (RA) implicate intestinal dysbiosis of bacteria as a contributing factor, though the mechanism(s) by which bacteria influence disease is not known. Our recent studies using the murine collagen-induced arthritis (CIA) model of inflammatory arthritis demonstrated a role of intestinal bacteria in influencing autoantibody pathogenicity through modulation of autoantibody glycosylation. As bacterial metabolites are potent immune modulators, we profiled intestinal metabolites generated during CIA to identify potential mediators of antibody glycosylation. We identified the bacteria-produced metabolite indole as significantly correlating with the development of disease. In this study, we aimed to further investigate the role of indole for antibody glycosylation during the development of CIA.

Methods: We utilized the murine collagen-induced arthritis (CIA) model in which mice are immunized with bovine type II collagen on days 0 and 21. To reduce the effect of microbe-produced metabolites during disease, we administered broad-spectrum antibiotics in the drinking water starting at day 21, which reduces intestinal bacteria >90% and CIA severity >95%. Indole was then added to this water at a concentration of 1 μM . Cecal contents with tissue were evaluated by LC-MS and 16S rRNA sequencing of bacteria. Cells in Peyer's patches, mesenteric LNs, and spleens evaluated by flow cytometry and qPCR. Serum antibodies were measured by ELISA. For ex vivo stimulation of B cells with indole, splenic B cells were negatively sorted 10 days following CII-immunization and differentiated in culture with LPS \pm indole. After 24 hours, RNA was isolated from cells and gene expression determined by qPCR.

Results: Profiling the metabolome during CIA identified the indole pathway as significantly altered and correlating with disease severity in CIA. Indole also correlated with the significant expansion of bacteria known to produce indole in the development of CIA. In mice protected from CIA by antibiotic administration (CIA+Abx) indole levels were significantly reduced ($P<0.0001$). Mice with CIA compared to CIA+Abx demonstrated significantly increased expression of β 1,4-galactosyltransferase 1 (GalT) and β -galactoside α 2, 6-sialyltransferase 1 (St6gal1), two enzymes important in mediating pathogenic antibody glycosylation. Administration of indole to mice with CIA+Abx resulted in significantly reversing the

protective effects of antibiotics both on disease severity and expression of GalT and St6Gal1. Treatment of CII-primed B cells with indole ex vivo also resulted in a significant induction of expression of these enzymes.

Conclusion: Our data demonstrate that the bacteria-produced metabolite indole significantly drives the development of CIA. While the glycosylation status of antibodies from mice in our treatment groups needs to be confirmed, these results strongly suggest that the mechanism is via induction of B cell glycosylation enzymes that modulate autoantibody effector function towards a proinflammatory profile. Targeting this pathway has potential clinical implications in treating and/or preventing RA.

Disclosure: W. Jubair, None; E. Alexeev, None; T. Lemke, None; M. Chriswell, None; S. Colgan, None; K. A. Kuhn, None.

Abstract Number: 66

Suppression of Inflammatory Arthritis, in Human Paraoxonase 1 Transgenic Mice, Correlates with Upregulation of the Hepatic Glutathione Pathway and Reduction of Bioactive Lipid Mediators

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Animal Models Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Paraoxonase 1 (PON1) is an HDL-associated protein, which hydrolyzes biologically active oxidized phospholipids and prevents oxidation of lipids in LDL and HDL. Increased lipid peroxidation and oxidative stress have been implicated in the pathogenesis of rheumatoid arthritis (RA), and we previously reported decreased inflammatory arthritis activity in PON1 transgenic (Tg) mice in 2 RA mouse models. The current work evaluated mechanisms for decreased inflammatory arthritis in PON1Tg mice using the K/BxN serum transfer model of RA.

Methods: The K/BxN serum transfer-induced arthritis model (STIA) was used in B6 mice homozygous for the PON1 human transgene [PON1Tg] and wild type littermate control mice [WT] (n= 10 per group). Non-STIA PON1Tg (n= 9) and WT (n=10) mice were also evaluated. Liquid chromatography–electrospray ionization, tandem mass spectroscopy was performed for a panel of 13 circulating bioactive lipid mediators (BLM) including TXB2, 6tl 2epi LTB4, LTB4, 15d-D12,14 PGJ2, 13 HODE, 9 HODE, 17S-HDHA, 15 HETE, 14 S-HDHA, 11 HETE, 12 HETE, 5 HETE, and 5-oxoETE. Next-generation RNA sequencing analysis was done on liver tissue. Histopathologic scoring of arthritic hind limbs was performed by a blinded reviewer as were the prior clinical arthritis activity scores.

Results: Marked reduction in histologic damage was observed in PON1Tg compared to WT mice (p values<0.0002; see Table) consistent with decreases in clinical arthritis scores. WT mice had significant increases in the majority of BLMs (11/13) after arthritis induction, however, PON1Tg mice did not have similar increases, and had significantly lower levels of 9/13 BLMs post-arthritis induction compared to WT mice (Table). Significant correlations were evident between lower levels of BLMs and lower clinical and histologic scores (r values = 0.5 - 0.8, p values < 0.05) for 10/13 BLMs. The hepatic glutathione metabolism pathway was 14-fold upregulated in PON1Tg mice versus WT mice after arthritis induction, controlling for baseline (non-arthritic) expression differences in PON1Tg and WT mice (Bonferroni p value < 1.5E-04). Increased expression of 7/8 genes in this pathway was significantly associated with decreases in circulating BLMs (r values = -0.5 - 0.8, p values <0.05; correlations of raw gene expression counts/various BLMs). Upregulation of GSTM3 (glutathione S-transferase mu 3) was highly correlated with both lower histologic damage scores (r = -0.8 - 0.9, p values <0.05) as well as trended with decreased clinical arthritis scores (r = -0.6, p = 0.09).

Conclusion: Overexpression of the human PON1 transgene in the KBxN STIA model of RA suppressed inflammatory arthritis, which correlated with upregulation of the hepatic glutathione pathway and reduction of circulating BLMs. Further investigation of these findings is warranted to evaluate potentially novel therapeutic targets for treatment of RA.

	PON1Tg	WT
Pre-arthritis		
TXB2	1.87±1.02	1.71± 0.82
6tl 2epi LTB4	0.17 ± 0.09 #	0.16 ± 0.10 #
LTB4	0.19 ± 0.04 #	0.16 ± 0.03 #
15d-D12,14 PGJ2	0.73 ± 0.29 *	0.43 ± 0.14 #
13 HODE	9.28 ± 5.49	6.83 ± 3.44 #
9 HODE	6.31 ± 2.91	3.84 ± 2.85 #
17S-HDHA	2.38 ± 1.98 #	2.27 ± 2.14 #
15 HETE	0.41 ± 0.30	0.99 ± 0.48
14 S-HDHA	17.35 ± 10.15 #	13.99 ± 14.49 #
11 HETE	0.63 ± 0.20	0.45 ± 0.22 #
12 HETE	33.62 ± 25.95 #	24.48 ± 18.11 #
5 HETE	3.51 ± 1.98 *	1.52 ± 0.89 #
5-oxoETE	0.73 ± 0.50	0.34 ± 0.26 #
Post-arthritis		
Inflammation (0-5)	1.5 ± 1.0*	4.5 ± 0.7
Cartilage Damage (0-5)	1.3 ± 0.9*	3.6 ± 0.8
Bone Erosion (0-5)	0.9 ± 0.9*	3.7 ± 0.9
TXB2	1.98 ± 0.52	2.32 ± 0.97
6tl2epi LTB4	0.42 ± 0.16	0.54 ± 0.24
LTB4	0.25 ± 0.04 *	0.32 ± 0.06
15d-D12,14 PGJ2	0.69 ± 0.24 *	1.15 ± 0.45
13 HODE	5.29 ± 2.79 *	14.38 ± 7.81
9 HODE	4.72 ± 1.69 *	12.34 ± 4.56
17S-HDHA	7.28 ± 4.19 *	13.22 ± 3.66
15 HETE	0.77 ± 0.39 *	2.45 ± 1.41
14 S-HDHA	50.86 ± 19.66	62.45 ± 15.37
11 HETE	0.73 ± 0.27 *	1.35 ± 0.37
12 HETE	64.50 ± 30.52	69.21 ± 20.85
5 HETE	4.34 ± 2.16 *	8.19 ± 2.40
5-oxoETE	0.75 ± 0.21 *	2.92 ± 3.27

Units are ng/ml (BLMs). PON1Tg= mice homozygous for the PON1 human transgene. WT= wild type littermate control mice. *p<0.05 compared to WT. # p<0.05 compared to Post-arthritis value of same group.

Disclosure: C. Charles-Schoeman, Bristol Myers Squibb, AbbVie, Octapharma, and Pfizer, 2,Regeneron-Sanofi, Pfizer, Octapharma, Amgen, and Gilead, 5; A. Shahbazian, None; J. Wang, None; X. Wang, None; E. Brahn, None; J. Papesh, None; V. Grijalva, None; S. T. Reddy, None.

Abstract Number: 67

Intestinal Inflammation and Netosis Associate with the Presence of Stool IgA ACPA in Subjects at-Risk for RA

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Anti-citrullinated protein antibodies (ACPA) and inflammation characterized by neutrophil extracellular trap (NET)osis have been detected at mucosal sites such as the lung and periodontium in individuals at-risk for RA. We postulated that the intestine is an additional site for inflammation and ACPA generation in subjects at-risk for future RA.

Methods: Stool was collected from 16 healthy controls, 13 subjects with early RA (eRA) (<1 year), and 34 subjects at-risk for the future development of RA. At-risk subjects included individuals without inflammatory arthritis at or prior to the study visit and were first-degree relatives (FDRs) of RA probands (10 serum CCP+ and 9 CCP-) or non-FDRs who were

CCP+ (N=15). Stool was tested by ELISA for CCP3 IgA, total IgA, myeloperoxidase (MPO)-DNANET remnants, and calprotectin. Isotype-specific antibody coating of stool bacteria was determined by flow cytometry. The murine collagen-induced arthritis (CIA) model was treated with broad-spectrum antibiotics after induction of disease (day 21) to interrogate the microbiome's role in stimulating intestinal inflammation and autoantibodies. Antibodies to collagen (CII) were measured by ELISA, and tissue neutrophils were assessed by flow cytometry.

Results: Stool IgA CCP3 was detected in 30% of at-risk subjects and 38% of eRA, and was significantly increased in serum CCP3 IgG+FDRs, while those in the eRA group demonstrated significantly increased IgA-coating of bacteria in the stool samples compared to the other groups (Table 1). Neutrophil-driven mucosal inflammation was present in at-risk subjects, reflected by high calprotectin and NET-remnant levels. MPO-containing NET remnants, which are reported to be induced by bacteria, significantly positively correlated with stool IgA CCP3 ($r=0.3$, $P=0.004$). In mice with CIA, antibiotic treatment significantly reduced disease severity >95%, neutrophil recruitment to the intestine, and mucosal anti-CII IgA. Mucosal anti-CII IgA significantly correlated with serum anti-CII IgG ($r=0.33$, $P=0.03$).

Conclusion: These data implicate a role of intestinal microbiota and inflammation in the induction of mucosal ACPA in at-risk subjects and anti-CII antibodies in CIA. Local neutrophil-associated inflammation strongly correlates with the generation of ACPA IgA in the intestine of at-risk subjects. In eRA, IgA coating of bacteria is increased, suggesting that the earlier generation of intestinal ACPA may lead to increased targeting of specific bacteria. The CIA model confirms the necessity of bacteria in driving the mucosal autoantibody response as mice depleted of bacteria using antibiotics resulted in reduced neutrophils and autoantibodies. While more specific mechanisms need to be defined, we propose that intestinal mucosal responses in at-risk individuals are significantly involved in the progression towards RA in a subset of individuals.

Table 1. Results of stool testing in study groups

Study Group	Stool CCP3 IgA (U/ml)	ACPA Index (U/ml CCP3 IgA ÷ U/ml total IgA)	IgA Coated Bacteria (% of total)	MPO-DNA complex (U/ml)	Fecal Calprotectin (mg/kg)
Healthy controls	301 ± 68	0.25 ± 0.03	9.1 ± 3.2	6,042 ± 639	115 ± 68
Serum CCP+ IgG FDR	1256 ± 627*	1.25 ± 0.50*	8.8 ± 2.0	12,342 ± 2,567	334 ± 139
Serum CCP- IgG FDR	530 ± 211	0.40 ± 0.16	4.8 ± 2.2	13,545 ± 3,214*	833 ± 395*
Serum CCP+ IgG non-FDR	344 ± 63	0.35 ± 0.06	5.6 ± 1.0	8,848 ± 2,184	311 ± 84
eRA	720 ± 249	0.41 ± 0.13	20.4 ± 6.5*	13,159 ± 2,899*	278 ± 160

All data are mean ± SEM. * $P<0.05$ as determined by ANOVA with Tukey's post-hoc analysis.

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Abstract Number: 68

A Genome-Wide Association Study Identifies rs116199914 As an Intergenic Variant Associated with Carotid Intima-Media Thickness in Spanish Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Cardiovascular (CV) disease is the most common cause of morbidity and mortality in patients with rheumatoid arthritis (RA) [1, 2]. Traditional CV risk factors and chronic inflammation do not fully explain the increased CV predisposition observed in patients with RA [3]. In this regard, cumulative knowledge suggests that genetic factors may play a relevant role in this phenomenon [4]. To shed light onto the genetic background influencing the development of CV disease in patients with RA, we performed a genome-wide association study (GWAS) in a cohort of Spanish patients diagnosed with this condition.

Methods: After quality control filters, 2,989 Spanish patients with RA who fulfilled the 2010 American College of Rheumatology classification criteria [5] were analyzed. In addition, data on subclinical atherosclerosis, obtained by carotid ultrasonography (by assessment of carotid intima-media thickness-cIMT-and presence/absence of carotid plaques), was available for 1,355 of these patients.

Results: rs116199914 was identified as an intergenic variant associated with cIMT values at the genome-wide level of significance (minor allele (G): $\beta=0.142$, $P=1.86E-08$). In addition, suggestive signals of potential relevance were observed when both the presence/absence of CV events and subclinical atherosclerosis were evaluated, although none of them reached the genome-wide level of significance. Finally, a molecular pathway enrichment and a predictive protein-protein relationship analyses, including these suggestive GWAS signals, revealed a potential functional enrichment of the collagen biosynthesis network regarding the presence/absence of carotid plaques (GO:0032964, $P=0.0497$).

Conclusion: Our study suggests that the rs116199914 genetic variant is implicated in the increased CV risk observed in Spanish patients with RA.

[1] *Arthritis Rheum* 2007;57:125-32; [2] *Best Pract Res Clin Rheumatol* 2016;30:851-69; [3] *Ann Rheum Dis* 2018;77:48-54; [4] *Autoimmun Rev* 2016;15:1013-30; [5] *Arthritis Rheum* 2010;62:2569-81.

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Possible Association of Early Inflammatory Arthritis with Viral Outbreaks Such As Influenza: Time Series Analysis of the Canadian Early Inflammatory Arthritis Cohort

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Disease clustering suggests a possible environmental cause. Rheumatoidarthritis (RA) is an autoimmune disease that may be triggered by environmental factors such as viruses. Influenza is a common viral infection worldwide. There is a laboratory confirmation that similar inflammatory cytokines and cells are involved in the pathogenesis of influenza and RA. Also, in subjects without RA, the presence of antibodies to influenza in recently exposed to influenza individuals is associated with the presence of rheumatoid factor. We estimated the distribution of early incident inflammatory arthritis over time. We examined whether and to what extent seasonal variations in influenza may be associated with inflammatory arthritis first symptom onset.

Methods: Canadian Early Arthritis Cohort (CATCH) is a prospective observational cohort study of adults with early (≤ 12 months) incident inflammatory arthritis. We included patients enrolled from January 2007 till January 2017. We used patient-reported date of first symptom onset as a proxy measure of IA onset in our study, and estimated the seasonal distribution of inflammatory arthritis (IA) onset for 10 years of observations. Influenza time series was based on laboratory confirmed influenza A & B retrieved from the Canadian Flu Watch surveillance program initiated in 2010. Bivariate analysis of influenza and IA was performed for 2010-2016 period using cross-correlations with different time lags, and time series Poisson regression with smoothing function to remove seasonality and long-term patterns in the exposure and outcome series. Both IA and influenza were recorded as monthly total frequencies.

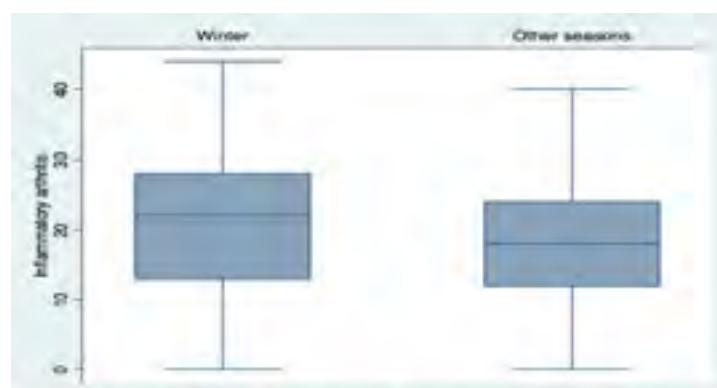


Fig. 1. Average onset of inflammatory arthritis aggregated by season, 2006-2016

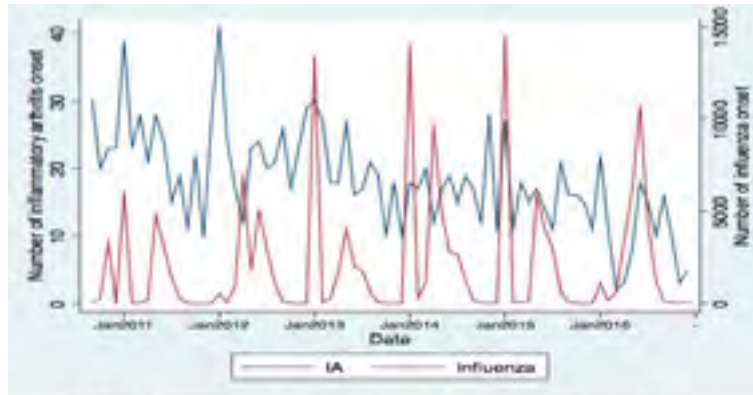


Fig. 2. Time series of inflammatory arthritis and influenza, 2010-2016

Results: 2519 patients with IA were included, 88% had confirmed RA. More IA onsets occurred in January though the difference between months was not significant. There were significantly more IA onsets in winter compared to other seasons (Figure 1). Bivariate time series analysis of IA and influenza revealed similar high-level patterns in the onsets in January (Figure 2). We found that influenza weakly correlated with IA onset. We estimated that every influenza onset was associated with on average 0.0023 % increase in IA onset ($p=0.04$).

Conclusion: Patient-reported IA symptom onset occurs more frequently in winter, when the immune system is more susceptible to infections. Peak periods of influenza outbreaks in Canada over 6 years were very weakly associated with an increase in IA onset.

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Abstract Number: 70

Colocalization of Malondialdehyde-Acetaldehyde Adducts (MAA) and Extracellular Matrix Proteins in Joint and Lung Tissues from Rheumatoid Arthritis Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Malondialdehyde-acetaldehyde adducts (MAA) are products of oxidative stress that modify self-proteins and stimulate potent cellular and humoral immune responses. We have previously demonstrated that MAA adducts are present in lung and joint tissues from rheumatoid arthritis (RA) patients and colocalize with citrullinated

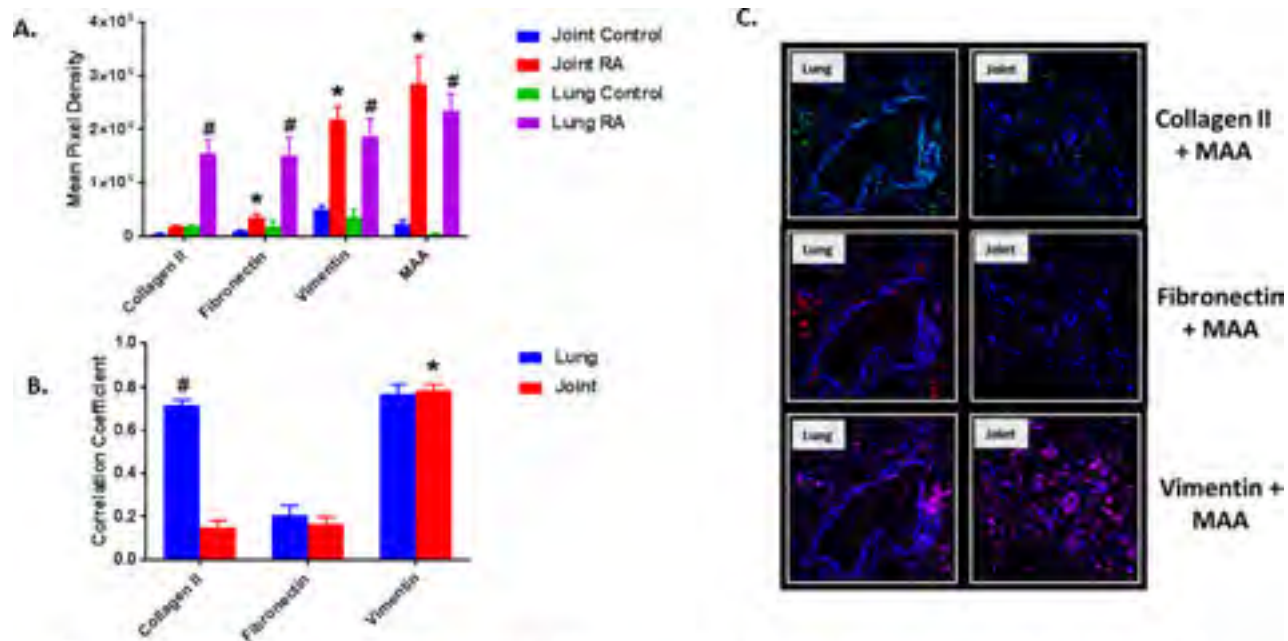


Figure 1 (A) Mean pixel density of malondialdehyde-acetaldehyde adducts (MAA) and extracellular matrix proteins in rheumatoid arthritis (RA) synovium and Lung compared to controls. (B) Correlation coefficients between Lung and joint tissue co-stained with MAA and Collagen II, Fibronectin, and Vimentin. (C) Representative lung RA-ILD and RA synovial tissue sections are depicted (blue = MAA, green = Collagen II, red = Fibronectin, purple = Vimentin).

proteins. Moreover, anti-MAA antibodies are associated with higher RA disease activity and extra articular features including interstitial lung disease (ILD). However, the adducted protein(s) driving these immune responses are unknown. Implicated as pathogenic target autoantigens; we characterized extracellular matrix (ECM) protein and MAA expression in RA lung and joint tissues.

Methods: Paraffin embedded joint tissues from osteoarthritis (OA) and RA patients (n=5 each) were stained for MAA, vimentin, fibronectin, and collagen II. Similarly, we stained non-paired lung tissues from subjects with RA-ILD and controls (n=3 each). Tissues were assessed with confocal microscopy and staining patterns were quantified using Zen and image J software. Co-localization of ECM proteins with MAA was determined using the Fiji plugin, Coloc2. Pearson's correlation coefficients were calculated and compared between disease groups for lung and synovium.

Results: MAA, vimentin, and fibronectin expression (but not collagen II) were all significantly higher in joint tissues from RA compared to OA patients (*P<0.001) **Fig 1A**. Colocalization of MAA with vimentin was significantly greater than that observed with other ECM proteins in RA synovium (*P<0.001) **Fig 1B/C**. In lung tissues, all 3 ECM proteins and MAA were all significantly increased in RA-ILD vs. normal controls (#P<0.03) **Fig 1A**. Colocalization of MAA with the ECM proteins (Collagen II and Vimentin) was increased in RA-ILD lung tissue. Similar to RA joint tissues, colocalization with MAA and vimentin was observed (R=0.77). However, collagen II was significantly increased (#P<0.001) in the lung compared to the joint **Fig 1B/C**.

Conclusion: Enhanced colocalization of critically important ECM proteins with MAA in diseased tissues, in addition to prior observations of increased anti-MAA antibody responses in RA, suggests a mechanistic role of MAA in RA synovial and lung disease. Moreover, these results suggest that interactions between MAA and ECM proteins are tissue dependent with MAA modification of vimentin potentially shared between the lung and synovium, while MAA modification of collagen may be more lung predominant.

Disclosure: G. M. Thiele, None; M. J. Duryee, None; J. D. McGowan, None; L. M. Duryee, None; L. W. Klassen, None; J. R. O'Dell, Medac, 5; B. R. England, None; T. R. Mikuls, BMS, Ironwood, Horizon, 2, Pfizer, Inc., 5.

Abstract Number: 71

Association of Shared Epitope and Poor Prognostic Factors in RA

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: There is a strong genetic association between RA and human leukocyte antigen (HLA) regions, particularly HLA-DRB1 alleles with the shared epitope (SE). SE alleles are associated with seropositivity, erosions and higher disease activity (DA) in RA. We evaluated the association between SE alleles and multiple poor prognostic factors (PPFs) of seropositive (anti-citrullinated protein antibody and/or RF) and erosive RA, and changes in DA.

Methods: We analyzed patients (pts) enrolled in a large sequential RA registry started in 2003; most had established RA and annual clinical evaluations. Pts with baseline (BL) data on SE status were included. A commercially available kit was used for HLA genotyping. HLA-DRB1 serotypes were assessed from DNA sequences using allele-specific polymerase chain reaction methods and categorized as pts with 0, 1 or 2 SE alleles. Association of multiple PPFs and SE status was evaluated using multinomial logistic models; association between change in DA and SE status was analyzed using linear regression models with age, sex, disease duration (DD), co-morbidities and biologic DMARDs as covariates.

Results: Of 689 pts with RA, 0, 1 and 2 SE alleles were reported in 241 (35.0%), 275 (40.0%) and 173 (25.1%) pts, respectively. At BL, pts with SE alleles (vs 0) were more likely to have PPFs and had longer DD and higher DA (Table 1). Odds ratio (OR) for seropositive erosive RA in pts with 2 and 1 SE alleles (vs 0) was 5.44 (95% CI 2.39, 12.39) and 2.87 (1.32, 6.23; Fig), respectively. OR for double seropositivity in pts with 2 and 1 SE alleles (vs 0) was 4.27 (95% CI 2.51, 7.28) and 2.56 (1.66, 3.94), respectively. In total, 551 pts had DA measures at BL and 1 year. After controlling for BL covariates, pts with SE (vs 0 SE) had a mean increase in DAS28 (CRP) of 0.24 ($p=0.031$), CDAI of 2.71 ($p=0.027$) and SDAI of 3.25 ($p=0.013$; Table 2).

Conclusion: Pts with SE alleles are more likely to have multiple PPFs; pts with 2 SE alleles are 5 times more likely to be seropositive with erosive RA and 4 times more likely to be double positive. Pts with SE alleles also had an increase in DA over time with standard-of-care treatment.

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Figure. Multinomial Model for Multiple PPF (Seropositive and Erosions)

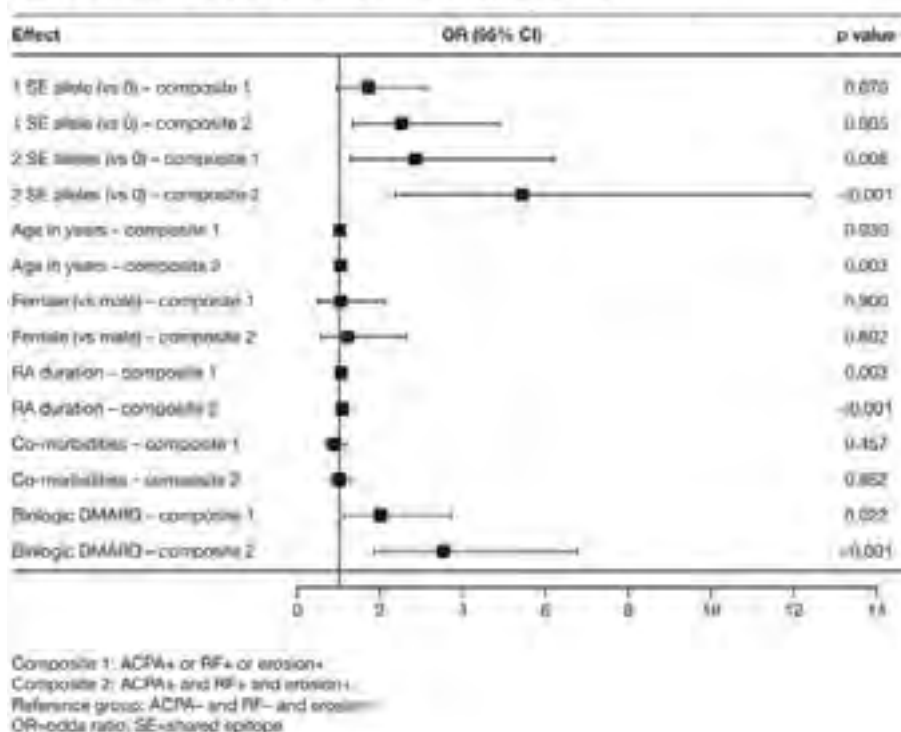


Table 1. Baseline Characteristics by SE Status

	0 SE alleles (n=241)	1 SE allele (n=275)	2 SE alleles (n=173)
Mean (SD) age, years	57.7 (13.6)	58 (13.9)	57.8 (13.6)
Female sex, n (%)	202 (83.8)	219 (79.6)	141 (81.5)
Mean (SD) RA duration, years	12.9 (12.1)	17 (13.3)	16.1 (12.2)
Biologic DMARDs, n (%)	83 (34.4)	145 (52.7)	83 (48.0)
ACPA+, n (%)	118 (49.0)	196 (71.3)	137 (79.2)
Erosions, n (%)	116 (48.1)	168 (61.1)	114 (65.9)
RF+, n (%)	120 (49.8)	195 (70.9)	128 (74.0)
Double positive, n (%)	100 (41.5)	174 (63.3)	121 (69.9)
DAS28 (CRP), mean (SD)	3.8 (1.5)	4.2 (1.6)	4.3 (1.6)

ACPA=anti-citrullinated protein antibody; SE=shared epitope

Table 2. Multivariate Analysis of Impact of SE Status on Change in DA

	DAS28 (CRP) model		CDAI model		SDAI model	
	Coefficient	p value	Coefficient	p value	Coefficient	p value
1 or 2 SE alleles (vs 0 SE)	0.24	0.031	2.71	0.027	3.25	0.013
Baseline DA	-0.41	<0.001	-0.46	<0.001	-0.48	<0.001
Age, years	0.01	0.271	0.04	0.367	0.04	0.406
Female (vs male)	0.11	0.435	2.52	0.099	2.12	0.198
No. of co-morbidities	0.11	0.003	1.25	0.003	1.42	0.002
Biologic DMARD (yes vs no)	0.41	<0.001	3.79	0.002	4.09	0.001
Adjusted R-square	0.23		0.27		0.29	

DA=disease activity; SE=shared epitope

Disclosure: E. Alemao, Bristol-Myers Squibb, 1, 3; J. Bryson, Bristol-Myers Squibb, 1, 3; C. K. Iannaccone, None; M. Frits, None; N. A. Shadick, Amgen, Mallinckrodt, Bristol-Myers Squibb, Sanofi-Regeneron, 2, Bristol-Myers Squibb, 5; M. Weinblatt, Amgen, Crescendo Bioscience, Bristol-Myers Squibb, Sanofi/Regeneron, 2, AbbVie, Ablynx, Amgen, Bristol-Myers Squibb, Canfite, Corrona, Crescendo, GSK, Gilead, Lilly, Lycera, Merck, Momenta, Novartis, Pfizer, Roche, Samsung, Set Point, UCB, Vertex, 5.

Abstract Number: 72

Altered Serologic Responses to Epstein Barr Virus Precede Clinical Disease Development in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

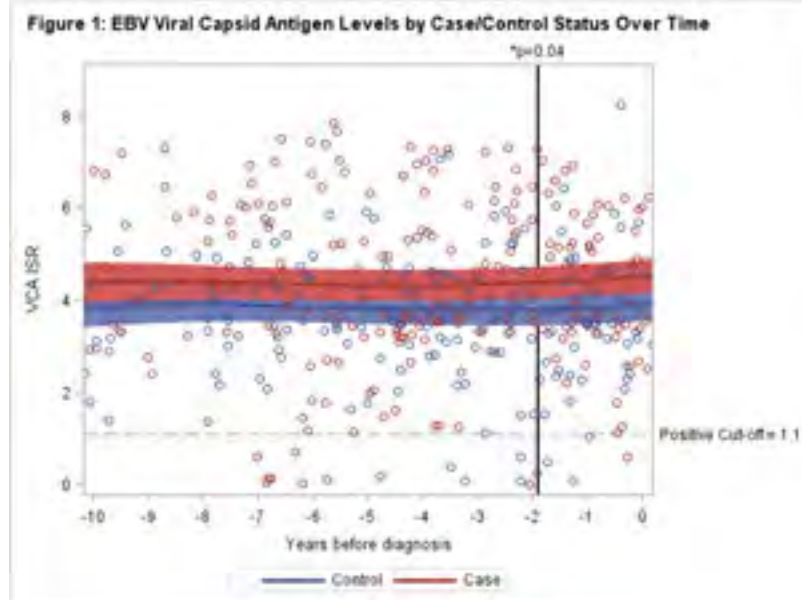
Session Type: ACR Poster Session A

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

Background/Purpose: EBV infects B cells and is associated with several autoimmune diseases, including RA. Prior studies have shown that patients with active RA have altered immune responses to EBV, including elevated anti-viral capsid antigen (VCA) antibodies that indicate recent reactivation. We hypothesized that the abnormal response to EBV occurs in the preclinical period and contributes to the initial development of autoimmunity in subjects who develop RA.

Methods: Serum from military subjects who developed RA (n=83) and controls matched for age, race, sex, region, and timing of blood draw (n=83) was obtained from Department of Defense Serum Repository as previously described (1). All RA subjects met 1987 ACR revised criteria for RA or were diagnosed by a board-certified rheumatologist. Sera were tested for anti-EBNA-1 IgG (2), anti-VCA IgG (Wampole, Cranbury, NJ), and anti-CCP3.1 and RF IgM (both Inova, San Diego, CA) by ELISA. Statistical analysis was by Chi-square, t-test, and ANOVA. A mixed model compared EBV levels at one-year intervals followed by 1 month intervals to identify the time when levels differed significantly between cases and

Fig 1. Mixed model analysis of VCA levels between cases and controls for 10 years before diagnosis of RA. VCA shows significant divergence between cases and controls at -1 year and 11 months (1.9 years) prior to RA diagnosis [Cases: mean[SE] = 4.41(0.18) and Controls: mean[SE] = 3.81(0.18)]



	RA Case	Control	p value
N	83	83	
Samples pre-diagnosis: N	243	243	
Samples post-diagnosis: N	47	47	
Samples per subject pre-diagnosis: mean (range)	2.9 (1-4)	2.9 (1-4)	
Samples per subject post-diagnosis: mean (range)	1 (1-1)	1 (1-1)	
Age at diagnosis: mean±SD	38.9 ± 10		
Sex: % male	59%	59%	
Race: % white	69%	69%	
VCA: % ever positive	95%	98%	0.68
VCA+ visits: % positive visits*	95%	97%	
VCA ISR mean ± SD†	4.44 ± 0.19	3.83 ± 0.14	0.02
Pre-diagnosis	4.39 ± 1.67	3.83 ± 1.24	0.02
Post-diagnosis	4.85 ± 1.89	4.30 ± 1.68	0.13
EBNA-1: % ever positive	99%	99%	1.00
EBNA-1+ visits: % positive visits	95%	97%	
EBNA-1 mean OD ± SD†	0.84 ± 0.03	0.77 ± 0.02	0.05
Pre-diagnosis	0.86 ± 0.29	0.79 ± 0.23	0.06
Post-diagnosis	0.74 ± 0.25	0.69 ± 0.20	0.27
RF IgM: % positive	70%	12%	0.0001
CCP3.1: % positive	72%	17%	0.0001

*2 visits missing VCA testing (1 case, 2 control)

†Average of repeated measures per individual (n=83 RA cases and n=83 controls)

controls ($P < 0.05$). Multiple comparison adjustment with a step down Holm-simulated method was used to control the family-wise type I error rate.

Results: Levels of VCA and EBNA-1 antibodies were significantly higher in RA cases vs controls over all visits, most notably in the pre-diagnosis period (Table 1). Analysis of EBV antibody levels in the 10 years prior to diagnosis showed VCA diverged 1.9 years before onset RA compared to controls (Fig 1), and EBNA-1 diverged at 3.5 years.

Conclusion: An altered immune response to EBV characterized by relatively elevated EBNA-1 and VCA antibodies is seen in pre-clinical RA. Elevated anti-VCA antibodies suggests that viral reactivation may contribute to the future development of RA. Further studies are needed to assess the complex lifecycle of EBV and immune regulation of viral infection in the pre-clinical period and the role in promoting RA-related autoantibody and classified disease development.

References: 1. Majka DS, et al. Ann Rheum Dis. 2008; 67(6):801-7.

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Abstract Number: 73

Circular RNAs Expression Profile in Chinese Rheumatoid Arthritis Patients at Different Disease Activity

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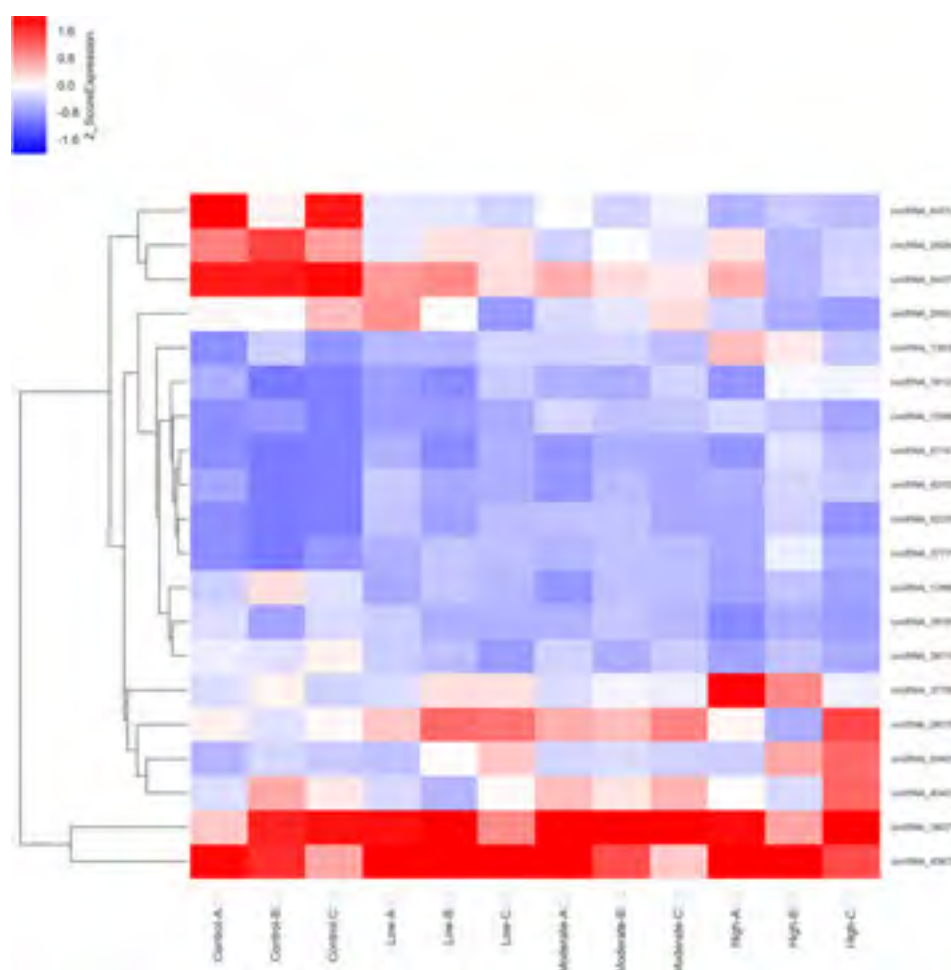
Session Date: Sunday, October 21, 2018

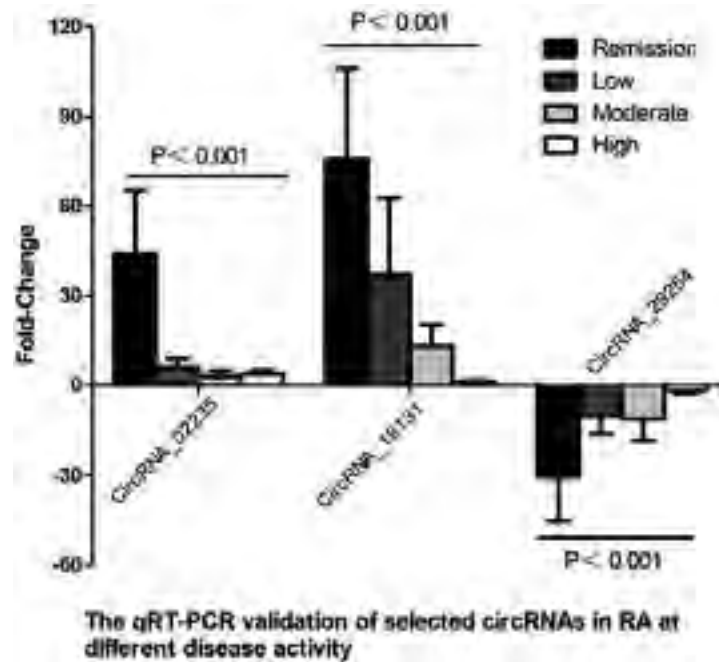
Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune-mediated chronic inflammatory joint disease, that is still no clear pathogenesis for patients to be cured in a timely manner. Circular RNAs (circRNAs) have been recently





Spearman correlation test of clinical variables and confirmed circRNAs from RA patients at different disease activity

	ESR	CRP	RF	Anti-CCP	HAQ	Pain_VAS	DAS28	CDAI	SDAI
CircRNA_02235	.004	-.309**	-.092	-.080	-.230*	.283**	-.363**	-.299**	-.350**
CircRNA_19131	-.159	-.407**	-.008	-.040	-.434**	.470**	-.501**	-.514**	-.542**
CircRNA_29264	-.073	-.332**	.001	.002	-.326**	.340**	.439**	-.397**	-.422**

Note: ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide antibody; HAQ: Health assessment questionnaire; Pain_VAS: Visual analogue scale pain score; DAS28: Disease activity score in 28 joints; CDAI: Clinical disease activity index; SDAI: Simplified disease activity index

* $P < 0.05$, ** $P < 0.01$

identified as non coding RNAs in most common model organisms and show potential as gene regulators. Here, we profiled the circRNAs expression of RA at different disease activity to improve our understanding of RA pathogenesis.

Methods: Expression profiling was performed by high throughput sequencing using whole blood RNA samples obtained from 12 RA patients. In each group there were 3 patients at low, moderate, high disease activity, respectively, as well as 3 healthy controls. Quantitative real time reverse-transcription polymerase chain reaction (qRT-PCR) was used to identify the differential circRNAs. Spearman correlation test assessed the correlation of circRNAs and clinical variables.

Results: Compared to health controls, a total of 155 circRNAs and 161 circRNAs were significantly upregulated and downregulated, respectively, in RA patients. qRT-PCR detection showed that the expression levels of downregulated circRNA_29264 (hsa_circ_0007889), upregulated circRNA_19131 (hsa_circ_0003123) decreased as the disease activity increased, upregulated circRNA_02235 was higher in remission than other disease activities. The correlation test showed the negative correlation among three circRNAs and C-reactive protein (CRP), health assessment questionnaire (HAQ), VAS pain score, disease activity score in 28 joints (DAS28), clinical disease activity index (CDAI) and simplified disease activity index (SDAI), respectively.

Conclusion: This work illustrates that circRNAs dysregulation may play a role in RA pathogenesis, and three key circRNAs show promise as candidate biomarkers for development of RA.

Disclosure: H. Liu, None; Q. Xie, None; G. Yin, None.

DNA Methylation of the Dual Specificity Protein Phosphatase 22 (DUSP22) Gene Promoter in Plasma of Patients with Seropositive and Seronegative RA

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: The Dual specificity protein phosphatase 22 (*DUSP22*) gene is aberrantly methylated in mononuclear cells in RA, and it has been associated with erosive disease. Increased serum IL-6 and phosphorylated STAT3 levels, which are negatively regulated by *DUSP22*, have been found in T cells of patients with anti-citrullinated peptide autoantibody (ACPA)-negative RA. Pathogenic mechanisms underlying different serotypes in RA are poorly understood. Here, we aim to determine whether plasma nuclear circulating cell-free DNA (ccfDNA) can be used to study DNA methylation of *DUSP22* and whether it is associated with serotype and other clinical features of RA.

Methods: This is an exploratory study in which we recruited 21 patients who satisfied the ACR criteria for RA. They were further classified in 14 seropositive (ACPA+ and/or RF+), and 7 seronegative patients (ACPA- and RF-). DNA was extracted from isolated plasma, bisulfite converted and pyrosequenced to determine DNA methylation levels in the promoter region of *DUSP22*. Statistical analysis was carried out to determine whether *DUSP22* DNA methylation in plasma correlated with serotype, index disease activity (CDAI), Simple Erosive Narrowing Score (SENS), Visual Analogue Scale (VAS), neuropathic pain (IDpain), Toronto Clinical Neuropathy Score (TCNS), Neuropathy Symptom Score (NSS), treatment (DMARDs, anti-TNF alpha), and disease duration. Variables were also analyzed by serotype status and the groups were compared using non-parametric tests.

Results: Hypomethylation of the *DUSP22* promoter was correlated with an increase in SENS ($p=0.02$), and NSS ($p=0.03$) in all RA patients. We found that *DUSP22* DNA methylation did not vary for the different treatment groups. While no statistically significant difference was determined in the DNA methylation of *DUSP22* between seronegative and seropositive patients, hypomethylation of *DUSP22* in seropositives was negatively and significantly correlated with years of disease ($p=0.002$), SENS ($p=0.04$), and NSS ($p=0.002$). We also found seronegative there was only significantly correlated with NSS ($p=0.017$).

Conclusion: While our study has a small samples size, it is the first study to demonstrate that DNA methylation can be measured in ccfDNA of RA patients. We also found that hypomethylation of *DUSP22* was correlated with erosive disease, disease duration and neuropathic pain in seropositive patients, and only with neuropathic symptoms in seronegative patients.

	ACPA – and RF-RA	ACPA+ and/or RF +RA	p-value
Demographics			
No. men	2	2	-
No. women	5	12	-
Men age (years)	57.3±6.4	59.0±14.0	
Women age (years)	61.0±8.3	56.7±13.1	
Hispanic	6	12	-
African American	1	2	-
Treatment			
DMARDs	6	9	-
Biologics +/- DMARDs	1	5	-
Clinical Characteristics			
% ACPA+	0	94.4%	-
% RF+	0	84.2%	-
Disease duration (years)	8.6±14.8	12.1±9.8	0.05
CRP	1.94±3.65	0.78±0.98	0.77

Table . (Cont'd)

	ACPA – and RF-RA	ACPA+ and/or RF +RA	p-value
WBC	7.4±2.2	6.8±2.0	0.48
CDAI	20.6±6.7	14.4±10.3	0.11
VAS	3.0±2.7	6.7±1.1	0.01
NSS	5.3±3.4	2.6±2.5	0.04
ID PAIN	4.3±1.4	2.0±1.6	0.008
TCNS	7.7±2.2	4.1±4.0	0.04
SENS	10.6±9.5	25.1±21.8	0.26
DUSP22 DNA methylation (%)	42.5±11.2	37.6±18.7	0.45
Rheumatoid arthritis treatment and DNA methylation of the DUSP22 promoter			
	DMARDs	Biologicals	p-value
% DUSP22 meth	39.7 ± 16.8	38.7 ± 16.7	0.851
Pearson correlation with DUSP22 DNA methylation without considering serotype status			
	% DUSP22 meth		p-value
Disease duration	-0.43		0.15
CRP	-0.09		0.69
WBC	-0.14		0.54
CDAI	-0.27		0.25
VAS	-0.08		0.72
NSS	-0.48*		0.03
ID PAIN	-0.22		0.3
TCNS	-0.15		0.52
SENS	-0.51*		0.02
Pearson correlation with DUSP22 DNA methylation considering serotype status			
	ACPA – and RF-RA	ACPA+ and/or RF +RA	
Disease duration	-0.03	-0.94*	
CRP	-0.47	0.14	
WBC	-0.18	-0.19	
CDAI	-0.46	-0.30	
VAS	-0.25	-0.18	
NSS	-0.80*	-0.76*	
ID PAIN	-0.7	-0.29	
TCNS	-0.37	-0.26	
SENS	0.18	-0.58*	

* $p \leq 0.05$

Disclosure: M. Rodriguez Alvarez, None; L. Delgado-Cruzata, None; E. Guzman, None; W. Tavarez, None; A. Bliese, None; T. Sabirov, None; M. J. Jimenez, None; C. A. Oviedo Hilario, None; M. E. Acosta, None; M. Albarracin, None; C. Cirilli, None; Z. Parra, None; C. Robles Hidalgo, None; C. Mesa, None; D. Bitinaite, None; S. Kadavath, None; I. El Hussein, None; G. Thomas, None; A. Kavaliauskas, None; K. Bolourian Kashi, None; M. Gebeyehu, None; D. Samip, None; P. Suri, None; M. Gold, None; S. Hinson, None.

Abstract Number: 75

Elevated Oxylipin Profile in Autoantibody-Positive Individuals at-Risk of Developing Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Preclinical phase of rheumatoid arthritis (RA) is characterized by presence of autoantibodies, including anti-citrullinated protein antibodies (ACPA), years before disease onset. Epidemiological observations suggest that high levels of total ω-3 fatty acids are significantly associated with lowering RA transition rate in autoantibody-positive individuals [1]. Fatty acids (FA) and their oxygenated eicosanoid metabolites (oxylipins) regulate systemic inflammatory

responses and pro-inflammatory gene expression leading to orchestration of chronic inflammatory cascade[2]. Over the last 15 years, we longitudinally followed genetically-susceptible Indigenous North American (INA) population with a disproportionately high RA risk (~2-3fold) and increased autoantibody prevalence. In this study, we examined the circulating levels of FA and their oxylipins in RA patients and their asymptomatic ACPA+ and ACPA- first-degree relatives (FDR) from this cohort to understand the role of these metabolites in preclinical RA pathogenesis.

Methods: Gas chromatography (GC) was used for FA estimation in serum samples from age-matched ACPA+ RA patients (N=10), ACPA- FDR (N=10), and ACPA+ FDR (N=53). Oxylipins were extracted and quantified using high performance liquid chromatography – tandem mass spectrometry (HPLC/MS/MS).

Results: We observed an overall increase in unsaturated and ω -6 FA levels in all the study subjects. The ω -3 index (% EPA + DHA) in these individuals was ~5-6% of total FA suggesting an intermediate risk category for coronary heart disease and inflammation. No significant differences were observed in circulating FA levels between RA patients and ACPA- FDRs. Serum eicosanoid profiling identified enrichment of 41 oxylipins (out of 77 mapped metabolites) in ACPA+ FDR compared to RA patients and ACPA- FDR (Mann-Whitney U test). Of these, 9-HODE and 13-HODE were significantly elevated in ACPA+ FDR compared to ACPA- FDR (~55-fold and ~41-fold respectively; $P < 0.0000000001$) and RA patients (~32-fold and ~22-fold respectively; $P < 0.0000000001$). While usage of NSAIDs had no effect on total oxylipin levels, samples stored at -20°C for >5yrs demonstrated significant oxylipin enrichment (*** $P=0.0006$). After correcting for duration of storage effects, we still observed an elevated oxylipin profile in ACPA+ FDR compared to other groups.

Conclusion: Our study demonstrates a distinct FA and oxylipin profile in asymptomatic ACPA+ FDR of INA RA patients and suggests that changes in the specific eicosanoids and their oxygenated metabolites are involved in the development of ACPA and/or the transition to clinically imminent RA in ACPA+ individuals.

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2. Brouwers, H., et al., *Lipid mediators of inflammation in rheumatoid arthritis and osteoarthritis*. Best Pract Res Clin Rheumatol, 2015. **29**(6): p. 741-55.

Disclosure: V. Anaparti, None; I. Smolik, None; T. Winter, None; X. Meng, None; H. Aukema, None; H. El-Gabalawy, None.

Abstract Number: 76

Whole Blood Targeted Bisulfite Pyrosequencing Identifies Differentially Methylated Regions within Major Histocompatibility Complex (MHC) of Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Human major histocompatibility complex (MHC) is strongly associated with rheumatoid arthritis (RA) pathogenesis. Epigenome-wide association study by Liu et al showed that differential DNA methylation within the MHC region can mediate RA genetic risk and contribute significantly to disease susceptibility [1]. Our study objective was to validate Liu et al study findings in an independent study cohort genetically predisposed for developing clinically imminent RA. Therefore, we sequenced MHC-specific methylated CpGs in autoantibody-positive RA patients and matched disease-free healthy controls from a high-risk indigenous North American (INA) population.

Methods: DNA was isolated from whole blood (WB) samples and targeted bisulfite pyrosequencing was used to profile methylated CpGs. Differentially methylated CpG loci (DMLs) were mapped and gene-annotated using R package. mRNA expression of identified genes with multiple DMLs was verified using quantitative real-time PCR (qPCR) in an independent cohort of RA patients and HCs.

Results: We identified 74 uniquely methylated CpG sites within the MHC region that were differentially methylated in the WB of RA patients ($q < 0.05$), compared to HCs. Of these, 36 DMLs were located on 19 genes. IPA network analyses showed these genes regulate NF- κ B complex and processes involved in antigen presentation, immune cell crosstalk and inflammation in autoimmunity and insulin-dependent diabetes mellitus. By qPCR, we also demonstrated a deregulated expression of mRNAs corresponding to *C6ORF10*, *TNXB* and *HCG18*.

Conclusion: Our results demonstrate presence of specific differentially methylated loci within the genomic region encompassing MHC region in whole blood DNA of indigenous RA patients. While some of these genes (*C6ORF10* and *TNXB*) confirm the findings of previous publication, we believe they might be involved in RA pathogenesis in high-risk INA individuals.

1. Liu, Y., et al., Epigenome-wide association data implicate DNA methylation as an intermediary of genetic risk in rheumatoid arthritis. *Nat Biotechnol*, 2013. **31**(2): p. 142-7.

Disclosure: V. Anaparti, None; I. Smolik, None; P. Agarwal, None; N. Mookherjee, None; H. El-Gabalawy, None.

Abstract Number: 77

Single Nucleotide Polymorphism in the Gene Encoding Peptidylarginine Deiminase 4 Correlates with Reduced Neutrophil Extracellular Traps and Anti-Histone Antibodies in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: In neutrophils, peptidylarginine deiminase 4 (PAD4) citrullinates histones allowing chromatin unraveling and neutrophil extracellular trap (NET) formation. NETs are increased and display proteins targeted by autoantibodies in rheumatoid arthritis. Interestingly, antibodies against citrullinated histones are among the first autoantibodies detected in rheumatoid arthritis. Thus, PAD4 may contribute to the development of rheumatoid arthritis by inducing NETs and ultimately autoantibodies. Murine studies have demonstrated that PAD4-deficient mice have reduced NETosis, autoantibodies, and inflammatory arthritis, but the effects of a loss of PAD4 in humans is unknown. Recently it has been shown that the G allele of single nucleotide polymorphism (SNP) rs2240335 in *PADI4* is associated with decreased expression of PAD4 in human neutrophils in healthy Caucasians. The purpose of this study is to determine if the G allele of rs2240335 correlates with reduced NETs and autoantibodies against citrullinated histones in humans, similar to the PAD4 knockout studies in mice.

Methods: DNA, plasma, and serum from subjects with rheumatoid arthritis, both anti-cyclic citrullinated peptide (CCP) antibody negative (n=44) and positive (n=71), and controls (n=28) were obtained from our biorepository. Subjects were ~90% Caucasian. DNA was genotyped at rs2240335. Plasma from controls homozygous at rs2240335 was subjected to an enzyme linked immunosorbent assay (ELISA) to quantify circulating NETs. Serum from rheumatoid arthritis subjects homozygous at rs2240335 was subjected to ELISA to quantify IgG that binds native histones and histones *in vitro* citrullinated with human PAD4. Results were compared between genotypes using a student's t test and verified by a permutation routine.

Results: The concentration of circulating NETs is significantly lower in controls homozygous for the G allele at rs2240335 compared to homozygotes for the T allele ($p=0.027$). In CCP+ rheumatoid arthritis subjects, there was no significant difference in anti-native and anti-citrullinated histone H1, H2A, H2B, H3, and H4 antibody levels between genotypes. However, for CCP- rheumatoid arthritis subjects, anti-citrullinated histone H2B ($p=0.036$) and H3 ($p=0.0041$) and anti-native histone H2A ($p=0.0064$), H2B ($p=0.0073$), and H3 ($p=0.030$) antibody levels were decreased in subjects with the GG genotype.

Conclusion: Similar to studies in PAD4-deficient mice, the G allele of SNP rs2240335, which has been shown to be associated with reduced PAD4 expression in human neutrophils, correlates with reduced NETosis in controls and reduced anti-histone antibodies in CCP- rheumatoid arthritis. Further studies are needed to determine if this allele is associated with rheumatoid arthritis risk in Caucasians.

Disclosure: A. M. Mergaert, None; M. Bawadekar, None; T. Q. Nguyen, None; S. J. Schrodi, None; M. A. Shelef, None.

Abstract Number: 78

Decreased B Cell Ataxia-Telangiectasia Mutated Expression and Receptor Diversity Identify a Subset of Rheumatoid Arthritis Patients with Increased Joint Erosion Prevalence

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: A skewed B cell receptor (BCR) repertoire was observed in some RA patients. In these patients, BCR κ light chains contain a higher percentage of downstream V κ and upstream J κ gene segments rather than the broader utilization of V κ -J κ gene segments seen in healthy donor (HD) controls. How this BCR phenotype occurs and whether it relates to erosive disease is unclear.

Methods: Peripheral blood B cells were obtained from 40 seropositive RA patients meeting ACR classification criteria. V κ and J κ gene segment usage was determined by PCR and allowed patients to be separated into two groups. Erosive disease prevalence was compared between the groups. Gene microarray was done on B cells from each group to determine candidate genes for further investigation and we developed *in vitro* and *in vivo* models based on this to investigate mechanisms for the observed differences.

Results: We identified a subgroup of RA patients whom we call group I in which BCR κ light chains contain a higher percentage of downstream V κ and upstream J κ gene segments compared to HD controls suggesting abnormalities in RAG-mediated BCR V(D)J rearrangement. BCRs in a second subgroup, group II, had broader utilization of V κ -J κ gene segments similar to that of HD. B cell gene array showed decreased ataxia-telangiectasia mutated (*ATM*) in group I vs group II. *ATM* is a key regulator of DNA double-strand break repair, RAG expression, and BCR κ locus allelic exclusion during RAG-induced V(D)J rearrangement. Intriguingly, group I RA patients had a higher prevalence of erosive disease despite no differences in age, disease duration, RF, or ACPA titers between the groups. To determine if lack of functional *ATM* independent of other RA disease factors could explain the increased erosive prevalence in group I, we pharmacologically inhibited *ATM* *in vitro* in HD control B cells and found increased pro-osteoclastogenic B cell *RANKL*, *IL6* and *TNF* expression and decreased anti-osteoclastogenic *OPG* and anti-inflammatory *IL10* expression. To determine if decreased B cell *ATM* expression in the absence of RA disease could account for the skewed BCR V κ -J κ segment usage in RA group I, we examined B cells from ataxia-telangiectasia (A-T) patients lacking *ATM*. BCRs from A-T patients showed the same skewed V κ -J κ gene segment usage seen in group I RA patients. We utilized the NSG “humanized” mouse model transplanted with non-RA human hematopoietic stem cells to examine developing human bone marrow B cells undergoing V(D)J recombination. *ATM* inhibition led to an increased immature B cell CD69⁺CXCR4⁺ phenotype indicative of retention in the bone marrow and an increased proportion of BCRs expressing λ light chains with evidence of κ chain deletion.

Conclusion: We have identified a novel way of subgrouping RA patients. Group I RA patients lack broad BCR V κ -J κ gene segment utilization, which can be explained by relatively insufficient B cell *ATM* expression. Lack of sufficient functional B cell *ATM* can also explain the increased erosive disease prevalence in group I compared to group II RA patients. Thus, subgrouping RA patients in the manner presented here has important implications for diagnosis, prognosis and treatment.

Disclosure: K. Mensah, None; J. N. Schickel, None; I. Isnardi, None; E. Meffre, None.

Rheumatoid Arthritis (RA)-Associated Autoantibodies Are Present in the Periodontal Exudate of Patients with and without RA

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Seropositivity for anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) is a hallmark of RA and can be present years before clinical onset has become apparent. Environmental factors, including smoking and chronic inflamed mucosal tissues of the lungs, gastro-intestinal tract or oral cavity (i.e. the periodontium), are suggested to contribute to initiation of these autoantibodies. While it is known that the inflamed periodontium contains citrullinated proteins and peptides, only Harvey et al. (2013) showed that IgG ACPA is indeed present in the periodontal exudate (n=9). As the IgA isotype is specific for mucosal immunity, we assessed in patients with and without RA whether IgA RF and IgA ACPA are present gingivocrevicular fluid (GCF), the periodontal inflammatory exudate.

Methods: RA patients fulfilling the ACR/EULAR 2010 classification criteria were recruited at the Rheumatology department of the Dr. Sardjito General Hospital, Yogyakarta, Indonesia. Patients without RA (non-RA) were recruited from the Oral Surgery department of the same hospital. Patients with diabetes or cardiovascular disease were excluded. Periodontitis was defined as periodontal inflamed surface area (PISA)>130 mm² (Leira et al. 2017). RF and ACPA were determined by ELISA in serum (IgM RF, IgA RF, IgG ACPA, IgA ACPA) and GCF (IgA RF, IgA ACPA). In addition, total IgA and IgG were determined in GCF. IgA ACPA seropositivity and IgA RF- and IgA ACPA positivity in GCF were defined as >mean+2SD of healthy controls (non-RA patients, never smokers, no periodontitis, n=88).

Results: In non-RA patients (n=151), PISA was correlated with total IgG and IgA in GCF (p<0.0001). IgA RF and IgA ACPA were present in GCF and correlated with total IgA in GCF (p<0.05 and p<0.01 respectively). In contrast to RA patients (n=72), IgA RF and IgA ACPA in GCF of non-RA patients were not correlated with IgA RF or IgA ACPA in serum. In non-RA patients, IgA ACPA positivity in GCF was more frequent in ever smokers (18%) than in never smokers (9.8%), the same held for presence or absence of periodontitis (18 and 9.3% IgA ACPA positivity in GCF respectively). Moreover, in non-RA patients PISA was correlated with IgA ACPA in serum (p<0.01) and GCF (p=0.05).

Conclusion: In non-RA patients, RA-associated autoantibodies are present in GCF, and are presumably the result of local formation due to periodontitis. Local production of autoantibodies may contribute to onset of RA.

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Leira et al. Acta Odontol Scand 2017 Nov 11:1-4

Disclosure: P. S. Rahajoe, None; M. J. de Smit, None; E. Eelsing, None; N. Kertia, None; A. Vissink, None; J. Westra, None.

Abstract Number: 80

Prediction of Future Development of Rheumatoid Arthritis in Patients with Seropositive Arthralgia

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Arthralgia in patients who are seropositive for rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) is a precursor to rheumatoid arthritis (RA) in some but not all patients. The factors which influence progression and outcomes in these patients remain to be fully defined. The aim of this study was to evaluate outcome and prognostic factors in a consecutive cohort of patients with seropositive arthralgia undergoing arthroscopy.

Methods: We performed a prospective study of consecutive patients seropositive for RF and/or ACPA, with arthralgia, presenting to our outpatient clinic. Demographic and clinical measures were collected and synovial biopsy was performed by needle arthroscopy to score macroscopic and microscopic changes. The degree of synovitis and vascularity were recorded on a 0–100-mm visual analog scale, and chondroscopy on a semi-quantitative scale from 0–3. Patients were then followed up at 3 monthly intervals and the time of diagnosis recorded. Mann-Whitney U test was used to compare groups. Spearman's Rank Correlation Coefficient was used to assess for associations between biometrics and demographic and clinical markers. GraphPad Prism Version 7 and IBM SPSS Statistics Version 24 were used for data analysis.

Results: 33 patients were recruited. Mean (SD) age was 54 (12) years. 22 (67%) were female. 27 (82%) were positive for RF and 30 (91%) for ACPA with 24 (73%) dual positive. Mean (SD) follow-up was 29 (10) months. Baseline characteristics are shown in Table 1. Final diagnosis was RA in 24 (73%), psoriatic arthritis in 2 (6%), connective tissue disease in 1 (3%), calcium pyrophosphate arthritis in 1 (3%), and remained seropositive arthralgia in 5 (15%). Baseline CRP was significantly higher in patients who developed rheumatoid arthritis than those who remained seropositive arthralgia, mean (SD) 9.63 (16.63) vs 1.40 (0.55) mg/dL ($p=0.005$). CRP was elevated in 9/24 RA patients (range 1–64 mg/dL), and 0/5 who remained seropositive arthralgia (range 1–2 mg/dL). Macroscopic synovitis and vascularity were both significantly higher in those who developed RA than in those who remained arthralgia only, mean (SD) 60 (25) vs 28 (13) mm ($p=0.009$) and mean (SD) 56 (26) vs 26 (13) mm ($p=0.012$) respectively. Baseline DAS28-CRP, tender joint count, swollen joint count, and patient global assessment were not different between the groups. Baseline synovial cell immunophenotyping did not predict final diagnosis.

Conclusion: The majority of seropositive arthralgia patients developed RA. Elevated baseline CRP and macroscopic synovitis and vascularity scores at arthroscopy predict the future development of RA.

Table 1. Baseline Characteristics of 33 Patients with Seropositive Arthralgia

Age, years	54 (12)
Sex, female, n (%)	22 (67%)
Tender Joint Count	3 (6)
Swollen Joint Count	0 (0)
Patient Global Assessment (mm)	47 (28)
DAS28-CRP	3.42 (1.34)
Arthroscopic synovitis (mm)	56 (26)
Arthroscopic vascularity (mm)	53 (26)

Data expressed as mean (SD) unless otherwise specified.

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Abstract Number: 81

Additive Effects of Functional Rheumatoid Arthritis (RA) LBH Risk Alleles on LBH Gene Transcription

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: *LBH* (Limb-bud and heart development gene) is dysregulated in RA, with a SNP associated with increased RA risk located in an upstream enhancer. This mutation decreases *LBH* gene transcription in FLS and *Lbh* deficiency in the passive K/BxN arthritis model increases disease severity. To understand the functional significance of *LBH* SNPs, we investigated the individual and combined effects of additional SNPs on *LBH* regulation.

Methods: FLS cultures were established from RA synovium obtained at the time of arthroplasty. Search of UCSC Genome Browser, NCBI dbSNP database and NIH GWAS Catalog identified two new *LBH*-associated SNPs, SNP1 and SNP2, that are modestly protective in RA. The two SNP1 (rs7579944) and SNP2 (rs1355208) are 300 bp apart in an intergenic region 9371 and 9071 bp upstream of the *LBH* TSS, respectively. Genomic DNA containing individual or combined RA Risk (Ref1 and -2) or RA Protective SNP1 and -2 alleles of *LBH* were cloned into minimal promoter pGL4.23-luciferase constructs. For luciferase assays, the control plasmids and single or combined Refs and SNPs plasmids (Ref1, SNP1, Ref2, SNP2, Ref1/Ref2 and SNP1/SNP2) were co-transfected into cultured RA FLS by nucleofection. Firefly luciferase activity was normalized to *Renilla*. Samples with minimal luciferase expression due to inadequate transfection efficiency were eliminated from the analysis.

Results: Transfection of FLS with 5 of the 6 constructs increased transcriptional activity of the minimal promoter by 2.2-2.6 fold, with no significant differences between Ref1, SNP1, Ref2, SNP2, or SNP1/SNP2 from each other. Surprisingly, the increase in luciferase activity was significantly less with risk-associated Ref1/Ref2 combination compared with the protective SNP1/SNP2 construct (1.8 ± 0.2 fold compared with 2.3 ± 0.2 fold of the minimal promoter, $p=0.0096$, $n=7$). This pattern remained the same after stimulation with TGF β 1 (1 ng/ml, 18 hr) or IL-1 β (2 ng/ml, 18 hr), even though these cytokines decrease the *LBH* gene expression in RA FLS. The NIH LDlink analysis tool showed that SNP1 and SNP2 have high linkage disequilibrium ($D>0.99$), with 44% of the population having the combined Refs and 39.7% having the combined RA protective SNPs.

Conclusion: The combination of two RA Risk *LBH*-associated SNPs significantly decreased transcriptional activity compared to the individual SNPs or combination of the two corresponding protective alleles. These results correlate with the protective effect of *LBH* in arthritis and suggest that the mechanism of RA protection with the combination SNP1/SNP2 is higher *LBH* transcription compared with the risk alleles. Therefore the genetic risk conferred by individual *LBH* alleles is additive and underscores the importance of their combinatorial contributions to RA susceptibility.

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

Abstract Number: 82

Analysis of Intestinal Microbiome Profile of Patients with Established Rheumatoid Arthritis and Healthy Controls

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: To describe the fecal microbiome profile in RA patients and analyze the mechanisms involved in the pathogenesis of RA

Methods: Design: Controlled, observational, cross-sectional study of established RA cohort.

Patients: Forty consecutive RA patients (ACR/EULAR 2010 criteria) >16 years, selected from a prospective inception cohort (diagnosis of RA between 2007-2011) and 40 sex-age matched healthy controls. Subjects with antibiotics, probiotics, initiation of a new therapy in the previous 3 months or other autoimmune diseases were excluded. Protocol: Cases and

controls were evaluated by a rheumatologist. Clinical data of disease activity were collected during the follow-up and analytical values were determined. Fecal samples were frozen within 24 hours of collection. All participants signed informed consent.

Main outcome: *Fecal samples exam.* Microbial DNA was extracted from fecal samples using QIAamp DNA stool Mini kit. The concentration and quality of DNA was determined by Nanodrop. **Secondary outcome:** Average DAS28-ESR during the follow-up, HAQ, RF, ACPA and erosive status. **Other variables:** Demographic, clinical-analytical and therapies (DMARDs).

Statistical analysis: Analysis of microbiota profile: UniFracPCoA(Principal Coordinate Analysis) was performed with the abundance data of operational taxonomic units (OTU) by means of the variance-covariance matrix implemented in Quantitative Insights Into Microbial Ecology(QIIME). The relative abundance of each OTU (taxa) was compared using a Wilcoxon test. The variations of abundance and diversity were compared by statistical analysis of an ANOSIM pathway with PAST and the differences were with $P < 0.05$. The calculation of α and β -diversity was carried out using QIIME.

Results: Most of subjects were women (75%) with a mean age of 59 years. In RA patients, the average DAS28 was 3.6 (table 1). β -diversity data showed that patients tend to differ from healthy subjects according to their microbiota ($p = 0.07$). Patients with RA exhibited decreased gut microbiome diversity compared with controls, although was not statistically significant. Regarding in species richness, the analysis suggested an increase of the *Collinsella aerofaciens* species and enterococcus genera in patients compared with controls. Likewise, an increase of arginine deaminase activity was observed, which belonged, in approximately 90%, to the RA genes of the genus *Collinsella*. Also, we observed a decrease in other bacterial lineages. On the other hand, RA patients showed an altered metabolic capacity for the transport of zinc and copper in comparison with controls.

Conclusion: These observations suggest a dysbiosis in RA patients, resulting from the abundance of certain bacterial (i.e. *Collinsella*) and decrease of other bacterial lineages. These alterations could influence in a significant way, by enzymatic or metabolic mechanisms, in the perpetuation of the autoimmunity of the disease.

Table 1.

VARIABLE	RA n=40	Control n=40	P - VALUE
Clinical characteristic			
Age (years), mean (SD)	58,5 (9,4)	58,5 (9,4)	0,998
Sex (female), n (%)	30 (75,0)	30 (75,0)	1,000
Smoke			0,018
Non-smoker, n (%)	15 (37,5)	24 (60,0)	
Ex-smoker, n (%)	16 (40,0)	5 (12,5)	
Smoker, n (%)	9 (22,5)	11 (27,5)	
Body mass index, mean (SD)	30,3 (5,6)	28,0 (4,9)	0,057
Obesity, n (%)	21 (52,2)	12 (30,0)	0,041
Laboratory characteristic			
Rheumatoid factor, n (%)	32 (80,0)	2 (5,0)	<0,001
Anti-cyclic citrullinated peptide, n (%)	28 (70,0)	0 (0,0)	<0,001
CRP, mg/l	5,02 \pm 4,5	5,17 \pm 7,03	0,911
ESR mm/h	17,12 \pm 11,8	12,17 \pm 9,4	0,041
Inflammatory activity			
Average DAS28 value, mean (SD)	3,6 (0,5)	-	-
DAS28 at index-date, mean (SD)	3,0 (1,1)	-	-
Average SDAI value, mean (SD)	13,3 (2,8)	-	-
SDAI at index-date, mean (SD)	9,7 (5,6)	-	-
Average CDAI value, mean (SD)	12,8 (2,7)	-	-
CDAI at index-date, mean (SD)	91 (6,1)	-	-
Average HAQ value, mean (SD)	0,89 (0,6)	-	-
HAQ at index-date, mean (SD)	1,06 (0,5)	-	-
Therapeutic regimen			
Glucocorticoids (%)	7,5	-	-
Sulfasalazine (%)	15	-	-
Leflunomide (%)	12,5	-	-
Methotrexate (%)	72,5	-	-
Hydroxychloroquine (%)	5	-	-
biologic disease-modifying antirheumatic drugs (%)	37,5	-	-

Disclosure: N. Mena-Vazquez, None; I. Moreno-Indias, None; P. Ruiz-Limon, None; M. Rojas-Gimenez, None; C. Fuego, None; S. Manrique-Arija, None; I. Ureña-Garnica, None; F. G. Jimenez-Nuñez, None; F. J. Tinahones, None; A. Fernandez-Nebro, None.

The Risk of Developing Rheumatoid Arthritis Based on HLA-DQ Genotypes

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: The strongest genetic risk for rheumatoid arthritis (RA) is contributed from the HLA region. RA-risk associated *HLA-DRB1* alleles including *04:01/4/5/8, *01:01, *10:01, and *14:02 code for the ‘Shared Epitope’ (SE) motif of the DRβ1 third hypervariable region. In an individual’s genotype, different combinations of SE and non-SE alleles contribute differently to RA-risk, as has been delineated in a table of Odds Ratios (OR) in a prior publication (1). Other studies have pointed to the importance in RA of specific *DQA1-DQB1* allele combinations in linkage disequilibrium (LD) with SE alleles that have been referred to as DQ5.1, DQ7.3, and DQ8 (2, 3). Interestingly, these particular DQ molecules, but not other DQs or DRs, bind certain peptides involved in autoantibody-positive RA (3). In the current study we investigated RA risk according to the DQ genotype and evaluated combinations of DQ molecules for hierarchy in RA risk.

Methods: 314 RA patients meeting 1988 ACR criteria and 316 controls from Washington State (USA) and the surrounding area were genotyped for *DRB1-DQA1-DQB1* haplotypes. *DQA1* and *DQB1* combinations were classified into 10 groups based on functional relevance and most frequent LD with *DRB1*: DQ5.1 (LD: *DRB1**01), DQ5.2/3 (LD: *DRB1**14 and *16), DQ6.1/2 (LD: *DRB1**15), DQ6.3/4/5/9 (LD: *DRB1**13, RA protective), DQ2 (LD: *DRB1**03 and *07, both RA protective), DQ7.3 (LD: *DRB1**04), DQ7.5/6 (LD: *DRB1**11 and *12), DQ8 (LD: *DRB1**04), DQ9 (LD: *DRB1**07 and *09), and DQ4 (LD: *DRB1**08). ORs for RA-risk were calculated for 48 of 55 possible combinations accounting for 97% of subjects.

Results: The genotypic OR [and 95% confidence intervals] for developing RA based on DQ ranged from 24.9 [4.63–259.0] to 0.16 [0.04–0.64]. The risk was generally significant when an individual carried simultaneously 2 of the 3 DQs in linkage with the SE (DQ5.1, DQ7.3 and DQ8), and was alleviated when the second DQ was no longer of those 3. DQ2 provided significant protection when combined with itself, DQ6.3/4/5/9, or DQ7.5/6, which are in linkage with *DRB1* alleles previously associated with protection against RA.

Conclusion: The risk of developing RA is influenced by both *HLA-DQ* alleles in the genotype. ORs varied according to particular combinations of DQ molecules. These observations considered along with recognition that HLA molecules present peptides derived from other (self) HLA molecules point to likely functional significance of *HLA-DQ* molecules in RA risk.

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Abstract Number: 84

ACPA-Positive Risk-RA Subject without Subclinical Arthritis Are in High Risk for Later Arthritis Onset, Especially Carriers of HLA-SE Risk-Gene

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Anti-citrullinated protein antibodies (ACPA) are predictive markers with pathological effects in rheumatoid arthritis (RA) development. Previous studies of ACPA-positive patients with musculo skeletal complaints (mainly arthralgia), but no arthritis, have shown increased risk for arthritis onset. However, these studies used clinical definition of arthritis, but did not exclude those subjects with ultrasound-detected subclinical arthritis. We aimed therefore to investigate risk factors for developing arthritis in ACPA-positive subjects with musculoskeletal complaints in the absence of any clinical and ultrasound signs of arthritis.

Methods: Patients presenting with musculoskeletal complaints and positive Anti-citrullinated protein antibody (ACPA) test in primary care were referred to the Rheumatology Clinic at Karolinska Hospital. Patients lacking arthritis by clinical and ultrasound examination (defined as synovial hypertrophy with Doppler activity) were recruited into the Risk-RA research program. A total of 66 subjects included between years 2015 up to December 2016 were analysed in this study. Blood samples from inclusion have been analysed for thirteen ACPA reactivities (citrullinated peptides from fillagrin, fibrinogen, alfa-enolase, vimentin, histones) using microarray based on ImmunoCap ISAC. DNA samples have been analysed for HLA-SE risk gene using DRlow-resolution kit (2-digit).

Results: A high proportion of the Risk-RA subjects, 41% (27 out of 66), developed clinical and/or ultrasound-detected arthritis during a median follow up of 8 months while 59% (39 out of 66) subjects didn't developed arthritis during a median follow up of 25 months.

No differences in characteristics at inclusion were observed between subjects developing and those not developing clinical and/or ultrasound-detected arthritis (table 1). Interestingly, subjects developing arthritis had higher concentration of anti-CCP and number of tender joints as compared to those not developing arthritis, but the difference did not reach statistically significance.

In contrast, subjects developing arthritis had a higher number of ACPA-reactivities (mean 6) than those not developing arthritis (mean 3, t test, $p < 0.05$). A significant difference in occurrence of a HLA-SE risk-gene was detected with subjects developing arthritis being more often carrier of such risk-gene (86%) as compared to those not developing arthritis (56%, chi-square test, $p < 0.05$). Cox proportional hazards regression accounting for the time of follow-up showed a HR for arthritis development of 1.1 for every increase in number of ACPA reactivities (95% CI 0.99-1.2, $p = 0.07$) and 4.9 (95% CI 1.5-16, $p = 0.01$) for HLA-SE carriers.

Conclusion: Subjects with ACPA-positive musculoskeletal complaints lacking any clinical and ultrasound signs of arthritis are at high risk to develop arthritis, especially among carriers of HLA-SE risk-gene. Table 1.

	Subjects (n=27) developing arthritis	not developing arthritis
Follow up time, months, median (1th -3th IQR; interval)	8 (4.9-19; 1.4-27)	25 (20-33; 11-43)
Females, n (%)	23 (85%)	33 (85%)
Age, mean (SD)	51 (14)	48 (16)
Current smokers, n (%)	3 (11%)	5 (13%)
Ever smokers, n (%)	18 (67%)	26 (68%)
ESR mm/h, mean (SD)	12 (7)	12 (12)
Pain VAS, mean (SD)	30 (24)	32 (27)
Tender joint count, 68-joint examination, mean (SD)	1.3 (3.1)	0.4 (1.4)
Anti-CCP concentration, times cut-off, median (1th -3th IQR)	11 (3.7-100)	70 (12-100)
Rheumatoid factor, IU/ml, median (1th -3th IQR)	19 (19-61)	19 (19-38)

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Abstract Number: 85

Antibodies to Citrullinated Protein Antigens (ACPAs) Induce Adipose Tissue Dysfunction Contributing to the Cardiovascular Disease Risk in Rheumatoid Arthritis. Modulation By Biological Dmards

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: 1) To test the relationship among ACPAs and levels of adipocytokines and atherosclerosis in RA patients. 2) To analyze the effects of ACPAs on the AT function: adipocyte differentiation, macrophage polarization and lipid accumulation, and 3) To evaluate the effects tocilizumab (TCZ) or infliximab (IFX) on the metabolic alterations induced by ACPAs on AT.

Methods: Human study: 75 RA patients and 40 healthy donors were included. Serum levels of adipocytokines were evaluated. Carotid intima media thickness (CMIT) was evaluated as atherosclerosis marker. **In vitro studies:** IgG-ACPAs were isolated from serum of RA patients. 3T3-L1 cells were treated with IgG-NHS or IgG-ACPAs alone or in combination with IFX or TCZ during several stages of the adipocyte differentiation. M0 macrophages were treated with IgG-NHS or IgG-ACPAs alone or in combination with IFX or TCZ. **Ex vivo experiments:** Subcutaneous AT samples were obtained from 8 obese patients through bariatric surgery. AT samples were treated *ex vivo* with IgG-NHS or IgG-ACPAs alone or in combination with bDMARDs. Protein and gene expression of molecules involved in adipogenesis, inflammation, insulin signaling and lipid accumulation was analyzed.

Results: RA patients had elevated levels of leptin/adiponectin ratio, visfatin and inflammatory markers in serum. These alterations were associated with the ACPAs levels. Disease activity and CMIT were associated with ACPAs, leptin/adiponectin ratio, levels of visfatin and inflammatory markers. IgG-ACPAs induced M1 polarization state and impaired insulin signaling in M0 macrophages. 3T3-L1 fibroblast treated with IgG-ACPAs at day 0 showed an impaired adipocyte differentiation. Genes involved in insulin signaling were reduced. Treatment with IFX and TCZ restore adipocyte differentiation and improved insulin signaling. In human AT, the treatment with IgG-ACPAs increased the inflammation, accompanied by a downregulation of genes involved in lipid accumulation, adipogenesis and insulin signaling. bDMARDs reverted inflammatory and metabolic alterations on human AT explants.

Conclusion: 1) ACPAs are related to high levels of adipocytokines in RA patients, suggesting its action on AT dysfunction, contributing to the increased CVD risk. 2) In vitro, ACPAs impairs AT function, acting in both, macrophages and adipocytes, inducing inflammation, impairing adipogenesis and lipid accumulation, and favoring an IR state. 3) TCZ and IFX might reverse the metabolic alterations induced in AT by ACPAs. 4) Targeting these autoantibodies would be an excellent therapeutic strategy to restore AT function and reduce the CVD related to RA. Funded by ISCIII(PI17/01316, CP15/00158 and RIER RD16/0012/0015) co-funded with FEDER.

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Abstract Number: 86

Age Dependent Effects of Cholesterol and Smoking on the Risk of Rheumatoid Arthritis in Women – Results from a Nested Case Control Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Table 1. Demographics and smoking history in women with incident RA, by age at inclusion in the PMP

	All	Lowest age tertile (29-48 years)	Middle age tertile (49-54 years)	Oldest age tertile (55-57 years)
n	139	48	47	44
Age at inclusion (years); mean (SD)	49.3 (7.5)	40.8 (6.0)	51.7 (3.2)	56.1 (0.3)
Time from inclusion to RA diagnosis (years); Median (IQR)	11 (7-17)	12 (8-19)	12 (7-15)	9 (6-13)
Current smoker	46 %	54 %	51 %	33 %

Table 2. Predictors of RA, by age at screening in pre-RA cases and matched controls. Bivariate conditional logistic regression

Age tertile	29-48 years	49-54 years	55-57 years
	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Total cholesterol (per SD)	1.56 (1.00-2.42)	1.95 (1.36-3.02)	1.30 (0.90-2.06)
Body mass index (per SD)	1.00 (0.76-1.30)	0.91 (0.68-1.36)	1.07 (0.68-1.68)
Current smoking at screening	2.29 (1.07-4.98)	2.11 (0.94-4.89)	0.98 (0.41-2.32)

Standard deviation (SD): body mass index 3.1 kg/m²; Total cholesterol 1.1 mmol/l

Session Type: ACR Poster Session A

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

Background/Purpose: Smoking is an established risk factor for rheumatoid arthritis (RA). A positive association between body mass index (BMI) and the risk of RA in women has been reported from several studies, but not from surveys of Scandinavian populations. Finally, a high serum cholesterol has been shown to predict RA in women, but not in men, possibly due to hormone related exposures. The objective of this study was to investigate the impact of described RA predictors in women in different age groups.

Methods: A total of 10902 women from a defined catchment area were included in a Preventive Medicine Program (PMP). Height and weight were measured as part of the health survey, and fasting blood samples were obtained. Serum total cholesterol (TC) was assessed by an enzymatic routine method. From this population, we identified individuals who developed RA after inclusion by linking the PMP register to the local community based RA register and to local and national patient administrative databases. In a structured review of the medical records, patients were classified according to the 1987 ACR criteria for RA. Four controls for each validated case, matched for sex, year of birth and year of screening, who were alive and free of RA when the index person was diagnosed with RA, were selected from the PMP register. The impact of TC, BMI and smoking on the risk of RA was examined in conditional logistic regression models, stratified by age (tertile).

Results: 139 women were diagnosed with RA and fulfilled the ACR criteria after inclusion in the PMP. These pre-RA cases were compared to 556 matched controls. There was a significant positive association between TC and subsequent development of RA in the two younger age groups, but not in the oldest group (Table). Current smoking was associated with a significantly increased risk of RA in the youngest age group (women aged 29-48 years), whereas there was no association among those aged above 55. BMI did not predict RA in either of the subgroups.

Conclusion: High cholesterol levels and smoking predict RA in an age dependent manner. The greater impact of these factors on the future risk of RA in younger women suggests that hormone related mechanisms contribute to the underlying pathways.

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Rheumatoid Arthritis Patients with Circulating Extracellular Vesicles Positive for IgM Rheumatoid Factor Have Higher Disease Activity

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune inflammatory disease that mainly affects synovial joints. Most research on RA has focused on cytokines as main effectors in disease progression however, cell-cell communication involves a much broader scope of responses. Cells can release additionally extracellular vesicles (EVs) and an important role of these EVs has been postulated as important communicators between resident and inflammatory cells [1]. B-cells also release EVs that contain the B-cell receptor on their surface which is an immunoglobulin that binds and presents antigens to T-cells [2]. The presence of IgM-RF in seropositive RA patients clearly points to a role of B-cells and plasma cells in the pathogenesis of this disease. In this study we investigate the presence of RF-IgM on circulating EVs and the relation to the severity of RA.

Methods: EVs were isolated from platelet-free plasma of 41 RA patients and 24 healthy controls (HC) by size exclusion chromatography. We quantified the particle and protein concentration, using NanoSight particle tracking analysis and micro-BCA. Tender (TJC) and swollen joints (SJC) were assessed by physicians and the global patient visual analogue score (VAS) was determined by the patient. IgM-RF, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were determined by standard laboratory blood tests in our hospital. Disease activity score (DAS28) was calculated.

Results: RA and HC pEVs were not different in particle size, protein content and particle concentration (115nm, 49fg, 3.5×10^{10} and 108nm, 45fg, 3.8×10^{10} , respectively). Between seronegative (RA-) and seropositive (RA+) patients, particle size, protein content per particle and amount of particles of pEVs were not statistically different (116nm, 39fg, 5.4×10^{10} and 114nm, 58fg, 1.8×10^{10} , respectively). In plasma of 28 out of 41 RA patients IgM-RF was detectable, and in 13 out of these 28 RA+ IgM-RF was also detected on their isolated pEVs (RF⁺pEVs). In RA- patients we did not find any RF present on pEVs. When comparing disease parameters we found no differences between RA+ and RA- patients, except for increased ESR levels in RA+ patients. However, RA+ patients with RF⁺pEVs showed significant higher levels of CRP and ESR and also VAS and DAS28 were significant increased compared to RA+ patients without RF⁺pEVs.

Conclusion: This study shows for the first time the presence of IgM-RF on pEVs in a subset of RA+ patients with a more severe disease. The presence of RF⁺pEVs may point to a higher B-cell involvement in the disease process in these patients.

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Lymphocyte DNA Methylation As a Mediator of Genetic Risk in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Genome-wide association studies (GWAS) have to date identified over 100 genomic loci at which single nucleotide polymorphisms (SNPs) confer an increased risk of developing rheumatoid arthritis (RA). These loci are enriched for lymphocyte-specific enhancer elements, consistent with a regulatory function of many causal variant(s). Epigenetic modifications have also been strongly implicated in RA pathogenesis, potentially impacting cell phenotype through altered gene expression. Here, we investigate the role of DNA methylation as a mediator of RA genetic risk.

Methods: CD4⁺ T- and B-lymphocytes were isolated by positive selection from fresh peripheral blood of drug-naïve patients attending an early arthritis clinic. Paired CD4⁺ T-lymphocyte-specific DNA and RNA were extracted from 43 RA and 60 disease control patients, respectively, and equivalent material from B-lymphocytes of 46 RA and 73 controls. Comparator groups were matched for age, sex, and acute phase response. Genotyping was performed using the Illumina Infinium Human CoreExome-24 array, and DNA methylation at >850,000 CpG sites quantified with the Illumina MethylationEPIC array. Gene expression profiling was measured using the Illumina Human HT-12 v4 BeadChip. Having first mapped genome-wide methylation quantitative trait loci (mQTLs) in *cis* (<1Mb), we focussed our analysis on known RA risk loci, and integrated paired normalised gene expression measurements for transcripts within 500kb of index CpGs. Finally, we performed an analysis of mQTLs acting in *trans*, seeking interactions between genotype and disease diagnosis to highlight RA-specific effects.

Results: CD4⁺ T lymphocyte *cis*-mQTLs colocalised with 30 independent ($r^2 < 0.8$) RA-associated SNPs, whilst in B lymphocytes such mQTL effects were present at 31 RA SNPs. A high proportion of these variants (>80%) appeared to function as *cis*-mQTLs in both cell types. CpG sites subject to *cis* effects at risk loci were depleted in regions associated with cell type-specific repressed chromatin marks, with enrichment at enhancer regions and those flanking transcription start sites suggesting active roles in transcriptional regulation. Linear regression identified putative regulatory effects of these CpG sites on gene expression, and causal inference testing highlighted genes for which risk SNPs most likely modulate gene expression via CpG methylation. Such effects, robust to false discovery rate, were particularly prevalent in CD4⁺ T lymphocytes, implicating *ANKRD55*, *ORMDL3*, and *FCRL3* amongst others as causal genes in this cell type. Similar effects were less robust in B-lymphocytes, albeit potentially implicating genes including *CCR6*. Our analysis of mQTLs acting in *trans* identified inter-chromosomal SNP-CpG associations, also revealing instances of differential effect sizes in RA patients and controls.

Conclusion: Here we demonstrate the utility of DNA methylation profiling as a tool for the prioritization of candidate genes following GWAS studies in RA, and highlight an important mechanism through which genetic variants may contribute to altered lymphocyte phenotype. The functional roles of highlighted genes in CD4⁺ T cells during RA pathogenesis await clarification.

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Abstract Number: 89

Anti-Nuclear Antibodies (ANA) and Air Pollution: Ultrafine Particles and Ozone

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Previous studies have suggested links between air pollution (particularly PM_{2.5}) and serum antibodies related to rheumatic diseases. No one has yet examined anti-nuclear antibody (ANA) positivity and ultrafine particles (UFP), or ozone (O₃), both of which can trigger systemic immune system activation.

Methods: Our analyses were based within the CARTaGENE cohort, 20,000 general population subjects drawn from the province of Quebec, Canada. We determined baseline ANA positivity on a random sample of these. Exposure to air pollutants were assigned by linking subjects' residential postal codes with estimated levels (determined by hybrid approaches including satellite imagery and modelling). We performed multivariable logistic regression models for the outcome of positive ANA, assessing for independent effects of UFP (available for Montreal only) and O₃ in separate models, adjusting for age, sex, smoking, and self-reported ancestry. As a sensitivity analysis, a final multipollutant model included both variables together with ambient PM_{2.5} variable (estimated using hybrid approaches including satellite imagery).

Results: ANA positivity at a titre of at least 1: 160 occurred in 713 (20%) of 3,578 randomly selected patients tested. The ANA positive subjects were more likely than ANA negative subjects to be female (63%, versus 49%) while average age (55.4 versus 54.0) and percent never-smokers (37% versus 40%) were similar. There was a trend for higher average UFP: exposure for ANA positive subjects (24606.28 particles / cm³, standard deviation, SD 4978.62) versus ANA negative (24328.35, SD 5075.62), while average ozone levels were very similar (22.5 versus 22.6 µg/m³). The multivariable model for UFP showed a trend to higher levels in the ANA positive group (1.008, 0.982, 1.034) while in the multivariable model for O₃ the OR was very close to the null value (0.996, 95% CI 0.965, 1.029). The multipollutant model results were very similar. In all models, risk factors for ANA positivity included older age and female sex, with trends for lower ANA positivity in French Canadians.

Conclusion: We saw a non-significant trend towards higher UFP levels in ANA positive versus negative subjects, while O₃ levels seemed very similar in the two groups. Expected trends for more ANA positivity with older age and female sex was seen. Further study of UFP levels with a larger sample size in in progress.

Pollution variables and ANA positivity: Odds ratios with 95% confidence intervals

Single pollutant model, Ozone, N=3346	Adjusted Odds Ratio	95%	CI
O ₃ (µg/m ³)	0.996	0.965	1.029
Age (continuous)	1.024	1.013	1.036
Female	1.778	1.492	2.118
Current (versus never or past) smoker	1.038	0.833	1.294
French Canadian Caucasian	0.843	0.703	1.012
Montreal	0.980	0.793	1.211
Ultrafine particles, N=1371			
UFP (1000 particles / cm ³)	1.008	0.982	1.034
Age (continuous)	1.028	1.011	1.045
Female	2.054	1.558	2.708
Current (versus never or past) smoker	1.119	0.802	1.561
French Canadian Caucasian	0.749	0.571	0.982
Montreal	NA	NA	NA
Multipollutant model N=1371			
Regional ambient PM _{2.5} (µg/m ³)	0.837	0.673	1.039
O ₃ (µg/m ³)	0.956	0.895	1.021
UFP (1000 particles / cm ³)	1.006	0.981	1.032
Age (continuous)	1.028	1.011	1.045
Female	2.080	1.576	2.745
Current (versus never or past) smoker	1.117	0.800	1.559
French Canadian Caucasian	0.735	0.559	0.965

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Abstract Number: 90

Deoxyribonuclease 1-like-3 Digests Self-DNA from Dead Cells and Prevents Autoimmunity

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Deoxyribonuclease 1-like-3 (DNase1L3) belongs to Deoxyribonuclease 1 (DNase1) family. This nuclease originally identified as one of apoptosis- and necrosis-related endonucleases that fragmentates intranucleosomal DNA. Unlike DNase1, DNase1L3 is able to digest protein-associated DNA in addition to naked DNA. Hence, DNase1L3 can degrade nucleosomal DNA more efficiently than DNase1, which is resistant to DNase1 because of the surrounding DNA-binding proteins such as histones. Mutations of *DNase1L3* gene that cause loss of function have been reported in murine models of systemic lupus erythematosus (SLE) and familial SLE with an autosomal recessive pattern of inheritance. A recent report showed that DNase1L3-deficient mice also developed features of SLE. In addition, several genetic variants of *DNase1L3* are associated with disease susceptibility to systemic sclerosis and hypocomplementemic urticarial vasculitis syndrome. The role of DNase1L3 in human immune systems is largely unknown. We aimed to clarify the expression and function of DNase1L3 in human immune cells.

Methods: We analyzed expression levels of DNase1L3 mRNA in each subset of human peripheral white blood cells, monocyte-derived dendritic cells and monocyte-derived macrophages. The effects of various stimuli on expression levels of DNase1L3 were tested in human immune cells. Nuclease activities of DNase1L3 was examined using various forms of DNA. We also analyzed the effect of secreted DNase1L3 on type 1 interferon production in plasmacytoid dendritic cells (pDCs) mediated by extracellular human DNA. Concentration of DNase1L3 in sera of systemic lupus erythematosus (SLE) patients was also measured.

Results: At steady states, pDCs expressed the highest levels of DNase1L3. In monocyte-derived cells, monocyte-derived dendritic cells (MoDCs) differentiated with interleukin (IL)-4 and granulocyte monocyte colony-stimulating factor (GM-CSF) showed markedly high expression of DNase1L3 mRNA in comparison with MoDCs differentiated with interferon-alpha (IFN α) and GM-CSF. Additionally, IL-4, not IL-13, induced expression of DNase1L3 mRNA in monocytes and monocyte-derived macrophages. As downstream of IL-4 signaling, insulin receptor substrate 2 and extracellular signal-regulated kinase 1/2 were required for the induction of DNase1L3 mRNA expression. DNase1L3 protein was distributed in the cytosol but not in the nucleus and could be secreted into the culture supernatant. The secreted DNase1L3 protein could digest not only naked DNA but also lipid-DNA complexes and protein-DNA complexes, which were only partially digested by DNase1. DNase1L3 could inhibit IFN α secretion from pDCs induced by apoptotic blebs more efficiently than DNase1. We developed enzyme-linked immunosorbent assay of DNase1L3 and identified co-relation between serum DNase1L3 and serum complement 4 in patients with systemic lupus erythematosus.

Conclusion: DNase1L3 is secreted by innate immune cells and may play a critical role in the tissue homeostasis by degrading self-DNA associated with various types of cell death.

Disclosure: S. Inokuchi, None; H. Mitoma, None; S. Kawano, None; M. Ayano, None; Y. Kimoto, None; M. Akahoshi, None; Y. Arinobu, None; K. Akashi, None; T. Horiuchi, None; H. Niro, None.

Abstract Number: 91

Type I IFN Production Is Induced By Non-Haematopoietic Tissue Cells but Not Plasmacytoid Dendritic Cells in Preclinical Autoimmunity and SLE

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: SLE is characterized by persistently high type I IFN activity. Plasmacytoid dendritic cells (pDCs) produce large amounts of IFNs in viral infections in response to nucleic acids and they have therefore been postulated to be the main source of type I IFNs in SLE. However, the precise role of pDCs in autoimmunity still remains unclear. The aim of this study was to investigate the source of type I IFN in patients with established SLE and preclinical autoimmunity.

Methods: Patients with SLE meeting 2012 ACR/SLICC criteria and healthy donors were recruited alongside therapy-naïve individuals presenting with ANA and 1 clinical symptom (At-Risk). IFN activity was evaluated by a score of IFN-responsive genes in the peripheral blood using TaqMan. pDCs were immunophenotyped and studied *in vitro* for production of cytokines and induction of T cell responses using flow cytometry. pDCs were sorted and sequenced using high-sensitive RNA sequencing. IFN expression was visualised in skin biopsies using *in situ* hybridisation. Keratinocytes were isolated from fresh skin biopsies and cultured *in vitro*; IFN production was measured by qPCR and ELISA.

Results: Most of SLE and At-Risk patients had increased IFN activity, which correlated with disease activity. In contrast, circulating pDCs were decreased in both SLE and At-Risk patients and their numbers did not correlate with any clinical features or IFN status. *In vitro* stimulation with TLR9 or TLR7 agonists revealed that pDCs from SLE and At-Risk patients could not produce IFN- α and TNF- α . In addition, they induced significantly less T cell activation and proliferation compared to pDCs from healthy donors. RNA-seq data analysis showed an upregulation of IFN-responsive genes in most of the SLE and At-Risk pDCs as well as pathways related to immune regulation and senescence but not transcripts of any IFN subtypes. Phenotypically, SLE pDCs were characterised by increased telomeric erosion. *In situ* hybridization revealed high IFN expression in the epidermis but not in lymphocyte-infiltrating areas of lesional biopsies from SLE patients. High expression of IFN was also observed in epidermis of At-Risk individuals without any signs of cutaneous inflammation. *In vitro* stimulation of freshly isolated keratinocytes from these also showed a notable increase in IFN production.

Conclusion: In SLE, non-haematopoietic tissue resident cells are a dominant source of IFN and this is present prior to clinically overt disease. Meanwhile, the professional IFN-producing pDCs have lost their immunogenic properties. These findings suggest an important role for tissue resident cells in autoimmunity and may facilitate novel therapeutic interventions.

Disclosure: A. Psarras, None; A. Alase, None; A. Antanaviciute, None; I. Carr, None; M. Wittmann, Novartis, 5, Janssen, 5, AbbVie Inc., 5, Celgene Corporation, 5; G. C. Tsokos, Janssen, 5, Silicon Pharmaceuticals, 9, ABPRO, 9; P. Emery, Bristol-Myers Squibb, 2, 5, Pfizer, Inc., 2, 5, Roche, 2, 5, Novartis, 5, UCB, Inc., 5, Abbott, 2, 5, Merck & Co., 2; E. M. Vital, Roche, 2, 5, GlaxoSmithKline, 2, 5, AstraZeneca, 2, 5.

Abstract Number: 92

Lupus Nephritis Serum Induces Neutrophil Chemotaxis Towards Glomerular Endothelial Cells in Vitro

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Title: Lupus Nephritis Serum Induces Neutrophil Chemotaxis towards Glomerular Endothelial Cells In Vitro :

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease associated with endothelial cell dysfunction (ECD), a key modulator of proliferative renal disease through upregulation of adhesion molecules, release of inflammatory chemokines, and ingress of neutrophils into glomerular tissue. Understanding how ECD processes lead to neutrophil influx across the endothelium is essential to finding therapeutic targets for SLE. Our previous studies showed that lupus serum induces neutrophil adhesion to glomerular endothelial cells. The aim of this study is to uncover the functional ability of SLE serum from patients with active disease to induce chemotaxis of neutrophils towards glomerular endothelial cells.

Methods: SLE patients meeting ACR criteria had serum collected and stored at -80°C during paired visits with lower and higher activity by SLE Disease Activity Index (SLEDAI) score. 15 SLE patients (5 SLE only, 5 SLE with hypertension (HTN), and 5 SLE lupus nephritis (LN) with HTN) and 10 healthy controls (5 with and 5 without HTN) were examined. To assess the functional ability of SLE serum to induce neutrophil chemotaxis, primary Human Renal Glomerular

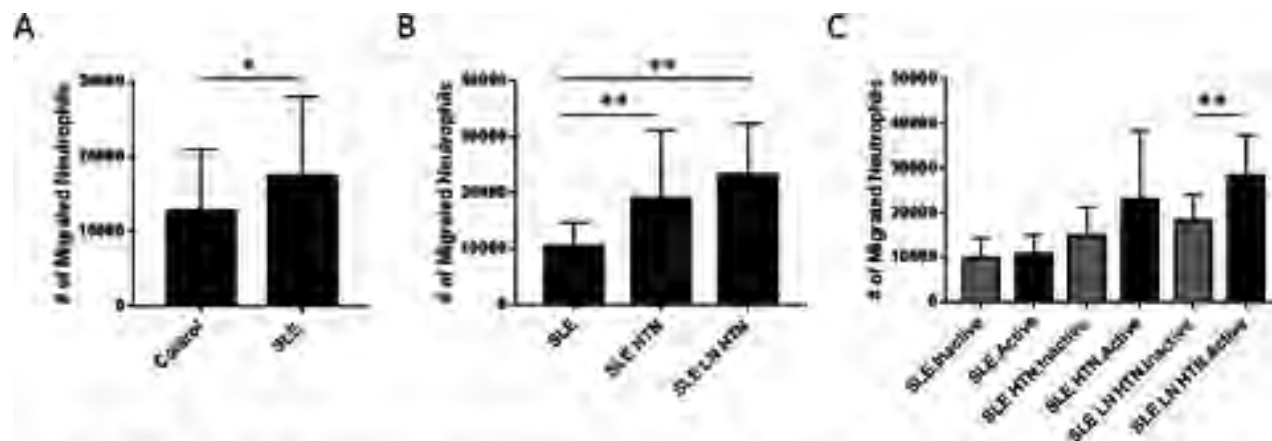


Figure 1. SLE serum increases neutrophil migration, which is enhanced with HTN and LN, along with disease activity in LN HTN cohorts. Number of neutrophils migrated towards CM from HRGECs treated with control (A), SLE (A,B,C), SLE HTN (B,C), or SLE LN HTN (B,C) serum. * $p \leq 0.05$, ** $p \leq 0.01$, as estimated using student's t test.

Endothelial Cells (HRGECs) were cultured in 10% SLE serum (or control serum) for 3 hours and washed, then conditioned media (CM) was collected. Neutrophils collected from healthy donors and stained with CalceinAM were then allowed to migrate through a transwell towards the CM for 1 hour. Migration towards CM was calculated as cells that migrated into the receiving wells based on fluorescence intensity. Groups were compared using student's test.

Results: SLEDAI scores from lower and higher activity paired visits were 0-6 and 4-14 (always ≥ 4 points higher than the inactive visit). HRGECs treated with SLE serum and HTN serum (SLE and control aggregated) induced significantly greater neutrophil chemotaxis than control serum ($p=0.027$) (Figure 1A) and non-HTN serum (not shown, $p=1.8 \times 10^{-7}$), respectively. HRGECs treated with SLE HTN serum and SLE LN HTN serum significantly promoted neutrophil migration compared to SLE serum (Figure 1B, $p=0.0007$, $p=4.173 \times 10^{-9}$) with only SLE LN HTN showing significant differences between inactive and active disease (Figure 1C, $p=0.001$).

Conclusion: This study suggests that circulating factors in SLE serum induce expression of mediators by glomerular endothelial cells that promote neutrophil migration, furthering our understanding of how ECD processes lead to renal inflammation in SLE. Furthermore, hypertension may be an independent and synergistic mediator of ECD induced by circulating factors in SLE.

Disclosure: D. Russell, None; M. Markiewicz, None; X. Zhang, None; J. C. Oates, None.

Abstract Number: 93

Biomarkers Associating Endothelial Function in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

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Session Type: ACR Poster Session A

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

Background/Purpose: The endothelium is a key element in the regulation of vascular homeostasis and its alteration is a precursor of vascular disease. Considering SLE is a systemic autoimmune disease with potentiated extensive vascular lesions, such as skin vessels, renal glomeruli, the cardiovascular system, brain, lung alveoli, and gastrointestinal tract

vessels. We aimed to assess serum levels of endothelial function related biomarkers including Ang1, Ang2, adam13, VEGF, Tie-2 and thrombomodulin in patients with systemic lupus erythematosus (SLE) and elucidate its correlation with clinical features, laboratory parameters, and the overall disease activity.

Methods: Disease activities were evaluated by SLE disease activity index (SLEDAI). Patient characteristics were obtained by retrospective chart review. Laboratory investigations included complete blood count, urine analysis, 24-h total urinary protein, assay of serum creatinine, ANA, anti-DNA, complement component C3, C4. Six biomarkers associated with endothelial function were tested through enzyme-linked immunosorbent assay (ELISA) measurement.

Results: This study comprised 80 children and adolescents with SLE. Serum levels of VEGF and Tie-2 were significantly increased in active SLE patients when compared with inactive SLE patients ($p < 0.05$). Angiopoietin-2 and Tie-2 serum levels were significantly increased in patients with low complement levels ($P < 0.05$). Although serum levels of Angiopoietin-1 and -2 were higher in active SLE patients when compared with inactive SLE patients, the difference did not reach statistical significance. While levels of VEGF, angiopoietin-2, and Tie-2 show no differences between patients with and without renal involvement ($p > 0.05$), serum angiopoietin-1 levels was negatively associated with neurological involvement ($P < 0.05$). Additionally, SLEDAI score positively associated with thrombomodulin levels ($P < 0.05$); and negatively associated with VW factor levels ($P < 0.05$). SLEDAI score positively correlated to serum levels of VEGF, Angiopoietin-2, and Tie-2 ($P > 0.05$) without statistical significance.

Conclusion: These six serum markers may be relevant to SLE pathogenesis. Its serum level seems to be potent biomarker for SLE activity as well as organ involvement. These biomarkers may be beneficial in disease monitoring and planning of future therapy.

Disclosure: W. F. Lee, None; C. Y. Wu, None; H. Y. Yang, None; J. L. Huang, None.

Abstract Number: 94

Circulating Soluble MICA Is Associated to Lupus Nephritis and to a TLR/IFN-I Signature in T Cells in a Cohort of Adult SLE Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: The MHC class I-related chain A (MICA) is a major ligand for the NKG2D receptor of NK and CD8 T cells. MICA expression at the cell surface is triggered by environmental stressors and label malfunctioning cells for their recognition by cytotoxic cells, which is followed by activation of programmed death in the MICA-labeled cells and their subsequent clearance by the immune system. Alterations in this recognition and also abnormal NK functions have been associated to defective apoptosis in SLE. The disruption of the MICA expression pathway is a major immune escape strategy of virus-infected or transformed cells to avoid immune surveillance. MICA can be shed from the cell surface and act as a soluble decoy receptor (sMICA) for cytotoxic cells. Our objective was to study circulating sMICA levels in relationship with innate molecular processes and clinical features in a cohort of patients with lupus.

Methods: 36 patients diagnosed with SLE and 13 healthy controls were recruited for a cross-sectional study. Circulating mononuclear cells were characterized by flow cytometry, and individual populations of monocytes, T and B lymphocytes were purified with magnetic bead sorting (Miltenyi MACS) for gene expression studies. A commercial ELISA (Diacalone) was used for detection of sMICA. Data are shown as median (CI95). The statistical analysis was done with non-parametric tests. An alpha value of 5% was considered significant.

Results: Globally, no differences in sMICA levels were found between patients and controls. However, in the lupus cohort, sMICA correlated with BILAG (p 0.428, p 0.023) and with SLEDAI scores (p 0.378, p 0.047). Interestingly, the up-regulation of sMICA was inversely associated to circulating NK counts (p 0.07), which were significantly lower in patients than in controls, and further decreased during active disease (p 0.01). Levels of sMICA were particularly high in patients

with active nephritis [aLN: 6.0 ng/ml (4.23-7.74), iLN 3.36 ng/ml (2.23-4.67) (p 0.029 vs aLN), healthy controls 3.0 ng/ml (1.66 - 4.39) (p 0.012 vs aLN)]. Furthermore, sMICA correlated with proteinuria (ρ 0.52, p 0.004) and with plasma creatinine (p 0.421, p 0.026). On the other hand, no association was observed with dsDNA antibodies or with complement levels. As regards activation of mononuclear cell subpopulations, sMICA levels were associated with the up-regulation of TLR2 (p 0.002) and TLR4 (p 0.003) in T lymphocytes, as well as with the transcripts of the interferon sensitive genes IFIT1 (p 0.035) and HERC5 (p 0.018) in these cells. An inverse association between sMICA and MICA gene expression levels in B lymphocytes approached significance (p 0.08).

Conclusion: Our data support an impairment in NK functions in active lupus, and a tight association between kidney flares and the up-regulation of sMICA. This molecule could come either from the innate activation of kidney cells or from PBMCs shedding. Disruption of the MICA pathway could account for a complement-unrelated process of damage in SLE.

Disclosure: M. Perez-Ferro, None; F. I. Romero-Bueno, None; C. Serrano del Castillo, None; R. Largo, None; G. Herrero-Beaumont, None; O. Sanchez-Pernaute, None.

Abstract Number: 95

Expression of SLAMF6 and Its Functional Significance in Podocytes of Lupus Nephritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

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Session Type: ACR Poster Session A

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

Background/Purpose: Systemic lupus erythematosus (SLE) is multisystem disorder that is caused by tissue damage resulting from antibody and complement-fixing immune complex deposition. Lupus nephritis (LN) is frequent complication and one of the most serious manifestations of SLE. The alteration of the structural protein in podocytes is known as a mechanism of proteinuria in LN. The signaling lymphocyte activation molecule family (the SLAM family) of type I transmembrane receptors consists of nine related members of the immunoglobulin superfamily and has been reported to mediate important regulatory signals between immune cells through their homophilic and heterophilic interactions (Nat Rev Immunol. 2003 Oct;3(10):813-21). The 1q23 region on human chromosome 1 including the SLAMF cluster of genes, containing SLAMF6 has been identified as a lupus susceptibility locus (Nat Rev Rheumatol. 2010 Jun;6(6):348-57). It has been shown that the expression of signaling lymphocyte activation molecule family 6 (SLAMF6) is enhanced in CD4⁺T cells of SLE patients and is involved in IL-17 production (J Immunol 2012; 188:1206-1212). We sought to examine the functional role of SLAMF6 in lupus podocytes.

Methods: We evaluated the co-expression of nephrin, a podocyte marker and SLAMF6 in kidney of normal controls and LN patients, also in B6 and MRL/*lpr* mice at the age of 8wk and 16wk by immunofluorescence analysis. We also examined nephrin positive SLAMF6 expression in isolated podocytes from B6 and MRL/*lpr* kidneys. Then, we analyzed the expression of SLAMF6 in CD4⁺T cells of isolated kidney and spleen in B6 and MRL/*lpr* mice. We treated human podocytes with IgG from healthy individuals and LN patients for 24 h and 48h and analyzed the expression of SLAMF6 by real-time PCR.

Results: In the histopathology, the expression of SLAMF6 was increased in nephrin positive area in LN patients and MRL/*lpr* mice compared to control. Although the expression of nephrin in MRL/*lpr* mice kidney at 16 wk old decreased compared to B6 mice at same age, the expression of SLAMF6 in podocytes increased in diseased MRL/*lpr* mice compared to B6 mice. Similarly, the expression of SLAMF6 in CD4⁺T cells increased in diseased MRL/*lpr* mice kidney and spleen compared to B6 mice. The level of SLAMF6 mRNA elevated in human podocytes exposed to LN-derived IgG.

Conclusion: The expression of SLAMF6 is enhanced in LN podocytes, suggesting that the possibility of cooperating with CD4⁺T cells contributing to its dysfunction. Further examination is needed to investigate in detail how SLAMF6 is involved in the development of LN in the future.

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Abstract Number: 96

The Liver X Receptor Modulates Inflammatory Cytokines Based on Lxr α Polymorphism in Monocyte-Derived Macrophages and Patients with Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Liver X receptors (LXRs) have emerged as important regulators of inflammatory gene expression. Previously, we had reported that an LXR α gene promoter polymorphism (-1830 T>C) is associated with systemic lupus erythematosus (SLE). Therefore, we assessed cytokine expression in relation to LXR α polymorphism in monocyte-derived macrophages and peripheral blood mononuclear cells (PBMC) from patients with SLE.

Methods: Macrophages were obtained after 72 hours of culture of human monocytes supplemented with phorbol 12-myristate 13-acetate. Cells were transfected with LXR α promoter constructs. Additionally, PBMC-derived macrophages from the patients with SLE were evaluated for pro-inflammatory cytokines in relation to the genotypes of LXR α -1830 T>C.

Results: The expression of LXR α was increased in macrophages; levels of pro-inflammatory cytokines, such as IL-1 β and TNF- α , were decreased with increased expression of LXR α . Production of pro-inflammatory cytokines varied depending on the expression of LXR α -1830 T>C genotype. In particular, decreased LXR α expression with increased pro-inflammatory cytokine expression was observed in monocyte-derived macrophages transfected with the TC genotype of LXR α -1830 T>C compared to those in cells transfected with the TT genotype. To verify the involvement of TLR in the expression of pro-inflammatory cytokines according to LXR α -1830 T>C genotype, various TLR agonists were treated in monocyte-derived macrophages transfected with the LXR α -1830 T>C. The levels of pro-inflammatory cytokines were further increased in TC genotype-transfected cells compared to those in TT genotype-transfected cells with treatment of TLR7 and TLR9 agonist. Pro-inflammatory cytokine levels were significantly decreased in TC genotype-transfected cells after treatment with TLR7 or TLR9 inhibitors. These results are consistent with those of an *ex vivo* study on PBMCs from patients with SLE with respect to the TC and TT genotypes of LXR α -1830.

Conclusion: These data suggest that expression levels of LXR α , according to LXR α -1830 T>C genotype, may contribute to the inflammatory response by induction of inflammatory cytokines in SLE.

Disclosure: C. H. Suh, None; W. Y. Baek, None; H. A. Kim, None; J. Y. Jung, None.

Abstract Number: 97

Enhanced IFN- α Production By Plasmacytoid Dendritic Cells Is Associated with Increased Toll-like Receptor 7 Retention in the Lysosomes and Exposure to Type I IFN in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Type I interferon (IFN) appears to contribute to the development of systemic lupus erythematosus (SLE). Overexpression of type I IFN regulated genes has been reported in patients with SLE. Although plasmacytoid dendritic cells (pDCs) is a major source of type I IFN including IFN- α and IFN- β , previous reports showed that IFN- α production by pDCs stimulated with a Toll-like receptor (TLR) 9 agonist or viruses was not increased in SLE compared to healthy controls (HC). In this study, we investigated another endosomal TLR-signaling pathway in SLE and the effect of type I IFN on TLR pathways.

Methods: Blood samples were obtained from HC and patients with SLE diagnosed according to the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Peripheral blood mononuclear cells (PBMCs) from SLE patients and HC were stimulated with a TLR9 agonist, CpG-A oligodeoxynucleotides -2216 (CpG-A ODN), or a TLR7 agonist, imiquimod. The proportion of IFN- α producing -pDCs was investigated by intracellular cytokine staining and flow cytometry. PBMCs were pretreated with IFN- α or IFN- β for 24 hours, and then IFN- α and IFN- β production by pDCs was assessed. Localization of TLR7 in cellular compartments in pDCs was investigated with or without pretreatment with IFN- α or IFN- β .

Results: As previously reported, the level of IFN- α production by pDCs stimulated with CpG-A ODN was reduced in SLE compared with HC. However, the proportion of IFN- α producing pDCs stimulated with imiquimod was significantly increased in SLE patients. The percentage of IFN- α producing pDCs stimulated with imiquimod was positively correlated with SLE disease activity index (SLEDAI) score, and the proportion of IFN- α producing pDCs stimulated with CpG-A ODN was negatively correlated with SLEDAI. Exposure to Type I IFN enhanced IFN- α production of TLR7-stimulated pDCs, but reduced that of pDCs activated with CpG-A ODN. TLR7 localization was increased in late endosome/lysosome compartments in pDCs from SLE patients. TLR7 localization was increased in late endosome/lysosome compartments of pDCs treated with either IFN- α or IFN- β both in HC and SLE.

Conclusion: IFN- α production by pDCs was increased upon stimulation with a TLR7 agonist in SLE patients. We found more TLR7 localization in late endosome/lysosome in lupus pDCs. Because IFN- α production requires TLR trafficking to lysosome-related organelle, enhanced IFN- α production by pDCs was partially due to TLR7 retention in the lysosomes in SLE. We also demonstrated that pretreatment with type I IFN enhanced IFN- α production by a TLR7 agonist-stimulated pDCs. In animal models of lupus, the role of TLR9 pathway in the pathogenesis is unclear but several reports indicated that TLR7 pathway is involved in the progression of autoimmune responses. Our study also indicates the importance of TLR7 pathway in SLE.

Disclosure: G. Murayama, None; A. Chiba, CHUGAI PHARMACEUTICAL CO., LTD., 8; A. Makiyama, None; K. Yamaji, None; N. Tamura, Chugai Pharmaceutical Co., LTD, 2, Astellas Pharma Inc., 2, ASAHI KASEI MEDICAL, 2, Sanofi K.K., 8, Bristol-Myers Squibb, 8; S. Miyake, TAIHO PHARMACEUTICAL CO., LTD, 5, Chugai Pharmaceutical Co., LTD, 8, AYUMI Pharmaceutical Co., LTD, 8, Astellas Pharma Inc., 8, Pfizer, Inc., 8, Sanofi K.K., 8, Bristol-Myers Squibb, 8.

Abstract Number: 98

Presence of Apoptotic Microparticle Containing Immune Complexes in Asymptomatic ANA+ Individuals Despite the Absence of Inflammation

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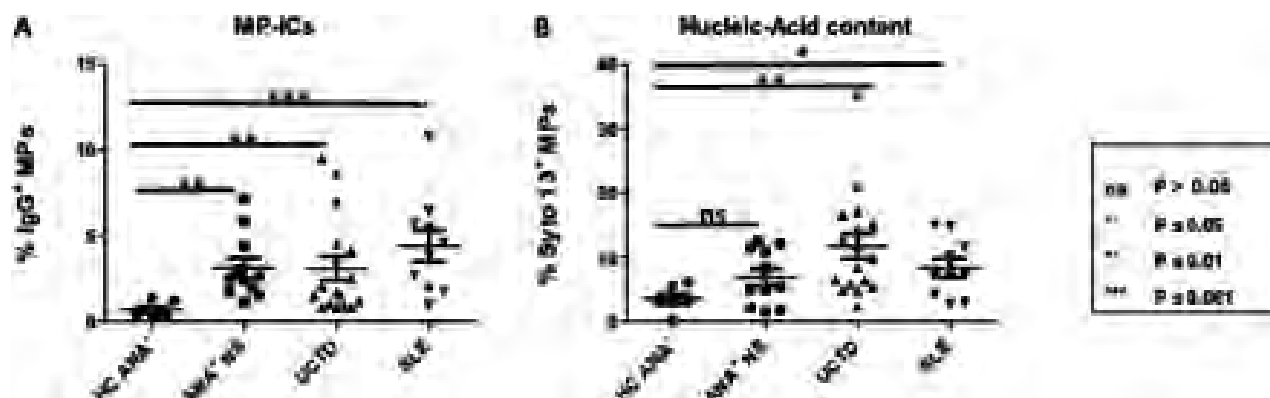
SESSION INFORMATION

Session Date: Sunday, October 21, 2018

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



Background/Purpose: Currently, little is known about what distinguishes asymptomatic Anti-Nuclear Antibody (ANA) positive individuals (ANA⁺NS) who will progress to Systemic Lupus Erythematosus (SLE) from those who will not. Preliminary data from our laboratory indicates that pro-inflammatory cytokines are increased in SLE but not in ANA⁺ NS. This finding suggests that the development of SLE is characterized by a change in the ability of the autoimmune response to elicit inflammation. Microparticles (MPs) are one of the sources of nuclear antigens in SLE. Previous studies have found increased levels of MP complexed with IgG (MP-ICs) in SLE as compared to healthy controls (HC) and have shown that these MP-ICs constitute a strong pro-inflammatory stimulus. In this study, we examined if ANA⁺NS individuals have MP-ICs to determine whether the lack of inflammation in these individuals results from the absence, or change in character, of their immune complexes.

Methods: Flow cytometry was used to examine the type, nucleic acid content, and IgG binding of peripheral blood Annexin V⁺ MPs in ANA⁻HC (n=7), ANA⁺NS (≥1:160 by IF, n=11), symptomatic ANA⁺ individuals lacking sufficient classification criteria for a connective tissue disease diagnosis (UCTD, n=17) and SLE patients (n=10, classified according to the 1997 American College of Rheumatology criteria). MP nucleic acid content was determined by staining with Syto13 which detects DNA and RNA. Eleven specific ANAs were detected using the Bioplex 2200 ANA Screen. The expression levels of five IFN- α induced genes were measured and summed to generate an IFN5 score.

Results: Consistent with previous studies, SLE patients had increased levels of MP-ICs (Figure 1A) that contained higher levels of nucleic acids (Figure 1B), as compared to ANA⁻ HC. Surprisingly, ANA⁺NS and UCTD patients had similar elevations in the amount of IgG coating their MPs to those seen in SLE (Figure 1A) and in a subset of these individuals the MP nucleic acid content was also higher than ANA⁻ HC (Figure 1B). There was a non-statistically significant trend to higher MP-ICs in ANA⁺ NS and UCTD individuals with specific ANAs and to higher IFN5 scores in those UCTD individuals with elevated Syto13⁺ MPs.

Conclusion: MPs appear to be a source of autoantigen in ANA⁺NS individuals. The results suggest that the differences in elaboration of pro-inflammatory factors between ANA⁺NS individuals and SLE patients do not result from a lack of immune complexes.

Disclosure: C. Muñoz-Grajales, None; D. Bonilla, None; A. Karanxha, None; D. Ferri, None; E. Silverman, None; S. Johnson, None; A. Bookman, None; Z. Touma, None; J. E. Wither, None.

Abstract Number: 99

DC-Hil⁺ Myeloid-Derived Suppressor Cells Are Elevated in the Peripheral Blood and Lesional Skin of Cutaneous Lupus Patients

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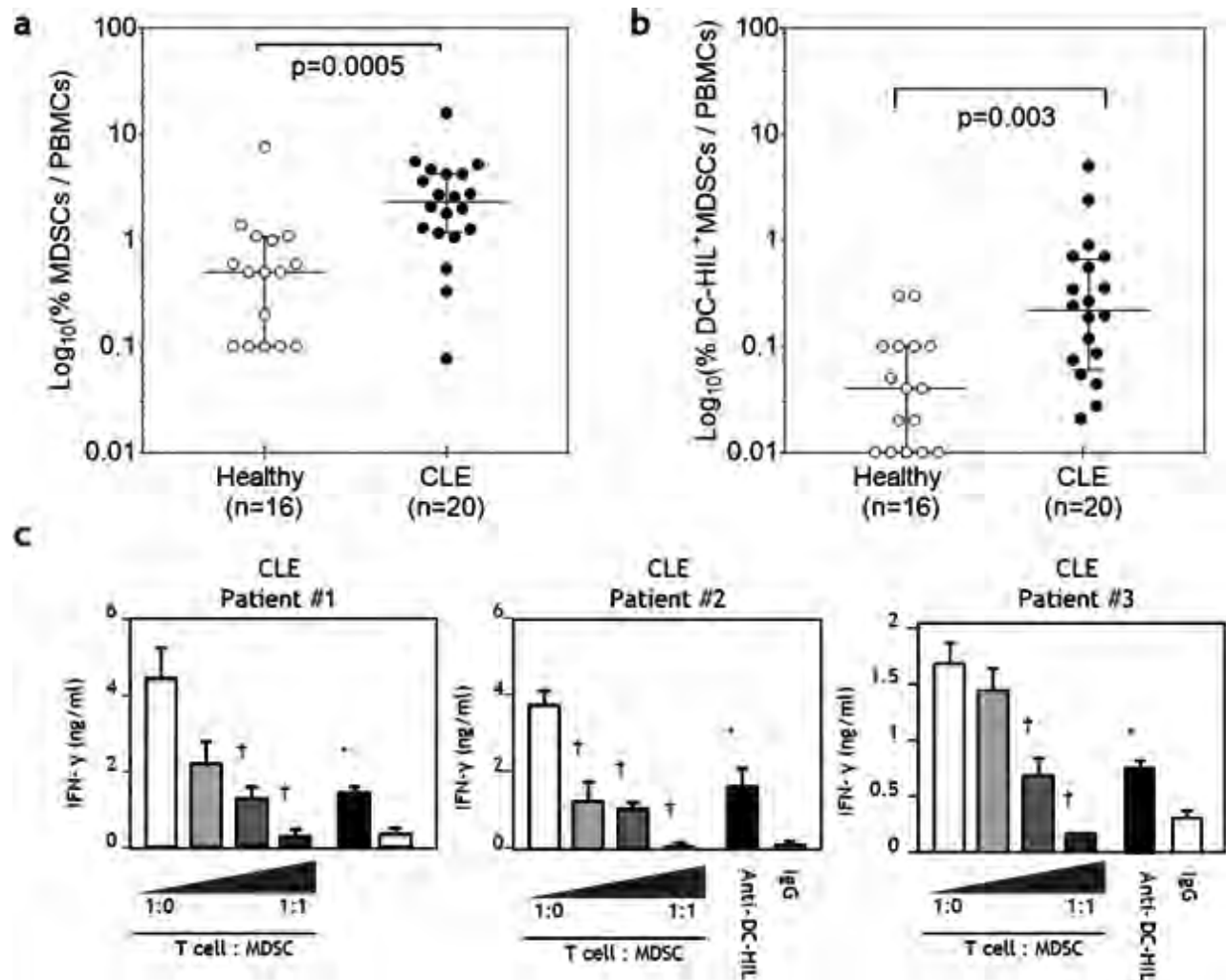
SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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



Background/Purpose: Myeloid-derived suppressor cells (MDSCs) are major T cell suppressors, and their dysfunction has been implicated in the pathophysiology of autoimmune diseases. MDSCs suppress T cells using multiple co-receptors including the DC-HIL receptor, which has been shown to be a major receptor in monocytic MDSCs (M-MDSCs). We previously showed that DC-HIL⁺ M-MDSCs from patients with psoriasis are expanded and functionally deficient, thus enhancing autoreactivity. However, the function of MDSCs in cutaneous lupus erythematosus (CLE) is poorly understood. We hypothesized that DC-HIL⁺ M-MDSCs are elevated in the peripheral blood and lesional skin of patients with CLE.

Methods: All patients were recruited through the UT Southwestern Cutaneous Lupus Registry. PBMCs from 20 CLE patients and 16 age- and gender-matched healthy controls were analyzed using flow cytometry. M-MDSCs were identified by the phenotype of CD14⁺ HLA-DR^{neg/low}. To investigate the suppressor function of M-MDSCs, freshly isolated autologous M-MDSCs and T cells were co-cultured at varying ratios. T cell function was measured by secretion of IFN- γ by ELISA. Anti-DC-HIL mAb (50 $\mu\text{g/mL}$) was added to the 1:1 co-culture to study the role of the DC-HIL receptor. Immunohistochemical staining of five CLE lesional skin biopsies and three control skin biopsies using anti-DC-HIL antibodies was performed to study the population of MDSCs in skin tissue.

Results: CLE patients had significantly higher %M-MDSCs amongst PBMCs (2.3% (IQR: 1.2%-4.2%)) compared to controls (0.5% (0.1%-1.1%)) ($p=0.0005$). Percent DC-HIL⁺ M-MDSCs amongst PBMCs was also elevated in CLE patients (0.22% (0.06%-0.67%)) compared to healthy controls (0.04% (0.01%-0.1%)) ($p=0.003$). MDSCs isolated from PBMCs of three additional CLE patients suppressed activated autologous T cells in a dose-dependent manner. Addition of anti-DC-HIL monoclonal antibody partially reversed the suppressor function, indicating that DC-HIL is a receptor involved in MDSC-mediated T-cell suppression in CLE. Compared with normal skin, CLE skin had increased DC-HIL⁺ cells ($p=0.04$), particularly at the dermal-epidermal junction. DC-HIL⁺ cells were in close proximity to CD3⁺ T cells at the dermal-epidermal junction, perifollicular, and perivascular areas.

Conclusion: In summary, DC-HIL⁺ M-MDSCs are expanded in CLE blood and skin, and display immunosuppressive properties. Their up-regulation in CLE blood may represent the body's response to limiting disease severity, since most patients had mild disease activity. Further studies are needed to discern whether these cells help contain the immune dysregulation to skin, since few CLE patients progress to SLE.

Disclosure: S. Florez-Pollack, None; L. C. Tseng, None; M. Kobayashi, None; G. Hosler, None; K. Ariizumi, None; B. F. Chong, Biogen Incorporated, 2, Daavlin Incorporated, 2, Celgene Corporation, 5, Pfizer Incorporated, 9.

Abstract Number: 100

Glycosphingolipids and Proteins in Urine Exosomes: Potential Biomarkers of Lupus Nephritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Exosomes, extracellular vesicles that are abundant in human urine and contain proteins from renal cells, are a potential source of biomarkers of renal disease in LN patients. We previously demonstrated that levels of Glycosphingolipids (GSL) glucosylceramide (GlcCer) and lactosylceramide (LacCer), and expression of a neuraminidase (NEU1) that mediates GSL catabolism, are elevated in the urine of human patients with nephritis compared to controls. Based on these results we hypothesized that lipids and proteins in the GSL catabolic pathway in urine exosomes could be used as biomarkers of therapeutic response and/or disease flare in LN patients.

Methods: Lipids and proteins were analyzed by mass spectrometry in exosome fractions isolated from urine in 1) a pilot study of lupus nephritis (LN) patients during quiescent disease (non-flare) and renal flare, and in non-nephritis lupus patients; and 2) LN patients that failed to respond or had a complete response to mycophenolate mofetil (MMF) treatment.

Results: In the LN flare versus non-flare versus non-nephritis pilot study, differences in GSL (GlcCers and LacCers) levels were observed among the three sets of samples. Differences in phospholipids were also observed. Proteomics results identified several abundant and known urine biomarkers for LN albumin and serotransferrin in the samples from LN patients. Additional known urine biomarkers in the LN samples included complement factors, anti-trypsin, and alpha-2-HS-glycoprotein/fetuin-A. Novel proteins that were differentially abundant (either higher or lower) in LN samples compared to non-nephritis lupus samples and/or in flare compared to non-flare samples also were identified and included lysosomal protective protein (cathepsin A), a co-factor for NEU1. In the treatment response study, significant differences in GlcCer levels in exosomes isolated from pooled urine samples collected at baseline (prior to MMF treatment) were observed between LN patients that responded compared to those that did not respond to therapy. These results are being validated in a cohort of MMF responder (30) and non-responder (30) LN patients using exosomes isolated from individual urine samples taken at baseline and at 3-, 6-, and 12-months post-treatment. Additional lipids and proteins that are differentially abundant in these urine exosome samples between responders and non-responders are being identified and validated.

Conclusion: Preliminary data suggest that lipid and protein molecules in urine exosomes may serve as early markers of disease flare and/or response to therapy in LN patients and may enhance the predictive power of current models of response to therapy.

Disclosure: T. K. Nowling, None; J. Rodgers, None; J. C. Oates, None; M. Janech, None; R. Drake, None.

Abstract Number: 101

Regulation of Monocyte Function By Epstein Barr Virus Interleukin-10 (vIL10) in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease characterized by periods of elevated and suppressed disease activity. Epstein Barr Virus (EBV) has been associated with SLE. EBV maintains latency in infected B cells and shows intermittent reactivation. Elevated concentrations of EBV Early Antigen (EA) IgG, a measure of viral reactivation, increase the probability of transitioning to SLE in unaffected family members, which underscores the importance of EBV reactivation in SLE autoimmune responses. Viral IL10 (vIL10), an EBV lytic protein, is a homolog of interleukin 10. Monocytes are one of the first cells to respond following infection and dysregulation of monocytes plays a dynamic role in the systemic autoimmune response in SLE. However, the effects of vIL-10 on monocyte function in the context of increased human or cellular IL10 (hIL10) have not been examined. In this study we examine whether vIL10 has similar inhibitory effects on monocytes as hIL10.

Methods: Plasma from 20 SLE patients (10 European American and 10 African American) with varying disease activity and 19 age, race and sex matched healthy unrelated controls were concentrated and vIL10 detected by western blotting. The band intensities were normalized to pooled sera from infectious mononucleosis patients. Plasma IL10 levels were measured by xMAP assays. Monocytes were enriched from peripheral blood mononuclear cells from healthy donors. STAT phosphorylation, cytokine secretion and expression of cell surface markers were determined by flow cytometry. Gene expression was by quantitative PCR.

Results: SLE patients had significantly higher levels of plasma vIL10 (8516 ± 3291 ; 6509 ± 1953 , $p=0.03$), and significantly higher levels of hIL10. No correlation was observed between vIL10 and hIL10. To determine the functional consequences of increased vIL10 in the presence of high levels of endogenous cellular IL10, we performed in vitro stimulation of monocytes with hIL10 in the presence or absence of vIL10. As expected, hIL10 induced phosphorylated STAT3 (pSTAT3), which is required for anti-inflammatory gene expression induced by IL10, while vIL-10 induced significantly lower pSTAT3. The presence of vIL10 reduced hIL10 induced pSTAT3 in a dose dependent manner, suggesting that vIL10 can act as a competitive inhibitor of hIL10 activity. vIL10 increased pro-inflammatory gene expression, but was unable to downregulate IL10R1 gene expression. However, neutralizing antibody to IL10R1 reduced pSTAT3 and inhibited upregulation CD163 induced by both hIL10 and vIL10, suggesting that vIL10 signals through IL10R1. We did not see any significant differences between the frequency of cells positive for intracellular hIL10 in monocytes stimulated with hIL10 or vIL10.

Conclusion: Lupus patients have increased levels of plasma vIL-10, possibly due to increased EBV reactivation. vIL10 signals through IL10R1 and can suppress hIL10 induced STAT3 phosphorylation. Suppression of hIL10 induced anti-inflammatory genes by vIL10, together with an increase in inflammatory gene expression may overcome the anti-inflammatory effect of IL10 and exacerbate autoimmune responses in SLE.

Disclosure: N. R. Jog, None; E. Chakravarty, None; J. M. Guthridge, None; J. A. James, None.

Abstract Number: 102

Estrogen Controls the Expression of Serine Arginine-Rich Splicing Factor 1 (SRSF1) in Human T Lymphocytes Via Transcriptional and Post-Transcriptional Mechanisms

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic debilitating autoimmune disease that primarily afflicts women in the childbearing years. Female hormones especially estrogen are implicated in the pathogenesis of disease, however the precise molecular mechanisms regulated by estrogen in immune cells are not well understood. We previously identified novel roles for the multifunctional protein serine/arginine-rich splicing factor 1 (SRSF1) in T cells. We

showed that SRSF1 promotes expression of the CD3zeta signaling gene and activates IL-2 production in normal T cells. T cell specific *Srsf1*-conditional knockout mice exhibit defects in T cell function and develop autoimmune disease. SRSF1 expression levels are decreased in T cells from SLE patients, and associate with severe disease activity. Importantly, overexpression of SRSF1 into SLE T cells rescues IL-2 production. These results imply that the SRSF1 is an important molecule in T cells and immune-mediated disease. However, not much is known about the regulation of SRSF1, and if hormones may contribute to its expression.

Methods: Peripheral blood was collected from healthy women in the follicular phase of the menstrual cycle. T cells were isolated by negative selection from peripheral blood. T cells were cultured (in RPMI without phenol red supplemented with charcoal-stripped serum), with increasing concentrations (0, 1nM, 10nM, 100nM) of beta-estradiol for 18 – 24 hours. To assess mRNA stability, transcription was blocked with actinomycin D, cells collected at 0, 0.5, 1, 1.5 and 2 hours, and *Srsf1* expression assessed by RT-qPCR. To assess posttranslational protein degradation mechanisms, the proteasome inhibitor MG132 or the lysosome inhibitor Bafilomycin A1 were added to cultures followed by western blots for SRSF1. The *Srsf1* promoter was cloned into a pGL3-luciferase plasmid. T cells were transfected by electroporation and luciferase activity measured by a luminometer.

Results: Exposure to estrogen led to a dose dependent increase in *Srsf1* mRNA expression, but decreased protein levels in T cells. This discrepancy between mRNA and protein levels suggests that estrogen controls SRSF1 at transcriptional and post-transcriptional levels and may upregulate transcriptional activity of its promoter but downregulate protein levels via mRNA decay, translation or protein degradation. Accordingly, estrogen increased luciferase activity of the *Srsf1* promoter-luciferase construct indicating that estrogen activates *Srsf1* transcription. Estrogen did not affect mRNA stability, however protein analyses showed that the proteasome is involved in the degradation of SRSF1. In silico analysis revealed microRNA (miR) target sites within the *Srsf1* 3' UTR, of which miR-21-5p, miR-27, and miR-200b-3p are known to be regulated by estrogen and to be dysregulated in SLE.

Conclusion: Our results suggest that estrogen can modulate the expression of SRSF1 via transcriptional and posttranscriptional mechanisms in human T lymphocytes, thus revealing a potential molecular link between hormones, immune cells and autoimmune disease.

Disclosure: J. F. Oviedo, None; E. N. Cravens, None; V. R. Moulton, None.

Abstract Number: 103

Identification of IL-17+ and IL-10+ TCR $\alpha\beta$ + CD4- CD8- double Negative (DN) T Cell Subsets in Lupus-Prone Mice and Patients with SLE and Their Significance in Predicting Renal Involvement

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: We have previously shown that DN T cells are expanded in both lupus-prone mice and patients with SLE and we have demonstrated that this population is an essential component of the immunopathogenesis of the disease. It still remains unknown whether the DN T cell pool consists of functionally heterogeneous subpopulations. In this study we ask whether DN T cells comprise distinct functional subsets.

Methods: Flow cytometry analysis was applied for the expression of cytokines, chemokine receptors, and T cell receptor (TCR) repertoire etc. IL-17-GFP B6 mice were crossed to MPL/lpr mice for 8 generations to generate IL-17-GFP MPL/lpr mice which were used to track IL-17⁺ DN T cells *in vivo* and sort IL-17⁺ DN T cells *ex vivo*. Cytokine capture assay was applied for *ex vivo* isolation of either IL-17⁺ or IL-10⁺ DN T cells. Metabolism-associated gene expression was quantified by RT-qPCR. Peripheral blood T cells from either healthy subjects or patients with SLE were assessed by flow cytometry analysis.

Results: Two distinct DN T populations were identified in both mice and humans based on the expression of two cytokines, IL-17 and IL-10. As expected, IL-17⁺ DN T cells were significantly increased in aging MRL/lpr mice (20 wks old) compared to either age matched control MRL/mpj mice or young MRL/lpr mice (12 wks old), a finding which is consistent with our previous report that DN T cells contribute to lupus pathogenesis by producing IL-17. Interestingly, the numbers of IL-10⁺ DN T cells in aging (20 wks old) mice were reduced compared to young (12 wks old) MRL/lpr mice. Flow cytometry analysis revealed that the predominant chemokine receptors expressed on IL-17⁺ and IL-10⁺ DN T cells were different. Higher levels of CCR6 expression were observed only on IL-17⁺ DN T cells and especially in those infiltrating the kidneys (64±11.4% in kidneys vs 19.3 ± 5.6% in spleens) but CCR4 expression was restricted on IL-10⁺ DN T cells. Furthermore, different TCR V beta repertoire usage (V β 5, 6, 8.1/8.2, 12) was observed in IL-17⁺ DN T cells while V β 14 and 15 were noted on IL-10⁺ DN T cells. Finally, different expression levels of metabolic genes were recorded between IL-17⁺ vs IL-10⁺ DN T cells. Consistently, increased percentage of IL-17⁺ DN T cells (7.0 ± 5.4% vs 4.1 ± 2.6 %) and reduced IL-10⁺ DN T cells (0.49 ± 0.65% vs 7.5 ± 1.6%) were observed in the peripheral blood from the subjects with SLE compared to healthy subjects.

Conclusion: We present evidence that two distinct subsets exist within the DN T cell population in lupus prone mice and patients with SLE. The ratio of IL-17⁺/10⁺ DN T cells increases as the disease progresses in MRL/lpr mice. The two subsets appear to utilize different TCR repertoire and express different cytokine receptors and metabolic enzyme patterns. We propose that the ratio between the two subsets represents a valid disease biomarker and particularly of impeding kidney involvement.

Disclosure: Y. Li, None; H. Li, None; V. C. Kyttaris, None; G. C. Tsokos, None.

Abstract Number: 104

Identification of a Gut Pathobiont Immunostimulatory Lipoglycan Antigen Linked to Lupus Nephritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: A transmissible agent has long been suspected in SLE. In a discovery cohort we found that, compared with healthy subjects, Lupus patients had a five-fold overall mean greater representation of the *Ruminococcus gnavus* species of the Lachnospiraceae family of anaerobic gram-positive cocci. Many SLE patients also displayed biomarkers of increased gut permeability that has been associated with bacterial translocation. In a patient, the relative fecal *R. gnavus* abundance directly correlated with serum levels of IgG anti-*R. gnavus* antibodies. This anti-bacterial immune response had features indicative of molecular mimicry with anti-native DNA antibodies, which are direct contributors to the pathogenesis of Lupus nephritis (LN). We therefore sought to isolate and characterize the responsible strain-associated antigen in the *R. gnavus* candidate pathobiont.

Methods: A panel of strains of the Lachnospiraceae family, and other anaerobic commensals, were evaluated by immunoblot, bead-based Luminex assay, as well as direct and competition ELISA. To isolate lipoconjugates from the candidate Gram-positive bacterial commensal strain, we applied a validated extraction protocol using a butanol separation with fractionation after passage over Hydrophobic Interaction Chromatography (HIC). Fractions were then evaluated for immunoreactivity and capacity to stimulate a human TLR2- transfected HEK reporter gene system.

Results: In an assay with a cutoff based on the mean+2SD of 55 healthy controls, we found that one of 8 independent *R. gnavus* isolates, which we termed RG2, displayed high level serum IgG reactivity with 30 of 50 active LN patients and only 4 of 36 patients without active renal disease (P<0.001 by *t* test). Fractionation of the RG2 extract by chromatography enabled the isolation of a lipoglycan, which by high-resolution NMR spectroscopy showed the presence of repetitive oligosaccharide building blocks. Sera from LN patients also displayed strong IgG reactivity with the lipoglycan, which was inhibitable by the nuclease-treated RG2 extract. In side-by-side analyses the lipoglycan had the same oligomeric immunoblot banding pattern of the parental bacterial extract, and in a HEK transfected reporter cell system displayed strong dose-dependent (range 2 to 2000 ng/ml) NFκB activation, compared to nonstimulated conditions. This activity was significantly inhibited by an anti-huTLR2 mAb at 10 ug/ml (P=0.006) but not isotype control. Further analyses of the exact

carbohydrate content, as well as the overall size and detailed structure of the isolated lipoglycan, are currently under study by NMR, MS, and GC/MS.

Conclusion: We have identified a gut commensal strain-associated cell wall lipoglycan, which appears to represent an immunodominant antigen in a candidate pathobiont implicated in the pathogenesis of LN. Moreover, the TLR2-activation potential of the lipoglycan pool may be due to the presence of lipopeptides, which will require further investigation. Our findings suggest a pathway by which continuous translocation of a bacterial mimic of DNA with innate immunostimulatory properties may contribute to the pathogenesis of LN.

Disclosure: G. Silverman, None; N. Gisch, None; A. Omarbekova, None; D. F. Azzouz, None.

Abstract Number: 105

Immunologic Properties of Cutaneous Lupus Erythematosus (CLE) Patients Refractory to Antimalarials Compared to Patients That Respond to Antimalarials

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Two major therapies for cutaneous lupus erythematosus (CLE) are the antimalarials, hydroxychloroquine (HCQ) and quinacrine (QC). HCQ is often the first-line therapy for CLE, but only half of patients show a response to it. While some of the patients that do not initially respond to HCQ benefit from the addition of QC, there is a subset of patients that are refractory to both antimalarials. Refractoriness poses a huge challenge because these patients will often continue to have active disease when they are initially started on antimalarials. To better characterize these refractory patients, we investigated the immunologic characteristics of patients that respond to antimalarials versus those that do not.

Methods: CLE patients were classified as HCQ-responders, HCQ/QC-responders, or HCQ/QC-nonresponders. Immunohistochemistry was used to characterize the inflammatory cell composition and cytokine expression in lesional skin biopsies from patients. Total RNA was extracted from these biopsies to analyze specific gene signatures. The patient's CLASI score – a measure of disease activity – at the time of the biopsy was also determined.

Results: Immunohistochemistry showed that myeloid dendritic cells (mDCs) were significantly higher in HCQ/QC-responders compared to HCQ-responders and HCQ/QC-nonresponders, while plasmacytoid dendritic cells, neutrophils, macrophages, and autoreactive T cells did not differ significantly among the three groups. The HCQ/QC-nonresponder group was distinct from the other groups in that their CLASI scores did correlate positively with the number of macrophages ($p < 0.05$, Figure 1). Staining also showed that IL-22 expression was significantly higher in HCQ/QC-nonresponders versus the HCQ- or HCQ/QC-responders while IL-17 expression was not significantly different between the responders and nonresponders. Analyzing their RNA expression demonstrated a high type I IFN signature (LY6E, OAS1, ISG15, MX1) in HCQ-responders but a low type I IFN signature and higher TNF-alpha expression in both HCQ/QC-nonresponders and HCQ/QC-responders.

Conclusion: An increased number of mDCs may contribute to HCQ-refractoriness and predict a better response to treatment with both HCQ and QC but do not contribute to HCQ/QC-refractoriness. The significant correlation between macrophages and CLASI scores in the HCQ/QC-nonresponders, a finding not seen in either HCQ or HCQ/QC-responders, may also indicate that macrophages are more involved in antimalarial-refractory skin disease. The difference between the responders and nonresponders is further confirmed by the cytokine staining and mRNA expression. Our data is an initial step in determining the activation pathways that account for the lack of response to antimalarials.

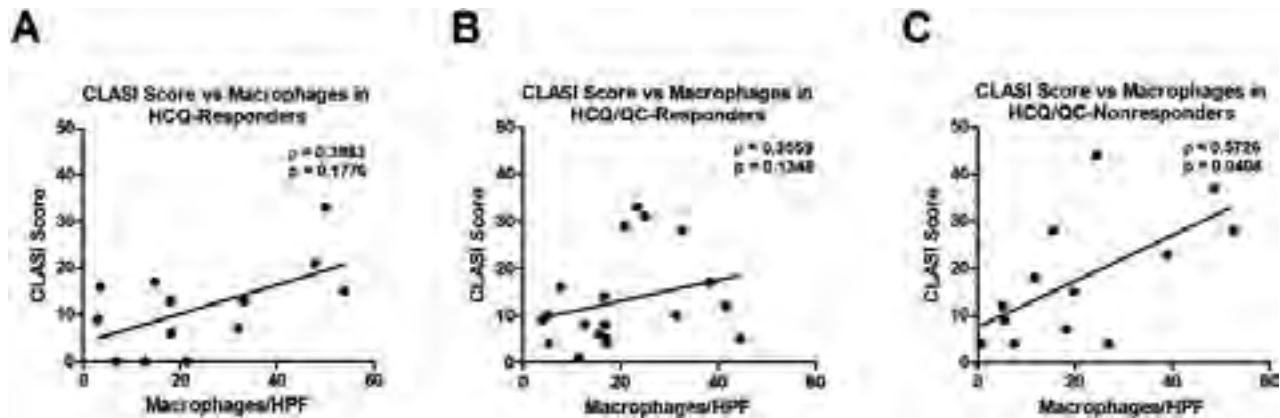


Figure 1: CLASI Score versus Macrophages in HCQ-Responders, HCQ/QC-Responders, and HCQ/QC-Nonresponders

Disclosure: M. Zeidi, None; K. Desai, None; H. J. Kim, None; V. P. Werth, None.

Abstract Number: 106

Highly Elevated Levels of Anti-Mitochondrial Antibodies in Systemic Lupus Erythematosus and Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: We recently described the phenomenon in systemic lupus erythematosus (SLE) in which mitochondria are extruded into the extracellular space during formation of neutrophil extracellular traps (NETs). NET formation has been demonstrated to be inflammatory and immunogenic, possibly including mitochondria. While poorly characterized, it is known that in both SLE and rheumatoid arthritis (RA) a small subset of patients are positive for anti-mitochondrial antibodies (AMAs). Frustratingly, current mitochondrial isolation techniques produce mitochondria that are wrapped in nuclear DNA (nuDNA), blurring the distinction of AMAs and anti-dsDNA antibodies, commonly seen in SLE. Here, we aim to perfect mitochondrial isolation, characterize the targets of AMAs, and determine their clinical implications in RA and SLE.

Methods: Mitochondria from HepG2 cells isolated by Dounce homogenization and subsequent DNase treatment were tested for nuDNA contamination by quantitative PCR (qPCR) of 16S rRNA and 18S rRNA genes and organelle purity by fluorescence-activated cell sorting (FACS). Isolated mitochondria were used to test sera from healthy individuals (HC, n=17), SLE patients (n=44), and RA patients (n=101) for anti-mitochondrial IgG antibodies via FACS and western blot (WB) methods. Finally, sera were tested for presence of AMA by immunocytochemistry using a HepG2 cell line with GFP-tagged mitochondria.

Results: Our mitochondrial isolation technique yielded over a 1,000-fold reduction in nuDNA over standard techniques, reducing the possibility of anti-dsDNA antibodies binding to residual nuDNA on the mitochondrial surface. Further, we did not observe any binding of propidium iodide, an impermeable DNA-binding dye, or anti-dsDNA antibodies, to the isolated mitochondria. Similarly, this technique produced particles that were 99.1% positive for mitochondria markers MitoView and MitoTracker. Using this ultrapure isolate, we found that SLE and RA patients had significantly elevated reactivity against isolated mitochondria compared to HC ($p < 0.0001$, 727 vs 333 MFI and 680 vs 400 MFI, respectively). Levels of AMAs were particularly elevated in patients with severe disease, including erosive disease (RA, $p = 0.01$) and nephritis (SLE, $p = 0.02$). AMA reactivity was confirmed with ICC using HepG2 cells with GFP-tagged mitochondria. Lastly, we found mitochondrial proteins near band sizes 15, 30, 35, 45, and 75kDa that were consistently labeled by SLE sera, indicating an unequal antigenicity between mitochondrial proteins.

Conclusion: Here, we introduce a highly effective method of mitochondrial isolation in which both nuDNA and non-mitochondrial organelle contamination are reduced to insignificant levels compared to previous methods. Subsets of SLE and RA patients have been reported to have AMAs, but they have not been well-characterized. In this study, we show a

tremendous increase in AMAs in SLE and RA patients and we illuminate that these AMAs target only a subset of mitochondrial proteins. Little is known about AMA targets, and it is expected that their identification will open new avenues for SLE and RA monitoring, stratification, treatment and prevention.

Disclosure: R. Moore, None; C. Lood, None.

Abstract Number: 107

Apolipoprotein L1 Risk Variants, Renal Histopathology, and Prognosis in African American SLE Nephritis Patients: A Cohort Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Apolipoprotein L1 (APOL1) risk variants (RV), G1 and G2, associate with CKD in African Americans (AA) and are evolutionarily preserved due to improved infectious resistance. Interferons (IFN) in SLE, have been shown to increase APOL1 expression and RV toxicity in endothelial cells and podocytes. Though RV homozygotes with SLE nephritis demonstrate advanced renal progression, associations with renal histopathologies have not been validated in SLE.

Methods: Herein, this cohort study tested the hypothesis that RV homozygosity (RV/RV) associates with specific clinical and biopsy features compared to reference allele (G0) homozygosity (G0/G0) or RV heterozygosity (RV/G0). Whole blood DNA for genotyping, kidney biopsy slides, and clinical reports from 77 AA SLE patients with biopsy-proven nephritis reviewed for: biopsy class, activity index (AI), chronicity index (CI) and clinical features across APOL1 genotype. RV-attributed mitochondrial morphology, was assessed on electron microscopy (EM) images. Analysis was confirmed by two blinded pathologists. As proof of concept, primary endothelial cells across genotype were given IFN to over-express APOL1, and features on EM were compared.

Results: The G0/G0, RV/G0, and RV/RV groups comprised 35%, 52%, and 12% of the cohort. There were no genotype differences in SLE history or demographics. Compared to G0/G0, and RV/G0 groups, the RV/RV had higher urine protein to creatinine ratios (uPCR) and creatinine (Cr) at biopsy (mean uPCR: 2.5; 2.7; 4.3 mg/L p=0.06 and Cr: 1.3; 1.03; 2.3 mg/dL p=0.01 respectively). Adjusting for dsDNA, AI, CI, and percent sclerotic glomeruli, the RVs independently associated with proteinuria at biopsy (OR=2.1, p=0.05). Paradoxically, the G0/G0 and RV/G0 vs the RV/RV group displayed higher AI and CI with a trend toward higher dsDNAs at biopsy (G0/G0 or RV/G0: AI: 5.3/24; CI: 2.6/12 dsDNA: 447 vs RV/RV: AI: 1.2/24; CI: 1.3/12; dsDNA: 69, p=AI: 0.004; CI: 0.01; dsDNA: 0.1). In 30% of the RV/RV cases, the reading pathologist commented that clinical severity was out of proportion to the biopsy lesion. The RV associated with ESRD in 7.9%, 3.9%, and 20% of the G0/G0, RV/G0, and RV/RV cases (OR: 5.7; p=0.03). On EM, RVs associated with mitochondrial condensation (mitochondrial area: G0/G0: 0.17; RV/G0: 0.09; RV/RV: 0.06 μm^2 ; p<0.01); this result was recapitulated in our cell culture model. IFN-treated endothelial cells increased APOL1 expression 18 fold across genotypes (p<0.01). Compared to G0/G0 and RV/G0 cells, RV/RV cells had mitochondrial areas: G0/G0: 0.08; RV/G0: 0.07; RV/RV: 0.04 μm^2 ; (p<0.01).

Conclusion: In this SLE cohort, APOL1 RVs associated with poorer prognosticators, initial proteinuria and creatinine, and ultimately progressive nephritis. These features were paradoxically out of proportion to the SLE lesion on biopsy. The literature supports RV-conferred podocyte and endothelial cell mitochondrial defects owing to a mitophagy deficiency. As evidenced by EM images from both SLE patient biopsies and primary cell cultures, these genes may confer intrinsic renal pathology. Consequently, traditional scoring of histopathologic severity may underestimate injury that associates with RV alleles.

Disclosure: A. Blazer, None; M. Wu, None; N. Schmidt, None; A. Engelbrecht, None; F. X. Liang, None; R. M. Clancy, None; J. P. Buyon, None; H. M. Belmont, Exagen, 2.

Sex-Specific Expression of CXorf21 Provide Molecular Explanation for the Fundamental Difference in Male and Female Immune Response: An Explanation for Female-Bias SLE Pathogenesis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Systemic lupus erythematosus (SLE) is complex autoimmune disorders characterized by B cell hyperactivity resulting in autoantibody and cytokine production. Approximately 90% of patients are female. We have produced data an X-chromosome gene dose effect increases susceptibility. Therefore, our objective is to functionally describe an X-linked protein which escapes X-inactivation, Chromosome X open reading frame 21 (*CXorf21*), to uncover any role this protein may have in the pathogenesis or susceptibility to SLE. Publicly available data predict CXorf21 is a dehydrogenase/reductase expressed almost exclusively in monocytes, B cells, and and other antigen-presenting cells. Additional studies show that CXorf21, a SLE risk allele, directly interacts with another SS/SLE-associated risk allele, *Slc15a4*. SLC15a4, a lysosomal proton-oligopeptide co-transporter, is necessary for endolysosomal antigen processing, TLR7- and NOD1-mediated cytokine as well as antibody production in dendritic cells and B cells.

Methods: We used quantitative real-time PCR, Western blot protein analysis, Bio-plex cytokine immunoassay, and pHrodo™ assay, as well as, *in vitro* CRISPR-Cas9 knockdown experiments to examine the role of CXorf21 in monocytes and B cell immunity.

Results: Our data show that CXorf21 basal gene and protein expression is elevated in female primary monocytes and B cells compared to male cells. We also found CXorf21 mRNA expression was higher in both male and female SLE-affected EBV-transformed B cells and female primary Sjogren's Syndrome patient's PBMC subsets compared to healthy male controls. Additionally, we found that following activation by TLR7 (Imiquimod) and NOD1 (iE-DAP) agonists *CXorf21*, *IFN-alpha*, and *NFkappaB* expression increases, in addition to an increase IL-6 and TNF-alpha cytokine production. This response is exaggerated in a female-specific manner. Successful knockdown of CXorf21, using CXorf21-specific gRNA (CRISPR-Cas9), abrogated both the expression levels and cytokine response in the female samples, but had not affect in male subjects. pHrodo™ lysosomal pH experiments revealed that knockdown of CXorf21 protein in healthy female monocytes resulted in an increased lysosomal pH. As result of the increase from acidic to a more alkaline lysosomal environment in the female samples (auto)antigen processing is perceived to be disrupted.

Conclusion: CXorf21 is over-expressed in female immune cells compared to male cells and is involved in a sex-dependent dimorphic response to activation through TLR7 and NOD1. We propose that CXorf21 via interaction with the lysosome proton cotransporter, SLC15a4, maintains the lysosomal pH gradient necessary for monocyte and B cell immune response. Thus, sexual dimorphic expression of CXorf21, based on escape of X chromosome inactivation, skews (auto)antigen processing and immune response by women compared to men. CXorf21 may be a major contributor to TLR7 disease pathogenesis, and sex bias of the diseases based on an X chromosome dosage effect.

Disclosure: R. H. Scofield, NIH, ept Veran Affairs, Lupus research Institute, 2, Dept of Veterans Affairs, University of Oklahoma, 3, Boston Pharmaceuticals, 5; V. M. Harris, None; B. T. Kurien, None; K. A. Koelsch, None.

Unique miRNA Signatures Detected in Extracellular Vesicles from Patients with Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Recent studies have identified distinct changes in cellular miRNA (miR) expression associated with systemic lupus erythematosus (SLE). We have previously shown that toll-like receptor TLR7 and TLR8 are significantly up-regulated in PBMCs of SLE patients. TLR7 and TLR8 bind to single-stranded RNA of viral origin to stimulate innate inflammatory responses. We have demonstrated that EV-encapsulated miR-21 induces both TLR8-mediated cytokine signaling and EV secretion in vitro. In another recent publication from our group, we also discovered that high mobility group box (HMGB)1 is a substrate for transglutaminase-2-mediated autoantigen complex formation and HMGB1 complexes are significantly up-regulated in both extracellular plasma and PBMCs of SLE patients. The objective of this study was to identify miR and other small RNA signatures that may be used as diagnostic biomarkers and potential therapeutic targets to limit either HMGB1 or TLR-induced inflammatory response in SLE.

Methods: Our pilot cohort consisted of four active female SLE patients meeting the revised criteria of the American College of Rheumatology and three age/sex matched healthy controls. Active disease was defined as a SLEDAI > 4 at the time of sample collection. Plasma-derived EVs were isolated by ultracentrifugation and small RNA libraries were prepared for RNA-sequencing (RNAseq). Global small RNA reads were analyzed and cross-referenced with a sequencing database (miR-Base) of known miRs. RNAseq reads with more or less than a 2-fold change when comparing healthy to SLE were characterized and considered statistically significant if $p < 0.05$.

Results: Analysis of our RNAseq data resulted in a large collection of statistically significant small RNA reads (< 25nt) that were up or down-regulated in SLE patients relative to healthy controls; 77% of these RNA reads were unique non-coding RNA sequences that did not align with a database of known miRs, which suggests that many of the SLE-associated small RNAs in EVs are long non-coding RNA (lncRNA), piwi interacting RNA (piRNA), or novel/undiscovered miRs. Conversely, 23% of the reads correlated with miRBase-aligned sequences for known miRs. Since our database analysis found that there are 47 predicted miRs targeting the 5030nt long mRNA sequence for HMGB1 and there are 121 known miRs predicted to target HMGB1, we cross-referenced our results to identify miRs that may inhibit its expression that were down-regulated in the plasma-derived EVs of SLE patients. Our analysis revealed that miR-142-3p, a previously characterized negative regulator of HMGB1, was down regulated over 15-fold in EVs from SLE patients when compared to healthy controls. In examining the dataset for miRs that may bind HMGB1 to facilitate EV trafficking, we found that let-7b-5p was up-regulated in SLE EVs more than 4-fold.

Conclusion: Our data demonstrate unique EV-derived small RNA signatures that may be targeted therapeutically or used as diagnostic biomarkers for SLE. Also, these results identify HMGB1-associated miRs that are dysregulated in SLE and a collection of miRs that may function as TLR7/8 agonists. Future studies will expand our cohort and validate miRs of interest in the context of HMGB1 and TLR7/8.

Disclosure: I. Okafor, None; N. A. Young, None; G. R. Valiente, None; E. Schwarz, None; P. Harb, None; C. Henry, None; W. Willis, None; E. Sullivan, None; K. Jablonski, None; L. C. Wu, None; N. I. Maria, None; A. Davidson, None; E. D. O. Roberson, None; W. Jarjour, None.

Single-Cell RNA-Seq Analysis of ANA+ Healthy and SLE Patients Show Variations in Activated Stress Response and Regulatory Pathways

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: One hallmark of the autoimmune disease Systemic lupus erythematosus (SLE) is the presence of antinuclear antibodies (ANAs). While the specificities and levels can indicate characteristics of SLE status, many individuals acquire ANAs either years prior to clinical diagnosis of SLE or fail to develop any further symptoms. At present, the mechanisms controlling further autoimmune progression in ANA+ healthy individuals remain unknown.

Methods: To ascertain potential differences in immune cell populations and/or their transcriptional state, we performed single cell RNA-seq on peripheral blood mononuclear cells from 30 patients, including African and European American individuals which were healthy ANA+ individuals with no other SLE criteria (n=10), active SLE patients (n=10), and healthy controls (n=10) with no autoantibodies. Transcriptomes were analyzed using canonical correlation analysis, followed cell population identification and by tSNE cluster visualization and differential gene expression within each cell population was assessed.

Results: Distinct cell population clusters could be identified for each of the disease classifications. EA ANA+ individuals showed an increase in the number of NK cells relative to SLE and healthy individuals while, in contrast, AA ANA+ individuals had lower numbers of NK cells. Specific populations of B cells could be identified for each disease classification in both AA and EA patients. For EA patients, stress response related genes such as *JUN* and *PPP1R15A* were upregulated in ANA+-specific B cells while SLE-specific B cells were marked by upregulation of pro-survival/proliferation genes such as *TCL1A*, *PCDH9* and *RALGPS2*. AA SLE patients demonstrated a proportional enrichment of plasma cells relative to both ANA+ and healthy individuals while *FCRL5*, a marker of dysfunctional B cells, was increased in SLE memory B cells. Overall, AA ANA+ cell populations showed an upregulation in a number of heat shock genes in ANA+ (*HSPA6*, *HSPA1A*, *DNAJB1*). Comparison of a list of candidate regulatory factors demonstrated dysregulation of several genes, including an upregulation of *TGFB* across all AA ANA+ cell clusters and a similar increase in CD46 in EA ANA+ clusters.

Conclusion: These data indicate that substantial transcriptional and cell population differences exist among immune cells from ANA+, SLE, and healthy individuals, including an apparent activated stress response programs in the cells from ANA+ individuals. Our results suggest that cells from ANA+ individuals may be actively regulating a response to autoantigen stimulation, whereas an exhaustion of that response may allow for transition to SLE.

Disclosure: M. C. Smith, None; S. Slight-Webb, None; S. R. Macwana, None; J. A. James, None; J. M. Guthridge, None.

BAFF Inhibition Attenuates Fibrosis in Bleomycin-Induced Scleroderma Model Via Modulating the Regulatory and Effector B-Cell Balance

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster I

Session Type: ACR Poster Session A

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

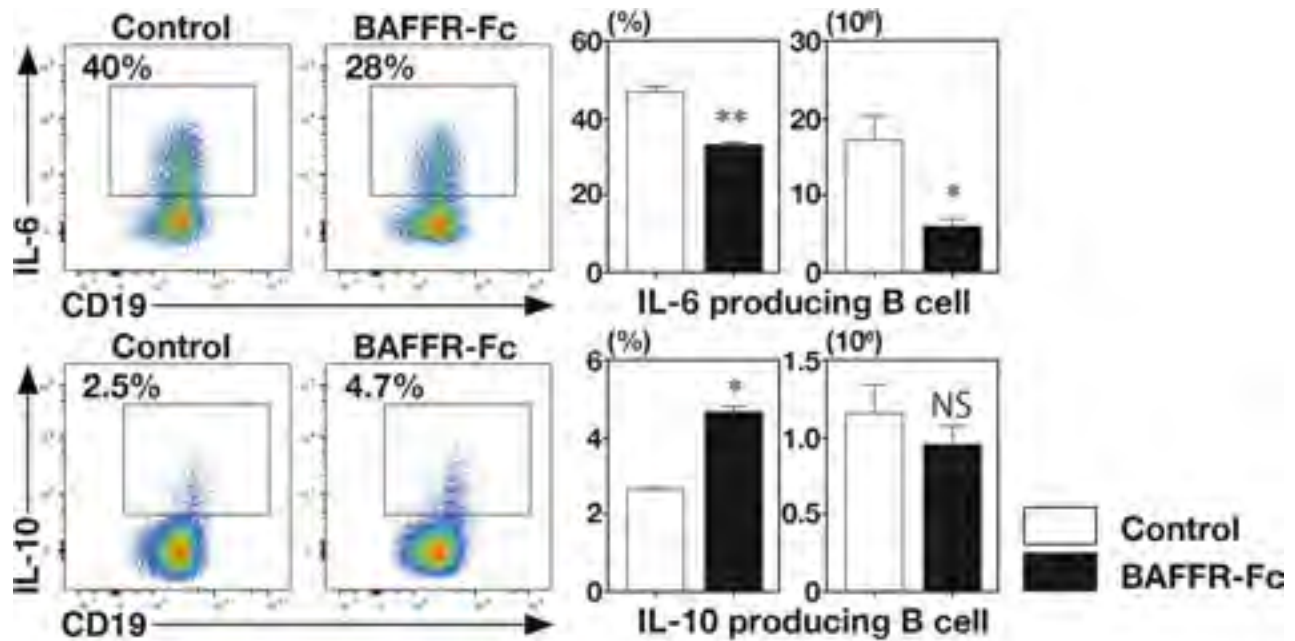


Figure 1

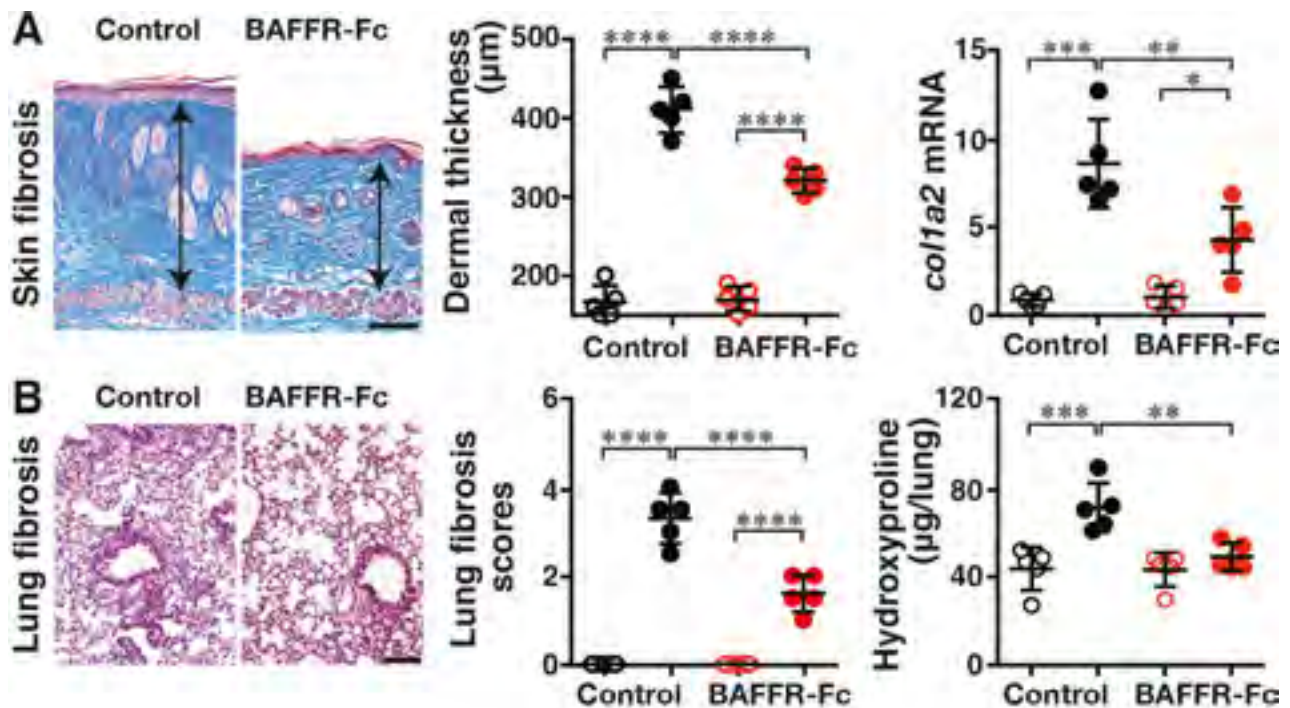


Figure 2

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune disease characterized by skin and lung fibrosis. Over 90% of patients with SSc are positive for autoantibodies. In addition, serum B cell activating factor (BAFF) level is correlated with SSc severity and activity. Thus, B cells are considered to play a pathogenic role in SSc. However, there are two opposing subsets: regulatory B cells (Bregs) and effector B cells (Beffs). IL-10-producing Bregs negatively regulate the immune response, while IL-6-producing Beffs positively regulate. Therefore, a protocol that selectively depletes Beffs would represent a potent therapy for SSc. The aim of this study was to investigate the roles of Bregs and Beffs in SSc, and to provide a scientific basis for developing a new treatment strategy targeting B cells.

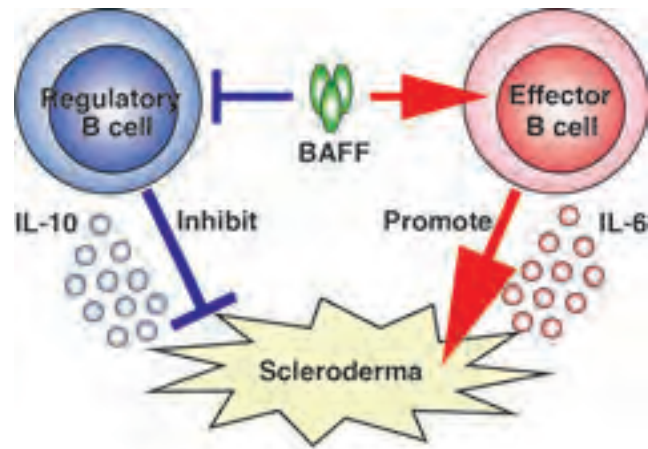


Figure 3

Methods: The bleomycin-induced scleroderma model was induced in the mice with a B cell-specific deficiency in IL-6 or IL-10. We also examined whether BAFF regulates cytokine-producing B cells and its effects on scleroderma model.

Results: Serum IL-6 levels gradually increased with the development of fibrosis in bleomycin-induced scleroderma mice, while serum IL-10 levels did not. IL-6-producing Beffs increased in Spleen and the inflamed skin of scleroderma model. The skin and lung fibrosis was attenuated in B cell-specific IL-6-deficient mice, whereas B cell-specific IL-10-deficient mice showed more severe fibrosis. BAFF stimulation increased Beffs and decreased Bregs. By contrast, BAFF antagonist (BAFFR-Fc) increased Bregs and decreased Beffs (Fig 1). Furthermore, BAFF antagonist attenuated skin and lung fibrosis in scleroderma model via modulating the regulatory and effector B-cell balance (Fig 2).

Conclusion: The current study indicates that Beffs play a pathogenic role in scleroderma model while Bregs play a protective role (Fig 3). BAFF inhibition is a potential therapeutic strategy for SSc via alteration of B cell balance.

Disclosure: T. Matsushita, None; T. Kobayashi, None; Y. Hamaguchi, None; M. Hasegawa, None; M. Fujimoto, None; K. Takehara, None.

Abstract Number: 112

Evidence for Altered Peroxisome Proliferator Activated Receptor (PPAR) Pathway Activity in a Transgenic Mouse Model of Scleroderma (TβRIIΔk-fib): Analysis of Mouse Skin, Lung and Explanted Cells

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SESSION INFORMATION

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Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster I

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

Background/Purpose: The T β RII Δ k-fib transgenic (TG) mouse model of scleroderma carries a fibroblast-specific TGF β receptor II mutation resulting in balanced up-regulation of TGF β signalling and replicates key fibrotic and vasculopathic features of scleroderma, including susceptibility to lung fibrosis and pulmonary hypertension. This study examines evidence of PPAR pathway perturbation in whole tissue or explanted cells from adult or neonatal TG mice compared with wildtype (WT) littermates. Lanifibranor (formerly known as IVA337) is a new chemical entity that activates all PPAR isoforms and is undergoing clinical trials in scleroderma at present.

Methods: Gene expression differences between whole skin biopsies, fibroblasts or aortic smooth muscle cells (aSMCs) from T β RII Δ k-fib and WT littermate mice (n=3 each group) were quantified using MouseRef-8v1.1 expression BeadChips (Illumina, USA). In total, 42 microarray gene expression profiles were analysed. After normalisation (global; Bioconductor Lumi), the genes were ranked according to differential expression. Data were expressed as pairwise analysis comparing the mean expression of two groups (t test), with FDR correction for multiple testing (number of tests/rank of p value). The PPAR pathway gene list obtained from http://software.broadinstitute.org/gsea/msigdb/cards/KEGG_PPAR_SIGNALING_PATHWAY was cross-referenced with each microarray. Within the GSEA cohort of genes the number with significant differential expression or a trend to difference (P<0.10) in analysis was determined. A total list of 12800 genes were tested.

Results: The genes within the PPAR pathway showing either significant difference (p<0.05) or trend of difference are summarised in Table 1 below. Overall, 11 genes showed significant difference between WT and TG explant cells and 82% (n=9) were reduced in the TG cells. 25 genes showed a trend of difference in ≥ 1 of the test substrates and the majority, 18 (72%), were down-regulated in TG mice. This suggested down-regulation of the PPAR pathway in the T β RII Δ k-fib mouse model. As shown in Table 1, there were most differences for the aSMCs and this is notable as the altered phenotype of these in culture is likely to reflect an altered in vivo environment, with elevated TGF β activity in the vessel wall rather than intrinsic SMC abnormalities; the SMC do not express the transgene.

Conclusion: As expected, whole tissue is less informative than explanted cells with whole skin showing no significantly differentially expressed genes. These results are not indicative of highly dysregulated PPAR pathway expression, although overall there is a signal that the PPAR pathway, assessed by GSEA, may be reduced in TG mice. This trend is seen most often in aSMC explant culture. This mouse model provides a potential platform for in vivo experiments to provide mechanistic support for trials of lanifibranor in scleroderma.

Table 1.

Adult whole skin	Adult whole lung	Adult skin cultured fibroblasts	Adult lung cultured fibroblasts	Neonatal skin cultured fibroblasts	Neonatal lung cultured fibroblasts	Aortic SMC culture
	ACADM ACSL4 PDPK1	ACADL RXRA	CPT1C SCD	ACAA1 ACSL1 CPT1C FABP5	ANGPTL4 APOA1 PDPK1	ACOX3 ANGPTL4 CPT2 FABP3 FABP5 FADS2 LPL NR1H3 PDPK1 PPARG SCP2

Italicised trend only (p<0.10), others p<0.05

Disclosure: E. C. Derrett-Smith, None; S. Xu, None; R. K. Hoyles, None; O. Lacombe, Inventiva, 3; P. Broqua, Inventiva, 3; J. L. Junien, Inventiva, 3; I. Konstantinova, Inventiva, 3; C. P. Denton, Roche, Actelion, GlaxoSmithKline, Sanofi-Aventis, Inventiva, SCL Behring, Boehringer-Ingelheim, Bayer., 5.

Abstract Number: 113

Epigenetic Changes in Dermal Fibroblasts By Inhibition of DOT1L Affect Cell Proliferation and Cell Cycle, but Have No Direct Effects on Collagen Deposition in in Vitro and In Vivo models of Fibrosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

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Session Type: ACR Poster Session A

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

Background/Purpose: Fibrosis is a key feature of systemic sclerosis, a devastating disease that is not well understood. The role of epigenetic factors in the pathophysiology is increasingly explored. Histone modifications such as histone methylation are dynamic epigenetic events that regulate signaling pathways and cellular processes. DOT1L is the unique H3K79-methyltransferase and methylates histone 3 at the Lysine residue at position 79. Inhibition of DOT1L in cartilage and bone has cell-type specific effects on Wnt-signaling, a pathway suggested to play an important role in fibrosis. We aim to study the role of DOT1L in fibrosis using different *in vitro* and *in vivo* models.

Methods: Primary cell cultures of healthy human dermal fibroblasts (breast and abdomen) were treated with DOT1L-inhibitor EPZ-5676 or vehicle for 14 days and stimulated with TGF- β after starvation. Smooth muscle alpha 2 actin (ACTA2) gene expression was measured by RT-qPCR. Western Blot was performed for dimethylated H3K79. Picrosirius Red staining measured collagen deposition. Proliferation was analyzed with 5-Bromo-2'-deoxy-uridine (BrdU) labeling. Flow cytometry was done using Propidium Iodide to analyze the cell cycle phases. Col1a2;Cre-ERT²;DOT1L^{fl/fl} mice (tamoxifen-inducible fibroblast specific DOT1L knockout mice) were injected subcutaneously with bleomycin (0.1mg) or vehicle (5 days/week, 4 weeks). Injected skin was analyzed by OH-proline assay for collagen content, and by histology for dermal thickness.

Results: The DOT1L-inhibitor EPZ-5676 reduced H3K79 dimethylation in all samples. DOT1L inhibition had a differential effect on ACTA2 expression: in breast dermal fibroblasts the increase of ACTA2 after TGF- β stimulation was reduced, while in abdominal dermal fibroblasts the increase of ACTA2 was more pronounced. After 48 hours of TGF- β , collagen deposition was higher in DOT1L-inhibitor exposed fibroblasts. After 72 hours of TGF- β stimulation however, collagen deposition was comparable between control and DOT1L inhibition. BrdU labeling assay showed more fibroblast proliferation with inhibition of DOT1L. Analysis of the cell cycle using flow cytometry revealed that DOT1L inhibition increased the proportion of cells in the G1/G0 phase, with fewer cells in S and M/G2 phase. *In vivo*, subcutaneous bleomycin increased dermal thickness and skin collagen content in mice. No difference was observed between mice with a conditional fibroblast-specific deletion of DOT1L or wild type mice.

Conclusion: In an *in vitro* model of fibrosis, the induction of ACTA2 with TGF- β in DOT1L-inhibited primary human dermal fibroblasts was dependent on the site of origin of the fibroblasts. DOT1L inhibition resulted in a more rapid increase in collagen deposition, but this did not result in detectable differences in collagen deposition at the end point of the experiments. DOT1L inhibition increased fibroblast proliferation but also led to a higher proportion of cells in the G0/G1 phase. In an *in vivo* murine model of skin fibrosis, no difference in bleomycin-induced skin thickness and collagen content was found when the DOT1L gene was deleted in fibroblasts.

Disclosure: N. Berghen, None; J. Cremer, None; E. de Langhe, None; R. Lories, None.

Abstract Number: 114

Antifibrotic Regulation By Response Gene to Complement 32 Protein

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

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Session Type: ACR Poster Session A

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

Background/Purpose: Pulmonary fibrosis is a serious problem in patients with scleroderma lung disease (SLD). Better therapies for pulmonary fibrosis are urgently needed. Identification of new therapeutic targets guides the development of innovative therapies for patients with pulmonary fibrosis. Previous research suggested that a protein termed Response Gene to Complement 32 (RGC-32) is involved in kidney fibrosis, but RGC-32 involvement in SLD or other forms of pulmonary fibrosis has not been explored in depth.

Methods: The levels of RGC-32 mRNA and protein in human lung tissues were studied by RNA-Seq, qRT-PCR, and Western blotting. A chronic bleomycin exposure model of pulmonary fibrosis was used to assess the effects of RGC-32 gene deficiency on collagen accumulation in the lungs *in vivo*. Experiments in primary human lung fibroblast cultures were used to investigate the effect of plasmid-based RGC-32 gene delivery on TGF- β -induced upregulation of collagen mRNA and protein.

Results: The RNA-Seq data suggested and qRT-PCR confirmed a significant decline in the levels of RGC-32 mRNA in the lung tissues of patients with SLD and idiopathic pulmonary fibrosis (IPF) compared with lung tissues from healthy controls. Similarly, RGC-32 protein levels were significantly decreased in SLD and IPF lung tissues based on western blotting analyses. These observations contrasted previous reports about RGC-32 involvement in several non-fibrotic diseases as well as in kidney fibrosis, all of which implicated elevated levels of RGC-32 in disease mechanisms. In an attempt to explain the striking difference between the commonly observed elevation of RGC-32 level in a variety of diseases and the observed decline in pulmonary RGC-32 mRNA and protein in patients with SLD and IPF, the possibility was considered that the decrease in RGC-32 in pulmonary fibrosis might be part of a failing protective feedback loop in which lower RGC-32 levels represent the organism's attempt to attenuate profibrotic signaling. To assess this possibility, germline-deficient (RGC-32^{-/-}) mice were challenged with bleomycin. The expectation was that if RGC-32 is a profibrotic mediator as suggested by the studies of kidney fibrosis, then RGC-32^{-/-} mice would be protected from bleomycin-induced fibrosis compared with their wild-type RGC-32^{+/+} strain background controls. However, RGC-32^{-/-} mice were not only not protected from fibrosis, but accumulated significantly more collagen in response to bleomycin challenge, indicating that RGC-32 acts protectively against fibrosis in the lungs. Further supporting this notion, overexpression of RGC-32 attenuated TGF- β -induced upregulation of collagen in primary human lung fibroblast cultures.

Conclusion: These combined data from human patients, the animal model, and cultured primary fibroblasts indicate that RGC-32 protects from fibrosis in the lung and that its loss in patients with SLD and IPF allows for a more severe fibrosis. Therapeutic restoration of pulmonary RGC-32 levels may be beneficial for patients with pulmonary fibrosis.

Disclosure: S. Atamas, None; V. Rus, None; V. Lockatell, None; H. Rus, None; I. Luzina, None.

Abstract Number: 115

CTLA4-Ig/CD86 Interaction on Cultured Human Fibrocytes and Fibroblasts from Systemic Sclerosis Patients

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SESSION INFORMATION

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Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster I

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Background/Purpose: CTLA4-Ig interacts with the cell surface costimulatory molecule CD86 and can downregulate the target cell activation [1]. Circulating fibrocytes (CFs) express markers of both hematopoietic cells (CD45, MHC class II) and stromal cells (collagen I and III), together with the chemokine receptors, which regulate their migration into inflammatory lesions (CXCR4, CCR2, CCR7) [2]. CFs can migrate into systemic sclerosis (SSc)-affected tissues and can differentiate into fibroblasts/myofibroblasts [2]. Skin fibroblasts (SFs) are involved in the excessive production of extracellular matrix (ECM) proteins which characterizes fibrosis in SSc [3].

The aim of the study was to compare CD86 expression on CFs, SFs and human macrophages (M) from SSc patients and to study the effects of CTLA4-Ig/CD86 interaction on SSc cultured CFs and SFs.

Methods: Peripheral blood CFs and M together with SFs were obtained from 8 “limited” cutaneous SSc patients (treated only with vasodilators, mainly cyclic prostanoids), after patient informed consent and local Ethics Committee approval for skin biopsies.

CFs and M were characterized by fluorescence-activated cell sorter analysis (FACS), for CD45, collagen type I (COL I), CXCR4, CD14, CD86, and HLA-DRII expression. After 8 days (T8) of culture, CFs were treated for 3 hrs and SFs were treated for 24 and 48 hrs, in the absence or in the presence of CTLA4-Ig (10, 50, 100 and 500 micrograms/ml).

Quantitative real-time polymerase chain reaction (qRT-PCR) for CD86 on CFs, SFs and M were performed. In addition, after CTLA4-Ig treatment, qRT-PCR for CD86, COL I, IL1beta, TGFbeta, α phaSMA, S100A4, CXCR2, CXCR4, CD11a was performed. The statistical analysis was carried out by the nonparametric Mann-Whitney U test.

Results: At gene level, SSc M highly expressed CD86 molecule. Notably, T8-cultured SSc CFs showed significantly higher CD86 gene expression, compared to SSc M ($p<0.05$). On the contrary, SSc SFs showed a very low CD86 gene expression, compared to both M and CFs (both $p<0.01$). After 3 hrs-CTLA4-Ig treatments, qRT-PCR of SSc CFs showed α phaSMA, COL I and CD11a gene expression significantly decreased ($p<0.01$, $p<0.05$ and $p<0.05$ respectively), whereas S100A4 gene expression resulted significantly increased ($p<0.01$), compared to untreated cells (CNT). CD86 and CXCR4 gene expression resulted decreased (not significantly) only after treatment with CTLA4-Ig 500 micrograms/ml. Otherwise, SSc CFs did not show any significant variations in TGFbeta, IL1beta and CXCR2 gene expressions, compared to CNT. SSc SFs treated with CTLA4-Ig did not show any significant modulation in the gene expression levels of CD86, compared to CNT.

Conclusion: In conclusion, CD86 expression on M and CFs in SSc patients might support their earlier and intensive activation in this disease when compared to resident SFs in the same patients. Therefore, SSc CFs seem to be more responsive to CTLA4-Ig treatment than SFs, thus a new therapeutic option for abatacept in SSc treatment should be taken into consideration based on its possible anti-fibrotic effect.

References: 1. Cutolo M et al. Arthritis Res Ther 2009;11:176-85; 2. Bucala R. Mol Med 2015;21:S3-5; 3. Asano Y. J Dermatol 2017; Epub ahead of print. Review.

Disclosure: M. Cutolo, Bristol Myers Squibb, 2; P. Montagna, None; S. Soldano, None; A. C. Trombetta, None; B. Ruaro, None; P. Contini, None; S. Paolino, None; C. Pizzorni, None; E. Alessandri, None; M. Patanè, None; A. Sulli, None; S. Scabini, None; E. Stratta, None; R. Brizzolara, None.

Abstract Number: 116

Identifying Matricellular Protein CYR61 As a Potential Anti-Fibrotic and Pro-Angiogenic Mediator in Scleroderma

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SESSION INFORMATION

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Background/Purpose: Vascular abnormalities represent a fundamental event in the pathogenesis of scleroderma (SSc) in that endothelial cell (EC) damage triggers a self-fueling process ending in pathological tissue fibrosis. In our previous study we identified CYR61 as a histone deacetylase 5-target gene in SSc ECs, and further confirmed its role in impaired angiogenesis in SSc. As CYR61 is also involved in fibrosis, we hypothesize that CYR61 is beneficial for SSc through its anti-fibrotic and pro-angiogenic properties. In this study, we examined the anti-fibrotic role of CYR61 in SSc fibroblasts, and also dissected the mechanism of its pro-angiogenic property in SSc ECs.

Methods: Dermal ECs and fibroblasts were isolated from biopsies from healthy subjects or patients with diffuse cutaneous SSc. CYR61 was determined by qPCR and ELISA. CYR61 was overexpressed using a CYR61 vector. Angiogenesis was assessed by an *in vitro* Matrigel tube formation assay. The scratch wound assay and gel contraction assay were used to evaluate fibroblast function. Cell proliferation was assessed by ki67 immunofluorescence, while superoxide production was measured using dihydroethidium. Cell senescence was analyzed by measuring p21. A t-test was used to compare differences between groups, and a p-value of <0.05 was considered significant.

Results: In both SSc ECs and fibroblasts, CYR61 levels were significantly lower compared to control cells. In SSc ECs, overexpression of CYR61 was accompanied with elevation of *NOS3* as well as increased secretion of CYR61 and VEGF. The cell surface receptor for CYR61 on ECs, integrin $\alpha v\beta 3$, was significantly elevated on SSc ECs. The proangiogenic properties of CYR61 was blocked by neutralizing antibodies for $\alpha v\beta 3$, as well as inhibitors for AMPK or AKT/NO signaling pathways. In SSc fibroblasts, overexpression of CYR61 led to significant decrease in profibrotic genes including *COL1A1* and *ACTA2* while increasing anti-fibrotic *PPARG*. CYR61 overexpression also resulted in increased secretion of matrix degrading MMP1 and 3, as well as pro-angiogenic VEGF. The anti-fibrotic effect of CYR61 was further demonstrated by delay in wound healing and inhibition of gel contraction. CYR61 led to early superoxide production followed by decrease in cell proliferation and cell senescence in SSc fibroblasts.

Conclusion: In this study we showed that deficiency in CYR61 potentially contributes to impaired angiogenesis and enhanced fibrosis in SSc ECs and fibroblasts. CYR61 overexpression in SSc ECs led to increase excretion of CYR61, which through binding to $\alpha\text{v}\beta 3$, activates the AMPK/AKT pathways to promote angiogenesis. CYR61 also induced pro-angiogenic VEGF expression to further increase its pro-angiogenic potential. In addition, CYR61-overexpressed SSc fibroblasts were converted from extracellular matrix-producing myofibroblasts into extracellular matrix-degrading senescent cells. Moreover, the ability of CYR61 to increase VEGF secretion in fibroblasts may modulate angiogenesis in SSc ECs. Taken all together, our data supports the beneficial role of CYR61 in SSc and warrants the use of CYR61 mimetics as a therapeutic option.

Disclosure: P. S. Tsou, None; D. Khanna, Eicos Sciences, 1,Pfizer, Inc., 2,Horizon, 2,BMS, 2,Actelion, 5,Bayer, 5,Bayer, 2, Corbus, 5,Cytos, 5,EMD Serono, 5,Genentech, Inc., 5,Sanofi-Aventis, 5,GSK, 5,Boehringer Ingelheim, 5; A. H. Sawalha, None.

Abstract Number: 117

Hypomorphic A20 Expression Modulates Fibrosis Susceptibility: Implications for Systemic Sclerosis?

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SESSION INFORMATION

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Background/Purpose: Multiple organ fibrosis, a hallmark of systemic sclerosis (SSc), remains poorly understood. Recent GWAS have uncovered consistent genetic linkage between TNFAIP3, encoding the ubiquitin-editing enzyme A20, and fibrotic SSc phenotypes. A20 has been previously implicated in negative regulation of innate immune cell activity, and hypomorphic variants are linked with autoimmunity in SLE, RA, IBD and Behcet syndrome. In view of its potential importance in SSc, we sought to characterize the regulation and role of A20 in the context of fibrosis and SSc pathogenesis.

Methods: We evaluated A20 expression in skin and lung biopsies from patients with SSc, and examined the effect of A20 gain- and loss-of-function in explanted human and mouse fibroblasts. Moreover, we generated transgenic mice with partial or fibroblast-specific deletion of A20, and analysed the effect on experimentally-induced fibrosis and associated transcriptome changes by RNA seq.

Results: Unbiased transcriptome analysis of SSc skin and lung biopsies revealed significantly decreased A20 levels and **robust anti-correlation with fibrotic TGF- β signaling ($r=-0.84$, $p<0.005$)**. Lesional skin myofibroblasts in SSc showed a notable absence of A20 expression. In vitro, A20 expression was markedly reduced in fibroblasts treated with TGF- β . Moreover, TGF- β abrogated the stimulation of A20 elicited by TLR4. Remarkably, ectopic A20 in skin and lung fibroblasts abrogated profibrotic responses and disrupted Smad signalling, and prevented myofibroblast differentiation in mesenchymal progenitor cells. Conversely, reduced A20 activity was associated with enhanced magnitude of fibrotic responses. A20 haploinsufficient mice, which show a partial reduction of A20 levels comparable to individuals harbouring A20 risk alleles, showed augmented bleomycin-induced skin and lung fibrosis, **increased tissue levels of F4/80, procollagen I and ASMA, and transcriptome signatures with altered fibrotic and inflammatory gene expression**.

Conclusion: We uncover a novel role for the SSc risk gene A20 as a fundamental checkpoint in modulating fibroblast activity and differentiation. Reduced A20 renders fibroblasts and transgenic mice susceptible to fibrosis. These observations suggest that reduced A20 in SSc patients carrying TNFAIP3 risk variants may underlie unchecked fibroblast activation and contribute to the pathogenesis of multiple organ fibrosis.

Disclosure: S. Bhattacharyya, None; W. Wang, None; B. M. Jeong, None; H. Abdala-Valencia, None; R. G. Marangoni, None; S. Berdnikovs Ph.D., None; J. Varga, BSM, 2,Pfizer, Inc., 2,Boehringer, 5,Mitsubishi, 5,Corbus, 5,Scleroderma Foundation, 6.

Pharmacological Inhibition of JAK/STAT Signaling By Tofacitinib Prevents Experimental Organ Fibrosis: Novel Therapy for Systemic Sclerosis

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Background/Purpose: Synchronous fibrosis in systemic sclerosis (SSc) leads to failure of the skin, lungs and other organs, and has no effective treatments. Myofibroblast activation underlies fibrosis in different organs, but the pathogenesis of fibrosis and the key extracellular cues driving the process remains poorly understood. Multiple intracellular pathways are triggered by cytokines and chemokines implicated in SSc. Of special interest is IL-6, which activates JAK/STAT signaling. A recent multi-ethnic GWAS identified strong associations of JAK-STAT variants with SSc. In order to illuminate the mechanisms linking these risk genes with disease pathogenesis, we investigated the IL6/JAK/STAT axis in SSc, and the effect of tofacitinib, a JAK/STAT inhibitor, in preclinical model of organ fibrosis.

Methods: We measured JAK/STAT expression and activity in SSc skin biopsies by immunohistochemistry and by unbiased transcriptome profiling. We defined a tofacitinib gene signature, and measured its activity in SSc. The effects of tofacitinib treatment were determined in explanted fibroblasts, and in a preclinical model of multiple organ fibrosis.

Results: We measured JAK/STAT expression and activity in SSc skin biopsies by immunohistochemistry and by unbiased transcriptome profiling. We defined a tofacitinib gene signature, and measured its activity in SSc. The effects of tofacitinib treatment were determined in explanted fibroblasts, and in a preclinical model of multiple organ fibrosis.

RESULTS: Expression of both phospho-JAK2 and phospho-STAT3 was significantly elevated in SSc skin biopsies (n=19) compared to matched healthy controls (n=10) (p<0.0001). Moreover, activated JAK/STAT expression showed significant negative correlation with pulmonary function (r=-0.48, p<0.01). We next analyzed gene expression signatures in transcriptome datasets comprised of 84 SSc and 12 healthy control skin biopsies, that clustered SSc biopsies into four distinct subsets. We found a significant correlation of the IL6/JAK/STAT signature (63 genes) with the inflammatory intrinsic subset, accounting for 40% of all SSc biopsies. The strength of an experimentally-derived “tofacitinib gene signature” of 39 genes was significantly reduced (p<0.001) in the same SSc biopsies, and was negatively correlated with TNF α and IFN α pathway scores. In fibroblasts, tofacitinib effectively inhibited induction of inflammatory and fibrotic genes induced by IL-6. Notably, tofacitinib treatment resulted in dramatic attenuation of bleomycin-induced skin and lung fibrosis in mice.

Conclusion: The JAK/STAT signaling pathway is markedly activated in a subset of SSc patients, and appears to contribute to disease progression. Blocking JAK/STAT activity with tofacitinib abrogates core fibrotic responses in fibroblasts, and prevents multiple organ fibrosis in mice. These results are the first to demonstrate that in SSc patients with genomic evidence of enhanced JAK/STAT pathway activity in target organs, tofacitinib treatment might be effective in slowing or reversing fibrosis.

Disclosure: S. Bhattacharyya, None; W. Wang, None; J. Wei, None; J. Varga, BSM, 2, Pfizer, Inc., 2, Boehringer, 5, Mitsubishi, 5, Corbus, 5, Scleroderma Foundation, 6.

Targeting Dysregulated CD38/NAD⁺ Homeostasis Mitigates Multiple Organ Fibrosis

Bo Shi¹, Wenxia Wang², Swati Bhattacharyya¹, Benjamin Korman³, Roberta Goncalves Marangoni¹, David Camp⁴, Paul Cheresch⁵, Guilherme de Oliveira⁶, Eduardo Chini⁷ and John Varga¹, ¹Northwestern University, Chicago, IL, ²Feinberg School of Medicine, Northwestern University, Chicago, IL, ³Department of Rheumatology, Northwestern University, Feinberg School of Medicine Scleroderma Program, Chicago, IL, ⁴Division of Pulmonary and Critical Care, Northwestern University, Chicago, IL, ⁵Northwestern University, CHICAGO, IL, ⁶Mayo Clinic of Medicine, Rochester, MN, ⁷Kogod Center on Aging, Mayo Clinic, Rochester, MN



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Background/Purpose: Persistent myofibroblast activation underlies unresolving multi-organ fibrosis in systemic sclerosis (SSc). We had shown that fibrosis is associated with reduced expression of NAD-dependent sirtuins (SIRT) 1 and 3. The activity of SIRT is determined by availability of NAD^+ , which in turn is regulated by CD38, the main NAD-consuming enzyme. We had shown that during chronological aging, up-regulation of CD38 drives cellular NAD^+ consumption, resulting in reduced SIRT activity, mitochondrial dysfunction, cellular metabolic collapse and senescence. We sought to test the hypothesis that biological aging is accelerated in SSc, and causes NAD^+ depletion and metabolic imbalance contributing to cellular senescence and fibrosis. We also hypothesize restoring NAD^+ homeostasis will prevent fibrosis in mouse model.

Methods: Expression and regulation of NAD^+ metabolic pathway enzymes and fibrotic pathway genes was examined in human and mouse SSc transcriptomes, tissue biopsies, and explanted fibroblasts. Cellular senescence was investigated by immunostaining. Fibrosis and inflammation induced by chronic subcutaneous bleomycin were examined in aged mice treated with the orally available NAD^+ precursor nicotinamide riboside (NR), and a novel potent and selective CD38 inhibitor (78c).

Results: The number of p16-positive senescent cells was elevated in SSc skin biopsies. Moreover, levels of CD38 transcript and protein were increased in SSc skin biopsies as well as explanted skin fibroblasts compared to matched controls. CD38 expression was also elevated in skin from mice with fibrosis. Notably, CD38 levels showed strong correlation with the TGF- β signature ($p < 0.0001$, $r = 0.42$) as well as Modified Rodnan skin score ($p < 0.003$, $r = 0.34$), while an anti-correlation with SIRT activity was observed. Overexpressing CD38 lowered cellular SIRT activity and augmented, while CD38 inhibition diminished, fibrotic responses in cultured fibroblasts. NR alone, or combined with the CD38 inhibitor 78c, abrogated TGF- β -mediated fibrotic responses and Smad-dependent transcriptional activity in fibroblasts. Treatment of aged mice with 78c alone, or combined with NR supplementation, attenuated fibrosis and inflammation in the skin and lungs. These anti-fibrotic effects were correlated with increased tissue levels of NAD^+ .

Conclusion: Expression of CD38 and other NAD-consuming enzymes is elevated in fibrotic skin. Elevated CD38 potentially causes cellular NAD^+ depletion and reduced SIRT activity with protein hyperacetylation. SIRT dysfunction in turn contributes to persistent fibroblast activation and senescence underlying unresolving fibrosis (Fig.1). Restoring NAD^+ homeostasis through CD38 inhibition and NR supplementation ameliorated fibrosis in mouse models and could represent a novel strategy for the treatment of SSc.

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Abstract Number: 120

An Orally Available Highly Selective 5-Hydroxytryptamine 2B Receptor Antagonist Ameliorating Pulmonary and Dermal Fibrosis in Preclinical Models of Systemic Sclerosis

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Background/Purpose: Serotonin or 5-hydroxytryptamine (5-HT) is well known as a stimulator of tissue fibrosis and a significant role of peripheral 5-HT_{2B} receptors in fibrosis has been suggested with the receptor being upregulated in fibrotic tissues. In addition, agonism of the 5-HT_{2B} receptor has been implicated in human tissue fibrosis caused by drugs known to activate the receptor. Pharmacologic inhibition of 5-HT_{2B} receptor signalling consequently represents a promising treatment strategy for fibrotic disorders including systemic sclerosis. 5-HT is released from platelets activated due to vascular damage, one of the first pathological events in systemic sclerosis. The local 5-HT concentration is increased and leads to activation of 5-HT_{2B} receptors on e.g. fibroblasts. This results in progression of myofibroblast differentiation leading to excessive extracellular matrix synthesis and eventually fibrosis. The objective of the present study was to evaluate a novel highly selective orally available 5-HT_{2B} receptor antagonist for its ability to reduce pulmonary and dermal fibrosis in the sclerodermatous chronic graft-versus-host disease model and dermal fibrosis in the tight-skin-1 model of systemic sclerosis.

Methods: The murine sclerodermatous chronic graft-versus-host disease (cGvHD) model was used to evaluate anti-fibrotic effects after therapeutic dosing of the 5-HT_{2B} receptor antagonist, AM1476. The compound was orally administered at 1, 10 and 30 mg/kg b.i.d. from day 21, several days after the first clinical signs of cGvHD, to day 49. Dermal thickness, myofibroblast counts, collagen production and number of phosphorylated Smad3 positive cells were used to evaluate dermal fibrosis. Effects on pulmonary fibrosis were measured using hydroxyproline content, Sirius Red staining and Ashcroft score. The tight-skin-1 model was used to evaluate anti-fibrotic effects after therapeutic treatment. AM1476 was orally administered at 10 mg/kg, b.i.d. from week 5 to week 10. Hypodermal thickening, myofibroblast counts and hydroxyproline content in skin biopsies were evaluated at the end of the treatment period.

Results: The 5-HT_{2B} receptor antagonist AM1476, significantly reduced all measured dermal and pulmonary fibrosis readouts in the cGvHD model using an oral therapeutic treatment approach. Therapeutic treatment of dermal fibrosis in the tight-skin model effectively and significantly reduced hypodermal thickening, number of myofibroblast and hydroxyproline content.

Conclusion: Inhibition of 5-HT_{2B} receptor activity resulted in pronounced anti-fibrotic effects in both pulmonary and dermal fibrotic tissues. The highly selective 5-HT_{2B} receptor antagonist AM1476 represents a promising drug candidate for treatment of fibrotic conditions and is currently in development for systemic sclerosis.

Disclosure: C. Wenglén, AnaMar AB, 3; H. Arozenius, AnaMar AB, 3; L. Pettersson, AnaMar, 3; G. Ekström, AnaMar AB, 3.

Abstract Number: 121

Inhibition of Nuclear Receptor Coactivator 3 Attenuates Fibrosis in Murine Models of Systemic Sclerosis

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Background/Purpose: Uncontrolled activation of fibroblasts releasing large amounts of extracellular matrix proteins is a key feature of systemic sclerosis (SSc). The nuclear receptor coactivators (NCOA) are named after their role as coactivators for nuclear hormone receptors, but are indeed modulating a large number of signaling pathways. In this study, we aimed to analyze whether targeting of NCOA3 may ameliorate fibrosis in preclinical models of SSc.

Methods: Fibroblasts were exposed to chronically high levels of TGF- β to mimic the situation in fibrotic diseases. The expression of different transcriptional cofactors in response to TGF- β stimulation was analyzed by quantitative real-time PCR. Protein levels were analyzed by Western Blot. Knockdown of NCOA3 was achieved via transfection with siRNA *in vitro*. For knockdown of NCOA3 *in vivo*, siRNA was premixed with atelocollagen for stabilization and injected subcutaneously at the site of bleomycin injections. Additionally, NCOA3 was targeted with the SRC3 inhibitor-2 (SI-2) in different murine models. The interaction of NCOA3 and TGF- β /SMAD signaling was analyzed by SMAD-responsive reporter as well as CoIP assays.

Results: SiRNA-mediated knockdown of NCOA3 strongly decreased the pro-fibrotic effects of TGF- β , with significant reductions in collagen protein, in the mRNA levels of *COL1A1* and *ACTA2* as well as significant decreases in the prototypical TGF- β target genes *PAIL* and *CTGF*. Knockdown of NCOA3 also ameliorated fibrosis in the bleomycin-induced dermal fibrosis model of SSc, with reductions of dermal thickening, of myofibroblast counts and of hydroxyproline content. Furthermore, pharmacological targeting of NCOA3 by the inhibitor SI-2 was able to ameliorate fibrosis in bleomycin-induced pulmonary fibrosis and in dermal fibrosis induced by overexpression of constitutively active TGF- β receptor type I (TBRI^{act}). Mechanistically, NCOA3 directly interacts with SMAD3 to promote TGF- β /SMAD3 signaling as shown by reporter studies and CoIP assays.

When we analyzed the expression levels of NCOA3 in SSc and in matched healthy individuals, we observed a modest, but statistically significant downregulation of NCOA3 expression, a phenotype that persisted also in cultured SSc fibroblasts. Stimulation of normal fibroblasts with chronically high levels of TGF- β also decreased the mRNA and protein levels of NCOA3. Given the profibrotic effects of NCOA3, the downregulation of NCOA3 in fibrotic SSc skin may be an endogenous regulatory attempt to counteract the increased activity of TGF- β /SMAD3 signaling.

Conclusion: We demonstrate in our study that inhibition of NCOA3 has profound anti-fibrotic effects and serves as a coactivator for the profibrotic effects of TGF- β /SMAD. Antagonizing NCOA3 augments an endogenous regulatory loop to reduce persistent fibroblast activation and tissue fibrosis in SSc.

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Abstract Number: 122

Metformin Inhibited the Development of Bleomycin-Induced Murine Scleroderma Via Restoring the Balance between Regulatory and Effector T Cells and Suppressing Spleen Germinal Center Formation

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Background/Purpose: Scleroderma is a multisystem connective tissue disease characterized by extensive tissue fibrosis and its three prominent cardinal features are vasculopathy, excessive collagen deposition and immunological abnormalities. Metformin (MET) has anti-inflammatory and anti-fibrotic effects. Therefore, we investigated the potential effect of metformin on fibrosis in a murine model bleomycin (BLM) of scleroderma.

Methods: A total of 50 mice were randomly divided into 5 group: MET treatment groups (200mg/kg, 100mg/kg, 50mg/kg), model group and control group. Scleroderma was induced in C57BL mice by subcutaneous injections of BLM daily, after 2 hours interval, different dose MET was intraperitoneally injected, while control group received with normal saline at corresponding time point. At the end of the fourth week, all mice were sacrificed and spleen tissues were collected for flow cytometry analysis. The skin samples were harvested for immunohistochemistry and quantify biological parameters (hydroxyproline content and RT-PCR).

Results: MET treatments markedly alleviated histopathological changes (dermal thickness and collagen deposition) and hydroxyproline contents compared with model group ($P < 0.05$). The abnormal differentiation of Th17 cells, Th1 cells, Th2 cells and follicular helper T (Tfh) cells was significantly inhibited by MET ($P < 0.05$), while the proliferation of Treg cells were upregulated ($P < 0.05$). Moreover, the expression levels of specific cytokines and transcriptions factors related to Th17 cells changed: interleukin-17A (IL-17A) and retinoic-acid-receptor related orphan receptors gamma t (ROR γ t) were decreased whereas fork head box protein 3 (Foxp3) was increased partly in a dose-depend manner. In addition, MET treatment inhibited spleen germinal center B cells formation ($P < 0.01$).

Conclusion: Our results indicate that MET can effectively alleviate the fibrotic disorders by modulating the balance between Treg cells and effector T cells and germinal center B cells formation.

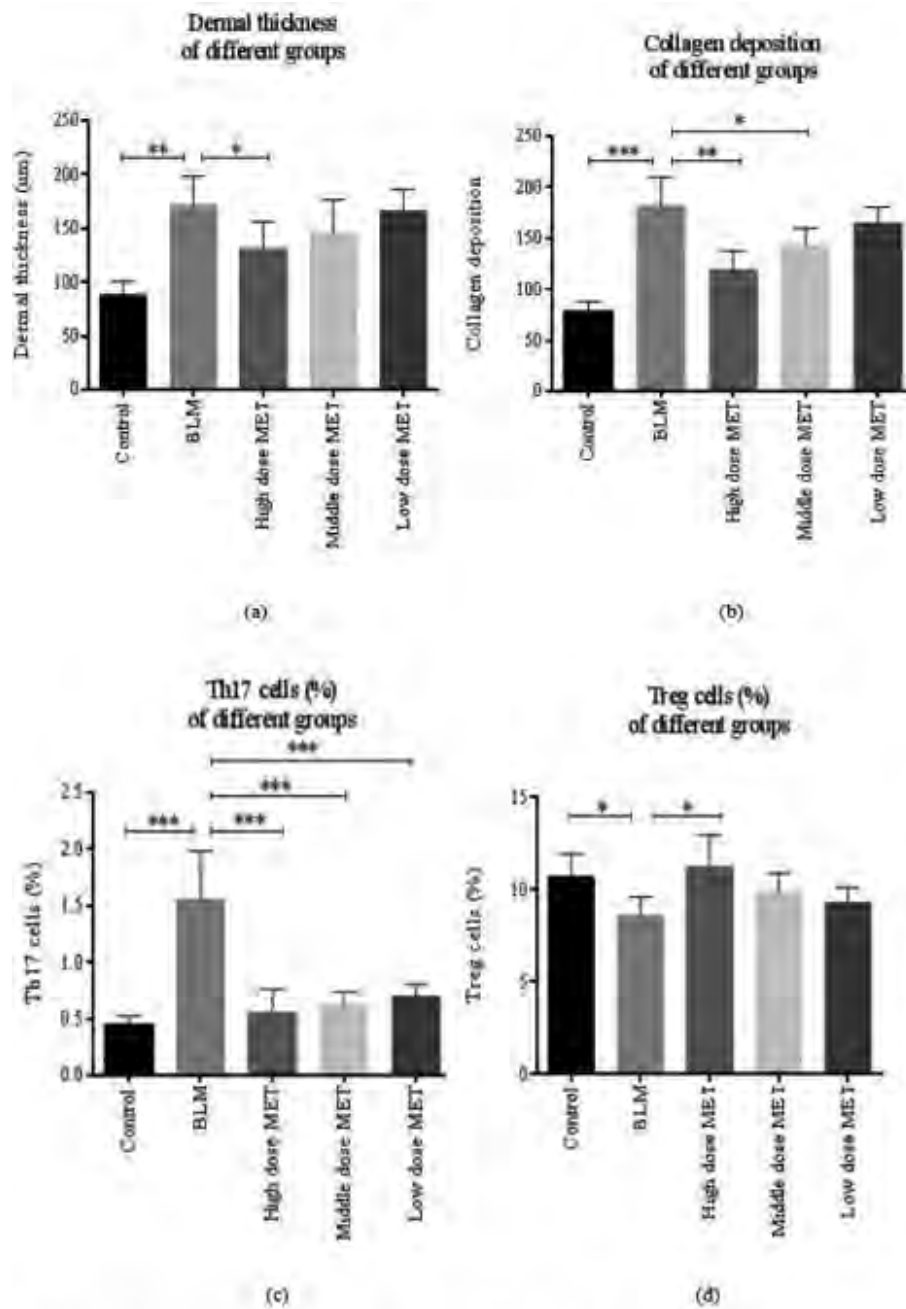


Figure legends. Therapeutic effects of metformin in BLM-treated mice. Scleroderma was induced in C57BL mice. Metformin (50mg/kg, 100mg/kg, 200mg/kg) was intraperitoneally injections in a 28 days. Mice were sacrificed in the end of the fourth weeks. Quantitative analysis of dermal thickness and collagen deposition in skin tissues

Disclosure: Y. Wang, None; Z. Liang, None; X. Zhao, None; C. Gao, None; J. Luo, None.

Non-Hematopoietic Derived TNF Drives Pulmonary Vasculopathy: A New Model of CTD-Associated Pulmonary Hypertension

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Session Type: ACR Poster Session A

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

Background/Purpose: Cardiopulmonary disease is a severe comorbidity in many connective tissue diseases (CTD). Rheumatoid arthritis, systemic sclerosis, and systemic lupus patients are all at increased risk of pulmonary complications and mortality secondary to these complications. Specifically, pulmonary arteriole vasculopathy can lead to right ventricle hypertrophy and eventually, right heart failure. Recently, TNF transgenic (TNF-Tg) mice with inflammatory erosive arthritis was described to have inflammatory interstitial lung disease with significant arteriole thickening, concomitant with right ventricle hypertrophy. However, the source of the pathogenic TNF in this model remains unknown. Thus, we performed adoptive transfer experiments to test the hypothesis that non-hematopoietic derived TNF mediates pulmonary vasculopathy in the setting of inflammatory arthritis.

Methods: Female TNF-Tg and WT littermates were treated with a 10 Gy split dose at 6 weeks of age, and syngeneic TNF-Tg or WT bone marrow was transferred back into the irradiated mice. Following bone marrow reconstitution, the mice were euthanized at 4-5 months of age for histology of the hearts and lungs. Histomorphometry was performed to assess, right ventricular (RV) area, lung cellular area, and pulmonary arteriole thickness.

Figure 1

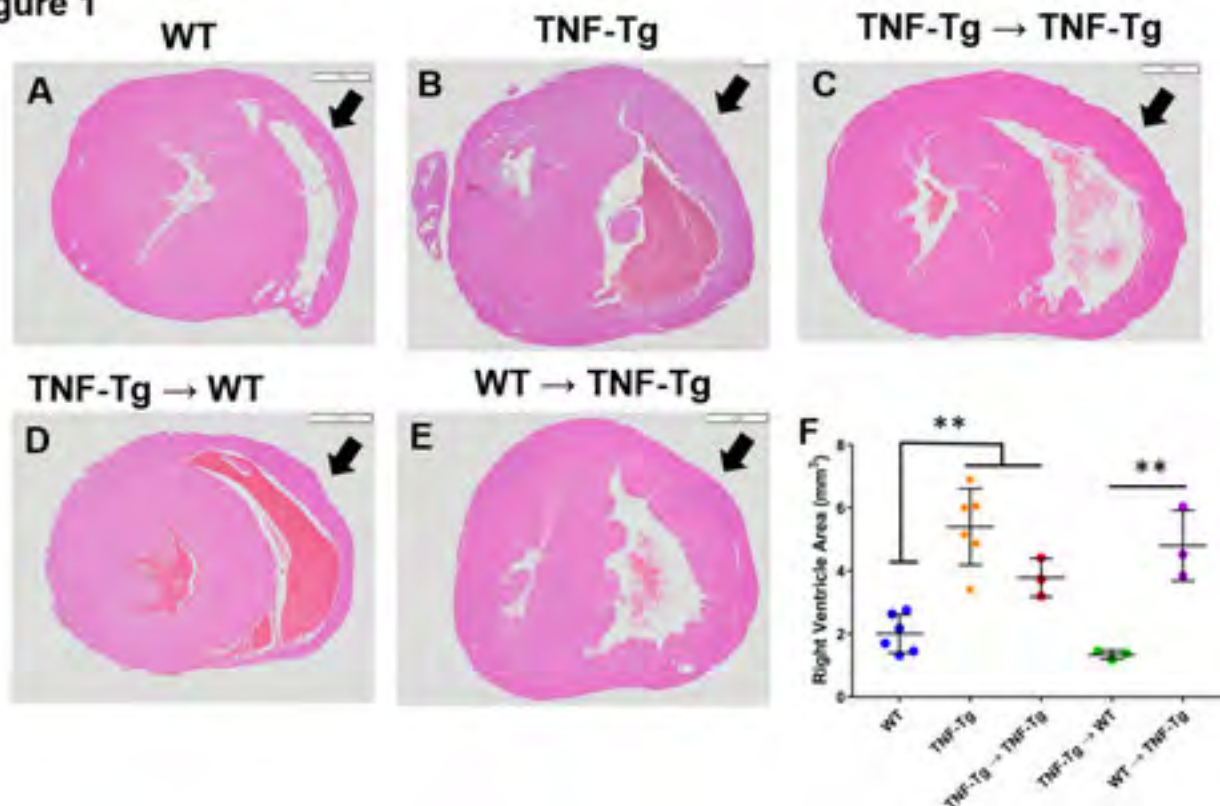
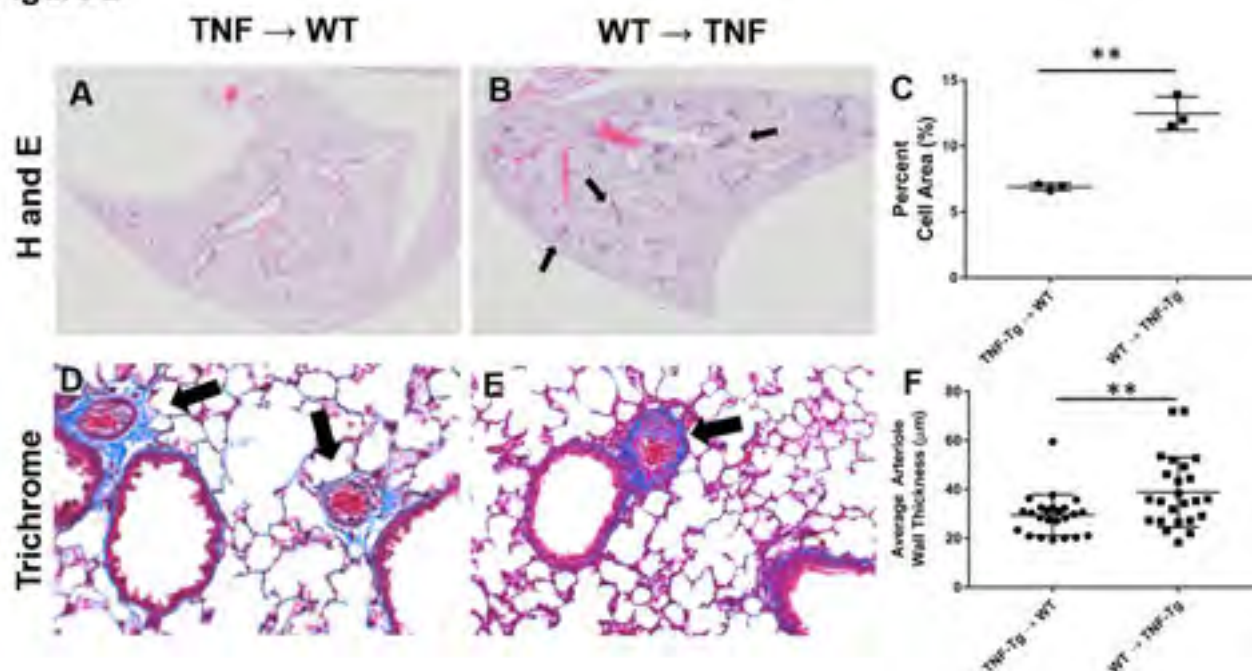


Figure 2



Results: Representative images (Figure 1A-E) of the hearts show an increase in RV area (Arrows) in the TNF-Tg and the TNF-Tg donor into TNF-Tg recipients (TNF-Tg → TNF-Tg) compared to the WT mice (5.4 ± 1.2 and 3.7 ± 0.6 vs 2.0 ± 0.6 mm², $p < 0.05$). However, the WT recipient of TNF-Tg bone marrow (TNF-Tg → WT) showed no signs of ventricular hypertrophy. In contrast, the TNF-Tg recipient of WT bone marrow (WT → TNF-Tg) displayed increased RV area compared to the TNF-Tg → WT mice (4.8 ± 1.1 vs 1.3 ± 0.1 mm³, $p < 0.05$). The lung cellular infiltrate is also reduced in the TNF-Tg → WT compared to the WT → TNF-Tg (Arrows, Figure 2 A-C, 6.8 ± 0.2 vs 12.5 ± 1.3 %, $p < 0.05$), as well as the pulmonary arteriole thickness (Arrows, Figure 2 D-E, 29.5 ± 8.4 vs 38.3 ± 14.2 μm, $p < 0.05$).

Conclusion: We have previously described significant cardiopulmonary disease in the TNF-Tg mouse. Here, we interrogated the role of the non-hematopoietic derived TNF to drive cardiopulmonary pathology associated with connective tissue disorders. These data suggest a critical role of tissue resident cells and their inflammatory profile in the development of vasculopathy and pulmonary hypertension.

Disclosure: R. Bell, None; M. D. L. L. Garcia-Hernandez, None; J. Rangel-Moreno, None; C. T. Ritchlin, AbbVie, Amgen, UCB, 2, AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer Inc, 5; H. Rahimi, None; E. Schwarz, None.

Abstract Number: 124

M10, a Small Fragment of the Hepatocyte Growth Factor Receptor, Attenuates Fibrotic Changes in a Murine Model of Scleroderma Lung Disease and in Human Lung Fibroblasts

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Interstitial lung disease (ILD) is the major cause of mortality among scleroderma (systemic sclerosis, SSc) patients. Extracellular matrix (ECM) deposition is a hallmark of this and other fibrotic lung diseases. TGFβ plays a crucial role in ECM gene expression via regulation of Ca²⁺/calmodulin-dependent protein kinases and matrix

metalloproteinases (MMPs). We recently demonstrated that M10 peptide, naturally derived from the cytosolic fragment of the hepatocyte growth factor receptor, blocks the TGF β -mediated canonical pathway via interaction with SMAD2 and reduces fibrosis *in vivo*. In this study, we investigate the efficacy of M10 in the regulation of intracellular Ca²⁺ levels, ECM proteins, and in the bleomycin-induced therapeutic mouse model of SSc-ILD.

Methods: Lung fibroblasts were derived from lung tissues of SSc patients and from matched normal lungs obtained at autopsy. Antifibrotic *in vivo* effects of M10 (10 mg/kg, intraperitoneal, every 48h) were studied in the bleomycin-induced therapeutic mouse model of SSc-ILD. Ca²⁺ was measured by FLIPR Tetra cellular screening system equipped with Molecular Devices ScreenWorks® software. Expression levels of collagen, connective tissue growth factor (CTGF, CCN2), fibronectin and tenascin were measured by immunoblotting and real-time PCR. Expression levels of matrix metalloproteinases (MMPs) were determined by human MMP antibody array. Statistical analysis was performed using GraphPad Prism 7 software.

Results: In both normal lung fibroblasts and SSc-ILD lung fibroblasts, an acute increase of intracellular Ca²⁺ was observed 15 sec following TGF β administration, with a second peak of delayed Ca²⁺ efflux at 60 sec. A high level of Ca²⁺ was maintained throughout the 10 min of the cellular screening process. In the presence of M10 peptide, TGF β -mediated Ca²⁺ was significantly ($p < 0.001$) reduced in both acute and delayed states maintaining overall lower amplitude. M10 peptide suppressed TGF β -mediated mRNA and protein expression of collagen I, CCN2, fibronectin, and tenascin. M10 peptide significantly induced the expression of MMP-10 in normal lung fibroblasts, whereas M10 peptide inhibited MMP-3 in SSc-ILD lung fibroblasts. In the bleomycin-induced therapeutic mouse model of SSc-ILD, M10 noticeably reduced collagen in lung parenchyma. A semi-quantitative evaluation of histopathology using the Ashcroft scale demonstrated a significant decrease in bleomycin-induced fibrosis in M10-treated mice as compared to mice treated with control (scrambled) peptide.

Conclusion: M10 peptide reduces ECM proteins, inhibits TGF β -mediated Ca²⁺ efflux and regulates MMPs demonstrating strong antifibrotic effects *in vitro* and *in vivo* in an animal model of lung fibrosis and should be considered as a potential therapeutic agent for systemic sclerosis and other fibrosing diseases.

Disclosure: T. Akter, None; I. Atanelishvili, None; A. Noguchi, None; G. S. Bogatkevich, None; R. Silver, None.

Abstract Number: 125

Monocyte Transcriptome Delineates SSc Patients with Functionally Distinct Patterns of Gene Dysregulation That Persist through Differentiation

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: The etiology and pathogenesis of SSc are poorly understood; however, an increasing body of evidence supports an early inflammatory phase that precedes, and may precipitate, fibrosis. Circulating monocytes are likely to play a role in the progression of SSc because they produce inflammatory cytokines, including interferon, that have previously been identified in SSc patients. Moreover, monocytes are precursors of macrophages that can reorganize the extracellular matrix (ECM), resulting in end-organ fibrosis.

Methods: We sequenced RNA from classical and nonclassical monocytes obtained from whole blood of patients enrolled in the Prospective Registry of Early Systemic Sclerosis (PRESS) cohort at one of 11 United States Scleroderma Centers and compared them with age-, sex-, and ethnicity-matched controls. The PRESS cohort includes patients with early (< 2 years' duration since first non-Raynaud symptom attributed to SSc) diffuse cutaneous SSc (swollen hands or sclerodactyly and at least one of the following: anti-topoisomerase I or anti-RNA polymerase III serum autoantibodies; proximal skin involvement; tendon friction rubs). Patients were 73% women, 67% white, and mean (SD) age was 51y (12); healthy

controls were 73% women, 67% white, and mean (SD) age was 52y (13). Skin biopsies collected through the Northwestern Scleroderma Patient Registry were used to examine gene expression in dermal myeloid cells.

Results: Based on RNA sequencing data from classical monocytes, we define three sub-groups of patients who are robustly delineated by upregulation of distinct functional pathways. Group 1 was defined by an interferon signature, group 2 exhibited marked increase in pro-inflammatory chemokines including CCL2 and proliferation markers, and group 3 samples upregulated genes associated with TGF β signaling and ECM remodeling. These sub-groups were recapitulated in nonclassical monocytes, although not all the same genes were up-regulated. Additionally, we found that expression of genes associated with monocyte maturation from classical to nonclassical phenotype differed in these three patient groups. Finally, we examined gene expression in myeloid cells isolated from the fibrotic skin of SSc patients and healthy control participants. Genes associated with patient groups 1 and 3 were generally more upregulated in patients than genes from group 2. This result bolsters previous findings regarding the importance of interferon and TGF β signaling in SSc skin disease and illustrates a relationship between disease-specific gene expression during maturation from blood-borne monocytes to tissue-resident myeloid cells.

Conclusion: Our study confirms the role of monocytes in SSc pathogenesis through the dysregulation of genes that have been previously reported in SSc patients. Future studies will integrate longitudinal data in order to determine whether the gene expression that defined patient groups in our study is stable over time and whether it predicts patient response to specific therapies.

Disclosure: J. L. M. Dunn, None; P. J. Homan, None; S. Dominguez, None; C. M. Cuda, None; K. Aren, None; M. A. Carns, None; T. M. Frech, None; D. Khanna, Eicos Sciences, 1, Pfizer, Inc., 2, Horizon, 2, BMS, 2, Actelion, 5, Bayer, 5, Bayer, 2, Corbus, 5, Cytos, 5, EMD Serono, 5, Genentech, Inc., 5, Sanofi-Aventis, 5, GSK, 5, Boehringer Ingelheim, 5; S. Assassi, Biogen Idec, 2, Bayer, 2, Boehringer Ingelheim, 2, 5, Momenta, 2; H. Perlman, Galvani, 5; M. Hinchcliff, None; D. R. Winter, None.

Abstract Number: 126

Direct Interaction between Autoreactive B Cells and Endothelial Colony Forming Cells Induces Cytokine Production from B Cells through B Cell Receptor and IL-6-JAK2-STAT3 Signaling Pathway, Suppressing Proliferation of Endothelial Colony Forming Cells in Systemic Sclerosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Systemic sclerosis (SSc) is a connective tissue disorder that is characterized by fibrosis and vascular damage in the skin and other visceral organs, with an autoimmune background. One of the cause of vasculopathy is thought to be the repair dysfunction of damaged vessels. Actually, endothelial progenitor cells in peripheral blood mononuclear cells (PBMCs) of SSc were reported to be reduced. However, the mechanism of these reduction is unclear. Recent studies have indicated that B cells play critical roles in systemic autoimmunity and disease expression through various functions such as activation of other immune cells in addition to autoantibody production. Several studies have also shown that B cells activated in SSc produce IL-6, which induces fibrosis. Indeed, Rituximab (RTX), a B cell depleting antibody, or Tocilizumab (TCZ), anti-IL-6 receptor (IL-6R) antibody, can ameliorate many autoimmune diseases including SSc. Here, we focused on the relationships between endothelial colony forming cells (ECFCs), and autoantigen-reactive B cells in SSc.

Methods: In SSc patients treated with RTX, TCZ, or oral steroid, we analyzed nailfold capillary changes over time. We also compared the number of ECFCs in PBMCs before and one year after treatment. In mouse study, we assessed the relationship between Topo I reactive B cells and ECFCs with or without contact, using topo I and complete Freund's adjuvant-induced SSc model mice (Topo I model). We also analyzed activated signaling pathway after contact with Topo I reactive B cells and ECFCs. Finally, the effect of B cell depletion treatment or anti-IL-6R antibody treatment to vasculopathy and ECFCs in Topo I model mice was assessed.

Results: Both B cell depletion treatment and anti-IL-6R antibody treatment improved ulcer healing, promoting neovascularization. The number of ECFCs in PBMCs of SSc patients, which was reduced before treatment, increased after one year of RTX treatment or TCZ treatment. In particular, the number of ECFCs after RTX treatment increased as many as healthy controls. In Topo I model mice, the number of ECFCs was reduced compared with controls. The experiment with recombinant cytokines or neutralizing antibody revealed that this reduction of ECFCs is caused by cytokines such as IL-6, TNF- α , CCL3, and CCL4 from Topo I reactive B cells, which were activated by direct interaction with ECFCs. In contrast, IL-10 production, which promotes colony formation of ECFCs, from Topo I reactive B cells was reduced compared with Topo I non-reactive B cells. This direct interaction activates B cell receptor (BCR) pathway such as SYK, BTK, PLC γ 2, TRAF6, and NF- κ B. In Topo I reactive B cells, IL-6-JAK2-STAT3 pathway is also activated. These results suggest that activated both BCR pathway and IL-6-JAK2-STAT3 pathway are crucial in activation of Topo I reactive B cells and suppression of ECFCs. Finally, both B cell depletion and anti-IL-6R antibody treatment also increased ECFCs, suppressing vasculopathy in Topo I model mice.

Conclusion: Decreased number of ECFCs is closely related to vasculopathy of SSc. Autoreactive B cells, these signaling pathways, cytokines, and drugs which can increase ECFCs can be novel therapeutic targets in vasculopathy of SSc.

Disclosure: T. Fukasawa, None; A. Yoshizaki, None; S. Ebata, None; K. Nakamura, None; Y. Asano, None; Y. Kazoe, None; K. Mawatari, None; T. Kitamori, None; S. Sato, None.

Abstract Number: 127

MiR-3606-3p Inhibits Systemic Sclerosis through Targeting TGF- β Receptor II

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Though transforming growth factor- β (TGF- β) plays a fundamental role in the pathogenesis of SSc, the mechanism by which TGF- β signaling acts in SSc remains largely unclear. The aim of this study is to clarify the underlying mechanism of TGF- β signaling over-activation in SSc, especially epigenetic manners.

Methods: Twenty SSc patients and twenty-one age, gender-matched healthy individuals were enrolled in this study. Luciferase analysis was used to evaluate the binding capacity of miRNA-3606-3p to TGFBR2. Western blot and qPCR were used to detect the expression of miRNA, TGFBR2, p-SMAD2/3 and collagen.

Results: Transcription level of *TGFBR2* was increased in both SSc skin samples and fibroblasts (**Fig. 1A and 1B**). In contrast, miR-3606-3p, a predicted miRNA of TGFBR2, was downregulated in SSc fibroblasts and skin tissues (**Fig. 1C and 1D**).

Based on the above findings, we then determined whether *TGFBR2* is the direct target for miR-3606-3p. Three *TGFBR2* 3'-UTR wild type-containing binding sites (site 1, site 2 and site 3) of miR-3606-3p were subcloned into the pmirGLO vector, and co-transfected with a luciferase construct containing miR-3606-3p mimics into primary dermal fibroblast cells. As illustrated in **Fig. 1E**, the relative luciferase activity was only significantly decreased in the *TGFBR2* 3'-UTR wildtype site 3 group, whereas there was no significant difference in the *TGFBR2* 3'-UTR wild type site 1 or site 2 group, suggesting that miR-3606-3p may selectively bind to the sequence containing site 3 of the *TGFBR2* 3'-UTR. Furthermore, overexpression of miR-3606-3p significantly diminished the level of *TGFBR2* mRNA (**Fig. 1F**) and TGFBR2 protein (**Fig. 1G**).

Next, we examined whether the repression of TGFBR2 mediated by miR-3606-3p would disrupt TGF- β /Smad signaling in fibroblasts. Western blot analysis showed that the transfection of primary fibroblast cells with miR-3606-3p mimics significantly reduced the protein levels of type I collagen and p-SMAD2/3 (**Fig. 1H**). We then analyzed the expression of type I collagen and p-SMAD2/3 in response to *TGFBR2* downregulation in the fibroblasts. Interestingly, siRNA-induced *TGFBR2* downregulation revealed similar results to those obtained via miR-3606-3p overexpression in the fibroblasts (**Fig. 1I**).

Conclusion: Our findings demonstrated that increased TGFBR2 could be responsible for the hyperactive TGF- β signaling observed in SSc. We identified a pivotal role for miR-3606-3p in SSc, which inhibits TGF- β signaling, at least partly, through TGFBR2 repression. The results suggest that the regulation of miR-3606-3p/TGFBR2 could be a promising therapeutic strategy for treatment of fibrosis.

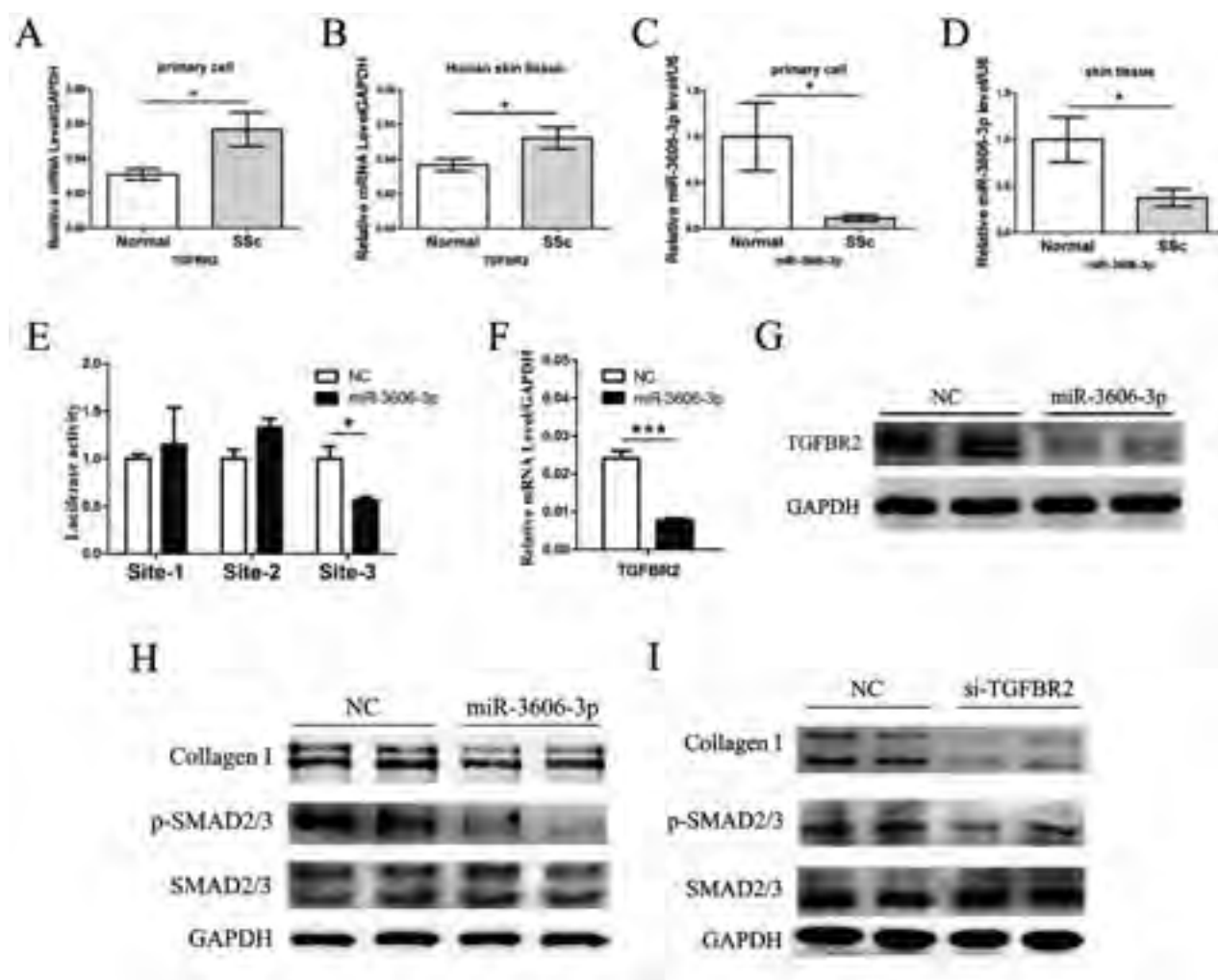


Figure 1

Disclosure: X. Shi, None; Q. Liu, None; W. Tu, None; X. Mei, None; L. Jin, None; W. Wu, None; J. Wang, None.

Abstract Number: 128

Inhibition of Prolyl-tRNA Synthetase As a Novel Therapeutic Target for Systemic Sclerosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Prolyl-tRNA synthetase (PRS), a member of aminoacyl tRNA synthetases (ARS), is an enzyme that conjugates amino acid proline to its tRNA to generate prolyl-tRNA to be used in protein synthesis. Since proline is one of major components of collagen, we hypothesized that suppression of PRS would down-regulate collagen synthesis, which could be beneficial in fibrosis. Systemic sclerosis (SSc) is an autoimmune disease that is characterized by progressive thickening of skin, caused by excessive accumulation of collagen.

Methods: Inhibitory activity of DWN12088 against PRS was assessed by aminoacylation assay. Fibroblasts were treated with DWN12088 either before or after treatment of transforming growth factor beta (TGF β), and then collagen and pro-fibrotic markers were assessed using western blot. 3D skin organoid was constructed using systemic sclerosis patient-derived dermal fibroblast and keratinocyte. For in vivo study, constructed patient-derived 3D skin organoid was engrafted to SCID mouse using tie-over dressing. After 2 weeks administration of DWN12088, degree of dermal thickness and collagen I (Col I) expression were determined by histological analysis.

Results: To validate our hypothesis, we investigated the expression levels of pro-fibrotic markers by overexpression or knockdown of PRS in vitro. We showed that PRS is closely related to the expression of Col I and alpha smooth muscle actin (α SMA). Interestingly, PRS protein expression is significantly increased in lung tissue of idiopathic pulmonary fibrosis (IPF) patients. We developed a novel selective inhibitor of PRS, DWN12088, which has IC₅₀ value of 74 nM against PRS. DWN12088 reduced TGF β -induced Col I and pro-fibrotic marker expression in various cell-lines and primary fibroblasts. This suggests that PRS may be a critical contributor of excessive accumulation of collagen, a main pathological hallmark of fibrosis. Using systemic sclerosis patient-derived dermal fibroblast, we developed 3D skin organoid in order to investigate efficacy of DWN12088. In this model, DWN12088 successfully decreased skin thickness, Col I, and α SMA. In a mouse xenograft model using the patient-derived 3D skin organoid, treatment of 10 mg/kg DWN12088 also showed decrease in skin thickness and collagen expression compared to control group.

Conclusion: PRS is an enzyme required during protein translation involving proline amino acid. In fibrotic condition, we observed that PRS is overexpressed, which may be responsible for over-production of collagen. Inhibition of PRS successfully inhibited formation of collagen and expression of pro-fibrotic markers in various cellular systems, systemic sclerosis patient-derived skin organoid model, and its mouse xenograft model. Therefore, DWN12088, a novel PRS inhibitor, may serve as a potential therapeutic agent in systemic sclerosis and other fibrotic diseases.

Disclosure: C. H. Lee, Daewoong Pharmaceuticals, 3; S. J. Yoon, Daewoong Pharmaceuticals, 3; M. Cho, Daewoong Pharmaceuticals, 3; J. S. Park, Daewoong Pharmaceuticals, 3; Y. Kim, None; J. H. Ju, None; D. J. Bae, None; C. S. Park, None; J. H. Kim, None; S. Kim, None; B. Lee, Daewoong Pharmaceuticals, 3.

Abstract Number: 129

Rnaseq Analysis of Human Skin in Organ Culture Identifies Collagen 22A1 As a TGF- β Early Response Gene

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Systemic sclerosis (SSc) is a complex multi-system autoimmune disease characterized by immune dysregulation, vasculopathy, and organ fibrosis. Skin fibrosis causes high morbidity and impaired quality of life in affected individuals. In this study, we identified genes that may be involved in the development of dermal fibrosis mediated by TGF- β in human skin maintained in organ culture.

Methods: To identify new genes regulated by TGF- β in human skin, we performed high-throughput RNA sequencing using ex vivo human skin samples treated with TGF- β or a vehicle control. We identified genes whose expression is altered in

human skin treated with TGF- β . Of these genes, COL22A1 showed the highest level of differential expression. The expression levels of COL22A1 and its time-dependent changes were evaluated using real-time PCR and immunoblotting (IB) in *ex vivo* human skin tissues and *in vitro* in normal human dermal fibroblasts. To investigate which TGF- β signaling cascades are involved in the induction of COL22A1 expression, normal skin fibroblasts were cultured with TGF- β in combination with specific inhibitors. Since COL22A1 was an early response gene, we sought to assess its role in the TGF- β -mediated response, thus normal skin fibroblasts were transfected with COL22A1 siRNA and then stimulated with TGF- β . Furthermore, we compared mRNA and protein levels of COL22A1 in skin fibroblasts from control donors and patients with the diffuse cutaneous form of SSc by using real-time PCR and IB.

Results: COL22A1 was most differentially expressed and its levels were significantly increased by TGF- β *ex vivo* and *in vitro*. TGF- β caused a significant increase in the expression levels of COL22A1 at earlier time points than other fibrosis associated genes. Further, TGF- β -induced COL22A1 expression was abrogated by ALK5 and MEK inhibition. Silencing of COL22A1 significantly reduced TGF- β -induced ACTA2 expression. Dermal fibroblasts from patients with diffuse cutaneous SSc showed significantly increased expression levels of COL22A1 compared with normal skin fibroblasts.

Conclusion: In conclusion, our findings suggest that the increased expression of COL22A1 is associated with the pathogenesis of fibrosis in SSc, and that the regulation of COL22A1 expression may have important implications for skin fibrosis. These results contribute novel insights into genes regulated under pro-fibrotic conditions in human skin, providing direct relevance to human dermal fibrosis.

Disclosure: T. Watanabe, None; L. Mlakar, None; J. Heywood, None; W. da Silveira, None; G. Hardiman, None; C. A. Feghali-Bostwick, GSK, Biogen, BMS, iBio Inc, 2, 7.

Abstract Number: 130

The Role of Cofilin, an Actin Associated Protein, in Activation of Systemic Sclerosis Vascular Smooth Muscle Cells

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by activation of the immune system, vascular dysfunction and tissue fibrosis. Vascular dysfunction in SSc is one of the most prominent features of the disease that generally manifest as Raynaud's phenomenon and vascular wall proliferation resulting in progressive fibro-proliferative vasculopathy seen in all involved organs. There is evidence for increased vascular smooth muscle cell (vSMC) proliferation, migration and resistance to apoptosis in SSc. In this study, we wished to understand the role of cofilin signaling pathways involvement in SSc-vSMC dysfunction. Cofilin is a member of the actin associated proteins that accelerates actin depolymerization at pointed ends and severs long actin filaments. It plays a crucial role in cell migration by promoting the rapid turnover of actin filaments through severing filamentous actin (F-actin) and depolymerizing actin filaments from the pointed end. Cofilin is inactivated by phosphorylation through LIM-Kinases (LIMK), and activated by dephosphorylation mediated by Slingshot phosphatases (SSH-1).

Methods: We isolated vSMC from 4mm punch skin biopsies from 3 patients with diffuse cutaneous SSc (dcSSc) and 3 healthy controls. We examined the expression levels of P-cofilin, total cofilin, P-LIMK and Total LIMK by western blot analysis. We used insulin at a concentration of 5nM, which activates LIMK by phosphorylation, to evaluate the effect of cofilin on vSMC migration that was examined by the scratch test assay.

Results: We demonstrate significant increase in SSc-vSMC migration compared to control cells that was noted at 2 hours and continued for 48 hours, with an average increase migration of 2.1 fold at 24 hours. The expression ratio of P-cofilin to total cofilin was 3.7 and 0.3 in control-vSMC and SSc-vSMC, respectively ($P < 0.01$). We also noted decreased ratio of phosphorylation of LIMK in SSc-vSMC (0.21) compared to control vSMC (0.55, $P < 0.01$). The addition of insulin increased the ratio of phosphorylation of LIMK by 2 folds at 24 hours, which was associated with 6 fold increase in phosphorylation of cofilin. Moreover, *in vitro* treatment of vSMC with insulin decreased SSc-vSMC migration potential and reverted SSc-vSMC migration to a pattern similar to control vSMC.

Conclusion: We provide an experimental evidence for the role of cofilin in increased migration of SSc-vSMC, which contribute to the abnormal phenotype of SSc-vSMC. We report *activation* of cofilin in SSc-vSMC as shown by decrease P-

cofilin in association with inactivation of LIMK by decreased P-LIMK levels in the cells. Furthermore, the addition of insulin activates LIMK by phosphorylation, which in turn inactivates cofilin. Indeed, the addition of insulin to SSc-vSMC cultures resulted in reduced SSc-vSMC migration to a level comparable to control vSMC migration rate.

Disclosure: S. Nada, None; B. Kahaleh, None; N. Altorok, None.

Abstract Number: 131

Myofibroblast Cells Expression of CD248 May Contribute to Exacerbate Microvascular Damage during Systemic Sclerosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

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Session Type: ACR Poster Session A

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

Background/Purpose: Microvascular rarefaction and tissue fibrosis are the hallmarks of Systemic Sclerosis (SSc). CD248, also known as endosialin, is a transmembrane glycoprotein expressed on key effector cells within the stroma of fibrotic tissue, including pericytes and fibroblast (FBs). The functional role of CD248 during fibrotic process is largely unknown, although it has been reported that in the experimental models of liver and kidney fibrosis, CD248^{-/-} mice are protected from myofibroblast accumulation and capillary rarefaction, probably inhibiting pericytes differentiation toward α SMA⁺ myofibroblasts. On these bases, CD248 may be considered an attractive therapeutic target in the pathologic processes in which vascular damage and fibrosis are strongly joined, as observed in SSc. The aim of this work was to investigate the expression of CD248 isoforms, in dermal fibroblasts and evaluate the functional contribute of this molecule to exacerbate the microvascular damage during SSc.

Methods: After ethical approval, skin biopsies were collected from SSc-patients and healthy controls (HC). CD248 expression was investigated in the skin and in cultured FBs before and after TGF β treatment, by immunohistochemistry, qRT-PCR and western-blot. Additionally, we assessed the role of CD248 expression on angiogenesis by employing endothelial cel/SSc-FBs organotypic cocultures where FBs were treated or not with lentiviral induced CD248 short-hairpin RNAs delivery.

Results: CD248 expression was increased in perivascular cells and fibroblasts in SSc-skin. We identified 2 different isoforms of CD248 molecule, one short isoform, which has been generally correlated with the activated status of CD248, and one long isoform. Both the isoforms were significantly increased in SSc-FBs compared to HC-FBs, with the short isoform was not expressed at all in HC-cells. TGF β treatment of SSc-FBs induced a significant increase of CD248 expression. Functionally, SSc-FBs, SSc-FBs, overexpressing CD248, suppressed angiogenesis in the organotypic model and, after silencing this molecule, the angiogenic phenotype was rescued.

Conclusion: The over-expression of short isoform of CD248, increased after TGF β treatment, may play a role in fibrotic process by modulating the molecular pathways leading to dermal FBs differentiation toward myofibroblast, responsible of the impaired extracellular matrix production and interfering with endothelial cells tube formation. The CD248 silencing may prevent these angiogenic alterations. Future study, targeting CD248, may open new therapeutic strategy to inhibit both myofibroblasts generation and microvascular damage.

Disclosure: P. Di Benedetto, None; R. Ross, None; P. Cipriani, None; F. Esteves, None; V. Liakouli, None; P. Ruscitti, None; F. Carubbi, None; O. Berardicurti, None; N. Panzera, None; S. Di Bartolomeo, None; C. Galloni, None; G. Mavria, None; F. Del Galdo, None; R. Giacomelli, None.

Novel Therapeutic Peptides Which Target CD206 Inhibit Macrophage Dependent Fibroblast Activation in Scleroderma

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Alternatively activated macrophages expressing CD206 are believed to promote fibrosis in a range of disorders including systemic sclerosis (SSc). Novel therapeutic peptides (RP) which enter the cell by binding CD206 may selectively inhibit this population of cells. We investigated the potential for RP peptides to suppress fibrosis in experimental mice and in model systems using SSc derived macrophages. sCD206 and CD206 cell surface expression were evaluated as biomarkers in SSc.

Methods: RP therapeutic peptides 10mg/kg were administered by twice daily subcutaneous injection during dermal and lung bleomycin fibrosis models, in wild type C57BL/6 female mice (n=10 mice per group). SSc macrophage viability was assayed by Presto Blue assay. SSc macrophage-fibroblast cross-talk was modelled using transfer of media followed by qPCR for collagen I. sCD206 was assayed by ELISA in plasma (n=40 healthy control (HC) and 40 diffuse SSc) and blister fluid (BF) (n=12 HC and 13 SSc). SSc monocyte-derived macrophages (n=17 SSc & 9 HC) were profiled by flow cytometry for CD206 (M2) and P2X7 (ATP receptor) expression, and by qPCR for arginase (M2) and IFN γ (M1).

Results: In mouse models, RP peptides inhibited both the dermal and lung fibrosis induced by bleomycin, and reduced plasma cytokines to basal levels (skin model; dermal thickness in controls 343, bleo 402, bleo +RP 345 μ m, $p<0.0009$, plasma IL-6 in bleo 101 pg/ml, bleo+RP 24, $p<0.00018$, plasma IL12p40 bleo 38, bleo+RP 0, $p<0.15\times10^{-7}$) (lung model; Ashcroft score bleomycin 5.8, bleo+RP 2.8, $p<0.0024$, plasma IL6 bleo 58, bleo+RP 7 $p<0.0005$, IL12p40 bleo 152, bleo+RP0, $p<0.00014$).

As a biomarker, sCD206 was elevated in SSc plasma (SSc median 683, HC 583 pg/ml, $p<0.024$), and BF (SSc median sCD206 42, HC 31 pg/ml, $p<0.041$). Both CD206 and P2X₇ were highly expressed by SSc macrophages (mean fluorescence SSc, 776.1 SD=409.1, 724.4 SD=455.3 vs HC 632.2 SD=73.7, 472.9 SD=25.4), correlating with modified Rodnan skin score ($p<0.05$, $r=0.51$). Double positive P2X₇ and CD206 cells were seen in a subgroup with higher skin scores. SSc macrophages had elevated arginase:IFN γ ratio (11.4 vs 5.9, $p=0.03$).

RP therapeutic peptides suppressed viability in SSc macrophage cultures with raised arginase:IFN γ ratio >8 , but had no effect on macrophages with lower arginase:IFN γ . Treatment of SSc macrophages with RP832c, as the lead candidate, effectively abolished macrophage-fibroblast cross-talk, reducing collagen I to basal levels (collagen I, basal 2830, TGF β stimulated 3026, SSc macrophage media treated 4186, RP832c 10 μ M macrophage media 3519, RP832c 100 μ M macrophage media 2475, relative expression to TBP, $p<0.0039$).

Conclusion: These data confirm the presence of activated CD206 positive macrophages in SSc, and demonstrate the potential for these cells to directly stimulate fibroblasts, inducing collagen I. Furthermore, the RP peptides suppress fibrosis and cytokines in mouse models and selectively inhibit highly activated SSc macrophages. RP832c, the lead compound, blocked SSc macrophage-fibroblast cross-talk and will be developed as a GLP therapeutic for clinical trials.

Disclosure: B. Ahmed Abdi, None; H. Lopez, Riptide Bioscience, 4; G. Martin, Riptide Bioscience, 4; C. Garvin, Riptide Bioscience, 4; J. Jaynes, Riptide Bioscience, 4; J. Stanway, None; C. P. Denton, Roche, Actelion, GlaxoSmithKline, Sanofi-Aventis, Inventiva, SCL Behring, Boehringer-Ingelheim, Bayer., 5; D. Abraham, None; S. Vigneswaran, None; S. Morris, None; R. J. Stratton, None.

GBR830, a True OX40 Antagonist Antibody with Potent Suppressive Effects on T Cell-Mediated Pathological Responses

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: OX40 (TNFRSF4, CD134) is a costimulatory receptor member of the NGFR/TNFR superfamily expressed predominantly on activated T lymphocytes. Ligation of OX40 by its ligand OX40L (TNFSF4, CD252) leads to enhanced T cell survival, proliferation, and effector function. Blocking the OX40/OX40L pathway is therefore highly attractive to treat a broad range of T cell-mediated autoimmune diseases. While several OX40 agonist antibodies are in clinical development for cancer, generation of a true OX40 antagonist is challenging. The studies presented herein characterize the preclinical profile, mechanism of action, and immunomodulatory capabilities of GBR 830.

Methods: T cell proliferation assay (inhibition or agonism); NFκB reporter cell assay; xenogeneic human graft versus host disease model in SCID mice; cynomolgus monkey T cell-dependent antigen response (T-DAR) model; and in vitro antigen reactivation model.

Results: GBR 830, a humanized IgG1 anti-OX40 antibody, recognizes the cysteine-rich domain 2 of OX40 that overlaps the binding region to OX40L. Consequently, GBR 830 blocks the binding of OX40L to OX40 and inhibits OX40L-mediated inhibition of T cell proliferation and NFκB signaling. In contrast to all other anti-OX40 antibodies tested, GBR 830 did not reveal any residual agonism even in a sensitive experimental setup. In a xenogeneic graft versus host disease model using immunodeficient mice reconstituted with human peripheral blood mononuclear cells, GBR 830 suppressed T helper cell-mediated responses. In a cynomolgus monkey T-DAR model to keyhole limpet hemocyanin, GBR 830 demonstrated a profound inhibitory effect on memory response but not on primary antibody response. In vitro vaccine (tetanus toxoid) or autoantigen reactivation assays showed that GBR 830 can inhibit memory T cell reactivation.

Conclusion: Overall, these data suggest that GBR 830 has immunomodulatory capabilities in T helper cell-mediated responses, applicable to a broad range of autoimmune pathologies. Accordingly, GBR 830 demonstrated positive results in a phase 2a clinical study in patients with moderate-to-severe atopic dermatitis (NCT02683928) and has the potential to address unmet medical needs in autoimmune and inflammatory diseases.

Disclosure: J. Macoin, Glenmark Pharmaceuticals SA, 3; S. Blein, Glenmark Pharmaceuticals SA, 3; T. Monney, Glenmark Pharmaceuticals SA, 3; P. Sancheti, Glenmark Pharmaceuticals Ltd, 3; V. Reddy, Glenmark Pharmaceuticals SA, 3; J. Back, Glenmark Pharmaceuticals SA, 3.

Exploration of T-Cell Signatures Following TCR Stimulation Using Single Cell RNA-Seq to Inform Treatment Response Studies in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: For rheumatoid arthritis (RA), as with many other rheumatic diseases, the importance of determining which therapy will work best, early in disease, to prevent further progression, is an important area of research. Progress in treatment response has been limited, possibly due to the complex interplay between various cell types. As such, specific T-cell signatures, determined by single cell RNA-Seq (scRNA-Seq), could be predictive of future response to treatments such as anti-TNF biologic therapies. Our aim was therefore to determine the optimal study design and to assess the potential of scRNA-Seq to identify T-cell signatures under resting and stimulated conditions to inform future studies.

Methods: Primary CD4⁺ T-cells were either stimulated using anti-CD3/CD28 beads or subjected to the same conditions without stimulation for 4 hours. Single cells were isolated using the 10X Genomics Chromium Controller with a target recovery of 6000 cells. Each scRNA-Seq library was sequenced on 4 Illumina HiSeq 4000 lanes (~200K reads/cell) and processed using the cellranger pipeline. Further quality control and cluster analysis was performed using Seurat.

Results: For the unstimulated sample 5,586 cells were recovered and after quality control and filtering, 5,387 cells remained. Similarly, for the stimulated sample, 4,621 cells were recovered and 4,473 remained. This resulted in an average of 1,094 and 1,456 genes per cell. Similar clusters were seen after downsampling the stimulated dataset to 1 lane (~379M reads, ~82K reads/cell), suggesting that CD4⁺ T-cells are defined by large gene expression changes rather than subtle variations, consistent with protein expression data. Cluster exploration allowed the identification of several typical CD4⁺ T-cell populations, including naïve, helper and regulatory. Furthermore, alignment of the two conditions in Seurat, identified classical and non-classical markers of activation, such as CD69, CCR7, MYC and PIM3. Finally, the relative cluster location and the expression of indicative markers suggested evidence of a progression from a naïve cell state to an 'active' effector state.

Conclusion: This data has provided important insights into future study design and confirmed the potential of scRNA-Seq to identify T-cell signatures. Importantly, despite obvious expression changes, cluster identity was maintained between stimulatory conditions. This implies it is possible to directly compare scRNA-Seq expression profiles between patient samples showing different disease activity without confounding the conclusions and enable the use of scRNA-Seq to investigate its predictive potential in RA treatment response. We are therefore in the process of expanding this work to study patient samples and different cell types. For example we have already generated similar data for monocytes on 3 RA samples and 3 healthy samples.

Disclosure: P. Martin, None; J. Ding, None; B. Mulhearn, None; S. Viatte, None; S. Eyre, None.

Abstract Number: 135

High Dimensional Analysis By Mass Cytometry and RNA-Sequencing Reveals Altered Frequency and Exhausted Features of CD4 T and MAIT Cells in Systemic Sclerosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune disease characterised by excessive fibrosis of skin and internal organs, and vascular dysfunction. Association of T and B cell subsets have been reported in SSc, however there is lack of systematic studies of functional relations between immune cell subsets in this disease. This lack of mechanistic knowledge hampers targeted intervention.

In the current study we ought to determine differential immune cell composition and heterogeneity in peripheral blood of SSc patients and its impact on disease severity and progression.

Methods: Mononuclear cells from blood of SSc patients with interstitial lung disease (ILD, n=10) or No ILD (n=10) and healthy controls (n=10) were analysed by mass cytometry using a 36 marker (cell-surface and intracellular) panel to aid in identification of major PBMC lineages including T cells, B cells, monocytes and NK cells and their subsets. Transcriptome analysis (m-RNA sequencing) was performed on sorted T and B cell subsets. Unsupervised clustering of mass cytometry data was performed using in-house developed analysis software MARVIS. This software combines dimension reduction and

clustering steps to identify all possible cellular subsets. Further, custom R scripts helped in identifying nodes that were differentially expressed between the study groups and also phenotype of these nodes.

Results: Unsupervised clustering performed revealed significant differences in the frequencies of T cell and B cell subsets. Most strikingly we identify a 3 fold decrease in frequencies of Va7.2+ CD161+ mucosal associated invariant T cells (MAIT) in SSc patients and 2 fold increase in total B cells, particularly CD19+ CD27- naive cells. A subset of memory CD8+ T cell, expressing CXCR3 was found to be increased in SSc patients as compared to healthy controls. Transcriptome analysis of sorted B cell and T cell subsets showed decrease in genes related to survival and increased expression of apoptotic genes in CD4,CD8 T and MAIT cells from SSc patients. Genes related to exhaustion and leukocyte migration were highly expressed in T cells from patients.

Conclusion: This study provides an in depth analysis of systemic immune composition in SSc with the potential to delineate mechanisms of pathogenesis and identify diagnostic and/or therapeutic targets. This is the first demonstration of altered frequencies of T cell subsets, particularly MAIT cells, in systemic sclerosis and also outlines exhaustive nature of these cells in the periphery of systemic sclerosis patients.

Disclosure: B. Paleja, None; A. H. L. Low, None; P. Kumar, None; S. Saidin, None; A. Lajam, None; C. Chua, None; L. Lai, None; S. Albani, None.

Abstract Number: 136

Alpn-101, a Dual ICOS/CD28 Antagonist, Potently Suppresses Disease in Multiple Mouse Models of Autoimmunity

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: CD28 and Inducible T-cell Costimulator (ICOS) are two related costimulatory molecules within the immunoglobulin superfamily (IgSF) expressed on T cells and interacting with CD80/CD86 and ICOS ligand (ICOSL), respectively. Both play critical roles in T cell activation and adaptive immunity, but when dysregulated can contribute to autoimmunity. We used our proprietary platform to create a variant Ig domain (vIgDTM), an engineered version of ICOSL capable of binding both ICOS and CD28 and blocking the interaction of these costimulatory molecules with their respective receptors. This ICOSL vIgD was fused to a human Fc lacking effector function (i.e. FcR binding and complement fixation) to create the therapeutic candidate ALPN-101, which has previously been shown to have potent immunosuppressive activity *in vitro*. We report here *in vivo* activity data in mouse models of autoimmune disease supporting the potent immunosuppressive activity of ALPN-101.

Methods: ALPN-101 was evaluated for immunosuppressive activity in multiple mouse models, including the collagen-induced arthritis (CIA) model with either prophylactic or therapeutic dosing. ALPN-101 was dosed a maximum of 4 times either prior to or just after disease onset. Comparator molecules were administered at molar equivalent doses in regimens matching ALPN-101.

Results: ALPN-101, when given either prophylactically or therapeutically, significantly attenuated disease activity in the collagen-induced arthritis model. ALPN-101 mediated significant disease reduction in CIA, matching or exceeding CD28-only or ICOS-only inhibitors. Similar effects were observed in additional disease models.

Conclusion: Efficacy *in vivo* of ALPN-101 is superior to wild-type ICOSL domains or CD28-only inhibitors. The increased efficacy of ALPN-101 was made possible by engineering the wild-type ICOSL IgSF to create a vIgD with altered affinity between ICOSL and ICOS and through specifically-directed alterations in ICOSL/CD28 binding. Preclinical development of ALPN-101 is underway to support clinical studies of this potentially first-in-class dual ICOS and CD28 inhibitor.

Disclosure: S. Dillon, Alpine Immune Sciences, 1, 3; K. Lewis, Alpine Immune Sciences, 1, 3; L. Evans, Alpine Immune Sciences, 1, 3; R. Swanson, Alpine Immune Sciences, 1, 3; J. Yang, Alpine Immune Sciences, 1, 3; M. Wolfson, Alpine Immune Sciences, 1, 3; M. Seaberg, Alpine Immune Sciences, 1, 3; K. Susmilch, Alpine Immune Sciences, 1, 3; S. Mudri, Alpine Immune Sciences, 1, 3; M. Rixon, Alpine Immune Sciences, 1, 3; S. Peng, Alpine Immune Sciences, 1, 3, 6; K. Swiderek, Alpine Immune Sciences, 1, 3.

Abstract Number: 137

Autoantibody-Inducing CD4 T (aiCD4 T) Cells Which Induce Systemic Lupus Erythematosus (SLE) Contain Follicular Helper T Cell in Addition to the Major IL-21-Producing CXCR5-ICOS^{hi}PD1^{hi} Population: Self-Organized Criticality Theory As the Cause of SLE

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: We have shown that repeated immunization with antigen induces systemic lupus erythematosus (SLE) in the mice otherwise not prone to spontaneous autoimmune diseases. We found that overstimulation of CD4 T cells led to the development of autoantibody-inducing CD4 T (aiCD4 T) cell which had undergone *de novo* T cell receptor (TCR) revision, capable of inducing variety of autoantibodies and stimulating CD8 T cells, driving them to become cytotoxic T lymphocyte (CTL). These CTLs then matured through antigen cross-presentation in dendritic cell (DC), after which they caused tissue injury identical to SLE. We have proposed Self-Organized Criticality Theory, explaining that systemic autoimmunity would be an inevitable consequence of over-stimulating host's immune system by repeated immunization with antigen to levels that surpass system's self-organized criticality. Since the aiCD4 T cell appeared to be included in CD45RB^{lo}122^{lo} CD4 T cell subset, we here further dissected the phenotype of the aiCD4 T cell by pursuing this subset, and found that aiCD4 T cells include not only follicular helper T (Tfh) cell but also IL-21-producing CXCR5⁺ICOS^{hi}PD-1^{hi} cell, and this subset seemed to be responsible for the induction of SLE.

Methods: BALB/c mice were repeatedly immunized with ovalbumin (OVA) and SLE was induced. CD45RB^{hi} or CD45RB^{lo} CD4 T cells in spleen of these mice were studied the expression of cell surface marker using flow cytometry. Splenic CD45RB^{hi} or CD45RB^{lo} CD4 T cells were also magnetically isolated and stimulated by anti-CD3 and anti-CD28 antibodies *in vitro*. After stimulation, IL-21 in culture supernatant were detected using ELISA. IL-21-producing CD4 T cell was also detected using flow cytometry.

Results: After repeated immunization with OVA, the CXCR5⁺PD-1^{hi} Tfh cell was significantly increased. A unique CXCR5⁺PD-1^{hi} CD4 T cell subset was also increased in the OVA-immunized mice. These subsets were, however, absent in the CD45RB^{hi} subset. The expression of ICOS was equally high in both subsets as compared with conventional CXCR5⁺PD-1⁻ CD4 T cells, however, the expression of Bcl-6 was lower in the CXCR5⁺ICOS^{hi}PD-1^{hi} CD4 T cells as compared with Tfh cells. The amount of IL-21 produced from CD45RB^{lo} CD4 T cell of OVA-immunized mice was significantly high as compared with CD45RB^{hi} CD4 T cell of OVA-immunized mice or whole CD4 T cell of control mice. IL-21-producing CD4 T cell was also significantly increased within CD45RB^{lo} subset after repeated immunization with OVA. We also found that CXCR5⁺PD-1^{hi} CD4 T cells produced much more IL-21 as compared with Tfh cells after repeated immunization with OVA.

Conclusion: The CXCR5⁺ICOS^{hi}PD-1^{hi} CD4 T cells that produce IL-21 were significantly increased in addition to Tfh cells in the mice repeatedly immunized with OVA. This novel CXCR5⁺ICOS^{hi}PD-1^{hi} CD4 T cells may behave as aiCD4 T cells, and drive B cells and CD8 T cells to induce a variety of autoantibodies and lupus tissue injuries by producing massive IL-21.

Disclosure: K. Tsumiyama, None; S. Shiozawa, None.

Distinct Roles of Tfh2, SLAMF7+ Tfh1 Cells and Th1 Cells in the Pathogenesis of IgG4-RD

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: IgG4-related disease (IgG4-RD) is a novel disease entity characterized by the infiltration of IgG4-secreting plasmablasts (PBs) and the generation of germinal centers in various affected organs. Several CD4+ T cell subsets including follicular helper T cells (Tfh), Th2 cells and Th1 (cytotoxic) cells have thus far been shown to be involved in the pathogenesis of IgG4-RD. Given the classic tenet that Th1 and Th2 are mutually exclusive, the above findings seem apparently contradictory and the underlying mechanism of this disease remain largely enigmatic. Here, we have thoroughly investigated the role of each CD4+ T cell subsets in patients with IgG4-RD.

Methods: Peripheral blood (PB) mononuclear cells were obtained from 21 patients with IgG4-RD and 10 healthy controls (HC). The phenotype of CD4+ T cells was analyzed by a flow cytometry. CD4+ T cells were categorized as Th1, Th2, Th17, Th1/17, Tfh1, Tfh2, Tfh17, and respective activated populations by expression of CXCR5, CXCR3, CCR6 and PD-1. The frequency of SLAMF7+ (cytotoxic CD4+) cells was also evaluated among CD4+ T cells subsets. The proportion of CD4+ T cell subsets relative to whole CD4+ T cells in patients with IgG4-RD was compared with that in HC. Moreover, the number of CD4+ T cell subsets was assessed for correlation with the titers of serum IgG4.

Results: The patients with IgG4-RD enrolled in this study were aged 66 ± 11 years and their titers of serum IgG4 were 372 ± 336 mg/dl. The frequency of Th1, Tfh1, Tfh2, and respective activated populations in patients with IgG4-RD patients was significantly increased compared with that in HC. Positive correlations were noted between the number of activated Tfh2 cells and the titer of serum IgG4 ($r=0.46$, $p=0.03$), while no correlations were observed between the number of any other activated subsets and the titer of serum IgG4, suggesting a critical role of this subset in generating IgG4-producing PBs. Notably, SLAMF7+ cells were almost exclusively observed in activated subsets of Th1 and Tfh1 cells in patients with IgG4-RD. This trend was more noticeable in patients with IgG4-RD than in HC. Moreover, the expression levels of SLAMF7 in activated Tfh1 cells were much higher than that in non-activated Tfh1 cells in patients with IgG4-RD ($13.99 \pm 5.59\%$ vs $0.81 \pm 0.56\%$, $p<0.0001$). Intriguingly enough, positive correlations were noted between the number of SLAMF7+ activated Tfh1 cells and the titer of serum IgG4 ($r=0.45$, $p=0.039$), while no correlations were observed between that of SLAMF+ activated Th1 cells and serum IgG4 ($r=0.11$, $p=0.63$).

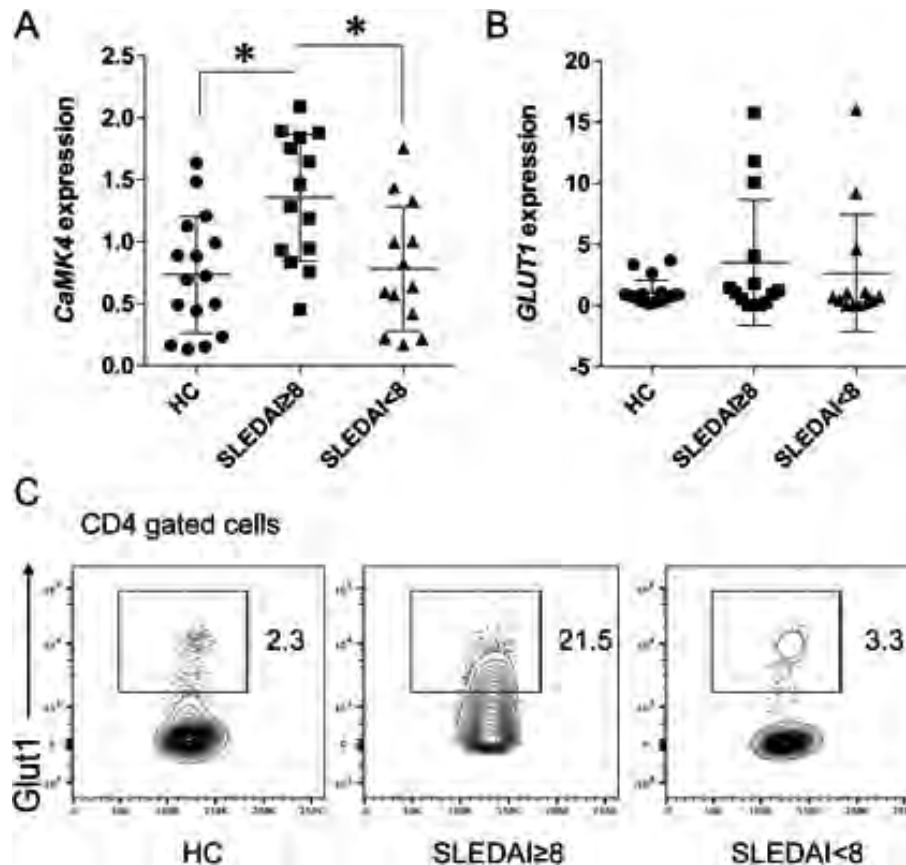
Conclusion: Together, these suggest that activated Tfh2 cells and SLAMF7+ activated Tfh1 cells were involved with the pathogenesis of IgG4-RD via generating IgG4-producing PBs, while Th1 cells, especially SLAMF7+ cells, contribute to another pathologic processes in this disease via antibody-independent mechanisms such as the production of cytokines and cytotoxic molecules. These results might reconcile the previous contradictory findings and expand our knowledge of this novel disease entity.

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Calcium/Calmodulin-Dependent Protein Kinase 4 Promotes GLUT1-Dependent Glycolysis in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Glycolysis is critical for T-cell effector functions, and increased glycolysis leads to autoimmunity. APT production by effector T cells is dependent on the mitochondria-independent glycolysis system. In addition, the expression of GLUT1, a major glucose transporter, is enhanced upon the activation of T cells.

We sought to clarify the significance of immunometabolism in the pathological condition of systemic lupus erythematosus (SLE) and to determine the effect of calcium/calmodulin-dependent protein kinase 4 (CaMK4) on T-cell metabolism.

Methods: We performed metabolomic profiling using capillary electrophoresis mass spectrometry in naive T cells from MRL/lpr mice treated with anti-CD3/28 antibodies in the absence or presence of a CaMK4 inhibitor (KN-93). We examined the expression of GLUT1 and CaMK4 in CD4⁺ T cells from healthy controls (HCs: n=34), patients with inactive SLE (n=18), and patients with active SLE (n=24) by flow cytometry and quantitative PCR. We performed in vitro experiments to determine the effect of KN-93 on the expression of GLUT1 during Th17 differentiation in T cells from SLE patients.

Results: CaMK4 inhibition significantly decreased the levels of glycolytic intermediates such as G6P, F6P, F1, 6DP, pyruvate, and lactate, whereas it did not affect the levels of the pentose phosphate pathway intermediates such as 6-PG, Ru5P, R5P and PRPP. As shown in Figure A, the mRNA expression of *CAMK4* in CD4⁺ T cells was significantly higher in the active SLE patients (SLEDAI ≥ 8) compared to the HCs and the inactive SLE patients (SLEDAI < 8). Although there was no significant difference in the gene expression of *GLUT1* among these three groups (Fig. B), the surface expression of GLUT1 was the highest in the SLE patients with SLEDAI ≥ 8 among the HCs and SLE patients (Fig. C). A functional analysis revealed that CaMK4 inhibition decreased the expression of GLUT1 during Th17 cell differentiation, followed by a reduction of IL-17 production.

Conclusion: Our results indicate that (1) the activity of CaMK4 could be responsible for glycolysis, which contributes to the production of IL-17, and (2) CaMK4 may contribute to an aberrant expression of GLUT1 in T cells from active SLE patients.

Disclosure: T. Koga, None; M. Umeda, None; Y. Endo, None; T. Shimizu, None; R. Sumiyoshi, None; S. Kawashiri, None; N. Iwamoto, None; K. Ichinose, None; M. Tamai, None; T. Origuchi, None; H. Nakamura, None; A. Kawakami, None.

Abstract Number: 140

Inhibition of Cathepsin S Leads to Suppression of SS-a/SS-B Specific T Cells from Patients with Primary Sjögren Syndrome

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Primary Sjögren syndrome (pSS) is an autoimmune disease characterised by an infiltration of T and B cells into exocrine gland tissue and its subsequent destruction. Antigen presenting cells, including B cells, foster T cell activation and anti-SS-A/SS-B producing plasma cells, eventually leading to disease progression and systemic complications. Cathepsin S (CatS) is crucially involved in MHCII processing in pSS mouse models and patients. In this translational study we investigated the *ex vivo* effects of the CatS inhibitor RO5459072 in different bio-compartments, including specific T cells, of pSS patients and healthy controls.

Methods: *Ex vivo* CatS activity was assessed in different bio-compartments of 15 pSS patients and 13 healthy controls and in presence or absence of RO5459072 using commercial activity and quantification assays. In addition, antigen (5µg/mL SS-A, 5µg/mL SS-B, 5µg/mL Influenza H₃N₂; 2µg/mL Tetanus Toxoid and 100ng/mL SEB) specific T cell responses were examined using 2x10⁵PBMC/well IFN-g/IL-17 Dual ELISPOT (48h incubation) and 5x10⁴ PBMC/well BrdU proliferation assays after (72h incubation) in presence or absence of RO5459072.

Results: pSS patients showed significantly higher CatS activity in tear fluid than healthy controls (two-tailed t-test p<0.01). RO5459072 significantly suppressed CatS activity in tears of pSS patients (two-tailed t-test p<0.01). CatS inhibition also exerted a strong and dose-dependent suppression of T cell responses towards SS-A and SS-B antigen in *ex vivo* derived pSS patient cells in Elispot and BrdU assays (Table 1).

Conclusion: CatS activity in tear fluid seems to be a relevant biomarker for pSS disease activity. RO5459072 is a potent inhibitor of CatS and the pSS associated relevant antigen specific T cell responses.

Table 1. Suppression of antigen specific T cell responses (Elispot) and suppression of cell proliferation (BrdU) in the presence of RO5459072 (1-100 µM).

Elispot - SFU/Million Cells (mean of triplicates)										
	SS-A				SS-B				SEB	
RO5459072	0µM	1µM	10µM	100µM	0µM	1µM	10µM	100µM	0µM	100µM
pSS 1	80	46.7	38.3*	41.7*	111.7	55	31.7	18.33	>1000	>1000
pSS 2	258.3	230	60*	23.3*	105	130	63.3	25*	>1000	>1000
pSS 12	30	23.3	15	6.7	73.3	38.3**	35**	33.3	>1000	>1000
pSS 15	23.3	18.3	15	3.9*	40	21.7	13.3	4.5	>1000	>1000

BrdU - Stimulation Index (mean of triplicates)										
	SS-A				SS-B				SEB	
RO5459072	0µM	1µM	10µM	100µM	0µM	1µM	10µM	100µM	0µM	100µM
pSS 3	1.405	1.617	1.598	0.363**	1.89**	1.978	2.505	0.991**	4.207****	0.924***
pSS 4	1.211*	1.301	1.085	0.329***	1.968*	1.86	1.255	0.473**	1.92*	0.238*
pSS 7	1.867*	1.806	1.769	1.008*	2.838**	2.568	1.749	0.95**	8.70**	2.841**
pSS 11	1.348	1.426	1.393	0.391**	1.932*	1.85	2.233	1.268*	6.711*	2.507*

IFN-g Spot Forming Units (SFU) were determined using an CTL Elispot reader. Results from unstimulated control conditions were subtracted from antigen specific results and expressed as SFU/Million PBMC and statistical analyses were applied. BrdU results are expressed as a Stimulation index, where absorbance results of the antigen condition is divided by the result of the untreated control the BrdU assay. One-tailed t-test, * p<0.05, ** p<0.01, ***p<0.001, ****p<0.0001

Disclosure: P. Hargreaves, Hoffmann La Roche, 2, 3; M. Theron, Hoffmann La Roche, 3; F. Kolb, Hoffmann La Roche, 3; M. Manchester, Hoffmann La Roche, 3; B. Reis, Hoffmann La Roche, 3; A. Tiaden, Hoffmann La Roche, 2; D. Kyburz, Hoffmann La Roche, 2; T. Manigold, Hoffmann La Roche, 2.

Abstract Number: 141

Lymphocyte Activation Gene 3 Plasma Level Is Increased and Associated with Progression in Early Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Lymphocyte activation gene 3 (LAG3) resembles CD4 and is a key checkpoint molecule leading to downregulation of T cell proliferation and antigen presentation via interactions with CD3 and MHC-II respectively. LAG3 is primarily expressed by activated T cells, regulatory T cells, and exhausted T cells. LAG3 plays an important role in maintaining immunological unresponsiveness to self-antigens. However, little is known about its pathogenetic role in autoimmune diseases, like rheumatoid arthritis (RA).

Methods: The plasma level of soluble (s) LAG3 was measured in 120 treatment naïve patients with early RA, with symptoms for an average of 3 months. This was done at baseline and after 12 months of treatment with either methotrexate + placebo or methotrexate + adalimumab. Treatment response was evaluated by DAS28CRP, total sharp score (TSS), erosion score (ES) and joint space narrowing (JSN). IgM-RF and anti-CCP status were also measured. Further, we examined paired plasma and synovial fluid samples from 38 RA patients with long standing disease (> 8 years) and plasma from healthy donors (HD, n=35). Human peripheral blood mononuclear cells (PBMCs) and synovial fluid mononuclear cells (SFMCs) were examined by flow cytometric analysis to characterize LAG3 and PD-1 expression on CD4+ T cells. Exhaustion status was assessed by IL-2 expression, after stimulation with CD3CD28 beads in a cell:bead ratio of 2:1 (suboptimal stimulation). Finally, SFMCs were stimulated with rhLAG3 for 48 hours.

Results: Plasma level of sLAG3 was increased in early RA patients (1725 ± 2285 pg/ml) vs HD (741 ± 381 pg/ml, $p < 0.001$). After 12 months of treatment, sLAG3 remains elevated compared with HD (1236 ± 1326 pg/ml, $p < 0.05$). The changes in sLAG3 were not affected by adding adalimumab to the methotrexate treatment. Baseline plasma levels of sLAG3 were strongly associated with autoantibody status, IgM-RF ($\rho = 0.38$, $p = 0.006$) and anti-CCP ($\rho = 0.38$, $p = 0.005$), but not to DAS28CRP, and inversely with CRP ($\rho = 0.38$, $p = 0.04$). Furthermore, baseline levels of sLAG3 were associated with progression in TSS after two years ($p < 0.05$) and changes in TSS (0-2 year) was also associated with change in sLAG3 ($\rho = 0.25$, $p < 0.05$). Highest levels of sLAG3 were observed in the synovial fluid from patients with chronic RA (3615 ± 2854 pg/ml), compared with plasma ($p < 0.001$). No correlation between sLAG3 in the two compartments was observed. Highest expression of LAG3 after suboptimal stimulation was observed in synovial IL-2-, FOXP3-, PD-1+, CD4+ T-cells. No biological effect was observed by addition of rhLAG3 to cultured PMBCs and SFMCs as assessed by production of TNFa, MCP-1 or IgM-RF.

Conclusion: sLAG3 in plasma is increased in early, untreated and longstanding RA despite a favorable response to intensive synovitis suppressive treatment. A high baseline sLAG3 level is associated autoantibody seropositivity and with radiographic progression at two years. These observations support that persistent CD4+ T cell activation is a key feature in the RA pathogenetic pathway.

Disclosure: J. M. Pedersen, None; A. Hansen, None; M. Hvid, None; K. Hørslev-Petersen, None; M. L. Hetland, None; K. Stengaard-Pedersen, None; M. Østergaard, None; B. K. Moeller, None; E. M. Hauge, None; P. Junker, None; B. Deleuran, None.

Abstract Number: 142

Peripheral CD4+CD25+Foxp3+T Regulatory Cells Absolutely Reduce in Patients with Systemic Lupus Erythematosus

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SESSION INFORMATION

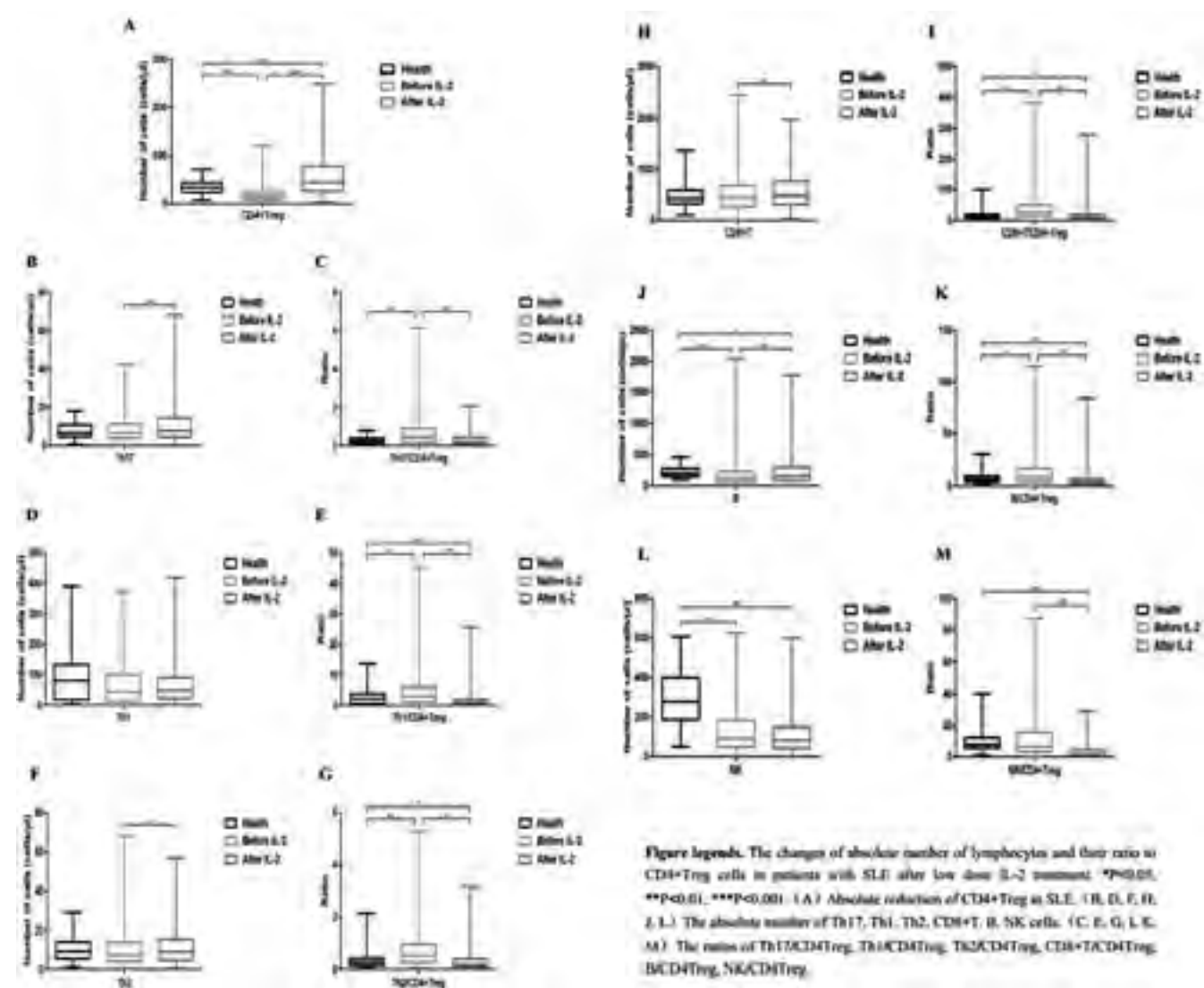
Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

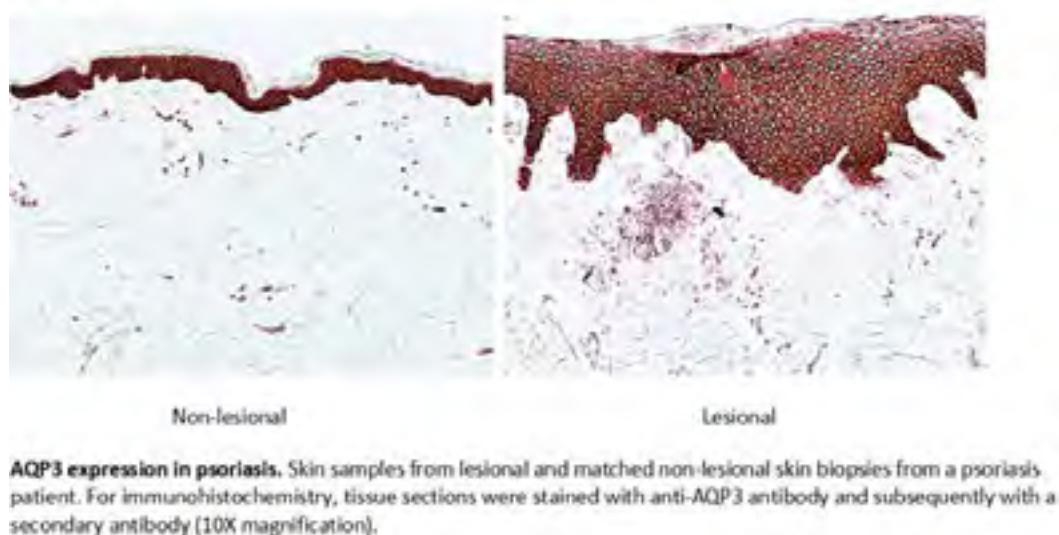
Background/Purpose: RegulatoryT (Treg) cells, with the capacity to suppress immune responses, and effector T (Teff)cells, to promote inflammation, have been intensively studied in recent years. However, previous reports describing the respective changes of Treg and Teff, especially T helper 17 cells (Th17) in patients with systematic lupus erythematosus



(SLE) were controversial. Here, we investigated the changes of both the absolute number and percentage of CD4+CD25+Foxp3+Treg(CD4Treg) and effector cells on a large scale and further the role of low-dose interleukin-2 (IL-2) on these changes in SLE.

Methods: A total of 235 SLE patients (219 women and 16 men), with mean age of 37.80±14.00 years, and 90 healthy volunteers, matched for patients' age and gender, were enrolled. The absolute number and percentage of subpopulation of peripheral blood (PB) lymphocyte in these patients were measured by flow cytometry combined with internal microsphere standard. And low-dose IL-2 was used among 127 patients at a dosage of 50 WIU every day for five days. Immunological and clinical assessments were performed again.

Figure 1:



Results: As compared to healthy controls, the absolute number of CD4Treg were significantly decreased in SLE. The median ratios of Th17/Treg in patients were greatly higher than those of healthy volunteers [0.42(0.19, 0.88) vs. 0.21(0.15, 0.34), $P<0.001$], while there was not significantly different about Th17. Besides, Th1, Th2, CD8+T, B cells and their respective ratios to Treg were like that of Th17 as well. Moreover, CD4Treg cells were negatively correlated with ESR and SLEDAI score. While no obvious correlation was seen between Th17 cells and SLEDAI score. After IL-2 therapy in SLE, there was a four-fold increase in CD4Treg [43.73(24.08, 74.22) vs. 11.95(7.51, 20.34), $P<0.001$], whereas Th17 cells were increased slightly. The ratio of Th17/Treg was decreased significantly in patients with IL-2 treatment [0.19(0.09, 0.41) vs. 0.52(0.23, 0.95), $P<0.001$], tended to balance and had no difference with healthy individual ($P=0.275$). Similarly, there were same trends in Th1, Th2, CD8+T, B and NK cells.

Conclusion: The reduction of CD4Tregs, rather than the elevation of effector cells, contributes to the imbalance of Teff/Treg, indicating that SLE is an autoimmune disease triggered by the defect of immunotolerance. More importantly, although low-dose IL-2 might promote the proliferation of various lymphocyte subpopulation, it mainly modulated the abundance and immunosuppression activity of Tregs, which effectively induced autoimmune tolerance and further improved clinical symptoms.

Disclosure: X. Q. Liu, None; N. L. Lai, None; Y. Duan, None; J. Chen, None; X. F. Li, None; C. Gao, None.

Abstract Number: 143

Aquaporin 3 (AQP3) Protein Is Highly Expressed in Psoriatic Plaques and AQP3 Gene Expression Strongly Induced By IL-23 in CD4+ Th17 Cells

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Th17, a subset of CD4⁺ helper T cells, provides protection against pathogens and malignancies, but also promotes immune-mediated-inflammation in a range of disorders including psoriasis, psoriatic arthritis, and axial spondyloarthritis. In our analysis of high throughput transcriptomic data, we identified *aquaporin 3 (AQP3)* as a novel gene in the promotion of Th17 differentiation and pathogenicity. *AQP3* encodes for a water channel protein highly expressed in the kidney and keratinocytes. Interestingly elevated AQP3 expression is reported in inflamed skin of patients with atopic dermatitis. Elevated *AQP3* was recently reported in a murine model of psoriasiform dermatitis but its importance in human psoriasis has not been examined. We investigated AQP3 expression in human psoriatic skin and analyzed the expression of AQP3 in human CD4⁺ T cells following cytokine exposure.

Methods: To validate our initial *in silico* findings, we conducted *in vitro* experiments with human naive T cells. To investigate key inducers of *AQP3* in CD4⁺ lymphocytes, we cultured naïve CD4⁺ T cells in the presence of IL1B, IL6, TGFβ1, and IL23, alone, or in combination, and monitored *IL17A*, *IL17F*, and *AQP3* mRNA expression levels by qPCR. We also analyzed AQP3 mRNA and protein levels in lesional and non-lesional skin from psoriasis patients compared to skin from healthy controls.

Results: We found that *AQP3* expression at 72 hours increased more than 7-fold in naive CD4⁺ T cells when cultured in the presence of Th17 differentiating conditions and correlated with IL-17A and IL-17F expression. When CD4⁺ lymphocytes were cultured in the presence of IL1B, IL6, and TGFβ1 or TGFβ3, a 5-fold increase in *AQP3* was observed, but no increased expression was noted when cells were cultured with the individual cytokines. Interestingly, IL23 dramatically increased AQP3 expression in naive CD4⁺ T cells (more than 15-fold) when combined with IL1B, IL6, and TGFβ1, but failed to do so when added alone. We also noted elevated mRNA (2.3 fold) and protein expression levels of *AQP3* in lesional psoriatic skin compared to non-lesional skin (figure 1). Expression levels were highest in the epidermis but also noted in cells infiltrating the dermis.

Conclusion: Expression of *AQP3* was elevated in Th17 cells compared to naive CD4⁺ T cells. IL23 greatly augmented *AQP3* expression in CD4⁺ T cells in the presence of IL1B, IL6, and TGFβ1. In addition, AQP3 protein expression is increased in the cells infiltrating the dermis and keratinocytes in psoriasis, a Th17-related disorder. These data suggest that AQP3 may be a cellular marker of a pathogenic Th17 subset and may provide insights into disease pathogenesis with the potential to serve as a therapeutic target.

Disclosure: A. Paine, None; M. D. L. L. Garcia-Hernandez, None; B. D. Korman, None; J. Duculan, None; M. Suarez-Farinas, None; J. G. Krueger, None; C. T. Ritchlin, AbbVie, Amgen, UCB, 2, AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer Inc, 5.

Abstract Number: 144

Small Molecule Inhibitor of Bcl-6 Reduces the Tfh Population in Peripheral Blood, Splenic Germinal Center and Ankle Joints in a Collagen-Induced Arthritis Mouse Model of RA

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) is a common autoimmune disease characterized by chronic joint inflammation, synovial hyperplasia and progressive destruction of cartilage and bone. T follicular helper (Tfh) cells, a CD4⁺ T cell subset, predominantly located in lymphoid follicles, regulate B cell survival and antibody production in germinal centers. Our previous studies have showed that circulating Tfh cells were significantly increased in active RA

patients, correlated with their anti-CCP antibody titer and disease activity. Here, we further investigated the role of Tfh cells in RA pathogenesis in mice with collagen-induced arthritis (CIA) and also examined the therapeutic effect of a small molecule inhibitor (SMI-Tfh) which selectively blocks the Tfh cell signature transcription factor Bcl-6.

Methods: CIA model was induced by administering chicken type II collagen in twenty-four DBA/1 mice. The joints were observed for score of swelling of paws and ankles. Disease progression was monitored daily and recorded by arthritis severity scores weekly. Following the onset of clinical arthritis, mice were treated with SMI-Tfh. Blood, spleen, and affected paws were collected at the end of the study. Pathological changes were examined by staining of tissue sections with hematoxylin and eosin. Immunofluorescent histochemistry (IHC) staining and flow cytometry analysis were performed to identify Tfh cells ($CD4^+CXCR5^+ICOS^+$) in spleen, paw, and blood. IHC results were analyzed by Image J and flow cytometry results were analyzed by FlowJo software. Statistical analysis was carried out using GraphPad Prism software and the significance was evaluated by t test.

Results: Our results showed paw-swelling onset between days 21-28 and with peak on day 42 after initial immunization in DBA/1 mice. Compared with the ankles of control mice, the joints of CIA mice had increased inflammatory cells in the synovial tissues and destruction of articular cartilage. Tfh cells ($CD4^+CXCR5^+ICOS^+$) were observed in the blood and the germinal centers of the spleen of CIA mice. Mice treated with SMI-Tfh had significantly reduced paw swelling. SMI-Tfh was nontoxic at the tested dose (50mg/kg). SMI-Tfh treatment also reduced inflammatory cell and Tfh cell infiltration in inflamed joints, and significantly inhibited the numbers of Tfh cells in the blood and in the germinal centers of spleen ($p<0.01$) in CIA mouse.

Conclusion: Tfh cells originating from splenic lymphoid follicles may contribute to the circulating Tfh cells in the peripheral blood in RA and play an important role in the development of active RA. The small molecule inhibitor SMI-Tfh selectively inhibits Tfh cells in the spleen and in the inflamed joints. It appears to decrease severity in inflammatory arthritis, and may be useful as a new and additional therapeutic modality for RA.

Disclosure: N. Bhatia, None; S. Bradley, None; C. McLeod, None; G. Olayemi, None; R. Quinet, None; W. E. Davis, None; J. Zakem, None; X. Zhang, None.

Abstract Number: 145

1,25(OH)₂D₃ and Dexamethasone Additively Suppress Synovial Fibroblast Activation By CCR6⁺ T-Helper Memory Cells and Enhance the Effect of Tnf α Blockade

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Despite improvement in treatment of rheumatoid arthritis (RA) over the past decades, insufficient treatment response and treatment resistance in many patients demonstrate the need to develop new therapeutic strategies. Chronic synovial inflammation could be suppressed by targeting activation of RA synovial fibroblasts (RASf) by for example IL-17A-producing CCR6⁺ T helper memory (memTh) cells. Previously, we have shown that dexamethasone (DEX) combined with the active vitamin D metabolite 1,25(OH)₂D₃ reduces pathogenicity of memTh cells. Therefore, we here studied the additive effect of 1,25(OH)₂D₃ and DEX on suppressing the pro-inflammatory loop between RASf and CCR6⁺ memTh cells and explored potential therapeutic applications.

Methods: CCR6⁺ memTh cells from PBMC of healthy donors or treatment-naïve early RA patients were cultured alone or with RASf from established RA patients for three days and treated with or without 1,25(OH)₂D₃, DEX or etanercept. Treatment effects were assessed using ELISA and flow cytometry.

Results: CCR6⁺ memTh produces less of the pro-inflammatory cytokines IL-17A, IL-22 and IFN γ upon exposure to 1,25(OH)₂D₃, and to a lesser extent by DEX. TNF α was only inhibited by the combination of 1,25(OH)₂D₃ and DEX. In contrast, in RASf cultures DEX was the strongest inhibitor of IL-6, IL-8 and tissue-destructive enzymes. As a result, 1,25

(OH)₂D₃ and DEX additively inhibited inflammatory mediators in CCR6+ memTh-RASF co-cultures. Interestingly, low doses of mainly DEX, but also 1,25(OH)₂D₃, combined with etanercept better suppressed synovial inflammation in this co-culture model compared to etanercept alone.

Conclusion: This study suggests that 1,25(OH)₂D₃ and DEX additively inhibit synovial inflammation through targeting different pro-inflammatory mechanisms. Furthermore, low doses of DEX and 1,25(OH)₂D₃ enhance the effect of TNF α blockade in inhibiting RASF activation, providing a basis to improve RA treatment.

Disclosure: W. Dankers, None; C. González-Leal, None; N. Davelaar, None; P. Asmawidjaja, None; A. Otten-Mus, None; J. Hazes, None; E. Colin, None; E. Lubberts, None.

Abstract Number: 146

Mesenchymal Stromal Cell Transferred Mitochondria Elicit an Immune Function Reprogramming That Entails T Regulatory Cell Commitment and Clinical Improvement of Graft Vs Host Disease

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Mesenchymal stromal cells (MSCs) are progenitor cells with suppressive capacities that have fueled ample translation for the treatment of immune mediated diseases including Graft versus Host Disease (GVHD), one of the human indications with regulatory approval. Paracrine effects of the MSC secretome contribute to these actions, but recent evidence suggests that cell-to-cell transfer of MSC mitochondria to different tissues (MitoT) exerts significant regenerative and restoring effects. We hypothesized that MitoT would also encompass immunocompetent cells, and provide the first evidence herein of MitoT to T cells, relating it to a novel immune reprogramming mechanism of MSC therapy, tested both *in-vitro* and *in-vivo*, in an animal model of GVHD.

Methods: MitoT was assessed by flow cytometry, qPCR and confocal microscopy of human mononuclear cells (PBMCs) previously co-cultured in vitro with mitotracker (mitochondrial stained) umbilical cord MSCs at different ratios and conditions. To assess the direct functional impact of MitoT we employed the artificial transfer of MSC-derived mitochondria ("Mitoception")¹ to PBMCs. Mitotracker-positive (Mito+) acceptor cells were sorted for further testing and compared to Mitotracker-negative (Mito-) sorted cells. Experimental readouts included target cell phenotype and function, immune-related gene expression by RNA sequencing and qPCR, and metabolic "Seahorse" analysis of OXPHOS and glycolytic functions. *In vivo* effects were tested in a humanized xenogenic model of GVHD in NSG immunodeficient mice.

Results: Dose-dependent MitoT was observed from MSCs to T and B lymphocytes, NK and Dendritic cells (100%), reaching 60%-90% in CD3+CD4+ cells according to their state of activation. Transfer was independent of proinflammatory MSC pre-treatment, inhibition of gap junctions, hemi-channels or nanotubule formation. The suppression of MitoT at 4°C and the detection of human-specific mitochondrial genes (qPCR) in murine MSC-cocultured lymphoid cells confirmed the mediation of an energy dependent process, not attributable to cell fusion.

Genetic analysis showed most significant changes of mRNA expression in Treg activation pathways, including FOXP3, IL2RA, CTLA4, TGF β and Runx1. Indeed, naïve Mito+ sorted T cells were driven towards a CD127^{low}, CD25⁺ FoxP3⁺ (Treg) functionally proven suppressor phenotype as opposed to Mito- cells (fold change of 14) (p<0.01). Preliminary metabolic analysis of MitoT+ PBMCs displayed a 50% increase in the Glycolytic/OXPHOS ratio, which is a hallmark of T cell activation.

In vivo testing of xeno-GVHD induced by human Mito+ cells as compared to non-treated cells, showed significant improvement in weight loss (p<0.05), gut (p<0.05) and liver (p<0.01) tissue damage, organ infiltrating CD4⁺, CD8⁺ (p<0.05) and IFN γ ⁺ cells (p<0.0001) as well as survival (p<0.05).

Conclusion: These findings present the first evidence of MitoT from MSC to T-lymphocytes and immune cell subpopulations, pointing to a new level of complexity of the immunoregulatory role of MSCs, widening the horizon of their clinical applications.

¹Patent application PCT/EP2015/066190. Fondecyt 1170852.

Disclosure: A. C. Court, None; A. Le-Gatt, None; P. Luz-Crawford, None; M. Kurte, None; M. I. Ortuzar, None; R. Elizondo, None; R. A. Contreras, None; K. Pino-Lagos, None; M. Khoury, None; F. E. Figueroa, None.

Abstract Number: 147

T Follicular Helper Cell Phenotype in RA Patients Receiving Rituximab

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: B and T cells contribute to tissue injury in rheumatoid arthritis (RA). Rituximab (RTX), an anti-CD20 monoclonal antibody, is used for the treatment of RA and results in rapid B-cell depletion. However, the therapeutic effect of RTX may not be entirely contingent on depletion of B cells; rather, we hypothesized a contributing factor is the dampening of their interplay with the T-cell drivers of their maturation in secondary lymphoid organs. The latter follicular helper T (Tfh) cells are represented in the blood as a circulating (cTfh) pool. Thus, we examined effects of RTX on cTfh cells in RA patients treated either for the first time (“naïve”) or on maintenance therapy (*i.e.*; received at least once prior; “maintenance”).

Methods: Blood was drawn from 5 naïve and 11 maintenance patients prior to the first infusion, at 2 weeks (prior to 2nd infusion, if given) and 12 weeks. Peripheral blood mononuclear cells were stained with antibodies conjugated with fluorochromes for flow cytometry—CD4, CD3, CD45RA, CXCR5, PD-1, ICOS, CCR7, CD127, CD25, TCR β , CD19, IgD, CD38, CD27, PSGL-1, CD138, and CD5—to determine naïve, activated, and memory CD4 T cells, cTfh and cTfh subsets (cTfh1, cTfh2, cTfh17) and conventional CD4 T helper cell subsets (Th1, Th2, Th17). Naïve and memory B cells, and plasma cells were also enumerated. Data were analyzed using FlowJo® software. Plasma was assessed for anti-citrullinated peptide antibody (IgG) titers (ACPA) using QuantaLite® ELISA kit. Disease activity (DA) was determined by chart review.

Results: Naïve compared to maintenance patients had more cTfh cells (CXCR5⁺PD-1^{hi}ICOS^{hi}; $5.65 \pm 0.68\%$ vs. $2.67 \pm 0.36\%$; among CD4 T cells), with a significant linear relationship between the percentage of cTfh and that of CD19⁺ B cells (Pearson’s correlation coefficient 0.52); more cTfh17 cells (CXCR3⁻CCR6⁺; $29.5 \pm 2.79\%$ vs. $21.42 \pm 1.16\%$; within the CD4⁺CD45RA⁻CXCR5⁺ population); and more PD-1^{lo} memory cTfh17 cells ($35.42 \pm 3.32\%$ vs. $21.88 \pm 1.27\%$), although their percentages and ACPA titers did not change over the course of therapy. Th17 cells were differentiated from cTfh17 cells by their expression of CXCR5⁻ rather than CXCR5⁺. Naïve compared to maintenance patients also had more Th17 cells (CD4⁺CXCR5⁻CXCR3⁻CCR6⁺; $19.35 \pm 1.54\%$ vs. $14.27 \pm 1.08\%$), in both the PD-1^{hi} effector ($16.38 \pm 1.82\%$ vs. $11.89 \pm 0.87\%$) and PD-1^{lo} memory subsets ($20.77 \pm 1.72\%$ vs. $13.91 \pm 1.07\%$). All naïve patients had moderate-to-high DA at baseline as compared to only 27% of maintenance patients; post-RTX, all naïve patients had either low DA or clinical remission as compared to 82% of the maintenance patients.

Conclusion: We found a higher percentage of cTfh cells in naïve compared to maintenance RA patients treated with RTX, consistent with prior studies showing that B-cell help is needed for Tfh-cell development. We also found a higher frequency of cTfh17 and Th17 cells in naïve compared to maintenance patients and correspondingly higher DA at baseline in naïve patients, suggesting that B-cell depletion results in reduced cTfh and Th17 cells, as DA improves. Future studies are needed to better understand these cTfh subsets and their correlation to B-cell depletion and DA in RA, as well as their potential as therapeutic targets.

Disclosure: B. Hsiao, None; J. Y. Choi, None; J. E. Craft, None.

High Level of CD38 Expression in SLE CD8 T Cells Dictates Decreased Cytotoxicity

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: CD38 is an ectonucleotidase that has the ability to degrade nicotinamide adenine dinucleotide (NAD). The percentage of CD38 expressing CD8 T cells are increased in patients with SLE in whom cytotoxic responses are known to be decreased. We sought to determine whether CD38 is responsible for the decreased cytotoxicity in T cells from patients with SLE.

Methods: We used sorted human primary CD8 T cells, TALL-104 and CRISPR-generated CD38 knock out Jurkat cells. Electroporation was performed using Amaxa. Cells were stimulated with anti-CD3/CD28 or P815 cells. Degranulation and cytotoxicity were assayed by flow cytometry (FCM). Expression of cytolytic molecules (granzymeB, perforin and IFN-g) and the transcription factors Eomes, T-bet and EZH2 were measured by FCM and qPCR. NAD production and protein acetylation were measured using colorimetric or Western blot techniques.

Results: Compared with CD38^{low}, CD38^{high}CD8 T cells displayed lower cytotoxicity as determined by the expression of CD107a, granzymeB, perforin and IFN-g. In addition, CD38^{high}CD8 T cells showed lower cytotoxicity against P815 cells. Eomes and T-bet, which regulate cytotoxic function of CD8 T cells, were decreased in CD38^{high}CD8 T cells, while EZH2 levels were increased. EZH2 known to repress Eomes and T-bet has been reported to have a higher suppressive capacity and stability when acetylated. SIRT1 is a NAD-dependent deacetylase and controls EZH2 acetylation. Consequent upon lower production of NAD, the levels of proteins acetylated on lysine residues increased in CD38^{high}CD8 T cells. Lower deacetylation activity of SIRT1 may cause higher acetylation of EZH2 and suppression of Eomes and T-bet in CD38^{high}CD8 T cells. Finally, overexpression of CD38 in CD38^{low}CD8 T cells or TALL-104 cells increased acetylated protein and decreased degranulation and cytotoxicity against P815 cells, which indicates that CD38 may reprogram cytotoxicity in CD8 T cells.

Normal: CD38^{low}→NAD[↑]→SIRT1 activity (deacetylase)[↑]→EZH2[↓]→Eomes, T-bet[↑]→Cytotoxicity[↑]

SLE: CD38^{high}→NAD[↓]→SIRT1 activity (deacetylase)[↓]→EZH2[↑]→Eomes, T-bet[↓]→Cytotoxicity[↓]

Conclusion: We present novel evidence that CD38^{high}CD8 T cells which are expanded in patients with SLE display decreased cytotoxicity. CD38 causes decreased NAD levels, higher acetylation of EZH2 and subsequent decrease of the cytotoxicity-linked transcription factors, Eomes and T-bet. Our data document the role of CD38 in the control of the cytotoxic response of CD8T cells and provide a molecular explanation for the known decreased cytotoxic responses in patients with SLE.

Disclosure: E. Katsuyama, None; A. Suarez-Fueyo, None; S. Bradley, None; M. Kono, None; L. Mulki, None; V. C. Kyttaris, None; G. C. Tsokos, None.

Deep Immune-Profilng of CD4+ T Cells in Behcet's Disease

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Functionality and immune-phenotypes of the human CD4⁺ T-cell compartment in Behcet's disease (BD) are under-investigated, but several lines of evidence point to its relevance in the pathogenesis and progression of the disease. We aimed to apply an unbiased single cell approach to dissect the immune-phenotype of CD4⁺ T cells in prototypical BD in order to identify cell populations of potential pathobiological relevance.

Methods: We determined single cell expression levels of CD3, CD4, CD8, CD127, CD25, CD45RA, CCR7, FoxP3, HELIOS, Ki76, HLA-DR, CD38, CD39 in PBMC by flow cytometry and computed the representation of all possible cell populations within CD4⁺ starting populations in PBMC from healthy (HD, n=25), BD (n=13), and diseased subjects with non-BD auto-immune uveitis (n=11, VKH, Sarcoidosis, and HLA-B27 associated uveitis). BD subjects met ISG criteria and were Arab or Chinese. 62% had pan-uveitis, 23% major vascular disease, and 7% parenchymal CNS disease. 46% were HLA-B51 carriers.

Results: Computation of all populations defined by 8 markers (CD127, CD25, CD45RA, CCR7, FoxP3, HELIOS, Ki67, HLA-DR) within the CD4⁺ T cell compartment yielded a total of 6,560 cell populations per subject out of which 45 reached significance ($p < 0.000001$) differentiating 3 groups (BD, non-BD uveitis, and HD). All of these populations comprised sub-types of the human regulatory T (Treg) cell compartment with strong predominance of non-proliferating, non-activated, FoxP3⁺Helios⁺ Treg carrying central-memory phenotypes (CD45RA⁻, CCR7⁺). 2-group testing of BD vs non-BD revealed 43 distinct cell populations at a significance level of $p \leq 0.002$ representing CD25⁺ non-Treg; comparison of BD vs HD uncovered 58 populations at significance level of $p \leq 0.0001$ representing FoxP3⁺Helios⁺ subpopulations, and non-BD vs HD identified 61 populations at $p \leq 0.001$, comprising CD25⁺CD127^{+/+} FoxP3^{+/+}, but consistently HELIOS⁻, presumably non-Treg populations. A separate analysis using 6 marker combinations (CD38, CD39, CD226, TIGIT, CD45RA, CCR7) within the CD3⁺CD4⁺CD8⁻CD127⁻CD25⁺ compartment which contains most human Treg, showed 48 populations ($p \leq 0.0001$) in 3-way comparison (BD, non-BD uveitis, and HD) pointing to high significance of TIGIT and CD226, and 18 populations with differential expression of CD39⁺ between BD and non-BD diseases subjects. TIGIT and CD226 co-expressing Treg (CD127⁻CD25⁺) subpopulations also reached significance ($p \leq 0.02$) in a longitudinal analysis of 7 BD subjects in active vs inactive disease states, as did 56 out of 6,560 populations within total CD4⁺CD3⁺ cells, mostly representing non-Treg cells in active disease.

Conclusion: Differential expression of CD4⁺ Treg and non-Treg cells shapes the immune-phenotype of BD vs HD and non-BD autoimmune diseases that have phenotypic overlap with BD (uveitis). Populations within the HELIOS⁺FOXP3⁺ compartment of non-activated, non-proliferating Treg had the highest significance when differentiating BD from HD, suggesting relevance of a true Treg phenotype. Non-Treg CD25⁺ cell populations seem more indicative of BD vs non-BD uveitic disease as well as of clinically active BD while populations with high CD39 expression may indicate non-BD states.

Disclosure: J. Nowatzky, None; A. Al-Obeidi, None; Y. Xia, None; O. Manches, None.

Abstract Number: 150

PD-1 Signaling Interferes with OX40L to Alter the Suppressive Function and Proliferation of CD4⁺ Regulatory T Cells in Lupus Mice

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: In systemic lupus erythematosus (SLE), the dysregulated production of autoantibodies is a consequence of disrupted T cell homeostasis. Programmed death-1 (PD-1), a negative regulator in T cells, limits certain T cell-mediated immune responses. Increased PD-1 expression on T cells inhibits cell activation and proliferation and its blockade reinstates immune cell function. Our laboratory has shown that attenuated, but not absent, PD-1 signaling enables CD4⁺ regulatory T cells (T_{reg}) to survive and suppress helper T cells T_h and B cells. Gene array data have shown that attenuated PD-1 expression in T_{reg} down-regulates several members of the TNF receptor family, including OX40L. It has been reported that OX40L is up-regulated in immune cells from patients with autoimmune disease by promoting follicular helper and effector memory T cells, and suppressing T_{reg} proliferation. We hypothesize that one mechanism by which PD-1 sustains T_{reg} proliferation and suppressive function is by reducing OX40L expression on T_{reg}.

Methods: We treated lupus-prone BWF₁ mice with a neutralizing Ab against PD-1 or control isotype-matched IgG intraperitoneally. OX40L, Foxp3 and PD-1 expression on T_{reg} from the spleens was measured by flow cytometry. T_{reg} were cocultured with unmanipulated CD4⁺CD25⁻ T_h and B cells, and cell proliferation/apoptosis of T_{reg}, T_h and B cells was measured with CFSE/Annexin V by flow cytometry. Cytokine production namely IFN γ (T_{h1}), IL-4 (T_{h2}), IL-17a (T_{h17}) and TGF- β (T_{reg}), and anti-dsDNA (B cells) in the culture media were measured by ELISA. To test the plasticity of these T_{reg}, we treated T_{reg} with agonistic vs antagonistic OX40L Ab *in vitro*, and set up the coculture experiments and determined cell proliferation and cytokine production as described above.

Results: OX40L expression was lower in PD1^{lo}T_{reg} from anti-PD1-treated mice when compared to PD1^{hi}T_{reg} from controls. OX40L^{hi}T_{reg}, irrespective to its Foxp3 expression, lost its ability to suppress T_h and B proliferation. PD1^{lo}T_{reg} treated with agonistic OX40L had attenuated suppressive function: there was decreased production of TGF- β , increased proliferation of T_h (T_{h1} predominant) and increased anti-DNA production. These T_{reg} also had increased apoptosis. Treating PD1^{hi}T_{reg} with antagonistic OX40L could not restore the suppressivity in T_{reg}.

Conclusion: Effective induction of T_{reg} is associated with low expression of PD-1, which permits cells to survive and perform cell suppressive function. Attenuated PD-1 expression in T_{reg} reduces OX40L expression on T_{reg}, which helps restore the suppressive capacity and proliferation of T_{reg}. Increased OX40L expression overrides PD-1 signaling to deactivate and induce apoptosis in Foxp3⁺T_{reg}, but reduced OX40L expression cannot recover T_{reg} suppressivity when PD-1 signal is high. The suppressive function induced by low PD-1 expression is influenced by the intensity of OX40L expression. PD-1 and OX40L signaling most likely crosstalk to regulate the suppressive capacity and survival of T_{reg} to achieve peripheral tolerance in SLE.

Disclosure: M. Wong, None; B. H. Hahn, Janssen Research & Development, LLC, 2.

Abstract Number: 151

Molecular Mechanisms of Pathogenic T Cell Resilience in Human Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: T-cell resilience is critical to the immune pathogenesis of human autoimmune arthritis. Autophagy is essential for memory T cell generation and is associated with pathogenesis in rheumatoid arthritis (RA). We have previously described that CD4⁺ T cells in patients with RA have an increased level of autophagy compared to their healthy controls. Here, we sought to explore at epigenetic and transcriptional levels the concept of persisting increased autophagy as the consequence of "autophagic memory", as one of the mechanisms conferring resilience to pathogenic T cells, in particular to a subset of CD4⁺ T cells (CPL: Circulating Pathogenic-like Lymphocytes), which are significantly more represented in patients with active arthritis and patients resistant to therapy with biologics.

Methods: Autophagy was assessed in CD4⁺ T cell subsets from autoimmune arthritis patients and healthy subjects using flow cytometry. RNA sequencing and methylation array analysis to understand the molecular mechanism of autophagic memory. Transcription-factor gene regulatory network analysis was built to identify key regulators. qPCR was used to confirm the gene expression level of key regulators.

Results: We demonstrated "Autophagic memory" as elevated autophagy levels in CD4⁺ memory T cells compared to CD4⁺ naive T cells and in Jurkat Human T cell line trained with starvation stress. We then showed increased levels of autophagy in pathogenic CD4⁺ T cells subsets from autoimmune arthritis patients. Using RNA-sequencing, transcription factor gene regulatory network and methylation analyses we identified MYC as a key regulator of autophagic memory. We validated MYC levels using qPCR and further demonstrated that inhibiting MYC increased autophagy.

Conclusion: The present study proposes the novel concept of autophagic memory and suggests that autophagic memory confers metabolic advantage to pathogenic T cells from RA and supports its resilience and long term survival. Particularly, suppression of MYC imparted the heightened autophagy levels in pathogenic T cells. These studies have a direct translational valency as they identify autophagy and its metabolic controllers as a novel therapeutic target.

Disclosure: P. Kumar, None; J. Y. Leong, None; B. Paleja, None; S. Saidin, None; J. van Loosdregt, None; T. Arkachaisri, None; A. Consolaro, None; M. Gattorno, None; A. Martini, None; G. W Williams, None; K. D Pischel, None; M. Lotz, None; S. Albani, None.

Abstract Number: 152

Polymorphonuclear Neutrophils and Regulatory T Lymphocytes (Treg) Cooperate to Sustain Treg Activity in Normal and Arthritic Contexts

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Polymorphonuclear neutrophils (PMN) are abundant and activated in rheumatoid arthritis (RA) joints. In addition to their pro-inflammatory role, PMN exert immunoregulatory functions and may thus affect T-cell responses. Regulatory T lymphocytes (Treg) play a key role in the control of autoimmunity but they are functionally deficient in RA. Very few data are available on Treg-PMN communication in normal conditions, and even less during inflammation, especially in RA. The aim of this study was to analyze the mechanisms controlling the interaction between Tregs and PMNs and the consequences on their activity.

Methods: Splenic Treg and bone marrow PMN (C57BL/6 mice) were purified by magnetic sorting. Treg and PMN of healthy donors and RA patients were freshly isolated by magnetic sorting from peripheral blood. Co-cultures were unstimulated or exposed to anti-CD3/anti-CD28 antibodies and/or LPS. CD4⁺FoxP3⁺ Treg (mouse and human), Ly6G⁺ (mouse) and CD66b⁺ (human) PMN were identified by flow cytometry. Cell activation was studied using antibodies against CD39, CD25, CTLA-4 (Treg) and CD11b (PMN). Treg maintenance was evaluated as the frequency of FoxP3 expression among CD4⁺ cells, and cell proliferation by CFSE staining followed by flow cytometry analysis. In some case, co-cultures were performed using Transwell (0.4 mm). Cytokine levels were quantified in culture supernatants by ELISA. Collagen-induced arthritis (CIA) was induced by immunization with type II collagen in complete Freund's adjuvant.

Results: Without stimulation of both Treg and PMN from naive mice, no effect on any cell type was observed in co-culture. In contrast, co-culture of activated Treg with activated PMN resulted in Treg proliferation and increased maintenance of FoxP3 expression, with higher CTLA4 but lower CD39 expression, sustained PMN activation evidenced by CD11b up-regulation, and higher secretion of MIP-2, IL-6 and IL-17 but not IFN- γ in naive mice. All these effects were lost in transwell experiments or when blocking JAK signalling. Nevertheless, transfer of supernatants from LPS-activated PMN also partly increases Treg maintenance. Most importantly, PMN sustain Treg suppressive effect on effector T cells (CD4⁺FoxP3⁻) proliferation. Similar results were observed in co-cultures of activated Treg/PMN isolated from CIA mice, although in vitro activation of PMN is not required. Likewise, human Treg-PMN co-cultures led to enhanced Treg maintenance with higher expression of CTLA4/CD25 in a cell contact-dependent manner in both healthy donors and RA patients. Secretion of IL-8 and IL-10 was enhanced in co-cultures.

Conclusion: Our results reveal the existence of a link between Treg and PMN, mainly leading to an activation of both cell types in normal or inflammatory conditions. Although cell contacts are clearly required, soluble mediators are also involved and probably as a second signal. Whether these synergistic interactions lead to a global suppressive or inflammatory milieu with functional modulation of either partner needs to be clarified, especially in RA patients.

Disclosure: M. Batignes, None; F. Santinon, None; M. C. Boissier, None; P. Decker, None; N. Bessis, None.

Chemotaxis of Vδ2 T Cells to the Joints Contributes to the Pathogenesis of Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: To explore the role of Vδ2 t cells in the pathogenesis of rheumatoid arthritis (rA)

Methods: Sixty-eight patients with RA, 21 patients with osteoarthritis and 21 healthy controls were enrolled in the study. All patients with RA fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism criteria for RA. Peripheral Vδ2T population, chemokine receptor expression and proinflammatory cytokine secretion were quantified by flow cytometry. The infiltration of Vδ2 T cells within the synovium was examined by immunohistochemistry and flow cytometry. The effect of tumour necrosis factor (TNF)-α and interleukin (IL)-6 on Vδ2 T migration was determined by flow cytometry and transwell migration assay.

Results: Peripheral Vδ2T cells, but not Vδ1 T cells, were significantly lower in patients with RA, which was negatively correlated with disease activity gauged by Disease Activity Score in 28 joints. Vδ2 T cells from RA accumulated in the synovium and produced high levels of proinflammatory cytokines including interferon-γ and IL-17. Phenotypically, Vδ2 T cells from RA showed elevated chemotaxis potential and expressed high levels of chemokine receptors CCR5 and CXCR3, which was driven by increased serum TNF-α through nuclear factor kappa B signalling. In vivo, TNF-α neutralising therapy dramatically downregulated CCR5 and CXCR3 on Vδ2 T cells and repopulated the peripheral Vδ2 T cells in patients with RA

Conclusion: High levels of TNF-α promoted CCR5 and CXCR3 expression in Vδ2 T cells from RA, which potentially infiltrated into the synovium and played crucial roles in the pathogenesis of RA. Targeting Vδ2 T cells might be a potential approach for RA.

Disclosure: X. Xinyue, None; W. MO, None; X. Zhang, None.

Epigenetic Editing of FOXP3 in Human T Cells Is Sufficient to Induce Overexpression and Create a Regulatory T Cell Phenotype in Vitro

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

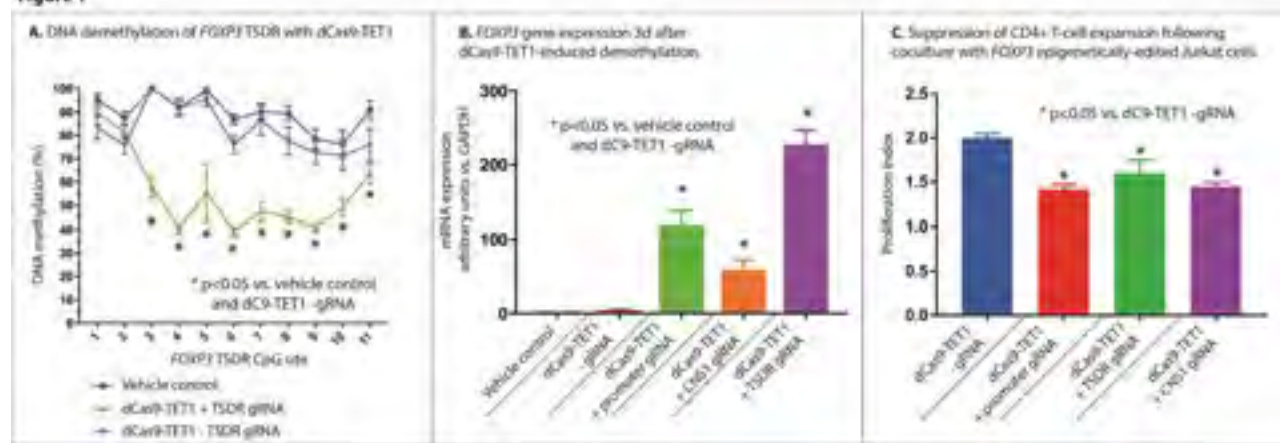
Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Defects in the number and function of naturally-occurring regulatory T cells (Tregs) have been identified in a variety of autoimmune diseases. The development of Tregs is marked by a variety of epigenetic modifications, most closely associated with demethylation of the *FOXP3* gene. Transfection of T cells with *FOXP3* transgenes has resulted in conversion to a Treg phenotype; however, the effects on cellular function of direct epigenetic editing of *FOXP3* has not yet been evaluated.

Figure 1



Methods: Guide RNA (gRNA) sequences targeting the human *FOXP3* promoter, TSDR, and CNS1 region were designed. An epigenetic editing SUNTAG (dCas9 + TET1) construct was used to demethylate genomic regions. Constructs containing dCas9 + TET1 + guide RNA sequences + fluorescent reporter were transfected by electroporation into Jurkat cells and cultured for 24 hours, then enriched by flow sorting. *FOXP3* and *CTLA4* gene expression was determined by qPCR and *FOXP3-TSDR* DNA methylation quantified by bisulfite pyrosequencing 3 days after transfection. Primary CD4+ T cells were isolated from human peripheral blood, stained with CellTrace reagent and combined with *FOXP3* epigenetically-edited Jurkat cells in a 1:1 ratio and stimulated with anti-CD3/anti-CD28 beads and 30U/mL rhIL-2 for 5 days. Suppression of T cell division was determined by flow cytometry.

Results: Epigenetic editing constructs targeting the *FOXP3* TSDR reduced DNA methylation (TSDR region, transfected: $55\% \pm 2$ mean \pm SEM vs. vehicle: 91 ± 3 , $p=8E-5$) (Figure 1), whereas constructs targeting the promoter and CNS1 did not reduce TSDR methylation. All gRNAs increased *FOXP3* expression (TSDR-targeted vehicle: 0.7 ± 0.2 , dC9-TET1+TSDR gRNA 230 ± 10 relative units vs. GAPDH, $p<0.0001$) (promoter-targeted: vehicle: 0.7 ± 0.2 , dC9-TET1+Prom. gRNA 120 ± 20 , $p=0.02$), (CNS1-targeted vehicle: 0.7 ± 0.2 , dC9-TET1 +CNS2 gRNA 59 ± 10 , $p=0.001$) (Figure 1). Furthermore, epigenetic editing of *FOXP3* resulted in increased expression of the Treg-related gene *CTLA4* (*FOXP3* prom.-targeted non-significant, dC9-TET1+*FOXP3* TSDR gRNA 6.4 ± 0.6 vs. vehicle: 1.6 ± 0.4 , $p=0.003$; dC9-TET1+*FOXP3*+CNS1 gRNA: 3.9 ± 5 vs. vehicle: 0.8 ± 0.3 , $p=0.009$). Epigenetically edited cells resulted in suppression of naïve T-cell proliferation by 20-30% (dC9+TET1+prom. gRNA=29% avg. suppression, $p=2E-5$, dC9+TET1+TSDR gRNA=20% avg. suppression, $p=0.008$, dC9+TET1+CNS1 gRNA=28% avg. suppression, $p=3E-5$, all vs. dC9+TET1-gRNA) (Figure 1).

Conclusion: Epigenetic editing of *FOXP3* using a dCas9-TET1 construct induces DNA demethylation, overexpression, and a regulatory T cell phenotype. Our data are intriguing but need confirmation, particularly to clarify the persistence of induced DNA methylation changes and resistance to phenotype switching. If confirmed, this approach has the potential to significantly improve upon current methods of T-reg generation.

Disclosure: C. Dunn, None; C. Velasco, None; M. Andrews, None; A. Rivas, None; M. A. Jeffries, None.

Abstract Number: 155

Polyfunctional Synovial T-Cell Responses and Synovial Invasiveness Repressed By Blockade of Phosphodiesterase 4

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Genetic and functional studies strongly support the role of T-cells in PsA pathophysiology. Effective targeting of T-cells requires a detailed understanding of their phenotypic and functional characteristics at the site of

inflammation. This study aims to understand the different components of T-cell responses in the PsA synovium compared to the peripheral blood and investigate the effects of targeting broader pro-inflammatory signalling pathways by interfering with phosphodiesterase 4 (PDE4).

Methods: PsA Synovial tissue cell suspensions, matched synovial fluid mononuclear cells (SFMC) and PsA peripheral blood mononuclear cells (PBMC) were stimulated with PMA and ionomycin in the presence of Brefeldin A and analysed for CD4, CD8, CD161, IL-17A, IFN γ , GM-CSF and TNF α expression by flow cytometry. PsA synovial cell suspensions were cultured in the presence of PDE4 inhibitor, Rolipram (10 μ M) for 8hr followed by analysis of intracellular cytokines. Polyfunctional cytokine expression was determined by SPICE analysis. The effect of Rolipram treatment on the spontaneous secretion of IL-6, IL-8, MCP-1, IL-1 β , RANTES, MMP-1 and MMP-3 was quantified by ELISA. Explants were also embedded in matrigel over a time-course of 1-21 days and synovial outgrowths assessed.

Results: PsA synovial infiltrating T-cells had increased frequencies of CD4 T helper subsets; Th1 ($p<0.05$), Th17 and exTh17 ($p<0.05$) compared to the peripheral blood. The production of GM-CSF, IL-17A and IFN γ , but not TNF α , was also higher in the synovial tissue compared to peripheral blood ($p<0.05$). Strikingly, polyfunctional cells co-expressing GM-CSF, TNF, IL17A and/or IFN- γ were significantly increased in the CD4, CD8, Th1, Th17 and exTh17 compartment of synovial T-cells. Analysis of disease activity revealed that polyfunctional cytokine expressing T-cells ($p<0.01$, $r=0.89$) and not monofunctional synovial T-cells ($p=0.267$, $r=-0.05$) are important to disease progression. Moreover, we revealed that PDE4 blockade can suppress the frequencies of these polyfunctional GM-CSF⁺TNF α ⁺IL-17A⁺ and/or IFN- γ ⁺ in CD8, CD4, Th1, Th17 and exTh17 cells (all $p<0.05$). Finally, using whole tissue synovial explants, which closely reflect the *in-vivo* inflamed microenvironment of the joint, we demonstrate that PDE4 blockade also inhibits the secretion of pro-inflammatory mediators and synovial invasiveness ($p<0.05$).

Conclusion: Immunophenotypic analysis of the synovial tissue of PsA patients shows accumulation of Th1, Th17 and exTh17 cells, with a specific increase in polyfunctional cells co-expressing GM-CSF⁺TNF α ⁺IL-17A⁺ and/or IFN- γ ⁺, exerting pleiotropic effects and disease progression. Neutralisation of these polyfunctional T-cells and synovial invasiveness by PDE4 may therefore produce optimal inhibition of pro-inflammatory signalling responses in the PsA synovium.

Disclosure: S. M. Wade, None; M. Canavan, None; T. McGarry, None; S. C. Wade, None; R. Mullan, None; D. J. Veale, None; U. Fearon, None.

Abstract Number: 156

Assessing the Role of Ascvd Score in Primary Thrombosis Prophylaxis Strategy Among Asymptomatic Antiphospholipid Antibody Carriers

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Primary thrombosis prophylaxis among asymptomatic antiphospholipid antibody (aPL) carriers is challenging. The presence of aPL does not always lead to thromboembolic events. Additional factors are needed to potentiate thrombus formation. A risk stratification tool to guide primary thrombosis prophylaxis among aPL positive carriers does not yet exist. Our study aims to evaluate the role of ASCVD score in primary thrombosis prophylaxis among asymptomatic aPL carriers.

Methods: This study included a convenience cohort of 198 persistent aPL positive patients who attended clinic at University of Texas Southwestern Medical Center. All patients had persistent high titer (≥ 99 percentiles) aPL. LA was tested by dilute Russell's viper venom time, partial thromboplastin time-LA and silica clotting time, with appropriate cut-offs established in the laboratory. ASCVD is calculated based on patients' age, total cholesterol, HDL, most recently documented systolic blood pressure, diabetes status, and smoking status. Pearson Chi-squared analysis was used to determine the association between increased ASCVD >10 and various thromboembolic events. Non-parametric comparison of ASCVD as a continuous variable was performed among different groups.

Results: Of the 198 aPL positive patients, 38 (19.2%) patients had arterial thrombosis, 72 (36.3%) had venous thrombosis, 7 had both arterial and venous thrombosis, and 95 (48.0%) were asymptomatic. Significantly higher 10-year CVD risk was

seen among aPL patients with arterial thrombosis compared to asymptomatic carriers ($P<0.0001$). When comparing thrombotic APS patients to asymptomatic aPL positive carriers, 10-year CVD risk $>7.5\%$ ($OR=2.202$, 95% CI 1.043–4.556, $P=0.042$) and 10-year CVD risk $>10\%$ ($OR=2.321$, 95% CI 1.089–5.153, $P=0.029$) were significantly associated with arterial thrombosis but not venous thrombosis or any thrombosis. There were no significant CVD risk differences observed between aPL patients with venous thrombosis/or any thrombosis and asymptomatic carriers.

Conclusion: Increased 10 year cardiovascular disease risk determined by ASCVD among aPL positive patients is significantly associated with arterial thrombosis but not venous thrombosis. Since the protective effect of aspirin against incident thrombosis in all aPL carriers is not supported by randomized controlled data, our result suggests that ASCVD may be useful in identifying a subgroup of aPL carriers who benefit from aspirin.

Disclosure: Y. Zuo, None; A. Udupa, None; J. Fan, None; U. E. Makris, None; D. Karp, None; Y. M. Shen, None.

Abstract Number: 157

Identifying Additional Risk Factors Associated with Thrombosis and Pregnancy Morbidity in a Unique Cohort of Antiphospholipid Antibody Positive Chinese Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Risk stratification of asymptomatic aPL carriers is difficult. Our objective was to identify additional clinical and epidemiological predictors of arterial thrombosis, venous thrombosis, and pregnancy morbidities in a large cohort of Chinese aPL carriers.

Methods: This cohort included 297 consecutive persistent aPL positive patients who attended the rheumatology clinic at Peking University People's Hospital. Among those, 85 had arterial thrombosis, 76 had venous thrombosis, and 34 experienced APS related pregnancy morbidities. 143 patients had at least one persistent positive aPL without any other criteria APS manifestations and were defined as aPL positive control patients. When assessing risk factors associated with pregnancy morbidities, only reproductive age (age <45) female controls were used. Pearson Chi-squared analysis and multivariable logistic regression were used to evaluate correlation between different risk factors and clinical manifestations.

Results: When comparing to asymptomatic aPL positive controls, additional risk factors associated with arterial thrombosis included: hypertension ($OR=2.368$, 95% CI 1.249 – 4.491, $P=0.0083$), smoking ($OR=6.137$, 95% CI 2.408 – 15.637, $P=0.0001$), and the presence of underlying autoimmune disease ($OR=4.401$, 95% CI 2.387– 8.113, $P<0.0001$). Additional risks associated with venous thrombosis included: smoking ($OR=4.594$, 95%CI 1.681 – 12.553, $P=0.029$) and the presence of underlying autoimmune disease ($OR=6.33$, 95%CI 3.355 – 11.94, $P<0.0001$). The presence of underlying autoimmune disease ($OR=3.301$, 95%CI 1.407 – 7.744, $P=0.0061$) is the only additional risk which demonstrated a significant association with pregnancy morbidity. A high frequency of thrombocytopenia and hypocomplementemia were observed in all +aPLs patients.

Conclusion: Hypertension is a potential predictor for arterial thrombosis. Smoking and the presence of underlying autoimmune disease are potential predictors for both arterial and venous thrombosis among aPL carriers. The presence of underlying autoimmune disease is an additional risk for APS related pregnancy morbidities in +aPL Chinese patients. This is the largest cross sectional comparison between Chinese APS patients and asymptomatic aPL carriers where we are able to identify additional risk factors for thromboembolic events and pregnancy morbidities. Our data may help physicians to risk stratify aPLs positive Asian patients.

Disclosure: Y. Zuo, None; C. Li, None; S. Zhang, None; U. Makris, None; D. Karp, None; Z. G. Li, None.

Incidence and Prevalence of Antiphospholipid Syndrome in a Health Management Organization (HMO): A 15-Year Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Antiphospholipid Syndrome (APS) is an unusual disease and there are scarce epidemiological data. Our objective was to assess incidence and prevalence rates of APS using data from a tertiary university hospital-based health management organization (HMO) in Latin America.

Methods: Different methods were used to ensure complete APS cases ascertainment: (a) patients with diagnosis of APS, recurrent abortions and/or fetal death in HMO electronic medical records, (b) patients with a Lupus anticoagulant, IgG/IgM anticardiolipin and/or IgG/IgM β 2glycoprotein positive test in laboratory database, (c) patients included in the Institutional Registry of Thromboembolic Disease of our hospital. Electronical medical records of all cases retrieved by these ascertainment methods were reviewed and definite APS was diagnosed if 2006 modified Sapporo Criteria were fulfilled. Possible APS was diagnosed if diagnosed by an experienced rheumatologist (in spite of absence of a second antibody determination). Global, age-specific, and sex-specific incidence and prevalence rates were calculated for members of the HMO. For the incidence study members with continuous affiliation ≥ 1 year from January 2000 to January 2015 were followed until he/she voluntarily left the HMO, APS was diagnosed, death, or study finalization. Prevalence was calculated on January 1st 2015.

Results: 53 incident cases of APS were identified during the study period. Patients' characteristics are shown in table 1. A total of 349,775 persons contributed a total of 2,073,438 person-years. Incidence rates are reported as cases per 100,000 person-years (py): APS overall incidence rate was 2.6 (95% CI 1.9-3.2), 2.9 (95% CI 2.0-3.9) and 2.0 (95% CI 1.1-3.0) in women and men respectively. In our population, age-specific incidence and prevalence rates in female patients peaked in the third decades of life and in male they peaked in the sixth decades. On January 1st 2015, 55 APS prevalent cases were identified from a denominator population of 135,750 HMO members. Prevalence rate was 40.5 per 100,000 persons (95% CI 29.8-51.2). LA was the most frequent antibody (71.7%); thrombotic events were more frequent than obstetric ones and only 2 women had both (5.6%).

Conclusion: Incidence and prevalence rates were similar of previous reports. Incidence and prevalence rates in women were higher in the young population, associated with obstetric morbidity.

Table 1. APS Incident cases characteristics

	APS patients(n=53)
Female, n (% , 95% CI)	36 (67.9 ,53.9-79.3)
Mean age at diagnosis, years (DS)	55.9 (17.1)
Mean age at first event, years (DS)	52.6 (17.5)
Global Incidence per 100,000 patients-year (% , 95% CI)	2.6 (1.9-3.2)
Definite cases (fulfilment of Sapporo criteria), n (%)	50 (94.3)
Probable cases, n (%)	3 (5.7)
Lupus anticoagulant +, n (% , 95% CI)	38 (71.7, 57.8-82.4)
IgG anticardiolipin +, n (% , 95% CI)	22 (42.3, 29.4-56.4)
IgM anticardiolipin +, n (% , 95% CI)	23 (44.2, 31.1-58.2)
IgG β 2glycoprotein +, n (% , 95% CI)	7 (28.0, 13.3-49.6)
IgM β 2glycoprotein +, n (% , 95% CI)	5 (20.0, 8.1-41.5)
LA + Anticardiolipin, n (% , 95% CI)	26 (49.1, 35.6-62.2)
Triple positive, n (% , 95% CI)	7/25 (28.0, 13.3-49.9)
Thrombotic event, n (% , 95% CI)	44 (83.0, 70.0, 91.1)
Deep venous thrombosis (DVT), n (% , 95%CI)	24 (45.3, 32.2-59.1)
Pulmonary thromboembolism (PTE), n (% , 95%CI)	7 (13.2, 6.3-25.7)
Stroke, n (% , 95%CI)	12 (22.6, 13.11-36.2)
Stroke + DVT or PTE, n (% ,95%CI)	1 (1.9, 0.2-12.9)
Obstetric morbidity, n/females (% , 95% CI)	11/36 (30.6, 17.4-47.9)

Table . (Cont'd)

	APS patients(n=53)
> or = 3 abortion 1 st trimester, n (% , 95% CI)	5 (9.4, 3.9-21.2)
Fetal loss > 10 weeks, n (% , 95% CI)	5 (9.6, 3.9-21.6)
Premature birth < 34 w, n (% , 95% CI)	1 (1.9, 0.2-13.3)
Thrombotic and obstetric event, n/females (% , 95% CI)	2/36 (5.6, 1.3-20.7)
Primary APS, n (% , 95% CI)	45 (84.9, 72.2-92.4)
Rheumatic disease associated, n (% , 95% CI)	8 (15.1, 7.6-27.8)
Mortality at 12.7 years, n (% , 95% CI)	1 (1.9, 0.2-13.3)
Follow-up time, median, years (IQR)	12.7 (9.1-15.3)

Disclosure: A. Luissi, None; M. Scolnik, None; E. R. Soriano, AbbVie, Bristol-Myers Squibb, GSK, Janssen, Novartis, Pfizer Inc, Roche, UCB, 2,AbbVie, Bristol-Myers Squibb, Eli Lilly, GSK, Janssen, Novartis, Pfizer Inc, Roche, Sanofi, UCB, 5,AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer Inc, Roche, Sandoz, UCB, 8.

Abstract Number: 159

The Frequency of Screening and Prevalence of Antiphospholipid Antibodies in the General Population

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

Session Type: ACR Poster Session A

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

Background/Purpose: The antiphospholipid syndrome (APS) is defined by vascular thrombosis or pregnancy morbidity in the presence of persistently circulating antiphospholipid antibodies (aPL). Those positive for multiple types of aPL have greatest future thrombotic risk. Little is known regarding testing patterns in a population-based sample and whether testing for aPL is done in accordance with the revised Sydney recommendations. We characterized patterns of aPL testing in a large general population sample.

Methods: We performed a retrospective analysis using TruvenHealth MarketScan® Research Databases, that integrate de-identified patient health data (contributed by large employers, managed care organizations, hospitals, EMR providers, Medicare and Medicaid) including laboratory results on a subset (over 1 million). We used MarketScan lab data from 2010-2015 to identify individuals tested for lupus anticoagulant (LA), anti-cardiolipin(aCL), and anti-beta2-glycoprotein1 (aGP1) antibodies. All subjects were required to be at least 18 years old, having continuous eligibility for medical benefits at least 12 months before and 3 months following the first aPL test.

Results: We identified 33,456 individuals who had had at least one aPL test performed. The distribution of testing is shown in Figure 1. In these 33, 456 individuals, only 6,391 (19%) had been tested for all three tests (LA, aCL, aGP1). Of those 33,456 tested at least once, 5786 (17.3%) were positive for at least one test and 255 of these 5,786 (10.6%) had a confirmatory second finding.

18,370 individuals had one or more LA test, among which 1,291 (7%) were positive initially. Among these 1,291 initially positive, only 996 (77%) were known to have been retested ≥12 weeks later.

24,964 individuals had one or more aCL test, among whom 3,753 (15%) were positive initially. Of those 3,753 initially positive, only 1,707 (45%) were re-tested ≥12 weeks.

11,456 individuals had one or more aGP1 test, among whom 1,304 (11%) were positive initially. Of those 1,304 initially positive, only 537 (41%) were re-tested ≥12 weeks.

Conclusion: In this retrospective claims analysis, and applying revised Sydney criteria for APS diagnosis, we determined that confirmatory aPL testing was performed ≥12 weeks in 77%,45%, and 41% of initially positive LA, aCL, and aGP1, respectively. In addition, in those individuals who had been tested at least once for any aPL, only 6,391 had been tested for all 3 aPL. These findings highlight that aPL testing may often be incompletely performed. Limitations of these analyses include the possibility that testing was done outside the window for which we had data. Further characterization of testing

patterns in individuals with known thrombotic events, pregnancy morbidity, systemic lupus, and other high-risk conditions is warranted and may help to inform local diagnostic practices.



Figure 1: Distribution of testing for LA, aB2GPI, and ACL

Disclosure: G. Egiziano, None; J. Widdifield, None; A. Rahman, None; E. Vinet, None; C. S. Moura, None; J. R. Curtis, Amgen Inc., 2, 5, AbbVie Inc., 2, 5, BMS, 2, 5, Corrona, LLC, 2, 5, Janssen, 2, 5, Eli Lilly, 2, 5, Myriad, 2, 5, Pfizer, Inc., 2, 5, Roche/Genentech, 2, 5, Radius, 2, 5, UCB, Inc., 2, 5; S. Bernatsky, None.

Abstract Number: 160

Pregnancy Outcomes of Antiphospholipid Antibody Positive Patients: Prospective Results from Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) Clinical Database and Repository (“Registry”)

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

Session Type: ACR Poster Session A

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

Background/Purpose: APS ACTION Registry was created to study the natural course of disease over 10 years in persistently antiphospholipid antibody (aPL) positive patients with or without systemic autoimmune diseases. The objective of this analysis was to describe the new pregnancy outcomes of the aPL-positive patients since the inception of the registry.

Methods: A web-based data capture system is used to store patient demographics, history, and medications. The inclusion criteria are positive aPL, based on the laboratory section of the Updated Sapporo APS Classification Criteria, tested at least twice within one year prior to enrollment. Patients are followed every 12±3 months with clinical data and blood collection. For this descriptive analysis, we identified patients who were recorded as “pregnant” during the prospective follow-up; new “aPL-related pregnancy morbidity” was defined as: a) live birth with small-for-gestational-age (SGA) infant with/without preeclampsia (PEC); b) preterm live birth (PTLB) ≤ 34th week of gestation due to PEC or eclampsia; or c) fetal death ≥ 10th week of gestation. Categorical variables were analyzed using chi-square test or Fisher’s exact test, and continuous variables using Student’s t-test or ANOVA.

Results: Since the inception of the registry in 2012, 55 pregnancies were recorded in 42 aPL-positive patients. Three pregnancies, ongoing at the time of data lock, were excluded. Of 40 patients included (mean maternal age: 32.9 ± 5.2 y; primary aPL/APS: 30 [75%]; systemic lupus erythematosus [SLE]: 10 [25%]), 10 (25%) did not fulfill clinical APS classification criteria, 5 (13%) had obstetric APS (OAPS), 12 (30%) thrombotic APS (TAPS), and 13 (33%) OAPS+TAPS. Pregnancy outcomes (Table) were not different between patients with or without TAPS, with and without OAPS, with or without APS, and with OAPS and with TAPS with one exception: term live birth occurred in 12/34 (35%) of pregnancies of patients with history of TAPS compared to 12/18 (67%) of pregnancies of patients without history of TAPS (*p*: 0.03). The analysis of all the pregnancy morbidity combined showed no significant difference between the groups. Forty-four of 52 (85%) pregnancies were treated with low dose aspirin (LDA) and/or low-molecular weight heparin (LMWH) (37 with LDA+LMWH): 5/52 (10%) due to OAPS only (LDA+LMWH: 5); 14/52 (27%) TAPS only (LDA+LMWH: 12); 16/52 (31%) OAPS and TAPS (LDA+LMWH: 13); and 9/52 (17%) despite no APS classification (LDA+LMWH: 7). Medications were not different among patients with different new pregnancy outcomes.

Conclusion: In our multi-center international prospective aPL-positive cohort, after excluding one-fourth of pregnancies complicated by pre-embryonic or embryonic losses before 10 weeks of gestation: a) five of 39 (13%) resulted in fetal deaths; and b) 34 of 39 (87%) resulted in live birth, while 12 of 39 (31%) patients had “aPL-related pregnancy morbidity”. Clinical and Laboratory Characteristics of Newly Pregnant Patients Included in AntiPhospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) Clinical Database and Repository (“Registry”), by Pregnancy Outcomes

	TLB n: 24 (46%)	PTLB* n: 10 (19%)	FD** n: 5 (10%)	PELS*** n: 13 (25%)	p
Additional Pregnancy Morbidity	SGA/PEC: 1 PEC: 1	SGA/PEC: 2 PEC: 3 SGA: 1	-	-	
History of Lupus	7 (29%)	2 (20%)	3 (60%)	2 (15%)	0.28
History of Thrombosis	12 (50%)	7 (70%)	4 (80%)	11 (85%)	0.16
History of Pregnancy	20 (83%)	7 (70%)	3 (60%)	10 (77%)	0.67
History of Pregnancy Morbidity	16 (67%)	2 (20%)	3 (60%)	9 (69%)	0.14
≥1 Fetal Death ≥ 10w	9 (38%)	1 (10%)	2 (40%)	5 (38%)	0.38
≥1 Preterm Delivery ≤ 34w	6 (25%)	2 (20%)	1 (20%)	4 (31%)	0.94
≥1 Pre-Emb/Emb Loss < 10w	8 (33%)	2 (20%)	2 (40%)	6 (46%)	0.25
Laboratory Category					
Lupus Anticoagulant (+) Only	9 (38%)	2 (20%)	4 (80%)	3 (23%)	0.10
Double aPL (+)	6 (25%)	2 (20%)	-	2 (15%)	0.80
Triple aPL (+)	9 (38%)	6 (60%)	1 (20%)	8 (62%)	0.26
Rx During Pregnancy					
No LDA / LMWH	1 (4%)	1 (10%)	2 (40%)	4 (31%)	0.06
LDA alone	1 (4%)	-	-	-	-
LMWH alone	5 (21%)	1 (10%)	-	-	0.53
LDA + LMWH	17 (71%)	8 (80%)	3 (60%)	9 (69%)	0.88
Hydroxychloroquine	14 (58%)	5 (50%)	3 (60%)	6 (46%)	0.90

TLB: term live birth; PTLB: preterm live birth; FD: fetal death; PELS: pre-embryonic or embryonic loss; SGA: small for gestational age; PEC: preeclampsia; LDA: Low-dose aspirin; LMWH: Low-molecular-weight-heparin. * 7/10 at or before 34w of gestation; ** 10-20w of gestation; 2, ≥20w; 3); ***3rd consecutive loss only for one patient

Disclosure: E. Sevim, None; D. Andrade, None; A. Banzato, None; M. Tektonidou, None; A. Ugarte, None; C. B. Chighizola, None; L. Ji, None; D. Branch, None; G. Ramires de Jesus, None; L. Andreoli, None; M. Petri, None; R. Cervera, None; J. S. Knight, None; T. Atsumi, None; D. Erkan, None.

Clinical and Laboratory Characteristics of Persistently Antiphospholipid Antibody Positive Patients: Retrospective Results from Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) Clinical Database and Repository (“Registry”)

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

Session Type: ACR Poster Session A

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

Background/Purpose: APS ACTION Registry was created to study long-term outcomes in persistently antiphospholipid antibody (aPL)-positive patients with/without other systemic autoimmune diseases (SAIDx). The primary objective of this analysis was to report the baseline demographic, clinical, and laboratory characteristics of aPL-positive patients enrolled since 2012. Secondly, we analyzed the association between aPL-profiles and aPL-related events at baseline.

Methods: A web-based data capture system is used to store patient demographics and aPL-related medical history. Inclusion criteria are positive aPL, based on the Updated Sapporo APS Classification Criteria, tested at least twice within one year prior to enrollment (IgA aCL/aβ₂GPI included whenever available). Patients are followed every 12±3 months with clinical data and blood collection. For this analysis, aCL and aβ₂GPI IgG/M/A positivity was defined as a titer of ≥40 U, based on local enrollment tests, and criteria and non-criteria (NC) aPL manifestations were retrieved (Table). To test the association between aPL profiles and clinical outcomes, we used chi-square test or Fisher's exact test for categorical variables.

Results: As of 12/2017, 714 patients were enrolled from 26 centers worldwide (mean age at entry: 45 ± 13y; female: 530 [74%]; white: 460 [64%]; and other SAIDx: 257 [36%]). Historically, 161 (23%) had aPL-positivity without APS; 393 (55%) thrombotic APS (TAPS); 66 (9%) obstetric APS (OAPS); and 94 (13%) TAPS+OAPS. 48% and 63% of TAPS patients had arterial and venous thrombosis, respectively (14% both); 1% had catastrophic APS. 81 of 161 (50%) and 263 of 553 (48%) of patients without and with clinical APS classification, respectively, had ≥1 NC aPL manifestation. Livedo (p=0.002) and skin ulcers (p=0.047) were more frequent in patients with TAPS+OAPS and TAPS (with/without OAPS), respectively (vs aPL-positive patients without APS). Based on inclusion aPL, 585 (82%) patients were tested for all three aPL; 222/585 (38%) were triple aPL-positive. Thrombosis, pregnancy morbidity, and NC aPL manifestation rates were similar across different aPL profiles except (Table): a) ≥3 consecutive (pre)embryonic losses and cardiac valve disease

differed when compared between triple-, double-, and single aPL-positive patients; and b) livedo was higher in isolated LA-positive patients compared to triple aPL-positive patients.

Conclusion: In our international aPL-positive cohort, at baseline: a) one-fourth of patients do not fulfill clinical APS classification criteria; b) almost half have at least one non-criteria aPL manifestation; c) livedo and skin ulcers are more common in thrombotic APS patients; and d) there is no association between the aPL-related criteria events and aPL profile. Future prospective registry analysis, accounting for potential confounders and using standardized core laboratory aPL test results, will help clarify aPL risk profiles.

Baseline Clinical Characteristics of 714 Patients Included in AntiPhospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) Clinical Database and Repository (“Registry”) Between 2012-2018, by Antiphospholipid Antibody (aPL) Profile

Baseline Clinical Characteristics	P ¹	LA only Positivity (134)	Triple* aPL Positivity (222)	Double* aPL Positivity (176)	Single* aPL Positivity (179)	P ²
Any Vascular thrombosis	0.29	100 (75%)	154 (69%)	114 (65%)	122 (68%)	0.61
- Arterial Thrombosis	0.51	40 (30%)	68 (31%)	60 (34%)	51 (29%)	0.24
- Venous Thrombosis	0.93	70 (52%)	107 (48%)	66 (38%)	82 (46%)	0.10
- Small Vessel Thrombosis	0.47	6 (4%)	13 (6%)	10 (6%)	7 (4%)	0.62
Transient Ischemic Attacks	0.53	9 (7%)	19 (9%)	17 (10%)	12 (7%)	0.60
Catastrophic APS	0.52	1 (1%)	2 (1%)	2 (1%)	0	0.38
Any Pregnancy Morbidity	0.22	51 (38%)	58 (26%)	60 (34%)	64 (36%)	0.64
- ≥ 1 Fetal Death ≥ 10 th w	0.33	26 (37%)	35 (60%)	31 (52%)	34 (53%)	0.60
- ≥ 1 Preterm Delivery <34 th w	0.21	11 (16%)	19 (33%)	18 (30%)	12 (19%)	0.20
- ≥ 1 Pre-Emb/Emb Loss < 10 th w	0.22	31 (44%)	28 (48%)	31 (52%)	38 (59%)	0.50
- ≥ 3 Pre-Emb/Emb Loss < 10 th w	0.17	9 (13%)	5 (9%)	3 (5%)	11 (17%)	0.041
Any Non-Criteria Manifestation	0.78	70 (52%)	116 (52%)	96 (55%)	87 (49%)	0.40
- Livedo Reticularis/Racemosa	0.032	23 (17%)	21 (9%)	24 (14%)	24 (13%)	0.34
- Persistent Thrombocytopenia	0.05	23 (17%)	54 (24%)	31 (18%)	27 (15%)	0.051
- Persistent Hemolytic Anemia	0.70	8 (6%)	14 (6%)	5 (3%)	9 (5%)	0.28
- Cardiac Valve Disease	0.06	8/112 (7%)	26/181 (14%)	14/149 (9%)	9/152 (6%)	0.037
- Skin Ulcers	0.77	5 (4%)	7 (3%)	7 (4%)	7 (4%)	0.89
- aPL-associated Nephropathy**	0.50	2 (2%)	7 (3%)	4 (2%)	2 (1%)	0.41

*Triple (LA+aCL+aβ₂GPI), double (two tests based on LA, aCL, or aβ₂GPI), and single (LA, aCL, or aβ₂GPI); ** Biopsy-proven.

p¹: comparison between triple aPL and LA only positivity; p²: comparison between triple, double, and single aPL positivity.

Note: Among 585 patients, only **one** patient included in the registry because of isolated IgA positivity; and b) only **three** patients switched groups because of IgA (groups were determined based on the highest isotype titer).

Disclosure: E. Sevim, None; D. F. Zisa, None; D. Andrade, None; V. Pengo, None; M. Tektonidou, None; A. Ugarte, None; M. Gerosa, None; L. Ji, None; M. Efthymiou, None; G. Ramires de Jesus, None; D. Branch, None; C. Nalli, None; S. Sciascia, None; H. M. Belmont, None; P. R. Fortin, None; M. Petri, None; E. Rodriguez-Almaraz, None; R. Quintana, None; J. S. Knight, None; R. Willis, None; T. Atsumi, None; M. L. Bertolaccini, None; D. Erkan, None; M. Barbhaiya, RRF, 2.

Abstract Number: 162

Mammalian Target of Rapamycin (mTOR) Pathway Assessment in Antiphospholipid Antibody Positive Patients with Livedo Reticularis/racemosa

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SESSION INFORMATION

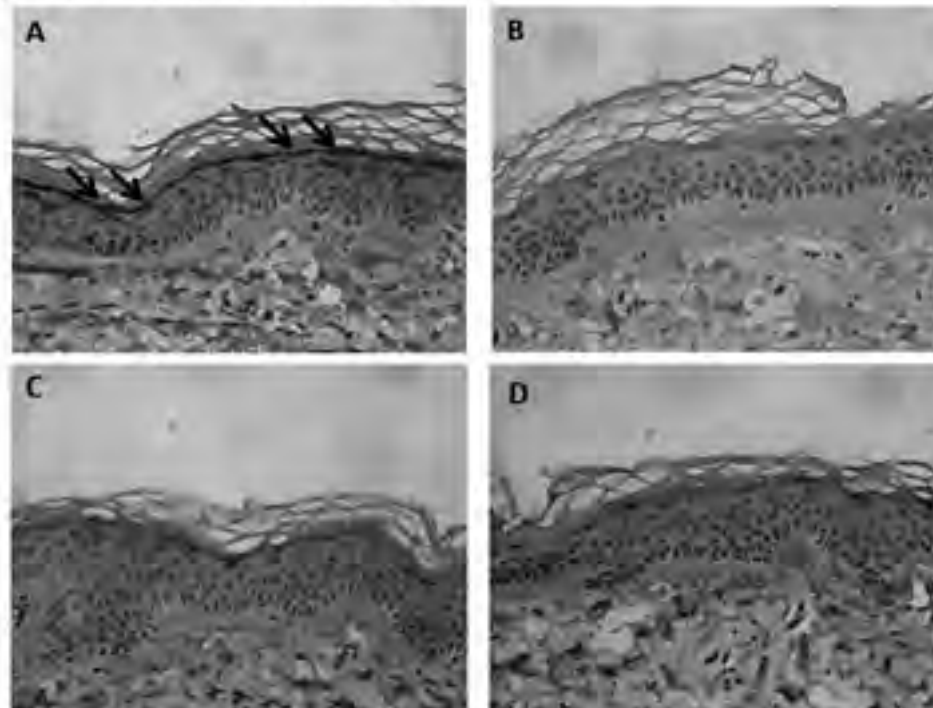
Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

Session Type: ACR Poster Session A

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

Figure: Increased mTOR Activity Suggested by the S6RP Staining (arrows) in the Central Skin Biopsy (A) of an Antiphospholipid Antibody-positive SLE Patient with Livedo, Compared to the Lesional Skin Biopsy (B) in the same patient (no similar mTOR activity was observed in the central [C] or lesional [D] skin biopsies of the aPL-negative SLE patient with livedo).



Background/Purpose: Endothelial proliferation is a key finding in antiphospholipid antibody (aPL)-positive patients with microthrombosis. The mTOR pathway plays a role in the endothelial proliferation leading to aPL-related nephropathy; however the role of mTOR pathway is not well determined in patients with livedo, which is purple discoloration of the skin due to reactive dilation of peripheral dermal venules triggered by reduced blood flow in the center. Thus, our primary objective was to investigate mTOR pathway activation in the skin biopsies of aPL-positive patients with livedo reticularis/racemosa; secondly, we investigated mTOR activation in peripheral blood mononuclear cells (PBMC).

Methods: This ongoing cross-sectional study includes patients with livedo reticularis/racemosa: a) those with persistent aPL-positivity (LA, aCL IgG/M ≥ 40 U, and/or α_2 GPIIgG/M ≥ 40 U) with/without systemic lupus erythematosus (SLE); and b) aPL-negative SLE patients as a control group. We collect demographics and aPL-related history. We perform two 5-mm skin biopsies on each patient, one from the erythematous-violaceous (lesional) and the second from a non-violaceous area (central). Specimens are stained for phosphorylated S6 ribosomal protein (P-S6RP) as a marker of mTOR complex-1 activity;,. We also collect PBMCs from aPL-positive patients to examine mTOR expression in monocytes assessed by flow cytometry. Unstimulated and lipopolysaccharide (LPS)-stimulated measurements are used to calculate the fold change in mTOR activation. Mann-Whitney-U test is used to compare the fold change between aPL-positive patients and sex- and age-matched healthy controls.

Results: As of May 2018, three aPL-positive SLE patients (all female and Caucasian; mean age: 40 ± 11.2 y; and 2 met APS clinical classification criteria) and one aPL-negative SLE control were enrolled. In all aPL-positive patients, but not in aPL-negative SLE control, there was increased mTOR activity in the non-violaceous area (central) of the skin (epidermis), compared to erythematous-violaceous (lesional) skin (Figure). Unstimulated, LPS-stimulated, and fold change mTOR measurements were not different in monocytes of aPL-positive patients, compared to the healthy control group (p: 0.57, p: 0.73, and p: 0.56, respectively).

Conclusion: Based on the preliminary results of our ongoing study, we found increased mTOR activity in the center of livedoid lesions of aPL-positive patients with SLE, compared to an aPL-negative SLE patient. However, there was no systemic mTOR activation in monocytes. Given the vascular stenosis occurring in arterioles located in the center leading to livedo at the periphery, our findings are consistent with the pathophysiology of livedoid lesions. Further analysis with increased number of patients will determine the clinical relevance of our findings.

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Development of New International Classification Criteria for Antiphospholipid Syndrome: Phase II Item Reduction Survey

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

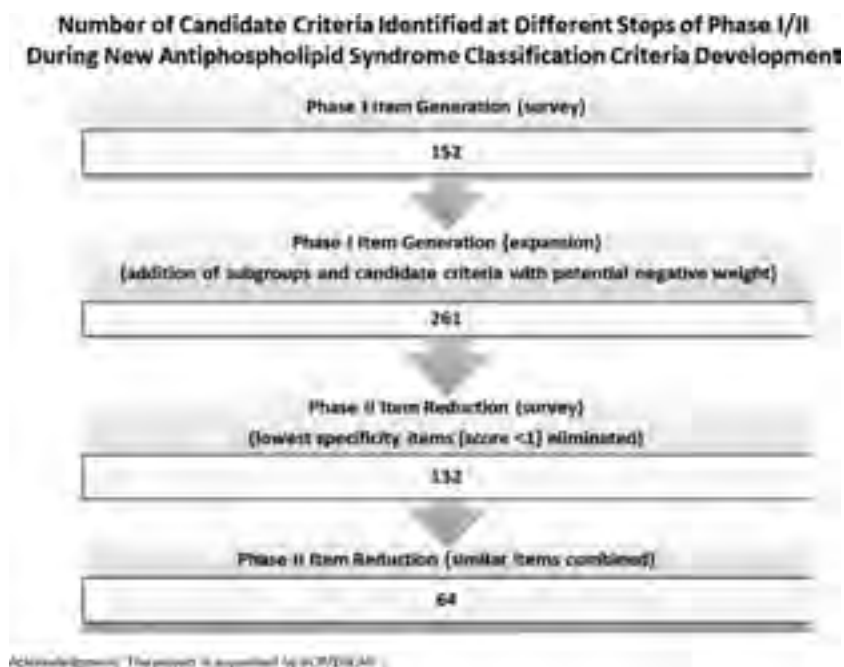
Session Type: ACR Poster Session A

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

Background/Purpose: An international multidisciplinary effort has been initiated to develop new rigorous, consensus-based criteria to identify patients with high likelihood of having APS. The methodological approach includes both expert-based and data-driven methods, and four phases: item generation (I); item reduction (II); item weighting and threshold identification (III); and classification criteria refinement and validation (IV). We have previously reported Phase I results (Barbhuiya M, et al. *Lupus* 2016;25[SupplS]:11); here we report our Phase II "Item Reduction" survey results. The aim of Phase II is to reduce the 261 Phase I items to approximately 20 items, considered to be the most important features distinguishing APS from other conditions.

Methods: 61 international physician-scientists experienced in APS were e-mailed a survey to rank each item generated in Phase I on a Likert scale (-5 to +5), with (-5) **extremely strongly against APS, i.e., more likely related to another disease entity; (0) not for or against APS; and (+5) extremely likely APS**. Experts were asked to "consider two patients who are exactly the same except that one has the clinical feature presented and the other does not. Please rate each feature in terms of how strong this feature is in differentiating APS from other similar conditions, i.e., specific for APS." An article reference library (n: 26), including mostly aPL/APS-related systemic reviews and meta-analyses, was provided. Mean survey scores for each item (\pm SD) were calculated. Items were ranked from highest to lowest mean score, and highest scoring items were grouped based on independent logical domains.

Results: Phase II survey response rate was 71%. Of 43 responders, 22 were rheumatologists, four hematologists, four nephrologists/cardiologists/neurologists/vascular specialists, four internists, three clinical immunologists, three pediatric rheumatologists, two pediatric hematologists, and one obstetrician. Mean item scores ranged from -2.29 to 4.65; items of



low specificity (score less than 1) were eliminated. The higher specificity items (n=132) were organized into seven clinical (cardiopulmonary, dermatologic, hematologic, neurologic, obstetric, renal/abdominal, and vascular), two laboratory (antiphospholipid antibody [aPL] ELISA and lupus anticoagulant), and one pathologic domains. Items overlapping or describing similar concepts were combined (n=64) (Figure).

Conclusion: Sixty-four candidate criteria identified using the Phase II item reduction survey will be further reduced and refined based on the ongoing project to develop new APS classification criteria, with the goal of better standardizing patients for APS research.

Disclosure: M. Barbhaiya, RRF, 2; S. Zuily, ACR/EULAR, 2; Y. Ahmadzadeh, None; R. P. Naden, None; K. Costenbader, None; D. Erkan, ACR/EULAR, 2.

Abstract Number: 164

Reliability of Lupus Anticoagulant and Anti-Phosphatidylserine/Prothrombin Autoantibodies in Antiphospholipid Syndrome: A Multicenter Study

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	Patients	S (42 Patients)
Demographic		
mean age (S.D.) at data collection	48.9 (13.9)	
SEX (males)	17	28.3
Clinical manifestations of APS		
Thrombosis	43	71.7
Arterial Thrombosis	25	41.7
Venous Thrombosis	27	45
Obstetric APS	1	1.7
Low Titer aPL and Thrombosis*	17	28.7
GAPSS mean (S.D.)	11 (8)	
aPL profile at diagnosis		
LA (positive, n)	37	79.2
ACA (IgG/IU)	32	58.3
anti-β2GPI (IgG/IU)	29	48.3
Antithrombotic Therapy		
VKA (warfarin)	26	51.1
LMWH	5	8.3
DOAC	8	13.3
None	27	45

Characteristics of the patients included in the study.

SD = Standard Deviation; APS = Antiphospholipid Syndrome; aPL = Anticardiolipin Antibodies; GAPSS = Clinical and Biological Score, 1-4 = None Anticardiolipin; ACA = Anticardiolipin Antibodies; anti-β2GPI = Anti-β2Glycoprotein I antibodies; VKA = Vitamin K antagonist; LMWH = Low Molecular Weight Heparin; DOAC = Direct Anticoagulant.

*Defined as levels of ACA IgG/IU or anti-β2GPI IgG/IU antibodies 25-40 UPL/MPU.

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Correct interpretation of lupus anticoagulant (LA) tests is crucial for diagnosis of antiphospholipid syndrome (APS). However, testing patients during vitamin K antagonist (VKA) or other anticoagulant treatment remains a contentious issue and has been discouraged by official guidelines because of interpretational problems affecting the mixing test.

Methods: We enrolled 60 patients who met one of the following inclusion criteria: 1) Fulfilled the diagnosis of thrombotic APS defined as per Sidney criteria; 2) Patients with thrombosis and suspected APS not completely fulfilling the laboratory criteria, as follows: a) and inconstant previous LA positivity; and/or b) low-medium titers aPL (defined as levels of aCL IgG/IgM or anti- β 2GPI IgG/IgM 10-30GPL/MPL aPL) with no LA positivity. aPL testing was performed in a blind fashion in 4 centers undergoing periodic external quality assessment.

Results: The mean age at was 50 years old (SD ± 11) (F:M71,7% : 28,3%). Forty-three patients (72%) had a confirmed diagnosis of thrombotic APS (arterial 58%; venous 56%), and 17 patients presented with thrombosis and inconstant LA positivity (N. 7; 41%) and/or with low-medium titers (N. 10;59%). Categorical agreement for LA among the centers, as expressed by Cohen's kappa coefficients, ranged between 0.41 and 0.60 (corresponding to moderate agreement). The correlation among quantitative results at the 4 sites for aPS/PT IgG was strong (Cohen's kappa coefficients=0.81–1. Spearman rho 0.84). We observed 27 (45 % of the total) cases (15/20, 75% patients on VKA) in which LA results were discordant (as defined by lack of agreement in ≥ 3 laboratories) or inconclusive. Conversely, in those cases, we observed a good correlation for aPS/PT IgG testing (Cohen's kappa coefficients=0.81–1, Spearman rho 0.86). aPS/PT testing showed an overall agreement of 83% (up to 90% in patients receiving VKA), providing an overall increase in test reproducibility of + 28% when compared to LA, becoming even more evident (+65%) when analyzing patients on VKA.

Conclusion: Despite the progress in the standardization of aPL testing, we observed up to 45% of discrepant results for LA, even higher in patients on VKA. Our findings highlight that some discordances in the reliability of LA testing still exist. The introduction of aPS/PT antibody testing into the diagnostic process of APS might represent a further diagnostic tool, especially when LA is not available or the results are uncertain.

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Abstract Number: 165

Clinical and Immunological Features of Antiphospholipid Syndrome in the Elderly: A Retrospective National Multicenter Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Antiphospholipid syndrome (APS) mainly affects women who are of child-bearing age. We aimed to describe the clinical and immunological features of APS patients diagnosed after the age of 60.

Methods: The Elderly-Phospholipid study is a national, multicenter, retrospective study involving all APS (2006 revised Sapporo criteria) patients followed in 5 French tertiary university centers including 4 national referral centres for lupus and APS. The clinical and serologic features of patients in whom APS was diagnosed after the age of 60 were analyzed and compared to APS patients included in the Euro-Phospholipid cohort.

Results: Sixty-one patients (40 women (65.6%); 68.2 ± 7 years at diagnosis) were included in the Elderly-Phospholipid study. 70.4% of the patients had primary APS. Stroke was the most common manifestation at diagnosis (36.1%) and during follow

up (9.8%). Lupus anticoagulant (LA), aCL and a β 2GPI antibodies were detected in 70.5%, 67.7% and 60.6% of patients, respectively. 37.7% patients were triple-positive for aPL antibodies. All patients were treated with antithrombotic treatment including antiplatelet agents (29.5%) and/or oral anticoagulants (82%). Over a 5.3 \pm 3.8 years follow-up, only 5 (8.2%) patients, all receiving oral anticoagulants, developed major bleeding. The mortality rate was 11.5% with a mean age at death of 77.2 \pm 6 years. The most common causes of death were infection, haemorrhage and malignancy. As compared to Euro-Phospholipid APS patients who had a mean age of 34 \pm 13 years at the onset of the disease, patients in the Elderly-Phospholipid study were more frequently male ($p<0.01$) and had a higher frequency of primary APS ($p<0.01$), stroke ($p<0.0001$) and LA ($p<0.05$).

Conclusion: Older patients with late APS onset have a distinct disease profile, with a higher frequency of LA antibody and arterial thrombosis.

Clinical features at disease onset in elderly patients with APS

	Elderly-Phospholipid (n=61)	Euro-Phospholipid* (n=1000)	P
Stroke, n (%)	22 (36.1)	131 (13.1)	<0.0001
Pulmonary embolism, n (%)	17 (27.8)	90 (9)	<0.0001
Thrombocytopenia, n (%)	13 (21.3)	219 (21.9)	ns
Deep vein thrombosis, n (%)	11 (18)	317 (31.7)	<0.05
Livedo reticularis, n (%)	7 (11.5)	204 (20.4)	ns
Transient ischemic attack; n (%)	6 (9.8)	70 (7)	ns
Epilepsy, n (%)	5 (8.2)	34 (3.4)	ns
Myocardial infarction, n (%)	4 (6.5)	28 (2.8)	ns
Hemolytic anemia, n (%)	3 (4.9)	66 (6.6)	ns
Superficial thrombophlebitis, n (%)	2 (3.3)	91 (9.1)	ns
CAPS, n (%)	1 (1.6)	6 (0.6)	ns

Immunologic findings in elderly patients with APS

	Elderly-Phospholipid (n=61)	Euro-Phospholipid* (n=1000)	P
Anticardiolipin antibodies, n (%)	41 (67.2)	879 (87.9)	<0.0001
IgG and IgM	5 (8.2)	321 (32.1)	<0.0001
IgG alone	25 (41)	436 (43.6)	ns
IgM alone	11 (18)	122 (12.2)	ns
AntiB2GPI antibodies, n (%)	37 (60.6)	na	
IgG and IgM	6 (9.8)	na	
IgG alone	21 (34.4)	na	
IgM alone	10 (16.4)	na	
Lupus anticoagulant, n (%)	43 (70.5)	536 (53.6)	<0.05
Alone	14 (22.9)	121 (12.1)	<0.05
With anticardiolipin antibodies	4 (6.6)	na	
With antiB2GPI antibodies	2 (3.3)	na	
Triple positive aPL	23 (37.7)	na	
Antinuclear antibodies, n (%)	33 (54)	597 (59.7)	ns
Anti-double-stranded DNA, n (%)	11 (18)	292 (29.2)	ns
Anti-Ro/SSA, n (%)	7 (11.5)	140 (14)	ns
Anti-La/SSB, n (%)	1 (1.6)	57 (5.7)	ns
Anti-Sm, n (%)	0 (0)	55 (5.5)	ns

ns, not significant ($p>0.05$); na, not available; CAPS, catastrophic antiphospholipid syndrome

*Arthritis Rheumatism, 2002, 46, 1019–1027, Ann Rheum Dis 2015;74:1011–1018

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Abstract Number: 166

Superior Sensitivity for Detection of Primary Antiphospholipid Syndrome By a 9-Test Panel in Patients with Deep Venous Thrombosis, Pulmonary Embolism, and Stroke or Transient Ischemic Attack

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

Table 1. Sensitivity and specificity of nine tests for detection of PAPS in 1835 patients comprised of 513 with PE, 583 with DVT, and 739 with S/TIA; ATH, all patients with thrombotic events; HC, healthy controls.										
TEST	$\alpha 2$ -IgG	$\alpha 2$ -IgM	$\alpha 2$ -IgA	aCL-IgG	aCL-IgM	aCL-IgA	HPPNA	DRVVT	PNP	All tests
PE+ TEST+	19	7	3	13	25	2	144	63	20	30
PE+ TEST-	250	255	194	417	396	250	205	189	45	20
Sensitivity (%)	4.9	2.7	1.5	3	5.0	0.8	41	25	30.8	50
p value vs HPPNA	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	-	<0.0001	NS	<0.0001
DVT+ TEST+	21	15	9	28	50	2	216	78	40	95
DVT+ TEST-	411	370	317	569	523	347	299	277	69	11
Sensitivity (%)	4.9	4.0	2.8	4.7	8.7	0.57	44.5	21.97	31	76.5
p value vs HPPNA	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	-	<0.0001	0.0026	<0.0001
S/TIA+ TEST+	18	15	10	28	33	3	22	135	26	39
S/TIA+ TEST-	351	354	334	655	627	381	204	296	55	15
Sensitivity (%)	4.9	4	2.9	4.1	5	0.78	9.7	31.3	32	72
p value vs PNP	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	NS	-	<0.0001
ATH+ TEST+	52	41	22	69	108	7	382	278	88	105
ATH+ TEST-	1012	979	845	1641	1540	978	678	702	188	40
HC+ TEST+	1	0	7	1	0	0	0	1	0	1
HC+ TEST-	8	40	208	99	40	496	40	39	40	39
p value	NS	NS	NS	NS	NS	NS	<0.0001	<0.0001	<0.0001	<0.0001
Sensitivity (%)	4.8	4.0	2.5	4.0	6.5	0.7	30.0	28.6	31.3	59.5
p value vs HPPNA	<0.0001	0.0006	<0.0001	<0.0001	<0.0001	<0.0001	-	<0.0001	NS	<0.0001
PPV (%)	98	100	76	99	100	100	100	100	100	99
Specificity (%)	98	100	97	98	100	100	100	98	100	98
p value vs HPPNA	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
NPV (%)	3.8	3.9	20.3	23.8	26.2	32.2	5.6	5.0	17.5	48.5

Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Antiphospholipid Syndrome (APS) is characterized by thrombotic events mediated by antiphospholipid antibodies (aPL). Most patients have primary APS (PAPS), while a significant minority has SLE (Ann. Rheum. Dis. 74, 1011). Although PAPS affects 0.5% of the population (Thrombosis Res. 151, S43), it may be underdiagnosed in the absence of SLE. Thus, we evaluated aPL testing in non-SLE patients with deep venous thrombosis (DVT), pulmonary embolism (PE), and stroke or transient ischemic attack (S/TIA).

Methods: 1835 patients were evaluated for PAPS at our Institution between 2010 and 2018: 513 were diagnosed with PE, 583 with DVT, and 739 with S/TIA. Lupus anticoagulants were assessed by hexagonal phase phospholipid neutralization assay (HPPNA) and diluted Russell viper venom test (DRVVT) using Stago protocols (Parsippany, NJ, USA). Platelet neutralization procedure (PNP) was performed, as earlier described (*Am. J. Clin. Pathol.* 79, 678). IgG and IgM antibodies to $\beta 2$ -glycoprotein 1 ($\alpha 2$ -IgG, $\alpha 2$ -IgM) and cardiolipin (aCL-IgG, aCL-IgM) were measured in house while IgA isotypes ($\alpha 2$ -IgA, aCL-IgA) were tested by LabCorp (Burlington, NC). Sensitivities, specificities, positive (PPV) and negative predictive values (NPV) were assessed by 2-tailed χ^2 tests using GraphPad software.

Results: In patients with PE, HPPNA was the most sensitive individual test for detecting APS (from 349/513 tested, 144/349 resulted in positive HPPNA (41%). 50/513 patients were assessed with all 9 tests; 30/50 had at least one positive result (sensitivity: 60%; $p < 0.0001$ relative to HPPNA). In patients with DVT, HPPNA was also most sensitive for detecting APS (from 485/583, 216/485 resulted in positive HPPNA (45%), $p < 0.01$ relative to all other individual tests). 47/583 patients were assessed with all 9 tests; 36/47 had at least one positive test (sensitivity: 76.6%; $p < 0.0001$ relative to HPPNA). In 739 patients with S/TIA, PNP was the most sensitive individual test for detecting APS (from 81/739, 26/81 resulted in positive PNP (32%). 54/739 patients were evaluated with all 9 tests; 39/54 had at least one positive test (sensitivity: 72%; $p < 0.0001$ relative to PNP). When combining patients with DVT, PE, and S/TIA (Table 1), the complete 9-test panel yielded the greatest sensitivity for detecting APS (105/151, 69.5%) relative to the most sensitive individual test, HPPNA (382/1060, 36%; $p < 0.0001$). The 9-test panel had similar specificity and PPV but markedly higher NPV at 46% over any individual test ($p < 0.0001$).

Conclusion: This study indicates that a 9-test aPL panel has superior sensitivity for detecting PAPS in patients with DVT, PE, or Stroke/TIA. However, the complete panel was only performed in 151 of 1835 patients with thrombotic events. These findings have major implications for diagnosis of PAPS patients who need lifelong anticoagulation for preventing potentially fatal thrombotic events.

Disclosure: K. Dziamski, None; K. Banki, None; A. Perl, None.

Recurrent Thrombosis in Patients with Antiphospholipid Antibodies Following an Initial Venous or Arterial Thromboembolic Event

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

Session Type: ACR Poster Session A

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

Background/Purpose: After an initial thromboembolic event (TE), several studies reported that patients with antiphospholipid syndrome (APS) manifest a high-risk for recurrent TE. A systematic review found that antiphospholipid antibody (aPL) positivity in patients with a first venous TE (VTE) predicted an increased risk of recurrent VTE, but the strength of the association was uncertain because of low quality studies. Few studies report on recurrent TE after a first arterial TE (ATE). We performed a systematic review to determine if the risk for recurrence was comparable between VTE and ATE in patients with APS.

Methods: We used the systematic review methodology developed by Cochrane and the Evidence-based Practice Centers and EPPI-Reviewer 4 software. The population of interest was APS patients who had a single VTE or ATE. Outcomes included recurrent VTE, ATE, and death. Studies that did not distinguish patients based on an initial VTE or ATE were excluded. Risk of bias was formally assessed. Aggregate recurrence rates were estimated using meta-analysis. Statistical heterogeneity of pooled analysis was assessed using the chi-squared and the I² statistics. A weighted 24-month rate was estimated using OpenMeta software.

Results: Table 1 demonstrates the number of articles. For patients with initial VTE, 10 studies described 257 patients on anticoagulation and 572 patients who had discontinued anticoagulation. For patients with initial ATE, 4 studies described 405 patients on anticoagulation and 370 patients who had discontinued anticoagulation. Patients with initial VTE who stopped anticoagulation were generally not treated with aspirin, whereas patients with an initial ATE who stopped anticoagulation took aspirin. Table 2 provides 2-year risk estimates of recurrent TE following an initial VTE or ATE. Limitations of studies included heterogeneous criteria for positive aPL definition and APS diagnosis, varying study designs (randomized trials vs. cohort studies), and small sample sizes. In addition, only 3 studies provided information about the same patients while taking anticoagulation as well as after stopping anticoagulation.

Conclusion: Compared to APS patients with an initial VTE, APS patients with an initial ATE have a higher risk for recurrent TE while taking anticoagulation, similar to the rate while not taking anticoagulation. Due to the limitations of literature, however, it is difficult to accurately estimate and compare recurrence rates for APS patients with different thrombotic phenotypes. Future studies need to clearly distinguish between different thrombotic manifestations of APS.

Table 1: The Number of Articles Identified at Each Stage of the Systematic Review

	VTE	ATE
# after the first search	3,137	1,694
# after the exclusion based on title and abstract screening	90	137
# after the exclusion based on full review	6	4
# after the inclusion of new studies based on manual review	13	5
# included in the final analysis	10	4

VTE: venous thromboembolism; ATE: arterial thromboembolism

Table 2: Overall Risk Estimates of Recurrent Thromboembolism (TE) in APS Patients Following an Initial Venous TE (VTE) and Arterial TE (ATE), Stratified by Long-term Anticoagulation (95% Confidence Interval)*

	VTE	ATE
On Anticoagulation	0.045 (0.020-0.070)	0.187 (0.101 – 0.274)
	13 Events in 257 Patients	81 Events in 405 Patients
No Anticoagulation (c/s antiplatelet Rx)	0.167 (0.085-0.250)	0.168 (0.129 – 0.206)
	105 Events in 572 Patients	62 Events in 370 Patients

* Results are provided as proportions and total number of events, and represent the rates over 24 months

Disclosure: T. Ortel, None; S. Meleth, None; D. Catellier, None; M. Crowther, None; D. Erkan, None; P. R. Fortin, None; D. Garcia, None; N. Haywood, None; S. R. Levine, None; M. J. Phillips, None; N. Whitehead, None.

Abstract Number: 168

IgG Anti-High-Density Lipoproteins Antibodies Discriminate between Arterial and Venous Events in Thrombotic Antiphospholipid Syndrome Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

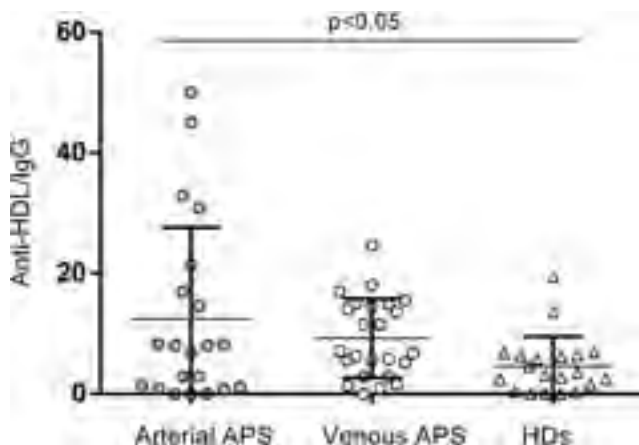
Session Title: Antiphospholipid Syndrome Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Reliable biomarkers for risk stratification in Antiphospholipid Syndrome (APS) are still lacking. Anti-high-density lipoproteins antibodies (anti-HDL) showed promising results in predicting the development of cardiovascular disease in autoimmune conditions. Nevertheless, the association between anti-HDL and clinical features of APS remains unclear.

Methods: This cross-sectional study included 60 thrombotic APS patients and 20 healthy donors(HDs). Clinical data were retrospectively collected (Figure 1). Serum levels of total IgG, IgG anti-HDL antibodies and complete aPL profile were assessed, including lupus anticoagulant, anti-cardiolipin, anti- β 2glycoproteinI, and anti-phosphatidylserine/prothrombin antibodies.



Patients Characteristics	APS patients (n=50)	HDs (n=20)
Female sex, n (%)	43 (71.9)	25 (75)
Age (mean, S.D.), years	50±10.6	45.1±11.6
Primary APS patients, n (%)	43 (71.9)	0 (0)
Concomitant diagnosis of SLE, n (%)	17 (28.3)	-
Disease duration since APS diagnosis (mean, S.D.), years	11.7±7.5	-
Thrombosis, n (%)	60 (100)	0 (0)
Venous thrombosis, n (%)	57 (61)	-
Arterial thrombosis, n (%)	20 (30)	-
Pregnancy morbidity, n (%)	1 (1.6)	0 (0)
Arterial hypertension, n (%)	22 (36.6)	1 (5)
Hyperlipemia, n (%)	19 (31.6)	0 (0)
Smoking, n (%)	5 (8.3)	2 (10)
LA, n (%)	14 (56.6)	0 (0)
aCL-IgG/IgM, n (%)	22 (36.6)	0 (0)
Anti-B2GPI-IgG/IgM, n (%)	22 (36.6)	0 (0)
aPS/PT-IgG/IgM, n (%)	29 (48.3)	0 (0)
Triple aPL positivity, n (%)	15 (25)	-
GAPSS (mean, S.D.)	12.3±5.5	-
Total cholesterol levels (mean, S.D.), mg/dl	187.4±51	145±32.2
LDL-cholesterol levels (mean, S.D.), mg/dl	84±9.1	72±15.8
Triglycerides levels (mean, S.D.), mg/dl	38.7±28.6	104±26.2
CRP levels (mean, S.D.), mg/dl	0.4±0.2	0.2±0.2
Statins, n (%)	20 (33)	0 (0)
Anti-thrombotic drugs, n (%)	19 (31.6)	1 (5)
HCQ, n (%)	15 (25)	0 (0)
Anticoagulant agents, n (%)	33 (55)	0 (0)
Antithrombotic agents, n (%)	36 (60)	0 (0)

APS means Antiphospholipid Syndrome; HDs, healthy donors; SLE, systemic lupus erythematosus; LA, lupus anticoagulant; aCL, anti-cardiolipin antibodies; anti-B2GPI, anti-B2 glycoprotein I antibodies; aPS/PT, antiphosphatidylserine/prothrombin antibodies; aPL, anti-phospholipid antibodies; GAPSS, Global Antiphospholipid Score; HDL, high-density lipoproteins; CRP, C-reactive protein; HCQ, hydroxychloroquine

Results: 43 patients (72%) were primary APS and 17 patients (28%) had a concomitant diagnosis of autoimmune disease. Thirty APS patients (50%) presented previous arterial events and 37 (61%) venous events. Higher levels of IgG anti-HDL were found in APS patients compared to HDs [mean 46 (\pm 70) vs. 14 (\pm 13)AU, respectively; $p < 0.001$], even after correcting for total IgG levels [mean 13 (\pm 16) vs. 4.6 (\pm 5), respectively; $p < 0.001$]. No association with traditional cardiovascular risk factors, except for smoking habit ($p < 0.0001$) was found. No differences in anti-HDL levels were observed between patients with primary APS and those with a concomitant autoimmune disease ($p > 0.050$). Patients who experienced at least one arterial event had significantly higher levels of anti-HDL antibodies when compared to patients with history of venous thrombosis [mean 53 (SD \pm 94) vs. mean 34 (SD \pm 29), respectively; $p = 0.046$] (Figure 2). This difference became stronger when adjusting for total IgG levels [anti-HDL/IgG: mean 13.1 (SD \pm 16.7) vs. mean 9.5 (SD \pm 6.6); $p = 0.007$]. In addition, patients tested positive for aPS/PT (IgG/IgM) antibodies had significantly higher levels of anti-HDL antibodies [mean 53.1 (SD \pm 81.1) vs. mean 20.7 (SD \pm 17.6), $p = 0.045$]. The levels of IgG anti-HDL antibodies were not influenced by pharmacological treatments (all $p > 0.050$).

Conclusion: Our study demonstrates that thrombotic APS patients have higher levels of IgG anti-HDL antibodies, supporting the emerging role of these autoantibodies in APS setting. Moreover, our findings suggest that anti-HDL represent a promising tool for risk management and assessment and a potential biomarker for lipid dysfunction and arterial thrombotic events.

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Prognosis of Patients with Antiphospholipid Syndrome Nephropathy

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Antiphospholipid syndrome (APS) is associated with several patterns of renal involvement. Among them, antiphospholipid nephropathy (APSN) is a rare but specific pattern resulting from microvascular lesions. APSN prognosis, outside lupus nephritis, is unknown. We aimed to describe the renal, vascular and general prognosis of patients with APSN.

Methods: We performed a retrospective multicenter study on patients with antiphospholipid antibodies associated with APSN lesions, and no other nephropathy. Patients were identified through a national call for medical reports. End-stage renal disease (ESRD)-free survival, thrombosis recurrence-free survival and overall survival were assessed. Factors associated with estimated glomerular filtration rate (eGFR) change were also analysed.

Results: Twenty-five patients were included : 18 (72%) women, median age 38.8 (24.6-68.7) years. Seventeen (68%) had APS according to revised Sapporo criteria, 22 (88%) with lupus anticoagulant, 14 (56%) with triple positivity. Median blood pressure was 132 (110-214) / 79.5 (60-124) mmHg, median eGFR was 47.8 (5.8-103) mL/min/1.73m², median proteinuria was 0.95 (0.14-5) g/day. On renal biopsy 13 (52%) had glomerular thrombotic microangiopathy, 17 (68%) fibrous intimal hyperplasia and 3 (12%) focal cortical atrophy. Moderate to severe interstitial fibrosis ($\geq 25\%$) was observed in 11 (44%) patients. Three patients developed ESRD after a median follow-up of 4.4 (0.4-38.3) years. ESRD-free survival at 5 years was 82.3% (IC95% 65.5%-100%). Two other patients presented a 30% decrease in eGFR. No factor was significantly associated with annual change in eGFR. However patients with interstitial fibrosis ($\geq 25\%$) seemed to have steeper eGFR decline (-0.08 (-4.42;7.005) ; 3.03 (-18.23;14.05) ; $p=0.06$). Thrombosis recurrence-free survival was 96% at 5 years (IC95% 88.7%-100%), 74% at 10 years (IC95% 51%-100%). One patient died during follow-up. Overall survival was 100% at 5 years and 90% at 10 years (IC95% 73%-100%).

Conclusion: The renal prognosis of isolated APSN is poor in this young population. Up to 20% of patients developed ESRD at 5 years. Severe lesions of renal fibrosis suggest a late diagnosis. The early detection of renal features could improve prognosis with the possibility of evaluating the efficacy of anti-proliferative treatments in APSN.

Disclosure: C. Rousselin, None; Z. Amoura, None; A. Karras, None; D. Guerrot, None; J. J. Boffa, None; G. Canaud, None; S. Faguer, None; E. Auxenfans, None; N. Jourde-Chiche, None; M. Lambert, None; T. Quémeneur, None.

Abstract Number: 170

Predictive Value of Antiphospholipid Antibodies in the Acute Phase of Deep Vein Thrombosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Deep vein thrombosis (DVT) is frequent and potentially life threatening disease with tendency to reoccur. Anticoagulant treatment of the first episode of DVT usually lasts 3 months. Antiphospholipid syndrome (APS) is an important cause of DVT. However, the APS can be confirmed only 24 weeks after DVT according to the current APS classification criteria. Thus, undiagnosed APS patients, who cease anticoagulant therapy after 3 months, might be exposed to a greater risk for recurrent venous thromboembolism. Studies evaluating the significance of positive antiphospholipid antibody (aPL) test in the acute phase of DVT are lacking. We aimed to evaluate whether positive aPL test at the time of acute DVT diagnosis is predictive of APS.

Methods: Patients with acute DVT, confirmed by compression ultrasound, were included into a 24-month prospective study. All patients were given anticoagulants. aCL IgG/IgM and anti-β2GPI IgG/IgM/IgA antibodies were determined by our in-house ELISA at inclusion and then every 4 weeks for the first 24 weeks. The last aPL measurement was performed 24 months after inclusion into the study. APS was confirmed if a patient tested positive (medium or high positive aCL and/or presence of anti-β2GPI) 12 and 24 weeks after DVT. Lupus anticoagulants (LA) were tested after cessation of anticoagulation.

Results: 196 patients (111 male, 85 female, age 54±2 years) included in the study had aPL titer assessed at least 5 times. Ultimately, 20/196 (10.2%) patients fulfilled APS classification criteria. Among these, 15/20 (75%) patients had medium or high titer aPL at the time of acute DVT (1 of whom had double positive aPL and 2 of them had multiple positive aPL at first aPL determination). Two patients (10%) had low positive aCL IgG and one had low titer aCL IgM. Two patients (10%) were negative for aPL, but had later fulfilled APS criteria due to positive LA. APS was not established in 176/196 (89.7%) patients. Among these, 146/176 (83%) patients were negative for aPL at inclusion, while 30/176 (17%) had low titer aCL IgM or aCL IgG. Altogether, diagnostically important aCL IgG/IgM and/or anti-β2GPI titer at the time of acute DVT had 83% specificity and 90.5% sensitivity for APS. Isolated low titer aCL IgG were more frequent in patients with APS than in patients without APS ($\chi^2=125.6$; $p<0.001$). Completely negative aCL IgG/IgM and anti-β2GPI in the acute phase of DVT had a negative predictive value of 98.6%.

Conclusion: Here we show that in acute phase of DVT, positive medium or high titer aCL IgG/IgM or anti-β2GPI is suggestive of APS. In these patients continuation of anticoagulation beyond the initial 3 months should be considered. Patients with negative aPL in the acute phase of DVT do not need further aPL testing; however, LA should be determined. Low aPL titre at the time of acute DVT deems further testing imperative.

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Abstract Number: 171

Flow Cytometric Assessment of the Mammalian Target of Rapamycin Pathway Using Antiphospholipid Syndrome As a Disease Model

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

Session Type: ACR Poster Session A

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

Background/Purpose: The mammalian target of rapamycin (mTOR) is a component of MTOR complex-1 that, when activated by upstream molecule protein kinase B (AKT) and another cell signaling pathway mitogen activated protein kinase p38 (p38/MAPK), is responsible for protective autophagy, cell proliferation and growth, and protein synthesis. These independent signaling pathways cross-talk and regulate each other. The mTOR pathway is responsible for the endothelial proliferation leading to chronic renal vascular lesions in antiphospholipid antibody (aPL)-positive patients.

Firstly, our team developed a flow cytometry-based assay that assesses the basal and responsive mTOR phosphorylation in peripheral blood monocytes of patients in relation to the activation of AKT and p38/MAPK . Secondly, based on this assay, we evaluated three antiphospholipid syndrome (APS) patients.

Methods: We assayed unstimulated and lipopolysaccharide (LPS)-stimulated whole blood, 30 minutes at 37C, for peripheral blood classical monocyte (HLA-DR⁺⁺CD14⁺CD16⁻), phosphorylated mTOR/AKT, and p38/MAPK analysis. Unstimulated and stimulated levels of phosphorylated mTOR/AKT and p38/MAPK were reported as percent positives and median fluorescence intensities, and compared against each other. Three APS patients, identified according to the Updated Sapporo Classification Criteria, were assessed with the assay. The mean results were compared with three age- and gender-matched healthy volunteers by the Mann-Whitney U test.

Results: All patients were male (mean age: 51 ± 18.5) with no other systemic autoimmune diseases. Patient #1 had history of arterial thrombosis, autoimmune hemolytic anemia, thrombocytopenia, white matter changes, aPL nephropathy, and livedo reticularis (on aspirin [ASA], azathioprine, and low dose prednisone). Patient #2 had arterial thrombosis, transient ischemic attacks, and microthrombotic APS with peripheral cyanosis, diffuse alveolar hemorrhage, and livedoid vasculopathy (on ASA, hydroxychloroquine, atorvastatin, and low-molecular-weight-heparin). Patient #3 had microthrombotic APS with livedoid vasculopathy (on mycophenolate mofetil and warfarin). All three patients had high mTOR levels both at baseline and after stimulation when compared to healthy controls (p: 0.02 and p: 0.007, respectively), which was independent of AKT and p38/MAPK activation (p: 0.02 and p: 0.03, respectively) (Table).

Conclusion: We developed a flow cytometry-based assay that assesses the activation of mTOR and related proteins; our preliminary analysis of three APS patients demonstrates that mTOR pathway is activated independent of AKT and p38/MAPK. Further clinical studies will determine the clinical utility of this assay.

Table: Flow Cytometric Detection of mTOR, AKT, and p38/MAPK in Monocytes of APS Patients and Healthy Controls Before and After Lipopolysaccharide Stimulation

		Patient 1	Patient 2	Patient 3	Patient Mean	Control Mean	p
% of mTOR-positive monocytes	Unstimulated	80	49	44	58	15	0.02
	Stimulated	95	96	87	93	76	0.007
	Fold Increase	1.6	2.3	2.0	1.9	2.5	0.29
% of AKT-positive monocytes	Unstimulated	10	4	7	7	2	0.06
	Stimulated	76	73	59	69	72	0.62
	Fold Increase	3.1	3.4	2.3	2.9	3.8	0.07
% of p38/MAPK- positive monocytes	Unstimulated	1	2	8	4	7	0.46
	Stimulated	29	50	80	53	67	0.45
	Fold Increase	1.8	3.4	9.0	4.7	4.5	0.93
% of mTOR- & AKT- positive monocytes	Unstimulated	11	3	6	6	2	0.11
	Stimulated	75	72	57	68	65	0.71
	Fold Increase	7.0	26.6	9.8	14.5	44	0.05
% of mTOR- & P38/MAPK- positive monocytes	Unstimulated	1	1	4	2	2	0.98
	Stimulated	17	44	78	47	59	0.56
	Fold Increase	21.5	35.5	19.3	25.3	31.4	0.38
% of AKT-independent mTOR-positive monocytes	Unstimulated	69	46	38	51	6	0.02
	Stimulated	20	24	30	25	11	0.03
	Fold Increase	0.3	0.5	0.8	0.5	0.8	0.37
% of p38/MAPK-independent mTOR-positive monocytes	Unstimulated	79	48	40	56	13	0.03
	Stimulated	78	52	8	46	16	0.25
	Fold Increase	1.0	1.1	0.2	0.8	1.1	0.64

Disclosure: A. Badger, None; E. Sevim, None; O. Alpan, None; D. Erkan, None.

Abstract Number: 172

Serum Chemokines and miRNA Levels and Its Association with Cumulative Organ Damage in Patients with Antiphospholipid Syndrome: A Bench to Bedside Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Recent evidence suggests that chemokines and miRNAs are involved in the pathogenesis of antiphospholipid syndrome (APS). However, the specific role of these molecules in both cumulative thrombotic damage and in risk of thrombosis is still not well understood. The aim of this study was to explore the association between autoimmunity related chemokines and miRNAs with cumulative organ damage as well as the clinical risk of thrombosis in patients with APS.

Methods: This cross-sectional study included patients with APS Sapporo/Sydney criteria from a single outpatient rheumatology clinic. Demographic, clinical and clinimetric data (DIAPS, Damage Index in patients with Thrombotic Antiphospholipid Syndrome; aGAPSS, adjusted Global Anti-Phospholipid Syndrome Score and SLEDAI, Systemic Lupus Erythematosus Disease Activity Index) were recorded. Serum samples were obtained in the same visit and levels of chemokines BLC (B lymphocyte chemoattractant), IP10 (IFN- γ -induced protein 10), MCP-1 (monocyte chemoattractant protein-1) and MIG (monokine-induced-by-IFN- γ) were measured by multiplex bead array technology (Luminex MAGPIX System). In addition, relative expression of miR-19, miR-20, miR-126, and miR-155 was measured by qPCR. Sera from healthy individuals were evaluated for reference. Normality analysis was performed with Kolmogorov-Smirnov test and comparisons were made with Mann-Whitney U test. Associations were evaluated with exact Fisher's test and Spearman rho coefficient. ROCs were used to investigate miRNAs cut-off points. IBM SPSS version 23.0 was used for calculations.

Results: Sixty five APS patients were included, mean age was 43 ± 14 years old, 73% were female and 53% primary APS. DIAPS correlates with number of thrombosis (0.381, $p=0.003$), anti-cardiolipin antibodies IgG (0.328, $p=0.030$), anti- β 2GPI IgG (0.366, $p=0.017$) and BLC (0.385, $p=0.015$). Anti-cardiolipin IgG (0.395, $p=0.010$) and BCL (0.359, $p=0.025$) also correlates with aGAPSS. SLEDAI correlates with miR-126 (0.637, $p=0.001$) in secondary APS. The tissue factor related miRNAs, miR-19 (AUC=0.812, $p<0.0001$) and miR-20 (0.834 $p<0.0001$) were able to differentiate patients from controls. Interestingly, $\text{miR-20} \leq 0.0198$ was associate to the presence of anticardiolipin ($p=0.048$) and a tendency of triple positivity ($p=0.093$) as well as recurrent thrombosis ($p=0.075$).

Conclusion: Our results suggest that BLC, miRNA-19 and miRNA-20 may be involved in the accrual damage in APS and risk of thrombosis. Wide and prospective studies to explore processes related to accumulation of chronic damage in APS are needed. The long time follow up for clinical end-points is the challenge for validating new potential circulating biological markers.

Disclosure: L. A. Martinez-Martinez, None; F. Sanchez-Muñoz, None; M. J. N. N. Chacon-Perez, None; Y. Juarez-Vicuña, None; N. M. Ornelas, None; A. Beltran-Cortez, None; R. A. Venegas Yañez, None; J. Fonseca Basurto, None; E. Aranda Cano, None; M. C. Amigo, None; L. M. Amezcua-Guerra, None.

Abstract Number: 173

The Efficacy of Treatment with Low Dose Aspirin and Low Molecular Weight Heparin in Pregnant Women with Criteria Anti-Phospholipid Antibodies

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Anti-phospholipid antibodies (aPL) are the biomarkers of anti-phospholipid syndrome (APS), a systemic autoimmune condition characterized by thrombosis and/or pregnancy morbidity (PM). The aim of this study was

to quantify the magnitude of the obstetric risk conveyed by criteria aPL, simultaneously assessing the efficacy of conventional treatment.

Methods: Data on 178 pregnancies in 60 women with persistent criteria aPL positivity (lupus anticoagulant, anti-cardiolipin and/or anti-b2GPI antibodies) were retrospectively collected (Table 1, Table 2). A weighted generalized estimating equations(GEE) model for repeated measures was applied to quantify the probability of PM conveyed by aPL, considering as covariates: number of positive aPL tests, low-dose aspirin (LDASA), low molecular weight heparin (LMWH) and their interaction; systemic autoimmune disease and age>35 years were inserted as confounders.

Results: Women with multiple aPL positivity had a probability of PM twice that of women with single aPL positivity. Women with single criteria aPL positivity had a probability of PM of 77%(95%CI 68-85), which raised to 86% (95%CI 76-93) in case of multiple aPL. Treatment with LDASA reduced the probability of PM to 29% (95%CI 11-57) in women with a single aPL test and to 44% (95%CI 17-75) in women with multiple positive tests. Among women with a single criteria aPL test receiving combo treatment, the probability of PM was 30% (95%CI 20-42). The association LDASA+LMWH reduced to 45% (95%CI 31-59) the probability of PM in women with multiple aPL tests.

Conclusion: This retrospective longitudinal cohort study showed that LDASA+LMWH allowed a significant decrease of PM in women with single but not multiple criteria aPL. Even though the association regimen led to a reduction of the probability of PM from 86% to 45% in patients with a high-risk aPL profile, it might be worth to add supplementary therapeutic tools.

Table 1.

	Criteria aPL (N of patients: 60)
Age at first conception, years	30.8 (5.78)
Systemic AD	28 (46.7%)
Organ-specific AD	11 (18.3%)
Pregnancy complications	16 (26.7%)
None	26 (43.3%)
≥ 3 PrL before 10 gw	10 (16.7%)
PrL after 10 gw	8 (13.3%)
Premature birth before 34 gw	
Thrombotic events	12 (20.0%)
Arterial	4 (6.7%)
Venous	7 (11.7%)
Arterial + venous	1 (1.6%)
LA	45 (75.0%)
aCL IgG/IgM	25 (41.7%)
anti-b2GPI IgG/IgM	30 (50.0%)
Number of positive aPL tests	
1	37 (61.7%)
2	6 (10.0%)
3	17 (28.3%)
aPL isotypes	
IgG	21 (60.0%)
IgM	9 (25.7%)
IgG + IgM	5 (14.3%)

Table 2.

	Criteria aPL (N of pregnancies: 178)
Pregnancy complications	
None	72 (40.5%)
≥ 3 PrL before 10 gw	68 (38.2%)
PrL after 10 gw	23 (12.9%)
Premature birth before 34 gw	15 (8.4%)
Treatments	
None	81 (45.5%)
LDASA [+ HCQ]	18 [8] (14.6%)
LDASA + LMWH [+ HCQ]	52 [14] (37.1%)
LMWH	4 (2.2%)
HCQ	1 (0.6%)

Disclosure: C. B. Chighizola, None; F. Pregnolato, None; M. G. Raimondo, None; C. Comerio, None; L. Trespidi, None; M. O. Borghi, EFPIA, 2; M. Gerosa, None; B. Acaia, None; W. Ossola, None; E. Ferrazzi, None; A. Bulfoni, None; P. L. Meroni, None.

Rivaroxaban Versus Warfarin As Secondary Thromboprophylaxis in Patients with Antiphospholipid Syndrome: A Randomized, Multicenter, Open-Label, Clinical Trial

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Long-term anticoagulation with vitamin K antagonists (VKAs) is the standard of care in thrombotic antiphospholipid syndrome (APS) but requires frequent monitoring and dose adjustment. Rivaroxaban, an orally active direct factor Xa inhibitor, provides more consistent anticoagulation but its use in APS is controversial.

Methods: This is a phase 3 non-inferiority open-label RCT. We randomly (1:1) assigned 190 patients with thrombotic APS (arterial or venous) receiving warfarin to receive either rivaroxaban (at a daily dose of 20 mg) or dose-adjusted acenocumarol (standard of care, normalized ratio (INR) 2-3 or 3.1 to 4.1 in those with recurrent thrombotic episodes). The per-protocol analysis was designed to determine the rivaroxaban noninferiority to warfarin for the primary endpoint of recurrent thrombosis. Secondary efficacy outcomes include time to thrombosis, type of recurrent events (arterial or venous), and overall causes of death. The primary safety outcome was major bleeding.

Results: In the primary analysis, thrombotic events occurred in 11 patients in the rivaroxaban group (11.6%; 4.59 patients-year) and in 6 patients in the VKAs group (6.3%; 2.26 patients-year) (hazard ratio, 1.93; 95% CI, 0.69 to 5.39; p=0.210). In the intention-to treat analysis, thrombotic events occurred in 12 patients in the rivaroxaban group (12.6%; 4.68 patients-year) and in 6 patients in the VKAs group (6.3%; 2.22 patients-year) (hazard ratio, 2.13; 95% CI, 0.77 to 5.88; p=0.144). In the per-protocol population and in the intention-to-treat population, patients in the rivaroxaban group had a higher rate of stroke (9 events (3.75 patient-year) and 10 events (3.90 patient-year), respectively, than those in the VKAs group (0 events) (hazard ratio in the rivaroxaban group, 16.16; 95% CI, 0.84 to 309.43; p=0.065, in the PP study and 20.04; 95% CI, 1.04 to 386.58; p=0.047 in the ITT study). Major and nonmajor clinically relevant bleeding occurred similarly in both groups (31.6% in the rivaroxaban and 26.3% in the VKAs), but with less intracranial hemorrhage and critically significant bleeding in the rivaroxaban group

Conclusion: In patients with APS, rivaroxaban could not demonstrate its noninferiority to VKAs for the prevention of recurrent thrombosis, and stroke occurred more frequently in the rivaroxaban group. There were no significant between-group difference in the risk of major bleeding, although critical bleeding occurred less frequently in the rivaroxaban (ClinicalTrials.gov number: 02926170)

Disclosure: J. Cortés-Hernández, None; L. Sáez-Comet, None; A. Riera Mestre, None; A. Castro Salomó, None; J. Cuquet Pedragosa, None; V. Ortiz-Santamaría, None; M. Mauri Plana, None; J. Ordi-Ros, None.

Deductive Anatomy By Self-Examination. Preliminary Evaluation of a Novel Method to Reinforce Knowledge of Musculoskeletal Anatomy at the 2018 Panlar Meeting

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

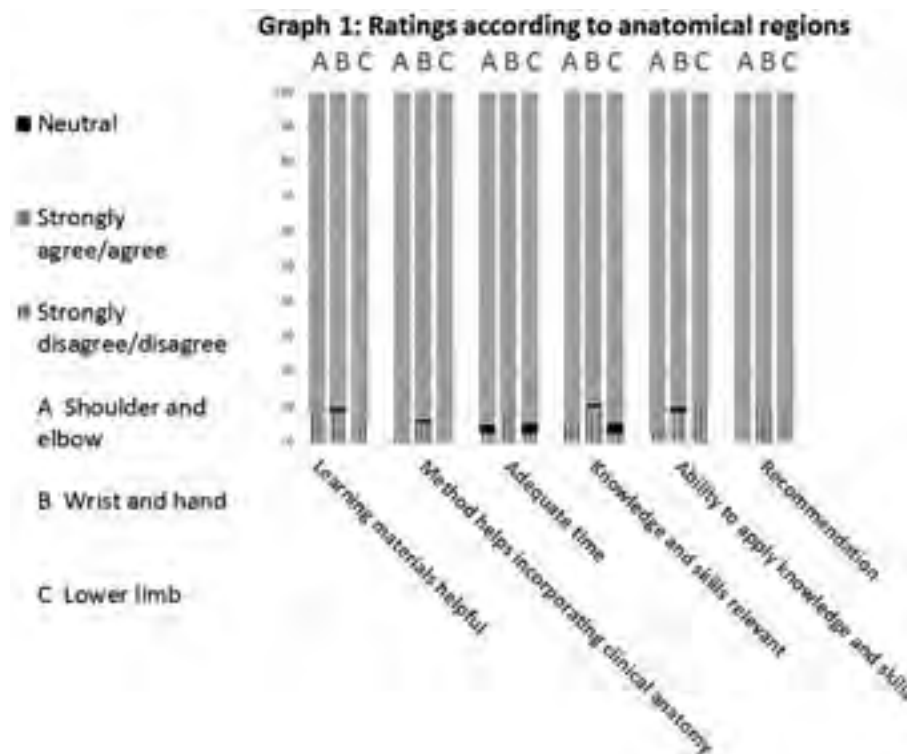
Session Time: 9:00AM-11:00AM

Background/Purpose: Traditionally, anatomy has been taught by dissection and textbooks of descriptive and topographic anatomy. Today, dissection is increasingly rare and emphasis is placed instead on peer examination with or without US, and CT or Magnetic Resonance Imaging-based images. Counter-current to this progressively technological evolution, the authors have developed a humanistic method of teaching and learning anatomy that involves self-examination and requires no technology. We have termed this deductive anatomy by self-examination (DASE) and it is based on inspection, palpation, and sensory input originating directly from the self-examined anatomical items.

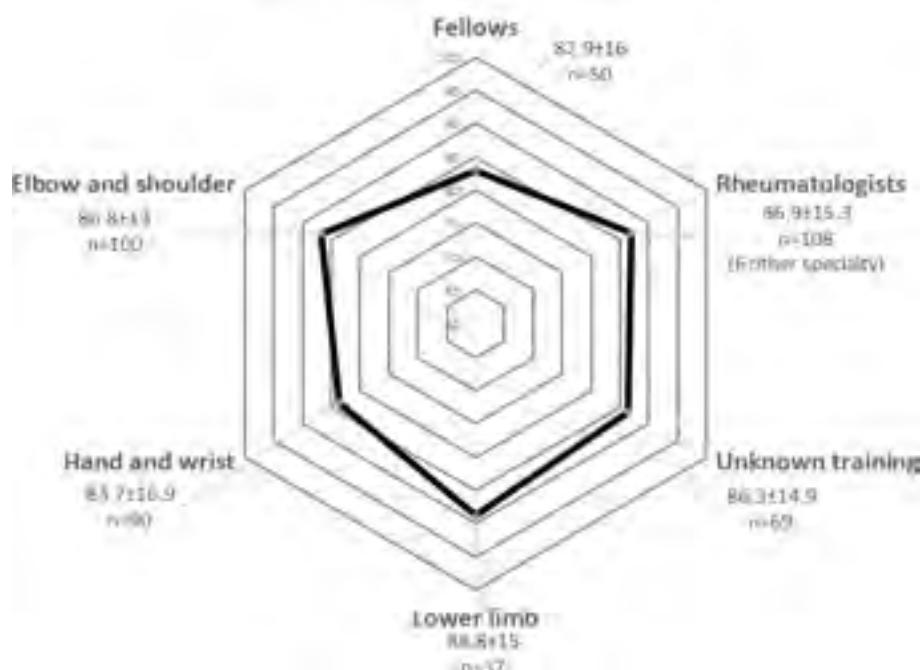
Methods: The authors gave three DASE seminars at the 2018 PANLAR Meeting in Buenos Aires. Seminars were 1 hour and 45 minutes duration, were given in consecutive days, and each dealt with different anatomical regions. Seminar #1 dealt with the wrist and hand (5 exercises), #2 dealt with the elbow and shoulder (7 exercises) and #3 dealt with the lower extremity (6 exercises). At the end of each seminar participants were invited to complete an anonymous evaluation that included rating five characteristics of the seminar on a Likert scale as well as a global evaluation.

Results: Ninety of 100 (90%) participants evaluated seminar #1, 100 of 120 (83%) seminar #2, and 37 of 60 (62%) seminar #3. Graph 1 shows the global ratings per anatomical region by rheumatologists, unspecified professionals, and fellows. In all instances, the acceptance rate was over 80%. A strongly agree rating was given by 60 to 92% of participants in the lower extremity seminar, 52 to 78% in the shoulder and elbow seminar, and 43 to 68% in the hand and wrist seminar. Graph 2 depicts the individual questions asked, and the participants recommendation, per anatomic region. Once again, scores were uniformly greater than 80% acceptance on questions regarding attendee's satisfaction and the technique's relevance and applicability. There was the suggestion that movies be included to facilitate the performance of the exercises.

Conclusion: DASE was well received by a variety of participants. There were no differences in the evaluation scores according to the anatomical region or participants' level of training. The authors believe that DASE holds promise as a supporting method to the usual teaching of anatomy. Exercises are self-performed, may be repeated as needed, cause no embarrassment, and have no cost. Problems inherent to its N=1 nature may be solved by peer examination. DASE is now being assessed in medical students.



Graph 2: Overall ratings of the seminar



Disclosure: M. A. Saavedra, None; V. Pascual-Ramos, None; J. J. Canoso, None; M. A. Sanchez-Valencia, None; R. A. Kalish, None; C. Hernandez-Diaz, None.

Abstract Number: 176

Deductive Anatomy By Self-Examination. a Novel Method to Reinforce Traditional Teaching of Musculoskeletal Anatomy

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Knowledge of musculoskeletal anatomy (MSA) is essential for physicians such as rheumatologists, orthopedic surgeons, physiatrists, generalists, and other professionals for whom a musculoskeletal-centered physical examination is a central component of their patient assessments. Teaching methods of MSA range from cadaver dissection to technology-heavy virtual anatomy. Large student classes, a shortage of instructors, and a dearth of available cadavers have shifted anatomical education from the former to the latter and other innovative methods. To these, we are adding deductive anatomy by self-examination (DASE), which is based on self-inspection, self-palpation, plus an additional channel the other ancillary methods lack, self-perception by the explored structure. The objective of this presentation is to introduce the concept of DASE and describe exercises using DASE that explore the upper and lower extremities.

Methods: DASE exercises follow a set pattern. 1. The targeted anatomical items involved are described. 2. The re-arrangement brought by the motion of the related joint(s) of the targeted items is hypothesized. 3. The targeted items are analyzed through inspection, palpation and the explored items perception during motion of one's own body part. 4. The new geometrical arrangement is understood. 5. The clinical applications of the exercise are correlated. Filmed exercises will be shown.

Results: Thirty-seven DASE exercises were designed by authors consensus. In the upper extremity, they included, as examples, the palpatory recognition of the lateral bands of the digital extensor mechanism, the action of interosseal and lumbrical muscles, a functional distinction of the flexor and the extensor wrist pulleys, and abstruse functions such as pronosupination and the external rotation of the humerus required for arm elevation. In the lower extremity, examples include the ischiotibial muscles and the hip abductors during ambulation, re-arrangement of items caused by knee flexion, and the co-ordination of leg muscles during ankle motion. The above exercises elucidate anatomic relationships during normal movement and help understand the deformities caused by joint, capsule, or tendon damage, some shoulder limitations, gait disorders, and more.

Conclusion: We propose DASE as an N=1 supplementary strategy to current teaching of MSA. DASE provides unlimited opportunities to reinforce knowledge at no cost, and the understanding of complex anatomical regions may be improved. Enthusiastic feedback obtained at recent seminars suggest the potential utility of DASE in medical school and postgraduate curricula at a time in which more active learning and teaching techniques are being encouraged and incorporated, but controlled studies of the educational outcomes and reproducibility will be needed.

Acknowledgement: We thank Fernando Peña for expert movies production.

Disclosure: J. J. Canoso, None; M. A. Saavedra, None; V. Pascual-Ramos, None; M. A. Sanchez-Valencia, None; R. A. Kalish, None.

Abstract Number: 177

A Needs Assessment to Inform Rheumatology Curriculum Re-Design for Internal Medicine Residents

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: In an effort to redesign our rheumatology curriculum for internal medicine (IM) residents, we sought to understand the correlations between IM resident in-training exam (ITE) scores, self-reported confidence, rheumatologists' perception of residents' proficiency, and diagnoses seen in rheumatology clinic.

Methods: All data was collected from a single academic medical center. We analyzed IM resident ITE scores on rheumatology-related educational objectives from 2010-2017. Objectives were divided into 10 categories defined by the ABIM Certification Examination Blueprint: RA, SpA, SLE, SSc, OA, crystalline arthritis, infectious arthritis, vasculitis, bone disease, and regional musculoskeletal. In spring 2018, we surveyed IM residents on their self-reported confidence and rheumatology fellows, faculty, and advanced practice providers (APPs) on their perceived proficiency of IM residents in these same 10 categories on a 10-point Likert scale. In addition, we tallied diagnoses seen by IM residents in rheumatology clinic from January-April 2018 in each of these categories. Pearson correlation coefficients were calculated between these measures.

Results: The average ITE score on rheumatology-related educational objectives was 66.3%. The lowest average score was in crystalline arthritis (55.9%) and the highest was in SLE (73.4%). Regarding survey data, everyone who received a survey responded (response rate 100%). The resident survey included 38 residents (17 interns, 21 upper-levels). The lowest average confidence was in vasculitis (3.68) and the highest was in OA (7.53). The rheumatologist survey included 22 respondents (7 fellows, 12 faculty, 3 APPs). The lowest average perceived proficiency was in SSc (3.80) and the highest was in OA (6.14). Of 143 diagnoses seen by IM residents in rheumatology clinic, the least common diagnosis category was infectious arthritis (n = 0) and the most common was RA (n = 40). There was a positive correlation between resident confidence and rheumatologists' perceived proficiency (r = 0.934, p < 0.001). In contrast, there was no statistically significant correlation between resident ITE scores and resident confidence (r = -0.474, p = 0.166), rheumatologist's perceived proficiency (r = -0.442, p = 0.201), or number of diagnoses seen in rheumatology clinic (r = -0.319, p = 0.369), all showing a trend towards a negative correlation. In particular, crystalline arthritis was second highest in resident confidence (6.95), third highest in perceived proficiency by rheumatologists (5.43), and the third most common diagnosis encountered by residents in rheumatology clinic (n = 16), though it had the lowest ITE scores.

Conclusion: IM resident confidence correlates with rheumatologists' perceptions of their proficiency in core rheumatology topics. However, ITE scores do not correlate with either of these measures. Thus, common diagnoses like crystalline arthritis and OA that are felt to be simple may be overlooked in IM resident education. When designing curricula, rheumatology educators should not rely on perceptions and instead must analyze objective assessments like the ITE to identify significant gaps in IM resident knowledge.

Disclosure: D. Leverenz, None; A. M. Eudy, None; L. Criscione-Schreiber, GlaxoSmithKline, 2.

Abstract Number: 178

The Impact of a Novel Immune Related Adverse Event Tumor Board on Interprofessional Clinical Confidence and Collaboration

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: The diagnosis and management of patients who develop immune related adverse events (irAEs) from checkpoint inhibitor therapy (ICI) requires multidisciplinary care and rheumatologists play an important role in their management¹. In September 2017 a new monthly conference was developed at our institution dedicated to the presentation and management of irAEs. This tumor board consists of clinicians from numerous departments with known interest and experience in irAEs. The goal is to discuss new and/or challenging cases of irAEs, review the extant literature and receive input on interprofessional management. On average, 6 cases are discussed at each conference. A survey was developed to assess its educational value to attendees and appraise its impact on confidence in managing irAEs.

Methods: In the 2nd quarter of 2018, an online survey was sent via e-mail to health care providers (HCPs) at the Cleveland Clinic. The survey population was made up of HCPs included on the monthly tumor board invitation. The survey questions aimed to assess the satisfaction with the educational value of this new conference, the perceived impact on irAE awareness, confidence level in diagnosing and management of irAEs, and perceived impact on patient care. Future educational needs were also assessed.

Results: The survey was sent to 37 HCPs with a response rate of 24/37 (65%). The majority of responders were oncologists followed by rheumatology HCPs (Table 1). 95.8% reported having seen a patient who developed an irAE from ICI with 29.2% seeing 1-2 patients per month. In terms of the clinical impact of this irAE tumor board, 66.7% reported a significant increase in their awareness of the scope and presentation of irAEs, and 41.7% reported significantly increased confidence in diagnosing and managing certain irAEs. Most (75%) felt that the conference format/content was superior to other conferences in terms of interest and practical content. When queried about what aspects they valued most, the most common response was the multidisciplinary nature of the conference.

Table 1. Tumor Board survey responses (N = 24)

Which advanced degree do you have?	DO/MD 83.3% NP 4.2% PA 0% RN 8.3% Other 4.2%
What type of medicine to you practice	Oncology 66.7% Rheumatology 12.5% Pulmonology 0% Gastroenterology 4.2% Hepatology 0% Endocrinology 4.2% Ophthalmology 0% Dermatology 4.2% Other 12.5%

How many years have you been practicing in your field?	< 5 years 33.3% 5-10years 29.2% > 10 years 37.5%
Have you seen patients who are treated with ICI and develop irAEs?	Yes 95.8% No 4.2%
Describe you primary role in irAEs from ICI	Prescriber/manager of ICI therapy 4.2% Management of irAEs 29.2% Both 54.2% Neither 12.5%
How many tumor board conferences have you attended	One 12.5% Two 16.7% Three or more 70.8%

Conclusion: irAEs are a new area of medicine that require multidisciplinary collaboration for investigation and optimal management. The multisystem involvement and autoimmune, inflammatory mechanisms of these complications makes rheumatologists valued, if not central, partners in both patient management and research. Novel venues for educational interchange are needed to further this evolving field. A regular conference solely dedicated to irAEs appears to have educational value as assessed by learner satisfaction and may increase skill and confidence in patient management.

1. Calabrese L, Mariette X The evolving role of the rheumatologist in the management of immune-related adverse events caused by cancer immunotherapy. *Ann Rheum Dis* 2017;77(3):317-8.

Disclosure: C. Calabrese, None; P. Funchain, None; P. D. Patil, None; L. H. Calabrese, Bristol-Myers Squibb, 5, 8, Genentech, Inc., 5, 8.

Abstract Number: 179

Swimming Against the Stream- the Fishbowl Discussion Method As an Interactive Tool for Medical Conferences – Experiences from the 11. European Lupus Meeting

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

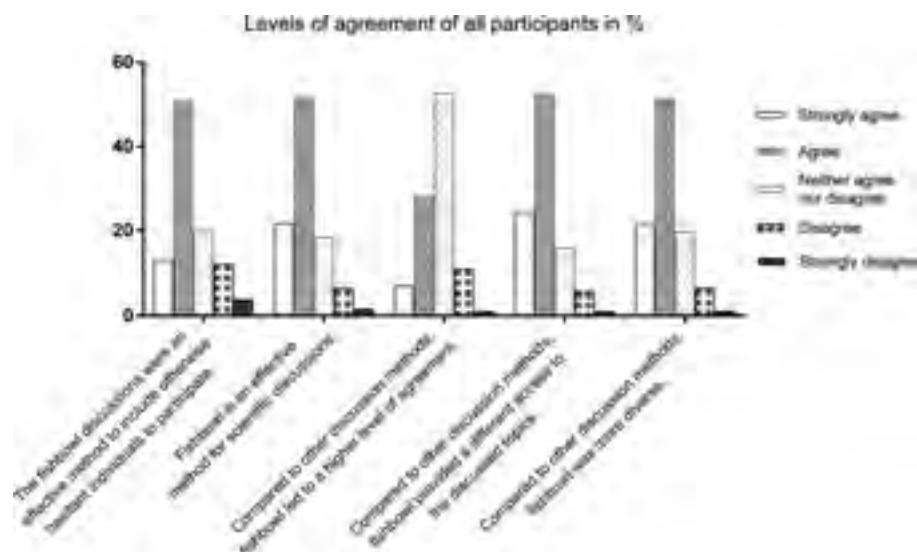
Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: A ubiquitous hierarchy pervades all levels of medicine. The high level of recognition and respect for experts and their opinions prevents exchange between the different levels of the hierarchy. Especially at medical conferences, discussions usually take place between experts, while patients, young doctors and students listen, and active participation often does not occur. The fishbowl method is an interactive and dynamic technique with a group of discussants sitting in an inner circle that contains an additional empty chair. Members from the auditorium can, at anytime, occupy the empty chair and join the discussion. It was our aim to introduce this method as an alternative to pure expert panels.

Methods: Ten discussion groups with different topics were formed in advance of the European Lupus Meeting 2018. The groups consisted of an SLE expert moderator, a SLE patient representative, a fellow in training and two international SLE experts. Each discussion lasted one hour and was protocolled on flipcharts by another fellow and a fourth SLE expert. The method was evaluated by participants and the auditorium in an online survey distributed via email after the conference among all attendees assessing feelings as active participants and opinions regarding the effectiveness of the method.



Results: A total of 169 attendees completed the online survey. 47 were members of the inner circle (8 moderators, 14 experts, 5 patient representatives, 20 fellows) and 122 were members of the audience. Only 15.5% had heard about the method before and 6.6% had participated in a fishbowl round before. 39 members of the audience participated actively, of whom the majority felt comfortable (28.7%) or even very comfortable (16.6%) with their role on the empty chair. 78.5% of all participants would recommend the method for future conferences. Levels of agreement regarding the effectiveness of the method are shown in Figure 1. Opinions did not differ between the inner circle and the audience.

Conclusion: The fishbowl discussions were overall excellently received and positively evaluated. Fishbowl provides a diverse and apparently effective method for scientific exchange. By reducing hierarchies and challenging traditions, active participation is facilitated and otherwise hesitant listeners can easily contribute to the discussion.

Figure 1

Disclosure: J. Mucke, None; H. J. Anders, None; M. Aringer, None; D. G. Chehab, None; R. Fischer-Betz, None; F. Hiepe, None; H. M. Lorenz, None; A. Schwarting, None; R. Voll, None; M. Schneider, None.

Abstract Number: 180

Back to Bedside Teaching: Completion of a Rheumatology Rotation Significantly Increases Internal Medicine Residents' Competency and Comfort with Comprehensive Knee Examinations

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Prior studies have elucidated the lack of competency and confidence in musculoskeletal (MSK) examination skills amongst medical trainees. A variety of teaching modalities have been studied, including lecture or workshop-based and peer-to-peer training, however, there remains a dearth of literature regarding the effectiveness of traditional bedside teaching versus dedicated workshops. The aim of this study was to determine if incorporating a MSK workshop into a 2 week clinical rotation in rheumatology would be an effective means to increase internal medicine residents' competency and comfort with knee examinations when compared to the rotation alone.

Methods: Informed consent was obtained from all participants. Each block of resident rotations during a 6 month period was randomized to workshop plus rotation versus rotation alone; the number of residents assigned to rheumatology varied biweekly, yielding unequal group sizes. Participants were tested on their knee examination skills at the start of their rotation using an objective structured clinical examination (OSCE) administered by trained rheumatology faculty. Those

randomized to the intervention group were provided a 1-hour workshop consisting of a didactic presentation, video and hands on application of skills. Immediately following the rotation, all residents were retested using the OSCE. Residents were administered a pre and post rotation survey assessing to what degree the rotation was beneficial in enhancing their comfort with knee examination skills. Comfort and helpfulness were measured using a 5-point Likert scale (1: not comfortable and 5: very comfortable). Paired and independent samples t-tests were used for pre and post as well as between group comparisons.

Results: Twenty residents participated in the study (12 received the workshop). For the group as a whole, there were significant improvements in pre and post-test OSCE scores (pre-test mean = 6.3 ± 2.2 , post-test mean = 11.3 ± 1.4 , $p < 0.001$), showing improvements of close to 80%. Comfort with examination also significantly improved post rotation (pre-level mean = 2.6 ± 0.8 , post-level mean = 4.1 ± 0.7 , $p < 0.001$), moving overall from “somewhat uncomfortable” to “comfortable” ranges. Interestingly, there was no significant difference in the change in OSCE scores ($p = 0.140$) or levels of comfort ($p = 0.560$) between the group that received the workshop and the group that completed rotation alone. Ninety-five percent of residents found completion of the rotation to be helpful in improving examination skills (mean helpfulness = 4.5 ± 0.7). This did not differ between groups ($p = 0.560$).

Conclusion: This study provides evidence that completion of a rheumatology rotation results in substantial improvement in resident competency and comfort with comprehensive knee examinations. In an educational era emphasizing organized interactive learning, it is of interest that we were unable to demonstrate that provision of a focused workshop improved outcomes beyond the rotation itself. These findings highlight the continued value of bedside teaching and the effectiveness of the rheumatology elective in helping to bridge known gaps in MSK education.

Disclosure: A. Kwiatkowski, None; N. Shakoor, Dr. Comfort/DJO, 7; J. A. Block, Gilead, 1, Novartis, 2, Pfizer, Inc., 2, Janssen, 2, GlaxoSmithKline, 5, Zynherba Pharmaceuticals, 5, Agios, Inc, 7, Daiichi Sankyo, Inc., 7, Omeros, Inc., 7; A. Manadan, None; S. Khandelwal, None.

Abstract Number: 181

Effectiveness of Elective Completion in Enhancing Board Preparedness and Comfort with Diagnosing and Treating Rheumatologic Conditions in a Cohort of Internal Medicine Residents at an Academic Medical Center

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Elective choice during residency is influenced by future career goals and perceived knowledge gaps. There is limited literature directly comparing elective exposures to outcomes on the American Board of Internal Medicine Certification Exam (ABIM-CE). Developing structured curricula within an elective experience has been shown to enhance ABIM-CE performance (Shanmugam et al, BMC Med Edu, 2012). Studies have shown outcomes on the in-training exam, a surrogate marker for the ABIM-CE, can be improved with conference attendance and self-directed reading. Comfort with managing specialty specific conditions after elective completion has not been well studied. The major aim of this study was to determine if completion of a 2 week rheumatology rotation improved residents' board preparedness and comfort with diagnosing and treating common rheumatologic diseases.

Methods: Informed consent was obtained from all participating residents. The curriculum was based equally on inpatient and outpatient experiences, with formal didactics. A 10 question pre-test using knowledge based multiple choice questions on a variety of rheumatologic principles was given at the start of the rotation. At rotation completion, a different 10 question post-test was administered. Residents completed a pre and post rotation survey assessing to what degree the rotation enhanced their board preparedness and comfort with diagnosing and treating rheumatologic conditions. Comfort was measured on a 5-point Likert scale (1: not comfortable and 5: very comfortable). Paired samples t-tests were used for pre and post comparisons and bivariate correlations were evaluated using Spearman's rho.

Results: Twenty residents participated in the study. There was no significant difference between individual pre and post rotation question test scores (pre-test mean = 8.1 ± 1.2 , post-test mean = 7.7 ± 1.2 , $p = 0.290$). Interestingly, comfort with board preparedness significantly improved (pre-level mean = 2.3 ± 1.2 , post-level mean = 3.5 ± 1.0 , $p < 0.001$), as did comfort with diagnosing (pre-level mean = 2.3 ± 1.2 , post-level mean = 3.5 ± 1.0 , $p < 0.001$) and treating (pre-level mean = 2.0 ± 0.9 ,

post-level mean = 3.7 ± 0.8 , $p < 0.001$) rheumatologic conditions (moving overall from “somewhat uncomfortable” to “comfortable” ranges). There was no correlation between composite test scores and comfort with board preparedness ($p = 0.280$). There was also no correlation between composite test scores and amount of independent reading time on rheumatology specific topics ($p = 0.718$).

Conclusion: This study shows that completion of a rheumatology elective greatly increases resident comfort with diagnosing and treating common rheumatologic conditions. Interestingly, while there was no improvement in ABIM style test scores, residents felt much more comfortable with the ABIM-CE after the rotation. The differences between subjective and objective findings warrant further investigation into the relationship between comfort and knowledge acquisition. Additionally, whether ABIM style questions truly capture clinically relevant knowledge or whether residents are not appropriately gauging board preparedness should be explored.

Disclosure: A. Kwiatkowski, None; N. Shakoar, Dr. Comfort/DJO, 7; J. A. Block, Gilead, 1, Novartis, 2, Pfizer, Inc., 2, Janssen, 2, GlaxoSmithKline, 5, Zynherba Pharmaceuticals, 5, Agios, Inc, 7, Daiichi Sankyo, Inc., 7, Omeros, Inc., 7; A. Manadan, None; S. Khandelwal, None.

Abstract Number: 182

Needs Assessment of a Structured Program for Fellows As Teachers: Rheumatology Program Directors' Perspective

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatology fellowship programs and program directors (PDs) are dedicated to didactic and clinical training of their fellows. Throughout fellowship training, fellows serve as teachers for residents, medical students, patients and families. However, structured teaching programs through which fellows themselves can acquire teaching skills are limited. Rheumatology program directors' interest in developing structured teaching programs has not been previously evaluated.

Methods: We conducted an in-person needs assessment of Rheumatology PDs attending the 2017 American College of Rheumatology national conference. The survey addressed questions regarding the availability of and interest in structured teaching programs for fellows.

Results: Fifty-seven of 94 Rheumatology PDs attending the meeting completed the survey (response rate 60.6%). The majority of PDs had >15 years of experience (38%) followed by 29% with 11-15 years of experience. Only 28% of programs required structured training in education and 33% of programs reported not having any structured training in teaching for their fellows. Over half of PDs (55%) reported that fellows are not trained in how to give feedback to medical students or residents, but almost all PDs (98.3%) believe that “fellows are a valuable resource for medical student/resident learning.” Additionally, majority of PDs (84%) agreed that [their] fellows could use additional instruction in teaching skills and 90% noted that this would be an asset to fellows for their future careers. Our survey also identified barriers to implementing teacher training programs as only 55.1% of PDs agreed that fellows have time for such programs and only 39.7% agreed that faculty have time to supervise fellow teaching.

Conclusion: This is the first evaluation of Rheumatology program directors' opinions regarding opportunities for their fellows to learn teaching and feedback skills. Less than a third of respondents reported having required structured training in education in their programs. PDs are interested in providing structured training opportunities on how to teach for fellows as they believe this will be an asset in their future careers. However, despite the need and interest in creating structured opportunities for teaching fellows how to teach, there are concerns about time available within the fellowship for fellows to receive this training, as well as time for faculty members to provide it. Future research based on this needs assessment should involve an efficient way to create a fellows-as-teachers curriculum.

Disclosure: P. Reid, None; E. Miloslavsky, Genentech, Inc., 2; A. Dua, None.

Needs Assessment of a Structured Teaching Program for Fellows As Teachers: Rheumatology Fellows' Perspective

Pankti Reid¹, **Eli Miloslavsky**² and **Anisha Dua**³, ¹Internal Medicine, rheumatology, University of Chicago, Chicago, IL, ²Division of Rheumatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, ³Medicine, University of Chicago, Chicago, IL

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Fellows are expected to teach patients, trainees and colleagues, regardless of what type of practice they join. The Accreditation Council for Graduate Medical Education (ACGME) Internal Medicine subspecialty milestones reflect that graduating fellows demonstrate the ability to teach effectively.¹ Yet, fellows frequently learn how to teach during their training through trial and error or observation.² Rheumatology fellows' experience and attitudes regarding teaching and teacher training have not been previously assessed. We evaluated fellows' interest in and access to training in education during their fellowship.

Methods: An anonymous survey was administered during the Fellows education session at the 2017 American College of Rheumatology national conference. The survey assessed fellows' career plans, interest and confidence in teaching, as well as experience with training in education during fellowship.

Results: Of the 150 surveys distributed, 107 were returned (response rate 71%). Seventy percent of those surveyed were adult rheumatology fellows, 12% were in pediatric rheumatology; 25% were 1st year fellows and 67% were 2nd year fellows. About 75% fellows demonstrated interest in pursuing a career that would involve teaching: 50% in "private practice with academic affiliation or teaching role" and 25% in "clinical educators in an academic program." Regarding fellowship training, over half reported that their program did not provide structured training in education, but notably, about 49% of programs were reported to "offer direct observation and feedback of [fellow's] teaching ability by attending physicians." Almost all fellows (94%) agreed or strongly agreed with the statement "If I had more time, I would do more teaching" and 97% felt that their "Teaching skills can be improved." About 88% of fellows reported that "learning how to teach effectively will be valuable to [his/her] career" and about 80% of fellows "would be willing to participate in a program to improve [their] teaching skills if no additional years of training required." Finally, while the majority (84%) of fellows felt confident in their ability to teach Rheumatology to a medical student/resident, 36% did not feel confident in their ability to give feedback to students/residents.

Conclusion: This is the first national needs assessment of rheumatology fellows' attitudes regarding experience as teachers. The majority of fellows are interested in pursuing careers where teaching would be a vital part of their profession and most felt that their teaching skills could be improved. However, over half of fellowship programs do not provide structured training in education, demonstrating a gap between fellows' needs and fellowship resources. Our study suggests a significant need to develop programs aimed at enhancing fellows' teaching skills.

1. Internal Medicine Subspecialty Milestones-ACGME <https://www.acgme.org/Portals/0/PDFs/Milestones/InternalMedicineSubspecialtyMilestones.pdf>
2. Miloslavsky EM, Boyer D, Winn AS, Stafford DE, McSparron JI. Fellows as Teachers: Raising the Educational Bar. *Ann Am Thorac Soc*. 2016 Apr;13(4):465-8. <https://doi.org/10.1513/annalsats.201601-026ps>. PubMed PMID: 26835749.

Disclosure: P. Reid, None; E. Miloslavsky, Genentech, Inc., 2; A. Dua, None.

Development of Focused Musculoskeletal Ultrasound Training for Primary Care Providers to Facilitate the Diagnosis of Gout: Initial Steps in an Educational Needs Assessment

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

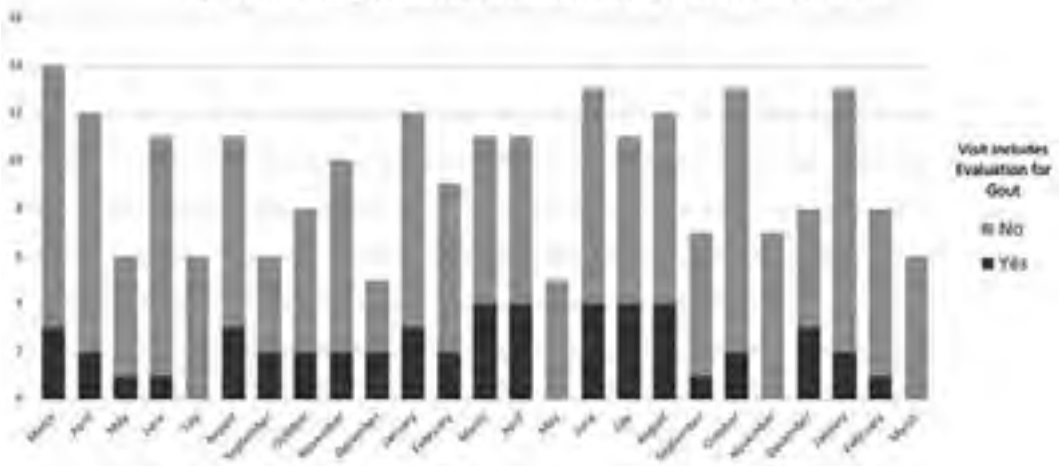
Session Time: 9:00AM-11:00AM

Background/Purpose: Gout is common in primary care settings, though establishing or excluding the diagnosis with confidence can be challenging, particularly if arthrocentesis is not feasible at the time. Musculoskeletal ultrasound (MSKUS) has emerged as a useful diagnostic tool, as identification of the double contour sign (DCS) is a rapid, relatively easy assessment that can help confirm the presence of gout. Although the practice of “point of care” ultrasound in several clinical conditions has expanded for some primary care providers (PCPs), the use of MSK US to specifically explore the diagnosis of gout remains largely associated with the subset of rheumatologists who have been trained in this technology. The purpose of our project was to contribute to a clinical and educational needs assessment, to inform the discussion and

Figure 1 – Description of Visits to the Rheumatology MSK US Clinic for the Evaluation of Gout

	Visits n (% of Total)	Time from Referral Request to Clinic Visit Average days [Range, SD]
Referral Request From		
Rheumatology Clinic	37 (71%)	31d [0 – 83, 23]
Primary Care Clinic	11 (21%)	24d [0 – 49, 15]
MSK Clinics	4 (8%)	26d [0 – 41, 14]
Primary Care Clinic Location		
Salt Lake City VA	29 (58%)	33d [0 – 83, 20]
Utah Community VA Clinics	16 (31%)	30d [0 – 69, 22]
Non-Utah Community VA Clinics	6 (12%)	15d [0 – 38, 13]
Total	52	29d [0 – 83, 21]

Figure 2 - Number of Patient Visits in the Rheumatology MSK US Clinic per Month



development of a potential training experience in MSK US for PCPs as well as health professions students and trainees at the Salt Lake City Veterans Affairs Medical Center (SLCVAMC) and University of Utah.

Methods: All consult requests and appointments in the SLCVAMC Rheumatology MSK US clinic from May 2016 to May 2018 were identified, and those specifically addressing the diagnosis of gout were reviewed. Quality indicators relevant to access to care, including the time from the consult request to the clinic visit were also collected, as well as the origin of the consult request (e.g., rheumatology clinic vs. primary care; rural primary care vs non-rural primary care).

Results: A total of 235 visits to the Rheumatology MSK US clinic were identified between May 2016 and May 2018; 52 (22%) of these included an evaluation for gout. Description of the gout MSK US visits is presented in Figure 1 and overall MSK US visits by type is presented in Figure 2. Out of the 52 patients for whom the visit included an evaluation for gout, 23 (44%) were confirmed.

Conclusion: Over 2 years, the availability in the MSK US clinic has been relatively unchanged, and is consistently near 30 days, a critical measure for VA health care systems. A substantial portion of these involves specific requests to consider the diagnosis of gout. As use of MSK US increases, there is likely to be a growing educational need within primary care. Rheumatologists should develop their role not only as content and technology experts in MSK US, but also as teachers for PCPs who are interested in learning how to perform and interpret this focused assessment to investigate the possibility of gout.

Disclosure: G. A. Kunkel, None; A. Barker, None; J. Timm, None; C. L. Koenig, None; M. J. Battistone, ABIM Rheumatology Exam Committee, 9.

Abstract Number: 185

Evaluating Medical Student Confidence and Performance of the Pediatric Musculoskeletal Exam

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Children commonly present with musculoskeletal complaints to primary care providers who work in a busy practice with diverse populations. Musculoskeletal complaints may result from mechanical causes including trauma or from inflammatory etiologies such as juvenile idiopathic arthritis. Pain may not be the presenting musculoskeletal complaint, which makes evaluation difficult. General knowledge of how to evaluate a patient with musculoskeletal complaints and how to do an appropriate musculoskeletal exam is necessary to effectively triage patients. However, many physicians report a lack of confidence and competence in the musculoskeletal examination due to limited training. Pediatric Gait, Arms, Legs, and Spine (pGALS) is a validated screening tool aimed at general practitioners to help discern normal from abnormal pediatric musculoskeletal findings. Its utilization at the medical student level has not been well described.

Methods: Graduating fourth year medical students were surveyed regarding their future specialty choice, confidence in pediatric exam skills (including the pediatric musculoskeletal exam), and the amount of pediatric musculoskeletal training they received in medical school. They performed a scored baseline pediatric musculoskeletal exam on a pediatric standardized patient presenting with chronic joint complaints consistent with juvenile idiopathic arthritis; the total score had a theoretic range from 0 to 42. Following the initial survey and baseline exam, they watched training videos in the pGALS assessment. After the pGALS intervention, they returned to complete a follow-up pediatric musculoskeletal exam and survey.

Results: 14 graduating medical students participated in the study. 11 planned to enter a pediatric residency. On the initial survey, participants were least confident in their pediatric musculoskeletal exam skills compared to all other pediatric exam skills. Prior to pGALS training, 21.4% of participants reported being confident or very confident in their pediatric

musculoskeletal exam skills, compared to 100% of participants reporting confidence after training ($p < 0.0001$). The average musculoskeletal exam score also increased significantly (pre: 22.1 ± 4.2 vs. post: 32.2 ± 4.9 , $p = 0.0001$). In regards to pediatric musculoskeletal training, there were no participants who felt that they received extensive education in the pediatric musculoskeletal exam. All participants desired additional training. 100% of participants felt that the pGALS training was beneficial to their education.

Conclusion: Graduating fourth year medical students may not be confident nor proficient at the pediatric musculoskeletal exam based on our analysis. While our study population was small, many of the student participants plan to enter pediatrics. Instruction in using a validated pediatric musculoskeletal screening tool, such as pGALS, may be a low cost and efficient way to improve medical student confidence and proficiency in the pediatric musculoskeletal exam. The information found from this study will be the basis for testing pGALS in a larger population at different centers.

Disclosure: K. Hays, None; N. M. Ruth, None; D. Kern, None; P. J. Nietert, None; L. Muhammad, None; M. Knoll Friesinger, None; P. McBurney, None.

Abstract Number: 186

The Accuracy and Potential Impact of a Diagnostic Decision Support System in Rare Disease Cases

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Diagnosis in rare diseases cases is often delayed by several years. Main factors for delayed diagnosis are believed to be lack of awareness and knowledge about rare diseases among health care professionals. Diagnostic decision support systems (DDSS) have the potential to enhance clinical diagnosis by assessing case data based on incorporated medical knowledge and by suggesting relevant differential diagnoses. DDSS can contribute to professional support and education by visualising medical information and reasoning. We report about the use of Ada/DX, a DDSS in development, in an outpatient clinic for rare inflammatory systemic diseases. Presenting preliminary results, we evaluate the system's diagnostic accuracy and assess the potential impact of this diagnostic and educational tool on the time to diagnosis.

Methods: This retrospective study is being conducted at the outpatient clinic for rare inflammatory systemic diseases at the Hannover Medical School, Germany. Ethical approval was obtained from the local ethics committee. To date, 82 (of a total 120) patient cases with confirmed diagnosis were included. The time of the visit of first documented symptoms and the time of diagnosis were identified. Time to diagnosis (TD) was calculated. Documented clinical evidence from the medical record was transferred to the DDSS and the disease suggestions in the DDSS were evaluated. Primary endpoint was the correctness of top disease suggestions for the visit of diagnosis. In these cases, secondary endpoints were the time to first correct top rare disease suggestion (T1R) and the time to first correct top 5 rare disease suggestion (T5R). The difference between TD and T1R and the difference between TD and T5R was calculated. Wilcoxon signed-rank test was conducted.

Results: On preliminary evaluation, primary accuracy of top suggestions of the DDSS at the time of diagnosis was 80.5% (71.9% to 89.1%, 95% CI). The table shows a comparison of the original time to diagnosis without the use of the DDSS and the time to correct disease suggestions with the use of the DDSS. (All times are expressed in months.)

	Mean	Std Dev	PCTL 25	PCTL 50	PCTL 75
Among all cases					
Time to diagnosis (TD) in medical record	57.8	84.2	2.3	18.0	74.5
Among cases with correct top suggestion at time of diagnosis					
Time to correct top rare disease suggestion (T1R)	25.0	50.6	0.0	3.0	21.0
Time to correct top 5 rare disease suggestion (T5R)	13.1	31.9	0.0	0.0	5.3
Time difference (TD - T1R)	29.6	70.5	0.0	1.0	19.3
Time difference (TD - T5R)	41.5	78.3	0.8	9.5	40.0

The Wilcoxon signed-rank test shows a significant difference for TD - T1R (z-score -5.37, $\alpha=0.05$, $p<0.001$) and TD - T5R (z-score -6.03, $\alpha=0.05$, $p<0.001$). Main reasons for incorrect DDSS disease suggestions were multi-morbidity (cases with multiple relevant diagnoses), atypical disease presentation and high level of case complexity.

Conclusion: The DDSS suggested the correct diseases based on information from the medical record in most of the analysed rare disease cases. The DDSS often suggested the correct diseases at times prior to the visit of diagnosis. DDSS could be used as educational tools that suggest relevant differential diagnoses in rare disease cases. They might help to reduce time to diagnosis and improve patient outcomes. Prospective research is needed to verify the results.

Disclosure: S. Ronicke, Ada Health GmbH, 3; M. C. Hirsch, Ada Health GmbH, 4; E. Türk, Ada Health GmbH, 3; K. Larionov, None; D. Tientcheu, None; A. D. Wagner, None.

Abstract Number: 187

Participant-Reported Effect of an Indigenous Health Continuous Professional Development Education Initiative

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Arthritis conditions are highly prevalent in Indigenous populations in Canada and patients experience severe outcomes. Patients avoid specialty care health systems due to experiences of racism, stereotyping and culturally unsafe environments. The 'Educating for Equity' program was designed as a continuing medical education (CME) intervention to incorporate skill-based teaching to re-center relationships and engage patient social realities, and was adapted as an educational intervention for rheumatologists.

Methods: Following introductory exposure to Indigenous health competency training, a half-day interactive workshop was delivered to 9 rheumatologists who were recruited through the Canadian Rheumatology Association membership. This half-day workshop provided content knowledge and skill practice through role playing case studies with instantaneous feedback on performance. Participants completed a pre-workshop survey which was repeated 3 months following the workshop to identify the strategies they used to address social issues and enhance therapeutic relationships, as well as a 15 question Likert-scaled Social Cultural Confidence in Care Survey (SCCCS). They were asked about the perceived impact of the intervention on their practice.

Results: Prior to the workshop, strategies to address social issues were primarily to involve allied health staff or local primary care providers, with few offering they would ask patients about social situations themselves. Strategies they used to enhance the therapeutic relationship were being open, available, and flexible, encouraging family participation in decision making, and sharing expectations for treatment effects while working to reach common ground and earn trust. Following the workshop, they were more likely to focus on relationship building with patients and their families, had enhanced awareness and confidence to explore the context of patient social reality in decision making, were serving as advocates for access to treatment, enquired about residential school experiences and patient cultural practices, and had changed their practices to be more patient-centered, with attention paid to space and time in the care environment. They valued the developing community of practice and were motivated to learn more about Indigenous health. There was no statistical improvement in the SCCC ratings, but trends to improvement in rankings were noted in this small group. Interactive group discussion and role playing were reported as the most effective part of the intervention.

Conclusion: This CME intervention had beneficial impact on self-reported confidence and enhanced practice strategies to engage with Indigenous patients. The next phase will incorporate reinforcement of principles and skills while providing training in facilitation to expand the community of practice.

Disclosure: C. Barnabe, None; R. B. Kherani, None; T. Appleton, None; R. Henderson, None; L. Crowshoe, None.

Pediatric Trainee Confidence and Exposure to Rheumatology

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: A small number of previous studies show residents have low levels of confidence in rheumatologic and musculoskeletal (MSK) skills. The objective of this study was to evaluate pediatric trainee exposure to and confidence in Rheumatology skills at our institution.

Methods: Fourth year medical students applying for pediatric residency and pediatric residents from a single institution completed an anonymous survey to evaluate confidence in MSK history, physical exam, rheumatologic lab interpretation and exposure to MSK pathology. Confidence levels were measured as continuous variables on a scale from 0 to 100. Survey responses were compiled and summarized using frequency with percentages for categorical variables and means and standard deviations and medians with interquartile range (IQR) for continuous variables. Group comparisons between the rheumatology rotation and patients seen/evaluated with arthritis were assessed using two-sample t-tests or Wilcoxon rank sum or one-way ANOVA with post hoc Tukey adjustment for multiple comparisons. The rating of sufficient exposure of residents with confidence in MSK history, physical exam, lab interpretation and diagnosing arthritis was assessed with Spearman correlations for continuous variables. Two-sided p-values <0.05 were considered statistically significant.

Results: All 20 medical students responded to the survey. Student confidence performing the MSK exam (p=0.03) and perceived ability to diagnose arthritis (p=0.07) was positively correlated with an increased perceived exposure to MSK pathology. This association was moderate-strong via Spearman correlation (0.49 and 0.41, respectively).

Table 1: Medical student confidence comparisons

	Medical Student Confidence		
	MSK History	MSK Physical Exam	Diagnosing Arthritis
Rheumatology rotation			
Yes (n=5), mean ± sd	62 ± 21.95	56.93 ± 14.56	55 ± 12.51
No (n=15), mean ± sd	59.73 ± 13.84	52.8 ± 22.62	45.4 ± 11.44
p-value	0.46	0.66	0.33
Seen/evaluated arthritis patients			
No (n=10), mean ± sd	60.6 ± 14.03	61.1 ± 15.85	54.1 ± 13.07
Yes (n=9), mean ± sd	58.89 ± 18.53	48.67 ± 15.43	51.22 ± 13.59
p-value	1.0	0.12	0.81
Correlation exposure vs confidence			
Medical student sufficient exposure	0.22	0.49	0.41
p-value	0.35	0.03	0.07

Table 2: Resident confidence comparisons

	Resident Confidence			
	MSK History	MSK Physical Exam	Lab Interpretation	Diagnosing Arthritis
Seen/evaluated arthritis patients				
No (n=16)	66.25 ± 27.17	52.69 ± 29.45	32.06 ± 15.74	25.12 ± 21.56
Yes (n=47)	70.64 ± 19.09	61.42 ± 20.44	56.25 ± 18.73	50.96 ± 24.83
p-value	0.88	0.32	<0.0001	0.001
Training year				
1 (n=18)	66.78 ± 19.03	59.11 ± 22.52	40.94 ± 13.48	30.78 ± 15.93
2 (n=22)	70.73 ± 16.66	59.5 ± 20.02	50.95 ± 22.94	46.28 ± 25.63
3 (n=19)	70.53 ± 23.19	57.16 ± 26.87	52.79 ± 20.22	49.47 ± 29.47
p-value	0.34	0.88	0.05	0.08
Correlation exposure vs confidence				
Resident sufficient exposure	0.58	0.65	0.41	0.47
p-value	<0.0001	<0.0001	0.0009	0.0001

Of 160 residents surveyed, 63 responded. Resident confidence in interpreting rheumatologic labs and diagnosing arthritis was greater in residents who reported seeing/evaluating new-onset arthritis patients ($p<0.0001$ and $p=0.001$, respectively). Greater level of perceived exposure to MSK pathology was associated with an increased level of confidence obtaining MSK history ($p<0.0001$), performing MSK exam ($p<0.0001$), interpreting rheumatologic labs ($p=0.0009$), and diagnosing arthritis ($p<0.0001$).

25% of residents and 50% of medical students reported no contact with a newly diagnosed arthritis patient.

Conclusion: Lack of perceived trainee exposure to MSK topics correlates to less confidence in MSK skills. Yet, many trainees had never examined a new arthritis patient. Further studies are needed to investigate strategies to increase trainee exposure and confidence in MSK skills. Future studies should also evaluate trainee competence.

Disclosure: J. Rutsky, None; A. Salvator, None; L. Ballenger, None; S. Cuff, None; K. Driest, None.

Abstract Number: 189

Evaluation of Rheumatology Lectures By Clinical Students in a Nigerian Medical School: Learning from the Learners

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

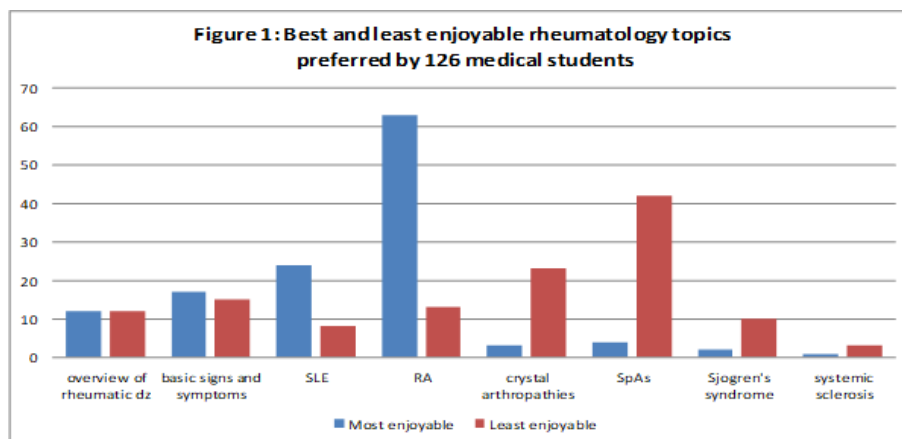
Session Type: ACR Poster Session A

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

Background/Purpose: There is a disparity between the enormous burden and the knowledge of rheumatic disorders among doctors and this is partly traceable to inadequate undergraduate rheumatology training. The situation is worse in sub-saharan Africa and Nigeria in particular where only 10 out of 30 medical schools teach rheumatology. To bridge the gap, specialist rheumatology residents are increasingly being utilized. Currently, there is no known student-based evaluation of rheumatology teaching effectiveness in Nigeria.

This study aims to identify the most and least enjoyable lectures preferred by the students, the proportion of students able to identify rheumatic conditions after the lectures as well as evaluate rheumatology teaching effectiveness using the augmented Stanford Faculty Development Program Questionnaire (aSFDPQ).

Methods: All 134 4th to 6th year medical students in the University of Uyo medical School, South-south Nigeria were asked to evaluate their rheumatology lectures using a self-administered questionnaire that included the likert-scale (aSFDPQ) instrument. Each class received about 3 one hour long didactic lectures during their 16-week medicine rotation. Mann whitney U test was used for ordinal data with $p<0.05$.



Results: A 94% response rate was obtained from 126 participants. 78 were male (61.9%). 63 students (50%) chose rheumatoid arthritis (RA) as their best topic because it was well explained (52.4%). 42(33.3%) cited spondyloarthropathies (SpAs) as their worst topic because it was difficult(30.1%). Twenty six students (20.6%) identified a rheumatic condition before the lectures compared with 57 (45.2%) after the lectures representing an increase of 24.6% ($p=0.001$). The mean aSFDPO score was 3.76 ± 0.47 . Highest scoring domains were: learning climate (4.03) and teacher's attitude (4.0). The least domain was Evaluation(3.39). Mann Whitney U domain values ranged from (1647.5<U<1869.5), ($0.257 < p < 0.990$) with no significant differences by gender ($p=0.825$) or class($p=0.162$). The mean global teacher rating was 74.64 ± 13.65 (range 40-100).

Conclusion: Rheumatoid arthritis was most enjoyed while spondyloarthritis was least understood by our students. There was a 24.6% increase in the proportion of students able to identify rheumatic conditions after the lectures. Although global teacher rating was good (74.6%), resident teaching effectiveness was suboptimal as assessed by total aSFDPO score<4.0. There is an urgent need for formal pedagogic training to improve rheumatology teaching effectiveness in Nigeria.

Table 1: Teaching skill evaluation of Rheumatology Resident

S/N		No. of items	Mean	SD	Minimum	Maximum	p value
1	Learning climate	8	4.03	0.57	2.00	5.00	0.257
2	Control of session	7	3.68	0.63	1.43	5.00	0.426
3	Communication of goals	8	3.61	0.64	1.50	5.00	0.475
4	Promoting understanding and retention	8	3.87	0.63	1.38	5.00	0.988
5	Evaluation	7	3.39	0.80	1.00	5.00	0.990
6	Feedback	7	3.57	0.69	1.00	5.00	0.372
7	Promoting self-directed learning	8	3.73	0.60	1.63	4.88	0.823
8	Teacher's knowledge	8	3.94	0.75	1.60	5.00	0.577
9	Teacher's attitude	7	4.00	0.65	1.43	5.00	0.392
	SFDPO (domains 1-8)	58	3.73	0.48	1.84	4.75	0.904
	aSFDPO (all domains)	65	3.76	0.47	1.79	4.78	0.825

Disclosure: A. Akpabio, None; M. Owolabi, None; V. Umoh, None; O. Adelowo, None.

Abstract Number: 190

An Innovative Pilot Educational Program to Inform Rheumatology Fellows about the Population of the Bronx: Issues Affecting and Resources Available to the Community

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: As noted in the 2015 ACR Workforce Study, few in the rheumatology identify as being from a community of color. Therefore, most rheumatologists do not have first-hand experience being part of these communities -- which are often those most affected by the rheumatic diseases. We therefore devised a community tour for our fellows to 1. better understand the community of patients they serve and 2. have an appreciation of the community resources available to the patients of the Bronx, NY.

Methods: In order to devise the tour, an assessment was done of the zip codes from patients seen in the Montefiore general arthritis clinic. We found that patients from across the borough were seen in clinic, therefore the decision was made to leave the neighborhoods where the clinics were located in order to bring the fellows to an area of the Bronx that they did not commonly visit. No traditional tourist sites were visited on the 3 hour tour. While on the tour, fellows learned about the history of the Bronx including several key events, such as the construction of the Cross Bronx Expressway, in addition to concepts such as "White Flight" and the discriminatory housing practice known as "Red-Lining." While on the tour the fellows visited 3 major community resources: Women's Housing and Economic Development Corporation (WHEDco); Institute for Family Health: Urban Horizons and Bronx Works. WHEDco provides award winning affordable housing, an Early Childhood Discovery Center, home-based childcare training institute and the Bronx Cook Space -- where street vendors can safely prepare food for purchase using shared industrial kitchen space. Institute for Family Health: Urban Horizons is a federally qualified health center that was created to address health disparities in innovative ways by

working with programs such as the CDC's REACH program. Bronx Works, located adjacent to housing court, offers in addition to eviction prevention and homelessness services, health insurance assistance, and youth programs.

Results: 5/7 fellows completed the post-tour survey. None of these 5 fellows had ever participated in something similar. 5/5 felt that the tour was: "Informative/Very Informative" and "Helpful/Very Helpful" All respondents "Recommend doing it next year" and felt that it "Enhanced their fellowship".

Conclusion: Most of the physicians that work for Montefiore do not live in the Bronx and many use public transit and local highways thus avoiding local streets and neighborhoods. This, in addition to the typical media portrayal of the Bronx, can lead to providers not engaging with the community outside of the clinical setting. This can also lead to the reinforcement of biases often faced by communities of color. By taking the fellows into the neighborhood and having them interact with community members it begins to give them a nuanced perspective of the patients they serve.

Disclosure: I. Blanco, None; H. Archer-Dyer, None.

Abstract Number: 191

Creation of an Immunology Series Video Library in Facilitating Basic Immunology Knowledge Acquisition and Retention Amongst Adult Rheumatology Trainees

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³Rheumatology, University of Toronto, Toronto, ON, Canada, Toronto, ON, Canada, ⁴University of Toronto, Toronto, ON, Canada, ⁵Rheumatology, University of Toronto, Toronto, ON, Canada, ⁶St. Michael's Hospital, Toronto, ON, Canada

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: A strong foundational knowledge in immunology is key to understanding complex rheumatologic disease processes. Indeed, an immunology curriculum delivered by Rheumatology training programs across Canada is required to meet the core competencies outlined by the regulatory college. With initial work completed by Mahendira *et al* (2015), a need for improving current immunology curricula was identified and high yield immunology teaching topics to be included in a national curriculum were established. In order to meet these needs, video illustration was chosen as a method of communicating complex immunological content to a geographically dispersed audience. Three short video clips were developed to highlight important immunology topics. The effectiveness of these videos in facilitating comprehension and knowledge acquisition amongst rheumatology trainees was assessed.

Methods: Immunology topics including "T cells", "Cytokines", and "Cytokine Receptors" were previously identified as essential to an immunology curriculum for Rheumatology trainees. Video content related to these topics was generated with the assistance of immunology, rheumatology, and medical education experts as well as a Biomedical Illustrator. The videos were piloted on adult rheumatology trainees, with pre- and post- video quizzes based on video content administered. To evaluate duration of knowledge retention, post- video quizzes were administered immediately after and six weeks following each video clip. The statistical significance of improvements in quiz performance was evaluated using paired t-testing. Qualitative feedback was also gathered to assess video content and design.

Results: Eight adult rheumatology trainees participated in video testing. The average pre test score for "T cells", "Cytokines" and "Cytokine Receptors" was 58.3% (+/- 36.5), 61.1% (+/- 19.7), and 38.9% (+/- 16.8), respectively. Immediate post test scores were significantly improved ($p < 0.05$) for "T cells" and "Cytokines" with averages of 90.3% (+/- 20.1) and 91.7% (+/- 15.4), respectively. Immediate post test scores for "Cytokine Receptors" were not significantly improved however scores did improve to meet departmental pass standards ($> 60\%$), with average post test scores being 62.5% (+/- 16.7). Six week post test scores continued to be above departmental pass standards for "T cells" and "Cytokines", with scores of 76.4% (+/- 16.2), 81.9% (+/- 10.2), respectively. Overall, video modules for "T cells" and "Cytokines" were well received with comments suggesting content was "easy to follow," "helpful," and a "great teaching resource." Post-test scores and qualitative data for "Cytokine Receptors" suggest the video was "too complex" and as such will be revised and re-piloted to better meet the needs of Rheumatology trainees.

Conclusion: Immunology video content is an effective tool for improving short term comprehension and knowledge retention amongst rheumatology trainees. We hope to continue to develop these educational deliverables, building an

Disclosure: M. Himmel, None; N. Haroon, None; W. Gu, None; A. Bookman, None; H. McDonald-Blumer, None; D. Mahendira, None.

Abstract Number: 192

Impact of Case-Based Simulation Training on the Confidence and Knowledge of Medical Residents to Perform Rheumatologic Procedures

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Simulation training is now widely used in various residency programs, especially in the field of critical care, to train and prepare residents for real life medical cases and procedures. Training in rheumatologic procedures such as arthrocentesis however, is a neglected part of many internal medicine residency programs. The purpose of this study was to explore the impact of simulation based training curriculum on the residents' confidence and knowledge to perform these procedures independently.

Methods: A case-based simulation training curriculum was developed in our internal medicine residency program based in an urban tertiary care center. The initial assessment consisted of surveying the participants' past experience with arthrocentesis and corticosteroid injections, current satisfaction with such training in their program and knowledge regarding the basic anatomical landmarks. Understanding the indications/contraindications of performing these procedures was also reviewed. The training sessions included faculty led, hands on, simulation based instruction using knee and shoulder anatomic models. The post-training questionnaire was provided to assess for any difference in outcome. Simulation models provided instant feedback by providing a sound when the needle was placed in the correct location. The training was not complete until all participants had located and inserted the needle in the appropriate location as verified by the auditory feedback.

Results: A total of 37 participants (54% men and 46% women), enrolled in the educational curriculum. 9 (24%) of the medical residents were Year-1, 13 (35%) Year-2, 12 (32%) Year-3; 3 participants were medical students and attending physicians. Among the medical residents, 28 (76%) participants were International Medical Graduates and 9 (24%) were American Medical Graduates. Analysis was completed using SAS 9.4 and paired t-test. Median post training satisfaction and confidence in the procedural skills were higher (p-value <0.05). There was also improvement in the mean post-training objective knowledge based questionnaire scores in 4 out of 8 areas (p-value <0.05). All 37 participants were interested in training in similar sessions in the future.

Conclusion: Simulation based training helps residents learn complex medical cases and practice invasive procedures in a safe environment. This study shows that use of knee and shoulder models to practice joint injections increases residents' confidence and satisfaction and improves their clinical skills. We feel that simulation based arthrocentesis training should be incorporated as part of the basic internal medicine curriculum.

Disclosure: S. Afroz, None; M. Duttuluri, None; R. Iyengar, None; Y. Ali, None.

Abstract Number: 193

Practice Improvement Using Virtual Online Training: A Novel App-Based Platform to Teach Clinical Reasoning in Rheumatology

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: The demand for rheumatologists continues to increase due to the high prevalence of rheumatic disease in a growing population. As outlined in ACR's 2015 Workforce Study, recruitment of the future workforce is a critical part of strategies to address the predicted shortage. ACR has identified graduate medical education and early exposure at the medical student level as key parts of recruitment strategies. Yet, the diminished amount of time allotted to introduce and study rheumatic disease in the undergraduate medical curriculum stands at odds with this recommendation and may reduce the likelihood of attracting students to rheumatology. While there has been some attention paid at the graduate medical education level, little attention has been focused on the undergraduate level, particularly the pre-clinical years. We developed an interactive virtual patient platform that presents rheumatology case scenarios. Virtual patient platforms combine case-based learning with new technology and are increasingly used in medical school curricula as an engaging, interactive instructional strategy and assessment tool. Virtual patient platforms can, in theory, support learners' development of clinical reasoning skills across health professions, but few studies provide evidence to support these claims. The development of clinical reasoning skills is of particular importance in rheumatology given the complex nature of rheumatic disease and diversity of clinical presentations.

Methods: We created a simulation platform, "Practice Improvement using Virtual Online Training" (PIVOT), to present virtual cases of patients. During their rheumatology block, 150 second-year medical students used PIVOT to work through a case of a young woman presenting with fatigue, joint pain, and low-grade fever, ultimately diagnosed with lupus. The case content (which included videos of the patient interview, photographs of exam findings, and lab results) was released via the app over four days. Each day, students worked in teams to answer 2-3 open-text questions and received timely feedback from an expert rheumatologist. Students also used a "differential diagnosis slider" to demonstrate their clinical reasoning by ranking diagnoses in order of likelihood.

Results: Individual responses to surveys were analyzed to measure user satisfaction. Use of the differential diagnosis slider and justifications for laboratory studies throughout the case measured clinical reasoning. The educational features most valued by learners included emphasis on clinical decision-making, working within a team, directed expert feedback, and support in "bridging the gap" between the pre-clinical and clinical years.

Conclusion: This application recognizes the evolving, iterative process of developing a differential diagnosis and encourages learners to engage in repeated hypothesis generation and refinement. Tracking the use of the differential diagnosis slider measures valuable information about the development of critical reasoning skills. This platform can be adapted for different learner levels in various settings. The asynchronous, technology-driven framework reflects the way healthcare providers increasingly interact in practice.

Disclosure: M. Lockwood, None; J. Mandal, None; S. Andreatta, None; M. Dall'Era, None.

Abstract Number: 194

A Survey on Gout-Related Knowledge Among Internal Medicine Residents

Sreelakshmi Panginikkod¹, Ahmad Raja², Ehsan Rajabirostami¹, Roshanak Habibi¹, Rasiya Hashim³, Sumia Matin Afridi⁴, Alvaro Altamirano Ufion⁵ and Venu Pararath Gopalakrishnan¹, ¹Internal Medicine, Presence Saint Francis Hospital, Evanston, IL, ²Presence Saint Francis Hospital, Evanston, IL, ³Presence Saint Joseph Hospital, Evanston, IL, ⁴Florida Hospital Orlando, Orlando, FL, ⁵Internal Medicine, Advocate Illinois Masonic Medical Center, Chicago, IL

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: The prevalence of gout has risen in recent decades despite advancements in therapeutic options due to several reasons, including lack of adherence to treatment guidelines by physicians and patients' poor perception and adherence to therapy. We aim to assess the beliefs and knowledge of gout management in Internal Medicine residents, to investigate the gaps, so that education programs can target these gaps and address them in a comprehensive fashion.

Methods: A cross-section survey of Internal Medicine residents from three residency programs in Chicago was conducted using a 20-item questionnaire based on current ACR guidelines on gout management. Residents were considered to have

“good” knowledge if 70% of the questions are answered correctly. Survey performance was compared to respondent’s year in residency, information on guidelines, number of teaching sessions attended, and number of gout patients cared for. We obtained adjusted relative risks (RRs) of good knowledge by estimating a multivariable Poisson regression model with robust variance estimates, adjusted for covariates. Analyses were conducted using Stata, version 14.2.

Results: Of the original sample of 150 residents, 126 (84%) responded to the survey. Good knowledge was demonstrated by only 40% of the respondents. In our survey, two-third of the residents reported that their teaching on gout management is inadequate. For acute gout attacks, 70% of the respondents recognized the right therapeutic options. Only half of the residents knew the correct dose of colchicine and other half opted regimens accounting for higher dose of >2 mg/day. During an acute attack, urate-lowering therapy (ULT) was continued by approximately three-quarters (73%) of the residents. Half of the respondents (50%) were aware that anti-inflammatory prophylaxis (54% colchicine) was indicated while initiating ULT, but only one-third offered the prophylaxis for ≥8 weeks. Approximately 60% of residents reported that allopurinol is initially dosed according to the renal function, but only one third (33%) were aware that it must be titrated to the target serum urate level. Less than half (46%) considered the target serum urate level to be less than 6 mg/dl. In multivariable regression analysis, gout related knowledge was found to be higher among residents who attended more than 3 teaching sessions (RR-3.1; P=0.03; 95% CI, 1.09 to 10.9) and who read the guidelines (ACR/ACP/EULAR) on management (RR-1.8; P=0.04; 95% CI, 1.87 to 4.00).

Conclusion: Our study suggests that better dissemination of knowledge on gout management to Internal Medicine physicians in training is needed. We have identified several areas that should be focused: 1) avoidance of high-dose colchicine; 2) initiating anti-inflammatory prophylaxis while starting urate lowering therapy and its duration; 3) initial dosing of allopurinol 4) target serum urate level; and 4) the need to titrate allopurinol to target serum urate level. Education programs targeting these knowledge gaps may lead to better management practices of the upcoming physicians and help in reducing the prevalence of this burdensome disease.

Disclosure: S. Panginikkod, None; A. Raja, None; E. Rajabirostami, None; R. Habibi, None; R. Hashim, None; S. Matin Afridi, None; A. Altamirano Ufion, None; V. Pararath Gopalakrishnan, None.

Abstract Number: 195

A Two-Year Educational Initiative to Teach Rheumatology through Social Media: The Rheumatology Image of the Week Project (#RheumIOW)

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: With 2 billion global active monthly users of Facebook and 330 million users of Twitter, social media platforms may be used to deliver educational content to today’s adult learner. The Rheumatology Image of the Week project (#RheumIOW) sought to leverage social media to disseminate educational micro-content about rheumatology topics. We recruited rheumatology Fellows-In-Training (FITs) to generate questions based on the ACR Image Library and shared these questions online. We previously showed FITs found question-generation to be a valuable educational experience and useful for learning rheumatology. In the present analysis, we explore the engagement of social media users with #RheumIOW during the two years of the project.

Methods: FITs created questions related to images from the ACR Image Library. Every Tuesday from August 2015-August 2017, one question, its accompanying image, and a link to the Image Library were shared via ACR accounts on Twitter, Facebook, and LinkedIn (Figure 1). Online engagement was measured using platform analytics.

Results: As of May 2018, ACR accounts on Twitter, Facebook and LinkedIn accounts had 15,800, 18,900, and 3,600 followers, respectively. Figure 2 shows clicks generated by platform over the two-year project period. There was a trend toward decreasing participation across all platforms over time with a decline of 40% in Facebook clicks, 59% in Twitter clicks, and 22% in LinkedIn clicks between the first and last six months of the project. Nevertheless, #RheumIOW posts had more engagement than most ACR posts during this time.

Conclusion: The #RheumIOW project sought to leverage social media to deliver educational micro-content on rheumatology topics. Our project was successful in engaging social media users to learn rheumatology and in driving users

to ACR's Image Library. Although ACR has similar numbers of followers on Twitter and Facebook, the latter generated 1.9 times more clicks for #RheumIOW posts. Facebook outperformed Twitter and LinkedIn in stimulating engagement with learners, which may help guide future educational projects. The decline in participation over time indicates that future educational interventions may be most effective when limited in duration. Educational outreach projects on social media may help to increase interest in rheumatology and could be used to recruit Millennials into the field.



Figure 1. #RheumIOWpost with question, associated image, and link to ACR Image Library.



Figure 2. Number of #RheumIOW clicks from August 2015 to August 2017.

Disclosure: J. Gosselin, None; J. S. Hausmann, None.

Abstract Number: 196

Immunology and Immunopharmacology at Point of Care: A Quality Improvement Teaching Initiative for Rheumatology Fellows

Nina Kello¹ and Anne Davidson², ¹Rheumatology, Northwell Health, Donald and Barbara Zucker School of Medicine, Manhasset, NY, ²Feinstein Institute for Medical Research, Manhasset, NY

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Immunology knowledge in the rheumatology community is important for a better understanding of disease pathogenesis and management, especially in an era of an expanding number of biologic therapies. Focus on immunology and immunopharmacology within rheumatology fellowship training programs varies depending on institution, as well as the involvement and availability of immunologists. The ACGME Program Requirements for Rheumatology requires “knowledge in pharmacokinetics, metabolism, adverse events, interactions, and relative costs of drug therapies used in the management of rheumatic diseases” and 5% of the rheumatology certification exam tests immunology and pharmacology. Immunology knowledge of rheumatology fellows and attendings has anecdotally been inadequate, though official data on immunology and immunopharmacology knowledge is lacking. We hypothesized that teaching and applying immunology in the clinic setting at “point of care” would promote a better understanding of immunopharmacology.

Methods: Over the course of 6 months, with the use of diagrams and flash cards, a brief (25min) tutorial covering the basic science behind a drug, followed by the pharmacology of said drug, was held at every fellow’s clinic by our immunologist and a senior fellow. Baseline immunology and immunopharmacology knowledge of the rheumatology fellows was determined with a pre-assessment test on the selected topic prior to each tutorial. The handouts were compiled into a book, which was available both in print and online and used on a regular basis when discussing patient management in clinic. The attending would initially model how to teach the material in a 3-5 minute format, and thereafter the fellow would use the same material to teach medical residents and students. A post-test assessment was performed 6 months after the lectures.

Results: Rheumatology fellows showed a significant improvement in test scores after our immunology tutorials, with pre-test scores ranging from 51-68% to post-test scores 82-95%. Post-test assessments not only evaluated improvement in knowledge, but also identified areas of weakness for repeat teaching.

Conclusion: Teaching immunology and immunopharmacology at “point of care” has proven to be an effective and well-liked tool to use in clinical practice among rheumatology fellows. Our innovative approach makes immunology clinically relevant and will indirectly improve patient care given better understanding of drug side effects and interactions. Our approach is interactive, convenient, time-efficient, flexible, easily updated, promotes the “fellow as teacher”, and can be used in the clinic even by programs with limited immunology expertise. We encourage application of this approach to future generations of rheumatology fellows within our fellowship program and beyond.

Disclosure: N. Kello, None; A. Davidson, None.

Abstract Number: 197

Improving Clinical Decisions for Gout Management: Effect of Online Case-Based Education

Nimish Mehta, Piyali Chatterjee-Shin and Karen Badal, Medscape, LLC, New York, NY

SESSION INFORMATION

Session Date: Sunday, October 21, 2018
Session Title: Education Poster
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Gout is a chronic condition with a considerable effect on patient health and quality of life. Despite the availability of multiple pharmacologic treatments and evidence-based management guidelines, treatment targets are often not achieved in patients with gout. A study was conducted to determine if online, case-based intervention could improve clinical decisions made by rheumatologists and PCPs regarding the management of patients with gout.

Methods: Educational design included 2 online, interactive, patient cases presented using a “test, then teach” approach to elicit cognitive dissonance, with evidence-based feedback provided following each learner response. Educational effectiveness was assessed with a repeated-pairs pre-/post-assessment study design with 3 case-based questions and 1 confidence question, in which each individual served as his/her own control. McNemar’s chi-squared test assessed differences from pre- to post-assessment. P values <.05 are statistically significant. Cramer’s V was used to calculate the effect size (<0.05 no effect; 0.06-0.15 noticeable effect; 0.16-0.26 considerable effect; >0.26 extensive effect). The activity launched 12/26/2017, with data collected through 1/18/2018.

Results: The analysis set consisted of responses from rheumatologists (n=73) and primary care physicians (PCPs, n=1053) who answered all assessment questions during the study period. Analysis of pre- vs post-intervention responses by demonstrated a significant improvement in overall competence of with considerable educational impact (rheumatologists: $V = .276$, $P < .0001$. PCPs: $V = .358$, $P < .0001$).

Average correct responses increase from 68% pre to 90% post education for rheumatologists, and 41% pre to 76% post for PCPs. Specific areas of improvement in clinical decisions include:

- Addition of allopurinol to colchicine in a patient with serum urate level of 9.2 mg/d
- Treatment with fixed-dose lesinurad/allopurinol combination therapy in a patient with adherence issues while maintaining target urate levels
- Switching from allopurinol to febuxostat in a patient with uncontrolled serum urate levels and hypersensitivity to allopurinol based on HLA-B*5801 positivity

Post-education, 18% of rheumatologists and 36% of PCPs were more confident in using a treat-to-target approach when prescribing urate-lowering therapy in gout.

Conclusion: This study demonstrated the success of online, interactive, case-based education on improving the evidence-based clinical decisions and confidence of rheumatologists and PCPs in selecting appropriate treatment for patients with gout using a treat-to-target approach.

Disclosure: N. Mehta, None; P. Chatterjee-Shin, None; K. Badal, None.

Abstract Number: 198

The Utility of a Coloring Book As an Adjunct Tool to Teach Musculoskeletal Sonoanatomy: A Pragmatic Randomized Control Trial

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Ultrasonography is an important modality to evaluate and diagnose a host of musculoskeletal and rheumatologic conditions. However, the interpretation of sonographic images is a challenging skill to acquire. Furthermore, there is a limited set of resources available to rheumatology fellows for self-study. To fill that gap, the investigators created a musculoskeletal ultrasound coloring book as an adjunct to didactic sessions, and assessed the utility of this book through a pragmatic randomized control trial.

Methods: The investigators prepared a coloring book using images obtained by scanning their own joints. Complete ultrasound scans of 10 joints were taken according to OMERACT protocols. Two sets of chapters were created: a 'control' chapter with faithful reproductions of the ultrasound images, and a 'coloring' chapter, with color inversions of black-and-white ultrasound images to enable participants to color in the spaces. Both have identical captions and interpretations underneath the images.

Participants were recruited from the University of Iowa Rheumatology Fellowship Program. All participants attended didactic hour-long weekly sessions and were administered four sets of distinct examinations: the pre-test, the immediate post-test, the 4-week post-test, and the 6-month post-test. Each participant was provided a copy of the modified coloring book which was composed of 5 randomly assigned 'control' chapters and 5 randomly assigned 'coloring' chapters. Participants were strongly encouraged to study the material prior to didactic sessions, follow along during sessions, and use the book chapters as resources thereafter. Test results were blinded to investigators until the end of the trial.

Results: 6 fellow physicians participated in 10 sessions each and appeared for each of the four 10-question exams. Therefore, the group had an overall total of 60 sessions, of which 30 were subject to intervention with the 'coloring' chapter and 30 were controls with the 'standard' chapter. The mean pre-test scores were 2.3 (SD = 1.9) for controls and 3.1 (SD = 1.4) for interventions. The mean post-test scores were 9.3 (SD=0.4) and 9.8 (SD=0.3) for controls and interventions, respectively. Mean 4-week post-test scores were 5.8 (SD=0.9) and 7.6 (SD=1.1), respectively, and 6-month post-test scores were 4.1 (SD=0.8) and 6.8 (SD=1.1), respectively. The differences between the pre-test, immediate post-test, and 4-week post-test scores were not statistically significant ($p=0.736$, $p=0.322$, and $p=0.210$, respectively). However, the difference between the mean 6-month post-test scores was statistically significant ($p=0.05$).

Conclusion: The musculoskeletal ultrasound coloring book is a useful adjunct to didactic sessions to promote six-month retention of sonoanatomy knowledge by fellow physicians. Further investigation is necessary to determine if this translates into greater fluency in interpretation of pathology, technique in obtaining images, and satisfaction. The investigators recommend implementation in multiple institutions to more definitively determine the utility of a musculoskeletal ultrasound coloring book as an adjunct to didactic sessions.

Disclosure: B. Kumar, None; M. Swee, None; M. Suneja, None.

Abstract Number: 199

Evaluating the Perception Among Rheumatologists of Maintenance of Board Certification Programs in the United States

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education Poster

Session Type: ACR Poster Session A

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

Background/Purpose: There continues to be a debate about the value and purpose of maintenance of certification programs (MOC) created by board-certifying organizations. Physicians, echoed by multiple societies including the American College of Rheumatology (ACR), have raised concerns questioning the recertification process. The goal of this survey study is to assess the impact, value, and purpose of maintenance of board certification in rheumatology.

Methods: A survey designed to assess the impact and perceived value of maintenance of board certification in rheumatology was sent via email to 3,107 rheumatologists within the US. The survey addressed issues related to how rheumatologists perceive negative and positive impacts of MOC, and how this program might affect various aspects related to rheumatology practice and patient access to care.

Results: A total of 515 rheumatologists completed the survey. With an estimated number of ~5,000 full-time practicing rheumatologists in the US, this sample size gives a margin of error of <5% with 95% confidence that the responses accurately reflect the views of rheumatologists. The majority (74.8%) did not think there is significant additional value in MOC, beyond what is already achieved from Continuing Medical Education, or that MOC is valuable in terms of improving patients care (63.5%). The majority felt that the primary reason for creating MOC is financial well-being of board certifying organizations (43.4%) or to satisfy administrative requirements in health systems (30%). Only 15.1% believed improving patient care was the primary reason for MOC. The majority of rheumatologists believed board certification should be a life-long credential (63.7%), and 75.2% favor a state legislation to remove MOC as a requirement for employment, insurance reimbursement, or securing clinical privileges. Notably, when asked about positive and negative impacts, the majority reported that MOC results in time away from providing patient care (74.6%), time away from family (74%), and psychological stress (69.7%). 65.6% perceived staying current with new knowledge as a positive impact of MOC. When asked about anticipated effects of requiring MOC, 77.7% reported physician burnout, 67.4% early physician retirement, and 63.9% anticipated an effect on reducing the overall number of practicing rheumatologist. Of interest, 58.9% believe board certification in rheumatology should be administered or overseen by other organizations such as the ACR. Of the respondents who reported participating in research activities, 39.6% believed MOC is adversely affecting their ability to perform research or research related activities.

Conclusion: The majority of rheumatologists in the US do not believe there is value for recertification and maintenance of certification in rheumatology. Negative impact was clearly more than any positive impact perceived. Importantly, there is evidence for lack of trust in board certifying organizations among rheumatologists, and the majority of rheumatologists believe MOC contributes to physician burnout, early retirement, and loss in the rheumatology work force. This is alarming given the current and predicted shortage in rheumatologists in the future.

Disclosure: A. H. Sawalha, None; P. Coit, None.

Validation of the Ers-RA Risk Score in a Dutch Population

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: The most frequent cause of death in patients with chronic rheumatoid arthritis(RA) is of cardiovascular (CV) origin. CV risk prediction scores in the normal population do not predict the CV risk in RA patients adequately due to the additional systemic inflammatory burden which is pathogenic for CV disease. Recently, Solomon et al developed the ERS-RA Risk Score, a newly and expanded CV risk score predicting the 10 year CV event risk in RA

Area Under the Curve	
Test Result Variable(s)	Area
ERS_RA_RISK_SCORE_70	0.04
ERS_RA_RISK_SCORE_80	0.05
ERS_RA_RISK_SCORE_90	0.05
ERS_RA_RISK_SCORE_100	0.05
ERS_RA_RISK_SCORE_110	0.04
ERS_RA_RISK_SCORE_120	0.03
ERS_RA_RISK_SCORE_130	0.03
ERS_RA_RISK_SCORE_CDAI>10	0.12

The test result variable(s):

ERS_RA_RISK_SCORE_70
ERS_RA_RISK_SCORE_80
ERS_RA_RISK_SCORE_90
ERS_RA_RISK_SCORE_100
ERS_RA_RISK_SCORE_110
ERS_RA_RISK_SCORE_120
ERS_RA_RISK_SCORE_130
ERS_RA_RISK_SCORE_CDAI>10

patients. This is based on a cohort from the Consortium of Rheumatology Researchers of North America registry. In this abstract we present the results of a validation test performed with the ERS-RA Risk Score in the Dutch CARRE study.

Objective: To perform a validation test of the ERS-RA Risk Score in the Dutch CARRE study.

Methods: We validated the ERS-RA Risk Score in the CARRE cohort by performing a ROC curve analysis. The CARRE study is a Dutch cohort study investigating CVD and its risk factors in RA-patients who have been followed prospectively for at least five years. RA patients registered at Reade (location Jan van Breemen institute in Amsterdam, the Netherlands) participated if they fulfilled the 1987 ACR classification criteria, were diagnosed between 1989 and 2001, and were aged between 50 and 75 years. In contrast to the cohort used in study of Solomon et al, the CARRE study used the HAQ instead of m-HAQ and the CARRE lacks the Predictor's Global Assessment to calculate the CDAI. However, to approximate the true outcome of the m-HAQ and the CDAI we conducted the following modifications of the CARRE cohort data. To calculate the CDAI we estimated the Predictor's Global Assessment as 70%, 80%, 100%, 110%, 120% and 130% of the Patient's Global Assessment. Furthermore, we approximated the m-HAQ score 50% lower than the HAQ score as described in a recent published article.

Results: The CARRE study included 352 RA patients with 60 CV events over a 10 year follow up period. The mean age was 63.3 years of which 121 (34%) male participants. The ROC curve analysis shows an area under the curve of 0.603-0.612 depending on the predicted Predictor's Global Assessment (see figure 1).

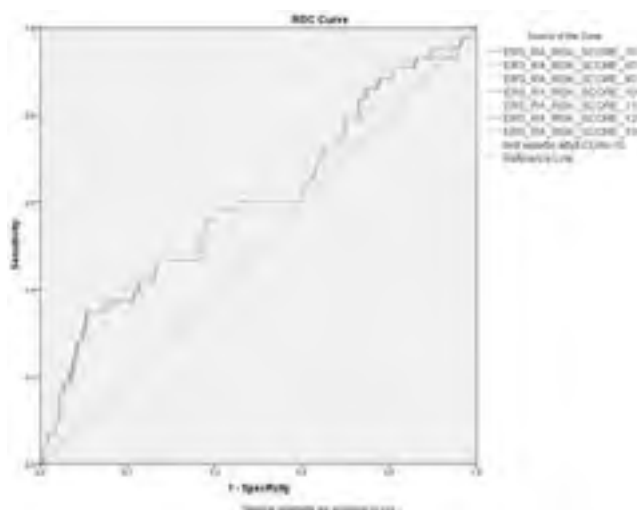


Figure 1. ROC curve analysis of the ERS-RA Risk score in the CARRE cohort with different approximated CDAI scores.

Conclusion: In conclusion, the ERS-RA Risk Score has a limited validity in the CARRE study, a Dutch RA cohort and can therefore not be used for risk prediction in Dutch RA patients.

Disclosure: M. Baniaamam, None; M. Nurmohamed, Pfizer, Abbvie, Roche, BMS, MSD, Mundipharma, UCB, Janssen, Menarini, Eli Lilly, and Celgene., 2, 5, 8.

Abstract Number: 201

Occupational Exposure to Coal and Silica Dust Is Associated with Elevated Risk of Rheumatoid Arthritis in Coal Mining Areas of US

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Exposure to inhaled mineral dust, particularly silica, has been associated with increased risk of RA and other autoimmune diseases. Coal mining leads to silica exposure, but the extent to which RA can be attributed to coal mining has not been estimated. We studied the association of RA with work-related coal and silica exposure in the Appalachian region of the US, given its geographic concentration of mining and data showing a high population prevalence of arthritis.

Methods: We conducted a random digit dial telephone survey within selected counties in the Appalachian region with the highest coal workers' pneumoconiosis mortality rates identified by NIOSH. Eligibility was limited to males, age ≥ 50 , with any work history. A brief structured telephone interview included demographics, occupational dust, work-related ergonomic exposures, and self-reported physician diagnoses of and treatment for arthritis, including RA. Only those reporting both a physician diagnosis of RA and glucocorticoid use for joint symptoms were considered to have RA for this analysis. We scored ergonomic exposures using a 13-item list of physical work hazards (e.g. lifting, bending, using power tools), each contributing 1 point. We used logistic regression analysis to estimate the risks of any arthritis and, separately, the subset meeting the study definition of RA associated with occupational coal dust and other occupational silica exposure, adjusting for high-levels of ergonomic exposure (≥ 11 items; 75th percentile), age, and smoking status (current/former/never). The models of RA risk exclude those reporting a diagnosis of arthritis who do not meet the study definition of RA.

Results: Among the 973 men, average age was 66 ± 10 years; 91% were white; 54% ever smokers. 266 (27%) reported coal mining work; 189 (19%) reported work-related silica exposure without coal mining. Arthritis was highly prevalent among the respondents, with 517 (53%) reporting a physician diagnosis of any arthritis and 112 (12%) RA. In the fully adjusted models (Table 1), coal mining was associated with elevated odds of both RA and any arthritis. Other silica exposure also increased the odds of any arthritis. Current smoking was associated with RA only.

Conclusion: In this population of older men living in areas in which coal mining and other occupational silica dust exposure is common, we found a high prevalence of self-reported arthritis, particularly of RA. While this study may overestimate the true prevalence of RA, the odds of any arthritis and RA associated with coal-mining remained markedly elevated after adjusting for ergonomic exposures and smoking. Given both the frequency of exposure and magnitude of risk, a substantial proportion of prevalent arthritis in this region may be attributable to occupational factors, a link that is not widely appreciated or acknowledged.

Table 1. Risk of arthritis associated with occupational coal dust and silica exposure among 973 men age ≥ 50 from US counties with high prevalence of coal mining.

	Model 1 (Adjusted for Age/Smoking)		Model 2 (Age/Smoking/Ergonomics)	
	All arthritis	RA	All arthritis	RA
	OR (95% CI)		OR (95% CI)	
Coal and Silica exposure				
Coal mining work	2.6 (1.9, 3.5)	4.4 (2.7, 7.2)	2.2 (1.6, 3.1)	3.5 (2.1, 6.0)
Other occupational silica exposure	2.0 (1.4, 2.8)	2.4 (1.3, 4.3)	1.7 (1.2, 2.4)	1.9 (0.99, 3.6)
None reported	(ref)	(ref)	(ref)	(ref)
Cigarette Smoking				
Current	1.3 (0.8, 1.9)	2.1 (1.1, 3.9)	1.2 (0.8, 1.9)	1.9 (1.0, 3.7)
Former	1.1 (0.8, 1.4)	1.2 (0.7, 1.9)	1.1 (0.8, 1.4)	1.2 (0.7, 1.9)
Never	(ref)	(ref)	(ref)	(ref)
Ergonomic exposure				
11-13 items			1.5 (1.1, 2.0)	1.8 (1.1, 3.0)
0-10 items			(ref)	(ref)

All arthritis: Self-reported physician diagnosis of arthritis.

RA: Self-reported physician diagnosis of RA + history of glucocorticoids.

Models of RA exclude 405 respondents with non-RA arthritis.

Ergonomic exposure dichotomized at the 75th percentile.

Disclosure: L. Trupin, None; E. H. Yelin, None; G. Schmajuk, None; P. Blanc, None.

Abstract Number: 202

Risk of Inflammatory Arthritis Development in the Family Members of Indigenous North American (INA) RA Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Background/Purpose: INA populations have a high prevalence of seropositive RA, often with severe disease. The risk of RA in family members of RA patients, particularly first-degree relatives (FDR), is estimated to be up to 4 times that of the general population. We prospectively followed a cohort of unaffected family members of INA RA patients to determine the incidence of inflammatory arthritis (IA).

Methods: Family members of INA RA probands were recruited and followed longitudinally between 2005-2017. At baseline, participants were examined to confirm absence of synovitis and questionnaires regarding joint symptoms, lifestyle, and comorbidities were administered. Serum was tested for ACPA (anti-CCP3 ELISA) and IgM RF seropositivity. Seropositive individuals were re-evaluated annually and seronegative individuals every three years. Participants were instructed to contact the investigators if symptoms suggestive of IA occurred and were re-evaluated at that time. Diagnosis of IA required one or more swollen joints deemed to represent synovitis by a study rheumatologist. Individuals included in the analysis had a least two visits, 6 months or more apart. To calculate the incidence of IA, number of IA cases was used as the numerator, and total years of follow-up of the entire cohort served as the denominator.

Results: 374 family members (314 from Manitoba, 60 from Alaska) were enrolled. The majority (75%) were FDR. Total follow-up time for the cohort was 1,940 person-years. 18 (4.8%) people developed IA after a mean of 4.8 (IQR 3.6-6.1) years, and 15/18 (83%) met the 2010 ACR/EULAR criteria for RA. Baseline cohort characteristics are in Table 1. The rate of IA development was 9.2 cases per 1000 person years of follow-up (0.9% annually). 6/18 of the IA group was ACPA and RF seronegative at baseline with a median time to transition of 5.6 (± 1.1) years, whereas the 5/18 who were ACPA/RF positive at baseline developed IA after 3.2 (± 2.2) years (Table 2). Interestingly, 7/12 relatives who were ACPA/RF positive at baseline had not developed IA after being followed for a mean of 5.1 years (± 2.2), and many individuals who were seropositive at any given time subsequently became seronegative.

Conclusion: This prospective longitudinal cohort study of the relatives of INA RA patients is the first to establish the incidence of IA in this high-risk population. As expected, ACPA+/RF+ seropositivity is associated with the highest rates of IA development and shortest latency period. Importantly, the lack of IA development in the majority of seropositive individuals, including ACPA+/RF+, suggests the transition to clinically detectable disease relates to other unknown factors.

Table 1. Baseline characteristics of individuals with longitudinal follow-up.

	Transitioner, n=18	Non-Transitioner, n=356	p-value
Female	14 (77.8)	234 (65.7)	0.29
Age (years), mean (SD)	30.0 (11.5)	37.1 (12.8)	0.02
Duration of follow-up (years), mean (SD)	4.8 (2.4)	5.2 (2.7)	0.57
History of smoking	16 (88.9)	272 (76.5)	0.24
Pack years smoking, med (IQR)	3.5 (1.2-12.0)	5 (0.8-12.6)	0.41
BMI (kg/m ²), mean (SD)	28.9 (7.9)	32.4 (7.1)	0.06
Diabetes	0 (0)	58 (19.5)	0.13
Any HLA shared epitope (SE)	8/15 (53.3)	114/192 (59.4)	0.65
HLA 1402 positive	9/15 (60.0)	93/234 (39.7)	0.07
HLA SE double positive	5/15 (33.3)	30/192 (15.6)	0.10
CRP (mg/L), med (IQR)	2.4 (1.1-5.7)	3.4 (1.7-7.0)	0.44
ACPA negative †	8 (44.4)	321 (91.2)	0.01
ACPA positive†	10 (55.5)	31 (8.8)	0.01
ACPA strong positive†	7 (38.9)	11 (3.1)	0.01
RF negative‡	11 (61.1)	295 (84.7)	0.02
RF positive‡	7 (38.9)	53 (15.2)	0.01
RF strong positive‡	4 (22.2)	11 (3.2)	0.01
RF and ACPA positive‡	5 (27.8)	7 (2.0)	0.01
Symptoms			
Hand pain	10/16 (62.5)	143/279 (51.3)	0.381
Other joint pain	10/15 (66.7)	155/280 (55.4)	0.390
Hand swelling	6/16 (37.5)	99/282 (35.1)	0.845
Other joint swelling	7/16 (43.8)	79/279 (28.3)	0.405
Hand stiffness	8/17 (47.1)	109/281 (38.3)	0.498
Other joint stiffness	8/16 (50)	114/280 (40.7)	0.407

Values are reported as n (%), unless otherwise noted.

* Strong positive values generated according to ACR definition. Strong positive ³x's upper limit of normal based on manufacturers cut-off.

† n=352 in non-transitioner subset

‡ n=348 in non-transitioner subset

Table 2. Baseline autoantibody groups and development of inflammatory arthritis.

	ACPA-/RF- n=285	ACPA-/RF+ n=48	ACPA+/RF- n=29	ACPA+/RF+ n=12
Time at risk, person-years	1472.1	276.2	137.3	51.5
Cases of IA (% in autoantibody group)	6 (2.1)	2 (4.2)	5 (17.2)	5 (41.7)
Cases of IA/ 1000 person years	4.1	7.2	36.4	97.1
Time to IA, years	5.6 (1.1)	5.5 (5.0)	4.7 (2.7)	3.2 (2.2)
Time to ACPA positivity, years	2.3 (1.7)	2.2 (n=1)	-	-
Number cases meeting ACR RA criteria	5/6	1/2	5/5	4/5

Values are reported as mean with standard deviation unless stated.
Seropositivity of ACPA and RF based on manufacturers cut-off level.

Disclosure: S. Tanner, None; I. Smolik, None; B. Dufault, None; C. Hitchon, Pfizer, Inc., 2; D. Robinson, None; E. Ferucci, None; H. El-Gabalawy, None.

Abstract Number: 203

Meat Consumption and Risk of Rheumatoid Arthritis in Women: A Population-Based Cohort Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Mixed results have been reported for the association between meat consumption and the risk of developing rheumatoid arthritis (RA). The aim of this study was to evaluate the association between red meat, particularly processed meat, and the risk of RA using data from a population-based cohort of women.

Methods: We prospectively followed 35,600 women aged 48-83 years from the Swedish Mammography Cohort (SMC), between 2003 and 2014. Meat consumption was assessed with a 96-item self-administered questionnaire in 1997. A corresponding questionnaire data from 1987 was available, enabling identification of long-term meat consumption. The relative risk (RR) of RA associated with meat consumption and its 95% confidence interval (CI) were estimated using Cox proportional hazard regression models. Multivariable models were adjusted for age, body mass index, educational level, physical activity, use of dietary supplements, energy intake, and smoking.

Results: During the 12 years of follow-up (381 456 person years), 368 new cases of rheumatoid arthritis were identified. Meat consumption was not associated with the development of RA in age-adjusted (RR=0.96 (95% CI: 0.69-1.32)) or multivariable adjusted (RR=1.08 (95%CI: 0.77-1.53)) models (**Table 1**). No association was observed either for consumption of type-specific meat, such as red meat (RR=1.08 (95% CI: 0.77-1.50)), processed meat (RR=0.84 (95% CI: 0.59-1.22)), or poultry (RR=0.88 (95% CI: 0.60-1.31)). , Women with a consistent long-term consumption of meat of >7 servings/week over a period of 10 years had no increased risk of RA, HR 1.19 (95% CI: 0.78-1.80), compared to women with a consistent consumption of <=4 servings/week.

Conclusion: In this large population-based cohort study, meat consumption, in total, by sub-types, or over time, was not associated with the risk of RA development in women.

Table 1. Relative risk of rheumatoid arthritis during follow-up (2003-14) of women in the Swedish Mammography Cohort by meat consumption in 1997.

	N of cases	N of person years	RR Adjusted for age	RR Multivariable adjusted*
Meat, overall				
<=4 servings/week	62	64 230	Ref	Ref
4-7 servings/week	97	113 706	0.84 (0.61-1.15)	0.88 (0.64-1.22)
7-10 servings/week	112	104 390	1.04 (0.76-1.42)	1.13 (0.81-1.56)
>10 servings/week	97	99 131	0.96 (0.69-1.32)	1.08 (0.77-1.53)
Read meat				
<=4 servings/week	83	87 288	Ref	Ref
4-7 servings/week	120	125 334	0.96 (0.73-1.27)	1.01 (0.76-1.35)

Table . (Cont'd)

	N of cases	N of person years	RR Adjusted for age	RR Multivariable adjusted*
7-10 servings/week	89	89 256	1.00 (0.74-1.35)	1.08 (0.79-1.47)
>10 servings/week	76	79 579	0.97 (0.71-1.32)	1.08 (0.77-1.50)
Processed meat				
<=1 servings/week	54	52 945	Ref	Ref
1-3 servings/week	110	121 488	0.84 (0.60-1.16)	0.86 (0.62-1.20)
3-6 servings/week	131	120 021	1.01 (0.73-1.39)	1.06 (0.76-1.46)
>6 servings/week	73	88 003	0.78 (0.55-1.11)	0.84 (0.59-1.22)
Poultry				
0 servings/week	47	52 122	Ref	Ref
<=1 serving/week	253	252 887	0.97 (0.71-1.33)	1.01 (0.73-1.40)
>1 serving/week	68	77 448	0.82 (0.56-1.19)	0.88 (0.60-1.31)

*Adjusted for age, alcohol intake, smoking, energy intake, dairy products and fish consumption

Disclosure: D. Di Giuseppe, None; L. Ljung, None; B. Sundstrom, None.

Abstract Number: 204

Investigating Asthma, Allergic Disease, Passive Smoke Exposure, and Risk of Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Several studies show an association between asthma and RA. However, none have controlled for allergic disease, urban environment, or passive smoke exposure. We aimed to determine the association of asthma, allergic disease, and passive smoke exposure with RA risk.

Methods: We performed a case-control study using a biobank at a single center, identifying cases of RA using a rules-based algorithm combining self-report with two diagnosis codes (PPV = 88%). We matched each case to three controls based on age, sex, and location of residence at index date of survey. Data on exposures were self-reported on biobank surveys. Unconditional logistic regression models calculated the relationship between each exposure and RA after adjusting for potential confounders.

Results: We identified 1,149 RA cases and 3,441 controls. Mean age at survey date was 62 years (SD 13), and 72% were female. Asthma was associated with RA even after adjusting for allergies, urban environment, and passive smoke exposure (Table 1). History of allergic disease was also associated with RA (Table 1). Passive home smoke exposure duration and pack-years were modestly associated with development of RA, but the association with passive work smoke exposure was not statistically significant (Table 1).

Conclusion: Asthma, allergic diseases, and passive smoke exposure at home may be associated with increased risk of developing RA. Future studies investigating the relationship between atopy and autoimmunity are needed.

Table 1. Association between asthma, allergy, passive smoke exposure and RA*

	1997-2001	2002-2006	2007-2011	2012-2016
RA	N=520	N=819	N=840	N=1400
CV mortality	100 (19.7%)	112 (15.0%)	130 (17.3%)	193 (16.5%)
Infection	174 (34.2%)	259 (34.8%)	308 (41.0%)	542 (46.4%)
Cancer	66 (13.0%)	112 (15.0%)	130 (17.3%)	189 (16.2%)
PsA	N= 21	N= 31	N= 52	N= 83
CV mortality	5 (23.8%)	7 (25.0%)	9 (19.6%)	13 (18.1%)
Infection	6 (28.5%)	10 (35.7%)	14 (30.4%)	28 (38.9%)
Cancer	3 (14.3%)	4 (14.3%)	14 (30.4%)	15 (20.8%)

Table 3. (Cont'd)

	1997-2001	2002-2006	2007-2011	2012-2016
AS	N=61	N=121	N=202	N=224
CV mortality	14 (23.3%)	18 (16.7%)	32 (18.0%)	38 (19.6%)
Infection	16 (26.7%)	31 (29.6%)	58 (36.0%)	83 (45.4%)
Cancer	12 (20.0%)	25 (23.1%)	27 (15.2%)	33 (17.0%)

Disclosure: T. T. Cheung, None; S. M. F. Tsoi, None; B. M. Y. Cheung, None; C. S. Lau, None.

Abstract Number: 205

Circulating Plasma Metabolites and Risk of Rheumatoid Arthritis in the Nurses Health Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) develops insidiously, often over many years. Given that diet and obesity have been associated with increased RA risk, we investigated whether metabolomic profiling of plasma could identify novel biomarkers associated with risk of developing RA among women.

Methods: Incident RA cases with plasma samples drawn prior to disease onset in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) cohorts were matched to controls at a 1:2 ratio based on age, race, menopausal status, post-menopausal hormone use, as well as blood-draw variables: fasting status, time of day, and date of blood draw.

Metabolite	NHSII #	OR	95% CI	P	OR	95% CI	P
Any time to diagnosis							
Serum Metabolites							
4-acetamidobenzoic acid	00981	0.793	(0.657, 0.952)	0.008	0.734	(0.585, 0.920)	0.003
C5-7 carnitine	00366	0.817	(0.692, 0.963)	0.016	0.730	(0.598, 0.895)	0.002
N-acetylglucosamine	13113	0.812	(0.704, 0.943)	0.031	0.647	(0.477, 0.876)	0.005
D3 carnitine	00688	0.840	(0.710, 0.995)	0.043	0.681	(0.506, 0.912)	0.010
N-acetylserine		0.817	(0.695, 0.962)	0.015			
N-acetylglutamate	00084	0.820	(0.696, 0.967)	0.019			
serine	01257	1.253	(1.037, 1.514)	0.020			
C18:1 n-7	00855	0.834	(0.707, 0.984)	0.030			
C18:1 n-7 phosphatidylcholine		0.835	(0.709, 0.980)	0.030			
choline	00902	0.846	(0.720, 0.999)	0.048			
N6-acetyl-L-lysine	00006	0.844	(0.714, 0.999)	0.048			
C7 carnitine	10228				0.695	(0.516, 0.930)	0.010
caffeine	11947				0.742	(0.493, 0.937)	0.016
C12:1 TAG	10517				0.320	(0.143, 0.698)	0.007
C18:0 SFA-misc	01348				0.741	(0.534, 0.977)	0.037
1,3-bis(sn)-sn-glycerol-3-phosphate	11103				0.762	(0.517, 0.914)	0.038
3-oxoheptanoic acid	10736				0.728	(0.485, 0.987)	0.046
Plasma Metabolites							
C18:1 n-7		1.234	(1.048, 1.452)	0.017	1.350	(1.096, 1.641)	0.017
C22:0 LPS (somer)		1.216	(1.034, 1.430)	0.015	1.377	(1.098, 1.711)	0.017
1,1,1,2,2-pentachloroethane D3 (somer)		1.232	(1.071, 1.478)	0.025			
C20:0 LPS (somer)		0.841	(0.709, 0.997)	0.040			
Carnitine-3-glucuronide (somer)					0.721	(0.543, 0.951)	0.024
Selenocysteine					0.722	(0.562, 0.946)	0.038
Selenomethionine-3-glucuronide (somer)	10357				0.747	(0.588, 0.962)	0.040
Selenomethionine-3-glucuronide (somer)					0.738	(0.559, 0.966)	0.041
1-1/2 years prior to diagnosis							
Carnitine	00870	1.772	(1.442, 2.207)	0.002	1.601	(1.350, 1.905)	0.010

*Statistically significant ORs for identifying metabolites

RA: all rheumatoid RA; SP: seropositive RA; OR: odds ratio per standard deviation; P: p-value

Untargeted liquid chromatography tandem mass-spectrometry molecular profiling of plasma samples drawn prior to RA onset from incident cases and matched controls participating in NHS and NHSII were collected. The final sample after quality control filtering consisted of a total of 256 pre-RA cases and 511 matched controls, measured across 437 unique, known metabolites. Conditional logistic regression was used to assess the association between individual metabolites and risk of RA, with adjustment for BMI and smoking. Subgroup analyses were also performed among case-control matched groups with 1) seropositive RA cases, and 2) with RA cases whose plasma was drawn between 1-5 years prior to diagnosis. Multiple comparison adjustments were made using the number of effective tests.

Results: Top metabolites associated with increased risk of incident RA included C18:1 lysophospholipid (OR: 1.23, 95% CI: 1.05-1.45), and C22:0 lysophosphatidylserine isomer (OR: 1.22, 95% CI: 1.03-1.43). 4-acetamidobutanoic acid (OR: 0.78, 95% CI: 0.66-0.93) and N-acetyltryptophan (OR: 0.83, 95% CI: 0.70-0.98), as well as C5 (OR: 0.84, 95% CI: 0.71-0.995) and C5:1 carnitines (OR: 0.82, 95% CI: 0.69-0.96) were shown to have a protective effect against incident RA. Although these metabolites did not survive adjustment for multiple comparisons, they were found to be marginally significant and shared consistent directions of effect in the seropositive-only RA analyses. In the 1-5 year period prior to RA diagnosis, homoarginine was identified as a significant risk factor for incident RA in both the full group (OR: 1.77, 95% CI: 1.24-3.53) and in the seropositive-only (OR: 3.01, 95% CI: 1.30-6.96) analyses.

Conclusion: We have identified several metabolic markers of incident RA. Further replication in an independent cohort is ongoing to confirm our findings.

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Abstract Number: 206

Impact of International Classification of Diseases 10th Revision Codes and Updated Medical Information on an Existing Rheumatoid Arthritis Phenotype Algorithm Using Electronic Medical Data

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SESSION INFORMATION

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Background/Purpose: Electronic medical records (EMRs) are increasingly being utilized for clinical research, where the phenotypes of interest are typically defined by algorithms. Almost a decade ago, a rheumatoid arthritis (RA) phenotype algorithm using codified and narrative data extracted from the EMR using natural language processing (NLP), was developed using machine learning approaches. The objective of this study was to evaluate the temporal portability of this algorithm, with the introduction of International Classification of Diseases (ICD), 10th revision codes, as well as a new EMR system (Epic) at our institution.

Methods: We studied subjects from the EMR of 2 large academic centers with ≥ 1 ICD9 RA code (714.x) or ICD10 RA code (M05.x, M06.x) and ≥ 2 clinical notes to create a database of all potential patients with RA ("RA Mart", n = 52,728). A random 100 subjects were selected from the RA Mart, and patients were classified as RA yes/no from medical record review to create the validation set. We first calculated the performance characteristics of using ≥ 2 RA ICD9 or ICD10 RA codes to define RA compared to RA classified from chart review. We then applied a previously published logistic regression algorithm for RA using ICD9 codes and data extracted using NLP from data fields specified in 2010. For example, this model would not include treatments approved after 2010. We then applied a modified algorithm incorporating ICD10 codes and additional medications to existing variable fields, e.g. number of RA ICD9 codes became number of ICD 9 or 10 RA codes. We compared performance characteristics of the original 2010 with the modified 2010 RA algorithm using the original published positive predictive value (PPV) as a benchmark.

Results: In the validation set, 41% of subjects were classified as RA. Among those with RA, mean age was 68, 76% female, and 59% were RF or anti-CCP positive; 7% of subjects only had ICD10 but not ICD9 codes. The PPV for

classifying RA using ≥ 2 ICD9 codes was 50%; and for using ≥ 2 ICD9 or ICD10 was 52% (Table). Using the exact data fields specified in the 2010 algorithm, we achieved a PPV of 93%. When the data fields were updated with new types of data, ICD10, new treatments, the PPV remained at 93%. In comparison, the published PPV of the algorithm was 94%, with a sensitivity of 63%.

Conclusion: We observed that an existing RA algorithm trained using machine learning approaches on EMR data was robust temporally, despite the introduction of new medical information which also updated the algorithm steps. At this time including ICD10 had a minimal impact on classification. The existing RA algorithm continued to perform significantly better than using ICD9 or ICD10 data alone at classifying RA.

Table. Performance characteristic of the published algorithm and modified algorithm to identify individuals with RA, as compared to codified data alone (n=100).

	≥ 2 ICD9 RA codes	≥ 2 ICD9 or ICD10 RA codes	Published algorithm	Modified algorithm
Sensitivity	0.80	0.93	0.68	0.66
Specificity	0.44	0.41	0.97	0.97
PPV	0.50	0.52	0.93	0.93

RA: rheumatoid arthritis

PPV: positive predictive value

Disclosure: S. Huang, None; J. Huang, None; T. Cai, None; K. P. Dahal, None; A. Cagan, None; J. Stratton, None; T. Cai, None; K. P. Liao, None.

Abstract Number: 207

Divergent Patterns of Cardiovascular Risk in Biomarkers of Lipids and Subclinical Myocardial Injury during Increased Inflammation in Rheumatoid Arthritis

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SESSION INFORMATION

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Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Inflammation is an independent risk factor for cardiovascular (CV) risk in rheumatoid arthritis (RA). Paradoxically, potentially cardioprotective decreases in inflammation is associated with increased low-density lipoprotein cholesterol (LDL-C). Few studies exist as to how increased inflammation modulates lipid parameters. This study's objective was to examine changes between lipids and markers of myocardial injury among RA patients demonstrating increased inflammation.

Methods: We studied a longitudinal, large academic medical center-based RA cohort, examining annually-collected clinical data, CRP and blood samples among patients with an increase in C-reactive protein (CRP) ≥ 10 mg/L CRP between any two time points at least one year apart. The first time point was defined as the baseline. Subjects on statin therapy one year before baseline or during the one-year follow-up period were excluded. For all subjects, we measured routine lipids: total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), LDL-C; advanced lipoprotein measures: apoA1, apoB, HDL cholesterol efflux capacity; myocardial injury markers: high sensitivity troponin T (hs-cTnT); myocardial strain: pro-BNP. The paired t-test was used to determine significant differences between baseline and follow-up.

Results: Among 1,443 unique RA patients we identified n=103 RA patients who experienced an ≥ 10 mg/L CRP increase in two consecutive years. Baseline characteristics of this cohort were as follows: mean age 59 years, 80% female, 72% positive for RF and/or anti-CCP antibodies; baseline treatment MTX 50.5%, tumor necrosis factor inhibitor 49.5%; a mean CRP increase of 35.9 mg/dL was found. On concurrent follow-up labs, TC, LDL-C, apoB and apoA1 were all significantly reduced (Table). HDL cholesterol efflux capacity was not significantly altered. Both biomarkers of myocardial strain and injury (pro-BNP, hs-cTnT) were significantly increased.

Conclusion: Among 103 RA patients experiencing significant increases in inflammation, markers of subclinical myocardial injury and strain were increased despite concurrent decreases in routine lipid levels, including ones predictive of reduced CV risk. These findings suggest that increases in inflammation in RA may promote subclinical cardiac damage and CV risk while other, accepted CV risk markers, i.e. LDL-C, may mislead clinicians in this setting.

Table. Lipid and myocardial biomarkers at baseline and follow-up after RA patients experienced increase in inflammation.

Biomarker	Baseline	Follow-up	p-value
Routine lipids, mean (SD)			
Total cholesterol (mg/dL)	192.1 (40.3)	177.0 (35.1)	<.0001
HDL-C (mg/dL)	59.1 (18.4)	57.0 (17.5)	0.2
LDL-C (mg/dL)	113.4 (32.4)	101.8 (29.2)	<.0001
Triglycerides (mg/dL)	112.1 (59.1)	101.1 (57.7)	0.003
Non-HDL (mg/dL)	133.0 (37.0)	120.0 (32.8)	<.0001
Total cholesterol/HDL-C	3.5 (1.1)	3.4 (1.7)	0.01
Advanced lipoprotein measures, mean (SD)			
apoA1 (mg/dL)	162.0 (34.6)	152.5 (33.3)	<.0001
apoB (mg/dL)	94.0 (24.0)	90.4 (23.2)	0.02
apoB/apoA1	0.60 (0.20)	0.62 (0.22)	0.3
HDL cholesterol efflux capacity	1.3 (0.40)	1.2 (0.40)	0.1
Markers of myocardial injury or strain			
Hs-cTnT (ng/mL)	8.3 (10.6)	9.8 (12.9)	0.0003
Pro-BNP (pg/mL)	197.4 (371.4)	298.9 (650.2)	0.001
Inflammatory markers and RA disease activity			
hsCRP (mg/L)	8.7 (14.7)	44.6 (47.7)	<.0001
RA Clinical Disease Activity Index (CDAI)	14.8 (12.5)	19.5 (17.0)	0.02

CDAI: ≤10, remission/low disease activity; >10 and ≤22, moderate disease activity; >22 high disease activity

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Abstract Number: 208

Antibodies to Citrullinated Protein Antigens Are Associated with Risk of Cardiovascular Disease in Community-Dwelling Women: The Multi-Ethnic Study of Atherosclerosis

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SESSION INFORMATION

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Antibodies to Citrullinated Protein Antigens are Associated with Risk of Cardiovascular Disease in Community Dwelling Women: The Multi-Ethnic Study of Atherosclerosis

Background/Purpose: Risk for cardiovascular (CV) events in patients with RA is double what it is for the general population. Antibodies to citrullinated proteins (ACPA) are detectable years before RA onset and in some individuals who do not develop RA. It is not known whether ACPA, in the absence of clinical RA, is associated with CV events. Among men and women without RA in a multi-ethnic community dwelling population, we investigated associations between ACPA and incident CV events.

Methods: Among a randomly selected subset of 1617 participants in the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective cohort study designed to determine risk factors and progression of subclinical and clinical cardiovascular disease, we measured ACPA using a multiplex array of 38 different individual ACPA. Each ACPA was defined as positive if > 95th percentile cut-off in MESA. The number of (+) ACPA were summed for each participant (range 0-38). We

Hazard Ratios and 95% Confidence Intervals for Associations between the Number of ACPA and Incident CV Events in Women and Men in MESA*			
	Women (n=814)	Men (n=803)	
Heart Failure			
Events / P-Y	27 / 3241650	38 / 3068642	
Event rate (per 1000 P-Y)	0.008	0.013	
Age and race adjusted	0.974 (0.89-1.07)	1.031 (0.89-1.08)	
Fully adjusted**	0.979 (0.89-1.08)	1.028 (0.88-1.08)	
Myocardial Infarction			
Events / P-Y	27 / 3252327	43 / 3042264	
Event rate (per 1000 P-Y)	0.008	0.014	
Age and race adjusted	1.060 (1.01-1.11)	0.946 (0.85-1.05)	
Fully adjusted**	1.068 (1.02-1.12)	0.942 (0.85-1.04)	
Angina			
Events / P-Y	25 / 3230606	51 / 2992645	
Event rate (per 1000 P-Y)	0.008	0.017	
Age and race adjusted	1.062 (1.01-1.11)	0.997 (0.94-1.06)	
Fully adjusted**	1.068 (1.02-1.12)	0.979 (0.92-1.04)	
Composite CV Events			
Events / P-Y	79 / 3189711	123 / 2936650	
Event rate (per 1000 P-Y)	0.025	0.042	
Age and race adjusted	1.034 (1.00-1.07)	0.977 (0.93-1.02)	
Fully adjusted**	1.039 (1.00-1.08)	1.043 (0.93-1.01)	
*For every (+)ACPA, there was a 7% higher risk of MI and angina, and 4% higher risk of CV events in women.			
**Fully adjusted for age, race, diabetes, SBP, eGFR, HTN med use, current smoking, and IL-6			

examined the association of the number of ACPA with all-cause mortality, incident heart failure, angina, MI, and a composite of all CV events using Coxproportional hazards models and adjusting for covariates and tested for interaction by sex.

Results: Mean age was 65 years. The sample was 50% women, 40% Caucasian; and 31% had ≥ 1 (+) ACPA. Among ACPA(+) participants, the median number (+) was 2 (IQR 1-6). ACPA(+) and ACPA(-) participants were similar in age, gender, and race/ethnicity, but ACPA(+) participants had higher IL-6 concentrations. Associations between number of ACPA and incident CV events differed significantly by sex ($p_{\text{interaction}} < 0.05$). In women, but not men, higher number of (+) ACPA was significantly associated with risk of angina, MI, and CV events. No associations were observed among men.

Conclusion: In a community-living population without RA, higher number of ACPA was associated with incident angina, MI, and CV events in women, but not men. To better understand mechanisms, future studies are needed to determine whether ACPA are associated with subclinical CVD markers in people without RA, but with RA-related autoimmunity, and whether these associations differ by sex.

Disclosure: J. M. Hughes-Austin, None; R. Katz, None; G. S. Firestein, None; M. H. Criqui, None; W. H. Robinson, None; J. H. Ix, None.

Abstract Number: 209

Development of an Algorithm for the Classification of Cardiovascular Comorbidity in Rheumatoid Arthritis: Data from the Ontario Best Practices Research Initiative

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Development of an Algorithm for the Classification of Cardiovascular Comorbidity in Rheumatoid Arthritis: Data from the Ontario Best Practices Research Initiative

Background/Purpose: Cardiovascular disease (CVD) is increased in rheumatoid arthritis (RA). The ability to accurately identify CVD is important for primary and secondary prevention strategies. RA registries collect comorbidity data, but discordance between physician-reported and patient-reported CVD often exists. Therefore, we aimed to develop an algorithm for the classification of CVD in a representative RA registry.

Methods: Data were collected from the Ontario Best-practices Research Initiative (OBRI), a clinical registry of RA patients followed in routine care in Ontario, Canada. Clinical information, including patient medication profile, was obtained at registry entry, through physician visits and patient telephone interviews. Cardiovascular disease (CVD) was defined as having ≥ 1 of myocardial infarction (MI), coronary artery disease (CAD), cerebral vascular accident (CVA), including transient ischemic attack and stroke), or peripheral arterial disease (PAD).

Results: An algorithm for classifying CVD and CVD risk factors was developed including the 2033 subjects with baseline data (Figure 1). At cohort entry, the prevalence of CVD was 5.3% (n=108) and the majority had physician reported CAD/MI (n=96, 4.7%) with lower prevalence of CVA (0.5%) or PAD (0.1%). Seventeen subjects (15.7%) were not identified as having CVD by physician-report but were classified as having CVD upon medication review.

Conclusion: An algorithm for classification of CVD has been successfully developed in a representative RA registry. Validation based on chart review is underway in a subsample to verify the findings. The discrepancy between physician and



* MI: myocardial infarction; CAD: coronary artery disease; PAD: peripheral artery disease; CVA: cerebral vascular accident (including stroke and TIA).

** Clinical judgement is applied at this step. Information taken into account includes whether the patient is on anti-platelet agents, anti hypertensives, cholesterol control medications, or nitroglycerin's. For uncertain cases, a second reviewer's opinion is used.

patient-reported CVD highlights the importance of utilizing information from multiple sources when classifying comorbidities. The classification of CVD risk factors is also underway to further validate the algorithm.

Figure 1. Classification of patients with cardiovascular disease.

Disclosure: K. Cui, None; M. Movahedi, None; C. Bombardier, Canada Research chair in Knowledge Transfer for Musculoskeletal Care, 6; Pfizer Research Chair in Rheumatology, 6; B. Kuriya, None.

Abstract Number: 210

Changes in Alcohol Use in Patients with Rheumatoid Arthritis: Associations with Disease Activity, Health Status, and Mortality

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Prior studies observed better disease control, quality of life, and physical function among patients with rheumatoid arthritis (RA) who drink alcohol. These studies may suffer from reverse causality due to discontinuation of use over time among those with poor health. We assessed factors associated with changes in alcohol use over time and the effects of discontinuation on disease activity and mortality in a large RA registry.

Methods: RA participants in FORWARD, the National Data bank for Rheumatic Diseases, were asked about alcohol use on semi-annual surveys (any v. none). Our disease activity measure was the Patient Activity Scale2 (PAS2). Logistic regression models with generalized estimating equations assessed associations between patient factors and alcohol use at the time of the next questionnaire among those reporting current regular alcohol intake. Multivariable logistic regression and Cox proportional hazards models illustrated survival of alcohol use over time by disease activity categories and assessed the risk of discontinuation of alcohol use on subsequent worsening of disease activity (>0.5 standard deviation change) and mortality.

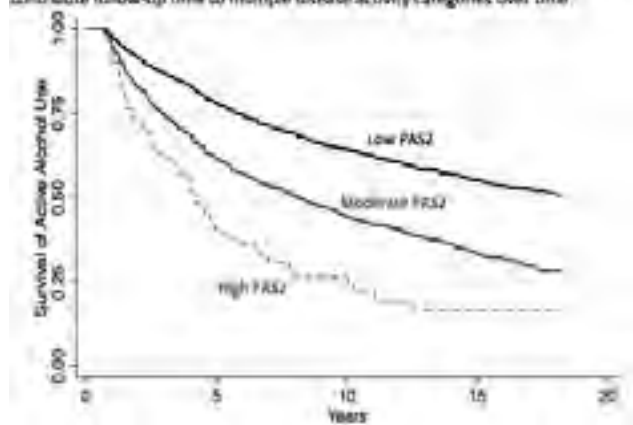
Results: In 121,280 observations (16,722 unique patients), alcohol users had lower PAS2 [β : -0.18 (-0.21, -0.15) $p < 0.001$]. Discontinuation of alcohol was common among drinkers (8.2% of observations). Higher disease activity was associated with future discontinuation of alcohol (Table, Figure). This was explained by other factors associated with discontinuation: older age, female sex, non-white race, obesity, comorbidity, work disability, low educational level and income, and poor physical/mental quality of life. Recent discontinuation (in prior 6 month interval) was not independently associated with a subsequent increase in PAS2 over the subsequent 6 months after adjustment [OR 1.03 (0.94, 1.13) $p = 0.58$]. Discontinuation was associated with a greater risk of death [HR 1.58 (1.25, 2.00) $p < 0.001$], but not independently of the above factors [HR 1.13 (0.86, 1.47) $p = 0.36$]. Sensitivity analyses limited only to moderate alcohol use were similar.

Conclusion: Higher disease activity, disability, comorbidity, and poor quality of life are associated with discontinuation of alcohol use in RA. Discontinuation of alcohol is not independently associated with worsening disease activity or greater mortality. These observations highlight a need to ensure that a behavioral exposure temporally precedes the outcome in epidemiologic studies and calls into question previously described benefits of alcohol consumption in RA.

Table: Associations between disease activity and discontinuation of alcohol use.

	Model 1 Odds of Discontinuation (N=7,937; Obs=52,345)		Model 2 Odds of Discontinuation (N=7,817; Obs=51,073)	
	OR (95% CI)	p	OR (95% CI)	p
Age <50	Reference		Reference	
Age 50-60	1.02 (0.92, 1.13)	0.71	1.01 (0.90, 1.12)	0.90
Age 60-70	1.08 (0.97, 1.20)	0.18	1.04 (0.93, 1.16)	0.13
Age 70-80	1.22 (1.09, 1.37)	0.001	1.12 (0.98, 1.27)	0.002
Age >80	1.54 (1.32, 1.80)	<0.001	1.27 (1.08, 1.51)	0.005
Male	0.69 (0.61, 0.77)	<0.001	0.72 (0.64, 0.81)	<0.001
White	0.69 (0.58, 0.82)	<0.001	0.73 (0.62, 0.87)	<0.001
BMI				
Low	1.04 (0.73, 1.49)	0.81	1.03 (0.71, 1.50)	0.86
Normal	Reference		Reference	
Overweight	1.10 (0.98, 1.23)	0.16	1.04 (0.93, 1.17)	0.47
Obese	1.57 (1.41, 1.75)	<0.001	1.37 (1.22, 1.54)	<0.001
Methotrexate	1.04 (0.97, 1.12)	0.28	1.05 (0.97, 1.13)	0.21
Prednisone	1.10 (1.03, 1.19)	0.008	1.06 (0.98, 1.14)	0.16
Any Biologic	0.92 (0.86, 0.99)	0.02	0.94 (0.87, 1.01)	0.08
PAS2				
Remission	Reference		Reference	
Low	1.36 (1.27, 1.44)	<0.001	1.07 (1.00, 1.15)	0.06
Mod-High	1.85 (1.37, 2.51)	<0.001	1.22 (0.90, 1.66)	0.19
Work Disability	--	--	1.18 (1.06, 1.32)	0.003
RDCI	--	--	1.02 (1.00, 1.04)	0.02
Liver Disease	--	--	1.23 (0.99, 1.53)	0.07
Physical QOL	--	--	0.99 (0.98, 0.99)	<0.001
Mental QOL	--	--	0.99 (0.99, 1.00)	0.001
Education ³ 16 yrs	--	--	0.84 (0.76, 0.93)	0.001
Income (Ref 0-25K)	--	--	Reference	--
35-55K	--	--	0.84 (0.77, 0.92)	<0.001
65-150K	--	--	0.72 (0.65, 0.79)	<0.001

Figure: Predicted survival of alcohol use among patient in different disease activity groups over long-term follow-up. PAS2 is evaluated as time varying- participants can contribute follow-up time to multiple disease activity categories over time.



Disclosure: J. Baker, Corrona, LLC, 5; H. Sayles, None; B. R. England, None; T. R. Mikuls, BMS, Ironwood, Horizon, 2, Pfizer, Inc., 5; K. Michaud, None.

Abstract Number: 211

Excess in Prevalence of Functional Disability in Patients with Rheumatoid Arthritis: Does Serologic Status Matter?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Despite the advances in treatment of rheumatoid arthritis (RA) over the recent decades, many patients with RA do not achieve remission or full physical functioning. Changing burden of functional disability (FD) in patients with RA has not been widely studied. We aimed to assess the prevalence of patient-reported FD in RA compared to subjects without RA over RA disease duration, age range and calendar time, and to define the effect of rheumatoid factor/ anti-cyclic citrullinated peptide (RF/CCP) positivity on the prevalence of FD in patients with RA.

Methods: This retrospective population-based cohort study included residents of a geographical area who met 1987 ACR criteria for RA in 1999-2013 and a cohort of subjects without RA from the same area matched by age and sex. Index date for each non-RA subject corresponded to incidence date of the matching patient with RA. Activities of Daily Living (ADL) were recorded annually over the past 20 years based on patient provided information about performing six ADLs without assistance including feeding oneself, dressing, using the toilet, bathing, walking and housekeeping. FD was defined as having difficulty with ≥ 1 of the six ADLs. Analyses were performed using age-, sex- and disease duration adjusted logistic regression models with random subject effects to account for multiple measures per patient.

Results: Five hundred eighty-six patients with RA (mean age 55 years, 70% females, 374 (64%) RF/CCP positive) and 531 non-RA subjects (mean age 56, 70% females) have completed 7,446 questionnaires (4,301 RA and 3,145 non-RA) from 1/5/1999 to 1/5/2018 on or following their RA incidence/index date. The prevalence of FD was significantly higher in the RA vs non-RA subjects, starting at RA incidence/index date (26% in RA vs 11% in non-RA subjects, $p < 0.001$), with persistent excess in prevalence over the entire follow-up time. Patients with RA compared to the non-RA subjects had at least a 15%-excess in the proportion of FD at any given age up to the 8-9th decade of life. The prevalence of FD overall was similar in RF/CCP positive vs negative patients with RA ($p = 0.67$). However, there was a significant interaction between RF/CCP positivity and disease duration ($p = 0.027$; Figure), suggesting that the prevalence of FD over disease duration is increasing in patients with RF/CCP and declining in those negative for RF/CCP.

Conclusion: Patients with RA have a significantly higher prevalence of FD over RA disease duration and across the age-range compared to their non-RA counterparts. RF/CCP positive patients are disadvantaged with an increasing burden of FD over their RA disease duration, while RF/CCP negative patients experience decline in FD, suggesting that additional vigilance and measures may be needed in management of patients with positive RF/CCP to help improve their FD profile.

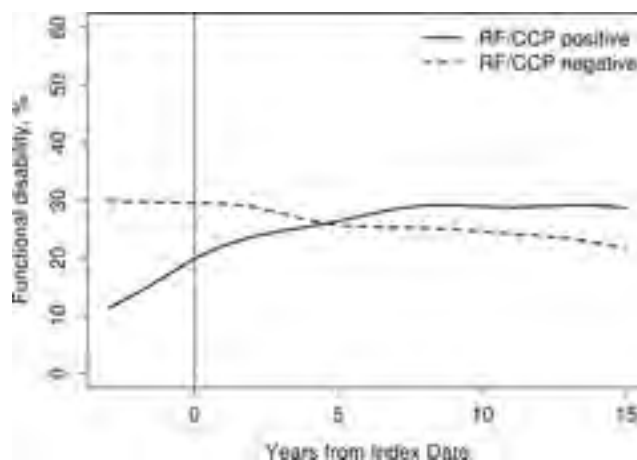


Figure.

Disclosure: E. Myasoedova, None; J. M. Davis III, None; S. J. Achenbach, None; E. L. Matteson, None; C. S. Crowson, None.

Mortality and Causes of Death in Patients with Inflammatory Arthritis in Hong Kong over 20 Years

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Patients with inflammatory arthritis have a higher mortality than the general population due to increased risks of cardiovascular diseases, infection and cancer. As the treatment of inflammatory arthritis and its associated complications has improved significantly over the past decades, many studies have demonstrated a better survival in patients with inflammatory arthritis. However, it is unknown if the survival of patients with inflammatory arthritis in Hong Kong has also improved. Therefore, the aim of this study was to determine the trend in the mortality and the causes of death of different inflammatory arthritis in Hong Kong.

Methods: The Hong Kong Hospital Authority is the only public healthcare service provider in Hong Kong. The Clinical Data Analysis and Report System (CDARS) captures diagnosis, medication prescriptions, laboratory parameters for all patients. Patients with a diagnosis of rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis from 1997 to 2016 were included in this analysis.

Patient demographics and causes of death were obtained. Results were analysed by R version 3.4.3 with package “epitools” version 0.5-10. Mortality rate and standardised mortality ratio (SMR) for all-cause mortality and cause-specific mortality were estimated every 5 years. Age and gender adjustment was conducted using census statistics provided by the Census and Statistics Department. A linear poisson regression analysis was performed to evaluate the change in SMR over time.

Results: 15445, 2165 and 4488 patients with RA, PsA and AS were included in this analysis respectively. Characteristics of the patients were summarised in Table 1. The SMR of RA, PsA and AS dropped significantly over 20 years (Table 2). There was a significant decrease in cardiovascular death in patients with RA and AS (Table 3; $p < 0.001$). However, infection remained the leading cause of death and the mortality due to infection increased over the past 20 years.

Conclusion: The mortality in patients with inflammatory arthritis in Hong Kong decreased significantly over the past 20 years.

Table 1. Characteristics of patients included in this study (cut-off date: 31/12/2016)

	RA	PsA	AS
n	15445	2165	4488
Age	61.9±0.1	55.86±0.27	49.6±0.22
Male (%)	2952 (19.1%)	1221 (56.4%)	3580 (79.8%)
Female (%)	12493 (80.9%)	944 (43.6%)	908 (20.2%)
Male:Female ratio	1:4.23	1.29:1	3.94:1

Table 2. Age and gender-adjusted mortality rate, standardized mortality ratio of inflammatory arthritis in 1997-2016

Year	1997-2001	2002-2006	2007-2011	2012-2016
RA				
Mortality rate (/1000 PY)				
Crude				
RA	46.86 [42.84-50.89]	35.24 [32.82-37.65]	26.20 [24.64-27.75]	22.31 [21.14-23.48]
AS	33.50 [25.10-41.91]	21.89 [17.99-25.78]	17.27 [14.89-19.65]	11.83 [10.28-13.38]
PsA	37.91 [21.70-54.13]	17.74 [11.49-23.98]	11.54 [8.41-14.68]	9.61 [7.55-11.68]
Age and gender-adjusted				
RA	21.46 [19.61-23.30]	13.28 [12.37-14.19]	18.75 [17.64-19.87]	14.73 [13.96-15.50]
AS	17.89 [13.40-22.39]	12.52 [10.29-14.75]	14.76 [12.72-16.79]	12.17 [10.58-13.77]
PsA	38.04 [21.77-54.31]	14.33 [9.28-19.37]	8.99 [6.54-11.43]	7.57 [5.94-9.20]
Age and gender-adjusted SMR				
RA	3.15 [2.89-3.43]	2.30 [2.15-2.46]	1.97 [1.86-2.10]	1.77 [1.68-1.87]
AS	3.78 [2.94-4.86]	2.57 [2.15-3.07]	2.55 [2.22-2.93]	1.84 [1.62-2.10]
PsA	5.98 [3.90-9.17]	2.24 [1.58-3.19]	1.50 [1.15-1.97]	1.25 [1.01-1.56]

Table 3. Cause of death in inflammatory arthritis patients in 1997-2016

	1997-2001	2002-2006	2007-2011	2012-2016
RA	N=520	N=819	N=840	N=1400
CV mortality	100 (19.7%)	112 (15.0%)	130 (17.3%)	193 (16.5%)
Infection	174 (34.2%)	259 (34.8%)	308 (41.0%)	542 (46.4%)
Cancer	66 (13.0%)	112 (15.0%)	130 (17.3%)	189 (16.2%)
PsA	N= 21	N= 31	N= 52	N= 83
CV mortality	5 (23.8%)	7 (25.0%)	9 (19.6%)	13 (18.1%)
Infection	6 (28.5%)	10 (35.7%)	14 (30.4%)	28 (38.9%)
Cancer	3 (14.3%)	4 (14.3%)	14 (30.4%)	15 (20.8%)
AS	N=61	N=121	N=202	N=224
CV mortality	14 (23.3%)	18 (16.7%)	32 (18.0%)	38 (19.6%)
Infection	16 (26.7%)	31 (29.6%)	58 (36.0%)	83 (45.4%)
Cancer	12 (20.0%)	25 (23.1%)	27 (15.2%)	33 (17.0%)

Disclosure: T. T. Cheung, None; S. M. F. Tsoi, None; B. M. Y. Cheung, None; C. S. Lau, None.

Abstract Number: 213

Excessive Risk of Major Cardiovascular Events in Sero-Positive Rheumatoid Arthritis and in Patients with Active Disease

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

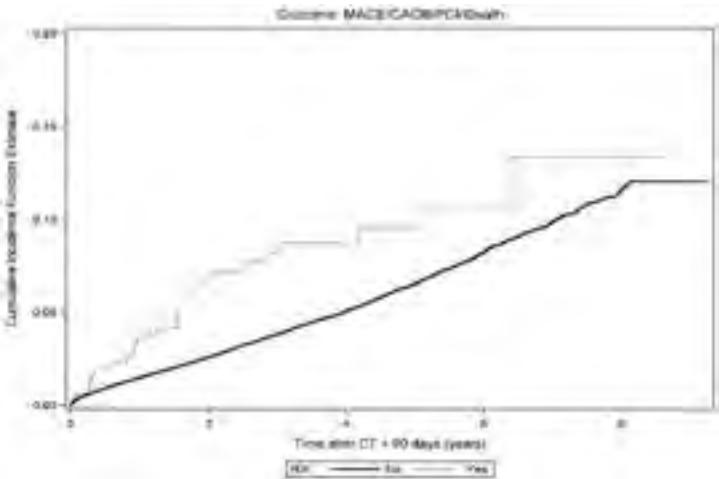
Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) is a known risk factor for the development of cardiovascular disease (CVD). However, the influence of RA on the prognosis after initial diagnosis and treatment for coronary artery disease (CAD) is unknown.

Objective: To examine the risk of major cardiovascular events (MACE) and all-cause mortality among RA and non-RA patients after referral to cardiac computed tomography (CCT) due to symptoms suggestive of CAD.



Methods: This was a follow-up study, using data from the Western Denmark Heart Registry [1] covering all diagnostic procedures in a catchment area with approximately 3.3 mill. inhabitants. The register provides information on clinical variables such as smoking, severity of stenosis and calcium score. Information on RA diagnosis and co-variables were identified through individual-level linkage of nationwide administrative registers. Outcome measures were *MACE alone* and a combined outcome (CO) including *MACE*, coronary artery bypass grafting, percutaneous coronary intervention, and *all-cause mortality*. Median time until events or censoring were 3.5 years (min/max: 0.0: 9.2).

In the studied region, RA-flares are controlled through escalation of disease modifying drugs and intra-articular or intramuscular glucocorticoid injections (GCI). Hence, the number of times a patient had received GCIs 3 years prior to the CCT were used as a surrogate marker of disease activity. Analyses were performed for overall RA and the serological subtypes: 'seropositive RA'(ICD-10: M05) and 'other RA'(ICD-10: M06).

Cox proportional hazard models were used to examine the association between RA and non-RA patients and the outcomes.

Results: *We included 42,257 patients, and identified 358 (0.8%) patients with RA. The incidence rate for revascularization, not related to the initial diagnosis, in RA and non-RA patients was 3.4 (95% CI 1.3-9.0) vs. 3.7 (95% CI 3.7-4.1)/1000 person-years. For both the CO and MACE an increased risk was seen in RA compared to non-RA (CO: hazard ratio (HR): 1.35 (95% CI: 0.93-1.96), MACE: HR 1.94 (95% CI: 1.18-3.19)). The risk was higher among patients who had received GCI more than one time during 3 years prior to the CT (CO: HR: 1.80 (95% CI: 1.1-3.0), MACE: HR 3.02 (95% CI: 1.62-5.65)) and in patients with sero-positive RA (CO: HR: 1.42 (95% CI: 0.93-2.16), MACE: HR: 2.45 (95% CI: 1.47-4.08)) (Fig.1).*

Conclusion: *We found a strong association between RA and cardiovascular events in the period after the initial diagnosis and treatment in this cohort of patients with a-priori risk of CAD referred for cardiac CT. These findings support that RA per se, but in particular, sero-positivity and inflammation related to flares increase the risk of CVD and mortality.*

1. Nielsen LH, Bottcher M, et al. The Western Denmark Cardiac Computed Tomography Registry: a review and validation study. Clinical epidemiology 2014.

Disclosure: A. de Thurah, None; I. Trolle Andersen, None; A. Bugge Tingaard, None; J. Therkildsen, None; A. Hammerich Riis, None; M. Böttcher, None; E. M. Hauge, None.

Abstract Number: 214

Exploring the Relation between Air Pollution and Disease Activity in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Disease remission is considered an achievable target in a significant proportion of patients with rheumatoid arthritis (RA). Nevertheless, diseases flares, that significantly contributes to damage progression and disability, remain unpredictable. Thus, factors able to potentially interfere on disease activity should be considered and assessed. The aim of our study is to evaluate the influence of particulate matter (PM) on disease activity and general health (GH) in patients with RA.

Methods: All consecutive patients with RA (ACR/EULAR Criteria 2010) resident in Lombardy (Italy) were enrolled in this cross-sectional design study. In each patient Disease Activity Score on 28 joints (DAS28), Simple Disease Activity Index (SDAI) and General Health (GH) were assessed. Data on daily pollutants concentration levels (PM2.5 e PM10) were derived from the Local Environmental Protection Agency (ARPA Lombardia) website. Continuous variables are expressed as mean±SD. Categorical variables are presented as absolute numbers and frequencies. Multivariable linear regression models were used to test the associations between the daily PM10 and PM2.5 exposure and disease activity (DAS28, GH and SDAI). The variables, which were significant with simple regression analysis (p-

value <0.05), were considered for adjustment in the multivariate model. β coefficients were reported for 10 $\mu\text{g}/\text{m}^3$ increments of PM concentrations. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results: 235 patients were enrolled in the study (patients' characteristics: age at visit 57.5 ± 13.9 years, disease duration 16.1 ± 11.9 , female 77.87%, rheumatoid factor positivity 51.91%, anti-citrullinated protein antibody positivity 48.94%, radiographic damage 41.28%). Multivariable linear regression models were adjusted for radiographic damage (DAS28, SDAI and GH), disease duration (DAS28 and SDAI) and age (GH). Increases of PM2.5 and PM10 exposure (9 day before the visit) were significantly associated with worsening of DAS28, SDAI and GH (table 1).

Multivariable linear regression model

	PM exposure	β	SE	95% CI		p-value
DAS28	PM ₁₀ Day -9	0,1169	0,0524	0,0137	0,2201	0,0266
	PM2.5 Day -9	0,1402	0,0665	0,0092	0,2713	0,0361
SDAI	PM ₁₀ Day -9	0,9703	0,4418	0,0995	1,8412	0,0292
	PM2.5 Day -9	1,1988	0,5607	0,0935	2,3040	0,0337
GH	PM ₁₀ Day -9	2,0574	0,9346	0,2152	3,8997	0,0288
	PM2.5 Day -9	2,3624	1,1848	0,0270	4,6979	0,0474

Conclusion: In our cohort of RA patients, there was significant evidence of the harmful effect on RA activity related to PM2.5 and PM10 exposure. Nevertheless, the association between day-to-day PM changes and disease activity do not confirm causation. Further studied are required to evaluate the influence of air pollution on RA activity.

Disclosure: T. Schioppo, None; V. Bollati, None; C. Favero, None; N. Ughi, None; I. Scotti, None; V. Merlino, None; O. De Lucia, None; A. Murgo, None; F. Ingegnoli, None.

Abstract Number: 215

A Decade Earlier- Onset of Symptoms of RA in the Indian (Asian) Cohort Compared to Dutch Cohort: Based on Meteor, a Global Database

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Reported symptom onset and diagnosis debut in rheumatoid arthritis (RA) patients may be influenced by environmental factors, genetics and gene-environmental interactions, but also by cultural and socioeconomic differences. We have shown high burden of RA in younger women in our population surveys.^{1,2} We aimed to compare symptom onset and diagnosis debut in an Indian and a Dutch cohort.

Methods: METEOR, an international database capturing daily clinical practice, has registered RA patients using a comprehensive online case record form for over two decades. 3500 Indian patients were registered from 2007-2012. We randomly selected a retrospective, cross sectional sample of 500 subjects to contain 125 subjects in each of the four disease duration a-priori categories [0-2, 2-5, 5-10, >10 years]. Using similar methods, a Dutch cohort (500 out of 7899 patients, registered between 2000-2012) was selected. Between group differences were compared using Chi-square & Mann-Whitney tests, p-values <0.05 were considered statistically significant.

Results: 85% and 72.5% of patients in the Indian and Dutch cohort were women. The mean age (SD) at symptom onset and diagnosis debut was 39.8 (11.7) and 43.8 (12.1) years respectively in the Indian cohort; these were 52.7 (14.1) and 53.2 (13.9) years in the Dutch cohort (p <0.001). Figure 1 shows the proportion of patients at onset of symptoms as per age groups. Mean disease duration (years) at Meteor entry was not significantly different (Indian 7.4, Dutch 7.2). 33% Indian women and 11% Dutch women in the study data belonged to 16-40 years age group (p<0.05). Indian patients were more often active-severe. 84.2% and 65.2% Indian respectively were RF and ACPA positive: this was 65.1% and 64.4% in the Dutch cohort.

Conclusion: The earlier age at onset in the Indian compared to the Dutch cohort is strikingly significant and merits further research. It has several important implications which are not merely confined to socioeconomic and health care disparities in the study populations.

Acknowledgement: Sponsored by METEOR (The Netherlands) and Arthritis Research Care Foundation (Pune India).

References :

- 1). Chopra A, Ghorpade R, Sarmukkadum S, et al. 5 million patients and not 0.34% is worrisome: Burden of rheumatoid arthritis in India. *Arthritis Rheumatism* 2012; 64: V 10 (Suppl):S23
- 2). Report of a WHO scientific group. The burden of musculoskeletal conditions at the start of the new millennium. Geneva (Switzerland): World Health Organization 2003. WHO Technical Report Series 919

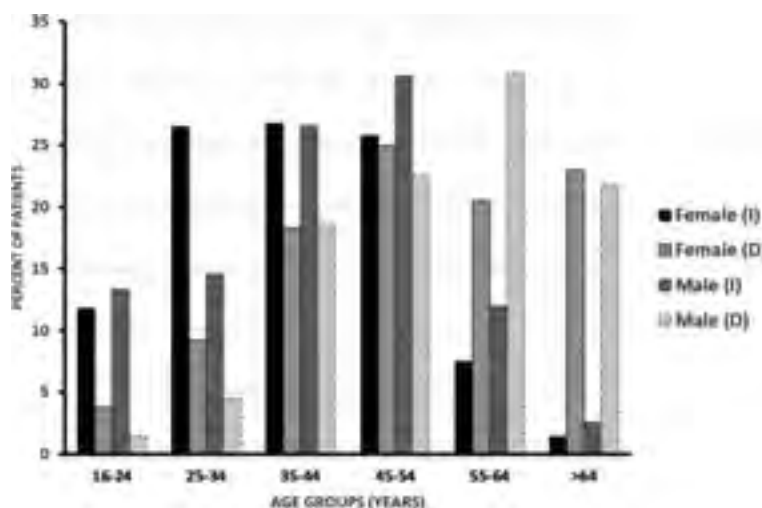


Figure 1. Proportion of patients (percent) in the Indian (I) and Dutch (D) cohort as per onset of symptoms of RA in different age groups

Disclosure: A. Chopra, None; M. Saluja, None; S. A. Bergstra, None; T. Kainifard, None; A. Venugopalan, None; T. W. J. Huizinga, Abblynx, Roche and Sanofi, 2, 5, 8.

Abstract Number: 216

Inflectra and Remicade Use and Cost in Canada Under Provincial Drug Plans in 2016

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Inflectra (infliximab) was the first biosimilar for inflammatory bowel disease and/or arthritis, approved by Health Canada on the belief that it is as safe and effective as its bio-originator Remicade. We assessed recent use of Inflectra versus Remicade (regardless of indication), within Canadian provincial publicly financed drug benefit programs.

Methods: We used aggregate claims data from the National Prescription Drug Utilization Information System (NPDUIS), for 2016. This contains public drug plans data from across Canada except Quebec. Aggregated data were obtained by province, sex, and age groups. We described patients for whom the public drug plan/program accepted at least part of 1 or more claims for Inflectra or Remicade, either towards a deductible (if applicable) or payment. We also calculated total number of claims and recorded amounts paid by the public drug plan (drug cost and pharmacy fees).

Results: In 2016, there were 218 beneficiaries with at least one Inflectra dispensation,, with a total of 856 claims approved. During this time, at least 12,912 individuals were dispensed Remicade, with a total of 80,862 approved claims. No other infliximab biosimilar was dispensed under public drug plans in 2016. Stratified information (sex, age group, province financing the claim) was available for 184 Inflectra and 12,904 Remicade users. Most patients were dispensed Inflectra in Ontario (146 /186, 79%) or in British Columbia (38/186, 21%). Excluding Quebec, other provinces with Inflectra dispensation were Alberta, Newfoundland and Labrador, New Brunswick, Saskatchewan, and Manitoba. There was a significantly higher proportion of seniors receiving Inflectra (71/184, 38%) versus Remicade (2362/12912, 18%) and more females (see Table).

The estimated total cost recorded according to public plans for Remicade in Canada (exclusive of Quebec) in 2016 was \$361,502,867 Canadian, representing an average cost per claim of Remicade of \$4,471 (versus Inflectra, \$1,934). If half of the Remicade claims had been Inflectra instead, the cost difference would have been over \$102.5 million. This does not consider undisclosed rebates/discounts which may have been in place.

The findings are limited in terms of our inability to stratify by indication. We were unable to establish if subjects were primarily new-users. No analyses of drug persistence (which may reflect safety and effectiveness) were done.

Conclusion: In 2016, there were 12,912 Remicade users and 218 Inflectra users in Canada, exclusive of Quebec; Remicade's recorded price tag was over \$361.5 million, not including rebates/discounts. Although cost savings of using biosimilars are potentially large, our estimates do not account for other considerations, such as safety and effectiveness, and rebates/discounts offered by drug companies.

Table

	Inflectra	Remicade
Number of beneficiaries	218	12,912
Number of accepted claims ^e	856	80,862
Program paid amount	\$1,655,245	\$361,502,867
Cost per claim	\$1,934	\$4,471
Female sex, N (%) beneficiaries	117 (64)	6,304 (49)
Age groups, beneficiaries N (%*)		
0-44	42 (23)	6,314 (49)
45-64	71 (39)	4,228 (33)
65-74	49 (27)	1,686 (13)
75+	22 (12)	676 (5)

* Percent exceeds 100 due to rounding

Disclosure: C. S. Moura, None; D. Choquette, None; G. Boire, Merck, BMS, Pfizer, 8,Amgen, BMS, Eli Lilly, Janssen, Pfizer, 9,Merck, Amgen, Abbvie, Novartis, BMS, Pfizer, 9; V. P. Bykerk, Amgen Inc., 5,Pfizer, Inc., 5,UCB, Inc., 5,Bristol-Myers Squibb, 5,Sanofi Genzyme, 5,Gilead, 5; C. Thorne, Amgen Inc., 2, 5, 9,Pfizer, Inc., 2, 5, 9,UCB, Inc., 9,AbbVie Inc., 2, 5, 9,Medexus/Medac, 2, 5, 8,Eli Lilly and Co., 9,Merck & Co., 9,Hospira, 5, 9,Janssen, 9,Sanofi Genzyme, 5, 9,Celgene Corporation, 9,CaREBiodam, 9,Centocor, 5,Novartis, 9; W. P. Maksymowych, AbbVie, Amgen, Eli Lilly, Janssen, Merck, Pfizer, Synarc, Sanofi and UCB Pharma, 2, 5, 8; P. Lakatos, None; T. Bessissow, None; L. Svenson, None; L. Targownik, None; W. Afif, None; S. Bernatsky, None.

Abstract Number: 217

Association between Comorbidities and Socioeconomic Status Among Patients with Rheumatoid Arthritis in Korea

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018
Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Increased prevalence of comorbidities in patients with rheumatoid arthritis (RA) compared to general population has been noted in several previous study. This study aims to systematically examine the effect of SES on the comorbidity distribution among Korean patients with RA.

Methods: A total of 1,088 (weighted n = 612,303) RA patients aged ≥ 19 years were selected from 2007-2015 Korea National Health and Nutrition Examination Survey which is a nation-wide survey annually conducted using questionnaires and medical examinations. Three components of SES including household equivalence income (below versus above median level), education (below versus above high school education), residence (rural versus urban) were stratified into low and high. The prevalence of the following comorbidities was compared between low and high group in terms of each component: stroke, myocardial infarction (MI), angina, hypertension, dyslipidemia (hypercholesterolemia and/or hypertriglyceridemia), diabetes, obesity, thyroid disease, osteoporosis, osteoarthritis, stress, depression, and suicide ideation.

Results: When stratified into low and high group of each SES component, patients of low income or low education were older and more comorbid than those of high income or high education, showing higher prevalence of stroke, MI, angina, hypertension, dyslipidemia, diabetes, osteoporosis, depression, and suicide ideation (all p-value < 0.05). To adjust confounding by age, we further stratified RA patients according to the median age value of 63 years. In the aged under the 63 years, low income was associated with depression, hypertension, diabetes, osteoarthritis, suicide ideation, obesity and hypertriglyceridemia (Figure 1) while the prevalence of these comorbidities was comparable in the aged above the 63 years. Low education showed a similar trend in the aged under the 63 years (Figure 2). In the aged above the 63 years,

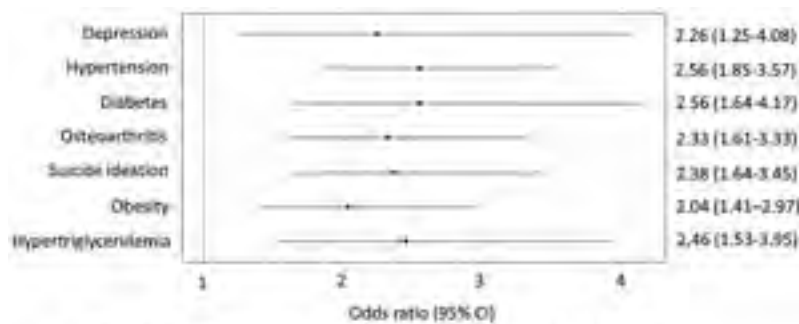


Figure 1. Association between income level and comorbidities in RA patients

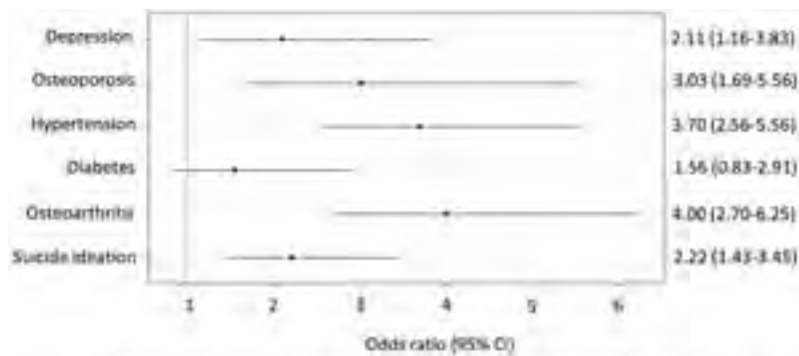


Figure 2. Association between education level and comorbidities in RA patients

low education was associated only with suicide ideation (p < 0.05).

Conclusion: Among Korean RA patients aged under the 63 years, higher prevalence of comorbidities was found in association with low income and/or low education. Recognizing the different prevalence of comorbidities by SES would be essential to provide optimal patient care and to improve the health outcome in patients with RA.

Risk of Serious Infection Associated with TNF Inhibitor Versus Triple Therapy in Rheumatoid Arthritis Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Treatment with tumor necrosis factor inhibitor (TNFi) with methotrexate or triple therapy (MTX, sulfasalazine, and sulfasalazine) is considered in patients with rheumatoid arthritis (RA) who have inadequate response to methotrexate (MTX) alone. One of the safety concerns of both these treatment strategies is serious infection. We compared the rate of serious infection among two treatment groups.

Methods: We used Truven Market Scan data (2003-2014) to conduct an observational cohort study among RA patients ≥ 18 years old with MTX prescription. We identified initiators of triple therapy when both HCQ and SSZ were newly added to MTX. TNFi initiators were identified when they newly started a TNFi in addition to MTX treatment. Index date was the first dispensing date of the last drug to complete triple therapy or a TNFi. We excluded patients with malignancy, dialysis, HIV, nursing home stay or hospitalized infection, and any prior use of study drugs except MTX during a 180-day baseline period before the index date. Outcome was defined as time to hospitalized bacterial or opportunistic infections based on inpatient diagnosis codes. In as-treated analysis, patients were followed from the day after index date until first of the following events: outcome occurrence, disenrollment, death, or drug switching or discontinuation. In an intention-to-treat (ITT) follow-up approach, we also followed patients until 180 days and 365 days after the index date without censoring on drug switching or discontinuation. For confounding adjustment, we used propensity score fine stratification weights that accounted for demographics, comorbidities, medication use, and healthcare utilization factors. A weighted Cox-proportional hazards model estimated the hazard ratio (HR) and 95% confidence interval (CI).

Results: We identified 45,305 TNFi initiators and 1,388 triple therapy initiators. Mean age was 53 (± 12) years in both groups. Patients in two treatment groups had similar baseline characteristics except that the TNFi group had more psoriasis and inflammatory bowel disease, underlying use of bisphosphonate, proton pump inhibitors, and more use of healthcare system. Two treatment groups had a similar incidence rate of outcome in as treated analysis (adjusted HR = 1.06, 95% CI 1.79-1.41). ITT analyses also showed consistent results (**Table**).

Conclusion: Among RA patients with inadequate response to MTX, the risk of serious infection was similar after starting a TNFi versus triple therapy adjusted for baseline confounding.

Table. Weighted incidence rates and HR of serious infections requiring hospitalization among patients who received combination therapy versus triple therapy

	TNFi + MTX					Triple therapy (reference group)			
	No. of patients	No. of outcome	Person-year	Incidence rate per 100 person-years (95% CI)	Weighted HR (95% CI)	No. of patients	No. of outcome	Person-year	Incidence rate per 100 person-years (95% CI)
As treated	45,305	2,124	72,246	2.93 (2.81, 3.06)	1.06 (0.79, 1.41)	1,388	47	1,671	2.81 (2.11, 3.74)
180 days ITT	45,305	686	20,449	3.35 (3.11, 3.61)	0.89 (0.59, 1.35)	1,388	23	611	3.76 (2.50, 5.66)
365 days ITT	45,305	1,165	37,635	3.09 (2.92, 3.27)	0.86 (0.63, 1.18)	1,388	40	1,106	3.62 (2.65, 4.93)

Disclosure: Y. Jin, None; E. H. Kang, None; R. J. Desai, None; A. Tong, None; S. C. Kim, Roche, Pfizer, and Bristol-Myers Squibb, 2.

Impact of Rheumatoid Arthritis on Influenza-Related Complications: A Population Based Cohort Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid Arthritis (RA) is associated with increased incidence of seasonal influenza and its complications. Population-based studies on outcomes are lacking. The aim of our study was to evaluate the impact of RA on in-hospital mortality, length of stay, and hospitalization costs in patients with influenza.

Methods: We examined National Inpatient Sample data from 2000-2012. We performed a case-control study in which we included all discharges with influenza as primary diagnosis and RA (ICD 9 coded as 714.xx) as secondary diagnosis as cases (discharges with any comorbidities were excluded); while those with influenza as primary diagnosis and no comorbidities including RA as controls. The main outcomes included in-hospital mortality, length of stay, and hospitalization costs to study the impact of RA on influenza patients.

Results: A total of 1097 discharges had influenza as the primary diagnosis for admission. A total of 543 patients had influenza with RA (study group), and 554 had influenza without RA (control group). (Table 1) Both the groups who had any comorbidities listed as a secondary diagnosis were excluded to exclude the impact of other comorbidities on outcomes. There was no difference in mortality in patients with influenza with or without RA (0.5% vs 0.2%, $P = .31$). However, patients with influenza and RA had increased length of hospital stay (3.8 vs 2.1 days, $P < .001$), and higher hospitalization costs (\$15,826 vs \$5,953, $P < .001$). On multivariate analysis, RA was independently associated with increased hospital stay and higher hospitalization costs; but not mortality.

Conclusion: RA appears to be associated with increased length of stay and hospitalization costs in patients with influenza.

Factor	Discharges of Influenza only(N=554)	Discharges of Influenza +RA(N=543)	P value
Age	44.5 (20.3)	67.6 (14.9)	< 0.001
Gender	241 (43.5)	125 (23.0)	<0.001
Male (%)			
Female (%)	313 (56.5)	418 (77.0)	
Length of stay (days)	2.1 (1.6)	3.8 (2.8)	<0.001
Total Charges (\$)	6263.2 (5952.8)	14137 (15826)	<0.001
Mortality (%)	1 (0.18)	3 (0.55)	0.306

Disclosure: P. G. K. Venkatesh, None; X. Zhu, None.

Non-Medical Switch to Biosimilars: What Have We Learned?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Biosimilars intend to be as effective and safe as the originator product and would increase patients' access to biological agents. The decision for switching to a biosimilar is not always promoted by the physicians and, although there is emerging evidence from randomized controlled trials concerning this issue, data from real world clinical practice is still lacking.

Our objective was to learn about physicians' and patients' perspectives concerning biosimilars in the context of non-medical switch.

Methods: A standardized questionnaire was conducted aimed at physicians' perspectives and to patients who experienced a switch to a biosimilar.

Results: The survey was applied to 51 physicians (39% male), both residents and specialists of rheumatology (public and private practice). All of them considered themselves to be at least reasonably informed about the concept of biosimilar and more than half (n=31; 61%) were reasonably familiar with its prescription. Among the factors influencing biosimilars prescription, efficacy was considered the most relevant (reduction of symptoms n=16, 31%; disease progression n=9, 18%), followed by safety (n=16, 31%) and cost (n=12; 24%). Even though the large majority believes that prescription of these therapies will increase in the near future (especially in RA, PsA and AS), they would prescribe them as first, second or third line therapy in only 22, 24 and 29%, respectively. Almost half the physicians (n=25; 49%) had only a mild to moderate degree of confidence in the switching process. Globally, economic reasons were assumed to have determined the switching process (costs n=17, 33%; savings n=16, 31%).

Regarding the 22 patients who answered the telephone survey, most of them (n=15; 68.2%) claimed to have been at least 'reasonably' informed about biosimilars. Several health care providers were involved in this process. The patients' main worries about switching were safety (n=11; 50%) and efficacy (n=6; 27.3%). Most patients were at least moderately confident about biosimilars' efficacy and safety (50% and 36.4%, respectively). Nearly half of the patients (n=10) accepted the switch without apprehension while the other half (n=11) believed they had no other choice, and 50% (n=11) considered that the switch was made by economic reasons. Globally, most patients didn't change the degree of satisfaction after switching to the biosimilar.

Conclusion: In this case-study, physicians seem to still be cautious about biosimilar prescription, worrying particularly about their efficacy. On the other hand, patients do not seem to have changed their satisfaction with biological agents (before and after the switch), yet still worry mostly about the safety of biosimilars. Economic issues were the main reason to justify the switching process in both physicians' and patients' perspectives. However, switching should remain a case-by-case clinical decision made primarily by the physician and patient on an individual basis.

Disclosure: J. Marona, None; S. Rodrigues Manica, None; C. Lopes, None; J. Lagoas Gomes, None; T. Costa, None; A. Neto, None; I. Silva, None; A. F. Mourão, None; S. Falcao, None; M. Mateus, None; P. Araújo, None; W. Castelhão, None; M. Costa, None; J. C. Branco, None; F. Pimentel-Santos, None.

Abstract Number: 221

Distal Interphalangeal Joint Involvement and Its Association with Disease Activity in Rheumatoid Arthritis (RA): Analysis Based on a Nationwide RA Database in Japan

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Distal interphalangeal (DIP) joint arthropathy is characteristic of both psoriatic arthritis and osteoarthritis, but it has long been pointed out that DIP joints can also be affected in rheumatoid arthritis (RA) since the report by McCarty et al. (Arthritis Rheum 9(2):325,1966). However, the clinical significance of DIP joint involvement in RA has yet to be elucidated in detail. The aim of this study was to examine the frequency of DIP joint involvement in RA, and its relationship with RA disease activity, using the National Database of Rheumatic Diseases in Japan (*NinJa*).

Methods: We used data of patients with adult-onset RA registered in *NinJa* in 2016 whose affected joint distribution data were available (n=12413). The relationship between DIP joint involvement and age, sex, age at RA onset, disease duration, stage, class, pain visual analog scale (VAS) score, tender joint count (TJC), swollen joint count (SJC), disease activity score in 28 joints-C-reactive protein level (DAS28-CRP), modified Health Assessment Questionnaire (mHAQ), rheumatoid factor, and anti-cyclic citrullinated peptide (anti-CCP) antibody were analyzed.

Results: The number of RA patients who presented with DIP joint involvement (tenderness or swelling in the second to fourth DIP joints) was 257 (2.0%). The number (mean \pm standard deviation) of affected DIP joints was 2.6 ± 2.3 with median of 1. DIP involvement was not related to age, age at RA onset, disease duration, stage III-IV, class 3-4, mHAQ, presence of rheumatoid factor or that of anti-CCP antibody. On the other hand, DIP involvement was significantly more frequent in women than in men (91.0% versus 80.1%, $p < 0.01$). Furthermore, pain VAS, TJC, SJC, and DAS28-CRP were significantly higher in RA patients with DIP involvement than in those without it, indicating the association of DIP involvement with high RA disease activity. Categorizing RA disease activity based on DAS28-CRP scores also revealed that DIP involvement was significantly associated with higher frequency of moderate and high disease activity and with lower frequency of remission status. Regarding the involvement of other joints in the hand, the number of affected DIP joints was significantly correlated with those of the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints with correlation coefficients of 0.24 and 0.14, respectively ($p < 0.01$).

Conclusion: We have demonstrated that DIP involvement was significantly associated with high disease activity in RA. It would thus be necessary to pay more attention to DIP joint involvement, albeit being observed infrequently, when evaluating disease activity in RA patients.

Disclosure: T. Sawada, None; S. Nishiyama, None; M. Tago, None; K. Tahara, None; E. Kato, None; H. Mori, None; H. Hayashi, None; T. Matsui, None; J. Nishino, None; S. Tohma, None.

Abstract Number: 222

Viral Exposures As a Risk Factor for Rheumatoid Arthritis: Summarizing the Evidence

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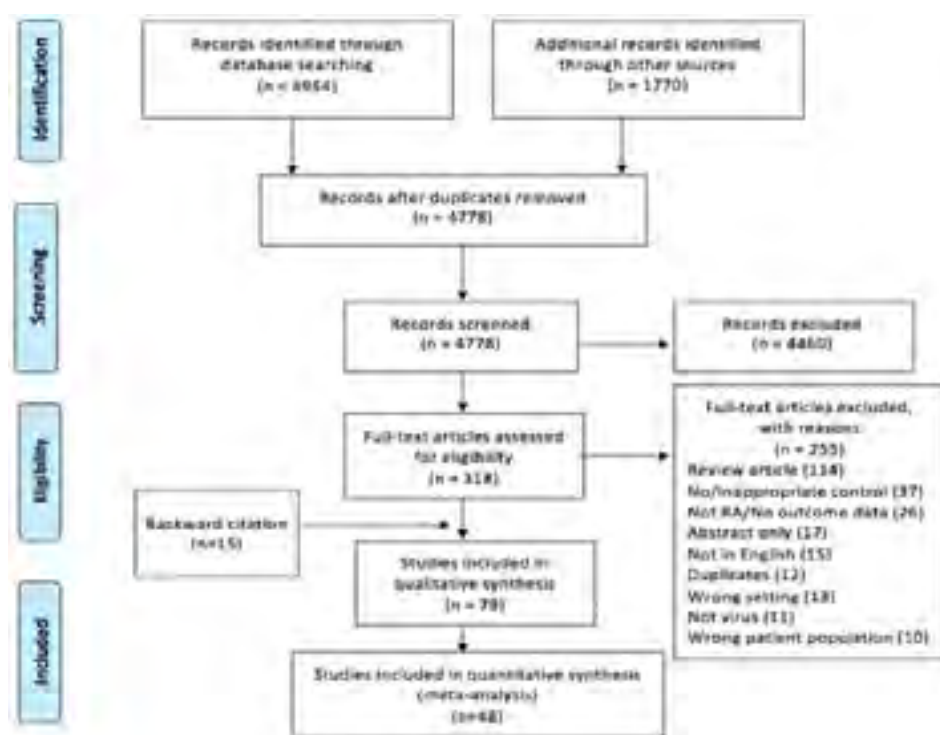
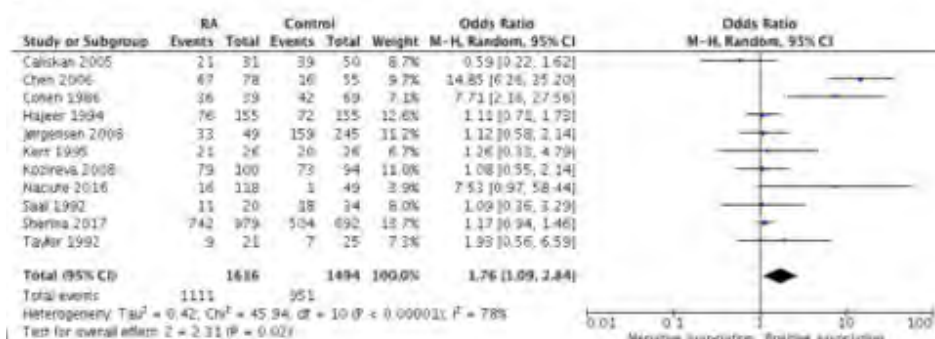


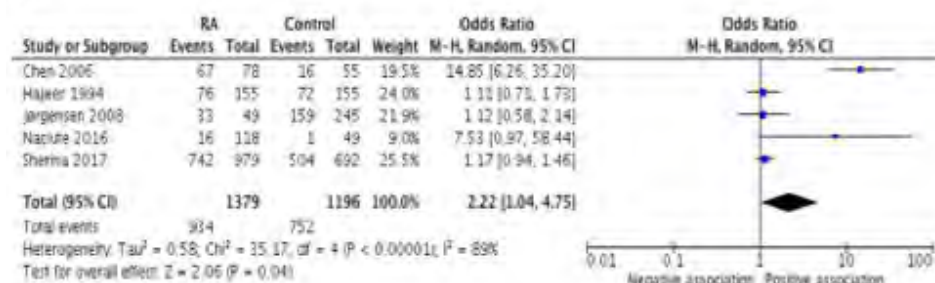
Fig.1 Flow chart of study selection

Fig. 2 Forest plots for cumulative odds ratio (95% CI) of serum IgG anti-PVB19 antibodies in RA cases and controls.

A



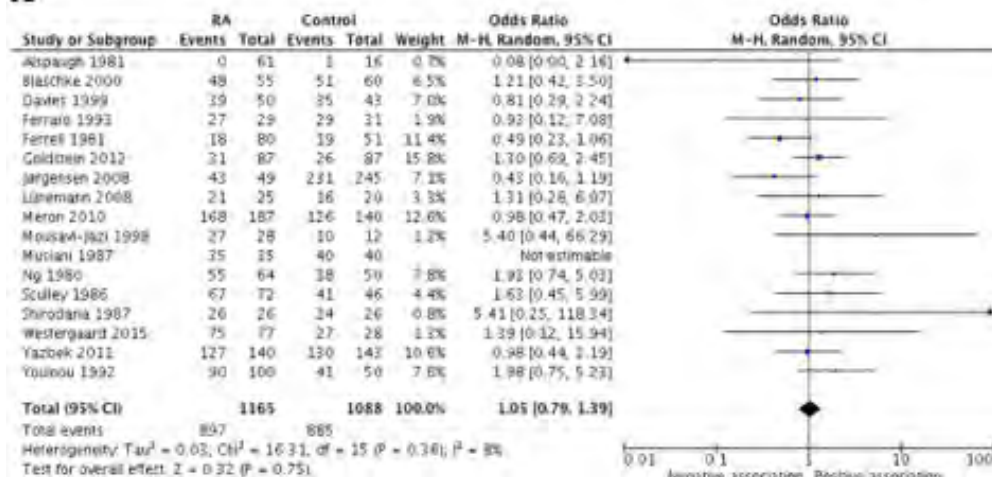
B



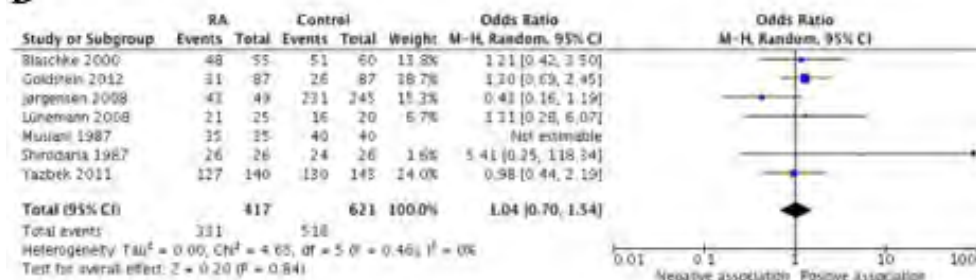
(A) Without matching of cases and controls (B) With matching of cases and controls.

Fig. 3 Forest plot for cumulative odds ratio (95% CI) of serum anti-EBNA IgG in RA cases and controls.

A



B



(A) Without matching of cases and controls (B) With matching of cases and controls.

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoidarthritis (RA) is an autoimmune disease with a complex etiology. Infections are viewed as environmental triggers of RA.

Different viral exposures have been implicated in the etiology of RA via several mechanisms of immune activation, such as molecular mimicry. The purpose of this systematic review was to summarize the evidence relating to the association between putative viral exposures and RA.

Methods: A systematic literature search was conducted using MEDLINE-OVID, EMBASE-OVID, PUBMED and Cochrane library databases. Articles were included if they were case-controls, cross-sectional or cohort studies and were published in English.

Results: Of 6724 citations, 78 studies were selected for review, 48 were meta-analysed (Figure 1). Studies had poor quality. Based on the IgG antibodies and viral DNA, the odds of parvovirus B19 (PBV19) infection were increased in RA patients compared to controls (odds ratio (OR) (95%CI) = 1.77 (1.11; 2.80), $p=0.02$, OR (95% CI) =3.53 (1.00; 12.53), $p=0.05$ for PVB19 IgG and DNA, respectively) (Figure 2). For Epstein-Barr virus (EBV), patients with RA had not significant OR of anti-Epstein-Barrnuclear antigen (EBNA) (N=17 studies, OR (95% CI) = 1.05 (0.79; 1.39), $p=0.75$), but significant OR of anti-viral capsid antigen (VCA) (OR (95% CI) = 1.5(1.07; 2.10), $p=0.02$) and anti-early antigen (EA) (OR (95% CI) = 2.74 (1.27;5.94), $p=0.01$) (Figure 3). Cytomegalovirus (CMV) was not associated with RA (OR(95% CI) = 1.24 (0.78; 1.95), $p=0.36$). Chronic hepatitis B (HBV) was not associated with RA in 5 case-control (OR (95% CI) = 1.37 (0.83; 2.25, $p=0.22$) and 1 cohort studies (HR 1.09 (0.74, 1.63), $p>0.05$). Chronic hepatitis C (HCV) was associated with increased risk of RA in 7 case-control studies (OR (95% CI)= 2.82 (1.35; 5.90, $p=0.006$) and 1 cohort study (HR 2.03 (1.27, 3.22), $p<0.01$). There is a risk of persistent arthritis after Chikungunya fever (OR(95% CI) = 90 (15.2; 134.3)).

Conclusion: Studies about the risk of RA after viral exposures suffer from inconsistent methodological quality. There is a risk of RA after PBV19 infection and possibly HCV but not EBV or HBV. Chikungunya virus is associated with the persistent inflammatory arthritis.

Disclosure: F. Kudaeva, None; J. E. Pope, None; M. Speechley, None.

Abstract Number: 223

The Effect of Concomitant Diabetes on RA-Related Outcomes: Results from the Acr's RISE Registry

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: The impact of concomitant comorbidities on RA outcomes is of high interest, and some evidence suggests that patients (pts) with RA and diabetes may have worse clinical outcomes and adverse events compared with pts with RA without diabetes. Therefore, we evaluated the effects of diabetes on change in HAQ score and infection in pts with RA, comparing those with diabetes to those without diabetes.

Methods: Using the ACR's Rheumatology Informatics System for Effectiveness (RISE) electronic health record-based registry, we identified pts with RA who had ≥ 1 rheumatologist visit with a valid HAQ measurement (index visit) in 2016. Eligible pts had ≥ 1 previous visit and a subsequent outcome visit with any HAQ measured at 12 months (± 3 months) after the index visit. Prior to the index visit, diabetes was identified based on ≥ 1 ICD-9 or ICD-10 diagnosis code, any medication for diabetes or elevated diabetes biomarkers (hemoglobin A_{1c}, random glucose). Mean HAQ change between the index and outcome visit was calculated based on HAQ categories at the index visit (0–0.5, 0.5–1 and 1–3). Generalized linear models were used to calculate the adjusted mean HAQ change controlling for potential confounders (e.g., demographics, conventional DMARDs, biologic DMARDs). First infection during follow-up was defined by ICD-9 or ICD-10 diagnosis codes or anti-infective medications. We calculated the incidence rate (IR) of

infections among pts with and without diabetes and compared hazard ratios (HR) using Cox regression adjusting for potential confounders.

Results: Among 457,950 pts in the 2016 RISE registry, there were 3897 pts with RA with diabetes and 18,689 without diabetes in the final cohort. Overall, the mean HAQ change between index and outcome visit was 0.03 in pts with diabetes and 0.002 in pts without diabetes ($p<0.01$). After stratifying on baseline HAQ and comparing with pts without diabetes, pts with diabetes and RA worsened more and improved less, depending on their baseline HAQ (Table 1). Among those with diabetes, we identified 935 infections, yielding an IR of 27.9 (95% CI: 26.2, 29.8) per 100 person years. For pts without diabetes, we identified 3989 infections with an IR of 24.4 (95% CI: 23.7, 25.2). After adjusting for potential confounders, the HR of infection among diabetes pts (HR: 1.09; 95% CI: 0.94, 1.26) was not significantly different to pts without diabetes.

Conclusion: Among pts with RA, those with diabetes had greater worsening, or less improvement, in their functional status. These results suggest additional interventions may be needed for pts with RA and diabetes to optimize this and other comorbidities.

Disclaimer: *This data was supported by the ACR's RISE Registry. However, the views expressed represent those of the authors, not necessarily those of the ACR.*

Medical writing assistance provided by Carol Keys, PhD (Caudex), funded by Bristol-Myers Squibb.

Table 1. HAQ Changes During Follow-up Among Patients With RA With or Without Diabetes, Stratified by Baseline HAQ Score

Baseline HAQ	Crude mean DHAQ score		Adjusted mean DHAQ score		Adjusted* mean difference of HAQ change (95% CI)
	Patients with RA and diabetes	Patients with RA without diabetes	Patients with RA and diabetes	Patients with RA without diabetes	
0-<0.5	0.23	0.17	0.24	0.18	0.06 (0.04, 0.08)
0.5-<1.0	0.10	0.02	0.32	0.26	0.06 (0.03, 0.09)
≥1.0	-0.30	-0.36	-0.40	-0.46	0.06 (0.01, 0.10)

* Adjusted for age, sex, race, conventional DMARD, biologic DMARD

Disclosure: H. Yun, Pfizer, Bristol-Myers Squibb, 2; F. Xie, None; L. Chen, None; S. Yang, None; L. Ferri, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; E. Alemao, Bristol-Myers Squibb, 1, 3; T. Curtice, Bristol-Myers Squibb, 1, 3; J. R. Curtis, AbbVie, Amgen, Bristol-Myers Squibb, Corrona, Janssen, Lilly, Myriad, Pfizer, Radius, Roche/Genentech, UCB, 2, 5.

Abstract Number: 224

Risk of Venous Thrombotic Events in Rheumatoid Arthritis Patients Initiating Tofacitinib or Adalimumab

Huifeng Yun, Fenglong Xie, Lang Chen and Jeffrey R. Curtis, University of Alabama at Birmingham, Birmingham, AL

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Recent concern has been raised for a risk for venous thromboembolism (VTE) associated with janus kinase inhibitors among patients with RA who are already known to bear increased risk for VTE based on their underlying conditions. We evaluated the risk of VTE, defined as the composite of pulmonary embolism (PE) or deep vein thrombosis (DVT) among RA patients initiating tofacitinib (Tofa) compared to patients initiating adalimumab (ADA).

Methods: Using 2010-2015 US Market scan claims data, we conducted a retrospective cohort study among RA patients (identified based on ≥ 1 ICD-9 RA diagnosis codes initiating Tofa or ADA). Patients were not allowed to have used Tofa or ADA prior to the date of initiation (index date) using all available data. Eligible patients must have had ≥ 12 months (baseline) prior health plan enrollment. Patients with history of other autoimmune disease, advanced kidney or liver disease, malignancy, HIV, hepatitis B/C, or pregnancy during baseline were excluded. Follow-up started from the index date and ended at the earliest date of: VTE, death, loss of medical/pharmacy coverage, switch to other biologic, or drug discontinuation (with a 90 day extension). PE was identified using inpatient diagnosis codes plus outpatient anti-coagulant treatment within 0-60 days; DVT was identified using inpatient/outpatient diagnosis codes and medication use as above. We calculated incidence rates per 100 patient-years of VTE for each drug and compared VTE risks during follow-up using

Cox regression, adjusting for potential confounders including age, gender, history of VTE, comorbidities and concurrent medications. Several sensitivity analyses were conducted using different exclusion criteria and outcome definitions (such as using only inpatient diagnosis and anti-coagulant use within 60 days to define DVT occurrence).

Results: We identified 6,022 ADA initiators (4,798 PY) and 2,155 for Tofa (1,523 PY). During median (IQR) follow up of 0.5 (0.3, 1.0) years, we identified 20 VTE events among tofa users with an IR of 1.31 (95% CI: 0.80-2.03) and 40 VTE events among ADA users with an IR of 0.83 (95% CI: 0.60-1.14). After adjustment for potential cofounders, the hazard ratio of VTE for Tofa users was 1.07 (95% CI: 0.54-2.14) referent to ADA users. Sensitivity analyses using different exclusion criteria and outcome definitions had a large impact on the number of events and absolute incidence rates, but minimal effect on the adjusted hazard ratios comparing the two therapies. For an example, using an outcome definition of inpatient VTE events with anti-coagulation within 60 days, the IR rate associated with tofacitinib was 0.65/100PY (95% CI: 0.31, 1.20) with similar adjusted HR to the main analysis (1.02, 95% CI 0.40-2.62).

Conclusion: In this comparison of tofacitinib vs. adalimumab based on 60 VTE events, we observed comparable risk between these two RA treatments.

Disclosure: H. Yun, Pfizer, Bristol-Myers Squibb, 2; F. Xie, None; L. Chen, None; J. R. Curtis, AbbVie, Amgen, BMS, Eli Lilly and Company, Janssen, Pfizer, Roche/Genentech, Corrona, UCB, Myriad, 2, 5.

Abstract Number: 225

U.S. Trends in Hospitalization Rates and Causes and in-Hospital Mortality in Rheumatoid Arthritis Patients, 2000-2014

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SESSION INFORMATION

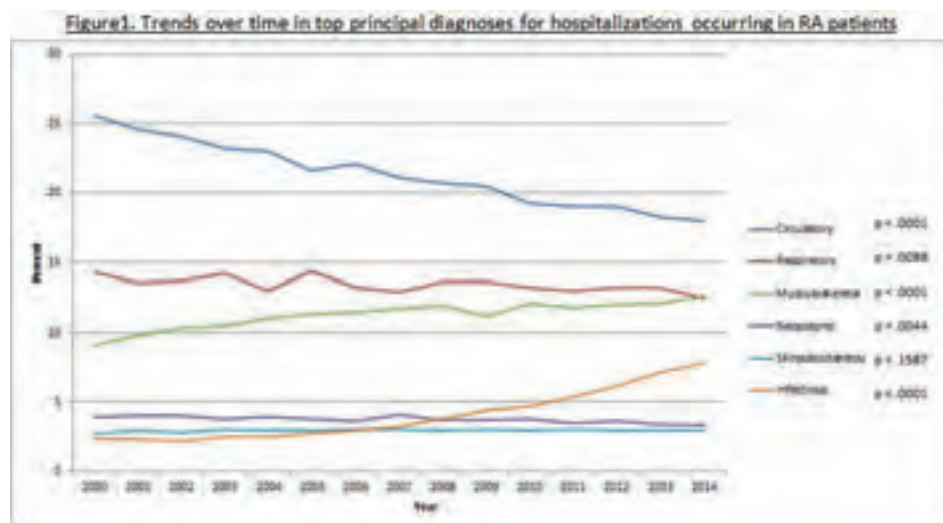
Session Date: Sunday, October 21, 2018

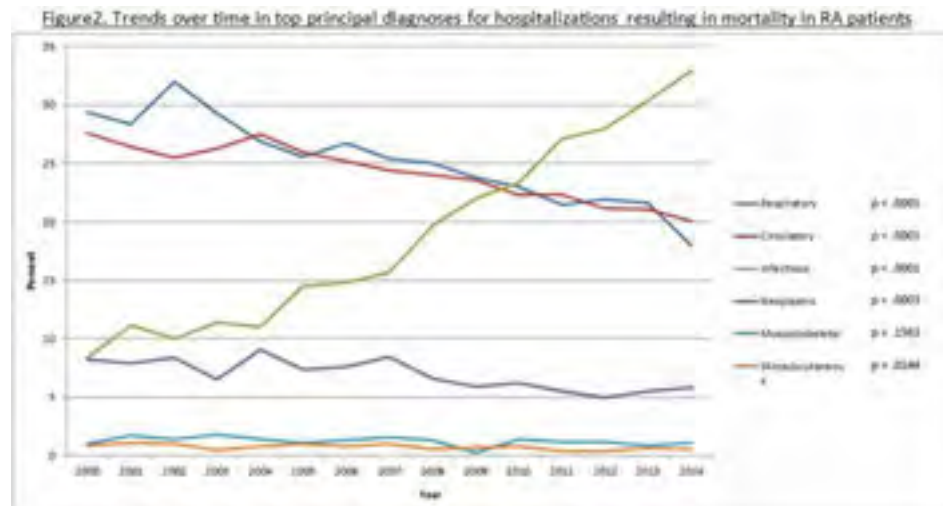
Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Over the past two decades, major advances have been made in the treatment of RA, allowing disease remission to become an achievable goal. Although studies have looked at the trends in hospitalization for RA, contemporary data on the principal diagnoses that lead to hospitalizations and in-hospital mortality in RA are lacking. The objective of this study was to evaluate national trends in hospitalizations, underlying causes, and in-hospital mortality in RA over the past 15 years.





Methods: We used the National Inpatient Sample (NIS) from 2000-2014 to study the temporal trends in RA hospitalizations in the US. All hospitalized adults with RA (ICD9-CM 714.0 and 714.2) were included. We examined trends over time using linear regression in SAS version 9.3.

Results: Between 2000 and 2014, there were 183,983 hospitalizations with a principal discharge diagnosis of RA. The annual rates of hospitalization for principal diagnosis of RA decreased from 76.5 admissions per 1 million adults in 2000 to 30 in 2014 ($P < 0.0001$ for trend), an admission rate reduction of 61%. Although overall annual hospitalization rates declined in the US as well in this time frame- from 14.5% to 12% (rate reduction of 16%) - the decline was not as significant as in RA. In-hospital mortality declined from 0.70% of all hospitalizations in 2000 to 0.41% in 2014 ($P < 0.0001$ for trend). The mean (\pm SD) age of hospitalized RA patients remained largely stable, 62.7 (\pm 30.7) in 2000 and 61.9 (\pm 32.3) years in 2014. When RA was listed as a non-primary diagnosis, the most frequent principal diagnoses for admission remained diseases of the circulatory system over the entire study period. However, the rates of hospitalization for RA patients for circulatory or respiratory system diseases significantly declined between 2000 and 2014, whereas hospitalization for infectious disease causes significantly increased (Figure 1). The most common principal diagnosis leading to in-hospital mortality changed from diseases of the respiratory system in 2000 to infectious and parasitic diseases in 2014 (Figure 2).

Conclusion: Both hospitalization rates and in-hospital mortality rates in U.S. patients with RA have declined significantly over the past 15 years. Diseases of the circulatory system continue to be the principal diagnosis associated with hospitalizations whereas infectious diseases account for the hospitalizations resulting in highest in-hospital mortality in RA in recent years.

Disclosure: N. Singh, None; Y. Gao, None; E. Field, None; P. Lenert, None; J. R. Curtis, Amgen Inc., 2, 5, AbbVie Inc., 2, 5, BMS, 2, 5, Corrona, LLC, 2, 5, Janssen, 2, 5, Eli Lilly, 2, 5, Myriad, 2, 5, Pfizer, Inc., 2, 5, Roche/Genentech, 2, 5, Radius, 2, 5, UCB, Inc., 2, 5; M. Vaughan-Sarrazin, None.

Abstract Number: 226

Representation of Elderly People and Women in Rheumatoid Arthritis and Osteoarthritis Trials: A Systematic Review and Meta-Analysis Comparing Clinical Trials with Population-Based Studies

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

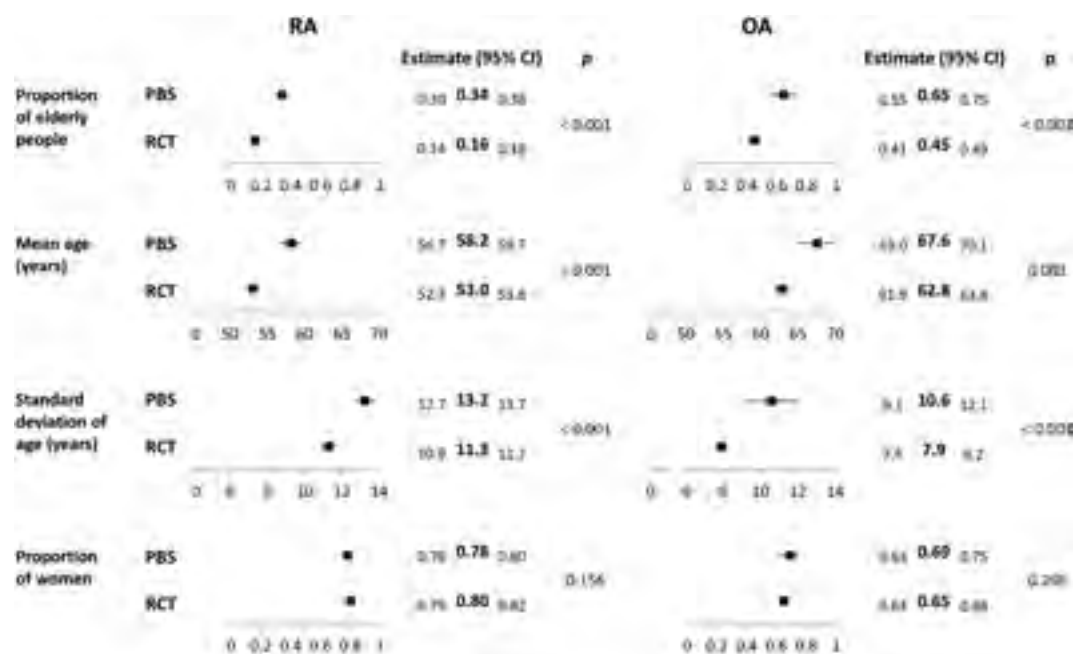


Figure 1. Meta-analyses' estimates of population-based studies (PBS) and randomized controlled trials (RCT) on rheumatoid arthritis (RA) and osteoarthritis (OA) for the proportion of elderly people, mean age, standard deviation of age, and the proportion of women. CI, confidence interval.

Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Elderly people (as commonly defined by an age of ≥ 65 years) and women have been reported to be underrepresented in clinical trials of various medical specialties from past to present. However, it has not yet been quantitatively assessed in rheumatology. Rheumatoid arthritis (RA) and osteoarthritis (OA) are two of the most common chronic rheumatic diseases, major contributors to global disability, and both tend to occur predominantly in the elderly and in women. We assessed whether randomized controlled trials (RCT) in RA and OA include adequate proportions of elderly people and women comparable to data from population-based studies including registries (PBS).

Methods: Our systematic review and meta-analysis was registered with PROSPERO (www.crd.york.ac.uk/prospero/; identifier CRD42018085409). Four systematic searches in MEDLINE (PubMed), extended by a hand search, yielded RCT in RA and OA on any intervention published in 2016 and 2017 and PBS in RA and OA published between 2013 and 2017. Random effects meta-analyses estimated the pooled proportion of elderly people (aged ≥ 65 years), the mean age and standard deviation (SD), and the proportion of women stratified by disease (RA and OA) and study type (RCT and PBS). The proportion of elderly people was estimated if it could not be abstracted from the original manuscript. Heterogeneity was evaluated with Cochran's Q and the I^2 -statistic. Finally, estimates of RCT and PBS were subsequently compared with two-sample Z-Tests.

Results: 265 RCT including over 50,000 participants and 53 PBS including over 520,000 participants were finally deemed eligible, and 260 RCT and 52 PBS were included in quantitative syntheses (i.e., meta-analyses). Heterogeneity was considerable in all meta-analyses with I^2 values between 96% and 100%. In both RA and OA, RCT included less elderly people (RA -0.18 [95% confidence interval -0.22 to -0.13] $p < 0.001$; OA -0.20 [-0.30 to -0.09] $p < 0.001$) and had lower mean ages (RA -5.2 years [-6.8 to -3.5] $p < 0.001$; OA -4.7 years [-7.5 to -2.0] $p = 0.001$) and SD (RA -1.9 years [-2.6 to -1.3] $p < 0.001$; OA -2.7 years [-4.2 to -1.2] $p < 0.001$) than did PBS (Figure 1). Five RCT analyzed the influence of age on outcome with conflicting results. Proportions of women were similar in RCT compared to PBS in both RA and OA (RA 0.02 [-0.01 to 0.05] $p = 0.156$; OA -0.04 [-0.10 to 0.03] $p = 0.269$).

Conclusion: While women are adequately represented in RA and OA RCT, the elderly are significantly underrepresented. This undermines the applicability of trials' results to the general population. It is urgent to improve the inclusion of elderly people in clinical trials and study age as a determinant for outcome.

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Rheumatoid Arthritis Patients Treated with Abatacept, Rituximab and Tocilizumab in Denmark and Sweden: Risk of Serious Infections

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SESSION INFORMATION

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Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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Background/Purpose: Safety concerns have been raised regarding the risk of serious infections (SI) with the different available biologic disease-modifying anti-rheumatic drugs (bDMARDs). Little is known about the risk of SI in patients with rheumatoid arthritis (RA) treated with non-tumor-necrosis-factor-inhibitors (non-TNFi) bDMARDs. In RA patients treated in routine care with the three non-TNFi, abatacept, rituximab and tocilizumab, we aimed to estimate 1) crude and adjusted incidence rates (IR) and 2) relative risks (RR) of SI during the first year since treatment start.

Methods: Collaborative observational cohort study conducted in Denmark (DK) and Sweden (SE) in parallel. RA patients in DANBIO (DK) and ARTIS/SRQ (SE) who started a non-TNFi treatment between 2010-2015 were included and their clinical characteristics at baseline were identified. Baseline comorbidities, reimbursed/dispensed antibiotic prescriptions and incident SI (hospitalization listing infection as major cause of admission) were identified through linkage to National Patient Registries and Prescription Drug Registries. IR of SI/100 patient years (adjusted for age and sex) and rate ratios (as estimates of RR, adjusted for additional covariates) during the first year since treatment start were assessed by Poisson regression.

Results: 8,987 treatment episodes were identified (abatacept 2,725/rituximab 3,363/tocilizumab 2,899). Differences in baseline characteristics between the three drugs were observed (Table). During the first year since treatment start, 456 SI were identified. Age/sex-adjusted IRs for SI were numerically different across treatments in each country (abatacept/rituximab/tocilizumab for SE 6.0/6.4/4.7 and for DK 7.1/8.1/6.1, respectively), but the confidence intervals (CI) were wide. Differences in the 1-year adjusted between-drug comparisons (=RR) were observed, but with 1 included in the CIs (Table).

Table Baseline characteristics, IR and RR of RA patients starting non-TNFi stratified by drug and country

Variable	ABA, N=2725		RTX, N=3363		TCZ, N=2899	
Country	DK	SE	DK	SE	DK	SE
Treatment episodes, n	830	1895	718	2645	1098	1801
Female gender, %	78	81	78	76	78	79
Age, years	55(5.0-6.7)	61(5.1-6.9)	61(5.2-6.9)	64(5.4-7.1)	59(5.0-6.7)	59(4.9-6.7)
Disease duration, yrs	7(3.1-8)	11(6-7.1)	11(5-9.9)	13(6-7.2)	8(2-5.6)	11(5-7.0)
DAS28	4.7(1.6-5.5)	4.9(4.1-5.7)	4.8(4.0-5.6)	5.0(4.1-5.8)	5.0(4.1-5.8)	5.1(4.2-6.0)
HAQ	1.4(0.8-1.9)	1.1(0.5-1.8)	1.5(1-2)	1.3(0.9-1.8)	1.4(1-2)	1.3(0.9-1.8)
CRP, mg/l	8(3-20)	8(4-21)	10(4-23)	10(4-25)	11(4-30)	11(4-30)
Previous cancer, %	1	4	0	11	0	4
Incidence rates (IR) of serious infections, 0-12 months						
Patient years (PY)	568	1477	571	2189	586	1426
Infections, n	80	100	60	156	35	86
IR (95%CI)/100 PY*	7.1(5.1, 9.9)	6.0(4.8, 7.5)	8.1(5.8, 11.0)	7.1(5.3, 9.7)	6.0(4.6, 8.3)	4.7(3.7, 6.2)
Risk Ratio (RR) for serious infections, 0-12 months**						
	ABA vs TCZ (ref)		ABA vs RTX (ref)		TCZ vs RTX (ref)	
Adjusted RR (95%CI)	1.15	1.13	0.88	0.86	0.82	0.77
	(0.69, 1.90)	(0.68, 1.54)	(0.55, 1.40)	(0.66, 1.13)	(0.50, 1.36)	(0.57, 1.01)

Numbers are medians (Q1-Q3) unless otherwise stated. End of follow-up was July 2015 in DK and December 2015 in SE.
 DK=Denmark, SE=Sweden, yrs=years
 *adjusted for age and gender, ** Adjusted for age, sex, DAS28, smoking, disease duration, HAQ, previous serious infection, previous cancer, previous chronic obstructive pulmonary disease and (titles) of antibiotic prescriptions.

Conclusion: Differences in baseline characteristics were observed. Numerical differences in IR between the three drugs were seen, and the relative risk of SI seemed to vary with drug. However, the findings should be interpreted with caution due to few events and risk of residual confounding.

Disclosure: K. Lederballe Grøn, BMS, 2; E. V. Arkema, None; B. Glintborg, AbbVie, Biogen, Pfizer, 2; F. Mehnert, None; M. Østergaard, Abbvie, BMS, Boehringer-Ingelheim, Celgene, Eli-Lilly, Hospira, Janssen, Merck, Novartis, Orion, Pfizer, Regeneron, Roche, UCB., 2, 5, 8; L. Dreyer, Eli Lilly and Co., 8; M. Nørgaard, None; N. S. Krogh, None; J. Askling, Abbvie, BMS, MSD, Pfizer, Roche, Astra-Zeneca, Eli Lilly, Samsung Bioepis, and UCB, Pfizer and Eli Lilly., 2, 5, 8; M. L. Hetland, Abbvie, Biogen, BMS, CellTrion, MSD, Novartis, Orion, Pfizer, Samsung and UCB, 2, 5.

Abstract Number: 228

Widespread Chronic Use of Proton-Pump Inhibitors and Potential for Drug-Drug Interactions in Rheumatoid Arthritis and Lupus Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Poor control of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) can lead to the use of corticosteroids and non-steroidal anti-inflammatories (NSAIDs), which in turn can affect patients' gastric mucosa and contribute to gastroesophageal reflux disease (GERD). GERD may be treated with acid-reducing agents including proton pump inhibitors (PPIs); PPIs are known to interact with a variety of drugs, potentially including investigational therapies in clinical trials. The prevalence of chronic PPI use in RA and SLE patients is not well-known, and therefore the potential for widespread drug-drug interactions in these patients is not well-understood. A better understanding of the details of concomitant medication use in these patient populations could guide more effective therapies in the future. We investigated the prevalence and type of chronic PPI use in RA and SLE populations, with the aim of helping clinicians and investigators to make appropriate treatment decisions, and to highlight the importance of PPI polypharmacy in clinical trial design.

Methods: A retrospective analysis of medication use in RA and SLE patients from 2012-2015 was done using Truven MarketScan® Claims Databases. Algorithms from the literature were used to identify RA and lupus cases, and to stratify by disease severity/line of treatment; these were pressure-tested using sensitivity analyses. Omnibus tests for between-strata differences in PPI use according to disease severity/line of treatment were carried out, followed by pairwise comparisons (n=15 for RA; n=3 for lupus) using Fisher's exact test correction for multiple comparisons via false discovery rate (FDR).

Results: Roughly one-third of RA and lupus patients in a large claims database were chronic users of PPIs. For SLE patients, this proportion increased with our measure of disease severity. For RA patients, higher use was observed in TNF-IR and BIO-IR patients. Following significant results from our omnibus tests and FDR correction of pairwise comparisons, all but the following four remained significant for RA: csDMARD vs. bDMARD/JAKi; TNF-IR vs. no treatment; TNF-IR vs. multiple treatment; and BIO-IR vs. multiple treatment. For lupus, mild vs. moderate and mild vs. severe comparisons remained significant. Results are given in Table 1.

Conclusion: Chronic use of PPIs is widespread among RA and lupus patients in the Market Scan database. Because PPIs may interact with a number of other medications, providers who treat RA and lupus patients should take care to assess concomitant medication use in these patients, and researchers designing clinical trials should carefully assess the prevalence of PPI use in comparator versus treatment arms to ensure that results are not unduly influenced by PPI use. In each case, attention should be paid to the particular type of PPI used, as pharmacokinetic characteristics of each PPI vary.

Table 1. Chronic PPI Use Among RA and SLE Patients.

	Chronic PPI use (n, %)
RA	
csDMARD	14,056 (34)
bDMARD/JAKi	8,838 (34)
TNF-IR	304 (40)
BIO-IR	268 (50)
No treatment	3,244 (37)
Multiple treatments	120 (44)

Lupus

Mild (n=1,436)	427 (30)
Moderate (n=782)	334 (43)
Severe (n=6)	5 (83)

Disclosure: D. Keebler, Genentech, Inc, 1, 3; N. Jones, Genentech, Inc., 3; M. McEnany, Genesis Research, 3.

Abstract Number: 229

Disability Status, Mortality, and Leading Causes of Death in Seropositive Rheumatoid Arthritis Patients: A Population-Based Study in Korea

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Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease that leads to functional disability and premature mortality. We aimed to identify the status of disability and mortality in patients newly diagnosed with seropositive RA who were followed up for up to 10 years, as compared with the general population in Korea.

Methods: We conducted a nationwide population-based study using a National Health Insurance Service-National Sample Cohort of a Korean population consisting of 1 million individuals who submitted medical care claims between 2002 and 2013. A RA diagnosis was defined as the diagnostic code for seropositive RA (*International Classification of Diseases* code M05) with the prescription of any disease-modifying anti-rheumatic drug (DMARD).

Results: The analysis included 1655 incident seropositive RA patients and 8275 non-RA controls, matched by age, sex, and income. In RA patients, the most commonly used DMARD was hydroxychloroquine (n=1180, 71.30%), followed by methotrexate (n=1150, 69.49%), leflunomide (n=434, 26.22%), sulfasalazine (n=598, 36.13%), and bucillamine (n=269, 16.25%). The most commonly used biologic DMARD was adalimumab (n=42, 2.54%), followed by etanercept (n=29, 1.75%), infliximab (n=14, 0.85%), and rituximab (n=8, 0.48%).

The disability rate in the first 10 years of the disease increased in RA patients compared with non-RA controls (odds ratio [OR] 2.27, 95% confidence interval [CI] 1.75–2.93, $p<0.0001$). The physical disability rate significantly increased (OR 3.81, 95% CI 2.80–5.18, $p<0.0001$). During the follow-up period, 88 RA patients (0.05%) and 200 non-RA controls (0.02%) developed disability regardless of cause and severity. Of these, 73 and 99 had physical disabilities (82.95% and 49.50% of all disabilities, respectively). The mortality rate in the first 10 years of the disease also significantly increased in the RA group compared with the non-RA controls (OR 1.33, 95% CI 1.05–1.69, $p=0.02$), especially in the death caused by infection (OR 4.39, 95% CI 1.59–12.12, $p<0.01$). During the follow-up period, 88 RA patients (0.05%) and 335 non-RA controls (0.04%) died. The main causes of death in the first 10 years of RA were malignancy (19.32%), cardiovascular disease (15.90%), RA itself (11.36%), and infection (7.95%). In the non-RA control group, the main causes of death were malignancy (36.41%), cardiovascular disease (21.50%), and respiratory disease (7.16%).

Conclusion: Seropositive RA patients had higher mortality and disability than the non-RA population in the first 10 years of the disease. Further study about the determinants of disability and mortality is needed.

Disclosure: I. A. Choi, None; J. S. Lee, None; E. Y. Lee, None.

Increased Prevalence of Coronary Artery Disease in Patients with Chest Pain and Seropositive Rheumatoid Arthritis: An Analysis from a Clinical Computed Tomography-Based Large-Scale Population Cohort

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Inflammation seems to play a central role in the development of atherosclerosis and inflammatory diseases seem to promote progression of coronary artery disease (CAD). Rheumatoid arthritis (RA) is associated with increased mortality, and evidence exists of a strong association between RA and premature cardiac events. However, knowledge of the severity and pattern of coronary artery calcifications in RA patients is still sparse. The aim of this study was to examine the prevalence and severity of CAD in RA patients from a large-scale cohort with chest pain referred for CAD rule out.

Methods: This was a cross sectional study in 39,534 patients from the Western Denmark Heart Registry. For each individual, data included cardiac CTs (CCT) with a registration of up to 40 variables including level of stenosis and calcification. RA patients were identified through linkage with the Danish National Patient Registry. All analyses were performed for overall RA and the serological subtypes: 'sero-positive RA' and 'other RA'. In the studied region, RA-flares are controlled through escalation of disease modifying drugs and intra-articular or intramuscular glucocorticoid injections (GCI). The number of times a patient had received GCIs 3 years prior to the CCT was used as a surrogate marker for disease activity. The prevalence of having a coronary artery calcium score (CACS) > 0 among RA and non-RA patients was assessed by estimating odds ratios (OR) with [95% CI], adjusted for gender, age, Charlsons co-morbidity index, hypertension, lipid-lowering treatment, body mass index and smoking status.

Results: A total of 337 (0.9%) patients with RA were identified; 268 (79.5%) being sero-positive. Women accounted for 73.9% of the RA patients compared to 54.4% of the non-RA patients. Non-obstructive CAD was present in 35.6% of the RA patients vs. 31.7% of the non-RA patients, and 15.4% of the RA patients had a CACS > 400 vs. 10.1% in non-RA patients. OR for having a CACS > 0 was 1.17 [0.91-1.50] 95% CI for overall RA, 1.33 [1.00-1.77] for sero-positive RA and 0.72 [0.42-1.24] for other-RA. Patients who had received >1 GCI 3 years prior to the CCT had an OR at 1.49 [0.99-2.27] for having CACS > 0.

Conclusion: Based on data from a large CCT database, coronary artery calcifications are more frequent in RA patients with seropositive disease and high disease activity RA. In particular, the occurrence of severe calcifications is more frequent. These findings support the hypothesis that inflammatory disease may accelerate the atherosclerotic process leading to increased coronary artery calcification and risk of cardiac events.

Disclosure: A. Bugge Tingaard, None; A. de Thurah, None; I. Trolle Andersen, None; A. Hammerich Riis, None; J. Therkildsen, None; E. M. Hauge, None; M. Böttcher, None.

Rates of Influenza Vaccination in a Cohort of Patients with Rheumatoid Arthritis and Psoriatic Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: The infections complicating rheumatic diseases cause significant morbidity and mortality. Rheumatoid arthritis and psoriatic arthritis patients are at increased risk of infection due to their altered immune system superimposed over the immunosuppressive effects of the treatment. The Center for Disease Control and Prevention is recommending that any person with rheumatoid arthritis should receive annual influenza vaccination. Despite these endorsements, the uptake of influenza vaccination in rheumatoid arthritis patients is low, and the rates of influenza vaccinations for psoriatic arthritis are largely unknown. The overall objective of this study is to understand the vaccination rate in our cohort of rheumatoid arthritis and psoriatic arthritis, and compare it with the literature reported rates in these populations. We also aim to understand the barriers for non-vaccination in a small subset of patients.

Methods: All the patients from the Rheumatology clinic with a clinical diagnosis of either psoriatic arthritis or rheumatoid arthritis were included in the analysis. The data was collected by retrospective chart review for the last 2 influenza season. Vaccination status was verified based on the electronic medical record documentation. We offered the questionnaire to 35 consecutive patients with rheumatoid arthritis and 17 with psoriatic arthritis whose record of vaccination is No. If the answer was No, the patients were subsequently asked about reasons for non-vaccination.

Results: We identified 526 patients with a diagnosis of psoriatic arthritis. The average age was 55.7. The gender distribution was 49.4% male, 50.6% females. Out of the 526 psoriatic arthritis patients, only 52.7% of them were “ever” vaccinated. This includes any reported vaccination since 2001. However, only 28.9% were vaccinated in the last 2 flu seasons. The Rheumatology clinic follows a total of 1489 patients with a diagnosis of rheumatoid arthritis. This subset of patients was slightly older than the PsA cohort, mean age 62.5, with 54.9% being female. The “ever” vaccination rate in this cohort was 61.3%. The vaccination rate in the last 2 winter seasons was much lower, only 37.4%. We compared the vaccination rates in the clinic, with the literature-reported vaccination rates in rheumatoid arthritis population. There was no difference in the vaccination rates between the PsA and RA cohort, and also no statistical difference between the vaccination rates in the 2 cohorts, based on sex. Among individuals with RA who ever received vaccination for influenza, the proportion of individuals who received the vaccine in the last two years was smaller in those younger than 65 compared with those older than 65, 51.7% and 63.7%, respectively ($p=0.0001$). Among individuals with PsA who ever received vaccination for influenza, the proportion of individuals who received the vaccine in the last two years was much higher in those older than 65 compared with those younger than 65, 38.7% vs. 4.02% respectively ($p=0.0001$).

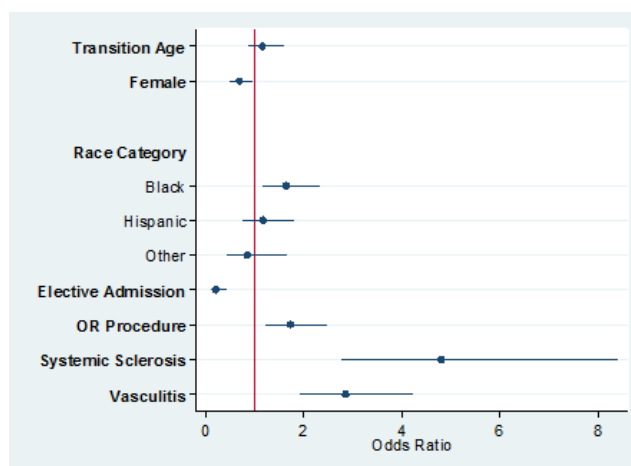
Conclusion: Our result indicate that the influenza vaccination rates in a cohort of PsA and RA patients are very low, less than half of them receiving the influenza vaccine.

Disclosure: A. Coca, None; J. Dolan, None; C. T. Ritchlin, AbbVie, Amgen, UCB, 2,AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer Inc, 5.

Abstract Number: 232

Inpatient Mortality in Transition-Aged Youth with Rheumatic Disease: An Analysis of the National Inpatient Sample

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Transition from pediatric to adult care is seen as a vulnerable time for youth with chronic diseases. In patients with rheumatic disease, studies show high rates of loss to follow up and increased disease activity in young adults compared to adolescents. However, there are no mortality data on young adults with rheumatic diseases. In this study, we sought to assess whether transitional age is a risk factor for inpatient mortality.

Methods: We analyzed the 2012-2014 National Inpatient Sample database, a representative sample of all discharges in the United States produced by the Agency for Healthcare Research and Quality (AHRQ). Individuals with rheumatic diseases were identified by International Statistical Classification of Disease – 9 (ICD-9) codes at time of discharge. Youth were divided by age into three age groups: pre-transitional age (11-17), transitional age (18-24) and post transitional (25-31). We fitted univariable and multivariable logistic regression models to assess whether transitional age was a risk factor for inpatient mortality. We also assessed whether sex, underlying disease, socioeconomic status, insurance type, and psychiatric comorbidity were risk factors for inpatient death. Due to NIS restrictions on reporting data cells with fewer than 10 outcomes, specific diagnoses were combined to form the following categories: inflammatory arthritis, systemic lupus erythematosus (SLE), systemic sclerosis (SS), connective tissue diseases other than SLE or SS, systemic vasculitis, and periodic fever syndromes.

Results: There were 21,488,293 individual hospital discharges in the NIS data sets from 2012-2014. Of these, 30,269 met our inclusion criteria of diagnosis and age. There were 195 inpatient deaths (0.7%). The Odds ratio for inpatient death of an individual in the transitional age range was 1.18 compared to the pre transitional and post-transitional age ranges in the multivariable model ($p=0.3$). Black race (OR=1.4, $p=0.06$), male sex (1.75, $p<0.001$), and a diagnosis of systemic sclerosis (OR= 4.81, $p<0.001$) or vasculitis (OR= 2.85 $p<0.001$) were the greatest risk factors of inpatient mortality.

Conclusion: Transitional age was not a risk factor for inpatient mortality in this study. We did identify other risk factors for inpatient mortality other than age. Further studies are required to assess if there is an increased risk of mortality in outpatients of the transitional age group.

Figure 1: Parsimonious multivariable logistic regression model including all covariates significant at the $p=0.05$ level. Transition age was forced into the model despite being non-significant. White Race was the referent racial category.

Disclosure: P. T. Jensen, None; K. Koh, None; R. Cash, None; S. P. Ardoin, None; A. Hyder, None.

Abstract Number: 233

TNF Inhibitors: Prevalence of Use and Predictors of Treatment Non-Persistence in the 2011-2016 Medicare Population

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Use of tumor necrosis factor inhibitor (TNFi) drugs is common among patients with rheumatic disease who do not respond to conventional therapies. The aims of this study were to (i) characterize the use of, and (ii) investigate factors associated with non-persistence to TNFis in a contemporary database of Medicare beneficiaries.

Methods: This study used claims data from 2010-2016 from a 20% Medicare sample. We identified all patients whose first (i.e., index) TNFi use occurred between 2011-2016 based on the presence of one or more Medicare Part D prescription or Part B injectable/IV drug claims for adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab. To identify baseline covariates, we required that patients have Medicare Parts A/B and D coverage for a baseline period of at least one year prior to the index TNFi claim. Comorbid conditions were defined based on a diagnosis code in at least one inpatient or two outpatient claims separated by 30 days or more. We defined non-persistence as a gap in supply of the index TNFi of more than 180 days. Factors associated with the rate of non-persistence were assessed using multivariable Cox proportional hazards regression.

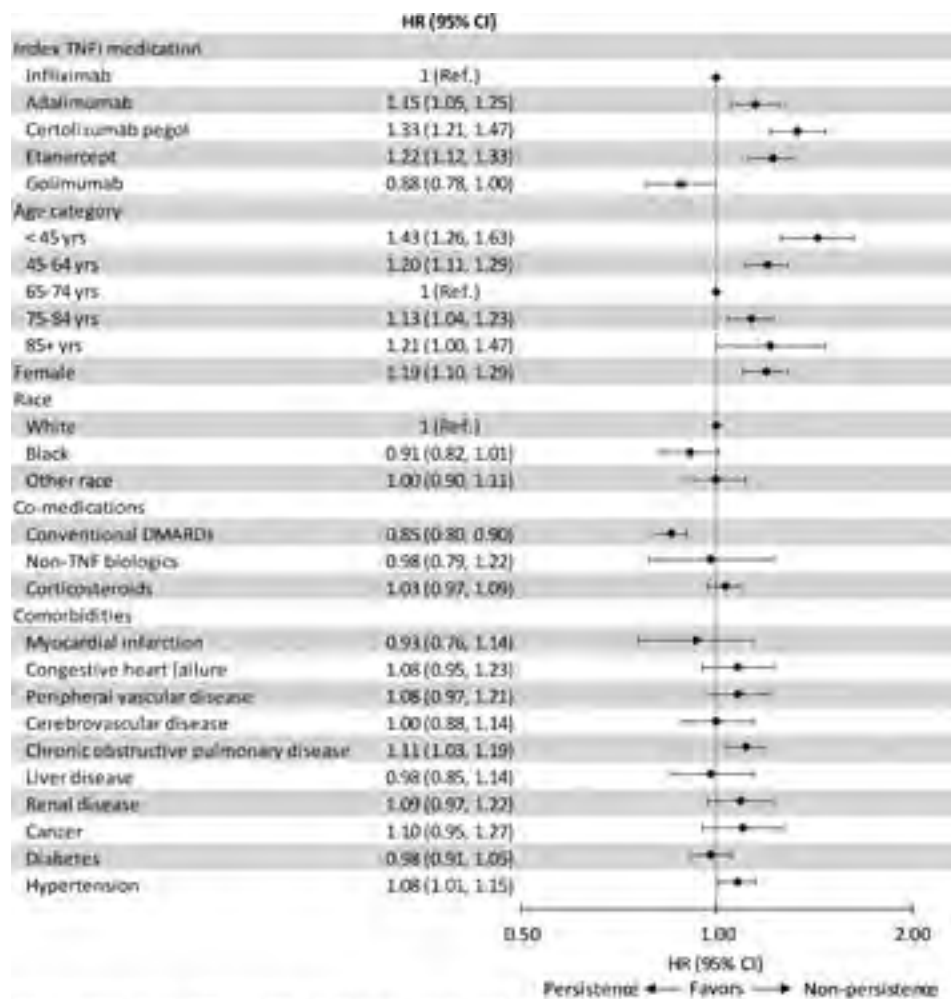


Figure. Hazard ratios (HR) and 95% confidence intervals (CI) for non-persistence to the index TNFi from a multivariable Cox regression model.

Results: We identified 15,622 patients initiating a TNFi from 2011-2016, with infliximab being the most common and golimumab the least common (**Table**). Mean age was 64 ± 13 years and 71% were female. History of rheumatoid arthritis (60%) was the most common TNFi indication, and 40% of patients had baseline concomitant use of each of conventional DMARDs and corticosteroids. Among 8,147 patients with rheumatoid arthritis and two or more TNFi claims, over a mean of 16.1 months of follow-up, we identified 2,937 (36%) patients who were non-persistent with the index TNFi. Female sex, chronic obstructive pulmonary disease, and hypertension were associated with a higher rate of non-persistence, and age 65-74 years and concomitant DMARD use were associated with a lower rate of non-persistence (**Figure**). In comparison to initiators of infliximab, rates of non-persistence were higher among initiators of adalimumab, certolizumab pegol, and etanercept, and lower among initiators of golimumab.

Table. Baseline characteristics of Medicare patients initiating a TNFi biologic medication.

	Adalimumab <i>N</i> = 4460	Certolizumab <i>N</i> = 1705	Etanercept <i>N</i> = 1130	Golimumab <i>N</i> = 8015	Infliximab <i>N</i> = 5613	Total <i>N</i> = 15023
Age, mean (SD) yrs	60 ± 14	60 ± 11	62 ± 13	60 ± 11	61 ± 12	61 ± 13
Age category, <i>N</i> (%)						
< 45 yrs	780 (16%)	78 (5%)	384 (12%)	41 (4%)	327 (6%)	1570 (10%)
45–64 yrs	1697 (36%)	765 (16%)	1187 (37%)	173 (17%)	902 (18%)	4224 (27%)
65–74 yrs	1568 (34%)	871 (51%)	1125 (30%)	528 (52%)	8672 (53%)	6764 (43%)
75–84 yrs	574 (12%)	410 (24%)	426 (13%)	238 (23%)	1005 (20%)	2653 (17%)
≥ 85 yrs	90 (2%)	81 (5%)	68 (2%)	35 (8%)	137 (3%)	411 (3%)
Female, <i>N</i> (%)	3198 (68%)	1130 (78%)	2320 (73%)	768 (79%)	3458 (69%)	11074 (72%)
Race, <i>N</i> (%)						
White	3513 (77%)	1470 (86%)	2482 (78%)	370 (86%)	4351 (86%)	12786 (82%)
Black	571 (12%)	113 (7%)	362 (11%)	87 (9%)	414 (8%)	1552 (10%)
Other (see)	485 (10%)	117 (7%)	345 (11%)	58 (6%)	278 (6%)	1284 (8%)
Indicated diseases, <i>N</i> (%) ^a						
Rheumatoid arthritis	2099 (45%)	1359 (80%)	2129 (67%)	926 (91%)	2858 (57%)	9371 (60%)
Psoriatic arthritis	390 (8%)	171 (10%)	351 (11%)	58 (6%)	480 (10%)	1450 (9%)
Ankylosing spondylitis	122 (3%)	42 (2%)	93 (3%)	15 (1%)	189 (4%)	461 (3%)
Crohn's disease	731 (16%)	120 (7%)	14 (0%)	< 1	805 (16%)	1696 (11%)
Ulcerative colitis	330 (7%)	74 (1%)	19 (1%)	23 (7%)	627 (12%)	1023 (7%)
Plaque psoriasis	985 (21%)	95 (6%)	637 (20%)	38 (4%)	349 (7%)	2104 (13%)
Hidradenitis suppurativa	90 (2%)	< 1	< 1	< 1	22 (0%)	< 123 (< 1%)
Uveitis	19 (0%)	< 1	< 1	< 1	28 (1%)	< 64 (< 1%)
Co-medication, <i>N</i> (%)						
Conventional DMARDs	1535 (33%)	754 (44%)	1352 (42%)	561 (55%)	2061 (41%)	6254 (40%)
Non-TNF biologics	17 (0%)	40 (2%)	31 (1%)	48 (5%)	87 (2%)	223 (1%)
Corticosteroids	1553 (33%)	796 (43%)	1221 (38%)	477 (47%)	2467 (49%)	6454 (41%)
Comorbid conditions, <i>N</i> (%)						
Myocardial infarction	126 (3%)	35 (2%)	109 (3%)	23 (2%)	170 (3%)	463 (3%)
Congestive heart failure	315 (7%)	114 (7%)	261 (8%)	67 (7%)	323 (6%)	1080 (7%)
Peripheral vascular disease	343 (7%)	168 (10%)	243 (8%)	75 (7%)	415 (8%)	1244 (8%)
Cerebrovascular disease	233 (5%)	100 (6%)	182 (6%)	55 (5%)	315 (6%)	885 (6%)
Chronic obstructive pulmonary disease	1055 (23%)	372 (22%)	810 (25%)	197 (19%)	1103 (22%)	3537 (23%)
Liver disease	225 (5%)	70 (4%)	187 (6%)	35 (3%)	231 (5%)	748 (5%)
Renal disease	368 (8%)	162 (10%)	277 (9%)	89 (9%)	442 (9%)	1338 (9%)
Cancer	209 (4%)	100 (6%)	153 (5%)	63 (6%)	334 (7%)	859 (5%)
Diabetes	1389 (30%)	396 (23%)	1000 (31%)	261 (26%)	1302 (26%)	4348 (28%)
Hypertension	2639 (57%)	1065 (62%)	1888 (59%)	649 (64%)	3062 (61%)	9303 (60%)

SD, standard deviation; DMARD, disease-modifying antirheumatic drug; TNFi, tumor necrosis factor inhibitor.

^aFrequencies shown in gray if disease not indicated for a specific TNFi drug.

Conclusion: TNFis are used among a diverse set of Medicare beneficiaries. In TNFi initiators with rheumatoid arthritis, there were differences in the rate of non-persistence by sex, age, co-medication, comorbid disease, and the type of TNFi. These findings suggest that there may be differences in the benefit and harm profiles (e.g., therapeutic response or adverse complications), or patient preferences in drug administration (e.g., once-monthly dosing for golimumab), between the TNFis.

Disclosure: N. S. Roetker, None; Y. Peng, None; K. M. Nieman, None; S. Li, None; D. T. Gilbertson, None.

Population-Based Estimates of Fatigue Prevalence Among Adults Aged >18 Years with and without Arthritis, United States, 2015-2016

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Fatigue is a common symptom among adults with arthritis and can severely impact quality-of life. This study's two objectives were to estimate the national prevalence of fatigue among US adults with and without arthritis and to describe differences in intensity, duration, sociodemographic and health-related characteristics in fatigue among adults with arthritis.

Methods: The National Health Interview Survey is an ongoing survey of the civilian, non-institutionalized population designed to gather nationally representative data on a variety of health topics. We analyzed 2015 and 2016 Adult Functioning and Disability Supplement data (sample sizes = 16,939 and 16,478, respectively). Doctor-diagnosed arthritis was defined as a "yes" to: "Have you ever been told by a doctor or other health care professional that you have arthritis, rheumatoid arthritis, gout, lupus or fibromyalgia?" The case finding question for fatigue was "In the past 3 months, how often did you feel very tired or exhausted?" (never, some days, most days, every day). Any fatigue was defined as positive answer some days, most days, or every day. Among those reporting any fatigue, intensity responses were a little, a lot, somewhere in between to "How would you describe the level of tiredness?" and duration responses were some of the day, most of the day, all day to "How long did it last?". Age-standardized prevalence (%) and 95% confidence intervals (CI) were calculated overall and by sociodemographic characteristics (age, sex, race/ethnicity, and education) and health-related characteristics (arthritis-attributable activity limitation (AAAL), self-rated health (excellent/very good, good, fair/poor), body mass index (BMI) (<25.0, 25.0-30 and 30.0+), number of co-morbid conditions, and physical activity level (inactive, insufficient, active). Analyses accounted for the complex survey design.

Results: Any fatigue was higher among adults with arthritis (80.4% CI 78.6-82.0) than without arthritis (60.8% CI 59.8-61.8; $p<0.01$). Adults with arthritis vs. no arthritis also reported significantly greater "fatigue on most days" (16.4%, CI=14.7-18.3 vs. 7.2%, CI=6.7-7.6) and "fatigue every day" (12.2%, CI=10.7-13.9 vs. 4.1%, CI=3.8-4.5). The highest prevalence of "fatigue every day" among adults with arthritis was observed for those with ≥ 3 co-morbid conditions (27.4%), reporting fair/poor health (25.9%) and being physically inactive (21.9%). "Fatigue every day" prevalence among adults with arthritis was significantly lower for those age 65+, college degree or higher, no AAAL, no co-morbid conditions, excellent/very good health, and physically active. Among adults with arthritis with any fatigue, 25.8% (CI=23.6-28.1) said their intensity was "a lot"; 24.1% (CI=21.9-26.5) reported a duration of "most of the day" and 12.4% (CI=10.7-14.4) "all of the day".

Conclusion: Among adults with arthritis about 4 in 5 report any fatigue, and among those 1 in four report intense ("a lot") fatigue and 1 in 3 report a duration of most or all of the day. Because pain is an important component of fatigue, exercise and self-management education interventions that lower pain levels may also improve fatigue.

Disclosure: J. M. Hootman, None; L. Murphy, None; M. Boring, None; D. Guglielmo, None.

Clinical Predictors and Risk of Methotrexate Induced Liver Fibrosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Methotrexate (MTX) is a highly effective therapy for patients with rheumatologic and dermatologic conditions. Its use infers significant reduction in morbidity and mortality; however, it has been associated with a range of liver related adverse events. The risk with current dosing remains unknown. The American College of Rheumatology and American Association of Dermatology guidelines identify alcohol use, diabetes, and obesity as risk factors for MTX-induced liver injury.

Methods: We aim to quantify the prevalence of liver fibrosis and its relationship to clinical features. This will include total lifetime dose and parameters associated with non-alcoholic fatty liver disease (NAFLD) including obesity and diabetes. We predict those with NAFLD will be at increased risk of liver injury while taking MTX. A retrospective cross sectional study was performed among patients with rheumatoid arthritis or psoriasis/psoriatic arthritis who were referred to hepatology between 2015-2018 for evaluation of liver injury in the setting of chronic MTX use. The primary outcome was the prevalence of liver fibrosis using Fibroscan ($\geq 6\text{kPa}$ = $\geq \text{F1}$ Fibrosis) or biopsy where available. Clinical predictive variables analyzed were demographics, co-morbidities, symptoms, physical exam findings, dose and duration of MTX use, laboratory values, and the controlled attenuation parameter (CAP) score, which is a method for measuring steatosis based on Fibroscan. Variables with a univariate $P < 0.2$ were included in a multivariable logistic regression model.

Results: 30% (11/37) of patients had RA and 70 % (26/37) had psoriasis. 38% (14/37) were determined to have liver fibrosis. Rates were much higher among those with psoriasis (11/14 patients). Clinical variables retained in the final regression model were weight, body mass index (BMI), CAP score, and the presence of NAFLD.

Conclusion: Early detection of liver toxicity ensures improved outcomes and prevents unnecessary cessation of methotrexate. Those with NAFLD have an increased risk of methotrexate hepatotoxicity. We recommend individuals with risk factors for metabolic syndrome be referred to hepatology and screened for NAFLD prior to initiation of methotrexate.

Disclosure: S. Oberholtzer, None; L. Worobetz, None.

Abstract Number: 236

Hypogammaglobulinemia and Infection Risk in Patients Treated with Rituximab

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Rituximab (RTX) is an effective immunosuppressive therapy for many autoimmune diseases. Secondary hypogammaglobulinemia (hypoIg) can occur mainly after repeated cycles of RTX. The risk of infection in these patients has been shown to be higher in some studies, especially with secondary hypoIgM. Our objectives are to determine whether low IgG or IgM levels associate with infection in RTX treated patients.

Methods: Retrospective observational study of patients with autoimmune diseases from a single center, treated with RTX (2x1000mg 2 weeks apart) between 2010-2017. Patients that did not complete one full RTX cycle were excluded. Exposures were demographical characteristics; previous/concomitant immunosuppressants and peripheral B cell CD19+ count. Outcomes were serum Ig levels (IgM, IgG and IgA) at baseline and 4-6 months after each cycle, hypoIg and serious infections (defined as requiring hospitalization and/or intravenous treatment). Fisher exact test was used to compare dichotomous variables; Wilcoxon rank sum test to compare continuous variables with skewed distributions; logistic regression for normal distributed continuous variables.

Results: 41 patients were included with a median age of 50.9 years (IQR 37.4, 64.9); median number of cycles of 4. Most patients had systemic lupus erythematosus (36.6%), rheumatoid arthritis (14.6%) and myasthenia gravis (14.6%). During all treatment period 18 patients (43.9%) developed hypoIgG, 22 (53.7%) hypoIgM and none hypoIgA. Lower baseline IgG and IgM levels were associated with hypoIgG ($p < 0.001$) and hypoIgM ($p = 0.03$), respectively. Moreover, after each RTX cycle median IgM levels tend to decrease ($p < 0.001$ until the 3rd cycle), while median IgG levels tend to remain stable after the 1st cycle. Incidence of hypoIgG was lower in patients treated hydroxychloroquine (HCQ) ($p = 0.01$). Other immunosuppressive therapy and clinical characteristics did not associate with hypoIg. 13 patients had a serious infection (incidence rate of infection of 19.2/100 patients-year). Incidence of infection was higher in elderly patients ($p = 0.02$) and

lower in patients treated with HCQ ($p=0.02$), and did not associate with hypoIgG or hypoIgM. Lower median levels of IgG were associated with a higher incidence of infection after the 2nd ($p=0.03$) and the 3rd ($p=0.02$) cycles. Analyzing the variation of IgG levels between baseline and each cycle, there was a tendency towards the occurrence of infection in relation with a higher % of negative variation of IgG levels, especially after the 3rd cycle, although not statistically significant ($p=0.06$).

Conclusion: a higher incidence of serious infections did not associate with low absolute IgM or IgG titers, but with the percentage of reduction of IgG levels, and not IgM, from baseline and each treatment. This can have a clinical impact in the decision to stop RTX treatment based on safety. HCQ showed a protective role for infection in patients treated with RTX, which can be explored in larger prospective studies.

Disclosure: J. Caetano, None; F. Batista, None; J. Delgado Alves, None.

Abstract Number: 237

The Risk of Serious and Opportunistic Infections in Rheumatologic Patients on Interleukin Inhibitors: A Systematic Review and Meta-Analysis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Interleukin (IL) inhibitors are increasingly being used for rheumatologic diseases. There are many controlled clinical trials assessing the efficacy of IL inhibitors, but there are few meta-analyses which have examined the pooled risk of infection with these drugs. Our objective was to assess the risk of serious infection and opportunistic infections in patients with rheumatologic diseases treated with IL inhibitor therapy (anakinra, brodalumab, canakinumab, secukinumab, tocilizumab, olokizumab, ixekizumab, ustekinumab, clazakizumab, and rilanocept).

Methods: Medline via Pubmed, Embase, conference proceedings from ASCO, AACR and ACR and reference lists from published systematic reviews related to rheumatologic diseases and interleukin inhibitors for were searched for RCTs using PICOS strategy. We extracted the incident data for serious infections and opportunistic infections. We conducted a fixed-effect meta-analysis via calculating a pooled odds ratio (Mantel-Haenszel methods with a continuity correction designed for sparse data) using STATA software version 14 (Stata Corp., College Station, Texas, USA). Heterogeneity was assessed using Q-statistic and quantified using I^2 statistic.

Results: The initial search of PubMed and Embase yielded 881 citations. We included 38 eligible RCTs that included 16,841 patients. We extracted data on serious infections (death or hospitalization), candidiasis, herpes zoster, and Pneumocystis carinii Pneumonia (PCP) as the main outcomes of interest. Serious infections were significantly more common with patients who received IL inhibitors compared to standard of care (OR 1.97, 95% CI 1.48-2.62) and the heterogeneity was minimal ($I^2 = 0\%$, $P = 0.99$). Moreover, we found that candidiasis also was significantly more common with patients who received IL inhibitors than standard of care (OR 5.41, 95% CI 2.04-14.33; $I^2 = 0\%$, $P = 0.99$). However, we found no significant difference between patients who received IL inhibitors or standard of care in terms of the risk of herpes zoster or PCP (OR 1.23, 95% CI 0.39-3.84; $I^2 = 0\%$, $p = 0.97$ and OR 0.99, 95% CI 0.10-9.65; $I^2 = 0\%$, $p = 0.70$, respectively). There was no increased incidence of secondary assessed opportunistic infections such as TB, non-TB mycobacterium, coccidioidomycosis, histoplasmosis, aspergillosis, cryptococcus, etc.

Conclusion: We found an increased risk of serious infections, and a significantly increased risk of candidiasis with the use of IL inhibitors, but there was no appreciable increase in the risk of herpes zoster or PCP. Other opportunistic infections were also found to have no appreciable increased risk. Patients and providers need to remain vigilant in recognizing the risk of serious and opportunistic infections with the use of IL inhibitors, and proper care must be taken to quickly identify and treat any infections as a result of IL inhibitor therapy.

Disclosure: A. Berlinberg, None; J. Bilal, None; A. Alhifany, None; W. Faridi, None; C. K. Kwoh, None.

Abstract Number: 238

IL Inhibitors Therapy in Rheumatic Diseases and the Risk of Malignancies: Systematic Review and Meta-Analysis of Rare Harmful Effects in Randomized Controlled Trials

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: Tumor necrosis factor alpha (TNF α) inhibitor therapy in patients with rheumatologic disorders is well known to increase the risk of malignancy. While the individual trials report these incident side effects with Interleukin (IL) inhibitor therapy, the subject has not been systematically investigated.

Objective: To investigate the risk of malignancies in patients with rheumatic diseases treated with interleukin (IL) inhibitor therapies (Anakinra, brodalumab, canakinumab, secukinumab, tocilizumab, olokizumab, ixekizumab, ustekinumab, clazakizumab, and rilanocept).

Methods: Medline via Pubmed, Embase, conference proceedings from ASCO, AACR and ACR and reference lists from published systematic reviews related to rheumatologic diseases and interleukin inhibitors for were searched for RCTs using PICOS strategy. We extracted the incident data for malignancies. We conducted a fixed-effect meta-analysis via calculating a pooled odds ratio (Mantel-Haenszel methods with a continuity correction designed for sparse data) using STATA software version 14 (Stata Corp., College Station, Texas, USA). Heterogeneity was assessed using Q-statistic and quantified using I² statistic.

Results: After screening 881 studies, 16841 patients from 38 eligible studies were analyzed. We found no significant difference between patients who received IL-inhibitors or placebo in terms of the risk of malignancies (OR 1.07, 95% CI 0.708-1.63; I²= 9.9%, P = 0.32). We conducted a sensitivity analysis to examine the risk of malignancies based on individual IL-inhibitors. We found no significant difference in the occurrence of malignancies in patients who received anakinra, Ixekizumab, Rilanocept, Secukinumab, Tocilizumab or Ustekinumab versus placebo (OR 0.20, 95% CI 0.06-0.66; I²= 0%, P = 0.97), (OR 1.28, 95% CI 0.30-5.5; I²= 4.9%, P = 0.35), (OR 2.18, 95% CI 0.22-21.23; I²= 0%, P = 0.75), (OR 2.43, 95% CI 0.71-8.27; I²= 0%, P = 0.98), and (OR 1.46, 95% CI 0.72-2.97; I²= 44%, P = 0.13), and (OR 2.14, 95% CI 0.25-18.37; I²= 0%, P = 0.67) respectively.

Conclusion: IL inhibitors therapies appear safe with regards to risk of malignancies for a follow up duration of up to 52 weeks. Long term data is required from cancer survivors to further ensure the safety of IL inhibitor therapies.

Disclosure: J. Bilal, None; I. B. Riaz, None; A. Berlinberg, None; A. Alhifany, None; G. Ortega, None; W. Faridi, None.

Abstract Number: 239

Outcomes of Hospitalizations and the Temporal Trends in Mortality from Acute Myocardial Infarction in Patients with RA and FM during 2005 to 2015

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

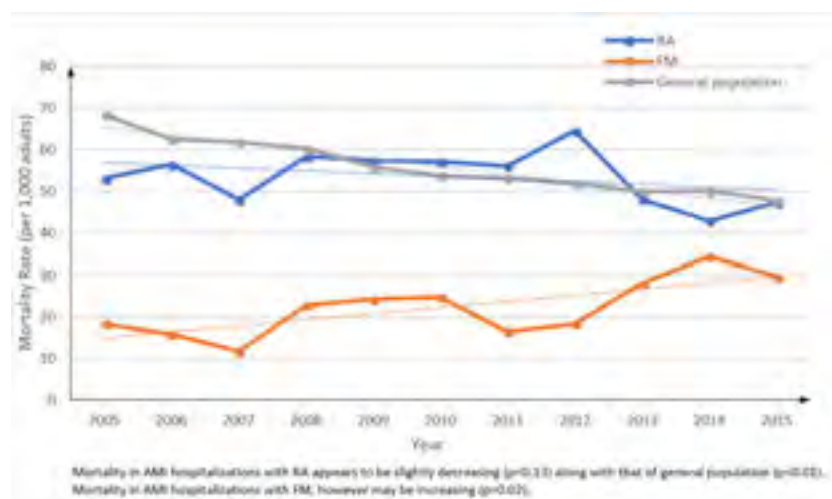
Session Title: Epidemiology and Public Health Poster I: Rheumatoid Arthritis

Session Type: ACR Poster Session A

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

Background/Purpose: RA is associated with an increased risk of coronary artery disease (CAD). This association is believed to be due to systemic inflammation and its role in atherogenesis. The non-inflammatory FM has also been reported as an independent risk factor for CAD. In this study, we evaluated the outcomes of patients hospitalized for acute myocardial infarction (AMI) in those with and without RA or FM in a nationally representative sample.

Methods: We used data from the National Inpatient Sample (NIS) for hospitalizations during the period 2005-2015 with adult AMI as the primary diagnosis and RA or FM as the secondary diagnosis using ICD-9 codes. The proportion who met ACR classification criteria cannot be determined with the NIS database. FM in the presence of immune-mediated or inflammatory rheumatic diseases was excluded. We used logistic regression to calculate the adjusted odds ratios for inpatient mortality from AMI with RA and with FM. We also investigated the unadjusted temporal trend of mortality rate in these groups and compared it to that of the general population.



Results: We identified a total of 1,363,041 AMI hospitalizations from 2005-2015 of which 18,383 (1%) had a diagnosis of RA and 8133 (0.6%) had a diagnosis of FM. Compared to patients without RA, hospitalized RA patients were older (70.4 vs. 67.4 years; $p < 0.01$) and predominantly female (62.8% vs. 39.1%; $p < 0.01$). Compared to patients without FM, FM patients were younger (63.9 vs. 67.4 years; $p < 0.01$) with an even higher proportion of females (81% vs. 39.1%; $p < 0.01$). After adjusting for age, gender, race, comorbidities and cardiac procedures, RA hospitalizations with AMI had similar adjusted inpatient mortality (aOR=0.94; 95% CI= 0.87-1.01; $p=0.14$) compared to non-RA hospitalizations while the adjusted odds-ratio for inpatient mortality due to AMI in FM hospitalizations was 0.67 (95% CI= 0.57-0.80; $p < 0.01$). The temporal trends of mortality rate (per 1,000 adults) in AMI hospitalizations in RA ($p=0.13$), FM ($p=0.02$) and the general population ($p < 0.01$) are shown in the figure.

Conclusion: Inpatient mortality in RA patients hospitalized for AMI was similar to that for non-RA patients even though the RA patients were older. The temporal trend of the unadjusted mortality rate in RA was similar to that of the general population and both were slightly decreasing. These findings may be related to strict cardiovascular risk factor modifications and in the case of RA, the availability of better DMARDs as well.

Compared to non-FM patients, patients with FM hospitalized for AMI had a lower inpatient mortality. The trend of AMI mortality rate in FM patients, however, was different from the other trends. Unlike that in RA or in general population, the AMI mortality rate in FM was increasing. This may be due to increased recognition of FM as a diagnostic entity or to the failure to recognize or treat CAD risk factors in the mostly female population.

Disclosure: A. Vafa, None; S. Fugar, None; J. P. Case, None.

Bi-Directional Associations between “Too Much Sitting” and Self-Reported Pain in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health Poster I – ARHP

Session Type: ACR Poster Session A

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

Background/Purpose: Epidemiological evidence indicates that sedentary behaviour, or “too much sitting”, is associated with poor health outcomes in the general population, including elevated systemic inflammation. In addition, regularly breaking up sitting with light-intensity physical activities - such as standing or walking (i.e., sedentary breaks), is proposed to confer positive effects on systemic inflammation, and the experience of bodily pain. Importantly, these relationships are observed to be independent of engagement in moderate-to-vigorous physical activity.

We propose sedentary behaviour may contribute to the progression of pertinent RA outcomes, and particularly those with an inflammatory origin (e.g., joint pain). However, these associations may be bi-directional in nature, and sedentary behaviour may represent a consequence, as well as a cause of RA outcomes. The aim of this study is therefore to explore potential bi-directional associations between sedentary behaviour patterns (sitting, standing, sedentary breaks), with self-reported pain in RA.

Methods: Patients with RA (n = 62, Mean age = 56 ± 13 years) were recruited to this study lasting 8-days. On Day 1, patients completed validated questionnaires to assess their experience of pain over the preceding 2-weeks (McGill Pain Questionnaire-Short Form). Following this, they were given an activPAL (accelerometer enabled posture sensor) to wear for the next 7-days to assess their sitting time (min/day), standing time (min/day) and frequency of sedentary breaks (number/day). On Day 8, participants completed the same pain questionnaire as on Day 1, but were asked to report their experience of pain over the previous 7-days.

Linear regressions examined the relationship between pain on Day 1 (independent variable) with sedentary behaviour patterns over the subsequent week (sitting, standing, sedentary breaks – dependent variables) [Model 1]. Next, the association between sedentary behaviour patterns (in the preceding 7-days - independent variables) and pain on Day 8 were investigated [Model 2]. Finally, to investigate directionality Model 2 was further adjusted for reported pain on Day 1 [Model 3].

Results: Pain on Day 1 significantly predicted time spent sitting in the subsequent 7-days (Model 1; $\beta = .27, p < .05$), but was not significantly linked to standing or sedentary breaks. Time spent sitting was significantly linked to the experience of pain on Day 8 (Model 2; $\beta = .26, p < .05$), but no relationships were demonstrated between standing and sedentary breaks with this outcome. The association between sitting time and pain on Day 8, was no longer significant following adjustment for baseline (Day 1) pain ($\beta = .06, p = .52$).

Conclusion: This is the first study to explore the potential bi-directional associations between sedentary behaviour patterns and pain in RA. Results suggest that sitting time may represent a consequence, rather than a cause of joint pain in these patients. However, the observed association between “too much sitting” throughout the week and subsequent pain (Day 8), may point to the potential of interventions targeting sitting time for minimising the risk of recurrent joint pain.

Disclosure: C. O'Brien, None; J. L. Duda, None; J. J. C. S. Veldhuijzen van Zanten, None; G. S. Metsios, None; G. D. Kitas, None; S. A. M. Fenton, None.

Is There a Relationship between Takotsubo Cardiomyopathy and Fibromyalgia? Insights from the National Inpatient Sample Database

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Takotsubo cardiomyopathy (TCM) or stress cardiomyopathy is an unusual but potentially fatal type of acute cardiomyopathy characterized by transient regional left ventricular systolic dysfunction. It is suggested to be related to stress-induced catecholamine release and is more common in females. Fibromyalgia is also characterized by chronic pain believed to be related to chronic emotional and physical stress. The aim of this study is to determine whether the prevalence of patients with FM is higher among patients hospitalized with TCM compared to the estimated prevalence of FM in the general population and to investigate the characteristics and outcomes of patients hospitalized with TCM and FM compared to patients with TCM and no FM.

Methods: We used data from the National Inpatient Sample (NIS) for hospitalizations during the period 2005-2015 with TCM as a primary diagnosis and FM as a secondary diagnosis using ICD-9 codes. The proportion who met ACR classification criteria cannot be determined with the NIS database. We calculated the prevalence of FM in TCM hospitalizations and compared the characteristics and outcomes of TCM hospitalizations with FM and without FM using SPSS software. The prevalence of FM in the general adult population was obtained from Centers for Disease Control and Prevention (CDC) and is about 2%.

Results: We identified a total of 8,164 TCM hospitalizations from 2005-2015 of which 238 (2.9%) had a diagnosis of FM. FM hospitalizations with TCM were younger (63.0 vs 66.2; $p < 0.01$) and with a higher proportion of females (99.6% vs. 91.5%; $p < 0.01$) compared to patients without FM. Common comorbidities and cardiovascular risk factors such as DM, HTN, and tobacco use were similar in both groups, however, obesity was more common in patients with FM (12.6% vs 9.0%; $p = 0.05$).

Patients with TCM and FM also had higher rates of depression and drug use compared to those without FM. The rates of severe inpatient complications including cardiac shock and cardiac arrest were similar in both groups. One patient died in the FM group (0.4%) while 105 patients (1.3%) died in the non-FM group ($p = 0.2$). The findings are summarized in the table.

Conclusion: About 3 percent of TCM hospitalizations have FM. This is slightly higher than the estimated national prevalence of this disorder in the general population by the CDC. Patients with FM presenting with TCM are younger with even higher proportion of females compared to the ones without FM. Inpatient mortality due to TCM, however, was not statistically different between two groups.

Given the similar presumed etiologies in these disorders, this study suggests that FM may be a risk factor for TCM, however, further investigations are required to establish the possible association between FM and TCM.

Variables*	TCM with FM vs. TCM without FM
Mean age (years)	63.0 vs. 66.2 ($p < 0.01$)
Female percentage	99.6 vs. 91.5 ($p < 0.01$)
Hypertension (%)	64.7 vs. 63.4 ($p = 0.6$)
Diabetes mellitus (%)	13.9 vs. 16.9 ($p = 0.2$)
Obesity (%)	12.6 vs. 9.0 ($p = 0.05$)
Depression (%)	34.9 vs. 15.3 ($p < 0.01$)
Tobacco use (%)	18.9 vs. 15.8 ($p = 0.2$)
Drug use (%)	5.9 vs. 2.6 ($p < 0.01$)
Alcohol use (%)	2.5 vs. 3.5 ($p = 0.4$)
Cardiac shock	2.9 vs. 4.3 ($p = 0.3$)
Inpatient mortality (%)	0.4 vs. 1.3 ($p = 0.2$)
Mean length of stay (days)	3.5 vs. 3.7 ($p = 0.3$)
Mean total charges (\$)	38253.8 vs. 41130.6 ($p = 0.3$)

* Demographic, Clinical Characteristics, and outcomes of TCM hospitalizations in patients with FM and without FM

Disclosure: A. Vafa, None; S. Fugar, None; C. Mbachii, None; A. K. Okoh, None; J. P. Case, None.

Abstract Number: 242

DHEA Deficiency in Fibromyalgia

Thomas Romano, Private Practice, Martins Ferry, OH

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Fibromyalgia (FM) is a common condition but often difficult to treat. This may be because co-morbidities are unrecognized and pose an impediment to a successful therapeutic outcome. This study examined the presence of one such co-morbidity in such patients.

Methods: 108 consecutive female FM patients, mean age 48.87 years treated in a private community-based rheumatology practice were evaluated. All fulfilled ACR 1990 and 2010 FM criteria. All complained of fatigue and decreased stamina. Blood samples were obtained on the initial visit and sent to a reference lab for measurement of dehydroepiandrosterone sulfate (DHEA-S) levels.

Results: Of the 108 FM patients tested, 83 (77%) had low-for-age DHEA-S levels. 6 had no detectable DHEA-S. The levels ranged from 0 to 679 mcg/dl, with 75 having levels under 100 mcg/dl. The mean DHEA-S level for the 108 patients was 96.8 mcg/dl, much lower than the expected level of 150 mcg/dl.

Conclusion: DHEA deficiency is a common co-morbidity in FM and levels should be measured especially if fatigue and decreased stamina are prominent symptoms.

Disclosure: T. Romano, None;

Abstract Number: 243

High Prevalence of Fibromyalgia Among Israel School Teachers

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Fibromyalgia Syndrome (FMS), characterized by widespread pain and fatigue, has frequently been associated with stress in various models, including workplace related stress. In the current study we have evaluated the prevalence of FMS symptoms among Israeli school teachers and have attempted to correlate such symptoms with work – related stress.

Methods: Individuals, all currently employed as school teachers in Israel, were recruited to the study. Participants were asked to answer a questionnaire evaluating symptoms of FMS, based on the current diagnostic criteria, which include the widespread pain index (WPI) and the symptom severity scale (SSS). Participants were further questioned regarding stressful experiences during their work and about post – traumatic symptoms as well as regarding work performance and motivation.

Results: 321 participants were recruited (79.4% female, 20.6 male). 30 individuals (9.3%) of the sample fulfilled current criteria for a diagnosis of FMS, with a rate of 11.4% among females and 1.5% among males. While specific symptoms such as fatigue and irritable bowel symptoms were negatively correlated with work performance, no significant difference was found between teachers with or without fibromyalgia regarding work attendance and performance. FMS symptoms were strongly correlated with work – related stress and were strongly correlated with Post Traumatic Stress Disorder

(PTSD) related symptoms. Motivation to work was significantly lower among teachers fulfilling FMS criteria, but other performance – related parameters did not differ between teachers fulfilling or not fulfilling FMS criteria.

Conclusion: Fibromyalgia symptoms are highly prevalent among Israeli school teachers, and may be related to stress encountered in the classroom. These results are relevant both for physicians treating individuals involved in educational careers as well as for educators and decision – makers involved in planning and managing educational strategies.

Disclosure: Y. Buskila, None; D. Buskila, None; G. Jacob, None; I. Weiss, None; J. N. Ablin, None.

Abstract Number: 244

A Qualitative Study Mapping the Behaviour Change Techniques Used in a Practice-Based Fibromyalgia Self-Management Programme

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Fibromyalgia (FM) is a complex long-term condition that affects up to 5.4% of the UK population. It is associated with chronic widespread pain, fatigue, stiffness, sleep problems, memory and concentration difficulties, and irritable bowel syndrome. FM can cause significant levels of disability, with individuals frequently using healthcare resources, and experiencing loss of work days. There is a lack of robust evidence for the effectiveness of pharmacological treatments for FM, with current guidelines all recommending non-pharmacological interventions. Allied Health Professionals at the Royal National Hospital for Rheumatic Diseases, Bath, UK, developed the manualised Fibromyalgia Self-Management Programme (FSMP); a non-pharmacological, multidisciplinary exercise and education group intervention. The main aims of the FSMP are to provide condition-specific, patient centred, education and exercise advice, supporting the development of core, self-management skills. The FSMP comprises 2.5 hour weekly sessions over six weeks or 4 hour weekly sessions over four weeks. Core components include education about FM, sleep hygiene, goal-setting, pacing, hydrotherapy, and dietary advice. As the FSMP was developed clinically there has been little opportunity for the clinical team to fully understand the mechanisms by which it is effective. To inform successful widespread implementation, this research aimed to map the FSMP to the Michie Behaviour Change Taxonomy (BCT) to determine the mechanisms that facilitate the patient's ability to self-manage FM.

Methods: Non-participatory observations were conducted of the four week and six week FSMP. Comprehensive field notes on the content of the course, therapist delivery, and any additional content not included in the manual were recorded. Subsequently, semi-structured interviews were conducted with both therapists (n=4) and patients (n=9). Observations and the review of the therapist manual data were deductively coded in NVIVO to the BCT using Framework Analysis. Interview data were analysed using Theoretical Thematic Analysis.

Results: Review of the course manual and session observations showed that the FSMP coded onto 12 of the 16 main areas of the taxonomy, encompassing 22 behaviour change techniques. Patient's interviews indicated that they had made substantial behaviour changes as a result of attending the course including; increased activity levels; pacing; better quality sleep and improved communication with family members. Patients reported positive changes to symptoms as a result of attending the course. Therapists highlighted four key challenges in delivering the course; fidelity between therapists; patient readiness and acceptance of FM; group management; and patient fatigue while attending the programme.

Conclusion: The FSMP uses a range of behaviour change techniques. Patients who attended the course made changes to their behaviour, which enabled them to manage their symptoms of FM more effectively.

Disclosure: J. Pearson, None; K. Whale, None; N. Walsh, None; S. Derham, None; J. Russell, None; F. Cramp, None.

Improvement in Fibromyalgia Symptoms and Skin Biopsy Results in Patients with Fibromyalgia and Small Fiber Neuropathy Treated with Intravenous Immune Globulin Infusion(IVIG)

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Small fiber neuropathy is often a challenging clinical problem; patients with small fiber sensory neuropathy commonly have severe complaints but only minimal objective abnormalities on examination. Because it affects mainly small, unmyelinated nerve fibers, standard electrophysiological testing is often normal, and skin biopsy was proven to be diagnostic with sensitivity in 88% of cases in one study. The purpose of this study is to assess the effectiveness of IVIG in the treatment of SFN in patients with Fibromyalgia both subjectively (patient reported improvement in symptoms) and objectively by measuring nerve fiber density through skin biopsy before and after 6 months of treatment.

Methods: Our study is an interventional open labelled treatment trial, involving 7 patients diagnosed with Fibromyalgia according to ACR criteria and had symptoms of SFN (ranging from chronic extremity pain, numbness or tingling) All the 7 patients were diagnosed by Small fiber neuropathy after undergoing a 3 mm punch skin biopsy (1 on the thigh and one on the lower leg, as approved by the American Academy of Neurology) and the decrease in nerve fiber density was used for diagnosis of SFN) All patients after being diagnosed with SFN on skin biopsy got 6 months of weight based IVIG treatment (2gm/kg). Objective effectiveness of IVIG therapy was assessed by a repeat post treatment biopsy after completing the 6 months of treatment. Subjective effectiveness was assessed by patient-filled FIQR questionnaires before and after treatment.

Patient demographics:

Age groups	42-68	
Male: Female ratio	1:6	
Prevalence of Fibromyalgia	7 of 7 patients	100%
Prevalence of Rheumatoid	3 of 7 patients	42.86%
Prevalence of Sjogren's disease	4 of 7 patients	57.14%
Prevalence of Sarcoidosis	1 of 7 patients	14.29%
Prevalence of vitamin D deficiency	3 of 7 patients	42.86%

Results: Revised Fibromyalgia Impact Questionnaire (FIQR) results before and after treatment:

Patient	FIQR score before treatment	FIQR score after treatment	Magnitude of improvement change
1	85	27	58
2	70	48	22
3	27	0	27
4	64	41	23
5	83	58	25
6	23.6	9.3	14.3
7	78	71	7

Nerve fiber diameter on skin Biopsy before and after treatment:

Pt	Pretreatment upper thigh nerve fiber diameter	Post-treatment upper thigh nerve fiber diameter	Magnitude of change in upper thigh nerve diameter	Pretreatment lower leg nerve fiber diameter	Post-treatment lower leg nerve fiber diameter	Magnitude of change in lower leg nerve diameter	Net change of nerve fiber diameter
1	3.9 mm	9.3 mm	+5.4 mm	5.3 mm	12.4 mm	+7.1 mm	+12.5 mm
2	5.0 mm	3.5 mm	-1.5 mm	0.4 mm	1.6 mm	+1.2 mm	-0.3 mm
3	3.6 mm	11 mm	+7.4 mm	0.4 mm	0.8 mm	+0.4 mm	+7.8 mm
4	4.3 mm	9.5 mm	+5.2 mm	0.3 mm	0.0 mm	-0.3 mm	+4.9 mm
5	2.6 mm	4.9 mm	+2.3 mm	1.2 mm	6.8 mm	+5.6 mm	+7.9 mm
6	4.6 mm	9.9 mm	+5.3 mm	5.5 mm	4.3 mm	-1.2 mm	+4.1 mm
7	3.0 mm	3.6 mm	+0.6 mm	1.5 mm	4.5 mm	+3 mm	+3.6 mm

Mean improvement changes of FIQR score is 25, mean improvement of upper thigh nerve diameter is 3.5 mm, and mean improvement of lower leg nerve diameter is 5.7 mm.

Conclusion: As shown in our study, IVIG has been proven to be very effective in improving SFN on both the clinical and the pathophysiologic levels and should be considered for the routine management of this underdiagnosed, yet very troublesome and crippling disease. Larger scale studies are definitely needed to confirm these results and facilitate the wider use of IVIG in treatment.

Disclosure: S. Metyas, None; H. Youssef, None; C. Chen, None; A. Quismorio, None; J. Bui, None.

Abstract Number: 246

Factors Associated with Disability in a Prospective Cohort of Complex Regional Pain Syndrome Type 1

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Complex regional pain syndrome (CRPS) is a form of chronic pain that usually affects an arm or a leg. CRPS typically develops after an injury, a surgery, a stroke or a heart attack. The pain is out of proportion to the severity of the initial injury. CRPS is uncommon, and its cause isn't clearly understood.

Methods: To estimate the percentage of patients with CRPS who develop disability and its associated factors. **Consecutive** patients older than 18 years old whose met Budapest criteria for CRPS type 1 were included. Demographic variables, time of follow-up, main cause of the disease and location, time between trauma and starting treatment were recorded from the electronic clinical history (ECH). Previous immobilization, type were recorded. of treatment, response to it and clinical manifestations. Disability was defined when there was a change in work activity.

Results: 98 patients were included with at least one year of follow up, 65.3% were women. The median age is 54 years (45-61), presented the following clinical patterns: pain 69.7%, inflammation 39.7%, dysautonomic phenomena 33.6% and motor alterations 21.4%. The main cause that triggered the SDRC was fracture in 60.2%, followed by 15.3% in contusion and 14.2% in soft tissue trauma, of which 66% corresponds to upper limb and 37% to lower limb. With respect to the diagnosis, a 3-step scintigraphy compatible with CRPS was obtained in 70.4% of the cases. In the radiographic evaluation, patchy osteopenia was the predominant pattern in 28.5% of the cases. Regarding the treatment, it was distributed: 74.4% received immobilization indication. 56% of patients received oral bisphosphonate and 32% EV. It was also found that 60% of patients used vitamin D and calcium, NSAIDs in 30%, corticosteroids in 23.4% and 29.5% of adjuvant medication during the course of the disease. 66.3% of patients performed rehabilitation as part of their treatment. 67.3% had some response to treatment and 50% had a good response to treatment. The prevalence of disability was 60%. In the univariate analysis, this was associated with: Precise indication of rehabilitation (0.001), Greater use of NSAIDs (p: 0.004) positivity in bone scintigraphy (0.044), dysautonomic phenomena (0.025), and negatively with good response to treatment (p: 0.000). In the logistic regression analysis using disability as a dependent variable, we found a significant and independent association with indication of rehabilitation (OR: 4.3 CI: 1.3-14) and response to treatment (OR: 0.078 CI: 0.023-0, 2).

Conclusion: 60% of the patients developed disability in their follow-up, they were associated independently with the indication of rehabilitation and in a negative way with a good response to treatment.

Disclosure: E. Sanchez Prado, None; A. Ruta, None; J. Torres Chichande, None; F. Salvatori, None; S. Magri, None; R. García Salinas, None.

Fibromyalgia Patients Often Receive Several Rheumatic Disease Diagnoses

Robert S. Katz¹ and Jessica L. Polyak², ¹Rush University Medical Center, Chicago, IL, ²Rheumatology Associates S.C., Chicago, IL

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: In a written office questionnaire, we asked patients the number of rheumatic disease diagnoses they had been given. We also asked about the length of time from the start of symptoms to receive a rheumatic disease diagnosis, how many doctors were seen, and whether the patient agrees with the current rheumatic disease diagnosis.

Methods: Patients were given an in-office questionnaire, which listed the following rheumatic disease diagnoses. They checked diagnoses that they had received by clinicians.

Results: We asked 155 Fibromyalgia patients and 106 non fibromyalgia rheumatic disease controls, how many diagnosis¹ they have previously been given. The mean age was 52.45 years for fibromyalgia patients and 50.39 years for non FMS rheumatic disease controls.

Conclusion: Fibromyalgia patients receive multiple rheumatic disease diagnoses more often than other rheumatic disease patients. Fibromyalgia can be difficult to diagnose as patients often report widespread pain and subjective joint swelling, yet the clinician does not find synovitis on exam. The use of the 2011 published ACR criteria sheet developed for the diagnosis may assist the clinician and the patient in making the diagnosis of fibromyalgia. Having at least 12 points on this 31-point scale suggests the likelihood of the patient having fibromyalgia.

		FMS (N=191)	Non-FMS (N=130)	Two- sided P- value
Number of Diagnoses	0 [n (%)]	27 (14.1)	25 (19.2)	0.0060*
	1 [n (%)]	110 (57.6)	86 (66.2)	
	2 [n (%)]	46 (24.1)	18 (13.9)	
	3 [n (%)]	7 (3.7)	0 (0)	
	4 [n (%)]	1 (0.5)	1 (0.8)	
	Mean (SD)	1.19 (0.737)	0.97 (0.634)	
	Median	1.0	1.0	
	Min, Max	0, 4.0	0, 4.0	
How many doctors did you see prior to diagnosis? ^{2,3}	N (number responded)	155 pts	106 pts	0.0042*
	Mean (SD)	3.12 (3.089)	2.06 (0.893)	
	Median	2.0	2.0	
	Min, Max	1.0, 20.0	1.0, 5.0	
How long before start of symptoms to diagnosis (months)? ¹	N (number responded)	148 pts	98 pts	0.3035
	Mean (SD)	43.23 (61.878)	45.07 (75.247)	
	Median	24.0	24.0	
	Min, Max	1.0, 504.0	1.0, 540.0	
Agree with diagnosis? ^{2,3}	Yes [n (%)]	141 (84.4%)	102 (90.8%)	0.0325*
	No [n (%)]	0 (0%)	2 (1.8%)	
	Unsure [n (%)]	26 (15.6%)	11 (10.4%)	

1. Non-parametric Wilcoxon Mann-Whitney U test was used to derive the two-sided p-value.

2. A Fisher exact test was used to derive the two-sided p-value.

3. 41 patients' results were missing from this analysis.

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

Abstract Number: 248

The Emotional Quotient in Fibromyalgia Patients Is Similar to Rheumatic Disease Controls

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: There is IQ, the intelligence quotient, and EQ, the emotional quotient. EQ refers to emotional intelligence or the emotional intelligence quotient, the ability to use emotional information to guide thinking and behavior. It also refers to the ability to adjust emotions to achieve one's goals.

We wondered whether patients with fibromyalgia might have a poor emotional quotient and not be able to handle their symptoms well. We administered an in-office questionnaire to evaluate EQ.

Methods: We administered an in-office questionnaire to patients with fibromyalgia and non-fibromyalgia rheumatic disease controls. Included were 10 questions, each graded 0-4, regarding social/emotional awareness. We compared the results from patients with fibromyalgia syndrome meeting the 2010 ACR criteria for the diagnosis and those with other rheumatic diseases.

Results: There were 160 females and 31 males in the fibromyalgia syndrome group, and 82 females and 48 males in the non-fibromyalgia rheumatic disease patient group. The mean age of the fibromyalgia patients was 52.45 years for females and 50.39 years for males. The mean age of the patients with other rheumatic disease was 55.23 years for females and 54.02 years for males. 66.5% of the FMS patients and 57.7% of the no-FMS patients were married. The mean HAQ scores in FMS patients was 3.1 and in non-FMS rheumatic disease patients was 1.7 (p 0.001). Patients with FMS had an emotional quotient scale of 33.0 compared with 32.0 for rheumatic disease controls, p 0.84. There was no statistically significant difference between the two groups.

Conclusion: There was not a statistically significant difference between patients with fibromyalgia and non-FMS rheumatic disease patients with regard to their emotional quotient or social/emotional awareness. It does not appear from the results of this study, that fibromyalgia patients are less equipped to handle their symptoms. Rather, their symptoms may overwhelm them because of the intensity, and not necessarily from an inability to cope with them emotionally.

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

Abstract Number: 249

Patients with Fibromyalgia May be Fearful of Developing Dementia Despite Lack of Concrete Evidence of Cognitive Decline

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Core features of cognitive dysfunction in fibromyalgia are memory loss and disturbance in mental clarity. The present study examines if disturbance in mental clarity, a core feature of fibromyalgia, shapes the fear of falling prey to Alzheimer's in rheumatic disease groups with and without fibromyalgia.

Methods: The self administered form of the new ACR criteria for fibromyalgia along with the Mental Clutter Scale were administered to 246 consecutive patients at a single office site. Scores on the new ACR criteria of ≥ 12 formed the fibromyalgia group. Scores ≥ 4 defined disturbance in mental clarity. Risk of Alzheimer's disease, as judged by the patient, was measured on a 0 to 100 chance scale.

Results: Perception of risk substantially increased with sharp reductions in mental clarity often referred to as brain fog, with risk increasing from 18.7 ± 20.7 to 46.2 ± 20.6 $p < 0.01$ in the fibromyalgia group, and from 22.0 ± 23.2 to 41.1 ± 25.3 , $p < 0.01$ in controls. The percentage of people who perceived high risk was significantly higher among fibromyalgia patients (40.6% vs. 19.3%, $p < 0.01$). The age of risk perception was very similar in the two groups (fibromyalgia 47.4 ± 9.9 vs. 49.6 ± 9.8 , $p = .38$).

Conclusion: Fear among people with fibromyalgia that Alzheimer's will strike them is often presumed to be due to the development of memory problems in their young years. This is the first known evidence of an association between perceived risk of Alzheimer's disease in fibromyalgia and poor mental clarity, a core component of cognitive dysfunction in fibromyalgia. At the average age of 47, the risk views of the fibromyalgia group will be a costly burden in the years to come. Yet, there is no evidence that the cognitive problems of fibromyalgia transition to Alzheimer's later in life. A better understanding of the cognitive problems of fibromyalgia among clinicians would be an important advance.

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

Abstract Number: 250

Fibromyalgia Patients Do Not Appear to Obsess about Their Symptoms Compared with Other Rheumatic Disease Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: We wanted to know if fibromyalgia patients tend to obsess about their symptoms, and whether this might aggravate the complaints that they experience. We administered an obsessive-compulsive disease scale (1-3 for each question), as part of a questionnaire to patients in an office rheumatology practice.

Methods: Patients in an office rheumatology practice were given a questionnaire, which included a scale of obsessive-compulsive symptoms. The obsessive-compulsive questions were the following (each question 1-3):

1. I am worried about dirt, germs, and viruses.
2. I wash my hands very often or in a special way to be sure that I am not dirty or contaminated.
3. I must check the stove or other electrical appliances that I have locked the door, to make sure that things have not disappeared.
4. I get a compelling urge to put my things in a special order.
5. Do you have unwanted ideas, images, or impulses that seem silly, nasty or horrible?
6. Do you persistently engage in actions or behaviors that you feel compelled to do, but seem to make little sense and are unrewarding?

Results: There were 160 females and 31 males in the fibromyalgia syndrome group, and 82 females and 48 males in the non-fibromyalgia rheumatic disease patient group. The mean age of the fibromyalgia patients was 52.45 years for females and 50.39 years for males. The mean age of the patients with other rheumatic disease was 55.23 years for females and 54.02 years for males. 66.5% of the FMS patients and 57.7% of the no-FMS patients were married. The mean HAQ scores in FMS patients was 3.1 and in non-FMS rheumatic disease patients was 1.7 ($p = 0.001$). Fibromyalgia syndrome (FMS) patients met the 2010 ACR criteria for the diagnosis.

The obsessive-compulsive scale symptom total was 15.7 in FMS patients and 15.7 in non FMS rheumatic disease patients. $p = 0.84$. The results were not statistically significant.

Conclusion: Patients with fibromyalgia do not appear to be more obsessive-compulsive compared to rheumatic disease controls. Though fibromyalgia patients often have intense subjective symptoms, they do not appear to become more obsessive about their health problems, compared to non FMS rheumatic disease patients.

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

Using the Stroop Word Naming Test and the Mental Clutter Scale in Fibromyalgia Patients to Evaluate the Symptoms of Fibrofog in Office Testing of Cognitive Complaints

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: We have found that the Stroop word naming test is useful in evaluating fibromyalgia patients with cognitive symptoms, especially in those describing word retrieval problems. It is possible that the slower processing of information may disturb the synchrony of neural circuits and lead to some of the symptoms of cognitive dysfunction in fibromyalgia patients. The Mental Clutter Scale is also valuable in the assessment of cognitive problems.

Methods: We administered the Stroop word naming test and the Mental Clutter Scale to rheumatic disease patients in a rheumatology office practice.

Results: There were 28 patients (27 females and 1 male), in the fibromyalgia syndrome group, and 42 (28 females and 14 males), in the non-fibromyalgia rheumatic disease patient group. The mean age of the fibromyalgia patients was 50.66 years for females and 45 years for males. The mean age of the patients with other rheumatic disease was 53.14 years for females and 48.86 years for males. Fibromyalgia syndrome (FMS) patients met the 2010 ACR criteria for the diagnosis. The mental clutter score in those with fibromyalgia was 3.8 ± 2.2 and was 2.2 ± 1.6 in patients with other rheumatic diseases, $p < 0.001$

Conclusion: Fibromyalgia patients have an abnormal Stroop word naming speed. The test is simple to administer. When attempting to evaluate patients with cognitive dysfunction, it can be a helpful test to screen for fibrofog. This test, in addition to the Mental Clutter Scale, can be given in the office, and can help to evaluate patients who are concerned about cognitive dysfunction.

One theory based on the abnormal Stroop test is that fibromyalgia patients appear to be “a beat behind” in their cognitive functioning. Perhaps, when they are sitting at a group meeting, they are not quite following the content because of a slowing of some neural circuits.

Disclosure: R. S. Katz, None; L. Kwan, None; J. Anilao, None; E. Mitchell, None; J. L. Polyak, None.

Publication Bias Regarding Scientific Studies about Fibromyalgia

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: It is estimated that approximately 5 million people in the United States suffer from Fibromyalgia. That's compared to 1.3 million adults with rheumatoid arthritis and about 250,000 with systemic lupus.

Methods: We reviewed six major rheumatology journals over a two-year period to assess the number of articles written regarding rheumatoid arthritis, lupus, osteoarthritis, ankylosing spondylitis, and psoriatic arthritis. The journals reviewed were Arthritis and Rheumatology; The Annals of Rheumatic Disease; The Journal of Clinical Rheumatology; Nature Reviews of Rheumatology; Arthritis Care and Research; and Seminars in Arthritis and Rheumatism.

Results: We found the number of publications for rheumatoid arthritis, lupus, osteoarthritis, psoriatic arthritis, ankylosing spondylitis, and fibromyalgia as the following:

Conclusion: Research papers regarding lupus appeared 13 times more often in these six rheumatology journals compared with fibromyalgia articles. Rheumatoid arthritis studies were 26 times more frequently included, compared to articles on fibromyalgia, in these journals.

Publication bias could have critical adverse consequences for the 5 million people in the United States that carry the diagnosis of fibromyalgia.

Journal editors need to carefully consider the origins of this bias, the damaging effects on treatment advances for patients who carry the diagnosis, and ways of ameliorating this situation.

Publication bias limits the amount of literature on fibromyalgia that clinicians can use to synthesize and learn from. It can also distort the importance of the disease entity in the mind of the reader.

Chi squared test of equal proportions between all groups

The FREQ Procedure

disease	Frequency	Percent
AS	141	5.35
FMS	20	0.76
H	1318	50.00
LUPUS	268	10.17
OA	299	11.34
PSA	66	2.50
RA	524	19.83
Total	2636	100.0

Chi-Square Test for Equal Proportions	
Chi-Square	3199.7109
DF	6
Pr > ChiSq	<.0001

Sample Size = 2636

Chi squared test of equal proportions between LUPUS and FMS

The FREQ Procedure

disease	Frequency	Percent
FMS	20	8.94
LUPUS	268	93.06
Total	288	100.0

Chi-Square Test for Equal Proportions	
Chi-Square	213.1536
DF	1
Pr > ChiSq	<.0001

Sample Size = 288

Chi-squared test of equal proportions between RA and FMS

The FREQ Procedure

diagnosis	Frequency	Percent
FMS	20	3.68
RA	524	96.32
Total	544	100.0

Chi-Square Test for Equal Proportions	
Chi-Square	166.9417
DF	1
Pr > ChiSq	<.0001

Sample Size = 544

Articles on lupus, with a prevalence of less than 300,000, appeared in these rheumatology journals 13 times compared with articles about fibromyalgia, with a prevalence of 5 million. It is likely that manuscripts of fibromyalgia face greater publication hurdles than other rheumatic diseases.

Disclosure: R. S. Katz, None; L. Kwan, None; F. Leavitt, None.

Abstract Number: 253

Fibromyalgia Patients Are Frequently Thought to be Challenging to Treat- Are They?

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Fibromyalgia patients can be time consuming to treat and difficult to manage. Especially challenging fibromyalgia patients tend to have many symptoms, ask many questions, are sometimes non-believing in their diagnosis. Some call this group 'catastrophizers'. We evaluated the difficulty of caring for fibromyalgia patients in a rheumatology office practice.

Methods: A rheumatologist and a rheumatology nurse both independently assessed the perceived difficulty of taking care of individual fibromyalgia patients. The difficulty of caring for each patient was discussed between the doctor and the rheumatology nurse until there was an agreement. Each patient met the 2010 ACR criteria for the diagnosis. Patients were rated on a scale of one through three to indicate how challenging and exhausting they were to treat. (1 = easy; 2= moderate; 3 = difficult) Factors considered included the patient's attitude and needs, the difficulty to treat, time spent compared with treating other rheumatic disease patients, and, in general, how challenging they were as patients.

Results: 350 fibromyalgia patients followed in a rheumatology office practice were evaluated. 132 (37.7%) patients were judged to be in Category One, easy to care for. 170 (48.6%) patients were considered to be in Category Two, moderately challenging for the rheumatologist and nurse. 48 (13.7%) patients were judged to be in Category Three, especially difficult to care for.

Conclusion: Most fibromyalgia patients (86.3%) were rated by the rheumatologist and nurse as moderate or easy to care for. These patients appreciated the care given and the expertise, and were willing to consider lifestyle changes and medication.

Only 13.7% of the fibromyalgia patients in this office practice were considered to be exhausting and especially challenging to care for.

Fibromyalgia patients have an undeserved reputation for being extremely difficult to care for. The majority are not.

Disclosure: R. S. Katz, None; L. Kwan, None.

Abstract Number: 254

The Lumbar Spine Is Straight in Fibromyalgia Patients

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Previously we investigated the lack of alordotic curve in the cervical spine seen on lateral view x-rays in patients with fibromyalgia compared with patients without fibromyalgia. One hypothesis is that the muscle pressure is increased in fibromyalgia, and that this can lead to straightening of the neck. We evaluated these changes in the lumbar spine.

*Two sample t-test to compare:
L-1 L-4 Cobb Angle between FMS & Non-FMS*

group	Method	N	Mean	Std Dev	Std Err	Minimum	Maximum
FMS		61	11.0000	7.3371	0.9394	0.0000	37.0000
NOFMS		19	18.7368	6.4291	1.4726	10.0000	33.0000
Diff (1-2)	Pooled		-7.7368	7.6333	1.8747		

Method	P-value
Pooled	<.0001

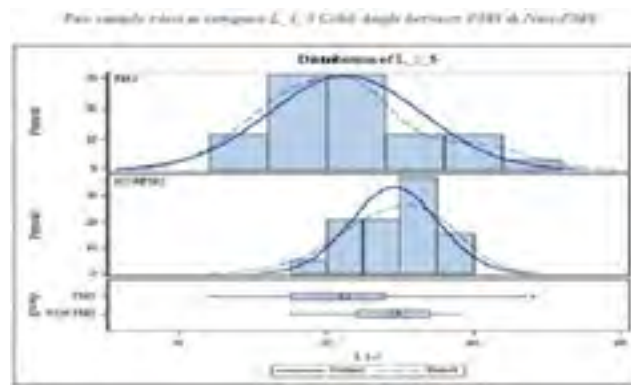
Equality of Variances				
Method	Num DF	Den DF	F Value	Pr > F
Folded F	60	18	1.31	0.5401

*Two sample t-test to compare:
L-1 L-5 Cobb Angle between FMS & Non-FMS*

group	Method	N	Mean	Std Dev	Std Err	Minimum	Maximum
FMS		61	22.3574	10.3996	1.3315	4.0000	48.0000
NOFMS		19	29.2105	6.0218	1.3820	15.0000	38.0000
Diff (1-2)	Heteroscedastic		-6.8531		1.0191		

Method	P-value
Heteroscedastic	0.0001

Equality of Variances				
Method	Num DF	Den DF	F Value	Pr > F
Folded F	60	18	2.08	0.0125



Methods: Patients with and without fibromyalgia who had x-rays of the lumbar spine had a measurement of the Cobb angle between the top of L1 to the bottom of L4 and the top of L1 to the bottom of L5.

Results: There were 61 patients (55 females and 6 males), in the fibromyalgia syndrome group, and 19 (11 females and 8 males), in the non-fibromyalgia rheumatic disease patient group. The mean age of the fibromyalgia patients was 47.90 years for females and 44.66 years for males. The mean age of the patients with other rheumatic disease was 60.72 years for females and 46.62 years for males. Fibromyalgia syndrome (FMS) patients met the 2010 ACR criteria for the diagnosis.

Conclusion: Fibromyalgia patients have a straight lumbar spine when compared to controls without fibromyalgia. A straight lumbar spine, in addition to a straight cervical spine, which has previously been reported, suggests increased muscle tension in fibromyalgia patients. Elevated muscle pressure may be the cause of pain in patients with fibromyalgia, and clinicians can use the straight cervical spine and straight lumbar spine as additional support for the diagnosis of fibromyalgia. A straight lumbar spine may also be a window into the etiology of fibromyalgia.

Disclosure: R. S. Katz, None; J. L. Polyak, None; B. J. Small, None; A. Farkasch, None.

Abstract Number: 255

Interpretation of Proverbs Compared with the Mental Clutter Scale in Fibromyalgia Patients Demonstrates Intact Intellectual Ability Despite the Symptoms of Fibrofog

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Fibromyalgia patients frequently have cognitive dysfunction (fibrofog). We compared cognitive ability using an interpretation of proverbs with reported poor mental clarity and other fibrofog symptoms.

Methods: Patients meeting the 2010 ACR criteria for fibromyalgia and rheumatic disease controls were given 10 proverbs to interpret. The proverbs were listed on a form, and five potential explanations were given the patients. Patients circled the correct response.

Table: List the proverbs: :

1. The pen is mightier than the sword.
2. People who live in glass houses should not throw stones.
3. Birds of a feather flock together.
4. There is no such thing as a free lunch.
5. The squeaky wheel gets the grease.
6. Too many cooks spoil the broth.

7. Necessity is the mother of invention.
8. A chain is only as strong as its weakest link.
9. You can lead a horse to water, but cannot make it drink.
10. Keep your friends close and your enemies closer.

Results: 109 fibromyalgia patients (mean age 50 y.o.) and 157 rheumatic disease control patients (mean age 53.5 y.o.) were given the list of the 10 proverbs. The fibromyalgia patients scored 73% of the answers correct. The rheumatic disease control patients scored 71% of the answers correct. There was no statistical difference between the two groups. On the mental clutter scale, the mean score for Fibromyalgia patients was 3.8 ± 2.2 ; and the mean score for rheumatic disease patients was 2.2 ± 1.6 , $p < 0.001$. A mental clutter score of 3.8 is an abnormal score and is associated with brain fog.

Conclusion: Proverb interpretation requires the ability to think abstractly and is often impaired in the early stages of dementia.

There was no relationship between the mental clutter scores and cognitive ability based on the interpretation of proverbs. This suggests that while fibromyalgia patients report a lack of mental clarity and other fibrofog symptoms, their intellectual function appears to be intact, and this likely reassures them that they are not developing dementia. Even with the difficulties they experience regarding memory, concentration, and mental foginess, fibromyalgia patients do not appear to be developing dementia.

Disclosure: R. S. Katz, None; L. Kwan, None.

Abstract Number: 256

The Effectiveness of Medications for Fibromyalgia Based on Patient Experiences

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: We asked patients with fibromyalgia to rank the effectiveness of medications they have tried.

Methods: In a rheumatology office practice, 95 patients (mean age 50.5) who met the 2010 ACR criteria for fibromyalgia (88 females and seven males) completed an in-office questionnaire regarding the effectiveness of various medications used to treat fibromyalgia. The medications included pregabalin, gabapentin, duloxetine, various muscle relaxants, sleep aids, stimulants, pain medications, and nonsteroidal anti-inflammatory medicines. Patients rated the medications on a 1 to 4 scale from not helpful to very helpful.

Results: See tables

Conclusion: There were much higher effectiveness results for pain medications, sleeping aids, stimulants, muscle relaxants, and anti-inflammatory drugs than for pregabalin and duloxetine, which are both FDA-approved medications. Fibromyalgia patients in this office survey concluded that the FDA approved medications for fibromyalgia were ineffective compared with other medications tried for this disorder.



Medications	Patient	Mean VAS (1-3)
Pain Medications	70	2.814
Sleeping Aids	72	2.778
ADD Medications	34	2.647
Stimulants	35	2.486
Muscle Relaxers	78	2.436
NSAIDs	81	2.304
Pregabalin	43	1.256
Duloxetine	44	1.023
Gabapentin	30	0.733

Disclosure: R. S. Katz, None;

Abstract Number: 257

Argentine Registry of Patients with Fibromyalgia

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Fibromyalgia (FM) has been reported in up to 5% of adult population and its treatment still represents a challenge. In Argentina, there are few records describing the different aspects of FM patients. Therefore, the aim of the study was to describe the frequency of FM patients consults in daily practice and to analyze these patient characteristics.

Methods: Multicenter, observational, cross-sectional study that included a total of 759 patients with FM (ACR 1990 and/or ACR 2010 criteria). The number of consultations performed from January to June of 2017 (both the total consultations and those of patients with FM) was recorded. For each patient with FM, we collected the following data: age, gender, health insurance provider, whether it was the first time consulting a physician, professional who referred the patient, duration of FM, presence of concomitant autoimmune disease, comorbidities and treatment. **Statistical analysis:** Descriptive analyses of the clinical characteristics were performed, using absolute numbers and proportions for categorical variables, and means and medians, standard deviation (SD) and interquartile range (IQR) for numerical variables. Frequency of FM consultations with the corresponding 95% confidence interval was determined. We compared demographic and disease characteristics according to health insurance provider, public care and presence of comorbidities by means of chi-square or T-student test.

Results: A total of 759 patients (12 children) from 15 rheumatology centers were included. According to the complete registries from 6 centers, from a total of 7350 visits in a 6-month period, the frequency of FM patients consults was 10.4% (CI95 9.7-11.1). Out of 747 adult patients, 95% were women, median age 52 (SD 12.6), 9% were consulting for the first time and 78% had a health insurance. Median duration of FM was 24 months (IQR 10-48). Most patients resulted from referrals from General Practice (54%) and Traumatology (28%). About 28% of the patients have a concomitant autoimmune disease, being RA and Hypothyroidism present in more than 30% of the cases. Hypertension and Osteoarthritis were the most frequent comorbidities reported. Most patients (96%) were on pharmacological treatment (80% Pregabalin). The most frequent non-pharmacological treatments were kinesiotherapy (40%) and physical activity (27%). Patients from the public health system (36%) showed higher probability of being referred by other specialists (69 vs 48%, $p<0.001$), longer duration of FM (55 vs 32 months, $p<0.0001$) and less number of doctors previously consulted (2 vs 3, $p<0.0001$). Out of 12 pediatric patients (all referred by other specialists), 11 were girls, mean age 13 (SD 3). Median duration of symptoms was 10 months (ICQ 7-48); 75% were treated with NSAIDs and 25% with Pregabalin; 92% were on kinesiotherapy and 85% on psychotherapy.

Conclusion: Until the date, this is the largest Argentine registry of FM patients, including a large number of patients (both adult and pediatric) and many participating centers. We believe that this registry could provide evidence-based socio-demographic data, useful not only for clinical trials but also to improve treatment strategies in FM.

Disclosure: J. Sosa, None; S. B. Papisidero, None; D. S. Klajn, None; M. P. Kohan, None; J. Á. Caracciolo, None; R. I. Trobo, None; C. Romeo, None; G. Casado, None; D. Gilberto, None; J. C. Calcagno, None; G. Pendón, None; F. Giordano, None; D. Pereira, None; A. Munarriz, None; D. Mónica, None; D. Scublinsky, None; A. Bohr, None; A. Perez Davila, None; I. Petkovic, None; S. Petruzzelli, None; J. Hofman, None; M. S. Espósito, None; V. Ortiz, None; S. Visentini, None; A. Vulcano, None; A. B. Pringe, None; M. Herrera Calvo, None; M. Hu, None; G. F. (Grupo de Estudio de la Sociedad Argentina de Reumatología), None.

Abstract Number: 258

Association of Sudoscan Values with Disease Duration in Female Patients with Fibromyalgia

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Fibromyalgia is characterized by chronic widespread pain. The patients with fibromyalgia complain of symptoms such as fatigue, sleep disturbance and intermittent palpitation, suggesting the potential contribution of autonomic dysfunction in the pathogenesis of the disease. Although dysfunction of autonomic nervous system is common in fibromyalgia patients, there is still a lack of simple methods for the assessment of autonomic dysfunction in the disease. Assessment of sudomotor function has been recently proposed to explore peripheral autonomic sympathetic function. In the present study, we investigated the sudomotor function by using a rapid, objective and non-invasive method in female patients with fibromyalgia.

Methods: Cross-sectional study included 23 female patients with fibromyalgia (mean age 51.1 ± 8.5 , disease duration 13.6 ± 14.7 months) and 29 age-matched healthy controls (HC) subjects. Electrochemical skin conductance (ESC) of hand and feet were measured with the SUDOSCAN (Impeto Medical, France). Fibromyalgia severity was assessed by fibromyalgia impact questionnaire (FIQ) and pain visual analogue scale (VAS). Toronto clinical neuropathy score (TCNS) was applied

in the enrolled subjects. During the sudomotor test, patients were asked to place their bare hands and feet on large electrodes. The test took 2~3 min to carry out without pain.

Results: Hand (58.8 ± 16.9 microSiemens (μS) vs. 64.9 ± 11.7 μS) and feet ESC values (65.8 ± 12.2 μS vs. 69.3 ± 9.4 μS) tended to be lower in female patients with fibromyalgia, compared to those of HC subjects, although the differences were not statistically significant. TCNS in fibromyalgia patients was significantly higher than HC subjects (7.4 ± 2.1 vs. 1.4 ± 0.9 , respectively). There was no association between the hand or feet ESC values and FIQ, pain VAS, TCNS, or body mass index. Interestingly, there were significant negative correlation between fibromyalgia duration and ESC values of hand and feet (spearman's correlation coefficient ; -0.523 and -0.635, respectively).

Conclusion: Our study identified that this quick and non-invasive method to assess sudomotor function might represent the pathologic changes of autonomic nervous system in female patients with fibromyalgia. Further longitudinal study with a larger number of participants is needed to elucidate the clinical significance of hand and feet ESC values in the disease.

Disclosure: K. M. Ko, None; S. J. Moon, None.

Abstract Number: 259

Prevalence of Attention Deficit Hyperactivity Disorder Among Patients with Fibromyalgia

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Chronic diseases involve cognitive aspects. Attention deficit hyperactivity disorder (ADHD) is a chronic condition, marked by persistent inattention, impaired concentration, hyperactivity, impulsivity, emotional lability, anxiety and disorganized behavior. Fibromyalgia (FM) includes a range of symptoms affecting memory, attention and concentration. High rates of comorbidity between ADHD and FM have been reported, as well as some evidence that patients with both conditions experience heightened symptom severity. In addition, recent studies suggest that vitamin D deficiency is associated with cognitive impairment.

Methods: Consecutive patients, older than 18 years, with diagnosis of fibromyalgia (2010 ACR criteria) seen at the outpatient Rheumatology Unit between May 2016 and April 2017, were included. During the inclusion visit the following data were collected: Revised Fibromyalgia Impact Questionnaire (FIQ-R), HAQ-A (Health Auto Questionnaire-simplified, Argentine validation); pain (Visual Analogue Scale, VAS), fatigue (VAS) and serum 25 -hydroxyvitamin D (25(OH)D) level. During the Neurology visit, the following tests were performed: Conners Continuous Performance Test II (CPT II), Wender-Utah Rating Scale (WURS) and Structured Clinical Interview for Personality Disorders (SCID-II). Descriptive statistics were calculated. Correlations were calculated between CPT II and pain, fatigue, FIQ-R, HAQ-A and 25(OH)D, using Spearman's test.

Results: 37 patients with FM were included. Patients' characteristics are shown in table 1. 73% (n=27) of the patients tested positive for adult ADHD. In 40.7% (11/27) of them, the diagnosis had been missed in childhood. Participants with both FM and a positive adult ADHD screening test did not score significantly higher on the FIQ-R (54.9 , $SD= 16.3$ vs 48.8 , $SD= 11.3$; $p= 0.3320$) and did not have lower vitamin D levels (27.4 ng/ml, $SD= 13.1$ vs 36.7 ng/ml, $SD= 9.6$; $p= 0.1050$). There was a very good positive correlation between ADHD and fatigue ($r= -0.9607$; $p= 0.0086$). No association was found between ADHD and severity of perceived cognitive symptoms ($p= 0.673$). There was no correlation with pain ($r= 0.1688$ $p=0.3325$), HAQ-A ($r= 0.1340$; $p= 0.4429$) or vitamin D level ($r= -0.3211$; $p=0.1176$). No correlation was observed between vitamin D levels and FIQ-R ($r= -0.1848$; $p= 0.3662$). The most frequent personality disorders found were narcissism (32,4%) and obsessive-compulsive disorder (32,4%).

Conclusion: The co-occurrence of adult ADHD in FM was highly prevalent. The diagnosis had been often overlooked in childhood. ADHD was associated with fatigue but not with pain, disease impact or functional capacity. Vitamin D levels were not associated with disease impact or dyscognition. Patients with FM should be assessed for the presence of adult ADHD. More investigations are needed to understand the impact of cognitive disorders in FM.

Table 1.

Characteristics	n= 37
Female, n (%)	34 (92)
Age (years), mean (SD)	58.5 (13.4)
Time from diagnosis (years), mean (SD)	3.9 (3.9)
HAQ-A, mean (SD)	0.74 (0.52)
Pain (VAS, 0-100), mean (SD)	68.6 (22.8)
Fatigue (VAS, 0-100), mean (SD)	72.2 (27.2)
FIQ-R, mean (SD)	53.4 (15.2)
25(OH)D, ng/ml, mean (SD)	29.9 (12.5)
Cognitive complaint, n (%)	25 (67.6)

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Abstract Number: 260

Outcome Expectations and Fibromyalgia: Perceived Benefits of Exercise Are Associated with Self-Efficacy and Physical Performance

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster – ARHP

Session Type: ACR Poster Session A

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

Background/Purpose: Outcome expectancy is recognized as a determinant of exercise engagement and adherence. Higher outcome expectations for exercise (OEE) have been shown to correlate with greater motivation to exercise in patients with osteoarthritis. However, little is known about which factors may influence OEE in fibromyalgia. This is the first study to examine the associations between baseline OEE and demographic, physical and psychosocial variables in patients with fibromyalgia.

Methods: This study is a cross-sectional, secondary analysis of data obtained at baseline evaluation from a single-center, 52-week, randomized comparative effectiveness trial of Tai Chi versus aerobic exercise for participants with fibromyalgia (n=226). Baseline measures included demographics, physical performance, outcome expectancy, self-efficacy, anxiety, depression, stress, social support, and pain coping. OEE was assessed with the 9-item Outcome Expectations for Exercise Scale, where a higher value indicates stronger expectation for a positive outcome. Independent t-test and chi-square test were used to determine the relationship between participant characteristics and high OEE (\geq median of 3.9). Statistical significance was set at $p < 0.05$.

Results: Participants had a mean age of 51.8 years and body mass index of 30.0 kg/m², 92.5% were female, 61.1% were white, and 36.0% possessed at least college-level education. Compared to the lower OEE group, individuals with a higher OEE were more likely to have a greater self-efficacy (5.7 ± 2.2 vs. 4.8 ± 2.0 ; $P=0.001$) and physical performance as assessed by 6-minute walk distance (meters) (423.8 ± 85.8 vs. 382.2 ± 77.6 ; $P<0.001$) or SF-36 physical component (31.8 ± 7.0 vs. 29.6 ± 8.0 ; $P=0.029$). There were no other significant associations.

Conclusion: Our study found that higher OEE was significantly associated with greater self-efficacy and physical performance. Future longitudinal research should explore how these relationships affect long-term exercise engagement for patients with fibromyalgia.

Disclosure: G. Chi, None; J. Marszalek, None; L. L. Price, None; R. R. Bannuru, Fidia, 8; C. Wang, None.

Mindfulness Is Associated with Sleep Quality Among Patients with Fibromyalgia

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster – ARHP

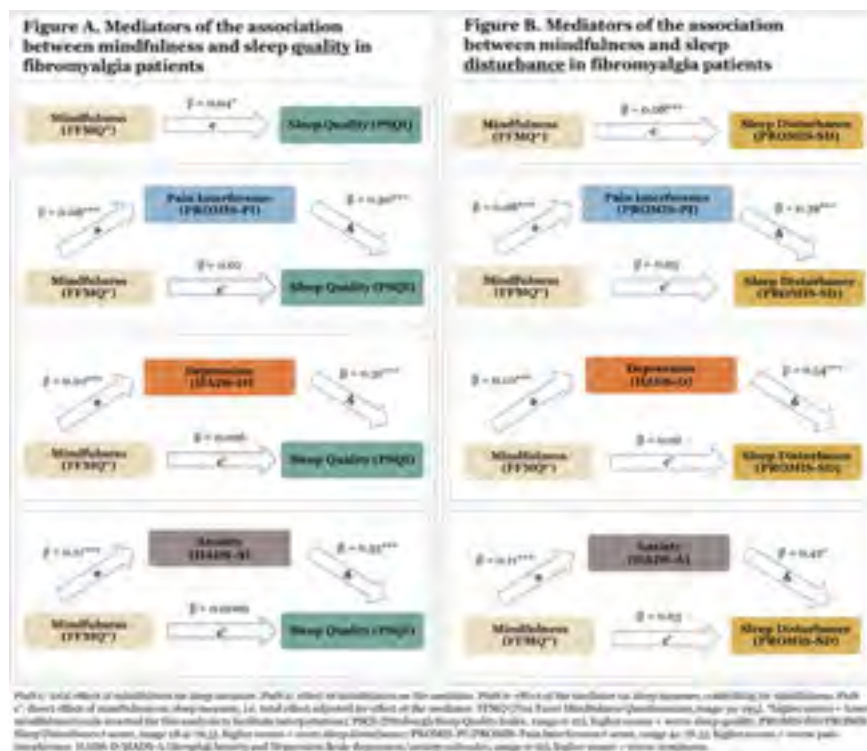
Session Type: ACR Poster Session A

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

Background/Purpose: Poor and disturbed sleep is an important disabling feature of fibromyalgia. Previous studies suggest higher mindfulness may be associated with better sleep quality in people with chronic health problems. However, the role of mindfulness in sleep problems in fibromyalgia remains understudied. We examine the relationships between mindfulness and sleep, psychological health, and pain interference in fibromyalgia patients.

Methods: A cross-sectional analysis of baseline data from a randomized controlled trial in fibromyalgia patients was performed. Measures included mindfulness (Five Facet Mindfulness Questionnaire), sleep quality (Pittsburgh Sleep Quality Index), sleep disturbance (PROMIS Sleep Disturbance), pain interference (PROMIS Pain Interference), anxiety, and depression (Hospital Anxiety and Depression Scale). Pearson correlations were used to examine associations among mindfulness, sleep quality, sleep disturbance, anxiety, depression, and pain interference. Mediation analysis was conducted to assess whether anxiety, depression, and pain interference mediated the association between mindfulness and sleep quality, and the association between mindfulness and sleep disturbance.

Results: A total of 177 patients with fibromyalgia were included (93% female, mean age: 52±12 years, 59% white, BMI: 30±7 kg/m²). Higher mindfulness in patients was associated with better sleep quality ($r = -0.23$, $p = 0.002$) as well as less sleep disturbance ($r = -0.24$, $p = 0.002$), pain interference ($r = -0.31$, $p < 0.0001$), anxiety ($r = -0.58$, $p < 0.0001$), and depression ($r = -0.54$, $p < 0.0001$). In addition, pain interference, depression, and anxiety mediated the association between mindfulness and sleep quality (**Figure A**), and the association between mindfulness and sleep disturbance (**Figure B**).



Conclusion: Higher mindfulness is associated with better sleep quality and less sleep disturbance, pain interference, anxiety, and depression in people with fibromyalgia. Further, higher mindfulness has a significant indirect effect on better sleep in fibromyalgia patients by way of lowering pain interference, depression, and anxiety.

Disclosure: M. Park, None; Y. Zhang, None; L. L. Price, None; R. R. Bannuru, Fidia, 8; C. Wang, None.

Abstract Number: 262

Shedding Light on Fibromyalgia: Emotional Regulation Processes and Executive Functions Join Together

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes Poster – ARHP

Session Type: ACR Poster Session A

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

Background/Purpose: Fibromyalgia (FM) is characterized mainly by the presence of generalized pain accompanied by emotional and cognitive symptoms. The evidence shows that in order to face the emotional consequences of pain, there must be an adequate capacity for self-regulation that is, in part, mediated by executive functions. However, this relationship between the emotional and the cognitive has been scarce studied in FM patients, whose shows a deficit in the use of emotional regulation strategies and executive functions. The purpose of the study was to compare the emotional regulation processes between FM and healthy subjects, and also to explore the relationship between emotional regulation and the processes of executive functions within FM patients.

Methods: 55 FM patients who satisfy the ACR criteria were included, and a healthy group matched by age and sex was also recruited. Both groups completed the Difficulties in Emotional Regulation Scale (DERS). Comparison of the groups was performed by the Student's t-test. For the second purpose of the study, 30 women in the FM group completed the measure of planning and monitoring with the Map of the Zoo (BADS: Behavioural Assessment of the Dysexecutive Syndrome the Map of the Zoo test). For the second purpose, a Spearman's Rho was carried out.

Results: The results found statistically significant differences in all the scales of the DERS ($p < .01$), showing that FM patients had greater difficulties in the emotional regulation process in comparison with a control group. The result of explore the relationship between executive function and emotional regulation showed a negative correlation between the emotional lack of control scale and the total score in formulating ($\rho = -.43$, $p = .04$) and the total score of planning (formulating and executing a plan) ($\rho = -.47$, $p = .03$), and between the interference emotional scale and the formulating ($\rho = -.45$, $p = .04$) and the total score of planning ($\rho = -.44$, $p = .04$).

Conclusion: The results of the present study indicate that, although FM patients do not differ from the control group in the attention or awareness given to their emotional states, they are not able to implement other strategies to regulate that emotional state. Moreover, these problems in the use of emotional strategies could be due to difficulties in the executive processes. Therefore, cognitive function impaired could potentiate alterations in psychological processes, so specific interventions could be designed in order to improve executive function and increasing the use of strategies for emotional regulation.

Disclosure: M. Redondo, None; A. Trucharte Martinez, None; G. Castillo Parra, None; L. Leon, None.

Abstract Number: 263

Racial Disparities in Total Knee Replacement Failure Are Not Explained By Poverty

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Healthcare Disparities in Rheumatology Poster

Session Type: ACR Poster Session A

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

Background/Purpose: U.S. blacks have a higher risk of revision total knee replacement (TKR) than whites, but whether this is mediated by poverty is unknown. The goal of this study was to evaluate racial disparities in TKR failure and determine whether community poverty modifies this risk.

Methods: All black and white NewYork (NY) State residents enrolled in a prospective single-institution TKR registry 2007-2011 were included. Institutional registry patients were linked to the NY Statewide Planning and Research Cooperative System (SPARCS) database (1/1/07-12/31/14) to capture patients who underwent revision TKR at another institution, and the reasons for revision. Patients were linked by geocoded addresses to their residential census tract (CT). Cox regression was used to assess predictors of TKR revision. Next, multivariable logistic regression was used to analyze predictors of TKR failure, defined in two ways: 1. TKR revision in NY State 2 years or less after the initial surgery or; 2. KOOS Quality of Life (QOL) that worsened or improved less than or equal to 7.5 points, or HSS Satisfaction Survey QOL rating of no improvement or worsening 2 years after surgery. Logistic regression was used to estimate the interaction between percent of the CT under the poverty line (CT poverty) and race on TKR failure.

Results: 4529 TKR in 4263 patients were included in the study. 137 (3.0%) required TKR revision, and 330 (17%) experienced TKR failure. Mean age was 68.0 ± 9.8 , 64.1% were female, 8.4% black. Cases came from 1687 unique census tracts and mean CT poverty was $7.7\% \pm 8.1\%$ (a poverty area is defined as 20% or higher). Median follow-up in SPARCS was 63 months. TKR revisions occurred a median of 15.3 months [IQR 8.0- 28.1] after the index surgery. Causes of TKR revision were septic in 26 (19%) and aseptic in 111 (81%) including mechanical failure (n=104, 75.9%), fracture (n=5, 3.7%), other causes (n=2, 1.5%). Compared to aseptic revisions, septic revision cases were older (67.5 vs. 62.4 years, $p=0.028$), had lower volume surgeons ($p=0.019$), and a shorter time to revision (6.3 vs. 17.6 months; $p=0.018$). In multivariable analysis, factors influencing the risk of TKR revision were younger age (HR 0.80 per 5 years; 95% CI 0.74 - 0.86) and disruption of the operative wound during the index surgery admission (HR 8.05; 95% CI 1.12 - 57.7). Three hundred thirty out of 1943 (17%) cases resulted in TKR failure at 2 years. In univariate analysis, risk factors for TKR failure included race, diabetes, and upper respiratory tract infection during the index surgery admission, TKR laterality, patient expectations score, and CT poverty, but in multivariable analysis only black race remained statistically significant (OR 2.18; 95% CI 1.26 - 3.79). There was no interaction between CT poverty and race on the risk of TKR failure.

Conclusion: Blacks are at higher risk than whites of TKR failure, defined as no improvement after TKR or the need for revision, and community level poverty does not modify this risk.

Disclosure: A. R. Bass, None; J. Szymonifka, None; L. A. Mandl, None; B. Y. Mehta, None; E. Y. Lai, None; S. Lyman, None; M. L. Parks, Zimmer Biomet, 2, 5; S. Z. Mirza, None; S. A. Dey, None; S. M. Goodman, Roche, Novartis, 4.

Abstract Number: 264

Relationships between Adverse Childhood Experiences and Health Status in Systemic Lupus Erythematosus

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Healthcare Disparities in Rheumatology Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Adverse childhood experiences (ACEs) such as abuse, neglect and domestic violence are associated with poor adult health status and immune dysregulation. The extent and impact of ACEs on patients with existing autoimmune disease are not known. We compared prevalence of ACE in SLE patients with the general population and investigated relationships between ACEs and health status in SLE patients.

Methods: Data derive from the California Lupus Epidemiology Study (CLUES), a diverse population based cohort of individuals with SLE. Participants completed the ACE questionnaire, a validated 10 item survey covering 3 domains (abuse, neglect and household challenges). We estimated prevalence of ACE in 270 CLUES participants compared to the general population using 2015 California Behavioral Risk Factor Surveillance System data (1:1 matching by county, age, sex and race/ethnicity). We examined 5 patient-reported outcomes (SLE activity, damage, depression, physical function and quality of life) and 3 physician-assessed measures (SLE disease activity, damage and severity indices). SLE outcomes were compared across ACE levels (0, 1, 2-3, ≥ 4) and domains using multivariable linear regression controlling for age, sex, race/ethnicity, disease onset <18 years, and education level. Domain effects were estimated in separate models. Statistical significance was $p < 0.05$.

Results: ACE levels and domains were similar for SLE patients and the general population. Six in 10 individuals (63.3%) with SLE reported ≥ 1 ACE and 19.3% had ≥ 4 ACEs. Nonzero ACE levels were more common ($>58\%$) in women, Latino and African American participants, those who did not graduate college and those with lupus nephritis. In adjusted models, higher overall ACE score was associated with greater patient-reported SLE activity and damage, higher levels of depressive symptoms, poorer physical function and quality of life, though not all measures reached statistical significance (Table 1). ACE levels did not predict worse physician-assessed SLE activity, damage or severity (Table 2). The results for all 3 ACE domains paralleled results for ACE score levels with worse patient-reported, but not physician-assessed outcomes.

Table 1. Mean (adjusted¹) patient-reported outcomes of activity, damage, depression and physical function and physician-reported outcomes of activity, damage and lupus severity, by ACE levels

Patient-Reported Outcomes					
ACE Level	SLAQ	BILD	PHQ	PROMISPF	SF-36 PCS
0	7.7 (8.4-8.1)	1.6 (1.9-1.3)	5.1 (5.3-4.9)	48.8 (47.3-50.3)	44.8 (42.9-46.7)
1	8.1 (8.8-7.5)	2.0 (1.8-2.3)	5.4 (4.3-6.4)	46.3 (46.1-46.5)	41.9 (39.9-43.9)
2-3	9.5 (7.9-11.1)	3.9 (2.3-5.4)	7.9 (6.2-9.4)	46.9 (44.7-49.1)	42.3 (38.9-45.7)
≥4	11.0 (11.2-10.8)	2.6 (2.0-3.2)	8.1 (6.9-9.3)	46.6 (42.4-50.7)	38.5 (35.1-41.9)
p<0.05	*		*		*
Physician-Assessed Outcomes					
ACE Level	SLEDAI	SDI	LSI		
0	2.5 (1.9-3.2)	1.7 (1.3-2.1)	8.9 (8.5-9.3)		
1	2.6 (1.8-3.4)	2.2 (1.7-2.7)	7.8 (6.6-9.0)		
2-3	3.7 (2.3-5.1)	2.1 (1.6-2.6)	8.8 (6.4-11.2)		
≥4	2.4 (1.8-3.0)	1.9 (1.3-2.4)	8.4 (6.0-10.8)		
p<0.05					

SLAQ - Systemic Lupus Activity Questionnaire; BILD - Brief Index of Lupus Damage; PHQ - Patient Health Questionnaire depression scale; PROMIS PF - Patient-Reported Outcomes Measurement Information System Physical Function; SF36 - Short Form-36 Physical Component Score; Quality of Life; SLEDAI - Systemic Lupus Erythematosus Disease Activity Index; SDI - Systemic Lupus Collaborating Clinics Damage Index; LSI - Lupus Severity Index.
Cells are means (95% confidence interval).
¹Adjusted for age, sex, race/ethnicity, disease onset <18 years, education level

Table 2. Mean (adjusted¹) patient-reported outcomes of activity, damage, depression and physical function and physician-reported outcomes of activity, damage and lupus severity, by ACE domain

Patient-Reported Outcomes					
ACE Domain	SLAQ	BILD	PHQ	PROMISPF	SF-36 PCS
None	7.7 (8.4-8.1)	1.6 (1.9-1.3)	5.1 (5.3-4.9)	48.8 (47.3-50.3)	44.8 (42.9-46.7)
Household Challenges	10.1 (8.9-11.2)*	2.1 (1.8-2.3)	6.6 (6.0-7.2)*	46.5 (45.0-47.9)*	40.7 (38.9-42.5)*
Neglect	10.6 (9.2-12.0)*	2.0 (1.4-2.5)	7.6 (6.4-8.8)*	46.7 (43.6-49.8)*	39.7 (37.3-42.1)*
Abuse	11.7 (10.3-13.1)*	2.2 (1.6-2.7)	7.7 (6.6-8.7)*	46.1 (44.3-47.9)*	39.2 (37.0-41.4)*
Physician-Assessed Outcomes					
ACE Domain	SLEDAI	SDI	LSI		
None	2.5 (1.9-3.2)	1.7 (1.3-2.1)	8.9 (8.5-9.3)		
Household Challenges	3.0 (2.5-3.5)	2.1 (1.9-2.4)	8.3 (6.9-9.7)		
Neglect	2.6 (1.9-3.4)	1.7 (1.2-2.2)	8.5 (6.5-10.5)		
Abuse	3.0 (2.4-3.7)	2.1 (1.6-2.5)	8.7 (6.4-11.0)		

SLAQ - Systemic Lupus Activity Questionnaire; BILD - Brief Index of Lupus Damage; PHQ - Patient Health Questionnaire depression scale; PROMIS PF - Patient-Reported Outcomes Measurement Information System Physical Function; SF36 - Short Form-36 Physical Component Score; Quality of Life; SLEDAI - Systemic Lupus Erythematosus Disease Activity Index; SDI - Systemic Lupus Collaborating Clinics Damage Index; LSI - Lupus Severity Index.
Cells are means (95% confidence interval).
¹Adjusted for age, sex, race/ethnicity, disease onset <18 years, education level. (Domain effects estimated in separate models, with ACE0 as reference group).
* $p < 0.05$.

Conclusion: ACEs were equally common among CLUES cohort and the general population. Accumulation of adverse experiences was associated with poorer patient-reported health measures, but not physician-assessed outcomes, in adulthood. Results reinforce the need to prevent ACEs and promote resilience when a history of ACE is ascertained.

Disclosure: K. DeQuattro, None; L. Trupin, None; J. Li, None; P. Katz, None; C. Lanata, None; E. H. Yelin, None; S. Rush, None; L. A. Criswell, None; L. Murphy, None; M. Dall'Era, None; J. Yazdany, None.

Abstract Number: 265

Disparities in Utilization and Direct Costs of Hospitalizations and Emergency Room Visits in SLE: The Georgia Lupus Registry

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Healthcare Disparities in Rheumatology Poster

Session Type: ACR Poster Session A

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

Background/Purpose: There is a lack of population-based statistics on utilization and costs of direct healthcare of systemic lupus erythematosus (SLE) in the US, which disproportionately impacts blacks. Data are limited to those from databases, such as Medicaid and commercial claims, which cannot validate SLE diagnoses on a larger scale. To overcome these limitations, we utilized a population-based registry to evaluate healthcare utilization and direct costs in SLE. **Methods:** The Georgia Lupus Registry is a Centers for Disease Control and Prevention-funded population-based registry of validated SLE patients in Atlanta, GA, from 2002–04. The state privacy exemption for public health surveillance allowed diagnoses to be validated without consent on a population level, using ≥ 4 ACR criteria or 3 ACR criteria with a final diagnosis of SLE by a board-certified rheumatologist. Validated incident patients were matched with the state Hospital Discharge Database from 2000–13, which captured all hospital and emergency room (ER) admissions. Direct costs were reported according to the latest Medicare reimbursement rates, regardless of insurance or lack thereof. Patients were censored at

Table 1. Description of Patients With Incident SLE by Hospitalization or Emergency Room Status

		Overall (n=187)	Hospital admissions			p-value	Emergency room visit			p-value
			No (n=66)	Yes (n=121)			No (n=79)	Yes (n=117)		
Demographics	Age at diagnosis	Mean \pm SD	40.6 \pm 16.4	39.7 \pm 14.6	40.9 \pm 17.0	0.34	43.6 \pm 15.6	39.9 \pm 16.5		0.2
	Sex					0.66				0.076
		Male	84 (13.1)	13 (14.4)	31 (12.6)		13 (19.0)	29 (11.3)		
		Female	292 (86.9)	77 (85.6)	215 (87.4)		64 (81.0)	228 (88.7)		
	Race					0.0062				0.0013
		Black	248 (73.8)	46 (62.3)	192 (78.0)		47 (39.3)	201 (78.2)		
Clinical (ACR criteria)		White	77 (22.9)	28 (31.1)	49 (19.9)		48 (32.0)	51 (19.8)		
		Other	19 (3.3)	6 (6.7)	3 (2.0)		6 (7.6)	3 (1.3)		
	Marital status					0.93				0.031
		Single	185 (56.9)	58 (62.3)	135 (57.2)		57 (49.3)	146 (63.9)		
		Married	129 (41.1)	39 (37.5)	99 (42.8)		18 (50.7)	91 (38.1)		
	Male sex					0.23				0.36
		No	272 (81.0)	69 (74.7)	203 (82.3)		63 (79.7)	209 (81.3)		
		Yes	84 (19.0)	21 (23.3)	43 (17.7)		16 (20.3)	48 (18.7)		
	Insurance					0.69				0.93
		No	288 (83.7)	76 (84.4)	212 (86.2)		68 (86.1)	220 (83.4)		
		Yes	48 (14.0)	14 (15.6)	34 (13.8)		11 (14.0)	47 (16.6)		
	Pharmaceutical					0.002				0.38
		No	275 (81.8)	64 (71.1)	211 (85.8)		63 (79.7)	212 (82.5)		
		Yes	81 (18.2)	26 (28.9)	35 (14.2)		16 (20.3)	45 (17.5)		
	Oral steroids					0.75				0.26
		No	281 (77.7)	71 (78.9)	210 (87.2)		63 (82.0)	196 (78.3)		
		Yes	73 (22.3)	19 (21.1)	54 (22.8)		16 (20.3)	45 (17.5)		
	Arthritis					0.39				0.46
		No	114 (34.3)	37 (36.0)	89 (36.2)		30 (38.0)	86 (33.5)		
		Yes	226 (65.7)	63 (70.0)	157 (63.8)		49 (62.0)	171 (66.5)		
	Seizure					<0.0001				0.016
		No	216 (64.0)	76 (84.4)	143 (57.2)		60 (75.9)	138 (63.3)		
		Yes	118 (35.3)	14 (15.6)	104 (42.8)		19 (24.1)	79 (36.7)		
	Renal disorder					0.05				0.82
		No	213 (60.3)	72 (80.0)	141 (57.8)		51 (64.6)	180 (70.0)		
		Yes	103 (30.7)	18 (20.0)	85 (34.2)		26 (32.9)	77 (30.0)		
	Neurologic disorder					0.16				0.81
		No	185 (56.8)	63 (69.4)	229 (89.4)		74 (89.7)	231 (89.9)		
		Yes	11 (3.3)	5 (5.6)	26 (10.6)		5 (6.3)	26 (10.1)		
	Hematologic disorder					0.063				0.92
		No	164 (48.3)	39 (42.3)	125 (51.3)		31 (39.3)	41 (16.0)		
		Yes	282 (83.7)	79 (77.7)	212 (86.2)		68 (86.1)	216 (84.0)		
	Immunologic disorder					0.12				0.93
		No	165 (51.3)	34 (37.9)	71 (28.9)		25 (31.6)	30 (11.1)		
		Yes	211 (68.7)	66 (62.1)	175 (71.1)		54 (68.4)	177 (68.9)		
	Anticoagulant therapy					0.075				0.36
		No	11 (4.3)	7 (7.8)	8 (3.3)		3 (3.7)	10 (3.9)		
		Yes	121 (35.3)	81 (89.2)	218 (86.7)		76 (96.3)	247 (96.1)		
	Number of ACR criteria	Mean \pm SD	4.6 \pm 1.4	4.3 \pm 1.2	4.7 \pm 1.4	0.014	4.4 \pm 1.1	4.7 \pm 1.4		0.15

Data are expressed as n (%), unless otherwise specified. Based on information from 2000 to 2013 SLE registry. Age at diagnosis.

Table 2. Description of Hospitalizations and Emergency Room Visits in Patients With Incident SLE Overall and by Sex, Race and ACR Renal Criterion

Admission type	Category	Subgroup	Cases, n	Total				Visit rate Number of visits per ten persons years (95% CI)	Charge rate		Stay rate	
				Total person-years	Total number of admissions	Total direct charges (US\$, 2015)	Total length of stay (days)		Direct charges per admission (US\$, 2015)	Direct charges per day (US\$, 2015)	Length of stay per person-year (days)	Length of stay per admission (days)
Hospitalization	Overall	Overall	136	3065	1255	\$6,365,119	5089	47 (29, 45)	18,793	44,912	6293	296
	Sex	Male	44	400	179	\$1,679,312	1483	43 (28, 52)	25,725	49,488	3953	366
		Female	292	2665	1076	47,685,807	3606	46 (28, 48)	17,892	44,318	6258	285
	Race	Black	248	2155	928	47,855,546	3670	50 (38, 53)	22,257	44,497	4084	362
		White	77	792	148	8,548,571	1140	39 (28, 25)	18,189	47,742	2607	344
		Other	11	118	9	118,636	19	7 (3, 13)	2481	42,434	3757	35
	ACR renal criterion	No	225	2278	947	24,702,032	4246	38 (28, 32)	11,154	17,314	3418	391
		Yes	111	886	308	11,663,087	4423	52 (42, 76)	17,427	15,395	9363	336
Emergency Room visit	Overall	Overall	136	3065	2004	\$4,818,097	2897	43 (32, 48)	1172	2404	2366	68
	Sex	Male	44	400	265	793,843	124	44 (38, 48)	1773	2891	2583	69
		Female	292	2665	1739	4,024,254	2773	43 (36, 48)	1342	2363	2363	68
	Race	Black	248	2155	1397	4,598,378	1949	50 (39, 62)	1980	2297	2196	37
		White	77	792	254	668,386	289	38 (22, 36)	863	3279	3307	38
		Other	11	118	15	44,293	19	11 (3, 19)	379	3407	3407	11
	ACR renal criterion	No	225	2278	1267	1,368,456	1332	18 (12, 62)	3166	1389	2326	40
		Yes	111	886	737	1,119,640	1759	54 (38, 96)	2050	3432	2266	40

All calculations from SLE diagnosis through 2015 or death. ACR renal criterion captured during the first year after SLE diagnosis. Charges are inflation adjusted to 2015 US\$.
SLE, Systemic Lupus Erythematosus.

death. **Results:** Of 336 incident patients, 86.9% were female, 73.8% black, 22.9% white and 58.9% unmarried; 246 (73.2%) were admitted to hospital and 257 (76.5%) to the ER (Table 1). Patients admitted to the ER and hospital were significantly more likely to be black and have serositis. Hospitalized patients were also more likely to have a renal disorder and meet a greater number of ACR criteria (Table 1). Overall, 1255 hospitalizations had a total cost of \$56,365,119 (Table 2). The hospitalization rate was higher in blacks and those with renal disorders. Charges per hospitalization were higher in whites compared with blacks and in those with renal involvement. Length of stay per admission was similar across all groups (6–8 days) (Table 2). There were 2004 ER admissions with a total cost of \$4,818,097. The ER admission rate was highest in the blacks and those with renal involvement. Charges per ER admission were similar by sex and in those with renal involvement, but were higher in whites compared with blacks (Table 2).

Conclusion: SLE has significant healthcare utilization and cost burden. A large proportion of patients are admitted to the ER or hospital. Blacks and those with early renal involvement have a higher rate of hospital and ER admissions. Despite having fewer hospital and ER admissions, whites incurred higher charges per admission than blacks. Further study of factors that drive healthcare utilization and cost is needed.

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Abstract Number: 266

Diagnostic Delays and Disparities in Access to Care in Systemic Lupus Erythematosus

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Healthcare Disparities in Rheumatology Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Systemic lupus erythematosus (SLE) presents heterogeneously and can be difficult to diagnose. Once diagnosed, prompt evaluation and treatment by a specialist can prevent morbidity. Few studies have systematically quantified delays in diagnosis and access to specialty care in SLE. Using a large cohort of individuals with confirmed SLE, we aimed to characterize patient-perceived delays in diagnosis and access to specialty care at SLE onset.

Methods: Data were derived from the California Lupus Epidemiology Study (CLUES), a population-based, longitudinal, multi-ethnic cohort of patients with SLE. Data were collected via annual telephone interviews and in-person clinical visits. Questions included time from onset of symptoms to seeing a doctor and to diagnosis of SLE, the number of doctors seen before SLE diagnosis, specialty of diagnosing physician, specialty of doctor giving incorrect diagnosis, and the time until first visit with a specialist (rheumatologist or nephrologist) if not initially diagnosed by one. We examined the relationships between these variables and race/ethnicity, poverty (<125% of federal poverty level; FPL), education (\leq high school, vocational/trade schooling, college, postgraduate), and self-assessed health literacy (adequate vs. limited, using a validated 4-item scale), testing the differences with chi-square tests.

Results: This study included 417 patients, 90% female with a mean age of 47 ± 14 years. 90% met $\geq 4/11$ ACR criteria for SLE; the balance had a physician diagnosis of SLE and/or lupus nephritis. The racial/ethnic distribution was 31% Caucasian, 35% Asian, 23% Hispanic and 11% African-American. Twenty-two percent had an education level \leq high school, 19% were $>125\%$ FPL, and 40% with low health literacy. Time from symptom onset to seeing a doctor varied, with 65% seen in < 6 months, 12% in 6-12 months, 7% in 1-2 years and 16% waiting >2 years. Time from symptom onset to receiving a diagnosis also varied, with 48% of participants waiting >6 months. 39% of patients received an incorrect initial diagnosis, most commonly from primary care physicians. There were no significant differences for any of these outcomes by race, education, health literacy or poverty level. For patients who were initially diagnosed with SLE by a non-specialist, racial/ethnic minorities and those with a high school education or less were more likely to wait longer than 3 months for a referral (both $p = 0.03$). Compared with those with less education, patients with higher levels of education saw more doctors before receiving a correct diagnosis (mean=2.1 vs 2.6; $p=0.02$).

Conclusion: Overall approximately half of this study's patients waited >6 months to receive a diagnosis of SLE, and 39% received an incorrect initial diagnosis. Access to specialty care varied significantly, with racial/ethnic minorities, and those with low education waiting longer to see a specialist. Those with a higher education level saw more doctors prior to receiving a diagnosis, which could potentially be explained by greater access to healthcare in general. This study suggests that efforts to decrease diagnostic delays and errors, particularly among at-risk populations with SLE, are warranted.

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Abstract Number: 267

Patterns of Access to Prescription Medications Among Lupus Cases and Controls in the Population-Based Michigan Lupus Epidemiology & Surveillance (MILES) Cohort

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Healthcare Disparities in Rheumatology Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Medication access and adherence are important issues in determining patient outcomes. We investigated sociodemographic factors and disparities associated with prescription medication access in a population-based cohort of lupus patients and controls.

Methods: Detailed data on prescription access and sociodemographics were collected at the MILES baseline visit by structured interview. We compared access between cases and frequency-matched controls (using chi-squared tests) and examined factors associated with access in separate multivariable logistic regression models.

Results: 654 participants (462 SLE cases, 192 controls) completed the MILES Cohort baseline visit; 584 (89.3%) female, 288 (44%) black, and mean age 53 years. SLE patients were significantly more likely than controls to report the following in the preceding 12 months to save money: skipping doses, taking less medicine, delaying filling prescriptions and asking their doctor for a lower cost medication (Table 1).

Table 1. Self-reported prescription access within the preceding 12 months in SLE cases compared to frequency-matched controls.

Questionnaire Item	SLE cases (n=462) n (%)	Controls (n=192) n (%)	p-value
Unable to get Rx's doctor felt necessary?	56 (12.1)	18 (9.4)	NS
Skipped med doses to save money?	62 (13.4)	12 (6.3)	0.008
Taken less medicine to save money?	70 (15.2)	11 (5.7)	0.001
Delayed filling a Rx to save money?	75 (16.2)	17 (8.9)	0.013
Asked doctor for lower cost medication to save money?	110 (23.8)	30 (15.6)	0.02
Bought Rx from another country to save money?	5 (1.08)	2 (1.04)	NS
Used alternative therapies to save money?	38 (8.2)	11 (5.7)	NS

NS=not significant

Based on multivariable models (Figure 1), having SLE was associated with several types of limitations in medication access, after adjusting for sex, race, age, insurance status, and income level. Household income below the US median was also associated with limitations in medication access, whereas private insurance was generally associated with improved access. Black persons were less likely to ask their doctor for lower cost alternatives.

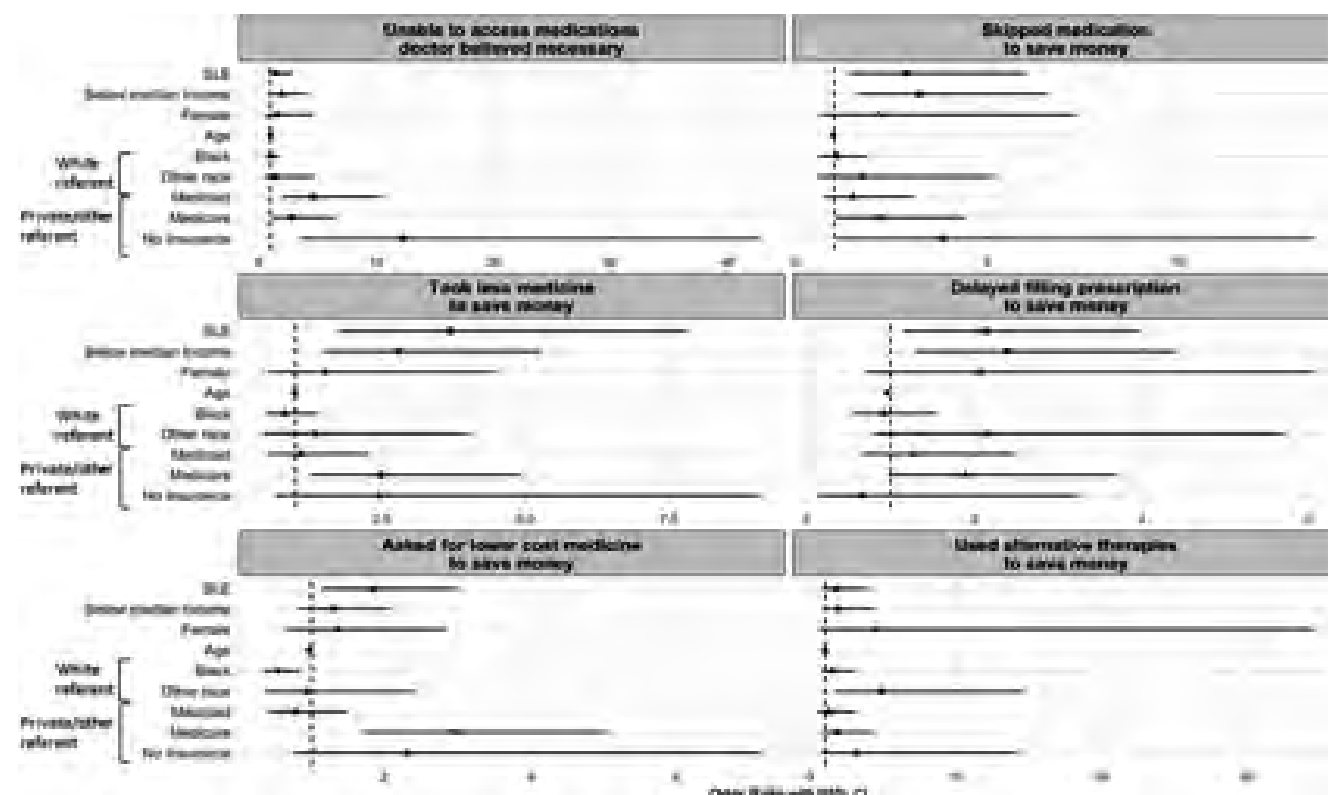


Figure 1. Forest plots from a series of multivariable models of factors associated with aspects of prescription medication access and adherence. Squares represent positive odds ratios (ORs), circles negative ORs, triangles not significant ORs; horizontal lines represent 95% CIs.

Conclusion: SLE patients were more likely than controls from the general population to experience limitations in prescription medication access, and less than 1 in 4 patients asked providers for lower cost medications. Further, disparities in access were found in association with income, race and insurance status. Consideration of medication costs in patient decision making could provide a meaningful avenue for improving patient access and adherence to medications.

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The Effect of Renaming Gout to Urate Crystal Arthritis on Illness and Treatment Perceptions in Māori (the Indigenous People of Aotearoa/New Zealand)

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Healthcare Disparities in Rheumatology Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Recent research has suggested that renaming gout to a pathophysiological illness label (urate crystal arthritis) avoids inaccurate lay perceptions of gout and promotes more effective management strategies. In Aotearoa/New Zealand, Māori (indigenous New Zealanders) have high prevalence of gout, with early onset and severe disease. It is unknown how a change in illness label would impact on indigenous New Zealanders who are disproportionately affected by gout. The aim of this study was to examine the effect of changing the illness label of gout on the perceptions of the disease and its management in Māori in Aotearoa/New Zealand.

Methods: Supermarket shoppers in rural and urban locations with large Māori communities were recruited into a study examining the perceptions of different types of arthritis. Participants were randomised 1:1 to complete a questionnaire examining the perception of the same disease description labelled as either 'gout' or 'urate crystal arthritis' (UCA). Participants rated likely causal factors for the disease, illness perceptions and the usefulness of various management strategies using Likert scales. Differences between the two illness labels were tested using independent sample t-tests.

Results: Completed questionnaires were available from 172 Māori participants. The gout-labelled illness was most likely to be viewed as caused by diet ($P=0.003$), whereas the UCA-labelled illness was most likely to be viewed as caused by aging ($P=0.001$). 'UCA' was seen as having a wider range of factors as responsible for the illness, with stress or worry, hereditary factors, chance and pollution more likely to be viewed as causes of 'UCA'. 'Gout' was less likely to be viewed as having a chronic timeline than 'UCA' (mean (SD) for 'Gout' 6.9 (2.8) and for 'UCA' 7.9 (2.4), $P=0.013$). 'Gout' was also viewed as better understood than 'UCA' (mean (SD) for 'Gout' 6.3 (3.1) and for 'UCA' 4.4 (3.3), $P=0.001$). Other illness perceptions did not differ between the illness label groups. Changing to a healthier diet was perceived as more helpful for 'Gout' compared to 'UCA' (mean (SD) for 'Gout' 8.5 (2.3) and for 'UCA' 7.3 (2.7), $P=0.003$). Participants also viewed stopping or restricting alcohol use as more helpful for 'Gout' than 'UCA' (mean (SD) for 'Gout' 8.1 (2.8) and for 'UCA' 7.0 (3.1), $P=0.017$). There were no differences between 'Gout' and 'UCA' in perceptions that adopting regular exercise, losing weight or taking long-term medications would be helpful for managing the illness ($P>0.23$ for all).

Conclusion: In an indigenous population that is disproportionately affected by gout, causal beliefs and management strategies for a gout-labelled illness are consistent with widely-held lay beliefs that gout is a disease caused by self-inflicted dietary excess. Renaming gout to urate crystal arthritis promotes more complex causal beliefs, a longer timeline for the disease, and is likely to avoid perceptions that dietary modification and alcohol restriction are the main strategies for effective management.

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Adverse Event Reporting Rates and Placebo/Standard-of-Care-Arm American College of Rheumatology Responses Vary By Region in Rheumatoid Arthritis Trials

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Healthcare Disparities in Rheumatology Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Clinical trials are becoming increasingly globalized, with more representation from Asia, Latin America, and the Russian Federation and Eastern Europe (RFEE).¹ Adverse event (AE) reporting rates and placebo (or standard-of-care arm) responses may differ by geographic region and level of economic development²⁻⁴; efficacy and safety may not be generalizable across regions. This potential heterogeneity and its implications for rheumatoid arthritis (RA) trials have not been studied in detail. The current study assessed potential regional differences in rates of ACR response and AE reporting using patient-level data (PLD) from RA trials in the TransCelerate initiative.⁵

Methods: We obtained PLD for all 17 RA trials available through TransCelerate as of August 2017 and analyzed data from 7 trials for which geographic information was available (NCT01198002, NCT01202760, NCT01202773, NCT01404585, NCT00605735, NCT00048581, NCT00647270). We grouped patients by region and evaluated differences in demographics, AE reporting rates, and ACR response. After a significant omnibus chi-square test result, pairwise comparisons were made between regions using Fisher exact test, with false discovery rate (FDR) correction for multiple comparisons. All patients were included in analyses of AE reporting. Only patients with data sufficient to calculate ACR scores were included in analyses of ACR response. Demographics for patients in each region are shown in the Table.

Results: The lowest rates of AE reporting and ACR50 response were seen in RFEE. The highest rate of ACR20 response was seen in Asia. After FDR correction, significantly lower 12-week and 52-week AE reporting rates were seen in RFEE than in Asia, Latin America, and the United States. Only the ACR50 response difference between RFEE and Latin America survived FDR correction; however, ACR20 rates in Asia remained significantly higher than in RFEE and the United States (Table).

Table. Regional Variations in Patient Demographics and Efficacy and Safety in Placebo/Standard-of-Care Arms of Clinical Trials in RA

Patient numbers and demographics	US	Latin America	Asia	RFEE
AE analysis, n	369	167	164	213
ACR response analysis, n	268	132	107	160
Female, %	81	89	88	81
Median age, years (SD; range)	55 (11; 21-78)	51 (12; 22-76)	52 (12; 18-83)	51 (12; 25-79)
Proportions of patients attaining ACR50/20 response at 12 weeks and/or reporting ≥1 AE at 12 and 52 weeks				
Patients, %	US	Latin America	Asia	RFEE
ACR50 response	6	9a	7	1
ACR20 response	17	24	29a b	15
AE at 12 weeks	53a	49a	51a	22
AE at 52 weeks	68a	58a b	65a	39

^a*p* < 0.05 vs RFEE. ^b*p* < 0.05 vs US. All *p* values corrected for multiple comparisons.

Conclusion: Patient-level data from placebo arms in the TransCelerate initiative revealed significant regional differences in AE reporting rates and ACR50/ACR20 response rates. Differences in Latin America, RFEE, and Asia were especially notable; future patient populations from these regions may show distinct efficacy/safety profiles regardless of treatment. Given the ongoing globalization of clinical trials, country- and region-specific treatment patterns, patient populations, and safety issues should be explored to avoid misguided inferences across regions. Capping recruitment by region to balance these factors may be warranted. *References:* 1. Drain PK et al. *Nat Rev Drug Discov.* 2014;13:166-7. 2. Contopoulos-Ioannidis D et al. *J Clin Epidemiol.* 2016;78(suppl C):10-21. 3. Yusuf S, Wittes J. *N Engl J Med.* 2016;375 :2263-71. 4. Xu X et al. *Arthritis Rheumatol.* 2016;68(suppl 10). 5. Gill D. *Nat Rev Drug Discov.* 2014;13:nrd4437.

Disclosure: K. Tuckwell, Roche/Genentech, 1, Genentech, Inc., 3; E. Teng, Roche/Genentech, 1, Genentech, Inc., 3; J. Chia, Genentech, Inc., 1, Genentech, Inc., 3; D. Lee, Genentech, Inc., 3; J. Galanter, Genentech, Inc., 1, Genentech, Inc., 3; J. Peake, Genentech, Inc., 3; D. Keebler, Roche, 1, Genentech, Inc., 3.

Abstract Number: 270

Gaps in Knowledge about the Ontario Trillium Drug Program

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Session Information**Session Date:** Sunday, October 21, 2018**Session Title:** Healthcare Disparities in Rheumatology Poster**Session Type:** ACR Poster Session A**Session Time:** 9:00AM-11:00AM

Background/Purpose: Medication costs for patients with a rheumatic disease can add up as they may be on numerous and/or costly medications including anti-inflammatory medications, disease-modifying anti rheumatic drugs and/or biologic medications. The number of biologic medications available to treat rheumatic diseases has steadily increased over the last decade. Biologic medications generally cost over 10,000 Canadian dollars annually. In Ontario, Canada, the Trillium Drug Program (TDP) funds patients who approximately spend greater than 4% of their after-tax household income on prescription drugs. From 2005 to 2015, the TDP has increased its coverage of medications that cost greater than \$10,000 annually, from 20 to 124 medications, respectively.¹ However, the gaps in knowledge about the TDP is not clear among resident physicians and patients. The purpose of the study was to determine what resident physicians and patients know about the TDP.

Methods: This research survey project was approved by the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board. Qualtrics survey software was used to distribute anonymous questionnaires to Queen's University residents (family medicine and core internal medicine) and patients at a private rheumatology clinic. Two types of patient surveys were completed: a general patient questionnaire and a specific questionnaire for patients on expensive biologic medications.

Results: 50/55 residents have heard of the TDP but only 11/50 residents know how a patient would apply for it. The general patient survey revealed that 18/27 patients have heard of the TDP but only 2/18 patients know how to apply for it. Of these two patients, one patient has applied. The other patient did not think that they would qualify for it and so has not applied. The survey of patients on expensive medications revealed that 3/7 patients have a private drug plan and 6/7 patients have heard of the TDP. All six of these patients have heard of this program through a healthcare professional. 5/6 of the patients know how to apply for the TDP. 4 of these 5 patients has applied to the TDP and one has not as they do not think they need it.

Conclusion: The survey results reveal that resident physicians and patients generally do not know how to apply to the TDP, although they have heard of the program. On the other hand, the patients who are on expensive medications generally do know how to apply to the TDP and have done so. This is likely due to guidance by a healthcare professional. Due to these gaps in knowledge about the TDP, we have created an information sheet to educate patients about the TDP.

Reference:

1. Tadrous M, Greaves S, Martins D *et al.* Catastrophic drug coverage: utilization insights from the Ontario Trillium Drug Program. CMAJ [Internet]. 2018 Mar 26;6(1):E132-E138. Available from: <http://cmajopen.ca/content/6/1/E132.full#ref-18>

Disclosure: A. Gupta, None; H. Khey Beldman, None; C. Avern, None; H. Avern, None.

Abstract Number: 271

Health Care Disparities for Infectious and Non-Infectious Uveitis in the US

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Session Information**Session Date:** Sunday, October 21, 2018**Session Title:** Healthcare Disparities in Rheumatology Poster**Session Type:** ACR Poster Session A**Session Time:** 9:00AM-11:00AM

Background/Purpose: Autoimmune disease like systemic lupus erythematosus and rheumatoid arthritis are influenced by health care disparities due to race, income, sex and age. Uveitis is a frequent association with rheumatic diseases including ankylosing spondylitis, Behcet's disease, and juvenile idiopathic arthritis. There is lack of national data regarding how health care disparities influence uveitis. The primary aim of our study is to compare the effect of race, income and insurance status in patients with infectious and non-infectious uveitis.

Methods: We used the National Inpatient Sample (NIS) for the years 2002-2013. We used ICD-9 codes to identify infectious, noninfectious uveitis cases and ocular complications. We collected information on patient's age, sex, race,

income quartile of median household income for patients' zip code and payer status. A multivariate logistic regression model was run to predict odds of developing infectious uveitis, non-infectious uveitis and ocular complications, adjusted for age, sex, race, income quartile of median household income for patient's zip code and payer status. To assess the effect of income irrespective of race, we ran a logistic regression model, excluding African Americans. Statistical analysis was done using SAS version 9.4.

Results: There were a total of 94,143,978 discharges, which included 15,296 total cases of uveitis, 4,538 cases of infectious uveitis and 10,758 cases of non-infectious uveitis. For a multivariate model odds of African Americans having infectious uveitis are five times: (OR = 5.37, 95% CI: 4.95-5.82) and having non-infectious uveitis are one and half times as compared to Caucasians: (OR = 1.43, 95% CI: 1.35-1.52). Odds of Medicare (OR = 2.21, 95% CI= 1.35-3.62) and Medicaid (OR = 1.7, 95% CI = 1.04-2.85) patients having complications from infectious uveitis are double and 1.7 times as compared to those with private insurance. Odds of Medicare (OR = 2.01, 95% CI= 1.46-2.71) and Medicaid (OR = 2.18, 95% CI = 1.51-3.16) patients having complications from non-infectious uveitis are double as compared to those with private insurance.

After excluding African Americans, patients with median household income for patient's zip code of \$ < 38,999 have 1.5 times odds of having infectious uveitis: (OR=1.54, 95% CI=1.38-1.71), as compared to those with median household income > \$63,000. Medicare patients have 1.6 times the odds (OR = 1.6, 95% CI= 0.83-3.06) and Medicaid patients double (OR = 2.05, 95% CI = 1.05-4) the odds having ocular complications from infectious uveitis. And Medicare patients have 1.7 times the odds (OR = 1.7, 95% CI= 1.21-2.46) and Medicaid patients double (OR = 2.35, 95% CI = 1.54-3.58) the odds having ocular complications from non-infectious uveitis as compared to those with private insurance.

Conclusion: African Americans have higher odds of developing infectious and non-infectious uveitis. Medicare and Medicaid patient have higher odds of developing complications from infectious and non-infectious uveitis. Uveitis should be added to the list of immune-mediated diseases which are affected by health care disparities. These disparities cannot be completely explained on the basis of racial or genetic factors.

Disclosure: K. Chauhan, Nowatski Eye Foundation, 2; S. Scaife, None; J. T. Rosenbaum, Alcon Research Institute, the Spondylitis Association of America (SAA), and Pfizer, 2,AbbVie, Gilead, Novartis, Regeneron, and UCB, 5.

Abstract Number: 272

Ethnic Disparities in Lupus Nephritis Outcomes in the Inland Empire: Findings from the Southern California Lupus Registry

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Session Information

Session Date: Sunday, October 21, 2018

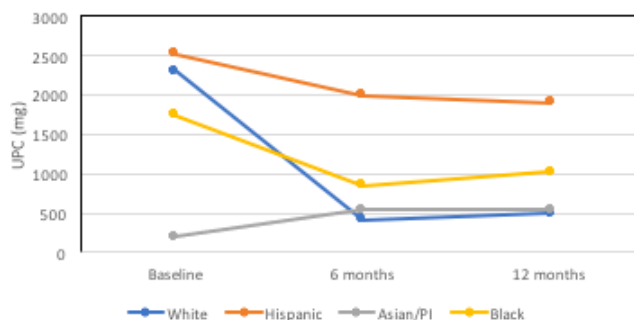
Session Title: Healthcare Disparities in Rheumatology Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Loma Linda University Health (LLUH) serves Riverside and San Bernardino County, which are the two largest counties by geographic size in California and make up the Inland Empire of Southern California. This underserved region of California comprises 50% Hispanic, 31.8% White, 8.7% Black, and 6.6% Asian/Pacific Islander (PI)

Figure 1: UPC Trend Over 12 Months in Different Ethnicities



residents. Prior studies have established differences in the incidence, clinical manifestations, and treatment response of SLE among ethnic groups. Of particular note are Hispanics, who have demonstrated greater prevalence of renal involvement and better response to certain therapies. However, the majority of these studies were conducted in Latin America and few have focused exclusively on lupus nephritis (LN). The objective of our study was to evaluate therapy management and response differences between LN patients of different ethnic backgrounds in the Inland Empire.

Methods: Data was obtained from the Southern California Lupus Registry (SCOLR), a registry that enrolled SLE patients June 2016 to June 2018 at LLUH. All LN patients were screened for inclusion. Exclusion criteria included patients with renal transplant and unknown LN class. Information obtained from the medical record included demographics, LN class, medications used, and the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) and urine protein-to-creatinine ratio (UPC) at baseline, 6 months, and 12 months. Simple descriptive statistical analyses were calculated to determine if observed differences were statistically significant, and a p-value ≤ 0.05 was considered significant.

Results: Thirty-five patients with LN were identified, of which there were 3 (8.6%) White, 18 (51.4%) Hispanic, 6 (17.1%) Asian/PI, and 8 (22.9%) Black. Baseline, 6 month, and 12 month SLEDAI were significantly lower in the Asian/PI cohort when compared to the other ethnic groups. In contrast, there was a trend towards higher baseline, 6 month, and 12 month SLEDAI and proteinuria levels in Hispanics when compared to the other ethnic groups (Figure 1). No significant association was found between change (between baseline and 6 months) in SLEDAI and ethnicity. All White patients had SLEDAI improvement over 6 months, while the majority of Asian/PI, Black, and Hispanic patients had no change or worsened disease activity. No association was found between medication type and ethnicity or between medication type and change in SLEDAI.

Conclusion: Asian/PI patients have significantly less disease activity whereas Hispanic patients trend towards greater disease activity than their counterparts. This study is the first endeavor to evaluate therapy management and response differences between LN patients of different ethnic backgrounds in Southern California. Further studies with greater power are needed to validate these findings.

Disclosure: K. Choi, None; A. Haghshenas, None; A. Benitez, None; L. Salto, None; K. Torralba, None; V. K. Sandhu, None.

Abstract Number: 273

Incidence of Systemic Lupus Erythematosus By Income: A Nationwide Study

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Healthcare Disparities in Rheumatology Poster

Session Type: ACR Poster Session A

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

Background/Purpose: The incidence of systemic lupus erythematosus (SLE) varies significantly across patients from different racial/ethnic backgrounds, and is highest in non-Caucasian populations. In addition, poverty has been associated with increased SLE severity and mortality, independent of race/ethnicity. How the incidence of SLE varies by income level, the main determinant of poverty, is unknown.

Methods: Using OptumLabs Data Warehouse, a large administrative database of commercially insured and Medicare Advantage beneficiaries, we identified adults with newly diagnosed SLE (ascertained using three ICD-9/10 codes at least 30 days apart) from 2013-2017. Patients had at least two years of enrollment prior to SLE diagnosis. Patients of ≥ 65 years were excluded due to difficulty in estimating income after retirement. Income was based predominately on self-report or when data were missing, derived rulesets were used. Income was missing in 5% of the sample. We estimated the incidence rate (IR) of SLE per 100,000 person-years stratified by income and racial/ethnic categories with age- and sex-adjusted adjustment to the 2010 US total population aged 18-64 years.

Results: We identified 2810 patients with newly diagnosed SLE. The average age (SD) was 44.9 (12.5), 62% of the patients were Caucasian, 16% Black, 15% Hispanic, 7% Asian/other, and 88% were female. The overall age-, sex- and race/ethnicity-adjusted IR was 3.4 (95% confidence interval: 3.3-3.5) per 100,000. SLE incidence was 8 times higher among women (9.1) than men (1.2). The incidence rate among Blacks was twice as high as that of Caucasians, and was moderately higher in Hispanic and Asian/other compared to Caucasians. SLE incidence was 12% higher in those with <\$40,000 household income than those with ≥\$40,000 income. Caucasians with <\$40,000 income had 20% higher SLE incidence than those with ≥\$40,000 income, but there was no evidence of a differential income effect among minorities.

Conclusion: The incidence of SLE is highest among Blacks, and Hispanics. Lower income is associated with higher incidence of SLE in Caucasians; this differential effect of income on disease incidence was not seen in minorities.

Table. Incidence Rates of SLE per 100,000 person years according to income

Income	Overall	Caucasian	Black	Hispanic	Asian/Other
<\$40,000	4.4	3.9	6.0	5.7	3.9
\$40000 - \$99,000	3.8	3.3	6.0	5.7	3.4
\$100,000+	3.8	3.2	5.9	5.4	3.8
Unknown	1.7	1.5	3.3	2.4	1.3
OVERALL	3.4	2.9	5.1	2.4	3.1

Disclosure: A. Duarte-Garcia, None; C. S. Crowson, None; R. McCoy, None; S. Schilz, None; H. Van Houten, None; L. Sangaralingham, None; V. R. Chowdhary, None; S. Amin, None; K. J. Warrington, GlaxoSmithKline, 2, Eli Lilly and Co., 2, Sanofi, 5; E. L. Matteson, None; N. Shah, None.

Abstract Number: 274

Socioeconomic Disparities in Disease Activity in Patients with Rheumatoid Arthritis

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Healthcare Disparities in Rheumatology Poster

Session Type: ACR Poster Session A

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

Background/Purpose: To develop a methodology for well-defined rheumatoid arthritis (RA) measurement as an outcome and provide a clear definition of social determinants related to disease activity. We then examine the association between racial and social factors and risk of higher RA disease activity among RA patients.

Methods: The patients studied were from the University of Pittsburgh's Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry. Since February 2010, RACER has enrolled patients older than 18 years who have been diagnosed with RA by a rheumatologist. The registry had data to enable generating Disease Activity-C Reactive Protein (DAS28-CRP) for patients' each visit. We conducted across-sectional study using the baseline data. Evaluation for difference between dichotomous variables of outcome (high vs. low DAS28-CRP) was done using Chi-square or Fisher exact tests. Comparisons of continuous variables were performed using t-test or the Wilcoxon test. The multiple logistic regression models were then constructed and adjusted for confounders selected by backwards selection and consideration of clinically relevant covariates.

Results: A total of 729 patients with information available on both baseline DAS28-CRP and a majority of social factors' were included for the analyses. The mean age was 59.5(SD=12.7) years, 78% were female, and median RA disease duration was 9.8 (IQR: 3.7, 19.1) years. 45% of patients had high DAS (N=326), about 64% had less than a college degree, 24% had annual income <\$25K, and 67% were not-working. High RA disease activity group patients were more likely to be black, smokers, with a higher BMI, lower education level, not working. They were also less likely to be married, with a lower annual income, with abnormal CRP and longer disease duration. For the multiple logistic regression model adjusted for selected confounders, we found that having higher BMI, annual income below \$25K, and being not working were statistically significantly associated with increases risk of higher RA activity (Table 2).

Conclusion: The objective of this study is to utilize the well-defined RA cohort to estimate whether there are differences in RA disease activity at baseline for different social and racial factors groups. Our results indicate that significant

differences in RA disease activity by social and racial groups may be a reflection of lack of early care and delay in seeking treatment, leading to a more serious and debilitating disease outcome. Outreach into the community at all levels addressing the need for early RA detection and treatment will be needed.

Disclosure: L. Zhu, None; E. Talbott, None; L. W. Moreland, None.

Abstract Number: 275

Health Equity: Access to Rituximab for Patients Comparing Variable Access in a Single Rheumatology Clinic

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Healthcare Disparities in Rheumatology Poster

Session Type: ACR Poster Session A

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

Background/Purpose: The purpose of our study is to investigate the difference in time to access of rituximab therapy between patients with rheumatoid arthritis (RA) compared to patients with other autoimmune diseases.

Methods: A retrospective chart review was performed on 236 patients under the care of rheumatologists out of the University of Alberta, who had received rituximab from October 2012 to October 2017. Data extracted included the method of drug coverage, the date determining when a patient would require rituximab for treatment and the date of first infusion. A Cuzick's test of trend was performed on three groups. The first group includes patients with autoimmune disease (not RA) receiving coverage through the Short Term Exceptional Drug Therapy (STEDT) program, Alberta's publicly funded special access program for high cost drugs. The second group includes patients with autoimmune disease (not RA) who receive non-STEDT funding, encompassing compassionate care and insurance. The third group includes RA patients followed by the Rheumatoid Arthritis Pharmacovigilance Program and Outcomes Research in New Therapies (RAPPORT) clinic at the University of Alberta whom all receive non-STEDT funding. Analysis was conducted using STATA 13.

Results: Of the 236 patients, 154 patients were identified as having RA and followed by the RAPPORT clinic. Eighty-two patients were identified as having other autoimmune diseases (vasculitis, dermatomyositis, systemic lupus erythematosus, myositis, sarcoidosis, Sjogren's and ankylosing spondylitis). Of these 82 patients, 54 had their rituximab covered through Alberta's STEDT program and 28 patients received coverage from non-STEDT programs. The median time to access was 36 days (QR: 25, 53) for RAPPORT patients, 30 days (QR: 17, 44) for STEDT patients with other autoimmune diseases and 45.5 days (QR: 33, 63) for non-STEDT patients with other autoimmune diseases. The Cuzick's test revealed a statistically significant trend between groups (p-value = 0.004).

Conclusion: Our analysis concludes that public funding through the STEDT program, allows quicker access to rituximab compared to alternative sources of funding including compassionate care and insurance. RA patients who also receive non-STEDT coverage also receive rituximab more quickly, having the benefit of a dedicated clinic familiar with drug application processes. The result of this study indicates evidence of medication health economic disparity between access for patients with different conditions. This is concerning for patients who require medications quickly, for disease control, such as vasculitis patients, who appear to have less equity in access to rituximab. Further analysis is necessary to determine causes for this disparity and expedite access.

Disclosure: R. Chu, None; C. Mallon, None; J. W. C. Tervaert, None; E. Yacyshyn, None.

Abstract Number: 276

Gender Differences in TNFi Treatment Adherence and Response in As Patients: A Prospective Longitudinal Cohort Study

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Healthcare Disparities in Rheumatology Poster

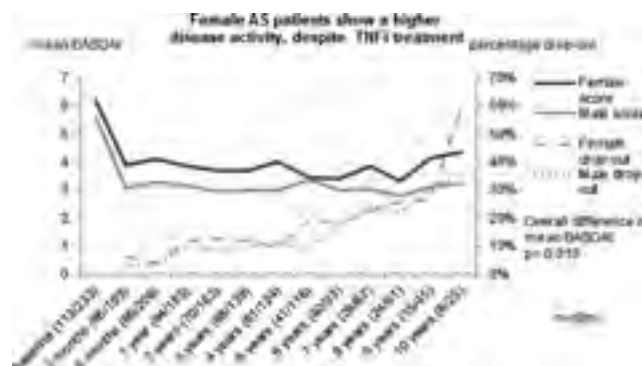
Session Type: ACR Poster Session A

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

Background/Purpose: Despite several observations of gender differences in TNF inhibitor (TNFi) treatment response and adherence in ankylosing spondylitis (AS) patients, limited studies were conducted. Our aim is to assess gender differences in TNFi treatment adherence and response in a longitudinal cohort study over a 10-year follow-up period in AS patients.

Methods: AS patients (fulfilling the modified New York Criteria) treated consecutively with TNFi were included in a prospective, observational cohort. Data were collected at baseline, screening, 3 and 6 months and thereafter every 6 months on demographics, lifestyle factors, inflammatory markers (C-reactive Protein (CRP)) and disease specific parameters (Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Metrology Index (BASMI)). TNFi response was defined by BASDAI50% response criteria (50% of the initial score or improvement of >2 points) and ASDAS response criteria (improvement of >1.1 points). Kaplan Meier Survival curves and Generalized Estimating Equations (GEE)-analyses were performed.

Results: In total 359 AS patients (33.4% females) were included with a mean follow-up of 5.1 years. Women showed a significant lower follow-up duration than men, 4.5 vs. 5.4 years. Patients who were lost to follow-up, were mostly still treated. Overall, females showed significantly higher disease activity scores, BASDAI (0.57 points) (figure 1) and ASDAS (0.27 points), compared to males over the entire follow-up period. According to both the BASDAI and the ASDAS response criteria, females had an overall significantly lower percentage of responders compared with males. In the secondary outcomes, females showed only a clinically relevant lower BASMI (higher mobility) than males (0.23 points).



Conclusion: Female AS patients showed a significantly lower follow-up duration, a lower improvement and a lower clinical response to TNFi according to the BASDAI and ASDAS response criteria.

Disclosure: S. Hoekstra, None; T. Rusman, None; M. T. Nurmohamed, AbbVie Inc., 2, 5, Pfizer, Inc., 2, 5, Merck & Co., 2, 5, Roche, 2, 5, BMS, 2, 5, UCB, Inc., 2, 5, Eli Lilly and Co., 2, 5, Celgene Corporation, 2, 5, Janssen, 2, 5; C. van Denderen, None; I. van der Horst-Bruinsma, AbbVie Inc., 2, 5, Pfizer, Inc., 2, 5, MSD, 2, 5, UCB, Inc., 2, 5.

Abstract Number: 277

Outcomes of Telemedicine for Rheumatoid Arthritis in the Alaska Native Population

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Session Information**Session Date:** Sunday, October 21, 2018**Session Title:** Healthcare Disparities in Rheumatology Poster**Session Type:** ACR Poster Session A**Session Time:** 9:00AM-11:00AM

Background/Purpose: In rheumatoid arthritis (RA), access to a rheumatologist is associated with improved quality of care and outcomes. Telemedicine has been proposed as a solution to the problem of limited access to rheumatologists given the workforce shortage and concentration of rheumatologists in urban areas. Rheumatology care using live video telemedicine has been implemented within the Alaska Tribal Health System. The purpose of this analysis is to evaluate the impact of telemedicine follow-up for RA on disease activity and functional status.

Methods: Study participants with a diagnosis of RA were recruited when seeing a rheumatologist, either in-person or by telemedicine. At the study visit, participants completed the Routine Assessment of Patient Index Data 3 (RAPID3) and a telemedicine perception survey and agreed to medical record review for disease characteristics and measures of quality and access to care. Participants also agreed to telephone contact at 6 and 12 months for follow-up surveys and RAPID3. This analysis describes the results as of the 6-month follow-up RAPID3.

Results: To date, 81 participants have completed the 6-month follow-up (41 telemedicine and 40 in-person). Demographics, disease characteristics and baseline RAPID3 and functional status were similar across groups. The telemedicine group had a higher mean number of rheumatologist visits in the preceding year (3.2 vs. 2.1, $p=0.002$). At the 6-month follow-up, the mean RAPID3 was lower in the in-person group (3.2 vs. 4.0, $p=0.04$), with no difference in functional status between groups. The change in RAPID3 and functional status over 6 months were no different in the telemedicine vs. in-person group. In multivariate linear regression, no factors (demographics, smoking status, disease characteristics, telemedicine vs. in-person group) were associated with change in RAPID3, but a worsening of functional status was more likely in smokers ($p=0.009$). The percent in low disease activity or remission at 6 months was low (16%) and did not differ by group. Multivariate logistic regression did not identify any factors associated with low disease activity or remission, although there was a non-significant trend toward lower odds of low disease activity or remission with a higher rheumatic disease comorbidity index ($p=0.079$).

Conclusion: Telemedicine can improve access to care in patients with RA. In this study, there was lower disease activity at 6 months in RA patients seen in-person compared to by telemedicine, but it was not significant in multivariate analyses. Based on this study to date, no significant differences are identified between telemedicine and in-person care on short-term outcomes in RA.

Disclosure: E. Ferucci, None; T. Choromanski, None; G. Day, None; S. Freeman, None.

Abstract Number: 278

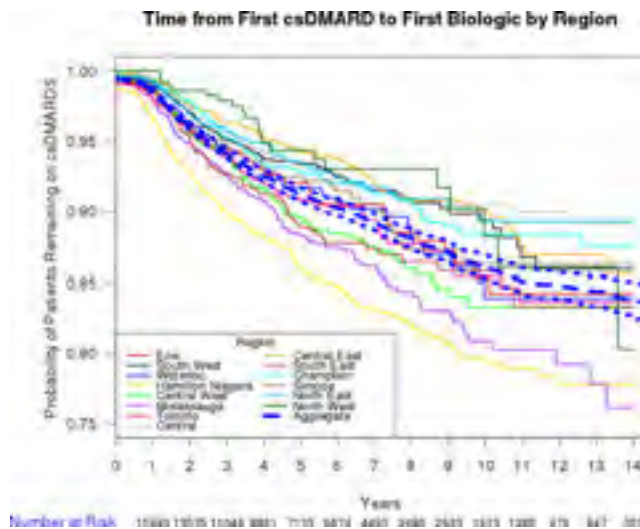
The Effect of Patient, Prescriber and Region on the Initiation of First Biologic for Rheumatoid Arthritis: A Longitudinal Population Study

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Session Information**Session Date:** Sunday, October 21, 2018**Session Title:** Healthcare Disparities in Rheumatology Poster**Session Type:** ACR Poster Session A**Session Time:** 9:00AM-11:00AM

Background/Purpose: Prescribing the first biologic for rheumatoid arthritis is an important decision for physicians, payers, and patients with costs and clinical implications. Our aim was to describe disparities in access to the first biologic prescribed to patients with rheumatoid arthritis in a single payer health care system (no insurance confounders) to explain the relative contributions of patient, prescriber and geographic region characteristics to receipt of first biologic.

Methods: Our study design is a population retrospective administrative data-based population study conducted in Ontario Canada. We used a time-series analysis to describe trends in rheumatologist preference and nested Cox proportional hazards models with random effects and time varying exposures to adjust for patient, physician and geographic area



characteristics. Patients had an incident RA diagnosis between 2001 to 2015 after 66 years of age in Ontario Canada and received at least one csDMARD or biologic. The main exposure was time from the first csDMARD prescription to the outcome of first biologic prescription, adjusted for patient, prescriber and geographic area variables. Patient covariates were age, sex, disease duration, socioeconomic status, distance to care and supply of care in the patient's area of residence. Prescriber covariates were year of graduation, specialty of practice, and the supply of rheumatologic care in the patient's geographic region. Patients were censored at death, move out of province or end of study follow-up.

Results: A total of 17,672 patients met the study inclusion criteria accruing 82,445.79 patient-years of follow up. Variables significantly associated with delayed receipt of first biologic medication, were older age, sex (male)(HR=0.76), lower socioeconomic status (HR=0.92), greater distance to nearest rheumatologist (HR=0.95). Rheumatologist preference for and use of biologics increased 2.5-fold in the study time period but have not kept pace with the number of new active RA patients (3 fold). Geographic area level differences in time to prescriptions of first biologic exists and widens over time with about a 10% difference from highest to lowest prescribing regions 2 years after first csDMARD prescription (Figure 1). Prescriber preference (after adjustment for patient and physician covariates) accounted for 65% of prescription variation while differences between the regions themselves contributed 4.6% to the overall prescription variation.

Conclusion: From a direct measurement of the total Provincial population of RA patients with identical medication coverage, variation in time to receipt of first biologic exist after adjusting for individual level patient, prescriber, and geographic area covariates. These findings illustrate systemic gaps in care and the influence of physician preferences that could be further optimized to improve patient outcomes.

Disclosure: M. Tatangelo, None; G. A. Tomlinson, None; M. Paterson, None; N. Bansback, None; T. Gomes, None; A. Kopp, None; V. Ahluwalia, None; C. Bombardier, None.

Abstract Number: 279

Variations and Disparities in Healthcare Teams Among Individuals with Lupus

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Healthcare Disparities in Rheumatology Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Given the systemic and complex nature of lupus, individuals with lupus are often cared for by a multi-disciplinary team, each provider playing a unique role in lupus treatment, maintenance, or preventive healthcare. The purpose of this study is to analyze the composition of healthcare teams for individuals with lupus across demographic variables.

Methods: This cross-sectional study draws from an online national needs assessment survey conducted between December 2015 and January 2016 among 3,022 adults who self-reported a lupus diagnosis. Respondents identified the type of healthcare providers who cared for their lupus and also the one provider who primarily treated their lupus. Multiple

logistic regression models were conducted to assess the association between self-reported demographic information and treatment team composition.

Results: The majority of respondents (Table 1) had a rheumatologist primarily treating their lupus (78.6%), while a lower percentage reported a primary care provider (PCP) or nephrologist as their primary doctor for lupus (12.9% and 3.3%, respectively). Specific care team compositions emerged when analyzing what provider is primarily responsible for treating the individual's lupus (Table 2). Groups with higher odds of having a rheumatologist in charge of their lupus care included: African Americans, females, and individuals with moderate or severe symptoms. Groups reporting higher odds of having a PCP in charge of their lupus care included rural respondents and respondents with public insurance. The analysis revealed that individuals whose symptoms were moderate to life threatening, who had public insurance and who were under 65 had higher odds of having a PCP on their treatment team. Significantly lower odds of having a PCP on the treatment team were observed among African American and Asian respondents.

Conclusion: The study supports exploring whether rural respondents and individuals with public insurance are experiencing barriers to accessing specialty care. The study also highlights disparities among some minorities who are less likely to have a primary care provider on their care team. Considering the complexity of lupus and its comorbidities, ensuring access to both specialty and primary care is essential.

Disclosure: The Lupus Foundation of America received funding from UCB Pharma to support study data collection.

Table 1. Background characteristics of respondents (n = 3,022)*

Characteristic	No. (%)
Sex	
Female	2823 (93.5)
Male	196 (6.5)
Geographic location	
Rural	560 (18.6)
(Sub)urban	2446 (81.4)
Insurance	
Private	1633 (65.7)
Medicaid/Medicare	851 (34.3)
Age	
Young adults (18-24)	81 (2.7)
Adults (25-64)	2604 (86.2)
Older adults (65-79)	337 (11.2)
Race/ethnicity	
White	1749 (57.9)
African American	544 (18)
Asian	90 (3)
Latino	399 (13.2)
Other races	240 (7.9)
Lupus treatment team	
PCP on lupus treatment team	2178 (72.1)
PCP primarily treating	385 (12.9)
Nephrologist primarily treating	98 (3.3)
Rheumatologist primarily treating	2345 (78.6)
Symptom severity at diagnosis	
Mild	456 (15.2)
Moderate	1114 (37.0)
Severe	1036 (34.5)
Life-threatening	401 (13.3)

* Individual items may not add to totals due to missing data.

Table 2. Logistic regression models of participant characteristics on treatment team composition

	Model 1	Model 2	Model 3	Model 4
	PCP on Treatment Team OR (95% CI)	Rheumatologist Primarily treating lupus OR (95% CI)	PCP Primarily treating lupus OR (95% CI)	Nephrologist Primarily treating lupus OR (95% CI)
Race§				
African American	0.76 (0.59 - 0.97)*	1.43 (1.05 - 1.94)*	0.49 (0.33 - 0.75)†	1.84 (0.98 - 3.47)
Asian	0.43 (0.26 - 0.72)†	0.57 (0.32 - 1.00)	0.27 (0.07 - 1.12)	8.51 (3.81 - 18.99)‡
Latino	0.81 (0.61 - 1.08)	0.85 (0.63 - 1.16)	0.87 (0.58 - 1.30)	2.53 (1.32 - 4.85)†
Other races	1.19 (0.81 - 1.74)	0.93 (0.64 - 1.35)	1.10 (0.72 - 1.71)	1.28 (0.48 - 3.43)
Sex¶				
Female	0.91 (0.61 - 1.34)	1.71 (1.18 - 2.49)†	0.85 (0.53 - 1.36)	0.82 (0.32 - 2.12)
Age group#				
25-64 age group	1.94 (1.13 - 3.33)*	0.89 (0.44 - 1.80)	1.96 (0.60 - 6.39)	1.46 (0.34 - 6.32)
65+ age group	1.44 (0.78 - 2.67)	1.00 (0.47 - 2.15)	1.84 (0.54 - 6.30)	1.27 (0.24 - 6.71)
Location**				

Table . (Cont'd)

	Model 1	Model 2	Model 3	Model 4
	PCP on Treatment Team OR (95% CI)	Rheumatologist Primarily treating lupus OR (95% CI)	PCP Primarily treating lupus OR (95% CI)	Nephrologist Primarily treating lupus OR (95% CI)
Rural	1.08 (0.84 - 1.39)	0.68 (0.53 - 0.87)†	1.70 (1.28 - 2.25)‡	0.76 (0.37 - 1.59)
Insurance††	1.49 (1.19 - 1.87)‡	0.52 (0.41 - 0.65)‡	2.00 (1.52 - 2.64)‡	1.35 (0.80 - 2.26)
Medicaid/Medicare Symptom severity ‡‡				
Moderate	1.34 (1.04 - 1.74)*	1.43 (1.07 - 1.92)*	0.88 (0.61 - 1.25)	0.34 (0.16 - 0.75)†
Severe	1.51 (1.16 - 1.98)†	1.38 (1.02 - 1.85)*	0.87 (0.61 - 1.26)	0.63 (0.32 - 1.25)
Life threatening	1.77 (1.26 - 2.49)†	1.29 (0.89 - 1.86)	0.51 (0.31 - 0.85)*	2.06 (1.07 - 3.98)*

* $P < .05$ † $P < .01$ ‡ $P < .001$

§ Reference group is white.

¶ Reference group is male.

Reference group is 18-24 age category.

** Reference group is suburban/urban.

†† Reference group is private insurance.

‡‡ Reference group is mild symptoms.

Disclosure: R. P. Daly, Lupus Foundation of America, 3; R. Partovi, Lupus Foundation of America, 3; P. Davidson, Lupus Foundation of America, 3.

Abstract Number: 280

Be Fierce. Take Control.TM an Evidence-Based Digital Lupus Awareness and Education Campaign for Young Minority Women at Risk for Lupus

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Healthcare Disparities in Rheumatology Poster – ARHP

Session Type: ACR Poster Session A

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

Background/Purpose: Lupus is a complex, chronic autoimmune disease that has significantly higher prevalence and incidence among minority women.[i] In an effort to reduce the time to diagnosis for populations with highest risk, ACR and the Lupus Foundation of America created a digital awareness and education campaign, *Be Fierce. Take Control.*, intended for African American and Latino women ages 18-25 who may be experiencing lupus symptoms to raise their awareness of lupus and provide evidence-based information on what to do next.

Methods: Formative research was conducted via web-based focus groups with 60 individuals meeting intended audience criteria to gather information on help and information seeking behavior, attitudes towards health care, and appropriateness of culturally relevant language. Using this information, a digital campaign involving mobile ads, videos and articles all directing to a campaign website was developed and tested for cultural relevancy, health literacy, scientific accuracy, and general appeal. Testing was completed using user panels, as well as a rigorous review and approval process by two lupus clinician/researchers. Campaign assets were finalized using feedback, and the campaign was launched in June 2017. Following the first year of launch, user testing was conducted with 10 individuals in the intended audience to provide detailed information on how users navigated the campaign website in order to improve user experience.

Results: The website received a total 114,866 page views in the first year. The majority of visitors read the home page, followed by a page providing reliable resources of next steps to take if lupus symptoms are suspected. 72% of visitors who responded to a helpfulness poll present on each page indicated that the web-content was helpful. User testing post-launch revealed 9 out of 10 users could describe lupus as an autoimmune disease after reviewing the site, and 7 out of 10 users had a better understanding of lupus and would be comfortable enough to approach a doctor about potential lupus symptoms. New updates were released in May 2018 based on these results. In addition, a series of lupus articles were released through a paid media partnership with A Plus media, receiving 345,145 views in the first three months. The partnership also included development and promotion of a video featuring NY Sharks women's football team, depicting the theme of being fierce in their lives with an underlying message on taking control of your health. The video gained

attention from celebrity influencers, generating over 2 million views with nearly a third of its YouTube viewers watching the entire video.

Conclusion: *Be Fierce. Take Control.* provides an example of a well-designed, culturally competent online resource to increase awareness and knowledge of lupus symptoms in African American and Latino women ages 18-25 who may be experiencing lupus symptoms. This is the first digital-only lupus campaign targeted to this audience, highlighting the importance of rigorous testing to ensure cultural relevance in health communication campaigns.

[i] Centers for Disease Control and Prevention. Lupus Detailed Fact Sheet. <https://www.cdc.gov/lupus/facts/detailed.html>. Published May 3, 2018. Accessed June 1, 2018.

Disclosure: R. P. Daly, Lupus Foundation of America, 3; N. Wanty, KDH Research and Communication, 3; M. Maloney, Lupus Foundation of America, 3, Centers for Disease Control and Prevention, 2; S. Boyd, American College of Rheumatology, 3, Centers for Disease Control and Prevention, 2; K. Tse, Lupus Foundation of America, 3; K. Goldstein, Ogilvy, 3.

Abstract Number: 281

Development of an African American Lupus Community-Based Patient and Provider Education Program: Lupus Conversations

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Healthcare Disparities in Rheumatology Poster – ARHP

Session Type: ACR Poster Session A

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

Background/Purpose: African Americans (AA) with lupus experience severe manifestations and outcomes, and a long journey to diagnosis and care. We developed and tested evidence-based, culturally appropriate, scalable lupus education modules, one targeting the diverse AA community and one targeting primary care providers (PCPs). This curriculum was designed to disseminate lupus-related education, reduce stigma, and promote healthcare-seeking norms.

Methods: Rheumatology, public health and behavioral health experts from 2 academic institutions in Boston and Chicago developed 2 learning modules. The first was a didactic and participatory community-based curriculum for Popular Opinion Leaders (POLs). Based on a CDC model, POLs are community leaders trained to disseminate information through their social networks. The goal was to provide predominately AA POLs with lupus education and dissemination materials to improve awareness and promote positive health-seeking behaviors in their communities. The second included videos geared towards PCPs using motivational interviewing principles to improve culturally competent provider communication skills. To prepare both modules, we conducted a literature review on lupus disparities, racial discrimination and social determinants of health. We engaged key academic and community-based AA stakeholders and experts in an iterative process regarding curriculum content, cultural competency, dissemination materials and implementation strategies. POL and physician modules and materials were piloted and reviewed by POLs in Boston and Chicago and by key community stakeholders. Central themes from curriculum feedback were extracted after review of detailed notes.

Results: The community-based POL curriculum included lupus education, POL model principles, community research methods, and dissemination strategies. The POL training was delivered in Boston (N=18) and Chicago (N=19) in four 2-3 hour sessions. Materials included slide presentations, videos, role-plays, data monitoring exercises, and palm cards to facilitate dissemination. Multiple themes from community feedback were extracted (**Table**). The provider curriculum included video web-based modules using actors with scripted scenarios, and “do over” patient-doctor scenarios to demonstrate flawed interactions and subsequent improvement, supplemented by didactic materials. Physician modules were reviewed by the POLs and stakeholders for feedback and were approved for CME credit.

Conclusion: We utilized an interdisciplinary approach involving community-based and academic stakeholders to develop educational modules specific for the AA community. We incorporated nuanced and diverse feedback from community members in 2 cities to develop this tool. Our next step is to facilitate national dissemination.

Table. Key Themes from Popular Opine Leader and Community Stakeholder Curriculum Feedback

	POL Curriculum	Health Provider Video	Dissemination Materials
Popular Opinion Leaders (POL) participating in pilot in Boston (N=18) and in Chicago (N=19)	Theme 1: Development of an “African-American” Specific Model -Concerns about meaning of a targeted “African American (AA) POL model” in setting of significant heterogeneity of the black community by culture, religion, language and socioeconomic status	Theme 1: Hair Loss as a Culturally Significant Symptom of Lupus -Important for providers to understand relevance of hair when treating African American lupus patients-Hair loss may not be most important symptom for all AA patients, need to consider pain, fatigue and kidney problems	Theme 1: Palm Cards as a Dissemination Tool -Palm card with information about lupus symptoms and contact information for Lupus Foundation of America (LFA) and Lupus Society of Illinois (LSI) was well received-Palm card needs more facts about lupus including an explanation that lupus is not contagious, especially in cases of discoid lupus, so that strangers would feel more comfortable talking with them
	Theme 2: Curriculum Content and Presentation -Need more information about clinical trials; Boston or Chicago specific lupus research, choosing a rheumatologist, environmental risk-factors, medications and how they work for different people/ co-morbidities, mental health and lupus -Pictorials, videos and other interactive methods were most effective learning tools	Theme 2: Perceived Discrimination -Discrimination is not always the main issue for AA lupus patients. Some doctors just don’t know enough about lupus and recognizing signs/symptoms-Important to highlight specific discrimination faced by female patients in medical system; providers are dismissive about their pain and equate fatigue with laziness -Female patients often feel more comfortable seeing female providers because they can better relate to their experience	Theme 2: Creating Materials for a Wider Audience - Need more information appropriate for school-aged children and families. - Need to engage men - Need dissemination materials in other languages (e.g. Spanish, Portuguese, French)
	Theme 3: Evaluation Methods -POLs reported feeling flustered and/or overwhelmed by multiple-choice format of pre/post-tests; were reluctant to hand in forms; key points should be clearly presented in slides -Other POLs reported test questions were too easy	Theme 3: Patient-Provider Communication -Providers need to build rapport and address patient’s concerns -Providers should be encouraged to be more open and candid with their patients about clinical tests, results and treatment o Individuals felt that meaning and significance of test results aren’t explained o Individuals felt side effects from medications were not appreciated and contributed to more problems	
Community Stakeholders with experience with academic-community partnerships (N=3)	Theme 1: Tailoring Curriculum to Target City -Importance of including city-specific information in curriculum content o Local statistics regarding demographics and lupus prevalence o Relevant research studies including clinical trials particularly involving local city	Theme 1: Patient Rights -Video highlights patients need to know that they have options when seeing a rheumatologist -It is important that patients have access to information about the treating physician - Partnerships between physicians and patients are important to highlight	Theme 1: Dissemination Tracking -Emphasis on working with the LFA and LSI to track effectiveness of dissemination by measuring changes in call volume and documenting callers who reference the palm cards
	Theme 2: Perception of Research -Include information about perception of research and clinical trials within the community	Theme 2: Cultural humility -The viewer should recognize that physicians should treat patients with empathy	Theme 2: Palm Card Content -Materials should include all available lupus related resources locally -Palm cards depicting AA families are more appealing to different audiences
		Theme 3: Colorism concept -In addition to attention on hair, need to consider incorporating this concept in future modules Theme 4: Diagnosis delays Video addresses a poor patient-doctor encounter but not delays to diagnosis that AA patients with lupus face Theme 5:Language-related feedback Language thought to be clear and easy to understand. Feedback that AA should not be described as “minorities” and term replaced with “underrepresented population”	

Disclosure: K. Mancera-Cuevas, None; C. Phillip, None; C. Leatherwood, None; C. Correia, None; J. Brucker, None; E. Freeman, None; G. Granville, None; K. Mimms, None; P. Canessa, None; C. H. Feldman, None; R. Ramsey-Goldman, None.

The Utility of Positive ANA Referrals at the University of Chicago

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Health Services Research Poster I – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

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

Background/Purpose: The ANA test is nonspecific and can be difficult to interpret without understanding the limitations of the test. Referrals to Rheumatology for positive ANA is a common practice that may lead to unnecessary resource utilization and contribute to delays in patients seeing a rheumatologist. At the University of Chicago, the current wait time for a new patient visit is over 60 days. The aim of this project is to evaluate the quality of our ANA referrals by analyzing how often these patients are diagnosed with an ANA-associated rheumatic disease (AARD) and the associated healthcare expenditures.

Methods: Charts were reviewed for patients referred to the University of Chicago outpatient rheumatology clinic over a 6-month period (April 2017-September 2017) with “positive ANA” as the reason for referral, or if “positive ANA” was a listed problem in the initial Rheumatology note’s plan. Demographic data, referral information, relevant rheumatologic labs and imaging were recorded. Patients’ final diagnoses were organized into the following categories: AARD, possible AARD (ongoing work-up at time of review) or no AARD. Positive predictive value for AARD was calculated using the total number of ANA referrals and the number of referrals diagnosed with AARD. Costs of lab tests and imaging were estimated using the Healthcare Bluebook and lab testing websites.

Results: Eighty-three patients referred for positive ANA were evaluated. The majority of patients were female (64/83,77%). Most patients were either Caucasian (36/83, 43%) or African American (36/83, 43%) with an average age of 40 years (range 19-85 years).

The majority of referrals were internal from University of Chicago providers (58/83,70%). Of these referrals, 50% came from primary care clinics. The six most common reasons for ordering an ANA were: joint pain, fatigue, neuropathy, rash, headache and interstitial lung disease. During initial rheumatologic visit, a total of 234 lab tests were ordered, with an

Lab Test	# of positive results/# total tests ordered (%)
ANA	4/4 (80%)
dsDNA	1/19 (0.5%)
C3/C4	5 (low C4)/39 (13%)
RNP/Smith	3/36 (8%)
SSA/SSB	3/39 (8%)
RF	1/14 (7%)
anti-CCP	0/14 (0%)
ANCA	0/4 (0%)
aPL	0/4 (0%)
ESR	0/22 (0%)
CRP	1/24 (4%)
ACE	0/3 (0%)
Scl-70	1/6 (17%)
Quantitative Igs	0/5 (0%)

Table 1. ACE= angiotensin converting enzyme

estimated cost of \$23,592. A total of 41 joint x-rays were ordered, with an estimated cost of \$3,731. Table 1 shows the most common lab tests ordered and the number of positive tests. The majority of tests were unremarkable. AARD was diagnosed in 5 patients (2 SS, 1 overlap CTD, 2 UCTD). Possible AARD included 7/83 (8%) patients and 71/83 (85%) had no systemic AARD. The positive predictive value (PPV) for AARD was 5.7%.

Conclusion: Our review shows that the PPV of diagnosing AARD in our system is very low and ANA referrals are contributing to unnecessary cost, resource use, and longer wait times for our clinic. As many referrals are internal, the next step of this project will be a multifold intervention including an educational component for primary providers and creating a decision-making support tool in our electronic medical record with the goal of improving the quality of referrals and creating more space for urgent patients to be seen.

Disclosure: V. Patel, None; A. Dua, None.

Abstract Number: 283

Benefits Accrued through the Implementation of Telerheumatology Services

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Health Services Research Poster I – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

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

Background/Purpose: Telerheumatology services were developed at the Southern Arizona VA Health Care System (SAVAHCS) to provide specialty care to remote Community Based Outpatient Clinics (CBOCs). The aims of this study were to examine the potential benefits of this telerheumatology program.

Methods: As part of a quality improvement initiative, we performed a review of the patients seen in the SAVAHCS' weekly telerheumatology clinics in Sierra Vista, Casa Grande, and Yuma, AZ from 2015 to 2017. At each of the CBOCs, we use high level audio-video technology to obtain the patient's history in an in-person visit, direct nurses on appropriate musculoskeletal exams, assist in making diagnoses, and, ultimately, carry out the patient's treatment plan. The nurses received training on recognizing common rheumatologic disorders and performing a focused musculoskeletal exam. We calculated the following: the miles saved based on an estimate of the distance that patients did not need to travel as a result of the telerheumatology visit; miles saved based on round trip miles from the patient's CBOC clinic to the SAVAHCS (i.e. 70 miles one way for both Casa Grande and Sierra Vista CBOCs and 240 miles one way for Yuma CBOC); and estimates of direct cost savings were generated using the reimbursement rate for beneficiary travel (0.415/mile).

We also evaluated the number of encounters and unique patients for the most common rheumatologic diagnoses by CBOC site and by year.

Results: Table 1 summarizes the total number of patient encounters, miles saved, and travel dollars saved by CBOC site and year.

Table 2 summarizes the number of unique rheumatologic diagnoses in each CBOC site and year. A patient may have more than one rheumatologic diagnosis associated with each visit.

Table 1: Summary of number of visits, miles saved and travel dollars saved by clinic site

Site	Year	Total # visits	Total Miles Saved	Travel Dollars Saved
Casa Grande, AZ	2015	22	3,080	\$1,278
	2016	32	4,480	\$1,859
	2017	46	6,440	\$2,673
Sierra Vista, AZ	2015	33	4,620	\$1,917
	2016	37	5,180	\$2,150
	2017	48	6,720	\$2,789
Yuma, AZ	2017	23	11,040	\$4,582
Total 2015-2017		233	41,840	\$17,364

Table 2: Summary of Rheumatologic Diagnosis Codes per year per site

Clinic Site	Sierra Vista			Casa Grande			Yuma	Total
Year	2015	2016	2017	2015	2016	2017	2017	
Rheumatologic Diagnosis								
Rheumatoid Arthritis	1	4	6		1	7	3	22
Osteoporosis	6	5	6			5	1	23
Osteoarthritis	2	2	6				1	11
Gout	3	3	2			2	2	12
Pseudogout	3							3
Psoriatic Arthritis	1	1	2				3	7
Polymyalgia Rheumatica	3	2				1	1	7
Giant Cell Arteritis	1	1	4					6
SLE/Discoid Lupus	1	2	2	1	1			7
Sjogren's/Sicca Syndrome	1	1	3		1	1		7
De Quervain's Tenosynovitis		1						1
Fibromyalgia/Chronic Pain Syndrome		2				2	1	5
Inflammatory Bowel Disease			1			1		2
Ankylosing Spondylitis			1			2	1	4
Sarcoidosis						1	1	2
Unspecified Joint Pain	4	5	10	2	2	4	6	33
Totals	26	29	43	3	5	26	20	152

Of note, the total number of rheumatologic diagnoses in Sierra Vista increased from 26 diagnostic codes in 2015 to 43 diagnostic codes in 2017. In Casa Grande, the number of rheumatologic diagnostic codes increased from 3 in 2015 to 26 in 2017.

Conclusion: Our telerheumatology program has demonstrated a year-to-year increase in the use of the provided services, based on the increase in patient visits and diagnostic codes. Overall, telerheumatology shows excellent potential in increasing access to underserved populations by decreasing travel-related costs, as well as decreasing the time and distance traveled to appointments.

Disclosure: A. Peck, None; A. Pender, None; C. K. Kwok, None.

Abstract Number: 284

Challenges and Barriers to Employment That Persons with Osteoarthritis Face at Work Due to Their Condition

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Health Services Research Poster I – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

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

Background/Purpose: To understand the challenges that people with osteoarthritis (OA) experience at work due to their condition, for the purpose of adapting to OA the content of Making It Work™, an online self-management program supporting workers with inflammatory arthritis (IA) to remain employed and lead healthy and productive lives at work.

Methods: Eight focus groups were conducted with 34 workers with OA (1 group with hand OA, 1 hip, 2 knee, and 4 multi-joint OA). Patients were recruited through arthritis consumer organizations, a teacher's benefit plan, and outpatient arthritis clinics. Eligibility criteria included, being currently employed, age 18–70 years, having been diagnosed with OA by a physician and reporting being affected by OA at work. Focus group were conducted using a standardized interview guide, led by an experienced facilitator and transcribed verbatim. Transcripts were analyzed independently by 2 researchers. A thematic analysis followed a general inductive approach to identify problems and organize them into topics and broad categories.

Results: The sample included 34 patients (mean age 55 years; OA duration: 8.2 yrs), working in education (n=23); health care (n=6); business (n=2); office/ clerical (n=3). Analysis revealed 4 main categories of problems or challenges:

1. Impact of OA : current symptoms (pain, psychological symptoms, fatigue due to constant pain and need for planning), impact of OA (functional limitations, interpersonal relationships, e.g., lack of understanding or fear of annoying others, reduced self-confidence, reduced social participation) and evolution of symptoms (variability, unpredictability).
2. Barriers to cope with OA: physical environment, lack of effective treatment, difficulty adapting having OA, other impacts (financial consequences, comorbidity).
3. Difficulties at work: impact of OA at work, e.g., safety issues, barriers at work [job characteristics (e.g., time constraints), job environment (e.g., limited work space or poor equipment), lack of support, reluctance to disclose (due to fear of stigmatization), difficulty commuting].
4. Adaptations to work done by patients without requesting job accommodations: modifying movement, activities or position, and planning work differently to avoid pain, addressing mobility and commuting issues (e.g finding parking close to work).

Conclusion: The study identified challenging issues meaningful to individuals working with OA. Though issues are similar to those described by IA patients, they are described differently, and their respective importance differs. Findings will be useful to vocational counsellors and other health professionals helping people with OA deal with employment issues related to their arthritis, and to people developing employment health services for arthritis.

Disclosure: A. C. Rat, None; A. Stewart, None; P. Rogers, None; D. P. Mosher, None; D. Lacaille, None.

Abstract Number: 285

Inflammatory Bowel Disease Is Associated with a Substantial Economic Burden in Patients with Psoriatic Arthritis and in Patients with Ankylosing Spondylitis

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Session Information

Session Date: Sunday, October 21, 2018

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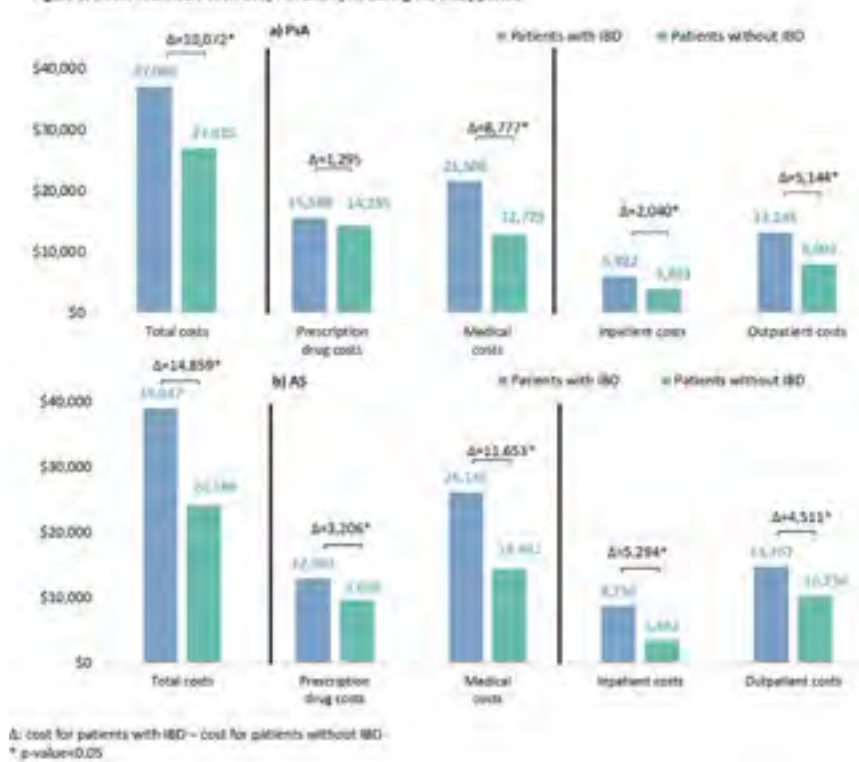
Background/Purpose: Psoriatic arthritis (PsA) and ankylosing spondylitis (AS) belong to a group of inflammatory arthritides known to share similar extra-articular manifestations, such as inflammatory bowel disease (IBD). Though, IBD, PsA, and AS individually present significant economic burden, it is not clear whether there is an incremental economic burden associated with IBD among patients with PsA or AS. This study aims to describe the prevalence and incidence of IBD and quantify the healthcare resource utilization (HRU) and direct healthcare costs associated with IBD among patients with PsA and AS.

Methods: Adult patients with ≥ 2 claims for PsA or AS were selected from a large US claims database (Q12007–Q32016). Prevalence and incidence of IBD, including Crohn's disease (CD), ulcerative colitis (UC), and IBD-related gastrointestinal (GI) disturbances (gastroenteritis/colitis/gastritis) were assessed during the 1-year period following the initial claim for PsA/AS (i.e., study period) in PsA patients and AS patients separately. Prevalence and incidence for each individual condition were also reported. HRU and costs (2017 US\$) were assessed during this period and compared between patients with (cases) and without (controls) IBD. Cases and controls were required not to have any IBD diagnosis during the 1-year period before their first claim for PsA/AS and were matched 1:1 on age, sex, region of residence, health plan type, index year, and employment status. The comparison of HRU and costs were conducted using Wilcoxon signed-rank test.

Results: We identified 22,205 PsA and 9,980 AS patients. IBD prevalence was 3.8% (CD: 1.0%; UC: 0.9%; GI disturbances: 2.5%) in PsA patients and 8.5% (3.8%; 2.7%; 4.2%) in AS patients. IBD incidence was 2.5% (0.4%; 0.3%; 2.0%) in PsA and 4.1% (1.0%; 0.8%; 2.9%) in AS. There were 464 PsA and 314 AS patients with IBD who were matched 1:1 with PsA and AS patients without IBD during the study period.

Patients with IBD had significantly higher HRU, including more outpatient (OP), emergency room, and inpatient (IP) visits, more IBD-related procedures (e.g., gastro-related endoscopy, abdominal/bowel imaging), and more corticosteroid use. In PsA, the mean annual total costs were \$37,086 for patients with IBD, 27% higher than for patients without IBD ($p < 0.001$; Figure 1); in AS, the costs were \$39,047 for patients with IBD, 38% higher than for patients without IBD

Figure 1. Direct healthcare costs in a) PsA and b) AS during the study period



($p < 0.001$). The difference in total costs was largely driven by the difference in medical costs (PsA: 87%; AS: 78%). Of the medical cost difference, 23% and 59% were accounted for by the differences in IP and OP costs, respectively, in PsA patients, while the percentages were 45% and 39% in AS patients.

Conclusion: IBD prevalence and incidence were 3.8% and 2.5% in PsA and 8.5% and 4.1% in AS, respectively. In both PsA and AS, IBD was associated with substantial economic burden, including higher HRU and healthcare costs.

Disclosure: M. J. Bergman, AbbVie Inc., 5, 8, BI, 5, Genentech, Inc., 5, GSK, 5, Horizon, 5, Janssen, 5, Novartis, 5, 8, Pfizer, Inc., 1, 5, Sanofi, 5, 8, Celgene Corporation, 8, JNJ, 1; P. Zueger, AbbVie Inc., 1, 3; J. Song, Analysis Group, Inc., 3; I. Pivneva, Analysis Group, Inc., 3; K. A. Betts, Analysis Group, Inc., 3; A. D. Joshi, AbbVie, Inc., 1, 3.

Abstract Number: 286

The Prevalence and Treatment Patterns of Women of Childbearing Age with Rheumatic Diseases

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Session Information

Session Date: Sunday, October 21, 2018

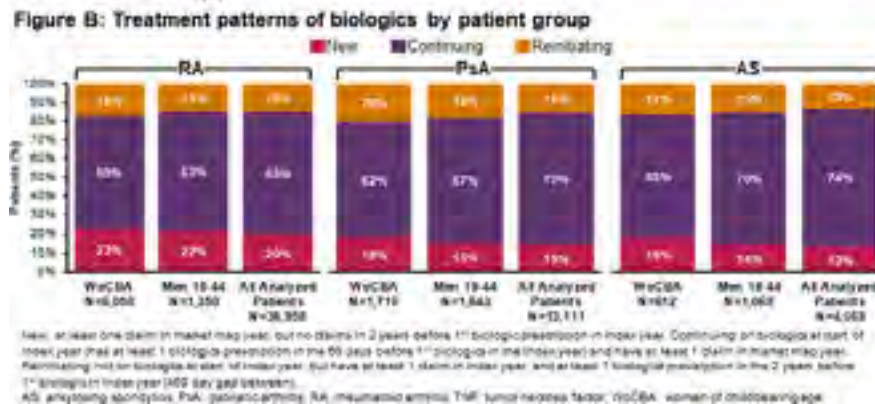
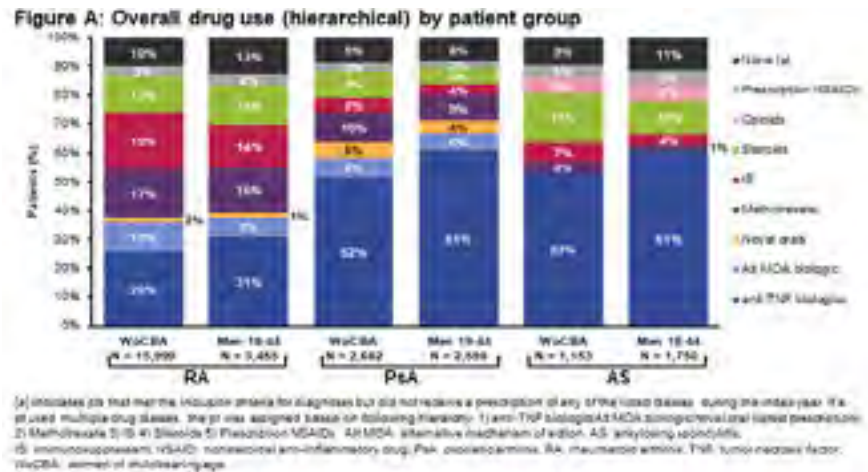
Session Title: Health Services Research Poster I – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

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

Background/Purpose: Emerging data on exposure of infants to therapeutics through placental transfer and breastmilk could impact the management of women of childbearing age (WoCBA) with rheumatic diseases (RD; including rheumatoid arthritis [RA], psoriatic arthritis [PsA] and ankylosing spondylitis [AS]). This descriptive study assessed differences in treatment patterns of patients (pts) with RD between WoCBA and comparator groups.

Methods: IMS PharMetrics claims were used to identify pts continuously enrolled between Jan 2014–Dec 2015 with: ≥ 2 RD diagnosis codes and ≥ 1 RD diagnosis or ≥ 1 RD medication claim between Jan–Dec 2015 (measurement period). Age/gender at the start of the measurement period were used to allocate pts to the following cohorts: WoCBA (aged 18–44



years), Women (45–65), Men (18–44), and Men (45–65). Outcomes assessed in the measurement period included % biologics utilization and treatment changes (discontinuation [≥ 60 -day gap with no additional biologic claims]; switch [initiation of new biologic within 60 days]; re-initiation of the same or new biologic [after gap ≥ 60 days]).

Results: Of the WoCBA pts analyzed, 15,999 had RA, 2,682 PsA and 1,153 AS. Biologic utilization among WoCBA pts with RD was lower compared with men in the same age group. Use of methotrexate was similar between genders for RA and PsA pts, but higher for WoCBA than for men with AS (**Figure A**). Across RD pt cohorts on biologic therapy, WoCBA had the highest proportion of new and reinitiating pts, and the lowest proportion of continuing pts (**Figure B**). Similarly, across RD indications, the WoCBA pt group on biologic therapy had one of the highest numbers of Switch, Reinitiate (new), and Discontinue events, compared to all other groups.

Conclusion: Despite the importance of disease control prior to, during and after pregnancy, trends show lower rates of biologic use in WoCBA pts. Further exploration is needed to better understand how treatment patterns among WoCBA pts are impacting their disease outcome and how to best optimize care.

The study was funded by UCB Pharma, conducted by Charles River Associates, medical writing by Julia Bárdos, Costello Medical, UK. We thank the patients, their caregivers and the investigators who contributed.

Disclosure: E. Lee, UCB Pharma, 3; R. Suruki, UCB Pharma, 3; B. Carpenter, Charles River Associates, 3; T. Harkness, Charles River Associates, 3; D. Luk, Charles River Associates, 3; M. Yassine, UCB Pharma, 3.

Comparison of Real-World Costs between Patients with Rheumatoid Arthritis Treated with Subcutaneously-Administered Biologics Previously Treated with Another Biologic

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Session Information

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

Background/Purpose: To compare real-world healthcare costs between patients with rheumatoid arthritis (RA) who were treated with subcutaneously (SC) administered biologics after previously using at least one other biologic agent.

Methods: Using the Truven Health MarketScan® Commercial and Medicare Supplemental data, adult RA patients initiating one of six SC biologics between January 1, 2014 and June 30, 2016 were identified. Episodes (patients could contribute more than one) of treatment were captured, starting with initiation of index SC biologic and ending with end of data, end of continuous enrollment, switch to new biologic, or gap of 90+ days without index medication. Per-month biologic costs and RA-related healthcare costs (defined as claims with an RA diagnosis code or drug code for RA medication) were measured during the variable-length episodes. Generalized estimating equations models (accounting for multiple episodes per person) were used to compare costs between biologic agents by year of initiation, adjusting for baseline demographics and clinical characteristics.

Results: The sample comprised 10,464 episodes (from 8,418 patients). Biologics and number of episodes, by year of initiation 2014, 2015, 2016, were: tocilizumab—758, 557, 279; abatacept—970, 754, 453; adalimumab—1327, 1070, 526; etanercept—968, 888, 461; certolizumab—360, 330, 174; golimumab—284, 196, 109. Biologic costs accounted for 91-95% of total RA-related costs. Mean adjusted per month biologic costs, by year of initiation—2014, 2015, 2016—were: tocilizumab—\$2900, \$2765, \$3065; abatacept—\$3219, \$3534, \$4510; adalimumab—\$3478, \$4609, \$5145; etanercept—\$3129, \$4222, \$4154; certolizumab—\$4196, \$4697, \$5780; golimumab—\$3237, \$3513, \$4335. Tocilizumab per month costs were significantly lower ($p < 0.05$) than abatacept (2015, 2016), adalimumab (2015, 2016), etanercept (2015, 2016), certolizumab (2014, 2015, 2016), and golimumab (2016).

Conclusion: Among RA patients treated with SC biologics after using at least one other biologic, patients treated with tocilizumab generally had lower real-world costs than those treated with other SC therapies.

Disclosure: J. H. Best, Genentech, Inc., 3; P. Juneau, Truven Health Analytics, an IBM Company, 3; A. Kong, Truven Health Analytics, an IBM Company, 3.

Burden of Illness of Treating Patients with Pemphigus vulgaris

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Background/Purpose: Pemphigus vulgaris (PV) is a rare autoimmune disorder that affects the skin and mucous membranes. Many patients with PV suffer from serious infections, and though rare, mortality is associated with complications of treatment of PV, including corticosteroids. This study aimed to estimate the burden of illness in patients with PV in the US.

Methods: A retrospective cohort of patients with a new diagnosis of PV was identified from the Truven Health Marketscan US commercial claims database between January 1, 2009 and September 30, 2016. Newly diagnosed PV patients were defined by one inpatient diagnosis or two outpatient diagnoses of Pemphigus NOS/PV ((PV), ICD-9/10 694.4/L10.0)) during the study period and no PV diagnosis in prior 12 months. One-year healthcare resource use and costs were calculated, and the most prevalent comorbidities in the PV population are described.

Results: A cohort of 631 PV patients was identified. The mean age of the cohort was 50 (SD=11) years and 55% were female. During the baseline period, the most frequently reported comorbidities were opportunistic infections (62.8%), hypertension (23.3%), and type 2 diabetes (12.8%); 58.3% of patients were prescribed corticosteroids. During the first-year after diagnosis of PV, outpatient visits were the most frequently reported resource use (mean=19.5; SD=17.5); mean length of inpatient stays, for patients with hospitalization, was 12.0 (SD=21) and mean ER visits were 0.33 (SD=0.8). Mean total costs in the year prior to diagnosis were \$16,420 (SD: \$39,781), comprised of pharmacy (\$2,500; SD=\$4,993), inpatient (\$5,423; SD=\$27,618), and outpatient (\$8,498; SD=\$17,121). Mean total costs during first year after diagnosis were \$30,742 (SD=\$69,875). Total costs were comprised of pharmacy (\$3,558; SD=8,858), inpatient (\$5,623; SD=\$18,108), and outpatient (\$21,561; SD=\$59,785). The mean cost [SD] of outpatient services during the first year after diagnosis was: durable medical equipment (\$1,107 [\$2,319]), evaluation and management (\$2,105 [\$2,386]), unclassified (\$8,717 [\$41,132]), imaging (\$1,454 [\$3,066]), other outpatient services (\$14,207 [\$48,573]), procedures (\$4,713 [\$17,383]), and tests (\$1,590 [\$2,604]).

Conclusion: Patients diagnosed with PV have high a comorbidity burden, particularly opportunistic infections. Healthcare costs almost doubled in the year following the diagnosis of PV compared to one year prior to diagnosis of PV.

Disclosure: J. H. Best, Genentech, Inc., 3; M. Michalska, Genentech, Inc., 3; I. Abbass, Genentech, Inc., 3.

Abstract Number: 289

Adherence of Etanercept in Iraqi Patients with Rheumatoid Arthritis: One- and Five-Year Data from a Local Registry

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Background/Purpose: Real-world data on adherence to TNF α inhibitors in patients with RA are missing from many regions, including the Middle East. This study evaluated the real-world 1- and 5-year adherence to etanercept (ETN) among Iraqi patients with RA.

Methods: This observational, retrospective study assessed patient data entered in the National Center of Rheumatology in Iraq database during the period May 2012 – May 2017. Individuals aged >18 years, with a diagnosis of RA, and who required treatment with ETN, with or without MTX, were identified and included in the analysis. Those previously treated with a different biologic or who were enrolled in a randomized clinical trial were excluded. Adherence was assessed for 1- and 5-year periods, with 1-year adherence defined as 7 consecutive patient visits. Demographics, Disease Activity Score 28 (DAS28), Clinical Disease Activity Index (CDAI) scores, and adverse events (AEs) data were also collected. Editorial support was provided by Charlene Rivera, PhD, and Vojislav Pejovic, PhD, of Engage Scientific Solutions and was funded by Pfizer.

Results: In total, data from 1293 individuals were collected. Approximately half (51.7%, n=668) were treated concomitantly with MTX and 40.4% were taking prednisolone. At baseline, the mean (\pm standard deviation) disease duration was 10.0 \pm 8.3 years, and mean CDAI and DAS28 scores were 27.6 \pm 13.0 and 5.7 \pm 2.0, respectively. The adherence to treatment at 1 year was 86.5% (n=1119) for all patients and 85.5% (n=571) for those also receiving MTX. Among patients who discontinued treatment at 1 year, 75.2% (n=112) did not specify a reason, 20.8% (n=31) reported lack of efficacy, and 4.0% (n=6) reported side effects as reasons for discontinuation. Patients who discontinued treatment at 1 year due to side effects or other unspecified reasons had significantly improved CDAI and DAS28 scores at the last follow-up visit compared with baseline scores (16.3 and 19.9 vs 26.3 and 26.3 for CDAI, respectively; 4.5 and 4.8 vs 5.4 and 5.5 for DAS28, respectively; p \leq 0.001). The adherence at 5 years was 61.3% (50.4% for patients treated concomitantly with

MTX). Among patients who discontinued treatment at 5 years, 84.6% did not specify a reason, 12.2% reported lack of efficacy, and 3.2% reported side effects as reasons for discontinuation. Average CDAI and DAS28 scores significantly decreased at the last follow-up visit compared with baseline among patients still on treatment at 5 years (19.9 vs 26.6 and 4.7 vs 5.6, respectively; $p=0.001$).

Conclusion: A majority of real-world Iraqi patients with RA were adherent to ETN treatment after 5 years. Furthermore, most patients tolerated treatment with ETN and had significant improvements in treatment scores at 5 years. Adherence was higher among patients in the total population compared with the subset receiving concomitant MTX.

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Abstract Number: 290

Emergency Department (ED) Utilization Among SLE Patients and Controls in the Population-Based Michigan Lupus Epidemiology & Surveillance (MILES) Cohort

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Background/Purpose: SLE patients frequent the emergency department (ED) irrespective of their access to care, which raises concerns regarding the quality of care in the ambulatory setting. We investigated the characteristics and patterns of ED utilization among MILES Cohort participants to identify opportunities to improve quality of care in SLE.

Methods: Data were derived from the baseline visit of MILES, a longitudinal, population-based cohort of SLE patients and controls in southeastern Michigan. Frequency of ED utilization in the preceding 12 months was categorized as none, 1-2 visits, or 3 or more visits. We used stratified multivariable ordered logistic regression to evaluate factors associated with increasing frequency of ED utilization. Variables determined *a priori* to be important, or with p -values <0.1 in univariate analysis, were included in multivariable models (listed in Table 2).

Figure 1: ED utilization in the preceding 12 months among MILES Cohort participants



Table 1. Characteristics of MILES Cohort participants

	SLE	Control	p-value
Number of participants	462	192	
Percentage of participants, %	70.6	29.4	
Demographics			
Age, mean years (SD)	53.5 (12.5)	53.6 (14.0)	0.781
Female, n (%)	430 (93.1)	154 (80.2)	<0.001
Race, n (%)			0.633
White	246 (53.2)	109 (56.8)	
Black	208 (44.6)	78 (40.6)	
Other	10 (2.2)	5 (2.6)	
Insurance, n (%)			0.245
Private/Commercial	90 (46.9)	90 (46.9)	
Medicaid	112 (24.2)	47 (24.5)	
Medicare	134 (29.0)	42 (21.9)	
Other	8 (1.7)	6 (3.1)	
No insurance	10 (2.2)	7 (3.6)	
Total Family Income in USD, n (%)			0.281
0-99,999	237 (51.3)	114 (59.4)	
100,000-99,999	100 (21.7)	57 (29.2)	
100,000 or more	98 (21.2)	33 (17.2)	
Unknown	27 (5.8)	8 (4.2)	
Education level, n (%)			0.756
Less than high school	41 (8.9)	16 (8.3)	
High school completion	46 (10.0)	26 (13.5)	
Some college	125 (27.1)	55 (28.7)	
Associate's	76 (16.5)	28 (14.6)	
Bachelor's	88 (19.1)	37 (19.3)	
All Higher Degrees	85 (18.4)	30 (15.6)	
Healthcare Resource Utilization in preceding 12mo, n (%)			
Unable to get necessary care	36 (7.8)	10 (5.2)	0.239
Last ambulatory care visit	453 (98.9)	172 (90.0)	<0.001
Mental healthcare visit	01 (19.7)	34 (17.7)	0.536
ED Utilization			
Number of ED visits in the past 12mo, mean (SD)	1.2 (1.1)	0.5 (1.6)	0.007
Frequency of ED visit, n (%)			<0.001
None	246 (53.5)	135 (70.7)	
1-2 ED visits	149 (32.5)	44 (23.0)	
≥3 ED visits	64 (14.0)	12 (6.3)	
Pain			
VAS pain score, mean (SD)	5.2 (2.5)	3.3 (2.8)	<0.001
Pain catastrophizing score, mean (SD)	7.9 (7.6)	4.4 (6.3)	<0.001
Current opioid use, n (%)	143 (31.0)	15 (7.8)	<0.001
Satisfaction with life score, mean (SD)	30.8 (8.1)	23.0 (7.7)	0.001

*VAS=visual analog pain scale

Results: Characteristics of the MILES Cohort participants (462 SLE patients and 192 controls) at baseline visit is summarized in Table 1. ED utilization grouped by frequency is shown in Figure 1, where SLE patients reported a total of 572 ED encounters and controls a total of 113 ED encounters. SLE patients reported higher pain scores and pain catastrophizing scores compared to controls, and more reported current opioid use ($p<0.001$). In stratified multivariable ordered logistic analysis, increasing frequency of ED utilization among SLE patients was associated with black race [OR 1.53(95% CI 1.01-2.31)], Medicaid coverage [2.35 (1.28-4.33)], and current opioid use [2.19(1.41-3.42)]. Among controls, black race [2.33 (1.08-5.03)] and higher pain catastrophizing scores [1.06 (1.00-1.12)] were associated with increasing frequency of ED utilization.

Conclusion: Factors associated with increasing frequency of ED utilization among SLE patients differ from those among controls from the general population. Although SLE patients experience high pain burden, only current opioid use is associated with frequent ED utilization. Opioid therapy is associated with high morbidity and mortality, and further study aimed at understanding opioid prescribing practices for SLE patients who frequent the ED is warranted to identify opportunities to improve quality of care.

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Table2: Results from stratified multivariable ordered logistic models analyzing factors associated with increasing frequency of PD utilization among SLE patients and controls of the MILES Cohort

Variables	SLE		Control	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	0.98 (0.96-1.00)	0.051	0.99 (0.96-1.02)	0.629
Sex				
Male	Reference	-	Reference	-
Female	0.87 (0.41-1.80)	0.701	1.43 (0.53-3.82)	0.480
Race				
White	Reference	-	Reference	-
Black	1.53 (1.01-2.31)	0.043*	2.33 (1.08-5.03)	0.031*
Other	2.81 (0.84-9.40)	0.092	1.25 (0.09-16.74)	0.867
Insurance				
Private	Reference	-	Reference	-
Medicaid	2.35 (1.28-4.33)	0.006*	2.65 (0.92-7.65)	0.071
Medicare	1.53 (0.90-2.61)	0.119	1.62 (0.58-4.51)	0.393
Other	2.79 (0.62-12.51)	0.179	1.40 (0.19-9.99)	0.733
No insurance	0.46 (0.08-2.46)	0.364	omitted	0.988
Income				
0-59,999	Reference	-	Reference	-
60,000-99,999	1.21 (0.71-2.08)	0.485	2.57 (0.93-7.67)	0.069
More than 100,000	0.93 (0.50-1.73)	0.827	1.05 (0.30-3.61)	0.942
Unknown	0.98 (0.41-2.37)	0.965	2.86 (0.36-19.68)	0.337
Higher Education	1.00 (0.87-1.17)	0.938	0.90 (0.68-1.19)	0.470
Healthcare Resource Utilization (12mo)				
Last ambulatory care visit	2.02 (0.21-19.29)	0.541	1.95 (0.40-9.51)	0.410
Mental healthcare visit	1.53 (0.93-2.51)	0.092	0.58 (0.21-1.60)	0.294
Pain				
VAS pain score	1.04 (0.94-1.14)	0.457	0.96 (0.84-1.10)	0.551
Pain Catastrophizing scale	1.03 (0.99-1.06)	0.105	1.06 (1.00-1.12)	0.044*
Current opioid use	2.19 (1.41-3.42)	0.001*	2.21 (0.70-6.93)	0.175
Satisfaction with Life Scale	0.93 (0.84-1.08)	0.273	0.88 (0.72-1.09)	0.239

*VAS=visual analog pain scale

* Statistically significant with p-value <0.05

Abstract Number: 291

Factors Associated with High-Dose Corticosteroid Use in SLE Patients Post Initiation of SLE Therapy

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Health Services Research Poster I – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

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

Background/Purpose: Systemic lupus erythematosus (SLE) therapies include non-steroidal anti-inflammatory drugs, antimalarials, systemic immunosuppressants, and biologics with corticosteroids as necessary. The majority of these current therapies are only partially effective in disease control. Despite treatment, patients may experience flares of disease activity, which can lead to progressive end-organ damage. Severe flares may require intensive immunosuppression, including with high-dose corticosteroids, with risk including end-organ damage. The objective was to understand the unmet need in SLE by quantifying use of high-dose (≥ 40 mg/day) corticosteroids and determining factors associated with its use.

Methods: This study utilized the Truven Marketscan® commercial claims database. Patients were indexed on first use of antimalarial, oral immunosuppressant or biologic during 2012-2013 (first use determined based on no claims for the 3 drug classes during the 1-year pre-index). Included patients had 2 recorded SLE diagnoses, were 18-50 years of age and had continuous medical and prescription enrollment from baseline through the 2-year follow-up. Patients with other pre-specified autoimmune disorders or cancers during the study period (baseline through follow-up) were excluded. During follow-up, fill of at least 1 high-dose corticosteroid prescription was assessed and associative logistic regression modeling performed.

Results: 1,401 patients (93% female; mean age 38.4 years) met the study criteria; 79% were indexed on an antimalarial, 15% on an oral immunosuppressive, 1% on a biologic and 5% on a combination of at least 2 of the aforementioned classes. 16% patients received a diagnosis code for nephritis or chronic kidney disease (CKD), 3% for myocarditis or pericarditis, and 13% for thrombocytopenia or leukopenia. During baseline, 56% of patients had at least 1 visit to a rheumatologist and 13% filled at least 1 high-dose corticosteroid prescription. During follow-up, 22% of patients had at least 1 high-dose corticosteroid prescription. Factors significantly associated ($p<0.05$) with high-dose corticosteroids during follow-up included: baseline rheumatologist visit ($OR=0.62$; 95% $CI=0.47-0.82$), number of SLE medication classes received during follow-up ($OR=1.85$, 95% $CI=1.36-2.51$), receipt of high dose corticosteroid during baseline ($OR=5.21$, 95% $CI=3.60-7.53$), nephritis or CKD ($OR=1.85$, 95% $CI=1.29-2.64$), myocarditis/pericarditis ($OR=3.38$, 95% $CI=1.75-6.55$), and thrombocytopenia/leukopenia ($OR=1.70$, 95% $CI=1.17-2.48$).

Conclusion: A number of baseline factors were associated with high-dose corticosteroid treatment during the follow-up period; one notable factor is the high percentage of patients using high-dose corticosteroids (≥ 40 mg/day). This indicates that important subsets of patients experience inadequate disease control with current therapies. This study reveals high-dose corticosteroid use is prevalent in SLE management broadly, underscoring the unmet need in this population.

Disclosure: K. Schroeder, Eli Lilly and Company, 1, 3; S. Gelwicks, Eli Lilly and Company, 1, 3; J. Paik, Eli Lilly and Company, 1, 3; R. W. Hoffman, Eli Lilly and Company, 1, 3.

Abstract Number: 292

Derivation of a National Rheumatoid Arthritis Cohort in the Veterans Health Administration and Validation with the Veterans Affairs Rheumatoid Arthritis Registry

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Table 1. Frequency of patients in the VA fulfilling RA algorithms from 1/2000 - 4/2018

Algorithm	Components	Number of Patients	N (%) VARR identified
1	RA diagnostic codes	171,946	2301 (98.5)
2	RA diagnostic codes + rheumatologist diagnosis	81,449	2400 (98.5)
3	RA diagnostic codes + rheumatologist diagnosis + DMARD	71,087	2347 (98.0)
4	RA diagnostic codes + (rheumatologist diagnosis + DMARD, OR all rheumatologist diagnoses)	80,373	2399 (98.4)
5	RA diagnostic codes + (rheumatologist diagnosis + DMARD, OR all rheumatologist diagnoses) + exclusion of Anky Spond and PsA	61,791	2300 (94.7)
6	RA diagnostic codes + (rheumatologist diagnosis + DMARD, OR all rheumatologist diagnoses) + positive antinuclear antibody + exclusion of Anky Spond and PsA	90,891	2488 (94.5)

Diagnostic codes were at least 1 ICD-9/ICD-10 for RA, 90 days apart
* Rheumatoid factor or anti-CCP antibody above reference value
Abbreviations: VARR, Veterans Affairs Rheumatoid Arthritis Registry; RA, Rheumatoid arthritis; DMARD, disease-modifying antirheumatic drug; Anky Spond, ankylosing spondylitis; PsA, psoriatic arthritis

Table 2. Characterization of National VA RA cohort by medication ever use and autoantibody status, compared to participants within the VARR registry

Algorithm	National VA				VARR patients identified by algorithm			
	% Any DMARD	% MTX	% RF positive	% CCP positive	% Any DMARD	% MTX	% RF positive	% CCP positive
1	74.7	51.2	15.9	56.1	99.5	83.2	84.0	83.8
2	85.0	58.8	18.1	58.9	99.5	86.2	84.0	83.8
3*	100.0	69.2	81.1	80.1	100.0	88.6	84.1	84.0
4	88.4	61.3	58.7	57.4	99.3	83.2	84.0	83.8
5	99.1	68.1	84.2	82.2	99.5	83.3	84.2	83.8
6	97.6	65.3	65.3	64.6	99.5	83.3	84.3	84.7

* Algorithm required DMARD prescription
DMARD and methotrexate % are those who had a prescription at any time during follow-up

Session Information

Session Date: Sunday, October 21, 2018

Session Title: Health Services Research Poster I – ACR/ARHP

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

Background/Purpose: The Veterans Health Administration health system represents the largest integrated healthcare system in the U.S. and maintains robust administrative and clinical data that can facilitate outcomes research of chronic diseases. Our objective was to compare the ability of a combination of available Veterans Affairs (VA) data sources to define a national cohort of rheumatoid arthritis (RA) patients and validate these potential cohorts using the Veterans Affairs Rheumatoid Arthritis (VARA) Registry.

Methods: We queried national VA data in the Corporate Data Warehouse within the VA Informatics and Computing Infrastructure from 2000 through April 1, 2018. We collected outpatient and inpatient diagnostic codes, diagnostic codes from non-VA providers, outpatient medications and IV infusions, non-VA medications, provider specialty, autoantibody status, and corresponding dates. We tested the performance of administrative-based algorithms with varying requirements for RA classification. We characterized cohort membership by DMARD use and autoantibody status, and then calculated the sensitivity of each algorithm in VARA where all participants (n= 2640) fulfilled 1987 ACR RA Criteria.

Results: Using an RA algorithm based only on diagnostic codes, we identified 121,946 unique patients in the VA (Table 1). More stringent algorithms requiring rheumatologist diagnosis, DMARD use, exclusion of other rheumatic diseases, and/or incorporating autoantibody results reduced the cohort size (60,845 in the most stringent algorithm). The application of additional criteria had a limited impact on the sensitivity, with the most stringent algorithm identifying 94.5% of VARA participants. The proportion receiving a DMARD consistently increased with more restrictive algorithms in the national cohort (Table 2). The most restrictive algorithm yielded 97.6% with DMARD use (69.3% for MTX). Similarly, autoantibody positivity increased with greater stringency of the algorithm with a frequency of anti-CCP positivity ranging from 56.1% in criteria using only diagnostic codes to 64.6%.

Conclusion: Administrative-based algorithms are highly sensitive for defining a national cohort of VA patients with RA. The characteristics of this newly assembled national cohort reflect those of an established RA registry with respect to DMARD use, suggesting reasonable specificity. Greater autoantibody positivity in VARA registry may be due to channeling of seropositive subjects into registry participation.

Disclosure: B. R. England, None; P. Roul, None; B. Sauer, None; S. Pei, None; G. W. Cannon, Amgen Inc., 2; J. F. Baker, Corrona, Bristol Myers Squibb, 5; T. R. Mikuls, BMS, Ironwood, Horizon, 2, Pfizer, Inc., 5.

Abstract Number: 293

Temporal Trends and Factors Associated with Bisphosphonate Drug Holidays

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Session Information

Session Date: Sunday, October 21, 2018

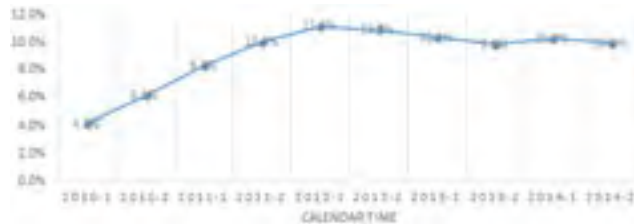
Session Title: Health Services Research Poster I – ACR/ARHP

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

Background/Purpose: Safety concerns related to osteoporosis (OP) medication use and temporary or permanent cessation of bisphosphonate therapy (e.g. ‘drug holidays’) have generated appreciable attention in the lay media and medical community. We examined trends and factors associated with BP drug holidays.

Methods: We assembled a cohort of women (‘OP cohort’) who had osteoporosis as diagnosed by a physician, fragility fracture, or were treated with any OP therapy using 2009-2015 Medicare data (100% sample). Women with Paget’s or malignancy were excluded. Use of any OP therapy was examined in 6 month calendar time intervals during which women had to remain alive with full medical & pharmacy coverage. We identified the subgroup of women (‘long term BP user cohort’) who had initiated BP therapy and were $\geq 80\%$ adherent with any BP for ≥ 3 years. Women were considered to



have taken a BP holiday if they had a gap in BP use > 12 months. We examined patterns of BP drug holidays over time, stratified in 6 month intervals and by cumulative duration of BP drug use.

Results: From a source population of more than 3 million women with osteoporosis, declining trends in use of all OP therapies were observed. Overall oral BP use fell by more than 50% from 2010 to 2014, although declines plateaued between 2012 and 2104. A total of 160,369 long-term BP users were identified, with mean (SD) age of 78.5 (7.5) years; 71% used alendronate and 51% used alendronate exclusively. Of these, 58,046 (36.2%) women had a BP drug holiday of >12 months. Approximately 10% of long term BP users discontinued each 6 month interval, reaching a peak in 2012 and continuing in a stable fashion thereafter (Figure). The timing of BP drug holidays peaked at a cumulative duration of 5-5.5 years of BP exposure. Numerous factors differed significantly between women taking drug holidays and those who did not including age, fragility fracture, and recent DXA.

Conclusion: Long term cessation of bisphosphonate therapy after 3-5 years of prior use has become increasingly common in the U.S. The impact on fracture risk and the optimal timing to restart remains of high importance.

Figure: Trends in Bisphosphonate Drug Holidays Over Time

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Abstract Number: 294

Physical Therapists' Ability to Recognize Inflammatory Arthritis Cases and Awareness of Importance for Their Prompt Referral to Rheumatology

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Session Information

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Background/Purpose: Early referral to rheumatology of persons with suspected inflammatory rheumatic disease is associated with better outcomes. Persons with undiagnosed rheumatic disease may directly consult a physical therapist (PT) in the Canadian private sector without physician referral.

Our objectives were: : 1) To investigate whether PTs can correctly identify new-onset inflammatory arthritis and differentiate between these cases and other musculoskeletal problems;
 2) To assess whether PTs are aware that persons with new-onset inflammatory arthritis should be seen promptly by a rheumatologist.

Methods: We sent a questionnaire to PTs in two Canadian provinces (Quebec and Alberta, where PTs are permitted to refer patients directly to medical specialists) describing four case scenarios (new-onset rheumatoid arthritis - RA; knee osteoarthritis - OA; new-onset ankylosing spondylitis - AS; and low back pain- LBP). Participants were asked to identify

probable diagnoses, and indicate their plan of action. Questionnaires were sent via professional licensing bodies and associations and completed through an online platform.

Results: There were 303 PTs who responded to the survey (290 in Quebec and 13 in Alberta). Most PTs (67.6%) were between 18 and 45 years of age, 77.9% were female and 76.4% had more than 5 years experience. The proportions who correctly identified each of the four cases were: 87.7, 82.8, 73.4, 100% respectively for RA, OA, AS, and LBP. The majority (77%) of respondents who correctly identified the case as RA/inflammatory arthritis indicated that it was very important or extremely important to refer to a rheumatologist. Similarly, 70.4% of those who correctly identified the case of AS/inflammatory arthritis said it was very important or extremely important to refer the patient to a rheumatologist. Of those who correctly identified the case of OA, 29.9% said that it was very or extremely important to do so. For the case of LBP, only 0.5% said that it was at least very important to refer to a rheumatologist. In terms of comfort level to refer to a specialist, the majority of respondents (63.1%) felt extremely or quite comfortable.

Conclusion: The majority of PTs correctly diagnosed the clinical cases and were aware of the importance of prompt referral to rheumatology of patients with suspected inflammatory disease. Most indicated that it was not very important to refer those with OA and the overwhelming majority would not refer those with LBP. The implications are that many PTs can distinguish between those with inflammatory and noninflammatory conditions and appropriately refer suspected inflammatory arthritis to rheumatology.

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Abstract Number: 295

Implementing a Staff Tobacco Cessation Protocol Increases Quit Line Referrals in a Community Rheumatology Practice

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Background/Purpose: Smoking remains the leading preventable cause of US mortality and predicts higher incidence, greater severity, and reduced treatment response in many rheumatologic conditions. Despite increased risk, few scalable rheumatology clinic interventions exist to support cessation; yet, all states have free tobacco quit lines. Our objective was to examine the impact of our 90-second electronic health record (EHR)-supported staff tobacco cessation protocol on state quit line referral rates in a community rheumatology clinic.

Methods: Using a pre-post implementation design, we implemented and evaluated our EHR-supported staff tobacco cessation protocol called Quit Connect with medical assistants at a community rheumatology practice between May 2015 and April 2018. The protocol included electronic health record prompts to *Ask* (assess smoking status and 30-day readiness to quit or cut back), *Advise* to quit and electronically *Connect* those willing to receive quit line support. Data sources included manually abstracted baseline data and post-implementation EHR protocol documentation. Clinic staff received a one-hour training session on the protocol components and monthly feedback on their fidelity. The effectiveness of the implementation was examined through manually abstracted EHR data using standardized manuals to determine delivery protocol components per patient visit (e.g. advice given, follow-up offered and quit line referrals). Post-implementation quit line referrals were compared to abstracted baseline rates using odds ratios (OR) with 95% confidence intervals.

Results: At baseline (n=100 visits with active smokers), tobacco use discussion was documented by providers 26% of the time. In 17% of these visits, cutting back or quitting was advised. Follow-up or referral to the quit line was never documented, although at three visits (3%), primary care follow up was advised.

Post-implementation, tobacco status was recorded at 5031 of 5117 visits (98%). Readiness to quit was asked at 595 of 607 visits (98%) with smokers. Among those asked, 129 (22%) expressed readiness to quit. Compared to baseline, where 3% (3/100) were recommended any follow up, post-intervention, 31% of smokers who were ready to quit (40/129) were offered referral to the quit line (OR 14.5, 95% CI 4.3-48.6, $p < 0.0001$). Of these, 93% (37/40; 28% of ready smokers) accepted referral. Challenges included >50% turnover of staff. Despite this, usual clinic and float staff were able to implement this protocol.

Conclusion: We demonstrated that Quit Connect, our 90-second staff tobacco cessation protocol, resulted in a 14-fold increase in referrals to the quit line in a community rheumatology clinic. Nearly one in four patients were ready to quit. Engaging staff to implement the protocol resulted in improved referral rates despite high staff turnover. Future studies should investigate scaling cessation protocols with rheumatology staff in diverse clinics to leverage free, state quit lines.

Disclosure: A. M. Chodara, None; E. Ramly, Pfizer, Inc., 2; D. White, Pfizer, Inc., 2; H. Johnson, Pfizer, Inc., 2; A. Gilmore-Bykovskiy, Pfizer, Inc., 2; C. M. Bartels, Pfizer, Inc., 2.

Abstract Number: 296

Does Care By a Multidisciplinary Team Improve Outcomes in Rheumatoid Arthritis? a Randomized Controlled Study

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Background/Purpose: Quality standards recommend an annual review by a multidisciplinary team (MDT) for all patients with rheumatoid arthritis (RA); however, this is based on expert opinion.

Methods: Single centre randomised single-blind controlled trial of MDT vs. routine rheumatologist review in established RA.

Primary outcome: Minimal clinically important difference (MCID) in quality of life (QOL) (increase in European QOL-5-Dimension-3-Level Singapore (EQ5D-SG) index by 0.1) at 6 months.

Secondary outcomes: Change in EQ5D-SG, pain, disease activity score in 28 joints (DAS28), physical function (modified Health Assessment Questionnaire, mHAQ), coping, self-efficacy (Rheumatoid Arthritis Self-Efficacy scale, RASE), Medication Adherence Report Scale (MARS), Disease Specific Knowledge (DSK) and physical activity.

Adult patients with RA were randomly assigned to a single visit to a 6-member MDT (rheumatologist, nurse, medical social worker, physiotherapist, occupational therapist and podiatrist) or usual care. MDT providers prescribed disease modifying anti-rheumatic drugs (DMARD) and counselled patients with respect to managing flares, medication adherence, coping, joint protection, exercise, footwear. Data were collected by face-to-face questionnaires, review of medical records and joint counts by a standardised blinded assessor at 0, 3 and 6 months. Paired and between-group t test with Bonferroni-Holm correction for multiple testing and logistic regression were used.

Results: 140 (power 95%, 10% attrition) patients (86.3% female, 53.4% Chinese, age 54.4 ± 12.7 years) were recruited. There were fewer females and seropositive patients in MDT (Table 1). The median (IQR) disease duration was 5.5 (2.4, 11.0) years and DAS28 was 2.87 (2.08, 3.66). There was more DMARD escalation in MDT (34.4% vs. 19.4%), and the mean patient experience score (1-10) was higher (8.9 ± 1.0 vs. 8.4 ± 1.0 , $p = 0.009$).

123 patients completed the study. 40.6% (MDT) vs. 34.3% patients achieved an MCID in EQ5D-SG, OR 1.3 (0.6, 2.7). Among the secondary outcomes, there were significant within group improvements in RASE and coping in the MDT arm, but not in the control arm (Table 2).

Conclusion: A single visit to a MDT in stable patients with established RA and low disease activity failed to achieve a MCID in EQ5D-SG index but did achieve small but significant improvements in coping and self-efficacy. Patients valued the MDT experience. Recommendation of MDT care needs to balance resource use with marginally improved outcomes.

Table 1: Baseline Characteristics

	Usual Care, n = 67	Multidisciplinary team care, n = 64
EQ5D Index (SG), mean (SD)	0.76 (0.29)	0.72 (0.27)
Age (years), median (IQR)	56.6 (46.7, 61.3)	56.5 (45.9, 62.6)
Gender, female (%)	61 (91.0)	52 (81.2)
Race		
Chinese	34 (50.7)	36 (56.2)
Malay	9 (13.4)	6 (9.4)
Indian	19 (28.4)	18 (28.1)
Other	5 (7.5)	4 (6.2)
Education level		
None/ Primary / Secondary	41 (61.2)	44 (68.7)
Vocational / Diploma	10 (14.9)	8 (12.5)
Degree	16 (23.9)	12 (18.7)
Socioeconomic status: Occupation		
Unpaid work/ unemployed	28 (41.8)	37 (57.8)
Manual	7 (10.4)	4 (6.2)
Technical/ Admin/ Manager	27 (40.3)	19 (29.7)
Professional	5 (7.5)	4 (6.2)
Language, English speaking (%)	59 (88.1)	55 (85.9)
BMI, median (IQR)	25.4 (20.9, 29.2)	24.9 (21.9, 29.2)
Ever-smoker (%)	10 (14.9)	12 (18.7)
Disease duration, years, median (IQR)	5.7 (2.4, 9.4)	5.3 (2.4, 13.0)
Seropositive (RF+ or ACPA+) (%)	51 (85.0)	41 (66.1)
Physical activity (minutes/ week), median (IQR)	52.5 (0, 210)	85 (0, 210)
Comorbidity		
Diabetes (%)	9 (13.4)	12 (19.0)
Charlson's comorbidity score, median (IQR)	3 (2, 4)	3 (2, 4)
DAS28-ESR, median (IQR)	2.9 (2.4, 3.4)	2.9 (2.1, 3.9)
mHAQ, median (IQR)	0.12 (0, 0.37)	0 (0, 0.12)
Pain, VAS (0-10)	2 (1, 5)	3 (0.5, 5)
Prednisolone dose (mg), median (IQR)	4 (2, 5)	3.8 (2, 5)
Proportion on methotrexate (%)	54 (81.8)	50 (79.4)
Proportion on biologics (%)	5 (7.8)	2 (3.4)
Medication adherence, MARS (5, worst – 25, best), median (IQR)	23 (21, 25)	24 (21, 25)
Self-Efficacy, RASE (28, worst – 140, best), median (IQR)	104 (98, 108)	103.5 (98, 109)
Coping, VAS (0, very well – 100, very poorly), median (IQR)	20 (0, 40)	30 (10, 50)
DSK (0-12), median (IQR)	6 (5, 7)	5 (4, 7.5)

Table 2: Secondary outcomes

		Baseline	6 months	Change	within group paired t test for change, p value	Between group t test for change, p value
EQ5D Index (SG) (-0.59, worse than death – 1, perfect)	Usual care	0.76 (0.69, 0.83)	0.73 (0.66, 0.81)	-0.03 (-0.09, 0.03)	0.36	0.04
	MDT care	0.72 (0.65, 0.79)	0.79 (0.72, 0.86)	0.07 (0.00, 0.15)	0.06	
DAS28-ESR (0-10)	Usual care	2.80 (2.56, 3.04)	2.90 (2.63, 3.17)	0.10 (-0.18, 0.38)	0.49	0.03
	MDT care	3.13 (2.84, 3.42)	2.79 (2.53, 3.06)	-0.34 (-0.61, -0.06)	0.02	
mHAQ (0, no disability – 3, fully disabled)	Usual care	0.22 (0.14, 0.30)	0.24 (0.15, 0.33)	0.02 (-0.05, 0.09)	0.60	0.27
	MDT care	0.12 (0.05, 0.18)	0.20 (0.12, 0.28)	0.08 (0.00, 0.17)	0.06	
Pain, VAS (0, no pain – 10, worst pain)	Usual care	3.1 (2.4, 3.8)	2.5 (1.9, 3.1)	-0.6 (-1.5, 0.3)	0.19	0.62
	MDT care	2.9 (2.2, 3.6)	2.1 (1.5, 2.7)	-0.9 (-1.6, -0.1)	0.02	
Medication Adherence, MARS (5, worst – 25, best)	Usual care	22.3 (21.5, 23.0)	22.7 (21.7, 23.6)	0.4 (-0.6, 1.4)	0.42	0.72
	MDT care	22.6 (21.8, 23.5)	23.3 (22.4, 24.2)	0.6 (-0.2, 1.5)	0.16	
Self-Efficacy, RASE (28, worst – 140, best)	Usual care	102.1 (99.6, 104.5)	103.8 (101.4, 106.2)	1.8 (-0.6, 4.1)	0.13	0.10
	MDT care	104.0 (101.2, 106.8)	108.3 (106.0, 110.7)	4.3 (2.3, 6.4)	<0.001*	
Coping, VAS (0, very well – 100, very poorly)	Usual care	25.1 (19.8, 30.5)	25.7 (20.9, 30.5)	0.5 (-5.7, 6.8)	0.86	0.02
	MDT care	31.2 (25.0, 37.5)	22.4 (17.4, 27.4)	-8.8 (-13.7, -4.0)	<0.001*	
DSK (0, none – 12, all)	Usual care	6.1 (5.5, 6.6)	6.4 (5.7, 7.1)	0.3 (-0.2, 0.8)	0.21	0.54
	MDT care	5.8 (5.1, 6.5)	6.4 (5.7, 7.2)	0.6 (-0.1, 1.4)	0.11	
Physical activity (min/ week)	Usual care	119.7 (77.5, 161.9)	100.3 (63.3, 137.4)	-19.4 (-56.8, 18.0)	0.30	0.35
	MDT care	186.3 (101.8, 270.8)	135.5 (82.7, 188.3)	-50.8 (-107.5, 5.9)	0.08	

All values are mean (95% CI)

* significant after Bonferroni-Holm correction

Disclosure: M. Lahiri, None; P. P. M. Cheung, None; P. Dhanasekaran, None; S. R. Wong, None; A. Yap, None; D. Tan, None; A. Santosa, None; P. H. Phan, None.

Hospitalization Rates Among Patients with Polymyalgia Rheumatica: A Population-Based Study from 1995-2017

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Session Information

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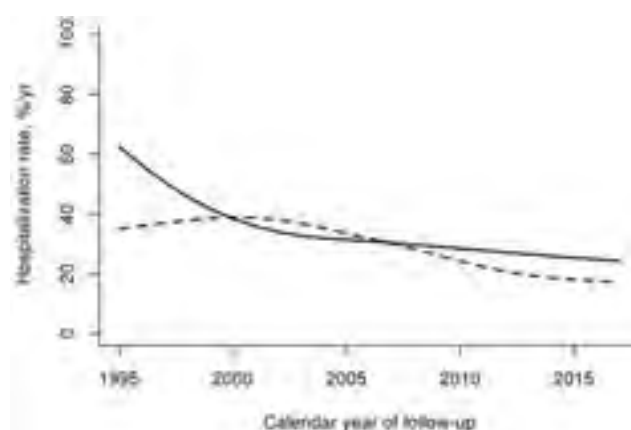
Background/Purpose: The study purpose was to determine whether patients with polymyalgia rheumatica (PMR) are at greater risk for all-cause hospitalizations compared to the general population.

Methods: The study cohorts included all incident cases of PMR in a geographically-defined area diagnosed between 1995 and 2014 and non-PMR subjects from the same underlying population with similar age, sex and calendar year of index. Patients were followed until death, migration, last contact or June 30, 2017. Discharge diagnoses were grouped together using Clinical Classification Software (CCS). Readmission was defined as a hospital admission date within 30 days of a prior discharge date. Person-year methods and rate ratios (RR) from Poisson regression models were used to compare hospitalization rates between the groups. Generalized linear models were used to analyze the length of stay (LOS).

Results: A total of 463 PMR and 459 non-PMR subjects (64% female; mean age 74.1 years for both) were followed for medians of 8.4 and 7.4 years, respectively.

The patients with PMR had 1398 hospitalizations and the non-PMR patients had 1207 hospitalizations. Both groups had similar rates of all-cause hospitalizations [rate ratio (RR) 1.03; 95% confidence interval (CI): 0.95–1.11]. The rate ratio of hospitalizations for PMR compared to non-PMR remained relatively stable over time except for marginally higher rate ratios in the 1995-1999 (RR 1.40; 95% CI: 1.01-1.96) and 2010-2017 (RR 1.17; 95% CI: 1.05-1.31) time period (Figure). The rate of hospitalization remained stable across disease duration. There were no significant differences in hospitalizations according to discharge diagnosis groupings for patients with PMR vs non-PMR. The average length of stay was 4.4 and 4.7 days, respectively, among the PMR and non-PMR hospitalizations ($p=0.16$). Readmission rates were similar among the PMR subjects with 215 readmissions (20% of 1063 subsequent hospitalizations) compared to the non-PMR subjects with 214 readmissions (24% of 904 subsequent hospitalizations; $p=0.07$).

Figure. Age and sex adjusted hospitalization rates across calendar year among patients with incidence PMR in Olmsted County (solid line) and age- and sex-matched comparators (dashed line)



Conclusion: In this analysis of all-cause hospitalizations in a population-based cohort, patients with PMR did not have higher hospitalization rates compared to the general population.

Disclosure: S. Raheel, None; C. S. Crowson, None; S. J. Achenbach, None; E. L. Matteson, None.

Factors Affecting Inpatient Mortality in Hospitalizations for Sepsis with Underlying Systemic Lupus Erythematosus: Data from the National Inpatient Sample 2010-2014

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Session Information

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Session Title: Health Services Research Poster I – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

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

Background/Purpose: Infections are associated with significant morbidity and mortality in systemic lupus erythematosus (SLE). Clinical outcomes of SLE patients hospitalized is variable due to variable demographic distribution. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection with significant increase in inpatient mortality. Data describing clinical outcomes and factors associated with poor outcomes of patients with sepsis with SLE is limited in current literature. Our objective is to evaluate factors affecting mortality in patients with sepsis and underlying SLE.

Methods: We used the National Inpatient Sample (NIS) available through Healthcare Cost and Utilization Project (HCUP) to estimate the number of hospitalizations for sepsis among adult patients with SLE in the US from 2010-2014. ICD-9 CM codes were used to identify the population. Logistic regression analysis was used to identify independent associations of in-hospital mortality. We described the associations as patient factors and hospital factors.

Results: We identified 35475 hospitalizations for sepsis with secondary diagnosis of SLE using NIS database from 2010-2014. There were 3557 inpatient deaths during these hospitalizations. Mean age of patients admitted with sepsis and SLE was 54.145 years. Analysis of the population with inpatient mortality, suggested increased odds of mortality with age, location & size of hospital and number of associated comorbidities. Odds of mortality were noted to decrease with female sex and insurance status, as reported in Table 1.

Conclusion: This study suggests increased risk of inpatient mortality in males, with increasing age and increase in number of comorbidities. Previous studies have shown similar results. Urban and large hospitals were found to be associated with higher mortality. This may represent higher likelihood of patients with comorbidities like SLE being referred or transferred to larger urban hospitals. Serious infections continue to be an important source of mortality in SLE. And factors affecting the mortality can guide us to implement guidelines for prevention and management of infections including but not limited to vaccinations, especially in high risk subgroup including males, older population with SLE and patients with multiple comorbidities.

Table 1: Factors associated with inpatient mortality in patients with sepsis and underlying SLE

Variable	Odds Ratio	P value
PATIENT FACTORS		
Age	1.027	0.000
Sex		
Male	Reference	
Female	0.752	0.010
Race		
White	Reference	
Black	0.906	0.310
Hispanic	0.799	0.084
Asian or Pacific Islander	0.908	0.701
Native American	0.957	0.914
Other	0.912	0.736
Charlson Comorbidity Index		
1		
2	1.397	0.008
3	1.414	0.005
>=4	2.312	0.000
Insurance Status		
Medicare	Reference	
Medicaid	0.724	0.004
Private	0.596	0.000

Self-Pay	0.461	0.005
Median household income quartiles for patient's ZIP Code (in dollars)		
\$1-38,999	Reference	
\$39000-47999	1.073	0.482
\$48000-62999	0.921	0.451
>\$63000	0.855	0.192
HOSPITAL FACTORS		
Teaching Status of Hospital		
Non-Teaching	Reference	
Teaching	1.101	0.243
Hospital Location		
Rural	Reference	
Urban	1.488	0.012
Hospital Region		
Northeast	Reference	
Midwest	0.7956	0.104
South	1.072	0.557
West	0.876	0.309
Hospital Bed-size		
Small	Reference	
Medium	1.280	0.088
Large	1.362	0.019

Disclosure: K. Chugh, None; K. Jatwani, None; J. Kaur, None; S. Jatwani, None.

Abstract Number: 299

A Comparison of Persistent Versus Limited Frequent Emergency Department (ED) Utilization Among Systemic Lupus Erythematosus (SLE) Patients

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Session Information

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Session Title: Health Services Research Poster I – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

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

Background/Purpose: Patients with SLE often require additional medical management outside of the outpatient setting from ED visits to hospital admissions. Previous studies in the general population showed that those who frequently visit the ED mostly do so over a limited time period(<12 months); however, a subgroup are persistent frequent ED users over years. We examined whether persistent and limited ED utilization in SLE patients are associated with patient characteristics, SLE history, long term opioid therapy (LTOT), and general health status.

Figure: Proportion of ED encounter in each encounter category group at discharge from either the ED or after ED-initiated hospitalization among SLE patients who frequented the ED between 2013-2016

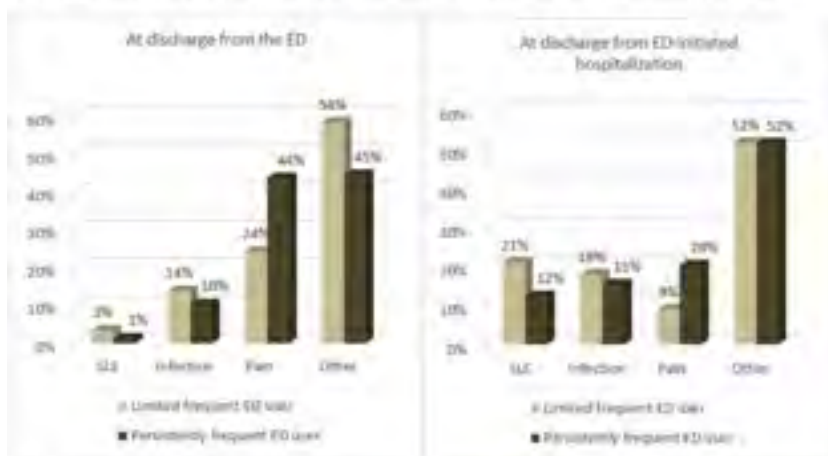


Table: Factors associated with persistently frequent ED use compared to limited frequent ED use

Variable	OR (95% CI)	p-value
Age	1.00 (0.96-1.03)	0.870
Female	1.61 (0.39-6.54)	0.508
Race		
African American	Reference	
Caucasian	0.22 (0.07-0.75)	0.015†
Hispanic/Latino	0.46 (0.15-1.38)	0.165
Insurance		
Medicaid	Reference	
Medicare	13.84 (3.14-61.05)	0.001†
Private/Commercial	1.48 (0.50-4.38)	0.481
Area of Deprivation Index	1.01 (0.97-1.05)	0.687
Depression	1.74 (0.60-5.070)	0.306
Number of co-morbidities	0.77 (0.55-1.08)	0.135
Long-term opioid therapy	3.16 (1.04-9.64)	0.043†
Other DMARD	0.39 (0.16-0.95)	0.038†

Other DMARD=disease modifying antirheumatic drug (exclude HCQ)

†statistically significant with p-values<0.05

Methods: We conducted a retrospective study of SLE patients who frequented the ED for ≥ 3 visits in a calendar year from 2013-2016. Limited use was defined as meeting criteria for frequent ED use for 1 out of the 4 years. Persistent users met these criteria for at least 2 out of the 4 years, consecutive or non-consecutive during the study period. Patient demographics, medical history, and ED encounter information were collected through in-depth electronic health record review. Each ED encounter was categorized into the following groups; SLE-, infection-, pain-related, or “other”. Multivariate logistic regression was used to evaluate factors associated with frequent ED utilization.

Results: We identified 52 limited users who had 335 ED encounters, and 77 persistent users who had 1143 encounters; average age 41.5 (SD 15.6), 116(90%) female, 76 (58%) with Medicaid insurance coverage, and 77 (60%) African American, 27 (21%) Caucasian, and 25 (19%) Hispanic/Latino. Persistent users had more than twice the average number of ED visits (mean 14.8, SD 8.8) compared to limited users (mean 6.4, SD 2.0), and had more ED-initiated hospitalizations(49% vs 40%, respectively). Pain-related ED visits were more common among persistent users (32%)than limited users (18%) (see Figure). In multivariate analysis, persistently frequent ED users were more likely to be African American, have Medicare insurance coverage and be on LTOT, but less likely to be on other DMARD, than their respective counterparts who are limited frequent ED users (see Table).

Conclusion: Among SLE patients who persistently frequent the ED, pain is a major cause for both ED utilization and ED-initiated hospitalizations. This group of SLE patients who account for a high volume of healthcare resource utilization may be amenable to targeted interventions to improve pain management and care coordination in the outpatient setting. Further research is needed to improve quality of care and reduce healthcare resource utilization among SLE patients who frequently utilize the ED.

Disclosure: J. Lin, None; J. Lee, None; L. G. Suter, None; L. Fraenkel, None.

Abstract Number: 300

Built-in-Electronic-Medical-Record Disease Activity Calculators and Treat-to-Target in Rheumatoid Arthritis

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Session Information

Session Date: Sunday, October 21, 2018

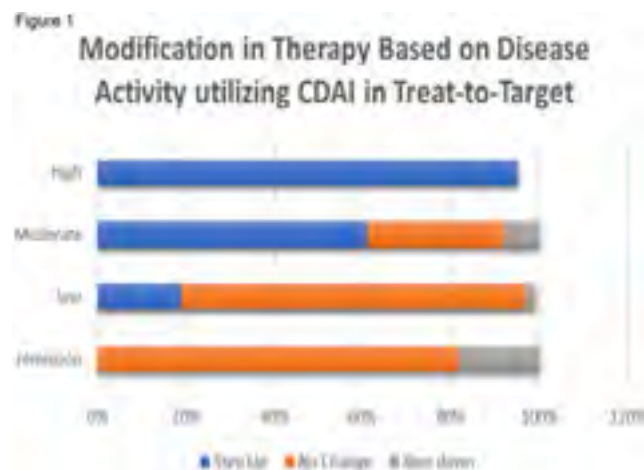
Session Title: Health Services Research Poster I – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

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

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory arthritis that, if undertreated, can lead to cumulative damage and disability. The goal of treatment is to achieve the lowest possible disease activity. The current recommendations from ACR is to adopt a “treat to target” strategy (1). In order to quantify disease activity and monitor it over time, disease activity score calculators (DAC) were developed.

Table 1 Disease Activity CDAI	Step up therapy	No change therapy	Step down therapy	Most Common Added Medication Class	RTF (mo)	ATF (mo)	Fellow	Junior faculty	Senior faculty
Remission 33	-	27 (81%)	6	-	3.7 ⁵	4	14 (42%)	18 (54%)	1 (3%)
Low 74	14 (19%)	58 (78%)	2	6 42% cDMARDs	3	4.8 ²	23 (31%)	43 (58%)	8 (11%)
Moderate 75*	46 (61%)	23 (31%)	6	19 41% bDMARDs	2	2.8	27 (36%)	46 (61%)	2 (3%)
High 22	21 (95%)	-	-	14 67% bDMARDs	1.7	2.89	15 (68%)	6 (28%)	1 (4%)
204 Encounters									
Table 2 DAS CRP									
Remission 17	3 (18%)	12 (70%)	2 (12%)						
Low 3	2 (67%)	1 (33%)	-						
Moderate 5	5 (100%)	-	-						
High 2	2 (100%)	-	-						
27 encounters									
Table 3 Reference CDAI Calculated Value									
Disease activity (DA)		Calculated CDAI value							
Remission		≤2.8							
Low		2.9-10							
Moderate		11-22							
High		>22							



DAC were validated, incorporating subjective and objective data such as: patient pain level, patient perception of disease activity (PtGA), provider perception of disease activity based on history and exam (PrGA), the swollen joint count(SJC), the tender joint count (TJC) and timely laboratory values. In a treat-to-target strategy, treatment is adjusted in accordance with disease activity scores to achieve remission (2).

The Clinical Disease Activity Index (CDAI), Disease Activity Score 28 (DAS 28), and DAS28-CRP are three methods that incorporate subjective and objective data. The result is classified into 4 groups: remission, low disease, moderate disease, and high disease activity. Adjustment of therapy may entail changing one anti-rheumatic drug to another, the addition of a new drug or the maintenance of current regimen.

Methods: Our study employs a before-after design, retrospectively examining the adoption of EMR-DAC, of patients >18 years of age, with an ICD9/10 code of RA, seen 18 months before and after introduction of the EMR-DAC in 3/2015 within the Drexel Rheumatology practices. We hypothesized that provider documentation of disease activity would increase after DAC were built into the EMR. We hypothesized that calculation of an objective score would lead to a higher rate of medication changes and decreased time to first biologic.

Results: Of the 900 patients seen in Drexel Rheumatology practice from 3/2015 to 9/2016, 23% had a CDAI documented. Preliminary CDAI data showed that of the 97 patients with moderate or high disease activity, 61% and 95% respectively had a change in therapy. In the DAS 28-CRP study group, 100% of the patients with moderate to high disease activity were started on additional therapy, with 75% prescribed or recommended a bDMARD and prednisone. 67% of the low disease activity patients were started on additional medications.

Conclusion: Our preliminary results show a low adoption rate of DACs, with CDAI being the most commonly used. Our data show DAC values do correlate with overall changes inpatient care in our practice and suggest that providers are incorporating the values in implementing a treat-to-target strategy.

Disclosure: A. Jayatilleke, None; S. Pompa, None.

Rheumatology Clinic Staff Needs for Partnering to Improve Blood Pressure and Tobacco Risk Management

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Session Information

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Session Type: ACR/ARHP Combined Abstract Session

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Background/Purpose: Patients with rheumatologic conditions are at a higher risk of cardiovascular disease (CVD) than peers. High blood pressure (BP) and tobacco use exacerbate CVD risk, yet many times these risk factors are unaddressed in patients in rheumatology clinics. We interviewed rheumatology clinic staff to identify facilitators and barriers to addressing high BP and tobacco to inform the development and dissemination of tailored CVD risk management protocols in specialty clinics.

Methods: Medical assistants, nurses, and scheduling staff from four adult rheumatology clinics in two health systems were interviewed by two expert facilitators in seven 60 minute focus groups (n=23 BP and n=14 tobacco group participants). We analyzed transcripts using qualitative content analysis with NVivo 11 software.

Results: We found systems- (Table 1) and person-level (Table 2) facilitators and barriers to addressing BP and tobacco. Across both health systems, rheumatology clinic staff's usual practices followed three process steps: (1) identify high BP or tobacco use, (2) follow-up within the clinic, and (3) follow-up across settings (i.e. with primary care and community resources). Focus groups identified the two key barriers as (1) lack of a system for follow-up, both within the specialty clinic and across settings, and (2) staff needs for talking points during patient interactions to address high BP and tobacco. Fragmented staff to provider communication and role perceptions were also reported as contributing to these barriers.

Conclusion: Our study identified addressable gaps in rheumatology staff's current processes for addressing high BP and tobacco including both risk identification and facilitating management. Future work should support systems of follow-up, talking points for staff discussions, and or improve staff and provider collaboration on CVD preventive care.

Table 1. Systems-level barriers and facilitators for blood pressure (BP) & tobacco (TOB) care

THEME	ILLUSTRATION
<i>Step 1. Identification of High BP or Tobacco Use</i>	
Standard check-in routine, time constraints	BP: "I mean <u>we barely have time</u> to get patients in... and then sometimes the providers come in when we're still rooming."
<i>Step 2. Follow-Up Within Specialty Clinic</i>	
No standard follow-up	BP: " <u>There is no system</u> thing that everybody does... they have come back and were like, 'Hey, did we ever recheck that blood pressure?' I noticed it was really high.' 'Well that was like 2 hours ago, and I didn't know that you wanted me to.'"
Physical reminders helped with BP rechecks	BP: "We give our providers stickers, so if it's a high blood pressure, we could write it on the stickers. <u>I don't know that we always do though.</u> "
EHR structure did not support nuance of cutting back.	
Educational materials provided	TOB: "When you give them this packet of [tobacco cessation] paperwork, it's kind of like <u>'Well, we care a little, but we don't have time to fully follow-up.'</u> "
Provider conversations rare	
<i>Step 3. Follow-Up Across Settings</i>	
No standard process for communication with primary care	TOB: "I usually just say, 'Do you want any information on quitting?'... And there's been people who have said yes, <u>but if it's in a specialty department where their PCP isn't there, it never gets addressed.</u> "

Table 2. Person-level barriers for specialty blood pressure (BP) and tobacco (TOB) care

THEME	ILLUSTRATION
<i>Provider</i>	
Providers' perception of roles and responsibilities for BP and tobacco management varied	BP: "But then a lot of times they are like, <u>'That's not my area, primary can take care of that.'</u> "

Table . (Cont'd)

THEME	ILLUSTRATION
<i>Nurse or medical assistant</i>	
Knowledge gaps about BP guidelines and tobacco treatments	BP: "Well they just start asking questions. <u>I'm not the doctor, so I don't feel like I... just try to down play it.</u> "
Staff verbiage needs about BP and tobacco management	TOB: " <u>I don't have the verbiage</u> to continue...Even when I tried to say, 'Are you interested? I have a card' ...I don't know where to go with it."
<i>Patient</i>	
Knowledge levels varied less knowledgeable about tobacco resources	BP: "[Patients] ask, ' <u>Well, what should [my BP] be?</u> ' I hear that all the time."
Patients appeared indifferent talking about BP and resistant during conversations about tobacco	TOB: "I've had, ' <u>Don't ask me that ever again</u> '...about if they're a smoker."

Disclosure: M. Tong, None; L. Block, None; A. Gilmore-Bykovskiy, Pfizer, Inc., 2; E. Ramly, Pfizer, Inc., 2; C. M. Bartels, Pfizer, Inc., 2.

Abstract Number: 302

Validity and Responsiveness of Inflammation and Joint Damage Scores Based on the Omeract Rheumatoid Arthritis MRI Scoring System

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Imaging of Rheumatic Diseases Poster I: MRI

Session Type: ACR Poster Session A

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

Background/Purpose: The RAMRIS scoring system is used to quantify synovitis, tenosynovitis, bone marrow edema (BME), bone erosions and joint space narrowing (JSN) on MRI examinations of the wrist and hand in clinical trials in RA. We explored methods to combine the MRI features into valid, responsive and feasible scores for a) *inflammation* and b) *joint damage*.

Methods: We analyzed baseline and 12-month MRI data (wrist and MCP 2-5) from the ARCTIC trial (derivation cohort, n=195, all fulfilling 2010 RA criteria) to assess five different approaches to the development of combined scores: **1) Unweighted summation:** RAMRIS synovitis, tenosynovitis and BME were summarized to an inflammation score. Erosions and JSN were summarized to a damage score. **2) Normalized summation:** Each component was transformed to the same scale before summation. **3) Weighted summation:** We divided each component into three joint, tendon or bone areas, which were individually weighted and summarized. Weights were calculated conditioned to give the highest standardized response mean (SRM) to the resulting score. **4) Adjusted weighted summation:** Weights from approach 3) were adjusted based on clinical experience and feasibility concerns (e.g. only whole numbers as adjustment weights). **5) Single site weighted summation:** As in 3, but weights calculated for each individual bone, joint and tendon. The combined scores were tested in pooled data from the CIMESTRA and OPERA trials (validation cohort, n=194, all fulfilling 1987 RA criteria, baseline and 12-month data for wrist and MCP 2-5). Validity was examined by assessing correlations to imaging, clinical and biochemical measures. Responsiveness was tested by calculating the SRM of the resulting combined score, and the relative efficiency using the score obtained by unweighted summation as reference.

Results: Patient characteristics, as well as baseline and follow-up RAMRIS scores were comparable between trials. Validity: All the combined scores were significantly correlated to other imaging, clinical and biochemical measures (**table 1**, all patients). Responsiveness: Inflammation scores combined by method 2, 3 and 4 had significantly higher responsiveness

compared to unweighted summation. For the damage score, there was a trend towards higher responsiveness for method 4 (figure 1, data from OPERA and CIMESTRA).

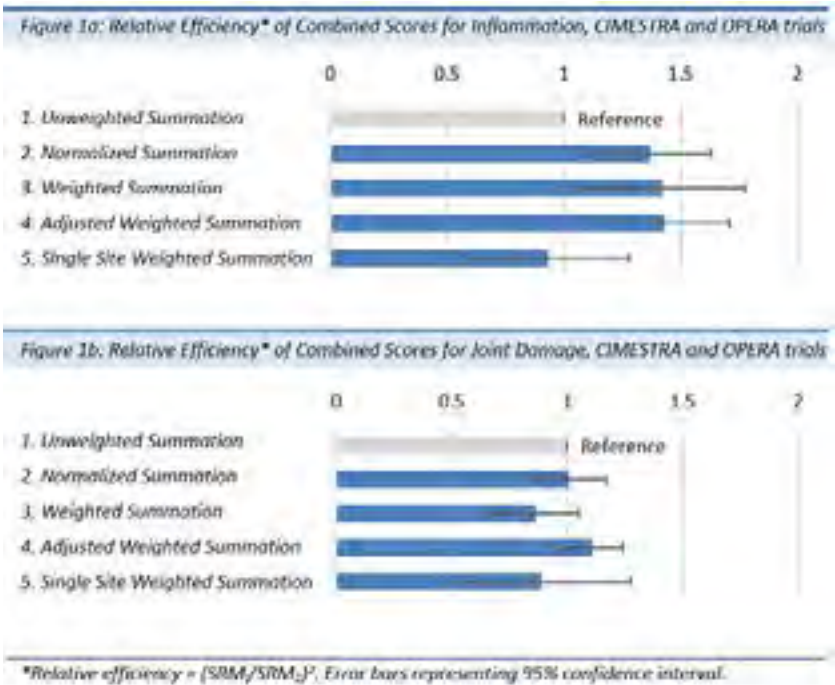


Table 1a: Spearman correlations of Combined Inflammation Scores to other disease measures (all patients)										
	DAS28	TJC28	SwC28	PGA	PhGA	CRP	ESR*	PFTS*†	USPD*	USBM*
1. Unweighted Summation	0.32	0.14	0.42	0.12	0.32	0.40	0.24	-0.26	0.49	0.54
2. Normalized Summation	0.36	0.18	0.46	0.14	0.35	0.43	0.24	-0.25	0.52	0.55
3. Weighted Summation	0.27	0.13	0.44	0.11	0.29	0.33	0.17	-0.29	0.47	0.52
4. Adjusted Weighted Summation	0.30	0.15	0.42	0.11	0.31	0.37	0.19	-0.28	0.50	0.54
5. Single Site Weighted Summation	0.29	0.14	0.45	0.11	0.29	0.32	0.21	-0.26	0.46	0.48

Table 1b: Spearman correlations of Combined Joint Damage Scores to radiographic outcomes (all patients)			
	vdHQS Erosions	vdHQS JSN	vdHQS Total
1. Unweighted Summation	0.43	0.33	0.40
2. Normalized Summation	0.41	0.32	0.38
3. Weighted Summation	0.41	0.34	0.40
4. Adjusted Weighted Summation	0.43	0.33	0.40
5. Single Site Weighted Summation	0.42	0.37	0.43

*ARCTIC only. Abbreviations: DAS28= Disease Activity Score, 28 joints. TJC28= Tender Joint Count, 28 joints. SwC28= Swollen Joint Count, 28 joints. PGA/PhGA= Patient's/Physician's Global Assessment. PFTS= PROMIS T-score. USPD= Ultrasound Power Doppler. USBM= Ultrasound B-Mode. vdHQS= van der Heijde Sharp Score † Negative correlation due to inverse scale of PROMIS T-score. Radiographic outcomes measured by vdHQS including hands, wrists and feet. All coefficients significant at the 0.05 level.

Conclusion: Combined RAMRIS scores assessing inflammation and damage with weighting of the individual components and adjustment for face validity and feasibility displayed the highest responsiveness. The discriminative properties of the proposed combined scores need to be tested in placebo-controlled clinical trials.

Disclosure: U. Sundin, None; M. Østergaard, None; D. Glinatsi, None; A. B. Aga, UCB, Inc., 5, AbbVie Inc., 5, Eli Lilly and Co., 5, Novartis, 5, Pfizer, Inc., 5; K. Hørslev-Petersen, None; M. L. Hetland, None; P. Junker, None; B. J. Ejbjerg, None; P. Bird, None; P. G. Conaghan, AbbVie Inc., 5, Bristol-Myers Squibb, 5, 8, GlaxoSmithKline, 5, Novartis, 5, 8, Pfizer, Inc., 5, 8, Roche, 5, 8; S. Lillegraven, None; E. A. Haavardsholm, AbbVie Inc., 2, Merck & Co., 2, Pfizer, Inc., 2, UCB, Inc., 2, Celgene Corporation, 5, Eli Lilly and Co., 5, Pfizer, Inc., 5, Roche, 5, UCB, Inc., 5.

The Value of the Simplified Ramris-5 in Early RA Patients Under Methotrexate Therapy Using High Field MRI

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Imaging of Rheumatic Diseases Poster I: MRI

Session Type: ACR Poster Session A

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

Background/Purpose: The aim of the study was to evaluate a simplified version of the Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) to five joints of the hand (RAMRIS-5) in patients with early rheumatoid arthritis (RA) before and after the initiation of a methotrexate (MTX) therapy using high-resolution, 3 Tesla (T), magnetic resonance imaging (MRI).

Methods: 28 RA patients according to 2010 ACR/EULAR criteria (Ø 56.8 years (range 39 - 74), seropositive, disease duration < 6 months (range 2 – 23 weeks) were prospectively assessed with baseline investigation including clinical assessment (DAS-28 and CRP) and 3T MRI of the clinical dominant hand, as well as 3 and 6 months after starting MTX therapy. MRI-scans were analysed according to RAMRIS and the simplified RAMRIS-5 (Figure-1).

Results: DAS-28, CRP, RAMRIS and RAMRIS-5 decreased significantly after initiation of a MTX therapy. There was a strong correlation between RAMRIS-5 and RAMRIS at baseline ($r=0.838$; $p<0.001$) and follow-up (3 months: $r=0.876$; $p<0.001$; 6 months: $r=0.897$; $p<0.001$).



Conclusion: 3T MRI based RAMRIS-5, a simplified and resource-saving RAMRIS score is a suitable tool to show changes in early RA and may be used for diagnosis and therapy monitoring in follow-up evaluations.

Figure 1

Disclosure: P. Sewerin, None; M. Frenken, None; D. B. Abrar, None; C. Goertz, None; C. Schleich, None; M. Schneider, None; B. Ostendorf, None.

Abstract Number: 304

Dynamic MRI in Rheumatoid Arthritis for the Assessment of Synovitis Promoting Cartilage Loss

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Imaging of Rheumatic Diseases Poster I: MRI

Session Type: ACR Poster Session A

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

Background/Purpose: To investigate the local inflammatory activity of the synovium by using dynamic magnetic resonance imaging (MRI) and cartilage biochemical composition of the MCP-joints 2 and 3 by using Delayed Gadolinium-Enhanced MRI (dGEMRIC) in patients with early rheumatoid Arthritis (eRA) treated with methotrexate.

Methods: MCP joints 2 and 3 of 28 patients with early RA (disease duration ≤ 6 months) were examined prior to methotrexate (baseline) as well as 3 and 6 months after the therapy-initiation. MRI perfusion parameters and dGEMRIC index were calculated. OMERACT RA MRI score (RAMRIS), including synovitis, bone marrow edema (BME) and erosion subscores, and clinical parameters (CRP and DAS28) were registered at all of the time points.

Results: Local perfusion in dynamic MRI decreased significantly after initiation of methotrexate-therapy and correlates significantly with the DAS28 improvement after 3 months ($p < 0.05$). The extent of local inflammation significantly correlated with dGEMRIC values at all of the time points evaluated ($p < 0.05$). Local inflammation and cartilage composite measurements showed significant correlation with BME subscore after 3 months and with RAMRIS and erosion subscore in the after 6 months ($p < 0.05$).

Conclusion: In patients with eRA, synovial local hyperperfusion measured by dynamic MRI correlated significantly with the local cartilage compositional and decreased significantly 3 and 6 months after initiating of methotrexate-therapy. Dynamic MRI seems to be a useful parameter for assessing therapy-success, since DAS28 and RAMRIS showed significant correlations. This is the first study showing that methotrexate is able to delay cartilage loss and underlines the priority of early treatment.

Figure 1: Overlay of native T1 image of digitus 2 and 3 with a color-coded map of dynamic MRI from blue - low perfusion to red - high perfusion of MCP D2 and D3. Picture A demonstrates the perfusion of MCP joints at baseline MRI prior to MTX therapy, while pictures B and C show the perfusion 3 and 6 months after MTX therapy. In this example, we found higher perfusion after 3 and 6 months compared to baseline MRI for both MCP joints.



Disclosure: P. Sewerin, None; A. Mueller-Lutz, None; M. Schneider, None; C. Schleich, None; B. Ostendorf, None; S. Vordenbäumen, None.

Abstract Number: 305

Introduction and Value of a Shortened Psamris-7 in Psa-Patients before and after Treatment Escalation to Bdmard Using High Resolution MRI

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Session Information

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Session Title: Imaging of Rheumatic Diseases Poster I: MRI

Session Type: ACR Poster Session A

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

Background/Purpose: The aim of the study was to evaluate a simplified version of the OMERACT Psoriasis Arthritis Magnetic Resonance Imaging Score (PsAMRIS) to seven regions of the clinically dominant hand in patients with psoriasis arthritis (PsA) before and after treatment escalation to biological Disease-Modifying Antirheumatic Drugs (bDMARDs) using high resolution, 3 Tesla (T) MRI.

Methods: 18 patients with PsA according to the CASPAR classification criteria (\bar{x} 47 years \pm 16) who qualified for bDMARD therapy due to inadequate Methotrexate (MTX) treatment, were prospectively assessed by both baseline investigation and 6 months after therapy escalation including clinical examination (CRP and DAS 28) and 3T MRI of the clinically dominant hand. Scans were analyzed by two independent experts (PS/CS) using the OMERACT PsAMRIS and the simplified PsAMRIS-7 which includes all distal interphalangeal joints (DIP), proximal interphalangeal joint (PIP) and metacarpophalangeal joint (MCP) of the index (PIP and MCP II).

Results: On average, PsAMRIS rating lasts 312 seconds (s; SD= 40.9); PsAMRIS-7 scoring was 116 s (SD=20.9), on average. We found no correlation between DAS28 and / or CRP to PsAMRIS ($r=-0.044$ / $r=-0.23$) or PsAMRIS-7 ($r=-0.094$ / $r=-0.13$). In contrast, there was a strong correlation between OMERACT PsAMRIS and the simplified PsAMRIS-7 at baseline ($r=0.871$; $p<0.01$) and after six months ($r=0.907$; $p<0.01$).

Conclusion: The simplified PsAMRIS-7, using 3T MRI, is a time and resource saving shortened version of the OMERACT PsAMRIS and a reliable tool for detecting morphological changes in PsA. Hence, the shortened PsAMRIS-7 may have the potential to apply in diagnosis and therapy monitoring of PsA patients. Therefore PsAMRIS-7 needs to be investigated in larger clinical studies.

Disclosure: P. Sewerin, None; D. B. Abrar, None; C. Goertz, None; M. Jung, None; M. Schneider, None; B. Ostendorf, None; C. Schleich, None.

Abstract Number: 306

The Role of Inflammation in the Evolution of MRI Erosions in the Feet of Patients with Early RA

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Imaging of Rheumatic Diseases Poster I: MRI

Session Type: ACR Poster Session A

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

Background/Purpose: Patients with aggressive RA develop early structural damage. As persistent inflammation is associated with bone erosions, assessing inflammatory activity may be key in treatment decision-making to slow or prevent further damage. This study aimed to determine the impact of inflammation on US and changes in erosions on MRI in early RA.

Methods: Patients with RA (ACR criteria, treatment naïve, symptom duration <2 years) were recruited and treated as per standard of care. The 2nd- 5th metatarsophalangeal joints (MTPJs) were imaged using US (Esaote MyLab70) at study entry, 6 weeks, 3-, 6- and 12-months follow-up. MTPJs were semi-quantitatively graded for synovial thickening (ST) and power Doppler (PD) (0-3, 3=severe inflammation). The most clinically symptomatic foot at baseline was imaged using a 1.0T peripheral MRI (GE Medical) at baseline, 12-months, and at a 24-49 months follow-up. MRI erosions were semi-quantitatively graded using the OMERACT-RAMRIS system (grade 0-10) for the metatarsal heads and phalanx bases. We characterized the number of MTPJs with low (grade <2) or high (grade ≥2) ST or PD during the majority of the first 12 months, and the number of erosions that were unchanged, improved or worsened by grade ≥1 over the follow-up.

Results: Forty-one patients were included [n=33 female, mean (SD) age=51.6 (10.3) years]. Of 32 patients with follow-up MRIs, total erosion score decreased (improved erosions) in 17 patients and increased (worsened) in 18. Ten patients had a simultaneous improvement and worsening of erosions in different MTPJs. At baseline, 12- and ≥24-months, 299, 308 and 242 metatarsal heads and phalanx bases were graded on MRI. Approximately 40% of joints had a grade ≥1 erosion at each visit, and 5-7% had grade ≥2 erosions. Of all baseline erosions, 28% improved and 27% worsened after 12-months; 40% improved and 29% worsened from baseline to post-24 months. Most changes were by grade 1, and the largest change was by grade 2. Joints with persistently low ST scores had more frequent erosion healing and fewer worsened erosions than joints with persistently high ST (Table 1). MTPJs with persistently high ST had more erosions that worsened than improved after 12 months, but approximately the same number had improved and worsened erosions after ≥24 months. Persistently high PD and erosion progression occurred very infrequently. Six patients were not treated with DMARDs or biologics throughout the study duration. Four of these patients had persistently high ST, of whom 3 had worsened total erosion scores.

Conclusion: Our findings suggested that more erosions worsened in joints with persistent severe inflammation than joints with low inflammation in early RA. The value of US inflammation for predicting erosion progression warrants further investigation, especially in populations with greater disease activity.

Table 1: MTPJs with persistently low or high inflammation during the first 12 months, and the progression of their MRI erosions after 12 months and after 24-49 months.

		MRI erosion BL to 12 months				MRI erosion BL to post-24 months			
ST	PD	Stable	Improve	Worsen	Sum	Stable	Improve	Worsen	Sum
Low	Low	71 (64%)	24 (22%)	16 (14%)	111	53 (55%)	29 (30%)	14 (15%)	96
	High	2 (100%)	0	0	2	2 (100%)	0	0	2
High	Low	24 (69%)	3 (9%)	8 (23%)	35	14 (56%)	5 (20%)	6 (24%)	25
	High	1 (50%)	0	1 (50%)	2	1 (50%)	0	1 (50%)	2
Sum		98	27	25	150	71	33	21	125

Disclosure: H. Zou, None; K. A. Beattie, None; S. Totterman, Qmetrics Technologies, 4; G. Ioannidis, None; M. Larche, AbbVie Inc., 2.

Abstract Number: 307

Tenosynovitis on MRI of Bilateral Hands and Its Concordance with Joint Swelling/Tenderness in Patients with Early Rheumatoid Arthritis

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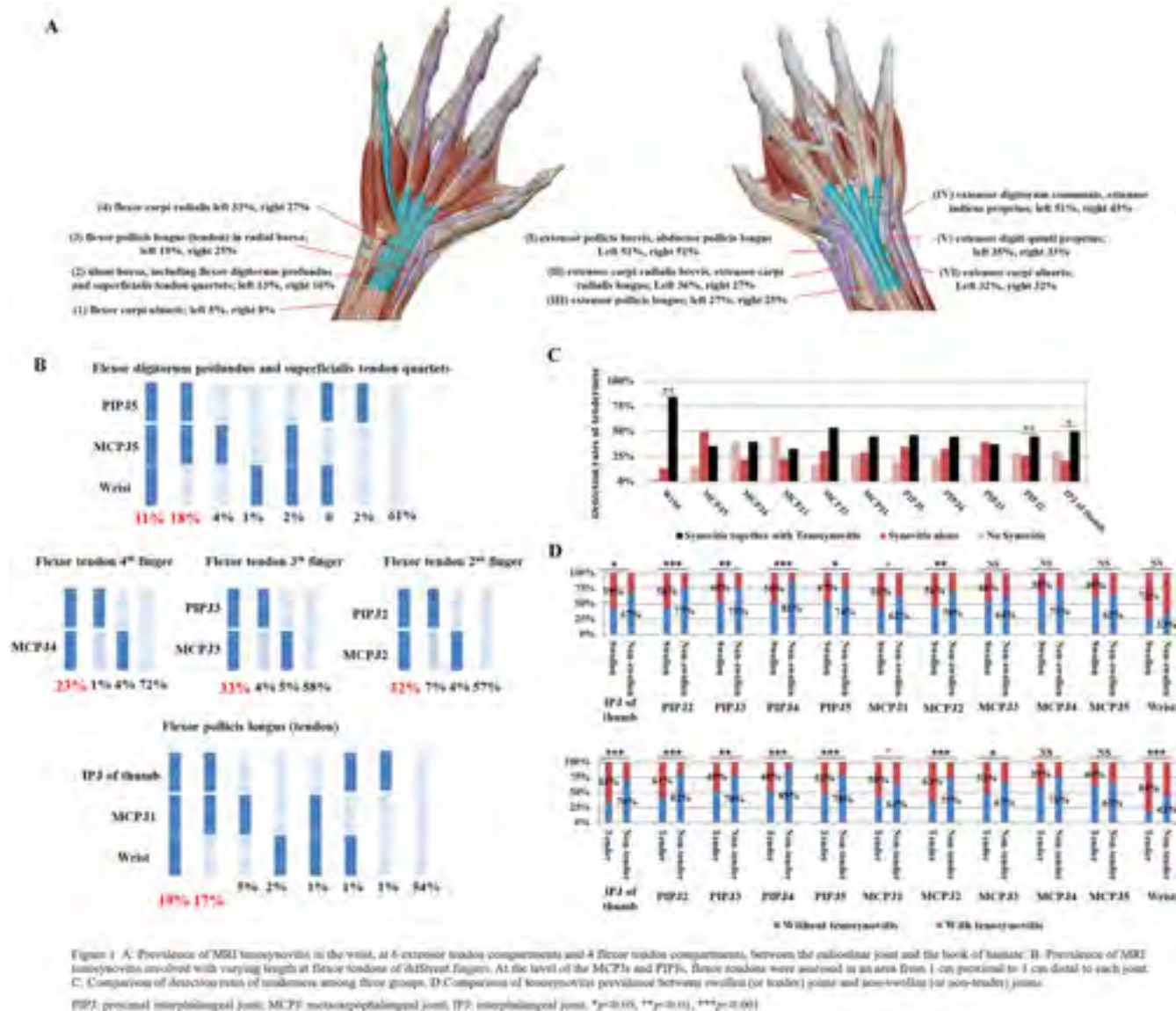
Session Information

Session Date: Sunday, October 21, 2018

Session Title: Imaging of Rheumatic Diseases Poster I: MRI

Session Type: ACR Poster Session A

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



Background/Purpose: The updated recommendations of Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) System in 2017 firstly recommended tenosynovitis with a standard score. However, there is no study on the novel score of tenosynovitis using bilateral-hands MRI and no data of MRI tenosynovitis on proximal interphalangeal joints (PIPs) either.

Objective: To explore the distribution of MRI tenosynovitis among bilateral hands and its concordance with joint swelling/tenderness in early RA patients.

Methods: Early active RA patients (DAS28-CRP ≥ 2.6 and disease duration ≥ 1 year) were recruited in our hospital during October, 2011 to March, 2018. Bilateral hands (including PIPJs, MCPJs and wrists) of each patient were scanned simultaneously on 3.0T whole-body MRI system with an 8-channel sense head coil. MRI tenosynovitis and synovitis were scored based on RAMRIS 2017. Clinical data were collected simultaneously.

Results:

- Among 75 patients recruited, the median age was 45 years old with 71% female. The median disease duration was 7 months and 85% had bony erosions.
- MRI tenosynovitis was detected in 84% of patients. Tenosynovitis in extensors occurred in 72% of wrists, which were higher than tenosynovitis in flexors (52%), of which the most frequent tenosynovitis was detected in extensor pollicis brevis, abductor pollicis longus (figure 1A). Tenosynovitis occurred alone or together with synovitis. For wrists, interphalangeal joints (IPJ) of thumb and PIPJ2, joints with both synovitis and tenosynovitis showed higher rates of tenderness than those joints with synovitis alone ($p < 0.05$, figure 1C).
- For PIPJ2-5 and IPJ of thumb, the prevalence of synovitis in swollen (or tender) joints were significantly higher than those in non-swollen (or non-tender) joints (all $p < 0.05$, figure 1D). Multivariate Logistic regression analyses

showed MRI tenosynovitis score was an independent risk factor respectively for swelling (or tenderness) of PIPJ2, PIPJ4, PIPJ5; tenderness of MCPJ1~4 and IPJ of thumb (OR 1.859~3.414, all $p<0.05$).

4. Tender wrists showed more tendon sheaths with tenosynovitis than non-tender wrists (3.6±3.1 vs. 2.3±2.9, $p=0.007$). ROC analyses showed that when there were ≥3 tendon sheaths with tenosynovitis, tenderness occurred in the wrist with 54% of sensitivity and 66% of specificity (AUC: 0.647, 95% CI: 0.559-0.735, $p=0.002$). Tenosynovitis score of flexor carpi radialis tendon was an independent risk factor for tenderness of wrists (OR 2.050, 95% CI: 1.103-3.812, $p=0.023$).

Conclusion: This study first reports distribution of MRI tenosynovitis among bilateral hands including PIPJs, and tenosynovitis score was an independent risk factor for tenderness of wrist, certain MCPJs or PIPJs.

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Disclosure: Y. Q. Mo, None; Z. H. Yang, None; J. W. Wang, None; X. Y. Du, None; Y. H. Xu, None; K. M. Yang, None; G. Z. Shi, None; J. Shen, None; L. Dai, None.

Abstract Number: 308

Carpal Bones Affection Frequency in Rheumatoid Arthritis By Magnetic Resonance Imaging

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Session Information

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Session Title: Imaging of Rheumatic Diseases Poster I: MRI

Session Type: ACR Poster Session A

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

Background/Purpose: Wrist joint between radio-ulna and first carpal row; scaphoid and triquetrum bones stabilize the central carpal column and support the flexion-extension or abduction-adduction movements¹. Rheumatoid arthritis (RA) chronic disease affects the hand-wrist small joints, causing disability. Magnetic resonance imaging (MRI) is the most sensitive diagnosis and disease follow-up method (96%)², that can demonstrates lesions since initial RA phases. Objective: Identify by MRI the most affected wrist bones in 3 different RA clinical phases.

Methods: Exploratory, non-blinded cohort; from Hospital “Dr. José E. González” since Nov. 2016-Feb. 2017, (approved by Ethics and Research Committees); 60 patients assessed by rheumatologists (ACR-EULAR 2010 criteria), were divided into 3 groups: Clinically Suspicious Arthralgia (CSA), 23 (38%); Early RA (ERA), 22 (37%) and RA 15 (25%); accepted to perform MRI 1.5T, dominant hand, simple T1, T1-gadolinium and STIR (coronal and axial sections) sequences; images were assessed by experimented radiologist

Results: Female was predominant with 83% (50); mean age 42 (19-70 years); we evaluated by OMERACT-RAMIRS 1,731 wrist sites of bones and joints, obtaining lesions (synovitis, erosions, osteitis) in 56% (964); synovitis was the most prevalent 46% (445) and Triquetrum bone the most affected in all 3 groups: CSA, 87% (20/23), ERA, 91% (20/22) and RA, 93% (14/15), see Table and Figure

Conclusion: The predominant Triquetral synovitis, could suggest us, be the first morphological site to be considered in the RA evaluation when it is clinically suspected; however further longitudinal studies are needed to conclude it



CSA (n=23)	Synovitis n (%)	Erosions n (%)	Osteitis n (%)
Triquetrum	20 (87)	21 (91)	2 (9)
Lunate	11 (48)	22 (96)	2 (9)
Capitate	10 (44)	21 (91)	4 (17)
TOTAL=288 (16%)	137 (48)	130 (45)	21 (8)
Active erosions		30 (26)	
ERA (n=22)			
Triquetrum	20 (91)	21 (96)	12 (55)
Lunate	16 (73)	21 (96)	12 (55)
Scaphoid	18 (82)	20 (91)	10 (46)
TOTAL=408 (24%)	181 (44)	154 (38)	73 (18)
Active erosions		52 (44)	
RA (n=15)			
Triquetrum	14 (93)	14 (93)	11 (73)
Scaphoid	14 (93)	14 (93)	7 (47)
Hamate	13 (87)	9 (60)	6 (40)
TOTAL=268 (15%)	127 (47)	78 (29)	63 (24)
Active erosions		35 (30)	

Disclosure: M. D. C. Larios-Forte, None; C. Skinner-Taylor, None; D. A. Galarza-Delgado, None; J. Esquivel-Valerio, None; J. Riega-Torres, None; D. Vega-Morales, None; I. Perez-Onofre, None.

Abstract Number: 309

Sub-Clinical Disease Activity in the Feet of Patients with Early Rheumatoid Arthritis: What Clinical Assessments Miss

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Imaging of Rheumatic Diseases Poster I: MRI

Session Type: ACR Poster Session A

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

Background/Purpose: Early diagnosis of RA and effective monitoring of disease activity are important for treatment decision-making. Early treatment strategies can be effective in preventing the development of erosive disease. The primary method of assessing disease activity with physical examination of swollen and tender joints has low accuracy and reliability but remains the cornerstone of assessment despite new imaging modalities. This study examines early RA disease activity in feet with clinical assessment and its correlation with findings on US and MRI, the latter being the reference standard.

Methods: Treatment naive patients with early RA (ACR criteria, <2 years of symptom duration) were recruited. The most clinically symptomatic foot was assessed for swelling and tenderness in the metatarsophalangeal joints (MTPJ) 2-5. The same foot was imaged by US (Esaote MyLab70, 6-18 MHz linear array probe) and a peripheral MRI (1.0 Tesla, GE Medical). US images were semi-quantitatively graded for synovial thickening (0-3) and Power Doppler (PD) (0-3), representing hypervascularization by the rheumatologist who performed clinical assessments. Based on OMERACT RA MRI scoring criteria, a radiologist blinded to clinical and US results semi-quantitatively graded MTPJ 2-5 for bone marrow edema (BME) (grade 0-3 per metatarsal head and phalanx base, max=24) and synovitis (grade 0-3 per MTPJ, max=12).

Results: Included in the analyses were 39 patients; 33 female (84.6%), mean (SD) symptom duration 12.2 months (10.9), 18 anti-CCP positive (46.2%), and 15 RF positive (38.5%). Mean CRP and ESR levels were 18.9 mg/L (30.7) and 28.4 mm/hr (22.4), respectively. Of the 31 swollen MTP joints, 81% had synovial thickening on US, and of these joints, 44% showed PD and 64% had synovitis or BME grade ≥ 2 on MRI. Of 125 MTP joints assessed as not swollen, 41% (51 joints) were found to have synovial thickening on US with 22% also showing PD and 38% with synovitis or BME grade ≥ 2 . Of the 39 patients, 18 had ≥ 1 swollen joint and, of this subset, 94% had synovial thickening, with 41% showing PD and 57% having synovitis or BME grade ≥ 2 . Of the 21 patients without swelling, 86% (18 patients) had synovial thickening in ≥ 1 joint, with 28% showing PD and 40% having synovitis or BME grade ≥ 2 .

Conclusion: In examining patients with early RA, joints with synovial thickening and PD on US are also found to have inflammation on MRI. Making treatment decisions based solely on clinical presentation might result in under treatment of a fairly high proportion of patients with sub-clinical inflammation. These findings are suggestive that US with evidence of synovial thickening and PD may be helpful as an adjunct to clinical examination in assessing disease activity.

Disclosure: F. Khokhar, None; H. Zou, None; M. Allen, None; S. Totterman, None; K. A. Beattie, None; M. Larche, AbbVie Inc., 2.

Abstract Number: 310

The Trajectory of Grade 1 Erosions in the Feet of Patients with Early RA

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Session Information

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

Background/Purpose: The identification of erosions plays a critical role in the management of RA, as the presence of erosions denotes more aggressive disease requiring more aggressive treatment. MRI can be used to visualize and monitor erosion progression in RA, and is often used as a gold standard in research. While the clinical significance of grade 1 erosions remains unknown, so too does the trajectory of these erosions over time. This study examined the course of grade 1 erosions (involving 1-10% of bone on MRI) in the feet of newly diagnosed RA patients after two or more years of treatment.

Methods: Patients newly diagnosed with RA (treatment-naïve, ACR criteria) were recruited. Participants were assessed at baseline, 1-year, and ≥ 2 years (24-49 months) after diagnosis. The most clinically symptomatic foot chosen at baseline was scanned using a 1.0T peripheral MRI at each visit. A radiologist, blinded to clinical results, semi-quantitatively scored erosions in the metatarsal head and the base of the phalanges of each of MTPs 2-4 (grade 0-10) according to OMERACT-RAMRIS criteria. All patients were treated as per standard of care, and therapy received after baseline assessment was noted. The location of each erosion was noted to ensure that changes over time corresponded to the original erosion. Erosions were compared after one year and ≥ 2 years and categorized as unchanged, worsened or improved. New erosions were also noted.

Results: This study included 41 patients [n=33 females, mean (SD) age 51.9 (10.3) years]. The baseline MRI found at least one grade ≥ 1 erosion in 35 of 41 patients (85%), in 103 MTP joint bones. The majority of the erosions were grade 1 [n=89 (86%)] at baseline. Comparing grade 1 erosions one year later, 20 (19%) had resolved, 77 (75%) remained unchanged, 6 (6%) had progressed, and there were 20 new grade 1 erosions. Comparing baseline grade 1 erosions to ≥ 2 years later, 16 (16%) had resolved, 87 (84%) remained stable, 0 had progressed, and there were 10 new grade 1 erosions. Of note, only one erosion progressed by more than 1 grade within a follow-up period (grade 1 to grade 3 after 1 year). In terms of treatment, by their final assessment, 6 patients had received no DMARDs/biologics, 20 were on a single DMARD, 8 on combination DMARDs, and 7 on biologic or biologic/DMARD combination. There was no consistent relationship identified between the type of therapy and the improvement, stability, or progression of erosions.

Conclusion: Grade 1 erosions on MRI are common in the MTP joints of early RA patients. The majority of erosions appear to resolve or remain stable following two or more years of treatment. This suggests that early standard treatment may be sufficient to manage small erosions. There does not appear to be any consistent relationship between change in these small erosions and the type of RA treatment chosen. The clinical relevance of these erosions remains unknown.

Disclosure: M. C. Yelovich, None; H. Zou, None; S. Deshauer, None; S. Totterman, Qmetrics Technologies, 4; K. A. Beattie, None; M. Larche, AbbVie Inc., 2.

Abstract Number: 311

Magnetic Resonance Imaging of the Cervical Spine in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis Presenting with Chronic Neck Pain – a Systematic Comparison of Clinical Assessments

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Imaging of Rheumatic Diseases Poster I: MRI

Session Type: ACR Poster Session A

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

Background/Purpose: Despite the differences in pathogenesis, neck pain associated with functional limitation of the cervical spine is a frequent clinical symptom of patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Here we compare inflammatory and structural findings obtained by magnetic resonance imaging (MRI) in patients with RA and AS who present with chronic neck pain.

Methods: A total of 107 patients (59 RA with 295 and 48 AS with 240 vertebral segments) were consecutively included if they had chronic neck pain (duration >3 months). All patients had clinical examinations for neck function and mobility, were asked to fill in disease specific questionnaires, also had laboratory examinations (CRP, ESR) and MRI of the cervical spine (CS) using contrast-enhanced MRI sequences (T1 pre- and post-Gadolinium, sagittal and axial images). An experienced rheumatologist examined all patients blinded to diagnosis and MR images. In addition, two experienced readers blinded to patients' diagnosis and clinical assessments evaluated the MRIs by describing the anatomical structures of the CS (vertebral body, intervertebral disc, facet joints) and the pattern of inflammatory activity in the bone marrow (vertebral edges vs. vertebral endplates).

Results: The RA group included more females (66.1%) and older patients (58.6 ± 11.4 years) in comparison to AS (68.8% males, mean age 47.9 ± 13.1 years), while there were no differences in the duration of neck pain. AS patients reported higher mean levels of neck pain on a 0-10 numerical rating scale (5.0 ± 3.6) as compared to RA patients (3.0 ± 3.1) ($p=0.003$), while the Northwick pain questionnaire didn't reveal any differences. There were numerically more patients with AS (n=11, 22.9%) than RA (n=9, 15.3%) ($p=0.166$) with bone marrow edema (BME) at the vertebral edges. The majority of lesions was located in the lower CS. In contrast, more patients with RA (n=18, 30.5%) than AS (n=3, 6.3%) had erosive osteochondrosis with endplate BME ($p=0.002$). Atlantoaxial synovitis was found in only 1 patient with RA (1.7%), while inflammatory changes around the dens axis were found in 2 (3.4%) and atlantodental synovitis in 5 (8.5%) RA patients but not in AS patients. In comparison, erosive changes in the dens axis region were found in 3 RA (5.1%) vs. 2 AS (4.1%) patients. No major differences related to the presence of facet joint osteoarthritis was found (78% in RA vs. 65% in AS). The prevalence of facet joint osteoarthritis was the only imaging finding correlating with clinical symptoms: $r=0.259$ ($p=0.049$) for RA and $r=0.416$ ($p=0.003$) for AS, respectively. Similarly, only facet joint osteoarthritis correlated with restriction of cervical rotation in patients with AS ($r=0.471$, $p=0.001$).

Conclusion: Both BME and chronic changes of the lower part of the CS but not of the atlantoaxial region are seen in patients with RA and AS who present with chronic neck pain. The pattern of BME involvement in patients with RA vs.

AS was different. Facet joint osteoarthritis was the only imaging finding that correlated with the magnitude of neck pain, in AS it also correlated with impaired cervical rotation.

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Abstract Number: 312

Diagnostic Value of MRI in Non-Radiographic Axial Spondyloarthritis

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Session Information

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

Background/Purpose: Few studies showed signs of inflammation at the MRI of the sacroiliac joints (SIJ) or spine in only 30% of the non-radiographic axial spondyloarthritis (nr-axSpA) patients ⁽¹⁾. Aims: 1) to evaluate inflammation at the MRI of the SIJ/ spine in TNF naïve nr-axSpA patients 2) consistency in case of absence of inflammation after 6 months and 3) evaluate gender differences

Methods: Consecutive patients with inflammatory back pain who were either HLA-B27 positive with ≥ 1 SpA-feature or HLA-B27 negative with ≥ 2 SpA-features, with high disease activity (BASDAI ≥ 4), had an MRI of the SIJ and spine. In case of absence of inflammation, the MRI was repeated after six months. MRI images were scored according to the Spondyloarthritis Research Consortium of Canada (SPARCC spine, range 0-108; SPARCC SIJ, range 0-72) method

Results: Included were 70 patients, of whom 37 (53%) females. Half of the patients (36/69, 52.2%) showed signs of inflammation on the first MRI: 27/69 patients (39.1%) at the SIJ, 14/46 patients (30.4%) at the spine and 4 patients (5.8%) on both sites and one patient missed the baseline MRI. Males had more often a positive MRI compared to females 62.5% vs. 43.2%. Patients with a positive MRI showed a median SPARCC score for SIJ of 8.0 (IQR: 1.8-23.5, higher in females) and for spine 6.5 (IQR: 2.8-10.8, higher in males). Only 4/33 patients (12.1%) showed a positive MRI after six months.

Conclusion: Fifty percent of the patients with nr-axSpA and high disease activity showed inflammatory lesions at the MRI of the SIJ and/or spine, which occurred more often in males compared to females. In most cases (87.9%) a MRI without inflammatory lesions remained negative after 6 months, indicating that a second MRI after a short period is not valuable.

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Abstract Number: 313

Do Musculoskeletal Ultrasound and Magnetic Resonance Imaging Identify Synovitis and Tenosynovitis at the Same Joints and Tendons? – a Comparative Study in Patients Presenting with Early Arthritis and Clinically Suspect Arthralgia

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Session Information

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Session Title: Imaging of Rheumatic Diseases Poster I: MRI

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

Background/Purpose: In the diagnostic process of RA, the use of advanced imaging techniques like musculoskeletal ultrasound (US) and magnetic resonance imaging (MRI) has been recommended. Unfortunately, research on its comparability is scarce. Therefore we aimed to compare findings of synovitis and tenosynovitis by US with MRI on joint- and tendon-levels in patients presenting with early inflammatory arthritis (IA) and clinically suspect arthralgia (CSA).

Methods: Seventy patients newly presenting to the rheumatology outpatient clinic (40 with recent-onset CSA, 30 with IA) underwent US and MRI of MCPs, wrist and MTPs at the same day. Grey-scale (GS) and power Doppler (PD) synovitis were scored according to Szkudlarek *et al* (combining synovial effusion and hypertrophy) and tenosynovitis by GS/PDUS was scored according to the OMERACT definition. Static images were also re-scored for GS synovitis according to the recently published EULAR/OMERACT score (considering synovial hypertrophy regardless of the presence of effusion) by two readers (ICC 0.92). MRI scans were scored according to the RAMRIS method. All scores ranged from 0-3. Analyses were performed on joint/tendon level. Synovitis and tenosynovitis scores were compared and test characteristics determined with MRI as reference. Cut-off for dichotomization were scores ≥ 1 and ≥ 2 for US and ≥ 1 for MRI.

Results: Compared to MRI, GSUS synovitis according to the EULAR/OMERACT (US cut-off ≥ 1) had a sensitivity ranging from 27-75% for the different locations (MCP, wrist, MTP joints) and a specificity of 80-98%. For the method according to Szkudlarek *et al* the sensitivity was between 68-91% and specificity 52-70%. When a US cut-off ≥ 2 was used, the sensitivity and specificity were 6-23% and 99-100%, respectively for the 'EULAR/OMERACT method' and 39-64% and 92-97% for the 'Szkudlarek method'. Synovitis by PDUS had a sensitivity of 30-54% and specificity of 97-99%. The sensitivity to detect tenosynovitis by GSUS ranged between 42-65% and the specificity 81-92%. For tenosynovitis by PDUS the sensitivity ranged between 16-35% and the specificity from 98-100%.

Conclusion: Ultrasound is less sensitive to detect synovitis and tenosynovitis compared to MRI in early arthritis and arthralgia. The high specificity implies that there were few 'false positive' results. The new EULAR/OMERACT method had a higher specificity than the method according to Szkudlarek *et al*, with MRI as a reference. Thus current data showed that MRI is more sensitive for the early detection of synovitis and tenosynovitis. However, US is more readily available to rheumatologists in many countries, it is inexpensive and logistically easier to arrange.

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Abstract Number: 314

Development and Preliminary Validation of an Omeract Magnetic Resonance Imaging (MRI) Scoring System for Ankle Enthesitis in Spondyloarthritis

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Background/Purpose: Enthesitis is a key feature in spondyloarthritis (SpA). MRI allows sensitive visualization of enthesal inflammation and damage, but no validated, internationally accepted MRI scoring systems exist. The objective of this study was to develop and perform preliminary validation of a novel OMERACT MRI scoring system for assessing ankle enthesitis in SpA patients.

Methods: A systematic literature review (SLR) of MRI studies on enthesitis in SpA identified key inflammatory and structural pathologies. Accordingly, pathologies to score and definitions of these were agreed by consensus within the OMERACT MRI in arthritis working group, followed by 3 internet-based multireader scoring exercises, with calibration sessions in between. In Exercise 1 the Achilles tendon and plantar fascia entheses in 10 ankle MRIs (sagittal T1-weighted (T1W) and sagittal and axial fat suppressed T2W images) were scored by 15 readers with varying expertise in ankle MRI. Each enthesis was assessed for peritendon hypersignal, intratendinous hypersignal, enthesal bone marrow edema, retrocalcaneal bursitis, tendon thickening, bone spur and erosion. Each parameter was scored 0-3 (no, mild, moderate, severe). After a calibration session leading to minor modifications, and development of reader rules, Exercise 2 comprised scoring of 16 ankle MRIs (specifications as above), by 15 readers. In Exercise 3, ankle MRIs (sagittal fat-suppressed T2W) of 21 patients before and after biological therapy were scored for the inflammatory variables by 10 readers, blinded to chronological order. Inter-reader agreement was calculated using single measure, two-way random effects, absolute agreement intraclass correlation coefficients (ICCs) for sum scores of inflammatory and structural lesions (patient level), and Cohen's kappa for scores at lesion level.

Results: Exercise 1: Mean pairwise inter-reader ICCs were 0.40 and 0.41 for inflammatory and structural variables, respectively. Exercise 2: Mean pairwise inter-reader ICCs were 0.64 (Range: 0.17 – 0.93) for inflammatory variables, while 0.45 (Range 0.08 – 0.91) for structural variables. Exercise 3: The mean pairwise inter-reader ICC for inflammatory variables was 0.81 (Range: 0.57 – 0.95) for baseline scores and 0.81 (Range: 0.57 – 0.92) for change scores. Table 1 shows ICCs and kappas for all readers and for 4 preselected readers (the participating radiologist and the 3 rheumatologists with highest interreader agreement in Exercise 2).

Conclusion: Initial steps in developing an OMERACT MRI enthesitis scoring system at the ankle have been performed, and good reliability (particularly for inflammatory variables) has been demonstrated.

Table 1: Inter-reader agreement on patient level (ICC for inflammation sum scores) and lesion level (kappa for inflammatory parameters) on baseline and change score in Exercise 3

		All readers together			Radiologist + Best 3 from Exercise 2		
		Mean	Median	Range	Mean	Median	Range
Patient level (ICC)							
Sum score of all parameters	Baseline	0.81	0.83	0.57 - 0.95	0.91	0.91	0.90 – 0.94
	Change	0.80	0.82	0.57 – 0.92	0.85	0.84	0.79 – 0.91
Lesion level (kappa values)							
All parameters	Baseline	0.68	0.67	0.45-0.85	0.81	0.81	0.76 – 0.85
	Change	0.48	0.48	0.24 – 0.68	0.57	0.58	0.46 – 0.65
Bone marrow edema	Baseline	0.86	0.86	0.75 – 0.97	0.88	0.89	0.84 – 0.92
	Change	0.53	0.52	0.30 – 0.82	0.54	0.47	0.45 – 0.76
Peri-tendon hypersignal	Baseline	0.62	0.64	0.29 – 0.87	0.78	0.79	0.68 – 0.87
	Change	0.47	0.49	0.16 – 0.75	0.53	0.50	0.42 – 0.75
Intra-tendon hypersignal	Baseline	0.51	0.55	0.02 – 0.89	0.81	0.79	0.77 – 0.89
	Change	0.41	0.41	0.09 – 0.64	0.52	0.54	0.35 – 0.63
Retro-calcaneal bursitis	Baseline	0.49	0.55	-0.12 – 0.93	0.60	0.57	0.42 – 0.78
	Change	0.26	0.24	-0.28 – 1.00	0.42	0.45	0.15 – 0.67

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Assessing the Value of Whole Body Magnetic Resonance Imaging As to Clinical Examination to Predict Remission and Relapse in Early Peripheral Spondyloarthritis

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Session Information

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Session Title: Imaging of Rheumatic Diseases Poster I: MRI

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Background/Purpose: Evaluation of disease activity and treatment response in peripheral spondyloarthritis (pSpA) is currently based upon clinical findings, laboratory tests and ultrasound examination. Whole-body magnetic resonance imaging (WB MRI) is a relatively new imaging technique that could offer additional information regarding the inflammatory status of joints, entheses and soft tissues. The objective of this study is to determine A) the value of WB MRI, performed at baseline, in relation to clinical remission in pSpA and B) the value of subclinical inflammation, detected by WB MRI, at time of clinical remission in predicting flare after treatment withdrawal in pSpA.

Methods: Clinical REmission in peripheral SPondyloArthritis (CRESPA) is a placebo-controlled trial of golimumab treatment in 60 early (symptom duration < 12 weeks) pSpA patients (pts). All pts underwent a modified WB MRI at baseline and at the time of clinical remission when treatment was withdrawn. The WB MRI was performed by scanning multiple locations individually (using different coils) in order to investigate SpA-specific locations in detail. Several anatomical sites of pelvis and lower limbs were evaluated for bone marrow edema (BME), synovitis and soft tissue inflammation (STI) by 3 readers, giving a score of 0 (no abnormalities), 1 (mild), 2 (moderate) or 3 (severe). For each site a mean of the scores of the 3 readers was calculated. For each patient at each time point, we calculated a sum score for synovitis, STI and BME separately adjacent to a total sum score. Changes scores are baseline minus remission sum scores.

Results: Pts reaching remission had lower baseline MRI synovitis (3,0 vs. 3,6), STI (2,1 vs. 2,2), BME (1,8 vs. 2,9) and total sum scores (7,0 vs. 8,7) than the non-remission group. However, these differences lacked statistical significance. At the time of clinical remission 10/45 (22%) and 11/45 (24%) pts had residual talocrural and subtalar synovitis respectively. However, there was no statistically significant difference between patients who relapsed after treatment withdrawal and those who remained in remission concerning synovitis sum scores ($p = 0.497$) as well as BME sum scores ($p = 0.741$) and STI sum scores ($p = 0.131$) at time of clinical remission (Table 1).

Table 1: BME, synovitis and STI presence in early pSpA pts who relapsed and did not relapse after stopping golimumab therapy

	Patients relapsed (n=20)	Patients not relapsed (n=25)
BME at baseline	1.9 (± 2.4)	2.0 (± 2.4)
BME at follow-up	1.3 (± 1.1)	1.4 (± 1.9)
Synovitis at baseline	2.4 (± 2.9)	3.6 (± 3.9)
Synovitis at follow-up	1.2 (± 1.4)	1.4 (± 1.4)
STI at baseline	1.9 (± 2.4)	2.3 (± 2.3)
STI at follow-up	0.9 (± 0.7)	1.1 (± 1.1)

Conclusion: There was no significant difference in inflammatory burden on baseline WB MRI between patients going into remission and those with ongoing disease activity. At remission, a substantial part of the participants showed residual ankle synovitis on MRI. However, residual inflammatory lesions detected by MRI did not differ significantly between patients who relapsed after treatment withdrawal and those in ongoing remission.

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Eligibility Rates in Axial Spondyloarthritis Clinical Trials Based on Imaging Criteria

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Session Information

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Background/Purpose: Axial Spondyloarthritis (AxSpA) encompasses both non-radiographic (nr-AxSpA) as well as radiographic ankylosing spondylitis (AS) which displays structural changes at the sacro-iliac joint (SIJ). Phase 2 and 3 clinical trials are currently ongoing requiring imaging-based eligibility of subjects based on the protocol specific target population for the type of disease (nr-AxSpA vs. AS). The currently accepted modified New York (mNY) criterion includes a radiographic assessment of the SI joint. In clinical trials the subjects deemed locally to be good candidates either for an AS or an nr-AxSpA trial have an SIJ X-ray examination read centrally to determine eligibility (mNY+ for AS and mNY- for nr-AxSpA). For nr-AxSpA trials, an MRI examination of the SIJ is also obtained to confirm inflammation per ASAS/OMERACT guidelines; mNY- with positive MRI (MRI+) subjects are deemed eligible for these trials. Therefore, for prospective trial design it is important to understand the percentages of subjects likely to be deemed eligible by central imaging review and how many subjects will screen-fail for either AS (mNY+) or nr-AxSpA (mNY-).

Methods: A total of 4782 subjects from seven trials were assessed for mNY +/- and/or MRI +/- . 2 studies (n=1419) had both an AS or and nr-AxSpA cohort and subjects were recruited according to mNY+ (for AS cohort) or mNY-/MRI+ (for nr-AxSpA cohort). 3 studies (n=821) had mNY+ as the imaging inclusion criteria and 2 studies (n=2496) had mNY- / MRI+ as the imaging inclusion criteria. The read model was either a single or double read. Percentage of subjects deemed either eligible for AS (mNY+) or nr-AxSpA (mNY-/MRI+) was calculated. We also calculated the percentage of subjects who were mNY- / MRI- or MRI+.

Results: As shown in Table 1, for AS studies requiring an mNY+ radiograph, 52.6% were eligible and 47.2% were ineligible. For nr-AxSpA studies which required a mNY- radiograph, 70.9% were eligible and 29% were ineligible. Further, when nr-AxSpA mNY- subjects were assessed for MRI positivity per ASAS/OMERACT guidelines, 39.7% were MRI+ (eligible) and 60.3% were MRI- (ineligible).

Table 1:

Type of AxSpA Population	Radiographic Inclusion Criteria	Total # Analyzed	# mNY+ (%)	# mNY- (%)
AS	mNY+	2240	1180 (52.6%)	1058 (47.2%)
nr-AxSpA	mNY-	3915	1134 (29%)	2778 (70.9%)
Distribution of nr-AxSpA subjects (mNY-) into MRI +/-				
	MRI Inclusion Criteria	Total # analyzed	MRI+	MRI-
nr-AxSpA	MRI+	2635	1046 (39.7%)	61 (60.3%)

Conclusion: The screen failure rate was high for both AS (47.2%) and nr-AxSpA (29%) studies. Further, not all mNY- subjects initially categorized as nr-AxSpA were MRI+; 60.3% of the mNY- pool did not qualify per the ASAS/OMERACT criteria for inflammation of the SIJ. Given that MRI positivity is increasingly being used to enroll "true" non-radiographic axial SpA subjects the failure rate is noteworthy. Overall, the data suggests that not all subjects screened locally will qualify to enter the trial when the radiographic criteria are applied centrally. This is due partly to the deliberate lack of clinical observations during central review of the SIJ imaging. In conclusion, these rates should be taken into consideration during prospective AS and nr-AxSpA trial design.

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Imaging Biomarker Based Patient Stratification: Initial Data and Validation in Four Most Common Knee Arthritic Diseases

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Background/Purpose: Biomarker science has advanced to aid in distinguishing between different forms of arthritis: inflammatory arthritides such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA) and OA. Biomarkers are also used to assess disease activity. Diagnostic serum biomarkers such as rheumatoid factor (RF) and cyclic-citrullinated peptide (CCP) and assays of disease activity such as C-reactive protein (CRP), and multi-biomarker assays have utility but lack complete sensitivity and specificity. Increasingly quantitative imaging biomarkers may fill an important gap in disease identification and assessment.

Objectives: 1) To investigate the association between imaging measures of inflammation in the synovium of the knee joint and systemic levels of CRP in patients with RA, PsA and OA. 2) Investigate how imaging and clinical markers correlate to IL-6 levels from joint fluid in different patient cohorts.

Methods: 38 patients with a flare of pain in the knee were recruited. 12 were diagnosed with RF positive (+) RA, 6 with RF negative (-) RA, 6 PsA, and 14 OA, according to ACR/EULAR criteria. CRP in blood and IL-6 levels from joint fluid were determined. Patients underwent MRI, including Dynamic Contrast Enhanced (DCE)-MRI exam prior to an ultrasound-guided arthrocentesis. MRI were scored for synovitis [1] and DCE-MRI were quantified using Dynamic Enhanced MRI Quantification (DEMRIQ) method, extracting the volume of enhancing voxels (Nvoxel), Initial Rate of Enhancement (IRE), Maximum Enhancement (ME). Inflammation was quantified as IRExNvoxels and MExNvoxels [2]. Correlation between all clinical scores and all imaging parameters was done using Spearman rho, with significance levels of $p < 0.05$.

Results: The imaging markers of perfusion in the synovium of the knee (MExNvoxels and IRExNvoxels) were the only imaging measures, which showed a very high association with CRP in both RF+ RA ($r = 0.92 / 0.97$, $p < 0.05$) and PsA patients ($0.93 / 0.99$, $p < 0.05$), whereas all other imaging markers of inflammation showed no statistical association with blood levels of CRP in these diseases. We found no association between CRP and any imaging assessed scores of inflammation in either RF- RA or OA. In addition, only RF+ RA patients showed a positive moderate to high association between MExNvoxels and IL-6 ($r = 0.66$, $p < 0.05$) in the knee joint aspirate.

Conclusion: Quantitative imaging and blood biomarkers of inflammation, such as DCE-MRI parameters and CRP, appear to relate differently to each other in the four most common knee arthritic diseases, RF + RA, RF- RA, PsA and OA. DCE-MRI may have specific utility in differentiating these conditions and their disease activity.

References: : [1] Guermazi A et al.; MRI-based semiquantitative scoring of joint pathology in osteoarthritis. *Nat Rev Rheumatol.* 2013 Apr;9(4):236–251

[2] Kubassova O et al.; A computer-aided detection system for rheumatoid arthritis MRI data interpretation and quantification of synovial activity. *European journal of radiology.* *Eur J Radiol.* 2010 Jun;74(3):e67-72.

Disclosure: O. Kubassova, None; M. Boesen, None; A. Taylor, None; R. Riis, None; L. Hornum, None; H. Bliddal, None; C. Ballegaard, None; E. M. Bartels, None.

Inflammatory Findings Detected By MRI at Enthesal Sites in the Pelvic Girdle of Patients with Polymyalgia Rheumatica Have Potential for a Diagnostic Test

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Imaging of Rheumatic Diseases Poster I: MRI

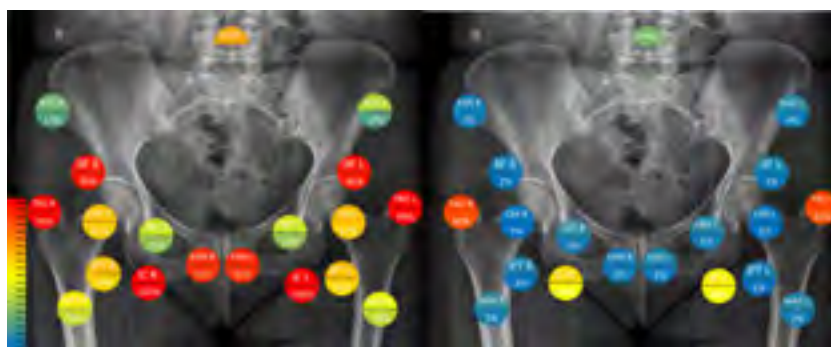
Session Type: ACR Poster Session A

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

Background/Purpose: Polymyalgia rheumatica (PMR) is a common inflammatory disease of the elderly. In the absence of a diagnostic test its differential diagnosis which is mainly based on clinical expertise, elevation of C-reactive protein and exclusion of other diseases can be challenging. Extracapsular inflammation in the pelvic and the shoulder girdle has recently been highlighted by studies using FDG-PET/CT and MRI. Based on our observations in the last years we have developed a scoring system for pelvic girdle MRI scans concentrating on characteristic findings in PMR and, thus, evaluated its use as a diagnostic test.

Methods: A total of 120 pelvic contrast enhanced MRI scans of patients with pelvic girdle pain was available. While 40 patients had PMR diagnosed by an expert rheumatologist, 80 were found to have other inflammatory or non-inflammatory causes of pain. Three radiologists fully blinded to the clinical diagnosis scored peritendinous contrast enhancement at 19 predefined sites: 9 tendinous sites bilaterally and the most caudal perispinous area of the lumbar spine. Five different patterns of involvement were evaluated. Inter- and intraobserver agreements were assessed by intraclass correlation coefficients (ICC).

Results: There were 55% and 62.5% females in the PMR and the control group, respectively. Their mean age was 64.2 ± 8.8 years, with no difference between groups. The interobserver ICC with 0.76 and the intraobserver ICC with 0.88-0.91 for the assessment of single sites were excellent. In the PMR group, 13.4 ± 2.7 sites were affected, but only 4 ± 2.3 in controls. Mostly bilateral peritendinitis at the proximal M. rectus femoris and the origins of M. adductor longus were the hallmark of pelvic involvement in PMR (Figure). A bilateral affection of these two sites discriminated patients with PMR from controls with a sensitivity of 100% and a specificity of 95%. If at least 4 sites including one of those two were bilaterally affected the specificity even improved to 97.5% without reducing sensitivity, this pattern performed best.



Conclusion: The MRI findings described here were found to be very characteristic and even specific for PMR. Thus, we think that contrast enhanced pelvic MRI is a valid imaging tool for diagnosing PMR. These results need to be confirmed in larger prospective studies.

Figure. Illustration of extracapsular inflammation in 19 predefined sites in PMR (left) and controls (right) superimposed on X-ray. The upper semicircle represents colour encoded relative frequency at individual site, the lower semicircle colour encoded and numeric frequency of bilateral affection.

Disclosure: M. Fruth, None; J. Kozik, None; P. Martin-Seidel, None; A. Seggewiss, None; B. Buehring, None; X. Baraliakos, None; J. Braun, None.

Patterns of Muscle Oedema, Atrophy and Fatty Replacement in the Idiopathic Inflammatory Myopathies: A Single-Centre Retrospective Review of Magnetic Resonance Imaging Data

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Imaging of Rheumatic Diseases Poster I: MRI

Session Type: ACR Poster Session A

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

Background/Purpose: Magnetic resonance imaging (MRI) has been used as a non-invasive tool to aid diagnosis and monitor disease activity in the idiopathic inflammatory myopathies (IIMs). Recent research has focused on whether radiological features may help subtype a patient with IIM, as this can be difficult to determine clinically and false negative results may occur with muscle biopsy. Herein, we describe the MRI findings in patients with IIM and identify radiological patterns that may discriminate between the subtypes of polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM) and necrotising autoimmune myopathy (NAM).

Methods: We retrospectively reviewed 114 lower-limb MRIs performed on 66 patients with IIM and 10 patients with non-inflammatory muscle histology (non-IIM) between 2009 and 2017 at the Royal Adelaide Hospital. Three patients did not satisfy EULAR/ACR criteria for IIM due to either normal creatinine kinase (CK) or strength, but had convincing clinical and histological features. A number of patients (n = 28) had serial images performed. Two musculoskeletal radiologists (SP, NB) independently quantified the degree of muscle oedema (MO), fatty replacement (MFR) and atrophy (MA). Clinical information was prospectively recorded. Ordinal logistic regression was performed analysing radiological grades for each IIM subtype. Spearman correlations were performed to evaluate associations between radiological grades and clinical parameters. Fisher's exact test was used to analyse categorical data. Grades were compared between time points using the Wilcoxon signed rank test.

Results: There was low inter-rater reliability ($\kappa < 0.60$) between radiologists for numerous muscular compartments and, as such, a finding was only considered convincing if it was statistically significant for both radiologists. Pelvic and adductor MO, MFR and MA and posterior thigh MA significantly increased the likelihood of NAM. Anterior thigh MA and MFR significantly increased the likelihood of IBM. Pelvic MO decreased the likelihood of PM. Radiological changes (MO, MFR or MA) in adductors, anterior thighs or posterior thighs significantly reduced the likelihood of a non-IIM diagnosis. Measures of disease activity by visual analogue scale, muscle strength and CK did not correlate with radiological muscle oedema. Follow up scans were performed at a median of 370 days (IQR 217-528 days) and the most striking observation was of stability in radiological grades in many muscular compartments. A significant increase in MA and MFR grades were observed in the anterior thigh and anterior lower limbs, due to progression in a minority of patients.

Conclusion: MRI patterns help discriminate between IIM subtypes. The observed stability over time in MA and MFR in multiple muscle compartments is reassuring and may reflect that these patients were treated intensively with suppression of inflammation, such that further muscle damage was not detected. Clinical disease activity assessments do not seem to reflect the degree of radiological muscle inflammation and, as such, MRI may be a useful adjunct for monitoring disease activity in clinical practice.

Disclosure: J. Day, None; N. Bajic, None; S. Gentili, None; S. Patel, None; V. Limaye, None.

Development of a Magnetic Resonance Imaging Atlas for the Classification of Osteoarthritis of the First Metatarsophalangeal Joint

Shannon Munteanu, Karl Landorf, Jade Tan, Maria Auhl, Jamie Allan, Andrew Buldt and Hylton B. Menz, School of Allied Health, La Trobe University, Bundoora, Australia

Session Information

Session Date: Sunday, October 21, 2018

Session Title: Imaging of Rheumatic Diseases Poster I – ARHP

Session Type: ACR Poster Session A

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

Background/Purpose: Osteoarthritis (OA) of the first metatarsophalangeal joint (MTPJ) of the foot is the most common form of foot OA. The condition is typically evaluated using plain film radiographs, however magnetic resonance imaging (MRI) may provide more detailed insights into the disease process. Therefore, the purpose of this study was to develop a standardised atlas of MRI features of first MTPJ OA and assess its reliability.

Methods: We selected representative images covering the spectrum of OA severity from a database of first MTPJ OA for the following features: osteophytes (dorsal and plantar metatarsal head and dorsal proximal phalanx), joint space narrowing (first MTPJ and first metatarsal-sesamoid joint), bone marrow lesions (first metatarsal, proximal phalanx and sesamoids), cysts (first metatarsal and proximal phalanx), effusion (dorsal and plantar), capsular thickening (dorsal and plantar) and cartilage loss. Thirty cases were then independently scored with the atlas by two raters (SEM and HBM) to determine inter-rater reliability. Statistical analysis was conducted using percentage agreement and Gwet's AC1 modification of the weighted kappa statistic (K_w) and were interpreted using the cut-offs proposed by Cohen (0-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial, 0.81-1.00 almost perfect). An *a priori* decision was made to exclude any observations with $K_w < 0.40$ from the atlas. Reliability of a combined score summing all observations was also assessed using the intra-class correlation coefficient (ICC).

Results: An example MRI from a participant with first MTPJ OA is shown in the figure, and inter-rater reliability results are presented in the table. Percentage agreement ranged from 57 to 96%, and K_w scores ranged from 0.13 to 0.91. Of the 15 features documented with the atlas, 14 (93%) demonstrated acceptable reliability. Only plantar capsular thickening did not reach the reliability threshold, with a K_w of 0.13. The ICC for the combined score was 0.89 (95% CI 0.78 – 0.95), and after excluding plantar capsular thickening, the ICC was 0.90 (95% CI 0.80 – 0.95).

Conclusion: With the exception of first MTPJ plantar capsular thickening, MRI features of first MTPJ OA can be reliably documented using our standardised atlas. The use of this atlas will assist in documenting the severity of first MTPJOA for epidemiological studies and for evaluating the effects of treatment in clinical trials.



Figure. Example MRI of first MTPJ OA, demonstrating osteophytes (OP), cyst (C) and bone marrow lesion (BML).

Table. Reliability results.

Variable	% agreement	Gwet's AC1 K_w	Interpretation
Osteophytes, dorsal metatarsal head ¹	91	0.72 (0.53 – 0.91)	Substantial
Osteophytes, plantar metatarsal head ¹	94	0.81 (0.68 – 0.94)	Almost perfect
Osteophytes, dorsal proximal phalanx ¹	86	0.54 (0.24 – 0.84)	Moderate
Joint space narrowing, 1st MTPJ ¹	95	0.88 (0.82 – 0.94)	Almost perfect
Joint space narrowing, 1st metatarsal-sesamoid ²	80	0.60 (0.30 – 0.91)	Moderate
Bone marrow lesions, metatarsal ³	96	0.87 (0.80 – 0.94)	Almost perfect
Bone marrow lesions, proximal phalanx ³	96	0.87 (0.76 – 0.98)	Almost perfect
Bone marrow lesions, sesamoids ²	67	0.40 (0.03 – 0.77)	Fair
Cysts, metatarsal ²	90	0.81 (0.58 – 1.00)	Almost perfect
Cysts, proximal phalanx ²	93	0.91 (0.78 – 1.00)	Almost perfect
Effusion – dorsal ²	83	0.76 (0.53 – 0.99)	Substantial
Effusion – plantar ²	80	0.67 (0.39 – 0.95)	Substantial
Thickening – dorsal ²	70	0.40 (0.05 – 0.75)	Fair
Thickening – plantar ²	57	0.13 (-0.24 – 0.51)	Slight
Cartilage loss ²	80	0.60 (0.29 – 0.91)	Moderate

¹ scored as none, mild, moderate or severe

² scored as present or absent

³ scored as none, <25%, 25-50%, >50%

Disclosure: S. Munteanu, None; K. Landorf, None; J. Tan, None; M. Auhl, None; J. Allan, None; A. Buldt, None; H. B. Menz, None.

Abstract Number: 321

In Rheumatoid Arthritis All Disease Activities Are Not Created Equal

Keith Knapp¹ and Gary Craig², ¹Discus Analytics LLC, Spokane, WA, ²Discus Analytics LLC., Spokane, WA

Session Information

Session Date: Sunday, October 21, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster I

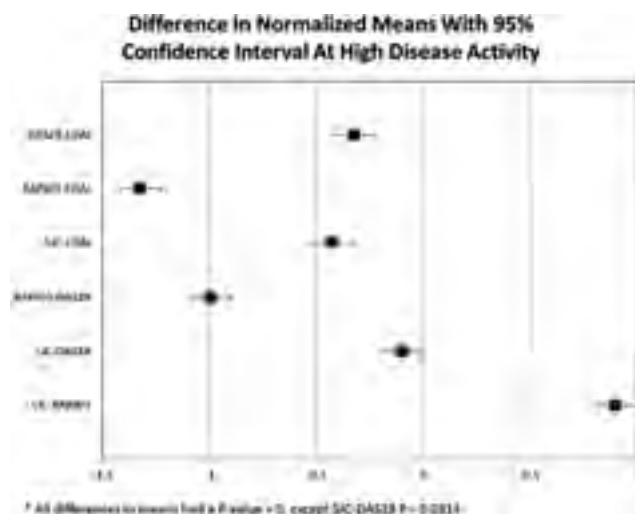
Session Type: ACR Poster Session A

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

Background/Purpose: Multiple composite RA disease activity (DA) metrics are approved for use; each reflect different aspects of disease. Many use similar measurements but their values are handled with different weighting, specifically the RAPID3(R3) measures patient functional capacity rather than clinical measures of inflammation. Despite their use varying by problem it has long been realized that these metrics are not perfectly comparable. Further it is important to understand the impact of each and to select usage appropriately. In this study we analyze scores from multiple DA metrics for concordance within each DA state: high, moderate (mod), low and remission (rem).

Methods: Pts > 18 years and clinically diagnosed with RA in the JointMan database between 1 Jan 2009 and 4 Mar 2018 were included. Encounters for the Pts having DAS28, CDAI, RAPID3 scores and swollen joint counts (sjc) were selected and further filtered into four cohorts, high, mod, low, and rem. Each cohort contained only encounters where the patient was in its named DA state using all metrics. Encounters where a patient was in two or more named DA states were excluded. All DA scores and the sjc were normalized to Z-Scores on which was performed an analysis of variance. A Tukey HSD post-hoc analysis compared the individual cohort results.

Results: 4996 pts over 33,551 encounters were initially included, only 17.8% (5996 encounters) had DA state agreement (1470 high, 1785 moderate, 620 low, 2121 remission). The F values for each DA cohort were: High 461.9, Mod 1638, Low 2457, Rem 4824 and all had a P-value < 10^{-16} . All four scores compared had significantly different means at all disease activity states. The difference in means between SJC and R3 (0.945) at the remission state was particularly noteworthy.



Conclusion: Our results(especially with the meager 17.8% DA state concordance) suggest potential for wide variance in assessing DA state even with closely related measures. This may confuse clinical assessment & understanding of medication responses. Further, the discrepancy between SJC, a measure commonly used at office visits by clinicians to consider medication changes, and the functional measure R3, is concerning given the widespread use of R3 as a reporting metric. Prudence should be used when reporting DA scores and states.

Disclosure: K. Knapp, Discus Analytics, 1, 2, 3; G. Craig, Premera/Blue Cross, Celgen, Genentech, Lilly, Novartis, 5, Discus Analytics LLC, 4, Abbvie, BMS, Celgene, Genentech, Novartis, Lilly, UCB, 8.

Swollen Joint Count Vs. RAPID3: Why a Discrepancy in Remission State?

Gary Craig¹ and Keith Knapp², ¹Discus Analytics LLC., Spokane, WA, ²Discus Analytics LLC, Spokane, WA

Session Information

Session Date: Sunday, October 21, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster I

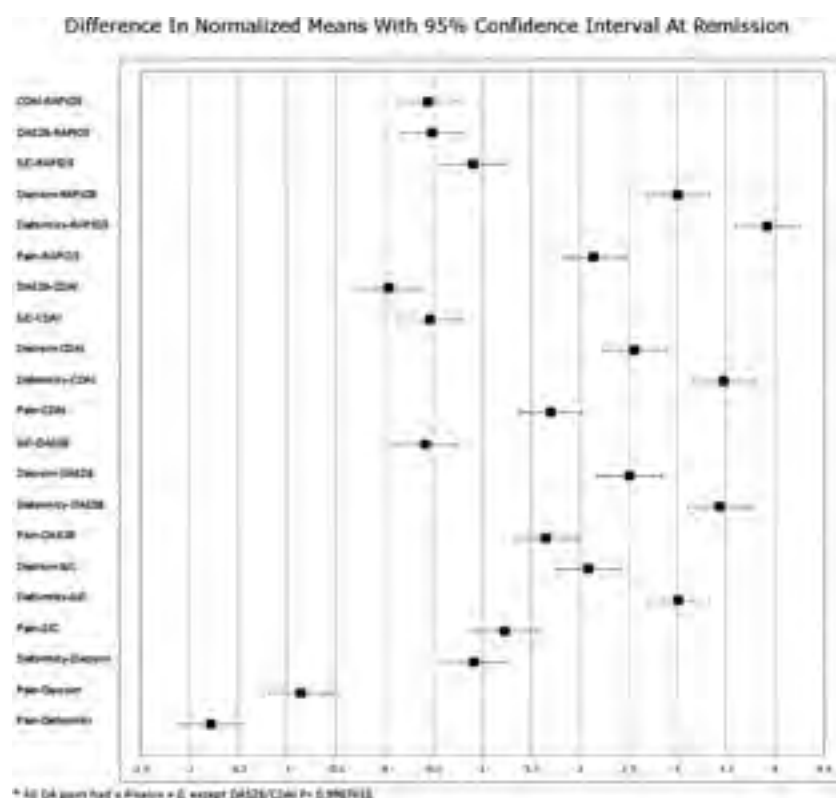
Session Type: ACR Poster Session A

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

Background/Purpose: RA patients (pts) often have multiple comorbidities, and with multiple disease activity (DA) metrics available selecting an appropriate metric is vital. It remains an outstanding question as to how much non-inflammatory disease impacts the composite DA metrics, further increasing the need to understand the impact of each metric. A companion study to this suggested a significant difference between between RAPID3(R3) and the swollen joint count (SJC). In this study we compare the DA scores at each DA state for RA patients without Fibromyalgia, re-examined the SJC/R3 relationship, and subsequently factored in damage.

Methods: Pts > 18 years and diagnosed with RA in the JointMan database between 1 Jan 2009 and 4 Mar 2018 were initially included. Pts having a diagnosis of Fibromyalgia were subsequently excluded. Encounters for the Pts having DAS28, CDAI, and RAPID3 scores were selected and further filtered into four cohorts, high, moderate (mod), low, and remission (rem). Each cohort contained only encounters where the patient was in its named DA state using all three metrics. Encounters where a pt was in two or more named DA states were excluded. All DA scores and the SJC were normalized to Z-Scores on which was performed an analysis of variance. A subsequent ANOVA sensitivity analysis with pain scores and counts of decreased range of motion and deformed joints was also completed. A Tukey HSD post-hoc calculation compared the individual DA results.

Results: 4659 pts over 31,383 encounters were initially included, only 18.2% (5709 encounters) had DA state agreement (1300 high, 1690 moderate, 616 low, 2103 remission). The F values for each DA cohort were: 441.4 high, 1469 mod, 2326 low, 4392 rem and all had a P-value < 10^{-16} . In the main analysis, for the pair-wise comparisons of each metric to the others, virtually all pairs had significantly different means at each disease activity state. The difference in means between SJC and R3 was 0.96 in high and 0.91 in remission. In the sensitivity analysis the difference in means between SJC and DAS28 was 0.05 in high and 0.42 in remission. Similarly the differences in means between composite scores and joints with deformities or decreased range of motion was also significant (P-value = 0).



Conclusion: When controlling for fibromyalgia patients, each metric and its DA state is consistently different from other metrics at the same DA state. The exception of SJC/DAS28 scores was not surprising as SJC trends closest to DAS28 scores than other metrics. The SJC/DAS28 pair had a high concordance of means in the high DA state. A disparity between SJC/R3 in remission exists when excluding FM and is not resolved when considering the potential RA related joint damage that might adversely affect the function scores of R3. This raises concern that R3 values at remission may unduly represent functional impairment from concordant non-RA musculoskeletal diseases.

Disclosure: G. Craig, Premera/Blue Cross, Celgen, Genentech, Lilly, Novartis, 5, Discus Analytics LLC, 4, Abbvie, BMS, Celgene, Genentech, Novartis, Lilly, UCB, 8; K. Knapp, Discus Analytics, 1, 2, 3.

Abstract Number: 323

Impact of Gains in Rheumatoid Arthritis Disease Activity Documentation on Outcomes over Time

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster I

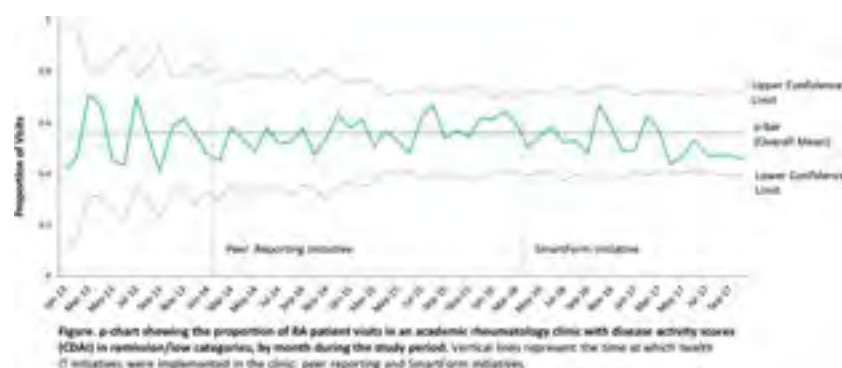
Session Type: ACR Poster Session A

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

Background/Purpose: Despite significant interest in using health information technology (IT) to improve processes of care such as documentation of disease activity in RA, few studies have evaluated the impact of process improvements on actual health outcomes. In this study, we assessed whether 2 health-IT initiatives that improved collection and documentation of RA disease activity scores in a large academic rheumatology clinic resulted in concomitant improvements in clinical outcomes over time.

Methods: We examined 2 initiatives designed to facilitate Clinical Disease Activity Index (CDAI) documentation: 1) a monthly peer report of physician Os performance on CDAI documentation, and 2) introduction of an electronic health record (EHR) SmartForm with an embedded CDAI calculator to make collection and tracking of disease activity scores more efficient. All adult RA patients with ³ 2 encounters in our rheumatology clinic with ³ 1 CDAI documented (64% of all RA encounters) between 1/2013 - 10/2017 were included. Data derived from our EHR data warehouse included demographics, encounter dates, and CDAI scores. We compared mean CDAI 12 months pre- and post-the peer reporting initiative and 19 months pre- and post- the SmartForm initiative with t-tests. Paired t-tests were performed on a subgroup of patients with ³ 1 CDAI pre- and post- each initiative to assess whether there was significant change in CDAI over time for the same patient. The proportion of visits with a low/remission CDAI (CDAI²10) each month were examined using a control chart.

Results: We included 920 RA patients with 7171 encounters over 5 years. 82% were female; mean age was 57±16, 50% identified as non-White, and 13% preferred a language other than English (e.g. Chinese or Spanish). Mean CDAI was stable pre- and post- the peer reporting initiative (12.4) and increased slightly after the SmartForm initiative (from 11.3 to 13.4, p<0.05). Paired t-test detected small disease activity improvements after the peer reporting initiative (n=237, mean CDAI from 12.0 to 10.7, p<0.05) but worse scores after the SmartForm initiative (n=341, mean CDAI from 11.2 to 12.7, p<0.05). Though these changes were statistically significant, they did not exceed the minimally clinically important



difference thresholds for CDAI. The overall proportion of visits with a CDAI in the low/remission category increased from 42 to 46% during the study period (Figure).

Conclusion: Although 2 quality improvement initiatives resulted in sustained improvements in disease activity score documentation, we did not see parallel gains in actual CDAI scores. These findings demonstrate that recording CDAI scores is not sufficient to improve disease activity without a comprehensive treat-to-target program. Additional efforts are underway in our health system to build a health-IT intervention to support providers and patients in improving RA outcomes.

Disclosure: J. Li, Pfizer, Inc., 2; J. Gandrup, None; L. Trupin, None; Z. Izadi, None; J. Yazdany, Pfizer, Inc., 2; G. Schmajuk, Pfizer, Inc., 2.

Abstract Number: 324

Three Health It Interventions Increased Documentation of RA Disease Activity Scores in an Academic Rheumatology Clinic: Results from an Interrupted Time Series Study

Julie Gandrup^{1,2}, Jing Li², Zara Izadi³, Milena Gianfrancesco², Torkell Ellingsen⁴, Jinoos Yazdany² and Gabriela Schmajuk^{5,6}, ¹Rheumatology, Odense University Hospital, Odense, Denmark, ²Medicine/Rheumatology, University of California, San Francisco, San Francisco, CA, ³Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, ⁴Department of Rheumatology, Odense University Hospital, Odense, Denmark, ⁵San Francisco VA Medical Center, San Francisco, CA, ⁶Medicine/Rheumatology, University of California - San Francisco, San Francisco, CA

Session Information

Session Date: Sunday, October 21, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster I

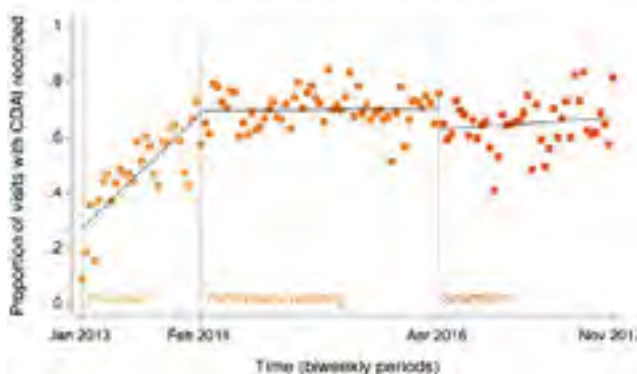
Session Type: ACR Poster Session A

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

Background/Purpose: Regular assessment of disease activity is a fundamental part of high quality RA care. Customization of electronic health records (EHRs) can facilitate the systematic collection of disease activity scores as part of a treat-to-target approach to RA treatment. We aimed to evaluate the overall impact of 3 health IT initiatives at the point of care on documentation of RA disease activity scores in an academic rheumatology clinic.

Methods: We studied 3 initiatives designed to facilitate documentation of a validated RA measure, the Clinical Disease Activity Index (CDAI), over a 5-year period (see Figure): 1) an Epic flowsheet to input and track scores using structured fields, 2) peer reporting of provider performance on their individual proportion of RA visits with documented CDAI, and 3) an Epic SmartForm that included a CDAI calculator alongside workflow changes to optimize CDAI documentation. The study included all adult RA patients with ³ 2 visits in a rheumatology clinic at a tertiary care center between June 2012-October 2017. Clinical data were retrieved from the EHR data warehouse. Interrupted time-series (ITS) analysis was used to assess whether the proportion of visits with a CDAI documented in the EHR changed following implementation of each initiative. Provider surveys assessing satisfaction with CDAI documentation workflows (1-10 scale) and time spent documenting disease activity were administered immediately before and 24 months after the third initiative.

Figure: Interrupted time series (ITS) analysis with each dot representing mean proportion of disease activity scores recorded in the electronic health record during two-week time periods. Vertical lines indicate onset of three health IT quality improvement initiatives.



Results: We included data from 995 unique patients with 8,040 encounters. Mean (SD) age was 58.9(16) years, 82% were female, and 66% were non-Hispanic White. Over 60 months, overall documentation of CDAI scores increased from 0% to 64%. After introduction of the flowsheet, ITS analysis showed an immediate increase in documentation(28.1%, $p<0.05$) (Figure), followed by a steady rise (1.4% increase per 2-week period, $p<0.05$). Documentation remained stable after peer performance reporting. The SmartForm was associated with a small immediate decrease (-7.8%, $p<0.05$), followed by a rise back to near pre-intervention levels. Provider satisfaction with documentation increased (from 5.4 ± 2.5 to 7.5 ± 1.4) after SmartForm implementation and average time for RA disease activity documentation decreased (from 6.5 ± 5.3 to 3.2 ± 1.9 minutes).

Conclusion: Introducing an EHR flowsheet improved documentation of CDAI, and additional culture and workflow changes maintained these gains. This study illustrates how EHR optimizations evolve in stages, with an initial focus on health IT and subsequent attentions to workflows and provider satisfaction. Overall, modifications to the EHR, culture, and workflows proved to be an effective method of driving increased documentation of disease activity without compromising provider satisfaction.

Disclosure: J. Gandrup, None; J. Li, None; Z. Izadi, None; M. Gianfrancesco, None; T. Ellingsen, None; J. Yazdany, Pfizer, Inc., 2; G. Schmajuk, Pfizer, Inc., 2.

Abstract Number: 325

A Comparison of RADAIS and RAPID3 Disease Measures

Ryan Jessee, Amanda M. Eudy and Megan E. B. Clowse, Department of Medicine, Division of Rheumatology and Immunology, Duke University, Durham, NC

Session Information

Session Date: Sunday, October 21, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Treat to target has been shown to improve outcomes in multiple rheumatology diseases although relies on accurate disease measures. Our academic clinic routinely measures RAPID-3 in all patients at clinic check-in. However, a previous survey of our providers found a low confidence in the accuracy of RAPID-3, often attributed to comorbidities. Therefore, we examined whether RADAIS-5, which includes questions that our providers felt were more specific for inflammatory arthritis activity, would be a more reliable measure of RA and more accurately predict medication changes in clinic.

Methods: We performed a cross-sectional study over a 4-month time period involving 100 randomly selected rheumatology clinic patients. Patients completed a RADAIS-5 and RAPID-3 questionnaire at the beginning of routine clinical visits. Therapy changes, comorbidities (osteoarthritis, fibromyalgia/chronic pain, and mood disorders), and diagnosis were recorded. Pearson correlation coefficients were calculated between RADAIS-5 and RAPID-3, and differences in disease activity scores by co-morbidities and diagnosis were estimated by t-tests.

Results: Inflammatory arthritis (IA), which included RA, PsA, IBD-related arthritis, and ReA, was the most common diagnosis ($n=45$). Both RADAIS-5 and RAPID-3 were highly correlated across diagnoses and comorbidities ($p<0.001$ for all,

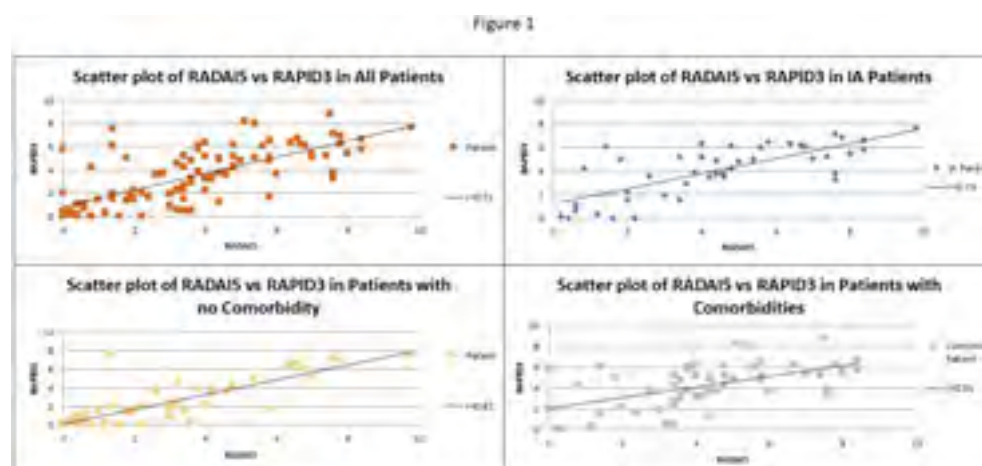


Figure 2

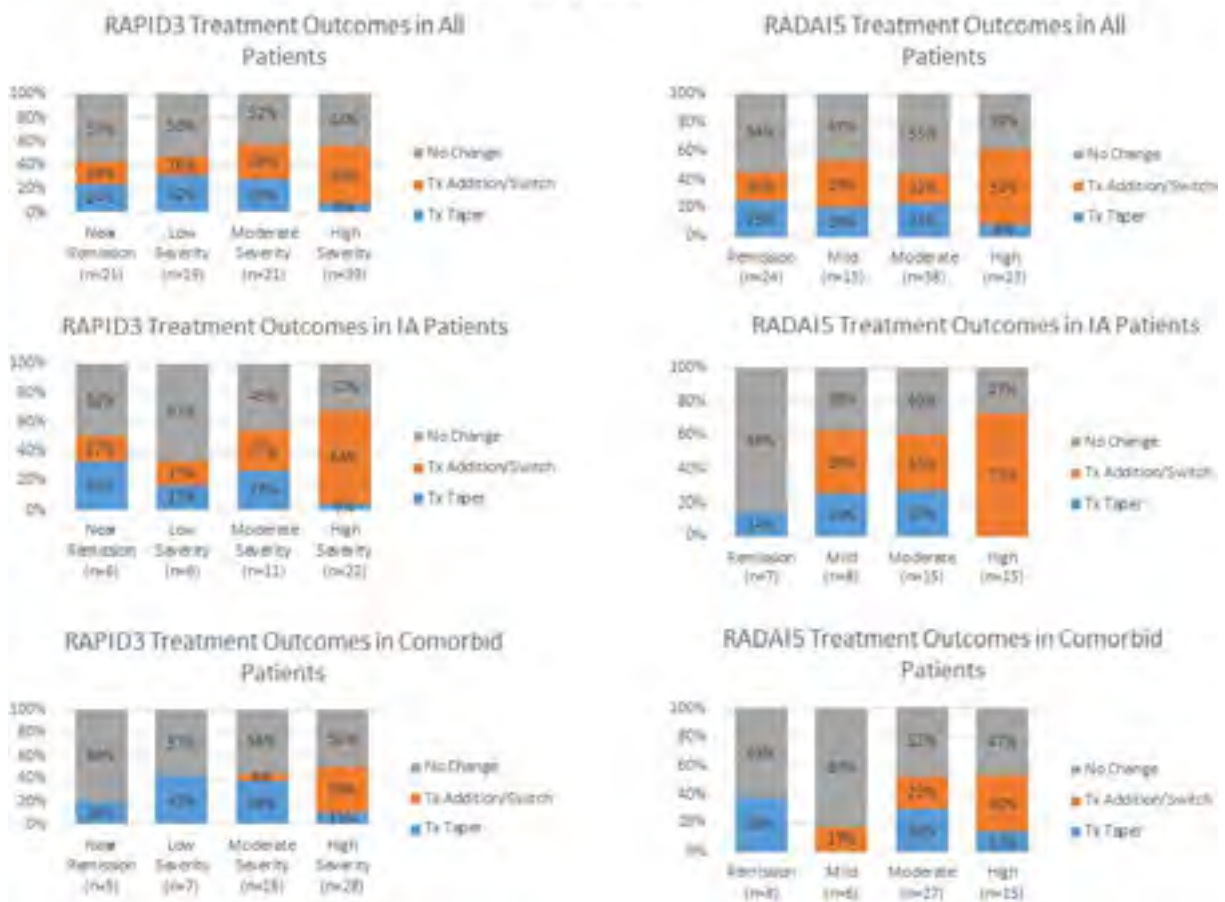


Figure 1). Comorbidities of OA, FM, and mood disorders uniformly resulted in higher disease activity measures ($p=0.01$). Across both measures, patients in remission had more medication tapering and patients with high disease activity had more treatment escalation ($p=0.1$), with this trend continuing when examining IA patients and comorbid patients (Figure 2). However, for patients with intermediate disease activity there was not a clear trend of management, and neither disease activity measure appeared to more accurately reflect medication change in these patients.

Conclusion: Our study confirms a high degree of correlation between RADAIS-5 and RAPID-3 across rheumatologic patients, although this relationship is weakened in patients with comorbid OA, FM, or mood disorders. Having one of these comorbid conditions clearly resulted in higher disability on both of the patient-reported measures. Based on the medication changes in this study, it does not appear that either measure provides clear guidance for patients with intermediate disease activity measurements. In order to improve patient care by incorporating patient-reported measures, additional work identifying approaches to decrease confounding by comorbid disease is essential.

Disclosure: R. Jessee, None; A. M. Eudy, None; M. E. B. Clowse, UCB Pharma, 5, Janssen, Pfizer, 2, 5, AbbVie, Bristol-Myers Squibb, 2.

Abstract Number: 326

Implementation of a Treat-to-Target Quality Improvement Program for Rheumatoid Arthritis Management Using Real-Time Patient Reported Outcome Measures

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Changing clinical practice patterns and incorporation patient-reported outcome measures (PROMs) for disease activity assessment into routine workflow is challenging. We sought to integrate a treat-to-target (TTT) approach for medication optimization for patients with RA in our practice through: 1) a reliable system to collect disease activity scores (PROMs) using iPads in the waiting room, 2) a multidisciplinary learning collaborative (LC) for providers focused on TTT, and 3) incorporation of patient perspectives on shared decision making (SDM) and treatment satisfaction.

Methods: At an academic medical center rheumatology clinic, patients completed a Routine Assessment of Patient Index Data 3 (RAPID3) survey via an online patient portal or an iPad. RAPID3 scores were uploaded to patient charts and were available for physicians to review during the visit. Rheumatologists were non-randomly allocated to either intervention (N=8) or control (N=13) groups. Intervention physicians attended monthly LC sessions between August 2017-June 2018 to discuss and develop TTT practices to use during visits with RA patients. Physician visit notes were retrospectively examined by 2 researchers to identify patients with medication changes and to calculate a “TTT score”. Mean TTT scores between intervention and control rheumatologists were evaluated using T-test. Phone calls were made to patients of physicians in the intervention group following a medication change to measure treatment satisfaction using the Treatment Satisfaction Questionnaire for Medication (TSQM) and use of SDM through the 9-item Shared Decision Making Questionnaire (SDM-Q-9). The TSQM and SDM-Q-9 questionnaires are both on 100 point scales and higher numbers reflect positive scores.

Figure: Comparison of Intervention Physician vs. Control Physician Cumulative Treat-to-Target Score Over Time



Results: From May 2017-April 2018, 2656 RA patients completed RAPID3 surveys with an average completion rate of 70%. Mean TTT scores among the intervention group rheumatologists were 9% higher than those in the control group (43% vs. 34%, $p=0.0042$) (Figure). 72 phone calls were completed to patients of rheumatologists in the intervention group with median[IQR] TSQM score components of 75[58, 92] (effectiveness), 92[83,100] (side effects), 100[89, 100] (convenience), and 83 [67, 100] (global satisfaction), and median[IQR] SDM-Q-9 score of 96[87, 00].

Conclusion: The results of this non-randomized, quality improvement study show feasibility and utility of electronic PROMs collection methods and real-time integration of PROMs survey scores into the electronic medical record. It also demonstrates the ability of a learning collaborative model to impact TTT practices within a large academic medical practice, as the non-randomized fashion mimics “real-world” experience.

Disclosure: M. Forman, None; C. Leatherwood, None; C. Xu, None; E. Ko, None; B. Lu, None; M. D. Iversen, None; D. Solomon, None; S. Desai, None.

The Patient Global Assessment and Common Composite Disease Activity Measures Vary Minimally When Patients Reflect on Their Arthritis or Their Global Health: Results from the Canadian Early Arthritis Cohort Study

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Session Information

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Background/Purpose: The patient global assessment (PtGA) is a core domain used in RA composite disease activity (CDA) measures for trials and treat-to-target paradigms. The PtGA is asked differently, either referring to the patient's global health or condition (PtGA-GH), or to their arthritis disease activity (PtGA-AR). Objectives of this study were to assess agreement between PtGA-GH vs. PtGA-AR ratings and between CDA indices calculated using both versions of the PtGA.

Methods: We included patients enrolled in the Canadian Early Inflammatory Arthritis Cohort (CATCH) study between 2011 and 2017 who met 1987 or 2010 ACR/EULAR criteria for RA and simultaneously completed both PtGA-GH and PtGA-AR using a 10 cm VAS (scored 0-10) at baseline, 6- and 12-months of follow-up. Descriptive statistics were used to summarize baseline cohort characteristics, PtGA ratings and CDA indices with differences compared using Wilcoxon-sign rank tests and chi-square tests. Agreement was assessed using intraclass correlation coefficients (ICC) for continuous measures and weighted kappa coefficients for categorical measures. Stratified analyses were also performed by age (older >65) and sex.

Results: Of 571 early RA patients who completed both PtGAs, 71% were female, 83% were white, 17% were current smokers, 17% were erosive, and 60% had completed high-school. Baseline mean(sd) age was 55(15), symptom duration was 5(3) months and comorbid conditions were 2(2). Agreement between PGA ratings, composite CDA measures and classification of remission using both PtGA-GH and PtGA-AR are summarized in Table 1. Mean(sd) PtGA-GH ratings were only marginally higher than PtGA-AR ratings and agreement was high between PtGA ratings at baseline and over the first year follow up (all ICCs > 0.8). Agreement in CDA scores calculated with either PtGA was even higher at baseline and over time (all ICCs > 0.95). There was also high concordance in classification of remission using either PtGA at all time points (all Kappa's > 0.85). Results of stratified analyses showed that relative to men, women tended to report slightly higher differences in PtGA-GH vs. PtGA-AR (all p's >0.0001) but overall agreement in PGA ratings, CDA scores and classification of remission was very high and similar in both sexes. Age stratified analyses, which reflects the comorbidities that increase with age, were similar to those in the whole sample.

Conclusion: Results from this large sample of early RA patients followed in a longitudinal study in typical practice settings, showed patients rated their PtGA-GH marginally higher their PtGA-AR, but this difference had minimal impact on composite disease activity indices and classifications of remission commonly used in patient care. These findings suggest common composite measures of RA disease activity can be calculated using either the PtGA-GH or PtGA-AR.

Table 1: Agreement PtGA Indices

Variable	Baseline PtGA - GH	PtGA - AR	6-months PtGA - GH	PtGA - AR	12-months PtGA - GH	PtGA - AR
Patient Global Assessment (0-10)						
Mean (SD)	5.7 (2.8)	5.2 (2.8)	3.0 (2.7)	2.8 (2.6)	2.7 (2.6)	2.4 (2.5)
ICC	0.80		0.88		0.88	
Composite Disease Activity Indices						
DAS28 ESR Mean (SD)	5.0 (1.3)	4.9 (1.3)	2.9 (1.4)	2.9 (1.4)	2.6 (1.4)	2.6 (1.4)
ICC	0.98		0.99		0.99	
Remission, Frequency (%)	23 (5%)	23 (5%)	193 (45%)	196 (46%)	243 (56%)	247 (57%)
Kappa (95% CI)	0.93 (0.91, 0.95)		0.97 (0.96, 0.98)		0.98 (0.97, 0.98)	

SDAI Mean (SD)	28.7 (14.4)	28.1 (14.4)	10.5 (10.4)	10.2 (10.4)	8.2 (9.8)	7.9 (9.7)
ICC	0.99		0.99		0.99	
Remission, Frequency (%)	6 (1%)	6 (1%)	143 (30%)	155 (32%)	192 (41%)	203 (43%)
Kappa (95% CI)	0.95 (0.93, 0.97)		0.95 (0.94, 0.97)		0.95 (0.94, 0.97)	
CDAI Mean (SD)	27.1 (13.7)	26.6 (13.7)	9.7 (10.3)	9.5 (10.3)	7.3 (9.2)	7.0 (9.1)
ICC	0.99		0.99		0.99	
Remission, Frequency (%)	5 (1%)	6 (1%)	158 (28%)	173 (31%)	210 (38%)	215 (39%)
Kappa (95% CI)	0.93 (0.909, 0.96)		0.92 (0.901, 0.94)		0.92 (0.90, 0.94)	
RAPID III Mean (SD)	4.6 (2.4)	4.5 (2.3)	2.5 (2.2)	2.4 (2.2)	2.2 (2.1)	2.1 (2.1)
ICC	0.97		0.98		0.98	
Remission, Frequency (%)	52 (9%)	53 (9%)	199 (36%)	206 (37%)	231 (41%)	237 (42%)
Kappa (95% CI)	0.85 (0.81, 0.89)		0.86 (0.83, 0.90)		0.85 (0.815, 0.89)	

Disclosure: V. P. Bykerk, Bristol-Myers Squibb, Pfizer Inc, Sanofi, UCB, 5; O. Schieir, Other, 2; M. F. Valois, Other, 2; E. C. Keystone, AbbVie, Amgen, Bristol-Myers Squibb, F. Hoffmann-La Roche Inc, Gilead, Janssen Inc, Lilly Pharmaceuticals, Pfizer Pharmaceuticals, Sanofi-Aventis, 2, AbbVie, Amgen, AstraZeneca Pharma, Biotest, Bristol-Myers Squibb Company, Celltrion, Crescendo Bioscience, F. Hoffmann-La Roche Inc, Genentech Inc, Gilead, Janssen Inc, Lilly Pharmaceuticals, Merck, Pfizer Pharmaceuticals, Sandoz, UCB, 5, Amgen, AbbVie, Bristol-Myers Squibb Canada, F. Hoffmann-La Roche Inc., Janssen Inc., Merck, Pfizer Pharmaceuticals, Sanofi Genzyme, UCB, 8; G. Boire, Merck & Co., 8, 9, BMS, 8, 9, Pfizer, Inc., 8, 9, Amgen Inc., 9, AbbVie Inc., 9, Novartis, 9, Eli Lilly and Co., 9, Janssen, 9; J. E. Pope, None; D. Tin, Multiple, 2; C. Hitchon, Pfizer, Inc., 2; C. Thorne, Amgen Inc., 2, 5, 9, Pfizer, Inc., 2, 5, 9, UCB, Inc., 9, AbbVie Inc., 2, 5, 9, Medexus/Medac, 2, 5, 8, Eli Lilly and Co., 9, Merck & Co., 9, Hospira, 5, 9, Janssen, 9, Sanofi Genzyme, 5, 9, Celgene Corporation, 9, CaREBiodam, 9, Centocor, 5, Novartis, 9; S. J. Bartlett, UCB, Inc., 5, Eli Lilly and Co., 5, Pfizer, Inc., 5; B. Haraoui, AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Merck, Pfizer, Roche, and UCB, 9, AbbVie, Amgen, BMS, Janssen, Pfizer, Roche, and UCB, 2, Amgen, BMS, Janssen, Pfizer, and UCB, 8.

Abstract Number: 328

Implementation of Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) Documentation in Systemic Lupus Erythematosus (SLE) Patients at an Academic Medical Center

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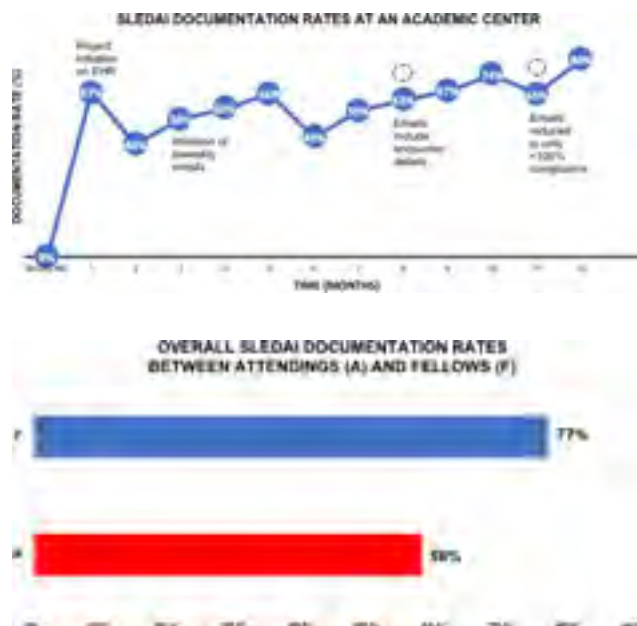
Session Information

Session Date: Sunday, October 21, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster I

Session Type: ACR Poster Session A

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



Background/Purpose: The 2008 European League Against Rheumatism (EULAR) Task Force on SLE management encourages the use of at least one of the SLE disease indices for the monitoring of disease activity. SLEDAI documentation is crucial to obtain for purposes of clinically meaningful translational and basic science research. This study aimed to 1) identify baseline SLEDAI documentation rates in an academic setting 2) determine if biweekly email feedback would improve documentation rates and 3) ascertain perceived barriers to documentation.

Methods: Chart review of all SLE encounters over a one-month period was performed at an academic center to ascertain a baseline SLEDAI documentation rate. Physicians were then instructed to document SLEDAI scores into a designated section of the electronic health record (EHR) at month 1. Chart review was repeated continuously for each provider over the next 12 months. Personalized SLEDAI documentation rates were emailed to each provider biweekly. Two Plan-Do-Study-Act (PDSA) cycles were performed over the 12-month period. Physicians completed a survey regarding documentation barriers at the close of the study.

Results: 704 SLE encounters were reviewed for this study. Pre-intervention, baseline SLEDAI documentation rates were 0%. Following the introduction of a designated section for documentation within the EHR, rates increased to 67%. After the initiation of personalized biweekly emails, collective documentation rates increased to 80% by 12 months. Rates continued to increase after emails included encounter details (PDSA 1), and after email frequency was reduced to contact only those providers who did not meet 100% compliance (PDSA 2). Fellows (77%) had higher documentation rates compared to attending physicians (58%) throughout the study. Survey results revealed that the majority of physicians (65%) believed SLEDAI documentation improved patient care, though 40% of physicians cited such documentation as a burden. Major barriers to documentation were cited to be forgetfulness and lack of time.

Conclusion: This quality improvement study demonstrates that a biweekly email feedback intervention increased SLEDAI documentation rates at an academic center, with higher documentation rates seen with rheumatology fellows. Additionally, physicians did perceive that increased documentation directly improved patient care. Major barriers to documentation were reported to be forgetfulness and lack of time.

Disclosure: S. H. Chung, None; H. H. Juo, None; J. Thomason, None; A. Bays, None.

Abstract Number: 329

Use of Inter-Professional Collaboration to Improve Adherence to American College of Rheumatology Recommendations for Use of Disease Activity Measures

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Session Information

Session Date: Sunday, October 21, 2018

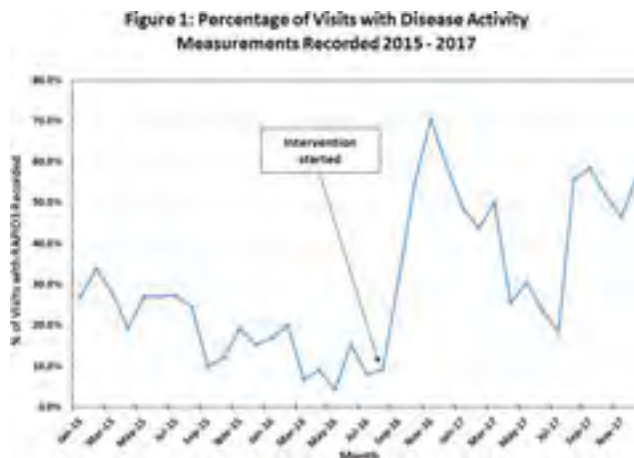
Session Title: Measures and Measurement of Healthcare Quality Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: “Treat to target” is the goal of therapy in the treatment of Rheumatoid Arthritis (RA) based on the 2015 American College of Rheumatology (ACR) guidelines. Disease specific patient-reported outcome measures are a critical component of patient care to assess disease activity and function. The ACR recommends that disease activity measurement be performed in the majority of encounters for RA patients. This can be difficult to achieve in a busy Rheumatology practice. We hypothesized that using a collaborative and team-based approach would help us collect these data more effectively.

Methods: Beginning in September 2016, we trained the medical assistants in the Rheumatology clinic at the MetroHealth Medical Center on the administration and collection of RAPID3 questionnaires for all patients with RA seen for an office visit. To evaluate the effectiveness of this educational intervention, we retrospectively abstracted data from the medical record (Epic) for all patients with a problem list diagnosis of Rheumatoid Arthritis and who were seen for an office visit in the Rheumatology clinic between January 1, 2015 and December 31, 2017. We calculated the percentage of visits in which a RAPID3 was collected. We then compared pre-intervention to post-intervention results, using Chi-square analysis to determine statistical significance.



Results: Between January 1, 2015 and December 31, 2017, there were a total of 4485 visits for persons with a diagnosis of RA (1552 visits in 2015, 1590 in 2016 and 1333 in 2017). Prior to the intervention, 17.8% of patient visits (474/2663) included a RAPID3. After initiation of the intervention, the percentage of visits with a RAPID3 increased rapidly (Figure 1) and overall post-intervention, 45.7% of visits (832/1822) for RA patients had a RAPID3 recorded (p-value < 0.001 for pre- to post-intervention comparison).

Conclusion: The use of inter-professional collaboration is an effective way to improve adherence to ACR recommendations and provide high-quality care for patients with RA. A similar strategy to what we employed in our clinic could easily be implemented in other busy Rheumatology practices.

Disclosure: E. Weinberger, None; D. Einstadter, None; M. Magrey, None.

Abstract Number: 330

The IMPACT of a Referral Algorithm for Axial Spondyloarthritis: Four Month Follow-up in Patient Reported Outcomes

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Session Information

Session Date: Sunday, October 21, 2018

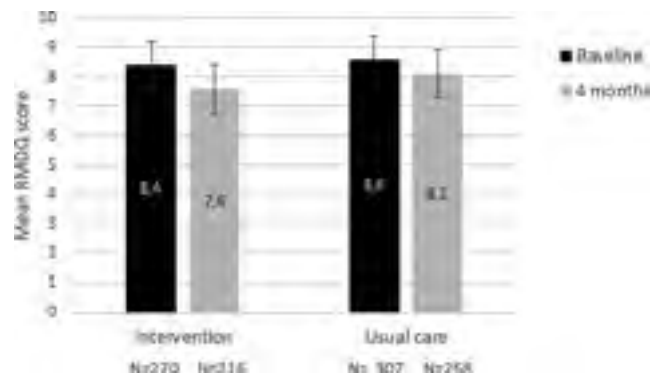
Session Title: Measures and Measurement of Healthcare Quality Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: A substantial amount of patients with chronic low back pain (CLBP) have axial spondyloarthritis (axSpA), but early recognition of these patients is difficult for general practitioners (GPs). As a result, several referral strategies have been developed to help physicians identify patients at risk for axSpA within the large group of CLBP patients. Most referral strategies were developed in secondary care patients. The only referral strategy that was developed and validated in primary low back patients is the CaFaSpA strategy. After model development and validation it is important to perform an impact analysis before implementation in daily clinical practice. The purpose of this study is to assess the impact of using a referral strategy on patient outcomes in young primary care patients with CLBP at risk for axSpA.

Methods: A clustered randomized controlled trial was performed in a primary care setting (ClinicalTrials.gov Identifier: NCT01944163). Each cluster contained the general practices from a single primary care practice and their included patients. Clusters were randomized to either the intervention (use of CaFaSpA referral strategy) or the control group



(usual care). Primary outcome was disability caused by CLBP, measured with the Roland Morris Disability Questionnaire (RMDQ) at baseline and 4 months. A linear mixed-effects model was used to analyze mean change in RMDQ score.

Results: In total 679 patients were included within 93 GP clusters. Sixty-four percent of our study population were female and mean age was 36 years. Median RMDQ score at baseline was 8 (IQR4-12) in both groups. Compared to baseline, mean RMDQ score decreased by 0.74 points at 4 months (intervention) and by 0.46 points (control)(**Figure 1**). This decrease did not significantly differ between groups($p=0.50$).

Conclusion: Although the CaFaSpA referral strategy can be used as a screening tool to identify axSpA patients but this strategy did not have an early impact on disability caused by CLBP.

Figure 1. Estimated mean RMDQ scores over time for the overall intervention and usual care group. Bars indicate 95% confidence intervals for the mean estimates.

Disclosure: M. Jamal, None; A. Korver, None; M. Kuijper, None; D. Lopes Barreto, None; F. van den Hoogen, None; C. W. Y. Appels, None; A. Spoorenberg, None; B. Koes, None; L. van Hoven, None; J. Hazes, None; A. E. Weel, None.

Abstract Number: 331

Development and Implementation of a Patient-Reported Outcomes Measurement Information System (MyRheum)

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Session Title: Measures and Measurement of Healthcare Quality Poster I

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Background/Purpose: There is a growing recognition of the potential value for measuring patient-reported outcomes (PROs) in patients with rheumatologic conditions. PROs measured at point of care can enhance shared decision making and facilitate treatment decisions, although the ability to collect and report PROs in real time is challenging because of technology and workflow barriers. Clinical disease activity measures are important for making treatment decisions in RA but do not measure patient domains of health important to patients. The Patient-Reported Outcomes Measurement Information System (PROMIS) measures patient status for different domains in people with a wide range of diseases and scores are standardized to the US general population.

We assessed the feasibility, patient/provider compliance and utility of electronically collecting PROs in patients in a large tertiary care rheumatology practice using PROMIS Global Health (GH), PHQ9, RAPID3 or SLAQ, the PROMIS domains: pain interference, fatigue and physical function, and a review of systems (ROS).

Methods: PROs are administered on a tablet at the patient's visit or through the patient portal (MyChart, Epic Systems) prior to their appointment through the Knowledge Program (Cleveland Clinic, Cleveland OH), an electronic platform that is integrated within the Epic electronic health record (EHR). PROMIS domains are administered using computer adaptive testing and scores are standardized on a T scale with a mean of 50 and SD of 10. Results are displayed within the EHR at

the time of the visit. The ROS is administered at every visit. PHQ9, if normal, is administered yearly and the remaining scales are completed at least 3 months apart.

Results: Since operational (8/2016–1/2018) MyRheum has administered 100,687 questionnaires in 29,238 patients at 53,608 visits (~30% using MyChart). More than 40,000 PROMIS GH and 50,000 RAPID3 scales have been collected. PROMIS GH physical and mental health summary scores were compared across 10 Cleveland Clinic disease areas (n=276,182). Mean PROMIS physical health summary score of rheumatology patients was 42.5, worse than all disease areas (mean score range 41.1 - 49.2) except neurology. Mean mental health summary scores of rheumatology patients was 47.4, which fell in the middle of the range of mean scores of the disease areas (39.6 to 50.3). Patient completion rates averaged 71% for 2017 with a small gradual decline over time. Nearly 1/3 were collected at home prior to the visit using My Chart.

Conclusion: The MyRheum system was successfully deployed in a tertiary care system with 27 rheumatologists in 10 locations. Cross departmental comparisons of diseases showed rheumatology patients had the second lowest self-reported physical health demonstrating the impact of our diseases and the need to measure PROs that assess this domain. The decline in participation requires further analysis. The creation of this large PRO biomarker databank demonstrates its practicality and provides a powerful platform for clinical care, research and value-based healthcare initiatives.

Disclosure: C. Deal, None; A. Abelson, None; L. H. Calabrese, None; G. Strnad, None; I. Katzan, None; M. E. Husni, None.

Abstract Number: 332

Components of Impaired Physical Function and Disability in a Non-Rheumatic Population. Normative Values of the Health Assessment Questionnaire Disability Index

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Session Information

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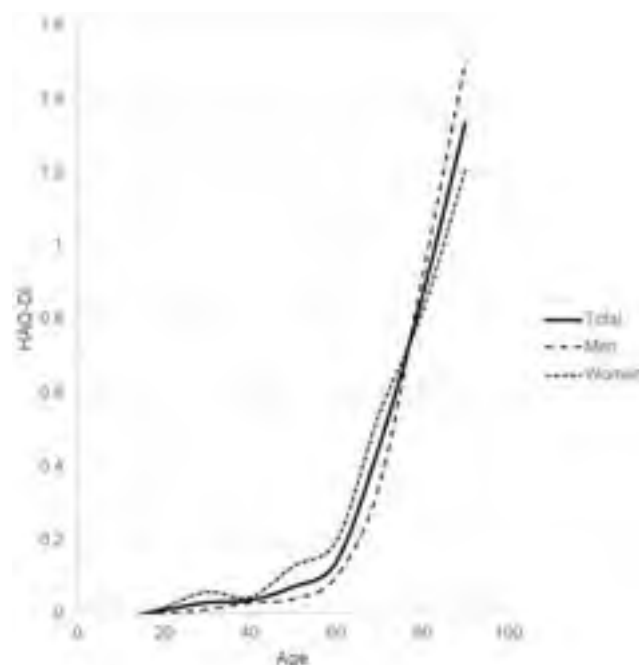
Background/Purpose: HAQ-Di is broadly used to measure disability in RA, its assessment might influence taking decision process. However, it cannot differentiate disability related to arthritis, accrual damage, age, personal behaviors or comorbidities. We aimed to determine factors related to disability in a non-rheumatic population and evaluate its contributing factors.

Methods: We ask outpatients attendees of clinical specialties or first contact physician to fill out the HAQ-Di and have and structured interview during their scheduled visit. Those older than 18 years who signed informed consent were included. Participants with any musculoskeletal disease, chronic pain, neurological or psychiatric condition, use of drugs that impaired mobility or mental status, as well as illness in terminal stage were excluded. Demographic variables, formal education, exercise, and the Charlson index were recorded. Pearson's correlation, chi square, Mann-Whitney-U or t-test were performed as appropriate. Contribution of each factor to the predicted disability was determined by forward stepwise multivariate regression modelling.

Results: A total of 1,506 subjects were included, their mean age was 54.7±15.8 years, 17% were younger than 40 years, 65% between 40 and 70 years, and 18% older than 70 years. One fourth were ever smokers, 40.7% female, BMI was 27.1±4.4 Kg/m², Charlson index 1.5±1.7, HAQ-Di was 0.17±0.45 for the whole population; 25.1% declared some disability (HAQ-Di value >0). HAQ-Di values above 0.1 started at the 55 years subjects and increase to 1.3 at 90 years; it was higher in women than in men (0.25±0.54 versus 0.12±0.37; p <0.001). HAQ-Di showed correlation with age r=0.47 (p<0.001), and Charlson index, r=0.52 (p<0.001). Subjects with less than 10 years of formal education had a higher HAQ-Di, 0.52±0.73, compared with those with >10 years, 0.09±0.3 (p<0.001). Those who practice exercise on daily basis had a HAQ-Di of 0.09±0.32, those who did not any exercise had 0.45±0.69 (p<0.001). A regression model including standardized age (mean age value=0.17), sex (1=man), diagnosis of hypertension (1=yes) and diabetes (1=yes) explained the 25% of the HAQ-Di and predicted a HAQ score of 0.45.

Conclusion: One fourth of outpatients attending a general Hospital had disability. The main determinant is the age, but there is a significant contribution of comorbidity, high blood pressure and diabetes. Moreover, those who practice exercise

on daily basis and those with higher education had the lowest HAQ-Di scores. We suggest that when HAQ-Di must be used in the RA population, they must be adjusted by age, sex and comorbidity.



Variable	Coefficient B	Standard error	t value	P value
Constant	0.17	0.02	9.5	<0.001
Z age	0.17	0.01	14.3	<0.001
Hypertension	0.14	0.3	4.8	<0.001
Sex	-0.04	0.02	-2.8	<0.001
Diabetes	0.06	0.03	2.1	0.04

Note: Z age= standardized age

Disclosure: C. A. Arce-Salinas, None; H. F. ESPINOSA-ORTEGA, None; O. Enriquez-Antonio, None.

Abstract Number: 333

Electronic Delivery of Patient-Reported Outcome Questionnaires on Tablet PCs at Clinic Visit: A Feasibility Study

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Session Information

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Session Title: Measures and Measurement of Healthcare Quality Poster I

Session Type: ACR Poster Session A

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Background/Purpose: Assessment of patient-reported outcomes (PROs) at clinic visits has emerged as an important component to determine disease activity in Rheumatoid Arthritis(RA). However, paper-based distribution, scoring and documentation on PROs is time-consuming and prone to human error. Modern electronic health record (EHR) systems allow for automatic integration of PRO data captured on tablets in the waiting room. Distribution, scoring, analysis and documentation of PRO questionnaires can be automated, thereby increasing the time a provider can spend with each patient.



Session Title: Measures and Measurement of Healthcare Quality Poster I

Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Patient-reported outcome measures (PROMs) are accepted modalities of gathering patient self-report of their health status in the realms of physical, mental and social well-being. PROMs are endorsed as metrics of quality of care. With the widespread implementation of electronic medical record (EMR) in the United States, PROM can be captured electronically. At the academic center, EMR in use is Epic® software which interfaces with the Patient-Reported Outcomes Measures System –PROMIS®. In a satellite clinic at UM rheumatology, the providers (n = 3) collectively opted to integrate PROMIS short form questionnaires [Adult Physical Function (PF) and Pain Intensity (PI)] into the EMR. However, the data collection of PROM via patient portals was low (5-10%). Our project aimed to examine collection rate of PROMs using portable devices (Tablets) at the time of check-in the clinic.

Methods: Between July 1, 2016, and March 31, 2018, patients seeking care at one rheumatology satellite clinic completed PROMIS® questionnaires (PF and PI), before the clinic visit. One week before the visit patients received a reminder on the EMR portal to complete the surveys. For patients who did not access questionnaire on the portal, they were able to complete at the time of appointment check-in on an Android-based Tablet. Those patients who could not complete by either portal or Tablet were assisted by a medical assistant (MA) using the office computer. The results were available on the EMR to the providers at the point of care.

Results: Of the total patients seen in rheumatology clinic, 87.2% completed the PROMIS® questionnaires, of which 82.4% used Tablets at check-in, 14.1% completed at home (portal), and 3.4% were assisted on a clinic desktop computer to complete the questionnaire (Table 1).

Conclusion: Use of tablets or other modalities in the clinic at check-in is associated with a high rate of PROMIS® questionnaire completion by patients. The routine use of PROM data collection at check-in may encourage patients to complete PROMIS® questionnaires on EMR portal accessed at home. Around 13% of patients did not complete questionnaires due to various reasons – lack of portal access, limited tablet availability at check-in, time constraints for MAs in a busy clinic, and rarely, patient refusal to complete. Given the increased acceptance, the routine of PROM data in the clinic using a tablet with EMR integration should be explored as a preferred modality.

Table 1: PROMIS® questionnaire completion rates

Quarter (year)	Total patients seen	Total N	Total %	Completed Questionnaires					
				At Home		In Office			
				Home Portal N	Home Portal %	Tablet N	Tablet %	Assisted by medical assistant N	Assisted by medical assistant N
Q3 (2016)	1127	941	83.5	83	8.8	817	86.8	41	4.3
Q4 (2016)	868	705	81.2	81	11.5	590	83.7	34	4.8
Q1 (2017)	866	825	95.3	104	12.6	708	85.8	13	1.6
Q2 (2017)	613	541	88.2	80	14.8	436	80.6	25	4.6
Q3 (2017)	764	656	85.9	112	17	532	81.1	12	1.8
Q4 (2017)	777	687	88.4	122	17.8	545	79.3	20	2.9
Q1 (2018)	747	671	89.8	130	19.4	514	76.6	27	4
Net	5762	5026	87.2	712	14.1	4142	82.4	172	3.4

Disclosure: V. Nagaraja, None; V. Oggenovski, None; D. Khanna, None.

Abstract Number: 335

Cross-Cultural Validity of Functional Status Assessment Measures for Rheumatoid Arthritis

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Session Information

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Table 1. Summarized characteristics of included studies by instrument.

Instrument	Number of Studies Included	Languages (number of studies)*	Cosmin Rating	Translation	Cultural Adaptation	Cross-Cultural Validity
HAQ-DI	29 included studies	20 languages: Arabic (3), Bengali, British English, Chinese, Danish, Dutch, Estonian, French, Italian, Japanese, Korean, Malay, Marathi, Persian (3), Portuguese, Spanish(4), Swedish, Swiss German, Thai(2), and Turkish(2).	Poor: 21, Fair: 6, Good: 2	27	26	1
MDHAQ, MHAQ, HAQII	8 included studies	8 languages: Arabic, Chinese, Dutch, Finnish, Hindi, Korean, Spanish, and Swedish.	Poor: 3, Fair: 4, Good: 1	7	4	1
PROMIS	2 included studies	1 language: Dutch (2)	Poor: 1, Good: 1	1	1	1

* in parenthesis is the number of studies per language, if greater than one. This includes dialects.

Background/Purpose: Functional Status Assessment Measures (FSAMs) are important outcome measures in Rheumatoid Arthritis (RA) as poor function is a predictor for mortality and associated with lower quality of life and work disability. FSAMs inform assessment and treatment as part of guideline-based care. The Health Assessment Questionnaire (HAQ) and its derivatives are standardized and validated FSAMs commonly used in RA. More recently the Patient-Reported Outcomes Measurement Information System (PROMIS) has been developed and includes FSAMs. The HAQ and PROMIS measures were developed and validated in English, but have been translated and culturally adapted for use in other countries. Our objective was to conduct a systematic review of the cross-cultural validity of FSAMs for RA including HAQ and HAQ-derived measures as well as PROMIS measures.

Methods: Four electronic medical databases (MEDLINE, EMBASE, Cochrane Library and CINHALL) were searched in accordance with a published strategy from the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) group. The references of each included article were then manually searched for additional relevant studies. Included studies were evaluated using the COSMIN tool for cross-cultural validity and were scored as excellent, good, fair or poor.

Results: Of 58 papers identified, by our search strategy and 3 identified by manual search, 39 were included: 29 described the translation, cultural adaptation or cross-cultural validity of the HAQ-DI, 8 other HAQ derivatives, and 2 the PROMIS measures, representing 22 languages (Table). Of the 39 papers reviewed, 35 described translation, 31 described cultural adaptation, and only 3, examined cross-cultural validity of translated versions. There was generally poor adherence to proposed guidelines for cross-cultural adaptations of measures. No studies were rated as excellent by the COSMIN tool, only 4 studies were rated as good, 10 were rated fair, and 25 were rated as poor. Two studies that looked at cross-cultural validity noted differential item functioning (DIF) between Dutch and US populations for the HAQ-II and PROMIS measures and a third study found DIF between Turkish and UK populations on the HAQ.

Conclusion: FSAMs have been widely used both in their validated English form and in many translated forms. This review highlights a paucity of data on the cross-cultural validity of FSAMs and the mostly poor or fair quality methods by which they were translated and adapted. This needs to be considered when using these measures for multinational clinical trials and for day-to-day use in practice.

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Abstract Number: 336

Physical Activity Monitors: New Tool to Assess Improvement in Myositis

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Background/Purpose: Physical activity monitors (PAM) are increasing being used to objectively quantify free-living movement in clinical research, especially musculoskeletal diseases. Given that patients with idiopathic inflammatory myopathies (IIM) have proximal muscle weakness which affects mobility, PAM may be a helpful tool for clinical assessment. We examined the validity, reliability and responsiveness of the activity measures obtained from a research grade PAM, Actigraph, as an outcome measures in IIM.

Methods: The 6 validated myositis core set measures (CSM; manual muscle testing [MMT], physician global disease activity [MD global], patient global disease activity [Pt. global], extra-muscular global disease activity [Ex-muscular global], HAQ and muscle enzymes) and 3 functional measures (six-minute walk [6MWD], timed up-and-go [TUG] and sit-to-stand tests [STS]) and Patient-Reported Outcome (PRO) Measurement Information System physical function short form (PROMIS-PF) were completed on outpatients with IIM [DM, PM, necrotizing myopathy (NM) or anti-synthetase syndrome] at baseline, 3 and 6 months. Patient were instructed to wear, Actigraph, a PAM device, on the waist for 7 consecutive days monthly for 6 months, and PAM measures including average of daily step count (controlled for length of time the device was worn) and average of maximum step counts in a minute (surrogate measure for speed of walking), were assessed. Pearson correlations were used for cross-sectional analysis with $\rho > 0.5$ considered strong, 0.35-0.5 moderate, and 0.2-0.35 weak correlation. We examined the test-retest reliability as well as responsiveness. Mixed liner model was used for longitudinal analysis and validation against all CSMs.

Results: Fifty patients [mean age, 53.6 (± 14.6); 30 females/20 males] were studied. Eleven of 50 had PM, 27 had DM, 7 had NM and 4 had anti-synthetase syndrome. Cross-sectional results at baseline showed Actigraph maximum steps per minute had moderate to strong correlation with MD global, MMT, Pt-global, HAQ and Ex-muscular global, whereas average daily steps showed moderate to strong correlation with MD global, Pt-global and HAQ. Both measures of actigraph showed significant longitudinal association with MD global, MMT, pt. global and HAQ demonstrating construct validity for the measure, whereas muscle enzyme and Ex-muscular global didn't show significant results (Table 1). There was significant association of both Actigraph measures with functional tests and patient reported outcomes (Table 1). Both measures increased significantly in patients with improvement and remained stable for patients with stable disease over 0, 3, and 6 months, demonstrating responsiveness and test-retest reliability of the measures.

Conclusion: Actigraph's average daily steps and maximum steps per minute both showed good construct validity, reliable and responsive longitudinally.

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Abstract Number: 337

Does a Best Practice Alert Improve RA Patient Referral to Preventative Cardiology?

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Background/Purpose: RA patients are at about 50% increased risk of cardiovascular disease (CVD)¹. Despite this risk, numerous studies show inadequate cardiovascular risk assessment of these patients. Preventive cardiology focuses on reducing CVD risk factors through a multidimensional approach that uses nutrition, exercise, and pharmacologic intervention. This study assesses referral rates of RA patients seen in outpatient rheumatology clinic and referred to the preventive cardiology department through the use of an electronic health record (EHR)based best practice alert (BPA).

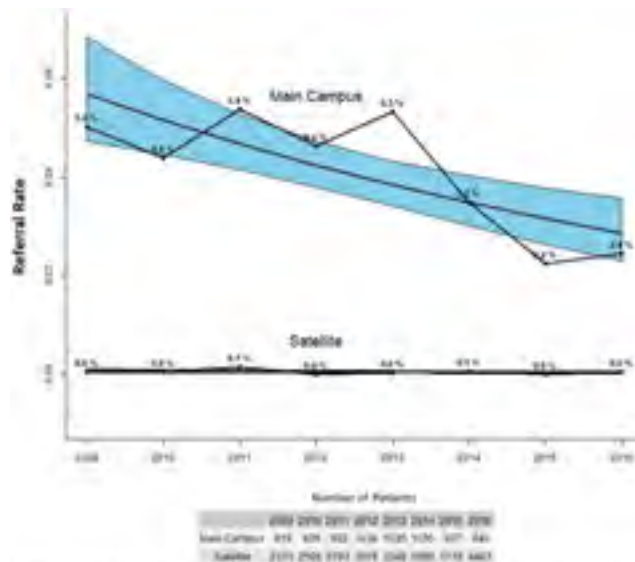


Figure 1. Referral rate to preventive cardiology from rheumatology clinics with and without electronic best practice alert from 2009-2016. The predicted referral rate with 95% confidence interval (blue) is shown with overlay of the observed referral rate for each year.

Methods: This retrospective cohort study compares referral rates to preventive cardiology with and without a BPA for RA patients with visits to rheumatology clinics on main and satellite campuses in a tertiary care system. The main campus uses a BPA that is triggered at least once a year for patients with a diagnosis code of RA, while the satellite campuses did not institute a BPA (usual care) for RA patients. Only patients with referral eligible visits (no referral in past 12 months) were included each year for analysis. Patients with a CVD diagnosis were excluded. The referral rate from when the BPA was implemented in 2009 to 2016 was determined for each year as the number of patients with referral divided by the number of patients with at least one referral eligible visit. A Poisson regression was conducted to examine the number of preventive cardiology referrals performed by campus locations with and without the BPA as a function of year.

Results: Overall, 12,916 RA patients (age: 55.3 (SD=15.0); 77.2% female) were seen across 90,810 clinical visits from 2009-2016. There were 2,714 (21%) main campus patients and 10,202(79%) satellite patients. The difference in referral rates between the main campus(with BPA) and satellite group (without BPA) was statistically significant($p<0.0001$). The main campus rate ranged from 2.2% to 5.4% with an average of 4.1% (Figure 1). The satellite referral rate ranged from 0% to 0.1% (Figure 1).

Conclusion: The EHR-based BPA was modestly effective in improving referral rates for RA patients to preventive cardiology compared to usual care. A multimodality approach is needed to further improve CVD risk factor management for RA patients. Future interventions such as laboratory focused BPAs assessing lipid profiles, interdisciplinary clinics between rheumatology and cardiology, and increased education targeted to physicians and patients to promote CVD risk management in RA should be explored.

References : Avina-Zubieta JA, Thomas J, SadatsafaviM, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. *AnnRheum Dis*. 2012;71(9):1524-1529. <https://doi.org/10.1136/annrheumdis-2011-200726>.

Disclosure: S. Smoker, None; E. Romich, None; A. Nowacki, None; M. E. Husni, None.

Abstract Number: 338

Implementation of an Automated Phrase to Increase Awareness of Cardiovascular Risk in Rheumatoid Arthritis Patients in an Urban Fellows Rheumatology Clinic

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Background/Purpose: Rheumatoid arthritis (RA) is a significant and well-established risk factor for atherosclerotic cardiovascular disease (ASCVD). Cardiovascular risk stratification is often left to the primary care provider (PCP), who may not be aware of the increased risk, leaving risk inadequately addressed. We aimed to increase documentation and identification of RA patients' ASCVD risk through the use of an automated phrase in an urban fellows' clinic.

Methods: RA patients were seen at a large public hospital serving a predominantly black underserved population. Providers imported an automated phrase into clinic notes for RA patients. The phrase included the 2013 American College of Cardiology/American Heart Association ASCVD 10-year risk score, along with associated risk factors. We compared demographic data, RA disease characteristics, ASCVD risk factors, and documentation of risk factors between the 8-week period before implementation (control) and the 8-week period after (study). All patients with a diagnosis of RA were included. Documentation of ASCVD risk was compared using chi-squared testing.

Results: A total of 343 RA patient encounters were reviewed (164 in study, 179 in control; 278 patients total). There were no differences between the study and control groups in terms of baseline demographics, RA characteristics, or ASCVD risk factors (Table 1). The automated phrase was used in 93 (56.7%) patient encounters during the study period. ASCVD risk score calculation was attempted in 71 (54.2%) study visits vs. 5 (3.4%) controls ($p < 0.0001$), and was successful in 47 (35.0%) study visits vs. 4 (2.7%) controls ($p < 0.001$). Tobacco use was documented in 99 (60.4%) study visits, vs. 38 (21.2%) controls ($p < 0.0001$). CDAI (clinical disease activity index) scores were documented in 109 (66.5%) study visits vs. 85 (47.5%) controls ($p = 0.005$). Documentation of diabetes status and smoking cessation interventions were not different between the two groups (Table 2).

Table 1: Demographic Data and Disease Characteristics Contributing to ASCVD Risk

	Study (n=127)	Control (n=151)	p value
Age – years	55.7 ± 13.6	58.5 ± 12.3	0.07
Female sex – no. (%)	109 (85.8)	117 (77.5)	0.07
Race – no. (%)			
Black or African-American	97 (76.4)	119 (78.8)	0.63
White	4 (3.1)	2 (1.3)	0.30
Hispanic	24 (18.9)	23 (15.2)	0.44
Other	2 (1.6)	7 (4.6)	0.15
PCP visits – no. (%)			
Patients with a PCP	109 (85.8)	136 (90.1)	0.28
PCP visit within 3 months	51 (40.2)	69 (45.7)	0.29
PCP visit within 6 months	86 (67.7)	98 (64.9)	0.31
PCP visit within 12 months	101 (79.5)	124 (82.1)	0.38
Pre-existing ASCVD – no. (%)	8 (6.3)	16 (10.6)	0.20
ASCVD 10-Year Risk Score			
Risk score (%)	10.19 ± 8.9	12.5 ± 7.5	0.62
No. (%) ≥ 7.5%*	20 (51.3)	3 (75)	0.32
Blood pressure (BP)			
Systolic BP – mmHg	131.4 ± 14.9	132.2 ± 17.4	0.41
Diastolic BP – mmHg	76.5 ± 11.1	81.3 ± 49.9	0.30
Systolic BP – mmHg ≥ 140	39 (30.7)	54 (35.8)	0.37
On anti-HTN – no. (%)	74 (58.3)	89 (58.9)	0.91
Lipids			
Lipid panel within 3 years – no. (%)	89 (70.1)	100 (66.2)	0.69
Total cholesterol – mg/dL	175.6 ± 43.4	177.2 ± 40.3	0.83
Triglycerides – mg/dL	113.6 ± 75.1	119.3 ± 71.0	0.56
High density lipoprotein – mg/dL	57.9 ± 21.0	54.5 ± 18.4	0.18
Low density lipoprotein – mg/dL	96.4 ± 35.6	100.2 ± 32.7	0.40
Statin Use			
No. (%)	46 (36.2)	53 (35.1)	0.85
Statin and risk ≥ 7.5% – no. (%)*	12 (60.0)	1 (33.3)	0.33
Diabetes			
No. (%)	34 (26.8)	31 (20.5)	0.22
Hgb A1C – %	7.5 ± 2.1	7.3 ± 1.9	0.65
Smoking – no. (%)	26 (20.5)	22 (14.6)	0.19
Body Mass Index (BMI)			
(kg/m ²)	29.8 ± 6.9	30.5 ± 7.1	0.40
Underweight (BMI < 18.5)	3 (2.4)	1 (0.7)	0.24
Normal (≥ 18.5, < 25)	28 (22.0)	32 (21.2)	0.99
Overweight (≥ 25, < 30)	42 (33.1)	51 (33.8)	0.90
Obese (≥ 30)	54 (42.5)	68 (45.0)	0.76
Aspirin use – no. (%)	60 (47.2)	69 (45.7)	0.81
Seropositive – no. (%)	121 (95.3)	137 (90.7)	0.14

Table . (Cont'd)

	Study (n=127)	Control (n=151)	p value
CDAI			
Mean \pm SD	10.6 \pm 11.7	12.4 \pm 12.9	0.41
CDAI $\geq 10^+$	26 (36.1)	29 (50.9)	0.13
Use of prednisone			
Current use – no. (%)	88 (69.3)	108 (71.5)	0.68
Current dose – mg/day	4.7 \pm 5.3	4.3 \pm 4.3	0.45
Dose ≥ 8 mg/day – no. (%)	27 (21.3)	21 (13.9)	0.11

Values are depicted as number (%) of individuals unless otherwise specified.

Plus-minus values are means \pm SD.

P values were calculated using two-sided T test for comparison of means and chi-squared testing for comparison of proportions.

Duplicate patient encounters were excluded from analysis.

* : Denominators include patients with a successfully calculated ASCVD 10-yr risk score calculation only (n = 39 for study and n= 4 for control).

^ : Denominators include patients with pre-existing ASCVD only (n=8 for study and n=16 for control).

+ : Denominators include patients with a calculated CDAI only (n= 72 in study and n= 57 in control).

Table 2: Implementation of the use of an automated phrase and documentation of ASCVD risk

	Study (n=164)	Control (n=179)	p value¶
Use of automated phrase – no. (%)	93 (56.7%)	0 (N/A)	N/A
ASCVD risk score documentation *			
Attempted – no. (%)	71 (54.2)	5 (3.4)	<0.0001
Calculated – no. (%)	47 (35.9)	4 (2.7)	<0.0001
Diabetes documentation			
Diabetes documented – no. (%)	33 (76.7)	27 (73)	0.362
Tobacco use documentation#			
Documented (all) – no. (%)	99 (60.4)	38 (21.2)	<0.0001
Documented (smokers)# – no. (%)	28 (77.8)	13 (50.0)	0.023
Intervention (smokers)# – no. (%)	16 (44.4)	7 (26.9)	0.416
CDAI documentation – no. (%)	109 (66.5)	85 (47.5)	0.005

Values are depicted as number (%) of patient encounters unless otherwise specified.

Documentation encounters included 278 patients; 4 patients were seen 3 times, 57 patients were seen twice, and the remaining patients were seen once.

¶ P values were calculated with chi-squared testing.

* : Denominators include patients eligible for ASCVD 10-yr risk score calculation only (patients ≥ 40 and ≤ 79 years and without pre-existing ASCVD; n = 131 for study and n=146 for control).

: Denominators differ from the totals, and include smokers only (n=36 in study and n=26 in control)

Conclusion: ASCVD risk factors were identified in our predominantly black RA population, including uncontrolled hypertension, high mean BMI, high disease activity, and high prednisone use. The use of an automated phrase increased ASCVD risk score, tobacco use, and CDAI score documentation. Although the majority of patients were seen by a PCP within the past 6 months, statins were under-prescribed, and a significant proportion of blood pressures were not at goal. PCPs may underestimate the increased ASCVD risk in RA. Further interventions are needed to increase awareness among PCPs using a multi-disciplinary approach.

Disclosure: L. A. Cassidy, None; J. Brandt, None; A. Gizinski, None; A. Khosroshahi, None; G. Bao, None; S. S. Lim, None.

Abstract Number: 339

Documenting Bone Health for Veterans with Rheumatoid Arthritis in an Outpatient Academic Clinic

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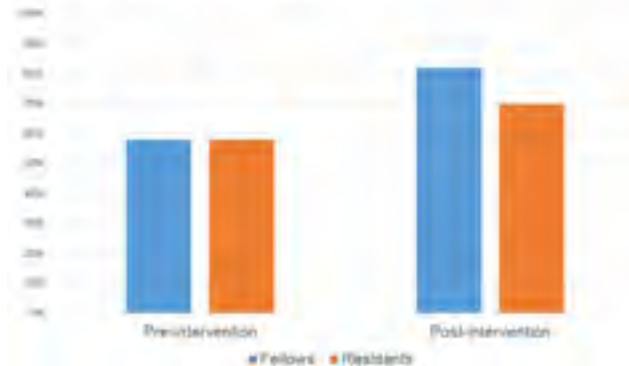
Background/Purpose: Rheumatoid arthritis (RA) increases the risk of bone density abnormalities such as osteoporosis, predisposing patients to fragility fractures and subsequent morbidity. Osteoporotic fractures incur an economic burden

Image 1: Intervention: "Bone health" prompt in the Rheumatoid arthritis office visit template.

The image shows a digital medical template for a Rheumatoid Arthritis (RA) office visit. It features several sections:

- Assessment:** A large text area for clinical notes.
- Bone Health:** A section with checkboxes for:
 - ☐ Normal Bone Density
 - ☐ Osteopenia
 - ☐ Osteoporosis
 - ☐ Last Exam
 - ☐ High Fracture
 - ☐ Disseminated
 - ☐ No Assessment
- Plan:** A large text area for treatment plans.
- Review checkboxes:** At the bottom, there are checkboxes for "Review this case only in" and "Review this document in", each followed by a text field for specifying the location.

Figure 1: Three-month documentation rate of bone health among fellows and residents pre- and post-intervention. Each bar represents data in n=50 patients.



reaching nearly \$17 billion annually. Consequently, rheumatologists should assess and manage bone health more attentively. Bone density assessment in RA patients is not always evaluated in routine clinical practice despite guidelines suggesting its importance. We have noted that trainees in the rheumatology clinic are not routinely documenting or managing bone health in our patients. The aim of this quality improvement project was to increase documentation of bone health in RA patients seen by residents and fellows in a high volume VA Medical Center outpatient rheumatology clinic from the baseline 3 month average of 58% to 70% (stretch goal 80%) during the time period of February to April 2018.

Methods: Pre-intervention documentation rate of bone health was measured by reviewing 50 fellows' and 50 residents' rheumatology RA clinic visit notes between August and October 2017 at a VA center serving a large metropolitan area. Patients seen by the authors were excluded. Intervention: In December 2018, a "Bone Health" prompt was added to the RA note template, reminding physicians to document bone health status, FRAX score, and recommendations (Image 1). In order to facilitate the intervention, fellows were educated about the importance of bone health documentation and informed about the QI project at a Grand Rounds conference. Additionally, flyers reminding all residents and fellows about the template were posted in exam rooms at the VA. Post-intervention data were collected between February and April 2018, using the same process.

Results: The pre-intervention documentation rate among both 1st and 2nd year rheumatology fellows and residents (Internal Medicine, PM&R) was 58%. The post-intervention rate improved among both fellows and residents to 82% and 70% respectively (n=50 patients per subgroup), meeting the set goal of our project (Fig 1).

Conclusion: Adding a "Bone Health" prompt to the RA office visit template improves the documentation rate of bone health, as shown by improvement in the post-intervention chart review. Fellows had a greater documentation rate in their post-intervention results than did residents, potentially due to more frequent exposure to this topic. In the future, we plan to analyze if the increased documentation rate translated into improved rates of guideline concordant management of decreased bone density in this vulnerable population.

Disclosure: B. Ahmed, None; R. Nayfe, None; A. Udupa, None; U. E. Makris, None; R. Arora, None; S. Reddy, None.

No Improvement in Time to Biopsy and Therapy in Lupus Nephritis Patients over Two Decades

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Background/Purpose: Proteinuria and urinary casts are good indicators of lupus nephritis (LN) yet six different LN guidelines recommend kidney biopsy to confirm LN. Therefore, kidney biopsy remains the gold standard for diagnosing LN and initiating therapy. Recent studies report an average wait time to see a specialist of 50 days which can delay biopsy and therapy in LN. There is limited information on wait times for confirming diagnosis and starting therapy in LN patients. We aimed to examine time to biopsy and therapy in LN patients and compare over two decades. We hypothesized that time to biopsy has not changed but therapy choices would differ in the decade after ALMS trial.

Methods: Our cohort study identified all incident LN patients with initial kidney biopsy from 1997-2017 at an academic center. Sociodemographics and reported details on the first biopsy in LN patients were abstracted from a comprehensive native kidney biopsy database. Biopsy reports were reviewed for LN class and chronicity as per International Society of Nephrology guidelines. Time to biopsy and therapy were defined as time from nephrology referral until biopsy, and time from biopsy until start or change in therapy respectively. Further, for two decades we compared change in time to biopsy over 1997-2007 vs. 2007-2017, rate of hospitalization while awaiting biopsy, and type of therapy initiated.

Results: Among 175 incident LN patients with initial native kidney biopsies, 79% were female, 72% White with median age of 24 years (2-77 years). Median times to biopsy and therapy were 52 days (24-155 days) and 7 days (0-18 days) respectively. 13% of the patients were hospitalized during the wait period. Over two decades, there was no significant change in time to biopsy (Fig 1) or hospitalization rates. Univariate and multivariate analyses showed 4 times higher odds of starting MMF in LN patients in the latter decade (OR 3.5, CI 1.2,10.8 p=0.02). Type of therapy was independent of race, proliferative LN and chronicity (Table 1). Limitations include examining only LN patients with kidney biopsy, and no data on LN patients on MMF without biopsy.

Conclusion: This is among the first studies to report wait times for diagnosing and starting therapy in LN (~60 days) with no improvement in the latter decade despite increased use of MMF after 2007. Observing wait times to undergo biopsy as a major barrier in provision of efficient care to LN patients we recommend system improvement strategies such as establishing multidisciplinary clinics. Future work will examine improvement in time to biopsy after establishing a multidisciplinary LN clinic.

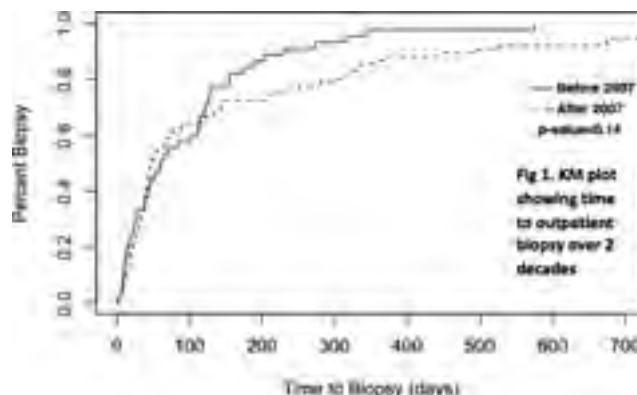


Table 1. Odds of Mycophenolate Therapy Choice using Logistic Multivariate Regression Model

Variables	Multivariate OR (95% CI)	p-value
Biopsy after 2007	3.50 (1.20,10.80)	0.02
Gender (Female)	0.43 (0.11, 1.50)	0.20
Lupus Duration >5 years	0.08 (0.01, 0.76)	0.03
Race (White vs non-White)	1.24 (0.36, 4.73)	0.74
LN (Proliferative vs non-proliferative)*	0.44 (0.13, 1.38)	0.17
Chronicity Present	0.67 (0.21,2.13)	0.49

* LN proliferative includes class 3,4 while non-proliferative includes classes 1,2,5

Disclosure: S. Garg, None; S. Panzer, None; T. Singh, None; C. M. Bartels, Pfizer, Inc., 2.

Abstract Number: 341

Setting Treatment Target for Joint Surgery in Lower Limbs in Patients with Long-Standing Rheumatoid Arthritis Based on Multicenter Prospective Cohort Study; Validation and Reliability of Objective Index of Activity Speed (Timed Up and Go test) for Measuring Physical Function

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Session Information

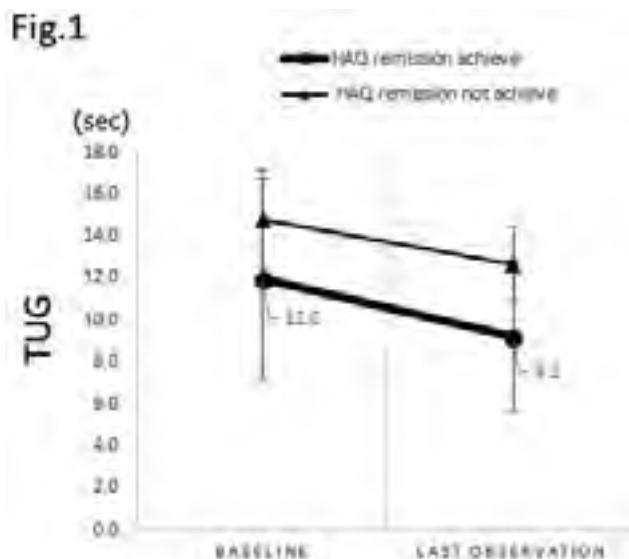
Session Date: Sunday, October 21, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Total management including reconstructive joint surgery and rehabilitation should be needed for further improvements of physical function for long-standing RA patients. It is very important to set treatment goal for



those management. The purpose of this study is to set treatment target using Timed Up and Go test (TUG) in relation to achievement of HAQ-DI remission ($\text{HAQ-DI} < 0.5$) with joint surgery in lower limbs.

Methods: Multicenter prospective observational cohort study was conducted among patients who underwent elective joint surgery for RA from April 2012 to March 2016 (Study registration: UMIN000012649). In this study, we collected data at baseline and at 6 or 12 months after the surgery. These data were as follow; age, sex, disease duration, drug therapies, and disease activity (DAS), TUG, and patient-reported outcome [HAQ-DI, EQ-5D (QOL), patient's global assessment (PtGA) and BDI-II (depression)]. Correlation between TUG and other variables were determined. Association between TUG and achievement of HAQ remission and cut-off values for HAQ remission were also determined using logistic regression analysis with adjustment of age and sex and ROC curve, respectively.

Results: Totally, 139 patients with elective joint surgery in lower limbs were analyzed. Mean age, disease duration, HAQ-DI and TUG were 65.4 years, 17.5 years, 1.022, and 12.7 seconds, respectively. Elective joint surgeries were total hip arthroplasty; 10.1%, total knee arthroplasty; 33.8%, total ankle arthroplasty or ankle fixation; 10.1%, and forefoot arthroplasty; 46.0%. The surgeries can significantly improve the outcome measures, including TUG, DAS, PtGA, pain, EQ-5D and BDI-II other than HAQ-DI. In this study, 45 of 139 patients (32.4%) had HAQ remission status at baseline. 18 of 94 patients (19.1%) who had $\text{HAQ-DI} > 0.5$ can achieve HAQ remission with the surgery. Notably, TUG at last observation was significantly associated with achievement of HAQ remission even after adjustment for age, sex, and DAS (1 second increasing of TUG, OR: 0.72, 95% CI: 0.53-0.97). The adjusted-TUG at last observation of patients with achievement of HAQ remission was 9.2 second (95% CI: 5.6-12.8) (Fig.1). Cut-off of TUG at observation for achievement of HAQ remission was 9.2 second based on ROC analysis (Fig.2). Importantly, We confirmed significant more improving of EQ-5D, HAQ-DI and TUG in patients who achieved TUG 9.2 second at last observation than in patients who did not (Fig.3).

Fig.2

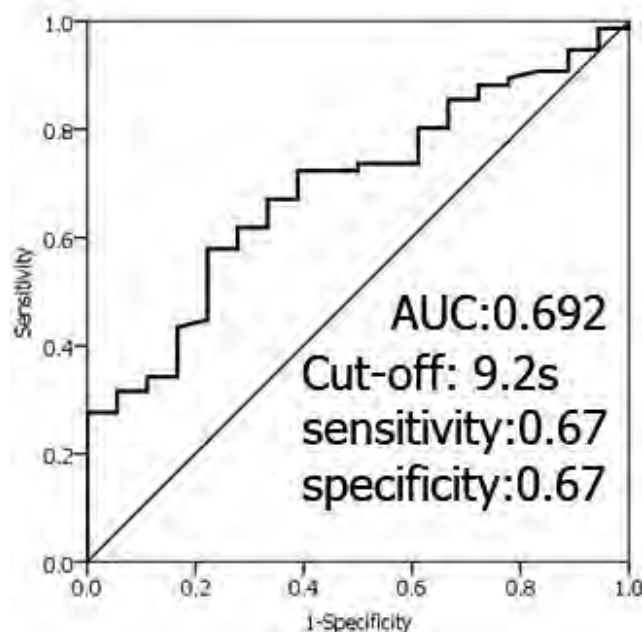
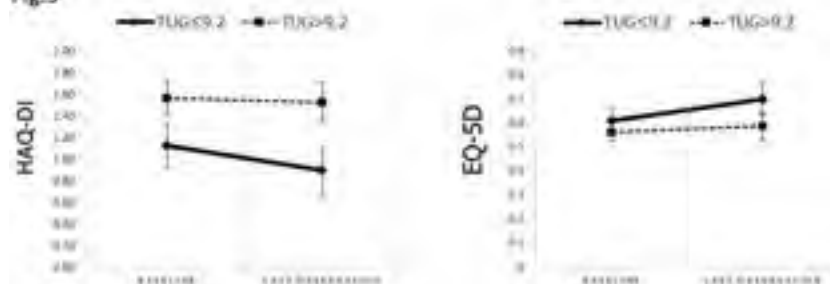


Fig.3



Conclusion: TUG was significantly associated with patient reported outcomes, HAQ-DI and EQ-5D. The cut-off values of TUG (9.2 seconds) should be important to achieve good QOL and physical function for patients with joint surgery in lower limbs and could be suitable target for surgical procedure.

Disclosure: T. Kojima, None; H. Ishikawa, None; M. Kojima, None; S. Tanaka, None; N. Haga, None; K. Nishida, None; M. Yukioka, None; J. Hashimoto, None; H. Miyahara, None; Y. Niki, None; T. Kimura, None; H. Oda, None; S. Asai, None; K. Funahashi, None; N. Ishiguro, None.

Abstract Number: 342

Optimizing the Dataset to Collect from Patients to Accurately Predict Their Status Prior to the Clinic Visit

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster I

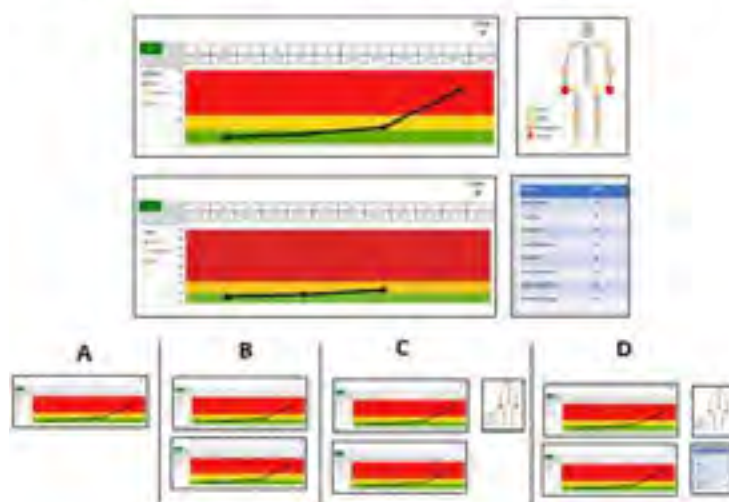
Session Type: ACR Poster Session A

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

Background/Purpose: Understanding a patient's status before entering the exam room, or accurately tracking status between visits, is vital to creating more efficient ways to apply patient care. We studied which patient-derived dataset resulted in the most accurate diagnosis for common clinical scenarios encountered in rheumatoid arthritis (RA) management.

Methods: 3 clinical cases were created for 4 RA scenarios: Acute Flare-RA, Chronic Active-RA, Acute Flare-Not RA, and Chronic Active-Not RA. To see which data most accurately predicted the clinical scenario, 4 datasets were developed (Figure 1): Dataset A (RAPID3), B (RAPID3 + CDAI), C (RAPID3 + CDAI + Homunculus), and D (RAPID3 + CDAI + Homunculus + Events). CDAI included only values from previous office visits, so the dataset could be derived without physician input. 12 rheumatologists were given randomly assembled packets with 48 cases (3 cases x 4 scenarios x 4 datasets). For each case, the rheumatologist decided which of the 4 RA scenarios the dataset represented, as well as how confident they were in their decision (10-point Likert scale). Comparisons were tested using a Generalized Estimating Equation for logistic regression. Post-hoc comparisons were tested for each incremental amount of data.

Figure 1: Datasets* Presented for Each Case Scenario; A = RAPID3; B = RAPID3 + CDAI; C = RAPID3 + CDAI + Homunculus; D = RAPID3 + CDAI + Homunculus + Events.



(*RAPID3 is a patient derived measure of disease activity, CDAI is a composite measure from patient and rheumatologist, Homunculus is a patient derived measure of severity of joint pain by location, and Events are important items that occurred since last visit, such as a new illness or symptom).

Table 1. Rheumatoid Arthritis and Doing Poorly - Correct Etiology by Clinical Phenotype for 4 Datasets. (Optimal Dataset shaded in green)

All Phenotypes	Dataset			
Response	A	B	C	D
Incorrect	135 (93.8%)	59 (41.0%)	20 (13.9%)	15 (10.4%)
Correct	9 (6.2%)	85 (59.0%)	124 (86.1%)	129 (89.6%)
Total	144	144	144	144
RA – Acute Flare	Dataset			
Response	A	B	C	D
Incorrect	31 (86.1%)	80 (83.3%)	10 (27.8%)	10 (27.8%)
Correct	5 (13.9%)	6 (16.7%)	26 (72.2%)	26 (72.2%)
Total	36	36	36	36
RA – Chronic Active	Dataset			
Response	A	B	C	D
Incorrect	32 (88.9%)	3 (8.3%)	2 (5.6%)	2 (5.6%)
Correct	4 (11.1%)	33 (91.7%)	34 (94.4%)	34 (94.4%)
Total	36	36	36	36
Not-RA – Acute	Dataset			
Response	A	B	C	D
Incorrect	36 (100%)	25 (69.4%)	7 (19.4%)	0 (0%)
Correct	0 (0%)	11 (30.6%)	29 (80.6%)	36 (100%)
Total	36	36	36	36
Not-RA – Chronic Active	Dataset			
Response	A	B	C	D
Incorrect	36 (100%)	1 (2.8%)	1 (2.8%)	1 (2.8%)
Correct	0 (0%)	35 (97.2%)	25 (69.7%)	35 (97.2%)
Total	36	36	36	36

Results: Across all scenarios (Table 1), there was an increase in percent correct as more clinical data was presented ($p<0.0001$). Post-hoc analysis showed improvement in % correct moving from dataset A to B (6.2% vs. 59.0%, $p<0.0001$) and B to C (59.0% vs. 86.1%, $p<0.0001$), but not C to D (86.1% vs. 89.6%, $p=0.4575$). Analysis of specific scenarios showed that dataset C was optimal for Acute Flare–RA and Acute Flare–Not RA. Dataset B was optimal for Chronic Active – RA and Chronic Active – Not RA. Level of confidence was high (8/10) and did not vary by dataset - indicating confidence in decision making regardless of the decision.

Conclusion: To our knowledge, this is the first study that shows the optimal data set to collect from patients between visits or before a visit to accurately diagnose the common clinical scenarios that affect patients with RA. The combination of RAPID3 (historical and current) + CDAI(historical) + pain Homunculus gave the greatest diagnostic accuracy across all clinical phenotypes. These results can inform the design of data collection systems that improve rheumatology efficiency, by empowering the rheumatologist before the visit, and driving return visits based on patient need rather than an arbitrary interval.

Disclosure: E. Newman, None; E. Thomas, None; A. Berger, None; H. L. Kirchner, None.

Abstract Number: 343

Low Rates of Immunizations in Cohort of Immunocompromised Patients in an Academic Rheumatology Practice

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Patients with rheumatologic disorders often require immunosuppression (e.g. DMARDs, biologics, or high doses of prednisone). These patients are at increased risk for infections. While live vaccines are contraindicated in the immunosuppressed, 2018 CDC guidelines support inactivated vaccine administration [1]. Despite recommendations for immunization [2], there is lack of evidence on whether vaccination rates are optimal. The purpose of this study was to investigate the rates of influenza, pneumococcal, and tetanus/diphtheria/pertussis (Tdap) vaccination in immunosuppressed individuals with rheumatologic disorders seen from 2012-2017 at a large academic rheumatology clinic.

Methods: Patients seen at a large urban academic medical center's rheumatology clinic between 2012-2017 were included if they had a diagnosis of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or vasculitis in addition to any of the following: prednisone ≥ 20 mg/day, a DMARD (except hydroxychloroquine), and/or a biologic agent. Deceased patients were excluded. Immunizations, medications, and comorbidities were recorded. Vaccination administration for Prevnar, Pneumovax, Influenza, or Tdap was assessed. Chi squared tests evaluated immunization patterns based on various factors including sex, comorbidities, physician experience level (< 10 years, ≥ 10 years), diagnosis, and age group (< 65 years, ≥ 65 years).

Results: Of 2366 patients reviewed, 1239 met inclusion/exclusion criteria. Results are shown in the Table. Vaccination rates were below 50% (except for receipt of flu vaccine once during the study period). More patients aged ≥ 65 years received Prevnar/Pneumovax than those < 65 years of age. Patients with SLE had higher rates of immunization versus those with RA or vasculitis. Presence of cardiopulmonary comorbidities generally increased rates. No significant difference was found in rates based on ethnicity, sex, non-cardiopulmonary comorbidities, or physician experience.

Conclusion: Infections contribute to morbidity and mortality for immunosuppressed patients, and guidelines recommend vaccination. The above results show strikingly low vaccination rates in this vulnerable population. Other risk factors for infection, including older age and cardiopulmonary comorbidities, were associated with higher vaccination rates. Rheumatologists may not be considering vaccination during their busy clinical practice. Education and quality improvement initiatives are needed to improve vaccination rates in Rheumatology clinics.

REFERENCE :

1. CDC- Immunization schedules. <https://www.cdc.gov/vaccines/schedules/hcp/adult.html>. May 31, 2018
2. Van Assen S, Agmon-Levin N, Elkayam O, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2011;70:414e22.

Table 1. Vaccination rates in immunocompromised patients

	Prevnar	Pneumovax	Td/Tdap	Flu (Ever)	Flu (Past Year, 2017)
Total [n (%)]	268 (22%)	558 (45%)	320 (26%)	747 (60%)	468 (38%)
Age [n (%)]					
≤ 65 years	144 (16%)	358 (40%)	230 (26%)	523 (59%)	326 (37%)
> 65 years	124 (35%)	200 (57%)	90 (26%)	224 (64%)	142 (41%)
p-value	$< 0.01^*$	$< 0.01^*$	0.95	0.09	0.20
Diagnosis [n (%)]					
SLE	98 (25%)	187 (47%)	120 (30%)	246 (62%)	165 (42%)
RA	149 (20%)	314 (43%)	182 (25%)	431 (59%)	269 (37%)
Vasculitis	21 (18%)	57 (50%)	18 (16%)	70 (61%)	34 (30%)
p-value	0.15	0.21	$< 0.01^*$	0.54	0.04*
Cardiac co-morbidity [n (%)]					
Yes	16 (33%)	35 (73%)	17 (35%)	36 (75%)	26 (54%)
No	252 (21%)	523 (44%)	303 (25%)	711 (60%)	442 (37%)
p-value	0.04*	$< 0.01^*$	0.12	0.03*	0.02*
Pulmonary co-morbidity [n (%)]					
Yes	29 (44%)	47 (71%)	27 (41%)	52 (79%)	34 (52%)
No	239 (20%)	511 (44%)	293 (25%)	695 (59%)	434 (37%)
p-value	$< 0.01^*$	$< 0.01^*$	$< 0.01^*$	$< 0.01^*$	0.02*

* Significant result

SLE = Systemic lupus erythematosus , RA = Rheumatoid arthritis

Disclosure: D. Cherny, None; N. Shakoar, Dr. Comfort/DJO, 7; T. Beck, None; S. Khandelwal, None.

Use of Lean Six-Sigma Methodologies to Improve Pneumococcal Vaccination Rates Among Immunocompromised Veterans with Rheumatologic Diseases: A Quality Improvement Project

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Pneumonia is a leading cause of morbidity and mortality in the United States among immunocompromised individuals with rheumatologic diseases. Despite the publication of Advisory Committee on Immunization Practices (ACIP) guidelines for pneumococcal vaccinations addressing the specific needs of this population, implementation of these guidelines has been inconsistent. At one Midwestern VA Rheumatology Clinic, pneumococcal vaccination rates were determined to be as low as 3%. From January to June 2018, we used Lean Six Sigma methodologies to improve the current process surrounding pneumococcal vaccination in the Rheumatology Clinic.

Methods: Current processes and improvement targets for pneumococcal vaccine administration were explored using Lean-six sigma methods: 1) interdisciplinary process mapping; 2) process maps analysis, Voice of the Customer (VOC), and brainstorming for value and flow analyses; 3) value stream maps and pilot testing utilizing PDSA (Plan-Do-Study-Act) cycles; and 4) post-implementation control and sustainability planning. The interprofessional team consisted of a nurse and physician leader, a physician champion, and clinic management. The first set of PDSA cycles involved educating providers and posting the ACIP guidelines in each patient room. The second set of PDSA cycles involved bundling and relocating supplies to a more convenient location. Outcome measures were defined as time required to administer vaccine and percentage of eligible patients who are up-to-date with pneumococcal vaccination. Balancing measures included total time spent in clinic and vaccine adverse reactions.

Results: Process mapping revealed eight barriers. Process redesign resulted in elimination of five of these barriers through workflow simplification. A nurse alert step was added to further improve efficiency. The VOC indicated value in the delivery of high quality care and improving vaccination rates, but without spending excess time in the vaccine administration workflow. Interim results show improvement in outcome measures, including reduced time required for vaccine administration from 15 to 7 minutes, and increased percentage of patients appropriately immunized from 3% to 21%. Vaccine administration added fewer than 15 minutes to total appointment time and no adverse reactions occurred.

Conclusion: A bundle of quality improvement efforts utilizing lean six sigma methodologies increased the pneumococcal vaccination rate from 3% to 21% and reduced the time required for vaccination from 15 to 7 minutes. Elements of the bundle included: (1) clinician education, (2) posting of an easy-to-read version of the guidelines for vaccine administration, (3) simplification of workflow for administration of pneumococcal vaccines, and (4) integration and bundling of supplies necessary for vaccination. This bundle can be replicated at other sites using similar methodologies. The investigators intend on continuing through more iterations of these PDSA Cycles to achieve a goal of at least 70% appropriate pneumococcal vaccination among immunocompromised patients at the Iowa City VA Rheumatology Clinic.

Disclosure: M. Swee, None; J. Wilson, None; B. Kumar, None.

Abstract Number: 345

Snap Crackle Pop: Healing the Cracks in Our Referral Process, Helping Pediatric Rheumatology Patients Get Care Sooner

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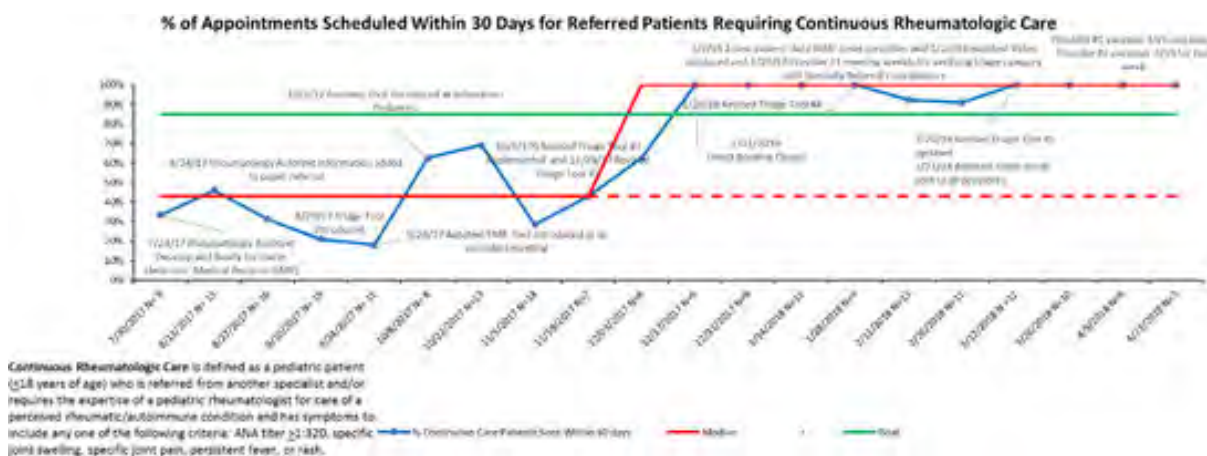
Session Information

Session Date: Sunday, October 21, 2018

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

We used a Key Driver Diagram to define our leading factors and guide our change ideas, and an aim statement and data management plan to guide the work and data collection. Our run chart captures biweekly change and demonstrates improvement over time.

The average number of patients scheduled within 30 days of referral over the first four months compared to the subsequent five months represents a **131% increase**. Our run chart shows a shift demonstrating non-random variation and improvement in our outcome measure. We have continuously met and exceeded goal of 85% since December 2017.



By investing time in creative problem-solving, streamlining, and clear communication, and by facilitating staff empowerment and ownership, this project achieved remarkable gains in patient access and care delivery. This result is a process that can be transferred to other settings, and holds great value given the universal challenges of supply/demand.

Abstract Number: 346

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Session Information**Session Date:** Sunday, October 21, 2018**Session Title:** Measures and Measurement of Healthcare Quality Poster I**Session Type:** ACR Poster Session A**Session Time:** 9:00AM-11:00AM

Background/Purpose: The growing use of cancer immunotherapy and checkpoint inhibitors has led to a steep rise in immune-related adverse events (irAEs). Despite expanding research efforts, definitive methods of predicting irAE onset or severity and reliable therapeutic approaches beyond steroids are lacking. Evaluation and management of irAEs requires a multidisciplinary approach. At the University of Chicago, we have developed a dedicated irAE pilot clinic with the aim to facilitate diagnosis and management for irAE patients in a timely fashion.

Methods: The pilot clinic was run by Rheumatology over seven months with one hour per week dedicated to new or follow up irAE patient visits. No limit was placed on organ involvement so a wide breadth of complications was observed and treated. The indications for referral included: irAE refractory to steroids with possible need for steroid sparing immunosuppression (IS), high severity irAE needing early steroid-sparing agent, and concern for any Rheumatologic irAE. Referrals were placed through an order in our electronic medical record system. Physicians were informed about the irAE clinic through multiple presentations at Hematology-Oncology grand rounds and fellow rounds and Internal Medicine conferences. In addition to the primary irAE clinic, we have developed a network of specified “point person” physicians within various medical subspecialties (Hepatology, Dermatology, Pulmonary, Nephrology, Neurology) to coordinate diagnostic procedures and discuss therapeutic options in each case.

Results: A total of fifteen new patients were evaluated; eight of these required more than one follow up. Oncologists referred twelve patients and three were new referrals after hospital discharge. Most of the patients were seen for possible Rheumatologic irAE (40%). About 33% were seen for irAE refractory to steroids and 27% for high severity irAE requiring Rheumatology assistance for steroid-sparing IS. Malignancy history ranged from melanoma, non-small cell lung cancer to gynecologic tumors. Patients were able to be seen within an average of 7 days (0-19 days) and 93% of the Oncologists noted utilization of and followed Rheumatology recommendations in patient's care. Of the evaluated patients, 3 were ruled out for irAE. The irAEs diagnosed included the following: 2 arthritis, 1 vasculitis, 1 myocarditis, 1 dermatitis, 3 pneumonitis, 2 hepatitis and 2 neurologic. Of those with irAEs diagnosed, 8 had serologies checked and all had some antibody positivity (5 of 8 with ANA >1:160, 2 with RF positive (1 also with CCP positive), 1 ANCA positive). The patient with dermatitis had eosinophilia on differential and 40% of patients with diagnoses of irAE had lymphopenia on their differential (patient without irAE did not have abnormality on differential).

Conclusion: A dedicated irAE clinic can help Oncologists streamline care of their high risk patients resulting in more efficient and effective care for challenging cases. In addition, creation of an irAE clinic cohort allows for trends to be identified such as the development of lymphopenia in association with irAE, serological findings, and which steroid-sparing strategies are most effective.

Disclosure: P. Reid, None; R. Jan, None.

Abstract Number: 347

Effectiveness of a Biopsychosocial Exercise Approach in Rheumatic Diseases

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Session Information**Session Date:** Sunday, October 21, 2018**Session Title:** Measures and Measurements of Healthcare Quality Poster – ARHP**Session Type:** ACR Poster Session A**Session Time:** 9:00AM-11:00AM

Background/Purpose: The trend towards biopsychosocial approaches is increasing today and studies on psychosocial effects of exercise are limited in the literature. There is a need for framed exercise programs to assess clinical effectiveness of biopsychosocial approaches. There is a specific approach named as Cognitive Exercise Therapy Approach (the authors request that the abbreviation stays as “BETY” as the original in Turkish), which has newly developed its biopsychosocial

assessment scale. The purpose of this study is to investigate the effectiveness of BETY in rheumatic patients comparing to a control group.

Methods: Twenty-nine patients with rheumatic diseases were included in this study. Patients were divided into two groups; BETY group (n=14) and control group (n=15). BETY Scale for biopsychosocial status, Hospital Anxiety and Depression (HADS) for depression and anxiety, Health Assessment Questionnaire (HAQ) for daily living activity evaluation were used pre- and post-treatment. BETY approach is performed in a period of one hour, 3 times a week for 12 weeks and includes clinical pilates exercises, dance therapy-authentic movement and pain management information. The control group did not take any exercise treatment.

Results: Mean age of the BETY group and control group was $48,86 \pm 8$ and $40,47 \pm 10,97$ respectively. There were significant improvements in BETY scale and HADS anxiety and depression scores in BETY group ($p < 0.05$). Although HADS depression score was changed ($p < 0.05$), no changes were recorded in control group in other parameters ($p > 0.05$) (Table.1.). There wasn't any change in the HAQ scores of both groups ($p > 0.05$).

Table 1. Comparison between two groups.

	BETY Group (n=14)			Control Group (n=15)			Between groups
	Age	BMI		Age	BMI		
	48,86±8	25,68±3,19		40,47±10,97	26,49±4,89		
	Before Median (25th-75th)	After Median (25th-75th)	p	Before Median (25th-75th)	After Median (25th-75th)	p	p
BETY Score	60 (47,25-82)	39 (30,75-48,75)	0,013	62 (54-78)	61 (47-76)	0,409	0,347
HAQ	9 (4,75-14,75)	4 (2,5-10)	0,068	13 (6-20)	11 (1-16)	0,624	0,363
HADS-A	9,5 (6,75-12,75)	5 (1,5-5)	0,002	10 (5-12)	10 (7-12)	0,778	0,001
HADS-D	8 (5-10)	4 (1,5-5)	0,014	10 (9-12)	9 (4-11)	0,014	0,235

Conclusion: BETY program was effective on anxiety, depression and biopsychosocial status of patients. This study is important in demonstrating the effectiveness of a framed biopsychosocial exercise approach. More detailed studies are needed in several patient groups.

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Abstract Number: 348

Psychometric Validation of the Arthritis Helplessness Index in Systemic Lupus Erythematosus

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Measures and Measurements of Healthcare Quality Poster – ARHP

Session Type: ACR Poster Session A

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

Background/Purpose: Helplessness is a relevant construct in systemic lupus erythematosus (SLE), an unpredictable chronic illness with no known cure characterized by relapsing and remitting features. However, no measure of helplessness has been validated in this population. The Arthritis Helplessness Index (AHI) is a 15-item self-report measure developed to assess perceptions of helplessness in coping with rheumatoid arthritis (RA). Since its development, the measure has been widely used across rheumatologic contexts and adapted into several variants. A single-factor total score, a bi-factor 7-item Internality and 5-item Helplessness version, and a 5-item Helplessness short-form have been proposed in the literature for RA patients. One potential challenge with using the AHI has been that multiple variants of the measure exist. Moreover, lack of a formal evaluation of the psychometric properties of the measure in SLE had precluded identification of the optimal form of the measure for this patient population. The present study examined the structural validity, reliability, and convergent validity of the Arthritis Helplessness Index in a sample of patients with SLE.

Methods: Patients with SLE ($N = 136$) receiving medical care at a private hospital completed the AHI and other self-report measures. The structural validity of the AHI was examined using confirmatory factor analysis. Internal consistency reliability was evaluated with Cronbach's coefficient alpha. Pearson product-moment correlations were used to examine convergent validity with measures of depression, anxiety, and mastery.

Results: The five-item AHI-Helplessness measure demonstrated a tenable factor structure ($CFI = 0.98$, $RMSEA = 0.06$, $SRMR = 0.04$). Internal consistency reliability was fair ($\alpha = 0.69$). Convergent validity was evidenced via significant correlations with measures of depression, anxiety, and mastery.

Conclusion: The results of the present study suggest that the 5-item AHI-Helplessness scale is a reliable and valid one-factor measure of helplessness for patients with SLE. Moreover, the results suggest that the 15-item AHI total score and 7-item AHI-Internality subscale should not be used in patients with SLE given the lack of structural validity.

Disclosure: S. Gholizadeh, None; D. R. Azizoddin, None; S. D. Mills, None; G. Z. Racaza, None; H. M. Kala'aukahi Potemra, None; D. J. Wallace, None; M. Weisman, None; P. M. Nicassio, None.

Abstract Number: 349

Improving the Performance of the Spanish Version of QOL-RA

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Measures and Measurements of Healthcare Quality Poster – ARHP

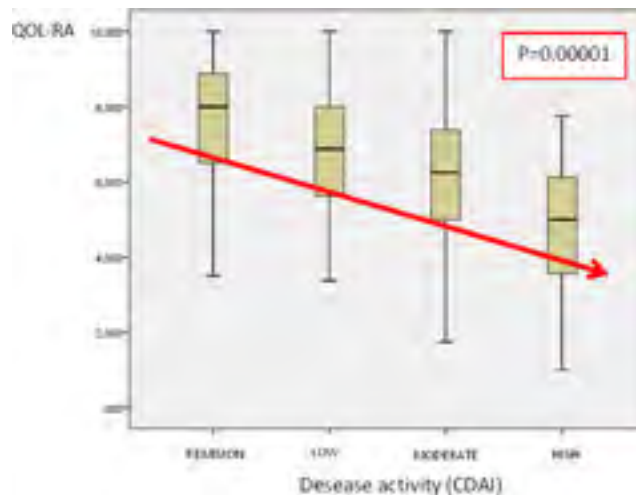
Session Type: ACR Poster Session A

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

Background/Purpose: We have recently validated the Quality of Life-Rheumatoid Arthritis Scale (QOL-RA). Redundancy between questions N° 3 and N° 6 was observed, and it was influenced by age and disease duration. For this reason, with the author's permission, we have changed these questions and developed a new version of Spanish QOL-RA. The aim of our study was to validate this Spanish version in patients with RA.

Methods: Across-sectional multicenter study was carried out. Patients ≥ 18 years old, with a diagnosis of RA according to ACR-EULAR 2010 criteria were included. Patients with difficulties in answering the questionnaire (illiterate, blind) and with decompensated comorbidities were excluded. Sociodemographic data, comorbidities, RA characteristics, disease activity current treatment were registered. Questionnaires were administered to assess quality of life by EQ-5D-3L and QOL-RA, functional capacity by HAQ-A and depression by PHQ-9. The time to complete and calculate both quality of life questionnaires was measured, and the difficulties that the patients presented to complete any item were recorded. The QOL-RA was re-administered in 20 patients to evaluate reproducibility. *Statistical analysis:* Student's T, ANOVA and χ^2 tests. Spearman correlation. Reliability by Cronbach's alpha. Reproducibility using ICC. QOL-RA linear tendency based on RA activity by multinomial logistic regression with completed factorial model. Multiple linear regression.

Results: 430 patients were included. 87.7% were females, with a median (m) age of 53.1 years (IQR 45-62) and m disease duration of 8.9 years (IQR 4-16). Disease activity by DAS28-ESR was m 2.9 (IQR 1.9-3.9). The median of QOL-RA was 6.6 (IQR 5.3-8) and it had a good correlation with EQ-5D-3L ($Rho: 0.6$), PHQ-9 ($Rho: -0.56$), HAQ-A ($Rho: -0.55$), CDAI ($Rho: -0.47$) and DAS28-ESR ($Rho: -0.4$). Worse QOL-RA was observed in current smokers (mean 6.1 ± 1.7 vs 6.6 ± 1.9 , $p = 0.016$), unemployed (mean 6.1 ± 1.8 vs 6.9 ± 1.8 , $p = 0.0001$), patients not doing physical activity (mean 6.3 ± 1.9 vs 7 ± 1.9 , $p = 0.0001$) and those with morning stiffness (mean 5.8 ± 1.9 vs 7.1 ± 1.7 , $p = 0.0001$). It showed very good reliability (0.97) and reproducibility (ICC = 0.96 IC 95% 0.90-0.99). Ceiling and floor effects were 2.8% and 0.7%, respectively. Only 0.9%



of the questionnaires presented at least one missing answer. There was no redundancy between questions. Patients with higher disease activity had a significant poorer quality of life. (Figure 1) In the multivariate analysis, using QOL-RA as dependent variable, adjusting by age, sex and disease duration, disability, disease activity, and the presence of depression were independently associated to worse quality of life.

Conclusion: This new version of QOL-RA demonstrated better construct validity, reproducibility and reliability compared to the original version and it was easy to complete and calculate.

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Abstract Number: 350

Clinical Correlates of Immune-Related Adverse Events for Patients with Melanoma Treated with Checkpoint Inhibitors and a Noted Significant Difference in Peripheral Lymphocyte Counts

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster I: Checkpoint Inhibitors, Retroperitoneal Fibrosis

Session Type: ACR Poster Session A

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

Background/Purpose: Checkpoint immunotherapy has become the standard of care in treating advanced melanoma. These medications have been associated with immune-related adverse events (irAEs). Accurate methods of predicting and managing irAEs are still lacking. Here, we aim to identify clinical correlates of irAEs from patients with melanoma previously treated with immunotherapy.

Methods: We retrospectively reviewed electronic medical records of patients with melanoma who were seen at The University of Chicago Medical Center between 1/2011-1/2017 and were treated with immune checkpoint inhibitors (ICIs). Other inclusion criteria included the following: ≥18 years old, ICI administered at least once, received systemic corticosteroids(CS). Patients' irAEs were graded based on the National Cancer Institute's Common Terminology Criteria for Adverse Events. Patients were excluded if they had low grade (1 or 2) irAEs and if systemic CS were used for reasons other than irAE management. Wilcoxon Mann-Whitney test and Chi-squared test of association were used to compare quantitative and categorical data (respectively) between patients with irAEs and patients without irAEs.

	Checkpoint inhibitor + irAE (22)	Checkpoint inhibitor, no irAE (87)	P value
Gender: female: Male	8 (40%): 12 (60%)	27 (46.25%): 43 (53.75%)	0.613 ^{ns}
Race			
White	18 (90%)	71 (80.75%)	
Hispanic	1 (5%)	0	
AA	1 (5%)	2 (2.5%)	0.199 ^{ns}
Other (All Asian, Pacific Islander)	0	3 (3.75%)	
Declined	0	4 (5%)	
Age at Melanoma dx: Age (Range, st dev)	58yo (20-75, 13.2)	58yo (17-91, 15.8)	0.815 ^{ns}
Smoking status			
Current	2 (9%)	5 (6.25%)	
Previous	7 (32%)	30 (37.5%)	0.888 ^{ns}
Never	11 (55%)	45 (56.25%)	
Pack-years (for those reported): Age (Range, st dev)	15.64pp (1-46, 21.8)	17.64pp (0-75-80, 17.8)	
Checkpoint inhibitor(s)			
PD-1/PD-1	10 (50%)	47 (59%)	
CTLA4	1 (11%)	8 (10%)	0.569 ^{ns}
Combination	7 (33%)	21 (24%)	
Other	0	4 (5%)	
Age at start of Checkpoint inhibitor: Age (Range, st dev)	58yo (30-86, 14.3)	60yo (19-94, 15.7)	0.456 ^{ns}
Lymphocyte abnormality			
Lymphopenia	10 (50%)	21 (24.35%)	0.022 ^{**}
abnormal absolute lymphocyte count on 2 measures in a row at least			
Lymphocytosis	2 (9%)	2 (2.5%)	
Normal	8 (40%)	57 (77.35%)	

^{ns} Fisher's Chi-squared test of association

^{**} Wilcoxon Mann-Whitney test

Results: Twenty patients with grade 3 or higher irAEs were identified and compared with 80 patients who received ICI therapy but did not have any irAEs. The irAEs were as follows: 4 transaminitis, 4 dermatitis, 3 arthritis, 3 colitis, 2 neurologic, 2 thyroiditis, 1 myocarditis, and 1 pneumonitis. Some patients had more than one high grade irAE with second irAE including iritis, Guillain-Barre syndrome, pancreatitis and adrenalin sufficiency (AI). From start of ICI, the average days to first irAE occurrence was 121 days (7-378 days). The average days to irAE after cessation of ICI was 61 days (0-375 days), excluding an outlier of a late AI at 1316 days. There was no statistically significant difference between irAE and non-irAE patients in terms of gender, race, age at melanoma diagnosis, age at ICI therapy, or type of ICI used (p values 0.615, 0.193, 0.315, 0.458 and 0.569, respectively). There was a statistically significant difference in peripheral absolute lymphocyte count (ALC) between the two groups; while 60% of patients with irAEs had ALC abnormalities (lymphopenia defined as ALC<900/uL, lymphocytosis>3300/uL), only 28.7% of the group without irAEs had any peripheral ALC abnormalities. The 3 irAE patients with eosinophilia (>600/uL) had dermatitis.

Conclusion: This cohort evaluated patients with Melanoma treated with ICIs and found no significant demographic differences between those who developed a high grade irAE compared with those who did not. There was a significant difference in ALC, with those patients who developed irAEs demonstrating an abnormal ALC. More research is needed to further validate and elucidate this observed association between peripherally lymphocyte count and development of irAEs.

Disclosure: P. Reid, None; T. Chongsuwat, None; A. Dua, None; J. Luke, None.

Abstract Number: 351

Rheumatic Immune-Related Adverse Events in Patients on ANTI-PD-1 Inhibitors: Fasciitis with Myositis Syndrome As a New Rheumatic Complication of Immunotherapy

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster I: Checkpoint Inhibitors, Retroperitoneal Fibrosis

Session Type: ACR Poster Session A

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

Background/Purpose: To evaluate the prevalence and type of rheumatic immune-related adverse events (irAEs) in patients receiving programmed cell death protein-1 (PD-1) inhibitors.

Methods: This is a single-center prospective observational study including all cancer patients receiving PD-1 inhibitors between January 2016 and January 2018. Patients who experienced new-onset rheumatic irAEs were referred to the department of rheumatology by oncologists or hematologists for standardized clinical evaluation and management. Patients

were remitted when they identified new clinically important symptoms during routine care or during a clinical trial. In general terms, only those with complications of moderate-severe intensity or unremitting were referred to us. Patients with mild and transient arthralgias that resolved with non-steroid anti-inflammatory drugs (NSAIDs) were not referred for evaluation (the incidence of arthralgia secondary to nivolumab in phase III trials ranges from 5 to 16%). The study only included cases in which there was a clear temporal relationship with the onset of treatment and they did not have any previous rheumatic disease that could explain the symptoms.

Results: During the period analyzed, we evaluated a total of 11 patients. No patient had pre-existing rheumatic or autoimmune disease. In this period, a total of 220 patients were treated with PD1 inhibitors in our center; therefore, the estimated minimum prevalence of rheumatic IRAEs related to these therapies in our population was 5%. The rheumatic IRAEs evaluated included 5 cases of oligo- or polyarthritis, 1 with a polymyalgia rheumatica-type syndrome, 2 cases of immunotherapy-induced sicca syndrome, 1 patient with a paraneoplastic acral vascular syndrome (the diagnosis was established after excluding other causes of blue digit syndrome) and 2 patients who presented symptomatic inflammatory myositis with fasciitis in lower extremities. These 2 patients developed abruptly the same clinical picture, characterized by symmetrical painful swelling of the lower limbs with a progressive induration and thickening of the skin and soft tissues. In both cases, the clinic was established acutely after the first doses of the anti-PD-1 immunotherapy. MRI in these patients demonstrated the presence of myositis and fasciitis involving the muscles of the thighs and legs. The temporal relationship and the rapid improvement of symptoms after withdrawal of the drug support a casual relationship, expanding the clinical spectrum of rheumatic IRAEs related with these agents (*fasciitis with myositis syndrome*). The median time to IRAE after anti-PD1 exposure was 8 weeks (range: 2–24). In 5 patients, immunotherapy was discontinued (due to the adverse effect in three and cancer progression in two). In general terms the symptoms resolved completely with symptomatic treatment. Disease-modifying antirheumatic drugs were needed for 2 patients.

Conclusion: Rheumatic IRAEs should be kept in mind during the follow-up and evaluation of patients treated with PD-1 inhibitors. The concomitant development of symptomatic inflammatory myositis with fasciitis in lower extremities appears to be a new adverse effect of anti-PD-1 immunotherapy.

Disclosure: F. J. Narváez, None; P. Juárez, None; J. Lluch, None; J. A. Narvaez, None; R. Palmero, None; X. Garcia del Muro, None; J. M. Nolla, None; E. Domingo-Domenech, None.

Abstract Number: 352

Polymyalgia Rheumatica-like Syndrome from Checkpoint Inhibitor Therapy: Case Series and Systematic Review of the Literature

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster I: Checkpoint Inhibitors, Retroperitoneal Fibrosis

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatic immune related adverse events (irAEs) from checkpoint inhibitor (ICI) therapy remain poorly understood. In our early experience with rheumatic irAEs we encountered patients presenting with polymyalgiarheumatica (PMR)-like clinical phenotypes. This entity has also been described in the literature. It is the purpose of this study to describe the cases of PMR-like syndrome secondary to ICI reported in the literature to date, and determine if they meet the 2012 EULAR/ACR criteria for PMR¹.

Methods: A systematic literature search was performed in PubMed andOvid Embase using the search terms: “polymyalgia rheumatica”[MESH] OR“polymyalgia rheumatic” AND “ immunotherapy” OR checkpoint inhibitor therapy”. We determined how many cases provided enough data to apply the EULAR/ACR criteria for PMR (age > 50, elevated ESR or CRP, and bilateral shoulder aching) and these cases were designated “A level”evidence. The remaining cases, with incomplete or insufficient data, were designated “B level” evidence.

Results: A total of 39 patients were included for analysis, including 6 cases from our center. Among these, 25 (64%) were designated A level. The remaining 14 (36%) were designated B level and thus censored from further evaluation. Within group A, 20 cases fulfilled complete EULAR/ACR criteria for a diagnosis of PMR. Three patients also met imaging

criteria. The main reason why patients did not meet criteria was because they had other joint involvement– most commonly knees, followed by elbows and hands. Two patients had low-positive rheumatoid factor. One case described a patient with RS3PE. In the whole group, the specific checkpoint inhibitor was reported in 24 cases. 7 were exposed to nivolumab, 4 to combination ipilimumab/nivolumab, 5 to pembrolizumab, 3 to ipilimumab and 5 to PD-1 or PD-L1 agents. Of note, 3 cases of giant cell arteritis have been described with ICI therapy: 2 in the setting of PMR and one isolated case.

Table. Cases from our irAE clinic

	sex	Tumor type	ICI	Age	Shoulder aching	Abnormal ESR/CRP	EMS > 45 min	Hip pain	Normal RF/ACPA	No other joints
1	M	RCC	Nivolumab	63	Y	N	Y	Y	Y	N
2	M	Melanoma	Ipi/nivo	69	Y	Y	Y	Y	Y	Y
3	M	Melanoma	Ipi/nivo	79	Y	Y	Y	Y	Y	Y
4	M	Melanoma	Pembro	57	Y	N	Y	Y	RF 35 IU/ml	N
5	M	Melanoma	Pembro	60	Y	Y	Y	Y	RF 45 IU/ml	N
6	M	Melanoma	Nivo	66	Y	Y	Y	Y	Y	N

Conclusion: In this combined analysis 36% of reported cases of PMR were based on incomplete reporting data making verification problematic. Of those with enough data for evaluation nearly 80% met current classification criteria for PMR. Among those with insufficient evidence atypical features (synovitis, positive serology) were present that may indicate an alternative inflammatory rheumatic manifestation of unclear nosology. Prospective registry-based studies with adequate assessment of data are urgently needed.

References : 1. Dasgupta B, et al. 2012 provisional classification criteria for polymyalgia rheumatic: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Ann Rheum Dis* 2012;71:484-492.

Disclosure: C. Calabrese, None; E. Kirchner, None; L. H. Calabrese, Bristol-Myers Squibb, 5, 8, Genentech, Inc., 5, 8.

Abstract Number: 353

Immune-Related Adverse Events Associated with Immunotherapy in Solid Organ Tumors. Study of 102 Cases from a Referral Single Center for Last 3 Years

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster I: Checkpoint Inhibitors, Retroperitoneal Fibrosis

Session Type: ACR Poster Session A

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

Background/Purpose: Immune checkpoint blockade therapy (ICTB) has shown remarkable benefit in different cancer types. Blockade of intrinsic down-regulators of immunity increases the activity of the immune system, which can lead to different immune-related adverse events. Our aim was to assess the immune-related adverse events in patients who received anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4), anti-programmed cell death 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1). Our aim was to assess the incidence, treatment and evolution of immune-related adverse events due to ICTB.

Methods: We set up an observational study of patients treated with Nivolumab and Pembrolizumab (anti-PD1), Atezolizumab (anti-PD-L1) and Ipilimumab (anti-CTLA-4) for solid organ tumors. All these patients were followed in a single reference University Hospital from March-2015 up to May-2018.

The main outcome was to determinate the incidence of immune-related adverse events of ICTB. The secondary objective was to assess the frequency and management of the rheumatological side effects.

Results: We studied 102 patients (63♂/39♀) with a mean age of 60.6±9.7 with lung (n=63), gastric (n=3), bladder (n=1), kidney (n=11), melanoma (n=21) and colon cancer (n=3). Only 7 patients had a previous diagnosis of an immune-mediated

disease: psoriasis (n=2), psoriatic arthritis (n=1), systemic lupus erythematosus (n=1), spondyloarthritis (n=1), rheumatoid arthritis (n=1) and skin lupus (n=1).

ICTB was performed as follows: pembrolizumab (n=35), nivolumab (n=52), atezolizumab (n=10) and ipilimumab (n=5). After a median of 5 [2.5-10.5] months since the ICTB onset, we observed 87 (85.3%) patients with different autoimmune adverse effects (n=95), summarized in **TABLE**. ICTB discontinuation was required in 39 patients. 36 patients received specific treatment (prednisone, antihistamine, levothyroxine and thiamazol), obtaining a good response in 31 cases (79.5%). ICTB was reintroduced in 28 patients (71.8%) after resolution of the adverse event, with an appropriate tolerance in all cases. Rheumatological side effects were observed in 11 patients (10.8%): inflammatory arthralgia (n=6), arthritis (n=4), and aortitis (n=1). 7 of them required a temporary withdrawal of the immunotherapy, 3 were treated with NSAIDs and other 4 with oral prednisone (one of them also needed intraarticular corticosteroids). From the 7 patients with previous diagnosis of an immune-mediated disease, only 1 patient with psoriasis suffered a worsening of skin symptoms and other with psoriasis arthritis had a monoarthritis episode.

Conclusion: In our study, the majority of autoimmune side effects due to ICBT were gastrointestinal, thyroiditis and cutaneous. The prevalence of rheumatological adverse effects was slightly higher than in pivotal studies. Most of them were with PD-1/PD-L1.

TABLE

Immune-Related Adverse Events	Anti CTLA-4 n=5	Anti PD-1 / PD-L1 n=97	TOTAL n=102
Gastrointestinal, n (%) (diarrhoea, colitis, mucositis)	1 (1.1)	38 (40)	39 (41.1)
Skin, n (%) (rash, erythema nodosum, psoriasis, vitiligo and alopecia)	1 (1.1)	12 (12.6)	13 (13.7)
Thyroid, n (%) (thyroiditis)	0 (0)	18 (18.9)	18 (18.9)
Articular, n (%) (arthralgia, arthritis)	0 (0)	10 (10.5)	10 (10.5)
Vasculitis, n (%) (aortitis)	0 (0)	1 (1.1)	1 (1.1)
LFTs alteration, n (%)	0 (0)	8 (8.4)	8 (8.4)
Nephritis, n (%)	0 (0)	6 (6.3)	6 (6.3)
TOTAL	2 (2.1)	93 (97.9)	95 (100)

+ LFT = liver function test.

Disclosure: J. L. Martín-Varillas, None; Í. González-Mazón, None; B. Atienza-Mateo, None; M. Delgado Ruiz, None; I. Bernat Piña, None; D. Prieto Peña, None; M. Calderón Goercke, None; L. Sánchez-Bilbao, None; E. Peña Sainz-Pardo, None; A. García Castaño, None; M. A. González-Gay, None; R. Blanco, None.

Abstract Number: 354

Rheumatic Complications of Immune Checkpoint Inhibitor Therapy: A Single Center Experience

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster I: Checkpoint Inhibitors, Retroperitoneal Fibrosis

Session Type: ACR Poster Session A

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Background/Purpose: Immune checkpoint inhibitors (ICIs) have led to improved outcomes in multiple cancers, but they are associated with immune-related adverse events (irAEs), including inflammatory arthritis. We report our single center experience with rheumatic irAEs.

Methods: Patients ≥18 years treated with an ICI at our institution from 2011-2018 and seen by rheumatology for evaluation of musculoskeletal symptoms following ICI were included. A rheumatologist evaluated all patients and confirmed the

diagnosis of irAE at the time of evaluation. Cases were reviewed by two rheumatologists to confirm the presence of a rheumatic irAE. Inflammatory arthritis was defined as joint pain with inflammatory features on history and physical exam without an alternative etiology. PMR was based on 2012 ACR/EULAR criteria. Patients with and without pre-existing rheumatic conditions were analyzed.

Results: Twenty-nine patients were evaluated by rheumatology for suspected rheumatic irAEs. Eighteen had confirmed inflammatory arthritis (n=12) or PMR (n=6) (**Table 1**). Six had inflammatory joint pain but no evidence of synovitis by exam, imaging or synovial fluid. Five had an alternative etiology identified (gout, fracture, infectious arthritis). Patients with pre-existing rheumatic conditions (n=6) (**Table2**) developed a flare of their underlying disease a median of 12 weeks following ICI (range 1-43 weeks). The mean initial prednisone dose was 25mg/day (range15-40mg), with a mean duration of use of 37.4 weeks (range 17-57 weeks). One patient with PMR/RA required tocilizumab; one patient with PsA required MTX. Two patients discontinued ICI.

Ten patients without a pre-existing rheumatic condition developed inflammatory arthritis and two developed PMR a median of 36 weeks following ICI (range 9-160 weeks, p=0.0485 compared to patients with pre-existing conditions). Patients with PMR were treated with prednisone. Patients with inflammatory arthritis were treated with systemic or IA steroids and in 8 cases with DMARDs, including HCQ or SSZ. The mean initial prednisone dose was 31.1mg/day (range 6-60mg), with a mean duration of use of 26.6 weeks(range 3-82 weeks). ICIs were discontinued in 5 patients.

Conclusion: We report 18 patients with inflammatory arthritis or PMR after ICI treatment. Our work highlights the differences between patients with and without pre-existing rheumatic conditions and describes the successful use of non-biologic DMARDs as treatment. Further studies are needed to determine the incidence of rheumaticirAEs, to improve classification and to identify the most effective treatment.

Patient Characteristics		N=18 (100%)
Sex		
Male		12 (66%)
Female		7 (39%)
Age (years) (median (IQR))		63 (48-80)
Pre-existing disease		
Autoimmune		16 (88%)
Type 1 Diabetes		2 (11%)
Endometriosis		1 (5%)
History of rheumatic disease		6 (33%)
Type of ICI when irAE developed		
PD-1 inhibitors		15 (83%)
Combination PD-1+CTLA-4		3 (17%)
Best response		
CR		9 (50%)
PR		17 (94%)
SD		5 (28%)
PD		2 (11%)
Number of patients with additional irAE		10 (56%)
Lymphopenia		2
Hypothyroidism		2
Pneumonitis		1
Necrosis		1
Colitis (Pseudomembranous)		1
Hepatitis		1

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Table 1. Characteristics of 18 patients who developed rheumatic irAEs following planned checkpoint inhibitor treatment

Rheumatologic irAE	Imaging or Synovial Fluid	Auto- antibodies	Treatment of irAE	Other irAE	irAE Response
Patients With Pre-Existing Rheumatic Conditions					
PMR/seronegative RA	Shoulder and hip x-rays OA	RF, CCP (-)	Prednisone	Colitis	Improved ICI continued
PMR/seronegative RA	None	ANA (-) RF, CCP (-)	Prednisone, tocilizumab Infliximab for colitis	Colitis	Partially improved Switch from spilimimab to pembrolizumab.
PMR	None	RF, CCP (-)	Prednisone	None	Improved Switch from nivolumab to pembrolizumab
PMR	None	Not checked	Prednisone	None	Improved ICI discontinued
Psoriatic Arthritis	None	Not checked	Prednisone, MTX	None	Improved ICI discontinued
Seronegative RA	None	ANA 1:160 RF, CCP (-)	Prednisone	None	Improved ICI continued
Patients Without Pre-Existing Rheumatic Conditions					
Inflammatory arthritis	Synovial fluid knee: 8,854 WBCs, 52% neutrophils; 11,006 WBCs, 6% neutrophils Knee x-rays without erosions	ANA 1:40 RF 35, CCP (-)	IA steroid injection, SSZ	Hypothyroidism	Ongoing ICI continued
Inflammatory arthritis	None	ANA 1:40 RF, CCP (-)	Prednisone, SSZ, HCQ	Hypothyroidism	Improved ICI discontinued
Inflammatory arthritis	Synovial fluid knee: 10,093 WBCs, 96% neutrophils	ANA 1:40 RF, CCP (-)	Prednisone, SSZ, HCQ Infliximab for colitis	Colitis	Improved ICI discontinued
Inflammatory arthritis/synovitis and fasciitis	MRI forearm peri- muscular edema in the fascial planes MRI femur signal intensity in the superficial and deep fascia	ANA (-) RF, CCP (-)	Prednisone, HCQ	Pneumonitis Colitis	Improved ICI continued initially, but then discontinued due to other irAEs
Inflammatory arthritis	Hand x-rays without erosions	ANA 1:40 RF, CCP (-)	Prednisone, HCQ	Colitis	Improved ICI continued with dose reduction
Inflammatory arthritis	Synovial fluid knee: 4,454 WBCs, 70% neutrophils Musculoskeletal ultrasound joint effusion, synovial thickening, positive color power doppler	ANA negative	Prednisone, IA steroid injection	Hepatitis	Improved ICI discontinued
Inflammatory arthritis	MRI wrist enhancing erosions, tenosynovitis	RF, CCP (-)	HCQ	None	Improved After ICI completed
Inflammatory arthritis	Synovial fluid knee: 14,940 WBCs, 99% neutrophils Knee x-rays without erosions	ANA 1:40 RF (-)	Prednisone	Hypothyroidism Myopathy	Improved After ICI completed
Inflammatory arthritis	Knee x-rays OA	ANA 1:160 RF, CCP (-)	Prednisone, IA steroids, HCQ	Colitis	Partially improved ICI discontinued
Inflammatory arthritis	Hand x-rays OA	ANA 1:160 RF, CCP (-)	Prednisone, IA steroids, SSZ, HCQ	Pneumonitis	Improved After ICI completed
PMR	Hip x-rays OA	RF, CCP (-)	Prednisone	None	Improved ICI temporarily held
PMR	None	ANA (-) RF (-)	Prednisone	Hypothyroidism	Improved ICI continued

Table 2. Description of rheumatic immune related adverse events of patients with and without pre-existing rheumatic disease

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Association of HLA-DRB1 Shared Epitope Alleles with Immune Checkpoint Inhibitor-Induced Inflammatory Arthritis

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Session Information

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Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster I: Checkpoint Inhibitors, Retroperitoneal Fibrosis

Session Type: ACR Poster Session A

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

Background/Purpose: Immune checkpoint inhibitors (ICI), an important type of cancer therapy, can cause adverse events through immune activation. Inflammatory arthritis (IA) due to ICI treatment is increasingly appreciated as prevalent and morbid, but genetic risk factors are not understood. In this pilot study, we aimed to evaluate the frequency of HLA class I and II alleles associated with traditional forms of inflammatory arthritis in a group of patients with ICI-induced IA as compared to population controls.

Methods: High resolution HLA typing was performed on 27 patients with ICI-induced IA and 726 controls who were prospective bone marrow donors at our institution. Genotyping at the shared epitope (SE) locus (HLA-DRB1) was also performed on 220 rheumatoid arthritis (RA) cases. Allele-positivity rates were compared using Fisher's exact test. The frequency of having at least one SE allele was compared between ICI-induced IA patients and both population and RA controls.

Results: The average age was 60.2 (SD 12.1) years and 12 patients (44.4%) were female. Patients were treated with ICIs targeting CTLA-4, PD-1, and/or PD-L1. Melanoma was the most common tumor type (N=9), followed by non-small cell lung cancer (N=6). Other tumor types were renal cell carcinoma, basal cell carcinoma, squamous cell carcinoma, Merkel cell carcinoma, mycosis fungoides, colon, endometrial, esophageal, and breast cancers. Of the included patients, 26 were of European descent and one was African-American. In the 26 patients of European descent, 16 (61.5%) had at least one SE allele, significantly different from the European descent bone marrow donor controls where 299 (41.2%) had at least one SE allele (OR=2.3, p=0.04). Of individual class I or II alleles, only the allele-positivity rate of DRB1*04:05 was statistically different between groups. There were trends toward higher allele-positivity rates for HLA A*03:01, B*52:01, and C*12:02 in ICI-induced IA (Table 1). The ICI-induced IA population did not differ significantly from RA cases of European descent in frequency of having at least one SE allele, but they were more likely to be negative for rheumatoid factor and anti-cyclic citrullinated peptide antibody (Table 2).

Conclusion: Patients with ICI-induced IA who were of European descent were more likely to have at least one shared epitope allele compared to bone marrow donor controls. Further statistically powered studies are warranted to establish whether immunogenetic framework modifies the risk of developing IA from ICI therapy.

Table 1: Comparison of allele-positivity rates for select HLA class I and II alleles and prevalence of having at least one SE allele in ICI-induced IA vs healthy control patients of European descent

HLA allele/s	Odds Ratio (95% CI) ICI-induced IA vs. controls	p-value*
A*03:01	2.2 (0.9, 5.1)	0.07
B*08:01	0.9 (0.3, 2.6)	0.56
B*15:01	2.2 (0.7, 5.9)	0.12
B*27:05	0.6 (0.0, 4.0)	1.00
B*52:01	5.0 (0.5, 24.1)	0.08
C*06:02	0.9 (0.3, 2.7)	1.00
C*12:02	5.4 (0.6, 26.8)	0.07
DQB1*03:01	0.4 (0.1, 1.1)	0.06
DQB1*03:02	1.4 (0.5, 3.8)	0.44
DRB1*03:01	1.1 (0.4, 2.9)	0.81
DRB1*04:05	8.6 (1.7, 43.4)	0.04
At least 1 SE allele	2.3 (1.0, 5.1)	0.04

* p-values < 0.05 significant (Bold)

Table 2: Frequency of shared epitope and autoantibodies in ICI-induced IA compared to ethnically matched RA patients

	ICI-induced IA (European descent) N= 26	RA (European descent) N= 220	p-value*
Positive for SE (at least 1 allele)	16 (61.5%)	145 (65.9%)	0.66
Number of shared epitope alleles	Two alleles: 2 (7.7%) One alleles: 14 (53.8%) Zero alleles: 10 (38.5%)	Two alleles: 52 (23.6%) One alleles: 93 (42.3%) Zero alleles: 75 (34%)	0.15
CCP positive	2 (7.7%)	142 (64.6%)	<0.01
RF positive	2 (7.7%)	122/215 (56.7%)	<0.01
RF and CCP double positive	0 (0%)	106/215 (49.3%)	<0.01

* Fisher's exact test was used. P-values <0.05 significant (bold). CCP: anti-cyclic citrullinated peptide antibodies. RF: rheumatoid factor.

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Abstract Number: 356

Immune Related Adverse Events from Immune Checkpoint Inhibitors: A Retrospective Analysis from 2004-2017 at the University of North Carolina at Chapel Hill

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Session Information

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Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster I: Checkpoint Inhibitors, Retroperitoneal Fibrosis

Session Type: ACR Poster Session A

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Background/Purpose: Immune checkpoint inhibitors (ICI) targeting CTLA-4, such as ipilimumab (anti-CTLA4), or PD-1/PD-L1, such as nivolumab and pembrolizumab are increasingly utilized in a wide variety of malignancies including melanoma, head and neck tumors, and small and non-small cell lung cancers. By upregulating the immune system to prevent evasion and promote destruction of cancer cells, these ICI may cause immune related adverse events (irAEs) which mimic autoimmune diseases such as inflammatory arthritis (RA, SLE, PMR), inflammatory bowel diseases (UC, Crohn's), and psoriasis. We sought to gain a better understanding of the range of irAEs that occur from ICI use at our institution including the type, severity, timing from onset of therapy, management, and ultimately how these impact patient outcomes. Better understanding of the irAEs provides a unique opportunity to explore and understand the pathogenesis of autoimmune diseases.

Methods: We identified patients who have received ipilimumab, nivolumab and/or pembrolizumab at UNC between January 2004 through July 9, 2017. We investigated the number of patients started on each immunotherapy and for which indication. Through chart review, we further investigated each type and severity of irAEs, their timing, management, duration, management of cancer therapy and cancer response.

Results: Between January 2004 and July 2017, 116 patients received ipilimumab (most frequently for melanoma in 91.3% of patients), 231 patients received pembrolizumab, and 444 patients received nivolumab. Immune related adverse events occurred in 72.4% of patients who received ipilimumab (52.6% of these patients also received nivolumab either in combination or monotherapy). The most frequent irAE was rash (40.5%), colitis (32.8%), thyroid disease (23.3%), musculoskeletal (MSK) (13.8%), hepatitis (12%) and hypophysitis/adrenal insufficiency (12%). The MSK irAEs were mostly asymmetric medium-large joint arthritis, clinically similar to a seronegative spondyloarthritis variant (68.8%) or proximal myalgias similar to PMR. Treatment of the MSK irAEs consisted of NSAIDs, mild to moderate doses of prednisone, intra-articular steroids, colchicine, hydroxychloroquine, apremilast (in a patient with psoriasis), and one patient eventually required knee replacement. Biologics were more frequently utilized in the treatment of severe grade 3-4 colitis with infliximab 5 mg/kg or vedolizumab. Other irAEs less frequently seen were pneumonitis (4.3%), ophthalmologic (4.3%), severe refractory peripheral neuropathy (4.3%), renal (2.3%), pancreatitis (1.7%), and appendicitis (0.9%).

Conclusion: Our findings among patients treated with ipilimumab and nivolumab were in line with prior studies evaluating the irAE secondary to ICIs with skin and GI manifestations being most frequent. In addition, most patients with MSK

irAEs had asymmetric medium-large joint involvement mimicking a seronegative spondyloarthropathy. We are currently evaluating other subsets including patients who received nivolumab monotherapy or pembrolizumab.

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Abstract Number: 357

Musculoskeletal Immune-Related Adverse Events with Use of Checkpoint Inhibitors in Malignancy: Experience in Sydney, Australia

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster I: Checkpoint Inhibitors, Retroperitoneal Fibrosis

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

Background/Purpose: The strategy of using monoclonal antibodies to inhibit checkpoints on T cells, and enhance T-cell activity against cancer cells has significantly improved the survival of patients with advanced malignancies, particularly using inhibitors of the checkpoints PD-1 and CTLA-4. Treatment can be complicated by inflammatory and immune-related adverse events (irAE). This large case series reports on eighteen patients' treated with checkpoint inhibitors at three sites in Sydney, Australia and the rheumatic irAE noted. The purpose of the case series is to add the Australian experience into the mix of this emerging clinical entity.

Methods: This study included 18 patients with advanced cancer (15 melanoma, 2 non-small cell lung cancer, 1 renal cell carcinoma) treated at Melanoma Institute Australia, Westmead Hospital or Royal North Shore Hospital, who were referred for rheumatological evaluation from 2013 to 2016. Data was collected retrospectively by medical chart review and examined for the nature of symptoms, time to onset of symptoms, duration of immunotherapy prior to onset of rheumatic irAE, management strategies and treatment outcomes.

Results: The patient characteristics, immunotherapy regimes and presentations are summarised in Table 1 below. Joints affected were mainly large joints associated with tenosynovitis and peri-articular symptoms. Time to onset of symptoms was variable. There were no sex differences. All of these patients had a negative rheumatoid factor (RF) and anti-cyclic citrullinated protein (anti-CCP) antibody. Most patients responded to NSAIDs or low dose prednisone and were able to remain on immunotherapy for their malignancy.

Conclusion: Immunotherapy has an important role in the treatment of advanced malignancies. In our study the rheumatic irAEs appear, in the majority, to be easily managed and patients can remain on treatment with their check point inhibitor. The underlying cause and pathogenesis of these adverse effects remains unknown. Interestingly, the grading systems or guidelines for classification of rheumatic irAEs are much less established than those for gastrointestinal or endocrine manifestations. There is limited experience in the management of rheumatic irAEs and no consensus guidelines on how best to manage these rheumatic irAEs. Progress is required on how to best classify, evaluate, stratify and manage these conditions.

Table 1: Patient characteristics, immunotherapy and presentation

Factor	
Age, median (range), years	61.5 (42 - 83)
Male, n (%)	12 (61.7)
Drug Therapy, n (%)	
Anti-PD-1	9 (50)
Ipilimumab (anti-CTLA-4)	2 (11)
Anti-PD-1 + ipilimumab	7 (39)
Type of Advanced Cancer, n (%)	
Melanoma	15 (83)
Non-small cell lung cancer	2 (11)
Renal cell carcinoma	1 (6)
Time to onset of rheumatological symptoms, median (range), months	4 (0.23-24)
Presentation of rheumatological irAE n (%)*	
Polyarthopathy, small joints	6 (33)

Table . (Cont'd)

Factor	
Polyarthropathy, large joints	12 (66)
Monoarthropathy	1 (5)
SLE-like	2 (11)
Sicca symptoms	1 (5)
Polymyalgia	4 (22)
Radiologic evidence of iRAE n (%) **	
Tenosynovitis	4 (22)
Arthropathy	2 (11)
Synovitis	2 (11)
Joint effusion	2 (11)
Nil	1 (5)

* Some patients presented with more than 1 iRAE

** Some patients had more than 1 radiological finding, some patients had no radiology completed

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Abstract Number: 358

Immunophenotypic Analysis of T Cells from Leukemia Patients with Immune Checkpoint Inhibitor-Associated Respiratory Complications

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Session Information

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Background/Purpose: Immune checkpoint inhibitor (ICI)-based combinations are showing encouraging results in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) treatment; however, ICIs can cause immune-related adverse events, inflammation of one or few organs. Ten percent of AML or MDS patients receiving an ICI develop respiratory complications, one of life-threatening immune related adverse events (irAEs) induced by ICIs. Understanding the mechanism by which pneumonitis occurs is important in risk stratification and early detection, however, this information remains elusive.

Methods: We performed flow cytometry and T cell receptor (TCR) analysis of cells isolated from bronchial alveolar lavage (BAL) fluid and matched blood from seven AML or MDS patients, who received ICI therapy, developed respiratory symptoms, and underwent a standard-of-care bronchoscopy (hereafter, ICI group). In parallel, we collected 22 BAL and matched blood samples from AML or MDS patients who had never been received an ICI. Six of these patients were determined to have documented bacterial or fungal pneumonia, based on the independent review of two independent pulmonologists and an infectious disease specialist, and served as controls.

Results: The ICI group patients developed respiratory symptoms 42.6 ± 62.6 days (mean \pm SD) after the first infusion of an ICI. TCR analysis showed that BAL T cells from the ICI group were clonally expanded compared to control BAL T cells. Immuno phenotyping revealed that BAL CD8⁺ T cells in the ICI group were expanded (ICI vs. control, % within live lymphocytes, mean \pm SD, 24.1 ± 18.3 vs. 5.8 ± 1.2 , $P = 0.02$). These cells were most likely effector memory or terminally differentiated effector memory cells. Compared to BAL CD4⁺ T cells in controls, Th1.17 (CXCR3^{hi} CCR6^{hi}) CD4⁺ T cells, known to be implicated in autoimmune diseases, were expanded in the ICI group (% within live CD4⁺ T cells, 49.4 ± 19.5 vs. 16.8 ± 11.0 , $P = 0.03$). IL-17 producing CD4⁺ T cells were also expanded in BAL in the ICI group (% within non-regulatory CD4⁺ T cells, 15.4 ± 4.8 vs. 7.6 ± 2.8 , $P = 0.03$). Although statistical significance was not reached, Th17 cell-related cytokines were detected in BAL fluid in ICI group at a frequency similar to, or slightly greater than controls. Immunophenotypic characteristics of T cells in blood were comparable between the ICI group and control.

Conclusion: These results suggest that Th1.17 CD4⁺ T cells may play a central role in ICI-associated pneumonitis. Understanding the biology of the Th1.17 CD4⁺ T cell will provide us therapeutic targets and reliable biomarkers of ICI-associated pneumonitis. Furthermore, characterization of Th1.17 CD4⁺ T cells may offer better insights into pneumonitis secondary to the autoimmune diseases.

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Abstract Number: 359

Characterization of Lymphoid Cells in Synovial Fluid from Cancer Patients with Immunotherapy-Induced Arthritis

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Session Information

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Background/Purpose: Checkpoint inhibitors (ICIs) are revolutionizing cancer treatment; however, ICI therapy is associated with immune-related adverse events (irAEs). irAEs can be life-threatening and/or severely impair quality of life, necessitating early termination of ICI treatment. Two percent of cancer patients who receive ICI treatment develop arthritis as an irAE (arthritis-irAE). Prompt diagnosis and early intervention are critical in the management of irAE; however, detailed characterization of immune cells in the inflamed tissues, the first step in elucidating the mechanisms of irAEs, is still lacking. Here, we characterize synovial immune cells isolated from patients with arthritis-irAE.

Methods: We analyzed synovial fluid from five patients with arthritis-irAE. As a control, we also analyzed one anonymous pediatric tonsil. We stained lymphoid immune cells with lineage-specific markers and measured effector cytokines in the CD4⁺ T cell populations.

Results: Arthritis developed an average of 270±375 days after the first ICI infusion. Two of the five patients developed arthritis after completion of ICI treatment. Arthritis was treated with systemic prednisone and/or local injection. Three patients achieved complete resolution of arthritis ("steroid responders") while two patients had suboptimal response and needed additional treatment ("steroid non-responders"). The most abundant lymphoid immune cells were CD4⁺ T cells (53.1±13.2% of live immune cells), followed by CD8⁺ T cells, NK cells, $\gamma\delta$ T cells, NK T cells, and B cells. Most CD8⁺ T cells were effector memory or terminally differentiated effector memory cells. All CD4⁺ T cell subsets were identified in the synovial fluid, including regulatory T cells (Treg), naïve T cells, Th1 (CXCR3^{hi} CCR6^{hi}), Th1.17 (CXCR3^{hi} CCR6^{hi}), Th17 (CXCR3^{lo} CCR6^{hi}), and follicular helper T cells (CXCR5⁺). Effector CD4⁺ T cell cytokines, including interferon gamma, IL-4, IL-17, and IL-21, were produced by both Tregs and non-Tregs. Interestingly, IL-17⁺ non-Treg cells were expanded in steroid non-responders compared to steroid responders, indicating that Th17 cells might play a critical role in persistent arthritis-irAE.

Conclusion: Our results suggest that arthritis-irAE can develop at any time during or after the ICI treatment. The observed expansion of IL-17⁺ non-Treg cells in synovial fluid from steroid non-responders suggests that Th17 cells might play a key role in the pathogenesis of arthritis-irAE. Understanding of Th17 CD4⁺ cell biology will provide therapeutic targets and reliable biomarkers for arthritis-irAEs.

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Sarcoidosis Induced By Immune Check Point Inhibitors

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Session Information

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Background/Purpose: Immune check point inhibitors (ICIs) targeting programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) have demonstrated improved survival for multiple cancers but have been associated with immune related adverse events (IRAEs). Granulomatosis have been rarely reported.

Methods: We described patients with granulomatous /sarcoid-like reactions among those receiving anti-PD-1(L1) antibody included in the prospective registry REISAMIC ("Registry of Severe Adverse Events of Immunomodulating Monoclonal Antibodies in Oncology") between June 2014 and December 2017.

Results: Out of 657 patients under ICIs, 7 cases (1%) developed sarcoid like reactions. ICI regimens included pembrolizumab (4 patients), nivolumab (3 patients) including one in association with ipilimumab, and one combined with an antiangiogenic tyrosine kinase inhibitor. Five patients had melanoma and 2 patients had renal cell carcinoma. Five patients had partial or complete response under immunotherapy while 2 patients had disease progression. Granulomatous reaction occurred at a median time of 4 months after beginning the ICI. None patient had preexisting sarcoidosis or autoimmune disease. Granulomatosis involved lymph nodes in 7 cases (including lung in 6 cases), skin in 3 cases, and uveitis in 1 case. Patients were often asymptomatic (mediastinal and hilar lymphadenopathy discovered on radiological evaluation). Three patients developed granulomatous lesions on scars. These clinical presentations were highly suggestive of sarcoidosis diagnosis, confirmed by histology (skin biopsy, pulmonary biopsy in 1 case each, ultra sounded guided endobrachial fine needle aspiration in 3 cases, mediastinoscopy in 1 case). All biopsies were performed in order to avoid cancer progression. No other alternative diagnosis was identified. Bronchoalveolar lavage revealed lymphocytic alveolitis in 2 patients. Pulmonary function tests, cardiac evaluation, and calcemia were normal. Angiotensin converting enzyme levels were in the normal range for 6 out of 6 patients. No patient needed corticosteroid treatment while 1 patient required hydroxychloroquine or cutaneous disease. Despite these IRAEs, immunotherapy was continued for 3 patients. Prognosis was good and lymphadenopathy and pulmonary infiltrate and skin granulomas improved in most cases particularly when ICI was stopped.

Conclusion: ICI induced sarcoidosis reactions are rare and most often benign.

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Abstract Number: 361

Risk Factors of Immune-Related Adverse Events in Patients Treated with Anti-Programmed Cell Death 1 Antibody Pembrolizumab

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster I: Checkpoint Inhibitors, Retroperitoneal Fibrosis

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

Background/Purpose: Immune checkpoint inhibitors have been established as a novel standard treatment for various types of malignancies. However, these new class of drugs have led to increased immune-related adverse events (irAEs) including rheumatic manifestations.

The aim of this study was to determine the risk factors of irAEs in patients treated with anti-programmed death 1 antibody pembrolizumab.

Methods: A retrospective medical record review was performed to identify all patients who received at least one dose of pembrolizumab at Samsung Medical Center, Seoul, Korea between June 2015 and December 2017. Three hundred and ninety-one patients were identified. Multivariate logistic regression model was used to identify risk factors of irAEs.

Results: The median number of cycles of pembrolizumab was two (range, 1-36). The primary malignancies included in the study were lung cancer (n=211, 54.0%), melanoma (n=74, 18.9%), lymphoma (n=53, 13.6%) and others (n=53, 13.6%). Sixty-seven (17.1%) patients experienced clinically significant irAEs; most commonly dermatologic disorders (n=39, 10.0%), pneumonitis (n=11, 2.8%), musculoskeletal disorders (n=10, 2.6%), followed by endocrine disorders (n=7, 1.8%). Fourteen patients (3.6%) experienced serious irAEs (\geq grade 3). Most common serious irAEs were pneumonitis (n=9, 2.3%). There were 4 deaths associated with irAEs, all of which were due to pneumonitis. In univariate logistic regression analysis, body mass index, number of cycles and cumulative dose of pembrolizumab, and baseline neutrophil-lymphocyte ratio were the risk factors of irAEs in pembrolizumab-treated patients. Multivariate logistic regression analysis was performed with variables that were significant in univariate analysis. Higher body mass index and multiple cycles of pembrolizumab were associated with higher risk of irAEs (body mass index: odds ratio [OR] 1.080, 95% confidence interval [95% CI] 1.005-1.161, $P = 0.035$; pembrolizumab cycle: OR 1.153, 95% CI 1.087-1.224, $P < 0.001$). Low neutrophil-leukocyte ratio tended to increase irAE risk, but not statistically significant in multivariate analysis (OR 0.953, 95% CI 0.902-1.007, $P = 0.089$).

Conclusion: To our knowledge, this is the first study to explore the risk factor for irAE in patients undergoing modern cancer immunotherapy. Our study demonstrate that BMI is associated with an increased risk of irAEs in patients treated with pembrolizumab. Also, the number of cycles of pembrolizumab was a risk factor for the development of irAEs. Further studies to investigate the potential mechanisms by which obesity raises irAEs are needed.

Disclosure: I. Y. Kim, None; Y. Eun, None; H. Kim, None; J. K. Ahn, None; E. J. Park, None; C. H. Jeon, None; J. Kim, None; H. S. Cha, None; E. M. Koh, None; J. Lee, None.

Abstract Number: 362

Immune Check Point Inhibitors, Auto-Antibodies, and Immune Adverse Reactions

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Session Information

Session Date: Sunday, October 21, 2018

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Background/Purpose: Immune checkpoint inhibitors (ICI) targeting cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) and its ligand PD-L1 have had substantial success in treating a variety of cancers. However, immune-related adverse events (irAEs) do occur and can cause significant morbidity and mortality. Although autoimmune (AI) processes share features of irAEs, little research has been done regarding the association between AI serologies and the risk of irAEs. The objective of our review is to determine whether positive AI antibodies (with or without presence of rheumatologic disease) were associated with irAEs and to characterize the nature, severity, and consequences of these irAEs.

Methods: We retrospectively evaluated charts of patients (pts) treated with ICIs at the Ohio State University Comprehensive Cancer Center between 2009 and 2017 under an IRB approved protocol. Those who had known rheumatic antibody testing associated with common rheumatic pathologies before, during or after treatment with ICI were identified. We collected information on pt demographics, clinical and treatment history, and test results to identify exacerbations of existing rheumatologic disease and irAE events. See table 1.

Results: A total of 15 patients were included in this study and received the CTLA-4 inhibitor ipilimumab (Ipi) or anti-PD-1 treatment with nivolumab (nivo) or pembrolizumab (see Table 1). Many were positive for more than one auto-Ab during their treatment course. Twelve pts (80%) had an irAE after a median of 3 cycles and 58% of those patients had documented evidence of positive antibodies prior to the onset of toxicity. Treatment included NSAIDs, steroids, treatment delay, and treatment cessation. Only 4 patients had pre-existing rheumatic diseases; several developed AI irAEs (often multiple) including: arthralgias, hypophysitis, Hashimoto's, and colitis. The pre-existing rheumatic disease patients with melanoma on Ipi had flares of their disease requiring steroids and/or cessation of therapy. A total of 9 patients had Ab drawn before treatment with ICI: 4 positive, and 5 negative. One patient with SCC and pre-existing Lupus suffered respiratory failure and died. None of 5 patients with negative ab had known rheum disease and 4 out of these 5 patients did not have complications. See table 1.

Conclusion: This study adds to the current knowledge about pts with pre-existing rheumatic disease who are treated with ICI. In our study all 4 pts with prior rheum disease developed complications related to treatment.. The role of routine testing for rheumatologic antibodies in unselected patients remains unclear, however close surveillance of patients with pre-existing disease is certainly warranted. Whether a specific profile or pattern of autoantibodies may be useful in the diagnosis and evaluation of suspected irAE remains an area of active investigation.

Table 1. Baseline characteristics (n = 15)

Characteristics	N
Median age	57
Male	9
Had pre-existing autoimmune disease	4
Cancer type	
Melanoma	9
Non Small Cell Lung Cancer	3
Pancreatic	1
Small Cell Lung Cancer	1
Squamous Cell Carcinoma	1
Immunotherapy	
Ipilimumab	9
Nivolumab	3
Pembrolizumab	3
Antibodies	
ANA	8
Anti-cardiolipin	5
RF	2
RNP	1
SSA-A	3
SSA-B	3
Anti-TPO	3
irAEs	
Flare of existing disease	3
Arthralgia	3
Colitis	2
Hashimoto's	2
Hypophysitis	2
Other	4
Grades	
1	7
2	5
3	3
4	1
Treatment & Outcomes	
No treatment	7
NSAIDs	2
Steroids	5
Levothyroxine supplementation	2
Treatment delay	3
Treatment discontinuation	3
Mortality	5

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Abstract Number: 363

Immune-Related Adverse Events in Cancer Immunotherapy: How Often Do We See Them?

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Session Information**Session Date:** Sunday, October 21, 2018**Session Title:** Miscellaneous Rheumatic and Inflammatory Diseases Poster I: Checkpoint Inhibitors, Retroperitoneal Fibrosis**Session Type:** ACR Poster Session A**Session Time:** 9:00AM-11:00AM

Background/Purpose: Over the years there has been a huge effort to change the traditional way to treat cancer, that was previously based on chemotherapy and/or radiotherapy. Enhancing the immune system with immunotherapy, instead of suppressing it, has achieved impressive results in some tumors, mainly metastatic melanoma, and nowadays several other tumors are being treated with it. Along with better results regarding tumor control, several immune-mediated adverse events have emerged

Methods: We included retrospectively all patients diagnosed with cancer that received immunotherapy (check point inhibitors) as part of their treatment between January 2014 and June 2018. Immunotherapy includes: monoclonal antibody to CTLA4 ipilimumab, IgG4 programmed death 1 (PD-1) inhibitor antibody nivolumab and pembrolizumab. There were no patients receiving IgG4 programmed death 1 ligand (PDL-1) inhibitor antibody atezolizumab, avelumab or durvalumab. We reported all immune-mediated adverse event (IMAE), time to first IMAE, treatment received, response to treatment, discontinuation of immunotherapy and deaths.

Results: A total of 27 patients, (54.5% males) were included. Type of tumor, name of check point inhibitor received, type of IMAE, time to first IMAE, treatment and response are summarized in table 1. We observed a total of 11 (40.7%, CI 95% 23.2-60.9) IMAE. Incidence density rate was 120.9 (100 person-year). The most frequent were hematologic and dermatologic adverse events. Most of the IMAE were mild to moderate, 27.3% required treatment, with 66% of response. Among the rheumatologic related IMAE, there were only arthritis and Sicca syndrome, the last one being the most frequent and generally mild, with no need for treatment. 2 patients presented with arthritis, one of them required methotrexate because of persistent arthritis. No specific autoantibodies were found. Only 1 out of 5 patients with rheumatic IMAE was sent to a rheumatologist for treatment, all others were managed by oncologists. No patients were evaluated by a rheumatologist before started immunotherapy.

Conclusion: immune-mediated adverse events related to check point's inhibitors are a new entity and oncologist and rheumatologist must be aware of them. Rheumatic IMAE had a frequency of 27.3%, with Sicca syndrome and seronegative arthritis as the only manifestations in our cohort.

TABLE 1. General Characteristics

	IMAE
Age, mean (SD)	65.8 (10.66)
Male, n (%)	6 (54.5)
Type of tumor, n (%)	
- Melanoma	4 (14.8)
- Lung	20 (74.1)
- Larynx	1 (3.7)
- Kidney	1 (3.7)
- NHL (non-Hodgkin lymphoma)	1 (3.7)
Check Point Inhibitor, n (%)	
- Ipilimumab	1 (3.7)
- Nivolumab	14 (51.8)
- Ipilimumab + Nivolumab	6 (22.2)
- Pembrolizumab	6 (22.2)
Type of IMAE, n (%)	
- Thyroiditis	1 (9.1)
- Pneumonitis	1 (9.1)
- Hematologic	4 (36.4)
- Dermatologic	5 (45.4)
- Arthritis	2 (18.2)
- Sicca Syndrome	3 (27.3)
- Pancreatitis	1 (9.1)
- Hepatitis	1 (9.1)
Time to onset to the 1 st IMAE (years)	0.17
Incidence density rate, 100 person-year	120.9 (CI 95% 69.2-180.2)
% discontinuation of immunotherapy	27.3
Treatment required, n (%)	3 (27.3)
Response to treatment, n (%)	2 (66.7)
Deaths, n (%)	3 (27.3)

TABLE 2. Rheumatologic IMAE

	N (%)	Pre-existent autoimmune disease	Fulfill criteria for specific rheumatic disease	Evaluation by rheumatologist n (%)	Use of steroids n (%)	Use of synthetic DMARD n (%)	Use of biologic DMARD n (%)
Arthritis/arthritis	2 (40)	0	0	1 (50)	1 (50)	1 (50)	0
Sicca Syndrome	3 (60)	0	0	0	0	0	0

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Abstract Number: 364

Elevated sCD40L As a Predictive Biomarker of Immune-Related Adverse Events in Patients Receiving Immune Checkpoint Inhibitors

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Session Information

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Background/Purpose: The clinical use of immune checkpoint inhibitors (ICI) has led to outstanding clinical outcomes in previously refractory cancers, but ICI have also been associated with off-target side effects collectively known as immune related adverse events (irAE). Any organ system can be affected by these events during or after cessation of these therapies. Although management of these adverse events with immunosuppression is usually successful, our understanding of the underlying pathophysiology is incomplete. Furthermore, our ability to predict which patients will develop irAE is limited. The purpose of this study was to identify predictive biomarkers of irAE in cancer patients initiating ICI.

Methods: Patients with advanced cancer scheduled to begin treatment with ICI were recruited from a tertiary care oncology centre. A detailed review of their electronic medical record was performed to record demographics, disease details, and treatment history (including drug names, start and stop dates, last dose, disease response). Serum was collected prior to initiating ICI therapy. Anti-nuclear antibodies (ANA) were detected using a common platform in the Mitogen Diagnostics Lab (Calgary, AB) and cytokines/chemokines were measured using a Human Cytokine/Chemokine 65-Plex panel (Eve Technologies, Calgary, Alberta). Subjects were followed prospectively and any irAE, defined by Common Terminology Criteria for Adverse Events (CTCAE), were recorded. Associations between clinical and serological biomarkers, and irAE were analyzed using *t* tests and ANOVA.

Results: A total of 26 patients with advanced cancer were enrolled in this study. The mean age was 60 years old and 9/26 (35%) were female. Cancer types included melanoma (n = 13), renal carcinoma (n = 7), non-small cell carcinoma (n = 2), ovarian cancer (n = 2), Merkel cell carcinoma (n = 1), anal carcinoma (n = 1). All patients received therapeutic blockade of either PD-1 (n = 22) or PD-L1 (n = 4). irAEs occurred in 15/26 (58%) of the patients as follows: dermatitis (n = 1), colitis (n = 3), hepatitis (n = 2), hypothyroidism (n = 6), pneumonitis (n = 2), and type 1 diabetes mellitus (n = 1). The distribution of irAE grades were as follows (CTCAE grade 1 irAEs were excluded): CTCAE grade 2 (n = 9) and CTCAE grade ≥ 3 (n = 6). While males developed more grade 2 irAEs (n = 8), females developed more severe grade 3 irAEs (n = 4). Tumor type and the presence of ANA were not found to predict the development of irAE. On the other hand, sCD40L (p = 0.0413), PDGF-A (p = 0.0215) and PDGF-B (p = 0.007) were significantly higher prior to initiating ICI in patients who developed irAE compared to those who did not.

Conclusion: These findings identify sCD40L, PDGF-A and PDGF-B as potential predictive biomarkers for the development of irAE in patients receiving ICI treatment for advanced cancer. Interestingly, although it has been shown that sCD40L is elevated in advanced cancers such as non-small cell lung cancer and also in various autoimmune disease, these data are the first to implicate it as a predictive biomarker for irAE development. The mechanisms by which these biomarkers participate in the onset of irAE needs to be explored.

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Abstract Number: 365

Monoclonal Gammopathy in Rheumatic Diseases

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Session Information

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Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster I: Checkpoint Inhibitors, Retroperitoneal Fibrosis

Session Type: ACR Poster Session A

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

Background/Purpose: To analyze the clinical spectrum, laboratory characteristics, and outcomes of monoclonal gammopathy (MG) in patients with rheumatic diseases.

Methods: Screening for the presence of MG was performed in 872 in patients with rheumatic diseases from January 2010 to July 2017. A total of 41 patients were enrolled. Their clinical and biological features in addition to outcomes were described. For each patient with primary Sjögren syndrome (pSS), 2 age- and sex-matched pSS patients without MG were selected as controls. Risk factors for the presence of MG and malignant hematological neoplasias were assessed.

Results: MG was observed in patients with SS, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, primary biliary cirrhosis, polymyositis, hypomyopathic dermatomyositis, psoriatic arthritis, ANCA-associated vasculitis, polyarteritis nodosa, and polymyalgia rheumatic, with SS the most frequent type. Serum M protein was detected in 37 patients. The monoclonal bands identified in serum were 16 IgG (5 κ , 11 λ), 11 IgA (6 κ , 5 λ), 6 IgM (5 κ , 1 λ), and 4 free λ chains. M components were observed in urine in the other 4 patients. High ESR, albumin/globulin inversion, rheumatoid factor positivity, hypergammaglobulinemia, and hypocomplementemia were common features, presented in more than half of the 41 patients. Patients with pSS, when complicated with MG, showed a higher rate of abnormal urine NAG (71.4 vs 15.8%, $P = 0.025$), higher levels of ESR [55.0 (53.5) mm/h vs 21.0 (31.8) mm/h, $P = 0.001$], ESSDAI [26.0 (25.0) vs 12.0 (9.0), $P = 0.006$], and ClinESSDAI scores [24.0 (25.0) vs 10.5 (10.0), $P = 0.011$]. Multivariate analysis revealed that the disease activity, assessed by either ESSDAI [adjusted OR 1.127 (95%CI 1.015–1.251), $P = 0.025$] or ClinESSDAI [adjusted OR 1.121 (95%CI 1.011–1.242), $P = 0.030$], was the only independent risk factor for the presence of MG. During the follow-up, 2 patients had transient serum M protein, 2 had isotype switch, 1 progressed to multiple myeloma (MM), and another 2 experienced renal injuries attributed by monoclonal or polyclonal plasma cell interstitial infiltration. Seven (17.1%) of the 41 MG patients presented hematological neoplasias, 4 with MM, 2 with smoldering multiple myeloma, and 1 with B cell lymphoma of mucosa-associated lymphoid tissue (MALT) type. The presence of light-chain MG was associated with the development of MM [OR 17.5 (95%CI 1.551–197.435), $P = 0.041$], but not with an increased risk of lymphoma or SMM.

Conclusion: MG was observed in patients with various rheumatic disorders, with SS being the most common type. The presence of MG might be associated with higher disease activity. The development of hematological neoplasias including MM and lymphoma was seen in this setting. Therefore, we recommend the screening for MG and close monitoring for potential malignant transformation in patients with rheumatic diseases as needed.

Disclosure: Y. Yang, None; Y. Jia, None; S. Chen, None; Y. Su, None; Z. G. Li, None.

Abstract Number: 366

Infectious Complications of Immunosuppressive Therapy in Patients with Common Variable Immunodeficiency (CVID) and Inflammatory Arthritis

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Background/Purpose: Common variable immunodeficiency (CVID) is one of the most common symptomatic primary immunodeficiency syndrome with an incidence of ~1 in 25,000 people. CVID is a heterogeneous collection of syndromes, which are all characterized by impaired B-cell differentiation, resulting in defective immunoglobulin production and an increased susceptibility to infection. Autoimmune conditions are common in CVID, and the prevalence of autoimmune-associated inflammatory arthritis in patients with CVID is estimated to be around 10%. This study aims to further delineate the features of autoimmune inflammatory arthritis in patients with CVID.

Methods: Using ICD-9 and ICD-10 diagnostic codes, we identified patients with CVID at the University of Virginia from 2007 to 2018. We then reviewed individual charts to identify the patients who met the Revised European Society for Immunodeficiency (ESID) criteria for CVID. From this cohort of patients, we identified those who met the criteria for any one among various autoimmune inflammatory arthropathies. We reviewed the charts of the patients who met all these criteria for details on the treatment and outcomes of both autoimmune inflammatory arthritis and CVID.

Results: A total of 95 patients met the strict criteria for CVID. Of these, six patients (6.31%) were found to have autoimmune inflammatory arthritis; four had rheumatoid arthritis (RA) and two had psoriatic arthritis (PsA). The male-to-female ratio was 1:1. All the patients were non-Hispanic and Caucasian. All the patients were non-Hispanic and Caucasian. The median time between the diagnoses of autoimmune arthritis (median age = 44.5 years) and CVID (median age = 52.5 years) was 129 months (10.7 years). Four patients (66.6%) were initially diagnosed with autoimmune arthritis and had rheumatoid arthritis. Of these, three patients were on methotrexate and two patients were managed with anti-TNF and abatacept. Five patients (83.3 %) received intravenous immunoglobulin (IVIG). Of all of the patients diagnosed with CVID and autoimmune arthritis, none developed a major infection (requiring a lengthy course of antibiotics or hospitalization) while on treatment. Two patients (33.3%) developed other autoimmune diseases, namely, autoimmune thrombocytopenia (ITP) and autoimmune thyroiditis.

Conclusion: Autoimmune inflammatory arthritis was present in 6.31% of the patients in our CVID cohort. Despite the majority of patients being on immunosuppressants and IVIG, none of them developed a major infection during the study. To our knowledge, this study is the first to address the risk of infection in patients with CVID who received immunosuppressants and IVIG. However, the conclusions were limited by the low sample size. Therefore, there is a need for a prospective longitudinal cohort study. Increased vigilance for autoimmune arthritis complications is important as survival outcomes are worse in CVID patients with non-infectious complications. Further evaluation of these patients to understand the mechanism underlying immune dysregulation is essential, as this may promote targeted therapies and improve clinical outcomes.

Disclosure: F. Alduraibi, None; M. Lawrence, None; L. Borish, None; A. Carlson, None.

Abstract Number: 367

Incidence of Inflammatory Bowel Disease (IBD) Among Patients (Pts) with Other Chronic Inflammatory Diseases (CID) Treated with Interleukin-17a (IL-17a) or Phosphodiesterase 4 (PDE4) Inhibitors

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Background/Purpose: IBD is often associated with other CID, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and psoriasis (PsO). Newer biologic agents such as IL-17a inhibitors and small molecule inhibitors targeting PDE4 have been shown to be useful to treat PsA and PsO with both, and AS with the former. However, real-world evidence of IBD co-occurrence in pts with CID treated with IL-17a/PDE4 inhibitors is scarce. To compare the incidence of IBD (i.e., Crohn's disease and ulcerative colitis) between pts with CID not treated with a biologic agent and those treated with IL-17a/PDE4 inhibitors.

Methods: Adults with ≥ 2 claims with a diagnosis of either RA, PsA, AS, or PsO and ≥ 12 months of continuous health plan enrollment pre- (baseline period) and post-index date (random date among CID claims) were selected from the MarketScan® Research Database (1/2010-7/2017). Pts with cancer treated with rituximab or ofatumumab, with a transplant, or with ≥ 2 baseline claims with a diagnosis of IBD were excluded. The 1-year and 2-year incidence of IBD (defined as ≥ 2 IBD claims) was evaluated post-index among pts with no baseline claim for biologics and pts treated with IL-17a/PDE4 inhibitors during the baseline period. Comparison of IBD incidence between the two cohorts was done using a logistic regression model adjusting for baseline characteristics (including type of CID).

Results: In total, 424,767 pts were not treated with biologics (mean age: 54.4 years; 63.0% female) and 2,489 were treated with IL-17a/PDE4 inhibitors (mean age: 50.3 years; 54.6% female). The 1-year incidence was 0.7% in pts treated with IL-17a/PDE4 inhibitors and 0.5% in pts not treated with biologics (unadjusted odds ratio [OR]=1.54, P=0.0680). Among pts with ≥ 2 years post-index (nobiologics: n=208,853; IL-17a/PDE4-4: n=362), the 2-year incidence was 1.7% in pts treated with IL-17a/PDE4 inhibitors and 0.8% in pts not treated with biologics (unadjusted OR=2.16, P=0.0625). After adjustment, pts treated with IL-17a/PDE4 inhibitors were more likely to develop IBD than pts not treated with biologics at both 1 year (adjusted OR=1.77, P=0.0187) and 2 years (adjusted OR=2.29, P=0.0477). Similar trends were found when excluding pts with RA only (1-year incidence: adjusted OR=1.80, p=0.0161; 2-year incidence: adjusted OR=2.32, p=0.0438).

Conclusion: Higher IBD incidence was found in CID pts treated with IL-17a/PDE4 inhibitors compared to those not treated with biologics.

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Abstract Number: 368

Synovial Analysis Using Leukocyte Esterase Reagent Strips

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster I: Checkpoint Inhibitors, Retroperitoneal Fibrosis

Session Type: ACR Poster Session A

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

Background/Purpose: The analysis of synovial fluid (SF) is an important tool to study joint diseases. SF is classified into non-inflammatory, inflammatory and septic according to white blood cell (WBC) count. This classification is essential to start the diagnostic process, and to determine whether a rheumatologist evaluation is required. When SF is removed, the WBC decreases with time; an inflammatory liquid could become a false non-inflammatory one in hours. Reagent strip testing of urine is a validated tool to diagnose urinary tract infection, via the detection of leukocyte esterase activity. It has been used to analyze other biological fluids occasionally. SF test immediately performed after an arthrocentesis using reagent strips could have potential benefits as a screening tool.

Methods: Prospective study. We analyzed SF samples collected successively from patients in a tertiary university Hospital (November 2015 to April 2018). All samples were tested within 1 hour after their collection. We analyzed: Visual appearance, WBC (measured by manual leukocyte method), synovial glucose and total protein. Leukocyte esterase was measured by reagent strip test. It was recorded semiquantitatively as a number of plus signs (negative, 1+, 2+ or 3+) using standard color chart found on the container's label. The cut-off for the WBC by manual leukocyte counting over than 2000 cells/mm was used to differentiate between inflammatory and non-inflammatory specimens. We decided to classify as inflammatory SF the ones with 1+ or more in the leukocyte esterase pad. We compared the WBC (reference standard diagnostic test) with the presence of leukocyte esterase using the leukocyte esterase reagent.

Results: 303 joint fluid samples were analyzed. According to manual leukocyte counting 147 (48.5%) were non-inflammatory and 156 (51.5%) inflammatory. Of the inflammatory fluids: 144 (92.3%) were positive according to leukocyte esterase reagent. Of the mechanical fluids: 95 (65.5%) were negative according to leukocyte esterase reagent. The sensitivity and specificity of leukocyte esterase reagent was 92.3% and 64.6% respectively. The PPV was 73.5% and NPV was 88.8%. The 12 false-negative results (negative by leukocyte esterase reagent but more than 2 000 leukocytes/mm³)

showed a predominance of mononuclear cells (62.2%), the median WBC count was 4017.7/mm³ and median polymorphonuclear cells percentage was 33.5%, all cultures were negatives. For inflammatory fluids: semi-quantitative results (negative, 1+, 2+ and 3+) were significantly different regarding the mean WBC, mononuclear cells, polymorphonuclear cells count and glucose. We found 20 hemorrhagic SF; the presence of erythrocytes did not alter the results.

Conclusion: Our results demonstrate that leukocyte esterase reagent strips are a rapid, cheap, and sensitive tool to identify inflammatory SF. Leukocyte esterase reagent strips had an excellent sensitivity but a poor specificity, so they could be used as a screening tool in primary care practice or in rural or poor areas. A positive result indicates an inflammatory process, so the patient should be referred to a rheumatologist.

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Abstract Number: 369

Association of Retroperitoneal Fibrosis with Malignancy and the Pathologic Features of Malignancy with Retroperitoneal Fibrosis

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster I: Checkpoint Inhibitors, Retroperitoneal Fibrosis

Session Type: ACR Poster Session A

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

Background/Purpose: Retroperitoneal fibrosis (RPF) is a periaortic sclerotic disease that encases adjacent structures, particularly the ureters. Because it is unclear whether RPF is associated with malignancy, we examined standardized incidence ratios (SIRs) of cancers in patients with RPF compared with age- and sex-matched general population. Subsequently, pathological differences between malignancy with RPF and malignancy without RPF were investigated.

Methods: Medical records of 111 patients diagnosed as having RPF by computed tomography, positron emission tomography (PET), and/or histological evaluation were reviewed. Forty one cases of cancers, which were confirmed by biopsies, were identified in 35 patients with RPF. Cancer incidence rates were calculated and compared with that observed in the Korean general population, computing the standardized incidence ratios (SIRs), which were then stratified according to RPF-cancer intervals. Cancer specimens with RPF (n=3) and cancer specimens without RPF (n=15), which were controls for age, sex, and cancer stage, were examined for the expression of interleukin (IL)-4, IL-10, PD-1, PD-L1, and IgG4/IgG by immunohistochemistry (IHC).

Results: The mean \pm SD age at RPF diagnosis was 59.2 \pm 15.0 years, and 69.4% of the patients were male. Ninety two cases (82.9%) showed peri-aortitis, and 65 cases (58.6%) presented with hydronephrosis. The cancer SIR (95% confidence intervals) in patients with RPF relative to age- and sex-matched individuals in the general population was 3.18 (2.23-4.41) [2.65 (1.70 - 3.94) in men; 5.34 (2.76 - 9.32) in women]. The most frequent cancer was unspecified urinary organ cancers with SIR of 733 (238 - 1711). SIRs of multiple myeloma [27.6 (3.34 - 99.6)], renal cell cancers [9.53, (1.15-34.4)] and adenocarcinoma of unknown primary cancers [16.9, (2.05 - 61.1)] were also significantly higher than in the general population. When stratified by RPF-cancer intervals, SIR was 10.4 (6.59 - 15.60) within 1 year of RPF diagnosis, while no significant increase in SIR was found out of 1 year around RPF. IHC analysis showed that the expressions of IL-4 and IL-10 in cancer tissues with RPF were higher than those in cancer tissues without RPF. However, there are no differences in the expression of PD-1, PD-L1 and IgG4/IgG between cancer tissues with RPF and those without RPF.

Conclusion: RPF was strongly associated with cancers within 1 year of RPF diagnosis. Immune environment of cancer tissues with RPF is different from that without RPF. That may contribute to the occurrence of RPF.

Disclosure: S. J. Lee, None; E. J. Nam, None; Y. W. Song, Astellas Pharma, Inc., 9; Y. M. Kang, None.

Rituximab in Idiopathic Retroperitoneal Fibrosis

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster I: Checkpoint Inhibitors, Retroperitoneal Fibrosis

Session Type: ACR Poster Session A

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

Background/Purpose: Retroperitoneal fibrosis (RPF) is a rare disease characterized by the proliferation of fibrous tissue in the retroperitoneum, most commonly surrounding the aorta from the renal vessels to the branching of the iliac arteries. RPF has a number of etiologies, which include idiopathic, IgG4-related, infectious, malignant, and drug-induced. However, the majority of cases are of either idiopathic or IgG4-related disease. Recent studies on IgG4-related disease have shown rituximab to possibly be an effective treatment. However, the current first-line treatment for idiopathic RPF (iRPF) is glucocorticoid therapy. Relapse rates vary widely in the literature after discontinuation of treatment, and DMARDs remain poorly studied. We sought to evaluate the efficacy of rituximab in idiopathic RPF by quantifying changes in iRPF diameter on imaging pre- and post-rituximab therapy in ten iRPF patients as well as response by lab parameters.

Methods: This study was approved by the ethics review board at the University of British Columbia. All except one patient had histopathologic proof of their idiopathic RPF diagnosis. All patients had clinical and imaging features consistent with the diagnosis. All patients were previously treated with rituximab (1000mg) in two doses approximately 2 weeks apart. Pre- and post-therapy contrast enhanced cross-sectional abdomen and pelvis imaging were compared, of which 17 were CTs and one was an MRI. In all patients, the thickest portion of the peri-aortic disease was measured in the axial plane. The presence of acute and/or long standing unilateral or bilateral back pressure related renal findings were also documented (e.g. hydronephrosis, presence of stents, and renal atrophy). Details of clinical visits including patient demographics, symptoms, biopsies and laboratory evaluations were also collected pre- and post-therapy. Statistical analysis was performed using a Student's t-test. A probability of $p < 0.05$ was considered statistically significant.

Results: A comparison of pre and post-rituximab imaging studies were available in nine patients and revealed a statistically significant decrease in iRPF diameter following treatment with rituximab. The RPF diameter around the aorta before and after therapy decreased from a mean of 16.4 ± 4.9 cm to 10.8 ± 6.5 cm, respectively ($p=0.016$). The craniocaudal iRPF mean length decreased from 110.1 ± 42.6 to 94.0 ± 47.3 ($p=0.027$). The GFR increased from 62.1 ± 13.1 to 64.8 ± 15.6 , the creatinine decreased from $108.9 \mu\text{mol/L} \pm 17.1$ to 105.4 ± 20.2 , and the CRP decreased from $15.7 \text{ mg/dl} \pm 16.4$ to 4.3 ± 5.2 when comparing mean values before to after therapy, respectively, but non-significantly.

Conclusion: There were statistically significant improvements in iRPF diameter following treatment with rituximab. Rituximab requires further study to establish its role in treating idiopathic RPF.

Disclosure: V. Boyeva, None; H. Alabsi, None; M. Seidman, None; R. Paterson, None; J. Kur, None; S. Chang, None; L. Chen, None; M. Carruthers, None.

Therapeutic Efficacy and Safety of Igaratimod in Treating Mild IgG4-Related Diseases

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster I: Checkpoint Inhibitors, Retroperitoneal Fibrosis

Session Type: ACR Poster Session A

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

Background/Purpose: To evaluate the therapeutic efficacy and safety of Iguratimod in the treatment of mild IgG4 related disease (IgG4-RD).

Methods: Thirty patients with newly diagnosed mild IgG4-RD were enrolled. One initial dose of diprospan, intramuscular injection, and Iguratimod, 25 mg, twice daily, at 0, 12 and 24 weeks, patients were followed up. Follow up indexes including physician global assessment (PGA), IgG4-RD responder index (IgG4-RD RI), serology and imaging, plasma cytokines and adverse drug effect. Flow cytometry technology was performed for the detection of T, B-cell subsets and plasma cells before and after treatment in patients.

Results: The ages of thirty-four patients with newly diagnosed mild IgG4-RD were 50.83 ± 10.24 years old, and disease duration was 31.5 (8-66) months. The ratio of male to female was 1:1. The IgG4-RD RI of patients assessed at 0 weeks was 10.47 ± 3.98 . There was a significant decrease of IgG4-RD RI in patients following up at 12 weeks and 24 weeks, which was 3.60 ± 2.44 , 3.13 ± 1.71 , $P < 0.0001$. Serum IgG and IgG4 levels at baseline were 22.16 ± 9.54 g/L and 12250(5568-15625) mg/L, respectively. The IgG level at week 12 and week 24 was 15.42 ± 6.15 g/L and 15.43 ± 5.93 g/L respectively, and the IgG4 level was 4725 (2738-8748) mg/L and 6020(2613-11450) mg/L, which showed significantly reduction of serum IgG and IgG4, P values were both < 0.0001 respectively. After treatment, CD3+CD8+ T cells, plasmablast/plasma cells (surface markers as CD19+CD24-CD38hi, CD19+CD27hiCD38hi, CD19+IgD-CD38hi), and CD19+IgD-CD38-CD27+ memory B cells all decreased significantly. The percentage of CD19+IgD+CD38+/- naïve B cells increased after treatment. there were no significance of CD4+CXCR5+ ICOS+ and CD4+CXCR5+PD-1+ TFH, CD19+ total B cells, CD19+CD24hiCD38hi regulatory B cells, CD138+CD38+ plasma cells, CD4+IFN- γ + Th1, CD4+IL17-A+ classical Th17 cells, CD4+ IL-17A+IFN- γ + Th1-like Th17 cells before and after treatment with Iguratimod. Of 30 patients, 23(76.7%) patients had complete remission of clinical symptoms, 3(10.0%) patients had partial remission, and 4 (13.3%) patients had no response to Iguratimod treatment. According to adverse drug reaction, 3 had oral ulcers, two had stomach discomfort, 1 had mild hair loss, and others were well tolerated and had no significant adverse drug reaction.

Conclusion: Iguratimod is effective for the treatment of mild IgG4-RD, it can improve the clinical symptoms of patients, reduce the serum IgG and IgG4 levels, and can also reduce the peripheral blood CD3+CD8+ T, especially plasmablasts/plasma cells, memory B cells, and up-regulate naïve B cells. Besides, Iguratimod can also reduce the plasma IFN- γ levels. So we recommend that it can be used as a first-line treatment for some patients with mild IgG4-RD.

Disclosure: W. Zhang, None; P. Zhang, None.

Abstract Number: 372

Arterial Involvement in Erdheim-Chester Disease: A Retrospective Cohort Study

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Session Information

Session Date: Sunday, October 21, 2018

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Session Type: ACR Poster Session A

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

Background/Purpose: Erdheim-Chester disease (ECD) is a rare histiocytosis of the "L" (Langerhans) group with multisystem involvement that can affect the large and medium sized arteries mimicking vasculitis. Aortic involvement is common but the frequency and outcome of aortic branch vessel abnormalities are less well described.

Methods: Patients diagnosed with ECD from January 1, 1998 to July 31, 2016 were retrospectively identified. Images containing information of arterial involvement within six months of diagnosis were considered baseline and compared to last follow-up studies. Two physicians independently reviewed the studies to evaluate for presence of abnormalities

attributable to ECD. Age and sex adjusted logistic regression models were used to examine associations between patient characteristics and vessel involvement at baseline.

Results: Among a cohort of 64 patients with ECD, 63 had baseline imaging of vascular structures. ECD involvement of at least one segment of the aorta was observed in 56%. Abnormalities were also observed in aortic arch branches (26%), visceral branch arteries (40%), iliofemoral arteries (31%), coronary (5%) and pulmonary (3%) arteries. Perinephric fibrosis was strongly associated with the identification of abnormalities in the thoracic aorta [OR 4.92 (1.54, 15.75); $p=0.007$], abdominal aorta [OR 7.57 (2.28, 25.07); $p=0.001$] and visceral branch arteries [OR 6.05 (1.52, 24.03); $p=0.01$] but not pelvic/lower extremity arteries.

A total of 47 patients had follow-up imaging of arterial structures. The majority of arterial segments affected at baseline did not have significant radiographic change during the follow-up evaluation. Partial response was observed in 11% of patients with baseline abnormalities seen in the infra-renal abdominal aorta and 6% of patients with baseline aortic arch, descending thoracic aorta, and supra-renal abdominal aorta involvement, respectively. The remainder of arterial segments had partial response detected at a frequency of less than 5%. Complete normalization of arterial abnormalities at follow-up was only observed in 9% or less of arterial segments involved at baseline. Development of arterial involvement after diagnosis in patients with normal baseline arteries was similarly infrequent but occurred most often in the pulmonary arteries (11%), celiac artery (9%), right iliac (7%), left iliac (7%) and right femoral (5%). Eight patients required intervention with arterial endovascular stenting or bypass. At last follow-up 12 (19%) patients were deceased. Of the 9 patients for which cause of death was known, only 3 patients died from cardiovascular causes.

Conclusion: Aortic and aortic branch vessel abnormalities are frequently observed in patients with ECD and are often asymptomatic. Partial and/or complete resolution of arterial findings is uncommon.

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Abstract Number: 373

The Effect of an Intensive Controlled 6-Month Exercise Program with Subsequent 6-Month Follow-up Period in Patients with Idiopathic Inflammatory Myopathies – Preliminary Data

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster I: Clinical Features and Disease Course

Session Type: ACR Poster Session A

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

Background/Purpose: Muscle inflammation and weakness, subsequent atrophy and permanent muscle damage in idiopathic inflammatory myopathies (IIM) lead to impaired function, reduced muscle strength, endurance and aerobic capacity, decreasing quality of life. Data on the effectiveness of non-pharmacological care in IIM are limited due to heterogeneity of studied interventions/outcomes. The aim of our study was to minimize the limitations of available studies and to determine the effect of an intensive exercise program on muscle strength and endurance and the quality of life in cohorts with a substantial number of IIM patients.

Methods: All patients were non-selectively consecutively recruited into intervention (IG) and control (CG) group and they had impaired skeletal muscle strength. They fulfilled the Bohan and Peter 1975 diagnostic criteria. Patients from both groups received educational material for home exercises, but only the IG underwent a six-month intensive ADL (activities of daily living) and muscle strength exercise program with a subsequent six-month follow-up period. All patients were evaluated by a physician and physiotherapist blinded to intervention at 0, 3, 6 and 12 months. Patients also filled out

patient reported outcomes/questionnaires and provided blood for routine laboratory analysis and biobanking. Data analysis was performed between groups and within the group.

Results: In total 27 patients were included in the IG and 23 patients in the CG. Compared to the observed statistically significant deterioration in the CG over the period of 0-6 months, we found a statistically significant improvement in IG in objectively assessed muscle strength and endurance as well as in subjectively assessed functional abilities (HAQ) and depression (BDI-II). During the follow-up period, there was a significant deterioration or stagnation of the achieved results in the IG. However, improved functional abilities during the intervention period persisted in the IG even in the follow-up period. Only numerical improvements in the IG compared to numerical deterioration in CG, that did not achieve statistical significance, during the intervention period, were observed in some subjectively assessed patient reported outcomes assessing quality of life and fatigue.

Conclusion: Our program led to a significant improvement in the observed parameters that was clinically significant in a substantial proportion of patients (in the IG) and prevention of the expected worsening in muscle strength and endurance (observed in the CG).

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Parameter (unit)	Intervention group Mean \pm SEM	Control group Mean \pm SEM	Intra-group analysis (Friedman+Dunn)		Inter-group analysis (2WA)
			Intervention gr.	Control group	
MMT8	m0: 54.7 \pm 2.6 m3: 60.7 \pm 2.4 m6: 69.1 \pm 1.9 m12: 64.0 \pm 2.5	m0: 63.6 \pm 2.0 m3: 57.9 \pm 1.8 m6: 54.2 \pm 1.9 m12: 56.5 \pm 2.2	m0-3: p<0.01 m3-6: p<0.0001 m0-6: p<0.0001 m6-12: p<0.05	m0-3: p<0.05 m3-6: NS m0-6: p<0.0001 m6-12: NS	p<0.0001
FI-2 (%)	m0: 30.0 \pm 4.4 m3: 46.9 \pm 4.7 m6: 70.6 \pm 4.9 m12: 58.4 \pm 5.8	m0: 38.3 \pm 5.3 m3: 29.6 \pm 4.6 m6: 26.1 \pm 4.1 m12: 25.7 \pm 3.6	m0-3: p<0.01 m3-6: p<0.0001 m0-6: p<0.0001 m6-12: p<0.05	m0-3: NS m3-6: NS m0-6: p<0.01 m6-12: NS	p<0.0001
HAQ	m0: 0.9 \pm 0.2 m3: 0.7 \pm 0.1 m6: 0.6 \pm 0.1 m12: 0.8 \pm 0.2	m0: 1.3 \pm 0.2 m3: 1.4 \pm 0.2 m6: 1.4 \pm 0.2 m12: 1.5 \pm 0.2	m0-3: NS m3-6: NS m0-6: p<0.01 m6-12: p<0.05	m0-3: NS m3-6: NS m0-6: NS m6-12: NS	p=0.0002
BDI-II	m0: 11.9 \pm 2.1 m3: 10.7 \pm 1.7 m6: 8.9 \pm 1.5 m12: 10.5 \pm 2.0	m0: 13.0 \pm 1.4 m3: 14.3 \pm 1.7 m6: 15.7 \pm 1.1 m12: 16.0 \pm 2.0	m0-3: NS m3-6: NS m0-6: p<0.05 m6-12: NS	m0-3: NS m3-6: NS m0-6: NS m6-12: NS	p=0.0025

Acronyms: SEM, standard error of the mean; Friedman, Friedman's test; Dunn, Dunn's post hoc test; 2WA, two way ANOVA, MMT-8, Manual muscle test-8; FI-2, Functional index-2; HAQ, Health assessment questionnaire; BDI-II, Beck's depression inventory-II; m0, month 0 (= at the baseline); m3, month 3 (= in the middle of the intervention period); m6, month 6 (= at the end of intervention); m12, month 12 (= at the end of a 6-month follow up period); p, p-value; NS, not significant

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Abstract Number: 374

Nailfold Microangiopathy in Dermatomyositis and Systemic Sclerosis: What Is Different?

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster I: Clinical Features and Disease Course

Session Type: ACR Poster Session A

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

Background/Purpose: Nailfold videocapillaroscopy (NVC) is a non invasive and useful method to assess peripheral microvascular status and evaluate patients with connective tissue diseases (1). Microvascular involvement was clearly

described in systemic sclerosis (SSc) (2-4), but may be detected also in patients with dermatomyositis (DM) (5,6). Only few studies described the main NVC changes over time in this last clinical condition (5,6). The aim of this retrospective study was to compare the NVC findings between DM and SSc at first NVC, and to identify NVC changes in patients with DM during a 3 year follow-up.

Methods: Twenty-four DM (mean age 54 ± 15 SD years; disease duration 4 ± 5 years; 4 males and 20 females) and 24 SSc patients, matched for age and disease duration at first NVC were retrospectively evaluated. NVC was yearly performed by the same operator, and capillary parameters scored as reported in the literature (2-4). Clinical aspects and treatments were recorded. Non parametric test were used to carry out statistical analysis.

Results: Nineteen out of 24 DM patients (79%) showed a NVC “scleroderma-like pattern”. Comparing at baseline DM with SSc patients, the giant capillary and microhaemorrhage scores were significantly higher in SSc than in DM patients (1.42 ± 0.58 vs 1.00 ± 0.72 , $p=0.04$, and 1.00 ± 0.66 vs 0.67 ± 0.56 , $p=0.05$ respectively), while capillary density, ramification (abnormally shaped capillaries, expression of angiogenesis) and disorganization scores were higher in DM patients (1.54 ± 0.72 vs 1.12 ± 0.85 , $p=0.05$; 1.79 ± 1.02 vs 0.79 ± 1.02 , $p=0.002$; 1.67 ± 0.82 vs 0.83 ± 1.01 , $p=0.004$, respectively). Accordingly, the absolute number of ramified capillaries was significantly higher in DM patients (1.92 ± 1.06 vs 0.88 ± 1.08 , $p=0.002$), while the absolute capillary number was significantly higher in SSc patients (6.83 ± 2.18 vs 5.62 ± 1.95 , $p=0.05$) at baseline. No statistically significant variations of all the capillaroscopic scores were observed during the 3 year follow-up in DM patients. By comparing DM patients with or without anti-Jo-1 antibody positivity, no statistically significant differences of the scores of the main capillary parameters were observed at baseline between the groups. However, anti-Jo-1 positive patients showed a statistically significant decrease of capillary ramifications at T2 (score 1.4 ± 1.1 vs 2.6 ± 0.7 , $p=0.05$) and T3 (1.0 ± 0.0 vs 2.6 ± 0.5 , $p=0.03$), when compared with the anti-Jo-1 negative group.

Conclusion: This study demonstrates that DM and SSc display different capillaroscopic features. The capillaroscopic manifestations of DM persist in contrast to the progressive changes described in SSc patients (4), and the anti-Jo-1 positivity do not seem to modify the DM NVC pattern.

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Abstract Number: 375

Only a Minor Proportion of Individuals with Anti-Aminoacyl-tRNA Synthetase Autoimmunity Presents with the Clinical Picture of “Antisynthetase-Syndrome”

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster I: Clinical Features and Disease Course

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

Background/Purpose: Antisynthetase Syndrome is a rare and severe autoimmune inflammatory disease that is associated with autoimmunity against aminoacyl-tRNA synthetase and clinical signs of arthritis, myositis and interstitial lung disease. The aim of this study was to test how many patients with positive anti-aminoacyl-tRNA synthetase autoimmunity present with clinical signs of Antisynthetase Syndrome.

Methods: In a first step, patients with unexplained musculoskeletal pain referred to the outpatient clinic of Department of Internal Medicine 3 of the University of Erlangen-Nuremberg were tested for anti-aminoacyl-tRNA synthetase autoantibodies Jo1, PL12, PL7, EJ and OJ using immunoblot technology. In a second step, patients tested positive for the respective autoantibodies were carefully examined for the presence of clinical signs of Antisynthetase Syndrome and followed up whether clinical changes of Antisynthetase Syndrome developed.

Results: 160 subjects with positive anti-aminoacyl-tRNA synthetase autoantibodies were identified. 50 subjects (31%) had reactivity against anti-Jo1, 38 against PL12 (24%), 29 against PL7 (18%), 23 (14%) against OJ and 9 (6%) against EJ. 11

(7%) subjects had reactivities against more than one aminoacyl-tRNA synthetase. Median age at onset was 51 years (20 to 81 years) and mean (SD) follow up was 82 (81) months. 27 (17%) of these subjects had clear evidence for Antisynthetase Syndrome presenting with at least one of the clinical triad findings of the syndrome: arthritis, myositis and interstitial lung disease. There was a clear preponderance of females (78%) developing Antisynthetase Syndrome. 8 patients (30% of those with clinical signs of Antisynthetase Syndrome) presented with arthritis, 23 (85%) had myositis and 16 (59%) exhibited interstitial lung disease. Arthritis presented in all cases as symmetrical polyarthritis; IgG-RF was positive in one third of the patients, while ACPA were tested negative. Radiographic erosions on plain radiographs were only observed in one patient. “Mechanic” hands and Raynaud syndrome were present in 2 (7%) and 7 (26%) patients with Antisynthetase Syndrome, respectively. Two patients with Antisynthetase Syndrome died due to their disease.

Conclusion: These results suggest that only a minority of individuals tested positive for anti-aminoacyl-tRNA synthetase autoantibodies develops Antisynthetase Syndrome. Individuals with positive autoimmunity but no clinical signs of Antisynthetase Syndrome may either represent pre-disease subjects, who may develop Antisynthetase Syndrome later in life or resemble “forme fruste” of the disease, presenting with only mild and unspecific musculoskeletal symptoms. Hence, further longitudinal observations are needed to determine the outcome of anti-aminoacyl-tRNA synthetase autoantibody carriers.

Table 2 Clinical and laboratory characteristics of Antisynthetase syndrome (ASSD) patients (n=27)

Age at onset, years, median (range)	51 (20-81)
Sex, N females (%)	21(78)
Median diagnostic delay, months (range)	1 (0-79)
Anti-Jo1 reactivity, N (%)	19 (70)
Anti-PL12 reactivity, N (%)	2 (7)
Anti-PL7 reactivity, N (%)	3 (11)
Anti-EJ reactivity, N (%)	1 (4)
Anti-OJ reactivity, N (%)	0 (0)
>1 autoantibody reactivities, N (%)	2 (7)
Disease related deaths, N (%)	2 (7)
Arthritis, N (%)	8 (30)
Myositis, N (%)	23 (85)
Interstitial lung disease, N (%)	16 (59)
Mechanic hands , N (%)	2 (7)
Raynaud syndrome, N (%)	7 (26)

Disclosure: J. Knitza, None; H. Schenker, None; G. Schett, None; J. Distler, None.

Abstract Number: 376

Antisynthetase Syndrome: Prevalence of Serositis in Autoantibody Subsets

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster I: Clinical Features and Disease Course

Session Type: ACR Poster Session A

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

Background/Purpose: Antisynthetase Syndrome(AS) is a relatively rare autoimmune disease characterized by interstitial lung disease (ILD), myositis, inflammatory arthritis, Raynaud phenomenon, and mechanic’s hands. Eight autoantibodies (Ab) to aminoacyl-transfer-RNA synthetases have been described so far: Jo-1, PL-7, PL-12, EJ, OJ, YRS, KS, and Zo. The morbidity and mortality in AS is mainly related to the pulmonary complications. However, little has been reported about the prevalence of serositis (pleural and/or pericardial effusions) in AS other than small cohort studies (15-20 patients) and case reports. The purpose of our study was to determine the prevalence of serositis in AS, its clinical significance, and its association with specific AS Ab subtype(s).

Methods: Clinical data were obtained by retrospective review of electronic medical records from 2004 – 12/2017. AS required diagnosis by a rheumatologist, and patients had to have one of the following AS Ab: Jo-1, PL-7, PL-12, EJ, and OJ. Pleural effusions were qualified as trace, small, medium, or large, based on the findings on chest X-ray and thoracic CT scan. Pericardial effusions were classified as trace, small, medium, large, ortamponade, based on echocardiographic findings. Patients grouped by AS Ab type were compared using Pearson chi-square tests or Fisher exact tests. Size measures were evaluated using Kruskal-Wallis tests that evaluate each measure as an ordered factor. *For all measures, aP-value of < 0.05 was considered significant.*

Results: A total of 93 patients were included in this study. The mean age was 57.5years; 63% were female. The largest subset of patients had Jo-1 Ab (N=62).Pleural effusions were present in 44% of patients, 75% of which were bilateral. Out of 90 patients with complete data available, 42.2% had pleural effusion(s) and 47% had a pericardial effusion, 10% of which were moderate to large, and one patient had tamponade physiology. Jo-1 patients were significantly less likely to have pleural effusions when compared to patients with other Ab (P=0.005). PL-12 had a higher frequency of pleural effusions relative to Jo-1 and PL-7, as well as, compared to all other Ab combined. No statistical comparisons were made between PL-7, EJ, and OJ Ab due to small sample sizes. Alternate causes of serositis were ruled out in all but two patients, who were found to have lung malignancy.

Table 1. Group Effusion Measures – jo1 vs. others

Factor	Other Antibodies (N=31)		Jo-1 (N=62)		p-value
	n	Statistics	n	Statistics	
Pleural Effusion Present	31	20(64.5)	62	21(33.9)	0.005^c
pleural effusion size	30		60		0.004^b
none		11(36.7)		41(68.3)	
trace		2(6.7)		2(3.3)	
small		12(40.0)		14(23.3)	
moderate		4(13.3)		1(1.7)	
large		1(3.3)		2(3.3)	
Pleural Effusion Size (Positive Only)	19		19		0.63 ^b
trace		2(10.5)		2(10.5)	
small		12(63.2)		14(73.7)	
moderate		4(21.1)		1(5.3)	
large		1(5.3)		2(10.5)	
unilateral or bilateral	20		20		0.47 ^c
Unilateral		6(30.0)		4(20.0)	
Bilateral		14(70.0)		16(80.0)	
Pleural Intervention	31	1(3.2)	62	1(1.6)	0.99 ^d
Pericardial Effusion Present	31	17(54.8)	59	25(42.4)	0.26 ^c
pericardial effusion size	31		59		0.30 ^b
none		14(45.2)		34(57.6)	
trace		9(29.0)		11(18.6)	
small		3(9.7)		9(15.3)	
moderate		2(6.5)		3(5.1)	
large		3(9.7)		1(1.7)	
tamponade		0(0.0)		1(1.7)	
Pericardial Effusion Size (Positive Only)	17		25		0.93 ^b
trace		9(52.9)		11(44.0)	
small		3(17.6)		9(36.0)	
moderate		2(11.8)		3(12.0)	
large		3(17.6)		1(4.0)	
tamponade		0(0.0)		1(4.0)	
Pericardial Intervention	31	4(12.9)	62	1(1.6)	0.041^d

Statistics presented as N (column %).

p-values: b=Kruskal-Wallis test, c=Pearson's chi-square test, d=Fisher's Exact test.

Table 2. Group Effusion Measures - pl12 vs. Other

Factor	Other Antibodies (N=76)		PL-12 (N=17)		p-value
	n	Statistics	n	Statistics	
Pleural Effusion Present	76	28(36.8)	17	13(76.5)	0.003^c
pleural effusion size	74		16		0.002^b
none		48(64.9)		4(25.0)	
trace		3(4.1)		1(6.3)	
small		19(25.7)		7(43.8)	
moderate		2(2.7)		3(18.8)	
large		2(2.7)		1(6.3)	
Pleural Effusion Size (Positive Only)	26		12		0.30 ^b
trace		3(11.5)		1(8.3)	
small		19(73.1)		7(58.3)	
moderate		2(7.7)		3(25.0)	
large		2(7.7)		1(8.3)	
unilateral or bilateral	27		13		0.17 ^c
Unilateral		5(18.5)		5(38.5)	
Bilateral		22(81.5)		8(61.5)	
Pleural Intervention	76	1(1.3)	17	1(5.9)	0.33 ^d
Pericardial Effusion Present	73	32(43.8)	17	10(58.8)	0.26 ^c
pericardial effusion size	73		17		0.23 ^b
none		41(56.2)		7(41.2)	
trace		15(20.5)		5(29.4)	

Table . (Cont'd)

Factor	Other Antibodies (N=76)		PL-12 (N=17)		p-value
	n	Statistics	n	Statistics	
small		11(15.1)		1(5.9)	
moderate		3(4.1)		2(11.8)	
large		2(2.7)		2(11.8)	
tamponade		1(1.4)		0(0.0)	
Pericardial Effusion Size (Positive Only)	32		10		0.68 ^b
trace		15(46.9)		5(50.0)	
small		11(34.4)		1(10.0)	
moderate		3(9.4)		2(20.0)	
large		2(6.3)		2(20.0)	
tamponade		1(3.1)		0(0.0)	
Pericardial Intervention	76	2(2.6)	17	3(17.6)	0.041 ^d

Statistics presented as N (column %).

p-values: b=Kruskal-Wallis test, c=Pearson's chi-square test, d=Fisher's Exact test.

Conclusion: Pleural and pericardial effusions were more common in patients with AS than previously thought. In this study, almost half of the patients had some degree of serositis. PL-12 had a higher frequency of pleural effusions than other AS Ab. Further research is necessary in this field.

Disclosure: A. Katz, None; J. Bena, None; S. Chatterjee, None.

Abstract Number: 377

Preliminary Validation of Rectus Femoris Muscle Ultrasound in Idiopathic Inflammatory Myopathy Patients

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster I: Clinical Features and Disease Course

Session Type: ACR Poster Session A

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

Background/Purpose: Muscle ultrasound (MUS) offers a cost effective, accessible option for detection of muscle inflammation and atrophy in patients with Idiopathic Inflammatory Myopathies (IIM). The goal of this study was to compare several MUS parameters in patients with IIM vs. healthy controls (CON), to examine their correlates with measures of IIM disease activity and damage, and to compare the sensitivity and specificity of MUS to magnetic resonance imaging (MRI).

Methods: MUS of the right mid-rectus femoris (RF) using the Acuson Sequoia was performed in 26 IIM patients (PTS) meeting probable or definite Bohan and Peter criteria (20 with juvenile dermatomyositis [JDM], 2 DM, 2 juvenile polymyositis [PM], and 2 juvenile overlap myositis) and compared to 30 age-, gender- and race-matched controls (CON). MUS parameters of IIM patients, evaluated by digital image processing software within regions of interest identified by radiologists, were correlated (Spearman rank) with IIM disease activity and damage assessments and semi-quantitative MRI short tau inversion recovery (STIR) and T1 scores. The area under the receiver operating characteristic (ROC) was used to compare sensitivity and specificity of MUS to MRI.

Results: The median age at diagnosis of IIM was 12.8 years, 69% were female, 77% were Caucasian. The median age of CON was 14.5 years, with similar genders and races as PTS. Median MD Global Disease Activity was 4.0 cm (10 cm VAS) and MD Global Disease Damage was 1.8 cm. There was a significant increase in RF echogenicity [median 48.5 in PTS vs. 39.3 CON, p=0.0004], but decrease in RF area (median 9.0 PTS vs 10.6 CON, p=0.038), RF contracted area (median 7.9 PTS vs. 9.9 CON, p=0.005) and vascular power Doppler (median 4.0 PTS vs. 1.0 CON, p=0.032) in IIM vs. CON. Mean

echogenicity of MUS correlated with MD Global Activity (r_s 0.46, $p=0.04$) and inversely with proximal MMT (r_s -0.54, $p=0.01$). RF area inversely correlated with MD global activity (r_s -0.46, $p=0.04$) and correlated with proximal MMT (r_s 0.57, $p=0.009$). Contracted RF area inversely correlated with MD Global Activity (r_s -0.56, $p=0.009$) and correlated with proximal MMT (r_s 0.76, $p<0.0001$) and CMAS (r_s 0.80, $p<0.0001$). MUS echogenicity correlated with both STIR (r_s 0.44, $p=0.03$) and T1 MRI sequences (r_s 0.46, $p=0.02$). T1 MRI correlated with the difference in RF area between the contracted and resting states (r_s 0.67, $p=0.002$). Several MUS measures inversely correlated with muscle atrophy on T1 MRI, including vascular color Doppler (r_s -0.49, $p=0.01$), RF contracted mean AP area (r_s -0.57, $p=0.003$), and RF contracted area (r_s -0.43, $p=0.03$). The area under the curve by ROC analysis of MUS echogenicity vs. STIR MRI was 0.75, and using an average of STIR and T1 MRI, improved to 0.81.

Conclusion: Several MUS parameters of RF differed between IIM vs. CON, including increased echogenicity, decreased resting and contracted area, and decreased vascular power Doppler. MUS also had moderate to strong construct validity with IIM disease activity, strength and MRI measures. MUS echogenicity has strong sensitivity and specificity compared to MRI, and is a promising imaging modality for IIM patients.

Disclosure: E. McBride, None; G. Mamyrova, Cure JM, 2; M. Harris-Love, None; A. Premkumar, None; D. Koziol, None; J. Yao, None; L. Yao, None; J. Shrader, None; M. Jain, None; R. Curiel, Cure JM, Bristol Myers Squibb, 2; F. W. Miller, None; L. G. Rider, Hope Pharmaceuticals, Bristol Myers Squibb, Lilly, 2.

Abstract Number: 378

Pulmonary Hypertension in Anti-Synthetase Syndrome

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Session Information

Session Date: Sunday, October 21, 2018

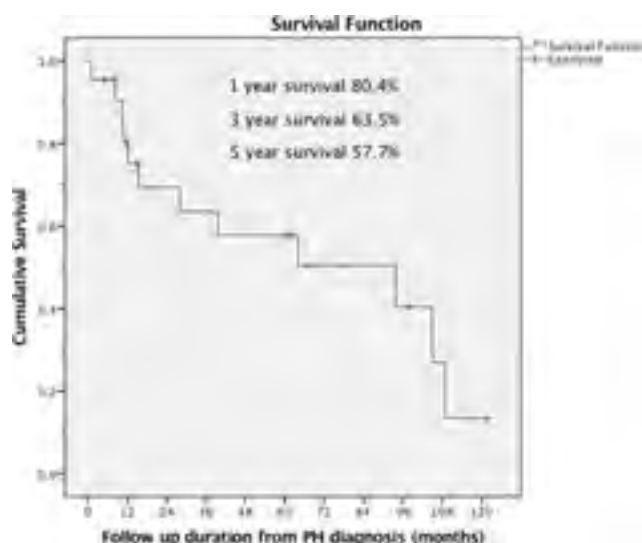
Session Title: Muscle Biology, Myositis and Myopathies Poster I: Clinical Features and Disease Course

Session Type: ACR Poster Session A

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

Background/Purpose: Clinical manifestations of anti-synthetase syndrome (ASS) include fever, Raynaud phenomenon, mechanic's hands, inflammatory arthritis, myositis and interstitial lung disease (ILD). Pulmonary hypertension (PH), although not part of the syndrome, when present may indicate a poor prognosis and has not been well studied.

Methods: We conducted a retrospective chart review of patients with ASS with Jo-1, PL-7, PL-12, EJ and OJ antibodies between 2003 - 2017. ASS patients with PH were selected for further review. PH was diagnosed by right heart catheterization (RHC) in all patients with mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg, and defined as severe if mPAP was ≥ 35 mmHg. Patients were classified as having pre-capillary PH if pulmonary capillary wedge pressure (PCWP) was ≤ 15 mmHg, post-capillary PH if PCWP was >15 mmHg, and combined pre- and post-capillary PH if PCWP was >15 mmHg with diastolic pressure gradient ≥ 7 mmHg and/or pulmonary vascular resistance (PVR) >3 Wood units. Patient



demographics, laboratory data, echocardiogram and RHC parameters, spirometry and DLCO were evaluated. Numerical variables were compared using Mann-Whitney test. Categorical variables were compared using either Pearson's chi-squared test or Fisher's exact test. Binary logistic regression analysis was used to identify factors associated with mortality. Survival function was estimated using the Kaplan-Meier method. A p-value of <0.05 was considered significant.

Results: We identified 177 patients with positive anti-Jo-1 antibody, and 36 patients with non-Jo-1 antibodies. Twenty-two (10.33%) had PH and the following antibodies: Jo-1 (18), PL-12 (2), EJ (1) and PL-7 (1). The median age was 51 years and the median follow-up duration was 6.89 years. The median duration from ASS onset to PH diagnosis was 36.17 months. Fifteen patients had pre-capillary PH, 3 had post-capillary PH and 4 had combined PH. Median forced vital capacity (FVC) at PH diagnosis was 48%, of which 3 patients had FVC \geq 70%. One patient had PH without ILD. Sixteen patients (72.7%) had severe PH. Sixteen out of 19 patients with pre-capillary PH were treated for pulmonary arterial hypertension and 9 of them received combination therapy. All 22 patients also received immunosuppressive therapy. Twelve patients (54.5%) died. Two patients with lung transplants survived. The deceased group had higher PVR ($p=0.024$) and higher rates of severe PH ($p=0.05$). Right ventricular dilation was associated with mortality ($p=0.046$). Survival was not affected by SS-A antibody positivity, presence of Raynaud phenomenon or pericardial effusion, New York Heart Association Functional Class, FVC at PH diagnosis, and duration from ASS onset to PH diagnosis. Survival analysis is shown in Figure 1.

Conclusion: PH is not uncommon in patients with ASS. Severity of PH at diagnosis was a predictor of mortality. Given this dismal prognosis, we recommend screening echocardiography in all ASS patients.

Disclosure: C. Carneiro, None; P. O-Charoen, None; S. Chatterjee, None.

Abstract Number: 379

Risk Factors of Venous Thromboembolism in Idiopathic Inflammatory Myopathies

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster I: Clinical Features and Disease Course

Session Type: ACR Poster Session A

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

Background/Purpose: Idiopathic inflammatory myopathies (IIM) are heterogeneous disorders characterised by skeletal muscle weakness and muscle inflammation. IIM includes dermatomyositis (DM), polymyositis (PM), antisynthetase syndromes (ASS), scleromyositis (SCM), inclusion body myositis (IBM), immune-mediated necrotizing myopathies (IMNM) and Overlap Syndromes (OS). Previous population-based studies have demonstrated a higher risk of venous thromboembolism (VTE) in IIM patients compared to healthy controls. In these works, IIM were only divided in PM and DM and few risk factors of VTE have been highlighted. The purpose of this study was to identify the VTE specific risk factors in IIM and analyse VTE occurrence in more recently defined subtypes of IIM.

Methods: All adults with IIM hospitalized in Internal Medicine units from Eastern France between 2004 and 2018 were enrolled. Demographic, clinical and laboratory data were retrospectively collected from medical records. Mann-Whitney test and Chi-square test were used for comparison of continuous and discrete variables, respectively. We computed a multivariate model to determine factors associated with VTE using a Cox analysis. VTE-free survival analysis was performed using log-rank test.

Results: 203 patients (55 male, 148 female) were involved. The mean age at diagnosis was 51 years \pm 16. VTE occurred in 12% of cases, mostly within the first year of follow-up (31%). At VTE diagnosis, conditions such as immobilization (20%), infection (10%), malignancy (20%), active disease (31%), treatment by intravenous immunoglobulins (17%) or by glucocorticoids (55%) were observed. In univariate analysis, we found that patients with VTE experienced more dysphonia ($p=0.037$) and received a greater number of therapeutic lines ($p=0.035$) compared to patients without VTE. In multivariate analysis, significant risk factors were personal history of pulmonary embolism (HR 13, $p=0.023$), dysphonia (HR 99,

p=0,00005), elevated C-reactive protein (HR 5.1, p=0.0081) and number of therapeutic lines (HR 2.7, p=0.023). We compared VTE-free survival in all IIM subtypes within the five years after diagnosis: a particular subgroup including DM, PM, ASS, OS and IMNM (group 1) presented a higher risk than another including SCM, IBM and unspecified myositis (group 2) (HR 4.21, p=0,048).

Conclusion: Common but also unexpected risk factors were reported here. Elevated C-reactive protein confirmed the link between inflammation and thrombosis mechanisms. Dysphonia and the number of therapeutic lines reflected a more severe disease. Among IIM, only those in group 1 (DM, PM, ASS, OS and IMNM) were associated with an increased risk of VTE. The identification of these subtypes should alert to VTE risk and lead to early apply prophylactic measures.

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Abstract Number: 380

A New Tool to Assess Muscle Strength in Polymyositis and Dermatomyositis: Hand-Held Dynamometry

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Session Information

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Session Title: Muscle Biology, Myositis and Myopathies Poster I: Clinical Features and Disease Course

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

Background/Purpose: Idiopathic inflammatory myopathies (IIM) are a group of systemic autoimmune diseases characterized by proximal muscle weakness, which is often assessed clinically using manual muscle testing (MMT). Studies have shown that patient's weight and examiner's experience and strength may play important roles in grading muscle strength with MMT. Therefore, more objective tools are required to quantify muscle strength in order to optimize treatment response in clinical trials and practice. Hand-held dynamometry (HHD) is a quantitative, inexpensive, compact device with reliability in several neuromuscular diseases. We aimed to assess reliability, validity and responsiveness of HHD in IIM.

Methods: The 6 validated myositis core set measures (CSM; manual muscle testing [MMT], physician global disease activity (MD-GDA), patient global disease activity (PT-GDA), extra-muscular global disease activity (EM-GDA), HAQ and muscle enzymes) and 3 functional measures (six-minute walk [6MWD], timed-up-and-go [TUG] and sit-to-stand tests [STS]) were completed on patients with IIM [DM, PM, necrotizing myopathy (NM) or anti-synthetase syndrome] at baseline, 3 and 6 months. At each visit strength was assessed using HHD (Micro FET2, Hoggan Health Industries, Draper, UT) on 3 consecutive attempts. HHD was validated and compared with MMT as well as other CSMs and functional tests. Spearman correlations were used with rho >0.5 considered strong, 0.35-0.5 moderate, and 0.2-0.35 weak. We examined the test-retest reliability as well as HHD responsiveness.

Results: Fifty patients [mean age, 53.6(±14.6); 30 females/20 males] were studied. Eleven of 50 had PM, 28 had DM, 7 had NM and 4 had anti-synthetase syndrome. HHD showed strong test-retest reliability (Rho: 0.96) and excellent internal consistency (Cronbach-α: 0.95). HHD correlated moderately with MMT score (R: 0.44, p=0.003). HHD showed moderate to strong correlation with muscle disease activity (R: -0.5, p: 0.0008) and MD-GDA (R: -0.4, p: 0.006), HAQ (R: -0.5, p: 0.0005), STS (R: 0.5, p: 0.0002), and 6MWD (R: 0.4, p: 0.005) (Table 1). Longitudinal change in HHD strongly correlated with total improvement score (R: -0.6, p=0.01) at 6 months. HHD scores changed significantly in physician-reported "moderately-better" and "a-little-better" groups (p=0.01) demonstrating responsiveness to change. HHD did not change longitudinally in patients who had stable disease demonstrating reliability. MMT and HHD showed similar correlations with the conventional CSM, however, effect size and standardized response mean (SRM) of HHD was higher than MMT (0.56 vs 0.20; 0.33 vs 0.20).

Conclusion: HHD demonstrates good test-retest reliability, construct validity and responsiveness in a large cohort of patients with IIM and a better effect size and SRM than MMT.
Table. Comparison of MMT and hand-held DM

	MMT		Hand-held DM	
	R	P value	R	P value
Physician global disease activity	-0.5	0.0001	-0.4	0.006
Patient global disease activity	-0.5	<.0001	-0.1	0.3
Extramuscular global disease activity	-0.7	<.0001	-0.5	0.0008
HAQ-DI	-0.6	<.0001	-0.5	0.0005
CK levels	-0.1	0.3	-0.03	0.8
Muscle disease activity	-0.7	<.0001	-0.5	0.0008
Peak sit-to-stand	0.5	0.0003	0.6	0.0002
Peak timed up-and-go	-0.1	0.4	-0.1	0.5
Six-minute walk test distance	0.55	0.0006	0.4	0.005
Effect size	0.20	0.56		
Standardized response mean	0.20	0.33		

Disclosure: D. Saygin, None; C. V. Oddis, None; S. Moghadam-Kia, None; D. Koontz, None; N. M. Neiman, None; R. Aggarwal, None.

Abstract Number: 381

Muscle Endurance Deficits in Myositis Patients Despite Normal Manual Muscle Testing Scores

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Background/Purpose: To assess muscle function in myositis patients, clinicians typically use manual muscle testing (MMT), a measure of maximal isometric strength. However, patients with high baseline strength and/or mild muscle impairment often report functional changes undetected by MMT. We investigated whether quantifying muscle endurance using the Myositis Functional Index-2 would identify muscle impairment uncaptured by MMT.

Methods: We reviewed the records of myositis patients from a large single-center cohort who had at least one FI2 muscle endurance assessment (n=128, 226 patient-visits). Patients with dermatomyositis (DM; n=31) and polymyositis (PM; n=39) met Bohan and Peter criteria. Patients with inclusion body myositis (IBM; n=58) met 2011 European Neuromuscular Centre diagnostic criteria for probable or definite IBM. MMT strength data were converted to a 0-10 scale using standard Kendall conversion.

Results: Composite FI2 endurance scores were similar in patients with IBM, DM, and PM, although IBM patients had diminished strength (Figure 1). At the population level, muscle endurance correlated with and evolved very similarly to strength overtime, inversely to serum creatine kinase (Figure 2). However, in patients with normal or near-normal strength (mean MMT >9.75/10; n=62), FI2 scores were typically abnormal and highly variable (mean FI2, 5.6/10; interquartile range, 3.3-7.8/10), suggesting the presence of muscle impairment not reflected by MMT. In an illustrative case, a DM patient with high baseline strength complained of flaring muscle weakness which was reflected by FI2 but not MMT scores (Figure 3).

Conclusion: Muscle endurance testing may identify muscle impairment inadequately described by MMT, particularly in patients with high MMT scores.

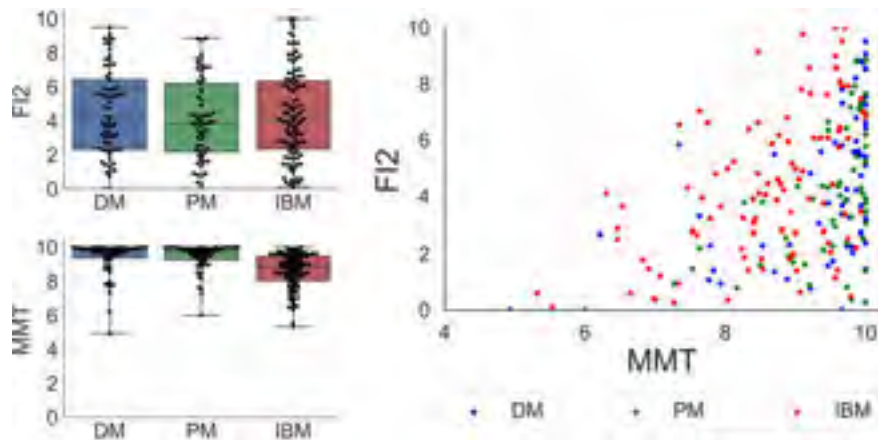


Figure 1: Composite FI2 endurance and MMT strength scores in myositis patients.

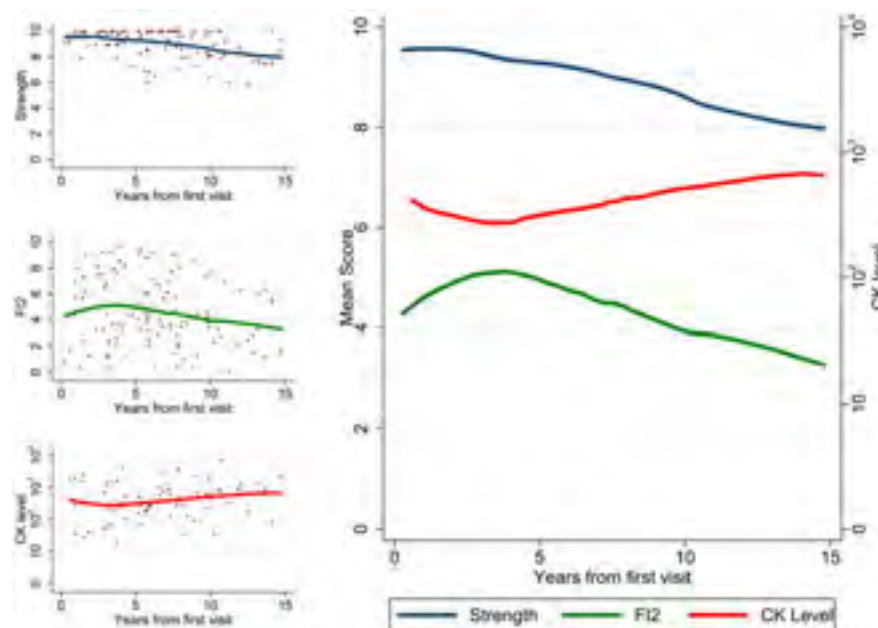


Figure 2: MMT and FI2 scores evolved similarly over time, inversely to serum CK levels. Locally-weighted regression of all myositis patient data.

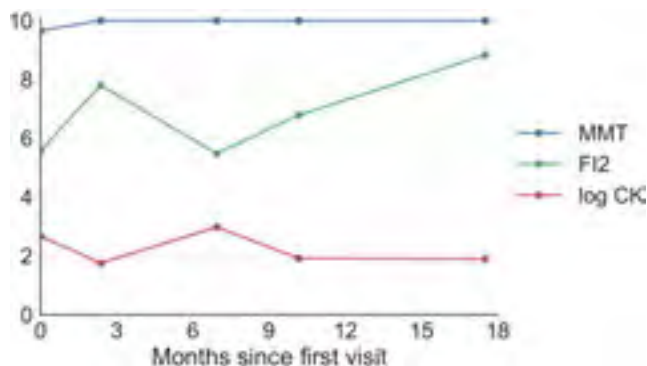


Figure 3: The evolution of MMT, FI2, and serum CK in a DM patient with a disease flare at month 7.

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Nailfold Capillary Changes in the Adult Newly Onset-Dermatomyositis: A Prospective Cohort Study

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Background/Purpose: There is currently no study in newly onset dermatomyositis (DM) regarding nailfold capillaroscopy (NC) findings, angiogenic cytokines, disease related clinical, laboratory and treatment features. Therefore, the aims of the present study were: (a) to analyze cross-sectionally and prospectively NC findings in newly onset-DM; (b) to correlate NC findings with serum angiogenic cytokines [angiogenin (ANG), vascular endothelial growth factor-1 (VEGF1)] and DM clinical and laboratory features.

Methods: Twenty-three patients with DM with less than 12 months of symptoms were included. All the patients met at least four of the five criteria of Bohan and Peter criteria, including classical cutaneous lesions (heliotrope rash and/or Gottron's papules) and the new European League Against Rheumatism / American College of Rheumatology (EULAR / ACR) classification criteria for DM. To assess serum cytokine levels, age, gender and ethnicity-matched 23 healthy volunteers were recruited as a control group. NC characteristics and DM activity parameters were analyzed. Additionally, 15 out of 23 patients were also assessed prospectively after a median duration of 3.21 years.

Results: A significantly higher serum ANG and VEGF1 levels ($P=0.017$ and $P<0.001$, respectively) were observed in DM patients compared to controls. Capillary density and avascular areas correlated positively ($r=0.6$; $P=0.016$) and negatively ($r=-0.59$; $P=0.019$) with serum level of ANG. Besides, capillary density correlated inversely with the number of enlarged ($r=-0.54$; $P=0.007$); giant capillaries ($r=-0.53$; $P=0.009$) and avascular areas ($r=-0.84$; $P<0.001$). The number of the enlarged capillaries correlated positively with patient ($r=0.49$; $P=0.016$) and physician VAS ($r=0.56$; $P=0.005$), presence of facial rash ($r=0.44$; $P=0.035$), giant capillaries ($r=0.76$; $P<0.001$) and microhemorrhages ($r=0.59$; $P=0.003$). Giant capillaries had positive correlation with physician ($r=0.50$; $P=0.014$) and cutaneous VAS ($r=0.42$; $P=0.046$), enlarged capillaries ($r=0.76$; $P<0.001$), avascular areas ($r=0.54$; $P=0.007$), microhemorrhages ($r=0.55$; $P=0.006$) and bushy capillaries ($r=0.42$; $P=0.044$) and negative with capillary density ($r=-0.53$; $P=0.009$). Microhemorrhages correlated positively with "V-neck" sign ($r=0.44$; $P=0.032$) and physician VAS ($r=0.48$; $P=0.02$). VEGF1 showed no relation to NC parameters neither with DM-related clinical and laboratory features. Longitudinally, all patients had major clinical response with significant improvement in the all NC parameters, except for enlarged and bushy capillaries.

Conclusion: The present data emphasize that NC may be a useful tool to assess disease activity in recently onset-DM and also reinforce the role of ANG in the angiogenesis process in this myopathy.

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Abstract Number: 383

Myositis Patients with Anti-U1-RNP and Anti-Ro52 Autoantibodies Are at Risk of Pericarditis, Glomerulonephritis, and Pulmonary Hypertension

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Background/Purpose: To define the clinical phenotype of myositis patients with anti-U1- ribonucleoprotein (RNP) autoantibodies.

Methods: The clinical features of 20 anti-U1RNP-positive patients were assessed and compared to those of 132 antisynthetase syndrome (ASyS), 178 dermatomyositis (DM), and 135 immune-mediated necrotizing myopathy (IMNM) patients.

Results: Twenty (4.6%) of 437 patients tested were anti-U1-RNP-positive; these were younger (~37 years) and more likely to be black (60%) than ASyS, DM, or IMNM patients. Muscle weakness, arthritis, interstitial lung disease (ILD), and DM-specific skin features eventually developed in 80%, 60%, 45%, and 60% of anti-U1-RNP-positive patients, respectively. Four of 7 (57%) anti-U1-RNP-positive patients had a necrotizing muscle biopsy. ILD was more severe in anti-U1-RNP-positive patients than in DM or IMNM. Glomerulonephritis and pericarditis occurred in 25% and 40% of anti-U1-RNP-positive patients, respectively, but rarely in the other groups. Pulmonary hypertension (PH) developed in 25% of anti-U1-RNP-positive, 20% of ASyS, and in <3% of DM and IMNM patients. Interestingly, glomerulonephritis, pericarditis and PH only occurred in anti-U1- RNP-positive patients with co-existing anti-Ro52 autoantibodies.

Conclusion: Muscle weakness and arthritis are the most common clinical features in anti- U1-RNP-positive patients; when present, ILD is severe. Pericarditis, glomerulonephritis and PH are relatively common in anti-U1-RNP-positive patients, and only developed in those anti-U1-RNP-positive patients with co-existing anti-Ro52 autoantibodies.

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Patients with Anti-Synthetase Syndrome Have a Similar Prevalence and Severity of Interstitial Lung Disease to Systemic Sclerosis

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Background/Purpose: Interstitial lung disease (ILD) is a significant cause of morbidity and mortality in connective tissue diseases (CTDs). The purpose of this study is to compare the prevalence, physiology, and radiographic findings in different CTDs to formulate rational screening/monitoring plans.

Methods: Patients diagnosed with dermatomyositis (DM), polymyositis (PM), anti-aminoacyl tRNA synthetase syndrome (ARS), limited cutaneous systemic sclerosis (lcSS), diffuse cutaneous systemic sclerosis (dcSS), or mixed connective tissue disease (MCTD) were identified from the MYSTIC cohort (VUMCIRB 141415); the presence of ILD was identified from chart abstraction. Radiographic patterns of ILD were ascertained from the initial CT scan. American Thoracic Society Criteria were used to grade severity by forced vital capacity (FVC) and diffusing lung capacity for carbon monoxide (DLCO) percentages; if multiple pulmonary function tests (PFTs) were available, the most severe value was used.

Results: Patient characteristics are shown in Table 1. Forty of 71 patients had ILD with the highest prevalence in dcSS (70%), ARS (64.2%), and lcSS (48%). Nonspecific interstitial pneumonia (NSIP) was the most common radiographic pattern (Table 2), but 27% of patients with lcSS had a usual interstitial pneumonia (UIP) pattern. Severe restriction was present in 43% of ARS patients and 33% of dcSS patients. Similarly, 86% of ARS patients and 66% of dcSS had severe

Table 1: Patient Characteristics						
	DM N = 17 (5%)	PM N = 3 (1%)	ARS N = 14 (5%)	lcSS N = 27 (10%)	dcSS N = 10 (4%)	MCTD N = 11 (4%)
Age Range (Mean)	27-71 (58.1)	44-68 (54.3)	53-70 (52.9)	21-81 (59.3)	19-80 (58.3)	23-65 (49.9)
Female	12 (70.6%)	2 (66.7%)	10 (71.4%)	23 (85.3%)	6 (60%)	8 (72.7%)
Caucasian	17 (100%)	3 (100%)	10 (71.4%)	22 (81.4%)	6 (60%)	6 (54.5%)
African American	0	0	4 (28.6%)	5 (18.5%)	1 (10%)	5 (45.5%)
Other	0	0	0	0	3 (30%)	0
ILD Present	5 (29.4%)	2 (66.7%)	9 (64.3%)	13 (48%)	7 (70%)	4 (36.4%)
Pulmonary Hypertension	1 (5.9%)	0	2 (14.3%)	10 (37%)	4 (40%)	2 (18.2%)
Supplemental Oxygen	2 (11.8%)	0	5 (35.7%)	6 (22.2%)	2 (20%)	1 (9%)

Table 2: Pulmonary Phenotypes						
Radiographic Patterns						
	DM N = 5 (5%)	PM N = 2 (2%)	ARS N = 9 (6%)	lcSS N = 11 (4%)	dcSS N = 6 (6%)	MCTD N = 4 (4%)
NSIP	1 (20%)	1 (50%)	5 (55.6%)	4 (36.4%)	5 (83.3%)	3 (75%)
Atypical for UIP	0	0	1 (11%)	0	0	0
Consistent with UIP	1 (20%)	0	1 (11%)	3 (27%)	1 (16.7%)	0
Other	3 (60%)	1 (50%)	2 (22%)	4 (36.4%)	0	1 (25%)
Physiologic Severity						
	DM N = 5 (5%)	PM N = 2 (2%)	ARS N = 9 (6%)	lcSS N = 13 (5%)	dcSS N = 8 (8%)	MCTD N = 3 (3%)
Restriction						
No Restriction	2 (40%)	0	1 (11%)	2 (15%)	0	1 (33%)
Mild - FVC 65-79%	1 (20%)	1 (100%)	1 (11%)	6 (46%)	2 (33%)	0
Moderate - FVC 50-64%	2 (40%)	0	2 (22.2%)	4 (31%)	2 (33%)	1 (33%)
Severe - FVC <50%	0	0	3 (33.3%)	1 (7.7%)	2 (33%)	0
Gas Exchange						
DLCO - 65-79%	2 (40%)	0	1 (11%)	2 (15%)	0	0
DLCO - 50-64%	0	1 (100%)	0	2 (15%)	2 (33%)	1 (33%)
DLCO - <50%	3 (60%)	0	6 (66.7%)	7 (54%)	4 (66.7%)	2 (66.7%)

gas exchange deficits. Supplemental oxygen use was 35.7% in ARS and 20% in dcSS. Despite the high prevalence of ILD in lcSS, physiologic severity was less than ARS or dcSS. FVC was mildly restricted in 46% of lcSS cases; only one patient had severe restriction. Fifty four percent of lcSS patients had severe reduction in DLCO, but this is likely due to concomitant pulmonary hypertension. Overall, ILD in dcSS and ARS was much more severe than lcSS, DM, PM, or MCTD.

Conclusion: In our cohort, ARS and dcSS had similar prevalence and severity of ILD. While expert opinion promotes screening and monitoring for ILD in systemic sclerosis (SSc), there are currently no clear recommendations for ARS. This data indicates that screening CT/PFTs are indicated for ARS as well as SSc.

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Abstract Number: 385

Sexual Dysfunction in Female Patients with Idiopathic Inflammatory Myopathies

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Background/Purpose: Idiopathic inflammatory myopathies (IIM) are characterized by inflammation and atrophy of skeletal muscles, pulmonary and articular involvement, which leads to functional impairment, reduced quality of life including sexual life. The aim of this study was to assess sexual functions/quality of life and pelvic floor function in female IIM patients compared to age-/sex-matched healthy controls (HC).

Methods: In total, 22 women with IIM [mean age: 55.1, disease duration: 7.9 years, dermatomyositis (DM, 8)/ polymyositis (PM, 10)/ necrotizing myopathy (IMNM, 3)/ inclusion body myositis (IBM, 1)], who fulfilled the Bohan/Peter 1975 criteria for DM/PM, and 22 healthy controls (mean age: 55.1 years) without rheumatic diseases filled in 12 well-established and validated questionnaires assessing sexual function/quality of life, pelvic floor function, fatigue, physical activity and depression. Data are presented as mean \pm SEM.

Results: Compared to HC, patients with IIM had significantly higher prevalence and greater severity of sexual dysfunction (FSFI, BISF-W: in all subscales as well as total scores), dysfunction of pelvic floor (PISQ-12), and worse sexual quality of life (SQoL-F) (table). Worse scores in IIM patients were associated with elevated muscle enzyme levels [lactate dehydrogenase: FSFI ($r=-0.524, p=0.0123$), BISFW ($r=-0.528, p=0.0115$)], greater fatigue [FIS: FSFI ($r=-0.434, p=0.0438$), BISF-W ($r=-0.488, p=0.0211$), SQoL-F ($r=-0.488, p=0.0070$), PISQ-12 ($r=0.643, p=0.0013$)], more severe depression [BDI-II: PISQ-12 ($r=0.474, p=0.0258$)], deteriorated quality of life [HAQ: PISQ-12 ($r=0.476, p=0.0252$)], and worse ability to perform physical activities [HAP: FSFI ($r=0.437, p=0.0417$), BISF-W ($r=0.451, p=0.0351$), PISQ-12 ($r=-0.494, p=0.0195$)].

Conclusion: Women with IIM reported significantly impaired sexual function, sexual quality of life and pelvic floor function than age-matched healthy controls. Worse scores in IIM were associated with disease activity, physical activity, fatigue, depression and quality of life.

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Questionnaire: score range	Idiopathic inflammatory myopathies (n=22)	Healthy controls (n=22)	p-value
FSFI: Female Sexual Function Index: 2(worst)-36(best)	14.2 \pm 2.7	23.5 \pm 2.5	p=0.0146
BISF-W: Brief Index of Sexual Function for Women: -16(worst)-75(best)	15.5 \pm 3.9	28.9 \pm 3.8	p=0.0193
PISQ-12: Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire short form: 0(best)-48(worst)	13.8 \pm 1.1	8.0 \pm 1.0	p=0.0003
PFIQ7: Pelvic Floor Distress Inventory Questionnaire – short form 7: 0(best)-300(worst)	15.8 \pm 4.5	5.6 \pm 2.3	p=0.1450
SQoL-F: Sexual Quality of Life Questionnaire – Female: 0(worst)-100(best)	54.9 \pm 6.0	83.1 \pm 3.4	p=0.0006
FSS: Fatigue Severity Scale: 9(best)-63(worst)	46.9 \pm 2.8	26.7 \pm 2.5	p<0.0001
FIS: Fatigue Impact Scale: 0(best)-160(worst)	60.6 \pm 6.9	29.0 \pm 4.2	p=0.0003
MAF: Multidimensional Assessment of Fatigue Scale: 1(best)-50(worst)	26.1 \pm 2.3	17.8 \pm 1.4	p=0.0129
BDI-II: Beck's Depression Inventory II: 0(best)-63(worst)	14.5 \pm 2.2	5.3 \pm 1.1	p=0.0003
HAP: Human Activity Profile – adjusted activity score: 0(worst)-94(best)	53.7 \pm 4.3	81.1 \pm 1.5	p<0.0001
HAQ: Health Assessment Questionnaire: 0(best)-3(worst)	1.0 \pm 0.2	0.0 \pm 0.0	p<0.0001

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Abstract Number: 386

Differences in Body Composition in Myositis Patients and Healthy Controls Are Associated with Disease Activity and Duration, Inflammatory Status, Skeletal Muscle Involvement and Physical Activity

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Background/Purpose: Skeletal muscle, pulmonary and articular involvement in idiopathic inflammatory myopathies (IIM) limit the mobility/self-sufficiency of patients, and can have a negative impact on body composition. The aim of this study was to assess body composition and physical activity of IIM patients and healthy controls (HC).

Methods: 54 patients with IIM (45 females; mean age 57.7; disease duration 5.8 years; polymyositis (PM, 22) / dermatomyositis (DM, 25) / necrotizing myopathy (IMNM, 7)) and 54 age-/sex-matched HC (45 females, mean age 57.7) without rheumatic/tumor diseases were included. PM/DM patients fulfilled Bohan/Peter criteria for PM/DM. Anthropometric parameters and body composition were assessed (by densitometry: iDXA Lunar, and by bioelectric impedance: BIA2000-M), and physical activity was evaluated using Human Activity Profile (HAP) questionnaire. Routine biochemistry analysis was performed after 8 hours of fasting. Disease activity was evaluated by MITAX and MYOACT activity score. Muscle involvement was evaluated by manual muscle test (MMT-8) and functional index 2 (FI2). Data are presented as mean±SD.

Results: Compared to HC, patients with IIM had a trend towards significantly increased body fat % (BF%) as assessed by iDXA (39.9±7.1 vs. 42.4±7.1 %, p=0.077), but significantly decreased lean body mass (LBM) as assessed both by iDXA (45.6±8.1 vs. 40.6±7.2 kg, p=0.001) and BIA (52.6±8.8 vs. 48.7±9.0 kg, p=0.023), and increased extracellular mass/body cell mass (ECM/BCM) ratio (1.06±0.15 vs. 1.44±0.42, p<0.001). Higher ECM/BCM ratio reflects worse muscle predispositions for physical exercise, aerobic fitness/performance, and deteriorated nutritional status. Compared to HC, IIM patients had significantly lower bone mineral density (BMD: 1.2±0.1 vs. 1.1±0.1 g/cm², p<0.001). Disease duration negatively correlated with BMD (r=-0.392, p=0.004) and LBM-BIA (r=-0.272, p=0.047). Disease activity assessed by both MITAX and MYOACT positively correlated with LBM-BIA (MITAX: r=0.294, p=0.031; MYOACT: r=0.335, p=0.013) and LBM-DXA (MITAX: r=0.341, p=0.012; MYOACT: r=0.368, p=0.007), similarly as with basal metabolic rate (BMR; MITAX: r=0.336, p=0.014; MYOACT: r=0.351, p=0.010), and fat free mass (FFM; MITAX: r=0.338, p=0.014; MYOACT: r=0.356, p=0.009). CRP was positively associated with BF% assessed both by DEXA (r=0.276, p=0.035) and BIA (r=0.306, p=0.025). Higher BF%-DEXA was associated with worse physical endurance (FI2: r=-0.311, p=0.026) and worse ability to perform physical activity (HAP: r=-0.292, p=0.032). MMT-8 score negatively correlated with ECM/BCM ratio (r=-0.385, p=0.006).

Conclusion: Compared to healthy age-/sex-matched individuals we found significant negative changes in body composition of our IIM patients, which are associated with their disease activity and duration, inflammatory status, skeletal muscle involvement, and physical activity. These data could reflect their impaired nutritional status and predispositions for physical exercise, aerobic fitness and performance.

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Abstract Number: 387

Increased Risk of Malignancy in Elderly Patients with Inflammatory Myositis

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Session Information

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Background/Purpose: The association between inflammatory myositis and malignancy is well established, however, the risk of malignancy in aged patients is known to be similar with general populations. We aimed to analyze the incidence of malignancy in elderly patients with inflammatory myositis, and to estimate the increased risk of malignancy of these patients compared to knee OA patients in Korea.

Methods: Patients with polymyositis (PM) and dermatomyositis (DM) over the age of 50 were identified from Korean nationwide claims database from January 2012 to December 2014 with excluding the patients who had history of any malignancy for a year prior to enrollment. They were observed until any malignancy was newly diagnosed or up to end of the study, December 2015. The crude incidence rate (IR) of malignancies in PM and DM patients over 50 years of age was estimated and we calculated age- and sex-adjusted standardized incidence ratio (SIR) by dividing the observed number of malignancies in patients with PM or DM by expected number of malignancies which was drawn from the incidence rate of malignancy in knee OA patients for cumulative person-years (PYs).

Results: A total of 683 patients with PM and 502 patients with DM over 50 years old were included. In PM patients, 46 cases of solid malignancy (217.7/10,000 PYs) and 4 of hematologic malignancy (18.2/10,000 PYs) occurred during 2,113 and 2,195 PYs of follow-up. On the other hand, the number of 36 solid malignancies (238.0/10,000 PYs) and 7 hematologic malignancies (44.7/10,000 PYs) were identified for 1,512 and 1,565 PYs of observation in patients with DM. Compared to patients with knee OA aged over 50 (n=5,476,302), the risk of overall malignancy was increased in both PM and DM patients; SIR was 1.4 (95% CI 1.0-1.8) in PM patients and 1.8 (95% CI 1.3-2.4) in DM patients, respectively. The risk of solid malignancy was also significantly increased than expected in patients with PM (SIR 1.4, 95% CI 1.0-1.8) and DM (SIR 1.6, 95% CI 1.1-2.1). However, the risk of hematologic malignancy was significantly increased in patients with DM (SIR 9.0, 95% CI 2.3-15.6), but not in those with PM (SIR 3.3, 95% CI 0.1-6.6).

Conclusion: We figure out that even in the elderly patients, inflammatory myositis is associated with increased risk of both solid and hematologic malignancies.

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Comparison of Anti-3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase and Anti-Signal Recognition Particle Necrotising Myopathies: A Single Centre Experience

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Background/Purpose: Immune-mediated necrotising myopathy (IMNM) is characterised by paucity of inflammation on muscle biopsy and is associated with antibodies to signal recognition particle (SRP) and 3-hydroxy-3-methylglutaryl-

coenzyme A reductase (HMGCR). IMNM patients tend to be more refractory to conventional immunosuppressive therapies. Previous case series suggested that a more severe clinical course and greater resistance to treatment in anti-SRP myopathy compared to anti-HMGCR. Thus, we aimed to analyse disease characteristics and treatment responses in a single-centre IMNM cohort based on SRP or HMGCR antibody status.

Methods: All subjects with a diagnosis of IMNM from 2008 to 2017 were included in this retrospective study. Patient electronic records were reviewed and disease subgroups based on antibody status (anti-SRP and anti-HMGCR) were analysed.

Results:

Subgroup	HMGCR	SRP
Number of patients, n (%)	17 (61)	11 (39)
Female, n (%)	13 (76)	6 (55)
Median age at onset, years (Interquartile range)	62 (57 - 71)	52 (31 - 55)
Ethnicity, n (%)	White British 12 (70.6) African-Caribbean 2 (11.8) South Asian 2 (11.8) Chinese 1 (5.8)	African 8 (72.7) African-Caribbean 2 (18.2) White British 1 (9.1)
Median peak creatine kinase, units/L (Interquartile range)	7030 (4143 – 19114)	9750 (3237 – 19022)
Statin exposure, n (%)	14 (82)	1 (9)
Type 2 diabetes, n (%)	11 (65)	0 (0)
Cardiac involvement, n (%)	0/5 (0)	2/6 (33)
Malignancy, n (%)	2 (12)	1 (9)
Rituximab, n (%)	2 (12)	5 (46)

28 patients had a diagnosis of IMNM, of which 39% had anti-SRP and 61% had anti-HMGCR myopathy. SRP patients were predominantly of African or African-Caribbean descent (91%) with more ethnic heterogeneity observed in the HMGCR group. 82% of HMGCR patients were exposed to statins compared to 9% of SRP subjects. Six SRP patients underwent cardiac MRI with two patients demonstrating cardiac involvement whilst myocarditis was not identified in anti-HMGCR myopathy. Two HMGCR patients were identified with malignancies (follicular thyroid carcinoma and low-grade non-Hodgkin's lymphoma) and one SRP patient was identified with prostate adenocarcinoma.

11 HMGCR and 4 SRP patients were initiated on 'triple therapy' – pulsed intravenous methylprednisolone (IVMP) followed by high dose oral prednisolone, intravenous immunoglobulin (IVIg) and an immunosuppressant (methotrexate or azathioprine). The remainder were initially commenced on either IVMP/prednisolone or IVIg dependent on patient factors (e.g. diabetes).

46% of SRP patients received rituximab therapy (6 months to 9 years post symptom onset) compared to 12% of HMGCR patients (4 to 6 years post symptom onset). 3 SRP patients responded well to rituximab clinically and biochemically (the other 2 patients were followed-up in local hospitals after their first dose of rituximab).

Conclusion: There were distinct features in our IMNM cohort based on antibody profile. Anti-SRP myopathy disproportionately affected more African and African-Caribbean patients. This group tended to have higher creatine kinase levels and cardiac complications were present in some. Anti-SRP myopathy was associated with a failure to respond adequately to conventional therapies requiring the addition of rituximab more frequently and earlier in the disease course. There is heterogeneity in therapy choice depending on clinician experience and patient factors suggesting the need for further prospective studies and standardised protocols.

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Risk Factors Associated with Mortality in Inflammatory Myositis: An Asian Perspective

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Background/Purpose: Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of autoimmune diseases with systemic involvement and excess mortality. We aim to describe the causes and evaluate predictors of mortality in patients at a tertiary-care academic medical institution in Singapore.

Methods: Medical records of patients newly diagnosed with IIM in the Department of Rheumatology and Immunology, Singapore General Hospital, between 2003-2017 were retrospectively reviewed. Patients recruited fulfilled the 2017 EULAR/ American College of Rheumatology (ACR) classification criteria[1] for polymyositis (PM), dermatomyositis (DM), immune-mediated necrotizing myopathy (IMNM) and amyopathic dermatomyositis (ADM). Demographics, disease manifestations and treatment for cases were collected using a standardized protocol. In-hospital cause of death was determined by two independent reviewers according to categories set apriori. Person-years follow-up was calculated from date of cohort entry to either death or censor date. Univariate Cox proportional hazard (PH) regression was used to examine the association between each variable and mortality. We included both variables that were reported to be associated with mortality in the literature or variables with $p < 0.1$ in the multivariate Cox regression model. We used the stepwise forward selection approach to select variables that were significant at $p < 0.05$.

Results: Of 100 patients (23% male, 76% Chinese), 58% and 40% fulfilled the definite and probable EULAR/ACR criteria for IIM respectively; 50% PM, 43% DM, 6% ADM and 1% juvenile myositis (Table 1). Mean age of diagnosis was 53.7 (SD 14.7) years, with 359.0 person-years follow-up from initial diagnosis. Of those who underwent a muscle biopsy (N=77), 99% had features consistent with that of an inflammatory myositis. 40% of all patients were positive for myositis-specific/associated antibodies. (Figure 1). Forty-one percent of all patients had interstitial lung disease (ILD). There were 26 deaths (26%), translating to mortality rate of 72.4 per 1000 patient years. 62% percent of deaths were due to infection (pneumonia [n=14], infective endocarditis [n=1], staphylococcus bacteraemia [n=1]), whilst 19% were due to ILD. In the multivariate analysis, Chinese ethnicity (HR 0.48 95% CI 0.24-0.96, $p = 0.039$) and male gender (HR 2.58 95% CI 1.22-5.50, $p = 0.014$) were independent predictors of mortality.

Conclusion: Pneumonia and ILD are the leading causes of death for IIM in this Asian cohort. Chinese and male gender were independent predictors of mortality.

Reference:

1. I.E. Lundberg, et al. 2017 EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. 2017. Ann Rheum Dis, 76 (12):1955-64.

Table 1: Baseline characteristics of patients recruited

Gender:	
Male, n (%)	23 (23.0)
Ethnicities:	
Chinese, n (%)	76 (76.0)
Non-Chinese, n (%)	24 (24.0)
Myositis subtypes:	
Polymyositis, n (%)	50 (50.0)
Dermatomyositis, n (%)	43 (43.0)
Clinically Amyopathic Dermatomyositis, n (%)	6 (6.0)
Juvenile Dermatomyositis, n (%)	1 (1.0)
Clinical features and investigations:	
Concomitant Autoimmune disease*, n (%)	21 (21.0)
Malignancy within 3 years of diagnosis, n (%)	16 (16.0)
Presence of ILD, n (%)	41 (41.0)
Asymptomatic, n (%)	12 (12.0)
HRCT changes:	
Nonspecific interstitial pneumonia, n (%)	26 (26.0)
Usual interstitial pneumonia, n (%)	13 (13.0)
Organising Pneumonia, n (%)	4 (4.0)
Electromyogram, n (%)	88 (88.0)
Muscle biopsy done, n (%)	77 (77.0)
Myositis-specific/associated antibodies(MSA/MAA):	
Patients with 1 MSA/MAA, n (%)	25 (25.0)
Patients with 2 MSAs/MAAs, n (%)	12 (12.0)
Anti-Jo-1, n (%)	14 (14.0)
Anti-Ro52, n (%)	14 (14.0)
Anti-MDA5, n (%)	5 (5.0)
Anti-SRP, n (%)	4 (4.0)
Anti-PM-Scl75, n (%)	4 (4.0)
Anti-TIF1g, n (%)	4 (4.0)
Laboratory results:	
ESR, mm/Hr, mean (SD)	40 (30)

Creatine Kinase, U/L, mean (SD)	2889 (4388)
Aldolase, U/L, mean (SD)	40 (47)
Alanine aminotransferase, U/L, mean (SD)	107 (115)
Aspartate aminotransferase, U/L, mean (SD)	140 (142)
Lactose Dehydrogenase, U/L, mean (SD)	1290 (837)

Abbreviations: ILD (Interstitial lung disease), HRCT (High-resolution computed tomography), ESR (Erythrocyte sedimentation rate)

* Autoimmune thyroiditis, Systemic sclerosis, Systemic lupus erythematosus, Rheumatoid arthritis, Sjögren syndrome, Microscopic polyangiitis

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Severe Axial and Pelvifemoral Muscle Damage in Immune-Mediated Necrotizing Myopathy Evaluated By Whole-Body MRI

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Background/Purpose: Immune-mediated necrotizing myopathies (IMNM) are a severe condition with early muscle damage attested by MRI of thigh muscles. Presence of damage in the other muscle groups, as well as the pattern and the severity of muscle damage in IMNM according to clinical and serological features remain to be clarified.

Methods: IMNM patients with a whole-body MRI (WB-MRI) (n=42) (anti-HMGCR, anti-SRP and seronegative) were included as well as 60 sIBM patients (as controls). Each muscle groups (n=55) were evaluated and fat replacement was estimated in T1 sequence using the Mercuri score (1= normal; 2= mild involvement, fat replacement <30%, 3=moderate involvement, 30-60%; 4=severe involvement, >60%). Overall lesion load was defined as the sum of all abnormal Mercuri scores (≥ 2) evaluated in each muscle groups (reported in percentage from minimum 0% to maximum 100%) and lesion load quotient was defined as the overall lesion load divided by disease duration (years) at WB-MRI. Multivariate analysis including MRI data but also age at first symptom, disease duration and treatment initiation delay were performed by principal component analysis (PCA) and hierarchical clustering analysis (HCA).

Results: IMNM patients (anti-HMGCR, n=25; anti-SRP, n=12 and seronegative, n=5) were aged 48.1 ± 15.8 years at WB-MRI and had a disease duration of 9.8 ± 8.1 years. Most severely affected muscle groups (mean Mercuri \pm SD) were located in the pelvifemoral (gluteus minimus: 2.71 ± 1.15 , gluteus medius: 2.6 ± 1.17 , great adductors: 2.55 ± 1.27 and perineal: 2.43 ± 1.42), lumbar (lumbar extensors: 2.19 ± 1.11) and to a lesser extent in the scapular region (subscapularis: 2.73 ± 1.16). Unsupervised analysis showed two subgroups of patients: one with a mild lesion load ($15 \pm 10\%$, n=32/42) and another with a severe lesion load ($60 \pm 10\%$, n=10/42; $p < 0.001$). In the first group, the mean disease duration before WB-MRI was 6.8 ± 6.0 years compare to 19.52 ± 5.7 years in the second ($p < 0.0001$). Correlational studies confirmed that disease duration was the most important predictor of muscle damage (e.g lumbar $r = 0.76$, and pelvifemoral muscle groups r ranging from 0.55 - 0.73 ; $p < 0.01$).

Nonetheless, multivariate analyses – adjusted for disease duration, age at first symptoms and treatment initiation delay - demonstrated a more severe involvement of the gluteus maximus ($p = 0.04$) and the great adductor ($p = 0.04$) in seropositive vs seronegative patients.

Overall lesion load quotient was similar in IMNM compared to IBM (14 ± 14.9 vs 9.4 ± 8 , $p = 0.3$), but muscle involvement pattern was different. Lesion load quotient was more severe in the trapezius ($p = 0.05$), infraspinatus ($p = 0.03$), psoas ($p = 0.0008$), iliac ($p = 0.0002$), longus adductor ($p = 0.01$) and pectinus ($p = 0.0003$) in IMNM compared to IBM.

Conclusion: IMNM is associated with a severe fatty replacement in the axial and pelvifemoral muscle groups. Disease duration and serological status are important predictor of muscle damage. IMNM and IBM patients seem to have comparable overall lesion load, but progression was more severe in some muscle groups.

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Risk Factors for Relapse in Inflammatory Myopathy

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Background/Purpose: Many inflammatory myositis patients experience relapse (relapse rate : 48~65%). Risk factors for relapse in inflammatory myositis remain uncertain. We investigate the relapse and related factors in patients with inflammatory myopathy.

Methods: Retrospectively, the patients who met the Bohan and Peter criteria for the diagnosis of dermatomyositis and polymyositis were collected in a tertiary hospital between Jan. 2005 to Dec. 2016. The relapse was defined as resuming glucocorticoid or dose up of glucocorticoid more than 50% due to myositis or skin aggravation after improvement of inflammatory myositis by initial treatment. We investigated factors associated with the relapse using Multivariate Cox proportional hazards models with backward elimination.

Results: We identified 138 patients (61 dermatomyositis, 3 inclusion body myositis, and 74 polymyositis), and high dose (1mg/kg) of glucocorticoid (median, 60mg [50.0-60.0], prednisolone equivalent) was given as an initial treatment for inflammatory myopathy. Glucocorticoid dose has been reduced less than 15 mg (prednisolone equivalent) until 5 months (median, [4-7]) after initial treatment. However, during glucocorticoid tapering, relapse occurred in 86 patients (62%) after 12 months (median, [7-25]) of initial treatment. Independent risk factors for relapse on multivariable analysis in the overall inflammatory myopathy patients included anti-Ro antibody positivity (adjusted HR 1.84, $p = 0.028$), elevated level of creatine kinase at 1 month after initial glucocorticoid treatment (adjusted HR 2.10, $p = 0.007$), administration of immunomodulators for maintenance (methotrexate, azathioprine, or cyclosporine; adjusted HR 0.41, $p = 0.003$).

Conclusion: Administration of immunomodulator for maintenance may help to reduce the risk of relapse in inflammatory myopathy.

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Autoantibody Profile and Clinical Characteristics in Patients with Idiopathic Inflammatory Myopathies

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Background/Purpose: Autoimmune myositis(AIM) is a constellation of rare chronic disease with progressive muscle weakness. Several autoantibodies are found to be highly correlated with IIM(myositis-associated autoantibodies, MAAs) or distinct clinical features amongIIM (myositis-specific autoantibodies, MSAs). In the current study, we evaluated autoantibody profiles using LIA and analyzed their association with clinical features among patients with autoimmune myositis in Korea.

Methods: Patients with idiopathic inflammatory myopathies were enrolled at seven tertiary care university medical centers. Autoantibodies were examined using EUROLINE assay (for 16 antigens including Mi-2alpha, Mi-2beta, TIF1gamma, MDA5, NXP2, SAE1, Ku, PM-Scl100,PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, Ro-52). Data on history, physical findings, and laboratory investigations were obtained by retrospective medical record review.

Results: A total of ninety-three patients were enrolled. Seventy-two percent (n=67) was women, and mean age at the diagnosis was 50.7 +/- 13.5 year-old. Patients with PM, DM, ADM, and OM were 37 (39.8%), 48 (51.6%), 6 (6.5%), and 10 (10.8%), respectively. Anti-Ro52antibody was the most common antibodies, and anti-TIF1gamma antibody was the most common MSA (Table 1). Positive anti-TIF1gamma antibody was significantly associated with the presence of malignancy and absence of interstitial lung disease (ILD). ILD was observed among 42 patients (45.2 %) and of those ILD,anti-MDA5 antibody was associated with bronchiolitis obliterans organizing pneumonia/cryptogenic organizing pneumonia (BOOP/COP) and anti-synthetase antibodies were associated with nonspecific interstitial pneumonia (NSIP, Table 2).

Conclusion: Myositis-specific autoantibodies were related with clinical manifestations. Especially, anti-MDA5 and anti-synthetase were associated with BOOP/COP and NSIP, respectively.

Table 1. Autoantibody profiles

Antigen	N	% (of total 93)
Mi-2 alpha	7	7.5
Mi-2 beta	5	5.4
TIF1 gamma	15	16.1
MDA5	11	11.8
NXP2	1	1.1
SAE1	2	2.2
Ku	4	4.3
PM-Scl100	1	1.1
PM-Scl75	8	8.6
Jo-1	13	14
SRP	12	12.9
PL-7	4	4.3
PL-12	1	1.1
EJ	4	4.3
OJ	6	6.5
Ro-52	37	49.3

Table 2. Clinical features and autoantibodies

Clinical features	autoantibodies	odds ratio	95% confidence interval	P
Malignancy	Anti-TIF1gamma	43.4	7.7-245.5	<0.01
ILD	Anti-TIF1gamma	0.3	0.7-1.0	=<0.05
ii	Anti-synthetase antibodies*	7.6	2.5-22.9	<0.01
ILD-BOOP/COP	Anti-MDA5	7	1.8-27.1	<0.01
ILD-NSIP	Anti-synthetase antibodies*	3.5	1.3-9.8	<0.05

* anti-synthetase antibodies include antibodies against Jo-1, PL-7, PL-12, EJ, and OJ

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Physical Activity Monitoring Using Wrist-Worn Accelerometer in the Assessment and Follow-up of Patients with Myositis

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Background/Purpose: Wrist-worn accelerometers allow the objective estimation of physical activity (PA) in daily life. Recently, the ENMC workshop on outcome measures in myositis suggested to implement PA monitoring for improving patient follow-up. This study aimed to evaluate PA monitoring in the assessment of myositis patients in daily clinical practice.

Methods: Included patients had a diagnosis of dermatomyositis (DM), immune-mediated necrotizing myopathy (IMNM) or overlap myositis (OM). They either had a new-onset or relapsing myositis, a stable disease on maintenance therapy or were undergoing immunosuppressant tapering. Patients were evaluated at baseline and 6 months (M6). IMACS core-set measures, ACR/EULAR improvement score, muscle endurance testing, deltoid and psoas strength using hand-held dynamometry, 14-days raw acceleration data (expressed both as mean daily Euclidean norm minus 1 g (ENMO) and as standard deviations from healthy control Z-score), and quality of life (QoL) questionnaires were recorded. Relationships between variables were investigated using Spearman correlation coefficient (ρ) and random forest (RF) regressions.

Results: Fifty-five patients (16 OM, 27 IMNM and 12 DM) were included. At baseline, 67% had ENMO Z-score lower than 1 (mean Z-scores -1.09 ± 0.94). At M0, ENMO mainly correlated with manual muscle testing 8 (MMT8, $\rho=0.44$, $p<0.001$), creatinine level ($\rho=0.43$, $p<0.001$), HAQ ($\rho=-0.53$, $p<0.0001$), and SF-36-physical functioning ($\rho=0.40$, $p<0.01$). According to RF regressions, most important features associated with ENMO Z-scores were HAQ, SF-36-physical functioning/energy/pain and disease duration.

At M6, ENMO changes mainly correlated to changes in muscle enzymes ($\rho=-0.44$, $p<0.01$), MMT8 ($\rho=0.44$, $p<0.01$), and depression score ($\rho=-0.44$, $p=0.013$). According to the RF regression, most important features associated with ENMO changes were absolute change in MMT8, HAQ, SF-36-physical functioning, physician global assessment, and depression score.

ENMO changes were correlated with ACR/EULAR improvement score ($\rho=0.48$, $p<0.01$) and all patients, except one, achieving a major improvement had an absolute change of ENMO >5 mg/day. Yet, only 50% with moderate improvement (ACR/EULAR) had an improvement in ENMO and variable changes in ENMO were observed in patients with unchanged and minimally improved status.

Conclusion: PA levels were smaller in myositis patients at baseline compared to healthy controls and were correlated with MMT8 and QoL. Patients with major ACR/EULAR improvements at follow-up were associated with consistent changes in PA, while other displayed heterogeneous changes in PA.

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In Patients with Suspected Idiopathic Inflammatory Myopathy, Does Pre-Biopsy Musculoskeletal MRI Result in Greater Yield of Diagnostic Biopsy Results? Summary of Data from a 10-Year Single Hospital Audit

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster I: Clinical Features and Disease Course

Session Type: ACR Poster Session A

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

Background/Purpose: The idiopathic inflammatory myopathies (IIM) constitute a potentially steroid-responsive group of conditions that must be differentiated from other causes of muscle weakness. Histopathology from muscle biopsy remains pivotal to diagnosis; however, muscle involvement in IIM is often patchy with associated risk of non-diagnostic biopsies. There has been mounting evidence for the use of magnetic resonance imaging (MRI) prior to biopsy to target biopsy site and improve diagnostic yield [1], though this is not routinely used. This single-centre 10-year clinical audit aimed to examine whether the use of MRI prior to muscle biopsy in patients with undifferentiated myopathy resulted in high rates of diagnostic results compared to selection of biopsy site based on clinical assessment of muscle involvement alone.

Methods: Patient admissions over a 10-year period with an ICD code of “myopathy” or “myositis” were extracted from the hospital iSOFT database and screened for eligibility. Each eligible case was assessed to determine (1) clinical localisation of muscle involvement (2) whether a musculoskeletal MRI was performed pre-biopsy (3) site of muscle biopsy (4) histopathology result (+/- electron microscopy/muscle markers) (5) congruence of muscle involvement by clinical assessment and selected biopsy site (6) congruence of muscle involvement on MRI and selected biopsy site.

Results: Forty-eight eligible cases were identified for inclusion in the study. Of these, 15 had musculoskeletal MRI performed prior to muscle biopsy and 33 did not. Of the patients who did not have an MRI, the biopsy was positive in 30 cases (91%) and negative in 3 (9%). In the patients who did undergo MRI, the result was positive in 12 (80%) and negative in 3 (20%). The selected biopsy site correlated with clinical sites of muscle involvement in 40 cases, 3 did not, and 5 lacked sufficient clinical documentation to determine this. Two of the three negative biopsies in the MRI group had been targeted appropriately; biopsy correlated to sites of involvement on MRI. One of these cases was ultimately given a clinical diagnosis of dermatomyositis.

Conclusion: Inflammatory myopathies are uncommon clinical conditions. Despite the limitations of a small sample size and retrospective analysis, our results suggest that clinical targeting for muscle biopsy site alone yields high rates of diagnostic results and doesn't support the use of MRI to target biopsy site. However the results are perhaps surprising, and therefore a prospective study would be of interest.

1. Day J, Patel S, Limaye V. The role of magnetic resonance imaging techniques in evaluation and management of the idiopathic inflammatory myopathies. *Semin Arthritis Rheum.* 2017;46(5):642-9.

Disclosure: J. Murdoch, None; M. Needham, None; H. Keen, None.

Abstract Number: 395

Systemic Lupus Erythematosus (SLE) with Inflammatory Myositis

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster I: Clinical Features and Disease Course

Session Type: ACR Poster Session A

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

Background/Purpose: The goal of this study was to identify specific clinical features of patients with SLE who have inflammatory myositis.

Methods: A retrospective chart review was performed of patients seen in the rheumatology clinic at a single center safety net hospital over a period of 4 months and who had an encounter diagnosis of SLE by ICD-10 code [M32.x]. Diagnosis of SLE was confirmed by one author (NB) using 2015 ACR/SLICC criteria. Cases of inflammatory myositis were defined by either muscle biopsy or with CK elevation/muscle weakness with or without confirming muscle MRI consistent with myositis. Data on patient demographics, clinical and laboratory features were extracted. Chi-square was used to analyze clinical features.

Results: Of 354 patients with an encounter diagnosis of SLE, 30 (8.5%) were diagnosed with myositis. Most (93%) were women; 56% were African American and 43% Hispanic. Half were diagnosed with SLE and myositis simultaneously, 30% developed myositis after SLE diagnosis (mean 5.5 years later) and 20% were diagnosed with myositis prior to SLE (mean 10.9 years earlier). Patients fell into two clinical categories, those with features of systemic sclerosis (60%) and those

without (40%). Among those with features of systemic sclerosis, 9 of 18 met the 2013 ACR/EULAR classification criteria for systemic sclerosis, while 9 of 18 did not but scored 5 or more criteria points. SLE patients with co-existing features of systemic sclerosis were more likely to have Raynaud's phenomenon and interstitial lung disease ($p < 0.05$) (Table 1 and 2). Muscle biopsy was performed in 16 patients, with 12 biopsies among 11 patients available for review (one patient underwent two biopsies over 3 years). Non-specific inflammatory changes were the most commonly observed muscle biopsy feature, followed by tubuloreticular inclusions by electron microscopy (Table 3). Autoimmune necrotizing myopathy was described in 4 of 12 muscle biopsies, three of whom lacked features of systemic sclerosis.

Conclusion: In our cohort of SLE patients at a large safety net hospital, the diagnosis of co-existing myositis was seen in 8.5% of patients, most of whom had overlap features of systemic sclerosis.

Table 1. Clinical features of patients with SLE and inflammatory myositis

Clinical Features, n (%)	SLE without Scleroderma Features (n=12)	SLE with Scleroderma Features (n=18)	All Patients (n=30)
Arthralgias	10 (83%)	17 (94%)	27 (90%)
Inflammatory arthritis	10 (83%)	16 (89%)	26 (87%)
Leukopenia or lymphopenia	11 (92%)	15 (83%)	26 (87%)
Myalgia	9 (75%)	16 (89%)	25 (83%)
Raynaud's	6 (50%)	18 (100%)*	24 (80%)
Thrombotic event or significant pregnancy morbidity	8 (67%)	10 (56%)	18 (60%)
Interstitial lung disease	2 (17%)	15 (83%)*	17 (57%)
Serositis	9 (75%)	8 (44%)	17 (57%)
Alopecia	7 (58%)	10 (56%)	17 (57%)
Oral/nasal ulcers	7 (58%)	8 (44%)	15 (50%)
Gottron's or heliotrope rash	6 (50%)	4 (22%)	10 (33%)
Nephritis	4 (33%)	6 (33%)	10 (33%)
Discoid lupus	3 (25%)	5 (28%)	8 (27%)
Myocarditis	1 (8%)	6 (33%)	7 (23%)

* $p < 0.05$ by chi-square

Table 2. Serological features of patients with SLE and inflammatory myositis

Serologic Marker, n (%)	SLE without Scleroderma Features	SLE with Scleroderma Features	All Patients
RNP	7/12 (58%)	16/18 (89%)	23/30 (77%)
Low C3 or C4	7/12 (58%)	14/18 (78%)	21/30 (70%)
Any APLS Ab	5/10 (50%)	10/14 (71%)	15/24 (63%)
Smith	6/12 (50%)	12/17 (71%)	18/29 (62%)
RF or CCP	5/10 (50%)	12/16 (75%)	17/26 (65%)
SSA	5/12 (42%)	11/18 (61%)	16/30 (53%)
dsDNA	5/12 (42%)	10/18 (56%)	15/30 (50%)
p-ANCA	2/8 (25%)	4/9 (44%)	6/17 (35%)
U2snRNP	0/6 (0%)	5/10 (50%)	5/16 (31%)
Ku	0/6 (0%)	2/10 (20%)	2/16 (13%)
Jo 1	0/6 (0%)	2/14 (14%)	2/20 (10%)
Mi2	1/6 (17%)	1/12 (8%)	2/18 (11%)
SRP	1/6 (17%)	0/10 (0%)	1/16 (6%)

* $p < 0.05$ by chi-square.

APLS: antiphospholipid antibody, RF: rheumatoid factor, CCP: anti-citrullinated peptide

Table 3. Muscle biopsy features of patients with SLE and inflammatory myositis

		Patients without scleroderma features						Patients with scleroderma features					
Muscle biopsy features		Pt 1	Pt 2	Pt 3	Pt 4	Pt 5 # 1	Pt 5 #2	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10	Pt 11
Autoimmune Necrotizing Myositis	Necrotic fibers with sparse mononuclear cell infiltrate	X	X	X					X				
	Myophagocytosis	X	X	X			X		X		X		
Polymyositis- related Changes	Endomysium inflammatory cells	X	X				X	X	X		X		
	Increase in endomyseal connective tissue	X	X					X		X			
Nonspecific Inflammatory Changes	Variable fiber size	X	X		X	X	X	X	X	X	X		
	Necrotic/regenerating muscle fibers	X	X	X	X	X	X	X	X	X	X		X
	MHC class 1 sarcolemmal upregulation (if stained)			X		X		X	X				
Dermatomyositis- related Changes	Perivascular inflammatory cells	X		X			X	X	X		X		
	Perifascicular atrophy	X		X			X			X	X		
	Perimyseal inflammation			X		X	X	X		X	X		
	Tubuloreticular inclusion by electron microscopy	X		X	X	X	X		X	X	X		
Neuropathic Changes	Denervation atrophy				X				X			X	X

Note: patient 5 had two biopsies performed. "X" denotes presence of biopsy finding.

Disclosure: N. Bitencourt, None; E. Solow, None; B. L. Bermas, UpToDate, 7.

Clinical, Physiologic, and Radiologic Features Associated with Severe MDA5-Associated Interstitial Lung Disease

Tracy Doyle¹, Priya Borker², Elaine Fletcher¹, David Murphy³, Rachna Madan³ and Paul F. Dellaripa⁴, ¹Brigham and Women's Hospital, Boston, MA, ²Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, Boston, MA, ³Brigham and Women's Hospital, Harvard Medical School, Boston, MA, Boston, MA, ⁴Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Session Information

Session Date: Sunday, October 21, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster I: Clinical Features and Disease Course

Session Type: ACR Poster Session A

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

Background/Purpose: Autoantibodies against melanoma differentiation-associated protein 5 (MDA-5) have been described in patients with dermatomyositis (DM) and progressive interstitial lung disease (ILD). Previous cohorts have shown a significant portion of these patients can develop rapidly progressive ILD. The goal of our study is to describe the

	n (%) or mean +/- SD		
	All Subjects n=15	Mild/Mod ILD n=8	Severe ILD n=7
Demographics			
Age	57 +/- 12	55 +/- 12	59 +/- 13
Female gender	11 (73%)	8 (75%)	5 (71%)
Caucasian race	12 (80%)	6 (75%)	6 (86%)
Ever smoking	5 (33%)	2 (25%)	3 (43%)
Pack years	18 +/- 20	24 +/- 30	12 +/- 11
Clinical Features			
Rash	13 (87%)	7 (88%)	6 (86%)
Fever	5 (33%)	3 (38%)	2 (29%)
Inflammatory arthropathy	8 (53%)	4 (50%)	4 (57%)
Raynaud's phenomenon	6 (40%)	5 (63%)	1 (14%)
Mechanic's Hands	7 (47%)	4 (50%)	3 (43%)
Myositis/muscle weakness	3 (20%)	0 (0%)	3 (43%)
Oral ulcers	3 (20%)	1 (13%)	2 (29%)
Abnormal capillary microscopy	4 (29%)	2 (25%)	2 (29%)
Nasal congestion	2 (13%)	0 (0%)	2 (29%)
Pneumomediastinum	4 (27%)	0 (0%)	4 (57%)
ILD	14 (93%)	7 (88%)	7 (100%)
Classification of Severe ILD			
FVC <50 at time of diagnosis	1 (7%)	0 (0%)	1 (14%)
Oxygen use for ILD	2 (13%)	0 (0%)	2 (29%)
Transplant evaluation for ILD	5 (33%)	0 (0%)	5 (71%)
Respiratory failure requiring MV	3 (20%)	0 (0%)	3 (43%)
Death due to ILD or MDA5 diagnosis	3 (20%)	0 (0%)	3 (43%)
Phenotype of MDA5 Disease			
CADM	4 (27%)	2 (25%)	2 (29%)
Vasculopathic skin lesions	6 (40%)	3 (38%)	3 (43%)
CADM/vasculopathy	3 (20%)	2 (25%)	1 (14%)
Other	2 (13%)	1 (13%)	1 (14%)
Laboratory Abnormalities			
Creatinine kinase	150 +/- 333	59 +/- 25	241 +/- 470
Aldolase	8 +/- 6	6 +/- 1	10 +/- 8
Erythrocyte sedimentation rate	54 +/- 35	35 +/- 20	72 +/- 40
C-reactive protein	23 +/- 33	3 +/- 2	41 +/- 37
Treatment			
Corticosteroids	15 (100%)	7 (100%)	8 (100%)
Rituximab	5 (33%)	1 (13%)	4 (57%)
Methotrexate	4 (27%)	3 (38%)	4 (57%)
Azathioprine	5 (33%)	4 (50%)	1 (14%)
Mycophenolate mofetil	8 (53%)	6 (75%)	2 (29%)
Cyclosporine	5 (33%)	1 (13%)	4 (57%)

Table 1: Baseline characteristics of MDA5-positive associated ILD subjects stratified by mild/moderate vs. severe disease			
	n (%) or mean +/- SD		
	All Subjects n=15	Mild/Mod ILD n=8	Severe ILD n=7
Demographics			
Age	57 +/- 12	55 +/- 12	59 +/- 13
Female gender	11 (73%)	6 (75%)	5 (71%)
Caucasian race	12 (80%)	6 (75%)	6 (86%)
Ever smoking	5 (33%)	2 (25%)	3 (43%)
Pack years	18 +/- 20	24 +/- 30	12 +/- 11
Clinical Features			
Rash	13 (87%)	7 (88%)	6 (86%)
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Abnormal capillary microscopy	4 (29%)	2 (25%)	2 (29%)
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FVC <50 at time of diagnosis	1 (7%)	0 (0%)	1 (14%)
Oxygen use for ILD	2 (13%)	0 (0%)	2 (29%)
Transplant evaluation for ILD	5 (33%)	0 (0%)	5 (71%)
Respiratory failure requiring MV	3 (20%)	0 (0%)	3 (43%)
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CADM	4 (27%)	2 (25%)	2 (29%)
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CADM/vasculopathy	3 (20%)	2 (25%)	1 (14%)
Other	2 (13%)	1 (13%)	1 (14%)
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Creatinine kinase	150 +/- 333	59 +/- 25	241 +/- 470
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Treatment			
Corticosteroids	15 (100%)	7 (100%)	8 (100%)
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Methotrexate	4 (27%)	3 (38%)	4 (57%)
Azathioprine	5 (33%)	4 (50%)	1 (14%)
Mycophenolate mofetil	8 (53%)	6 (75%)	2 (29%)
Cyclosporine	5 (33%)	1 (13%)	4 (57%)

phenotypic, physiologic, and radiologic features of this cohort and to identify important factors that may predict prognosis in terms of disease severity and outcomes.

Methods: A retrospective single center observational longitudinal study characterized clinical characteristics, lung function, HRCT findings, and outcomes of MDA5-positive patients referred to a tertiary hospital. Patients who met the following criteria were defined as severe ILD: (1) baseline FVC <50% with ILD as known cause; (2) oxygen use due to ILD; (3) lung transplant evaluation due to ILD; (4) respiratory failure requiring mechanical ventilation for ILD; (5) death due to ILD or MDA5 diagnosis. CT scans were reviewed by 2 radiologists to determine ILD pattern and a semi-quantitative CT severity score.

Results: Fifteen MDA5-positive cases were identified between 2007 to 2018; 4 (27%) had clinically amyopathic DM (CADM), 6 (40%) had vasculopathic skin lesions, and 3 (20%) had both CADM/vasculopathy. Seven subjects (47%) developed severe ILD, of which 3 died from hypoxemic respiratory failure and 1 from failure to thrive. Those with severe disease had lower FVC%, TLC%, DLCO%, and CT ILD score at baseline and 1 year of following up, and were more likely to have a cryptogenic organizing pattern on CT. Smoking history, myositis, oral ulcers, nasal congestion, pneumomediastinum, and higher levels of inflammatory markers were more likely to be found in the severe group, whereas Raynaud's phenomenon and non-specific interstitial pneumonia pattern on CT were more common in the mild/moderate group.

Conclusion: Our data supports that MDA5Ab-associated ILD seems to follow a bimodal pattern, which can be severe and/or progressive in a significant number of cases, but may be treatable and stabilized in certain patients. Although CADM and ulcerative and nodular lesions consistent with vasculopathy were found in equal frequency in the entire cohort and in

Table 2: Physiologic and radiographic features of MDA5-positive associated ILD subjects stratified by mild/moderate vs. severe disease			
	n (%) or mean +/- SD		
	All Subjects n=15	Mild/Mod ILD n=8	Severe ILD n=7
Baseline PFTs			
FEV1%	72 +/- 17	78 +/- 14	64 +/- 20
FVC%	70 +/- 19	77 +/- 15	60 +/- 20
FEV1/FVC	83 +/- 11	80 +/- 12	86 +/- 9
TLC%	78 +/- 22	85 +/- 22	87 +/- 19
DLCO%	48 +/- 14	54 +/- 7	38 +/- 20
1-Year PFTs			
FEV1%	81 +/- 20	90 +/- 11	63 +/- 24
FVC%	79 +/- 21	83 +/- 23	62 +/- 24
FEV1/FVC	82 +/- 6	81 +/- 5	84 +/- 7
TLC%	79 +/- 18	85 +/- 15	66 +/- 20
DLCO%	58 +/- 13	63 +/- 13	49 +/- 8
CT			
Baseline ILD score	72 +/- 66	44 +/- 46	92 +/- 74
1-year ILD score	86 +/- 70	50 +/- 67	130 +/- 64
NSIP	6 (40%)	4 (57%)	2 (29%)
COP	2 (14%)	0 (0%)	2 (29%)
NSIP and COP	3 (21%)	1 (14%)	2 (29%)

the severe ILD subgroup, risk factors for severe disease appear to be smoking history, myositis, oral ulcers, nasal congestion, pneumomediastinum, and higher levels of inflammatory markers.

MDA-5 = melanoma differentiation-associated gene 5; CADM = clinically amyopathic dermatomyositis; ILD = interstitial lung disease

Disclosure: T. Doyle, None; P. Borker, None; E. Fletcher, None; D. Murphy, None; R. Madan, None; P. F. Dellaripa, up to date, 7, Genentech, Inc., 9.

Abstract Number: 397

Myositis-Specific Autoantibodies and Their Clinical Associations

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster I: Clinical Features and Disease Course

Session Type: ACR Poster Session A

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

Background/Purpose: Myositis-specific autoantibodies (MSAs) have been shown to predict clinical features and have prognostic implications in patients with idiopathic inflammatory myopathies (IIMs), with anti-melanoma differentiation-associated gene 5 antibody (anti-MDA5 Ab) and anti-transcriptional intermediary factor antibody (anti-TIF1γAb) being associated with potential life-threatening complications. However, testing of autoantibodies in inflammatory myopathy is not routinely performed in Hong Kong due to its cost and limited availability. The aim of the study is to investigate the prevalence of MSAs and their associated complications.

Methods: A total of 201 consecutive patients with IIMs being followed up in the Rheumatology clinics of participating regional hospitals from July 2016 to January 2018 were recruited. Clinical characteristics, treatment history and disease

complications such as interstitial lung disease (ILD), rapidly progressive interstitial lung disease (RP-ILD) and malignancies were documented. Immunoblot assay was used to detect the presence of MSAs in all the participants.

Results: Out of the 201 patients with IIMs, 122 (60.7%) had dermatomyositis while 79 (39.3%) had polymyositis. Around 63.2% patients had at least one MSA positive. The most common MSAs were anti-MDA5 Ab (28, 13.9%) and anti-TIF1 γ Ab (28, 13.9%), followed by anti-Jo-1 Ab (25, 12.4%). Anti-MDA5 Ab was present exclusively in dermatomyositis and was strongly associated with digital ulcers, clinically amyopathic dermatomyositis (CADM) and RP-ILD (all $p < 0.001$). Anti-TIF1 γ Ab was strongly associated with refractory rash and malignancy (both $p < 0.001$). Anti-Jo-1 Ab was strongly associated with interstitial lung disease (ILD) ($p = 0.001$) and was negatively associated with malignancy ($p = 0.006$). Multivariate analysis showed that independent risk factors of development of RP-ILD included anti-MDA5 Ab positivity (OR 14.5, $p = 0.001$), CADM (OR 13.9, $p = 0.015$) and history of pulmonary tuberculosis (OR 12.2, $p = 0.026$). By Cox regression with adjustment of confounders, independent risk factors for malignancy included anti-TIF1 γ Ab positivity (HR 3.55, $p = 0.002$), dermatomyositis (HR 3.82, $p = 0.009$) and family history of cancer (HR 3.40, $p = 0.038$). In 45 newly diagnosed IIM patients, 32 (71.1%) had dermatomyositis and 13 (28.9%) had polymyositis. Kaplan Meier analysis showed that the 6-month mortality in patients with anti-MDA5 Ab was 47.5%, compared to 11.1% in those without anti-MDA5 Ab. Anti-MDA5 was associated with significantly lower survival ($p = 0.002$).

Conclusion: The local data on MSA profiles and their clinical associations were established. Anti-MDA5 Ab was associated with CADM, RP-ILD and poorer survival, while anti-TIF1 γ Ab was associated with malignancy in Hong Kong Chinese patients with IIMs, especially nasopharyngeal carcinoma. MSA testing enables early confirmation of these diseases with potentially life-threatening complications, and will have an important impact on the management of pulmonary disease and vigilance of malignancy screening.

Disclosure: V. T. L. Wong, None; H. So, None; R. W. K. Ip, None; V. W. Lao, None; S. H. Pang, None; L. S. Tam, None; P. Wong, None; L. H. P. Tam, None; T. O. Lam, None; M. Y. Law, None; I. C. Yim, None; T. L. LAI, None; P. M. L. Lee, None; R. M. L. Yip, None.

Abstract Number: 398

Muscle Function and Health-Related Quality of Life in Patients with Polymyositis and Dermatomyositis

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster – ARHP

Session Type: ACR Poster Session A

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

Background/Purpose: Poly- and dermatomyositis (PM/DM) are idiopathic inflammatory muscle diseases characterized by reduced muscle function. Oral glucocorticoids and DMARD's are the usual treatment options and physical exercise plays an important role in the treatment as well. Despite an often beneficial effect of treatment, most patients are left with sustained muscle impairment and reduced quality of life. It is not known how muscle impairment differ between patients with newly onset PM/DM and patients with established PM/DM. The aim of this study is to investigate muscle function as to maximal isometric strength (MVIC) and isometric muscular endurance (ME) in patients with newly onset, active and established PM/DM. A further aim is to investigate possible correlations between muscle function and health related quality of life (HRQoL).

Methods: All patients diagnosed with PM or DM ($n = 5$, all female) during 170901 and 180401 at Karolinska University hospital in Solna who met the inclusion criteria were asked to participate. Patients with established PM/DM ($n = 6$, all female) were identified through patient register at the same clinic, selected to match recent onset disease group as to age and gender. A dynamometer from Biodex was used to assess MVIC and ME starting with three warm-up 4-sec contractions followed by three similar maximal contractions, all with a 3-minute rest in-between. Thereafter six sets of twelve submaximal repetitions, starting on 20 % of MVIC and increasing by 10 %/set, finishing on 70 % of MVIC. Each set ended with a new maximal contraction registered as percentage of initial MVIC. The participants reported HRQoL using SF-36. Statistical significance was set to $p < 0.05$, Mann-Whitney U-test was used to compare groups and Spearman's rho for correlations.

Results: Median age for patients with recent onset PM/DM was 36 (min–max 19–64) years and for established disease 61 (42–66) years. Diagnosis duration was 4 (1–6) months and 126 (85–433) for the two groups, respectively. Patients with recent onset disease had a median MVIC of 73 (53–127) Nm and patients with established disease had 58 (41–82) Nm ($p=0.22$). ME were 83 (63–94) % and 91 (85–98) % for patients with recent onset disease and established PM/DM, respectively ($p=0.08$). The correlations between ME and General Health was ($r_s=0.54$, $CI=-0.08-0.87$) with correlations to Physical Function, Physical Role Function, and Social Function varying between ($r_s=0.40$, $CI=-0.26-0.81$) and ($r_s=0.48$, $CI=-0.17-0.84$). Correlations between MVIC and Vitality, Physical Role function, Emotional Function and Social Function varied between ($r_s=-0.49$, $CI=-0.84-0.16$) and ($r_s=-0.34$, $CI=-0.78-0.33$). Correlations to remaining domains were lower.

Conclusion: No significant differences were found between the groups regarding MVIC and ME. However, there was a trend towards reduced ME in patients with recent onset PM/DM compared to established disease. Correlations between muscle function and HRQoL were moderate at best. Further research is needed with more patients to reach statistical power and improved matching of patients and controls.

Disclosure: K. Andreasson, None; L. Alemo Munters, None; H. Alexanderson, None.

Abstract Number: 399

Musculoskeletal Comorbidities after Total Knee Replacement for Osteoarthritis

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Session Information

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Background/Purpose: For patients undergoing total knee replacement (TKR) for osteoarthritis (OA), preoperative musculoskeletal (MSK) complaints in areas beyond the index knee are common; however, the risk for new MSK comorbidities after TKR is not well studied.

Methods: We used data from the Adding Value in Knee Arthroplasty (AViKA) prospective cohort study on patients undergoing elective TKR for OA at a tertiary academic center. Preoperative questionnaires included demographics, data for Charlson Comorbidity Index, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain and Function Scales, Mental Health Inventory-5 (MHI-5), Pain Catastrophizing Scale (PCS), and presence of MSK symptomatic areas by region (neck, hands/wrists/arms/shoulders, back, hips, non-index knee, and ankles/feet). Follow-up questionnaires including data on incident symptomatic areas were distributed at 3, 6, 12, 24, 36, and 48 months post-TKR. Cumulative incidence (number of new cases per number of subjects at risk) and incidence rates (number of new cases per person time) were calculated for each symptomatic area. We used Poisson regression models to identify factors associated with incident MSK symptomatic areas. Covariates with two-sided p -values < 0.05 , or incidence rate ratio (RR) < 0.8 , or $RR > 1.25$ in univariate analyses were incorporated in the final parsimonious models.

Results: Among 308 patients undergoing elective TKR for OA, 87% were younger than 75 years and 60% were female. One-quarter of subjects had at least one symptomatic area at baseline, and of those, non-index knee was the most common presurgical symptomatic area (10%). The cumulative incidence of any new MSK symptomatic area over 4 years was 45%, while the incidence rate was 192 per 1000 person-years (95% CI 153-242 per 1000 person-years). Cumulative incidence was highest for non-index knee (23%) and back (15%); incidence rates for non-index knee and back were 69 per 1000 person-years (95% CI 52-92 per 1000 person-years) and 53 per 1000 person-years (95% CI 38-74 per 1000 person-years) respectively. Based on the final Poisson model (Table), variables associated with developing an incident MSK symptomatic area after TKR included female sex (RR 1.51, 95% CI 1.13-2.04), body mass index ≥ 35 (RR 1.34, 95% CI 1.03-1.74), baseline index knee WOMAC function score ≥ 41 (RR 1.49, 95% CI 1.12-1.97), and symptoms consistent with anxiety/depression (MHI-5 < 68) (RR 1.41, 95% CI 1.10-1.82).

Conclusion: Incident MSK comorbidities, particularly in the non-index knee and back, will occur in roughly half of elective TKR recipients in the four years following TKR. Factors associated with incident MSK comorbidities include female sex,

obesity, worse baseline index knee functions cores, and anxiety/depression. Further study is needed to examine the long-term impact of these incident comorbidities on postoperative rehabilitation and quality of life.

Predictors of Incident MSK Comorbidity by Univariate and Multivariate Poisson Regression

Demographics	No Incident MSK Comorbidity N (%)	Any Incident MSK Comorbidity N (%)	Univariate RR (95% CI)	Multivariate	
				RR (95% CI)	P-value
Age					--
< 65 years	71 (44)	52 (40)	1.0 (ref)	--	
65-75 years	69 (43)	61 (47)	1.11 (0.84-1.46)	--	
> 75 years	22 (14)	18 (14)	1.06 (0.71-1.59)	--	
Sex					0.006
Male	77 (48)	38 (29)	1.0 (ref)	1.0 (ref)	
Female	85 (53)	93 (71)	1.58 (1.18-2.13)	1.51 (1.13-2.04)	
BMI (kg/m ²)					0.03
<35	135 (85)	89 (70)	1.0 (ref)	1.0 (ref)	
≥35	24 (15)	39 (30)	1.56 (1.21-2.00)	1.34 (1.03-1.74)	
Medical comorbidities					
Charlson comorbidity index					--
0-1	100 (67)	73 (59)	1.0 (ref)	--	
≥2	49 (33)	51 (41)	1.21 (0.93-1.57)	--	
Orthopedic comorbidities					
# of problematic areas at baseline					--
0-1	151 (93)	116 (89)	1.0 (ref)	--	
≥2	11 (7)	15 (11)	1.33 (0.93-1.90)	--	
Baseline WOMAC paina					--
0-40	102 (64)	59 (46)	1.0 (ref)	--	
≥41	57 (36)	70 (54)	1.50 (1.16-1.94)	--	
Baseline WOMAC functiona					0.006
0-40	97 (60)	48 (37)	1.0 (ref)	1.0 (ref)	
≥41	65 (40)	82 (63)	1.69 (1.28-2.21)	1.49 (1.12-1.97)	
Mental health comorbidities					
MHI-5 scoreb					0.008
0-67	22 (14)	36 (27)	1.54 (1.19-1.98)	1.41 (1.10-1.82)	
68-100	140 (86)	95 (73)	1.0 (ref)	1.0 (ref)	
PCS scorec					--
<16	129 (80)	90 (70)	1.0 (ref)	--	
≥16	32 (20)	38 (30)	1.32 (1.01-1.73)	--	

* Subjects with 0 follow-up questionnaires were excluded from the analysis.

a - WOMAC scores were transformed to a 0 to 100-point scale (100 worst).

b - MHI-5 = Mental Health Inventories 5 score. Scores transformed to 0 to 100-point scale (0 worst).

c - PCS score = Pain catastrophizing scale score. Score ≥ 16 was considered high pain catastrophizing.

Disclosure: M. Zhang, None; F. Selzer, None; E. Losina, Samumed, 5; JBJS, 5; J. E. Collins, None; J. N. Katz, None.

Abstract Number: 400

Predictors of Response to a Single Intra-Articular Injection of Mannitol-Modified Cross-Linked Hyaluronic Acid (HANOX-M-XL) in Patients with First Metatarsophalangeal Joint Osteoarthritis (hallux rigidus)

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Background/Purpose: To investigate the potential predictors of response to a single intra-articular injection of mannitol-modified cross-linked hyaluronic acid (HANOX-M-XL) in patients with first metatarsophalangeal joint osteoarthritis (FMP-OA).

Methods: Observational, single-arm, prospective multicentre trial, with a 3 month follow-up (N° EudraCT 2015-AO1904-45). Inclusion criteria: patients with symptomatic hallux rigidus, not relieved by analgesics and / or non-steroidal-anti-

inflammatory drugs (NSAIDs) and / or foot orthotic) with radiological evidence of FMP-OA (joint space narrowing and/or osteophyte). Main exclusion criteria: Patients with hallux valgus, microcrystalline or inflammatory arthritis, viscosupplementation of the target joint in the last 3 months, intra-articular corticosteroids in the previous month, planned surgery within the 3 months of follow-up. All patients received a single, imaging guided (ultrasonography or fluoroscopy), intra-articular injection, of 1 ml of HANOX-M-XL, in the FMP joint. Data obtained at baseline: age, sex, weight, height, symptoms duration, bilaterality, previous and current treatments for OA, concomitant therapies, patient self-assessment of pain (11-point numeric scale 0-10), Menz radiological classification (stage 1 to 4). Outcome measures: patient self-assessment of pain at day 90, patient's perception of effectiveness ((0=not effective to 3= very effective), changes in analgesic intake, safety. The primary endpoint was the pain variation between the date of injection and month 3. The secondary outcome measures were the patient assessment of effectiveness and the decrease in pain killer use. Predictors of efficacy were studied in uni-variate and multivariate analysis from the intent-to-treat (ITT) population.

Results: Sixty-five subjects(72.3% women, mean age 60, mean symptom duration 24.9 months) were included in the trial. Nine (13.5%) were lost to follow-up. X-ray grade was 1 in 28 patients, 2 in 29, 3 in 6. There was no statistically significant correlation between the radiological stage and the pain score at baseline ($p = 0.69$). At baseline and end-point, the average pain was respectively 6.5 ± 1.8 and 2.8 ± 2.3 . The pain score mean difference was highly significant (-3.1 ± 2.9 ; $p < 0.0001$). The average pain score at end-point was 2.0 ± 1.9 in X-ray stage 1, 3.1 ± 2.3 in stage 2 and 3.3 ± 2.4 in stage 3. The between-group difference was statistically significant ($p=0.001$). In multivariate analysis, pain decrease was unrelated to age, gender, disease duration, pain score at baseline, bilaterality, and imaging guidance but remained related to X-ray stage ($p=0.02$). Adverse events (AEs) were reported by 15 patients (22.7%). All were a transient increase of the big toe pain, that occurred within the very next hours after injection and lasted a few days. All AEs have been resolved in 3 to 7 days.

Conclusion: This prospective study, from the largest cohort ever published in FMP visco supplementation, showed that the clinical outcome of a single injection of 1 ml of HANOX-M-XL, performed under imaging guidance, was significantly better in patients with mild joint space narrowing. However the majority of patients with more advanced OA were also significantly improved.

Disclosure: T. Conrozier, LABRHA SAS, 5, 8; A. Charpentier, None; M. Bossert, None; S. Mellac-Ducamp, None; L. Galois, None.

Abstract Number: 401

Quality of Systematic Reviews Comparing Conventional Vs. Computer-Assisted Joint Replacement

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Session Information

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Background/Purpose: An increasing number of total jointreplacement (TJR) procedures are performed as computer-assisted total joint replacement (CA-TJR). Effectiveness of computer-assisted total joint replacement (CA-TJR) compared to conventional TJR has been evaluated by multiple systematic reviews with conflicting results. We evaluated the quality of systematic reviews comparing CA-TJR to conventional TJR.

Methods: We searched MEDLINE, EMBASE, the Cochrane, and Epistemonikos to identify systematic reviews published through May 2017. One reviewer conducted title and abstract screening of all resulting citations. Full-text articles that met inclusion criteria were retrieved and assessed independently by two reviewers using the AMSTAR 2 tool (Sheet al., 2017). AMSTAR 2 has seven critical and 9 non-critical domains. Systematic reviews are rated as high (no critical or non-critical flaws), moderate (non-critical flaws only), low (1critical flaw), or critically low quality (>1 critical flaw).

Results: Of 384 citations originally identified, 38 systematic reviews were included (Figure 1). Based on the AMSTAR2 tool, 37 studies were rated critically low and one study was rated low. The low rating was due to failure in meeting AMSTAR 2 criteria on the following critical domains (Figure 2): 37 (89%) reviews did not report the protocol registration; 32 (84%) studies did not justify excluding individual studies; 27(68%) studies did not account for risk of bias in primary studies when interpreting the results; 20 (52%) failed to use comprehensive literature search strategy; 17 reviews with meta-analyses failed to justify the use of appropriate methods for statistical combination of results from

randomized controlled trials (48%) and non-randomized studies (44%), and 16 (42%)meta-analyses did not use satisfactory techniques to assess risk of bias of RCTs; and 16 (42%) studies failed to report publication bias. The non-critical weaknesses are shown in figure 3.

Conclusion: Despite the large number of published systematic reviews about the relative effectiveness of CA-TJR, quality of these reviews was critically low, thus significantly weakening the conclusions derived from these reviews.

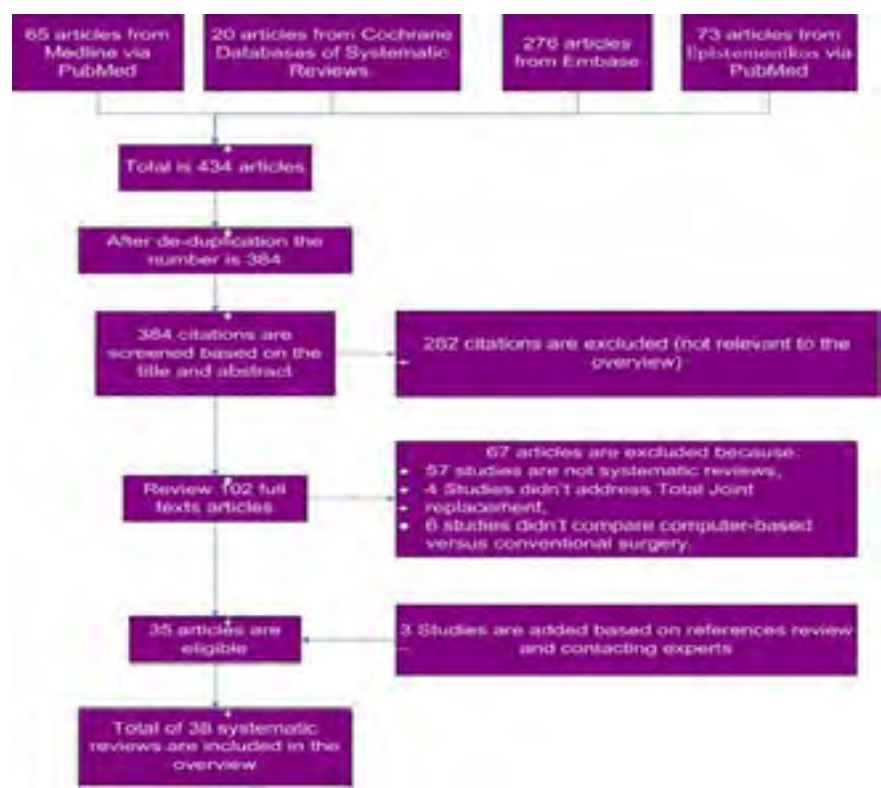


Figure1: Flow Diagram of Study Selection

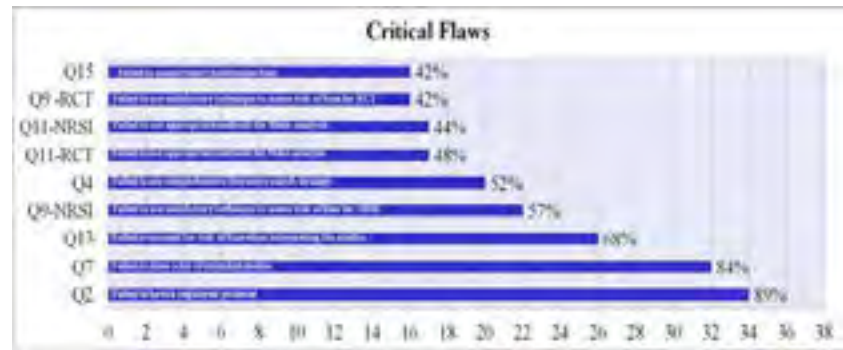


Figure2



Figure3

Disclosure: M. Hasan, None; M. Zhang, None; H. Ghomrawi, None.

Abstract Number: 402

Preoperative Physical Function Influences on Stair Climbing Ability 1 Month after Total Knee Arthroplasty

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Background/Purpose: This study was undertaken to identify preoperative physical performance factors predictive of stair climbing ability 1 month following total knee arthroplasty.

Methods: In this prospective cohort study, we assessed a total of 84 patients (8 males and 76 females; average age 72.0 ± 6.0 years) who underwent a primary unilateral total knee arthroplasty (TKA). Before and 1 month after TKA, patients completed physical performance tests including stair climbing test (SCT), 6-minute walk test (6MWT), timed up and go test (TUG), isometric knee flexor and extensor strength of the surgical and non-surgical knees, and instrumental gait analysis for spatiotemporal parameters. Self-reported disease-specific physical function measured by using the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) and self-reported quality of life measured by using Euro QOL five dimensions (EQ-5D) questionnaire.

Results: In the bivariate analyses, the postoperative SCT-ascent had a significant positive correlation with the SCT-ascent ($r=0.29$, $p=0.01$), SCT-descent ($r=0.28$, $p=0.01$), TUG ($r=0.37$, $p<0.01$), preoperative age ($r=0.25$, $p=0.02$), and a significant negative correlation with the preoperative 6MWT ($r=-0.33$, $p<0.01$), peak torque (PT) extensor of surgical knee ($r=-0.29$, $p=0.01$), PT flexor of surgical knee ($r=-0.26$, $p=0.02$), PT extensor of the non-surgical knee ($r=-0.26$, $p=0.02$), PT flexor of the nonsurgical knee ($r=-0.25$, $p=0.02$). The postoperative SCT-descent had a significant positive correlation with the SCT-ascent ($r=0.28$, $p=0.01$), SCT-descent ($r=0.40$, $p<0.01$), TUG ($r=0.38$, $p<0.01$), preoperative age ($r=0.27$, $p=0.01$), WOMAC function ($r=0.30$, $p<0.01$), and a significant negative correlation with 6-MWT ($r=-0.33$, $p<0.01$), PT extensor of surgical knee ($r=-0.23$, $p=0.04$), PT flexor of surgical knee ($r=-0.24$, $p=0.03$), PT extensor of the nonsurgical knee ($r=-0.25$, $p=0.03$), PT flexor of the nonsurgical knee ($r=-0.23$, $p=0.03$). In the linear regression analyses, the postoperative SCT-ascent had a significant positive correlation with the preoperative TUG ($\beta=0.28$, $p<0.01$), PT extensor of surgical knee ($\beta=-0.23$, $p=0.03$) and the postoperative SCT-descent had a significant positive correlation with preoperative SCT-descent ($r=0.28$, $p=0.01$), and the age ($\beta=0.20$, $p=0.04$).

Conclusion: This study demonstrated that preoperative physical function influenced on postoperative stair climbing ability 1 month after TKA. Using variables easily measured before surgery, it may be possible to predict with good accuracy for postoperative stair climbing ability. In addition, these results could be of importance in determining variable preoperative rehabilitation strategies to improve stair climbing ability, especially focusing on balance, endurance and strengthening exercises.

Disclosure: J. Kim, None; B. R. Kim, None.

Abstract Number: 403

Comparison of Radial Extracorporeal Shock Wave Therapy and Traditional Physiotherapy in Rotator Cuff Calcific Tendinitis Treatment

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Background/Purpose: Radial Extracorporeal Shock Wave Therapy (rESWT) has more recently been used in the treatment of a number of musculoskeletal conditions. The purpose of this study is to investigate the efficacy of rESWT on pain, range of motion (ROM) and functionality besides conventional physiotherapy methods in the treatment of chronic rotator cuff calcific tendinitis (RCCT).

Methods: We studied 80 patients with chronic RCCT. The patients were randomly divided into 2 groups: rESWT group (n=40) treated with conventional physiotherapy and rESWT and control group (n=40) treated only with a conventional physiotherapy program. The traditional physiotherapy program included ultrasound, transcutaneous electrical nerve stimulation, shoulder joint ROM and stretching exercises, and ice applications. All patients received a total of 20 treatments for 4 weeks, 5 days a week. rESWT was applied once a week in total for 4 weeks. Before and after treatment, all patients were evaluated for age, height, weight, body mass index (BMI), pain intensity with a visual analogue scale, shoulder ROM and functional disability status with the shortened version of the Disabilities of the Arm, Shoulder and Hand questionnaire (QuickDASH). The SPSS 22.0 was used for the statistical analysis. A p value of <0.05 was considered statistically significant.

Results: The mean age of the participants was 53.29 ± 9.57 years and the mean BMI value was 26.09 ± 2.99 kg/m². Although all the parameters of the patients in both groups improved significantly, it was determined that patients in the rESWT group had a statistically significant improvement in pain, ROM and QuickDash scores ($p < 0.001$, $p < 0.001$, $p < 0.001$, respectively).

Conclusion: We assume that rESWT is an effective and noninvasive method of reducing pain and increasing ROM and functional status without the need for surgery.

Disclosure: T. Duymaz, None; D. Sindel, None.

Abstract Number: 404

Interleukin 17A– a Translational Target to Treat Supraspinatus Tendinopathy

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Background/Purpose: Shoulder tendinopathy is a multi factorial disorder that accounts for a high proportion (approx. 30%) of referrals to orthopaedic surgeons. Experimental evidence points to the importance of the interleukin 17 (IL-17) cytokine family in the pathogenesis of several immune inflammatory diseases. Given our previous findings of a role for IL-17A in tissue remodeling events in tendinopathy we hypothesized that blockade of IL-17A may provide a therapy for tendinopathy.

Methods: We confirmed evidence of IL-17 family expression in supraspinatus tendinopathy and thereafter, explored mechanisms whereby IL-17A mediated inflammation and tissue remodelling in human tenocytes. Torn supraspinatus tendon (established pathology) and matched intact subscapularis tendon (representing ‘early pathology’) along with control biopsies were collected from patients undergoing shoulder surgery. In tendon biopsies, expression of IL-17A was assessed by qRT-PCR and immune histochemistry. In isolated tenocytes, effects of IL-17A blockade by secukinumab were assessed following IL-17A and TNF activation by whole transcriptome AmpliSeq or multiplex cytokine assays. Finally, we assessed the translational effects of IL-17A blockade on structure/function in a rat model of rotator cuff tendinopathy of the supraspinatus tendon using magnetic resonance imaging (MRI) and gait analysis.

Results: *IL-17A blockade reduces proinflammatory signature in human tenocytes.* Transcriptomic datasets showed the presence of the IL-17 family members IL-17A-E and receptors IL-17RA & IL-17RC throughout the spectrum of tendinopathy. Furthermore IL-17A significantly elevated production of the proinflammatory cytokines IL-6, IL-8, CXCL-1 and CCL-2 in tenocytes. Importantly, IL-17A blockade by secukinumab significantly reduced the expression of these proinflammatory cytokines.

IL-17A blockade significantly improves tendon structure and function in vivo. The pharmacological effects of IL-17A blockade on MRI/ gait abnormalities were assessed 4 weeks after the surgical induction of tendinopathy and following once weekly dosing of anti-IL-17A antibody. The induction of tendinopathy significantly increased the MRI T2 signal in tendinopathy and triggered gait abnormalities by significant alteration of front-hind ratios of footprint contact areas. IL-17A blockade normalized both, altered MRI T2 signals ($p < 0.01$, $n = 4$) and gait abnormalities ($p < 0.05$, $n = 8$).

Conclusion: Our study provides evidence that IL-17A operates as a cytokine modulator in human supraspinatus tendinopathy and that blockade significantly improves tendon structure and function in a rodent model of supraspinatus tendinopathy. Based on these results we have commenced a randomised multicenter trial of the effect of IL-17A blockade with secukinumab in patients with rotator cuff tendinopathy (NCT03344640).

Disclosure: N. L. Millar, Novartis, 5; M. Akbar, None; E. Weber, Novartis, 3; F. Kolbinger, Novartis, 3; F. Raulf, Novartis, 3; O. Leupin, Novartis, 3; S. Carter, Novartis, 3; N. Beckmann, Novartis, 3; L. Mindeholm, Novartis, 3; I. B. McInnes, AbbVie Inc., 5, BMS, 2, 5, Astra Zeneca, 2, 5, Eli Lilly and Co., 5, Janssen, 2, 5, Celgene Corporation, 2, 5, Leo, 2, Novartis, 5, Pfizer, Inc., 5, Oxford Biodynamics, 2, UCB, Inc., 2, 5; M. Schieker, Novartis, 3.

Abstract Number: 405

Feasibility of Enabling Self-Management and Coping with Arthritic Pain Using Exercise (ESCAPE-Pain) Programme for Knee Osteoarthritis in Malaysia

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Background/Purpose: In Malaysia around one in ten older people are diagnosed with osteoarthritis (OA), with the knee being one of the most commonly affected areas. This can lead to functional limitations, impaired activities of daily living and reduced quality-of-life. Our systematic review of the literature concludes that a programme integrating exercise, education and active coping strategies, known as Enabling Self-management and Coping with Arthritic Pain using Exercise (ESCAPE-pain) provides the best evidence for implementation. Thus, this study aims to evaluate the feasibility of the ESCAPE-pain programme among patients with knee OA in the Malaysian healthcare context.

Methods: A pragmatic, feasibility randomised controlled trial (RCT) was conducted recruiting patients with knee osteoarthritis from two hospitals in Malaysia. Participants were randomised to receive ESCAPE-pain intervention plus usual care ($n = 36$) (intervention group) or usual care only ($n = 36$) (control group). Outcomes were measured for physical function (TUG), knee injury and osteoarthritis outcome scores (KOOS), mental wellbeing (Short-WEMWBS), exercise health beliefs and self-efficacy (ExBeliefs) and fear of falling (Short-FES-I) at baseline, six-week and after 12-week of intervention.

Results: There were no significant differences in baseline characteristics between the groups ($p > 0.05$). Recruitment rate showed 90.5% (72/105) and retention rate at 12-week was 87.5% (63/72). Attendance to intervention programme at ≥ 10 of 12 sessions was high (82.4%). Using modified intention-to-treat analysis, repeated measures ANOVA showed no significant changes ($p > 0.05$) for TUG or KOOS between intervention and control groups. However, better outcomes ($p < 0.05$) were reported after 12 weeks for health beliefs, mental wellbeing, and fear of falling among patients in intervention group. Satisfaction survey among participants revealed that the ESCAPE-pain programme is easy to follow, straightforward and tolerable for future implementation.

Conclusion: The findings of this study indicate that the ESCAPE-pain programme is feasible for patients with knee OA in Malaysia. As a feasibility study, this is not powered to detect significant differences on primary KOOS outcomes,

nonetheless participants reported positive views towards exercise with significant improvements in belief in performing activities, mental wellbeing and reduced fear of falling.

Disclosure: M. K. Che Hasan, None; E. Stanmore, None; C. Todd, None.

Abstract Number: 406

Limiting the Risk of Osteoarthritis after Anterior Cruciate Ligament Injury: Are We Missing the Opportunity to Intervene?

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Orthopedics, Low Back Pain and Rehabilitation Poster – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

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

Background/Purpose: Fifty percent of people with anterior cruciate (ACL) injury develop knee osteoarthritis (OA) within 6-10 years, even with ligament reconstruction. Despite evidence that targeted exercise, appropriate physical activity and weight management effectively limit symptomatic knee OA, only 27% (62/233) of Australians and Americans with ACL reconstruction 1-5 years previously, remembered discussing OA risk with any health care professional (HCP). We conducted a survey to understand what Canadian sports orthopedic surgeons, primary care physicians (PCPs) and physiotherapists (PTs) managing non-elite athletes with ACL injury do or do not tell their patients about their OA risk.

Methods: We surveyed practicing sports orthopedic surgeons, PCPs and PTs who provide care to non-elite athletes with acute ACL injury.

The electronic survey was distributed through an e-blast and newsletter link by the Canadian Academy of Sport and Exercise Medicine (CASEM) (many members are PCPs with specialty training in sports) and the Sports and Orthopedic Divisions of the Canadian Physiotherapy Association. Orthopedic surgeons were contacted via telephone and or email and completed the survey via fax, mail or online. The survey included four sections: practitioner demographics; frequency and specific factors discussed; when post-injury risk factors are discussed; and, recommendations for how and with whom risk factors and their management should be discussed.

Results: There were 98 PCP, 263 PT, and 140 orthopedic surgeon respondents. All Canadian provinces and 2 of 3 territories were represented. Seventy-five or more of each provider group had greater than 5 years' experience treating people with ACL injury. Seventy to 77% of physicians reported that they always discussed OA risk but only 35% of PTs do (Table 1). All groups reported that patient activity level (i.e. activities perceived as detrimental to knee health), ACL re-injury and simultaneous injury to other structures in the knee were most often the reason for discussing OA risk. A high proportion of providers discussed OA risk as part of initial management with many fewer respondents reporting such discussions 3-6 months after injury. Despite a lower proportion of PTs reporting always discussing OA risk, 80% of the physicians and 99% of the PTs indicated that PTs were best suited to provide OA risk information.

Conclusion: These results suggest that there is communication gaps as HCPs, particularly PTs, who routinely manage people with ACL injury do not consistently discuss OA risk post injury. Discussions occur only early post injury when the focus is likely on ACL recovery. Subsequently, there is a lack of emphasis on managing OA risk at final follow-up, when it's likely most important. Educational strategies for health professionals are needed to develop care pathways inclusive of support for OA risk management post ACL injury.

Table 1:

	Primary Care Sports Physician (n=98) % (95% CI)	Physiotherapist (n=263) % (95% CI)	Orthopedic Surgeon (n=140) % (95% CI)
Discuss OA risk factors:			
Never	1.0 (0.2, 5.3)	9.1 (6.2, 13.2)	0.7 (0.1, 3.9)
Sometimes	27.5 (19.7, 37.1)	57.0 (51.0, 62.9)	22.1 (16.1, 29.7)

Table . (Cont'd)

	Primary Care Sports Physician (n=98) % (95% CI)	Physiotherapist (n=263) % (95% CI)	Orthopedic Surgeon (n=140) % (95% CI)
Always	71.4 (61.8, 79.4)	33.8 (28.4, 39.8)	77.1 (69.5, 83.3)
Factors influencing OA risk discussion (yes):			
Age	36.5 (27.5, 46.4)	49.6 (43.2, 55.9)	52.2 (43.9, 60.3)
Sex	36.5 (27.5, 46.4)	6.1 (3.7, 10.0)	16.1 (10.9, 23.1)
Body weight	46.9 (37.2, 56.8)	52.6 (46.2, 59.0)	53.6 (45.3, 61.7)
Activity level	51.0 (42.2, 60.8)	67.7 (61.3, 73.6)	55.5 (47.1, 63.9)
Type of acute management	37.1 (27.8, 47.5)	36.6 (30.4, 43.2)	46.3 (38.2, 54.7)
Concurrent joint injury	71.3 (61.4, 79.5)	83.5 (78.0, 87.8)	88.4 (82.0, 92.7)
Revision ACL reconstruction	63.3 (53.0, 72.6)	71.8 (65.4, 77.4)	80.6 (73.1, 86.4)
Timing of OA risk discussion (yes):			
Initial ACL management	79.6 (70.3, 86.5)	64.6 (58.1, 64.6)	94.1 (88.8, 97.0)
3-6 months post-injury	43.0 (33.4, 53.2)	49.3 (42.7, 55.9)	13.2 (8.5, 20.0)
>6-12 months post-injury	24.7 (17.1, 34.4)	29.3 (23.6, 35.7)	15.4 (10.3, 22.5)
>12 months post-injury	19.4 (12.6, 28.5)	19.1 (14.4, 24.9)	11.8 (7.4, 18.3)

Disclosure: A. Davis, None; R. Wong, None; K. Steinhart, None; J. Astephen Wilson, None; L. Cruz, None; D. Cudmore, None; T. Dwyer, None; L. Li, None; P. MacDonald, None; P. Marks, None; L. Nimmon, None; D. Ogilvie-Harris, None; N. Urquhart, None; J. Chahal, None.

Abstract Number: 407

Digital Disruptive Technology for Rehabilitation Following Elective Surgery for Low Back Pain, Knee and Hip Osteoarthritis: A Systematic Review and Meta-Analysis

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Session Information

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Background/Purpose: The global uptake of digital health technologies in rehabilitation is increasing, but their effectiveness warrants further investigation. We aim to evaluate the effects of digital solutions used in musculoskeletal rehabilitation for people who underwent orthopaedic surgeries.

Methods: Six databases were searched from the earliest records to October 2017. Eligible studies were randomised controlled trials (RCT) that investigated the effectiveness of disruptive digital technology-based intervention, solo or in combination with other interventions, compared with a control group for people who underwent elective total knee/hip replacement (TKR/THR) or lumbar spinal surgeries. Two researchers independently reviewed the studies as per the Cochrane methodology for the systematic literature review. Study quality was assessed using the Physiotherapy Evidence Database (PEDro) scale (0-10). Trials deemed clinically homogeneous were grouped in meta-analyses. Meta-analyses were performed using random-effects model, and results expressed as mean differences (MD), or standardised MDs (SMD) with 95% confidence interval (CI). The primary outcomes included visual analogue scale (VAS) for pain and functional assessments: the timed up-and-go (TUG) and 6-minute walk test (6MWT).

Results: We identified 19 eligible RCTs with 15 trials (n=1706) for people who underwent TKR, 3 trials (n=383) for THR and 1 (n=60) for lumbar discectomy. There were 3 types of digital rehabilitation interventions involved in this review: telerehabilitation relying on either telephone counselling (8 trials, n=1130) or videoconferencing (4 trials, n=384), game-based therapy (5 trials, n=308) and software (3 trials, n=327). Seven studies were rated as good quality (a PEDro score of 7 or greater).

The pooled analysis of VAS pain data included 5 trials (n=438) assessing post TKR rehabilitation and 1 trial (n=60) assessing post lumbar discectomy rehabilitation. The results showed that, compared to usual care, disruptive technology-based interventions are more effective in reducing pain (MD = -0.19; 95% CI: -0.35, -0.02) for people undergoing TKR. Results of TUG were available from 2 trials (n=207) assessing post TKR rehabilitation and 1 trial (n=72) in THR. Compared to usual care, the intervention showed significant effects in TUG for people who underwent TKR (MD: -7.03;

95% CI: -11.18, -2.88). Pooled estimates from 2 trials (n=258) for people undergoing TKR showed the digital-enabled rehabilitation was not superior to usual care in the 6MWT (MD: -29.36; 95% CI: -65.71, 6.99).

Three trials for people who underwent TKR investigated patient compliance via exercise diaries, leaving inconclusive results. No difference in rates of hospital readmissions or treatment-related adverse events were observed.

Conclusion: There is moderate quality evidence that current digital-enabled rehabilitation shows small but significant effects over usual rehabilitation in reducing pain and improving mobility post TKR. No evidence was observed for people undergoing THR or lumbar spinal surgery rehabilitation. Digital rehabilitation is technically feasible, well-accepted and can be used safely in people undergoing musculoskeletal surgeries.

Disclosure: X. Wang, None; M. Ferreira, None; D. J. Hunter, Merck Serono, Flexion, Tissuegene, 5; G. Vesentini, None; D. Pozzobon, None.

Abstract Number: 408

State or Trait: Pain Catastrophizing and Widespread Pain Following TKR and Their Associations with Pain Relief

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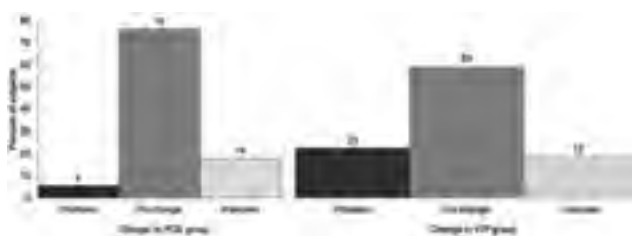
Background/Purpose: Pain catastrophizing and widespreadpain (WP) —constructs reflecting cognitive processes during the pain experience—predictdisability, pain chronicity/severity, and lower quality of life in a range of conditions. Gaps remain in our understanding of the extent to which each is a stable(trait) or dynamic (state) variable. We assess a) the stability of pain catastrophizing and WP from before to after TKR and b) whether changes in these measures could be explained by changes in pain.

Methods: We used data from a prospective study of TKR recipients ages 40+. Questionnaires included a body pain diagram to assess WP, the Pain Catastrophizing Scale (PCS; 0-52, 52=worst), and WOMAC Pain (0-100,100=worst). To calculate WP score, we summed the number of body regions, excluding the index knee, in which a subject attested to pain in the past week(maximum=7).

We divided subjects into 3 WP groups (0 vs. 1-2 vs. ≥3pain regions) and into low and high PCS groups (≤16 vs. >16) at baseline and 12 months post-TKR. We assessed changes in group membership from baseline to 12 months. To assess whether changes in PCS and WP were associated with knee pain relief, we created 4 groups by amount of WOMAC pain improvement: <10,10-29, 30-49, ≥50. Changes in PCS score and WP were compared across these groups using ANOVA.

Results: 176 subjects completed the scales at baseline and 12 months; 64% were female, mean age was 66, and baseline median WOMAC pain was 40.

The number of subjects in the high PCS score group diminished from 45 (26%) pre- to 23 (13%) post-TKR. Mean PCS score diminished from 11 (SD:10) to 6 (SD: 8). The number of subjects in each WP group was similar pre- and 12months post-TKR. However, 73 subjects (41%) changed group and were similarly likely to worsen (55%) and to improve (45%). As Figure 1 depicts, most changes in PCS group were in the direction of improvement while, for WP group, similar proportions worsened and improved.



Improvements in PCS score were associated with WOMAC pain reductions. The group with most pain relief (≥ 50 points) had a greater mean improvement in PCS score (11 (SD:12)) than the group with least pain relief (4(SD: 12)) ($p = 0.02$). We did not find a statistically significant association between change in WP and change in WOMAC.

Conclusion: 71% of those with baseline high PCS improved sufficiently to join the low PCS group after TKR. PCS score improvements were associated with pain relief, suggesting that the present measure of catastrophizing reflects state-like aspects that diminish along with pain. In contrast, WP scores were as likely to increase as to decrease after TKR, regardless of knee pain relief. The findings urge caution in interpreting PCS and WP as trait measures in MSK pain research.

Figure 1. Percent of subjects changing PCS or WP group membership from baseline to 12 months

Disclosure: E. Lape, None; F. Selzer, None; J. E. Collins, None; E. Losina, Samumed, LLC, 5, Journal of Bone and Joint Surgery, 9; J. N. Katz, Journal of Bone and Joint Surgery, 9, Osteoarthritis Research Society International, 6.

Abstract Number: 409

Unique Skeletal Muscle Relaxant Tolperisone in a Crossover Driving Simulation Study: No Evidence of Sedation Compared to Cyclobenzaprine and Placebo

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Session Information

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Background/Purpose: Tolperisone is a centrally-acting muscle relaxant being developed in the US as a treatment for acute and painful symptoms of neck and low back muscle spasms. Tolperisone historically has shown both muscle relaxant and analgesic effects without sedation in placebo-controlled and head-to-head clinical studies in Europe and Asia. The present study explores the impact of tolperisone on driving simulation endpoints, self-reported sleepiness, and cognition compared to placebo and cyclobenzaprine.

Methods: The study was a 3-way, randomized, blinded, crossover study assessing the safety and cognitive effects of tolperisone in 31 healthy volunteers. Treatment groups included 450 mg tolperisone administered three-times-a-day (150 mg TID), 30 mg cyclobenzaprine (10 mg TID), and placebo (TID). Participants spent the first three days of three consecutive weeks in the research unit. Dosing occurred in the morning (AM) and at midday (PM) on Days 1-3 and at bedtime on Days 1 and 2. Subjects were administered a digit symbol substitution test followed by 100 km (60 minute) of simulated driving on Day 1 one hour after their midday dose (at drug T_{max}), and again the morning of Day 2 (pre-dosing) to assess next day residual effects. They were also tested the morning of Day 3 (post-dose) to assess the drug at steady-state. Subjects returned to the clinic on Days 7 and 14 to repeat these procedures.

Results: For the primary endpoint of Standard Deviation of Lateral Position (SDLP) over 100-km of driving, tolperisone was no different than placebo, whereas cyclobenzaprine showed significant impairment ($p < 0.001$). Results from secondary endpoints, including cognitive test findings, support this conclusion.

The distribution of SDLP for the placebo and tolperisone test conditions showed symmetry around zero, while cyclobenzaprine was markedly different; a subset of subjects in this study had a level of impairment associated with increased crash risk, as demonstrated by SDLP values above 4.4 cm in this test paradigm (consistent with normative Blood Alcohol Concentration (BAC) levels of above 0.05%).

Secondary measures confirmed the finding of absence of sedation for tolperisone relative to placebo: Digit Symbol Coding Day 1 $p = 0.84$, Day 2 $p = 0.21$, Day 3 $p = 0.12$; and Karolinska Sleepiness Scale: Day 1 $p = 0.47$, Day 2 $p = 0.47$, and Day 3 $p = 0.49$. Additional measures of driving indicated no impairment for tolperisone versus placebo.

Of note in this study, patients taking cyclobenzaprine perceived a distinct lack of effect discrimination and reported feeling safe to drive on Days 2 and 3, while demonstrating impairment based on their SDLP and other secondary endpoint outcomes.

Conclusion: Tolperisone at a dose of 150 mg TID was found to have no impact, compared to placebo, on various measures of driving, self-reported sleepiness, and cognition, in contrast to the widely used muscle relaxant cyclobenzaprine at a dose of 10 mg TID. Because of its long half-life and anticholinergic activity, cyclobenzaprine is not recommended for use in the

elderly and has been associated with an increase in falls and injury. Data from this study confirms impairment in cognition and driving for healthy subjects taking cyclobenzaprine.

Disclosure: J. Caron, Neurana Pharmaceuticals, 3; T. Wessel, Neurana Pharmaceuticals, 1; G. Kay, None.

Abstract Number: 410

Experience of Finding Footwear and Factors Contributing to Footwear Choice in People with Gout

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Background/Purpose: Gout frequently affects the foot, particularly the first metatarsophalangeal joint and Achilles tendon. People with gout commonly wear ill-fitting footwear that lacks cushioning and support, which may further contribute to foot pain and disability. Currently, there is limited understanding about the footwear experience in people with gout and what variables contribute to their footwear choice. The aim of this study was to understand footwear characteristics, experience of finding appropriate footwear, and factors contributing to decisions about footwear choice in people with gout.

Methods: We conducted a web-based survey of people visiting a gout patient education website. All survey participants self-reported a diagnosis of gout and were resident in the United States. The 14-item survey included questions to elicit demographic and clinical characteristics, type of footwear worn, level of difficulty in finding appropriate footwear, and factors contributing to choices about footwear.

Results: There were 83 survey respondents. Respondents were predominately European ethnicity (n=70, 84%), male (n=48, 58%), and aged between 46-75 years old (n=61, 73%). Thirty-nine percent (n=32) were newly diagnosed (<12 months), 43% (n=35) had gout for 1-10 years, and 19% (n=16) had disease for more than 10 years. Most respondents (81%) had experienced at least one flare in the past three months. Medications included non-steroidal anti-inflammatory drugs (n=24, 29%), allopurinol (n=34, 41%), colchicine (n=24, 29%), and corticosteroids (n=9, 11%). Gout flares in the feet were reported by 77 (93%) respondents, mostly in the big toe joint (n=59, 73%), and 73 (88%) reported current foot pain. Tophi affecting the feet were reported by 29 (35%) respondents. Questions about footwear were completed by 76 participants. The majority of respondents (n=49, 64%) reported that they had difficulty in finding footwear. Closed-in athletic shoes (n=66, 88%), sturdy walking shoes or boots (n=60, 79%), and casual closed-in slip-on shoes (n=48, 63%) were the most frequently worn footwear. Orthopaedic or customised shoes were worn least often (n=12, 16%). Comfort, fit, support, and ease to put on/off were the features most often rated as important or very important features when choosing footwear (Table).

Conclusion: For people with gout, foot involvement is almost universal, and difficulty finding suitable footwear is a common experience. Comfort, fit, support, and ease of donning shoes are the key features that people with gout consider important when choosing footwear.

Table: Features of importance in choosing footwear, n=76

Features	Not important	Slightly important	Important	Very important
Comfort	1 (1)	1 (1)	13 (17)	61 (80)
Style	8 (11)	30 (39)	28 (37)	10 (13)
Fit	0 (0)	1 (1)	22 (29)	53 (70)
Support	4 (5)	12 (16)	21 (28)	39 (51)
Cost	10 (13)	20 (26)	29 (38)	17 (22)
Weight	9 (12)	34 (45)	27 (36)	6 (8)
Color	19 (25)	23 (30)	28 (37)	6 (8)
Material	14 (18)	33 (43)	21 (28)	8 (11)
Fastenings	21 (27)	27 (36)	19 (25)	9 (12)
Non-slip	11 (14)	22 (29)	29 (38)	14 (18)
Heel height	23 (30)	19 (25)	11 (14)	23 (30)
Ease to put on/off	2 (3)	17 (22)	27 (36)	30 (39)

Disclosure: A. Brenton-Rule, None; N. Dalbeth, None; L. Edwards, None; K. Rome, None.

Abstract Number: 411

Kinesiophobia and Physical Function Among Adults with Knee Osteoarthritis: Before and after Strength Training Classes

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Background/Purpose: Approximately 14 million people in the United States have been clinically diagnosed with symptomatic knee OA. Rising from a chair, negotiating stairs and walking can be compromised. Exercise, a widely recommended firstline treatment to improve pain and daily function among adults with OA is underutilized. Thus, identifying factors that restrict movement and exercise among adults with knee OA is critical. Kinesiophobia, or fear of movement due to pain and potential physical harm, has been proposed to be an important factor restricting movement and willingness to perform exercise among adults with chronic pain, however its relationship with painful knee OA is not well understood. This study examined the relationship of kinesiophobia with commonly used knee osteoarthritis performance-based measures before and after an evidence-based exercise class.

Methods: We used secondary data analysis from a randomized controlled trial before and after a 6-week group strength training class that met twice weekly for 1 hour. Participants were ≥ 50 years with knee pain and self-reported doctor diagnosed knee OA. Kinesiophobia was measured using the 17-item Tampa Scale of Kinesiophobia (TSK). Performance measures included timed-up-and-go (TUG), sit-to-stand 5 and 10 repetitions, and negotiation of 10 steps. We measured quadriceps strength with isokinetic testing, and pain and function with the WOMAC. For data analysis we used simple linear regression with TSK, or change in the TSK, being the independent and performance measures, or their changes, as the dependent variable, and paired T-tests.

Results: 68 participants had baseline data of which 55 had after exercise class data. Higher TSK was associated with slower stair climb ($p=0.02$) and time in the 5 sit-to-stand ($p=0.03$) at baseline. TSK decreased after the exercise class (mean change -0.58) but did not attain statistical significance ($p=0.47$). Change in TSK was associated with change in self-reported physical function ($p=0.02$), but not with pain or physical performance measures.

Conclusion: Among this cohort of adults with knee osteoarthritis, kinesiophobia was associated with negotiating stairs and rising from a chair, two critically important functional activities commonly restricted by osteoarthritis. Future research addressing the impact of kinesiophobia and efficacy of interventions to modify said impact is warranted.

Table 1. Simple linear regression baseline variables

Baseline dependent variables (seconds)	Baseline TSK independent variable				
	Slope	Standard Error	95% Confidence Limits	P-value	R ²
Stair negotiation (n=62)	0.53	0.23	0.08, 0.98	0.02	0.08
adjusted*	0.46	0.21	0.04, 0.88	0.03	0.24
Sit-to-stand 5 reps. (n=62)	0.20	0.09	0.01, 0.39	0.03	0.08
adjusted	0.18	0.09	0.00, 0.36	0.05	0.16
Sit-to-stand 10 reps. (n=59)	0.17	0.18	-0.19, 0.53	0.32	0.02
adjusted	0.15	0.18	-0.21, 0.51	0.41	0.08
TUG (n=62)	0.07	0.05	-0.29, 0.18	0.16	0.16
adjusted	0.06	0.05	-0.04, 0.16	0.22	0.15

* adjusted for age, sex and pain

Table 2. Simple linear regression of change scores before and after exercise class

Change score dependent variables	Change score TSK independent variable				
	Slope	Standard Error	95% Confidence Limits	P-value	R ²
Stair negotiation n=55	0.09	0.17	-0.24 to 0.43	0.58	0.006
Sit-to-stand 5 n=55	0.01	0.07	-0.13 to 0.15	0.86	0.006

Table . (Cont'd)

Change score dependent variables	Change score TSK independent variable				
	Slope	Standard Error	95% Confidence Limits	P-value	R ²
Sit-to-stand 10 n=51	-0.03	0.13	-0.30 to 0.23	0.80	0.0013
TUG n=55	0.01	0.04	-0.06 to 0.08	0.77	0.0014
Quad strength n=54	-.003	0.002	-0.007 to 0.0009	0.12	0.05
WOMAC function n=54	0.54	0.22	0.09 to 0.99	0.02	0.10
WOMAC pain n=54	0.14	0.07	-0.01 to 0.30	0.07	0.06

Disclosure: A. Ledingham, None; M. P. LaValley, None; K. Baker, None; J. Keysor, None.

Abstract Number: 412

Efficacy of Shoe-Stiffening Inserts for First Metatarsophalangeal Joint Osteoarthritis: Preliminary Findings from the Simple Randomised Controlled Trial

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Background/Purpose: This trial assessed the efficacy of shoe-stiffening inserts for reducing pain associated with first metatarsophalangeal joint (MTPJ) osteoarthritis (OA).

Methods: One hundred participants (45 men 55 women, mean age 57.5, SD 10.3 years) with first MTPJ OA received rehabilitation therapy and were randomised to receive either (i) full-length carbon fibre shoe-stiffening inserts (Figure 1) (intervention group) or(ii) sham shoe inserts (control group). The primary outcome measure was the footpain domain of the Foot Health Status Questionnaire (FHSQ) assessed at 12 weeks. Secondary outcome measures included the function domain of the FHSQ, severity of first MTPJ pain, general health status, use of rescue medication and co-interventions, adverse events, physical activity levels and global change in symptoms ('moderately better' or above considered a successful outcome). FHSQ and global change in symptoms at 12 weeks are presented here. Multiple imputation was used to replace missing data. FHSQ pain scores were analysed using analysis of covariance with the intervention group and baseline scores entered as independent variables, and global change in symptoms was analysed using absolute and relative benefit, and number needed to treat.

Results: Data were available for 91 participants at week 4 and 85 participants at week 12. FHSQ pain scores improved in both groups. There was a statistically significant difference in FHSQ pain in favour of the intervention group at 12 weeks (adjusted mean difference 7.4 points, 95%confidence interval [95% CI] 1.3 – 13.5, p=0.018). See Figure 2. Participants in



Figure 1. Full-length carbon fibreshoe-stiffening insert.

the intervention group were also more likely to report that their pain was at least moderately better (successful treatment) at 12 weeks compared to the control group (61 versus 34%; absolute benefit increase 27% [95% CI 6 – 45], relative benefit increase 79% [95% CI 11 – 189]). The number needed to treat was 4 (95% CI 2 – 18).

Conclusion: Carbon fibre shoe stiffening inserts are effective at reducing pain in people with first MTPJ OA.

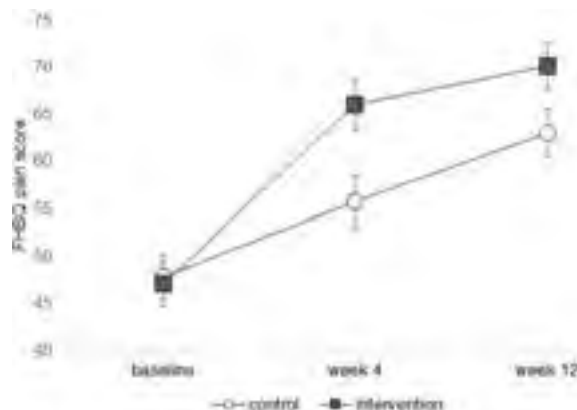


Figure 2. Foot Health Status Questionnaire(FHSQ) scores at baseline, week 4 and week 12 for the control and intervention groups. Higher scores indicate less foot pain.

Disclosure: S. Munteanu, None; K. Landorf, None; J. McClelland, None; E. Roddy, None; F. Cicuttini, None; A. Shiell, None; M. Auhl, None; J. Allan, None; A. Buldt, None; H. B. Menz, None.

Abstract Number: 413

S100A8 & S100A9: Alarmin Mediated Inflammation in Tendinopathy

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Background/Purpose: Alarmins, also referred to as damage associated molecular patterns (DAMPs), are endogenous molecules mobilized in response to tissue damage and are known to activate the innate immune system in the early stages of disease. The molecular mechanisms that regulate inflammatory and remodelling pathways in tendinopathy are largely unknown therefore identifying early immune effectors is essential to understanding the pathology.

S100A8 and S100A9 are low molecular weight calcium binding proteins constitutively expressed by cells of myeloid origin. Under pathological conditions they are released in other cell types in response to environmental triggers and cellular damage. Based on our previous investigations highlighting tendinopathy as an alarmin mediated pathology we sought evidence of S100A8 & A9 expression in human tendinopathy and thereafter, to explore mechanisms whereby S100 proteins may regulate release of inflammatory mediators and matrix synthesis in human tenocytes.

Methods: Torn supraspinatus tendon (representing established pathology) and matched intact subscapularis tendon (representing ‘early pathology’) biopsies were collected from patients undergoing arthroscopic shoulder surgery. Control samples of healthy hamstring tendon were collected from patients undergoing anterior cruciate ligament (ACL) reconstruction. S100A8 & A9 expression was analyzed at transcript and protein level using quantitative RT-PCR and immunohistochemistry, respectively. Primary human tenocytes were cultured from hamstring tendon tissue obtained during hamstring tendon ACL reconstruction. The *in vitro* effect of recombinant human S100A8 & A9 on human tenocytes was measured using quantitative RT-PCR and release of inflammatory mediators was measured at a protein level by ELISA.

Results: Immunohistochemical staining of tendinopathic tissues indicated the presence of S100A8 and S100A9 in tendinopathy with early diseased tissue displaying a distinct increase in S100A8 and S100A9 expression compared with control and established pathology. These findings were mirrored by data obtained at transcript level from both early and late pathology. Treating tenocytes with exogenous S100A8 & A9 significantly increased protein release of IL-6, IL-8 and CCL2 and an induction of CCL20 and CXCL10 release was observed. However, no alterations in genes associated with matrix remodelling were observed at a transcript level.

Conclusion: We have confirmed the presence of S100A8 and S100A9 in tendinopathy and propose that S100A8 & A9 participate in early pathology by modulating the stromal microenvironment and influencing the inflammatory profile of tenocytes. S100A8 and S100A9 may participate in a positive feedback mechanism involving enhanced leukocyte recruitment and release of pro-inflammatory cytokines from tenocytes that perpetuates the inflammatory response within the tendon in the early stages of disease. This, in turn, may contribute aberrant matrix remodelling and support a detrimental transition from acute to chronic inflammation. Selectively targeting DAMP signalling in early disease provides scope for novel translational strategies in the management of tendon disorders.

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Abstract Number: 414

Comparison of Physical Activity Measures Derived from the Fitbit Flex and the Actigraph GT3x+ in an Employee Population with Chronic Knee Symptoms

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Session Information

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Background/Purpose: There is increasing public health interest in the objective measurement of free-living physical activity in persons with arthritis, but research grade wearable monitors can be expensive. We therefore sought to examine the accuracy of the affordable personal monitor (Fitbit Flex) by comparing that output with data from the GT3X+

Table 1. Definitions of Fitbit Flex and ActiGraph GT3x+ Measured Activity Intensity Level

Physical Activity Intensity	Fitbit* (worn on non-dominant wrist)	ActiGraph** (worn on waist)
Light	Slightly Active (Activity between 1.5-3 METs)	Light 100-2019 cpm (counts per minute)
Moderate (bouted)	Fairly Active (Activity between 3-6 METs in at least 10 min bout)	Moderate 2020-5999 cpm in at least 10 min bout
Vigorous (bouted)	Very Active (Activity ≥6 METs or ≥145 steps/minute in at least 10 min bout)	Vigorous 6000 cpm and above in at least 10 min bout
MVPA (bouted)	Active Minutes (Fairly Active + Very Active Min ≥ 3 METs in at least 10 min bout)	MVPA (bouted) 2020 cpm and above in at least 10 min bout
Non-sedentary	Slightly Active + Fairly Active + Very Active	Light + Moderate (unbouted) + Vigorous (unbouted)

* Thresholds based on Fitbit MET minute calculations

** Thresholds based on vertical counts per minute (cpm) by TriAxio

† Pate, R. P., Barrigan, D., Gould, K. W., Moore, J. C., Telford, T., McDowell, M. Physical Activity in the United States measured by accelerometers. Medicine and Science in Sports and Exercise 2008;40(1):183-83.

accelerometer (amount of time spent in light, moderate, and vigorous PA) worn simultaneously for 7 days; high accuracy would support substitution with this less expensive personal activity monitor in future arthritis research.

Table 2. Comparison of Data from Fitbit Flex and ActiGraph GT3x+ Worn Simultaneously for Seven Days (N=226 days from 35 persons)

Physical Activity Intensity	Fitbit Obtained Data Mean \pm SD (min/day)	ActiGraph GT3x+ Obtained Data Mean \pm SD (min/day)	Difference (95% CI) (min/day)	Spearman correlation (95% CI)
Light	201.8 \pm 117.7	229.5 \pm 86.2	-27.7 (-51.3, -4.1)	0.52 (0.43, 0.62)
Moderate (bouted)	17.4 \pm 23.6	18.8 \pm 27.1	-1.3 (-4.9, 2.3)	0.47 (0.36, 0.58)
Vigorous (bouted)	20.8 \pm 27.7	0.2 \pm 1.7	20.6 (17.0, 24.2)	0.34 (0.01, 0.28)
MVPA (bouted)	28.2 \pm 42.4	19.7 \pm 27.5	8.5 (4.7, 22.2)	0.67 (0.56, 0.74)
Non-sedentary	240.0 \pm 133.5	278.4 \pm 91.1	-38.4 (-49.5, -19.2)	0.57 (0.47, 0.65)

Methods: Subjects (n=35) with chronic knee symptoms were recruited for a pilot intervention study using Fitbits to increase physical activity in employees with chronic knee symptoms at an urban insurance corporation. Subjects simultaneously wore for 7 days a Fitbit Flex (wrist-worn) and ActiGraph GT3x+ (waist-worn) as part of 12-week post-intervention follow-up evaluation. Fitbit Flex data was regularly stored on a research storage service (Fitabase) by participants. Correlation tables were constructed to examine the association between the amount of time spent in activity intensity categories (Light, Moderate, Vigorous, and Moderate/Vigorous – the last three categories in bouts of 10 min or more). Due to discrepancy in wear time (Fitbit worn for 24 hours/day, ActiGraph unit was not), sedentary minutes were not included for comparison. Comparisons were calculated by matching Fitabase data from calendar days Fitbit was worn with data from valid monitoring days (≥ 10 hours wear time) of the ActiGraph.

Results: Participants at baseline were primarily female (69%), Caucasian (57%), with mean age 52 years, BMI 32 kg/m². Table I provides an overview of the definitions and distinctions of each measured activity intensity level. Table 2 provides the comparison of data from Fitbit Flex and ActiGraph GT3x+, including Spearman correlations, within each of the activity intensity categories.

Conclusion: The individual intensity category correlations for the two devices are not strong. However, the bouted Moderate-Vigorous activity categories are moderately well correlated. One potential confounder includes the wrist vs waist location of the monitoring device during data collection. This moderate correlation of moderate/vigorous intensity between devices is reassuring to consumers/researchers using the Fitbit to track bouted higher intensity activities, but may not support substitution of the ActiGraph with the Fitbit in population studies that seek to accurately measure all levels of activity and sedentary time.

Disclosure: P. Semanik, None; J. Lee, None; C. PELLEGRINI, None; J. Song, None; D. D. Dunlop, None; R. W. Chang, None.

Abstract Number: 415

1-Year Outcomes from a Novel Physical Therapist-Administered Physical Activity Intervention after Total Knee Replacement: A Pilot Study

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Session Information

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Background/Purpose: Physical activity (PA) does not increase after total knee replacement (TKR) despite improvements in pain and function. A potential solution to this problem is to deliver a PA intervention during outpatient physical therapy (PT) that uses activity trackers, i.e., Fitbits and steps goals. We previously reported the 6-month preliminary effectiveness of our randomized controlled pilot trial. The aim of this abstract was to report on the long-term preliminary effectiveness and retention of PA at the 1-year follow-up.

Methods: Patients undergoing outpatient PT after a unilateral TKR were randomized to a control or intervention group. Both groups received standard PT. The intervention group additionally received a Fitbit Zip, step goals during PT, and monthly phone calls after discharge (DC). A physical therapist created and progressed individualized weekly step goals from baseline to DC from PT. For 6 months (6m) after DC from PT, research assistants called participants once a month to progress the weekly step goal and encourage the participants to continue tracking their steps/day. After 6m, the PA intervention was discontinued and the Fitbit was returned. The primary outcome was PA, quantified as steps/day and minutes/week in MVPA measured with an ActigraphGT3X at DC, 6m, and 1-year. For this analysis, we compared PA between the control and intervention group at 1-year after PT discharge with at-test.

Results: Of the 43 people enrolled, to date 19 people have completed the 1-year follow-up (mean(SD) age = 67.0 (7.0) years, BMI = 31.5 (5.9) kg/m², 53.4% women, days from TKR to PT = 13.8 (21.3)). At 1-year, those in the intervention (n=9) walked 5719 (1757) steps/day and spent 122.3 (101.9) min/week in MVPA, whereas the control (n=10) group walked 3959 (2009) steps/day and spent 46.7 (73.4) min/week in MVPA (Figure 1). The intervention group accumulated 1,760 more steps/day (p=0.13) and spent 75.6(p=0.24) more minutes/week in MVPA at 1-year than the control group.

Figure 1. MVPA/week between groups & sample size at baseline, DC, 6m, 1-year

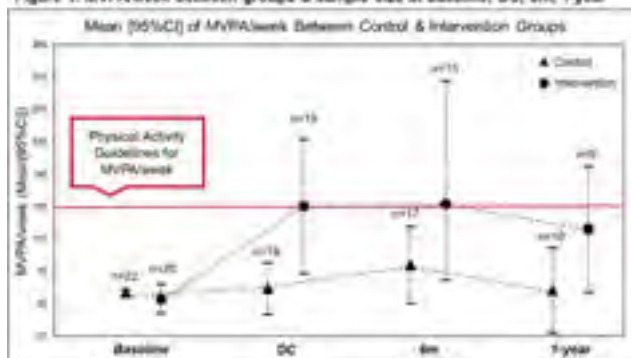
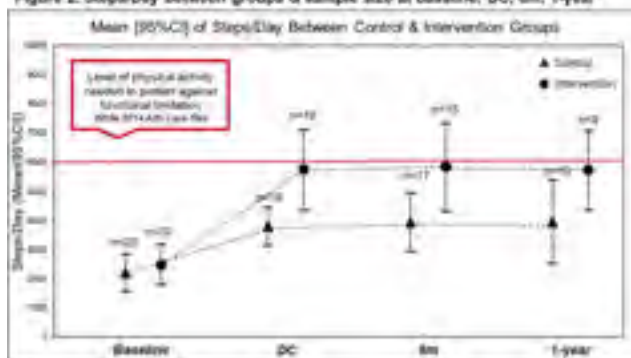


Figure 2. Steps/Day between groups & sample size at baseline, DC, 6m, 1-year



Conclusion: The preliminary results indicate a physical therapist-administered PA intervention may increase PA after TKR. At 1-year, the intervention approached clinically meaningful levels of PA for steps/day, i.e. walking close to 6,000 step/day which is a benchmark known to protect against the development of functional limitation, and spent close to 150 min/week in MVPA, which is recommended dose from the 2008 Physical Activity Guidelines for Americans.

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The Association of Biomechanical Change and Pain Catastrophizing with the Chronic Low Back Pain

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Session Information

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Background/Purpose: Low back pain (LBP) is commonly characterized by symptom duration. Acute LBP is defined as pain lasting < 3 months and chronic LBP is defined as “pain on at least half the days in the past 6 months”. Identifying mechanisms that discriminate chronic versus non-chronic is important to prevent transitions to chronic pain states, thus, improving the LBP prevalence, disability rates and health care costs.

Biomechanical changes are one potential mechanism; prior research suggests that persons with acute LBP use more pelvic rotation and less lumbar flexion or a *stiff* spine when compared to healthy controls. Pain catastrophizing, the exaggerated and negative orientation of pain, predicts disability among persons with acute and chronic LBP.

The aim of this study was to examine the association of lumbo-thoracic ratio (LTR), representing the level of stiffness of lumbar spine, with pain catastrophizing, assessing whether this association varies between individuals with chronic and non-chronic LBP at baseline, 2.5 and 6 months.

Methods: A sample of 29 adult patients with provider diagnosed acute LBP (<3 months) and telephone access completed questionnaires and biomechanical data at baseline, 2.5 and 6 months along with weekly questionnaires. The NIH Task Force of Research Standards for Chronic LBP's was used to classify participants as chronic vs. non-chronic.

Biomechanical measures. Participants completed trunk forward bending and backward return tasks at slow and fast self-selected paces. Lumbar flexion was calculated as the difference between the thoracic and pelvic rotations and was then used to calculate the LTR at that time instant as the ratio of lumbar flexion over thoracic rotation.

Pain catastrophizing measured with the *Pain Catastrophizing Scale* (PCS) (Cronbach's $\alpha=.94$; range: 0-52).

Analysis. Linear regression models were used to evaluate whether the association between PCS and LTR varied by chronic LBP status using an interaction term.

Results: At the 2.5 month follow-up, significant differences in the association of PCS with LTR of fast-paced tasks were identified between those with chronic and non-chronic LBP ($F=5.0$; $p=.04$ for both interaction terms); for those with chronic LBP, an increase in PCS was associated with an increase in LTR ($p=.006$), while among those without chronic LBP there was no association between PCS and LTR ($p=.23$). The association between PCS and LTR did not differ by chronic LBP status at baseline or 6 months; at each of these time points, regardless of chronic LBP status, there was a positive association between PCS and LTR of fast-paced tasks.

Conclusion: The relationship identified between PCS and LTR is a possible contributor to the development of chronic LBP.

Disclosure: E. Salt, None; A. Wiggins, None; M. K. Rayens, None; Q. Hooker, None; I. Shojaei, None; B. Barzgari, None.

Patient Reported Outcomes Pre and Post Intervention in Older Veterans with Chronic Back Pain

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Background/Purpose: Chronic back pain is the second most common reason for a physician’s visit and results in significant physical and psychosocial consequences in older adults. Identifying appropriate and reliable patient reported outcome measures is critical for research and clinical purposes. The NIH’s Patient Reported Outcomes Measurement Information System (PROMIS) instruments provide robust patient reported outcome(PRO) measures; however, these have not been evaluated alongside “legacy”instruments in older adults with chronic back pain to expand our understanding of treatment response. In this pilot trial, we used epidural steroid injections(ESI) as a vehicle intervention to better understand our PRO. This study aims to evaluate whether legacy and/or PROMIS biopsychosocial measures change according to those who responded or were non-responders to ESI.

Table 1: Analysis of Variance (ANOVA) for PROMIS and Legacy Measures

Corresponding Measures	Descriptive Statistics Mean (SD)						ANOVA p-value for factor *indicates those with significant values		
	Responder (R)			Non Responder (NR)					
L: Legacy P: PROMIS	N	Pre-ESI	Post-ESI	N	Pre-ESI	Post-ESI	Interaction	R vs NR	Pre-ESI vs Post-ESI
Pain Interference									
L: Brief Pain Inventory	14	5.98 (2.81)	4.39 (3.05)	28	5.50 (2.62)	5.77 (2.18)	0.0321*	0.5435	0.1230
P: Pain Interference	14	65.77 (6.30)	60.53 (7.67)	26	67.27 (6.14)	65.0 (5.42)	0.2572	0.0726	0.0061*
Pain Behavior									
L: SF-36 Bodily Pain	14	23.5 (12.59)	38.4 (15.77)	29	28.95 (17.24)	31.31 (11.88)	0.0350*	0.8253	0.0045*
L: Pain Catastrophizing	14	1.72 (1.18)	1.68 (1.39)	29	1.48 (1.14)	1.74 (1.15)	0.3494	0.8021	0.5034
L: Fear Avoidance Belief Questionnaire	14	67.14 (14.12)	55.14 (22.91)	29	67.27 (18.83)	70.48 (16.67)	0.0095*	0.1458	0.1233
P: Pain Behavior	14	59.89 (3.39)	57.35 (7.62)	26	60.30 (5.00)	60.47 (3.81)	0.1857	0.1880	0.2487
Depression/ Anxiety									
L: PHQ- Depression subscale	14	2.07 (2.13)	1.5 (1.83)	29	1.52 (1.99)	2.24 (2.15)	0.0143*	0.8799	0.7645
L: PHQ- Anxiety subscale	14	1.5 (2.1)	1.28 (1.81)	29	1.48 (2.11)	1.69 (2.14)	0.3570	0.7631	0.9870
P: Emotional distress: depression	14	52.22 (11.95)	50.29 (10.84)	26	51.08 (9.84)	52.15 (10.25)	0.3226	0.9112	0.7754
P: Emotional distress: anxiety	14	58.24 (9.79)	51.58 (12.89)	26	58.25 (11.03)	56.58 (11.41)	0.1516	0.4571	0.0197*
Fatigue									
L: FACIT- fatigue	14	26.86 (8.85)	39.36 (8.43)	29	23.55 (11.50)	25.55 (9.25)	<0.0001*	0.6390	0.0098*
P: Fatigue	14	61.27 (10.51)	55.48 (8.69)	24	60.22 (9.44)	60.82 (10.35)	0.0179*	0.4845	0.0521
Sleep									
L: MOS Sleep	14	36.36 (21.32)	37.79 (22.79)	29	43.01 (20.28)	40.63 (22.84)	0.3726	0.9684	0.0558
P: Sleep disturbance	13	56.45 (14.52)	51.31 (14.81)	22	57.39 (12.96)	55.25 (15.19)	0.4476	0.9050	0.0824
Social									
L: MOS Social Support	14	4.51 (0.76)	4.91 (0.32)	29	4.14 (0.90)	4.20 (0.91)	0.1848	0.0252*	0.0762
P: Satisfaction with social roles	14	39.13 (9.05)	48.45 (11.13)	23	40.15 (8.02)	39.96 (8.76)	0.0036*	0.1711	0.0051*
P: Social isolation	14	43.41 (8.28)	42.51 (12.21)	23	47.67 (11.83)	45.93 (12.20)	0.8046	0.2775	0.4464

Methods: We enrolled a convenience sample of older Veterans (age 60+) with chronic backpain with/without leg pain scheduled for lumbar ESI. Subjects completed “legacy” instruments and corresponding PROMIS computer adaptive test (CAT) item banks pre-and post-ESI in the following domains: pain interference, behavior and intensity; functional status; depression and anxiety; fatigue; sleep and social functioning. The effects of ESI on bio-psychosocial measures using legacy and PROMIS were assessed using a two-way analysis of variance (ANOVA) with one repeat factor (pre/post ESI) and one between factor (responder/non-responder). We defined responders vs non-responders to ESI based on the accepted minimally important significant difference for the Roland Morris Disability Questionnaire, used in back pain trials.

Results: Participants included 71 Veterans who were on average 67 years old, 94% men, 73% non-Hispanic white, 17% African American. Patients were obese with a mean BMI 32.25% reported multi-site pain and 59% were diagnosed with depression, anxiety and/or PTSD. The majority (69%) reported pain duration ≥ 5 years with 93% reporting associated radiculopathy. The time between pre and post ESI assessments ranged between 3-8 weeks (based on routine follow-up appointment). Two-way ANOVA results showed that ESI responders (compared to non-responders) reported significant improvement in several domains from legacy (pain interference and behavior, depression and fatigue) and PROMIS (fatigue and social) measures. Table 1 includes legacy and PROMIS mean values (+SD) as well as ANOVA results for the interaction and factor effects.

Conclusion: These results suggest that responders to ESI showed improvement in several domains, more commonly among legacy than PROMIS measures. Fatigue was the only variable that improved using both instruments. Further research in a larger and gender diverse sample is warranted to gain a better understanding of PRO that may improve in older adults with chronic back pain receiving ESI.

Disclosure: R. Nayfe, None; M. Chansard, None; L. S. Hynan, None; E. M. Mortensen, None; U. E. Makris, None.

Abstract Number: 418

Dose-Response Relationship between Neuromuscular Electrical Stimulation and Muscle Function in Patients with Rheumatoid Arthritis

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Background/Purpose: Neuromuscular electrical stimulation (NMES) is a viable intervention to improve impaired muscle function of patients with rheumatoid arthritis (RA). However, there is limited evidence about dose-response of NMES to promote muscle function in these patients. The purpose of this study was to investigate the dose-response relationship between NMES and muscle function in patients with RA and to establish the minimal NMES intensity to promote improvements.

Methods: This was a secondary analysis of pre to post NMES intervention from a randomized study. Participants were adults diagnosed with RA. Participants underwent 36 NMES treatment sessions for the quadriceps muscles over 16 weeks. Muscle function was assessed pre- and post-intervention by the following 3 measures: quadriceps cross-sectional area and muscle quality were quantified using computed tomography, and strength via an isokinetic dynamometer. NMES intensity was calculated in percentage dividing NMES-elicited quadriceps muscle torque by maximum voluntary isometric contraction (MVIC). Improvements in muscle function were calculated using paired samples t-test. Dose-response relationship was determined using curve estimation regression statistics. The minimum NMES intensity was defined as the one sufficient to significantly improve all muscle function measures.

Results: Twenty-four subjects (48 legs) participated (75% female, 58[8] years old, and BMI of 32[7] kg/m²). Quadriceps cross-sectional area, muscle quality and strength improved pre-post intervention ($p < .001$) (Table 1). Associations between NMES and muscle quality ($r^2 = 0.20$) and strength ($r^2 = 0.23$) were significant, but between NMES and muscle cross-sectional area was not ($r^2 = 0.02$). The minimum NMES intensity necessary to improve all measures of muscle function ranged from 11% to 20% of MVIC (Table 2).

Conclusion: The minimum NMES intensity for significant gains in muscle function is around 15%. Larger NMES intensities may promote better muscle quality and strength in patients with RA.
Table 1: Muscle function pre and post NMES.

Variables	Baseline	Follow-up	Change	95% CI of Change
Quadriceps Cross-sectional Area (cm ²)	48.8 (8.5)	52.4 (8.5)	3.6 (2.8)	2.8; 4.4
Quadriceps muscle quality (HU)	45.9 (4.6)	47.4 (5.1)	1.5 (2.3)	0.8; 2.2
Quadriceps Strength (Nm)	144.6 (33.9)	158.6 (36.3)	14.1 (19.8)	8.3; 19.9

Table 2: NMES dose-response of quadriceps muscle function outcomes.

Intensity (% MVIC)	Muscle Cross-sectional Area		Muscle Quality		Muscle Strength	
	Change in cm ²	95% CI	Change in HU	95% CI	Change in Nm	95% CI
1 to 10 (n=8)	3.23	1.85; 4.61	0.15	-0.89; 1.18	1.16	-7.60; 9.91
11 to 20 (n=7)	3.43	2.40; 4.45	1.18	0.42; 1.95	11.08	4.60; 17.57
21 to 30 (n=13)	3.59	2.45; 4.74	1.87	1.01; 2.73	17.63	10.37; 24.89
31 to 40 (n=6)	3.80	2.61; 4.99	2.40	1.51; 3.29	22.56	15.01; 30.12
41 to 50 (n=4)	3.98	2.76; 5.19	2.58	1.67; 3.49	24.12	16.41; 31.83
51 to 60 (n=10)	4.15	2.34; 5.96	2.48	1.12; 3.84	22.89	11.39; 34.38

Disclosure: G. J. Almeida, None; S. S. Khoja, None; S. R. Piva, None.

Abstract Number: 419

Effect of Changes in Physical Activity on Cartilage Degradation in Knee Osteoarthritis

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Background/Purpose: Guidelines recommend 150 minutes a week in moderate-intensity physical activity (PA) to improve health in knee osteoarthritis (KOA). Despite that, individuals with KOA do not engage in the recommended amount of PA and physicians refrain from prescribing the PA recommendations due to concerns that large amounts of PA may worsen KOA. Only few studies have investigated the effects of PA on cartilage health and this issue needs further clarification. Serum biomarkers have been validated to identify cartilage degradation. The aim of this study was to determine the associations between changes in PA and changes in concentration of a biomarker of cartilage degradation.

Methods: This is a secondary analysis from a randomized trial that compared the effects of an intensive exercise program (comprehensive behavioral intervention [CBI]) to a less intensive program (standard of care exercise [SCE]) on physical function and PA after total knee replacement. Subjects with available serum and PA measured at baseline and 3-month follow-up were included. Blood samples were collected in the morning after a 12-hour fasting. Samples were frozen for future analysis. Cartilage degradation was assessed by analyzing the concentration of cartilage oligomeric matrix protein (COMP) using standardized enzyme-linked immunosorbent assay (ELISA). Daily time in moderate PA was assessed using the Sensewear Armband activity monitor worn for 7 days. Pearson correlation coefficients were used to determine associations between changes in PA and changes in COMP.

Results: Data on 33 subjects were available and analyzed. Subjects were 67±6 years old, 67% female and 92% white, with BMI of 30±4 kg/m². They had mild pain on surgical (2±2) and non-surgical (3±3) knees, and moderate functional limitations (17.9±9.5) measured by the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) physical function subscale. Demographics between CBI (n=14) and SCE (n=19) were similar at baseline. Forty three percent of the subjects in the CBI arm improved PA above the standard error of measurement (11 minutes of moderate PA per day) and experienced an increase in COMP (145±418 ng/ml), while only 26% of the subjects in the SCE improved PA and showed a slight decrease in COMP (-49±725 ng/ml), suggesting that perhaps more PA may increase cartilage degradation. However, upon further assessment of the direct associations between changes in PA and COMP, we observed negative associations between changes in PA and changes in COMP in the CBI (r=-.65; p=.012) and in the SCE (r=-.45; p=.056), indicating that individuals who increased PA actually had a decrease in COMP concentration.

Conclusion: These preliminary results indicate that moderate PA does not seem to contribute to cartilage degradation in individuals with KOA and strengthen to body of evidence in this area. In this study, individuals with KOA appear to

engage in activities of low impact such as brisk walk, which may not be detrimental to the knee joint. A larger study is warranted to validate our findings. Participation in moderate PA could be encouraged by physicians since its benefits outweigh the harms.

Disclosure: G. J. Almeida, None; C. Moore-Patterson, None; C. N. Smith, None; P. Jayabalan, None; S. R. Piva, None.

Abstract Number: 420

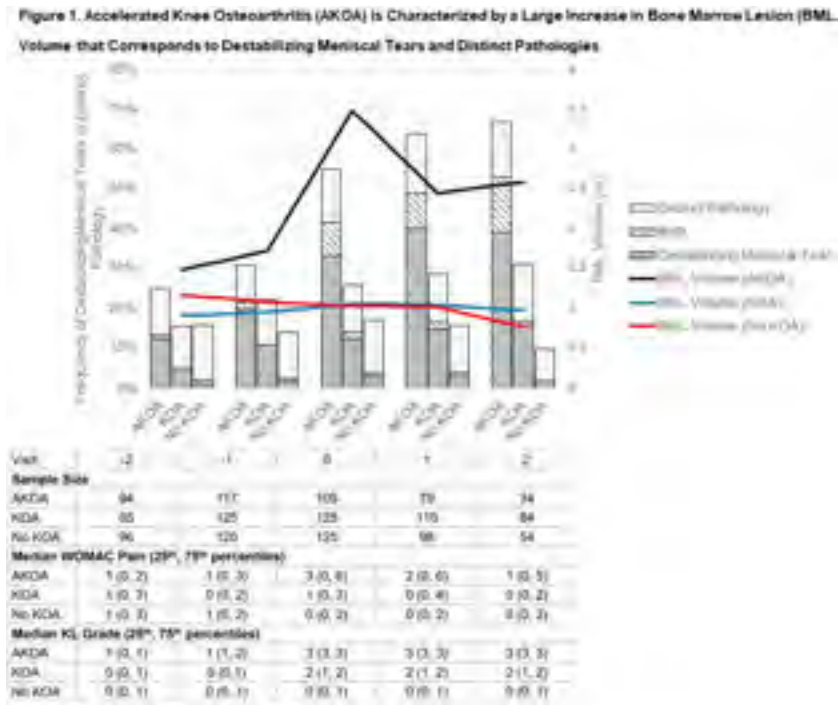
Accelerated Knee Osteoarthritis Is Characterized By Destabilizing Meniscal Tears and Pre-Radiographic Structural Disease Burden

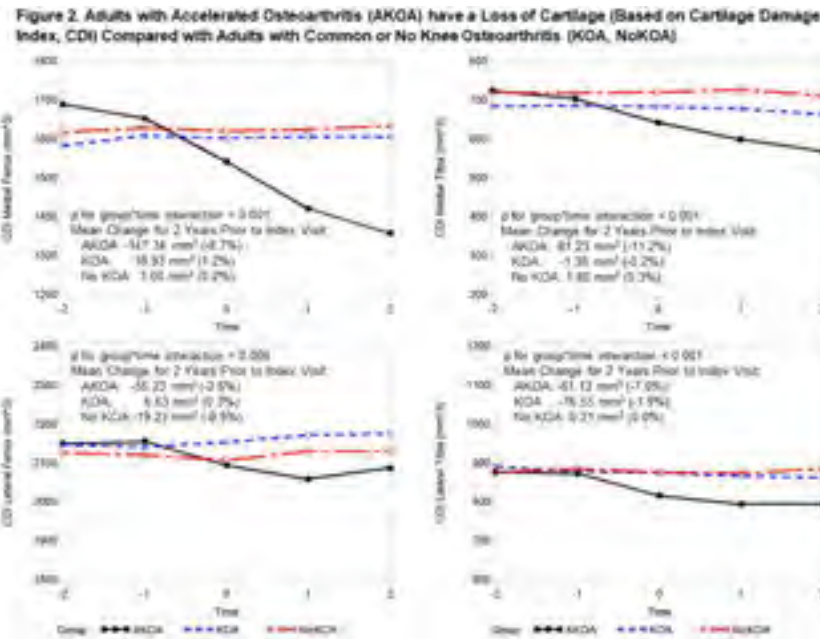
Jeffrey B. Driban¹, Julie Davis², Bing Lu³, Lori Lyn Price^{4,5}, Robert J. Ward⁶, James MacKay⁷, Charles B. Eaton⁸, Grace H. Lo⁹, Mary Barbe¹⁰, Ming Zhang¹¹, Jincheng Pang¹², Alina Stout¹³, Matthew Harkey¹³ and Timothy E. McAlindon¹⁴,
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Session Information

Session Date: Sunday, October 21, 2018
Session Title: Osteoarthritis – Clinical Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: A subset of adults who develop knee osteoarthritis (KOA) quickly progress from no radiographic disease to advanced-stage disease often in ≤ 12 months. Adults with accelerated KOA (AKOA) have greater pain and disability than those with common KOA even prior to radiographic onset. AKOA may be a unique endotype of KOA consequent on specific pathologies, as opposed to rapid evolution of common KOA; however, this hypothesis is untested. Hence, we aimed to determine if incident AKOA is preceded and characterized by distinct pathologic changes (e.g., subchondral bone damage), destabilizing meniscal tears (e.g., root/anchor tears) or other secondary feature changes; such





as, diffuse meniscal pathology, greater quantitative changes in bone marrow lesions (BMLs) and articular cartilage than adults with common or no KOA.

Methods: We selected 3 sex-matched groups from the Osteoarthritis Initiative who had a knee without radiographic KOA at baseline (Kellgren-Lawrence [KL]<2): *AKOA* developed KL grade ≥ 3 ≤ 48 months, *common KOA* increased radiographic scoring ≤ 48 months without meeting AKOA criteria, and *no KOA* had the same KL grades at baseline and 48 months. Observation period was up to 2 years before and after an index visit, which was when the AKOA or common KOA criteria were met (no KOA index visit was matched to AKOA). Radiologists reported meniscal and other distinct pathological findings. We quantified BML volume and cartilage damage on magnetic resonance (MR) images. We performed linear mixed models –adjusting for sex and factors related to missing MR data.

Results: Overall the groups were predominantly female (63%), overweight, and 33% reported frequent knee pain within a year of baseline. At 1 year before the index visit, >75% of adults with AKOA had multiple meniscal regions affected (diffuse pathology; vs common KOA: OR=3.19, 95% CI=1.70 to 5.97). By the index visit, adults with AKOA were twice as likely to have distinct pathology than those with common KOA (OR=2.19, 95% CI=1.01, 4.77; Figure 1). The most common distinct pathology affected the subchondral bone (i.e., subchondral fracture, acute attrition), which was found in 12.3% of adults with AKOA, 0.8% with common KOA, and 1.6% with no KOA. Diffuse meniscal pathology was ubiquitous in AKOA; including 42% with a destabilizing meniscal tear (common KOA: 14%). These changes corresponded to larger BMLs and greater cartilage loss (Figure 1 and 2).

Conclusion: AKOA is characterized by destabilizing meniscal tears in a knee with greater pre-radiographic disease (e.g., diffuse meniscal pathology, large BMLs, greater cartilage loss)

Disclosure: J. B. Driban, None; J. Davis, None; B. Lu, None; L. L. Price, None; R. J. Ward, None; J. MacKay, None; C. B. Eaton, None; G. H. Lo, None; M. Barbe, None; M. Zhang, None; J. Pang, None; A. Stout, None; M. Harkey, None; T. E. McAlindon, None.

Abstract Number: 421

What Do Patients with Osteoarthritis Think of Their Preoperative Education before Total Hip Replacement Surgery: Qualitative Study

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Session Information**Session Date:** Sunday, October 21, 2018**Session Title:** Osteoarthritis – Clinical Poster I**Session Type:** ACR Poster Session A**Session Time:** 9:00AM-11:00AM

Background/Purpose: Osteoarthritis (OA) is the most common joint disorder and one of the main causes of pain and disability in adults. The hip is one of the major joints affected by OA. OA of the hip can be observed in 7% to 27% of the population. When patients do not benefit from conservative treatments, Total Hip Replacement (THR) surgery is recommended. THR increases every year (> 50K in Canada in 2017). Providing preoperative education regarding THR decreases patients' anxiety and improves rehabilitation. So far, preoperative education is mostly developed based on clinicians' perspectives. Therefore, this study aimed to investigate patients' perspectives on the quality of current preoperative education and the educational gaps that they face.

Methods: In total, 46 patients with hip OA and 16 of their family caregivers/friends participated in in-person focus groups or telephone interviews. Patients answered questions regarding gaps in, and quality of, the preoperative education they received, the barriers to receiving preoperative education, and their main concerns before THR. Each focus group or interview was transcribed verbatim. The transcriptions were coded and analyzed using NVivo, is a software for analyzing qualitative research. To conduct the analyses and investigate the phenomenon that we were interested in (i.e., preoperative education), as patients and their family members experience it in their daily lives, the eidetic phenomenologic approach was used.

Results: Five themes were identified: 1) People learn in different ways: explains different methods participants use to gather information regarding THR, 2) Pre-op was useful but: provides information regarding patients' opinions on quality of preoperative education, 3) Never got a definitive answer: explains the educational gaps that exist in current preoperative education, 4) The biggest worry: indicates patients' concerns before THR and 5) Had to struggle to get the information: indicates barriers that patients face in receiving preoperative education.

Conclusion: These findings enhance our knowledge on the current educational gaps that patients experience and the reasons why some patients cannot receive preoperative education. These findings can be used to develop preoperative education that addresses patients' educational needs and facilitate their access to preoperative education.

Acknowledgment: We would also like to acknowledge Colleen O'Melinn and Halima Elmi for their contributions of recruitment, data collection and data analysis on this study.

Disclosure: S. Mohammadi, None; W. Watson, None; B. Grazys, None; M. Westby, None; W. Miller, None.

Abstract Number: 422

Efficacy and Safety of a Fixed-Dose Combination of Nimesulide/Pantoprazole Compared with Naproxen/Esomeprazole for Pain Relief in Patients with Osteoarticular Diseases and Dyspeptic Symptoms

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Session Information**Session Date:** Sunday, October 21, 2018**Session Title:** Osteoarthritis – Clinical Poster I**Session Type:** ACR Poster Session A**Session Time:** 9:00AM-11:00AM

Background/Purpose: NSAIDs are one of the most used drug classes in the world.¹ However, its use may be associated with potentially limiting adverse events (AEs), especially gastrointestinal toxicity.² Concomitant use of proton-pump inhibitors, including fixed-dose combination regimens, have emerged as an alternative to minimize gastrointestinal AEs.³ This study investigated the safety and efficacy of fixed-dose combination of naproxen/esomeprazole and nimesulide/pantoprazole to determine if both regimens are equally suited to relieve pain in patients with osteoarticular disease and dyspeptic symptoms.

Methods: This was a multi-center, randomized, double-blind, active-controlled, parallel-group, non-inferiority phase 3 study. Patients were assigned to receive either nimesulide/pantoprazole (100mg/20mg) twice daily or naproxen/esomeprazole (500mg/20mg) twice daily for 14 days. The primary endpoint was the mean change in modified Western Ontario and

McMaster Universities Osteoarthritis Index (WOMAC)⁴ pain subscale. Safety assessment was performed by the mean visual analog scale (VAS) of dyspeptic symptoms. This study is registered at ClinicalTrials.gov: NCT01670552.

Results: A total of 490 patients were enrolled and randomized (399 completed). The baseline characteristics are presented in Table 1. Mean changes in the modified WOMAC are presented in Table 2. The difference in mean change in the modified WOMAC after 7 days of treatment between the 2 groups was 2.33 mm (95% CI, -1.22 to 5.89 mm). After 14 days of therapy, the difference was 0.45 mm (95% CI, -3.29 to 4.19 mm). Overall frequencies of AEs were similar in the 2 groups.

Conclusion: The present study demonstrated non-inferiority of a 14-day regimen with a fixed-dose combination of nimesulide/pantoprazole compared to naproxen/esomeprazole for the treatment of osteoarticular pain. The results of the study show that the gastrointestinal adverse effects related to NSAID use may be reduced by the use of a fixed-dose combination of nimesulide/pantoprazole.

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3. Scheiman JM. The use of proton pump inhibitors in treating and preventing NSAID-induced mucosal damage. *Arthritis Res Ther*. 2013;15(Suppl 3):S5.
4. Bellamy N. WOMAC osteoarthritis index user guide. Version V. Brisbane, Aust. 2002.

Disclosure: E. de Almeida Macêdo, EMS Pharma Inc., 3; H. Pott Junior, EMS Pharma Inc., 3; M. Scheinberg, EMS Pharma Inc., 5; C. Ecclesato, EMS Pharma Inc., 3; R. Bleuel Amazonas, EMS Pharma Inc., 3.

Abstract Number: 423

Accelerated Knee Osteoarthritis Is Characterized By Pre-Radiographic Degeneration of the Extensor Mechanism and Cruciate Ligaments: Data from the Osteoarthritis Initiative

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Degeneration of knee ligaments and tendons, which may be signs of joint instability and abnormal joint loading, may antedate the onset of radiographic accelerated knee osteoarthritis (AKOA) and contribute to prodromal joint symptoms that are common among adults with AKOA. We assessed whether adults with incident AKOA are more likely to have degenerative knee ligaments or tendons compared to adults with common or no KOA at timepoints prior to and after the onset of disease.

Methods: We classified 3 sex-matched groups of Osteoarthritis Initiative participants who had a knee without radiographic KOA at baseline (Kellgren-Lawrence [KL] < 2): 1) incident AKOA: ≥ 1 knee progressed to KL grade ≥ 3 within 48 months, 2) incident common KOA: ≥ 1 knee increased in radiographic scoring within 48 months but not meeting AKOA criteria, and 3) no KOA: both knees had the same KL grade at baseline and 48 months. The observation period included up to 2 years before and after when the accelerated or common KOA criteria were met (index visit; no KOA index visit was matched to AKOA). Two musculoskeletal radiologists read magnetic resonance images and reported degenerative signal changes for cruciate and collateral ligaments, extensor mechanism, and proximal gastrocnemius tendons. A degenerative appearance was defined as the presence of abnormal intrinsic high-signal intensity within the substance of the ligaments or tendon

without discrete tear. We used generalized linear mixed models with group (3 levels) and time (up to 5 levels) as independent variables.

Results: Table 1 provides the descriptive characteristics of each group. Regardless of time, adults with AKOA had twice the odds of having degenerative cruciate ligaments than those with no KOA (OR=2.10, 95% CI=1.18 to 3.74). A weaker association, which was not statistically significant, was found for those with AKOA versus those with common KOA (OR=1.73, 95% CI=0.99 to 3.02). Adults with common KOA had similar odds of having a degenerative cruciate ligament as those with no KOA (OR=1.21, 95% CI=0.68 to 2.17). Adults with accelerated or common KOA had twice the odds of having degenerative extensor mechanism than no KOA (OR=2.13 and 2.16, respectively). Collateral ligaments and proximal gastrocnemius tendons were not statistically significant.

Conclusion: Degenerative cruciate ligaments and extensor mechanism precede radiographic onset of AKOA. Hence, AKOA may be preceded by knee instability, which may help identify high-risk patients and novel prevention strategies.

Table 1. Descriptive Characteristics of those with Accelerated Knee Osteoarthritis (AKOA), Common Knee Osteoarthritis (KOA), or No KOA at Osteoarthritis Initiative Baseline

Variables (means, SD; except where noted)	AKOA (n=125)	Common KOA (n=125)	No KOA (n=125)
Females (n, %)	79 (63%)	79 (63%)	79 (63%)
Index knee KL Grade=0 (n, %)	42 (34%)	71 (57%)	92 (74%)
Patellofemoral Osteoarthritis (MR-based) (n, %)	88 (75%)	84 (69%)	80 (66%)
Frequent knee pain in past 12 months (n, %)	44 (35%)	49 (39%)	30 (24%)
Age (years)	62.5 (8.5)	58.4 (8.4)	57.3 (8.2)
Body mass index (kg/m ²)	29.7 (4.6)	28.1 (4.4)	26.9 (4.4)
Global impact rating (0 to 10; higher score=greater impact)	1.7 (1.9)	1.1 (1.5)	0.8 (1.1)
How many days limited activities in past 30 days (0 to 30)?	3.2 (7.3)	1.7 (4.8)	1.4 (4.3)
WOMAC pain (0 to 20; higher score=more pain)	2.3 (3.1)	1.8 (2.3)	1.6 (2.4)

Note: SD = standard deviation, KL = Kellgren-Lawrence, MR = Magnetic resonance

Table 2. Frequency of Degenerative Ligaments/Tendons Among Those with Accelerated Knee Osteoarthritis (AKOA), Common Knee Osteoarthritis (KOA), and No KOA

Frequency [n (%)]	Visit	AKOA	Common KOA	No KOA
Cruciate Ligaments	-2	39 (43)	14 (22)	25 (26)
Group effect (p = 0.03)	-1	50 (43)	34 (28)	30 (24)
Group*time Interaction (p = 0.24)	Index	49 (47)	35 (28)	30 (24)
	1	41 (51)	33 (31)	25 (26)
	2	17 (47)	27 (33)	11 (21)
Collateral Ligaments	-2	22 (24)	6 (9)	12 (13)
Group effect (p = 0.43)	-1	28 (24)	19 (15)	17 (14)
Group*time Interaction (p = 0.06)	Index	28 (26)	19 (15)	17 (14)
	1	24 (30)	20 (18)	15 (15)
	2	8 (22)	17 (20)	8 (15)
Extensor Mechanism	-2	40 (43)	26 (40)	21 (22)
Group effect (p = 0.01)	-1	50 (43)	48 (39)	30 (24)
Group*time Interaction (p = 0.43)	Index	47 (45)	51 (41)	32 (26)
	1	36 (46)	46 (42)	26 (27)
	2	11 (31)	33 (39)	17 (32)
Proximal Gastrocnemius Tendon	-2	46 (50)	25 (38)	39 (41)
Group effect (p = 0.71)	-1	54 (46)	54 (44)	51 (41)
Group*time Interaction (p = 0.12)	Index	50 (47)	56 (45)	51 (41)
	1	37 (46)	50 (45)	41 (42)
	2	15 (42)	40 (48)	20 (38)

Disclosure: J. Davis, None; M. Harkey, None; R. J. Ward, None; J. MacKay, None; L. L. Price, None; C. B. Eaton, None; G. H. Lo, None; M. Barbe, None; T. E. McAlindon, None; J. B. Driban, None.

Abstract Number: 424

Occult Extractable Synovial Fluid in Inflammatory and Non-Inflammatory Arthritis of the Knee

Noelle Rolle¹, Irum Jan², Wilmer Sibbitt Jr¹, Philip Band³, William Hayward⁴, Maheswari Muruganandam¹, N. Suzanne Emil¹, Monthida Fangtham¹, Roderick Fields¹ and Arthur Bankhurst¹, ¹Rheumatology, University of New Mexico Health Sciences Center, Albuquerque, NM, ²Internal Medicine, University of New Mexico Health Sciences Center, Albuquerque, NM, ³NYU School of Medicine, New York, NY, ⁴The Department of Exercise and Sport Sciences, New Mexico Highlands University, Las Vegas, NM

Session Information

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: We hypothesized that mechanical compression of the knee in rheumatoid arthritis(RA) and osteoarthritis (OA) would mobilize occult extractable fluid and improve arthrocentesis success.

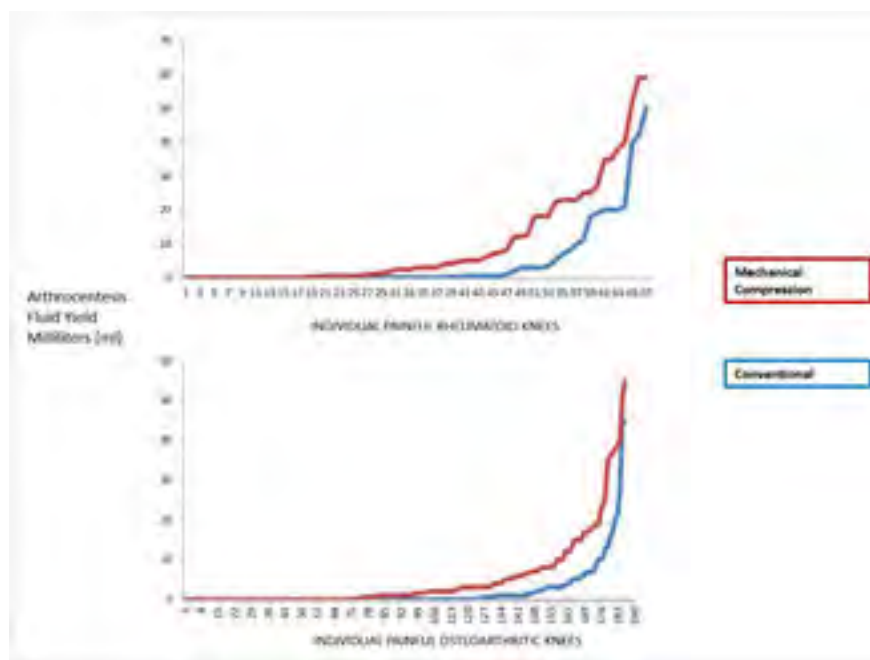


Manual Compression



Mechanical Compression

Methods: 186 consecutive knees with grade II-III OA and 67 knees with RA were included. Conventional arthrocentesis was performed and success and volume (milliliters) determined; the needle was left intra-articularly, and mechanical compression was applied with an elastomeric knee brace. Arthrocentesis was then resumed until fluid return ceased. Fluid was characterized as to volume and cell counts.



Results: In the RA knee mechanical compression decreased failed diagnostic arthrocentesis from 56.7% (38/67) to 26.9% (18/67) (-47.4%, $p = 0.003$), and increased absolute arthrocentesis yield from 4.7 ± 10.3 ml to 9.8 ± 9.8 ml (108% increase, 95% CI -8.5 < -5.1 < -1.7 $p = 0.0038$). Total extractable fluid yield was 96% greater in RA (9.8 ± 9.8 ml) than OA (5.0 ± 9.4 ml, $p = 0.0008$), and occult extractable fluid was 77% greater in RA than OA (RA: 5.3 ± 8.7 ml, OA 3.0 ± 5.5 ml, $p = 0.046$). Large effusions (≥ 5 ml) in RA were associated with an increase in neutrophils in synovial fluid ($p = 0.04$) but not radiologic arthritis grade ($p = 0.87$). In contrast, in the OA knee large effusions were associated with more severe arthritis grade ($p = 0.0001$) but not synovial fluid neutrophil count ($p = 0.96$).

Conclusion: Mechanical compression improves the success of diagnostic and therapeutic knee arthrocentesis in both RA and OA. Large effusions in RA are associated with inflammatory synovial fluid but not arthritis grade; in contrast, large effusions in OA are associated with more severe arthritis grades.

Disclosure: N. Rolle, None; I. Jan, None; W. Sibbitt Jr., None; P. Band, None; W. Hayward, None; M. Muruganandam, None; N. S. Emil, None; M. Fangtham, None; R. Fields, None; A. Bankhurst, None.

Abstract Number: 425

Efficacy, Safety, and Tolerability of ONO-4474, an Orally Available Pan-Tropomyosin Receptor Kinase Inhibitor, in Japanese Patients with Moderate-to-Severe Osteoarthritis of the Knee: A Randomized, Placebo-Controlled, Double-Blind, Parallel-Group Comparative Study

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: ONO-4474 is an orally available, peripheral-specific, pan-tropomyosin receptor kinase (pan-Trk) inhibitor currently under development for treatment of musculoskeletal pain in OA patients. This study assessed the efficacy, safety, and tolerability of ONO-4474 in Japanese patients with OA of the knee with inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs).

Methods: Male and female Japanese patients with moderate-to-severe OA of the knee and inadequate response to NSAIDs, who were aged 40 to <75 years with a body mass index between 18.5 and <39.0 kg/m² were recruited in this study. After a 14-day screening period, patients entered a 28-day, double-blind treatment period and were randomized to receive ONO-4474 200 mg/day (100 mg twice daily after meals) or placebo. Patients then entered a 14-day follow-up period. The primary efficacy endpoint was change in knee pain during walking, assessed over 24 hours, calculated as the difference in posterior mean of changes in VAS₂₄ scores from baseline versus placebo at Week 4. Other efficacy endpoints included WOMAC scores, Patients' Global Assessment (PGA) scores, and frequency of rescue treatment use. Safety endpoints were vital signs, 12-lead ECG, laboratory tests, neurological examinations, Columbia Suicide Severity Rating Scale (C-SSRS), and adverse events (AEs).

Results: The full analysis and safety analysis sets included 110 patients (ONO-4474 and placebo, both n = 55). The difference in posterior mean change in VAS₂₄ from baseline \pm posterior standard deviation (95% confidence interval [CI]) (ONO-4474 group – placebo group) was -5.8 ± 4.4 mm [$-14.3, 2.8$] at Week 4 and the posterior probability that the difference was less than 0 mm was 90.6%, indicating an improvement with ONO-4474 versus placebo. At Week 4, the difference for ONO-4474 versus placebo in the least-squares (LS) mean changes in WOMAC total and pain scores from baseline \pm standard error [95% CI] were -3.6 ± 3.5 mm [$-10.5, 3.3$] and -4.1 ± 3.8 mm [$-11.7, 3.5$]. The difference in the LS mean change of PGA from baseline \pm standard error [95% CI] was -6.4 ± 4.5 mm [$-15.4, 2.6$]. Fewer patients in the ONO-4474 group than the placebo group required rescue therapy. Treatment-emergent AEs (TEAEs) occurred in 41.8% of patients in the ONO-4474 group and 18.2% in the placebo group. The most common TEAE in the ONO-4474 group was myalgia (7.3%). In the ONO-4474 group, TEAEs related to the peripheral and central nervous system included dizziness and hypoaesthesia (3.6% each), and dysaesthesia, dysgeusia, feeling abnormal, skin warm, and hypoaesthesia oral (1.8% each), while TEAEs related to the musculoskeletal system included myalgia (7.3%), arthralgia (5.5%), and pain in extremity (1.8%). Four patients in the ONO-4474 group and one patient in the placebo group withdrew from treatment because of TEAEs, none of which were considered serious, and those patients recovered or were recovering after drug discontinuation. There were no clinically significant changes in vital signs, 12-lead ECG, laboratory tests, or C-SSRS scores.

Conclusion: ONO-4474 may be a tolerable and effective analgesic in patients with moderate-to-severe OA of the knee.

Disclosure: N. Ishiguro, Ono Pharmaceutical Co., Ltd., 5; Astellas Pharma Inc., 2, 8; AbbVie GK, 2; Asahi Kasei Corporation, 2; CHUGAI PHARMACEUTICAL CO., LTD., 2; DAIICHI SANKYO COMPANY, LIMITED, 2, 8; Eisai Co., Ltd., 2; KAKEN PHARMACEUTICAL CO., LTD., 2; Medical Corporation SANJINKAI, 2; Medical Corporation TOUKOUKAI, 2; Mitsubishi Tanabe Pharma Corporation, 2; Otsuka Pharmaceutical Co., Ltd., 2; Pfizer Japan Inc., 2, 8; Takeda Pharmaceutical Company Limited, 2; Zimmer Biomet G.K., 2; Eli Lilly Japan K.K., 8; Taisho Toyama Pharmaceutical Co., Ltd., 8; Bristol-Myers Squibb Company, 8; S. Oyama, Ono Pharmaceutical Co., Ltd., 3; R. Higashi, Ono Pharmaceutical Co., Ltd., 3; K. Yanagida, Ono Pharmaceutical Co., Ltd., 3.

Abstract Number: 426

The Association of Dietary Patterns with Knee Symptoms and MRI Detected Structures in Patients with Knee Osteoarthritis (OA)

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Session Information

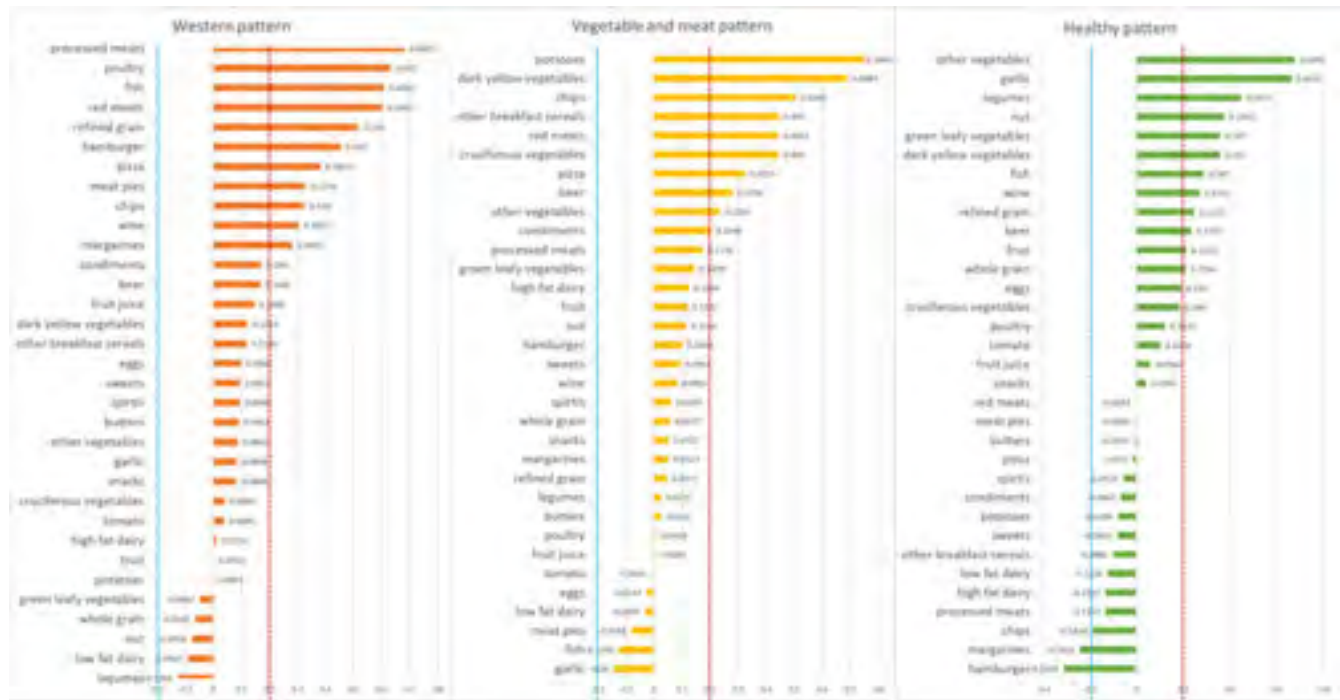
Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM The association of dietary patterns with knee symptoms and MRI detected structures in patients with knee osteoarthritis (OA)

Abstract



Background/Purpose: This study aimed to examine the cross-sectional and longitudinal associations of dietary patterns with knee symptoms and structures in knee OA patients.

Methods: Participants were from a subset of a randomised, placebo-controlled trial in Tasmania, who had symptomatic knee OA and vitamin D deficiency at baseline and received 50,000 IU vitamin D₃ (N= 129) or placebo (N= 132) monthly for 24 months (aged 63.0 ± 7.2 years). Baseline diet was assessed by the Anti-Cancer Council of Victoria food frequency questionnaire. At baseline and 24 months, knee symptoms were assessed using WOMAC index and knee structures using MRI. Factor analysis was used to identify dietary patterns. Each participant received a score for each dietary pattern, with a higher score indicating a greater intake of food composing that pattern. Associations between dietary pattern scores and knee OA outcomes were examined using multivariable linear regressions with adjustment for age, sex, BMI/change in BMI, treatment arm, total energy intake and physical activity.

Results: Three dietary patterns were identified: “western pattern”, characterised by high intakes of processed food, chips and wine, “vegetable and meat pattern”, characterised by high intakes of vegetables, red meat and beers, and “healthy pattern”, characterised by high intakes of vegetables, legumes, nuts, fish, fruits and whole grain. Participants with higher healthy pattern or vegetable and meat pattern scores had lower baseline WOMAC function scores (β : -54.0, 95% CI: -99.9 to -8.1 and -58.7, -10.9 to -0.8, respectively), and also had lower baseline total WOMAC scores (β : -69.4, 95% CI: -131.4 to -7.4 and -76.5, -144.7 to -8.3, respectively). Baseline western pattern scores were not associated with either total WOMAC or WOMAC function scores. Healthy pattern or vegetable and meat pattern scores were not associated in WOMAC scores over 24 months, but higher western pattern scores were associated with increased total WOMAC scores and WOMAC function scores (β : 118.4, 95% CI: 25.2 to 111.6 and 101.8, 36.2 to 167.4, respectively) over 24 months. In multivariable analyses, dietary patterns were not significantly associated with any knee structure cross-sectionally or longitudinally.

Conclusion: These results suggest that maintaining a healthy dietary pattern may have beneficial effects on knee function, whereas maintaining a western pattern may contribute to increased functional disability over time in knee OA patients. The evidence does not suggest that dietary patterns affect knee structure.

Figure 1. Rotated factor loading for the three dietary patterns.

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One Year Efficacy and Safety of One or Three Injections of Hylan G-F 20 for Knee Osteoarthritis: A Systematic Literature Review and Meta-Analysis

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Hylan G-F 20 is indicated for the treatment of pain in knee osteoarthritis (OA) in patients who failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics. The 26-week efficacy and safety of 1 or 3 injections of hylan G-F 20 have been widely reported, but there is limited research focusing on the long-term effects. A systematic literature review (SLR) and meta-analysis were conducted to determine the 1-year efficacy and safety of hylan G-F 20 for knee OA.

Methods: A SLR was conducted by searching MEDLINE, Embase, and Cochrane CENTRAL and manual searching of relevant conference proceedings (published January 1, 1995 through May 4, 2017). Eligible studies were randomized controlled trials, non-randomized controlled trials, non-randomized non-controlled trials, and observational studies that investigated 1-year efficacy and safety of 1 or 3 injections of hylan G-F 20 for knee OA. Cohort analyses of both Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain and Physical Function at 1 year were conducted for 1 or 3 injections of hylan G-F 20 using standardized mean change (SMC). Direct meta-analysis of WOMAC Pain and WOMAC Physical Function at 1 year were conducted for 1 injection of hylan G-F 20 vs. appropriate care (e.g. medications, education/counseling, weight loss, arthroscopy, etc.) or physical therapy using either reported or calculated endpoints or change from baseline values.

Results: The search retrieved 1,591 references; 22 met criteria for inclusion and were used to assess safety, 8 of which were included for efficacy analyses. Combined cohort analysis of 1 and 3 injections for WOMAC Pain at 1 year showed a decrease in SMC (95% confidence interval; p-value; I^2) of -0.89 (-1.15, -0.62; $p<0.0001$; 90.76%). Results of separate analyses for 1 and 3 injections were -1.17 (-1.86, -0.47; $p<0.001$; 96.87%) and -0.79 (-1.04, -0.53; $p<0.0001$; 81.35%), respectively. The cohort analysis results for WOMAC Physical Function at 1 year for combined, 1 injection, and 3 injections were -0.91 (-1.14, -0.67; $p<0.0001$; 88.14%), -1.03 (-1.60, -0.45; $p<0.001$; 95.78%), and -0.86 (-1.13, -0.58; $p<0.0001$; 83.39%), respectively. Comparative meta-analysis of 1 injection of hylan G-F 20 vs. appropriate care or physical therapy showed a mean difference (95% confidence interval; p-value; I^2) of -4.10 (-6.18, -2.02; $p<0.001$; 76.3%) for WOMAC Pain and -8.97 (-11.64, -6.31; $p<0.0001$; 0%) for WOMAC Physical Function at 1 year. Total adverse event (AE) rates at 1 year varied across the 22 studies, with 0-2% reported having serious/severe AEs, 3-19.6% for treatment-related AEs, 0.25-4.65% for drug discontinuation due to AEs, and 0-9.68% for withdrawals due to AE.

Conclusion: The evidence shows that both 1 and 3 injections of hylan G-F 20 are effective at reducing WOMAC Pain and Physical Function, with statistically significant improvements at 1 year compared to baseline and standard of care. Relatively low rates of AEs further strengthen the evidence in favor of using hylan G-F in knee OA. It is likely that additional research will continue to illustrate differences in long-term efficacy and safety between hylan G-F 20 and other comparators.

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Significant Pain Reduction with Oral Methotrexate in Knee Osteoarthritis; Results from a Randomised Controlled Phase III Trial of Treatment Effectiveness

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Session Information

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Session Title: Osteoarthritis – Clinical Poster I

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

Background/Purpose: Current treatments for osteoarthritis (OA) are severely limited. Synovitis is prevalent in OA and is associated with pain. The slow-acting anti-rheumatic drug methotrexate (MTX) is the gold-standard treatment for synovitis in inflammatory arthritides. The primary aim of the PROMOTE trial was to determine the effectiveness of MTX versus placebo as an analgesic treatment for knee OA.

Methods: PROMOTE was a multi-centre, randomised, placebo-controlled trial with 12 months follow-up. Participants with symptomatic (visual analogue scale (VAS) pain $\geq 4/10$) and radiographic tibiofemoral knee OA, fulfilling clinical ACR criteria, were recruited across UK primary and secondary care. Participants were randomized on a 1:1 basis to MTX or placebo, in addition to ongoing usual care, with dose escalation from 10mg to 25mg over 8 weeks and maintenance at 25mg (or the highest tolerated dose) for the remainder of the study. The primary endpoint was average knee pain during the previous week (numerical rating scale [0-10], NRS) at 6-months. Secondary endpoints included WOMAC, quality-of-life and adverse events. Linear mixed models compared outcomes between groups on an intention-to-treat (ITT) basis. In a sub-study, contrast-enhanced MRI of the index knee was performed at baseline and 6 months.

Results: Of 207 patients screened, 155 participants (64% women, mean age 60.9 years, 50% K-L Grade 3-4) were randomized. Primary endpoint data at 6 months were available for 134 patients (86%); only ITT data are presented. At 6 months, average knee pain (as measured by NRS) was 6.2 in the placebo group and 5.1 in the MTX group, with a baseline adjusted treatment difference of -0.83 points (95% CI -1.55 to -0.10; $p=0.025$), equivalent to a standard effect size of 0.36. Statistically significant differences at 6 months were seen for WOMAC stiffness and physical function, but not pain. Treatment benefits were reduced by 12 months. 94 patients had analysable MRI data at baseline and 80 at 6 months; no change in synovial volume was found. Four serious adverse events were reported (MTX: 2 [not defined as possibly related], placebo: 2).

Conclusion: MTX added to usual care demonstrated significant reduction in knee OA pain at 6 months, and suggests improvements in WOMAC stiffness and function. Despite a moderate standard effect size, the treatment effect was smaller than thresholds considered clinically meaningful. Further analyses will explore predictors of response to understand if subsets with enhanced response can be identified.

We acknowledge Arthritis Research UK for funding support.

Table 1: Selected PROMOTE outcomes at baseline and 6 months follow-up (primary endpoint)

	Month	MTX		Placebo		Adjusted Difference at 6 months (95% CI)	p-value
		N	Mean (SD)	N	Mean (SD)		
Average Knee Pain NRS (0-10)	M0	77	6.4 (1.78)	78	6.8 (1.62)	-0.83 (-1.55 to -0.10)	0.025
	M6	66	5.1 (2.32)	68	6.2 (2.30)		
WOMAC Pain	M0	77	10.5 (3.49)	78	11.7 (3.77)	-0.95 (-2.17 to 0.27)	0.126
	M6	66	8.1 (4.56)	68	9.9 (4.38)		
WOMAC Stiffness	M0	77	4.6 (1.57)	78	4.9 (1.97)	-0.60 (-1.18 to -0.01)	0.045
	M6	66	3.6 (1.80)	68	4.4 (2.05)		
WOMAC Physical Function	M0	76	35.4 (10.98)	78	37.0 (13.54)	-5.01 (-8.74 to -1.29)	0.008
	M6	66	26.4 (14.73)	68	32.5 (15.32)		
EQ-5D Utility	M0	77	0.57 (0.19)	78	0.48 (0.25)	0.0227 (-0.040 to 0.085)	0.476
	M6	66	0.63 (0.21)	68	0.53 (0.27)		
Height adjusted synovial volume	M0	47	130 (106.8)	47	127 (115.8)	14.89 (-18.19 to 47.96)	0.373
	M6	42	132 (115.8)	38	116 (108.8)		

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The Potential Clinical Relevance of Imaging Biomarker Data from Short-Term Interventional Trials in Osteoarthritis: A Comparison of the Cathepsin K Inhibitor Miv-711 Phase 2a MRI Knee Joint Data and KL-Matched 5577 Knee Control Data from the Osteoarthritis Initiative

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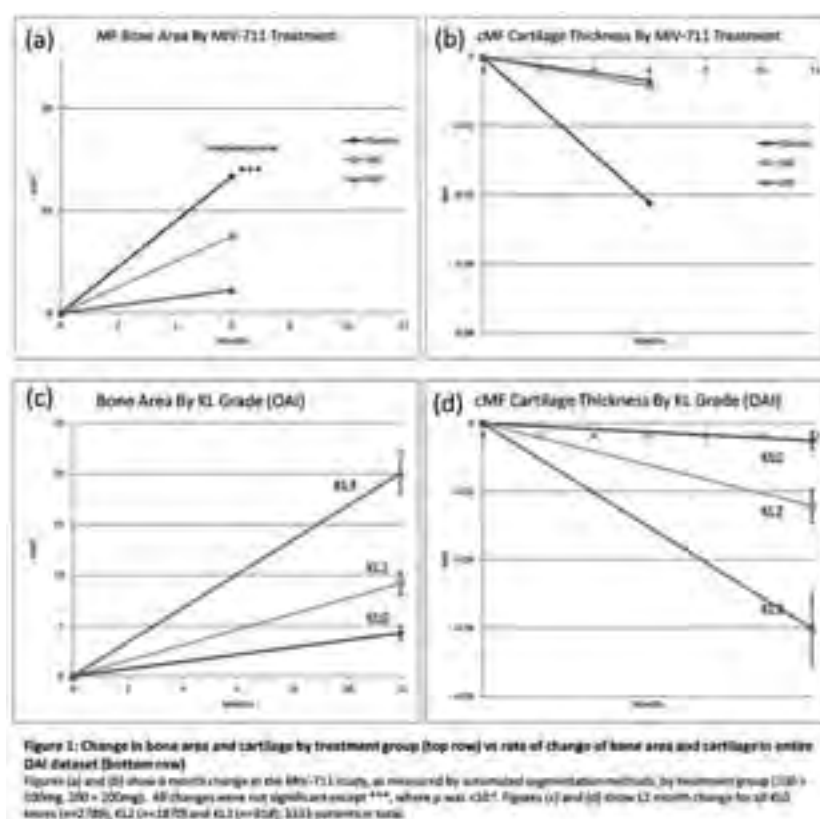
Session Information

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical Poster I

Session Type: ACR Poster Session A

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



Background/Purpose: New imaging biomarkers using supervised machine learning offer opportunities to demonstrate effects of potential DMOADs on joint structure in short, small trials based on superior reliability. MIV-711, a cathepsin K inhibitor, demonstrated substantial effects vs placebo on both joint bone area and cartilage thickness following 6 months' treatment. The Osteoarthritis Initiative (OAI) provides an opportunity to contextualize the short-term interventional trial data against a large prospective cohort.

Methods: In the MIV-711-201 study (ACR 2017, abstract 14L), patients with ACR knee OA, KL2-3 and pain ≥ 4 & <10 on 0-10 NRS were enrolled at 6 European sites and randomised to receive MIV-711 100mg or 200mg or matched

place boqd for 6 months. 244 participants were enrolled, 69% women, mean age 62, mean BMI ~32, (evaluable for imaging; 100mg n=72, 200mg n=71, placebo n=68). 3D bone area of the medial femoral condyle (MF) and cartilage thickness in the central medial femur (cMF) were measured using automated segmentation of MR images and active appearance modelling. Rates of change were compared against annual change from all knees with KL grade 0 (normal), 2 or 3 from the OAI cohort using the same method (n =2789, 1870, 918 for KL0,2,3; 3333 patients in total).

Results: In the MIV-711-201 quantitative MRI data, mean changes in MF bone area (mm²) were 13.4 (7.48, 19.28); 7.54 (-1.19, 16.27); 2.22 (-3.92, 8.37) for the placebo, 100mg and 200mg groups respectively (95% CI, Figure 1a). cMF cartilage thickness (mm) mean changes were -0.042 (0.001, -0.085), -0.008 (0.034, -0.051), -0.007 (0.044, -0.058) for the placebo, 100mg and 200mg respectively (95% CI, Figure 1b). These data are in good agreement with the corresponding published data based on manual segmentation. OAI MF bone area change (mm²) over 12 months was 4.26, 9.177, 20.09 (mm²) for KL0, 2 and 3 respectively (equates to 2.13, 4.59, 10.05 over 6 months assuming linear change, Figure 1c). OAI cMF cartilage change over 12 months was -0.005, -0.024, -0.060 (mm) for KL0, 2 and 3 respectively (equates to -0.0025, -0.012, -0.03 over 6 months assuming linear change, Figure 1d). The MIV-711 placebo group changes in bone and cartilage were similar to that expected for a group of KL3 knees (OAI). The MF bone area rate of change in the 200mg group was comparable to the rate found in OAI normal (KL 0) knees and both the 100mg and 200mg doses reduced cartilage loss area change by around 80% to a rate comparable to that seen in OAI normal knees.

Conclusion: This comparison strongly suggests that the 6-month MIV-711 treatment effects found on cartilage and bone measures has structural relevance when compared to the natural progression seen over 12 months in OAI KL3 patients. Should such beneficial structural effects be maintained over time, the already observed signals on clinical symptoms could become manifest clinical benefits.

Disclosure: P. G. Conaghan, Medivir AB, 5, Novartis Pharmaceutical Co., 5, Flexion Therapeutics, 5, Abbvie, 5, Infirst, 5, Merck Serono, 5, ONO Pharmaceutical Co., 5, Galapagos, 5, GlaxoSmithKline, 5; M. A. Bowes, Imorphics Ltd, 3; S. R. Kingsbury, None; A. Brett, Stryker Corporation, 1, 3; G. Guillard, Imorphics Ltd., 3; A. Jansson, Medivir AB, 1, 3; C. Wadell, Medivir AB, 1, 3; R. Bethell, Medivir AB, 1, 3; J. Öhd, Medivir AB, 1, 3.

Abstract Number: 430

Prevalence of Intra-Articular Mineralization on Knee CT in Persons with or at Risk of Knee Osteoarthritis

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Session Information

Session Date: Sunday, October 21, 2018

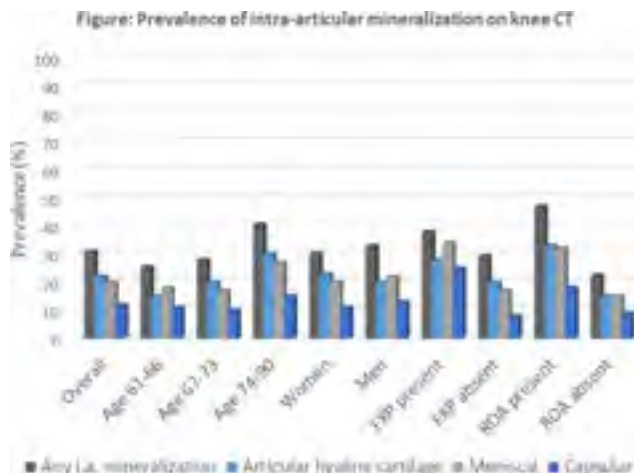
Session Title: Osteoarthritis – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: While intra-articular (i.a.) mineralization can be visualized on knee radiographs, the sensitivity of its identification is low with this modality, hampering efforts to understand its pathogenic role and consequences in knee OA. Computed tomography (CT) is highly sensitive for the detection and localization of i.a. mineralization. We report the prevalence of CT-detected i.a. mineralization in older adults with or at risk of knee OA.

Methods: Bilateral knee CT scans, PA knee radiographs and standard questionnaires to ascertain frequent knee pain are being obtained during the current study visit in the Multicenter Osteoarthritis (MOST) Study, a NIH-funded longitudinal cohort study of persons with or at risk of knee OA. Axial CT images with coronal and sagittal 2D reformats were scored by a musculoskeletal radiologist using an ordinal score (0-3) for degree of mineralization in each of the WOMBS subregions of cartilage and meniscus, as well as the soft tissue, capsule, and vasculature. A second MSK radiologist read a random sample of 50 subjects. Prevalence of i.a. mineralization was computed for the total



sample, and stratified by age, sex, and presence of frequent kneepain and radiographic knee OA (ROA) (Kellgren and Lawrence grade ≥ 2).

Results: To date, 150 subjects (300 knees) have been scored during the ongoing study visit (53% female, mean age 71, mean BMI 29.8). Overall, 9% of knees had chondrocalcinosis on radiograph, while CT-detected mineralization was present in 31% of knees in cartilage, meniscus, and/or capsule. The prevalence in specific locations was: 22% articular cartilage, 20% meniscal, and 12% capsular (Figure). 24% of knees without chondrocalcinosis on radiograph had articular cartilage and/or meniscal mineralization detected by CT. Of the knees with CT-detected articular cartilage mineralization, the majority had it present in 1-3 WORMS cartilage subregions (out of 14), and 63% also had meniscal mineralization. For the knees with meniscal mineralization, the majority had it in 5 or 6 WORMS meniscus subregions (out of 6), and 60% also had articular cartilage mineralization. Articular and meniscal mineralization increased with age, was similar among men and women, and was more prevalent in those with frequent knee pain and ROA (Figure). Capsular mineralization was similar across age and gender, but more prevalent in those with frequent knee pain and ROA. Overall, 47% of knees had vascular calcification, which increased with age and was more prevalent in men.

Conclusion: CT of the knee provides greater visualization of i.a. mineralization than radiographs, including locations within the hyaline articular cartilage, meniscus, and soft tissue, as well as its co-localization. These data will provide opportunity to evaluate the longitudinal relation of i.a. mineralization to adjacent articular tissue pathology and overall OA progression.

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Abstract Number: 431

Early Pre-Radiographic Structural Pathology Precedes the Onset of Accelerated Knee Osteoarthritis: Data from the Osteoarthritis Initiative

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Session Information

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Session Title: Osteoarthritis – Clinical Poster I

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

Background/Purpose: Individuals that develop accelerated knee osteoarthritis (AKOA) have more frequent knee pain, decreased physical function, and are more likely to receive a knee replacement when compared to adults with a gradual onset of knee osteoarthritis (OA). Therefore, developing prognostic tools that provide earlier signs of individuals at risk for the development of AKOA are needed to lessen the burden of this disease. The purpose of this analysis was to determine which pre-radiographic structural pathologies precede the development of AKOA.

Methods: The sample comprised participants from the Osteoarthritis Initiative (OAI) who had at least one radiographically normal knee at baseline (Kellgren-Lawrence [KL] grade ≤ 1). Participants were classified into 2 groups based on radiographic disease progression from baseline to 48 months: AKOA (KL grade change from ≤ 1 to ≥ 3) and No AKOA. Magnetic resonance images were assessed for the presence of 9 semi-quantitative structural pathologies and separated into tertiles for 3 quantitative pathologies at the OAI baseline (Table). For the quantitative pathologies, we converted the tertiles to a dichotomous variable to compare the worst tertile (i.e. largest bone marrow lesion and effusion, smallest cartilage damage index) to the combination of the other two tertiles. Logistic regressions were used to determine which pre-radiographic structural pathologies were more likely to antedate the development of AKOA compared to individuals not developing AKOA.

Results: Overall the groups were predominantly female (63%), overweight, and 33% reported frequent knee pain within a year of baseline. At the OAI baseline visit, degenerative cruciate ligaments (odds ratio [OR]=2.2, 95% confidence interval [CI]=1.3,3.5), infrapatellar synovitis (OR=2.0, 95%CI=1.2,3.2), medial meniscal pathology (OR=2.1, 95%CI=1.3,3.4), lateral meniscal pathology (OR=2.4, 95%CI=1.5,3.8) and larger quantitative knee effusion (OR=2.2, 95%CI=1.4,3.4) were more likely to antedate the development of AKOA when compared to those that did not develop AKOA (Table).

Table. Baseline Pre-Radiographic Structural Pathologies Associated with Accelerated Knee Osteoarthritis (OA) Over the Next 4 Years

Structural Pathologies			Group		Univariate Odds Ratio (95% CI)
			AKOA (n=113) n (%)	No AKOA (Reference, n=241) n (%)	
Semi-Quantitative	Degenerative Cruciate Ligaments ^a	Absence	66 (58%)	181 (75%)	Reference
		Presence	47 (42%)	60 (25%)	2.15 (1.34, 3.45)*
	Degenerative Collateral Ligaments ^a	Absence	86 (76%)	208 (86%)	Reference
		Presence	25 (22%)	33 (14%)	1.97 (0.95, 4.06)
	Degenerative Extensor Mechanism	Absence	64 (57%)	163 (68%)	Reference
		Presence	49 (43%)	78 (32%)	1.60 (1.01, 2.53)
	Degenerative Gastrocnemius/Tendon	Absence	64 (57%)	146 (61%)	Reference
		Presence	49 (43%)	95 (39%)	1.18 (0.75, 1.85)
	Infrapatellar Synovitis	Absence	63 (56%)	172 (71%)	Reference
		Presence	50 (44%)	69 (29%)	1.98 (1.24, 3.15)*
	Medial Meniscal Pathology	Absence	35 (31%)	118 (49%)	Reference
		Presence	78 (69%)	123 (51%)	2.14 (1.32, 3.43)*
Quantitative	Lateral Meniscal Pathology	Absence	64 (57%)	182 (76%)	Reference
		Presence	49 (43%)	59 (24%)	2.39 (1.47, 3.79)*
	Medial Meniscal Extrusion	Absence	90 (80%)	210 (87%)	Reference
		Presence	23 (20%)	31 (13%)	1.73 (0.98, 3.03)
	Lateral Meniscal Extrusion	Absence	109 (96%)	238 (99%)	Reference
		Presence	4 (4%)	3 (1%)	2.91 (0.54, 13.23)
	Effusion Volume ^a	Smallest	83 (74%)	176 (73%)	Reference
		Larger	30 (26%)	65 (27%)	2.18 (1.38, 3.43)*
	Bone Marrow Lesion Volume ^a	Smallest	78 (69%)	161 (67%)	Reference
		Larger	35 (31%)	80 (33%)	0.90 (0.58, 1.46)
	Cartilage Damage Index ^a	Larger	78 (70%)	153 (63%)	Reference
		Smallest	34 (30%)	88 (37%)	0.84 (0.52, 1.38)

*Statistically significant; $p \leq 0.004$. ^aComparing the worst tertile (i.e. largest effusion/bone marrow lesion, smallest CDI) to the other 2 tertiles.

^bAnterior and posterior cruciate ligaments were grouped together as there were too few to analyze separately.

^cMedial and lateral collateral ligaments were grouped together as there were too few to analyze separately.

Conclusion: The presence of early ligamentous degeneration, synovitis, meniscal pathology, and large effusion precedes the onset of AKOA and may be prognostic biomarkers.

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Abstract Number: 432

Relation of Patellofemoral Joint Alignment, Morphology, and Radiographic Osteoarthritis to Frequent Anterior Knee Pain

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Session Information

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

Background/Purpose: Radiographic patellofemoral osteoarthritis (OA) is prevalent in approximately 25% of population-based samples and 39% of individuals with knee pain. Discordance between knee OA features and pain is common yet not well understood. It may in part be explained by mechanical factors, such as patellofemoral alignment or bony morphology, that could cause pain by altering joint load. It may also be due to factors that influence pain perception, such as psychosocial or central mechanisms. We aimed to compare within-person, between-knee alignment, morphology and presence of patellofemoral OA in individuals with unilateral frequent anterior knee pain, to determine if these variables explain pain discordance.

Methods: We evaluated a subsample from the Multicenter Osteoarthritis Study (MOST), a cohort of 3026 individuals aged 50–79 years who had, or were at risk of, knee OA at baseline. We identified individuals who presented at the 60-month clinic visit with discordant patellofemoral pain. We defined this as: (i) a response of ‘yes’ to the question “During the past 30 days, have you had pain, aching, or stiffness in your knee on most days?” for one knee, but ‘no’ to the same question regarding the contralateral knee; and (ii) this pain was reported to be isolated to the anterior knee region using a knee pain map. For those not meeting inclusion criteria at the 60-month visit, we also included participants who met the same criteria at 84-months.

We measured alignment and morphology using MR images (patellar tilt angle, bisect offset, sulcus angle, lateral trochlear inclination) and lateral radiographs (Insall-Salvati ratio). Patellofemoral OA was defined on lateral view radiographs as any osteophyte \geq grade 2, or joint space narrowing \geq 1 plus any osteophyte, sclerosis or cyst \geq 1.

We modelled the odds of having pain using conditional logistic regression, which enables within-person, between-knee comparisons. Within-person matched pairs (i.e. knees) removes the effect of person-level risk factors that may contribute to pain (e.g. age, sex, BMI, kinesiophobia, depression, genetics, and other known/ unknown factors) that could otherwise explain pain variability among people.

Results: Inclusion criteria were met in 136 participants, 115 with history of surgery/ injury data, 97 with bilateral radiographs and 71 with MR images. The mean age ($n=71$) was 69 (8) years, BMI 30.2 (5.3) kg/m², 47 (66%) women. Alignment and morphology measures did not differ between knees. Odds of having patellofemoral OA was significantly increased in knees with pain compared to those without (OR 6.6 [95% CI 1.5, 29.7], as was history of surgery or injury (OR 2.1 [1.2, 3.6]).

Conclusion: In individuals with unilateral frequent anterior knee pain, odds of having patellofemoral OA were higher in knees with pain than without. Alignment and morphology measures did not differ by knee. Dynamic alignment may be more relevant to pain outcomes.

Table. Odds of each exposure in knees with pain compared to knees without pain

	Crude Prevalence	Crude Odds Ratio (95% CI)	*Adjusted Odds Ratio (95% CI)
Structure variables			
PFROA ($n=97$)			
Painful	27 (28%)	7.50	6.63
Contralateral	14 (14%)	(1.72, 32.80)	(1.48, 29.69)

Table . (Cont'd)

	Crude Prevalence	Crude Odds Ratio (95% CI)	*Adjusted Odds Ratio (95% CI)
TFROA (n=97)			
Painful	44 (45%)	1.55	1.17
Contralateral	38 (39%)	(0.72, 3.30)	(0.49, 2.80)
Surg/inj (n=115)			
Painful	50 (44%)	2.05	
Contralateral	30 (26%)	(1.19, 3.55)	
Alignment/ morphology (n=71)			
Sulcus angle		1.03 (0.97, 1.09)	
Lateral trochlear inclination		1.02 (0.92, 1.13)	
Bisect offset x 100%		0.99 (0.94, 1.05)	
Patellar tilt angle		0.94 (0.86, 1.03)	
Insall Salvati ratio x 100%		0.95 (0.90, 1.00)	

* For PFROA, we included history of surgery or injury and TFROA as covariates; for TFROA, we included history of surgery or injury and PFROA.

Disclosure: E. Macri, None; T. Neogi, None; I. Tolstykh, None; C. E. Lewis, None; J. Torner, None; M. C. Nevitt, None; J. J. Stefanik, None.

Abstract Number: 433

Impact of Bariatric Surgery on Rheumatic Diseases: A Systematic Review and Meta-Analysis

Marie Moly¹, Bernard Combe¹, Thomas Barnetche², Claire Daien¹, Jacques Morel³, Cédric Lukas¹, Cécile Gaujoux-Viala⁴ and Charlotte Hua⁴, ¹Rheumatology, University Hospital Lapeyronie, Montpellier, Montpellier, France, ²Rheumatology, University Hospital Pellegrin, Bordeaux, Bordeaux, France, ³Department of Rheumatology, University Hospital Lapeyronie, Montpellier, Montpellier, France, ⁴Rheumatology, University Hospital Carémeau, Nîmes, Nîmes, France

Session Information

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Obesity increase the incidence of rheumatic diseases (1-3). Bariatric surgery (BS) improve obesity-related comorbidities (4). The aim of our study was to assess currently available literature the impact of BS on rheumatic disease such inflammatory rheumatic disease, gout, musculoskeletal disorder and surgical management of osteoarthritis.

Methods: We systematically searched literature (via Pubmed, Embase, Cochrane library and abstracts from recent ACR and EULAR congresses) for studies evaluating the effects of BS on rheumatic diseases. A meta-analysis was performed with Review Manager Software, with random effects models, whenever methodologically possible and relevant. Data were extracted by one investigator and independently checked by another.

Results: The literature search revealed 399 articles and abstracts of potential interest, and further examination resulted in 124 studies include in systematic review and 24 studies fulfilling required criteria for preplanned analyses regarding the impact of BS on rheumatic diseases. For musculoskeletal disorder, the mean difference between before and after BS was -468.14 (95% confidence interval[95% CI] -646.76 ; -289.51) for WOMAC function, -95.18 [-127.06 ; -63.29]for WOMAC pain, 30.45 [22.02 ; 38.87] for SF36 physical function, 22.91 [16.58; 29.24] for SF36 bodily pain (Figure 1). For surgical management of osteoarthritis incidence of reoperation, the Odd ratio (OR) was 1.41 [0.88;2.27] and for incidence of infection the OR was 0.91 [0.53;1.59]. For gout, the effect size was 0.83 [0.79;0.87] for hyperuricemia before and after, the mean difference between before and after BS was -1.45 [-1.95; -0.94] for uric acid (Figure 2).

Conclusion: This study supports the interest of BS in rheumatology, with improvement of function and pain in musculoskeletal disorders, decrease of acid uric level.

References:

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Figure 1 Forest plot for the mean difference between before and after BS for WOMAC function (A), WOMAC pain (B), SF36 physical function (C) and SF36 bodily pain (D)

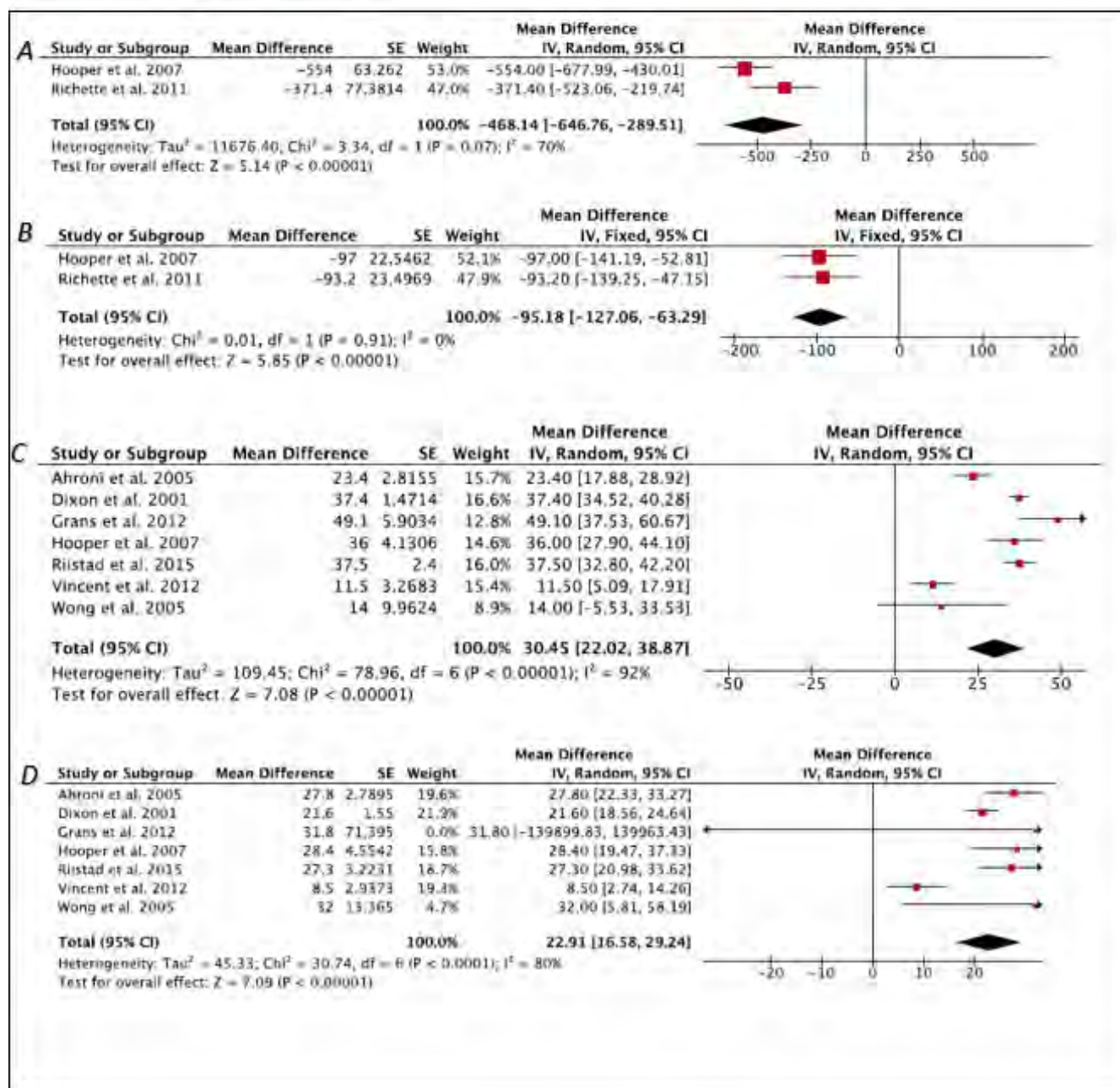
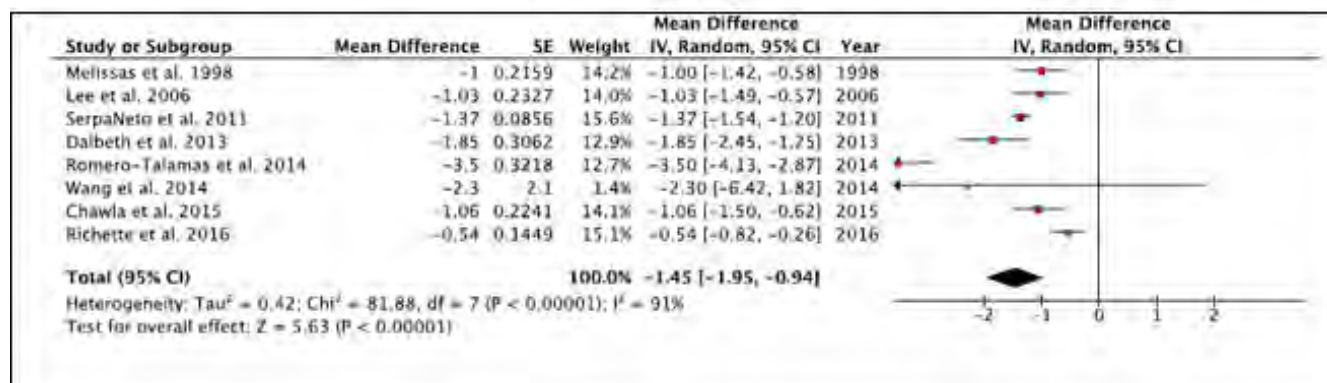


Figure 2: Forest plot for the mean difference between acid uric (mg/dl) before and after BS



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Disclosure: M. Moly, None; B. Combe, None; T. Barnetche, None; C. Daien, None; J. Morel, None; C. Lukas, None; C. Gaujoux-Viala, None; C. Hua, None.

Abstract Number: 434

Trends in Procedure Type, Patient Characteristics, and Outcomes Among Persons with Knee Osteoarthritis Undergoing Bariatric Surgery, 2005-2014

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical Poster I

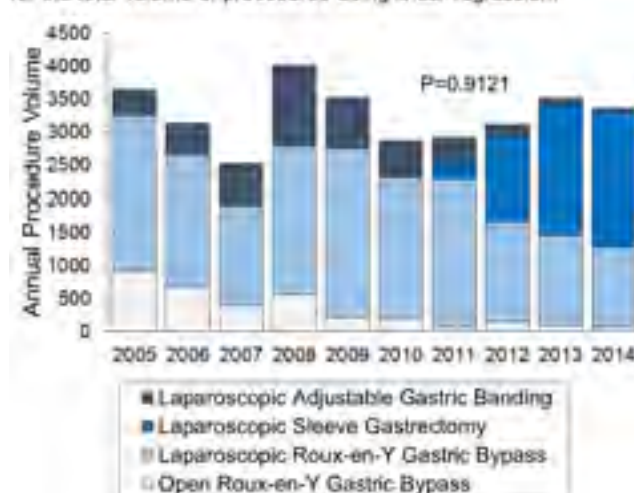
Session Type: ACR Poster Session A

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

Background/Purpose: Bariatric surgery, the most effective treatment for losing weight and maintaining weight loss among morbidly obese persons, has been evolving as a treatment for morbidly obese patients with knee OA (KOA). The purpose of this study was to evaluate trends in the volume and distribution of surgical approaches, patient characteristics, and inpatient outcomes among persons with KOA undergoing bariatric surgery from 2005-2014.

Methods: We used the National Inpatient Sample data from 2005 to 2014 to identify bariatric procedure discharges with documented comorbid KOA. We abstracted hospital setting, procedure, demographic and clinical patient characteristics, and inpatient surgical outcomes from each discharge. We calculated descriptive characteristics and the Elixhauser Comorbidity Index, a comorbidity metric designed for use with administrative datasets. Inpatient outcomes included complication rates, length of stay (LOS), and costs. We examined temporal trends on distribution of surgery types, hospital and patient characteristics, and surgical outcomes using linear regression and the Cochran-Armitage test for trend.

Figure. Distribution of bariatric procedure types among persons with knee osteoarthritis undergoing bariatric surgery between 2005 and 2014. The bars represent the estimated volume of each type of bariatric surgery procedure, and the p-value was obtained for the total volume of procedures using linear regression.



Results: The national volume of persons with KOA undergoing bariatric surgery from 2005-2014 remained consistent at a total of about 3,300 procedures annually. The procedure distribution changed over time; the most commonly-performed procedure shifted from laparoscopic Roux-en-Y gastric bypass (RYGB) (65%) in 2005-2006 to laparoscopic sleeve gastrectomy (LSG) (58%) in 2013-2014 (Figure). The median age and Elixhauser Index increased from 46 to 50 years and 1.6 to 2.0, respectively. From 2005-2014, the median costs (2017 USD), adjusted for LOS, Elixhauser Index, hospital location and teaching status, and bed size, for laparoscopic RYGB and laparoscopic banding procedures decreased from \$15,100 to \$13,700 ($p<0.0001$) and \$14,100 to \$10,100 ($p=0.0001$), respectively, whereas the adjusted costs of open RYGB did not change significantly. The adjusted costs of LSG did not change significantly between 2011, when the procedure code was introduced, to 2014. Inpatient complication rates decreased significantly from 5.2% to 1.7%, and inpatient mortality remained at 0.0%-0.1%.

Conclusion: The volume of persons with KOA undergoing bariatric surgery remained unchanged from 2005-2014. Less invasive procedures, such as LSG, are utilized more frequently over time, likely leading to a decrease in inpatient complication rates associated with bariatric surgery. Decreases in the costs of older laparoscopic techniques (RYGB and banding) may be due to improved surgical technology, whereas the cost of open RYGB has not changed over the decade. There were no significant cost changes during the four-year period of evaluation for LSG, a relatively new procedure. Mortality rates remained low despite an increase in age and number of concomitant comorbidities.

Disclosure: Y. Gong, None; F. Selzer, None; B. Deshpande, None; E. Losina, Samumed, 5, JBJS, 5.

Abstract Number: 435

Is Frailty Associated with Worse Outcomes after Total Joint Replacements?

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: To determine whether frailty is associated with clinical outcomes 1-year after total hip or total knee replacement, (TKR and THR).

Methods: Community-dwelling patients ≥ 65 yo scheduled for elective TKR or THR were recruited from a musculoskeletal specialty hospital. Frailty was measured using validated criteria. A variety of instruments including Hip/Knee Injury and Osteoarthritis Outcome Score (HOOS/KOOS) and PROMIS-29 were administered pre-operatively and at 1-year. Preoperative dependence was measured with Katz ADL scores. Regression models were created by considering all variables which were significant at the 0.05 level in univariate models, and then performing backward selection to retain variables with 0.05 significance. Age and gender were forced in to all models.

Results: 740 subjects enrolled, 303 THR/437 TKR. Median age 72 years (range 65-94), 95.1% Caucasian, 63.5% female, 7.5% frail. 327 cases with 1 year data, (93% of eligible). There were no differences in percentage of frail and non-frail patients meeting OMERACT-OARSI responder criteria at 1-year, ($p=0.09$). In univariate analyses being frail was associated with worse HOOS/KOOS outcomes at 1-year in all subscales except HOOS pain; however, these relationships were no longer significant in multivariate analyses. Controlling for age, gender, and which joint was replaced, only pre-operative PROMIS-29 pain intensity predicted being an OMERACT-OARSI responder at 1-year, (OR 1.6; 95%CI 1.3-2.0). There were no predictors of being an OMERACT-OARSI responder in TKR. Interestingly, among THR, stronger baseline grip strength- a component of the frailty phenotype- was associated with decreased odds of being an OMERACT-OARSI responder, (OR 0.46; 0.23-0.93) and an increased likelihood of having worse HOOS pain at one year ($p=0.02$). Having fewer Katz ADL dependencies pre-operative strongly predicted better HOOS ADL scores at 1-year ($p<0.001$). No frailty components were associated with functional outcomes in TKR.

Conclusion: Frailty does not appear to be independently associated with 1-year outcomes in THR and TKR patients, although currently only a small absolute number of frail patients have completed 1-year follow-up. The finding that stronger grip strength is associated with worse outcomes is intriguing. Whether this reflects a ceiling effect of the OMERACT-OARSI responder criteria or is a clinically meaningful difference will be explored as the study progresses.

Disclosure: L. A. Mandl, None; C. N. Cornell, Exactech, 5; M. B. Cross, acelity, 5, acelity surgical advisory board, 5, bone and joint journal 360, 6, exactech, 5, intelligoint, 1, 5, journal of orthopaedics and traumatology, 6, theravance biopharma, 5, zimmer, 5; A. Gonzalez Della Valle, None; M. P. Figgie, None; S. A. Jerabek, stryker, 5; J. Do, None; M. Sasaki, None; N. Hupert, None; J. Szymonifka, None; S. K. Magid, None.

Abstract Number: 436

Structural Effects of Intra-Articular Sprifermin in Symptomatic Radiographic Knee Osteoarthritis: A Post-Hoc Analysis of Cartilage Morphology over the 2-Year Treatment-Period of a 5-Year Randomized, Placebo-Controlled, Phase II Study

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¹Radiology, Boston University School of Medicine, Boston, MA, ²EMD Serono Research & Development Institute, Inc. (a business of Merck KGaA, Darmstadt, Germany), Billerica, MA, ³EMD Serono Research & Development Institute, Inc. (a business of Merck KGaA, Darmstadt, Germany), Billerica, MA, ⁴Boston University School of Medicine, Boston, MA, ⁵University of Maryland School of Medicine, Baltimore, MD, ⁶Department of Radiology, University of Erlangen-Nuremberg, Erlangen, Germany, Erlangen, Germany

Session Information

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical Poster I

Session Type: ACR Poster Session A

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

Table 1: Cartilage morphology change from baseline to 24 months, ITT analysis set

Compartment	Assessment approach	Placebo (n=100) Mean (SD), CV	Sprifermin (10 mg) (n=111) Mean (SD), CV	Sprifermin (10 mg) (n=111) Mean (SD), CV	Sprifermin (10 mg) (n=111) Mean (SD), CV	Sprifermin (10 mg) (n=111) Mean (SD), CV	P-value ¹
Entire Knee	Delta Sum	1.81 (0.89, 0.24)	1.78 (1.25, 0.22)	1.22 (0.66, 0.74)	1.21 (0.82, 0.78)	-0.58 (0.57, 0.26)	0.0301 [*]
Entire Knee	Delta Subregion	0.79 (0.48, 0.69)	0.60 (0.65, 0.49)	0.60 (0.37, 0.43)	0.59 (0.53, 0.78)	-0.53 (0.53, 0.78)	0.0304 [*]
LFTJ	Delta Sum	0.29 (0.55, 0.50)	0.37 (0.25, 0.48)	0.45 (0.15, 0.67)	0.23 (0.12, 0.34)	-0.22 (0.05, 0.38)	0.1028
LFTJ	Delta Subregion	0.18 (0.36, 0.58)	0.21 (0.13, 0.43)	-0.24 (0.15, 0.35)	0.12 (0.07, 0.22)	-0.19 (0.04, 0.32)	0.0777
MFTJ	Delta Sum	0.86 (0.32, 0.41)	0.77 (0.38, 0.38)	0.52 (0.26, 0.78)	0.81 (0.41, 0.21)	0.48 (0.23, 0.72)	0.2274
MFTJ	Delta Subregion	0.40 (0.20, 0.58)	0.34 (0.21, 0.68)	0.28 (0.12, 0.38)	0.39 (0.23, 0.58)	-0.23 (0.11, 0.34)	0.0007
PFJ	Delta Sum	0.44 (0.21, 0.72)	0.43 (0.20, 0.67)	0.22 (0.05, 0.44)	0.15 (0.02, 0.28)	0.27 (0.04, 0.51)	0.0073
PFJ	Delta Subregion	0.21 (0.0, 0.31)	0.21 (0.10, 0.36)	-0.10 (0.01, 0.20)	0.06 (0.01, 0.18)	0.28 (0.04, 0.32)	0.1736

Table 2: Bone marrow lesion change from baseline to 24 months, ITT analysis set

Compartment	Assessment approach	Placebo (n=100) Mean (SD), CV	Sprifermin (10 mg) (n=111) Mean (SD), CV	Sprifermin (10 mg) (n=111) Mean (SD), CV	Sprifermin (10 mg) (n=111) Mean (SD), CV	Sprifermin (10 mg) (n=111) Mean (SD), CV	P-value ¹
Entire Knee	Delta Sum	0.09 (0.26, 0.93)	0.39 (0.07, 0.78)	0.09 (0.39, 0.38)	0.18 (0.24, 0.54)	-0.09 (0.40, 0.92)	0.1887
Entire Knee	Delta Subregion	0.06 (0.25, 0.92)	0.21 (0.07, 0.48)	-0.05 (0.24, 0.23)	0.07 (0.26, 0.38)	-0.13 (0.41, 0.12)	0.1083
LFTJ	Delta Sum	0.13 (0.02, 0.27)	0.28 (0.08, 0.48)	-0.01 (0.21, 0.21)	0.20 (0.04, 0.27)	0.17 (0.04, 0.28)	0.2984
LFTJ	Delta Subregion	0.10 (0.02, 0.23)	0.18 (0.04, 0.33)	-0.02 (0.17, 0.11)	0.13 (0.01, 0.23)	0.07 (0.05, 0.18)	0.2585
MFTJ	Delta Sum	0.05 (0.25, 0.58)	0.14 (0.10, 0.38)	0.12 (0.13, 0.38)	0.13 (0.17, 0.43)	0.00 (0.12, 0.24)	0.9817
MFTJ	Delta Subregion	-0.02 (0.22, 0.18)	0.12 (0.05, 0.21)	0.08 (0.12, 0.28)	0.18 (0.05, 0.28)	0.08 (0.07, 0.23)	0.3211
PFJ	Delta Sum	-0.18 (0.30, 0.18)	-0.06 (0.26, 0.13)	-0.13 (0.34, 0.08)	-0.21 (0.45, -0.02)	-0.26 (0.58, -0.02)	0.0121 [*]
PFJ	Delta Subregion	-0.08 (0.22, 0.12)	-0.11 (0.28, 0.07)	-0.11 (0.30, 0.07)	-0.22 (0.40, -0.04)	-0.28 (0.48, -0.02)	0.0006 [*]

¹ p-values using Jonckheere-Terpstra (symptomatic) test

Background/Purpose: Sprifermin, a recombinant human fibroblast growth factor 18, is currently being investigated as a potential disease-modifying OA drug. Sprifermin treatment leads to a dose-dependent increase in femorotibial cartilage thickness, as well as medial and lateral compartment cartilage, over two years¹. The aim of this post-hoc analysis was to evaluate the potential effects of sprifermin on additional knee structural endpoints, based on semi-quantitative MRI assessment over 24 months.

¹Hochberg MC, et al. *Arthritis Rheumatol.* 2017; 69 (suppl 10).

Methods: Patients aged 40–85 years with symptomatic radiographic primary femorotibial OA according to ACR criteria, Kellgren-Lawrence Grade 2 or 3, and medial minimum joint space width ≥ 2.5 mm in the target knee were randomized (1:1:1:1) to receive double-blinded sprifermin (30 μ g or 100 μ g) or placebo, administered as three weekly intra-articular injections in 6- or 12-month cycles. 1.5 or 3 Tesla MRIs were acquired at baseline, 6, 12, 18 and 24-month follow-up visits using a standard protocol (NCT01033994).

MRIs were read using the Whole-Organ Magnetic Resonance Imaging Score (WORMS) system by three trained musculoskeletal radiologists at baseline, 12 and 24 months. Analyses of all sprifermin and placebo arms included multiple MRI-defined OA features and multi-dimensional assessments: (a) delta-subregional approach (the difference in the *number of subregions* with worsening as compared to improvement) and (b) delta-sum approach (absolute *scores of all subregions*). Analyses were performed on a whole knee level and separately for medial, lateral, and patellofemoral compartments. To test for potential dose-response effects, the Jonckheere-Terpstra (asymptotic) test was used. P-values were not adjusted for multiple testing.

Results: In total, 549 patients were included. A dose-dependent treatment effect for sprifermin on cartilage morphology (i.e., less worsening of cartilage damage) was observed for the entire knee from baseline to 24 months using both delta sum and delta subregion approaches (Table 1). For bone marrow lesions (BMLs), a dose-dependent treatment effect (improvement of BMLs) was observed from baseline to 24 months for the patello-femoral joint, using both delta sum and delta subregion approaches, but not in the other compartments (Table 2). No significant changes from baseline to 24 months were reported in Hoffa-synovitis, effusion-synovitis, menisci, or osteophytes.

Conclusion: Sprifermin has a positive effect on cartilage morphology based on semi-quantitative assessment, in addition to the previously reported effect on cartilage thickness based on 3D morphometry. Sprifermin was also associated with BML improvement in the patello-femoral joint. There were no significant effects associated with sprifermin on the other joint tissues assessed, and no additional safety concerns.

Disclosure: A. Guermazi, Merck Serono, 5, Genzyme, 5, AstraZeneca, 5, TissueGene, 5, OrthoTrophix, 5, Boston Imaging Core Lab (BICL), LLC, 9; J. Kraines, EMD Serono, 3; A. Aydemir, EMD Serono, 3; S. Wax, EMD Serono, 3; M. Crema, Boston Imaging Core Lab (BICL), LLC, 1; M. C. Hochberg, Bioberica, 5, EMD Serono, 5, Novartis Pharma AG, 5, Plexxikon, 5, Pfizer, Inc., 5, Proximagen, 5, Regeneron, 5, Samumed, LLC, 5, Theralogix LLC, 5; F. Roemer, BICL, 4.

Abstract Number: 437

Does Reduction in Mechanical Knee Joint Loading Explain the Beneficial Effects of Weight Loss in Overweight or Obese Patients with Knee Osteoarthritis?

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Knee osteoarthritis (KOA) is traditionally considered a local joint pathology. The effect of obesity on the pathogenesis of KOA is predominantly attributed to increase mechanical joint loading (local effect). Weight reduction, a well-established recommendation for overweight or obese patients with KOA, is hypothesized to improve OA symptoms via reduction in mechanical joint loading. We sought to confirm or refute the latter hypothesis.

Methods: This is a secondary data analysis of a previously completed 18-month randomized controlled trial in KOA that compared combination diet-induced weight loss plus exercise vs. diet only vs. exercise only. In this analysis, the primary outcomes were self-report measures on pain severity (WOMAC pain) and function (WOMAC function) at the end of the study (month-18). The primary independent variables were changes in weight (kg) and knee joint compressive force (N)

from baseline to month-6. Regression models were adjusted for gender, race, treatment group assignment, and baseline measures on BMI, number of comorbid illnesses, and SF36 mental component summary score (SF36 MCS).

Results: From the 454 subjects enrolled in the original study, 329 (72.4%) subjects had available baseline and follow-up WOMAC data. This cohort had the following baseline characteristics (mean \pm SD): age= 66 years \pm 6.3; BMI =33.5 \pm 3.6; weight (kg) = 92.7 \pm 14.5; 70% females; 85% Whites; SF36 MCS= 57.1 \pm 7.3; WOMAC pain (range 0-20) = 6.3 \pm 3.0; and WOMAC function (range 0-68) = 23.3 \pm 10.8. The mean changes (SD) in weight and knee joint compressive force from baseline to month 6 were -6.3 (6.7) kg and -60.2 (651) N, respectively.

After controlling for potential covariates, the change in weight (β coefficient= 0.06, $p=0.03$) from baseline to month-6 was a significant predictor of WOMAC pain at month-18. The change in knee joint compressive force was not ($p=0.68$). Additionally, the change in weight ($\beta= 0.29$, $p=0.001$) was a significant predictor of WOMAC function at month-18. Again, the change in knee joint compressive force was not ($p>0.10$).

Interestingly, gender, race, number of comorbid illnesses, and SF36 MCS were not significant in both multivariable models for WOMAC pain and function.

Conclusion: Weight loss was temporally associated with improvement in OA symptoms through mechanisms other than reduction in mechanical joint loading. Extra-articular mechanisms (e.g., peripheral inflammation from adipokines and central sensitization) of weight loss in KOA should be explored.

Disclosure: D. Ang, None; D. Beavers, None; S. P. Messier, None.

Abstract Number: 438

What Characterizes Osteoarthritis: Ultrasound-Detected Inflammation but Not Osteophytes Is More Common in Hand Osteoarthritis Than in Painless Bony Enlargements

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: To study structural and inflammatoryultrasound lesions in elderly subjects with hand osteoarthritis (HOA) as wellas in pain-free subjects with bony enlargements of finger joints.

Methods: Prospective study of 331 subjects [mean age 75.2 (\pm SD 7.2) years, 49.5%female], of the Bruneck Study cohort, recruited from the official population register by random sampling. Sixteen joints (wrist, CMC, MCP1-5, PIP1-5,DIP2-5) were clinically evaluated for the presence of bony enlargements, soft tissue swelling and tenderness. Ultrasound of the dorsal and palmar side of these joints was conducted using a GE Logic E ultrasound device. Osteophytes, synovial hypertrophy and/or joint effusion (SH/E), Power Doppler (PD), and erosions were subjectively graded from 0 to 3 in accordance with prior publications. The Health Assessment Questionnaire (HAQ), the Short Form Score for the Assessment and Quantification of Chronic Rheumatic Affections of the Hands (SF-SACRAH) and the Functional Index for Hand Osteoarthritis (FIHOA) were used to assess functional impairment of hands. We defined two groups according to the presence or absence of HOA: Group A were subjects fulfilling the ACRcriteria (n=89, 26.9%) whereas group B were individuals with bony enlargements at finger joints, but without any hand pain, aching, tenderness or soft tissue swelling (which are entry parameters for the ACR criteria). A global ultrasound sum score was calculated for each group by summing all semi quantitative scores of the investigated US abnormalities.

Results: Eighty-nine subjects (26.9%) fulfilled the ACR criteria for HOA, 176 subjects(53.2%) were in group B. Sixty-six patients (19.9%) did neither fulfill the definition of group A nor that of group B and were excluded. Osteophytes were the most common finding in both groups (n=89, 100% and n=175, 99%,respectively), whereas SH/E (n=83, 93% and n=119, 68%, respectively, p<0.001) and PD (n=29, 33% and n=23, 13%, respectively, p<0.001) were more frequent in group A as compared to group B. Erosions were the least common finding (n=15, 17% and n=24, 14%, respectively, p>0.2). Grade 2 or 3ultrasound changes were more frequently observed in group A than in group B(see Table 1). In group A, the SF-SACHRA correlated with the global SH/E (corr_{coeff}0.46,p<0.001) and the osteophyte score (corr_{coeff}0.27, p=0.036). The FIHOA score correlated with the osteophyte score (corr_{coeff}0.39,p=0.0028) as well as with the PD score (corr_{coeff}0.4, p<0.001).There was no association between ultrasound findings and the level of pain.

Conclusion: US-verified SH/E and PD were more common in patients with clinical HOA as compared to subjects with bony enlargement without pain. This indicates that inflammation might drive clinical symptoms in people with degenerative joint disease at hands. Whether US signs of structural changes and inflammation in a symptomatic subjects precedes clinical HOA needs to be investigated by future studies.

		Osteophytes	SH/E	Erosion	Power-Doppler
Group A (n = 89)	none	0%	6 (6.7%)	74 (83.1%)	60 (67.4%)
	<= G1	15 (16.9%)	44 (49.4%)	4 (4.5%)	11 (12.4%)
	<= G2	32 (36%)	28 (31.5%)	9 (10.1%)	16 (18%)
	<= G3	42 (47.2%)	11 (12.4%)	2 (2.2%)	2 (2.2%)
Group B (n = 176)	none	1 (0.6%)	57 (32.4%)	152 (86.4%)	153 (86.9%)
	<= G1	58 (33 %)	76 (43.2%)	11 (6.2%)	13 (7.4%)
	<= G2	75 (42.6%)	38 (21.6%)	12 (6.8%)	10 (5.7%)
	<= G3	42 (23.9%)	5 (2.8%)	1 (0.6%)	0 (0%)
p-value	(A vs B)	p <0.001	p <0.001	p=0.45	p <0.001

Disclosure: N. Gasperi, None; A. Adinolfi, None; A. Kleyer, None; M. Hagen, None; C. Gasperi, None; M. Weger, None; S. Kiechl, None; J. Willeit, None; G. Schett, None; A. Iagnocco, None; A. Gasperi, None; A. Mayr, None; C. Dejaco, None.

Abstract Number: 439

Articular Cartilage from Osteoarthritis Patients Shows Extracellular Matrix Remodeling over the Course of Treatment with Sprifermin (Recombinant human fibroblast growth factor 18)

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical Poster I

Session Type: ACR Poster Session A

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

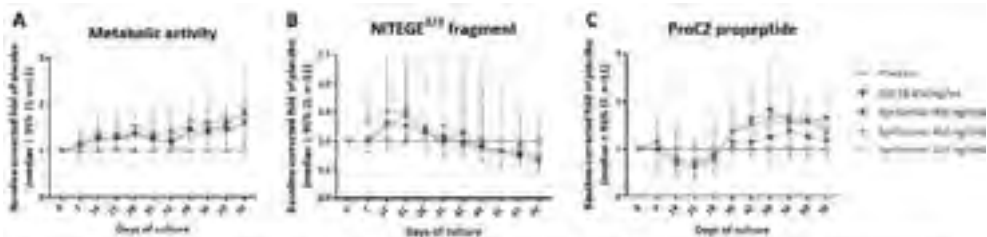
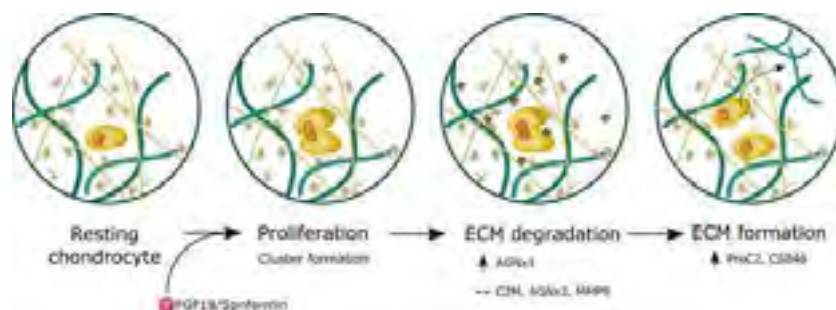


Figure 1. Human OA articular cartilage tissue explant cultures. Human OA articular cartilage explants were cultured for 20 days with weekly administration of Sprifermin or FGF18. (A) Metabolic activity was measured weekly by Molarblue, ALP (n=11). (B) and ProC2 (C), were measured in the conditioned medium collected weekly during culturing. Values are mean \pm SEM of 11 patients. Data from each patient were baseline corrected and normalized to placebo before patient data were combined.



Background/Purpose: Sprifermin, a truncated form of human fibroblast growth factor 18 (FGF18), is being investigated as a potential cartilage and disease-modifying OA drug. *In vitro*, Sprifermin induces chondrocyte proliferation and extracellular matrix (ECM) production. Here, we characterized the ECM remodeling of human knee OA articular cartilage in response to long-term Sprifermin treatment.

Methods: Full depth articular cartilage explants from OA patients ($n_{\text{patients}}=11$) were cultured for 70 days. Freshly prepared media with either Sprifermin (900, 450, 225 ng/mL), FGF18 (450 ng/mL), IGF-1 (100 ng/mL, positive control) or placebo formulation (negative control) was added once weekly ($n_{\text{explants/treatment/patient}}=2$). Metabolic activity was measured weekly by AlamarBlue. Biomarkers of ECM remodeling were quantified in conditioned media using well-described ELISAs; exProC2 reflecting type II collagen formation and exAGN1 reflecting aggrecanase-mediated aggrecan degradation. Data were baseline-corrected and normalized to placebo for each individual patient and reported as mean \pm standard errors of the mean (SEM).

Results: In human OA articular cartilage cultured *ex vivo*, the positive control IGF-1 induced ProC2 and increased metabolic activity in all patient explants as well. All investigated doses of Sprifermin and FGF18 continuously increased metabolic activity compared to placebo over the 70 days of treatment (fig. 1A). The aggrecan degradation biomarker exAGN1 was increased by the investigated doses of Sprifermin and FGF18 as compared to placebo (fig. 1B). exAGN1 release peaked at 21 and then gradually decreased in presence of Sprifermin and FGF18, indicating a shift of a catabolic to an anabolic phenotype as cause of treatment. Type II collagen formation, measured by exProC2, was initially (day 7-28) decreased by Sprifermin and FGF18 compared to placebo, but from day 35 to 70 exProC2 increased in a dose dependent manner, with sprifermin superior to FGF-18 (fig. 1C). The increase in exProC2 release from Sprifermin (900 ng/mL)-treated explants were 1.5-fold of placebo at day 49.

Conclusion: The data indicate that human knee OA articular cartilage explants increase their metabolic activity and formation of type II collagen in response to long-term treatment with Sprifermin and FGF18. The induction of cartilage formation is preceded by cartilage degradation, indicating that a catabolic process is needed to make room of proliferation of chondrocyte and renewal of cartilage (fig. 2).

Figure 2. Schematic illustration of sprifermin effects on articular cartilage

Disclosure: D. Reker, Nordic Bioscience, 3; C. S. Thudium, Nordic Bioscience, 3; A. S. Siebuhr, Nordic Bioscience, 3; T. Gantzel, None; C. Ladel, Merck KGaA, 3; M. Michaelis, Merck KGaA, 3; M. A. Karsdal, Nordic Bioscience, 1, 3; A. Gigout, Merck KGaA, 3; A. C. Bay-Jensen, Nordic Bioscience, 1, 3, IMI APPROACH, 2.

Abstract Number: 440

Assessing Inappropriate Pain Management in Adults with Hip or Knee Osteoarthritis Treated with Different Opioid Intensity Regimens: Results from a Retrospective Database Analysis

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical Poster I

Session Type: ACR Poster Session A

Background/Purpose: Opioids are often prescribed for osteoarthritis (OA) pain management despite the need for balancing their risks and benefits. Since there are no standard criteria for defining inappropriate pain management (IPM), this study examined prevalence of potential criteria that may be indicative of IPM in OA patients (pts) treated with opioids.

Methods: Data were from a US employer-sponsored insurance claims database (2011-2016). Pts were community-dwelling adults (≥ 18 yr) diagnosed with hip/knee OA who filled an opioid prescription (index event) within 30 days of OA diagnosis; had continuous enrollment 6 months pre- and 12 months post-index; and no pre-index joint surgery. Opioid regimen intensity in the 3-month post-index period was defined by frequency (intermittent: ≤ 4 d/wk; daily: >4 d/wk), average daily dose in morphine milligram equivalents (MME: <50 MME/d=low, ≥ 50 MME/d=high), and short- or long-acting opioids (SAO, LAO), providing 6 increasing intensity regimens: intermittent-low-dose SAO, intermittent-high-dose SAO, daily-low-dose SAO, daily-high-dose SAO, LAO, and LAO+SAO. Potential IPM, defined based on existing literature and clinical input (Table 1), comprised 3 clinical categories (Opioid Use, Miscellaneous Drug Use, Medical Service Use). Descriptive analysis characterized prevalence of potential IPM over the 12-month post-index period.

Results: The study included 271,512 pts (61.5% knee; 11.1% hip; 27.4% both); mean age 59.8 yr; 62.7% women. IPM was observed in 52.6% of pts during the post-index period; 30.7% in Miscellaneous Drug Use, 27.7% in Opioid Use, and 14.4% in Medical Service Use. LAO+SAO had the highest IPM (85.4%); intermittent SAO regimens had the lowest (42.7%-44.7%; Table 2). IPM in the intermittent dose regimens was driven by Miscellaneous Drug Use; IPM in the higher intensity regimens was driven by Opioid Use. The top 2 IPM criteria in each clinical category were generally similar across opioid intensity regimens (Table 2).

<i>Clinical category/criterion</i>	<i>Definition</i>
<i>Opioid Use</i>	
Multiple opioids	≥ 4 prescriptions for unique opioids in any 90-day period
Early refills	≥ 1 opioid prescription fill when $>10\%$ of an existing prescription should have remained available
Excessive post-surgical opioid use	Opioid prescription fill >90 days after any OA surgery
Pre-surgical opioid use	Any opioid use within 60 days prior to joint surgery
Concomitant long-acting opioid use	≥ 2 occurrences during any ≥ 7 day period of overlapping prescription fills for unique long-acting opioids
History of substance abuse	Receives opioids despite history of substance abuse
Post-index opioid abuse	≥ 1 diagnoses of opioids abuse disorder (dependence/abuse) after receiving opioids
History of opioid abuse	≥ 1 diagnoses of pre-index opioid overdose
Opioid overdose	≥ 1 diagnoses of post index opioid overdose
<i>Miscellaneous Drug Use</i>	
Excessive muscle relaxant use	≥ 3 fills for unique muscle relaxants within any 90-day period among patients with comorbid chronic low back pain
Excessive non-opioid dose	Exposure to acetaminophen or aspirin >4 g/d, or ibuprofen >3.2 g/d
Multiple NSAIDs	≥ 2 NSAIDs used concomitantly except for cardiovascular aspirin (75-325mg/d)
NSAIDs despite contraindications	NSAIDs (single drug or combined with SAO) despite contraindications
NSAID adverse events	Gastrointestinal or cardiovascular events, renal failure, hepatotoxicity after NSAID use
Too many hyaluronic acid or corticosteroid injections	≥ 3 hyaluronic acid or corticosteroid injections in a 12-month period
<i>Medical Service Use</i>	
OA-related visits with multiple specialists	≥ 4 OA-related visits to pain medicine specialists, orthopedists, rheumatologists, anesthesiologists in any 90-day period
Excessive OA-related office visits	≥ 4 office visits with an OA diagnosis within a 90-day period
OA-related inpatient admissions	Any inpatient stay with an OA principal diagnosis without corresponding joint surgery
OA-related ED visits	An ED visit with a primary diagnosis for OA
Repeated OA-related joint surgeries	≥ 2 of the same OA procedures in a 90-day period

ED, emergency department; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis

Conclusion: This study suggests potential criteria indicative of IPM were observed in the majority of OA pts treated with opioids. IPM generally increased with higher opioid intensity regimens; drivers of IPM differed between low and high intensity regimens. The study was limited by the data source and retrospective design such that it could not be determined if IPM resulted from the index opioid treatment regimen itself, patient/physician behavior, or other factors. Nevertheless, study findings reinforce physician need for evaluating pain management with opioids in OA pts individually to ensure optimal health outcomes.

Table 2. Adults in each opioid intensity regimen meeting any potential criterion of inappropriate pain management and top 2 criteria in each clinical category.

Opioid regimen	Any criterion, %	Opioid use		Miscellaneous drug use		Medical service use	
		Criterion	%	Criterion	%	Criterion	%
Intermittent low-dose SAG (n=145,425)	44.7	Any criterion	15.3	Any criterion	43.7	Any criterion	13.6
		Early refill	8.4	Too many hyaluronic acid/corticosteroid injections	22.3	OA-related visits with multiple specialists	9.3
		Pre-surgical use	6.9	NSAID adverse events	7.3	Excessive OA-related office visits	4.1
Intermittent high-dose SAG (n=44,669)	42.7	Any criterion	10.0	Any criterion	26.1	Any criterion	14.1
		Early refill	7.9	Too many hyaluronic acid/corticosteroid injections	18.6	OA-related visits with multiple specialists	10.3
		Pre-surgical use	6.9	NSAID adverse events	5.2	Excessive OA-related office visits	3.0
Daily low-dose SAG (n=41,178)	73.0	Any criterion	46.5	Any criterion	34.2	Any criterion	14.4
		Early refill	30.0	Too many hyaluronic acid/corticosteroid injections	23.9	OA-related visits with multiple specialists	8.6
		Excessive post-surgical opioid use	8.8	NSAID adverse events	8.6	Excessive OA-related office visits	6.3
Daily high-dose SAG (n=10,137)	81.8	Any criterion	68.0	Any criterion	36.2	Any criterion	19.0
		Early refill	41.0	Too many hyaluronic acid/corticosteroid injections	22.1	Excessive OA-related office visits	10.2
		Excessive post-surgical opioid use	13.0	NSAID adverse events	8.3	OA-related visits with multiple specialists	9.7
LAC (n=5,819)	66.9	Any criterion	40.4	Any criterion	30.9	Any criterion	16.1
		Early refill	27.0	Too many hyaluronic acid/corticosteroid injections	19.8	OA-related visits with multiple specialists	9.6
		Pre-surgical use	8.9	NSAID adverse events	3.3	Excessive OA-related office visits	6.9
LAC+SAG (n=13,673)	85.4	Any criterion	75.3	Any criterion	34.2	Any criterion	21.3
		Early refill	62.9	Too many hyaluronic acid/corticosteroid injections	20.0	OA-related visits with multiple specialists	11.5
		Multiple episodes	21.0	NSAID adverse events	8.5	Excessive OA-related office visits	10.6

LAC, long acting opioid; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; SAG, short acting opioid

Disclosure: N. P. Katz, Teva, Regeneron, 5; K. Gandhi, Teva, 1, 3; W. Wei, Regeneron, 1, 3; A. Huang, STATinMED Research, 3, 5; L. Wang, STATinMED Research, 3, 5.

Abstract Number: 441

The Presence of Neuropathic Pain Does Not Influence the Response to Hyaluronic Acid (HA) in Patients with Knee Osteoarthritis but HA Injections Modify Pain Phenotype

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Session Information

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Session Title: Osteoarthritis – Clinical Poster I

Session Type: ACR Poster Session A

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Background/Purpose: Twenty to forty percent of patients with symptomatic knee osteoarthritis (OA) described neuropathic pain (NP). Several studies have shown that hyaluronic acid (HA) is an effective treatment of pain-associated knee OA. However, the impact of NP in the response to HA in knee OA is unknown as well as the impact of HA injections on the neuropathic profile of pain.

Our main objective was to assess the effect of NP according to DN4 score (10 items; NP if DN4 \geq 4) in the response to HA in patient with moderate to severe symptomatic knee OA. Our secondary objectives were to assess the correlations between NP and baseline clinical and radiographic characteristics of knee OA patients and the effects of HA injections on NP.

Methods: We conducted a post-hoc analysis from the 2012 HAPPYVISC study, a multicenter randomized, double-blind, non-inferiority prospective trial comparing the efficacy of 3 weekly intra-articular injections of 2 different HA at 24 weeks. At baseline, demographic, anthropometric, clinical data (VAS Pain, WOMAC score, NP assessed by DN4, presence or lack of synovial effusion) radiologic data (OARSI score for joint space narrowing [JSN]) were recorded. The symptomatic effect of HA was assessed by PGA, WOMAC, DN4 and OMERACT-OARSI response. All patients from intention-to-treat population with fully available DN4 data were included. Mann-Whitney and chi-square tests and multivariate logistic regression analysis were used.

Results: 187 patients were included. As baseline characteristics and treatment effectiveness were similar between the 2 HA groups, their data were pooled. Mean age was 64.7, sex ratio was 0.8, mean BMI was 27.7 and mean disease duration was 46.5 months. At baseline, mean VAS pain, WOMAC pain, WOMAC function were respectively 5.8, 9.7 and 27.3. Intra-articular effusion was present in 59 patients (31.6%). 79 patients (42.2%) had a OARSI grade 3 JSN. NP was present in 20 patients (10.7%). Most common positive DN4 items were tingling (36.9) and burning (36.4%). NP was significantly associated with pain intensity according to WOMAC pain score ($p = 0.02$). A significant association between baseline burning and VAS pain intensity was also found ($p = 0.01$).

At 24 weeks, 132 patients (70.6%) were OMERACT-OARSI responders. We found a significant association between OMERACT-OARSI response and overweight, obesity, and OARSI grade ($p=0.01$; $p=0.0003$; $p=0.04$). The presence of NP according to DN4 score at baseline did not impact the rate of OMERACT-OARSI responders to HA ($p=0.32$). On the other hand, the prevalence of patients with NP decreased by 50% ($n=10$) at 24 weeks after HA injections and there was an improvement of more than 75% of absolute DN4 value in 64 patients (34.2%). Most improved DN4 items were itching (90%), hypoesthesia to pinprick (88%), and burning (50%).

Conclusion: NP is frequently described by symptomatic knee OA patients and is associated with pain severity. While NP does not influence HA response, AH reduces NP especially itching, sting hypoesthesia and burning.

Disclosure: E. Tiendrebeogo, None; T. Conrozier, None; X. Chevalier, None; F. Eymard, None.

Abstract Number: 442

Patient Factors Associated with Gaps in Osteoarthritis Care

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Session Information

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

Background/Purpose: Exercise, weight loss, simple analgesic medications and joint injections are effective non-surgical treatments for knee osteoarthritis (OA) to reduce pain and improve function. While these treatments are recommended in international guidelines and appropriate for virtually all patients, they are substantially under used. Furthermore, many patients receive opioid analgesia in place of recommended therapies. Reduced mobility due to knee OA increases risk for CV events, diabetes, and all-cause mortality; while opioid use for chronic non-cancer pain is associated with increased mortality without added therapeutic benefit. Currently, little is known about patient factors that influence use of recommended non-surgical OA care, as well as non-recommended care such as opioids, and thus which patients to target in implementation strategies.

Methods: Knee OA patients were assessed prior to orthopaedic surgical consultation using a standardized online questionnaire that assessed: sociodemographic factors (age, sex, education, income, employment, and Lubben social network score), medical comorbidities, OA disease severity (pain numeric rating scale, WOMAC pain scale, KOOS-physical function score, Gignac coping efficacy scale, and pain catastrophizing scale), and non-surgical therapies used (both

ever tried and currently using). Comprehensive non-surgical treatment was defined as use of analgesia (acetaminophen, NSAIDs or injection) *plus* exercise or physical therapy *plus* weight loss if BMI ≥ 25 kg/m². Multivariate logistic regression was used to assess the relationship between patient factors (sociodemographics, comorbidities, and OA severity) with lack of current use of comprehensive treatment, as well as with current use of opioid analgesia for knee OA.

Results: 2,220 patients were included: mean age 65.6 ± 9.1 years, 58.8% female, mean BMI 32.7 ± 6.6 kg/m², mean WOMAC pain $11.6/20 \pm 3.6$ and mean KOOS-PS $56.5/100 \pm 17.7$. 654 (29.5%) patients were currently using comprehensive treatment; 609 (27.4%) tried and stopped and 957 (43.1%) never used. 635 (28.6%) patients were currently using opioid analgesia for knee OA. In multivariate analysis, lack of use of comprehensive care was significantly associated with older age (OR 1.02, 95% CI 1.01-1.04), male sex (1.67, 1.34-2.08), high school education or less (1.25, 1.01 – 1.56; 1.82, 1.30-2.55), lower social support (0.97, 0.95-0.99), and higher BMI (1.03, 1.01-1.04). Use of opioids was significantly associated with comorbid hypertension (1.26, 1.01-1.59), depression (1.69, 1.30-2.20), other painful joints (1.27, 1.01-1.59), and worse physical function on the KOOS-PS (1.02, 1.01-1.03).

Conclusion: In a cohort with moderate-to-severe knee OA, less than one third were using comprehensive non-surgical OA treatment and over one quarter were using opioid analgesia. Sociodemographic factors including lower level of education and social support were associated with less uptake of comprehensive treatment, suggesting that clinicians should be aware of these barriers to care. Medical comorbidity and lower function, but not pain severity, were associated with opioid use, meriting further research to better understand opioid prescribing in OA.

Disclosure: L. King, None; D. A. Marshall, None; G. Hawker, None.

Abstract Number: 443

Impact of Intra-Articular Steroid Injection on Bone Marrow Lesions in Osteoarthritis of the Hip: An Assessment Using the Outcome Measures in Rheumatology Hip MRI Inflammation Scoring System

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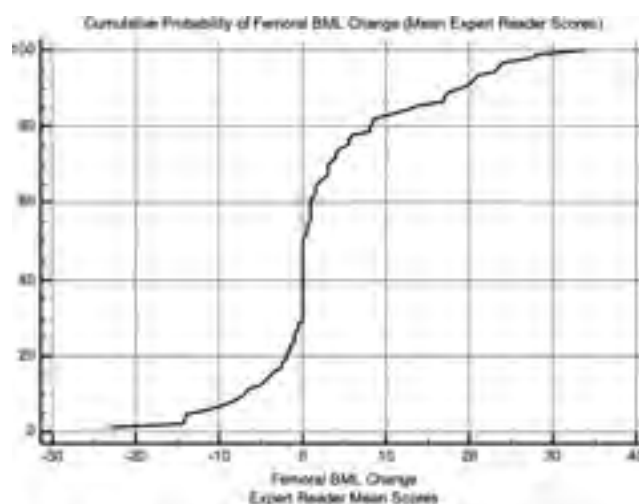
Session Information

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Background/Purpose: Intra-articular (I/A) steroid injection is an effective treatment for alleviating symptoms in osteoarthritis (OA) of the hip but the impact of this treatment on imaging findings relevant to prognosis, such as bone marrow lesions (BML) on MRI, has not been reported. The OMERACTHip MRI Inflammation Scoring System (HIMRISS) is a validated method for semi-quantitative assessment of BML in hip OA¹. We aimed to assess the impact of I/A steroid on BML in a multi reader exercise of MRI scans from a prospective cohort.

Methods: We assessed MRI scans from both hips of 90 patients at baseline and 8 weeks after I/A steroid injection. In HIMRISS, BML is scored as 0/1 (absent/present) in 100 regions on a web-based grid overlay slice-by-slice on coronal hip MRI. T1/STIR sequences were read blinded to timepoint by 8 readers (2 radiology fellows, 3 rheumatologists, 3 MSK radiologists) after review of validated HIMRISS methodology and calibration tools and attaining pre-specified scoring proficiency for assessment of status and change scores (intra-class correlation coefficient (ICC) > 0.80) versus expert reader consensus scores. Readers each scored HIMRISS BML in all 360 hips.

Results: Subjects were 56% male, age 59±13 (mean±SD) years, symptom duration 4.4±4.5 years, K-L OA grade 1/2/3/4 in 20%/28%/34%/18%, 24% taking NSAID. Although mean change in femoral BML was small (potential range 0-100), a significant increase was noted after injection. Moreover, change in BML greater than smallest detectable change (SDC) was noted in 30-40% of cases among readers with worsening score being more frequent (mean 22.2%) than improvement (10.0%) (Figure). In univariate analysis, worsening of femoral BML by >SDC was associated with NSAID use (OR=3.78 (1.37 to 10.45), P=0.01) and this remained significant in multivariate analysis adjusted for age, gender, BML, baseline femoral BML score (OR=4.25 (1.31 to 13.83), P=0.02).

Conclusion: Following I/A steroid injection for hip OA, extent of BML is more likely to deteriorate than improve and deterioration may be associated with concomitant NSAID use.

1. Maksymowych WP, et al. J Rheumatol 42:370-8, 2014

Table. OMERACT HIMRISS BML scores (mean(SD)) in femoral head and the entire hip joint at baseline and 8 weeks after I/A steroid injection.

SRM: standardized response mean

SDC: smallest detectable change

	Baseline	8 weeks	Change	P value	SRM	% change > SDC
All readers						
Fem BML	18.9(17.4)	21.1(18.7)	2.2 (9.2)	0.02	0.24	44.4%
Fem BML	14.2 (13.0)	15.5 (13.6)	1.3 (6.5)	0.06	0.20	41.1%
Central slices						
Fem BML	4.8 (4.7)	5.7 (5.4)	0.9 (3.1)	0.01	0.30	33.3%
Ant-Post slices						
Total HIMRISS	29.1(23.1)	31.2(24.8)	2.1 (10.0)	0.05	0.21	35.6%
Expert readers						
Femoral BML	16.1 (16.7)	19.2 (18.5)	3.0 (9.9)	<0.001	0.31	32.2%
Fem BML	11.8 (12.4)	13.7 (13.2)	1.9 (7.0)	0.01	0.27	32.2%
Central slices						
Fem BML	4.4 (4.8)	5.5 (5.6)	1.1 (3.4)	<0.001	0.33	25.6%
Ant-Post slices						
Total HIMRISS	26.3 (22.6)	29.0 (24.6)	2.7 (11.0)	0.02	0.25	33.3%

Figure. Cumulative probability plot of change in femoral BML scores at 8 weeks after I/A steroid injection in 90 patients with hip OA.

Disclosure: W. P. Maksymowych, CaRE rthritis, 9; R. G. Lambert, None; M. Pianta, None; Z. Al-Ani, None; D. Lindsay, None; U. Weber, None; S. J. Pedersen, None; S. Wichuk, None; K. Steer, None; G. Bostick, None; J. Paschke, None; J. L. Jaremko, None.

Abstract Number: 444

Trajectories of Sport or Recreational Activities over Eight Years and Associated Factors in Persons at Risk for Knee Osteoarthritis

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Session Information

Session Date: Sunday, October 21, 2018

Background/Purpose: Participation in exercise, sport or recreational activities offers multiple health benefits, promotes wellbeing and weight management, and preserves function and quality of life. Staying physically active is important for persons at high risk for knee OA, but without radiographic disease, for helping to prevent the downward spiral of functional decline and disability onset associated with OA development and progression. Understanding how activity levels evolve over time and associated baseline modifiable factors will inform strategies for activity promotion. In persons at high risk for knee OA, we identified distinct trajectories of weekly hours spent in strenuous activities over 8 years and baseline factors associated with membership in each trajectory.

Methods: Weekly hours engaged in strenuous activities, such as jogging, swimming, cycling, singles tennis, aerobic dance, skiing (downhill or cross-country) or other similar activities were estimated using items in the PASE (Physical Activity Scale for the Elderly) questionnaire over 8 years. OAI Participants with KL 0 in both knees and with ≥ 3 time points of PASE data were included. We used latent mixture modeling with zero-inflated Poisson distribution to identify groups with a similar underlying trajectory of weekly hours spent in strenuous activities. Multinomial logistic regression was used to model associations of baseline predictors with membership in each trajectory. Multivariable models were created by including variables with $p \leq 0.20$ in the univariate model. Backward selection (removing variables with multivariable $p > 0.20$) was used to create final models.

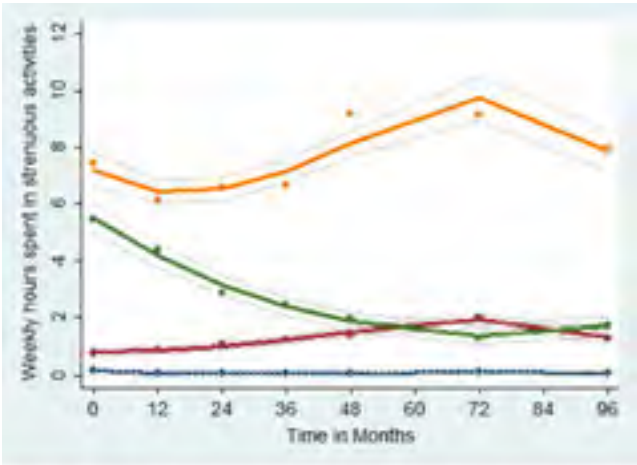


Figure 1. Four distinct trajectories of weekly hours spent in strenuous sport or recreational activities over 8 years. 594 participants (49.8%) were in Group 1 (a persistently low group, blue line), 354 (29.7%) were in Group 2 (red line), 151 (12.7%) were in Group 3 (green line), and 95 (7.5%) were in Group 4 (a high group, orange line). The dots are actual hours at each time point; the solid lines are estimated hours across 8 years; the dotted lines are 95% confidence intervals.

Results: Among 1194 OAI participants [age: 58.4 (SD 8.9) years, BMI: 26.8 (4.5) kg/m², 58.4% women], we identified 4 distinct trajectories of weekly hours spent in strenuous activities (Figure 1). Nearly 50% of the participants reported zero hour and 30% reported 1-2 hours per week over 8 years. As shown in the table, being older, greater BMI, and more severe knee pain were each associated with reduced likelihood, and being a college graduate and having stronger knees with an increased likelihood of being in the high trajectory (Gr. 4 vs. 1). Depressive symptoms were associated with a reduced likelihood of being in Gr. 3 vs. 1 or Gr. 2 vs. 1 (Table).

Conclusion: In persons at high risk for knee OA, we identified 4 distinct trajectories of weekly hours spent in strenuous activities over 8 years. Reducing BMI, knee pain, and depressive symptoms and improving knee strength may potentially facilitate continued participation in exercise, sport, or recreational activities.

Table 1. Associations of baseline predictors (independent variables) with membership in each of the weekly hours spent in strenuous activities trajectory groups (reference group: membership in Group 1 – persistently low)

Multinomial logistic regression models results for relative risk ratios (95% confidence intervals)				
n = 1194				
Baseline predictors	Group 2 n = 354	Group 3 n = 151	Group 4 n = 95	
Age (per 5-year increase)	0.84 (0.77, 0.92)	0.90 (0.81, 1.01)	0.85 (0.73, 0.99)	
BMI (per 5-kg/m ² increase)	0.94 (0.80, 1.11)	0.75 (0.60, 0.95)	0.66 (0.48, 0.90)	
Other Races (reference: White)	1.78 (1.14, 2.78)	1.15 (0.64, 2.07)	1.23 (0.55, 2.74)	
Depressive symptoms (yes vs. no)	0.49 (0.28, 0.88)	0.38 (0.16, 0.92)	0.83 (0.36, 1.92)	

WOMAC pain (range: 0-20) (per 4-unit increase)	0.67 (0.53, 0.85)	0.60 (0.42, 0.85)	0.49 (0.30, 0.79)
Knee extensor strength (Newton) (range: 27-880) (per 60-Newton increase)	0.94 (0.89, 1.06)	1.06 (0.94, 1.13)	1.27 (1.13, 1.43)
Education level (college graduate and above vs. non-college graduate)	1.68 (1.23, 2.29)	2.51 (1.58, 3.98)	1.90 (1.06, 3.41)

Disclosure: A. H. Chang, None; J. Lee, None; O. Almagor, None; J. S. Chmiel, None; J. Szymaszek, None; L. Sharma, None.

Abstract Number: 445

Interleukin-1 β Inhibition with Canakinumab Associates with Reduced Rates of Total Hip and Knee Replacement (THR/TKR) and Osteoarthritis (OA) Symptoms: Exploratory Results from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: In osteoarthritis (OA), there are no therapeutics to prevent disease progression. Canakinumab, a monoclonal antibody targeting interleukin-1 β , reduced inflammation and cardiovascular events in the CANTOS trial (Ridker et al. 2017). CANTOS included 10,061 men and women with a history of myocardial infarction and high-sensitivity C-reactive protein (hsCRP) ≥ 2 mg/L who were randomized to placebo or one of three doses of canakinumab (50 mg, 150 mg, or 300 mg) given sc once every 3 months. Median follow-up was 3.7 years.

Methods: We conducted a post-hoc exploratory analysis of CANTOS data to evaluate potential effects of canakinumab on rates of OA-related adverse events (AE) and incident TKR/THR (ARGUS) in the full CANTOS cohort and in a subgroup with a medical history of OA. The high-level term Osteoarthropathy (OAP) was used to search the AE database, (no adjudication of OA was pursued). A time to event analysis was done for first occurrence of TKR/THR as well as for OAP-related AEs. The drug-treated groups were compared to placebo by two-sided log-rank test. Second, the analyses were repeated with pooled drug-treated groups and hazard ratios for pooled drug vs placebo computed by Cox proportional hazards regression (CPH).

Results: In all patients, incidence rates of TKR/THR were 1.41%, 0.88%, 0.66%, and 0.80% in the placebo and canakinumab 50 mg, 150 mg, and 300 mg groups, respectively. The relative risk reduction (RRR) for pooled treatment vs placebo was 45% computed by CPH, $p < 0.001$. For OA-related adverse events, comparable incidence rates were 7.0%, 5.2%, 5.1%, 6.0%, respectively. The RRR for pooled treatment vs. placebo was 23% computed by CPH, $p = 0.002$. In the subgroup of 1569 CANTOS participants with OAP at baseline, incidence rates of TKR/THR were 6.25% and 3.36% in the placebo and combined canakinumab groups respectively (RRR vs placebo 45%, $p < 0.013$, Figure 1). Incidence rates for OA-related adverse events were 20.7%, 16.6%, 12.4%, 15.0%, respectively (RRR vs. placebo across groups 31%, $p = 0.003$, Figure 2).

Conclusion: In an exploratory analysis of the CANTOS trial, canakinumab treatment was associated with reduced rates of THR/TKR and OA symptoms. Effects were most apparent among those with a prior history of OA. An additional responder analysis based on hsCRP lowering at 3 months is currently ongoing.

References: Ridker PM, Everett BM, McFadyen JG, et al., Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119-31

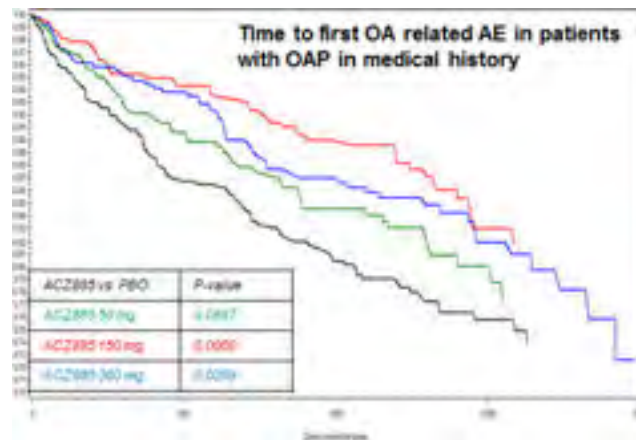


Figure 1



Figure 2

Disclosure: M. Schieker, Novartis Pharma AG, 1, 3, University of Munich, 3; L. Mindeholm, Novartis Pharma AG, 1, 3, 5; J. Praetstgaard, Novartis Pharma AG, 1, 3; C. Scotti, Novartis Pharma AG, 1, 3; D. Solomon, None; T. Thuren, Novartis Pharma AG, 1, 3; K. Dreyer, Novartis Pharma AG, 1, 3; R. Roubenoff, Novartis Pharma AG, 1, 3; P. M. Ridker, Novartis Pharma AG, 2, 5.

Abstract Number: 446

Participation in American Football Is Associated with Increased Risk for Knee Pain and Osteoarthritis: Data from the Osteoarthritis Initiative

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Male youth commonly participate in American football. Little data inform whether this is associated with knee pain or osteoarthritis (OA) later in life. We aimed to evaluate the relationship of football participation with these outcomes using data from the Osteoarthritis Initiative (OAI), hypothesizing that it is associated with a higher prevalence of knee pain, knee OA, and symptomatic knee OA.

Methods: This is a retrospective cross-sectional study of OAI participants with knee x-ray readings, symptom assessments, and completed surveys on lifetime physical activity. A modified version of the Historical Physical Activity Survey Instrument identified those who played football. Posterior-Anterior semi-flexed knee radiographs were scored for Kellgren-Lawrence (KL) grade (0-4). Radiographic OA (ROA) was defined as KL ≥ 2 . Frequent knee pain within a person required at least one knee to have frequent kneepain. Symptomatic radiographic OA (SOA) required that at least one knee had both ROA and frequent knee pain. Anyone with a total knee replacement was classified as having frequent knee pain, ROA, and SOA. Since 98% of the subjects who participated in football were men, we restricted this study to men only. Using logistic regression, we evaluated the association of any history of football participation during 2 age periods: ages 12 – 18 and over the participants' lifetime, with the prevalence of ROA, frequent knee pain, and SOA as the outcomes. Outcome Definitions. All outcomes were person-based definitions. Exposure Definitions. For the 12-18 age range and any history of American football participation, we looked at the exposure in two ways: (1) dichotomously (non-participants versus participants) and (2) 4 groups: non-participants and 3 levels of participation (low, medium, and high tertiles of football participation). The Cochran-Armitage trend test was used to evaluate for a dose response relationship. We performed analyses both unadjusted and adjusted for age, BMI, and history of knee injury.

Results: 1166 men were included with a mean age of 63.7 (SD 9.2) years and BMI of 28.6 (SD 4.2) kg/m². 31% (365/1166) played football at some time in their lives, 95% (346/365) played between 12-18 years old, with 65% (223/346) playing at least 5 years during that age range.

The ORs for SOA from lowest to highest football participation were 1.2, 1.5, and 2.2 respectively (p for trend = 0.004) (Table). Findings were similar for football from ages 12 –18 years and for outcomes of knee pain and ROA (Table).

Conclusion: This is the first large epidemiologic study to suggest that football participation, especially in the teen years, is detrimental to knee health, independent of knee injury. A limitation to this study is that the exposure of football was ascertained retrospectively. Prospective studies evaluating football players are warranted.

Table. Table of knee pain, knee OA, and symptomatic knee OA prevalence based on history of football participation status and associated odds ratios			
Football Time Period	Prev. of outcome	Unadjusted Odds Ratios	Adjusted Odds Ratios*
Any History of Football Participation			
Outcome of Frequent Knee Pain			
No (n = 801)	35.80%	Referent	Referent
Yes (n = 365)	46.30%	1.7 (1.4-2.2)	1.6 (1.3-2.1)
Low (n = 141) (7.5 - 47.5)	44.30%	1.4 (1.0-2.0)	1.6 (0.9-2.9)
Middle (n = 120) (47.5 - 104)	47.50%	1.6 (1.1-2.4)	1.6 (1.1-2.3)
High (n = 104) (75 - 150)	56.80%	2.6 (1.7-3.9)	2.2 (1.4-3.4)
		p for trend=0.0001	p for trend=0.0008
Football Participation from Ages 12 - 18 years old			
No (n = 800)	36.00%	Referent	Referent
Yes (n = 346)	49.70%	1.8 (1.4-2.3)	1.8 (1.3-2.3)
Low (n = 113) (7.5 - 47.5)	45.30%	1.5 (1.0-2.2)	1.6 (0.9-2.3)
Middle (n = 117) (47.5 - 110)	49.60%	1.8 (1.2-2.8)	1.8 (1.2-2.4)
High (n = 116) (77.5 - 150)	54.30%	2.1 (1.4-3.2)	2.0 (1.3-3.0)
		p for trend=0.0001	p for trend=0.001
Any History of Football Participation			
Outcome of Radiographic Knee OA			
No (n = 792)	26.70%	Referent	Referent
Yes (n = 365)	61.30%	2.3 (1.9-2.7)	2.2 (1.8-2.6)
Low (n = 141) (7.5 - 47.5)	57.00%	1.9 (0.7-4.5)	0.9 (0.6-1.3)
Middle (n = 120) (47.5 - 75)	62.50%	1.9 (0.9-3.9)	1.3 (0.8-1.9)
High (n = 104) (75 - 150)	71.50%	2.0 (1.3-3.2)	1.9 (1.2-3.2)
		p for trend=0.01	p for trend=0.04
Football Participation from Ages 12 - 18 years old			
No (n = 800)	26.80%	Referent	Referent
Yes (n = 347)	63.20%	2.3 (1.9-2.7)	2.2 (1.8-2.6)
Low (n = 113) (7.5 - 47.5)	59.00%	1.1 (0.7-1.8)	1.0 (0.7-1.3)
Middle (n = 116) (47.5 - 110)	62.90%	1.3 (0.9-1.9)	1.3 (0.9-1.9)
High (n = 118) (77.5 - 150)	67.80%	1.6 (1.1-2.4)	1.5 (1.0-2.3)
		p for trend=0.02	p for trend=0.04
Any History of Football Participation			
Outcome of Symptomatic Radiographic Knee OA			
No (n = 792)	23.00%	Referent	Referent
Yes (n = 365)	35.00%	1.6 (1.2-2.1)	1.5 (1.1-2.0)
Low (n = 141) (7.5 - 47.5)	28.90%	1.3 (0.8-1.9)	1.2 (0.8-1.7)
Middle (n = 120) (47.5 - 75)	34.20%	1.6 (1.0-2.3)	1.5 (1.0-2.3)
High (n = 104) (75 - 150)	44.90%	2.5 (1.6-3.8)	2.2 (1.4-3.4)
		p for trend=0.0001	p for trend=0.004
Football Participation from Ages 12 - 18 years old			
No (n = 800)	23.30%	Referent	Referent
Yes (n = 347)	34.80%	1.6 (1.2-2.1)	1.5 (1.1-2.0)
Low (n = 113) (7.5 - 47.5)	31.00%	1.4 (0.9-2.1)	1.3 (0.8-2.0)
Middle (n = 116) (47.5 - 110)	31.90%	1.3 (0.9-2.0)	1.2 (0.8-1.9)
High (n = 118) (77.5 - 150)	42.30%	2.1 (1.4-3.3)	2.1 (1.5-3.1)
		p for trend=0.002	p for trend=0.001

*Adjusted for age, BMI, prior knee injury

Disclosure: G. H. Lo, None; T. E. McAlindon, None; A. Kriska, None; L. L. Price, None; B. Rockette-Wagner, None; L. A. Mandl, None; C. B. Eaton, None; M. C. Hochberg, None; R. D. Jackson, None; C. K. Kwoh, None; M. C. Nevitt, None; J. B. Driban, None.

Abstract Number: 447

Discriminating between Central & Peripheral Pain Sensitization Using a Slowly Repeated Evoked Pain Protocol

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pain Mechanisms – Basic and Clinical Science Poster

Session Type: ACR Poster Session A

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

Background/Purpose:

- In a prior study, the response of pain sensitization by fibromyalgia (FM) patients to a protocol of Slowly Repeated Evoked Pain (SREP)* was strongly associated with clinical pain. However, this protocol needs further investigation regarding its underlying mechanisms and clinical usefulness.

* *SREP differs from Temporal Summation of Pain (TSP) in which the frequency of painful stimuli is usually around 0.33 Hz in TSP, whereas it is 10 times slower (0.03 Hz) in SREP.*

- This study explored the central vs. peripheral origin of the pain sensitivity observed in response to SREP protocol when this was applied to patients with chronic pain characterized by central sensitization (FM) vs. characterized by peripheral sensitization (rheumatoid arthritis, RA) vs. healthy controls (HC).

Methods:

- Fifty-nine patients with FM, 30 with RA, and 50 HC matched in socio-demographic variables participated in this study.
- Potential group differences of psychological factors were controlled: Clinical Pain (McGill Questionnaire), Anxiety and Depression (HADS), and Catastrophization (CSQ).
- Participants were instructed in the use of a Visual Analogue Scale (VAS) to assess the pain caused by a pressure algometer on the nail of the third finger.
- Threshold and tolerance were obtained to calculate the intensity of the pain stimulus individually for each participant. Then, a series of 9 pain stimuli of 5s duration and low-moderate intensity was applied at a 30s interval.
- SREP sensitization index was quantified as the difference in pain scores between the 9th and 1st painful stimuli.

Results:

- The repeated measures ANOVA showed a significant increase in subjective pain ratings of the SREP series exclusively for the FM group (see Figure).
- Logistic regressions revealed an acceptable diagnostic accuracy of SREP index to discriminate between FM & AR and FM & HC, but not between AR & HC (see Table).

Conclusion:

- SREP seems to be based on central processes rather than to be related to peripheral sensitization.
- SREP could be presented as a simple tool that would allow in a complementary way to explore the level of central pain sensitization in patients with chronic pain.
- Potential clinical utility of SREP warrants further investigation.

Disclosure: M. Romero, None; S. Bruehl, None; G. A. Reyes del Paso, None; P. De la Coba, None.

Tizanidine, a Frequently Used Muscle Relaxant, Is Associated with Severe Hypotension: Role of Cytochrome P450 1A2 Inhibition in Routine Clinical Practice

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pain Mechanisms – Basic and Clinical Science Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Tizanidine, a muscle relaxant widely used for musculoskeletal pain, can lower blood pressure and is metabolized by the cytochrome P450 1A2 (CYP1A2). As a result, strong CYP1A2 inhibitors raise plasma concentrations of tizanidine 10-33 fold, thus potentially increasing the risk of tizanidine side effects. Despite this concern, there is limited information about the clinical consequences of this drug-drug interaction in routine clinical practice. We tested the hypothesis that when used in combination with strong CYP1A2 inhibitors, tizanidine is associated with higher rates of severe hypotension than the active comparator, cyclobenzaprine.

Methods: In this retrospective cohort study in the de-identified electronic health record database at Vanderbilt University Medical Center, we studied patients 18 years of age or older who had received tizanidine or cyclobenzaprine concurrently with the strong CYP1A2 inhibitors ciprofloxacin or fluvoxamine. We extracted demographic variables (including age, race, and sex) and the specific CYP1A2 inhibitor drug, and we used ICD-9 codes, which were collapsed according to the categories described in the Charlson/Deyo modified score. The primary outcome was severe hypotension, defined as systolic blood pressure (SBP) ≤ 70 mm Hg. To examine the association between severe hypotension and the concurrent use of tizanidine and a strong CYP1A2 inhibitor, we built two multivariate logistic regression models: (1) adjusted for age, sex, and race; (2) adjusted by a logarithmically transformed propensity score, defined as the probability of assignment to tizanidine given demographics, Charlson score, specific strong CYP1A2 inhibitor, and current use of antihypertensives (by class).

Results: The cohort was comprised of 1,626 patients prescribed tizanidine and 5,012 prescribed cyclobenzaprine concurrently with a strong CYP1A2 inhibitor. Severe hypotension occurred more often in the tizanidine group [2.03% (n=33)] than the cyclobenzaprine group [1.28% (n=64)]; OR= 1.60, p=0.029. This difference remained statistically significant after adjustment for a log-transformed propensity score (OR= 1.57, p=0.049). The highest risk for severe hypotension was among patients receiving tizanidine and a strong CYP1A2 inhibitor who had a Charlson score of 3 or more [OR=10.60 (95% C.I. 4.19-26.81)] or who received three or more concurrent anti-hypertensives [OR=5.64 (95% C.I. 2.30-13.81)].

Table: Association between concurrent prescription of tizanidine and a CYP1A2 inhibitor and severe hypotension (SBP ≤ 70 mm Hg)

	Tizanidine (n=1,626)	Cyclobenzaprine (n=5,012)	p-value
Windows with event (SBP ≤ 70 mm Hg)	33	64	
Rate of Event (%)	2.03	1.28	0.032
Unadjusted Odds Ratio (95% CI)	1.60 (1.05, 2.45)	Reference	0.029
Adjusted Odds Ratio – adjusted for age, race, and sex	1.69 (1.08, 2.64)	Reference	0.021
Adjusted for logarithmically transformed PS	1.57 (1.0, 2.45)	Reference	0.049

Conclusion: Strong CYP1A2 inhibition increases the risk of severe hypotensive episodes associated with the use of tizanidine. Clinicians should avoid co-prescribing tizanidine with strong CYP1A2 inhibitors, particularly in patients with higher comorbidity indices and in those who receive three or more antihypertensive agents.

Disclosure: S. Chaugai, None; A. Dickson, None; M. Shuey, None; Q. Feng, None; K. Barker, None; J. Luther, None; C. M. Stein, None; C. P. Chung, None.

Pain Processing in Chronic Low Back Pain Individuals with or without Sick Leave

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pain Mechanisms – Basic and Clinical Science Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Chronic low back pain (LBP) is one of the most common musculoskeletal complaints in industrialized societies. It affects 80% of the adult population at some time in their lives and chronic LBP (CLBP) remained one of the most common causes of disability among adults in the past 20 years. One of the reasons for relatively low impact of current available treatment is the lack of a better pathophysiologic understanding of CLBP, reflected in the inconsistent response to the commonly used drug and non-drug treatments. Pain definition *per se* is at the very basis of the problem, due to its complexity and subjective experience encompassing the interpretation of nociceptive stimuli influenced by many factors. Some of the CLBP characteristics are reflected in brain processes probed by functional magnetic resonance imaging (fMRI). With that in mind we performed a study comparing neuronal correlates between CLBP with or without sick-leave

Methods: Cross-sectional observational study comparing CLBP with or without sick leave with 74 volunteers divided into three groups: CLBP and sick leave [CLBP_L]; CLBP without sick leave [CLBP_NL]; controls without pain]. fMRI was used during performance of two paradigms: pain and attention.

Results: After acute painful stimulation (figure 1, 2), higher response at the anterior cingulate and superior frontal gyrus was observed in CLBP_NL vs. CLBP_L ($p < 0,001$) and at the frontal pole and paracingulate region, comparing control vs. CLBP_L ($p < 0,001$) showing a gradual modulation of these areas. We also observed a higher brain activity in the CLBP_NL compared to CLBP_L in superior frontal gyrus ($p = 0,047$).

Conclusion: Our results confirm and extend previous studies showing that chronic pain is associated with altered neuronal plasticity in brain areas that extend beyond somatosensory regions to include areas processing emotions. The lower activation of the superior frontal gyrus in the CLBP_L group in both tests (pain and attention) suggests a chronic preexisting activation in these areas. These results indicate that the modulation of acute pain and attention participates in the mechanism propagating chronic pain perception.



Figure 1 and 2

1
 fMRI analysis in pain paradigm in CLBP_NL comparison > CLBP_L
 (Anterior Cingulum and the superior frontal gyrus / mediumright)
 Values% BOLD Effect

Variable	CLBP_NL	CLBP_L	Valor p
BOLD Effect	0,10 [0,04; 0,22]	-0,09 [-0,23; -0,02]	<0,001

2

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Injection Site Reaction Associated with Subcutaneous Biologic Agents and Methotrexate. Analysis from the Rhumadata® Clinical Database and Registry

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pain Mechanisms – Basic and Clinical Science Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Injection Site Reaction (ISRs) are associated with the subcutaneous (SC) route of administration of all biologic agents, and 3% to 15% of patients reports it. ISRs include pain, itching, redness, swelling or a combination of any of those. Rhumadata® has collected the intensity of pain associated with SC injections. We report here the results and compare levels of pain across agents.

Methods: As part of the patient reported outcomes (PROs), one question on pain intensity was asked to patients exposed to SC methotrexate or a biologic agent administered with a device or a syringe. The same question was asked at all visits making multiple answers available for the same patient. The intensity of pain was described using the following scale: 1- none, 2- negligible, 3- mild, 4- moderate, 5- severe, 6- extremely severe and 7- intolerable. Pain levels associated with adalimumab (ADA), etanercept (ETA), certolizumab (CERTO), golimumab (GOLI), denosumab (DEN), abatacept (ABA), tocilizumab (TOCI) and methotrexate (MTX) are presented.

Results: A total of 12,843 injection pain assessments were extracted. 7,347, 2,117 and 3,319 were performed on patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) respectively. Women represented 76%, 44% and 50% of these cohorts. Mean ages at treatment initiation were 53.0(SD=12.1), 41.6(12.4) and 48.7(11.6). Severe, very severe or intolerable pain was reported for 3.12%, 9.23% and 6.21% of SC injections performed on patients with RA, AS and PsA respectively. Multivariate logistic regression showed that women (OR=2.09, 95% CI=[1.42, 3.08]) were more likely to report severe, very severe or intolerable pain than men, as were patients with longer disease duration (OR=1.04, 95% CI=[1.02, 1.06]). Patients diagnosed later (Age at diagnosis OR=0.98, 95% CI=[0.97, 1.00]) were less likely to report high levels of pain. Subjects treated with ADA (OR=6.31, 95% CI=[3.13, 12.72]) and ETA (OR=4.37, 95% CI=[2.42, 7.90]) were more likely to report more pain than patients using MTX. Patients using CERTO (OR=0.26, 95% CI=[0.12, 0.54]) and GOLI (OR=0.11, 95% CI=[0.06, 0.23]) were less likely to report severe, very severe and intolerable pain than patients injected with ADA. Primary diagnosis (RA, AS and PsA) are similarly associated with reported pain levels. Stopping MTX or bDMARD treatment for an ISR-pain is extremely rare.

Conclusion: The intensity of pain associated with subcutaneous route of administration varies with gender, age (age at diagnosis and disease duration at injection) and administered medication.

Disclosure: D. Choquette, None; L. Bessette, None; J. Brown, None; B. Haraoui, AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Merck, Pfizer, Roche, and UCB, 2, 5, 8; F. Massicotte, None; J. P. Pelletier, None; J. P. Raynauld, None; M. A. Rémillard, None; D. Sauvageau, None; A. Turcotte, None; É. Villeneuve, None; L. Coupal, None.

Abstract Number: 451

The Frequency of Neuropathic Pain in Patients with Low Back Pain and the Relationship with Demographic Characteristics: A Cross-Sectional Study

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pain Mechanisms – Basic and Clinical Science Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Low back pain (LBP) is one of the most challenging chronic pain conditions. The path physiology of LBP is complex and contains nociceptive and neuropathic pain (NP) pathways. NP may be associated with leg pain, sensory and motor deficits, disability and lower quality of life. The aim of this study was to evaluate the prevalence of NP in patients with LBP and the relationship of NP with demographic characteristics, body mass index (BMI) and pain duration.

Methods: 440 outpatient patients who applied to the PMR clinic of our research hospital with LBP from January 2017 to July 2017 were enrolled in the study. All the patients were evaluated with respect to NP. Data were collected using a structured questionnaire (demographics and LBP duration). Douleur Neuropathique 4 (DN4) questionnaire was used to identify NP. The main type of pain was recorded (tingling, numbness, burning etc.). Any difference in demographic characteristics or duration of pain were investigated between the patients with and without NP. Binary logistics regression modeling was used to obtain a subset of sociodemographic factors that were independently associated with NP. Data were analyzed using NCSS 10 (2015. Kaysville, Utah, USA).

Results: 193 (43, 9 %) of the 440 LBP patients had NP according to DN4 (score of $DN4 \geq 4$) (95% confidence interval 39%-49%). Mean age of the patients was 44.8 years (± 13.7 , min 18, max 85). 263 (59, 8%) of the patients were female. The median duration of LBP was 24 months (with extremes of 3 days and 30 years). 343 (77, 9%) of the patients had chronic LBP (more than 3 months). The average BMI was $27, 98 \pm 4, 54$. 275 patients (62,9%) were not officially employed (housewife, retired, student etc.), 35 patients (7,7%) were office holder, 130 patients (29,6%) were high-activity worker. The most common types of pain were numbness (62% of the patients with NP), and burning (21%). Gender distribution of the patients with and without NP was similar ($p=0,237$). The patients with NP were older ($p<0,001$), had higher BMI ($p=0,005$) and longer LBP duration ($p<0,001$) and had lower educational level ($p=0,018$). NP was significantly more common in unemployed patients and less common in high activity employees ($p=0,001$). Logistic regression analyses identified that high-active workers' risk of having NP was 1,76 times lesser than other groups (office workers, housewives and retired patients) ($p=0,039$, $OR(95\%CI)=1,76(1,03-3,02)$). Odds ratio of employment was not different in general ($p=0,099$). The predictive value of longer pain duration of having NP was close to significance ($p=0,056$).

Conclusion: In our group, nearly half of the patients with LBP had accompanied NP. NP was remarkably more common in patients with low socioeconomic status and patients who perform high levels of physical activity at workplace had interestingly lower NP scores compared to patients with less physically active lifestyles. Our results showing NP being more common in sedentary patients may suggest that emphasizing exercise training as a therapeutic intervention in LBP management could also be beneficial to NP also.

NP is associated with higher levels of pain and disability, clinicians should be mindful of NP management while LBP is being treated.

Disclosure: B. Erhan, None; K. Gumussu, None; B. Kara, None; G. T. Bulut, None; E. Yılmaz Yalcinkaya, None.

Abstract Number: 452

Features of Peripheral and Central Sensitization and Neuropathic Pain Are Seen in Both Osteoarthritis and Rheumatoid Arthritis

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pain Mechanisms – Basic and Clinical Science Poster

Session Type: ACR Poster Session A

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

Background/Purpose: OA and RA are among the most common chronic painful rheumatic diseases. Appreciation of the role of pain sensitization in OA has revolutionized the management of chronic pain with neuroactive agents. By contrast, pain in RA has conventionally been considered to be “inflammatory”, with the belief that treatment with disease-modifying anti-rheumatic agents (DMARDs) aborts the painful experience. A number of patients with RA, however, continue to experience pain despite optimal control of inflammation. Thus, we aimed to test the hypothesis that pain in RA, similar to OA, includes signs of peripheral and central sensitization and neuropathic features.

Methods: After consent, patients with physician diagnosis of symptomatic OA of the hips and/or knees (VAS pain score at the sites $\geq 3/10$), active or DMARD-naïve RA (escalation or change in RA therapy, synovitis on physician exam at the reference clinic visit), and control (45 yrs or older, without pain ≥ 1 month, no arthritis or neuropathy or joint replacement history) were recruited and asked to fill a pain DETECT (PD-Q) questionnaire ¹. Quantitative sensory tests (QST) including pressure pain thresholds (PPT) using an algometer and temporal summation (TS) using von Frey monofilament (60 g), were performed on all subjects at right and left radial styloids, tibial tuberosities, and medial knees. Sensitization is present when there is low PPT using an algometer (peripheral= diseased site; central= no diseased site) and an increased in pain score after repeated controlled stimulation with von Frey monofilament (central) ². Demographic data, PD-Q scores and results from QST were compared between groups using analysis of variance (ANOVA). PD-Q scores were classified as ≤ 12 -unlikely neuropathic vs >12 -likely neuropathic. Correlations between PD-Q scores and QST results were analyzed using Spearman's rho.

Results: Participants included 25 OA, 20 RA, and 19 controls. Patients with OA were older and had higher BMI than RA and control subjects ($p < 0.001$). PD-Q scores were in the "likely neuropathic" range in 32% of OA and 40% of RA vs 0% of control subjects ($p < 0.001$). Both OA and RA had lower PPT vs control at all tested sites. OA and RA patients exhibited significantly higher TS vs control subjects. PD-Q final score and component questions were associated significantly with PPT ($\rho = -0.244$ to -0.448 , $p < 0.05$), but not to TS results.

Table: Demographic, clinical, and QST data of patients with symptomatic hip and/or knee OA, active or DMARD-naïve RA, and control subjects

Variable (s)	OA (n=25)	RA (n=20)	Control (n=19)	p all groups
Age	65.2 (10.2)	53.2 (10.7)	52.9 (10.4)	<0.001
BMI, kg/m ²	32.8 (9.6)	25.9 (7.0)	26.6 (4.3)	0.007
%Female patients	88%	65%	58%	0.063
Pain detect final score	8.6 (6.4)	11.9 (9.2)	1.4 (2.5)	<0.001
Likely neuropathic, % patients	32%	40%	0%	0.009
PPT Left radial styloid, lbf	4.5 (2.7)	4.0 (1.5)	5.6 (2.6)	0.121
PPT Right radial styloid, lbf	4.5 (2.8)	3.6 (1.4)	5.6 (2.4)	0.037
PPT Left medial knee joint, lbf	4.6 (2.8)	4.4 (2.7)	7.7 (3.3)	0.001
PPT Right medial knee joint, lbf	4.5 (2.8)	4.1 (2.4)	7.7 (3.2)	<0.001
PPT Left tibial tuberosity, lbf	5.2 (2.9)	5.4 (2.5)	8.9 (2.8)	<0.001
PPT Right tibial tuberosity, lbf	6.1 (3.6)	5.0 (2.7)	11.1 (9.9)	0.005
TS left radial styloid, % patients	68.0%	75.0%	57.9%	0.385
TS right radial styloid, % patients	76.0%	85.0%	42.1%	0.009
TS left tibial tuberosity, % patients	76.0%	60.0%	26.3%	0.004
TS right tibial tuberosity, % patients	68.0%	85.0%	36.8%	0.006

Data are reported in mean (standard deviation) unless specified. Abbreviation: lbf, pound-force.

Conclusion: Both OA and RA exhibited evidence of neuropathic features on a PD-Q questionnaire and peripheral and central sensitization on QST. To our knowledge, this is the first study evaluating sensitization in both OA and RA compared to control and demonstrating similar pain patterns and degrees of sensitization in both disease groups. The clinical and treatment implications of these findings warrant attention and further investigation.

Reference: 1. Curr Med Res Opin, Vol.22, No. 10 (2006); 2. Curr Osteoporosis Rep (2015).

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Abstract Number: 453

Profound Changes in the NaV1.8 Nociceptive Innervation of the Murine Knee Joint after Destabilization of the Medial Meniscus

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pain Mechanisms – Basic and Clinical Science Poster

Session Type: ACR Poster Session A

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

Background/Purpose: We aimed to compare the nociceptive innervation of healthy and osteoarthritic mouse knees.

Methods: Destabilization of the medial meniscus (DMM) or sham surgery was performed in the right knee of 10-week old male C57BL/6 Na_v1.8-tdTomato mice. These mice express a bright red fluorescent tomato reporter in all neurons that express the voltage-gated sodium channel, Na_v1.8, which is expressed by approximately 75% of dorsal root ganglion (DRG) sensory neurons, including >90% of C-nociceptors (pain-sensing neurons) and C-low-threshold mechanoreceptors, as well as a lower percentage of A δ -nociceptors and A β afferents. Sixteen weeks after surgery, mice were perfused transcardially with paraformaldehyde, knees were collected, post fixed and decalcified (DMM, sham, and 26-week-old naïve mice, n=5/group). Twenty- μ m thick sections were cryosectioned and collected at mid-joint level. Na_v1.8-tdTomato signal was quantified using ImageJ. In order to confirm innervation patterns, we also used (1) Wild type C57BL/6 mice (n=3/group) immunostained for PGP9.5, and (2) C57BL/6-Pirt-GCaMP3 mice (n=3/group). These mice express the green fluorescent calcium indicator, GCaMP3, in ~90% of all sensory DRG neurons through the Pirt promoter.

Results: In 26-week old naïve knees, Na_v1.8 expressing sensory neurons were observed in the lateral synovium and insertions of the cruciate ligaments, while medial synovium showed less innervation. Sixteen weeks after DMM surgery, mice had severe OA joint damage (cartilage degeneration score = 12.8 ± 1.9 , compared to 0.4 ± 0.49 after sham surgery). DMM, but not sham-operated knees showed profound neuroanatomical changes in the nociceptive innervation. We detected an increase in Na_v1.8 innervation of the medial synovium compared to age-matched naïve and sham-operated controls. The lateral synovium and the cruciate ligaments showed no changes. We also observed changes in the subchondral bone (SCB) innervation of the tibia and femur in the medial compartment, characterized by the presence of channel-like structures containing Na_v1.8 expressing fibers pointing toward the calcified cartilage. These nerves were also observed to a lesser extent in sham and naïve knees. Finally, Na_v1.8 signal was detected in osteophytes. Findings in Pirt-GCaMP3 mice and PGP9.5 staining in WT mice confirmed the above findings.

Conclusion: The Na_v1.8 nociceptive innervation of the mouse knee profoundly changes at late stage experimental osteoarthritis, most notably an increase in the medial synovium and the presence of Na_v1.8 neurons in the SCB of the medial compartment. Ongoing studies are aimed at characterization of these nerves. The functional significance of these neuroanatomical changes associated with joint damage needs to be further investigated.

Disclosure: A. Obeidat, None; R. J. Miller, None; R. E. Miller, None; A. M. Malfait, None.

Abstract Number: 454

Effects of Prolonged Chemogenetic Inhibition of Nociceptors in a Murine Surgical Model of Osteoarthritis

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pain Mechanisms – Basic and Clinical Science Poster

Session Type: ACR Poster Session A

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

Background/Purpose: The aim of this study was to investigate the effects of prolonged chemogenetic inhibition of Na_v1.8 nociceptors on pain-related behaviors and cellular changes in the dorsal root ganglia (DRG) in a murine model of OA. After destabilization of the medial meniscus (DMM), mice develop pain-related behaviors in association with progressive joint damage, including knee hyperalgesia and mechanical allodynia in the ipsilateral hindpaw. In addition, cellular changes occur in the DRG, including increased numbers of macrophages 8 and 16 weeks after DMM, compared to sham and naïve age-matched controls.

Chemogenetic silencing of nociceptors involves the use of Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), also termed Pdi, genetically targeted to the Voltage-Gated Sodium Channel 1.8 (Na_v1.8). Na_v1.8 is expressed by the majority of nociceptors. Activation of Pdi with the synthetic chemical agonist clozapine N-oxide (CNO) inhibits the neuronal activity of these nociceptors (Miller RE et al, *Arthr Rheum* 2017).

Methods: CNO- or saline-loaded Alzet minipumps were implanted into the peritoneal cavity of 10-week old male Na_v1.8-Pdi C57BL/6 mice, which allows for chronic release of CNO or saline for up to 6 weeks. Three days after implantation, DMM surgery was performed on the right knees of these mice.

A blinded observer performed the following behavioral tests after surgery: Knee hyperalgesia was measured using a Pressure Application Measurement (PAM) device (Ugo Basile), and mechanical allodynia in the ipsilateral hind paw was measured using von Frey fibers and the up-down staircase technique. To assess cellular changes in the peripheral pain pathway, L4 DRG sections were immunostained with the macrophage marker, F4/80. The total number of macrophages per DRG section was quantified using ImageJ and normalized to the area of each DRG.

Results: Evaluation of knee hyperalgesia 2, 4 and 6 weeks after DMM surgery in saline (n=5) and CNO (n=11) implanted Nav1.8-Pdi mice revealed that CNO-implanted mice had significantly less knee hyperalgesia at 4 (p= 0.0004) and 6 (p= 0.01) weeks after DMM, compared to saline-implanted mice. Mechanical allodynia was assessed at 6 weeks after DMM surgery, and CNO-implanted mice had significantly less mechanical allodynia compared to saline-implanted mice (p= 0.03). Macrophage infiltration in the ipsilateral L4 DRG was significantly attenuated in CNO-implanted mice compared to vehicle controls (p=0.03).

Conclusion: The results showed that prolonged (*i.e.*, 6 weeks) chemogenetic inhibition of nociceptors in Nav1.8-Pdi mice significantly attenuated knee hyperalgesia and mechanical allodynia. In addition, prolonged chemogenetic inhibition also affected cellular changes in the DRGs, with fewer macrophages in CNO-implanted mice. This suggests that prolonged blockade of nociceptor activity can attenuate pain-related behaviors and influence cellular changes in the DRGs in murine OA. Histological assessment of the knee joints is ongoing.

Disclosure: P. B. Tran, None; S. Ishihara, None; R. E. Miller, None; R. J. Miller, None; A. M. Malfait, None.

Abstract Number: 455

Metabolic Syndrome and Trajectories of Pain Severity and Number of Painful Sites in Knee Osteoarthritis: Data from a 10.7-Year Prospective Study

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pain Mechanisms – Basic and Clinical Science Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Metabolic syndrome (MetS) has been suggested as having a role in osteoarthritis (OA) pathogenesis. No study has assessed whether MetS and its components are associated with pain severity and number of painful sites (NPS) and their courses over time. We aimed to examine the association of MetS and its components with trajectories of pain severity and NPS in people with radiographic knee OA (ROA) over 10.7 years.

Methods: 1,099 participants (mean age 63 years) from a population-based older adult cohort study were recruited at baseline. 875, 768 and 563 participants attended years 2.6, 5.1 and 10.7 follow-up, respectively. Data were collected on demographic, psychological, lifestyle and comorbidities, blood pressure, glucose, triglycerides, and high-density lipoprotein (HDL) cholesterol. MetS was defined based on National Cholesterol Education Program-Adult Treatment Panel III criteria. ROA was assessed by X-ray. Knee pain was measured by Western Ontario and McMaster Universities Osteoarthritis Index pain questionnaire at each time-point. Presence/absence of pain at the neck, back, hands, shoulders, hips, knees and feet was collected by questionnaire at each time-point. Group-based trajectory modelling was applied to identify pain trajectories. Multi-nominal logistic regression was used for the analyses.

Results: 60% of participants had ROA and 32% had MetS at baseline. Three pain severity trajectories were identified in those with ROA: 'Marginal pain' (50%), 'Mild pain' (35%) and 'Moderate pain' (15%). Three NPS trajectories were identified: 'Low NPS' (10%), 'Medium NPS' (38%), and 'High NPS' (52%). In univariate analyses, MetS was associated with increased risk of both 'Mild pain' (relative risk: 1.47, 95%CI: 1.10–1.96) and 'Moderate pain' (2.22, 95%CI 1.54–3.20) relative to 'Marginal pain'. It was also associated with increased risk of both 'Medium NPS' (2.25, 1.11 to 4.54) and 'High NPS' (3.36, 1.70–6.63) compared to 'Low NPS'. In multivariable analyses, abdominal obesity was associated with increased risk of both 'Mild pain' (1.70, 1.17–2.49) and 'Moderate pain' (2.75, 1.63–4.64), and MetS and low HDL were associated with 'Moderate pain'. Abdominal obesity was the only component associated with increased risk of both 'Medium NPS' (2.82, 1.39–5.70) and 'High NPS' (3.60, 1.79–7.24), and MetS was only associated with increased risk of

'High NPS'. However, these associations became non-significant after further adjustment for body mass index, but hypertension became protective with 'Mild pain'.

Conclusion: MetS is predominantly associated with trajectories of pain severity and number of painful sites through abdominal obesity, suggesting that weight loss is the most important way of controlling OA pain.

Disclosure: F. Pan, None; J. Tian, None; F. Cicuttini, None; G. Jones, None.

Abstract Number: 456

Effect of Local and Systemic CCR2 Blockade on Knee Hyperalgesia in a Mouse Model of Osteoarthritis

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Session Information

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Session Title: Pain Mechanisms – Basic and Clinical Science Poster

Session Type: ACR Poster Session A

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

Background/Purpose: Surgical destabilization of the medial meniscus (DMM) in the mouse knee results in slowly progressive osteoarthritis (OA), characterized by moderate joint damage by week 8 and severe joint damage by week 16 after surgery. Progressive joint damage is associated with pain-related behaviors, including knee hyperalgesia and mechanical allodynia in the ipsilateral hindpaw (Miller RE et al. PNAS, 2012).

Knee hyperalgesia occurs in the early stages of experimental OA, week 2-8 after DMM surgery (Miller RE et al. Arthr Rheum 2017). We have previously shown that C-C Chemokine Receptor 2 (CCR2) signaling plays a key role in persistence of mechanical allodynia in this model, but has no effect on joint damage (Miller RE et al. PNAS, 2012). Here, we aimed to assess the effect of CCR2 blockade on knee hyperalgesia in the early phase of the disease.

Methods: DMM or sham surgery was performed on the right knee of 10-week old male C57BL/6 wild type (WT) or *Ccr2* null mice. Two, 4, and 8 weeks after surgery (n= 4-12/time point), knee hyperalgesia was measured by Pressure Application Measurement (PAM), as described (Miller RE et al. Arthr Rheum, 2017).

To study the effect of systemic pharmacological blockade of CCR2, CCR2 antagonist (5mg/kg) (CCR2RA, RS504393, Tocris) or vehicle control (100% DMSO₄) was injected intraperitoneally (i.p.), 4 or 8 weeks after surgery in WT mice. Knee hyperalgesia was assessed hourly for 3 hours after injection.

To study the effect of local CCR2 blockade in the knee, 5µL of CCR2RA (0.4mg/kg) (BMS CCR2 22, RD Systems) (n=4) or 5µL of vehicle control (50% EtOH) (n=3) were injected intra-articularly (IA) 7 weeks after DMM surgery in WT mice. Knee hyperalgesia was measured hourly for 4 hours.

In addition, MCP-1 (5µL of 100ng/µL), the ligand for CCR2, or vehicle control (5µL PBS in 0.1% BSA) were injected IA in the right knee of 10-week old naïve WT and *Ccr2* null mice (n=4/group), and knee hyperalgesia was assessed up to 24 hours after injection.

Results: WT mice developed knee hyperalgesia 2 weeks after DMM but not sham surgery, and this was maintained until week 8. In contrast, *Ccr2* null DMM mice were protected from hyperalgesia up to week 8 (p<0.0001 at week 2, 4, and 8). Systemically administered CCR2RA alleviated established hyperalgesia in WT mice, 4 and 8 weeks after DMM (p<0.0001 compared to vehicle). Likewise, IA injection of CCR2RA into the knee joint 7 weeks after DMM reversed hyperalgesia (p<0.05 compared to vehicle).

IA administration of MCP-1, but not vehicle, rapidly induced knee hyperalgesia in naïve WT mice (p<0.001 compared to vehicle control), but not in *Ccr2* null mice.

Conclusion: These findings suggest a role for MCP1-CCR2 signaling in the development of knee hyperalgesia after DMM surgery. Furthermore, the findings with IA injection of MCP-1 or CCR2RA suggest that the effect is mediated by CCR2 present in the intra-articular space and that CCR2 is important for early OA knee pain.

Disclosure: S. Ishihara, None; R. E. Miller, None; R. J. Miller, None; A. M. Malfait, None.

Neuropathic Pain in Patients with Knee Osteoarthritis (Preliminary Report)

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pain Mechanisms – Basic and Clinical Science Poster – ARHP

Session Type: ACR Poster Session A

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

Background/Purpose: There are limited studies in the literature indicating that neuropathic pain occurs in knee osteoarthritis (OA) (1). The aim of this cross sectional study was to evaluate frequency of neuropathic pain in knee OA patients and to determine the relation with disease variables.

Methods: Twenty knee OA patients who were not having any comorbid disease and/or using drugs that would cause neuropathy, were recruited to the study. Demographic properties (age, sex, disease duration) and clinical characteristics (functional status by WOMAC and pain intensity by VAS) recorded. The neuropathic property of knee pain was assessed by both LANSS and DN4 scales. Descriptive statistics was used for clinical variables and frequency of neuropathic pain. The difference of clinical variables between patients with and without neuropathic pain, were examined using t tests and chi square tests for continuous and categorical variables respectively. Correlation coefficients of clinical variables and neuropathic pain scores determined by LANSS and DN4, were analyzed with Spearman correlation analyses. The significance threshold was set as p values less than 0.05.

Results: Twenty knee OA patients (11 female, 9male) with a mean age of 55±18 years were included to the study. 11 patients (55%) were defined as having neuropathic pain depending on the LANSS (scores≥12) and DN4 (scores≥4) questionnaire scores. The mean scores of LANSS scale and DN4 were correlated with WOMAC scores

Conclusion: In conclusion neuropathic pain may be common in knee OA patients. Diagnosis and treatment of neuropathic pain are warranted in order to increase functional disability in patients suffering from knee OA.

References :

1. Dimitroulas T, Duarte RV, Behura A3, Kitas GD, Raphael Neuropathic pain in osteoarthritis: a review of pathophysiological mechanisms and implications for treatment. *Semin Arthritis Rheum.* 2014 Oct;44(2):145-54.

Disclosure: P. Borman, None; F. Kaygisiz, None; A. Yaman, None.

Validation of the 2012 Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria Compared to the 1997 Acr Criteria and 2017 Candidate Weighted Criteria for Lupus in Pediatric Patients

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – Clinical Poster I: Lupus, Sjögren's Disease, and Myositis

Session Type: ACR Poster Session A

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

Background/Purpose: Different classification criteria for systemic lupus erythematosus (SLE) have been proposed over many years. The most widely used and accepted criteria have been the 1997 ACR criteria. In 2012, the SLICC criteria were published in an attempt to improve clinical relevance of SLE criteria and address concerns with the 1997 ACR

criteria. In 2017, a new candidate weighted criteria were proposed at the ACR meeting that included entry criteria. Our aim was to validate the 2012 SLICC criteria compared to 1997 ACR and 2017 weighted criteria for SLE in pediatric-onset SLE.

Methods: Retrospective chart review of patients with a clinical diagnosis of SLE diagnosed before the age of 19 years at our tertiary care center between 2002 and 2017. The ACR and SLICC classification criteria were applied to these patients. The 2017 weighted criteria were also applied for patients diagnosed after October 2014 as this was the date our laboratory began using the ANA Hep2 assay, which is an entry criterion for the new weighted criteria. We excluded patients diagnosed at another center and those for whom no records were available for review. All criteria sets were compared against a gold standard of physician diagnosis. Autoimmune controls were defined as patients who were referred for serologies positive for ANA but who did not fulfill criteria for diagnosis of SLE at the initial visit, or were diagnosed with another autoimmune disease.

Results: There were 150 patients (82% female) who were diagnosed with SLE over the past 15 years. The mean age at diagnosis was 13 ± 2.7 years, with 23% Asian, 28% Black, 26% White, and 26% Caucasian, and 23% Other; 24% also identified as Hispanic. The sensitivity for the 1997 ACR criteria was 90.3 (CI: 0.84-0.95) and specificity was 95.9 (CI: 0.90-0.99). The sensitivity for the 2012 SLICC criteria was 99.3 (CI: 0.96-0.99) and specificity was 95.7 (CI: 0.90-0.99). The 2017 weighted criteria did not produce significant results as the patient sample size compared was too small.

Conclusion: The 2012 SLICC criteria were more sensitive than, but with similar specificity as, the 1997 ACR criteria. These findings are comparable with the observed statistics seen in the adult population. Further patient samples are needed to determine the test characteristics for the new weighted candidate criteria.

Disclosure: M. Ma, None; J. Cerise, None; B. A. Eberhard, None; J. Hui-Yuen, None.

Abstract Number: 459

Readmission Rate within 30 Days of Hospitalization Due to New Onset Lupus Nephritis and Associated Risk Factors: The Importance of Intravenous Pulse Methylprednisolone Therapy

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – Clinical Poster I: Lupus, Sjögren's Disease, and Myositis

Session Type: ACR Poster Session A

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

Background/Purpose: There is a paucity of data regarding the early hospital readmission rates in newly diagnosed childhood lupus nephritis (cLN). We conducted a retrospective study to characterize the early hospital readmission rates in cLN and identify risk factors associated with these readmissions.

Methods: 76 cLN cases evaluated from 1/1/2008 to 4/2/2017 were included in the study. The readmission rate within 30 days following a hospitalization due to newly diagnosed cLN was calculated. The characteristics of the early readmitted cases were compared with those of whom were not early readmitted using chi-square, fisher exact test, independent t-test or Mann-Whitney U tests as appropriate; variables with a P-value <0.10 were included in a multivariable analysis using stepwise linear logistic regression.

Results: The 30-day readmission rate following hospitalization for cLN was 1 per 5.8 admissions (17.1%). Clinical characteristics of these cases are listed in tables 1, 2 and 3. Not receiving pulsed methylprednisolone (30.8% vs 3.2%, $p < 0.001$), stage 2 hypertension on day 1 (76.9% vs 41.3%, $p = 0.019$), higher white blood cell count on admission ($5.7 \times 10^3/\text{mm}^3$ vs $5.0 \times 10^3/\text{mm}^3$, $p = 0.022$) and at discharge ($13.7 \times 10^3/\text{mm}^3$ vs $8.8 \times 10^3/\text{mm}^3$, $p = 0.23$), diuretic treatment (69.2% vs 34.9%, $p = 0.021$), anti-hypertensives other than angiotensin-converting enzyme inhibitors (76.9% vs 49%, $p = 0.042$) and albumin infusions (46.2% vs 12.7%, $p = 0.004$) predicted early readmission in univariable analysis. In multivariable analysis the absence of treatment with pulsed methylprednisolone was a risk factor for early readmission (OR=21.4 (2.89-158.82) $p = 0.002$) whereas not receiving intravenous albumin had a protective effect (OR=0.12 (0.026-0.51) $p = 0.004$).

Conclusion: One in 5.8 children (17.1%) hospitalized for newly diagnosed cLN were readmitted within 30 days of discharge. Not receiving pulsed steroids and receiving intravenous albumin on admission increased the risk of hospital readmission in newly diagnosed cLN.

Table 1.-Distribution of nephritis classes between groups. ERG: Early readmitted group, NERG: Not early readmitted group. P value=0.151

Nephritis class	All lupus nephritis patients (n/%)	ERG (n/%)	NERG (n/%)
I	1 /1.3	0/0	1/1.6
II	5/ 6.6	0/0	5/7.9
III	9/11.8	0/0	9/14.3
III/V	5/6.6	0/0	5/7.9
IV	27/35.5	6/46.2	21/33.3
IV/V	20/26.3	3/23	17/27
V	9/11.8	4/30.8	5/7.9

Variable	Patients with lupus nephritis	ERG	NERG	P value
Number of patients	76	13	63	
Age (years) ^a	14.2 (11.6-15.9)	13.9 (11.5 - 15.2)	14.3 (11.9 - 16.0)	0.793
Length of stay (days) ^a	6 (3.25-9.0)	7.0 (4.0-9.0)	6.0 (3.0-9.0)	0.608
Gender (n/%)	.	.	.	0.040
Female	62/81.6	8/61.5	54/85.7	
Male	14/18.4	5/38.5	9/14.3	
Ethnicity (n/%)	.	.	.	0.622
African American	47/61.8	8/61.5	39/61.9	
White	9/11.8	1/7.7	8/12.7	
Hispanic	15/19.7	4/30.8	11/17.5	
Asian	3/3.9	0/0	3 /4.8	
Other	2/2.6	0 /0	2 /3.1	
Insurance (n/%)	.	.	.	0.574
Medicaid	44/57.9	9/69.2	35/55.5	
Private insurance	28/36.8	4/30.8	24/38.1	
Tricare insurance	3/3.9	0/0	3 /4.8	
None	1/1.3	0/0	1/ 1.6	

Table 2. - Demographic and health insurance coverage characteristics. . ERG: Early readmitted group, NERG: Not early readmitted group.

^aMedian and interquartile ranges.

Variable	Total (n=76)	ER (n=13)	NER (n=63)	P
Stage 2 HTN on admission (n/%)	36/47.36	10/76.9	26/41.3	0.019
Treated with Pulsed MPN (n/%)	70/92.1	9/69.2	61/96.8	0.007
Treated with albumin infusion (n/%)	14/18.34	6/46.2	8/12.7	0.011
Treated with diuretics (n/%)	31/40.78	9/69.2	22/34.9	0.022
Treated with Non-ACE anti-HTN (n/%)	39/51.31	10/76.9	29/46	0.042
WBC on admission (x 10 ³ /mm ³)	5.0 (3.7-7.2)	5.7 (4.1-9.1)	5.0 (3.4-6.6)	0.022
WBC on discharge (x 10 ³ /mm ³)	9.2 (6.6-14.6)	13.7 (9.2-16.4)	8.830 (6.0-13.9)	0.023
Discharged on NSAID	6 (7.9%)	3 (23.1%)	3 (4.8%)	0.059
Lymphocyte count (x 10 ³ /mm ³)	1.3 (0.9-1.9)	1.3 (1.2-2.3)	1.2 (0.7-1.7)	0.074
Serum albumin (g/dL)*	2.2 ± 0.6	1.9 ± 0.6	2.2 ± 0.5	0.099
New lupus diagnosis (n/%)	35/46.1	9/69.2	26/41.3	0.066
Arthritis (n/%)	29/38.2	7/53.8	22/34.9	0.224
Cutaneous involvement (n/%)	42/55.3	7/53.8	35/55.6	0.910
Mucosal involvement (n/%)	16/21.1	3/23.1	13/20.6	1
Neurologic involvement (n/%)	7/9.2	0/0	7/11.1	0.596
Pericarditis (n/%)	24/31.5	7/53.8	17/27	0.155
Pleuritis (n/%)	31/40.7	6/46.2	25/39.7	0.443
Ascites (n/%)	13/17.1	2/15.4	11/17.5	0.682
Anasarca (n/%)	15/19.7	4/30.8	11/17.5	0.273
BMI (percentile)	75.3 (44.3-88.7)	73.1 (45.9-88.1)	76.6 (43.5-89)	0.896
Weight change at discharge (Kg.)	-0.1 (-1.1 to +1.8)	-0.9 (-2.9 to 1.3)	0 (-0.8 to 2)	0.245
Treated with cyclophosphamide (n/%)	39/51.3	9/69.2	30/47.6	0.156
Treated with mycophenolic acid (n/%)	21/27.6	3/23.1	18/28.6	1
Treated with HXQ (n/%)	43/56.6	5/38.5	38/60.3	0.148
ACE inhibitor on discharge (n/%)	26/34.2	3/23.1	23/36.5	0.524
Hemoglobin (g/dL)*	10.4 ± 1.9	10.4 ± 2.0	10.3 ± 1.9	0.895
Platelet count (x 10 ³ /mm ³)*	251.5 ± 124.6	217.8 ± 99.8	258.5 ± 128.7	0.287
ESR (mm/hr)*	88.3 ± 38.4	88.7 ± 38.8	88.3 ± 38.7	0.969
Serum creatinine (mg/dL)	0.9 (0.7-1.5)	1 (0.6-1.45)	0.9 (0.7-1.5)	0.983
EGFR (ml/min/1.73 m2) *	69.4 ± 35.5	64 ± 27.2	70.5 ± 37.1	0.550
AKI on admission (n/%)	49/64.5	9/69.2	40/63.5	0.762
UPCR (mg/mg)	2.89 (1.17-4.96)	4.22 (1.50-5.49)	2.68 (1.16-4.96)	0.481
C3 (mg/dL)	39 (22-54.5)	30 (20-62.5)	39 (23-53)	0.994

Table . (Cont'd)

Variable	Total (n=76)	ER (n=13)	NER (n=63)	P
C4 (mg/dL)	5 (3-9.25)	5 (3.5-19.5)	5 (3-8)	0.403
Days between discharge and readmission	49.5 (15.5-255.5)	12 (5-18)	132 (35-318)	<0.001
Days between SLE DX and nephritis DX	5.5 (2-45.25)	1 (-0.5-21.5)	1 (0-18)	0.127
Days between nephritis symptoms onset and biopsy	19 (8-43)	18 (10-61)	19 (17.7-37.7)	0.726
SLEDAI-2K	22 (19-29)	22.0 (19.0 - 29.5)	23.0 (19.0 - 9.0)	0.837
SLEDAI-renal	12 (8-12)	12 (8-12)	12 (8-12)	0.897
NIH Activity index (0-24)	6 (2.75-11)	6 (1.5-11)	6 (2.5-11)	0.678
NIH Chronicity index (0-12)	1 (0-4)	1 (0-4)	1 (0-3.5)	0.970
Admitted to PICU (n/%)	12/15.8	1/7.7	11/17.5	0.679

Table 3. - Clinical and laboratory characteristics of patients admitted with a new diagnosed of lupus nephritis. Values represent number and percentage, median and interquartile range or mean \pm SD BMI: Body mass index, HXQ: Hydroxychloroquine, ACE: Angiotensin-converting enzyme, EGFR: Estimated glomerular filtration rate, AKI: Acute kidney injury defined as EGFR < 80 ml/min/1.73 m², UPCR: Urine protein: creatinine ratio in spotted urine, DX: Diagnosis, SLEDAI-2K: SLE disease activity index 2000, NIH: National Institute of Health, PICU: Pediatric intensive care unit.

Disclosure: A. A. Herrera Guerra, None; S. Prahalad, None; K. A. Rouster-Stevens, None; R. Garro, None; L. Bryan, None; Y. Hong, None.

Abstract Number: 460

Immunomodulatory Medication Use for Youth with Newly-Diagnosed Systemic Lupus Erythematosus

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – Clinical Poster I: Lupus, Sjögren's Disease, and Myositis

Session Type: ACR Poster Session A

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

Background/Purpose: To examine immunomodulatory medication use for youth with systemic lupus erythematosus (SLE) during their first year of care.

Methods: We conducted a retrospective cohort study using administrative claims for 2000 to 2013 from Clinformatics™ DataMart (OptumInsight, Eden Prairie, MN) for youth ages 10-24 years with an incident diagnosis of SLE (≥ 3 International Classification of Diseases, Ninth Revision codes for SLE 710.0, each >30 days apart). We determined the proportion of subjects filling a prescription for an immunomodulatory medication, defined as hydroxychloroquine or an immunosuppressant (excluding glucocorticoids), within 3, 6, and 12 months after the first SLE diagnosis code (index date). We used a Cox proportional hazards regression model to examine associations between time to immunomodulatory prescription fill within 12 months and demographic and disease factors (age, race/ethnicity, household education level, region, history of seizures/stroke, history nephritis).

Results: We identified 650 youth with an incident diagnosis of SLE. In the 12 months following the index date, 511 (79%) of youth had a prescription fill for an immunomodulatory medication. For those with a prescription fill for hydroxychloroquine in the first year (n=457, 70%), 374 (58%) and 407 (63%) of youth filled the medication within 3 months and 6 months from the index date, respectively (Table). For those with a prescription fill for an immunosuppressant (n=221, 34%) in the first year, 114 (18%) and 162 (25%) of youth filled the medication within 3 months and 6 months from the index date, respectively (Table). Location in the Northeast region was significantly associated with a longer time to immunomodulatory prescription fill within 12 months, compared to location in the South (HR=0.69, 95% CI 0.50-0.94). There were no statistically significant associations for the other demographic and disease factors.

Conclusion: Among youth with newly-diagnosed SLE, hydroxychloroquine use is prevalent although not universal, and immunosuppressant use is notably low during the first year of care. As poorly controlled SLE disease activity can lead to organ damage, further work is needed to identify potential factors contributing to suboptimal immunomodulatory medication use in this population.

Table: Immunomodulatory Medication Use in Youth with Newly-Diagnosed SLE, N=650

Proportion with prescription fills after first SLE diagnosis code, n (%)	Within 3 months	Within 6 months	Within 1 year
Immunomodulatory medication (hydroxychloroquine or immunosuppressant)	428 (66)	460 (71)	511 (78)
Hydroxychloroquine	374 (58)	407 (63)	457 (70)
Immunosuppressant	114 (18)	162 (25)	221 (34)
Immunosuppressant medications include: mycophenolate mofetil, azathioprine, leflunomide, methotrexate, tacrolimus, and oral cyclophosphamide.			

Disclosure: A. M. Davis, None; M. S. Klein-Gitelman, None; J. Faerber, None; H. Katcoff, None; Z. Cidav, None; D. Mandell, None; A. M. Knight, None.

Abstract Number: 461

Ofatumumab Use in Childhood-Onset Systemic Lupus Erythematosus: A Single-Center Experience

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – Clinical Poster I: Lupus, Sjögren's Disease, and Myositis

Session Type: ACR Poster Session A

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

Background/Purpose: Ofatumumab is a fully human anti-CD20 monoclonal antibody that has been approved for the treatment of chronic lymphocytic leukemia. It has been increasingly used in the treatment of autoimmune hemolytic anemia, rheumatoid arthritis, and nephrotic syndrome. There are limited case series reporting the off-label use of ofatumumab in SLE, with minimal data in childhood-onset SLE (cSLE). In majority of these reports, ofatumumab was used as alternative B-cell depletion therapy for patients who have become intolerant of rituximab due to development of severe infusion reactions. We describe our center's experience with the use of ofatumumab in cSLE patients who have become rituximab-intolerant.

Methods: A retrospective case series analysis of cSLE patients who met the ACR classification criteria for SLE and who received ofatumumab at our center was completed after IRB approval. Collected data include patient demographics, clinical presentation and course, medications, prior use of and reaction to rituximab, and response to ofatumumab therapy.

Results: Nine patients were included (females: 6, Hispanic ethnicity: 5, African-American: 3, Asian: 1). At the time of the first ofatumumab infusion, median age was 16 years (range: 11-18) and median disease duration was 39.6 months (16.2-139). All patients had received rituximab (median cumulative dose: 3g [0.5-9], median number of infusions received: 3 [0.5-13]) and developed severe infusion reactions precluding retreatment. Significant combination immunomodulatory therapy was also received pre-ofatumumab: plasmapheresis in 3 patients, cyclophosphamide in 2, IVIG in 3, mycophenolate mofetil in all 9, and cyclosporine in 1. Indications for ofatumumab included renal flare in 6 patients, extrarenal flare in 2, and both renal and extrarenal flare in 1. Ofatumumab (median cumulative dose: 1g [0.3-2.9], median number of infusions received: 2 [1-4]) was well-tolerated in all 9 patients. Within 6 months post-ofatumumab, partial renal response was achieved in 5 of 7 patients with renal flare. Clinical improvement was noted in all. B-cell depletion was achieved in 7 patients who were tested 3 months post-ofatumumab. In 5 patients tested, median B-cell repletion time was 6 months (range: 4-12). Three patients received a second course of ofatumumab within a median time of 18 months (5-19) due to disease flare. Two patients developed serious adverse events: 1 had septic shock 3.5 months after ofatumumab (only received one dose due to early B-cell depletion; also had significant prior immunomodulatory therapy) and 1 had an anaphylactic reaction after the third ofatumumab dose (previously also developed anaphylaxis after first rituximab infusion).

Conclusion: In this retrospective review we describe our center's experience with the use of ofatumumab in nine patients with childhood-onset SLE who had become intolerant of rituximab due to severe infusion reactions. Our patient outcomes

suggest that ofatumumab is a safe and well-tolerated alternative therapy to rituximab. Further studies in a larger cohort are warranted to determine long-term safety, efficacy, and the appropriate dosing regimen in cSLE patients.

Disclosure: A. C. Sagcal-Gironella, None; E. Muscal, None; A. A. Ramirez, None; M. Marcus, None; M. Gillispie, None; W. B. Lapin, None; M. M. De Guzman, None.

Abstract Number: 462

Steroid Use in Pediatric Proliferative Lupus Nephritis

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – Clinical Poster I: Lupus, Sjögren's Disease, and Myositis

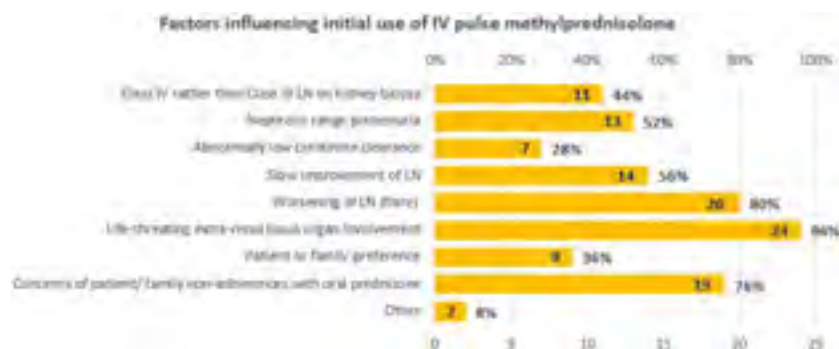
Session Type: ACR Poster Session A

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

Background/Purpose: Corticosteroids (CS) are the mainstay of childhood-onset lupus (cSLE) and proliferative lupus nephritis (LN) therapy. However, there are no widely accepted CS dosing regimens for LN. We aim to identify the CS treatment approaches employed by providers for newly diagnosed pediatric proliferative LN in response to common and challenging clinical scenarios.

Methods: Pediatric rheumatologists and nephrologists attending the 2018 Childhood Arthritis and Rheumatology Research Alliance (CARRA) meeting participated in a working group addressing CS use in newly diagnosed pediatric LN. Participants responded to 3 scenarios in live polling and 12 questions of CS management in small groups. A post meeting survey was sent to each participant.

Results: In total, 51 physicians participated in the working group and 25 answered the survey. Of the 51 participants, 42 (82%) reported prednisone to be the oral CS of choice to treat newly diagnosed pediatric LN and 64.7% favored liquid prednisolone if swallowing pills is problematic. Once daily dosing was the preferred regimen (15/25, 60%) to help patients with adherence. Some (8/25, 32%) use a twice daily regimen for prednisone doses >2mg/kg/day or 60mg. A 3-4 times daily regimen was considered for hospitalized patients with severe disease manifestations by 6/25, 24%. Factors leading to the use of intravenous (IV) pulse methylprednisolone during the initial 12 months of therapy for proliferative LN are shown in Figure 1. Laboratory results prompting a CS dose change are shown in Table 1 (Panels A/B). Side effects such as weight



Panel A. Which laboratory results would cause you to start decreasing (or tapering) corticosteroids in your patient with proliferative LN?					
	Normal	>50% improvement	25-50% improvement	Any improvement	Not important for my decision
Complement C3 and C4	3 (12%)	5 (20%)	4 (16%)	9 (36%)	4 (16%)
Anti-dsDNA antibodies	2 (8%)	4 (16%)	4 (16%)	9 (36%)	8 (32%)
Proteinuria	0 (0%)	7 (28%)	7 (28%)	8 (32%)	3 (12%)
ESR	1 (4%)	2 (8%)	4 (16%)	8 (32%)	10 (40%)
Urinary cellular casts	3 (12%)	5 (20%)	1 (4%)	5 (20%)	11 (44%)

Panel B. Which changes in laboratory tests would cause you to increase corticosteroid doses in your patient with proliferative LN during the initial 12 months of therapy?					
	Newly abnormal	>50% worsening	25-50% worsening	Any worsening	Not important for my decision
Complement C3 and C4	4 (16%)	7 (28%)	10 (40%)	1 (4%)	3 (12%)
Anti-dsDNA antibodies	5 (20%)	3 (12%)	8 (32%)	1 (4%)	8 (32%)
Proteinuria	0 (0%)	10 (40%)	11 (44%)	2 (8%)	2 (8%)
ESR	2 (8%)	4 (16%)	4 (16%)	1 (4%)	14 (56%)
Urinary cellular casts	5 (20%)	3 (12%)	3 (12%)	9 (36%)	5 (20%)

gain (20/25, 80%), difficult to control blood pressure (19/25, 76%) or hyperglycemia (21/25, 84%) were reported as reasons to taper CS. In patients with inactive LN on mycophenolate mofetil, the extra-renal features that prompt an increase in CS are new/worsening neuropsychiatric disease (24/25, 96%), cardiac (23/25, 92%), or pulmonary involvement (23/25, 92%). In cases of non-adherence, all physicians would discuss reasons for non-adherence with 72% choosing to start/increase the frequency of IV steroids.

Conclusion: Prescribed CS dosing regimens vary widely in the U.S. when used for the treatment of children with proliferative LN. Decisions on initial CS dosing regimens and subsequent management strategies remain provider dependent.

Figure 1.

Table 1.

Disclosure: N. Chalhoub, None; J. Deng, None; N. M. Ruth, None; S. P. Ardoin, None; M. Gilbert, None; T. Hennard, None; L. Hiraki, None; P. T. Jensen, None; A. M. Knight, None; R. Kunder, Gilead Sciences, Inc, 3; L. Lewandowski, None; S. H. L. Lim, None; A. Merritt, None; S. I. Savani, None; M. B. Son, None; E. von Scheven, None; S. E. Wenderfer, None; H. I. Brunner, None.

Abstract Number: 463

Percentage of Glomerular Crescents Predicts Renal Outcomes in Childhood-Onset Lupus Nephritis

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Session Information

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Background/Purpose: Outcomes for childhood-onset crescentic lupus nephritis are unclear. The revised classification system for lupus nephritis by the Renal Pathology Society clearly distinguishes between cellular, fibrocellular, and fibrous crescents. A revised activity index includes cellular and fibrocellular crescents and uses thresholds of 25% and 50% glomerular involvement to distinguish between mild, moderate, and severe. The revised chronicity index includes scores for <25%, 25-50% and >50% fibrous crescents.

Methods: The objective was to test the validity of the 25% and 50% thresholds for crescentic involvement in childhood-onset crescentic LN. We identified 69 patients in the Midwest Pediatric Nephrology Consortium's pediatric glomerulonephritis with crescents registry (21% of total). Enrollment in the retrospective IRB-approved registry includes patients <21 years old with >1 crescentic glomerulus on kidney biopsy from 15 centers from 2004-16 with at least 1 year of follow-up data. All biopsies sampled from >10 glomeruli. The primary outcome was end stage kidney disease (ESKD) at 1 year. Secondary outcomes included estimated glomerular filtration rate (eGFR) at 1 year and change in eGFR over time. Crescents were defined as cellular/fibrocellular or fibrous based on local pathologist.

Results: The median age at time of biopsy was 14.0 years (range 6-20) and median follow up was 3.0 years (range 1-11.3). A median of 27 glomeruli were sampled per biopsy (IQR 19-35). The median percentage of cellular crescents was 16.4% (IQR 10-38%, max 96%) and fibrous crescents was 0% (IQR 0-5%, max 56%). The cumulative incidence of ESKD was 1.5% at one year and 9% (n=6 patients) at last follow up. Median time to ESKD was 27.6 months (range 5-131). Outcomes stratified well by both percentage of cellular glomerular crescents and by percentage of fibrous crescents (Table 1). Median change in eGFR was +18mL/1.73m²/min (IQR -7 to +42) at 1 year and -3.1 mL/min/1.73m²/year (IQR -16 to +6) at latest follow-up. There were only three subjects with >25% fibrous crescents and only one with >50%.

Cellular crescents	#	Renal survival	eGFR at biopsy	Δ eGFR/yr	Follow-up (yr)
<25%	42	100%	67 (50-105)	+2.8	3.2
25-50%	15	93%	58 (46-81)	+4.5	2.7
>50%	11	82%	30 (19-51)	+8.8	1.8
Fibrous crescents	#	Renal survival	eGFR at 1year	Δ eGFR/yr	Follow-up (yr)
<25%	64	92%	92 (74-100)	+3.2	3.0
<10%	57	93%	93 (78-102)	+2.7	3.0
None	45	91%	92 (74-102)	+3.2	3.0
>1	23	91%	92 (81-100)	+2.8	2.8
>10%	10	80%	69 (28-91)	-2.4	3.8
>25%	3	67%	52 (26-79)	-15.4	2.3

Conclusion: We show utility for the thresholds for cellular crescents used in the 2018 revised NIH activity index in children with lupus nephritis. For fibrous crescents, thresholds of 10% and 25% better discriminate renal outcomes. We propose inclusion of a pediatric arm for future studies intended to generate evidence-based definitions for classification of lupus nephritis.

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Abstract Number: 464

The Long Term Outcomes in Chinese Children Diagnosed with Systemic Lupus Erythematosus and Biopsy Proven Lupus Nephritis – a 18-Year Cohort

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – Clinical Poster I: Lupus, Sjögren's Disease, and Myositis

Session Type: ACR Poster Session A

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

Background/Purpose: Renal disease occurs in 50-70% of all childhood onset systemic lupus erythematosus (cSLE). The prevalence of LN is higher in children and the manifestations are usually more severe than the adult counterparts. Yet there are few reports on long term outcomes in cSLE patients with LN. This study aimed to study long-term outcomes in Chinese cSLE patients with biopsy proven LN.

Methods: We completed retrospective chart reviews of all patients diagnosed and followed with SLE and biopsy proven LN from Jan 2000 to Feb 2018 in 3 regional hospitals in Hong Kong. All the patients met either the ACR or SLICC classification criteria (after year 2012) for SLE. Patients with LN were classified according to WHO criteria or INS/RPS criteria (after year 2003). The outcomes including chronic kidney disease (CKD) stages, dialysis, renal transplant and death were retrieved from patient charts at 6 time points: the year of diagnosis (Y0), one year after diagnosis (Y1), Y5, Y10, Y15 and last follow up (Y last) of patients.

Results: Our cohort included 104 cSLE patients with biopsy proven LN (Table 1). Majority (85.6%) had LN diagnosed within 2 years of SLE diagnosis. Thirty-two patients had second renal biopsies. None of the Class V LN transformed to proliferative LN in their second renal biopsies and 9 (28.1%) transformed from non-proliferative to proliferative LN with a mean of 5.87 years from the 1st to 2nd renal biopsy. There were total 144 biopsies in the study cohort period. Cyclophosphamide (CYC) was used as induction therapy in 38/99 (38.38%) of proliferative LN (Class III/IV +/- V) episodes in 36 patients vs Mycophenolate mofetil (MMF) in 28/99 (28.3%) episodes in 28 patients. Three patients required transient dialysis during the course and none required long term dialysis. Two patients had renal transplant and 5 patients died. The outcomes of death and renal transplant are worst in patients with proliferative LN without using either CYC or MMF as induction therapy and are best in non-proliferative LN as expected (Table 2 and 3).

Conclusion: The renal outcome of LN in cSLE is suboptimal with close to 30% of patients have significant proteinuria and 18.2% have abnormal renal function (CKD stage 2 or above) at their last visit. Patients with non-proliferative LN have best outcomes followed by proliferative LN treated with CYC or MMF in the induction phase.

Table 1. Basic demographic and distribution of classes of LN

Feature	Value or count
Sex	
Male	Male 11 (10.6%)
Female	Female 93 (89.4%)
Mean/median age of diagnosis of SLE (years)	12.98/13 (IQR 5, SD 3.39)
Mean/median age of diagnosis of LN (years)	13.7/14.5 (IQR 4.75, SD 3.22)
Mean/median duration of follow up (years)	8.66/9 (IQR 7, SD 4.55)
Histologic class on first renal biopsy n (%)	
Total N = 104	
II	8 (7.69)
III	20 (19.23)
IV	35 (33.65)
V	8 (7.69)
II+III	5 (4.80)
II+V	11 (10.58)
III+V	10 (9.62)
IV+V	5 (4.81)
VI	1 (0.96)
Unable to classify	1 (0.96)
Histologic class on second renal biopsy n (%) Total N = 32	
II	1 (3.13)
III	5 (15.63)
IV	7 (21.88)
V	4 (12.5)
II+V	6 (18.75)
III+V	5 (15.63)
IV+V	4 (12.5)

Table 2. Outcome of non-proliferative and proliferative LN.

	Non-proliferative LN N = 20		Proliferative LN	
		CYC induction (per 100-patient years) N=36	MMF induction (per 100-patient years) N = 28	Non CYC or MMF (per 100-patient years) N=20
CKD stage \geq 4 at Y last	0	0.835	0.971	0
Nephrotic range of proteinuria at Y last	0.613	0.557	1.456	0
Transient dialysis	0	0.557	0	0.658
Renal transplant	0	0	0.485	*0.658
Death	0	0.835	0	1.316

* same patient with renal transplant

Table 3. Outcome at different time points.

CKD stage and degree of proteinuria	Y0 (n=104)	Y1 (n = 104)	Y5 (n=82)	Y10 (n = 44)	Y15 (n =16)	Y last (n = 99)
Normal (eGFR >90 ml/min/1.73m2)	55	86	69	31	9	81
2 (eGFR 60-89 ml/min/1.73m2)	25	13	8	6	1	12
3 (eGFR 30-59ml/min/7.73m2)	17	2	3	3	2	2
4 (eGFR 15-29 ml/min/1.73m2)	5	2	1	2	1	3
5 (eGFR <15 ml/min/1.73m2)	0	0	0	0	1	1
Significant proteinuria UPCr ratio >500mg/g but \leq 2000mg/g	35	25	13	7	4	23
Nephrotic proteinuria UPCr ratio >2000mg/g	60	6	3	4	1	6
Cumulative death	0	0	1 (censored)	2 (censored)	4 (censored)	5 (censored)
Cumulative renal transplant	0	0	1 (renal transplant at Y4)	1	2 (one renal transplant at Y 13)	2 (both alive at CKD stage 2)
Missing data	2	1	1	2	No	No

Y (n): number of year reference to the date of first renal biopsy which confirmed lupus nephritis e.g Y1: one year after diagnosis of LN; UP Cr ratio: Urine protein to creatinine ratio

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Abstract Number: 465

Seasonal Variation in Cutaneous Flares for Pediatric Lupus

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Session Information

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Session Title: Pediatric Rheumatology – Clinical Poster I: Lupus, Sjögren's Disease, and Myositis

Session Type: ACR Poster Session A

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

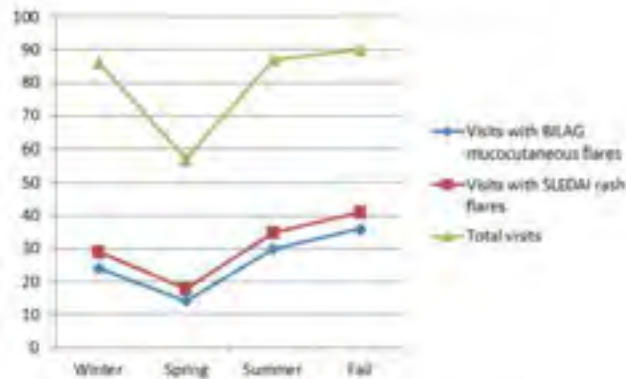
Background/Purpose: Exposure to sunlight has been proposed as a possible environmental trigger for lupus flares, particularly cutaneous disease. Contradictory findings exist regarding seasonal variation in cutaneous disease activity, with particular gaps in knowledge around pediatric and minority patient populations.

Our objectives for this study were to study the relationship between sun exposure and cutaneous lupus flares in a racially and ethnically diverse pediatric lupus population. Based on prior studies, we hypothesized that higher rates of cutaneous flares would be present in summer/fall compared to winter/spring seasons.

Methods: We retrospectively reviewed 12 years of data from patients enrolled in the Pediatric Einstein Lupus Cohort at the Children's Hospital at Montefiore from the Bronx, New York. We selected patients that had any history of mucocutaneous disease by indicated by BILAG scores of A-D, as opposed to E, at any point during follow up. We defined cutaneous flares by two methods: (1) mucocutaneous BILAG criteria A or B and (2) SLEDAI-2K inflammatory rash criteria. Chi-square tests were used to compare flare rates during summer/fall vs winter/spring and to compare flare rates during each season.

Results: We examined 320 visits for 90 individual patients. The average age of participants at included visits was 16.8 ± 3 years; 82% of patients were female; 52% were Hispanic and 43% Black. Among included visits, 33% had represented BILAG-mucocutaneous flares and 38% represented SLEDAI-rash flares. Total visits and flare visits were not evenly

Figure 1. Seasonal distribution of cutaneous flare visits and total visits in the Pediatric Einstein Lupus Cohort



distributed throughout the year; more total visits and more flare visits were observed during summer/fall (Figure 1). The rate of visits with BILAG-mucocutaneous flares was 37% in the summer/fall vs 27% in winter/spring ($p = 0.04$). The rate of visits with SLEDAI-rash flares was 43% in summer/fall vs 33% in winter/spring ($p = 0.05$) (Table 1). In contrast, there was no significant association between specific seasons and BILAG-mucocutaneous flares or SLEDAI-rash flares, though the highest flare rates were observed during fall (40%, 46% of visits, respectively).

Conclusion: Our results show a modestly increased rate of cutaneous flares during summer/fall months when compared with winter/spring months in a racially and ethnically diverse sample of children with SLE. More studies are needed to better understand the relationship between sun exposure and disease flare in minority race/ethnicities with pediatric lupus to inform disease activity prevention counseling.

Table 1. Rates of cutaneous flare in pediatric lupus patients

	Summer/Fall visits (N = 177)	Winter/Spring visits (N = 143)	p value:
Mucocutaneous flare visits by BILAG	66 (37%)	38 (27%)	0.04
Inflammatory rash flare by SLEDAI	76 (43%)	47 (33%)	0.05

Disclosure: T. Tanner, None; M. Dionizovik-Dimanovski, None; D. Wahezi, None; T. Rubinstein, None.

Abstract Number: 466

Improving Pneumococcal Vaccination Rates in Childhood-Onset SLE Patients at a Large Tertiary Care Center: The Path to Creating a More Sustainable Model of Vaccination with the Help of EMR

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – Clinical Poster I: Lupus, Sjögren's Disease, and Myositis

Session Type: ACR Poster Session A

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

Background/Purpose: *Streptococcus pneumonia* is a leading cause of illness in children worldwide and can lead to death in those with an immune suppressed status. Given the pathophysiology of systemic lupus and therapies needed to induce and maintain remission, these patients are more susceptible to pneumococcal infections compared to healthy counterparts. As recommended by the CDC/HHS, a simple preventative measure by immunization with the pneumococcal polysaccharide vaccine (PPSV23) is key in risk reduction for this population. The purpose of this QI initiative was multidimensional: first to increase pneumococcal vaccination rates in childhood-onset systemic lupus erythematosus (cSLE) patients at our institution and second to examine the effectiveness of various interventions to ensure continued vaccination success.

Methods: Initial undertaking for this QI project was started in summer 2015 with utilization of a plan-do-study-act model. Baseline immunization rates of PPSV23 for eligible patients were assessed through chart review. These included all

children ≥ 2 to <18 years old with cSLE (with and without immunosuppression) and were evaluated in rheumatology clinics within 6 months of the initial cycle. Interventions included a presentation to rheumatology providers and nurses, pre-visit planning and placing paper reminders on clinic schedules. Various interventions were analyzed based on chart review and provider feedback, which led to identification of barriers to successful vaccination.

Results: The pre-intervention to post-intervention PPSV23 immunization rates for 111 eligible cSLE patients increased from 4.5% to 47.1% during a 27-week cycle. Out of the patients who did not receive PPSV23, the reason was unknown in 70.2%, declined in 10.8%, and due to lack of follow up in rheumatology clinic during cycle 1 in 18.9%. Of the patients with an unknown status, 52.5% did not receive the vaccination due to lack of vaccination reminder and 47.4% of providers deferred vaccination to the next visit due to lack of time. The reason for a lack of vaccination reminder included changing clinic schedules (i.e. clinic add-ons) in 65.8% and oversight in 34.1%. All providers specified that they needed reminders in the patient's EMR rather than on paper, as this would also circumvent changing clinic schedules. To date, the total number of cSLE patients at our institution is 548 (aged 2 years to 18 years old). Since initiation of this project, 60.4% of cSLE patients have received the PPSV23 vaccine.

Conclusion: Our study shows that the main barrier to cSLE patient's receiving PPSV23 vaccination is provider oversight, lack of clinic time, and/or ineffective reminders. To increase vaccination success, a best practice advisory (BPA) alert in each cSLE patient's EMR is being created. Ongoing work has centered on developing BPA parameters regarding variables such as PPSV23 vaccination status, age, and prior vaccination with the PCV13, a prerequisite to receiving the PPSV23. We hope this work will reduce vaccine preventable illnesses that would otherwise consume provider time, resources and unnecessary health care costs.

Disclosure: S. Singla, None; M. M. De Guzman, None.

Abstract Number: 467

The Prevalence and Clinical Features of Co-Occurring Autoimmunity in Children with Systemic Lupus Erythematosus: The Childhood Arthritis and Rheumatology Research Alliance (CARRA) Legacy Registry

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Session Information

Session Date: Sunday, October 21, 2018

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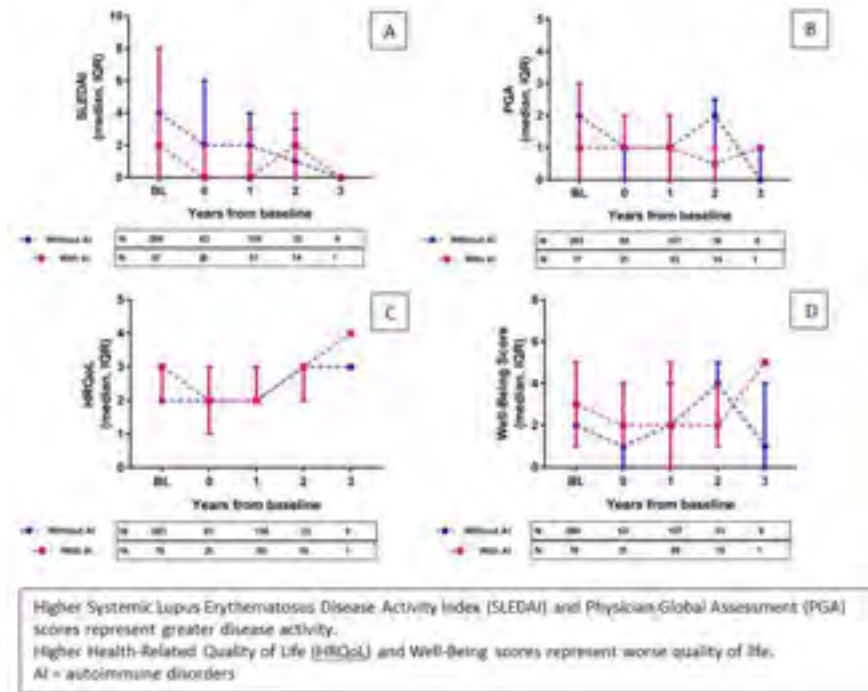
Session Time: 9:00AM-11:00AM

Background/Purpose: The co-occurrence of autoimmune disorders (AI) with systemic lupus erythematosus (SLE) in adults is associated with poor disease outcomes. We describe the co-occurrence of other AI in children with SLE (cSLE) and evaluate the relationship between comorbid AI and lupus disease outcomes using the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Legacy Registry.

Methods: The CARRA Legacy Registry is a multicenter prospective, observational, longitudinal database of children with defined rheumatic conditions including SLE. Subjects were enrolled from May 2010 through July 2014 at anytime during their disease course and data were collected at 6-month interval follow up visits from 60 clinical sites in the US and Canada. 1285 subjects met the American College of Rheumatology (ACR) 1997 criteria for SLE. We defined comorbid AI as the presence of any of the following diseases: Hashimoto's thyroiditis, Celiac disease and type 1 diabetes mellitus. Disease outcomes were assessed by measures of disease activity and impact on quality of life (QoL). Comparisons by AI status were made using chi-square, Fisher's exact, two-sample t-tests, Wilcoxon rank sum tests, and mixed effects models as appropriate.

Results: Data on the co-occurrence of AI were available in 388 (30%), unknown in 31 (2%), and missing in 866 (67%) at the baseline visit. The prevalence of comorbid AI was 20% (n=79). When comparing subjects with AI (n=79) to those without AI (n=309), subjects with AI were significantly younger at onset of lupus and had more 1st degree relatives with AI (Table 1). Subjects without AI had significantly more renal disease at the time of enrollment. During follow up visits, the average Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score over time was significantly lower among subjects without AI. There were no significant differences over time in the Physician Global Assessment (PGA) level of

Figure 1: Disease activity and quality of life over time based on comorbid autoimmune disorders



disease activity by comorbid AI. Overall, there were no significant differences in the QoL measures or their trajectory over time based on the presence of comorbid AI (Figure 1).

Conclusion: Among children with SLE, the co-occurrence of another AI is associated with younger age at presentation, but is not associated with poor disease outcomes. Our study was limited by missing data on our variables of interest. Future plans include validating our results using the new prospectively collected CARRA Registry that has more complete data on comorbid AI and lupus disease outcomes.

Table 1: Baseline comparison by comorbid autoimmune disorders

	All subjects with available data on AI (n = 388)		Without AI (n = 309)		With AI (n = 79)		p-value*
	N	%	N	%	N	%	
Ethnicity							0.750
Hispanic	103	26.55	79	26	22	28	
Race							0.4434
White	216	55.67	172	56	45	57	
African American	106	27.32	82	27	23	29	
Asian	33	8.51	28	9	5	6	
Other	7	1.8	5	2	2	3	
Sex							0.2475
Female	308	79.38	248	80	59	75	
Insurance							0.4457
Yes	364	93.81	287	93	78	99	
Smoking							>0.9999
No	262	67.53	215	69	50	63	
AI in 1st degree relative							0.0069
No	214	55.15	181	59	32	41	
Yes	146	37.63	108	35	39	49	
Age at primary disease onset (n=383) mean, sd	11.41	3.802	11.60	3.778	10.61	4.56	0.0406
Time in years to SLE Dx (n=382), median (IQR)	0	(0,1)	0	(0,1)	0	(0,1)	0.9670
Renal disease	167	43.04	140	46	26	33	0.0357
SLEDAI (n=352), median (IQR)	4	(0,8)	4	(0,8)	2	(0,8)	0.1834

Numbers of missing data: Ethnicity 1 (0.26%), Race 19 (4.9%), Insurance 14 (3.61%), Smoking 122 (31.44%), AI in 1st degree relative 28 (7.22%).

AI = autoimmune disorders

* after excluding missing data

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Baseline Features and Outcomes of Pediatric-Onset Discoid Lupus Erythematosus: Interim Data Analysis of a Multicenter Retrospective Cohort Study

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Session Information

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Session Type: ACR Poster Session A

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

Background/Purpose: Discoid lupus erythematosus(DLE) is rare in children. Prior studies suggest 25-30% of children with skin-limited DLE are diagnosed with systemic lupus erythematosus (SLE) over time. Biomarkers and risk factors to identify those at highest risk are unknown. This multicenter, retrospective study aims to characterize baseline features and outcomes in pediatric patients with skin-limited DLE, as well as risk factors for the progression of DLE to SLE. Baseline characteristics of all patients with DLE and initial study findings are presented in this interim analysis.

Methods: Nine of 18 committed clinical sites, including pediatric dermatologists and rheumatologists, retrospectively reviewed all medical records of patients ≤ 18 years of age with clinical and/or histopathologic findings consistent with DLE. Baseline data were collected on all patients, including demographics, dates of DLE onset and diagnosis, distribution of DLE, and family history of SLE. For patients with skin-limited DLE, rates of progression to SLE based on American College of Rheumatology (ACR) and Systemic Lupus International Collaborating Clinics (SLICC) classification criteria were evaluated.

Results: Clinical records for 205 patients have been reviewed to date, with 50% of participating sites reporting. Baseline data are presented in Table 1. African-American females were most commonly affected. Median age at DLE diagnosis was 11.8 years, with median time from DLE onset to diagnosis of 0.5 years. Most patients (76%) had localized disease (i.e. head/neck only); 20% had a family history of SLE in a 1st degree relative. Most patients had skin-limited DLE at baseline, with only a minority exhibiting ≥ 4 ACR classification criteria (n = 56; 27%) or ≥ 4 SLICC classification criteria (n = 46; 22%). Initial treatments are presented in Table 2. Patients with skin-limited DLE and at least one follow-up visit (n=115) had median follow up of 3.1 years (range 0.1-12.5 years, 393 total patient-years). During this period, a minority met criteria for SLE diagnosis, utilizing ≥ 4 ACR classification criteria (n = 16; 14%) and ≥ 4 SLICC classification criteria (n = 24; 22%).

Conclusion: This study represents the largest investigation of pediatric DLE performed to date. Utilizing both ACR and SLICC classification criteria for SLE, most patients (>73%) presented with skin-limited DLE, with a low cumulative incidence of SLE using both ACR and SLICC classification criteria. Further analysis may help to determine risk factors for progression to SLE and inform the creation of consensus guidelines for treating children with DLE.

Table 1. Baseline data for 205 patients with DLE (skin-limited DLE and SLE)

<i>N</i> (%)	
Gender	
Female	142 (69%)
Male	63 (31%)
Race/Ethnicity*	
Black or African American	82 (40%)
White	61 (30%)
Hispanic or Latino	34 (17%)
Asian	14 (7%)
Native Hawaiian or Other Pacific Islander	2 (1%)
American Indian or Alaskan Native	1 (0.5%)
Unknown or not reported	15 (7%)
1st degree family member with diagnosis of SLE	42 (20%)
Distribution of DLE lesions	
Localized (head/neck only)	155 (76%)
Generalized (both above/below the neck)	46 (22%)
Isolated (below the neck ONLY)	4 (2%)
Median (IQR)	
Age at presentation of DLE, years	10.8 (7.2-13.6)
Age at DLE diagnosis, years	11.8 (8.0-14.4)

* Participants could designate more than 1 race/ethnicity category

Table 2. Medications at baseline for patients with DLE (Skin-Limited and SLE)

Medication	<i>N</i> , (%)
Topical steroids	132 (65%)
Hydroxychloroquine	118 (58%)
Other immunomodulatory medications	59 (29%)
á Prednisone/Methylprednisolone	46 (22%)
á Mycophenole mofetil	16 (8%)
á Rituximab	5 (2%)
á Methotrexate	4 (2%)
á Dapsone	4 (2%)
á Azathioprine	4 (2%)
á Quinacrine	1 (0.5%)
á Thalidomide	1 (0.5%)
Topical calcineurin inhibitors	40 (20%)
None	13 (6%)

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Abstract Number: 469

Clinical Characteristics and Treatment of 25 Children with Systemic Lupus Erythematosus Complicated with Thrombotic Microangiopathy in China

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – Clinical Poster I: Lupus, Sjögren's Disease, and Myositis

Session Type: ACR Poster Session A

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

Background/Purpose: Thrombotic microangiopathy (TTP) is a rare disease involving multiple organ systems. It is caused by extensive platelet thrombosis in the terminal arterioles and anterior capillaries, leading to clinical manifestations of microvascular hemolysis, thrombocytopenia, and organ dysfunction. Syndrome. TTP may be secondary to infection, malignancy, drugs, pregnancy, and autoimmune diseases. When TTP occurs in SLE patients, similar clinical symptoms may appear in TTP and SLE, and the symptoms in the early stages of the onset are lack of specificity, which mask each other and lead to delayed diagnosis. Although the incidence of SLE with TTP is not high, but the disease is serious, rapid progress, the fatality rate as high as 33.9-62.5%. This study investigated the clinical and laboratory characteristics, diagnosis, treatment, and prognosis of children with systemic lupus erythematosus (SLE) complicated with thrombotic microangiopathy (TTP).

Methods: Twenty-five children with SLE combined with TTP (SLE-TTP) were selected and their clinical symptoms, laboratory tests, renal pathological features, SLE disease activity indicators and treatment outcomes were analyzed retrospectively.

Results: 25 children with SLE-TTP, including 8 males (32%) and 17 females (68%). The onset age was 9-18 years, with a median age of 14 years. Among them, 9 cases were SLE first (25%), 1 case was TTP first (4%), and 15 cases were concurrent (60%). The mean SLE disease activity score (SLEDAI) was 22.4 points. Of the 25 children with SLE-TTP, all had thrombocytopenia, microvascular anemia, systemic symptoms in 21 cases (84%), cutaneous symptoms in 10 cases (40%), and digestive symptoms in 10 cases (40%). Nine cases had edema (36%), neurological symptoms in 9 cases (36%), respiratory symptoms in 6 cases (24%), joint pain in 5 cases (20%), and renal impairment in 19 cases (76%). Ten of these children completed a renal biopsy and found 8 pathological lesions of the kidney. Which type IV and TMA each accounted for 20% of renal pathological lesions. The most common treatment for children with SLE-TTP is immunosuppressive therapy with glucocorticoid pulse therapy (13 cases, 52%), followed by plasma exchange combined with glucocorticoid pulse therapy and immunosuppressive agents (10 cases, 40%). A total of 11 patients had plasma exchange (44%) with an average of 8.0 times. More than 80% of patients used plasma exchange and glucocorticoid therapy, and all patients achieved remission. Among the 25 cases, one case died (4%), and the remaining 15 cases (60%) were followed up at regular clinics without relapse.

Conclusion: SLE-TTP is often the first or concurrent SLE event, accompanied by middle-to-severe lupus activity. The main clinical manifestations of systemic symptoms in children with SLE-TTP included neurological symptoms, edema, and gastrointestinal symptoms. Renal pathology was mainly wolf kidney type IV or IV+TMA (40%). Severe SLE-TTP infection is an important risk factor for SLE-TTP. More than 92% of the patients were treated with immunosuppressants and glucocorticoids, and 40% of them needed plasmapheresis for effective remission.

Disclosure: J. Li, None;

Abstract Number: 470

Pro-Inflammatory High Density Lipoprotein Function Is Associated with Accelerated Carotid Intimal Medial Thickness Progression in Childhood-Onset SLE

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – Clinical Poster I: Lupus, Sjögren's Disease, and Myositis

Session Type: ACR Poster Session A

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Background/Purpose: Patients with childhood-onset(cSLE) are at significantly increased risk of death from cardiovascular disease when they reach early adulthood. The Atherosclerosis Prevention Pediatric Lupus Erythematosus (APPLE) trial was a randomized placebo-controlled trial evaluating the effect of atorvastatin on subclinical atherosclerosis over 3 years, as measured by carotid intima-media thickness (CIMT). Results showed a trend toward reduced CIMT progression in the atorvastatin treated group and that children with SLE have CIMT progression rates greater than children with familial hypercholesterolemia. Additional subgroup analyses showed that post pubertal children with elevated C-reactive protein benefited from statin therapy. Although traditional risk factors play an important role in atherosclerosis progression, they do not fully account for the increased risk seen in SLE and additional biomarkers are needed to identify high risk individuals. Since completion of the APPLE trial, pro-inflammatory high density lipoprotein function (piHDL) function has been identified as a biomarker predictive of both the presence and progression of subclinical atherosclerosis in adult women with SLE. Although higher levels of HDL cholesterol are generally considered to be protective against atherosclerosis, HDL may become inflammatory (piHDL) in the setting of chronic inflammation and promote LDL oxidation and atherosclerosis. This is the first study to evaluate piHDL function as a predictor of accelerated CIMT progression in cSLE.

Methods: Stored baseline plasma from the APPLE trial placebo group (n=94) was tested for piHDL function using a cell-free assay based on piHDL function. Plasma samples were stored at -80°C and had not been previously thawed. Baseline and last follow-up mean common CIMT measurements recorded in the APPLE trial were used to calculate the rate

of CIMT progression. Accelerated CIMT progression was defined as > 0.002 mm/year. Univariate logistic regression was performed to determine the association between baseline piHDL function and accelerated CIMT progression.

Results: The cohort was 87% female with a mean age of 15.7 years (standard deviation ± 2.4). The median piHDL function was 1.04 FU, interquartile range 0.49-2.08, similar to values seen in adult women with SLE. Univariate logistic regression showed that every one point increase in piHDL function was associated with a modest yet statistically significant 1.69-fold increased odds of accelerated mean-mean common CIMT progression (95% CI 1.08-2.65, $p = 0.22$).

Conclusion: piHDL may be a useful biomarker to aid in identifying cSLE patients at increased risk for atherosclerosis progression. Further study is underway to evaluate the predictive role of piHDL function as part of a biomarker panel in cSLE.

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Abstract Number: 471

Early Signs of Diastolic Impairment in Children with Incident Systemic Lupus Erythematosus

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Session Information

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Session Title: Pediatric Rheumatology – Clinical Poster I: Lupus, Sjögren's Disease, and Myositis

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Background/Purpose: The timing and etiology of diastolic impairment in pediatric-onset systemic lupus erythematosus (pSLE) are poorly understood, and the role of screening echocardiography remains unclear. We compared left ventricular diastolic function at pSLE diagnosis with controls and determined the prevalence of abnormal echocardiographic findings.

Methods: Echocardiograms of children with pSLE ages 5-18 years performed within 1 year of diagnosis and age- and sex-matched controls with structurally normal hearts (evaluated for benign murmurs or chest pain during the same period) were re-read by two blinded cardiologists. Baseline characteristics, SLE disease activity index (SLEDAI), and cardiovascular symptoms/signs were abstracted by chart review. Diastolic indices (E/A ratio, e' , E/e' , and isovolumetric relaxation time (IVRT)) were compared using linear mixed effects models adjusted for systemic hypertension. Other abnormalities, including pericardial effusion and valvular disease, were also evaluated. Pearson's correlation was used to identify factors associated with worse diastolic indices.

Results: 85 children with incident pSLE had baseline echocardiograms, of which 61% were for screening, 15% were for cardiovascular symptoms/signs, and 23% were for other indications. Median time from SLE diagnosis to echocardiogram was 6 days (interquartile range 1-70). Prior glucocorticoid exposure was minimal (Table 1). Diastolic indices were significantly worse in pSLE cases compared to controls (with lower E/A, lower e' , higher E/e' and longer IVRT) even after adjustment for hypertension (Table 2). 6 pSLE cases (7%) met cutoffs for abnormally low e' and 32 (47%) had prolonged IVRT, though none met international criteria for Grade I diastolic dysfunction. Mild to moderate pericardial effusions, aortic and mitral insufficiency were present in 15%, 17%, and 6% of all pSLE cases, respectively, including 8%, 15%, and 3% of asymptomatic pSLE cases ($n = 61$). SLE disease activity, but not presence of effusion, was correlated with worse E/e' ($p = 0.31$, $p = 0.02$), septal e' (-0.30 , $p < 0.01$), and IVRT (0.50 , $p < 0.01$).

Conclusion: Subclinical echocardiographic findings were prevalent in a group of children with incident SLE, with worse diastolic indices at diagnosis compared to peers without SLE, independent of long-term glucocorticoid use or hypertension.

Future longitudinal studies using echocardiography will determine whether these measures of diastolic function worsen over time and if they are prognostic of future cardiac complications.

Table 1. Baseline demographic and disease characteristics

	pSLE	Controls	p-value
	(N=85)	(N=85)	
Age, mean (SD)	14.6 (2.9)	14.6 (2.9)	-
Female, n (%)	68 (80)	68 (80)	-
Race, n (%)			
White	50 (59)	28 (33)	<0.01
African American	15 (18)	32 (38)	
Asian	6 (7)	17 (20)	
Other	14 (16)	8 (9)	
Ethnicity, n (%)			
Non-Hispanic	76 (89)	68 (80)	0.17
Hispanic	6 (7)	11 (13)	
Body Mass Index, mean (SD)	21.0 (4.2)	22.0 (4.8)	0.15
Body Surface Area	1.5 (0.3)	1.5 (0.3)	0.85
Hypertension, n (%)	18 (21)	0 (0)	<0.01
Serositis, n (%)	20 (24)	-	-
Nephritis	37 (44)	-	-
Neurologic	9 (11)	-	-
Antiphospholipid antibodies	51 (60)	-	-
SLEDAI*, mean (SD)	16.8 (9.1)	-	-
Cumulative prednisone dose (mg)¶, median [IQR]	60 [0-1652]	-	-
Duration of prednisone use (days), median [IQR]	0 [0-3]	-	-
Cardiac symptom#, n (%)	24 (28)	-	-
Cardiac exam abnormality^	9 (11)	-	-

* SLEDAI < 5: low disease activity; 6-10: moderate; 11-19: high; maximum 105

¶ Cumulative oral prednisone dose prior to echocardiogram

Chest pain, dyspnea, palpitations

^ Murmur, rub, gallop, tachycardia

Table 2. Left ventricular diastolic function in pSLE cases versus controls

	Controls N = 85	SLE N = 85	Unadjusted			Adjusted for hypertension		
	mean (SD)		β*	95% CI	p	β*	95% CI	p
E/A, mitral	2.2 (0.6)	1.9 (0.5)	-0.2	[-0.4, -0.1]	0.01	-0.2	[-0.4, -0.01]	0.04
e' (septal)	12.4 (1.6)	11.4 (2.2)	-1.1	[-1.8, -0.4]	<0.01	-0.9	[-1.7, -0.1]	0.02
e' (lateral)	17.0 (3.2)	14.8 (3.3)	-2.3	[-3.5, -1.1]	<0.01	-1.9	[-3.3, -0.5]	0.01
E/e' (average)	6.6 (1.3)	7.3 (1.7)	0.9	[0.3, 1.5]	0.01	0.9	[0.2, 1.6]	0.02
IVRT ^	59.8 (12.0)	67.9 (16.7)	7.0	[1.9, 12.2]	0.01	4.4	[-1.2, 10.0]	0.12

Comparison of mean diastolic indices in 85 SLE cases and 85 age and sex-matched controls.

Decreased mitral inflow E/A ratio (abnormal <1), decreased tissue Doppler septal e' (<7 cm/s), decreased lateral e' (<10 cm/s), elevated E/e' (>14) and prolonged IVRT (>70 msec) correspond to impaired relaxation.

* Mean differences in linear mixed effects models, with or without adjustment for systemic hypertension

^ IVRT = isovolumetric relaxation time

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Abstract Number: 472

Libman Sacks Endocarditis in Pediatric Systemic Lupus Erythematosus: Clinical Features and Complications

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – Clinical Poster I: Lupus, Sjögren's Disease, and Myositis

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Background/Purpose: Libman-Sacks endocarditis (LSE) is a rare manifestation of pediatric-onset systemic lupus erythematosus (pSLE). It is difficult to differentiate LSE from infective endocarditis (IE) in immunosuppressed patients.

Data remain scarce on the diagnosis of LSE and disease course. We aim to describe the diagnosis, evaluation and management of endocarditis in pSLE.

Methods: A retrospective chart review was conducted of all patients who fulfilled ACR lupus classification criteria and were diagnosed with pSLE and either LSE or IE. Data were collected on demographics, laboratory results, echocardiogram findings, clinical features, and treatment. Descriptive statistics were used.

Results: We describe 6 patients (4 females) with pSLE and endocarditis, with a mean age at diagnosis of 11.6 +/- 3.3 years (Table 1). Three patients were White, 2 Black, and 1 Asian. The mean disease duration from pSLE diagnosis to diagnosed cardiac involvement was 1.4 +/- 2.8 years. Four patients had biopsy-proven lupus nephritis. All patients had positive serologies for ANA and anti-dsDNA antibodies. Five patients had anti-cardiolipin (aCL) antibodies at pSLE diagnosis and 3 had aCL antibodies at endocarditis diagnosis. Four patients were on treatment with steroids, 2 were on hydroxychloroquine, and 2 were treatment-naïve. One patient was treated with Cyclophosphamide, Rituximab, and plasmapheresis for pulmonary hemorrhage. The mean SLEDAI at diagnosis of endocarditis was 10.5 +/- 6.4. Two patients had baseline echocardiograms at the time of pSLE diagnosis; both were normal.

Two patients had LSE, with involvement of mitral and aortic valves on echocardiogram. Two patients had isolated IE without LSE, more commonly involving the tricuspid valve. Two patients were on antibiotics prior to obtaining blood cultures so overlying IE could not be ruled out. The only other concurrent clinical manifestation of lupus was arthritis in 2 patients. No patients had an increase or change in immunosuppression specifically for treatment of LSE. Five patients received prophylactic anti-coagulation. One patient was placed on subacute bacterial endocarditis prophylaxis. The most severe complications were pulmonary embolus (one definite, one possible), distal emboli and Roth spots (2 patients).

Conclusion: This is the largest case series of endocarditis in pSLE to date. Our data demonstrate endocarditis (LSE and/or IE) is more frequently diagnosed early in disease course, often in conjunction with other end-organ manifestations. As pSLE can have a more severe disease course than adult-onset SLE, our data suggest that endocarditis occurs in patients whose disease is either newly diagnosed or not well-controlled. Obtaining an echocardiogram at pSLE diagnosis with annual echocardiograms for surveillance may be useful. Anti-phospholipid antibodies play a role in LSE and should also be monitored.

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Table 1.

Patient	Age at SLE diagnosis (years)	Sex	Race/Ethnicity	Age at diagnosis of cardiac condition (years)	SLEDAI at cardiac diagnosis	Cardiac Diagnosis	Echo findings	Anti-coagulation	Complications
1	6	M	White/Hispanic	7	13	Libman Sacks Endocarditis (LSE) vs Infective Endocarditis (IE) — persistent fevers	Thickened mitral valve and mitral valve nodules	Low-dose aspirin	-Multiple small train emboli -Left sided Roth spot
2	10	M	Black/non-Hispanic	10	10	LSE vs IE—persistent fevers	Libman-Sacks endocarditis on aortic valve leaflet	Low dose Aspirin at Libman-Sacks diagnosis	none
3	12	F	White/Hispanic	13	21	IE (<i>S. aureus</i>)	Mitral & tricuspid vegetations (TEE)	Heparin x 3 day	-Septic emboli to foot -Bilateral Roth spots -Abnormal V/Q scan
4	13	F	Black/non-Hispanic	21	5	LSE	Libman-Sacks endocarditis on mitral valve	Low dose Aspirin at Libman-Sacks diagnosis	Moderate mitral regurgitation
5	14	F	Asian/non-Hispanic	14	11	LSE	Non-obstructive Libman-Sacks nodule on aortic valve	No	none
6	15	F	White/Hispanic	15	3	IE (<i>S. aureus</i>)	Echodensities on tricuspid valve	Heparin → Low-dose anticoagulation started after pulmonary embolus	Pulmonary embolus

A Weighty Diagnosis: Weight Change and Risk Factors in Early Juvenile Systemic Lupus Erythematosus

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – Clinical Poster I: Lupus, Sjögren's Disease, and Myositis

Session Type: ACR Poster Session A

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Background/Purpose: SLE is a chronic, multisystem autoimmune condition with multiple comorbidities due to inflammation and treatment, including metabolic syndrome, poor cardiac outcome, and poor quality of life. Obesity is more prevalent in children with jSLE compared to the general population. Obesity induces inflammation and independently contributes to lower functional status. Corticosteroid (CS) use is associated with weight gain. Obesity is also more prevalent in youths of lower socioeconomic status (SES). This study aims to retrospectively study weight change in an inception cohort of jSLE and potential contributors.

Methods: A retrospective chart review of jSLE was conducted at a single medical center. Inclusion criteria were an ICD-9 or ICD-10 diagnosis of jSLE prior to 18 years of age and multiple visits in the first year of jSLE. Baseline data included demographics and serologies. Variables collected from each visit included: time from diagnosis; age; weight, height, and BMI with percentiles and Z-scores; documentation of fatigue, gastrointestinal, psychiatric, or musculoskeletal symptoms; albumin; SLEDAI; and current medications with CS dose in mg/kg of prednisone. A mixed effect model was used to determine associations between BMI change and individual factors.

Results: Interim analysis included 16 patients, who were predominantly female, Hispanic, and on Medicaid (Table 1). Average age of diagnosis was 13.81 years. There was an average 0.064 ± 0.007 kg/m² increase in BMI per week ($p < 0.001$). Clinically, the number of obese and seriously obese patients increased from 25% to 43.75%. CS dose and SLEDAI were inversely associated with BMI ($p < 0.001$, $p = 0.017$). There was a trend towards association between higher BMI and fatigue ($p = 0.168$), gastrointestinal ($p = 0.074$), psychiatric ($p = 0.801$), and no musculoskeletal symptoms ($p = 0.403$).

Conclusion: There is a statistically significant trend towards increasing weight in the first year of jSLE and an increased rate of obesity. Increasing BMI was significantly associated with lower CS dose and SLEDAI and was associated with a more positive review of symptoms. Future study will expand this cohort, examine the impact of growth, and direct prospective studies.

Table 1. Patient characteristics.

Gender	
Female	15 (93.8%)
Male	1 (6.2%)
Ethnicity	
Asian	3 (18.8%)
Black	3 (18.8%)
Latino	3 (18.8%)
White	7 (43.8%)
Insurance	
Medicaid	12 (75%)
Private	4 (25%)
Average age at diagnosis	13.81 (SD 1.31)

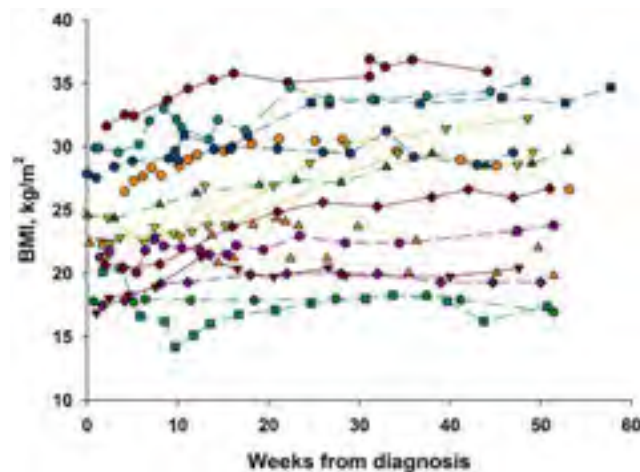


Figure 1. Change in patient BMI.

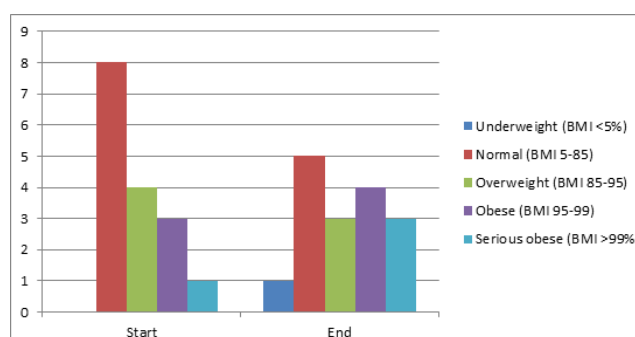


Figure 2. Change in BMI status.

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Lupus Impact Tracker (LIT) As a New Tool in Assessing Patient Reported Outcome in Pediatric Lupus

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Session Information

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Session Title: Pediatric Rheumatology – Clinical Poster I: Lupus, Sjögren's Disease, and Myositis

Session Type: ACR Poster Session A

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Background/Purpose: Patient Reported Outcome (PRO) measures for Quality of Life (QoL) in patients with lupus are useful supplements to the physician-derived indices of disease activity in estimating disease-impact and true patient-burden. PRO tools in pediatric lupus to date either capture QoL insufficiently or are too time-consuming to be used in routine clinical practice. Lupus Impact Tracker (LIT) is a practical, brief, 10-item, unidimensional, PRO tool, validated in adults, covering the concepts of cognition, lupus medications, physical health, pain/fatigue impact, emotional health, body image, and planning/desires/goals. We propose to determine the psychometric properties of LIT and its correlation with physician derived disease activity in pediatric and young adult patients with lupus.

Methods: This is a prospective, observational, pilot study where patients aged between 12 and 25 years, fulfilling the 1997 ACR classification criteria for SLE, were enrolled. Patients completed LIT alongside 3 consecutive, routine clinical visits. Data were collected on demographics, and clinical and laboratory disease-parameters including disease activity (SLEDAI) and damage (SLICC-ACR) indices.

Intraclass correlation coefficients (ICC) were calculated between serial LIT scores for test-retest reliability. Spearman correlation coefficients were calculated between LIT scores and SLEDAI and Kruskal-Wallis tests for association between LIT scores and SLEDAI-based groups (mild/moderate/severe). Using a Bonferroni type adjustment, a p-value <0.01 was considered significant.

Results: Of 28 patients completing 3 visits, 79% were female, 36% African American, 36% Asian, and 14% Latino. The mean (SD) age at enrollment was 17.25 (2.7) years, with a mean (SD) disease duration of 4.02 (2.79) years. Mean (SD) SLEDAI scores were 4.04 (3.3), 3.61 (2.8), and 4.29 (3.8) for the first, second and third visits. Mean (SD) LIT scores were 31.52 (27.2), 23.66 (23.4), and 24.91 (24.6) for the first, second and third visits. Intra-class correlation (ICC) between LIT scores at visit 1 and visit 2 was 0.696, and between LIT scores at visit 2 and 3 was 0.815, demonstrating moderate to high test-retest reliability. LIT and SLEDAI scores were moderately correlated at visit 3 with Spearman correlation coefficient of 0.69, but only weakly at visits 1 and 2 (0.205 and 0.203 respectively). No significant association was found between LIT and SLEDAI-severity groups (Kruskal Wallis $P=0.28$, 0.20, 0.74 at visits 1, 2 and 3 respectively).

Conclusion: This is the first pediatric study to show LIT as a simple, practical instrument to assess QoL, with moderate to high test-retest reliability. In conformity with some studies in adult lupus, it has only low to moderate correlation with physician derived disease activity. While this can be partly due to inclusion of patients with stable and low SLEDAI scores in this pilot, it also supports that PRO measures are supplementary rather than surrogate to disease activity indices based on clinical and serologic parameters alone. Results of correlation of LIT scores with other validated pediatric PRO measures will be reported next with a larger sample size.

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Abstract Number: 475

Adolescents' Perspectives on Living with Childhood-Onset Systemic Lupus Erythematosus

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Background/Purpose: Non-adherence to medical recommendations in childhood-onset systemic lupus erythematosus (cSLE) is estimated to be between 40-50%. For patients with cSLE, non-adherence results in increased hospitalizations, preventable disease damage, disease flares, and higher health care costs. Currently there are no published data regarding adolescent patients' perspectives on the management of cSLE, including barriers to treatment adherence. The aim of this study was to characterize the adolescent's perspective on the management of cSLE and its impact on their lives.

Methods: Ten adolescents diagnosed with cSLE per ACR SLE classification criteria were recruited from a pediatric rheumatology clinic and cSLE patient registry. Participants' characteristics are summarized in Table 1. Two separate focus groups were conducted and led by trained facilitators to discuss topics around living with cSLE and its management. The sessions were audio-taped, transcribed, and coded for themes by three independent coders.

Results: Focus group transcript analyses revealed seven major themes: 1) Barriers/Facilitators of treatment adherence, 2) Symptoms Impacting Daily Life, 3) Lack of Understanding/Knowledge about cSLE, 4) Impact on personal relationships, 5) Self-care and management, 6) Worry about the Future, and (7) Relationship/communication with healthcare providers. Adherence barriers included the number, taste, timing and side effects of oral medications. Adherence facilitators were desire to avoid being sick/in pain/hospitalized, use of pill boxes, reminder apps, and storage/location of pills. Fatigue, pain, and mood significantly impacted daily life for these adolescents. All adolescents described difficulties at school, including absenteeism related to disease flares and hospitalizations, missed schoolwork, bullying, and/or the general lack of awareness and understanding of cSLE among educators and peers. They emphasized the role of healthcare providers in helping increase schools' awareness and understanding of cSLE. Future worries were quality of life, transition to college, and job opportunities. All adolescents wanted direct communication with, and between, their providers.

Conclusion: While adherence was identified as a significant problem, some adolescents also noted strategies to improve self-management. All adolescents desired increased knowledge/understanding from the public regarding cSLE, especially aimed at school advocacy. Important next steps are to identify modifiable factors, with the long-term goal of developing interventions to improve the overall well-being and self-management for adolescents with cSLE.

Table 1: Participant demographical and disease characteristics

Characteristic	Adolescent (n = 10)
Demographics	
Female, No. (%)	10 (100)
Age, mean (SD), y	16.1 (1.6)
Race/Ethnicity, No. (%)	
White non-Hispanic	7 (70)
Black non-Hispanic	3 (30)
Other, non-Hispanic	-
Hispanic	-
cSLE characteristics	
Disease duration, mean (SD), y	2.7 (2.5)
SLEDAI _{2K} , mean (SD)	4 (4.19)
Presence of lupus nephritis, No. (%)	2 (20)
Comorbidities, No. (%)	7 (70)

¥SLEDAI_{2K} score from clinic visit preceding focus group session. Range of scores is 0-14 for participants.

‡ dyslipidemia, hypovitaminosis D, ADHD, anti-phospholipid abs.

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Abstract Number: 476

A Better Understanding of Childhood Sjögren Syndrome: Evaluation of the 2016 Acr/EULAR Classification Criteria for Use in Diagnosing Sjögren Syndrome in Children

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Background/Purpose: Clinical presentation of Sjögren syndrome in children differs from adults: dryness symptoms are more common in adults, while parotitis is more common in children. Criteria developed for adult classification have demonstrated low sensitivity when applied to pediatric populations, and no child-specific criteria have been established. The latest adult classification criteria have not yet been evaluated for use in children. Our objective was to evaluate the applicability of these new criteria for use in children.

Methods: Retrospective chart reviews were conducted to collect individual patient level data for children diagnosed with Sjögren syndrome (based on clinical diagnosis at age <18 years). Data including clinical features, laboratory values, imaging studies, and test items in the 2016 ACR/EULAR criteria were collected, and de-identified data were entered into a REDCap database. This study was approved by the Institutional Review Boards or equivalent regulatory bodies at individual affiliate institutions.

Results: To date, 144 children with Sjögren syndrome were included from 11 institutions across 4 countries (data collection is ongoing). This constitutes the largest childhood Sjögren syndrome patient series to date. The majority of children (88%) were female with a mean age of 11.7 years at diagnosis (range 1–17.8 years). Twenty-three children (16%) also had another autoimmune disease (18 with SLE, 4 with uveitis, 1 with subacute cutaneous lupus). Frequency of clinical features were as follows: 54% with parotitis, 54% with dry eyes, 54% with dry mouth, 52% with arthralgias without arthritis, 29% with arthritis, 21% with lymphadenopathy, 18% with cytopenias, 14% with fevers, 13% with cutaneous vasculitis, 10% with weight loss, and <10% each with recurrent vaginitis, myositis, pulmonary, renal, or neurologic manifestations. Only 6 children had testing for all 5 items included in the 2016 ACR/EULAR criteria. Most children (93%) had testing for anti-SSA antibodies, but fewer underwent minor salivary gland (MSG) biopsy (46%), Schirmer testing (40%), ocular surface staining (OSS, 15%), or measurement of unstimulated whole saliva flow (UWSF, 13%). While most children studied

(95.8%) were missing at least one data point, 38 of 144 children (26%) met the 2016 ACR/EULAR classification criteria for Sjögren syndrome. Of these 38 children: 35 (92%) had positive anti-SSA antibodies; 29 (76%) had positive Schirmer test; 22 (58%) had positive MSG biopsy; 4 (11%) had positive UWSF; and 1 (3%) had positive OSS. Of the 106 children not meeting criteria: 70 (66%) had positive anti-SSA antibodies; 10 (9%) had positive MSG biopsy; 8 (8%) had positive Schirmer test; and 4 (4%) had positive UWSF.

Conclusion: Criteria items from the 2016 ACR/EULAR criteria are not routinely assessed in children diagnosed with Sjögren syndrome making formal retrospective assessment of criteria difficult. Prospective study of these criteria along with defining child-specific normal values and adding child-specific criteria items (such as recurrent parotitis) are warranted. Establishing criteria for childhood Sjögren syndrome is a key step toward better understanding and treating this condition.

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Early Treatment with Intravenous Pulse Methylprednisolone or Methotrexate Is Associated with Decreased Medication Requirements at 12 and 24 Months in Patients with Juvenile Dermatomyositis: A Propensity Score Analysis

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Background/Purpose: Daily oralprednisone has been the main therapy in juvenile dermatomyositis(JDM), and combination therapy with methotrexate (MTX) introduced soon afterdiagnosis has been increasingly used. There have been few randomized studies toprovide evidence for therapeutic choices in JDM. We therefore evaluated effectsof initial therapies on treatment outcomes using propensity score analysis in large North American JDM registry.

Methods: We examined outcomes associated with 3 treatments used in the first3 months after diagnosis in 286 JDM patients: high (≥ 2 mg/kg/d) vs. lowdaily prednisone dose; pulse intravenous methylprednisolone (IVMP) vs. none;MTX vs. none. The 4 outcomes, achievement of half of the initial prednisonedose, prednisone discontinuation, treatment escalation at 12 and 24 months, anddevelopment of calcinosis, were evaluated by Coxproportional hazards and logistic regression. We accounted for differences in useof initial therapies by creating propensity score models that were matched 1:1 for patients with and without each therapy. Differences inthe propensity score model covariates were examined by Chi-square and Wilcoxonrank sum tests. Initial hazard models did not includethe use of other medications, while final models adjusted for duration of othermedications received.

Table1: Cox proportional Hazards modeling of relative hazard of 3 outcomes in the first 12 and 24 months of treatment, by initial pulse intravenous methylprednisolone.

Outcome	Time	IVMP not received (N=75), n (%)	IVMP received (N=75), n (%)	HR (95% CI) initial model	HR (95% CI) final model
Time to half of initial prednisone dose	12 months	26 (37%)	25 (29%)	0.96 (0.56-1.67)	0.75 (0.39-1.43)
	24 months	43 (57%)	41 (51%)	0.93 (0.61-1.43)	0.84 (0.52-1.34)
Time to prednisone discontinuation	24 months	21 (28%)	23 (31%)	1.19 (0.66-2.15)	1.41 (0.76-2.63)
Time to treatment escalation	12 months	30 (40%)	20 (27%)	0.62 (0.35-1.09)	0.48 (0.26-0.88) [#]
	24 months	44 (59%)	29 (39%)	0.58 (0.36-0.93) [#]	0.49 (0.29-0.80) [#]

IVMP received group showed significant difference ($p < 0.05$) compared to IVMP not received group.
Abbreviations: IVMP, intravenous methylprednisolone; HR, Hazard ratio

Table2: Cox proportional Hazards modeling of relative hazard of 3 outcomes in the first 24 months of treatment, by receipt of prednisone and methotrexate in combination in the first 3 months vs. prednisone alone.

Outcome	Time	Prednisone (N=48), n (%)	Prednisone and MTX (N=48), n (%)	HR (95% CI) initial model	HR (95% CI) final model
Time to half of initial prednisone dose	12 months	19 (40%)	16 (33%)	0.83 (0.43–1.61)	0.56 (0.23–1.38)
	24 months	28 (58%)	28 (58%)	0.84 (0.49–1.45)	0.48 (0.23–0.98)[‡]
Time to prednisone discontinuation	24 months	7 (15%)	17 (35%)	2.83 (1.18–6.55)[‡]	2.05 (0.57–7.30)
Time to treatment escalation	12 months	14 (29%)	14 (29%)	1.04 (0.50–2.18)	0.66 (0.22–1.92)
	24 months	19 (40%)	18 (38%)	0.98 (0.51–1.87)	0.50 (0.22–1.10)

[‡] Prednisone and MTX in combination group showed significant difference (P<0.05) compared to Prednisone group.
Abbreviations: MTX, methotrexate; HR, hazard ratio

Results: Of 286 patients, 169 received high dose prednisone, 83 received IVMP, and 90 received MTX in the first 3 months. The propensity score models had good fit, indicated by reduced model AIC values compared to intercept only models, and each of the covariates was balanced between treatment groups within each of the propensity score quartiles. High doses of prednisone had no effect on the likelihood of achieving the 3 treatment outcomes compared to lower doses of prednisone. Patients receiving initial pulse IVMP were less likely to have a treatment escalation at 12 and 24 months compared to those not receiving pulse IVMP (Table 1). Patients receiving prednisone/MTX in combination in the first 3 months were more likely to achieve prednisone discontinuation at 24 months in a model without adjustment for other medications received (Table 2). These 3 initial therapies had no association with the development of calcinosis at ≥ 24 months.

Conclusion: Initial pulse IVMP therapy and prednisone in combination with MTX in the first 3 months of treatment are associated with reduced requirements for future treatment in JDM patients. There was no association of initial prednisone dose with these outcomes. Pulse IVMP and MTX in combination with prednisone are recommended in the early treatment of JDM patients.

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Abstract Number: 478

Evidence Based Recommendations for Corticosteroid Tapering/Discontinuation in New Onset Juvenile Dermatomyositis Patients: Results from the Paediatric Rheumatology International Trials Organisation

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Background/Purpose: At present no clear evidence based guidelines exist to standardize the tapering and discontinuation of corticosteroids (CS) in juvenile dermatomyositis (JDM). Aim of our study is to provide evidence-based recommendations for CS tapering/discontinuation through the analysis of the patients in the PRINTO new onset JDM trial, and to identify predictors of clinical remission (CR) and CS discontinuation.

Methods: New onset JDM children were randomized to receive either prednisone (PDN) alone or in combination with methotrexate (MTX) or cyclosporine (CSA). We stratified patients according to CR into two major groups. Group 1 included

those on CR, who could discontinue PDN, with no major therapeutic changes (MTC) (reference group). Group 1 was compared with those who did not achieve CR, without or with MTC (group 2 and 3, respectively). PRINTO/ACR/EULAR JDM core set measures (CSM) and their median changes over time were compared in the 3 groups. A logistic regression model with odds ratios (OR) and 95% confidence intervals (CI) was used to identify predictors of CR with PDN discontinuation.

Results: 139 children were enrolled. The reference Group 1 showed at least a 50% decrease in the CSM already in the first 2 months when compared to the other two groups. The achievement of a PRINTO JDM 50-70-90 response at 2 months (ORs range 4.5-6.9) from treatment start, an age at onset >9 years (OR 4.6) and the combination therapy PDN+MTX (OR 3.6) increase the probability of achieving CR ($p<0.05$). (Table)

Conclusion: This is the first proposal of evidence based specific cut-offs for corticosteroid tapering/discontinuation based on the change in JDM CSM of disease activity.

Table	OR (95% CI)	p [#]
Responder at 2 months:		
Printo-50 (vs. not responder/Printo-20)	5.41 (1.37 - 21.32)	0.0076
Printo-70 (vs. not responder/Printo-20)	6.90 (1.91 - 24.99)	0.0017
Printo-90 (vs. not responder/Printo-20)	4.46 (1.08 - 18.38)	
Age at onset > 8.53 years (≤ 8.53 years)	4.64 (1.69 - 12.71)	
Treatment group: PDN+MTX (vs. PDN / PDN+CSA)	3.63 (1.30 - 10.09)	0.0116
AUC of the model: 0.80		

OR: Odds Ratio; 95% CI: 95% Confidence Interval; P[#]: Likelihood Ratio test

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Abstract Number: 479

Intravenous Immunoglobulin in Combination with Intravenous Methylprednisolone in the Treatment of Calcinosis Associated with Juvenile Dermatomyositis (JDM)

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Background/Purpose: Calcinosis is a major complication of JDM and is associated with disability and poor quality of life. There are no known effective treatments for calcinosis; current therapy is based on anecdotal retrospective studies. Our aim was to introduce a systematic evaluation of calcinosis and assess the response to IV Immunoglobulin (IVIG) in combination with IV Methylprednisolone (IVMP) in JDM patients (pts).

Methods: A retrospective review was conducted of 11 pts with probable or definite JDM with calcinosis treated with IVIG and IVMP, added to ongoing immunosuppressive therapy. The evaluation of treatment response was based on change at follow-up in 9 potential body areas with calcinosis (head, upper and lower extremities, chest, back, abdomen, buttocks); total number of calcinosis lesions, their size and consistency; associated signs of inflammation (erythema, warmth, tenderness) in the lesions; and impact on function (limitation of joint range of motion (ROM) and Child Health Assessment Questionnaire (CHAQ) scores).

Results: The median age at baseline was 14 years, median disease duration was 4 years [IQR 3-8] (Table 1). The median duration of IVIG treatment to documented clinical improvement in calcinosis was 16 months [IQR 9-60], with monthly

IVIG dose ranging from 1- 2 gm/kg and IVMP dose ranging from 1mg/kg to 30 mg/kg/dose with IVIG. The median [IQR] number of anatomic areas with calcinosis was 6.0[1.0-7.0] pre- and 8.0 [2.0-8.0] post-treatment, with 4 pts(36%) having fewer anatomic areas involved with calcinosis after treatment, 4 (36%) with additional areas involved and 3 (27%) with no change at follow-up. A decrease in the total number of calcinosis lesions was documented in 6 pts (55%), while 3 (27%) had an increase and 2 (18%) had no change in the number of lesions. Among the 6pts with fewer calcinosis lesions, 3 exhibited a decrease in size of calcinosis while 2 had softening of the lesions. The median [IQR] number of areas with inflammation was 2.0 [1.0-6.0] pre- and 1.0 [0.0-3.0] post-treatment, with improvement in calcinosis-related signs of inflammation noted in 6 pts (55%), while 3 (27%) had increased inflammation and 1 (9%) had no change. Nine of 10 pts with restricted ROM at baseline due to calcinosis demonstrated improved ROM at the final evaluation visit (p=0.001). The median [IQR] number of restricted joints was 3.0 [1.0-5.0] pre- and 2.0 [0.0-2.0] post-treatment (p=0.047). CHAQ scores improved from median of 0.9 [0.19-1.9] pre- to 0.10 [0.0-0.69] post-treatment (p=0.05).

Conclusion: These data suggest that the combination of IVIG and IVMP was effective in improving calcinosis in a subset of JDM pts, as evident in improvement in the extent of calcinosis, associated inflammation, and physical function. This study also highlights the need for objective tools to assess calcinosis to aid in the evaluation of treatment responses.

Table. Eleven JDM Patients with calcinosis treated with IVIG and IVMP

ID	Age (yrs.)	IVIG duration (Mths.)	N. of anatomic areas with calcinosis		Calcinosis lesion number and characteristics		N. of areas with signs of inflammation		N. of restricted joints due to calcinosis		N. of joints with improved ROM Final	CHAQ Score (0-3)		Therapies administered while on IVIG and IVMP
			Initial	Final	Initial	Final	Initial	Final	Initial	Final		Initial	Final	
1	12	12	7	4	> 17 calcinosis lesions Most lesions are firm Few lesions are hard	13 calcinosis lesions (4 are new)	6	3	3	2	2	1.75	NA	Prednisone, Hydroxychloroquine, Methotrexate, Lansoprazole, Sucralfate, Potassium phosphate, Magnesium oxide, Calcium carbonate, Alendronate, Pamidronate, Vitamin D
2	14	14	4	5	11 calcinosis lesions	2 lesions are hard	3	2	1	1	1	0.375	0.5	Methotrexate, Adalimumab, Colchicine, IV Pamidronate, Calcium and Vitamin D
3	9	6	7	6	20 deep plaques and nodular lesions	16 calcinosis lesions (6 are new) 1 lesion decreased in size Lesions are more superficial	6	0	6	4	6	1.125	0.75	Prednisone, Methotrexate, Hydroxychloroquine, Colchicine, Cyclosporine, Cyclophosphamide, Calcium, Calcitriol, Alendronate, Ranitidine, Amlodipine
4	15	16	7	8	15 nodular and plaque like lesions	26 calcinosis lesions	2	4	5	2	3	0.125	0.0	Aluminum hydroxide, Amlodipine
5	12	17	3	2	Two large plaques on posterior thighs and punctate calcification on left elbow	Lesions on elbow resolved No new lesions	2	0	5	0	5	2.66	0.125	Hydroxychloroquine, Methotrexate, Cyclosporin, Alendronate, Gabapentin
6	14	8	1	1	One large plaque	Decreased in size Tenderness and warmth resolved, but still fluctuant	1	1	2	1	1	0.675	0.0	Prednisone, Methotrexate, Infliximab, Pamidronate
7	17	9	5	5	7 calcinosis lesions	18 lesions (5 are new) Some lesions become smaller and softer	0	0	0	0	0	0.0	0.0	Hydroxychloroquine, Prednisone, Methotrexate, Rituximab, Alendronate, Topical Sodium Thiosulfate
8	14	60	6	8	8 calcinosis lesions	At least 24% of patient's body surface area is covered with calcinosis	0	1	3	3	3	2.1	1.0	Hydroxychloroquine, Methotrexate, Deflazacort, Azathioprine, Colchicine, Pamidronate, Probenicid
9	18	78	1	1	2 tender nodules	Large plaque on thigh	1	0	1	0	0	1.8	NA	Prednisone, Methotrexate, Mycophenolate mofetil, Hydroxychloroquine, Amlodipine, Gabapentin
10	4	66	8	2	17 tender plaques and nodules	2 single nodular lesions (one is new) No tenderness No other lesions	3	2	3	2	1	1.125	0.083	Prednisolone, Methotrexate, Cyclophosphamide, Rituximab, Adalimumab, Abatacept, Colchicine, Pamidronate
11	16	19	6	8	8 nodular lesions	16 calcinosis lesions 11 lesions are tender	1	2	1	2	0	NA	1.625	Methotrexate, Prednisone, Colchicine, Azathioprine

Disclosure: M. Phillpotts, None; E. Alshaikh, None; Y. Aleatany, None; O. Y. Jones, None; G. Mamyrova, Cure JM, 2; L. G. Rider, Hope Pharmaceuticals, Bristol Myers Squibb, Lilly, 2; R. Curiel, Cure JM, Bristol Myers Squibb, 2.

Abstract Number: 480

Analyze Myositis with Ultrasound and Exercise (AMUSE) Kids- Initial Analysis of Longitudinal Data

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – Clinical Poster I: Lupus, Sjögren's Disease, and Myositis

Session Type: ACR Poster Session A

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

Background/Purpose: There is an unmet need for more objective disease outcome measures in Juvenile Myositis (JM) patients. This pilot study sought to test the reliability, validity and responsiveness of muscle ultrasound (US) modalities as outcome measures in JM subjects.

Methods: This prospective, consecutive observational JM cohort (using Bohan and Peter criteria) had clinical, functional and muscle US data collected at baseline, 3 and 6 months. US modalities assessing muscle consistency and perfusion [i.e. GrayScale with Echogenicity and Muscle Thickness, Power Doppler, 2D Shear wave® Elastography, and Contrast Enhanced US with Lumason® (CEUS)] were performed unilaterally on the proximal vastus lateralis (VL) at each study visit before and after all exercises including functional measure tests. Spearman correlation was utilized to evaluate the relationship of baseline US VL data pre- and post-exercise to International Myositis Assessment and Clinical Studies Group (IMACS) validated Core Set Measures (CSM). Descriptive statistics for VL US longitudinal measurements were performed and graphed to visualize trends. Subjects were characterized as change vs no change, guided by ACR/EULAR myositis response criteria and designated as 'active' or 'inactive' disease (PRINTO definition and physician judgement).

Results: Eleven enrolled subjects included primarily Caucasian females (mean age 10.7 ± 4.2 years) with a mean disease duration of 36 ± 23.7 months. At baseline, several US measures had fair to strong correlations ($r_s \geq 0.30$) with CSM, with most associations being stronger post-exercise (Table 1). Longitudinal assessment confirmed this post-exercise trend with disease status. The 'no change' subjects demonstrate consistent muscle US values over time (reliability) (Fig 1). Patients with initial 'active' disease showed an increase in elastography following exercise, reflecting an increase in muscle stiffness (Fig 1A), and a decrease in degree of perfusion post exercise, measured by Peak Intensity CEUS, over time (Fig 1B).

Figure 1: Descriptive longitudinal of change vs no change patients and median values of US measurements of Elastography, Peak Intensity, and Time to Peak

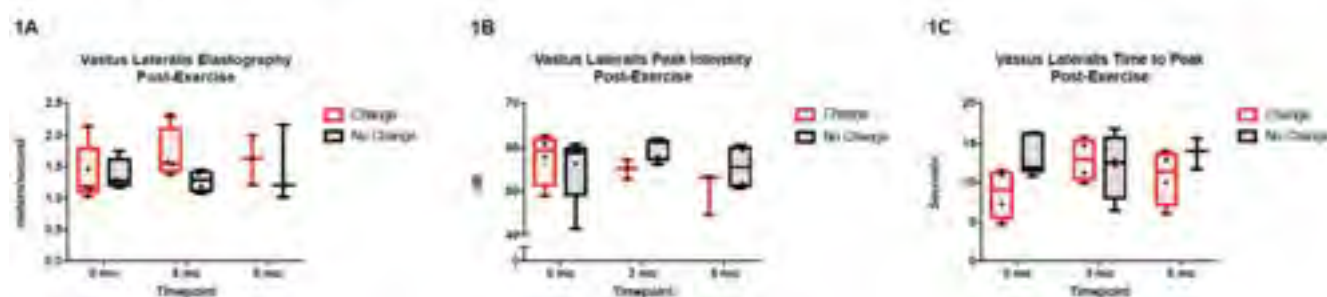


Table 1. Spearman correlation coefficients of different ultrasound modalities of the vastus lateralis muscle pre/post exercise and the PROMIS SF, Core Set Measures, and functional tests in 11 JM patients¹ at their baseline study visit.

	Core Set Measures							Functional Tests		
	PROMIS SF Pt/Parent	CHAQ SDI	Pt/Parent Global	MDAS	MD Global	CMAS	MMTB	STS	TUG	6MWD
Echogenicity Pre	-.10	.32	.14	.39	.05	-.46	-.76**	-.13	.32	-.19
Echogenicity Post	-.10	.32	.14	.39	.05	-.46	-.76**	-.13	.32	-.19
Muscle Thickness Pre	-.28	-.13	-.13	-.80	-.08	-.49+	.08	-.32	-.15	.42
Muscle Thickness Post	-.42	-.05	-.11	-.29	-.01	.80	.12	-.30	-.10	.52+
Elastography Pre	-.28	-.23	-.20	.09	-.05	-.23	.08	.67	-.20	-.44
Elastography Post	.36	-.26	.36	.04	.32	-.11	.86	.32	-.17	-.11
Power Doppler Pre	-.31	.33	-.21	.43	-.21	-.60	-.41	-.26	-.16	-.10
Power Doppler Post	-.18	.00	.00	-.15	.53+	.09	-.25	-.86**	-.03	-.12
CEUS T _p Pre	-.32	.06	-.27	.23	-.34	-.28	-.03	.35	-.05	-.17
CEUS T _p Post	.00	-.05	-.63+	-.39	-.12	-.20	.27	.67	.38	-.13
CEUS I _p Pre	.01	-.45	-.48+	-.18	-.25	.35	.51+	-.02	-.60	.87+
CEUS I _p Post	-.04	-.20	-.09	-.28	.46	-.11	.11	-.09	-.35	.15
CEUS AUC Pre	.30	.23	.09	.30	.46	.11	-.08	-.34	.61*	-.21
CEUS AUC Post	-.18	-.21	.11	.12	-.46	.08	.08	.04	.10	-.03

Due to low sample size, Spearman's correlation coefficients were interpreted as follows: fair ($\geq 0.3, < 0.5$), moderate ($\geq 0.5, < 0.7$), strong ($\geq 0.7, < 0.9$) or very strong (≥ 0.9) and were considered significant at the .01 level **, the .05 level *, and at the .15 level +. Abbreviations: Pre (Pre exercise), Post (Post exercise), CEUS (Contrast Enhanced Ultrasound), T_p (Time to Peak), I_p (Peak Intensity), AUC (Area Under the Curve), CHAQ (Childhood Health Assessment Questionnaire), Pt (Patient), Patient-Reported Outcome Measurement Information System Mobility Short Form (PROMIS-SF), MDAS (Myositis Disease Activity Scale), CMAS (Childhood Myositis Assessment Scale), MMTB (Manual Muscle Testing B), STS (Sit to Stand), TUG (Time Up and Go), 6MWD (6 Minute Walk Distance)

Additionally, the speed of perfusion on Time to Peak CEUS increased in subjects who clinically improved in their disease status (change group) (Fig1C).

Conclusion: Following exercise in active JM patients, the VL remains stiffer with less capillary enhancement compared to stable patients, likely reflecting residual vasculopathy. In patients showing clinical improvement, speed of perfusion (T_p CEUS) increases over time and may be useful as a future treatment response measure. Further longitudinal analysis is underway with healthy controls to strengthen these findings.

Disclosure: L. Tasan, None; E. Brunner, None; J. Squires, None; R. Aggarwal, None; C. V. Oddis, None; C. K. Zigler, None; K. Schollaert-Fitch, None; E. Mirizio, None; K. S. Torok, None.

Abstract Number: 481

Stepping It up: The Use of Physical Activity Monitors As an Outcome Measure in Juvenile Myositis

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – Clinical Poster I: Lupus, Sjögren's Disease, and Myositis

Session Type: ACR Poster Session A

Background/Purpose: The use of physical activity monitors (PAM), which objectively quantify free-living movement, may enhance assessment of disease activity in juvenile myositis (JM) clinical trials and complement traditional core set measures (CSM) of disease activity. We examined the validity, reliability and responsiveness of the average daily step counts (ADSC) obtained from a commercially available PAM, Fitbit® One, as outcome measures in patients with JM.

Methods: JM patients age 3-17 were enrolled from rheumatology clinic. The following evaluations were performed at baseline, 1, 3 and 6 months: a) CSMs including Manual Muscle Testing (MMT), Childhood Health Assessment Questionnaire (CHAQ), MD global disease activity (MD-global), Extra-muscular global disease activity (Ex-Mus global), muscle enzyme, patient/parent global disease activity (pt-global), Childhood Myositis Assessment Scale (CMAS), Disease Activity Score (DAS), b) Patient-Reported Outcome (PRO) Measurement Information System Mobility Short Form (PROMIS-SF), and c) office functional tests: Sit-to-Stand (STS), Timed Up and Go (TUG) and Six Minute Walk Distance (6MWD). Fitbit® One was worn for 7 consecutive days monthly for 6 months, and PAM measures, including ADSC were assessed. Pearson Correlation assessed the relationship between Fitbit® ADSC and current CSMs, PROs and functional tests. Reliability and responsiveness of PAM measures were determined.

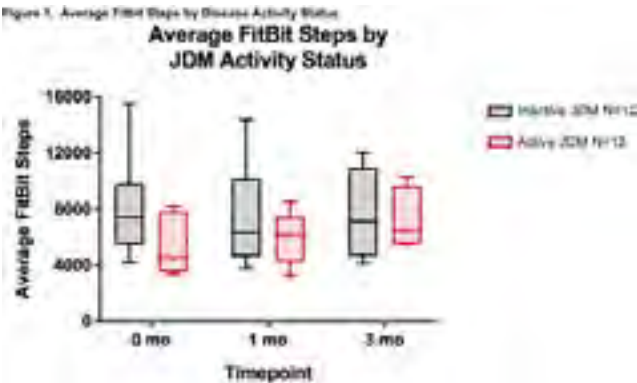


Table 1. Pearson correlation analyses of Fitbit® steps in free-living environment with CSMs¹, PROs² and functional tests.

	Average Fitbit Steps		
	Pearson's r	Sig. (2-tailed)	N
Core Set Measures			
MD global	-0.51	0.045*	17
MMT ³	0.54	0.03*	17
Parent/Patient Global Assessment: Disease Activity	-0.48	0.05*	17
Ex-Mus global ⁴	-0.47	0.06	17
CMAS ⁵	0.22	0.40	17
DAS ⁶	-0.36	0.15	17
Functional Tests			
6MWD ⁷	0.18	0.48	17
STS (highest)	0.57	0.04	17
TUG (highest)	0.15	0.56	17

¹Core Set Measures (CSM), ²Patient Reported Outcomes (PRO), ³Manual Muscle Testing (MMT), ⁴Extra-muscular global disease activity (Ex-Mus global), ⁵Childhood Myositis Assessment Scale (CMAS), ⁶Disease Activity Score (DAS), ⁷Six Minute Walk Distance (6MWD), ⁸Sit to Stand (STS), ⁹Timed Up and Go (TUG). *P < 0.05.

Results: A total of 17 JM participants have been enrolled, including 5 active and 12 stable, 76.5% female, 94% White with mean (SD) age of 11.5 years (3.4). As the study is ongoing, this data represents baseline, 1 and 3-month time points. Fitbit® ADSC showed moderate to strong correlation at baseline with key CSMs including MD global, MMT, pt-global, Ex-Mus global, but no to weak correlation with CMAS and functional tests (Table 1). Patients with stable disease at baseline and follow-up (1 and 3 months) showed no significant change in Fitbit® ADSC over time demonstrating strong test-retest reliability, whereas patients with active disease demonstrated Fitbit® ADSC increase longitudinally associated with clinical improvement (Figure 1).

Conclusion: Fitbit® ADSC had moderate to strong correlation with key JM CSMs except CMAS and functional test. ADSC also demonstrate preliminary reliability and responsiveness. Continued analysis of longitudinal data will help to determine the utility of a commercially available PAM as an outcome measure in JDM.

Disclosure: E. Brunner, None; L. Tasan, None; K. S. Torok, None; B. Rockette-Wagner, None; C. K. Zigler, None; K. Schollaert-Fitch, None; D. Koontz, None; C. V. Oddis, None; R. Aggarwal, None.

The Association of Short-Term Ultraviolet Radiation Exposure and Calcinosis in Juvenile Dermatomyositis in the Childhood Arthritis & Rheumatology Research Alliance Registry

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – Clinical Poster I: Lupus, Sjögren's Disease, and Myositis

Session Type: ACR Poster Session A

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

Background/Purpose: JDM is an autoimmune systemic vasculopathy characterized by myositis and skin rash. Some myositis specific antibodies (MSAs) are associated with clinical manifestations in JDM, including extensive photosensitive rash and a chronic disease course. Prior research demonstrates a link between UV radiation (UVR) and certain MSAs. However, it is unclear if UVR worsens disease severity in JDM. We investigated the association between UVR and development of calcinosis, which we used as a proxy for severe disease. Understanding the role of UVR in disease severity may help clinicians develop interventions to limit UV exposure and poor outcomes in JDM.

Methods: This was a cross-sectional study of JDM subjects in the U.S. multi-center Childhood Arthritis & Rheumatology Research Alliance (CARRA) registry enrolled from 2010-15. We excluded subjects missing date of symptom onset or zip code. Mean UV index (UVI) in the calendar month prior to symptom onset in each subject's zip code was calculated from daily satellite solar noon measurements. The primary outcome was history of calcinosis. Chi-squared and Kruskal-Wallis tests were used to compare subject characteristics stratified by UV quartiles. Multivariate logistic regression was used with adjustment for sex, race, age, interval to diagnosis, disease duration, and latitude. Race was dichotomized as black or non-black. Interaction between race and UVI was evaluated.

Results: Among subjects (n=522), 11% identified as black and 89% as non-black, of which 79% identified as white. Overall, mean UVI was 4.9 (± 2.6) and 11% had calcinosis. Stratified by UV quartiles, clinical and demographic characteristics were similar. In a multi-variate analysis, there was no significant relationship between mean UVI and calcinosis (see Table 1 for OR's). Black race was associated with a 3-fold greater odds of calcinosis. However, when accounting for a statistically significant interaction between race and UVI, black subjects were less likely to develop calcinosis at the mean UVI. At higher UVI levels, the odds of calcinosis steadily increased in the non-black subjects. Additional statistically significant risk factors for calcinosis in our model included male sex, older age at disease onset, longer disease duration, and delay in diagnosis.

Conclusion: In the CARRA JDM registry, we found that black subjects living in areas with lower UVI, had a 3-fold greater odds of calcinosis compared to non-black subjects. However, non-black subjects living in areas with moderate to high UVI, had increased risk of calcinosis beyond those of black subjects suggesting that lighter skinned individuals with JDM may be more susceptible to UVR and subsequent development of calcinosis. Our data suggests UVR is an important factor associated with calcinosis but also highlights the complex interplay between genes and environment present in autoimmune conditions like JDM.

Table 1: Multivariate logistic regression model of mean UVI as a predictor of Calcinosis

Predictor	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Female sex	0.62	0.34-1.14	0.11	0.48	0.25 - 0.95	0.03*
Age at disease onset (per year)	1.01	0.94-1.09	0.71	1.10	1.01 - 1.20	0.03*
Disease duration (per year)	1.23	1.13-1.33	<0.001*	1.30	1.18 - 1.44	<0.001*
Diagnosis interval (per month)	1.03	1.01-1.05	0.005*	1.04	1.01 - 1.06	<0.001*
Mean UVI	0.94	0.84-1.05	0.25	1.03	0.89 - 1.19	0.66
Black race	3.22	1.54-6.41	0.001*	3.35	1.22 - 8.17	0.01*
Mean UVI*Black race	0.69	0.48-0.95	0.03*	0.67	0.45 - 0.94	0.02*
Mean latitude	1.00	0.94-1.07	0.91	1.00	0.92 - 1.09	0.99

* indicates p-value <0.05. Model adjusted for sex, age, disease duration, diagnosis interval, race and latitude.

Disclosure: J. Neely, None; C. S. Long, None; H. Sturrock, None; S. Kim, None.

Correlation between Disease Activity and Hip Score in Patients with Rheumatoid Arthritis after Total Hip Arthroplasty

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: The Disease Activity Score including 28 joints (DAS28), the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) were developed in order to provide a quantifiable measure of rheumatoid arthritis (RA) activity. Although inflamed hip joints greatly impact activities of daily living (ADL) and walking ability, the hip joint was not included in the DAS28, SDAI or CDAI assessments. This study aimed to assess the correlation between a hip score and disease activity in patients with RA after THA.

Methods: We analyzed the effect of RA disease activity on a hip function score in an observational cohort of RA patients after THA. Thirty-three registered RA patients who had undergone THA (44 joints) between 1997 and 2016 and who had been followed for more than 1 year were included. Hip function was recorded and RA disease activity was measured on the same day. The mean age of the patients was 66.8 years (range, 41–84 years). They were followed for a mean of 7.9 years (range, 1–19) after surgery. The Japanese Orthopedic Association (JOA) hip score was used as a clinical outcome measure for hip dysfunction. The JOA hip score accounts for: ‘pain’ (up to 40 points), ‘range of motion’, ‘ability to walk’, and ‘activities of daily living (ADL)’ (each up to 20 points), such that a higher score indicates less pathology. The mean duration of disease following RA diagnosis for this patient group was 22.9 years (range 2–47 years). The RA disease progression was assessed by Steinbrocker radiographic stages, 9 patients (11 THA) were in stage II, 4 patients (7 THA) were in stage III, and 20 patients (26 THA) were in stage IV. More than half of the studied patients had advanced to Steinbrocker radiographic stage IV. RA disease activity were measured using the DAS28, SDAI and CDAI. RA functional assessment was measured using the modified health assessment questionnaire (mHAQ).

Results: The mean JOA score for hip function was 83.8 (range, 39–99) at the final follow-up. The mean DAS28-ESR, DAS28-CRP, SDAI, CDAI and mHAQ measuring RA disease activity levels were 3.87 (range, 0.77–6.04), 2.39 (range, 1.03–5.21), 8.89 (range, 0.23–27.33) and 7.67 (range, 0.1–23.90), respectively, at the final follow-up. There was a significant negative correlation between the JOA hip score and all disease activity assessments observed after THA (DAS-ESR [P = 0.0012]; DAS-CRP [P = 0.0036], SDAI [P = 0.0023], CDAI [P = 0.0016] and mHAQ [P < 0.0001]). There were significant JOA score changes among the parameters of ADL (DAS-ESR [P = 0.0081]; DAS-CRP [P = 0.0245]), SDAI [P = 0.0116] and CDAI [P = 0.0187] and mHAQ [P < 0.0001]) and the ability to walk (DAS-ESR [P = 0.0012], DAS-CRP [P = 0.0011], SDAI [P = 0.0011], CDAI [P = 0.0007] and mHAQ [P < 0.0001]). Thus, ADL and ability to walk are correlated with RA disease activity.

Conclusion: We found significant negative correlations between JOA hip scores and all disease activity assessments in RA patients treated with THA. We conclude that THA may have a positive secondary systemic effect on RA disease activity, and tight control of RA disease activity may improve hip function for RA patients after THA.

Disclosure: H. Wakabayashi, None; M. Hasegawa, None; A. Sudo, None.

Abstract Number: 484

Rheumatoid Arthritis Patients Have Lower Preoperative Expectations but Greater Clinical Improvement after Total Knee Arthroplasty Compared to Osteoarthritis Patients

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Preoperative patient expectations of Total Knee Arthroplasty (TKA) influence postoperative outcomes and satisfaction. Rheumatoid Arthritis (RA) may lower preoperative expectations after TKA compared to patients with knee osteoarthritis (OA). As RA patients undergoing primary TKA have lower expectations, but comparable knee specific clinical outcomes when compared to OA patients we hypothesized that satisfaction would also be comparable.

Methods: A retrospective review of 76 RA patients who underwent primary TKA from 2007-2011 were matched 1:2 with a cohort of 152 OA patients based on age, gender, ASA score, and Charlson Comorbidity Index score. The Hospital for Special Surgery Knee Replacement Expectations Survey (HSS-KRES), Visual Analogue Scale Pain (VAS), Knee injury and Osteoarthritis Outcome Score (KOOS), and the Short Form-12 (SF-12) were compared at baseline and at two years post-op. Minimum Clinically Important Difference (MCID) was calculated for KOOS and SF-12 subdomains.

Results: RA patients had significantly lower preoperative expectations (mean HSS-KRES 68.8 vs 77.7, $p=0.03$), higher VAS pain (66.2 vs 59.8, $p=0.05$), worse KOOS pain, knee symptoms, and activities of daily living limitations at baseline ($p<0.01$). At 2 years, the RA group had larger improvement in VAS pain (-53.7 vs -44.8, $p=0.02$) and these 3 KOOS domains ($p<0.05$), achieving comparable scores to OA patients. RA patients had a significantly higher proportion of patients achieve MCID (11.96) for KOOS symptoms (98.4% vs 77.2%, $p<0.001$). There was no significant difference between satisfaction rates with over 85% of RA and OA patients either somewhat satisfied or very satisfied at 2 years follow-up.

Table 1. Characteristics and Comparison between OA and RA

		OA N=152			RA N=76			p-value ¶
		N	Mean	Std	N	Mean	Std	
Total expectation score	Baseline	116	77.79	18.16	50	68.84	25.84	0.030
Visual Analogue Scale		149	59.8	24.21	76	66.25	21.15	0.030
LEAS		150	9.38	2.75	76	8.39	2.77	0.013
KOOS Pain		149	44.9	17.1	75	38.99	16.66	0.015
KOOS Symptoms		147	48.25	17.65	73	36.53	19.54	<.0001
KOOS ADL		149	51.41	18.84	76	42.38	18.76	0.001
KOOS Sports and Rec		119	19.21	20.54	55	17.58	27.75	0.698
KOOS QOL		148	22.21	15.74	72	19.73	14.87	0.266
SF-12 PCS		144	33.25	8.59	72	28.63	7.81	<.001
SF-12 MCS		144	50.17	12.29	72	47.21	12.54	0.100
Visual Analogue Scale	2 Year	143	14.85	21.47	72	10.83	14.19	0.102
LEAS		148	11.29	3.12	74	10.41	3.23	0.050
KOOS Pain		148	84.63	17.53	71	84.94	16.60	0.900
KOOS Symptoms		97	77.20	17.57	64	80.38	16.47	0.251
KOOS ADL		149	83.52	16.92	73	82.46	19.47	0.676
KOOS Sports and Rec		75	57.75	27.10	48	66.31	30.44	0.106
KOOS QOL		94	66.84	25.69	62	69.46	26.45	0.540
SF-12 PCS		135	45.22	10.87	68	39.89	10.55	0.001
SF-12 MCS		135	53.63	8.84	68	48.93	11.30	0.003
Visual Analogue Scale	Delta (2 year - baseline)	140	-44.83	30.23	72	-53.77	21.54	0.014
LEAS		146	1.86	3.39	74	2.01	2.91	0.745
KOOS Pain		145	40.07	19.64	70	46.01	22.24	0.048
KOOS Symptoms		93	28.98	23.23	62	45.20	21.69	<.0001
KOOS ADL		146	32.11	17.88	73	40.29	22.77	0.008
KOOS Sports and Rec		64	36.97	27.78	35	49.51	36.46	0.058
KOOS QOL		91	43.77	26.25	59	51.24	26.02	0.090
SF-12 PCS		129	12.14	10.44	65	11.15	8.85	0.511
SF-12 MCS		129	2.89	9.74	65	2.14	12.50	0.758

Table 2. Comparison of baseline, 2-year and delta expectation scores, pain, and patient reported outcome measures. OA: Osteoarthritis cohort; RA: Rheumatoid Arthritis cohort; N: number of patients; ColPctN: percentage of patients; Std: stand deviation; p-value ¶: obtained using Two-sample t-test

Conclusion: While RA patients had lower baseline expectations compared to OA patients they achieved meaningful improvement in KOOS and SF-12 subdomains and there was no difference in satisfaction compared to OA patients after TKA. These findings may be used for preoperative counseling prior to TKA.

Disclosure: J. Blevins, None; Y. F. Chiu, None; S. Lyman, None; S. M. Goodman, Roche, Novartis, 4; L. A. Mandl, None; P. K. Sculco, Lima, 5; M. P. Figgie, None; A. McLawhorn, Ethicon and Intellijoint, 5.

Abstract Number: 485

Bone Loss in Different Sites over Time in Patients with Rheumatoid Arthritis

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Session Information

Session Date: Sunday, October 21, 2018

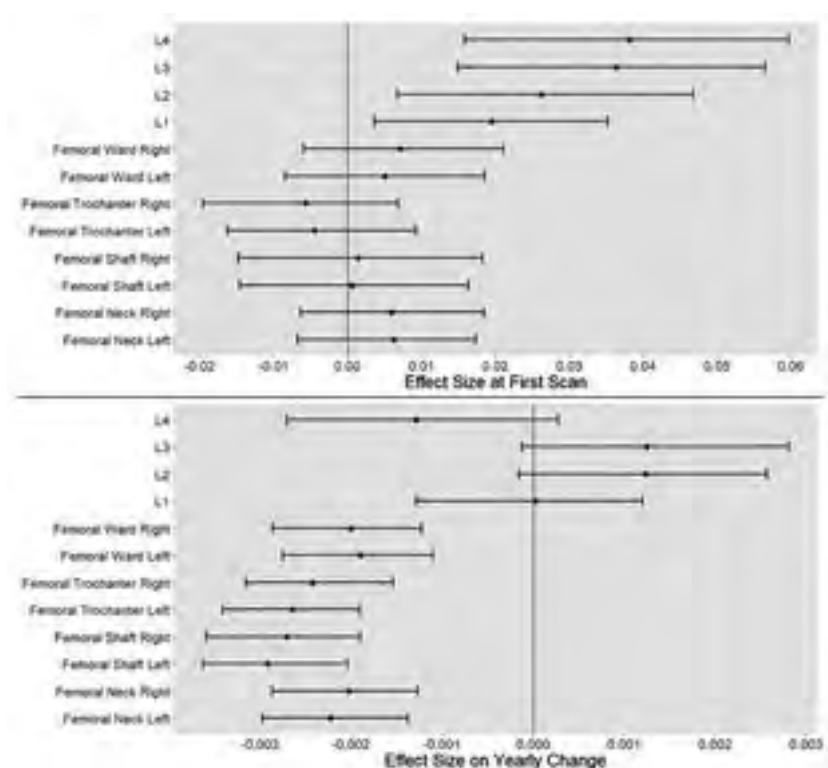
Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) is described as an independent risk factor for osteoporosis and is included in models, including the FRAXTM tool which uses bone mineral density (BMD) as well as demographics to predict fracture risk. Most dual X-ray absorptiometry (DEXA) scans only measure the non-dominant hip. Published data are from existing datasets that are X-sectional and the influence of factors on progression of BMD loss in different sites has not been studied. We aimed to test the hypothesis that bone loss over time is more pronounced in patients with RA, compared to those without.

Methods: We used data from patients referred for DEXA in the North West of England from June 2004 and October 2016. Patients have their FRAXTM risk factors assessed and their BMD measured in both femoral necks, shaft, trochanter and Ward's triangle in addition to L1-L4 in the lumbar spine (LS). Patients attending for multiple scans in this period without a diagnosis of RA were used as a comparator group. A longitudinal mixed-effects model was fitted, with BMD at each site as



the exposure, adjusting for all risk factors for OP in addition to fitting interaction terms for bisphosphonate use in addition to calcium/vitamin D use.

Results: 6941 patients were included, 6169 (88.9%) were females. Of whom 1270 (20.5%) were menopausal. Mean age was 63 years (SD 11.3 years) and 749 patients with RA (named the RA group) had multiple scans and were compared to the 6192 without an RA diagnosis. There is an average of 2.35 scans per patient (SD 0.64 scans), an average of 4.26 years apart (SD 1.88 years). Patients in the RA group had significantly higher average BMD in the lumbar spine than those in the non-RA group. There was no significant difference in the bone mineral density of the femur between the RA and non-RA groups. Conversely, patients in the RA group lost BMD faster in the femur than the non-RA group, but BMD loss in the lumbar spine was not significantly different between groups.

Figure 1. Showing the results of the longitudinal analysis for average BMD (top) and bone loss over time (bottom)

Conclusion: The average BMD in the lumbar spine is higher in the RA group than in the non-RA group, but bone loss appears to be increased in the femur at all sites of measurement. The most likely explanation is increasing OA in the lumbar spine causing slower loss of BMD. This is clinically significant because bone loss in the hip is used as a predictor for fracture and the rapid bone loss seen would necessitate reducing the interval between scans in this group of patients. Limitations of the study include lack of information about length of disease and specific treatments history for the RA patients.

Disclosure: R. Tribbick, None; M. Massarotti, None; J. G. Kerns, None; F. Dondelinger, None; M. Bukhari, None.

Abstract Number: 486

The Electrophysiologic and Sonographic Evaluation of Peripheral Nerves in Rheumatoid Arthritis Patients

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: The compression neuropathies due to arthritis, tenosynovitis and deformities in the joints, mononeuritis multiplex are very common in patients with rheumatoid arthritis (RA). No previous study investigated function and morphology of peripheral nerves in patients with RA. This study was aimed to compare the morphology and electrophysiology of median, ulnar and tibial nerves in patients with RA to healthy controls.

Methods: Fifteen female patients (20-60 years) were diagnosed with RA at least 1 year before according to ACR criteria and 12 healthy women (matched for age and body mass index) were enrolled. A total of 30 RA patient extremities and 24 healthy controls were included. Patients with an additional disease (diabetes, hypothyroidism, uremia, Lyme, sarcoidosis, leprosy, Guillain Barre syndrome, neurotoxic drug use, etc.), which may be caused by polyneuropathy, were excluded. Disease activity was assessed by using the clinical disease activity index (CDAI), DN4-neuropathic pain questionnaire, with or without neuropathic pain. The patients and the control group were assessed by three independent researchers. After clinical assessment of the clinician (SUD), the patients were referred to the electrodiagnosis laboratory. Nerve conduction studies (NCS) were performed by the same electrodiagnostician (ZO) who was blinded to clinical findings. The patients who had an electrodiagnostic abnormality were excluded. Patients were referred to ultrasonographic assessment, which was done by a third blinded researcher (SSO). In the electromyography (ENMG) measurement; median (motor and sensory), ulnar (motor and sensory), tibial (motor), and sural (sensory) nerve conduction studies were performed bilaterally.

Results: Sonographic measurements of nerve cross-sectional area of the median nerve at level of wrist, ulnar nerve at wrist and midpoint of forearm, and cubital tunnel and tibial nerve at the level of the both ankle and poplitea were statistically bigger in patient with RA than the control group ($p < 0.05$) (Table 1). Cubital tunnel syndrome (6 in RA patients, 2 in control group; $p < 0.05$) and carpal tunnel syndrome (4 in RA patients, 2 in control group; $p < 0.05$) were observed significantly more in RA patients than control group in ENMG study.

	Patients with RA mean \pm standard deviation	Control group mean \pm standard deviation	p
Median nerve cross sectional area			
Wrist	10.8 \pm 3.8	9.6 \pm 4.2	0.896
Mid forearm	8.2 \pm 2.6	7.1 \pm 3.4	0.231
Elbow	14.4 \pm 4.7	10.3 \pm 4.9	0.828
Ulnar nerve cross sectional area			
Wrist	5.2 \pm 2.7	3.1 \pm 1.3	0.005
Mid forearm	7.2 \pm 3.1	4.3 \pm 1.5	0.001
Elbow	10.6 \pm 3.2	7.9 \pm 3.4	0.016
Tibial nerve cross sectional area			
Ankle	6.1 \pm 3.1	3.9 \pm 1.7	0.044
Poplitea	29.9 \pm 12.1	17.3 \pm 6.4	0.003

Conclusion: In summary, there are morphological changes in the peripheral nerves of RA patients, although their functions are not impaired yet. Therefore, it is important to evaluate the peripheral nerves sonographically in RA patients.

Disclosure: S. Sahin Onat, None; Z. Özisler, None; A. Orhan, None; S. Ünsal-Delialioglu, None; S. Ozel, None.

Abstract Number: 487

Cognitive Impairment in Rheumatoid Arthritis Patients: A Case-Control Study

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis in adults. Extra-articular manifestations of RA can occur in about 40% of patients, either in the beginning or during the course of their disease. Recent studies have suggested that RA may have an important relation in the development of cognitive and neurological dysfunction. However, the bond between RA and the brain is still uncertain. The purpose of this study was to assess the frequency and the clinical predictors of cognitive impairment in rheumatoid arthritis (RA) patients.

Methods: A cross-sectional and case-control study was performed including consecutive RA patients seen in a rheumatology outpatient clinic of referral tertiary hospital. The control group included 100 healthy subjects. We registered clinical and demographic data including age, sex, level of education, time of disease, time of diagnosis, drugs in use, cardiovascular risk factors and other comorbidities. Functional capacity was assessed using the Health Assessment Questionnaire (HAQ). Neurological appraisal was made with standardized questionnaires: Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and the Hospital Anxiety and Depression (HAD). Analysis of the data was performed using chi-square and t-tests and a multivariate analysis (SPSS 22.0). Significance level was set as <0.05.

Results: We included 200 patients (166 were female) with a mean age of 57.4 (\pm 11.4) years; Among these patients, 163 (81.5%) used corticosteroids, 148 (74%) methotrexate, 16 (8%) sulfasalazine, 91 (45.5%) leflunomide, 35 (17.5%) chloroquine and 57 (28.5%) biologic therapy. The mean age of RA diagnosis was 43.0 (\pm 13.6) years. In both univariate and multivariate analysis, compared to the control group, patients with RA presented significant lower MMSE (21.9 \pm 3.9) and MoCA (17.0 \pm 4.4) scores (p <0.05). Adjusting for level of education, just 61 and 50 patients presented normal MMSE and MoCA scores (p <0.01), respectively. Cognitive decline was associated with higher HAQ scores (functional outcome due to RA) and prolonged time of disease (p <0.05). No correlation was found between sex, disease-modifying antirheumatic drugs, rheumatoid factor, C-reactive protein levels and the neurological impairment. The mean HAD score was 17.7 (\pm 7.7) and anxiety and depression were more prevalent in RA patients than in control group (p <0.01).

Conclusion: Patients with rheumatoid arthritis may present with cognitive decline and dementia as extra-articular manifestations of the disease. Neurological impairment is usually disregarded and might be under-diagnosed in RA patients. Future studies are necessary in order to better understand the relationship between RA and the brain.

Disclosure: B. Rizkallah Alves, None; B. KUSZNIR VITTURI, None; B. AZEREDO COUTINHO NASCIMENTO, None; F. SOBOLEWSKI CARNEIRO DE CAMPOS, None; D. Yukito Torigoe, None.

Abstract Number: 488

Rheumatoid Meningitis: Meningeal Biopsy Is Not Essential for Diagnosis

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid meningitis (RM) is a rare complication of RA with a high mortality rate if untreated. Traditionally RM has been a diagnosis of exclusion. Although there are no established diagnostic criteria for RM, current clinical practice relies on a meningeal biopsy for diagnosis¹. Previous reports have stressed on the critical importance of a biopsy before rendering a diagnosis of RM². Our study aimed to review the clinical history of RM at our institution and assess the role of meningeal biopsy in RM patients.

Methods: An administrative database search with the key terms “rheumatoid arthritis”, “pachymeningitis”, “leptomeningitis”, “chronic meningitis”, and “meningitis not otherwise specified” was conducted within the Mayo network from 1990-2017 to identify RM patients. Patients were only included if the RA was diagnosed by a rheumatologist and RM was diagnosed both by a rheumatologist and neurologist. A retrospective chart review was undertaken to obtain complete clinical history, testing, imaging, histopathology, treatment and outcome.

Results: Fourteen patients with a diagnosis of RM were identified. Mean age was 67 years and 57% were males. RA disease duration ranged from many years to new onset RA diagnosed concurrently with RM. No patient had seronegative disease. RA disease activity was controlled in 10/11 (91%) of the patients at RM diagnosis. Subcutaneous nodules were present in 4/13 (31%) and erosions in 3/10 (30%) patients. Headache, seizure and hemiparesis were the most common presentations of RM. No patient had cranial neuropathies. Cerebrospinal fluid cell count and protein levels were normal in 3/14 (21%) patients. All patients demonstrated enhancement of the pachymeninges, leptomeninges or both, with 12/14 (86%) having a fronto-parietal predominance on MRI. Comprehensive clinical workup excluded other conditions. Of the 10 patients undergoing biopsy, 10/14 (80%) showed nonspecific findings of inflammation or necrosis and none showed vasculitis or rheumatoid nodules. Infectious organisms and specific histological changes of IgG4 disease were absent. Corticosteroids, rituximab and methotrexate were used for treatment. 10 of the 12 (83%) patients who underwent repeat imaging showed complete or near complete resolution of abnormalities. The four RM patients treated without undergoing a biopsy did similarly well.

Conclusion: RM can present at any time in RA and occurs in well controlled RA. MRI shows fronto-parietal meningeal enhancement. Biopsy is negative for pathognomonic features of RM. Patients with suspected RM without biopsy do equally well with treatment. In contrast to the previous literature, our study shows that clinical evaluation, testing and imaging in RA patients with meningitis, in the absence of atypical features e.g. seronegative disease, is sufficient to diagnose RM without a biopsy. Biopsy should not delay treatment. RM responds well to immunosuppressive treatment.

References:

1. Kato T, Hoshi K, Sekijima Y, et al. Rheumatoid meningitis: an autopsy report and review of the literature. Clin Rheumatol. 2003;22:475–480.
2. Lattanzi S, Cagnetti C, Di Bella P, et al. Leptomeningeal inflammation in rheumatoid arthritis. Neurol Neuroimmunol Neuroinflamm. 2014;1:e43.

Disclosure: F. Aslam, None; A. Parsons, None; M. Grill, None; B. Goodman, None.

Self-Reported Depression in Patients with Rheumatoid Arthritis Is Undertreated and Associated with Poorer Clinical Status and Lower Rates of Remission in Routine Care

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Depression in patients with rheumatoid arthritis (RA) may be pre-existent, amplified, or newly-developed after onset of RA. Together with other comorbidities, socioeconomic factors, education level or affective factors can influence perception of pain, functional disability, and health status. The prevalence of depression in RA patients has been estimated to be 19% over 5 years and affect remission rates according to a classical composite index (Leblanc-Trudeau, C et al. Rheumatology 2015;54:2205-14). We compared patient self-reported scores included in the Multidimensional Health-Assessment Questionnaire (MDHAQ) and levels of remission according to RAPID3 in patients who reported depression versus no report of depression.

Methods: All patients, regardless diagnoses, complete a MDHAQ at each visit in the waiting area before seeing the rheumatologist at all visits. The 2-page MDHAQ includes physical function (FN) in 10 activities of daily living, three 0-10 visual analogue scales (VAS) for pain (PN), patient global estimate (PATGL), fatigue (FT), RADAI self-report joint count, a review of 60 symptom checklist, three 0 to 3.3 scores for depression, anxiety, and sleep quality, and demographic data. RAPID3 (0-30) is the sum of 0-10 scores from FN, PN, and PATGL; remission corresponds to a RAPID3 value ≤ 3 . Patients with RA (physician ICD9 and ICD10 diagnosis) were classified according to self-report of checking depression as part of a symptoms checklist. A retrospective chart review was conducted to evaluate the percentage of patients with treatment or specialist evaluation for depression. Demographic and clinical characteristics were compared according to self-reported depression status using Student t-test and chi-square test.

Results: Overall 464 RA patients were included in the analysis, of which 118 (25%) self-reported depression in the last month. Only 37 (31%) of all patients reporting depression had evidence in the medical record of treatment and/or specialist evaluation for depression. Mean age (SD) was 55.5 (14.9) and 86% were female, with no difference between depression groups. Patients reporting depression had lower education level (12.5 vs 14.3, $p < 0.001$) and poorer scores for physical function, pain, and patient global leading to higher RAPID3 and lower percentage of patient in remission (12.4 vs 4%, $p < 0.001$) (Table). Depressed patients also reported higher scores for fatigue, number of painful joints, number or symptoms, and more difficulty with sleep, and anxiety (Table).

Table: MDHAQ/RAPID3 patient self-report scores in patients with rheumatoid arthritis according of their depression status. Data are presented as mean (SD) and percentages. Comparisons by Student t-test and chi-square test.

	No self-reported depression N= 346 (75%)	Self-reported depression N= 118 (25%)	p
Demographic variables			
Age, years	55.4 (14.9)	55.8 (15.1)	0.80
Female, %	84%	91%	0.08
Education level, years	14.3 (3.1)	12.5 (3.4)	<0.001
MDHAQ/RAPID3: Patient self-report scores			
Physical function (0-10)	2.4 (2.0)	3.4 (1.9)	<0.001
Pain (0-10)	5.3 (3.0)	6.8 (2.6)	<0.001
Patient global estimate (0-10)	4.9 (3.0)	6.6 (2.7)	<0.001
RAPID3 (0-30)	12.6 (7.2)	16.6 (6.4)	<0.001
% patients in RAPID3 remission	12.4%	4%	<0.001
Fatigue (0-10)	4.2 (3.2)	6.3 (3.0)	<0.001
Self-reported joint pain-RADAI (0-48)	12 (10)	18 (12)	<0.001
Review of Symptoms (0-60)	8 (7)	18 (9)	<0.001
Sleep problems (0-3.3)	1.1 (0.9)	1.9 (0.9)	<0.001
Dealing with depression/feeling blue (0-3.3)	1.1 (0.9)	1.9 (0.9)	<0.001
Dealing with anxiety/being nervous (0-3.3)	0.1 (0.4)	0.7 (0.4)	<0.001

Conclusion: The prevalence of self-reported depression in our RA patients was 25%, with only 31% treated for this condition. RA patients with self-reported depression exhibit higher scores for all MDHAQ patient-reported outcomes,

including to a lower rate of RAPID3 remission. MDHAQ/RAPID3 may be useful to identify patients with depression in busy clinical settings.

Disclosure: I. Castrejón, None; M. Riad, None; J. R. Chua, None; T. Pincus, Medical History Services, LLC., 7, 9.

Abstract Number: 490

Catastrophizing in Rheumatoid Arthritis

Soraya Benamar¹, Charlotte Hua², Jacques Morel³, Françoise Barchechath-Flaisler⁴, Bernard Combe³, Cédric Lukas³ and Cécile Gaujoux-Viala⁵, ¹Rheumatology, Department of Rheumatology, Nîmes University Hospital and Montpellier University EA 2415, Nîmes, France, ²Department of Rheumatology, Nîmes University Hospital and Montpellier University EA 2415, Montpellier, France, ³University Hospital Lapeyronie, Department of Rheumatology, Montpellier, France, ⁴Rheumatology, Department of Rheumatology, Nîmes University Hospital and Montpellier University EA 2415, Nîmes, France, ⁵Department of Rheumatology, Nîmes University Hospital and Montpellier University EA 2415, Nîmes, France

Session Information

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Several studies pay a particular attention to catastrophizing. Catastrophizing is a negative cognitive and affective response based on inadequate expression of pain. The objective was to assess catastrophizing level in rheumatoid arthritis (RA) and to determine if there is a link between catastrophizing and physical pain intensity, disease activity, disability, depression and quality of life.

Methods: We performed a systematic review of literature and search the following databases : PUBMED-MEDLINE, COCHRANE and EMBASE until April 2018. All observational, cross-sectional and randomized control studies investigating catastrophizing in patients with rheumatoid arthritis were included. Statistical analysis defined pooled mean catastrophizing level, using the Pain Catastrophizing Scale (PCS) and assessed the association with disease activity (DAS28), pain (Numerical Rating Scale NRS) and quality of life (SF36).

Results: On 1494 articles concerning catastrophizing and rheumatic disorders, 22 articles concerned RA patients. Finally, 7 were selected in the meta-analysis including 601 RA patients (mean age 57.4 years old, 67.7% female, mean pooled DAS 28 = 3.4 and mean pooled VAS = 3.8). Mean pooled catastrophizing level at baseline was 14.7 (sd = 11.4) in RA patients. In one study, a RA sample identified 22% of high catastrophizers (defined by PCS > 30). There is a significantly positive correlation between pain catastrophizing and disease activity in 3 studies (r between 0.22 and 0.39, all p<0.01) (Table). Pain is strongly associated with catastrophizing (r=0.71 (p<0.01) for NRS; r = -0.43 (p<0.01) for SF-36 Bodily Pain). Higher PCS scores were significantly associated with higher levels of distress i.e. lower SF-36 Mental Health score (r= -0.52 (p<0.01)). Moreover catastrophizing is significantly associated with reduced physical function (r=-0.35 (p<0.01) for SF36 Physical Function) (Table).

Conclusion: Catastrophizing is rarely measured but it's a common psychological trait which is clearly associated with disease activity, pain, mental health and physical function. It would be interesting to early detect it in order to adapt pharmacologic and non-pharmacologic treatment.

Table 1 : Correlation coefficient between Pain Catastrophizing Scale(PCS) and variables of interest in RA patients

	DAS 28	Pain	Mental Health	Physical Function
PCS	r = 0.33 (p<0.002) r = 0.39 (p< 0.01) r = 0.22(p<0.01)	r = 0.71 (p<0.01)* r = -0.43 (p<0.01)°	r = -0.52 (p<0.01)	r = -0.35 (p < 0.01)

Results are expressed by correlation coefficient (r) and significance level (p)

* Numerical Rating Scale

° SF-36 Bodily Pain

Disclosure: S. Benamar, None; C. Hua, Abbvie, BMS, Pfizer, 5; J. Morel, Abbvie, BMS, Celgene, Janssen, Medac, MSD, Novartis, Pfizer, Sanofi, Schering, Roche- Chugai, UCB, 5; F. Barchechath-Flaisler, Roche Pharmaceuticals, 5; B. Combe, Pfizer, UCB, BMS, Janssen, Lilly, MSD, Roche-Chugai, Abbvie, Novartis, 2, 5, 8; C. Lukas, Abbvie, BMS, Celgene, Janssen, MSD, Novartis, Pfizer, Sanofi, Schering, Roche- Chugai, UCB, 5; C. Gaujoux-Viala, Abbvie, BMS, Celgene, Janssen, Medac, MSD, Nordic Pharma, Novartis, Pfizer, Sanofi, Roche- Chugai, UCB, 2, 5.

Cognitive Impairment Is Associated with Disease Activity in Patients with Rheumatoid Arthritis

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Session Information

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Session Type: ACR Poster Session A

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

Background/Purpose: Intact cognitive function is important for executing several tasks on day-to-day basis in people with chronic diseases, including rheumatoid arthritis (RA). A number of studies have reported a high prevalence of cognitive impairment in patients with RA. Chronic systemic inflammation in RA may play an important role in the pathogenesis of cognitive impairment, in addition to the traditional risk factors. Our objective was to investigate the association between disease activity and cognitive impairment in patients with RA.

Methods: All patients who were of Thai nationality, aged of 18 years old or older, diagnosed of RA according to the ACR 1987 revised criteria for the classification of RA or the 2010 Rheumatoid arthritis classification criteria, literate, and had at least a visit of follow-up were included in this study. A total of 464 patients from the RA registry of 2 academic centers, Siriraj and Phramongkutklao hospital were included. Demographics, clinical and laboratory data related to disease activity (Disease activity score 28 or DAS28), functional status (Health assessment questionnaire or HAQ) were collected. Cumulative disease activity of DAS28 was calculated by the sum of serial measurement of DAS28 divided by the total times of clinic visits from first to last measurement. Cognitive function was assessed using the Thai version of the Montreal cognitive assessment (MoCA-T). Subjects were classified as cognitively impaired if they scored less than 25, a cutoff point validated in Thai population. Univariate and multivariate analyses were performed to identify factors associated with cognitive impairment.

Results: Most subjects (85%) were female with the mean age \pm SD of 59.2 ± 11.4 years old and median (range) educational level of 9 (4-14) years. The median duration of follow-up (range) was 5.2 (2.2-5.9) years. They were long-standing RA [median disease duration (range) of 9.9 (5.1-16.6) year], had moderate cumulative disease activity [mean DAS28 \pm SD of 3.5 ± 0.81], and mild functional impairment [median HAQ (range) 0.5 (0.13-1.10)]. Seventy percent was classified as having cognitive impairment. Patients with cognitive impairment significantly impaired in all domains, especially in visuospatial/executive, language, and abstraction. In multiple logistic regression analyses, old age (> 60 years) [RR 3.43, 95% CI 2-5.9, $p < 0.001$], low education (< 6 years) [RR 9.9, 95%CI 4.9-19.9, $p < 0.001$], and high cumulative disease activity (mean DAS28 > 2.6) [RR 2.2, 95%CI 1.04-4.4, $p = 0.038$] were independently associated with cognitive impairment.

Conclusion: Besides traditional risk factors, high cumulative RA disease activity is associated with cognitive impairment. Therefore, treat-to-target aiming at low disease activity or remission may be beneficial for preventing cognitive decline in RA patients.

Multiple logistic regression analysis to identify factor related to cognitive impairment in RA

Factors	RR	95%CI	P-value
Age > 60 years	3.43	2.01 – 5.86	< 0.001
Smoking	1.75	0.75 – 4.09	0.197
Education < 6 years	9.88	4.91 – 19.86	< 0.001
Unemployment	1.11	0.67 – 1.86	0.678
DAS28 > 2.6	2.15	1.04 – 4.42	0.038
HAQ > 0.5	1.05	0.65 – 1.69	0.857
Anxiety	2.29	0.92 – 5.69	0.075

Disclosure: W. Katchamart, None; P. Narongroeknawin, None; N. Phutthinart, None; V. Srinonprasert, None; W. Muangpaisan, None; S. Chaiamnuay, None.

All Site Cancers and Lymphoma Incidence in US Veterans with Rheumatoid Arthritis 2001-2015

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Session Information

Session Date: Sunday, October 21, 2018

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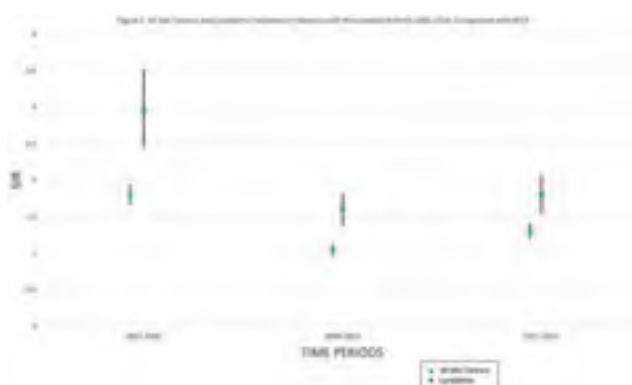
Session Type: ACR Poster Session A

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

Background/Purpose: Patients with rheumatoid arthritis(RA) have a modest increased risk of overall cancer and of lymphoma. The purpose of our study was to report trends in the incidence of all site cancers and lymphoma in US Veterans with RA relative to US population-based rates from the Surveillance, Epidemiology, and End Results (SEER) Program.

Methods: In order to identify RA patients in the national VA, we used the following algorithm: ≥ 2 RA diagnostic codes at least 30 days apart, rheumatologist diagnosis of RA, and either a DMARD prescription or positive autoantibody test (RF or anti-CCP) within the VA Corporate Data Warehouse between 1/2001-12/2015; exclusion criteria included patients with diagnostic codes for psoriatic arthritis or ankylosing spondylitis. Diagnoses of all site cancers (includes all cancers -in situ and malignant)were identified from the VA Central Cancer Registry (VACCR) and mortality data from the National Death Index. The study period was divided into three 5-yearintervals: 2001-2005, 2006-2010, and 2011-2015. Person-years of follow-up for RA patients was calculated from the index date (first fulfilling the RA algorithm) to the earliest of death, the development of any cancer (for trendsin all site cancer), or development of lymphoma (for trends in lymphoma), or theend of the study period (12-31-2015). Rates of all site cancer and lymphoma forthese time intervals in 5-year age groups (20-24 through 85+) were obtained from SEER*Stat version 8.3.5. Standardized incidence ratios (SIRs) were calculated for each time period by dividing the observed number of cancers in RA patients to the expected numbers obtained by applying the SEER rates.

Results: We identified 50,870 male US Veteranswho fulfilled our RA algorithm and eligibility criteria. The mean (SD) age was64 (11) years, 80% were white, 13% black, 60% were current or former smokers,65% were RF positive and 62% were anti-CCP positive. Among these patients, 4435all site cancers and 461 lymphomas were observed. Relative to SEER, the highest SIRs were observed in 2001-2005 for both all site cancers (1.8, 95% CI 1.7-1.9)and lymphomas (2.9, 95% CI 2.4-3.5). We observed a decrease in SIRs for bothtypes of cancers in 2006-2010 and then a slight increase in the last time period(Figure 1).



Conclusion: To our knowledge, this is the first study evaluating incidence trends of all site cancers and lymphoma in a national cohort of veteran RA patients. We observed higher rates of both all site cancers and lymphomas, in the veteran RA population compared to the SEER population, but the trend was toward decreasing risk over more recent years compared to a similarly-aged non-RA population.

Figure1.Trends in All Site Cancer and Lymphoma Incidence in veteran RA patientscompared with the US general population

Disclosure: N. Singh, None; Y. Gao, None; B. R. England, None; P. Roul, None; E. Field, None; J. F. Baker, Corrona, Bristol Myers Squibb, 5; B. Sauer, None; T. R. Mikuls, BMS, Ironwood, Horizon, 2,Pfizer, Inc., 5; G. W. Cannon, Amgen Inc., 2; J. R. Curtis, AbbVie, Amgen, BMS, Janssen, Pfizer, Roche/Genentech, Corrona, UCB, 2, 5; M. Vaughan-Sarrazin, None; C. Lynch, None.

Abstract Number: 493

Trends in the Incidence of SOLID Tumors in Patients with Rheumatoid Arthritis in Spain. a National Observational Cohort Study

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Session Information

Session Date: Sunday, October 21, 2018

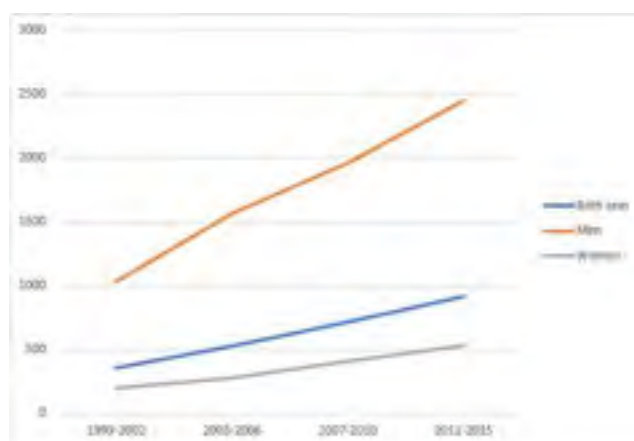
Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: During the last 20 years, the treatment in rheumatoid arthritis (RA) has changed. Considering the increasing use of biological immunomodulators to treat chronic inflammatory conditions and the concern that immune modulation may alter cancer risk and progression, it's important to know the tumors incidence in patients with RA. The objective of this study was to analyze the incidence and trend of hospital admissions for solid tumors in patients with RA in Spain during the period between 1999 and 2015.

Methods: This is a retrospective population based study. We have analyzed a national administrative database that includes a Minimum Basic Data Set (MBDS) of hospital admissions of RA patients during the period 1999 to 2015. We selected the MBDS for solid tumors (breast, colon, pancreas, prostate, lung, pleura, melanoma, ovary, cervix, uterus, bladder and kidney). Cases were identified by the presence in primary and secondary diagnosis of ICD9 codes. The population at risk was estimated through the population census of the National Institute of Statistics, with an estimated prevalence of RA



of 0,5% (0,8% in women and 0,2% in men). Crude and adjusted rates of the solid tumors were calculated, and the trend was analyzed using the Generalized Linear Model (GLM) with the year as the analysis variable.

Results: 338.343 RA hospital admissions were detected in the study period, being 18.401 (5,4%) due to solid tumors. The main clinical-demographic characteristics are shown in the next table.

	Total	Women	Men	<i>P value</i>
N (%)	18.401 (5,4)	8689 (3,8)	9712 (8,6)	<i>P</i> <0,001
Age, mean (SD)	69,98 (11,21)	68,62 (12,3)	71,20 (9,99)	<i>P</i> <0,001
In-hospital exitus n (%)	2455 (13,34)	1035 (11,9)	1420 (14,62)	<i>P</i> <0,001
Charlson Index, mean (SD)	5,72 (2,95)	5,63 (2,95)	5,80 (2,95)	<i>P</i> <0,001
Stay, mean (SD)	10,94 (11,6)	10,76 (11,6)	11,1 (11,77)	<i>P</i> =0,051

The solid tumor adjusted rate during the study period was 647,53/10⁵ inhabitants/yr (366,97/10⁵ in women and 1792,99/10⁵ in men; relative risk men:women =4,8). This rate increased from 305,65/10⁵ in 1999 to 993,19/10⁵ inhabitants/yr in 2015 (814,06/10⁵ in 1999 to 2535,5/10⁵ in 2015 in men and from 181,68/10⁵ in 1999 to 607,71/10⁵ in 2015 in women). The annual age-adjusted rate increased significantly: 7,37% (6,52% in men and 8,02% in women; *p*≤0,001). Figure 1.

Conclusion: There was an increasing incidence of hospital admissions due to solid tumors in RA in Spain during the period 1999-2015. An annual rate increase of 7.37%, is estimated.

Disclosure: V. Villaverde García, None; M. Fernández, None; R. Mazzucchelli, None; C. Macia-Villa, None; G. Candelas, None; J. Quirós, None; M. Peña, None; E. Perez-Fernandez, None; N. Crespi, None; A. Garcia-Vadillo, None; C. Barbadillo, None; J. L. Morell-Hita, None; H. Godoy, None; M. Espinosa, None; C. Morado-Quinoá, None; C. Martinez-Prada, None; M. Galindo, None; O. Guzon-Illescas, None; A. Herranz, None.

Abstract Number: 494

Arterial Wall Inflammation Declines after 6 Months of Anti-Inflammatory Therapy with Methotrexate and/or Adalimumab in Rheumatoid Arthritis Patients

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Patients with rheumatoid arthritis (RA) have an elevated cardiovascular (CV) disease risk, mostly explained by both an increased prevalence of traditional CV risk factors and the presence of systemic inflammation that accelerates atherosclerosis. There is accumulating evidence that anti-inflammatory treatment for RA reduces this CV risk. A non-invasive tool for detecting arterial wall inflammation in atherosclerosis is 18F-Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography (18F-FDG-PET/CT). In this study we investigated the effect of anti-inflammatory treatment with methotrexate (MTX) and/or adalimumab on arterial wall inflammation in RA assessed by 18F-FDG-PET/CT.

Methods: 18F-FDG-PET/CT was done in patients with active early RA starting MTX (n=25) and active established RA starting adalimumab (n=24) before and after 6 months of therapy, and in osteoarthritis controls (OA; n=29). 18F-FDG uptake in arterial wall was determined by standardized uptake values (SUV). Volumes of interest covering the arterial segment with the highest 18F-FDG were defined to derive the maximum SUV (SUVmax) in the ascending, descending and abdominal aorta and the aortic arch. Global arterial uptake was estimated using the mean SUVmax of the arterial segments.

Results: Mean age was 65±9 for early RA, 61±7 for established RA and 63±5 years for OA controls. Median disease duration was 2.1 (interquartile range (IQR) 1.3-3.3) weeks for early RA and 6.9 (IQR 1.8-13.9) years for established RA. DAS28 was 4.9±1.0 and 4.4±1.0 at baseline and declined to 3.1±1.3 and 2.8±1.4 after 6 months therapy, respectively. At baseline mean SUVmax was 1.86±0.38 for early RA, 1.68±0.43 for established RA and 1.56±0.41 for OA controls. SUVmax tended to decline more in early RA patients when compared to established RA (1.86±0.38 to 1.79±0.43 (-3.7%) and 1.68±0.43 to 1.63±0.43 (-3.0%), respectively). SUVmax in most arterial segments declined after 6 months of therapy (Table 1). The most prominent decline in SUVmax was in the abdominal aorta in established RA patients (-9.8%).

Conclusion: A decline in global arterial SUV max and in most of arterial segments was found in both early and established RA patients after 6 months of MTX and/or adalimumab, suggesting that anti-inflammatory therapy with either MTX and/or adalimumab decreases arterial wall inflammation and thus CV risk in RA.

Table 1. Arterial 18F-FDG uptake

	OA	Early RA			Established RA		
	Baseline	Baseline	6 months MTX	Δ	Baseline	6 months adalimumab	Δ
SUVmax	1.55±0.44	1.82±0.38	1.77±0.38	-2.7%	1.69±0.61	1.60±0.44	-5.3%
ascending aorta							
SUVmax descending aorta	1.57±0.42	1.93±0.53	1.81±0.47	-6.2%	1.65±0.39	1.71±0.47	+3.6%
SUVmax	1.62±0.43	1.84±0.44	1.81±0.58	-1.6%	1.73±0.61	1.56±0.45	-9.8%
abdominal aorta							
SUVmax	1.51±0.48	1.85±0.48	1.76±0.45	-4.9%	1.66±0.40	1.64±0.59	-1.2%
aortic arch							
Mean SUVmax over 4 segments	1.56±0.42	1.86±0.38	1.79±0.43	-3.7%	1.68±0.43	1.63±0.43	-3.0%

Disclosure: A. Blanken, None; R. Agca, None; A. Voskuyl, None; R. Boellaard, None; C. van der Laken, None; M. Nurmohamed, AbbVie, Pfizer, Merck, Roche, BMS, UCB, Eli Lilly, Celgene and Janssen, 2, 5, 8.

Abstract Number: 495

Characteristics of Metabolic Syndrome in Men and Women with Early Rheumatoid Arthritis

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

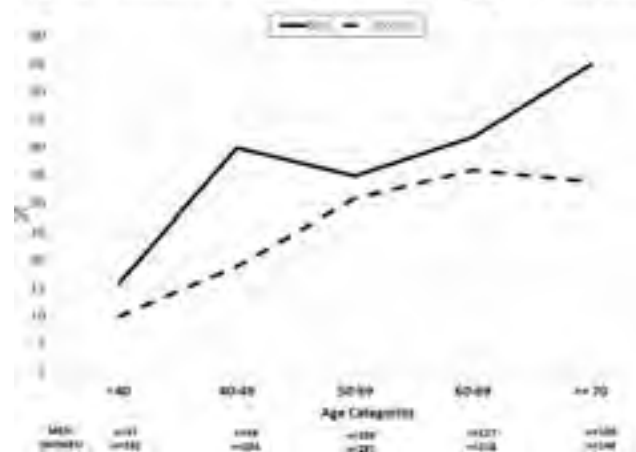
Prevalence and Characteristics of Metabolic Syndrome in Men and Women With Early Rheumatoid Arthritis

B. Kuriya, O. Schieir, M.F. Valois, J.E. Pope, G. Boire, L. Bessette, G. Hazlewood, J.C. Thorne, D. Tin, C. Hitchon, S. Bartlett, E.C. Keystone, V.P. Bykerk and L. Barra, on behalf of CATCH investigators.

Background/Purpose: Metabolic syndrome (MetS) increases the risk of cardiovascular disease (CVD) and is highly prevalent in established RA but data on the prevalence in early RA (ERA) are conflicting. Furthermore, there are limited data on potential differential expression of MetS by sex in RA. Our aim was to estimate the prevalence and characteristics of MetS among men and women with ERA.

Methods: The Canadian Early Arthritis Cohort (CATCH) is a multicenter observational study of ERA patients. Participants (n=1536) with confirmed ERA (symptoms <12 months) and complete baseline data for MetS components were included to estimate the prevalence of MetS according to the 1999 World Health Organization definition, requiring ≥2 of 5

Figure. Prevalence of MetS at baseline by age group and sex.



components (BMI ≥ 30 , or BP $\geq 140/90$, or HDL level ≤ 1.0 mmol/L in women or ≤ 1.0 mmol/L in men, or triglyceride level ≥ 2.0 mmol/L, or random glucose ≥ 6.1 mmol/L). Sex-stratified logistic regression was used to identify clinical, laboratory and treatment variables associated with MetS.

Results: The study sample was 71% female, mean age was 54 (SD 15) years, mean DAS28-ESR at cohort entry was high 5.1 (SD 1.4) and the majority was treated with csDMARDs (87%), at or before, the baseline visit. At baseline, 462 (30%) met criteria for MetS; prevalence was higher in men 180 (41%) than women 282 (26%); $p < 0.0001$. Age and sex stratified prevalence of MetS is shown in the Figure. The most frequent MetS components in men were hypertension (60%), glucose intolerance (39%), obesity (BMI ≥ 30 , 36%) and low HDL (36%); and in women were hypertension (47%), obesity (30%) and glucose intolerance (23%). These components were all significantly higher in men than women ($p < 0.05$). In univariable analysis, MetS was significantly associated with higher mean uric acid, creatinine and alanine aminotransferase levels in women; and higher mean creatinine in men. These associations were no longer significant after adjustment in multivariable logistic regression.

Conclusion: The prevalence and characteristics of MetS were different in male and female ERA patients. Further investigation is needed to determine if different strategies for CVD risk management in men and women with ERA and MetS is required.

Figure. Prevalence of MetS at baseline by age group and sex.

Disclosure: B. Kuriya, None; O. Schieir, Other, 2; M. F. Valois, Other, 2; J. E. Pope, AbbVie Inc., 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Lilly, 5, Merck & Co., 5, Novartis, 5, Pfizer, Inc., 5, Roche, 5, Sanofi, 5, Sandoz, 5, Celltrion, 5, United Chemicals Belgium, 2; G. Boire, Merck & Co., 8, 9, BMS, 8, 9, Pfizer, Inc., 8, 9, Amgen Inc., 9, AbbVie Inc., 9, Novartis, 9, Eli Lilly and Co., 9, Janssen, 9; L. Bessette, Amgen, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Lilly, Novartis, 2, 5, 8; C. Thorne, Amgen Inc., 2, 5, 9, Pfizer, Inc., 2, 5, 9, UCB, Inc., 9, AbbVie Inc., 2, 5, 9, Medexus/Medac, 2, 5, 8, Eli Lilly and Co., 9, Merck & Co., 9, Hospira, 5, 9, Janssen, 9, Sanofi Genzyme, 5, 9, Celgene Corporation, 9, CaRE Biodam, 9, Centocor, 5, Novartis, 9; D. Tin, None; C. A. Hitchon, None; G. Hazlewood, None; S. J. Bartlett, UCB, Inc., 5, Lilly, 5, Pfizer, Inc., 5, Novartis, 5; E. C. Keystone, AbbVie, Amgen, Bristol-Myers Squibb, F. Hoffmann-La Roche Inc, Gilead, Janssen Inc, Lilly Pharmaceuticals, Pfizer Pharmaceuticals, Sanofi-Aventis, 2, AbbVie, Amgen, AstraZeneca Pharma, Biotest, Bristol-Myers Squibb Company, Celltrion, Crescendo Bioscience, F. Hoffmann-La Roche Inc, Genentech Inc, Gilead, Janssen Inc, Lilly Pharmaceuticals, Merck, Pfizer Pharmaceuticals, Sandoz, UCB, 5, Amgen, AbbVie, Bristol-Myers Squibb Canada, F. Hoffmann-La Roche Inc., Janssen Inc., Merck, Pfizer Pharmaceuticals, Sanofi Genzyme, UCB, 8; V. P. Bykerk, Amgen Inc., 2, BMS, 2; L. Barra, None.

Abstract Number: 496

Heart Failure Risk Among Patients with Rheumatoid Arthritis: Association with Anti-Rheumatic Drugs

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) is associated with increased risk of coronary artery disease (CAD), but the association with heart failure (HF) is less characterized. We aimed to identify factors associated with HF risk among patients with RA.

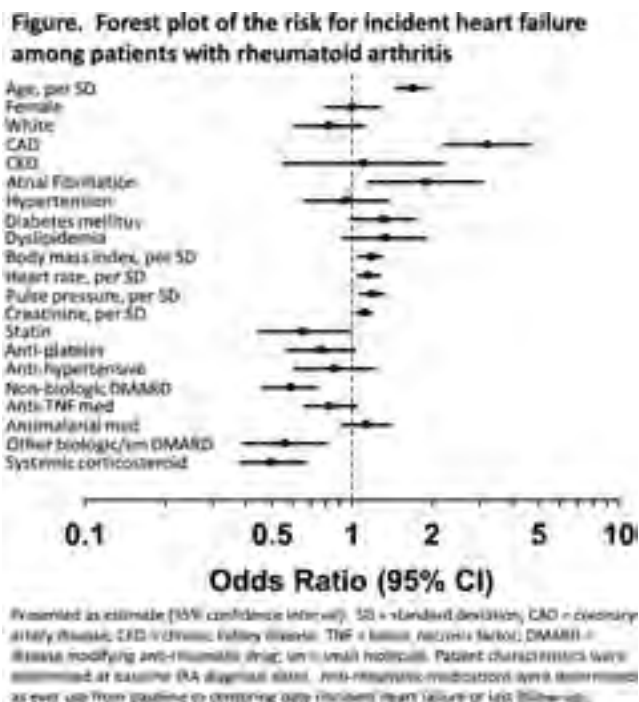


Table. Characteristics of rheumatoid arthritis patients according to incident heart failure status

	No heart failure N = 8,970 (94.5%)	Incident heart failure N = 522 (5.5%)	P*
Baseline at RA diagnosis			
Age, years	58 (46, 65)	63 (54, 71)	< 0.001
Female	76	73	0.06
White	89	96	0.06
Coronary Artery Disease	2.9	12.3	< 0.001
Atrial Fibrillation	1.2	5.3	< 0.001
Hypertension	64	75	< 0.001
Dyslipidemia	23	30	< 0.001
Chronic Kidney Disease	1.1	2.9	0.001
Diabetes mellitus	11	20	< 0.001
Body mass index, kg/m ²	28 (24, 33)	29 (25, 34)	0.009
Heart rate, bpm	78 (71, 86)	79 (70, 89)	0.08
Pulse pressure, mmHg	50 (40, 60)	55 (48, 68)	< 0.001
Creatinine, mg/dl	0.81 (0.70, 0.98)	0.90 (0.77, 1.12)	< 0.001
Statin	19	23	0.012
Anti-platelet	16	23	< 0.001
Anti-hypertensive	32	59	0.002
Ever Use of Medication			
Non-biologic DMARD	83	67	< 0.001
Anti-TNF	45	28	< 0.001
Antimalarial	42	35	0.11
Other biologic/small molecule DMARD	17	6.9	< 0.001
Systemic Corticosteroid	50	81	< 0.001

Values are percentage or median (25th, 75th percentiles). DMARD = disease-modifying anti-rheumatic drug. TNF = tumor necrosis factor. *Unadjusted.

Methods: Using the Vanderbilt University Medical Center electronic health record, we retrospectively identified 9,492 adult RA patients (median age 56 years, 76% female, 89% white) without prevalent HF at RA diagnosis. RA diagnosis was defined as ≥ 2 RA specific ICD-9 codes (714.0-714.2) that were ≥ 14 days apart and an anti-rheumatic medication prescription. Medication categories were: non-biologic disease modifying anti-rheumatic drug (DMARD) [azathioprine, cyclophosphamide, leflunomide, methotrexate, sulfasalazine]; anti-tumor necrosis factor (TNF) [adalimumab, certolizumab, etanercept, golimumab, infliximab]; antimalarial [chloroquine, hydroxychloroquine, quinacrine]; other biologic/small molecule DMARD [abatacept, anakinra, rituximab, tocilizumab, tofacitinib]; and systemic corticosteroid. Incident HF was defined as ≥ 1 ICD-9 code (428.x or 425.x) with diuretic use within 90 days. The associations between demographic, clinical factors, and medications with the risk of incident HF were quantified with multivariable-adjusted logistic regression.

Results: Over a median 5.0 (range: 0.1 to 27) years of follow-up, a total of 522 RA patients (5.5%) developed incident HF (Table). Increasing age, CAD, a trial fibrillation, as well as higher body mass index, heart rate, pulse pressure, and creatinine at baseline (first RA ICD-9 code) were each associated with greater HF risk (Figure). The risk of HF varied by use of anti-rheumatic medication class before HF. Non-biologic DMARDs, other biologic/small molecule DMARDs, and systemic corticosteroids were associated with lower HF risk, $p \leq 0.001$ for all. Anti-TNF agents and antimalarials were not associated with the risk of HF, $p \geq 0.10$ for both.

Conclusion: RA patients are at risk for HF. Established cardiovascular disease or traditional risk markers are associated with increased risk. Anti-rheumatic medications variably associate with HF risk, with lower risk observed among patients taking non-biologic or other biologic/small molecule DMARDs or systemic corticosteroids.

Disclosure: M. Ahlers, None; C. M. Stein, None; C. P. Chung, None; M. J. Ormseth, None; E. Farber-Eger, None; D. Gupta, None.

Abstract Number: 497

Increased Concentration of Large Very Low Density Lipoprotein Particles Associates with Progression of Carotid Atherosclerosis in Rheumatoid Arthritis

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

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

Background/Purpose: Patients with rheumatoid arthritis (RA) have a marked increase in cardiovascular (CV) morbidity and mortality compared to the general population. Conventional lipid profiles are insufficient to stratify CV risk in this population, and may not capture many of the lipoprotein abnormalities which predispose to atherosclerosis (ATH). Nuclear magnetic resonance (NMR) spectroscopy simultaneously quantifies the number, size, and composition of lipoprotein particles, providing a better understanding of the modifications in each lipoprotein. The current work investigated the relationship of lipoprotein profiles by NMR spectroscopy with progression of carotid ATH in a longitudinal cohort of patients with RA.

Methods: The study population included 119 RA patients who had carotid ultrasounds performed at 2 time points separated by a mean \pm SD of 5.5 ± 1.2 years at a single academic center. The number and type of carotid plaques were assessed, and an ATH score provided by the same radiologist for all scans. Fasting blood was collected for lipoprotein analysis, inflammatory markers, and lipoprotein particle profiles measured by NMR spectroscopy (Liposcience Inc. Raleigh, North Carolina, USA). Traditional cardiovascular risk factors, medication use, and RA disease characteristics were assessed for all patients at baseline and follow-up visits.

Results: In RA patients without baseline carotid ATH, mean large very low density lipoprotein (VLDL) particle concentrations were significantly higher in patients with incident plaque formation over the follow-up period, compared to patients without incident plaque formation ($p < 0.05$). Similar trends were noted in evaluation of all RA patients with plaque progression regardless of baseline ATH status. In multivariate analysis controlling for significant traditional CV risk factors, RA disease characteristics, medication use, and the presence of carotid plaque on baseline ultrasound, large VLDL concentrations remained significantly associated with increased risk of carotid plaque progression measured by ≥ 1 unit increase in carotid ATH score ($p < 0.05$). Similar results were noted when defining ATH progression by ≥ 1 new carotid

plaque from the baseline scan. Triglyceride levels were also significantly associated with plaque progression in univariate analysis, but did not remain significant in multivariate analysis. Mean total, LDL, and HDL cholesterol levels were not associated with carotid ATH progression in this cohort.

Conclusion: The current work suggests a relationship between large VLDL particles and cardiovascular risk in RA patients as assessed by the progression of carotid ATH over 5 year longitudinal follow-up. Further CV outcome studies may be warranted to determine if large VLDL particles are a useful biomarker of CV risk in patients with RA.

Disclosure: I. Golub, None; J. Wang, None; A. Shahbazian, None; J. Moriarty, None; C. Charles-Schoeman, Bristol Myers Squibb, AbbVie, Octapharma, and Pfizer, 2, Regeneron-Sanofi, Pfizer, Octapharma, Amgen, and Gilead, 5.

Abstract Number: 498

Trends in the Incidence of Cardiovascular Diseases in Patients with Rheumatoid Arthritis in Spain: A National Observational Cohort Study of Hospital Discharges

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Session Type: ACR Poster Session A

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

Background/Purpose: Cardiovascular diseases (CVDs) are a worldwide health problem, with an increased risk in Rheumatoid Arthritis (RA) due to its inflammatory context, comorbidities and the use of risk medications as corticosteroids or NSAIDs. The introduction of biological therapies and new therapeutic strategies have emerged in the last decades implying an important change in the management and evolution of RA, and also a greater awareness among rheumatologists about cardiovascular risk. However, the trend of CVDs in RA in Spain is unknown. Our objective was to analyze the incidence and trend of hospital admissions for CVDs in patients with RA in Spain during the period between 1999 and 2015.

Methods: We performed an observational retrospective population study analyzing the Spanish national administrative database that includes a Minimum Basic Data Set (MBDS) of hospital admissions of patients with RA during the period 1999 to 2015. We selected the MBDSs for CVDs, myocardial infarction (MI), ischemic heart disease (IHD), congestive heart failure (CHF), cerebrovascular disease (CeVD) and aortic aneurysm (AA). Cases were identified by the presence in primary and secondary diagnosis of ICD 9 codes. The population at risk was estimated through the population census of the National Institute of Statistics, with an estimated prevalence of RA of 0.5% (0.8% in women and 0.2% in men). Crude and adjusted rates of the selected CVDs were calculated, and the trend was analyzed using the Generalized Linear Model (GLM) with the year as the analysis variable. Statistical analysis was made using SPSS statistical package version 20 (SPSS Inc, Chicago, IL).

Results: 338,343 RA hospital admissions were detected in the period, being 207,597 (61.3%) due to CVDs. Table 1 summarizes the data of the six subgroups of CVDs along the seventeen years period. Mean age was similar in all groups. Deaths during admission were greater in CHF and CeVD. AA group presented the lowest diabetes mellitus percentage. Age-adjusted rates during the period for all groups were greater in men than in women: Relative Risk (RR) around 2 in CVD, CHF and CeVD, around 5 in MI and IHD, and 12 in AA. An annual increase in all group rates was found with an estimation of 5-7% in CVD, MI, IHD, CHF and CeVD and 9% in AA. Table 1. Trends data of cardiovascular diseases in Spanish Rheumatoid Arthritis in-patients during 1999-2015 period. Age adjusted rates expressed as rate per 10⁵ inhabitants/year. SD standard deviation. CI 95% confidence interval 95%.

Conclusion: CVDs were the first cause of hospital admissions in Spain in RA patients during the period 1999-2015. Moreover, in that period there was an increasing incidence of hospital admissions due to CVDs in all the studied

	Cardiovascular disease	Myocardial infarction	Ischemic heart disease	Congestive heart failure	Cerebrovascular disease	Aortic aneurysm
Total admissions	207597	12294	37691	31765	18445	2144
Men (%)	71724 (34.5)	6808 (55.4)	19845 (52.6)	9970 (31.4)	4509 (35.3)	1492 (69.6)
Women (%)	135873 (65.5)	5486 (44.6)	17846 (47.4)	21795 (68.6)	13936 (64.7)	652 (30.4)
Mean age (SD)	73.69 ± 11.83	72.24 ± 10.38	73.38 ± 9.77	77.6 ± 9.2	74.8 ± 10.39	74.52 ± 9.06
Deaths (%)	14649 (7.1)	1164 (9.5)	2818 (7.5)	4224 (13.3)	2282 (12.4)	204 (9.5)
Diabetes mellitus (%)	396.39 (19.3)	2971 (24.2)	9404 (25)	6681 (21)	3748 (20.3)	258 (12)
Age-adjusted rate	7407.36	448.82	1348.95	1353.25	664.15	322.88
Men	13275.48	1266.00	3685.64	1873.95	1221.71	1425.31
Women	5830.59	237.65	772.92	950.36	524.58	116.13
Age-adjusted rate increase 1999-2015	3795.03 → 9070.71	212.71 → 553.56	680.78 → 1776.24	542.62 → 1779.70	350.13 → 934.61	30.13 → 130.06
Men	4489.95 → 18200.59	598.73 → 1527.98	1704.03 → 4769.61	868.77 → 2889.88	629.66 → 1720.68	115.07 → 437.35
Women	3038.71 → 7993.63	118.33 → 352.81	425.63 → 1892.64	446.93 → 1491.47	276.35 → 733.72	18.10 → 54.83
Annual increase % estimation (CI 95%)	5.68 (1.868-1.064)	5.02 (1.041-1.059)	5.28 (1.044-1.062)	6.8 (1.054-1.082)	6.3 (1.054-1.072)	9.1 (1.076-1.107)
Relative risk men : women	2.28	5.33	4.7	1.97	2.36	12.27

subgroups, being strikingly higher in men after age-adjusted rates. An annual rate increase is estimated in all the different studied subgroups oscilating between 5 and 9%annual increasing.

Disclosure: C. Macia-Villa, None; R. Mazzucchelli, None; E. Perez-Fernandez, None; J. Quirós, None; J. L. Morell-Hita, None; N. Crespi, None; M. Peña, None; C. Barbadillo, None; M. Espinosa, None; H. Godoy, None; M. Fernández, None; M. Galindo, None; A. Garcia-Vadillo, None; O. Guzon-Illescas, None; A. Herranz, None; C. Martinez-Prada, None; C. Morado-Quínoa, None; V. Villaverde García, None.

Abstract Number: 499

Low Inflammatory Burden and Statin Exposure Inhibit Progression and Induce Regression of Early Coronary Plaques in Rheumatoid Arthritis

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Early atherosclerotic lesions appear as non-calcified plaques (NCP) on a non-invasive coronary artery evaluation by computed tomography angiography (CCTA). Advanced,more vulnerable lesions appear as mixed/ partially calcified plaques (MP) or calcified plaques (CP). We evaluated the role of inflammation, medication exposure and cardiac risk factors (CRFs) on NCP generation and progression in RA patients with a follow-up evaluation of coronary anatomy with CCTA.

Methods: Ninety-nine participants underwent a repeat CCTA assessment within 83±3.6 months. All coronary lesions were counted and characterized as NCP, MP, or CP; prevalence, number, stenotic severity and burden of individual NCP plaques on both baseline and follow-up scans was recorded. Patients were subsequently classified into four groups according to plaque disposition: NCP-negative (no NCP at any time), NCP-positive (NCPpresent at both times), disappearing-NCP (present at baseline, absent at follow-up), or new-NCP (absent at baseline, present at follow-up). A Multinomiallogistic regression model evaluated predictors independently associated with classification of patients into the respective NCP groups compared to the NCP-negative group.

Results: Overall NCP prevalence was lower at follow-up compared to the baseline assessment (26.5% vs. 52.4%, p<0.001, table 1); 21 of 99(21%) patients showed disappearance or development of new NCP lesions. In the NCP-positive group, 68% of the follow-up NCP plaques derived from original NCP lesions, with the vast majority (93%) displaying identical

Table 1. Changes in numbers of all and NCP coronary plaques from baseline scan

NCP-Groups	n	n-total plaques		N (%) NCP plaques		
		baseline	Flu	baseline	Flu	p
NCP-negative	35	26	52	0 (0%)	0 (0%)	-
NCP-positive	43	113	154	74 (62.7%)	62 (40.3%)	0.038
Disappearing NCP	17	43	40	24 (55.8%)	0 (0%)	<0.001
New NCP	4	0	7	0 (0%)	5 (71.4%)	0.048
All	99	187	253	98 (52.4%)	67 (26.5%)	<0.001

Table 2. Predictors of dynamic change of coronary non-calcified plaque in RA.

Group	Predictors	OR (95% CI)	p-value
NCP-negative		Ref	ref
NCP-positive	AUC-CRP	0.94 (0.90-0.99)	0.016
	Statin exposure (years)	1.21 (1.0-1.43)	0.046
Disappearing NCP	AUC-CRP	0.95 (0.90-1.01)	0.11
	Statin exposure (years)	1.26 (1.01-1.58)	0.04
New NCP	AUC-CRP	1.01 (0.67-1.05)	0.63
	Statin exposure (years)	0.97 (0.77-1.19)	0.40

stenotic severity and burden; 29% were incident NCP plaques. Of baseline NCP lesions, 18% receded. In the disappearing group, 75% of the original NCP plaques receded, whereas 16% transitioned to more stable calcified plaques (CP). Patients in the NCP-positive group displayed lower cumulative inflammatory burden [area under the curve for c-reactive protein (AUC-CRP), $p=0.016$] and longer duration of statin exposure compared to the NCP-negative ones (table 2, $p=0.046$). NCP disappearance was mostly predicted by lengthier statin exposure ($p=0.04$).

Conclusion: Lower inflammatory burden and longer statin exposure inhibit NCP growth or progression to more advanced, vulnerable plaques. Lengthier statin exposure may further induce regression of such early atherosclerotic lesions.

Disclosure: G. Karpouzas, None; S. Ormseth, None; E. Hernandez, None; M. Budoff, None.

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Abstract Number: 500

Impact of Inflammation and Biologic Treatments on Generation and Progression to Advanced Calcified Coronary Plaques in Rheumatoid Arthritis

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Session Information

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

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Background/Purpose: In early atherogenesis inflammation drives and co-localizes with intimal calcification. In chronic, advanced plaques inflammation and calcification are inversely correlated and spatially distinct; advanced calcification is considered a stabilizing physiologic process rendering plaques less prone to rupture. We evaluated the role of inflammation, biologic treatments and cardiac risk factors on the de-novo generation and progression of advanced, calcified coronary plaques (CP) in patients with rheumatoid arthritis (RA).

Methods: Ninety-nine participants with a baseline non-invasive evaluation of coronary anatomy with computed tomography angiography (CCTA) underwent a repeat assessment within 83 ± 3.6 months. Coronary lesions were counted and defined as non-calcified (NCP), mixed (MP) or calcified (CP). The prevalence, number, stenotic severity and burden of individual CP plaques was recorded. Patients were classified into three groups according to plaque disposition: CP-negative (no CP at any time), CP-positive (CP present at both times), and new-CP (absent at baseline, present at follow-up). A Multinomial logistic regression model evaluated predictors independently associated with patient classification into the CP-positive or New-CP groups compared to the CP negative group.

Table 1. Changes in numbers of all and NCP coronary plaques from baseline scan

CP-Groups	n	n-total plaques		N (%) CP plaques		p
		baseline	FU	baseline	FU	
CP-negative	61	56	61	0 (0%)	0 (0%)	-
CP-positive	18	80	105	38 (43.6%)	61 (58.1%)	0.44
New-CP	20	40	76	0 (0%)	45 (59.2%)	<0.001
Disappearing-CP	2	11	11	2 (18.2%)	0 (0%)	0.46
All	99	187	253	37 (19.8%)	106 (41.8%)	<0.001

Table 2. Predictors of dynamic change of coronary non-calcified plaque in RA

Groups	Predictors	OR (95% CI)	p-value, n/
CP-negative	Age	1.36 (1.13-1.62)	<0.001
	Diabetes	8.03 (0.80-809.26)	0.076
	Hyperlipidemia	12.51 (1.45-106.31)	0.022
	Erosions	0.60 (0.13-6.18)	0.62
	AUC-CRP	1.10 (1.03-1.19)	0.008
CP-positive	Biologic exposure (years)	0.78 (0.54-1.14)	0.20
	Age	1.18 (1.07-1.31)	0.001
	Diabetes	0.29 (0.02-4.15)	0.33
	Hyperlipidemia	0.96 (0.28-3.39)	0.93
	Erosions	0.17 (0.04-0.73)	0.017
New-CP	AUC-CRP	1.08 (1.03-1.14)	0.002
	Biologic exposure (years)	1.21 (1.03-1.57)	0.030

Results: CP prevalence was higher at follow-up compared to baseline (42.3% vs. 19.8%, $p<0.001$, table 1); 21 of 99 (21%) patients developed new CP lesions. In the CP-positive group, 43% of the lesions at follow-up were unchanged from baseline, 16% derived from progression of MP, 3% from NCP and 23% were incident CP lesions. In the New-CP group, 73% of lesions were incident CP, 13% derived from NCP and 13% from MP. CP-positive patients were older, with greater baseline hyperlipidemia and higher inflammatory burden [area under the curve for c-reactive protein (AUC-CRP), $p=0.008$] compared to the CP-negative ones (table 2). New CP subjects were older, had greater frequency of baseline erosions, higher inflammatory burden ($p=0.002$) and lengthier biologic exposure ($p=0.015$) vs. the CP-negative group.

Conclusion: Higher inflammatory burden promotes generation, maturation and early calcification of coronary plaques in patients with RA. Higher duration of biologic exposure, through systemic and/ or local inflammatory control, fosters advanced calcification and stabilization of atherosclerotic plaques.

Disclosure: G. Karpouzas, None; S. Ormseth, None; E. Hernandez, None; M. Budoff, None.

Predictors of Change in Coronary Plaque Burden and Composition in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

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Background/Purpose: We previously reported higher prevalence, burden and more vulnerable occult coronary plaque composition in patients with rheumatoid arthritis (RA) compared to age and gender-matched non-autoimmune disease controls. We now explore the predictors of change in coronary atherosclerosis burden and plaque composition in RA patients with a follow-up non-invasive interrogation of coronary anatomy.

Methods: One hundred participants with a baseline 64-slice coronary computed tomography angiography (CCTA) for atherosclerosis interrogation, underwent a follow-up assessment in a mean of 83±3.6 months. Plaque load was evaluated with 3 quantitative scores: segment involvement score (SIS) reflected the number of segments with plaque; segment stenosis score (SSS) reported the cumulative stenosis grade conferred by plaque over all evaluable segments and the plaque burden score (PBS) described the cumulative plaque size over all evaluable segments. Plaque composition was defined as non-calcified (NCP), mixed (MP) or calcified (CP). Coronary artery calcium score (CAC) was quantified by the Agatston method. Multivariate linear and logistic regression models evaluated independent determinants of change in total, NCP, MP and CP plaque burden; multinomial logistic regression models compared predictors of individual plaque type burden progression or regression against non-progressors.

Results: Total plaque burden increased in 41%, remained stable in 41% and decreased in 18%. Duration of prednisone exposure in-between studies, and age independently predicted total plaque burden change (all p<0.05). NCP regression was predicted by lower prednisone and higher statin duration exposure, whereas NCP progression was forecasted by longer prednisone and shorter biologic DMARD inter-scan exposure, older age, and higher prevalence of HTN compared to

Table 1. Predictors of coronary plaque burden and composition change in RA

Change	predictors	Regression	OR (95% CI)	
			Stability	Progression
NCP	Prednisone exposure (yrs)	0.72 (0.52-0.99)*	Ref	1.09 (0.84-1.43)
	Statin exposure (yrs)	1.25 (1.05-1.47)**	Ref	0.91 (0.68-1.22)
	MP	1.14 (1.04-1.24)**	Ref	1.10 (1.03-1.16)**
SIS	Age	-	Ref	1.13 (1.05-1.22)***
	Hypertension	-	Ref	3.39 (1.11-10.38)*
	Body Mass Index	-	Ref	1.13 (1.01-1.26)*
SSS	AUC-hsCRP	-	Ref	1.05 (1.01-1.09)*
	Age	1.00 (0.94-1.06)	Ref	1.10 (1.01-1.20)*
	Prednisone exposure (yrs)	0.55 (0.39-0.89)*	Ref	1.46 (1.06-2.00)**
PBS	Biologic exposure (yrs)	1.01 (0.84-1.21)	Ref	0.65 (0.44-0.97)*
	Hypertension	1.83 (0.60-5.65)	Ref	0.17 (0.03-1.00)
	MP	1.19 (1.07-1.31)***	Ref	1.11 (1.04-1.18)***
CP	Body Mass Index	1.15 (1.00-1.32)*	Ref	1.08 (0.96-1.16)
	Age	-	Ref	1.11 (1.04-1.19)**
	Hypertension	-	Ref	3.37 (1.14-9.97)*
CAC	AUC-hsCRP	-	Ref	1.05 (1.02-1.10)**
	Age	1.01 (0.95-1.07)	Ref	1.11 (1.01-1.21)*
	Hypertension	1.55 (0.50-4.78)	Ref	0.08 (0.01-0.71)*
MP	Prednisone exposure (yrs)	0.54 (0.33-0.86)**	Ref	1.65 (1.14-2.39)**
	Age	1.09 (1.01-1.19)*	Ref	1.07 (1.00-1.13)*
	Age	1.23 (1.09-1.38)***	Ref	1.15 (1.07-1.24)***
CP	Body Mass Index	1.05 (0.68-1.25)	Ref	1.15 (1.03-1.28)*
	AUC-hsCRP	1.05 (0.99-1.12)	Ref	1.06 (1.02-1.10)**
	Age	-	Ref	1.11 (1.05-1.19)***
	Hypertension	-	Ref	3.53 (1.32-9.42)*
	AUC-hsCRP	-	Ref	1.03 (1.00-1.07)*

*p<0.05 **p<0.01 ***p<0.001

non-progressors (all $p < 0.05$). CP-progressors were older, with higher cumulative inflammatory burden [area under the curve for c-reactive protein (AUC-hsCRP)], more obese and with greater prevalence of hypertension, and (all $p < 0.05$) than non-progressors. Finally, CAC increase was independently predicted by older age, hypertension and cumulative inflammatory burden (all $p < 0.05$).

Conclusion: Cardiac risk factors, inflammation and duration of exposure to medications such as prednisone, biologics and statins significantly and differentially impacted coronary plaque burden and composition change over time in RA.

Disclosure: G. Karpouzas, None; S. Ormseth, None; E. Hernandez, None; M. Budoff, None.

Abstract Number: 502

Implications of Coronary Artery Calcium Score and Its Change over Time As Markers of Coronary Plaque Vulnerability and Patient Risk in Rheumatoid Arthritis

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SESSION INFORMATION

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Background/Purpose: Atherosclerotic plaque calcification is considered a stabilizing physiologic process; calcified coronary plaques (CP) are less prone to rupture and yield lower risk of cardiovascular events compared to non-calcified (NCP) or the more vulnerable partially calcified, mixed plaques (MP). Interestingly, higher coronary artery calcium score (CACS) and its progression associate with higher event risk in general patients. Likewise, we reported that CACS predicted cardiac events in rheumatoid arthritis (RA) patients independently of risk factors or cardiac risk scores. To address this paradox, we evaluated the contribution of MP burden to CACS as well the influence of change in MP burden on CACS progression in RA patients with a baseline and follow-up evaluation of coronary anatomy with computed tomography angiography (CCTA).

Table 1. Contribution of Mixed and Calcified plaque burden and their change on CACS and its change over time in patients with rheumatoid arthritis

CCTA		Beta	p-value	Raw RW (95% CI)	Rescaled RW
Baseline	Model 1				
	SSS-MP	.564	.000	0.258 (0.085-0.472)	38.6%
	SSS-CP	.532	.000	0.480 (0.232-0.662)	63.9%
	Model 2				
	SSS-MP	.548	.000		
	SSS-CP	.518	.000		
	Age	.062	.082		
Follow-up	Gender	-.007	.83		
	Model 1				
	SSS-MP	.418	.000	0.250 (0.112-0.396)	38.6%
	SSS-CP	.634	.000	0.399 (0.235-0.554)	61.5%
	Model 2				
	SSS-MP	.399	.000		
	SSS-CP	.610	.000		
Change (Follow-up - Baseline)	Age	.085	.970		
	Gender	-.030	.48		
	Model 1				
	SSS-MP change	.388	.000	0.106 (0.017-0.251)	27%
	SSS-CP change	.585	.000	0.288 (0.115-0.483)	73%
	Model 2				
	SSS-MP change	.314	.010		
Change (Follow-up - Baseline)	SSS-CP change	.538	.000		
	Age	.341	.008		
	Gender	-.053	.53		

Model 1: Unadjusted; Model 2: age and gender adjusted

Beta: standardized coefficient; RW: Relative Weight; Raw RWs indicate the contribution of each predictor in a model for the total variance explained (sum to R^2) after accounting for the effects of intercorrelations among variables; Rescaled RWs represent the % contribution of each predictor to the total explainable variance; 95% CI: 95% Confidence Interval

Methods: Ninety-nine patients underwent a repeat CCTA within 83 ± 3.6 months from baseline. Total number of segments with plaque (segment involvement score-SIS) and cumulative stenosis severity rendered by plaque over all evaluable segments (segment stenosis score-SSS) we computed for all participants. Coronary lesions were defined as non-calcified (NCP), mixed (MP) or calcified (CP). Generalized Linear Models predicted the contribution of MP and CP plaque burden to the baseline and follow-up CACS as well as the influence of change in the burden of the respective lesions on CACS progression.

Results: Mixed and calcified plaque burden (SSS-MP and SSS-CP respectively) strongly correlated with CACS at both baseline ($r_{mp}=0.75$ and $r_{cp}=0.77$, $p<0.001$) and follow-up ($r_{mp}=0.57$ and $r_{cp}=0.68$, $p<0.0001$), whereas non-calcified plaque did not ($r_{ncp}=-0.03$, $p=0.85$ and -0.16 , $p=0.30$ respectively). Both MP and CP burden comparably and significantly contributed to CACS magnitude at both times; MP accounted for 36.5% and 38.5% of explainable variance in CACS while CP accounted for 63.5% and 61.5% of it at baseline and follow-up respectively. Likewise, change in MP and CP burden from baseline to follow-up significantly contributed to and justified 27% and 73% of explainable CACS change variance respectively.

Conclusion: The vulnerable MP and the more stable CP burden and their change significantly and collectively contributed to CACS at any time as well its progression respectively in patients with RA. Therefore, the MP burden and its change epitomize the vulnerability components within the higher baseline and progressing CACS scores yielding higher cardiovascular event risk.

Disclosure: G. Karpouzas, None; S. Ormseth, None; E. Hernandez, None; M. Budoff, None.

Abstract Number: 503

Waist Circumference Based Abdominal Obesity Versus Body Mass Index in Rheumatoid Arthritis: Influence on the Risk of Diabetes and Cardiovascular Disease

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

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Background/Purpose: Adipose tissue deposited around the mesentery is highly associated with insulin resistance and cardiovascular disease (CVD). Compared to BMI, waist circumference (WC) has been shown to be a better marker of adiposity around the abdomen in the general population. However, it is not known if it is similarly associated with CVD and type 2 diabetes (T2D) in RA patients. We sought to determine whether WC is a better T2D and CVD predictor than BMI.

Methods: RA patients with ≥ 1 year participation in FORWARD, National Databank for Rheumatic Diseases without baseline T2D from 1998 through 2017 were assessed for T2D (self-report or initiating of antidiabetic medication) and CV events (myocardial infarction, stroke and heart failure validated from hospital/ death records). WC was measured by the patients according to World Health Organization (WHO) 2008 measurement guideline. $WC \geq 102$ cm in men and ≥ 88 cm in women was considered as abdominal obesity. BMI was categorized according to WHO classification. Cox proportional hazard models with adjustment for sociodemographics, comorbidities, RA severity measures and treatment (DMARDs and glucocorticoids) constructed to estimate T2D and CVD risk. WC and BMI were evaluated in different models. WC and BMI interaction in the same model was also assessed.

Results: The study included 2,177 RA patients (mean [SD] age 66 [12] years) of which 28% were obese ($BMI \geq 30$ kg/m²) and 52% had abdominal obesity. During a median (IQR) 5.9 (2.6-11.1) years of follow-up, 229 incident T2D cases and 94 CV events were observed. The incidence rate (95%CI) of T2D was slightly higher in obese patients than patients with abdominal obesity (33.4 [27.8-40.1] vs. 24.1 [20.6-28.2]); but, CVD incidence (8.6 [6.5-11.1] vs. 8.7 [6.1-12.4]) was similar. In adjusted models both obesity (HR 1.86 [1.33-2.59]) and abdominal obesity (HR 1.59 [1.19-2.13]) were significantly associated with incident T2D, however the risk with obesity was higher than the abdominal obesity. For the CVD, neither BMI based obesity nor WC based abdominal obesity were significantly associated with increased risk (Table). When women and men analyzed separately, abdominal obesity was a more prominent predictor of T2D in women (HR 1.75 [1.25-2.44]) than men (1.05 [0.54-2.06]). In analysis of interaction of BMI and WC in normal weight and overweight patients, abdominal obesity in the presence of normal weight tended to increase the T2D risk.

Conclusion: Both BMI based obesity and WC based abdominal obesity were strong risk factors for T2D in RA patients but BMI predicted T2D better. Neither of them was associated with CVD. Obesity in RA can have a paradoxical effect in RA in terms of mortality which might be areas on why obesity and abdominal obesity were not associated with CVD, the leading cause of death in RA. Regardless, WC measurement in RA might be helpful in particularly nonobese female patients to estimate T2D risk.

Table. Association of waist circumference and body mass index with incident type 2 diabetes and cardiovascular disease in RA patients

	Type 2 Diabetes		Cardiovascular Disease	
	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
Waist circumference based abdominal obesity	1.94 (1.48-2.57)	1.59 (1.19-2.13)	1.31 (0.87-1.98)	1.09 (0.69-1.72)
Body mass index				
Underweight: <18.5 kg/m ²	0.56 (0.14-2.28)	0.50 (0.12-2.08)	0.63 (0.10-4.67)	0.75 (0.10-5.62)
Normal weight: 18.5-24.9 kg/m ²	Referent	Referent	Referent	Referent
Overweight: 25-29.9 kg/m ²	0.95 (0.66-1.38)	0.82 (0.56-1.21)	1.54 (0.94-2.54)	0.87 (0.51-1.49)
Obese ≥30kg/m ²	2.49 (1.83-3.39)	1.86 (1.33-2.59)	1.45 (0.86-2.44)	1.09 (0.61-1.94)
Waist circumference and body mass index interactions[†]				
Normal weight without abdominal obesity	Referent	Referent	Referent	Referent
Normal weight+abdominal obesity	1.46 (0.79-2.71)	1.30 (0.68-2.47)	1.18 (0.45-3.12)	0.86 (0.31-2.37)
Overweight without abdominal obesity	1.01 (0.60-1.72)	0.97 (0.56-1.69)	1.50 (0.77-2.93)	0.80 (0.37-1.71)
Overweight + abdominal obesity	1.13 (0.71-1.78)	0.84 (0.51-1.39)	1.45 (0.78-2.67)	0.71 (0.36-1.42)

*Adjusted for age, sex, disease duration, socioeconomic status (employment and education level, insurance, location of residency), ethnicity, smoking, hypertension comorbidity index, HAQ, NSAIDs, statins, glucocorticoids, prior count of csDMARDs and bDMARDs, prior CVD history and DMARDs
[†]Only includes normal weight and overweight patients

Disclosure: G. Ozen, None; S. Pedro, None; K. Michaud, None.

Abstract Number: 504

Views of Primary Care Physicians and Rheumatologists Regarding Screening and Management of Hyperlipidemia Among Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Screening and management of hyperlipidemia in rheumatoid arthritis(RA) is suboptimal, despite RA patients' high risk for cardiovascular disease(CVD) mortality. Our purpose was to identify barriers to screening for hyperlipidemia among patients with RA from the viewpoint of primary care physicians (PCPs) and rheumatologists.

Methods: We recruited rheumatologists and PCPs nationally to participate in moderated, structured group teleconference discussions using the nominal group technique. The groups had either only PCPs or only rheumatologists. Participants generated lists of barriers to screening and management for hyperlipidemia in patients with RA, within the same session. Each participant was allowed 6 votes to rank items: 3 votes for the most important item, 2 for the second most important, and 1 to the third most important. Investigators characterized items and totaled the votes as themes and sub-themes.

Results: Twenty-six rheumatologists participated in 1 of 3 groups (group size ranged from 7-11) and 22 PCPs participated in 1 of 3 groups(group size ranged from 4-9). The items generated across the 6 separate groups were categorized into physician-, patient- and system-level barriers. Table 1 lists the barriers for hyperlipidemia screening and Table 2 lists the barriers for management of hyperlipidemia for both rheumatologists and PCPs.

The largest number of barriers for rheumatologists were at the physician level (e.g. 'ownership' of hyperlipidemia screening and management), with 83% of the priority votes for screening and 89% for treatment. Patient-level barriers received the majority of votes among the PCPs groups (44% for screening and 69% for management).

Table 1: Screening for hyperlipidemia: List of themes and sub-themes of barriers for rheumatologists and primary care physician (PCPs) to screen patients with RA, with their respective priority votes

<i>Category</i>	<i>Subcategory</i>	<i>Rheumatologist (% votes)</i>	<i>PCP (% votes)</i>
Physician Level	Total Votes	83.0	42.5
	Lack of time	34.0	1.7
	Conflict regarding ownership of hyperlipidemia screening	25.9	10.8
	Lack of training and knowledge of hyperlipidemia guidelines	17.9	19.2
	Focus only in RA	4.9	--
	Physician prioritization of RA symptomology over preventive measures	--	10.0
	Lack of physician knowledge about RA	--	0.8
Patient Level	Total Votes	7.5	44.2
	Effect of RA and its treatment	2.5	9.2
	Patient prioritization of RA symptomology over preventive measures	2.5	9.2
	Patient expectations	1.9	--
	Patient already on multiple medications	0.6	0.0
	Side effects of RA medications and RA drug interactions	0.0	--
	Comorbidities	0.0	--
	Patient's barriers with transportation	0.0	--
	Multiple blood draws	0.0	8.3
	Side effects of statins and drug interactions with statins	0.0	5.0
	Barriers from the patient	--	0.0
	Poor patient compliance with medical care	0.0	9.2
	Patients' lack of awareness of CVD risk	--	3.3
System Level	Total Votes	9.9	13.4
	Lack of care coordination	6.8	11.7
	Financial barriers (limited insurance coverage, cost of repeating labs)	3.1	--
	Lack of financial incentive for screening	--	1.7

Note: RA = rheumatoid arthritis; CVD = cardiovascular disease; 0% = that sub-theme emerged during the brainstorming session but did not receive votes; "--" = the sub-theme did not emerge in the respective group.

Conclusion: Our data showed that rheumatologists are conflicted about whether management of CVD risk reduction strategies among patients with RA should fall within the role of the rheumatologist or PCP. PCPs are more concerned about the overall effect of RA and its treatment in the context of screening and managing hyperlipidemia. These findings improve our understanding of why RA patients are not consistently screened and treated for hyperlipidemia. To address this gap, there is a need to develop strategies that clarify the specific roles of the PCP and rheumatologist and develop solutions that target key barriers.

Disclosure: I. Navarro-Millán, None; A. Cornelius-Schecter, None; R. O'Beirne, None; M. Morris, None; S. Goodman, None; A. Cherrington, None; L. Fraenkel, None; J. R. Curtis, None; M. M. Safford, None.

Table 2: Management of hyperlipidemia: List of themes and sub-themes of barriers for rheumatologists and PCPs to treat hyperlipidemia among patients with RA with their respective priority votes

<i>Category</i>	<i>Subcategory</i>	<i>Rheumatologist (% votes)</i>	<i>PCP (% votes)</i>
Physician Level	Total Votes	89.0	25.0
	Conflict regarding ownership of hyperlipidemia management	37.7	0.0
	Lack of training and knowledge of hyperlipidemia guidelines	32.1	--
	Lack of time	13.0	0.8
	Focus only in RA	6.2	--
	Prioritize non-pharmacologic measures (diet and exercise)	--	4.2
	Lack of training and knowledge of hyperlipidemia guidelines	--	18.3
	Difficulty implementing lifestyle modifications for patients with pain	--	1.7
Patient Level	Total Votes	5.6	69.2
	Patient already on multiple medications	2.5	8.3
	Side effects of statins	2.5	--
	Side effects of RA medications and RA drug interactions	0.6	--
	Comorbidities	--	6.7
	Effect of RA and its treatment	--	5.8
	Side effects of statins and drug interactions of statins	--	42.5
	Patients' lack of awareness of CVD risk	--	1.7
	Priority of RA symptomology over preventive measures	--	4.2
System Level	Total Votes	5.6	5.8
	Financial barriers (limited insurance coverage, cost of additional medications, cost of repeating labs)	5.6	0.0
	Lack of care coordination	--	5.8

Note: RA = rheumatoid arthritis; CVD = cardiovascular disease; 0% = the sub-theme emerged during brainstorming session but did not receive votes; "--" = the sub-theme did not emerge in the respective group.

Abstract Number: 505

Impact of Biological Treatment on Left Ventricular Regional Dysfunction in Rheumatoid Arthritis Patients Determined with Global Circumferential and Longitudinal Strain Values Using Cardiac Magnetic Resonance Imaging

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Congestive heart failure (CHF) is a major contributor to morbidity and mortality in patients with rheumatoid arthritis (RA). Myocardial disease is typically clinically silent, only manifesting as myocardial dysfunction after an extended preclinical phase. Feature-tracking (FT) cardiac magnetic resonance (CMR) imaging can be used to assess early left ventricular (LV) dysfunction. It is critically important to differentiate between the effects of disease and those of biological treatment on LV regional function, since this distinction may have important implications for long-term management of RA. This study aimed to assess LV regional function in RA patients and to determine the impact of biological treatment using global circumferential and longitudinal strain values, assessed by CMR.

Methods: RA patients and controls without cardiac symptoms were enrolled, and those with no history and/or clinical findings of systemic and pulmonary hypertension, coronary artery disease, valvular heart disease, atrial fibrillation, diabetes mellitus, and dyslipidemia underwent non-contrast CMR. Patients with RA were administered non-biologic disease-modifying antirheumatic drugs (nbDMARDs) or biologic DMARDs (bDMARDs). All subjects underwent evaluation of LV regional function, as measured by CMRI. LV global longitudinal peak systolic strain (GLS) is a prognostic indicator of adverse cardiovascular outcomes in various patient populations, and global circumferential peak systolic strain (GCS) is a predictor of CHF in the general population. GLS and GCS were calculated in the 16 LV segments. Group comparisons were made using the Wilcoxon rank sum test, Fisher's exact test, and Steel test where appropriate.

Results: We compared 100 patients with RA (86% women; mean age, 55.3±10.3 years) with 30 healthy controls (100% women; mean age, 55.7±4.5 years). No statistically significant differences in cardiovascular risk (CV) factors were observed in the characteristics between the patients and the healthy controls. GCS was significantly reduced by 27% in the RA group compared to controls (p=0.017). Furthermore, GCS was significantly lower by 17% in the nbDMARD group than in the bDMARD group (p=0.035). GCS in the RA group was associated with the Simplified Disease Activity Index (SDAI) (p=0.05). GCS in the RA group was not associated with CV risk factors or other RA status. GLS in the RA group was significantly reduced by 22% compared to the control group (p=0.027). GLS in the RA group was not associated with CV risk factors or RA status. GLS was lower by 16% in the nbDMARD group than in the bDMARD group (p=0.049). GLS tended to be associated with the SDAI.

Conclusion: This prospective study assessed LV regional dysfunction in RA, using global circumferential and longitudinal strain values on CMR. Subclinical LV regional dysfunction of GCS and GLS was prominent in RA patients without cardiac symptoms. Biologic treatment may normalize LV regional dysfunction, associated with a reduction in disease activity in RA patients.

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Abstract Number: 506

Clinical and Sonographic Characteristics of Carotid Intima-Media Thickness in Rheumatoid Arthritis Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) is a chronic and systemic disease with high cardiovascular (CV) risk. Carotid intima-media thickness (CMT) is an independent surrogate marker of subclinical atherosclerosis. Several instruments may underestimate CV risk in RA (1). Objectives: to describe demographic and clinical characteristics, CV risks and carotid ultrasound (US) measurements; to assess the differences among three RA-groups according to CMT and to assess the usefulness of CV risk scores as predictors of higher CMT.

Methods: All patients fulfilled 1987 ACR and/or 2010 ACR/EULAR classification criteria. Subjects between 40-75 years old were included. CV risk was calculated by seven scales. Carotid US was performed by an on-call-certified radiologist and reviewed by two radiologists. Carotid plaque (CP) = CMT ³0.12 cm or a ³50% focal increase of CMT compared to the surrounding normal arterial wall. Three RA-groups were created according to CMT.

Results: One hundred RA-patients were included, demographic data are in figure 1. CMT: 25 had <0.079 cm (group 1), 38 had 0.08-0.09 cm (group 2) and 37 had CMT ³0.09 cm (group 3). Six scores had statistically significant result. The highest sensitivity to detect increased CMT was obtained by SCORE-moderate risk (75.7%) and the highest specificity was 100% with Framingham-lipids-high risk.

Conclusion: CIMT can be used as an independent surrogate marker of subclinical atherosclerosis in RA-patients. Different CV risk scores did not predict the presence of CP.

Reference: 1. Galarza-Delgado DA., et al. “Assessment of six cardiovascular risk calculators in Mexican mestizo patients with rheumatoid arthritis according to the EULAR 2015/2016 recommendations for cardiovascular risk management.” Clinical rheumatology 36.6(2017):1387-1393.

Figure 1. Baseline characteristics

A.				
	CIMT ² 0.079 cm (n=25)	CIMT ² 0.08-0.09 cm (n=38)	CIMT ³ 0.1 cm (n=37)	P
Age, years, mean ± SD	53.1 ± 8.1	54.2 ± 8.7	61.5 ± 6.9	<0.01
Women, n (%)	24 (96)	37 (97)	35 (95)	NS
Body mass Index, kg/m ² , mean ± SD	28.8 ± 5.5	28.4 ± 5.6	29.6 ± 5.0	NS
Disease variables				
Disease duration, years, mean ± SD	12.8 ± 9.7	14.8 ± 7.5	12.9 ± 8.7	NS
Diagnosis delay, months, median (Percentile 25-75)	7.1 (2.0-24.3)	5.0 (2.1-36.5)	12.2 (5.0-12.4)	NS
CRP, mg/L, median (Percentile 25-75)	0.7 (0.5-1.0)	1.0 (0.6-1.3)	0.9 (0.6-1.1)	NS
ESR mm/H, median (Percentile 25-75)	34 (15-44)	21 (13-32)	24 (14-36)	NS
RF IgG, IU/ml, median (Percentile 25-75)	6.8 (0-24.9)	8.6 (5.3-13.1)	9.5 (3.9-18.1)	NS
RF IgM, IU/ml, median (Percentile 25-75)	163.3 (54.7-200)	76.6 (35.2-200)	194.3 (56.8-200)	NS
RF IgA, IU/ml, median (Percentile 25-75)	34.1 (14-135)	39.4 (11.5-93.5)	59.5 (18.5-179)	NS
antiCCP, U/ml, median (Percentile 25-75)	85.9 (2.6-198)	27.2 (4-197)	106.7 (4.4-196)	NS
DAS28-CRP, mean ± SD	3.4 ± 1.2	3.2 ± 1.2	3.2 ± 1.4	NS
CDAI, mean ± SD	16.6 ± 12.5	12.5 ± 10.0	13.1 ± 12.1	NS
SDAI, mean ± SD	17.5 ± 12.5	13.5 ± 10.1	13.9 ± 12.2	NS
Methotrexate user, n(%)	23 (92)	37 (77)	21 (78)	NS
Prednisone user, n(%)	18 (72)	23 (48)	14 (52)	NS
Cardiovascular risk calculator				
OMNIBUS, mean (SD)	2.1 ± 2.2	3.7 ± 3.7	8.8 ± 8.1	<0.01
FRS-Lipids, mean ± SD	4.2 ± 2.8	6.5 ± 4.7	11.2 ± 9.6	<0.01
FRS-BMI, mean ± SD	6.5 ± 4.7	9.6 ± 8.0	15.7 ± 12.7	<0.01
SCORE, mean ± SD	0.5 ± 1.0	0.7 ± 0.9	1.7 ± 1.4	<0.01
ERS-RA, mean ± SD	5.7 ± 4.2	8.3 ± 7.6	10.8 ± 7.8	NS
QRISKII, mean ± SD	4.4 ± 3.7	7.0 ± 5.7	13.7 ± 8.7	<0.01
RRS, mean ± SD	1.5 ± 1.1	2.4 ± 2.1	5.0 ± 5.5	<0.01
Ultrasound Variables				
Plaque, n (%)	0	6 (13)	7 (26)	<0.01
Bilateral plaque, n (%)	0	0	16 (59)	<0.01
CIMT, mm, mean ± SD	0.06 ± 0.01	0.08 ± 0.01	0.1 ± 0.08	<0.01

B.							
CV risk	CIMT <0.09	CIMT >0.09	Total	Sensitivity	Specificity	PPV	NPV
OMNIBUS, high risk,	6	14	20	37.8	90.5	70	71.3
FRS-Lipids, high risk, n(%)	0	3	3	8.1	100	100	64.9
FRS-BMI, high risk, n (%)	6	8	14	21.6	90.5	57.1	66.3
SCORE, moderate risk, n(%)	24	28	56	75.7	61.9	53.8	81.3
RRS, moderate and High, n (%)	1	3	4	8.1	98.4	75	64.6

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = Rheumatoid Factor; antiCCP = Anti-cyclic citrullinated peptide; DAS28-CRP = disease activity score; CDAI = Clinical Disease Activity; CDAI = Clinical Disease Activity Index; SDAI = Simplified Disease Activity Index; ACC-AHA 2013 = The American College of Cardiology and American Heart Association Os 2013; FRS-lipids = Framingham Risk Score using lipids; FRS-BMI = Framingham Risk Score using lipids; SCORE = Systemic Coronary Risk Evaluation; ERS-RA = Extended Risk Score-Rheumatoid Arthritis; RRS = Reynolds Risk Score; CIMT = Carotid Intima-Media Thickness; PPV = Positive Predictive Value; NPV = Negative Predictive Value.

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Abstract Number: 507

Echocardiographic Markers of Right Ventricle Dysfunction in Hispanic Patients with Rheumatoid Arthritis: A Case-Control Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Screening for cardiovascular (CV) disease in patients with rheumatoid arthritis (RA) remains controversial, however, there is agreement in considering echocardiography as the most immediate and simple approach to obtain reliable markers of right ventricle (RV) performance. (1) When RV systolic function adaptation fails, the RV becomes uncoupled from pulmonary circulation and dilates to preserve flow output at a price of systemic congestion. It has been reported that evaluation of RV functional state by using the relationship between the tricuspid annular plane systolic excursion (TAPSE) and the pulmonary artery systolic pressure (PASP) as a surrogate for the RV length-force, is of clinical prognostic relevance. (2) Objective: Assess RV function by TAPSE/PASP ratio in RA-patients and as compared to controls.

Methods: A case-control study with Hispanic RA-patients aged 40 to 75 years that fulfilled the 2010 ACR/EULAR criteria and matching controls were included. Exclusion criteria: poor acoustic window, prior atherosclerotic CV disease and overlap syndromes. Patients were matched using age, sex and CV comorbidities. Transthoracic echocardiogram was performed by a board-certified cardiologist, and reviewed by two cardiologists. TAPSE was measured as the total displacement of the tricuspid annulus (mm) from end-diastole to end-systole and PASP was estimated using the modified Bernoulli equation, according to ASE's guidelines.

Results: A total of 76 RA-patients and 52 matched controls were included. Demographic and clinical characteristics of both groups are shown in Table 1. As shown in Table 2, the mean TAPSE/PASP ratio was significantly lower in RA-patients than controls (0.89 ± 0.29 vs 1.02 ± 0.28 , $P=0.016$). TAPSE/PASP ratio showed significant correlation with age ($r=-0.24$, $P=0.03$) and null correlation with disease duration ($r=0.2$, $P=0.08$) and DAS 28-CRP ($r=0.05$, $P=0.69$).

Conclusion: TAPSE/PASP was reduced in RA-patients compared to controls. This ratio correlates with RA-patients age. TAPSE/PASP estimated by echocardiography may detect early RV dysfunction in RA. Larger studies are needed to determine the utility of TAPSE/PASP ratio to detect CV disease in Hispanic RA-patients.

- 1). Fine NM, et al. Evaluation of myocardial function in patients with RA using strain imaging by speckle-tracking echocardiography. *Ann Rheum Dis.* 2014;73(10):1833–9.
- 2). Guazzi M, et al. Tricuspid annular plane systolic excursion and pulmonary arterial systolic pressure relationship in heart failure. *AJP Hear Circ Physiol.* 2013;305(9):H1373–81.

Table 1. Demographic and Clinical characteristics

	RA (n=76)	Control (n=52)	P
Women, n (%)	74 (97.4)	46 (88.5)	0.041
Age, mean \pm SD	55.71 \pm 8.84	53.86 \pm 6.14	NS
Disease duration (years), mean \pm SD	10.43 \pm 8.55	-	-
DAS 28-CRP, mean \pm SD	3.34 \pm 1.34	-	-
BMI, mean \pm SD	29.11 \pm 5.42	28.31 \pm 4.37	NS
Hypertension, n (%)	26 (34.2)	12 (23.1)	NS
Active smoking, n (%)	6 (7.9)	6 (11.5)	NS

NS- Non-significant

Table 2. Echocardiographic findings

	RA (n=76)	Control (n=52)	P
TAPSE, mean \pm SD	22.8 \pm 3.1	23.9 \pm 3.1	0.052
PASP, mean \pm SD	27.14 \pm 6.34	24.68 \pm 5.44	0.024
TAPSE/PASP, mean \pm SD	0.89 \pm 0.29	1.02 \pm 0.28	0.016

TAPSE - Tricuspid annular plane systolic excursion, PASP - Pulmonary artery systolic pressure

Disclosure: J. R. Azpiri-López, None; D. A. Galarza-Delgado, None; I. J. Colunga-Pedraza, None; J. A. Davila-Jimenez, None; E. E. Abundis-Marquez, None; A. H. Guillen-Lozoya, None; F. J. Torres-Quintanilla, None; A. Valdovinos-Bañuelos, None; R. Ramos-Cázares, None; R. Vera-Pineda, None; J. A. Cardenas-de la Garza, None; R. I. Arvizu-Rivera, None; A. Martínez-Moreno, None.

Non-Invasive Evaluation of Left Atrial Pressure in Hispanic Patients with Rheumatoid Arthritis: A Case-Control Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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Background/Purpose: In the last several years a higher prevalence of heart failure has been described in Rheumatoid arthritis (RA) patients, particularly heart failure with preserved ejection fraction (HFpEF). Elevated left atrial pressure (LAP) may not only be a pathophysiologic substrate of symptoms in patients with HFpEF, it may also be direct prognostic markers.(1) Several studies have emphasized the importance of left atrial function in RA-patients. (2) Objective: to compare the LAP and diastolic left ventricle (LV) filling patterns between RA-patients and controls.

Methods: A case-control study with RA patients aged 40 to 75 years that fulfilled the 2010 ACR/EULAR criteria and matching controls were included. Exclusion criteria: poor acoustic window, prior atherosclerotic cardiovascular (CV) disease and overlap syndromes. Patients were matched using age, sex and CV comorbidities. Transthoracic echocardiogram was performed by a board-certified cardiologist, and reviewed by two cardiologists. LAP was estimated using the Nagueh-formula [$1.24 * (E/E') + 1.9$] and ASE's guidelines were used to define elevated LAP and diastolic LV filling patterns.

Results: A total of 80 RA-patients and 54 matched controls were included. Demographic and clinical characteristics are shown in Table 1. As shown in Table 2, the mean LAP was not significantly higher in RA-patients than controls (12.9 ± 3.6 vs 12.2 ± 2.5 , $P=0.18$). The difference between elevated LAP prevalence was not significant among both groups (8.8% vs 5.6% , $P=0.49$). Abnormal diastolic LV filling pattern was more prevalent in RA-patients compared to controls. LAP showed null correlation with disease duration ($r=0.06$ $P=0.64$) and DAS 28-CRP ($r=0.01$ $P=0.93$).

Conclusion: Left atrial pressure values were not different in Hispanic RA-patients evaluated when compared to controls and did not correlate with disease activity and duration. RA-patients had abnormal relaxation more frequently than controls.

- Hasenfuss G, et al. Rationale and Design of the Reduce Elevated Left Atrial Pressure in Patients With Heart Failure Trial. *J Card Fail*. 2015;21(7):594–600.
- Maloberti A, et al. Association Between Atrial, Ventricular and Vascular Morphofunctional Alterations in RA. *High Blood Press Cardiovasc Prev*. 2018;25(1):97–104.

Table 1. Demographic and Clinical characteristics

	RA (n=80)	Control (n=54)	P
Age, mean \pm SD	55.3 \pm 8.6	53.5 \pm 6.3	0.182 (NS)
Women, n (%)	78 (97.5)	49 (90.7)	0.085 (NS)
Disease duration, mean \pm SD	10.5 \pm 8.5	-	-
DAS 28-CRP, mean \pm SD	3.3 \pm 1.31	-	-
DM type 2, n (%)	7 (8.8)	7 (13)	0.434 (NS)
Hypertension, n (%)	28 (35)	11 (20.4)	0.067 (NS)
Smoking, n (%)	6 (7.5)	6 (11.1)	0.473 (NS)

DAS 28-CRP - DAS 28 using C reactive protein, DM type 2 - Diabetes mellitus type 2, NS - Non-significant

Table 2. Echocardiographic findings

	RA (n=80)	Control (n=54)	P
LAP (mmHg), mean \pm SD	12.9 \pm 3.6	12.2 \pm 2.5	0.178 (NS)
Elevated LAP, n (%)	7 (8.8)	3 (5.6)	0.490 (NS)
E/E', mean \pm SD	8.88 \pm 2.87	8.3 \pm 2.06	0.206 (NS)

Table . (Cont'd)

		RA (n=80)	Control (n=54)	P
E/A, mean \pm SD		1.05 \pm 0.29	1.06 \pm 0.32	0.855 (NS)
Diastolic LV filling pattern	Normal, n (%)	66 (82.5)	51 (94.4)	0.042
	Impaired relaxation, n (%)	10 (12.5)	2 (3.7)	0.08 (NS)
	Pseudonormal, n (%)	4 (5)	1 (1.9)	0.346 (NS)
	Restrictive, n (%)	0 (0)	0 (0)	NS

LAP - Left atrial pressure, LV - Left ventricle, NS - Non-significant

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Abstract Number: 509

Cardiovascular Disease Risk Factors May Negatively Impact Rheumatoid Arthritis Disease Outcomes: Findings from the Ontario Best Practices Research Initiative

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis increases the risk of cardiovascular disease (CVD). Less is known about the direct influence of CVD on RA outcomes, but higher comorbidity burden has been suggested to adversely affect RA treatment response. We tested our hypothesis that CVD risk factors (RFs) alone, in the absence of CVD, are associated with higher disease activity and disability in RA.

Methods: The Ontario Best Practices Research Initiative (OBRI) is a clinical registry of RA patients followed in routine care. RA subjects with complete data to calculate disease activity according to the Disease Activity Score-28 (DAS28), Clinical Disease Activity Index (CDAI), 28 swollen joint count (SJC28) and functional status (Health Assessment Questionnaire Disability Index [HAQ-DI]) at cohort entry were selected. Patients were divided into mutually exclusive groups by baseline CVD status as: (1) no CVD/no CVD RFs; (2) CVD; (3) no CVD but CVD RFs including hypertension (HTN), dyslipidemia (DLP), diabetes (DM), or smoking. We performed separate linear regression analyses, adjusted for baseline clinical and demographic variables, to determine the independent effect of CVD status on disease outcomes at baseline.

Results: Of 2033 patients examined, 54% had no CVD, 5% had CVD and 41% had CVD RFs alone. The most common RF was HTN (23%) followed by current smoking (17%), DM (12%) and DLP (5%). The majority had 1 CVD RF (34%) with decreasing frequency of 2 (8%), 3(2%) or all 4 (0.3%) risk factors. Subjects with CVD or CVD RFs were significantly older, had less education, higher ESR, higher joint counts, higher pain scores and greater number of non-CVD comorbidities. In cross-sectional analyses, having a CVD RF was associated with significantly higher composite disease activity scores (DAS28 and CDAI), and HAQ-DI scores (Table). No association between CVD status and swollen joint count was observed.

Conclusion: Even in the absence of CVD, traditional CVD risk factors are associated with greater RA disease severity and disability. Self-perceived impact of comorbidity (patient global assessment of health) may be driving this relationship. Investigation into the magnitude of effect for the individual CVD RFs, and whether differences in RA treatment patterns by CVD status may mediate this relationship is warranted. This will help determine if CVD RFs are truly poor prognostic markers for RA outcomes.

Table. Multivariable linear regression of disease activity outcomes and functional status at baseline according to CVD status.

	β - coefficient (95% CI); p-value			
	DAS28-ESR	CDAI	SJC-28	HAQ-DI
No CVD / No CVD RFs	Ref	Ref	Ref	Ref
CVD	0.39 (0.03, 0.75); 0.03	2.29 (-0.85, 5.43); 0.15	0.76 (-0.39, 1.92); 0.20	0.15 (-0.19, 0.31); 0.08
CVD RFs / No CVD	0.28 (0.11, 0.44); 0.001	1.70 (0.25, 3.14); 0.02	0.39 (-0.14, 0.92); 0.15	0.20 (0.12, 0.27); <0.0001

Models adjusted for age and gender; furthermore, variables that were significantly associated with both CVD status and disease outcomes were also considered (e.g. education, other comorbidities, annual household income, and health insurance coverage)

Disclosure: K. Cui, None; M. Movahedi, None; C. Bombardier, Pfizer, Inc., 2; B. Kuriya, None.

Abstract Number: 510

Lipid Profile and Cardiovascular Risk in Subjects at Risk for Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease associated with an increased cardiovascular (CV) risk that is already present at the time of diagnosis. However, it is unclear at what point in the period before diagnosis of RA the CV risk increases. Therefore, we assessed CV risk factors and the 10-year risk of CV mortality in a cohort of subjects at risk for RA and analyzed associations with anti-citrullinated protein antibody (ACPA) status and arthritis development.

Methods: In a cohort of 555 consecutive arthralgia patients with positivity for rheumatoid factor (RF) and / or ACPA, demographics, medical history, medication use and comorbidities were assessed. Lipid profile was determined and blood pressure was measured. The 10-year CV risk according to the European Heart SCORE was calculated for patients of whom data were complete.

Results: ACPA positive patients (n=348) were younger (mean age 48.3 vs 51.5, p=0.002), had higher CRP levels (median 2.3 mg/l vs 2.0, p=0.007) and had lower cholesterol (mean level 5.2 mmol/l vs 5.6, p<0.001), HDL (mean level 1.0 mmol/l vs 1.2, p<0.001) and LDL levels (mean level 3.5 mmol/l vs 3.7, p=0.021) than ACPA negative patients. Patients who developed arthritis (n=188) had a higher heart rate (68 beats per minute vs 63, p=0.048) and lower cholesterol (mean level 5.2 vs 5.5, p=0.006), HDL (mean level 1.0 vs 1.1, p=0.003) and ApoB levels (mean level 0.8 g/l vs 0.9, p=0.011) compared to patients who did not develop arthritis. In ACPA positive patients, lower LDL was predictive for the development of arthritis.

The European Heart SCORE was calculated in 144 patients (median 1, IQR 0-2). 43.8% had a low risk (SCORE<1%), 48.7% a medium risk (SCORE 1-<5%) and 7.7% had a high to very high 10-year risk (SCORE ≥ 5%) of cardiovascular mortality. The Heart SCORE was not associated with ACPA status or arthritis development.

Conclusion: Similar lipid abnormalities as known in RA patients with untreated disease were also present in seropositive arthralgia patients at risk for RA. In ACPA positive patients, LDL predicted development of arthritis. However, arthralgia patients who developed arthritis did not have a higher CV risk score than those who did not develop arthritis. Also, despite differences in lipid profile, the CV risk score does not differ between ACPA positive and ACPA negative patients at risk for RA. Overall, differences in lipid profile were too small to have an effect on the 10 year risk of CV mortality as calculated by the European Heart SCORE.

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Identifying Vulnerable Plaque in Rheumatoid Arthritis Using Novel Microbubble Contrast-Enhanced Carotid Ultrasonography and Serum Biomarkers of Inflammation and Atherosclerosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

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

Background/Purpose: Rheumatoid arthritis (RA) patients have an elevated risk of cardiovascular (CV) disease unexplained by traditional CV risk factors. Markers of systemic inflammation, including those elevated in RA, are associated with increased plaque vulnerability. Neovascularization of the vasa vasorum (VV) is a key early feature of vulnerable plaque that is also associated with inflammation in the general population. RA-related factors may promote vulnerable plaques with increased VV neovascularization, leading to elevated CV risk. Microbubble contrast-enhanced ultrasound (CU) is a novel technique validated for quantifying VV neovascularization, which is not measured by traditional imaging techniques. Increased carotid adventitial vasa vasorum density (aVVD) indicates increased plaque vulnerability. We use CU to measure and compare aVVD in RA subjects and non-RA control subjects. We further examine correlations of aVVD with biomarkers of inflammation and atherosclerosis.

Methods: We performed a cross-sectional study of RA (n=87) and non-RA control subjects (n=101). All RA patients met 2010 ACR classification criteria. Subjects were assessed for traditional cardiovascular risk factors. Nitrite, CD40L, E-selectin, MMP-9, ICAM-1, VCAM-1, CRP, and ESR were measured in serum. CU was performed along the common carotid arteries bilaterally. CU images were analyzed using Myocardial Contrast Echocardiography 2.9 software. aVVD was quantified as the ratio of mean common carotid artery adventitial to lumen video intensity using maximum of both sides. Demographic data, CV risk factors, and biomarker levels were compared between RA and control subjects using Wilcoxon rank-sum or chi-square tests. Association of aVVD with biomarkers and CV risk factors, stratified by case status, was examined using Pearson and Spearman correlation, respectively, and linear regression models adjusted for number of CV risk factors and age.

Results: RA subjects were older (59.6 ± 12.0 versus 56.1 ± 14.8 years; $p = 0.01$) and had higher number of CV risk factors (40.2% versus 20.6% had ≥ 3 risk factors; $p = 0.003$) compared to controls. aVVD was higher in RA subjects (0.64 ± 0.14 versus 0.61 ± 0.15 ; $p = 0.02$). In RA subjects, MPO was lower (422.8 ± 516.4 versus 604.4 ± 455.1 ng/mL; $p = 0.0002$) and ESR was higher (21 ± 16 versus 16 ± 13 mm/hr; $p = 0.01$). The other biomarkers did not differ significantly between groups. aVVD was correlated with MPO ($r = -0.33$, $p = 0.001$) and CRP ($r = 0.25$, $p = 0.02$) in control subjects, associations which remained significant after adjusting for number of CV risk factors and age. No significant correlations were found between aVVD and biomarkers in RA patients. Number of CV risk factors was not significantly correlated with aVVD in RA and controls.

Conclusion: Using the novel CU technique, we found that aVVD is significantly higher in RA compared to control subjects, suggesting CU may quantify increased plaque vulnerability in RA patients with subclinical atherosclerosis. The differences in correlation of aVVD with biomarkers of atherosclerosis and traditional CV risk factors between RA and control subjects suggests RA-related differences in atherosclerotic progression.

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Incidence of First Cardiovascular Event in Spanish Patients with Chronic Inflammatory Rheumatic Diseases: Prospective Data from an Observational Multicentric Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: To determine the incidence and risk factors implicated in the development of first cardiovascular event (CVE) in patients with chronic inflammatory rheumatic diseases (CIRD) attending rheumatology clinics after 2.5 years of follow-up.

Methods: Analysis of data after 2.5 years of follow-up in an observational prospective study [CARDiovascular in rheumatology (CARMA) project] that includes a cohort of patients with CIRD [rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA)] and another cohort of matched individuals without CIRD attending outpatient rheumatology clinics from 67 hospitals in Spain. The cumulative incidence per 1000 patients and the incidence density per 1000 patient-months of non-fatal CVE were estimated in both cohorts at 2.5 years from the start of the project. Weibull proportional hazard model was used to calculate the Hazard Ratio (HR) and 95% confidence interval (95% CI) of the risk factors involved in the development of CVD events. Losses to follow-up and their causes were also analyzed.

Results: The total number patient who completed the follow-up visit at 2.5 years was 2,598 (89.2% of those who started the study). Seven patients had died due to CVE and 23 because of non-CVE. The higher number of losses to follow-up was found in the control group (15.81%), because many of them were not periodically follow-up at the outpatient clinics. Cardiovascular cumulative incidence in patients with CIRD 15.30 cases per 1000 patients (95% CI: 12.93-17.67), being higher in AS patients 22.03 (95% CI: 11.01-33.04). The higher risk of developing a first CVE during the 2.5 years of follow-up was in patients with AS (HR: 4.11, 95% CI: 1.07-15.79; p: 0.04), those with older age (HR:1.09; 95% CI: 1.05-1.13, p <0.001), higher systolic blood pressure (HR: 1.02; 95% CI: 1.00-1.04, p = 0, 01) and longer duration of the rheumatic disease (HR: 1.07; 95% CI: 1.03-1.12), p <0.01). In contrast, female gender was a protective factor (HR: 0.43; 95% CI: 0.18-1.00, p = 0.05).

Conclusion: Patients with AS prospectively followed-up at rheumatology outpatient clinics show higher risk of developing a first CVE than those with RA or PsA. Besides traditional CVD risk factors a longer time course of the disease is a risk factor for the development of CVD in patients with CIRD.

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Low Serum IGF1 Is Associated with Higher Cardiovascular Morbidity in the Middle-Aged Women with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Since low serum IGF1 is generally attributed to inflammation and RA severity, we analyze if serum levels of IGF1 is associated with cardiovascular (CV) risk in women with rheumatoid arthritis (RA).

Methods: The risk of developing of CV disease within 10 years was calculated in a cohort of 184 female RA patients (median age 53 years, range 21-71) with no history of CV events, using the Framingham strategy. A 5-year follow-up of new CV events was completed by a structured interview in all the patients. The reported CV events were confirmed through the Swedish National Patient Register. The CV risk and CV event-free survival curves were compared with respect to serum IGF1 levels, where IGF1 levels below the median of the total cohort were considered low.

Results: The RA women with low IGF1 (n=96, median 110 pg/ml) had significantly higher CVR compared to those with normal IGF1 (n=88, median 181 pg/ml) with the predicted risk of 7.2 % and 3.3 %, respectively (p<0.001). In age-adjusted groups, CVR was significantly higher in females ≤50 years with low IGF1 (p<0.001). At 5-year follow up, 12 (6.5%) patients experienced CV event. A Kaplan-Meier analysis showed that the CV events occurred with higher frequency in the patients with low IGF1 at baseline (p=0.029). After 5 years the risk of having experienced a cardiovascular event was 5 times higher in patients with low IGF1 at baseline (RR 4.583; CI95% 1.033-20.34; p=0.027). At baseline the IGF1 low group had high prevalence of hypertension (24% vs. 8.5%, p=0.004) and higher BMI (p=0.008). The atherogenic index (total cholesterol/HDL) (2.8 vs 3.0) and smoking (15% vs. 14%) was similar between the groups. With exception for disease duration, the groups were similar in RA-related CVR factors as seropositivity (91% vs 92%), disease activity measured by DAS28 (median 3.20 vs 2.90), or systemic inflammation measured by serum IL6 and IL1b. The prevalence of treatment with MTX monotherapy was higher in the IGF1low group (56% vs. 39%, p=0.024), while the use of TNFi and other biologics was similar within the groups.

Conclusion: Female patients with RA, IGF1 levels in the normal low range are associated with higher CVR and experienced higher frequency of CV events. This increase in CV disease seems to be independent of the RA-related characteristics.

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Cardiovascular Risk Management in Seropositive Rheumatoid Arthritis: What Can We Do Better?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

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Background/Purpose: The increased risk of cardiovascular disease (CVD) in rheumatoid arthritis (RA) has been well established. While the reasons for an increased risk of CVD in RA remain unclear, it is imperative to carefully manage cardiovascular risk factors in RA patients. The purpose of this study was to compare CVD risk management in seropositive RA patients compared with non-RA patients in a large healthcare system.

Methods: The study design was a matched retrospective cohort comparing subjects with seropositive RA and non-RA patients drawn from the outpatient population receiving care within the Fairview Health System in Minnesota between 1/1/2005 and 12/31/2015. A cohort of 732 adult subjects with seropositive RA was identified from electronic medical records, and matched with a cohort of 2994 non-RA patients based on age and sex. Demographic characteristics and multiple clinical measures of cardiovascular risk, including BMI, outpatient blood pressure, smoking status, serum lipids and hemoglobin a1c, were ascertained from electronic medical record. Mortality was assessed from medical and state records. Chi-square tests were used for categorical variables and t-tests or Wilcoxon-Mann-Whitney tests for continuous variables. Generalized estimating equation models were used for longitudinal analyses.

Results: The mean age at baseline was 56 years in both RA and non-RA cohorts, and the majority of patients were female (79% RA, 80% non-RA). Participants in the two cohorts were largely white (82% RA, 85% non-RA), and overweight or obese (baseline BMIs of 25 or greater in 69% RA, and 71% non-RA patients). RA patients, on average, lived in zip codes with a lower median household income than non-RA patients (65,100 vs 67,700, $p<0.01$). Patients had a minimum of one year follow up (mean 6 years RA, 5.7 years non-RA). There were more deaths in the RA cohort than non-RA cohort during the follow-up period (15% vs 10%, $p<0.01$). RA patients and non-RA patients, on average, had blood pressure readings, cholesterol and A1C measurements in the normal range, and there was no difference in these parameters between cohorts in longitudinal analyses. Mean systolic blood pressure was 125 and mean diastolic blood pressure was 73 in both RA and non-RA patients. Mean HDL, LDL, Total cholesterol, and A1C were 55 ± 1 , 104 ± 2 , 188 ± 2 , and 6.7 ± 0.1 , respectively, for RA patients and 53 ± 0.4 , 103 ± 1 , 183 ± 1 , and 6.9 ± 0.05 for non-RA patients. However, there was a higher percentage of current smokers among RA patients (24% vs. 14%, $p<0.01$).

Conclusion: While most CVD risk factors were well managed in seropositive RA patients and in non-RA controls, we found an excess of active smoking in RA patients compared with the non-RA cohort, indicating an area of potential practice improvement.

Disclosure: M. McElwee, None; P. Boersma, None; H. Hashmi, None; A. K. Shmagel, None.

Abstract Number: 515

How Knowledgeable Are Patients with Rheumatoid Arthritis about Cardiovascular Disease?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

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

Background/Purpose: Despite dramatic change in treatment options in recent years, cardiovascular disease (CVD) mortality has not improved in rheumatoid arthritis (RA) and remains the leading cause of mortality in RA. Rates of screening and treatment for modifiable CVD risk factors in RA remains poor (27-45%). The primary objective was to evaluate baseline cardiovascular risk awareness (CVRA) in patients with RA.

Methods: Consecutive patients at two academic centers with a diagnosis of RA of at least 3 months' duration were enrolled. Patients completed questionnaires on demographics, RA characteristics, active treatment and CVRA. CVRA was measured using the Heart Disease Knowledge Questionnaire (HDKQ; 30 items), and the Heart Disease Fact Questionnaire- RA (HDFQ-RA; 13 items). Descriptives for the study group and total correct response rates (%) were obtained for each tool. We then performed linear regression analysis with demographics (age, gender, ethnicity, and race), disease features (RA medications, RAPID3) and lifestyle (self-reported smoking and sedentary status) as independent variables to assess for correlates of CVRA.

Table 1 Cardiovascular risk awareness (CVRA) in rheumatoid arthritis patients	
Baseline CVRA items with <50% correct response rate	
Heart Disease Knowledge Questionnaire-RA	
	AR (n=167)
Women are less likely to get heart disease after menopause than before.	48.1
Having had rheumatoid arthritis increases the risk of getting heart disease.	58.5
The most important cause of heart attacks is stress.	55.7
Smokers are more likely to die of lung cancer than heart disease.	46.1
The healthiest exercise for the heart involves rapid breathing for a sustained period of time.	43.1
Sudden trouble seeing in one eye is a common symptom of having a heart attack.	37.2
Atrial defibrillation is a procedure where hardened arteries are opened to increase blood flow.	36.5
Margarine with liquid soyflower oil is healthier than margarine with hydrogenated soy oil.	34.7
Men and women experience many of the same symptoms of a heart attack.	40.1
Total Mean	60
Total SD	19
Heart Disease Fact Questionnaire	
	AR (n=167)
Anti-inflammatory medications such as diclofenac or ibuprofen taken by patients with rheumatoid arthritis may increase their chance of heart disease.	28.3
Having lots of inflammation ("flares") of rheumatoid arthritis adds to the increased chance of heart disease.	40.1
Total Mean	75
Total SD	19

Table 2. Predictors of baseline CVRA						
Variable	Univariate			Multivariate		
	B	95% CI	P	B	95% CI	P
HDKQ						
Non Caucasian Race	-0.34	-0.13, -0.08	<0.001	-0.13	-0.12; 0.01	0.10
Hispanic Ethnicity	-0.31	-0.22, -0.08	<0.001	-0.11	-0.13; 0.01	0.18
Educational Level	0.50	0.02, 0.04	<0.001	0.40	0.02; 0.03	<0.001
Self-Reported Smoking status	-0.20	-0.17, -0.02	<0.001	-0.05	-0.10; 0.05	0.53
Prednisone dose baseline	-0.20	-0.07, 0.01	0.005	-0.14	-0.06; 0.002	0.07
HDFQ-RA						
Non Caucasian Race	-0.20	-0.13, -0.02	0.011	-0.06	-0.09; 0.04	0.53
Hispanic Ethnicity	-0.23	-0.18; -0.04	0.003	-0.12	-0.14; 0.01	0.18
Education Level	0.41	0.01; 0.03	<0.001	0.14	0.01; 0.03	<0.001
Self-Reported Smoking status	-0.20	-0.17, -0.02	0.01	-0.10	-0.13; 0.04	0.26

HDKQ: Heart Disease Knowledge Questionnaire, HDFQ-RA: Heart Disease Fact Questionnaire Rheumatoid Arthritis

Results: 167 RA patients participated. Mean (SD) age was 57.6±13.8 years; 87% were women. Thirty-seven percent were Caucasian and 40% African American. Forty-three percent were taking NSAIDS routinely, 60% methotrexate, and nearly 50% were on some dose of corticosteroid. Mean (SD) RAPID3 score was 11.8 (7.6). Self-reported CVD risks were: smoking (18%), hypertension(44%), diabetes mellitus (25%), High cholesterol (44%), overweight (46%), sedentary lifestyle (45%) and poorly controlled RA (48%).

Mean (SD) total correct response rates for HDKQ and HDFQ-RA at baseline were 60 (19) and 75 (19). For individual items, the correct response ratio was less than 50 for 9/30 HDKQ, and 2/10 HFFQ-RA items. Of note, participants performed poorly on the two items (role of NSAIDS and active RA) pertaining specifically to RA and increased CVD risk (Table 1). Determinants of poor CVRA on univariate analysis were less education, Hispanic ethnicity and Non-Caucasian Race (Table 2). On multivariate analysis, education was the sole independent predictor of CVRA, after adjusting for race, ethnicity, lifestyle and medication (Table 2).

Conclusion: General and RA specific understanding of CVRA is poor among RA patients. Education (not ethnicity/ race, or RA activity and medications) was the sole independent predictor of CVRA after adjusting for other variables. Interventions to improve CVRA should target those at risk and they need to be aligned to their educational level.

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Abstract Number: 516

Microalbuminuria in Rheumatoid Arthritis: Investigating the Association with Diffuse Functional and Morphological Alterations of the Retinal Microvasculature, the Dermal Capillary Network and the Coronary Microcirculation

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Increased urinary albumin excretion (UAE) is an early marker of renal microvascular damage that correlates with cardiovascular risk and corresponds to a state of generalized microvascular impairment, even below the threshold values usually considered for microalbuminuria (30-300 mg in a 24h urine sample). However, data regarding prevalence of microalbuminuria are conflicting in patients with rheumatoid arthritis (RA), a disease characterized by excess cardiovascular risk. Moreover, it remains unclear whether it corresponds to a state of generalized microvascular dysfunction in this particular group of patients. We investigated for the first time whether microalbuminuria is associated with other forms of microvascular impairment located in the dermal capillary network, the retinal and the coronary microvasculature.

Methods: 24h urine samples were obtained from RA and non-RA individuals to estimate UAE. Morphological changes in the retinal microvasculature were evaluated from retinal photography. Retinal images were processed with specifically designed computerized software that calculates retinal arteriolar and venular diameters, to obtain central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE), as well as their ratio (arteriovenous ratio, AVR). Functional assessment of the coronary artery network was based on measurement of the subendocardial viability index (SEVR), a non-invasive estimate of microvascular coronary perfusion, using radial artery applanation tonometry. Dermal capillary rarefaction was evaluated with nailfold capillaroscopy applied in the distant phalanx of the fingers, using semi automated software that calculates capillary density in the obtained images.

Results: A total of 111 individuals were studied, of whom 74 were RA patients with long-standing disease [9 (4–16.5) years], moderate disease activity (DAS score: 3.6 ± 1.4), and relatively low levels of systemic inflammation, and 37 were matched controls. Patients with RA presented narrower retinal arterioles, shown by decreased CRAE (78.0 ± 8.9 vs 87.4 ± 10.0 μm , $p < 0.001$) and AVR (0.69 ± 0.10 vs 0.78 ± 0.10 , $p < 0.001$); impaired coronary microvascular perfusion, shown by decreased SEVR (140.6 ± 22.3 vs 150.7 ± 21.6 %, $p = 0.038$), and pronounced capillary rarefaction, reflected in a lower number of dermal capillaries per visual field (132.5 ± 28.2 vs 151.2 ± 25.6 , $p = 0.007$), compared to controls. By contrast, neither UAE [5.1 ($2.8 - 10.8$) vs 6.5 ($3.0 - 11.7$) mg/24h] nor prevalence of microalbuminuria (11.0 vs 8.1%) differed between patients and controls ($p = \text{ns}$ for both). In the RA group, UAE was not significantly associated with inflammation or other disease-related parameters, nor with any of the studied microvascular indices of the coronary microcirculation, the retinal microvasculature, and the dermal capillary network.

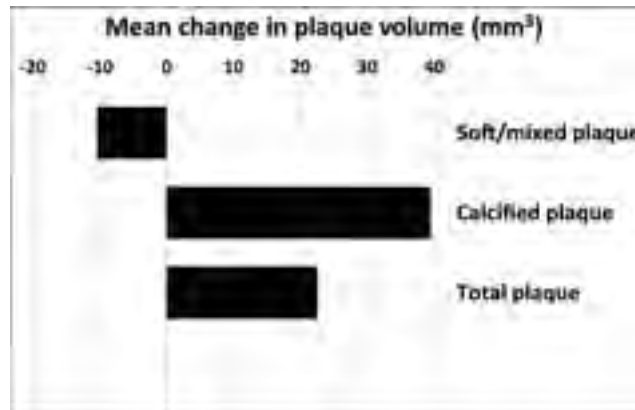
Conclusion: In our population of RA individuals, microalbuminuria was not associated with morphological and functional alterations in distal microvascular beds. Increased UAE in RA patients might be primarily considered as a manifestation of compromised function of the renal microvasculature, rather than a marker of generalized microvascular dysfunction.

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Abstract Number: 517

Effects of Statin-Treatment on Coronary Plaques in Patients with Inflammatory Joint Diseases

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

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Effects of Statin-treatment on Coronary Plaques in Patients with Inflammatory Joint Diseases

Background/Purpose: Statins have an established preventive effect on coronary artery disease in the general population. The effect of statins on coronary plaque progression and characteristics in patients with inflammatory joint diseases (IJD) is unknown. Our aim was to evaluate the change in coronary atherosclerosis in long-term statin-treated patients with IJD.

Methods: Sixty-eight patients with IJD and carotid artery plaque(s), underwent coronary computed tomography angiography before and after 4.7 (range 4.0-6.0) years of statin treatment. The treatment target for low density lipoprotein cholesterol (LDL-c) was ≤ 1.8 mmol/L. Changes in coronary artery calcification (CAC) and coronary artery plaque volume (calcified, mixed/soft and total) from baseline to follow-up were assessed using the 17-segment model of the American Heart Association. Linear regression analysis was used to identify predictors of atherosclerotic progression.

Results: Coronary plaques were present in 42% of the patients at baseline and in 51% at follow up. Mean CAC score increased with 173 ± 284 , calcified plaque volume with 39.4 ± 78.3 mm³ and total plaque volume with 22.8 ± 54.6 mm³ ($p < 0.01$, for all) (Figure 1). Mean mixed/soft plaque volume decreased with -10.4 ± 27.5 mm³ ($p < 0.01$). At follow-up, 51% of the patients had obtained LDL-c treatment target. Compared to patients above LDL-c target, patients with an LDL-c ≤ 1.8 mmol/L experienced reduced median progression of both CAC (21 [2-143] vs. 69 [16-423], $p < 0.01$) and total plaque volume (0.08 [-1.0-13.9] vs. 13.0 [0.0-60.8], $p = 0.02$) (Table 1).

Conclusion: We revealed a progression of atherosclerotic plaque volume in statin-treated patients with IJD, mainly due to calcifications. However, soft, unstable plaques were reduced, probably as a result of an alteration in plaque composition from mixed/soft plaques into calcified, stable plaques. Patients with recommended LDL-c levels at follow-up experienced a reduced atherosclerotic progression compared to patients with LDL-c levels above the treatment target. Our results support the importance of treatment to guideline recommended lipid targets in IJD patients.

Figure 1

Table 1

	LDL ≤ 1.8 mmol/L n=34	LDL > 1.8 mmol/L n=34	p-value*
LDL-c level baseline, mean \pm SD	3.7 \pm 0.9	4.4 \pm 1.0	<0.01
LDL-c level follow-up, mean \pm SD	1.5 \pm 0.2	2.4 \pm 0.7	<0.01
Change LDL-c level, mean \pm SD	-2.2 \pm 0.9	-1.9 \pm 1.3	0.38
Change in Calcium score, median (IQR)	21 (2, 143)	69 (16, 423)	<0.01
Change in soft/mixed plaque, median (IQR)	0 (-3.5, 0.0)	0 (-15.7, 0.0)	0.71
Change in calcified plaque, median (IQR)	1.7 (0.0, 17.3)	13.4 (1.5, 107.6)	0.02
Change in total plaque volume, median (IQR)	0.08 (-1.0, 13.9)	13.0 (0.0, 60.8)	0.02

* independent samples t-test

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Cardiometabolic Risk Factors Impact on the Cardioprotective Effect of Apelin on Systolic and Diastolic Function, in Patients with Rheumatoid Arthritis

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Background/Purpose: The rheumatoid arthritis (RA) population demonstrate a significantly increased incidence of cardiac events. Cardiac dysfunction in RA may occur as a result of impaired filling during diastole, or as contractile insufficiency (systolic dysfunction). Chronic systemic inflammation may be the underlying cause of cardiac alterations, and also impact significantly on traditional cardiovascular risk profiles. Apelin is an endogenous peptide known for its vasoactive effects, inotropic action and general cardioprotective function. Apelin may prove to be particularly beneficial within the RA population.

This study aimed to determine the association of apelin concentrations with measures of cardiac geometry, systolic and diastolic function, independent of traditional risk factors and inflammation in RA patients.

Methods: 186 RA patients were included, where demographic, anthropometric and RA disease characteristics were recorded. Cardiac structure and function was assessed using two-dimensional directed M-mode echocardiography, Pulsed Doppler, and tissue Doppler imaging. Circulating cytokine concentrations were determined using immunoturbidimetric methods. Apelin-13 concentrations were quantified using a solid-phase sandwich ELISA technique. The association of apelin concentrations with stroke volume, ejection fraction, endocardial and midwall fractional shortening, relative wall thickness, left ventricular mass, mitral inflow (E/A), lateral and septal e', left ventricular filling pressures (E/e'), and left atrial volume index (LAVI) were determined in comprehensively adjusted multivariate and backward regression analyses.

Results: Apelin concentrations were not independently associated with cardiac geometry, diastolic or systolic function ($p > 0.05$) in all patients. Body mass index impacted on apelin-ejection fraction and apelin-fractional shortening relations (interaction $p = 0.02$, for both), and hypertension impacted on apelin-E/A ratio, apelin-stroke volume, apelin-ejection fraction, apelin-endocardial fractional shortening and apelin-midwall fractional shortening relations (interaction $p = 0.03$, $p = 0.01$, $p = 0.02$, $p = 0.01$ and $p = 0.03$, respectively). In stratified analyses, apelin was associated with improved ejection fraction and endocardial fractional shortening in patients with a BMI $\geq 25 \text{ kg/m}^2$, but not in those with a BMI $< 25 \text{ kg/m}^2$. Apelin concentrations were associated with an improved E/A ratio (partial $r = 0.31$; $p = 0.04$), stroke volume (partial $r = 0.29$; $p = 0.03$), ejection fraction (partial $r = 0.39$; $p = 0.01$), endocardial fractional shortening (partial $r = 0.40$; $p = 0.003$) and midwall fractional shortening (partial $r = 0.31$; $p = 0.02$) in hypertensive but not normotensive patients.

Conclusion: Apelin concentrations are associated with improved active relaxation in hypertensive patients only. The inotropic effects of apelin is paradoxically increased in the presence of adverse metabolic risk factors. The vasoactive and cardioprotective effects of apelin may be particularly beneficial in those with adverse cardiometabolic risk profiles.

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Marginal Structure Modeling of Association between Disease Activity and Hospitalized Infection Among Patients in a Rheumatoid Arthritis Registry

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Background/Purpose: Higher disease activity might be associated with a higher risk of developing infections among patients with rheumatoid arthritis (RA). Since no randomized trial has been conducted using disease activity as the main exposure, this association may be confounded due to the effects of other RA treatments or comorbidities. To examine the association between RA disease activity and hospitalized infection using data from the U.S. Corrona RA registry linked to Medicare claims data for outcome ascertainment. We hypothesized that patients who started in moderate disease activity and subsequently attained low disease activity or remission had lower rates of infection.

Methods: Using CORRONA RA patients with Medicare coverage in 2006-2014, we identified eligible patients who had at least one visit with moderate disease activity based on the clinical disease activity index (CDAI between 10 and 22). Hospitalized infection was assessed in Medicare data. Follow-up started at the second Corrona visit and ended at the earliest date of: hospitalized infection, high disease activity (CDAI >22), loss to follow-up, or 12/31/2014. We calculated the incidence rate of hospitalized infection for patients in remission, low and moderate disease activity and estimated the effect of CDAI on hospitalized infection by controlling for time-dependent confounders using marginal structural models (MSM). Each observation was weighted using stabilized inverse-probability-of-treatment weights (IPTW), truncated at the 1st and 99th percentile.

Results: A total of 1,618 RA patients were eligible for analysis, for which 212 hospitalized infections were identified over mean follow-up of 2.2 years. These patients had mean (SD) age of 69.0 (10.0) years and 77.2% were female. The crude incidence of hospitalized infection was 4.0 per 100 person years for patients in remission, 7.1 for low disease activity and 7.5 for moderate disease activity. Using MSMs, and referent to being in remission, the hazard ratio of hospitalized infection associated with moderate disease activity was 1.19 (95% CI: 0.42-3.42) and for low disease activity was 0.78 (95% CI: 0.37-1.67). Baseline factors that were significantly associated with an increased risk for infection included older age, duration of RA, glucocorticoid use, and history of hospitalized infection.

Conclusion: In rheumatoid arthritis patients, the crude incidence of hospitalized infection was higher for patients in low or moderate disease activity compared to those in remission. However, these differences were greatly attenuated after controlling for confounding using marginal structural models to account for the interplay of disease activity, RA treatments, treatment switching, and other potential confounders.

Table: Events, absolute incidence rate and hazard ratios of hospitalized infection by disease activity

Disease activity	Events	Incidence rate per 100 person years	Unadjusted Hazard Ratio (95% CI) without weight*	Adjusted HR (95% CI) without IPTW weighting**	Unadjusted HR (95% CI) with stabilized weights†	Adjusted HR (95% CI) with stabilized weights†
Moderate	105	7.5	1.89 (1.32-2.71)	1.59 (1.09-2.32)	1.56 (0.61-4.01)	1.19 (0.42-3.42)
Low	95	7.1	1.69 (1.19-2.38)	1.50 (1.04-2.15)	0.86 (0.37-1.96)	0.78 (0.37-1.67)
remission	13	4.0	Ref	Ref		Ref

* Without adjustment and without weight

** Adjusted baseline and time-varying characteristics, but did not apply weight

† Adjusted baseline and time-varying characteristics with stabilized weight

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Abstract Number: 520

Factors Associated with the Development of Severe Respiratory Infections in Patients with Rheumatoid Arthritis Included in a Vaccination Program

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Background/Purpose: Rheumatoid arthritis (RA) patients are at increased risk of infections particularly respiratory infections. These may be augmented due to RA itself and to immunosuppressive drugs, specially biologic therapy. Vaccination programs are designed to decrease infections. In RA patients underwent to Vaccination program previously to start a new or a change in biologic therapy from October 2011; our aim was to assess the incidence of severe respiratory infections and to determine the underlying basal risk factors for the development of these complications.

Methods: Retrospective study of 401 patients diagnosed with RA who were invited to participate in a protocolled vaccination program from October 2011 to October 2016 in a referral center. The follow-up was made until June 2017 with a minimum follow-up period of 8 months and maximum of 5.5 years. Serious infections were defined as those that required hospitalization or at least one dose of intravenous antibiotic treatment at the emergency room. Information was retrieved from the hospital records. Only 7 patients refused vaccination (2%). Information was not obtained in 4 of the remaining 394 patients. Therefore, these 4 patients were not included in the assessment.

Results: We finally studied 390 patients (307♀/83♂), mean±SD age 61.28±12.9 years that were vaccinated and followed-up. The main features at the time of vaccination were: median diseased duration (4 years), positive rheumatoid factor (56.7%), subcutaneous nodules (4.9%), erosive arthritis (36.9%), pulmonary fibrosis (3.8%), secondary Sjögren syndrome (5.1%), other extraarticular manifestations (14.6%) and rheumatoid vasculitis (5.6%). Most patients had received immunosuppressive drugs before the vaccination program. The most frequently used were systemic corticosteroids (n=228), methotrexate (n=362) and biologic agents (40.3%). During the follow-up, 42 patients (10.7%) had required hospital admissions due to infections, 17 of them were severe respiratory infections (4.35%). The remaining 25 admissions were in the setting of urinary tract infections (n=12), intraabdominal infections (7), skin and soft tissues (12) and articular (1). Also 12 of these patients had zoster herpes. The presence of anti-citrullinated protein antibodies (ACPA) was associated with an increased frequency of admissions due to these infections (TABLE). It was also the case for the presence of a history of biologic therapy prior to vaccination. No association of severe respiratory infection with rheumatoid factor, erosions or pulmonary fibrosis was found.

Conclusion: Vaccinated patients with RA present a low incidence of severe respiratory infections. Positivity for ACPA and the use of biologics prior to vaccination are associated with increased risk of severe respiratory infections in these patients. Therefore, vaccination should be performed prior to the onset of biologic treatment.

TABLE.

Admission for severe respiratory infections	Crude OR (CI 95%)	p	Adjusted OR* (CI 95%)	p
RF positivity	2.13 (0.67 – 6.83)	0.2011	2.26 (0.69-7.84)	0.1799
ACPA positivity	3.73 (1.04-13.43)	0.0441	4.49 (1.2-16.83)	0.0259
Erosions	2 (0.71-5.64)	0.1898	2.16 (0.75-6.25)	0.1573
Rheumatoid vasculitis	1.48 (0.40-5.42)	0.5527	1.38 (0.37-5.22)	0.6336
Pulmonary fibrosis	4.27 (0.87-20.91)	0.2932	2.45 (0.46-13.05)	0.2932
Biologic treatment before vaccination	3.02 (1.01-9.02)	0.0476	2.61 (0.85-8.07)	0.0947

* adjusted by age and sex.

Disclosure: L. C. Domínguez-Casas, None; P. Rodríguez-Cundín, None; V. Calvo-Río, None; N. Vegas-Revenga, None; V. Portilla, None; F. Antolin, None; M. Rebollo-Rodrigo, None; A. Corrales, None; D. Prieto Peña, None; M. Calderón Goercke, None; M. A. González-Gay, None; R. Blanco, None.

Abstract Number: 521

The Lung in an English Cohort of Rheumatoid Arthritis Patients – an Overview of Different Types of Involvement and Treatment

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Background/Purpose: Lung disease is described in 5–20% of pts (pts) with RA and affects parenchyma, pleura, airways and vasculature; drug-induced pulmonary disease also occurs. It is associated with a higher mortality and identification of safe and effective drugs is essential.

Methods: Retrospective analysis of the electronic records from RA cohort followed at University College Hospital. Lung involvement was based on high resolution computed tomography. Demographic data, smoking status, complementary exams at baseline/follow-up and therapies used were analysed. A sub-analysis of pts treated with rituximab (RTX) evaluated response at 12, 24 and 36 months. Declines of 15% in gas transfer from baseline and/or 10% in forced vital capacity were recognized.

Results: From 1129 RA pts, 87 (7.7%) had documented lung involvement. Mean age at last follow-up was 68.3±12 years, 74.7% were female and 85.1% Caucasian. Median diseased uration was 14 (IQR 8-29) years. 54% of pts had erosive disease. RF was positive in 88.1% and ACPA in 87.8%. 23 pts had positive ANAs (25 missing data) and 4 anti-Ro52, 2 anti-Scl70, 2 anti-PL12. Secondary SS occurred in 6.9%, cutaneous rheumatoid nodules in 5.7% and cutaneous vasculitis in 1.1%. 11.5% and 43.7% were current and previous smokers, respectively. Mean interval between articular and pulmonary symptoms was 12.3 years; 2 pts had lung disease as a prior manifestation. Types of lung involvement are shown in table 1. At last follow-up appointment 22 pts were still on MTX and 27 had previously received it. MTX-acute pneumonitis occurred in 2 pts, both in the 1st year of treatment.

Table 1 – Characterization of different types of lung involvement

	Female	Mean age at lung disease diagnosis (mean±SD)	Interval between RA and lung disease diagnosis (median [IQR])	Smoking habits	Positive RF	Positive ACPA
NSIP (n=18)	61.1%	66.3±12.5	1 [0-15]	76.5%	88.9%	88.2%
UIP (n=18)	61.1%	66.8±13	1 [0-13.5]	52.9%	87.5%	94.1%
OP (n=4)	100%	57±7.1	10 [4.25-21]	25%	100%	100%
Isolated bronchiectasis (n=31)	87.1%	63.7±9.3	17 [5.5-24.5]	45.2%	83.3%	78.6%
Obliterative bronchiolitis (n=2)	50%	74.5±3.5	30.5	50%	50%	100%
Panbronchiolitis (n=2)	100%	48.5±15.5	8.5	50%	100%	100%
Rheumatoid nodules (n=4)*	100%	45.8±11.4	6.5 [2.5-15.75]	75%	100%	75%
Pleural effusion (n=3)*	66.7%	41±9.3	13	66.7%	100%	100%

Note – 5 patients had evidence of interstitial lung disease in high resolution computed tomography, but with an unspecified pattern; 1 patient had evidence of small airways disease secondary to RA without any specific pattern

*1 patient had concomitantly pleural effusion and rheumatoid nodules

Legend: NSIP - nonspecific interstitial pneumonia; UIP - usual interstitial pneumonia; OP – organizing pneumonia

Table 2 – Disease outcomes after treatment with rituximab

Time of reevaluation	12 months			24 months			36 months		
ILD pattern	OP	NSIP	UIP	OP	NSIP	UIP	OP	NSIP	UIP
TLCO stable/ improvement	2/2 100%	7/9 77.8%	1/3 33.3%	1/1 100%	5/5 100%	1/2 50%		2/2 100%	1/2 50%
TLCO decline		2/9 22.2%	2/3 66.7%			1/2 50%			1/2 50%
FVC stable/ improvement	2/2 100%	7/9 77.8%	2/3 66.7%	1/1 100%	4/5 80%	1/2 50%		2/3 66.7%	1/2 50%
FVC decline		2/9 22.2%	3/3 100%		3/5 60%	1/2 50%		1/3 33.3%	1/2 50%
HRCT stable/ improvement		3/3 100%	1/3 33.3%		3/3 100%		2/2 100%	2/2 100%	
HRCT worsening			2/3 66.7%			1/1 100%			

Legend: ILD - interstitial lung disease; NSIP - nonspecific interstitial pneumonia; UIP - usual interstitial pneumonia; OP – organizing pneumonia; TLCO - gas transfer; FVC - forced vital capacity; HRCT - high resolution computed tomography

RTX was used in 26 pts (57.8%) with ILD (14 nonspecific interstitial pneumonia-NSIP, 8 usual interstitial pneumonia-UIP, 2 organising pneumonia-OP). The mean number of cycles was 4 (range 1-12). Two pts were concomitantly receiving MMF and 1 AZA. RTX treatment outcomes are shown in table 2.

In the cohort there were 18 (20.7%) deaths. Seven of them were related to ILD (4 UIP, 3 NSIP) and occurred 8.8 years after the ILD diagnosis. Two were due to infection, but none was felt to be directly related to immunosuppressive therapy.

Conclusion: Lung disease occurred in 7.7% of our cohort, with ILD being the commonest presentation (51.7%).

MTX was widely used in pts with lung disease with only 2 cases of acute pneumonitis. Although the number of ILD-pts treated with RTX was small, the drug improved/stabilized the disease in most NSIP and OP pts. UIP pattern was associated with disease progression, despite RTX, and worse outcome.

Disclosure: A. C. Duarte, None; M. J. Leandro, Genentech, Roche Basel, 2, 5; J. Porter, GSK, 2.

Abstract Number: 522

Analysis of Sequential Development of Pulmonary Lesions in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: We previously reported that there was patterns of coexistence of pulmonary lesions and airway disease (AD) were common abnormalities of patients with pulmonary involvement. However, it remains unknown through what pathways various pulmonary lesions develop. The purpose of this study was to determine the sequential development of pulmonary lesions in RA. For this purpose, we examined the pattern of newly emerging pulmonary lesions and relationship between pre-existing and new lesions.

Methods: A retrospective cohort study. Subjects were consecutive 208 RA patients who started bDMARDs in our department and received HRCT scan before and during the therapy. Based on HR-CT, pulmonary abnormalities were classified 20 lesions such as ground-glass opacity (GGO), reticular pattern, and bronchiolitis. We recorded their existence

Newly-emerging pulmonary lesions and pre-existing lesions

	Newly-emerging lesions										Total
	ground-glass opacity	consolidation	reticular pattern	interlobular septal thickening	curved linear opacity	nodular pattern	small nodular pattern	bronchiolitis	bronchiectasis		
None	1	2	2	1	3	2	1	6	0		42
ground-glass opacity	-	1	0	0	0	1	0	0	0		12
consolidation	1	-	1	0	0	2	1	0	0		16
reticular pattern	5	4	0	0	2	4	1	2	2		41
bronchiolitis	1	1	1	0	0	1	0	1	1		14
bronchiectasis	1	0	0	0	1	1	0	1	1		5
curved linear opacity	1	0	0	0	-	0	0	1	0		14
nodular pattern	1	4	2	1	1	-	0	2	2		30
small nodular pattern	0	1	2	2	0	1		1	0		23
bronchiolitis	1	5	0	0	0	1	1	-	1		34
bronchiectasis	2	2	0	0	2	1	1	0	2		18
low attenuation areas	1	2	0	0	1	2	1	1	1		28
Total	20	15	6	8	9	11	5	11	11		

Red; >50% of newly emerging lesions, Yellow; >=25% and numbers>2. Overlapping pulmonary lesions were frequently found.

and changes during the therapy. Cluster analysis was conducted according to new lesions by Ward method. A checkerboard analysis of pre-existing and new lesions was conducted.

Results: Subjects were 208 RA patients, M/F; 64/144, mean age; 59.2 years old, disease duration; 7.9 years. bDMARDs used for the longest period were TNF inhibitors in 79.8% of the subjects. Pulmonary abnormalities were found in 146 (70.2%) of RA patients (ILD 81, (38.9%); nodular lesions 45, (21.6%); and AD 115, (55.3%)) at the entry. During the observation period (3.26; 2.61 years), new pulmonary lesions were found in 31.3% of patients and the incidence was 10.0/100-person year. New lesions were frequently occurred in patients with pre-existing pulmonary lesions. Cluster analysis of new lesions showed 7 clusters; Cluster 1: nodular lesions developed mainly patients with AD and reticular pattern, Cluster 2; curved linear opacities with/without reticular pattern which occurs in patients without pre-existing diseases or bronchiolitis with nodules, Cluster 3; bronchiectasis developed in patients with bronchiolitis, Cluster 4; consolidation developed in patients with pre-existing pulmonary diseases, particularly AD, Cluster 5; bronchiolitis occurred in patients with bronchiectasis, Cluster 6; no new pulmonary lesions and Cluster 7; GGO developed in patients with AD and fibrotic ILD. Similarly, a checkerboard analysis of pre-existing and new lesions revealed followings (Fig.1); 1) in patients without pre-existing lesions, bronchiolitis or curved linear opacities occurred, 2) patients with bronchiolitis developed bronchiectasis, 3) reticular pattern occurred in patients with AD (bronchiolitis/bronchiectasis), and 4) patients with AD with reticular pattern developed GGO and/or consolidation.

Conclusion: Pulmonary lesions were developed in several patterns, not at random. Pre-existing pulmonary lesion induced new pulmonary lesions. Airway diseases, particularly bronchiolitis, might be an important lesion that induce ILD (and nodular lesions).

Disclosure: A. Tanaka, None; K. Kurasawa, None; Y. Takamura, None; T. Miyao, None; R. Yamazaki, None; S. Arai, None; T. Owada, None; R. Maezawa, None; M. Arima, None.

Abstract Number: 523

The Prevalence and Clinical Characteristics of Rheumatoid Arthritis with Interstitial Lung Disease in the San Joaquin Valley of Central California

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid Arthritis (RA) is an autoimmune disease of systemic inflammation primarily involving the small synovial joints. Approximately 1.5 million adults in the United States have RA. Interstitial Lung Disease (ILD) is present in 35% of RA cases, and pulmonary complications are responsible for 10-20% of RA-related deaths. Currently, the burden of RA-ILD in the San Joaquin Valley is unknown. This study aims to enhance understanding of this unique condition and its representation in our community; consequently creating the framework for a database of RA-ILD patients.

Methods: In this retrospective, case-control study medical records from CRMC, ACC and URA during January 2013-May 2017 were reviewed to identify and analyze subjects with both RA and ILD. Statistical analysis using Pearson's Chi Square and Logistic Regression was employed to compare characteristics of subjects with RA-ILD (cases) to those with ILD alone (controls).

Results: 4767 subjects with ILD were identified. 34 of these were diagnosed with RA, giving RA a prevalence of 0.7% within the ILD population. 528 subjects with RA were identified. 34 of these were also diagnosed with ILD giving ILD a prevalence of 6.4% within the RA population. The majority of RA-ILD subjects were Hispanic males. 50% were smokers with an average of 37 pack years. The majority had been prescribed steroids, with an average maintenance dose of 6mg prednisone daily. All were prescribed a non-biologic DMARD, with hydroxychloroquine being the most common; while only 32% were prescribed a biologic DMARD. CCP and RF were tested in 93% of cases, and 75% were positive. There was a significant relation between RA-ILD and ILD alone with regards to CCP positivity [$X^2(2, N=44)=12.37, p=0.002$], RF positivity [$X^2(2, N=46)=10.73, p=0.005$], steroid use [$X^2(1, N=81)=11.15, p=0.01$], biologic DMARD therapy [$X^2(1, N=81)=11.56, p=0.01$], and non-biologic DMARD therapy ($p<0.001$). Subjects with a positive CCP were 52 times more likely to have RA-ILD than CCP negative subjects (OR 52.01; CI 1.83 - 1473.63; $p=0.02$). RF positivity was also strongly

associated with RA-ILD (OR 16.68; CI 1.25 - 223.16; p=0.03). In both groups, restrictive pulmonary disease was most common. The average % DLCO of the RA-ILD group was 43% whereas that of the control group was 91%.

Conclusion: This investigation elucidated significant clinical characteristics and treatment patterns among RA-ILD patients in the Central Valley. The high rate of CCP positivity in patients with RA-ILD may support that CCP is linked to aggressive RA with more frequent extra-articular manifestations. Further research is needed to investigate the risk of RA development in the ILD population with CCP positivity. Our RA-ILD population may have more severe pulmonary disease compared to ILD alone, reflected by a much lower average %DLCO. Future studies should examine the effects of anti-TNF therapy on pulmonary function in RA-ILD. Routine TB and cocci screening and pulmonary function testing in this population may be indicated as a result of this study. Standardized coding for RA-ILD may improve our ability to capture more patients and increase the sample size, which was a limiting factor in this study.

Disclosure: C. Yuvienco, None; M. White, None; K. Heber, None; R. Jain, None.

Abstract Number: 524

Clinical Course of Interstitial Lung Disease in Rheumatoid Arthritis Patients in Clinical Practice

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Interstitial lung disease (ILD) is the extra-articular manifestation that most frequently worsens the course of Rheumatoid arthritis (RA) disease. Purpose: To describe the characteristics of RA patients with ILD. To assess the incidence rate of functional respiratory impairment in these patients.

Methods: This is a longitudinal prospective study. A cohort of RA patients diagnosed of ILD since Feb 2007 until Mar 2018 were recruited and followed up until lost of follow-up or end of study (May 2018) in a multidisciplinary team, carried by a pneumologist and a rheumatologist in a Tertiary Hospital in Madrid. The main variable was functional respiratory impairment: decline in percent predicted FVC of $\geq 10\%$ since the previous visit. Pulmonary function was measured at baseline and in follow-up visits every 3-6 months. Covariables: a) sociodemographic, b) clinical (basal comorbidities, ILD type (non specific interstitial pneumonia [NSIP]; usual interstitial pneumonia [UIP], Others); c) pulmonary function tests (FVC%, DLCO%); d) laboratory tests (ESR, rheumatoid factor, anti-CCP); e) therapy (corticoids, disease modifying antirheumatic drugs (DMARDs) such as Azathioprine (AZA), Mycophenolate, Leflunomide (LEF) and Biologic Agents (anti-TNFs, Abatacept, Rituximab). Survival techniques were used to estimate the incidence rate (IR) of functional impairment, expressed per 100 patient-years with their respective confidence interval [95 % CI].

Results: We included 43 patients, 63% were women, with a mean age at ILD diagnosis of 70 ± 9.6 years. The most frequent comorbidities at baseline were: hypertension (65%), peripheral vascular disease (18.6%), and cerebrovascular disease (13.9%). 42% of the patients never smoked. Rheumatoid factor and anti-CCP was positive in 85% and 82% of the patients respectively, and the baseline ESR was 43 ± 26 . 32.5% had NSIP and 63% had UIP. The median values of FVC% were 103[84-111]. During the follow-up, 77% of the patients used corticoids; and regarding DMARDs patients used Mycophenolate (n=4), AZA (n=18), LEF (n=16), TNFs (n=6), RTX (n=20) and ABA (n=5). Functional impairment occurred in 16 patients (37%) with an IR of 17 [11.4-25.3] (141.4 patient-years of follow-up). 50% of the patients achieved functional deterioration at 4.6 years since the diagnosis of ILD. Concerning the ILD types, IR for UIP was 18 [10.6-30.3] and for NSIP 15.7 [8.4-29.2]. The IR in patients taking corticoids was 15.3 [9.8-24.1]; LEF 13.2 [6-29.4]; AZA and Mycophenolate 17.4[8.3-36.6]; RTX 10.9[4-29.2].

Conclusion: Our RA patients were in their seventies and had active disease signs (higher ESR and Rheumatoid Factor positive) at the diagnosis of ILD. The most common radiological pattern was the usual interstitial pneumonia. The pulmonary function was mild at ILD diagnosis, maybe reflecting that our patients are diagnosed early in time. Functional impairment occurred in 37% of patients with an incidence rate of 17% patient-years, being 4.5 years the median time free of impairment. The crude incidence of functional impairment varies among therapies, being 10% for RTX. These results show the complexity of these patients and the need of further multicentric observational studies.

Abstract Number: 525

Low Interstitial Lung Disease Event Rate in Patients with Rheumatoid Arthritis: Pooled Post Hoc Analysis of Data from the Tofacitinib Clinical Development Program

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018
Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Interstitial lungdisease (ILD) is a common extra-articular manifestation of RA,¹ and treatment-induced ILD is more common in Asia than the rest of the world.²

Methods: We aimed to investigate incidence rates (IR; patients [pts] with events per 100 pt-years [PY]) of ILD events in pts with active RA, receiving tofacitinib 5 or 10 mg twice daily in a post hoc analysis of data pooled from 2 Phase (P)1, 10 P2, 7 P3/4, and 2 long-term extension(LTE) trials (ORAL Sequel LTE main study database locked at time of analysis: March 2017). No pts with pre-existing ILD were included. Potential ILD events were adjudicated by three independent pulmonologists as ‘probable’ (compatible adverse event [AE] with supportive clinical evidence) or ‘possible’ (compatible AE with no supportive clinical evidence). ILD IRs at 6-month intervals and by pt age and region are described. A

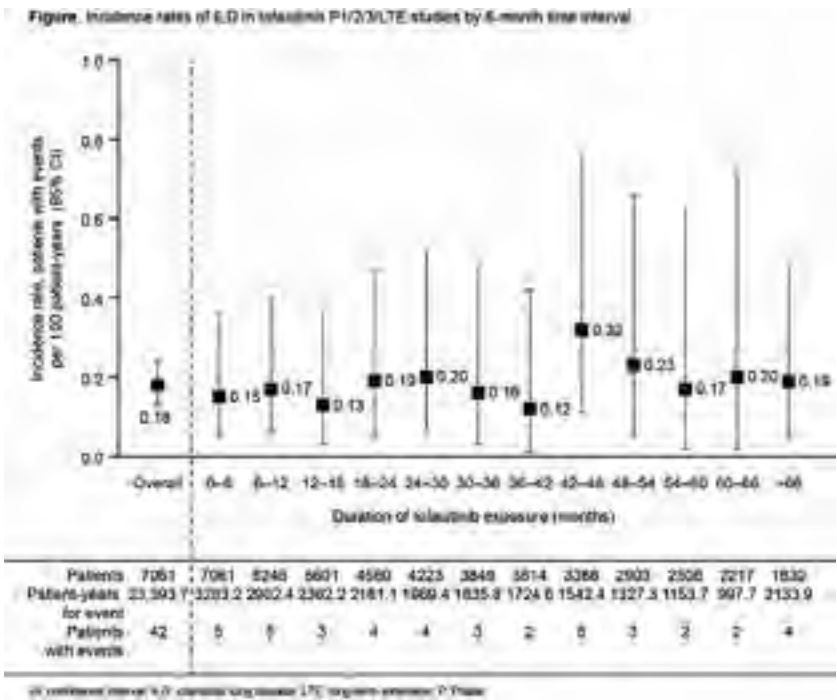


Table. Incidence rates (patients with events per 100 patient-years) for interstitial lung disease in tofacitinib Phase 1/2/3/4 and LTE trials						
P1/2/3/4 trials (placebo-controlled cohort)						
	n (%)	Placebo N=1136 PY	IR (95% CI)	n (%)	AB tofacitinib* N=6163 PY	IR (95% CI)
	1 (0.1)	311.04	0.32 (0.01, 1.79)	7 (0.1)	5281.01	0.13 (0.05, 0.37)
P1/2/3/4/LTE trials (pooled analysis set)						
	n/N1 (%)	AB tofacitinib N=7061 PY		IR (95% CI)		
Overall	42/7061 (0.6)	23,393.69		0.18 (0.13, 0.24)		
Dose						
5 mg BID	15/3064 (0.5)	8397.52		0.18 (0.10, 0.29)		
10 mg BID	27/3995 (0.7)	14,996.66		0.18 (0.12, 0.26)		
Age						
<65 years	12/6042 (0.5)	20,454.07		0.16 (0.11, 0.22)		
≥65 years	10/1019 (1.0)	2939.62		0.34 (0.16, 0.63)		
Race						
White	23/4576 (0.5)	15,433.47		0.12 (0.09, 0.22)		
Black	2/219 (0.9)	608.07		0.33 (0.04, 1.19)		
Asian	13/1566 (0.8)	5095.32		0.26 (0.14, 0.44)		
Other	4/700 (0.6)	2256.82		0.18 (0.05, 0.45)		
Region						
Asia	14/1673 (0.8)	5525.16		0.25 (0.14, 0.43)		
Non-Asia	28/5388 (0.5)	17,868.53		0.16 (0.10, 0.23)		
North America	9/1743 (0.5)	5092.44		0.18 (0.08, 0.34)		
Europe	10/2762 (0.4)	8756.87		0.11 (0.05, 0.21)		
Latin America	9/1221 (0.7)	3980.42		0.23 (0.10, 0.43)		
Rest of world	4/400 (0.0)	29.16		0.00 (0.00, 9.43)		

*Includes all patients who advanced to tofacitinib during index studies.
BID, twice daily; CI, confidence interval; IR, incidence rate; LTE, long-term extension; N1, number of patients in subgroup; P, Phase; PY, patient-years of risk period of tofacitinib exposure

descriptive case-matched control (ratio of pts with vs without ILD events 1:5, matched by age and gender) analysis identified potential ILD risk factors.

Results: Out of 7061 pts (PY of exposure = 23,394), 42 (0.6%) had an ILD event; median time to ILD event was 1144 days. The IR for ILD with both doses of tofacitinib treatment was 0.18 (Table; Figure). In a placebo-controlled cohort analysis in tofacitinib P2/3/4 studies, ILD event IRs were numerically lower with tofacitinib vs placebo (Table). IRs were numerically higher in pts aged ≥65 vs <65 years, and in Asian vs non-Asian countries; 95% confidence intervals were wide and overlapped. IRs generally remained stable over time, although the number of events was small in each interval (Figure). There were 17/42 (40.5%) serious AEs of ILD; 35/42 events (83.3%) were mild to moderate in severity. In the case-matched control analysis (case 42 vs control 210), the ILD group had a numerically higher proportion of pts who were Asian (31.0% vs 17.6%), smokers/ex-smokers (50.0% vs 39.5%), RF-positive (89.2% vs 71.0%), anti-CCP antibody positive (54.8% vs 46.7%), had received prior MTX (90.5% vs 79.5%), non-MTX csDMARDs (61.9% vs 55.2%), TNF inhibitors (26.2% vs 18.6%), and concomitant glucocorticoids (71.4% vs 52.9%), and had higher baseline mean ESR (57.0 vs 46.9 mm/hr) and CRP (25.4 vs 15.4 mg/L) vs controls.

Conclusion: Across P1/2/3/4/LTE studies, ILD events following tofacitinib treatment were low, and were associated with known risk factors.

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Bronchiectasis in RA Is a Crucial Risk Factor of Hospitalised Pneumonia Associated with bDMARDs As Well As Interstitial Lung Disease

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Interstitial lung disease (ILD) is a risk factor of pneumonia in RA patients treated with biological DMARDs (bDMARDs) [1-4]. Bronchiectasis (BE) is a well-known risk for severe pneumonia in general population[5]. However, BE is not fully examined as a risk for severe pneumonia during bDMARDs-treatment. We investigated types of respiratory diseases in RA patients before treatment with bDMARDs and correlated them to severe pneumonia during the treatment with special attention to ILD and BE.

Methods: This was a retrospective study. RA patients in Jichi Medical University, who satisfied the American Rheumatism Association 1987 criteria, were examined for their lungs by high-resolution computed tomography (CT) before starting bDMARDs and divided into three groups by a rheumatologist and a pulmonologist: normal, BE and ILD group. The patients with other lung diseases were excluded. The patients who had both BE and ILD were put into a group of the main lesion of the two. The log-rank test was used to compare the survival curves from the three groups for the differences in the probabilities of severe pneumonia requiring hospitalization. Hazard ratios (HR) on the risk of severe pneumonia between two of the three groups were determined by Cox proportional hazard model with covariates.

Results: A total of 494 patients were examined by chest CT before treatment with bDMARDs from 2003 to 2013. There were 348 patients in normal, 30 in BE and 49 in ILD group. Sixty-seven patients with the pulmonary lesions other than BE and ILD were excluded. Fourteen patients developed severe pneumonia which required hospitalization; 2 in normal (0.57%), 4 in BE (13%) and 8 in ILD (16%). Eleven and 3 patients developed bacterial and pneumocystis pneumonia, respectively. The log-rank test showed differences between the groups ($p < 0.00001$). The pneumonia-free rate of BE was lower than that of normal group (HR 26.79, 95% CI 5.11-196.32). The pneumonia-free rate of ILD was also lower than that of normal group (HR 30.25, 95% CI 7.27-204.54). No difference was shown for the pneumonia-free rates between BE and ILD.

Conclusion: This study suggested that BE in patients with RA is a risk factor of severe pneumonia during the treatment with bDMARDs to the extent comparable to ILD. The frequency of pneumonia in patients with normal lungs is very low.

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Long-Term Follow up of Subclinical Interstitial Lung Disease in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Using of high-resolution computed tomography(HRCT) has increased the early detection of interstitial lung disease(ILD) in asymptomatic and undiagnosed individuals. This study was to identify asymptomatic lung disease and to analyze long-term prognosis of subclinical rheumatoid arthritis-associated ILD(RA-ILD).

Methods: 1502 patients with RA were treated and followed them up for seven years or until development of symptomatic ILD. All patients were performed chest radiological examinations at the initial presentation. The HRCT findings which include (1) ground glass opacity, (2) air-space consolidation, linear opacity including (3) septal line and (4) non-septal line, (5) honeycomb lung, (6) traction bronchiectasis, (7)pleural irregularity, and (8)pleural effusion were scored as the CT scoring system. The extent of involvement of each abnormality was assessed independently for each of the three zones of each lung. The HRCT extent score was represented the sum of the score of each lung. HRCT parameters which included the extension score, ACPA and the clinical features at the initial presentation were retrospectively analyzed.

Results: 92(6.1%) out of 1,502 RA patients had abnormal chest radiological findings which consist with ILD. 5 out of 92 patients had shortness of breath and showed a rapidly progressive ILD (5.4%) at the presentation. The rest of 87 (54 women, 33 men) had subclinical RA-ILD who were either asymptomatic or have symptoms and physiologic abnormalities that are as yet unrecognized as being due to RA-ILD at the presentation. 12(13.8%) out of 87 subclinical RA-ILD patients developed symptomatic RA-ILD after diagnosed RA (28.4+/-16.1 months). There was no difference in the positive rates of anti-CCP2 and HRCT findings at the presentation between stable subclinical RA-ILD and later-developing clinical RA-ILD. However there was a difference in the HRCT finding which showed progression of ground-glass attenuation (HRCT score 2.1+/-0.7 vs. 0.1+/-0.3, $p<0.001$). These 12 cases were treated with immunosuppressant which include tacrolimus, azathioprine and MMF. And all cases showed stable ILD on HRCT after treatment of immunosuppressant.

Conclusion: Subclinical RA-ILD, which is detectable on HRCT, should be considered in RA even in absence of chest symptoms. HRCT finding focused on progression of ground-glass attenuation is a sensitive technique for detection of later-developing clinical RA-ILD in subclinical group.

Disclosure: M. Yamasaki, None;

Progression in Interstitial Lung Disease – Comparison of Rheumatoid Arthritis with Idiopathic Pulmonary Fibrosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid Arthritis (RA) is a common autoimmune condition characterised by symmetrical inflammatory small joint polyarthropathy and loss of function. Systemic manifestations of RA are relatively common and thought to occur in upto 40% of patients. Interstitial lung disease (ILD) is a systemic complication of rheumatoid arthritis (RA) and is associated with significant increase in mortality compared to patients who do not have ILD. Idiopathic pulmonary fibrosis (IPF), previously known as cryptogenic fibrosing alveolitis, also has a poor prognosis, with median

survival of 3-5 years from diagnosis in the era before any specific treatments were found³. More recently, there have been new treatment options for these patients with Perfenidone and Nintedanib licensed and NICE approved for treatment of IPF. Although it is believed that the prognosis of rheumatological ILD is better, there are not enough data on progression to able to confidently prognosticate these patients. The purpose of this study was to assess the differences in progression in patients with IPF compared to RAILD.

Methods: The Coventry ILD database was set up in 2011; all patients with ILD were added to this. This study retrospectively looked at the patients who had been entered in this registry. Other forms of ILD like Connective Tissue Disorder related ILD (CTD-ILD) were excluded from this study. Data were anonymised prior to extraction for the study and only data available prior to the use of Perfenidone and Nintedanib were utilised. Statistics were performed using R software which is freely downloadable from the internet.

Results: This study included 185 patients of which 55 had IPF and 37 had RAILD. As this is not a matched study, there are significant differences in the presentations of patients in the different arms. Table 1 illustrates the main differences in the study population. The mean age in the IPF group was 72.4 where as for RAILD the mean age was 65.7 with standard deviation of 9.1 and 9.6 respectively. This difference is statistically significant. FVC values were 84.7% and 95% operated and these differences were statistically significant. TLCO values were much lower in IPF patients with values of 48.2 compared with 61.5 in patients with RAILD. Univariate analysis revealed a number of variants including diagnosis, age, sex, TLCO; but multivariate analysis only showed TLCO as the significant variant. Median follow up was 41 months.

Table 1: Baseline characteristics demonstrating that RA has higher FVC at presentation.

Category	IPF	nonIPF IIP	Rheumatoid	P
Number	49	48	34	
Age	72.4 (9.1)	70.8 (9.6)	65.7 (9.6)	0.006
FEV1	84.1 (17.1)	80.6 (20)	88.9 (17.7)	0.133
FVC	84.7 (20.6)	84 (19.3)	95.0 (18.1)	0.026
Tlco	48.2 (14.6)	52.2 (18.1)	61.5 (17.1)	0.002

Outcome: Median 5 year survival was 48% for IPF and 81% for RAILD. Median 50% survival was 4.5 years for IPF and 9 years for RAILD.

Conclusion: Significant gaps remain in our understanding of the natural course of RAILD and IPF. Our study suggests that the biggest single factor influencing outcome is TLCO at baseline.

Disclosure: S. Dubey, None; F. Woodhead, Roche, 2,Boehringer, 2.

Abstract Number: 529

Chest Computed Tomography Abnormalities in Patients with Rheumatoid Arthritis By Serologic Status

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Lung involvement in rheumatoid arthritis (RA) has been recognized as an important contributor to morbidity and mortality. While interstitial lung disease (ILD) is a well-recognized manifestation more common in seropositive RA, the association between RA and other respiratory outcomes such as chronic obstructive pulmonary disease (COPD) and bronchiectasis are less understood. The purpose of this study was to describe imaging abnormalities in clinically-indicated chest computed tomography (CTs) of patients with RA and compare abnormalities based on serologic status.

Methods: We identified patients within a single-center registry composed of 1,500 RA patients with prospective measures of RA characteristics and detailed clinical data who had clinically-indicated chest CTs. We extracted data by reviewing the

initial clinically-indicated chest CT report occurring after baseline study visit. We described the proportion of patients with imaging findings and impression in the report from the attending radiologist. We further stratified the characteristics by RA serostatus (seropositive as rheumatoid factor and/or anti-cyclic citrullinated peptide positivity; seronegative as both negative). We compared patients with seropositive RA to seronegative RA using t-tests or Wilcoxon rank-sum tests for continuous variables and chi-square tests or Fisher's exact tests for categorical variables.

Results: We analyzed 188 patients with chest CTs performed after study baseline. The mean age was 64.3 years (SD 11.9), 79.8% were female, mean RA duration was 21.4 years (SD 13.3), mean body mass index (BMI) was 27.5 kg/m² (SD 6.3), 60.1% were ever smokers, and 73.4% were seropositive. Most CTs were obtained to rule out respiratory illness (43.1%), followed by malignancy (24.5%). The most common chest CT pattern abnormalities were: pulmonary nodules (38.8%), opacities (24.5%), and pleural effusions/thickening (18.1%). The most common final impressions for the chest CTs were: pulmonary nodules (30.3%), atelectasis (21.3%), and ILD (16.0%). Only 11.7% of chest CTs had completely normal final impressions. There were no statistically significant differences between seropositive and seronegative RA, including ILD (p=1.0), bronchiectasis (p=0.21), and COPD (p=0.78).

Conclusion: A wide variety of chest CT abnormalities were present at high prevalence in both seropositive and seronegative RA patients with few having normal findings. While we found no differences based on serostatus in these clinically-indicated chest CTs, there may be differences in the subclinical natural history of lung disease based on RA serostatus and disease activity. The pathogenesis, clinical manifestations, and outcomes of patients with pulmonary abnormalities warrant further research.

Table. Chest computed tomography (CT) findings in patients with seronegative vs. seropositive rheumatoid arthritis (RA)

	All patients (n = 188)	Seronegative RA (n = 50)	Seropositive RA (n = 138)	p value
Demographics				
Age (Mean, SD), years	64.3 (11.9)	63.6 (13.7)	64.5 (11.2)	0.90
Female (n, %)	150 (79.8)	37 (74.0)	113 (81.9)	0.33
RA duration (mean, SD), years	21.4 (13.3)	16.8 (14.4)	23.1 (12.5)	<0.001
BMI (mean, SD), kg/m ²	27.5 (6.3)	27.6 (6.0)	27.5 (6.4)	1.00
Ever smoker (n, %)	113 (60.1)	29 (58.0)	84 (60.9)	0.85
CT Patterns (n, %)				
Normal	24 (12.8)	9 (18.0)	15 (10.9)	0.30
Pulmonary nodules	73 (38.8)	18 (36.0)	55 (39.9)	0.76
Consolidation	46 (24.5)	8 (16.0)	38 (27.5)	0.15
Pleural abnormalities	34 (18.1)	8 (16.0)	26 (18.8)	0.82
Ground-glass opacities	32 (17.0)	11 (22.0)	21 (15.2)	0.38
Bronchiectasis	31 (16.5)	7 (14.0)	24 (17.4)	0.74
Lymph node enlargement	26 (13.8)	6 (12.0)	20 (14.5)	0.84
Fibrotic changes	24 (12.8)	7 (14.0)	17 (12.3)	0.95
Emphysema	21 (11.2)	6 (12.0)	15 (10.9)	1.00
Pulmonary embolism	7 (3.7)	3 (6.0)	4 (2.9)	0.39
CT Diagnosis per Report (n, %)				
Normal	22 (11.7)	8 (16.0)	14 (10.1)	0.40
Pulmonary nodules	57 (30.3)	15 (30.0)	42 (30.4)	1.00
Atelectasis	40 (21.3)	14 (28.0)	26 (18.8)	0.25
ILD	30 (16.0)	8 (16.0)	22 (15.9)	1.00
Bronchiectasis	27 (14.4)	4 (8.0)	23 (16.7)	0.21
Infection	24 (12.8)	5 (10.0)	19 (13.8)	0.66
Pleural effusion	18 (9.6)	5 (10.0)	13 (9.4)	1.00
COPD	17 (9.0)	5 (10.0)	12 (8.7)	0.78
Lymphadenopathy	16 (8.5)	2 (4.0)	14 (10.1)	0.24
Malignancy	10 (5.3)	1 (2.0)	9 (6.5)	0.30
Pulmonary embolism	7 (3.7)	3 (6.0)	4 (2.9)	0.39
Other	32 (17)	6 (12.0)	26 (18.8)	0.38

BMI: body mass index

COPD: chronic obstructive pulmonary disease

ILD: interstitial lung disease

Disclosure: S. Huang, None; T. Doyle, None; A. Marshall, None; C. K. Iannaccone, None; J. Huang, None; M. E. Weinblatt, Amgen Inc., 5, Bristol-Myers Squibb, 5, Crescendo Bioscience, 5, UCB, Inc., 5, Amgen Inc., 2, Bristol-Myers Squibb, 2, Crescendo Bioscience, 2, Sanofi/Regeneron, 2; P. F. Dellaripa, up to date, 7, Genentech, Inc., 9; E. Karlson, None; N. A. Shadick, Bristol-Myers Squibb, 5, Amgen Inc., 2, Mallinckrodt, 2, UCB, Inc., 2, Crescendo Biosciences, 2, Sanofi, 2, Bristol-Myers Squibb, 2, DxTerity, 2; J. A. Sparks, None.

RA-Voice: Evaluating Laryngeal Involvement in Rheumatoid Arthritis Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Laryngeal involvement is not uncommon in connective tissue diseases including Rheumatoid Arthritis (RA). Its prevalence has been estimated between 5% and 70% of patients and, in post mortem series, between 45% and 88% of patients. The crico-arytenoid joint is the most commonly affected site. Dysphonia, cough, dryness symptoms, foreign body sensation and odynophagia are among the symptoms of laryngeal involvement although, quite often, it is asymptomatic.

With this study, the authors aimed to evaluate laryngeal involvement in RA patients and healthy sex and age matched controls and evaluate results within the RA patients group according to disease activity and duration of disease.

Methods: This is a cross-sectional study that evaluated laryngeal involvement in RA. Patients were accessed using video laryngostroboscopy (VLS) and objective changes were recorded using the reflux finding score (RFS). The Reflux Symptom Index (RSI), was used to evaluate laryngopharyngeal symptoms and Vocal cord impairment was accessed using the Voice Handicap Index-10 (VHI-10). Statistical analysis was performed using non-parametric tests, given the small sample size and non-normal distribution of the variables.

Results: We enrolled 48 RA patients, with mean disease duration of 13 years, and 30 healthy sex and age matched controls. Two males were active smokers in each group and, in RA group, 4 males and 3 females were previous smokers. 77.8% of the patients were being treated with Metotrexate, 6.25% were receiving concurrent medication with prednisolone above 7.5 mg daily, 14.58% were also medicated with AINE's on demand and 66.67% used proton pump inhibitors, mostly as a preventive measure.

Compared with controls, RA patients presented higher median values in the RFS ($p < 0.0001$) and RSI ($p = 0.0002$) but differences in the VHI-10 were non-significant.

Within the RA group, there were no significant differences in the RFS, RSI nor VHI-10 when comparing patients with DAS 28 3V above vs below 2.6 at the time of evaluation. However, we found significant differences regarding the RSI when evaluating patients according to duration of disease, with patients with longer disease duration having higher scores (0-5 vs 6-10 years $p = 0.03$; 0-5 vs 11-15 years $p = 0.047$; 0-5 vs >15 years $p = 0.015$).

Even though no differences were found regarding the RFS, patients within the > 15 years of disease duration, presented a higher median score (median scores for: < 5 years = 2.5, 6-10 years = 3, 11-15 years = 4, > 15 years = 7).

Conclusion: We found significant differences between RA patients and healthy controls regarding self-perceived laryngeal symptomatology (RSI) and findings on VLS (RFS), with patients scoring higher.

RA patients with longer disease duration had more symptoms and more alterations on laryngeal examination but there were no significant differences according to disease activity.

Current evidence, as identified in the present study, suggests that laryngeal manifestations in RA patients may be under diagnosed and a multidisciplinary team approach is necessary to improve the overall patient management.

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Association of Rheumatoid Arthritis and Other Autoimmune Diseases

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

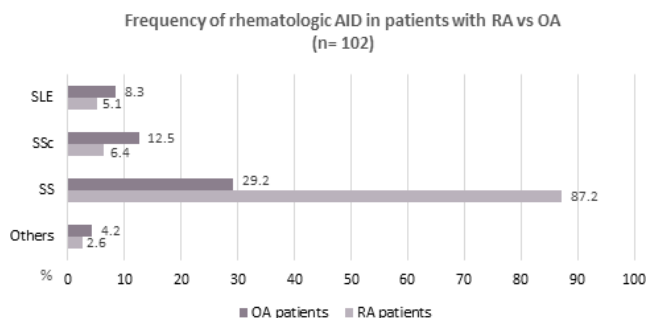
Session Type: ACR Poster Session A

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

Background/Purpose: The coexistence of different autoimmune diseases (AID) has been well established in the literature. In our knowledge, there is no study assessing specifically the association between RA and other AID. The aim of our study was to determine the frequency of AID in RA patients and to compare this frequency between patients with and without RA or other rheumatologic AID.

Methods: Multicenter, observational, analytical, retrospective study, including consecutive patients with diagnosis of RA (ACR/EULAR 2010 criteria). Patients with initial diagnosis of primary osteoarthritis (OA) were used as control group.

Results: A total of 1549 patients from 23 centers were included: 831 RA [84% women, mean age 55.2 (\pm 13.6)] and 718 OA [82% women, mean age 67 (\pm 11.1)]. Mean age at RA symptoms onset was 45.5 (\pm 13.4). Most patients (90.5%) were treated with DMARDs and 34.3% with biologic drugs. The frequency of AID in the RA group was 22% (n=183). RA patients showed higher frequency of rheumatologic AID (9.4 vs 3.3%, p <0.001), and lower frequency of non-rheumatologic AID than OA patients (15.3 vs 20.5%, p = 0.007). The most frequent rheumatologic AID was Sjögren's Syndrome (SS), with a higher prevalence in RA patients (87.2 vs 29.2%, p <0.001). There was no difference in the frequency of other pathologies. The frequency of rheumatologic AID in RA patients was higher in those with erosive RA (11 vs 6.8%, p =0.048). No association with gender, age, nodular RA or seropositivity was observed. A lower age at RA diagnosis was associated with lower age at thyroid AID (39 vs 48.2, p =0.0001) and SS diagnosis (41.3 vs 57.1, p < 0.0001). Family history of



AID was higher in RA patients (24.4 vs 13.4%, $p < 0.001$). In the control group, family history of AID was associated with higher frequency of non-rheumatologic AID (36.2 vs 20.9%, $p = 0.005$), mostly thyroid diseases.

Conclusion: The frequency of AID in RA patients was 22%. Rheumatologic AID were more frequent in RA patients, mostly in those with erosive RA, whereas non-rheumatologic AID prevailed in OA patients. Family history of AID, mainly rheumatologic ones, was higher in RA patients.

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Abstract Number: 532

Relationship between Insulin Sensitivity and Beta Cell Secretion in Non-Diabetic Rheumatoid Arthritis Subjects

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: In non-diabetic healthy individuals insulin secretion and insulin sensitivity are linked by a negative feedback loop characterized by a hyperbolic function. We aimed to study the association of traditional insulin resistance (IR) factors with insulin secretion and sensitivity, and to determine whether the hyperbolic equilibrium of this relation is preserved in patients with rheumatoid arthritis (RA).

Methods: Cross-sectional study encompassing 361 non-diabetic individuals, 151 RA and 210 controls. Insulin, C-peptide and IR indexes by homeostatic model assessment (HOMA2) were assessed. A multivariable analysis was performed to evaluate the differences in the correlation of traditional IR-related factors with glucose homeostasis molecules, as well as IR indexes between patients and controls. Non-linear regression analysis was used to assess the hyperbolic relation of insulin sensitivity and secretion.

Results: HOMA2-S% was lower in RA patients than in controls after adjusting for traditional IR-related factors and prednisone intake (105 ± 53 vs. 108 ± 75 , $p=0.006$). Insulin (9.8 ± 6.5 vs. 13.0 ± 13.4 U/ml, $p=0.007$) and C-peptide serum levels (1.53 ± 0.77 vs. 3.37 ± 2.94 ng/ml, $p=0.000$) were found to be up-regulated in RA patients. The insulin to C-peptide ratio was lower in RA patients (0.14 ± 0.07 vs. 0.08 ± 0.02 , $p=0.000$) after multivariate adjustment including glucocorticoids. Traditional IR-related factors strongly correlated with glucose, insulin, C-peptide, and IR indexes in both patients and controls. However, Pearson's correlation coefficients were lower in patients. This shows that the variability in glucose homeostasis molecules or IR indexes had a weaker association with traditional IR-related factors in RA patients. Linear relations between glucose homeostasis molecules (glucose, insulin and C-peptide) and HOMA2 indexes showed high values that reached statistical significance. However, the relation of C-peptide with insulin, HOMA2-IR with C-peptide, and the relation of HOMA2-%B with insulin and C-peptide were lower in patients with RA than in controls. Hepatic insulin extraction, as assessed by the insulin:C-peptide molar ratio, was lower in patients after multivariable analysis (0.08 ± 0.02 vs. 0.14 ± 0.07 , $p=0.000$). The association between insulin sensitivity and secretion showed a different hyperbolic relation in patients: the variability explained by the curve (non-linear $r^2=0.690$ vs. $r^2=0.899$, $p=0.000$) and beta coefficients ($-0.87[95\%CI -0.95--0.78]$ vs. $-0.98[95\%CI -1.04--0.92]$ ng/ml, $p=0.034$) were lower in RA.

Conclusion: The traditional factors associated with IR in healthy individuals are less related to IR in RA patients. Insulin sensitivity and secretion yield a different hyperbolic equilibrium in RA.

Disclosure: E. Delgado-Frías, None; B. S. Tejera, None; R. Lopez-Mejías, None; D. V. G. AM, None; A. Jiménez-Sosa, None; J. M. Olmos, None; J. L. Hernández, None; J. Llorca, None; M. A. González-Gay, None; I. Ferraz-Amaro, None.

Abstract Number: 533

Association between Inflammation and Changes in Kidney Function in Patients with Early Rheumatoid Arthritis

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: One of the most severe visceral manifestations of RA is nephropathy. The key symptoms of renal dysfunction (RD) are microalbuminuria (MA), β -2-microglobulinuria (β -2M), reduced renal blood flow (RBF) and decreased glomerular filtration rate (GFR).

The aim of our study was to examine whether tumor necrosis factor- α (TNF α) can induce and maintain decrease RD and whether this is associated with severity of RA.

Methods: The median age of the group of 35 (28 female, 7 male) participants with early eRA was 50.71 ± 2.25 years, with median disease duration 9.21 ± 0.43 months. TNF α was from ELISA Kits, R&D Systems (USA), MA and β -2M were from ORGenTec GmbH (Germany). The ratio of albumin-creatinine (AB/CR) in the morning portion of urine and the glomerular penetration index (GPI), reflecting the average concentration of AB in the glomerular ultrafiltration, were also calculated by formula: $GPI = P \cdot V / GFR$, where P - of excreted AB urine concentration (mg/l); V - minute diuresis (ml / min.). The serum and urine CR concentration was determined by a unified method using the Jaffe color reaction (Popper method).

Results: The severity of tubular damage in early eRA is associated with TNF- α expression, especially in the patients with TNF- α above 250 pg/mL, when MA rates were significantly higher ($\chi^2=12,3$ in $p<0,01$). We identified robust data that patients with high TNF α , the number of reported cases of MA was significantly higher. We evaluated not only the stage but also the nature of the dependence, describing the functional relationship between the numerical variables. We have performed of regression analysis, while the serum range of TNF α was considered as an independent variable and as a dependent variable - index characterizing the severity of RD (index of MA). We identified that in the eRA patients with

high TNF α , the number of reported cases of MA was significantly higher ($\chi^2=12,3$ with $p<0,01$). The obtained dependence showed the dynamics of expression of RD in eRA with a progressive deterioration which did associate with the levels of TNF α expression, and variety of the β -2M urine rates in the interval 200–350 $\mu\text{g/L}$.

Conclusion: In this study we have confirmed, that overexpression of TNF- α is involved in the induction of RD, which is manifested by decrease of GFR and increase of urinary excretion of microproteins. At the same time, the dynamics of MA and β -2M values was reliably determined by the stage of disease activity, which reflects the RA severity.

Disclosure: G. Prytkova, None; D. Rekalov, None; D. Nikitina, None.

Abstract Number: 534

Increased Insulin Resistance and Impaired Beta-Cell Function in Patients with Rheumatoid Arthritis: The Role of Glucocorticoid Therapy?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Increased insulin resistance and impaired β -cell function have been demonstrated in rheumatoid arthritis(RA). The aim of the study was to analyze the association of these metabolic disturbances with glucocorticoid (GC) therapy.

Methods: The study population included 127 non-diabetic subjects: 90 RA pts (mean age 52.4 ± 9.9 yrs, disease duration 9 yrs, range 4-13) and 37 matched controls (mean age 49.0 ± 7.5 yrs). All pts were on disease modifying anti-rheumatic drugs (methotrexate in 93.3%), biologic therapy in 27.8%, and GC in 65.6%, none on GC >10 mg/day (median dose 5 mg/day, range 5-10, during 4 yrs (range 2-6yrs), cumulative GC dose was 9.1 g (5.5-16.4 g). Clinical work-up included determination of the body mass index (BMI), waist circumference (WC), blood pressure (BP), disease activity (mDAS28-SE), inflammation markers, lipids, glucose, specific insulin, and C peptide. The updated-computer Homeostasis Model Assessment was used to calculate insulin resistance (HOMA2-IR) and β -cell function (HOMA2-%B). HOMA2-IR >1 was defined as increased insulin resistance. Lack of compensatory rise of HOMA2-%B implied impaired β -cell function.

Laboratory	RA pts (N=90)	Controls (N=37)	RA pts with GC vs. without GC	Controls vs. RA pts with GC	Controls vs. RA pts without GC
Age (years)	52.4 \pm 9.9	49.0 \pm 7.5	ns	ns	Ns
BMI (kg/m ²)	25.7 \pm 4.3	26.2 \pm 4.3	ns	ns	Ns
Hypertension (%)	28/90 (31.1)	8/37 (21.6)	ns	ns	Ns
Triglycerides (mmol/L)	1.2 (0.8-1.5)	1.0 (0.8-1.4)	ns	ns	Ns
Blood glucose (mmol/L)	4.8 \pm 0.6	4.7 \pm 0.8	ns	ns	Ns
Insulin (pmol/L)	68 (50-103)	55.3 (36-69)	ns	0.003	0.072
C-peptide (pmol/L)	785 (520-1010)	600 (450-880)	ns	0.037	0.217
logHOMA2-IR	1.4 (1.0-2.3)	1.2 (0.8-1.4)	ns	0.003	0.05
HOMA2-IR >1	67/90 (74.4)	20/37 (54.2)	ns	0.026	0.024
HOMA2-%B	148 (116-190)	141 (114-158)	ns	0.140	0.642
DAS 28-SE	4.0 \pm 1.5		ns		
DAS 28-CRP	4.2 \pm 1.5		ns		
Duration of GC therapy (years)	4 (2-6)		ns		
Cumulative dose of GC (g)	9.1 (5.5-16.4)		ns		

Results: Increased insulin resistance ($\log\text{HOMA2-IR}>1$) was detected in 74.4% of RA pts and in 54.2% of controls, $p=0.025$. RA pts had also higher values of $\log\text{HOMA2-IR}$ than controls 1.4 (range 1.0-2.3) vs. 1.2 (range 0.8-1.4); $p=0.008$; which was followed with impaired β cell function: HOMA2-\%B 148 (116-190) vs. 141 (114-158) $p=0.186$. Univariate regression revealed association of $\log\text{HOMA2-IR}$ with all insulin resistance risk factors: age, BMI, WC, BP, and triglycerides, while multivariate analysis demonstrated that beside BMI, and triglycerides, **daily dose of GC was an independent risk factor for $\log\text{HOMA2-IR}$ (β 0.191, 95% CI 0.020-0.361, $p=0.029$)**. On the other hand, statistical difference was not found for duration of GC therapy and cumulative GC dose. Analyzing patients with and without GC therapy statistical difference was not found regarding any parameters of glucose metabolism, as well as all classic insulin resistance risk factors (Table 1). In comparison with controls, higher insulin resistance was found for RA pts with GC therapy, which was not followed with differences in B cell function. Patients without GC therapy also had higher insulin resistance, but the statistical significance was borderline. Both RA groups had significantly higher number of subjects with increased insulin resistance than controls.

Conclusion: There was no significant difference in insulin resistance between RA pts with and without GC therapy. Daily dose has more significant influence than duration of GC therapy and cumulative GC dose but this therapy does not play a principal role in increased insulin resistance in RA pts.

Disclosure: G. Ristic, None; V. Subota, None; D. Stanisavljevic, None; B. Glisic, None; M. Petronijevic, None; D. Stefanovic, None.

Abstract Number: 535

Is There Achilles Tendon Damage in Rheumatoid Arthritis Patients?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Ankle involvement is common in Rheumatoid Arthritis (RA). It has been reported that more than 90 % of patients develop ankle symptoms over the course of the disease. In spite of this, it remains a neglected anatomical area since clinical implications of ankle involvement appear to be continuously underestimated. We analyzed the ultrasound (US) features of the Achilles Tendon (AT) and entheses in patients with RA and compared these to healthy athletes. Relations between these findings and clinical and physical therapy parameters were identified.

Methods: Consecutive patients aged ≥ 18 with RA according to ACR/EULAR 2010 criteria were included. We consigned socio-demographic data, disease duration, physical activity and Body Mass Index (BMI). Clinical evaluation relied on the Disease Activity Score 28 (DAS28), Health Assessment Questionnaire (HAQ), Routine Assessment of Patient Index Data 3 (RAPID 3), as well as on a visual analog scale (VAS), and entheses pain. Separately, AT thickness and echogenicity were examined bilaterally with US in 60 ankle regions. US examinations were performed by two experienced rheumatologists. To evaluate AT involvement, we used the Madrid Sonographic Enthesitis Index (MASEI) evaluating elementary lesions: bursitis, calcification, erosion, Power Doppler (PD), thickening of tendon, and structural change. Statistical analysis: Standard descriptive results were expressed as the mean \pm standard deviation (SD). Chi-square Test and Fisher's exact test were used for categorical variables whereas T test for the continuous variables.

Results: A total of 60 ankles from 30 patients with RA and 36 ankles from 18 healthy controls were assessed. The mean (\pm SD) age was 58.3 ± 9.5 years and disease duration were 14.5 ± 5.9 years in RA patients. 30% of patients with RA had foot and ankle pain at visit. The mean (\pm SD) DAS28, HAQ and RAPID3 were 3.46 ± 0.9 , 0.9 ± 0.6 , and 11 ± 6.5 respectively. 26.7% were obese. 30% of RA patients performed physical activity. At least 1 AT lesion was found in US of all RA patients. The most frequent US abnormality in RA patients was tibialis posterior tenosynovitis followed by peroneus longus tenosynovitis. A statistically significant difference was found between RA patients and healthy controls in mean (\pm SD) MASEI (3.56 ± 2.4 vs. 2.33 ± 1.7 , $p=0.01$), and subitem scores such as: structural changes (0.66 ± 0.4 vs. 0.2 ± 0.4 , $p<0.01$), erosion (0.8 ± 1.3 vs. 0.02 ± 0.16 , $p<0.01$) and PD (0.3 ± 0.9 vs. 0.02 ± 0.16 , $p=0.03$).

Conclusion: Achilles tendon involvement is rather frequent in RA patients. The MASEI score was significantly higher in patients with RA compared with athletes.

Disclosure: M. N. Fornaro, None; T. Cazenave, None; M. C. Orozco, None; M. V. Martire, None; E. Reyes, None; H. Schmulevich, None; G. Citera, Novartis, Pfizer Inc, 2, AbbVie, Bristol-Myers Squibb, Eli Lilly, Genzyme, Novartis, Pfizer Inc, Roche, 5; M. G. Rosemffet, None.

Abstract Number: 536

Prevalence and Relative Factors for Frailty in Patients with RA from a Prospective Observational Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

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

Background/Purpose: Frailty is defined as degradation of physical and cognition function in elderly adult. The characteristics of frailty include not only physical problems as co-morbidity and disability, but also mental and social problems. It is unclear of relationship between frailty and disease activity of patients with rheumatoid arthritis (RA). We investigated the relative factors about frailty in patients with RA from a prospective observational study.

Methods: 95 from 100 patients entered the CHIKARA study (Correlation research of sarcopenia, skeletal muscle and disease Activity in Rheumatoid Arthritis) were investigated by frailty check list (maximal score is 25). According to reported article, frailty was defined from 8 to 25 and pre-frailty was from 4 to 7, and normal was from 0 to 3. We investigated relationship of disease activity in frailty, pre-frailty and normal groups, and analyzed the relative factors for frailty.

Results: The prevalence of frailty, pre-frailty, and normal was 19%, 39% and 42%, respectively. The character of groups indicated at Table 1. Frailty group was the oldest of three groups. Disease activity score 28 erythrocyte sedimentation rate (DAS28ESR) and matrix metalloproteinase 3 (MMP3) of frailty group was higher than those of pre-frailty and normal groups. Whereas, modified health assessment questionnaire (mHAQ) of frailty group was lower than those of pre-frailty and normal groups. Normal was 66.6% and frailty was 6.7% in remission patients. However, Normal was 13.3% and frailty was 46.7% in moderate and high disease activity patients. The prevalence of frailty was increased with disease activity. The relative factors for frailty in patients with RA indicated at Table 2. Age, locomotive syndrome, DAS28ESR, mHAQ, and Steinbroker class were related positively and leg muscle score and grip strength were related negatively by univariate analysis. Steinbroker class (odds ratio: 3.25 95%CI: 1.11-9.51, P=0.031) and mHAQ (odds ratio: 1.29, 95%CI: 1.13-1.46, P<0.001) were independent relative factors by multivariate analysis.

Conclusion: It was revealed that frailty involved disease activity and physical function in patients with RA. Control of disease activity is important to prevent not only disease progression, but also frailty.

Table 1. The character of frailty, pre-frailty, and normal in patients with RA

	Frailty (19%)	Pre-frailty (39%)	Normal (42%)	P value
Age, years	72.5 ± 10.3	68.6 ± 11.3	60.7 ± 16.4	0.01
Leg muscle score	84.9 ± 5.9	86.2 ± 6.4	93.2 ± 9.7	<0.001
Grip, kg	12.6 ± 6.9	17.7 ± 7.1	18.1 ± 6.2	0.013
Locomotive 5 score	11.1 ± 5.8	6.4 ± 4.9	2.6 ± 4.0	<0.001
MMP3, ng/dl	143.7 ± 122.0	95.9 ± 66.0	88.6 ± 52.0	0.033
DAS28ESR	3.62 ± 0.97	3.27 ± 1.02	2.83 ± 0.96	0.015
mHAQ	0.9 ± 0.7	0.4 ± 0.2	0.1 ± 0.1	<0.001
Sarcopenia, %	39	41	18	0.063

Table 2. Relative factors for frailty in patients with RA

	Univariate		Multivariate	
	R value	P value	Odds ratio	95%CI
Age, years	0.203	0.048		
Locomotive syndrome	0.397	<0.001		
Leg muscle score	-0.222	0.031		
Grip strength, kg	-0.272	0.008		
DAS28ESR	0.228	0.026		
mHAQ	0.413	<0.001	1.29	1.13-1.46
Steinbrocker class	0.331	0.001	3.25	1.11-9.51

Disclosure: M. Tada, None; Y. Yamada, None; K. Mandai, None; N. Hidaka, None.

Abstract Number: 537

Increased Risk of Incident Chronic Kidney Disease Among Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis of Cohort Studies

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Patients with rheumatoid arthritis (RA) may have a higher risk of developing chronic kidney disease (CKD) compared with general population. However, the data on this risk are still limited and not well-characterized. This systematic review and meta-analysis was conducted with the aim to comprehensively investigate the risk of incident CKD among patients with RA by reviewing all available studies.

Methods: A systematic review was performed using MEDLINE and EMBASE database from inception to April 2018 to identify all cohort studies (either retrospective or prospective) that compared the risk of incident CKD in patients with RA versus individuals without RA. Point estimates and standard errors from each study were extracted and combined together using the random effect, generic inverse variance method of DerSimonian and Laird. Visualization of funnel plot was used for evaluation for publication bias.

Results: Of 2,580 retrieved articles, a total of 4 retrospective cohort studies with 1,627,981 participants met the inclusion criteria and were included into the meta-analysis. The risk of incident CKD was significantly increased among patients with RA with the pooled risk ratio of 1.52 (95% CI, 1.28-1.80). The statistical heterogeneity of this study was high with an I^2 of 82%. The forest plot of this systematic review and meta-analysis is shown as figure 1. The funnel plot was relatively symmetric and, thus, did not suggest the presence of publication bias in favor of positive studies (figure 2) although interpretation of the funnel plot was limited by the relatively small number of included studies.

Conclusion: A significantly increased risk of incident CKD among patients with RA compared with individuals without RA was demonstrated in this study.

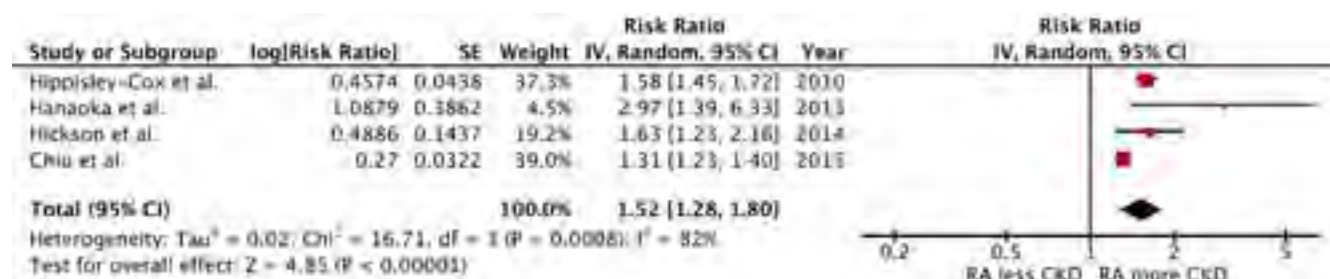


Figure 1: Forest plot

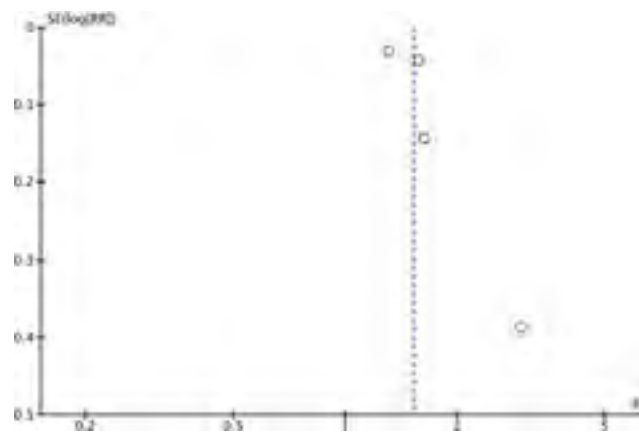


Figure 2:Funnel plot

Disclosure: P. Ungprasert, None; S. Raksasuk, None.

Abstract Number: 538

Type 1 Diabetes in RA: Comparison with Type 2 and Its Association with RA Severity and Treatment

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: DMARD treatment for Rheumatoid Arthritis (RA) has been shown to improve the glucose control and reduce the incidence of diabetes, usually assumed to be type 2 (T2D) in adults. While rare in adults, type 1 diabetes (T1D) can improve with DMARD treatment. We sought to differentiate the prevalence of T1D from T2D and examine the association of diabetes type with DMARDs, and other factors in patients with RA.

Methods: Participants in Forward, The National Databank for Rheumatic Diseases, during 1999-2018 who reported having diabetes and completed new questions added in 2017 regarding the type of diabetes, age of diagnosis, and treatments. Participants were characterized at the earliest time point available after diabetes diagnosis (baseline): either at enrollment into Forward or at the time of diagnosis during followup. Differences by diabetes type were assessed by statistical tests (Chi², T-test). Logistic generalized estimating equation (GEE) models were used in both univariate and multivariable manner to investigate associations between diabetes type and demographics, clinical measures, and RA treatment. Best models were found by QIC criterion.

Results: Of the included 700 diabetic RA patients, 8.6% (60) were of T1D, while the remaining 640 were T2D (91.4%). The onset age for T1D was 36 years (SD 22) vs 54 years (SD 13) for T2D. The majority of T1D was diagnosed before RA diagnosis (63.3%) whereas T2D was diagnosed mostly after RA diagnosis (71.6%). Patients with T1D tended to be younger, have higher education, lower BMI, worse HAQ, and more likely to smoke than patients with T2D (Table 1). These factors were significant in longitudinal models, although no RA severity measures were associated with diabetes type. Patients with T1D were slightly more likely to receive nonTNFi bDMARDs compared to patients with T2D although this was attenuated in the multivariable model (Table 2).

Conclusion: Surprisingly, the percentage of patients with RA reporting T1D was about double that expected in the population (~4% in the general population¹). These patients were younger and tended toward greater use of non TNFi bDMARDs. Future studies should account for type of diabetes due to important differences in impact of auto-immune diseases by treatments.

¹American American Diabetes Association

Table 1 –Patients characteristics by diabetes type at baseline.

Variables	Diabetes		P-value
	T1D	T2D	
Age	57.5 (11.3)	61.7 (9.8)	0.00
Onset age of diabetes	35.6 (22.0)	54.2 (12.8)	0.00
Education	14.6 (2.4)	13.9 (2.4)	0.02
Female sex	81.7	75.9	0.33
White ethnicity	83.3	88.3	0.26
Employed	30.0	26.0	0.50
Smoking			
Current	8.3	3.7	0.08
Ever	43.3	43.7	0.95
RA duration (years)	17.7 (14.2)	15.7 (12.4)	0.24
Diabetes duration (years)	21.9 (17.3)	7.5 (9.1)	0.00
RD comorbidity index	3.1 (1.7)	2.9 (1.8)	0.64
BMI	29.3 (8.7)	33.3 (7.5)	0.00
HAQ disability	1.33 (0.8)	1.11 (0.7)	0.02
PAS	4.54 (2.3)	4.07 (2.2)	0.12
Pain scale	4.91 (2.9)	4.51 (2.9)	0.30
Fatigue scale	5.08 (3.2)	4.80 (3.0)	0.49
Sleep scale	4.67 (3.2)	3.94 (3.2)	0.10
Global severity	4.28 (2.5)	4.01 (2.5)	0.42

Table 2 –Association of T1D with RA disease characteristics, outcomes and DMARDs compared to T2D (OR (95%CI) from logistic GEE models)

Variables	Age & sex adjusted			Multivariable		
	OR	95%CI	P-value	OR	95%CI	P-values
Age (years)	0.96	(0.95 - 0.96)	0.00	1.00	(1.00 - 1.01)	0.06
Sex (male)	0.64	(0.529 - 0.78)	0.00	0.82	(0.37 - 1.82)	0.63
Onset age of diabetes	0.93	(0.91 - 0.95)	0.00	0.95	(0.93 - 0.97)	0.00
Education	1.16	(1.01 - 1.32)	0.04	1.12	(0.98 - 1.27)	0.09
RA duration	1.03	(1.01 - 1.05)	0.00			
Diabetes duration	1.08	(1.06 - 1.10)	0.00			
RD comorbidity index	1.00	(1.00 - 1.01)	0.04			
BMI	0.99	(0.99 - 0.99)	0.00	0.99	(0.98 - 0.99)	0.00
HAQ disability	1.00	(0.99 - 1.01)	0.18			
PAS	1.00	(0.99 - 1.00)	0.16			
Pain scale	1.00	(0.99 - 1.00)	0.22			
Fatigue scale	1.00	(0.99 - 1.00)	0.45			
Sleep scale	1.00	(1.00 - 1.00)	0.25			
Global severity	1.00	(1.00 - 1.00)	0.15			
White	0.69	(0.33 - 1.41)	0.31	0.61	(0.23 - 1.60)	0.31
Employed	0.99	(0.98 - 1.01)	0.59			
Current smoking	2.51	(0.90 - 6.70)	0.08			
Ever smoking	1.06	(0.61 - 1.83)	0.84	3.12	(0.75 - 13.02)	0.12
Lifetime Biologic count	1.02	(1.00 - 1.03)	0.026			
Diabetes treatment	1.02	(1.00 - 1.03)	0.02	0.97	(0.95 - 0.99)	0.04
RA treatment	csDMARD ref.			0.96	(0.49 - 1.89)	0.91
TNFi	0.99	(0.98 - 1.01)	0.30	1.01	(0.98 - 1.03)	0.52
NonTNFiDMARDs	1.01	(0.99 - 1.03)	0.09	1.03	(0.99 - 1.07)	0.14

Disclosure: S. Pedro, None; G. Ozen, None; K. Michaud, University of Nebraska Medical Center and FORWARD, The National Databank for Rheumatic Diseases, 3, University of Nebraska Medical Center and FORWARD, The National Databank for Rheumatic Diseases, 3, Rheumatology Research Foundation and Pfizer, 2, Rheumatology Research Foundation and Pfizer, 2.

Abstract Number: 539

Thyroid Function in Early Versus Established Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

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Background/Purpose: Thyroid dysfunction is common in rheumatoid arthritis (RA). Subclinical hypothyroidism is the first most common, followed by clinical hypothyroidism. Thyroid dysfunction in RA had been found to increase the risk of cardiovascular disease. Subclinical hypothyroidism is defined as increased serum thyroid stimulating hormone (TSH) concentration with normal serum free thyroxine (T4) level. The aim of this study was to compare the thyroid function in early RA patients (of less than one-year duration of RA symptoms) versus established RA patients (of more than or equal to one-year duration of RA symptoms).

Methods: We recruited 35 early RA patients (ERA) and 52 established RA patients attending specialized rheumatology clinic. All the patients had no clinical evidence of thyroid dysfunction. Patients with diabetes, pregnancy, renal and liver impairment were excluded. Fasting Free thyroxine (FT4), Free triiodothyronine (FT3), and thyroid stimulating hormone (TSH) were assessed in all the participants. t-test was used to compare the RA disease characteristics and the thyroid function between early and established RA. P value of <0.05 was considered significant.

Results: Rheumatoid arthritis patients had been recruited through a specialized rheumatology clinic, 35 were with new onset rheumatoid arthritis (early RA; ERA of less than a year of RA symptoms onset) and 52 were with established RA (of more than a year of RA symptoms onset). The mean RA duration was 7.4 ± 2.0 months for ERA and 96 ± 92 months for the established RA group. There were no significant differences in age (45.76 ± 2.45 years for ERA vs. established RA respectively, $p=0.49$), or in gender distribution (31 F and 4 M in ERA vs. 46 F and 6 M in established RA, $p=0.9$) between the two groups.

ERA compared to the established RA group had more active RA as manifested by more swollen 28- joints (5.7 vs 1.7 , respectively, $p=0.001$), more tender 28-joints (17 vs 11 , respectively, $p=0.01$), higher DAS-28-ESR score (5.8 vs 4.5 , respectively, $p=0.0001$), higher DAS 28-CRP score (5.1 vs. 3.9 , respectively, $p=0.001$), and longer morning stiffness duration (in minutes) ($p=0.04$). As well, ERA had lower HDL level (1.4 vs 1.2 , respectively, $p=0.04$). On the other hand, established-RA patients had RA disease onset at an earlier age than the EAR group (36.5 vs 44 years, respectively, $p=0.02$).

While the mean TSH, T3 and T4 were within normal range in both groups, there were significant differences in the mean values between ERA and established RA. TSH was 2.12 ± 1.52 in ERA vs. 5.8 ± 8.3 in established RA (NR: 0.27 - 4.2 mIU/L), $p=0.04$. Mean FT3 was 4.54 ± 0.53 in ERA vs. 3.61 ± 1.13 in the established RA (NR: 4 - 6.8 pmol/L), $p=0.04$. Average FT4 was 17.7 ± 4.77 in ERA vs. 15.3 ± 2.51 in the established RA (NR: 12 - 22 pmol/L), $p=0.01$.

Conclusion: RA patients with more than a year of RA symptoms are at a higher risk of silent autoimmune thyroid disease than their age sex matched RA patients with new onset RA; of less than a year of RA symptoms onset. Regular assessment of thyroid function might be an important part in the routine biochemical and immunological profile screening of RA.

Disclosure: S. Hannawi, None; I. Al Salmi, None; H. Hannawi, None.

Abstract Number: 540

Echocardiographic Abnormalities in Rheumatoid Arthritis Patients Compared to Age, Sex and Traditional Cardiovascular Risk Factors Matched Controls

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease of the joints with several extra-articular features. Cardiovascular disease (CVD) mortality accounts for 40-50% of all deaths in RA. Apart from

atherosclerotic heart disease other cardiac abnormalities had been found to be prevalent in RA; including, pericarditis, heart failure, coronary vasculitis and valve disease. Due to scarcity of data regarding cardiac disease in the Middle East population, we studied echocardiographic features in RA patients compared to their age, sex, and traditional CVD risk factors matched controls.

Methods: In a cross-sectional study, we recruited 39 RA patients meeting the 1987 revised criteria of RA and 37 age, sex and traditional CVD risk factors matched controls. Standard trans-thoracic echocardiography examination was carried out by a specialties cardio-sonographer who was blinded to the status of the participants. Left ventricular dimensions, wall geometry, ejection fraction, diastolic parameters, right ventricular size and function, valve structure and function, pericardium, pulmonary pressures and aortic root dimensions were assessed by echocardiography. t-test and chi-2 test were used to compare the echocardiographic findings between the two groups. P value of <0.05 was considered significant.

Results: Thirty-nine RA patients (34 F, 4 M) and 37 controls (32 F, 5 M) were studied. Among RA, 27 (69%) were rheumatoid factor positive. The two groups were similar in terms of age ($p=0.86$), gender ($p=0.71$), and traditional cardiovascular risk factors (hypertension ($p=0.61$), diabetes mellitus ($P=0.51$), hyperlipidemia ($p=0.75$), history of smoking ($p=0.97$), and obesity by body mass index definition ($p=0.77$)).

No significant difference was found between RA and the controls in term of left ventricular ejection fraction, wall geometry, diastolic parameters, right ventricular size and function, valves diseases, pulmonary pressures, pericardium and aortic root dimensions. However, left ventricular end-diastolic diameter (43.11 ± 1.14 vs. 39.35 ± 0.84 mm respectively, $p=0.01$), end-systolic diameter (24.39 ± 0.70 vs. 26.96 ± 0.96 mm, respectively, $p=0.03$) and Left ventricular mass index (79.83 ± 5.11 vs. 63.64 ± 3.15 , respectively, $p=0.01$) were significantly higher in RA patients than in the controls.

Conclusion: Patients with rheumatoid arthritis have higher left ventricular end-diastolic and end-systolic dimensions, and greater left ventricular mass index compared to their age, sex and traditional CVD risk factors-matched controls. As the increase in the left ventricular mass index is a predictor of cardiac sudden death, echocardiography might be a simple non-invasive tool for cardiac risk screening in RA.

Disclosure: S. Hannawi, None; K. Naeem, None; H. Hannawi, None; I. Al Salmi, None.

Abstract Number: 541

Prevalence of Sjögren's Syndrome in Patients with RA Enrolled in a Large Observational US Registry

Leslie R Harrold¹, Ying Shan², Sabrina Rebello², Neil Kramer³, Sean E. Connolly⁴, Evo Alemao⁴, Sheila Kelly⁴, Tammy Curtice⁴, Joel Kremer⁵ and Elliot Rosenstein³, ¹University of Massachusetts, Worcester, MA, ²Corrona, LLC, Southborough, MA, ³Overlook Medical Center, Institute for Rheumatic & Autoimmune Diseases, Summit, NJ, ⁴Bristol-Myers Squibb, Princeton, NJ, ⁵Albany Medical College and the Center for Rheumatology, Albany, NY

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Session Type: ACR Poster Session A

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

Background/Purpose: Sjögren's syndrome is a known co-existing autoimmune disease in patients with RA, but its prevalence and impact on RA are poorly understood. The aims of this study were to assess the prevalence of secondary Sjögren's syndrome (sSS) and to compare the baseline characteristics of patients with RA, with and without Sjögren's syndrome, in a national sample of patients with RA.

Methods: We identified adult patients with rheumatologist-diagnosed RA (ARA 1987 or ACR/EULAR 2010 criteria) from a large observational US registry (Corrona RA), with at least one visit assessing the presence of sSS (yes/no) between Apr 22, 2010 and Feb 28, 2018. Patients who had an sSS diagnosis were compared with those who never had a diagnosis. In those without a diagnosis, patients had to be enrolled for at least 12 months to ensure complete data capture. The index date was the date of first capture of sSS diagnosis (sSS patients) or first visit in patients with a negative sSS diagnosis (non-sSS patients). Patients with missing sSS information were excluded. The primary outcome was the unadjusted prevalence of Sjögren's syndrome in patients with RA. Baseline characteristics and the prevalence by RA disease duration were assessed by sSS status.

Results: A total of 24,528 patients met the inclusion criteria, of whom 7870 (32.1%) had a diagnosis of sSS. The unadjusted overall rate for the prevalence of Sjögren's syndrome in patients with RA was 0.30 (95% CI: 0.29, 0.31). Compared with patients without sSS, patients with sSS were more likely to be older, female and seropositive (both cyclic

citrullinated peptide positive and RF+), and had a longer duration of RA, higher disease activity (CDAI score), and a higher incidence of co-morbidities (cardiovascular disease, malignancies and serious infections), erosive disease and subcutaneous nodules at the index date (Table 1). The rate of sSS increased with increasing RA disease duration (Table 2).

Conclusion: This study suggests that patients with sSS and RA have a higher disease burden than those with RA alone. sSS was associated with seropositivity, more severe RA, and a greater incidence of other extra-articular manifestations and co-morbidities. A higher prevalence of sSS was observed as the duration of RA increases. Professional medical writing and editorial assistance was provided by Claire Line, PhD, at Caudex, and was funded by Bristol-Myers Squibb.

Table 1. Baseline Characteristics at Index Date

	Patients with sSS + RA (n=7870)	Patients with RA only (n=16,658)
Age, years, mean (SD)	62.5 (11.9)	59.2 (13.1)
Sex, female	6617 (84.4)	12,229 (73.8)
Duration of RA, years, mean (SD)	13.6 (11.0)	9.5 (9.2)
Co-morbidities		
CV disease*	1219 (15.5)	1710 (10.3)
Malignancy†	1223 (15.5)	1821 (10.9)
Serious infections‡	795 (10.1)	845 (5.1)
Cyclic citrullinated peptide positive, n/m (%)	1999/3420 (58.5)	4076/7451 (54.7)
RF+, n/m (%)	2983/4296 (69.4)	6338/9492 (66.8)
Erosive disease, n/m (%)	2480/6650 (37.3)	4230/12,406 (34.1)
Subcutaneous nodules, n/m (%)	2700/7869 (34.3)	2886/16,640 (17.3)
CDAI, mean (SD)	13.4 (12.8)	11.3 (11.9)
Number of prior biologics/tsDMARDs		
0	2583 (32.8)	7593 (45.6)
1	2656 (33.7)	5592 (33.6)
≥2	2631 (33.4)	3473 (20.8)
Number of prior csDMARD		
0	367 (4.7)	1704 (10.2)
1	2984 (37.9)	8016 (48.1)
≥2	4519 (57.4)	6938 (41.6)

Data are n (%) unless otherwise stated

* History of coronary artery disease, myocardial infarction, coronary heart failure requiring hospitalization, acute coronary syndrome, unstable angina, cardiac revascularization procedure, cardiac arrest, ventricular arrhythmia, stroke, transient ischemic attack or other CV event

† History of lung cancer, breast cancer, lymphoma, skin cancer (melanoma and squamous) or other cancer

‡ Infection required hospitalization or IV treatment

csDMARD=conventional synthetic DMARD; CV=cardiovascular; n/m=number of patients by total number of patients in the analysis;

sSS=secondary Sjögren's syndrome; tsDMARD=targeted synthetic DMARD

Table 2. Prevalence of Sjögren's Syndrome in Patients with RA by Disease Duration

Disease duration, years	n (%)
0-1	533 (14.4)
2-3	637 (23.2)
4-5	732 (28.9)
6-10	1538 (29.8)
>10	3637 (38.8)

Disclosure: L. R. Harrold, Corrona, LLC, 1,Pfizer, 2,Roche, Bristol-Myers Squibb, 5,Corrona, LLC, University of Massachusetts Medical School, 3; Y. Shan, Corrona, LLC, 3; S. Rebello, Corrona, LLC, 3; N. Kramer, None; S. E. Connolly, Bristol-Myers Squibb, 1, 3; E. Alemao, Bristol-Myers Squibb, 1, 3; S. Kelly, Bristol-Myers Squibb, 1, 3; T. Curtice, Bristol-Myers Squibb, 1, 3; J. Kremer, Corrona, LLC, 1, 3,AbbVie, Bristol-Myers Squibb, Genentech, Lilly, Novartis, Pfizer, 2,Genentech, Inc., 8; E. Rosenstein, Amgen, Bristol-Myers Squibb, Horizon, 5,Up-To-Date, 7,AbbVie, Amgen, Bristol-Myers Squibb, 8.

Abstract Number: 542

Incidence and Prevalence of Interstitial Lung Disease in the US Population and in Patients with RA By Anti-Citrullinated Protein Antibody Status

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster I: Comorbidities

Background/Purpose: Interstitial lung disease (ILD) is recognized as the most common pulmonary extra-articular manifestation of RA. The hazard ratio for 30-year risk of ILD in patients with RA (vs a matched cohort of patients without RA) is 8.96 (95% CI: 4.02, 19.94).¹ A recent meta-analysis concluded that anti-citrullinated protein antibody (ACPA) positivity was associated with an increased risk of lung disease (pooled odds ratio: 2.6).² The objective of this analysis was to evaluate the prevalence and incidence of ILD by ACPA levels in general and in the population with RA.

Methods: Data from July 1, 2002, to September 30, 2017, from administrative claims database Optum[®] Clinformatics[™] Data Mart were used. Patients with ACPA test information were included in the analysis; the date of the test was the index date for the general cohort and first RA diagnosis date was index date for the RA cohort. The RA cohort comprised patients having ≥ 2 claims for RA and an ACPA test. Patients in the general and RA cohorts were divided into groups based on median ACPA titer values. Identification of patients with ILD was based on a published algorithm that included a two-step process: an initial diagnosis code of ILD, then a code for chest X-ray or CT scan on or after the first ILD diagnosis, and a second chest X-ray or CT scan after the first scan. Incidence rates (IRs) and prevalence rates were calculated for both cohorts and by subgroups based on ACPA levels.

Results: A total of 177,728 patients with ACPA information were identified (overall cohort); of those 20,746 (11.7%) and 156,982 (88.3%) were ACPA+ and ACPA-, respectively. A total of 9827 patients with RA had ACPA information (RA cohort); of whom 2927 (29.8%) and 6900 (70.2%) were ACPA+ and ACPA-, respectively. The prevalence of ILD in the overall cohort was 5.3% versus 8.2% in the RA cohort. The ILD IRs were higher in the ACPA+ versus the ACPA- group in the overall cohort (13.3 vs 8.4 per 1000 patient-years) as well as in the RA cohort (12.9 vs 11.7 per 1000 patient-years). In addition, the ILD IRs were greater for patients with higher ACPA titers in the overall cohort (Table 1).

Conclusion: The prevalence of ILD in patients with RA was higher than that in the general population. The ILD prevalence and IRs were higher in ACPA+ patients and increased with ACPA titer in the overall cohort. Further analysis with a larger RA cohort is required to confirm these findings.

References:

1. Bongartz T, et al. *Arthritis Rheum* 2010;**62**:1583–91.
2. Zhu J, et al. *J Rheumatol* 2014;**41**:1282–9.

Table 1. Incidence and prevalence of ILD by ACPA status and titers

	Total patients	Patients with ILD	Prevalence, %	Incident ILD	IR per 1000 PY
Overall cohort					
N	177,728	9466	5.3	2778	9.0
ACPA- patients	156,982	7871	5.0	2308	8.4
ACPA+ patients	20,746	1595	7.7	470	13.3
By ACPA titer groups for ACPA+ patients in overall cohort					
Group 1 (≤ 41.30)	10,379	753	7.3	213	12.1
Group 2 (> 41.30)	10,367	842	8.1	257	14.5
RA cohort					
n	9827	807	8.2	263	12.0
ACPA- patients	6900	559	8.1	184	11.7
ACPA+ patients	2927	248	8.5	79	12.9
By ACPA titer groups for ACPA+ patients in RA cohort					
Group 1 (≤ 52.00)	1473	127	8.6	40	13.0
Group 2 (> 52.00)	1454	121	8.3	39	12.7

ACPA=anti-citrullinated protein antibody; ILD=interstitial lung disease; IR=incidence rate; PY=patient-years

Disclosure: E. Alemao, Bristol-Myers Squibb, 1, 3; R. Indrakumar, Mu-sigma, 5; A. Rao, Mu Sigma for Bristol-Myers Squibb, 5; Y. Bao, Bristol-Myers Squibb, 1, 3.

Abstract Number: 543

Disease Severity Among Bio-Naive RA Patients on Csdmards

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Background/Purpose: Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD) are recommended as the first-line treatment for patients with rheumatoid arthritis (RA). Guidelines recommend escalation of treatment to combinations of csDMARD and/or biologics for those with moderate to high disease activity despite treatment with csDMARDs. We sought to characterize disease burden among RA patients who had been on a csDMARD for at least six months and who had not transitioned to a biologic.

Methods: We identified patients enrolled in the US Corrona RA Registry between 06/01/2014 and 1/30/2018 who had been receiving csDMARD continuously for at least 6 months, remained biologic naïve, were in moderate or high disease activity (Clinical Disease Activity Index [CDAI] >10) and had at least one follow-up visit. Disease activity was assessed in the subset of patients with a 6 month follow-up visit (+/- 3 months) comparing those who achieved remission/low disease activity (CDAI≤10) to those who remained in moderate/high disease activity (CDAI>10) in terms of demographics, lifestyle factors, comorbid conditions and disease characteristics using descriptive statistics.

Results: There were 525 patients who met study inclusion criteria, with a mean age of 65 (SD 13), mean duration of RA of 11 years (SD 11), and mean duration of csDMARD therapy of 397 days (SD 210). In those with a 6 month visit (n=409), more than half (n=219) remained in moderate/high disease activity (54%) at follow up. Those who achieved remission/low disease activity (n=190) were similar to those in moderate/high disease activity (n=219) at their 6 month visit with respect to age, BMI, comorbid conditions (history of serious infection, cardiovascular disease, malignancy), duration of RA and prednisone dosage. Baseline swollen and tender joint counts were higher in those who did not achieve remission/low disease activity; a higher proportion of those reaching remission/low disease activity were college educated or higher (39%) compared with 27% (Table). Over the 6-month period, treatment acceleration occurred in <30% of patients. Dose escalation of the csDMARD, initiation of another csDMARD and initiation of abiotic DMARD occurred in 57 (14%), 33 (8%) and 42 (10%) of the total population of patients respectively.

Conclusion: Substantial numbers of patients on csDMARDs have persistent moderate/high disease activity over 6 months of follow-up. These observations indicate that there is considerable need for a treat to target approach to care to prevent joint damage and physical disability and maximize long-term health-related quality of life.

Table

Characteristics		Remained in Moderate/ High Disease activity N=219	Achieved Remission/ Low Disease Activity N=190	P value
Age	N	218	189	0.979
	Mean(SD)	65.99 (12.47)	65.80 (12.72)	
BMI	N	219	189	0.098
	Mean(SD)	29.64 (6.96)	28.62 (6.65)	
Education	N	214	181	0.011
College and above	n (%)	57 (26.64)	70 (38.67)	
Work status	N	216	184	0.032
Full Time	n (%)	38 (17.59)	50 (27.17)	
Part Time	n (%)	20 (9.26)	21 (11.41)	
At home	n (%)	14 (6.48)	10 (5.43)	
Disabled	n (%)	36 (16.67)	15 (8.15)	
Retired	n (%)	108 (50.00)	88 (47.83)	
History of serious infection	N	219	190	0.722
	n (%)	17 (7.76)	13 (6.84)	
History of cardiovascular Disease*	N	219	190	0.689
	n (%)	39 (17.81)	31 (16.32)	
History of Malignancy**	N	219	190	0.305
	n (%)	30 (13.70)	33 (17.37)	
Duration of RA	N	219	189	0.523
	Mean(SD)	10.41 (10.30)	11.33 (11.35)	
Prednisone Use	N	219	190	0.559
None	n (%)	182 (83.11)	154 (81.05)	
< 5 mg	n (%)	10 (4.57)	15 (7.89)	
5 mg to <10 mg	n (%)	20 (9.13)	16 (8.42)	
10 mg or greater	n (%)	7 (3.20)	5 (2.63)	
Tender Joint Count (28)	N	219	190	0.020
	Mean(SD)	6.76 (6.99)	5.14 (5.53)	
Swollen Joint Count (28)	N	219	190	0.016
	Mean(SD)	6.08 (5.48)	4.69 (4.25)	

* History of cardiovascular disease includes history of cardiac arrest, myocardial infarction, acute coronary syndrome, unstable angina, coronary artery disease, ventricular arrhythmia, congestive heart failure, cardiac revascularization procedure, other cardiovascular event, stroke, transient ischemic attack, hemorrhage (with or without hospitalization), deep vein thrombosis, peripheral arterial disease, pulmonary embolism, carotid artery disease.

** History of malignancy includes history of lung cancer, breast cancer, skin cancer, lymphoma or other cancer.

Disclosure: L. R. Harrold, Corrona, LLC, 1, Pfizer, Inc., 2, Corrona, LLC, 3, Roche and Bristol Myers-Squibb, 5; J. Griffith, AbbVie Inc., 1, AbbVie Inc., 3; H. J. Litman, Corrona, LLC, 3; H. Feng, Corrona, LLC, 3; C. A. Schlacher, AbbVie Inc., 3; J. Kremer, Corrona, LLC, 1, Corrona, LLC, 3, AbbVie, Amgen, BMS, Genentech, Lilly, Regeneron, Sanofi, Pfizer, 5, AbbVie, Genentech, Lilly, Novartis, Pfizer, 2.

Abstract Number: 544

Does Anti-Citrullinated Protein Antibody Status Modify Treatment Effect of Certain Biologic DMARDs?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Multiple therapeutic options with different mechanistic actions are available to treat patients (pts) with RA. However, selecting therapies by the characteristics of pts with RA is not a fully established practice. Recent evidence suggests that anti-citrullinated protein antibodies (ACPA) status is associated with a differential treatment response to abatacept (ABA), but not to TNF inhibitors (TNFi).^{1,2} The objective of this analysis was to generate additional evidence on the association of biologic (b)DMARD treatment (ABA and TNFi) effect by ACPA status.

Methods: Data from two RA registries were used to address the research objective. One of the registries was an RA disease-specific registry and provided data for the treatment effect of initiating TNFi; the other was a product-specific RA registry and provided treatment effect of ABA initiation. Pts were evaluated by a rheumatologist annually in the RA disease-specific registry and every 3 months in the product-specific registry.^{3,4} The disease-specific registry was a single-center registry and the product-specific registry was a multi-center and multi-country registry. Descriptive statistics were used to summarize baseline demographics, disease activity measures and serostatus for both cohorts. Percentage change and mean change in disease activity from baseline to 12 months by ACPA status were assessed for pts with data available at baseline and follow-up.

Results: Data for a total of 797 TNFi and 2350 ABA pts were available and were included in the analysis. The average (SD) age was 54.9 (13.9) years for pts in the TNFi cohort and 57.8 (12.6) years for pts in the ABA cohort. ACPA information was available for 92% of TNFi and 83% of ABA pts; 70% and 67% of pts in the TNFi cohort and the ABA cohort were ACPA+, respectively. ACPA+ pts in both cohorts had longer disease duration (Table 1). ACPA+ ABA pts had a significantly greater mean change in disease activity on CDAI, SDAI and SJC compared with ACPA- ABA pts. Similar reduction in disease activity was not observed between ACPA+ and ACPA- TNFi pts (Table 2).

Conclusion: ACPA status is associated with a differential treatment response to abatacept, but not TNFi. These findings are consistent with other studies reported in the literature and could be due to the different mechanism of action of abatacept and TNFi.^{1,2}

References:

1. Harrold LR, et al. *J Rheumatol* 2018;**45**:32–9.
2. Sokolove J, et al. *Ann Rheum Dis* 2015;**74**:983–4.
3. <https://www.brasstudy.org/>
4. Nüßlein HG et al. *BMC Musculoskeletal Disorders* 2014;**15**:14.

Table 1. Baseline Characteristics by ACPA Status Within Treatment Cohort

	ABA pts (n=2350)			TNFi pts (n=797)		
	ACPA+ pts (n=1304)	ACPA- pts (n=635)	p value	ACPA+ pts (n=508)	ACPA- pts (n=223)	p value
Age, years	58.3 (12.2)	57.2 (13.3)	0.151	56.3 (13.6)	52.8 (13.7)	0.003
Duration of RA, years	11.1 (9.0) n=1299	9.2 (9.1) n=633	<0.0001	15.5 (11.8)	9.9 (10.1) n=222	<0.0001
Female, n (%)	1022 (78.4)	536 (84.4)	0.002	431 (84.8)	182 (81.6)	0.275
BMI	26.7 (5.3) n=1260	27.9 (5.9) n=607	<0.0001	26.9 (6.2) n=403	26.6 (5.6) n=150	0.863

Table . (Cont'd)

	ABA pts (n=2350)			TNFi pts (n=797)		
	ACPA+ pts (n=1304)	ACPA- pts (n=635)	p value	ACPA+ pts (n=508)	ACPA- pts (n=223)	p value
DAS28 (CRP)	4.9 (1.3) n=325	4.9 (1.1) n=124	0.688	3.8 (1.7) n=376	3.1 (1.6) n=153	<0.0001
CDAI	28.3 (12.1) n=1164	29.8 (12.7) n=546	0.057	21.7 (17.5) n=374	14.9 (14.9) n=151	<0.0001
SDAI	30.0 (12.9) n=1092	31.5 (13.3) n=509	0.044	22.5 (18.1) n=370	15.4 (15.6) n=150	<0.0001
Number of swollen joints	6.6 (5.2) n=1294	6.8 (5.7) n=632	0.711	7.2 (7.6) n=418	4.6 (6.4) n=168	<0.0001
Number of painful joints	9.2 (6.6) n=1290	10.5 (7.5) n=620	0.003	7.9 (8.5) n=418	4.9 (6.8) n=168	0.0003

Values are mean (SD) unless otherwise stated

ABA=abatacept; ACPA=anti-citrullinated peptide antibody; pt=patient; TNFi=TNF inhibitor

Table 2. Change in Disease Activity at 12 Months by ACPA Status by Treatment Cohort

	ABA pts			TNFi pts		
	ACPA+ pts (n=1209)	ACPA- pts (n=578)	p value for change	ACPA+ pts (n=469)	ACPA- pts (n=203)	p value for change
DAS28 (CRP)	-1.6 (1.4) n=243	-1.5 (1.1) n=89	0.297	-0.2 (1.2) n=278	-0.3 (1.1) n=109	0.365
CDAI	-15.6 (12.5) n=1035	-13.6 (12.6) n=476	0.001	-2.3 (11.9) n=277	-3.2 (8.7) n=112	0.271
SDAI	-15.9 (12.9) n=883	-14.7 (13.3) n=391	0.016	-2.4 (12.6) n=261	-3.1 (9.0) n=104	0.426
SJC	-4.2 (5.0) n=1183	-3.8 (5.3) n=562	0.013	-1.6 (6.0) n=377	-1.8 (5.2) n=140	0.584
Number of painful joints	-5.5 (6.4) n=1178	-5.3 (7.0) n=551	0.391	-1.3 (6.5) n=337	-1.0 (5.0) n=140	0.725

Value are mean change (SD) unless otherwise stated

ABA=abatacept; ACPA=anti-citrullinated peptide antibody; pt=patient; TNFi=TNF inhibitor

Disclosure: E. Alemao, Bristol-Myers Squibb, 1, 3; Y. Elbez, Bristol-Myers Squibb, 5; Y. Saini, Mu-sigma, 5; S. E. Connolly, Bristol-Myers Squibb, 1, 3; A. Rao, Mu Sigma for Bristol-Myers Squibb, 5; C. K. Iannaccone, None; M. E. Weinblatt, Amgen, Crescendo Bioscience, Bristol-Myers Squibb, Sanofi/Regeneron, 2, AbbVie, Ablynx, Amgen, Bristol-Myers Squibb, Canfite, Corrona, Crescendo, GSK, Gilead, Lilly, Lycera, Merck, Momenta, Novartis, Pfizer, Roche, Samsung, Set Point, UCB, Vertex, 5; N. A. Shadick, Amgen, Mallinckrodt, Bristol-Myers Squibb, Sanofi-Regeneron, 2, Bristol-Myers Squibb, 5.

Abstract Number: 545

How to Treat Rheumatoid Arthritis Patients When Methotrexate Has Failed? Results from the Meteor Registry

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: After failure of initial methotrexate(MTX) treatment in rheumatoid arthritis (RA) patients, various treatment options can be considered. To date, evidence about the preferred follow-up strategy is sparse. We aimed to compare consecutive DMARD treatment regimes in daily practice in RA patients who failed on initial MTX monotherapy.

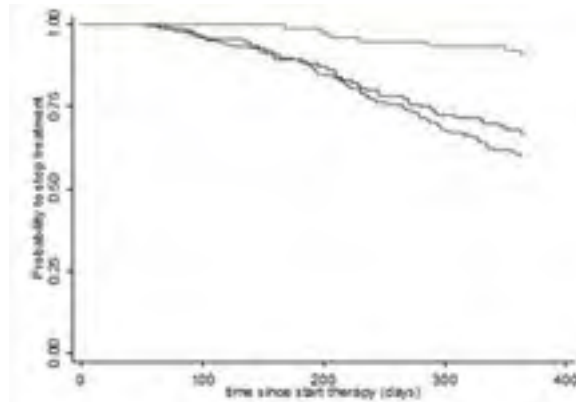


Figure 1. Kaplan-Meier curve showing the probability to stop treatment over time. The figure is based on unadjusted data. Blue line = csDMARD(s), red line = csDMARD(s) + glucocorticoid, green line = bDMARD ± csDMARD(s).

Table 1. Adjusted changes in DAS over time for each medication group (in patients=528)*

Maximum follow-up duration	6 months	95% CI	1 year	95% CI
csDMARD(s)	-0.75	-1.11; -0.42	-0.39	-0.66; -0.13
csDMARD(s) + glucocorticoid	-0.96	-1.32; -0.69	-0.40	-0.62; -0.23
bDMARD (± csDMARD(s))	-2.00	-2.65; -1.35	-0.91	-1.32; -0.60

*Results given for a linear mixed model analyses and were adjusted for multiple propensity scores. Missing data were imputed using multiple imputation by chained equations (MICE) due to the proportion of missing data. The actual timing of follow-up visits differed per patient. Parameter estimates represent the unit of change in DAS per year.

Methods: Newly diagnosed RA patients who had failed initial MTX treatment were selected from METEOR, an international, observational registry. Subsequent DMARD treatment regimens were categorized as: 1) csDMARD(s) only (143 patients), 2) csDMARD(s) + glucocorticoid (278 patients) and 3) bDMARD ± csDMARD(s) (89 patients). We selected follow-up visits until switch to yet another treatment strategy occurred or until a maximum follow-up duration of 1 year. Linear mixed model analyses were performed to analyze treatment responses per treatment group (DAS) after a maximum follow-up duration of 6 and 12 months. Differences in time to stop treatment between treatment groups after a maximum follow-up duration of 1 year were estimated using Cox regression. Analyses were adjusted for multiple propensity scores, to correct for confounding by indication.

Results: Median follow-up duration on studied treatment was 6.9 (IQR4.1; 9.4) months for patients receiving csDMARD (s), 7.8 (IQR 5.0; 10.2) months for patients receiving csDMARD(s) + glucocorticoid and 9.0 (IQR 6.2; 10.9)months for patients receiving treatment including a bDMARD.

We found differences in treatment response between the 3 treatment groups, both after 6 months ($p=0.001$) and after 1 year ($p=0.029$). Adjusted treatment effects over time stratified for treatment groups are shown in table 1. Both after 6 months and after 1 year, patients receiving a bDMARD experienced most decrease in DAS per year, followed by patients receiving csDMARD(s) + glucocorticoid and by patients receiving treatment with csDMARD(s) alone. Results of the Cox regression showed that patients receiving treatment including a bDMARD had a lower hazard for discontinuing treatment (i.e. failing or intolerance) compared to patients receiving csDMARD(s) alone [HR (95% CI) 0.38 (0.24; 0.60)], but there were no differences between csDMARD treatment with- or without a glucocorticoid [HR (95% CI) 0.89 (0.66; 1.20), figure 1].

Conclusion: In this analysis of worldwide common practice data, RA patients who had failed initial treatment with MTX monotherapy had a better DAS response and treatment survival after a subsequent switch to a bDMARD containing treatment regimen than to a regimen with csDMARD(s), with or without glucocorticoids.

Disclosure: S. A. Bergstra, None; L. L. Winchow, None; E. Murphy, Roche, 5, AbbVie and UCB, 9; A. Chopra, None; K. Salomon-Escoto, None; J. E. Fonseca, AbbVie Inc., 2, 8, Pfizer, Inc., 2, 8, Merck & Co., 2, 8, Bayer, 2, 8, Janssen, 2, 8, Roche, 2, 8, UCB, Inc., 2, Novartis, 2, 8; C. F. Allaart, None; R. B. M. Landewé, None.

Abstract Number: 546

Baricitinib: Early Vs. Delayed Start in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Baricitinib (bari) is an oral JAK1/JAK2 inhibitor approved for the treatment of moderately to severely active RA in adults in over 40 countries including European countries, the United States, and Japan. In the 52-week Phase 3 RA-BEAM study, bari 4 mg once daily (QD) showed clinical improvements compared to placebo (PBO) and to adalimumab (ADA) in MTX-inadequate-responder (IR) patients (pts).¹ The objective of this analysis was to assess if pts who receive bari early attain added clinical improvement compared to pts with a delayed start of therapy.

Methods: In RA-BEAM 1305 pts (mean disease duration 8.7 years) were randomized 3:3:2 to PBO, bari-4 mg QD, or ADA 40 mg every 2 weeks. At Week 16 or subsequent visits, IRs (lack of $\geq 20\%$ reduction in tender and swollen joint count) were rescued to open-label bari-4mg. At Week 24 PBO pts were switched to bari-4 mg. Patients initially randomized to bari-4 mg were considered the early start group for this analysis and PBO pts switched at Week 24 or rescued at Week 16 or later were considered delayed start. Change from baseline using mixed model repeated measures and mean scores were assessed for the Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), DAS28-hs CRP, DAS28-ESR, HAQ-DI, and modified total Sharp score (mTSS) to compare the early vs delayed start groups between Weeks 24 and 52.

Results: In the early and delayed start groups, 35 (7.2%) and 128 (26.2%) pts were rescued to bari between Weeks 16 and 24, respectively. The early start group had significantly greater change from baseline up to Week 32 and showed greater and more rapid reduction through the first 4 weeks ($>50\%$ reduction) for CDAI compared to the delayed start group (Figure 1). At Week 24, the delayed start group showed a CDAI reduction similar to the reduction achieved by the early start group between Weeks 4 and 8 giving the early start group a 4 to 5 month advantage in disease improvement compared to the delayed start group. After receiving bari, the delayed start group also showed a rapid improvement in CDAI and caught up to the early start patients by Week 40. Similar results were seen for SDAI, DAS28-ESR, and DAS28-hsCRP. However, the early start pts had significantly greater improvement in HAQ-DI still maintained at Week 40 (Figure 1) and a significant advantage from Weeks 16 to 52 (Figure 2) for mTSS.

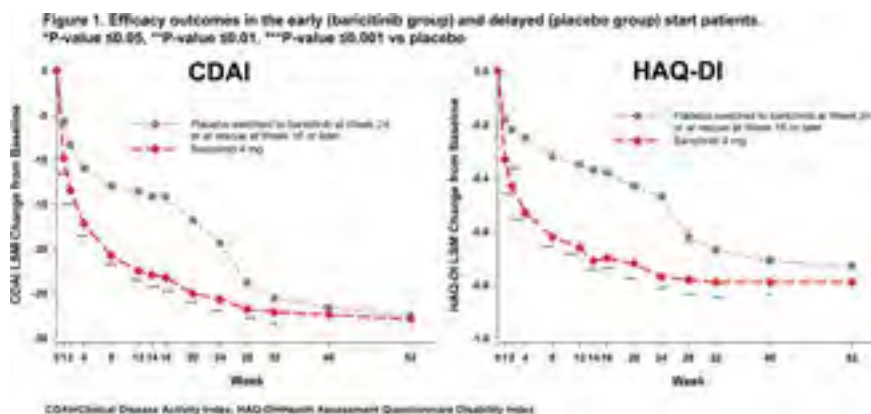
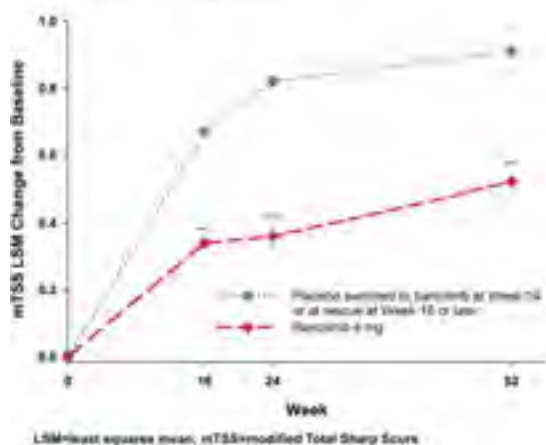


Figure 2. Structural outcomes in the early (baricitinib group) and delayed (placebo group) start patients. *P-value ≤ 0.05 , **P-value ≤ 0.01 , ***P-value ≤ 0.001 vs placebo



Conclusion: While overall disease activity improvement was similar, early start of bari treatment provided faster efficacy. A delay of up to 6 months in bari treatment had an impact on HAQ-DI and structural damage progression.

Reference: 1. Taylor PC et al. *N Engl J Med* 2017;376:652–62

Disclosure: P. C. Taylor, Celgene, Eli Lilly and Company, Galapagos, UCB, 2,AbbVie, Eli Lilly and Company, Galapagos, GlaxoSmithKline, Pfizer, UCB, Biogen, Sandoz, Novartis, Janssen, 5; Y. Tanaka, Mitsubishi-Tanabe, Bristol-Myers, Eisai, Chugai, Takeda, Abbvie, Astellas, Daiichi-Sankyo, Ono, MSD, Taisho-Toyama, 2,Daiichi-Sankyo, Astellas, Eli Lilly, Chugai, Sanofi, Abbvie, Pfizer, YL Biologics, Bristol-Myers, Glaxo-Smithkline, UCB, Mitsubishi-Tanabe, Novartis, Eisai, Takeda, Janssen, Asahi-kasei, 5; A. Cardoso, Eli Lilly and Company, 1, 3; J. Zhong, None; Y. F. Chen, Eli Lilly and Company, 1, 3; J. L. Workman, Eli Lilly and Company, 1, 3; L. D. C. Morales, None; M. Schiff, Abbvie, Amgen, Antares, BMS, Eli Lilly and Company, JJ, Novartis, Novo, Nordisk, Pfizer, Roche, UCB, 5,Abbvie, BMS, 8.

Abstract Number: 547

Corticosteroid Bridging Strategies with Methotrexate Monotherapy in Early Rheumatoid and Undifferentiated Arthritis; A Comparison of Efficacy and Toxicity in 2 Clinical Trials

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: What is the optimal glucocorticoid (GC) bridging therapy with MTX monotherapy in early arthritis?

Methods: In trial A, early RA and UA (arthritis in ≥ 1 joint(s), < 1 year symptoms) patients were randomised to 3 different treatment arms. Here we used data of arm C where patients were treated with prednisone (15 mg/day, tapered to 0 in 10 weeks) and MTX (25mg/week).

In trial B, RA and UA (arthritis in ≥ 1 joint and ≥ 1 other painful joint) patients were treated with prednisone (60 mg/day, tapered in 7 weeks to 7.5 mg/day, continued to 4 months) and MTX (25 mg/week). We compared changes in DAS and HAQ and percentages with DAS ≤ 2.4 and with DAS < 1.6 at first evaluation (3 months in trial A, 4 months in trial B).

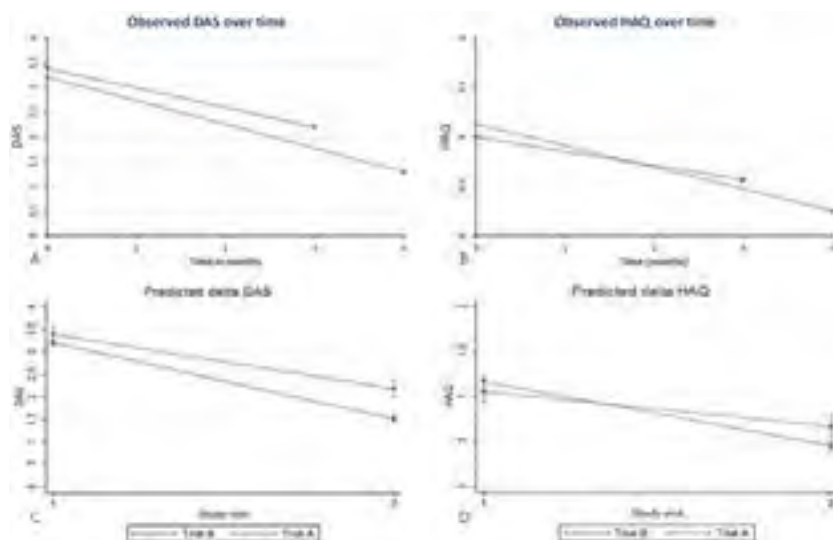


Figure 1A: Observed DAS over time, B: Observed HAQ over time, C: Predicted delta DAS, D: Predicted delta HAQ. All predictors are from multiple imputed models, adjusted for age, gender, body mass index, presence of ACPA, presence of rheumatoid factor, symptom duration, effect over time (in DAS) and baseline DAS (for binary outcomes). DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire.

After multivariate normal imputation we applied generalized estimating equations (GEE) for linear outcomes and logistic regression models for binary outcomes, adjusted for potential baseline confounders (figure 1). Adverse events were compared using binominal probability test.

Results: At baseline, patients in trial A (n=97) were more often APCA positive (77% vs 56%) and less often had UA (2% vs 20%) than in trial B (n=610). Baseline DAS, HAQ and symptom duration were comparable.

At the first evaluation time point (median 3.0 (IQR 2.98-3.2) months in trial A, 4.0 (3.8-4.2) in trial B), DAS and HAQ had decreased significantly less in trial A (DAS β 0.500 (95% CI 0.276; 0.725), and HAQ 0.330 (0.189; 0.470) (figure 1). Fewer patients in trial A achieved DAS<1.6 (29% vs 63%) (adjusted OR 0.215 (95% CI 0.124; 0.373) and DAS \leq 2.4 (56% vs 81% (adjusted OR 0.249 (0.143; 0.435)). Presence of ACPA was positively associated with achieving DAS<1.6 in trial B, but not in trial A. Reported serious adverse events were 23 per 100 patient years in trial A and 8 in trial B (table 1). Table 1. Most frequently reported adverse events, per 100 patient years

	Trial A (n=97)	Trial B (n=610)	p
Malaise	42.9	9.45	0.000
Gastrointestinal symptoms	97.6	48.7	0.004
Hypertension	0.00	9.95	0.091
Hyperglycaemia (>7.8mmol/l)	0.00	8.46	0.130
Infections	46.9	39.8	0.582
Skin rashes	27.3	7.96	0.014
Hair loss	23.4	9.45	0.074
Headache	31.2	8.95	0.008
Depression/feeling sad	31.2	11.9	0.031
Bone marrow depression	15.6	0.00	0.000
High creatinine (above normal)	11.7	0.00	0.001
Liver enzymes (above normal)	35.1	22.4	0.229
Dizziness	3.90	5.47	0.837
Dyspnoea	0.00	3.48	0.432

Conclusion: In early arthritis patients, MTX with prednisone 60 mg/day tapered in 7 weeks to and continued at 7.5 mg/day was associated with better early clinical outcomes and fewer (serious) adverse events although slightly more hypertension and hyperglycaemia than MTX with prednisone 15mg daily tapered to nil in 10 weeks.

Disclosure: E. G. Brilman, None; J. A. van der Pol, None; P. H. de Jong, Pfizer Inc., 2; A. E. Weel, Pfizer Inc, 2; J. Hazes, Pfizer Inc, 2; T. W. J. Huizinga, BMS, 2, EU, 2, Arthritis Foundation, 2, IMI, 2, LUMC, 3, Abblynx, 5, Merck & Co., 5, UCB, Inc., 5, BMS, 5, Biotest AG, 5, Janssen, 5, Pfizer, Inc., 5, Novartis, 5, Roche, 5, Sanofi-Aventis, 5, Abbott, 5, Consulting Bioscience, 5, Galapagos, 5, Nycomed, 5, Boehringer, 5, Takeda, 5, Zydus, 5, Epirus, 5, Eli Lilly and Co., 5; C. F. Allaart, Abb Vie, 2.

Abstract Number: 548

Persistence in Low Disease Activity or Remission with Etanercept Monotherapy in Patients with Rheumatoid Arthritis: Results from the Corrona Registry

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Monotherapy with etanercept (ETN) maybe a viable therapeutic option for maintenance of patients with rheumatoidarthritis (RA) who prefer to eliminate potential burdens or side effects of combination therapy. Our objective was to compare persistence of low disease activity (LDA)/remission in patients with RA who were on combination therapy with ETN and a conventional synthetic disease-modifying antirheumatic drug (csDMARD; most commonly methotrexate) who then either discontinued the csDMARD or continued on combination therapy.

Methods: This analysis included RA patients from the Corrona registry during 10/1/2001–8/31/2017. ETN monotherapy (Mono) patients were initially treated with ETN + csDMARD combination therapy, achieved Clinical Disease Activity Index

(CDAI) LDA/remission (score ≤ 10), and discontinued the csDMARD (index visit). The index visit for the comparator combination therapy (Combo) group (patients who continued on combination therapy) was selected as the date that had a similar time interval from the initiation visit as the Mono group. Propensity score (PS) matching (1:2 without replacement) was used to ensure balanced groups and included variables selected a priori (baseline CDAI, RA duration, duration in LDA/remission before index) and variables not originally balanced between the Mono and Combo groups. Cox regression was used to compare persistence in LDA/remission between the groups, overall and at specific timepoints, adjusted for any covariates that remained imbalanced after PS matching. Patients were censored if disease activity increased to moderate or severe, ETN was discontinued, or a csDMARD was reinitiated (in patients in the Mono group).

Results: We identified 182 Mono and 403 Combo patients. After matching, 120 Mono and 207 Combo patients were eligible (45 on Mono had >3 years ETN before index date and could not be matched). After PS matching, characteristics at index visit were similar between groups except prednisone dose (mean [standard deviation] 6.2 [2.6] for Mono, 4.7 [3.4] for Combo; standardized difference 0.488). Models indicated that a substantial proportion of both Mono and Combo groups remained in LDA/remission through 24 months after the index date (Table). The overall persistence in LDA/remission between Mono and Combo groups was not statistically different ($P = 0.057$).

Conclusion: Approximately 3 of 4 patients with RA remained on ETN Mono and maintained LDA/remission for 2 years after csDMARD discontinuation. Although Combo persistence was numerically greater than Mono, the high level of persistence with ETN Mono following achievement of LDA/remission and discontinuation of csDMARD suggests that ETN Mono may be a viable option for patients who cannot adhere to or tolerate csDMARDs. Persistence in LDA/Remission*

Time after index visit	ETN Mono (N = 120)	ETN + csDMARD Combo (N = 207)
6 months	0.88	0.96
12 months	0.77	0.92
18 months	0.75	0.89
24 months	0.75	0.86

* Models were adjusted for sex, race, age group, insurance type, anti-cyclic citrullinated peptide antibody status, and prior csDMARD use.

Disclosure: D. A. Pappas, Corrona, LLC, 3, Novartis, 9; Y. Shan, Corrona, LLC, 3; T. Lesperance, Amgen Inc., 5; S. Rebello, Corrona, LLC, 3; E. Karis, Amgen Inc., 1, Amgen Inc., 3; G. Kricorian, Amgen Inc., 1, Amgen Inc., 3; W. Hua, Corrona, LLC, 3; N. A. Accortt, Amgen Inc., 1, Amgen Inc., 3; S. Stryker, Amgen Inc., 1, Amgen Inc., 3.

Abstract Number: 549

Unmet Treat-to-Target Goals with Available Targeted Immunomodulators in the Management of Rheumatoid Arthritis: Real World Evidence from the Corrona Registry

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Targeted immunomodulators (TIMs) have revolutionized the therapy of RA and made low disease activity (LDA) a realistic goal for patients. Given the multiple therapy options available, our goal was to quantify and describe the current state of unmet need by examining the proportion and characteristics of patients with moderate/high disease activity using real world registry data.

Methods: We identified patients in the Corrona RA registry ≥ 18 years old with ≥ 1 -year follow-up from 01/2012 to 06/2017. In a cross-sectional cut, we evaluated the percentage of patients with moderate or high disease activity (Clinical Disease Activity Index [CDAI] > 10) at the last registry visit. Then, we estimated the number of patients on continuous therapy (no interruption in therapy > 30 days) with a TIM ≥ 6 months before the last registry visit. Demographic/disease characteristics and treatment history were described. Patient reported outcomes (PROs) and disease activity in the 12 months before the last visit were assessed. PROs included mHAQ, pain, fatigue, Patient Global Assessment (PtGA), and morning (AM) stiffness duration. Percentages of patients with improvement \geq minimum clinically important difference (MCID) from index visit to last registry visit were estimated.

Results: Of 30,100 patients with ≥ 1 year of follow-up, 10,400 (35%) had CDAI >10 at the last registry visit. Of these 5,090 were on continuous therapy with a TIM ≥ 6 months. In this cohort, mean age was 61 years, 81% were female, 87% were white, mean duration of RA was 14 years, 69% and 58% were seropositive for RF and CCP, respectively. Mean CDAI was 21.2, mean mHAQ was 1.2; 35% of patients had high disease activity (CDAI >22), 88% reported having AM stiffness and in 56% its duration was >1 hr. Approximately 39%, 26%, and 16% of patients were treated with their first, second, and third TIM, respectively; 85% were on the same TIM for ≥ 12 months. Out of 5,090 patients, 3,625 patients had a registry visit within 12 months prior to their most recent visit (index visit). Mean PRO scores at index and last registry visits are shown in **Table 1**; $<25\%$ reported improvements \geq MCID in CDAI or PRO scores (**Table 2**).

Conclusion: For 35% of patients followed in the Corrona RA registry, LDA was not achieved. Half had been on a TIM >6 months. In most of these patients, disease activity remained high and patients had significant pain, fatigue, AM stiffness, and reduced physical function. These data clearly indicate that there is an unmet need for new effective therapies to help patients meet treat-to-target goals.

Table 1. PRO Measures in Patients on TIMs ≥ 6 Months

	Index Visita n=3,625	Last Visit n=5,090
mHAQ, mean \pm SD	1.1 \pm 0.7	1.2 \pm 0.7
Pain VAS, mean \pm SD	47.7 \pm 27.3	53.2 \pm 26.3
Fatigue VAS, mean \pm SD	50.6 \pm 28.3	55.0 \pm 27.8
Duration AM stiffness (min), mean \pm SD	90.3 \pm 170.0	105.0 \pm 202.2
Patients with AM stiffness, n (%)		
None	559 (15.7)	614 (12.2)
<30 min	517 (14.5)	704 (14.0)
30–60 min	636 (17.9)	902 (17.9)
>60 min	1836 (51.5)	2801 (55.5)

^a Registry visit ≥ 12 months before the last visit (9-15-month window was used, if there was >1 visit in the range, the visit closest to 12 months was the index visit).

Table 2. Patients Who Reported Improvement in CDAI or PROs \geq MCIDa From Index Visitb to Last Registry Visit

Outcome, n (%)	On TIM ≥ 6 months n=3,625
CDAI	707 (19.7)
mHAQ	652 (23.5)
Pain	789 (21.9)
Fatigue	612 (22.2)
PtGA	776 (21.5)

^a MCID was defined as change in CDAI >6 for patients starting in moderate disease activity, CDAI >12 for patients starting in high disease activity, decrease of ≥ 0.25 points for mHAQ, and decrease of 10 points for pain, fatigue and PtGA.

^b Registry visit ≥ 12 months before the last visit (9-15-month window was used, if there was >1 visit in the range, the visit closest to 12 months was the index visit).

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Disclosure: D. A. Pappas, Corrona, LLC, 3, Novartis, 9; N. Tundia, AbbVie Inc., 3, AbbVie Inc., 1; Y. Shan, Corrona, LLC, 3; H. J. Litman, Corrona, LLC, 3; J. Kremer, Corrona, LLC, 3, AbbVie Inc., 2, 5.

Abstract Number: 550

Biologic Discontinuation in Rheumatoid Arthritis: A Population Based Study 1999-2017

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SESSION INFORMATION

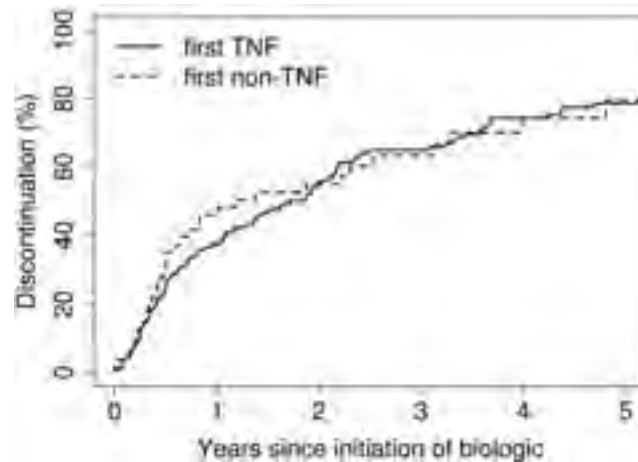
Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Discontinuation of biologic medications in rheumatoid arthritis (RA) can be used as a proxy for drug efficacy when direct measures of disease activity are not available. Recent data comparing the discontinuation rates of



different biologics, specifically tumor necrosis factor (TNF) vs. non-TNF, have been mixed. Further, most of the existing data on this topic comes from controlled trials or cohorts of referred patients. Our objective was to determine drug discontinuation rates for TNF and non-TNF biologics and identify predictors and indications for discontinuation in a population based cohort.

Methods: We retrospectively studied 606 patients with incident RA from 1999-2013 in a geographically well-defined population. All patients met the 1987 American College of Rheumatology classification criteria for RA and were followed until July 1, 2016. Discontinuation rates were estimated using cumulative incidence adjusted for the competing risk of death. Cox models were used to examine potential predictors of discontinuation.

Results: 156 patients were treated with at least one biologic medication (mean age at first biologic: 52 years; 71% female; median years from RA diagnosis to first biologic: 1.3; median follow-up: 6.0 years). Cumulative incidence for time to discontinuation for first TNF biologic was 38% at 1 year (95% confidence interval [CI], 30-47%) and 56% at 2 years (95% CI, 48-65%). For first non-TNF biologic, these values were 46% at 1 year (95% CI, 34-62%) and 55% at 2 years (95% CI, 42-71%). The most common reasons for discontinuation of any first biologic were inefficacy (43%), adverse effects (15%), and achievement of therapeutic goal (13%). The frequencies of each reason were similar between TNF and non-TNF treated patients. Potential predictive factors for discontinuation, including age, sex, years from RA diagnosis, rheumatoid factor/anti-citrullinated protein antibody positivity, smoking, and obesity, did not reach statistical significance with the exception of age ≥ 65 years, which was associated with increased risk for discontinuing non-TNF biologics (hazard ratio: 3.06; 95% confidence interval: 1.52-6.16).

Conclusion: Discontinuation rates were similar between TNF and non-TNF biologics. We did not identify any significant predictors of drug discontinuation apart from age in this population.

Disclosure: M. Richter, None; E. L. Matteson, Roche, 2, Bristol-Myers Squibb, 2, Up-To-Date, 7, Eli Lilly and Co., 2, Novartis, 2; J. M. Davis III, None; S. J. Achenbach, None; C. S. Crowson, None.

Abstract Number: 551

Leflunomide As a Concomitant DMARD Choice for the Biological Treatment Era of Rheumatoid Arthritis

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SESSION INFORMATION

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Background/Purpose: Methotrexate and leflunomide are anchor conventionalsynthetic DMARDs (csDMARDs) for rheumatoid arthritis (RA) treatment. Although methotrexate is the usual recommended concomitantcs DMARD along with biological DMARDs (bDMARDs), leflunomide is an alternative treatment option. Objective of this study was to describe leflunomide survival with concomitant bDMARDs use.

Methods: TReasure is a multicenter,web-based registry of RA and spondyloarthritis patients receiving targeted treatments. As of May 2018, 1401 RA patients were recorded. Age, sex, disease duration, BMI, initial bDMARDs, acute phase reactants, swollen and tender joint counts (28 joints), patient global assessment of disease activity, pain VAS, DAS-28, CDAI, and SDAI were recorded before starting bDMARDs. Patients starting a bDMARD were divided into two groups. Group 1 included patients receiving concomitant leflunomide with or without other csDMARDs combined with leflunomide. Group 2 consisted of patients using other concomitant csDMARDs or combinations that did not include leflunomide. DAS-28 disease state at the last recorded visit was compared. Retention rate of leflunomide was calculated by Kaplan-Meier analysis.

Results: Overall, 1401 patients, 444 of which (31.6%) using leflunomide with their first bDMARD were included. Demographic data and baseline disease activity are given in table 1. Initial bDMARDs in group 1 were anti-TNF drugs 275 (61.9%), abatacept 77 (17.3%), rituximab 59 (13.3%), tofacitinib 20(4.5%), and tocilizumab 13 (2.9%). At the baseline visit leflunomide was combined with hydroxychloroquine [266 (59.9%)],methotrexate [83 (18.7%)], or sulfasalazine [67 (15.1%)]. Median (Q1-Q3)duration of treatment with leflunomide was 28 (7-54) months. DAS-28 activity state at the last visit for group 1 and group 2 were; high in 8.8% vs. 8.5%, moderate in 36.7% vs. 33.3%, low in 20.2% vs. 18.0%, and remission in 34.3% vs. 40.1%respectively (p=0.31). Median (Q1-Q3) DAS-28 score at the last visit was not significantly different between groups [3.05 (2.31-3.96) vs. 2.86 (2.18-3.82), p=0.11]. Five-year survival of bDMARDs with concomitant leflunomide was around 80% (figure 1).

Conclusion: Leflunomide was one of the major concomitant csDMARDs in our RA biological registry. It was combined with both anti-TNF and other biologics. Retention rate of bDMARDs with concomitant leflunomide was satisfactory and disease activity with leflunomide was not significantly different from that with other synthetic DMARDs.

Figure 1. Leflunomide retention rate while using bDMARD

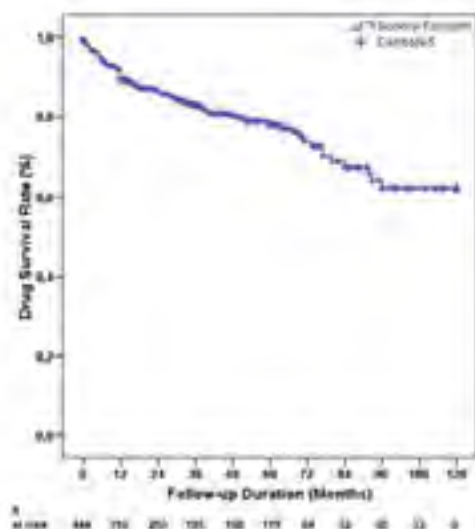


Table 1. Demographic features and baseline disease activity assessments

	bDMARDs with leflunomide n=444	bDMARDs without leflunomide n=957	P
Female, n (%)	368 (82.9)	746 (78.0)	0.033
Age	56 (43-61)	53 (39-61)	<0.001
Disease duration (years)	11 (7-16)	8 (5-15)	<0.001
Rheumatoid factor, (%)	76.7	62.9	<0.001
Anti-CCP, (%)	68.3	59.7	0.16
DAS	29.0 (24.8-32.9)	27.7 (24.1-32.1)	0.001
ESR	36 (20-51)	31 (16-53)	0.018
CRP	17.6 (7.5-35.8)	14.1 (6.3-39.9)	0.11
PGA	60 (50-80)	70 (50-80)	0.09
Pain	70 (50-80)	70 (50-80)	0.44
HAQ-DI	0.9 (0.50-1.35)	0.9 (0.55-1.35)	0.94
SJC	3 (2-5)	3 (2-5)	0.54
TJC	7 (4-10)	6 (3-10)	0.29
CDAI	28 (14-33)	25 (14-31)	0.33
SDAI	54 (33-68)	45 (26-66)	0.31
DAS-28	4.31 (3.74-5.72)	4.58 (3.85-5.76)	0.76

Data were given as median (Q1-Q3)

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Drug Tolerability and Discontinuation Reasons of 7 Biologics in 4466 Treatment Courses of Rheumatoid Arthritis -the Answer Cohort Study-

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Background/Purpose: Drug tolerability indicates both the patient's and doctor's satisfaction and useful summary measure of overall treatment effectiveness and toxicity. Although more than 5 years have passed since 7 biologics became available for patients with rheumatoid arthritis (RA) in our country, we still lack reliable evidence in directly compared drug tolerability and discontinuation reasons of 7 biologics in a real-world setting of RA.

Methods: In this 7-center, retrospective study, 4466 biologics treatment courses from 2009 to 2017 (female 82.7%, baseline age 57.6y, Bio naïve 63.6%, disease duration 7.8y, rheumatoid factor positivity 76.3%, anti-cyclic citrullinated peptide

antibody (ACPA) positivity 82.7%, disease activity score assessing 28 joints with CRP 3.9, modified Health Assessment Questionnaire 0.7, methotrexate 8.2 mg/week (limited to 16mg/week in our country), prednisolone 6.5 mg/day, number of each agent; tocilizumab (TCZ) 895, etanercept (ETN) 891, infliximab (IFX) 748, abatacept (ABT) 681, adalimumab (ADA) 558, golimumab (GLM) 464, and certolizumab pegol (CZP) 229) were included. Reasons for discontinuation of each biologic were analyzed and classified into 4 major categories: 1) inefficacy (both primary and secondary); 2) toxic adverse events (infection, skin or systemic reaction, hematologic, pulmonary, renal, cardiovascular complications and malignancies); 3) remission; and 4) nontoxic reasons (patient preference, change in hospital, desire for pregnancy, etc.). The judgment and reasons for discontinuation (only one reason were allowed to cite) depended on the decisions of each attending physician. Drug tolerability at 36 months were evaluate by Kaplan-Meier method for each discontinuation reasons, and adjusted by potent confounding factors (sex / age / ACPA positivity / switched biologics numbers) using a Cox proportional hazards model.

Results: The causes of 7 biologics treatment discontinuation at 36 months were as follows. Drug inefficacy (45.4%), nontoxic reasons (22.4%), toxic adverse events (21.0%), and remission (11.2%). Adjusted cumulative incidence rates of each agent and discontinuous reason at 36 months were as follows. Drug inefficacy (TCZ 22.5%, ABT 26.1%, GLM 32.3%, CZP 33.5%, ETN 37.7%, ADA 38.6%, and IFX 38.7%; Cox P < 0.001), toxic adverse events (CZP 6.2%, ABT 7.4%, ETN 11.1%, TCZ 11.8%, ADA 14.9%, GLM 16.4%, and IFX 17.0%; Cox P = 0.0049), and remission (ETN 3.1%, ABT 4.8%, CZP 5.3%, TCZ 5.8%, GLM 6.8%, ADA 10.2%, and IFX 10.7%; Cox P = 0.0018). Overall adjusted tolerability excluding nontoxic reasons and remission were ABT 68.5%, TCZ 68.3%, CZP 62.3%, GLM 56.5%, ETN 55.4%, ADA 52.2%, and IFX 50.9% (Cox P < 0.001).

Conclusion: TCZ and ABT showed lower inefficacy and higher overall retention, ABT and CZP showed lower toxic adverse events, and ADA and IFX showed higher bio-free induction due to remission compared to other biologics in background-adjusted models. These novel findings may contribute to adequate biologics selection in the clinical practice of RA.

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Channeling to Treatment and Associated Changes in Disease Activity Over 12 Months in Patients With RA Treated With Abatacept Versus Other DMARDs in Real-World Community Practice Settings

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Background/Purpose: Abatacept (ABA), a selective T-cell co-stimulatory modulator, has shown efficacy similar to TNF inhibitors (TNFi) for RA management in clinical trial settings, but different patient (pt) subtypes have shown a differential response to treatments in real-world and clinical trial settings. Additional data comparing the characteristics and associated clinical responses in pts receiving ABA versus other DMARDs in real-world community practice settings are needed.

Methods: We analyzed data from 24,602 pts with RA exposed to DMARDs from January 1, 2014 to September 30, 2017 in the United Rheumatology Database, which provides electronic medical record data from 120 community-based rheumatology providers. Baseline (BL) differences in demographics, disease activity and laboratory measurements were analyzed descriptively between pts receiving ABA versus TNFi, conventional (c)DMARDs and biologic (b) or targeted synthetic (ts)DMARDs of other mechanisms of action (other b/tsDMARDs) as first- or later-line therapy. Mean changes from BL to Year 1 (using records dated closest to Year 1) in CDAI scores were assessed using multivariate linear regressions adjusting for BL covariates (age, sex, smoking status, BMI, Charlson Comorbidity Index, CDAI score and number of prior treatments). Exposure was treated similarly to an intent-to-treat analysis (first observation carried forward).

Results: At BL, ABA pts (vs all other DMARD pts) had higher low- and high-density lipoprotein levels, and were more likely to have a history of type 1 or 2 diabetes (Table 1). ABA pts also had higher BL disease activity (CDAI; mean [SD]: 20.3 [13.0]) versus other b/tsDMARD (19.9 [13.4]), TNFi (18.1 [13.2]) and cDMARD pts (14.4 [12.4]; Table 1). After adjusting for BL covariates, the reduction in least square mean (LSM) CDAI from BL was greater in ABA pts (−5.6) than other b/tsDMARD pts (−3.4); this difference suggested a trend toward significance (2.2 [95% CI: −0.2, 4.6]; p=0.07). The reduction in LSM CDAI was comparable between ABA and TNFi pts (Table 2).

Conclusion: Pts with RA receiving abatacept (vs other DMARDs) in community practice settings tend to have higher disease activity and a history of diabetes, which have been associated with worse clinical response to treatment. Nonetheless, mean changes in disease activity from BL to Year 1 in pts receiving abatacept versus other b/tsDMARDs were larger in magnitude, although the difference was not statistically significant. Additional analyses with a larger pt population are warranted. Writing support provided by Bu Reinen, PhD (Caudex), funded by Bristol-Myers Squibb.

Table 1. Baseline Characteristics of Patients With RA in the United Rheumatology Database*

Baseline characteristics	Abatacept	Other b/tsDMARD	TNFi	cDMARD
n	3584	3481	7711	9826
Age, years, mean (SD)	61.0 (13.5)	59.7 (13.2)	59.4 (13.8)	63.5 (13.9)
Sex, n (%)				
Female	2921 (81.5)	2804 (80.6)	5812 (75.4)	7376 (75.1)
History of smoking, n (%)				
No	706 (19.7)	824 (23.7)	1511 (19.6)	2116 (21.5)
Yes	994 (27.7)	1148 (33.0)	2018 (26.2)	2826 (28.8)
Unknown	1884 (52.6)	1509 (43.3)	4182 (54.2)	4884 (49.7)
BMI, kg/m ²				
n	2094	2170	4364	5142
Mean (SD)	30.3 (6.8)	30.1 (6.7)	29.7 (6.6)	29.1 (6.1)
Diabetes, n (%)	406 (11.3)	288 (8.3)	609 (7.9)	533 (5.4)
Hypertension, n (%)	881 (24.6)	943 (27.1)	1727 (22.4)	2050 (20.9)
Charlson Comorbidity Index				
n	3584	3481	7711	9826
Mean (SD)	1.0 (1.4)	1.0 (1.2)	0.8 (1.1)	0.6 (0.6)
HDL				
n	54	111	60	52
Mean (SD)	62.0 (20.4)	60.5 (21.8)	57.1 (17.2)	58.9 (16.8)
LDL				
n	56	102	54	40
Mean (SD)	110.0 (38.4)	106.4 (32.8)	102.5 (32.9)	100.1 (37.9)
RF titer				
n	108	91	193	467
Mean (SD)	73.1 (142.4)	99.9 (127.8)	75.9 (114.4)	65.2 (109.7)
ACPA titer ≥20				
n	32	31	97	175
Mean (SD)	109.7 (138.4)	87.9 (64.5)	103.6 (93.6)	84.7 (77.5)
RAPID3 (0–30)				
n	1049	966	1678	1679
Mean (SD)	8.3 (6.4)	8.3 (6.5)	7.3 (6.3)	6.2 (5.6)
CDAI				
n	559	564	820	564
Mean (SD)	20.3 (13.0)	19.9 (13.4)	18.1 (13.2)	14.4 (12.4)
Prior RA treatment (United Rheumatology records only), n (%)				
0	1627 (45.4)	1478 (42.5)	4047 (52.5)	7866 (80.1)
1	883 (24.6)	962 (27.6)	2519 (32.7)	1662 (16.9)
≥2	1074 (30.0)	1041 (29.9)	1145 (14.8)	298 (3.0)

* Other b/tsDMARDs: infliximab, etanercept, adalimumab, certolizumab pegol and golimumab; TNFi: tocilizumab, rituximab and tofacitinib; cDMARD: methotrexate, sulfasalazine, azathioprine, tacrolimus, gold thiomalate, leflunomide, aurothioglucose, auranofin, cyclosporine, penicillamine, cyclophosphamide and hydroxychloroquine
ACPA=anti-citrullinated protein antibody; b/tsDMARD=biologic or targeted synthetic DMARD; cDMARD=conventional DMARD; HDL=high-density lipoprotein; LDL=low-density lipoprotein; RAPID3=Routine Assessment of Patient Index Data 3; TNFi=TNF inhibitor

Table 2. Changes in CDAI Over 12 Months in Patients With RA**†

	n	Baseline, LSM (95% CI)‡	Year 1, LSM (95% CI)‡	Change from baseline, LSM (95% CI)‡§	Difference in change, LSM (95% CI)‡§	p value
Abatacept	164	21.0 (18.5, 23.5)	13.6 (11.7, 15.6)	−5.6 (−7.4, −3.8)	Ref	Ref
Other b/tsDMARD	108	19.8 (17.0, 22.6)	15.5 (13.3, 17.7)	−3.4 (−5.5, −1.4)	2.2 (−0.2, 4.6)	0.07
TNFi	180	18.8 (16.4, 21.1)	12.5 (10.7, 14.3)	−6.2 (−7.8, −4.5)	−0.5 (−2.7, 1.7)	0.64
cDMARD	116	16.0 (13.2, 18.9)	12.3 (10.0, 14.5)	−5.6 (−7.7, −3.5)	0.0 (−2.6, 2.7)	0.98

* Includes patients who had CDAI measurements at both baseline and Year 1

† Other b/tsDMARDs: infliximab, etanercept, adalimumab, certolizumab pegol and golimumab; TNFi: tocilizumab, rituximab and tofacitinib; cDMARD: methotrexate, sulfasalazine, azathioprine, tacrolimus, gold thiomalate, leflunomide, aurothioglucose, auranofin, cyclosporine, penicillamine, cyclophosphamide and hydroxychloroquine

‡ Calculated by multivariate linear regression adjusted for age, sex, smoking status, BMI, Charlson Comorbidity Index and number of prior treatments

§ Further adjusted for baseline CDAI

b/tsDMARD=biologic or targeted synthetic DMARD; cDMARD=conventional DMARD; LSM=least square mean; TNFi=TNF inhibitor

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Abstract Number: 554

Are There Any Associations between ANA Development and Poor Treatment Response to Bdmards in RA Patients?

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Background/Purpose: It has been well known that anti-TNF- α treatment for RA patients is associated with ANA development. We previously reported that ANA development along with ANA levels at base line were associated with poor outcomes of infliximab (IFX)(1). However, no replication studies have been reported. In addition, whether the findings are true to general biologic DMARDs (bDMARDs) is uncertain. Here, we evaluate an association between poor treatment response and ANA development during bDMARDs treatment in RA patients and analyze correlates of ANA development.

Methods: Japanese RA patients treated with (n=657) or without (n=211) bDMARDs (IFX, etanercept ETN, adalimumab ADA, golimumab GLM, certolizumab pegol CZP, tocilizumab TCZ, abatacept ABT) as a first line bDMARD were enrolled from a single center cohort. The study participants were not registered in the previous study (1). ANA was measured by indirect immunofluorescence assays at multiple time points of treatment. We conducted multiple logistic linear regression analysis to assess effects of ANA development on treatment outcomes. We further analyzed correlates of ANA development by using patients with RA who were treated by MTX but not by bDMARDs as controls.

Results: ANA development (≥ 2 times baseline levels) at 3 months and at 6-12 months after bDMARDs initiation were significantly associated with insufficient response within a year (odds ratio (OR)=3.51, p=0.020) and between 12 and 24 months (OR=3.16, p=0.038), respectively. The associations remained significant after conditioning on each bDMARD use (OR=3.16-3.56, p<0.05), indicating the observed association was not limited to IFX use. The use of IFX was a risk for ANA development (OR=6.36, p<0.001), and the use of other TNF- α inhibitors (TNFi) also showed the same trends as IFX use (OR=1.68, p=0.214). On the other hand, the use of non-TNFi bDMARDs was not associated with ANA development (OR=0.792, p=0.675).

Conclusion: ANA development could be a marker of poor treatment response in RA patients undergoing bDMARDs treatment. Undefined common factors among RA patients treated with bDMARDs might influence ANA development and subsequent poor treatment outcome.

Reference:

1. Yukawa N, Fujii T, Kondo-Ishikawa S, Yoshifuji H, Kawabata D, Nojima T, et al. Correlation of antinuclear antibody and anti-double-stranded DNA antibody with clinical response to infliximab in patients with rheumatoid arthritis: a retrospective clinical study. *Arthritis Res Ther.* 2011;13(6):R213.

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Three Year Outcomes of Patients with Elderly-Onset Rheumatoid Arthritis Treated with a Therapeutic Strategy Targeting Low Disease Activity, and Impact of Adverse Events on Physical Function

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

Background/Purpose: The aim of this study was to evaluate three year outcomes of patients with elderly-onset RA (EORA) who were treated with a therapeutic strategy targeting low disease activity (LDA), and clinical factors associated with physical dysfunction in patients who achieved LDA.

Methods: Data of 197 MTX-naïve EORA (mean age 74.9) from a prospective, monocentric registry were analyzed. Treatment was adjusted targeting LDA defined by DAS28-ESR or simplified disease activity index (SDAI). Treatment was initiated with non-biologic DMARDs (nbDMARDs), followed by biologic DMARDs such as TNF inhibitors, tocilizumab, or abatacept. Primary outcomes were obtained from SDAI and the HAQ disability index (HAQ-DI). Serious adverse events (SAEs) during three years of observational period were assessed at all visits. Associated factors of physical dysfunction (HAQ-DI >0.5) in patients who achieved SDAI-LDA at week 156 or at dropout were examined using multivariate logistic regression models.

Results: MTX was administered in 167 (85%) of the 197 patients, and dose-dependent adverse drug reactions were observed in 100 patients, and 158 patients received mean 8.5 mg/week of MTX at week 24, and 35% of them received a biologic DMARD with or without MTX at week 52, 36% at week 104, and 33% at week 156. Median dose of 3.5mg/day of prednisolone (PSL) were administered with DMARDs in 17% of the patients at week 156. Adherence to the treat-to-target (T2T) strategy was observed in 81%, 87%, 91% at week 24, 52, and 104 weeks, respectively. At week 56, 104, and 156, SDAI-LDA was achieved in 73%, 82%, and 88% by last observation carried forward analysis, SDAI-remission in 36%, 50%, and 56%, and HAQ-DI ≤0.5 in 68%, 71%, and 72%, respectively. Clinically relevant radiological progression (CRRP: Δ modified total sharp score [mTSS] /year >the smallest detectable change [2.1]) was observed in 28% at week 52. Infection requiring hospitalization occurred in 31 patients during the observational period, extra-articular manifestations in 13, ischemic heart disease in 9, malignancy in 11, and bone fracture in 20. Twenty-nine (15%) of the 197 patients dropped from the study for aging (dementia or sarcopenia) in 11, patient decision in 6, exacerbation of interstitial lung disease in 5, infection in 4, malignancy in 2, and sudden death in 1, and 18 of the 29 patients achieved LDA at dropout. HAQ-DI ≤0.5 was not achieved in 46 of the 173 patients who achieved LDA at week 156 or at dropout. Multivariate analysis showed older age (odds ratio (OR) 1.15, 95% confidence interval (CI) 1.07-1.23), SAEs occurred during the observational period (OR 3.96, 95%CI 1.76-8.92), and higher SDAI (OR 1.16, 95%CI 1.02-1.33) were significantly associated with risk of non-achievement of HAQ-DI ≤0.5 in patients who achieved SDAI-LDA. Comorbidities at baseline, mTSS at baseline, and CRRP at week 52 were not significant. Infection requiring hospitalization, ischemic heart disease, and bone fracture were significant among the SAEs.

Conclusion: The patients with EORA can achieve clinical remission and normal physical function by therapeutic strategy targeting LDA. SAEs under T2T strategy of EORA have great impact on physical dysfunction in patients who achieved treatment goals.

Disclosure: T. Sugihara, Chugai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co. Ltd., Mitsubishi-Tanabe Pharma Co., Astellas Pharma Inc., Bristol Myers Squibb K.K., Pfizer Inc. and Abbvie Japan Co., Ltd., 5; T. Ishizaki, None; H. Baba, None; T. Matsumoto, None; S. Iga, None; T. Kusuda, None; M. Tsuchida, None; M. Kamiya, None; Y. Komiya, None; F. Hirano, Chugai Pharmaceutical Co., Ltd.; Ono Pharmaceuticals; Mitsubishi Tanabe Pharma Co.; UCB Japan; CSL Behring; Towa Pharmaceutical Co., Ltd.; Abbvie Japan Co., Ltd.; Japan Blood Products Organization; Ayumi Pharmaceutical Co.; Sumitomo Dainippon Pharmaand, a, 2, 5; T. Hosoya, None; N. Miyasaka, None; M. Harigai, Chugai Pharmaceutical Co. Ltd., Teijin Pharma Co. Ltd., 2, 5.

Treatment Initiation and Duration in DMARD Naïve Rheumatoid Arthritis Patients: Analysis of US Health Plan Claims

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: The ACR treat-to-target approach for rheumatoid arthritis (RA) recommends regular assessments of disease activity and adjustment of medication regimen until efficacy goals are met. Given recent advances in pharmacologic therapy, this study assessed recent treatment patterns in RA patients (pts) who had newly initiate da DMARD.

Methods: Adult pts with ≥2 claims for RA, initiating first DMARD between 1/2012–9/2016 (index date; ID) were identified in fully-adjudicated commercial medical and pharmacy health insurance claims, including self-insured, full-risk, and Medicare policies for approximately 40 million lives annually. Those with 12-months continuous enrollment pre- and post-ID and without DMARD claims 12 months pre-ID were selected. Initial utilization of conventional synthetic DMARDs (csDMARDs), TNF inhibitors (TNFi), anti-IL6 pathway antibodies, other biologic DMARDs (bDMARDs), and JAK inhibitors (JAKi), as monotherapy and in combination with csDMARDs, was summarized with descriptive statistics. Median therapy duration was assessed with Kaplan-Meier method. End of treatment was defined as drug discontinuation, switch to a new therapy, or addition of another DMARD.

Results: Among 26,808 identified pts (74.2% female; mean age 51.9±11.0 yrs), 97.7% of pts initiated monotherapy and 2.3% started combination therapies. The most commonly-prescribed monotherapies were csDMARD (91.3%) and TNFi (6.6%). The most commonly-prescribed treatments in combination with csDMARDs included TNFi (88.0%) and other bDMARDs (7.3%). The median duration of csDMARD monotherapy was 230 days. The median treatment duration (combination vs monotherapy) was: 225 vs. 206 days (TNFi), 227 vs. 203 days (anti-IL6), 198 vs. 182 days (other bDMARDs), and 347 vs. 301 days (JAKi). JAKi treatment had the longest therapy duration when combined with csDMARDs (347 days), and other therapies lasted for a median of 182-230 days. As monotherapy, JAKi duration was 301 days, and other therapies lasted for a median of 198-227 days.

Conclusion: Real-world data from US longitudinal healthcare claims showed that in RA pts newly initiating DMARDs, the median duration of therapy was less than a year, suggesting a need for a treatment with improved response durability. Duration of JAKi therapy was longer than median duration of other therapies. Further research is needed to determine the reasons for the longer persistence of JAKi therapy and why persistence is low with RA therapies overall.

Therapy initiated by DMARD naïve patients	N	% within monotherapy and combination therapy subgroups	Median length of therapy (days) ¹	% of subjects still on index therapy at day 360	Mean Age (SD)	Female (N, %)	Mean CCI (SD)
Monotherapy	26182		227	38.3%	51.9 (11.0)	19429 (74.2)	1.3(1.1)
initiating csDMARD	23852	91.1%	230	38.6%	52.0 (10.9)	17730 (74.3)	1.3(1.1)
initiating TNFi	1739	6.6%	205	35.8%	50.6 (12.2)	1237 (71.1)	1.5(1.0)
initiating anti-IL6	99	0.4%	196	30.3%	54.5 (11.0)	75 (75.8)	1.5(1.0)
initiating other bDMARDs	398	1.5%	182	32.7%	53.2 (11.8)	312 (78.4)	1.6(1.2)
initiating JAKi	94	0.4%	301	46.8%	52.2 (9.3)	75 (79.8)	1.7(1.1)
		100.0%					
Combination therapy	626		224.5	37.1%	51.1 (11.0)	460 (73.5)	1.3 (1.0)
initiating csDMARD in combination with TNFi	551	88.0%	225	37.0%	51.2 (10.9)	401 (72.8)	1.3 (0.9)
initiating csDMARD in combination with anti-IL6	16	2.6%	227	43.8%	48.2 (14.7)	15 (93.8)	1.1(0.9)
initiating csDMARD in combination with other bDMARDs	46	7.3%	198	32.6%	49.2 (11.5)	37 (80.4)	1.5(1.5)
initiating csDMARD in combination with JAKi	13	2.1%	347	46.2%	54.7 (8.8)	7 (53.9)	1.7 (1.0)
		100.0%					
Total monotherapy + combination therapy ²	26808				51.9 (11.0)	19889 (74.2)	1.3(1.1)

¹ Median days were derived from Kaplan-Meier analysis. LOT = length on therapy. Median days on 1st LOT were longer for patients on combination than on monotherapy (p<0.0001).

² One patient initiating csDMARD in combination with other biologic DMARDs and TNFi, two patients initiating other biologic DMARDs in combination with TNFi, and two patients initiating TNFi in combination with JAKi were removed from the analysis due to insufficient sample size to form cohorts.

Abstract Number: 557

The Impact of Combination with Conventional Synthetic DMARDs on Drug Retention and Clinical Effectiveness of Tofacitinib, Anti-Tumor Necrosis Factor Therapy and Biologics with an Alternative Mode of Action in Patients with Rheumatoid Arthritis. a Cohort Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Co-medication with conventional synthetic DMARDs (csDMARDs) is currently recommended with all targeted therapies (bDMARDs and tsDMARDs) for the management of rheumatoid arthritis (RA). However, targeted DMARDs are often used as monotherapy,

Primarily because of intolerance to methotrexate and other csDMARDs. Our aim was to analyze the impact of combination with csDMARDs on the effectiveness of tofacitinib (TOFA), Tumor Necrosis Factor inhibitors (TNFi) and biologic agents with an alternative mode of action (OMA, abatacepter tocilizumab) in a large cohort of patients with RA.

Methods: In an observational cohort study (SCQM), we included all RA patients initiating a new therapy with TOFA, TNFi, or OMA between August 2013 and March 2018, who had at least one follow-up visit. We analyzed whether the effectiveness of TOFA, TNFi and OMA was modified by concomitant csDMARDs therapy at baseline (COMBI) compared to monotherapy (MONO). The primary outcome was drug maintenance, defined as the time from initiation to discontinuation of treatment. A secondary outcome was low disease activity (LDA) state based on the CDAI at 12 months. We used Kaplan–Meier curves to display drug maintenance and Cox proportional hazard models to analyze the hazard for treatment discontinuation. We adjusted for potential confounders (gender, age, disease duration, seropositivity, BMI, smoking, baseline CDAI number of distinct previous bDMARDs). We applied multiple imputation to account for missing baseline covariate data.

Results: A total of 2503 treatment courses were included, 436 on TOFA, 1244 on TNFi, and 823 on OMA. On average, patients on TNFi were younger, less prior bDMARD and received more COMBI. MTX was by far the most commonly prescribed COMBI with all three targeted therapies (88%-90%). (Table)

In multivariable adjusted models, TOFA maintenance was not different in MONO- compared to COMBI-therapy (Hazard Ratio (HR)_{MONO}: 1.05 (95%CI: 0.77 - 1.45)), nor was OMA maintenance (HR_{MONO}: 1.04 (95%CI: 0.84 - 1.30)). On the contrary, TNFi maintenance was significantly decreased in MONO (HR_{MONO}: 1.28 (95%CI: 1.07 - 1.53)).

Low disease activity (LDA) at 12 months was achieved in 47%, 44% and 40% of patients treated respectively with TOFA, OMA or TNFi. The likelihood of reaching LDA with TOFA or with OMA was not significantly modified by MONO (OR_{MONO}: 1.13 (95%CI: 0.70 - 1.83), OR_{MONO}: 1.04 (95%CI: 0.84 - 1.30), respectively), while the likelihood of LDA was significantly reduced for TNFi in MONO (OR_{MONO}: 0.66 (95% CI: 0.49- 0.89)).

Conclusion: In this 'real world' cohort, combination therapy with csDMARDs did not improve drug-maintenance and effectiveness of TOFA or OMA, whereas TNFi appeared to require comedication for optimal treatment results. Our results suggest that usefulness of concomitant csDMARDs varies according to the type of targeted therapy.

Table – Patient and disease characteristics at treatment initiation

	TOFA (N=436)	TNFi (N=1244)	OMA (N=823)	<i>p</i> value
Female sex [%]	80	75	76	NS
Age [yrs]	59	54	59	< 0.001
Tobacco Smoking ever [%]	31	30	27	NS
BMI [kg/m ²]	26.5	26	26.3	NS
Seropositivity [%]	69	66	75	< 0.001
Disease duration [yrs]	12	9	11	< 0.001
CDAI (bl)	22	21	21	NS
Concomitant csDMARDs (@ bl)				<0.001
None [%] (= MONO)	45	29	40	
Including MTX [%]	49	64	53	
Other csDMARDs [%]	6	7	7	
Concomitant csDMARDs (@ 1 yr)				<0.001
None [%] (= MONO)	49	29	44	
Including MTX [%]	42	64	49	
Other csDMARDs [%]	9	7	6	
Prior bDMARD use				<0.001
None [%] (= Bio-naïve)	33	60	38	
1 prior bDMARD [%]	26	25	32	
≥ 2 prior bDMARDs [%]	41	15	30	

Disclosure: A. Finckh, Pfizer, Inc., 2, 8, MSD, 2, 8, Roche, 8, AB2 Bio Ltd., 5, Eli-Lilly, 5, 8, BMS, 7, AbbVie Inc., 5; C. Tellenbach, None; A. Scherer, None; B. Moeller, None; A. Ciurea, None; I. von Mühlhnen, None; C. Gabay, AB2 Bio, Pfizer and Roche, 2, AB2 Bio, AbbVie, Bristol Myers Squibb, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, UCB, 5, 8; D. Kyburz, None; R. Mueller, Pfizer, Inc., 5; P. Hasler, Pfizer, Inc., 5; P. Zufferey, None.

Abstract Number: 558

Major Reduction of Ultrasound Detected Synovitis during Subcutaneous Tocilizumab Treatment; Results from a Multicenter 24 Weeks Study of Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Ultrasound (US) is sensitive for detection of synovitis (assessed by Grey Scale (GS) and power/color Doppler). Presence of Doppler activity is found to predict erosive progression. Clinical disease activity in rheumatoid arthritis (RA) is usually evaluated by Composite Disease Activity Scores (CDAS) like CDAI, SDAI and DAS28. Treatment with subcutaneous tocilizumab (TCZ-SC), an IL-6 inhibitor, causes rapid fall in ESR and CRP. Thus, use of CDAS, which includes ESR or CRP, may not give correct information about the inflammatory activity, while this could potentially be better reflected by use of US. The present purpose was to explore the longitudinal response of TCZ-SC on US synovitis in comparison with CDAS in patients with RA.

Methods: This is a multi-country (Denmark, Finland, Norway, Sweden), open-label, single-arm study (part of TOZURA (1)), enrolling patients (pts) with inadequate response to csDMARDs. Pts received TCZ-SC 162 mg qw for 24 weeks as monotherapy or in combination with a csDMARD. Stable oral NSAIDs and corticosteroids (CS) (≤10 mg/day prednisone or equivalent), were allowed. US examination (36 joints and 4 tendons, scored according to the Norwegian US atlas (2)) and clinical (examiner's and patient's global VAS, 28 TJC, 28 SJC and ESR/CRP) were performed at baseline, 4, 12 and 24 weeks. Sum scores of GS/Doppler and CDAS were calculated, and remission by US (defined as sum score Doppler of 0, 1, 2 or 3) and CDAS (including Boolean) was explored.

Results: 110 pts were followed with US assessments (83% female, mean (SD) age 55.6 (12.1) years, RA duration 8.7 (9.5) years, 81% anti-CCP positive and 62% with erosive disease). Already after 4 weeks US, clinical variables and CDAS

decreased significantly ($p < 0.001$), and ESR/CRP reached normal levels (table 1). At 24 weeks, CDAI, SDAI and Boolean remission was found in 34.7%, 33.7% and 27.4%, while DAS28(ESR), being more influenced by low ESR, showed remission in 83.5%. US showed major reduction of synovitis after 24 weeks, where stringent Doppler remission criteria showed remission in more than half of the patients (sum score 0; 53.3%, 1; 65.6%, 2; 75.6% and 3; 78.9%).

Conclusion: The different CDAS showed large discrepancies in number of patients in remission. US detected synovitis was markedly reduced with the initial effect seen already after 4 weeks, and with more than half of the patients achieving absence of Doppler activity after 24 weeks.

References: 1. EULAR 2017 Abstract SAT0199
2. Hammer HB et al, ARD, 2011

	Baseline Median (IQR) n=110	4 weeks Median (IQR) n=102	12 weeks Median (IQR) n=95	24 weeks Median (IQR) n=91
Sum score GS	21 (13-36)	16 (8-30)	12 (5-21)	9 (3-19)
Sum score PD	8 (2-20)	4 (1-10)	1 (0-4)	0 (0-2)
Tender joint count	8 (5-12)	4 (1-9)	2 (0-5)	1 (0-3)
Swollen joint count	6 (2-10)	2 (0.5-6)	1 (0-2.5)	0 (0-2)
Patient's global VAS (0-100)	55 (36-70)	32 (18-49)	16 (7-31)	12 (4-28)
Assessor's global VAS (0-100)	35 (25-49)	17 (11-31)	10 (5-18)	5 (2-11)
CRP (mg/L)	5.5 (2.6-13.1)	0.2 (0.2-0.4)	0.2 (0.2-0.6)	0.2 (0.2-0.4)
ESR (mm/h)	21 (12-34)	4 (2-7)	3 (2-5)	3 (2-5)
DAS28(ESR)	5.0 (4.3-5.8)	3.1 (2.1-3.8)	2.1 (1.5-2.9)	1.6 (1.1-2.4)
CDAI	23.8 (17.1-31.2)	12.9 (7.3-21.9)	7.2 (3.6-11.4)	4.3 (1.8-9.8)
SDAI	29.8 (21.1-45.0)	13.3 (7.6-23.2)	7.7 (3.8-12.6)	4.6 (2.2-10.2)

Disclosure: H. B. Hammer, AbbVie, Novartis, BMS, Pfizer, UCB, Roche, MSD, 8; I. M. J. Hansen, None; P. Järvinen, None; M. Leirisalo-Repo, None; M. Ziegelsch, AbbVie Inc., 8; B. Agular, Roche, 3; L. Terslev, Danish Rheumatism Association, 2, 8, AbbVie Inc., Roche, Novartis, 8.

Abstract Number: 559

Radiographic Progression Based on Baseline Demographics and Disease Characteristics from Three TNF-Alpha Inhibitor Biosimilar Studies in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

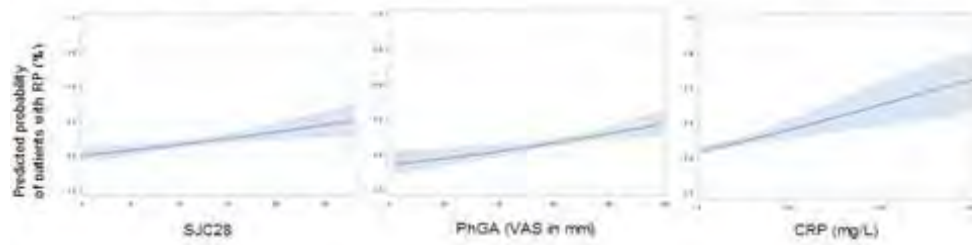
Session Type: ACR Poster Session A

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

Background/Purpose: SB4, SB2, and SB5 are biosimilars of reference etanercept, infliximab, and adalimumab, respectively. Radiographic data were assessed using the modified Total Sharp Score (mTSS) at week 0 and final week (week 52 for etanercept and adalimumab and week 54 for infliximab) in phase III biosimilar studies.¹⁻³ The purpose of this analysis is to identify baseline demographics and disease characteristics that are associated with radiographic progression (RP) and build a matrix model to show the proportion of patients with RP by the identified baseline factors.

Methods: Patients who had radiographic data were pooled. RP was defined as a change in mTSS > 0 from week 0 to final week. The three baseline factors that had the strongest Pearson's correlation coefficient with the change in mTSS were selected, and univariate logistic regression analysis was performed to assess the association between each baseline factor and predicted probability of patients with RP. Then, multivariate logistic model was fitted to develop a matrix that shows the proportion of patients with RP in each tertile of baseline factors.

Figure 1. Predicted Probability (with 95% Confidence Limits) of Patients with RP Based on SJC28, PGA, and CRP



CRP, C-reactive protein in mg/L; PhGA, physician global assessment; SJC28, 28 swollen joint count; VAS, visual analogue scale

Figure 2. Matrix Model of the Proportion of Patients with RP based on SJC28, CRP and PhGA

SJC28	>17	11-17	<10	CRP (mg/L)	PhGA (VAS in mm)
	33 (14, 49)	28 (24, 32)	15 (9, 21)		
	28 (12, 40)	28 (24, 32)	15 (9, 21)		
	16 (10, 27)	28 (24, 32)	15 (9, 21)		
CRP (mg/L)	>17	11-17	<10	CRP (mg/L)	PhGA (VAS in mm)
	33 (14, 49)	28 (24, 32)	15 (9, 21)		
	28 (12, 40)	28 (24, 32)	15 (9, 21)		
	16 (10, 27)	28 (24, 32)	15 (9, 21)		
PhGA	>17	11-17	<10	CRP (mg/L)	PhGA (VAS in mm)
	33 (14, 49)	28 (24, 32)	15 (9, 21)		
	28 (12, 40)	28 (24, 32)	15 (9, 21)		
	16 (10, 27)	28 (24, 32)	15 (9, 21)		

Data are represented in % (95% CI)

CRP, C-reactive protein in mg/L; PhGA, physician global assessment; SJC28, 28 swollen joint count; VAS, visual analogue scale

Color scheme: green < 20%, yellow 20-30%, and red > 30% predicted probability of patients with RP

Table 1. Baseline Demographics and Disease Characteristics

	Total Number of Patients (n=1371)	p-value of Pearson's Correlation Coefficient with the Change in mTSS
Baseline mTSS	37.9 (36.8)	NA
Age, yr	51.4 (12.0)	0.38
Female, n (%)	1120 (81.7%)	0.24
RA Disease duration, yr	5.9 (4.9)	0.94
MTX dose, mg/week	15.2 (4.4)	0.94
SJC28	11.0 (5.3)	0.0041
PhGA	15.1 (8.3)	0.13
HAQ-DI	1.3 (0.6)	0.03
DAS28 (ESR)	4.3 (0.8)	0.02
SDAI	19.9 (11.8)	0.004
CDAI	28.5 (11.4)	0.009
PhGA, mm	61.9 (23.5)	0.048
Patient global VAS, mm	61.9 (23.6)	0.13
Patient pain VAS, mm	62.0 (23.5)	0.13
CRP, mg/L	13.3 (19.1)	0.033
ESR, mm/h	44.4 (20.4)	0.12
RP positive n (%)	1038 (75.4%)	0.73

NA, Not applicable; this parameter is not applicable.

CRP, C-reactive protein in mg/L; DAS28, disease activity score by 28 joints; ESR, erythrocyte sedimentation rate; SJC28, 28 swollen joint count; HAQ-DI, Health Assessment Questionnaire; MTX, methotrexate; PhGA, physician global assessment; SJC28, 28 swollen joint count; SDAI, Simplified Disease Activity Index; VAS, visual analogue scale; VAS, mm.

Results: A total of 1371 patients had radiographic assessments. The mean change in mTSS was 0.41 and the number of patients who had RP was 376 patients (27.4%). The swollen joint count 28 ([SJC28], p -value = 0.0041), C-reactive protein ([CRP], p -value=0.033), and Physician Global Assessment ([PhGA], p -value = 0.048) had the strongest correlation with RP (Table 1). Predicted probability of patients with RP as a function of SJC28, CRP, and PhGA is displayed in Figure 1. The proportion of patients with RP increased as baseline levels of each factor worsened (Figure 2). The proportion of patients with RP was greatest (37%, 95%CI: 32, 43) in the highest tertile of each category (SJC28 >17, CRP >30, and PhGA >80) and least (12%, 95% CI: 8, 20) in the lowest tertile of each category (SJC28 < 10, CRP <5, and PhGA <50).

Conclusion: A pooled radiographic assessment data showed that baseline SJC28, CRP, and PhGA are associated with RP, and the proportion of patients with RP increases as each baseline factor worsened.

References:

1. Smolen JS et al. *Rheumatology*. 2017 Oct 1;56(10):1771-1779
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Abstract Number: 560

Impact of Formulary Copayment Change on Treatment Patterns in Rheumatoid Arthritis Patients on Etanercept

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) is a chronic disease that requires long-term treatment to improve or maintain disease activity. Tumor necrosis factor inhibitors (TNFi), a class of biologic disease-modifying antirheumatic drugs (bDMARDs), are effective at treating symptoms and inhibiting joint progression. Although treatment changes are not recommended in patients with stable disease, health plans have recently enacted formulary changes with higher copayments that could disrupt patient access to TNFis. Our purpose was to describe impacts of formulary copayment changes on TNFi use among patients with RA using the TNFi etanercept (ETN).

Methods: This retrospective observational cohort analysis used the IBM Watson Health Market Scan Commercial database. The study population included adults (aged 18–64 years) with RA, with 6 months continuous ETN use (no gap ≥ 45 days) during 1/1/2013–12/31/2015 (defined as stable use period), and continuous plan enrollment ≥ 6 months before and ≥ 12 months after index date (first date after a patient's 6-month stable-use period). ETN persistence, bDMARD switching, refill gaps, and treatment effectiveness (using a validated effectiveness algorithm) were described for patients with or without formulary change during 12 months after index. Average ETN copayment was calculated at the drug plan-level. Formulary change was defined as a monthly increase of $> \$40$ to account for copay changes attributable to ETN wholesale acquisition costs between 2014–2015. This amount also corresponded to the 90th percentile of average plan-level changes in ETN copayments in the database, representing an average change in copay by a payer.

Results: A total of 1,970 patients met study inclusion criteria (mean age 50.3 years, standard deviation 9.5; 77.8% female). Of these, 133 (6.8%) patients had a formulary change during follow-up. Overall, most patients (60.3%) persisted on ETN for the 12-month follow-up period; 13.0% switched from a bDMARD, and 26.7% discontinued (gap of ≥ 45 days). Nearly half (48.0%) of all patients were considered effectively treated according to the validated algorithm. Compared to patients without a formulary change, those with a formulary change more likely to switch biologics (19.5% vs 12.6%, $P = 0.021$) and tended to be less likely to be persistent (54.1% vs 60.7%, $P = 0.135$), and less likely to be effectively treated (42.1% vs 48.4%, $P = 0.161$) (Table). Patients with a formulary change also tended to be more likely to discontinue bDMARDs for at least 12 months (10.5% vs 7.9%; $P = 0.293$).

Conclusion: Using a combination of health plan- and patient-level data, this retrospective administrative claims database analysis identified a cohort of stable ETN patients and found a significant association between changing formulary status and switching bDMARD therapy for RA and negative trends for persistence and treatment effectiveness. Treatment Patterns Following Formulary Change

	Mean copay change amount		P-value
	≤ \$40	> \$40	
Total stable ETN users, n (%)	1,837 (93.2)	133 (6.8)	
Copay, mean (median) US \$	-\$4.48 (-\$1.0)	\$68.53 (\$45.25)	
Treatment pattern, n (%)			
Persistent following formulary change	1,115 (60.7)	72 (54.1)	0.135
Nonpersistent following formulary change	722 (39.3)	61 (45.9)	
Gap	491 (26.7)	35 (26.3)	0.917
Restart	345 (18.8)	21 (15.8)	0.392
Restart as % of those with gap	345 (70.3)	21 (60.0)	0.202
Discontinuation (no restart in 12 months)	146 (7.9)	14 (10.5)	0.293
Switch	231 (12.6)	26 (19.5)	0.021
Prior gap	62 (3.4)	5 (3.8)	0.813
No prior gap	169 (9.2)	21 (15.8)	0.013
Any gap (with or without switch)	553 (30.1)	40 (30.1)	0.995
Effectively treated	889 (48.4)	56 (42.1)	0.161

Disclosure: H. Oko-osi, Amgen Inc., 1,Amgen Inc., 3; M. Bonafede, None; M. Gharaibeh, Amgen Inc., 3,Amgen Inc., 1; J. Manjelijskaia, Truven Health, 3; L. Lopez-Gonzalez, None; D. H. Collier, Amgen Inc., 3,Amgen Inc., 1; B. S. Stolshek, Amgen Inc., 3,Amgen Inc., 1.

Abstract Number: 561

U-Act-Early Trial 3 Years Follow-up: Radiographic Joint Damage and Use of Bdmards over 5 Years in Early RA Patients Treated-to-Target with Strategies Initiating Tocilizumab, Methotrexate or Their Combination

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: The U-Act-Early trial was a 2-year multicentre, double-blind, randomized, placebo-controlled trial in early (DMARD-naïve) RA patients treated to the target of remission, with step-up strategies starting with tocilizumab (TCZ), methotrexate (MTX) or their combination (TCZ+MTX)¹, here labelled as TCZ, MTX and TCZ+MTX, respectively. When sustained remission (SR, DAS28 <2.6 AND 28 swollen joint count ≤4 for ≥24 weeks) was achieved, medication was tapered and stopped. During the trial, both TCZ arms showed less progression of joint damage than the MTX arm. Patients were subsequently followed for 3 additional years, during which treatment was open and accordance with usual care. The objective is to evaluate progression of radiographic joint damage and biological (b)DMARD use over 5 years in the TCZ, MTX and TCZ+MTX arms as initiated in the U-Act-Early trial.

Methods: 226 of the 317 patients included in U-Act-Early (79 TCZ, 72 MTX, 75 TCZ+MTX) participated in the follow-up. Radiographs of hands and feet were taken at baseline U-Act-Early, after 2 and 5 years. A professional reader scored the radiographs in chronological order, applying the Sharp vander Heijde (SvdH) method. During follow-up medication data was collected every 3 months for the first year and every 6 months thereafter. We analysed change in total SvdH score and in SvdH erosion and joint space narrowing (JSN) scores over 5 years, and bDMARD use over time. Differences between the arms in median change in radiographic scores over time were tested with the van Elteren test, correcting for baseline DAS28 level (<5.1 or ≥5.1) and centre.

Results: Baseline characteristics at start of U-Act-Early of the patients included in this follow-up were not significantly different from those of all patients included in U-Act-Early, suggesting no selective dropout. The median (interquartile range) changes in total SvdH scores over 5 years were 0 (0-1) for TCZ, 0 (0-2) for MTX and 0 (0-1) for TCZ+MTX

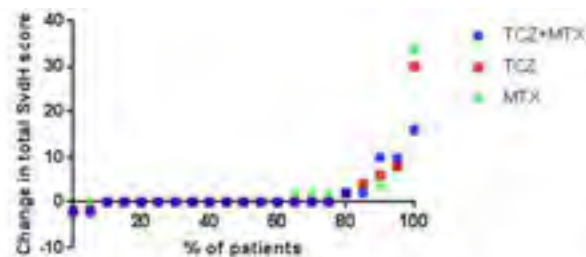


Figure 1 Cumulative probability plot for absolute change in total Sharp van der Heide score over 5 years per strategy arm as randomised in U-Act-Early

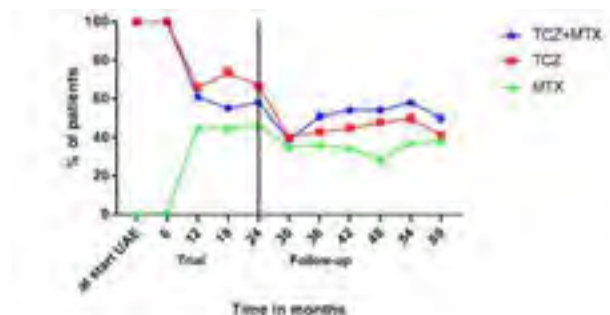


Figure 2 Percentages of patients who used at least one biological DMARD at any time-point over 5 years per strategy arm as randomised in U-Act-Early

	TCZ+MTX	TCZ	MTX	P-value ¹
SwH score				
Total	0 (0-1) (-2 to 1)	0 (0-1) (-2 to 30)	0 (0-2) (0 to 35)	TCZ+MTX vs. MTX: 0.41 TCZ vs. MTX: 0.05
Erosions	0 (0-0) (0 to 1)	0 (0-1) (-2 to 17)	0 (0-1) (0 to 35)	TCZ+MTX vs. MTX: 0.62 TCZ vs. MTX: 0.80
Joint space narrowing	0 (0-0) (-2 to 0)	0 (0-0) (-1 to 14)	0 (0-1) (0 to 4)	TCZ+MTX vs. MTX: 0.03 TCZ vs. MTX: 0.11

¹ Van Erchemt had no statistical significance (P=0.28) for TCZ vs MTX and MTX vs TCZ+MTX.

(Figure 1 and Table), with a borderline statistically significant difference for TCZ and MTX ($p=0.05$), but not for TCZ+MTX and MTX ($p=0.41$). No differences were shown for the erosion scores over 5 years (TCZ vs. MTX; $p=0.80$ and TCZ+MTX vs. MTX; $p=0.62$); for JSN scores there was a statistically significant difference for TCZ and MTX ($p=0.03$), but not for TCZ+MTX and MTX ($p=0.11$). During U-Act-Early, bDMARD use decreased in both TCZ arms and increased in the MTX arm, but during follow-up it remained higher in both TCZ arms (Figure 2).

Conclusion: Progression of radiographic joint damage over 5 years was low: >70% of patients had no progression at all, without differences between strategy arms, probably due to convergence of treatment strategies resulting from the treat-to-target principle applied in each arm². Use of bDMARD remained higher in both TCZ arms.

References:

1. Bijlsma JWJ, et al. *Lancet*. 2016;388:343-55.
2. Smolen JS, et al. *Ann Rheum Dis*. 2017;76:960-77.

Disclosure: M. M. Verhoeven, None; M. J. de Hair, None; P. M. Welsing, None; A. Pethö-Schramm, F Hoffmann-La Roche, 3; M. E. Borm, Roche Nederland BV, 3; X. M. Teitsma, None; J. van Laar, Arthrogon, MSD, Pfizer, Eli Lilly, BMS, Astra Zeneca, Roche-Genentech, 2, 5; F. P. Lafeber, None; J. W. J. Bijlsma, Roche, AbbVie, Bristol-Myers, Squibb, Merck Sharp and Dohme, Pfizer, UCB, 2, 5; J. W. G. Jacobs, None.

Low Inflammation on Magnetic Resonance Imaging in Patients with Rheumatoid Arthritis That Achieved Sustained Clinical Remission on Adalimumab

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: ACR and EULAR recommend bDMARD tapering in patients (pts) with rheumatoid arthritis (RA) who achieved stable clinical remission. Yet, there are limited systematically collected data on objective magnetic resonance imaging (MRI)-assessed levels of musculoskeletal inflammation, especially tenosynovitis, in RA pts in stable clinical remission with previous data derived from a range of cohorts with differing definitions of clinical remission. The purpose of the analysis was to evaluate within the PREDICTRA study the extent of disease control, in particular MRI inflammation, in RA pts in DAS28-based stable clinical remission attained on adalimumab (ADA) at the standard dosing of 40 mg every other week (eow).

Methods: PREDICTRA is a multicenter, randomized, double-blind study generating data on pt and disease characteristics that may predict the clinical course of ADA dose-tapering for RA pts in stable clinical remission. RA pts with DAS28-CRP or -ESR <2.6 for ≥6 months following treatment with originator ADA 40 mg eow for ≥12 months in clinical practice were eligible to enter a 4-week (wk) open-label lead-in study period with continued standard ADA dosing. Pts must have had confirmed DAS28-ESR <2.6 at the beginning and end of the lead-in period and quality-verified MRI of the most affected or, if both equally affected, the dominant hand to be eligible for randomization. Study assessments included multiple measures of disease activity (SJC28 and 68, TJC28 and 68, DAS28, CDAI, SDAI, patient's and physician's global assessment of disease activity), physical function (HAQ-DI, SF-36 PCS), and OMERACT RAMRIS scores for synovitis, tenosynovitis, bone marrow edema and erosions. Data of the randomized pts at the end of the lead-in period are presented.

Results: Of the 149 pts that entered the lead-in period, 122 (82%) were randomized. The randomized pts were 75% female, mean age 59.7±10.3 years, RA duration 12.8±9.8 years, prior ADA exposure 5.1±3.0 years, and DAS28 remission duration 2.2±2.1 years. Most pts received concomitant methotrexate (83.6%; mean dose 13.2 mg weekly) and few received concomitant corticosteroids (9.8%; mean dose 3.2 mg daily). Very low disease activity was observed in terms of clinical measures and MRI inflammation scores (synovitis [3.5±3.13], osteitis [1.0±2.01], tenosynovitis [2.7±2.7]). The mean MRI erosion score was low given the disease duration, and physical function scores were within normal ranges (**Table**).

Conclusion: Pts with long-standing RA randomized to the tapering phase of the PREDICTRA study based on sustained DAS28-based clinical remission on prior standard dose ADA therapy showed very low levels of clinical disease activity and normal physical function. This concurred with low MRI inflammation scores, especially for osteitis and tenosynovitis, the latter pathology being reported for the first time in RA clinical remission pts.

Table: Summary of Patient Characteristics

Patient Characteristic (N=122)	Mean (SD)*
Duration of prior adalimumab, years	5.1 (3.0)
Duration of remission, years	2.2 (2.0)
Concomitant csDMARDs dose, mg	
Methotrexate (weekly)	13.2 (5.5)
Hydroxychloroquine (daily)	228.6 (75.6)
Sulfasalazine (daily)	750.0 (288.7)
Concomitant oral corticosteroids dose, mg (daily)	3.2 (1.7)
Anti-cyclic citrullinated peptide (ACCP), Unit	286.6 (206.4)
ACCP positive, n (%)	63 (52.9)
Rheumatoid factor (RF), KU/L	139.5 (395.4)
RF positive, n (%)	90 (76.3)
C-reactive protein (CRP), mg/L	5.3 (28.0)
Erythrocyte sedimentation rate (ESR), mm/hr	11.4 (8.4)

Table . (Cont'd)

Patient Characteristic (N=122)	Mean (SD)*
Tender joint count (TJC) 68	0.3 (0.6)
Swollen joint count (SJC) 66	0.1 (0.3)
DAS28 (ESR)	1.7 (0.6)
Clinical Disease Activity Index (CDAI)	1.3 (1.4)
Simplified Disease Activity Index (SDAI)	1.8 (3.0)
Patient's Global Assessment of Disease Activity –VAS, 0-100 mm	6.4 (8.9)
Physician's Global Assessment of Disease Activity – VAS, 0-100 mm	3.7 (5.0)
Pain – VAS, 0-100 mm	8.5 (11.5)
HAQ-DI	0.3 (0.4)
SF-36 MCS	54.4 (7.7)
SF-36 PCS	50.1 (7.8)
MRI OMERACT scores	
Synovitis, Range 0-24	3.5 (3.1)
Osteitis, Range 0-75	1.0 (2.0)
Tenosynovitis, Range 0-30	2.7 (2.7)
Erosion, Range 0-250	21.4 (26.9)

* All values are Mean (SD) unless otherwise specified

ACCP = Anti-cyclic citrullinated peptide; CRP = C-reactive protein; ESR = Erythrocyte sedimentation rate; EAMs = extra-articular manifestations; HAQ-DI = Health Assessment Questionnaire – Disability Index; IBD = inflammatory bowel disease; MCS = mental component summary; OMERACT = Outcome Measures in Rheumatology; PCS = physical component summary; Pts = patients; RF = rheumatoid factor; SD = standard deviation; SF-36=Short form 36-item health survey; VAS = Visual Analogue Scale.

Disclosure: P. Emery, AbbVie, Bristol-Myers Squibb, Lilly, Merck, Novartis, Pfizer, Roche, Sandoz, and UCB, 2, 5; G. R. Burmester, AbbVie, Bristol-Myers Squibb, Lilly, MSD, Novartis, Pfizer, Roche, Sandoz, and UCB, 2, 5; E. Naredo, AbbVie, Roche, Bristol-Myers Squibb, Pfizer, UCB, Lilly, Novartis, Janssen, and Celgene GmbH, 8, AbbVie Inc., 9; I. Lagunes Galindo, AbbVie Inc., 1, 3; Y. Zhang, AbbVie Inc., 1, 3; X. Wang, AbbVie Inc., 1, 3; M. Hojnik, AbbVie Inc., 1, 3; P. G. Conaghan, AbbVie, Bristol-Myers Squibb, Lilly, Novartis, Pfizer, and Roche, 5, 8.

Abstract Number: 563

Efficacy and Safety of Abatacept in Combination with MTX in Early, MTX-Naïve, Anti-Citrullinated Protein Antibody–Positive Patients with RA: Primary and 1-Year Results from a Phase IIb Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: In patients (pts) with early (disease duration ≤ 24 months [mths]), MTX-naïve RA and poor prognostic factors including anti-citrullinated protein antibody (ACPA) positivity (+), abatacept (ABA) + MTX vs MTX was superior at achieving DAS28 (CRP) < 2.6 at 12 mths.^{1,2} The AVERT-2 trial (clinicaltrials.gov, NCT02504268) further investigates the ability of ABA + MTX to induce validated metrics of remission in pts with ACPA+ early RA (disease duration ≤ 6 mths).

Methods: Pts were randomized (3:2) to double-blind, weekly SC ABA 125 mg + MTX vs MTX for 56 weeks (wks). Key inclusion criteria: age ≥ 18 years; RA diagnosis ≤ 6 mths (ACR/EULAR 2010 criteria); ACPA+; TJC and SJC ≥ 3 ; CRP > 0.3 mg/dL (ULN)/ESR ≥ 28 mm/h; SDAI > 11 ; DMARD naïve. Primary endpoint: proportion of pts in SDAI remission (SDAI ≤ 3.3) at Wk 24 in the first 375 pts randomized (primary analysis population). Hierarchically tested secondary endpoints: DAS28 (CRP) < 2.6 at Wk 24 and SDAI ≤ 3.3 at Wk 52 (primary analysis population), and change from baseline (CfB) in total Sharp/van der Heijde score (SHS; X ray) and Boolean remission at Wk 52 (all randomized pts). Comparisons were made using logistic regression for binary outcomes and rank-based non-parametric analysis of covariance for X ray data.

Results: In the primary analysis population, 225 pts received ABA + MTX and 150 received MTX. Overall, 752 pts were randomized to ABA + MTX (n=451) and MTX (n=301); 63 and 68 discontinued, respectively, by Wk 52. Baseline characteristics were similar across treatment arms in each population (Table 1). The proportion of pts achieving SDAI \leq 3.3 at Wk 24 was 21.3% for ABA + MTX and 16.0% for MTX (primary analysis population; p=0.2359; Table 2). Nominally significant benefits in favor of ABA + MTX were observed for all secondary endpoints including mean CFB in total SHS at Wk 52 in all randomized pts (0.5 vs 2.5; nominal p<0.0001; Table 2). Safety profiles were similar across treatment arms; no new safety signals were identified.

Conclusion: Abatacept + MTX vs MTX in ACPA+, early RA did not meet the primary endpoint of a statistically significant difference in SDAI \leq 3.3 at Wk 24 in the primary analysis population, but did so at Wk 52. Consistent with previous studies,^{1,2} the benefits of abatacept + MTX vs MTX were seen for the composite endpoint of DAS28 (CRP) <2.6 at Wk 24 in the primary analysis population, and for the other secondary endpoints in all randomized pts.

References:

- Emery P, et al. *Ann Rheum Dis* 2015;**74**:19–26.
- Westhovens R, et al. *Ann Rheum Dis* 2009;**68**:1870–7.

Medical writing assistance provided by Sharon Gladwin, PhD (Caudex), funded by Bristol-Myers Squibb.

Table 1. Baseline Characteristics

	Primary analysis population (n=375)		All randomized patients (n=752)	
	ABA + MTX (n=225)	MTX monotherapy (n=150)	ABA + MTX (n=451)	MTX monotherapy (n=301)
Age, years	50 (13)	50 (15)	49 (13)	49 (14)
Female, n (%)	170 (75.6)	121 (80.7)	349 (77.4)	243 (80.7)
RA duration, months	1.3 (1.5)	1.3 (1.4)	1.2 (1.4)	1.3 (1.4)
TJC (28 joints)	13.8 (7.0)	13.4 (6.7)	13.2 (6.8)	13.7 (6.8)
SJC (28 joints)	10.4 (6.0)	11.1 (5.9)	10.0 (5.7)	10.7 (5.9)
Pain	66.2 (21.4)	65.6 (22.6)	66.5 (22.5)	65.4 (22.4)
HAQ-DI	1.6 (0.7)	1.6 (0.6)	1.6 (0.7)	1.6 (0.7)
Patient Global Assessment	65.3 (21.5)	63.0 (23.7)	65.7 (22.7)	62.7 (24.1)
Physician Global Assessment	66.3 (18.4)	66.4 (20.6)	65.1 (18.5)	66.1 (19.8)
RF+, n (%)	210 (93.3)	136 (90.7)	420 (93.1)	279 (92.7)
CRP, mg/dL	2.3 (3.1)	1.9 (2.1)	2.0 (2.7)	1.9 (2.2)
DAS28 (CRP)	5.7 (1.1)	5.6 (1.0)	5.6 (1.1)	5.6 (1.0)
SDAI	39.6 (14.7)	39.6 (14.1)	38.2 (14.1)	39.4 (13.8)
Total SHS	NC	NC	9.8 (16.3)	13.0 (19.8)
CS* at Day 1, n (%)	96 (42.7)	52 (34.7)	208 (46.1)	93 (30.9)

Data are mean (SD) unless otherwise indicated

Pain and Patient and Physician Global Assessment were measured by visual analog scale (0–100 mm)

* Oral and/or injectable

CS=corticosteroids; NC=not calculated; SHS=Sharp/van der Heijde score

Table 2. Primary and Secondary Efficacy Endpoints

	ABA + MTX	MTX monotherapy	Adjusted OR* (95% CI)	p value
SDAI \leq 3.3 at 24 weeks (primary analysis population)	21.3 (48/225)	16.0 (24/150)	1.4 (0.8, 2.5)	0.2359
DAS28 (CRP) <2.6 at 24 weeks (primary analysis population)	38.7 (87/225)	25.3 (38/150)	1.9 (1.2, 3.1)	0.0112†
SDAI \leq 3.3 at 52 weeks (primary analysis population)	29.8 (67/225)	15.3 (23/150)	2.3 (1.4, 4.0)	0.0021†
Mean (SD) CFB in total SHS at 52 weeks (all randomized)	0.5 (2.3) n=450	2.5 (6.2) n=300	–	<0.0001†
Boolean remission at 52 weeks (all randomized)	21.5 (97/451)	11.6 (35/301)	2.1 (1.4, 3.2)	0.0006†

Data are % (n/N) unless otherwise indicated

For binary outcomes, patients with missing values due to discontinuation or other reasons and those who took a high dose of corticosteroids within 42 days of the 12-month assessment were imputed as non-remitters

For CFB in total SHS, imputation was performed by linear extrapolation for patients with available data at baseline and the time of discontinuation

* Based on logistic regression and adjusted for treatment arm, Japan vs rest of world (yes/no) and baseline measure

† Nominal p value only as the primary endpoint in the statistical hierarchy did not reach significance

CFB=change from baseline; OR=odds ratio; SHS=Sharp/van der Heijde score

Disclosure: P. Emery, Bristol-Myers Squibb, AbbVie, Pfizer, MSD, Novartis, Roche and UCB, 5, AbbVie, Bristol-Myers Squibb, Pfizer, MSD and Roche, 2; Y. Tanaka, Mitsubishi-Tanabe, Bristol-Myers Squibb, Eisai, Chugai, Takeda, AbbVie, Astellas, Daiichi-Sankyo, Ono, MSD, Taisho-Toyama, 2, Daiichi-Sankyo, Astellas, Eli Lilly, Chugai, Sanofi, AbbVie, YL Biologics, Bristol-Myers Squibb, GSK, UCB, Mitsubishi-Tanabe, Novartis, Eisai, Takeda, Janssen, Asahi Kasei, 8; V. P. Bykerk, Amgen, Pfizer, Bristol-Myers Squibb, UCB, Roche, Regeneron, 5, Amgen, Bristol-Myers Squibb, 2; T. W. J. Huizinga, Abbott Laboratories, Biotest AG, Bristol-Myers Squibb, Crescendo Bioscience, Inc, Novartis Pharmaceuticals Corporation, Pfizer Inc, Roche, sanofi-aventis, Schering-Plough, UCB, Inc., Eli Lilly, 5, EU & Dutch Arthritis Foundation, 2, Abbott Laboratories, Biotest AG, Bristol-Myers Squibb, Novartis Pharmaceuticals Corporation, Pfizer Inc, Roche, sanofi-aventis, Schering-Plough, 8, Abbott Laboratories, Roche, 9; G. Citera, Bristol-Myers Squibb, Pfizer, AbbVie, Roche, Eli Lilly, Genzyme, 5; M. Nys, Bristol-Myers Squibb, 1, 3; S. E. Connolly, Bristol-Myers Squibb, 1, 3; A. Johnsen, Bristol-

Myers Squibb, 1, 3; **R. Fleischmann**, AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, EMD-Serano, Eli Lilly, Merck, Novartis, Pfizer, Roche, Sanofi-Genzyme, UCB, 2, AbbVie, ACEA, Amgen, Bristol-Myers Squibb, GSK, Eli Lilly, Novartis, Pfizer, Sanofi-Genzyme, UCB, 5.

Abstract Number: 564

Levels of CXCL13 and sICAM1 Correlate with Disease Activity Score in Rheumatoid Arthritis (RA) Patients Treated with Tocilizumab (TCZ)

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: The biomarkers CXCL13 and sICAM1 have been associated with outcomes in patients with RA treated with TCZ. This study evaluated the association of CXCL13 and sICAM1 with disease activity and response to TCZ in early RA and DMARD-IR patients.

Methods: Patient subsets from the FUNCTION (early RA) and LITHE (DMARD-IR) clinical trials were selected based on baseline and Week 24 sample availability; serum CXCL13 and sICAM1 levels were measured. Correlations between CXCL13 and sICAM1 levels and DAS28-ESR at baseline, and between change in CXCL13 and sICAM1 levels and change in DAS28-ESR at Week 24, were determined. Changes in CXCL13 and sICAM1 levels from baseline to Week 24 were compared between treatment arms using Welch *t* test. The effect of treatment, baseline DAS28-ESR and baseline CXCL13 and sICAM1 levels on the likelihood of DAS28-ESR remission and ACR50 response at Week 24 was determined via logistic regression. DAS28-ESR remission and ACR50 rates were compared against CXCL13 and sICAM1 status (high vs low median values) within each trial arm using a Cochran-Mantel-Haenszel test.

Results: Overall, 458 of 872 patients from FUNCTION (TCZ+ MTX, n = 160; TCZ monotherapy [TCZ-mono], n = 157; placebo [PBO] + MTX, n = 141) and 287 of 791 patients from LITHE (TCZ + MTX, n = 137; PBO + MTX, n = 150) were included. In these patient subsets, mean disease duration in FUNCTION was significantly shorter than in LITHE (0.45 vs 8.65 years). At baseline, correlation of serum CXCL13 levels with DAS28-ESR was moderate in the early RA population and weak in the DMARD-IR population (Table). Correlation between baseline serum sICAM1 levels and DAS28-ESR was low in both populations. Serum levels of CXCL13 decreased significantly at Week 24 in all treatment arms in both populations; sICAM1 levels decreased significantly at Week 24 in the TCZ-mono arm in patients with early RA and the TCZ + MTX arms in both populations but not in the PBO + MTX arms. Change in CXCL13 levels correlated moderately with change in DAS28-ESR at Week 24 in both populations (Table). Change in sICAM1 levels correlated moderately with change in DAS28-ESR at Week 24 in the DMARD-IR population but weakly in the early RA population. Although the treatment arm had a significant effect on the likelihood of DAS28-ESR remission and achievement of ACR50, the effect of baseline levels of CXCL13 and sICAM1 were not significant. DAS28-ESR remission and ACR50 response rates at Week 24 within each treatment arm of the early RA and DMARD-IR populations were not significantly different between patients with high vs low baseline CXCL13 and sICAM1 levels.

Conclusion: The association of baseline CXCL13 levels with RA disease activity was stronger in the early RA population than in the DMARD-IR population. Baseline levels of CXCL13 and sICAM1 did not predict response to TCZ at Week 24, suggesting that although these biomarkers are associated with disease activity, they do not predict response to TCZ in all RA populations.

Table. Correlation Between Serum CXCL13 and sICAM1 Levels and DAS28-ESR

	Baseline						Week 24*					
	CXCL13			sICAM1			Δ CXCL13			Δ sICAM1		
	n	r	P value	n	r	P value	n	r	P value	n	r	P value
FUNCTION (early RA)	458	0.36	< 0.0001	458	0.14	0.0029	458	0.33	< 0.0001	458	0.16	0.0005
LITHE (DMARD-IR)	282	0.21	0.0003	282	0.17	0.0040	202	0.33	< 0.0001	202	0.26	0.0002

CXCL13, C-X-C motif chemokine ligand 13; DAS28-ESR, Disease Activity Score in 28 joints per erythrocyte sedimentation rate; DMARD-IR, inadequate response to disease-modifying antirheumatic drugs; RA, rheumatoid arthritis; sICAM1, soluble intercellular adhesion molecule 1.

* Correlation between change in CXCL13 and sICAM1 levels from baseline to Week 24 and change in DAS28-ESR from baseline to Week 24; all patients combined.

Disclosure: K. Tuckwell, Genentech, Inc., 3; C. Gabay, AB2 Bio, Pfizer and Roche, 2, AB2 Bio, AbbVie, Bristol Myers Squibb, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, UCB, 5, 8; T. Sornasse, Genentech, Inc., 3; R. Laubender, Roche Diagnostics, 3; J. Wang, Roche Products Ltd., 3; M. Townsend, Genentech, Inc., 3.

Abstract Number: 565

Genetic Polymorphism in Dihydrofolate Reductase Impacts Methotrexate Polyglutamation in Adult Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

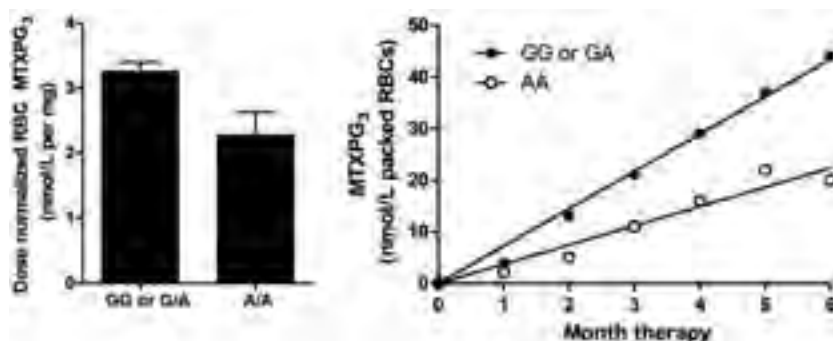
Session Type: ACR Poster Session A

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

Background/Purpose: Methotrexate (MTX) is anti-folate activated to MTX polyglutamates (MTXPGs). MTX metabolism includes multiple enzyme-mediated reactions and genetic polymorphisms in these genes are linked to MTX disposition and effects. The objective of this study was to examine the influences of variant in the dihydrofolate reductase gene (DHFR: rs1382539 G/A) on MTX polyglutamation and clinical efficacy in rheumatoid arthritis (RA).

Methods: Two US based cohorts of consented adult RA were analyzed, a first cohort of 187 patients (median age 65 years under median 15mg/weekly MTX) evaluated at a single visit for MTXPG levels (>3 months), and a second cohort consisting of 38 patients (mean age 55 years) enrolled in adose escalation study (starting 7.5 mg/week) for 6 months (206 study visits). RBCMTXPG levels (MTXPG₁ [MTX] up to 5 glutamic residues [MTXPG₅]) were measured using liquid chromatography. MTXPG₃ (the preponderant MTXPG species) was expressed as nmol/L packed RBC; percent long-chain MTXPG₃₋₅ (over total MTXPG₁₋₅) and dose normalized MTXPG₃ levels (polyglutamation rate, nmol/L per mg) were also estimated. Real-time PCR was used to genotype the rs1382539 G/A variant in *DHFR*. Differences in MTXPG accumulation by genotypes were analyzed using Mann-Whitney test. Linear mixed effect with random intercept and fixed slope were used to analyze the impact of the variant on longitudinal changes in MTXPG levels and response (per DAS-28).

Results: In the first cohort, carriers of the rs1382539 A/A genotype (n=15 patients [8%], mean age 64±12 years under 15 mg/week) presented with 15 nmol/L lower MTXPG₃ levels (median 26 nmol/L [IQR: 18-55] vs 41 nmol/L [IQR: 28-60]; p=0.04) than those with G/G or G/A genotypes (total 173 patients mean age 64±12 years under 15 mg/week), respectively. Similarly, 16% lower long-chain MTXPG₃₋₅ (median 36% [IQR 18-48%] vs median 52% [IQR 40-68%]; p<0.01) and 0.8 nmol/L per mg lower MTX polyglutamation rate (median 2.1 nmol/mg MTX [IQR 1.2-3.1] vs 2.9 nmol/mg MTX [IQR 2.0-4.3]; p=0.02; Figure) were measured in carriers of the A/A genotype vs G/G or G/A genotypes, respectively (Figure, panel A). In the second cohort, linear mixed effect models revealed that carriers of the rs1382539 A/A genotype (n=4 patients [10%]) also presented with lower RBC MTXPG₃ levels (estimate=-11±5 nmol/L; p=0.03), lower percent long-chain MTXPG₃₋₅ (estimate=-15±1%; p=0.02) and lower polyglutamation rate (estimate=-0.9±0.4 nmol/mg; p=0.01) than carriers of the G/G or G/A genotype (Figure, panel B). While the rs1382539 variant was not significantly associated with clinical efficacy (p>0.05), lower RBC MTXPG₃ level and percent long-chain MTXPG₃₋₅ levels associated with higher DAS28 in the cohort (p<0.05).



Conclusion: Our data indicate that the rs1382539 G/A variant in DHFR impacts MTX polyglutamation in adultRA, and may indirectly contribute to clinical efficacy in some patients.

Disclosure: T. Dervieux, exagen, 3; M. Grosjean, None; C. Jiang, None; K. Brady, Exagen Diagnostics, 3; K. Schmiegelow, None; J. Kremer, None; J. Yang, None.

Abstract Number: 566

Capillary Blood Based Methotrexate Polyglutamate Assay for Monitoring Low Dose Methotrexate Therapy in Rheumatic Diseases

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

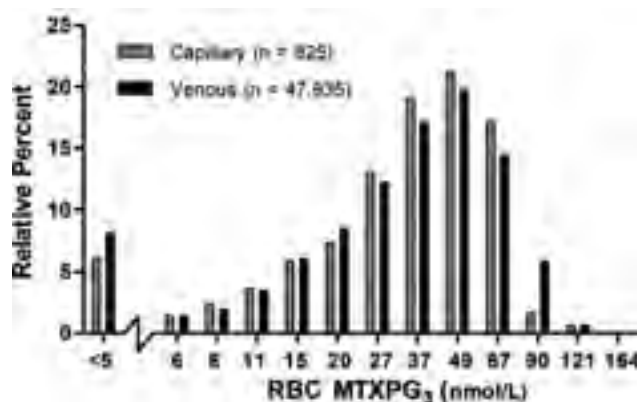
Session Type: ACR Poster Session A

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

Background/Purpose: The red blood cell (RBC) Methotrexate (MTX) polyglutamate (MTXPG₃) assay is a helpful therapeutic drug monitoring (TDM) tool in autoimmune rheumatic diseases. Our objective was to transition the RBC MTXPG assay from venous blood to capillary blood collected by fingerstick.

Methods: Adult subjects with Rheumatoid Arthritis (RA) (mean age 62±13 [SD]) treated with low dose weekly MTX therapy (mean dose 17±5 mg/week [SD]) were enrolled from two rheumatology practices in the United States. Clinical staff consented subjects and collected paired specimens: a capillary blood specimen (10µl) collected by fingerstick on volumetric absorptive microsampling device (Neoteryx, Torrance, CA, USA), and a venous blood specimen (10 ml) collected in EDTA containing tubes. Dried capillary blood and venous blood were shipped overnight to a CAP/CLIA accredited clinical laboratory. RBC MTXPG₃ levels from capillary and venous blood were measured using validated liquid chromatography coupled with high sensitivity tandem mass spectrometry. Patient reported outcomes (PROs) comparing venipuncture and fingerstick collection methods were obtained at the time of the visit. RBC MTXPG₃ levels from capillary blood were compared to historical levels estimated from a database of venous blood specimens collected from patients on MTX therapy and assessed for compliance, defective activation to polyglutamates (RBC MTXPG₃ <5nmol/L), or in adequate response to MTX.

Results: In the 106 RA subjects enrolled, mean (SD) RBC MTXPG₃ levels recovered from dried capillary blood and venous blood specimens were similar (30±18 nmol/L vs 33±19 nmol/L, respectively) (R²=0.89; slope=1.10). PROs indicated that the fingerstick collection method was convenient and non-inferior to venipuncture, but only a minority of subjects (37%) were comfortable with self-collection of the capillary blood specimen at home. Following one year of testing, capillary RBC MTXPG₃ (36±20 nmol/L RBC) levels from a population of 679 patients (mean age 58±15 years; n=825 capillary blood specimens) were similar to RBC MTXPG₃ (38±24 nmol/L) levels estimated from the database of patient specimens collected using venipuncture (mean patient age 58±15 years; n=47,935). Potential for poor compliance (RBC MTXPG₃ ≤5 nmol/L RBC) was detected in 7.0% (n=54) and 8.5% (n=4,224) patient specimens collected using the fingerstick and venipuncture based method, respectively (Figure).



Conclusion: Measurement of capillary blood MTXPG₃ levels can be applied to the TDM of MTX in clinical rheumatology practice. PROs suggest that patient training will be required before transitioning from office-based to home-based specimen collection.

Disclosure: T. Dervieux, Exagen, 3; K. Brady, Exagen Diagnostics, 3; D. Stimson, Exagen Diagnostics, 3; Y. Qu, Exagen Diagnostics, 9; T. O'Malley, Exagen Diagnostics, 3; R. Apilado, Exagen Diagnostics, 3; S. Reddy, None; P. Chitkara, None; J. Conklin, Exagen Diagnostics Inc., 3; R. Alexander, Exagen Diagnostics, Inc., 3; C. Ibarra, Exagen Diagnostics, 1, 3.

Abstract Number: 567

Non-Surgical Periodontal Therapy Plus Short-Term Antibiotic Treatment May Improve Clinical Disease Activity: A Pilot Study in Difficult to Treat Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Autoimmunity against citrullinated peptides is a hallmark of rheumatoid arthritis (RA). Chronic periodontitis (CP) is a known major source of citrullinated peptides. Here, we investigated potential associations between the treatment of CP, the reduction pathogenic periodontal microbes, the autoantibody repertoire and RA disease activity.

Methods: We evaluated ten patients with DAS28_{CRP} ≥ 4.2 for the presence and severity of CP. All patients had active disease and were positive for rheumatoid factor and anti-cyclic citrullinated peptide antibody (ACPA). Each had an inadequate response to at least two conventional and two biological disease modifying anti-rheumatic drugs. Periodontal scaling and root planing (SRP) was performed in conjunction with one week of amoxicillin and metronidazole therapy, if significant CP was indicated by clinical attachment level (CAL) loss ≥ 5mm at ≥ 2 separate sites.

The primary outcome was mean DAS28 improvement >1.2 from baseline to month 3, corresponding to good clinical response. Secondary clinical outcomes included periodontal pocket depth (PD), CAL, and bleeding on probing (BOP). The presence of major periodontal pathogens was assessed by semiquantitative polymerase chain reaction in the subgingival biofilm at baseline, month 3 and 6. Sera were longitudinally tested for antibodies against native and citrullinated peptides from enolase, fibrinogen, vimentin, and tenascin-C.

Results: Eight patients had CP requiring treatment. In these patients, DAS28 improved upon SRP by mean (+/- SD) 0.74 +/- 0.93, p=0.049, thereby failing the predefined significance at a group level. Nevertheless, moderate and transient DAS28 response >0.6 at month three was achieved in three patients, and prolonged good clinical response was observed in a fourth patient at month 3 and 6. The clinical signs of CP improved in parallel, PD by 1.8 +/- 1.5 mm (mean +/- SD), p=0.018, CAL by 0.7 +/- 0.6 mm, p=0.051, and BOP by 36 +/- 24%, p=0.018. Furthermore, the microbial burden was significantly reduced upon SRP in the biofilm for the following bacteria: *P. gingivalis*, *Treponema denticola* and *Tannerella forsythia*, p<0.05 for all. However, the serum concentrations of all tested autoantibodies remained unchanged at group level, and the changes in the microbiota and titers of autoantibodies could not specifically be associated with improvement of arthritis symptoms in individual patients.

Conclusion: Successful treatment of CP reduced the burden of specific microbial species in the periodontal biofilm, and improvement of clinical RA disease activity could be observed in individual patients. This finding could support the hypothesis of RA inflammation being permanently triggered by chronic periodontal infections. However, clinical responses in this small interventional pilot study did not track back to changes in the microbiota or in the antigen specific immune response, suggesting patient improvement is not directly linked to these aspects of disease.

Disclosure: B. Moeller, None; P. Bender, None; S. Eick, None; K. Midwood, None; J. Potempa, None; S. Reichenbach, None; A. Schwenzer, None; P. M. Villiger, None; A. Wong, None.

Change in RF and Anti-CCP Isotype Levels in RA Patients Treated with Anti-TNF, Abatacept, Rituximab or Tocilizumab and Correlation with Clinical and Radiographic Outcomes: Data from a Randomized Trial

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: In rheumatoid arthritis (RA), little is known about the prognostic relevance of the change in autoantibody (ab) levels. Seroconversion was reported to be associated with a better clinical and radiological outcome in MTX-insufficient responders (IRs) treated with abatacept (1). The ROC randomized study (2) offered the opportunity to investigate changes in RF and anti-CCP levels in 1st anti-TNF-IR patients treated either with a 2nd anti-TNF, abatacept, rituximab or tocilizumab.

Objective: To evaluate the effects of bDMARDS on rheumatoid factor (RF) and IgG, A and M anti-CCP ab in RA, and associations between changes in serological status and clinical and radiological responses.

Methods: Ab titres (IgM-RF, IgG, A and M-anti-CCP) were determined by ELISA at baseline and month 6 in respectively 230, 220, 242 and 241 patients enrolled in the ROC randomized trial. The association between changes in ab titers with clinical response was assessed at months 6 and 12. Radiographs of the hands and feet were analyzed at screening and at months 12. The van der Heijde-modified Sharp scoring method was used to assess the mean change from baseline in total Sharp score (TSS) and to determine radiographic progression.

Results: Seroconversion of IgM-RF (patients with IgM-RF present at baseline, and then that became undetectable after treatment) was observed in only 4 patients (2%), of IgG antiCCP in 15 (7%), of IgA in 17 (7%) and of IgM in 16 patients (7%).

No significant difference in the proportion of patients converted to seronegative status was observed between patients treated with a 2nd anti-TNF or with a non-TNF targeted therapy. In the non anti-TNF group, seroconversion of IgA anti-CCP was significantly more frequent in rituximab (24%) than in abatacept (7%) or tocilizumab-treated patients (4%) (p=0.007). Seroconversion of RF was associated with a significantly more frequent remission (75% of patients with a DAS28-ESR<2.6 at month 6 among seroconverted patients vs 22% in patients who remained RF positive, p=0.01). IgA anti-CCP seroconversion was associated with a better therapeutic response (good EULAR response in 59% of seroconverted patients at month 12 vs 25% in patients who remained IgA anti-CCP positive, p=0.004). Seroconversions of IgM and IgG anti-CCP were not associated with any clinical or radiological response.

RF levels decreased irrespectively of the biologic used whereas a significant decrease of anti-CCP isotypes was only observed with rituximab. The decrease of RF was correlated with the decrease of polyclonal B-cell activation markers (total IgG, IgA, IgM, kappa and lambda free light chains of immunoglobulins (FLCs), whereas IgG, IgA, IgM-anti-CCP were not correlated with total IgA, G, M or FLCs. Changes in RF or anti-CCP levels were not associated with clinical or radiographic outcome.

Conclusion: Seroconversion of RF and anti-CCP was infrequent. Seroconversion of RF was significantly associated with a more frequent DAS28-remission and seroconversion of IgA anti-CCP with a better EULAR response.

Disclosure: R. Felten, None; M. A. Alyanakian, None; L. Chatenoud, None; J. Sibilia, None; F. Gandjbakhch, None; C. Lukas, None; J. E. Gottenberg, None.

Clinical and Sociodemographic Characteristics of Patients with Rheumatoid Arthritis (RA) Starting Triple Therapy and a Combination of a TNF Inhibitor and Methotrexate from a Large US Registry

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SESSION INFORMATION

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Session Type: ACR Poster Session A

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Background/Purpose: The combination of methotrexate (MTX), hydroxychloroquine (HCQ) and sulfasalazine (SSZ) has been called Triple Therapy (Triple) and has been compared with a combination of TNF inhibitors and MTX (TNFi + MTX). We sought to examine the use of Triple in a large US registry and compare the clinical and sociodemographic characteristics of the patients starting either therapy to determine if there were clinically relevant differences at initiation.

Methods: All eligible initiations in the Corrona registry from 2001-2017 were considered. Initiation of Triple was defined as initiation of one or more of the three drugs resulting in the first time use of all three drugs. Initiation of TNFi+MTX was defined as the initiation of TNFi resulting in the first time use of TNFi + MTX. Initiations were in patients who were biologic/small molecule naïve. Sociodemographic, clinical and disease characteristics were compared at time of initiation between the therapies. Patients initiating Triple who later initiated TNFi+MTX were not included in the TNFi+MTX cohort. Standardized mean differences (SMDs) were used to compare patients initiating Triple vs TNFi+MTX therapy; |SMDs| >0.15 were considered clinically relevant.

Results: From 2001- 2017, we identified 3452 TNFi+MTX and 226 Triple eligible initiations. Table 1 describes patient characteristics with |SMDs|>0.15. Triple initiators were older, had longer disease duration, were more likely to have Medicare coverage, and more likely to be RF+ or CCP+. Triple initiators had a history of more comorbidities than TNFi+MTX initiators. TNFi +MTX initiators had higher disease activity measures than Triple initiators: CDAI and all its components, patient fatigue and mHAQ. There were larger differences in MD Global and joint counts (|SMDs|>0.30) than Pt Global and Pt Fatigue (|SMDs| < 0.19). At start of therapy patient pain and prednisone, analgesic and NSAID use were not different (|SMDs| <0.15).

Conclusion: Utilization of Triple was not common over a period of 16 years covered by the registry. Pts started on triple were older, had less severe RA and a higher comorbidity burden. These differences are likely to impact response to treatment as it appears that rheumatologists channeled pts with more severe RA to TNFi + MTX, while pts with a h/o comorbidities were more likely to receive Triple.

Table 1. Clinically relevant standardized differences (SMDs) between groups, all initiators

Variable	Triple		TNFi + MTX		SMD	P value
	N	Proportion or Mean	N	Proportion or Mean		
Age	225	59.94	3429	56.66	0.250	0.0003
Medicare Insurance	215	0.34	3248	0.27	0.178	0.01
Duration RA	224	8.64	3414	6.36	0.267	0.0001
RF+ or CCP+	160	0.82	2234	0.75	0.160	0.05
Hx Malignancy	226	0.15	3452	0.04	0.475	<0.0001
Hx Serious Infections	226	0.06	3452	0.03	0.209	0.002
Charlson Index	226	1.32	3452	1.21	0.230	0.008
CDAI	218	14.9	3332	20.66	-0.404	<0.0001
28 Tender Joint Count	218	4.14	3332	6.70	-0.370	<0.0001
28 Swollen Joint Count	218	4.50	3332	6.45	-0.314	<0.0001
Patient Global (0-100)	218	36.48	3332	40.60	-0.152	0.03
MD Global (0-100)	218	26.12	3332	34.53	-0.370	<0.0001
mHAQ (0-3)	224	0.39	3363	0.48	-0.185	0.007
Pt Fatigue (0-100)	119	36.53	1770	42.18	-0.187	0.05

Disclosure: J. Kremer, Corrona LLC, 1, 3; J. L. Palmer, Corrona LLC, 1, 3; G. W. Reed, Corrona, 1, 3; D. A. Pappas, Corrona, LLC, 3, Novartis, 9; L. R. Harrold, Corrona, LLC, 1, Pfizer, Inc., 2, Roche, Bristol-Myers Squibb, 5, Corrona, LLC, University of Massachusetts Medical School, 3; J. Greenberg, Corrona LLC, 1, Corrona LLC, 3, Eli Lilly, Genentech, Janssen, Pfizer Inc, 5; J. R. Curtis, AbbVie, Amgen, Bristol-Myers Squibb, Corrona, Janssen, Lilly, Myriad, Pfizer, Radius, Roche/Genentech, UCB, 2, AbbVie, Amgen, Bristol-Myers Squibb, Corrona, Janssen, Lilly, Myriad, Pfizer, Radius, Roche/Genentech, UCB, 5.

Abstract Number: 570

Evaluation of CXCL13, sICAM1, MMP-3 and S100A8/A9 As Serum Biomarkers in Patients with Rheumatoid Arthritis Treated with Subcutaneous Tocilizumab

D. James Haddon, Thierry Sornasse, Michael J. Townsend, Jinglan Pei and Margaret Michalska, Genentech, Inc., South San Francisco, CA

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Session Type: ACR Poster Session A

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

Background/Purpose: Serum levels of C-X-C motif chemokine ligand 13 (CXCL13) and soluble intercellular adhesion molecule-1 (sICAM-1) have been associated with outcomes in patients with rheumatoid arthritis (RA) treated with tocilizumab (TCZ); levels of matrix metalloproteinase-3 (MMP-3) and S100A8/A9 have also been associated with disease activity and joint damage. This study evaluated the association of CXCL13, sICAM-1, MMP-3 and S100A8/A9 levels with disease activity and response to TCZ in patients with RA who achieved low disease activity with 24 weeks of TCZ + methotrexate (MTX) treatment and were subsequently randomized to TCZ monotherapy (mono) or TCZ + MTX in the COMPACT trial (NCT01855789).

Methods: US patients with RA who had an inadequate response to MTX received initial combination therapy of MTX plus TCZ 162 mg subcutaneous for 24 weeks. Patients who achieved Disease Activity Score in 28 joints – erythrocyte sedimentation rate (DAS28-ESR) ≤ 3.2 at Week 24 were randomized 1:1 to receive either TCZ mono or continue TCZ + MTX until Week 52. Randomized patients were included in the present study based on baseline, Week 24 and Week 40 sample availability; serum levels of CXCL13, sICAM-1, MMP-3 and S100A8/A9 were measured by immunoassay. Spearman correlations between CXCL13, sICAM-1, MMP-3 and S100A8/A9 levels and DAS28-ESR at baseline, Week 24 and Week 40 were analyzed. Changes in CXCL13, sICAM-1, MMP-3 and S100A8/A9 levels from baseline to Week 24 (open-label period) were determined using Wilcoxon test. Mean changes in CXCL13, sICAM-1, MMP-3 and S100A8/A9 levels from Week 24 to Week 40 (randomized period) were compared between treatment arms using analysis of covariance.

Results: Of 296 randomized patients, 249 were included (TCZ mono, n = 126; TCZ + MTX, n = 123). Biomarker levels were well balanced across treatment arms at baseline and Week 24 (randomization). At baseline, there were weak to mild correlations between DAS28-ESR and biomarker levels (CXCL13 [r = 0.13, P = 0.0411], sICAM-1 [r = 0.20, P = 0.0015], MMP-3 [r = 0.19, P = 0.0021], S100A8/A9 [r = 0.25, P = 0.0001]). Significant reductions in biomarker levels were observed from baseline to Week 24 (open-label period) in all patients (P < 0.0001). CXCL13, sICAM-1, MMP-3 and S100A8/A9 levels were relatively stable between Week 24 and Week 40 (randomized period), with no significant differences between TCZ mono and TCZ + MTX (Table).

Conclusion: In agreement with previous studies, the association between baseline disease activity and CXCL13, sICAM-1, MMP-3 and S100A8/A9 levels was weak to mild; TCZ + MTX treatment from baseline to Week 24 (open-label period) resulted in significant reductions in all biomarkers. Changes in levels of CXCL13, sICAM-1, MMP-3 and S100A8/A9 from Week 24 to 40 (randomized period) were similar between treatment groups, consistent with the finding of non-inferiority of TCZ mono compared with TCZ + MTX in patients with RA who achieve low disease activity with TCZ + MTX.

Table. Changes in Serum Biomarker Levels from Week 24 to Week 40 (Randomized Period) in Patients Receiving TCZ as Monotherapy or in Combination With MTX

Estimated Mean Change From Week 24 to 40* (95% CI)	TCZ Mono (n = 126)	TCZ + MTX (n = 123)	Difference, TCZ Mono Minus TCZ + MTX (95% CI)
CXCL13 (pg/mL)	−0.02 (−0.05 to 0.01)	−0.04 (−0.07 to −0.00)	0.02 (−0.02 to 0.05)
sICAM-1 (pg/mL)	0.01 (−0.01 to 0.02)	−0.01 (−0.03 to 0.01)	0.01 (−0.01 to 0.03)
MMP-3 (ng/mL)	0.04 (0.01 to 0.08)	0.03 (−0.00 to 0.07)	0.01 (−0.03 to 0.05)
S100A8/A9 (ng/mL)	0.01 (−0.05 to 0.07)	−0.05 (−0.12 to 0.01)	0.06 (−0.01 to 0.13)

ANCOVA, analysis of covariance; CXCL13, C-X-C motif chemokine ligand 13; DAS28-ESR, Disease Activity Score in 28 joints calculated with erythrocyte sedimentation rate; MMP-3, matrix metalloproteinase-3; mono, monotherapy; MTX, methotrexate; q2w, every 2 weeks; qw, once a week; sICAM-1, soluble intercellular adhesion molecule-1; TCZ, tocilizumab; TNFi, tumor necrosis factor inhibitor.

* ANCOVA model for estimated mean included log10 transformed Week 24 biomarker value as a covariate, treatment group and the following randomization stratification factors: DAS28-ESR remission status at Week 24 (< 2.6, ≥ 2.6 to ≤ 3.2), patient TNFi exposure (yes or no), baseline weight-by-dosing group (< 80 kg q2w, 80 to < 100 kg q2w, 80-to < 100 kg qw, ≥ 100 kg qw).

Disclosure: D. J. Haddon, Genentech, Inc., 3; T. Sornasse, Genentech, Inc., 3; M. J. Townsend, Genentech, Inc., 3; J. Pei, Genentech, Inc., 3; M. Michalska, Genentech, Inc., 3.

Abstract Number: 571

United States Rheumatology Practice-Based Real-World Evidence of Methotrexate Utilization and Response to Therapy in Rheumatoid Arthritis Patients Treated with Intravenous Golimumab

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: AWARE (Comparative and Pragmatic Study of Golimumab IV Versus Infliximab in Rheumatoid Arthritis) is a nongoing Phase 4 comparator study designed to provide a real-world assessment of intravenous golimumab (GLM) and intravenous infliximab (IFX) in patients (pts) with rheumatoid arthritis (RA). The primary objective of AWARE is to assess the incidence of infusion reactions, the concomitant use of methotrexate (MTX) is also reported. The FDA approved label for GLM states that it is indicated for the treatment of patients with moderately to severely active RA in combination with MTX; however prospectively obtained real world evidence based data on the rate of GLM use without MTX has not been reported. Here we compare patient demographics, disease characteristics, response to therapy and discontinuation of GLM treated patients with and without concomitant MTX from an interim analysis (IA) of the AWARE study.

Methods: AWARE is a prospective, noninterventional, observational, multicenter 3-year study conducted in the US. RA pts (1,200 adults) were enrolled at the time of initiating treatment with GLM or IFX. All treatment decisions including MTX utilization are made at the discretion of the treating rheumatologist. Imputations of CDAI data were not performed at this IA. Data shown are mean ± standard deviation.

Results: 678 GLM pts were enrolled; of these 487 (71.8%) were GLM Plus-MTX and 191 (28.2%) were GLM No-MTX. Demographics are shown in the table. Response to therapy was assessed with CDAIs and shown in the figure below.

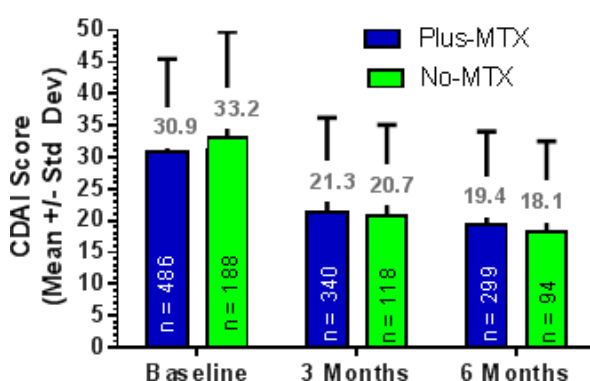
	GLM Plus-MTX	GLM No-MTX
Number of Patients	487	191
Age (years)	61.7 ± 12.85	58.7 ± 14.55
Sex (% Female)	87.1%	81.7%

Table . (Cont'd)

	GLM Plus-MTX	GLM No-MTX
Disease Duration (yr)	9.0 ± 9.67	9.6 ± 10.74
Baseline CDAI	30.9 ± 14.58	33.2 ± 16.61
Race		
White	86.2%	87.4%
African American	8.6%	8.4%
Other	5.1%	4.2%
Weight (kg)	83.6 ± 24.55	84.0 ± 22.21
BMI (kg/ m ²)	31.0 ± 8.45	30.8 ± 7.89

Overall, 92.6% of GLM Plus-MTX and 91.5% of GLM No-MTX pts had a baseline (BL) categorical CDAI disease activity of moderate or high, and 7.4% of GLM Plus-MTX and 8.5% of GLM No-MTX pts had a BL categorical CDAI disease activity of low or remission. Discontinuation from the study during the period of this IA was similar between the GLM Plus-MTX (173/487; 35.5%) and GLM No-MTX (64/191; 33.5%). 7.9% of GLM No-MTX pts reported leflunomide use.

**CDAI Score Among Patients Treated with
Golimumab IV: Plus-MTX or No-MTX**



Conclusion: At BL 28.2% of pts on GLM did not report concomitant MTX use. The demographics of the GLM Plus-MTX pts did not differ remarkably from GLM No-MTX pts. The reported early response to treatment, assessed by CDAI score after 3 months and 6 months was similar in the GLM Plus-MTX and GLM No-MTX groups. These preliminary IA data suggest that in a real-world rheumatology practice setting, use of GLM with or without concomitant MTX led to similar CDAI scores at 3 and 6 months in RA pts with predominantly moderate to high BL CDAI disease category.

Disclosure: A. Broadwell, Janssen Research & Development, LLC, 2; V. Bray, Janssen Research & Development, LLC, 2; D. Conaway, Janssen Research & Development, LLC, 2; J. Schechtman, Janssen Research & Development, LLC, 2; A. J. Kivitz, Janssen Research & Development, LLC, 2; D. Parenti, Janssen Scientific Affairs, LLC, 3; S. Black, Janssen Scientific Affairs, LLC, 3; S. Xu, Janssen Research & Development, LLC, 3; W. Langholff, Janssen Research & Development, LLC, 3; S. Kafka, Janssen Scientific Affairs, LLC, 3.

Abstract Number: 572

Combining Tocilizumab with Methotrexate Improves Sustainability. Real World Evidence Report from Quebec Database Rhumadata®

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Biologic therapy targeting TNF have consistently demonstrated better efficacy and effectiveness when combined with a conventional synthetic DMARD (csDMARD), most frequently methotrexate. Although pre-clinical protocols have shown the short-term efficacy of tocilizumab (TOCI) in monotherapy in very selected patients suffering from rheumatoid arthritis (RA), little is known on the long-term comparative sustainability of monotherapy (Mono) versus combo therapy (Combo). We evaluate here the comparative sustainability of tocilizumab in patients with rheumatoid arthritis initially treated with or without MTX.

Methods: Data from RHUMADATA® patients with RA prescribed TOCI either as an initial or second biologic was analyzed. Patients were followed until treatment discontinuation, loss to follow-up or April 22nd, 2018. The characteristics of selected patients were tabulated and the TOCI discontinuation rates of patients undergoing initial mono and combo therapy compared using Kaplan-Meier methods and Cox regression models adjusting for potential confounders.

Results: A total of 122 patients with RA received TOCI in first or second intention. Of those, 44(36.1%) and 78(63.9%) initially received mono and combo therapy respectively. Most patients were women (77%), mean age at diagnosis was 45.0 (SD=12.8) years, and the average age at treatment initiation was 54.5 (SD=11.8) years. HAQ and DAS28(4)-CRP at treatment initiation were respectively 1.21 (SD=0.57) and 4.64 (SD=1.01). Forty-nine and 11 percent of patients concomitantly received hydroxychloroquine (HCQ) and sulfasalazine (SSZ) respectively. Age-adjusted Carlson's comorbidity index (ACCI) at baseline was 2.5 (SD=1.1), and 79% were RF-positive and 75% ACPA positive. Significant differences in retention rates between mono and combo TOCI therapy were observed (log-rank p-value =0.0002). Mean retention time for mono and combo-therapy were respectively 2.77(SE=0.41) and 5.13(SE=0.43) years. Use of MTX remains significant (p-value<.0001) after adjusting for gender, age and disease duration at treatment initiation, HAQ, DAS28(4)-CRP, RF and ACPA, ACCI, and concomitant use of HCQ and SSZ.

Conclusion: Combining tocilizumab with MTX significantly improves its sustainability.

Disclosure: D. Choquette, None; L. Bessette, None; J. Brown, None; B. Haraoui, Amgen Inc., 2, 9, Pfizer, Inc., 2, 8, 9, UCB, Inc., 2, 8, 9, AbbVie Inc., 2, 9, Bristol-Myers Squibb, 2, 9, Eli Lilly and Co., 9, Merck & Co., 9, Sandoz, 9, Hoffmann-La Roche, 2, 9, Janssen, 2, 9; F. Massicotte, None; J. P. Pelletier, None; J. P. Raynauld, None; M. A. Rémillard, None; D. Sauvageau, None; A. Turcotte, None; É. Villeneuve, None; L. Coupal, None.

Abstract Number: 573

Subcutaneous Tocilizumab in Monotherapy or in Combination with DMARD in Patients with Moderate to Severe Active Rheumatoid Arthritis: Observational Study to Describe Real-World Drug Retention Rate at 12 Months, Interim Analysis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: In France, tocilizumab (TCZ) subcutaneous (sc) 1st prescription and yearly renewal are restricted to hospital. Monitoring may be done by both office-based or hospital rheumatologists. The objective is to describe 12-month drug retention rate, efficacy and tolerance of TCZ sc in real life in rheumatoid arthritis (RA) patients(pts).

Methods: Prospective, multicentre, observational 18-month study including pts with moderate/severe active RA requiring TCZ sc as prescribed in real life. *Primary endpoint:* drug retention rate of TCZsc at 12 months in pts followed by hospital- and office-based rheumatologists. *Secondary end points:* pts characteristics, concomitant treatments, adherence using the Compliance Questionnaire for Rheumatology (CQR5), efficacy and safety of TCZ sc. *Statistical analysis:* pts with ≥ 1 TCZ injection were analyzed for safety. Pts fulfilling inclusion and non-inclusion criteria were analyzed for efficacy.

Results: 291 pts were recruited, 288 were analysed for safety and 281 for efficacy. At baseline: mean age 56.2 ± 12.5 years, females: 74.4%, at least 1 co-morbidity: 71%, mean RA duration 9.5 ± 9.0 years, RF/ACPA +: 83.5%, erosive RA: 61.2%,

mean DAS28ESR 4.76 ± 1.22 . Past RA treatments included DMARDs in 94.3%, mainly MTX (90.4%), and biologics in 63.3%. TCZ Mono (i.e. without csDMARD) was initiated in 42% and TCZ Combo in 57% of the pts, 84.9% of the latest received MTX (mean dose 17.2 ± 4.4 mg/w). 151 pts completed M12, 26 pts had no M12 visit collected yet. 104 (37.1%) pts withdrew: AE 19.4%, lack of efficacy 11.1%.

At M12, drug retention rate was 63.3% in all pts, 61.8% in Mono, 64.1% in Combo (Fig.1). 2 Mono pts had an ongoing csDMARD, 6 Combo pts had no csDMARD. Total number of TCZ injections was 33.3 ± 23.3 done by pt himself in 53.9%, at home in 92.7%. Adherence to TCZ sc was high in 85.4% of the 82 pts who fulfilled the CQR5. 47.3% used prednisone at 13.1 ± 12.8 mg/day in the Mono and 8.4 ± 4.7 in the Combo group.

At M12, 89% of the pts were followed at hospital, 11% by mixed or office-based rheumatologists. Mean DAS28ESR in all, Mono and Combo were 1.89 ± 1.08 , 1.67 ± 1.03 , 2.05 ± 1.11 respectively. DAS28 remission and LDA were respectively 71.8% in all, 77.1% in Mono, 67.2% in Combo and 16.4% in all, 14.6% in Mono, 18.0% in Combo. No new safety signal was reported. 218 (75.7%) pts had at least one adverse event (AE), 41 (14.2%) had at least one serious AE including 7 serious infections.

Conclusion: In this 12-month interim analysis, drug retention rate was 63.3% in patients receiving TCZ sc in real life, with no difference between Mono and Combo groups. DAS28 remission/LDA was 88.2% in all patients, 91.7% in Mono and 85.2% in Combo. No new safety signal occurred. Final analysis will include remaining missing data.

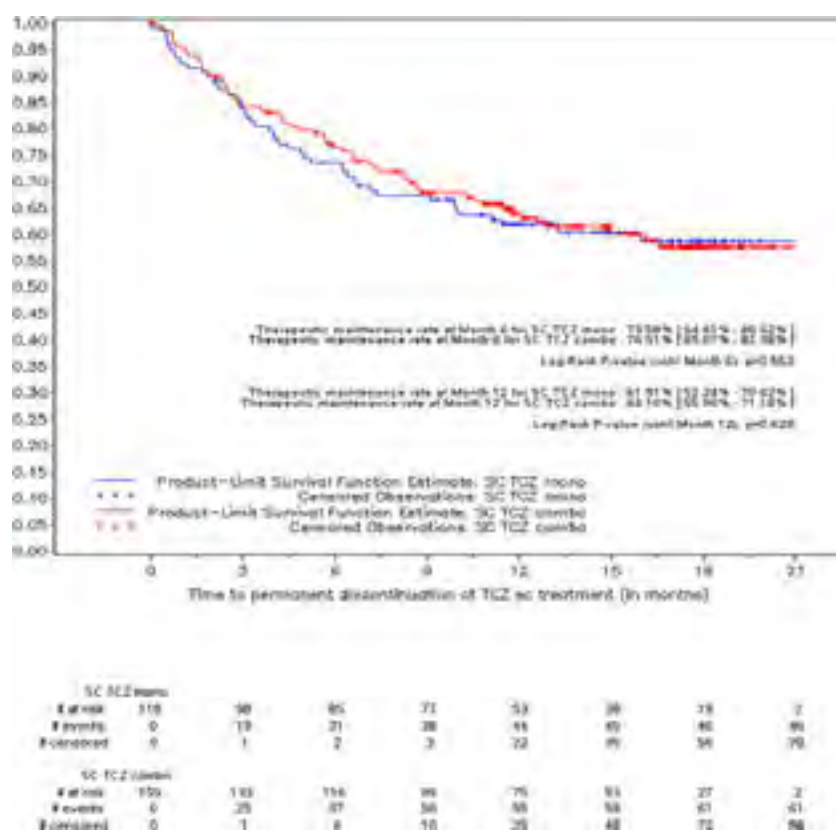


Fig. 1. Kaplan-Meier curve of the drug retention rate in Mono and Combo groups - Efficacy population

Disclosure: P. Hilliquin, Roche SAS, 5, Chugai Pharma France, 5; T. Barnette, Roche SAS, 5, Chugai Pharma France, 5; G. Baudens, Roche SAS, 5, Chugai Pharma France, 5; R. Niarra, Roche SAS, 3; I. Idier, Chugai Pharma France, 3; A. Sarau, Roche SAS, 5, Chugai Pharma France, 5.

Abstract Number: 574

Longitudinal Efficacy Analysis of Patients with Active Rheumatoid Arthritis and Inadequate Response to Conventional Synthetic Dmards: Response Following Rescue from Baricitinib 2mg to 4mg Once-Daily

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Alto, CA, ³Eli Lilly and Company, Indianapolis, IN, ⁴Keio University School of Medicine, Tokyo, Japan, ⁵Paris Descartes University, Hôpital Cochin, Paris, France, ⁶Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria, ⁷University of Alabama at Birmingham, Birmingham, AL

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Baricitinib (bari), an oral selective Janus kinase 1/2 inhibitor, has shown clinical efficacy in patients (pts) with RA and an inadequate response to conventional synthetic DMARDs.¹ Baricitinib is approved for treating moderate-severe RA in over 40 countries. The two objectives of these analyses were to evaluate the percentage of pts, originally randomized to 2 mg or 4 mg in the Phase 3 RA-BUILD study, and rescued in the study and/or in RA-BEYOND (the long-term extension study); and to assess the clinical benefits post-rescue.

Methods: RA-BUILD was a 24-week study evaluating once daily bari 4 mg (N=227) and 2 mg (N=229) compared to placebo (N=228). Pts with <20% improvement in tender joint count or swollen joint count (SJC) at Weeks 14 and 16 compared to baseline were rescued to bari 4 mg at Week 16; at Week 20, rescue was based on investigators' decision. Pts not rescued continued blinded treatment in RA-BEYOND and those with Clinical Disease Activity Index (CDAI)>10 at or after 3 months in RA-BEYOND were eligible for rescue to bari 4 mg, but not required. Once rescued, change in background medications was allowed. In RA-BEYOND, unrescued pts achieving sustained CDAI ≤10 were randomized to bari 2 mg or maintained at 4 mg. Descriptive longitudinal data analysis was based on observed data from pts randomized to bari 2- or 4-mg in RA-BUILD, including data up to 1 April 2017 in RA-BEYOND. Percent rescued and overall response rates in achieving CDAI ≤10, and pain (visual analogue scale ≤10, 20 or 40 mm), were evaluated from time of original randomization to bari 4 mg and 2 mg in RA-BUILD. Median change over time in CDAI, HAQ, SJC28 and pain after rescue from 2 to 4 mg was evaluated using pt data at time of rescue (reset as Week 0).

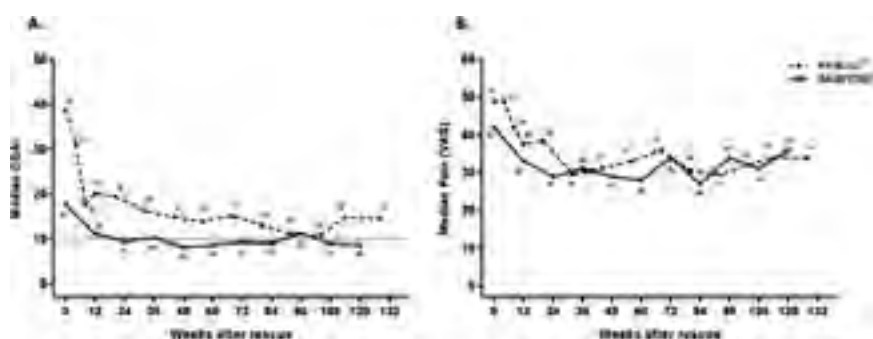


Figure 1. Median CDAI (A) and Median Pain (B) after rescue in patients rescued from bari 2 mg to 4 mg. Observed values. Numbers are indicated for each data point. RA-BUILD dataset includes patients rescued only in RA-BUILD and those rescued in both RA-BUILD and RA-BEYOND. RA-BEYOND data set includes patients rescued only in RA-BEYOND.

Table. Mean and median clinical outcome values in patients originally on bari 2 mg rescued to bari 4 mg in RA-BUILD or RA-BEYOND								
	CDAI		HAQ-DI		Pain (VAS)		SJC28	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
RA-BUILD¹								
At time of rescue (N=21)	30.99	30.76	1.38	1.38	52.10	49.00	10.48	10.00
Week 128 after rescue ² (N=15)	13.96	14.50	1.04	1.13	35.53	34.00	2.80	2.00
RA-BEYOND³								
At time of rescue (N=97)	19.97	17.70	1.14	1.12	45.26	42.00	4.11	3.00
Week 120 after rescue ² (N=45)	10.47	8.60	1.02	1.00	35.56	30.00	1.90	2.00

¹Includes patients rescued only in RA-BUILD and those rescued in both RA-BUILD and RA-BEYOND.
²Includes patients rescued only in RA-BEYOND.
³15 of the patients achieved CDAI≤10 after rescue to bari 4 mg in RA-BUILD.
⁴15 of the patients achieved CDAI≤10 after rescue to bari 4 mg in RA-BEYOND.
CDAI = Clinical Disease Activity Index; HAQ-DI = Health Assessment Questionnaire; VAS = Visual Analogue Scale; SJC28 = Swollen Joint Count based on 28 joints; VAS = visual analogue scale.

Results: The percentage of pts on bari 4 mg “rescued” in RA-BUILD was 36% compared to 52% in pts originally assigned to bari 2 mg. In RA-BEYOND, 7% of pts originally randomized to 4 mg were rescued after dose tapering to 2 mg. Clinically meaningful response rates in CDAI (≤ 10) and pain improvement increased and stabilized over time in the bari-treated population. Pts rescued in RA-BEYOND, after being treated with bari in RA-BUILD had less disease activity compared to pts rescued in RA-BUILD at the time of rescue (Table). Pts on 2 mg rescued to bari 4 mg in RA-BEYOND demonstrated improved disease control with the majority achieving CDAI ≤ 10 and pain reduction (Figure).

Conclusion: Fewer pts originally assigned to bari 4 mg in RA-BUILD required rescue compared to pts assigned to 2 mg. Disease activity assessed by CDAI and patient-reported pain improved in many pts after rescue from 2 to 4 mg of bari.

References: 1. Dougados, M et al. *Ann Rheum Dis*. 2017;76:88

Disclosure: R. Fleischmann, AbbVie, Amgen, AstraZeneca, Aventis, BMS, Celgene, Eli Lilly and Company, Genentech, GSK, Janssen, Merck, Pfizer, Regeneron, Roche, Sanofi, UCB, 2, AbbVie, Akros, Amgen, BMS, Celgene, Eli Lilly and Company, Genentech, GSK, Janssen, Pfizer, Sanofi-Aventis, UCB, 5; M. C. Genovese, AbbVie, Eli Lilly and Company, Galapagos, Gilead, Pfizer, 5; A. Cardoso, Eli Lilly and Company, 1, 3; L. Sun, Eli Lilly and Company, 1, 3; Y. F. Chen, Eli Lilly and Company, 1, 3; C. D. Walls, Eli Lilly and Company, 1, 3; D. E. Schlichting, Eli Lilly and Company, 1, 3; T. Takeuchi, Astra Zeneca K.K., Eli Lilly Japan K.K., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Co., Abbvie GK, Nipponkayaku Co.Ltd, Janssen Pharmaceutical K.K., Astellas Pharma Inc., Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co, Ltd., Taisho Toyama, 5, AbbVie GK., Bristol-Myers K.K., Chugai Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Astellas Pharma Inc, Diaichi Sankyo Co., Ltd., Eisai Co., Ltd., Sanofi K.K., Teijin Pharma Ltd., Takeda Pharmaceutical Co., Ltd., Novartis Pha, 8; M. Dougados, Abbvie, Pfizer, Eli Lilly and Company, Novartis, UCB, Merck, Roche, BMS, UCB, 2, 5; J. S. Smolen, AbbVie, Janssen, Eli Lilly and Company, MSD, Pfizer, Roche, 2, AbbVie, Amgen, Astra-Zeneca, Astro, BMS, Celgene, Celltrion, Chugai, Gilead, Glaxo, ILTOO, Janssen, Eli Lilly and Company, Medimmune, MSD, Novartis-Sandoz, Pfizer, Roche, Samsung, Sanofi-Aventis, UCB, 5; J. R. Curtis, AbbVie, Amgen, BMS, Eli Lilly and Company, Janssen, Pfizer, Roche/Genentech, Corrona, UCB, Myriad, 2, 5.

Abstract Number: 575

Time to Discontinuation of Biologic Therapy By Mechanism of Action in Rheumatoid Arthritis: Results from a Rheumatoid Arthritis Cohort

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Patients with rheumatoid arthritis (RA) may discontinue their biologic disease modifying antirheumatic drug (bDMARDs) due to non-response, loss of response or adverse events. However, time to discontinuation may be related to mechanism of action. We aimed to compare drug survival of tumor necrosis factor inhibitors (TNFi) versus non-TNFi/TOFA in patients initiating bDMARD treatment in a Canadian (Ontario) observational cohort.

Methods: Patients enrolled in the Ontario Best Practice Research Initiative (OBRI) who started their first bDMARD therapy within 30 days before or any time after OBRI enrolment were included. Patients were excluded if they had less than 2 visits during this period of time. Patients were followed from bDMARD start until discontinuation/switching, death, lost to follow-up, or last visit, whichever came first. Time to discontinuation of bDMARD due to (1) any reason, (2) non-response, physician, and patient decision, (3) non-response, and (4) adverse events (AEs) were assessed using Kaplan-Meier survival analysis for TNFi versus Non-TNFi/TOFA users. Cox proportional hazards regression model was also used to compare TNFi versus Non-TNFi/TOFA users adjusting for the effect of potential confounders. To deal with missing data, multiple imputation by chained equations was performed.

Results: A total of 796 patients were included of whom 130 (16.3%) received non-TNFi and 756 (83.7%) received TNFi (Table 1). TNFi included: Etanercept, Adalimumab, Certolizumab, Golimumab, and Infliximab. Non-TNFi/TOFA and Tofa

included: Abatacept, Rituximab, Tocilizumab, and small molecule Tofacitinib. Mean (SD) age and disease duration were 56.2 (12.8) years and 8.3 (9.0) years, respectively, and the majority were females (79.8%).

Over a mean (SD) follow-up of 2.4 (2.0) years, bDMARD discontinuation was reported for 291 (36.6%) due to any reason, 229 (28.8%) due to non-response, AEs, physician, and patient decision, 110 (13.8%) due to non-response, and 81 (10.2%) due to AEs, respectively.

There was a significant difference in time to discontinuation due to any reason (Logrank $p=0.0002$); non-response, AEs, physician, and patient decision (Logrank $p=0.04$) between TNFi and non-TNFi/TOFA users. However, there was no significant difference in bDMARD discontinuation due to non-response (Logrank $p=0.36$) and AEs (Logrank $p=0.06$). After adjusting for potential confounders, difference in discontinuation remained significant between the TNFi and non-TNFi/TOFA group for any reason [HR: 0.62 (0.46-0.84)] and non-response, AEs, physician, and patient decision [HR: 0.67 (0.47-0.94)].

Conclusion: The analysis demonstrates that patients initially started on non-TNFi/TOFA therapy are significantly more likely to discontinue their therapy earlier for any reason and due to non-response, AEs, physician and patient decision compared to TNFi therapy. Lack of response is likely not driving this, however AEs and, to an even greater degree, patient and physician preference likely influenced the results.

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Abstract Number: 576

An Analysis of Early Introduction of Adalimumab and Subsequent Bio-Free Condition in the Patients with Rheumatoid Arthritis

Satoshi Ito¹, Yoichi Kurosawa^{1,2}, Eriko Hasegawa^{1,2}, Daisuke Kobayashi^{1,2}, Shinji Taniguchi¹, Asami Abe¹, Hiroshi Otani¹, Kiyoshi Nakazono¹, Akira Murasawa¹, Ichiei Narita² and Hajime Ishikawa¹, ¹Department of Rheumatology, Niigata Rheumatic Center, Shibata, Japan, ²Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: HOPEFUL-1 trial showed efficacy of combination therapy with adalimumab (ADA) plus methotrexate (MTX) in MTX naïve patients with active early rheumatoid arthritis (eRA). In that trial, early introduction of ADA significantly reduced the joint destruction. However, although the biological disease-modifying antirheumatic drugs (bDMARDs) are the most effective treatment of RA, the costs are much higher than those of conventional synthetic DMARDs (csDMARDs). In recent years, HOPEFUL-2 trial and HIT-HARD trial showed the possibility of successful bio-free in patients with eRA. / To analyze efficacy of early introduction of ADA and bio-free condition in RA patients in real world.

Methods: Among 172 patients (M35, F137) who received ADA, 44 patients (M12, F32) started ADA as an early introduction. In this study, the definition of early introduction was within 3 months from the start of MTX. Four patients switched to tocilizumab due to inefficacy and 3 patients achieved clinical remission (CR). Four patients discontinued ADA due to side effects. We analyzed 30 patients who were followed up more than 52 weeks with the mean age of 54.0 ± 14.9 years old, the mean disease duration of 11.8 ± 22.7 months.

Results: The mean DAS28-CRP decreased from 4.67 ± 1.38 to 1.73 ± 0.48 ($p<0.001$) after initiation of ADA. Twenty six patients achieved CR (86.6%), and 16 patients (53.3%) achieved bio-free condition. One patient relapsed and re-started ADA. After achieving CR again, the patient wanted bio-free condition with the adjustment of csDMARDs. Therefore, tacrolimus was raised from 1.5mg/day to 3mg/day and ADA was discontinued again. The mean duration of bio-free condition was 20.9 ± 14.7 months. MTX (mg/week) was significantly increased from 7.3 ± 1.9 to 8.8 ± 3.2 ($p<0.001$). The number of csDMARD other than MTX were changed from 0.9 ± 0.6 to 1.3 ± 0.9 ($p=0.008$). One patient discontinued bucillamine due to proteinuria. Prednisolone dose (mg/day) was decreased from 6.1 ± 3.5 to 2.9 ± 1.8 ($p<0.001$). Six patients with CR did not want bio-free condition. Six patients with sustained CR wanted bio-free condition and discontinuation of ADA was already scheduled.

Conclusion: Early introduction of ADA was effective and subsequent bio-free condition might be a good choice in terms of medical cost.

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Disclosure: S. Ito, None; Y. Kurossawa, None; E. Hasegawa, None; D. Kobayashi, None; S. Taniguchi, None; A. Abe, None; H. Otani, None; K. Nakazono, None; A. Murasawa, None; I. Narita, None; H. Ishikawa, None.

Abstract Number: 577

Expanded Autoantibody Profiles Predict Treatment Response to Biologic Therapy in Rheumatoid Arthritis

Ted R. Mikuls¹, Amrita Bath², Bryant R. England³, Michael J. Duryee⁴, Carlos D. Hunter⁴, Joel Kremer⁵, Dimitrios A. Pappas^{6,7}, William H. Robinson⁸, Jeffrey R. Curtis⁹ and Geoffrey M. Thiele¹⁰, ¹Internal Medicine, Division of Rheumatology, VA Nebraska-Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE, ²Rheumatology, University of Nebraska Medical Center, Omaha, NE, ³Rheumatology, VA Nebraska-Western Iowa Health Care System & University of Nebraska Medical Center, Omaha, NE, ⁴Internal Medicine Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE, ⁵Albany Medical Center, Albany, NY, ⁶Columbia University, New York, NY, ⁷Corrona, LLC, Waltham, MA, ⁸Stanford University, Palo Alto, CA, ⁹University of Alabama at Birmingham, Birmingham, AL, ¹⁰University of Nebraska Medical Center, Omaha, NE

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

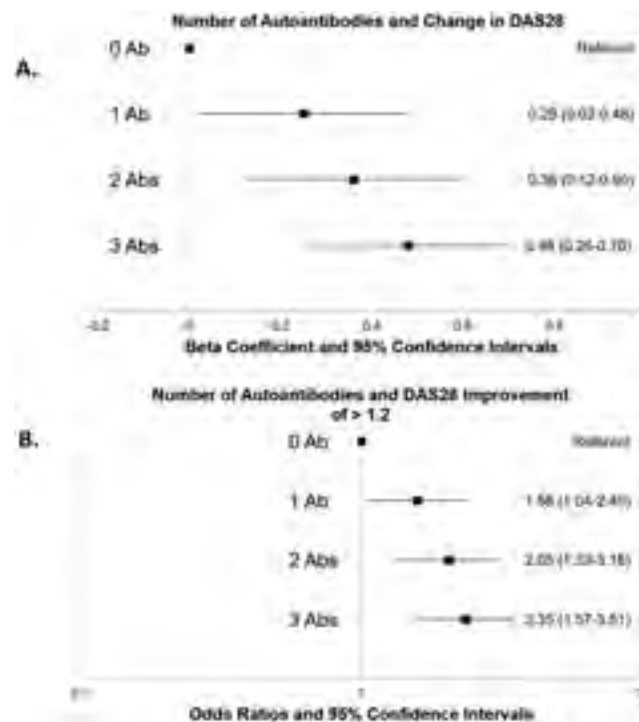
Session Time: 9:00AM-11:00AM

Background/Purpose: Although biologics represent a major advance in rheumatoid arthritis (RA), many patients fail to achieve adequate responses to these agents. As previous studies have suggested that individual autoantibodies may selectively predict treatment response, we examined whether combined positivity to three well-characterized RA-related autoantibodies predicts treatment response among RA patients initiating biologics.

Methods: We examined data and banked serum from the Comparative Effectiveness Registry to study Therapies for Arthritis and Inflammatory Conditions (CERTAIN), a prospective RA cohort study. We examined a subset (n=1224) of enrolled patients including: biologic naïve anti-TNF initiations (35%), biologic exposed rituximab (10%) and tocilizumab (24%) initiations, and abatacept (31%) initiations regardless of previous biologic exposure. RF, anti-CCP and IgG antibodies to malondialdehyde-acetaldehyde (MAA) were measured centrally using banked enrollment serum. RF and anti-CCP positivity were defined per the manufacturer while anti-MAA positivity was defined as values >33rd percentile (to approximate the frequency of positivity for RF/anti-CCP). Response to therapy was evaluated at 6 months post biologic initiation. The relationship between the number of baseline autoantibodies (Abs) positive (range 0 to 3) with treatment response was examined using linear (DAS28 change) and logistic regression (>1.2 DAS28 change) accounting for age, sex, race/ethnicity, education, smoking, body mass index, concomitant DMARDs, baseline DAS28, and prior biologic use.

Results: Patients (n=1224) were predominantly Caucasian (89%) and female (79%) and had a mean age of 57 yrs. Most were RF (60%) or anti-CCP positive (55%) and biologic naïve (59%). Compared to those with no Abs positive, those positive for Abs achieved a significantly greater response (Figure). In separate univariate analyses, all 3 Abs were associated with DAS28 improvement with similar effects (β coef 0.29-0.31). After adjusting for covariates, patients positive for all 3 Abs had an average improvement in disease activity of 0.48 units (95% CI 0.26-0.70) compared to those with no Abs (A). Likewise, those with 3 positive Abs were 2.35 times more likely (95% CI 1.57-3.51) to achieve an improvement >1.2 DAS28 units during treatment (B). Associations between Ab positivity and treatment response were dose-dependent (trend $p < 0.001$ in both models) and did not differ substantially across biologics.

Conclusion: An expanded Ab profile appears to significantly predict RA treatment response to biologic treatment in a dose-dependent fashion. Additional work that incorporates these serologic profiles with additional biomarkers or other



informative patient characteristics could allow for the accurate prediction of treatment response, thus providing an opportunity to personalize RA management.

Figure:

Disclosure: T. R. Mikuls, BMS, Ironwood, Horizon, 2, Pfizer, Inc., 5; A. Bath, None; B. R. England, None; M. J. Duryee, None; C. D. Hunter, None; J. Kremer, None; D. A. Pappas, Corrona, LLC, 3, Novartis, 9; W. H. Robinson, None; J. R. Curtis, Amgen Inc., 2, 5, AbbVie Inc., 2, 5, BMS, 2, 5, Corrona, LLC, 2, 5, Janssen, 2, 5, Eli Lilly, 2, 5, Myriad, 2, 5, Pfizer, Inc., 2, 5, Roche/Genentech, 2, 5, Radius, 2, 5, UCB, Inc., 2, 5; G. M. Thiele, None.

Abstract Number: 578

Effect of Disease Duration and Other Patient Baseline Characteristics on Outcomes in Tocilizumab-Treated Rheumatoid Arthritis Patients: A Pooled Analysis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Tocilizumab (TCZ) efficacy and safety in rheumatoid arthritis (RA) have been well established by numerous phase 3 and 4 studies and observational studies. The purpose of the present analysis was to explore the extent to which disease duration, inflammation, disease burden, and other baseline factors explain variations in outcomes in studies of RA patients treated with TCZ.

Methods: This was a pooled analysis of methotrexate-inadequate responding (IR)/conventional synthetic (cs) DMARD-IR patients with RA allocated to TCZ (intravenous or subcutaneous, monotherapy + combination therapy) in phase 3 and 4 studies. Endpoints were change from baseline to week 24 in Clinical Disease Activity Index (CDAI) and quality of life

(Health Assessment Questionnaire–Disability Index [HAQ-DI]) and week 24 ACR50 and CDAI remission (≤ 2.8). Using a combination of clinically informed and mathematically driven variable selection techniques, models (with study included as a random effect to account for intracorrelation of observations within each study) were built to optimize fit and explain outcome variance. Analysis of covariance and logistic regression were used for CDAI/HAQ-DI change from baseline and for ACR50/CDAI remission, respectively.

Results: The analyses were performed on 5462 patients from 12 studies. Analysis of baseline characteristics (before TCZ administration) revealed that patients with longer disease duration had been exposed to more cs DMARDs and had worse HAQ-DI than patients with shorter disease duration. Statistical modeling of clinical outcomes showed that disease duration accounted for <2% of the variation in HAQ-DI and CDAI change from baseline. Baseline CDAI explained 32% of the variation in CDAI change from baseline. Patients with higher baseline values tended to have greater improvements, likely due to having more “room” for improvement and to a higher risk for regression to the mean resulting from the fact that inclusion criteria for most trials required defined thresholds of disease activity, including joint counts. Baseline HAQ-DI, neither an inclusion criterion itself nor influenced by other inclusion criteria, explained 15% of the variation in HAQ-DI change from baseline. The odds of achieving ACR50 decreased by 9.2% if disease duration was doubled. The odds of achieving CDAI remission decreased by 15% per 5 additional years of disease duration and decreased by 22% per 10 additional score units of CDAI at baseline.

Conclusion: In this pooled analysis of TCZ-treated RA patients, disease duration explained statistically significant but practically small variations in clinical outcomes. These findings support that TCZ treatment outcomes are not heavily influenced by disease duration or other baseline characteristics.

Disclosure: A. Rubbert-Roth, Roche, 9; D. Aletaha, Roche, 2, Roche, 5, Roche, 8; J. Devenport, Genentech, Inc., 3; P. N. Sidiropoulos, Genentech, Inc., 3; Y. Luder, F. Hoffmann-La Roche, 1, F. Hoffmann-La Roche, 3; M. Edwardes, None; J. W. G. Jacobs, None.

Abstract Number: 579

Changes in DNA Methylation Identify Response to Treatment with Methotrexate and TNF Inhibitors Among RA Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

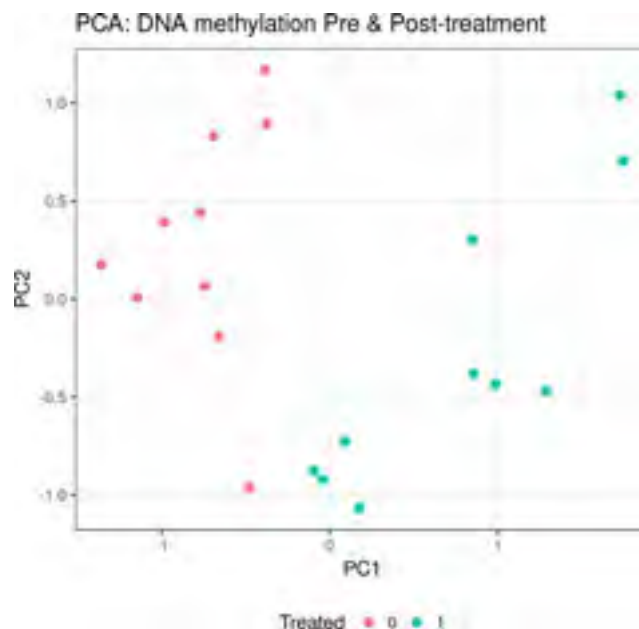
Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Epigenetic modifications including DNA methylation are implicated in the development and progression of autoimmune diseases, such as rheumatoid arthritis [MIM 180300]. Evidence indicates that exogenous exposures, such as smoking, diet, and medications can change DNA methylation and that changes in DNA methylation contribute to immune cell autoreactivity. Methotrexate (MTX) and anti-TNF agents (a-TNFs) are effective treatments for RA. It is believed they reverse epigenetic modifications that cause T-cell autoreactivity, improving RA symptoms among some patients. Changes in DNA methylation associated with response to these treatments are potential biomarkers for prediction of treatment response.

Methods: We conducted a study to identify DNA methylation profiles that may serve as biomarkers of response to treatment with MTX and a-TNFs for RA. Blood samples, clinical data, and disease severity scores (DSS) were collected from 30 treatment naive individuals with RA at baseline and after 3-6 months of treatment with: MTX (n=10), a-TNFs (n=10), or MTX and a-TNFs (n=10). DSS included the Simple Disease Activity Index, Clinical Disease Activity Index, and the C-reactive protein and Erythrocyte Sedimentation Rate Disease Activity Scores. Genome-wide methylation profiles were generated using Illumina's Infinium Human Methylation EPIC BeadChip from PBMC samples. Quantile normalization and background subtraction with dye-bias normalization were performed using minfi and CpGs with high detection p-values and cross-reactive probes, and CpGs measuring SNPs were excluded. Treatment response was defined as difference in DSS from baseline to post treatment measurements. Differentially methylated positions (DMPs) and differentially methylated regions (DMRs) associated with, i) treatment, and ii) treatment response, were identified with limma and bumpHunter, respectively, using surrogate variables to adjust for blood cell proportions, batch effects, and genetic ancestry. Next, due to small sample size, baseline methylation levels in the top 1000 DMPs and 100 DMRs (by p-value, no multiple testing correction) identified in pre- and post-treatment analyses were used to predict observed treatment response. Principal component analysis (PCA) was done with the top DMPs and DMRs to identify treatment and treatment response clusters.



Results: Preliminary results found 38 DMPs associated with treatment ($p < 0.0001$), 28 of which were hypomethylated. PCA found distinct clusters for study subjects pre- and post-treatment. Additionally, subjects clustered by treatment arm using baseline methylation only.

Conclusion: These results indicate that treatment with MTX and a-TNFs alter DNA methylation and may be used as biomarkers treatment response. Further research is needed with larger sample size.

Disclosure: C. Adams, None; K. Marker, None; M. Krueger, None; L. Barcellos, None; L. A. Criswell, None.

Abstract Number: 580

Clinical Effectiveness of Tofacitinib 11mg Once Daily (QD) Versus Tofacitinib 5mg Twice Daily (BID) in the Corrona US RA Registry

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA, originally approved at 5 mg twice daily (BID). In 2016, an extended-release (XR) dose of tofacitinib 11 mg once daily (QD) was approved. Limited clinical or real-world data exist comparing efficacy outcomes between 11 mg QD and 5 mg BID doses. We aimed to compare the efficacy of these formulations.

Methods: Treatment effectiveness at 6 (± 3) months(mos) after initiation (baseline) was evaluated in an observational cohort of patients(pts) initiating tofacitinib 5 mg BID or 11 mg QD between February 2016 and March 2018, identified from the Corrona US RA Registry. The primary outcome was achievement of a minimum clinically important difference (MCID) in Clinical Disease Activity Index (CDAI) improvement at approximately the 6-mo visit following initiation. The MCID was dependent on baseline disease activity (≥ 2 if low baseline CDAI [≤ 10], ≥ 6 if moderate baseline CDAI [$10 < \text{CDAI} \leq 22$], and ≥ 11 if high baseline CDAI [> 22]). Secondary outcomes included: CDAI change from baseline to 6-mo visit, Pt Pain, and Pt Fatigue; achievement of low disease activity (LDA; CDAI ≤ 10) in pts without baseline LDA, or remission (CDAI ≤ 2.8) in pts without baseline remission, at 6 mos; and improvement \geq MCID in HAQ (≥ 0.22) at 6 mos. Outcomes were compared between groups in unadjusted analyses and adjusted linear and logistic regression models (covariates: age, sex, baseline CDAI, duration of RA [apriori decision], and additional covariates with standardized

Table 1. Patient baseline characteristics, and unadjusted and adjusted 6-month primary and secondary outcomes, of patients initiating tofacitinib 11 mg QD and 5 mg BID in the Corrona US RA Registry

	Tofacitinib 11 mg QD (N=196)	Tofacitinib 5 mg BID (N=138)	p value*
Baseline demographic and clinical characteristics			
Age, mean (SD) years	60.1 (11.8)	60.8 (11.4)	-
Female, n (%)	154 (78.6)	110 (79.7)	-
Duration of RA, mean (SD) years	14.0 (11.2)	14.5 (10.1)	-
CDAI, mean (SD)	18.0 (13.5)	17.5 (13.9)	-
Prednisone use, n (%)	63 (32.1)	46 (33.3)	-
Tofacitinib monotherapy, n (%)	80 (40.8)	64 (46.4)	-
Line of therapy, n (%) ^b	1 st , 2 nd , 3 rd , 4 th	4 (2.9), 8 (5.8), 35 (25.4), 91 (65.9)	-
Primary outcome ^c			
Patients with CDAI improvements ≥MCID from baseline to 6-month visit, n (%)	46 (23.5)	29 (21.0)	0.79
Improvement ≥MCID in CDAI from baseline to 6-month visit, OR (95% CI)	1.23 (0.70, 2.15)		0.47
Secondary outcomes ^d			
Continuous outcomes: change from baseline to 6-month visit, LSM (95% CI)			
CDAI	-2.30 (-4.32, -0.28)	-1.84 (-3.95, 0.27)	0.69
HAQ	-0.04 (-0.13, 0.05)	-0.04 (-0.14, 0.05)	0.93
Patient Pain	-4.26 (-8.71, 0.19)	-2.35 (-7.01, 2.30)	0.46
Patient Fatigue ^e	-0.51 (-4.88, 3.86)	1.15 (-3.42, 5.72)	0.51
Binary outcomes: measured at 6-month visit, OR (95% CI)			
Achievement of LDA ^f	1.64 (0.78, 3.46)		0.19
Achievement of remission ^g	1.53 (0.48, 4.93)		0.47
Improvement in HAQ ≥0.22 ^h	1.34 (0.69, 2.59)		0.39

*p value for primary outcome from adjusted logistic regression model; p values for binary secondary outcomes from chi-squared tests; ^bLine of therapy: 1st-line patients naïve to csDMARDs and all biologic DMARDs; 2nd-line patients naïve to biologic DMARDs, but not csDMARDs; 3rd-line patients exposed to one prior biologic DMARD; 4th-line+ patients exposed to more than one prior biologic DMARD; ^cAdjustment covariates were age, gender, duration of RA, CDAI, prior number of non-TNFi, and prior number of biologic DMARDs; ^dFor continuous outcomes, the LSM (95% CI) are from an adjusted linear regression model; ^eDefined from 0 (no problem) to 100 (major problem); ^f6-month CDAI ≤10 among those without LDA at baseline (CDAI >10); ^g6-month CDAI ≤2.8 among those without remission at baseline (CDAI >2.8); ^hImprovement in HAQ calculated only for patients with baseline HAQ ≥0.22 (N=79 11 mg QD; N=87 5 mg BID)

BID, twice daily; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; CI, confidence interval; HAQ, Health Assessment Questionnaire; LDA, low disease activity; LSM, least squares mean; MCID, minimum clinically important difference; OR, odds ratio; QD, once daily; RA, rheumatoid arthritis; SD, standard deviation; TNFi, tumor necrosis factor inhibitor

differences>0.2). An exploratory analysis (limited sample size) was conducted to examine 6-mo outcomes in pts who switched to 11 mg QD after 5 mg BID initiation.

Results: 791 pts initiated tofacitinib (11 mg QD: n=460; 5 mg BID: n=234), of whom 334 pts (11 mg QD: n=196; 5 mg BID: n=138) had a registry visit and thus CDAI data at 6 mos after initiation. Baseline characteristics are shown in the Table. There were no significant differences in the proportion of pts with CDAI improvements ≥MCID between formulations with and without adjustment (23.5% vs 21.0%; oddsratio 1.23; 95% confidence interval 0.70, 2.15; covariates added in the model were prior number of non-TNF inhibitors and biologic DMARDs). There were no significant differences in the odds of achieving LDA, remission or improvement in HAQ ≥0.22 between formulations with adjustment (Table). Similar proportions of pts initiating 11 mg QD and 5 mg BID remained on tofacitinib at 6 mos (61.2% vs 67.4%; p=0.43). There were 135 switchers (5 mg BID to 11 mg QD); their post-6-mo outcomes were similar to those at the time of switch.

Conclusion: Results suggest that pts with RA who initiated treatment with tofacitinib 11 mg QD achieved comparable efficacy outcomes with pts who initiated with 5 mg BID. Although currently available person years of exposure is limited, data do not suggest the emergence of any new or unexpected safety risks for the XR formulation.

Disclosure: S. Cohen, Pfizer Inc, 2,Pfizer Inc, 5; H. J. Litman, Corrona, LLC, 3; C. Chen, Pfizer Inc, 1,Pfizer Inc, 3; T. Lukic, Pfizer Inc, 1,Pfizer Inc, 3; A. Madsen, Pfizer Inc, 1,Pizer Inc, 3; L. Takiya, Pfizer Inc, 1,Pfizer Inc, 3; K. J. Dandreo, Corrona, LLC, 3; T. Blachley, Corrona, LLC, 3; J. Greenberg, Corrona, LLC, 1,Corrona, LLC, 3,Eli Lilly, Genentech, Janssen, Pfizer Inc, 5.

Abstract Number: 581

Comparative Analysis of Outcomes Among Patients with Rheumatoid Arthritis Initiating Tofacitinib in Combination with Oral MTX Who Discontinue, Interrupt, or Persist with MTX

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018
Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA, in combination with MTX or other non-biologic (nb)DMARDs, or as monotherapy. Two pooled open-label long-term extension studies previously showed that patients (pts) discontinuing concomitant MTX or glucocorticoids (GC) could maintain favorable treatment response.¹This analysis of real world data assessed characteristics of pts who discontinued MTX after tofacitinib treatment.

Methods: This retrospective cohort study included pts aged ≥18 years in the Truven MarketScanTM US Commercial and Medicare Supplemental claims database with ≥2 tofacitinib claims (first = index) with <60-day gap between 1/1/2014–1/31/2017, ≥2 oral MTX claims (one ≤90 days post-index) with <60-day gap, and an RA diagnosis on or within 12 months pre-index. Pts were continuously enrolled for ≥12 months pre-/post-index with no prior claim for tofacitinib 12 months pre-index. Pts were assigned to mutually exclusive cohorts for analysis by 12-month post-index MTX persistence: “persistent” (MTX-P; ≤60-day gap), “discontinued” (MTX-D; >60-day gap) and “interrupted” (MTX-I; >60-day gap with ≥1 subsequent MTX claim 12 months post-index). Outcomes at 12 months post-index were tofacitinib persistence (<60-day gap), adherence (proportion of days covered), effectiveness (composite measure; defined in Table)^{2,3} and RA-related costs. Two sample tests (t-test, chi-squared) were applied separately to MTX-P vs combined MTX-D and MTX-I, and pair-wise among the 3 cohorts, with no adjustment for multiple comparisons or imbalances in baseline covariates.

Results: 479 pts met inclusion criteria (MTX-P: 337 [70%]; MTX-D: 94 [20%]; MTX-I: 48 [10%] in the 12-month post-index period). Demographic and baseline clinical characteristics were similar among cohorts, aside from differences in the proportion of males and all-cause out-of-pocket costs (p<0.05; Table).

Table. Baseline demographics and clinical characteristics, and outcomes of patients with RA treated with tofacitinib and MTX during the 12-month post-index period

	MTX-P (N=337)	MTX-D (N=94)	MTX-I (N=48)
Baseline demographics and clinical characteristics			
Male, n (%)	38 (11.3)	17 (18.1)	11 (22.9)
Age (years) (mean) (SD)	66.4 (10.4)	65.0 (9.4)	66.1 (9.4)
Line of therapy, n (%)			
0 prior DMARDs	96 (28.5)	25 (26.6)	11 (22.9)
1 prior DMARD	109 (32.3)	40 (42.6)	20 (41.7)
2 prior DMARDs	96 (28.5)	22 (23.4)	14 (29.2)
≥3 prior DMARDs	41 (12.2)	7 (7.4)	3 (6.3)
Adherence to all payor treatment (days) (SD)	247.8 (192.9)	229.6 (200.1)	221.9 (167.9)
RA-related pay of payor treatment (cost) (SE) (SD)	200.3 (157.3)	188.6 (100.7)	182.8 (134.4)
Outcomes of interest			
Effectiveness, n (%)	227 (67.4)	57 (60.6)	27 (56.3)
Adherence (PAC) (days) (SD)	30.8 (5.1)	33.7 (5.3)	34.6 (5.3)
Effectiveness ^{2,3} n (%)	121 (35.9)	33 (35.1)	9 (18.8)
RA-related total cost (SE) (SD)	41,802.9 (2,700.0)	40,708.4 (15,708.7)	81,084.3 (29,676.9)
Out-of-pocket costs	11,449.1 (2,312.5)	11,421.4 (14,127.9)	28,147.9 (13,741.2)
Monthly costs	954.1 (192.6)	951.8 (1176.9)	13,786.9 (34,245.0)

¹The time to next group treatment receipt was censored on date of therapy discontinuation. ²Effectiveness is a composite measure based on outcomes from outcomes originating in DMARDs, outcomes of DMARDs, and GC therapy, and 11 GC outcomes. ³Costs include costs included pharmacy and medical costs. ⁴For MTX-P vs MTX-D, ⁵For MTX-P vs MTX-I, ⁶For MTX-P vs MTX-D, ⁷For MTX-P vs MTX-I, ⁸For MTX-P vs MTX-D, ⁹For MTX-P vs MTX-I, ¹⁰For MTX-P vs MTX-D, ¹¹For MTX-P vs MTX-I, ¹²For MTX-P vs MTX-D, ¹³For MTX-P vs MTX-I, ¹⁴For MTX-P vs MTX-D, ¹⁵For MTX-P vs MTX-I, ¹⁶For MTX-P vs MTX-D, ¹⁷For MTX-P vs MTX-I, ¹⁸For MTX-P vs MTX-D, ¹⁹For MTX-P vs MTX-I, ²⁰For MTX-P vs MTX-D, ²¹For MTX-P vs MTX-I, ²²For MTX-P vs MTX-D, ²³For MTX-P vs MTX-I, ²⁴For MTX-P vs MTX-D, ²⁵For MTX-P vs MTX-I, ²⁶For MTX-P vs MTX-D, ²⁷For MTX-P vs MTX-I, ²⁸For MTX-P vs MTX-D, ²⁹For MTX-P vs MTX-I, ³⁰For MTX-P vs MTX-D, ³¹For MTX-P vs MTX-I, ³²For MTX-P vs MTX-D, ³³For MTX-P vs MTX-I, ³⁴For MTX-P vs MTX-D, ³⁵For MTX-P vs MTX-I, 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Tofacitinib persistence, adherence and effectiveness over 12 months were similar between MTX-D and MTX-P. RA-related total and pharmacy costs were lower in MTX-D vs MTX-P ($p<0.001$ and $p<0.05$, respectively).

Conclusion: This analysis of US-based claims data showed that pts who initiate tofacitinib with oral MTX can discontinue MTX with similar persistence, adherence and effectiveness, and lower RA-related total/pharmacy costs 12-months post-index vs MTX-persistent pts. Further analysis with a larger sample size is needed to confirm the robustness of these findings; further investigation is also needed regarding the MTX-I group as interpretation of this group is limited by the small sample size. Findings are limited by the use of claims data which may reflect MTX discontinuation/interruption related to pt choice without physician knowledge.

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2. Curtis JR et al. *Arthritis Res Ther* 2011; 13: R155.
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Abstract Number: 582

Baseline Power Doppler and Multi-Biomarker Disease Activity Score Predict 12-Week Disease Activity Response to Tofacitinib

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Point of care tailored treatment strategies are of value to improve rheumatoid arthritis (RA) patient outcomes. Musculoskeletal ultrasound (MSUS) is increasingly used as a modality by which rheumatologists diagnose and monitor the progression of RA. The multi-biomarker disease activity (MBDA) blood test is a commercially available assay that measures twelve inflammatory biomarkers to score RA disease activity on a scale of 1-100. This pilot study evaluated whether baseline MSUS and MBDA scores or their early changes, are predictive of 12-week clinical response in RA patients treated with tofacitinib.

Methods: 25 RA patients who met entry criteria (including baseline disease activity score using ESR [DAS28]>3.2 and power Doppler US [PDUS] score >10) were treated with open-label tofacitinib at the approved dose of 5 mg PO BID and assessed at baseline, 2 weeks and 12 weeks. MSUS was performed at each visit scoring 34-joints for PDUS and GSUS. Other metrics examined were MBDA score, clinical disease activity index (CDAI), disease activity score (DAS28). Associations between MBDA score /PDUS/GSUS at baseline or their changes from baseline to 2 or 12 weeks, and the change in DAS28/CDAI from baseline to 12 weeks, were assessed using Pearson correlation coefficients.

Results: Mean age was 52 years, mean disease duration 10.4 years, 88% of patients were female, 40% Caucasian, and 96% were RF/CCP positive. At baseline, the mean (SD) DAS28 was 6.26 (1.2) and CDAI was 40 (13.2). There was significant improvement in PDUS, GSUS, MBDA score, DAS28, and CDAI over 12 weeks (all $p<0.0001$). Correlations of 12-week changes in MBDA score or MSUS with 12-week changes in CDAI or DAS28 were all significant (correlation coefficients 0.44-0.58), except for GSUS with DAS28 (Table 1). Changes from baseline to 2 weeks in PDUS or GSUS were associated with significant DAS28 response at 12 weeks (Table 1). Baseline PDUS, GSUS and MBDA score were significant predictors of 12-week CDAI or DAS28 responses, except for GSUS with DAS28 response (Table 1).

Conclusion: This study showed that RA patients treated with tofacitinib for 12 weeks demonstrated significant responses with clinical, imaging, and biomarker end-points. In addition, baseline PDUS and MBDA score were predictive of the

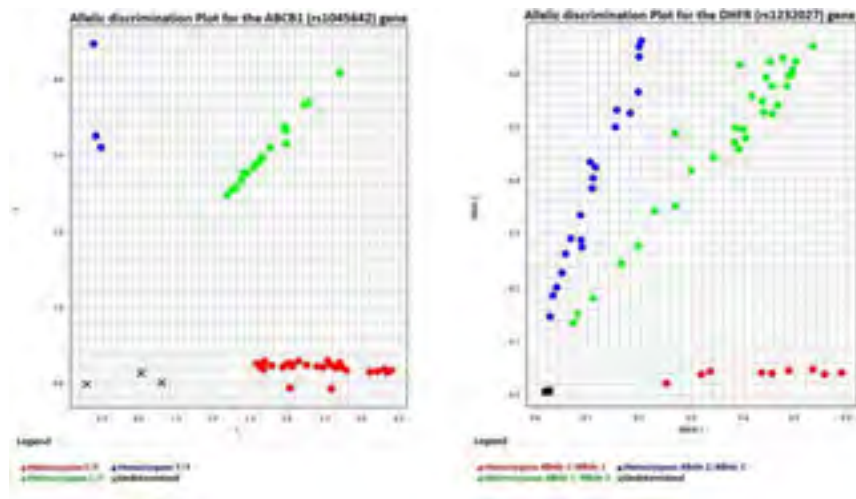


Table 1: Correlations coefficients for associations of Biomarker or Imaging Measures with 12-Week Changes (Δ) in Clinical Disease Activity Measures

Associations of 12-Week Δ MBDA score/MSUS with 12-Week Δ CDAI/DAS28		
	CDAI (0-12 week)	DAS28 (0-12 week)
PDUS (0-12 week)	0.56**	0.56**
GSUS (0-12 week)	0.47*	0.34
MBDA score (0-12 week)	0.44*	0.59**
Associations of 2-Week Δ MBDA score/MSUS with 12-Week Δ CDAI/DAS28		
	CDAI (0-12 weeks)	DAS28 (0-12 weeks)
PDUS (0-2 weeks)	0.37	0.42*
GSUS (0-2 weeks)	0.44*	0.42*
MBDA score (0-2 weeks)	0.22	0.29
Associations of Baseline MBDA score/MSUS with 12-Week Δ CDAI/DAS28		
	CDAI (0-12 weeks)	DAS28 (0-12 weeks)
PDUS Baseline	0.55**	0.46*
GSUS Baseline	0.47*	0.25
MBDA score Baseline	0.44*	0.50*

*p<0.05, **p<0.01

DAS28 and CDAI response at 12 weeks. This is the first study to evaluate early MSUS and MBDA changes as predictors of clinical response in RA patients treated with tofacitinib.

Disclosure: A. Razmjou, None; J. Brook, None; G. Kaeley, None; D. Elashoff, Genentech, Inc., 2, Pfizer, Inc., 2, mallinkrodt, 2, Amgen Inc., 5; V. K. Ranganath, Genentech, Inc., 2, Pfizer, Inc., 2, mallinkrodt, 2, Amgen Inc., 5.

Abstract Number: 583

Identification of a Protein Profile Useful to Predict Response to Methotrexate in Early Rheumatoid Arthritis Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Among the best known disease-modifying antirheumatic drugs, Methotrexate (MTX) is one of the most effective and widely used medications. It is used as a general first-choice drug in rheumatoid arthritis (RA), although some patients will not respond to this treatment and it is not free from side effects. The purpose of this work is to identify circulating proteins that could be useful to predict the patient's response to MTX.

Methods: Serum samples from patients enrolled in the Pathobiology of Early Arthritis Cohort (PEAC) were collected before treatment with MTX. Response to therapy was determined after 6 months by calculating the initial and final DAS28 of the patients. Their classification was performed following the EULAR response criteria. Sixty samples at baseline from this cohort (30 good responders and 30 non-responders) were depleted from the 14 most abundant proteins by affinity chromatography to remove background. Then, they were analysed by reversed-phase nanoliquid chromatography coupled to mass spectrometry using a SWATH strategy in a tripleTOF MS (Sciex). The quantitative data obtained in this proteomic analysis were processed using the ProteinPilot 5.0.1 and PeakView 2.1 software (Sciex). Machine learning analyses were performed on a train set of 30 samples (15 responders and 15 non-responders) via support vector machine (SVM) using the Classyfire, e1071 and caret R packages. Results were verified in an independent set of 24 samples by a two-stage support vector machine (TSSVM) with RBF kernel and 10 cross-fold validation for each meta-model.

Results: The proteomic analysis led to the identification and quantification of 229 proteins that were common between the screening and validation sets. Independent screening and validation data sets were pre-processed by PCA for dimension reduction. Then, results were analyzed by machine learning tools, leading to the definition of a panel of 8 proteins (one of them involved in MTX metabolism and two in the regulation of the immune response) that classifies at baseline the groups of responders and non-responders to MTX with strong agreement (Kappa>0.80), very high accuracy and good relevant metrics (Table 1).

Conclusion: We have defined a panel of circulating proteins useful to predict the response to MTX therapy in rheumatoid arthritis patients.

Table 1. Metrics of the classification performance of the 8-protein panel identified in this work to predict response of the patient to MTX. Cut-off for significance was p-value < 0.05.

Train set							
Accuracy	95% CI	p-value	Kappa	Sensitivity	Specificity	Pos pred value	Neg predvalue
0.9333	(0.7793 -0.9918)	1.108e-05	0.8667	0.8824	1.0000	1.0000	0.8667
Validation set							
Accuracy	95% CI	p-value	Kappa	Sensitivity	Specificity	Pos pred value	Neg predvalue
0.9583	(0.7888 -0.9989)	0.0007722	0.9091	1.0000	0.9375	0.8889	1.0000

Disclosure: C. Ruiz-Romero, None; F. Picchi, None; L. González, None; R. Hands, None; V. Calamia, None; P. Fernández, None; M. Camacho, None; R. Paz, None; C. Bessant, None; C. Pitzalis, None; F. J. Blanco, None.

Abstract Number: 584

Changes in CD4+ T and B Cell Profile As Indicator of Clinical Remission to TNF Inhibitors in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: TNF inhibitors (TNFi) are widely used for the treatment of rheumatoid arthritis (RA). This study aims to analyse the profile of peripheral blood mononuclear cells (PBMC) after 6 months (m) of treatment with TNFi in order to find cellular biomarkers of response.

Methods: This was a prospective bi-center pilot study including 50 RA patients under TNFithrapy. PBMC were isolated from patients at baseline and 6m of treatment, andflow-cytometry analysed. Clinical activity at baseline and 6m of TNFi

treatment was assessed by DAS28. Clinical remission (DAS28^{2.6}) after 6m of treatment was considered as optimal response. The association between clinical remission and the percentage of change (Δ ,6m-0m) within each PBMC subset was analysed through multivariate log-regression model (odds ratio; 95% CI). All the analyses were adjusted by sex, age, concomitant-methotrexate, rheumatoid-factor and baseline-DAS28.

Results: Increased percentage of CD4+ T cells (Δ CD4+) was found after 6m of TNFi treatment in optimal responders; while suboptimal responders showed decreased percentage of this cell population (OR: 1.08; 95% CI: 1.01-1.16; p: 0.017). In addition, the percentage of B cells after 6m of TNFi treatment (Δ CD19+) decreased in optimal responders (OR: 0.7; 95% IC: 0.54-0.96; p: 0.024). This effect was essentially promoted by naïve B cells (OR: 0.7; 95% IC: 0.47-0.93; p: 0.017). The other PBMC subsets (monocytes, NK and CD8+ T cells) did not show statistical differences.

Conclusion: Our results demonstrate that CD4+ T and B cells may be useful as cellular biomarkers of response to TNFi in RA patients.

Funding: ISCIII (PI16/00474; PI16/01092)

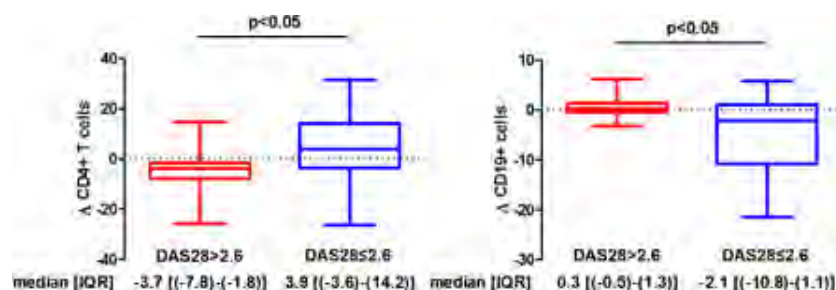


Figure Legend: Percentage of change of CD4+ T cells and CD19+ B cells after 6m of TNFi treatment according to clinical remission achievement (DAS28^{2.6}). The U Mann-Whitney test was applied considering p-value < 0.05 as significant difference.

Disclosure: B. Hernández-Breijo, None; I. Gañán-Nieto, None; C. Sobrino, None; V. Navarro-Compán, None; A. Martínez, None; C. García-Hoz, None; J. Bachiller, None; M. G. Bonilla Hernán, None; G. Roy, None; M. Vázquez, None; A. Balsa, None; L. M. Villar, None; D. Pascual-Salcedo, None; E. Rodríguez-Martín, None; C. Plasencia, None.

Abstract Number: 585

The Role of Genetic Polymorphisms on the Response to Methotrexate Variations Among Rheumatoid Arthritis Patients in Saudi Arabia

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

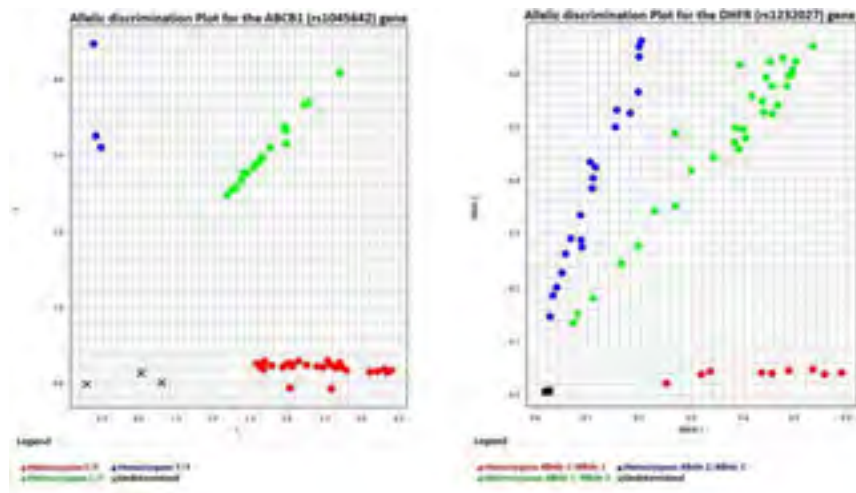
Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Low dose methotrexate (MTX) is one of the most commonly used disease-modifying anti-rheumatic drug for rheumatoid arthritis (RA) with excellent efficacy and safety profile. However, it is implicated in significant inter-patient clinical response variability. Genetic polymorphisms have been suggested to play a role in this clinical response variations. In this study we investigated the association between key pharmacogenetics of methotrexate [ABCB1, DHFR] genes and the efficacy /tolerability of the drug among patients with RA at a tertiary center in Saudi Arabia, which may aid in an individualized risk assessment and prediction of treatment outcomes.

Methods: A total of hundred patients with RA who received low-dose MTX therapy for at least six months were selected. Clinical and demographic characteristics were collected, Red blood cell MTX PG concentration were measured and



common polymorphisms in folate pathway enzymes were performed through genotyping procedure. The efficacy of MTX in treating RA was measured by counting the number of tender, swollen joints, scoring the visual analogue scale (VAS), scoring modified Health Assessment Questionnaire (mHAQ).

Results: The allelic frequencies of rs1045642 were 76.8 % for C, 6.0% for T, and 17.2 % for C/T, while, the allelic frequencies of rs1232027 were 50.9 for G/A, 32.5 % for G, 16.6 % for A. The study did not demonstrate any association between the polymorphism in ABCB1 gene and either toxicity or efficacy of MTX, while revealed an association between (rs1232027) polymorphism in the DHFR gene and certain adverse effects which are; nausea, lung infection, skin nodules, menstrual irregularities, oral ulcers in patients with RA ($P < .05$). In this study, we did not find a correlation between MTX dose and plasma level. Moreover, MTX plasma level was not correlated with toxicities detected in patients on MTX. On top of that, ABCB1 (rs1045642) and DHFR Gene (rs1232027) polymorphism were not associated with the risk of delayed elimination of MTX.

Conclusion: The ABCB1 gene polymorphism is not a predictor of either toxicity or efficacy of MTX treatment in RA patients. while DHFR gene polymorphism might be a reliable predictor of toxicity to MTX treatment. Sofar, published data still inconsistent between variable studies. Further meticulously designed studies that include more genetic polymorphisms and larger sample size are needed for more accurate results that lead to further integration of pharmacogenetics into clinical practice and better outcomes.

Toxicity	GG	GA	AA	Pearson Chi-Square
Nausea	71.4%	14.3%	14.4%	0.029
Hair loss	48.1%	30.4%	21.4%	0.162
Photosensitivity	55.6%	22.2%	22.2%	0.209
Skin nodules	58.7%	28.7%	13%	0.006
Lung infection	33.5%	59%	7.5%	0.017
Menstrual irregularities	33.3%	40%	26.7%	0.057
Bone ache	53.2%	35.4%	11.3%	0.256
Deformity	60.1%	39.9%	0	0.294
Oral Ulcers	59.9%	29.9%	10%	0.027

Percentage of genotypes of DHFR Gene (RS1232027) in MTX-induced toxicities

Disclosure: S. Attar, None; M. Hagrass, None; A. Abuzenadah, None; O. Fath Aldin, None; R. Attar, None; R. Alraddadi, None; M. Sulaiman, None; A. Aseri, None.

Abstract Number: 586

Effectiveness, Tolerability, and Safety of Tofacitinib in Rheumatoid Arthritis: A Retrospective Analysis of Real-World DATA from the ST. Gallen and-Aarau RA-Cohort

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Tofacitinib is an oral JAK inhibitor approved for the treatment of RA. Efficacy and safety of tofacitinib have been shown in several randomized clinical trials. Aim of the study presented here was to assess the clinical tolerability and effectiveness of tofacitinib among RA patients in real life.

Methods: Consecutive patients between June 2013 and April 2017 with RA who fulfilled the ACR/EULAR 2010 criteria were included in a prospectively designed analysis of retrospective data. Patients were initiated on tofacitinib 5mg bid. The primary objective was to analyze the safety of tofacitinib in a real-life cohort. Safety was assessed by the reasons to stop tofacitinib during follow up and changes of liver enzymes, hemoglobin, and creatinine. The secondary outcome was to analyze the frequency of and time to achieve low disease activity (LDA) and remission as defined by DAS28. Patients were stratified according to previous treatment with biologic agents (bio-naïve versus bio-experienced).

Results: Overall, 144 patients were treated with tofacitinib. 83.9% of patients were pre-exposed to at least one biologic agent. The average DAS28 at the initiation of tofacitinib was 4.42. 50.4% were rheumatoid factor and 49.0% were ACPA positive. The mean follow up was 1.22 years (range 4d – 3.7 years). 89 (61.8%) patients remained on tofacitinib during follow-up. The median time to stop tofacitinib was 95 days (range 4-1106). Reasons to stop tofacitinib were: insufficient response (n=23), gastrointestinal symptoms (n=18), infection (n=5), myalgia (n=2), remission (n=2), headache (n=2), cough, blue finger syndrome, intolerance, heartburn, psoriasis, and increased liver enzymes (all n=1). Increased ALAT or ASAT > 2x ULN were detected in 3.3% and 4.4%, respectively. These elevated transaminase levels were transient in 50 and 60% of the cases, respectively. Hemoglobin decrease of >10% was detected in 15.1% of the patients and decreased lymphocytes < 500/μl in 3.4%. An increase of creatinine >20% was detected in 9.4%. 58.2% and 49.5% of all patients achieved LDA or remission after a median survival time of 319 and 645 days, respectively. These rates were significantly higher in patients naïve to biologic agents as compared to patients pre-exposed to biologics (LDA: naïve 100% after mean 92d, pre-exposed 34.8% after 434d, p <0.001; remission: naïve 83.3% after 132d, pre-exposed 44.9% after 692d, p=0.001).

Conclusion: Tofacitinib is a safe and effective treatment option for patients with RA. Tofacitinib may induce high rates of LDA and remission in patients with active disease, even after use of one or more biologics, though the rate is significantly higher in patients naïve to biologics. Tofacitinib may be a valuable option in a treat to target approach. Our data point to benefits of an early use of tofacitinib in the therapeutic strategy.

Disclosure: R. Mueller, Pfizer, Inc., 5; C. Hasler, None; F. Popp, None; F. Mattow, None; M. Durmisi, None; A. Rubbert-Roth, None; A. Souza, None; N. Graf, None; H. Schulze-Koops, None; P. Hasler, Pfizer, Inc., 5; J. von Kempis, UCB, Inc., 5.

Abstract Number: 587

The Superiority of a Treat to Target Strategy over Conventional Treatment with Fixed Csmdard and Corticosteroids: A Multi-Centre Randomized Controlled Trial in RA Patients with Inadequate Response to Conventional Synthetic Dmards, and a New Therapy with Certolizumab Pegol

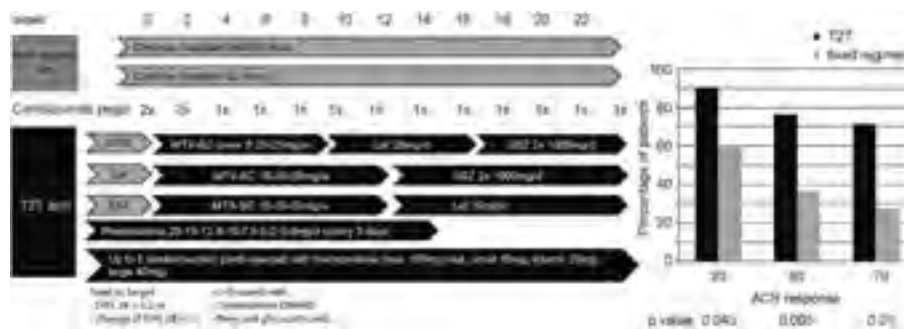
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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A



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

The superiority of a treat to target strategy over conventional treatment with fixed csDMARD and corticosteroids: a multi-centre randomized controlled trial in RA patients with inadequate response to conventional synthetic DMARDs, and anew therapy with certolizumab pegol.

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Background/Purpose: Treatment of rheumatoid arthritis (RA) includes the use of conventional (cs), biologic (b) disease-modifying anti-rheumatic drugs (DMARDs) and oral or intraarticular (IA-) glucocorticoids (GCs).

To analyse whether a treat to target (T2T) strategy optimizing csDMARD, oral and IA-GC treatment as an adjunct new therapy to a new certolizumab pegol (CZP) therapy in RA patients improves effectivity in RA patients.

Methods: 43 patients with active RA (≥ 6 tender, ≥ 6 swollen joints, ESR ≥ 20 mm/h or CRP ≥ 7 mg/l) despite csDMARD treatment for ≥ 3 months and naïve to bDMARDs were randomized to CZP (200 mg/2 weeks after loading with 400 mg at weeks 0-2-4) plus a treat to target strategy (T2T, n=21) or to CZP added to the established csDMARD therapy (fixed regimen, n=22). The T2T strategy consisted of changing the baseline csDMARD therapy (1) SC-methotrexate (dose: 15 \Rightarrow 20 \Rightarrow 25 mg/week, depending on the initial dose) \Rightarrow leflunomide (20 mg/d) \Rightarrow sulfasalazine (2x1000 mg/d) plus (2) oral GCs (20-15-12.5-10-7.5-5-2.5-0 mg/d tapered every 5 days) and (3) injections of ≤ 5 affected joints with triamcinolone. DMARD modification and an addition of oral GCs were initiated depending on the achievement of low disease activity (DAS28 < 3.2). The primary objective was defined as the ACR50 response at week 24.

Results: ACR 50 was achieved in 76.2% of the T2T as compared to 36.4% of the fixed regimen patients (p=0.020). ACR 20 and 70 responses were achieved in 90.5% and 71.4% of the T2T patients and 59.1% and 27.3% of the fixed regimen patients, respectively (p=0.045 and p=0.010, resp.). The adverse event rate was similar for both groups (T2T n=51; fixed regimen n=55).

Conclusion: Treat to target management with optimization of csDMARDs, oral and IA-GCs of RA patients in parallel to a newly established CZP treatment was safe and efficacious in comparison to a fixed regimen of csDMARDs background therapy. UCB Pharma funded this study. Gebro Pharmaceuticals provided the csDMARDs and GCs for the study.

Disclosure: R. Mueller, UCB, Inc., 5; M. Spaeth, None; C. von Restorff, None; C. Ackermann, None; J. von Kempis, UCB, Inc., 5.

Abstract Number: 588

Acr Hybrid Analysis: Blinded Data from the Ongoing Phase IIb Trial with the EP4 Receptor Antagonist CR6086 in DMARD-Naïve Patients with Early Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: The ACR Hybrid, officially recommended by the ACR as a revision to the ACR20/50/70 response criteria, combines the ACR20/50/70 scores with the mean percent change in all 7 ACR core components, thus providing a percent improvement from baseline on a continuous scale. Despite the demonstrated higher sensitivity to patient-reported improvement than the ACR20 criterion [1], its application is still limited in clinical trials [2], possibly because the scientific community is not yet familiar with its use. Data from an ongoing drug trial in DMARD-naïve patients with early rheumatoid arthritis (RA) were used to compare the ACR Hybrid scores versus the traditional efficacy measures (ACR20/50/70) and DAS28.

Methods: To assess the validity of the ACR Hybrid measure, we used blinded data from the ongoing trial with the EP4 receptor antagonist CR6086 in early rheumatoid arthritis, DMARD-naïve patients (the CREATIVE study). This is a randomized, placebo-controlled, double-blind, dose response, Phase IIb, multicentre trial of CR6086 administered for 12 weeks in combination with methotrexate (NCT03163966). The study consists of a baseline evaluation and 4 post-baseline visits at the following time-points: weeks 3, 6, 9 and 12. The ACR Hybrid score was obtained calculating the mean percent change from baseline across the 7 ACR core set measures for each patient/visit and determining whether patients achieved ACR20, 50, or 70 responses at that visit. The ACR Hybrid scores were compared with ACR20/50/70 outcomes and DAS28 calculated at each post-baseline visit. Missing data were not imputed. Results are presented as number of visits, regardless of patients and time-points.

Results: A total of 146 patients newly diagnosed with RA by the 2010 ACR/EULAR classification criteria had been randomized in EU/non-EU countries at the time of the data cut-off (May 2018). Overall, 376 post-baseline visits were available for the analyses. ACR20 response was achieved in 157/376 (42%) visits, while mean percent changes in ACR core measures $\geq 20\%$, and therefore positive ACR Hybrid scores, were observed in 250 visits (i.e. 66% of total) (Table). Similarly, ACR50 response was achieved in 66/376 (18%) visits, while mean improvements in ACR core measures $\geq 50\%$ were observed in 87 visits (i.e. 23% of total). ACR Hybrid scores and percent change from baseline in DAS28 were highly correlated (Spearman's correlation -0.85).

Conclusion: Analysis of blinded data from an ongoing Phase IIb drug trial in early RA, DMARD-naïve patients encourages the use of the ACR Hybrid score and supports its role as a valuable endpoint in clinical trials. By increasing the sensitivity of the analysis, this new measure of RA response might facilitate the demonstration of differences between treatments.

Table. Number of visits by ACR Status and mean percent change in ACR core set measures

ACR Status	Mean percent change in ACR core set measures			
	<20	$\geq 20, < 50$	$\geq 50, < 70$	≥ 70
Not ACR20	122	91	6	0
ACR20 but not ACR50	4	66	20	1
ACR50 but not ACR70	0	6	22	4
ACR70	0	0	8	26

[1] Ward MM et al. Arthritis Rheum. 2014; 66(9): 2339–2343.

[2] van Vollenhoven RF et al. Arthritis Care Res (Hoboken). 2011; 63:128–134.

Disclosure: C. Vitalini, Rottapharm Biotech, 3; B. Barbetta, Rottapharm Biotech, 3; G. Giacobelli, Rottapharm Biotech, 3; N. Brambilla, Rottapharm Biotech, 3; M. D'Amato, Rottapharm Biotech, 3; F. Girolami, Rottapharm Biotech, 3; L. C. Rovati, Rottapharm Biotech, 3.

Abstract Number: 589

DAS28-CRP Versus DAS28-ESR and Thresholds for Disease Activity Category: Blinded Data from the Ongoing Phase IIb Trial with the EP4 Receptor Antagonist CR6086 in DMARD-Naïve Patients with Early Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: In most patients with rheumatoid arthritis (RA) the 28-Joint Disease Activity Score (DAS28) values calculated using C-reactive protein (CRP) are lower than those calculated using erythrocyte sedimentation rate (ESR). Since validated thresholds for categorizing disease activity are available for DAS28-ESR only, their application for DAS28-CRP has become common in clinical practice and clinical trials. Recently, Fleischmann et al. proposed new DAS28-CRP cut-offs for definition of remission, low and high disease activity [1, 2]. We aimed to evaluate here the use of the newly proposed thresholds for categorizing disease activity in relation to the validated DAS28-ESR cut-offs in DMARD-naïve patients with early RA.

Methods: We used blinded data from the ongoing trial with the EP4 receptor antagonist CR6086 in early rheumatoid arthritis, DMARD-naïve patients (the CREATIVE study). This is a randomized, placebo-controlled, double-blind, dose response, Phase IIb, multicentre trial of CR6086 administered for 12 weeks in combination with methotrexate (NCT03163966). The study consists of a baseline evaluation and 4 post-baseline visits at the following time-points: weeks 3, 6, 9 and 12. DAS28-CRP and DAS28-ESR were determined at each visit and their correlation was analysed using Spearman's coefficient. Agreement between the newly proposed DAS28-CRP thresholds for remission (<2.4), low (≤ 2.9) and high disease activity (>4.6) and the validated DAS28-ESR cut-offs (<2.6 , ≤ 3.2 and >5.1 , respectively) was determined by κ coefficient, sensitivity and specificity. Results are presented as number of visits, regardless of patients and time-points.

Results: A total of 146 patients newly diagnosed with RA by the 2010 ACR/EULAR classification criteria had been randomized in EU/non-EU countries at the time of the data cut-off (May 2018). Overall, data for the analyses were available for 527 visits. DAS28-CRP values were generally lower than DAS28-ESR values, but the 2 measures were highly correlated (Spearman's correlation 0.94). Based on the validated DAS28-ESR cut-offs, remission was determined in 17 visits, low disease activity in 22 visits, moderate disease activity in 202 visits, and high disease activity in 286 visits. The corresponding values obtained applying the newly proposed DAS28-CRP thresholds were 18, 27, 181 and 301 visits, respectively. A good agreement was reached against the validated DAS28-ESR cut-offs ($\kappa=0.67$) and sensitivity was particularly high for the high disease activity category (90%).

Conclusion: Analysis of blinded data from the ongoing Phase IIb trial with CR6086 indicated that the newly proposed DAS28-CRP thresholds for remission, low and high disease activity are consistent with the validated DAS28-ESR cut-offs, thus supporting their use in clinical trial and clinical practice.

[1] Fleischmann R et al. Ann Rheum Dis. 2015; 74:1132–1137.

[2] Fleischmann RM et al. RMD Open 2017;3:e000382.

Disclosure: C. Vitalini, Rottapharm Biotech, 3; B. Barbetta, Rottapharm Biotech, 3; G. Giacobelli, Rottapharm Biotech, 3; N. Brambilla, Rottapharm Biotech, 3; M. D'Amato, Rottapharm Biotech, 3; F. Girolami, Rottapharm Biotech, 3; L. C. Rovati, Rottapharm Biotech, 3.

Abstract Number: 590

Advances in Therapeutic Management with First Biological Therapy in Rheumatoid Arthritis throughout 15 Years

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: In the last two decades the treatment in patients with rheumatoid arthritis(RA) has undergone major advances, especially due to the appearance of new therapies, the use of the “treat to target” strategy and a better understanding of the “window of opportunity” concept. However, data from clinical practice confirming the benefits of using these strategies are scarce. Our purpose was to investigate whether the proportion of patients (pts) with RA in maintained remission (R) or low disease activity (LDA) after starting a first biological agent has increased over time and which factors are associated with this change.

Methods: Analysis of a database from a prospective cohort including 365 pts with RA starting a 1st biological agent (BA) (TNF inhibitor, abatacept or tocilizumab) in a tertiary hospital between 2000-2014. Demographic, clinical and analytical data were collected at the beginning of treatment and clinical activity (DAS28) was measured every 6 months. For this study, 3 groups were established according to BA initiation date: interval 1 (i1) (between 2000-2004), (i2) 2005-2009 and (i3) 2010-2014, with a minimum follow-up of 2 years at all pts. For each interval, the percentage of pts achieving maintained (at least 3 consecutive visits) R (DAS28 <2.6) or LDA (DAS28 <3.2) was determined. In addition, all variables collected were compared between groups by ANOVA and chi-square test.

Results: Out of the 365 pts initiating a 1st BA, 133 started in i1, 122 in i2 and 110 in i3. Of these, 38% (n=137) achieved maintained R/LDA. This percentage increased significantly in successive intervals (31% in i1 vs, 38% in i2 vs 45% in i3, p=0.02). Baseline characteristics of pts achieving R/LDA are shown in table 1A. For patients in i2 and i3, compared to the previous interval (i1 and i2 respectively), a significant higher frequency of use of BA with different mechanisms of action (0% in i1 vs 2.2% in i2 vs 34% in i3, p <0.001), women (56% in i1 vs 76% in i2 vs 84% in i3, p = 0.01) and concomitant methotrexate (56% in i1 vs 74% in i2 vs 81% in i3, p=0.03) was found. On the other hand, the percentage of optimized pts increased significantly over time (13% in i1 vs 32% in i2 vs 56% in i3, p <0.001; table 1B).

Conclusion: The percentage of pts with RA achieving maintained R/LDA after initiating a 1st BA has progressively increased over time. This is probably related to a greater use of BAs with different mechanisms of action and concomitant methotrexate. The sustained control of disease activity may allow using more frequently optimized doses of BA.

Disclosure: P. Bogas, None; C. Plasencia, None; V. Navarro-Compán, None; D. Benavent, None; G. Gonzalez, None; M. G. Bonilla Hernán, None; I. Monjo, None; J. Molina, None.

	2000-2004 (n=41)	2005-2009 (n=46)	2010-2014 (n=98)	p value
Table 1A: Characteristics at the beginning of biological therapy				
Non-TNFi BA (Tocilizumab)	0%	2.2%	34%	<0.001
Age (years)	52 ± 11.1	51 ± 15.7	54 ± 12.1	0.5
Sex (female)	58%	78%	84%	0.01
Non smokers	54%	61%	45%	0.6
BMI (Kg/m ²)	26.5 ± 4.7	25.9 ± 4.4	26 ± 5.6	0.5
Disease duration (years)	8.2 ± 6.3	10.7 ± 7.8	7.8 ± 6.1	0.1
RF +	85%	80%	79%	0.7
Anti-CCP +	65%	84%	85%	0.9
DMARDs (MTX/SZP/LEFL)				0.02
- Methotrexate	56%	74%	81%	0.03
- Leflunomide	7%	4%	6%	0.6
- Sulfasalazine	37%	35%	35%	0.7
CPR	7.3 ± 10.6	12.1 ± 12.7	8.7 ± 11.4	0.001
ESR	33 ± 20.5	34 ± 20.5	19 ± 10.2	<0.001
DAS28	5.2 ± 1.4	4.8 ± 1.1	4.7 ± 1.1	0.2
HAQ	6.1 ± 5.6	7.3 ± 5.8	7.5 ± 4.5	0.8
Table 1B: Follow-up characteristics				
Follow-up time (years)	4.0 ± 2.9	4.7 ± 2.4	4.6 ± 2.6	0.06
Time under biologics (years)	3.8 ± 2.1	4.4 ± 2.6	4.1 ± 2.7	0.2
DAS28 > 3.2 at end of interval (%)	22%	10%	7.5%	0.1
Optimized at the end of interval (%)	13%	32%	56%	<0.001

Evaluation of MRI Ramris Score and Clinical Response in Patients with ACPA Positive Undifferentiated Arthritis Treated with Infliximab Versus Placebo

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Patients (Pts) with Undifferentiated Arthritis (UA), positive for ACPA antibodies are at high risk of progressing to Rheumatoid Arthritis (RA). TNF play a key role in the pathogenesis of RA. Very early treatment with the combination of Methotrexate and Infliximab (IFX) in a small cohort of UA showed a benefit in clinical symptoms and reduction of MRI evidence of synovitis and erosions. We assess whether IFX as a monotherapy is more effective than placebo (Pbo) in UA Pts positive for ACPA. Here we evaluate the clinical response, the MRI RAMRIS score and the risk to develop RA.

Methods: This was a randomized, double-blind, Pbo-controlled, two-arm parallel design study of 12 months to the primary endpoint (proportion of Pts who developed RA by ARA 2007 criteria). Pts with UA and symptomatic clinical synovitis of ≥ 1 joints and ACPA positivity were randomized 1:1 to IFX (3 mg/kg) or Pbo at week 0, 2, 6, 14 and 22, after which treatment was terminated. NSAIDs/stable low-dose oral corticosteroids (≤ 5 mg/day) were permitted but no DMARDs. Disease activity measures (DAS28CRP) were evaluated at BL, Wks 2 and 4, and every 4 Wks until Wk 52. OMERACT RAMRIS scores (components: erosion, osteitis, synovitis, tenosynovitis) and peritendinitis scores were evaluated at BL and Mth 4. Pts who developed RA at any time were discontinued and could receive standard of care.

Results: 28 Pts were randomized (mean age: 48 +/- 12 yrs; mean UA duration: 0.34 +/- 0.53 yr; mean CRP: 1.67 +/- 2.23 mg/dL). By 1 yr, 11/15 (73%) Pts treated with IFX developed RA vs 10/15 (67%) Pbo-treated Pts (Kaplan Meier, log rank $p=0.868$). At Wk 14, ACR 20, 50, 70 responses were observed respectively in 71.4%, 42.9%, 28.6% Pts treated with IFX vs 21.4%, 0%, 0% treated with Pbo. Remission DAS28CRP rate was observed in 50% in the IFX group vs 21.4% in the Pbo group. Pts in the IFX arm experienced significantly greater improvements in RAMRIS score versus Pbo at Wk 16 (graph). Furthermore, the difference in the RAMRIS score observed at Wk 14 was statistically different in the group of Pts who did not develop RA after 1 yr.

Conclusion: In this small randomized cohort of UA ACPA positive Pts, we noted a significant difference in the RAMRIS scoring after 4 months in the IFX group vs Pbo. This is the first study to report a worsening of disease activity based on the RAMRIS scores in the Pbo group but changes were minimal and not observed in all Pts. IFX has higher efficacy but did not prevent the progression to definite RA. Further analyses are ongoing to determine MRI predictors for severity.

Disclosure: T. Kirchgesner, None; B. Vande Berg, None; T. Sokolova, None; L. Meric de Bellefon, None; A. Nzeusseu Toukap, None; M. Stoeniou, None; P. Durez, None.

Improved Response to Etanercept Is Associated with Serum Vitamin D Levels in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Although treatment of rheumatoid arthritis (RA) has significantly improved during the past decades, many patients do not adequately respond or become resistant to current treatments. It is currently unknown why some patients respond well and others do not, and how the response rate could be improved. Vitamin D has strong immunomodulatory properties and it has been shown RA patients have a lower serum 25(OH)D level than healthy individuals. Moreover, vitamin D levels are correlated with disease severity. Interestingly, in vitro studies have shown that vitamin D augments the suppressive effects of etanercept in a simplified model for synovial inflammation. This suggests that vitamin D could improve the therapeutic response to etanercept in RA patients. Therefore we studied if etanercept response is related to serum vitamin D (25(OH)D) levels in RA patients.

Methods: For this study, data were used from the tREACH trial, a multicenter stratified single blinded randomized clinical trial. RA patients, according to the 2010 classification criteria, who started with etanercept within the first 12 months of the study were included in the analysis. Serum vitamin D (25(OH)D) levels were determined at the start of treatment (Tstart) and 3 months later using the LIAISON® 25 OH Vitamin D TOTAL assay. Correlation coefficients between vitamin D levels and the disease activity score (DAS) were calculated. Treatment response was determined with the EULAR response criteria, and difference in response rates was assessed using Chi-Square tests.

Results: 91 patients started etanercept in the first 12 months of the study, of which 24 did not have serum for 25(OH)D measurements at start of treatment and three months later. A total of 67 patients was included, of which 82% was female. At baseline, 45 (67%) and 48 (73%) were positive for rheumatoid factor and anti-citrullinated protein antibodies, respectively. DAS after etanercept treatment was weakly inversely correlated with serum 25(OH)D after treatment ($r=-0.29$, $p=0.02$) and the change in 25(OH)D during treatment ($r=-0.25$, $p=0.04$). After correcting for DAS and serum 25(OH)D at the start of treatment the aforementioned correlations were still found. Importantly, EULAR response rate was significantly lower in patients who were vitamin D-deficient at the start of treatment (34.6% vs 59.4%) and in patients with decreasing 25(OH)D levels during treatment (39.2% vs 57.7%).

Conclusion: RA patients with a serum 25(OH)D level below 50 nmol/L at the start of etanercept treatment or decreases during treatment have a lower EULAR response rate. Therefore, increasing serum 25(OH)D level in vitamin D deficient patients may be important to achieve optimal effects of TNF α blocking therapy.

Disclosure: W. Dankers, None; P. H. de Jong, None; S. Heil, None; S. van den Berg, None; A. Weel, None; J. Hazes, None; E. Colin, None; E. Lubberts, None.

Abstract Number: 593

Predictors of Persistence of Biologic Drug Step-Down Strategies in Inflammatory Arthritis: An Observational Study in Clinical Practice up to Seven Years of Follow-up

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Recommendations and guidelines for the management of Rheumatoid Arthritis (RA) and spondyloarthritis (SpA) with bDMARD include dose-tapering as an adequate option for patients on persistent remission. Although data regarding these strategies has increased in recent years, there is scarce evidence about their long-term effectiveness.

Our aim was to analyze the persistence of bDMARD dose-reduction in clinical practice and evaluate its predictors in patients with inflammatory arthritis with up to seven years of follow-up.

Methods: Prospective longitudinal study from June 2011 to April 2018. From a cohort of 153 patients with chronic inflammatory arthritis treated with bDMARD (TNF inhibitors, rituximab, tocilizumab, and abatacept) we recruited those with RA and SpA receiving reduced-dose regimens.¹

Variables analyzed were: persistence of bDMARD dose-reduction, outcomes of patients requiring its withdrawal, predictors of persistence reported in the literature such as glucocorticoid (GC) and previous bDMARD use, disease activity and duration of disease at dose reduction as well as demographic and clinical features. A logistic regression model was used to identify factors associated with persistence on reduced-dose regimen after 7 years of follow-up

Results: 56 patients (RA:33; SpA:23) on tapered bDMARD (etanercept 51.8%, adalimumab 32.1%, Infliximab 3.6% and tocilizumab 12.5%) at study entry were included. Their clinical and laboratory features are shown in table 1.

After a mean follow-up on tapered-dose of 4.4 ± 2.6 years, 42.9% of subjects overall remained treated with this strategy (RA: 36.4%; SpA: 52.2%).

From those who required discontinuation of the step-down regimen, 15 (48.4%) achieved the therapeutic objective and 7 (22.6%) failed after returning to standard dose respectively. bDMARD were discontinued in 4 (12.9%) patients due to sustained disease remission (RA=3; SpA=1), 3 (9.7%) due to adverse events and 2 (6.4%) due to other reasons.

No significant differences in the different variables analyzed were found between patients continuing vs discontinuing reduced-dose regimens. Only disease duration at dose-reduction was associated with persistence of bDMARD step-down strategy overall (AOR: 1.13; 95% CI 1.01-1.26; p 0.02) in multivariate analysis.

Conclusion: A significant proportion of patients with RA and SpA (36.4% and 52.2% respectively) can be maintained with reduced doses of bDMARD after a long-term follow-up. Disease duration was the only predictor of dose-tapering persistence overall.

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Table 1. Demographic and clinical features at bDMARD dose-reduction.

	Total n: 56	Continue tapered bDMARD n: 24	Withdrawn tapered bDMARD n:32
Age	52.3 \pm 14.3	53.9 \pm 13.9	51.1 \pm 14.7
Female	32 (57.1%)	10 (41.7%)	22 (68.7%)
Smoking status (ever smokers)	25%	23.8 %	26.1%
Diagnostics			
RA	33	12 (36.4%)	21 (63.6%)
SpA	23	12 (52.2%)	11 (47.8%)
Mean disease duration (mean \pm sd)			
RA	14.4 \pm 6.8	18.5 \pm 7.9	12.1 \pm 4.9
SpA	13.9 \pm 6.3	13.9 \pm 7.5	13.9 \pm 5
Disease activity (mean \pm sd)			
RA (DAS28)	2.3 \pm 0.5	2.3 \pm 0.3	2.3 \pm 0.6
AS (BASDAI)	1.6 \pm 1.6	1.7 \pm 1.8	1.5 \pm 1.7
Antibody Status (RA)			
RF	28 (85%)	9 (75%)	19 (90.5%)
ACPA	29 (88%)	9 (75%)	20 (95.2%)
Number of positive Ab (RA)			
0	4 (12%)	3 (25%)	1 (4.7%)
1	1 (3%)	0	1 (4.7%)
2	28 (85%)	9 (75%)	19 (90.5%)
Erosive disease (RA)	24/33	9/12	15/21
CRP (mg/dl) (median, IQR)			
RA	0.05 (IQR:0.28)	0.07 (IQR:0.27)	0.05 (IQR:0.28)
SpA	0.06 (IQR:0.26)	0.03 (IQR:0.17)	0.06 (IQR:0.25)
ESR (median, IQR)			
RA	9 (IQR:6)	9 (IQR:5)	9 (IQR:9)
SpA	10 (IQR:10)	7 (IQR:7)	12 (IQR: 8)
bDMARD Naive			
RA	28 (85%)	11 (91.7%)	17 (81%)
SpA	17 (73.9%)	9 (75%)	8 (72.7%)
Concomitant csDMARD			
RA	19 (57.6%)	7 (58.3%)	12 (55%)
SpA	5 (21.7%)	1 (8.3%)	4 (36.3%)
Concomitant GC			
RA	8 (24.2%)	2 (16.7%)	6 (28.6%)
SpA	2 (9%)	0	2 (18.2%)

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Abstract Number: 594

Identification of Tocilizumab Treated RA Patients, Whom Are Not Likely to Show Long-Term Clinical Benefit; Reanalysis of the Biomarker Sub-Study of LITHE

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

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Background/Purpose: To cilizumab, anti-interleukin 6 receptor (IL-6R) therapy, is an effective treatment of rheumatoid arthritis (RA). However, a significant amount of patients do not respond adequately long term and would most likely benefit from changing treatment at an early time point. Biomarkers reflecting joint tissue degradation (e.g. C1M) are direct measures of joint health and have been shown to be prognostic of structural progression, as well as pharmacodynamics markers of tocilizumab response. We investigated whether lack of early changes in biomarkers, in response to tocilizumab, were predictive of lack of long-term(52 week) clinical benefit.

Methods: Pooled biomarker data from the two treatment arms (4 and 8 mg/kg tocilizumab + MTX) were included in this reanalysis of the LITHE (a phase III randomized placebo controlled study, NCT00106535) biomarker study (N=380). Patients had moderate-severe RA and were DMARD-IRs. Biomarkers reflecting tissue degradation were selected; type I, II, III, IV and VI collagen metabolites C1M, C2M, C3M, C4M and C6M. Missing biomarker data(<5%) were imputed using KNN. Patients were dichotomized into quartiles using 16-week %-suppression in the biomarkers. Long-term clinical benefit was assessed by ACR20 and ACR50 at week 52. Escape patients were annotated as ACR non-responders. Mann-Whitney was used to compare level of biomarker suppression between responders and non-responders. Logistic regression was used to predict lack of response, adjusting for age, sex, BMI and baseline biomarker level.

Results: There were a total of 196 (50.5%) ACR20 and 266 (70.0%) ACR50 non-responders at week 52. There were significant differences in the median levels of biomarker suppression between ACR non-responders and responders: i) C1M; ACR20, 28 vs. 47% (p=0.0004), ACR50, 34 vs. 45% (p=0.02), ii) C2M; ACR20, 7 vs. 13%(p=0.007), ACR50, 8 vs. 13% (p=0.02), iii) C3M; ACR20, 14 vs. 28% (p=0.0008),ACR50, 17 vs. 30% (p=0.009), iv) C4M; ACR20, 20 vs. 30% (p=0.0001), ACR50, 22 vs. 29% (p=0.04), and v) C6M; ACR20, 36 vs. 53% (p=0.0004), ACR50, 37 vs. 56%(p=0.004). C1M was the best marker for prediction of whom would not respond totocilizumab. Patients with a 38 to 60% suppression in C1M were 2.0 times more likely to achieve an ACR50, whereas patient with less than a 38% suppression were 3.2 to 3.7 more likely not to achieve an ACR50 response and 3.7 to 5.6 more likely not to achieve an ACR20 response (table). The remaining markers could predict lack of ACR50 with ORs from 1.9 to 2.9 and ACR20 with ORs from 2.4 to 3.0, if the marker actually increased from baseline to 16 weeks (Q4, table).

	ACR20				ACR50			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
C1M								
N suppression	<40	40-58	59-5	increase	<40	40-58	59-5	increase
OR (95%-CI)		2.0 [1.1, 3.8]	3.7 [1.8, 7.4]	4.7 [1.8, 12.6]		2.0 [1.1, 2.7]	5.6 [2.3, 10.7]	3.7 [1.9, 7.3]
P		0.028	0.0009	0.0014		0.022	<0.0001	0.0001
C2M								
N suppression	<10	10-50	50-0	increase	<10	10-50	50-0	increase
OR (95%-CI)		1.2 [0.7, 2.2]	1.6 [0.9, 3.0]	1.8 [1.0, 3.6]		1.3 [0.7, 2.3]	1.3 [0.7, 2.2]	2.4 [1.3, 4.3]
P		ns	ns	0.027		ns	ns	0.0050
C3M								
N suppression	<18	18-27	27-0	increase	<18	18-27	27-0	increase
OR (95%-CI)		1.3 [0.7, 2.3]	1.9 [1.0, 3.7]	2.8 [1.4, 5.6]		1.4 [0.8, 2.5]	2.2 [1.2, 3.9]	2.8 [1.5, 5.1]
P		ns	0.045	0.0017		ns	0.013	0.0014
C4M								
N suppression	<62	62-29	29-0	increase	<62	62-29	29-0	increase
OR (95%-CI)		1.2 [0.6, 2.1]	1.5 [0.8, 3.0]	1.9 [0.9, 4.0]		1.5 [0.8, 2.7]	2.4 [1.3, 4.6]	3.0 [1.5, 5.8]
P		ns	ns	0.070		ns	0.0047	0.0011
C6M								
N suppression	<45	45-45	45-15	increase	<45	45-45	45-15	increase
OR (95%-CI)		0.7 [0.5, 1.0]	1.7 [0.9, 3.5]	2.1 [1.1, 4.0]		1.2 [0.7, 2.2]	2.2 [1.2, 4.2]	2.7 [1.4, 5.2]
P		ns	ns	0.030		ns	0.013	0.0044

Conclusion: We found that lack of early inhibition in tissue turnover biomarkers, especially C1M, were predictive of long term lack of clinical benefit. This indicates that biomarkers associated with joint tissue health may be used as patient monitoring and risk-assessment tool for anti-IL6 effect.

Disclosure: A. C. Bay-Jensen, Nordic Bioscience, 1, 3, IMI APPROACH, 2; C. S. Thudium, Nordic Bioscience, 3; C. Christiansen, Nordic Bioscience, 1, 4; M. A. Karsdal, Nordic Bioscience, 1, 3.

Abstract Number: 595

Predictive VALUE of CD19 SERUM Levels for LONG TERM Therapeutic Response and Utility As Biomarker for Optimization, in Rheumatoid Arthritis Patients Treated with Rituximab

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Rituximab (RTX) is directed against CD20 antigens in B lymphocytes (BL), producing selective depletion of BL, not affecting mature plasmatic cells, without immediate effect on immunoglobulin (Ig) levels.¹ RTX retreatment decrease serum Ig levels which could increase infection risk.² Current guidelines recommend optimization of biologic therapy once remission has achieved in rheumatoid arthritis (RA) patients. A serum biomarker able to predict what patients would maintain remission after optimization in RTX treated RA patients is lacking. In previous studies, RA patients with good response to RTX show significant decreases in DAS28 scores associated to maintained BL depletion.³ Purpose: to analyze the predictive value of CD19 serum level prior to RTX infusion for the long term maintenance of therapeutic response, and it's utility as a biomarker for optimization in RA patients treated with RTX.

Methods: all RA patients treated with RTX in our center during 2016 and 2017 for at least 6 months, and with 12 months follow-up, were included. Demographic data, clinical data related to RA, including activity parameters (DAS28, HAQ, ESR, RCP), number of infections, optimization and serum levels of lymphocytic subpopulations (CD19, CD3 and CD56) and immunoglobulins (Ig) prior to each RTX cycle were collected. Optimization was defined as any dose decrease (lower dose for cycle and/or increase interval between cycles). Recurrent infections were defined as three or more infections per year. Descriptive statistics, correlation between basal levels of CD19, CD3 or CD56, and activity parameters or Ig levels at 6, 12 and 18 months, and association studies between lymphocyte subpopulations and optimization or recurrent infections were performed.

Results: Thirty patients (25 females, 55±11 years) with RA (24 RF/aCCP +, 13±9 years from disease onset), were included. At RTX initiation, DAS28 was 5.4±1.2, 28 patients (93%) were treated with any DMARD, 25 (83%) with prednisone (5±2 mg/d), and 19 (63%) had received previous biologic therapy. After 57±39 months of RTX (accumulated dose 14±10g), 22 patients had been optimized (at 37±32 months, DAS28 3.2±1.4) and 6 had stopped RTX. CD19 levels were lower than 2% in 22 patients (79%), including 9 with undetectable levels. CD19 levels (cells/mm³) were lower in optimized patients (21 vs 4, p=.02), and were correlated with DAS28 6 and 12 months later (r=0.4; p=.02), and with ESR 6 months later (r=0.6; p=.002). CD19 levels did not correlate with Ig levels, and were not associated with recurrent infections. CD3 and CD56 levels did not show any relevant association.

Conclusion: In RA patients treated with RTX for more than 12 months, CD19 levels correlate with long term therapeutic response, being low or undetectable levels predictors of good outcome, without association with Ig levels or increased infections. Our results suggest that CD19 levels before every RTX cycle might be a useful biomarker to select candidate patients for optimization with this therapy.

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2. Bredemeier M, et al. Clin Rheumatol 2015;34:1801-1805.
3. Cambridge G et al. J Autoimmun 2016;70:22-30.

Disclosure: S. Melchor, None; E. Rodriguez-Almaraz, None; J. L. Pablos, None; P. Carreira, None.

Combination of Intra-Articular Steroid Injection and Tofacitinib More Effective Than Tofacitinib in Rapid Radiographic Progression Patients with Rheumatoid Arthritis

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

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Background/Purpose: Treatment of rheumatoid arthritis (RA) should aim at full remission. However, we experienced that rapid radiographic progression (RRP) existed despite initial tofacitinib and methotrexate combination therapy in early RA (unpublished data). In RRP, initial tofacitinib and methotrexate might be inadequate. To compare remission and radiographic non-progression in RRP patients treated with tofacitinib or with tofacitinib plus intra-articular steroid injection.

Methods: We designed a single-blind(X ray reader and assessment physician), randomized controlled trial. We screened 48 RRP (CRP> 10 mg/L, RF +, and ACPA+) early (disease duration<6 months) RA patients for inclusion. 39 were randomly allocated tofacitinib group (T group) or tofacitinib plus intra-articular steroid injection group (T plus I group). All patients were taking methotrexate (from 10 to 22mg a week). For T plus I group, palpate examinations of both MP and PIP joints, wrists, elbows, shoulders, and knees were performed every 4 weeks. If swollen joints were existed, intra-articular steroid injections were intensified in each swollen joints. Co-primary endpoints were proportion of patients showing clinical remission (SDAI <3.3) and radiographic non-progression (Δ modified total Sharp score ≤ 0.5) at 52 weeks. Analysis was by intention-to-treat with last observation carried forward to missing data.

Results: The characteristics of each group at baseline were not significantly different. Clinical remission at 52 weeks was achieved by more patients in the T plus I group (29.2%) than in the T group (21.3%) ($p<0.05$). Radiographic non-progression at 52 weeks was achieved by more patients in the T plus I group (33.4%) than in the C group (23.7%) ($p<0.05$).

Conclusion: Results of this reveal that combination of intra-articular steroid injection and tofacitinib can achieve a high clinical and radiological remission rate in early RRP RA.

References:

1. Effectiveness of initial treatment allocation based on expert opinion for prevention of rapid radiographic progression in daily practice of an early RA cohort. Durnez A, et al. Ann Rheum Dis. 2011 Apr;70(4):634-7. Epub 2010 Dec 21.
2. A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. Visser K, et al. Ann Rheum Dis. 2010 Jul;69(7):1333-7. Epub 2010 May 24.

Disclosure: K. Kume, None; K. Amano, None; S. Yamada, None; T. Kanazawa, None; K. Hatta, None.

Characteristics of Patients and Predictors of Composite Disease Activity Scores for Switching to Monotherapy Vs Continuing TNF Inhibitor and Methotrexate Combination Therapy in RA: A Retrospective Analysis of the Brigham and Women's Rheumatoid Arthritis Sequential Study Registry

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SESSION INFORMATION

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Background/Purpose: Biologics in combination with methotrexate (MTX) are being incorporated earlier in rheumatoid arthritis (RA) therapy to prevent long-term damage and maintain patient function. While some patients transition off TNF inhibitor (TNFi) + MTX combination therapy (Combo) to monotherapy (TNFi mono or MTX mono), differences in patient characteristics and attainment of disease control for the Combo and monotherapy groups are unclear.

Methods: Data were obtained from a prospectively collected cohort at a single academic medical center from 2003 to 2016. At study visits every 6 months, a range of patient and treatment variables were recorded. This analysis included patients who received Combo while in the cohort and were followed; patients were categorized into three groups: continued Combo, switched to TNFi mono, or switched to MTX mono. Baseline was the date of first recorded use of Combo or following entry to the cohort. Index was the date a patient switched to monotherapy, or for continuing Combo patients, baseline + 24 months (based on average time to switch in monotherapy groups). Predictors of disease activity scores at index were analyzed with ANCOVA.

Results: TNFi + MTX was used by 341 patients, with 46% remaining on Combo and 31% and 23% switching to TNFi mono or MTX mono, respectively. Half (51%) of the switches to monotherapy occurred in the first year after baseline, with an average time to switch of 23.4 months. Patient characteristics at index were significantly different across groups for mean age (older for switch to MTX mono) and biologic initiation era (less in late era for switch to MTX mono); nonsignificant trends were seen for gender and disease status (Table 1). Disease Activity Score 28-joint with C-reactive protein (DAS) at index was predicted by early TNFi initiation era ($p=0.0072$), longer disease duration ($p<0.0001$), and higher baseline DAS score ($p<0.0001$), but not by treatment group (Table 2). Other disease activity measures had similar predictors at index, except Rheumatoid Arthritis Disease Activity Index (RADAI), which was predicted by higher baseline RADAI score ($p=0.0004$) and marginally by treatment group ($p=0.0503$) (Table 2).

Conclusion: Over half the patients on Combo transitioned to TNFi mono or MTX mono, a majority during the first year of combo therapy on study. Patients switching to MTX mono were older than patients continuing Combo or switching to TNFi mono, but not much different in disease activity or time on therapy. Disease duration and baseline disease activity had the greatest influence on disease activity at the time of medication change.

Table 1. Demographic and Disease Characteristics at Index (Date of the Switch)

Characteristic at index*	Continued Combo TNFi + MTX (n = 157)	Switched to TNFi Mono (n = 105)	Switched to MTX Mono (n = 79)	p†
Age (years)	61.17 ± 11.83	59.36 ± 15.07	64.9 ± 12.92	0.0256
Female	140 (89.2%)	85 (81.0%)	63 (79.7%)	0.0831
White	144 (87.8%)	99 (90.0%)	76 (88.4%)	0.3099
Disease status by DAS (n = 123)	(n = 84)	(n = 60)		
Remission (DAS < 1.6)	39 (31.7%)	21 (25.0%)	13 (21.6%)	0.4748‡
Low (1.6 ≤ DAS ≤ 2.4)	32 (26.0%)	28 (33.3%)	15 (25.0%)	
Moderate (2.4 < DAS ≤ 3.7)	29 (23.6%)	22 (26.2%)	15 (25.0%)	
High (DAS > 3.7)	23 (18.7%)	13 (15.5%)	17 (28.3%)	
Biologic initiation era				
Late (2012-2016)	32 (20.4%)	13 (12.4%)	5 (6.3%)	0.0153‡
Intermediate (2006-2011)	27 (17.2%)	11 (10.5%)	13 (16.5%)	
Early (2003-2005)	98 (62.4%)	81 (77.1%)	61 (77.2%)	
Time from baseline to switch, months		23.4 ± 24.5	23.5 ± 22.2	0.9357
<1 year	–	56 (53.3%)	38 (48.1%)	
1-2 years	–	23 (22.0%)	13 (16.4%)	
2-3 years	–	7 (6.6%)	16 (20.3%)	
3-4 years	–	9 (8.6%)	4 (5.1%)	
>4 years	–	10 (9.5%)	8 (10.1%)	
Treatment duration, months				
Time on TNFi before index	28.2 ± 20.5	29.7 ± 28.4	24.6 ± 23.2	0.3350
Time on MTX before index	34.3 ± 25.0	28.6 ± 27.1	35.2 ± 29.2	0.1541

Data are presented as mean ± SD or n (%)

Abbreviations: DAS, Disease Activity Score 28-joint count with C-reactive Protein; MTX, methotrexate; TNFi, tumor necrosis factor inhibitor

* For each patient who continued combination therapy, the index date was calculated as their baseline date plus 24 months (the average time to switch in the other groups)

† Significant values ($p < 0.05$) are **bolded**; p by ANOVA for means (F-tests) and Chi-square for frequency counts

‡ P-value across all categories

Table 2. Predictors of Disease Activity Scores at Index

	DAS (N = 251)		RAPID3 (N = 211)		SDAI (N = 227)		CDAI (N = 245)		RADAI (N = 113)	
	Est*	p*	Est*	p*	Est*	p*	Est*	p*	Est*	p*
Treatment										
Switch to TNFi mono	−0.01	.9741	0.09	.9164	0.11	.9451	0.25	.8697	−0.77	.0503
Switch to MTX mono	0.20	.2986	−0.95	.3032	1.99	.2865	2.66	.1218	−0.70	.1479
Continued combo	
Age (per 10y)	0.0008	.8955	0.040	.1913	−0.002	.9772	−0.02	.7715	0.00	.8103
Gender										
Male	−0.04	.8462	1.01	.3110	−0.80	.6865	0.04	.9831	−0.23	.6231
Female	
College graduate										
Yes	0.09	.5947	0.49	.5184	1.06	.5049	−0.16	.9141	−0.30	.4422
No	
Marital status										
Married	0.09	.5622	−0.50	.5111	0.28	.8574	−2.36	.0930	−0.09	.8068
Other	
Biologic era										
Early†	0.65	.0072	2.10	.0941	6.08	.0112	5.58	.0115	0.65	.1889
Intermediate†	0.26	.3528	2.01	.1549	3.30	.2199	1.60	.5137	0.67	.1962
Late†	
Disease duration	0.03	<.0001	0.09	.0063	0.30	<.0001	0.30	<.0001	0.03	.1274
Steroid use										
No	−0.16	.3172	−0.67	.3634	−1.05	.4888	−0.70	.6183	−0.48	.2133
Yes	
Narcotic use										
No	0.47	.1030	−0.01	.9902	5.24	.0707	5.41	.0361	−0.08	.9105
Yes	
Baseline score	0.32	<.0001	0.46	<.0001	0.32	<.0001	0.31	<.0001	0.34	.0004

Positive values are higher/worse disease activity, negative values are lower/better disease activity

Abbreviations: CDAI, Clinical Disease Activity Index; DAS, Disease Activity Score 28-joint count with C-reactive protein; MTX, methotrexate; RADAI, Rheumatoid Arthritis Disease Activity Index; RAPID3, Routine Assessment of Patient Data 3; SDAI, Simplified Disease Activity Index; TNFi, tumor necrosis factor inhibitor

* Significant values ($p < 0.05$) are **bolded**; estimate (Est) and p by analysis of covariance

† Era of biologic initiation: early (2003-2005), intermediate (2006-2011), or late (2012-2016)

Disclosure: N. A. Shadick, Bristol-Myers Squibb, 5, Amgen Inc., 2, Mallinckrodt, 2, UCB, Inc., 2, Crescendo Biosciences, 2, Sanofi, 2, Bristol-Myers Squibb, 2, DxTerity, 2; M. E. Weinblatt, Amgen Inc., 5, Bristol-Myers Squibb, 5, Crescendo Bioscience, 5, UCB, Inc., 5, Amgen Inc., 2, Bristol-Myers Squibb, 2, Crescendo Bioscience, 2, Sanofi/Regeneron, 2; C. K. Iannaccone, None; M. Frits, None; T. Davis, Health Analytics, 3; C. Young, Health Analytics, 3; D. H. Collier, Amgen Inc., 3, Amgen Inc., 1; M. Gharaibeh, Amgen Inc., 3, Amgen Inc., 1; B. S. Stolshek, Amgen Inc., 3, Amgen Inc., 1.

Abstract Number: 598

Real-World Experience of Effectiveness and Safety of Certolizumab Pegol for Rheumatoid Arthritis in Japan: Single-Center Retrospective Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Certolizumab-pegol (CZP) is a sixth antitumor necrosis factor inhibitor for rheumatoid arthritis (RA) in Japan. Several clinical trials were conducted to evaluate the efficacy and safety of CZP, such as J-RAPID, HIKARI and C-OPERA study. They clarified the efficacy and safety of CZP for RA. However, the target population of most clinical trials is limited by the inclusion and exclusion criteria of the studies. Thus, the target populations are different between those in clinical trials and in daily practice. We investigated the effectiveness and safety of CZP for RA in daily practice.

Methods: Patients who started CZP after April 1, 2013 were investigated in this retrospective study. Retention rate, change in disease activity and safety of CZP obtained through medical records and the data from Institute of Rheumatology, Rheumatoid Arthritis (IORRA) cohort were analyzed. The missing data were complemented by using the last-observation-carried-forward (LOCF) method. Effectiveness was assessed by 28-joint Disease activity score (DAS28) and the factors associated with therapeutic response at 12 weeks with CZP by using logistic regression analysis. Retention rate was assessed by Kaplan-Meier method. Patients were followed until August 31, 2017.

Results: Consecutive 143 RA patients who started CZP at our institute were enrolled. Women were 93%. The median (interquartile range) age was 48 (36-59). Disease duration was 7 (3-14) years, and treatment periods were 39 (15-100) weeks. DAS28 was 3.7 (2.8-4.3) at baseline. Bio-naïve patients were 42%. Methotrexate (MTX) was used in 68% and the median dose was 10 (8-12) mg/week. Prednisolone was used in 39% and the median dose was 5 (4.0-8.8) mg/day at baseline. Patients who wanted to be pregnant were 42 (31% among women). The number of patients who could not continue CZP was 89 (62%), due to lack of effectiveness 51, marked effectiveness 2, pregnancy 5 and side effects 13. The DAS28 at 12 weeks was decreased from 3.6 to 2.9 ($p<0.01$). The DAS28 at 12 weeks was more decreased in bio-naïve subset than bio-switch subset significantly ($p<0.01$) and same tendency was detected in patients with MTX subset than without MTX ($p<0.01$). Bio-naïve might be the factor for achieving good response at 12 weeks (χ^2 2.2, $p=0.08$). The retention rate was 80% at 12 weeks and 47% at 52 weeks. A greater percentage of patients in bio-naïve subset adhered to CZP than that of patients in bio-switch subset ($p=0.04$). Similarly, the retention rate of CZP with MTX subset was significantly higher than that without MTX subset ($p=0.03$).

Conclusion: Patients who wanted to be pregnant was over 30% among women who used CZP. CZP was more effective in patients with bio-naïve and patients treated with CZP concomitant with MTX. The fact that seen in trial was ascertained in daily practice.

Disclosure: N. Sugitani, None; E. Tanaka, Abbvie, Ayumi Pharmaceutical, Bristol Myers Squibb, Chugai Pharmaceutical, Eisai Pharmaceutical, Nippon Kayaku, Pfizer, Takeda Pharmaceutical, and UCB Pharma, 5, 8; E. Inoue, None; E. Sugano, None; K. Saka, None; M. Ochiai, None; R. Yamaguchi, None; Y. Shimizu, None; N. Sugimoto, None; K. Ikari, Astellas, AbbVie, Bristol-Meyers, Chugai, Janssen Pharmaceutical, Lilly, Takeda, and Tanabe-Mitsubishi, UCB, 5, 8; A. Nakajima, Eisai, Bristol-Meyers, Novartis, Astellas, Noppon-Shinyaku, Pfizer, Ayumi, Daiichi-Sankyo, Taisyo-Toyama, Tanabe-Mitsubishi, Chugai, janssen, 5, 8; A. Taniguchi, abbVie, Eisai, Jansen, Teijin, Novartis, Eli Lil, 5, 8; H. Yamanaka, AbbVie, Eisai, Bristol-Meyers, Novartis, Behringer, Astellas, Kaken, Noppon-Shinyaku, Pfizer, UCB, Ayumi, Ono, Daoochi-Sankyo, Taisyo-Toyama, Takeda, Tanabe-Mitsubishi, Chugai, Teijin Pharma, Torii, YLbio, 5, 8.

Abstract Number: 599

Comparative Effectiveness in Pain and HAQ-DI Improvement for Baricitinib Versus Adalimumab, Tocilizumab, and Tofacitinib Monotherapies in Csdmard-Naïve Rheumatoid Arthritis Patients: A Matching-Adjusted Indirect Comparison (MAIC)

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

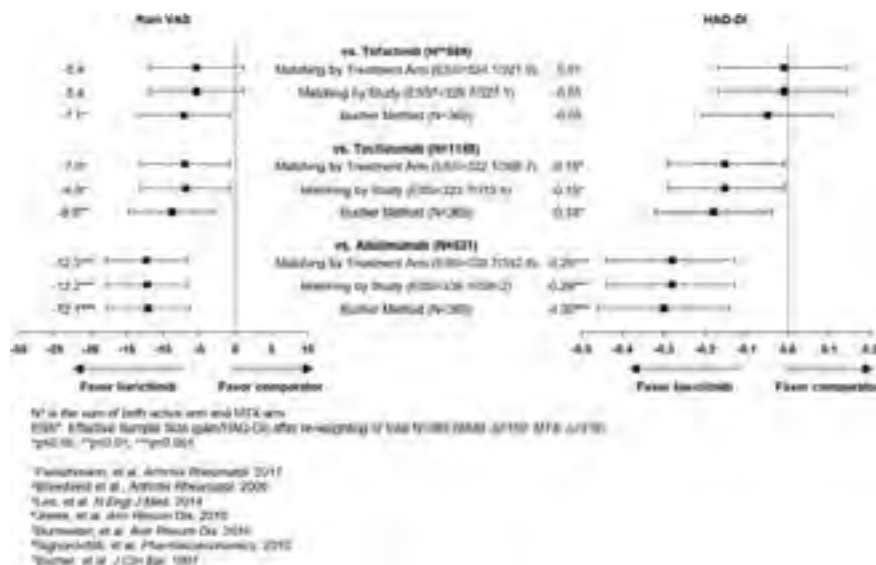
Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: In Phase 3 trial (RA-BEGIN), baricitinib (BARI) monotherapy demonstrated superiority to MTX in pain reduction and HAQ-DI improvement in treatment of csDMARD-naïve active RA patients.¹ No prospective head-to-head(H2H) trial data are available comparing BARI monotherapy vs. bDMARD monotherapy in csDMARD-naïve RA patients.

The objective was to assess pain and HAQ-DI for BARI monotherapy from a randomized, MTX-controlled trial vs adalimumab (ADA), tocilizumab (TCZ), and tofacitinib (TOFA) monotherapy from similar randomized, MTX-controlled trials in csDMARD/bDMARD naïve RA patients using matching-adjusted indirect comparison (MAIC).



Methods: Individual patient data from the RA-BEGIN BARI 4 mg arm were weighted to match baseline characteristics of the ADA arm from PREMIER,² TOFA 5 mg arm from ORAL-START,³ and TCZ 8 mg/kg arm from combination of AMBITION and FUNCTION,^{4,5} respectively; MTX arms were also matched between trials. Method of moments was used to determine weights for age, gender, baseline disease scores, and baseline values of the outcome variable. Mean change on pain VAS and HAQ-DI at Week 24 for BARI were adjusted for the above baseline characteristics with the weighted linear model, and then indirectly compared vs. respective published results for Week 24 TCZ and TOFA and for Week 26 ADA data. Statistical significance of the weighted treatment effect was assessed with the bootstrap method. Sensitivity analyses included MAIC with study level matching⁶, Bucher's method without matching adjustment⁷, and inclusion of disease duration as an additional matching variable.

Results: Across trials, the mean baseline pain VAS ranged from 58.7 to 65.2 with a 6-month mean change in pain of -28.3 to -33.5 for the MTX arm, indicating comparability between trials. Similar HAQ-DI and changes in HAQ-DI for the MTX arm were observed. At Week 24, BARI showed numerically greater improvement over MTX in pain than that for TCZ, ADA, and TOFA; statistically significant pain improvement were observed for BARI vs ADA and TCZ with all 3 matching methods but only with the Bucher method for TOFA (Figure). BARI-treated patients showed significantly greater improvement in HAQ-DI at Week 24 than TCZ and ADA but not TOFA (Figure). Sensitivity analyses showed consistent results.

Conclusion: This indirect comparison of different studies in cs/bDMARD-naïve RA patients, after adjusting for differences in baseline characteristics, suggest a greater pain reduction and improved physical function for BARI monotherapy vs. TCZ and ADA monotherapy. There is suggestion of greater pain reduction for BARI monotherapy vs. TOFA monotherapy, but no differences in improved physical function between the JAK inhibitors. A H2H clinical trial would be needed to confirm these results.

Disclosure: B. Fautrel, AbbVie, Biogen, BMS, Celgene, Janssen, Eli Lilly and Company, Medac, MSD, NORDIC Pharma, Novartis, Pfizer, Roche, Sanofi-Aventis, SOBI, UCB, 5; AbbVie, MSD, Pfizer, 2; B. Zhu, Eli Lilly and Company, 1, 3; P. C. Taylor, Celgene, Eli Lilly and Company, Galapagos, UCB, 2; AbbVie, Eli Lilly and Company, Galapagos, GlaxoSmithKline, Pfizer, UCB, Biogen, Sandoz, Novartis, Janssen, 5; M. van de Laar, AbbVie, Janssen, Eli Lilly and Company, MSD, Pfizer, BMS, 2; P. Emery, Eli Lilly and Company, AbbVie, BMS, MSD, Novartis, Pfizer, Roche, Samsung, Sandoz, UCB, 5; F. de Leonardi, Eli Lilly and Company, 1, 3; C. L. Gaich, Eli Lilly and Company, 1, 3; C. Nicolay, Eli Lilly and Company, 1; Z. Kadziola, Eli Lilly and Company, 1, 3; I. de la Torre, Eli Lilly and Company, 1, 3; R. Fleischmann, AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, Genentech, GlaxoSmithKline, Janssen, Eli Lilly and Company, Merck, Pfizer, Regeneron, Roche, Sanofi, Aventis, UCB, 2; AbbVie, Akros, Amgen, Bristol-Myers Squibb, Celgene, Genentech, GSK, Janssen, Eli Lilly and Company, Pfizer, Sanofi-Aventis, UCB, 5.

Early Versus Delayed Treatment in Patients with Rheumatoid Arthritis (RA) in Routine Care at a Single US Academic Center: Better Response According to MDHAQ (MultiDimensional Health Assessment questionnaire) for Patients Starting Treatment in the Initial 6 Months

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Delay in initiation of disease-modifying anti-rheumatic drug (DMARD) therapy may be a major contributing factor toward poor outcomes in patients with rheumatoid arthritis (RA). Many patients, however, undergo delay in diagnosis and treatment initiation in routine care regardless of rheumatologists' awareness. In this study, we aim to evaluate improvement according to multidimensional health assessment questionnaire (MDHAQ) scores in DMARD-naïve RA patients with and without delay in initiation of treatment.

Methods: We retrospectively reviewed all DMARD-naïve RA patients seen at a single academic site from 2011/16 who had an MDHAQ form at baseline visit and 6-month follow-up MDHAQ. Disease duration was derived from symptom onset to the time of first visit at our rheumatology clinic. We classified patients as "no delay" (<6 months) or "delay" (>6 months) to treatment according to the ACR definition ¹. Demographic, clinical data and the change from baseline to follow-up were compared in no delay versus delay groups using t-tests; %change from baseline in each group was also calculated. Mean change in MDHAQ scores in each group were compared with minimal clinically important improvement (MCII) ².

Results: Seventy-four patients were included; 33 (45%) with no delay and 41 (55%) with delay. By definition, median symptom duration at the first visit was significantly higher for the delay group (23 vs 2.2 months). No significant differences were seen in age, gender, ethnicity, rheumatoid factor, anti-cyclic citrullinated peptide antibody, type of DMARD initiated, and glucocorticoid dosage for both groups. Median interval from baseline to follow-up was not significant in both groups (6 months). Routine assessment of patient index data (RAPID3) and component scores improved in both groups at follow-up, greater improvement was noted in no delay vs delay (RAPID3 % change: -39% vs -29%, respectively. RA disease activity index (RADAI) self-reported joint counts of 48 joints also improved in both groups at follow-up with greater improvement in no delay vs delay (-46% vs -31%). Mean change in RAPID3, physical function and patient global assessment scores from baseline to follow-up in each group met the minimal clinically important improvement thresholds, but not pain (table).

Table. Changes in patient reported clinical variables included in the MDHAQ

	Early Treatment (<6m) N=33	Delayed Treatment (>6m) N=41	MCII threshold
RAPID3 (0-30)			3.8
Baseline	14.5 (5.7)	15.6 (6.7)	
Change at 6 months	-5.6 (6.4)	-4.6 (6.3)	
% Change from baseline	-39%	-29%	
MDHAQ-Function (0-10)			0.375 (HAQ)
Baseline	2.8 (2.0)	2.9 (2.3)	
Change at 6 months	-1.3 (2.0)	-0.9 (1.9)	
% Change from baseline	-46%	-31%	
MDHAQ-Pain (0-10)			2
Baseline	6.6 (2.5)	6.9 (2.6)	
Change at 6 months	-2.6 (2.8)	-1.8 (2.7)	
% Change from baseline	-39%	-26%	
MDHAQ-PATGL (0-10)			1.8
Baseline	5.9 (2.4)	6.4 (2.7)	
Change at 6 months	-2.6 (3.3)	-2.1 (3.2)	
% Change from baseline	-44%	-33%	
RADAI self-reported joint counts (0-48)			na
Baseline	13 (9)	16 (12)	
Change at 6 months	6 (10)	5 (10)	
% Change from baseline	-46%	-31%	

Data presented as mean (SD) and percentage (%) change from baseline comparing results between groups. MCII; minimal clinically important improvement; RAPID3, routine assessment of patient index data 3; PATGL, patient global assessment.

Conclusion: A clinically significant improvement was seen in all DMARD –naïve RA patients after treatment initiation, according to MDHAQ questionnaire. However, greater improvement was seen when treatment was initiated <6 months of symptom onset, emphasizing the importance of early referral and initiation of DMARD. Further studies confirming these results in other larger cohorts are needed. MDHAQ is useful in detecting meaningful clinical changes in early RA patients.

References:

1. Arthritis Care Res (Hoboken), 2016 Jan.
2. Ann Rheum Dis, 2015 Sep.

Disclosure: J. R. Chua, None; M. Riad, None; S. Hassan, None; N. Shakoob, Dr. Comfort/DJO, 7; J. A. Block, Gilead, 1, Novartis, 2, Pfizer, Inc., 2, Janssen, 2, GlaxoSmithKline, 5, Zynherba Pharmaceuticals, 5, Agios, Inc, 7, Daiichi Sankyo, Inc., 7, Omeros, Inc., 7; I. Castrejón, None.

Abstract Number: 601

At Which Point and for Which Reasons Are Oral MTX Formulations Switched to Injectable Ones in RA Patients? Combined Results from 3 Independent Observational and Clinical Trials

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: MTX is considered as a cornerstone in RA treatment since the 1990s and its injectable forms have proven their enhanced clinical and pharmacological efficacy and safety in case of insufficient response or poor tolerance of oral formulations. Few data are available considering the timepoint at which the formulation switch is performed in current practice.

The objective of this work was to investigate across 3 independent trials if there was a consistency in patterns of MTX oral -> injectable switches in terms of RA characteristics, MTX dosages (before and after the switch) and reasons of passage.

Methods: Three trials were considered for this work: 1/ STRATEGIE (observational study designed to investigate the therapeutic strategies used in current practice in RA patients insufficiently responding to initial MTX monotherapy), 2/ APRiM (observational study aimed to investigate the treatment adherence of RA patients switching from oral to injectable MTX or between two different MTX prefilled syringes) and 3/ SELFi (phase III randomized trial aiming to compare a new MTX autoinjector to the historical MTX prefilled syringe in terms of treatment adherence and functional capacity in RA patients at 6 months). In all three studies we selected baseline data concerning patients switching from oral to injectable MTX at the inclusion visit.

Results:

	STRATEGIE N = 151	APRiM N = 270	SELFi N = 98
RA duration, years (mean ± SD)	4.9 ± 6.1	6.6 ± 8.1	4.5 ± 5.9
(median (min;max))	2.8 (0.0; 29.0)	3.0 (0.0; 40.0)	2.0 (0.2; 30.5)
MTX treatment duration, years (mean ± SD)	3.6 ± 4.5	3.3 ± 4.2	2.5 ± 2.8
(median (min;max))	1.9 (0.0; 24.3)	1.4 (0.0; 23.6)	1.4 (0.1; 15.4)
DAS28 (mean ± SD)	4.4 ± 0.9	3.9 ± 0.9	3.5 ± 1.2
MTX oral dosage at V0, mg/wk (mean ± SD)	15.3 ± 3.7	15.0 ± 4.1	14.8 ± 3.8
MTX injectable dosage at the end of V0, mg/wk (mean ± SD)	17.0 ± 4.0	16.3 ± 3.8	17.0 ± 4.0
Distribution MTX dosage unchanged / raised / reduced	50% / 45% / 5%	62% / 34% / 4%	51% / 42% / 7%

Conclusion: Our work showed a consistent pattern across 3 independent trials concerning the oral/injectable MTX switch. It generally occurs at 15mg/wk, the new injectable dosage being either unchanged or very slightly raised as compared to the last oral one. Surprisingly, the MTX route of administration seems to be modified mostly for efficacy reasons, safety issues being anecdotal.

Disclosure: R. M. Flipo, NordicPharma, 5; A. Saraux, Nordic Pharma, 5; C. Hudry, Nordic Pharma, 5; C. Gaujoux-Viala, NordicPharma, 5; E. Senbel, Nordic Pharma, 5; S. Tropé, Nordic Pharma, 6; E. Zinovieva, Nordic Pharma, 3; A. Courbevet, Nordic Pharma, 3; H. Herman-Demars, Nordic Pharma, 3.

Individualised Infliximab Treatment: A Treatment Strategy Based on Therapeutic Drug Monitoring

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

Background/Purpose: The purpose is to develop an individualised treatment strategy based on Therapeutic drug monitoring (TDM) in order to optimise efficacy of Infliximab (INX) treatment. Targeted therapies have greatly improved the treatment of patients' inflammatory joint diseases, but a significant proportion of patients either do not respond sufficiently to therapy or lose efficacy over time. An extensive individual variation in serum drug concentrations suggests both under- and overtreatment of a substantial proportion of patients. Many patients develop anti-drug antibodies (ADAb) during therapy, contributing to reduced drug levels, inefficacy and adverse events. TDM can probably increase effectiveness of treatment with INX and other biological drugs.

Serum (MIL) low (ng/ml)	<2.0 and high ADRs (≥ 10 ug/L)	<2.0	2.1 – 2.9	3.0 – 6.6	6.7 – 10.0	>10.0
Action	Switch to oral hydrocortisone (200)	Increase dose of prednisone based on weight (200 mg/d)	Consider increasing dose	Random	Consider decreasing dose	Decrease dose
Guideline for action		Increase the dose by increasing the dose by 2-2.5 mg/kg to a max dose of 32 mg/kg or by decreasing the dose interval by 2 weeks to a min of 4 weeks	Consider increasing the dose based on clinical judgement and the patient's factors given below*	Within target range Continue with the same dose and dosing interval	Consider to decrease the dose based on clinical judgement and the patient's factors given below*	Decrease the dose by increasing the dose interval by 2 weeks to a min of 3 weeks or by decreasing the given dose by 2-2.5 mg/kg

*Patient factors to be considered when making the treatment decisions in the yellow boxes:
Disease activity and trend (disease activity, the trend of the trough level over time, previous drug interval changes, availability of alternative drug, diagnosis (RA patients are expected to have lower trough levels due to lower recommended dosing)

Methods: The treatment strategy has been developed by the steering committee of the NORwegian DRUG Monitoring study (NOR-DRUM), based on a systematic literature research (SLR), unpublished data and expert opinion. A SLR was performed in May 2016. In Norway neutralising ADAb are measured with an “in house” assay. For this assay, ADAb levels >50 µg/L are defined as “high”. This cut-off is based on own s-INX and ADAb data (Diakonhjemmet Hospital during 2015-2016) and clinical experience. The proposed strategy has been developed through a series of meetings in the project group consisting of national leading experts in this field (both clinicians experienced with TDM and laboratory physicians) and with additional input from international key experts in the scientific advisory board of the NOR-DRUM study.

Results: The treatment strategy from infusion number 4 onwards is depicted in the Figure. The therapeutic range for serum INX (through levels) is defined as 3-8 µg/ml (Figure, green zone). During the induction phase (infusion 1-3) the recommendation is to keep the level >20 µg/ml at infusion 2 and >15 µg/ml at infusion 3. A guideline for action according to levels outside the therapeutic range is given in the Figure. If the patients develop high levels of ADAb the recommendation is to switch therapy.

Conclusion: An individualised treatment strategy based on TDM has the potential to optimise therapy with infliximab and other biological drugs by: 1) prevention of treatment failure by identification of patients with drug levels below the therapeutic range, 2) reduction of overtreatment, which predispose to side effects and increase costs, and 3) early identification of ADAb development, with the possibility to detect treatment failures prior to a clinical flare and to prevent hypersensitivity reactions. The real life efficacy of this strategy is being investigated in an ongoing randomised clinical trial, NOR-DRUM (NCT03074656).

Disclosure: S. W. Syversen, None; G. L. Goll, AbbVie, Boeringer Ingelheim, Eli Lilly, Novartis, Pfizer, Orion Pharma, Roche, Sandoz, 5; K. K. Jørgensen, Tillots, Celltrion, Intercept, Sandoz, 5; J. Gehin, Roche, 5; C. Mork, None; T. Kvien, AbbVie, Biogen, BMS, Boehringer Ingelheim, Celgene, Celltrion, Eli Lilly, Epirus, Hospira, Merck-Serono, MSD, Mundipharma, Novartis, Oktal, Orion Pharma, Hospira/Pfizer, Roche, Sandoz and UCB, 5, 8, AbbVie, BMS, MSD, Pfizer, Roche, UCB, 2; J. Jahnsen, Orion Pharma, 5, Celltrion, 5, Janssen, 5, Pfizer, Inc., 5, MSD, 5, AbbVie Inc., 5, Takeda, 5, Napp Pharma, 5, Roche, 5, Boeringer Ingelheim, 5, Astro Pharma, 5, Mundi Pharma, 5, Sandoz, 5; N. Bolstad, None; E. A. Haavardsholm, Pfizer, Eli Lilly, Janssen-Cilag, Roche, Celgene, Pfizer, UCB, Roche, AbbVie, MSD, Eli Lilly, 5, Pfizer, UCB, Roche, MSD, AbbVie, 2.

Abstract Number: 603

Rheumatologists Beliefs in the Effectiveness of Other Methotrexate-Based Treatment Approaches May Explain the Low Use of Triple Therapy: A Bayesian Belief Elicitation

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Triple therapy (MTX, sulphasalazine (SSZ), hydroxychloroquine (HCQ)) has evidence to support its use from randomized trials (RCTs) but is not commonly used. The objective of this study was to quantify rheumatologists' beliefs about the effectiveness of common initial MTX-based treatment approaches for early rheumatoid arthritis (RA).

Methods: Rheumatologists completed a Bayesian belief elicitation exercise using a validated approach. In 1-on-1 interviews, each rheumatologist was asked to consider the probability that a typical patient with moderate-severe early RA would have an ACR50 response within 6 months, with each of 4 treatments: oral MTX, subcutaneous (sc) MTX, MTX + HCQ, or triple therapy. Rheumatologists were asked to think how they would typically use these treatments in practice, including their preferred dosing and use of any additional treatments (steroids, NSAIDs). In the belief elicitation exercise, participants were given 20 chips, each representing 5% of their total weight of belief. They were asked to distribute the 20 chips across a grid of possible values of the probability of an ACR50 response, placing more chips on values they believed more likely. The parametric distributions best fitting the chip counts were used to calculate pairwise relative risks for each participant. These distributions were averaged for the overall group and separately for subgroups that had optimistic or pessimistic beliefs regarding the relative effect of triple therapy to oral MTX (top and bottom quartiles).

Table 1: Pairwise treatment effects of the elicited distributions

Intervention	Comparator, relative risk, median (95% credible interval)			
	Oral MTX	Subcutaneous MTX	Dual therapy (MTX + HCQ)	Triple therapy
<i>Overall group</i>				
Oral MTX	1	—	—	—
Subcutaneous MTX	1.38 (0.82, 5.89)	1	—	—
Dual therapy (MTX + HCQ)	1.61 (0.87, 6.21)	1.16 (0.68, 3.7)	1	—
Triple therapy (MTX + HCQ + SSZ)	1.87 (0.74, 6.54)	1.29 (0.45, 3.74)	1.11 (0.34, 1.79)	1
<i>Triple therapy optimistic subgroup</i>				
Oral MTX	1	—	—	—
Subcutaneous MTX	1.52 (0.94, 6.22)	1	—	—
Dual therapy (MTX + HCQ)	1.90 (1.19, 6.33)	1.24 (0.72, 3.8)	1	—
Triple therapy (MTX + HCQ + SSZ)	2.35 (1.47, 6.84)	1.45 (0.96, 3.87)	1.14 (0.85, 1.87)	1
<i>Triple therapy pessimistic subgroup</i>				
Oral MTX	1	—	—	—
Subcutaneous MTX	1.20 (0.66, 2.05)	1	—	—
Dual therapy (MTX + HCQ)	1.25 (0.71, 2.67)	1.08 (0.60, 1.54)	1	—
Triple therapy (MTX + HCQ + SSZ)	1.26 (0.34, 2.05)	1.09 (0.18, 1.65)	1.05 (0.13, 1.57)	1

Results: The 38 rheumatologists who completed the belief elicitation exercise were from a variety of practice types (50% academic, 26% community, 24% both). The practice duration ranged from 1-42 years and 58% were female. The overall pooled RR for was highest for triple therapy vs. MTX (Table 1): relative risk (RR), median (95% credible interval): 1.87 (0.74-6.54). Triple therapy, however, was similar in perceived effectiveness to MTX + HCQ [RR 1.11 (0.34-1.79)]. For the optimistic subgroup, both triple therapy and MTX + HCQ were perceived as statistically superior to oral MTX [RR for triple therapy: 2.35 (1.47-6.84); RR for MTX+HCQ: 1.90 (1.19-6.33)], and similar to each other [RR triple therapy vs MTX+HCQ: 1.14 (0.85-1.87)]. Subcutaneous MTX was perceived as more effective than oral MTX, although the credible interval was wide. The pessimistic subgroup perceived all treatments to be similar.

Conclusion: There is variation in rheumatologists' beliefs regarding MTX-based DMARD treatments. Many consider triple therapy to be effective, but similar to other treatments, particularly MTX + HCQ, for which little RCT evidence exists. This may explain the low use in practice, and supports a randomized trial evaluating these treatments.

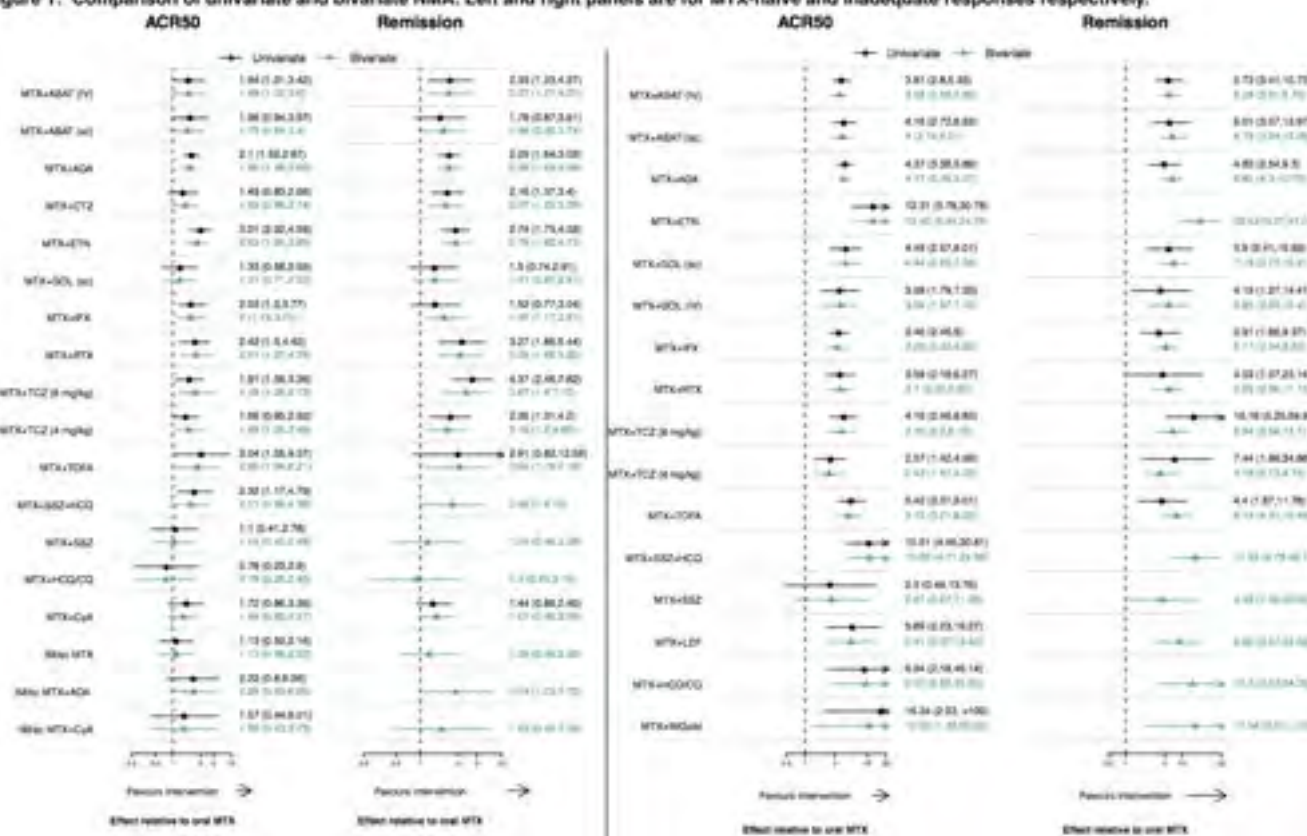
Disclosure: G. Pokharel, None; R. Deardon, None; S. Johnson, Roche, Bayer, Boehringer, BMS, NIH, Merck, 9; G. A. Tomlinson, None; G. Hazlewood, None.

Abstract Number: 604

Combining Observational and Randomized Controlled Trial Data Evidence to Jointly Estimate Remission and Response for Biologic and Non-Biologic Therapies in Rheumatoid Arthritis: A Bivariate Network Meta-Analysis

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Figure 1: Comparison of univariate and bivariate NMA. Left and right panels are for MTX-naïve and inadequate responses respectively.



SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Remission is the goal of rheumatoid arthritis (RA) treatment, but ACR responses are more commonly measured in clinical trials. As such, data on remission are lacking for some treatments, or may be imprecise. The objective of this study was to jointly estimate remission and ACR50 responses for methotrexate (MTX)-based treatment options in early RA.

Methods: We conducted a Bayesian bivariate network meta-analysis (NMA) to compare methotrexate monotherapy and methotrexate-based DMARD combinations for RA. The correlation between the outcomes was derived from an observational study (CATCH cohort), whereas the treatment outcomes were derived from randomized trials that formed the connected network of evidence. The analyses were conducted separately for MTX-naïve and MTX-inadequate response populations in a Bayesian framework with uninformative priors. Comparisons were made to a univariate NMA that estimated each outcome separately.

Results: From the incident RA cohort study, the correlation between ACR50 response and DAS28 remission at 6 months was moderate (Pearson correlation coefficient 0.58) for the 900 patients in the CATCH cohort who had moderate-high disease activity at baseline. For MTX-naïve patients, the NMA included 74 trials in total; 39 measured both outcomes, whereas 64 and 49 measured only ACR50 response or remission respectively. Two treatments that were not statistically superior to methotrexate alone for remission in the univariate NMA, were in the bivariate model [Figure 1: bivariate odds ratio (OR) (95% credible interval (CrI)): MTX +infliximab 2.0 (1.2, 3.7), MTX + tofacitinib 2.7 (1.0, 6.2)]. Six treatments had no data for remission in the univariate model, but could be estimated in the bivariate approach. Of these, only triple therapy (MTX + sulphasalazine +hydroxychloroquine) was superior to MTX alone for remission (OR (95%CrI): 2.5(1.0, 6.1)). In the MTX-IR analysis, all 16 treatments were superior to MTX alone for both ACR50 response and remission in both the univariate and bivariate models, but the CrI were usually more precise in the bivariate approach and remission could be estimated for several treatments not possible in the univariate model, including triple therapy (OR (95%CrI): 17.5 (6.8,46.1)).

Conclusion: By borrowing the strength across treatments and outcomes, a bivariate NMA allowed the estimation of both ACR50 response and remission for all treatment comparisons. In particular, our results add data on remission for several

MTX-based DMARD combinations (including triple therapy and biologic combinations) not demonstrated in the univariate NMA model.

Disclosure: G. Pokharel, None; R. Deardon, None; C. Barnabe, None; V. P. Bykerk, Amgen Inc., 5, Pfizer, Inc., 5, UCB, Inc., 5, Bristol-Myers Squibb, 5, Sanofi Genzyme, 5, Gilead, 5; S. J. Bartlett, UCB, Inc., 5, Lilly, 5, Pfizer, Inc., 5, Novartis, 5; L. Bessette, Amgen Inc., 2, 5, 8, Bristol-Myers Squibb, 2, 5, 8, Janssen, 2, 5, 8, Roche, 2, 5, 8, UCB, Inc., 2, 5, 8, AbbVie Inc., 2, 5, 8, Pfizer, Inc., 2, 5, 8, Merck & Co., 2, 5, 8, Celgene Corporation, 2, 5, 8, Sanofi, 2, 5, 8, Eli Lilly and Co., 2, 5, 8, Novartis, 2, 5, 8; G. Boire, Merck & Co., 8, 9, BMS, 8, 9, Pfizer, Inc., 8, 9, Amgen Inc., 9, AbbVie Inc., 9, Novartis, 9, Eli Lilly and Co., 9, Janssen, 9; C. Hitchon, Pfizer, Inc., 2; E. C. Keystone, Amgen Inc., 2, 5, 8, Bristol-Myers Squibb, 2, F. Hoffmann-La Roche Inc, 2, Janssen, 2, Lilly Pharmaceuticals, 2, Pfizer Pharmaceuticals, 2, Sanofi-Aventis, 2, AstraZeneca, 5, Biotest, 5, Bristol-Myers Squibb, 5, Crescendo Bioscience, 5, F. Hoffmann-La Roche Inc, 5, Genentech Inc, 5, Janssen Inc, 5, Lilly Pharmaceuticals, 5, Merck & Co., 5, 8, Pfizer Pharmaceuticals, 5, UCB, Inc., 5, Bristol-Myers Squibb, 8, F. Hoffmann-La Roche Inc, 8, Janssen Inc, 8, Pfizer Pharmaceuticals, 8, Sanofi Genzyme, 8, UCB, Inc., 8; J. E. Pope, Amgen Inc., 5, 9, Pfizer, Inc., 5, 9, UCB, Inc., 5, 9, AbbVie Inc., 5, Bristol-Myers Squibb, 5, 9, Actelion, 5, Eli Lilly and Co., 5, Merck & Co., 5, 9, Bayer, 5, 9, Roche, 5, 9, Novartis, 5, Sanofi, 5, Celtrion, 5, Seagen, 9, Genzyme, 5; D. Tin, None; C. Thorne, Amgen Inc., 2, 5, 9, Pfizer, Inc., 2, 5, 9, UCB, Inc., 9, AbbVie Inc., 2, 5, 9, Medexus/Medac, 2, 5, 8, Eli Lilly and Co., 9, Merck & Co., 9, Hospira, 5, 9, Janssen, 9, Sanofi Genzyme, 5, 9, Celgene Corporation, 9, CaREBiodam, 9, Centocor, 5, Novartis, 9; G. Hazlewood, None.

Abstract Number: 605

Clinical Outcomes of Golimumab As Second Line TNF Inhibitor Treatment in Patients with Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA) or Ankylosing Spondylitis (AS) – Subanalysis of a Non-Interventional Study in Germany

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Golimumab (GLM) has demonstrated efficacy and safety in patients (pts.) with active RA after treatment with at least one TNFi in a RCT. However, data on effectiveness and patient-reported outcomes (PROs) under daily clinical practice conditions are required.

The aim is to assess the effectiveness of GLM as second line bDMARD therapy in patients with established RA, PsA or AS who had received TNFi pretreatment.

Methods: Subanalysis of the non-interv., prospective, 24-month (24 mo) study GO-NICE in pts. with established RA, PsA or AS starting with GLM 50mg SC once monthly as second line TNFi after one previous TNFi in a real life setting in Germany (158 sites). Disease activity was assessed with DAS28, PsARC and BASDAI. PROs included QoL (EQ-5D-3L), functionality (FFbH), and fatigue (FACIT-F).

Results: 358 pts. were eligible. They had previously received ADA (177), CZP (3), ETA (119), or IFX (59). 147 pts. (41.1%) completed the study until month 24.

RA pts. (n=98): Mean age 55.6 yrs., 73 (74.5%) patients were female, 67 (68.4%) were rheumatoid factor (RF) positive, and 71 (74.0%) had anti ccp-antibodies at BL. DAS28 score at BL dropped significantly from 5.0 to 4.2 after 3 months (m3) to 2.8 points (m24) (p<0.0001 vs. BL), (in bDMARD-naïve patients: 5.0, 3.6 to 2.9). After 3m of treatment, 47.4% of pts. had LDA or were in remission (DAS28 ≤3.2), after 24 mo 62.5%.

PsA pts. (n=134): Mean age 50.8 yrs., 68 (50.7%) were males, 120 pts. (89.6%) had extra-articular manifestations at BL. The proportion of pts. achieving a response (PsARC) was 51.3% at m3, and 52.1% at m24, respectively, (bDMARD-naïve: 64.0%, and 77.7%).

AS-pts. (n=126): Mean age 45.2 yrs., 79 (62.7%) were males, 101 (80.2%) were HLAB27+, 44 pts. (35.5%) had extra articular manifestations at BL. The BASDAI dropped significantly from 4.9 at BL to 3.1 (m3) to 2.9 within 24 months (p<0.0001 vs. BL), (bDMARD-naïve: 5.0, 2.5 to 2.0).

An improvement of quality of life (QoL) was seen after 6 months and was maintained over 24 months: The pts.' health status (EQ VAS) improved significantly ($p<0.001$ vs. BL) from 48.4 to 64.4 (RA), from 47.8 to 62.9 (PsA) and from 45.5 to 60.8 (AS). The functional ability (FFbH) improved significantly ($p<0.05$ vs. BL) from 63.4 to 73.5 points (RA), and from 67.4 to 76.2 (AS), changes at m24 vs. BL in pts. with PsA were n.s. The mean fatigue score (FACIT-F) increased significantly ($p<0.003$ vs. BL) from 30.8 to 38.2 points (RA), and from 28.8 to 34.4 points (AS), changes at m24 vs. BL in pts. with PsA were n.s. No new safety signals were detected.

Difference BL to m24 [STD] p	RA: DAS28	AS: BASDAI
(2 nd line, after one TNFi)	-2.23 \pm 0.30 [-2.82, -1.64] <.0001	-2.02 \pm 0.32 [-2.65, -1.39] <.0001
(bDMARD-naïve)	-2.10 \pm 0.15 [-2.39, -1.81] <.0001	-2.89 \pm 0.20 [-3.29, -2.49] <.0001

Conclusion: GLM 50 mg SC once monthly as second-line TNFi in pts. with RA, PsA or AS who had previously received pretreatment with another TNFi was also effective and showed remarkable improvements in clinical parameters, patient-reported quality of life, functionality, and fatigue parameters within 3 (and 6) months. These effects were maintained over 24 mo. Overall results were consistent with those in patient who received GLM as first TNFi.

Disclosure: K. Krüger, MSD Sharp Dohme GmbH, 9,AbbVie Inc., 9,BMS, 9,Celgene Corporation, 9,Janssen, 9,Lilly, 9, Pfizer, Inc., 9,Sanofi-Aventis, 9,UCB, Inc., 9; G. R. Burmester, AbbVie, BMS, Lilly, MSD, Pfizer, Roche, 5; S. Wassenberg, AbbVie, Chugai, Janssen Biologics, MSD, Novartis, Pfizer, Roche, and UCB, 5; A. Thiele, MSD Sharp Dohme GmbH, 9, Biogen, 9,Celgene Corporation, 9,Chugai, 9,Hexal, 9,Janssen, 9,Lilly, 9,Novartis, 9,Pfizer, Inc., 9,UCB, Inc., 9; M. H. Thomas, MSD Sharp & Dohme GmbH Germany, 3.

Abstract Number: 606

Similiar Efficacy of Tofacitinib on Disease Activity in Rheumatoid Arthritis Patients with and without Previous Biologicals; Results from the Turkbio Registry

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Tofacitinib, a JAK3 inhibitor has been used to treat patients with rheumatoid arthritis (RA) in Turkey since 2015. The aim of this study was to investigate the drug survival, its efficacy and safety in patients with RA based on the database from the Turkish TURKBIO registry.

Methods: A total of 180 patients (152 female, median age: 54.5 years) were treated with tofacitinib for RA. Drug survival was assessed. In 118 patients with available data, treatment response was evaluated using the number of sensitive and swollen joints, VAS values, DAS28, HAQ scores and CRP levels at weeks 12, 24, 48 and 60.

Results: At baseline, RA patients had a median (Q1-Q3) disease duration of 14 (8-19) years. 75 patients (42%) had used ≥ 1 biologics previously. The other demographic and clinical features of the patients were shown in Table 1. Median (Q1-Q3) follow-up period was 137 weeks. After 48 and 137 weeks, 75% and 48% of the patients respectively, maintained tofacitinib (Figure 1). The most common reason for drug discontinuation was ineffectiveness of treatment (63%), followed by adverse events (23%). After 12 weeks, all disease activity parameters were reduced significantly compared to the baseline and most of them continued to be reduced until week 60. No difference was observed in disease activity

parameters between the groups with and without previous ≥ 1 biologics at weeks 0, 12 and 24 (Table 2). Remission rate was (43%) at week 60 (observed data), (Table 2).

A total of 9 adverse events (4 infection, 3 allergic reaction, 2 rash) were observed during the follow-up period.

Conclusion: The results of this long-term observational study suggest that tofacitinib might be an effective and safe treatment option in RA patients. Treatment with this drug may provide good response rates in RA patients refractory previous biologics.

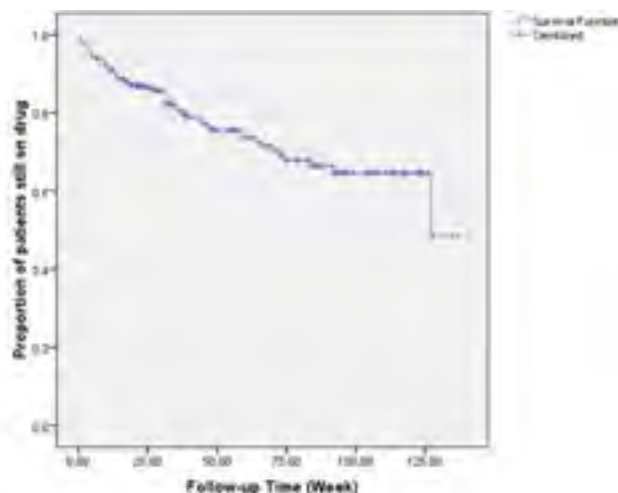


Figure 1 . Drug survival of tofacitinib 180 patients

Table 1. Demographic and clinical features of patients with RA on tofacitinib treatment at baseline

Demographic and clinical features features		RA Patients (n=180)
Age (yrs); Median (Q1-Q3)		54.5 (44 - 61)
Female sex, n (%)		153 (85%)
Disease duration (yrs); Median (Q1-Q3)		14 (8-19)
Rheumatoid factor positivity, n (%)		77 (70%)
CCP positivity, n (%)		39 (61%)
Number of previous DMARDs, n (%)		
	Methotrexate	83 (46)
	Leflunomide	87 (48)
	Sulfasalazine	35 (19)
	Hydroxychloroquine	51 (28)
	Azathioprine	3 (2)
Number of previous biologics, n (%)		
	Etanercept	31 (17)
	Adalimumab	34 (19)
	Rituximab	18 (10)
	Abatacept	29 (16)
	Golimumab	11 (6)
	Infliximab	9 (5)
	Certolizumab	10 (6)
≥ 1 Previous TNFi, n (%)		57 (32)
≥ 1 Biologic drug of any kind, n (%)		75 (42)
Mtx co-medication, n (%)		88 (49)
Glucocorticoid co-medication, n (%)		95 (53)

Table 2. Disease activity parameters at baseline and weeks 12, 24, 36, 48 and 60 (observed data)

		Week 0 [Baseline]	Week 12	Week 24	Week 36	Week 48	Week 60	*p	**p	***p
Patients with response data, (n)		118	39	41	31	32	28			
Disease activity level, n (%)	Remission	7 (6)	17 (43)	10 (24)	16 (52)	12 (43)	17 (61)			
	Low	8 (7)	8 (21)	8 (20)	5 (16)	4 (14)	0 (0)			
	Moderate	64 (54)	14 (36)	12 (29)	7 (23)	10 (38)	8 (29)			
	High	29 (24)	1 (3)	1 (3)	1 (4)	2 (7)	3 (11)			
DAS28, Median (Q1-Q3)		4.4 (3.7-5.1)	2.8 (2-3.5)	3 (2.4-3.6)	2.3 (1.9-3.3)	3.1 (1.9-4.2)	3.1 (1.9-4.1)	<0.001	<0.001	<0.001
Swollen joint count (0-28): Median (Q1-Q3)		2 (0-4.3)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0.8)	0 (0-0)	<0.001	<0.001	<0.001
Tender joint count (0-28): Median (Q1-Q3)		4 (2-10)	0 (0-1.3)	0 (0-2)	0 (0-0)	0 (0-2)	0 (0-0)	<0.001	<0.001	<0.001
CRP (mg/L): Median (Q1-Q3)		11 (4.7-23)	4.8 (3-12.8)	4.3 (3-10.3)	4 (3-9)	6 (3-12)	9 (3-17.5)	0.005	0.015	0.110
Patient global score (0-100): Median (Q1-Q3)		62.5 (40.3-80)	44 (12.5-60)	30 (20-50)	27 (12.5-31.5)	30.5 (15.8-69.5)	27.5 (13.8-46.3)	<0.001	0.001	<0.001
HAQ score: Median (Q1-Q3)		1 (0.8-1.5)	0.5 (0-1.3)	0.6 (0.1-1.3)	0.5 (0.1-0.8)	0.6 (0.2-1.2)	0.6 (0-1)	0.003	0.008	0.001

*p value for week 0 vs 12; **p value for week 0 vs 48; ***p value for week 0 vs 60.

Disclosure: B. Zengin, None; N. Inanc, None; S. Akar, None; G. Can, None; E. Dalkilic, None; A. Tufan, None; S. Senel, None; S. S. Koca, None; H. Yarkan, None; Y. Pehlivan, None; Z. Erturk, None; B. Goker, None; H. Direskeneli, None; M. Birlik, None; N. Akkoc, None; F. Onen, None.

Abstract Number: 607

Clinical and Functional Response to Tofacitinib and Adalimumab in Patients with Rheumatoid Arthritis: Probability Plot Analysis of Results from the ORAL Strategy Trial

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

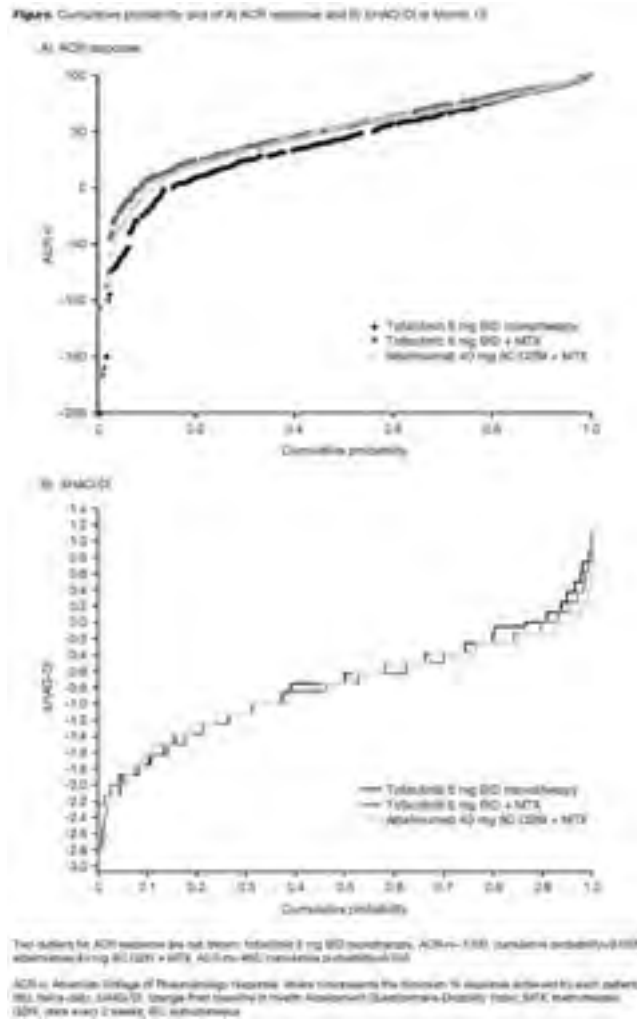
Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. ORAL Strategy (NCT02187055), a 12-month, global, Phase 3b/4 study, demonstrated that in patients with RA and an inadequate response to MTX, tofacitinib + MTX was non-inferior to adalimumab + MTX, while tofacitinib monotherapy was not non-inferior to either combination based on American College of Rheumatology (ACR) 50 response rates at Month 6.¹ This post hoc analysis aimed to assess the clinical and functional efficacy across treatments in the ORAL Strategy trial using cumulative probability plots.

Methods: Efficacy was evaluated between patients who received tofacitinib 5 mg twice daily (BID) as monotherapy (N=384), tofacitinib 5 mg BID + MTX (N=376), and adalimumab 40 mg subcutaneously once every 2 weeks + MTX (N=386) based on ACR responses and changes from baseline in Health Assessment Questionnaire-Disability Index (ΔHAQ-DI) at Month 12. Cumulative probability plots for ACR-n (where ACR is the % improvement from baseline in ACR components, and n represents the minimum % achieved by each patient) and ΔHAQ-DI are presented. The area under the curve (AUC) was calculated for ACR-n up to Month 12 (in months), and an analysis of covariance model was used to assess treatment effects in terms of the AUC of ACR-n at Month 12; there was no adjustment for multiplicity for this post hoc analysis.



Results: The cumulative probability plots of ACR responses at Month 12 indicated that the proportion of patients who achieved responses of ACR20, ACR50, and ACR70 was similar for tofacitinib + MTX and adalimumab + MTX, but was numerically smaller for tofacitinib monotherapy (Figure A). Responses of approximately \geq ACR80 were achieved by a similar proportion of patients in each treatment group. Least squares mean (standard error) AUC of ACR-n up to Month 12 (in months) was similar for tofacitinib + MTX (437 [35]) and adalimumab + MTX (402 [35]), but was smaller for tofacitinib monotherapy (319 [35]; $p < 0.05$; data not shown). The cumulative probability plots of Δ HAQ-DI suggested that, in general, reductions from baseline in HAQ-DI were similar across treatment groups (Figure B), although a slightly higher proportion of patients who received tofacitinib monotherapy reported an increase in HAQ-DI vs other treatments.

Conclusion: These data support the primary ORAL Strategy findings,¹ indicating that in patients with RA, clinical efficacy, based on ACR response, was generally similar for tofacitinib + MTX and adalimumab + MTX, while a smaller proportion of patients who received tofacitinib monotherapy achieved ACR response in general, and particularly for $<$ ACR80. Functional efficacy, based on Δ HAQ-DI, was generally similar across all treatment groups. Cumulative probability analyses for CDAI will be further evaluated.

1. Fleischmann et al. Lancet 2017; 390:457–68.

Disclosure: T. Takeuchi, AbbVie, Asahi-kasei, Astellas, AYUMI, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe Nipponkayaku, Novartis, Pfizer Japan Inc, Takeda, 2, AbbVie, Astellas, AstraZeneca, Chugai, Eli Lilly Japan, GSK, Janssen, Mitsubishi-Tanabe, Nipponkayaku, Novartis, Taiho, Taisho Toyama, UCB Japan, 5, AbbVie, Astellas, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Novartis, Pfizer Japan Inc, Sanofi, Takeda, Teijin, 8; J. S. Smolen, AbbVie, AstraZeneca, Eli Lilly, Janssen, MSD, Pfizer Inc, Roche, 2, AbbVie, Amgen, AstraZeneca, Astro, Bristol-Myers Squibb, Celgene, Celltrion, Chugai, Eli Lilly, Gilead, GSK, ILTOO, Janssen, Medimmune, MSD, Novartis, Pfizer Inc, Roche, Samsung, Sanofi, UCB, 5; R. Fleischmann, Pfizer Inc, 2, Pfizer Inc, 5, Pfizer Inc, 8; N. Iikuni, Pfizer Inc, 1, Pfizer Inc, 3; H. Fan, Pfizer Inc, 1, Pfizer Inc, 3; K. Soma, Pfizer Inc, 1, Pfizer Inc, 3; E. Akylbekova, IQVIA, a paid contractor to Pfizer, 3; T. Hirose, Pfizer Inc, 1, Pfizer Inc, 3.

Abstract Number: 608

Half Dose Reduction of Methotrexate in Patient with RA Who Achieved Clinical Remission

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Recently, it is recommended that tapering csDMARDs could be considered if a patient is in persistent remission. However, the methods of tapering csDMARDs including MTX without RA flare is not established. In this study, we determine whether half dose reduction of MTX in RA patient who achieved clinical remission is possible without flare by using clinical disease activity and MRI images of hand.

Methods: Out patient of department of Rheumatology on our hospital were included in this study. Inclusion criteria was the following: diagnosis of RA was based on 2010 ACR/EULAR classification criteria; achieving clinical remission defined by DAS28-CRP over 4 weeks; been treated with methotrexate and was reduced by half according to the patient wishes; MRI images of hand was available at reduction of MTX. The exclusion criteria were as follows: been treated leflunomide or tacrolimus, tsDMARDs and bDMARDs; oral prednisolone more than 5mg/day. In this study, disease flare was defined as DAS28-CRP of ≥ 2.3 at two sequential visits, dose increase of MTX and add-on other DMARDs. MRIs of the patient's dominant wrist and 2nd–5th metacarpophalangeal (MCP) joints were obtained using 1.5 T whole-body MRI unit (Achieva 1.5T, Philips Healthcare, Best, The Netherlands) with contrast enhancement. The MR image sets were assessed for bone erosions, synovitis and bone marrow edema according to the original OMERACT RAMRIS.

Results: Fifteen patients were enrolled in this study (10 female). The mean (\pm SD) age, disease duration, MTX dose before reduced and DAS28-CRP at baseline was 66.6 ± 9.8 y, 6.0 ± 3.6 y, 8.8 ± 3.4 mg/w and 1.32 ± 0.26 . Thirteen patients were positive for anti-CCP antibody and RF. Subclinical MRI inflammation was detected in all patients. The median (range) synovitis, bone edema and bone erosion score were 2(0-7), 0(0-4) and 7(1-22). Two patients experienced disease flare at week 16 and these patients had significantly higher MRI synovitis score (4.5 vs. 1.9 $p < 0.05$). Higher score of DAS28-CRP at baseline independently predicted higher MRI synovitis score ($\beta = 4.454$, 95% CI 0.930-7.988, $p < 0.05$). Analysis of the ROC curve identified the most sensitive and specific cut-off value for MRI synovitis score to be 5 (AUC = 0.923, 95% CI 0.077-1.000, $p < 0.05$).

Conclusion: Baseline DAS28-CRP could predict baseline MRI synovitis score. However, even if in clinical remission, it is reported subclinical remission would remain and depending on degree of it, radiographic progression can progress. Hence, not only clinical evaluation but also MRI evaluation is important before reduction of DMARDs. We conclude that half dose reduction of MTX for the RA patient who achieved clinical remission and had low grade MRI synovitis score might be a beneficial option of tapering MTX.

Disclosure: T. Suzuki, None; T. Ando, None; S. Shinagawa, None; M. Mizushima, None; T. Shibata, None; K. Kawahata, None.

Abstract Number: 609

Multi-Biologic Usage in Rheumatoid Arthritis Is Not Infrequent in the Routine Practice

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Biologic DMARDs (bDMARDs) have proven efficacy in rheumatoid arthritis (RA) however, some patients inadequately response to multiple bDMARDs. This study aims to determine the risk factors for ≥ 2 switches between bDMARDs in RA patients.

Methods: Hacettepe University Rheumatology Biologic Registry (HUR-BIO) is a monocentric registry of bDMARDs including 1609 RA patients by May 2018. The recorded bDMARDs in HUR-BIO were anti-TNF treatments (adalimumab, etanercept, infliximab, golimumab, certalizumab), rituximab, abatacept, tocilizumab, and tofacitinib. Demographic, clinical data and baseline disease activity (DAS-28, swollen and tender joint counts (28 joints)), and functional status were assessed. Six hundred and ninety-four patients with at least 3 control visits were enrolled to analyze. Flow-chart of switching among bDMARDs was shown in Figure. Baseline demographic and clinical risk factors for ≥ 2 switches of bDMARDs were analyzed by using univariate and multivariate analyses.

Results: One hundred and fifty-eight (22.7%) patients had ≥ 2 switches between bDMARDs for any reason. Among this group, 40.5%, 39.2%, 15.1%, 3.8%, 0.6% of patients were treated with 3,4,5,6 and 7 bDMARDs, respectively. Baseline demographic, clinical and laboratory data of patients were shown in Table 1. In multivariate analysis, longer follow-up duration (OR: 1.21, 95%CI: 1.06-1.37) and rheumatoid factor (RF) negativity (OR: 2.10, 95% CI: 1.13-3.89) was found as independent risk factors for ≥ 2 switches of bDMARDs. The analyses were performed again in a subgroup of patients including patients with ≥ 2 switches due to primary or secondary inefficacy (n=85) and patients without any switches (n=336). Patients with ≥ 2 switches were younger (46.2 (11.3) vs 49.5 (11.9), $p=0.02$), had higher number of swollen joint counts (3.8 (2.5) vs 2.9 (2.5), $p=0.04$), and longer follow-up duration (6.3 (3.9) vs 4.0 (2.6), $p<0.001$). Multivariate analysis failed to demonstrate any risk factor in this subgroup.

Conclusion: High prevalence of more than two switches among bDMARDs in our cohort implicates that there is still an unmet need in the treatment of RA patients. Multi-biologic usage of bDMARDs may be related with RF seronegativity.

Table 1. Baseline features of RA patients according to numbers of bDMARDs switching

	≥ 2 switching (n=158)	< 2 switching (n=536)	p
Female, n (%)	134 (84.8)	422 (78.7)	0.09
Age, years	45.8 (12.2)	49.4 (11.9)	0.001
Disease duration, years	7.6 (7.3)	7.6 (7.4)	0.96
Follow-up duration, years	6.6 (3.8)	4.5 (2.9)	< 0.001
RF +, n (%)	41/155 (60.0)	354/522 (67.8)	0.07
Anti-CCP +, n (%)	239/380 (62.8)	65/108 (60.3)	0.60
BMI, kg/m ²	29.4 (6.8)	29.5 (5.7)	0.92
ESR, mm/hr	38.0 (25.6)	38.0 (25.9)	0.97
CRP, mg/dL	3.4 (4.3)	3.4 (5.3)	0.99
DAS-28	5.1 (1.0)	5.1 (2.6)	0.74
SJC	4 (2.5)	3 (2.4)	0.008
TJC	7.5 (4.4)	6.4 (4.1)	0.07
HAQ-DI	1.09 (0.65)	1.00 (0.62)	0.37

All data were given as mean (standard deviation)



Figure: Flow-chart of switching among bDMARDs

Figure: Flow-chart of switching among bDMARDs

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Abstract Number: 610

4 Years Follow-up of a Cohort of Patients with Rheumatoid Arthritis in Sustained Clinical Remission with Optimization of Biological Therapy

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Once sustained clinical remission is achieved under treatment with biological therapies, the most efficient strategy is optimization. Searching for the lowest effective dose for each patient could minimize the risk of adverse effects related to biologics and improve the cost-effectiveness of RA treatment.

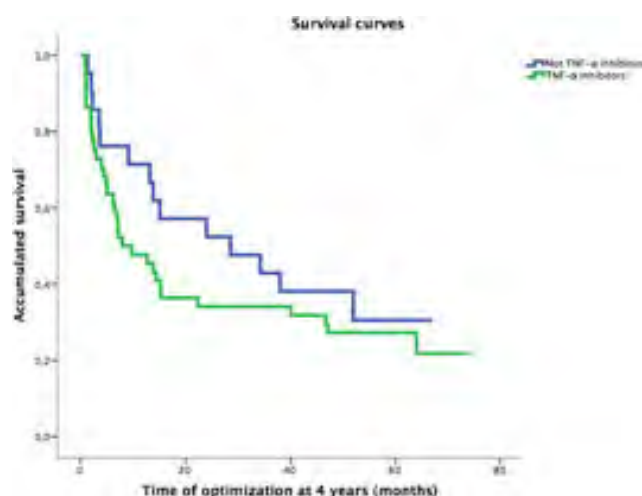
Our objectives are 1) to prove that an optimization strategy in patients with RA and sustained clinical remission under biological treatment maintains the proportion of patients with DAS28^{2,6} after 4 years, 2) to assess the maintenance of the effectiveness of the optimization at 4 years and 3) to analyze the time until relapse.

Methods: Open observational prospective study that included 70 patients with RA (CREATE registry) in clinical remission at least for 6 months, under treatment with tapered dose of biological therapy (TNF- α inhibitors, abatacept and tocilizumab). Treatment effectiveness was assessed with the main variable DAS28^{2,6}.

Statistical analysis included a descriptive study of variables and a confidence interval of 95% (95% CI) was estimated. For bivariate analysis, we used Student t-test for independent samples, repeated measures analysis of variance and mixed analysis of variance, and as a post-hoc contrast, Sidak adjustment. The log-rank test was used to compare the time until relapse according to the biological therapy.

Results: The mean age of the patients was 56,9 (13,7) years, 78,6% were women, 68,8% were RF positive and 66,7% ACPA positive; the mean DAS28 at the beginning of the optimization was 2,24 (0,73).

After 4 years, 27,7% (95%CI:16,82%-38,58%) of patients maintained clinical remission with the optimized dose, with a DAS28 2,15 (0,81). Through the first year, the percentage of relapses was 15,71%, in the second year, 7,35% and 4,61% relapsed during the third year.



	DAS28 at baseline Mean (SD)	DAS28 at 1 year Mean (SD)	DAS28 at 2 years Mean (SD)	DAS28 at 3 years Mean (SD)	DAS28 at 4 years Mean (SD)	P
Global (n=62)	2,24 (0,73)	2,54 (0,83) ^a	2,44 (0,7)	2,43 (1,14)	2,56 (1,14)	NS
No relapse (n=22)	2,05 (0,87)	2,43 (0,73)	2,2 (0,71)	1,7 (1,02)	2,15 (0,81)	NS
Relapse (n=40)	2,34 (0,62)	2,59 (0,88)	2,53 (0,68) ^b	2,72 (1,06) ^c	2,76 (1,22)	NS

Statistically significant differences with: a) DAS28 at baseline (p=0,047); DAS28 at 2 years from the group no relapse (p=0,028); (c) DAS28 at 3 years from the group no relapse (p=0,025)

The median time of optimization strategy until relapse was 13,83 (3,18) months (95%CI:7,6-20,06). No significant differences were found at comparing the survival curves of the optimized patients until relapse for 4years according to the biological therapy (TNF-_α inhibitors vs. no TNF-_α inhibitors) (log-rank test:0,865, p:0,352).

Conclusion: At the end of the study, most of the patients maintained DAS28 levels of low disease activity and half of them reached clinical remission, including those who had suffered a relapse and had turned back to the previous dose of biologic treatment. In view of this outcomes, optimization strategy in real clinical practice is possible and effective in patients with persistently controlled RA, in order to keep the therapeutic goal.

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Abstract Number: 611

Influence of Dose Titration of Concomitant Steroid and Methotrexate during Biologic Therapy in Patients with Rheumatoid Arthritis in Daily Practice Based on the IORRA Cohort

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: After the introduction of Biological Disease-Modifying Anti-Rheumatic-Drugs (bDMARDs) for the treatment of patients with active rheumatoid arthritis (RA), clinical remission has become an achievable and realistic therapeutic goal. In clinical trials, remission rates in patients receiving bDMARDs are assessed under a fixed-dose regimen of steroid and/or methotrexate (MTX). However, in daily practice, the dose of concomitant MTX and/or steroid is often titrated according to the patient's response to therapy; thus, remission rates might be influenced by this titration. To examine usage situation of concomitant MTX and steroid use and remission rate in RA patients receiving bDMARDs in daily practice.

Methods: We have established a large observational cohort of RA patients, IORRA (Institute of Rheumatology, Rheumatoid Arthritis), in our institute since October 2000. Essentially all RA patients who attend our clinic are asked to complete questionnaires every 6 months. Clinical information, including physician's evaluations and laboratory data, is collected biannually (April and October). As a result, more than 5000 RA patients were registered. All RA patients who commenced treatment with bDMARDs from 2012 to 2016 were extracted from the IORRA database. The 28-joint Disease Activity Score (DAS28), remission rate based on the ACR/EULAR remission criteria, and frequencies of use and doses of MTX and steroid before treatment and 2 years after initiation of each bDMARDs were calculated.

Results: Average DAS28 before and 2 years after the initiation of infliximab (IFX: n=39), etanercept (ETN: n=199), adalimumab (ADA: n=101), tocilizumab (TCZ: n=261), abatacept (ABT: n=123), golimumab (GLM: n=128) and certolizumab pegol (CZP: n=87) were 3.5/2.7, 3.4/2.7, 3.5/2.8, 3.8/2.4, 3.8/3.3, 3.7/2.8, and 3.6/2.9, respectively. The DAS28 remission rates were 56.4%, 57.3%, 53.3%, 64.0%, 23.6%, 50.1%, and 46.0%, respectively. The proportion of patients taking MTX decreased among ETN (78.4% to 59.3%) and TCZ (73.2% to 61.3%) users, while that and MTX dose increased among IFX (79.5% [9.0mg/week] to 84.6% [11.1mg/week]) and ADA (78.7% [9.8mg/week] to 85.3% [12.2mg/week]) users. The frequencies of use and average dose of steroid in patients treated with bDMARDs (n=912) before treatment and 2 years after initiation of bDMARDs were 43.1% (3.9 mg/day) and 42.0% (3.7 mg/day), respectively. The proportion of patients taking steroid did not change over time except for ETN user, and 42.0% of bDMARD users were still treated with steroid.

Conclusion: MTX and steroid use and doses in daily practice were well adjusted after the initiation of bDMARDs, with adjustment varied depending on the bDMARD. Despite increasing remission, our study revealed steroids have been used approximately 42.0%.

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Abstract Number: 612

Anti-Drug Antibodies Detected By Competitive ELISA Can Predict Treatment Failure in Patients Taking Adalimumab

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: A reduced clinical response in patients taking TNF-alpha inhibitors is influenced by their immunogenicity and therefore the importance of therapeutic drug monitoring has been increasingly recognized in the recent years. Many different methods used in routine analysis of anti-drug antibodies (ADA) differ in their reported levels and types of the detected antibodies. Bridging ELISA (bELISA), mostly used in routine analysis, cannot differentiate between neutralizing and non-neutralizing ADA and cannot detect IgG4, which is possible with competitive ELISA (cELISA) and Reporter Gene Assay. The latter is costly and labour-intensive, while cELISA is only emerging. It has been clinically observed that many patients with negative bELISA lose response over time despite dose optimisation.

We aimed to test whether cELISA detects anti-adalimumab (anti-ADL) antibodies in patients negative in bELISA and if anti-ADL antibodies, as detected by cELISA, can better predict a subsequent loss of response compared to bELISA.

Methods: Sera of patients with inflammatory bowel or chronic rheumatic diseases treated with ADL, having undetectable ADL levels and negative anti-ADL levels in bELISA, were collected and tested with *in-house* cELISA (sampling time). Only samples from patients who continued with the therapy were included, meaning they had received at least one more application of the drug after sampling time (n=16).

In cELISA, samples were incubated with a fixed amount of added drug and the neutralizing capacity of the samples was determined using a plate with pre-coated TNF-alpha. Kaplan-Meier analysis and Log Rank test were performed in order to make a comparison between the group of samples negative in both assays and the group of samples negative in bELISA, but positive in cELISA, according to clinical status on follow-up (observation time).

Results: The samples negative in bELISA were all subsequently tested by cELISA whereby 5/16 were detected as positive and 11/16 as negative samples. Follow-up of patients revealed an 80% loss of response in patients with negative bELISA and positive cELISA, and a 45% loss of response in patients negative for both ELISAs. The Kaplan-Meier analysis and Log Rank test both showed statistically significant differences between the group of samples negative in both assays and the group of samples negative in bELISA, but positive in cELISA ($p=0.024$). Patients with positive cELISA experienced a shorter time period before treatment failure compared to patients negative in both assays.

Conclusion: Positive anti-ADL antibodies in cELISA can predict treatment failure in patients taking ADL, who had undetectable levels of ADL and negative anti-ADL antibodies, as detected by bELISA. Thus, cELISA shows clear benefit for clinical utility over bELISA alone.

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Abstract Number: 613

Interim Analysis of Baseline Characteristics and Preferences of Administration Route of Rheumatoid Arthritis Patients Who Are Bio-Naïve or Switched between Advanced RA Treatments; A Multicenter, Prospective, Observational Study

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SESSION INFORMATION

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Session Type: ACR Poster Session A

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

Background/Purpose: To describe the baseline characteristics, patient and physician preferences of rheumatoid arthritis patients treated with biologics or targeted therapies in a real world setting.

Methods: This is an interim analysis of a multicenter, prospective, observational study. We have recruited patients who were prescribed advanced RA treatments for the first time (bio-naïve) or needed a switch in their current advanced treatments (bio-experienced). The patients were classified as RA, according to ACR 2010 criteria. The patients will be followed for 12 months and will be evaluated with EQ-5D (EuroQol 5 Dimension), HAQ, DAS28-4(ESR), CQR-19 (Compliance Questionnaire for Rheumatology) and WPAI (Work Productivity and Activity Impairment) every three months. Target recruitment is 590 patients. For this analysis, database was locked by March 2018 with 370 patients.

Results: We have included the data from the baseline visits of 370 moderate to severe RA patients in this analysis. Baseline patient characteristics for demographic findings, disease state and compliance (CQR) are shown in Table 1. Among the bio-naïves, 58% declared that they would prefer using advanced treatments orally after the failure of conventional synthetic DMARDs, while 24% of them preferred SC and 17% IV infusion. Among the bio-experienced

patients 46% (n=39) preferred oral intake, 31% (n=26) SC injection and 23% (n=19) IV infusion. In 54.0% of the cases, the drug administration routes in the physicians' prescriptions were in concordance to the patients' preference, whereas in 38.4% physicians prescribed drugs with different routes of administration. In 7.6% of the cases, patient preference is not known. In binary logistic regression analyses, patient and physician preferences for the route of administration were independent of baseline characteristics (Table 2).

Conclusion: Oral drug intake is the preferred route of administration for patients and physicians in advanced rheumatoid arthritis treatment. Patient and physician preferences for the route of administration were not related to the demographic or clinical variables.

Table 1: Baseline patient characteristics for demographic findings and disease activity scores.

Sample Size (N)	370
Mean Age (SD)	49,6 (11,8)
Female (%)	76%
Mean HAQ Score (SD)	0,92 (0,64)
Mean DAS28-4(ESR) Score (SD)	4,96 (1,19)
Mean CQR Score (SD)	71,1 (12,1)

Table 2: Binary logistic regression analyses of factors effecting patient's and physician's administration route preferences.

INDEPENDENT VARIABLES	P	
	Patient's preference	Physician's preference
Sample Size (N)	351	340
Gender	0.165	0.178
Age	0.337	0.745
Education level	0.998	0.490
Bio-experienced	0.087	0.583
Disease duration	0.427	0.140
DAS28-4 (ESH)	0.138	0.956
HAQ	0.589	0.107
EQ5D VAS	0.211	0.541
Restricted daily activities	0.226	0.122
CQR - surveyed prior to prescription	0.370	0.193

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Abstract Number: 614

Disease Activity One Year after Addition of Bucillamine or Sulfasaladine to Methotrexate in Japanese Patients with Rheumatoid Arthritis : Propensity Score Analysis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Bucillamine (BUC) is a small-molecule disease-modifying antirheumatic drug (DMARD) developed in Japan. The efficacy of combination therapy with BUC and methotrexate (MTX) has been demonstrated in comparison with that of placebo in rheumatoid arthritis (RA). However, its efficacy in comparison with other DMARDs such as sulfasalazine (SSZ) has not been elucidated.

Purpose: To assess the disease activity at 1-year after addition of BUC in comparison with SSZ to MTX in typical clinical practice.

Methods: We analyzed data from 16,988 cases of clinically diagnosed RA registered in a large database (NinJa: National Database of Rheumatic Diseases by iR-net inJapan) from April 2012 to March 2017 (1). The dataset was clinical information at a certain point within each year, and the point was any point selected by a registered physician. In this

Table1: Patients' Characteristics in Full and Propensity-Score Matched Cohorts

according to Initiation of bucillamine or sulfasalazine

Characteristics	Full cohort			Propensity Score-Matched Cohort		
	BUC(n=134)	SSZ(n=169)	P-value	BUC(n=117)	SSZ(n=117)	P-value
Sex:male (%)	25(18.7)	39(23.1)	0.008	21(17.9)	22(18.8)	0.702
Age (mean [SD])	62.84(11.03)	59.57(12.02)	0.272	61.64(10.82)	61.78(11.79)	0.912
Disease duration at Initiation (SD) (y)	10.6(10.19)	9.59(9.72)	0.223	9.83(9.87)	9.97(9.73)	0.919
ESCR (mean [SD])	2.49(3.41)	2.12(2.96)	0.113	2.20(2.95)	2.48(2.95)	0.096
TJC28 (mean [SD])	2.2(3.08)	2.69(4.27)	0.129	2.38(3.24)	2.33(3.50)	0.916
PGA0-10 (mean [SD])	2.62(2.25)	2.90(2.35)	0.030	2.62(2.25)	2.88(2.31)	0.002
HASQ (mean [SD])	0.34(0.49)	0.26(0.41)	0.36	0.30(0.45)	0.33(0.44)	0.613
MTX mg/wk (mean [SD])	8.76(3.05)	8.98(3.14)	0.668	8.70(3.08)	8.95(3.19)	0.682
PSL mg/d (mean [SD])	1.99(2.80)	1.62(2.66)	0.12	1.73(2.37)	1.65(2.70)	0.38
CRP mg/dL (mean [SD])	0.61(0.86)	0.79(1.42)	0.158	0.59(0.85)	0.65(0.96)	0.659
RF positive (patients, %)	58 (43.28)	62 (48.52)	※	51 (43.59)	57 (48.72)	※
ACPA positive (patients, %)	35 (26.11)	50 (29.59)	※	31 (26.49)	30 (25.64)	※

CRP: C-reactive protein; BUC: bucillamine; HASQ: The modified Health assessment questionnaire

MTX: methotrexate; PGA: patients' global assessment; PSL: prednisolone

SD: standard deviation; ESCR: erosive joint count; SSZ: sulfasalazine; TJC: tender joint count

study, we compared two groups of patients who received BUC or SSZ in addition to MTX in the earlier year. We excluded patients who started receiving biological DMARDs, and BUC or SSZ the year prior to the study period, and those whose regimens were changed to other DMARDs such as tacrolimus. Baseline characteristics were compared using the *t* test, Wilcoxon test, or chi-square test. Chi-square analysis was conducted for outcomes. The predicted probability of BUC treatment was calculated by fitting a logistic regression model by using all clinically relevant variables as presented in Table 1. Moreover, to reduce the effect of treatment-selection bias and potential confounding in this observational study, we performed rigorous adjustment for significant differences in the baseline characteristics of the patients with propensity-score matching by using the following algorithm: 1:1 optimal match with a 0.2 caliper and no replacement. We used the standardized difference to measure covariate balance, whereby a standardized mean difference of >0.1 represents meaningful imbalance. The outcome was remission rate with disease activity score in 28 joints based on C-reactive protein level (DAS28-CRP) in the year after initiation of BUC or SSZ therapy.

Results: The groups that received BUC and SSZ in addition to MTX included 134 and 169 patients, respectively. Table 1 shows the results of the pre- and post-propensity score matching of the patients characteristics. In each group, 117 patients were compared after score matching. The remission rates of DAS28-CRP in the following year were 48.7% (57/117 patients) and 51.3% (60/117 patients; *P* =0.79), and the drug use frequency rates in the following year were 74.4% (87/117 patients) and 71.8% (84/117 patients; *P* =0.93), in the BUC and SSZ groups, respectively.

Conclusion: Combination therapy with BUC or SSZ and MTX for rheumatoid arthritis did not show a significant difference in disease activity. Further studies are needed.

Disclosure: G. Kidoguchi, None; K. Tokunaga, None.

Abstract Number: 615

The Comparative Observational Study about Efficacy, Safety and Adherence between Tocilizumab and Infliximab in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Since 2003 in Japan, biologic agents have become widely used for RA patients in whom csDMARDs were ineffective. Tocilizumab (TCZ) was approved for marketing for use in patients with RA in Japan ahead of other countries in 2008. Randomized controlled trials have been shown the efficacy and safety of TCZ in patients with RA. Infliximab (IFX) is the first approved TNF inhibitor in Japan and it has abundant evidences for RA treatment. There have been few reports about the head to head comparison between IL-6 inhibitor and TNF inhibitors in patients with RA. We investigated the efficacy, safety, and adherence in RA patients treated with TCZ or IFX in real clinical practice.

Methods: One hundred sixty-one patients with RA treated with TCZ or IFX were retrospectively observed for 12 months in Saitama Medical University Hospital since 2008 to 2016. We compared the baseline characteristics, disease activity, physical disability, drug continuation rate, and adverse events between the patients treated with TCZ or IFX.

Results: In TCZ group (n=89) compared with IFX group (n=72), we found longer disease duration (TCZ vs. IFX: 9.8 vs. 6.4years p=0.001), lower rate of biologic-naïve patients (27.0% vs. 94.4% p<0.001), fewer MTX-users (66.3% vs. 100% p<0.001), and lower dose of MTX (5.8 vs. 8.5mg/week p<0.001). Age of disease onset, rate of female, DAS28-ESR4, HAQ-DI, RF, MMP-3, and daily dose of PSL were similar between the groups. DAS28-ESR4 and HAQ-DI significantly decreased for one year in both groups. The patients who achieved remission or low disease activity in CDAI were more in TCZ group than IFX group (83.8% vs. 62.5% p=0.016). There was no significant difference in the drug continuation rate (80.9% vs. 75.0%). In the patients who discontinued TCZ or IFX during one year of observational period, the rate of adverse events or lack of efficacy was not significantly different between the groups. We also investigated the efficacy, safety and drug continuation rate of TCZ (n=24) or IFX (n=68) as a first biologic for RA. The prevalence of patients who achieved remission or low disease activity in CDAI were more in TCZ group than IFX group (95.0% vs. 61.7% p=0.007), and there was no significant difference in the drug continuation rate (83.3% vs. 77.9%). The rate in lack of efficacy was lower in TCZ group than IFX group (0% vs. 10.3%) and there was no difference in adverse events between the groups (16.7% vs. 11.8%).

Conclusion: TCZ-treated patients, who, despite, had longer disease duration, were less biologic-naïve, and fewer MTX-users, showed equivalent or greater efficacy, drug continuation rate, and safety comparing with those treated with IFX.

Disclosure: M. Matsuda, None; Y. F. Asanuma, None; Y. Nakao, None; H. Yazawa, None; T. T. Wada, None; N. Kouzu, None; T. Mimura, None.

Abstract Number: 616

Supplementation of Methotrexate (MTX) with Ticagrelor Therapy Suppresses Disease Activity in Patients with Moderate to Very Active Ra; Further Evidence That Adenosine and Its Receptors Mediate the Anti-Inflammatory Activity of MTX

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Low dose weekly MTX remains the anchor drug for treatment of Rheumatoid Arthritis. The principal mechanism by which MTX suppresses inflammation in Rheumatoid Arthritis is thought to be enhanced adenosine release from cells which suppresses inflammation by stimulating adenosine receptors on T cells, macrophages and other inflammatory cells (Nature Rev Rheumatol 13:41, 2017). Many patients do not respond to low dose MTX and studies in mice suggest that MTX resistance may be due to inadequately increased adenosine release (Clin Exp Rheumatol 31:433, 2013). Because adenosine is primarily taken up by cells from the extracellular space via the nucleoside transporter ent1 we asked whether an agent that blocks adenosine uptake could enhance the effect of MTX in the treatment of RA. We therefore carried out an open label 1 month study, adding an inhibitor of adenosine uptake via ent1, ticagrelor (a P2Y12 inhibitor that is approved for inhibition of platelet aggregation to prevent severe cardiovascular events) (Nat Rev Cardiology12:156,2014), to patients who were poorly controlled with low dose methotrexate therapy for RA. (NCT02874092)

Methods: Patients (5 female/1 male, mean age 49.6 years) who all met ACR criteria for RA and had active disease, as defined by DAS28 (ESR) > 3.6 and who were on stable doses of MTX monotherapy (for a minimum of 12 weeks), were recruited from the Bellevue Hospital Center Arthritis Clinic. Patients had no known contraindication to ticagrelor and had no history of coronary artery disease. After giving informed consent patients entered an open label protocol in which they were administered Ticagrelor (90mg) twice daily for one month in addition to their stable dose of MTX. Disease activity was reassessed and change in activity from the start of the trial was noted. This study was approved by the NYULMC-Bellevue IRB.

Results: Five of six patient achieved an improvement in their DAS28(ESR) >0.6. Half of the patients (3 patients) achieved a reduction in DAS28 (ESR) >1.2, 2 patients achieved a reduction in DAS28 (ESR) >0.6 but less than 1.2 and 1 patient showed no improvement. Four of six patients had a reduction in their tender joints and all had a reduction in swollen joints. No patients reported any adverse reactions, including excessive bleeding.

Conclusion: The results of this small open label trial suggest that treatment with ticagrelor enhances the effect of MTX on RA and may be a useful addition to the therapeutic armamentarium. Moreover, these results offer further support for the hypothesis that enhanced adenosine release at inflamed sites mediates the anti-inflammatory effects of MTX therapy. The limitations of this trial include the fact that it was an open label trial in a small group of patients but the results support further study of ticagrelor in combination with MTX.

Subject	Baseline DAS	Baseline Tender Joints	Baseline Swollen Joints	Baseline ESR	One Month DAS	One Month Tender Joints	One Month Swollen Joints	One Month ESR	
30yo Female	5.96	18	17	10	4.15	5	5	14	
70yo Female	5.73	9	10	42	4.03	3	5	20	
44yo Male	5.13	6	12	18	5.38	7	9	26	Inconsistent Ticagrelor compliance
58yo Female	6.17	8	9	75	5.33	6	8	50	
63yo Female	5.32	1	11	95	4.64	2	5	50	ESR after 3 months from baseline
33yo Female	5.91	11	11	19	3.11	1	2	18	

Disclosure: P. B. Rosenthal, None; J. S. Berger, Astra Zeneca, Janssen, 2; B. N. Cronstein, Cantic Biopharma, Regenosine, 1, NIH Arthritis foundation, Astrazeneca, 2, Horizon Pharmaceuticals, Regenosine, 5, Patent issued and pending, 9.

Abstract Number: 617

Long-Term Outcome of Rituximab in Rheumatoid Arthritis: Real World Experience

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Rituximab is an effective treatment for rheumatoid arthritis (RA). Data on long-term outcomes following rituximab treatment are limited. The aim of this study was to evaluate the long-term efficacy of, and identify predictors of response to, rituximab in our centre.

Methods: We conducted an observational study of RA patients treated with rituximab from 2003-2016. Demographic and clinical characteristics, including response to treatment, were assessed with tender joint count, swollen joint count, erythrocyte sedimentation rate, and C-reactive protein. Arthroscopy was performed in patients where clinically indicated. Univariate and multivariable logistic regression models were established to evaluate baseline predictors of treatment response. Remission was defined as DAS28-CRP <2.6 or meeting the 2011 ACR/EULAR remission criteria.

Results: 114 RA patients were treated with rituximab. Mean (range) age was 62 (49-75) years. 73% were female, 85% were rheumatoid factor (RF)+, 64% anti-citrullinated protein antibody (ACPA)+, 59% RF+ and ACPA+. Median (IQR) disease duration was 13.5 (7,24.3) years and number of prior conventional synthetic DMARDs (csDMARDs) was 1 (0,2) and biologic DMARDs was 1 (0,2). Baseline characteristics of patients are shown in Table 1. 34 were receiving rituximab monotherapy, 80 were receiving combination therapy with a csDMARD. At last follow-up median (IQR) duration of rituximab treatment was 3.1 (1.8, 6.1) years. 68 (60%) patients maintained remission, 14 (12%) were primary non-responders (7% RF-, 50% ACPA-, 7% RF-ACPA-), 25 (22%) secondary non-responders (24% RF-, 40% ACPA-, 12% RF-ACPA-), and 7 (6%) stopped rituximab due to adverse events (3 hypersensitivity reactions, 2 recurrent LRTIs, 1 neutropenia, 1 severe herpes zoster). Of the 68 patients in remission, 26 (38%) were on rituximab monotherapy and 42 (62%) were receiving combination therapy with a csDMARD. Of the 39 biologic naïve patients, 24 (62%) were in remission and 15 (38%) were not; rituximab achieved equally good outcomes in patients who had previously failed a biologic. No significant baseline predictors of treatment response were identified using logistic regression modelling. In the 44 patients who had an arthroscopy, baseline ESR ($p=0.312$), CRP ($p=0.590$), patient global assessment ($p=0.934$), DAS28-CRP ($p=1$), TJC ($p=0.750$), SJC ($p=0.848$), macroscopic synovitis ($p=0.490$), macroscopic vascularity ($p=0.936$), and histologic inflammation ($p=0.146$) did not predict response to rituximab.

Conclusion: Rituximab is an effective long-term treatment, with 60% remission, for many of our RA patients, including those who have previously failed a biologic. In this cohort, no baseline demographic, clinical, or serological characteristics accurately predict response to rituximab.

Table 1: Baseline characteristics of 114 rituximab treated patients

N=114	
Age, years, mean (+SD)	62 (+13)
Female, n (%)	83 (73)
Disease duration, years, median (IQR)	13.5 (7, 24.3)
Previous csDMARDs, median (IQR)	1 (0, 2)
Previous bDMARDs, median (IQR)	1 (0, 2)
Serology, n (%)	
RF+	97 (85%)
ACPA+	73 (64%)
RF+ACPA+	67 (59%)
RF-ACPA-	13 (11%)

Disclosure: C. Low, None; R. Conway, None; F. Young, None; E. S. Molloy, None; A. B. Mongey, None; O. FitzGerald, None; A. G. Wilson, None; U. Fearon, None; D. J. Veale, None.

Abstract Number: 618

Blood Lymphocytes Subtypes As Biomarkers for Early Identification of Optimal Responders to Anti-TNF Treatment in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: TNF inhibitors (TNFi) are the most common biological agents used as disease-modifying treatment in rheumatoid arthritis (RA). Although these drugs have contributed to change the natural history of RA, approximately 30-50% of patients do not respond to this therapy. Early identification of optimal responders is crucial in the clinical setting. We aimed to study if baseline percentages of different leukocyte subsets in peripheral blood (PBMCs) can contribute to identify RA patients who will respond to TNFi.

Methods: This was a prospective bi-center pilot study including 50 RA patients under TNFi therapy. Clinical activity was assessed at baseline and 6 months of treatment by disease activity score 28 (DAS28), considering optimal responders if they reached remission at 6 months ($DAS28 \leq 2.6$). PBMCs were obtained before treatment and different leukocyte subsets were evaluated by flow cytometry in a FACSCantoII instrument. All the analyses were adjusted by sex, age, concomitant methotrexate, baseline DAS28 and rheumatoid factor through a multivariate log-regression model (odds ratio; 95% CI).

Results: Optimal responders showed higher percentage of B cells (OR=1.28;95%; CI:1.06-1.54;p=0.011) and naive B cells (Bn; OR=1.50; 95%; CI:1.11-2.04;p=0.009) at baseline. We established cut-off values by ROC curves and analyzed the ability of both variables in predicting clinical response. Best results were obtained with Bn. Showing more than 2.55% of these cells associated with optimal response.

Conclusion: Our results suggest that basal Bn percentages may contribute to identify optimal responders to TNFi in RA. Although our data should be validated in larger cohorts.

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Abstract Number: 619

Patterns of Change of a Second Biological Dmard in a Cohort of Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Evaluate the survival of the 2nd biological disease modifying drug (bDMARD) and to determine the causes of suspension of the 2nd bDMARD.

Methods: Patients ≥ 18 years of age who met ACR/EULAR 2010 criteria for Rheumatoid Arthritis (RA) and who had started their first biological disease modifying antirheumatic drug (bDMARD) between 01/2006 and 12/2017 were included. Socio-demographic variables, comorbidities, smoking status, date of onset of symptoms, the time elapsed between the interruption of the first bDMARD and the start of the second and the response to it. Variables were compared with Chi2, Student's T test and ANOVA. Cumulative survival was evaluated using Kaplan Meier curves and their comparisons using log rank.

Results: 347 patients were included, with a median age of 57.8 years (IQR: 48-65), 89.6% were women, 96.5% had positive RF and 60.8% positive anti-CCP. 70.6% had health coverage, 16.3% were smokers and 51.2% had comorbidities. 53.9% discontinued the 1st bDMARD of which 27.6% started a 2nd one (Abatacept 41.2 %, Etanercept 25%, Adalimumab 16.7%, Tocilizumab 14.6%, Certolizumab 6.3% and Rituximab 1%). The mean time between 1st bDMARD discontinuation and initiation of the 2nd was 9.5 months. 41.3% discontinued the 2nd bDMARD, being the causes of discontinuation: inefficacy 35.9%, lack of provision 30.8% and adverse events (AE) 20.5%. The median survival time of the 2nd bDMARD was 11 months (95% CI: 4-17.9), with no significant difference between the different drugs. In patients who had a TNF inhibitor agent as 1st bDMARD and the cause of discontinuation was lack of provision, 86.9% of them restarted a TNF inhibitor, while a change in mechanism of action was preferred in patients who discontinued due to AE (69.2%) or due to inefficacy (77.7%). There was no difference in the survival of the 2nd bDMARD to its use in monotherapy or combined with csDMARD. When the cause of suspension of the 1st bDMARD was AE, the survival of the 2nd bDMARD was significantly lower

(mean: 3.6 months) compared to those who stopped the 1st bDMARD due to inefficiency (mean 21.5 months) or due to lack of provision (mean:20.5 months), (Log Rank test: $p = 0.03$).

Conclusion: The survival of the 2nd bDMARD was 11 months, with no differences between drugs. The most frequent cause of suspension of treatment was inefficacy. The only factor associated to a decreased survival of the 2nd bDMARD was the discontinuation of the 1st bDMARD due to adverse event.

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Abstract Number: 620

Efficacy of a Second Tumor Necrosis Factor Inhibitor (TNFi) in the Treatment of Rheumatoid Arthritis (RA)

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Table 1

Rate of sustained or transient response to 1st and 2nd TNFi based on demographic and clinical data

	Total	Response (Sustained or Transient) n (%)	No Response n (%)	Response Not Determined	P ¹
TNFi 1	322	234 (72.7)	83 (25.8)	5 (1.6)	
Age, mean	56.0	56.2	55.0		0.44
BMI, mean	31.4	31	55		0.15
Insurance					
Private	176	129 (73.3)	45 (25.6)	2 (1.1)	0.89
Federal	146	105 (71.9)	38 (26.0)	3 (2.1)	
Females	241	174 (72.2)	62 (25.7)	5 (2.1)	0.95
Males	81	60 (74.1)	21 (25.9)	0 (0.0)	
CCP +	141	105 (74.5)	32 (22.7)	4 (2.8)	0.08
CCP -	141	94 (66.7)	46 (32.6)	1 (0.7)	
RF +	187	144 (78.7)	39 (20.9)	4 (2.1)	<0.01
RF -	115	72 (62.6)	42 (36.5)	1 (0.8)	
On Methotrexate	265	186 (70.2)	74 (27.9)	5 (1.2)	0.07
Off Methotrexate	54	45 (83.3)	9 (16.7)	9 (0.0)	
Time to 1 st TNFi <3 months	26	23 (88.5)	3 (11.5)	0 (0.0)	0.21
Time to 1 st TNFi >3 months	285	200 (70.2)	80 (28.1)	5 (1.8)	
TNFi 2	322	202 (62.7)	96 (29.8)	24 (7.5)	
Age, mean	56.0	56.0	55.1		0.58
BMI, mean	31.4	31.0	32.3		0.14
Insurance					
Private	176	111 (63.1)	53 (30.1)	12 (6.8)	0.96
Federal	146	91 (62.3)	43 (29.5)	12 (8.2)	
Females	241	161 (66.8)	62 (25.7)	18 (7.5)	<0.01
Males	81	41 (50.6)	34 (42.0)	6 (7.4)	
CCP +	141	91 (64.5)	39 (27.7)	11 (7.8)	0.29
CCP -	141	83 (58.9)	47 (33.3)	11 (7.8)	
RF +	187	123 (65.8)	47 (25.1)	17 (9.1)	<0.03
RF -	115	66 (57.4)	44 (38.3)	5 (4.3)	
On Methotrexate	265	166 (62.6)	78 (29.4)	21 (7.9)	0.64
Off Methotrexate	54	33 (61.1)	18 (33.3)	3 (5.6)	
Time to 1 st TNFi <3 months	26	23 (88.5)	3 (11.5)	0 (0.0)	<0.01
Time to 1 st TNFi >3 months	283	172 (60.8)	89 (31.4)	22 (7.8)	

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: The response rate of TNFi in RA is variable and to some extent unpredictable, making treatment decision-making quite complex. Some insurance carriers require RA patients to have failed 2 different TNFi agents prior to a trial of a biologic agent with an alternate mechanism of action (MOA). This study retrospectively analyzed our 4282 RA patient database to evaluate patients who failed to respond adequately to an initial TNFi and look for clinical predictors of response to a 2nd TNFi.

Methods: A retrospective manual chart review of the electronic health record (EHR) was performed on 322 RA patients seen over the course of four years who were noted to have been prescribed more than one TNFi. Age, gender, body mass index (BMI), insurance provider, RA diagnosis length, cyclic citrullinated peptide antibody (CCP) and rheumatoid factor (RF) positivity, concomitant disease modifying anti-rheumatic drug (DMARD) therapy, length of time between diagnosis of RA and start of 1st and 2nd TNFi, efficacy of 1st and 2nd TNFi as evidenced by sustained or transient reduction in clinical disease activity index (CDAI) or impression of the treating rheumatologist, and reason for discontinuation were recorded. Patients who did and did not respond to their 1st and 2nd TNFi were compared using Pearson's chi-square or Fisher's exact tests and Student's t-tests or Wilcoxon rank-sum tests. Comparisons of responses to 1st and 2nd TNFis were made with McNemar's tests. A multivariable logistic regression model that included age, BMI, and statistically significant characteristics from the bivariate analysis was used to model response to a 2nd TNFi.

Results: Whether there was no response or transient achievement of response to a 1st TNFi as measured by CDAI or treating rheumatologist is displayed in Table 1. RF positive patients were more likely to respond than RF negative patients. Whether there was a transient response or not could not be determined in 5 patients (1.6%). Response rates to the 2nd TNFi are displayed in Table 1. Response to the 2nd TNFi could not be determined in 24 patients (7.5%). Response rates to the 2nd TNFi were greater in females vs males and in RF positive vs. RF negative patients. The predilection for female response was independent of age, BMI, and seropositivity. If the time to 1st TNFi was three months or less from initial diagnosis of RA, sustained response to 2nd TNFi was more likely compared to longer times.

Conclusion: In RA patients who failed to achieve or sustain a clinical response to an initial TNFi, female patients, patients with +RF, and patients whose diagnosis of RA was within three months of 1st TNF initiation were more likely to have a clinical response to a 2nd TNF agent. In the absence of these criterion, our data suggest a significantly reduced response to a 2nd TNFi. In these individuals, a stronger consideration for choosing a biologic with alternative MOA could be given.

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Abstract Number: 621

Practical Optimization of Methotrexate Dose Improves Disease Control of Rheumatoid Arthritis Despite Reduction or Discontinuation of Oral Glucocorticoids

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Short-term glucocorticoids (GCs) along with methotrexate (MTX) has been recommended for newly onset patients with rheumatoid arthritis (RA) in EULAR recommendation 2016. However, it is not always easy to taper or stop oral GCs in clinical practice due to patients' fear of relapsed pain or fatigue. As well, some patients disagree to increase MTX dose for fear of adverse events. This study was conducted to clarify whether GCs could be reduced without impaired disease control by optimizing MTX dose in RA patients with stable medication in Japanese clinical practice setting.

Methods: Seventy patients with RA who regularly visit our outpatient clinic for ≥ 1 yr with stable medication were enrolled during Sep.-Oct. 2016. Clinical characters, disease activity, and medications at entry and 1 year after were collected. Therapeutic strategy was to increase MTX up to 16mg/w with reducing prednisolone (PSL) as much as possible based on patient's consent. Using biological or targeted synthetic DMARDs was permitted in case of uncontrollable disease. Wilcoxon's signed-rank test and chi-square test were used for statistics.

Results: Clinical characters (median [IQR]) were; age 62 [51, 68] yrs; female 69%; disease duration 6.8 [3.4, 13.7] yrs. Rate of MTX was elevated from 57 to 62%, and dose (mean \pm SD) was increased from 9.8 \pm 3.2 to 11.6 \pm 3.7 mg/w ($p < 0.0001$) for users only, whereas PSL users was decreased from 56 to 26%, and decreased from 2.0 \pm 3.1 to 0.8 \pm 1.8 mg/d ($p = 0.0004$) for all patients. Biological or targeted synthetic DMARDs were used for 16 patients, and newly started for 2 patients (tocilizumab and tofacitinib). Median CDAI, SDAI, and DAS28 were suppressed from 5.7 to 3.8, 6.2 to 3.9, and 2.92 to 2.77, and remission rate were increased from 24 to 39%, 27 to 41%, and 36 to 41%, respectively.

Conclusion: Oral GCs were successfully reduced or withdrawn without deteriorated disease control of RA with optimized MTX dose. However, use of oral GCs might delay clinical decision-making of starting biological or targeted synthetic DMARDs.

	Baseline	1-Year	p-value
%MTX	57%	67%	0.2226
MTX[mg/w] for users	9.8 \pm 3.2	11.6 \pm 3.7	<0.0001
%PSL	56%	26%	0.0003
PSL[mg/d] for all patients	2.0 \pm 3.1	0.8 \pm 1.8	0.0004
CDAI value	6.9 \pm 5.9	5.3 \pm 5.3	0.0177
CDAI remission	24%	39%	0.0687
SDAI value	7.8 \pm 7.0	5.7 \pm 5.8	0.0038
SDAI remission	27%	41%	0.075
DAS28 value	3.19 \pm 1.15	2.97 \pm 1.13	0.0837
DAS28 remission	36%	41%	0.4874

Disclosure: S. Hirata, AbbVie, Ayumi, Eli Lilly, UCB, Bristol-Myers Squibb, UCB, 9, AbbVie, Eisai, Tanabe-Mitsubishi, 9, AbbVie, Astellas, Ayumi, Bristol-Myers Squibb, Chugai, Eisai, Eli Lilly, Jansen, Kissei, Pfizer, Sanofi, Takeda, Tanabe-Mitsubishi, UCB, 8; K. Araki, None; H. Kohno, None; K. Yukawa, None; T. Tokunaga, None; T. Kuranobu, None; K. Oi, None; Y. Yoshida, None; T. Sugimoto, None; K. Oda, None; T. Nojima, None; E. Sugiyama, None.

Abstract Number: 622

DMARD Withdrawal in RA Patients Achieving Therapeutic Response with Certolizumab Pegol Combined with Dmards: Results from a Canadian Randomized Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

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Session Type: ACR Poster Session A

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

Background/Purpose: The efficacy and safety of certolizumab pegol (CZP) in the treatment of adult patients with moderate to severe rheumatoid arthritis (RA), when administered either in combination with methotrexate (MTX) or as monotherapy, has been previously shown in several controlled clinical trials. However, a detailed assessment of CZP in combination with a wide range of non-biologic disease-modifying drugs (nbDMARDs) used in clinical practice compared to switching to monotherapy after achieving a response when added to nbDMARD(s) is lacking. The objective of this trial was to compare the effectiveness and tolerability of CZP given as add-on to nbDMARDs, including MTX and others, or as monotherapy after achieving a DAS28 (ESR) improvement of ≥ 1.2 .

Methods: RA patients who had CZP added in clinical practice to their existing DMARD regimen due to inadequate response to their nbDMARD(s) were eligible. At 3 or 6 months, those patients who achieved a change in DAS28 of ≥ 1.2 were randomized to continue combination therapy (Combination group) or withdraw nbDMARD therapy (Monotherapy

group) and be followed up to 18 months. A sample size of 125 randomized patients was estimated to be required to have 100 randomized (50 per group) to detect a difference of 15% in response.

Results: A total of 124 patients were enrolled, of whom 81 were randomized to continue combination therapy (n=37) or withdraw nbDMARDs (n=44). No significant differences were observed between-groups in baseline age (58.4 vs. 54.2 years), gender (84% vs. 71% female), race (87% vs. 91% Caucasian), rheumatoid factor status (58% vs. 60% positive), or prior biologic experience (16% vs. 11%).

At 18 months, upon adjusting for baseline scores, similar improvements were observed between groups in DAS28 (ESR) (-2.1 vs. -2.1) (Figure 1). Furthermore, the odds of achieving DAS28 LDA (OR [95%CI]: 1.08 [0.36-3.23]), Δ DAS28 \geq 1.2 (1.59 [0.51-4.89]), LDA and/or Δ DAS28 \geq 1.2 (1.36[0.43-4.36]), and remission (1.00 [0.35-2.89]) were not different between the Combination and Monotherapy groups. Similarly, no differences were observed between groups at 12 months of treatment with respect to these outcomes.

Conclusion: The results suggest that, among RA patients achieving a therapeutic response when on combination therapy with certolizumab pegol and nbDMARDs, nbDMARDs could be withdrawn without significant impact on treatment effectiveness over the next year.

Figure 1. DAS28 (ESR) Scores

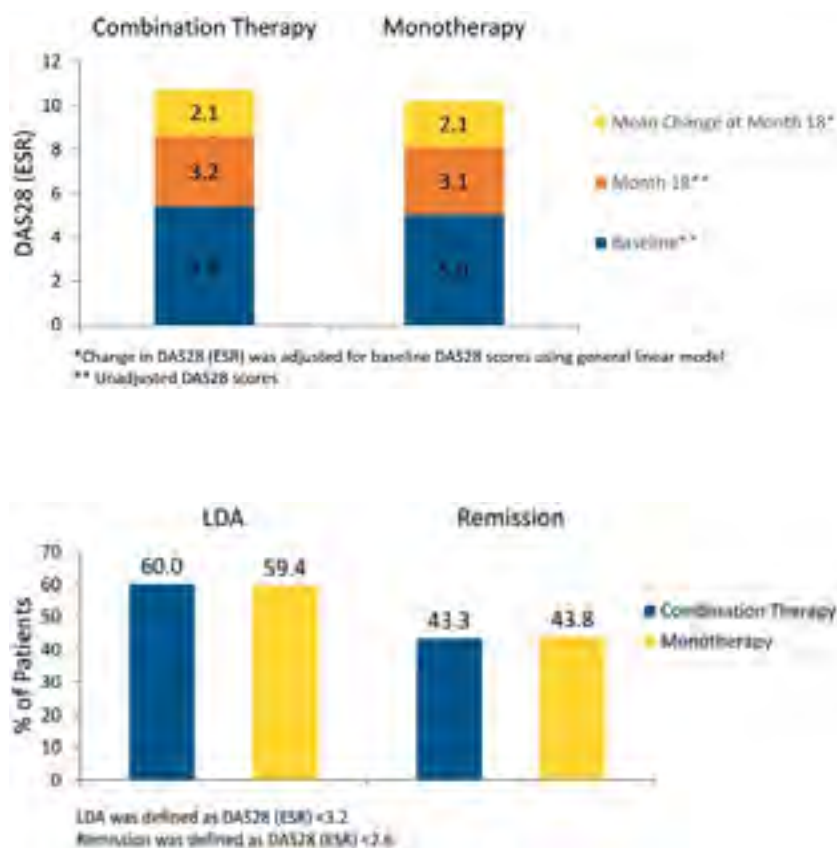


Figure 2. Proportions of Patients Achieving LDA and Remission at Month 18

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Step-Down-Bridge Versus Tight-Step-up Therapy in Patients with Early Rheumatoid Arthritis Lacking Poor Prognostic Factors: An Economic Point of View

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: In the Care in early RA (CareRA) trial, COBRA Slim, a combination of methotrexate (MTX) with a moderate-dose prednisone step-down-bridge scheme, showed a positive efficacy/tolerability balance in so-called low risk patients (Verschueren et al., 2015). The purpose of this piggy back study is to perform an economic evaluation on the 2 year data of CareRA.

Methods: Patients with early RA (≤ 1 year) naïve to DMARDs were stratified based on classic poor prognostic factors (RF/ACPA +, high disease activity, erosions), into high and low risk. Low risk patients were randomized to MTX with a step down bridge glucocorticoid (GC) scheme (COBRA Slim) or MTX without GC (Tight Step Up –TSU-). The treat to target principle was applied, with a low disease activity (DAS28CRP ≤ 3.2) threshold. Clinical and patient-reported data were collected at each visit (≥ 10 times in 2 years).

For cost-effectiveness analysis, direct costs of consultations, RA medication (systemic GCs, cs- and bDMARDs, analgesics) and hospitalization costs for serious adverse events over 2 years were considered. As benefits, proportion of patients with DAS28CRP < 2.6 at year 2 and area under the curve (AUC) DAS28CRP over 2 years were used. Missing data were imputed per item with expectation maximization.

For cost-utility analysis, utilities were calculated using a validated mapping algorithm (mixed adjusted censored model) for reconstructing EQ-5D scores based on age, sex, HAQ and VAS pain at relevant study visits. Quality-adjusted life years (QALYs) were determined as the time-weighted average of all available EQ-5D scores.

Incremental cost-effectiveness ratios (ICERs) were calculated to compare both treatment strategies. Bootstrapping corrected for bias with 1000 replications was used.

Results: From the initial CareRA cohort (n=379), cost/benefit data for a 2 year economic analysis of 326 patients was available and of these patients 75 belonged to the Low Risk group: 41 TSU and 34 COBRA Slim. Number of consultations were comparable (± 12). Hospitalization costs were > 2 times higher in TSU than in COBRA Slim. The mean hospitalization cost for COBRA Slim was 445.32 (CI 213.09-720.53) and 1067.12 (CI 242.34-2273.66) for TSU. There was an outlier in TSU accounting for 26318.43.

Numerically COBRA Slim (79.4% DAS28CRP < 2.6) showed a better effectiveness than TSU (75.6%). The cost-effectiveness analysis showed a dominating ICER for COBRA Slim compared to TSU (mean -167.85/1% remission gained, mean -2195.16/unit improvement of DAS28CRP AUC over 2 years).

More QALYs were gained with COBRA slim (1.72) compared to TSU (1.59), with significant differences in time (p < 0.05). Cost-utility analysis resulted in an ICER of -3938.54 per QALY.

A sensitivity analysis, leaving out the outlier, resulted in a mean ICER of 0.99/1% remission gained, 12.88/unit improvement of DAS28CRP AUC over 2 years and 23.12 per QALY.

Conclusion: COBRA Slim, a combination of MTX with a step down bridge GC scheme, seems more effective and results in a better quality of life than a tight step up approach. Based on this economic analysis, intensive step down remission induction strategies such as COBRA Slim should also be considered in patients with early RA lacking classical poor prognostic factors.

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Easy Accessibility of Biologics and Its Impact on Disease Activity and Quality of Life in Kuwaiti Patients with Rheumatoid Arthritis

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SESSION INFORMATION

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Session Type: ACR Poster Session A

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

Background/Purpose: Prescribing biologics for patients with rheumatoid arthritis (RA) may be restricted by many factors other than the physician's clinical judgment. In Kuwait, patients with RA have a free and a rapid access to biologics as they are provided within a week after being prescribed by their treating rheumatologists. The cost of treatment is fully covered by The Ministry of Health for Kuwaiti patients (KP) while non-Kuwaiti patients (NKP) have to follow a strict and a long protocol and if approved, biologic treatment will then be partially covered by a charity organization. The purpose of this study is to evaluate whether accessibility to treatment affects the rate of biologic prescription and whether this has an impact on disease activity and quality of life in patients with RA.

Methods: Data were extracted from The Kuwait Registry for Rheumatic Diseases (KRRD). Adult patients who satisfied the ACR classification criteria for RA from four major hospitals in Kuwait were evaluated from February 2013 through May 2018. All KP were selected. Demographic data, treatment agents, disease activity tools and HAQ-DI scores were studied and were compared with NKP using appropriate statistical methods.

Results: A total of 1,511 RA patients were included with 7,893 hospital visits. 795/1,511 (52.6%) were KP. Among KP 555/795 (69.8%) were females with a mean age of 54.5±13 years and a disease duration of 8.9±7.5 years (0-52). 73.5% had a positive rheumatoid factor and 58.9% had positive anti-citrullinated protein antibodies. 446 (56.1%) were on methotrexate and 53 (6.7%) were on steroid therapy. 389/795 (48.9%) were on biologic treatment, and 124/389 (31.9%) used them as monotherapy. For the total KP the mean values for DAS28 was 2.67±1.2, CDAI 4.03±5.6, SDAI 7.75±5.4, VAS pain 1.67±2.4, tender joints 2.95±5.5, swollen joints 0.41±1.8, ESR 28.4±22.4, CRP 5.52±4.9 mg/dL and HAQ-DI 0.88±0.77. Comparing KP with NKP, NKP had lower prescription for biologic therapy (8.9% vs 48.9%, $p<0.001$, higher methotrexate (74.9% vs 56.1% $p<0.001$) and higher steroid therapy (14% vs 6.7%, $p<0.001$). With regard to RA activity, NKP had higher DAS28 ($p=0.004$), higher ESR ($p=0.014$), more swollen joints ($p<0.001$) and higher HAQ-DI ($p<0.001$).

Conclusion: In the setting of easy accessibility to treatment, biologics were prescribed by rheumatologists in a much higher rate than when approval is preceded by a strict and a long protocol. This may explain the lower disease activity and the lower rate of steroid use and its positive impact on physical function.

Disclosure: A. Al-Herz, None; K. Saleh, None; A. Al-Awadhi, None; W. Al-Kandari, None; E. Hasan, None; A. Ghanem, None; Y. Ali, None; H. Alhajeri, None; S. Hayat, None; A. Aldei, None; M. Hussain, None; I. Nahar, None; F. Abutiban, None; A. Alenizi, None; K. Mokaddem, None; A. Khadrawy, None; A. Fazal, None; A. Zaman, None; G. Mazloun, None; Y. Bartella, None; S. Hamed, None; R. Alsouk, None; A. Al-Saber, None.

Tapering of Biological Antirheumatic Drugs in Rheumatoid Arthritis Patients Is Achievable and Cost Effective in Daily Clinical Practice: DATA from the Brussels UCL RA Cohort

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SESSION INFORMATION

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Session Type: ACR Poster Session A

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

Background/Purpose: Several studies have demonstrated that Rheumatoid Arthritis (RA) patients achieving low disease activity or remission are able to taper biological disease-modifying antirheumatic drugs (bDMARDs). The aim of this study is to evaluate the proportion of patients in whom the bDMARD can be tapered in daily practice and to analyse the characteristics of these patients. Another objective is to determine which bDMARDs are more adapted to dose reduction and the cost saving.

Methods: Inclusion criteria were RA patients from our Brussels UCL cohort treated with a bDMARD for at least one year. A dose reduction was proposed by the senior physician when sustained low disease activity or remission was achieved. Patient characteristics and baseline features before the introduction of the current bDMARD were collected as well as flares if happened. We also calculated, for each bDMARD, the proportion of patients who received a decreased dose and the annual cost.

Results: Data from 332 eligible RA patients were collected, 140 patients (42,1%) had a tapered regimen and 192 received a full dose of bDMARD. In the decreased dose group, age at diagnosis (43.1 vs 38.7 years, $p=0.004$), HAQ (1.3 vs 1.5, $p=0.048$), RF (83.3 vs 72.9%, $p=0.026$) and disease duration at the bDMARDs introduction (9.7 vs 12.1 years, $p=0.034$) were statistically different. As expected, the current DAS28-CRP was lower (2.26 vs 2.64, $p=0.001$) in the decreased dose group and interestingly, more patients receiving a decreased dose were treated with a combination of methotrexate when the bDMARD was introduced (86.7% vs 73.8%, $p=0.005$). No difference between groups was observed for gender, ACPA, erosion, number of previous bDMARDs, time to first conventional synthetic DMARD and biological DMARD, baseline DAS28-CRP and use of glucocorticoids. In our cohort, anti-TNF agents were the most commonly prescribed medications (anti-TNF 68%, tocilizumab 15%, rituximab 10%, abatacept 7%). Only 15 patients experienced a flare during the follow-up. Adalimumab, etanercept and rituximab were the most frequent decreased bDMARD and were associated with the most important reduction of annual cost. Figure: Proportion of patients with decreased dose for each bDMARD

Conclusion: In daily practice, tapering of bDMARDs in RA patients with low disease activity or remission is an achievable goal in a large proportion of patients, thereby reducing annual drug cost. The combination with methotrexate could be a positive predictive factor for the success of bDMARD tapering but further prospective research in daily practice are needed to confirm this result.

Disclosure: S. Dierckx, None; B. R. Lauwerys, None; T. Sokolova, None; L. Meric de Bellefon, None; M. Stoenoiu, None; A. Nzeusseu Toukap, None; F. A. Houssiau, None; A. Avramovska, None; P. Durez, None.

Abstract Number: 626

The Comparative Effectiveness of Cycling Tumor Necrosis Factor Inhibitor (TNFi) Versus Swapping to a Nontnfi on Patient-Reported Functional Ability of Patients with Rheumatoid Arthritis

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

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Background/Purpose: Data on patient-reported functional ability to evaluate the optimal strategy for patients who have failed to first TNFi is scarce. Patient-reported outcomes are a critical component of assessing whether clinicians are improving the wellbeing of patients. We conducted a systematic review and meta-analysis to evaluate the comparative effectiveness of two strategies, cycling versus swapping, on patient-reported functional ability and other patient-reported outcomes.

Methods: Four electronic databases were searched (MEDLINE, EMBASE, Cochrane Library, and Web of Sciences). Sources of gray literature (unpublished records) were searched through clinicaltrials.gov and other websites. The selection process, risk of bias assessment, and data extraction were performed by two independent reviewers. We included controlled trials evaluating patient reported outcomes in patients either cycling to a second TNFi or swapping to a targeted drug with an alternative mechanism of action. Other outcomes reported included pain, patient global assessment, fatigue, and quality of life.

Results: We included 13 studies reporting data on 4,394 patients. The reported cycling strategies were adalimumab, certolizumab, etanercept, golimumab, or infliximab; swapping strategies were abatacept, rituximab, tocilizumab, or tofacitinib. For the individual comparisons, TNFi versus disease modifying antirheumatic drug (DMARD), there was a statistically significant increase in functional ability from baseline to 14 weeks, favoring those patients receiving the cycling strategy (Mean Difference (MD) -0.20, 95% CI -0.34 to -0.06; scores ranging from 0 to 3). Differences favoring cycling when compared to a DMARD were also observed for pain, fatigue, and patient global assessment. Similarly, when comparing nonTNFi versus DMARD, there was a statistically significant increase in functional ability from baseline to 24 weeks, favoring those patients receiving the swapping strategy (MD -0.31, 95% CI -0.35 to -0.27; scores ranging from 0 to 3). Differences favoring cycling when compared to a DMARD were also observed for pain, sleep, fatigue, patient global, and quality of life (SF-36 physical and mental components). Three RCTs directly compared the two strategies. There was no statistically significant differences in the functional disability reported between those patients assigned to the cycling strategy compared with those assigned to the swapping strategy at 12, 24, 36 or 52 weeks (MD at 52 weeks -0.05, 95% CI -0.18 to 0.09; score ranging from 0-3).

Conclusion: Although evidence from previous reports suggest that swapping may be more effective than cycling when evaluating some clinical outcomes our results suggest that with the current evidence both strategies are equally effective in improving functional disability and other patient-reported outcomes.

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Abstract Number: 627

Corticosteroid Utilization before and after Initiation of Biologic Dmards between Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory, systemic autoimmune disease that causes several health problems, such as pain, joint destruction and loss of function. Thanks to the quick anti-inflammatory effects of the Glucocorticoids (Gc), Gc are the most common remedy used for the patients who suffer from RA. The present study aims to elucidate the effects of corticosteroid usage before the initiation of biologic disease-modifying antirheumatic drugs (DMARDs) to inform clinicians regarding the proper use of the required medications.

Methods: TReasure is a multicenter, web-based registry of RA where the information concerning spondyloarthritis patients who receive the targeted treatments could be found. As of May 2018, in the context of the present study, 1,209 RA patients were recorded. Age, sex, smoking habits, disease duration, BMI, initial bDMARDs, acute phase reactants, swollen and tender joint counts (28 joints), patient global assessment of disease activity, pain VAS, DAS-28, CDAI, and SDAI were recorded before patients started to use bDMARDs. In this study, corticosteroid doses were classified as follows: low as < 2.5, medium as 2.5 to 7.5 and high as ≥ 7.5 mg/day.

Results: 1,209 RA patients in the TReasure database used steroid therapy (Table 1). 420 (34.7%) of the patients discontinued steroid treatment after 90 ± 84.62 months (30-120) of follow-up. No statistically significant difference was found in the initial clinical characteristics of the patients who used or did not use Gc were evaluated (except the patients who were older or who had a lower ESR). The mean age of the patient who took Gc was 55 (45-62), RF positivity was 71.8%, CCP positivity was 64.9% and disease duration was nine years. Initially, low dose corticosteroids was used in 3.7%, medium dose corticosteroids in 61.7% and high dose in 34.6% of the patients. On the final treatment, low dose corticosteroids were used in 11.3%, medium dose corticosteroids in 64.3% and high dose in 24.4% of the patients (Figure 1, Table 2).

Conclusion: In the biologic registry, the administration of the Gc was stopped approximately in 35% of the patients. When the doses of the steroids usage were scrutinized, patients who received biologic DMARDs used fewer steroid dose. In 1/3 of the patients, Gc treatment was initiated with above 7.5 mg. In approximately 20% of the patients, the dose was reduced to 2.5 mg. However, 60% of the patients were using 2.5-7.5 mg Gc. Gc is frequently used as a bridge therapy because of its quick anti-inflammatory effects until the effects of DMARDs occur. However, it is notable that the corticosteroid usage was associated with more comorbidities before the initiation of biologic DMARDs among patients with RA. Our findings suggest that low and moderate doses of steroids are preferred more.

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Abstract Number: 628

Longitudinal Changes in Relative Market Share Proportions of Biologic and Targeted Synthetic Disease-Modifying Anti-Rheumatic Drugs for Treatment of Rheumatoid Arthritis: Descriptive Data from the Ontario Best-Practice Research Initiative Database

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018
Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: For patients with Rheumatoid Arthritis (RA) who do not achieve adequate clinical response with combined conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), the next step in goal-directed therapy is initiation of either biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs). bDMARDs include tumour-necrosis factor inhibitors (TNFi) or non-TNFi classes. Since inception of Ontario Best Practice Research Initiative (OBRI), new treatment options have become available. We aimed to describe the evolution of relative use of non-TNFi vs. TNFi in Ontario-based practices from 2008-2017.

Methods: Adult patients with RA enrolled in the OBRI who started therapy with bDMARDs or tsDMARDs anytime during, or up to 30 days before, enrollment were included. Using descriptive analysis of data from each year between 2008 and 2017, the relative proportion of the population treated with TNFi and non-TNFi therapy was measured for (i) all patients and (ii) those initiating their first bDMARD/tsDMARD. TNFi included: Etanercept, Adalimumab, Certolizumab, Golimumab, and Infliximab. Non-TNFi included: Abatacept, Rituximab, Tocilizumab, and Tofacitinib.

Results: A total of 1,057 patients were included of whom 653 were bDMARD/tsDMARD naïve. In 2008, the relative non-TNFi use was 3/56(5.4%) in all patients and 0/31 (0%) in treatment-naïve patients. By 2013 the proportion non-TNFi use increased to 135/562 (24%) in all patients and 11/92(12.0%) in treatment-naïve patients. This increasing trend in relative non-TNFi utilization continued in both groups until 2016 when relative use was 224/679(33.0%) in all patients and 17/56 (30.4%) in treatment-naïve. This was followed by 144/426 (33.8%) and 4/15 (26.7%), respectively in 2017.

Conclusion: This descriptive analysis of data from the OBRI cohort shows an increase in the use of non-TNFi therapies. The overall trend towards greater use of non-TNFi therapies as first line agents after combined csDMARDs may be partially explained by the presence of guidelines that allow clinicians to select any of the above options as first line advanced therapies. Future analyses evaluating patient-, disease- and concomitant drug use-specific determinants of physician decision-making will be conducted.

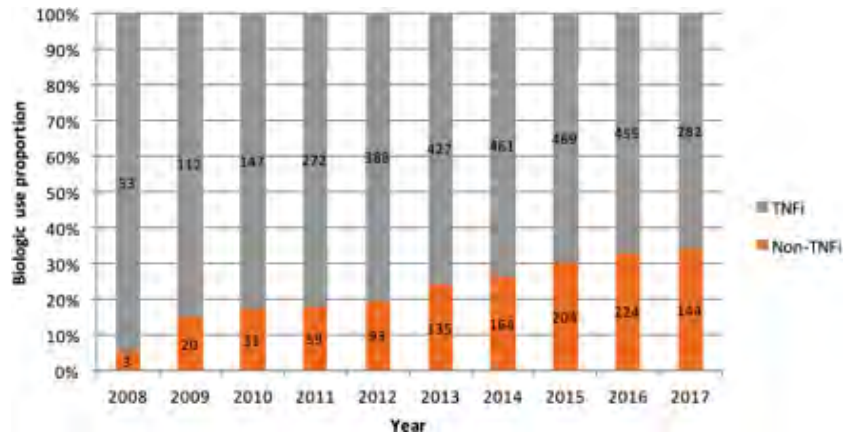


Figure 1: Proportion of biologic use according to mechanism of action by calendar year (n=1057)

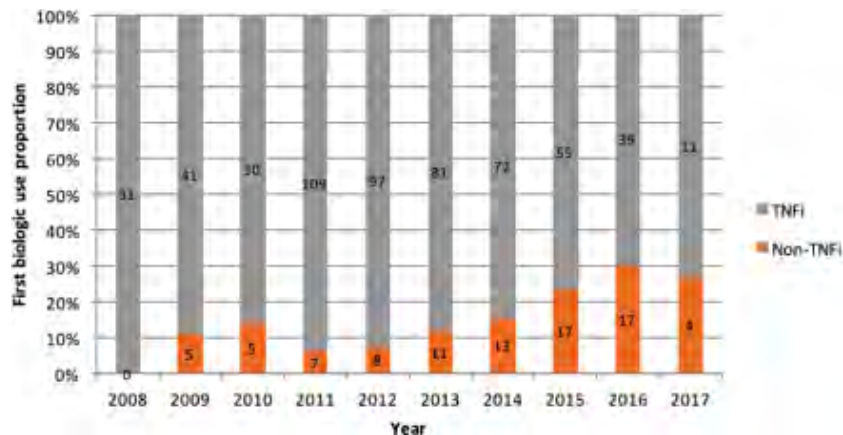


Figure 2: Proportion of first biologic use in biologic naïve patients according to mechanism of action by time period (n=653)

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Abstract Number: 629

Real-World Use of Tofacitinib Compared with Tumor Necrosis Factor Inhibitors in a Cohort of 211 Patients with Rheumatoid Arthritis: Data from a Drug-Based Registry Study in Taiwan

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I: Strategy and Epidemiology

Session Type: ACR Poster Session A

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

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Tofacitinib was approved in December 2014 for RA under Taiwan's National Health Insurance (NHI) reimbursement system. A drug-based registry (XTRA; established July 2016) collects real-world short- and long-term effectiveness, safety, treatment patterns, and persistence in RA patients newly prescribed tofacitinib or a TNF inhibitor (TNFi).

Methods: This observational study within the XTRA Registry comprises a 24-month enrollment plus 36-month follow-up period (August 2016 to August 2021). Patients receive standard care for RA according to the treating rheumatologists and NHI reimbursement criteria (Disease Activity Score 28-ESR [DAS28-ESR]>5.1; failure of 2 DMARDs including MTX; no tuberculosis). The tolerance and effectiveness of tofacitinib were assessed using Work Productivity and Activity Index-RA (WPAI-RA), HAQ-DI, DAS28-ESR, and Clinical Disease Activity Index (CDAI) scores at baseline and 24-week intervals. Comparisons with TNFi used Chi-square test for categorical variables and Student's t test for continuous variables, with no adjustment for multiplicity.

Results: As of January 2018, 211 patients were enrolled in the registry (n=113 tofacitinib; n=98 TNFi [etanercept, adalimumab, or golimumab]). Demographic characteristics were similar between tofacitinib initiators and TNFi initiators. TNFi initiators had higher baseline median DAS28-ESR and CDAI scores (6.16 and 36.6, respectively) vs tofacitinib initiators (5.74 and 28.7, respectively) (p<0.05). Tofacitinib initiators comprised 69.9% who had not previously received TNFi. More tofacitinib initiators (30.1%) than TNFi initiators (2.0%) received ≥1 previous TNFi (p<0.05). Persistence at the end of the first year was similar for tofacitinib initiators (88.5%) and TNFi initiators (90.8%). Numerically decreased functional impairment and improved productivity over time measured by WPAI-RA were seen for both tofacitinib and TNFi initiators. At Week 24, a similar proportion of tofacitinib initiators (23.3%) achieved CDAI low disease activity (LDA; 2.8<CDAI≤10) vs TNFi initiators (20.8%); similar effectiveness was also shown for tofacitinib in terms of DAS28-ESR<3.2 (LDA; 20.7% vs 18.0%). At Week 48, TNFi initiators and tofacitinib initiators achieved CDAI LDA (37.0% and 31.8% of patients), DAS28-ESR<2.6 (remission; 7.4% and 4.2%), and DAS28-ESR LDA (29.6% and 16.7%), respectively. The incidence rate of all-cause adverse events (AEs) was numerically higher in tofacitinib initiators vs TNFi initiators (44.9 vs 33.1 events/100 patient-years).

Conclusion: This drug-based registry is an effective tool for collecting real-world data from RA patients. Preliminary data showed meaningful effectiveness and patient-reported outcomes in both tofacitinib and TNFi initiators. The incidence and types of AEs in this real world setting under the same reimbursement criteria in the 6 medical centers across Taiwan were comparable with the known safety profile of tofacitinib. Additional data from this registry will provide pertinent information on these advanced therapies among patients with severe RA.

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Is Treatment Adherence of RA Patients to Injectable MTX Influenced By Previous MTX Route of Administration?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I – ARHP

Session Type: ACR Poster Session A

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

Background/Purpose: Previous studies have shown, that switching from oral to subcutaneous (SC) MTX can lead to improved efficacy and bioavailability (especially for doses $\geq 15\text{mg/wk}$) as well as to a decreased frequency of adverse gastrointestinal effects in patients with RA. Furthermore, some reports consider that this switch may improve treatments adherence and persistence [1]. The purpose of the present study was to investigate the treatment adherence of RA patients switching from oral to injectable MTX or between two different MTX prefilled syringes.

Methods: APRiM is a prospective, observational, multicenter study, which included adult patients with confirmed RA diagnosis (ACR/EULAR 2010 criteria) already treated by either oral MTX and requiring route modification (Gr1), or SC MTX in prefilled syringe (PFS) and eligible for a device switch (to an other PFS) (Gr2). The main objective of the study was to estimate at 6 months the proportion of patients with strong or improved to maximum treatment adherence evaluated by Morisky self-assessment (8: strong/maximum adherence, 6-7: medium adherence, <6 : poor adherence) in both groups.

Results: Between June 2016 and June 2017, 110 rheumatologists, at 90% with private practice, included 466 pts, 433 of which composed the analyzable baseline set. Pts baseline characteristics Gr1/Gr2 were [mean (SD)]: age: 59.2 (13.0) / 61.5 (12.2) yrs; RA duration: 6.5 (7.9) / 9.9 (10.5) yrs; MTX use duration: 3.6 (4.6) / 6.0 (5.1) yrs; DAS28: 3.9 (0.9) / 3.2 (1.2); Erosive RA: 37% / 53%. All pts were receiving MTX at a mean (SD) dose of 15.1 (4.0) / 15.6 (4.0) mg/wk. Mean (SD) Morisky's scores were 6.5 (2.0) / 6.6 (1.8) for respectively Gr1 / Gr2 at baseline, they improved up to 6.9 (1.8) / 7.0 (1.5) at 6 months. Treatment adherence remained strong or improved to max for 48% of patients in both Gr1 and Gr2. Interestingly, when rheumatologists were asked to estimate their patients' adherence, they reported respectively 77% and 84% [Gr1 / Gr2] of patients with "no missed injections". No new safety signals were identified during this study.

Conclusion: The results of the observational study APRiM revealed that less than 50% of patients are perfectly adherent to injectable MTX treatment, irrespectively of whether was their previous MTX way of administration. Though, this proportion seems to be highly overestimated by the rheumatologists. This underlies the importance of patient/physician effective communication.

[1] Bello et al., Open access Rheumatol. 2017

Disclosure: R. M. Flipo, NordicPharma, 5; E. Senbel, Nordic Pharma, 5; S. Tropé, Nordic Pharma, 6; E. Zinovieva, Nordic Pharma, 3; A. Courbeyrette, Nordic Pharma, 3; H. Herman-Demars, Nordic Pharma, 3.

A Self-Determination Theory Based Intervention to Promote Autonomous Motivation for, and Engagement in Physical Activity in Rheumatoid Arthritis: Theoretical Process Evaluation of a Randomised Controlled Trial

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster I – ARHP

Session Type: ACR Poster Session A

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

Background/Purpose: Moderate-to-vigorous physical activity (MVPA) is recommended for the treatment and management of physical and psychological health in Rheumatoid Arthritis (RA). However, most people living with RA are insufficiently active to accrue health benefits. Interventions are therefore required to support physical activity (PA) behaviour change in this population.

Using theory to develop interventions, can inform what may be the strategies undergirding behavioural change, and provide a framework for testing the efficacy of the theory post-intervention in terms of hypothesised mechanisms. Self-determination theory (SDT) suggests that social environments which foster autonomous motivation toward a behaviour (i.e., intrinsic and personally identified reasons), will promote better uptake and maintenance of the behaviour. This study reports the theoretical process evaluation of an SDT-based exercise intervention for people with RA, which aimed to increase MVPA engagement and optimise psychological well-being.

Methods: Patients with RA (n = 115) were randomised to an SDT-based psychological intervention + RA exercise programme (experimental group, n=59), or a RA exercise programme only (control group, n =56), delivered over 3-months. The SDT-based psychological intervention involve done-on-one consultations with a PA advisor, trained in strategies to promote autonomous motivation for PA (Table 1). Validated questionnaires assessed autonomous and controlled motivation for PA (Behavioural Regulation in Exercise Questionnaire-2), psychological well-being (Subjective Vitality Scale), and daily MVPA (International Physical Activity Questionnaire). Assessments were conducted at baseline (T1) and the end of the exercise programme (T2). Path analyses examined the hypothesised theoretical process model (Figure 1).

Results: Participants were excluded from analyses due to missing baseline data (n = 36), or as extreme outliers (n = 6). The hypothesised model (n = 73), demonstrated an excellent fit to the data [χ^2 (26) = 34.10, p = .13, CFI = .96, RMSEA = .07]. The intervention promoted higher autonomous motivation and lower controlled motivation for PA at T2. In turn, changes in autonomous motivation from T1 to T2, significantly positively predicted changes from T1 to T2 in MVPA and subjective vitality. Controlled motivation did not significantly predict either outcome.

Conclusion: An SDT-based psychological intervention providing support for PA, may promote MVPA and more optimal psychological functioning in RA patients who are engaged in a tailored exercise programme.

Figure 1. Theoretical process model

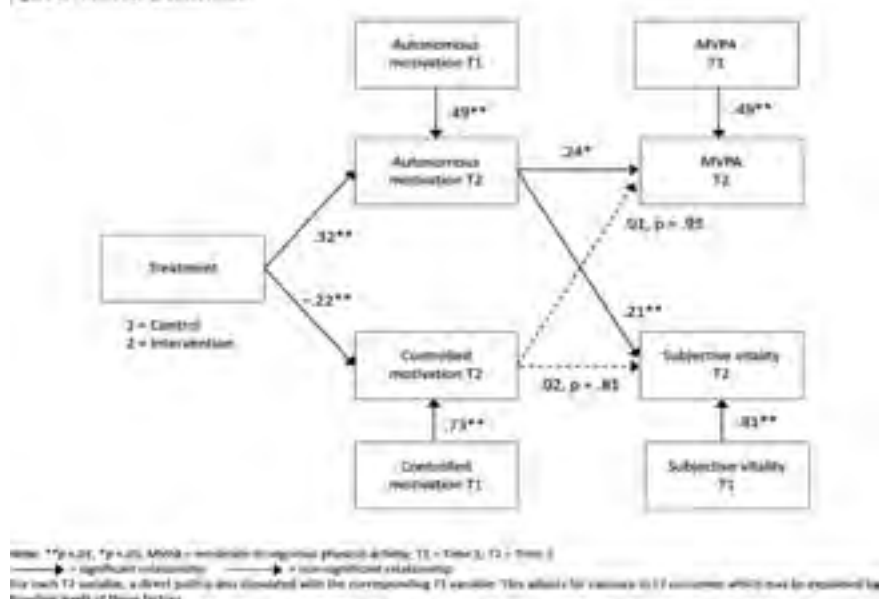


Table 1 Psychological intervention content for each contact with participants

Consultation	Contact	Duration	Behaviour change techniques
Baseline	Face-to-face	60 mins	<ul style="list-style-type: none"> • Elicit and acknowledge positive and negative experiences and emotions towards physical activity • Clarify the patient's knowledge regarding the benefits associated with increasing physically active behaviour specific to RA; gear discussions of these benefits to what is personally meaningful to the patient • Provide additional information requested by the patient • Encourage reflection on the links between physically active behaviour and personally meaningful life goals or events • Decisional balance • Patient centred goal setting
1 month	Telephone	10 mins	<ul style="list-style-type: none"> • Support attempts to change behaviour • Normalise failed attempts to be physically active • Problem solve to formulate strategies for enhancing self-efficacy • Elicit solutions to PA barriers • Review goals
2 month	Telephone	10 mins	<ul style="list-style-type: none"> • Encourage attempts made to be physically active • Brainstorm solutions to PA barriers • Discuss patient goals for last period of programme
3 month	Face-to-face	30 mins	<ul style="list-style-type: none"> • Recognise the institutionalisation of individual's PA participation • Have patients verbalise feelings towards physical activity • Discuss plans to be physically active in the future • Information regarding where it is possible to be physically active
5 month	Telephone	10 mins	<ul style="list-style-type: none"> • Discuss successful and failed attempts to maintain PA behaviour post exercise programme

Note: RA = Rheumatoid Arthritis; PA = physical activity.

Image reproduced/edited with permission from: Rouse PC, Veldhuijzen Van Zanten JCS, Metsios GS, Mtoumanis N, Yu C, Kouttsakis T, Fenton SAM, Coast J, Mistry H, Kitas GD, Duda JL. Fostering autonomous motivation, physical activity and cardiorespiratory fitness in rheumatoid arthritis: protocol and rationale for a randomised control trial. *BMC Musculoskeletal Disorders* 2014; 15:445.

Disclosure: S. A. M. Fenton, None; J. J. C. S. Veldhuijzen van Zanten, None; G. S. Metsios, None; P. C. Rouse, None; N. Ntoumanis, None; C. A. Yu, None; G. D. Kitas, None; J. L. Duda, None.

Abstract Number: 632

Interpretation of Symptoms Should Take into Account Gender in Psoriatic Arthritis: An Analysis of 451 Patients

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: Treatments targets in psoriatic arthritis (PsA) are remission (REM) or Low Disease Activity (LDA) which are usually defined based on objective disease activity but also patient-reported outcomes (PROs). The objective was to analyze if there was a gender difference for PROs in PsA, a real-life setting and if this difference was associated with disease activity.

Methods: ReFlap (NCT03119805) is a cross-sectional study in 14 countries of consecutive adult patients with definite PsA and more than 2 years of disease duration. Each patient underwent articular, enthesal and skin assessment and composite measures i.e. clinical Disease Activity in Psoriatic Arthritis (cDAPSA) and Minimal Disease Activity (MDA) were assessed. PROs were collected: Patient Global Assessment (PGA) (range 0-10), Health Assessment Questionnaire, HAQ-DI (0 - 3) and the Psoriatic Arthritis (PsA) Impact of Disease questionnaire (PsAID12) (comprising 12 questions including pain and fatigue with a final 0 – 10 score where 0 is perfect). Differences in scores between men and women were calculated and p-values were computed.

Results: Of 466 patients, 451 could be analyzed: 226 (50.1%) were men, mean age (standard deviation) was 53.1 (12.7) years, mean disease duration was 11.1 (8.2) years, 62.9% were taking conventional synthetic DMARDs and 60.6% a biologic. Disease activity was moderate: 9.5% had a Body Surface Area of psoriasis (BSA) $\geq 5\%$, mean Tender Joint Count (TJC 0-68) was 4.6 (9.4), mean Swollen Joint Count (SJC 0-66) was 2.1 (6.3). Overall, 62.1% patients had cDAPSA levels ≤ 13 and 37.9% fulfilled MDA5/7 (i.e. remission and low disease activity). Concerning PROs, mean PGA was 4.1 (2.9), mean HAQ-DI was 0.66 (0.67) and mean PsAID12 was 3.4 (2.5). According to gender, PROs were significantly higher in women: 4.7 (2.8), 0.86 (0.69) and 4.1 (2.5) in females versus 3.4 (2.9), 0.46 (0.60) and 2.7 (2.3) in males for PGA, HAQ-DI and PsAID12, respectively (all $p < 0.001$). When comparing components of PsAID12 scores, they were systematically higher in women (all $p < 0.01$) except skin problems (2.9 (3.0) females, 2.5 (2.6) males, $p=0.23$). Conversely, objective measures of disease activity didn't differ by gender: SJC 2.1 (5.7) females, 2.0 (6.8) males, $p=0.14$; BSA $\geq 5\%$: 8.4% females, 10.6% males, $p=0.49$, except for TJC: 5.4 (9.2) females, 3.8 (9.5) males, $p<0.001$ and CRP $>5\text{mg/L}$: 38.7% females, 30.1% males, $p=0.045$. MDA5/7 was less often reached in women: 25.8% females versus 50.0% males, $p<0.001$.

Conclusion: A significant gender difference was observed in this cross-sectional analysis of unselected PsA patients from 14 countries, with females reporting worse symptoms although musculoskeletal and skin disease activity was similar. This gender difference has to be taken into account when targeting remission or low disease activity, and in the overall management of PsA activity and impact.

Disclosure: C. Gorlier, None; L. Gossec, None; D. Puyraimond-Zemmour, None; L. C. Coates, None; U. Kiltz, None; Y. Y. Leung, None; P. Palominos, None; J. D. Cañete, None; R. Scrivo, None; A. R. Balanescu, None; E. Dernis, None; S. Tälli, None; A. Ruyssen-Witrand, None; M. Soubrier, None; S. Z. Aydın, None; L. Eder, None; I. Gaydukova, None; E. Lubrano, None; P. Richette, Fidia, 5, 8; M. E. Husni, None; M. de Wit, None; J. S. Smolen, None; A. M. Orbai, None.

Abstract Number: 633

The Effect of Guselkumab on Dactylitis: Results from a Phase 2 Study in Patients with Active Psoriatic Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

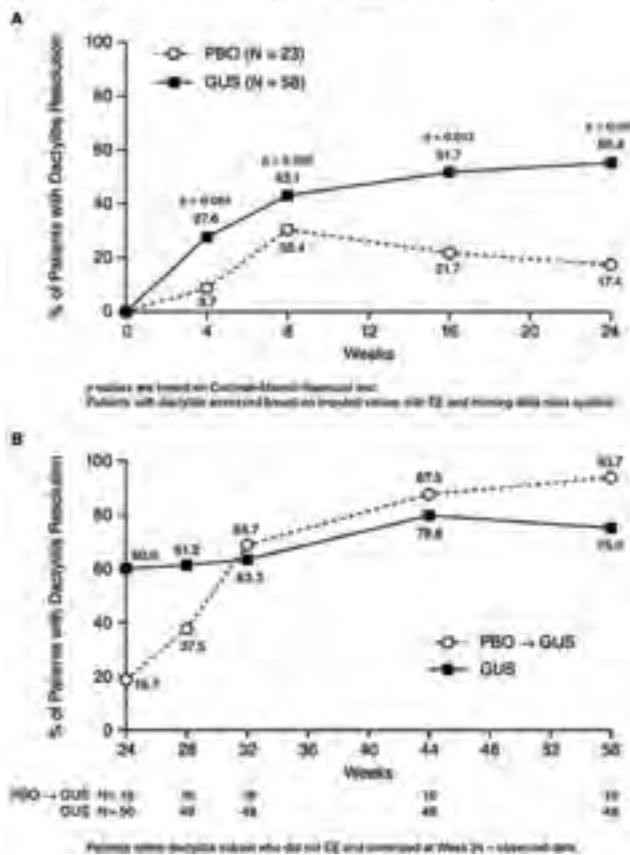
Session Type: ACR Poster Session A

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

Background/Purpose: In a Ph2 study, GUS was shown to be safe & effective in pts w/active PsA. We evaluated effect of GUS on dactylitis in subset of pts w/dactylitis at baseline (BL) from Ph2 GUS PsA study.

Methods: Pts w/active PsA & $\geq 3\%$ BSA of plaque PsO, despite current or previous treatment, were randomized 2:1 to 100mg SC GUS at wks0,4 then q8w or PBO during a 24wk double-blind treatment (tx) period. At wk16, pts w/ $<5\%$

Figure. Proportion of Patients with Dactylitis Resolution over Time



improvement in swollen & tender joint counts (SJC/TJC) early escaped (EE). At wk24, PBO group (grp) crossed over to GUS (wks24, 28→ q8w) (PBO→GUS) & GUS grp continued GUS (GUS→GUS)) thru wk44. Dactylitis was assessed by scoring each digit from 0-3(0=absent, 1=mild, 2=mod, 3=sev), for combined score of 0-60. Sensitivity analysis of change from BL thru wk24 in dactylitic digits was performed(combined score 20). Dactylitis scores during 24wk double-blind tx was analyzed using LOCF imputation for missing data & EE. Dactylitis after wk24 was evaluated using observed data.

Results: Of 149 pts,81 presented w/dactylitis at BL(PBO N=23,mean[SD]=3.9[3.01];GUS N=58, mean[SD]=6.5[6.15]) & 66 continued to active tx period(PBO→GUS N=16;GUS→GUS N=50).The dactylitis subset was similar to overall population in BL characteristics except for higher median values for # of SJC, # of TJC,&CRP. At wks16&24, GUS grp had significantly greater reduction in dactylitis score (wk24 mean [SD] change from BL, PBO:-0.4[6.06]; GUS:-3.8[4.93]; p=0.006)&a greater % of pts w/dactylitis resolution vs PBO grp(Figure). Consistent results were obtained w/# digits w/ dactylitis (wk24 mean [SD] change from BL, PBO:-0.2[3.04];GUS:-2.1[2.21];p=0.003). Improvement in dactylitis seen at wk24 was maintained in GUS→GUS grp(wk56:mean[SD] change from BL=-5.5[4.84],75% of pts w/resolution)& the values for the PBO→GUS grp(wk56:mean[SD]change from BL=-4.4[3.50],93.7% of pts w/resolution)approached those of GUS→GUS grp. Improvement in dactylitis was greater in ACR20/ACR50 responders vs non-responders in GUS-txd pts (Table) &was significantly correlated with improvement in TJC(R=0.38,p=0.004),SJC(R=0.50,p<0.0001),&HAQ-DI score(R=0.33, p=0.013).

Conclusion: GUS is efficacious in resolving symptoms of dactylitis in pts w/active PsA. This effect on dactylitis is correlated with improvement in joint symptoms & physical function.

Table 1. Change in Dactylitis Score in ACR20/50 and PASI75 Responders and Non-responders

	Mean (SD) change from BL in Dactylitis Score at Wk24		
	Non-responders	Responders	p-value
ACR 20	-1.76(7.595), n=21	-4.94(4.666), n=36	0.044
ACR 50	-2.44(6.213), n=36	-6.05(5.133), n=21	0.027
PASI 75	-4.00(2.858), n=13	-3.70(6.736), n=44	0.924

Disclosure: D. D. Gladman, Janssen Research & Development, LLC, 2; W. H. Boehncke, Janssen Research & Development, LLC, 2; A. B. Gottlieb, Janssen Research & Development, LLC, 2; P. Helliwell, Janssen Research &

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Abstract Number: 634

Spinal Mobility Measures Allow Discrimination of Subgroups of Different Activity and Severity in Early Axial Spondyloarthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: Spinal mobility has been mostly investigated in cohorts of patients with established AS. However, it was scarcely studied in the early phases of the disease and how the impairment in mobility across different measures behaves as compared to normal subjects. The purpose of this study was to investigate 1) which spinal mobility measures (SMMs) are most frequently impaired and in which order; 2) which SMMs are most discriminative of activity and severity in early axial Spondyloarthritis (axSpA).

Methods: All SMM measurements of patients from the DESIR (5-year data) and SPACE (data from Leiden University Medical Center, 2.6 (1.9) years of follow-up) cohorts and with a clinical diagnosis of axSpA (level of confidence $\geq 7/10$) were analyzed. SMMs were considered impaired when falling below pre-defined cut-offs, derived from normal individuals¹. The proportion of patients with each of the SMMs impaired was calculated, for both baseline and all observations. The BASMI, being a composite index, was not considered in the ranking of impairment of spinal mobility and only the level of impairment is presented. The same analysis was conducted in subgroups to contrast patient and disease characteristics potentially influencing spinal mobility, like treatment with biologics (ever/never), disease activity (with/without low disease activity over time, i.e., ASDAS <2.1 in $\geq 2/3$ of visits) and the presence of baseline syndesmophytes (yes/no).

Results: We included 328 (54% males, mean (SD) age of 32 (8) years) and 148 (64% females, mean (SD) age of 30 (9) years) patients from the DESIR and SPACE cohorts, respectively. No strict and fixed order of impairment in SMMs was seen in both cohorts. Considering patients in whom all SMMs were assessed, in DESIR, the most frequently impaired SMM (below 2.5th percentile) was mSchober (42%), followed by Lateral Spinal Flexion (LSF; 37%), Tragus-to-wall (16%), Cervical rotation (16%) and Chest expansion (11%). In SPACE, the order of impairment was: LSF (36%), mSchober (14%), Chest expansion (13%), Cervical rotation (11%) and Tragus-to-wall (3%). LSF and mSchober captured the

Table 1. Impairment of each of the spinal mobility measures and of the BASMI score in patients with early axSpA from the DESIR cohort, stratified by subgroups to contrast patient and disease characteristics potentially influencing spinal mobility ‡

	Without ASDAS ≥ 2.1 in $\geq 2/3$ of visits (n=118)	Ever treated with biologics (n=321)	With syndesmophytes at baseline (n=62)
mSchober (cm)	485 (42)	589 (36)	76 (37)
Lateral Spinal Flexion (cm)	460 (37)	563 (44)	57 (36)
Tragus-to-wall (cm)	171 (16)	150 (16)	22 (37)
Cervical rotation (degrees)	177 (16)	142 (17)	18 (29)
Chest expansion (cm)	169 (11)	151 (11)	11 (18)
BASMI-modified (0-10) †	451 (42)	378 (43)	29 (45)
	With ASDAS <2.1 in $\geq 2/3$ of visits (n=65)	Never treated with biologics (n=53)	Without syndesmophytes at baseline (n=64)
mSchober (cm)	304 (51)	481 (33)	46 (34)
Lateral Spinal Flexion (cm)	343 (27)	346 (28)	232 (34)
Tragus-to-wall (cm)	74 (11)	86 (15)	73 (11)
Cervical rotation (degrees)	39 (8)	75 (8)	63 (13)
Chest expansion (cm)	75 (15)	78 (11)	11 (7)
BASMI-modified (0-10) †	154 (24)	227 (25)	234 (38)

Legend: mS: spinal mobility measure (SMM) most frequently impaired; orange: 2nd SMM most frequently impaired; yellow: 3rd SMM most frequently impaired; light green: 4th SMM most frequently impaired; dark green: SMM least frequently impaired.
 † Impairment was defined as a value below the 2.5th percentile in normal individuals, and is presented at the observation level (n (%)) of all 5-year observations.
 ‡ BASMI-modified: calculated with cervical rotation in sitting position and 10-cm Schober's test, using the linear method (sum of the five scores: Lateral Spinal Flexion, 10-cm Schober's test, Cervical rotation, intermammary distance and Tragus-to-wall distance).

majority of patients with ≥ 1 SMM impaired (86% and 78% for DESIR and SPACE, respectively). LSF and BASMI best discriminated between subgroups of patients, with higher impairment in patients ever treated with biologics, with higher disease activity and presence of baseline syndesmophytes (Table 1, data from DESIR). Similar results were obtained in the SPACE cohort.

Conclusion: LSF and mSchober are the most impaired SMMs, together allowing the identification of the majority of patients with impaired spinal mobility in early axSpA. LSF and BASMI discriminate best between subgroups of patients, reflecting a worse spinal mobility in patients with more active and severe disease.

¹Ramiro S et al. Ann RheumDis. 2015 Jun;74(6):1218-24.

Disclosure: M. L. Marques, None; S. Ramiro, None; F. van Gaalen, None; P. Goupille, None; M. Dougados, None; D. van der Heijde, None.

Abstract Number: 635

Measuring Spinal Mobility over Time in Early Axial Spondyloarthritis: Can We Do It Reliably?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

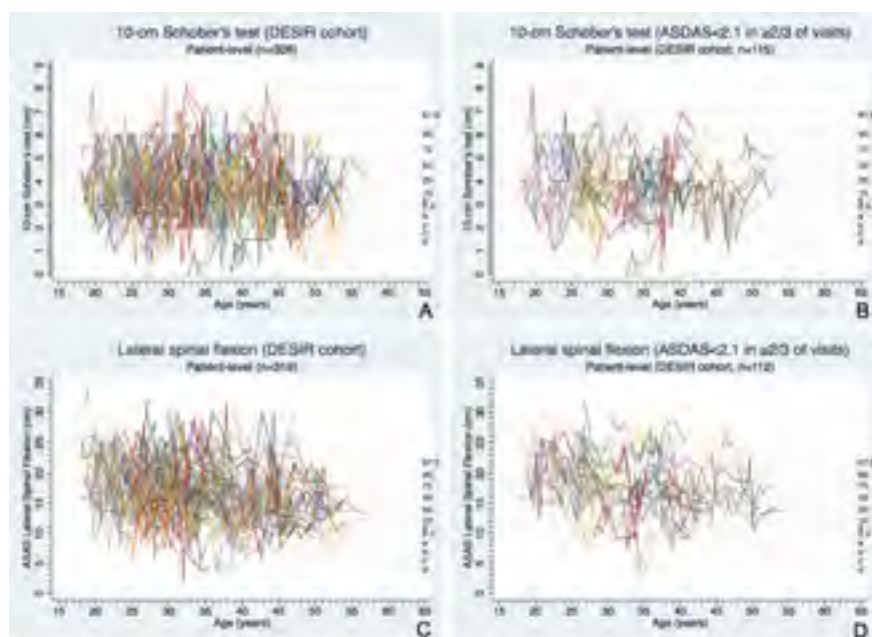


Figure 1. Measurements of 10-cm Schober's test and Lateral Spinal Flexion in DESIR cohort axSpA patients in function of age: A) 10-cm Schober's test in all axSpA patients; B) 10-cm Schober's test in axSpA patients with low disease activity in at least 2/3 of visits; C) Lateral Spinal Flexion in all axSpA patients; D) Lateral Spinal Flexion in axSpA with low disease activity in at least 2/3 of visits. The dotted lines represent the percentile curves derived from the normal individuals (percentiles indicated) and also the help-lines (a' to d'), derived to accommodate impaired values of patients with axSpA. The colored lines represent all the real measurements of Schober's test and Lateral Spinal Flexion, for each patient, over time.

Background/Purpose: The use of spinal mobility measures (SMMs), at the individual level and in the follow-up of patients with early axSpA has not yet been studied. The purpose of our study was to investigate the longitudinal use of SMMs and the relation with mobility curves of healthy individuals in patients with early axSpA.

Methods: All SMMs of patients from the DESIR (5-year data) and SPACE (data from Leiden University Medical Center, 2.6 (1.9) years of follow-up) cohorts and with a clinical diagnosis of axSpA (level of confidence $\geq 7/10$) were analysed. All available SMMs were plotted for each patient in function of age, and together with the percentile curves derived for healthy volunteers, the mobility curves¹. A subgroup analysis was performed in patients with low disease activity over time (ASDAS < 2.1 in $\geq 2/3$ of visits), in order to control for the influence of disease activity on spinal mobility. Intra- and inter-observer reliability were analyzed using Intraclass Correlation Coefficients (ICC) and the Smallest Detectable Change (SDC) in the SPACE cohort.

Results: We included 328 (54% males, mean (SD) age of 32 (8) years) and 148 (64% females, mean (SD) age of 30 (9) years) patients from the DESIR and SPACE cohorts, respectively. The mean number of observations with assessment of SMMs was 7 (1.1) and 4 (1.7) per patient in DESIR and SPACE cohorts, respectively. A high variability in SMMs within the same patient over time was observed, with very discrepant values for the same SMM from visit to visit, even when restricting the analysis to patients with low disease activity over time. Figure 1 shows the results for 10-cm Schober's test and Lateral Spinal Flexion (LSF) in the DESIR cohort. The results were strikingly similar for all the SMMs and in both cohorts. The reliability of SMMs was only "fair" to "good" (inter-reader ICC (2,1): 0.55-0.84; intra-reader ICC (2,1): 0.49-0.72). The obtained SDCs reflect that large variations in SMMs are needed to capture a true change beyond measurement error (e.g. 1.4 cm for 10-cm Schober's test; 5.1 cm for LSF; 2.2 cm for Chest expansion and 12.2 degrees for Cervical rotation).

Conclusion: There is a high variation of SMMs from visit to visit, which impairs the use of spinal mobility measures, at the individual level in the follow-up of patients with axSpA. It should be tested if reliability can be improved to reduce at least part of the variability.

¹Ramiro S et al. Ann Rheum Dis. 2015 Jun;74(6):1218-24.

Disclosure: M. L. Marques, None; S. Ramiro, None; F. van Gaalen, None; P. Goupille, None; M. Dougados, None; D. van der Heijde, None.

Abstract Number: 636

Remission/Low Disease Activity Is a Reasonable Treatment Target in PsA: Results from a Routine Care European Cohort of PsA Patients Treated with Ustekinumab or TNF Inhibitors

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SESSION INFORMATION

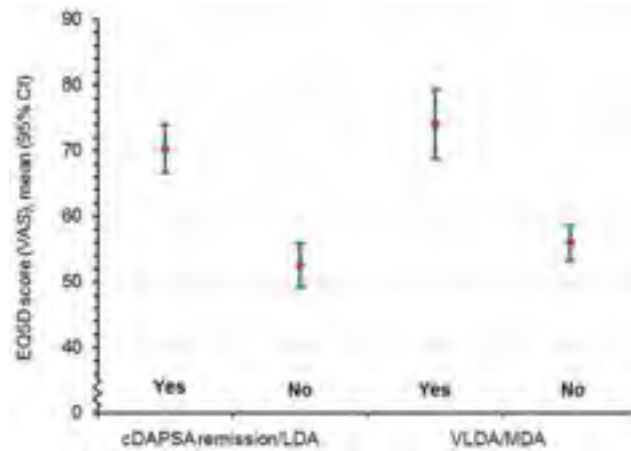
Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: The link between treatment recommendations for PsA (to aim for a state of remission or low disease activity (LDA))^{1,2} and patient-important outcomes has been little explored. The objective of this analysis was to investigate the potential of remission or LDA according to the clinical Disease Activity Index for PsA (cDAPSA) and achievement of very low/minimal disease activity (VLDA/MDA) during treatment with ustekinumab (UST) or TNF inhibitor (TNFi), as well as the association between these outcomes and health-related quality of life (HRQoL).



Methods: PsABio (NCT02627768) is an ongoing real-world observational study in eight European countries where PsA patients receive 1st-, 2nd- or 3rd-line biologics (either UST or TNFi). Of 563 UST- or TNFi-treated patients enrolled Dec 2015 – Aug2017, 303 had data available at 6 months and were analyzed here. Disease states were defined using cDAPSA ≤ 4 for remission and ≤ 13 for LDA (data available for 250 patients) and VLDA 7/7 and MDA 5/7 criteria (data available for 206 and 260 patients, respectively), and HRQoL using EQ5D (data available for 249 patients with MDA availability). Available observed data are presented, with no imputation of missing data.

Results: For the 303 patients analyzed, mean age was 49.7 (standard deviation, SD 12.8) years, mean disease duration was 7.2 (SD 8.2) years, and 50.5% were women. The table shows data at 6 months for cDAPSA remission, cDAPSALDA, VLDA, and MDA in UST- and TNFi-treated patients. cDAPSA remission/LDA and VLDA/MDA achievement (Yes vs No) were associated with better HRQoL based on mean (95% confidence interval, CI) EQ5D visual analog scale (VAS) at 6 months, as shown by non-overlapping CIs in the figure. Assessment of Psoriasis Skin Disease (68/299=22.7%) was the most frequently missed MDA component, while enthesitis was the least frequently missed (6/299=2.0%). The other five components were all missed with equal frequency (8–9%).

	UST-treated patients n/N (%)	TNFi-treated patients n/N (%)
cDAPSA remission (cDAPSA ≤ 4)	25/126 (19.8)	25/124 (20.2)
cDAPSA LDA (including remission) (cDAPSA ≤ 13)	64/126 (50.8)	66/124 (53.2)
VLDA	11/102 (10.8)	12/104 (11.5)
MDA (including VLDA)	38/132 (28.8)	38/128 (29.7)

Conclusion: Remission and/or LDA appeared to be reachable outcomes in this real-world study, since among patients treated with UST or TNFi for 6 months, cDAPSA remission/LDA was achieved by approx. 50% of patients, and VLDA/MDA by approx. 30% of patients, irrespective of the type of therapy. Furthermore, these disease states were associated with improved HRQoL, making these outcomes patient-relevant.

1. Gossec L, et al. *Ann Rheum Dis*.2016;75(3):499–510.
2. Smolen JS, et al. *Ann Rheum Dis*.2017;77(1):3–17.

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How to Define Remission and Low Disease Activity in Psoriatic Arthritis? an Analysis of 419 Patients with a Double Perspective, Based on Composite Scores and Patients' and Physicians' Perspectives

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

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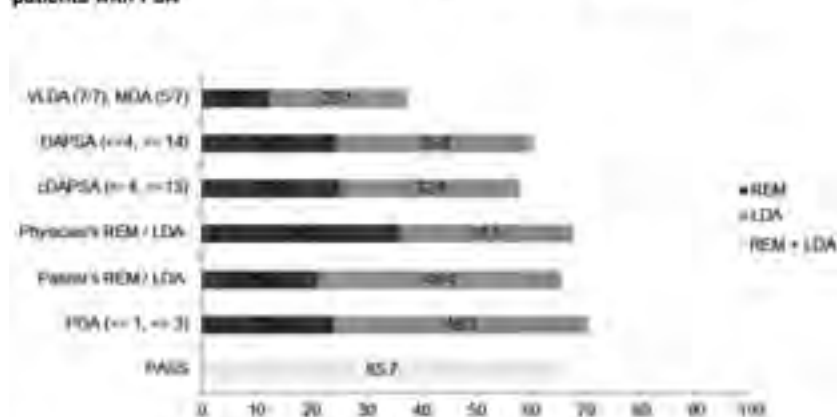
Session Time: 9:00AM-11:00AM

Background/Purpose: Remission (REM) or minimal/low disease activity (LDA) is the treatment goal in Psoriatic Arthritis (PsA). There is no consensus on definitions of REM/LDA. Recently, composite measures of disease activity have been compared but this comparison did not address the patient's perspective (ref).

The objectives were to assess frequency of REM/LDA using different definitions, and agreement between these definitions according to the patient's and physician's perspectives.

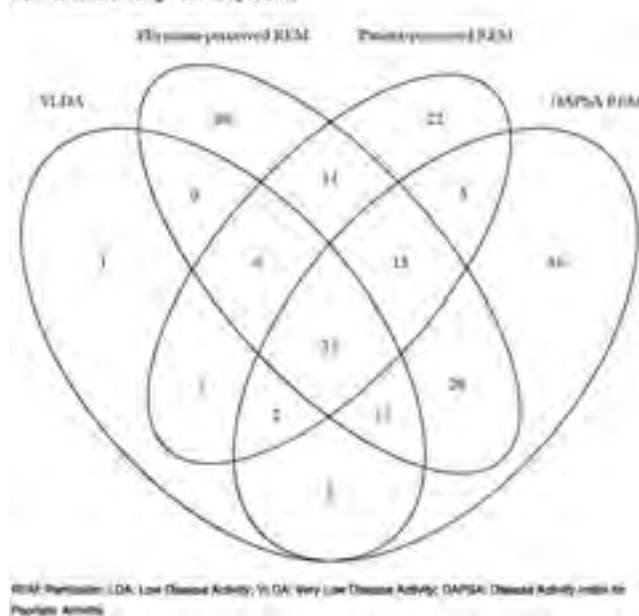
Methods: ReFlap (NCT03119805) is a cross-sectional study in 14 countries of consecutive adults with definite PsA and more than 2 years of disease duration. REM and LDA were defined using Very Low Disease Activity (VLDA), Minimal

Figure 1 Prevalence of REM/LDA according to different definitions in 419 patients with PsA



REM: Remission; LDA: Low Disease Activity; VLDA: Very Low Disease Activity; MDA: minimal disease activity; DAPSA: Disease Activity Index for Psoriatic Arthritis; cDAPSA: clinical DAPSA; Physician's REM/LDA: physician's single question for REM/LDA; Patient's REM/LDA: patient's single question for REM/LDA; PGA: patient global assessment; PASS: Patient Acceptable Symptom Status.

Figure 2 Venn diagram representing the number of patients meeting different REM criteria among 419 PsA patients.



Disease Activity (MDA), Disease Activity in Psoriatic Arthritis (DAPSA), clinical DAPSA (cDAPSA) and Patient Global Assessment (PGA). Furthermore, REM and LDA were assessed using specific single questions for the physician and the patient (Figure 1: physician and patient REM/LDA).

Proportions achieving each REM/LDA criterion were calculated. The agreement between the tested definitions was assessed by Venn diagram and calculation of kappa and prevalence-adjusted and bias-adjusted kappa (PABAK).

Results: Of 466 patients, 419 had data available for all definitions of REM/LDA: 212 (51.3%) were male, mean age was 53.9 ± 12.6 years and mean disease duration 11.3 ± 8.4 years, 59.0% were taking a biologic. Disease activity was moderate: 9.5% had a Body Surface area of psoriasis $\geq 5\%$, mean Tender and Swollen Joint Counts were respectively 4.9 ± 9.7 and 2.3 ± 7.2 . The frequency of REM varied from 12.2% (VLDA) to 21.0% (Physician REM question) and of LDA from 25.1% (MDA) to 46.3% ($\text{PGA} \leq 3$) (Figure 1). Agreement was moderate between the composite scores for REM (kappa DAPSA/VLDA 0.57, cDAPSA/VLDA 0.59). Agreements were lower for LDA whatever the definition used. Agreement between patient-defined REM/LDA and composite scores was only moderate. In particular, 36/88 (40.9%) of patients in patient-perceived REM were not in REM according to any composite score. Moreover, agreement between patient and physician REM occurred in 58/148 (39.0%) patients (Figure 2).

Conclusion: In this unselected population, REM/LDA was frequently attained. VLDA/MDA was a more stringent definition than DAPSA-based REM/LDA. Patient-assessed REM/LDA was similar in terms of prevalence to DAPSA, though agreement between patients and composite scores was only moderate. Further studies of patients' expectations are needed.

Reference. van Mens LJJ *et al.* Ann Rheum Dis. 2018

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Abstract Number: 638

Diagnostic Delay and Associated Factors in Axial Spondyloarthritis across Europe. Results from the European Map of Axial Spondyloarthritis Survey

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

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

Background/Purpose: Axial Spondyloarthritis (axSpA) is a chronic inflammatory disease associated with a long diagnostic delay (DD); however, recent data suggests improvements¹. The purpose was to assess the evolution of DD over time as reported by European axSpA patients and to identify factors associated with DD.

Methods: Between July 2017 and February 2018, 2846 axSpA patients participated in the European Map of Axial Spondyloarthritis (EMAS) survey across 13 countries. DD was patient-reported and defined as the time between symptom onset and formal diagnosis. Socio-demographics (gender, country, education, and relationship status), disease characteristics (report of extra-articular manifestations, HLA-B27 positive and axSpA subtype) and year of onset were assessed using bivariate Mann-Whitney and Kruskal-Wallis homogeneity tests and Pearson correlation coefficient. Moreover, a stepwise forward linear regression was conducted using variables that were significantly associated with DD.

Results: Of the 2846 patients, 61.4% were female. The mean age was 43.9 (SD 12.3) years. 85.5% self-reported having AS (n=2394/2800), 73.9% were HLA-B27 positive (n=1282/1735), and 50.7% had received biologic treatment (n=953/1880). The mean DD was 7.4 (SD 8.4) years with a median of 4.0 years. The bivariate analysis showed that DD was associated with the female gender, participant's country and year of onset but not associated with educational level, relationship status or disease characteristics (Table 1). Stepwise forward regression also showed that all the variables with bivariate association had significant explanatory power over DD. There was a significant correlation between year of onset and DD; the more recent the disease onset, the shorter the DD (Pearson correlation -0.55; p<0.001) (Figure 1).

Conclusion: Despite recent progress in the field of axSpA, DD remains high in Europe (7.4 years). However, EMAS results show that DD is decreasing over time. The strongest factors associated with a longer DD were in order: female gender, country and earlier year of onset. Increased understanding of the factors associated with DD is needed to support earlier diagnosis.

1. Sørensen et al. Diagnostic delay in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis: results from the Danish nationwide DANBIO registry. *Annals of the Rheumatic Diseases* 2015;74:e12.

Table 1. Diagnostic delay by patient characteristics and significance in bivariate and multivariable analyses

Variable	Mean (SD) DD if YES	Mean (SD) DD if NO	P-value Bivariate	Beta (95% CI) multivariable
Gender, Male	6.1 (7.4)	8.2 (8.9)	<.0001	2.53 (1.87-3.19)
Relation status, In relationship	7.5 (8.5)	7.2 (8.1)	.876	NA
Country	NA	NA	<.0001	.219 (0.12-0.32)
Year of onset	7.44	<.0001	.001 (0.000-0.002)	
Subtype, AS vs other	7.3 (8.2)	7.8 (9.4) to 8.3 (9.6)	.760	NA
HLA B27+	8.3 (8.3)	9.0 (9.3)	.775	NA
Extra-articular manifestations, Uveitis	8.0 (8.3)	7.6 (8.4)	.098	NA
Extra-articular manifestations, Crohn's disease	7.7 (8.7)	7.5 (8.4)	.786	NA
Extra-articular manifestations: Psoriasis	7.2 (8.8)	6.1 (7.6)	.239	NA

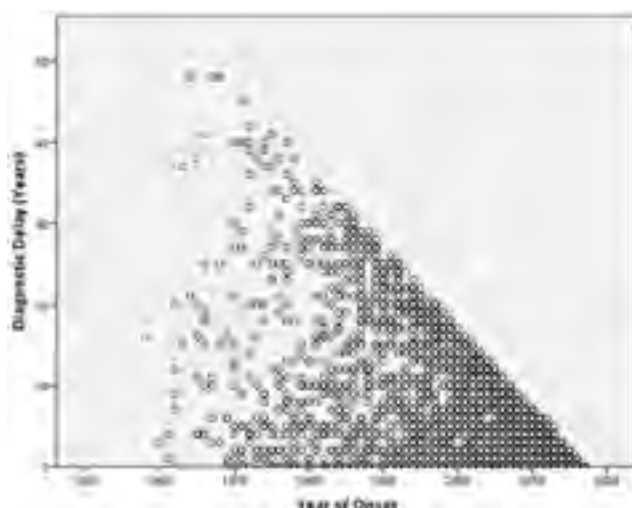


Figure 1. Scatter diagram for year of disease onset and diagnostic delay (N: 2,652)

Disclosure: L. Gossec, None; M. Garrido-Cumbrera, None; D. Poddubnyy, None; D. Galvez-Ruiz, None; C. Bundy, None; C. J. Delgado Dominguez, None; R. Mahapatra, None; P. Plazuelo-Ramos, None; S. Makri, None; V. Navarro-Compán, None.

Abstract Number: 639

Is a Primary Good Response to Nsaids Predictive of the Subsequent Response to the First TNF Inhibitor in Patients with Early Axial Spondyloarthritis ?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: Good response to NSAIDs is a SpA feature included in classification criteria for axial spondyloarthritis (axSpA). Among patients eligible for a TNF inhibitor (TNFi), some patients may have never responded to NSAIDs (NSAIDs non-responders) while others primary responded before secondary failure (NSAIDs responders). Our aim was to determine if the primary NSAIDs response is an independent predictive factor of a subsequent good response to the first TNFi in patients with early axSpA.

Methods: *Patients:* Subjects from the prospective observational DESIR cohort of early axSpA cohort who started a TNFi over the 5 years of follow-up.

NSAIDs response and TNFi response definitions: NSAIDs response was defined by the item “good response to NSAIDs according to Amor’s criteria” at the inclusion visit. TNFi response was defined by the BASDAI50 response between the “baseline” visit (last cohort visit before TNFi initiation) and the “follow-up” visit (visit taking place after at least 8 weeks of TNFi treatment).

Analysis

We compared the characteristics of the NSAIDs responder to the non-responders and their response to the first TNFi. We performed a multivariate logistic regression modeling the impact of an NSAID response to the TNFi response. We included known predictive factors of TNFi response in this model (age, gender, HLAB-B27, activity of the disease [ASDAS-CRP], CRP, X- ray and MRI sacroiliitis). To account for selection bias and for confirmation purpose, we applied a propensity score with Inverse Probability Weighting (IPW) method to predict TNFi response (SAS, version 9.2).

Results: Among the 708 patients of the cohort, 236 were included in the analysis. At baseline, the main characteristics were the following: 106 (44.9%) males, mean age 33.9 ± 8.9 years, mean BASDAI 54.4 ± 17.3 and 202 (85.6%) were NSAIDs responders. The NSAIDs responder and non-responder groups were comparable at M0 except for HLA-B27 positive status: 59.9% vs 41.2%, $p = 0.041$, history of psoriasis: 17.8% vs 35.3%, $p = 0.019$ and BASDAI: 53.0 ± 18.1 vs 61.8 ± 13.2 , $p = 0.001$, in responder and non-responder patients, respectively. The percentage of TNFi responders was 32.2% (65/202) and 23.5% (8/34) in the NSAIDs responder and non-responder groups, respectively (univariate analysis (OR 1.5 [IC95%: 0.7-3.6], $p = 0.313$).

The multivariate logistic regression found the following independent factors of the TNFi response: gender [adjusted OR (aOR) = 2.9 [CI95%: 1.4–6.0], $p=0.004$], age [aOR = 0.9 [CI95%: 0.91-0.99], $p=0.026$], HLA-B27 status [aOR = 2.5 [CI95 %: 1.2–5.3], $p = 0.02$], ASDAS-CRP score [aOR=1.6 [CI95 %: 1.1–2.4], $p = 0.016$], and MRI sacroiliitis [aOR = 2.0 [CI95 %: 1.0–4.2], $p = 0.054$]. Response to NSAIDs was not significantly associated to the response to the TNFi [aOR = 1.93 [CI95 %: 0.6-6.3], $p = 0.275$]. The IPW aOR confirmed the non-association between NSAIDs good response and TNFi good response: 1.60 [CI95%: 0.7–3.3], $p = 0.20$.

Conclusion: NSAIDs good response, according to the Amor’s criteria, does not seem to be an independent predictive factor of the subsequent TNFi response in early axSpA patients.

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Increasing Rates of Arthroplasty for Psoriatic Arthritis in the United Kingdom between 1995 and 2010

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SESSION INFORMATION

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Session Type: ACR Poster Session A

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

Background/Purpose: Arthroplasty requirements among patients with psoriatic arthritis (PsA) are not well known. This information is of importance to clinical and policy stakeholders for health system planning, and may serve as a surrogate for estimating the efficacy of disease-modifying therapy. Moreover, arthroplasty rates may be used as a proxy measure of how advanced medical therapy has contributed to the prevention of advanced-stage disease, as has been done previously for rheumatoid arthritis.

Methods: We utilized The Health Improvement Network (THIN), a large general practice medical records database in the United Kingdom to assess rates of first primary total arthroplasty among patients with PsA and the general population between the years 1995 and 2010. Linear regression was used to estimate arthroplasty rates for the two cohorts over the study period, and Poisson regression was used to determine incidence rate ratios (IRRs) between the PsA and general population cohorts, adjusted for age and sex. Chi-square tests were used to compare incidence rates across years between the two cohorts.

Results: We identified 5,619 patients with incident PsA and 5,090,814 eligible patients from the general population between 1995 and 2010. In total, 187 first primary total arthroplasties were documented in patients with PsA, and 80,165 first primary total arthroplasties were documented in the general population. A trend of increased arthroplasty rates were observed for both the PsA ($R^2=0.809$, $p<0.0001$) and general population ($R^2=0.890$, $p<0.0001$) cohorts over the study period. After adjustment for age and sex, PsA patients had a first arthroplasty incidence rate twice that of the general population (IRR=2.01, 95%CI 1.73-2.34, $p<0.0001$), notably beyond year 2003 when biologic therapies were introduced (Fig. 1).

Conclusion: Both general population and PsA patients have experienced increased rates of first arthroplasty from 1995 to 2010, although the overall incidence rate was significantly higher for those with PsA. There are a number of possibilities that could explain this finding such as patients living longer with PsA, or new biologic therapies making PsA patients better surgical candidates. Further research exploring these possibilities will be needed in the coming years.



Figure 1. Incidence rates (with 95% Confidence intervals) of first arthroplasty are shown for both the psoriatic arthritis cohort (blue circles) and the general population cohort (orange squares). The incidence rate of arthroplasty has increased for both groups from 1995 to 2010. *indicates significant difference in incidence rates by Chi-square test. Evaluation of the overall incidence rate ratio (IRR) revealed PsA patients had an incidence rate of first arthroplasty twice that of the general population (IRR 2.01, 95%CI 1.73-2.34, $p<0.0001$).

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Abstract Number: 641

Construct Validity of the Swollen and Tender Joint Counts for the Measurement of MSK Disease Activity in Psoriatic Arthritis

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SESSION INFORMATION

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Background/Purpose: Joint counts are central to the measurement of musculoskeletal disease activity in psoriatic arthritis (PsA). Few studies have addressed whether the three most commonly used joint counts: 66/68-Swollen and Tender Joint Counts (SJC66/68TJC), SJC28/TJC28 and SJC76/TJC78, are valid for the measurement of musculoskeletal disease activity. To test the construct validity of the joint counts, we examined the correlations between the joint counts and other variables associated with MSK disease activity. We hypothesized that joint counts would be strongly correlated (ρ 0.8-1) with each other, moderately correlated (ρ 0.6-0.8) with the physician global assessment (PhGA), and mildly correlated (ρ 0.4-0.6) with patient global assessment (PtGA), pain, health assessment questionnaire disability index (HAQ-DI) and C-reactive protein (CRP).

Methods: Data were requested from 8 phase III randomized controlled trials (RCTs) and the Tight Control of Psoriatic Arthritis (TICOPA) trial. A priori, a standardized protocol was designed to study construct validity. Spearman's correlation coefficients were calculated (all data were skewed/nonparametric) at baseline and the primary endpoint (12-16 weeks for most RCTs, 24 weeks for TICOPA) between the following variables: TJC28, TJC68, TJC78, SJC28, SJC66, SJC78, PtGA, pain, PhGA, HAQ-DI and CRP. We also calculated Spearman's correlation coefficients between changes in each of the variables from baseline to follow up.

Results: The SJC28 was moderately to strongly correlated with SJC66 and SJC76 at baseline and follow up and changes in SJC28, SJC66, and SJC76 were moderately correlated (Table). Similarly, the TJC28 was strongly correlated with TJC68 and TJC78 at both time points as well as among changes in the joint counts between baseline and follow up. There were mild-to-moderate correlations between SJC and TJC at both time points and similarly changes in joint counts were moderately correlated. The joint counts had low to moderate correlations with PhGA in all three scenarios and correlations with PtGA and pain were low to moderate, depending on the RCT. Finally, correlations between joint counts and CRP were low in all three scenarios.

Conclusion: These results indicate that SJC and TJC have construct validity and replicated most of the pre-hypothesized relationships with other variables of importance in RCTs. While good correlation between TJC and SJC subsets were

Table. Correlation among disease activity measures at baseline, follow up and change in disease activity measures between baseline and the primary endpoint.

Baseline	TJC68	SJC66	TJC28	SJC28	TJC78	SJC76
SJC66	0.6 (0.53-0.66)					
TJC28	0.86 (0.83-0.90)	0.53 (0.48-0.58)				
SJC28	0.52 (0.46-0.6)	0.81 (0.66-0.88)	0.68 (0.5-0.7)			
TJC78	0.99	0.51	0.85 (0.84-0.85)	0.51 (0.43-0.58)		
SJC76	0.53	0.98	0.52 (0.46-0.58)	0.81 (0.8-0.82)	0.58 (0.52-0.63)	
Physician global	0.32 (0.11-0.54)	0.29 (0.06-0.55)	0.29 (0.13-0.46)	0.25 (0.12-0.40)	0.09 (0.09-0.14)	0.22 (0.19-0.25)
Patient global	0.28 (0.16-0.47)	0.17 (0.11-0.37)	0.27 (0.16-0.37)	0.15 (0.01-0.25)	0.28 (0.11-0.28)	0.16 (0.10-0.16)
Patient pain	0.25 (0.13-0.45)	0.14 (0.05-0.35)	0.24 (0.18-0.36)	0.15 (0.07-0.25)	0.22 (0.15-0.22)	0.13 (0.13-0.16)
CRP	0.04 (-0.03-0.16)	0.13 (-0.01-0.25)	0.04 (-0.02-0.17)	0.11 (-0.02-0.22)	0.0 (-0.04-0.04)	0.01 (-0.02-0.15)
HAQ	0.4 (0.33-0.51)	0.23 (0.18-0.45)	0.41 (0.28-0.51)	0.27 (0.18-0.39)	0.39 (0.25-0.39)	0.17 (0.17-0.20)
Follow up						
SJC66	0.58 (0.44-0.65)					
TJC28	0.91 (0.85-0.93)	0.55 (0.44-0.62)				
SJC28	0.54 (0.39-0.62)	0.88 (0.78-0.95)	0.6 (0.54-0.71)			
TJC78	0.99	0.48	0.83 (0.82-0.84)	0.47 (0.37-0.56)		
SJC76	0.51	0.98	0.51 (0.45-0.56)	0.69 (0.64-0.73)	0.56 (0.5-0.62)	
Physician global	0.54 (0.34-0.69)	0.45 (0.13-0.55)	0.5 (0.35-0.67)	0.35 (0.22-0.47)	0.4 (0.33-0.46)	0.36 (0.33-0.39)
Patient global	0.5 (0.28-0.60)	0.33 (0.2-0.42)	0.5 (0.25-0.59)	0.28 (0.17-0.40)	0.3 (0.28-0.32)	0.24 (0.22-0.25)
Patient pain	0.49 (0.25-0.59)	0.34 (0.18-0.40)	0.51 (0.25-0.60)	0.28 (0.15-0.36)	0.32 (0.24-0.4)	0.25 (0.2-0.29)
CRP	0.19 (0.09-0.24)	0.24 (0.12-0.29)	0.17 (0.10-0.21)	0.2 (0.09-0.27)	0.15 (0.12-0.18)	0.11 (0.10-0.11)
HAQ	0.55 (0.26-0.55)	0.26 (0.21-0.35)	0.37 (0.25-0.57)	0.19 (0.10-0.33)	0.3 (0.25-0.34)	0.22 (0.21-0.22)
Change between baseline and primary endpoint						
SJC66	0.63 (0.49-0.65)					
TJC28	0.85 (0.81-0.91)	0.54 (0.43-0.61)				
SJC28	0.5 (0.33-0.59)	0.82 (0.68-0.87)	0.61 (0.57-0.68)			
TJC78	1.0	0.65	0.9 (0.89-0.9)	0.57 (0.55-0.58)		
SJC76	0.65	0.99	0.60	0.84 (0.83-0.85)	0.65	
Physician global	0.46 (0.29-0.53)	0.42 (0.26-0.52)	0.41 (0.25-0.51)	0.35 (0.24-0.43)	0.52 (0.51-0.52)	0.5 (0.48-0.52)
Patient global	0.36 (0.31-0.51)	0.27 (0.25-0.35)	0.34 (0.17-0.48)	0.21 (0.13-0.33)	0.45 (0.40-0.50)	0.32 (0.30-0.35)
Patient pain	0.35 (0.26-0.51)	0.28 (0.24-0.33)	0.34 (0.20-0.5)	0.26 (0.14-0.36)	0.49 (0.47-0.5)	0.34 (0.32-0.36)
CRP	0.14 (0.06-0.20)	0.12 (0.06-0.22)	0.1 (0.05-0.15)	0.11 (0.01-0.25)	0.09 (0.07-0.11)	0.15 (0.05-0.24)
HAQ	0.3 (0.26-0.46)	0.23 (0.22-0.29)	0.32 (0.19-0.51)	0.21 (0.20-0.32)	0.4 (0.35-0.45)	0.26 (0.24-0.27)

The median and range of the Spearman correlation coefficients are presented for the 9 trials examined.

identified, the TJC68/SJC66 is recommended by the GRAPPA-OMERACT working group for measurement of peripheral arthritis in PsA.

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Abstract Number: 642

Cost of Illness Analysis before and after Initiation of Tumour Necrosis Factor α Inhibitors in Patients with Axial Spondyloarthritis

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Background/Purpose: Tumour necrosis factor- α inhibitors (TNFi) are an effective but rather expensive treatment option in axial spondyloarthritis (axSpA) patients who fail conventional treatment. The aim of this study was to analyse the changes in the cost of illness after initiation of TNFi in patients with axSpA.

Methods: Patients with axSpA newly exposed to TNFi between 2011 and 2015 were identified from claims data of a large statutory health insurance fund (BARMER). Direct healthcare costs and productivity costs were analysed the year before (baseline period) and the year after (follow-up period) the first initiation of TNFi. Direct healthcare costs comprised costs for outpatient care, i.e. costs for services performed in an outpatient setting (visits to physicians, laboratory visits, visits to physical therapists, emergency department visits, outpatient hospital services), inpatient care, i.e. cost for performed services and administered drugs during inpatient hospital stays, and pharmacotherapy, i.e. costs for drug prescriptions in the outpatient setting.

Productivity costs comprised costs due to absence from paid work and were calculated using the friction cost method (FCM) and the human capital approach (HCA).

Results: Data from 1,452 persons were included in the analyses. The mean age was 44.6 years and 47.9% were female. AxSpA-related pharmacotherapy use (Fig. 1) and admissions to hospital as well as duration of inpatient treatment (Tab. 1) significantly decreased in the follow-up period compared to the baseline period. Mean total costs increased from 8,072 to 29,959 using the HCA and from 6,377 to 28,162 using the FCM (Tab. 2). Excluding costs for TNFi, total costs decreased by 15% to 6,876 or by 20% to 5,080 based on whether the HCA or the FCA was used.

Conclusion: Overall healthcare resource utilisation and productivity cost decreased in axSpA patients after initiation of TNFi. The increase in pharmacotherapy costs driven by TNFi was partly offset by significantly lower costs for outpatient and inpatient care, as well as significantly lower productivity costs. However, the effect of TNF-blocker therapy on the patient's disease activity, function or quality of life could not be assessed in this analysis.

Disclosure: I. Redeker, None; F. Hoffmann, None; J. Callhoff, None; H. Haibel, None; J. Sieper, None; A. Zink, None; D. Poddubnyy, None.

Figure 1 Percentage of patients receiving axSpA-related pharmacotherapy the year before and the year after the first initiation of TNFi.

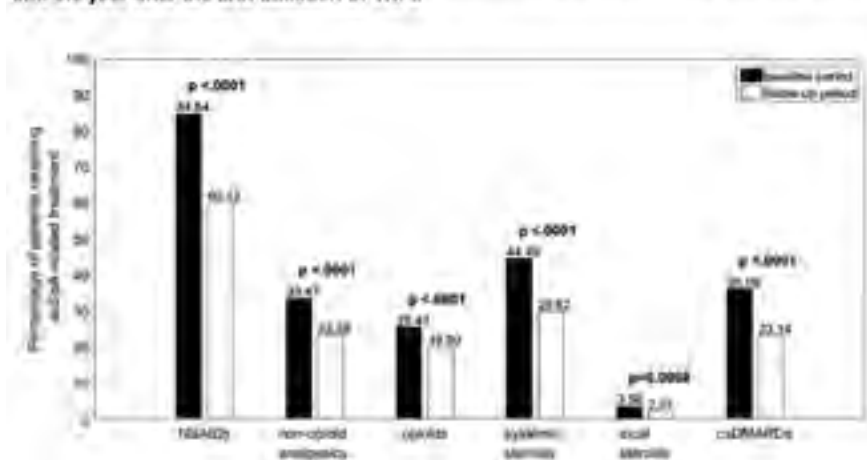


Table 1 Percentage of patients with hospital admission and duration of hospital stay the year before and the year after the first initiation of TNFi in patients with axSpA.

	Baseline period	Follow-up period	P-value
Hospital admission for any reason, n/N (%)	629/1452 (43)	411/1452 (28)	<.0001
AxSpA-related hospital admissions, n/N (%)	251/1452 (17)	87/1452 (6)	<.0001
Days of hospital stay for any reason; mean \pm SD [median], N=788	12 \pm 36 [8]	7 \pm 39 [1]	<.0001
Days of hospital stay with axSpA-related hospital admission; mean \pm SD [median], N=281	13 \pm 8 [10]	3 \pm 6 [0]	<.0001

Table 2 Direct healthcare costs and productivity costs in Euro the year before and the year after the first initiation of TNFi in patients with axSpA (N=1452).

	Costs (€), mean±SD baseline period	Costs (€), mean±SD follow-up period	P-value
Outpatient care*	1,402±1,008	1,381±1,054	0.0285
visits to rheumatologists	161±158	249±221	<.0001
Inpatient care	1,890±3,681	1,134±3,558	<.0001
with diagnosis of axSpA	612±1582	135±714	<.0001
Pharmacotherapy	1,201±2,939	23,957±5,480	<.0001
excluding costs for TNFi	1,201±2,939	875±1,721	<.0001
NSAIDs	130±159	83±151	<.0001
non-opioid analgesics	21±77	12±46	<.0001
opioid analgesics	118±517	123±364	0.3352
systemic steroids	23±52	17±54	<.0001
local steroids	1±6	1±4	0.0091
csDMARDs	159±366	97±278	<.0001
Direct healthcare costs	4,494±5,245	26,473±6,872	<.0001
excluding costs for TNFi	4,494±5,245	3,390±4,698	<.0001
Productivity costs, FCM	1,883±2,943	1,680±2,334	0.0021
Productivity costs, HCA	3,578±7,211	3,486±7,806	0.0458
Total costs, FCM	6,377±6,401	28,152±7,609	<.0001
excluding costs for TNFi	6,377±6,401	5,080±5,813	<.0001
Total costs, HCA	8,072±9,734	29,959±10,679	<.0001
excluding costs for TNFi	8,072±9,734	6,876±9,626	<.0001

TNF, Tumour Necrosis Factor; axSpA, axial Spondyloarthritis; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; csDMARDs, conventional synthetic Disease-Modifying Anti-Rheumatic Drugs; FCM, Friction Cost Method; HCA, Human Capital Approach; SD, Standard Deviation.
*excluding costs for pharmacotherapy.

Abstract Number: 643

Remission in Psoriatic Arthritis: Definition and Predictors

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Background/Purpose: No validated definition of remission exists for psoriatic arthritis (PsA) to date. We previously identified 17.6% of our patients as having remission (no actively inflamed joints for 12 months). However, we did not take into account the other domains of the disease. We aimed to test the concept of remission as the absence of disease manifestations in PsA, determine the frequency of remission in our PsA cohort, and identify predictors for remission.

Methods: Patients followed at the PsA clinic between 2000 and 2015 were included. Patients are assessed at 6- to 12-month intervals according to a standard protocol, which includes the information necessary for minimal disease activity (MDA) assessment. Remission was defined as a visit that patients had no tender or swollen joints, no inflammatory back pain, no tender enthesal sites, minimal skin involvement with BSA<1%, patient pain on visual analog scale (VAS) score of

<15, patient global disease activity VAS score of <20, Health Assessment Questionnaire (HAQ) score <0.5. We used imputation to determine remission status for each patient and did a sensitivity analysis including only visits with all information available. We fit a Weibull regression model with interval/right censored and left truncated data adjusted for sex and disease duration at baseline. Both multivariable full model and reduced model with Hazard Ratio (HR), 95% confidence interval (CI) estimates, and p-value are provided in Table1.

Results: 985 patients (57% males, mean age 47.4 yrs Table) were included. Using imputation 175 (18.2%) patients had remission at least once and 107 (10.9%) achieved sustained remission. For the sensitivity analysis, using only patients who had complete data, 109 (10.9%) patients achieved remission at least once, and 48(4.9%) sustained remission for 2 consecutive visits. Using baseline variables with imputation, only BMI was significant and lowered the chance of remission. In the sensitivity analysis no baseline variables were significant. Using a model with time varying covariates higher BMI lowered the chance of remission, while use of biologics increases the chance of remission. Similar results were obtained with the sensitivity analysis.

Conclusion: We defined remission as a state of no clinical activity. Remission occurred in 18% of patients with PsA at least once and was sustained in 11%. High BMI reduced and use of biologic agents increased the chance of sustained remission.

Table1. Weibull regression model for first remission, adjusted by gender and disease duration

Covariate	Multivariable full model		Multivariable reduced model	
	HR 95% CI	p-value	HR 95% CI	p-value
Age	1.02 (0.94, 1.11)	0.53		
Age at Diagnosis of PsA	0.98 (0.90, 1.07)	0.7048		
BMI	0.97 (0.93, 1.00)	0.0824	0.96 (0.92, 0.99)	0.02
Axial	0.85 (0.85, 1.99)	0.2276		
NSAIDs	0.71 (0.46, 1.10)	0.1224		
DMARDs	1.14 (0.74, 1.75)	0.5592		
Biologics	1.69 (1.11, 2.57)	0.0150	1.73 (1.15, 2.61)	0.009
Diabetes	0.57 (0.24, 1.34)	0.1984		
Infection	1.60 (1.00, 2.56)	0.0518		
Depression/Anxiety	0.60 (0.31, 1.16)	0.1302		
Elevated ESR	0.68 (0.41, 1.13)	0.1400		
Gender (male vs female)	1.10 (0.72, 1.68)	0.6696	1.10 (0.73, 1.67)	0.64
Disease Duration	0.95 (0.87, 1.04)	0.2967	0.97 (0.95, 1.00)	0.05

CI – confidence interval; BMI-Body Mass Index; NSAIDs- nonsteroidal anti-inflammatory drugs; DMARDs- disease modifying anti-rheumatic drugs; ESR- erythrocyte sedimentation rate

Table 2. Weibull regression model for sustained remission, adjusted by gender and disease duration

Covariate	Multivariate Full model		Multivariate reduced model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.19 (1.08, 1.30)	0.0002		
Age at Diagnosis of PsA	0.86 (0.79, 0.94)	0.0012		
BMI	0.97 (0.93, 1.02)	0.2199		
Axial	0.72 (0.44, 1.19)	0.1989		
NSAIDs	0.74 (0.45, 1.21)	0.2358		
DMARDs	0.78 (0.48, 1.26)	0.3052		
Biologics	2.11 (1.29, 3.47)	0.0030	1.76 (1.10, 2.84)	0.0195
Diabetes	0.82 (0.36, 1.86)	0.6308		
Heart Condition	0.66 (0.09, 4.81)	0.6786		
Infection	0.92 (0.48, 1.75)	0.7927		
Depression/Anxiety	0.52 (0.24, 1.15)	0.1062		
Elevated ESR	0.77 (0.44, 1.35)	0.3634		
Gender (male vs female)	1.18 (0.72, 1.93)	0.5096	1.27 (0.78, 2.05)	0.3317
Disease Duration	0.82 (0.74, 0.90)	<0.0001	0.96 (0.93, 1.00)	0.0239

CI – confidence interval; BMI-Body Mass Index; NSAIDs- nonsteroidal anti-inflammatory drugs; DMARDs- disease modifying anti-rheumatic drugs; ESR- erythrocyte sedimentation rate

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Influence of Inflammation and Structural Damage on Global Functioning in Patients with Axial Spondyloarthritis – Using the ASAS Health Index in Routine Care

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Background/Purpose: To investigate the relationship between spinal mobility and self-report global functioning as assessed by the ASAS Health Index (ASAS HI), and to study the influence of structural and inflammatory spinal changes on global functioning.

Methods: Patients from the outpatient clinic of our hospital suffering from axial or peripheral SpA completed questionnaires assessing disease activity and functioning (ASAS HI, pain, BASDAI, ASDAS, BASFI). Axial inflammation as detected by magnetic resonance imaging (MRI) was assessed by the Berlin score, structural damage by the modified Stokes ankylosing spondylitis (AS) Spine Score (mSASSS) and spinal mobility by the Bath AS Metrology Index (BASMI). Imagings were scored by two independent readers. Correlations between the ASAS HI and other health outcomes were analysed by Spearman's test. Logistic regression analyses were performed to investigate the association between functioning and other clinical characteristics.

Results: A total of 203 patients (76 non-radiographic (nr)-axSpA, 115 AS patients, and 12 with peripheral SpA (pSpA) were included: 63.5% male, mean (SD) age 46.6 (14.1), symptom duration 18.8 (12.8) years, and 76.4% HLA-B27 positive. The mean values of clinical assessments were ASAS HI 7.9 (4.0), BASDAI 5.0 (2.2), ASDAS 2.8 (1.1), BASMI 3.3 (1.8), pain 6.0 (2.6), and BASFI 5.0 (2.6). Elevated CRP levels were found in 37.4% of the patients, while 59.1% of the AS patients had syndesmophytes and 11.3% a bamboo spine. The median (IQR) mSASSS value was 3.8 (IQR 1.0-22.1) in AS und 0.0 (IQR 0.0-1.4) in nr-axSpA patients. The mean Berlin Score for patients with axSpA was 5.3 (SD 7.1). Patients received a treatment with NSAIDs (62.7%), DMARDs (20.9%) and/or biologics (49.4%). A significant correlation of the ASAS HI was found for BASMI ($r=0.5$), BASDAI ($r=0.7$), ASDAS ($r=0.5$), BASFI ($r=0.8$), BMI (0.3) and Berlin Score (0.3). ASAS HI did not correlate with radiographic damage (mSASSS $r=0.2$, presence of bamboo spine $r=0.2$) and CRP ($r=0.07$). Stratifying patients by symptom duration (cut-off 3 years) did not affect these results. Logistic regression showed influence of obesity but not of inflammation or structural damage on global functioning (Table 1).

Table 1: Association between clinical characteristics of patients with SpA and functioning status

	Univariable		Multivariable	
	OR (CI)	p	OR (CI)	p
Age	1.04 (1.02-1.06)	0.001	-	NS
Male sex	0.47 (0.24-0.93)	0.003	0.09 (0.01-0.71)	0.022
BMI	1.10 (1.03-1.18)	0.006	1.24 (1.05-1.48)	0.013
BASDAI, 0-10	1.35 (1.17-1.57)	<0.001	-	NS
ASDAS	2.51 (1.76-3.57)	<0.001	-	NS
BASFI, 0-10	2.03 (1.66-2.48)	<0.001	1.85 (1.19-2.87)	0.006
BASMI, 0-10	2.0 (1.56-2.54)	<0.001	-	NS
mSASSS, 0-72	1.02 (1.00-1.05)	0.089	-	NS
Berlin Score, 0-72	0.98 (0.91-1.04)	0.490	-	NS

Conclusion: The influence of obesity on functioning is remarkable in patients with SpA. In contrast, the influence of structural damage and spinal inflammation on functioning was limited in this study, probably due to the relatively low mSASSS and MRI scores. Further studies with inclusion of more severely affected patients are needed to study the association of functioning, spinal mobility, obesity and radiographic damage over a broader range of affected patients.

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Real World Secukinumab Study in Ankylosing Spondylitis and Psoriatic Arthritis – Comorbidities and Extraarticular Manifestations: Incidence and Status throughout a Non-Interventional Study in Germany

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Background/Purpose: Patients with psoriatic arthritis (PsA) or ankylosing spondylitis (AS) may suffer from extraarticular (EA) manifestations (uveitis, psoriasis) and have higher rates of comorbidities like cardiovascular diseases (CVD) and depression than the normal population. Comorbidities should be kept in mind when managing patients with PsA and AS, as they can contribute to increased mortality and influence disease activity¹. The aim of this interim analysis is to evaluate the incidence of selected EA manifestations and comorbidities at baseline and the impact of secukinumab on the status of these attributes compared to baseline.

Methods: The presence and severity of uveitis and psoriasis as well as coronary heart disease (CHD), stroke, heart insufficiency, and depression were documented according to clinical routine at baseline and at week 4, 16, 24 and 52 under treatment with secukinumab. Depressed mood has been evaluated by Becks Depression Inventory (BDI-II), plaque psoriasis via PASI score. At baseline 486 patients were included and observed up to 52 weeks, at the time of analysis not all patients have already reached the end of the study, therefore the results are presented as observed.

Results: As expected, plaque psoriasis was very frequent in PsA patients (63.3%), but also present in AS patients (11.5%) at baseline. For PsA patients, median PASI improved from 5.0 at baseline to 0.0 at week 52. Half of patients with available PASI achieved clear skin at week 52 (Tab 1).

Uveitis was more frequent in AS patients than in PsA patients (6.2% vs 0.9%). Only 1 AS patient and 2 PsA patients experienced new onset of uveitis.

At baseline, the following patients reported previous CHD (PsA 8.9%, AS 3.5%), heart failure (PsA 3.3%, AS 0.7%) and stroke (PsA 2.4%, AS 0.0%). Of these cardiovascular comorbidities none worsened (as observed at each scheduled visit) with secukinumab treatment for all patients observed up to 52 weeks. During the study two PsA patients were newly diagnosed with CHD and heart insufficiency throughout week 52. No new stroke occurred.

Depression was common in both populations (PsA 15.4%, AS 12.2%) at baseline. Up to week 52 median BDI-II improved from 12.0 to 6.0 (AS patients) and from 9.0 to 6.0 (PsA patients [Tab 1]).

Conclusion: Incidence of CVD and depression in PsA and AS patients is generally comparable to the published literature^{2,3}. However, in contrast to other studies⁴, previous uveitis was less frequently reported in SpA patients, particularly in the AS group. Cardiovascular comorbidities remained overall stable under secukinumab up to wk 52. Plaque psoriasis and depressive mood improved with secukinumab treatment.

	Baseline	Week 4	Week 16	Week 28	Week 40	Week 52
PASI 100 n(%)	0 (0.0)	7 (13.0)	23 (34.3)	28 (47.5)	18 (41.9)	15 (50.0)
PASI 75 n(%)	0 (0.0)	9 (16.7)	26 (38.8)	33 (55.9)	21 (48.8)	18 (60.0)
BDI-II (AS patients)	12.0	9.0	8.0	8.0	7.5	6.0
BDI-II (PsA patients)	9.0	8.0	7.5	8.0	7.0	6.0

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Do Ethnicity, Degree of Family Relationship, and the Spondyloarthritis Subtype in Affected Relatives Influence the Association between a Positive Family History for Spondyloarthritis and HLA-B27 Carriership? Results from the Worldwide ASAS Cohort

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Session Type: ACR Poster Session A

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

Background/Purpose: The Assessment of SpondyloArthritis international Society (ASAS) defines a positive family history (PFH) of spondyloarthritis (SpA) as presence of ankylosing spondylitis (AS), acute anterior uveitis (AAU), reactive arthritis (ReA), inflammatory bowel disease (IBD), and/or psoriasis in first (FDR)- or second (SDR)-degree relatives. In two European cohorts (SPACE and DESIR) a PFH of AS and AAU, but not other subtypes, were associated with HLA-B27 carrier ship in patients suspected of axial SpA (axSpA)¹. As the importance of ethnicity or degree of family relationship is unknown, we investigated the influence of ethnicity, FDR or SDR on the association between a PFH and HLA-B27 carrier ship in patients suspected of axSpA.

Methods: Univariable analyses were performed among patients suspected of axSpA in the ASAS cohort at baseline. Each disease (AS, AAU, psoriasis, IBD, ReA) in a PFH according to the ASAS definition was a determinant in separate models with HLA-B27 carrier ship as outcome. Analyses were stratified for self-reported ethnicity (white, Asian, and other), FDR, and SDR. Analyses were repeated in multivariable models to investigate independent associations.

Results: In total, 594 patients were analysed. Patients had a mean (SD) age of 33.7 (11.7) years, 46% were male; 52% was HLA-B27+, 59% were white, 36% were Asian, and 5% had another ethnicity. A PFH was reported by 23% of the patients; a PFH of AS was the most (15%) and PFH of AAU (1%) the least often reported family history among all patients. A PFH in first-degree relatives was reported in 19% of patients and in second-degree relatives in 4%. A PFH was associated with HLA-B27 carrier ship in patients with a white (OR:2.3, 95%CI:1.4-3.9) or Asian ethnicity (OR:3.1, 95%CI:1.6-5.8) and with a PFH in FDR (OR:2.9, 95%CI:1.8-4.5), but not with a PFH in SDR (OR:1.7, 95%CI:0.7-3.8) or in other ethnicities (Table 1). A PFH of AS was positively associated with HLA-B27 carrier ship in all subgroups (white OR:7.1, 95%CI:2.9-17.1; Asian OR:5.7, 95%CI:2.5-13.2; FDR OR:7.8, 95%CI:3.8-16.0; SDR OR:3.7, 95%CI:1.2-11.6). A PFH of AAU, ReA, IBD, or psoriasis was never positively associated with HLA-B27 carrier ship. In the multivariate analysis, similar results were found.

Conclusion: In the international ASAS cohort, a PFH of AS, but not of AAU, ReA, IBD, or psoriasis, was associated with HLA-B27 carrier ship irrespective of ethnicity or degree of family relationship. These data, in combination with data from two European cohorts, show that a PFH of AS and possibly a PFH of AAU can be used to identify patients who are more likely to be HLA-B27 positive and therefore have an increased risk of axSpA.

References: 1. Ez-Zaitouni et al (2017), AR&T2017;19(1):118.

Disclosure: M. van Lunteren, None; A. Sepriano, None; R. B. M. Landewé, None; J. Sieper, None; M. Rudwaleit, None; D. van der Heijde, None; F. van Gaalen, None.

Table 1 Univariable associations between each subtype of a positive family history and HLA-B27 carriage in chronic back pain patients suspected of axSpA included in the ASAS cohort (n=534).

	HLA-B27+ n=310	HLA-B27- n=284	OR (95% CI)	p-value
Positive family history according to ASAS definition				
<i>Stratified by self-reported ethnicity</i>				
White	54	26	2.3 (1.4-3.9)	0.001
Asian	38	14	3.1 (1.6-5.8)	0.001
Other ethnicities*	2	1	2.3 (0.2-25.0)	0.509
<i>Stratified by degree of family relationship</i>				
First-degree relatives	79	31	2.9 (1.8-4.5)	<0.001
Only second-degree relatives	15	10	1.7 (0.7-3.8)	0.212
Positive family history of ankylosing spondylitis				
<i>Stratified by self-reported ethnicity</i>				
White	37	6	7.1 (2.9-17.3)	<0.001
Asian	35	7	5.7 (2.5-13.2)	<0.001
Other ethnicities*	2	0	n.a.	n.a.
<i>Stratified by degree of family relationship</i>				
First-degree relatives	61	8	7.8 (3.8-16.0)	<0.001
Only second-degree relatives	13	4	3.7 (1.2-11.6)	0.023
Positive family history of acute anterior uveitis				
<i>Stratified by self-reported ethnicity</i>				
White	4	0	n.a.	n.a.
Asian	2	1	1.9 (0.2-20.7)	0.614
Other ethnicities*	0	0	n.a.	n.a.
<i>Stratified by degree of family relationship</i>				
First-degree relatives	5	1	4.7 (0.5-40.1)	0.162
Only second-degree relatives	1	0	n.a.	n.a.
Positive family history of reactive arthritis				
<i>Stratified by self-reported ethnicity</i>				
White	2	2	0.9 (0.1-6.5)	0.924
Asian	1	1	0.8 (0.03-2.9)	0.102
Other ethnicities*	0	0	n.a.	n.a.
<i>Stratified by degree of family relationship</i>				
First-degree relatives	1	2	1.4 (0.2-8.2)	0.735
Only second-degree relatives	0	3	n.a.	n.a.
Positive family history of inflammatory bowel disease				
<i>Stratified by self-reported ethnicity</i>				
White	2	7	0.3 (0.05-1.2)	0.089
Asian	0	2	n.a.	n.a.
Other ethnicities*	0	1	n.a.	n.a.
<i>Stratified by degree of family relationship</i>				
First-degree relatives	1	7	0.1 (0.02-1.0)	0.054
Only second-degree relatives	1	2	0.3 (0.03-2.9)	0.294
Positive family history of psoriasis				
<i>Stratified by self-reported ethnicity</i>				
White	16	15	1.0 (0.5-2.0)	0.938
Asian	7	2	0.9 (0.3-6.5)	0.926
Other ethnicities*	0	2	n.a.	n.a.
<i>Stratified by degree of family relationship</i>				
First-degree relatives	15	14	1.0 (0.3-2.1)	0.949
Only second-degree relatives	3	4	0.7 (0.2-3.1)	0.520

Statistically significant results are printed in bold. * Self-reported ethnicity was missing for 5 patients, who are included in this category, and other ethnicities are black, East Indian, Hispanic/Latino, mixed, or Turkish. ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; HLA-B27, human leukocyte antigen B27; n.a., not applicable; OR, odds ratio.

Abstract Number: 647

Validation of a New Electronic Spinal Mobility Index for Patients with Axial Spondyloarthritis Based on Inertial Motion Unit (IMU) Sensors

Philip Gardiner¹, Dawn Small², Eithne Boyle², Ann Marie Conlon², José António P. da Silva³, Joan Condell⁴, Antonio Cuesta-Vargas⁵, Eduardo Collantes-Estévez⁶ and Juan Luis Garrido-Castro⁷, ¹Rheumatology, Western Health and Social Care Trust, Londonderry, United Kingdom, ²Western Health and Social Care Trust, Londonderry, United Kingdom, ³Department of rheumatology, Centro Hospitalar e Universitário de Coimbra (SRHUC), Coimbra, Portugal, ⁴Ulster University, Coleraine, United Kingdom, ⁵University of Malaga, Malaga, Spain, ⁶Rheumatology service, IMIBIC/Reina Sofia Hospital/University of Cordoba, Cordoba, Spain, ⁷IMIBIC, Cordoba, Spain

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: Spinal mobility is a major problem for people with axial spondyloarthritis (axSpA). The BASMI has been widely used for measuring spinal mobility but it lacks responsiveness to change and requires clinical expertise to perform. Inertial Motion Unit (IMU) sensors are now available to measure spinal movement without requiring significant operator expertise. Our objective in this study was to test the reliability of these new tools in patients with axSpA and to develop a composite measurement tool analogous to the BASMI.

Methods: The study included 40 patients with axSpA fulfilling ASAS classification criteria (12 females, 28 males) with a mean age of 48 (27-41). Subjects had a wide range of severity of axSpA. ViMove IMU sensors (DorsaVi©) were used to obtain ROM measurements at the cervical and lumbar spine. Intra-rater and inter-rater reliability of BASMI and IMU tests were assessed by intraclass correlation coefficients (ICC) (two-way model, single measure, absolute agreement) with a 95% CI. Based on these observations we developed a novel scoring system named 'IMU-ASMI'. It includes four measurements of maximum ROM (degrees) carried out in both lumbar and cervical regions: flexion, extension, averaged L/R values for lateral flexion and rotation. Maximum spinal ROM values in normal subjects taken from an earlier criterion validity study are taken as reference in the composite IMU-ASMI score calculation.

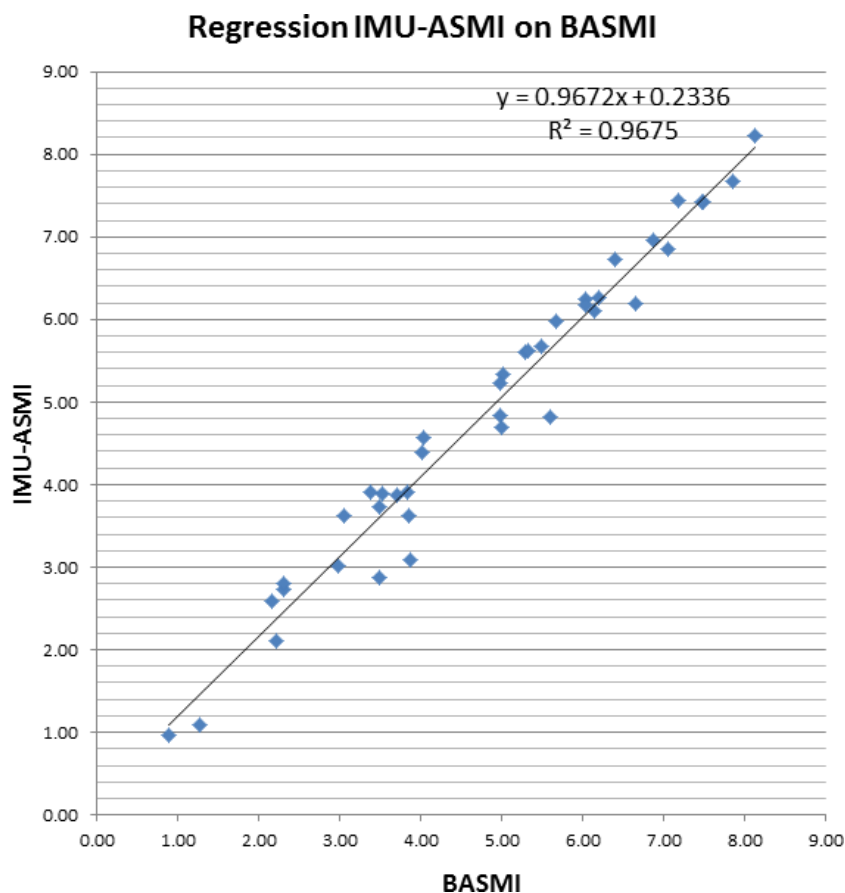
Results: The mean BASMI was 5.0 (range 0.7 to 8.2, SD 1.9). The mean IMU-ASMI was 5.1 (range 0.4-8.9, SD 2.1). The mean difference between the two scores was 0.04, SD 0.17.

The ICC results demonstrate that a sensor based IMU-ASMI has excellent reliability (table). The R^2 on the regression analysis was 0.97, indicating a close relationship between the BASMI and IMU-ASMI (Figure).

	BASMI		IMU-ASMI	
	ICC (2,1)	95% CI	ICC (2,1)	95% CI
Intra-rater	0.97	0.95-0.99	0.95	0.91-0.96
Inter-rater	0.95	0.91-0.98	0.93	0.85-0.98

Conclusion: IMU sensors can be used to accurately and reliably measure spinal mobility in patients with axSpA. We present a novel IMU-ASMI score based on combining sensor data on spinal mobility including an assessment of lumbar rotation. The score compares favorably with the BASMI linear scale, and the sensor technology on which it is based on will allow tests of spinal mobility to be carried out by non-experts in the community setting. Further studies are planned to test the sensitivity to change of the IMU-ASMI compared to BASMI.

Acknowledgements: This study was funded by FOREUM (<http://www.foreum.org/>). Physiotherapist Stephanie Keys also performed spinal mobility tests during this study.



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Abstract Number: 648

Performance of an Online Self-Referral Questionnaire Compared to a Physician-Based Referral Approach to Identify Patients with a High Probability of Axial Spondyloarthritis: Results from the Optiref Study

Fabian Proft¹, Laura Spiller¹, Mikhail Protopopov¹, Valeria Rios Rodriguez¹, Burkhard Mucbe¹, Judith Rademacher¹, Susanne Lueders², Anne-Katrin Weber¹, Inge Spiller¹, Joachim Sieper^{3,4} and Denis Poddubnyy^{3,4}, ¹Charité Universitätsmedizin Berlin, Berlin, Germany, ²Department of Rheumatology and Clinical Immunology, Charité Universitätsmedizin Berlin, Berlin, Germany, ³German Rheumatism Research Centre, Berlin, Germany, ⁴Charité Universitätsmedizin Berlin, Berlin, Germany

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: The diagnostic delay in axial spondyloarthritis (axial SpA) has been reported to be 9 years and still remains unacceptably high. One of the major reasons for this delay is a late referral of patients with suspicion of axial SpA by primary care (PC) physicians, dealing with patients with chronic back pain (CBP). Physician-based referral programs have performed well in recognition of patients with high probability of axial SpA among CBP patients. However, there is still an unmet need for patients who do not receive a referral recommendation to a rheumatologist because of lack of awareness on the PC level. The objective of this study was to develop and evaluate an online self-referral tool for CBP patients with suspicion of axial SpA.

Methods: Patients with CBP were included in the Identification of the Optimal Referral Strategy for Early Diagnosis of Axial Spondyloarthritis (OptiRef) Study and assessed by a rheumatologist if they either 1) were referred by a physician using the Berlin referral tool (CBP > 3 months and CBP onset < 45 years of age + at least 1 of the following 3 parameters: inflammatory back pain (IBP), HLA-B27 positivity, sacroiliitis on imaging), or 2) completed an online self-referral and indicated the presence of CBP > 3 months with onset < 45 years of age + at least 1 additional SpA parameter. Rheumatologist then performed a structured assessment of SpA features and made the diagnosis of axial SpA/non-axial SpA.

Results: A total of 362 patients were included in the study on a 1:1 ratio either referred by a physician using the Berlin referral tool or via the online self-referral tool. A total of 71 patients (39.9%) in the physician-referral group and 35 patients (19.3%) in the self-referral group were finally diagnosed with axial SpA ($p < 0.001$). Patients who were included via the online referral tool had a longer symptom duration, were more often females, less often HLA-B27 positive and had less often elevated CRP as compared to physician-referred patients (table 1a).

In patients diagnosed with axial SpA the patients referred by a physician were more often male ($p = 0.041$), HLA-B27 positive ($p < 0.001$) and showed more often advanced radiographic changes in the sacroiliac joints leading to the diagnosis of radiographic axial SpA (=ankylosing spondylitis) ($p = 0.033$). All other demographic and clinical characteristics did not differ between the two groups (table 1b).

Conclusion: The self-referral strategy resulted in the diagnosis of axSpA in 19% of the patients as compared to 40% with a referral done by a physician. However, the proportion of axSpA among self-referred patients was clearly higher than the expected 5% prevalence of axSpA in patients with CBP. The online self-referral tool can be used, therefore, in addition to a physician based referral program to improve the early diagnosis and to increase awareness of axSpA.

Disclosure: F. Proft, None; L. Spiller, None; M. Protopopov, None; V. Rios Rodriguez, None; B. Mucbe, None; J. Rademacher, None; S. Lueders, None; A. K. Weber, None; I. Spiller, None; J. Sieper, None; D. Poddubnyy, None.

Table 1a: patient characteristics in the whole OptiRef-cohort

	Whole cohort n=362	Berlin trial n=181	Self-referral n=181	p-value
Diagnosis of axSpA	106 (29.3%)	71 (39.2%)	35 (19.3%)	<0.001
Age	37.0 ± 10.3	37.4 ± 11.7	36.6 ± 9.1	0.916
Male:sex	179 (49.4%)	101 (55.8%)	78 (43.1%)	0.016
Back pain duration, years	7.9 ± 7.6	6.5 ± 6.9	9.2 ± 9.1	<0.001
PS	5.1 ± 2.6	5.3 ± 2.7	4.8 ± 2.5	0.055
HLA-B27	241 (66.6%)	104 (57.5%)	37 (20.4%)	<0.001
CRP elevation	53 (14.6%)	35 (19.3%)	18 (10.0%)	0.010
BP	204 (56.4%)	103 (56.9%)	101 (55.8%)	0.852
NSAID	164 (45.3%)	85 (47.0%)	89 (49.2%)	0.657
Smoking	97 (26.8%)	53 (29.3%)	44 (24.3%)	0.270
Uveitis ever	25 (6.9%)	16 (8.8%)	9 (5%)	0.147
Psoriasis ever	35 (9.7%)	14 (7.7%)	21 (11.6%)	0.213
CED ever	6 (1.7%)	2 (1.1%)	4 (2.2%)	0.410
Peripheral arthritis ever	49 (13.5%)	18 (9.9%)	31 (17.1%)	0.046
Dactylitis ever	2 (0.6%)	0 (0%)	2 (1.1%)	0.249
Enthesitis ever	51 (14.1%)	20 (11%)	31 (17.1%)	0.077

Table 1b: patient characteristics of axial SpA patients in the OptiRef cohort

	axSpA only n=106	Berlin trial n=71	Self-referral n=35	
radiographic axSpA (AS)	52 (49.1%)	40 (56.3%)	12 (34.3%)	0.003
Age	33.4 ± 9.4	33.9 ± 10.7	32.5 ± 6.2	0.893
Male:sex	65 (62.3%)	40 (56.3%)	17 (48.6%)	0.041
Back pain duration, years	6.6 ± 6.2	6.5 ± 6.4	6.8 ± 5.4	0.465
PhGA	44.42 ± 21.5	47.46 ± 20.3	38.3 ± 23.3	0.066
PS	4.96 ± 2.67	5.16 ± 2.66	4.51 ± 2.66	0.18
BASDAI	4.17 ± 1.95	4.22 ± 1.96	4.09 ± 1.93	0.479
BASFI	2.74 ± 2.17	3.03 ± 2.33	2.19 ± 1.74	0.132
ASDAS-CRP	2.45 ± 0.97	2.48 ± 0.98	2.41 ± 0.96	0.626
HLA-B27	84 (79.2%)	64 (90.1%)	20 (57.1%)	<0.001
CRP Elevation	41 (38.7%)	27 (38%)	14 (40.0%)	0.932
BP	89 (84%)	60 (84.5%)	29 (82.9%)	0.828
NSAID	71 (67%)	49 (69%)	22 (62.9%)	0.658
Smoking	30 (28.3%)	22 (31%)	8 (22.9%)	0.359
mNP positive	49 (46.2%)	38 (53.5%)	11 (31.4%)	0.077
active sacroitis by MRI	58 (54.7%)	43 (60.6%)	15 (42.9%)	0.191
Uveitis ever	18 (17%)	17 (24.1%)	6 (17.1%)	0.475
Psoriasis ever	11 (10.4%)	5 (7%)	6 (17.1%)	0.109
CEL ever	3 (2.8%)	1 (1.4%)	2 (5.7%)	0.209
Peripheral arthritis ever	17 (16%)	12 (16.9%)	5 (14.3%)	0.78
Dactylitis ever	1 (0.9%)	0 (0%)	1 (2.9%)	0.152
Enthesitis ever	15 (14.2%)	9 (12.7%)	6 (17.1%)	0.535

Abstract Number: 649

Ankylosing Spondylitis Disease Activity Score (ASDAS) Based on a Quick Quantitative CRP Assay Performs Similarly Well to ASDAS Based on Conventional CRP in Patients with Axial Spondyloarthritis

Fabian Proft¹, Burkhard Muehe¹, Laura Spiller¹, Valeria Rios Rodriguez¹, Judith Rademacher¹, Anne-Katrin Weber¹, Susanne Lueders², Mikhail Protopopov¹, Inge Spiller¹, Joachim Sieper³ and Denis Poddubnyy^{3,4}, ¹Charité Universitätsmedizin Berlin, Berlin, Germany, ²Department of Rheumatology and Clinical Immunology, Charité Universitätsmedizin Berlin, Berlin, Germany, ³Charité Universitätsmedizin Berlin, Berlin, Germany, ⁴German Rheumatism Research Centre, Berlin, Germany

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Figure. Comparison of the disease activity state ascertainment by ASDAS-routine-CRP vs. ASDAS-quick-CRP (A) and ASDAS-routine-CRP vs. ASDAS-ESR (B).

A

		ASDAS-quick-CRP (n=50)			
		Inactive disease (<1.3)	Low Disease Activity (1.3 - <2.1)	High disease activity (2.1 - <3.5)	Very high disease activity (>3.5)
ASDAS-routine-CRP	Inactive disease (<1.3)	4 (8%)	1 (2%)	0	0
	Low Disease Activity (1.3 - <2.1)	1 (2%)	10 (20%)	0	0
	High disease activity (2.1 - <3.5)	0	0	24 (48%)	2 (4%)
	Very high disease activity (>3.5)	0	0	0	8 (16%)

B

		ASDAS-ESR (n=48)			
		Inactive disease (<1.3)	Low Disease Activity (1.3 - <2.1)	High disease activity (2.1 - <3.5)	Very high disease activity (>3.5)
ASDAS-routine-CRP	Inactive disease (<1.3)	2 (4.2%)	3 (6.3%)	0	0
	Low Disease Activity (1.3 - <2.1)	0	8 (16.7%)	3 (6.3%)	0
	High disease activity (2.1 - <3.5)	0	1 (2.1%)	17 (35.4%)	6 (12.5%)
	Very high disease activity (>3.5)	0	0	2 (4.2%)	6 (12.5%)

Background/Purpose: The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite index to assess disease activity in patients with axial spondyloarthritis (axSpA). According to the treat-to-target (T2T) recommendations for SpA, and the ASAS/EULAR management recommendations for axSpA, the C-reactive protein (CRP)-based ASDAS is the preferred instrument for the assessment of disease activity in the process of making decision on modification of axSpA treatment in clinical routine. Currently, measurement of CRP by routine lab methods takes hours to days what challenges the feasibility of T2T approaches in clinical-routine and studies. The objective of this study was to compare the performance of the ASDAS based on a quick CRP assay (ASDAS-quick-CRP) with the ASDAS-routine-CRP and with the erythrocyte sedimentation rate (ESR)-based ASDAS in the assessment of disease activity in patients with axSpA.

Methods: This cross-sectional study was performed in patients referred with a suspicion of axSpA as part of the OptiRef study. Briefly, referred patients underwent an assessment of SpA features by a rheumatologist. CRP was measured in the central lab (routine turbidimetric assay, lowest detection level: 0.3mg/l) and locally by ESR and a quantitative quick-CRP test (QuickRead go®, Orion Diagnostica Oy, lowest detection level: 5mg/l, test duration approx. 2 min.). If the quick-CRP was below the limit of detection, the value of 2mg/l was used. In patients with the final diagnosis of axSpA, ASDAS-routine-CRP, ASDAS-quick-CRP and ASDAS-ESR were calculated.

Results: A total of 137 patients had available routine and quick CRP levels; 50 patients of them were diagnosed with axSpA. Mean±SD routine / quick CRP serum levels were 3.6±7.0 mg/l and 5.0±7.2 mg/l, respectively, in the entire group, and 6.2±8.3 mg/l and 7.4±8.4 mg/l, respectively, in patients with axSpA. There was no significant difference ($p=0.11$) in the mean values of ASDAS-CRP (2.7 ± 1.0) and ASDAS-quick-CRP (2.8 ± 1.0), while the ASDAS-ESR (2.9 ± 1.0) was significantly higher than ASDAS-routine-CRP ($p=0.02$). In 46 of the 50 cases of axSpA (92%) the status scores for disease activity showed no difference between ASDAS-routine-CRP and ASDAS-quick-CRP – figure. For ASDAS-ESR compared to ASDAS-routine-CRP, only 33/48 patients (68.8%) were assigned to the same DAC.

Conclusion: ASDAS-quick-CRP performed similarly well to ASDAS-routine-CRP with an agreement on the status score for disease activity of 92%, that was clearly better than the agreement of 68.8% between ASDAS-ESR and ASDAS-routine-CRP. With a duration of approximately 2 minutes the quick-CRP test is, therefore, feasible for immediate decision making as a part of clinical routine or clinical trials.

Acknowledgements: The OptiRef project was supported by an unrestricted research grant from Novartis. The “QuickRead go” was provided free of charge by Orion Diagnostica Oy.

Disclosure: F. Proft, None; B. Muche, None; L. Spiller, None; V. Rios Rodriguez, None; J. Rademacher, None; A. K. Weber, None; S. Lueders, None; M. Protopopov, None; I. Spiller, None; J. Sieper, None; D. Poddubnyy, None.

Abstract Number: 650

Can Disease Activity in Patients with Psoriatic Arthritis be Adequately Assessed By a Modified Disease Activity Index for Psoriatic Arthritis (DAPSA) Based on 28 Joints?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

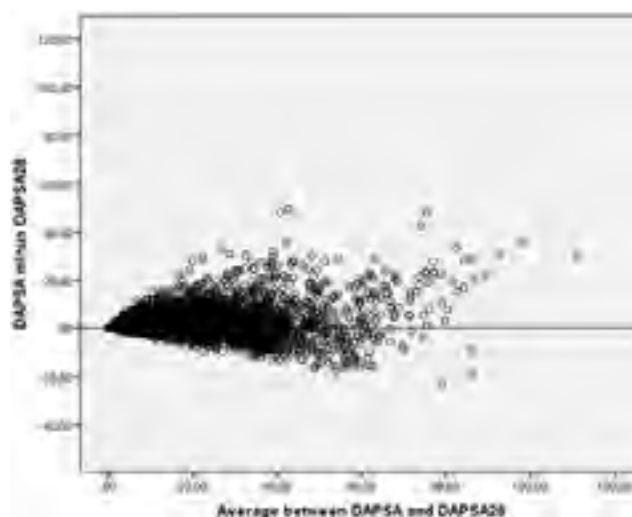
Session Time: 9:00AM-11:00AM

Background/Purpose: Many registries routinely collect only 28 joint count, although 66/68 joint count has higher face validity in PsA. We aimed to compute and test the validity of a simplified Disease Activity index for Psoriatic Arthritis (DAPSA) using 28 instead of 66/68 joint count.

Methods: We included PsA patients from the Danish national quality registry DANBIO, divided into examination (n=3157 patients, 24160 visits) and validation cohorts (n=3154 patients, 24160 visits) according to odd/even IDs. We defined: $DAPSA_{28} = (28TJC \times \text{conversion factor}_1) + (28SJC \times \text{conversion factor}_2) + \text{patient global [0-10VAS]} + \text{pain [0-10VAS]} + \text{CRP [mg/dL]}$. Identification of conversion factors was performed by Generalized Estimating Equations in the examination cohort, and *criterion, correlational and construct validity* explored in the validation cohort.

Results: Mean (SD) age: 52.0 (13.8) years, 54.4% females. *Conversion factor*₁ = 1.6, 95%CI(1.6-1.7), *conversion factor*₂ = 1.6, 95%CI (1.5-1.6), leading to:

$DAPSA_{28} = (28TJC + 28SJC) \times 1.6 + \text{patient global [0-10 VAS]} + \text{pain [0-10 VAS]} + \text{CRP [mg/dL]}$. *Criterion validity:* Physician's global and DAPSA/DAPSA₂₈ were similarly correlated ($r=0.63/r=0.61$, $p<0.001$). DAPSA/DAPSA₂₈ had comparable discriminative power, expressed as standardized mean difference (DAPSA, 0.90; DAPSA₂₈, 0.93) to distinguish between patients in high (starting bDMARD) and low (not starting/changing s/bDMARD for ≥ 60 days) disease activity. Agreement between DAPSA/DAPSA₂₈ disease activity states was best for remission/low disease activity (Table).



		DAPSA(n=6421) n(%) stratified by DAPSA disease activity states			
		DAPSA≤4	DAPSA>4 and ≤14	DAPSA>14 and ≤28	DAPSA>28
DAPSA28 (n=6421)	DAPSA28≤4	1135(98.4)	126(5.6)	4(0.2)	0(0)
	DAPSA28>4 and ≤14	18(1.6)	2073(91.5)	345(17.8)	14(1.3)
	DAPSA28>14 and ≤28	0(0)	66(2.9)	1509(77.9)	248(23.3)
	DAPSA28>28	0(0)	0(0)	80(4.1)	803(75.4)

Kappa with quadratic weighting of DAPSA/DAPSA28 disease activity states was high; 0.92 95%CI (0.92-0.92). Standardized response means for DAPSA/DAPSA28 were -0.96/-0.92 (n=572) for visits after bDMARD start. *Correlational validity:* Baseline DAPSA/DAPSA28 had strong correlation with DAS28 (r=0.87/r=0.93), SDAI (r=0.92/r=0.99), p<0.001. Bland-Altman plot showed better agreement between DAPSA/DAPSA28 for low than high disease activity (figure). *Construct validity:* DAPSA/DAPSA28 were similarly correlated to HAQ; r=0.60/0.62, p<0.001. DAPSA/DAPSA28 discriminated patients reporting their symptom state acceptable (n=1140) vs. not acceptable (n=1045) equally well: mean (SD) 9.1(8.7)/8.4(8.0) and 24.2(14.9)/22.5(13.8), respectively.

Conclusion: DAPSA28 showed good criterion, correlational and construct validity. Agreement between DAPSA and DAPSA28 was better for low than high disease activity levels. The original DAPSA should be preferred in PsA. However, data sets with only 28 joint counts available can be used to calculate DAPSA28.

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Abstract Number: 651

Analysis of the Different Value of Magnetic Resonance Imaging Changes in the Sacroiliac Joints for a Diagnosis of Axial Spondyloarthritis As Judged By Rheumatologists and Radiologists

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Session Type: ACR Poster Session A

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Background/Purpose: Classification of axial spondyloarthritis (axSpA) by the imaging arm of the ASAS criteria relies partly on the detection of a bone marrow edema (BME) in the magnetic resonance imaging (MRI) of the sacroiliac joints (SIJ) suspicious of SpA. Here we evaluate different types of MRI changes possibly relevant for a diagnosis of axSpA as judged by radiologists taking the rheumatologist's diagnosis as gold-standard.

Methods: Consecutive patients <45 years were included if they presented with chronic low back pain (duration >3 months) and underwent complete diagnostic workup including SIJ-MRI. All clinical and laboratory information including images but no radiological reports was available for experienced rheumatologists to make a diagnosis of axSpA or non-axSpA. In parallel, two experienced musculoskeletal radiologists, blinded to patients' demographics and symptoms (except for back pain) evaluated all MR images without knowledge of the rheumatologist's diagnosis, by quantification of BME, fat metaplasia, erosions, sclerosis and ankylosis based on the Berlin SIJ score. The radiologists also stated whether the patient is likely to have axSpA or not, solely based on MRI findings.

Results: A total of 100 patients were recruited. The rheumatologist diagnosed axSpA in 54 patients (mean age 31.5±8.0 years, 77.8% HLA-B27+, mean symptom duration 36.4±42.0 months), while 46 patients were diagnosed as non-specific back pain (age 33.6±7.1 years, 17.4% HLA-B27+, mean symptom duration 25.5±31.6 months). According to the radiologists, 38 patients were identified as axSpA, 34 of which were also diagnosed as axSpA by the rheumatologist (overall agreement with the clinical diagnosis: 63%), and 4 patients were thought to have axSpA by the radiologist but not

by the rheumatologist (disagreement with the clinical diagnosis: 8.7%). Similarly, the quantification of MRIs showed higher scores in patients diagnosed as axSpA by the rheumatologist. Only few patients had sclerosis or ankylosis. From the radiologist's perspective, the calculated odds ratio (OR) for identification of axSpA by MRI only was 3.1 (95% CI:1.4-7.1) for the presence of BME, 3.5 (95% CI:1.4-9.0) for fat metaplasia, 2.8 (95% CI:1.1-7.0) for erosions, 2.0 (95% CI:0.7-5.5) for ankylosis. For the combination of BME and any structural change, the OR was 3.7 (95% CI:1.6-8.5).

Conclusion: This study reveals a discrepancy between the rheumatologist's and the radiologist's identification of axSpA, confirming that a diagnosis of axSpA in daily practice should not rely on imaging findings only. Nevertheless, the overall specificity of the radiologists was acceptable, although the sensitivity was relatively low. These data suggest also that not only BME but also fat metaplasia and erosions are of value to diagnose axSpA, beyond classification. The combination of MRI changes seems to enhance the discriminative diagnostic performance. Finally, it will be important to define clinically relevant cut offs for the MRI scores.

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Disease Interception in Psoriasis Patients with Subclinical Joint Inflammation By Interleukin 17 Inhibition with Secukinumab – Data from a Prospective Open Label Study

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Background/Purpose: Musculoskeletal changes precede the onset of psoriatic arthritis (PsA). A subset of psoriasis patients is characterized by arthralgia as well as inflammatory changes in the joints visible by MRI assessment. These patients have a high risk to progress into PsA. The objective of the study was to test the concept of a very early intervention in PsA we exposed psoriasis patients with subclinical joint inflammation to the anti-interleukin (IL)-17A antibody secukinumab. We hypothesized that IL-17A inhibition disrupted the early link between skin and joint disease in Psoriasis.

Methods: Psoriasis (but not PsA) patients were included in the open prospective 24-weeks “Interception in Very Early PSA” (IVEPSA) study. To fulfill the inclusion criteria patients had to have a PASI score greater than 6 or nail or scalp involvement as well as inflammatory or erosive changes in MRI or high-resolution peripheral quantitative computed tomography (HRpQCT) at baseline. Patients received treatment with secukinumab 300 mg sc. for 24 weeks. MRI scans and HRpQCT of the dominant hand were performed at baseline and at 24 weeks. MRI was scored according to PsAMRIS. HRpQCT evaluated for erosions and enthesophytes.

Results: 20 patients (median age 49.5 years (IQR 42.8, 59), 70% males) with a median disease duration of 14 years (IQR 5, 20), were included into the study. At baseline, 85% reported arthralgia assessed by a Visual Analogue Scale (VAS) and 40% had tender joints on examination (TJC78). 83.3% had at least one inflammatory lesion in the MRI, 66.7% synovitis, 55.6% tendinitis/enthesitis, 27.8% osteitis and 16.7% periarticular inflammation. Erosions were present in 72.2% and 58.8% in the MRI and HRpQCT, respectively, while enthesophytes were found in 33.3% and 41.2%. One patient was discontinued early due to lack of improvement (wk12) and one patient was unable to perform the follow-up MRI. Psoriatic skin disease (total PASI and BSA) significantly improved (both $p < 0.05$) and also arthralgia (VAS pain, tender joint count) significantly declined after secukinumab treatment (both $p < 0.05$). Total PsAMRIS score and synovitis subscore significantly improved at wk24 ($p = 0.005$ and $p = 0.008$, respectively). Importantly, improvement in total PsAMRIS score significantly correlated with the improvement in arthralgia ($p < 0.05$). Finally, neither erosions nor enthesophytes in MRI and HRpQCT progressed during the 24 weeks of treatment. There was no new safety signal in the study.

Conclusion: IL-17 inhibition by secukinumab over 24 weeks led to resolution of inflammation and no progression of bone changes in the joints in psoriasis patients with subclinical peripheral joint involvement. These data suggest that very early disease interception in PsA is a feasible approach. IVEPSA also provides the guide for further very early interventions in PsA providing concepts for imaging-based identification and the sensitivity to change of subclinical inflammation to biological disease modifying anti-rheumatic drug therapy.

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Abstract Number: 653

Validation of Assessments in Spondyloarthritis International Society MRI Lesion Definitions in Axial Spondyloarthritis: Data from the Echography in Spondyloarthritis Cohort

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Background/Purpose: The diversity of MRI lesions in the sacroiliac joints of patients with axial spondyloarthritis (axSpA) has only recently been appreciated and consistent terminology, descriptions, and definitions have not yet been internationally accepted. The ASAS MRI group has generated updated consensus lesion definitions (ASAS_MRI_defⁿ) and these now require validation to support widespread adoption for clinical practice and research. We aimed to assess the distribution by diagnosis, reliability of detection, and construct validity of active and structural lesions as defined by the ASAS-MRI group (ASAS_MRI_defⁿ) on MRI scans from the ECHOSPA cohort.

Methods: Consecutive outpatients with age <50 years and symptoms >3 months suggestive of SpA were enrolled in the French ECHOSPA cohort study. MRI scans from 412 of the 470 recruited cases were available for evaluation by 2 readers and an adjudicator. ASAS_MRI_defⁿ were recorded in an ASAS consensus-derived eCRF that comprises global assessment (active and/or structural lesion typical of axSpA present/absent) and detailed scoring of individual lesions (SPARCC SIJ inflammation, SPARCC SIJ structural). Definite lesions were defined according to confidence ≥ 3 (0-4 scale). Reliability of detection of lesions assessed as present/absent by global assessment was analyzed using kappa and detailed scoring of SIJ quadrants by intra-class correlation coefficient (ICC). For construct validity we calculated optimal cut-offs for bone marrow edema (BME) and erosion that defined active and structural lesion typical of axSpA, respectively.

Results: At baseline, mean age of the 412 cases with MRI scans was 39.3 years, mean duration of symptoms was 2.5 years, 41.3% were HLA-B27 positive, and 63.2% were female. Active and structural lesions typical of axSpA were present in 9.7% and 10.8%, respectively, and ASAS positive MRI in 9.3%. Subchondral BME (13.6%) and erosion (9.4%) were the most frequent active and structural lesions, respectively. Active but not structural lesions were present in 3.0% while the converse was evident in 4.0%. Both active and structural lesions were present in 6.9% while either active or structural lesions were present in 13.8%. AxSpA was diagnosed at baseline in 88.1% and all categories of active and structural lesions were higher in those with axSpA. Substantial κ values (95%CI) were evident for detection of these lesions with comparable reliability for active and structural lesions: active lesion (0.76(0.65-0.88)), ASAS positive MRI (0.78 (0.66-0.89)), structural lesion (0.76(0.65-0.87)). Detailed scoring per SIJ quadrant that reflect expert opinion as to what constitutes an active or structural lesion typical of axSpA are provided in the Table.

Conclusion: SPARCC BME score of ≥ 3 and Erosion Score ≥ 2 may optimally reflect active and structural lesions typical of axSpA, respectively. MRI lesions defined by the ASAS-MRI group can be reliably detected.

Table.

Number of SIJ Quadrants	Active Lesion Typical of AxSpA	
	Sensitivity	Specificity
BME Score ≥ 2	100%	90.27%
BME Score ≥ 3	100%	95.14%
BME Score ≥ 4	97.5%	96.76%

	Structural Lesion Typical of AxSpA	
	Sensitivity	Specificity
Erosion Score ≥ 2	84.09	99.15
Fat metaplasia ≥ 2	27.27	98.02
Backfill ≥ 2	11.36	100
Ankylosis ≥ 2	4.55	99.72

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MRI Lesion Definitions in Axial Spondyloarthritis: A Consensus Reappraisal from the Assessments in Spondyloarthritis International Society

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Background/Purpose: There has been substantial progress in the characterization of MRI lesions in the sacroiliac joints (SIJ) and spine in axial spondyloarthritis (axSpA) since the last consensus-based reports from ASAS^{1,2}. In particular, new data have emerged regarding structural lesions and the considerable evolution in their appearance according to the degree of inflammation. There is as yet a lack of international consensus on standardized definitions of all the lesions reported to date. Consequently, the ASAS MRI group was convened to evaluate the literature describing the spectrum of MRI lesions in axSpA and to generate a consensus update on standardized definitions for MRI lesions.

Methods: The literature pertaining to MRI lesion definitions in axSpA was discussed at 3 meetings of the ASAS MRI group attended by 26 investigators (21 rheumatologists, 5 radiologists). The group reviewed the literature for MRI lesion definitions and decided by consensus which definitions would be retained, which required modification, and which required a new definition. The group also agreed on a set of reference images, a study design (ASAS MRImagine) for multi-reader assessment of lesion definitions using MRI scans from the ASAS classification cohort, a PowerPoint-based reader calibration module, and a study-specific interactive eCRF incorporating links to reference images for recording MRI data.

Results: For definitions denoting signs of activity in the SIJ, there are no revisions to the most current ASAS definition of a positive MRI and for subchondral bone marrow inflammation¹. Definitions for capsulitis and enthesitis are revised. A new definition, *joint space enhancement*, denotes increased signal on contrast-enhanced images in the joint space of the cartilaginous portion of the SIJ. This replaces the term 'synovitis' and a separate definition describes what constitutes joint

space fluid. For signs of structural change in the SIJ, the definition for sclerosis unchanged. A revised definition for a fatty lesion incorporates characteristics typical of axSpA, and for erosion requires both loss of cortical bone as well as adjacent marrow matrix on a T1W image. A new definition, *fat metaplasia in the joint space* (*'backfill'*), denotes the reparative change on aT1W image at the site of erosion when signs of activity recede. The new definition for ankylosis stresses the continuity of bright marrow signal across the joint space on a T1W image while for bone bud, the signal does not bridge the joint. Spinal lesion definitions are divided into those that occur in defined central and lateral sagittal slices. The revised definition of a vertebral corner inflammatory lesion divides this into a regular (type A) and dimorphic (type B) lesion. A new definition for corner erosion requires both loss of cortical bone as well as adjacent marrow matrix. New definitions for new bone growth require bright signal on T1W images extending from the vertebral corner marrow or endplate, which may (ankylosis) or may not (bone spur) be continuous with the adjacent vertebra.

Conclusion: The ASAS MRI group has generated a consensus-based update on MRI lesions in axSpA.

1. Lambert et al. Ann Rheum Dis 2016; 75:1958-1963
2. Hermann et al. Ann Rheum Dis 2012; 71:1278-1288

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Abstract Number: 655

Diagnostic Performance of MRI Lesions in the Sacroiliac Joints According to Updated Assessments in Spondyloarthritis International Society Lesion Definitions: A Central Reader Assessment of MRI Scans from the Assessments in Spondyloarthritis Classification Cohort

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Background/Purpose: The ASAS MRI group has generated updated consensus lesion definitions (ASAS_MRI_def^m) for the spectrum of MRI lesions in the SIJ. Their relative performance as diagnostic indicators requires assessment to understand their value in clinical practice when assessing patients referred with undiagnosed back pain. We aimed to determine optimal quantitative SPARCC cut-offs for specific MRI lesions reflecting diagnosis of axSpA in patients with undiagnosed back pain recruited to the ASAS Classification Cohort (ASAS-CC)¹ and diagnosed by local rheumatologist expert opinion.

Methods: ASAS_MRI_def^m were recorded in an eCRF that comprises global assessment (active or structural lesion typical of axSpA present/absent), links to reference images, and detailed scoring of lesions per SIJ quadrant (SPARCC SIJ inflammation, SPARCC SIJ structural). MRI images were available from 278 of the 495 cases that had MRI performed in the ASAS-CC and were evaluated by 7 experienced readers from the ASAS-MRI group. Detailed SPARCC scoring data was based only on assessment of images in DICOM format. We calculated sensitivity and specificity for varying numbers of SIJ quadrants with bone marrow edema (BME), erosion, and fatty lesions for diagnosis of axSpA as determined by the local rheumatologist at baseline and after a mean 4.4 years of follow up. Lesion cut-offs were tested according to data based on majority agreement ($\geq 4/7$ readers) and from any 2 central readers.

Results: Lesion cut-offs based on BME were most sensitive for diagnosis at baseline and follow up but erosion- and fatty-lesion based cut-offs were more specific (Table). There was a consistent improvement in the sensitivity and specificity

performance of cut-offs based on erosions and fatty lesions according to diagnosis at baseline and then at follow up after 4.4 years but not for cut-offs based on BME. This improvement was also consistently observed in data based on majority agreement of central readers. Sclerosis based cut-offs performed least well but specificity was still 90% at follow up.

Conclusion: The ASAS consensus definitions for active and structural lesions and scoring cut-offs based on the presence of these lesions in 2-3 SIJ quadrants have comparable diagnostic performance. However, diagnostic performance consistently improves for erosion and fatty lesion based cut-offs after follow up.

1. Rudwaleit et al. Ann Rheum Dis 2009;68:777-831.

Table. Sensitivities and specificities of cut-offs for SIJ lesion scores (number of SIJ quadrants) according to presence of axSpA according to diagnostic ascertainment of local physician in ASAS classification study.

MRI lesion cut-offs*	axSpA at Baseline (n 237)		axSpA at Follow up (n 143)	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Any 2 central reader data				
BME Score ≥ 2	50.00 (40.6 - 59.4)	82.46 (70.1 - 91.3)	46.48 (34.5 - 58.7)	86.36 (65.1 - 97.1)
BME Score ≥ 3	40.52 (31.5 - 50.0)	94.74 (85.4 - 98.9)	33.80 (23.0 - 46.0)	90.91 (70.8 - 98.9)
Erosion Score ≥ 2	35.34 (26.7 - 44.8)	92.98 (83.0 - 98.1)	33.80 (23.0 - 46.0)	95.45 (77.2 - 99.9)
Erosion Score ≥ 3	31.03 (22.8 - 40.3)	92.98 (83.0 - 98.1)	33.80 (23.0 - 46.0)	95.45 (77.2 - 99.9)
Fatty lesion (any) ≥ 2	34.48 (25.9 - 43.9)	92.98 (83.0 - 98.1)	38.03 (26.8 - 50.3)	95.45 (77.2 - 99.9)
Fatty lesion (any) ≥ 3	31.90 (23.6 - 41.2)	94.74 (85.4 - 98.9)	35.21 (24.2 - 47.5)	95.45 (77.2 - 99.9)
Sclerosis ≥ 2	32.76 (24.3 - 42.1)	82.46 (70.1 - 91.3)	29.58 (19.3 - 41.6)	90.91 (70.8 - 98.9)
Sclerosis ≥ 3	28.45 (20.5 - 37.6)	82.46 (70.1 - 91.3)	26.76 (16.9 - 38.6)	90.91 (70.8 - 98.9)
Majority agreement ($\geq 4/7$) central reader data				
BME Score ≥ 2	36.21 (27.5 - 45.6)	92.98 (83.0 - 98.1)	29.58 (19.3 - 41.6)	90.91 (70.8 - 98.9)
BME Score ≥ 3	32.76 (24.3 - 42.1)	100.00 (93.7 - 100.0)	28.17 (18.1 - 40.1)	95.45 (77.2 - 99.9)
Erosion Score ≥ 2	26.72 (18.9 - 35.7)	96.49 (87.9 - 99.6)	29.58 (19.3 - 41.6)	100.00 (84.6 - 100.0)
Erosion Score ≥ 3	24.14 (16.7 - 33.0)	96.49 (87.9 - 99.6)	29.58 (19.3 - 41.6)	100.00 (84.6 - 100.0)
Fatty lesion (any) ≥ 2	20.69 (13.7 - 29.2)	98.25 (90.6 - 100.0)	21.13 (12.3 - 32.4)	100.00 (84.6 - 100.0)
Fatty lesion (any) ≥ 3	18.97 (12.3 - 27.3)	98.25 (90.6 - 100.0)	21.13 (12.3 - 32.4)	100.00 (84.6 - 100.0)
Sclerosis ≥ 2	18.10 (11.6 - 26.3)	91.23 (80.7 - 97.1)	18.31 (10.1 - 29.3)	90.91 (70.8 - 98.9)
Sclerosis ≥ 3	16.38 (10.2 - 24.4)	91.23 (80.7 - 97.1)	15.49 (8.0 - 26.0)	90.91 (70.8 - 98.9)

* Based on SPARCC scoring and number of SIJ quadrants

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What Is the Level of Agreement between Local and Central Readers in the Detection of Active and Structural MRI Lesions Typical of Axial Spondyloarthritis? Data from the Assessments in Spondyloarthritis Classification Cohort Study

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SESSION INFORMATION

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Session Type: ACR Poster Session A

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Background/Purpose: There has been no central reader evaluation of MRI scans from the ASAS Classification Cohort (ASAS-CC)¹ to compare detection of lesions between central and ASAS-CC local site readers. Local readers reported active MRI lesions typical of axSpA in the SIJ of 61.6% and 2.2% of patients diagnosed with axSpA and non-axSpA back pain, respectively. Structural lesions were recorded but not reported. We aimed to compare the frequencies of active and structural lesions from the ASAS-CC according to diagnostic category and agreement for their detection between ASAS-CC local site readers and central readers from the ASAS-MRI group.

Methods: MRI lesions were recorded in an eCRF that included wording of lesions defining active and structural lesions typical of axSpA that was exactly the same as in the original ASAS-CC eCRF permitting comparisons between central and local site readers. In addition, lesions that met the criteria for an ASAS positive MRI were recorded by central readers. MRI images were available from 276 of the 495 cases who had MRI performed in the ASAS-CC and also had a local rheumatologist expert opinion diagnosis. Image quality was considered sufficient to record global data by 7 central readers in all cases. Lesion frequencies were assessed descriptively according to majority agreement ($\geq 4/7$) of central reader data and also any 2 central readers. Agreement for detection of MRI lesions was compared using the kappa coefficient.

Results: Significant differences in lesion frequencies were observed according to diagnostic category (Table 1). However, the frequency of active lesions reported by local readers (61%) was greater than for central readers (43.2%). Structural lesions were also more frequently reported by local readers (42.1%) compared to central readers (34.7%) but less so than active lesions. Agreement for detection of active lesions was good but poor for structural lesions (Table 2).

Conclusion: Local readers may have overestimated the presence of MRI lesions in the ASAS-CC, particularly active lesions. Agreement for detection of structural lesions was limited. The impact on diagnosis by the local rheumatologist cannot be deduced.

1. Rudwaleit et al. Ann Rheum Dis 2009;68:777-831.

Table 1. Central MRI reader assessment according to diagnostic ascertainment of local physician in the ASAS classification study for all 276 cases with MRI scans of SIJ and baseline local clinical and imaging assessment.

		Local Rheumatologist Diagnosis		
Reader	MRI Lesion Type	AxSpA (n=199)	Not AxSpA (n=77)	P value
ACTIVE LESIONS				
Local	Active lesions typical of axSpA	114 (61.0%)†	3 (4.2%)†	<0.0001
Central (≥4/7 agreement)	Active lesions typical of axSpA	86 (43.2%)	3 (3.9%)	<0.0001
Central (≥4/7 agreement)	ASAS MRI positive	79 (39.7%)	2 (2.6%)	<0.0001
Central (any 2 readers)	Active lesions typical of axSpA	96(48.2%)	7 (9.1%)	<0.0001
Central (any 2 readers)	ASAS MRI positive	92 (46.2%)	6 (7.8%)	<0.0001
STRUCTURAL LESIONS				
Local	Structural lesions typical of axSpA	77 (42.1%)#	6 (8.5%)#	<0.0001
Central (≥4/7 agreement)	Structural lesions typical of axSpA	69 (34.7%)	6 (7.8%)	<0.0001
Central (any 2 readers)	Structural lesions typical of axSpA	94 (47.2%)	10 (13%)	<0.0001

[†] Total with clinical and MRI data = 258

[#] Total with clinical and MRI data = 254

Table 2. Agreement between central and local readers for active and structural lesions typical for axSpA.

Local Reader		Central Readers			
		Active lesion (any 2 readers)		Active Lesion (≥ 4 readers)	
		Yes	No	Yes	No
Active lesion	Yes	85	32	78	39
	No	14	127	8	133
Kappa (95% CI)		0.64 (0.54-0.73)		0.62 (0.53-0.72)	
Structural lesion	Yes	58	25	43	40
	No	41	130	27	144
Kappa (95% CI)		0.44 (0.32 to 0.55)		0.38 (0.25 to 0.50)	

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First Validation of Consensus Definitions for MRI Lesions in the Sacroiliac Joint By the Assessments in Spondyloarthritis International Society MRI Group

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Background/Purpose: The diversity of MRI lesions in the sacroiliac joints of patients with axial spondyloarthritis (axSpA) has only recently been appreciated and consistent terminology, descriptions, and definitions have not yet been internationally accepted. The ASAS MRI group has generated updated consensus lesion definitions (ASAS_MRI_defⁿ) and these now require validation to support widespread adoption for clinical practice and research. We aimed to assess the reliability of detection of active and structural lesions as defined by ASAS_MRI_defⁿ on MRI images from the ASAS Classification Cohort (ASAS-CC) by 7 experts in MRI interpretation from the ASAS-MRI group.

Methods: ASAS_MRI_defⁿ were recorded in an eCRF that comprises global assessment (lesion present/absent), links to reference images, and detailed scoring (SPARCC SIJ inflammation, SPARCC SIJ structural). MRI images were available from 278 of the 495 cases that had MRI performed in the ASAS-CC. MRI images were available in a variety of formats (DICOM(n=175), JPEG (n=71), DICOM film (n=32)) and sequences, axial and semicoronal orientations, from 278 of the 495 cases who had MRI performed in the ASAS-CC. Image quality was considered sufficient for global assessment in all cases by all readers. Detailed SPARCC scoring data was based only on assessment of images in DICOM format (n=175). Detection of lesions assessed as present/absent by global assessment was analyzed using kappa. Reliability of detailed scoring was analyzed by intraclass correlation coefficient (ICC).

Results: Reliability of detection of active lesions was comparable irrespective of image format but structural lesions were detected more reliably on DICOM images (Table). In particular, the most frequently detected structural lesion, erosion, was detected to a comparable degree of reliability on DICOM images as the most frequently detected active lesion, subchondral inflammation. Fat metaplasia in the joint space (backfill) and ankylosis were also reliably detected despite low frequency of occurrence in this cohort. For detailed scores based on SPARCC methodology, mean (SD) was BME4.0(9.9), erosion 2.0(2.2), fatty lesion 1.1(3.3), backfill 0.4(3.2), ankylosis 0.05(0.2). Mean ICC was BME-0.84, Erosion-0.55, Fatty lesion (any)-0.61, Fatty lesion (>1cm depth)-0.55, Sclerosis-0.73, Fat metaplasia in joint space-0.36, Ankylosis-0.97.

Conclusion: The reliability of the ASAS_MRI_defⁿ was substantial for the most frequently detected lesions and comparable between active and structural lesions.

Table. Kappa values for detection of MRI lesions in the SIJ of patients in the ASAS-CC by 7 central readers.

	All images (n=278) Mean kappa of all reader pairs (95% CI)	DICOM images only (n=175) Mean kappa of all reader pairs (95% CI)
Active lesions typical of axSpA	0.74 (0.65-0.82)	0.70 (0.58-0.82)
Active lesions typical of axSpA (confidence ≥3) (-4(not SpA) to +4 (SpA) NRS scale)	0.77 (0.68-0.86)	0.80 (0.69-0.92)
ASAS positive MRI	0.75 (0.66-0.83)	0.73 (0.61-0.84)
ASAS positive MRI (confidence ≥3) (1-4 scale)	0.77 (0.68-0.86)	0.79 (0.67-0.90)
Structural lesions typical of axSpA	0.64 (0.54-0.75)	0.71 (0.59-0.83)
Structural lesions typical of axSpA (confidence ≥3) (-4(not SpA) to +4 (SpA) NRS scale)	0.62 (0.50-0.74)	0.75 (0.62-0.88)
Subchondral inflammation	0.65 (0.56-0.74)	0.60 (0.49-0.72)
Inflammation in erosion cavity	0.30 (0.13-0.47)	0.37 (0.15-0.58)
Capsulitis	0.40 (0.14-0.66)	0.55 (0.18-0.90)
Joint fluid	0.36 (0.21-0.50)	0.41 (0.23-0.59)
Enthesitis	0.21 (0.05-0.37)	0.23 (0.03-0.45)
Sclerosis	0.43 (0.30-0.55)	0.48 (0.33-0.63)
Erosion	0.55 (0.44-0.66)	0.61 (0.47-0.75)
Fatty lesion (any)	0.59 (0.47-0.71)	0.61 (0.46-0.76)
Fatty lesion >1cm	0.59 (0.43-0.75)	0.66 (0.47-0.84)
Fat metaplasia in joint space	0.46 (0.27-0.66)	0.50 (0.26-0.74)
Bone bud	0.13 (-0.05-0.30)	0.11 (-0.06-0.29)
Ankylosis	0.53 (0.21-0.83)	0.58 (0.25-0.89)

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Construct Validation of the Screening for Inflammatory Pain in the Lower Back Questionnaire: Data from the Screening in Axial Spondyloarthritis in Psoriasis, Iritis, and Colitis Cohort

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Background/Purpose: The 10-item SIMPLE screening questionnaire for axSpA is a patient self-report standardized questionnaire developed by rheumatologists from the Spondyloarthritis Research Consortium of Canada and patient consumers. It elicits responses to domains comprising inflammatory back pain (IBP). We aimed to test the construct validity of the items comprising this questionnaire by comparing responses with those elicited independently by rheumatologists and by evaluating their association with severity of back pain and diagnosis of axSpA.

Methods: The multicenter Screening for Axial Spondyloarthritis in Psoriasis, Iritis, and Colitis (SASPIC) Study is aimed at early detection of axial SpA in consecutive patients presenting with undiagnosed back pain to the rheumatologist. Consecutive patients ≤ 45 years of age with ≥ 3 months undiagnosed back pain with any one of psoriasis, acute anterior uveitis (AAU), or colitis undergo routine clinical evaluation by a rheumatologist for axSpA. Patients first complete the SIMPLE questionnaire and then the rheumatologist independently of any patient data determines the presence or absence of a diagnosis of axial SpA. Agreement between patient and physician reporting of questions reflecting IBP domains was analyzed using the kappa statistic. Proportions of patients reporting to the various IBP domain questions were compared according to back pain score ≥ 5 or < 5 (0-10NRS) using the chi-square. Associations between patient responses for different IBP domain items and a diagnosis of axSpA were analyzed by regression.

Results: 234 patients (51.3% male, mean age 34.6years, mean symptom duration 7.0 years, mean back pain duration 7.1 years, B27+36.3%) were referred with AAU (29.9%), psoriasis (18.8%), Crohn's colitis (32.1%), ulcerative colitis (19.2%). Patients responded to SIMPLE items reflecting stiffness, nocturnal awakening, improvement with exercise, and response to NSAID significantly more frequently when back pain score was ≥ 5 . Agreement between patient and physician reporting for IBP domains was substantial for duration of stiffness ($\kappa=0.57$) and nocturnal awakening ($\kappa=0.63$), but less for effect of exercise ($\kappa=0.30$), effect of rest ($\kappa=0.44$), and response to NSAID ($\kappa=0.31$). Most of the SIMPLE items were significantly associated with diagnosis of axSpA with the exception of items describing alleviation of symptoms by exercise and NSAID therapy (Table).

Conclusion: Patient reporting to IBP domains of stiffness and nocturnal pain are congruent with physician reporting and associate strongly with final diagnosis of axSpA. Reporting of impact of exercise and NSAID is variable and dependent on level of back pain.

Table.

SIMPLE ITEM	Odds Ratio (95%CI)	P value
Back stiffness yes and most noticeable - When I get out of bed	2.07 (1.20, 3.64)	0.01
Amount of Stiffness - 60 min or more duration	2.92 (1.60, 5.37)	0.00053
Nocturnal Awakening - Often	4.00 (2.26, 7.20)	0.00000024
Nocturnal Awakening - After several hours of sleep	2.50 (1.44, 4.38)	0.0012
Time of Day Symptoms are worst - Morning	2.72 (1.57, 4.77)	0.00042
Effect of Rest – Makes it worse	2.46 (1.39, 4.36)	0.0019

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Comparison of MRI and Conventional Radiography for Detection of Structural Changes Typical for SpA – Data from the Assessment of Spondyloarthritis International Society Cohort

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Table 1. Comparison of MRI with conventional radiographs for the detection of structural damage in the sacroiliac joints at the patient level (n=199)

		Radiographic sacroiliitis fulfilling the mNY criteria		Absolute agreement	Kappa value
		No (n=97)	Yes (n=102)		
Presence of structural lesions typical for SpA on MRI according to the global assessment	No (n=134)	85 (42.7%)	49 (24.6%)	69.3%	$\kappa=0.39$
	Yes (n=65)	12 (6.0%)	53 (26.6%)		
Presence of any structural changes (erosions, sclerosis, ankylosis or fat metaplasia) on MRI	No (n=120)	77 (38.7%)	43 (21.6%)	69.3%	$\kappa=0.37$
	Yes (n=79)	20 (10.1%)	59 (29.6%)		
Presence of erosions or sclerosis or ankylosis on MRI	No (n=124)	79 (39.7%)	45 (22.6%)	68.3%	$\kappa=0.37$
	Yes (n=75)	18 (9.0%)	57 (28.6%)		
Presence of erosions on MRI	No (n=141)	85 (42.7%)	56 (28.1%)	65.8%	$\kappa=0.32$
	Yes (n=58)	12 (6.0%)	46 (24.1%)		
Presence of sclerosis on MRI	No (n=163)	90 (45.2%)	73 (36.7%)	59.8%	$\kappa=0.21$
	Yes (n=36)	7 (3.5%)	29 (14.6%)		
Presence of ankylosis on MRI	No (n=195)	97 (48.7%)	98 (49.2%)	50.8%	$\kappa=0.04$
	Yes (n=4)	0 (0.0%)	4 (2.0%)		
Presence of fat metaplasia on MRI	No (n=157)	90 (45.2%)	67 (33.7%)	62.8%	$\kappa=0.27$
	Yes (n=42)	7 (3.5%)	35 (17.6%)		

mNY criteria – modified New York Criteria for ankylosing spondylitis; SpA – spondyloarthritis; MRI – magnetic resonance imaging

Table 2. Comparison of MRI with conventional radiographs for the detection of structural damage in the sacroiliac joints at the single joint level (n=398)

		Definite radiographic sacroiliitis (grade ≥ 2)		Absolute agreement	Kappa value
		No (n=209)	Yes (n=199)		
Presence of any structural changes (erosions, sclerosis, ankylosis or fat metaplasia) on MRI	No (n=272)	184 (46.2%)	88 (22.1%)	71.6%	$\kappa=0.42$
	Yes (n=126)	25 (6.3%)	101 (25.4%)		
Presence of erosions or sclerosis or ankylosis on MRI	No (n=283)	187 (47.0%)	96 (24.1%)	70.4%	$\kappa=0.39$
	Yes (n=115)	22 (5.5%)	93 (23.4%)		
Presence of erosions on MRI	No (n=312)	192 (48.2%)	120 (30.2%)	65.6%	$\kappa=0.29$
	Yes (n=86)	17 (4.3%)	69 (17.3%)		
Presence of sclerosis on MRI	No (n=345)	201 (50.5%)	144 (36.2%)	61.8%	$\kappa=0.21$
	Yes (n=53)	8 (2.0%)	45 (11.3%)		
Presence of ankylosis on MRI	No (n=393)	209 (52.5%)	184 (46.2%)	53.8%	$\kappa=0.03$
	Yes (n=5)	0 (0.0%)	5 (1.3%)		
Presence of fat metaplasia on MRI	No (n=330)	195 (49.0%)	135 (33.9%)	62.6%	$\kappa=0.23$
	Yes (n=68)	14 (3.5%)	54 (13.6%)		

MRI – magnetic resonance imaging

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Background/Purpose: The objective of the study was to compare magnetic resonance imaging (MRI) and conventional radiography of the sacroiliac joints (SIJs) for detection of structural lesions typical for axial spondyloarthritis (axSpA) in an international multireader exercise with central reading of images in the ASAS cohort.

Methods: Patients with symptoms suggestive of SpA from the international ASAS Cohort who had both radiographs and T1-weighted MRIs of SIJs available for central reading were included in the study. MRI scans were assessed for structural changes compatible with axSpA (global statement) and separate changes such as erosion, sclerosis, fat metaplasia and ankylosis, by 7 central readers. Structural changes were considered as present if recorded by the majority of readers (at least 4 out of 7). Similar to MRIs, radiographs of the SIJs were scored by 3 different central readers according to the grading system of the modified New York (mNY) criteria. At the patient level, presence of definite structural damage on radiographs was defined as fulfillment of the radiographic criterion of the mNY criteria (sacroiliitis of at least grade 2 bilaterally or at least grade 3 unilaterally); at the single joint level, radiographic structural damage was defined as presence of sacroiliitis grade 2 in the opinion of at least 2 readers. Absolute agreement (percentage of patients / joints with or without structural changes on both MRI and radiography) and Kappa coefficient of agreement between MRI and radiography were determined.

Results: Overall, 199 patients (contributing 398 joints) were included. 149 (74.9%) had a diagnosis of axSpA by a local rheumatologist. Based on central reading, 102 (51.3%) had definite radiographic sacroiliitis according to them NY Criteria,

while 65 (32.7%) had structural changes suggestive of SpA on MRI according to the global assessment. The absolute agreement between MRI and radiographic assessment was 69.3% and kappa was 0.39 (Table 1). Structural lesions scored positive on x-rays could not be confirmed in a relative high percentage (48.1%) on MRI. At the single joint level, the absolute agreement between MRI and radiography was 70.4% and kappa was 0.39 (Table 2). Among structural lesions, erosions on MRI showed the best discriminative capacity regarding the structural damage on radiographs (Tables 1 and 2).

Conclusion: There was only modest agreement between MRI and conventional radiography in terms of detection of structural changes typical for SpA in the SIJs. Erosions on MRI showed the best agreement with the presence of definite structural damage on radiographs.

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Progression of Radiographic Sacroiliitis in Patients with Axial Spondyloarthritis from the Assessment of Spondyloarthritis International Society Cohort on Central Reading – Five-Year Data

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Background/Purpose: It is known that radiographic progression of sacroiliitis in axial spondyloarthritis (axSpA) is quite slow, with only few predictors of such progression identified. An analysis of data from the Assessment of Spondyloarthritis International Society (ASAS) Cohort, based on local assessment of radiographs, revealed surprisingly high rate of regression from radiographic axSpA (r-axSpA) to non-radiographic axSpA (nr-axSpA). The objective of the study was to analyze the rates and predictors for radiographic progression of sacroiliitis in patients with axSpA from the ASAS Cohort, based on the central reading of radiographs.

Table. Factors associated with progression from non-radiographic axial spondyloarthritis to radiographic axial spondyloarthritis in the ASAS cohort after central reading.

Parameter at baseline	Univariable analysis OR (95% CI)	Multivariable model 1 OR (95% CI)	Multivariable model 2 OR (95% CI)	Multivariable model 3 OR (95% CI)
Male sex	3.85 (0.60 to 23.83)	-	-	-
Age at baseline, years	0.85 (0.75 to 0.96)	-	-	0.88 (0.76 to 1.05)
HLA-B27 status	4.24 (0.76 to 23.57)	-	-	-
Active lesions on MRI*	15.08 (1.68 to 135.54)	28.55 (1.85 to 441.70)	21.99 (1.31 to 360.13)	7.82 (0.37 to 168.14)
Chronic lesions on MRI*	5.83 (1.14 to 29.90)	-	1.99 (0.19 to 21.14)	4.90 (0.27 to 88.61)
Elevated CRP (local lab)	2.15 (0.46 to 9.99)	-	-	-
Sacroiliitis sum score	16.81 (2.29 to 123.66)	35.08 (2.32 to 530.99)	31.80 (2.15 to 470.16)	18.96 (1.15 to 312.11)

*MRI was assessed by local rheumatologists. ASAS - The Assessment of Spondyloarthritis

International Society, OR = odds ratio, CI = confidence interval, HLA-B27 = human leukocyte antigen B27, MRI = magnetic resonance imaging, CRP = C-reactive protein

Methods: A total of 205 patients included in the ASAS Cohort and diagnosed with axSpA by local rheumatologists, with baseline pelvic radiographs available for central reading, were included in the current study. Among them, 106 patients had a pelvic radiographs available at follow-up (mean follow-up time 4.4 ± 0.8 years). Images were independently assessed by 2 central readers (MP, FP), blinded for the chronology of the radiographs, according to the grading system of modified New York criteria (grade 0-4). In case of discrepancy in classification (nr-axSpA or r-axSpA), the final classification was defined by adjudicator (DP). Sacroiliitis sum score (0-8) was calculated based on scoring results of all readers as the sum of the mean scores of all readers for both joints. The primary outcome was the proportion of patients progressing from nr-axSpA to r-axSpA at follow-up. Predictors of progression were investigated in univariable and multivariable logistic regression analyses.

Results: Among 106 patients, 49 (46.2%) were classified as nr-axSpA, 57 (53.7%) as r-axSpA at baseline. The agreement between primary readers in classification (nr-axSpA or r-axSpA) was moderate to substantial ($\kappa=0.54$ – baseline, $\kappa=0.63$ – follow-up); between local and central readers – poor to moderate ($\kappa=0.18$ – baseline, $\kappa=0.58$ – follow-up). At follow-up, 8 (7.5%) patients progressed from nr-axSpA to AS, 6 (5.7%) were reclassified from AS to nr-axSpA. The sacroiliitis sum score increased in 43 (40.6%) patients, decreased in 21 (19.8%) and did not change in 42 (39.6%). Logistic regression analysis showed an association of active and chronic changes on baseline MRI, existing structural damage in sacroiliac joints at baseline and younger age with higher odds for progression from nr-axSpA to r-axSpA.

Conclusion: There was a low but still detectable progression from nr-axSpA to r-axSpA in the ASAS cohort over 4.4 years of follow-up. Active and chronic changes on MRI, initial structural damage on radiographs, and younger age at baseline were associated with higher odds for progression from nr-axSpA to r-axSpA.

Disclosure: M. Protopopov, 2016 ASAS Research Internship Grant, 2; F. Proft, None; A. Sepriano, None; R. B. M. Landewé, None; D. van der Heijde, None; J. Sieper, None; M. Rudwaleit, None; D. Poddubnyy, None.

Abstract Number: 661

Bridging the Gap between Symptom Onset and Diagnosis in Axial Spondyloarthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: Axial spondyloarthritis(axSpA) is diagnosed an average of 9 years after symptom onset (1), partly because inflammatory back pain (IBP) can be difficult for primary care providers to differentiate from mechanical back pain (MBP). Untreated, axSpA can result in irreversible structural damage, functional loss and reduced quality of life. We evaluated a stratified screening process for early axSpA identification. Objectives: 1) measure time to diagnosis by a rheumatologist; 2) measure referral wait times from primary care physician (PCP) to rheumatology screening; 3) determine the incremental precision and accuracy of a stratified screening process from primary to rheumatology care.

Methods: Adults (18+ years) with low back pain visited their PCP or a dedicated interprofessional back pain model of care (www.isaac.org) and underwent primary screening, consisting of a standardized clinical assessment that incorporated ASAS criteria for IBP. At the primary care level, patients with back pain >3 months duration, onset age <50 years, with at least one other IBP feature were referred for a secondary screen by a physiotherapist with advanced rheumatology training. This screen included standardized history, physical examination and baseline investigations. The likelihood of axSpA risk (vs MBP) was determined at each screening level and defined as low, medium, or high. Precision and accuracy of primary and

secondary screens were measured against the clinical judgement of a rheumatologist with axSpA expertise. The utility of HLA-B27 was assessed as an independent screen. Sensitivity, specificity and predictive values were calculated.

Results: 410 patients underwent primary and secondary screening over a 3-year period. Mean age: 36.9 years (± 9.8); 55% female; average back pain duration 7 years (± 7.2). HLA-B27 was present in 14.4% of patients. Meantime from onset of back pain to diagnosis for patients with medium or high risk (as per rheumatologist) was 6 years (± 6.3), with a median delay of 3 years. Median wait time from primary to secondary screen was 22 days. AxSpA risk assignment by rheumatologist was: 63.6% MBP or low risk and 36.4% medium or high risk, with 18.0% of all patients receiving a final diagnosis of axSpA. HLA-B27 performed poorly as an independent screen (28% sensitivity). The best combination of sensitivity, specificity, and predictive values was found with the secondary screen (see table 1).

Conclusion: The inclusion of a secondary screening process utilizing a stratified inter professional model can shorten time to diagnosis, with high precision and accuracy in patients with axSpA. Findings provide a platform to bridge the gap between onset of back pain and diagnosis and thereby improve long-term outcomes in this patient population.

References:

1. Feldtkeller E, Bruckel J, Khan M. Scientific contributions of ankylosing spondylitis patient advocacy groups. *Curr Opin Rheumatol.* 2000; 12:239-47

Table 1. Precision and accuracy§ of screening strata for axial spondyloarthritis (axSpA) (n=410)

Screening test	Sensitivity	Specificity	PPV	NPV
<i>Primary Screen</i>				
AxSpA IBP* score 3+	73 (67, 78)	44 (39, 49)	41 (36, 46)	75 (70, 80)
AxSpA IBP* score 4+	43 (36, 50)	67 (63, 72)	42 (35, 48)	69 (64, 73)
AxSpA IBP* score 5+	21 (15, 27)	87 (84, 90)	47 (37, 57)	67 (63, 71)
<i>Independent Screen</i>				
HLA-B27 present	28 (22, 35)	94 (91, 96)	71 (62, 80)	71 (67, 74)
<i>Secondary Screen</i>				
Interprofessional (i.e. advanced physiotherapist) risk of axSpA	68 (62, 74)	90 (88, 93)	80 (74, 85)	84 (81, 87)

§ Criterion standard for precision and accuracy: clinical judgment of medium or high risk of axSpA by a rheumatologist with expertise in axSpA
Figures presented are percentages (95% confidence interval)

PPV=positive predictive value

NPV-negative predictive value

* AxSpA IBP = axial spondyloarthritis inflammatory back pain characteristics based on ASAS criteria (i.e. age of onset < 50 years; back pain duration > 3 months; morning stiffness > 30 minutes; better with activity/exercise (not with rest); nocturnal back pain)

Disclosure: L. Passalent, None; K. Sundararajan, None; A. V. Perruccio, None; C. Hawke, None; N. Haroon, None; R. D. Inman, None; Y. R. Rampersaud, None.

Abstract Number: 662

Radiographic Progression of Structural Joint Damage in Patients with Active Psoriatic Arthritis Treated with Ixekizumab for up to 3 Years

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

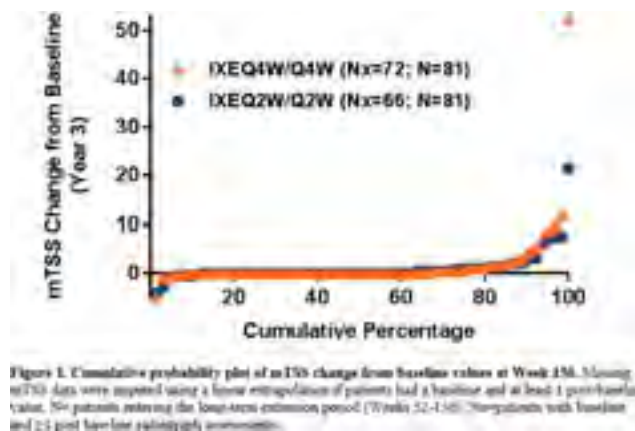
Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: Ixekizumab (IXE), an IL-17A antagonist, was shown to be superior to placebo (PBO) in inhibiting the progression of structural joint damage in patients (pts) with PsA treated for 24 weeks (wks).¹ We assessed the progression of structural joint damage in PsA patients with IXE for up to 3 years

Methods: SPIRIT-P1 (NCT01695239) is a Phase3 clinical trial investigating IXE treatment in biologic DMARD-naïve pts with active PsA. Pts must have had ≥ 1 joint erosion on the hand and foot radiographs confirmed by central reading *or* had a C reactive protein level > 6 mg/L at screening. 417 pts were randomized to 80 mg IXE every 2 (Q2W; N=103) or 4 wks (Q4W; N=107) following a 160 mg initial dose, PBO (N=106), or 40 mg adalimumab Q2W (ADA; active reference arm; N=101) for 24 wks. PBO and ADA pts were re-randomized (1:1) to IXEQ2W or IXEQ4W at Wk 16 (inadequate responders) or 24. Analyses are presented for either only pts who entered the long-term extension (LTE; wks 52-156) or



were intent-to-treat (ITT; wks 0-156). Radiographs were scored independently by 2 readers blinded to time point and clinical data. All pts were assessed for structural joint damage using the van der Heijde modified PsA Total Sharp Score (mTSS, 0-528 scale, average of readers). For LTE patients, data is presented as linear extrapolation or as observed. For linear extrapolation, any missing post-baseline data were imputed if pts had a baseline and ≥ 1 post-baseline value (i.e. Wk 52, 108, or 156). For ITT patients, post-hoc data is presented from a mixed model for repeated measures (MMRM).

Results: Of pts initially randomized (N=417), 300 pts (72%) entered the LTE (Wks 52-156) and 243 pts completed SPIRIT-P1 (58%). Adverse events and lack of efficacy were the primary reasons for discontinuation. 260 LTE pts had radiographs. Of LTE pts, mean mTSS change from baseline values at Wk 52, 108, and 156 for all 6 treatment groups are presented (Table). Wk 156 mean (SD) mTSS change from baseline values (linear extrapolation) were 1.7 (6.6) and 1.0 (3.2) for pts initially randomized to IXEQ4W and IXEQ2W. The Wk 156 cumulative probability plot is presented (Figure 1). For ITT patients, Wk 156 least squares mean (SE) mTSS change from baseline values (MMRM) were 1.9 (0.4) and 0.9 (0.4) for pts initially randomized to IXEQ4W and IXEQ2W. For LTE pts initially randomized to IXE, the majority of pts had Wk 156 mTSS change from baseline values (linear extrapolation) ≤ 0 (IXEQ4W: 67%; IXEQ2W: 62%) or ≤ 0.5 (IXEQ4W: 74%; IXEQ2W: 70%).

Conclusion: Over a 3 year period, minimal changes in mTSS were observed in the majority of PsA pts treated with IXEQ2W or IXEQ4W.

1 Mease P et al. 2017 ARD 76(1):79

Table. Radiographic Progression of Structural Joint Damage (Long-Term Extension Population)

	PBO/ IXEQ4W (N=31)	PBO/ IXEQ2W (N=33)	ADA/ IXEQ4W (N=39)	ADA/ IXEQ2W (N=35)	IXEQ4W/ IXEQ4W (N=81)	IXEQ2W/ IXEQ2W (N=81)
Baseline (Week 0), Mean (SD)						
mTSS	9.6 (11.0)	28.6 (42.4)	18.1 (28.2)	18.3 (32.7)	19.7 (33.1)	15.7 (31.4)
mTSS, Change from Baseline, Mean (SD), Linear Extrapolation ^a						
Week 52	Nx=26 0.2 (0.6)	Nx=29 0.9 (1.9)	Nx=34 0.1 (1.0)	Nx=32 -0.1 (2.4)	Nx=72 0.6 (2.3)	Nx=65 0.3 (1.5)
Week 108	Nx=27 0.4 (0.8)	Nx=29 1.2 (2.1)	Nx=34 0.3 (1.3)	Nx=32 0.4 (3.3)	Nx=72 1.1 (4.1)	Nx=66 0.6 (2.1)
Week 156	Nx=27 0.6 (1.3)	Nx=29 1.4 (2.5)	Nx=34 0.3 (1.4)	Nx=32 0.5 (3.6)	Nx=72 1.7 (6.6)	Nx=66 1.0 (3.2)
mTSS, Change from Baseline, Mean (SD), Observed						
Week 52	n=26 0.2 (0.6)	n=29 0.9 (1.9)	n=34 0.1 (1.0)	n=32 -0.1 (2.4)	n=72 0.6 (2.3)	n=65 0.3 (1.5)
Week 108	n=27 0.4 (0.8)	n=29 1.2 (2.1)	n=33 0.3 (1.3)	n=32 0.4 (3.3)	n=69 1.2 (4.2)	n=66 0.6 (2.1)
Week 156	n=25 0.5 (1.2)	n=28 1.4 (2.6)	n=30 0.2 (1.3)	n=28 0.6 (3.8)	n=60 1.6 (7.1)	n=61 1.0 (3.3)
Percentage of Non-Progressors in mTSS at Week 156, n (%), Linear Extrapolation ^a						
mTSS change ≤ 0	Nx=27 20 (74%)	Nx=29 13 (45%)	Nx=34 27 (79%)	Nx=32 23 (72%)	Nx=72 48 (67%)	Nx=66 41 (62%)
mTSS change ≤ 0.5	Nx=27 22 (82%)	Nx=29 17 (59%)	Nx=34 30 (88%)	Nx=32 24 (75%)	Nx=72 53 (74%)	Nx=66 46 (70%)
mTSS change ≤ 1.85	Nx=27 23 (85%)	Nx=29 20 (69%)	Nx=34 32 (94%)	Nx=32 27 (84%)	Nx=72 60 (83%)	Nx=66 56 (85%)

N=patients entering the long-term extension period (Weeks 52-156); Nx= patients with non-missing change from baseline mTSS after linear extrapolation; n=patients with change from baseline mTSS; SD=standard deviation

^a Missing mTSS data were imputed using a linear extrapolation if patients had a baseline and at least 1 post-baseline value (i.e. Week 52, 108, or 156). 0% were linear extrapolated at Week 52, 1.5% at Week 108, and 10.8% at Week 156.

Disclosure: D. van der Heijde, Imaging Rheumatology BV, 3,AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Daiichi, Eli-Lilly, Galapagos, Gilead, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi and UCB Pharma, 5; V. Chandran, Abbvie, Amgen, Celgene, Eli-Lilly, Janssen, Novartis, Pfizer, UCB, 5,AbbVie Inc., 2; R. Fleischmann, AbbVie, Amgen, AstraZeneca, BMS, Celgene,EMD-Serano, Eli Lilly, Merck, Novartis, Pfizer, Roche, Sanofi-Genzyme, UCB, 2,AbbVie, ACEA, Amgen, BMS, GSK, Eli Lilly, Novartis, Pfizer, Sanofi-Genzyme, UCB, 5; O. Benichou, Eli Lilly and Company, 1, 3; S. Rathmann, Eli Lilly and Company, 1, 3; C. Shuler, Eli Lilly and Co., 1,previous employee Eli Lilly and Co., 3.

Abstract Number: 663

Relative Contributions of Improvements in the Psoriasis Area and Severity Index (PASI) and Disease Activity Index for Psoriatic Arthritis (DAPSA) to Improvements in Quality of Life and Function in Patients with Psoriatic Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

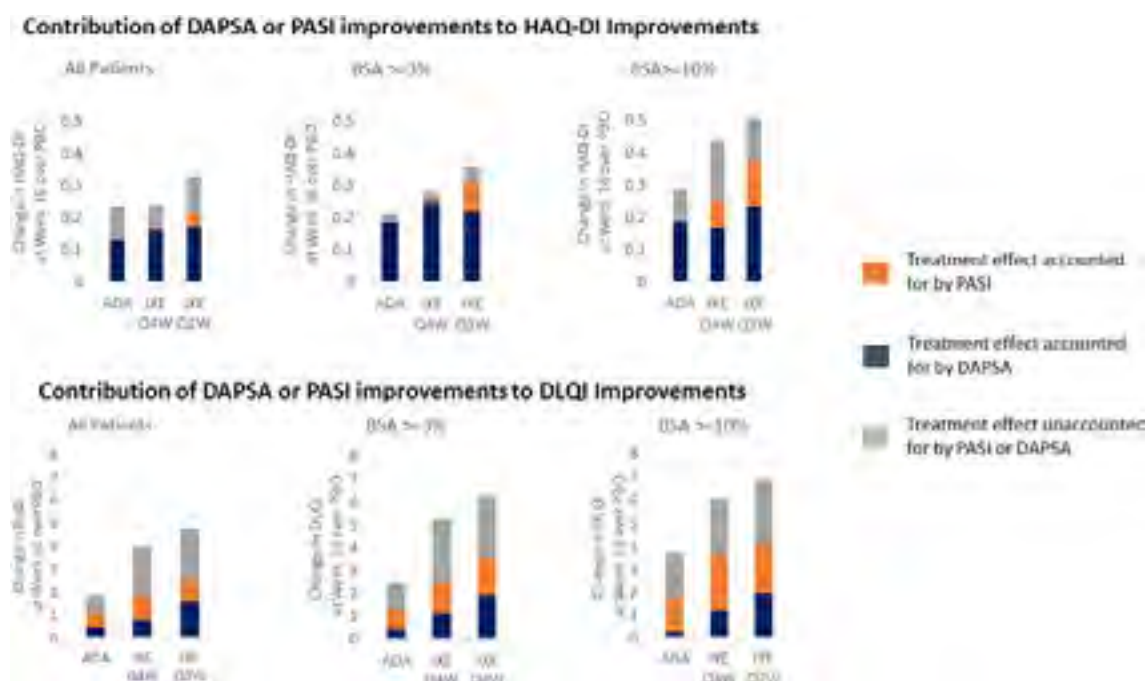
Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: Psoriatic arthritis (PsA) is a heterogeneous inflammatory condition characterized by the clinical domains of arthritis, enthesitis, dactylitis, spondylitis, and psoriasis. While it is known that both psoriasis and articular/periarticular symptoms have a meaningful impact on lives of PsA patients, it is not known the degree to which improvements in these symptoms independently contribute to improvements in quality of life (QoL) or function. This analysis quantifies the contributions of improvements in joint related symptoms (Disease Activity Index for PsA [DAPSA]) and skin related symptoms (Psoriasis Area and Severity Index [PASI]) to improvements in function(Health Assessment Questionnaire and Disability Index [HAQ-DI]) and skin-related quality of life (Dermatology Life Quality Index [DLQI]) using a multi-mediator analysis.

Methods: This analysis included data from a Phase 3 randomized clinical trial (SPIRIT-P1; NCT01695239) in biologic DMARD-naïve patients who met criteria for PsA who were randomly assigned to treatment groups (ixekizumab 80 mg



every 4 weeks [IXEQ4W, N=107], every 2 weeks [IXEQ2W, N=103], adalimumab [ADA, N=101] or placebo [PBO, N=106]). In this analysis, a multiple mediation model¹ was employed to assess the 'direct' and 'indirect (mediation)' effects of treatment on the DLQI and HAQ-DI at week 16 using percent improvement in DAPSA and PASI as the mediators. In the model, the indirect effects represent how much of the improvements in HAQ-DI or DLQI can be attributed to improvements in PASI or DAPSA. The direct effects represent the mean improvement in HAQ-DI or DLQI that cannot be accounted for by DAPSA or PASI improvements. Analyses were conducted on the intent-to-treat population and in patients with $\geq 3\%$ and $\geq 10\%$ body surface area (BSA) psoriasis involvement. Missing data was imputed using the last observation carried forward.

Results: The relative contributions of DAPSA or PASI improvements to improvements in HAQ-DI and DLQI for each treatment arm over placebo are shown in the Figure. Improvements in DAPSA accounted for the majority of improvements observed in HAQ-DI, and improvements in PASI accounted for the majority of improvements in DLQI. In patients with moderate (BSA $\geq 3\%$) or severe (BSA $\geq 10\%$) psoriasis, PASI had higher levels of contribution to both HAQ-DI and DLQI.

Conclusion: These results indicate that improvements in both joint and skin symptoms play a role in improving different aspects of function and QoL for PsA patients. While DAPSA was the most substantial contributor to improvements in HAQ-DI, the skin also plays a role, potentially through the effect of skin symptoms such as itching and skin pain on some domains of the HAQ-DI such as grooming or hygiene.

¹Preacher KJ, Hayes AF. *Behavior Research Methods*. 2008; 40(3):879-891.

Disclosure: A. Ogdie, Novartis, Pfizer Inc, 2, AbbVie, Bristol-Myers Squibb, Celgene, Corrona, Eli Lilly, Novartis, Pfizer Inc, Takeda, 5; P. Sunkureddi, Eli Lilly and Co, 2, 8; B. Zhu, Eli Lilly and Company, 1, 3; A. Spraberry, Eli Lilly and Co., 1, 3; W. Malatestinic, Eli Lilly and Co., 1, 3; Y. Dong, Eli Lilly and Company, 1, 3; D. Shrom, Eli Lilly and Co., 1, 3.

Abstract Number: 664

Prevalence and Factors Associated with Peripheral Manifestations in Spondyloarthritis. an Ancillary Analysis of the ASAS-Comospa Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

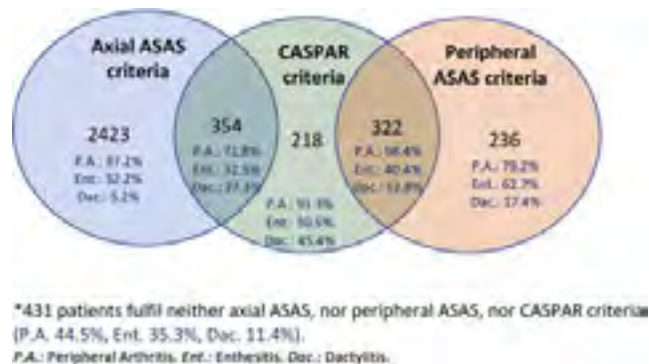
Session Time: 9:00AM-11:00AM

Background/Purpose: Peripheral manifestations (arthritis, enthesitis and dactylitis) can be observed in patients with Spondyloarthritis (SpA), but the factors associated with their presence are not well known. Studies are needed in order to thoroughly evaluate these symptoms. For this, we conducted an analysis aiming to: a) describe the prevalence of peripheral manifestations in patients with SpA in a world-wide population; b) determine the factors associated with the presence of these manifestations.

Methods: Data from the ASAS-COMOSPA study were analysed. The prevalence of each peripheral manifestation was evaluated with regard to the criteria fulfilled by the patient (ASAS axial, ASAS peripheral, CASPAR) and with regard to the time of occurrence of axial symptoms (before/concomitant/after). Factors associated with the presence of these peripheral manifestations were also explored by univariate and multivariate logistic regression.

Results: Out of the 3984 patients included in ASAS-COMOSPA, 2562 (64.3%) reported, at least, one peripheral manifestation. Among these, 2051 patients (51.5% from the total database) had current or past history of peripheral arthritis, being more frequent among patients who met CASPAR and Peripheral ASAS criteria (see Figure 1). Involvement was more frequently oligoarticular (40.2%) and appearing after axial symptom onset (48.9%). Multivariate analysis showed that patients from South America [OR 2.01, (95%CI 1.54 – 2.64)], the presence of enthesitis [OR 2.48, (95%CI 2.13 – 2.88)], dactylitis [OR 6.62, (95%CI 4.09 – 8.93)], skin psoriasis [OR 3.79, (95%CI 2.90 – 4.96)], HLAB27+ [OR 0.81, (95%CI 0.69 – 0.94)] and inflammatory back pain (IBP) [OR 0.81, (95%CI 0.69 – 0.94)] were associated with peripheral arthritis.

A total of 1506 (37.8%) and 618 (15.6%) patients reported enthesitis and dactylitis, respectively. Both occurred after axial symptoms onset in 58.3% and 60.8% of the patients, respectively. Similar results than peripheral arthritis were obtained in



the multivariate analysis regarding these two peripheral manifestations, with exception of IBP and HLAB27+, which were not associated with enthesitis.

Conclusion: Peripheral manifestations appear in 64% of patients with SpA and in more than 50% after axial symptoms onset. Peripheral arthritis, were more frequently mono- or oligo- rather than poly-articular, and the presence of psoriasis or any of the three peripheral manifestations acts as risk factor for the development of other peripheral symptoms.

Figure 1: Venn diagram.

Disclosure: C. López-Medina, None; A. Molto, None; M. Dougados, None.

Abstract Number: 665

Impact of Peripheral Manifestations on Patient-Reported Outcomes (PROs) and Treatment in Spondyloarthritis. Data from ASAS-Comospa

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: Peripheral manifestations (arthritis, enthesitis and dactylitis) are frequent in patients with Spondyloarthritis(SpA). However, little is known regarding the impact of these manifestations on patients' disease perception and treatments. In this analysis, we aimed to evaluate the impact of the presence of peripheral manifestations on patient-reported outcomes (PROs) and treatment.

Methods: Data from the ASAS-COMOSPA study were analysed. Patients who reported peripheral arthritis were divided into three groups: current, past history and no history. The impact of the presence of peripheral arthritis on VAS-G (Global Visual Analogue Scale), BASDAI (Bath Ankylosing Spondylitis Activity Index), BASFI (Bath Ankylosing Spondylitis Functional Index), work and activity impairment was evaluated through the use of the ANOVA one factor test. Finally, NSAIDs, corticosteroids and DMARDs intake were compared among patients with and without peripheral articular involvement.

A similar statistical analysis was performed for enthesitis and dactylitis.

Results: Among the 3984 patients included in the ASAS-COMOSPA study, 1333 (33.5%), 718 (18%) and 1933 (48.5%) patients had current, past history and no history of peripheral arthritis, respectively. Patients with current peripheral arthritis showed higher levels in VAS-G, BASDAI, BASFI, as well as in work and activity impairment, in comparison to the other two groups, being these differences statistically significant ($p < 0.01$). Patients with peripheral articular involvement at the time of the visit showed higher mean scores in all questions of the BASDAI questionnaire, in contrast to those with past history and/or no history ($p < 0.001$). Impact on treatment is shown in table 1. Regarding enthesitis, 642 (16.1%), 864 (21.7%) and 2478 (62.2%) patients had current, past history and no history of enthesitis, respectively. Patients with current enthesitis showed significant higher levels in all PROs against the other two groups of patients ($p < 0.05$), as well as higher scores in all the BASDAI questions ($p < 0.001$).

	Current or past history of arthritis			Current or past history of enthesitis			Current or past history of dactylitis		
	Yes = 2051 n (%)	No = 328 n (%)	p-value	Yes = 1506 n (%)	No = 2478 n (%)	p-value	Yes = 618 n (%)	No = 3366 n (%)	p-value
% of patients using NSAIDs	1858 (90.6)	1690 (87.4)	<0.001	1402 (93.1)	2146 (86.6)	<0.001	568 (91.9)	2980 (88.5)	0.013
% patients using csDMARDs	1581 (77.1)	790 (40.9)	<0.001	1062 (70.5)	1309 (52.8)	<0.001	492 (79.6)	1879 (55.8)	<0.001
% patients using bDMARDs	987 (48.1)	755 (39.1)	<0.001	750 (49.8)	992 (40.0)	<0.001	330 (53.4)	1412 (41.9)	<0.001
% patients using corticosteroids	1048 (51.1)	475 (24.6)	<0.001	738 (49.0)	785 (31.7)	<0.001	330 (53.4)	1193 (35.4)	<0.001

Finally, 171 (4.3%), 447 (11.2%) and 3366 (84.5%) patients had current, past history and no history of dactylitis, respectively. The same results as the other two peripheral manifestations were obtained regarding impact on PROs and BASDAI questions

Conclusion: The presence of any of the three peripheral manifestations at the time of the visit was associated to higher scores in all PROs. Patients with peripheral involvement showed greater use of NSAIDs, corticosteroids and DMARDs than those without peripheral manifestations.

Table 1. Impact on treatment

Disclosure: C. López-Medina, None; A. Molto, None; M. Dougados, None.

Abstract Number: 666

Inflammation on MRI of the Sacroiliac Joints Is Highly Associated with Structural Damage in Axial Spondyloarthritis Patients in Clinical Practice: Data from the ASAS and DESIR Cohorts

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: The effect of MRI-detected inflammation on the development of radiographic damage at the sacroiliac joints (SIJ) level in patients (pts) with axial SpA (axSpA) has been previously shown when images were scored by trained central readers¹. Central reading decreases measurement error, but does not translate easily to what is usually done in clinical practice. We aimed to test the possible effect of MRI-SIJ inflammation on structural damage in X-SIJ, when both are assessed by local readers as in daily clinical practice.

Methods: Pts with axSpA from both the ASAS and DESIR cohorts were included. MRI-SIJ and X-SIJ were obtained at baseline (BL), and X-SIJ at follow-up (ASAS: mean 4.4years; DESIR: 5 years) and scored by local readers (rheumatologists/radiologists). Images were taken unblinded to other imaging information and clinical characteristics.

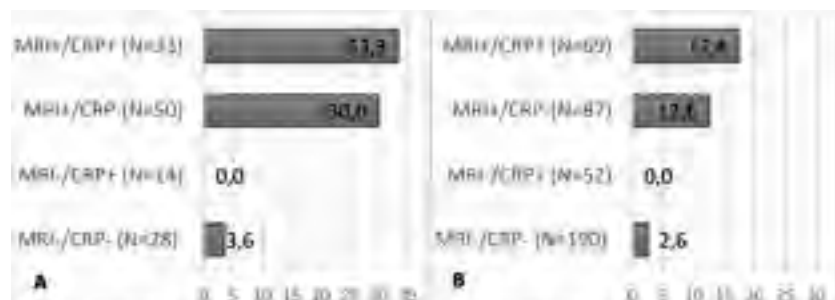


Figure. Net progression from mNY-negative to mNY-positive according to baseline objective inflammatory markers in the ASAS (A) and DESIR (B) cohorts (ASAS: N=125; 25 patients miss baseline MRI-SIJ; DESIR: N=398; 6 patients miss baseline MRI-SIJ and 17 patients miss baseline CRP).

Table. Effect of inflammation on MRI-SIJ at baseline on X-SIJ structural damage at follow-up.

Predictor	Outcome	mNY
		OR (95% CI)
Sacroiliitis on MRI-SIJ (ASAS-cohort)		3.1 (1.3; 7.9) *
Sacroiliitis on MRI-SIJ (DESIR-cohort)		7.4 (4.3; 12.7) *

* Adjusted for gender, HLA-B27, CRP, symptom duration.

Readers had the option to view the BL image when scoring the follow-up image. Bone Marrow Edema (BME) at MRI-SIJ was assessed either without a formal definition (ASAS) or according to the ASAS definition (DESIR). Structural damage in the X-SIJ was defined according to the mNY criteria. The % of structural net progression (number of ‘progressors’ minus the number of ‘regressors’ divided by the total number of pts) was assessed in subgroups according to CRP and BME status at BL. The effect of BME on MRI-SIJ on X-SIJ damage was evaluated in logistic regression models adjusted for potential confounders selected *a priori* on clinical grounds (gender, HLA-B27, CRP, symptom duration, variables available in both cohorts).

Results: In total, 125 (ASAS-cohort) and 415 (DESIR-cohort) pts had complete 5-year X-SIJ data available. Remarkably, but not unexpectedly, the % of ‘improvements in X-SIJ’ was impressive both in the ASAS and DESIR cohorts (8.8% and 5.5% respectively), yielding a total % of net progression that was higher in the former than in the latter (19.2% and 6.3%). Net progression in X-SIJ ranged from 0.0% to 33% and from 0% to 17.4% according to the presence of objective signs of inflammation at BL in the ASAS- and DESIR-cohorts, respectively (figure). In the multivariable analysis, the presence of baseline BME at MRI-SIJ both in the ASAS (OR=3.1 [95%CI: 1.3-7.9]), and DESIR cohorts (OR=7.4 [95% CI: 4.3-12.7]) was highly associated with X-SIJ structural progression at follow-up (table).

Conclusion: Our results, obtained in two independent cohorts, show that despite the expected increased ‘noise’ (measurement error) invoked by local reading, inflammation on MRI-SIJ still clearly associates with the development of radiographic damage in axSpA.

Disclosure: A. Sepriano, None; S. Ramiro, None; R. B. M. Landewé, None; M. Dougados, None; D. van der Heijde, None; M. Rudwaleit, None.

Abstract Number: 667

Assessment of Radiographic Sacroiliitis on Antero-Posterior Lumbar Radiographs As Compared to Conventional Pelvic Radiographs in Patients with Axial Spondyloarthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

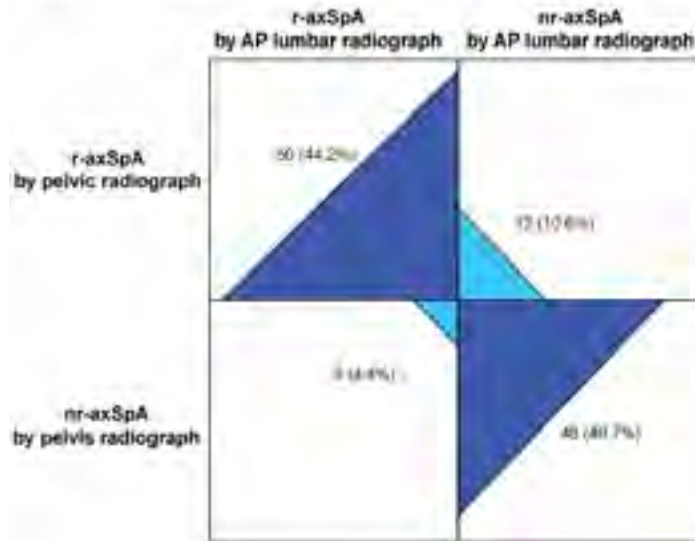
Session Type: ACR Poster Session A

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

Background/Purpose: EULAR guidelines consider conventional radiograph of sacroiliac joints (SIJs) as the first recommended imaging method in case of suspected axial spondyloarthritis (axSpA). However, it is not clear whether sacroiliac joints can be reliably assessed on anteroposterior (AP) lumbar radiographs, which are often performed as a part of the diagnostic work-up in patients presented with back pain. The aim of the study is to investigate reliability and validity of radiographic sacroiliitis assessment on AP lumbar radiographs as compared to conventional pelvic radiographs in patients with axSpA.

Methods: Patients from the GERman SPondyloarthritis Inception Cohort (GESPIC) were selected based on the availability of sets of pelvic and AP lumbar radiographs with visible SIJs at baseline and after 2 years of follow-up. Two trained readers (ML and VR) scored the images independently and in a random order according to the radiographic system of the modified New York (mNY) criteria (grade 0 to 4). The sacroiliitis sum score (0-8) was calculated as a sum of the mean grades of 2 readers for the right and left SIJ. We assessed intra- and inter-reader reliability using intraclass correlation coefficients (ICC) of the sacroiliitis sum scores.

Figure. Classification as non-radiographic or radiographic axial spondylarthritis based on sacroiliitis assessment on conventional pelvic and anteroposterior lumbar radiographs.



Results: A total of 226 sets radiographs were scored from 113 patients included in the present study. The intra-observer agreement was good to excellent for the sacroiliitis sum score of pelvic vs. AP lumbar radiographs at baseline (ICC 0.80 for ML and 0.74 for VR) and at year 2 (ICC 0.81 for ML and 0.77 for VR). The inter-observer agreement for pelvic and AP lumbar radiographs was also good to excellent: ICC at baseline: 0.81 and 0.73, respectively, at year 2: 0.76 and 0.79, respectively.

A total of 62 (54.9%) and 55 (48.7%) patients were classified as r-axSpA at baseline based on evaluation of pelvic and AP lumbar radiographs, respectively. The absolute agreement on the classification was 84.9% (figure). A total of 17 patients (12 (10.6%) with nr-axSpA and 5 (4.4%) with r-axSpA) were classified differently based on assessment of AP lumbar as compared to conventional pelvic radiographs (figure).

After 2 years of follow-up, progression from nr- to r-axSpA occurred in 7 patients (6.2%) and 8 patients (7.1%) classified as nr-axSpA at baseline based on pelvic or AP lumbar radiographs assessment, respectively. Regression from r- to nr-axSpA occurred in 4 patients (3.5%) and 3 patients (2.7%) on pelvic or AP lumbar radiographs, respectively, giving respective net progression rates of 2.7% and 4.4%.

Conclusion: Radiographic sacroiliitis can be assessed on AP lumbar radiographs with a similar reliability as on conventional pelvic radiographs.

Disclosure: V. Rios Rodriguez, None; M. Llop Vilaltella, None; M. Protopopov, None; J. Sieper, None; H. Haibel, None; M. Rudwaleit, Abbott, Bristol Myers Squibb, Janssen, MSD, Pfizer, Roche, UCB Pharma, 5; D. Poddubnyy, None.

Abstract Number: 668

Progression of Unilateral Grade 2 Sacroiliitis in a Psoriatic Arthritis Cohort

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Session Type: ACR Poster Session A

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

Background/Purpose: Axial psoriatic arthritis (axPsA) lacks a universally accepted definition. Initial studies required \geq unilateral grade 2 sacroiliitis (Uni2SI) but recent studies have required the modified radiographic New York ankylosing

spondylitis criteria (NYC) (bilateral grade 2 or unilateral grade 3 or 4 sacroiliitis). Our aims were: 1) assess the prevalence of axial involvement in a PsA cohort according to “at least Uni2SI”, 2) assess the radiographic progression of Uni2SI, 3) identify risk factors associated with progression, 4) define axPsA.

Methods: PsA patients participating in a prospective observational cohort were classified according to their worst sacroiliitis ever observed during their follow-up. The baseline features of patients with only uni2SI were compared to patients with NYC. The progression of Uni2SI was assessed in a sub-group of patients with: uni2SI on one of their radiographs and following x-rays. A comparison was made between the “non-progressors” and “progressors” (=patients who developed NYC over time). T-test, Wilcoxon rank sum test and Chi-square tests were used for descriptive analyses. Logistic regression identified risk factors associated with NYC compared to Uni2SI. Risk factors associated with radiographic progression of Uni2SI were identified in a survival analysis with interval censoring. P<0.05 was considered statistically significant.

Results: At least Uni2SI was detected in 612/1354 patients (45%). NYC sacroiliitis was observed in 477 patients (35%). Radiographic progression of Uni2SI was assessed in 154 patients, 80 (52%) progressed to NYC sacroiliitis within 5.5 years. The progressors were diagnosed at a younger age (35.6, 38.9, p=0.05), had less degenerative disc disease (DDD) (OR= 0.47, p=0.02), worse peripheral radiographic damage (OR=1.02, p=0.03) and psoriasis (OR=1.09, p=0.01) compared to non-progressors. Other demographic, clinical and radiographic variables were not associated with NYC sacroiliitis (table). In a survival analysis, patients with an elevated erythrocyte sedimentation rate (ESR) were more likely to progress (HR = 1.83, p=0.02), while patients with longer disease duration were less likely to progress (HR=0.95, p=0.02).

Patients with NYC vs “non-progressors” (unilateral grade 2 as reference group) Regression Analysis

Variable at baseline	Univariate			multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age of diagnosis	0.98	0.96-1	0.05			
Age at x ray *	0.99	0.97-1	0.23	0.99	0.97- 1.01	0.45
Male sex*	1.54	0.93-2.54	0.09	1.67	0.94- 2.95	0.08
HLA-B*27 positivity	1.11	0.59-2.09	0.75			
Smoking	0.93	0.56-1.54	0.78			
Tender and swollen joints	1	0.98-1.03	0.86			
Clinically damaged joints	1.01	0.98-1.04	0.33			
Modified Steinbrocker score	1.01	1-1.02	0.03	1.02	1- 1.03	0.03
Inflammatory back pain	1.29	0.59-2.81	0.53			
Syndesmophytes	1.46	0.87-2.45	0.15			
Degenerative disc disease	0.47	0.28-0.79	0.004	0.47	0.25- 0.87	0.02
SPARCC enthesitis score	0.83	0.64-1.09	0.19			
PASI	1.07	1.02-1.13	0.01	1.09	1.02- 1.17	0.01
Nail disease	0.86	0.48-1.53	0.61			
Elevated ESR	1.48	0.9-2.45	0.12			
Biologics	1.86	0.78-4.46	0.16			
NSAIDS	1.06	0.62-1.82	0.82			

* adjusted variables

PASI=psoriasis area severity index; ESR=erythrocyte sedimentation rate; SPARCC=spondyloarthritis Research Consortium of Canada; NSAIDS=non-steroidal anti-inflammatory drugs

Conclusion: Only half of patients with Uni2SI progressed to NYC sacroiliitis. Young patients with a short disease duration elevated ESR and with less DDD are at increased risk of progressing. Therefore, we recommend using the NYC for the definition of axPsA.

Disclosure: J. Feld, None; J. Y. Ye, None; V. Chandran, AbbVie Inc., 2,AbbVie Inc., amgen, celgene, eli lilly, Janssen, Novartis, Pfizer and UCB, 5,Eli Lilly and Co., 9; R. D. Inman, None; N. Haroon, AbbVie Inc., Amgen, Janssen, Novartis, UCB, 5; R. J. Cook, None; D. D. Gladman, Abbvie, Amgen, BMS, Celgene, Eli Lilly and Company, Janssen, Novartis, Pfizer, UCB, 5,Abbvie, Amgen, Celgene, Janssen, Novartis, Pfizer and UCB, 2.

Abstract Number: 669

High Prevalence of Axial Spondyloarthritis in Patients with Acute Anterior Uveitis and Chronic Back Pain – Preliminary Results of a Prospective Observational Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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Background/Purpose: Acute anterior uveitis (AAU) can be associated with axial spondyloarthritis (axSpA). Previous studies even described undetected axSpA in 40% of the patients with noninfectious AAU. Currently, axSpA patients still suffer an important diagnostic delay. The objective was to investigate whether referral of all patients with AAU and chronic back pain results in a high prevalence of newly diagnosed axSpA patients.

Methods: In April 2017 the prospective (ongoing) observational Sp-EYE study was started to include all patients with noninfectious AAU and chronic back pain (≥ 3 months, started $<$ age of 45 years) who were referred from nine Ophthalmology clinics to the Rheumatology department of the VU university medical center. Exclusion criteria were: history of a rheumatic or other known systemic disease associated with uveitis. At the Rheumatology department sociodemographic, clinical (e.g. duration of back pain, extra-articular manifestations, BASMI), laboratory (HLA-B27, C-reactive protein) and radiographic parameters were collected, as well as patient reported outcome parameters (e.g. BASDAI, ASDAS, ASAS Health Index). The diagnosis of axSpA was made by the rheumatologist. According to the ASAS criteria, diagnosed patients were classified into radiographic or non-radiographic axial spondyloarthritis.

Results: In the first year, 42 patients were referred to the Rheumatology department, of whom 32 (median age 35 years; 47% female) met all the inclusion criteria. See also table 1. At referral, 63% of the patients already had a history of more than one AAU and the median back pain duration was 11 years (table 1). AxSpA was diagnosed in 10 patients (31%, all HLA-B27 positive), of whom four fulfilled the criteria for radiographic and six for non-radiographic axSpA. Another 11 patients (34%, six HLA-B27 positive) were considered to be suspicious for early axSpA. An ASDAS-CRP score corresponding to a high disease activity ($\text{ASDAS} \geq 2.1$) was found in 57% of the patients with a new diagnosis or a suspicion for axSpA. Treatment was started in 20 patients, mostly with nonsteroidal anti-inflammatory drugs (in 18). In one patient a tumor necrosis factor alpha inhibitor was started shortly after diagnosis, because of the severity of the axSpA.

Conclusion: In this study the referral of noninfectious AAU patients with chronic back pain led to a notably high number of new diagnoses of axSpA (31%). Another third of the patients was considered to be suspicious for beginning axSpA, requiring further follow up. These results stress the importance of systematic referral of AAU patients from the ophthalmologist to the rheumatologist in order to improve early recognition of axSpA.

Table 1. Patient and disease characteristics at referral.

	Overall (N=32)		Definite AxSpA (N=10)		Suspicion of early axSpA (N=11)		No suspicion of axSpA (N=11)	
Age (years)	35	(29-48)	35	(30-53)	31	(27-42)	41	(34-54)
Gender – male (%)	17	(53)	8		5		4	
Back pain								
Age start back pain	24	(17-34)	29	(22-36)	20	(16-27)	24	(15-36)
Years since onset back pain	11	(5-23)	8	(4-19)	12	(2.8-21)	15	(5-24)
Currently back pain (%)	28	(88)	9		10		9	
Inflammatory back pain (clinically)	9	(28)	7		2		0	
Inflammatory back pain (ASAS)	20	(63)	9		8		3	
SpA characteristics								
Acute anterior uveitis	32	(100)						
Number of AAU	2	(1-4)	3	(2-10)	2	(1-3)	1	(1-3)
>1 AAU attacks at referral	20	(63)	8		7		5	
HLA-B27 positive (%)	20	(63)	10		6		4	
SpA features (ASAS) – amount	3	(± 1)	4.5	(4-5)	3	(2-4)	2	(1-3)
Sacroiliitis - mNY criteria	4	(13)	4		0		0	
Disease activity								
C-reactive protein > 7 mg/L	6	(19)	4		0		2	
BASMI score	1.7	(1.2-2.7)	3	(2-5.2)	1.4	(1.2-2.0)	1.4	(0.6-2.0)
Back pain, NRS	4	(1-6)	2	(2-6)	5	(3-6)	4	(1-6)
Patient global disease activity, NRS	5	(2-7)	5	(2-6)	7	(2-7)	5	(2-6)
BASDAI	3.0	(2-5)	2.2	(1.6-4.2)	4.0	(2.8-6.3)	3	(2-4)
ASDAS-CRP	2.2	(1.8-2.7)	2.0	(1.6-4.2)	2.3	(2.0-2.8)	2.0	(1.1-2.8)
ASDAS-CRP ≥ 2.1	16	(50)	4		8		4	
ASAS Health Index	4	(2.5-6)	3	(2-4)	6	(3.5-9)	5	(1-6)
Treatment started								
NSAID*	18	(56)	10		5			
DMARD **	1	(3)	0		1			
TNF inhibitor	1	(3)	1		0			

All values are reported as numbers (percentage), mean (\pm standard deviation) or median (with 1st and 3d quartile). *Two patients (both diagnosed with axSpA) already chronically used a nonsteroidal anti-inflammatory drug. **In one patient methotrexate was started because of persistent anterior uveitis and enthesitis.

AxSpA, axial spondyloarthritis; AAU, acute anterior uveitis; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score – C-reactive Protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Score; BASMI, Bath AS Metrology Index; DMARD, disease modifying antirheumatic

drug; mNY, modified New York criteria for sacroiliitis; nrs, numerical rating score (0-10); NSAID, nonsteroidal anti-inflammatory drug; SpA, spondyloarthritis; TNF, tumor necrosis factor.

Disclosure: R. van Bentum, None; F. Verbraak, None; S. Wolf, None; S. Tan, None; I. van der Horst-Bruinsma, AbbVie Inc., 2, 5, Pfizer, Inc., 2, 5, MSD, 2, 5, UCB, Inc., 2, 5.

Abstract Number: 670

Low Rate of Spinal Radiographic Progression over 2 Years in Ankylosing Spondylitis Patients Treated with Secukinumab: A Historical Cohort Comparison

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

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Background/Purpose: Secukinumab, a fully human monoclonal antibody that neutralizes IL-17A, improved signs and symptoms of ankylosing spondylitis (AS) in patients (pts) in the MEASURE 1 core trial at 2 years and through 4 years in the extension study.^{1,2} A low radiographic progression rate was also reported through 2 years (Δ mSASSS at Year 2=0.3).¹ Comparison of anti-TNF agents with historical NSAID-treated cohorts have not shown a significant benefit at 2 years in reducing radiographic progression.^{3,4} This retrospective analysis compared spinal radiographic progression over 2 years in the MEASURE 1 cohort of secukinumab-treated AS pts (C1; NCT01358175) vs a historical cohort of biologic-naïve AS pts (ENRADAS [C2; NCT00715091]).⁵

Methods: Baseline (BL) and 2-year X-ray data from the 2 cohorts were compared. Only data from pts with X-rays at BL (up to Day 30) and Year 2 (Days 31–743) were included (n=168 [C1], n=69 [C2]). X-rays were independently re-evaluated using the mSASSS by 2 reviewers (and an adjudicator for the top 10% of cases with the highest difference in Δ mSASSS between readers) who were blinded to sequence and treatment; averaged values (or the adjudicated score) were analysed.

Radiographic status at Year 2			
	C1 (MEASURE 1) N=168	C2 (ENRADAS) N=69	Odds ratio (95% CI), p-value
BL mSASSS, Mean (SD)	9.55 (14.14)	9.85 (13.78)	
mSASSS at Year 2, Mean (SD)	10.15 (14.70)	10.35 (14.65)	
Δ mSASSS over 2 years, LS mean (SE)	0.55 (0.14)	0.50 (0.22)	p=0.185
No progression (Δ mSASSS ≤ 0), %	61%	50%	1.43 (0.78, 2.60), p=0.243
No progression (Δ mSASSS < 0), %	62%	73%	1.84 (0.60, 5.77), p=0.593
Sensitivity analyses			
	MEASURE 1 (N=201; ENRADAS (N=122) n (% of N)	LS mean change (SE) from Baseline in mSASSS	Difference in LS means (SE) (MEASURE 1 vs. ENRADAS) p-value
Sensitivity analysis set 1 (BL to Day 30-817)	M: 178 (89%) E: 62 (51%)	M: 0.66 (0.153) E: 0.72 (0.225)	-0.03 (0.272) p=0.9175
Sensitivity analysis set 2 (All patients)*	M: 201 (100%) E: 122 (100%)	M: 0.64 (0.165) E: 1.06 (0.212)	-0.43 (0.280) p=0.1140
Sensitivity analysis set 3 (All patients, time-adjusted)*	M: 201 (100%) E: 122 (100%)	M: 0.66 (0.168) E: 0.99 (0.217)	-0.31 (0.280) p=0.2636
LS, least squares; CI, confidence interval; E, ENRADAS; LS, least squares; M, MEASURE 1; SE, standard deviation; SD, standard deviation			

The primary outcome was to compare the % pts with no radiographic progression (Δ mSASSS at Year 2 ≤ 0) in C1 vs C2. The difference between C1 and C2 was analysed using a logistic regression with cohort as a factor and BL mSASSS as a covariate. Sensitivity analyses were performed to assess the robustness of the comparison between the two cohorts using sensitivity analysis set 1 (BL to Days 640–819) and sensitivity analysis set 2 (all subjects with BL and post-BL X-rays [time-adjusted and unadjusted]).

Results: BL demographics were comparable across cohorts, with mean age 40.9 vs 42.6 years, and gender 72.8% vs 66.7% male in C1 vs C2, respectively. Over 2 years, least squares (LS) mean Δ mSASSS was 0.55 for C1 vs 0.89 for C2 ($p=0.185$) and % pts with no radiographic progression (Δ mSASSS at Year 2 ≤ 0) was slightly higher in C1 vs C2. Mean changes from BL in mSASSS were numerically lower in the MEASURE 1 vs ENRADAS cohorts across all the analyses performed (Table).

Conclusion: Over 2 years, a numerically lower rate of progression was seen in secukinumab-treated pts vs a control cohort of biologic-naïve AS pts. Further research is needed to understand the impact of IL-17A inhibition with secukinumab on spinal disease progression in AS pts; SURPASS (NCT03259074), an ongoing H2H study powered to compare differences in spinal radiographic progression with secukinumab vs biosimilar adalimumab, will help answer these questions.

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Abstract Number: 671

Validation of the Rexspa (Reductive X-Ray Score for Psoriatic Arthritis) in an Argentinean Cohort of Patients with Psoriatic Arthritis

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SESSION INFORMATION

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Session Type: ACR Poster Session A

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

Background/Purpose: There are many scores available to measure radiographic joint damage in patients with PsA, but most of them were developed for RA and then modified for PsA. These scores don't evaluate juxtaarticular bone proliferation, which is included as an item in the CASPAR criteria. The aim of our study was to validate the Reductive X-Ray Score for Psoriatic Arthritis (ReXSPA) score in a cohort of patients with PsA.

Methods: A cross-sectional study was carried out, patients ≥ 18 years old with PsA according to CASPAR criteria were included. Sociodemographic data, comorbidities, clinical characteristics, morning stiffness, pain and patient and physician global assessments (by NVS), joint count (66/68), dactylitis, enthesitis (MASES), cutaneous psoriasis (PASI), ESR and CRP were consigned. The self-questionnaires HAQ-A, BASDAI, BASFI, PsAQoL and DLQI were administered. The composite DAPSA and CPDAI indices were calculated and the presence of MDA was assessed. All patients underwent X-

rays of the hands and feet in the anteroposterior view. Two blind readers for the clinical characteristics of the patients and previously trained, scored them by Sharp van der Heijde modified for PsA (PsA-SvdHm) and ReXSPA indexes (ICC>0.94). The ReXSPA score evaluates a total of 22 joints in hands and feet. It values joint narrowing and erosion according to PsA-SvdHm and proliferation by Ratingen score. Time to read and calculate both scores were measured. *Statistical analysis:* Student T and Chi² test. Spearman correlation. Lineal regression analysis.

Results: A total of 66 patients were included, half of them were female, median (*m*) age of 56 years (IQR 43-62.3) and *m* disease duration of 8 years (IQR 4-14.3). 132 X-Rays were scored according to PsA-SvdH [*m* 35 (IQR: 16.3-72.5)] and ReXSPA [*m* 22 (IQR: 7-46.3)]. Time to read them was significantly shorter with ReXSPA than PsA-SvdH (mean 5.8±2.1 vs 7.5±2.5 minutes, *p*<0.0001), as well as, time to calculate them (mean 26.5±14.7 vs 55.3±38.3 seconds, *p*<0.0001), respectively. The correlation between both indexes was excellent (Rho: 0.93). In the multivariate analysis, using both radiographic scores as dependent variable, the association with disease duration remained significantly associated with both of them, and in the case of ReXSPA also with age.

Conclusion: The ReXSPA index has shown validity and a very good correlation with PsA-SvdH. It is quicker to read and calculate. Subsequent longitudinal evaluations will allow to demonstrate the validity of these findings and to determine if the evaluation of bone proliferation adds an additional advantage.

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Abstract Number: 672

Activation of NLRP3 Inflammasomes in Peripheral Blood Mononuclear Cells of Patients with Ankylosing Spondylitis

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: NLRP3 inflammasome is a molecular platform triggering activation of inflammatory cytokines including interleukin-1b (IL-1b). This study aimed to assess the expression of NLRP3 inflammasome complex and pro-inflammatory cytokines in patients with ankylosing spondylitis (AS).

Methods: Peripheral blood mononuclear cells (PBMCs) and serum from 23 male patients and gender-matched 30 healthy controls were consecutively collected. The mRNA expression for target genes including NLRP3, caspase-1, IL-1b, IL-17A, and IL-23 from PBMCs were evaluated by quantitative real-time polymerase chain reaction (qRT-PCR). Clinical information related with AS patients were collected including Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), peripheral arthritis, enthesitis, and extraarticular manifestations. Statistical analyses were performed using Spearman's correlation coefficient and Mann-Whitney *t* test.

Results: Higher mRNA expression of NLRP3, caspase-1, IL-1b, IL-17A, and IL-23 in AS was noted than those in controls (*p* = 0.010, *p* = 0.029, *p* = 0.005, *p* = 0.046, and *p* = 0.002, respectively). Patients treated with biological diseases modifying antirheumatic drugs (bDMARDs) showed significantly lower caspase-1, IL-1b, and IL-17A mRNA levels than those without bDMARDs, but not in IL-23 and NLRP3. NLRP3 mRNA levels were significantly associated with IL-23, IL-17A, caspase-1, and IL-1b (*p* < 0.05 of all). Increased NLRP3, caspase-1, IL-1b, IL-17A, and IL-23 mRNA expression in PBMC cultured with LPS was marked attenuated by antioxidants.

Conclusion: This study suggests that inflammatory response by activation of NLRP3 inflammasome might be involved in the pathogenesis of AS.

Disclosure: S. K. Kim, None; J. Y. Choe, None.

Chronic Back Pain (CBP) in First Degree Relatives (FDRs) of Patient with Ankylosing Spondylitis (AS): Comparison with the US Population, HLA-B27 Frequency and Persistence of Symptoms over Time

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

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Background/Purpose: We examined first degree relatives (FDRs) of patients with ankylosing spondylitis (AS) patients with chronic inflammatory back pain (CIBP), non-inflammatory CBP (NICBP) and no CBP for clinical features (comparing those with and without CIBP and with people participating in NHANES 2009-2010 with CBP. We examined HLA-B27 alleles and persistence of IBP over time in those with CBP.

Methods: 548 FDRs of 302 AS probands were divided into 3 groups, excluding those with a diagnosis of AS at baseline visit and, within each group, blood relatives: 1) No CBP (only subjects > 40 years of age at study visit who never had CBP) (n=159); 2) NICBP (n=79), and 3) CIBP (n=152). The white FDRs with CBP between ages 20 and 69 years were compared with 772 participants in NHANES 2009-2010 with CBP, to whom the same questionnaire was administered. HLA-B allele typing was carried out by single stranded conformation polymorphism analysis. FDRs were invited to return for a second visit either by mail or by repeat clinical evaluation.

Results:

1) FDRs with CIBP were younger than those with NICBP (45.1 years versus 55.6 years, $p=0.0002$), and had higher frequency of heel pain (52.7% versus 43.4%, $p=0.005$). HLA-B27 occurred in 57% of FDR's with CIBP compared 49.4% with NICBP ($p=n.s.$) and 39.6% of those >40 years of age at assessment with no CBP ($p=0.005$, OR=1.9).
2) Comparing 206 unrelated white FDRs (there were too few nonwhite FDR's available for meaningful analysis) with 772 white participants in NHANES 2009-2010 with CBP, there were no significant differences in features of IBP, in fact some features (pain improving as the day progresses, AM stiffness, awakening the second half of the night) were less common in FDRs with CBP compared with the general population (Table 1). On the other hand, other features of SpA (earlier age at CBP onset, uveitis, psoriasis) were more frequent in FDRs of AS patients.

Variable	AS-FDR with CBP% (N=206)	NHANES with CBP% (N=772)	*p	**p
Male	40.5	45.9	0.19	0.20
Morning stiffness >30 minutes	44.3	48.6	0.0008	0.0042
Back pain decreases as the day progresses	19.4	22.7	<0.0001	<0.0001
Back pain awakens after 4 hours sleep	57.2	74.8	<0.0001	<0.0001
Heel pain > 2 weeks	35.5	19.6	<0.0001	<0.0001
Iritis/uveitis	4.5	0.59	<0.0001	0.0005
Psoriasis	9.6	5.3	0.026	0.029
Age at CBP onset (years)	29.0+/-13.8	32.7+/-14.1	0.0006	0.0038

*p-value based on univariable model ** p-value based on multivariable model (adjusted for age and gender)

3) Of 23 patients with CIBP at baseline seen again 67.04+/- 31.02 months later, 16 (73%) still had CIBP, whereas only four (33%) of 13 NICBP patients (31%) seen 61.23 +/- 31.84 months later were still symptomatic. Of the remaining nine, three (23%) developed CIBP and six (46%) had symptoms resolve. Of the 13 without CBP at baseline seen 75.5 +/- 29.9 months later, 11(85%) remained asymptomatic, two (15%) developed CIBP and none developed noninflammatory CBP.

Conclusion: These data suggest FDRs of AS patients with CIBP have a younger age at onset, a higher frequency of heel pain, and higher frequency of HLA-B27 than those FDRs who do not develop CBP and compared to the general US population (though other features of CIBP were not more frequently seen). CIBP in FDRs of AS patients remains stable and chronic over time in most, suggesting a need for long term diagnostic and treatment approaches in this group.

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Defining the Therapeutic Target in Psoriatic Arthritis: MDA Versus Dapsa

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: T2T guidelines for psoriatic arthritis (PsA) propose using DAPSA or MDA to define the therapeutic target, but with differences in preference among experts. Objective: To determine the performance of MDA and DAPSA in the evaluation of disease activity in PsA patients.

Methods: Patients with PsA according to CASPAR criteria ≥ 18 years old were included. Sociodemographic data, comorbidities and current treatment were registered. Morning stiffness, pain, patient's (PtGA) and physician's global assessment (PGA) were consigned. Joint count (66/68), dactylitis, enthesitis (MASES), Psoriasis (PASI) and axial mobility (BASMI) were evaluated. ESR (mm/h) and CRP (mg/dl) were determined. Self-questionnaires were performed to assess: quality of life (PsAQoL, ASQoL), functional capacity (HAQ, BASFI) and disease activity (BASDAI). The composite indices were calculated: DAPSA, DAPSA-ESR, DAS28, CDAI, SDAI, CPDAI, and minimal disease activity (MDA). *Statistical analysis:* Descriptive statistics. Student's T test and ANOVA. Chi² test, Fisher exact test.

Results: 129 patients were included, 52.7% were male, with a median age of 56 years (IQR: 44-65). The median disease duration was 12 years (IQR: 7-18) and the median psoriasis duration was 21 years (IQR: 14-30). 58.9% had peripheral joint involvement, 2.3% axial involvement and 38.8% presented mixed involvement. The median of DAPSA was 13.3 (IQR: 7.4-21.7) and according to its cut-off values 3.9% of the patients were in remission, 26% in low disease activity, 55.8% in moderate and 14.3% in high disease activity. 31 patients (24%) met the MDA criteria. The cohort was dichotomized according to DAPSA: in those in remission and low activity, T2T group (10 and 56 respectively, total 66 patients) and in those with moderate and high disease activity, no T2T group (43 and 20 respectively, total 63 patients). We observed that 100% of patients who met MDA criteria were in remission and low disease activity categories by DAPSA. On the other hand, among patients who did not meet the MDA criteria, 46% had moderate and high disease activity according to DAPSA, while 35% (34 patients) were in low disease activity. The main reasons because of these patients did not meet MDA criteria, were: pain ≥ 15 mm (100%), PtGA ≥ 20 mm (79%) HAQ-A ≥ 0.5 (62%) and PASI ≥ 1 (56%). Of the 34 MDA/DAPSA discordant patients, a therapeutic change was made only in 11 of them, and they were: change of pharmacological treatment (55%), joint infiltration (27%) and consultation with the dermatologist due to skin disease activity (18%). The only variable associated with a therapeutic change was higher joint tender count in the univariate analysis, however, it did not remain significant in multivariate analysis, after adjusting for confounding variables.

Conclusion: The agreement of MDA and DAPSA was good in our cohort of PsA patients. In 60% of the discordant patients, treatment was not modified. It seems that both composite indexes are effective for monitoring T2T in daily clinical practice.

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Quantitative Ultrasound of the Calcaneus Has a Role to Play in Detecting Low Bone Mineral Density in Axial Spondyloarthritis Patients

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Background/Purpose: Axial spondyloarthritis (axSpA) patients have an increased risk of developing osteoporosis compared to matched controls. Dual energy x-ray absorptiometry (DXA) is the technique of choice to detect low bone mineral density (BMD). Quantitative ultrasound (QUS) of the calcaneus measures 3 parameters of bone: speed of sound (SOS), broadband ultrasound attenuation (BUA) and stiffness index (SI; composite of SOS and BUA) and can predict fragility fractures in postmenopausal women. QUS is cheap, portable and does not use any ionising radiation. It also provides information on bone microarchitecture, as well as bone mineral density (BMD). Few studies have investigated the use of QUS in axSpA. We aimed to investigate relationships between DXA and QUS in a well characterised axSpA cohort.

Methods: Patients fulfilling modified New York (mNY) or Assessment of Spondyloarthritis International Society (ASAS) criteria were consecutively recruited from rheumatology clinics in this twin-centre cross-sectional study. DXA assessed BMD at the spine, hip and radius. QUS of the calcaneus generated SOS, BUA and SI. Patients had a detailed assessment that included demographics, clinical exam, laboratory assessment and validated measures of disease severity (BASDAI, ASDAS-CRP, BASMI, mSASSS) collected. SPSS was used for statistical analysis.

Results: A total of 107 patients were included: 76% male, 81% mNY criteria, median (IQR) age 51.5 (17.8) years, disease duration 23.5 (20.4) years, BASDAI 3.9 (3.6), ASDAS-CRP 2.1 (1.5) and BASMI 4.1 (3.2). Fragility fracture prevalence was low (6%).

Using DXA, 16.3% had osteoporosis, 41.3% of the cohort had osteopenia and 42.3% had normal BMD as per WHO criteria. Using QUS, 2.9% of the cohort had osteoporosis, 33.7% had osteopenia and 63.5% had normal BMD. Sensitivity of the QUS was 72% in detecting low BMD, specificity was 51%, positive predictive value was 71% and negative predictive value was 53%.

There was no difference in QUS parameters in the fractured versus non-fractured group; however fragility fractures occurred uncommonly in this cohort.

Each QUS parameter (BUA, SOS, SI) was compared with DXA measurements: BUA correlated significantly ($p<0.05$) with all DXA sites (spine $r=0.39$, femoral neck $r=0.33$, total hip $r=0.37$, radius $r=0.34$), as did SI (spine $r=0.32$, femoral neck $r=0.36$, total hip $r=0.35$, total forearm $r=0.37$). There was no correlation between SOS and DXA measurements.

In univariate regression analysis, age, gender, BMI, and QUS parameters BUA and SI were independently associated with BMD by DXA. In multivariate regression models, when controlling for age, gender and BMI, both BUA and SI remained independent predictors of BMD at all DXA sites.

Conclusion: Quantitative ultrasound of the heel is independently associated with DXA measurements of BMD in this axSpA cohort. To become clinically useful, more research is needed to determine the subgroup of patients it performs most accurately in, as well as its association with fracture risk. However, QUS of the calcaneus is a promising tool which may be incorporated in assessment for low BMD in axSpA.

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A Novel Role for the Psoriatic Arthritis Impact of Disease Questionnaire

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Background/Purpose: Psoriatic arthritis (PsA) is an inflammatory arthritis that occurs in about 30% of patients with Psoriasis (Ps). Recently, a new Patient Reported Outcome Measure (PROM), Psoriatic Arthritis Impact of Disease (PsAID) was specifically developed for PsA Patients. The two versions of the PsAID, PsAID-9 and PsAID-12, are scored on a Numeric Rating Scale (NRS) of 0-10. The Minimal Disease Activity (MDA) is a composite outcome measure for PsA patients, which uses the Health Assessment Questionnaire (HAQ) as one criterion. However, the HAQ does not correlate well with measures of disease activity as PsA disease duration increases, and its use in the assessment of disease activity has been questioned.

Our objectives were to 1) validate the PsAID within our patient cohort, 2) determine if the PsAID can replace any of the other PROMs administered in the clinic, and 3) determine if the PsAID can replace the HAQ in the MDA.

Methods: Patients were recruited from a single psoriatic arthritis clinic. All patients completed the PsAID and 10 other PROMs. Various measures of disease activity were recorded by a physician at each visit. Descriptive statistics (mean, median, SD, min, max) were calculated for all PROMs. PsAID cut-offs for use in the MDA were generated based on Remission (REM) and Low Disease Activity (LDA) disease states in the Clinical Disease Activity for Psoriatic Arthritis Index (cDAPSA).

Results: 115 patients completed the PsAID. There were 70 males, 45 females, with a mean PsA duration of 18.7 (± 11.6) years. Mean scores of PsAID-9 and PsAID-12 were 3.4 (± 2.4) and 3.2 (± 2.3) respectively. The PsAID correlated moderately well with 9 of the PROMs administered in the clinic ($R^2 = 0.51-0.78$). Four PsAID cutoffs were generated for use in the MDA: REM PsAID-9, REM PsAID-12, LDA PsAID-9, and LDA PsAID-12. All four versions of the PsAID MDAs had a sensitivity greater than 85% with the HAQ MDA, and three versions of the PsAID MDA had a specificity greater than 85% with the HAQ MDA.

Conclusion: Our cohort had lower mean PsAID scores than previously reported series suggesting that our patients are monitored carefully. The only moderate correlations with other PROMs suggest that the PsAID cannot replace any of these PROMs. The high sensitivity and specificity of the PsAID MDA with the HAQ MDA suggest that the PsAID is an effective replacement for the HAQ in the MDA.

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Structural Damage Characteristics of Patients with Ankylosing Spondylitis in China

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Background/Purpose: Structural damage is a major cause of poor outcomes in patients with ankylosing spondylitis(AS). In China, structural damage characteristics of AS are rarely reported. We evaluated radiographic changes in sacroiliac (SI), spine and hip joints in Chinese AS patients, and compared structural damage with other races.

Methods: This study included 283 AS patients per the modified New York criteria. Computed tomography (CT) scans and lumbar/cervical X-rays were used to detect structural damage in SI joint and spine. Disease severity was assessed by BASRI-SI, BASRI-spine and BASRI-hip scored by a trained rheumatologist and a musculoskeletal radiologist where the inter-rater reliability (average kappa: 87.3%) was excellent. Adjusted median BASRI spine score per severity of hip arthritis was calculated using median regression.

Results: There were respectively 94 (33.2%), 98 (34.6%) and 91 (32.2%) patients with mild (BASRI-SI average: 2), moderate (2.5-3.5) and severe (4) structural damage of SI joint. 91.2% and 90.1% patients displayed bilateral symmetric sacroiliitis in the first decade and the whole duration, respectively. In patients with asymmetric sacroiliitis, more injuries were detected in left sacroiliac joints than the right. In early AS, more cervical and lumbar involvement was separately detected in 10.2 % and 21.8 %patients. In the whole duration, 68.9% patients had equal lumbar and cervical involvement. Median BASRI-spine was 4. 28 (9.8%) patients progressed to complete spinal fusion. The frequency of hip joint involvement was 41.2%. Higher hip scores were associated with worse BASRI-spine scores. Compared with the results from US AS patients (n=769) [PMID:20971774], our patients had more symmetric structural damage in SI joints and more cervical involvement in early disease. Comparing hip involvement with other races (24% for Spanish, 29% for Belgian, and 36% for Ibero-American) [PMID:19605374] revealed Chinese AS patients (41.2%) had more hip structural damage.

Table 1. Symmetric and Asymmetric Sacroiliac Involvement by AS Duration

Duration of Symptoms (years)	Symmetric Involvement	One-Grade Difference	Two-Grade Difference
	N (%)	N (%)	N (%)
0-9.9	134 (91.1)	13 (9.0)	0
10-19.9	85 (90.4)	9 (9.6)	0
20-29.9	37 (86.4)	4 (10.6)	1 (2.7)
30-39.9	3 (75)	1 (25)	0
≥ 40	1 (100)	0	0
All	233 (90.1)	27 (9.5)	1 (0.3)

Table 2. Comparison of Equal, Greater or Lesser Cervical- and Lumbar- Involvement by AS

Duration of Symptoms (years)	Cervical Equal Lumbar	Cervical > Lumbar Involvement	Lumbar > Cervical Involvement
	N (%)	N (%)	N (%)
0-9.9	100 (68)	13 (10.2)	32 (21.8)
10-19.9	58 (37.4)	9 (9.5)	31 (30)
20-29.9	20 (54.1)	8 (16.2)	14 (29.7)
30-39.9	2 (50)	1 (25)	1 (25)
≥ 40	1 (100)	0	0
All	195 (68.5)	31 (11)	77 (26.5)

Table 3. Median BASRI Spine Scores and Median Difference in BASRI Spine Scores per Score of Worst Hip

Hip Score	No. of Patients	Median BASRI Spine Score	Unadjusted Difference	Difference Adjusted for Disease Duration	Difference Adjusted for Disease Duration, Sex and Age of Onset
0	138	4 (1, 12)	Reference case	Reference case	Reference case
1	97	5.3 (2.5, 7)	+1.3 (-0.66, 3.6)	+1.36 (0.62, 2.09)	+1.66 (0.31, 2.77)
2	21	8 (5, 11)	+4 (1.65, 6.37)	+3.24 (1.88, 4.28)	+3.77 (1.75, 5.38)

Note: Data in parentheses are 95% confidence intervals. Hip score according BASRI-hip modified (0: normal, 1: nonsymmetric/oligoarticular, 2: severe, 3: complete joint fusion, 4: joint replacement).

Conclusion: Chinese AS patients had more symmetric structural damage in SI joints, more cervical involvement in early disease and more hip structural damage than reported in patients of other races. Using a more sensitive method of detection of SI and hip joint severity (CT scans) may explain part of these results.

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Abstract Number: 678

Ultrasonographic Evaluation of Achilles Tendon in Early Axial Spondyloarthropathy: Is There Any Difference between Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthropathy?

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: Along with emergence of the term of ‘non-radiographic axial SpA’ (nr-AxSpA), studies comparing AS and nr-AxSpA in terms of genetic, epidemiologic, and clinical issues have accrued. The aim of this study is to evaluate the achilles tendon enthesopathy with ultrasound (US) in AS and nr-AxSpA patients and controls. We also aimed to compare these groups in terms of associations between disease activity parameters and ultrasonographic achilles enthesitis signs.

Methods: A total of 24 AS and 20 nr-AxSpA patients fulfilling the ASAS (Assesment of Spondyloarthritis International Society) criteria for AxSpA, and 30 controls were enrolled. All SpA patients were newly diagnosed and on NSAID treatment. Demographic characteristics and ESR, CRP, HLA-B27, and indices of BASDI BASFI, BASMI, MASES (Maastricht Ankylosing Spondylitis Enthesitis Score), ASDAS-CRP, and mSASSS (Modified Stoke Ankylosing Spondilitis Spinal Score) scores were noted. Ultrasonographic evaluation of achilles tendon was performed in prone position by two rheumatologists blind to patients’ clinical data. For the distribution of the categorical data, chi square and Fisher’s exact test were used. For comparison of mean or median values of continuous values Mann Whitney U and ANOVA tests were used. Kruskal-Wallis Test was used for comparison of non-parametric data. Spearman’s correlation analysis was applied for determination of correlations between clinical and US parameters.

Results: The mean age and body mass index were similar between AS and nr-axSpA groups. However, the mean age of the control group was lower. HLAB27 positivity, extra-articular and peripheral involvement, disease activity, functional status, mean mSASSS, ultrasonographic gray scale (GS) and total scores (TS) were similar between AS and nr-axSpA groups. In GS, tendon echotexture scores were significantly different across all groups (0.81 ± 0.38 in AS, 0.58 ± 0.47 in nr-axSpA, 0.17 ± 0.91 in controls; $p=0.000$). Enteseal calcification and bone profile scores were similar in AS and nr-axSpA groups but higher than controls ($p:0.01$). When the correlations between US findings and disease activity and functional status were considered, Power Doppler (PD) score and MASES total scores were positively correlated in AS group ($p=.045$; $r: 0.41$).

Conclusion: In this study, AS and nr-axSpA patients were found to be similar in various clinical, functional, and radiologic aspects indicating that these two entities are different phenotypic reflections of the same disease spectrum rather than two distinct diseases. The positive correlation between PD and MASES scores in AS patients substantiate the performance of MASES in evaluation of enteseal activity.

Table 1: Ultrasound findings of AS and nr-axSpA patients and controls

		n	Mean	SD	Median	Min.	Max.	p
GS	AS	24	5.92	3.46	4.50	2.00	14.00	< 0.001
	nr-AxSpA	20	4.05	2.80	3.50	0.00	9.00	
	Control	30	1.73	1.89	1.00	0.00	7.00	
PD	AS	24	0.29	1.08	0.00	0.00	5.00	0.12
	nr-AxSpA	20	0.00	0.00	0.00	0.00	0.00	
	Control	30	0.00	0.00	0.00	0.00	0.00	
Total Score	AS	24	6.21	4.25	4.50	2.00	19.00	< 0.001
	nr-AxSpA	20	4.05	2.80	3.50	0.00	9.00	
	Control	30	1.73	1.89	1.00	0.00	7.00	

GS: Gray Scale; PD: Power Doppler; SD: standard deviation

Disclosure: S. Vahidfar, None; I. Sunar, None; S. Ataman, None; G. Yılmaz, None; J. M. AZARABADI, None; A. Bölükbaşı, None.

Abstract Number: 679

Ultrasonographic Research of the Relationship between Nail Disorders and Peripheral Arthritis or Enthesitis in Patients with Psoriasis and Psoriatic Arthritis

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SESSION INFORMATION

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Table 1.

	proximal nail fold (mm)	nail bed (mm)	proximal nail fold + nail bed (mm)	Pvalue*
Control (n=15)	1.11 ± 0.24	1.57 ± 0.33	2.18 ± 0.36	
Psoriasis (n=25)	1.23 ± 0.27	1.33 ± 0.47	2.55 ± 0.58	0.016
Psoriatic arthritis (n=35)	1.33 ± 0.35	1.25 ± 0.38	2.58 ± 0.56	0.014
Rheumatoid arthritis (n=23)	1.14 ± 0.27	1.14 ± 0.33	2.27 ± 0.46	0.732
Ulcerative colitis (n=28)	1.21 ± 0.28	1.22 ± 0.33	2.43 ± 0.49	0.059
Crohn's disease (n=13)	1.11 ± 0.25	1.14 ± 0.37	2.25 ± 0.48	0.378

* Comparison with control, Adjusted by height and body weight

Table 2.

	proximal nail fold (mm)	nail bed (mm)	proximal nail fold + nail bed (mm)	Pvalue*
Psoriasis (n=25)	1.23 ± 0.27	1.33 ± 0.47	2.55 ± 0.58	0.513
Psoriatic arthritis (n=35)	1.33 ± 0.35	1.25 ± 0.38	2.58 ± 0.56	
Psoriasis or Psoriatic arthritis with nail disorders (n=41)	1.34 ± 0.34	1.36 ± 0.46	2.68 ± 0.62	0.002
Psoriasis or Psoriatic arthritis without nail disorders (n=19)	1.18 ± 0.27	1.11 ± 0.29	2.29 ± 0.41	

* Adjusted by height and body weight

Background/Purpose: Although skin lesion is the most typical findings in patients with psoriasis (PsO), nail psoriasis is also one of the important clinical manifestation. Moreover, nail disorders in PsO are known as a risk factor for psoriatic arthritis (PsA). However, pathological feature and the relationship with inflammation of the soft tissue around the nail is unknown. The aim of this study was to compare the soft tissue thickness around the nail in patients with PsO, PsA and healthy control or other rheumatic diseases by using ultrasonography. The relationship between nail disorders and peripheral arthritis or enthesitis in patients with psoriasis was also analyzed.

Methods: Ultrasonographic assessment was performed in 25 PsO · 35 PsA · 15 healthy control · 23 rheumatoid arthritis (RA) · 28 ulcerative colitis (UC) and 13 Crohn's disease (CD) patients and included in this analysis. Ultrasonographic examination was performed by using HI VISION Ascendus (Hitachi Medical Corporation, Japan) with a multifrequency linear transducer (18-6 MHz) and the gray scale (GS) and power Doppler (PD) findings were assessed. The distance between the proximal nail fold on the dorsal side of the nail matrix and the nail bed on the volar side of the nail matrix was measured by electric caliper. The soft tissue thickness around nail was compared between groups and the relationship between nail disorders and peripheral arthritis or enthesitis in patients with psoriasis was also analyzed.

Results: The distance between the proximal nail fold and the nail bed was 2.58 ± 0.56 mm in PsA and 2.55 ± 0.58 mm in PsO patients ($p=0.603$). Among the 60 patients who combined PsO and PsA patients, 41 patients with nail psoriasis and 19 patients without nail psoriasis was compared. The distance was 2.68 ± 0.62 mm in patients with nail psoriasis and 2.30 ± 0.41 mm in without nail psoriasis ($p<0.001$), which was also swelling compared with control, RA, UC and CD group. The relationship between nail disorders and peripheral arthritis or enthesitis was not found in patients with psoriasis and psoriatic arthritis.

Conclusion: Soft tissue thickness around the nail in patients with PsO and PsA was compared with other rheumatic diseases by ultrasonographic assessment. In patients with PsO and PsA with nail psoriasis, soft tissue swelling around nail was observed. However, the relationship between nail disorders and peripheral arthritis or enthesitis was not found in patients with psoriasis and psoriatic arthritis.

Disclosure: T. Okano, None; K. Inui, None; K. Mandai, None; Y. Yamada, None; T. Koike, None; H. Nakamura, None.

Abstract Number: 680

Unmet Needs in the Treatment of Ankylosing Spondylitis. a Long-Term Observational Study from a Single University Center

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SESSION INFORMATION

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

Background/Purpose: Despite the progress in the treatment of ankylosing spondylitis (AS), a significant number of patients does not achieve low disease activity (LDA). The aim of this study was to estimate the size of unmet needs in the treatment of AS, using non-steroidal anti-inflammatory drugs (NSAIDs), and/or anti-cytokine therapy, in a long-term observational study.

Methods: Between January 2003 and December 2017, 220 patients with AS were diagnosed and followed-up in a tertiary outpatient rheumatology clinic. All patients fulfilled the 1984 modified New York criteria for AS. They were followed-up at predefined times and were naïve to biological treatment with anti-tumor necrosis factors (anti-TNFs) and interleukin (IL)-17 inhibitors. The patients were treated according to the European, United States and Canadian guidelines for AS. More specifically, NSAIDs including selective inhibitors of cyclooxygenase-2 were introduced. In addition, the following anti-TNFs were used: adalimumab (ADA), certolizumab, etanercept (ETN), golimumab and infliximab (INF). We also used secukinumab. During follow-up, clinical and laboratory findings, as well as treatment decisions and strategies, adverse drug reactions, reasons of termination or changing therapy, disease complications and comorbidities were all recorded. Disease activity was measured using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS), using the C-reactive protein.

Results: All patients had an active disease (BASDAI>4 and ASDAS> 2.1) and received at least two NSAIDs for 3 months. The anti-TNF of first choice was INF (51%), followed by ADA (27%) and ETN (22%). During the follow-up period, 18 patients were lost and 4 never received anti-TNF therapy due to various comorbidities. Thus, the final results are referred to 198 patients. Among them 12 (6%) continued receiving NSAIDs with significant clinical improvement and sustained LDA. However, 4 patients from this group never achieved LDA neither received anti-TNF therapy because they refused such treatment. On the other hand, 186 (94%) were treated with anti-TNFs. The majority of them demonstrated sustained LDA for a long period of time. However, from this group, 16 patients never achieved LDA despite they received 2 or 3 anti-TNFs or IL-17 inhibitors. Thus a total of 20 (10.1%) patients in our study never achieved LDA.

Conclusion: This is the first study aiming to estimate the gap and the size of unmet needs in AS patients using the international guidelines and recommendation for AS treatment. We found that the size of gap and unmet needs for AS treatment is 10%.

Disclosure: E. Pelechas, None; E. Kaltsonoudis, None; P. V. Voulgari, None; A. Drosos, None.

Abstract Number: 681

Identification of Treatment Naïve Patients with Psoriatic Arthritis Who Will Require a TNF Inhibitor

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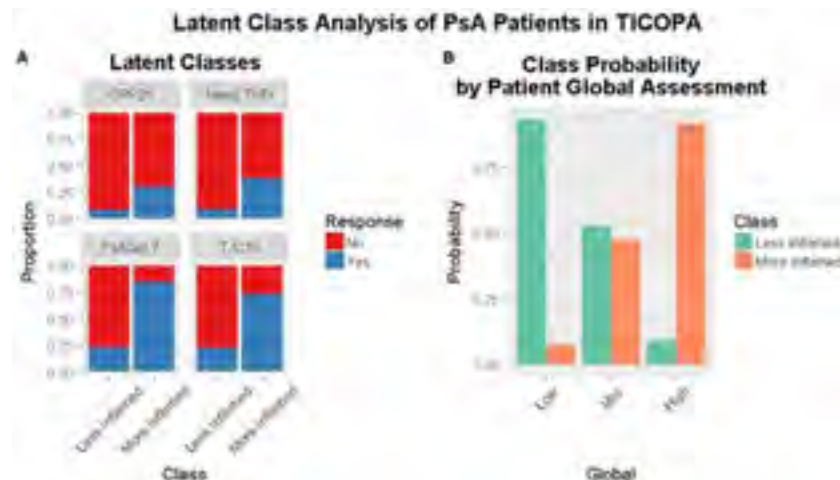
Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory disease that affects the skin, joints, and soft tissues. No metrics exist to indicate whether an untreated patient is unlikely to respond to oral therapies and will require therapy with a biologic. The objective of this study was to predict TNFi prescription among treatment naïve patients initiating methotrexate. We further aimed to identify subgroups of patients at baseline that would likely need a TNFi.

Methods: Data from the Tight Control of Psoriatic Arthritis (TICOPA) trial was used. In TICOPA, patients with at least one tender and swollen joint who were treatment naïve were randomized into one of two arms: intensive management and standard of care. We used all available baseline data to build models to predict the need for a subsequent TNFi within the 48 week study. We first applied a standard prediction modeling approach using stepwise Cox regression models. However, because of correlation among baseline variables (i.e., collinearity) and instability of the models, we decided to apply novel “machine learning” methods (e.g., tree-based classification, clustering methods, and latent class analysis, LCA) using R 3.4.4 with imported packages. Target categorical variables were cut from continuous variables after graphical exploration and trial analyses.

Results: Among the 188 participants who agreed to share data for additional studies, 44 initiated a TNFi during the 48-week study period. Exploration with comparison tests, stepwise regression, and tree-based models identified the PsAQoL score and the Patient Global Assessment (PtGA) as valuable predictors of TNFi prescription. Using LCA, we were able to define a two-class model (Figure 1A) that classified patients who were more and less likely to require a TNFi. In addition to receipt of a TNFi, these classes were defined by a CRP ≥ 25 , PsAQoL ≥ 7 , and TJC ≥ 10 (the most predictive and non-redundant set of variables). We termed the classes “Less Inflamed” and “More Inflamed” for simplicity. Importantly, PtGA was a strong predictor of being in one of these classes; as PtGA increased, the likelihood of being the “more inflamed” class increased. Dividing PtGA into Low (≤ 40), middle (40-70), and high (≥ 70) categories accurately predicted class membership (Figure 1B). In summary, PtGA was single best predictor of requiring a TNFi; baseline PtGA ≥ 70 has a HR of 2.62 (1.42-4.80) for requiring a TNFi and correctly classifies 76% of patients.

Conclusion: At baseline, participants in the TICOPA trial could be classified into two groups, “more inflamed” and “less inflamed” based on three variables and patient global was the single best predictor of class and receipt of a TNFi. The



baseline patient global assessment of treatment naïve patients with PsA yields valuable prognostic information and is an important tool for clinical decision-making in this population.

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Abstract Number: 682

Nonsteroidal Anti-Inflammatory Drug Use and Hypertension in Ankylosing Spondylitis

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Background/Purpose: Cardiovascular morbidity and mortality are increased in Ankylosing Spondylitis (AS). Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first line pharmacological therapy in AS; however, their propensity to increase blood pressure and potentially increase cardiovascular burden may limit their long-term use in an already at-risk population. Our objective was to determine the association of NSAID use and hypertension in AS.

Methods: We included 1069 adults with AS meeting the modified New York criteria from a longitudinal cohort with available NSAID and antihypertensive medication use data. Hypertension was defined by antihypertensive medication use. NSAID use was defined by the validated NSAID index and categorized according to no use or low vs. high NSAID use (index < 50 vs. ≥50). We conducted a comparison of baseline characteristics for patients with and without hypertension, using a chi-square test for categorical variables and Student's t-test or its nonparametric counterpart, as appropriate, for continuous variables. We assessed the association between NSAID use and hypertension at baseline with a multivariable logistic regression analysis.

Results: At baseline, the cohort was 74.1% male, 80.4% white, with a mean age 43.2 ± 14.2 years, and median disease duration of 16.0 years (interquartile range (IQR) = [8,27]) (Table 1). At baseline, 22.8% of patients had hypertension. After adjustment for age, gender and other covariates, the multivariable results found high compared to low dose NSAID use (adjusted OR 2.1, 95%CI 1.1-3.8) was associated with hypertension at baseline.

Conclusion: Compared to AS patients without hypertension, those with hypertension were significantly older, had longer disease duration, and more cardiovascular disease. Although there was no significant difference between any NSAID use versus no use, the multivariable analysis found a significant association between hypertension and high compared to low NSAID use. These data suggest a relationship between NSAID use and comorbid hypertension in AS, which may be dose-dependent and conditional upon the decision to initiate treatment.

Table 1 –Baseline characteristics of patients with and without hypertension

Variables	All patients N=1069	Hypertension (-) n=825 (77.2%)	Hypertension (+) n = 244 (22.8%)	p value
Baseline NSAID index with 3 categories:				0.0001
NSAID index=0, %	365 (34.1)	266 (32.2)	99 (40.6)	
0< NSAID index <50, %	337 (31.5)	287 (34.8)	50 (20.5)	
NSAID index≥50%	367 (34.3)	272 (33.0)	38 (38.9)	
Male gender, %	792 (74.1)	593 (71.9)	199 (81.6)	0.002
Age, mean±SD	43.24 (14.2)	39.50 (12.5)	55.9 (12.0)	<0.0001
White race, %	859 (80.4)	647 (78.4)	212 (86.9)	0.004
Education beyond high school, %	857 (81.4)	657 (80.8)	200 (83.3)	0.4
Disabled, %	81 (7.6)	49 (5.9)	32 (13.1)	0.0002
HLA-B27 positive, %	872 (83.0)	675 (83.3)	197 (81.7)	0.6
Disease duration (years), med (IQR)	16.0 (8.0, 27.0)	13.0 (6.0, 22.0)	29.0 (20.0, 39.0)	<0.0001
BASDAI (0-10), med (IQR)	3.6 (1.8, 5.9)	3.6 (1.6, 5.7)	3.9 (2.2, 6.2)	0.01
CRP (mg/dl), med (IQR)	0.4 (0.2, 1.1)	0.5 (0.2, 1.1)	0.4 (0.2, 0.9)	0.7
ESR (mm/hr), med (IQR)	11.0 (5.0, 22.0)	11.0 (5.0, 23.0)	11.0 (6.0, 20.0)	0.5
Analgesic use, %	290 (27.1)	196 (23.8)	94 (38.5)	<.0001
Ever smoker, %	468 (44.8)	332 (41.2)	136 (56.9)	<.0001
Cardiovascular disease, %	86 (8.2)	32 (4.0)	54 (22.4)	<.0001
TNFi use, %	440 (41.2)	328 (39.8)	112 (45.9)	0.09

med: median; IQR: interquartile range

Table 2 – Multivariable analysis – Factors associated with hypertension at baseline

Variables	Adjusted Odds Ratio (95% CI)	p value
Baseline NSAID index with 3 categories		0.05
Low vs. no use	0.7 (0.4, 1.3)	0.3
High vs. no use	1.5 (0.9, 2.4)	0.1
High vs. low	2.1 (1.1, 3.8)	0.02
Male vs. female	1.3 (0.7, 2.2)	0.5
Age (year):		<.0001
35-49 vs. ≤34	2.8 (1.3, 6.1)	0.01
≥50 vs. ≤34	9.2 (4.1, 21.0)	<.0001
Cardiovascular disease vs. no cardiovascular disease	4.3 (2.2, 8.5)	<.0001

Variables adjusted in this model included age, gender, race, education, disease duration, BASDAI, disability, CRP, mSASSS, TNFi use, and cardiovascular disease.

Disclosure: J. Liew, None; J. D. Reveille, Janssen, 5, Eli Lilly and Co., 2, 5, UCB, Inc., 5, Novartis, 5; M. Ward, None; M. Lee, None; M. Brown, None; M. H. Rahbar, None; M. Weisman, GSK, Lilly, Novartis, Baylx, Celltrion. All are consulting fees, 5, 6; L. S. Gensler, AbbVie Inc., 2, Amgen Inc., 2, Novartis, 2, 5, UCB, Inc., 2, Galapagos, 5, Janssen, 5, Eli Lilly and Co., 5, Pfizer, Inc., 5.

Abstract Number: 683

Spanish Validation of the Gepard Questionnaire for the Detection of Psoriatic Arthritis in Argentinean Patients with Psoriasis

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SESSION INFORMATION

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Background/Purpose: Psoriatic Arthritis (PSA) is preceded by the presence of cutaneous psoriasis (PS) in approximately 80% of the cases. We consider relevant to have tools that allow the detection of PSA in that population. The aim of this study was to evaluate the validity and performance of an adapted version of the GEPARD questionnaire in Spanish (GEPARDa) in a group of Argentinean patients with PS.

Methods: Adults >18 years who were able to read and understand Spanish were included. The questionnaire was translated from the original language (German) by two independent translators and retranslation into Spanish was made by another two translators. The performance of the questionnaire was evaluated in its new version (GEPARDa) as a diagnostic test.

Results: 83 patients were included, 55 (66.3%) were women, with a mean age of 50.7 (SD 6.3). Of the patients evaluated, 29 (34.9%) had PSA, 15 (18%) were diagnosed with PSA after referral by dermatology, 18 (21.6%) had PS without joint involvement, 6 patients had PS associated with osteoarthritis (OA) (7.22%) and 15 (18%) were diagnosed with OA. The differences in the means of the GEPARD questionnaire among the different groups were statistically significant between patients with known PSA and patients with PS, PS and OA and OA. There were no differences between patients with PSA and newly diagnosed PSA (Table 1). The area under the curve, considering as the gold standard the CASPAR criteria, was 0.9554 DS 0.01 (95%CI 0.91-0.99). A score of 6 was determined to be the better cut-off point for distinguishing PSA from non- PSA. With this value, sensitivity was 88.64%, specificity of 89.74%, LR + of 8.6 and LR - 0.12. Five false negatives were found. 4 patients had a false positive diagnosis. Table 2 shows the relationship of the variables studied and the positivity of the GEPARDa questionnaire. After the multivariate analysis, the variable that was associated with the positivity of the questionnaire was the DAS28 (OR 2.93, 95%CI 0.13-0.91, p: 0.03).

Conclusion: The GEPARDa version is an excellent tool for the detection of PSA in argentine patients with PS.

TABLE 1. Differences of GEPARDa in the evaluated groups.

Variables	PSA	PSA new diagnosis	PS	PS + OA	OA
Median (IQR)	9 (7-10.5)	8 (5-12)	1 (0.2.75)	4 (3-5)	4 (3-5)
p-value (vs APS)		1	<0.001	0.60	<0.001
mean (SD)	8.9 (2.3)	8.6 (3.11)	1.78 (2.4)	4 (1.09)	4.13 (1.4)
p-value (vs PSA)		0.99	<0.001	<0.001	<0.001

TABLE 2. Associations between GEPARDa ≥ 6 and studied variables.

Variables	GEPARDa ≥ 6	GEPARDa <6	p -value
Female n	27	28	0.48 (−0.29-0.13)
Age m (DS)	49.9 (15.3)	51.5 (15.2)	0.62 (45-54)
Years of education mean (SD)	13.17(4.5)	12.93 (4.1)	0.82 (12.14-15)
Intergluteo Commitment n	20	9	0.21 (−0.2-0.41)
Scalp Commitment n	25	11	0.12 (0.18-0.45)
Ungueal commitment n	19	6	0.6 (0.08-0.47)
Smoking n	14	8	0.62 (0.47-3.6)
Pack/years mean (SD)	3.05(5.84)	3.32 (6.49)	0.85 (1.7-4.6)
Body max index mean (SD)	26.72	25.4	0.47 (24.3-27.9)

Disclosure: M. V. Martire, None; M. P. Girard Bosch, None; S. Scarafia, None; V. L. Cosentino, None; M. J. Tapia, None; E. Kerzberg, None; N. Estrella, None; C. Troitiño, None; J. Marin, None; F. A. Sommerfleck, None; H. Maldonado Ficco, None; E. Catay, None; M. Benegas, None; E. R. Soriano, AbbVie, Bristol-Myers Squibb, GSK, Janssen, Novartis, Pfizer Inc, Roche, UCB, 2, AbbVie, Bristol-Myers Squibb, Eli Lilly, GSK, Janssen, Novartis, Pfizer Inc, Roche, Sanofi, UCB, 5, AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer Inc, Roche, Sandoz, UCB, 8.

Week 24	Polyarthritis		Enthesitis				Dactylitis			
ITT, NRI	≥5TJC and/or ≥5SJC		INV judgement		LEI >0		INV judgement		LDI-B >0	
	SPIRIT-P1 (n=306)	SPIRIT-P2 (n=356)	SPIRIT-P1 (n=186)	SPIRIT-P2 (n=273)	SPIRIT-P1 (n=182)	SPIRIT-P2 (n=221)	SPIRIT-P1 (n=134)	SPIRIT-P2 (n=86)	SPIRIT-P1 (n=93)	SPIRIT-P2 (n=62)
ACR20, %										
Placebo	43.7	29.9	33.3	29.4	33.3	26.1	41.0	40.0	50.0	42.9
Ixekizumab	63.1	52.7	62.8	52.7	61.6	49.3	64.2	51.5	70.8	50.0
<i>p</i> -value	0.0012	< 0.0001	0.0002	0.0004	0.0004	0.0012	0.0137	0.3668	0.0548	0.6380
ACR50, %										
Placebo	19.4	11.1	14.0	9.4	14.0	11.6	17.9	20.0	21.4	28.6
Ixekizumab	44.8	34.3	43.4	35.6	43.2	32.9	47.4	36.4	53.8	39.6
<i>p</i> -value	< 0.0001	< 0.0001	0.0001	< 0.0001	0.0001	0.0009	0.0015	0.1713	0.0039	0.4530
ACR70, %										
Placebo	7.8	1.7	3.5	0.0	3.5	0.0	7.7	0.0	10.7	0.0
Ixekizumab	28.6	16.7	26.4	14.9	26.4	13.8	33.7	18.2	40.0	20.8
<i>p</i> -value	< 0.0001	< 0.0001	0.0003	0.0002	0.0003	0.0012	0.0019	0.0398	0.0052	0.0622
MDA_{low}, %										
Placebo	18.4	5.1	7.0	2.4	7.0	1.4	15.4	0.0	17.9	0.0
Ixekizumab	36.0	25.1	33.3	23.9	33.6	21.7	40.0	27.3	47.7	27.1
<i>p</i> -value	0.0016	< 0.0001	0.0001	< 0.0001	0.0001	0.0001	0.0058	0.0086	0.0067	0.0285
DAPSA Remission, %										
Placebo	5.8	1.7	0.0	1.2	0.0	1.4	0.0	0.0	0.0	0.0
Ixekizumab	19.7	10.0	18.6	9.0	18.4	8.6	23.2	13.6	30.8	14.6
<i>p</i> -value	0.0013	0.0045	0.0005	0.0153	0.0005	0.0445	0.0010	0.0809	0.0009	0.1292
DAPSA LDA, %										
Placebo	23.3	17.1	17.5	16.5	17.5	13.0	28.2	10.0	28.6	7.1
Ixekizumab	34.0	26.8	34.3	26.1	32.0	22.4	30.5	25.8	26.2	22.9
<i>p</i> -value	0.0547	0.0432	0.0279	0.0815	0.0427	0.1046	0.7897	0.1367	0.8094	0.1887

Results are expressed as proportions of patients in the intent-to-treat population calculated using non-responder imputation. *P*-value for differences between ixekizumab and placebo by Chi-square tests or Fisher's exact tests.

Abbreviations: ACR20/50/70=20/50/70% improvement from baseline in ACR criteria; ACR=American College of Rheumatology; DAPSA=Disease Activity Index for PsA; INV=investigators; ITT=intent-to-treat; LDA=low disease activity; LDI-B=leeds dactylitis index-basic; LEI=leeds enthesitis index; MDA=minimal disease activity; NRI=non-responder imputation; PASI=psoriasis area severity index; PsA=psoriatic arthritis; SJC= swollen joint count; TJC=tender joint count.

inadequate response or intolerance to TNF inhibitors (SPIRIT-P2) were randomized to IXE Q4W (N=122) or Q2W (N=123), or to PBO (N=118). Patients fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria and had active disease with ≥ 3 TSJ and ≥ 3 SJC. Patients were classified according to the following phenotypes of PsA¹: polyarthritis (≥ 5 TJC and/or ≥ 5 SJC), oligoarthritis (< 5 TJC and < 5 SJC), DIP joint only, enthesitis and dactylitis according to either the investigator's judgment or a scale-based definition. In each phenotype ACR 20, 50 and 70 response criteria, Minimal Disease Activity Psoriasis Area Severity Index (MDA_{PASI}), and Disease Activity Psoriatic Arthritis (DAPSA) remission and low disease activity (LDA) response criteria were assessed to evaluate IXE effect at week 24 combining both doses. For each phenotype with a sufficient sample size, the IXE- and PBO-treated patients' baseline characteristics were assessed. Treatment effects of IXE and PBO were compared using Chi-square tests (or Fisher's exact tests if appropriate) within each phenotype.

Results: The most frequent phenotypes were: polyarthritis (N=662), enthesitis (investigator: N=459; LEI>0: N=403), and dactylitis (investigator: N=220; LDI-B>0: N=155). Too small sample sizes due to inclusion criteria^{2,3} or low frequency were observed for "DIP joint only", oligoarthritis and arthritis mutilans phenotypes (N=22, N=17 and N=15; respectively). Baseline patient characteristics were generally balanced between treatment arms and similar between the 3 most frequent phenotypes, with no difference in disease activity and duration. Efficacy of IXE was consistent across the different phenotypes for various outcomes at week 24: ACR20/50/70, MDA_{PASI}, DAPSA remission and DAPSA-LDA in SPIRIT trials irrespective of previous biologic DMARD use (Tab.1). Response rates were consistent to overall efficacy reported with IXE in SPIRIT trials²⁻⁴.

Conclusion: Treatment responses with IXE at week 24 were consistent regardless of the phenotypes.

References:

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Abstract Number: 685

Changes in Key Laboratory Values with Tofacitinib 5mg BID Treatment in Patients with Psoriatic Arthritis and Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of psoriatic arthritis (PsA) and rheumatoid arthritis (RA). In most countries where tofacitinib is approved, 5mg twice daily (BID) is the only recommended dose for PsA and RA. An important component of any product labeling is information on the need for laboratory monitoring. This post hoc analysis aimed to provide information on the effect of tofacitinib 5 mg BID on laboratory values in PsA and RA patients (pts).

Table 1. Changes in essential aminoacids and total levels, for 1996 year and 1997 year, among those and some countries, based on Health CT is the average information of all RCD group studies conducted in

	PSA ¹ (data cut-off: January 25, 2017) (N=148)						PSA ² (data cut-off: March 2, 2017) (N=148)					
	Mean (SE)		Mean (SE) change from baseline				Mean (SE)		Mean (SE) change from baseline			
	BL	S11	S12	S16	S19	S112	BL	S11	S12	S16	S19	S112
Diagnosis, g/gL	13.88 (0.07)	40.31 (0.04)	0.88 (0.00)	-0.04 (0.00)	0.03 (0.00)	0.10 (0.00)	12.79 (0.03)	0.10 (0.01)	0.11 (0.02)	0.21 (0.02)	0.17 (0.00)	0.27 (0.02)
Neutrophils, 10 ⁹ /mm ³	4.49 (0.00)	4.39 (0.00)	-0.33 (0.00)	-0.70 (0.00)	-0.33 (0.00)	-0.33 (0.00)	4.34 (0.00)	-0.79 (0.00)	-0.63 (0.00)	-0.69 (0.00)	-0.63 (0.00)	0.49 (0.00)
Eosinophils, 10 ⁹ /mm ³	1.44 (0.00)	0.99 (0.00)	-0.03 (0.00)	-0.05 (0.00)	-0.05 (0.00)	-0.11 (0.00)	1.83 (0.00)	0.17 (0.00)	0.00 (0.00)	0.01 (0.00)	-0.04 (0.00)	-0.13 (0.00)
Bilirubin, mg/dL	0.40 (0.01)	0.47 (0.01)	0.04 (0.00)	0.04 (0.01)	0.04 (0.00)	0.04 (0.00)	0.41 (0.01)	0.07 (0.00)	0.04 (0.01)	0.05 (0.00)	0.07 (0.00)	0.07 (0.00)
ALT, U/L	25.94 (0.01)	0.10 (0.01)	2.93 (0.00)	3.79 (0.00)	4.10 (0.00)	4.10 (0.00)	20.90 (0.00)	5.50 (0.02)	0.10 (0.00)	3.14 (0.00)	0.27 (0.00)	0.34 (0.01)
AST, U/L	21.97 (0.01)	0.07 (0.00)	3.77 (0.00)	3.81 (0.01)	3.49 (0.00)	3.80 (0.01)	20.00 (0.00)	3.04 (0.00)	0.04 (0.00)	4.43 (0.00)	4.80 (0.00)	3.34 (0.00)
CRP, mg/L	12.00 (0.00)	1.20 (0.00)	-0.10 (0.00)	-7.25 (0.00)	-7.30 (0.00)	-6.20 (0.00)	0.00 (0.00)	-1.37 (0.00)	-1.77 (0.00)	-1.21 (0.00)	-12.91 (0.00)	12.13 (0.00)
Creatine kinase, U/L	89.87 (0.00)	80.37 (0.00)	80.87 (0.00)	81.60 (0.00)	84.13 (0.00)	84.07 (0.00)	79.14 (0.00)	51.76 (0.00)	40.86 (0.00)	80.90 (0.00)	80.42 (0.00)	63.87 (0.00)
Serum creatinine, mg/dL	0.81 (0.00)	0.03 (0.00)	0.02 (0.00)	-0.01 (0.00)	0.00 (0.00)	-0.04 (0.00)	-0.71 (0.00)	0.00 (0.00)	0.04 (0.00)	0.06 (0.00)	-0.06 (0.00)	0.07 (0.00)
	Mean (SE)		Mean (SE) % change from baseline				Mean (SE)		Mean (SE) % change from baseline			
	BL	S11	S12	S16	S19	S112	BL	S11	S12	S16	S19	S112
LDL-c, mg/dL	115.72 (0.70)	7.30 (0.00)	0.03 (0.00)	-0.01 (0.00)	-0.03 (0.00)	-0.00 (0.00)	113.70 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
HDL-c, mg/dL	55.50 (0.02)	0.10 (0.00)	0.14 (0.00)	-0.04 (0.00)	0.07 (0.00)	0.07 (0.00)	55.07 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Total cholesterol, mg/dL	200.70 (2.00)	7.00 (0.00)	-7.02 (0.00)	0.72 (0.00)	0.00 (0.00)	0.00 (0.00)	197.51 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
TG, mg/dL	645.42 (3.50)	0.00 (0.00)	0.71 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	625.04 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)

[illegible]

Further studies are necessary to assess the role of individual

Smoking is the "most preventable cause of death and disability," and tobacco causes about 44% of all deaths in the United States.

Chemical-induced T_H1 and T_H2 profiles assigned to respectively T_H1 and T_H2 as assessed from pleural to peritoneal T_H1 and T_H2 in the spleen section, where Day 1 is the first day of infection; T_H1 and T_H2 cells were from L.TE, spleen which express in spleen section in 1:12 months.

Abbreviations: AIT, agitated intravenous infusion; BIA, twice daily; BI, baseline; CYP, C-reactive protein; HD, *in*-high-dose (aggravated-inflamed); LD, *in*-low-dose (aggravated-inflamed); LTZ, long-term treatment; M, month; N, number of patients included in the analysis. Stated as percent for each laboratory parameter at each time point to show that if due to missing values. PNA, patients' infection; RA, rheumatoid arthritis; SE, standard error; TO, toxyphoid.

Methods: For analysis of pts with active PsA treated with tofacitinib 5 mg BID, data were pooled from 2 Phase 3 studies and an ongoing long-term extension (LTE) study (data cut-off, January 25, 2017; database not locked; data may change). For analysis of pts with moderate or severe RA treated with tofacitinib 5 mg BID, data were pooled from 8 Phase 2, 7 Phase 3, and 1 LTE studies (data cut-off, March 2, 2017 for LTE; database not locked; data may change). All PsA and most RA pts received a background conventional synthetic DMARD. Data (to Month 12) for pts receiving constant tofacitinib 5 mg BID were evaluated, comprising pts who received tofacitinib 5 mg BID across studies, either at randomization or following switch from placebo. Pts in the placebo groups who switched to tofacitinib 5 mg BID at Month 3 were included from the time they first received tofacitinib. Pts who switched tofacitinib dose were excluded. Change from baseline in hematologic (hemoglobin, neutrophils, lymphocytes) and lipid (LDL-cholesterol, HDL-cholesterol, total cholesterol, triglyceride) levels and key liver tests (bilirubin, ALT, AST) were analyzed. Although not addressed in the product labeling, creatine kinase, creatinine, and C-reactive protein levels were also assessed. Pts meeting protocol-defined discontinuation criteria for laboratory values were evaluated.

Results: The constant tofacitinib 5 mg BID group comprised 348 PsA pts and 3,040 RA pts. Table 1 presents mean/percentage changes (SE) from baseline for laboratory values. Following initial increases/reductions, key laboratory values remained stable to Month 12 in both PsA and RA, except for a reduction in lymphocyte levels, which stabilized at later time points (data not shown). In both PsA and RA, $\leq 3.0\%$ of patients met discontinuation criteria for any laboratory values (Table 2).

Conclusion: In this post hoc analysis of laboratory data with tofacitinib 5 mg BID, changes in key laboratory values were similar for PsA and RA, and discontinuations due to protocol criteria being met for laboratory values were infrequent. These results provide further information on the effect of tofacitinib on laboratory values in PsA and RA.

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Table 2. Number (%) of patients in the constant-tofacitinib 5 mg BID group meeting protocol-defined discontinuation criteria for laboratory values		
Reason for discontinuation, n (%)	PA (data cut-off, January 25, 2017) (N=348)	RA (data cut-off, March 2, 2017) (N=3,040)
Two sequential hemoglobin ≤ 8.0 g/dL or a decrease of $\geq 30\%$ from BL	0	10 (<1.0)
Two sequential neutrophil counts $< 500/\text{mm}^3$	N/A	0
Two sequential neutrophil counts $< 1,000/\text{mm}^3$	0	N/A
Two sequential lymphocyte counts $< 500/\text{mm}^3$	0	24 (<1.0)
Two sequential platelet counts $< 75,000/\text{mm}^3$	0	3 (<1.0)
Two sequential AST or ALT elevations $> 3 \times \text{ULN}$ with ≥ 1 total bilirubin value $> 2 \times \text{ULN}$	0	2 (<1.0)
Two sequential AST or ALT elevations $> 3 \times \text{ULN}$ accompanied by elevated INR/consistent with hepatic injury	0	2 (<1.0)
Two sequential AST or ALT elevations $> 5 \times \text{ULN}$ regardless of total bilirubin or accompanying symptoms	1 (<1.0)	15 (<1.0)
Two sequential increases in serum creatinine $> 50\%$ over the average of screening and baseline values	N/A	00 (3.0)
Two sequential increases in serum creatinine $> 50\%$ and an increase > 0.5 mg/dL over average of screening and baseline	1 (<1.0)	N/A
Two sequential creatine kinase elevations $> 10 \times \text{ULN}$	0	N/A
A confirmed positive urine pregnancy test in a woman of childbearing potential	0	N/A
A patient may have met multiple criteria; each patient is counted once for each row		
Constant tofacitinib 5 mg BID; patients assigned to tofacitinib 5 mg BID, or advanced from placebo to tofacitinib 5 mg BID in the index studies, where Day 1 is the first dose of tofacitinib 5 mg BID		
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; BL, baseline; INR, international normalized ratio; N, number of patients included in the analyses; n, number of patients meeting criteria for discontinuation; N/A, not applicable; PSA, prostate-specific antigen; RA, rheumatoid arthritis; ULN, upper limit of normal		

Abstract Number: 686

Five-Year Efficacy and Safety of Apremilast Treatment in Subjects with PsA: A Pooled Analysis of the 3 Phase III Studies

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: Long-term apremilast (APR) efficacy and safety were evaluated for up to 5 yrs in adults with active PsA in the phase III PALACE 1-3 studies.

	Outcomes at Wk 260	
	APR30 n=329*	APR20 n=304*
ACR20, n/m (%)	215/320 (67.2)	202/298 (67.8)
ACR50, n/m (%)	144/324 (44.4)	142/287 (47.8)
ACR70, n/m (%)	86/325 (27.4)	75/300 (25.3)
Swollen joint count (0-76), mean % change from BL	-82.3	-86.0
Tender joint count (0-76), mean % change from BL	-72.7	-73.1
MASES [‡] of 0, n/m (%)	136/218 (62.4)	117/182 (64.3)
Dactylitis count [‡] of 0, n/m (%)	114/141 (80.9)	114/131 (87.0)
cDAPSA (0-154) ≤13, n/m (%)	108/328 (60.4)	106/302 (64.9)
HAQ-DI (0-3), mean change from BL	-0.42	-0.37
HAQ-DI MCI of ≥0.35, n/m (%)	173/329 (52.6)	148/303 (48.2)
PASI-50 [§] , n/m (%)	98/149 (65.8)	76/138 (55.9)
PASI-75 [§] , n/m (%)	65/149 (43.6)	59/136 (41.2)

Data as observed. *The n reflects the number of subjects with data available at Wk 260, regardless of when subjects started taking APR (BL, Wk 16, or Wk 24); actual number of subjects having data available for each end point may vary. †Denominators vary slightly due to availability of sufficient data for each level of ACR response assessment. ‡Examined among subjects with enthesitis at BL and having data at Wk 260. ‣Examined among subjects with dactylitis at BL and having data at Wk 260. ․Examined among subjects with psoriasis involvement of the body surface area ≥3% at BL and data at Wk 260. n/m=number of responders/number of subjects with sufficient data for evaluation. MASES=Maastricht Ankylosing Spondylitis Enthesitis Score. cDAPSA=Clinical Disease Activity in Psoriatic Arthritis. MCI=minimal clinically important difference. PASI-50/75=≥50/≥75% reductions from BL. Psoriasis Area and Severity Index.

Methods: Subjects were randomized (1:1:1) at baseline (BL) to placebo (PBO), APR 30 mg BID (APR30), or APR 20 mg BID (APR20). PBO subjects were re-randomized (1:1) to APR30 or APR20 at Wk 16 (early escape) or Wk 24. Double-blind APR treatment continued to Wk 52; subjects could continue APR during an open-label, long-term treatment phase for up to an additional 4yrs. Efficacy and safety were assessed and reported as observed.

Results: A total of 1,493 subjects were randomized and received ≥1 dose of study medication (PBO: n=496; APR30: n=497; APR20: n=500). Of those randomized to APR30 at BL, 44.5% (221/497) completed 260 wks of treatment. Among APR30 subjects entering Wk 52, 63.2% (331/524) completed 260 wks, regardless of when APR was started (BL, Wk 16, or Wk 24). At Wk 52, ACR20/50/70 response rates were 55.3%/26.1%/11.9% for APR30 subjects. Sustained response rates were observed with continued APR30 treatment at Wk 260 (Table). Marked swollen joint count improvements were seen, with a mean percent reduction of 82.3% at Wk 260; tender joint count reduction was 72.7%. At Wk 260, 62.4% (136/218) of APR30 subjects with BL enthesitis achieved a Maastricht Ankylosing Spondylitis Enthesitis Score of 0; 80.9% (114/141) with BL dactylitis achieved a dactylitis count of 0. A HAQ-DI minimal clinically important difference of ≥0.35 was achieved by 52.6% of APR30 subjects at Wk 260; 60.4% achieved low disease activity or remission, defined as a Clinical Disease Activity in Psoriatic Arthritis score ≤13. Sustained improvements in psoriatic skin involvement were observed with continued treatment at Wk 260 in APR30 subjects with ≥3% BL body surface area involvement, with 65.8% (98/149) and 43.6% (65/149) of subjects, respectively, achieving ≥50%/≥75% reductions from BL Psoriasis Area and Severity Index score. APR 20 results were similar (Table). Consistent efficacy results were seen across the individual studies. During the 0- to ≤52-wk APR-exposure period, adverse events (AEs) occurring in ≥5% of APR30-exposed subjects were diarrhea, nausea, headache, upper respiratory tract infection, and nasopharyngitis. Most diarrhea and nausea AEs were reported within the first 2 wks of treatment and usually resolved within 4 wks; gastrointestinal AE frequency decreased with longer APR30 exposure, and frequency of other common AEs decreased/remained stable with prolonged exposure. Serious AE rate during Wks >208 to ≤260 was 5.8%, consistent with earlier periods.

Conclusion: APR demonstrated sustained, clinically meaningful improvements in PsA signs/symptoms, physical function, and associated psoriasis in the subjects continuing treatment over 5 yrs. APR continued to demonstrate a favorable safety profile and was generally well tolerated at 5 yrs.

Disclosure: A. Kavanaugh, Abbott, Amgen, AstraZeneca, BMS, Celgene Corporation, Centocor-Janssen, Pfizer, Roche, UCB, 2; D. D. Gladman, AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 2, 5; C. J. Edwards, Celgene Corporation, Pfizer, Roche, Samsung, 2, 5, Abbott, GSK, Pfizer, Roche, 8; G. Schett, Abbott, Celgene Corporation, Roche, UCB, 2, 5; B. Guertel, Celgene Corporation, 3; N. Delev, Celgene Corporation, 3; L. Teng, Celgene Corporation, 3; M. Paris, Celgene Corporation, 3; P. J. Mease, Abbott, Amgen, Biogen Idec, BMS, Celgene Corporation, Eli Lilly, Genentech, Janssen, Novartis, Pfizer, Roche, UCB, 2, 5, Abbott, Amgen, Biogen Idec, BMS, Eli Lilly, Genentech, Janssen, Pfizer, UCB, 8.

Clinical Characteristics of Spondyloarthritis Patients in Japan in Comparison to Other Regions of the World

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: To delineate clinical characteristics of patients with spondyloarthritis (SpA) in Japan in comparison to other areas of the world.

Methods: Utilizing the COMOSPA data, an international cross-sectional observational study of SpA patients we analyzed information on demographics, disease characteristics, comorbidities, and risk factors. Patients were classified by region: Japan, other Asia (China, Singapore, South Korea, and Taiwan), and non-Asian countries (Europe, Americas, and Africa); patient characteristics, including diagnosis and treatment, were compared.

Results: Among 3984 patients included in the study, 161 were from centers in Japan, 933 from other Asian countries, and 2890 from other regions. Of SpA patients in Japan, 28.6% had peripheral SpA, whereas presenting symptoms were more predominantly axial in other Asian countries. This trend was explained by the predominance of PsA patients among Japanese SpA patients. In contrast to the relatively low number in Japan, 54% of patients from other Asian countries had pure axial SpA without peripheral features. HLA B27 testing, which is considered an integral part of the classification of axial SpA, was only performed in 62% of Japanese axial SpA patients. More than half of Japanese axial SpA patients were classified using imaging criteria.

Conclusion: There is substantially more peripheral SpA in Japan compared to other parts of Asia, and other regions of the world. Aside from ethnic differences, increasing recognition of PsA, as well as a potential under-diagnosis of axial SpA due to the insufficient use of HLA B27 testing in Japan, may partly explain regional discrepancies.

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Real Life Analysis of a Latin America Tertiary Spondyloarthritis Single-Center: High Frequency of Peripheral Involvement and Use of Synthetic Dmard

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Background/Purpose: The use of synthetic DMARDS (sDMARDS) in spondyloarthritis (SpA) has been increasingly questioned and restricted to peripheral disease, on the other hand, the use of immunobiological agents for the treatment of SpA has been further improved by anti-TNF and the release of new drugs with other mechanisms such as secukinumab (anti-IL17, SEC) and ustekinumab (anti-IL12/23, UST). The objective of our study is to describe clinical and treatment data of a SpA patients cohort followed at the outpatient clinic of a Brazilian single center.

Methods: 516 SpA patients evaluated from January 2017 to January 2018. Data from electronic medical records were assessed including diagnosis, disease characteristics, treatment and disease activity at the last visit.

Results: Among all patients, 195 (37.8%) were classified as Ankylosing Spondylitis (AS), 198 (38.3%) as psoriasis arthritis (PsA), 66 (12.8%) as axial non-radiographic or peripheral SpA, 42 (8.1%) as SpA related to inflammatory bowel disease and 15 (3.0%) as reactive arthritis patients. From all SpA patients 190 (36.8%) have no axial disease, with isolated peripheral arthritis. Regarding treatment, 321 (62.2%) patients were under sDMARDS as monotherapy or in association [156/321 (48.6%) methotrexate (MTX); 125/321 (38.9%) sulfasalazine (SSZ)]; 298 (57.7%) patients used NSAIDs. Concerning biological therapy 204 (39.5%) patients received biological DMARDS (bDMARDS) [68 infliximab (IFX), 59 adalimumab (ADA), 35 etanercept (ETA), 6 golimumab (GOL), 2 certolizumab pegol (CTZ), 23 secukinumab (SEC), 10 ustekinumab (UST), 1 rituximab (RTX)]. Patients with isolated peripheral involvement presented higher frequency of sDMARD use (78.4% vs. 51.4%, $P < 0.001$) compared to patients with axial disease, but with similar use of biological drug (37.1% vs. 45.7%, $P = 0.13$) and combined treatment of bDMARD and sDMARD (26.7% vs. 25%, $P = 0.73$). Forty-three AS patients (43/52, 82.7%) were HLA-B27 positive; 152/195 (77.9%) received NSAIDs; 95/195 (48.7%) used sDMARDS (23.1% MTX and 72.6% SSZ) and 79/195 (40.5%) used bDMARDS (31 INF, 22 ADA, 19 ETA, 3 GOL, 3 SEC, 1 UST). Among the 198 PsA patients, 148/198 (74.7%) have isolated peripheral disease; 146/198 (73.7%) used sDMARDS (78.8% MTX and 26.7% LNF) and 77/198 (38.9%) received bDMARDS (24 IFX, 18 ADA, 10 ETA, 19 SEC, 6 UST, 1 RTX). In relation to disease activity, 25/125 (20%) of AS patients had ASDAS ≥ 2.1 and 42/198 (21%) of PsA patients presented active arthritis in the last visit.

Conclusion: The description of epidemiological and clinical data of this cohort reinforces high prevalence of peripheral disease in Brazilian SpA patients. This fact could explain the wide use of sDMARDS in these patients. The frequency use of bDMARDS is in parallel with literature data including non-antiTNF drugs as SEC and UST.

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Association of Kinesiophobia, Aerobic Exercise, Functional Impairment and Disease Activity of Patients with Rheumatoid Arthritis and Spondyloarthritis

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Background/Purpose: Rheumatoid arthritis (RA) and spondyloarthritis (SA) are the most common chronic inflammatory rheumatism, leading to functional disability, but also cardiovascular mortality. Aerobic exercise (AE) is one of the most effective non-pharmacological resources for cardiovascular rehabilitation while the patients RA and SA have difficulty to join the practice of physical exercise. It can be explained by the presence of kinesiophobia, fear that the movement exacerbates the pain and disease. The objective was to compare the level of AE of patients with RA and SA with healthy subjects and to verify the association between kinesiophobia, the level of activity of the disease and the functional disability.

Methods: Fifty RA patients and fifty SA patients followed by the rheumatology department of the University Hospital of Besancon and fifty healthy age-matched subjects were included. The main inclusion criteria: between 18 and 80 years old and without orthopedic surgery <1 year. The disease activity (DAS-28 and ASDAS), the functional disability (HAQ and BASFI), the level of AE (SQUASH questionnaire) and kinesiophobia (TSK questionnaire) were evaluated. The control group answered to the SQUASH questionnaire. The t-test was used to compare inflammatory rheumatism groups with the control group (healthy subjects). The Pearson Correlation Test for each group (RA and SA) was used to verify the associations between variables.

Table 1: Demographic Characteristics of Patients with RA and SA and Healthy Subjects.

	RA	SA	Healthy Subjects
Age (years)	62.8 (10.8)	47.3 (12.7)	55.7 (13.4)
Height (m)	1.66 (0.10)	1.70 (0.1)	1.70 (0.1)
Weight (Kg)	72.4 (16.5)	71.8 (14.7)	71.7 (14.8)
Aerobic Exercises (SQUASH)	3706.9 (2958.3)	5448.0 (3655.6)	5503.5 (3095.9)
Kinesiophobia (TSK)	42.7 (7.8)	40.6 (7.5)	-
Functional disability (HAQ/BASFI)	1.0 (0.6)	4.3 (2.4)	-
Disease activity (DAS28/ASDAS)	3.0 (1.1)	1.6 (1.1)	-

Results: The level of AE is significantly higher in healthy subjects ($p = 0.022$). In the RA group, kinesiophobia is associated with disease activity, functional disability and level of AE. In the SA group, kinesiophobia is associated only with the functional disability.

Table 2: Results of Pearson Correlation Test between variables

		Aerobic Exercise	Kinesiophobia	Functional Disability	Disease Activity
RA	Aerobic Exercise	-	$r = -0.280^*$	$r = -0.414^{**}$	$r = -0.149$
	Kinesiophobia	$r = -0.280^*$	-	$r = 0.522^{**}$	$r = 0.327^*$
	Functional Disability	$r = -0.414^{**}$	$r = 0.522^{**}$	-	$r = 0.531^*$
SA	Aerobic Exercise	-	$r = -0.165$	$r = -0.40$	$r = -0.064$
	Kinesiophobia	$r = -0.165$	-	$r = 0.345^*$	$r = 0.224$
	Functional Disability	$r = -0.040$	$r = 0.345^*$	-	$r = 0.737^{**}$

* $p < 0.005$; ** $p < 0.005$

Patients have a low level of AE compared to healthy subjects. However, only the RA group has an association between kinesiophobia and AE. In the SA group, functional disability appears to be a factor limiting the practice of AE.

Conclusion: RA and SA patients need to be encouraged and better informed about the benefits of physical exercise.

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Abstract Number: 690

Subcutaneous Secukinumab Provides Sustained Inhibition of Radiographic Progression in Patients with Active Psoriatic Arthritis: 52-Week Results from a Phase 3 Study

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

Background/Purpose: Secukinumab (SEC), a fully human anti-interleukin-17A monoclonal antibody, significantly improved signs and symptoms and inhibited radiographic progression versus placebo (PBO) at Week (Wk) 24 in patients (pts) with psoriatic arthritis (PsA) in the FUTURE 5 (NCT02404350) study.¹ Here, we report the effects of SEC on radiographic progression, additional efficacy endpoints and safety through 52 wks in the FUTURE 5 study.

Methods: Pts (N=996) with active PsA, were randomized (2:2:2:3) to subcutaneous (sc) SEC 300mg with loading dosage (LD; n=222), 150mg with LD (n=220), 150mg without LD (n=222), or PBO (n=332). All groups received SEC or PBO at baseline (BL), Wks 1, 2, 3, and 4, and then every 4 wks. At Wk 16, PBO non-responders were switched to SEC 300mg or 150mg; remaining PBO pts were switched at Wk 24. Radiographic progression, as assessed by mean change in van der Heijde-modified total Sharp score for PsA (mTSS), was based on hand/wrist/foot radiographs obtained at BL, Wk 16 (non-responders), Wk 24 and Wk 52, assessed by two blinded readers (plus an adjudicator if required). Pts were stratified based on anti-TNF status (naïve/inadequate response [IR]). Radiographic data was analyzed by linear extrapolation at Wk 24 for all PBO non-responders and for all other pts with missing Wk 24 radiographs; Wk 52 radiographic data are based on observed data. In addition, radiographic data for the overall population was analyzed by linear mixed effects model at Wk 24. Additional assessments at Wk 52 included ACR20/50, PASI75 and resolution of dactylitis and enthesitis. Statistical analyses used non-responder imputation for these clinical variables. Safety analyses included all pts who received ≥ 1 dose of SEC.

Results: 91.9% (204/222; 300mg LD), 91.4% (201/220; 150mg LD) and 86.9% (193/222; 150mg No LD) pts completed 52 wks of treatment. Inhibition of radiographic progression was sustained through 52 Wks (Table). Proportions of pts with no radiographic progression (change from BL in mTSS ≤ 0.5) with SEC at 52 Wks were 92% (300 mg LD), 85% (150 mg LD), and 87% (150 mg No LD). Mean changes from baseline in mTSS by linear mixed effects model at Wk 24 were 0.03 (P<0.01; 300mg LD), 0.14 (P<0.05; 150mg LD) and -0.10 (P<0.001; 150mg No LD) vs. 0.51 (PBO). Clinical responses were also sustained or improved through 52 Wks (Table). Over the study (mean SEC exposure of 309.0 days), exposure adjusted incidence rates with SEC for selected AEs were: serious infections (1.6), *Candida* infections (2.2), crohn's disease (0.2), ulcerative colitis (0.1), major adverse cardiovascular event (0.2) and malignant/unspecified tumors (0.5).

Conclusion: Secukinumab provided sustained inhibition of radiographic progression through 52 wks. Clinical responses were also sustained or improved through 52 wks. The safety profile was consistent with that previously reported.¹

References: 1 Mease PJ, et al. *Ann Rheum Dis.* 2018;77:890-897.

Variable	Week	Secukinumab 300 mg LD N = 222	Secukinumab 150 mg LD N = 220	Secukinumab 150 mg No LD N = 222	Placebo N = 332
mTSS-structural progression mean change from BL (n)	24	0.02* (217)	0.13* (213)	-0.10* (216)	0.50 (296)
	52	-0.03 (207)	0.13 (203)	0.21 (195)	-
mTSS-structural progression in anti-TNF-naïve: mean change from BL (n)	24	-0.04* (152)	0.08* (149)	-0.20* (151)	0.48 (214)
	52	-0.14 (147)	0.18 (147)	0.18 (141)	-
mTSS-structural progression in anti-TNF-IR: mean change from BL (n)	24	0.16 (65)	0.23 (66)	0.31 (59)	0.54 (82)
	52	0.03 (60)	0.15 (61)	0.26 (54)	-
ACR20, % responders	16	82.6*	55.5*	59.5*	27.4
	52	60.9	64.1	66.8	-
ACR50, % responders	16	39.6*	26.9*	32.0*	6.1
	52	46.8	41.4	43.2	-
PASI75, % responders	16	78.0*	66.0*	58.1*	12.3
	52	74.5	63.2	59.8	-
Resolution of enthesitis ¹ , %	16	55.7†	54.6*	41.9	26.4
	52	70.7	63.1	61.2	-
Resolution of dactylitis ² , %	16	65.9*	57.5*	58.3*	32.3
	52	65.5	72.5	60.9	-

*P < 0.0001, †P = 0.001, ‡P < 0.01, §P < 0.05 (unadjusted P-values vs. placebo).
¹Data from pts with enthesitis at BL: N = 140 (300mg LD), 141 (150mg LD), 129 (150mg No LD) and 192 (placebo).
²Data from pts with dactylitis at BL: N = 122 (300mg LD), 60 (150mg LD), 160 (150mg No LD) and 124 (placebo).
 ACR, American College of Rheumatology response criteria; LD, loading; mTSS, modified total Sharp score; N, number of pts randomized; n, number of pts with data at baseline and Week 24/52; PASI, psoriasis area and severity index; pts, patients; TNF, tumour necrosis factor.

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Abstract Number: 691

A Service Evaluation of Reporting Standards of Computer Tomography Defined Sacroiliitis Suggestive of Axial Spondyloarthritis in Inflammatory Bowel Disease Patients Imaged for Non-Musculoskeletal Indications

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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Background/Purpose: A combined service evaluation by the rheumatology and radiology department was undertaken to understand the frequency and reporting standards of Computer Tomography-defined Sacroiliitis (CTSI) in patients with Inflammatory Bowel Disease (IBD) imaged for non-musculoskeletal indications.

Methods: CT scans of the abdomen and pelvis were identified retrospectively from the radiology imaging system (RIS) between January 2010 and December 2017. The results were then filtered to ages between 18 to 55 year olds, which is commonly considered to be the population with the highest diagnostic yield for axial spondyloarthritis (axSpA). Only scans of patients with confirmed IBD (Crohn's disease (CD) or Ulcerative Colitis (UC)) were evaluated. For patients who have undergone multiple scans, the most recent CT scan was used as the index scan. CT scan evaluation was undertaken by 3 radiology trainees (trained and under supervision of a senior musculoskeletal radiologist) in order to identify incidental CTSI, highly suggestive of axSpA^(1,2).

Results: A total of 301 unique scans of confirmed IBD patients (mean age 36; male 49.2%) were evaluated. The frequency of CTSI using the maximum sensitive criterion of a validated CT screening tool⁽¹⁾ was 19.9% (60/301). In 53 UC and 248 CD patients, the percentage of CTSI were 17.0% UC (9/53) and 20.6% CD (51/248) respectively. Of the 60 positive scans, 15/60 were reported as sacroiliitis but no reference was made for further rheumatological assessment; of these 15, seven had no previous diagnosis of axSpA. Of the remaining 45 CTSI; 26 were unidentified despite a bone evaluation having apparently been undertaken, 17 did not mention a bone evaluation, 2 were unidentified despite the SI joints having been reviewed.

Conclusion: An estimated 20% of selected IBD patients' scans have sacroiliitis indicative of possible underlying axSpA diagnosis but these were not reported in 75% of cases. There is a need to raise the awareness of this association and perhaps the utilisation of a validated CT tool may advance reporting excellence. Further assessment of this select group may help differentiate between asymptomatic sacroiliitis and a potential hidden burden of axSpA among IBD patients undergoing CT scanning for non-musculoskeletal indications.

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1. Chan J, Sari I, Salonen D, Inman RD, Haroon N. Development of a Screening Tool for the Identification of Sacroiliitis in Computed Tomography Scans of the Abdomen. *J Rheumatol* 2016;43:1687–1694.
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Disclosure: C. S. E. Lim, None; S. B. L. Low, None; B. Dhillon, None; S. Azegami, None; A. P. Toms, None; K. Gaffney, None.

TNF Inhibitor Dose Tapering in Axial Spondyloarthritis: A Systematic Review and Meta-Analysis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: Patients with axial spondyloarthritis (axSpA) who have achieved a stable disease state and are undergoing treatment with tumour necrosis factor inhibitor (TNFi) therapy may opt for a dose reduction. Lowering the standard dosing regimen presents several potential risks including disease relapse. We investigated the efficacy of adjusting (reducing or withdrawing) the standard TNFi dose for the treatment of axSpA.

Methods: CENTRAL, Embase, and MEDLINE databases were searched (up to February 2018) along with trial registries and reference lists of relevant articles^{1,2}. All randomized controlled trials (RCTs) evaluating a method of TNFi dose adjustment were assessed for eligibility. Data were pooled in RevMan 5.3 using a random-effects model for the following outcomes: Assessment of SpondyloArthritis international Society 40% (ASAS40) improvement criteria, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), C-reactive protein (CRP), remission, relapse and quality of life (QoL).

Results: 297 full-texts were reviewed for eligibility and 6 RCTs (737 participants) were included in the meta-analysis. There were higher ASAS40 rates with standard TNFi treatment as compared to an adjusted dose (risk ratio [RR] 0.63; 95% confidence interval [CI] 0.51 to 0.78; 3 studies; 538 participants; moderate quality evidence). There were no differences in the mean BASDAI (mean difference [MD] 0.40; 95% CI -0.11 to 0.91; 4 studies; 319 participants; moderate quality evidence) and mean CRP (MD 0.68; 95% CI -1.49 to 2.85; 4 studies; 319 participants; low quality evidence) between the standard and adjusted doses. There were higher rates of remission in the standard dose as compared to the adjusted dose (RR 0.65; 95% CI 0.56 to 0.77; 5 studies; 694 participants; low quality evidence). There were fewer events of disease relapse (i.e. BASDAI >4) in the standard versus adjusted dose (RR 1.20; 95% CI: 0.58 to 2.48; 2 studies; 156 participants; low quality evidence). QoL was not pooled due to clinical heterogeneity.

Conclusion: To our knowledge, this is the first review to incorporate a meta-analysis on TNFi dose adjustment in an axSpA population. Overall, this review found that axSpA patients who have achieved stable disease might experience little benefit or harm from TNFi withdrawal or reduction. The published data to date leave unclear the risk/benefit ratio of withdrawing treatment. Individualizing this decision is an important research question for future studies.

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Disclosure: D. O. Lawson, None; M. Eraso, None; L. Mbuagbaw, None; T. Aves, None; A. Leenus, None; M. Joanes, None; A. Omar, None; R. D. Inman, None.

Combining Adalimumab with Methotrexate Does Not Improve Long Term Sustainability in Patients with Psoriatic Arthritis. Real World Evidence Report from the Quebec Database Rhumadata®

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

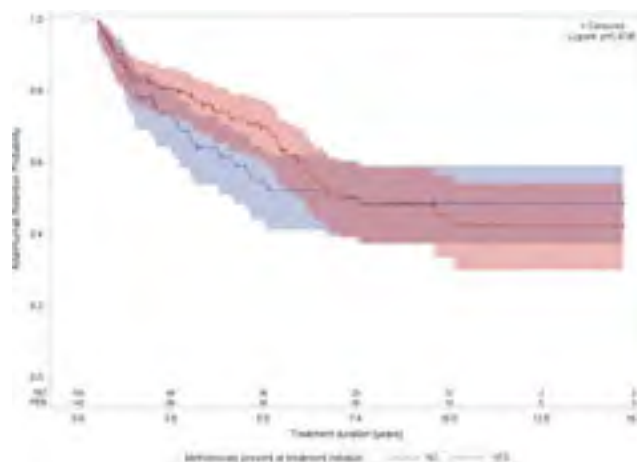
Background/Purpose: Psoriatic Arthritis (PsA) is a musculoskeletal inflammatory condition associated with psoriasis. It has a heterogeneous set of clinical manifestations which include peripheral arthritis, axial involvement, enthesitis, dactylitis, skin, and nail disease. In current practice, the treatment of PsA involves initiating a conventional synthetic DMARD (csDMARD), usually followed by an initial Tumor Necrosis Factor inhibitor (TNFi) and then a second TNFi before considering other classes of biological DMARD (bDMARD). The efficacy of TNFi in patients with PsA has been documented in randomized clinical trials (RCTs) for several of these agents, including adalimumab (ADA), etanercept, infliximab, adalimumab, golimumab, and certolizumab, compared with placebo. However, little is known about the utility of combining a TNFi with MTX (C) versus TNFi monotherapy (M) in psoriatic arthritis and studies to this day show conflicting results. We evaluate here the comparative sustainability of ADA used in first or second intention in patients with PsA initially treated in C or M.

Methods: Data from all RHUMADATA® patients with PsA prescribed ADA either as an initial or second TNFi was analyzed. Patients were followed until treatment discontinuation, loss to follow-up or February 21st, 2018. Only patients who were treated for at least six months were included. The characteristics of selected patients were tabulated, and the ADA discontinuation rates of patients who initiated C and M were compared using Kaplan-Meier estimates and multivariate Cox models adjusting for potential confounders.

Results: A total of 247 patients with PsA received ADA in first or second intention. Of those, 105(42.5%) and 142(57.5%) received treatment without and with MTX respectively. There was a statistically significant difference in populations in table 1 for the age at diagnosis (M:39.8±11.7; C: 43.5±11.4; p=0.012). No significant differences in retention rates between M and C therapy were observed (see figure below). Mean retention time for M and C therapy were respectively 5.06 (SE=0.29) and 6.82(SE=0.35). Subanalysis looking at ADA in first and in second intention showed similar results.

Conclusion: Combining MTX to ADA does not improve sustainability in patients with PsA.

Disclosure: O. Benryane, None; L. Coupal, None; D. Choquette, None.



Combining Etanercept with Methotrexate Does Not Improve Long Term Sustainability in Patients with Psoriatic Arthritis. Real World Evidence Report from the Quebec Database Rhumadata®

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

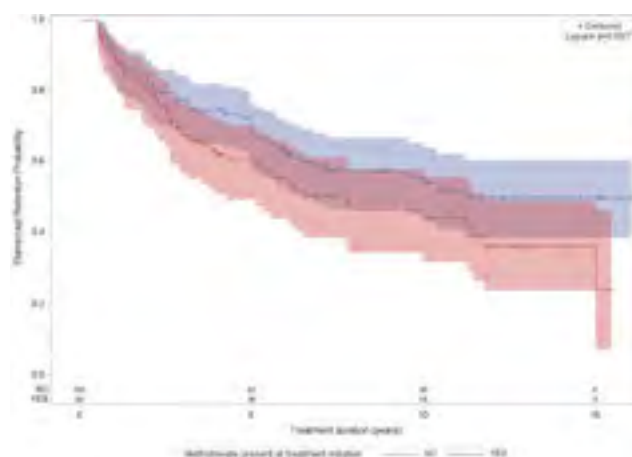
Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic Arthritis (PsA) is a musculoskeletal inflammatory condition associated with psoriasis. It has a heterogeneous set of clinical manifestations which include peripheral arthritis, axial involvement, enthesitis, dactylitis, skin, and nail disease. In current practice, the treatment of PsA involves initiating a conventional synthetic DMARD (csDMARD), usually followed by an initial Tumor Necrosis Factor inhibitor (TNFi) and then a second TNFi before considering other classes of biological DMARD (bDMARD). The efficacy of TNFi in patients with PsA is documented in randomized clinical trials (RCTs) for several of these agents, including etanercept (ETA), infliximab, adalimumab, golimumab, and certolizumab, compared with placebo. However, little is known about the utility of combining a TNFi with MTX (C) versus TNFi monotherapy (M) in psoriatic arthritis and studies to this day show conflicting results. We evaluate here the comparative sustainability of ETA used in first or second intention in patients with PsA initially treated in C or M.

Methods: Data from all RHUMADATA® patients with PsA prescribed ETA either as an initial or second TNFi was analyzed. Patients were followed until treatment discontinuation, loss to follow-up or February 21st, 2018. Only patients who were treated for at least six months were included. The characteristics of selected patients were tabulated, and the ETA discontinuation rates of patients who initiated C and M were compared using Kaplan-Meier estimates and multivariate Cox models adjusting for potential confounders.

Results: A total of 195 patients with PsA (according to CASPAR criteria) received ETA in first or second intention. Of those, 102 (52.3%) and 93 (47.7%) received treatment without and with MTX respectively. There were statistically significant differences in populations in table 1 for the BASDAI (M: 5.8 ± 2.8 ; C: 3.9 ± 2.3 ; $p=0.03$) and BASFI (M: 5.0 ± 3.0 ; C: 2.8 ± 2.0 ; $p=0.011$) scores, both being higher in the M group. No significant differences in retention rates between M and C therapy were observed (see figure below). Mean retention time for M and C therapy were respectively 7.12 (SE=0.42) and 8.25 (SE=0.68) years. The main reason for treatment cessation was inefficacy, followed by adverse events. There were more adverse events in the C group (26.1% vs 9.3%). Sub-analysis looking at ETA in first and in second intention showed similar results.

Conclusion: Combining MTX to ETA does not improve sustainability in patients with PsA.



Disclosure: O. Benryane, None; L. Coupal, None; D. Choquette, None.

Abstract Number: 695

Tumor Necrosis Factor Inhibitor Persistence and Reasons for Discontinuation in US Veterans with Axial Spondyloarthritis

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

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Background/Purpose: Although tumor necrosis factor inhibitors (TNFi) have favorably altered the treatment landscape for patients with axial spondyloarthritis (AxSpA), permanent therapy is infrequent. Further, the extent to which patients continue individual TNFi agents is uncertain and the reasons for discontinuation of TNFi remain obscure.

Objective: To determine TNFi persistence and reasons for discontinuation in patients with axial spondyloarthritis

Methods: A retrospective cohort analysis was performed of US veterans enrolled from 2007 to 2017 in the Department of Veterans Affairs (VA) Program to Understand the Long term outcomes in SpondyloArthritis Registry (PULSAR), who met ASAS criteria for AxSpA and were treated with TNFi. Enrollment sociodemographic variables, HLA-B27 status,

Figure 1: TNFi Persistence estimates in AxSpA Cohort

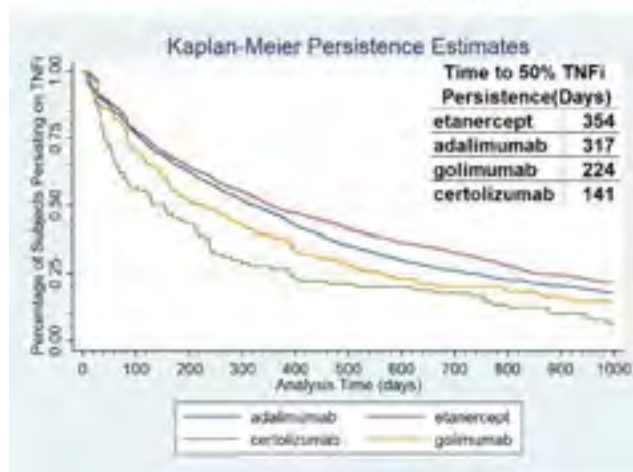
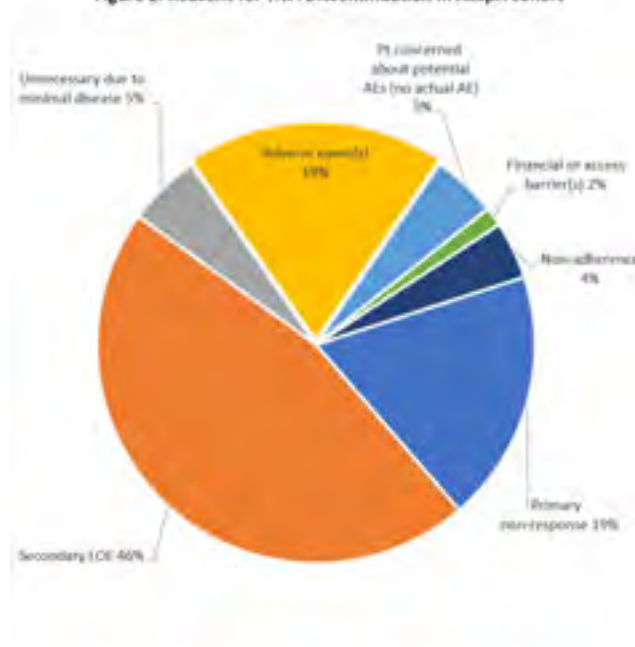


Figure 2: Reasons for TNFi Discontinuation in AxSpA cohort



erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were collected. Corporate Data Warehouse Pharmacy files provided courses of injectable TNFi agents (etanercept, adalimumab, certolizumab, and golimumab). Individual TNFi persistence was first compared with unadjusted Kaplan-Meier plots, and then multivariable Cox proportional hazards regression applied, including a term for the course sequence (accounting for the order of the TNFi, [STATA]). Reasons for discontinuation (primary non-response [< 6 months TNFi exposure], secondary [> 6 months TNFi exposure] loss of efficacy (LOE), adverse event, patient averseness, financial/access, minimal disease, non-adherence) were obtained by physician chart review.

Results: The cohort of 229 patients were of mean age 53.2 years, and mainly white (69%) men (93.8%). HLA-B27 was positive in 73.4%, with mean CRP of 1 [1.4] mg/dl and ESR 17.9 [17.8] mm/hr. Individual TNFi persistence was highest for etanercept ($p < 0.05$), accounting for TNFi sequence. At approximately 3 years, persistence for any TNFi was $< 25\%$ (Figure 1). Secondary LOE was the most common reason for discontinuation, accounting for nearly half of all courses. In 20% of instances, primary non-response and adverse events accounted for TNFi discontinuation (Figure 2), while patient risk averseness, non-adherence and drug access were infrequent ($< 5\%$) reasons.

Conclusion: Etanercept has the best TNFi persistence among VA AxSpA patients, but discontinuation is common, mainly due to loss of efficacy. The contributing factors for discontinuation, including specific administration guidelines, comorbidities or anti-drug antibodies are potential areas for further inquiry

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Abstract Number: 696

Efficacy and Safety of Novel Targeted Synthetic DMARD and Biological DMARD in Active Psoriatic Arthritis: A Systematic Review, Meta-Analysis, and Network Meta-Analysis

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Background/Purpose: Many targeted synthetic DMARD (tsDMARD) and biological DMARD (bDMARD) were recently approved for treatment of active psoriatic arthritis (PsA), but their comparative efficacy and safety remain unknown. This study aims to compare the efficacy and safety of recently generated tsDMARD and novel bDMARD in active PsA.

Methods: Randomized clinical trials (RCT) evaluating the efficacy and safety of tsDMARD including tofacitinib (TOF) and apremilast (APR), and bDMARD such as ustekinumab (UST), secukinumab (SEC), ixekizumab (IXE), clazakizumab (CLA), and abatacept (ABA) for active PsA, who received a diagnosis of PsA at least 6 months previously, fulfilled the Classification Criteria for Psoriatic Arthritis, and had active plaque psoriasis and active arthritis (≥ 3 swollen and ≥ 3 tender or painful joints) at screening, were identified by comprehensive systemic literature review. Pairwise meta-analysis and Network meta-analysis (NMA) using a random effects model were performed to estimate pooled odds ratios (ORs) and 95% confidence intervals (CIs) of attaining 20% or 50% improvement in ACR criteria (ACR20 or ACR50) and 75% improvement in psoriasis area and severity index (PASI75), any adverse events (AE) and serious adverse events (SAE) across trials.

Results: We deemed 15 RCT eligible, including 6004 participants and 17 treatments. For efficacy, pairwise meta-analysis showed that all treatments except CLA 200mg/25mg monthly were superior to placebo in achieving ACR20, all except CLA 200mg monthly and ABA 125mg weekly were superior in achieving ACR50, and TOF, APR 30/20mg twice daily, UST, SEC 300mg/150mg monthly and IXE were superior in achieving PASI75. For safety, TOF 10mg twice daily, APR 30mg/20mg twice daily, and IXE were more likely to have any AE, but no significant differences were seen for pooled SAE among the various treatments. NMA showed SEC 300mg monthly to be more efficacious in achieving ACR20 and ACR50, whereas UST 90mg 12 weekly had the highest efficacy in achieving PASI75. SEC 75mg monthly and UST 90mg 12 weekly had the lowest probability of pooled AE and SAE, respectively. Regarding the overall efficacy in both articular and cutaneous aspects and overall risk-benefit profile, SEC and UST ranked higher than other interventions.

Conclusion: Secukinumab and Ustekinumab may be the safest and most efficacious (for arthritis and psoriasis, respectively) for active PsA among the new targeted synthetic and biological DMARD.

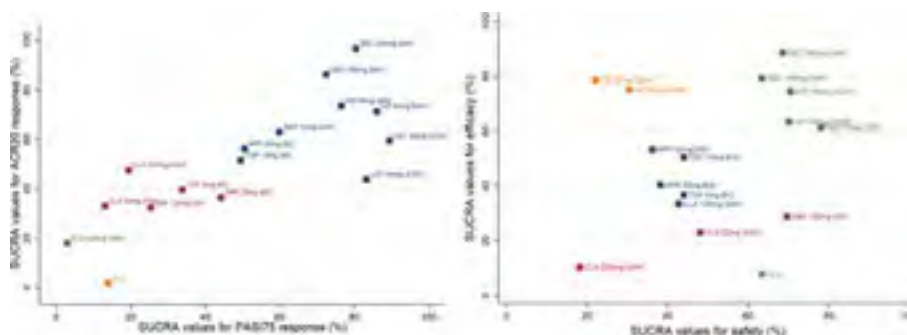


Figure 1: Clustered ranking plot for efficacy and safety

Each color represents a group of treatments that belong to the same cluster. Treatments lying in the upper right corner are more effective or/and safer than the other treatments. (Efficacy= 50% ACR20 response and 50% PASI75 response; Safety= 50% AE and 50% SAE). QD: daily; BID: twice daily; QW: weekly; Q2W: every 2 weeks; Q4W: every 4 weeks; Q12W: every 12 weeks; PLA: placebo.

Disclosure: C. Lu, None; B. I. Wallace, None; W. Fu, None; Y. Liu, None.

Abstract Number: 697

Clinical Results of Patients with Peripheral Psoriatic Arthritis Not Receiving Biological Therapy in a Multidisciplinary Unit

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Background/Purpose: We consider multidisciplinary management necessary, especially in a subgroup of patients with Psoriatic Arthritis (PsA) for complexity, cutaneous and / or joint involvement. Despite the limited evidence of efficacy of methotrexate (MTX) and other classical synthetic DMARDs (csDMARDs) in these patients, they are commonly prescribed in our multidisciplinary unit (following the recommendations of experts, in peripheral PsA). Objective: To assess joint and cutaneous involvement in patients with peripheral psoriatic arthritis not receiving biologics in our multidisciplinary unit (visited for at least 6 months)

Methods: We review clinical the records of 199 PsA patients visited in our multidisciplinary unit and select 74 patients with the above mentioned criteria; we collect epidemiological and clinical data, and joint and skin activity evaluation by DAPSA, PASI, BSA and PGA (in plaque psoriasis) and proportion of patients that achieve MDA (minimum disease activity) as a therapeutic goal. Data were analyzed using SPSSv23.

Results: 74 patients, 63.5% males, aged mean (SD) 54.8(14.0) years. 56 peripheral PsA and 18 mixed (peripheral predominance); with mean 94.9(92.4) months of disease; 35.1% with previous clinical enthesitis and 37.8% previous dactylitis. Cutaneous disease consisted mainly (82.4%) in plaque psoriasis, 9.5% affecting folds, 4.1% onychopathy. 52.7% have received a previous DMARD of (31.1% MTX, 9.5% leflunomide) and 23.0% PUVA; 4.1% have received previous biological treatment. Current treatment: 83.8% DMARDs (68.9% MTX and 5.4% leflunomide) with a mean follow-up of 60.6(55.0) months. Disease activity: Skin plaque psoriasis was mainly controlled: 73.4% low PASI level (23.4% moderate) median PASI 3.0 [1.5-5.0]; 50.0% mild BSA, median BSA 3.0[1.0-6.0]. 73.1% PGA of very mild or mild-moderate disease. 87.0% of patients met DAPSA criteria of remission-low disease activity (DAPSA median 3.15[1.34-6.71]; 55.9% achieved DAPSA <4); 75.7% were in low activity / remission according to medical judgement. Overall 63.9% of patients achieved MDA; 15.3% (10 patients) had relative” contraindications” to biological therapy (6 cases of recent cancer, 2 HBV infection).

Conclusion: Over half of PsA patients from our multidisciplinary unit achieve low cutaneous and articular disease activity under csDMARDs, mainly Methotrexate. The use of targeted DMARDs such as apremilast in this scenario before biological therapies may improve disease outcomes in a subgroup of patients, corresponding with the efficacy shown in different domains of the psoriatic disease. Further research is needed to compare clinical results between csDMARDs and Apremilast.

Disclosure: C. Pérez-Velásquez, None; M. L. Garcia Vivar, None; S. Perez Barrio, None; E. Galindez-Agirregoikoa, None; E. Ruíz Lucea, None; I. Torre-Salaberri, None; O. Fernández-Berrizbeitia, None; A. R. Inchaurre Pellejero, None; J. Blanco Madrigal, None; E. Guerrero Basterretxea, None; I. Calvo Zorrilla, None; O. Ibarguengoitia, None; D. Montero, None; N. Rivera-García, None; M. J. Allande Lopez Linares, None; I. Gorostiza-Hormaetxe, None.

Abstract Number: 698

Discontinuation of Methotrexate or TNF Inhibitors in Patients with Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis

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Background/Purpose: Methotrexate and TNF inhibitors (TNFi) are commonly used in the treatment of RA, PsA, and other SpA. While MTX is a mainstay of RA treatment, its efficacy and tolerability have not been as well studied in spondyloarthritis. Our aims were 1) to assess the rates of MTX and TNFi discontinuation in patients with PsA and ankylosing spondylitis (AS) compared to patients with RA, hypothesizing that MTX discontinuation, but not TNFi discontinuation, would occur sooner in patients with PsA or AS; and 2) to determine whether concomitant methotrexate use was associated with later TNFi discontinuation in PsA and AS.

Table: Rates of MTX and TNF inhibitor discontinuation by disease and results of adjusted models

Methotrexate discontinuation								
	N	PY	Time to discontinuation		Early discontinuation (within 90 days)		Late discontinuation (after 90 days)	
			Median persistence (years)	aHR (95% CI)	N (%)	aOR (95% CI)	Median persistence (years)	aHR (95% CI)
RA	28812	24271	1.10	Ref	6783 (23.5%)	Ref	1.84	Ref
PsA	3021	2528	0.92	1.10 (1.05-1.16)	739 (24.4%)	1.00 (0.97-1.16)	1.59	1.13 (1.06-1.21)
AS	2019	1496	0.70	1.30 (1.23-1.38)	632 (30.8%)	1.41 (1.28-1.56)	1.36	1.27 (1.18-1.38)
TNF inhibitor discontinuation								
	N	PY	Time to discontinuation		Early discontinuation (within 90 days)		Late discontinuation (after 90 days)	
			Median persistence (years)	aHR (95% CI)	N (%)	aOR (95% CI)	Median persistence (years)	aHR (95% CI)
RA	24594	24106	1.27	Ref	4442 (17.4%)	Ref	1.81	Ref
PsA	6946	6734	1.50	0.96 (0.92-0.99)	1121 (16.1%)	0.98 (0.87-1.01)	2.04	0.97 (0.93-1.02)
AS	3978	3506	1.14	1.11 (1.05-1.16)	758 (19.0%)	1.17 (1.07-1.28)	1.75	1.09 (1.02-1.16)

Adjusted hazard ratio (aHR) and adjusted odds ratio (aOR) from multivariable Cox or logistic regression models adjusted for age, sex, and year. TNF inhibitor models also adjusted for which TNF inhibitor patients received. RA = rheumatoid arthritis, PsA = psoriatic arthritis, AS = ankylosing spondylitis, PY = person-years

Methods: This retrospective study using OptumInsight administrative data 2000-2014 evaluated adults with RA, PsA, or AS (based on two diagnosis codes and DMARD use) with no prior biologic use who received a first ever MTX prescription or first ever TNFi prescription or infusion, requiring 6 months of preceding data (baseline) and at least 90days of follow up. Cox proportional hazards were used to compare time to medication discontinuation over the next two years between patients with RA, PsA, or AS, adjusting for age, sex, and calendar year. We also assessed rates of early discontinuation (within 3 months) and late discontinuation (after 3months).

Results: We identified 33,882 patients initiating MTX and 36,518 initiating a TNFi. Median MTX persistence was 1.05years and 24% of patients discontinued MTX within 90 days. Discontinuation occurred sooner in patients with PsA [aHR 1.10 (1.05-1.16)] and AS [aHR 1.30(1.23-1.38)] vs. RA (Table). Early MTX discontinuation was more common in AS, and late discontinuation was more common in both PsA and AS (Table). Median TNFi persistence was 1.29 years and 17% of patients discontinued within 90 days. TNFi discontinuation occurred sooner in patients with AS [aHR 1.11 (1.05-1.16)] but later in patients with PsA [aHR 0.96 (0.92-0.99)] vs. RA (Table). Associations between AS and sooner TNFi discontinuation, however, were attenuated and no longer significant after adjustment for concomitant medications, comorbidities, and healthcare utilization (not shown). Among TNFi initiators, concomitant use of MTX was associated with longer TNFi persistence in RA, PsA, and AS (all $p < 0.001$, p for interaction 0.85). Depression, anxiety, chronic pain, opioid use, and greater comorbidity burden were associated with sooner discontinuation of MTX and TNFi in all groups.

Conclusion: TNFi and especially MTX discontinuation are common, with greater discontinuation in patients with mental health disorders, comorbidities, and chronic pain. Patients with PsA and AS discontinue MTX sooner than patients with RA but continue TNFi at similar rates, possibly indicating poorer tolerability or efficacy of MTX in spondyloarthritis. Use of MTX, however, is associated with less TNFi discontinuation in all disease groups.

Disclosure: M. D. George, Bristol Myers Squibb, 2; J. F. Baker, Corrona, Bristol Myers Squibb, 5; A. Ogdie, Pfizer, Inc.; Novartis, 2, Abbvie, Amgen, BMS, Corrona, Lilly, Novartis, Pfizer, Takeda, 5.

Abstract Number: 699

New Onset/Recurrence of Inflammatory Arthralgia/Spondyloarthritis in Patients Treated with Vedolizumab for Intestinal Bowel Disease

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: Vedolizumab (VDZ) is a monoclonal antibody approved for inflammatory bowel disease, with a gut-specific mechanism of action, binding to $\alpha 4\beta 7$ integrin expressed on gut-homing T lymphocytes. Few cases of flare or new occurrence of rheumatic disorders in patients treated with VDZ were reported in literature (1-2). A small cohort study (3) did not report new induction or flare of arthritis and/or sacroiliitis and some patients with active SpA showed some improvement in symptoms after VDZ. Our purpose is to observe the possible role of VDZ in new onset/recurrence of rheumatic manifestations.

Methods: Observational study of a series of 7 patients with IBD who developed inflammatory arthralgia after treatment with VDZ.

Results: Four out of 7 patients were women and 6 patients had been diagnosed with Crohn's disease (CD), 1 with ulcerative colitis (UC). The mean duration of IBD was of 14 years. The mean age was 49.8 years (range 24-63). None of the patients had previous history of arthritis/spondyloarthritis. One patient who was previously treated with Infliximab and Mesalazine, during the course of the treatment suffered from an episode of arthritis with spontaneous remission, 9 years before starting VDZ. Six patients out of 7 had previously been treated with biologic therapy, in 2/6 patients VDZ was the 2nd-line biologic therapy and in 4/6 patients the 3rd-line. Six patients fulfilled the ASAS criteria for spondyloarthritis (4-5), 1 was classified as unspecified inflammatory arthralgia. The mean number of infusions of VDZ received before the onset of symptoms was 3 (range 1-6) and the mean time of exposure to VDZ was 11 weeks (range 1-32). Five patients had high levels of inflammation with mean CRP of 15.6 mg/L (range 0.6-42.2). Three patients with back pain performed a MRI that showed sacroiliitis. In 2 cases HLA-B27 was investigated with negative result. Four patients discontinued VDZ, 3 restarted the previous biologic therapy with Adalimumab and 1 was started on Infliximab.

Conclusion: This is the longest series collected so far regarding rheumatic manifestations developed after onset of VDZ treatment for IBD. Further studies are needed to investigate the role of VDZ in rheumatic diseases.

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Disclosure: S. Tamanini, None; M. Fredi, None; C. Bazzani, None; M. G. Lazzaroni, None; M. Fernandes, None; C. Nalli, None; A. Tincani, Bristol-Myers Squibb, 2, UCB, Inc., 5; F. Franceschini, None.

	Gender	Age	IBD	Concomitant therapy	ASAS criteria	Rheumatic features	Radiological findings
1	F	47	CD	None	Yes	Back pain, foot arthritis, family history of psoriasis	MRI: BME (bone marrow edema) of the right SI joint, enthesopathy of great trochanter US (ultrasound) left foot + 1 MTP joint synovitis, flexor digitorum longus and tibialis posterior tenosynovitis
2	F	50	CD	None	No	Shoulder pain	US: bursitis/subacromial subdeloid
3	M	55	CD	None	Yes	Back pain, family history of psoriasis	MRI: active bilateral sacroiliitis and erosions, enthesopathy of great trochanter, trochanteric bursitis
4	F	44	CD	VDZ	Yes	Polyarthritis, psoriasis	MRI: enthesopathy of great trochanter
5	M	44	UC	Mesalazine	Yes	Knee arthritis, family history of psoriasis	MRI: none
6	M	31	CD	Mesalazine	Yes	Back pain and wrist arthritis	MRI: BME of the SI joints and erosions US: right wrist synovitis
7	F	59	CD	VDZ	Yes	Knee arthralgia and arthritis, family history of psoriasis	MRI: left knee effusion US: enthesopathy of the ischio femoral

Immunogenicity of Originator and Biosimilar Infliximab: Anti-Drug Antibody Occurrence, Cross-Reactivity and Epitope Specificities across Six Diseases. Analyses from a Norwegian Randomized Switching Trial

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: The NOR-SWITCH study was funded by the Norwegian government to investigate switching from originator infliximab (INX) to biosimilar CT-P13, in spondyloarthritis (SpA), rheumatoid arthritis (RA), psoriatic arthritis (PsA), plaque psoriasis (Ps), Crohn's disease (CD) and ulcerative colitis (UC). Previously, the primary analyses of the pooled indications have been published¹. Anti-drug antibodies (ADAb) are associated with treatment failure and have been a concern in switching. Here, we investigate immunogenicity of infliximab in patients treated with originator INX vs patients switched to CT-P13; between patients with different inflammatory diseases; and the epitope specificities of ADAb.

Methods: The study was a 52-week randomized, double-blind, non-inferiority, phase IV trial and included adult patients with SpA, RA, PsA, UC, CD or Ps on originator INX. Patients were randomized 1:1 to either continued INX or switch to CT-P13 treatment. Assays for drug serum levels and neutralizing ADAb are fully automated on the AutoDELFIATM (PerkinElmer, Waltham, MA) immunoassay platform. Immunogenic infliximab-epitopes were identified by ELISA and comparison of sera from patients with CD, UC, SpA, RA, PsA or Ps was performed.

Results: 20 patients entered the study with detectable ADAb (9 in INX arm, 11 in CT-P13 arm). 36 patients (17 in INX-arm, 19 in CT-P13 arm) developed incident ADAb during the 52-week main study period with no consistent difference between diseases though numbers are small. 36 patients' and 15 control sera were tested for epitope specificity. No Ps patients developed ADABs in our study. All anti-CT-P13 and anti-INX sera were cross-reactive with INX and CT-P13, respectively. ADAb concentrations against INX or CT-P13 were strongly correlated (r values 0.92 - 0.99, $p < 0.001$ for all experiments, Spearman's correlation test). ADAb-negative controls (10 healthy individuals, 5 patients with RA) were negative for both INX and CT-P13. Recognition of 5 different batches of CT-P13 and INX by IgG4 ADAb were similar between all tested sera. ADAb in 60%-79% of patients recognized 7 synthetic peptides, with no significant differences between CT-P13 and INX ADAb. However, two epitopes were specifically recognized in UC and CD but not in rheumatic patients. Patients with detectable ADAb at any time were more likely to discontinue study drug treatment (7/26 (26.9 %) in INX arm, 5/30 (16.7 %) in CT-P13 arm) than patients without detectable ADAb (17/214 (7.9 %) in INX arm, 13/210 (6.2 %) in CT-P13 arm) ($p = 0.001$).

Studies on a possible association between HLA and ADAb responses are ongoing.

Conclusion: ADAb occurred to a similar degree in the two study arms and ADAb to originator INX also recognized CT-P13. The majority of patients show no consistent difference in epitope specificity between RA, SpA, PsA, UC and CD patients. However, two specific minor epitopes are only recognized by IBD patients which might reflect the importance of HLA background for ADAb response.

Table 1. ACR 20/50/70 and PASI 75/90 response rates at Week 24 among biologic-naïve PsA patients¹

	ACR response rates			PASI response rates	
	ACR 20	ACR 50	ACR 70	PASI 75	PASI 90
PBO	21.7% (19.8%, 23.7%)	7.4% (6.1%, 8.8%)	2.9% (2.2%, 3.9%)	7.8% (5.4%, 11.0%)	3.0% (1.9%, 4.7%)
ABA	43.6% (28.1%, 61.0%)	13.4% (6.4%, 26.3%)	4.1% (1.5%, 11.6%)	12.3% (6.5%, 21.3%)	5.3% (2.4%, 10.6%)
ADA	56.0% (47.6%, 64.3%)	33.7% (24.7%, 44.6%)	23.2% (13.6%, 38.0%)	51.1% (38.7%, 63.4%)	33.5% (22.9%, 45.5%)
APR	39.0% (29.8%, 49.3%)	14.8% (7.4%, 28.2%)	3.3% (1.1%, 9.6%)	--	--
CZP	54.2% (41.6%, 66.8%)	25.2% (15.5%, 39.4%)	18.9% (8.4%, 41.7%)	--	--
ETN	57.6% (42.3%, 72.0%)	48.2% (27.8%, 72.4%)	10.6% (3.2%, 36.5%)	26.0% (12.8%, 43.7%)	13.6% (5.6%, 27.2%)
GOL	68.4% (53.4%, 81.3%)	41.3% (23.0%, 66.3%)	30.8% (10.6%, 75.2%)	73.7% (56.2%, 88.0%)	57.1% (38.2%, 76.2%)
INF	63.5% (47.4%, 77.8%)	58.7% (34.1%, 83.6%)	38.0% (13.9%, 80.8%)	76.7% (59.8%, 89.1%)	60.8% (41.9%, 78.2%)
IXE	52.1% (39.2%, 64.9%)	31.0% (19.6%, 45.6%)	19.3% (9.4%, 36.3%)	68.0% (51.9%, 81.7%)	50.6% (34.3%, 67.6%)
SEC 150	64.8% (53.6%, 75.0%)	40.4% (27.2%, 56.3%)	28.1% (13.5%, 54.6%)	50.9% (36.4%, 66.2%)	33.3% (21.1%, 48.4%)
SEC 300	62.7% (45.8%, 77.4%)	36.6% (20.5%, 57.3%)	24.4% (9.4%, 53.8%)	61.1% (40.3%, 79.8%)	43.2% (24.2%, 64.7%)
TOF	47.5% (34.9%, 60.5%)	30.8% (19.4%, 45.4%)	13.0% (6.1%, 26.4%)	32.0% (20.6%, 44.9%)	17.9% (10.1%, 28.2%)
UST 45	41.6% (32.3%, 51.7%)	21.8% (13.3%, 34.4%)	14.8% (6.2%, 35.6%)	51.7% (38.6%, 65.0%)	34.2% (22.8%, 47.4%)
UST 90	47.7% (38.0%, 57.8%)	24.6% (15.3%, 38.0%)	17.2% (7.5%, 39.6%)	58.8% (45.3%, 71.4%)	40.8% (28.3%, 54.6%)

[1] PASI 75 and PASI 90 responses for APR and CZP were not reported among biologic-naïve population.

Methods: A systematic literature review was conducted to identify Phase 3 randomized controlled trials (RCTs) for TIMs approved for the treatment of active PsA in the US, including tumor necrosis factor- α inhibitors (adalimumab [ADA], certolizumab pegol [CZP], etanercept [ETN], golimumab [GOL], and infliximab [INF]), interleukin-17 inhibitors (secukinumab [SEC] and ixekizumab [IXE]), an interleukin-12/23 inhibitor (ustekinumab [UST]), a phosphodiesterase-4 inhibitor (apremilast [APR]), a selective T cell costimulation modulator (abatacept [ABA]), and a Janus kinase inhibitor (tofacitinib [TOF]) in active PsA. Joint (ACR 20/50/70) and skin (PASI 75/90) responses at Week 24 were estimated via a Bayesian network meta-analysis (NMA) among biologic-naïve patients. Treatment costs were based on Wholesale Acquisition Cost as of April 18, 2018 and included drug acquisition and administration costs. Incremental costs per responder relative to placebo were calculated as incremental treatment costs during 24 weeks divided by response rate difference vs. placebo.

Results: Fourteen RCTs that reported ACR and/or PASI responses at Week 24 among biologic-naïve PsA patients were included. INF, ETN, and GOL had higher ACR 50 response compared with other TIMs (Table 1). In terms of ACR 20 and ACR 70, GOL, INF, and SEC 150 mg had higher efficacy than other TIMs. With respect to PASI responses, INF, GOL, and IXE had higher efficacy than other TIMs. In terms of cost-effectiveness, when considering skin and joint responses together, INF (\$47,899 for ACR 50/\$42,522 for PASI 90), GOL (\$79,982/\$50,238), and ADA (\$111,259/\$96,149) were associated with lower incremental costs per additional ACR 50 or PASI 90 responder than other TIMs (Figure 1).

Conclusion: At Week 24, INF, GOL, and ADA had the lowest incremental cost per responder for joint and skin outcomes among all TIMs approved for PsA in biologic-naïve patients.

Disclosure: V. Strand, AbbVie, Amgen, BMS, Celgene, Celltrion, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, Sandoz, and UCB, 5; M. E. Husni, Celgene, AbbVie, Genentech, Bristol-Myers Squibb, Pfizer, Novartis, and Janssen, 5; J. Griffith, AbbVie Inc., 1, 3; Y. Song, AbbVie, 5; R. Singh, AbbVie Inc., 1, 3; J. Zhao, AbbVie, 5; K. A. Betts, AbbVie Inc., 5.

Abstract Number: 702

Effect of Biologics on Radiographic Progression of Peripheral Joints in Patients with Psoriatic Arthritis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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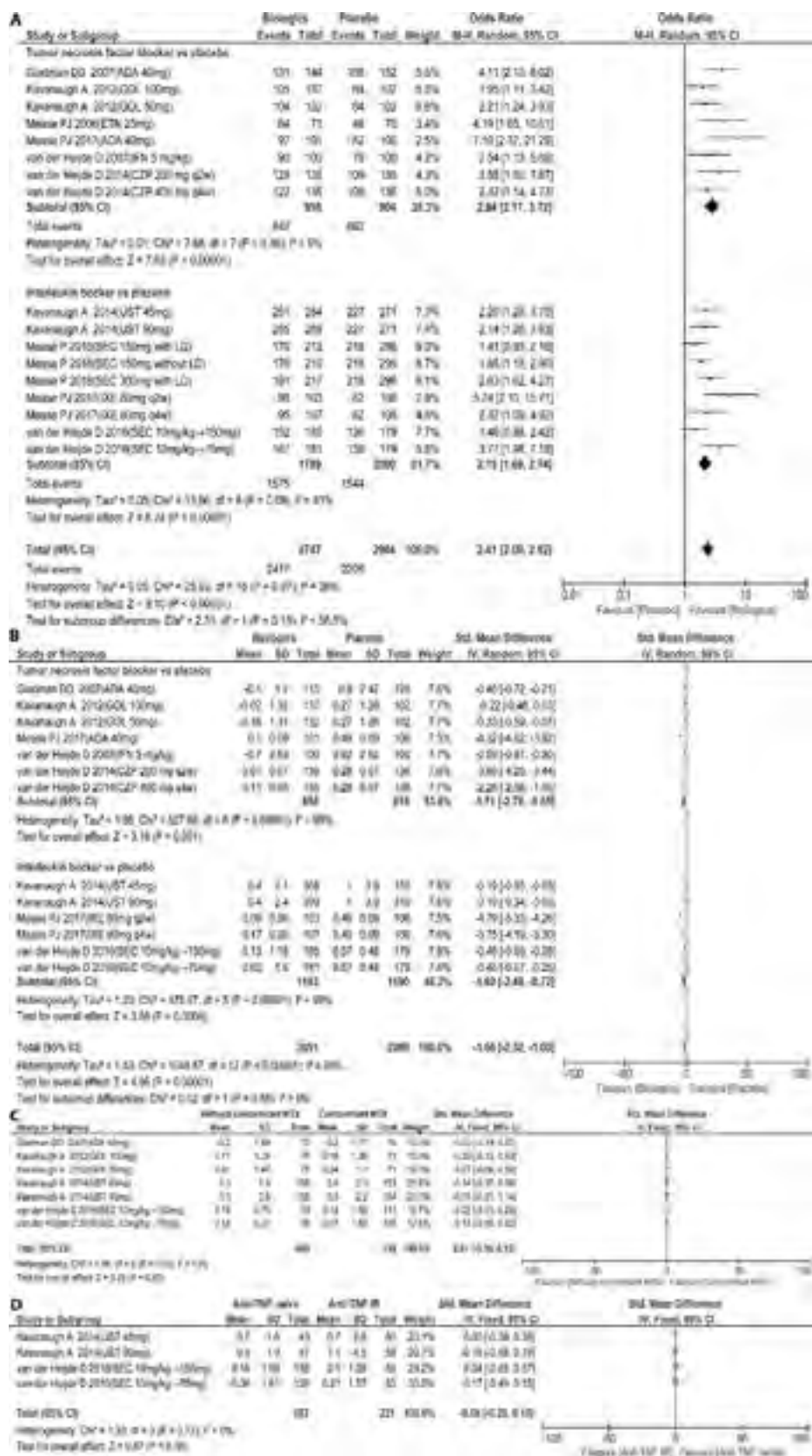
SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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



Background/Purpose: Psoriatic arthritis (PsA) often leads to structural damage with resultant disability and reduced quality of life. Biologic disease modifying anti-rheumatic drugs (bDMARDs), including tumor necrosis factor alpha (TNF- α), interleukin (IL), phosphodiesterase type 4 (PDE-4) and Janus kinase (JAK) antagonists have shown clinical efficacy in PsA.

The aims of this study are to determine the efficacy of the following drug combinations in preventing radiographic progression in peripheral joints of PsA patients, namely 1) bDMARDs versus placebo 2) concomitant methotrexate (MTX) versus bDMARD monotherapy 3) IL blockers in anti-TNF-naïve patients versus anti-TNF-failure patients.

Methods: Systematic review of articles published up to May 2018 in Medline and Web of Science, and abstracts from the two last European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) meetings. Primary endpoint was the proportion of patients without radiographic progression (non-progressors) at week 24. Secondary endpoint was the mean change in total radiographic score [modified total Sharp score (mTSS) or modified van der Heijde-Sharp score (mvdH-SS)] at week 24. Odds ratio (OR) and standardized mean difference (SMD) with 95% CIs across studies were synthesized. Subgroup analyses were performed on pre-specified study-level characteristics. We assessed the quality of evidence using the GRADEpro. This study was registered with PROSPERO, number CRD42018095272.

Results: Nine studies (10 RCTs, 4,478 patients), 8 drugs (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, secukinumab, ustekinumab, ixekizumab) and 16 treatments were evaluated. Tofacitinib and apremilast were not included as complete radiographic data was not available. (1) Patients treated with bDMARDs were more likely to achieve radiographic non-progression compared with placebo (OR for pooled: 2.41, 95% CI: 2.00, 2.92; OR for TNF blocker: 2.84, 95% CI: 2.17, 3.72; OR for IL blocker: 2.15, 95% CI: 1.69, 2.74; Figure 1A), and have significantly lower radiographic progression (SMD for pooled: -1.66, 95% CI: -2.32, -1.00; SMD for TNF blocker: -1.71, 95% CI: -2.76, -0.65; SMD for IL blocker: -1.60, 95% CI: -2.49, -0.72; Figure 1B). (2) In patients receiving bDMARDs, concomitant MTX use was not superior to monotherapy (SMD: 0.01, 95% CI: -0.09, 0.12; Figure 1C). (3) The effect of IL blockers (ustekinumab, secukinumab) on radiographic progression were not influenced by prior anti-TNF therapy (SMD: -0.08, 95% CI: -0.25, 0.10; Figure 1D).

Conclusion: Biologic DMARDs can retard radiographic progression in PsA compared with placebo. Concomitant MTX treatment does not improve this effect. Prior anti-TNF therapy does not influence the radiographic efficacy of IL blockers.

Disclosure: D. Wu, None; P. Wong, None; J. F. Griffith, None; J. Yue, None; L. S. Tam, None.

Abstract Number: 703

Articular Manifestations in Patients with Inflammatory Bowel Disease Treated with Vedolizumab

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

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

Background/Purpose: Vedolizumab is a humanised IgG1 monoclonal antibody anti- $\alpha 4\beta 7$ integrin agent used in inflammatory bowel disease (IBD). It modulates gut inflammation by preventing leukocyte migration to gastro-intestinal mucosa. Vedolizumab is effective on IBD but has been incriminated in occurrence of articular manifestations. Our study aimed at describing rheumatic manifestations and their risk factors occurring in IBD patients treated by vedolizumab.

Methods: In this retrospective monocentric study, we identified through a systematic electronic search all IBD patients treated by vedolizumab in rheumatology and gastroenterology of our hospital. We collected all the cases of incident articular manifestations occurring in the follow-up of these patients. Characteristics of articular manifestations were



analyzed and classified as inflammatory or not, and characteristics of patients who presented inflammatory articular manifestations were compared to those of patients without.

Results: Between february 2013 and june 2017, we indented 112 patients treated by Vedolizumab (56 women, mean age 39.9 ± 16 years, mean disease duration = 9.1 ± 7.8). The IBD was Ulcerative Colitis (UC) in 59 (52.7%), Crohn's disease (CD) in 49 (43.8%), and undetermined colitis in 4 (3.6%). Only 4 (3.6%) had a history of spondyloarthritis and 14 (12.5%) of peripheral arthralgias associated with IBD. 102 (91.1%) patients previously received anti-TNF : one in 49.1%, two in 35.7% and three lines or more in 6.3%). At initiation of vedolizumab, 55 (49.1%) received a DMARD (azathioprine in 19.6%, purinethol in 11.6%, methotrexate in 7.1%).

After a mean follow up duration of 11.4 ± 8.6 months, 32 (28.6%) of the patients presented articular manifestations (figure).

We studied several risk factors for developing articular symptoms. Among them, only the previous history of articular manifestation was associated with an increased risk of occurrence of inflammatory manifestations (4.8% vs. 12.5%; $p=0.007$). The use of corticosteroids or methotrexate was not significantly associated with a lower incidence of articular manifestations.

Conclusion: Occurrence of articular manifestations in patients treated with vedolizumab for IBD is quite infrequent. Half of the manifestations were not of inflammatory origin. About 5% of the patients presented early reversible inflammatory arthralgias that did not require treatment discontinuing. Only 10% of the patients present persistent inflammatory rheumatic manifestations that evolved in most of cases in parallel to IBD, but were considered as occurring paradoxically in only 3 patients.

Disclosure: A. Dupré, None; M. Collins, None; F. Carbonnel, None; X. Mariette, None; R. Seror, None.

Abstract Number: 704

Metabolomics Analysis of Insulin Resistance in Mild/Inactive Non-Diabetic Systemic Lupus Erythematosus Women

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: SLE patients present a higher prevalence of insulin resistance (IR) and metabolic syndrome (MetS) than age- and sex-matched healthy controls. Advances in technology are enabling evaluation for the prevention and early detection of those morbidities. Quantose IR is a simple test for IR based on a single fasting blood sample and may have value as an early indicator of risk for the development of prediabetes and type 2 diabetes mellitus (T2DM). The objective of this study was to evaluate IR in non-diabetic SLE women using metabolite markers identified using high-throughput metabolomic techniques.

Methods: SLE patients were consecutively enrolled in a cross-sectional study. A metabolomic approach using ultra-high performance liquid chromatography coupled with high-resolution mass spectrometry (UHPLC-HRMS) was developed in serum samples from non-diabetic SLE women. Activity (SLEDAI-2K) and damage (SLICC) index scores, as well as carotid intima-media thickness (IMT), were determined in SLE patients. Patients with a Quantose IR score of ≥ 63 were defined as IR. MetS was evaluated according to the NCEP-ATP III criteria.

Results: We enrolled 70 SLE patients with a mean \pm SD age of 39.3 ± 10.6 years and median disease duration of 11 years (IQR: 8-14). Forty-five of 70 (64.2%) and 27 (38.5%) SLE patients were found to have IR and MetS, respectively. The median Quantose IR score was 69 (IQR 52.7-80.0). Patients with IR had a higher body mass index (BMI) than those without IR (27 vs. 23.7; $p = 0.001$). Hypertension was more frequently found in patients with IR (33.3% vs. 8.0%; $p = 0.02$). The SLICC index and disease activity were not associated with the Quantose IR Score. The prevalence of a Quantose IR score ≥ 63 was higher in patients with MetS (81.5% vs. 53.5%; $p = 0.02$). Quantose IR score also correlated with the number of metabolic syndrome criteria ($r = 0.35$, $p = 0.003$). Carotid IMT values were not correlated with the IR index.

Conclusion: In non-diabetic SLE women, the prevalence of IR based on Quantose IR was 64.2% using UHPLC-HRMS. Although, some traditional IR factors, such as BMI and hypertension were associated with IR in these patients, SLE-related factors were not. Moreover, Quantose IR score may be related to MetS in those patients.

Disclosure: C. Mendoza Pinto, None; M. García-Carrasco, None; G. Díaz-Merino, None; P. Soto-Santillan, None; R. Mejía-Ocampo, None; P. Munguía-Realpozo, None; A. Ruiz-Arguelles, None.

Abstract Number: 705

Prevalence of Cervical Human Papillomavirus Infection in Women with Systemic Lupus Erythematosus: A Systematic Review and Meta-Analysis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Human papillomavirus (HPV), a common sexually-transmitted infection, is considered a necessary cause of cervical cancer.

The objectives of this systematic review and meta-regression were: 1) to compare the prevalence of cervical HPV infection between SLE patients and healthy controls and 2) to evaluate the relationship between cervical HPV infection and traditional and SLE-related risk factors for cervical HPV infection in these patients.

Methods: We conducted a systematic literature review (PubMed, Cochrane library, Embase, Virtual Health Library and SciELO databases) following PRISMA guidelines and meta-regression to investigate the pooled prevalence of cervical HPV infection in adult women with SLE. The included articles were independently evaluated by two investigators who extracted information on study characteristics, defined outcomes, risk of bias and summarized strength of evidence [Quality of evidence using the Oxford Centre for evidence-based medicine (EBM) Levels of Evidence] Using meta-regression, we further analyzed whether factors such as multiple sexual partners and immunosuppressive therapy were associated with HPV prevalence. We evaluated the quality of evidence included using the Oxford Centre for evidence-based medicine (EBM) levels of evidence. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for studies providing data on HPV prevalence in women with SLE and in healthy controls.

Results: A total of 687 articles were identified; 9 full-text articles examining the prevalence of cervical HPV infection in SLE women were included, comprising 751 SLE women. Eight studies employed PCR using general primers. The HPV prevalence varied from 3.1% to 80.7%. From the random effects meta-analysis, the pooled prevalence of cervical HPV infection in SLE vs. controls was 34.15% (95% CI: 19.6%-52.5%) vs. 15.3% (95% CI 0.79-27.8%), OR = 2.87 (CI 95% 2.20-3.76) $p < 0.0001$ (Fig. 1), with large between-study heterogeneity ($I^2 = 95.4\%$). When only SLE women were evaluated, meta-regression showed no significant differences between patients with and without a background of multiple sexual partners and any immunosuppressive therapy. In addition, the prevalence of cervical HPV infection did not significantly differ between SLE patients on azathioprine or cyclophosphamide.

Conclusion: This meta-analysis suggests that the prevalence of cervical HPV infection was higher in SLE women than in healthy controls. However, multiple sexual partners and any immunosuppressive therapy or specific immunosuppressive treatment (azathioprine and cyclophosphamide) were not associated with cervical HPV infection prevalence in these patients.

Disclosure: C. Mendoza Pinto, None; N. Molano-González, None; A. Rojas-Villarraga, None; V. Vallejo-Ruiz, None; S. Méndez-Martínez, None; M. García-Carrasco, None.

Abstract Number: 706

Increased Incidence and Prevalance of Resistant Hypertension in Patients with Systemic Lupus Erythematosus: A Retrospective Cohort Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Resistant hypertension (RHTN) is associated with increased risk of cardiovascular events in the general population. Patients with systemic lupus erythematosus (SLE) have increased cardiovascular risk, but little is known about RHTN in patients with SLE. We first compared the risk of RHTN in SLE patients and matched controls, then defined factors associated with RHTN in SLE, and finally calculated the risk of mortality associated with RHTN in SLE.

Methods: We used a validated algorithm (94% PPV) to identify adults with SLE from de-identified electronic health records at an academic medical center. We established a control cohort matched by age, race, and sex, with a 5:1 control-case ratio. Follow-up began with first SLEICD9 code (cases) or first ICD9 code (controls) and continued until RHTN or last visit. A RHTN diagnosis required simultaneous use of 3 antihypertensives including a thiazide diuretic and a mean outpatient blood pressure $\geq 140/90$ in the 6 months after therapy, or simultaneous use of ≥ 4 antihypertensives. We extracted demographic and comorbid variables using computer programming and included values closest to a patient's first relevant ICD9 code. We defined end-stage renal disease (ESRD) by an ESRD ICD9 or dialysis CPT code. We ascertained mortality by Social Security death files and hospital records. We used Cox proportional hazards models to compare risk of RHTN between groups, in incident cases only.

Results: We studied 1044 SLE patients and 5241 control subjects (Table). RHTN developed in 106 SLE patients (10%) and 278 controls (5%), with an incidence rate of 14.7 cases/1000 person-years in SLE compared to 7.4 in controls [HR 1.66, 95% CI, 1.26-2.21] (Figure). Patients with SLE had a higher risk of RHTN after adjustment for age, sex, race, calendar year, creatinine, and ESRD [HR 1.50, 1.12-2.00]. Among these patients, black race [HR: 3.20 CI: 2.48-4.12] and ESRD [HR: 5.76 95% CI: 3.85-8.62] were associated with RHTN. Finally, 25% of SLE patients with RHTN died compared to 10% of SLE patients without RHTN; this association remained significant after adjustment for age, sex and race [HR 2.83 CI: 1.65-4.87].

Conclusion: SLE Patients have a 1.7-fold higher risk of developing RHTN compared to frequency-matched controls. RHTN is an important comorbidity for clinicians to recognize in SLE, as it is associated with a 2.8-fold higher mortality risk.

Table. Baseline Characteristics

	N	Patients with SLE (N=1044)	Matched Controls (N=5241)	p value
Demographics				
Age at first ICD9 code (years)	6285	41 [30-53]	42 [31-54]	0.15
Female (%)	6285	941 (90.1)	4728 (90.2)	0.94
Race	6285			
White (%)		720 (69.0)	3678 (70.2)	
Black (%)		245 (23.4)	1167 (22.3)	
Other or Unknown (%)		79 (7.6)	396 (7.6)	0.69
Ethnicity	6285			
Hispanic (%)		29 (2.8)	149 (2.8)	0.87
BMI (kg/m ²)	5466	26.7 [23.1-32.2]	27.8 [23.5-33.4]	<0.001
Person years of observation time	6285	5.8 [2.7-10.0]	6.1 [2.3-11.2]	0.92
Renal Function				
Creatinine (mg/d)	5793	0.8 [0.7-1.0]	0.8 [0.7-0.9]	<0.001
GFR (ml/min/1.73m ²)	5781	85.8 [85.1-107.6]	89.6 [74.5-107.5]	<0.001
Lipid Concentrations				
Total Cholesterol (mg/dL)	2862	180.0 [152.0-208.0]	189.0 [181.0-218.0]	<0.001
HDL-C (mg/dL)	2755	51.0 [39.0-64.0]	53.0 [44.0-67.0]	<0.001
LDL-C (mg/dL)	2861	99.0 [78.8-124.0]	106.0 [84.0-131.0]	<0.001
Triglycerides (mg/dL)	2832	125.5 [88.0-182.0]	102.0 [69.0-155.0]	<0.001

^ Chi-squared tests were used for categorical variables; Wilcoxon-rank sum for continuous. p<0.05 considered significant. Values are shown as median [IQR] or n (%).

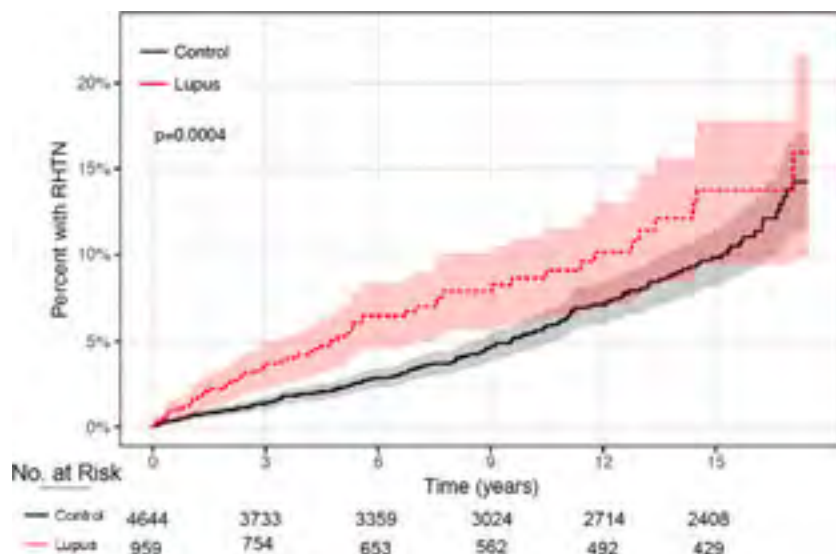


Figure. Cumulative Incidence of RHTN

Disclosure: J. S. Gandelman, None; O. A. Khan, None; M. Shuey, None; J. E. Neal, None; A. Dickson, None; A. Barnado, None; L. Wang, None; W. Dupont, None; C. M. Stein, None; C. P. Chung, None.

Abstract Number: 707

Subclinical Parameters of Arterial Stiffness and Arteriosclerosis Correlate with QRISK3 in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: It is well known that cardiovascular diseases (CVD) are a major contributor of death in systemic lupus erythematosus (SLE) as well in other rheumatic illness. In the last decades, there has been a growing development of different methodologies with the purpose of early detection of CVD. The aim of this study is to correlate the usefulness of subclinical parameters of vascular aging and QRISK3-2017 score for early detection of CVD in SLE.

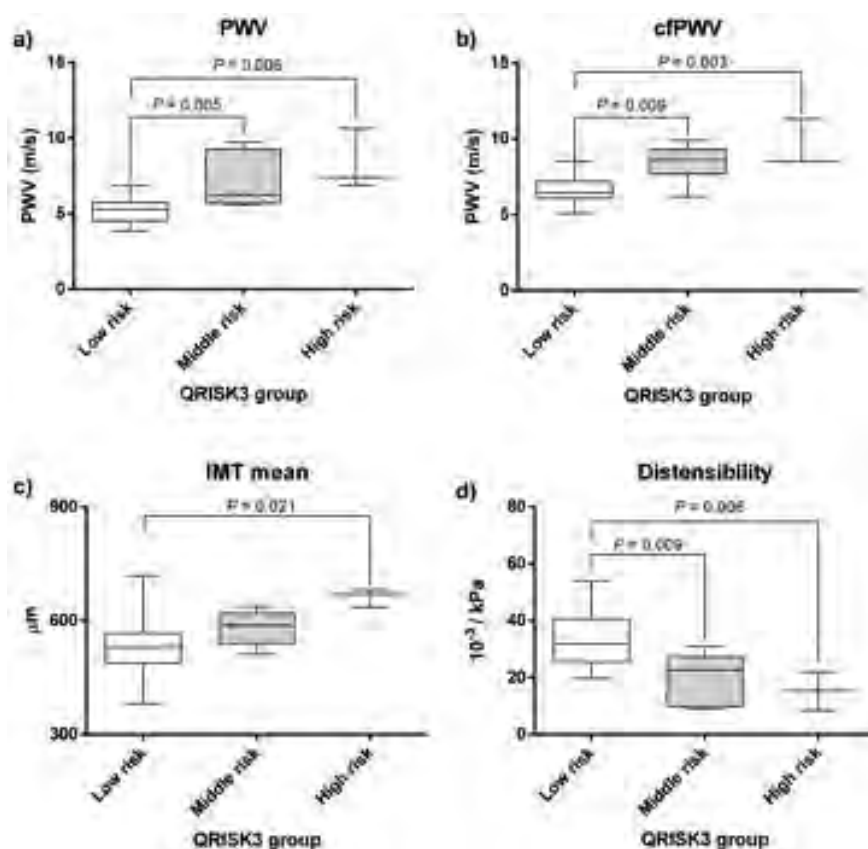


Table 1. Clinical and demographic characteristics in lupus and control subjects

Variable	Study group		P
	Lupus n = 50	CS n = 82	
Age (years)	33.6 ± 12.4	37.6 ± 12.9	0.076
Male / Female (n)	41 / 9	59 / 23	0.215
BMI, kg/m ²	25.6 ± 4.0	27.4 ± 5.0	0.026
Disease duration (years)	6.4 ± 4.8	—	—
SLEDAI	5.9 ± 4.2	—	—
SLICC	1.0 ± 1.2	—	—
Scholarship			
Basic (n, %)	22 (44%)	—	—
Upper secondary (n, %)	16 (32%)	—	—
Higher (n, %)	12 (24%)	—	—
Alcoholism (n, %)	0	0	N.S.
HT (n, %)	5 (10%)	0	0.007
DM2 (n, %)	3 (6%)	0	N.S.
Treatment			
Azathioprine (n, %)	24 (48%)	—	—
Chloroquine (n, %)	34 (68%)	—	—
Methotrexate (n, %)	10 (20%)	—	—
Mycophenolate Mofetil (n, %)	8 (16%)	—	—
Corticosteroids (n, %)	49 (98%)	—	—
Corticosteroids (mg, \bar{x} ± SD)	8.4 ± 9.6	—	—
ANAs (n, %)	50 (100%)	—	—
Anti-dsDNA (n, %)	22 (44%)	—	—
Complement			
C3 (mg/dL, \bar{x} ± SD)	83.6 ± 21.3	—	—
C4 (mg/dL, \bar{x} ± SD)	20.3 ± 11.8	—	—
Carotid plaque (n, %)	0	0	N.S.
cIMT mean (μm)	519 ± 89	542 ± 113	N.S.
PWV (m/s)	5.5 ± 1.5	5.8 ± 1.3	N.S.
cfPWV (m/s)	7.1 ± 1.3	7.0 ± 1.2	N.S.
Distensibility, (10 ⁻³ / kPa)	32.0 ± 12.2	32.1 ± 13.0	N.S.

Methods: Clinical assessment including systemic lupus erythematosus disease activity index (SLEDAI) and systemic lupus international collaborating clinics/ american college of rheumatology damage index (SLICC/ACR DI), laboratory measurements, carotid ultrasound examination, carotid intima media thickness(cIMT) measurement, carotid distention and diameter analysis, arterial stiffness measurement measured by tonometry and QRISK3-2017 were done. All results were analyzed by SPSS 24 software.

Results: We observed correlation between QRISK3 and mean cIMT ($r_s = 0.651$, $P < 0.001$), PWV ($r_s = 0.627$, $P < 0.001$), cfPWV ($r_s = 0.651$, $P < 0.001$) and distensibility($r_s = 0.555$, $P = 0.001$). Consistent with above, SLE patients in middle and high risk QRISK3-2017 showed increased arterial stiffness versus low risk group.

Conclusion: We encourage to the rheumatology community to assess cardiovascular risk in SLE patients with QRISK3-2017 risk calculator as an alternative method at the outpatient clinic along a complete cardiovascular evaluation when appropriate.

Disclosure: M. Vazquez-Del Mercado, None; F. Perez-Vazquez, None; E. Gomez-Bañuelos, None; E. Chavarria-Avila, None; A. Llamas-Garcia, None; K. I. Arrona-Rios, None; G. I. Diaz-Rubio, None; S. Duran-Barragan, None; R. E. Navarro-Hernandez, None; B. Jordan-Estrada, None; N. Prado-Bachega, None; M. A. A. Gonzalez-Beltran, None; C. G. Ramos-Becerra, None; F. Grover-Paez, None; D. Cardona-Muller, None; E. G. Cardona-Muñoz, None.

The Montreal Cognitive Assessment Test. a Useful Tool in Screening of Cognitive Impairment in Patients with Systemic Lupus Erythematosus short Title: Cognitive Impairment in SLE

Nicolas Paez-Venegas¹, Bethel Jordan-Estrada², Efrain Chavarria-Avila², Felipe Perez-Vazquez², Eduardo Gomez-Bañuelos³, Rafael Medina-Davalos¹, Jose A. Ontiveros-Gonzalez⁴, Gustavo I Diaz-Rubio², Rosa E Navarro-Hernandez² and Monica Vazquez-Del Mercado³, ¹Instituto Jalisciense de Salud Mental, ZAPOPAN, Mexico, ²Centro Universitario de Ciencias de la Salud, Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético, Universidad de Guadalajara, Guadalajara, Mexico, ³Servicio de Reumatología, 004086 PNPC CONACyT, Hospital Civil de Guadalajara Dr. Juan I. Menchaca, Guadalajara, Mexico, ⁴Hospital Civil de Guadalajara Dr. Juan I. Menchaca, Guadalajara, Mexico

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Systemic lupus erythematosus (SLE) is an inflammatory, chronic and multisystemic disease, which can be related with a long range of neuropsychiatric manifestations, including cognitive impairment. Cognitive evaluations based on screening tests in SLE, might identify early cognitive alterations. Objective. The aim of this study was to evaluate and to compare the efficacy of three screening test for cognitive impairment, Montreal Cognitive Assessment (MoCA), Mini Mental State Examination (MMSE), Cognitive Symptom Inventory (CSI) against the gold standard (neuropsychological battery), and identify the most efficient screening test, in a group of patients with SLE.

Methods: This is an observational cross-sectional study that recruited 44 patients from august to December 2017, diagnosed with SLE according to Systemic Lupus International Collaborating Clinics (SLICC) criteria 2012, without medical or psychiatric comorbidities, evaluated by MoCA, MMSE, CSI and the gold standard. These evaluations were performed to detect the presence and degree of cognitive impairment. Statistics were done using SPSS software.

Results : The MoCA test showed the highest correspondence (AUC = 99.4% $p < 0.001$), sensitivity(84%) and specificity (100%) with the gold standard. Followed by MMSE (AUC = 92.6%, $p < 0.001$) sensitivity (54.8%), specificity (100%), and finally, CSI(AUC = 30.6%, $p < 0.05$) had the lowest sensitivity (54.8%) and specificity(30.76%).

Conclusion: The MoCA is a brief, easily applicable screening test, highly effective for detecting cognitive impairment in SLE patients. It could be useful in the clinical follow-up as a tool for early detection of cognitive alterations, and could facilitate a timely diagnosis.

Disclosure: N. Paez-Venegas, None; B. Jordan-Estrada, None; E. Chavarria-Avila, None; F. Perez-Vazquez, None; E. Gomez-Bañuelos, None; R. Medina-Davalos, None; J. A. Ontiveros-Gonzalez, None; G. I. Diaz-Rubio, None; R. E. Navarro-Hernandez, None; M. Vazquez-Del Mercado, None.

Table 1. Clinical and demographic characteristics of SLE patients

Age (years)	34.1 ± 10.4
Male / Female (n)	7 / 37
Single / Married (n)	16 / 28
Education (years)	11.8 ± 3.9
Disease duration (years)	9.5 ± 4.9
Pharmacological treatment	
Azathioprine (n, %)	14 (15.9)
Chloroquine (n, %)	10 (11.3)
Prednisone (n, %)	9 (11.3)
Mycophenolate (n, %)	7 (9.09)
Methotrexate (n, %)	4 (9.09)
SLEDAI ($\bar{x} \pm DE$)	6.5 ± 4.6
ANA (n, %)	2 (4.54%)
Anti dsDNA (n, %)	14 (31.8%)
Anti-Sm (n, %)	2 (4.54%)
Anti-RNP (n, %)	4 (9.09%)
Anti-Ro 52 (n, %)	3 (6.18%)
Anti-La (n, %)	1 (2.27%)
Lupus Anticoagulant (n, %)	4 (9.09%)
Anti B2GP1 (n, %)	1 (2.27%)
ACL IgG, IgM (n, %)	1 (2.27%)
Low C3, C4 (n, %)	8 (18.1%)

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index;
dsDNA: double-strand DNA; ANAs: Antinuclear antibodies

Table 2 Correlations between the instruments used to assess cognitive impairment

Tool	CSI	MMSE	MoCA
	$r = 0.310$	$r = 0.678$	$r =$
Neuropsychological Battery	$p < 0.05$	$p < 0.001$	$r = 0.786$ $p < 0.001$
CSI	$r = 0.505$ $p < 0.001$	$r = 0.397$ $p < 0.01$	
MMSE		$r = 0.886$ $p < 0.001$	

CSI: Cognitive Symptom Inventory; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment

Abstract Number: 709

Differential Characteristics of Lupus Psychosis and Steroid Psychosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

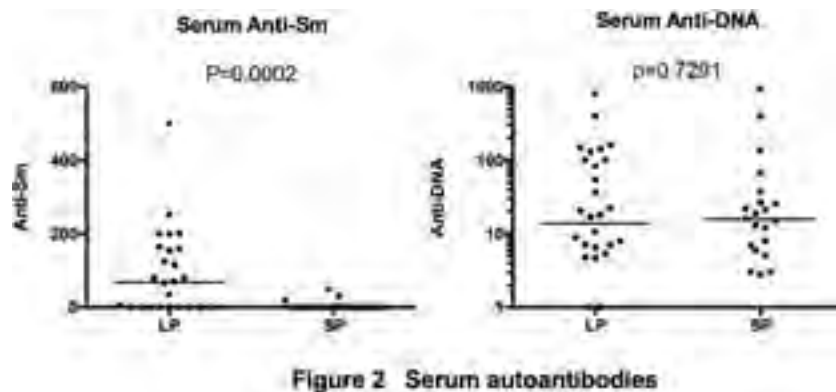
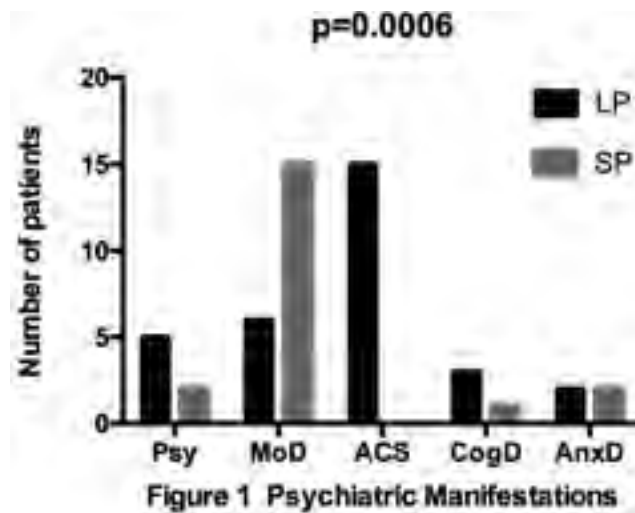
Session Type: ACR Poster Session A

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

Background/Purpose: Psychiatric manifestations are relatively common in patients with systemic lupus erythematosus (SLE). Since there are a number of factors causing psychiatric manifestations other than SLE, the diagnosis of lupus psychosis (LP) is often difficult. Especially, it has been sometimes challenging to discriminate steroid psychosis (SP) from LP, since LP usually occurs after the initiation or increase of steroid. The current studies were therefore designed to clarify the differences in clinical features between LP and SP.

Methods: Multicenter retrospective cross-sectional study was performed with 51 SLE patients who presented psychiatric manifestations between 1992 and 2001. The diagnosis of LP and SP was confirmed by retrospective review of the clinical records. Demographic features, clinical manifestations, serum autoantibodies and cerebrospinal fluid IL-6 were compared between LP and SP.

Results: Thirty-one and 20 patients were judged by review of the clinical records as LP and SP, respectively, in the retrospective study. There were no significant differences in age and gender between the 2 groups. However, the prevalence of acute confusional state was significantly higher in LP, whereas the prevalence of mood disorder was predominant in SP (Figure 1). Eleven of the 31 patients with LP were complicated with seizure disorders, whereas no patients with SP presented seizure. Of note, CSF IL-6 levels were elevated above the cut-off value of 4.3 pg/ml in 27 of 31 patients with LP, but in none of 7 patients with SP. Finally, serum anti-Sm antibodies, but not anti-DNA or anti-phospholipid antibodies, were significantly elevated in 31 patients with LP compared with 20 patients with SP (Figure 2).



Conclusion: These results in the current studies highlight the differences in clinical and laboratory features between LP and SP. Thus, acute confusional state and complication of seizure are characteristic of LP, whereas the most prevalent manifestation of SP is mood disorder. Moreover, the data also suggest that CSFIL-6 as well as serum anti-Sm antibodies might be effective tools for differential diagnosis of LP from SP.

Disclosure: S. Hirohata, None; Y. Kanai, None; A. Mitsuo, None; Y. Tokano, None; H. Hashimoto, None.

Abstract Number: 710

An Analysis of Cell-of-Origin in Diffuse Large B-Cell Lymphoma in Systemic Lupus Erythematosus, Including Molecular and Clinical Factors Associated with Survival

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Systemic lupus erythematosus (SLE) is associated with increased risk of diffuse large B-cell lymphoma (DLBCL). DLBCL is routinely classified by cell-of-origin (COO), with non-germinal centre B-cell (GCB) indicating poorer prognosis in the general population. We studied COO subtyping in SLE patients diagnosed with DLBCL, and overall survival.

Methods: We evaluated 20 cases of SLE with DLBCL. In tissue microarrays, immunohistochemistry analysis was performed (BCL2, MYC, BCL6, CD10, CD20, FOXP1, GCET1, MUM1). We examined associations between molecular and clinical features, including overall survival (time to death, all-cause).

Results: Of the 20 DLBCL SLE cases (Table 1), 12/20 cases (60%) were classified as non-germinal centre B-cell (GCB) whereas 8/20(40%) were classified as GCB using Hans or Choi algorithms. MYC and BCL2 protein expression was positive in 6/20 (30%) and 8/20(40%) SLE cases, respectively with 2/20 (10%) co-expressing both markers. The median survival for all 20 cases was 39 (mean 64) months. As expected, non-GCB cases had worse survival. In both univariate and multivariable Cox proportional hazards models, both non-GCB type and nodal status (any nodal involvement versus none) were associated with lower survival (Table 2). Stratification of cases by nodal status revealed that SLE duration at DLBCL diagnosis was much longer in cases presenting with nodal-only involvement and that BCL2 expression tended to be greater in patients presenting with extra-nodal involvement only. We were unable to detect any molecular or clinical features differing by COO subtype. SLE patients presenting exclusively with extranodal DLBCL were associated with better survival despite higher BCL2 protein expression (which normally indicates poor prognosis).

Conclusion: We present novel data characterizing DLBCL in SLE. Sixty percent of the DLBCL in SLE patients were non-GCB. The nodal and extranodal distribution was similar between patient with SLE and the general population, but extranodal disease occurred more often with short SLE duration and was associated with longer over-all survival. Since non-GCB DLBCL rely on the activation of the NF- κ B and JAK-STAT pathways, future assessments of the links between SLE and DLBCL could focus on genetic factors related to the TNF superfamily (TNFSF4), TNF- α , TNF Alpha Induced Protein 3, and other related pathways.

Table 1. Descriptive features of the SLE-DLBCL (n=20) subjects

Variable	Median [IQR]
Sex (female)	2/20 (90)
Age at SLE Diagnosis	45 [36-54]
Age at time of DLBCL diagnosis	58 [48-66]
SLE duration at DLBCL diagnosis	11 [5-18]
Variable	N (%)
Diagnosed after 1991	12 (60)
Nodal-only involvement	10 (50)
Only extranodal involvement	7 (35)
MYC positive	6 (30)
BCL2 positive	8 (40)
BCL6 positive	7 (35)
Dual positive, MYC and BCL-2	2 (10)
Non-germinal B-cell origin (Hans)	12 (60)

Table 2. Cox proportional hazards ratio (HR) for survival in SLE-DLBCL (n=20).

Variable (reference)	Unadjusted HR (95%CI)	Adjusted* HR (95%CI)
Sex (female)	2.64 (0.95-7.37)	4.49 (1.06-19.0)
Year of DLBCL diagnosis (years)	0.97 (0.92-1.02)	0.94 (0.88-1.01)
Any nodal-involvement	0.29 (0.10-0.98)	0.09 (0.03-0.26)
Non-germinal B-cell origin cell type(Hans)	0.28 (0.08-0.93)	0.08 (0.02-0.43)

* The adjusted model included all four variables in this table.

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Recurrence of Lupus Nephritis in Renal Transplant Recipients

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

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

Background/Purpose: Recurrence of lupus nephritis in the graft is a concern in lupus patients with end stage renal disease who undergo renal transplantation. The recurrence of lupus nephritis has been variable among different studies depending on the patient characteristics, immunosuppressive regimens and indications of renal biopsy. One of the major change is the use of posttransplant immunosuppressive regimen consisting of tacrolimus and mycophenolate mofetil instead of cyclosporine and azathioprine in addition to prednisone. Many of the previous studies reported the recurrence of lupus nephritis where cyclosporine and azathioprine were used as posttransplant regimen. We investigated the recurrence of lupus nephritis among our patients to see if the new posttransplant regimen has impacted the recurrence.

Methods : All recipients, who were transplanted between 2006-2017 in our center, with end stage renal disease secondary to lupus nephritis have been included in the study (n=38). Medical records of all 38 patients were reviewed retrospectively in the electronic medical record and information from the United Network for Organ Sharing Network (UNOS) were also reviewed retrospectively. Demographic information, transplant and dialysis related information have been recorded including kidney biopsy, graft loss and survival. The result of the indication biopsies has also been recorded. Association between recurrent lupus nephritis and survival and graft loss were examined using survival models.

Results : The overall mean \pm SD age at baseline was 42 \pm 13 years; 89% were female; 89% were African-American; the previous time on dialysis was median of 4 years (IQR: 2-8 years), 80% received hemodialysis and 31% received living donor transplantation in the cohort. All our patients received the standard immunosuppressive regimen consisting of prednisone, tacrolimus and mycophenolate mofetil. Four (11%) of the 38 patients had biopsy proven lupus nephritis recurrence. Total of 10 patients (26%) had graft loss or death during the median follow up time was 1,230 days (IQR: 460-2,227 days). Patient with recurrence showed trend for increased risk for graft loss or death (Hazard Ratio: 3.14, 95% Confidence Interval: 0.65-15.24) compared to the recipient without recurrence in our unadjusted proportional Cox regression model.

Conclusion: Recurrence rate of lupus nephritis in our patient population is much lower compared to previous data from different immunosuppressive era. Patient with recurrent disease showed trend for increased risk for graft loss or death. The current standard of posttransplant immunosuppressive regimen may have played role in lower relapse rate.

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Abstract Number: 712

Higher Prednisolone Dose during Treatment of Tuberculosis Correlates with Mortality during Tuberculosis Treatment in Systemic Lupus Erythematosus Patients: A Retrospective Cohort Study

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

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

Background/Purpose: Tuberculosis (TB) has complex interplay with systemic lupus erythematosus (SLE). In addition, SLE, corticosteroid, and immunosuppressants are associated with TB infection. However, the prognostic factors of TB in

Table 1. Comparison of Baseline Characteristics between the Survival Group and the Mortality Group during TB treatment			
(n=number of patients)	Survival Group (n=26)	Mortality Group (n=7)	p-value
Age, year, median (IQR)	57.5 (46.0-66.0)	44.0 (29.3-52.5)	0.0009
Female gender, n (%)	18 (69.2)	6 (85.7)	0.6418
TB within one year of SLE diagnosis, n (%)	9 (34.6)	4 (57.1)	0.3774
SLEDAI-2K, median (IQR)	4 (0-5)	7 (3-12)	0.1260
TB type			
Extrapulmonary + disseminated TB, n (%)	13 (50)	4 (57.1)	1.0000
Corticosteroid Use			
Average PGN dose 30 days before TB diagnosis, median (IQR)	15.6 (5.7-23.6)	55.2 (45.3-116.2)	0.0010
Average PGN dose 30 days before TB diagnosis, mg/kg/day, median (IQR) [#]	0.3 (0.1-0.5)	1.0 (0.5-2.3)	0.0010
Average PGN dose during TB treatment, mg/day, median (IQR)	11.7 (5.0-18.0)	56.2 (35.4-73.9)	0.0005
Average PGN dose during TB treatment, mg/kg/day, median (IQR) [#]	0.2 (0.1-0.3)	1.3 (0.6-1.5)	0.0002
steroid pulse therapy 6 months before TB diagnosis, n (%)	4 (15.4)	4 (57.1)	0.0419
steroid pulse therapy during TB treatment, n (%)	8 (31.2)	0 (0)	1.0000
DMARD before TB diagnosis			
Cyclophosphamide 6 months before TB diagnosis, n (%)	3 (11.5%)	6 (85.7%)	0.0009
Hydroxychloroquine, n (%)	20 (76.9%)	7 (100%)	0.3008
Methotrexate, n (%)	2 (7.7%)	1 (14.3%)	0.5235
Sulfasalazine, n (%)	3 (11.5%)	0 (0)	1.0000
Azathioprine, n (%)	11 (42.3%)	1 (14.3%)	0.2235
Leflunomide, n (%)	1 (3.8%)	1 (14.3%)	0.5845
DMARD during TB treatment			
Cyclophosphamide during TB treatment, n (%)	1 (3.8%)	2 (28.6%)	0.1067
Hydroxychloroquine, n (%)	22 (84.6%)	7 (100%)	0.5552
Methotrexate, n (%)	1 (3.8%)	1 (14.3%)	0.3845
Sulfasalazine, n (%)	3 (11.5%)	0 (0)	1.0000
Azathioprine, n (%)	8 (30.8%)	0 (0)	0.5591
Leflunomide, n (%)	3 (11.5%)	1 (14.3%)	1.0000
Comorbidities			
Heart Failure, n (%)	4 (15.4%)	1 (14.3%)	1.0000
CCr<30, n (%)	1 (3.8%)	2 (28.6%)	0.1067
ESRD, n (%)	0 (0)	1 (14.3%)	1.0000
Diabetes mellitus, n (%)	1 (3.8%)	0 (0)	1.0000
Hypertension, n (%)	8 (30.8%)	3 (42.9%)	0.1454
Intestinal lung disease, n (%)	1 (3.8%)	0 (0)	1.0000
Stroke, n (%)	1 (3.8%)	0 (0)	1.0000
Liver cirrhosis and COPD, n (%)	0 (0)	0 (0)	

[#] p < 0.05

[#] Body weight (kg) on the entry date of the cohort was used to adjust the dose of prednisolone

CCr, creatinine clearance rate; COPD, chronic obstructive pulmonary disease; DMARD, disease modifying anti-rheumatic drug; ESRD, end stage renal disease; IQR, interquartile range; PGN, prednisolone; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; TB, tuberculosis

Table 1 Univariate and Multivariate Analysis for Risk Factors of Mortality during TB Treatment in SLE Patients with Tuberculosis by Cox Proportional Hazards Model

Risk Factors	Univariate Analysis			Multivariate Analysis		
	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Age	0.95	0.90-1.00	0.0572			
SLEDAI-2K	1.13	0.97-1.31	0.1156	0.82	0.66-1.02	0.0792
Steroid pulse therapy 6 months before TB diagnosis	5.68	1.25-25.71	0.0242*	1.49	0.27-8.31	0.6504
Average PDN dose 30 days before TB diagnosis > 0.5 mg/kg/day #	15.25	1.82-127.78	0.0120*	2.08	0.15-28.89	0.5841
Cyclophosphamide 6 months before TB diagnosis	22.18	2.65-185.43	0.0042*	34.05	1.80-642.96	0.0186*
Average PDN dose > 0.5 mg/kg/day during TB treatment#	23.61	2.82-197.42	0.0035*	33.18	1.63-674.28	0.0227*

* $p < 0.05$
Body weight (kg) on the entry date of the cohort was used to adjust the dose of prednisolone
CI, confidence interval; PDN, prednisolone; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; TB, tuberculosis

patients with SLE have not been fully investigated. The aim of this study was to evaluate the effects of corticosteroid and immunosuppressants on the prognosis of TB in SLE patients.

Methods: This retrospective cohort study was conducted by reviewing the medical records between January 1, 2006 and December 31, 2016. SLE patients with TB infection were screened via ICD codes. Only those fulfilled the ACR 1997 classification criteria of SLE and presented with microbiological or typical histological evidence of TB were enrolled. Patients with history of organ transplantation, HIV, incomplete history of immunosuppressive agents, and those without taking anti-TB regimen were excluded. The primary outcome was mortality during TB treatment.

Results: 5388 patients with ICD codes of SLE were screened, and 88 patients with ICD codes of TB were identified. After review of the medical records, 32 patients and 33 episodes fulfilled the inclusion criteria and were enrolled. The mortality during TB treatment was 21.2% (7/33). In comparison with the patients in the survival group (n=26), the patients in the mortality group (n=7) had younger age at diagnosis (44.0 vs 57.5, $p=0.0384$), higher average prednisolone dose 30 days before TB diagnosis (55.3 mg/day vs 15.6 mg/day, $p=0.0010$), higher average prednisolone dose during TB treatment (56.3 mg/day vs 11.7 mg/day, $p=0.0001$), more steroid pulse therapy 6 months before the TB diagnosis (4/7, 57.1% vs 4/26, 15.4%, $p=0.0418$), and more cyclophosphamide pulse therapy 6 months before the TB diagnosis (6/7, 85.7% vs 3/26, 11.5%, $p=0.0005$). There was no significant difference between the two groups in SLEDAI-2K (7 vs 4, $p=0.1261$). The multivariate analysis by Cox proportional hazard model revealed that average dose of prednisolone more than 0.5 mg/kg/day during TB treatment (HR 33.18, 95% CI 1.63-674.28, $p=0.0227$) and cyclophosphamide 6 months before the diagnosis of TB (HR 34.05, 95% CI 1.80-642.96, $p=0.0186$) were associated with higher mortality during TB treatment.

Conclusion: This retrospective cohort study finds that the mortality during TB treatment correlates with prednisolone dose during TB treatment and cyclophosphamide use 6 months before TB diagnosis.

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Abstract Number: 713

Soluble ST2 and CXCL-10 May Serve As Biomarkers of Diastolic Dysfunction in SLE and Correlate with Disease Activity and Damage

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SESSION INFORMATION

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Background/Purpose: Subclinical myocardial dysfunction has been reported to occur early in SLE. The pathogenesis and prognosis of this finding is not clear. The study aims to search for biomarkers of subclinical myocardial dysfunction which may serve for early detection and better understanding of myocardial dysfunction pathogenesis in SLE.

Methods : A cross sectional study of 57 consecutive patients with SLE and 18 controls was performed. Demographic, clinical and cardiovascular risk factor data were obtained by questionnaires and review of patient charts. Serum samples were obtained to determine serum soluble ST2 (sST2), CXCL-10 and high sensitivity troponin (hs-troponin) levels. All participants underwent an Echo Doppler study including comprehensive diastolic function assessment.

Results: Cardiovascular risk factors were more frequent in the SLE group including hypertension, hyperlipidemia, chronic renal failure and smoking. SLE disease activity (SLEDAI) positively correlated with sST2, CXCL-10 and hs-troponin levels ($p=0.001$; $p<0.001$; $p=0.008$, respectively). Disease damage, measured by the SLE damage index (SDI) positively correlated with sST2 and CXCL-10 levels ($p=0.002$; $p<0.001$, respectively). Looking at tissue echo-Doppler, several measures of diastolic dysfunction negatively correlated with log CXCL-10: including E/A; E/e'_{lateral} and E/e'_{septal} ($p=0.04$, $p=0.003$, $p=0.029$, respectively) while E/e' positively correlated with CXCL 10 ($p=0.001$). Diastolic dysfunction parameters also correlated with log sST2 levels, a negative correlation was seen with E/e'_{lateral} and a positive correlation was seen with E/e' ($p=0.001$, $p=0.006$ respectively). Systolic dysfunction parameters positively correlated with hs-troponin: LVED, LVES, IVS, LVMASS and LVMASS index ($p=0.007$, $p=0.002$, $p=0.002$, $p=0.001$, $p=0.001$ respectively). In a multivariate analysis, log sST2 and log CXCL-10 were significantly different in SLE patients as compared to controls, independent of cardiovascular risk factors ($p=0.005$; $p=0.004$ respectively) and independent of each other ($p=0.003$, $p=0.018$, respectively).

Conclusion: Soluble ST2 and CXCL-10 levels were found to correlate with disease activity and accrued damage in SLE and may serve as sensitive biomarkers for early detection of diastolic dysfunction, independent of traditional cardiovascular risk factors, supporting the hypothesis that disease activity has an independent role in the development of myocardial dysfunction in SLE.

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Abstract Number: 714

A Predictive Clinical-Immunological Index for Infections Unveils Novel Innate and Adaptive Immunity Abnormalities As Key Risk Factors for Infections in a Cohort of Patients with Systemic Lupus Erythematosus

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Background/Purpose: Patients with systemic lupus erythematosus (SLE) have multiple innate and adaptive immune response abnormalities. It is unknown whether they play a key role in the development of infections, which was the aim of the present study. Until now, a tool to predict infections that encompasses the clinical and immunological features characteristic of SLE patients was lacking.

Methods: A prospective cohort study of 55 SLE patients with less than 5 years since diagnosis was undertaken in a tertiary care center. Patients were prospectively followed up during a twelve-month period, looking for the primary outcome that was the development of infection, defined as the presence of characteristic clinical features with response to antibiotic treatment, with or without microbiological isolation. Severe infections were defined as those requiring hospital admission for at least 72 hrs, IV antibiotic treatment or causing death. We registered relevant clinical data and performed immunophenotyping by flow cytometry. We analyzed the number of neutrophil extracellular traps (NETs) and their LL-37 expression by confocal microscopy. Repeated measure analysis for the immunosuppressive therapy, mean adjusted SLEDAI score for disease activity. Relative risks (RR) for infection adjusted for clinical and immunological features. The study was approved by the institutional ethics and research committees.

Results: During 12 months of follow-up, 18 patients (32%) presented 19 infectious events in a median time of 21.5 weeks (IQR 4-24), 12% were severe. The main causes of infection were community-acquired pneumonia (23%), superior respiratory tract (23%) and urinary tract infections (17%), herpes zoster virus (17%), gastroenteritis (11%) and cellulitis (5%). In comparison to their baseline immunological parameters, there was a higher expression of LL-37 in LPS induced NETs and a higher amount of LDGs during the infectious events. After univariate and multivariate analysis, we developed an index to predict infection in SLE patients assigning a score according to the RR absolute values. The index parameters were cyclophosphamide use, absolute numbers of B cells, total Th17 lymphocytes and expression of TLR2 in monocytes measured with multi-parametric flow cytometry. We validated the index retrospectively in a nested case-control study and at baseline. In the case-control analysis, a score ≥ 2 was able to predict infection in the following 3 months (AUC= 0.79; likelihood ratio = 2.22, P=0.015). The same cutoff point at baseline predicted infection in the following year (AUC= 0.84; likelihood ratio = 2.0, P=0.012).

Conclusion: Our compound clinical-immunological index is able to predict the development of infection in SLE patients, taking into account the use of cyclophosphamide, absolute numbers of peripheral Th17 and B cells as well as TLR2 expression in monocytes. By alerting clinicians about patients who are more prone to develop infections, there could be a closer follow-up of these patients, with a targeted, multidisciplinary approach.

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Abstract Number: 715

Septic Shock Among Patients with Systemic Lupus Erythematosus: Short and Long-Term Outcome and Cost. Analysis of the French Nationwide Database

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Background/Purpose : Infection is a leading cause of death and ICU admission in systemic lupus erythematosus (SLE) patients. Our aim was to investigate the outcome and costs of septic shock among SLE patients and to evaluate the main determinants of mortality.

Methods: We performed a retrospective analysis of all SLE patients hospitalized with a first episode of septic shock in France from January 1st, 2010 to December 31st, 2015 by extracting data from the PMSI database (*Programme de Médicalisation des Systèmes d'Informations*) which compiles all data concerning hospital discharges in France. SLE and septic shock diagnoses were based on ICD10 classifications. We assessed the lupus phenotype with diagnostic codes used before or during septic shock hospital stays. Severity of ICU stay was assessed by Simplified acute Physiology score (SAPS II) and procedure use were systematically recorded. Healthcare use and hospital costs were assessed at 1-year for septic shock survivors. Factors associated with 30-day and 1-year in-hospital mortality were studied using Cox regression models.

For multivariate analysis, we used sex, chronic kidney disease (CKD) and all variables that had a significance level < 0.20 as covariates.

Results: One thousand sixty eight (1,068) first ICU stays for septic shock were extracted from 130,150 hospital stays of SLE patients. In oonstrictors (epinephrine, norepinephrine) were used in 913(85.6%) patients, invasive mechanical ventilation for 369 (34.6%) and dialysis for 342 (32.0%). Thirty-day and 1-year post admission mortality rates were 30.9% (n=330) and 43.4% (n=463), respectively. Within one year, 30-day post septic shock survivors (n=738) were re-admitted (mean [SD]) 6.42[17.3] times for 64.1[48.9] days with a total cost of 14 431€ [20 444€] and 12 (1.6%) required chronic hemodialysis. Factors associated with death are shown in Table 1. At1-year, the main determinants of death were (HR [IC95]) Simplified Acute Physiology Score (SAPS II) (1,022 [1,017-1,026]), Charlson-age adjusted comorbidity index (1,166 [1,106-1,228]), an associated Goujerot-Sjögren syndrome(1,392 [1,021-1,899]) and fungal infection (1,371[1,056-1,781]).

Conclusion: For SLE patients septic shock is associated with poor short- and long-term outcomes and heavily increased healthcare use at 1-year. We found that independently of severity of the acute illness, Goujerot-Sjögren associated syndrome is a main determinant of 1-year death. Other characteristics of the SLE phenotype were not associated with short and 1-year prognosis.

Table 1: Analysis of first septic shock stays : characteristics and prognosis

Table 1	Univariate HR	Sex	Univariate HR	p	Adjusted HR	p
Age (mean ± SD)**	55.9 (± 26.4)	0.30	1.023 (1.016-1.030)	<0.0001	-	-
		0.365	1.023 (1.017-1.030)	<0.0001	-	-
Sex (M/F %)	81.0/258 (75.4/24.6%)	0.30	1.029 (0.799-1.326)	0.3123	1.121 (0.879-1.467)	0.1998
		0.365	0.942 (0.709-1.260)	0.2121	1.176 (0.909-1.485)	0.1777
Respiratory condition						
Chronic kidney disease (GFR < 30 ml/min/1.73m ²)	273 (25.6%)	0.30	1.096 (0.863-1.395)	0.4586	0.926 (0.734-1.185)	0.5422
		0.365	1.181 (0.960-1.448)	0.1044	1.041 (0.846-1.276)	0.704
Cancer (%)**	512 (48.5%)	0.30	1.749 (1.300-2.352)	0.0032	-	-
		0.365	1.680 (1.279-2.205)	0.0010	-	-
Diabetes (%)**	128 (12.3%)	0.30	0.751 (0.523-1.083)	0.1292	-	-
		0.365	0.933 (0.704-1.237)	0.631	-	-
Capillary leak syndrome (%)**	454 (42.5%)	0.30	1.131 (0.813-1.605)	0.2644	-	-
		0.365	1.221 (1.017-1.465)	0.0323	-	-
Charlson Age adjusted comorbidity index (mean ± SD)	4.0 (± 1.4)	0.30	1.236 (1.149-1.328)	<0.0001	1.252 (1.085-1.424)	<0.0001
		0.365	1.122 (1.064-1.180)	<0.0001	1.166 (1.106-1.228)	<0.0001
Physiological Status (SAPS II)						
Light (SAPS II)	283 (26.5%)	0.30	0.874 (0.680-1.123)	0.2955	-	-
		0.365	0.922 (0.748-1.136)	0.4464	-	-
Severe (SAPS II)	241 (22.6%)	0.30	0.608 (0.367-1.024)	0.0563	-	-
		0.365	0.978 (0.782-1.215)	0.8064	-	-
Intermediate (SAPS II)	100 (9.4%)	0.30	0.755 (0.506-1.127)	0.1689	0.868 (0.539-1.420)	0.5999
		0.365	0.783 (0.569-1.075)	0.1708	0.834 (0.584-1.183)	0.285
Severe (SAPS II)	67 (6.2%)	0.30	1.449 (1.016-2.048)	0.0404	1.512 (1.040-2.193)	0.031
		0.365	1.328 (0.879-1.805)	0.0708	1.362 (1.015-1.899)	0.0365
Organ failure (SAPS II)						
SAPS II	47.0 (± 21.4)	0.30	1.037 (1.023-1.052)	<0.0001	1.025 (1.020-1.030)	<0.0001
		0.365	1.034 (1.020-1.049)	<0.0001	1.033 (1.017-1.049)	<0.0001
Infection (%)						
Bacterial (%)	313 (29.7%)	0.30	1.341 (0.989-1.856)	0.0685	1.130 (0.877-1.451)	0.3443
		0.365	1.325 (0.992-1.663)	0.06	1.071 (0.870-1.318)	0.535
Fungal (%)	49 (4.6%)	0.30	0.732 (0.388-1.403)	0.0053	0.744 (0.389-1.005)	0.0128
		0.365	0.899 (0.349-1.083)	0.2551	0.863 (0.736-1.005)	0.1
Other (%)	257 (24.1%)	0.30	0.789 (0.563-1.107)	0.0288	0.721 (0.542-0.958)	0.0343
		0.365	0.753 (0.559-1.046)	0.0149	0.701 (0.553-0.889)	0.0094
Other (%)	214 (20.3%)	0.30	1.245 (0.868-1.605)	0.0676	1.113 (0.868-1.441)	0.4292
		0.365	1.186 (0.955-1.472)	0.1258	1.114 (0.895-1.389)	0.1297
Other (%)						
Myelodysplastic syndrome	61 (5.7%)	0.30	0.448 (0.231-0.868)	0.0174	-	-
		0.365	0.470 (0.246-0.798)	0.0054	-	-
GV disease	405 (38.3%)	0.30	0.780 (0.608-1.048)	0.0151	-	-
		0.365	0.847 (0.704-1.028)	0.0298	-	-
Fungal	146 (13.7%)	0.30	1.096 (0.779-1.539)	0.2272	1.229 (0.894-1.708)	0.1965
		0.365	1.309 (1.026-1.670)	0.0301	1.371 (1.056-1.781)	0.0179
Documented infection	701 (65.6%)	0.30	0.779 (0.624-0.978)	0.0275	0.757 (0.582-0.986)	0.0367
		0.365	0.940 (0.776-1.138)	0.1343	0.928 (0.752-1.141)	0.4723

* SAPS II : Simplified Acute Physiology Score

** Age, cancer, diabetes and (stroke-vascular) condition are considered to be part of Charlson -age adjusted index and germ variables to be part of documented infection

Disclosure: A. Mageau, None; K. Sacre, None; A. Perozziello, None; S. Ruckly, None; C. Dupuis, None; L. Bouadma, None; T. Papo, None; J. F. Timsit, None.

Soluble CD163 Is a Biomarker Associated with Accelerated Carotid Atheroma in SLE Patients at Otherwise Low Risk for Cardiovascular Disease

Clemence David¹, Gillian Divard¹, Rachid Abbas¹, Brigitte Escoubet¹, Marie-Paule Chauveheid¹, Diane Rouzaud¹, Anne Boutten¹, Thomas Papo¹, Monique Dehoux¹ and Karim Sacre², ¹Université Paris-Diderot, Paris, France, ²Bichat Hospital, Paris Diderot University, Paris, France

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Our study aimed to determine whether sCD163, a soluble macrophage marker upregulated in numerous inflammatory disorders, might be predictive of accelerated atherosclerosis associated with SLE.

Methods: The presence of carotid plaques was prospectively assessed by repeating ultrasound analysis in 63 consecutive SLE patients asymptomatic for cardiovascular disease (CVD) and 18 volunteer health-workers (controls). Ultrasound was performed at baseline and during follow up by a single investigator. Serum level of sCD163 was determined at baseline using ELISA. The primary outcome was the presence of a carotid plaque. Factors associated with carotid plaques were identified through multivariate analysis.

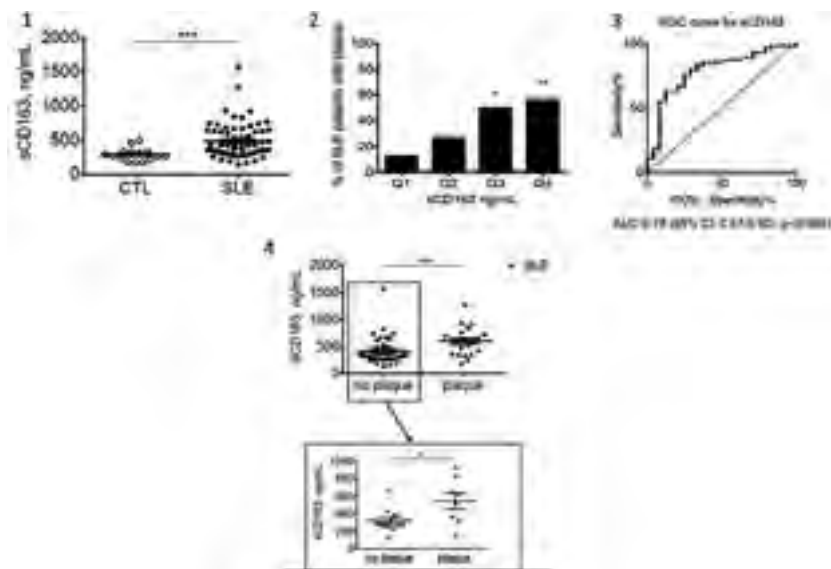
Results: Despite a low risk for cardiovascular events according to Framingham score in both groups ($2.1\% \pm 3.8$ in SLE vs $2.1\% \pm 2.9$ in controls; $p=0.416$), ultrasound study at baseline showed a carotid plaque in 23 (36.5%) SLE patients versus 2 (11.1%) controls ($p=0.039$). Multivariate analysis showed that SLE status increased the risk for carotid plaque by a factor of 9 ($p=0.017$). In SLE patients, sCD163 level was high ($483.7 \text{ ng/ml} \pm 260.8$ versus $282.1 \text{ ng/ml} \pm 97.5$ in controls; $p<0.001$) and independently associated with carotid plaques as assessed by stratification based on sCD163 quartile values ($p=0.009$), receiver operating characteristic (ROC) ($p=0.001$) and multivariate analysis ($p=0.015$). Eventually, sCD163 at baseline was associated with the onset of carotid plaque during follow up (3 ± 1.4 years) in SLE patients who had no carotid plaque at first evaluation ($p=0.041$).

Conclusion: Since sCD163 is associated with developing carotid plaque in SLE, it may be a useful biomarker for accelerated atherosclerosis in SLE patients at apparent low risk for CVD

1. Serum level of sCD163 in SLE patients (black rounds) and controls (white rounds).

2. Percentage of SLE patients (black bars) with carotid plaque according to serum level of sCD163 divided by quartile values

3. ROC curves of sCD163 for prediction of carotid plaque in SLE patients. AUC, area under the curve; CI, confident interval



4. Serum level of sCD163 measured at baseline in SLE patients with or without carotid plaque at first vascular assessment (black rounds, top). Serum level of sCD163 measured at baseline in SLE patient who had no carotid plaque (square box) at first assessment and in whom carotid plaque did or did not occur during follow up (black round, bottom).

Disclosure: C. David, None; G. Divard, None; R. Abbas, None; B. Escoubet, None; M. P. Chauveheid, None; D. Rouzaud, None; A. Boutten, None; T. Papo, None; M. Dehoux, None; K. Sacre, None.

Abstract Number: 717

The Burden of Chronic Kidney Disease in Systemic Lupus Erythematosus (SLE): A Nationwide Epidemiologic Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

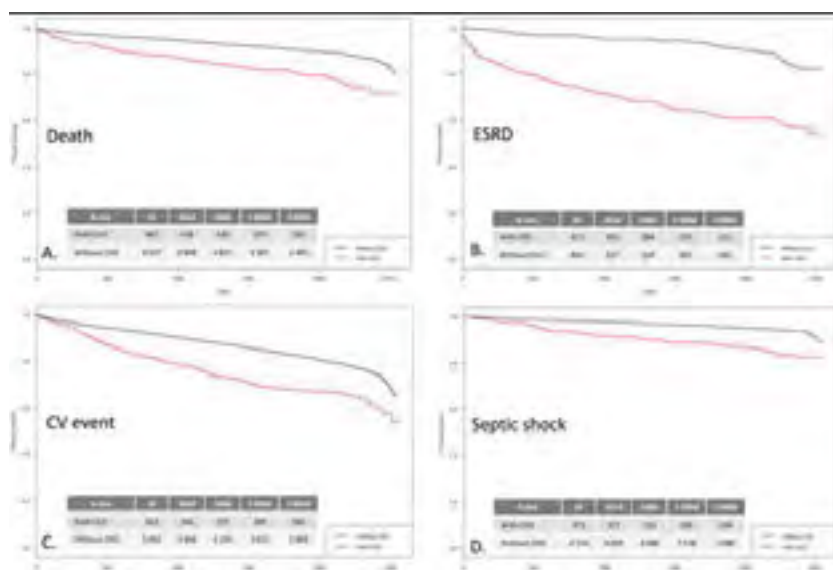
Session Type: ACR Poster Session A

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

Background/Purpose: Lupus nephritis occurs in about 50% of SLE patients. We aimed to analyze the impact of chronic kidney disease (CKD) on major clinical outcomes in SLE by using a nationwide medico-administrative database.

Methods: We performed a retrospective cohort study to analyse hospital stays' characteristics of SLE population in France from January 1st, 2009 to December 31st, 2015. We extracted data from the PMSI database (Programme de Médicalisation des Systèmes d'Informations) which compiles hospital discharges of all French healthcare facilities. PMSI uses International Classifications of Diseases 10th revision (ICD-10) to encode diagnosis. All the diagnosis and procedures performed during hospital stays associated with or following a "M32" diagnosis code, which defines the SLE population, were identified. Factors associated with major clinical outcomes such as death, end-stage renal disease (ESRD), septic shock, and cardiovascular event were assessed. Kaplan-Meier method was used to represent survival without major clinical outcomes according to the presence of CKD (eGFR <60mL/min/1.73m²) at first stay.

Results: From 2009 to 2015, 145 794 hospital stays associated with SLE diagnosis corresponding to 26 320 unique SLE patients were identified. Mean age [SD] at first stay was 46.7 [+/-17.2] and 85.6% were female. Among patients with kidney disease at first stay, 20.8% developed end-stage renal disease (ESRD) during follow up. Overall, from 2009 to 2015, death, septic shock, and cardiovascular event occurred in 6.7%, 4.5% and 10.5% of SLE patients, respectively. CKD identified at first stay in 2009 was significantly associated with the occurrence of death (RR 2.4 [2.0-2.9]), ESRD(RR 4.02 [2.86-5.65]), septic shock (RR 3.1 [2.3-4.2]), and cardiovascular event (RR 1.9 [1.6-2.3]) between 2009 and 2015.



Conclusion: Our results confirm at a nationwide level that CKD is a major risk factor for overall morbidity and mortality in SLE patients, highlighting the need for early pre-CKD lupus nephritis diagnosis. Occurrence of death (A), ESRD (B), cardiovascular event (C) and septic shock (D) between 2009 and 2015 according to CKD status (eGFR <60mL/min/1.73m²) at first stay in 2009. Blue lines represent the outcome in patients without CKD at first stay. Red lines represent the outcomes in patients with CKD at first stay

Disclosure: A. Mageau, None; J. F. Timsit, None; A. Perozziello, None; S. Ruckly, None; C. Dupuis, None; L. Bouadma, None; T. Papo, None; K. Sacre, None.

Abstract Number: 718

Assessing Dyspnea in Patients with Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Lungs can be affected in up to 50% of systemic lupus erythematosus (SLE) patients. Our aim was to assess the prevalence and degree of dyspnea in a SLE cohort using questionnaires and to see if they correlate with lung involvement.

Methods: Consecutive patients with SLE by 1997 ACR criteria in the Lupus Clinical Repository at a single academic center were given the UCSD Shortness of Breath Questionnaire (UCSD SOBQ) and the Dyspnea-12 Index (D-12). These questionnaires have been validated in connective tissue disease-related interstitial lung disease (ILD) cohorts but not in SLE. UCSD SOBQ is a 24-item tool (scores 0-120) assessing dyspnea severity with activities of daily living and its psychological impact. D-12 is a 12-item scale (scores 0-36) incorporating “physical” and “affective” aspects of dyspnea severity. Scores >50 were considered high for UCSD SOBQ and >12 for D-12. Demographics and SLE disease characteristics were recorded. Lung involvement was ascertained with medical record review by two rheumatologists. Correlation between dyspnea scores and lung involvement was determined using the Spearman’s Rank Order Correlation or Wilcoxon rank sum test, as appropriate, with SAS 9.4. A p value of <0.05 was considered significant.

Results: 50 SLE patients completed questionnaires (95% female, mean age 44 ± 14 years, mean disease duration 18 ± 10 years). 42% were White, 16% Latino, 12% Black, 10% Asian, and 20% other. Mean ±SD SLE disease activity (SLEDAI-2K) was 3.8±4. 98% of subjects were ANA positive, with about 1/3 positive for anti-dsDNA (27%), anti-RNP (33%), and anti-Smith (33%). Fewer were positive for Anti-Ro(17%), anti-La (6%) and anti-centromere (4%). 48/50 (96%) of subjects had abnormal UCSD SOBQ scores consistent with some degree of dyspnea. 37/50 (74%) had both abnormal UCSD SOBQ and D-12 scores. The median score was 24 (8-52) for UCSD SOBQ and 3 (0-8) for D-12. 13 had high UCSD SOBQ (score > 50), 10 had high D-12 (score > 12), and 8 had high scores on both indexes. 8 had lung involvement (7 ILD, 1 pleurisy) with all but 1 having a high UCSD SOBQ score, and 5 of them having both high UCSD SOBQ and D-12 scores. 3 had high scores on both indexes without SLE related lung involvement (2 heart failure, 1 unidentifiable cause). 3 had high UCSD SOBQ without high D-12 scores and no SLE related lung involvement (1 asthma, 2 unidentifiable cause). 2 had high D-12 without high UCSD SOBQ scores and no SLE related lung involvement (1 asthma, 1 unidentifiable cause). High UCSD SOBQ (p = 0.002) and D-12 scores (p = 0.004) were strongly associated with SLE lung involvement. High UCSD SOBQ scores correlated with higher SLE disease activity (SLEDAI-2K) (p = 0.03) and high D-12 scores with positive anti-dsDNA (p = 0.03). There were no significant associations with age, sex, SLE disease duration, or other autoantibodies.

Conclusion: Dyspnea was prevalent in our SLE cohort. UCSD SOBQ and D-12 questionnaires captured the majority of SLE patients with known lung involvement, with UCSD SOBQ being potentially more sensitive than D-12. These questionnaires may be useful tools to screen for dyspnea and possibly identify subclinical shortness of breath in SLE patients.

Disclosure: C. C. J. Lee, None; L. J. Forbess, None; D. J. Wallace, None; C. Jefferies, None; M. Ishimori, None.

Men and Sexual Function: An Overlooked Issue in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

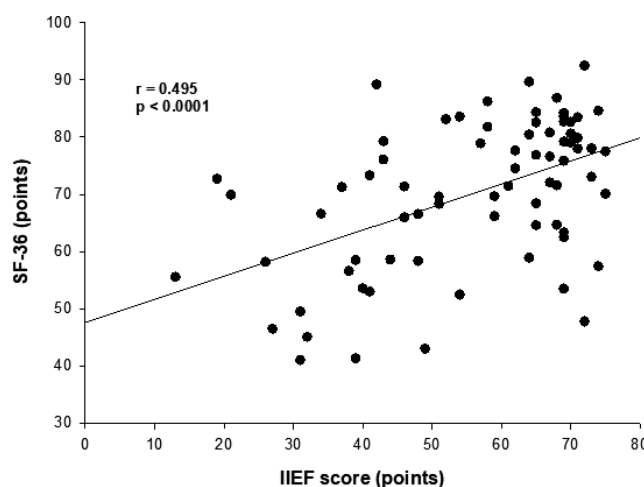
Background/Purpose: Whereas SLE is uncommon in men, the disease is usually more severe and requires more aggressive immunosuppression in male patients. There are multiple studies regarding sexual aspects in women with SLE, but information about sexual function in male patients is quite scant. The impact that the SLE-associated physical and psychological aspects have in these patients has not been previously addressed.

Methods: We performed a transversal study in a third-level referral center in Mexico City (between January and May 2018). We included men aged ≥ 16 years who fulfilled ACR criteria for SLE and who were sexually active in the previous six months. Patients with other autoimmune diseases (except for APS) or chronic viral infections were excluded. All subjects answered the International Index of Erectile Function-15 (IIEF-15) and the SF-36 (which determines generic health-related quality of life) questionnaires. Other clinical, serological and demographic variables were measured. Oxidized LDL was quantified by ELISA.

Results: We included 73 male SLE patients. Mean age was 37.8 ± 2.7 years and disease duration was 9.0 ± 7.3 years. SLEDAI score at the time of the study was 4.3 ± 4.1 points; most patients (87.7%) were taking immunosuppressive therapy. Comorbidities were present in 54.7% of subjects, with dyslipidemia and hypertension being the most prevalent (31.5% each).

Global IIEF-15 score was 56.4 ± 15.2 (range 5-75 points) and global SF-36 score was 70.1 ± 12.9 (range 0-100 points). There was a positive correlation between both scores (see Fig. 1). There was also a weak correlation between oxidized LDL levels and global IIEF-15 ($r=0.321$, $p=0.036$). Regarding erectile function, 37 subjects (50%) had some degree of dysfunction. These patients were older (34.7 ± 12.1 vs 40.9 ± 12.7 years, $p=0.037$), had a lower education degree ($p=0.002$) and a higher prevalence of type 2 diabetes mellitus ($p=0.016$) than those without erectile dysfunction. The rest of the variables are shown in Table 1.

Interestingly, 86% of patients said they would be willing to consult a specialist if any degree of sexual dysfunction was detected.



Conclusion: Global sexual function, and especially erectile function, is impaired in men with SLE. Most patients with sexual dysfunction are young and sexually active, and this should be considered by their rheumatologists, in order to inquire about this issue in regular visits. Further research is required to determine the physiopathogenic mechanisms underlying this condition, but endothelial damage and SLE-associated neuropsychological features could play a role.

Table 1

Variable	Mean \pm SD
Demographic	
Age (years)	37.8 \pm 12.7
Body mass index (m ² /kg)	26.6 \pm 4.8
Less than 10 years of schooling (n, %)	17/73 (23.2)
Time since SLE diagnosis (years)	9.0 \pm 7.3
Clinical Features	
Total score IIEF-15 (reference interval: 5-75 points)	56.47 \pm 15.2
Erectile function (reference interval: 1-30 points)	22.68 \pm 7.6
Intercourse satisfaction (reference interval: 0-15 points)	10.4 \pm 3.6
Orgasmic function (reference interval: 0-10 points)	7.7 \pm 2.9
Sexual desire (reference interval: 2-10 points)	7.4 \pm 1.8
Overall satisfaction (reference interval: 2-10 points)	8.1 \pm 1.6
Total score SF-36 (reference interval: 0-100 points)	70.14 \pm 12.9
Physical component summary score (reference interval: 0-100 points)	72.2 \pm 17.6
Mental component summary score (reference interval: 0-100 points)	68.0 \pm 11.2
Secondary antiphospholipid syndrome (n, %)	22/73 (30.1)
SLEDAI score (points)	4.3 \pm 4.1
Others comorbidities (n, %)	40/73 (54.7)
Laboratory features	
Hemoglobin (mg/dl)	15.4 \pm 2.43
Leukocytes (mm ³) (x10 ³)	5.69 \pm 2.2
Absolute lymphocyte count (mm ³)	1333.5 \pm 760.6
Absolute neutrophil count (mm ³)	3661.3 \pm 1759.4
Neutrophil-to-lymphocyte ratio	3.9 \pm 5.7
Platelets (cells/μl) (x10 ³)	216.3 \pm 77.2
Serum creatinine (mg/dl)	1.4 \pm 1.7
C3 levels (reference interval: 87-200 mg/dl)	104.9 \pm 32.8
C4 levels (reference interval: 19-52 mg/dl)	19.5 \pm 11.6
Anti-dsDNA antibodies (reference interval: \leq 9.6 UI/ml)	249.1 \pm 796.0
Use of immunosuppressive treatment (n, %)	64/73 (87.7)
Prednisone (n, %)	41/73 (56.2)
Current dose (mg/day)	5.30 \pm 7.9
Azathioprine (n, %)	26/73 (35.6)
Current dose (mg/day)	36.3 \pm 54.8
Antimalarial (n, %)	48/73 (65.8)
Current dose (mg/day)	150.3 \pm 123
Mycophenolate mofetil (n, %)	27/73 (37)
Current dose (mg/day)	616.4 \pm 887.9
Cyclophosphamide exposure previous 6 months (n, %)	7/73 (9.5)
Cumulative dose (previous 6 months) (mg)	417 \pm 1466
Anticoagulation (n, %)	11/73 (15.0)
Non-immunosuppressive treatment (n, %)	56/73 (76.7)

Disclosure: J. Campos-Guzmán, None; A. Barrera-Vargas, None; D. Gómez-Martín, None; J. Alcocer-Varela, None; S. Govea-Peláez, None; M. A. Gómez-Sámano, None; D. Cuevas-Ramos, None; D. M. Padilla-Ortíz, None; J. Merayo-Chalico, None.

Abstract Number: 720

Interleukin-6 Level in Cerebrospinal Fluid As a Biomarker for Systemic Lupus Erythematosus Patients with Longitudinally Extensive Transverse Myelitis like Neuromyelitis Optica Spectrum Disease

Yasuhiro Hasegawa¹, Yoshiyuki Arinuma¹, Kazuma Ino¹, Takumi Muramatsu¹, Junichi Kondo¹, Yu Matsueda¹, Takayuki Hoshiyama¹, Toshihiro Tono¹, Tatsuhiko Wada¹, Tatsuo Nagai² and Sumiaki Tanaka¹, ¹Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Sagamihara, Japan, ²Kitasato University, Department of Rheumatology and Infectious Diseases, Sagamihara, Japan

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Background/Purpose: Demyelinating syndrome in NPSLE includes the wide range of lesions similar to multiple sclerosis (MS). Recently, the diagnostic criteria for neuromyelitis optica spectrum disease (NMOSD) has been established, independently of MS. Clinically, longitudinally extensive transverse myelitis (LETM) as is described in the definition of NMOSD can be observed even in patients with SLE. IL-6 in cerebrospinal fluid (CSF) has been reported as one of biomarkers in NMOSD, but in lupus patients with LETM, the utility of CSF IL-6 for a diagnosis and as a surrogate marker after treatment has not been demonstrated. The aim of this study is to reveal the characteristic of lupus patients with NMOSD-like lesions, especially focusing on CSF IL-6.

Methods: SLE patients who had admitted to Kitasato University hospital due to a diagnosis and a treatment for NPSLE since 2004 to 2018 were exhaustively collected. Of collected NPSLE patients, patients who were classified as demyelinating syndrome were recruited for this analysis. To be compared with characteristics of patients with NMOSD not involving other autoimmune diseases, these patients were divided into two groups according to the lesions by magnetic resonance imaging: patients with LETM as is defined in international consensus diagnostic criteria for NMOSD and patients with brainstem and/or spinal cord lesions other than LETM. Clinical data including CSF IL-6 based on their medical charts were reviewed. The IL-6 levels in CSF were compared with non-parametric tests.

Results: Total 77 NPSLE patients admitted for 14 years. Of 77 patients, 12 patients (15.6%) had some brainstem and/or spinal cord lesions like demyelinating syndromes in NPSLE. 7 patients had LETM and of 7 patients with LETM, 2 patients were positive for anti-aquaporin 4 antibody. Of remained 5 patients, 1 patient had as small and punctuated lesion in brainstem and 4 patients had spinal cord lesion unlike LETM. The median level in CSF IL-6 in these 12 patients was 29.10 pg/ml, which was significantly decreased to 3.75 pg/ml ($p=0.008$) after treatment (Figure 1A). In patients with LETM, the median level of CSF IL-6 was 18.7 pg/ml, which tended to be decreased ($p=0.065$) after treatment (Figure 1B). Interestingly, patients with LETM positive for anti-Sm antibody had higher CSF IL-6 level (Figure 1B).

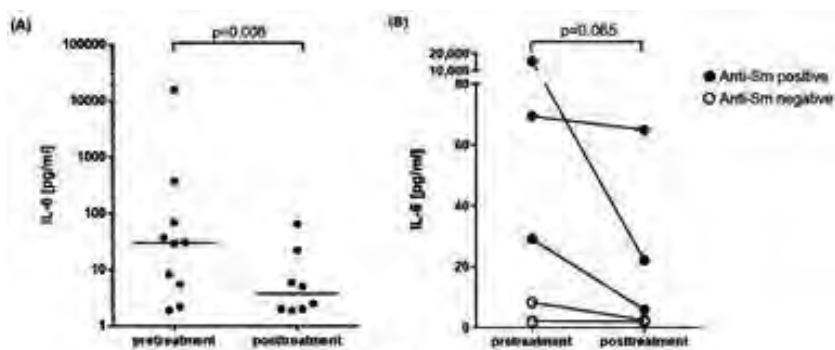


Figure 1 The change of IL-6 levels in CSF by treatment

Conclusion: IL-6 in CSF could be one of biomarkers in SLE patients with LETM, presumably depending on causes of LETM including autoantibodies.

Disclosure: Y. Hasegawa, None; Y. Arinuma, None; K. Ino, None; T. Muramatsu, None; J. Kondo, None; Y. Matsueda, None; T. Hoshiyama, None; T. Tono, None; T. Wada, None; T. Nagai, None; S. Tanaka, None.

Abstract Number: 721

The Burden of Renal Arteriosclerosis in Lupus Nephritis: A Cohort Study Examining Prevalence and Predictors of Renal Arteriosclerosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Cardiovascular disease (CVD) is significantly accelerated in young systemic lupus erythematosus (SLE) patients including those with lupus nephritis (LN). Despite literature suggesting that renal arteriosclerosis is an early predictor of CVD, presence of arteriosclerosis often overlooked in LN biopsies. Hence, we aimed to examine the prevalence of renal arteriosclerosis in kidney biopsies of LN patients by age group and in comparison to published rates in healthy adult kidney donors. We hypothesized that renal arteriosclerosis burden will be greater and will accelerate at a younger age in LN patients compared to healthy donors.

Methods: Our cohort study identified all consecutive LN patients who underwent kidney biopsy between 1994 and 2017 at an academic center. Data were abstracted from a comprehensive native renal biopsy database including sociodemographics and reported details regarding the first biopsy in SLE patients. SLE diagnosis was validated using SLICC 2012 and SLE duration was recorded from electronic health records. Biopsy reports were reviewed for LN class and chronicity as classified per International Society of Nephrology guidelines. The primary outcome of interest, renal arteriosclerosis (without arteritis or thrombi) was classified into four categories based on BANFF criteria for donor kidney biopsies: none, mild, moderate, severe. Prevalence of (A) any renal arteriosclerosis and (B) moderate-severe arteriosclerosis was calculated. Further, we compared predictors of the presence of any renal arteriosclerosis (vs. absence) using multivariate logistic regression.

Results: Among 189 incident LN patients with kidney biopsies, 78% were female, 78% white and median age was 25 years (2-79 years). Prevalence of any renal arteriosclerosis and moderate-severe renal arteriosclerosis was 31.8% and 7.4% respectively in LN patients (Table 1). Respective rates of 51.7% (any) and 10.8% (mod-severe) in ages 40-49 were comparable to healthy kidney donors ages 70-79.

Univariate analysis in LN patients showed that age, chronicity and ever smoking were positive predictors of renal arteriosclerosis. Multivariate analysis showed a peak of 11 times greater odds of renal arteriosclerosis in LN patients ages 40-49 compared to younger patients (OR 11.7, CI 1.6, 246.0), and chronicity predicted nearly three times greater odds of arteriosclerosis (OR 2.9, CI 1.2, 7.1). LN class and SLE duration were not predictors of arteriosclerosis.

Conclusion: Findings showed significantly greater burden of renal arteriosclerosis in LN patients two to three decades earlier than in healthy kidney donors. Quantifying renal arteriosclerosis burden in LN is important as a potential early predictor of CVD in SLE. Future work will compare prevalence and predictors of renal arteriosclerosis in SLE, vasculitis and non-glomerulonephritis biopsies and long-term CVD outcomes.

Table 1. Prevalence of Any or Moderate-Severe Arteriosclerosis in LN by Age Groups

Age groups	Prevalence Any arteriosclerosis	Prevalence Moderate-severe	Control Prevalence* (Any, Moderate-severe)
Overall (n=189)	31.8%	7.4%	(32%, 3.3%)
0-9 years (n=16)	6.3%	6.3%	NA
10-19 years (n=66)	22.2%	0	NA
20-29 years (n=33)	17.9%	0	(10%, 0%)*
30-39 years (n=17)	35.3%	11.8%	(19%, 2%)
40-49 years (n=29)	51.7%	10.8%	(37%, 2.3%)
50-59 years (n=12)	59.0%	25.0%	(44%, 7%)
60-69 years (n=12)	66.7%	33.3%	(51%, 6.5%)
70-79 years (n=4)	50.0%	25.0%	(82%, 9.1%)

* Comparator group ages 18-29. Control data source: Rule et al *Ann Intern Med.* 2010 May 4; 152(9): 561-7

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Abstract Number: 722

Increased Blood Pressure Visit-to-Visit Variability in Patients with Systemic Lupus Erythematosus: Association with Inflammation, Comorbidities and Increased Mortality

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Table: Factors associated with blood pressure variability in patients with SLE

Variable	Spearman coefficient	p-value
Age	0.15	<0.001
Creatinine	0.14	<0.001
C-reactive protein	0.12	0.002
Charlson score	0.18	<0.001
C3	-0.05	0.13
C4	0.003	0.94
Body mass index	-0.007	0.84

Background/Purpose: Patients with systemic lupus erythematosus (SLE) have increased mortality compared to the general population. As outcomes related to disease control have improved, this mortality difference has been explained increasingly by higher rates of cardiovascular and renal disease. Blood pressure visit-to-visit variability (BPV) has emerged as a risk factor for cardiovascular and renal outcomes in the general population but little is known about this relationship in SLE. We hypothesized that SLE patients have greater BPV than control subjects and that BPV is associated with higher comorbidity burden and increased mortality in SLE.

Methods: We identified a cohort of patients with SLE using a previously validated algorithm (PPV 94%) from a de-identified version of an academic medical center's electronic health record(EHR) and then frequency-matched (age, race, and sex) SLE patients to a control group in a ~5:1 control-case ratio. We excluded patients with fewer than three visits or age <18 years at the time of the first relevant ICD9 code (710.0 for SLE, any code for controls). We extracted demographic variables (age, race, and sex), ICD9 codes, laboratory results, and outpatient blood pressure values from the EHR. We compared BPV in SLE patients and controls. The primary outcome was systolic blood pressure coefficient of variation. Secondary outcomes included standard deviation, average real variation, and successive variation for both systolic and diastolic blood pressure. Second, we examined the association between BPV with clinical characteristics and mortality in patients with SLE.

Results: 899 patients with SLE and 4172 controls met inclusion criteria. Age, sex, and race were similar among the SLE and control groups. Patients with SLE had higher systolic BPV 9.7% [7.8-11.8] than the control group 9.2% [7.4-11.2], $p<0.001$ measured by coefficient of variation. All other measures of BPV were significantly higher in patients with SLE than in controls. In SLE patients, BPV correlated significantly with age, creatinine, C-reactive protein, and the Charlson comorbidity score; but not with C3, C4, and body mass index (Table). There was no statistically significant difference in BPV by sex, but Caucasian SLE patients [9.6%(7.9-11.4)] had lower BPV than SLE patients who were African-American [10.3%(7.9-12.9)] or patients from other races [10.4% (7.6-12.3)], $p=0.015$. Over a median follow-up of 6.5 years, 91 patients died. After adjustment for age, sex, race, and baseline Charlson comorbidity score, higher BPV was associated with death in patients with SLE [OR=1.24, 95%CI 1.16-1.33, $p<0.001$].

Conclusion: SLE patients had a higher BPV than the control group. In patients with SLE, higher BPV was associated with older age, higher creatinine, inflammation, comorbidity index, and mortality.

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Abstract Number: 723

Patient-Reported Cognitive Screen Does Not Identify Cognitive Sub-Domains: Exploration of the Subscale Structure of the Perceived Deficits Questionnaire in a Systemic Lupus Erythematosus Cohort

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Identifying patients with Systemic Lupus Erythematosus related cognitive impairment (SLE-CI) is critical as SLE-CI can negatively affect employment, quality of life, and disease self-management. Evidence-based and resource-efficient SLE-CI screening instruments are needed. The patient-reported 20-item Perceived Deficits Questionnaire (PDQ-20) is a potential instrument. However, our previous analyses questioned the PDQ-20 purported four-factor structure: attention/concentration, retrospective memory, prospective memory, and planning/organization. The purpose of this study is to explore the PDQ-20 factor (subscale) structure in an SLE cohort.

Methods: This study used PDQ-20 data from consecutive patients aged 18-65 years who met the ACR classification criteria for SLE in a single Canadian rheumatology center. Exploratory factor analyses (EFA) included squared multiple correlations and the maximum likelihood method to extract factors, followed by a varimax (orthogonal) rotation. Subsequent confirmatory factor analyses (CFA) was completed on identified factor structures. The validity of the results was tested with the assumption that each item had one factor pathway, with factor correlations considered. The sample size met standards for EFA ($>5 \times \text{items}$) and was sufficient to perform CFA (power=0.99).

Results: Participants who did ($n=177$) and did not return ($n=31$) the PDQ-20 did not statistically significantly differ in age, age at SLE diagnosis, education or employment status. EFA without any restriction resulted in 5 factors. However, one factor included only one item (Q19. Forget to take your medication). The EFA scree-plot and eigenvalues (factor 1=119.38) provided strong support for a single factor model. Four factors had eigenvalues over 1, with each factor having 4-6 items, which pulled for examination of a new four-factor model. Overall hypothesis test rejected the assumption of no common factor (Tucker and Lewis coefficient = 0.94). CFA results indicated adequate model fit for the new four-factor model (standardized root mean square residual=0.04; root mean square error of approximation=0.08; Bentler comparative fit index=0.93; all item factor loadings statistically significant with standardized factor loading range 0.56-0.88). Lagrange Multiplier statistics in the CFA found alternate item-factor pathways that significantly improved the model by adding or removing pathways. Correlations between the new four factors were all statistically significant with high interrelatedness (range: 0.80-0.92).

Conclusion: Results indicate that the PDQ-20 has one factor. Some results support a four-factor model distinct from the original PDQ-20 subscales. However, this new model exhibits high correlations between factors and multiple item pathways, and it does not correspond with a theoretical cognitive conceptual structure. This may be due to the recruitment of multiple cognitive domains in items related to everyday living activities. Evidence from this analysis and our previous CFA of the original PDQ-20 factor structure indicates that the PDQ-20 has one factor and should be interpreted using the total score and not subscales.

Disclosure: L. Engel, None; J. Su, None; E. Nalder, None; Y. Goverover, None; M. Gignac, None; C. Tartaglia, None; N. Anderson, None; Z. Touma, None.

Abstract Number: 724

Are Traditional Biomarkers of Lupus Associated with Renal Pathology in Lupus Nephritis?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Traditional biomarkers for systemic lupus erythematosus (SLE) and lupus nephritis (LN) include serum creatinine (Cr), complement levels (C3/C4), double-stranded DNA antibody (dsDNA), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), urine red blood cells (uRBC), and urine protein/Cr ratio (uPCR). However, these clinical parameters have limited specificity for active LN and are inconsistent predictors of renal pathology. Whether these biomarkers are associated with LN class has important implications in therapeutic decision-making. The objectives of this study are: 1) to determine whether these biomarkers are associated with LN on renal biopsy; 2) to determine whether they can distinguish between LN classes; and 3) to assess correlation between these biomarkers and activity and chronicity indices on renal biopsy.

Methods: Using the University of Pittsburgh Health Sciences Tissue Bank (HSTB) and Renal Pathology Department stored biopsy specimens, we identified 37 cases of LN diagnosed on renal biopsy from 2010-2016. Using the electronic database, we obtained LN classes and biomarkers checked within a few days to a month of biopsy date for each sample. Descriptive summaries, correlations, Fisher's exact test, and rank-sum tests were used to evaluate the relationship between the biomarkers and LN.

Results: Of the 37 LN samples, 1 had class I, 3 had class II, 10 had class III, 15 had class IV, and 13 had class V (5 with isolated class V) LN. Excluding samples with missing data, 14 (47%) had Cr >1.3 mg/dL. There were 17 (56.7%) with low C3, 18 (60.0%) with low C4, and 16 (59.3%) with dsDNA positivity. Of the 11 samples negative for dsDNA, 8 had class III or IV, and 3 had class I, II, or V LN. Overall mean \pm SD ESR was 53.3 ± 35.6 mm/h and CRP was 1.2 ± 2.5 mg/dL. Hematuria was variably reported, but only 11 (37.9%) had >5 RBC/hpf on urinalysis. Mean \pm SD uPCR was 2.6 ± 2.9 mg/g Cr. Comparison of biomarkers between classes III and IV vs. other classes (I, II, V, and II+V) showed significantly greater proportion with low C3 (66.7% vs. 16.7%; $p=0.027$) and significantly higher activity index (7.2 ± 3.8 vs. 1.0 ± 0.7 ; $p=0.002$) in class III-IV vs. other classes. Comparison of biomarkers for class V only vs. classes III and IV with or without class V (III, IV, III+V, and IV+V) showed significantly lower proportion with low C3 (0.0% vs. 66.7%; $p=0.008$) and significantly lower activity index (0.5 ± 0.7 vs. 7.2 ± 3.8 ; $p=0.034$) in class V vs. class III-IV. There was no significant correlation between any biomarker and activity index. There was borderline significant correlation between CRP ($\rho -0.4$, $p=0.058$) and uPCR ($\rho 0.4$, $p=0.057$) and chronicity index.

Conclusion: Traditional biomarkers of SLE and LN are imperfect predictors of LN class on renal biopsy. Surprisingly, only C3 was significantly different between LN classes, and none were significantly correlated with activity and chronicity indices. Because clinical laboratory and urine biomarkers do not distinguish LN classes well, renal biopsy is necessary to reliably diagnose LN class. Given the lack of associations between traditional biomarkers and renal pathology, more specific LN biomarkers are urgently needed.

Disclosure: K. Liang, None; K. P. Liang, None; Y. Li, None; A. Hurd, None; D. Landsittel, None; S. Bastacky, None.

Abstract Number: 725

Preliminary Population-Based Incidence and Prevalence Estimates of Primary Discoid Lupus and Cutaneous Lupus Erythematosus from the Manhattan Lupus Surveillance Program

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: The extant epidemiologic data of primary discoid lupus erythematosus (DLE) and primary cutaneous lupus erythematosus (CLE) remains limited with few published estimates for the general population and scant data regarding racial/ethnic populations in the U.S. DLE is associated with considerable morbidity given it tends to occur on the face, scalp, and ears and is associated with scarring and permanent alopecia. The Manhattan Lupus Surveillance Program (MLSP) is a population-based registry comprised of patients with Systemic Lupus Erythematosus (SLE) and related diseases treated in New York County (Manhattan) that was developed to determine the incidence and prevalence of SLE among Manhattan residents. Leveraging MLSP data we provide estimates of the prevalence and incidence of DLE and CLE during 2007 and 2007-09, respectively, in Manhattan across the major racial/ethnic populations (Black, Latino, Asian, White).

Methods: MLSP cases were identified from hospitals and associated lupus clinics, rheumatologists, and state population databases. Case screening was performed using a Manhattan address and ICD-9 codes, including 695.4 for DLE. Charts were abstracted and final diagnosis coded. DLE was defined as a diagnosis of primary DLE. CLE was defined as either a diagnosis of DLE, subacute cutaneous lupus erythematosus (SCLE), lupus profundus, chilblain lupus, or lupus tumidus. All diagnoses required notation by a rheumatologist, dermatologist, or pathologist. Patients who met ACR criteria for SLE were excluded.

Results: There were 74 prevalent and 26 incident primary DLE cases, resulting in preliminary age-adjusted overall prevalence and incidence rates of 4.4 and 0.5 per 100,000 person-years. Overall age-adjusted prevalence and incidence rates were 2 and 8 times higher among women compared with men, respectively. The age-adjusted prevalence of DLE was significantly higher among Blacks (15.1) and Latinos (4.8) compared with Whites (0.6) and Asians (0.6). The age-adjusted incidence of DLE was significantly higher among Blacks (1.8) compared with Whites (0.1) and Latinos (0.4). Diagnoses of SCLE, lupus profundus, chilblain lupus, and lupus tumidus were rare and thus the age-adjusted overall prevalence and incidence rates of CLE were similar to DLE (4.5 and 0.6 per 100,000 person-years, respectively). CLE, with 77 prevalent and 31 incident cases, had similar gender and racial ethnic differences.

Conclusion: Using data from a large population-based registry revealed substantial racial/ethnic and gender disparities in DLE and CLE among Manhattan residents. These data are consistent with the evidence of similar disparities among SLE patients with DLE and suggest Blacks are disproportionately affected whether they have the systemic or primary form. These data also provide epidemiologic estimates for DLE and CLE for the major racial/ethnic populations in the U.S.

Table 1: Age-adjusted rates of DLE and CLE among Manhattan residents, overall and by sex and race/ethnicity

	Prevalent Cases, 2007 Rate per 100,000 person-years (95% Confidence Interval)	Incident cases, 2007-2009 Rate per 100,000 person-years (95% Confidence Interval)
Primary DLE		
Total	4.4 (3.4-5.5)	0.5 (0.3 -0.7)
Male	2.5 (1.5 -3.9)	0.1 (0.0 -0.3)
Female	5.9 (4.4-7.8)	0.8 (0.5-1.3)
Race/ethnicity		
Non-Latino White	0.6 (0.2-1.4)	0.1 (0.0-0.4)
Non-Latino Black	15.1 (10.4-21.1)	1.8 (0.9-3.2)
Latino	4.8 (2.9-7.5)	0.4 (0.1-0.9)
Non-Latino Asian	0.6 (0.0-3.5)	0.6 (0.1-1.7)
Primary CLE		
Total	4.5 (3.6-5.7)	0.6 (0.4 -0.8)
Male	2.5 (1.5 -3.9)	0.1 (0.0 -0.3)
Female	6.2 (4.4-8.1)	1.0 (0.7-1.5)
Race/ethnicity		
Non-Latino White	0.6 (0.2-1.4)	0.1 (0.0-0.4)
Non-Latino Black	15.1 (10.4-21.1)	1.8 (0.9-3.2)
Latino	5.7(3.5-8.6)	0.4 (0.1-0.9)
Non-Latino Asian	0.6 (0.0-3.5)	0.6 (0.1-1.7)

There were 77 CLE cases (31 incident) and 74 DLE cases (26 incident).

Rates are per 100,000 Manhattan residents. Denominator data is based on 2007-2009 intercensal population estimates from the NYC DOHMH Bureau of Epi Services (2000-2014 files).

Data are age adjusted to the US 2000 Standard Population.

Cases were assigned to one of five mutually exclusive race/ethnicity categories: non-Latino white, non-Latino black, non-Latino Asian, Latino, and non-Latino other. Non-Latino cases identified with more than one race were categorized as non-Latino other.

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Abstract Number: 726

Anti-Retinoblastoma Protein Antibody Is Protective Against Lupus Nephritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Retinoblastoma protein (RB) regulates nucleosome/chromatin structures and is linked to tumor suppression. It regulates the cell cycle by repression of E2F transcription factor and stabilization of heterochromatin. Because SLE is the prototypic autoimmune disease with autoantibodies against the nucleosome and chromatin, the presence of anti-RB antibodies and the association with disease manifestations were examined.

Methods: 222 SLE patients from the Hopkins longitudinal cohort seen consecutively in clinic were studied (85% female, 94% Caucasian, mean age 51 years). Anti-RB antibodies were assayed by immunoprecipitation of ³⁵S-methionine-labeled protein generated by in vitro transcription and translation from full length human cDNA. Odds ratios and p-values for univariate analyses were calculated using Fisher's exact t-test. Exact logistic regression and odds ratios were calculated for the multi-variate model due to a cell frequency of zero for proteinuria ever and positive anti-RB antibody status.

Results: Anti-RB antibodies were present in 8.6% of these SLE patients, 6.3% with medium-high titer. Univariate associations with SLE manifestations for the medium-high titer positive patients are included in Table 1.

Table 1. Association of Anti-RB antibodies with SLE Manifestations

	Anti-Rb Positive (N=14)	Anti-Rb Negative (N=203)	p-value	OR (95% CI)
Vasculitis ever	0 (0.0%)	34 (16.8%)	0.1338	N/C
Proteinuria ever	0 (0.0%)	75 (37.0%)	0.0028	N/C
Hematuria ever	1 (7.1%)	43 (21.2%)	0.3103	0.29 (0.04, 2.25)
Renal SLE ever (Hematuria OR Proteinuria)	1 (7.1%)	81 (39.9%)	0.0145	0.12 (0.01, 0.9)
Stroke ever	2 (14.3%)	3 (1.5%)	0.0347	11.11 (1.69, 72.94)
Anemia ever	1 (7.1%)	124 (61.1%)	<0.0001	0.05 (0.01, 0.38)
Anti-Ro	4 (28.6%)	65 (32.2%)	1.0000	0.84 (0.25, 2.79)
Anti-La	1 (7.1%)	31 (15.4%)	0.6988	0.42 (0.05, 3.36)
Anti-RNP	1 (7.1%)	36 (17.7%)	0.4731	0.36 (0.05, 2.82)
Anti-Smith	1 (7.1%)	35 (17.2%)	0.4745	0.37 (0.05, 2.92)
Anti-dsDNA	6 (42.9%)	126 (62.1%)	0.1679	0.46 (0.15, 1.37)
RVVT	2 (14.3%)	69 (34.0%)	0.1525	0.32 (0.07, 1.49)
Anticardiolipin	9 (64.3%)	124 (61.1%)	1.0000	1.15 (0.37, 3.55)
Coombs	1 (7.1%)	33 (16.3%)	0.7021	0.40 (0.05, 3.13)

N/C=odds ratio was not calculated due to zero cell frequencies

Of note, medium/high titer anti-RB antibodies were never found in patients with proteinuria (p=0.0028). We next constructed a multi-variate model for proteinuria.

Table 2. Anti-RB antibodies Remain Negatively associated in a Multi-variate Model for Proteinuria

Variables	OR (95% CI)	p-value
Anti-RB	0.112 (0, 0.558)	0.016
Gender (Female)	0.417 (0.172, 0.999)	0.0498
Ethnicity (Caucasian)	0.288 (0.06, 1.144)	0.0833
Anti-dsDNA	1.806 (0.873, 3.808)	0.1192
Anti-Sm	1.273 (0.505, 3.154)	0.7127
Low complement	2.111 (1.04, 4.377)	0.0377

Conclusion: Anti-RB antibodies are a novel specificity not previously described in SLE. These antibodies are strongly negatively associated with lupus nephritis, even in multivariate models that include other variables (female gender, Caucasian ethnicity, anti-dsDNA, anti-Sm, and low complement). Intriguingly, anti-RB antibodies are positively associated with stroke in SLE. Additional studies are warranted to understand the mechanism of this finding.

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Abstract Number: 727

Increased Risk of Coronary Artery Disease Among Patients with Class III Lupus Nephritis: A Retrospective Study of Patients at the University of North Carolina at Chapel Hill

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Table 1. Odds Ratios and 95% CI of Coronary Artery Disease by Lupus Nephritis Class

LN class categories (n)*	OR (95% CI)
<i>Demographic + CAD + LN factors model with all classes**</i>	
Class 2 (n = 4)	2.90 (0.71, 11.9)
Class 3 (n = 18)	2.00 (0.98, 4.06)
Class 4 (n = 153)	1.31 (0.72, 2.37)
Class 5 (n = 97)	1.41 (0.75, 2.65)
Class 6 (n = 5)	2.76 (0.32, 23.8)
Classes 3 and 5 (n = 67)	2.45 (1.22, 4.90)
Classes 4 and 5 (n = 53)	1.58 (0.67, 3.76)
Classes 3 and 4 (n = 8)	0.86 (0.56, 26.5)
<i>Demographic + CAD + LN factors model with combined class III*</i>	
Any class 3 involvement (n=143)	2.35 (1.44, 3.86)
Other class involvement (n=333)	1.45 (0.87, 2.16)

* Three categories had n=1 and one category had n=0, however none of these patients had CAD. For these reasons, these subjects were not included in this analysis (n=9). 123 patients were missing LN class information.

** Adjusted for: **age, sex, 5-level race-ethnicity, HTN, DLP, DM, smoking history, steroid use, DMARDs use**. Model covariates—covariates in bold were independently significant with CAD at 0.05.

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Patients with systemic lupus erythematosus (SLE) are at an increased risk for developing coronary artery disease (CAD) compared to their cohorts without lupus. There have been several studies published that suggest that the presence of lupus nephritis (LN) is independently associated with CAD. However, none of these studies have looked at this association by class of LN. The purpose of our study was to define the characteristics of patients with SLE seen at the University of North Carolina Hospitals (UNCH); assess whether the presence of LN is independently associated with CAD; and evaluate whether this association varies according to specific LN classes.

Methods: A retrospective cross-sectional analysis was performed using medical records of patients 18 years and older with SLE at UNCH from April 4, 2014 to December 31, 2017. Subjects were identified using ICD-9 and ICD-10 codes specific for SLE. LN class was defined by ISN/RPS classification and determined based on review of renal biopsy and clinic notes. CAD was the outcome of interest and was defined by ICD codes for unstable angina, ST segment elevation myocardial infarction (STEMI), or non-STEMI. To determine the association between LN and CAD among SLE patients, logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI).

Results: The sample consisted of 3732 patients, 12% men with a mean (standard deviation) age of 48 (15.2) years; 43% White, 38% Black. Seventy percent had hypertension (HTN), 42% had dyslipidemia (DLP), 23% had diabetes mellitus (DM), and 38% had a history of smoking. Sixteen percent had LN (n=598) and 14% had CAD. When adjusting for age, sex, race/ethnicity, HTN, DLP, DM, smoking, steroid use, and disease-modifying antirheumatic drugs (DMARDs) use, the odds of having CAD were significantly higher for SLE patients with LN compared to patients without LN [OR 1.58, 95% CI (1.18, 2.14)]. In the LN analyses (Table 1), combined class III and V was significantly associated with CAD and class III alone was strongly associated with CAD. In several statistical models, class III was either strongly or significantly associated with increased risk of CAD. To better study the relationship between class III LN and CAD, all subjects with evidence of class III LN either alone or in combination were combined and the odds of CAD assessed. In this analysis any class III involvement was significantly associated with CAD compared to subjects without LN.

Conclusion: The results of our study confirm the findings of previous studies that LN is significantly associated with CAD after controlling for demographic, CAD, and lupus-specific factors. Ours is the first to study this association by LN class. We have shown that there may be an unexplored association between class III LN and CAD. We believe that our study reveals a critical area of further investigation and potential clinical intervention.

Disclosure: E. Y. Sun, None; C. Alvarez, None; S. Z. Sheikh, None.

A Higher Activity Index at Initial Renal Biopsy Is Associated with Rapid Progression to Renal Failure in Patients with Refractory Lupus Nephritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Lupus nephritis (LN) is a major cause of morbidity and mortality affecting ~50% of systemic lupus erythematosus (SLE) patients. Up to 30% of patients with LN progress to end stage renal disease (ESRD). Blacks and Hispanics develop LN earlier and have worse prognosis compared with whites. It remains controversial whether a higher activity index (AI) at the initial renal biopsy correlates with poor renal outcomes. We sought to investigate the association between AI and progression to renal failure in refractory LN patients of predominantly black and Hispanic backgrounds.

Methods: This study included sixty-one SLE patients meeting 1997 SLE ACR classification criteria and followed at the Columbia University Lupus Center, with a first renal biopsy performed between 1994 and 2015, and at least one subsequent biopsy due to refractory disease. Demographics, clinical, laboratory, and histopathologic characteristics were ascertained. Renal failure was defined as ESRD requiring renal replacement therapy (dialysis or transplant). Logistic regression models were constructed using STATA/SE 13.0 to evaluate for predictors of progression to renal failure within 5 years.

Results: Of the 61 patients, 51 (84%) were female, 26 (43%) Hispanic, and 18 (30%) black. The mean age at SLE diagnosis was 26 ± 12 years (Table 1). Twenty-two patients (36%) progressed to renal failure. Fibrinoid necrosis on first renal biopsy was associated with renal failure in unadjusted [OR 4.13 (CI 1.21- 14.05), $p=0.024$] and multivariate analyses (adjusting for age, sex, race, and serum creatinine at time of first biopsy) [OR 4.21 (CI 1.18 – 15.05), $p=0.027$]. Among the 22 patients with renal failure, 11 progressed to renal failure in less than 5 years and the median time from first renal biopsy to renal failure was 4.8 years (3.5-7.9). AI on the first renal biopsy significantly predicted progression to renal failure within 5 years in unadjusted [OR 1.24 (CI 1.01- 1.51), $p=0.038$] and multivariate analyses (adjusting for age, sex, race, and serum creatinine at time of first biopsy) [OR 1.26 (CI 1.004 – 1.58), $p=0.046$]. Chronicity index was not significantly associated with rapid progression to renal failure.

Conclusion: In a predominantly Hispanic and black cohort of refractory LN patients, 36% progressed to renal failure with half of them progressing in less than 5 years. AI on the first renal biopsy was an independent predictor of faster progression to renal failure and should prompt aggressive therapy.

Table 1. Patient Characteristics

	SLE (n=61)*
<i>Demographics</i>	
Female	51 (84)
Age Lupus Diagnosis, years	26 ± 12
Age at First Renal Biopsy, years	29 ± 13
Race	
Hispanic	26 (43)
Black	18 (30)
White	9 (15)
Asian	4 (6)
Other	4 (6)
<i>Co-morbidities</i>	
Hypertension	22 (40)
Diabetes	3 (5)
Smoking	2 (4)
Congestive Heart Failure	2 (3)
<i>Progression</i>	
Renal Failure (Dialysis or Renal Transplant)	22 (36)
Serum Creatinine (sCr) > 1.4 mg/dL	32 (53)
Renal Failure or sCr>1.4 mg/dL	34 (56)

Table . (Cont'd)

Table 1. Patient Characteristics	SLE (n=61)*
Time to Renal Failure, years	4.8 (3.5 – 7.9)
Characteristics at 1 st Renal Biopsy	
Proteinuria Prot:Cr (gm)	2.3 (1.4 – 4.4)
Serum Cr (mg/dL)	0.9 (0.7 – 1.4)
C3	56 (38 – 82)
C4	10 (6 – 12)
ds-DNA antibody titer	419 (100 – 2200)
Activity Index	8 (4 – 13)
Fibrinoid Necrosis	15 (25)
Number of Crescents	5 ± 10
Wire Loop	13 (22)
Chronicity Index	2 (0 – 3)
Lupus Nephritis Class	
II	4 (6.6)
III	6 (9.8)
IV	15 (24.6)
V	2 (3.3)
III/V	17 (27.9)
IV/V	17 (27.9)

* Reported as mean ± standard deviation, median (interquartile range) or number (% total). C3 = Complement 3, C4 = Complement 4, ds-DNA = double stranded DNA, ESRD = End Stage Renal Disease, Prot:Cr = protein to creatinine ratio, Renal Failure = end stage renal disease or transplant

Disclosure: S. Wang, None; S. Tanner, None; T. Kapoor, None; T. Perez, None; V. D. D'Agati, None; A. Askanase, None; R. Winchester, None; L. Geraldino-Pardilla, None.

Abstract Number: 729

Atherosclerotic Vascular Events in SLE – an Evolving Story

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Atherosclerotic vascular events(AVEs) are a major cause of mortality and morbidity in systemic lupus erythematosus (SLE) with a prevalence of 8-12%. We aimed to determine the changing pattern of AVE occurrence over the decades and to discern the effect of change in management of both classic risk factors for AVE and SLE.

Methods: Inception patients who entered the Lupus Clinic between 1975 and 1987 and followed to 1992 (Cohort 1) and between 1999 and 2011 and followed to 2016 (Cohort 2) were studied. AVEs (MI, angina, congestive heart failure, pace maker insertion, transient ischemic attack, stroke), attributed to atherosclerosis, and occurring during the 17 years, were identified. Lupus disease activity and therapy as well as hypertension, hypercholesterolemia, hyperglycemia and smoking were assessed. Analysis included descriptive statistics on baseline characteristics, traditional risk factors over the follow up, outcome rates by each 100 person years; Kaplan-Meier cumulative AVE curves, as well as competing risk Cox models adjusted by Inverse Probability Weights (IPW).

Results: There were 234 patients in Cohort 1 and 262 in Cohort 2. At enrollment the two cohorts were similar other than a greater number of Caucasians in Cohort 1 and more use of antimalarials and immunosuppressives in Cohort 2. Cohort 2 patients were more often treated with anti-hypertensives, lipid lowering therapy and smoking cessation and more often used antimalarials and immunosuppressives during the years of follow-up. 28(12%) of patients in Cohort 1 had an AVE compared with 10 of 262 (3.8%) in Cohort 2. The rate per 100 patient-years of follow-up was 1.9 in Cohort 1 and 0.44 in Cohort 2 (P < 0.0001) (Table). Percent of time with normal risk factors over the 17 year period was better in Cohort 2 (Table). The hazard ratio from IPW weighted model is 0.38 (95%CI: 0.22, 0.66) comparing cohort 2 to Cohort 1, a reduction of 62% in the risk for AVE in Cohort 2 (p = 0.0007).

Conclusion: The incidence of AVE in SLE in the modern era has declined in large part due to more effective management of classic coronary artery disease risk factors and SLE disease activity and treatment.

Table: Outcomes and management of risk factors and disease activity in SLE

Variable	Cohort 1 1975 - 1987	Cohort 2 1999 - 2011	P values
Number of patients	234	262	NA
Outcomes			
Follow-up time	6.5 ± 4.8 1462.0	8.3 ± 4.7 2288	
Person-years of FU			
Number of AVEs	28 (12.0%)	10 (3.8%)	0.001
Years from enrolment to AVE	3.8±4.3	5.9±4.2	NS
Incidence of AVE per 100/patient years	1.9	0.44	< 0.0001
Classic Risk Factors			
Percent years with Normal BP	72.0%	86.7%	0.0001
Percent years with Normal Cholesterol	39.7%	72.3%	0.0001
Percent years with Normal glucose	84.8%	93.2%	0.0001
Percent of years Smoked	24.7%	11.3%	0.0001
Disease Related Factors			
AMS within 5 years of enrolment	5.7±5.2	4.5±3.4	0.003
Alive at end of 17 years of follow-up	183 (78.2%)	247 (94.3%)	< 0.001

Disclosure: M. Urowitz, None; J. Su, None; D. D. Gladman, None.

Abstract Number: 730

Accrual of Atherosclerotic Vascular Events over 10 Years in a Multicentre Inception SLE Cohort

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: The prevalence of atherosclerotic vascular events (AVE) in published literature of an inception cohort with SLE is 10%. We aimed to investigate the annual occurrence and the associated factors of AVE in a multinational multiethnic inception cohort of patients with SLE.

Methods: A large 33-centre multinational inception cohort of SLE patients was followed yearly according to a standardized protocol between 2000-2018. Patients entered the cohort within 15 months of SLE diagnosis (≥4 ACR criteria). Patients followed for at least 10 years were identified. AVEs are described and attributed on a specialized form. Diagnosis of AVE is confirmed using standard clinical criteria, relevant laboratory data and imaging. Attribution to atherosclerosis (AS) is made on the basis of SLE being inactive at the time of the event, and/or the presence of typical AS changes on imaging or pathology and/or evidence of AS elsewhere. Analysis included descriptive statistics, rate of AVE's per 100 patient-years of follow-up and univariable and multivariable models.

Results: Of the 1847 patients enrolled in the cohort, 659 were followed for a minimum of 10 years (90.1% female, 46.3% Caucasian, 14.0% Black, 17.9% Asian, 18.4% Hispanic and 3.5% other). At enrolment mean age was 33.68 ± 12.75 years and SLEDAI-2K 5.75 ± 5.74. Disease duration at enrolment was 5.55 ± 4.21 months. The prevalence of AVEs, increases over time and is illustrated in table 1. The rate of AVEs per 100-patient years was 0.34. This was similar to the rate found in the entire cohort (N=1847) of 0.35. Associated univariate risk factors for AVE were older age at enrolment, male sex, Caucasian ethnicity, smoking, hypertension, and high cholesterol (Table 2). In multivariable analyses, associated risk factors for AVE were older age at enrolment [hazard ratio and 95% confidence interval [HR (95%CI)] [1.09 (1.06, 1.12)], smoking [1.03 (1.00, 1.06)] and steroid use [4.74 (1.08, 20.88)].

Conclusion: The prevalence of AVE in this study is much lower compared to previously published data. This may be due to more judicious use of glucocorticoids and improvements in treatment of cardiac risk factors. Although only a small number of classic risk factors showed positive associations in multivariable analysis all risk factors should be closely monitored and treated as they are in the general population.

Table 1. Cumulative annual prevalence of AVEs over time (n=659)

Follow-up	AVE
1	3 (0.46%)
2	4 (0.6 %)
3	8 (1.2%)
4	9 (1.3%)
5	11 (1.7%)
6	11 (1.7%)
7	13 (1.9%)
8	15 (2.3%)
9	16 (2.4%)
≥10	28 (4.3%)

Table 2. Univariate analysis of associated factors for AVE

Predictor	Hazard Ratio (95% CI)	p value
Age at enrolment (mean ± SD)	1.09 (10.6, 1.12)	<0.001
Gender (F)	0.24 (0.10, 0.55)	<0.001
Caucasian vs. non-Caucasian	3.81 (1.52, 9.54)	0.004
Follow up years from enrolment to last visit	0.81 (0.65, 1.01)	0.065
Smokers (ever)	2.47 (1.11, 5.49)	0.027
Smoking years *	1.06 (1.04, 1.09)	<0.001
Hypertension*	3.65 (1.09, 12.19)	0.036
Hypertensive years*	1.03 (0.89, 1.20)	0.652
High cholesterol*	8.99 (1.22, 66.38)	0.031
Years with high cholesterol*	1.20 (1.03, 1.39)	0.019
High glucose*	1.68 (0.77, 3.68)	0.196
Years with high glucose*	1.09 (0.78, 1.51)	0.632
Glucocorticoid treatment ever	1.85 (0.82, 4.19)	0.140
Positive anticardiolipin or Lupus anticoagulant*	2.21 (0.52, 9.36)	0.283
Antimalarial treatment ever	0.46 (0.18, 1.14)	0.093
Immunosuppressive treatment ever	0.90 (0.41, 1.98)	0.789

* within 10 years of diagnosis

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Abstract Number: 731

Clinical Characteristics and Neurophysiological Patterns of Peripheral Neuropathies in Patients with Systemic Lupus Erythematosus: A Single Center Experience

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: The prevalence of peripheral neurological manifestations in Systemic Lupus Erythematosus (SLE) ranges between 5% and 27% and are a major cause of morbidity. The aim of this study is to compare clinical characteristics and neurophysiologic patterns of peripheral neuropathies (PNP) in patients with SLE.

Methods: A retrospective study was performed. We included patients with SLE (SLICC 2012 criteria), who presented a PNP associated to SLE according to ACR 1999 nomenclature, since January 2015 to December 2017. Patients were classified according to the neurophysiologic pattern by the Neuromuscular Clinic Disorders at our Institute in 3 groups: 1. Sensory or sensory motor axonal neuropathy (ANP). 2. Mononeuropathy single or multiplex (MNP), and 3. Demyelinating neuropathy (DNP). The medical records were reviewed by an expert rheumatologist. Demographic characteristics: gender, age, Body Mass Index (BMI), and comorbidities (Diabetes Mellitus [DM] and Hypertension [HT]) were compared. Lupus characteristics: SLICC criteria, time between SLE diagnosis and PNP, ACR / 2012 criteria, disease activity (SLEDAI-2K),

cumulative damage (ACR/SLICC-DI), and treatment were compared between the PNP groups. One year after the event, disease activity, cumulative damage, treatment, and a new neurophysiologic study performed, and death was reviewed. Statistical analysis: Continuous variables were compared using Mann-Whitney U, categorical variables were compared using Chi-squared test and Fisher exact test as appropriate. Kruskal-Wallis test for multiple comparisons.

Results: Forty one PNP were included, 17 (41.5%) ANP, 16 (39%) MNP, and 8 (19.5%) DNP. Patients with ANP had lower BMI than MNP and DNP ($p < 0.05$). Eleven patients had a comorbidity, DM in 3 (7.31%) and HT in 9 (21.9%). No difference was found between age, sex and time between SLE diagnosis and PNP. Patients with DNP presented more cutaneous manifestations (alopecia and chronic cutaneous lupus) compared with MNP (50% vs 12.5%, $p < 0.046$; 25% vs 0%, $p < 0.037$, respectively). Patients with MNP had more synovitis compared with ANP (100% vs 76.5%, $p < 0.038$). Disease activity was similar between the groups, the median SLEDAI 2-K was 6 (IQR 2.5-12.5). However, renal and pleuritis manifestations were more frequently present in the DNP group comparing with MNP and ANP ($p < 0.05$). Cumulative damage was similar between the 3 groups, the median SLICC-DI was 0 (IQR 0-1). Pulses of methylprednisolone, cyclophosphamide, and higher doses of prednisone were used in the MNP and DNP than in the ANP group ($p < 0.05$). One year after, 100% of patients were alive, SLEDAI-2K and SLICC-DI scores were similar between groups. DNP was more frequently revalued with a new neurophysiologic study than the other groups ($p < 0.05$).

Conclusion: ANP were the most frequent PNP. Patients with PNP have moderate disease activity at the time of presenting the PNP. The DNP and MNP were considered more severe and received more aggressive treatment than the ANP.

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Abstract Number: 732

Impact of Disease Course on Atherosclerotic Vascular Events, Osteoporosis and Osteonecrosis in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: We have shown that disease course over time in systemic lupus erythematosus (SLE) follows three distinct patterns (prolonged remission, relapsing remitting and persistently active). The impact of these patterns on the development of specific co-morbidities, such as atherosclerotic vascular events (AVEs), osteoporosis and osteonecrosis is not known. The aim of the present study was to assess the incidence of such co-morbidities in lupus patients in the long term.

Methods: The inception patients of our long-term longitudinal cohort (enrolled within 18 months of diagnosis), with at least 10 years of follow-up and no time interval >18 months between consecutive visits, were investigated. Prolonged remission (PR) was defined as a clinical SLEDAI-2K=0 [serology (anti-dsDNA antibodies and C3/C4 levels) excluded], achieved within five years since enrolment and maintained for ≥ 10 years after that. Relapsing-remitting (RR) pattern was defined based on ≥ 2 remission periods (one remission period equals two consecutive visits with a clinical SLEDAI-2K=0), while patients with no remission were categorized as persistently active (PA). Incidence rates for AVEs (angina, myocardial infarction, re-vascularization procedure, transient ischemic attack, stroke, peripheral vascular disease), osteoporosis (according to the WHO definition) and osteonecrosis (confirmed radiologically) were calculated at 10 years and at the end of follow-up (median 17.5 years).

Results: Of 267 patients who fulfilled the inclusion criteria, 27 (10.1%) achieved PR, 180 (67.4%) were RR and 25 (9.4%) PA. At enrollment, there were no significant differences in demographic, clinical, immunological and therapeutic characteristics among the groups. At 10 years, PA patients had received significantly more glucocorticosteroids [39.4 ± 24.3 g vs. 16.6 ± 10.7 g and 27.3 ± 18.4 g for the PR and RR groups, $p < 0.001$]. The incidence rates of AVEs, osteoporosis and osteonecrosis at 10 years and for the entire duration of follow up are given in Table 1.

Table 1. Incidence rates (/100 patient-years) of AVEs, osteoporosis and osteonecrosis in all patients

	PR (n=27)	RR (n=180)	PA (n=25)	<i>p</i>
Age at enrolment (mean±SD)	39.2 ± 14.1	35.2 ± 13.4	37 ± 13.9	0.142
At 10 years				
AVEs (incidence, n, %)	0	2.7	4.3	0.002
Osteoporosis (incidence, n, %)	0.4	7.6	8.5	<0.001
Osteonecrosis (incidence, n, %)	8.5	10.3	12.4	0.142
At the end of follow-up				
AVEs	0.75	6.4	8	<0.001
Osteoporosis	6.6	14.1	12.3	0.004
Osteonecrosis	10.7	16.5	18	0.001

P value from ANOVA (Analysis of Variance) for age and Cochran-Armitage trend test for all rates (between PR and the other groups). No differences were observed between the RR and PA groups.

Conclusion: Disease course had a significant impact on the rates of atherosclerotic vascular events, osteoporosis and osteonecrosis over time. Patients who had achieved prolonged remission developed significantly fewer such co-morbidities whereas the differences between the RR and PA patients were not statistically significant.

Disclosure: K. Tselios, None; D. D. Gladman, None; Z. Touma, None; J. Su, None; N. Anderson, None; M. Urowitz, None.

Abstract Number: 733

Advanced Chronic Kidney Disease in Lupus Nephritis: Factors Leading to Progression

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Advanced chronic kidney disease (CKD) carries an increased risk for progression to end-stage renal disease (ESRD) and renal replacement therapy. However, the rate of progression and the predictors that drive the decline of renal function in lupus nephritis (LN) are not known. The aim of the present study is to define such factors in patients with LN and advanced CKD.

Methods: Patients with advanced LN-related CKD for two consecutive clinic visits were retrieved from our long-term longitudinal lupus cohort. Advanced CKD was defined according to the Kidney Disease Improving Global Outcomes as CKD stage 3b (eGFR=30-44ml/min/1.73m²) and stage 4 (eGFR=15-29ml/min/1.73m²), while ESRD was defined as eGFR<15ml/min/1.73m² or initiation of dialysis. All individuals were followed until the progression to ESRD or the last visit and were divided into two groups (“progressors” and “non-progressors”). Demographic, clinical, immunological and therapeutic variables were compared at baseline (the second visit of advanced CKD). Multivariable Cox regression analysis was performed for the identification of predictors for transition to ESRD. Statistical analysis was performed with SAS 9.4; *p*<0.05 was considered significant.

Results: One hundred eighteen patients (74 with CKD 3b and 44 with CKD 4) were included. Mean time from LN to advanced CKD was 5.6 years. There were no differences between groups at baseline, concerning demographic, clinical and immunological variables. Patients with CKD 4 more often had a proliferative LN (class III or IV) (50% vs. 29.7%, *p*=0.053). Rates of and time to progression are shown in Table 1.

Table 1. Rates and time to progression for all patients

Variable	CKD 3b (n=74)	CKD 4 (n=44)
Age at CKD	44.7±13.4	40.8±13.6
Progression to ESRD (% , n)	5.4% (4)	56.8% (25)
Time to ESRD (y, median)	4.5	3.1
Progression to CKD 4 (% , n)	21.6% (16)	Not applicable
Time to progression to CKD 4 (y, median)	4.8	Not applicable

Patients who did not progress (n=73, 61.9%) had a mean follow-up of 5.8 years (range 0-26.7). Their eGFR remained unaltered (from a median of 38.6 at baseline to 37.1ml/min/1.73m² at the last visit). Multivariable analysis for predictors of progression to ESRD is shown in Table 2.

Table 2. Predictors for transition to ESRD from CKD stages 3b and 4

	HR	Lower 95%CI	Higher 95%CI	p
Anti-dsDNA (+) at baseline	5.28	1.91	14.57	0.001
Glucocorticosteroids at baseline	4.17	1.01	17.15	0.048
Cumulative GCS dose (from LN to CKD)	1.01	1.00	1.02	0.04
Treated with IS (MMF or AZA) at baseline	0.21	0.07	0.60	0.004
CKD 4 (compared to CKD 3b)	27.5	2.9	96.3	<0.0001

GCS: glucocorticosteroids, IS: immunosuppressives, MMF: mycophenolate mofetil, AZA: azathioprine

Conclusion: Only 24.6% of our patients developed ESRD, while another 21.6% of the CKD 3b patients progressed to CKD 4. Risk factors for ESRD included abnormal anti-dsDNA antibodies at the time of CKD as well as treatment with glucocorticosteroids and higher cumulative dose (for the treatment of LN). Immunosuppressive treatment at the time of CKD was protective. Renal function remained stable in approximately 73% of the CKD 3b and 43% of the CKD 4 patients over 6 years of follow-up.

Disclosure: K. Tselios, None; D. D. Gladman, Abbvie, Amgen, BMS, Celgene, Eli Lilly and Company, Janssen, Novartis, Pfizer, UCB, 5, Abbvie, Amgen, Celgene, Janssen, Novartis, Pfizer and UCB, 2; J. Su, None; M. Urowitz, None.

Abstract Number: 734

The Role of Micro-RNA 142-3p Expression in Lupus Nephritis in an Egyptian Cohort

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Background/Purpose: Micro-RNAs play an important role in regulating gene expression at the posttranscriptional level. Recent data have shown that microRNAs are critical for the development and function of immune system, both innate and adaptive immunity.^(1,2) MicroRNAs are differentially expressed in patients with systemic lupus erythematosus (SLE), especially in association with lupus nephritis.^(3,4) The heterogeneity of patient ethnicity and variety in detection method may in part explain some of the discrepancies of positive micro-RNA list in SLE patients in different studies. Testing serum or urine microRNA expression would offer a promising tool to illustrate the pathogenesis of SLE, provide novel biomarkers and potential therapeutic option.⁽⁵⁾

Methods: Expression levels of micro-RNA-142-3p extracted from peripheral blood mono-nuclear cells determined using quantitative reverse transcription–polymerase chain reaction assay. A total of 90 plasma samples were obtained from 30 SLE patients without clinical and laboratory evidence of lupus nephritis, 30 SLE patients with lupus nephritis and 30 healthy control subjects.

Results: The expression of micro-RNA-142-3p in SLE patients was significantly lower than the expression in normal healthy control, p<0.001. In addition the Roc curve of micro-RNA-142-3p showed that micro-RNA-142-3p expression levels can significantly discriminate between lupus patients with and without lupus nephritis at a cut off level $\leq 5.7 \times 10^{-6}$ with a sensitivity of 83.33% and specificity of 90%. We also found a significant correlation between micro-RNA-142-3p expression levels and the pathological activity index of renal biopsy, while there was no significant correlation between micro-RNA-142-3p expression level and the pathological chronicity index.

Conclusion: The expression level of micro-RNA-142-3p could be considered a diagnostic marker of SLE. Also, the expression level of micro-RNA-142-3p could be considered a potential biomarker for recognition of renal involvement in SLE patients.

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Disclosure: M. Elkhaila, None; M. Zehairy, None; M. Tayel, None; A. Elkeriaie, None; D. Elkaffash, None; N. Baddour, None.

Abstract Number: 735

Serum Albumin at One Year Predicts Long-Term Renal Outcome

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Lupus nephritis remains a major cause of morbidity/mortality in SLE. Our cohort has shown that 20% of SLE patients with lupus nephritis onset in the first year will have end-stage renal disease (ESRD) by year ten. Population studies have shown no improvement in lupus nephritis outcomes in the last decades. Clinical trials of lupus nephritis cannot address long-term renal outcomes. We addressed whether serum albumin at 12 months after renal biopsy predicted long-term renal outcome.

Methods: 87 patients with biopsy-proven lupus nephritis were included in the analyses. Of the 87 patients, 79 (91%) were female, 49 (56%) were African American, 24 (28%) were Caucasian, and 14 (16%) were “other”. At the time of biopsy, 33 (38%) were under 30 years of age, 38 (44%) were from 30-44, and 16 were 45 years of age or older. The median age was 32.9. The median values of albumin at biopsy and 1-year post were 3.7 and 3.9 respectively. ISN/IRP class was 24% III, 23% IV, 23% V, and 30% mixed. Albumin levels were classified as low (<3.4g/dL), medium(3.5-4.3g/dL) and high (>4.3g/dL).Kaplan-Meier curves were plotted to assess the association between albumin levels and risk of developing renal event. Renal outcomes were 1 ESRD, 6 renal insufficiency, and 14 doubling creatinine.

Results: Serum albumin at 12 months post renal biopsy was associated with poor renal outcomes during follow-up ($p = 0.0098$). Among those with low serum albumin one year after biopsy, an estimated 43% will progress to renal failure, renal insufficiency, or a doubling of creatinine within 5 years (95% confidence interval 16%-71%). In contrast, among those with high serum albumin, an estimated 13% will progress (95% CI 1%-29%).

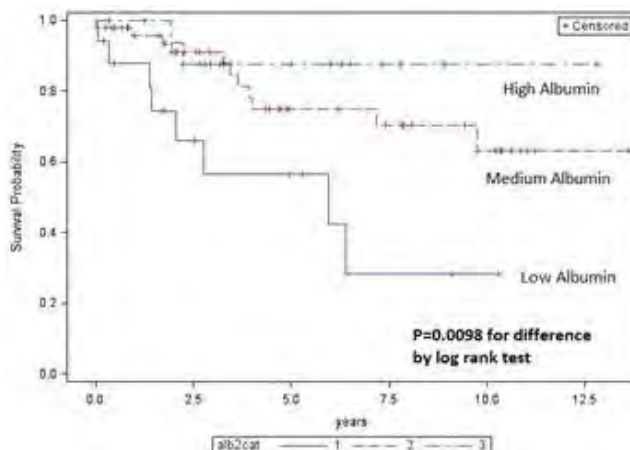


Figure 1: Plot of the probability of remaining renal-event free, by albumin levels one year after biopsy

	SLE cohort (N=76,354)				LN cohort (N=11,068)				IRR compared with SLE	
	Event	PT	Incidence per 100PY	95% CI	Event	PT	Incidence per 100PY	95% CI	Incidence rate ratio	95% CI
Herpes zoster	4,784	763,208	1.6	1.6 1.7	955	17,557	2.4	2.4 2.7	1.6	1.5 1.7
Disseminated zoster	582	375,582	0.3	0.2 0.2	157	89,352	0.4	0.3 0.5	1.9	1.6 2.3

Conclusion: Serum albumin 12 months post biopsy predicted good renal outcome in a linear fashion. This surrogate for renal outcome is readily available from lupus nephritis randomized clinical trials (and from some large databases, as well). Serum albumin should be added to urine protein/crds validated surrogates for long-term renal outcome in lupus nephritis.

Disclosure: V. Domingues, None; D. Goldman, Merck & Co., Pfizer, 1; L. S. Magder, None; M. Petri, EMD Serono, 5, Exagen, 2, Janssen, 5, GSK, 5, AstraZeneca, 2, Inova Diagnostic, 5, Novartis, 5, Amgen Inc., 5, Decision Resources, 5, Medscape, 5, Eli Lilly and Co., 5, Quintiles, 5.

Abstract Number: 736

Herpes Zoster and Disseminated Zoster in Systemic Lupus Erythematosus and Lupus Nephritis: Incidence Rates in Real-World Claims Data

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Disseminated zoster is a highly morbid complication of varicella zoster reactivation (herpes zoster) that is typically associated with immunosuppression. Systemic lupus erythematosus (SLE) and lupus nephritis (LN) are associated with increased risk of herpes zoster [1,2] but rates of disseminated zoster in these populations have not been described. The objective of this study was to compare the rates of herpes zoster and disseminated zoster infections in patients with SLE and LN using population-based claims data.

Methods: We conducted a retrospective cohort study using the Truven Healthcare MarketScan® Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits database between 2000 and 2014. Patients with SLE (SLE cohort) and SLE and LN (LN cohort) were identified using modifications to validated algorithms using claims data [3,4]. All patients received medical care in the U.S. and had 6 months of continuous medical and drug coverage ± index date. End of study was the first of end of enrollment or end of database. Incident herpes zoster cases were identified using ICD-9 codes 053.xx. Incidence rate ratios (IRR) and 95% confidence intervals (CI) were calculated.

Results: SLE and LN cohorts included 76,354 and 11,068 patients, respectively. Mean age was 48.1 and mean enrollment duration was 6.3 years. For patients in the SLE cohort there were 4284 incident cases of herpes zoster, of which 582 (14%) were considered disseminated. The LN cohort had increased rates of herpes zoster (IRR 1.6, 95% CI 1.5 to 1.7) and disseminated zoster (IRR 1.9, 95% CI 1.6 to 2.3) compared with the SLE cohort (Table 1).

Conclusion: In this population-based analysis of claims data, the rate of herpes zoster in SLE was consistent with prior reports [1] and the presence of LN was associated with increased risk of herpes zoster and disseminated zoster compared with SLE. A substantial minority of herpes zoster cases were associated with dissemination. Further characterization of the relative contributions of age, immunosuppressive therapies, and disease factors is warranted.

1. Chakravarty EF et al. Lupus, 2013;22:238-44. 2. Chen D et al., Exp Ther Med, 2017;14:6222-8. 3. Chibnik LB et al. Lupus, 2010;19:741-3. 4. Arkema EV et al. BMJ open, 2016;6:e007769.

Disclosure: K. Belendiuk, Genentech, Inc., 3; Y. Ding, Genentech, Inc., 3; D. Chawla, Genentech, Inc., 3; M. Cascino, Genentech, Inc., 3.

Atherogenic Index of Plasma in Women with Systemic Lupus Erythematosus and Rheumatoid Arthritis: A 10-Year Potential Predictor of Cardiovascular Disease

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are characterized by an increased frequency of cardiovascular diseases (CVD). Early diagnosis of these complications can reduce morbidity and mortality. Atherogenic index of plasma (AIP) is a new parameter in assessing the CVD risk¹. Previous work supports the utility of AIP and demonstrates that it is more closely associated with CVD risk than individual cardio-metabolic factors. However, no research yet has evaluated the relationship between AIP and the long term CVD risk in SLE and RA patients. The purpose of this study was to investigate whether AIP is associated with long term CVD risk among women with SLE and RA and to further determine its predictive value.

Methods: This was a cross-sectional study of 59 SLE and 99 RA women diagnosed according to the ACR criterion and carried out in the rheumatology department. For each patient, long-term risk of CVD was calculated using the Framingham risk score (FRS); AIP was derived according to the logarithmic (triglycerides/high-density lipoproteins cholesterol). At the same time, clinical, and biochemical data were obtained and disease activities were calculated. The relationship between FRS as a dependent variable and the AIP as an independent one was examined using linear regression analysis.

Results: The mean age of the SLE patients was 36.7 ± 9.1 years and of the RA was 47.9 ± 8.8 years. The mean disease duration for SLE and RA was 5.2 ± 3.8 and 8.4 ± 7.8 years, respectively. The mean body mass index for both groups was over 27.8 kg/m^2 . Nearly 70% of SLE patients were using prednisone with a mean daily dose of 9.1 mg; 29% of RA patients were receiving prednisone with a mean daily dose of 5.1 mg. The mean FRS% in SLE was 4.8 ± 4.5 , while in RA women was 6.4 ± 5.6 . 8.6% of SLE and 23.2% of RA patients were at a moderate to high risk of CVD. In SLE, mean AIP was 0.02 ± 0.27 while in RA it was 0.00 ± 0.4 . Among SLE patients, AIP showed significant association with FRS ($r=0.45$; $p<0.01$), triglyceride ($r=0.46$; $p<0.01$) and mild positive association with disease activity score ($r=0.29$; $p=0.03$), while FRS was significantly linked to uric acid level ($r=0.49$; $p<0.01$). In RA, AIP was associated with FRS ($r=0.26$; $p=0.01$), waist circumference ($r=0.27$; $p<0.01$), triglyceride and total cholesterol ($r=0.66$, $p<0.01$ and $r=0.38$, $p<0.01$; respectively). Serum uric acid was significantly associated with both FRS ($r=0.43$; $p<0.01$) and AIP ($r=0.27$; $p<0.01$) in women with RA. In multivariate regression analysis, an independent relationship between AIP and risk of CVD in both SLE ($\beta=6.0$, 95% CI: 1.87–10.13; $p<0.01$) and in RA ($\beta=1.64$, 95% CI: -0.64–3.93; $p=0.01$) was detected. SUA remained significant CVD predictor in both SLE and RA ($p=0.03$ and $p=0.01$; respectively).

Conclusion: Higher atherogenic index of plasma was potentially and strongly associated with risk of long term CVD risk among women with SLE and RA patients. AIP level can be a good marker for the CVD risk, thus control and monitor of AIP can improve the outcome in these populations.

Reference: 1- Joob B, Wiwanitkit V. Atherogenic Index of Plasma for the Assessment of Cardiovascular Risk Factors. *Annals of African Medicine*. 2017;16(3):148.

Disclosure: N. Hammam, None; T. A Gheita, None.

Two Clinical Phenotypes of Chinese SLE-PAH Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Pulmonary arterial hypertension (PAH) is a severe complication of systemic lupus erythematosus (SLE), which is the most common underlying disease of CTD associated PAH. However its pathogenesis is still unknown. Both inflammatory mechanisms and endothelial dysfunction are involved. According to the guidelines, immunosuppressive therapy and pulmonary vasodilators were two common strategies in our clinical practice, but the responses to two therapies vary in different reports, indicating different underlying mechanisms in different patients. In order to identify homogeneous groups of SLE-PAH patients, we conducted this retrospective study.

Methods: From 2011 to 2016 in Ren Ji Hospital, SLE-PAH patients were identified based on right heart catheterization (mPAP \geq 25 mmHg at rest, PAWP $<$ 15 mmHg and PVR $>$ 3 WU) or echocardiography (peak tricuspid regurgitation velocity (TRV) $>$ 3.4 m/s) excluding pulmonary hypertension due to left heart disease and pulmonary thrombosis. We distinguished two clusters according to multiple correspondence analysis and k-cluster analysis, which were defined as Vasculitic and Vasculopathic type. Kaplan-Meier survival curve of two clusters were made. Multivariate logistic regression was performed to identify predictors of clusters. Prediction model was established and ROC curve was made to find the optimal cut-off value.

Results: In a total of 108 SLE-PAH patients, two clusters with homogenous clinical features were identified. The Vasculitic Cluster were more likely to have pericarditis, LN, NPSLE, anemia, thrombocytopenia, as well as higher disease activity, and receiving higher doses of prednisone together with immunosuppressants, while the Vasculopathic type tended to have less systemic manifestations with lower disease activity, and were more likely given vasodilators in clinical practice. Overall, it seemed that the Vasculitic subtype was more severe with poorer outcome than the other subtype evidenced by the significantly higher mortality in survival curve (37.8% vs 18.3%, $p=0.026$) (Figure 1). Upon multivariate logistic regression, three predictors (SLEDAI $>$ 9, hypertension and early onset of PAH $<$ 2.99 years since SLE) were identified to distinguish Vasculitic SLE-PAH patients. Prediction model with these three factors were built, and ROC curve identified that score \geq 2 had a prediction rate of 89.5% with sensitivity of 91.9% and specificity of 94.4% (AUC 0.949, $p<0.0001$).

Conclusion: In this retrospective cohort study, two clusters with different prognosis were identified. The Vasculitic type had more systemic manifestation and higher disease activity as well as poorer outcome than the Vasculopathic type. The prediction model combining three factors established in our study might help stratify the patients and guide the therapy in clinical practice.

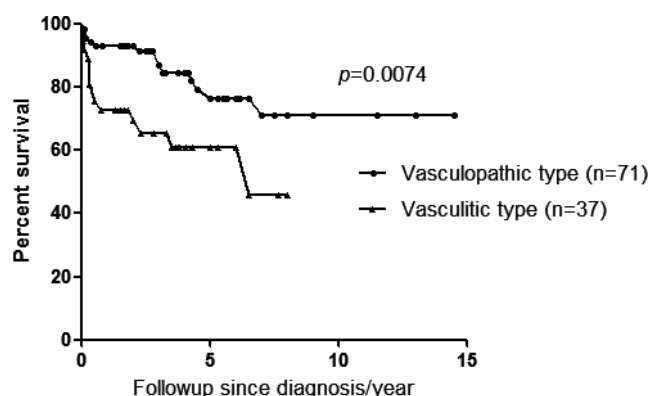


Figure 1. Survival Curve of 108 SLE-PAH in two distinct clusters.

Disclosure: F. Sun, None; W. Wu, None; L. Guo, None; Z. Chen, None; X. Wang, None; T. Li, None; S. Ye, None.

Urine and Plasma Soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1) Differentially Correlates with Renal and Non-Renal Systemic Lupus Erythematosus (SLE): A Prospective, Case-Control Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Elevated levels of sTREM-1 have been previously found in patients with SLE. A prospective, case-control, longitudinal study aimed to assess the value of urinary and plasma levels of sTREM-1 in evaluating disease activity in patients with active renal and non-renal SLE.

Methods: 15 patients with active renal lupus (ARL), 15 patients with active non-renal lupus (ANRL), and 30 patients with inactive lupus (IL), defined by baseline score of Safety of Estrogen in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) \geq or $<$ 6 and renal-SLEDAI \geq 4 or 0. Urine and plasma samples were collected and kept at -70°C until assayed for sTREM-1 levels using commercial ELISA. Urinary values were normalized for creatinine (Cr.) excretion. Plasma and urine samples of healthy individuals served as healthy control (HC).

Results: Compared to HC (urine: $n=13$; plasma: $n=72$), baseline mean urine sTREM-1 level (UsTREM-1) was significantly higher in ARL ($62.38 \pm 85.14 \text{ pg/mg Cr.}$ vs. $3.05 \pm 7.19 \text{ pg/mg Cr.}$, $p=0.0015$) but not in ANRL, whereas plasma sTREM-1 (PsTREM-1) was significantly higher in patients with ANRL ($361.47 \pm 187.79 \text{ pg/ml}$, 312.15 pg/ml vs. $228.76 \pm 85.23 \text{ pg/ml}$, $p=0.009$) and not in the ARL group. Moreover, UsTREM-1 level significantly discriminated between ALN and ANRL or IL ($p=0.0056$) as well as the ratio of urine-to-plasma sTREM-1 ($p=0.0083$), whereas PsTREM-1 was significantly higher in ANRL compared to ARL or IL ($p=0.014$). Baseline SELENA-SLEDAI score correlated with UsTREM-1 ($p=0.0005$) and PsTREM-1 ($p=0.006$) while renal-SLEDAI correlated only with UsTREM-1 ($p=0.013$). Elevated UsTREM-1 level positively correlated with higher ESR ($r=0.35$, $p=0.03$), serum anti-dsDNA antibody titer ($r=0.39$, $p=0.006$), SELENA-SLEDAI and renal-SLEDAI scores ($r=0.48$, $p=0.0005$ and $r=0.36$, $p=0.013$, respectively) and inversely correlated with lower serum C3 level ($r=-0.39$, $p=0.005$). Elevated PsTREM-1 level positively correlated with age ($r=0.25$, $p=0.005$), serum creatinine ($r=0.33$, $p=0.0006$), higher ESR ($r=0.4$, $p=0.007$), serum anti-dsDNA antibody ($r=0.59$, $p<0.0001$) and SELENA-SLEDAI score ($r=0.38$, $p=0.006$) but not with renal-SLEDAI score and serum C3 and C4 levels. Receiver operating characteristic (ROC) curves analysis of the area under the curve (AUC) displays that PsTREM-1 level differentiates between overall active SLE and IL: $\text{AUC} = 0.74$, $95\% \text{CI } 1.001 - 1.010$, $p=0.01$.

Conclusion: Our data suggest that UsTREM-1 level correlates with ARL while elevated PsTREM-1 correlates with ANRL. Urine and plasma sTREM-1 might be clinically used as a biomarker for the assessment of renal and non-renal disease activity in SLE. We suggest that renal innate immune activation and particularly TREM-1 play a role in the pathogenesis of lupus nephritis.

Disclosure: Y. Molad, None; M. Egbaria, None; A. Dortort-Lazar, None; E. Pokroy-Shapira, None; S. Oren, None; Y. Edel, None; V. Kliminski, None.

Can Monocyte Chemo-Attractant Protein-1 differentiate Different Histological Classes in Lupus Nephritis?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Lupus Nephritis one of the commonest manifestations of SLE. Despite being the gold standard in Lupus nephritis, renal biopsy is an invasive procedure with potential complications and difficult to repeat. Current treatment guidelines prioritize the histological class of lupus nephritis. Monocyte chemo-attractant Protein-1(MCP-1) a chemokine produced locally during active nephritis was shown in many previous studies as a promising biomarker for activity. This study investigates its usefulness to define histological classes.

Methods: This is a case-control study conducted at a tertiary care center in North India. Cases were patients of SLE satisfying the criteria for active lupus nephritis, defined as proteinuria > 1 gm/24 hours and/or active sediments in the form of hematuria [RBC > 5/hpf] or presence of cellular casts and undergoing kidney biopsy (n=36). Controls were patients of SLE without active LN (less than 500 mg/24 hours proteinuria and no active sediments. These were further divided into Control group I, those who had previously had lupus nephritis and were treated (n=11) and Control group II, those who never had nephritis (n=15)]. Urinary MCP-1 measurement was done using Sandwich ELISA kit. This was normalized for urinary creatinine excretion(pg/mg).

Results: Mean age in cases was 31.1 ± 10.2 years and in control-I was 34.6 ± 8.0 and control II was 36.3 ± 10.4 yrs respectively ($p=0.3$). Urinary MCP-1 values in cases (1214 ± 1467.1 pg/mg) were significantly higher compared to controls (184.5 ± 186.8 pg/mg, $p<0.001$). However, no significant difference was observed between control group I (170.5 ± 150.8) and control group II (194 ± 214 , $p=0.7$). Urinary MCP-1 levels showed significant correlation when compared with classical disease markers like 24-hour proteinuria, 24-hour PCR, Spot PCR and SLEDAI. A cut off value of MCP-1 of 339 pg/mg on ROC curve has sensitivity and specificity of 80% and 92% respectively for differentiating active from inactive nephritis. However, there was no significant difference of Urinary MCP-1 levels among different classes of nephritis ($p=0.593$) (Figure 1). Urinary MCP-1 levels did not show significant correlation with Renal activity index calculated on renal biopsy.

Conclusion: Urinary MCP-1 was not associated with different histological classes of lupus nephritis.

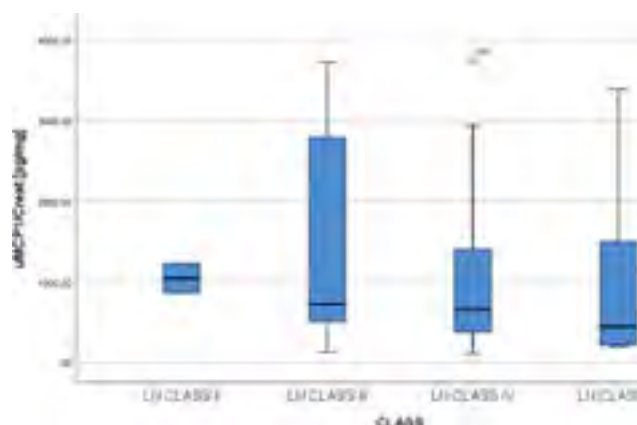


Figure 1: Box-plot depicting Urinary MCP-1 (normalized to urinary creatinine) across various histological classes. Box-plots show median and interquartile range, whiskers denote 1.5xIQR

Disclosure: V. Dhir, None; R. K. Gone, None; A. Sandhu, None; A. Sharma, None; S. Sharma, None; R. Nada, None; S. Jain, None; M. Rath, None.

Abstract Number: 741

Cardiovascular Risk Re-Classification Using Carotid Ultrasound in Systemic Lupus Erythematosus Patients Is Related to the Damage Produced By the Disease

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Systemic lupus erythematosus (SLE) is associated with an increased in the prevalence of atherosclerosis. Composite scores of cardiovascular risk factors in patients with SLE have been found to underestimate cardiovascular risk. Besides, ultrasound of the carotid arteries has been proposed as a reclassification risk tool in inflammatory diseases. The main purpose of our study was to analyze the impact of ultrasound carotid assessment in the cardiovascular risk stratification of patients with SLE.

Methods: This cross-sectional study encompassed 276 SLE patients. Lipid profile, SCORE risk calculation, and disease activity (SLEDAI), severity (Katz), and damage (SLICC) indexes were assessed. Carotid intima-media thickness (cIMT) and carotid plaques were determined through ultrasound evaluation. Reclassification of SCORE after ultrasound carotid assessment was performed. A multivariable regression analysis, adjusted for classic cardiovascular related factors, was performed to evaluate how risk reclassification is influenced by disease characteristics in SLE patients and to describe potential predictors of this risk reclassification.

Results: Patients had a mean \pm SD age of 51 ± 12 years. The median SLE disease duration was 18 ± 10 years and SLICC and Katz indexes were, respectively, 1 (interquartile range –IQR- 0-2) and 2 (IQR 1-4). Thirty-four percent of the patients were categorized as having no activity based on the SLEDAI index, while 31%, 17%, and 8% were classified, respectively, in the mild, moderate, and high or very high categories. According to the SCORE risk stratification system, 184 (67%) and 73 (27%) patients were respectively in low and moderate categories. Additionally, only 16 (6%) patients were considered in high or very high risk categories. However, after carotid ultrasound assessment, 37% (100) of the patients were considered to be in the very high risk category. Exactly, 64 patients, 43 in both the low and moderate category, moved into very high category. Patients that experienced reclassification compared to those that did not were older (48 ± 11 vs. 57 ± 9 years, $p=0.000$) and had more hypertension (31 vs 56 %, $p=0.000$). Gender, BMI, waist circumference and the presence of dyslipidemia, smoking or diabetes did not shown differences. Lipid profile disclosed no differences between reclassified or non reclassified subjects. Disease duration was related to reclassification after multivariable analysis (OR 1.04 [95% CI 1.00-1.07], $p=0.025$). Similarly, a SLICC higher or equal to 1 (OR 2.48 (95% CI 1-15-5.34), $p=0.020$) and *log* SLICC (OR 1.63 (1.01-2.64), $p=0.045$) disclosed statically significant relation to reclassification after multivariable adjustment. These relations were also found when SLICC was used without the cardiovascular item that its contains although in the case of *log* SLICC the significant was not completely found (OR 1.56 (95% CI 0.95-2.64), $p=0.077$).

Conclusion: Reclassification into very high SCORE category is frequent after carotid ultrasound assessment in SLE patients. This reclassification can be independently explain by the damage produced by the disease and makes candidates for more intensive preventive interventions to one out of every three patients evaluated.

Disclosure: J. C. Quevedo, None; I. Rúa-Figueroa, None; H. Sanchez-Perez, None; B. S. Tejera, None; D. V. G. AM, None; A. Gonzalez-Delgado, None; I. Ferraz-Amaro, None.

Abstract Number: 742

Moderate to Severe Depression in Patients with Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Depression is among the most common neuropsychiatric manifestations in SLE with a prevalence reported to be up to 75% in some studies. Depression in SLE patients has been shown to adversely affect health-related quality of life and increase work disability. The causes of depression in SLE are unclear and various sociodemographic and disease-specific factors have been identified. However, conflicting results have been reported in part because of methodologic issues and failure to account for all potentially important covariates. In this study, we examined the association of moderate to severe depression with socioeconomic status, disease activity, disease severity, treatment, and cognitive performance in patients with SLE.

Methods: Patients with SLE fulfilling the American College of Rheumatology criteria were recruited. All patients had detailed sociodemographic data collected and were evaluated for depression with the Beck Depression Inventory (BDI), for disease activity (SLEDAI-2K), SLE damage with the SLICC Damage Index (SLICC-DI), pain (10 cm visual analogue scale), and cognitive function by the Automated Neuropsychologic Assessment Metrics (ANAM), a symbol-based computerized testing program measuring multiple cognitive domains. Prednisone and immunosuppressive use as well as use of other potentially psychoactive medications were captured as well.

Results: In total, 99 patients were evaluated. Mean age was 46.4 (± 12.1) years with a female preponderance (93% vs 7% men). BDI score ranged from 1 to 52 (mean 17 ± 12). Moderately or severely depressed patients, defined by a BDI score ≥ 20 or BDI ≥ 29 respectively, comprised 31.3% of patients; of these 13.1% had moderate and 18.2% severe depression. Cognitive dysfunction was identified in 24.5%. Mean SLEDAI-2K scores were 5.1 (± 4.7) and mean SLICC-DI scores were 2.4 (± 2.1). Low annual income defined as $< \$20,000/\text{year}$ was reported by 37% of patients and mean pain severity was 3.5/10 (± 2.4). Using logistic regression, SLEDAI-2K scores and pain severity were found to be independently correlated with moderate to severe depression in patients with SLE (p-values of 0.0078 and < 0.0001 respectively). Low annual income showed a potential association (p=0.0902) and, in multiple linear regression using the actual BDI scores, was significantly associated (p=0.04). No independent associations were found between cognitive dysfunction, SLICC-DI, demographic or treatment characteristics (including prednisone) and depression in our group of SLE patients.

Conclusion: Patients' pain severity, disease activity as measured by SLEDAI-2K and low-income level are associated with the development of moderate to severe depression in patients with SLE. The first two of these are potentially modifiable.

Disclosure: N. Chalhoub, None; M. Luggen, None.

Abstract Number: 743

Outcome of Stroke in Patients with Systemic Lupus Erythematosus: A Nested Case-Control Study

Chi Chiu Mok, Lap Kiu Tsoi and Yat Pang Fu, Medicine, Tuen Mun Hospital, Hong Kong, Hong Kong

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: To evaluate the outcome of stroke in patients with systemic lupus erythematosus (SLE) in comparison with non-SLE patients.

Methods: Patients who fulfilled ≥ 4 SLICC/ACR criteria for SLE and had a history of cerebrovascular accident (stroke) were retrieved from our SLE database. The outcome of stroke in these patients was evaluated retrospectively and compared with a group of randomly selected age and gender matched non-SLE patients (in a 1:3 ratio) admitted to our stroke unit within the same time period. The type and pattern of stroke, atherosclerotic risk factors and previous history of stroke were compared between the two groups of patients. The primary outcome of interest was the 90-day functional outcome as assessed by the modified Rankin scale (mRS) (score 0-2 = functional independence; score 3-6 = functional dependence). Secondary outcomes included all-cause mortality, 30-day stroke mortality, stroke recurrence and stroke complications. Factors independently associated with a poor functional outcome (mRS 3-6) was studied by logistic regression.

Results: 40 SLE patients (age 53.7 ± 11.5 , 87.5% women) with stroke were identified (stroke prevalence 0.39/100 patient-year) and 120 non-SLE control patients (age 52.8 ± 14.8 , 87.5% women) with stroke were randomly selected. All were ethnic Chinese. The prevalence of atherosclerotic risk factors was similar between the two groups, except SLE patients had a higher atherogenic index (Log serum [triglyceride/HDL-cholesterol]). Ischemic stroke was more common in SLE than non-SLE patients (90% vs 63%; $p=0.001$). Among patients with ischemic stroke, SLE patients had more extensive infarction (defined as diffuse white matter lesions, multiple infarcts involving >1 major vascular territory or one single major vessel $>50\%$ involvement) than controls on CAT scan (69.4% vs 28%; $p<0.001$). Significantly more SLE patients had functional dependence (mRS score 3-6) at 90 days post-stroke than controls (32.5 vs 8.3 %; $p<0.001$; unadjusted OR 14.2). Logistic regression showed that SLE was an independent risk factor for a poor stroke outcome after adjustment for age, sex, history of stroke, various atherosclerotic risk factors and the type of stroke (ischemic vs hemorrhagic) (OR 10.1 [2.7–38.0]; $p=0.001$). In a subgroup of patients with ischemic stroke, SLE remained an independent factor for a poorer functional outcome after adjustment for the same covariates and the extent of stroke (OR 14.0 [2.0–96.2]; $p=0.007$). Although there was no significant difference in the 30-day stroke mortality between SLE and non-SLE patients (5% vs 2.5%; $p=0.43$), SLE patients had a higher incidence of post-stroke epilepsy (22.5% vs 3.3%; $p=0.001$). Upon a follow-up of 7.5 ± 5.2 years, SLE patients had a lower stroke recurrence free survival (59.5% vs 85.7%; $p<0.001$) and a higher rate of all-cause mortality (34.6% vs 15.1%; $p<0.001$).

Conclusion: Stroke in SLE patients is more likely to be ischemic in origin and more extensive than matched controls. Short-term functional outcome of stroke is poorer in SLE patients. Over 7.5 years, stroke recurrence, post-stroke epilepsy and all-cause mortality is significantly more frequent in SLE than non-SLE patients.

Disclosure: C. C. Mok, None; L. K. Tsoi, None; Y. P. Fu, None.

Abstract Number: 744

Association of PCSK9 Serum Levels with Lipid Metabolism Dysregulation, Activity/Damage Scores and Subclinical Atherosclerosis in SLE Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Cardiovascular disease is one of the major causes of morbidity and mortality in patients with systemic lupus erythematosus (SLE). SLE patients are characterized by a lipid metabolism dysregulation. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease that regulates cholesterol metabolism through low-density lipoprotein (LDL) receptor degradation. PCSK9 has been linked to cardiovascular risk (CVR) in general population. The purpose of this study is to examine whether PCSK9 levels are related to disease activity, damage and severity scores; abnormalities in the lipid profile; and the subclinical atherosclerosis that occur in SLE patients. If this were shown to be the case, PCSK9 would be a link between the disease and the lipid metabolism dysregulation that occurs in SLE patients

Methods: Cross-sectional study that encompasses 195 SLE patients. PCSK9 and lipoproteins serum concentrations were assessed. Activity (SLEDAI), severity (Katz) and damage (SLICC) index scores, and carotid ultrasound sonography were evaluated. A multivariable analysis, adjusted for standard CVR factors, was performed to evaluate the association of PCSK9 with SLE related dyslipidemia, subclinical atherosclerosis and activity/damage status

Results: In the univariate analysis, body mass index (BMI), waist circumference, traditional CVR factors and triglycerides were strongly related with PCSK9 serum levels. On the contrary, HDL cholesterol and apolipoprotein A levels showed a negative association. LDL cholesterol exhibited a trend to a negative association (beta coeff. -0.30, 95% CI -0.67-0.069, p=0.11). The presence of carotid plaques and cIMT were not associated with PCSK9 levels although a trend was observed (beta coeff. 20.21, 95% CI -2.47 - 42.72, p=0.081 and beta coeff. 71.19, 95% CI -18.38 - 160.76, p=0.12 respectively).

Regarding SLE data, patients with longer disease duration (beta coeff. 1.25, 95% CI 0.15-2.35, p=0.026) and higher C reactive protein (CRP) levels (beta coeff. 1.42, 95% CI 0.61-2.22, p=0.00) disclosed higher PCSK9 levels.

Prednisone intake was positively associated with PCSK9 levels (beta coeff. 35.48, 95% CI 14.29-56.6), p=0.001), and patients that were taking any DMARD or hydroxychloroquine disclosed significant lower levels of PCSK9 (beta coeff. -27.91, 95% CI -54.5 - -1.32, p=0.040 and beta coeff. -39.21, 95% CI -62.21 - -16.21, p=0.001 respectively). Higher values of SLICC index (beta coeff. 9.66, 95% CI 4.47-14.84, p=0.000) and patients that were in the high/very high SLEDAI activity category (beta coeff. 62.98 95% CI 18.10-107.86, p=0.006) disclosed significant higher values of PCSK9.

When multivariate analysis was performed (adjusted by BMI, waist circumference, gender, hypertension, dyslipidemia, CRP levels and atherogenic index) these positive associations with both SLICC index and SLEDAI activity and the use of prednisone were maintained, as well as negative associations with LDL levels and the use of hydroxychloroquine.

Conclusion: PCSK9 serum levels are independently related to SLE activity and damage scores. This would imply that the mechanisms leading to lipid metabolism dysregulation in SLE patients may be mediated or be a consequence of PCSK9.

Disclosure: H. Sanchez-Perez, None; J. C. Quevedo, None; I. Rua-Figueroa, None; B. Tejera-Segura, None; D. V. G. AM, None; A. Gonzalez-Delgado, None; F. Díaz-González, None; I. Ferraz-Amaro, None.

Abstract Number: 745

Prolonged Remission and Influence on Damage Accrual and Infection for Patients with Systemic Lupus Erythematosus: A Multi-Center Cohort Study from China

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

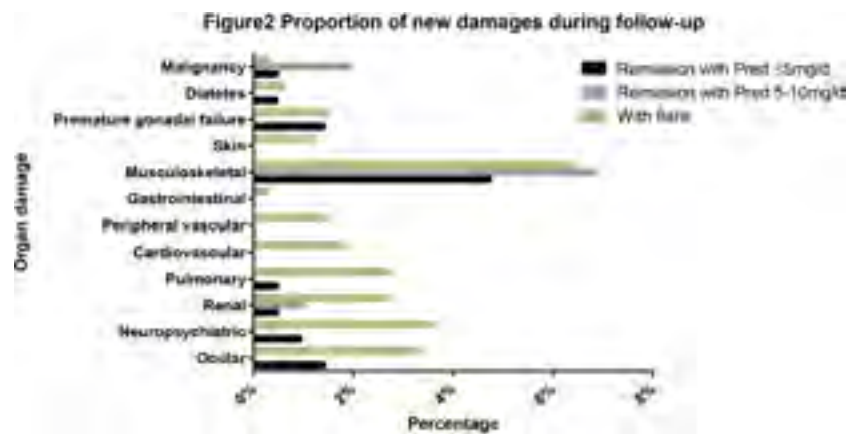
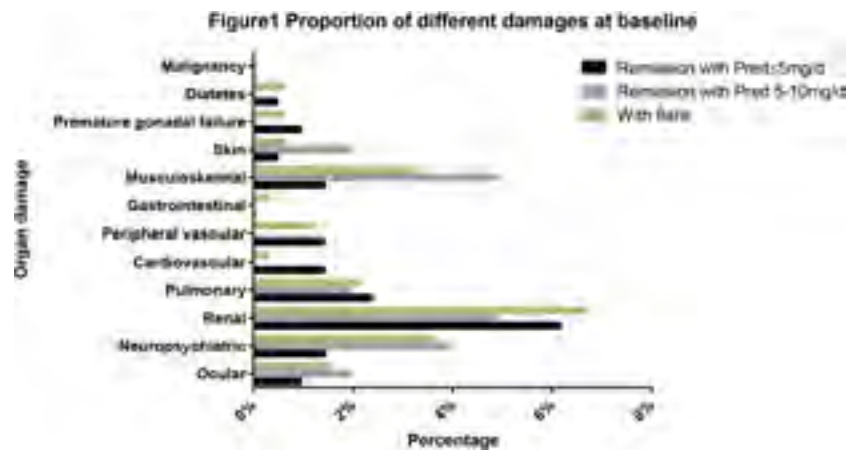
Session Time: 9:00AM-11:00AM

Abstract:

Background/Purpose: To study how many patients with Systemic Lupus Erythematosus (SLE) maintained remission in CSTAR(Chinese SLE Treatment and Research group) registry cohort, and further explore the influence of remission on organ damage accumulation and infection, which is the major cause of death in our cohort.

Methods: Patient recruitment started from April 2009 to February 2010. They were followed up yearly at clinic. Baseline data mainly included demography, clinical manifestations, activity (SLEDAI-2K), organ damages (SLICC/Damage Index). Logistic regression model was performed to study the effect of remission on damage and severe infection occurrence.

Results: A total of 687 patients were regularly followed up with intact data. Among them, 357 patients never experienced disease flare during follow-up. Finally, 74 (10.8%) patients developed into prolonged remission off steroids for at least 1 year, and 23(3.3%) patients of them were treated without steroids since enrolled. 137(19.9%) patients achieved persistent



remission with prednisone $\leq 5\text{mg/d}$ at the endpoint. Logistic regression analysis showed that disease flare was associated with new damage [OR 2.385, $p < 0.001$] and severe infection [OR 1.833, $p = 0.006$].

Conclusion: Prolonged remission should be a treating target for Chinese SLE patients and it can be achieved for nearly half of the patients now. To avoid disease flare may reduce the probability of new damage and severe infection. Appropriate strategies to maintain remission deserve more investigations in future.

Key words: Systemic lupus erythematosus, Remission, Organ damage, Infection

Table 1 Baseline Characteristics for Patients

	Remission with pred $\leq 5\text{mg/d}$ n=211 (%)	With flare N=330 (%)
Male	7.58	9.10
Serositis	21.8	16.4
Lupus nephritis	52.6	58.8
Hematological involvement	43.6	52.1
Interstitial lung disease	3.32	5.45
Pulmonary arterial hypertension	1.90	2.42
Neuropsychiatric involvement	7.58	7.58
Anti-dsDNA	55.0	56.7
Anti-SM	20.4	19.4
Anti-RNP	13.3	14.5
Anti-SSA	28.4	27.0
Anti-SSB	12.3	10.9
Anti-rRNP	10.4	14.8
APL	31.3	36.7
Low complement	57.4	63.9
Baseline organ damage	15.6	17.3

Disclosure: Z. Wang, None; J. ZHAO, None; Y. Wang, None; M. Li, None; X. Zeng, None.

Impact of Nephritis on the Outcomes of SLE Patients Hospitalized with Acute Myocardial Infarction; Insights from the National Inpatient Sample Database

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose : Early cardiovascular disease is an important cause of mortality in SLE. Previous studies have shown that lupus nephritis (LN) was associated with an increased risk of cardiovascular events in SLE patients. The primary aim of the present study was to assess the role of nephritis in mortality of SLE patients hospitalized with acute myocardial infarction (AMI) in a nationally representative sample.

Methods: We used data from the National Inpatient Sample (NIS) for the period 2005-2015 with adult AMI as a primary diagnosis and SLE, nephritis, chronic kidney disease (CKD) and end-stage renal disease (ESRD) as secondary diagnoses using ICD-9 codes. There is no specific ICD-9 code for LN and its classes. The proportion who met ACR classification criteria cannot be determined with the NIS database.

We compared the characteristics of AMI hospitalizations in SLE patients with and without nephritis and used logistic regression to calculate the odds ratios for inpatient mortality from AMI in SLE patients with nephritis. We compared this to AMI in SLE patients with all kidney disease (AKD) (defined as having ESRD or CKD or nephritis) and without kidney disease. AKD in SLE population is most likely due to LN¹.

Results: We identified a total of 4810 AMIs from 2005-2015 in patients with SLE. Among these, 245 had a discharge diagnosis of nephritis and 837 had AKD.

AMI hospitalizations with SLE and nephritis were younger (50.3 vs. 61.3 years; $p < 0.01$) with a higher proportion of males (24.9% vs. 19%; $p < 0.05$) and a higher proportion of African-Americans (36.7% vs. 22.3%; $p < 0.01$) compared to patients with SLE without nephritis. The findings for SLE and AKD were similar: younger and with a higher proportion of males and African-Americans. The findings are summarized in the table.

The unadjusted inpatient mortality from AMI in SLE and nephritis was not statistically different from that in SLE patients without nephritis, even after adjusting for age, gender, race, comorbidities and invasive cardiac procedures (a OR=1.28; 95% CI=0.5-2.7; $p = 0.52$). The adjusted odds-ratio for inpatient mortality from AMI in SLE and AKD, however, was 1.84 (95% CI=1.27-2.67; $p < 0.01$).

Conclusion: Patients with SLE and nephritis presented with AMI at a younger age compared to patients with SLE and no nephritis. The former group of SLE patients did not have a statistically different inpatient mortality due to AMI. However, AMI hospitalizations with SLE and AKD were associated with an increased probability of inpatient mortality compared to the ones with SLE and no kidney disease. Given that the most kidney diseases in SLE patients appear to be related to LN¹, this study suggests that LN is an independent risk factor for inpatient mortality due to AMI.

Variables*	SLE with nephritis vs. SLE without nephritis	SLE with AKD vs. SLE without kidney disease
Mean age (years)	50.3 vs. 61.3 ($p < 0.01$)	57.6 vs. 61.4 ($p < 0.01$)
Female percentage	75.1 vs. 81.0 ($p < 0.05$)	75.9 vs. 81.7 ($p < 0.05$)
Hypertension (%)	80.8 vs. 68.6 ($p < 0.01$)	81.8 vs. 66.5 ($p < 0.01$)
Complicated diabetes mellitus (%)	15.5 vs. 4.3 ($p < 0.01$)	11.4 vs. 3.5 ($p < 0.01$)
Anemia (%)	45.3 vs. 22.7 ($p < 0.01$)	42.4 vs. 19.9 ($p < 0.01$)
Non-ST elevation MI (%)	75.9 vs. 70.5 ($p = 0.06$)	79.0 vs. 69.0 ($p < 0.01$)
Percutaneous coronary intervention (%)	33.5 vs. 41.8 ($p < 0.01$)	30.9 vs. 43.6 ($p < 0.01$)
Coronary artery bypass graft (%)	3.7 vs. 7.0 ($p < 0.05$)	6.6 vs. 6.9 ($p = 0.75$)
Mean length of stay (days)	6.2 vs. 5.0 ($p < 0.01$)	6.5 vs. 4.3 ($p < 0.01$)
Mean total charges (\$)	66717.7 vs. 66493.8 ($p = 0.96$)	73320.5 vs. 65069.4 ($p < 0.01$)
Unadjusted odds-ratio for inpatient mortality	1.24 (CI=0.72-2.12; $p = 0.43$)	1.45 (CI=1.06-1.97; $p < 0.01$)
Adjusted odds-ratio for inpatient mortality	1.28 (CI=0.59-2.77; $p = 0.52$)	1.84 (CI=1.27-2.67; $p < 0.01$)

* Demographic, Clinical Characteristics and outcomes of AMI hospitalizations in SLE patients with and without nephritis as well as SLE patients with and without all kidney disease.

Reference:

1. Plantinga LC, Drenkard C, Pastan SO, et al. Attribution of cause of end-stage renal disease among patients with systemic lupus erythematosus: the Georgia Lupus Registry. *Lupus Sci Med*. 2016; 3(1):e000132.

Disclosure: A. Vafa, None; S. Fugar, None; C. Mbachi, None; J. P. Case, None.

Abstract Number: 747

The Influence of Depression on Clinical Features of Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Depression occurs commonly among patients with SLE. In this study, we used two separate scales to assess depression and determined differences in clinical characteristics and patient-reported disease activity in patients with and without symptoms of depression.

Methods: Patients meeting ACR or SLICC criteria for SLE in a university rheumatology clinic were included. At each visit, patients completed a series of questionnaires: Systemic Lupus Activity Questionnaire (SLAQ), Patient Health Questionnaire (PHQ-9), and the ACR Fibromyalgia (FM) Diagnostic Criteria 2011. To meet criteria for FM, patients had (1) widespread pain score ≥ 7 and symptom severity score ≥ 5 or (2) widespread pain score ≥ 3 and symptom severity score

Table 1. Clinical characteristics of SLE patients with depression.

	PHQ-9*			SLAQ*		
	No Depression n=122 n (%)	Depression* n=53 n (%)	p-value	No/Mild Depression n=172 n (%)	Moderate/Severe Depression n=36 n (%)	p-value
Fatigue	68 (55.7%)	46 (86.8%)	<0.0001	92 (53.8%)	30 (83.3%)	0.001
Muscle Weakness	39 (32.0%)	32 (60.4%)	0.0007	54 (31.4%)	21 (58.3%)	0.004
Muscle Pain	48 (39.3%)	39 (73.6%)	<0.0001	72 (41.9%)	24 (66.7%)	0.01
Swollen Joints	38 (30.9%)	36 (67.9%)	<0.0001	56 (32.8%)	25 (69.4%)	<0.0001
Stiff Joints	62 (50.4%)	37 (69.8%)	0.02	85 (49.7%)	25 (69.4%)	0.04
Anxiety	14 (11.5%)	21 (39.6%)	<0.0001	12 (7.0%)	24 (66.7%)	<0.0001
Forgetfulness	30 (24.6%)	30 (56.6%)	<0.0001	39 (22.8%)	22 (61.1%)	<0.0001
Patient reported flare	60 (53.1%)	44 (89.8%)	<0.0001	85 (54.5%)	27 (81.8%)	0.004
Fibromyalgia	15 (12.1%)	29 (54.7%)	<0.0001	31 (18.0%)	14 (38.9%)	0.01
	Mean (SD)	Mean (SD)	p-value	Mean (SD)	Mean (SD)	p-value
Clinical SLEDAI	1.7 (2.4)	2.8 (2.9)	0.008	1.8 (2.5)	2.1 (2.3)	0.6
Full SLEDAI	3.8 (3.2)	5.3 (5.3)	0.02	4.2 (4.1)	4.5 (4.3)	0.7
PGA (0-3)	0.4 (0.5)	0.7 (0.6)	0.0004	0.5 (0.6)	0.6 (0.6)	0.2
Patient-reported disease activity (0-10)	3.9 (2.7)	6.3 (2.2)	<0.0001	3.8 (2.8)	6.0 (2.6)	<0.0001
SLAQ	10.1 (5.6)	18.3 (6.1)	<0.0001	10.1 (6.6)	18.0 (6.2)	<0.0001
Fibromyalgia Widespread Pain Score	3.4 (3.3)	7.0 (5.2)	<0.0001	3.7 (3.9)	5.6 (5.1)	0.01
Fibromyalgia Symptom Severity Score	3.7 (2.1)	6.5 (1.6)	<0.0001	3.6 (2.5)	6.0 (1.9)	<0.0001

*Depression defined as Patient Health Questionnaire (PHQ-9) score ≥ 10

†Depression defined as patient response of moderate or severe to the SLAQ item "feeling depressed" in the previous month

≥ 9 . Physician measures of disease activity collected at each visit included SLEDAI and physician global assessment (PGA). Depression was defined as PHQ-9 score ≥ 10 . As part of the SLAQ, patients were asked if they were “feeling depressed” in the prior month, with responses of none, mild, moderate, or severe. Differences in clinical characteristics and patient-reported disease activity in patients with and without depression were analyzed by Fisher’s exact test and t-tests.

Results: The analysis included 208 patients with SLE (92% female, mean age 45 years, 22% with FM). Of 175 patients who completed the PHQ-9, 30% met criteria for depression. Of the 208 patients who completed the SLAQ, 47% reported experiencing any depression (mild, moderate, or severe) in the previous month, while 17% reported moderate to severe depression.

Among patients with FM, 66% reported depression by PHQ-9, 33% reported mild depression by SLAQ and 31% reported moderate to severe depression. In contrast, among those without FM, 18% reported depression by PHQ-9, 20% reported mild depression, and 13% reported moderate or severe depression by SLAQ.

Patients with depression reported more fatigue, muscle weakness, muscle pain, swollen joints, stiff joints, anxiety, and forgetfulness (Table 1). Further, patients with depression had higher overall SLAQ scores, patient-reported disease activity, widespread pain scores, and symptom severity scores. Among patients who met PHQ-9 criteria for moderate-severe depression, clinical SLEDAI, full SLEDAI, and PGA scores were higher than patients without depression.

Conclusion: These data suggest that SLE patients with depression are more symptomatic and have higher perceived disease activity. They also demonstrate a strong association between depression, FM, and some SLE symptoms that often confounds trials and clinical care decisions. Together, these findings suggest that identifying methods to distinguish between these symptoms and target therapy to the underlying pathology will improve the quality of life for patients living with SLE and the comorbid symptoms of fibromyalgia and depression.

Disclosure: A. M. Eudy, None; J. Rogers, AstraZeneca, 5; L. Criscione-Schreiber, GlaxoSmithKline, 2; D. Pisetsky, None; K. Sun, None; J. Doss, None; M. E. B. Clowse, AstraZeneca, 5.

Abstract Number: 748

Long-Term Survival of Renal Transplantation Due to Lupus Nephritis. Comparative Study with Non-Autoimmune Transplantation. Study from a Single Center

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SESSION INFORMATION

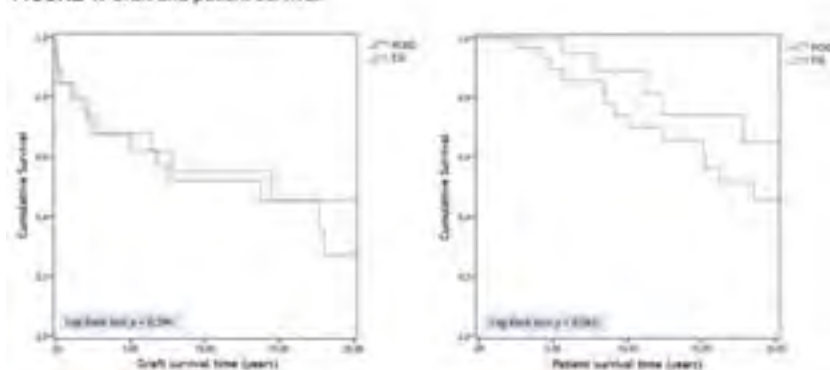
Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

FIGURE 1. Graft and patient survival.



Background/Purpose: Lupus nephritis (LN) is a severe complication of systemic lupus erythematosus, affecting up to 40% of patients. Unfortunately, about 20% of LN develop end stage renal disease (ESRD) and need replacement therapy. Renal transplantation (RT) may be required. However, concerns about LN recurrence after RT has been reported. In a series of patients with RT due to LN our aim was to assess a) long-term post-transplant survival and, b) comparison of post-transplant survival with a control group due to a non-autoimmune nephropathy, a polycystic kidney disease (PCKD).

Methods: We studied 2 groups of patients with first RT: a) LN and b) PCKD (control group). All these patients were transplanted in a single reference University Hospital. The main outcome variables were a) graft and patient survival up to 20 years and b) evolution of renal function (serum creatinine and proteinuria) in the first 5 years. Cumulative survival rates after RT were estimated by the Kaplan-Meier method and compared between groups using the log-rank test. Mann-Whitney test or chi²/Fisher's exact test were used to compare quantitative or qualitative variables, respectively.

Results: We included 53 patients with RT; a) LN group (21), b) PCKD group (32). No significant differences at baseline were observed between both groups regarding sex and cardiovascular risk factors. Significant differences were found in terms of age at RT, with a mean of 39.80±11.27 years in LN group and 46.59±5.01 years in PCKD group (p=0.004). Renal biopsy was performed in 16 LN patients: type II LN (25%), type III (25%) and type IV (50%), according to the World Health Organization and International Society of Nephrology/Renal Pathology Society classification. From 48 patients (of 53) in which a renal biopsy was performed during the first-year post-transplant, rejection was found in 21 cases (43.7%) with no significant differences between both groups (p=0.444). The evolution of serum creatinine and proteinuria after RT is shown in TABLE. Significant differences were found in creatinine levels at the 6th month post-transplant (p=0.032), not so in the rest of measurements. In LN group, 3 patients (14.3%) developed a lupus flare: 2 cases of extrarenal disease and only 1 case with histological recurrence in the graft. No significant differences were found in patient or graft survival between both groups in 20 years of follow-up (Figure 1).

Conclusion: RT may be a safe alternative therapy for ESRD in LN patients and can provide a long-term survival.

TABLE 1. Evolution of creatinine and proteinuria levels after renal transplant.

Serum Creatinine mg/dL	1 Month		6 Months		1 Year		3 Years		5 Years	
	PCKD	SLE	PCKD	SLE	PCKD	SLE	PCKD	SLE	PCKD	SLE
N	28	17	26	15	26	17	22	14	18	13
Mean	2.48±2.12	1.92±1.41	1.82±0.71*	1.47±0.59*	1.89±1.03	2.03±1.56	1.74±1.12	2.26±2.51	2.06±1.75	2.64±3.30
Proteinuria mg/24 h	PCKD	SLE	PCKD	SLE	PCKD	SLE	PCKD	SLE	PCKD	SLE
N	24	15	24	12	25	17	21	13	16	11
Mean	313.38±218.59	581.67±1032.80	372.67±375.79	651.67±679.01	322.84±314.93	1426.35±4413.40	378.81±383.91	409.46±335.64	871.81±1498.35	487.36±474.62

* p<0.05

Disclosure: L. Sánchez-Bilbao, None; B. Atienza-Mateo, None; J. L. Martín-Varillas, None; M. de Cos-Gómez, None; Í. González-Mazón, None; D. Prieto Peña, None; M. Calderón Goercke, None; J. C. Ruiz San Millán, None; E. Rodrigo Calabia, None; M. A. González-Gay, None; R. Blanco, None.

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Is Lupus Nephritis Onset Delayed in Older Caucasian Females with Less Aggressive Pathology?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Lupus Nephritis (LN) usually presents within 5 years of SLE diagnosis, however the minority of patients with late-occurring nephritis are poorly characterized. Factors associated with high risk for early nephritis include male gender, Hispanic and African American race, and childhood-onset SLE (Jacobsen et. al. 1998, Seligman et. al. 2002). Since proliferative nephritis is a more aggressive class of nephritis than membranous and mesangial nephritis, we hypothesized that female gender, Caucasian race, adult-onset SLE, and membranous pathology would be associated with a later or more insidious onset of nephritis.

Characteristic	Total (n = 278)	≤ 5 Years (n = 197)	> 5 Years (n = 81)	>10 Years (n = 45)	>15 Years (n = 22)
Female (n, %)	242 (87.05)	167 (84.77)	75 (92.68)	42 (93.33)	21 (95.45)
Race/Ethnicity (n, %)					
Black/African American	121 (43.53)	84 (41.12)	40 (49.38)	21 (46.67)	12 (54.55)
Hispanic/Latino	112 (40.29)	90 (45.68)	22 (27.16)	12 (26.67)	3 (13.64)
White/Caucasian	27 (9.71)	17 (8.63)	10 (12.35)	7 (15.56)	5 (22.73)
Asian	18 (6.47)	9 (4.57)	9 (11.11)	5 (11.11)	2 (9.09)
Age at SLE (median, IQR)	25.45 [19.12, 33.20]	25.84 [19.49, 39.03]	25.16 [18.31, 30.22]	24.36 [16.12, 39.34]	24.5 [19.19, 27.03]
Age at Lupus Nephritis (median, IQR)	29.78 [21.25, 39.43]	35.86 [20.49, 38.49]	58.24 [30.02, 44.78]	42.34 [33.06, 48.88]	45.38 [38.34, 51.75]
Histopathologic Class (n, %)					
I	35 (11.87)	24 (12.18)	9 (11.11)	6 (13.33)	5 (22.73)
II	65 (23.38)	45 (22.84)	20 (24.69)	14 (31.11)	7 (31.82)
III+IV	41 (14.75)	25 (12.69)	16 (19.75)	5 (11.11)	1 (4.55)
IV	54 (23.02)	48 (24.37)	15 (18.52)	7 (15.56)	3 (13.64)
IV+V	24 (8.63)	16 (8.12)	8 (9.88)	4 (8.89)	1 (4.55)
V	51 (18.32)	38 (19.29)	13 (16.05)	9 (20.00)	5 (22.73)
Proliferative (II, III+IV, IV, IV+V)	194 (69.78)	135 (68.53)	58 (72.84)	30 (66.67)	12 (54.55)

Table 1. Characteristics of the LN cohort. The initial group is the total cohort, followed by the cohort divided into ≤ 5 years between SLE and first LN biopsy and > 5 years. All >10 years patients are also included within the > 5 years group, and > 15 years patients are also in >5 years and >10 years groups. Time between SLE and biopsy was analyzed as a continuous outcome variable to prevent unnecessary loss of power.

Methods: A single large urban medical center was the source for retrospective record review of patients who underwent kidney biopsy between 1999 and 2015. Patients with biopsy-proven LN were evaluated to determine whether gender, race, age at SLE diagnosis, age at first biopsy, or histopathologic classification were associated with the time (years) between SLE diagnosis and first renal biopsy.

Results: 630 patients were screened. After elimination of duplicates, those without initial biopsy, biopsy findings other than lupus nephritis, and unknown date of SLE diagnosis, 293 subjects had adequate data available for analysis. Those with late onset SLE, diagnosis after age 50 (n=15), were excluded from further analysis due to known differences in this subgroup. The remaining 278 patients had characteristics shown in Table 1. Twenty-nine percent of patients in this cohort developed nephritis more than 5 years after initial SLE diagnosis, including 50% of Asian, 37% of Caucasian, 33% of African American, and 20% of Hispanic LN patients. Multivariable linear regression identified greater age at first biopsy and race as the strongest predictors of time between SLE diagnosis and first renal biopsy. Hispanic patients were more likely to present with LN earlier in their course and Asian patients were more likely to present later, with African American and Caucasian groups between them. The model accounts for 27% of the variability in the time elapsed between diagnosis and biopsy. Histopathologic class did not make a significant contribution, and proliferative nephritis was noted in similar numbers of patients who developed LN after 5 years (73%) and those in the early presenting group (69%, p=0.6).

Conclusion: Surprisingly, more than a quarter of known LN patients at this large US center present after 5 years of SLE, higher than expected based on low numbers of late onset nephritis in other cohorts. This appears to be more common in Caucasian and Asian subgroups. Older patients are more likely to develop nephritis later, but aggressive histopathology is not less likely in later presentations. The data underscore the importance of remaining vigilant about nephritis risk in patients of diverse demographics five years and more after diagnosis with SLE.

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Positive Remodeling Index and Low Attenuation Non-Calcified Coronary Plaques: Markers of Vulnerable Coronary Plaques in Systemic Lupus?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

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

Background/Purpose: Accelerated atherosclerosis leading to premature coronary artery disease remains the major cause of late death in SLE. Positive remodeling index and presence of low attenuation noncalcified plaque (<30 Hounsfield units) are characteristic vessel changes in unstable coronary plaques. We sought to characterize noncalcified plaque lesions in patients with systemic lupus erythematosus and to identify high risk lesions.

Methods: A total of 66 patients who met the ACR or SLICC classification criteria for SLE had CT angiogram studies. Of these, 30 patients had two CT angiogram studies. Coronary plaque area was measured by manual tracing for the difference between the area within the external elastic membrane and the area of the vessel lumen at the site of maximal luminal narrowing as observed on a cross-sectional coronary CT angiography image. Each noncalcified plaque detected within the vessel wall was evaluated with the minimum CT density and vascular remodeling index (RI). Total low density plaque volume per patient and low density/high density noncalcified plaque ratio were then compared by patient characteristics which included age, sex, ethnicity, BMI, smoking, SLEDAI, PGA, anti-dsDNA, low complement, current prednisone, current hydroxychloroquine, current NSAID use, history of cardiovascular event, hypertension, lupus anticoagulant, antidiolipin, hypercholesterolemia, and methotrexate use.

Results: All patients had at least one plaque with a positive remodeling index (>10%), and 83.1%(n=271) of total identified plaques had a positive remodeling index. Low density noncalcified plaque volume was associated with age ($p<0.01$) and body mass index ($p<0.01$). African Americans had significantly more ($p<0.05$) low density noncalcified plaque compared to patients of other ethnicities. The low density/high density noncalcified plaque ratio did not correlate with any patient characteristics and was on average 46% (SD=10). There were only 5 cardiovascular events in the studied group and there were no differences in remodeling index or low density noncalcified plaque observed in this group, but the number of events was small.

Conclusion: Positive remodeling index and low attenuation noncalcified plaques are common in patients with lupus and are significantly more likely to be seen among African American patients, patients with a BMI>30, and age over 60. These characteristic vessel changes, seen in unstable coronary plaques, may identify patients at need for more frequent noninvasive cardiac monitoring.

Disclosure: G. Stojan, None; L. Magder, None; M. Petri, None.

Coronary Plaque Burden in Patients with Lupus Compared to Healthy Volunteers

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

Background/Purpose: Accelerated atherosclerosis leading to premature coronary artery disease remains the major cause of late death in SLE. We sought to characterize non calcified and calcified plaque lesions in patients with systemic lupus erythematosus and to compare the findings with a group of healthy controls.

Methods: A total of 70 patients who met the ACR or SLICC classification criteria for SLE were included in the study. All patients underwent coronary CT angiography. A total of 100 non-matched healthy controls were included in the study. Coronary plaque area was measured by manual tracing for the difference between the area within the external elastic membrane and the area of the vessel lumen at the site of maximal luminal narrowing as observed on a cross-sectional coronary CT angiography image.

Results:

Table 1. Mean plaque volume (95% CI, in mm³) between study groups at baseline

	SLE group (N=70)	Control group (N=100)	p-value
Total plaque volume	1547.88 (1435.54, 1660.22)	432.96 (338.62, 527.29)	<0.0001
Calcified plaque volume	29.79 (-36.16, 95.74)	265.27 (209.89, 320.66)	<0.0001
Non-calcified plaque (NCP) volume	1518.09 (1427.73, 1608.45)	167.68 (91.81, 243.56)	<0.0001

Table 2. Mean(SD) of Calcified and Non-calcified Plaque, in each cohort, by age and sex

Sex	Age	Non-calcified Plaque					Calcified Plaque				
		JHU		UCLA		p	JHU		UCLA		p
		n	Mean(SD)	n	Mean(SD)		n	Mean(SD)	n	Mean(SD)	
Female	<44	18	1324.44 (464.69)	0	- (-)	-	18	0 (0)	0	- (-)	-
	45-59	25	1416.36 (429.85)	3	244.83 (125.38)	<.0001	25	2.00 (4.83)	3	138.50 (186.60)	0.3327
	60+	16	1562.06 (560.33)	21	111.04 (109.35)	<.0001	16	16.38 (28.54)	21	162.39 (165.96)	0.0007
Male	<44	2	1549.00 (548.71)	2	203.20 (287.37)	0.0916	2	0 (0)	2	122.20 (66.75)	0.2347
	45-59	4	1670.75 (290.82)	22	227.97 (268.13)	<.0001	4	0.50 (1.00)	22	250.30 (265.18)	0.0002
	60+	5	1919.60 (489.46)	52	215.31 (225.93)	0.0013	5	77.60 (69.37)	52	355.44 (400.42)	<.0001

Conclusion: SLE patients on average have a significantly higher burden of non calcified plaque (p<0.0001) compared to controls, while surprisingly, the calcified plaque burden is lower (p<0.0001). The limitation of our study is the comparatively older age of the control group as well as the gender discrepancy, with males being predominant among the controls. Nevertheless, this discrepancy even further highlights the burden of high risk non calcified plaque in SLE.

Disclosure: G. Stojan, None; M. Budoff, None; L. Magder, None; J. Li, None; A. Zadeh, None; E. Barr, None; M. Petri, None.

Prevalence and Predictors of Peripheral Vascular Disease in a Cohort of Systemic Lupus Erythematosus (SLE) Patients

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Background/Purpose: Low Ankle-brachial index (ABPI) < 0.9 demonstrating peripheral vascular disease (PVD), is a marker of subclinical cardiovascular disease and it is an inexpensive and easy method in which to assess peripheral vascular disease (PVD). Cardiovascular morbidity in systemic lupus erythematosus (SLE) is at least as frequent as in age- and sex-matched type-1 diabetes mellitus patients, making SLE a cardiovascular disease equivalent. Therefore, aggressive screening and management of cardiovascular risk factors should be performed to reduce this risk and improve long term mortality from vascular events.

Methods: The present study evaluated prevalence and risk factors for peripheral vascular disease in patients with SLE in a sub-Saharan country, Ghana. Secondly, it examined the correlates with disease characteristics, activity indices and traditional risk factors of atherosclerosis.

A prospective cohort of 77 Ghanaian female patients with SLE had clinical, laboratory parameters, disease activity, damage indices, treatment and traditional risk factors for atherosclerosis evaluated between those with and without PVD measured using ankle brachial pressure index (ABPI).

Results: The prevalence of PVD was 22.73% with a mean age of 30.94 (SD \pm 8.22) years (range: 20 – 60 years). Women with normal ABPI were older than those with abnormal ABPI, but this was not statistically significant (31.5 verses 28.5 years, $p = 0.192$).

From the multiple logistic regression model, prednisolone dosage, waist to height ratio (WHR), low density lipoprotein (LDL) as well as educational level were the statistically significant factors associated with higher prevalence of PVD ($p < 0.05$). A unit increase in WHR decreased the odds of developing PVD by 0.0013 (95% CI: 0.00 – 0.18). Increase in prednisolone dosage increases the patient's odds of developing PVD by 0.88 (95% CI: 0.79 - 0.99). Each one unit rise in patient's LDL increased their odds of getting PVD by 0.52 (95% CI: 0.27 - 0.98). Patients odds of being diagnosed with PVD increased by 0.85 (95% CI: 0.76 - 0.96) for each year after diagnosis. Higher educational level was associated with lower odds of developing PVD. Patients with tertiary education had 99% (AOR: 0.01, 95% CI: 0.00 - 0.47) lower odds of developing PVD.

Conclusion: There is an increase prevalence of PAD in this Ghanaian cohort of SLE patients compared to the general public but lower than other SLE cohorts, despite being younger than other SLE cohorts and female. Traditional cardiovascular factors as well as disease related factors like disease duration and prednisolone use are associated. Follow up studies would see the impact of this on disease outcome and organ damage, especially on their neurocognitive effect which has not been studied previously.

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Young SLE Patients Have Higher Coronary Artery Calcium Scores Compared with Population Controls

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Background/Purpose: Cardiovascular disease (CVD) is a leading cause of death in systemic lupus erythematosus (SLE). The coronary artery calcium (CAC) score is a surrogate for atherosclerosis that strongly predicts incident coronary artery disease and major CVD events, independent of traditional Framingham risk factors. The prevalence of CAC deposition in SLE patients over the age of 45 is higher compared to the Multi-Ethnic Study of Atherosclerosis (MESA) cohort; however, data on patients <45 years of age is limited. We evaluated CAC scores in younger SLE patients, compared to healthy controls from the Coronary Artery Risk Development in Young Adults (CARDIA) cohort.

Methods: We identified 45 SLE patients who met 1997 ACR classification criteria, with no known coronary artery disease, and who had a non-contrast chest CT performed as part of their routine clinical care with images retrievable for calculation of CAC using the Agatston score. Demographics, disease characteristics, and comorbidities were ascertained. Prevalence of any calcification - defined as CAC>0 - was reported and compared with data from the CARDIA cohort, a large biracial U.S. cohort of patients ages 33 to 45 at time of chest CT scan for CAC determination. Additionally, within our SLE cohort, we investigated the relationship between disease characteristics and presence of coronary artery calcification.

Results: The 45 SLE patients were 39±14 years old, 89% female, 38% Hispanic, and 38% African American, with a disease duration 9±7 years. Patients met on average 5±1 ACR-SLE classification criteria; all had positive ANA titers; and 58% had elevated dsDNA titers. The average SLE disease severity index¹ was moderate (5±3), 42% had lupus nephritis, and 36% tested positive for antiphospholipid (APL) antibodies. CAC>0 was noted in 47% of all patients, with 41% of patients age <45 and 56% of patients age ≥45 having positive CAC. Out of the patients with positive CAC, 81% of patients had CAC scores between 1 and 100 and 19% had CAC scores >100. When compared with the CARDIA subjects, more SLE patients aged<45 had a CAC>0 (41.4% vs 9.6%, p-value <0.00001). Additionally, 45% of SLE patients ages 18 to 32 and 5 years median SLE disease duration, had abnormal CAC scores; the youngest of whom was 21 years old. There were no significant differences in SLE disease duration, SLE severity index, lupus nephritis, APL positivity, BMI, smoking status, presence of hypertension or diabetes between patients with and without CAC.

Conclusion: Young SLE patients have significantly higher CAC scores compared with the general population. A positive CAC score was seen in 41% of SLE patients <45 year-old and 45% of SLE patients <32 years old. Our data suggest that subclinical atherosclerosis in SLE develops as early as the second decade of life, and warrants screening and cardio-protective interventions.

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Determinants of Major Neurocognitive Disorder (Vascular Dementia) in SLE: The Importance of Treatment Adherence of SLE Disease Activity and Cardiovascular Risk Factors

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Background/Purpose: Factors associated with neuropsychiatric damage in SLE has been described. Yet, determinants of progression of small vessel related brain injury, and major neurocognitive disorder-vascular dementia (MCD) is not well understood. The purpose of this study is a case-control analysis that compare neuropsychiatric lupus (NPSLE) patients with MCD and those who have not developed MCD.

Methods: A nested case-control study of 24 NPSLE subjects with MCD out of the SLE cohort at the University of Maryland between 1995 and 2018, were identified according to the 2007 American College of Rheumatology proposed response criteria for severe neurocognitive impairment in SLE (> 2.0 SD below the mean compared to normative data) that interferes with daily functioning leading to loss of independence. For each NPSLE patient with MCD, 3 age- and gender- matched NPSLE subjects with no MCD were randomly selected from the same cohort, and assigned an index date of the NP events corresponding to the MCD group ($n = 72$).

Results: 24 NPSLE cases with MCD [mean age 48.8 ± 18.5 years, African American (71.0 %), mean level of education 11.7 years, mean SLE duration of 15 years] were compared to 72 NPSLE patients with no MCD [mean age 44.8 ± 17.1 years, African American (69.4 %), mean level of education 12.3 years, mean SLE duration of 13 years]. Baseline data including, severity of NPSLE events, structural neuroimaging findings of cortical and subcortical infarcts, hypo perfusion with watershed infarction, periventricular white matter hyper intensity, cardiovascular disease risk factors and Framingham risk score, cytotoxic or immune therapy, glucocorticoid, anticoagulation or aspirin use were not significantly different among both groups. Similarly, autoantibodies of phospholipid, ribosomal-P, anti-neuronal antibodies, NR2 and NMDA, were similar among both groups. Higher disease activity, glomerulonephritis and depression were more frequent among MCD group than in comparators. Independent predictors of MCD included baseline lacunar infarcts based in the caudate, thalamus, cerebellum, and peri-Sylvian regions (OR 5.0, 95% CI: 1.2-20.3, $P < 0.012$), regional volume loss (OR 20.0, 95% CI: 2.2-182.4, $P < 0.001$), and cerebral atrophy (OR 1.8, 95% CI: 1.2-2.7, $P < 0.001$). Medication non-adherence for SLE disease activity (OR 2.0, 95% CI: 1.1- 3.9, $p < 0.012$), uncontrolled dyslipidemia (OR 16.3, 95% CI: 2.9-91.8, $P < 0.001$), uncontrolled hypertension (OR 7.3, 95 % CI: 1.6-33.1, $P < 0.003$), and alcoholism (OR 4.4, 95% CI: 0.9-25.2, $p < 0.076$) were independent predictors of MCD progression. Hydroxychloroquine use was associated with slow progression of MCD (OR 3.0, 95% 1.4-6.7, $P < 0.001$).

Conclusion: Despite a similar prevalence of vascular risk factors at baseline, the risk of MCD is higher in NPSLE patients who do not adhere to medications related to SLE and control of cardiovascular risk factors than in matched comparable group. Understanding the complexity of medication non adherence in SLE need to be identified, and patient-tailored interventions focusing on patients' specific barriers to adherence are needed. This observation deserve further study to confirm the use of hydroxychloroquine as an intervention to slow progression of MCD.

Disclosure: J. A. Mikdashi, None.

Elevated Serum Procalcitonin at Baseline Correlates with Reduced Survival in Patients with Lupus Myocarditis

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Background/Purpose: Myocarditis is a severe manifestation of systemic lupus erythematosus (SLE). Ethnicity is believed to play an important role in influencing the outcome. We aimed to describe the clinical features and outcomes of lupus patients with myocarditis in a North Indian population.

Methods: Clinical records of SLE patients fulfilling 2012 SLICC criteria presenting to the Rheumatology Clinic and inpatient services (from November 2014 to November 2017) were screened for a clinical and laboratory diagnosis consistent with lupus myocarditis (LVEF <50%, absence of massive pericardial effusion, severe pulmonary artery hypertension, significant regional wall motion abnormality or primary valvular disease). Demographic data, clinical features and echocardiography findings were noted. Cardiac outcomes as well as survival were assessed using Kaplan Meier survival analysis and Cox regression analysis.

Results: 37 patients with SLE who had features consistent with lupus myocarditis were included. The median duration of follow up was six and half months. 12 patients (32%) presented with lupus myocarditis at first presentation; the median duration between the diagnosis of SLE and diagnosis of myocarditis was seven and half months. All patients received corticosteroids and hydroxychloroquine while 27 patients received additional cyclophosphamide. Ten deaths (27.7%) were noted, of these 9 died during the initial presentation while one patient died two months' later of disseminated varicella infection. The deaths were attributed to disease activity alone in 2 patients, activity with infection in 5 patients and infection alone in remaining 3 patients. Among the survivors, mean ejection fraction rose from $33 \pm 8\%$ at baseline to $48 \pm 11\%$ at last follow up in 70% of patients (n=20). Raised serum procalcitonin at presentation (> 0.9 ng/ml) ($p=0.049$), higher blood urea ($p=0.038$) and low serum complement C3 (< 50 mg/dl) (0.002) were associated with increased mortality. Patients with raised serum procalcitonin at presentation had reduced survival (mean survival 2.5 months, C.I. 0.1 to 4.8 months) as compared to those without (mean survival 49.2 months, C.I. 38.2 to 60.2 months) ($p=0.014$).

Conclusion: Lupus myocarditis is associated with high mortality in Indian SLE patients. Elevated serum procalcitonin at presentation is associated with reduced survival in these patients.

Table1 showing baseline characteristics of all patients with myocarditis.

	Results
Duration of symptoms in days	15 (71)
Time from diagnosis of SLE to myocarditis in months [median (range)]	7.5 (0-84)
Follow up in months [median (range)]	6.5 (0-60)
dsDNA positivity	26/37 (70.2%)
Crackles on auscultation	17/23
Anemia (<10 g/dl)	26/33
Thrombocytopenia ($<150 \times 10^9/L$)	10/33
Leucopenia ($<4 \times 10^9/L$)	6/33
Hypoalbuminemia (<35 g/L)	32/34
Proteinuria (>0.5 gm/24hr or dipstick $>2+$)	22/28
Raised serum creatinine (>1.4 mg/dl)	13/36
Raised procal (>0.9 ng/ml)	8/26
Low C 3 (50-150 mg/dl)	10/22
Low C4 (16-38 mg/dl)	16/22
SELENA-SLEDAI	N=30
No flare (≤ 3)	3
Mild or moderate flare (3-12)	14
Severe flare (>12)	13

Disclosure: A. Dhooria, None; A. Gawalkar, None; K. Santosh, None; A. MB, None; A. Sharma, None; S. Sharma, None; S. Jain, None; V. Dhir, None.

Abstract Number: 756

Peripheral Neutrophil CD64 Index Combined with Biomarkers Improves the Ability of Diagnosing Bacterial Infection in Patients with SLE

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Patients with Systemic lupus erythematosus (SLE) are prone to bacterial infection owing to disease activity, abnormal immune function and long-term immunosuppressive therapy. Differentiating bacterial infection from disease relapse in SLE is challenging based on clinical signs and symptoms due to similar clinical presentation. Microbial culture is the gold standard for diagnosing bacterial infection, but it is time-consuming and the positive culture ratio is low. The role of several biomarkers including C-reactive protein (CRP), procalcitonin (PCT) and white blood cell count (WBC) for diagnosing bacterial infection is controversial. The study is aimed at evaluating the significance of neutrophil CD64 (nCD64) index, complement C3, complement C4, CRP, PCT, WBC, lymphocyte subsets, CD4⁺T subsets and their combination in differentiating bacterial infection from disease relapse in SLE.

Methods: Thirty-six hospitalized SLE patients with bacterial infection and 45 with lupus flare without infection were retrospectively studied. Bacterial infection was proven by positive cultures or typical clinical symptoms and signs combined with positive response to antibiotics. Lupus flare was considered as three points greater than the patient's previous SLEDAI. C3, C4, CRP and PCT were detected by immunoturbidimetry. Lymphocyte subpopulations, CD4⁺T subsets and nCD64 index were measured by flow cytometry. WBC was detected by blood cell analyzer.

Results: The levels of nCD64 index ($p=0.034$), CRP ($p=0.049$) and WBC ($p=0.028$) were significantly higher in the infected group and C3 ($p=0.001$), C4 ($p=0.016$) and B cells ($p=0.010$) were lower. The areas under the receiver operating characteristic (ROC) curves (AUC) for the above six biomarkers had no significant difference [nCD64 index: 0.619 (CI 0.504-0.724), CRP: 0.608 (CI 0.492-0.715), WBC: 0.625 (CI 0.510-0.730), C3: 0.658 (CI 0.540-0.764), C4: 0.646 (CI 0.526-

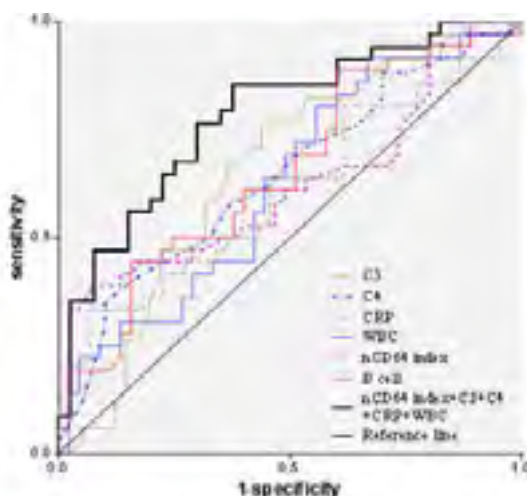


Figure 2 Comparison of ROC curves of C3, C4, CRP, nCD64 index, WBC and B cells as biomarkers in differentiating bacterial infection from disease relapse in SLE.

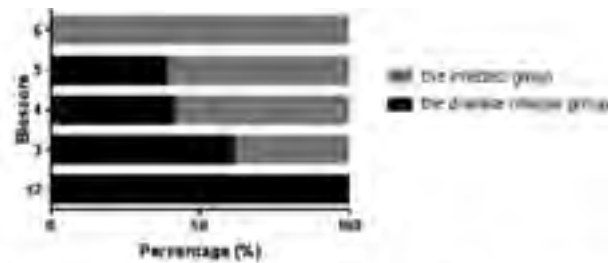


Figure 2 Distribution of the infected and the disease relapse SLE patients at bioscore range 0-6. One point was added once the value of C3, C4 or B cells was below the normal reference range of laboratory or the value of CRP, WBC or nCD64 index was above the cut-off value in the normal reference interval, with 0 being the minimum score and 6 being the maximum score. Six individuals were excluded due to some indicators were not detected. The value of patients with bioscore of less than 2 ($n=10$) were in the disease relapse group. Eleven (39.29%) of 28 patients with bioscore of 1 were infected. Thirteen (39.10%) of 33 patients with bioscore of 2 were infected. Thirteen (39.10%) of 33 patients with bioscore of 3 were infected. Eight (61.54%) of 13 patients with bioscore of 4 were infected. The whole of patients with bioscore of 5 ($n=2$) were infected.

Table 1 The demographic data and various markers of the infected group and the disease relapse group

	Infected group ($n=16$)	Disease relapse group ($n=45$)	<i>p</i>
Age	41.00 (28.25,56.75)	39.00 (26.00,46.50)	0.055
Gender			
female	4 (11.11%)	7 (15.56%)	0.400
male	32 (88.89%)	38 (84.44%)	
Weight (kg)	59.84 \pm 10.96	58.53 \pm 10.59	0.302
C3 (g/L)	0.46 (0.29,0.55)	0.56 (0.43,0.69)	0.001
C4 (g/L)	0.08 (0.03,0.12)	0.11 (0.06,0.17)	0.016
CRP (mg/L)	7.93 (3.35,23.15)	4.81 (2.02,10.48)	0.049
PCT (ng/mL)	0.19 (0.02,0.79)	0.09 (0.01,0.21)	0.160
nCD64 index	1.06 (0.75,3.13)	0.92 (0.73,1.17)	0.034
WBC ($\times 10^9/L$)	4.43 (3.42,8.01)	3.75 (2.46,6.72)	0.028
T cell (cell/ μ L)	727.50 (414.00,935.00)	722.68 (427.06,1141.00)	0.243
B cell (cell/ μ L)	89.56 (56.28,162.00)	130.00 (79.50,315.38)	0.010
NK cell (cell/ μ L)	58.50 (32.50,99.00)	49.00 (28.51,136.00)	0.470
Th cell (cell/ μ L)	263.50 (110.75,477.25)	276.00 (159.09,497.48)	0.213
Ts cell (cell/ μ L)	364.00 (193.25,506.43)	384.00 (234.50,543.30)	0.142
Th1 cell (cell/ μ L)	13.08 (11.72,84.63)	46.00 (15.53,95.60)	0.303
Th2 cell (cell/ μ L)	4.50 (2.40,8.07)	4.94 (2.48,9.20)	0.291
Th1/2 cell (cell/ μ L)	4.51 (2.27,7.31)	4.17 (2.08,9.30)	0.412
Treg cell (cell/ μ L)	13.49 (3.99,23.13)	12.46 (4.66,27.37)	0.492
Th1/Th2	3.00 (2.61,11.96)	8.22 (4.96,14.00)	0.274
Th1/2/Treg	0.30 (0.17,0.69)	0.40 (0.17,0.80)	0.434

Continuous variables were reported as Mean \pm standard deviation (M \pm SD) or median and interquartile range (IQR) and analyzed by the *t* test or Mann-Whitney U test for independent samples. Categorical variables were expressed as numbers and proportions and compared with Chi-square test.

0.754), B cells: 0.652 (CI 0.538-0.754)] and the best combination was nCD64 index, CRP, WBC, C3 and C4. The bacterial infection rate in patients with bioscore $\leq 2, 3, 4, 5$ and 6 were 0.00%, 39.29%, 59.10%, 61.54% and 100.00%, respectively.

Conclusion: The combination of nCD64 index, C3, C4, CRP, WBC and B cells in a bioscore is useful to diagnose bacterial infection in SLE.

Disclosure: M. Feng, None; Z. Liang, None; X. Zhao, None; C. Gao, None; J. Luo, None.

Urinary Galectin-3 Binding Protein As a Novel Biomarker of Renal Disease Activity in Lupus Nephritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Lupus nephritis (LN) is one of the most common and severe manifestations of systemic lupus erythematosus (SLE). This study investigates urinary galectin-3 binding protein (G3BP) levels in LN patients and their association with renal disease activity both clinically and pathologically.

Methods: A total of 44 biopsy-proven active LN, 27 active non-nephritis SLE and 24 inactive SLE patients were recruited. All of them fulfilled the 1997 ACR classification criteria for SLE. 28 Age matched healthy controls were recruited. Urinary G3BP was tested by ELISA. rSLEDAI was the total score of the four kidney-related parameters in SLEDAI.

Results: Urinary G3BP levels were significantly increased in active LN patients, and discriminated LN patients (27.65 (12.68-62.04)) from active non-nephritis SLE (6.35 (1.84-14.25), Area Under the Curve (AUC): 0.81 ($P<0.001$)), inactive SLE (7.62 (3.58-23.57), AUC: 0.74 ($P=0.001$)), and healthy controls (1.89 (1.31-5.54), AUC: 0.89 ($P<0.001$)) (Tab.1 and Fig. 1). Urinary G3BP performed better in discriminating active LN from active non-LN nephritis SLE than conventional markers, such as C3 (AUC: 0.51), C4 (AUC: 0.59), and anti-dsDNA (AUC: 0.51). Correlation analysis showed a significant negative correlation between urine G3BP and hemoglobin ($r=-0.29, P=0.005$), positive correlation between urine G3BP and

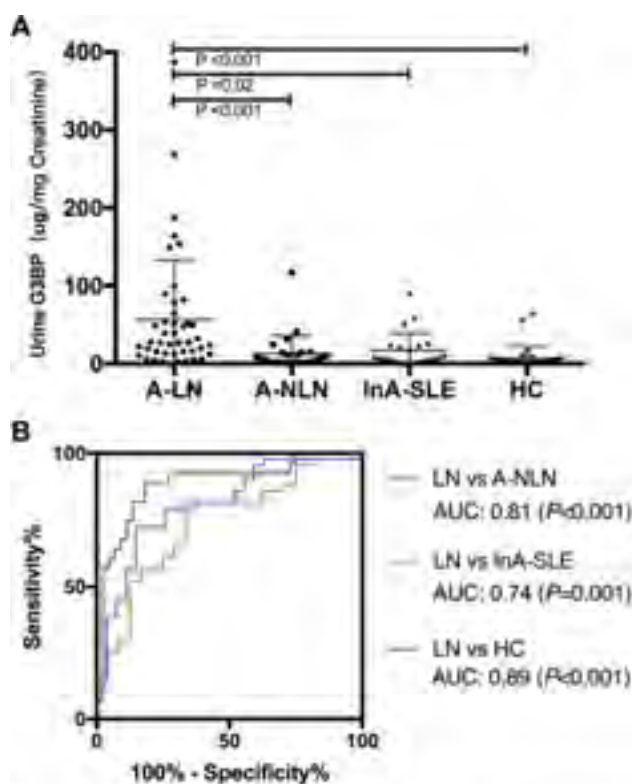


Figure 1. Urinary G3BP level is significantly increased in active LN patients. A. Group comparison. B. Receiver Operating Characteristic (ROC) curve.

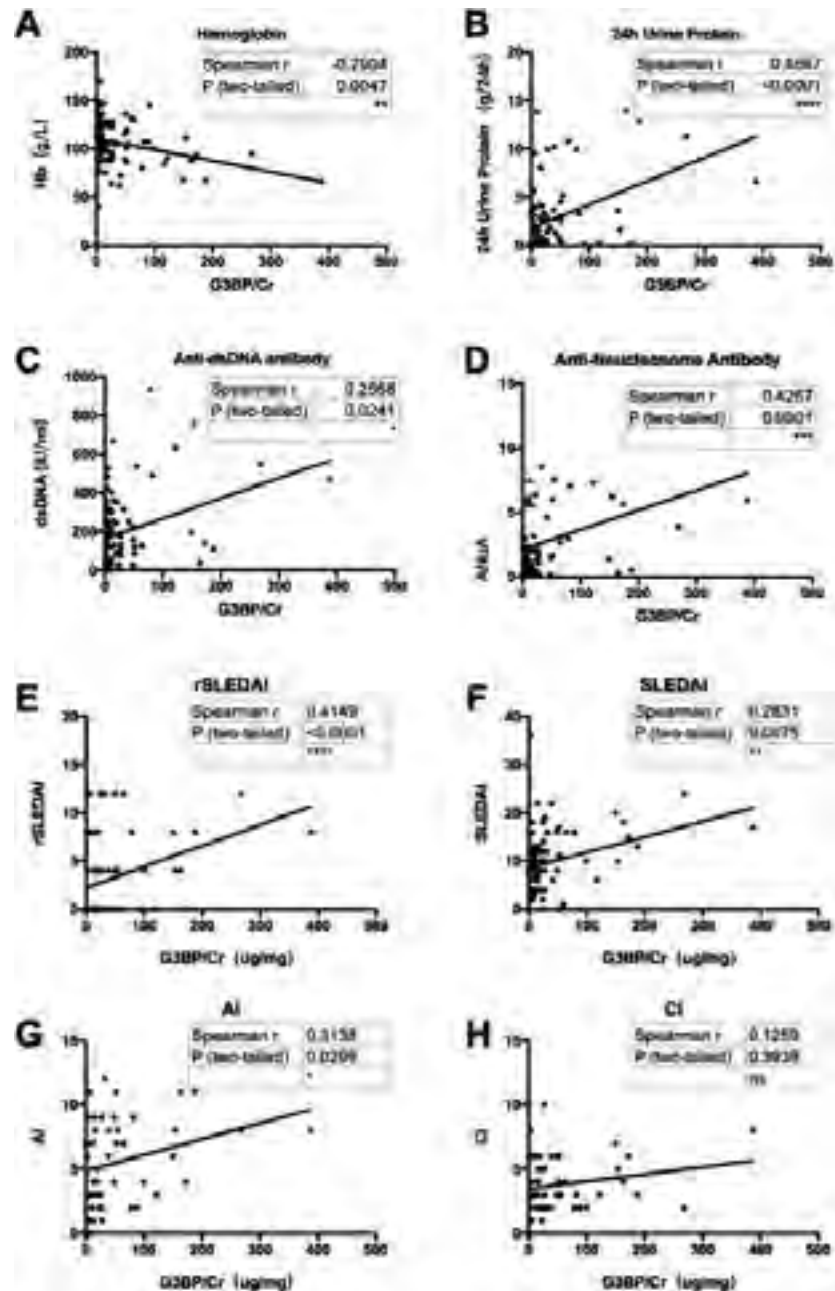


Figure 2. Correlation analysis between urinary G3BP and A. Hemoglobin; B. 24-hour urine protein; C. Anti-dsDNA antibody level; D. Anti-nucleosome antibody level; E. rSLEDAI; F. SLEDAI; G. Activity Index (AI); H. Chronicity Index (CI)

24-hour urine protein ($r=0.46$, $P<0.001$), anti-dsDNA antibodies ($r=0.26$, $P=0.02$) and anti-nucleosome antibodies ($r=0.43$, $P<0.001$) (Fig.2A-2D). Moreover, renal disease activity as assessed by rSLEDAI correlated with urine G3BP levels ($r=0.41$, $P<0.001$) (Fig. 2E). In 44 biopsy-proven active LN patients, urine was collected one day before the biopsy day. These previous concurrent samples revealed urinary G3BP levels were significantly elevated in Class III and Class IV LN over Class V LN (32.59 (15.75-80.46) vs 4.54 (3.83-19.09)). More importantly, urinary G3BP correlated with pathological renal activity index (AI), suggesting the measurement of G3BP levels in urine is useful in monitoring the progression of renal pathologies in patients with LN (Fig. 2G-H).

Conclusion: Our data suggest urinary G3BP as a biomarker for renal pathologies in patients with LN. These findings should be confirmed in a larger cohort to further validate the utility of urinary G3BP as a biomarker.

Disclosure: H. Ding, None; C. Ling, None; R. Bassi, EMD Serono, 3; S. L. Okitsu, EMD Serono, 3; J. A. DeMartino, EMD Serono, 3; Merck Co., 1; N. Shen, None.

Abstract Number: 758

Cutaneous Lupus Erythematosus Patients with a Negative ANA Meeting ACR and/or SLICC Criteria for Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

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Background/Purpose: Systemic lupus erythematosus (SLE) is a disorder that is heterogeneous and can be difficult to diagnose. One hallmark of the disease is the presence of anti-nuclear antibodies (ANA), a feature that has been incorporated into multiple classification criteria over the years. In this study, we use a database of cutaneous lupus erythematosus (CLE) patients to determine how many have a negative ANA and meet criteria for SLE using ACR and/or SLICC criteria.

Methods: We used a database of 454 CLE patients at the University of Pennsylvania that contained information including ANA status and the presence of features of SLE. The database was searched for patients who had a negative ANA and whether or not they met SLE criteria using the ACR and/or SLICC criteria.

Results: Of the 406 active patients with a known ANA, 147 had a negative ANA (36.2%) and 39 of all patients who had multiple ANAs checked (n = 114) had an ANA that fluctuated (34.2%). 30 ANA negative patients met SLE criteria (20.4%) and 19 patients with fluctuating ANA met SLE criteria (48.7%). Of all patients who had either a negative or a fluctuating ANA and met criteria for SLE (n = 49), 40 patients had involvement of at least 1 organ system other than skin (81.6%), and 22 patients had involvement of at least 2 organ systems other than skin (44.9%). Of the 40 patients with non-mucocutaneous organ involvement, 35 patients had arthritis, 14 patients had leukopenia, 9 patients had renal involvement, 4 patients had serositis, 3 patients had neurologic involvement, and 1 patient had thrombocytopenia.

Conclusion: Our results demonstrate that a positive ANA is not always present in patients with SLE involving non-mucocutaneous organ systems. If a positive ANA was a requirement for diagnosing SLE, many patients, who warrant treatment or should be included in clinical trials, would be excluded. This should be taken into consideration when devising SLE classification criteria to be used for clinical trials.

Disclosure: M. Tarazi, None; C. Kushner, None; R. Gaffney, None; V. P. Werth, None.

Abstract Number: 759

Comparison of Length of Stay and Total Hospital Charges for Hospitalizations for Sepsis in Patients with Systemic Lupus Erythematosus: A Study of National Inpatient Sample Database 2010 to 2014

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Sepsis is a systemic inflammatory response syndrome caused by an infection with at least one acute organ failure and is major public health concern.¹ Serious infectious diseases are recognized as major causes of morbidity and mortality in patients with systemic lupus erythematosus (SLE). Hospitalization of patients with SLE is a major cause of healthcare costs², but limited research is available examining cost differences of complications associated with lupus including severe infections and sepsis.

Methods: We analyzed hospitalizations for sepsis among adults in the Nationwide Inpatient Sample (NIS). Patients were stratified into two groups based on the status of SLE; using ICD-9 CM diagnostic codes. Descriptive statistics were represented as means/medians for continuous and as frequencies and percentages for categorical variables. A survey weighted multivariate regression analysis was used to adjust for confounders when calculating length of stay and total charges.

Results: There were an estimated 35475 adult hospitalizations for sepsis with secondary diagnosis of lupus, from 2010 to 2014. On univariate analysis, the average age of patients admitted with sepsis in the general population was 67.154 ± 0.064 years, whereas in the SLE population, the average age was 54.145 ± 0.225 years ($p < 0.0001$). Among the general population, 51.47% of all patients with sepsis were females; whereas among the SLE population, 87.79% of the population were females ($p < 0.0001$). Septic patients with secondary diagnosis of lupus had significantly higher length of stay and total cost per hospitalization. When adjusted for patient factors affecting population with SLE including age, gender and race, length of stay was still found to be significantly high by a coefficient of 0.27 (p value = 0.01). Similar results were noted in total hospital cost with average \$3541 increase in charges, for patients with sepsis and lupus, when adjusted for age, gender and race.

Conclusion: From our study, SLE is associated with higher cost burden and length of stay in patients admitted with sepsis. This may reflect decreased immune response from the disease itself as well as use of immunosuppressive drugs, resulting in longer stay in hospitals. Inpatient hospital charges associated with sepsis can be decreased with early and aggressive intervention. Rheumatology providers should have low threshold to screen patients for infections to prevent progression of infections to sepsis. This will help reduce healthcare utilization and costs in patients with underlying SLE.

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2. Anandarajah AP et al. Lupus. 2017 Jun;26(7):756-761. <https://doi.org/10.1177/0961203316676641>. Epub 2016 Nov 12. PubMed PMID: 27831537.

Table 1: Characteristics of patients admitted with Sepsis with secondary diagnosis of SLE from 2010-2014

Characteristics	Patients with sepsis without Lupus (n=4466146)	Patients with sepsis without Lupus (n=5475)	P value
Age in years (mean \pm SE)	67.154 \pm 0.064	54.145 \pm 0.225	0.000
Sex (%)			0.000
Males	48.53	12.21	
Females	51.47	87.79	
Race (%)			0.000
White	71.86	52.34	
Black	13.32	27.77	
Hispanic	8.85	13.42	
Asian or Pacific Islander	2.78	2.89	
Native American	0.7	0.98	
Other	2.49	2.6	
Length of Stay per hospitalization in days (Mean \pm SE)	7.38804 \pm 0.272	7.80936 \pm 0.105	0.000
Total Charge per hospitalization in dollars (Mean \pm SE)	65554.5 \pm 623	72183 \pm 1522	0.000

Disclosure: K. Chugh, None; S. Jatwani, None; K. Jatwani, None; J. Kaur, None.

Abstract Number: 760

Diagnosing SLE Arthritis with Dynamic Diffuse Optical Spectroscopy

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

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

Background/Purpose: SLE arthritis is difficult to evaluate because of the sometimes-evanescent nature of the symptoms and limitations of physical exams and imaging studies. Dynamic diffuse optical spectroscopy (dDOS) can be used to assess changes in light absorption through tissues during transient venous occlusion. The optical signal reflects changes in blood perfusion and has diagnostic value in rheumatoid arthritis. The current study explored the use of dDOS in SLE arthritis.

Methods: 11 SLE patients (ACR criteria) with active arthritis and 4 controls were evaluated. A dDOS sensor module was developed (Fig. 1). Hemodynamic effects were obtained by inflating a BP cuff to 40 mmHg x 60 seconds. Light at 3 wavelengths ($\lambda = 530, 655, 940\text{nm}$) was used to illuminate joints at 8 different points. Transmitted light intensities

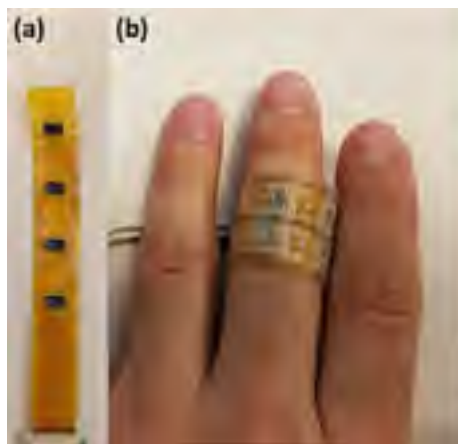


Fig. 1: Two dDOS sensor module bands (1a) wrapped around a PIP joint for measurement (1b). Each band contains 4 measurement heads (black dots). Each of the measurement heads includes 3 light-emitting diodes at three different wavelengths ($\lambda = 530\text{nm}$, 655nm , and 940nm , power = 2mW) and one Si-photodetector.

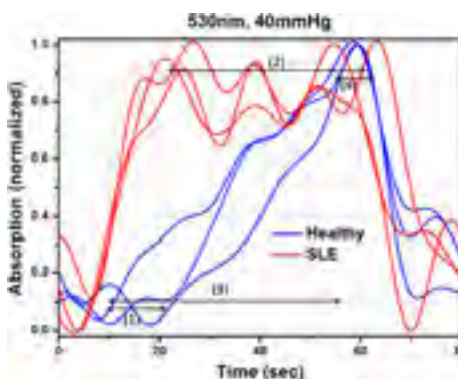


Fig. 2: Representative raw data for one healthy subject (blue) and one SLE arthritis subject (red). (1) and (2) are respectively the rise and the plateau times for a SLE patient, while (3) and (4) are respectively the rise and the plateau times for a healthy patient. It can be seen that SLE arthritis joints display a faster rise time (time needed to increase from 10% to 90% of the maximum value) and a longer plateau time than healthy joints.

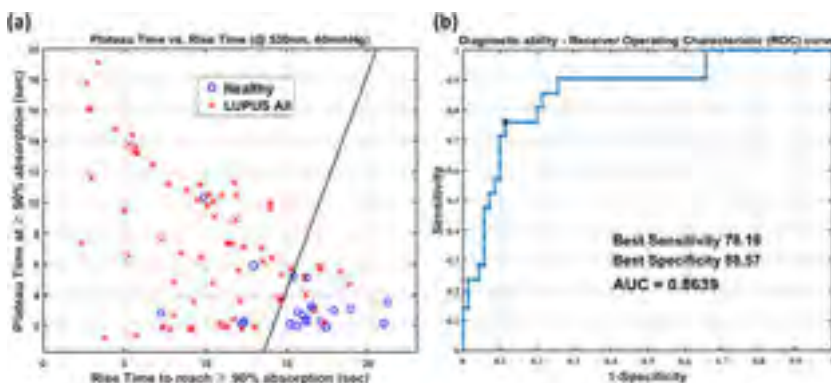


Fig. 3: Discriminant and ROC analysis which demonstrate the high specificity and sensitivity of dDOS when taking into account the rise time and the plateau time of the absorption signal (see Fig. 2).

were measured with Si-photodetectors at 8 other positions (total 8x8x3=192 signal traces). Swollen, tender and healthy joints were examined by the same assessor.

Results: SLE patients and normal controls dDOS data were available for analysis from 66 and 24 proximal interphalangeal (PIP) joints, respectively (PIPs 2-4). Best results were obtained at 530 nm with cuff inflation at 40 mmHg. A representative measurement of 3 SLE arthritis and 3 normal joints is shown in Fig. 2, highlighting differences in rise and plateau time. Given the pronounced effects at $\lambda = 530\text{nm}$, we speculate that altered vessel physiology paired with already-increased blood pooling in the affected inflamed joints resulted in quicker increase in light absorption (rise time) that is maintained longer (plateau time) compared to normal joints. The AUC for dDOS was consistent with excellent discrimination, AUC = 0.8639, sensitivity = 76.19, specificity = 88.57 (Fig. 3).

Conclusion: dDOS can evaluate SLE arthritis with high sensitivity and specificity. Rise and plateau time of the optical traces correlate strongly with swollen and tender joint count. The advantages of dDOS are non-invasiveness, objectivity (eliminates inter-rater variability and operator dependency), low cost, and high speed of performance (~5 min per area of scanning) compared to US and MRI. dDOS has the potential to bring much-needed objectivity to the quantification of SLE arthritis.

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Abstract Number: 761

Protein/Creatinin Urinary Index Has Concordance with 24 Hour Urinary Proteinuria in Patients with Systemic Lupus Erythematosus

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SESSION INFORMATION

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Background/Purpose: Twenty-four hour proteinuria (24hp) has been the gold standard for the screening and follow up of glomerular disease. The use of protein/creatinin urinary index (PCI) in a spot urine sample, has been proposed as an alternative to 24hp due to its low cost and simple recollection of the sample. This method has been validated in patients with diabetic and non-diabetic nephropathy, with less data in patients with Systemic Lupus Erythematosus (SLE). The aim of this study was to measure the correlation and concordance between these two methods in patients with SLE

Methods: Paired samples of 24hp (in grams in 24 hours) and PCI (first urine sample, expressed in mg/g) in SLE diagnosed patients with or without lupus nephropathy, collected between June 2015 and May 2018, in Señor del Milagro's Hospital at Rheumatology Unit were included for the analysis. PCI value is 1000 times higher than 24hp. Walser's index (WI) which evaluates the quality of the collected sample on 24hp, calculated with estimated and measured urine creatinine, age and weight was performed. A WI between 0.75 and 1.25 reflects well collected 24hp. Qualitative data was expressed in frequency and percentages, quantitative data in medians and interquartile range (IQR) or media and standard deviation (SD) depending on its distribution. Spearman test was performed to assess correlation between 24hp and PCI was. In order to analyze concordance between PCI and 24hp, the PCI was multiplied by 1000. Interclass Concordance Coefficient (ICC), with (Cronbach's alpha) was calculated. Receiver operating curves (ROC) with under the curve area (UCA) were calculated for 24hp values of ≥ 0.3 , 0.5, 1 and 3.5 grams per 24 hours, in order to calculate IPC cut points. A p value < 0.05 was considered significant.

Results: 68 patients, 60 (88.2) female, median age 33 years (IQR: 27-48), and 187 paired urine samples were included. Spearman's correlation between the 2 methods was 0.84. ICC was > 0.9 for the whole sample, 0.92 when WI was acceptable (n=88) and only dropped to 0.88 in the context of "non-acceptable" WI (n=99). Considering only acceptable WI samples, ROC curves showed cut points of 333 mg/g, 407 mg/g, 984 mg/g and 3013 mg/g had good sensitivity and specificity (S 77, Sp 87 or higher) to predict 24hp of 0.3 g, 0.5 g, 1 g and 3.5 g.

Conclusion: In this sample of SLE patients, 24ph and PCI had a good ICC and correlation, considering an acceptable WI. The use of PCI could replace 24ph in the assessment of glomerular disease in SLE patients.

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Abstract Number: 762

Aquaporin-4 Immunoglobulin G Antibody Positive Neuromyelitis Optica Spectrum Disorder and Systemic Autoimmune Diseases Overlap Syndrome: A Single Center Experience

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SESSION INFORMATION

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

Background/Purpose: The coexistence of neuromyelitis optica spectrum disorder (NMOSD) with other systemic autoimmune diseases is well recognized, especially with systemic lupus erythematosus (SLE) and Sjögren syndrome (SS). However, literature is scarce, limited to case reports and multicentric case series. The objective of this study is to describe the clinical and radiological characteristics and outcomes of patients with AQP4-IgG seropositive NMOSD coexisting with SLE and SS in a single center.

Methods: This was a retrospective study that included patients with concurrent diagnosis of AQP4-IgG seropositive NMOSD according to the 2015 International Consensus Diagnostic Criteria, and SLE according to the ACR revised criteria or SS according to the AECG criteria who regularly attended a tertiary referral center in Mexico City (2003-2018). We collected demographics, clinical (neurological events, number of relapses, remission, treatment, follow-up [date of last visit to a rheumatologist and/or neurologist] and disability according to the Expanded Disability Status Scale [EDSS]), laboratory (cerebrospinal fluid (CSF) analysis) and imaging data of NMOSD, as well as clinical and serological data of the overlapping autoimmune disease. We assessed disease activity in SLE and SS using SLEDAI-2K and ESSDAI respectively, and accrual damage with the SLICC/ACR-DI and SSDDI respectively.

Results: We included 11 patients, 10 (90.9%) women with a mean age at diagnosis of 36 ± 15 years. Seven (63.6%) had SLE and 4 (36.6%) primary SS. Five (45.5%) patients had also another systemic or organ-specific autoimmune disease. In 8 (72.7%) patients NMOSD followed SLE/SS onset, 2 (18.2%) had a simultaneous presentation, and in 1 (9.1%) NMOSD preceded SS diagnosis. The mean time from diagnosis of SLE/SS to the first neurological event was 54.6 months. The mean SLEDAI-2K and ESSDAI at first neurological event was 3.1 (mainly hypocomplementemia and high anti-dsDNA) and 14.3 points (mainly renal and peripheral nerve involvement) respectively. During follow-up, 10 patients (90.9%) experienced myelitis, 5 (45.5%) optic neuritis, 2 (18.2%) each experienced area postrema syndrome, acute brainstem syndrome and cerebral syndrome; being the median number of neurological events 4 (1-8). Three patients (27.3%) had antiphospholipid antibodies. None of the patients had pleocytosis or low CSF glucose and 3 had high CSF proteins. All patients had longitudinally extensive transverse myelitis on MRI, 3 (27.3%) optic nerve findings and 6 (54.5%) NMOSD-typical brain lesion patterns. Nine (81.8%) patients went into either total or partial NMOSD remission at a mean follow up of 6.5 ± 5.3 years. At last follow up the median EDSS, SLICC/ACR-DI and SSDDI was 2.5 (1-10), 2 (0-7) and 2 (0-3) points respectively; 4 (36.4%) patients had sequelae and 1 patient was death.

Conclusion: Patients with SLE or SS with clinical features of NMOSD should be tested for AQP4-IgG. In our cohort, AQP4-IgG seropositive NMOSD arose in the context of low SLE activity and in the context of SS with extraglandular features; and the disability and accrual damage at last follow up appeared to be mild.

Disclosure: E. Martín Nares, None; G. Hernandez-Molina, None; H. Frago-Loyo, None.

Comparison of Clinical Characteristics and Outcome between Isolated and Classic Lupus Nephritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Lupusnephritis (LN) is a serious manifestation of systemic lupus erythematosus(SLE). Rarely, patients may present with LN alone and have no extra-renalclinical manifestations of lupus (isolated lupus nephritis, ILN). We aimed to describe the clinical characteristics of patients presenting with isolated LN and to study their treatment outcome and long term survival and its predictors compared to classic LN.

Methods: Subjects were identified by searching a pathologic renal biopsy database. Clinical records were reviewed for exclusion of infectious and secondary causes. Cases with isolated LN were defined per 2012 SLICC criteria; classic SLE patients had lupus nephritis along with extra-renal manifestations of lupus. Complete response (CR) was defined as proteinuria <0.5 g/24 h and serum creatinine(sCr) within 125% of the baseline value after the start of induction therapy. Partial response (PR) was defined as reduction of proteinuria of >50% (and at least <3.0 g/24 hours) plus sCr within 125% of the baseline value after the start of the induction therapy.

Results: 30 patients with isolated LN and 134 patients with classic LN were identified. The median age at the time of biopsy was 41 and 39 years, for the ILN and LN group, respectively. Majority were Caucasian; female to male ratio was 3:1 in ILN and 2:1 in the LN group. The median duration from renal symptoms to biopsy was 5.2 months for ILN and 1.2 for the LN group (p=0.013). Mean sCr was 1.7 mg/dl and 1.3 mg/dl and 24hour proteinuria 8.5 and 4.9 g, respectively. A greater percentage of patients with ILN had hypertension at onset (83% versus 35% in LN, p<0.001) and interstitial fibrosis in biopsies (97% ILN versus 69% LN, p=0.018). The outcomes and survival among 18 ILN and 72 LN patients of class 3, 4 or mixed are noted in Table.

	ILN	LN
Complete response (95% CI)		
12 mo	23 (10, 54)	42 (32, 55)
5 year	48 (29, 80)	67 (57, 80)
10 year	62 (39, 99)	70 (59, 83)
Complete and/or partial (95% CI) response		
12 mo	51 (32, 80)	58 (48, 71)
5 year	69 (50, 95)	82 (73, 92)
10 year	85 (64, 100)	88 (79, 98)
ESRD/Renal transplant (95% CI)		
12 mo	6 (0, 40)	4 (1, 13)
5 year	12 (3, 45)	17 (10, 30)
10 year	30 (13, 71)	27 (17, 44)
Survival (95% CI)		
12 mo	94 (84, 100)	99 (96, 100)
5 year	88 (74, 100)	94 (87, 100)
10 year	64 (40,100)	87 (77, 100)

Conclusion: The response rates and 10 year survival tended to be higher in the LN group compared to ILN. Possible late recognition and/or under treatment of this subset may be underlying the differences.

Disclosure: K. Bugdayli, None; C. S. Crowson, None; L. Zand, None; M. P. Alexander, None; L. D. Cornell, None; V. R. Chowdhary, None.

Cardiovascular Disease in SLE at One Center between 1981 and 2016. a Population-Based Study Highlighting the Importance of Disease Duration and Age at Diagnosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Active inflammatory processes characterize early SLE disease, while later morbidity to a considerable extent consists of consequences of organ damage, particularly cardiovascular disease (CVD). In this study, we report on the frequency of acute myocardial infarctions and stroke in incident SLE cases in a defined population over an extended time.

Methods: The current study includes SLE patients followed at the Department of Rheumatology in Lund, Sweden, diagnosed 1981 through 2006. First, we compare incidence rates of acute myocardial infarctions (AMI) and cerebrovascular incidents (CVI) between all incident SLE cases within 8 counties, through the years 1998-2016, and the population. This time constraint is due to the availability of reliable electronic health care information for the population only from 1998 and forward. Second, we describe AMI and stroke incidence patterns in SLE patients 1981-2016 in an extended cohort. Only the first events of AMI and CVI respectively, both among SLE patients and in the population, were used for calculations.

Results: In all, 276 SLE patients were included in the study. From the defined 8 counties 175 SLE patients were studied and thus 101 patients from outside this region were included. Overall, 38 AMI and 44 CVI were recorded in 72 SLE patients, thus 10 patients had suffered both from an AMI and a CVI. The incidence rate-ratio for AMI was 3.0 in SLE overall (CI 1.3-6.9 (99.9%) $p<0.001$) compared with the population. Significantly increased rate-ratios of AMI were seen in women <40 and between 40-59 years of age, while for males only the age group 40-59 years had an increased incidence of AMI. SLE patients with a higher age at diagnosis (>54 years) had a shorter disease duration before suffering an AMI compared to SLE patients diagnosed at a younger age (median 7 years vs 18 years, $p<0.05$). The incidence rate-ratio for CVI in SLE overall was 3.2 (CI 1.6-6.6 (99.9%) $p<0.001$) compared to the population. An increased CVI incidence was only significant for women in the age group 40-59 years. Males were few and had only 2 events in the higher age group.

Conclusion: SLE patients are at risk of developing early myocardial infarctions and cerebrovascular incidents compared with the population. Patients with a younger age at SLE diagnosis may develop AMI after a longer disease duration compared to older patients.

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Predictors of End-Stage Renal Disease in Lupus Nephritis

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SESSION INFORMATION

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

Background/Purpose: End-stage renal disease (ESRD) is the most important complication of lupus nephritis (LN) and greatly affects mortality. Its incidence has been estimated at 11% at 5 years and 17% at 10 years after LN diagnosis. The identification of certain predictive factors is of importance for risk stratification and proper management. The aim of the present study was to define the factors associated with ESRD development in a defined cohort of LN patients.

Methods: Patients with LN (class II-V according to the International Society of Nephrology/Renal Pathology Society classification) were recruited from our long-term longitudinal cohort. Individuals with ESRD (estimated glomerular filtration rate, $eGFR \leq 15$ ml/min/1.73m²) at the first two clinic visits after enrolment were excluded. Patients were followed until the occurrence of ESRD (defined as two consecutive visits with an $eGFR \leq 15$ ml/min/1.73m² or initiation of dialysis) or last visit. They were divided in two groups (ESRD or not) and compared as per the demographic, histopathological, clinical and therapeutic variables. Statistical analysis was performed with SAS 9.0; $p < 0.05$ was considered significant. Time-dependent Cox regression analysis was performed for the identification of predictors.

Results: LN was diagnosed in 560 patients, 43 of whom developed ESRD (7.7%) after 7.5 ± 6.4 years of follow up. There were no differences in demographic variables at baseline. Concerning the histopathologic class, diffuse proliferative LN (class IV) was more frequent in the ESRD patients (51.2% vs. 28.4%, $p = 0.033$). Baseline serum creatinine was higher in the ESRD patients (152 ± 94 vs. 85 ± 41 mmol/L, $p < 0.001$); consequently $eGFR$ was lower (61 ± 37 vs. 93 ± 37 ml/min/1.73m² respectively, $p < 0.001$). Hypertension was more frequent in the ESRD patients (58.1 vs. 38.3%, $p = 0.015$). Concerning laboratory values, initial proteinuria was more severe in the ESRD patients (3.2 ± 2.5 vs. 1.9 ± 2.8 g/day, $p = 0.027$) whereas hemoglobin was lower (113 ± 18 vs. 120 ± 20 g/L, $p = 0.02$). There were no differences in therapeutic variables (dose of glucocorticosteroids, type and dose of immunosuppressives and antimalarials). Patients with ESRD were using angiotensin converting enzyme inhibitors or angiotensin receptor blockers more frequently (34.9 vs. 21.3%, $p = 0.04$). Multivariable Cox regression analysis revealed that hypertension (HR=10.1, 95%CI=4.34-23.8, $p < 0.001$), baseline serum creatinine (HR=1.009, 85%CI=1.008-1.01, $p < 0.001$) and initial prednisone dose (HR=1.016, 95%CI=1.001-1.031, $p = 0.03$) were associated with a higher probability for ESRD development. On the contrary, normal hemoglobin at baseline was protective (HR=0.97, 95%CI=0.95-0.99, $p < 0.001$).

Conclusion: Initial serum creatinine and hypertension were the most important predictors for the development of ESRD in patients with LN. These findings reinforce the importance of regular monitoring of serum creatinine even in asymptomatic patients as well as the need for strict control of hypertension in LN.

Disclosure: M. Deeb, None; K. Tselios, None; D. D. Gladman, Abbvie, Amgen, BMS, Celgene, Eli Lilly and Company, Janssen, Novartis, Pfizer, UCB, 5, Abbvie, Amgen, Celgene, Janssen, Novartis, Pfizer and UCB, 2; J. Su, None; M. Urowitz, None.

Abstract Number: 766

Neutrophil Extracellular Traps Are a Source of Extracellular High Mobility Group Box-1: Association with Clinical and Histopathological Features in Patients with Lupus Nephritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

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

Background/Purpose: Current evidence suggests that neutrophils play an important role in the pathophysiology of lupus nephritis (LN) mainly through the secretion of type I IFN and the production of Neutrophil Extracellular Traps (NETs). This type of cell death releases proinflammatory molecules, including High Mobility Group Box-1 (HMGB1). HMGB1 acts as an alarmin once released into the extracellular space and induces the synthesis of proinflammatory cytokines through its interaction with diverse receptors. Elevated levels of this protein have been associated with global disease activity as well as LN. However, the precise source of extracellular HMGB1 has not been addressed. The aim of this study was to analyze the expression of HMGB1 in NETs of patients with LN and its association with clinical and histopathological characteristics of the disease.

Methods: Twenty-three patients with LN confirmed by biopsy as well as 14 SLE patients with active disease (SLEDAI ≥ 6) and no evidence of LN were included. Clinical and laboratory features were obtained. NETs and the expression of HMGB1 were assessed by immunofluorescence and confocal microscopy. Besides, serum HMGB1 levels were measured by ELISA.

Results: 81% of the patients were women and the mean age was 30.6 years. Patients with LN were characterized by a higher expression of HMGB1 in NETs compared to patients without LN (Spontaneous: 57 vs 30.4, $p=0.027$; LPS: 55.8 vs 24.9, $p=0.005$), even though, we did not find differences in serum HMGB1 levels ($p=0.920$) nor the amount of NETs (Spontaneous: $p=0.230$, LPS $p=0.263$). Nonetheless, we found a positive correlation between serum HMGB1 and HMGB1 expression in LPS-induced NETs ($r=0.447$, $p=0.017$). The expression of HMGB1 in spontaneous NETs correlated with serum creatinine ($r=0.481$, $p=0.003$), proteinuria/creatinuria index ($r=0.34$, $p=0.039$), % of glomerular filtration rate descent ($r=0.543$, $p=0.001$), SLEDAI score ($r=0.508$, $p=0.001$), anti-DNAbs ($r=0.514$, $p=0.001$) and diverse histopathological findings of active LN in the renal biopsy as shown in Table 1.

Conclusion: Our findings support the hypothesis that NETs are a relevant source of extracellular HMGB1 in patients with LN. The positive correlation between HMGB1 from spontaneous NETs and histopathologic findings of active proliferative LN suggest the role of this alarmin in the pathophysiology of renal damage in SLE.

Table 1: Correlations between the mean fluorescence intensity of HMGB1 in spontaneous NETs and histopathological findings in renal biopsies.

Feature	Rho	p value
Activity Index	0.581	0.001
% of fibrinoid necrosis	0.621	0.002
% of cellular crescents	0.641	0.001
% of leukostasis	0.452	0.030
% of endocapilar proliferation	0.455	0.029
% of wire loop lesions	0.420	0.046

Disclosure: L. P. Whittall, None; D. Gómez-Martín, None; J. Torres-Ruiz, None; A. Zentella Dehesa, None; M. Tapia-Rodríguez, None; J. Alcocer-Varela, None.

Abstract Number: 767

Tobacco and Systemic Lupus Erythematosus Relationships: Pay Attention to the Retina!

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SESSION INFORMATION

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Session Type: ACR Poster Session A

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

Background/Purpose: Only a few studies have analyzed the influence of tobacco smoking in SLE in a quantitative way. Furthermore, scanty information exists regarding smoking and damage in SLE patients, considering the damage by organs, in a separate manner. The objective of this study was to carry out a cross-sectional analysis of the smoking habit in a well characterized, monocentric, cohort and to analyze the influence of tobacco on SLE phenotype, activity and specific damage. Additionally, we inquired about the degree of patient weakness regarding the impact of the tobacco use in SLE.

Methods: Consecutive SLE-patients (ACR-97 criteria) attendant our Lupus clinic throughout 2017 were included. At the time of the last visit, activity (S SLEDAI), cumulative clinical data and comorbidities were retrospectively collected and damage (SLICC/ACR damage index (SLICC/ACR DI) was calculated. To determine patients' smoking exposure, we used a standard model questionnaire and the pack-year (PY) was calculated. Patients ever smoking versus never smoking were compared, using only cumulative variables. A regression model was built to identify factors associated with retinal damage

Results: 216 patients included. Mean age 49 years (± 12.7), 93% females, median disease duration of 17 years (p25-p75: 9-25). 53% of the patients recognized to having ever smoked and 23% were active smokers. Medium PY: 13 (6-20.5). Sixty-one percent of all patients recalled being informed of the negative effects of smoking on their disease. However, only 54.8% of current smokers admitted to having been informed, compared to 83.3% of non-smokers ($p < 0.001$). In the bivariate analysis, a statistically significant association between tobacco any time and discoid lupus [$p = 0.002$; OR:3.5 (IC95% 1.5-8.9)] and photosensitivity [$p = 0.01$; OR:2.06 (IC95% 1.16-3.7)] was found. Regarding SDI, a trend was identified ($p = 0.08$) with a significant association with retinal damage, adjusted by age (OR 1.03, CI95% 1-1.07, $p = 0.04$) when the comparison was made considering the SDI organ by organ. Regarding comorbidity, the only one significant association that we found was peripheral arteriopathy ($p = 0.007$). When the comparison was carried out using PY, a statistically significant association was found with global SDI > 0 ($p = 0.002$) and retinal damage ($p = 0.02$), as well as with discoid lupus ($p = 0.01$), photosensitivity ($p = 0.03$) and peripheral arteriopathy ($p = 0.01$), suggesting a dose-response relationship. In a multivariate analysis exploring factors associated to retinal damage, just smoking ever and SDI remain statistically significant.

Conclusion: Smoking is associated to cutaneous manifestations and damage in SLE patients as well as peripheral arteriopathy, with a dose-response relationship. There is a specific association, not previously reported, between retinal damage and smoking. If confirmed, this association should be considered when planning the ophthalmologic monitoring for antimalarials use. It is imperative to optimize the patient education about the impact of tobacco consume in SLE.

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Abstract Number: 768

Spinal Cord Syndromes Associated with Systemic Lupus Erythematosus: Differentiating Lupus Myelitis, Neuromyelitis Optica, and Multiple Sclerosis

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Non-infectious myelitis in SLE is caused by heterogeneous disease processes including SLE myelitis, comorbid multiple sclerosis (MS), or anti-aquaporin-4 antibody (AQ4) mediated neuromyelitis optica (NMO). These conditions with different treatments and prognosis are difficult to differentiate. We compared the demographic, clinical, laboratory, and radiographic characteristics of these 3 conditions in SLE patients at a large academic institution.

Methods: We searched the Brigham and Women's Hospital Lupus Center Registry comprised of 2,297 patients with ≥ 4 1997 ACR revised criteria for SLE. Neurologic diagnoses within this population were identified by text string searches within electronic medical records for the terms "myelitis", "NMO", "neuromyelitisoptica", and "multiple sclerosis" between January 1, 2000 and December 31, 2015. Each subject was then reviewed by an attending neurologist to confirm the diagnosis of myelitis, NMO, or MS. To be classified as NMO, subjects required a positive AQ4 antibody and a neurologic syndrome typical of NMO (myelitis +/- optic neuritis). To be classified as MS, subjects required 2 separate neurologic syndromes typical of MS with characteristic brain lesions. Demographic, clinical, laboratory, and radiographic data were extracted. Characteristics of these 3 groups were compared using Fisher's exact test for categorical variables and analysis of variance for continuous variables. Wilcoxon rank-sum test was used for SLEDAI-2K score, ESR, and CRP level as these values were not normally distributed.

Results: Fifteen subjects with SLE (0.7%) met criteria for a spinal cord syndrome: 7 had myelitis, 3 had NMO, and 5 had MS (Table). The median SLEDAI-2K score at time of neurologic syndrome presentation was higher in myelitis subjects (8, IQR 7-16) compared to subjects with NMO (6, IQR 0-14) or MS (2, IQR 0-4), $p = 0.02$. Subjects with myelitis were also more likely to have elevated anti-dsDNA antibodies at presentation (86%) compared to subjects with NMO (33%) or MS (0%), $p = 0.03$. In all 3 groups, 100% of subjects who had a repeat MRI of the spine ≥ 6 months after spinal disease onset had persistent lesions. One year after spinal disease onset, all subjects were either in American Spinal Injury Association Impairment Scale (AIS) category D (in complete motor loss, $\geq 4/5$ strength) or category E (normal function).

Conclusion: Compared to subjects with SLE + NMO and subjects with SLE + MS, subjects with SLE myelitis had higher SLE disease activity at myelitis onset as indicated by SLEDAI-2K scores and elevated anti-dsDNA antibody levels. Studies involving larger populations should be conducted to differentiate these 3 conditions.

Table. Comparison of subjects with SLE myelitis, SLE +NMO, and SLE + MS at neurologic event presentation*

	SLE myelitis (n=7)	SLE + NMO (n=3)	SLE + MS (n=5)	p-value
Demographic Characteristics				
Age, mean \pm SD years	41 \pm 10	46 \pm 14	40 \pm 13	0.80
Sex				0.67
Female	5 (71)	3 (100)	5 (100)	
Male	2 (29)	0 (0)	0 (0)	
Race				1.00
White	6 (86)	3 (100)	5 (100)	
Black	1 (14)	0 (0)	0 (0)	
Years since SLE onset, mean \pm SD	10 \pm 11	22 \pm 15	16 \pm 3	0.23
Clinical Characteristics				
SLE flare	3 (43)	0 (0)	0 (0)	0.25
Median SLEDAI-2K score (IQR)	8 (7-16)	6 (0-14)	2 (0-4)	0.02
Sensory loss	6 (86)	1 (33)	3 (60)	0.39
Weakness	4 (57)	2 (67)	1 (20)	0.41
Bowel or bladder symptoms	3 (60)	1 (33)	1 (20)	0.77
Optic neuritis	2 (29)	2 (67)	0 (0)	0.13
Full response to acute treatment	1 (14)	0 (0)	1 (20)	1.00
Recurrence of disease	1 (14)	1 (33)	0 (0)	0.67
AIS Category E (normal) at 1 year	3 (43)	1 (50)	3 (60)	1.00
Laboratory Characteristics				
Elevated anti-dsDNA antibody	6 (86)	1 (33)	0 (0)	0.03
Hypocomplementemia	4 (57)	1 (33)	1 (33)	1.00
Antiphospholipid antibody positive	5 (71)	0 (0)	1 (20)	0.15
Median ESR in mm/hr (IQR)	19 (12-45)	22 (13-34)	11 (5-20)	0.24
Median CRP in mg/L (IQR)	7 (2-13)	5 (2-8)	0.6 (0.6-2)	0.07
Oligoclonal bands in CSF	2(67)	0 (0)	2 (100)	0.23
MRI Characteristics				
Single spinal lesion	5 (71)	1 (50)	1 (25)	0.39
Contrast-enhancing lesion(s)	4 (67)	1 (50)	1 (25)	0.48
Longitudinally extensive myelitis	2 (29)	1 (50)	1 (25)	1.00
Persistent lesion(s) after \geq 6 months	6 (100)	1 (100)	4 (100)	N/A

* Unless indicated otherwise, values are the number (%).

AIS=American Spinal Injury Association Impairment Scale

Note: missing values were excluded from analyses.

Disclosure: J. Williams, None; C. Speyer, None; D. Kreps, None; K. Costenbader, None; S. Bhattacharyya, None.

Abstract Number: 769

Herpes Zoster in Systemic Lupus Erythematosus: Prevalence and Risk Factors

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

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Background/Purpose: Herpeszoster (HZ) commonly observed in the elderly and in immune-compromised patients. The prevalence of HZ is 3.6-19.9% in previously reported data. The higher prevalence of HZ in Systemic Lupus Erythematosus (SLE) patients is aggravated by the concomitant use of immunosuppressant and glucocorticoids (GCs). The objective of this study is to determine the prevalence and describe the characteristics of HZ in an SLE cohort.

Methods: A patient questionnaire was developed to examine HZ in SLE patients. It includes different questions on patient' demographics, the onset of HZ in relation the SLE onset, pain related to HZ, history of varicella zoster vaccine, anti-viral therapy for HZ, and several estimated risk factors for HZ. The survey was distributed to consecutive SLE

patients attending the Lupus Clinic from January 2016 to April 2018. All patients were evaluated according to a standard protocol which includes assessment of disease activity (SLE Disease Activity Index 2000 [SLEDAI-2K]). Analysis included descriptive statistics.

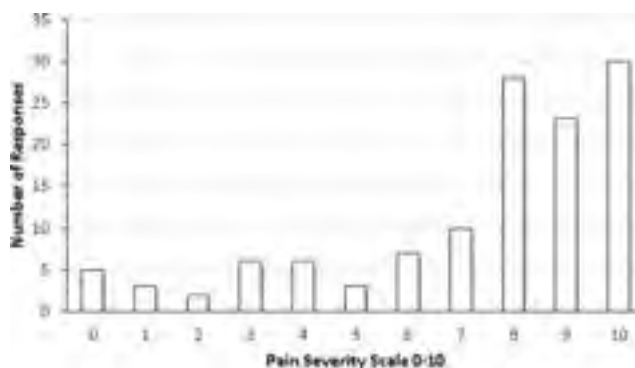
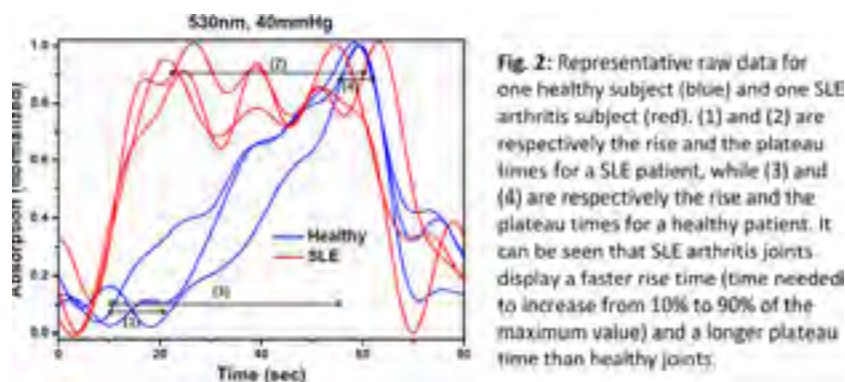


Figure 1. HZ Pain Severity as Reported by SLE Patients (N=123)



Results: Of 912 patients who visited the clinic within that period, 412 patients completed the survey. The prevalence of HZ was 127 (30.8%) at a mean age of 47.4 ± 13.7 years. Of these 127 patients, 32 (25.2%) patients experienced recurrent HZ event, occurring within 12.2 ± 12.1 years from the 1st HZ event. The demographic features of SLE patients with and without HZ are presented in Table 1.

HZ occurred in the first 5 years post SLE diagnosis in 43.1% of patients, 18.1% reported HZ from 6-10 years and 38.2% reported HZ occurrence ≥ 10 years post SLE diagnosis. Mean SLE duration at first HZ was 9.6 ± 9.8 years. Most (78.8%) of those who developed HZ were not vaccinated prior to HZ. 97.6% of HZ was confirmed by physician and 78% received anti-viral therapy. HZ pain, itching or tingling in the rash area was reported in 96.7% of patients. The majority of the patients reported pain (95.9%) and 74.0% scored between 7 and 10 (Fig. 1).

Eighty patients (62.9%) reported taking prednisone at the time of HZ. Of those, 32 patients reported a mean prednisone dose of 23.3 mg/day (range, 3–60 mg). Seventy-two patients (56.7%) were on immunosuppressant (Azathioprine 31.5%, Mycophenolate mofetil 14.17%, Methotrexate 6.3% and cyclophosphamide 4.72%).

Conclusion: The HZ prevalence of 30.8% was higher than previously published data in SLE. HZ can be an early comorbidity in SLE, with 43.1% of cases occurring within 5 years of SLE diagnosis and 57% after 10 years of SLE diagnosis.

Table 1. Demographic characteristic at study visit of patients with and without HZ

Characteristic	Patients who had HZ (N=127)	Patient who never had HZ (N=285)	P value
Sex (F)	118 (92.9%)	257 (90.2%)	0.369
Age in years at SLE diagnosis (mean \pm SD)	30.1 ± 13.1	31.0 ± 11.3	0.482
Age in years at study visit (mean \pm SD)	51.9 ± 14.5	47.4 ± 13.7	0.002
SLE duration at study visit (mean \pm SD)	21.8 ± 13.2	16.3 ± 11.5	<0.001
Ethnicity			0.003
Black	15 (11.8%)	62 (21.8%)	
Caucasian	86 (67.7%)	165 (57.9%)	
Chinese	17 (13.4%)	19 (6.7%)	
Others	9 (7.1%)	39 (13.6%)	
SLE duration at 1 st HZ	9.6 ± 9.8	-	-
Age at first HZ	47.8 ± 14.1	-	-

Table 1. (Cont'd)

Characteristic	Patients who had HZ (N=127)	Patient who never had HZ (N=285)	P value
Recurrent shingles HZ	32 (25.2%)	-	-
Year from 1 st HZ event to 2 nd HZ event	12.2 ± 12.1	-	-
Mean SLEDAI-2K (mean ± SD)	7.5 ± 7.1 (71/127)	-	-

Disclosure: H. Al Rayes, None; N. Anderson, None; D. Bonilla, None; J. Su, None; Z. Touma, None.

Abstract Number: 770

Cognitive Function Trajectories Are Associated with the Depressive Symptoms Trajectories in SLE over Time

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: We have shown that cognitive function followed particular trajectories over time in SLE, with some patients having persistently low scores and others normal scores. This study aims to: 1) describe the association between cognitive function trajectories and depressive symptoms trajectories and 2) identify baseline factors associated with trajectory membership.

Methods: Data were from the University of California San Francisco Lupus Outcomes Study, in which participants are followed longitudinally via annual telephone surveys. The Hopkins Verbal Learning Test-Revised (HVLTR; measures verbal memory) was administered in years 2-7, providing up to 6 of observation. Age- and education-stratified z-scores were derived for HVLTR delayed recall. The Center of Epidemiologic Studies Depression Scale (CES-D; score range 0–60; score ≥ 24 represents depression) was administered yearly.

Combined trajectory modelling for HVLTR and CES-D was performed. Models with up to 6 classes were assessed. The best model was determined by a combination of clinical plausibility and statistical criteria. Univariate/multivariable logistic regression analyses examined baseline (year 2) factors associated with class memberships, including sex, ethnicity, disease duration, treatments, fatigue, and self-reported disease activity.

Results: 755 patients (mean age 35 ± 13 years at SLE diagnosis) were studied. 4 latent classes were identified: 1-low CES-D scores and low cognitive scores (no depression + cognitive impairment; 20%), 2-lowest CES-D scores and highest normal cognitive scores (no depression + normal cognition; 48%), 3-highest CES-D scores and lowest cognitive scores (depression + cognitive impairment) (9%), and 4-high CES-D scores and normal cognitive score (depression + normal cognition; 23%) (Figure 1).

Figure 1. Cognitive function trajectories and the depressive symptoms trajectories in SLE

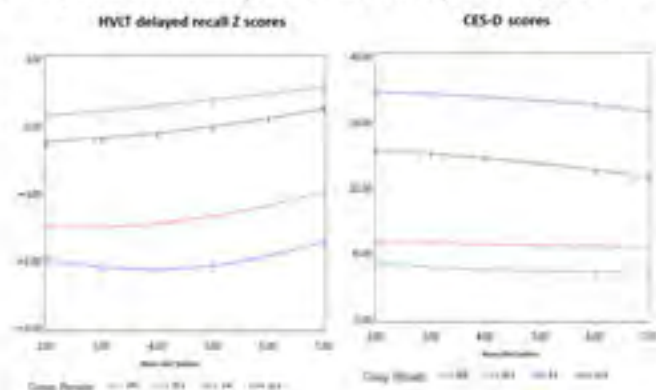


Table 1 shows the association between baseline variables and membership in classes 2 and 3. Caucasian ethnicity and education were associated with normal cognitive function. SLE disease activity and duration, fatigue, and methotrexate use (reflecting disease activity) were associated with cognitive impairment.

Conclusion: 4 distinct classes of combined cognitive function and the depressive symptoms were identified. Cognitive function was associated with depression status in 32% of patients (class 2 and 3). The results also confirmed that other factors predicted the latent class membership; such as ethnicity, education, disease activity and fatigue. These results highlight different aspects relevant for assessing and managing cognitive function over time in SLE.

Table 1. Baseline factors associated with normal cognitive function and absence of depression (comparing class 2 and 3 in univariate and multivariate analysis)

	HVLT-R delayed recall		P values
	Univariate	Multivariate	
Female	0.5 (0.2, 1.8)	---	
Caucasian	1.9 (1.1, 3.3)	5.9 (2.4, 14.7)	0.0001
Disease duration, year	1.0 (0.98, 1.02)	---	
Education	2.2 (1.8, 2.8)	2.3 (1.6, 3.1)	<0.0001
SLE activity	0.6 (0.5, 0.7)	0.7 (0.6, 0.8)	0.0004
Smoking, ever	0.8 (0.4, 1.2)	---	
Oral glucocorticoids	0.9 (0.5, 1.5)	---	
Methotrexate	0.6 (0.3, 1.7)	0.2 (0.06, 0.9)	0.03
Plaquenil use	0.8 (0.5, 1.3)	0.5 (0.2, 1.02)	0.06
Fatigue score	0.93 (0.91, 0.94)	0.93 (0.90, 0.95)	<0.0001

Tabled values are odds ratios (95% confidence intervals)

Disclosure: Z. Touma, None; J. Su, None; P. Katz, None.

Abstract Number: 771

Does Cognitive Function Change over-Time in Systemic Lupus Erythematosus?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Cognitive impairment (CI) is a common neurobehavioral manifestation of SLE. In our recent systematic review, the prevalence of CI was 38% (95% CI: 33-43%). Studies assessing CI in SLE are mostly cross-sectional and do not provide longitudinal data. Therefore, we aim to report the prevalence of CI and the change over-time in an SLE cohort using a comprehensive battery (CB) of tests.

Methods: Consecutive consenting SLE patients, aged 18-65 years, who attended a single centre (Jul 2016-Apr 2018) were recruited. Patients were administered the CB at baseline (T0), 6 months (T1) and 12 months (T2) which evaluates the following cognitive domains: simple attention and processing speed, visual-spatial construction, verbal fluency, learning and memory (visuospatial and memory), executive functioning (untimed and timed) and manual motor speed and dexterity. Patient scores were compared to a normative sample of age- and gender-matched healthy controls to obtain z-scores. CI was operationalized on the CB as a z-score of ≤ -1.5 (as compared to controls) on ≥ 2 domains. We determined the status of cognitive function based on the CB at T0, T1 and T2.

Results: Of the 220 patients (89.1% female), the mean age at SLE diagnosis was 28.3 ± 10.5 and disease duration at enrolment was 14.1 ± 10.4 years (Table 1). The prevalence of CI at T0 in 220 patients was 40.9%. Of the 220 patients, 124 had a 6 month follow-up with a CI prevalence of 29.8% and 71 patients had a 12 month follow-up with a CI prevalence of 35.2%. CI status over 6 months for T0 and T1: Of the 220 patients, 123 had both a T0 and T1 assessment. Sixty-two(50.4%) patients remained non-CI and 30 (24.4%) patients remained CI. Twenty-four(19.5%) patients transitioned from CI to non-CI at T1 and 7 (5.7%) patients transitioned from non-CI to CI at T1. CI status over 12 months for T0, T1 and T2: Of the 220 patients, 56 patients had 3 assessments at T0, T1 and T2. Of these, 41 (73.2%) patients remained stable across all three time points. Of the 41 patients, 30 patients remained non-CI and 11 patients remained CI over all three time points. Of 56, 15 (26.8%) patients changed CI status from CI to non-CI or vice versa (Table 2).

Conclusion: Cognitive function status in SLE patients fluctuates over time, with 26.8% of patients showing a change in status over a 12-month period. Our results advocate for close monitoring of cognitive function inpatients with SLE.

Table 1. Cohort characteristics at enrolment (n=220)

Characteristic	Value (N=220)
Gender (Female)	196 (89.1%)
Ethnicity:	
Asian	18 (8.2%)
Black	45 (20.5%)
Caucasian	128 (58.2%)
Other	25 (11.4%)
Age:	
18-29	38 (17.3%)
30-39	57 (25.9%)
40-49	55 (25.0%)
50-59	50 (22.7%)
60-69	20 (9.1%)
Education:	
Grade 8	9 (4.2%)
High School	39 (18.4%)
College	73 (34.4%)
University	91 (42.9%)
Age at SLE diagnosis (mean \pm SD)	28.3 ± 10.5
Age at enrolment (mean \pm SD)	42.4 ± 12.1
Disease duration at enrolment (mean \pm SD)	14.1 ± 10.3

Table 2. CI status at T0, T1 and T2 (N=56)

CI Status	Frequency (%)
Non-CI at all visits	30 (53.6)
CI at all visits	11 (19.6)
Transitioned from non-CI at T0 or T1 to CI at T2	6 (10.7)
Transitioned from CI at T0 or T1 to non-CI T2	9 (16.1)

Disclosure: Z. Touma, None; R. Green, None; C. Tartaglia, None; L. Ruttan, None; S. Lombardi, None; N. Anderson, None; J. Su, None; K. Colosimo, None; M. Vitti, None; J. E. Wither, None; M. J. Fritzler, Inova Diagnostics Inc., BioRad, Euroimmun GmbH, Mikrogen GmbH, Dr. Focke Laboratorien GmbH, ImmunoConcepts, SKF Canada, Amgen and Pfizer, 5,ImmunoConcepts, Inova Diagnostics, Euroimmun GmbH, and Alexion Canada, 7; D. Beaton, None.

Abstract Number: 772

Cytomegaloviral or Pneumocystis Jiroveci Pneumonia Increases Mortality Rate in Systemic Lupus Erythematosus Patients with Pulmonary Hemorrhage: Evidence from Bronchoalveolar Lavage Fluid Analysis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: To evaluate the role of cytomegaloviral or Pneumocystic jiroveci pneumonia (CMV/PJP) in SLE patients with pulmonary hemorrhage (PH).

Methods: We retrospectively examined hospital records for 27 SLE patients with PH who received bronchoalveolar lavage fluid (BALF) analyses. Clinical profile and mortality rates were compared between groups with and without CMV/PJP. Risk factors for PH-related mortality were analyzed.

Results: Among 27 SLE patients with PH, 15 patients had pathogens from BALF samples, and eight patients had CMV/PJP (Table 1). Although CMV/PJP was treated, the 90- and 180-day mortality rates of SLE patients with CMV/PJP were higher than those without these infections (90-day: 62.5% vs. 10.5%, $p = 0.011$; 180-day: 75% vs. 10.5%, $p = 0.002$). Risk factors for 90- and 180-day mortality were presence of CMV/PJP (OR 14.2, 95% CI 1.83-109.9; OR 25.5, 95% CI 2.91-223.3) and use of pulse methylprednisolone for PH treatment (OR 12.0, 95% CI 1.48-97.2; OR 8.5, 95% CI 1.13-63.9). Factors increasing the 90-day mortality rate were duration of mechanical ventilation exceeding 14 days (OR 11.1; 95% CI 1.11-112.0) and use of aggressive immunosuppression close to PH onset (OR 7.56; 95% CI 1.09-52.4) (Table 2). Three of the seven patients receiving aggressive immunosuppression died with the presence of CMV/PJP.

Conclusion: Due to the high prevalence of CMV/PJP and its association with mortality, routine BALF analysis is recommended in all suitable SLE patients with PH. Use of aggressive immunosuppression does not benefit SLE patients with opportunistic infections during PH attack.

Table 1. Baseline characteristic of PH of SLE patients.

Parameter	CMV - PJP - (n = 19)	CMV or PJP + (n = 8)
Age at hospitalization, years	33.2 (28.3 iV 43.7)	34.2 (32.7 iV 56.0)
Female sex	18 (94.7)	8 (100)
Duration of SLE > 3 years	14 (73.7)	5 (62.5)
History of lupus nephritis	17 (89.5)	7 (87.5)
SLEDAI-2K score	12 (7 iV 19)	11.5 (3.3 iV 20.3)
BAL procedure after PH onset, days	5 (3 iV 6)	5.5 (0.75 iV 20)
Hemosiderin-laden macrophage in BALF	8 (50)	5 (71.4)
Laboratory data		
WBC count, $10^3/\text{g/L}$	8.29 (4.8 iV 11.3)	6.45 (1.58 iV 15.42)
Lymphocyte count, $10^3/\text{g/L}$	0.58 (0.35 iV 1.00)	0.29 (0.19 iV 0.69)
Hemoglobin, g/dL	7.2 (6.0 iV 8.0)	7.1 (6.6 iV 7.9)
Platelet count, $10^9/\text{L}$	87 (57 iV 171)	134 (92 iV 190)
Serum IgG, mg/dL	934 (699 iV 1530)	874 (565 iV 874)
Serum creatinine, mg/dL	2.27 (1.21 iV 4.25)	2.51 (1.83 iV 4.67)
C3, mg/dL	47.6 (34.0 iV 67.0)	59.4 (46.3 iV 79.4)
C4, mg/dL	12.4 (5.1 iV 17.8)	15.1 (9.4 iV 28.7)
Anti-dsDNA antibody positivity	9 (47.4)	3 (37.5)
Background medications		
Prednisolone equivalent, mg/day	10 (5 iV 15)	17.5 (11.3 iV 23.8)
Hydroxychloroquine	4 (21.1)	2 (25)
Azathioprine	4 (21.1)	2 (25)
Mycophenolate	3 (15.8)	2 (25)
Calcineurin inhibitors	2 (10.5)	1 (12.5)
Cyclophosphamide*	3 (15.8)	0
Rituximab**	1 (5.3)	1 (12.5)
Ventilator usage	15 (78.9)	7 (87.5)
APACH II score†	26 (22 iV 27)	24 (24 iV 28)
SOFA score†	9 (8 iV 11)	8 (6 iV 12)
ECMO usage†	0	2 (33.3)
Treatment for PH		
Plasmapheresis	11 (57.9)	4 (50)
IVIg	2 (10.5)	4 (50)‡
IV pulse methylprednisolone	2 (10.5)	4 (50)‡
Cyclophosphamide	0	1 (12.5)

Values are presented as median (interquartile range) or number (percentage).

* Within 3 months or * 6 months before PH.

† Only for patients ever supported with MV.

‡ $p < 0.05$ vs. patients without CMV pneumonia or PJP.

Table 2. Risk factor analysis for 90-day and 180-day mortality rates in SLE patients with PH

Variable	90-day mortality			180-day mortality		
	OR	95% CI	p	OR	95% CI	p
SLEDAI-2K > 10	0.89	0.16-5.08	0.895	0.58	0.11-3.10	0.527
PDN > 7.5 mg/day	2.14	0.20-22.5	0.525	2.69	0.26-27.8	0.406
Serum IgG < 751 mg/dL	0.92	0.12-6.83	0.932	0.92	0.12-6.83	0.932
Bacteremia	5.83	0.87-38.9	0.069	3.61	0.64-20.3	0.145
Pathogens in BALF						

Table 2. (Cont'd)

Variable	90-day mortality			180-day mortality		
	OR	95% CI	p	OR	95% CI	p
Bacteria	0.74	0.11-4.87	0.757	1.30	0.23-7.32	0.766
CMV/PJP	14.2	1.83-109.9	0.011*	25.5	2.91-223.3	0.003*
MV >14 days	11.1	1.11-112.0	0.041	5.14	0.81-32.8	0.083
Treatment of PH						
Plasmapheresis	7.33	0.74-72.6	0.089	3.33	0.53-20.9	0.199
Pulse MP	12.0	1.48-97.2	0.020	8.50	1.13-63.9	0.038
IVIg	1.60	0.22-11.5	0.640	1.25	0.18-8.73	0.822
Aggressive IS close to PH	7.56	1.09-52.4	0.041	5.33	0.83-34.1	0.077

* The only factor that remained significant when selecting variables with $p < 0.05$ in multi variable analysis. (90-day, OR: 14.2, 95% CI: 1.83, 109.9; $p = 0.011$; 180-day, OR: 25.5, 95% CI: 2.91, 223.3, $p = 0.003$)

ANCA, anti neutrophil cytoplasmic antibody; APACHE II, Acute Physiology and Chronic Health Evaluation II; BAL, bronchoalveolar lavage; ECMO, extracorporeal membrane oxygenation; IgG, immunoglobulin G; IVIg, intravenous immunoglobulin; IS, immuno suppression; MV, Mechanical ventilation; MP, methylprednisolone; PDN, prednisolone; PH, pulmonary hemorrhage; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SOFA, sequential organ failure assessment; WBC, white blood cell.

Disclosure: C. C. Lai, None; Y. S. Sun, None; D. F. Huang, None.

Abstract Number: 773

Exploring the Relation between Immunoglobulins Level and Infection Risk in Adult Patients with Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Infection is a major cause of mortality in all stages of disease in systemic lupus erythematosus (SLE). Several risk factors for infection have been identified in SLE such as immunosuppressive medications and prednisone. Yet these do not fully explain the increased risk for infection. We have recently identified a possible association between low immunoglobulin levels and infection risk. The aim of this study was to determine whether acquired low levels of immunoglobulins (Ig) increase the risk of clinically relevant infections within two years in adults with SLE.

Methods: SLE patients in a long term observational study are followed at 2-6 month intervals according to a standard protocol which includes demographics, clinical, laboratory and therapeutic information. Disease activity is measured by the SLEDAI-2K, and damage by the SLICC/ACR damage index (SDI). Ig are measured yearly with quantification of IgG, IgA and IgM. The Low Ig was defined as at least two consecutive or non-consecutive immunoglobulin levels below normal. Baseline was defined by the first visit when low Ig was detected. Controls were patients who never having low Ig levels. The outcome was clinically relevant infection defined as an infection requiring use of antibiotics within 2 years from baseline. Cases and controls in this cohort study were matched on age and decade and then adjusted for potential confounding using propensity score. Primary analysis was time to event using cox-regression model tested for proportional hazard assumption. Restricted cubic spline function was used to address non-linearity. Results were further confirmed using inverse probability weighted treatment (IPWT).

Results: We identified 437 in the exposure group (221 consecutive and 227 non-consecutive) and 656 matched controls. Baseline characteristics are presented in the following table:

Variables at Index	Unit	Non-Low immunoglobulins	Low immunoglobulins	P-value
Disease Duration	Mean \pm SD	7.6 \pm 8.0	11.2 \pm 9.1	0.0001
Ethnicity	Black	90 (13.7%)	58 (13.3%)	0.4
	Caucasian	436 (66.5%)	292 (66.8%)	
	Chinese	57 (8.7%)	50 (11.4%)	
	Others	73 (11.1%)	37 (8.5%)	
SLEDAI-2K	Mean \pm SD	5.9 \pm 5.9	6.2 \pm 6.3	0.02
SDI	Mean \pm SD	0.5 \pm 1.0	1.2 \pm 1.6	<.001
Had Lupus Nephritis before the index.	Yes (%)	117 (17.8%)	196 (44.9%)	<.001
Proteinuria	Yes (%)	74 (11.3%)	112 (25.6%)	<.001
Any Low complement	Yes (%)	274 (41.8%)	162 (37.1%)	0.27
Increase DNA binding	Yes (%)	315 (48.0%)	187 (42.8%)	0.25
Leukopenia	Yes (%)	21 (3.2%)	18 (4.1%)	0.36
Antiphospholipids Antibodies	Yes (%)	168 (26.2%)	62 (15.2%)	0.0001
Prednisone use	Yes (%)	349 (53.2%)	332 (76.0%)	<.001
Oral Prednisone dose (mg/day)	Mean \pm SD	15.3 \pm 14.6	16.8 \pm 16.8	0.06
Immunosuppressant use	Yes (%)	152 (23.2%)	201 (46.0%)	<.001
Biologics treatment	Yes (%)	1 (0.2%)	5 (1.1%)	0.10

All immunoglobulins showed evidence of non-linearity. Proportional hazard assumption was satisfied for immunoglobulins and propensity score. A total of 97 events (47 in exposure group and 50 in non-exposure group). IgG and IgA showed increased hazard at very low levels (1.2 g/l and 1.25 g/l respectively) after adjustment for propensity score or weighted using IPWT. All three Ig showed decreased hazard of infection for normal ranges after adjustment of propensity score.

Conclusion: Our data suggest that very low IgG and IgA are important risk factors for infection independently from all known confounders including prednisone and immunosuppressives. Acquiring low immunoglobulins in SLE patients usually occurs later in the disease and is more likely to be seen among active patients with proteinuria and history of lupus nephritis. We recommend incorporating immunoglobulins measurement in clinical care of adult patients with SLE.

Disclosure: I. Almaghlouth, None; J. Su, None; E. Pullenayegum, None; S. Johnson, Roche, Bayer, Boehringer, BMS, NIH, Merck, 9; D. D. Gladman, Janssen Research and Development, LLC, 2; M. Urowitz, None.

Abstract Number: 774

Clinical Variables and Serologic Markers of Disease Activity Do Not Aid in Early Recognition of Patients with Tubulointerstitial Disease Who Have No Significant Renal Impairment at Time of Biopsy

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Tubulointerstitial damage (TID), defined as tubulointerstitial inflammation (TII) or interstitial fibrosis/tubular atrophy/ (IF/TA) is associated with poor renal outcomes in lupus nephritis (LN)¹. Glomerular damage is thought to initiate downstream changes that culminate in TID². However, some SLE patients with advanced TID have no significant renal impairment to prompt a renal biopsy, complicating their early recognition. Therefore, we studied whether patients with TID and either none or mild renal impairment at the time of biopsy differ from patients with TID and significant renal impairment. The objective was to identify potential factors that may aid in the early recognition of patients with TID before overt renal dysfunction.

Methods: We identified all patients who fulfilled ACR and/or SLICC criteria for SLE and had an index renal biopsy between 2005 and 2017 with moderate/severe TID. Moderate/severe TID was defined as IF/TA and/or TII involving $\geq 25\%$ of the biopsied tissue. Significant renal impairment was defined as glomerular filtration rate (eGFR) < 60 mL/min/1.73m² at the time of biopsy. The following variables were compared: SLE duration, LN class, history of diabetes, hypertension (HTN) and Sjogren's syndrome, medications (steroids, hydroxychloroquine, immunosuppressives, non-steroidal anti-

inflammatory drugs), demographics and laboratory data (complement, dsDNA, antiphospholipid antibodies, anti-Ro/La, anti-Sm/RNP).

Results: A total of 65 patients with moderate/severe T1D were included. Among these patients, 19 (29%) had moderate/severe T1I alone, 25 (38%) had moderate/severe IF/TA alone, and 21 (32%) had moderate/severe T1I accompanied by moderate/severe IF/TA. Among the 40 patients with moderate/severe T1I with or without accompanying IF/TA, 16 (40%) had eGFR ≥ 60 and 24 (60%) had eGFR < 60 . Compared to patients with eGFR < 60 , those with eGFR ≥ 60 had a longer disease duration [median (IQR): 55 (30, 68) vs 17 (3, 26) months, $p=0.002$], and were less likely to have anti-Ro/La antibodies (6% vs 35%, $p=0.04$). Among the 46 patients with moderate/severe IF/TA with or without accompanying T1I, 14 (30%) had eGFR ≥ 60 and 32 (70%) had eGFR < 60 . Compared to patients with eGFR < 60 , those with eGFR ≥ 60 were younger [28 (16, 33) vs 45 (30, 55) years, $p=0.002$] and had a higher proportion of Black patients (72% vs. 36%, $p=0.02$). In this group, patients were more likely to be on steroids at the time of biopsy (100% vs 70%, $p=0.03$) and HTN was seen less frequently (38% vs 74%, $p=0.03$). There was no association between eGFR ≥ 60 and LN class or routine serologic markers of disease activity among patients with moderate/severe T1I or IF/TA.

Conclusion: Moderate/severe T1I and/or IF/TA frequently occur in the absence of significant renal impairment and identifiable markers of early disease, hindering its timely recognition. At the time of biopsy, a large proportion of patients with eGFR ≥ 60 will already have moderate/severe T1D. New biomarkers to aid in the early identification of these patients are needed. Clinically, mild impairment in eGFR may aid the decision to biopsy earlier for prompt detection of tubular damage.

References

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Disclosure: A. Londono Jimenez, None; B. Goilav, None; M. Salgado Guerrero, None; K. A. Lynch, None; W. B. Mowrey, None; A. R. Broder, None.

Abstract Number: 775

Endomyocardial Biopsies in the Diagnosis of Myocardial Involvement in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Myocardial dysfunction is reported in over half of systemic lupus erythematosus (SLE) patients, yet the underlying pathogenesis remains poorly understood. Endomyocardial biopsies (EMBs) are considered the gold standard for diagnosing cardiac involvement and myocarditis in inflammatory conditions, including SLE. However, EMBs are rarely performed in clinical practice and most of the histopathology reports in the literature consist of post-mortem data. We sought to describe the histopathologic findings of EMBs in SLE patients with active cardiac symptoms.

Methods: A retrospective review of histopathology reports was performed on SLE patients at Columbia University Medical Center who underwent EMBs from 1994-2017. SLE patients were identified by ICD-9 & 10 codes. EMBs, performed for evaluation of unexplained low ejection fraction suspicious for myocarditis, were similarly identified by procedure codes for cardiac pathology. Out of 1,994 SLE patients identified by ICD codes, 59 had cardiac pathology reports. The diagnosis of SLE was confirmed in 41/59 patients by chart review using ≥ 4 revised 1997 ACR classification criteria or SLICC classification criteria. Eleven histopathology reports were EMBs and the remaining were valvular specimens. Demographics, SLE characteristics, and cardiovascular disease risk factors were ascertained by chart review.

Results: Data from eleven SLE EMBs patients was reviewed (Table 1). Mean age was 37 ± 17 ; 82% were female, and median disease duration was 2.5 years (0-25.5). Anti-dsDNA and anti-SSA/Ro antibodies were present in 64% and 45%, respectively. Forty-five percent had hypertension, 27% had coronary artery disease, 9% had hyperlipidemia, and 36% had end-stage renal disease; none had diabetes or smoked. One patient had antiphospholipid antibody syndrome on anticoagulation. Mean ejection fraction was 37%. On histopathology, 91% had mild interstitial fibrosis, 82% had myocyte hypertrophy, 27% had organized blood clots, and 27% had a mild infiltration of lymphocytes and macrophages without

clear evidence of myocarditis. None of the patients had vasculitis, endocarditis, ischemia, or amyloid deposition. Glycogen storage was observed in one patient.

Conclusion: EMBs are rarely performed in SLE. Inflammatory infiltrates were present in only 27% of all SLE EMBs and non-specific interstitial fibrosis and myocyte hypertrophy were the most common findings. These data suggest that EMBs have limited value in the diagnosis of cardiac involvement in lupus and support the need for alternative diagnostic approaches to SLE heart disease.

Table 1. Patient Characteristics.

	SLE EMBs (n=11)
Demographics	
Age, years, mean \pm SD	37 \pm 17
Female, n (%)	9 (82)
Race/Ethnicity (n=7)	
Non-Hispanic White, n (%)	0
Non-Hispanic Black, n (%)	2 (29)
Hispanic, n (%)	3 (43)
Asian, n (%)	2 (29)
SLE Characteristics	
SLE duration, years, median (IQR)	2.5 (0-25.5)
Lupus nephritis, n (%)	5 (45)
End-stage renal disease, n (%)	4 (36)
Antiphospholipid syndrome, n (%)	1 (9)
ANA, n (%)	11 (100%)
ds-DNA, , n (%)	7 (64)
SSA/Ro, n (%)	5 (45)
SSB/La, n (%)	3 (27)
Sm, n (%)	5 (45)
RNP, n (%)	5 (45)
Anti-malarials, n (%)	4 (36)
Steroids, n (%)	4 (36)
Mycophenolate mofetil, n (%)	4 (36)
Azathioprine, n (%)	0
Methotrexate, n (%)	0
Cyclophosphamide, n (%)	0
B cell therapy, n (%)	0
Cardiovascular Risk Factors and Assessments	
Smoking, n (%)	0
Hypertension, n (%)	5 (45)
Diabetes, n (%)	0
Hyperlipidemia, n (%)	1 (9)
Statin use, n (%)	3 (27)
Coronary artery disease, n (%)	3 (27)
Mean ejection fraction on echocardiogram, %	37%
Valvular abnormalities on echocardiogram, n (%)	3 (27)
Histopathology	
Myocyte hypertrophy, n (%)	9 (82)
Mild interstitial fibrosis, n (%)	10 (91)
Myocardial inflammatory infiltration, n (%)	3 (27)
Organized blood clot, n (%)	3 (27)
Endocarditis, n (%)	0
Vasculitis, n (%)	0
Ischemia, n (%)	0
Amyloid deposition, n (%)	0
Glycogen storage, n (%)	1 (9)

Disclosure: L. Geraldino-Pardilla, None; T. Kapoor, None; T. Perez, None; A. Askanase, None.

Abstract Number: 776

MMP7 and CXCL12: Two Promising Biomarkers in Lupus Nephritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Lupus nephritis (LN) is one of the most serious complications of Systemic lupus erythematosus (SLE). Early diagnosis of renal impairment, combined with a strict follow-up of patients, is important to avoid morbidity and mortality. Yet, current conventional biomarkers (proteinuria, urinary protein/creatinine ratio, estimated glomerular filtration rate, serum anti-dsDNA antibody titers, serum complement levels) reflect systemic rather than renal activity of the disease, or, in the case of proteinuria, remain elevated as a consequence of chronic damage. The aim of this study was to identify new biomarkers reflecting intra-renal activation of immune cells and renal tubular cell damage, the main determinants of impaired renal function in LN.

Methods: Using transcriptomic data generated in LN versus control renal biopsies in the context of the PRECISESADS study, we identified candidate biomarkers that correlated with intra-renal infiltration by immune effectors or histological evidence of tubular damage, and were potentially secreted in the serum: IL34, MMP7, RANTES, SLA2, CXCL12, CCL19 and CCL21. We evaluated concentrations of these eight biomarkers in sixty-seven LN and in eight control sera. IL34, MMP7, RANTES and SLA2 were evaluated by ELISA and CXCL12, CCL19 and CCL21 using a Bioplex assay. Biological indices of disease activity were retrieved from the patients files.

Results: Serum IL34 (p value: 0.0288), MMP7, CXCL12, CCL19 and CCL21 (p values: <0.0001) concentrations were significantly higher in LN patients than in controls. Strikingly, serum MMP7 and CXCL12 concentrations were negatively correlated with eGFR (p values: 0.0135 and 0.0190 respectively), while this was not the case for anti-dsDNA antibody titers, serum C3 or urinary protein/creatinine ratio. Accordingly, serum MMP7 and CXCL12 concentrations were significantly higher in patients with an eGFR < 50 mL/min/1.73 m² compared to > 50 mL/min/1.73 m² (p values: 0.0020 and 0.0336, respectively).

Conclusion: Adequate management of LN will be served by the identification of biomarkers reflecting intra-renal rather than systemic inflammation. By opposition to conventional biomarkers, MMP7 and CXCL12, which are produced in the kidney itself, displayed a significant negative correlation with eGFR in LN. Confirmation of these results in independent cohorts of samples is pending.

Disclosure: S. Goletti, None; S. Nieuwland, None; F. A. Houssiau, None; B. R. Lauwerys, None.

Abstract Number: 777

Electrocardiographic Abnormalities Are Associated with the Occurrence of Strokes in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Systemic lupus erythematosus (SLE) patients have a 10-fold higher risk for myocardial infarctions and a 3-fold higher risk for congestive heart failure and strokes, making cardiovascular disease (CVD) the leading cause of death in SLE. In the general population, nonspecific ST-T and QTc abnormalities are strong predictors of CV mortality. Yet, studies exploring the value of the ECG in identifying SLE patients at increased risk for cardiovascular events (CVE) are lacking. Therefore, we investigated the association between electrocardiographic (ECG) abnormalities and CVE in SLE.

Methods: We retrospectively reviewed 12-lead ECG data preceding a diagnosis of cardiovascular event (defined as myocardial infarction, congestive heart failure, and/or stroke) in 81 SLE patients, compared with ECG data from 269 SLE patients lacking a diagnosis of CVE. Patients were identified by ICD-9 & 10 codes for SLE, and the diagnosis was ascertained by chart review confirming ≥ 4 revised 1997 ACR or SLICC classification criteria. CVE were similarly confirmed by chart review including cardiology notes, diagnostic tests, and procedure data confirming the events. Nonspecific ST-T abnormalities were defined by the Minnesota code, and the QT interval was calculated and adjusted for heart rate by Bazett's formula. Regression models were constructed to test the association of ECG abnormalities with CVE.

Figure 1. Association of ECG non-specific ST-T changes with Strokes in SLE.

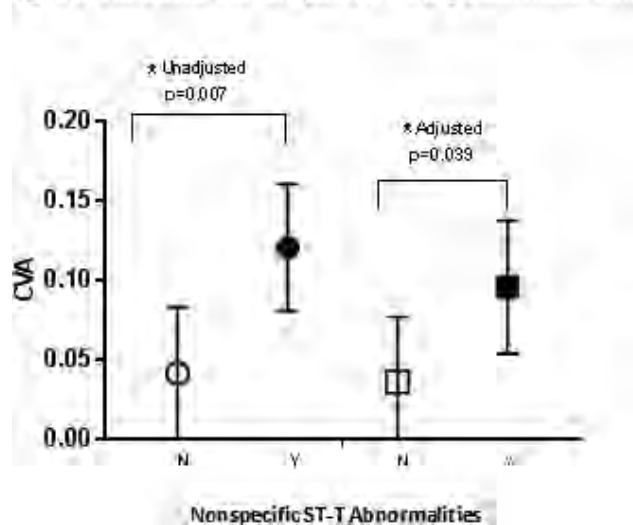
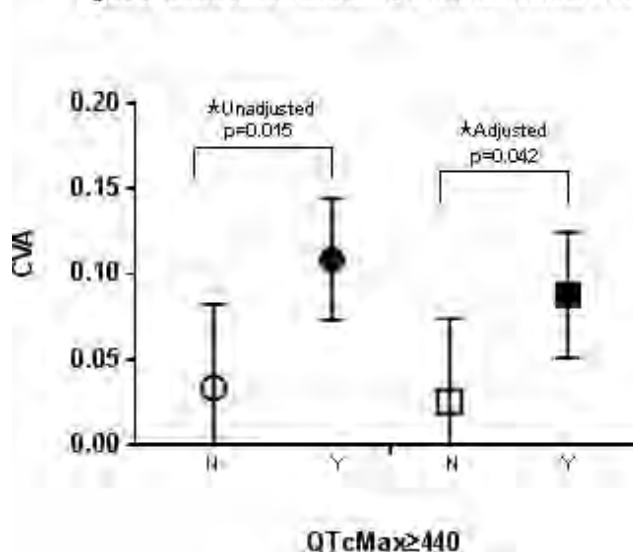


Figure 2. Association of maximum QTc ≥440 with Strokes in SLE.



Results: The mean age was 47 ± 15 years, 90% were female, 43% Hispanic and 40% were black. Sixty-five percent had hypertension, 8% had diabetes, 16% had a history of smoking, and 17% had hyperlipidemia. Mean disease duration at the time of the CVE was $12 (\pm 10)$ years. Nonspecific ST-T abnormalities were seen in 65% and 48% of patients with and without CVE, respectively (OR=2.05, $p=0.006$). Mean QTc length was 435 and 431 ms in those with and without CVE, respectively ($p=0.0102$); and the maximum QTc length was 464 and 431 ms, respectively ($p=0.0207$). After adjusting for confounders, the association between any CVE and ECG abnormalities lost significance. However, strokes remained significantly associated with nonspecific ST-T changes (OR=2.45, 95% CI: 1.01, 5.98; $p=0.05$) and a maximum QTc ≥ 440 ms (OR= 3.05, 95% CI: 1.02, 9.10; $p=0.045$) after adjusting for hypertension (Figures 1 & 2).

Conclusion: ECG nonspecific ST-T abnormalities and a maximum QTc ≥ 440 ms were associated with a 2-3-fold higher risk for strokes in SLE patients. This study supports the use of ECG to identify SLE patients at risk for stroke.

Disclosure: T. Perez, None; C. Dependier, None; J. Li, None; L. Geraldino-Pardilla, None.

Rates of Herpes Zoster Virus Infection in SLE Patients on Immunosuppression

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

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

Background/Purpose: Increased incidence of herpes zoster (HZ) has been reported in patients with autoimmune diseases. SLE in particular is known to be associated with a 2-fold increased risk of HZ compared with the general population.¹ ² Previously available live attenuated zoster vaccine was contraindicated in SLE patients on immunosuppression, or required significant treatment delay, resulting in relatively low vaccination rates. The recently approved recombinant zoster vaccine (RZV) can be safely administered to SLE patients on immunosuppression and recent immunization guidelines recommend RZV vaccination for patients with chronic medical conditions³. Therefore, it is important to define the HZ burden and to identify SLE patients who may benefit from HZ vaccination. We aimed to estimate HZ rates and to compare SLE patients with and without HZ.

Methods: Retrospective EMR chart analysis identified all patients with the new diagnosis of SLE, defined as having at least 2 ICD codes for SLE 1-6 months apart between 1/1/2006 and 12/31/2017 and no previous visits with SLE codes in our tertiary care center within 1 year prior. HZ infection was ascertained using ICD codes. HZ rates were calculated in subgroups stratified by SLE-specific medications. We used univariate analyses to compare patient demographics, laboratory parameters and SLE-specific medications between SLE patients with and without HZ.

Results: Out of 1646 patients who met inclusion criteria, 89 (5.4%) were diagnosed with HZ after the initial SLE diagnosis. There were no statistically significant differences between HZ+ and HZ- patients in demographics, baseline leukocyte cell counts, or ICD diagnosis codes for heart failure, cancer, lung disease or diabetes (Table). HZ+ patients were more likely to be on immunosuppressive medications, hydroxychloroquine (HCQ) and corticosteroids (CS). The rate of HZ among 307 patients on CS alone was 8%. The rate of HZ in 230 patients on HCQ +/- CS without other immunosuppressives was 4.8%. The rate of HZ among 161 patients on mycophenolate mofetil (MMF) +/- HCQ +/- CS without other immunosuppressives was 12%. The rate of HZ among 348 patients on non-MMF immunosuppressives +/- HCQ +/- CS without MMF was 4%.

Conclusion: This study demonstrates that among SLE patients treated with MMF, HZ rates were significantly higher when compared to patients receiving other immunosuppression, regardless of CS use. Therefore, HZ vaccination should be considered in all individuals with SLE on MMF.

References :

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Comparisons of SLE patients with and without HZ infection

	HZ POS (n=89)	HZ NEG (n= 1557)	p-value
Age(years), median (IQR)	42 (26, 58)	41 (27, 54)	0.25
Male sex, n(%)	12 (13)	178 (11)	0.56
Black race, n(%)	36 (40)	600 (39)	0.92
Hispanic, n(%)	31 (35)	558 (36)	0.52
WBC at time of first SLE diagnosis, median (IQR)	6.2 (4.3, 8.1)	6.0 (4.4, 8.5)	>0.99
Lymphocyte count at time of first SLE diagnosis, median (IQR)	1.25 (0.8, 2.1)	1.4 (1.0, 2.1)	0.15
ANC at time of first SLE diagnosis, median (IQR)	3.7 (2.6, 6.1)	3.8 (2.5, 5.8)	0.62
Cancer, n(%)	45 (2.89)	2 (2.25)	0.72
CHF, n(%)	52 (3.3)	5 (5.6)	0.25
Lung Disease, n(%)	251 (16.1)	16 (18.0)	0.64
Diabetes, n(%)	6 (7)	98 (6)	0.87

Table 1. (Cont'd)

	HZ POS (n=89)	HZ NEG (n= 1557)	p-value
Mycophenolate Mofetil (MMF), n(%)	38 (43)	301 (19)	<0.001
Non-MMF immunosuppressives*, n(%)	39 (44)	494 (32)	0.02
Hydroxychloroquine, n(%)	49 (55)	540 (35)	<0.001
Corticosteroids, n (%)	78 (88)	1016 (66)	<0.001

* methotrexate, leflunomide, azathioprine, cyclosporine, tacrolimus

Disclosure: I. Gendlina, None; A. Londono Jimenez, None; K. A. Lynch, None; W. B. Mowrey, None; Y. Balagula, None; A. R. Broder, None.

Abstract Number: 779

Cerebrospinal Fluid Biomarkers for Diagnosing Neuropsychiatric SLE: A Systematic Review and Meta-Analysis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Current guidelines recommend that in suspected neuropsychiatric SLE (NPSLE), the initial diagnostic workup should be similar to that in non-SLE patients presenting with the same manifestations. We aimed to synthesize the current best evidence regarding whether any additional cerebrospinal fluid (CSF) biomarker could be particularly beneficial in diagnosing patients with suspected NPSLE.

Methods: We completed a comprehensive search within PubMed, Embase, and CINAHL. We used a highly-sensitive search strategy comprising 67 keywords representing NPSLE and its 19 syndromes as well as CSF biomarkers. We also carried out forward and backward citation checking of the included studies and the relevant reviews using the Web of Knowledge Science Citation Index. We included the studies of the diagnostic test accuracy of any CSF biomarker for diagnosing NPSLE among patients with SLE, in which they used the ACR case definitions or other validated tools as their reference standards. Two investigators (SFA, GZ) independently replicated data extraction by using a standard form, which included an assessment of study quality as well as participant-level data to populate 2×2 contingency tables (true positives, true negatives, false positives and false negatives).

Results: We screened 2851 records and eventually included the data from 30 studies. Among the investigated 46 CSF biomarkers, only anti-NR2 and anti-neuronal antibody were shown to be highly accurate by more than one study (Figure 1). Also, anti-Smith, anti-RNP, α -klotho, fibroblast growth factor, IFN- γ , and interleukins 2, 5, 15, and 17 were

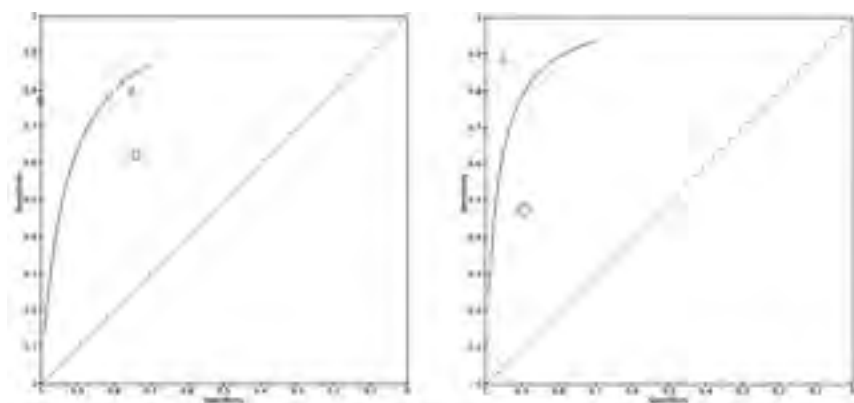


Figure 1. Pooled SROC plots representing the diagnostic accuracy of anti-NR2 (Left) and anti-neuronal antibody (Right).

Disclosure: S. F. Ahmadi, None; G. Zahmatkesh, None; M. Majed, None; S. Desai, None.

Abstract Number: 780

Urine Metabolomic Profile in Lupus Nephritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

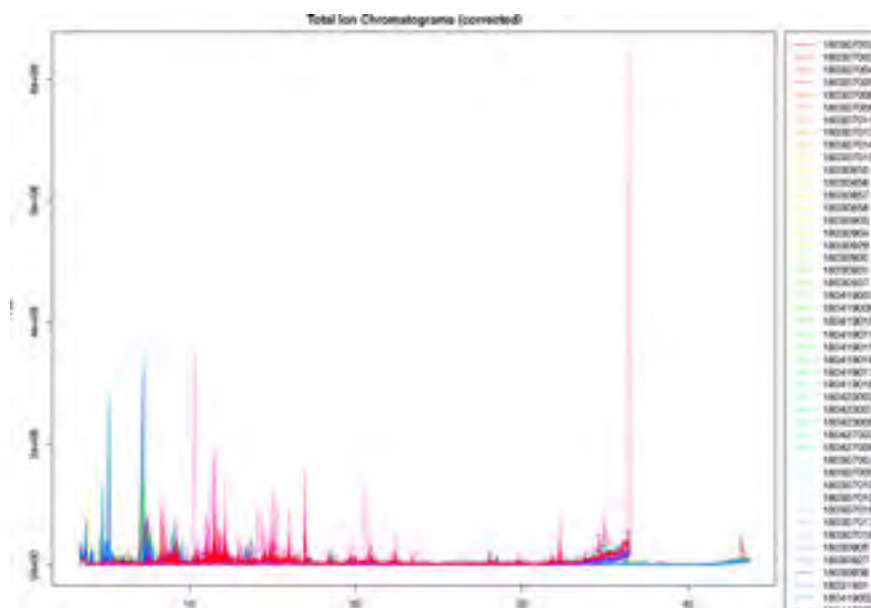
Session Time: 9:00AM-11:00AM

Background/Purpose: Lupus nephritis(LN) develops in 50-60% of lupus patients. The consequence of this entity is renal failure, that can arise in 10-15% of patients and an increase of the hazard ratio for mortality (HR 2.28). Proliferative lupus nephritis is the most aggressive clinical form. The criteria for diagnosis of LN are easy to apply, but not specific for determine the class of LN.

The aim of the study was to find a metabolomic profile in the urine of lupus patients to diagnose proliferative and/or membranous classes of LN.

Methods: This was a cross-sectional study. We included lupus patients with and without proliferative and/or membranous lupus nephritis. We used urine samples for the detection of metabolites using mass spectrometry thru gas chromatography (coupled with electronic nose). For baseline characteristics we used t test or U Mann-Whitney depending on the distribution of the variables; and X2 for categorical variables. For the detection and selection of the metabolites we used principal component analysis and random forest.

Results: We included 73 lupus patients, 35 had lupus nephritis; in this group the most common class of LN was IV. The patients with lupus nephritis were younger and had higher SLE activity at baseline. Sex distribution between the groups were similar. Due to these variety of the disease more patients with LN received steroid and cyclophosphamide pulses.



In the preliminary results of metabolomics we found 242 metabolites, of which 15 were match lupus nephritis, and thus can be considered as a metabolomic fingerprint.

	Lupus with nephritis (n: 35)	Lupus without nephritis (n: 38)	p value
Age	28.5 (13.1)	35 (14.6)	0.04
Females (%)	32 (82.1)	35 (92.1)	0.31
Weight	60.1 (11.8)	65.4 (16.4)	0.1
SLEDAI	13.7 (8.1)	3.7 (2.6)	< 0.0001
Evolution median (IQR)	24 (50)	54 (102)	0.005
Prednisone	29 (74)	27 (71)	0.74
Dose of prednisone median (IQR)	5 (10)	5 (0)	0.055
Cyclophosphamide	23 (59)	0	< 0.0001
Methylprednisolone pulse,	21 (53.8)	0	< 0.0001
Active sediment	31 (79.5)	-	NA
Nephritis class			NA
III	4	-	
IV	24	-	
III/V	3	-	
IV/V	5	-	
V	3	-	
Activity index	7 (6)	-	NA
Chronicity Index	2 (4)	-	NA

Conclusion: These preliminary results show a viable method for obtaining new biomarkers for the diagnosis of the different lupus nephritis classes.

Disclosure: D. Herrera Van Oostdam, None; C. Abud-Mendoza, None; M. Rodriguez Aguilar, None; R. Flores Ramirez, None; M. Pierdant Pérez, None; C. E. Vallín Orozco, None; M. U. Martinez-Martinez, None.

Abstract Number: 781

Simultaneous Identification of Two Biomarkers in ACTIVE LUPUS Nephritis: Autophagy in Treg CELLS and Prolactin Receptors in B Lymphocytes

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SESSION INFORMATION

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Background/Purpose: Recent studies suggest that autophagy defects contributes to systemic lupus erythematosus (SLE) pathogenesis. Prolactin (PRL) is associated with active SLE and stimulates the immune cells by binding to receptor (PRL-R). Prolactin decreases the suppressor function exerted by Treg cells favoring an inflammatory microenvironment in SLE. The objective is simultaneously identify the expression of autophagy in Treg lymphocytes and PRL-R in B lymphocytes of SLE patients.

Methods: We included 40 patients with SLE (ACR criteria) divided into two groups: Group 1: patients with remission SLE (SLEDAI<4), Group 2: patients with active SLE (SLEDAI > 4). The affected organs and the treatments received were obtained. As a control group, we included healthy individuals. A fasting peripheral blood sample was taken from all patients and controls. The cells were separated and labeled with specific antibodies: Treg cells: CD25⁺, FoxP3⁺,

Atg14⁺ (autophagy marker), and B lymphocytes: CD19⁺, PRL-R⁺. Analysis was performed by flow cytometry. ANOVA test was used for statistical analysis.

Results: We included 40 patients, divided in 20 inactive, 20 active SLE patients and 20 healthy controls. 80% of our population were female. Evolution time in inactive SLE patients was 8.72 ± 1.16 years and inactive SLE patients was 5 ± 0.95 years. SLEDAI was higher in active SLE patients than inactive SLE patients. In both active and inactive SLE groups, kidney was the most affected major organ (55% and 25% respectively). Sixty percent of inactive SLE patients and 35% of active patients had Chloroquine. The expression of autophagy, Treg cells Prolactin receptors and B-lymphocytes are shown in Figures 1 and 2.

Conclusion: The increase of autophagy in Treg and PRL-R in B lymphocytes participate in active lupus glomerulonephritis. Autophagy and PRL-R may be new therapeutic targets in SLE. This results suggest that may be a connection between autophagy, PRL-R, Treg and B cells if any.

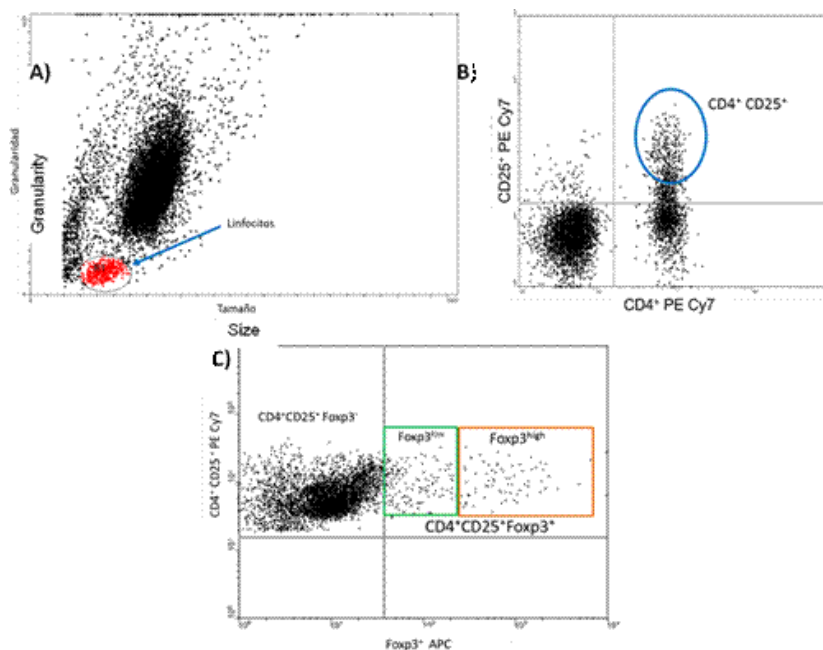


Fig.1: A) Dot plot in logarithmic scale of peripheral blood mononuclear cells (PBMC) of a SLE patient. B) Dot plot of the percentage of CD4 + CD25 + expression for Treg lymphocytes. C) Dot plot of the percentage of CD4 + CD25 + expression for Treg lymphocytes

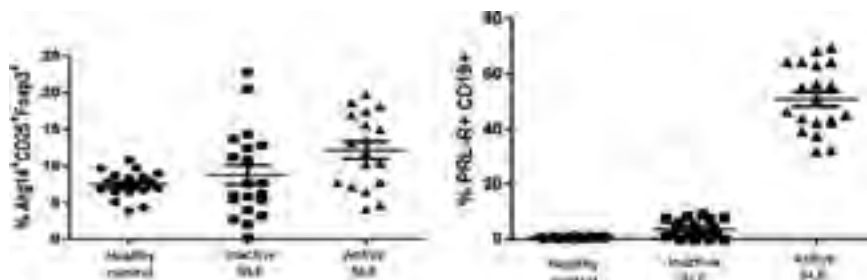


Fig. 2: Left: autophagy (%) in Treg cells inpatients and controls: A: Healthy control vs. Inactive SLE: 7.44 vs 8.74 $p = >0.9999$ B: Healthy control vs. Active SLE: 7.44 vs 12.11 $p = <0.05$. Right: prolactin Receptor in Blymphocytes, in Active and Inactive patients and healthy controls: A:Healthy Controls vs Inactive SLE: 0.62 vs 3.56 $p = 0.7463$. B: Healthy Controls vs Active SLE: 0.62 vs 50.79 $p = <0.0001$

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Cognitive Impairment and Health-Related Quality of Life in a Lupus Cohort

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Patients with systemic lupus erythematosus (SLE) are commonly affected by cognitive impairment (CI), with a meta-analysis finding a prevalence of 38%. Despite this high prevalence, there is limited data regarding the clinical impact of CI on patients with SLE. We hypothesize that the presence of CI is associated with a significant reduction in Health-Related Quality of Life (HRQoL) scores. Specifically we postulate effects on the domains of mental health, planning, and social functioning given the known effects of CI on these areas of function in other patient populations.

Methods: This single-center, cross sectional study of English-speaking SLE patients who presented in clinic from Ju 2016 to Apr 2017. Patients completed a comprehensive 2-hour neuropsychological battery, the Medical Outcomes Study Short Form 36 (SF-36) and Lupus Quality of Life (LupusQoL). CI was operationalized on the comprehensive battery as a z-score of ≤ -1.5 (as compared to controls) on ≥ 2 domains and/or $z \leq -2.0$ on ≥ 1 domain. Propensity scores were generated to balance covariates. Linear regression models were calculated for SF-36 and LupusQoL domain scores with respect to presence of CI.

Results: 171 participants were included in this study. 64 (37.4%) were found to have CI. Patient demographics are represented in table 1. Unadjusted patient characteristics by presence of CI are represented in Table 2. Linear regression models revealed that patients with CI showed statistically significantly lower scores in SF-36 Physical Component Summary score (PCS), SF-36 Mental Health, SF-36 Physical Functioning, SF-36 Social Functioning and LupusQoL Planning (Table 3).

Conclusion: Similar to previous studies, in our SLE cohort CI is prevalent, even with a high rate of post-secondary education. Our data demonstrate that CI is associated with significantly lower HRQoL scores. In addition to the expected decrease in Mental Health, Social Functioning, and Planning domains, a decrease in SF-36 PCS was also observed. This unexpected finding may be secondary to how patients interpret the PCS items, namely the effects of health on daily work activities. LupusQoL, a specific HRQoL measure for SLE, did not demonstrate a decrease in Physical Health scores but lower scores in Planning.

Table 1. Patient demographics at enrolment

Characteristic	N=171
Gender (F)	154 (90.1%)
Mean age (years) (Mean \pm SD)	42.7 \pm 12.1
Disease duration (Mean \pm SD)	14.5 \pm 10.3
Ethnicity	
Asian	15 (8.8%)
Black	34 (19.9%)
Caucasian	104 (60.8%)
Other	18 (10.5%)
Education level	
High school not completed	9 (5.5%)
Secondary school	32 (19.4%)
Post-secondary studies	124 (75.1%)
Employment status	
Employed or full time student	98 (57.3%)
Retired	5 (2.9%)
Homemaker	12 (7.0%)
Unemployed	56 (32.8%)

Table 1. (Cont'd)

Characteristic	N=171
SLE SLICC damage index (Mean \pm SD)	1.2 \pm 1.6
Treatment	
Antimalarials*	156 (91.2%)
Immunosuppressives*	148 (86.5%)
Glucocorticoids*	124 (72.5%)
Prednisone dose mg/day	6.32 \pm 7.00
(Mean \pm SD) Median (IQR)	5 (2-8)
Cognitive impairment	
(z-score of -1.5 in \geq 2 domains)	64 (37.4%)
Cognitive battery domains (z-score of -1.5 or less)	
Motor speed and dexterity	38 (22.2%)
Attention and processing speed	46 (26.9%)
Visual-spatial	51 (30.0%)
Verbal Fluency	6 (3.5%)
Learning and memory	77 (45.0%)
Executive function	12 (7.0%)

* Treatment within 1 year

Table 2. Characteristics by cognitive impairment (un-adjusted differences)

Characteristic	Cognitive Impairment ¹		p-Value
	No (N=107)	Yes (N=64)	
Gender (F)	97 (90.7%)	57 (89.1%)	0.73
Age at CI study enrolment (Mean \pm SD)	42.2 \pm 12.2	43.4 \pm 12.1	0.53
Disease duration at CI study enrolment (Mean \pm SD)	15.3 \pm 10.7	13.3 \pm 9.5	0.23
Ethnicity			0.005*
Asian	11 (10.3%)	4 (6.3%)	
Black	14 (13.1%)	20 (31.3%)	
Caucasian	66 (61.7%)	38 (59.4%)	
Other	16 (15.0%)	2 (3.1%)	
Education			0.17
Secondary education in-completed	3 (2.9%)	6 (9.7%)	
Secondary education	20 (19.4%)	12 (19.4%)	
Post-secondary education	80 (77.7%)	44 (71.0%)	
Employment status			0.97
Employed student	62 (57.9%)	36 (56.3%)	
Unemployed	34 (31.8%)	22 (34.4%)	
Homemaker	8 (7.5%)	4 (6.3%)	
Retired	3 (2.8%)	2 (3.1%)	
SLE organ damage index before HRQoL test (Mean score \pm SD)	1.1 \pm 1.6	1.3 \pm 1.7	0.67
Mean Lupus QoL Domain scores (Mean score \pm SD)			
Physical health	57.4 \pm 20.9	53.4 \pm 18.3	0.20
Pain	57.3 \pm 22.7	54.2 \pm 20.3	0.36
Planning	62.5 \pm 20.8	54.1 \pm 21.6	0.01*
Intimate relationship	59.5 \pm 26.1	52.0 \pm 29.5	0.13
Burden to others	50.6 \pm 25.3	46.6 \pm 23.1	0.30
Emotional health	59.6 \pm 19.1	56.9 \pm 19.2	0.38
Body image	60.3 \pm 20.5	60.4 \pm 19.8	0.98
Fatigue	47.0 \pm 22.2	41.4 \pm 22.0	0.11
Mean SF-36 Domain Scores (Mean score \pm SD)			
Bodily Pain	60.6 \pm 27.1	51.5 \pm 26.3	0.03*
General Health	44.4 \pm 24.0	41.7 \pm 23.6	0.46
Mental Health	67.4 \pm 21.2	60.3 \pm 22.4	0.04*
Physical Functioning	71.1 \pm 28.3	59.6 \pm 24.5	0.008*
Role Emotional	59.5 \pm 43.0	58.3 \pm 47.1	0.86
Role physical	54.0 \pm 42.5	39.8 \pm 45.4	0.04*
Social Functioning	71.3 \pm 27.8	60.5 \pm 29.3	0.01*
Vitality	45.2 \pm 26.6	39.5 \pm 22.7	0.15
Physical Score	41.2 \pm 11.6	37.0 \pm 10.8	0.01*
Mental Score	45.0 \pm 11.9	43.1 \pm 13.1	0.32

p values are from un-paired t-tests, Chi-Square tests and trend tests for more than two categories

* p <0.05

¹ CI is defined by z-score of -1.5 in \geq 2 domains

Table 3. Linear regression model: Estimated reduction of SF-36 and LupusQoL scores based on presence of cognitive impairment¹

HRQoL Tool	Domain	Estimated Score Reduction	95% Confidence Interval	p value
SF-36	Physical component score	-3.7	-7.2 to -0.2	0.04*
	Mental component score	-2.2	-6.1 to 1.7	0.26
	Bodily pain	-8.0	-16.0 to 0.4	0.06
	Global health	-3.0	-10.0 to 4.5	0.43
	Mental health	-7.4	-14.0 to -0.6	0.03*
	Physical functioning	-9.6	-18.0 to -1.4	0.02*
	Role emotional	0.2	-14.0 to 14.1	0.98
	Role physical	-13.0	-26.0 to 1.0	0.07
	Social functioning	-11.0	-20.0 to -1.9	0.01*
	Vitality	-6.4	-14.0 to 1.5	0.11
	Physical health	-2.9	-9.1 to 3.3	0.35
	Pain	-2.4	-9.2 to 4.4	0.49
	Planning	-7.9	-15.0 to -1.3	0.01*
Lupus QoL	Intimate	-7.0	-17.0 to 2.8	0.16
	Burden	-4.3	-12.0 to 3.4	0.27
	Emotional	-2.5	-8.5 to 3.5	0.42
	Body image	-0.3	-6.7 to 6.1	0.92
	Fatigue	-5.7	-13.0 to 1.3	0.10

¹ CI is defined by Z-score of -1.5 in two or more domains of the comprehensive cognitive battery

* p ≤0.05

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Abstract Number: 783

Procalcitonin and CXCL9 As Potential Biomarkers for Pneumonia in Patients with Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster I: Clinical Manifestations and Comorbidity

Session Type: ACR Poster Session A

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

Background/Purpose: Pneumonia is an important cause of death in patients with SLE. In general population, recommendations encourage the use of procalcitonin for management of pneumonia, however, evidence in patients with SLE is scant. The aim is to investigate the diagnostic and prognostic utility of procalcitonin and selected chemokines/cytokines in patients with SLE and pneumonia.

Methods: Cases: We studied 46 constitutive SLE patients (SLICC 2012 criteria) with pneumonia (respiratory symptoms + compatible image study) in a single tertiary care center, from Dec 2014 – Dec 2015. Patients were prospectively evaluated and samples for cultures and respifinder-22 (PCR for 18 viral + 4 bacterial pathogens) were obtained. Follow-up: 30 days after discharge. Basal procalcitonin determination on admission and in 42 (91%) patients a second sample 48-72 hrs later. Control groups: We included 27 active SLE and 24 inactive SLE patients (SLEDAI 2-K), without evidence of infection and a single procalcitonin measurement.

In 58 unselected patients (17 pneumonia, 23 active, and 18 inactive) we obtained serum for cytokines/chemokines determination by luminometry (IFN γ , IL-10, IL-12, IL-17, IL-1 β , IL-2, IL-21, IL-23, IL-5, IL-6, IL-8, TNF α , BAFF, IP-10, and CXCL-9).

Statistics analysis: Student-T test, Mann-Whitney U, Wilcoxon signed-rank test, Chi-squared test, Fisher exact test or Kruskal-Wallis test were used as appropriate.

Results: We included 97 patients, 83 women (86%). SLEDAI 2k: 1 ± 1.2 inactive vs 8.8 ± 4.5 active vs 8.2 ± 5.7 pneumonia. Patients with pneumonia had a shorter time from diagnosis (pneumonia 6 ± 8 years; $p < 0.001$; active 9 ± 6 years; inactive 14 ± 7 years).

Thirteen (28%) patients with pneumonia had a negative outcome (mechanical ventilation, shock or death). In 25 (54%) patients, a causal germ was identified. Patients with pneumonia had higher procalcitonin levels vs control groups ($p < 0.001$) whereas no differences were seen between active vs inactive patents. Thirty two patients (70%) with pneumonia had positive basal procalcitonin (> 0.5 $\mu\text{g/L}$) vs 0.0 $\mu\text{g/L}$ in control groups ($p < 0.001$); sensitivity 70% (95% CI: 54 - 82%), specificity 100% (95% CI: 93 - 100%). Twelve (38%) patients with positive basal procalcitonin had negative outcome vs one (7%) with procalcitonin ≤ 0.5 $\mu\text{g/L}$ ($p = 0.072$). Procalcitonin levels diminished in the second determination: median 0.95 (IQR 0.25 - 6.98) vs 0.36 (0.11 - 1.7), $p < 0.001$. In this determination, 16 patients had procalcitonin < 0.25 $\mu\text{g/L}$; two of them (12%) had negative outcome; 11 of 26 patients with procalcitonin > 0.25 $\mu\text{g/L}$ had a negative outcome (42%); $p = 0.084$.

Among the cytokines/chemokines evaluated, only CXCL9 was significantly higher in pneumonia vs control groups: median 1614 (IQR 905 - 2527) vs 641 (247 - 1096) active SLE and 313 (179 - 522) inactive SLE ($p < 0.001$).

Conclusion: Patients with SLE have a high rate of complications secondary to pneumonia. Procalcitonin is useful for diagnosis of pneumonia with a high specificity, even when comparing vs active SLE patients. CXCL9 is a potential biomarker for pneumonia in patients with SLE.

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Abstract Number: 784

Prediction of Hospital-Acquired Bacterial Infections in Patients with SLE

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SESSION INFORMATION

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Session Type: ACR Poster Session A

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Background/Purpose: Patients with SLE have an increased risk of serious infections, including nosocomial infections, which are associated with potentially modifiable adverse outcomes. Our objective is to develop a prognostic prediction model of hospital-acquired bacterial infections in patients with SLE.

Methods: A retrospective cohort of patients with SLE, classified according to the ACR criteria of 1987, with an age ≥ 16 years, hospitalized for ≥ 4 days for reasons other than bacterial infection in a university hospital between 2011 and 2016 was analyzed. Potential predictors were clinical and laboratory variables obtained during the first hours of hospitalization and selected by review of the medical literature. We compared the episodes in which at least one bacterial infection requiring intravenous antibiotics was diagnosed between days 3 and 15 of hospitalization with those who did not present this outcome. The significant variables in the univariate analysis and with absent data $\leq 20\%$ were included in a multivariate logistic regression model and finally the best performance prediction model was chosen with the most reasonable number of predictors.

Results: 579 hospitalizations were included, 12.4% ($n = 72$) developed the outcome, the most frequent nosocomial bacterial infection was bacteremia ($n = 24$), followed by urinary tract infections ($n = 19$) and pneumonia ($n = 13$). The main isolated bacteria were Escherichia coli ($n = 16$) and Staphylococcus aureus ($n = 15$). Table 1 presents the univariate analysis with selected independent variables. The variables incorporated in the final prediction model were: age, first neutrophil count of hospitalization, SLEDAI calculated on admission, use of central catheter in the first 72 hours, mean glucocorticoid dose in last month and use of antimalarial in last 3 months (table 2). By Receiver Operator Characteristic (ROC) analysis, it was demonstrated that the discrimination capacity of our model was acceptable (area under the ROC curve = 0.7475).

Conclusion: Our model predicts the risk of developing hospital-acquired bacterial infections in patients with SLE, using relatively simple clinical and laboratory data. One of the most important findings was that the use of antimalarials was associated with a significant reduction in the probability of nosocomial bacterial infection. External validation is required to corroborate the results and prospective studies are necessary to evaluate their clinical usefulness and impact.

Table 1. Characteristics of patients. Univariate analysis

Variable	Absent data	Total (n = 579)	Hospital-acquired bacterial infections (n = 72)	Without Hospital-acquired bacterial infections (n = 507)	p
Sex (women)	0 (0%)	512 (88.4%)	64 (87.7%)	448 (88.5%)	0.829
Age (years)	0 (0%)	32 (23)	37 (25)	31.5 (22)	0.085
Duration of the disease (months)	12 (2%)	48 (103)	36 (108)	48 (102)	0.270
Charlson Comorbidity Index	5 (0.8%)	2 (2)	2 (2)	2 (2)	0.572
Leukocytes (cells/mm3)	2 (0.3%)	7000 (4300)	7900 (5400)	6800 (4100)	0.089
Lymphocytes (cells/mm3)	2 (0.3%)	1200 (1200)	900 (1100)	1200 (1100)	0.045
Neutrophils (cells/mm3)	2 (0.3%)	4700 (3600)	5700 (5000)	4600 (3500)	0.007
CRP (mg/dl)	96 (16.6%)	1.5 (3.3)	2.45 (4.44)	1.26 (2.99)	< 0.001
ESR (mm/hour)	234 (40%)	54 (63)	60 (61)	54 (64)	0.729
Creatinine (mg/dl)	15 (2.6%)	0.8 (0.96)	0.97 (82.5)	0.8 (0.76)	0.073
Proteins in urinalysis (mg/dl)	143 (25%)	37.5 (150)	112.5 (125)	25 (150)	0.107
Albumin (g/dl)	259 (44.7%)	3 (1.2)	2.45 (1.35)	3.1 (1.15)	< 0.001
Complement C3 (mg/dl)	118 (20.4%)	69 (53)	65 (61)	71 (52)	0.113
Complement C4 (mg/dl)	122 (21.1%)	11.7 (13)	10.6 (18)	11.9 (12.7)	0.612
Anti DNA (titles)	155 (26.8%)	1:20 (160)	0 (160)	1:20 (160)	0.374
Antiphospholipid antibodies	0 (0%)	141 (24.4%)	13 (17.8%)	128 (25.3%)	0.163
Active lupus nephritis	0 (0%)	209 (36.1%)	34 (46.6%)	175 (34.6%)	0.046
Neuropsychiatric lupus	0 (0%)	27 (4.7%)	2 (2.7%)	25 (4.9%)	0.404
SLEDAI	0 (0%)	6 (12)	6 (13)	5 (11)	0.112
Bladder catheter	0 (0%)	16 (2.8%)	6 (8.2%)	10 (2%)	0.002
Central catheter	0 (0%)	37 (6.4%)	15 (20.6%)	22 (4.4%)	< 0.001
Alveolar hemorrhage	0 (0%)	10 (1.7%)	3 (4.1%)	7 (1.4%)	0.095
Mean glucocorticoid dose in last month -prednisolone equivalent- (mg)	0 (0%)	10 (15)	10 (20)	8.75 (15)	0.458
Methylprednisolone pulses	0 (0%)	96 (16.6%)	21 (28.8%)	75 (14.8%)	0.003
Cyclophosphamide in last month	0 (0%)	57 (9.8%)	10 (13.7%)	47 (9.3%)	0.237
Mycophenolate in last month	0 (0%)	94 (16.2%)	12 (16.4%)	82 (16.2%)	0.960
Azathioprine in last month	0 (0%)	85 (14.7%)	11 (15.1%)	74 (14.6%)	0.920
Rituximab in last 6 months	0 (0%)	10 (1.7%)	3 (4.1%)	7 (1.4%)	0.095
Antimalarial in last 3 months	0 (0%)	268 (46.3%)	21 (28.8%)	247 (48.8%)	0.001
Dialysis	0 (0%)	64 (11.1%)	12 (16.4%)	52 (10.3%)	0.117

Table 2. Variables included in the final prediction model of hospital-acquired bacterial infections in patients with SLE

Variable	OR	p	IC 95%
Age	1.0272	0.005	1.0083-1.0465
Neutrophils	1.0001	0.001	1.00005-1.00018
SLEDAI	1.0531	0.003	1.0175-1.0901
Central catheter	5.0763	0.000	2.3690-10.8775
Antimalarial	0.4293	0.005	0.2389-0.7717

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Correlation between Nailfold Capillary Number and Blood Perfusion in Systemic Lupus Erythematosus Patients

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Background/Purpose: Numerous articles have investigated peripheral microcirculation in primary Raynaud's phenomenon (RP) (1,2). Reports evaluating peripheral microcirculation in systemic lupus erythematosus (SLE) are scanty, but the interest is increasing (3). The aim of this study was to investigate possible correlations between morphological and functional aspects of microcirculation in different skin areas of the hands and face in SLE patients and to compare the results with primary RP (PRP) patients and healthy subjects (HS).

Methods: 14 SLE patients without RP (ACR criteria) (4) (mean age 53 ± 14 SD years, mean disease duration 7 ± 4 years), 14 PRP patients (LeRoy criteria) (5) (mean age 53 ± 17 years, mean RP duration 6 ± 5 years) and 14 HS (mean age 50 ± 17 years) were enrolled during the winter period, after informed consent. Nailfold video capillaroscopy (NVC) and laser speckle contrast analysis (LASCA) were performed in the three groups of patients. The absolute nailfold capillary number (CN) per linear millimeter at first distal row was assessed by NVC. Blood perfusion (BP) was detected by LASCA at the level of fingertips, periungual areas, dorsum and palm of both hands and face. The average BP was calculated as perfusion units (PU) (2). Patients were not taking vasodilator drugs since at least one month before study entry. Statistical analysis was performed by non parametric tests.

Results: SLE patients showed a positive correlation between nailfold CN and BP in all areas of hands ($p < 0.0001$), but no statistically significant correlation was observed between nailfold CN and BP at the level of face ($p = 0.10$). In both PRP and HS no statistically significant correlation was observed between nailfold CN and BP in all examined areas ($p = 0.70$ and $p = 0.20$, respectively). SLE patients showed a statistically significant lower nailfold CN than both PRP and HS (median 9.1 vs 10.3 vs 11.0, respectively, $p < 0.0005$). Conversely, no statistically significant difference of nailfold CN was observed between PRP and HS. PRP patients showed a statistically significant lower BP than both SLE and HS at the level of fingertip (median 90, 114, 187 PU, respectively; $p < 0.0001$), periungual (median 74, 100, 141 PU, respectively, $p < 0.0001$), dorsal (median 61, 72, 128 PU, respectively, $p < 0.0001$), and palm areas (median 76, 96, 124 PU, respectively, $p < 0.0001$). Conversely, PRP, SLE and HS patients showed similar BP values at the level of face (median 141, 139, 137 PU, respectively, $p = 0.30$).

Conclusion: This study demonstrates a correlation between morphological and functional microvascular features in SLE patients. SLE patients without RP have a subclinical microangiopathy, showing lower nailfold CN and BP than HS. Conversely, PRP patients show only a functional dysfunction, having a lower peripheral skin BP than both SLE patients and HS. The clinical value of this finding is undergoing further analysis, and open the door to new clinical insight.

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Disclosure: A. Sulli, None; B. Ruaro, None; C. Pizzorni, None; V. Smith, None; S. Paolino, None; V. Tomatis, None; M. Pendolino, None; M. Cutolo, None.

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Comparison of Nailfold Microvascular Damage in Mixed Connective Tissue Disease Versus Systemic Sclerosis Patients during a Three Year Follow-up

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: In systemic sclerosis (SSc), capillary abnormalities progress in a clearly defined sequence called the “scleroderma patterns” (Early, Active, Late) (1-3). On the contrary, characteristic nailfold capillary abnormalities are not present in mixed connective tissue disease (MCTD) (1,2). Until today, few studies described the main nailfold video capillaroscopy (NVC) changes in MCTD (4,5). The aim of this retrospective study was to compare nailfold capillary abnormalities in MCTD and SSc patients at first NVC visit, and to monitor MCTD capillary changes over a three year follow-up.

Methods: Ten patients (mean age 50 ± 19 years, mean disease duration 6.4 ± 4.2 years) affected by MCTD (Kasukawa’s criteria) who performed their first NVC were enrolled. Main capillary parameters (scores of capillary ramifications, enlarged capillaries, giant capillaries, microhemorrhages, number of capillaries, as well as absolute number of normal and total capillaries per linear millimetre) were evaluated in MCTD patients by NVC at baseline (T0, first NVC), and during a three year follow-up. Furthermore, NVC parameters were compared at T0 with 10 random SSc patients with the same disease duration (6.4 ± 4.2 years) and similar age (51 ± 17 years). Statistical analysis was performed by non parametric tests. The patients were receiving different immunosuppressive treatments.

Results: The scores of enlarged capillaries, giant capillaries and microhemorrhages were found significantly higher in patients with SSc versus MCTD patients at T0 (2.50 ± 0.5 vs 1.90 ± 0.6 $p=0.04$, and 1.63 ± 0.7 vs 0.70 ± 0.7 $p<0.02$, 1.25 ± 0.7 vs 0.70 ± 0.7 $p=0.05$, respectively). Moreover, the absolute number of total capillaries and normal capillaries were found significantly lower in SSc patients versus MCTD patients (5.8 ± 1.9 vs 7.6 ± 1.6 $p=0.04$ and 0.45 ± 1.0 vs 3.03 ± 2.9 $p=0.009$). On the contrary, no statistically significant difference was observed for the other capillary parameters (including capillary ramifications) between the two groups of patients. No statistically significant variation of the scores as well as of the absolute value of the above reported capillary parameters was observed during the 3 years of follow-up in MCTD patients. No statistically significant correlation was observed between capillary parameters and MCTD clinical aspects (Raynaud phenomenon, dysphagia, dyspnoea, sclerodactily, sicca syndrome, teleangiectasias and arthralgia) at first visit and during follow-up.

Conclusion: In a limited cohort of MCTD patients with an average disease duration of 6.4 years and a follow-up of three years, the nailfold microangiopathy does not seem to be significantly progressive. Patients with MCTD seem to show less enlarged/giant capillaries, and larger absolute number of total and normal capillaries than SSc patients.

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Abstract Number: 787

Longitudinal Follow-up of Anti-Topoisomerase I Positive Patients within the Leiden Systemic Sclerosis Cohort – Prognosis Infaust?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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

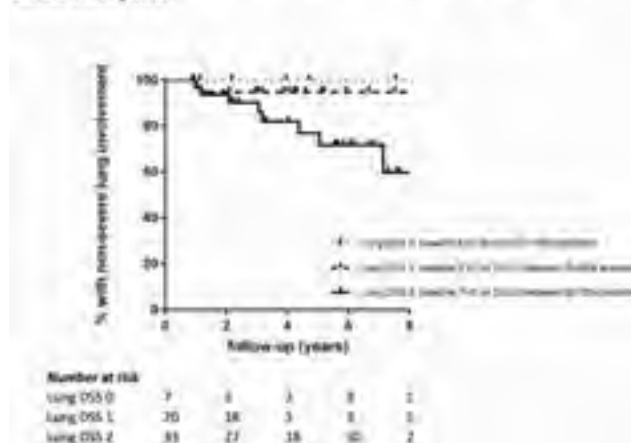
Background/Purpose: SSc is known for its heterogeneous disease course in which anti-topoisomerase I antibodies (ATA) are associated with dcSSc and interstitial lung disease and therefore regarded as marker for high-risk disease. In this study we aimed to describe disease course in ATA+ SSc patients.

Methods: Data of ATA+ patients included in the Leiden Systemic Sclerosis cohort (CCISS) between April 1st 2009 and May 1st 2016 were collected. Medsger Disease Severity Scale(DSS), providing a 0-4 score on 9 organ systems (0 normal to 4 severely affected; organ systems: general, peripheral vascular, skin, joint/tendon, muscle, GI tract, lung, heart and kidney) were calculated in all patients at baseline. Maximum disease score was determined, taking disease duration into account by stratifying the patients in 3 groups: 1. incident cases, 2. early disease, disease duration since first non-Raynaud ≤ 5 years,

Figure 1. Systemic Sclerosis maximum disease severity scores according to disease duration



Figure 2. Kaplan Meier curves for time to development of severe lung involvement (FVC or DLCO % predicted <50%) according to baseline lung disease severity scale



3. Prevalent disease, disease duration since first non-Raynaud > 5 years. Disease progression over time with specific focus on pulmonary involvement was assessed. For this purpose Kaplan Meier analysis assessing deterioration towards severe lung involvement (Lung DSS ≥ 3) was performed in patients with non-severe lung involvement (Lung DSS ≤ 2), with stratification for baseline severity score.

Results: Ninety-five patients were included in the current study. At baseline, median disease duration since first non-Raynaud symptom was 2.7 years (IQR 0.7-9.3). Evaluation of disease severity at baseline showed that mild / moderately severe disease (DSS scale 0, 1 and 2) was present among all subgroups including in 36% of patients with disease duration > 5 years (Figure 1). Longitudinal follow-up was available in 85 patients, with a median follow-up time of 3.2 years. Disease progression occurred in 48 patients (57%) and 2/49 lcSSc patients developed dcSSc over time. Of the 60 patients with non-severe pulmonary involvement at baseline, 9 (15%) developed severe pulmonary involvement over time, in which baseline Medsger Disease Severity Scale was a significant predictor (Figure 2).

Conclusion: ATA+SSc has a heterogeneous disease course, in which more than one-third of patients never develop severe organ involvement. Patients with normal lung function tests including FVC $\geq 70\%$ at baseline are unlikely to develop severe lung disease during follow-up. These data show that additional characteristics are needed to identify patients in need of therapy targeting SSc-related ILD.

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Clinical and Echocardiographic Associates of All-Cause Mortality and Cardiovascular Outcomes in Patients with Systemic Sclerosis

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SESSION INFORMATION

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Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Cardiac events are an important cause of mortality in Systemic Sclerosis (SSc), but its diagnosis remains challenging. Left ventricular global longitudinal strain is a novel parameter derived from speckle tracking echocardiographic analysis which has been proposed to identify patient at higher risk of cardiac events. We aimed to identify clinical and echocardiographic (including GLS) parameters associated with all-cause mortality and cardiovascular events in SSc patients.

Methods: 408 SSc patients (344 females, age 54±14 yrs.) were prospectively evaluated at baseline and follow-up (FU time 3.3 yrs. [IQR 1.8 to 5.5]). Cardiovascular events included: heart failure, cardiac infarction, coronary interventions, device implantation, arrhythmias, cerebral infarction, peripheral ischemic vascular disease.

Results: All-cause mortality (n=37) or cardiovascular events (n=57) occurred in 84 patients. At baseline, these patients were older (59±14 vs. 53±14 yrs., p<0.001), more often male (24 vs. 13%, p=0.018), more often had skin pigment changes (21 vs. 5%, p=0.011), coronary artery disease (11 vs. 3%, p=0.001), holter abnormalities (45 vs. 24%, p<0.001), increased ESR (24 [IQR 14 to 46] vs. 11 [IQR 6 to 25], p<0.001), worse NT-proBNP (151 [IQR 60 to 644] vs. 82 [IQR 51 to 145] ng/L, p<0.001), worse lung function test results (FVC 92±19 vs. 104±21%, p<0.001; DLCO 55±17 vs. 70±19%, p<0.001), worse left ventricular diastolic function (E/E-prime ratio 9.9 [IQR 6.7 to 10.2] vs. 7.8 [IQR 6.4 to 9.7], p<0.001), higher systolic pulmonary artery pressure (31±12 vs. 25±7mmHg, p<0.001) and lower GLS (-18.8 [IQR -20.3 to -19.5] vs. -21.1 [IQR -22.1 to -20.0]%, p<0.001). In a multivariate cox-regression analyses, age (HR 1.029, 95%CI 1.006 to 1.052), female sex (HR 0.527, 95%CI 0.302 to 0.922), NT-proBNP (HR 1.000, 95%CI 1.000-1.001), DLCO (HR 0.973, 95%CI 0.961-0.986) and GLS (HR 1.281, 95%CI 1.172-1.399) were independently associated with outcome. After dividing patients into groups according to median GLS (-20.9%) and elevated NT-proBNP (>200 ng/L), survival rates were lower and cardiovascular events increased when GLS was impaired and worsened when NT-proBNP was elevated (Log-rank p<0.001).

Conclusion: In SSc patients, next to age, DLCO and NT-proBNP, GLS strongly associates with all-cause mortality and cardiovascular events, indicating that these parameters reflect relevant cardiac involvement in SSc, and as such can contribute to risk stratification and patient management.

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The Relationship between YKL-40 and Vascular Endothelial Growth Factor in Angiogenesis in Systemic Sclerosis Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Systemic sclerosis (SSc) is an intractable, connective tissue disease that causes fibrosis of the skin and organs and its prognosis is affected by pulmonary arterial hypertension (PAH). SSc presents with Raynaud's phenomenon as the initial set of symptoms and is often accompanied by nailfold capillary abnormality. SSc is thought to cause microvascular disorder from the early stage. The chitinase-like protein YKL-40 has been implicated in inflammation, tissue remodeling, and angiogenesis in malignant tumors. A previous study in our department demonstrated elevated blood levels of YKL-40 in Japanese SSc patients. Globally, there are no reports examining the relationship between YKL-40 and vascular endothelial growth factor (VEGF) in SSc patients. Immunohistochemical (IHC) staining has not shown a relationship between YKL-40 and SSc in detail. We examined the relationship between YKL-40 and VEGF, which has an important role in angiogenesis.

Methods: We conducted a retrospective analysis of 84 SSc patients who were referred to our institution for treatment between August 2014 and April 2017. We excluded infection and malignant tumor complications. Controls were 15 healthy individuals. We measured serum YKL-40 levels and VEGF levels by ELISA and examined the correlation between YKL-40 age percentile, which was age-corrected for serum YKL-40 levels, and VEGF levels. Additionally, skin biopsy tissues from 7 SSc patients and 7 healthy individuals were also subjected to IHC staining with anti YKL-40 antibody.

Results: Our patient group included 11 men and 73 women with a mean age of 63.1 ± 13.4 years and a mean disease duration of 9.6 ± 9.8 years. The modified Rodnan total skin thickness score was 6.4 ± 6.9. Diffuse cutaneous SSc was identified in 20 patients; limited cutaneous SSc was identified in the other 64 patients. The 15 healthy individuals included 2 men and 13 women with a mean age of 59.7 ± 14.7. YKL-40 age percentile and VEGF levels in SSc patients (56.3 ± 30.2 and 410.0 ± 307.3 pg/ml, respectively) were significantly higher than in healthy individuals (24.9 ± 17.4 and 295.0 ± 154.5 pg/ml, respectively). The correlation coefficient (0.41) showed a mild correlation between YKL-40 age percentile and VEGF levels in SSc patients. Furthermore, staining of the blood vessel wall of the superficial dermis was found in specimens obtained from all SSc patients.

Conclusion: YKL-40 appears to reflect regeneration after capillary injury in SSc patients, with capillary vessels of the superficial dermis staining with IHC. There is a correlation between serum YKL-40 and VEGF levels in SSc patients.

Disclosure: T. Furukawa, None; K. Matsui, None; M. Kitano, None; N. Azuma, None.

Abstract Number: 790

Gastrointestinal Symptom Burden and Quality of Life in Systemic Sclerosis: Understanding the Role of Diet

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Systemic sclerosis (SSc) is a chronic autoimmune disease affecting multiple organ systems including vascular, musculoskeletal, cardiac, renal, pulmonary, and gastrointestinal (GI). 90% of SSc patients experience GI impairment and severe complications including impaired digestion, emptying, absorption, and peristalsis. The role of diet in SSc is not clear with few studies demonstrating prevalence of fructose intolerance and higher prevalence of celiac disease in undifferentiated connective tissue disease with SSc like features. Currently no consensus on dietary interventions in SSc exists. We aim to examine the impact of diet on symptom burden and quality of life measures in SSc.

Methods: An international randomized controlled single-blind study (IRB #748566) compared effects of a 4-week intervention of gluten-free (GF) vs Mediterranean (M) vs low FODMAP (LF) diets with no restriction on portion/calories. Medication changes were controlled for during the intervention period. Inclusion required a negative celiac test and a checklist from the subject's rheumatologist confirming ACR/EULAR SSc criteria. Telephone counseling provided diet instruction and support. Patient reported outcomes measures (PROMs) included the Geissen SSc Gastrointestinal (GGI),

SSc Gastrointestinal Tract (GIT), SF-36 and adherence questionnaires and were completed via REDCap at 0, 4, and 8 weeks. Data was analyzed by repeated measures analysis and linear mixed model analysis.

Results: Enrollment is ongoing with 51 subjects enrolled and 29 reaching completion (8, 9 and 12, respectively in the GF, M, and LF groups). Of these 29, there were no differences in age, gender, race, or ethnicity. There were no differences between diet groups at 0, 4 or 8 weeks in GGI, GIT, or SF-36. Statistically significant improvements for all groups occurred in the GGI daytime heartburn ($p=0.04$), nighttime heartburn ($p=0.01$), difficulty swallowing ($p=0.01$), and constipation items ($p=0.006$); in the GIT bloating domain ($p=0.02$) and overall combined score ($p<0.005$); and in quality of life (QoL) SF-36 role physical ($p=0.02$) and vitality ($p=0.01$) domains. Largest improvements occurred immediately post-intervention (week 4) with waning at week 8 though still significant. Mean adherence was 78.3% with the GF group demonstrating higher adherence (97.2%) than the M and LF groups (73.7% and 72.4% respectively) ($p<0.005$).

Conclusion: Though no differences related to diet emerged, statistically significant improvements in GI and QoL PROMs occurred in all groups suggesting that increased awareness and purposeful nutrition selection may impact GI symptom burden and overall QoL. Further inquiry is needed with larger sample sizes to determine if premeditated/structured nutrition selection is a worthwhile application in SSc care.

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Abstract Number: 791

Safety and Suitability of a Direct Thrombin Inhibitor, Dabigatran Etexilte, in Scleroderma-Associated Interstitial Lung Disease (SSc-ILD) Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Studies from our laboratory and others have shown thrombin to be a fibrogenic mediator implicated in the pathogenesis of ILD, including scleroderma-associated ILD (SSc-ILD). Thrombin activity is high in SSc-ILD bronchoalveolar lavage fluid (BALF), and normal lung fibroblasts transform to a myofibroblast phenotype upon exposure to thrombin. Dabigatran etexilate (Pradaxa[®]) is a selective thrombin inhibitor approved for the prevention of thromboembolic complications. On the basis of strong preclinical in vitro and animal data demonstrating that thrombin inhibition can ameliorate lung fibrosis, we have conducted a single-site, open-label study to establish the safety of Dabigatran etexilate in SSc-ILD patients.

Methods: Dabigatran etexilate was administered orally in a dose of 75 mg twice daily for 6 months to 15 patients with SSc-ILD having no contraindication to anticoagulant therapy (ClinicalTrials.gov Identifier NCT02426229). Safety and tolerability of Dabigatran etexilate were monitored by history, PE, questionnaires and laboratory studies during the treatment period. Plasma, BALF, skin and lung fibroblasts were obtained before and after treatment.

Results: 15 patients fulfilling the 2013 ACR/EULAR classification criteria have been enrolled: 13 have completed, 1 subject is still enrolled, and 1 subject was withdrawn due to noncompliance. Baseline characteristics are as follows: 13 females and 2 males; 6 African Americans and 9 Caucasians; 5 limited and 10 diffuse cutaneous SSc; age 47.5 ± 9.6 years (mean \pm SD); disease duration 4.1 ± 3.3 years; modified Rodnan Skin Score 16.0 ± 10.3 ; SSc Health Assessment Questionnaire 1.4 ± 0.6 ; UCLA SCTC GIT score 0.79 ± 0.58 ; Baseline Dyspnea Index 7.9 ± 3.1 ; FVC % predicted 70.6 ± 15.4 ; DLCO % predicted 54.3 ± 14.1 .

Overall, Dabigatran etexilate has been well tolerated. There have been no serious adverse events. Mild adverse events include: fatigue ($n=1$), epistaxis ($n=3$), menorrhagia ($n=2$) and cystitis ($n=1$). One moderate adverse event occurred in a subject with headache found to be unrelated to study medication. Monthly laboratory monitoring has shown no clinically significant change in CBC, CMP, PT/INR or PTT, but did show the expected prolongation of thrombin time (TT).

Exploratory analysis before and after Dabigatran etexilate treatment revealed that the most profound reduction in thrombin activity was observed in a patient having high BALF thrombin activity at baseline, and this patient also demonstrated the greatest reduction in collagen type I and α -smooth muscle actin in skin fibroblasts, as well as reduction of α -smooth muscle actin in lung fibroblasts.

Conclusion: Our data suggest that Dabigatran etexilate at a dose of 75 mg twice daily is safe and well tolerated in patients with SSc-ILD. Exploratory analysis suggests that SSc-ILD patients with high BALF thrombin activity may have the greatest potential to benefit from treatment with Dabigatran etexilate. A randomized controlled trial is warranted to establish safety and determine the efficacy of Dabigatran etexilate in patients with SSc-ILD.

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Abstract Number: 792

Evaluation of Esophageal Dysmotility in Systemic Sclerosis: Clinical VALUE of Computed Tomography

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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Background/Purpose: Esophageal dysmotility is common in Systemic Sclerosis (SSc), affecting 50-80% of patients, usually associated with poor prognosis. SSc leads to atrophy and fibrosis of the smooth muscle of the esophagus, modifying peristaltic contractions and motility. Manometry is considered the gold standard for the diagnosis of esophageal motility disorders, but dilation can also be observed with computed tomography (CT), even if its diagnostic validity is still unknown. /Purpose: To compare esophageal dilation observed with CT to manometry, in patients with SSc and to confirm whether CT can be used in the assessment of esophageal dysmotility.

Methods: Forty six patients meeting the 2013 ACR/EULAR Classification Criteria for SSc, and 53 healthy controls were included and retrospectively studied. Patients with overlapping syndromes, active infections or with longstanding diabetes were excluded. Epidemiological and clinical data were collected from medical records. All patients and controls had undergone at least one manometry and one CT, requested in daily clinical practice for another purpose. The most recent exams were selected for the study. Esophageal involvement was assessed using manometry (aperistalsis, inefficient peristalsis, nonspecific dysmotility and normal peristalsis) and compared with the largest coronal esophageal luminal diameters proximally, near the carina, and distally observed by CT. Data analysis was performed by STATA. All patients signed written informed consent, approved by the Research Ethics Committee.

Results: The sample included 76 women (10 dcSSc, 28 lcSSc, 3 MCTD, 35 controls) and 23 men (3 dcSSc, 2 lcSSc, 18 controls). Esophageal dysmotility was seen in 40/46 patients with SSc (87%) by manometry (defined as inefficient peristalsis or aperistalsis). Esophageal dilation (≥ 10 mm) was present proximally in 23/44 patients (52.3%), distally in 35/46 patients (76.1%), and near the carina in 26/44 patients (59.1%). Esophageal dilatation at any level was statistically associated with esophageal dysmotility ($p < 0.05$). The areas under the ROC curves suggest that the esophageal proximal diameter in the coronal plane is good for detecting esophageal dysmotility (0.798, 95%CI 0.705-0.890), with the distal diameter (0.759, 95% CI 0.661-0.857) and the carinal diameter (0.712, 95%CI 0.607-0.816), being slightly lower. A proximal diameter ≥ 7.5 mm provides a specificity of 87.2% (95% CI: 76.7–96.7) and a sensitivity of 65.3% (95% CI: 51.9–78.6) for esophageal dysmotility, enabling correct classification of 75% of the patients. A distal diameter ≥ 12.9 mm provides a specificity of 76.6% (95% CI: 64.5–88.7) and a sensitivity of 71.2% (95% CI: 58.8–83.5), correctly classifying 73% of the patients.

Conclusion: CT, a less invasive technique than manometry, can be an acceptable diagnostic tool for esophageal dysmotility in SSc, when the maximum proximal or distal esophageal diameter are ≥ 7.5 mm and 12.9mm, respectively. CT done in the daily clinical practice could be exploited when manometry is not preferred in selected patients with SSc. More studies need to be carried out to confirm this results.

Disclosure: C. Sobrino, None; C. Pijoan-Moratalla, None; N. Almeida-Arostegui, None; L. Gorospe-Sarasúa, None; C. de la Puente-Bujidos, None.

Abstract Number: 793

Clinical Associations of Anti-U11/U12 (RNPC-3) Autoantibodies in Patients with Systemic Sclerosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Anti-nuclear antibodies (ANA) are present in approximately 90% of sera from systemic sclerosis (SSc) patients and play an important role in the diagnosis and prognosis of SSc. Besides the classical autoantibodies that are part of the classification criteria (anti-Scl-70, anti-centromere, anti-RNA Pol III), several other antibodies can be found in SSc, albeit with lower prevalence, some of which clearly associate with disease phenotypes. Anti-U11/12 Ribonucleoprotein (RNP) antibodies have been reported in a small portion of patients with pulmonary fibrosis. RNPC-3, also known as U11/U12 Small Nuclear Ribonucleoprotein 65 KDa Protein has been reported as an autoantibody target with strong association with malignancy in patients with SSc. Here we aimed to study the prevalence of anti-RNPC-3 antibodies in SSc and controls.

Methods: A total of 613 well characterized SSc patients from two different sites (Barcelona, n=225; and Milan, n=388) were used to establish sero-clinical associations. In addition, a variety of disease controls (rheumatoid arthritis, n=50; systemic lupus erythematosus, n=50; infectious disease, n=50; healthy individuals, n=50) were included to assess autoantibody specificity. All samples were tested on particles coated with recombinant RNPC-3 along with classical SSc markers (Scl-70, centromere, RNA Pol III) using a novel particle-based multi-analyte technology (PMAT, Inova Diagnostics, San Diego, USA). Disease subtype [limited (lcSSc) or diffuse SSc (dcSSc)] and clinical manifestations were retrieved from each site and included digital ulcers (39.2%), interstitial lung disease (ILD, 37.7%), scleroderma-related malignancy (16.7%), and calcinosis (22.7%).

Results: In the total cohort, anti-RNPC-3 showed a prevalence of 3.1% (n=19) in SSc with 99.5% specificity, while the prevalence in each SSc cohort was 4.9% and 2.1% in the Spanish and Italian sites, respectively. Anti-RNPC-3 antibodies were found at very high titers in SSc versus controls ($p<0.0001$) and the majority of the positives (13/19, 68.4%) were negative for the classical SSc markers (anti-Scl-70, anti-centromere, anti-RNA Pol III). When analyzing against clinical manifestations in SSc, anti-RNPC-3 antibodies showed a strong association with ILD both in prevalence (Fisher Exact $p=0.0062$) and antibody levels (Wilcoxon-Mann-Whitney, $p=0.0153$), however the marker was not significantly associated with the other manifestations analyzed (cancer, ulcers, calcinosis). Although the marker showed higher prevalence in dcSSc (6.5% vs. 3.1% in lcSSc), the difference did not reach significance.

Conclusion: Our study confirms the presence of anti-RNPC-3 autoantibodies in patients with SSc. In addition, this study of Spanish and Italian SSc patients confirms the association of anti-RNPC-3 with ILD as previously reported in a North American cohort. In contrast, we were unable to confirm the associations with cancer. Further studies are needed to verify the clinical utility of the marker and to further investigate the putative association with cancer.

Disclosure: L. Beretta, None; M. Mahler, Inova Diagnostics, 3; C. Bentow, Inova Diagnostics, 3; A. Seaman, Inova Diagnostics, 3; F. Roup, Inova Diagnostics, 3; M. Amio, Inova Diagnostics, 3; K. Norvell, Inova Diagnostics, 3; J. Milo, Inova Diagnostics, 3; S. Encabo, Inova Diagnostics, 3; J. Perurena, None; M. Sanz, None; A. Guillen, None; A. Marín, None; V. Fonollosa, None; E. Callejas, None; C. P. Simeón, None.

Identification of an Immunodominant Epitope on Rnpc-3 As a Target of Autoantibodies in Patients with Systemic Sclerosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Anti-nuclear antibodies (ANA) are present in approximately 90% of sera from systemic sclerosis (SSc) patients and play an important role in the diagnosis and prognosis of that disease. Besides the classical autoantibodies that are part of the SSc classification criteria, several other antibodies can be found, albeit with lower prevalence, some of which clearly associate with disease phenotypes. Anti-U11/U12 Ribonucleo protein(RNP) antibodies have been reported in a small portion of patients with pulmonary fibrosis. RNPC-3, also known as U11/U12 Small Nuclear Ribonucleoprotein 65 kDa Protein has been reported as an autoantibody target with strong association with malignancy in SSc patients. The aim of this project was to analyze the B-cell epitopes of anti-RNPC-3 antibodies and to study the prevalence of anti-RNPC-3 antibodies in SSc and controls.

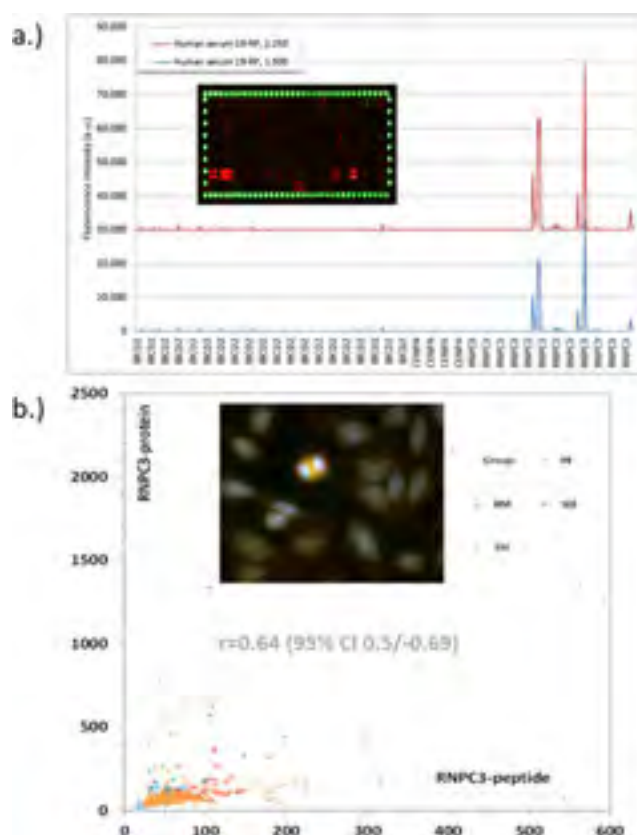


Figure1 Epitope mapping of RNPC-3 using solid phase peptide arrays (a) and correlation of peptide reactivity with RNPC-3 protein along with co-localized IIF pattern (b).

Methods: Two SSc sera with anti-RNPC-3 antibodies, assayed by an addressable laser bead-based immunoassay (ALBIA) with recombinant RNPC-3, were used for epitope discovery with peptide arrays covering the full-length aminoacid sequence of human RNPC-3. As controls, three samples with anti-centromere antibodies were included as well as peptides derived from CENP-A and BICD2. The identified candidate epitopes were subsequently utilized to synthesize synthetic,

biotinylated, soluble peptides for testing using a novel particle-based multi-analyte technology (PMAT). To analyze the marker in SSc, sera from 88 SSc patients were included where 32 cases had documented cancer. Sera from 64 systemic lupus erythematosus (SLE) patients, 65 idiopathic inflammatory myopathies (IIM), and 20 health individuals (HI) were included as a comparator group. Co-localization by indirect immunofluorescence (IIF) of human anti-RNPC3 with rabbit anti-RNPC3 (rabbit polyclonal) was performed.

Results: Epitope mapping revealed an immunodominant epitope in the C-terminus of the protein (see Figure). The reactivity to recombinant RNPC-3 (rRNPC-3) and to the RNPC-3 derived peptide (pRNPC-3) were highly correlated (Spearman's $\rho=0.64$, 95% Confidence interval 0.58-0.69; $p<0.0001$). Autoantibodies to both rRNPC-3 and pRNPC-3 tended to be higher in SSc and SLE compared to IIM and HI. When the cohort of patients with known history of cancer was compared with an unselected SSc cohort, no significant difference was found. Experiments performed by IIF confirmed the speckled pattern shown in previous studies.

Conclusion: Our study is the first to report a linear epitope on RNPC-3 as a target of autoantibodies in patients with SSc. Further studies are needed to validate the association of anti RNPC-3 antibodies with cancer as well as the utility of the novel RNPC-3 derived peptide.

Disclosure: M. Mahler, Inova Diagnostics, 3; C. Bentow, Inova Diagnostics, 3; J. Milo, Inova Diagnostics, 3; M. Hudson, None; M. Baron, None; M. Choi, None; M. J. Fritzler, Inova Diagnostics Inc., BioRad, Euroimmun GmbH, Mikrogen GmbH, Dr. Focke Laboratorien GmbH, ImmunoConcepts, SKF Canada, Amgen and Pfizer, 5, ImmunoConcepts, Inova Diagnostics, Euroimmun GmbH, and Alexion Canada, 7.

Abstract Number: 795

Frequency and Clinical Associations of Rare Antibodies in a Large Connective Tissue Disease Cohort

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Background/Purpose: Connective tissue diseases (CTDs) are characterised by specific autoantibodies which are useful for diagnosis. Rare antibodies have been described in CTDs in several case series. We assessed the frequency and clinical features of CTD patients attending our centre, positive for at least one of these antibodies (Jo-1, PCNA, XR, PL-4, PL-7, PL-12, SRP, Ku, Mi-2, EJ, SL, PmScl, rRNP, Th/To, NuMa-1, OJ and hnRNP). Rare antibody was defined as an antibody found in less than 5% of our patient population.

Methods: The immunology results for 5828 patients obtained over the past 17 years were analysed and patients with the rare antibodies were identified. Clinical data including diagnosis and frequency of organ involvement were obtained from medical records and patient review.

Results: 758 patients (12.5%) were positive for at least one rare antibodies. Clinical information confirming a diagnosis of a CTD was available for 514 patients. The most common rare antibody was PmScl (3.1%) and least common was OJ (0.01%). The majority of patients with rare autoantibodies demonstrated overlap syndromes (32.1%), the second most common diagnosis was scleroderma (SSc) (31.0%). The least common diagnosis was UCTD (1.1%). Further analyses of major organ involvement by antibody subtype revealed 82.4% of PL-7+ patients had interstitial lung disease (ILD). ILD was also frequently seen in PL12+ (75%), Jo-1+ (70.8%), SRP+ patients (66.7%) and Mi-2 (57%). PCNA, NuMa1, OJ and hnRNP were not associated with ILD. Pulmonary arterial hypertension (PAH) was most frequently seen in XR+ patients (31.8%), followed by Th/To+ (25%) and Jo-1 (15.3%) patients. None of our patients with PL-12 developed PAH. Inflammatory myositis (IM) was found in all Jo1+ and SRP+ patients, and in the majority of PL-7+ (88.2%) patients. Inflammatory arthritis was more commonly seen in hnRNP+ (100%), PCNA+ (57.1%), SL+ (38.3%),

and PL-12+ (33.3%) patients but not reported in EJ+, Mi-2+ and PL-4+ patients. Glomerulonephritis was reported in significant proportion of rRNP+ (60%), PCNA+ (42.9%), and PL-4+ (45.5%) patients. Scleroderma renal crisis was diagnosed in three (3.8%) SL+ patients.

Conclusion: Our data from a large cohort of patients with CTDs suggest that rare antibodies associate with characteristic features, in particular ILD and inflammatory myositis. A majority of these patients fulfil the criteria for overlap syndrome and SSc.

We noted some associations not reported in current literature between these antibodies and fibrotic and vascular features of CTDs. In contrast to previous findings, ILD was frequently reported in our Mi-2+ patients. Anti XR has not previously been associated with PAH or ILD, whereas we noted a frequency of 31.8% and 40.9% respectively.

Given the rarity of these antibodies, it is important to understand the clinical impact they may have in risk stratifying our patients at diagnosis especially given the high proportion of patients with overlap CTD features.

Disclosure: K. E. N. Clark, None; C. Campochiaro, None; L. V. Host, Roche, 2, Australian Rheumatology Association (ARA), 2, Arthritis Australia, 2, ARA Western Australia, 2; A. Sari, None; S. I. Nihtyanova, None; C. Fonseca, None; C. P. Denton, Roche, Actelion, GlaxoSmithKline, Sanofi-Aventis, Inventiva, SCL Behring, Boehringer-Ingelheim, Bayer., 5; V. H. Ong, None.

Abstract Number: 796

Demographic and Clinical Features of Systemic Sclerosis Patients with Anti-U1RNP Antibodies: A European Scleroderma Trials and Research (EUSTAR) Analysis

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SESSION INFORMATION

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Background/Purpose: Anti-U1RNP antibodies can be detected in patients with systemic sclerosis (SSc). However, their prevalence and clinical correlation with organ-specific complications have not been well characterized. The aim of the current study was to investigate the demographic and clinical features of SSc patients with anti-U1RNP antibodies using the European Scleroderma Trials and Research (EUSTAR) database.

Methods: SSc patients in the EUSTAR database with available data on anti-U1RNP antibodies were analyzed. Patients had to fulfill the 1980 American College of Rheumatology (ACR) or the 2013 ACR/European League Against Rheumatism (ACR/EULAR) classification criteria. Clinical characteristics were collected at the visit when the status of anti-U1RNP antibodies was first recorded.

Demographic and clinical parameters were compared between patients positive and negative for anti-U1RNP antibodies in univariate analysis followed by Bonferroni correction. Associations between anti-U1RNP status and involvement of multiple organs were tested in multivariate logistic regression models. Multiple imputation was used before regression analysis to handle missing values.

Results: A total of 8391 patients were eligible for this analysis, among which 408 (4.9%) patients were positive for anti-U1RNP antibodies. Of the 8391 patients, the majority was female (84.9%), the median age was 57.0 years (IQR: 46.0-66.0). The median disease duration was 7.0 years (IQR: 3.0-13.0). Thirty-one percent patients had diffuse cutaneous involvement.

In univariate analysis, SSc patients positive for anti-U1RNP antibodies were significantly younger at disease onset (mean 37.9 vs 46.6 years), had higher prevalence of synovitis (19.3% vs 13.4%), pulmonary hypertension assessed by

echocardiography (24.7% vs 15.9%), lung fibrosis diagnosed by chest X-ray or high-resolution computer tomography (53.1% vs 42.0%), proteinuria (12.6% vs 5.6%), erythrocyte sedimentation rate (ESR) >25mm/h (46.4% vs 31.4%) and hypocomplementemia (15.7% vs 7.1%) than those negative for anti-U1RNP antibodies.

By multivariate analysis, anti-U1RNP antibodies were confirmed to be independently associated with synovitis [odds ratio (OR) 1.47, 95% confidence interval (CI) 1.10 to 1.96], lung fibrosis (OR 1.36, 95% CI 1.06 to 1.76), pulmonary hypertension on echocardiography (OR 2.20, 95% CI 1.62 to 2.99), proteinuria (OR 2.27, 95% CI 1.56 to 3.31) and ESR>25mm/h (OR 2.11, 95% CI 1.65 to 2.71). In addition, there was a negative association with diffuse cutaneous involvement (OR 0.58, 95% CI 0.45 to 0.75).

Conclusion: This is the largest cohort of SSc patients positive for anti-U1RNP antibodies reported so far. It defines characteristic features associated with this specific subtype of SSc-patients. The detection of anti-u1RNP antibodies in SSc patients should be more emphasized and might be helpful for risk stratification during clinical practice.

Disclosure: W. Wu, None; P. Hoederath, None; E. Hachulla, None; P. Airò, None; G. Valentini, Abbvie, BMS, Lilly, MSD, Pfizer, Sanofi, 2, 8; M. Matucci Cerinic, Actelion, Bayer, ChemomAb, Inventiva, 2, 5; F. Cozzi, None; G. Riemekasten, None; Y. Allano, None; P. Carreira, None; S. Jordan, None; O. Distler, Actelion, Bayer, Boehringer Ingelheim, Mitsubishi Tanabe Pharma, Roche, 2, Actelion, AnaMar, Bayer, Boehringer Ingelheim, ChemomAb, espeRare foundation, Genentech/Roche, GSK, Inventiva, Italfarmaco, Lilly, medac, MedImmune, Mitsubishi Tanabe Pharma, Novartis, Pfizer, Sanofi, Sinoxa, UCB, 5, Patent mir-29 for the treatment of systemic sclerosis licensed, 9.

Abstract Number: 797

Absolute Reduction of Peripheral CD4⁺ Regulatory T Cells in Patients with Systemic Sclerosis and Its Restoration By Short-Term and Low Dose IL-2 Treatment

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

Background/Purpose: The aim of the present study was to investigate whether the imbalance of CD4⁺ T subsets can be corrected by supplementing low dose interleukin -2 (IL-2).

Methods: The PB samples from 21 patients with SSc as well as 30 healthy control subjects were analyzed for lymphocyte subsets using flow cytometry. Patients given a small dose of IL-2 (50WU) for a 5-day course based on standard treatment (including glucocorticoids, immunosuppressants, biologics, or combination). Using directly the percentages from flow cytometry combined with internal standard beads calculated absolute number of peripheral lymphocyte subsets and their ratio to Treg cells from the subjects in each group before and after IL-2 treatment.

Results: Notably, Treg cells rapidly increase after treatment with low doses IL-2. However, before treatment, the ratios of Th17/Treg($p<0.001$) and Th2/Treg($p=0.01$) were significantly higher. After treatment, although Th17 and Th2 cells increased, Treg cells increased more, so the ratios returned to normal. Similarly, after treatment, the numbers of Th1, CD8⁺ T, NK and B cells all increased to some extent, but the ratios of these T cells to Treg cells still were low i.e. they were balanced for the increase in Treg cells after treatment was more pronounced.

Conclusion: Short-term low-dose IL-2 treatment can promote the proliferation of Treg cells mainly and restore the balances of various cell subsets with Treg cells.

Disclosure: L. Shang, None; J. Luo, None; C. Gao, None; J. Yuan, None; Q. Li, None; X. Liu, None; H. Gao, None; X. F. Li, None.

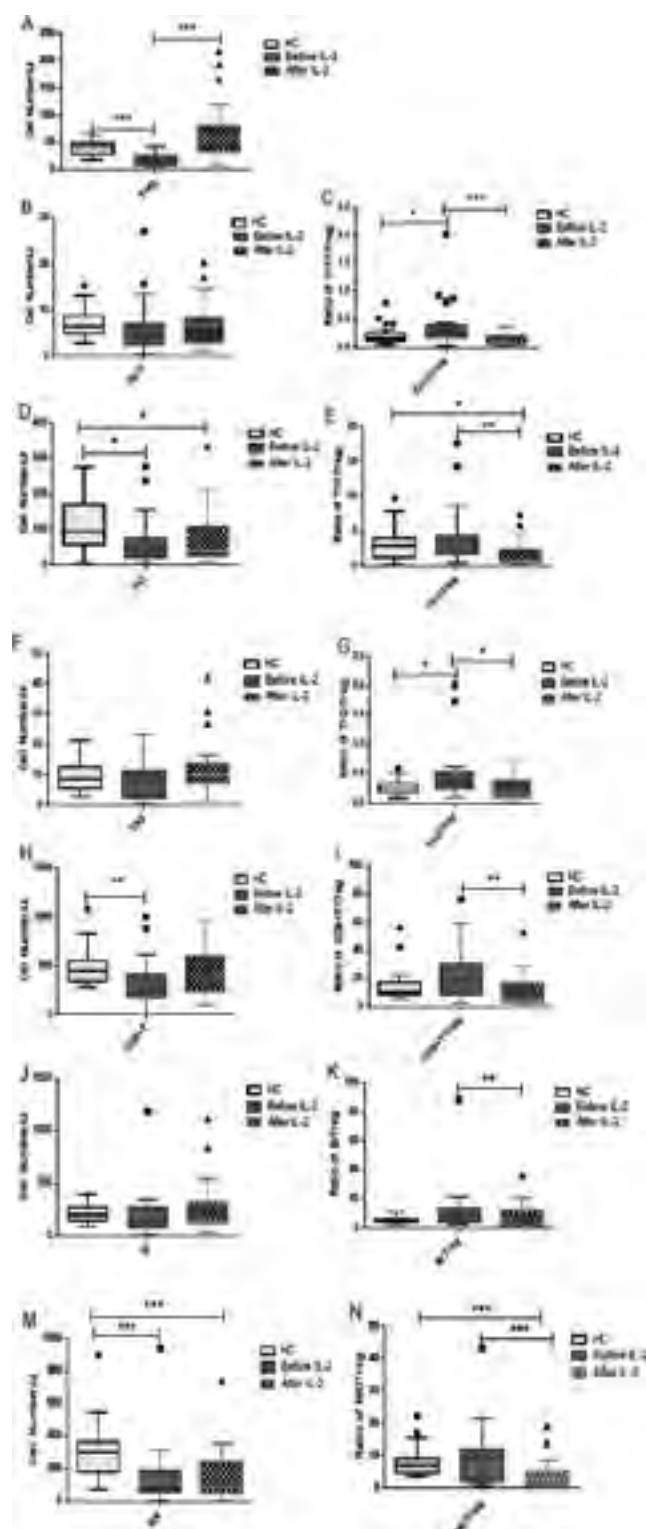


Fig. 1. Changes of CD4⁺ T cell subpopulations before and after treatment with low-dose IL-2 and healthy control subjects. (A) Significant increase in Treg cells after IL-2 treatment. (B, F, and J) Absolute number of Th1, Th2, and Th17 cells in PB of SLE patients before and after IL-2 treatment were not significantly different from those in healthy controls. (D, H, and L) The absolute numbers of Th1, CD8⁺ T, and NK cells in PB of patients with SLE were significantly reduced before IL-2 treatment while Th1 and NK were increased after the treatment. (C, E, G, I, K, M, and N) The all ratios of Th1/Th2, Th1/Th17, Th2/Th17, CD8⁺ T, total B, and IL-17⁺ Treg cells after IL-2 treatment were significantly decreased. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. PB, PB.

Predominant Fasciitis and Mild Intramuscular Edema on Muscle Magnetic Resonance Imaging in Scleroderma-Associated Myopathy

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Background/Purpose: Skeletal myopathy in systemic sclerosis is poorly defined. The spectrum of muscle histopathology in systemic sclerosis has been previously studied and shown to be heterogeneous. There has been little data to describe the imaging findings in scleroderma muscle disease. The purpose of this study is to determine whether there are unique muscle magnetic resonance imaging (MRI) features of scleroderma associated myopathy.

Methods: This retrospective, cross-sectional study included 25 patients with SSc and biopsy proven fibrosing myopathy or inflammatory myopathy as previously described (1). These patients also had coronal and axial T1-weighted images and short tau inversion recovery (STIR images) of the thighs as part of routine clinical care. A small subset (n=15) also had axial diffusion weighted imaging (DWI) using 2 b-values (0 and 800 s/mm²) and apparent diffusion coefficient (ADC) mapping. Two musculoskeletal radiologists, blinded to histopathological finding, reviewed the MR studies in consensus and semi-quantitatively evaluated for the presence of intramuscular edema, fascial edema, fatty replacement and atrophy on all sequences using equidistant 4-point scoring system (0 = absence, 1 = mild, 2 = moderate, 3 = maximal) for 36 individual skeletal muscles in each patient. Pairwise comparisons for categorical variables between the fibrosing and non-fibrosing groups were made using χ^2 test.

Results: There were 12 patients with fibrosing myopathy and 13 patients with an inflammatory myopathy with available MRI data. On STIR sequences, patients with a fibrosing myopathy more often had mild intramuscular (48% (170/355) vs. 36% (176/485), p=.0005) but more prominent fascial edema (16% (46/294) vs. 9% (47/496), p=.0005) when compared with the inflammatory myopathy group. Whereas, on T1-weighted sequences, patients with an inflammatory myopathy more often had evidence of chronic muscle damage such as mild fatty replacement (36% (182/504) vs. 27% (82/306), p=0.008) and atrophy (44% (217/498) vs. 34% (104/306), p=0.005) when compared with a fibrosing myopathy. On DWI, patients with SSc-associated fibrosing myopathy more often had elevated signal for both low and high b-value images.

Conclusion: Thigh muscle MRI may be a useful imaging biomarker to distinguish fibrosing myopathy from inflammatory myopathy in systemic sclerosis.

Reference:

1. Paik JJ, Wigley FM, Shah AA, Corse AM, Casciola-Rosen L, Hummers LK, et al. Fibrosing myopathy in systemic sclerosis associates with higher mortality. *Arthritis Care Res* 2017.

Disclosure: J. J. Paik, None; S. Ahlawat, None; F. DelGrande, None; L. K. Hummers, None; F. M. Wigley, None; A. A. Shah, Bristol-Myers Squibb, 5; A. Mammen, None; L. Fayad, None.

Progressive Lung Fibrosis in Patients with Systemic Sclerosis-Associated Interstitial Lung Disease in the Eustar Database

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Background/Purpose: Systemic sclerosis (SSc) carries a high risk for interstitial lung disease (ILD). Patients with SSc-ILD are prone to develop progressive lung fibrosis, but there are no validated algorithms for early detection of these patients. We assessed the frequency of progressive fibrosis in patients with SSc-ILD in the EUSTAR database and parameters associated with progression of fibrosis over a 12-month follow-up.

Methods: Patients registered in the EUSTAR database since 2010 who were ≥18 years old; fulfilled SSc classification criteria; had recordings for disease duration, baseline and 12+/- 3 months follow-up for lung function, and radiographic assessments for ILD (on HRCT or x-ray) were eligible for this longitudinal study. Significant progressive fibrosis was defined as FVC decline >10% or FVC decline 5-10% and DLCO decline ≥15% from baseline to a follow-up visit at 12+/- 3

Figure: Characteristics associated with significant progressive fibrosis in SSc-ILD patients in (A) uni- and (B) multivariable logistic regression

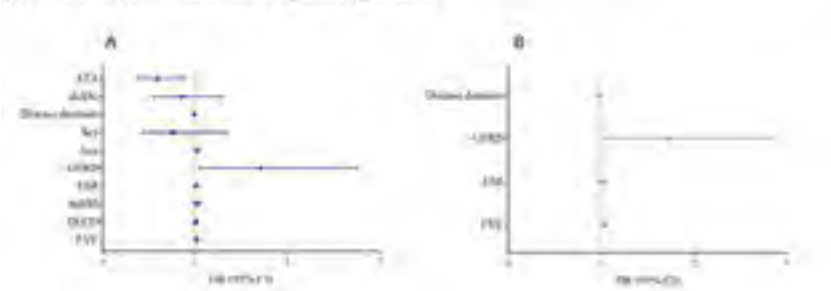


Table: Demographic and clinical characteristics of SSc-ILD patients in subgroups by FVC change

	Significant progressive fibrosis (n=111, 13%)	Moderate progressive fibrosis (n=116, 13.6%)	Stable lung fibrosis (n=415, 48.7%)	Moderate improvement in lung fibrosis (n=200, 23.5%)
Age, yrs (SD)	59 (13.4)	55 (12.1)	55 (13.5)	58 (12.1)
Male, n (%)	18 (15.9)	17 (16.0)	81 (19.9)	34 (18.0)
Disease duration, yrs	9.2 (7.6)	9.6 (8.4)	10.2 (8.3)	9.0 (8.6)
Disease duration > 3 yrs, n (%)	27 (23.9)	27 (25.5)	70 (17.2)	50 (26.5)
Diffuse cutaneous SSc, n (%)	51 (45.1)	45 (42.5)	186 (45.6)	78 (41.3)
Limited cutaneous SSc, n (%)	58 (51.3)	43 (40.6)	180 (44.1)	81 (42.9)
Anti-topoisomerase I Ab, n (%)	48 (42.5)	35 (31.9)	221 (56.9)	93 (49.2)
Anti-centromere Ab, n (%)	19 (16.8)	20 (18.9)	60 (14.7)	40 (21.2)
FVC % predicted	95.7 (23.1)	89.2 (21.4)	85.2 (20.6)	85.1 (19.5)
DLCO % predicted	62.4 (17.8)	58.2 (16.5)	58.4 (19.5)	59.0 (16.8)
ΔFVC % predicted	-17.1 (8.0)	-7.0 (3.4)	0.3 (2.5)	11.0 (7.3)
ΔDLCO % predicted	-6.7 (16.6)	1.0 (10.0)	-0.4 (11.3)	2.4 (1.7)
mRSS	10.9 (8.0)	9.2 (8.3)	9.6 (7.6)	9.9 (8.9)
ΔmRSS	0.5 (4.2)	-0.4 (3.2)	-0.4 (4.6)	-1.2 (5.3)
ESR	29.3 (23.8)	23.1 (21.9)	26.0 (19.0)	23.9 (20.8)
GERD, n (%)	87 (77)	68 (64.2)	268 (65.87)	118 (62.4)
Immunosuppressant, n (%)	8 (7.1)	9 (8.3)	50 (12.3)	21 (11.1)

Values are mean (standard deviation) unless otherwise stated. yrs, years; Ab, Antibody; FVC, (forced vital capacity; mRSS, modified Rodan SSa score; ESR, erythrocyte sedimentation rate; GERD, gastro-esophageal reflux disease; Δ, difference between first assessment and 12-month follow up. Lung function assessments were assessed in diffuse cutaneous SSc patients.

months. Moderate progressive fibrosis was defined as FVC 5-10% decline without DLCO decline $\geq 15\%$ over this time period. Significant improvement in fibrosis was defined as improvement of FVC $> 10\%$, or improvement of FVC 5-10% and DLCO improvement $\geq 15\%$ from baseline to a follow-up visit at 12 \pm 3 months. Moderate improvement in fibrosis was defined as improvement in FVC ≥ 5 -10% without DLCO improvement $\geq 15\%$ over this time period. Stable lung fibrosis was defined as $< 5\%$ change in either direction. Lung function declines were assessed as absolute changes in % predicted. Candidate predictors of significant progressive fibrosis were selected by expert opinion and logistic regression was applied.

Results: A total of 826 SSc patients met the eligibility criteria including measurements for lung function after 12 \pm 3 months follow-up. Of these, 106(12.8%) showed significant progressive lung fibrosis, 113 (13.7%) moderate progressive lung fibrosis, 408 (49.4%) stable lung fibrosis, 189 (22.9%) moderate improvement in fibrosis and 10 (1.2%) significant improvement in fibrosis. Demographic and clinical characteristics by subgroup are shown in the Table. Baseline FVC, erythrocyte sedimentation rate (ESR), gastroesophageal reflux disease (GERD) and disease duration were significantly associated with the development of significant progressive fibrosis over 12 \pm 3 months in uni- and multivariable modeling (AUC 0.67) (Figure). Age, sex, antibody profile and SSc subtype were not associated with significant progressive fibrosis in SSc-ILD.

Conclusion: This study provides novel insights regarding progressive fibrosis in patients with SSc-ILD in the large EUSTAR database.

Disclosure: A. M. Hoffmann-Vold, Boehringer Ingelheim, 2, Oslo University Hospital, Dept of Rheumatology, 3, Actelion, Boehringer Ingelheim, 5; Y. Allanore, None; M. Alves, Boehringer Ingelheim, 3; N. Graf, Astellas and Biotronik AG, 5; P. Airò, None; L. Ananyeva, Roche and Boehringer Ingelheim, 5; L. Cziráj, None; S. Guiducci, None; E. Hachulla, Actelion, GSK, Pfizer, Bayer, 2, Actelion, GSK, Pfizer, Bayer, 5; M. Li, None; C. Mihai, Actelion, Geneva, Roche, and Rofarm, 5; P. Sfikakis, None; G. Valentini, AbbVie, BMS, Lilly, Pfizer, Sanofi, 2, 5; O. Kowal-Bielecka, Bayer and Roche, 5; O. Distler, Actelion, Bayer, Boehringer Ingelheim, Mitsubishi Tanabe Pharma, and Roche, 2, Actelion, AnaMar, Bayer, Boehringer Ingelheim, ChemomAb, espeRare foundation, Genentech/Roche, GSK, Inventiva, Italfarmaco, Lilly, medac, MedImmune, Mitsubishi Tanabe Pharma, Novartis, Pfizer, Sanofi, Sinoxa, and UCB, 5, Patent, 9.

Abstract Number: 800

Assessment of Recent Evidence to Support Treatment Recommendations in Patients with SSc-ILD

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Systemic Sclerosis (SSc) is a chronic autoimmune disease characterized by fibrosis of skin and internal organs with an estimated worldwide prevalence of 110-430 cases/million. SSc involves the lung, with Interstitial Lung Disease (ILD) being the leading cause of death. The objective of this systematic literature review (SLR) was to review the available scientific evidence to guide decisions on screening; treatment initiation, change or escalation; disease progression and influence on subsequent treatment decisions in SSc-ILD.

Methods: The SLR was conducted according to NICE, CRD and IQWiG guidance for undertaking reviews in healthcare, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology. To update on most recent developments, the search strategy covered literature published from 2016-2018. Population, Intervention, Comparator and Outcomes criteria (PICO) were used to select publications at title/abstract and full-text screening. Data was extracted in six categories: screening/risk stratification; current treatments; treatment initiation/escalation; disease progression; treatment algorithms and biomarkers for ILD in SSc. The quality of evidence extracted was assessed using GRADE 2007 criteria.

Results: After title and abstract screening of the initial 887 citations found, 260 publications were full-text screened and 163 included in the analysis.

Although evidence was most prolific in the screening/risk stratification category for SSc-ILD, the information extracted in the biomarkers category showed a higher grade of evidence (average medium/high vs medium/low). Although HRCT and

DLCO still remain as main screening tools, some biomarkers are already in use for diagnosis and prognosis of SSc-ILD. These include genetic- (ALOX5AP gene polymorphisms), cellular- (neutrophil/lymphocyte ratio), and plasma biomarkers (antibodies such as ATA, ACA, anti-CXT, or chemokines such as CCL18, KL6, CCL-2 or IL-10). Evidence on lung disease progression was also graded medium/low, and the lowest volume and weakest evidence was observed in the current treatment; treatment algorithms; and treatment initiation/escalation categories. Immunosuppressive drugs (mycophenolate mofetil, cyclophosphamide, azathioprine and rituximab) were used as the recommended therapeutic approach.

Conclusion: This SLR found that the identification, validation and application of biomarkers as the main field of interest in SSc-ILD research, reflecting progress for early diagnosis and subsequent prognosis of this disease. In contrast, there was a dearth of robust evidence and no clear consensus on therapeutic interventions, highlighting the need for further evidence to support treatment options.

Disclosure: A. M. Hoffmann-Vold, None; T. Maher, GSK, 2, 5, UCB, Inc., 2, 5, 6, Boehringer Ingelheim, Astra Zeneca, Roche, Bayer, Biogen Idec, Cipla, Prometic, Sanumed, 5, Apellis, 1; E. Philpot, IQVIA, 3; A. Ashrafzadeh, IQVIA, 3; D. Jha, IQVIA, 3; M. Alves, Boehringer Ingelheim, 3; O. Distler, Actelion, Bayer, Boehringer Ingelheim, Mitsubishi Tanabe Pharma, Roche, 2, Actelion, AnaMar, Bayer, Boehringer Ingelheim, ChemolmAb, espeRare foundation, Genentech/Roche, GSK, Inventiva, Italfarmaco, Lilly, medac, MedImmune, Mitsubishi Tanabe Pharma, Novartis, Pfizer, Sanofi, Sinoxa, UCB, 5, Patent mir-29 for the treatment of systemic sclerosis licensed, 9.

Abstract Number: 801

Cardiac Autonomic Modulation at Rest and during Orthostatic Stress in Systemic Sclerosis Patients

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SESSION INFORMATION

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Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Autonomic dysfunction is a marker of myocardial involvement in systemic sclerosis (SSc) and heart rate variability (HRV) is impaired in SSc patients (1). The aim of the present study was to investigate autonomic HRV both at rest and during active standing in very early (EaSSc), limited (lcSSc) and diffuse cutaneous (dcSSc) patients.

Methods: Sixty-nine SSc patients (18M/51F, mean age 58 ± 12 yrs) and 36 age-matched healthy controls (HC) (13M/23F, age 57 ± 12 yrs) underwent recording of ECG and respiration in supine and orthostatic position. Spectral analysis of HRV identified different oscillatory components: total power (TP), index of global autonomic variability, low frequency (LF), marker of sympathetic modulation, and high frequency (HF), marker of vagal modulation. LF/HF was calculated as index of sympatho-vagal balance. Unpaired t-test and ANOVA were used to compare HRV parameters between the groups.

Results: Our case series included 12 EaSSc, 39 lcSSc and 18 dcSSc, aged 54 ± 8 , 59 ± 12 and 58 ± 12 yrs with a prevalence of anti-Topo-I/anticentromere antibodies equal to and 8/67%, 28/54% and 44/11%, respectively. SSc patients had a predominant sympathetic modulation and lower vagal control compared to HC at rest (low HF and high LF and LF/HF, Table 1). In SSc subgroups analysis in which parameters of HRV both at rest and in response to orthostatic stress (Δ ORT%), were significantly different in diffuse cutaneous (dcSSc) and limited cutaneous (lcSSc) patients compared to HC (Table 2).

Conclusion: SSc patients have a decreased vagal and an increased sympathetic modulation at rest as well as a blunted autonomic response to orthostatic challenge. These alterations were present in definite forms of SSc but not in EaSSc, suggesting that autonomic dysfunction follows the development of fibrosis. Further studies are needed to better establish the relationship between myocardial fibrosis and autonomic dysfunction.

Table 1. Comparison of HRV indexes at rest between SSc and age-matched healthy control group.

	SSc	HC	p-value
Spectral analysis			
Total power (ms ²)	933±1107*	1769±1973	<0.01
LFn (n.u)	57±22. *	38±22	<0.001
HFn (n.u)	34±19*	57 ±21	<0.001
LF/HF	3.27 ±4.23*	1.12 ±1.60	<0.001

HFun: high frequency normalized unity; LFun: low frequency normalized unity

Table 2. HRV indexes at rest and HRV adjustments from orthostatic stress between SSc sub-types and age-matched HC

	DcSSc	LcSSc	EaSSc	HC	p-value
Spectral analysis					
Total power (ms²)					
SUP	439±248	1553 ±2858	1430±1173*	1769 ±1973*	0.04
ΔORT%	0.08 ±0.68	0.38 ±1.35	0.31 ±1.23	0.82 ±3.40	0.97
LFn (n.u)					
SUP	61±20	58 ±22	54 ±25	38 ±22*#	<0.01
ΔORT%	0.18 ±0.98	-0.07 ±0.48	0.45 ±0.92	1.42 ±2.09*#	<0.001
HFn (n.u)					
SUP	34 ±18	32 ±16	42 ±25	57 ±21*#	<0.001
ΔORT%	-0.05 ±0.63	0.01 ±0.69	0.35 ±1.84	-0.40 ±0.51	0.09
LF/HF					
SUP	3.01 ±3.02	3.20 ±3.40	3.74 ±5.81	1.12 ±1.60*#	<0.001
ΔORT%	0.93 ±2.71	1.22 ±3.85	4.54 ±8.85	9.08 ±13.92*#	<0.01

SUP: supine position; ORT: Orthostatic position HFun: high frequency normalized unity; LFun: low frequency normalized unity; ΔORT%: (HRV in SUP position – HRV in ORT position) / HRV in SUP position); ANOVA one-way for independent measures and Tukey post-hoc test;

*differences from DcSSc, #differences from LcSSc, \$differences from EaSSc. α<0.05.

1. Cozzolino D et al. Rheumatology (Oxford) 2002; 41: 586–8.

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Abstract Number: 802

Prognostic Significance of Bicaudal D2 Antibodies in Sistemic Sclerosis (SSc) Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

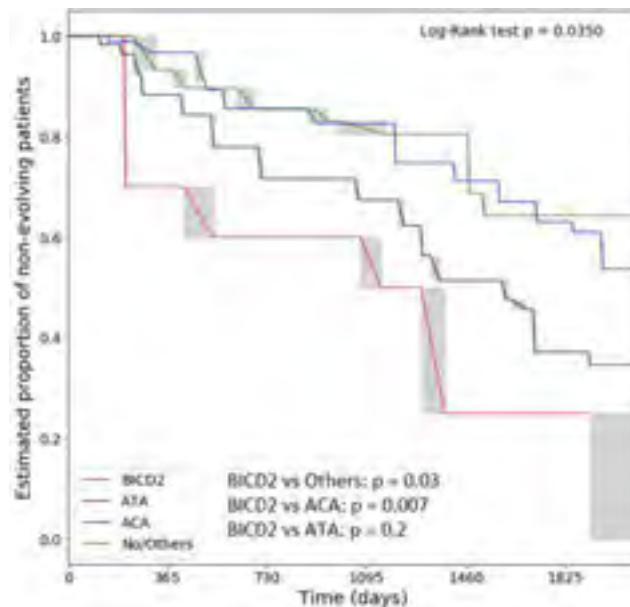
Session Type: ACR Poster Session A

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

Background/Purpose: Antibodies (Ab) toward Bicaudal D homolog 2 (BICD2) can be found in 25% of Systemic Sclerosis (SSc) sera, mostly in association with anti-centromere (ACA) or anti-topoisomerase I (ATA)abs, but also in isolation. Anti-BICD2 single specificity has been associated with myositis and interstitial lung disease (ILD), however its prognostic significance is unclear. A retrospective-prospective study was conducted to evaluate disease evolution in anti-BICD2+ patients.

Methods: Serum samples from 288 SSc (ACR/EULAR 2013 criteria) collected between 2012 and 2014 were stored at -80° C and sent for Ab determination to Inova Diagnostics (San Diego, CA). Samples were tested using a novel particle-based multi-analyte technology (PMAT) and with CTD Essential (which includes DFS70, dsDNA, RNP, Sm, Ro60, Ro52, SS-B, Jo-1, Scl-70, Centromere, Ribo-P) and CTD Comprehensive (RNA Pol III, Th/To, Ku, BICD2, PM/Scl; both test research use only).

Clinical data regarding major organ complications were retrospectively collected; time of evolution from baseline to new clinical manifestations was recorded. For dcSSc subjects evolutions included death, new digital ulcers, worsening of lung function(forced vital capacity, FVC loss > 10% or diffusing capacity for carbonmonoxide, DLCO loss > 15%), progression



of ILD on high resolution computed tomography, HRCT, development of pulmonary hypertension (PAH); evolution for lcSSc included progression of skin thickening as well as dcSSc categories; evolution for definite SSc without skin fibrosis included the appraisal of skin fibrosis and the above categories. Survival analysis for interval-censored data with 1.000-fold permutations was used.

Results: Our cohort included: 30 (10.4%) definite non-cutaneous SSc, 216 (75%) lcSSc and 42 (14.5%)dcSSc, mostly females (95.5%), aged 60 ± 12.7 years and with disease duration of 14 ± 13 years. Anti-BICD2 Ab were found in 49 subjects (17%), in 10 (3.5%) as a single-specificity, in 8 (2.8%) in associations with ATA, in 31 with ACA (10.8%). Patients were followed for a median of 4.0 (interquartile: 2 – 5.1) yrs until the first sign of evolution. Single anti-BICD2 Ab positivity was associated with myositis (3/10 vs. 11/278, $p=0.0089$) and weakly with dcSSc (4/10 vs. 38/278, $p=0.045$). Ab specificity was associated with different pattern of progression (Figure): Anti-BICD2+ patients had shorter evolution times compared to anti-BICD2- patients ($p=0.03$), ACA+ subjects ($p=0.007$) but were similar to ATA+ subjects ($p=0.2$). Crude mortality trended to be higher in anti-BICD2+ than anti-BICD2- patients (3/10 vs. 27/278, $p=0.074$).

Conclusion: We confirm the association between anti-BICD2 Ab and myositis in SSc and its overall prevalence. Anti-BICD2+ patients have a worse prognosis and higher rates of disease progression compared to ACA+ subjects and behave similarly to ATA+ subjects.

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Abstract Number: 803

Treating Interstitial Lung Disease and Skin Involvement in Systemic Sclerosis with Oral Versus Intravenous Cyclophosphamide: Preliminary Efficacy and Safety Data from 2 Randomized Clinical Trials and 1 Registry

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Background/Purpose: Two randomized controlled trials showed modest but significant effects for oral (po) CYC (superior to placebo and equal to mycophenolate mofetil). A number of European centres seem to prefer intravenous (IV) CYC based on a presumed better safety profile. However, no direct comparisons of these two administration methods have been published. In this context, our goal was to compare the relative efficacy and safety of **po versus IV CYC(IV) for treating ILD and/or skin involvement in SSc.**

Methods: Patients were derived from the EUSTAR database and Scleroderma Lung Studies I and II, receiving ≥ 6 months of **po** or IVCYC ,all with 12 months follow-up. **Serious (SAEs) and non-serious adverse events (AEs) and efficacy (change in ppFVC, ppDLCO, mRSS) were analyzed at end of treatment (EoT) and at follow-up (FU).** Analysis included descriptive statistics and linear regressions

Results: Between the 149 po versus 153 IV CYC patients there were baseline statistical differences in ethnicity, previous DMARD exposure, previous and concomitant steroid exposure and dosage, current/previous smoking, digital ulcers and arterial hypertension (Table 1).

Efficacy: after adjusting for significant baseline **ppFVC, ppDLCO** and mRSS, at EOT vs baseline and at FU vs EOT, changes in **ppFVC, ppDLCO** and mRSS were similar for both groups (p=NS, Table 2). In a multivariate analysis, route of administration had no impact on efficacy.

Safety: there was more leukopenia (22.1% vs 1.3%, $p<0.001$), haemorrhagic cystitis (5.5% vs 0%, $p=0.011$) and alopecia (19.5% vs 1.3%, $p<0.001$) at EOT visit after po than IV CYC. In contrast, there were more SAEs and need for oxygen supplementation at FU in the IV vs po group (19.3% vs 9.4%, $p=0.025$, and 7.2% vs 2%, $p=0.049$). The median cumulative CYC dosage was significantly higher in the po group [39.4 mg vs 9.2 mg, $p<0.001$). No significant differences were found for deaths, anemia, **thrombocytopaenia, gastro-intestinal bleeding, serious infections, malignancies, need for total parenteral nutrition, new onset of cardiomyopathy or amenorrhea.**

Table 1 - Differences between po and iv group at baseline

	Oral CYC (149 pts)	Intravenous CYC (153 pts)	p
Male gender, n(%)	26 (17.4)	29 (19.0)	>0.999
Caucasian race, n(%)	104 (69.8)	146 (95.4)	<0.001
Afro-american race, n(%)	23 (15.4)	0 (0)	<0.001
Diffuse skin subset, n(%)	89 (59.7)	80 (52.3)	0.487
mRSS at baseline, median (IQR)	13 (7-20)	12 (6-20)	0.487
ATA positive, n (%)	60 (40.3)	86 (56.2)	0.177
ACA positive, n (%)	4 (2.7)	9 (5.9)	0.396
ARA positive, n (%)	14 (9.4)	9 (5.9)	0.51
Previous steroid exposure, n(%)	43 (28.8)	70 (45.7)	0.001
Previous DMARD exposure, n(%)	35 (23.5)	62 (40.5)	0.001
Steroid treatment at baseline, n(%)	51 (34.2)	113 (73.9)	<0.001
Steroid dosage at baseline (mg), median (IQR)	0 (0-5)	5 (0-10)	<0.001
CYC treatment duration (days), median (IQR)	365 (165-366)	343 (194-314)	0.815
CYC daily dose (mg), median (IQR)	106.6 (91.1-132.3)	35.3 (29.3-40)	0.001
CYC cumulative dosage (g), median (IQR)	39.4 (32.7-47.1)	9.2 (5.6-13.6)	<0.001
Steroid treatment at EoT, n(%)	55 (37.2)	113 (73.9)	<0.001
Steroid dosage at EoT (mg), median (IQR)	0 (0-5)	5 (2.25-10)	<0.001
DMARD treatment started at EoT, n(%)	52 (34.9)	45 (29.4)	<0.001
Smoking history, n(%)	21 (14.1)	19 (12.4)	0.815
Arthritis, n (%)	29 (19.4)	31 (20.3)	0.209
RAH, n(%)	0 (0)	5 (3.3)	0.159
Muscle involvement, n (%)	14 (9.4)	22 (14.4)	0.216
Cardiomyopathy, n (%)	8 (5.4)	15 (9.8)	0.194
GERD, n (%)	114 (76.5)	132 (87.7)	0.578
Intestinal malabsorption, n (%)	9 (6.0)	13 (8.5)	0.508
Bacterial overgrowth, n (%)	12 (8.1)	12 (7.8)	>0.999
ILD prevalence, n(%)	125 (87.4)	143 (95.5)	0.111
SpFVC at baseline, median (IQR)	89 (60-75)	83 (68-96)	<0.001
DLCO at baseline, median (IQR)	51 (40-63)	56 (40-71)	0.622
History/presence of digital ulcers, n(%)	40 (26.8)	64 (42.5)	0.008
History/presence of arterial hypertension, n(%)	40 (26.8)	25 (16.3)	0.005

Subsidiary visit, CYC=cyclophosphamide, DMARD=disease modifying antirheumatic drug, both end of treatment visit, IV=intravenous, Diffuse lung diffusion of carbon cycle, ILD=interstitial lung disease, RAH=right ventricular arterial hypertension, mRSS=modified Rodan skin score, ATA=anti-topoisomerase I antibodies, ACA=anti-centromere antibodies, ARA=anti-RNA polymerase III antibodies, IQR=interquartile range

	END of E			T0 vs END		
	Oral CYC (349 [44])	Intravenous CYC (355 [44])	P	Oral CYC (349 [44])	Intravenous CYC (355 [44])	P
Change in mRSS	-3.0 ± 5.3	-1.9 ± 5.9	0.528	-1.4 ± 6.4	-0.8 ± 5.6	0.795
Change in %FVC	-0.1 ± 6.5	-0.8 ± 11.3	0.629	-0.5 ± 11.6	-1.1 ± 10.3	0.655
Change in %DLCO	-1.3 ± 11.5	-0.3 ± 11.0	0.798	-0.8 ± 11.0	-1.9 ± 11.3	0.588
Serious adverse events, n (%)	21 (14.5)	21 (14)	>0.999	13 (9.4)	29 (15.3)	0.076
Death, n (%)	0 (0)	0 (0)	N.A.	0 (1.5)	7 (4.7)	0.683
Discontinuation <30000, n (%)	1 (1.4)	0 (0)	0.085	1 (0.7)	0 (0)	0.966
Discontinuation <100, n (%)	2 (1.4)	1 (0.7)	0.972	1 (0.7)	1 (0.7)	>0.999
Leukocytes <2500, n (%)	32 (22.1)	2 (1.3)	<0.001	0 (0)	2 (1.1)	0.525
Concomitant Glucocorticoids, n (%)	4 (2.8)	2 (1.3)	0.643	2 (1.3)	1 (0.7)	0.916
Glucocorticoids >10mg, n (%)	4 (2.8)	0 (0)	0.013	1 (0.7)	0 (0)	0.989
Serious infections, n (%)	1 (1.4)	7 (4.5)	0.094	3 (2)	9 (5.5)	0.154
Cancer risk diagnosis, n (%)	2 (1.4)	2 (1.3)	>0.999	6 (4.4)	4 (2.7)	0.647
Organic supplementation number, n (%)	4 (2.7)	12 (8)	0.079	3 (2)	11 (7.3)	0.049
Total parenteral nutrition, n (%)	2 (1.4)	0 (0)	0.403	3 (2)	1 (0.7)	0.566
Cardiomyopathy new diagnosis, n (%)	3 (1.4)	13 (9.3)	0.154	3 (2)	1 (0.7)	0.084
Arterial hypertension, n (%)	6 (4)	6 (3.9)	<0.999	0 (0)	0 (0)	N.A.
Allopurinol, n (%)	28 (15.5)	2 (1.3)	<0.001	1 (0.7)	0 (0)	0.888

CYC=cyclophosphamide, DMARD= disease modifying ant rheumatic drug, FVC=forced vital capacity, DLCO=lung diffusion of carbon monoxide, mRSS= modified Rodan skin score, IQR=inter-quartile range

Conclusion: This hypothesis generating study is limited by the different source data, patients' selection (i.e. presence of active ILD and absence of PAH for SLSI and SLS 2), post-treatment medications (higher dosage corticosteroids, more csDMARD and O2 in IV-CYC) and short follow-up duration. It showed similar efficacy of one year of oral versus IV CYC. AEs were more frequent with po CYC but more SAEs were noted for IV-CYC. Well-controlled studies are warranted to confirm and extend our data.

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Abstract Number: 804

Prevalence of Echocardiographic Abnormalities in Patients with Systemic Sclerosis

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SESSION INFORMATION

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Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: To determine the prevalence of echocardiographic abnormalities and to identify associated clinical and laboratory features in a large systemic sclerosis (SSc) cohort.

Methods: The sample comprised 117 patients with SSc (ACR/EULAR 2013 criteria) treated at a tertiary university hospital that does not attend pediatric populations. In the routine clinical management of these patients, a transthoracic Doppler echocardiogram (TTE) is performed every 1 or 2 years. In each study, we investigated the presence of myocardial systolic dysfunction, diastolic myocardial dysfunction, valve disease, and pulmonary arterial hypertension (PAH) defined as a systolic pulmonary artery pressure (PAP) ≥ 40 mmHg and tricuspid regurgitation velocity (TRV) greater than 2.5 m/s.

Results: The sample included 104 women (89%) and 13 (11%) were men, with a mean age of 59 ± 15 years (mean ± standard deviation; range 19–86) and a median disease duration of 6.5 years (interquartile range [IQR], 25th-75th: 3–14 yrs). Twenty one patients (18%) had diffuse cutaneous scleroderma, eighty-nine (76%) had limited cutaneous involvement, 1 (0.8%) had a systemic sclerosis sine scleroderma, and six (5%) had prescleroderma.

The main TTE findings observed were:

- Left ventricular (LV) systolic dysfunction was present in 5.1% (6/117) of subjects, whereas LV diastolic dysfunction was present in 11.1% (13/117). Factors independently associated with LV diastolic dysfunction on multivariable analysis included arterial hypertension, disease duration, advanced age, and the limited cutaneous SSc subtype.

- Subclinical valve disease: 10.2% (12/117) of patients had valve dysfunction involving the mitral and/or the aortic valves. Valve dysfunction was mild or moderate in all cases, except in 3 patients (2.56%) who presented severe aortic stenosis. The age of these three patients were 52, 59 and 78 yrs. Antiphospholipid (APL) antibodies were positive in only 1 of these patients.
- TTE criteria for PAH: 11.1% (13/117). Right heart catheterization (RHC) confirmed the diagnosis of PAH in all cases except one (false positive). The median disease duration at PAH diagnosis was 6 years (IQR: 1.5 -14.5 yrs). Factors independently associated with PAH on multivariable analysis included the limited cutaneous SSc subtype and more severe peripheral vascular disease (Raynaud's phenomenon and digital ulcers).

Conclusion: In addition to the presence of PAH, it is also relatively common the presence of LV diastolic dysfunction (11.1%) and subclinical valve disease (10.2%).

The high frequency of severe aortic stenosis observed in our cohort (its prevalence in the general population is 0.3-0.5%) deserves a case-control study to investigate whether this complication is related or not to the activity of the disease.

Disclosure: J. Lluch, None; F. J. Narváez, None; P. Juárez, None; J. M. Nolla, None.

Abstract Number: 805

Diastolic Dysfunction in Scleroderma: An Investigation into Associated Risk Factors and Impact on Survival

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Scleroderma heart disease often goes unrecognized until severe clinical manifestations are present. Diastolic dysfunction (DD) may identify patients at risk for cardiac complications by identifying patients with myocardial fibrosis. The aims of this study were to 1) determine the prevalence of non-valvular DD in scleroderma, 2) assess risk factors for DD in scleroderma, and 3) evaluate the impact of DD on survival.

Methods: A total of 754 subjects with scleroderma seen between November 1st, 2007 through October 31st, 2017 were included in this retrospective cohort study. Echocardiograms were excluded if there was moderate to severe mitral or aortic valve disease, a primary cardiomyopathy, a recent myocardial infarction, or if subjects were admitted to an intensive care unit. The most recent analyzable echocardiogram for each subject was included. DD was defined according to the 2016 American Society of Echocardiography (ASE)/European Society of Cardiovascular Imaging (EACVI) guidelines. Univariable logistic regression assessed risk factors for DD, and a multivariable regression model was constructed of covariates with a p-value of ≤ 0.1 . Inclusion of all traditional DD risk factors in the multivariable model was planned a

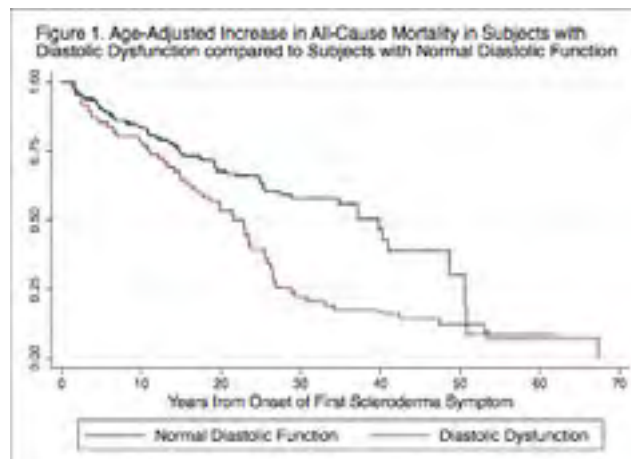


Table 1. Association of Cardiovascular Risk Factors and Scleroderma Characteristics with Diastolic Dysfunction by Logistic Regression

Cohort Characteristics & Autoantibodies	Univariable			Multivariable		
	OR	95% CI	P-value	OR	95% CI	P-value
Age	1.11	1.09 – 1.13	<0.001	1.12	1.08 – 1.17	<0.001
Female sex	1.2	0.7 – 2.0	0.56	1.3	0.5 – 3.9	0.59
White race vs. non-white race	1.1	0.7 – 1.6	0.74			
Hypertension	2.6	1.7 – 4.1	<0.001	2.1	0.9 – 4.5	0.07
Coronary Artery Disease	6.3	2.8 – 14.1	<0.001	5.3	1.0 – 27.2	0.046
Renal Disease (Cr ≥ 1.3 ever)	2.4	1.5 – 3.9	<0.001	2.0	0.8 – 4.9	0.14
Ever Smoker	1.6	1.1 – 2.3	0.02	0.9	0.4 – 2.0	0.89
COPD	2.6	1.4 – 4.7	0.002	1.3	0.5 – 3.5	0.62
Obesity (BMI ≥ 30 kg/m ²)	1.9	1.2 – 2.9	0.003	6.7	2.6 – 17.2	<0.001
Diabetes	1.7	0.8 – 3.7	0.140	0.3	0.0 – 1.9	0.34
Disease duration from onset first symptom (RP or non-RP)	1.04	1.02 – 1.05	<0.001	1.00	0.96 – 1.03	0.81
Limited cutaneous	1.6	1.1 – 2.5	0.02	1.2	0.5 – 2.8	0.73
RP with digital ischemia	0.9	0.6 – 1.3	0.70			
Severe GI disease	1.0	0.7 – 1.4	0.92			
Weakness (MMT*≤4)	1.2	0.7 – 1.8	0.50			
Myositis	0.8	0.5 – 1.3	0.32			
Tendon Friction Rubs	0.8	0.5 – 1.4	0.46			
Synovitis	1.3	0.9 – 2.0	0.21			
Telangiectasias	1.5	0.7 – 3.3	0.31			
Calcinosis	1.2	0.9 – 1.8	0.26			
Sicca symptoms	1.3	0.9 – 2.0	0.18			
PVC <70 ever	1.3	0.9 – 1.9	0.20			
Anti-Topoisomerase I	0.6	0.4 – 1.1	0.10	0.6	0.2 – 1.9	0.42
Anti-Centromere	0.9	0.6 – 1.5	0.80			
Anti-RNA Polymerase III	0.8	0.4 – 1.4	0.41			
Anti-Ro52	2.2	1.3 – 3.5	0.002	2.7	1.2 – 6.2	0.02
Anti-Kae	1.1	0.2 – 5.2	0.94			
Anti-P(hSc)	0.5	0.2 – 1.5	0.22			
Anti-Th/To	0.7	0.1 – 3.1	0.61			
Anti-Nor90	1.8	0.3 – 10.4	0.47			
Anti-Fibrillarin	0.9	0.2 – 3.0	0.81			

*MMT= manual muscle testing

priori. A Kaplan-Meier curve evaluated for differences in survival among those with and without DD, and a log-rank test for equality of survivor functions evaluated for significance.

Results: The prevalence of DD was 18.8%. Mean age at time of echocardiogram was 67.4 years(STD 9.7). Traditional DD risk factors including age, hypertension, coronary artery disease (CAD), renal disease, ever smoker, COPD, and obesity ($\geq 30\text{kg/m}^2$) were significantly associated with DD on univariable analyses (Table 1). Disease duration, limited cutaneous disease, and presence of anti-Ro52 autoantibody were significantly associated with DD on univariable analysis (Table 1). Only age, CAD, obesity, and a positive anti-Ro52 autoantibody were associated with DD on multivariable model (Table 1). An increase in age-adjusted all-cause mortality was seen in subjects with DD compared to those with normal diastolic function ($p<0.0001$)(Figure 1).

Conclusion: Patients not only with traditional cardiac risk factors but also with a positive anti-Ro52 autoantibody are at higher risk for DD. Given the poor survival associated with DD in this population, aggressive control of modifiable risk factors as well as further investigation into treatments is warranted.

Disclosure: A. M. Hinze, NIH T32 Research Award, 2; L. K. Hummers, None; F. M. Wigley, Scleroderma Research Foundation and Martha McCrory Professorship, 2; M. Mukherjee, Scleroderma Foundation, 2; A. A. Shah, None.

Estradiol Levels Are Elevated in Older Men with Diffuse Cutaneous SSc and Are Associated with Decreased Survival

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune disease characterized by excessive extracellular matrix deposition (ECM), leading to dermal and internal organ fibrosis. As in other autoimmune diseases, SSc is more prevalent in women. However, men have more severe disease. Considering the sex-based disparity in disease severity, estradiol (E2), an estrogen form with pro-fibrotic effects in different organs, may play a role in SSc pathogenesis. We previously reported that post-menopausal women with diffuse cutaneous (dc)SSc have higher serum E2 levels compared to healthy controls of similar age. Our objective was to examine serum E2 levels in dcSSc males in relation to disease characteristics (i.e. autoantibody profile and internal organ involvement) and its impact on survival.

Methods: We measured serum E2 levels in 83 dcSSc men >50 years old from the University of Pittsburgh Scleroderma Center and healthy controls of similar age. Using statistical modeling, we examined the associations between circulating E2 levels, internal organ involvement, autoantibody profiles, and survival.

Results: Male dcSSc patients had significantly higher serum E2 levels compared to healthy male controls. Male dcSSc patients also had higher serum E2 levels compared to dcSSc post-menopausal women of similar age. Male dcSSc patients with high serum E2 levels had significantly more heart involvement and worse survival. Using Cox regression modeling for risk of death, increasing serum E2 levels in anti-Scl-70 antibody positive dcSSc males were associated with an increased risk of death.

Conclusion: DcSSc male patients have higher levels of E2 compared to healthy controls and dcSSc post-menopausal women. Elevated serum E2 levels in dcSSc males >50 are associated with heart involvement and, if anti-Scl-70 antibody positive, worse survival. Our current study expands on our previous work, implicating E2 in the pathogenesis of SSc-associated fibrosis and extends our findings to an association between E2 levels, internal organ involvement, and overall survival. These data suggest an important role for estrogen imbalance in SSc.

Disclosure: D. Baker Frost, None; B. J. Wolf, None; C. Peoples, None; K. Silver, None; M. Laffoon, None; T. A. Medsger Jr., None; C. A. Feghali-Bostwick, GSK, Biogen, BMS, iBio Inc, 2, 7.

The Effects of DNA Methylation on Differential Expression in Dermal Fibroblasts from African-American Patients with Systemic Sclerosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: The etiology and reasons underlying the ethnic disparities in systemic sclerosis (SSc) remain unknown. African-Americans (AA) are disproportionally affected by SSc, yet dramatically underrepresented in research. The role of DNA methylation in disease risk remains unclear. Previously, we conducted DNA methylation analysis in AA SSc patients and found 17 genes and 11 promoters showed significant differential methylation levels between cases and controls. In this study, we seek to determine expression differences in some of the candidate protein-coding and RNA genes previously identified.

Methods: RNA was isolated from cultured primary dermal fibroblasts isolated from 12 AA SSc cases and 14 AA controls. All patients met the 2013 ACR/EULAR classification criteria for SSc, most (93%) presenting with diffuse cutaneous SSc. Transcript levels of steady state RNA of 5 protein coding genes, 2 non-coding and 1 long-coding (lnc) RNAs were analyzed using QRT-PCR. Values were normalized to the house-keeping gene, β 2-microglobulin, to determine magnitude of fold change. Statistical differences were noted between the groups using the Mann-Whitney test.

Results: QPCR analysis revealed 2 of the 5 protein coding genes and the lncRNA had significant differences in transcript levels between primary dermal fibroblasts from AA SSc patients and healthy controls. Both protein coding genes *DLX5* and *TMEM140* were significantly increased, while the lncRNA *MGC12916* was significantly decreased in primary dermal fibroblasts from AA SSc patients compared to healthy controls.

Conclusion: Differential gene expression of *DLX5* and *TMEM140* has been reported in previous studies with SSc patients. Our current study shows that gene body hypermethylation in *DLX5* and promoter hypermethylation in *TMEM140* is correlated with its overexpression in AA SSc patients relative to healthy controls. However, gene body hypermethylation of lncRNA *MGC12916* is correlated with its under expression in AA SSc patients relative to healthy controls. While previous studies reported both differential methylation and gene expression in *DLX5* only, these results are the first to report both differential methylation and gene expression of *DLX5*, *TMEM140* and lncRNA *MGC12916* in AA SSc patients, prompting further research in determining their role regarding SSc susceptibility in this cohort.

Disclosure: D. Baker Frost, None; W. da Silveira, None; I. Atanelishvili, None; R. C. Wilson, None; E. S. Hazard, None; J. C. Oates, None; G. S. Bogatkevich, None; C. A. Feghali-Bostwick, GSK, Biogen, BMS, iBio Inc, 2, 7; G. Hardiman, None; P. S. Ramos, None.

Abstract Number: 808

Mean Number of Nailfold Capillaries Is Associated with Disease Activity at 6 Months Follow-up in Systemic Sclerosis Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Nailfold capillaroscopy (NFC) is essential in the evaluation and classification of systemic sclerosis (SSc). The mean number of capillaries is considered a promising tool for assessing vascular involvement in SSc, however there is no consensus yet over how many digits should be analyzed and how.

Objective: Investigation of the associations of the mean number of capillaries, measured by NFC, with disease activity (by the EScSG activity score) and vascular involvement (digital ulcers (DUs) or history of DUs) in a single-center cohort of SSc patients.

Methods: 68 SSc patients (mean (SD) age 52.9 (11.0) years, disease duration 9.2 (7.1) years and diffuse cutaneous involvement 22 (34.2%)) fulfilling the ACR/EULAR 2013 classification criteria, were included. NFC and extensive assessment per the recommendations of EUSTAR were performed in all patients. 54 patients had a follow-up at 6 months. 8 digits were examined (II to V of both hands) by NFC; 4 images for each finger were saved. The NFC images were assessed by 2 experienced raters independently, scoring the mean number of capillaries in all fingers (m_nr/pat), in the 3rd finger of the dominant hand (m_nr/3rd dom) and in the 4th finger of the non-dominant hand (m_nr/4th non-dom) for each patient. Moreover, 'early', 'active', 'late' Cutolo patterns were also recorded.

Results: 2176 images were scored at baseline and 1728 at FU. The m_nr/pat at baseline ranged between 3.4-9.1, mean(SD) 5.6(1.7) for rater 1, respectively 3.3-8.9, 5.2(1.4) for rater 2.

There was good to excellent correlation (Spearman's rho) at baseline and FU of the m_nr/pat with m_nr/3rd dom, m_nr/4th non-dom and Cutolo patterns, and fair correlation of m_nr/3rd dom with m_nr/4th non-dom and Cutolo patterns. We found significant differences of all mean scores of capillaries between patients with and without history of DUs (Mann Whitney U test) (table 1). Using linear regression adjusted for age, gender and history of DUs, mean number of capillaries was associated with disease activity at FU (table 2).

Table 1. Differences in mean number of capillaries in patients with and without history of DUs

	History of DUs min-max; mean (SD)	Without history of DUs min-max, mean (SD)	p*
m_nr/pat rater 1	3.4-8.6; 5.04 (1.4)	3.4-9.1; 6.4 (1.8)	0.016
m_nr/3 rd dom rater 1	2.5-9.8; 4.9 (1.79)	2.3-10.3; 6.2 (2.3)	0.033
m_nr/4 th non-dom rater 1	2.0-9.0; 4.8 (1.5)	2.5-11.5; 6.0 (2.1)	0.017

* Mann-Whitney U test

Table 2. Associations between mean number of capillaries at baseline and disease activity (ESSG score 2003) at FU (linear regression)

Predictors	B (95% CI)	p
m_nr/pat rater 1	-0.03 (-0.40, 0.34)	ns
m_nr/pat rater 2	-0.45 (-0.834, -0.07)	0.022
m_nr/3 rd dom rater 1	-0.23 (-0.47, 1)	0.056
m_nr/3 rd dom rater 2	-0.33 (-.62, -0.03)	0.032
m_nr/4 th non-dom rater 1	-0.11 (-0.34, 0.12)	0.346
m_nr/4 th non-dom rater 2	-0.27 (-0.57, 0.02)	0.070

Conclusion: The mean number of capillaries had a good association with the history of DUs and predicted disease activity at 6 months follow-up. The m_nr/pat performed better in our analysis than the m_nr/3rd dom and m_nr/4th non-dom, however these could be used alternatively in clinical practice as they are less time consuming.

This work is part of the QUANTICAP project.

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Abstract Number: 809

The Lymphangiogenic Factors VEGF-C, CCL21 and Ang-2 Are Associated with Pulmonary Arterial Hypertension in Systemic Sclerosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Background/Purpose: Systemic sclerosis (SSc) is characterized by abnormalities in vascular pathways and lymphatic vessels with pulmonary hypertension as a major complication. Vascular endothelial growth factor C (VEGF-C), acting through its cognate receptor VEGFR3 is a major growth factor for lymphatic vessels under physiological conditions. Recent studies have shown that patients with SSc have altered levels of two VEGF-C regulating proteins; the angiogenic factor Ang-2 and the chemokine CCL21, also found to be associated with PAH development. We assessed the characteristics of VEGF-C in SSc patients and investigated serum levels of VEGF-C, CCL21 and Ang-2 segregated by pulmonary arterial pressure.

Methods: SSc patients from the Oslo University Hospital (n=371) and controls (n=100) were included; and sera analyzed for VEGF-C, CCL21 and Ang-2 by Luminex kits from Millipore. SSc patients with clinically suspect PH were referred to right heart catheterization. Mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg in the absence of significant interstitial lung disease (ILD) was defined as PAH; mPAP of 20-24mmHg in the absence of significant ILD borderline PAH. Descriptive statistics and logistic regression analysis were performed and tested by the goodness-of-fit with area under the curve (AUC).

Results: The mean age of SSc patients was 54 ± 14.1 years, 80% were female and 74% had limited cutaneous SSc. Serum levels of VEGF-C were lower in SSc than in controls (2.0 ± 0.7 ng/ml vs. 2.4 ± 0.7 ng/ml, $p < 0.001$) (Table 1). In patients with low levels of VEGF-C (< 2.3 ng/ml) PAH was 3.5-fold more frequent than inpatients with high levels of VEGF-C (14.7 % vs 4.2 %, $p = 0.005$). 167 patients were assessed by RHC. Patients with PH-ILD (n=27), borderline PH-ILD (n=3) and post-capillary PH (n=14) were excluded from the study, while the remaining 123 patients were included in the investigation of lymphangiogenic factor expression; including 28 patients with PAH, 45 borderline PAH and 50 with no PAH. CCL21, Ang2 and VEGF-C levels in these groups are shown in Figure 1. VEGF-C (OR 0.99, 95%CI 0.997-0.998, $p = 0.001$, AUC=0.79), CCL21 (OR 1, 95%CI 1-1.003, $p = 0.050$, AUC=0.69) and Ang-2 (OR 1, 95%CI 1-1.0001, $p = 0.49$, AUC=0.67) were associated with PAH compared to no PAH patients.

Conclusion: VEGF-C is associated with ssc-PAH, making it a possible maker for the development of PAH. This study also demonstrates dysregulation of lymphangiogenetic factor expression of multiple targets in sera of SSc-PAH patients.

Table 1: Longitudinal clinical and demographic data

	OUPH (n=371)	PAH (n=28)	Borderline PAH (n=45)	No PAH (n=50)
Age at disease onset, yrs	52 (15.5)	59 (13.8)	52 (13.6)	51 (15.8)
Time from onset to PH, yrs	7 (8.4)	7 (8.4)	10 (10.5)	n.a.
Females, no (%)	312 (84.1)	23 (82.0)	32 (71.1)	49 (98.0)
Deceased, no (%)	91 (24.5)	14 (50.0)	11 (24.4)	10 (20.0)
Limited cutaneous SSc, no (%)	270 (73)	26 (92.9)	23 (57.5)	44 (88.0)
Anti-Centromere Ab, no (%)	191 (52.3)	24 (85.7)	23 (57.5)	33 (66.0)
Mean VEGF-C level, ng/ml	2.0 (0.7)	1.6 (0.7)	1.9 (0.7)	2.3 (0.6)

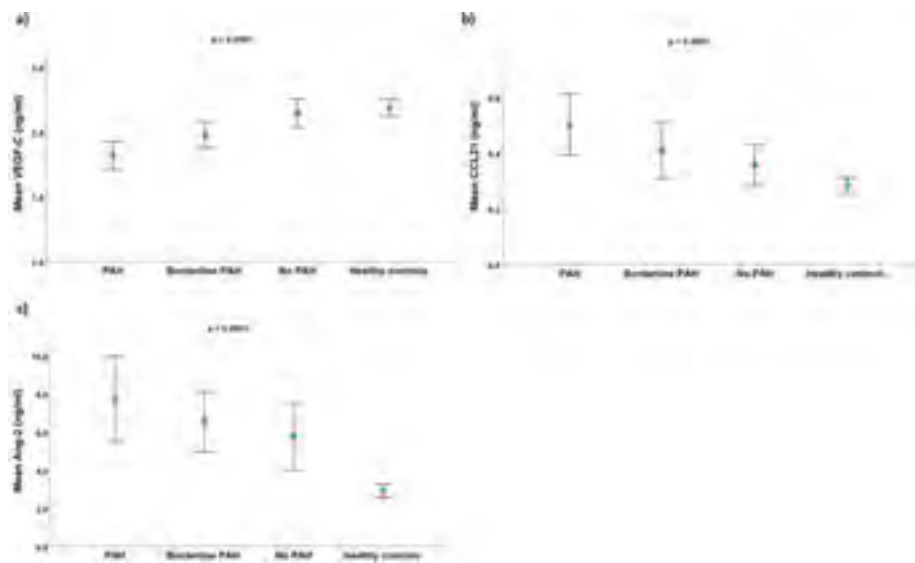


Figure 1: VEGF-C(a), CCL21 (b) and Ang-2 (c) serum levels

Disclosure: H. Didriksen, None; H. Fretheim, None; V. Palchevskiy, None; A. K. Andreassen, None; T. Garen, None; O. Midtvedt, None; E. Gude, None; J. A. Belperio, None; Ø. Molberg, None; A. M. Hoffmann-Vold, None.

Abstract Number: 810

Sexual Dysfunction in Women with Systemic Sclerosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: Impaired sexual function is common among women with chronic illnesses, including Systemic Sclerosis (SSc). Studies of sexual functioning among women with SSc have concluded that sexual impairment is common, according to comparisons with both the general population and women with other chronic diseases. There are no studies in our country that evaluate the impact of SSc in this area.

Objectives: To evaluate sexual impairment in women with SSc. To investigate sociodemographic, disease characteristics and psychological variables associated with sexual impairment in women with SSc.

Methods: Observational, analytical, cross-sectional study. We included women between 20 and 59 years of age diagnosed with SSc according to 2013 American college of rheumatology/European league against rheumatism classification criteria, from 5 public rheumatology centers of Argentina, between April 2017 and April 2018. We excluded patients with severe chronic diseases or other autoimmune rheumatologic diseases. Sexual impairment was assessed using the Spanish version of Female Sexual Function Index (FSFI) questionnaire, which has been validated among Latin American women aged 20 to 59 years. Higher subscale or total scores indicate better sexual function. A cutoff score of 26.55 is proposed as a criterion for impaired sexual function. We used Hospital Anxiety and Depression Scale (HADS) questionnaire to evaluate anxiety and depression. For the descriptive analysis, the continuous variables were reported as mean and standard deviation or median and interquartile range (IQR). The categorical variables were reported as percentage. A multiple linear regression model was performed, taking sexual dysfunction as the dependent variable, adjusted for possible confounders. The performance of the model was evaluated (assumptions, atypical observations, multicollinearity).

Results: We included 46 patients. The mean age was 44.78 years (+/- 9.84) and 39.13% were postmenopausal women. The mean FSFI score was 21.07 (+/- 8). Eighty percent presented sexual dysfunction and 13.04% of them correspond to sexually inactive patients due to the disease. The variables that showed significant association with sexual dysfunction in the univariate analysis were: dyspnea (β coefficient: -2.91. CI 95%: -5.79 to -0.04), VAS pain (β coefficient: -0.08. CI 95%: -0.15 to -0.005), VAS fatigue (β coefficient: -0.09. CI 95%: -0.17 to -0.01), body image satisfaction (β coefficient: 4.34. CI 95%: 0.80 to 7.88), age (β coefficient: -0.28. CI 95%: -0.51 to -0.05) and fibromyalgia (β coefficient: -14.73. CI 95%: -21.99 to -7.47). The variables that showed significant and independent association in the multivariate analysis were: body image satisfaction (β coefficient: 4.11. CI 95%: 1.10 to 7.13), age (β coefficient: -0.25. CI 95%: -0.45 to -0.05), fibromyalgia (β coefficient: -11.37. CI 95%: -18.26 to -4.48).

Conclusion: We found that sexual dysfunction is frequent between women with Systemic Sclerosis, and that is in concordance with other studies. According with our results, patients with greater body image satisfaction, younger and without fibromyalgia had better sexual function.

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Identification of Risk Factors for Gastric Antral Vascular Ectasia (GAVE) Among Systemic Sclerosis Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

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

Background/Purpose: Gastric Antral Vascular Ectasia(GAVE) is a vascular manifestation of systemic sclerosis (SSc) characterized by erythematous streaks and longitudinal rugal folds in the stomach on upper endoscopy. Estimates on the prevalence of GAVE in SSc patients range from 1-22%. GAVE can lead to iron deficiency anemia or acute gastrointestinal (GI) bleeding. Endoscopic laser therapy is effective in the treatment and prevention of GI bleeding related to GAVE. We aimed to identify risk factors for GAVE to improve early identification and treatment of these patients.

Table 1: Results

	SSc-GAVE, n (%) (n=17)	SSc-non GAVE, n (%) (n=306)	p Value
Sex			
Male	1 (6)	35 (11)	0.7
Female	16 (94)	271 (89)	
Race			
White/Caucasian	12 (71)	184 (60)	0.26
African American	1 (6)	8 (3)	
Asian	2 (12)	41 (13)	
Pacific Islander	0 (0)	1 (0.3)	
Other or mixed	2 (12)	60 (20)	
Unknown	0 (0)	10 (3)	
SSc Subtype			
Limited	8 (47)	185 (61)	0.13
Diffuse	9 (53)	118 (39)	
Smoking Use			
Never	8 (47)	207 (68)	0.14
Current	5 (29)	87 (28)	
Past	4 (24)	42 (14)	
History of ulcerations	6 (35)	98 (32)	0.79
Cause(s)			
Cause(s)	5 (29)	60 (20)	0.35
Raynaud's phenomenon	16 (94)	189 (62)	1
Scleroderma renal crisis	4 (24)	11 (4)	0.63
PAH	3 (18)	57 (19)	1
ILD	5 (29)	187 (61)	0.86
DLCO	15 (88)	242 (79)	0.54
Cancer History	2 (12)	51 (17)	0.69
Tumor(s)	13 (76)	207 (68)	0.60
Positive ANA	13 (76)	255 (83)	0.63
ANA Pattern			
Centromeric	3 (25)	33 (11)	0.13
Nucleolar	4 (40)	41 (14)	
Heterogeneous	1 (8)	40 (14)	
Speckled	3 (25)	43 (15)	
Mixed	0 (0)	29 (10)	
Positive anti Centromere	3 (18)	59 (19)	0.29
Positive anti Scl-70	3 (18)	60 (20)	1
Positive anti U3-RNP	2 (12)	25 (8)	0.37
Positive anti RNA Pol III	7 (41)	35 (11)	0.03
Positive anti PM-Scl	1 (6)	35 (11)	0.23
Creatine kinase (median, range)	83 (4.9-379)	62 (20-1334)	0.99
Alkalase (median, range)	4.3 (2.3-11.3)	5.3 (2.1-15.3)	0.05
Hemoglobin (median, range)	95.4 (78.7-103.3)	98.9 (74.9-153.7)	0.06
FVC % Predicted (median, range)	94 (85-114)	87 (73-134)	0.33
DLCO % Predicted (median, range)	72 (17-104)	75 (8-151)	0.74
RVSP on TTE (median, range)	43 (19-88)	28 (14-115)	0.54

Term: PAH=pulmonary arterial hypertension; ILD=interstitial lung disease; GERD=gastroesophageal reflux disease; FVC=forced vital capacity; DLCO=diffusing capacity of the lung for carbon monoxide; RVSP=right ventricular systolic pressure

Methods: We performed a retrospective analysis of prospectively collected data on SSc patients with and without GAVE seen at Stanford between 2004 and 2018. All patients fulfilled 2013 ACR/EULAR classification criteria for SSc. We collected and compared data on demographics, clinical features, autoantibodies, and laboratory findings in those with and without GAVE. We used Fisher's exact test to compare categorical variables, and Wilcoxon rank-sum test for continuous variables. Multivariate logistic regression including variables with p-value less than 0.1 was performed to identify predictors of GAVE.

Results: A total of 323 patients with SSc were included in this study, of whom 17 (5.3%) had GAVE. GAVE was significantly associated with scleroderma renal crisis (SRC), negative ANA, positive anti-RNA Polymerase III antibody, lower aldolase, and a trend toward lower hematocrit (Table 1). Given the high correlation between SRC and anti-RNA Polymerase III, only the latter was included in the multivariate logistic regression model. ANA negativity (OR 4.76 (95% CI 1.43 - 15.82), p=0.01) and anti-RNA polymerase III positivity (OR 4.5 (95% CI (1.13 - 17.92), p=0.03) remained significant predictors of GAVE.

Conclusion: We found a prevalence of GAVE of 5.3% in our cohort. A negative ANA or positive anti-RNA polymerase III antibody increases the risk of GAVE by more than 4-fold. Further studies are necessary to determine whether patients with these antibody profiles should undergo screening endoscopies for GAVE.

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Abstract Number: 812

Inflammatory Stays Inflammatory: A Subgroup of Systemic Sclerosis Characterized By High Morbidity and Inflammatory Resistance to Cyclophosphamide

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

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Session Type: ACR Poster Session A

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Background/Purpose: Elevated levels of C-reactive protein (CRP) in systemic sclerosis (SSc) have been linked to early inflammatory stages of the disease. This study has been set to investigate CRP levels in a longitudinal cohort of SSc patients and to correlate these findings with comorbidities and disease characteristics.

Methods: In this retrospective study patients with SSc were recruited from the outpatient clinic of the Department of Rheumatology and Clinical Immunology, University Medical Center Freiburg. Only patients with at least three consecutive visits over at least one year were included in this study. CRP serum levels were measured at every visit and categorized as positive if CRP concentrations were ≥ 5 mg/l. Subjects with elevated CRP levels at more than 80% of visits were defined as inflammatory SSc. The longitudinal CRP profile was correlated to comorbidities and disease characteristics.

Results: A total of 1,815 consecutive visits of 131 SSc patients were analyzed. Over the observed time span (91 [136-56] months) 18.3% (n=24) of patients had continuously elevated CRP levels (inflammatory SSc), whereas in 29% (n=38) CRP levels were always in the normal range. There was no association between disease duration and CRP levels at first visit (p>0.5). Inflammatory SSc was associated (p<0.05) with anti-topoisomerase I-antibodies, diffuse cutaneous SSc (dcSSc), pulmonary fibrosis, rheumatoid arthritis, and cardiac arrhythmia (p<0.05). Moreover, patients with inflammatory SSc revealed higher modified Rodnan skin scores (mRSS), and lower FCV, TLC, and DLCO (p<0.001). Even treatment with cyclophosphamide (CYC) did not alter CRP levels (n=12, median dose 4.5 g (3-10), median CRP before CYC 18.0 mg/l, after CYC 17.7 mg/l, p=0.754).

Conclusion: Inflammatory SSc is characterized by a more severe disease phenotype and high morbidity. Even treatment with CYC does not alter CRP levels in these patients.

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Abstract Number: 813

Prevalence of Gastroesophageal Disease in Systemic Sclerosis and Its Impact on Lung Disease: Fact or Fiction

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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Background/Purpose: Systemic sclerosis (SSc) patients frequently have upper gastrointestinal (GI) symptoms, with GI involvement being the leading cause of morbidity. Meanwhile, interstitial lung disease (ILD) and pulmonary hypertension (PH) are the leading cause of mortality in SSc. Reflux disease may play a role in ILD through chronic microaspiration and/or altered pulmonary mechanics in ILD can potentiate the impact of reflux. A potential causality between the two variables has yet to be established.

We investigated the prevalence of esophageal motility disorders and reflux in SSc patients and evaluated the relationship between GI characteristics and pulmonary outcomes.

Methods: This retrospective chart review was carried out at the University of California, Los Angeles (UCLA). Patients included in the study were diagnosed with systemic sclerosis and evaluated in SSc-GI clinic. Esophageal evaluation was carried out using at least one of the following modalities: high-resolution esophageal manometry (HREM), ambulatory pH testing and/or EGD. Data, collected within 1 year of the GI procedures, included: patient demographics, scleroderma characteristics, motility data, presence of ILD defined by HRCT, PH, oxygen requirement, and pulmonary function tests (PFTs) completed within one year of the index GI study. Statistical analyses included descriptive, ANOVA or Chi square testing as appropriate.

Results: Our study cohort included 122 patients, mean age \pm SD of 66 ± 9 at GI evaluation. 93% of patients were female, 68% had limited and 32% had diffuse cutaneous disease.

Most patients underwent HREM and EGD. Approximately 70% of the patients had absent contractility on manometry, while another 24% had ineffective esophageal motility. Hiatal hernia was found in one third of patients. Of those who underwent EGD, 37% had erosive esophagitis, while only 23% had a definitive diagnosis of GERD based on EGD. A portion of our cohort completed ambulatory pH testing, with 68% of studies demonstrating GERD. ILD was noted in 55% of patients.

We found no correlation between patient FEV1, FVC and/or DLCO and esophageal motility disorders based on HREM or the diagnosis of GERD based on EGD/pH studies. There were no significant differences in the PFTs and different HREM diagnoses, between patients with and without a diagnosis of GERD, or between patients with ILD with normal and abnormal motility. Our preliminary data did not reveal any correlation between esophagitis or hiatal hernia and ILD per HRCT findings.

Conclusion: Our study is one of the largest single-center cohorts of SSc patients characterizing esophageal motility, reflux and PFTs. The majority of our patients demonstrated abnormal motility, a finding believed to contribute to reflux. Over half of our cohort had lung involvement. There was no association found between esophageal dysmotility and/or GERD with PFTs. Similarly, preliminary data support a similar trend with HRCT findings of ILD. Given the lag time between discernable PFT changes and radiographic findings on HRCT, additional characterization of GI disease and early radiographic findings of ILD and PFT changes overtime is helpful and underway.

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NON Diffuse SSc, Peripheral Neuropathy, Concomitant Sjogren Syndrome and ANTI-RNA Polymerase III Represent Risk Factors for the Higher Frequency of Cancer in a Large Single Cohort of Patients with Systemic Sclerosis

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SESSION INFORMATION

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Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster I

Session Type: ACR Poster Session A

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

Background/Purpose: A higher prevalence of cancer has been described in patients with systemic sclerosis (SSc), but the magnitude of this risk and the type of cancer vary among reports. Risk factors predisposing the development of malignancies in SSc patients are not well defined. **The purpose** of our study was to analyze the frequency and risk factors associated with cancer in a large single cohort of patients with SSc.

Methods: All cases of cancer diagnosed in a cohort of 662 patients classified as SSc according to the ACR/EULAR criteria, attended in a single referral scleroderma outpatient clinic in Brazil between 2010 and 2017, were reviewed and evaluated regarding demographic, clinical and laboratory features. We used the Brazilian National Cancer Institute database to compare the cancer prevalence in SSc patients with the expected rate of cancer in the general population, and to estimate the risk of each cancer in this group, pairing by age. Taking into account that all sample proportions have an observed incidence higher than the general population, the one-tail proportion test was used to compare the cancer incidence in the sample and the population. A logistic regression model was performed to find risk factors for cancer. Statistical significance was considered when $p \leq 0.05$.

Results: ± 13.91 years; $p \leq \pm 9.24$ years; $p = 0.029$). When the frequency of cancer by gender in the SSc patients was compared with the predicted frequency of cancer in the Brazilian general population, it was found a significant association among female gender and cancer in general ($p < 0.001$), as well as with breast ($p < 0.001$), uterus ($p = 0.023$), lung ($p = 0.013$), colon ($p = 0.007$), esophagus ($p = 0.012$), stomach ($p = 0.042$), lymphoma/leukemia ($p = 0.007$), thyroid ($p = 0.004$) and melanoma ($p = 0.022$); male gender was only associated with cancer in general ($p = 0.013$). Multivariate logistic regression identified non diffuse SSc (OR 10.7, 95%CI 2.1-54.8, $p = 0.004$), Sjogren syndrome (OR 3.4, 95%CI 1.4-8.5, $p = 0.007$), peripheral neuropathy (OR 4.4, 95%CI 1.5-13.2, $p = 0.009$) and anti-RNAPolIII positivity (OR 5.1, 95%CI 1.2-22.7, $p = 0.032$) as significant risk factors for cancer occurrence.

Conclusion: This study confirmed a higher frequency of cancer in a large SSc cohort and pointed out that non diffuse SSc, peripheral neuropathy, concomitant Sjogren syndrome and anti-RNA polymerase III positivity represent risk factors for the development of cancer in SSc.

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Classic and Atypical Polymyalgia Rheumatica, Are Different Syndromes? Study of 93 Patients with PET/CT from a Single Center

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Vasculitis Poster I: Non-ANCA-Associated and Related Disorders

Session Type: ACR Poster Session A

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

Background/Purpose: Polymyalgia rheumatica (PMR) is a common inflammatory rheumatic disease of the elderly whose diagnosis is usually based on clinical, analytical and ultrasound findings. However, sometimes patients who present symptoms resembling PMR donot complete fulfill the 2012 EULAR/ACR criteria. It is not well known if these atypical patients behave as those who fulfill criteria. In these cases, Positron Emission Tomography/computed tomography (PET/CT) could be a useful tool to assess if these patients have a similar pattern of 18F-FDG uptake to those who fulfill criteria.

Objectives: Our aims were: **a)**to compare clinical and analytical features in patients with classic PMR to a typical PMR, **b)** to asses if findings in PET/CT differ between both groups.

Methods: Retrospective study of 93 patients with PMR and their respective PET/CT scans from a single University referral center. We considered two groups: **a)** Classic PMR: patients who fulfilled the 2012 EULAR/ACR criteria; and **b)** A typical PMR: patients with symptoms resembling classic PMR but did not fulfill the 2012 EULAR/ACR criteria.

Results: We evaluated 93 patients (30 men/63 women) with a meanage±SD of 69.2±10.8 years. A PET/CT was performed in all of them. Eighty (86%) patients had classic PMR and 13 (14%)atypical PMR. The comparative study is shown in the **TABLE**. Both groups were receiving similar doses of Prednisone at the time of PET/CT performance. Patients with atypical PMR were younger and had shorter duration of symptoms. Pain in the pelvic girdle was more frequent in patients with atypical PMR (100% vs 65%)while shoulder girdle pain was higher in patients with classic PMR (23.1% vs72.5%). No significant differences were found in PET/CT findings between classic and atypical PMR, although large vessel involvement was slightly more frequent in patients with atypical PMR.

Conclusion: Patients with a typical PMR used to be younger with a shorter evolution of symptoms and had predominantly pelvic girdle affection. Despite these differences, the pattern of F-FDG uptake in PET/TC was similar in classic and atypical PMR.

TABLE

	Classic PMR (n=80)	Atypical PMR (n=13)	P
Sex (<i>women</i>), n (%)	55 (68.8)	8 (61.5)	0.61
Age (<i>years</i>), mean ± SD	70.9±9.8	58.3±10	< 0.01
Duration of symptoms (months), median [IQR]	13.0 [6.0-38.0]	6.0[4.0-11.0]	< 0.01
Clinical symptoms, n (%) *			
Neck pain	16 (20.0)	2 (15.4)	0.63
Shoulder girdle pain	58 (72.5)	3 (23.1)	0.02
Pelvic girdle pain	52 (65.0)	13 (100)	0.03
Morning stiffness	19 (23.8)	4 (30.8)	0.68
Inflammatory low back pain	15 (18.8)	3 (23.1)	0.79
Diffuse lower limb pain	27 (33.8)	3 (23.1)	0.51
Laboratory markers, *			
Hb (g/dL), mean ± SD	12.7 ± 1.4	12.3 ± 1.6	0.14
Platelet count (x10 ⁹ /l), mean ± SD	280 ±85.3	276 ±99.5	0.19
CRP (mg/dL), median [IQR]	0.9[0.6-1.3]	0.7 [0.3-1.5]	0.31
ESR (mm/1 st h), median [IQR]	35 [12.0-65.1]	30 [15.7-58.8]	0.21
F-FDG uptake, n (%)			
Cervical interspinous bursae	10 (12.5)	1 (7.7)	0.62
Shoulders	47 (58.8)	5 (38.5)	0.21
Sternoclavicular joints	34 (42.5)	6 (46.2)	0.81
Hips	36 (45.0)	6 (46.2)	0.98
Lumbar interspinous bursae	29 (36.2)	5 (38.5)	0.88
Pubic symphysis	2 (2.5)	2 (15.4)	0.09
Subtrochanteric bursae	20 (25.0)	2 (15.4)	0.45
Ischial tuberosities	22 (27.5)	2 (15.4)	0.36
Knees	37 (46.2)	6 (46.2)	0.99
Large vessel involvement	49 (61.3)	10 (76.9)	0.27
Corticosteroids therapy			
Dose of Prednisone (mg), mean	10.0 [5.0-15.0]	10.0 [8.1-15.0]	0.99

* At the time ofPET/TC performance

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Abstract Number: 816

Development of Thoracic Aortic Aneurysms in Patients with Polymyalgia Rheumatica: Under diagnosed Giant Cell Arteritis?

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SESSION INFORMATION

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Session Title: Vasculitis Poster I: Non-ANCA-Associated and Related Disorders

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Background/Purpose: Polymyalgia Rheumatica (PMR) and Giant Cell Arteritis (GCA) are close-related entities. Imaging studies have suggested that subclinical inflammation of the large arteries is frequent in patients with apparently isolated PMR. Our objective was to compare characteristics of PMR patients who developed a thoracic aortic aneurysm (TAA) during follow-up with those who did not, in order to identify clinical features that may predict aortic involvement in clinical PMR patients.

Methods: All electronic medical records of PMR patients diagnosed after year 2000 (fulfilling ACR 2012 criteria) from a university hospital-based health management organization (HMO) were reviewed. Patients with a previous diagnosis of aortic aneurysm, those who developed clinical GCA or other rheumatic disease after PMR diagnosis and those lost in follow-up or without appropriate thoracic images after diagnosis, were excluded. A case-control study (PMR-TAA versus PMR without TAA) was performed and patients' characteristics were compared. A multivariate logistic regression analysis was performed to identify risk factors for TAA.

Results: 350 PMR patients were included (724 were excluded for the reasons mentioned in methods) and 50 (14.3%, 95% CI 10.9-18.4) developed a TAA during a median follow up of 5.4 years (IQR 2.9-7.9). 18 TAA were located at the aortic root and 32 at ascendant aorta, with a medium size at diagnosis of 4.3 cm (SD 0.33). No ruptures or dissections occurred but 5 patients (10 %, 95% CI 4.2-22.1) required surgery. Patients' characteristics are shown in Table 1. Traditional cardiovascular risk factors and clinical characteristics of PMR were similar across groups, except for less statins use and longer treatment with steroids in PMR-TAA group. In the multivariate logistic regression analysis, being a male (OR 4.4, CI 2.3-8.6, p <0.001) and months of corticosteroid treatment, (OR 1.02, 95% CI 1.01-1.03, p 0.01) were associated with an increased risk of TAA. Statins use seemed to be protective, although did not reach statistical significance (OR: 0.48, 95% CI 0.23-1.002; p=0.051).

Conclusion: 14.3 % of apparently isolated PMR developed a thoracic aortic aneurysm. Screening with thoracic images in PMR male patients and those PMR patients requiring a prolonged corticosteroid use may be advisable.

Table1. Demographic characteristics in PMR patients with and without thoracic aortic aneurysm.

	PMR with Thoracic aortic aneurysm (n=50)	PMR without aneurism (n=300)	P
Age at PMR diagnosis, media (SD)	75.3 (7.4)	75.0 (8.1)	0.84
Female, n (%), CI)	25 (50.0, 36.3-63.7)	239 (79.7, 74.7-83.9)	<0.001
Follow up after PMR diagnosis, years, median (IQR)	6.7 (4.1-10.4)	5.2 (2.7-7.5)	0.003
Arterial hypertension, n (%), CI)	36 (72.0, 57.9-82.8)	215 (71.7, 66.3-76.5)	0.96
Diabetes, n (%), CI)	4 (8.0, 2.9-15.7)	27 (9.0, 6.2-12.8)	0.82
Ever smoker, n (%), CI)	16 (32.0, 20.5-46.2)	79 (26.3, 21.6-31.6)	0.40
Dyslipidemia, n (%), CI)	18 (36.0, 23.8-50.2)	150 (50.0, 44.3-55.7)	0.07
Obesity, n (%), CI)	12 (24.0, 14.1-37.9)	93 (31.0, 25.9-36.5)	0.32
Cardiovascular event previous, n (%), CI)	8 (16.0, 8.1-29.1)	30 (10.0, 7.1-13.9)	0.21
Abdominal aortic aneurysm, n (%), CI)	1 (2.0, 0.3-13.2)	2 (0.7, 0.2-2.6)	0.34
Statin use, n (%), CI)	12 (24.0, 14.1-37.9)	128 (42.7, 37.1-48.4)	0.01
Aspirin use, n (%), CI)	12 (24.0, 14.1-37.9)	30 (10.0, 7.1-13.9)	0.21
Beta Blocker use, n (%), CI)	12 (24.0, 14.1-37.9)	77 (25.7, 21.0-30.9)	0.80

Table 1. (Cont'd)

	PMR with Thoracic aortic aneurysm (n=50)	PMR without aneurism (n=300)	P
Erythrocyte sedimentation rate at diagnosis, media (SD)	53.9 (21.9)	54.6 (24.0)	0.84
Hemoglobin at diagnosis, media (SD)	12.3 (1.5)	12.2 (1.3)	0.84
Shoulder girdle pain at diagnosis, n (%), CI)	49 (98.0, 86.8-99.7)	282 (94.0, 90.6-96.2)	0.25
Pelvic girdle pain, n (%), CI)	38 (76.0, 62.1-85.9)	231 (77.0, 71.9-81.4)	0.88
Arthritis at diagnosis, n (%), CI)	6 (12.0, 5.4-24.4)	24 (8.0, 5.4-11.7)	0.35
Initial corticosteroid dose, prednisone/d, media (SD)	10.2 (5.7)	9.3 (4.2)	0.21
Months with corticosteroid treatment, median (IQR)	22.8 (17.3-46.2)	19.5 (14.2-32.7)	0.02
Recurrences while corticosteroid tapering, n (%), CI)	21 (42.0, 29.1-56.1)	105 (35.0, 29.8-40.6)	0.34
More than one recurrence, n (%), CI)	8 (16.0, 8.1-29.1)	73 (24.3, 19.8-29.5)	0.19
Relapses after finishing corticosteroids, n (%), CI)	7 (14.0, 6.7-26.8)	33 (11.0, 7.9-15.1)	0.54
Methotrexate use, n (%), CI)	4 (8.0, 2.9-19.7)	16 (5.3, 3.3-8.5)	0.45

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Abstract Number: 817

Current Diagnostic Delays in Vasculitis and Factors Associated with Time to Diagnosis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Vasculitis Poster I: Non-ANCA-Associated and Related Disorders

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

Background/Purpose: Despite recent advancements in the evaluation and management of vasculitis, patients with vasculitis continue to encounter diagnostic delays. These delays are often associated with substantial morbidity and mortality. This study sought to describe the diagnostic journey of patients with vasculitis from the onset of symptoms to diagnosis, and identify factors associated with time to diagnosis.

Methods: Patients enrolled in an online registry completed a two-stage mixed-methods study: Stage 1: Survey consisting of open-ended questions about patients' diagnostic journeys and the perceived factors associated with rapid or delayed diagnosis; and Stage 2: Survey with specific questions based on data from Stage 1 and additional investigator-identified factors. Multivariate linear regression analysis was used to identify factors associated with time to diagnosis. Factors were divided into patient-related factors and healthcare-related factors. Patient Research Partners participated in idea conception, study design, and patient-engagement.

Results: 375 patients with vasculitis participated in Stage 1 and 456 patients participated in Stage 2. The median age (IQR) was 59 (24). 72% were females and 94% Caucasians. The majority (74%) of patients sought medical attention within 3 months of their symptoms and 85% were seen by a health care provider within 3 months. The mean time to diagnosis of vasculitis (\pm SD) was 3.3 ± 7 years with IgA-vasculitis having the shortest time (0.3 ± 0.5 years) and Behcet's disease having the longest time (20.4 ± 15 years) (Table 1). 313/456 (73%) of patients were misdiagnosed initially (33% were diagnosed with infections, 29% with an autoimmune disease, and 11% with a "fake" illness). The median (IQR) number of misdiagnoses was 5 (3). 40% of diagnoses were made in a hospital setting (35% inpatient and 5% emergency room [ER]). Only 2% of diagnoses were made at a specialized vasculitis center. More than half of patients had at least 1 ER visit prior to diagnosis, with 5% of patients having > 10 ER visits. Unemployment, time to travel to a medical center greater than 1 hour, being initially misdiagnosed, and delays in seeing a specialist were all associated with longer times to diagnosis (Table 1). 373/456 (82%) of patients reported that a delayed diagnosis had negative consequences on their health: 55% of patients thought it made their condition worse, 16% lost their job, and 11% became disabled.

Conclusion: Patients with vasculitis encounter substantial delays in achieving an accurate diagnosis and these delays are associated with negative health consequences. Both patient-related factors and healthcare-related factors are associated with diagnostic delays. Future efforts should focus on mechanisms to address modifiable factors and shorten delays in diagnosis for patients with new-onset vasculitis.

Table 1. Time to diagnosis and factors associated with time to diagnosis of vasculitis

Time to diagnosis		
Disease type	Number of patients	Mean time to diagnosis (years \pm SD)
Behcet's disease	17	20.4 \pm 15
Central nervous system vasculitis	16	0.6 \pm 1
Cryoglobulinemic vasculitis	15	2.6 \pm 5
Eosinophilic granulomatosis with polyangiitis	60	5.0 \pm 8
Giant cell arteritis	23	1.7 \pm 6
Granulomatosis with polyangiitis	162	1.7 \pm 3
IgA-vasculitis	18	0.3 \pm 0
Microscopic polyangiitis	48	2.5 \pm 5
Polyarteritis nodosa	21	1.5 \pm 2
Takayasu's arteritis	24	2.0 \pm 4
Urticarial vasculitis	13	5.6 \pm 7
Other	39	7.3 \pm 16
Factors associated with time to diagnosis		
Factors	Coefficient (95% CI)	p-value
Patient-related factors		
Female gender	-1.5 (-4.0 - 0.5)	0.15
Caucasian race	-1.5 (-6.0 - 3.0)	0.54
Single or Divorced or Widow(er)	1.1 (-1.0 - 3.2)	0.29
Employed	-2.4 (-4.0 - -0.4)	0.02
Household income >\$50,000/year	-1.5 (-4.2 - 0.6)	0.18
Patient location (North America)	1.2 (-2.0 - 3.8)	0.76
Charlson score >1	-1.5 (-3.9 - 0.4)	0.12
Time to travel to healthcare site >1 hour	2.6 (0.6 - 4.5)	<0.01
Healthcare-related factors		
Specialist involved initially	-1.3 (-3.1 - 0.6)	0.18
Lab studies ordered initially	0.2 (-1.6 - 2.0)	0.80
Misdiagnosis	2.3 (0.1 - 4.5)	0.03
Referral delays due to insurance	-0.3 (-2.5 - 2.5)	0.98
Time to see a specialist > 1 month	2.4 (0.3 - 4.6)	0.03

A positive coefficient indicates a longer time to diagnosis and a negative one indicates a shorter time to diagnosis. CI: confidence interval; \$ are US dollars.

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Abstract Number: 818

Visual Involvement in Giant Cell Arteritis: A Prospective Multi Center Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Vasculitis Poster I: Non-ANCA-Associated and Related Disorders

Session Type: ACR Poster Session A

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

Background/Purpose: Under reporting of visual impairment attributable to GCA is likely; certificates of visual impairment do not include GCA as a category. Delayed presentation, recognition and treatment are in most cases the reasons that sight loss (SL) is still present in 15-25% of patients at diagnosis. A “Yellow card reporting system” enabled us to characterise the spectrum and severity of visual involvement (VI) attributable to GCA.

Methods: We recorded patients prospectively, with new or relapsing diagnosis of GCA who presented with or without VI over a period of 2 years. We collected demographic information, symptomatology at presentation, medical history, date/dose of initiation of steroids, response to treatment, laboratory results, confirmatory investigations as ultrasound of temporal arteries, biopsy or /and PET, presence of VI with or without loss of acuity, persistence of visual symptoms and findings from formal ophthalmology assessment. SL was defined as symptomatic loss of acuity, field of vision or diplopia ascribable to ischaemic complications of GCA. Patients with transient visual symptoms were not considered to have SL. Analyses were performed using chi-squared and rank sum tests

Results: 388 patients were enrolled from 19 sites. 135 (35%) presented with VI. Patients with VI had mean age of 75.9 (SD 9.3) years, were predominantly females 95 (70%) and all were Caucasian. Headache (84% vs 92%, $p=0.012$) and scalp tenderness (61% vs 75%, $p=0.005$) were less common, but jaw (57% vs 46%, $p=0.040$) and tongue claudication (13% vs 4%, $p=0.004$) were more common at presentation in patients with VI than in those without. Median duration of symptoms prior to diagnosis was 2.0 (IQR 1.0-4.0) weeks. Information was missing regarding type and severity of VI from 4 patients. 33/131 presented with diplopia, 51 with arteritic ischemic optic neuropathy (AION), 7 with central retinal artery occlusion (CRAO); changes were permanent in 36/58 and 5 patients experienced AION as manifestation of recrudescing disease. Headache (75% vs 92%, $p<0.001$) and myalgia/stiffness (25% vs 44%, $p=0.011$) were less common in patients who presented with AION/CRAO than those without. Patients with AION/CRAO were older [mean age 80.9 (SD 6.7) years] compared to those without [73.2 (SD 8.7) years, $p<0.001$]. History of hypertension was more common (70% vs 46%, $p=0.001$) and hemoglobin levels were lower (mean 119.9 mg/dl (SD 16.5) vs 124.4 (SD 15.4), $p=0.018$). Patients with SL presented quicker with median duration of symptoms of 2.0 (IQR 1.0-4.0) vs 3.0 (IQR 1.4-6.0) weeks ($p=0.016$). 44/92 patients who presented with SL had at least unilaterally reduced visual acuity: counting fingers (3), hand movements (4), no light perception (7), light perception (3), 1 reported as blind and 25 had variable severity of unilateral visual acuity loss (from 6/18 to 6/120 based on Snellen chart).

Conclusion: Visual symptoms often leading to SL in GCA require urgent management. Patients with VI were older, without 'typical symptoms' such as headache and polymyalgia but more likely to have ischaemic symptoms, such as jaw and tongue pain and hypertension. Recognition of VI associated features should be embodied in public and professional awareness programs to prevent permanent SL in GCA.

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Abstract Number: 819

Use of Takayasu Arteritis Damage Score (TADS) to Measure Damage in Takayasu Arteritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Vasculitis Poster I: Non-ANCA-Associated and Related Disorders

Session Type: ACR Poster Session A

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

Background/Purpose: Takayasu Arteritis (TA) in India frequently present with complications, indicating the need for a specific damage index to capture the accumulation of disease-related scars over time. Takayasu Arteritis Damage Score (TADS) devised by us is a clinical index for use in these circumstances.

Methods: Disease extent in TA is assessed using the comprehensive tool, Disease Extent Index for Takayasu Arteritis (DEI.Tak). We modified this established score, using a large database of cases previously assessed by us. Items persisting for more six months, related to accumulating scars, were selected while omitting those used infrequently to produce a shorter form with 42 items focused on CVS, particularly pulse loss and vascular interventions. Drug-related damage were also included. This new TADS form was compared to Vasculitis Damage Index (VDI) and PGO using paper cases. It was then applied to analyze a cohort of 286 cases followed in one clinic over 2 decades.

Results: The increase in damage/scars over time correlated closely with disease duration, continuing to increase over 20 years. TADS also related to poor outcomes such as pulse loss. In a cohort of 286 TA patients, the mean age at onset of TA symptoms was 33.74 years (8-42). 142 vascular interventions were performed in 102 of this cohort (34 men, 68 women, mean disease duration 8.9 years). The procedures performed were: Carotid angioplasty + stenting - 29, vertebral angioplasty + stenting-6, grafts from ascending aorta to Carotids-4, subclavian angioplasty + stenting- 22, renal angioplasty + stenting-31, Aortic angioplasty + stenting - 15, coronary angioplasty + stenting- 22 and CABG Surgeries-14. The mean

follow up period was 144 months. Associated clinical features and drug therapy were recorded. Peri-operative complications included infections- 5.2%, Stroke- 8.8%, Myocardial infarction-4.6% and renal failure-4.8%. Drug toxicity and damage were seen in 30%. There were no deaths due to the procedures and TADS scores continued to rise. The patency of stents at 5 and 10 years were 92% and 83% respectively. In the majority (84.7%), drug therapy was also continuing. 32/286 patients died and the scores in fatal disease were higher than in non-fatal cases (7.4 Vs 4.8).

Conclusion: Damage is a significant factor in TA. Vessel occlusion is a major feature of TA, often requiring vascular interventions. Recording the new disease-specific damage score, TADS helps delineate features associated with pulse loss, long-term stent patency, drug induced damage and mortality.

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Abstract Number: 820

Incidence And Seasonal Variation Of Biopsy-Proven Giant Cell Arteritis – Revisited: A 20-Year Population-Based Study From Sweden

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SESSION INFORMATION

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Session Type: ACR Poster Session A

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

Background/Purpose: To investigate the incidence rate and seasonal variation of biopsy-proven giant cell arteritis (GCA) in a well-defined population in southern Sweden.

Methods: The study area was the County of Skane with a total population of 1,324,565 as of December 2016 (37% aged ≥ 50 years). Patients who underwent temporal artery biopsy (TAB) between 1997 and 2016 and lived in Skane at time of TAB were identified using the database at the Departments of Pathology serving Skane. All pathology reports of all TABs performed in the region during the 20-year period were retrieved and reviewed. Only patients with TAB positive GCA were included. The study period was divided into 4 five-year periods to study possible fluctuation of the incidence over time. Date of TAB was used to study possible seasonal variations in the incidence of TAB+GCA. The seasons were defined as follow: winter (December-February), spring (March-May), summer (June-August) and autumn (September-November). Incidence rates per 100,000 persons aged ≥ 50 years are presented.

Results: A total of 5886 TABs were identified during the study time. Of these, 1202 patients (864 females, 72%) were found to have a positive TAB during the 20-year period. The mean age at diagnosis was 75.1 years (SD 8.0) for all patients, 75.4 years (SD 7.8) for women and 74.5 years (SD 8.5) for men. The annual incidence rate of biopsy-proven GCA per 100000 persons in the age group ≥ 50 years was estimated to 13.7 (95% CI 12.9-14.4) and was higher among women (18.4 vs. 8.2 for men, $p=0.04$). There was a decline in the incidence rate over time: 15.8 during period 1 (1997-2001) vs. 12.2 in period 4 (2012-2016), $p<0.01$ (Table 1). The incidence rate of performed TABs declined during the study period, 76.4 (95% CI 72.6-80.6) during period 1 vs. 58.4 (95% CI 55.4-61.5) during period 4, $p<0.01$. There was a seasonal variation in the diagnosis of GCA, with more patients diagnosed during spring and summer compared to autumn and winter (331 patients diagnosed during spring, 319 during summer, 282 during autumn and 270 during winter, $p=0.04$).

Conclusion: The incidence rate of biopsy-proven GCA decreased over time. Similarly, the number of performed TABs decreased during the study period. A possible explanation for this may be an increased use of imaging studies in diagnosing GCA. We also observed a seasonal variation, with more patients diagnosed during spring and summer, possibly due to season related exposures, e.g. infections.

	All	95% CI	Men	95% CI	Women	95% CI
Period 1 (1997–2001)	15.8	14.1 - 17.6	7.9	6.1 - 9.7	15.8	14.1 - 17.6
Period 2 (2002–2006)	13.2	11.6 - 14.7	8.0	6.3 - 9.8	17.6	15.2 - 20.1
Period 3 (2007–2011)	13.6	12 - 15.1	7.4	5.8 - 9.1	19.0	16.5 - 21.5
Period 4 (2012–2016)	12.2	10.8 - 13.6	9.2	7.5 - 11	15.0	12.8 - 17.1
1997-2016	13.7	12.9 - 14.4	8.2	7.3 - 9	18.4	17.2 - 19.7

Disclosure: P. Stamatis, None; C. Turesson, None; J. A. Nilsson, None; A. Mohammad, None.

Abstract Number: 821

Comparison of Aortitis Vs Non-Inflammatory Aortic Aneurysms Among Patients Who Undergo Open Aortic Aneurysm Repair

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SESSION INFORMATION

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Background/Purpose: Distinguishing aortitis-induced aneurysms from more common non-inflammatory aortic aneurysms is difficult. Aortitis is often incidentally diagnosed upon histologic review after surgical repair of an aneurysm. Earlier detection of aortitis will allow for more prompt therapeutic intervention and possibly improve surgical outcomes. This study examined surgically diagnosed aortitis and identified patient characteristics and imaging findings associated with the disease.

Methods: This is a single-center, case-control study. Cases had biopsy-proven, newly-diagnosed, non-infectious aortitis following open aortic aneurysm surgical repair at the University of Pennsylvania Hospital System between 2012 and 2017. Controls were matched by year of open aortic aneurysm repair and lacked significant inflammation on pathology. Comorbidities, demographics, and laboratory prior to surgery were collected. Radiologic imaging (CT or MRI), including location of aneurysm, size, and rate of progression prior to surgery were also reviewed. The data was compared between aortitis and non-aortitis controls using Wilcoxon signed rank and chi-square or Fisher's exact tests. Backward stepwise logistic regression was used to determine factors independently associated with aortitis.

Table 1. Characteristics of Patients

Characteristic	Aortitis (n=20)	Control (n=11)	P-value
Age at time of surgery	67 (57, 79)	68 (58, 79)	0.78
Female	55%	31%	0.04
White Race	65%	77%	0.36
General Characteristics			
Co-morbidities			
Hypertension	85%	81%	0.74
Coronary artery disease	10%	57%	<0.01
Hyperlipidemia	50%	55%	0.79
Diabetes mellitus	15%	13%	0.96
Smoking history			0.66
Never	35%	47%	
Former	45%	47%	
Current	17%	7%	
BMI	28 (26, 30)	27 (25, 30)	0.89
Pre-surgical Imaging Findings (CT or MRI)			
Location of aneurysm that underwent repair			0.35
Ascending aorta	90%	73%	
Aortic arch	0%	9%	
Descending thoracic aorta	10%	13%	
Abdominal aorta, infrarenal or suprarenal	0%	3%	
Largest diameter of aneurysm, cm	5.7 (5.5, 6)	5.2 (4.9, 5.8)	0.01
Imaging abnormalities of aneurysm			
Wall thickening	15%	0%	0.07
Stenosis/Narrowing	4%	4%	0.98
Calcification or atheroma	17%	50%	0.03
Rate of change in aneurysm, mm/year	3.7 (1.6, 9.1)	-1.3 (-14.0, 1.2)	0.01
	N = 7	N = 7	
Values expressed as median (interquartile range) or percentage			

Table 2. Factors Independently Associated with Aortitis in Multivariate Analysis

	Odds ratio (95% CI)	P-value
Diameter of aneurysm, per cm	8.9 (2.5 – 31.9)	< 0.01
Calcifications and/or atheroma on imaging	0.1 (0.02 – 0.6)	0.01
Location of aneurysm in ascending aorta	76.4 (1.7 – 3393.6)	0.02

Results: 62 patients were included: 31 patients with aortitis and 31 controls (**Table 1**). Compared to controls, patients with aortitis were less likely to have a history of coronary artery disease prior to surgery (10% vs 58%, $p < 0.01$), calcification or atheroma on imaging (27% vs 58%, $p = 0.03$), and calcific atherosclerosis on pathology (35% vs 69%, $p < 0.01$). Aortitis patients had significantly larger aneurysmal diameters at the time of surgery and, among patients with serial imaging, a faster rate of growth of the aneurysm. Multivariable analysis revealed that aortitis is independently associated with a larger diameter of the aneurysm, absence of calcifications or atheroma on imaging, and location of aneurysm in the ascending aorta (**Table 2**).

Conclusion: The study revealed that among patients who undergo open surgical repair of an aortic aneurysm, those with a larger aneurysm diameter, no prior history of coronary artery disease, or absence of atherosclerosis on imaging are more likely to have histologic evidence of aortitis. Patients with these risk factors may benefit from referral to a rheumatologist for further evaluation and assistance with post-operative management.

Disclosure: L. Quimson, None; B. Rea, None; R. L. Rhee, None.

Abstract Number: 822

Immuno-Inflammatory Markers and MR-Angiographic Imaging to Detect Disease Activity in Takayasu Arteritis

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SESSION INFORMATION

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Background/Purpose: There is an unmet need for tools to quantify local disease activity in TAK.

Methods: Sera of 21 TAK patients, aged between 18 and 56 years and fulfilling the 1990 ACR criteria, were analyzed and compared with age/sex-matched controls (CTRL). Serum levels of 45 biomarkers were quantified using luminex technology. Vasculitis activity was scored in MR-angiography of 15 patients, which had MRA performed within 4 months to serum collection, from 0 (normal) to 3 (intense late enhancement). Disease activity was defined by the NIH criteria (1994).

Results: 4/21 patients showed active disease according to NIH criteria, and MRA signals of 10/15 TAK patients indicated vessel wall inflammation. Most serological molecules did not differ between the TAK cohort and the CTRL or remained undetectable in both cohorts. However, MMP-3 ($p=0.007$), sIL-6R ($p=0.010$), IL-11 ($p=0.021$) and APRIL ($p=0.001$) were elevated in the 22 TAK patients compared to CTRL. BAFF ($p=0.035$) and IFN α ($p=0.025$) directly correlated with MR-vasculitis activity, whereas YKL-40 (AUC=0.897), sILR2 (AUC=0.971) and CD163 (AUC=1) were associated with clinical disease activity. MRA signal intensity did not correlate with clinical disease activity ($p=0.51$).

Conclusion: Our data suggest that YKL-40, sILR2 and CD163 on one side and BAFF and IFN α on the other side may serve as biological mirrors of clinical disease activity and vessel wall inflammation, respectively. The clinical utility of these markers will have to be assessed in a prospective setting.

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Survival of Biopsy Proven Giant Cell Arteritis in Northern Italy: Correlation with Clinical, Laboratory and Histopathological Findings

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Session Type: ACR Poster Session A

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

Background/Purpose: To correlate survival with clinical, laboratory and histopathological findings in a population based cohort of patients with biopsy-proven giant cell arteritis (GCA) living in the Reggio Emilia area during a 26 years period

Methods: In this population-based study, all patients living in the Reggio Emilia area who underwent temporal artery biopsy (TAB) for suspected GCA from January 1, 1986 to December 31, 2012 were identified. A pathologist with expertise in vasculitis and blinded to clinical data and final diagnosis reviewed all TABs. Based on the localization of the inflammation, positive TABs were classified into 4 categories: small vessel vasculitis (SVV), with inflammation limited to small periadventitial vessels devoid of muscular coat; vasa vasorum vasculitis (VVV), with inflammation surrounding the adventitial vasa vasorum; inflammation limited to adventitia (ILA), with inflammation spreading from vasa vasorum to the adventitia without extension to the media; transmural inflammation (TMI), with external elastic lamina disruption and extension of the inflammation to the media. Histopathologic features evaluated were: the severity of inflammation and intimal hyperplasia, both graded on a semiquantitative scale (mild=1, moderate=2 severe=3), the presence of intraluminal acute thrombosis, calcifications, giant cells, fibrinoid necrosis and laminar necrosis. Information about clinical manifestations, laboratory findings, treatment and disease course were collected. Patients were followed from GCA diagnosis to death, migration or December 2013. Survival was estimated with the Kaplan-Meier method. Univariate and multivariate Cox proportional hazards models were used to evaluate potential predictors of survival at diagnosis.

Results: 281 patients (206 female, 73.3%) with biopsy-proven GCA were identified in the study period. 120 patients (84 female, 70%) died during a median follow-up period of 96 (IQR 55, 143) months. At univariate analysis, the presence of polymyalgia rheumatica (PMR) (HR 0.54, 95% CI 0.37-0.79, p=0.002), higher level of hemoglobin (HR 0.84, 95% CI 0.74-0.96, p=0.011) at disease onset, long-term remission (HR 0.47, 95% CI 0.26-0.86, p=0.015) and ILA or VVV at TAB (HR 0.48, 95% CI 0.24-0.97, p=0.041) were associated with lower mortality, while the evidence of large vessel involvement at imaging studies performed at diagnosis was associated with increased mortality (HR 5.84, 95% CI 1.57-21.8, p=0.009). Multivariate analysis confirmed the association between lower mortality and PMR (HR 0.54, 95% CI 0.36-0.81, p=0.003), higher level of hemoglobin (HR 0.83, 95% CI 0.69-0.99, p=0.049) at disease onset, and ILA or VVV at TAB (HR 0.38, 95% CI 0.17-0.82, p=0.014), and between increased mortality and large vessel involvement at imaging studies performed at diagnosis (HR 5.31, 95% CI 1.39-20.26, p=0.014).

Conclusion: PMR at diagnosis and only adventitial inflammation at TAB seem to identify subsets of biopsy-proven GCA patients with more benign disease, while large vessel involvement at diagnosis a subset with reduced survival.

Disclosure: L. Boiardi, None; P. Macchioni, None; F. Muratore, None; M. Catanoso, None; A. Cavazza, None; P. Mancuso, None; L. Cimino, None; G. Restuccia, None; C. Salvarani, None.

Comparing Childhood- Versus Adult-Onset Polyarteritis Nodosa

Michele Iudici¹, **Pierre Quartier**², **Christian Pagnoux**³, **Etienne Merlin**⁴, **Christian Agard**⁵, **Achille Aouba**⁶, **Pascal Roblot**⁷, **Pascal Cohen**¹, **Benjamin Terrier**¹, **Luc Mouthon**¹, **Loïc Guillevin**¹ and **Xavier Puéchal**¹, ¹National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP-HP, Université Paris Descartes, Paris, France, ²AP-HP, Institut des Maladies Génétiques (IMAGINE), and Université Paris-Descartes, Necker-Enfants Malades Hospital, Paris, France, ³Division of Rheumatology, Division of Rheumatology, Mount Sinai Hospital, Toronto, ON, Canada, ⁴CHU, Clermont-Ferrand, France, ⁵Nantes Hôtel Dieu, Nantes, France, ⁶Caen, Caen, France, ⁷CHU, Poitiers, France

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Vasculitis Poster I: Non-ANCA-Associated and Related Disorders

Session Type: ACR Poster Session A

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

Background/Purpose: To investigate differences between childhood (cPAN)- and adult-onset polyarteritis nodosa (aPAN) patients.

Methods: cPAN patients' clinical findings at onset and outcomes were compared to those of aPAN patients from the French Vasculitis Study Group registry matched for year of enrollment and initial systemic versus cutaneous disease. Their information on medications, disease activity and damage were collected. Kaplan-Meier relapse-free survival curves and the log-rank test were used to analyze cPAN versus aPAN differences for predefined outcomes.

Results: Twenty-one children with systemic and 13 with cutaneous PAN were compared with 84 systemic- and 27 cutaneous-matched aPAN patients. Median follow-up exceeded 5 years for both groups. At study entry, mononeuritis multiplex was less frequent in systemic cPAN than systemic aPAN ($P=0.04$), and purpura and myalgias were less frequent in cutaneous cPAN than cutaneous aPAN ($P<0.03$). During follow-up, systemic cPAN relapsed more often than matched systemic aPAN ($P<0.0001$), while relapse rates were similar for cutaneous disease ($P>0.05$). Mostly minor relapses, predominantly involving the skin, occurred in all 4 groups. At last visit, damage accrual was comparable for cPAN and aPAN patients, but fewer systemic cPAN patients were treatment-free (15% versus 42%; $P=0.03$). Two (6%) cPAN and 8 (7%) aPAN patients died.

Conclusion: Systemic PAN is equally severe in children and adults and carries a higher risk of relapse. The main cutaneous PAN features seem not to be influenced by age at disease onset.

Disclosure: **M. Iudici**, None; **P. Quartier**, Novartis and SOBI, 5, AbbVie, Lilly, Novartis and SOBI, 8, AbbVie, BMS, Novartis, Pfizer, Sanofi, 9, AbbVie, Novartis, Pfizer, SOBI, 9; **C. Pagnoux**, None; **E. Merlin**, None; **C. Agard**, None; **A. Aouba**, None; **P. Roblot**, None; **P. Cohen**, None; **B. Terrier**, None; **L. Mouthon**, None; **L. Guillevin**, None; **X. Puéchal**, None.

Assessment of Damage and Prognosis in Patients with Adult IgA Vasculitis: Retrospective Multicentered Cohort Study

Ummugulsum Gazel¹, **Ahmet Omma**², **Alper Sari**³, **Dondu Uskudar Cansu**⁴, **Ayten Yazici**⁵, **Ayşe Cefle**⁵, **Cemal Bes**⁶, **Omer Karadag**⁷, **Haner Direskeneli**⁸ and **Fatma Alibaz-Oner**¹, ¹Rheumatology, Marmara University School of Medicine, Istanbul, Turkey, ²Rheumatology, Ankara Numune Education and Research Hospital, Ankara, Turkey, ³Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Turkey, ⁴Rheumatology, Osmangazi University, School of Medicine, Eskisehir, Turkey, ⁵Rheumatology, Kocaeli University, Faculty of Medicine, Kocaeli, Turkey, ⁶Department of Rheumatology, Health Sciences University Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey, ⁷Rheumatology, Hacettepe University, Faculty of Medicine, Ankara, Turkey, ⁸Rheumatology, Marmara University, School of Medicine, Istanbul, Turkey

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Vasculitis Poster I: Non-ANCA-Associated and Related Disorders

Session Type: ACR Poster Session A

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

Background/Purpose: IgA Vasculitis is a leukocytoclastic vasculitis involving small vessels with depositions of immune complexes containing IgA. IgA Vasculitis is a predominantly pediatric vasculitis. There is limited data for the prognosis of adult IgA Vasculitis, with also no damage assessment. In this study, we aimed to evaluate the clinical characteristics, treatment, outcome and damage of patients with adult IgA Vasculitis.

Methods: We assembled a retrospective cohort of patients with adult IgA Vasculitis from tertiary Rheumatology Centers in Turkey. The demographics, clinical characteristics, treatment and outcomes of patients were abstracted from medical records. Birmingham Vasculitis Activity Score (BVAS), prognostic Five Factor Score (FFS) and vasculitis damage index (VDI) were calculated.

Results: The study included 103 (male/ female: 67/36) patients with adult IgA Vasculitis. The mean age was 42.6 ± 17 years. Infection history within 6 weeks before presentation was present in 40 (38.8%) patients (32 upper respiratory tract, 3 urinary tract, 2 gastrointestinal, 3 others). Cutaneous manifestations and arthritis/arthralgia were the most common clinical manifestations (Table 1). Ninety-two (89.3%) patients were treated with oral glucocorticoids (GC). Pulse GC treatment was also given to 29 (28.1%) patients. As additional immunosuppressive agents, azathiopirine was given to 36 (34.9%) and pulse cyclophosphamide to 13 (12.6%) patients. Fifty-nine patients (58.2%) had follow-up of mean 35.6 months. Eleven (18.6%) patients relapsed during follow-up. While 5 relapses were major, six of them were minor relapses. At the last visit, disease status was evaluated as active or treatment failure by the treating physician in 7 (11.8 %) patients. The rate of chronic renal failure was 8.3 % (n=5). Mortality was 1.6% (n=1) during follow-up, due to pneumonia. The mean VDI score was 0.3 in the last visit. Twelve (20.3%) patients had at least one damage item at the end of follow-up period.

Conclusion: Our results showed that approximately one fifth of patients with adult IgA Vasculitis had relapses during follow-up and had at least one damage item at the end of follow-up. Although, 31% of patients had $\text{FFS} \geq 1$, the mortality rate was observed to be very low in the present study.

Table 1: Baseline clinical characteristics of patients with adult Henoch Schönlein Purpura

Adult Henoch Schönlein Purpura (n=103)	
Laboratory parameters	
Anemia (<12 mg/dl for female, <13 mg/dl for male) (n, %)	36 (35%)
Erythrocyte Sedimentation Rate (mm/hour) *	34.7 ± 22
C-reactive protein (mg/l) †	18 (1-297)
Proteinuria (>300mg/24 hours)	47 (45.6 %)
Creatinine (mg/dl)*	0.8 ± 0.3
Hepatitis B positivity (n)	8/97 (8.2 %)
Hepatitis C positivity (n)	0/97
ANA positivity	21/97 (21.7%)
RF Positivity	5/88 (5.7%)
c-ANCA positivity	2/97 (2.1%)
p-ANCA positivity	1/95 (1.1 %)
Clinical Manifestations, n/103 (%)	
Fever	24 (23.3%)
Weight loss	26 (25.2%)
Myalgia/Weakness/Leg tenderness	44 (42.7%)
Arthritis and/or arthralgia	87 (84.5%)
Neurologic manifestations	1 (0.9%)
Testicular pain or tenderness	4 (3.9%)
Recent onset or severe hypertension	2 (1.9%)
Cutaneous Manifestations	97 (94.2%)
Peripheral limb edema	14 (13.6%)
Gastrointestinal manifestations	71 (68.9%)
Cardiac manifestations	5 (4.8%)
Ocular manifestations	3 (2.9%)
Pulmonary manifestations	3 (2.9%)
FFS=0	71 (68.9%)
FFS=1	24 (23.3%)
FFS=2	5 (4.9%)
FFS=3	3 (2.9%)
BVAS score at diagnosis*	6 ± 3

ANA: Anti nuclear antibody, FR: Rheumatoid factor, ANCA: Antineutrophilic cytoplasmic antibody, FFS: Five Factor Score, BVAS: Birmingham Vasculitis Activity score. *Mean \pm SD †Median (Minimum-maximum)

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Does Anti-Glomerular Basement (anti-GBM) Antibody Positivity Correlate with Relapse in Patients with Anti-GBM Disease?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Vasculitis Poster I: Non-ANCA-Associated and Related Disorders

Session Type: ACR Poster Session A

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

Background/Purpose: Anti-GBM disease is characterized by rapidly progressive glomerular nephritis with or without pulmonary hemorrhage. It is usually monophasic in nature and disease severity correlates with antibody titer. The disease is mediated by pathogenic antibodies directed against the non-collagenous region of the $\alpha 3$ chain of type IV collagen. Despite the known pathogenicity of anti-GBM antibodies, and the correlation of disease severity with their titers, there is conflicting reports on whether anti-GBM antibody positivity correlates with disease relapse on long term follow up. The objective of this study was to assess for correlation of anti-GBM antibody positivity and disease relapse in patients with anti-GBM disease.

Methods: Patients seen in a single academic center between 1997 and 2017 were initially screened for the presence of anti-GBM disease by ICD 9/10 code for anti-GBM disease or Goodpasture's syndrome. 435 patients were identified. Patients were then included in the study if the diagnosis was confirmed by a board certified rheumatologist or nephrologist at our institution and had positive anti-GBM antibodies or biopsy results consistent with a diagnosis of anti-GBM disease. Relapsing disease was defined as recurrence of glomerulonephritis or pulmonary hemorrhage after the initial presentation that necessitated a change in therapy. The primary endpoint of this study was anti-GBM antibody positivity at the time of relapse. All charts were reviewed for baseline demographics, clinical manifestations, anti-GBM antibody and ANCA positivity at the time of initial presentation; these were compared between those with relapsing and non-relapsing disease. Results were analyzed using a two tailed standard t-test. These same characteristics were also examined in the relapsing cohort at the time of relapse.

Results: 40 patients were confirmed as having anti-GBM disease at our institution. Mean follow up from disease onset to the date of last follow up was 56.2 months. 8 patients had relapsing disease and 32 patients had non-relapsing disease. Baseline characteristics and clinical manifestations were similar between groups (Table1). Patients with relapsing disease had a statistically higher incidence of ANCA co-positivity as compared to non-relapsing patients (62.5% vs. 21.7% respectively p value- 0.03).

In patients with relapsing disease, only 14.7% (1/7 tested patients) had positive anti-GBM antibodies at the time of their relapse.

Conclusion: In this study, anti-GBM positivity did not correlate with disease relapse in patients with anti-GBM disease. Patients with relapsing disease had a higher incidence of ANCA positivity, consistent with previous investigations. In patients with newly diagnosed anti-GBM disease, ANCAs should be obtained to assess for the risk of relapse and to help guide long term follow up and treatment. Larger studies are needed to validate our results.

Table 1: Baseline demographics, clinical features and laboratory values at baseline and at the time of relapse of anti-GBM disease

		Non-relapsing anti-GBM disease (n=32)	Relapsing anti-GBM disease (n=8)	p-value
Baseline characteristics	Length of follow up, mos (range)	62.79 (2-228)	26.29 (3-78)	0.16
	Time to diagnosis, days (range)	30 (1-182)	62 (5-243)	0.33
	Age, Yr (range)	46.06 (17-78)	41 (14-62)	0.52
	Male Gender (%)	53.1	37.5	0.44
	Non-Smoking Status (%)	43.8	50.0	0.61
	Renal involvement (%)	93.8	100	0.48
	Peak creatinine mg/dL (range)	7.24 (0.8-17.6)	5.37 (1.6-13.7)	0.33
	Pulmonary hemorrhage (%)	30.0	37.5	0.69
	Positive Anti-GBM antibodies (%) PPosi	73.9 (17/23)a	37.5 (3/8)	0.07
	Positive ANCA (%)	21.7(5/23)a	62.5 (5/8)	0.03
Characteristics at time of relapse	Time to relapse, weeks (range)		77.14 (6-480)	
	Positive Anti-GBM antibodies (%) Posit		14.3 (1/7)a	
	Positive ANCA (%)		75 (3/4)a	
	Renal involvement (%)		83.3	

Table 1. (Cont'd)

	Non-relapsing anti-GBM disease (n=32)	Relapsing anti-GBM disease (n=8)	p-value
Peak creatinine mg/dL (range)		3.42 (2.7-4.85)	
Pulmonary hemorrhage (%)		71.4	

Values are expressed as mean (range) or percent

^a Incomplete data available. Number of positive patients out of total tested represented in parentheses

Disclosure: N. Droz, None; A. Katz, None; J. Sedor, None; R. A. Hajj-Ali, None.

Abstract Number: 827

Rituximab Therapy for Systemic Rheumatoid Vasculitis: Indications, Outcomes and Adverse Events

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Vasculitis Poster I: Non-ANCA-Associated and Related Disorders

Session Type: ACR Poster Session A

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

Background/Purpose: Rheumatoid vasculitis (RV) is a rare systemic inflammatory process affecting small to medium sized blood vessels in patients with rheumatoid arthritis (RA). RV confers high morbidity and mortality, and evidence regarding safe, effective treatment options is lacking. Our study aims to characterize the indication, outcomes and adverse effects of rituximab treatment in a large single center cohort of RV patients.

Methods: Patients evaluated with systemic RV from 2000 to 2017 who were treated with rituximab were retrospectively identified through direct medical chart review. Patients who received rituximab for an indication other than RV, were treated at an outside institution, or for whom follow-up information was unavailable were excluded. Clinical characteristics, treatment, outcomes and adverse effects were analyzed.

Results: 17 patients with RV who were treated with rituximab were identified. Mean age at RV diagnosis was 59.2 (range:38-77), 59% were female, 94% were Caucasian and 76% had positive rheumatoid factor (RF). At time of initiating rituximab therapy, the median BVAS/RA was 4.0 (IQR, 2.0-7.5). RV presented in the skin in 9 patients (53%, ulcers and/or leukocytoclastic vasculitis), as mononeuritis multiplex in 2 (12%), inflammatory ocular disease in 2 (12%), and affected multiple organ systems in 4 (24%).

Rituximab was used as first-line induction therapy in 8 (47%) patients, first-line for relapse in 4 (24%), second-line in 2 (12%), and third- or fourth-line or in combination with another agent in 3 (18%). 15 patients had follow-up information recorded at 3 and 6 months from rituximab use. At 3 months, 2 (13%) had achieved complete remission (CR), and 10 (67%) had achieved partial remission (PR). At 6 months, 6 patients (40%) had achieved CR, 8 (53%) had achieved PR, and 1 patient had no response (NR). 8 of 13 patients with available records (62%) had CR at 12 months, and 5 patients (38%) had PR.

There were no significant differences in age, sex, smoking status, BMI, duration of RA, baseline RA characteristics, DAS28-CRP(3) or BVAS-RA baseline scores, RA treatments prior to development of RV, or type of RV presentation when compared between groups who did and did not achieve complete remission at 6 months.

10 (59%) of 17 patients experienced no adverse effects, 4 (24%) of 17 experienced mild adverse effects (infusion reaction, rash, infection requiring oral antibiotics) and 3 (18%) of 17 required hospitalization; 2 with infection requiring IV antibiotics and 1 with pneumocystis pneumonia. There were no deaths as a result of rituximab use.

Conclusion: Systemic RV is difficult to treat effectively. Complete remission of RV was achieved in 62% of patients and partial response in 38% within 12 months of rituximab use. Rituximab represents an effective treatment option for RV with an acceptable side effect profile. Further evidence is needed to inform treatment for patients with RV.

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Medium and Small-Sized Vessel Involvement in Hypereosinophilic Syndrome

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Vasculitis Poster I: Non-ANCA-Associated and Related Disorders

Session Type: ACR Poster Session A

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

Background/Purpose: Primary systemic vasculitis, especially eosinophilic granulomatosis with polyangiitis and polyarteritis nodosa, can be associated with blood and tissue eosinophilia. Conversely, eosinophilia in the context of hypereosinophilic syndrome (HES) may involve various organs, including blood vessels. While HES-related superficial and/or deep venous thromboses have been extensively reported, little is known about its medium- and small-sized-vessel involvement.

Methods: This multicenter retrospective study concerned patients with medium/small-sized-vessel vasculopathy and eosinophilia $>1,000/\text{mm}^3$. Patients with cardiac embolism or preexisting thrombophilia and those with primary systemic vasculitis (as defined by the 2012 revised International Chapel Hill Consensus Conference) were excluded.

Results: Among 13 patients with eosinophilia and medium- and/or small-sized-vessel involvement, 1 had mononeuritis multiplex with biopsy-proven eosinophilic vasculitis and 1 had retinal vasculitis and coronary spasm. For the remaining 11 patients (median age: 43 (21–62) yr), clinical characteristics included distal ischemia (digital ischemia and/or necrosis for 9 and pulse abolition with paresthesia for 2), with splinter hemorrhages for 5, purpura for 2 and Raynaud's syndrome for 2. Eosinophilia had been detected before vasculopathy onset for 6 patients and concomitantly for 5. Their etiological work-ups for eosinophilia, including the search for the FIP1L1-PDGFR α fusion transcript and T-cell lymphoproliferative disorders, were unremarkable. At vasculopathy diagnosis, median eosinophil count was $5,500/\text{mm}^3$ ($2,500\text{--}9,000/\text{mm}^3$). Doppler ultrasonograms of 9 patients revealed arterial thrombosis in 5 and/or stenosis in 4. Magnetic resonance imaging, CT angiography or arteriography, obtained for 7 patients, showed thrombosis and/or vascular involvement. Two patients had histological evidence of small-vessel vasculitis. First-line therapies included glucocorticoids (GCs) for 9, antiplatelet drugs for 9, anticoagulants for 7, iloprost for 3, immunosuppressants for 2 and anti-eosinophil drugs for 2. Eight of the 11 patients entered remission but 3 of them relapsed and 1 required high-dose GCs. Seven (63%) patients received further-line treatments, including immunosuppressants for 4 and/or anti-eosinophil drugs (interferon- α , imatinib, hydroxycarbamide or cyclosporine) for 5. Despite initially severe disease, 10 patients had complete remissions when their eosinophil counts normalized and 1 required transmetatarsal amputation prior to remission. During follow-up, clinical status always corresponded to blood eosinophilia.

Conclusion: Medium- and small-sized-vessel vasculopathy associated with eosinophilia is a rare entity, frequently manifesting with distal ischemia that may not fulfill primary systemic vasculitis criteria but is consistent with HES. Despite initially severe disease, favorable outcomes were obtained for most cases with immunosuppressants and/or anti-eosinophil drugs.

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DNA Damage and Repair in Patients with Cryoglobulinemic Vasculitis Treated with Direct Anti-HCV Drugs

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

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Session Type: ACR Poster Session A

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

Background/Purpose: Direct Acting Antiviral(DAA) agents were shown to be effective for treatment of HCV induced Cryoglobulinemic Vasculitis (HCV/CV+). Some reports showed failure of DAAs to reduce Hepatocellular carcinoma (HCC) development in HCV patients or the high risk of HCC. Although HCV replication results in hepatic stress which is associated with DNA damage, the impact of DAA on the host response to DNA damage is unknown. Our aim was to assess DNA damage and repair in CV patients treated with DAAs.

Methods: This study included 32 Egyptian patients with HCV/CV+ diagnosed according to the validated 2014 classification criteria of CV. We applied 3 DAA protocols: Sofosbuvir(SOF) plus Ribavirin (RBV) plus pegylated interferon (p-IFN) for 3 months (8 patients), SOF plus RBV for 6 months (13 patients) or SOF plus Daclatasvir for 3 months (11 patients). We measured DNA damage levels in peripheral blood cells as well as DNA repair genes (TOP1, TOP2A, TDP1, TDP2, XRCC1 and PARP1) in 3 groups: healthy individuals (n=9), HCV patients without CV (HCV/CV-) (n=13) and in HCV/CV+ patients: before and at end of treatment (EOT) (n=32), at 6 months; 3 months follow up from EOT (n=19) and at 12 months follow up (n=23). Data is reported as mean \pm SEM. *= $p<0.05$, **= $p<0.005$.

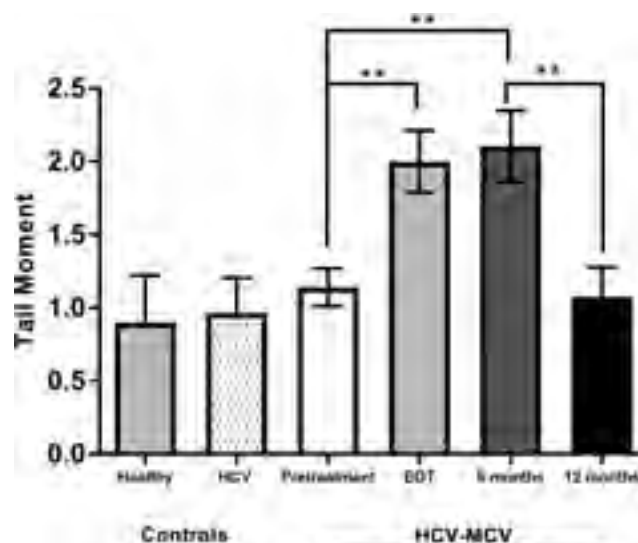


Figure 1: DNA damage levels: Healthy individuals (n=9), HCV-CV patients (n=13), HCV+CV at pretreatment (n=32), EOT (end of treatment) (n=32), 6 months (n=19) and 12 months (n=23).

Results: All patients showed viral clearance without recurrence, in all 3 protocols. All Patients improved clinically and serologically at EOT. After 12 months, only articular and constitutional manifestations as well as cryocrit % showed significant relapse (P value 0.009, 0.006, 0.002 respectively). HCV/CV+ patients showed increasing levels of double-strand breaks (DSBs) at EOT ($p < 0.05$) and at 6 months point ($p < 0.05$). However, at 12 months point, DSBs returned to pretreatment levels (**Figure 1**).

We found no studies investigating DNA repair genes during HCV infection. We report reduced expression of all tested DNA repair genes in HCV/CV+ patients compared to patients with HCV/CV- (**Figure 2**).

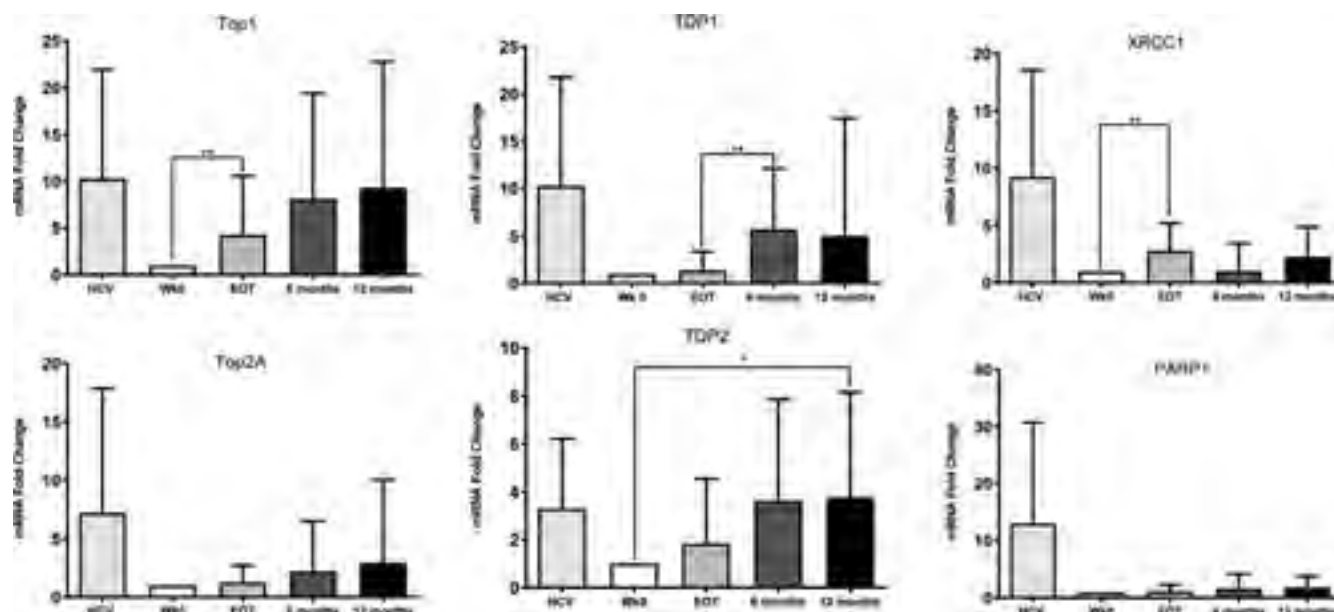


Figure 2: Repair genes expression levels: HCV-CV patients (n=13), HCV+CV at pretreatment (n=32), EOT (end of treatment) (n=32), 6 months (n=19) and 12 months (n=23).

Conclusion: The reported elevated levels of chromosomal breaks and the reduced expression of all tested DNA repair genes with DAAs in treating HCV/CV+ instigate deeper and more extended studies to understand the nature of our findings and evaluate the safety of these drugs.

Disclosure: M. T. Hegazy, None; W. Allam, None; M. A. Hussein, None; N. Zoheir, None; L. Quartuccio, None; P. Cacoub, Abbvie, Astra Zeneca, Bristol-Myers Squibb, Gilead, Glaxo Smith Kline, Janssen, Merck Sharp Dohme, Roche, Servier and Vifor, 5; W. Doss, None; M. I. Ellawindi, None; M. Fawzy, None; L. Guillevin, None; A. El Ray, None; M. E. S. El Raziky, None; M. El Serafy, None; S. El Khamisy, None; G. Ragab, None.

Abstract Number: 830

Primary Central Nervous System Vasculitis with Tumor-like Presentation

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Vasculitis Poster I: Non-ANCA-Associated and Related Disorders

Session Type: ACR Poster Session A

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

Background/Purpose: The aim of this study was to determine the frequency of ML in a large cohort of patients with PCNSV and compare the presenting clinical, laboratory, and imaging features in those with ML to those without.

Methods: We retrospectively studied a cohort of 191 consecutive patients with PCNSV who were seen at the Mayo Clinic, Rochester, MN over a 35- year period (1982-2017). The diagnosis of PCNSV was based on brain/spinal cord biopsy or

cerebral angiography. Cerebral biopsy specimens were reviewed by one pathologist (CG) without knowledge of clinical information. Comprehensive information about clinical manifestations at presentation and during the follow-up, laboratory investigations, radiological imaging, results of CNS biopsy or autopsy, type of, duration of, and response to treatment, number of relapses, functional status at last follow-up, and cause of death were recorded. We compared PCNSV patients with tumor-like presentation to those without.

Results: 13/191 (6.8%) patients had tumor-like presentation. In all 13 patients PCNSV diagnosis was established by cerebral biopsy (stereotactic in 10, open-wedge in 3). 4 patients had cerebral angiography, and vasculitis was suggested in one patient. A granulomatous inflammatory histologic pattern was found in 11 biopsies, accompanied by vascular deposits of β -amyloid peptide in 7. In the other 2 biopsies a lymphocytic vasculitis was observed. The 13 patients with tumor-like presentation were compared with the 178 patients without. The patients with ML were more frequently males (77% vs 44%, $p = 0.04$), were less likely to present with transient ischemic attacks (TIA) (0 vs 27.5%, $p = 0.023$) and more likely to present with seizures (46% vs 17%, $p = 0.022$). No significant differences in the CSF findings and ESR levels (normal in 100% and 82% of the patients, respectively) at diagnosis were observed in the two groups. Gadolinium-enhancing lesions were more frequently observed in patients with ML (77% vs 37%, $p = 0.007$). The frequencies of PCNSV recurrence (38% vs 29%), patients not requiring therapy at last follow-up (15% vs 25%), response to therapy (100% vs 74%), and poor outcomes (modified Rankin disability score ≥ 4) at last followup (8% vs 26%) were not significantly different in the two groups. No differences in survival were observed between the 2 groups ($p = 0.57$). Considering all 191 patients, univariate Cox proportional hazards modeling showed an increased mortality rate in those with increasing age (hazard ratio, HR, 1.4), cerebral infarction on initial MRI (HR 2.95), and angiographic large vessel involvement (HR 3.2), while mortality rate was lower in those with gadolinium-enhancing lesions on MRI (HR 0.3).

Conclusion: Tumor-like presentation represents a small subgroup of patients with PCNSV, and are often associated with vascular deposits of β -amyloid at biopsy, have seizures as presenting manifestation and gadolinium-enhancing cerebral lesions on MRI. As in PCNSV without ML, treatment response and prognosis was favorable in most patients.

Disclosure: C. Salvarani, None; R. D. Brown Jr., None; T. J. H. Christianson, None; C. Giannini, None; J. Huston III, None; G. G. Hunder, None.

Abstract Number: 831

No More HCV RNA in Serum and Cryoprecipitate in Patients with Persisting HCV-Cryoglobulinemia Vasculitis after Daa-Induced Sustained Virological Response

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Vasculitis Poster I: Non-ANCA-Associated and Related Disorders

Session Type: ACR Poster Session A

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

Background/Purpose: In addition to high antiviral efficacy, the new anti-HCV regimens (DAA) can improve most systemic manifestations of patients with HCV-mixed cryoglobulinemia vasculitis(HCV-CryoVas). However, 6 to 12 months after DAA, 50% to 61% of HCV-CryoVas patients still have detectable cryoglobulinemia and some of them still complain of CryoVas manifestations. The aim of the present study was to search for the presence of HCV RNA in serum and cryoprecipitate of HCV-CryoVas patients who had a sustained virological response after DAA and who remain cryoglobulin-positive.

Methods: Samples of patients who had systemic manifestations of CryoVas, including 15 HCV-infected and 4 HCV-noninfected patients were analyzed. All HCV-infected patients received all-or alinterferon-free combinations for 12 to 24 weeks. Cryoglobulins were precipitated during 7 days at 4°C, then cryoprecipitates were washed. Cryoglobulins were quantified by spectrophotometry and identified by immunofixation. HCV RNA viral loads were performed on sera and cryoprecipitates (after dilution) by the automated Roche Cobas® 6800 platform (limit of detection: 15 IU/mL).

Results: HCV-infected CryoVas patients were aged 59±10 yrs, 9 females, 44% cirrhotics, 69% genotype 1 and 30% treatment-naïve. Patients received DAAs, i.e. SOF/RBV (N=7), SOF/DACLA (n=6), SOF/SIME (n=2), and SOF/DACLA/RBV (N=1). Three groups of HCV patients were defined based on the presence of HCV RNA (in serum and/or cryoprecipitate) and clinical manifestations of CryoVas (**Table 1**). Group 1 included samples of 5 patients with symptomatic CryoVas before DAAs. They all showed HCV positive viral load in serum and cryoprecipitate. Other patients with either both positive cryoglobulin and symptomatic CryoVas (group 2, n=4) or positive cryoglobulin and no symptom of vasculitis (group 3, n=6) proved all negative for the presence of HCV RNA in serum and cryoprecipitate after sustained virological response to DAAs. In addition, 4 HCV-seronegative patients who had symptomatic CryoVas were all negative for the presence of HCV RNA in their serum and cryoprecipitate.

Conclusion: HCV-CryoVas patients who have a sustained virological response after DAA and who remain cryoglobulin-positive (symptomatic or not) do not have HCV RNA particles in their cryoprecipitate anymore. In such cases, the cryoglobulin production with or without vasculitis manifestations became autonomous and independent of HCV antigenic stimulation.

Table 1

Age (years) gender				HCV RNA (IU/mL)	
				serum	cryoprecipitate
Group 1					
71/F*	Yes	2	Yes	59 400	1824
53/M*	Yes	2	Yes	27 892	8320
68/F*	Yes	2	Yes	344 378	14 275
65/M*	Yes	2	Yes	1610	15 100
62/F*	Yes	2	Yes	7639	96 000
Group 2					
75/F	Yes	2	Yes	< 15	undetectable
54/M	Yes	2	Yes	< 15	undetectable
71/F*	Yes	2	Yes	< 15	undetectable
62/F*	Yes	2	Yes	< 15	undetectable
Group 3					
68/F*	Yes	2	No	< 15	undetectable
56/F	Yes	3	No	< 15	undetectable
53/M*	Yes	2	No	< 15	undetectable
30/M	Yes	2	No	< 15	undetectable
53/M	Yes	2	No	< 15	undetectable
65/M*	Yes	2	No	< 15	undetectable

* Patients with samples analyzed before and after DAA-therapy. Cryo: cryoglobulin. IU: International Units

Disclosure: P. Cacoub, Abbvie, Astra Zeneca, Bristol-Myers Squibb, Gilead, Glaxo Smith Kline, Janssen, Merck Sharp Dohme, Roche, Servier and Vifor, 5; E. Todesco, None; P. Ghillani-Dalbin, None; L. Musset, None; D. Saadoun, Medimmune, Abbvie, Bristol Meyer Squibb, Roche, Servier, Gilead, AstraZeneca and Glaxo Smith Kline, 5.

Abstract Number: 832

Immunoglobuline a Vasculitis: Comparison between Pediatric and Adult Population

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Vasculitis Poster I: Non-ANCA-Associated and Related Disorders

Session Type: ACR Poster Session A

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

Background/Purpose: Immunoglobuline A (IgA) Vasculitis, formerly known as Henoch-Schönlein purpura, is a small-vessel leukocytoclastic vasculitis due to deposition of IgA1, a subclass of IgA. Although it is mainly a pediatric disease, it can

affect adults with an incidence rate of 1-8 cases/1000000 patients/year and it is reported to have a more aggressive course and worse renal outcome. There are scarce studies analyzing this association, and none in our region. The purpose of the study is to describe the different features of the disease (clinical, laboratory, treatment and prognosis) both in pediatric and adult patients, and evaluate the differences between these groups, especially regarding renal outcome.

Methods: We performed a retrospective review of the electronic medical records of all the patients with IgA vasculitis that were followed in a university hospital between 01/01/2000 and 05/01/2018. We included all patients that fulfilled the EULAR/PRINTO/PRES 2010 criteria (European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society), and collected and analyzed demographic, clinical, treatment and histopathologic information available on their medical records. We considered pediatric patients those who were under 20 years when they were diagnosed.

Results: One-hundred eighteen patients were included, being 107 pediatric and 11 adults.

Table 1 shows demographic information, clinical manifestations, predisposing factors, treatment used, relapses, kidney outcome and deaths in both groups.

In our cohort, the adult group had more renal involvement. Kidney biopsy was performed in 5/8 of the affected patients, with confirmatory histopathology for IgA vasculitis in all of them.

Since adults showed more severe clinical manifestations, significantly more corticosteroids and immunosuppressants were used in this group.

As a consequence of the vasculitis, 2 of the affected adults suffered from chronic kidney disease, one of them required kidney transplant. No pediatric patient presented chronic kidney disease.

Finally, 2 deaths were found, both in the adult group, but only one related to the disease.

Conclusion: In our cohort, adult patients with IgA vasculitis suffered a more aggressive disease, with more renal involvement and required more intense treatment.

Table 1.

	Pediatric Patients (n=107)	Adult Patients (n=11)	P
Male, n (% , 95% CI)	61 (57.0, 47.3-66.2)	8 (72.7, 39.5-91.6)	0.31
Age at diagnosis, years, median (IQR)	6.2 (4.4-9.5)	39.7 (27.6-72.3)	<0.001
Follow-up, years, median (IQR)	7.3 (1.5-11.4)	9.3 (0.3-15.6)	0.47
Initial Clinical Manifestations			
- Purpura, n (% , 95% CI)	107 (100)	11 (100)	1
- Abdominal pain, n (% , 95% CI)	62 (57.9, 48.3-67.0)	5 (45.4, 19.1-74.6)	0.43
- Proctorrhagia, n (% , 95% CI)	12 (11.2, 6.4-18.8)	1 (9.1, 1.1-46.9)	0.83
- Intussusception, n (% , 95% CI)	0 (0)	0 (0)	1
- Scalp edema, n (% , 95% CI)	45 (42.1, 32.9-51.7)	1 (9.1, 1.1-46.9)	0.03
- Arthritis, n (% , 95% CI)	30 (28.0, 20.2-37.4)	2 (18.2, 4.2-52.9)	0.48
- Arthralgia, n (% , 95% CI)	57 (53.3, 43.7-62.6)	2 (18.2, 4.2-52.9)	0.03
- Renal involvement, n (% , 95% CI)	39 (36.4, 27.8-46.1)	8 (72.7, 39.5-91.6)	0.02
Predisposing Factors			
Upper respiratory tract viral infection, n (% , 95% CI)	24 (44.4, 31.5-58.2)	2 (33.3, 6.9-76.9)	0.60
Streptococcal infection, n (% , 95% CI)	26 (48.2, 34.9-61.7)	0	0.02
None recognizable, n (% , 95% CI)	4 (7.4, 2.7-18.6)	4 (66.7, 23.1-93.0)	<0.001
Unknown, n (% , 95% CI)	53 (49.5, 40.0-59.1)	5 (45.4, 19.1-74.6)	0.79
Initial Treatment			
- Watch and wait, n (% , 95% CI)	52 (48.6, 39.1-58.1)	1 (9.1, 1.1-46.9)	0.01
- NSAIDs, n (% , 95% CI)	35 (32.7, 24.4-42.3)	2 (18.2, 4.2-52.9)	0.32
- Corticosteroids, n (% , 95% CI)	36 (33.6, 25.2-43.2)	9 (81.8, 47.0-95.8)	0.002
- Immunosuppressants, n (% , 95% CI)	1 (0.9, 0.1-6.5)	2 (18.2, 4.2-52.9)	0.001
Relapses, n (% , 95% CI)	18 (16.8, 10.8-25.3)	1 (9.1, 1.1-46.9)	0.51
Chronic kidney disease at the end of follow-up, n (% , 95% CI)	0	2 (18.2, 4.2-52.9)	< 0.001
Death, n (% , 95% CI)	0	2 (18.2, 4.2-52.9)	< 0.001

Disclosure: M. Brom, None; I. J. Gandino, None; M. Scolnik, None; V. Scaglioni, None; M. Britos, None; C. De Cunto, None; E. R. Soriano, AbbVie, Bristol-Myers Squibb, GSK, Janssen, Novartis, Pfizer Inc, Roche, UCB, 2,AbbVie, Bristol-Myers Squibb, Eli Lilly, GSK, Janssen, Novartis, Pfizer Inc, Roche, Sanofi, UCB, 5,AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer Inc, Roche, Sandoz, UCB, 8.

11 Patients with Relapsing Polychondritis Presenting with Severe Airways Disease in One Centre in UK

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Vasculitis Poster I: Non-ANCA-Associated and Related Disorders

Session Type: ACR Poster Session A

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

Background/Purpose: Relapsing polychondritis (RP) is a multi-system disease characterised by episodes of progressive inflammation and subsequent degeneration of cartilage and connective tissue throughout the body. RP can be associated with significant morbidity and increased mortality. Respiratory manifestations include large and small airway disease. Tracheobronchomalacia is one of the severe forms of respiratory involvement and can lead to sudden death due to collapse of the airways. RP is a rare condition with incidence of around 1 in a million. We present 11 patients who presented with severe airways disease, and subsequently were diagnosed as relapsing polychondritis from one centre in UK with catchment area of around 500,000.

Methods: The index case was diagnosed at Louise Coote Unit with RP on the basis of tracheobronchomalacia, bilateral auricular chondritis, nasal chondritis, costochondritis and inflammatory arthritis.

All patients had presented to the difficult airways clinic at University Hospital Coventry and Warwickshire NHS Trust (UHCW) in Coventry with severe breathlessness, cough and monophonic wheeze or been admitted as emergency with severe 'exacerbation of asthma'. RP was diagnosed using the McAdam criteria) and disease activity assessed using the Relapsing Polychondritis Disease Activity Index (RPDAI). Tracheobronchomalacia was usually initially suspected on clinical examination particularly the presence of fixed inspiratory or harsh monophonic inspiratory and expiratory wheeze. Diagnosis of tracheobronchomalacia was confirmed by a combination of lung function testing, inspiratory and expiratory CT and bronchoscopy.

Results: All patients had three or more of the six diagnostic clinical features described by McAdam et al. (1976). There was considerable delay from the onset of respiratory symptoms to the diagnosis of RP. Flow-volume loops demonstrated flattening of usually expiratory curves (intrathoracic). CT showed obvious dynamic major airway collapse on expiratory films in the majority. Other manifestations of autoimmunity, such as anti-phospholipid syndrome, or other autoimmune conditions were present in 5 patients.

Patients were initially treated with a combination of oral prednisolone and methotrexate or azathioprine. 3 patients were treated with IV Cyclophosphamide, although none responded. Five patients have been treated with continuous positive airway pressure (CPAP) to palliate airway collapse. Anti-TNF treatment was tried in 3 patients (Infliximab in one with good response, Etanercept in another 2 without response). One of these has now been switched to Abatacept, whilst the other is due to start Secukinumab.

Conclusion: Obstructive small or large airways disease is a common presentation for relapsing polychondritis which is contrary to previous reports.

Monophonic wheeze should encourage investigations for tracheobronchomalacia.

Disclosure: S. Dubey, None; G. Pink, None; A. Ali, None; N. Hart, None; P. Murphy, None; J. Shakespeare, None; C. Gelder, None; C. Taylor, None; D. D'Cruz, GlaxoSmithKline, 5, 8.

Clinical Characteristics of IgA Vasculitis in Children and Adults: A Retrospective Cohort Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Vasculitis Poster I: Non-ANCA-Associated and Related Disorders

Session Type: ACR Poster Session A

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

Background/Purpose: Differences in both presentation and outcome based on age of diagnosis have been described in patients with IgA vasculitis (IgAV) but data are limited due to cohort size and follow-up duration. The aim of this study was to describe the clinical characteristics and outcome of a large single-institution cohort of biopsy-proven IgAV.

Methods: Patients with biopsy-proven IgAV from 1997 to 2016 were retrospectively identified. Clinical characteristics, laboratory parameters and outcomes were abstracted from direct medical chart review. Proteinuria was classified as non-nephrotic (≥ 0.2 g/d, ≤ 3.5 g/d) or nephrotic (> 3.5 g/d). Microscopic hematuria was defined as ≥ 5 RBCs/hpf or $\geq 2+$ on dipstick. Disease activity at each follow-up visit was categorized as complete response (normalization of all baseline abnormalities due to IgAV), partial response, non-response (lack of improvement of any abnormalities due to IgAV) or relapse (development of clinical signs of IgAV after a symptom-free period of at least one month). Prevalence of disease activity was estimated using multi-state models, which account for competing risks.

Results: A total of 243 IgAV patients were identified (97% Caucasian, 58% male). 174 patients were adults (> 21 years) and 69 were < 21 years. ACR criteria were met in 98% of adults and 100% of patients < 21 years. Compared to patients < 21 years, adults at baseline had more frequent ulcerative skin lesions (11% vs. 1%; $p=0.02$) and nephrotic-range proteinuria (22% vs. 3%; $p=0.007$) but less commonly had abdominal pain (34% vs. 61%; $p<0.001$), ischemic gastrointestinal involvement (10% vs. 20%; $p=0.04$) and arthralgias (38% vs. 61%; $p<0.001$). Frequency of baseline microscopic hematuria was similar between groups (47%). 8 adults, but no patients < 21 years, presented with end-stage renal disease. Oral (80%) and topical (23%) corticosteroids were the most common initial treatments used. Conventional immunosuppressive drugs were used at diagnosis in only 12% of patients.

Dialysis was required in 13 patients (8 adults) and renal transplant was performed in 4 cases (1 adult). Of 137 patients with hematuria during the study, 72% had complete resolution of hematuria by 1 year after onset, compared to 50% of 179 patients with proteinuria. The prevalence of disease activity state at each follow-up time point is shown in figure 1. During 389 person-years of follow-up, 29 deaths were observed. Five year survival rates (95% CI) for patients aged < 21 , 21-50, and 51+ years were 100%, 94% (87, 100) and 40% (26, 63), respectively ($p<0.001$). Standardized mortality ratio for patients aged 21-50 years at diagnosis was 5.62 (0.68, 20.3) and 7.60 (5.0, 11.1) for those 51 or older.

Conclusion: IgAV in adults is associated with more severe skin and kidney involvement, poorer renal outcome and increased mortality compared to patients diagnosed before 21 years of age.

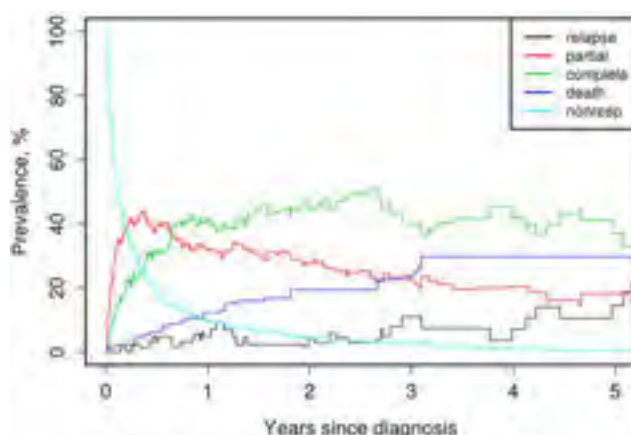


Figure 1: Prevalence of IgA vasculitis disease state at each study time point during follow-up. Overall, patients spent 40% of time in complete response during the first 5 years after diagnosis, 20% in partial response, 6% in relapses, and 8% in non-response (nonresp). At 5 years after diagnosis 30% of the cohort was deceased.

Disclosure: M. Villatoro-Villar, None; C. S. Crowson, None; K. J. Warrington, GlaxoSmithKline, 2, Eli Lilly and Co., 2, Sanofi, 5; A. Makol, None; S. R. Ytterberg, None; M. J. Koster, None.

Abstract Number: 835

Withdrawn

Abstract Number: 836

Genetic Risk Score Prediction in Ankylosing Spondylitis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: ACR Abstract: Plenary Session I

Session Type: ACR Plenary Session

Session Time: 11:00AM-12:30PM

Background/Purpose: The diagnosis of ankylosing spondylitis (AS) is delayed by on average 8–11 years after the onset of symptoms, and there is increasing evidence that early intervention in the disease can lead to better outcomes for patients. Early diagnosis of AS is challenging and the performance is still imperfect, even with magnetic resonance imaging (MRI). Whilst genetic risk scores (GRS) utilising only genomewide-significant associated SNPs capture only a small proportion of total heritability and consequently have modest discriminatory capacity, polygenic risk scores involving hundreds to many thousand SNPs capture a higher proportion of overall disease heritability and have greater discriminatory capacity and accuracy in disease-risk prediction.

Methods: In this study, we developed two polygenic GRS, one for AS based on European-descent samples (7,742 AS patients and 14,542 controls), and a second based on East Asian-descent samples (6,001 AS patients and 4,943 controls). AS was defined according to the Modified New York Criteria and all the samples were genotyped using Illumina CoreExome microarrays involving ~270,000 SNPs after quality control. The European-GRS involved 3,947 SNPs and East Asian-GRS 8,659 SNPs. Validation was performed using 10-fold cross-validation in the originator population, and also tested in Turkish (873 patients and 961 controls) and Iranian case-control cohorts (430 AS patients and 761 controls). Genetic risk scores were calculated using the adaptive MultiBLUP algorithm (Speed and Balding, Genome Res, 2014). Discriminatory capacity was tested by receiver operating characteristic analysis, and reported as area under the curve (AUC), with sensitivity and specificity reported at the best Matthews correlation coefficient.

Results: For the European GRS the AUC was 0.92 (83% sensitivity, 92% specificity), compared with 0.87 by using imputed HLA-B27 status alone ($P=2.4 \times 10^{-10}$ vs GRS). In the East Asian cohort, the AUC is 0.95 (91% sensitivity, 95%

specificity). The risk score in AS patients is significantly higher than the score in controls in both cohort ($p < 2.2 \times 10^{-15}$). Both models showed moderate discriminant capacity in other ethnics groups (European model AUC 0.85, 0.85 and 0.78 in the Turkish, Iranian and East Asian cohorts respectively; East Asian model AUC 0.84, 0.87 and 0.88 in the Turkish cohort, Iranian and European cohorts respectively).

Conclusion: Our results indicate that in AS GRS has high discriminatory capacity and could be of clinical utility in early diagnosis. Given that the AUC for MRI imaging is currently thought to be 0.90, this data suggests that genetic test scoring performs at least as well as the current gold standard imaging procedure. Given the cost of a SNP microarray is <\$US50, this test is potentially far cheaper than MRI and less expensive than traditional HLA-B27 testing.

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Abstract Number: 837

Efficacy of High-Dose Versus Standard-Dose Influenza Vaccine in Seropositive Rheumatoid Arthritis Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: ACR Abstract: Plenary Session I

Session Type: ACR Plenary Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Rheumatoid arthritis (RA) patients have 2.75 fold increased risk of influenza and influenza-related illness than age-matched healthy controls. For this reason, RA patients are a priority group for annual vaccination. Although vaccination is currently the most effective intervention against influenza and its associated complications, vaccine induced antibody responses and protection in RA are low. It is unknown if the use of a high dose vaccine (high dose trivalent inactivated influenza vaccine: HD-TIV) can improve protection over that conferred by the standard vaccine (standard dose quadrivalent inactivated influenza vaccine: SD-QIV) in RA.

Methods: We conducted a treatment-stratified, randomized, modified double-blind, active-controlled trial in adult seropositive RA patients (rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies) to assess antibody responses to either SD-QIV (15 µg of hemagglutinin (HA) per strain) or HD-TIV (60 µg of HA per strain) (NCT02936180). Subjects were recruited at a tertiary care center during the 2016–2017 (year 1) and the 2017–2018 (year 2) Northern-Hemisphere influenza seasons. They were stratified by the treatment received for 3 months prior to enrolment and during the study: DMARDs (Group 1-G1), anti-cytokine therapy (G2), anti-B-cell therapy and small molecules (G3). Seroconversion (SC) and seroprotection (SP) rates were assessed using pre- (Day 0 – D0) and post-vaccine (D28) serum hemagglutination inhibition (HI) titers. SC was defined as at least a four-fold HI antibody increase from D0. SP rate was defined as percent with HI titres $\geq 1:40$ at D28. Vaccine strains were A/HongKong/4801/2014(H3N2), B/Brisbane/60/2008 in Y1/2 with A/California/7/2009(H1N1) in Y1 and A/Michigan/45/2015(H1N1) in Y2.

Results: A total of 279 seropositive RA patients were enrolled. 140 (50.2%) received SD-QIV and 139 (49.8%) received HD-TIV. The mean age (\pm SD) was 61.0 ± 12.9 and 80% were female. According to treatment, 138 (49.5%) patients were in G1; 92 (33%) in G2 and 49 (17.6%) in G3. SP rates pre-vaccine were comparable between HD-TIV and SD-QIV groups. Overall responses to vaccination were consistently higher with the HD-TIV. SC (H3N2 22.3% vs 8.6%; B/Bris 44.6% vs 28.6%; H1N1 51.1% vs 30.0%) and SP rates (H3N2 48.5% vs 30.9%; B/Bris 60.9% vs 50.7%; H1N1 80.4% vs 73.5%) were seen in patients that received the HD-TIV compared to the SD-QIV. In logistic regression models including age, vaccine type, treatment (G1, G2 and G3); Charlson comorbidity index, and RA duration; vaccine dose and age were the only predictors of the influenza vaccine sero response. Patients that received HD-TIV were 2.8 times more likely to

H3N2 seroconvert (odds ratio 2.84; 95% confidence interval 1.38 - 5.87), 2 times more likely to B/Bris seroconvert (1.91; 1.15-3.17), and 2.3 times more likely to H1N1 seroconvert (2.33; 1.42-3.85).

Conclusion: In seropositive RA patients, the use of HD-TIV substantially improves the immune response to vaccination compared to SD-QIV. This is the first study documenting a successful intervention to enhance vaccine responses in immunocompromised hosts.

Disclosure: I. Colmegna, None; M. Useche, None; K. Rodriguez, None; M. Hudson, None; S. Bernatsky, None; H. Nedjar, None; E. Rahme, None; B. Ward, None.

Abstract Number: 838

Efficacy and Safety of Combined Immunosuppressive Therapy with High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Disease Accompanied By Anti-MDA5-Positive Dermatomyositis -a Multicenter Prospective Study –

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SESSION INFORMATION

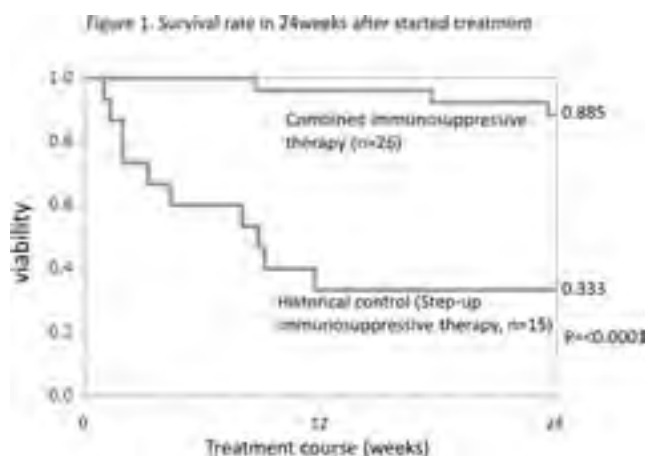
Session Date: Sunday, October 21, 2018

Session Title: ACR Abstract: Plenary Session I

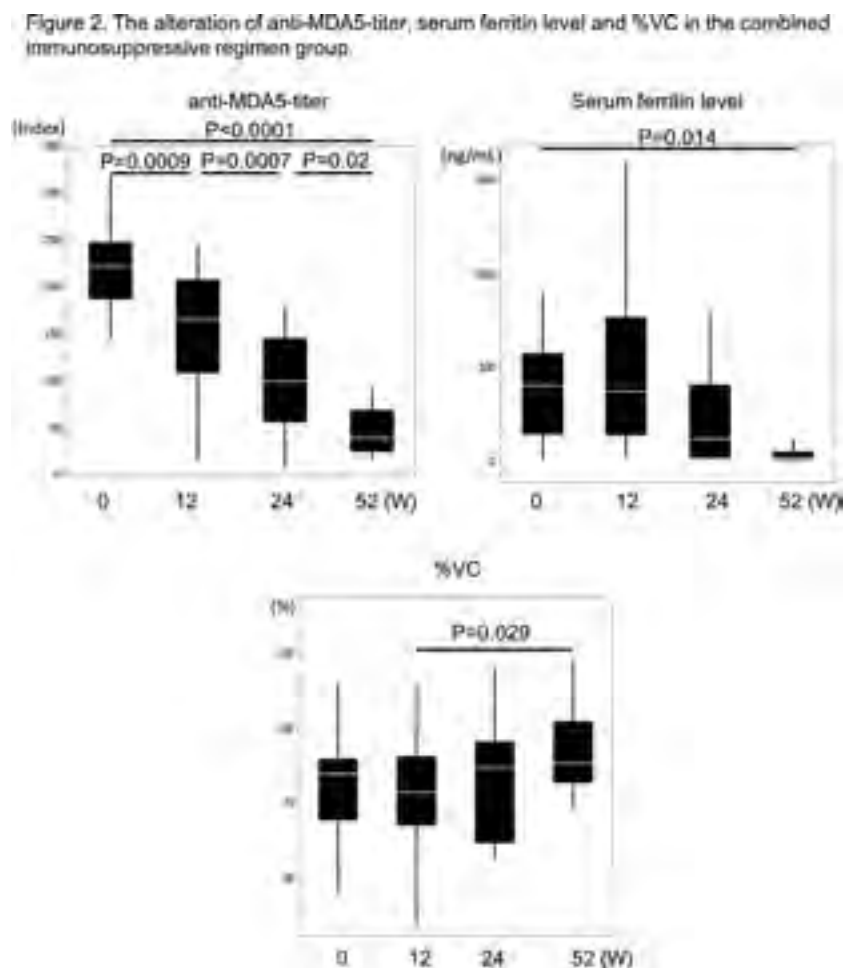
Session Type: ACR Plenary Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Interstitial lung disease (ILD) accompanied by anti-melanoma differentiation-associated gene 5 (MDA5)-positive dermatomyositis (DM) is often rapidly progressive and associated with poor life prognosis in Japanese patients. However, the standard treatment for such intractable cases had not been established, although some case reports have suggested possible efficacy of combined immunosuppressive therapy. Therefore, we evaluated the efficacy and safety of combined immunosuppressive regimen as a prospective trial for anti-MDA5-positive DM with ILD.



Methods: Anti-MDA5 was detected by protein-immunoprecipitation using ^{35}S -methionine-labeled HeLa cells. Newly onset adult Japanese anti-MDA5-positive DM patients with ILD were enrolled in multi-centers from July 2014 to September 2017. They were treated with combined immunosuppressive regimen of high-dose glucocorticoids (GC), tacrolimus, and intravenous cyclophosphamide. Plasmapheresis was also added if the patients got worse and needed oxygenation even after the regimen started. As the primary endpoint, their six-month survival was compared with a historical control of anti-MDA5-positive DM with ILD who received step-up treatment started with high-dose GC and gradually intensified by the addition of immunosuppressants. The alteration of serum ferritin level, anti-MDA5 titer (MESACUPTM anti-MDA5 test), and respiratory functions were also compared before and after treatment.



Results: The combined immunosuppressive regimen group (n=26) showed significantly better survival than the historical control (n=15) (6-month survival; 89% and 33%, respectively, $p<0.0001$) (Figure 1). At week 52, anti-MDA5-titer and serum ferritin level were decreased and %vital capacity was increased (Figure 2). During 52 weeks, cytomegalovirus reactivation was frequently observed in the combined immunosuppressive regimen group (90% vs 33%, respectively, $p=0.0002$). When the survived (18 cases) and the deceased (4 cases) in combined immunosuppressive regimen group were compared, frequency of skin ulcer (11% vs 75%, respectively, $p=0.01$), positivity of CRP (39% vs 100%, respectively, $p=0.01$), and serum ferritin level (468.3 ± 561.8 ng/mL vs 2050.3 ± 1772.8 ng/mL, respectively, $p=0.01$) before treatment were significantly higher in the deceased patients.

Conclusion: Early treatment with combination immunosuppressive therapy improves the survival of anti-MDA5-positive DM with ILD. Opportunistic infections such as cytomegalovirus reactivation should be carefully monitored and treated during the treatment.

Disclosure: H. Tsuji, None; R. Nakashima, Medical & Biological Laboratories Co., Ltd., 9; Y. Imura, None; M. Yagita, None; H. Yoshifuji, None; S. Hirata, None; T. Nojima, None; E. Sugiyama, None; K. Hatta, None; Y. Taguchi, None; M. Katayama, None; S. Akizuki, None; K. Murakami, None; M. Hashimoto, Astellas, 2, Bristol-Myers Squibb, 2, Mitsubishi-Tanabe, Chugai, Ayumi, and UCB Japan, 3; M. Tanaka, Mitsubishi-Tanabe, Chugai, AYUMI and UCB Japan, 3, Pfizer, Astellas, AbbVie GK, Taisyo Toyama, Takeda and Eisai, 9; K. Ohmura, None; T. Mimori, Acterion, Astellas, Asahi Kasei Pharma, Ayumi, Chugai, Daiichi Sankyo, Eisai, JB, Mitsubishi-Tanabe, MSD, Nippon Shinyaku, Pfizer, Sanofi, and Takeda,

Abstract Number: 839

Fibromyalgia Is Identified in Routine Care on Indices Derived from an MDHAQ (MultiDimensional Health Assessment Questionnaire) with Robust Agreement with 2011 Revised Fibromyalgia Criteria Questionnaire

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: ACR Abstract: Plenary Session I

Session Type: ACR Plenary Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Fibromyalgia (FM) generally is easily diagnosed, but maybe complex, particularly in patients who meet criteria for other rheumatic diseases. FM criteria have been revised in 2011, based entirely on a patient self-report questionnaire. However, these criteria generally are rarely used in routine clinical care because it is not feasible to use multiple patient questionnaires in busy clinical settings. An MDHAQ (multi-dimensional health assessment questionnaire) documents change in status in all rheumatic diseases in which it has been studied, and includes scales for pain, fatigue, symptom checklist, self-report painful joint count, and RAPID3 which are similar to the FM criteria questionnaire. We analyzed 5 indices based on MDHAQ scales for agreement with 2011 FM criteria in patients seen in routine clinical care.

Methods: All patients with all diagnoses complete an MDHAQ at all visits in routine care at one setting. The FM criteria questionnaire was added over a 3-month period to be completed by consecutive patients. The poly symptomatic distress (PSD) scale is derived from the FM questionnaire and indicates degree of FM symptoms. All MDHAQ scores were analyzed initially for agreement with FM Criteria questionnaire according to receiver operator characteristic (ROC) curves for area under the curve (AUC), and compiled into indices of 3 or 4 measures based on the highest results. The indices were then analyzed for AUC and cut points based on specificity and sensitivity identify to score 0 or 1 for a 0-3 index of 3 measures or 0-4 index of 4 measures, and correlations.

Results: Five different MDHAQ-FM indices were developed from the 5 MDHAQ scales with the highest AUC vs 2011. Criteria: symptom checklist, self-report painful joint count, fatigue, RAPID3, and pain scale. Three indices of 3 measures, termed MDHAQ-FM3, all included symptom checklist and self-report painful joint count; MDHAQ-FM3-P added a pain VAS, MDHAQ-FM3-F a fatigue VAS, and MDHAQ-FM3-R a RAPID3 score. Two MDHAQ-FM4 indices added fatigue VAS to symptom checklist and self-report painful joint count; MDHAQ-FM4-P included a pain VAS, MDHAQ-FM4-R RAPID3. The five different MDHAQ FM indices all agreed with the 2011 criteria with ROC AUC higher than 0.924 ($p=0.21$ for 5 indices), Correlations for 2011 criteria were all higher than 0.83 ($p<0.001$), and Agreement of the 5 indices with FM criteria was greater than 84.3% (table), these findings indicates robust capacity to identify FM similarly to the FM Criteria questionnaire.

	Contents:					Compared to 2011 FM Criteria		
	Pain VAS 0-10	Fatigue VAS 0-10	RAPID3 0-30	Symptom checklist 0-16	Self-report painful joint count 0-54	AUC for ROC Curves	Corre-lation With (PSD)	% Agreement
Cut-point for	≥6	≥6	≥16	≥16	≥16			
MDHAQ-FM3-P	+			+	+	0.924	0.832	84.3%
MDHAQ-FM3-F		+		+	+	0.937	0.854	86.6%
MDHAQ-FM3-R	+		+	+	+	0.928	0.839	84.5%
MDHAQ-FM4-P		+		+	+	0.927	0.852	85.9%
MDHAQ-FM4-R		+	+	+	+	0.932	0.849	86.9%

Conclusion: The MDHAQ identifies patients with FM similarly to the FM criteria questionnaire. Further longitudinal data will help to identify an optimal MDHAQ-FM index. Since MDHAQ also is useful in all rheumatic diseases in which it is been studied, it would appear a feasible and informative addition to routine clinical care in each patient at each visit.

Disclosure: J. Schmukler, None; J. R. Chua, None; M. Riad, None; I. Castrejón, None; T. Pincus, Medical History Services, LLC., 7, 9.

Abstract Number: 840

The CCL21/CCR7 Axis Drives Vascular, Inflammatory and Destructive Remodeling in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Cytokines and Cell Trafficking

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The synovial tissue of rheumatoid arthritis (RA) patients exhibits abundant expression of CCL21, produced excessively by RA fibroblasts and macrophages. While CCR7 mediates CCL21-driven T cell migration, we previously identified a novel angiogenic function of CCL21 in RA as well. We now reveal that in RA, macrophage expression of CCR7 is significantly increased, which further supports the importance of the CCL21/CCR7 pathway. In this study, we aim to determine the range of CCL21/CCR7 function and explore its activity on CCR7+ macrophages, contributing to the progression of inflammatory and destructive RA.

Methods: Expression of CCR7 on healthy (NL) versus RA immune cells was examined by flow cytometry and quantitative PCR. To evaluate CCL21-stimulated myeloid cell behavior, we performed monocyte chemotaxis, osteoclastogenesis assays and Western blot analysis for signaling. We also defined macrophage polarization through flow cytometry and ELISA. Intra-articular adenoviral delivery of CCL21 in mice was used to evaluate and confirm the arthritic effects of CCL21 in vivo.

Results: The percentage of double-positive CD14+CCR7+ is 2-fold higher in macrophages derived from RA compared to NL peripheral blood (NL: $19.38 \pm 2.7\%$; RA: $43.14 \pm 2.2\%$). We find that in vitro M1 polarized cells express higher levels of CCR7, which corroborates the high expression of CCR7 on macrophages isolated from RA synovial fluid. Confirming the clinical significance of CCL21/CCR7, monocyte chemotaxis induced by RA synovial fluid is considerably reduced in the presence of either anti-CCR7 or anti-CCL21 neutralizing antibody. Recombinant CCL21 stimulates RA monocyte chemotaxis dose-dependently, through CCR7 and activation of NF κ B, ERK and MAPK p38 signaling. CCL21 also affects myeloid cell differentiation and polarization. We observed an increase of M1 polarized macrophages upon CCL21 stimulation. Additionally, CCL21 ligation to CCR7 promotes osteoclast formation. Accordingly, local expression of CCL21 induces joint swelling and osteoclastic bone erosion in wild type mice, but not in CCR7-deficient mice. Histological analysis demonstrates that F4/80+ cell numbers are elevated in CCL21-treated arthritic joints. iNOS expression in the joint is increased 36-fold by CCL21. Elevated intra-articular production of M1-associated inflammatory factors confirms that local CCL21 expression promotes macrophage polarization to an M1 phenotype. We also noted that TRAP+ osteoclast numbers are 10-fold higher in CCL21 arthritic mice compared to the placebo non-arthritic group.

Conclusion: Our findings emphasize the diverse function of CCL21 and CCR7, increased even more by the pathogenic upregulation of CCR7 expression on RA macrophages. Given that CCL21/CCR7 activation potentiates RA joint inflammation, destruction and neovascularization, this pathway may be an attractive target for therapy.

Disclosure: K. Van Raemdonck, None; K. Palasiewicz, None; S. Umar, None; S. Shahrara, None.

Abstract Number: 841

TNFR2 Inactivation Reduces Psoriatic Inflammation in Mice Via Down-Regulating Dendritic Cell Expansion and Inhibiting IL-23/IL-17 Pathways

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Cytokines and Cell Trafficking

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Tumor necrosis factor- α (TNF), a potent proinflammatory cytokine, activates two receptors: TNFR1 and TNFR2. Anti-TNF biological agents neutralize TNF, thus preventing both TNFR1 and TNFR2 activation. These anti-TNF agents are used in treating inflammatory diseases including psoriasis and psoriatic arthritis. However, potentially life threatening adverse effects that include reactivation of tuberculosis and malignancies are associated with their long-term use. The adverse effects are associated with inhibition of TNFR1, not TNFR2, signaling. It is not clear whether inactivation of both TNF receptors is necessary for inhibiting psoriatic diseases. Here, we used a mouse model to identify the contributions of TNFR1 and TNFR2 in psoriasis.

Methods: We applied imiquimod (IMQ) (4 mg/day/mouse for 4 days) to 10-12-week-old wild type (WT), TNFR1 knockout (KO), and TNFR2KO mice ($n = 6$ each). Erythema, scaling, and thickness of the IMQ- or vehicle-treated area was assessed by PASI (Psoriasis Area and Severity Index). Epidermal thickness was measured using ImagePro software on H&E stained skin. We compared the psoriasis-related gene expression in the untreated vs. IMQ-treated skin using qPCR and immunohistochemistry. Fluorescence-activated cell sorting (FACS) was used to compare immune cell expansion in the lymph nodes.

Results: In WT, the cumulative score of skin inflammatory phenotype (erythema + scaling + thickness) peaked at day 5 with a cumulative score of 7.0 ± 1.3 . TNFR2 knock-out (TNFR2KO) did not show any sign of skin inflammation. TNFR1KO mice exhibited low level of inflammation with a cumulative score of 2.5 ± 0.8 . Histology revealed significant keratinocyte hyperplasia and leukocyte infiltration in the WT upon IMQ application. These inflammatory responses were significantly blunted in TNFR2KO, but not in TNFR1KO, mice. As expected, the IL-17 family of genes and genes encoding IL-22 and IL-23 are upregulated in IMQ-treated skin compared to untreated WT skin. Compared to WT mice, the IMQ induction of these genes was reduced significantly in TNFR2KO mice. Fold increases in mRNA levels upon IMQ: IL-17A (WT, 22.3 ± 4.1 vs TNFR2KO, 15.6 ± 2.3), IL-17C (WT, 31 ± 3.3 vs TNFR2KO, 11.2 ± 2.2), IL-17F (WT, 51.8 ± 3.8 vs TNFR2KO, 8.9 ± 1.7), IL-22 (WT, 33.6 ± 3.3 vs TNFR2KO, 9.4 ± 1.2) and IL-23 (WT, 101.8 ± 12.5 vs TNFR2KO, 14.2 ± 3.2). The effect of TNFR1 inactivation on IMQ induction of these genes was minimal. Importantly, our FACS analysis showed IMQ-induced CD11c⁺ and CD11b⁺ dendritic cell expansion, a critical component in T_H na \cdot ve cell to T_H17 differentiation, is inhibited in TNFR2KO, but not in TNFR1KO, mice. Immunohistochemistry studies showed reduced number of infiltrated T_H17 cells upon IMQ in TNFR2KO skin compared with WT or TNFR1KO mice.

Conclusion: Psoriatic inflammation in mice is critically dependent on TNFR2 via T_H17 cell expansion and IL-23/IL-17 induction. Selective inhibition of TNFR2 while retaining TNFR1 may block the psoriasis and psoriatic arthritis, as both share many common inflammatory pathways, and may lead to improved safety compared to the current anti-TNF therapy.

Disclosure: U. M. Chandrasekharan, None; J. Harvey, None; V. Rai, None; C. Braley, None; M. Lee, None; J. Hsieh, None; R. Jaini, None; A. Fernandez, None; P. DiCorleto, None; M. E. Husni, None.

Abstract Number: 842

Interleukin 17 Receptor D (IL-17RD) Is Regulated By Pro-Inflammatory Cytokines and Plays a Role in the Development of Collagen-Induced Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Cytokines and Cell Trafficking

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Interleukin-17 Receptor D (IL-17RD) otherwise known as similar expression of fibroblast growth factor genes (SEF) is often described as an inhibitor of multiple signaling cascades. IL-17RD is a member of the IL-17 receptor family. In contrast to the other IL-17 receptors, IL-17RA, -RB, -RC and -RE, little is known about the ligand

and function of IL-17RD. We hypothesized that IL-17RD is a brake that needs to be removed in order to develop auto-immune arthritis. However, the functional role of IL-17RD in auto-immune arthritis is still unknown and is the purpose of this study.

Methods: Human synovial fibroblasts from Rheumatoid Arthritis (RA) patients were stimulated with tumor necrosis factor α (TNF α), interleukin 1 β (IL-1 β) or IL-17A for multiple time points. IL-17RD expression levels were measured via qPCR. Collagen induced arthritis (CIA) was induced in IL-17RD knockout mice and wildtype littermates. At days 1 and 21, mice were immunized intradermally with chicken collagen type II in complete Freund's adjuvant (CFA). Mice were scored 3 times a week for clinical disease defined as swollen joints with a maximum score of 8. Due to ethical reasons, mice were removed from the experiments when they reached a score of 6. CD4⁺ memory T cells, CD8⁺ memory T cells, CD19⁺ B cells and monocytes were isolated from WT spleens and analysed for IL-17RD expression. Blood neutrophil migration assays were performed in vitro using WT and IL-17RD deficient (IL-17RD KO) mouse synovial fibroblasts.

Results: We show that IL-17RD is regulated by pro-inflammatory cytokines and plays a role in the development of collagen-induced arthritis (CIA). IL-17RD expression was decreased in human synovial fibroblasts from rheumatoid arthritis (RA) patients upon stimulation with TNF α or IL-1 β but not IL-17A. Interestingly, CIA incidence was significantly reduced in IL-17RD knockout (IL-17RD KO) mice compared to wildtype littermates (C57BL/6N) without affecting CIA severity in mice developing clinical manifest disease. Besides very low or absent IL-17RD expression in immune cells, no altered cytokine production was observed in LPS stimulated monocytes or α CD3 and α CD28 activated CD4⁺ T cells from IL-17RD KO mice versus WT controls. However, lower production of CXCL2 was detected by IL-17RD deficient synovial fibroblasts when stimulated with TNF α and IL-17A. Additionally, less neutrophils were attracted by these IL-17RD deficient synovial fibroblasts.

Conclusion: These data show the downregulation of baseline IL-17RD expression by pro-inflammatory cytokines in synovial fibroblasts and how IL-17RD deficiency reduces CIA incidence. This indicates that IL-17RD is likely a brake that is removed in an inflammatory environment but contradictorily lowers the chance of developing auto-immune arthritis.

Disclosure: M. Molendijk, None; A. Otten-Mus, None; P. Asmawidjaja, None; D. Baeten, None; E. Lubberts, None.

Abstract Number: 843

Localization of the Voltage-Gated Sodium Channel 1.7 in Peripheral Monocytes Contributes to Activation of BAFF Signaling in Monocytes of Patients with Primary Sjögren's Syndrome

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Cytokines and Cell Trafficking

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: In our previous study, we have reported that IL-6 production was robustly increased in BAFF-stimulated peripheral monocytes of patients with primary Sjögren's syndrome (pSS) and was positively and significantly correlated with the expression level of BAFF-receptor (BR3). We also found that the proportion of BR3-positive monocytes to total monocytes was positively and significantly correlated with the serum IgG level of pSS patients. In vitro analysis showed that IgG production by B cells was enhanced by co-cultured BAFF-stimulated monocytes probably through stimulation of B cells with IL-6 produced by the monocytes. These data collectively suggest that abnormal activation of monocytes is involved in the pathogenesis of pSS. It has been reported that the pathways via voltage-gated sodium channels in monocytic lineage are involved in production of inflammatory cytokines, such as IL-6 in inflammatory pain diseases. In this study, we investigated the localization and the expression level of ion channels, such as Nav1.7, a voltage-gated sodium channel, in peripheral monocytes in patients with pSS in an attempt to discriminate the disease from other autoimmune diseases, such as active RA and active SLE.

Methods: The expression level of Nav1.7 in peripheral monocytes was analyzed by FACS using whole blood samples from patients with pSS (n = 28), active RA (n = 15), active SLE (n = 37) and healthy controls (HC; n = 15). Monocytes were prepared from whole blood samples and stimulated with recombinant human soluble BAFF (sBAFF) in the presence or absence of an inhibitor against Nav1.7. The amount of IL-6 in the culture supernatants and the expression level of Nav1.7 in the cells were analyzed by ELISA and qPCR, respectively.

Results: FACS analysis revealed that the expression level of Nav1.7 in pSS monocytes was significantly higher than those of active RA ($p = 0.005$), active SLE ($p < 0.001$) and HC ($p < 0.001$). In addition, the expression level of BR3 in pSS monocytes was significantly higher than those of HC ($p = 0.048$), RA ($p = 0.037$) and SLE ($p = 0.024$). Interestingly, the expression level of Nav 1.7 in pSS monocytes was significantly and positively correlated with that of BR3 in the cells ($p = 0.02$). Moreover, a specific inhibitor against Nav 1.7 suppressed IL-6 production by sBAFF-stimulated peripheral monocytes in a dose dependent manner. In addition, qPCR analysis indicated that Nav 1.7 expression in pSS monocytes was induced upon stimulation with sBAFF.

Conclusion: Our results strongly suggest that the crosstalk between BAFF signaling and sodium channel is involved in activation of pSS monocytes and can be a therapeutic target for pSS.

Disclosure: K. Yoshimoto, None; Y. Ikeda, None; K. Suzuki, None; T. Takeuchi, None.

Abstract Number: 844

Differential Roles of $\text{TNF}\alpha$ -TNFR1 and $\text{TNF}\alpha$ -TNFR2 in the Differentiation and Function of Induced $\text{CD4}^+\text{Foxp3}^+$ Treg Cells in Autoimmune Diseases

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SESSION INFORMATION

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Session Title: Cytokines and Cell Trafficking

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Tumor Necrosis Factor (TNF) α exerts its pro-inflammatory or anti-inflammatory function. This study hypothesizes that TNF α has multi-function through binding the different receptor 1 and 2 (TNFR1 and TNFR2) and different signal pathways affect the development and function of induced regulatory T cells (Tregs) and Th cells.

Methods: iTreg and Th cells were differentiated *in vitro* and *in vivo* in the presence or absence of TNF. We also used TNFR1^{-/-} and TNFR2^{-/-} mice to investigate the requirement of TNFR1 or TNFR2 expression on these cells with differentiation, proliferation and function.

Results: TNF α facilitated iTreg differentiation and suppressive function *in vitro*. TNFR2 deficiency hampered iTreg differentiation, proliferation and function, while TNFR1 deficiency decreased the differentiation of inflammatory T cells such as Th1 and Th17 cells but maintained the regulatory capabilities of iTregs *both in vitro* and *in vivo*. Additionally, TNFR1^{-/-} iTregs expressed an increased level of TNFR2, while TNFR2^{-/-} iTregs expressed an elevated level of TNFR1. In human, Tregs from patients with multiple sclerosis (MS) and Rheumatoid Arthritis (RA) expressed an ascending level of TNFR1 but a decreased level of TNFR2.

Conclusion: TNF α may enhance the differentiation, proliferation and function of iTregs *via* TNFR2 signaling while promote Th cell *via* TNFR1. The expression of TNFR2 on Tregs might be downregulated in some autoimmune diseases, accompanied by an increased level of TNFR1. Thus, our results suggest that TNFR2 agonists or TNFR1-specific antagonists hold a potential promise for clinical application in treating patients with autoimmune diseases.

Disclosure: S. ZHENG, None; S. J. Yang, None; J. Wang, None; R. June, None.

Abstract Number: 845

New Insights in Lupus Dermatitis: Differential Regulation and Roles of Tissue-Resident Dendritic Cell Subsets in the Pathogenesis of Autoimmune Skin Inflammation

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Cytokines and Cell Trafficking

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Acquired or self antigens in tissues are taken to lymphoid organs to elicit protective immunity or tolerance, respectively. This is accomplished by dendritic cells (DC) that reside in tissues. Here, we used the skin model of tissue-resident DC to investigate mechanisms of tissue-DC migration and its role in lupus dermatitis. Skin harbors at least three subsets of DC: Langerhans cells (LC) that reside in the epidermis, langerin-expressing dermal DC that reside in the dermis (LangdDC), and langerin⁻ dermal DC. Here, we investigated the roles of skin-resident DC subsets in lupus dermatitis.

Methods: 1. To evaluate skin DC migration in lupus-prone MRL-Fas^{lpr/lpr} (MRL-lpr) and MRL-Fas^{+/+} (MRL+/+) mice and control C3H, B10.BR and B6 mice, we: a) applied fluorophores (FITC/TRITC) to the skin of mice and detected FITC/TRITC⁺ cells in the skin-draining lymph nodes to track in vivo migration of skin-resident DC; b) verified in vivo migration of skin DC at the steady state (without any external manipulation) using langerin-driven eGFP knock-in mice in the lupus and control backgrounds; c) assessed in situ migration where skin explants were floated on a culture medium containing chemokines in a culture chamber, followed by staining and counting for DC in the epidermis (for DC that have not emigrated), dermis (for DC that are migrating through lymphatics), and in culture wells (for DCs that have migrated out). 2. We treated MRL mice with glycolipid α GalCer that ameliorates lupus dermatitis and determined its effect on skin DC migration. 3. We investigated mechanisms of skin DC migration using TCR $\gamma\delta^{-/-}$ and CD40L^{-/-} mice and respective blocking antibodies. 4. We used diphtheria toxin receptor knock-in MRL mice to conditionally ablate LC and/or LangdDC, and determined the effect on lupus disease.

Results: We found a reduced migration of LC but increased trafficking of LangdDC to skin-draining lymph nodes in lupus dermatitis-prone MRL-lpr and MRL+/+ mice as compared to control mice. Such altered pattern of migration of these two skin DC subsets was corrected by α GalCer treatment. However, α GalCer did not increase LC migration through its well-known target iNKT cells but increased epidermal $\gamma\delta$ T cells that were otherwise reduced in lupus mice compared to controls. Epidermal $\gamma\delta$ T cells increased LC migration in vitro. The role of $\gamma\delta$ T cells in modulating LC migration was confirmed using knockout animals as well as blocking antibodies. CD40L deficiency or antibody blockade abrogated the ability of $\gamma\delta$ T cells to enhance LC migration. Finally, conditional ablation of LC worsened lupus dermatitis; this effect was abrogated when both LC and LangdDC were ablated together. LC depletion or α GalCer treatment did not affect kidney or lung disease.

Conclusion: The two skin DC subsets play opposite, balancing roles in the pathogenesis of lupus dermatitis: LC protect and LangdDC harm. The two skin DC are also regulated differently: LC migrate less, but LangdDC traffic more, to skin-draining lymph nodes of lupus mice that also have less epidermal $\gamma\delta$ T cells. $\gamma\delta$ T cells regulate LC migration via CD40-CD40L interaction. α GalCer that corrects these defects ameliorates dermatitis.

Disclosure: R. R. Singh, None; M. A. Gutierrez, None; P. Kim, None; D. Randhawa, None; R. Philips, None; J. K. King, None; A. Eriksson, None.

Abstract Number: 846

CD14 Deficiency Dampens Osteoclastogenesis and Alters Bone Remodeling in a Murine Model of Osteoarthritis

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SESSION INFORMATION

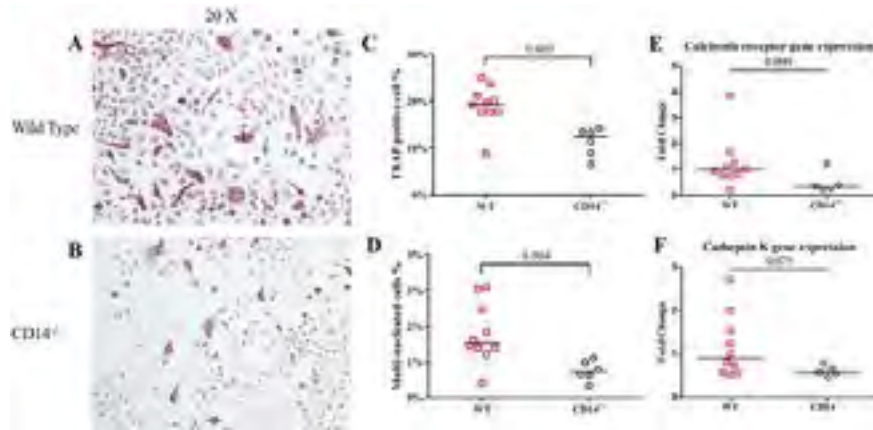
Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Pathogenesis of osteoarthritis (OA) is accompanied by chronic inflammation evidenced by macrophage infiltration into the joint. CD14 is expressed by monocyte/macrophage lineage cells, and is a co-receptor that



facilitates Toll-like receptor (TLR) signaling. Upon binding, the CD14/TLR complex can activate cytokine production and promote chronic inflammation. Given that CD14 is expressed by osteoclast precursors, and TLR signaling influence osteoclast development and activation, we hypothesized that CD14 may play a role in bone remodeling after joint injury in a murine post-traumatic knee OA model.

Methods: 10-12 week old male mice from CD14^{-/-} and congenic C57BL/6 (WT) controls were subjected to destabilization of medial meniscus (DMM), sham surgery or left un-operated. Mice were sacrificed at 6 and 19 weeks post-surgery, knees isolated, and cartilage and bone histopathology evaluated with the modified OARS score. Micro-CT was used to measure subchondral bone mineral density (BMD) and trabecular thickness (TbTh). In separate experiments, bone marrow was isolated from tibias and fibulas of WT and CD14^{-/-} mice. Non-adherent cells were isolated after 24-hour initial culture, and then media containing M-CSF (35 ng/ml) and RANKL (100 ng/ml) was added to promote osteoclast differentiation. After 8 days, TRAP⁺ (tartrate-resistant acid phosphatase) staining was assessed, and mRNA expression of calcitonin receptor and cathepsin K were measured using quantitative PCR.

Results: 6 weeks after DMM surgery cartilage histology was similar in the two strains, but at 19 weeks degeneration was significantly less in CD14^{-/-} mice compared to WT (7.125 vs 16.22, p=0.0002). Micro-CT analysis showed age-related increases in BMD and TbTh in WT mice (12.8% increase at 19 weeks compared to baseline, p=0.006) but not in CD14^{-/-} mice. CD14^{-/-} mice were also protected from surgery-related increases in BMD, which were observed in WT mice 6 week post-DMM: (7.3% increase in WT BMD vs. naive, p=0.04; 2.0% increase in CD14^{-/-} BMD DMM vs. naive, p=ns). In response to M-CSF and RANKL, cells from CD14^{-/-} mice showed less TRAP staining, reduced numbers of multi-nucleated cells, and lower expression of calcitonin receptor and cathepsin K compared to WT mice (Fig 1).

Conclusion: CD14 deficiency protects mice from subchondral bone changes after joint injury, and reduces the capacity of precursors to differentiate into osteoclasts. Bone remodeling is dependent on both bone resorption and anabolism, therefore it is possible that the defect in osteoclastogenesis in this strain is related to the ability of subchondral bone to remodel in response to age and joint injury. Additional studies are underway to confirm this. This study brings attention to pathologic bone remodeling in osteoarthritis models, and these results suggest a possible new therapeutic target to explore.

Figure 1

Disclosure: C. Zhou, None; V. Nguyen, None; R. Smalley, None; N. Sambamurthy, None; G. R. Dodge, None; C. Scanzello, None.

Abstract Number: 847

Basic Calcium Phosphate Crystals Induce Osteoarthritis-Associated Changes in Chondrocyte Phenotype through Activation of Calcium/Calmodulin Kinase 2

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Basic calcium phosphate crystals (BCP) are frequently found in osteoarthritic joints. Whether BCP crystal deposition is a cause or consequence of osteoarthritis (OA) pathology remains contentious. In OA, chondrocytes undergo a phenotype shift resulting in increased production of cartilage degrading enzymes (particularly matrix metalloproteinase 13, MMP13) and production of abnormal extracellular matrix components (eg type X collagen, COL10), disrupting cartilage integrity and leading to cartilage loss. The purpose of this study was to determine whether BCP crystals can induce the OA-associated phenotype change in chondrocytes.

Methods: Primary human chondrocytes were exposed to 50µg/ml BCP crystals (equivalent to the concentration present in synovial fluid in patients with OA) for up to 48h. Chondrocyte phenotypic marker expression (*SOX9*, *RUNX2*, *IHH*, *MMP13*, *COL10A1*) was measured by RT-qPCR, ELISA and immunocytochemistry. BCP crystal-induced signalling pathway activation was identified using western blotting, pharmacological inhibitors and RNA interference. Intracellular calcium levels were measured using the calcium-sensitive dye, Fluo4.

Results: Exposure to BCP crystals resulted in changes in chondrocyte phenotypic markers indicating cells were adopting a more OA-like phenotype. Expression of *SOX9* was lower, and *RUNX2*, *IHH* and *MMP13* higher, in BCP crystal-exposed cells compared to untreated controls. COL10 (a late-stage marker of the osteoarthritic chondrocyte phenotype) was detected at both the RNA and protein level in BCP crystal-exposed but not in untreated cells. BCP crystal exposure resulted in a rapid increase in intracellular calcium levels that was abolished by co-treatment with an antagonist preventing the release of calcium from intracellular stores. The BCP-induced increase in intracellular calcium was dependent on free Ca^{2+} in the extracellular environment and activity of the extracellular calcium sensing receptor (CaSR, a receptor for calcium first messenger signalling and activator of calcium release from intracellular stores). Exposure to BCP crystals resulted in activation of the calcium-sensitive enzyme, calcium/calmodulin kinase 2 (CaMK2) by a mechanism dependent on CaSR activity and the release of calcium from intracellular stores. Inhibition of CaMK2 activity or knockdown of either of the CaMK2 isoforms expressed by human chondrocytes (δ and γ) mitigated the ability of BCP crystals to induce OA-associated changes in chondrocyte phenotype.

Conclusion: BCP crystal exposure results in OA-like changes in chondrocyte phenotype by CaSR-mediated activation of CaMK2. Increased CaMK2 activity has been observed in osteoarthritis and is implicated in the disease-associated change in chondrocyte phenotype. Our data indicate the presence of BCP crystals within osteoarthritic joints may contribute to the increased CaMK2 activation seen in disease and may promote OA progression by inducing disease-associated changes in chondrocyte phenotype.

Disclosure: J. Rong, None; B. Pool, None; M. Zhu, None; J. Munro, None; G. M. McCarthy, None; J. Cornish, None; N. Dalbeth, Horizon, 5, Kowa, 5, Amgen Inc., 2, AstraZeneca/Ironwood, 2, AbbVie Inc., 8, Pfizer, Inc., 8, Janssen, 8; R. Poulsen, Research grants from the Health Research Council of NZ and Arthritis, NZ, 2.

Abstract Number: 848

A2A Adenosine Receptor Stimulation Switches TGF- β Signaling to Promote Chondrocyte Proliferation and Cartilage Regeneration

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: We previously found that intra-articular injections of liposomal preparations of adenosine completely prevent progression and reverse cartilage loss in post-traumatic OA. TGF- β signaling plays dual and opposing roles in cartilage health and chondrocyte life depending on the signals activated downstream. Activation of downstream signaling pathways for TGF- β leading to localization of phospho-SMAD2/3 associated with maintenance of cartilage. In contrast nuclear localization of phospho-SMAD1/5/8 results in chondrocyte hypertrophy. Here we report that intraarticular

injections of liposomal adenosine and A2AR agonist reverse OA in a different OA model and explore the role of TGF β signaling in this phenomenon.

Methods: Obesity-induced OA model: C57Bl6 mice (5-6 for each group, 12 weeks old) were fed a 60% fat diet (HFF mice) for 3 months, after which received intraarticular injections (10 μ l) of empty liposomes (LIPO) or liposomes containing the A2AR agonist CGS21680 (LIPO-CGS) or LIPO-Adenosine into the knee every 10 days for 4 injections. PTOA was induced in Sprague Dawley rats following non-surgical rupture of anterior cruciate ligament (ACL). Four weeks later rats were injected in the knee with 100ul of saline, LIPO or LIPO-CGS every 10 days (6 injections). RNA was isolated from chondrocytes in knee cartilage of rats treated as described above (3 from each group X 3 replicates) and subjected to RNAseq analysis. TC28a2 human chondrocyte cell line was used for *in vitro* experiments.

Results: LIPO-CGS and LIPO-Adenosine reversed OA in the obesity-induced OA model. Mouse knees had an OARSI score of 5.17 ± 1.84 before treatment. Treatment with LIPO-Ado and lipo-CGS decreased OA severity (OARSI score 1.33 ± 0.81 and 1.83 ± 0.98 , respectively, $p < 0.001$ vs pre-treatment). RNAseq revealed an increase in aggrecan, TGF β 2 and 3 and TGF β receptor 2 expression in chondrocytes from knees treated with LIPO-CGS. TGF- β expression was increased in deep layers of cartilage in the Lipo-CGS-treated rats and there was notable nuclear localization of phospho-SMAD2/3 in these chondrocytes. In contrast, phospho-SMAD1/5/8 was expressed in the nuclei of chondrocytes in the saline and LIPO-treated rats but not in the LIPO-CGS treated rats. Identical changes were observed in the knees of obese mice. To determine whether the effect of A2AR stimulation on TGF β signaling was direct or indirect we studied the effect of CGS21680 on nuclear phospho-SMAD expression in TC28a2 cells and found that CGS21680 increased nuclear phospho-SMAD2/3 and reduced nuclear phospho-SMAD1/5/8, as detected by immunofluorescence.

Conclusion: Administration of an A2AR agonist to established OA knees reverses OA in rats and mice and shifts TGF β signaling from ALK1/SMAD1/5/8 to ALK5/SMAD2/3 in OA chondrocytes after activation of A2AR in 2 OA animal models. These findings suggest a novel approach to the treatment of OA with the potential to reverse the changes in cartilage that characterize OA.

Disclosure: C. Corciulo, Regenosine, 1,Intellectual property, 9; C. Castro, None; S. Jacob, None; D. Fenyó, None; O. Kennedy, None; B. N. Cronstein, Cantic Biopharma, Regenosine, 1,NIH Arthritis foundation, Astrazeneca, 2,Horizon Pharmaceuticals, Regenosine, 5,Patent issued and pending, 9.

Abstract Number: 849

Constructing a Macrophage Infiltration Timeline in a Murine Model of Osteoarthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

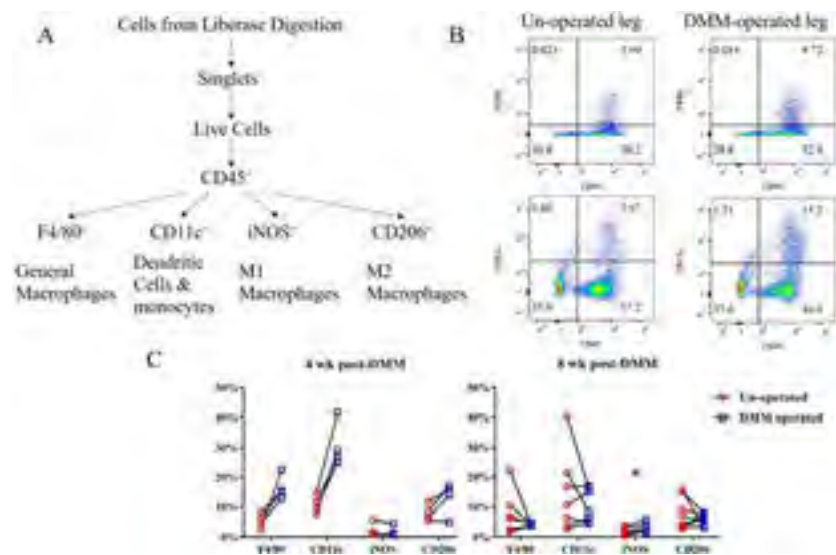
Session Title: Osteoarthritis and Joint Biology – Basic Science

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Macrophage infiltration in synovium (SM) and intra articular fat pads (FP) is common in Osteoarthritis (OA), and can contribute to catabolic cytokine and protease production as well as symptoms. However, whether macrophages are targets for therapy in OA is unclear, as macrophages can also promote tissue repair. The purpose of this study is to characterize the timeline and subtypes of macrophages in SM and FP in a commonly used murine model of post-traumatic OA.

Methods: C57BL/6 male mice (10-12 wks old) were subjected to destabilization of medial meniscus (DMM) on the right leg. For gene expression analysis, groups of mice were sacrificed pre-DMM (baseline), and post-DMM at 1, 2, 4, 8 and 16 weeks. Anterior SM and FP (combined) was dissected. Tissues were pooled from 4-5 mice per sample to obtain adequate mRNA, cDNA synthesized by routine methods, and CD68 (a pan-macrophage marker) mRNA transcript number quantified using the QX200TM Droplet Digital PCR System (BioRad). Additional mice were sacrificed 4 and 8 weeks post-surgery and SM/FP dissected for cellular analysis. Tissues from 4 knees were pooled, cells isolated enzymatically, and stained with the Live/Dead™ Fixable Violet Dead Cell Stain Kit (Invitrogen) and the following antibodies: CD45-PerCP Cy5.5, CD11c-Super Bright 645,F4/80-APC, iNOS-Alexa Fluor 488, CD206-PE. Multicolor flow cytometry was performed



and data analyzed with FlowJo software (Version 10). Gating strategy is outlined in Fig 1A, and cells were expressed as percent of the CD45+ population.

Results: CD68 mRNA level increased in DMM-operated limbs compared to preoperative levels, peaking at 4 weeks (21.61 ± 3.02 , Baseline: 2.24 ± 0.42). Levels remained significantly elevated compared to the un-operated limb up to 16 weeks (DMM: 4.77 ± 0.31 , contralateral: 0.90 ± 0.26). Percentages of F4/80+ macrophages and CD11c+ cells (expressed by murine monocytes and dendritic cells) in SM/FP were increased at 4 weeks post- DMM but not at 8 weeks (Fig 1B & C). iNOS+ cells (primarily expressed on M1 macrophages) were slightly elevated compared to the un-operated side only at 8 weeks ($p=0.02$). Percentage of CD206+ cells (expressed on M2 macrophages) were similar in DMM and un-operated knees at either 4 or 8 weeks (Fig 1C).

Conclusion: Changes in macrophage populations can be detected in SM/FP tissues after DMM surgery by both gene expression and flow cytometry. CD68 gene expression was most pronounced early at 4 weeks, and paralleled changes in F4/80+ and CD11c+ cells. Flow cytometry of M1 and M2 markers suggested a slight increase in iNOS+ (M1-type) cells at 8 weeks and CD206 at 4 weeks. Additional work is being pursued to further characterize macrophage phenotypes, and confirm gene expression seen at the chronic stage (16 weeks). These observations will be used to plan timing of interventions to better understand the pathologic roles of macrophage subtypes in OA.

Figure 1

Disclosure: C. Zhou, None; V. Nguyen, None; N. Sambamurthy, None; M. Dodge, None; C. Scanzello, None.

Abstract Number: 850

Long Term Efficacy of Cartilage Repair Induced By scSOX9 in Situ with Bone Marrow-Derived Mesenchymal Stem Cells

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Microfracture induces fibrocartilage or fibro-hyaline cartilage both are biomechanically inferior to hyaline cartilage. We reported previously that a super positively charged SOX9 (scSOX9) improved the quality of microfracture induced cartilage repair by inducing mesenchymal stem cell differentiation into chondrocytes and promoting hyaline-like cartilage. Here we examined the long-term efficacy of cartilage repair induced by microfracture with scSOX9 by assessing biomechanical property of the repaired cartilage.

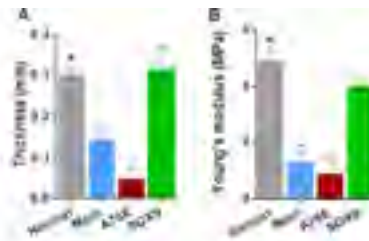


Figure 1. Mechanical property of repaired cartilage. (A) Thickness of reparative tissue in patellar groove. (B) Mechanical Young's modulus at 50 μ m indentation amplitude of representative control and treated patellar grooves. Data are presented for each region as the averaged of all control (n = 8) and all treated patellar grooves (n = 6-8). *p<0.05 and ***p<0.001 (compared with SOX9 group), # Not significant (compared with SOX9 group). Mem: collagen membrane only; A76E: scSOX9-A76E mutant; SOX9: super positively charged SOX9.

Methods: A cartilage defect was created at the right femoral trochlear groove in NewZealand female rabbits and microfracture was performed. scSOX9 was administered at the site of microfracture via a collagen membrane. Cartilage repair was assessed at 12 weeks by gross morphology, histology and matrix components. The distal femur was extirpated for biomechanical test.

Results: Cartilage defect in rabbits was treated with microfracture with collagen membrane only; with a SOX9 mutant, scSOX9-A76E or with scSOX9 respectively. Rabbits were observed for 12 weeks post-surgery. scSOX9 treated group induced hyaline-like cartilage while collagen-membrane only induced fibrocartilage and mutant scSOX9-A76E poorly induced cartilage repair. The cartilage matrix in scSOX9 treated group showed highly enriched proteoglycan content. The thickness of repaired cartilage induced by scSOX9 was comparable to that of normal cartilage in the same area. Whereas, collagen membrane only induced a thinner layer of cartilage, and scSOX9-A76E treated group showed even worse repaired tissue. In consistent with the histological data and the thickness of the repaired cartilage, the mechanical property of scSOX9 induced cartilage was also similar to that of normal cartilage (Figure1).

Conclusion: This long term *in vivo* study demonstrated that when administered at the site of microfracture, scSOX9 was able to induce reparative tissue with features of hyaline cartilage and near normal biomechanical properties. scSOX9 induced cartilage repair was enduring in long term. Together, this technology has potential to translate into clinical use for cartilage repair to prevent progression to osteoarthritis.

Disclosure: X. Zhang, None; S. Wu, VivoScript, Inc, 3; Y. Zhu, VivoScript, Inc, 3; C. Q. Chu, VivoScript, Inc, 2.

Abstract Number: 851

Integrin Mac-1 Potentiates Neutrophil Adhesion and NET Release in Antiphospholipid Syndrome

Gautam Sule¹, William J. Kelley¹, Srilakshmi Yalavarthi¹, Alison Banka¹, Andrew Vreede², Omolola Eniola-Adefeso¹ and Jason S. Knight³, ¹University of Michigan, Ann Arbor, MI, ²Rheumatology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, ³., University of Michigan, Ann Arbor, MI

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: While the role of antiphospholipid antibodies in activating endothelial cells has been extensively studied, the impact of these antibodies on the adhesive potential of leukocytes has received considerably less attention. Mac-1 is a heterodimeric beta-2 integrin primarily expressed by myeloid-lineage cells. In its activated state, Mac-1 mediates cell-cell interactions by engaging a variety of surface molecules, including the endothelium-expressed glycoprotein ICAM-1. Here, our goals were (1) to determine the extent to which APS neutrophils adhere to healthy, resting endothelial cells

under physiologic flow conditions, and (2) to identify potential therapeutic targets by elucidating the molecules required for that adhesion.

Methods: Primary APS patients (meeting Sydney criteria) and non-autoimmune controls were matched for age and gender. Freshly isolated human umbilical vein endothelial cells (HUVECs) were utilized within five passages. Samples were introduced into a flow channel via a programmable syringe pump, and perfused across a resting HUVEC monolayer. After 15 minutes of perfusion, the chamber was flushed, and the remaining adherent cells were quantified. Flow cytometry was used to identify differentially-expressed molecules on the surface of APS neutrophils. Neutrophil extracellular trap (NET) release was assessed in static neutrophil-HUVEC cultures.

Results: Pre-treating control neutrophils with APS plasma resulted in increased adhesion as compared with control plasma (>2.5-fold for n=12 plasma samples; p<0.05). This was true under both venous conditions (low shear) and conditions representative of the microvasculature (pulsatile flow and higher shear). Control neutrophils treated with APS plasma demonstrated upregulation of CD64, CEACAM-1, beta-2 glycoprotein I, and activated Mac-1 on the neutrophil surface, as well as shedding of L-selectin. Upregulation of activated Mac-1 and shedding of L-selectin were also triggered by IgG purified from APS plasma. For these changes to be meaningful clinically, we reasoned that they should be present on neutrophils in the peripheral blood of APS patients. Indeed, perfusion of anticoagulated blood through the flow chamber resulted in increased adhesion of patient neutrophils as compared with controls (>5-fold for n=18 patients; p<0.05). Similarly, patient neutrophils demonstrated upregulation of CD64, CEACAM-1, beta-2 glycoprotein I, and activated Mac-1 on the neutrophil surface. A monoclonal antibody specific for activated Mac-1 reduced the adhesion of APS neutrophils to HUVECs in the flow-chamber assay (>2-fold reduction for n=5 patients; p<0.05). Importantly, the same monoclonal antibody reduced NET release in neutrophil-HUVEC co-cultures.

Conclusion: APS neutrophils have an increased adhesive potential, which is dependent upon the activated form of Mac-1. This may lower the threshold for both neutrophil-endothelium engagement and NET release in patients, and thereby have implications for events such as venous thrombosis. Studies are underway to determine the extent to which Mac-1 is a viable therapeutic target in preclinical models of APS.

Disclosure: G. Sule, None; W. J. Kelley, None; S. Yalavarthi, None; A. Banka, None; A. Vreede, None; O. Eniola-Adefeso, None; J. S. Knight, None.

Abstract Number: 852

Antigenic Property of Prothrombin/HLA-DR Complex on Procoagulant Cells in Patients with Antiphospholipid Syndrome

Naoki Ohnishi¹, Yuichiro Fujieda¹, Ryo Hisada¹, Hiroyuki Nakamura¹, Masaru Kato¹, Kenji Oku¹, Toshiyuki Bohgaki¹, Olga Amengual¹, Shinsuke Yasuda¹, Hisashi Arase² and Tatsuya Atsumi¹, ¹Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan, ²Department of Immunochemistry, Research Institute for Microbial Disease, Osaka University, Suita, Japan

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

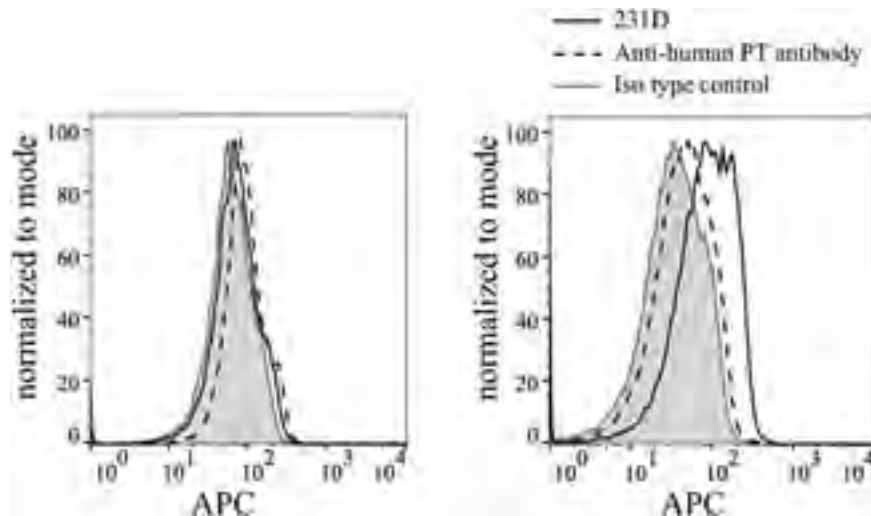
Session Title: Antiphospholipid Syndrome

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Antiphospholipid syndrome (APS) is characterized by thrombosis and/or pregnancy morbidity and the presence of antiphospholipid antibodies (aPL). Phosphatidylserine-dependent antiprothrombin antibodies (aPS/PT) recognize the phosphatidylserine/prothrombin(PS/PT) complex, and are highly associated with APS. Recently, it has been reported that misfolded beta2-glycoprotein I (beta2-GPI) are transported to the cell surface by human leukocyte antigen (HLA) class II molecules and are targeted by autoantibodies in patients with APS [1, 2]. APS patients with anti-beta2-GPI are highly likely to share the thrombophilic pathophysiology with those with aPS/PT, therefore we hypothesized that misfolded prothrombin(PT), likewise beta2-GPI, are transported to the cell surface by HLA class II molecules in procoagulant cells, consequently being targeted by aPS/PT.

Methods: 1) The interaction of PT with HLA-DR was analyzed by flow cytometry(FCM) using PT / HLA-DR overexpressed HEK293T cells. 2) PT synthesis from monocyte was investigated in phorbol-12-myristate-13-acetate (PMA) treated THP-1 cells by western blotting (WB) and FCM. 3) Cell surface transportation of synthesized PT with HLA-DR was evaluated by FCM in PMA-treated THP-1 cells.



Results: 1) PT protein in the presence of transcribed HLA-DR was detected on the cell surface and PT/HLA-DR complex was recognized by a mouse monoclonal aPS/PT (231D). 2) PMA treated THP-1 cells synthesized PT which showed stronger binding to 231D than to control monoclonal anti-PT antibody, the latter recognizes PT in the absence of phosphatidylserine (Fig). 3) 231D binding to PT/HLA-DR complex was confirmed in THP-1 cells co-stimulated with PMA and interferongamma. No binding was observed between control monoclonal anti-PT antibody and PT/HLA-DR complex.

Conclusion: Structurally altered PT is transported to the cell surface by HLA class II molecules in monocyte after PMA stimulation, indicating that PT/HLA-DR complexes may be targets for aPS/PT.

References: [1]Tanimura K,et al. Beta2-Glycoprotein I/HLA class II complexes are novel autoantigens in antiphospholipid syndrome. Blood 2015. [2] Arase N, et al. Novel autoantibody against the beta2-glycoproteinI/human leucocyte antigen-DR complex in patients with refractory cutaneousulcers. Br J Dermatol 2018
Figure. Prothrombinexpression in PMA treated THP-1 cells

Disclosure: N. Ohnishi, None; Y. Fujieda, None; R. Hisada, None; H. Nakamura, None; M. Kato, None; K. Oku, None; T. Bohgaki, None; O. Amengual, None; S. Yasuda, None; H. Arase, None; T. Atsumi, None.

Abstract Number: 853

Enhanced Type I Interferon Gene Signature in Primary Antiphospholipid Syndrome: Association with Earlier Disease Onset and Preeclampsia

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

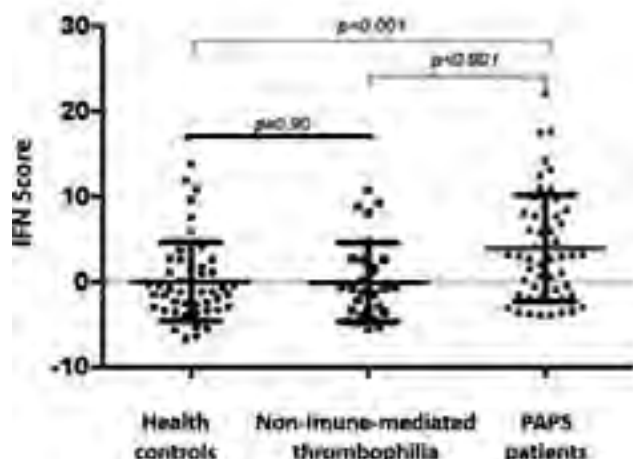
Session Title: Antiphospholipid Syndrome

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Primary antiphospholipid syndrome (PAPS) is an autoimmune vasculopathy mediated by autoantibodies with thrombosis as its main clinical manifestation. The presence of antiphospholipid antibodies, while relevant to confirm the diagnosis, does not seem to be sufficient to fully explain the pathophysiology and a second trigger is usually needed. Besides the hypotheses of viral infections and inflammatory insult as possible triggers, type II interferon (IFN) has been pointed as a possible protagonist. Recently, two studies have demonstrated that a relevant percentage of PAPS patients have an up-regulation of IFN genes in peripheral blood mononuclear cells (PBMC).However, 20% and 28%

Figure 1. Comparison of IFN-Score in PAPS patients, healthy controls and non-immune-mediated thrombophilia



of patients in these 2 cohorts, had anti-dsDNA positive antibodies, a highly specific Systemic Lupus Erythematosus (SLE) autoantibody. The aim of this study is to determine the prevalence of type I IFN signature in PBMC of patients with PAPS without specific SLE autoantibodies and search for it with clinical and laboratorial associations.

Methods: 53 PAPS patients (according to Sydney's criteria) were consecutively selected and age-matched with 50 healthy controls. A third group, with non-immune-mediated thrombophilia patients, was also included. The expression of 41 IFN induced genes was analysed using real time quantitative PCR (TaqMan Low Density Array). A principal component analysis (PCA) was used to determine which genes should compose the IFN signature and z-score was calculated. The IFN signature score cut-off was defined with a ROC curve, as the point that maximized both the specificity and sensitivity. Clinical and laboratorial features were analysed searching for associations with IFN signature.

Results: 11 IFN genes were highly expressed in primary APS patients. After PCA, 6 genes remained in the IFN signature: DNAJA1, IFIT5, IFI27, MX1, IFI6, TYK2. The type I IFN signature was present in 49% of patients with primary APS compared to 14.0% of healthy controls and 17% of non-immune-mediated thrombophilia patients ($p < 0.0001$). The mean IFN score was significantly higher in PAPS patients (4.0 fold higher, $p < 0.0001$) than in controls (**Figure 1**). A higher IFN signature was associated with a younger age at the first APS event ($p = 0.023$) and with the presence of obstetric events, especially with preeclampsia ($p = 0.032$). Treatment with statins was associated with lower levels of IFN scores ($p = 0.026$).

Conclusion: Our result indicates that PAPS patients, without lupus specific antibodies, have an enhanced type I IFN gene signature, not observed in non-immune mediated thrombophilia. We also provide novel data demonstrating that this overexpression of type I IFN-regulated genes is associated with an earlier onset of APS events and preeclampsia. Further studies are necessary to determine if this subgroup of patients will benefit of interventions targeting the type I IFN signalling pathway.

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Abstract Number: 854

First and Recurrent Thrombosis Risk after 1897 Patient-Years of Follow-up: Prospective Results from Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) Clinical Database and Repository ("Registry")

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: APS ACTION Registry was created to study the natural course of disease over 10 years in persistently antiphospholipid antibody (aPL)-positive patients with/without other systemic autoimmune diseases (SAIDx). Previously, we reported the annual recurrent and first thrombosis risk in persistently aPL-positive patients as 2.63% and 1.68%, respectively (*Arthritis Rheumatol* 2017;69:sup10).

Methods: A web-based data capture system is used to store patient demographics and aPL-related history. The inclusion criteria are positive aPL based on the laboratory section of the Updated Sapporo APS Classification Criteria, tested ≥ 2 within 1 year prior to enrollment. Patients are followed every 12 ± 3 months and receive advice on cardiovascular disease and thrombosis prevention at each visit. Based on patients who completed 1, 2, 3, 4, and 5 year follow-up visits, we report the incident thrombosis risk in persistently aPL-positive patients with/without a history of thrombosis. We also compare the characteristics of patients with/without new thrombosis.

Results: As of 5/2018, 735 patients were included: aPL/APS without SAIDx: 472 (no APS: 87; thrombotic APS [TAPS]: 272; obstetric APS [OAPS]: 51; and TAPS+OAPS: 62); and aPL/APS with SAIDx: 263 [no APS: 72; TAPS: 136; OAPS: 19; and TAPS+OAPS: 36]. Of 735 patients, 572, 473, 396, 264, and 71 completed 1, 2, 3, 4, and 5 year follow-up visits, respectively. Mean follow up was 2.6 years (1308 patient-years [pt-y]) and 2.54 years (589 pt-y) for those with and without a history of thrombosis, respectively. Based on 45 recurrent events in 36 patients, and 9 initial events since the inception of the registry (Table), the incident thrombosis risk was 2.75 and 1.53 per 100 pt-y in patients with and without history of thrombosis, respectively. Demographics, concomitant lupus diagnosis, aPL-profile, medications, and non-aPL thrombosis risk factors were not different between APS patients with (n: 36) or without (n: 376) recurrent thrombosis, and between aPL-positive patients with (n: 9) or without (n: 184) initial thrombosis except: APS patients with recurrence (vs those without recurrence), were younger (40.6 ± 13.2 vs 45.71 , p 0.04) and more likely to receive direct oral anticoagulants (3/36 [8%] vs 9/376 [2%], p 0.04) or no antiplatelet/anticoagulants (6/36 [17%] vs 15/376 [4%], p 0.001).

Conclusion: Based on approximately 2000 patient years of follow-up, the incident thrombosis risk in persistently aPL-positive patients remains relatively low (2.75 and 1.53 per 100 pt-y in patients with and without history of thrombosis, respectively) and commonly associated with LA- and/or triple aPL-positivity as well as non-aPL thrombosis risk factors and sub-therapeutic international normalized ratios. Future cox proportional analysis of APS ACTION registry will better determine the risk of thrombosis in persistently aPL-positive patients based on different risk profiles.

Table: Clinical and Laboratory Characteristics of Patients with Recurrent and Initial Events Since the Inception of AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking (APS ACTION) Clinical Database and Repository ("Registry")

N (%)	# of APS Patients with Recurrent Events n: 36	# of aPL-positive Patients with Initial Events n: 9
Mean age (registry entry) (\pm SD)	40.58 ± 13.20	38 ± 14.47
Female	27 (75%)	8 (89%)
Other Autoimmune Diseases	9 (25%)	3 (33%)
aPL Profile		
Triple aPL-positive	17 (47%)	2 (22%)
Double aPL-positive	10 (28%)	2 (22%)

Table . (Cont'd)

N (%)	# of APS Patients with Recurrent Events n: 36	# of aPL-positive Patients with Initial Events n: 9
Single aPL positive (aCL or a β ₂ GPI)	1 (3%)	3 (33%)
Single aPL positive (LA)	8 (22%)	2 (22%)
LA-positive with/without aCL/a β ₂ GPI	31 (86%)	6 (67%)
N (%)	# of Recurrent Events n: 45*	# of Initial Events n: 9
New Events		
Venous Thrombosis	23 (51%)	5 (56%)
Arterial Thrombosis	19 (42%)	3 (33%)
Microthrombosis	3 (7%)	1 (11%)
Antiplatelet & Anticoagulant Treatment		
VKA Only	21 (47%)	-
LMWH Only	6 (13%)	-
VKA + Antiplatelet Agent	5 (14%)	-
LMWH + Antiplatelet Agent	3 (9%)	-
Antiplatelet Agent only	2 (4%)	4 (44%)
None	5 (11%)	5 (56%)
Other Treatments		
Hydroxychloroquine	17 (38%)	3 (33%)
Statin	13 (29%)	1 (11%)
Direct Oral Anticoagulants	3 (9%)	-
Non-aPL Risk Factors at the Time of Events		
Sub-therapeutic INR (<2)**	19/26 (73%)	-
CVD Risk Factors***	33 (73%)	4 (44%)
Immobilization/surgery	8 (18%)	3 (33%)
Homozygous MTHFR Polymorphism	1/15 (7%)	-
Estrogen-containing OCP Use	1 (7%)	-

LA: lupus anticoagulant; **aCL:** anticardiolipin antibody; **a β ₂GPI:** anti- β 2-glycoprotein-I antibody; **VKA:** vitamin K antagonists; **LMWH:** low-molecular weight heparin; **INR:** international normalized ratio; **CVD:** cardiovascular disease; **OCP:** oral contraceptive pill. *: 2 events in 2 patients, 3 in 2 patients, and 4 in 1 patient; **: unknown in one patient, mean INR in 19 patients = 1.58; ***: **CVD Risk Factors:** Hypertension, Hyperlipidemia, Diabetes Mellitus, Obesity, Current Smoking, Family History of Early CVD, and Renal Failure

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Abstract Number: 855

IgG Antiphospholipid Antibodies, -a Common but Neglected Finding in Patients with Myocardial Infarction

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SESSION INFORMATION

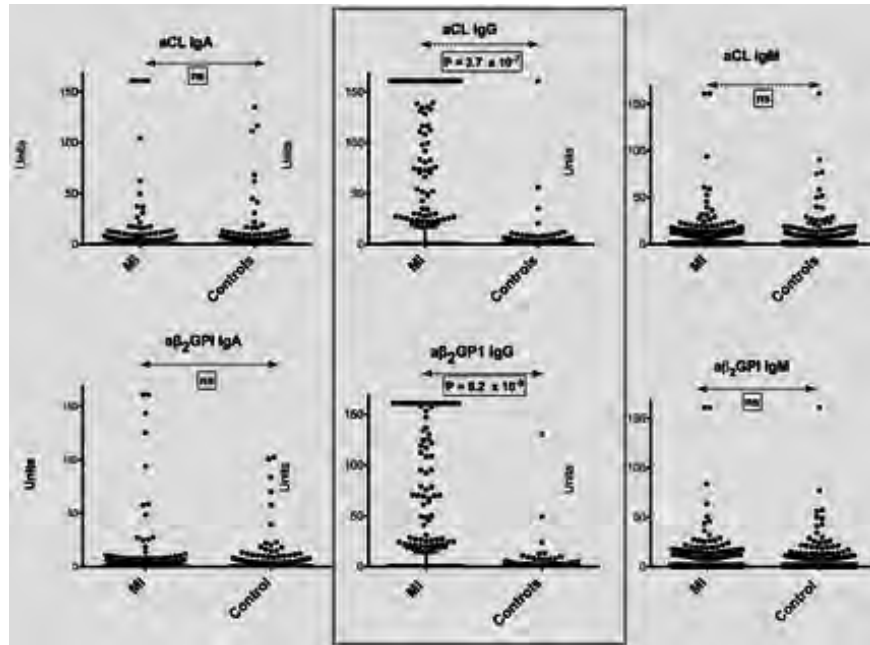
Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The antiphospholipid syndrome (APS) is present when arterial, venous or microvascular thrombosis or obstetric morbidity concur with confirmed positive tests for antiphospholipid antibodies (aPL). Long-term anticoagulation prevents new thrombotic events in most APS patients. Information on the occurrence of pro-thrombotic



aPL in myocardial infarction (MI) is conflicting due to limited size, selected populations and/or non-standardized methods in previous studies.

Methods: 805 patients (age <75years; 6-10 weeks after a first MI) and 805 age- (mean 62 ± 8 years), sex- (male 81%) and area-matched controls, free from MI, were examined. Associations between a PL positivity [anti-cardiolipin (aCL) and anti- β_2 glycoprotein-I (anti- β_2 GPI), IgG, IgM and IgA] and MI were studied by paired statistical analyses (paired Student's t-test, McNemar's test). Additionally, aPL positive MI patients and 6 APS patients, defined according to the Sydney criteria, were tested on a peptide ELISA regarding reactivity to specific domains of the β_2 GPI protein.

Results: Positivity for IgG anti-CL and IgG anti- β_2 GPI was noted in 10.9% versus 0.9% [$p < 0.0001$] and in 10.4% versus 0.9% [$p < 0.0001$] among MI patients and controls respectively, and many MI patients had high IgG titers. aPL of IgM and IgA isotypes did not differ (figure). IgG positivity for anti-CL and anti- β_2 GPI was highly correlated ($r_{\text{Spearman}} = 0.85$) and these antibodies were therefore evaluated combined as aPL IgG positivity ($n = 88$). Using this definition aPL IgG positivity remained associated with MI after adjustment for traditional cardiovascular risk factors (present smoking, hypertension, diabetes and body mass index) [adjusted OR 8.9 (95% CI: 4.6-17.3)]. Anti- β_2 GPI antibodies from MI patients usually recognized one domain of the β_2 GPI protein, while antibodies from APS patients targeted several domains.

Conclusion: In a large representative cohort of patients with a first-time MI and matched controls, we report a strong independent association between IgG aPL positivity and MI, suggesting that IgG aPL could be an important risk factor for MI in the general population. If long-term cohort studies can confirm causality for IgG aPL, our results may alter handling, treatment and outcomes for many patients with MI.

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Abstract Number: 856

Integrated mRNA and microRNA Transcriptomes of Monocytes from Antiphospholipid Syndrome Patients Identifies Molecular Networks Related to Their Atherothrombotic Status. Modulatory Effects of In Vivo Ubiquinol Supplementation

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Antiphospholipid Syndrome

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: 1. To characterize the mRNAs and microRNAs transcriptomes of monocytes, key immune cells in the atherothrombotic pathology of Antiphospholipid Syndrome patients (APS). 2. To evaluate the role of antiphospholipid antibodies (aPL) in the regulation of these processes. 3. To investigate the short-term effects of *in vivo* ubiquinol (reduced coenzyme Q10 [Qred]) supplementation.

Methods: Monocytes from peripheral blood of 30 APS patients and 30 healthy donors were purified by negative immunomagnetic selection. Then, gene expression microarray (Agilent G4112F platform) and nCounter microRNA expression arrays (Nanostring) were performed. Functional categorization of altered genes and miRNAs was made using IPA software, and interaction networks were identified. Genes and miRNAs integrating the networks were validated in the whole APS cohort, as well as on a set of thrombotic non-autoimmune patients. Predicted miRNA-mRNA interactions were tested by microRNA over-expression experiments. The short-term effects of *in vivo* Qred supplementation on the monocyte transcriptomes profiles were further analyzed.

Results: Microarray identified 518 altered genes in APS monocytes. Relevant biofunctions on which these genes were involved included hematological and cardiovascular system development and function, inflammatory response, and embryonic development, among others. Gene alterations were validated in the whole cohort, demonstrated to be stable along the time, divergent of the gene profile in monocytes from non-autoimmune thrombotic patients, and associated to clinical parameters, including thrombotic recurrences and early atherosclerosis. Analysis of miRNA profiles showed altered expression of 22 miRNAs in APS monocytes. Fifty-four genes were inversely correlated and predicted as CVD-related target genes of 19 differentially expressed miRNAs. Association of these genes and miRNAs with the occurrence and type of thrombotic events, obstetric complications and presence of atheroma plaques were demonstrated. Transfection studies further confirmed the relationship between specific miRNAs and their identified target genes. *In vitro* studies demonstrated the specific modulation of several genes/miRNAs by aPLs. *In vivo* Qred supplementation of APS patients reversed the monocytes' altered gene/miRNA profiles.

Conclusion: 1. Gene and microRNA expression profiles allowed the identification of relevant genes and pathways altered in monocytes of APS patients, associated with the pathogenesis of the disease and modulated, at least partially, by aPLs. 2. Specific microRNA-miRNA regulatory networks control the biological processes and factors related to the CV pathology in APS and are modified by *in vivo* Qred supplementation.

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Disclosure: C. Perez-Sanchez, None; L. Pérez Sánchez, None; A. M. Patiño-Trives, None; M. Luque Tevar, None; L. Scudeler, None; A. Ibáñez-Costa, None; P. Ruiz-Limon, None; Y. Jiménez-Gómez, None; I. Arias de la Rosa, None; M. C. Abalos-Aguilera, None; P. Segui, None; N. Barbarroja, None; J. M. Villalba, None; E. Collantes Estevez, None; M. J. Cuadrado, None; M. A. Aguirre Zamorano, None; C. Lopez-Pedrerá, None.

Abstract Number: 857

An Interactive Rheumatology Curriculum for Interprofessional Teams Using a Novel Mobile App

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education

Figure 1: Students' Impressions of the Interprofessional Rheumatology Curriculum



Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: The demand for rheumatologic care far exceeds the current supply of rheumatology providers, and this gap is expected to increase. Early exposure to rheumatology cases is an important way to inspire interest in our specialty among trainees in various health professions. The ability to work effectively in interprofessional (IP) teams is a critical skill for the next generation of rheumatology providers. We created a novel curriculum that A) provides health professions students with early exposure to illustrative rheumatology cases using an innovative patient simulation app, and B) allows students to practice collaborating in IP teams.

Methods: In this pilot curriculum, 16 medical students and 16 pharmacy students collaborated in pairs over the course of 2 weeks on a virtual patient case of a young woman with lupus. The case was presented using PIVOT (Practice Improvement using Virtual Online Training) – an interactive mobile app that allows students to review case content (i.e. videos of the patient interview, radiographic images, and lab results), refine their clinical reasoning skills (with tools such as the differential diagnosis slider which allows students to rank diagnoses in order of likelihood), and communicate with their teammate via mobile chat to formulate several IP collaborative care plans. The plans were graded for accuracy and completeness, and students were able to review expert plans written by faculty rheumatologists and pharmacists. At the end of the case, students completed a feedback survey that included both quantitative (Likert scale) and qualitative (open-text) assessment of the curriculum. We calculated descriptive statistics for the Likert scale data, and performed structured thematic analysis of the open-text data to identify common themes.

Results: All 16 interprofessional teams successfully completed the case and submitted 3 collaborative care plans. All 32 students completed the post-curriculum survey, and Likert scale scores are summarized in Figure 1. Thematic analysis of the open-text questions revealed that students particularly valued 1) the opportunity to learn from their medical/pharmacy teammate's unique approach to the case, 2) the team chat platform which allowed them to communicate with their teammate in real time, and 3) the opportunity to learn from faculty expert care plans.

Conclusion: We successfully developed a novel IP rheumatology curriculum for medical and pharmacy students using PIVOT, an interactive mobile application. The curriculum was well-received by the students, who reported that it improved their understanding of lupus as well as their ability to communicate effectively in IP teams. Based on the success of this pilot, we plan to utilize the PIVOT platform to develop additional rheumatology cases and to involve more health professional trainees, including nursing and physical therapy students.

Disclosure: J. Mandal, None; M. Dall'Era, None; S. Andreatta, None; L. Floren, None.

Abstract Number: 858

Measuring Cognitive Load during Arthrocentesis Training: Our Initial Experience

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Cognitive load theory is increasingly recognized as a meaningful construct in medical education and considers learning to be limited by availability of working memory. Demands on working memory are defined as cognitive load (CL), which is characterized as *intrinsic* (IL—related to the inherent difficulty of the task), *extrinsic* (EL—factors unrelated to the task), and *germane* (GL—deliberate cognitive processes used to acquire skills). Optimal learning conditions limit IL and EL, and increase GL. The Cognitive Load Inventory for Colonoscopy (CLIC) was developed as a tool to measure CL during procedural training in colonoscopy. The purpose of this study was to examine the initial experience with an adaptation of the CLIC to measure CL during arthrocentesis training.

Methods: From 2016 to 2018, 149 learners participated in a previously validated knee injection objective structured clinical examination (OSCE) during the MSK Education Week at the Salt Lake City VA. Immediately after the OSCE participants completed the CLIC adapted for arthrocentesis (Fig 1). 131 participants (3 fellows, 80 residents, 48 students) completed all activities and were used for data analysis. We used chi-squared analysis to compare CL to OSCE results. Only one question for EL (E5) was analyzed as other questions had no variance. We used unpaired T-test to compare different domains of cognitive load across fellows, residents and students.

Results: High IL (IL4) was associated with worse OSCE score ($p=0.04$). There was no association between internal distraction (E5) and OSCE score. High GL for no touch technique (G3) was associated with better scores for skin sterileprep ($p=0.01$) and sterility of procedure ($p=0.04$). High GL in controlling supplies (G4) was associated with better needle technique ($p=0.04$). Residents compared to fellows had significantly lower GL for controlling supplies (1.7 vs 2.9,

Figure 1. Cognitive Load Questionnaire

Intrinsic Load (IL)

1. How difficult was it to appropriately position the patient and manage their level of comfort?
2. How difficult was it to identify the relevant anatomy and landmarks?
3. How difficult was it to physically manipulate and control the needle and syringe?
4. Overall, how difficult was the procedure? (global)

Extrinsic Load (EL)

Effectiveness of teacher

1. How clear were your preceptor's instructions?
2. How effective was the manner in which my supervisor provided instructions or teaching?

External/Internal Distractions

3. How distracted did you feel by other people present in the room?
4. How distracted did you feel by the environment (ie, my pager going off, environmental noise, layout of the room)
5. How distracted did you feel by things on your mind unrelated to the procedure?

Germane Load (GL)

Preparation for procedure

1. How much mental effort did you invest learning how to position the patient and manage their level of comfort?
2. How much mental effort did you invest learning how to identify the relevant landmarks?

Performance of procedure

3. How much mental effort did you invest learning how to adequately disinfect the injection site and maintain the no-touch technique?
4. How much mental effort did you invest learning how to control or manipulate the needles and other supplies in this procedure?

Global

5. Overall, how much mental effort did you invest learning during this procedure?

Global (Glob)

During the procedure you've just completed, to what extent was your mind occupied by the following three activities?

1. The overall difficulty of the procedure? – I
2. Thoughts or distractions not essential to performing this procedure? – E
3. My efforts to understand learn knee aspiration/injection technique? – G

p=0.03) and significantly higher perception of global IL (2.3 vs 1.3, p=0.046), but not global EL or GL. There was no significant difference between residents and students in any domain.

Conclusion: We have adapted a previously validated tool to measure CL during arthrocentesis training. High IL was associated with worse performance and high GL with better performance on the OSCE which is consistent with cognitive load theory. IL and EL were likely lower than in the clinic as the OSCE took place directly following didactics and distractions were more limited than in a clinical setting. We would like to measure CL in the clinic setting to understand barriers to learning arthrocentesis.

Disclosure: E. Jaffe, None; A. Barker, None; M. J. Battistone, ABIM Rheumatology Exam Committee, 9.

Abstract Number: 859

Using Online Simulation of Pediatric Musculoskeletal Cases to Evaluate How Knowledge of Costs Affects Diagnostic Workup

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: With rapid rise in healthcare costs, there is increased emphasis to teach cost-conscious care in graduate medical education. Our objective was to develop online cases to teach high-value care and diagnostic evaluation of musculoskeletal (MSK) complaints to pediatric residents and rotating medical students.

Methods: Six online cases of common pediatric MSK complaints were developed utilizing a branched storyboard approach. Access and instructions on using the online modules were distributed during two scheduled lunchtime teaching conferences at University Hospitals Cleveland Medical Center.

Learners completed the modules in either one of two groups, those who saw the itemized costs of diagnostic tests and those who did not, to determine whether displaying costs would affect decision-making behavior and ability to arrive at a correct diagnosis. All learners completed a post-simulation survey. Measured outcomes included presumed diagnosis, cost of evaluation, diagnostic testing utilized, and perceptions towards the learning platform and high-value care. Simulation outcomes were assessed using paired t-tests. Survey data between the two groups were analyzed with Chi-squared tests. Outcomes separated by training year were analyzed using ANOVA and a post-hoc Tukey test.

Results: A total of 39 residents and medical students participated in the pilot and completed the survey. Learners were randomly assigned to complete the simulated cases with costs (n=19) or no costs (n=20) displayed next to orderable tests during the diagnostic workup. Overall, learners who were able to see costs of diagnosis spent less money on diagnostics (\$1511.11 mean per learner versus \$2311.35, p = 0.01). Arrival at the correct diagnosis was associated with lower costs in 3 of 6 cases (Table 1). When compared to the no cost group, learners in the group that had access to costs reported feeling more knowledgeable about the price of diagnostic tests post-simulation (p=0.04) and were more likely to factor costs into

Table 1: Costs vs. Correctness

Case	Correct diagnosis	Mean cost of work up	95% CI	Incorrect diagnosis	Mean cost of work up	95% CI	P-value
Rheumatic fever	17/39	\$701.29	\$559.13-\$843.46	22/39	\$599.55	\$404.45-\$794.64	0.30
Lyme arthritis	10/39	\$294.93	\$197.29-\$372.58	9/39	\$528.00	\$276.62-\$779.37	0.01*
Transient synovitis	24/39	\$237.83	\$134.22-\$341.44	15/39	\$520.80	\$311.82-\$727.77	<0.01*
Osgood-Schlatter	35/39	\$112.97	\$88.15-\$137.79	4/39	\$210.00	\$458.11-\$878.31	0.10
Anterior longitudinal ligament	33/39	\$410.33	\$250.60-\$560.01	6/39	\$277.33	\$133.98-\$468.68	0.75
Benign growth pain	36/39	\$66.72	\$36.66-\$96.79	3/39	\$201.67	\$14.28-\$389.06	0.01*

their practice moving forward ($p=0.03$). Third year residents demonstrated a statistically significant increase in number of cases diagnosed correctly as opposed to medical students.

Conclusion: Our data showed that those who made incorrect diagnoses often spent more money, stressing the need for proper clinical training to prevent wasted healthcare costs. Overall, learners expressed preference for using online cases as a learning tool and recognized high-value care as an important component of patient care after completion of the simulation. This suggests that simple interventions that challenge learners to integrate costs into decision-making can be the basis for changing future practice.

Disclosure: A. Yip, None; S. Morris, None; M. Buchner, None; A. Robinson, None.

Abstract Number: 860

Efficacy of a Web-Based Module to Educate Internal Medicine Housestaff on Gout

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Gout is a leading form of inflammatory arthritis. There is a paucity of data that examines the efficacy of teaching internal medicine (IM) residency trainees about the diagnosis and management of gout.

Methods: The Johns Hopkins Physician Education & Assessment Center was established to deliver an internet-based curriculum in Ambulatory Medicine to subscribing internal medicine residency training programs. A didactic module on the diagnosis and management of gout, including clinical manifestations, epidemiology, risk factors, pathophysiology and therapeutic approaches to gout care was added to the curriculum in 2017. This module included a pre-test and post-test, both consisting of 10 multiple-choice questions. We examined baseline (pre-test) and post-test scores after completing the gout module according to postgraduate year (PGY) of training, program size, and month of year the module was completed, for participating trainees in 2017 and 2018.

Results: A total of 3,612 trainees (PGY1 1334; PGY2 1273; PGY3 1005) at 148 IM residencies completed the gout module. Overall, mean score on the pre-test exam was 71% compared to 88% on the post-test exam ($p<0.001$). Aggregate pre-test scores did not differ, meaningfully or statistically, by PGY year. Further, scores were higher at the start of the academic year (i.e., July, August) than at its conclusion (i.e., April, May). While baseline knowledge of diagnosis and management of gout was not different between PGY1 and PGY3 trainees, PGY1 residents had higher baseline knowledge on the pathophysiology/epidemiology content area; mean PGY1 score was higher than the PGY3 score, at 53% compared to 50% ($p<0.05$), respectively. Both groups improved to a mean score of 85% on the post-test exam. Further, the figure

Table. Mean (SD) pre-test and post-test scores by content area according to PGY status.

	PGY-1	PGY-2	PGY3
Pre-test			
Pathophysiology/Epidemiology	53.0 (29.4)	51.1 (29.6)	50.1 (29.4)*
Clinical	72.7 (23.5)	71.4 (23.2)	73.1 (24.0)
Treatment	80.2 (25.3)	79.7 (26.9)	80.8 (28.2)
Post-test			
Pathophysiology/Epidemiology	84.9 (18.6)	84.8 (19.4)	84.9 (19.7)
Clinical	90.2 (18.7)	90.4 (18.6)	89.6 (18.8)
Treatment	89.5 (20.1)	91.3 (17.7)*	91.7 (18.3)**

* $p<0.05$ compared to PGY-1 as reference group

** $p<0.01$ compared to PGY-1 as reference group

and table below, demonstrate the ability of all trainees, regardless of PGY status, to increase their knowledge score after module completion, overall and in each content area.

Conclusion: This web-based gout curriculum is effective at increasing subject knowledge for all trainees, overall and by content-specific areas. Yet, inasmuch as baseline knowledge of gout was not higher at each successive year of training, this suggests a lack of effective training on the diagnosis and management of gout during IM residency training. Further, enrollment in the gout module earlier, rather than later, in residency training may enable earlier acquisition of gout knowledge, and improved patient outcomes in gout-related care.

Disclosure: A. C. Gelber, None; O. Tang, None; U. Haque, None; A. Bertram, None; S. Sisson, Johns Hopkins PEAC, 7.

Abstract Number: 861

Critical Appraisal Self-Efficacy and Learning Behavior in Rheumatology Trainees

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Critical appraisal self-efficacy, defined as confidence in one's ability to appraise the clinical literature, may impact trainees' ability to optimally use and incorporate literature in practice. Self-efficacy has been shown to influence behavior to engage in subsequent related tasks.¹ Little is known about critical appraisal self-efficacy in rheumatology trainees or how it relates to learning behaviors.

Methods: All ACGME-accredited rheumatology training programs were invited to enroll trainees in an online learning tool for epidemiology and biostatistics (epi/biostats): Hospital for Special Surgery Critical Literature Assessment Skill Support – Rheumatology (HSS CLASS-Rheum). Once enrolled, trainees completed a Baseline Questionnaire in order to access 10 educational modules. The Baseline Questionnaire included the 6 items most relevant to critical appraisal self-efficacy from the validated 92-item Clinical Research Appraisal Inventory (CRAI),¹ as well as 5 other critical appraisal self-efficacy items developed internally. Items ranged from 0 (no confidence) to 10 (total confidence). Analyses were performed with t-tests, Pearson correlations, and Cronbach's alpha.

Results: 33/150 programs enrolled in HSS CLASS-Rheum, and 118/125 trainees (94%) completed the Baseline Questionnaire: 63.6% female; 54.2% Caucasian, 31.4% Asian, 4.2% African American; 8.5% Hispanic/ Latino; 47.5% in 1st year of fellowship, 42.4% 2nd year; 55% had prior courses in epi/biostats.

The mean score of the 6 items from the CRAI was 4.28 (range 0.5-8.17; 10 highest possible score). These 6 items demonstrated internal consistency (Cronbach's alpha 0.95) and a strong correlation with our internally developed critical appraisal self-efficacy items ($r=0.84$; $p<0.001$). Trainees had significantly lower scores on the 6 CRAI items if they had no previous coursework in epi/biostats (3.6 vs. 4.8; $p<0.001$), rated their understanding of epi/biostats lower than their peers (3.3 vs. 4.9; $p<0.001$), reported being less likely to refer to studies to answer clinical questions (3.8 vs. 4.8; $p=0.002$), or were planning to enter private practice (3.9 vs. 4.6; $p=0.04$). Trainees who went on to complete at least 1 of the HSS CLASS-Rheum modules had higher baseline scores on these 6 CRAI items (4.5 vs. 3.6; $p=0.02$).

Conclusion: These data suggest that the 6 CRAI items may serve as a useful measure of critical appraisal self-efficacy in rheumatology trainees. Higher scores on these 6 items were associated with prior training in epi/biostats, better self-reported understanding of epi/biostats, as well as with positive learning behaviors including self-reported utilization of the medical literature and objective use of the HSS CLASS-Rheum learning tool. Prospective studies are needed to validate these items as a measure of critical appraisal self-efficacy, evaluate the effect of educational interventions on critical appraisal self-efficacy, and measure the impact of improved critical appraisal self-efficacy on learning behaviors.

References:

1. Mullikin EA, Bakken LL, Betz NE. Assessing research self-efficacy in physician-scientists: the clinical research appraisal inventory. *Journal of Career Assessment* 2007; 15:367-87.

Disclosure: J. Aizer, None; M. D. Tiongson, None; J. Schell, None; J. R. Berman, None; S. A. Paget, Medscape, 5; L. A. Mandl, None.

Abstract Number: 862

Addressing the Pediatric Rheumatology Workforce Shortage: Results from the American College of Rheumatology Annual Pediatric Residents Program

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Education

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The recent ACR Workforce Survey has projected that the current workforce shortage in pediatric rheumatology will worsen in the coming decades. Contributing to this shortage is lack of exposure to pediatric rheumatology in medical school and residency. In 2001, the American College of Rheumatology (ACR) established the annual Pediatric Rheumatology Residents Program to address this workforce shortage. This program introduces pediatrics and internal medicine-pediatrics residents to subspecialty rheumatology training by providing an opportunity for the residents to attend the ACR/Association of Rheumatology Health Professional (ARHP) annual meeting. The program focuses on residents who have an interest in pediatric rheumatology but are undecided about a subspecialty. The residents are paired with a pediatric rheumatology faculty mentor, attend special interactive sessions such as fellow/faculty panels and guided poster tours, and are recommended to attend pediatric rheumatology-specific sessions at the annual meeting. The goal of the program is to encourage residents to pursue pediatric rheumatology fellowship training. We were interested in learning how successful this program was at achieving its stated goals.

Methods: We reviewed data collected from resident applications and annual post-meeting electronic surveys for all program years to determine the number of residents who went on to pediatric rheumatology fellowship training. We also looked at how important individual sessions were to the residents' career decision-making.

Results: The inaugural program included 22 pediatric residents, 8 of whom pursued pediatric rheumatology fellowship training (36%). Over the subsequent 17 years, the program has sponsored 21-26 pediatric residents per year. The percentage of residents who pursued pediatric rheumatology training is shown in Figure 1 and varied between 13-73%.

End of program evaluations resident response rates were >95%. On program evaluations, residents noted that the faculty and fellow interactions were important and >90% of residents reported that faculty mentoring at the sessions was important in making decisions about the specialty.

Conclusion: The ACR Pediatric Rheumatology Residents Program has been successful in recruiting previously undecided residents to pursue fellowship training by providing opportunities for the residents to interact with pediatric rheumatologists and gain exposure to clinical and research sessions at the annual ACR/ARHP meetings. Continuation of this program is vital to address the deepening workforce shortage in pediatric rheumatology.

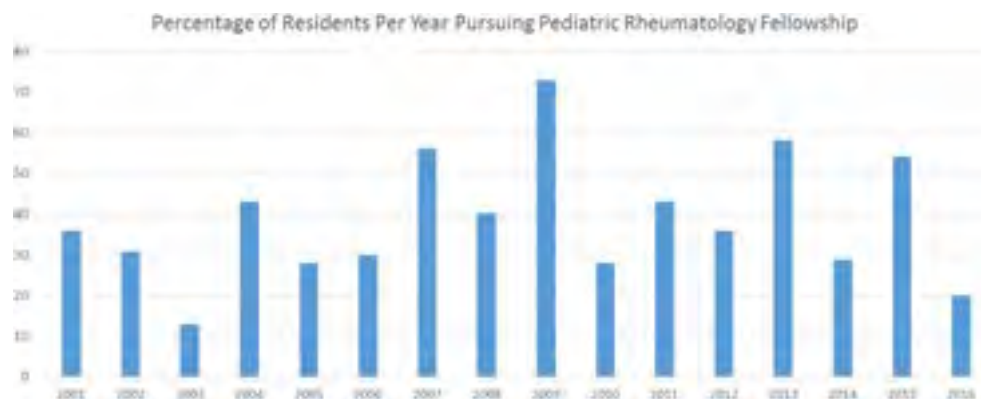


Figure 1

Disclosure: S. Sule, None; J. Mehta, None; N. Bitencourt, None; A. Cooper, Swedish Orphan Biovitrum, 9; J. Cooper, None; C. Figueroa, None; L. Hiraki, None; N. M. Ruth, None; M. Twilt, None; J. M. Anderson, None; S. P. Ardoin, None.

Abstract Number: 863

Combining Cardiac Magnetic Resonance and Right Heart Catheterization to Evaluate Right Ventricular Function for the Prognosis Prediction in Patients with Connective Tissue Diseases and Pulmonary Hypertension

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

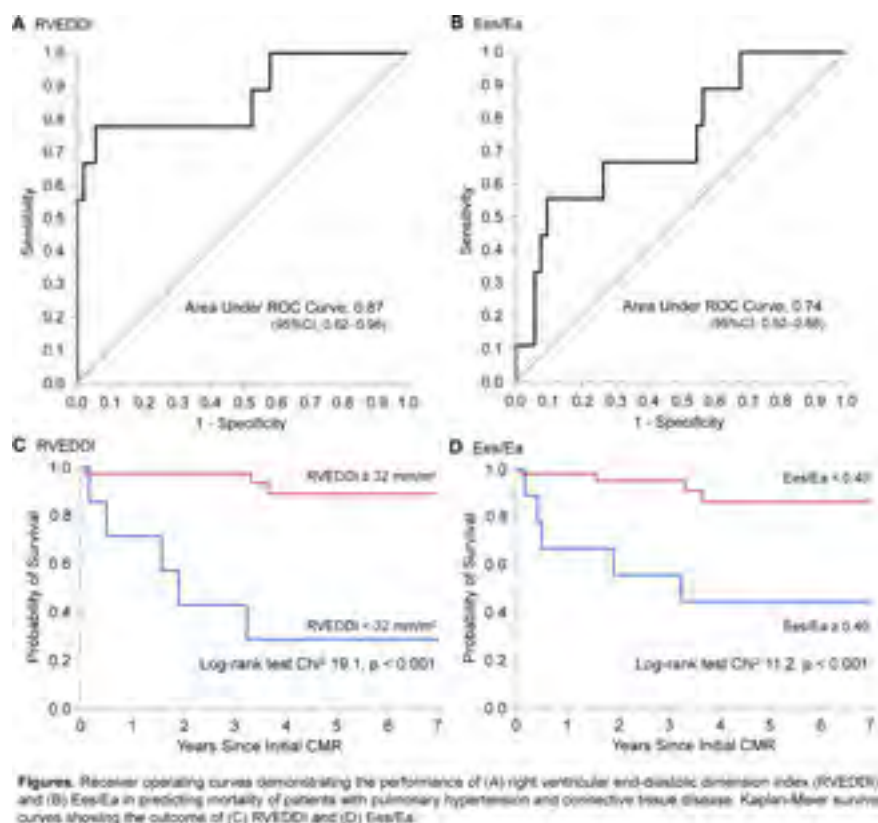
Session Title: Imaging of Rheumatic Diseases I: MRI and CT

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Pulmonary arterial hypertension associated with connective tissue diseases(CTD-PAH), particularly PAH associated with systemic sclerosis (SSc-PAH), has a poor prognosis compared with other PAH. The pathogenesis of CTD-PAH is complex, comprising not only pulmonary arteriopathy but also venous and interstitial involvements. In addition, recent studies have shown that right ventricular(RV) dysfunction is more pronounced in CTD-PAH than in other PAH despite similar or even lower pulmonary arterial (PA) pressure in CTD-PAH patients. The present study aimed to precisely evaluate RV function, including RV-PA coupling by combining cardiac magnetic resonance (CMR) and right heart catheterization(RHC) and to analyze its prognostic value in CTD patients with pulmonary hypertension (PH).

Methods: This is a single center retrospective analysis comprising 84 CTD patients, including SSc, systemic lupus erythematosus, and mixed connective tissue disease, who underwent both CMR and RHC from January 2008 to March 2018. End-systolic elastance (Ees, mPAP/RV end-systolic volume index), pulmonary arterial elastance [Ea, (mPAP-PAWP)/SV index], and Ees/Ea were calculated as load-independent parameters of RV systolic function, RV afterload, and RV-PA coupling metrics, respectively. The prognostic value of each parameter was evaluated by area under the ROC curves (AUCs) and Kaplan-Meier curves.



Results: Of 84 patients, 54 had PAH, 11 had non-PAH PH due to left heart disease, severe interstitial lung disease (ILD) and venous thromboembolic disease, and 19 did not have PH. Nine patients deceased during a median follow-up period of 25 months. In patients with PH (n=65), RV end-diastolic dimension (RVEDDI) and Ees/Ea strongly predicted the mortality with AUC of 0.87 and 0.74, respectively (Figure A and B). The 2-year overall survival rate was significantly lower in patients with either RVEDDI of >32 mm/m² or Ees/Ea of <0.40 compared with other patients (62% vs 98%, $p<0.001$) (Figure C and D). Notably, 2-year survival of patients with both RVEDDI of >32 mm/m² and Ees/Ea of <0.40 was only 20%. In multivariate Cox proportional hazards regression analyses using propensity score to control confounding factors including age, sex, PAH, SSc, and ILD, RVEDDI still significantly predicted the mortality (hazards ratio 11.1, 95% confidence interval 1.82-70.6). In SSc-PAH patients (n=24), compared with other CTD-PAH patients, RVEDDI was significantly higher ($p=0.004$), and Ees was significantly lower ($p=0.013$), indicating RV impairment in systolic function as well as diastolic function.

Conclusion: RV dimension and RV-PA coupling, which can be evaluated by combining CMR and RHC, strongly predicted the prognosis of CTD patients with PH. More pronounced impairment of these parameters observed in SSc-PAH patients is consistent with the less favorable outcome of those patients.

Disclosure: N. Abe, None; M. Kato, None; H. Nakamura, None; A. Noguchi, None; Y. Fujieda, None; K. Oku, None; T. Bohgaki, None; O. Amengual, None; S. Yasuda, None; T. Atsumi, None.

Abstract Number: 864

The Diagnostic Utility of the Relation between MRI Bone Marrow Edema and Other Types of MRI Lesions in the Sacroiliac Joints in Axial Spondyloarthritis

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Copenhagen, Rigshospitalet, Copenhagen, Denmark, ⁸King Christian 10th Hospital for Rheumatic Diseases, University of Southern Denmark, Institute of Regional Health Research, Graasten, Denmark, ⁹Dept. of Clinical Biochemistry, Rigshospitalet, University of Copenhagen, Glostrup, Glostrup, Denmark, ¹⁰Copenhagen Center for Arthritis Research, Dept. of Rheumatology, Rigshospitalet, University of Copenhagen, Glostrup, Glostrup, Denmark

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Imaging of Rheumatic Diseases I: MRI and CT

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: MRI detected bone marrow edema (BME) plays a central role in the ASAS (Assessment of Spondyloarthritis International Society) classification criteria for axial spondyloarthritis (axSpA). However, several studies have shown that BME in the sacroiliac joints (SIJs) is also present in other conditions^{1, 2}. The aim of the study was to investigate the utility of the relation between MRI BME and different types of MRI lesions in the sacroiliac joint to separate patients with axSpA from persons with other conditions.

Methods: The MASH study is a prospective cross-sectional study of 204 participants, aged ≤ 45 yrs. The study included 41 patients with axSpA, 46 women with and 14 without pain related to pregnancy or postpartum within 12 months after delivery, 25 patients with lumbar disc herniation, 26 persons with hard physical labor (cleaning assistants), 23 long-distance runners (≥ 30 km/week) and 29 healthy men. Participants with pain should all have VAS pain > 2 (on a scale 0-10) for ≥ 2 months. Participants in the non-axSpA groups were not allowed to have any clinical SpA features or rheumatological conditions. All participants underwent clinical, laboratory and MRI examination including semi-coronal STIR and T1-weighted sequences of the SIJs. MRIs were evaluated for BME, erosion, fat, ankylosis, and sclerosis according to the SPARCCMRI definitions of lesions^{3,4} by two independent readers. In each of the nine slices of the cartilaginous compartment, the left and right SIJs were separately assessed for presence of BME in relation to each of the above mentioned structural lesions (range of total score per patient: 0-18).

Results: The table shows the clinical characteristics within each participant group, and MRI results based on the mean scores of the two readers. BME located adjacent to joint space, adjacent to erosions and adjacent to fat were more frequent in patients with axSpA, but these lesions were also seen in the other study groups, mainly women with postpartum pain. When increasing amounts of lesions were required (higher cut-offs), almost only AxSpA patients fulfilled the requirements (table). BME adjacent to sclerosis was most frequent in women with postpartum pain, whereas BME adjacent to ankylosis was only seen in patients with axSpA.

Conclusion: BME located adjacent to joint space, adjacent to erosion and adjacent to fat was most frequent, but did not exclusively occur in patients with axSpA, whilst BME adjacent to sclerosis was most frequent in women with postpartum pain. Detailed analysis of lesions and their anatomical location may help differentiate axSpA from other conditions.

References:

1. Weber et al. AR2010;62(10):3048-3058
2. Seven et al. Annrheumdis-2018-eular.2586
3. Maksymowych et al. AR 2005;53:703-9.
4. Maksymowich et al. J Rheumatol. 2015;42:79-86.

Clinical characteristics and relations between MRI BME and other MRI lesions

	AxSpA (N=41)	Post-partum with pain (N=46)	Post-partum without Pain (N=14)	Disc herniation (N=25)	Cleaning staff (N=26)	Long distance Runners (N=24)	Healthy men (N=30)
Age (years)	30.9 30.5 (19; 44)	32.6 32.5 (26; 41)	33.1 32.5 (27; 41)	35.2 37.0 (21; 43)	39.1 39.0 (28; 45)	32.7 32.0 (22; 43)	30.9 30.0 (20; 45)
Male sex	25 (61)	0 (0)	0 (0)	11 (44)	0 (0)	19 (79)	30 (100)
HLA-B27 positive	33.0 (80.5)	5.0 (10.9)	1.0 (7.1)	0 (0)	0 (0)	1.0 (4.3)	4.0 (13.8)
CRP (mg/L)	11.4 6.0 (0.3; 58)	1.6 0.8 (0.3; 7.1)	2.4 0.7 (0.3; 13)	2.2 0.9 (0.3; 14)	2.6 1.0 (0.3; 20)	1.4 0.4 (0.3; 7.6)	0.9 0.3 (0.3; 4.9)
Body mass index (kg/m²)	23.1 22.7 (18.3; 31.7)	25.0 24.0 (17.3; 37.1)	22.1 21.1 (11.8; 31.6)	26.2 25.2 (19.6; 34.9)	26.3 25.3 (20.5; 35.8)	23.0 22.8 (19.0; 25.8)	25.0 24.8 (19.5; 31.4)
Childbirths	1.7 2.0 (0; 2)	1.5 1.0 (1; 4)	1.9 2.0 (1; 3)	1.6 2.0 (0; 3)	2.5 2.5 (0; 5)	0.5 0 (0; 2)	NA
Low back pain (VAS, 0-100 mm)	37.5 37.0 (0; 100)	54.6 59.5 (0; 98)	3.9 0 (0; 19)	54.7 62.0 (3; 96)	7.8 0 (0; 68)	2.4 0 (0; 15)	1.3 0 (0; 12)
BME adjacent to joint space	5.0 4.0 (0; 15.5)	2.1 0.5 (0; 13) ‡	1.0 0 (0; 5.5) ‡	0.3 0 (0; 2) §	0.2 0 (0; 2.5) §	0.2 0 (0; 1.5) §	0.2 0 (0; 1.5) §
	1.2	0.1	0	0	0	0	0

Table . (Cont'd)

	AxSpA (N=41)	Post-partum with pain (N=46)	Post-partum without Pain (N=14)	Disc herniation (N=25)	Cleaning staff (N=26)	Long distance Runners (N=24)	Healthy men (N=30)
BME adjacent to fat	0 (0; 10)	0 (0; 3.5) §	0 (0; 0.5) †	0 (0; 0) §	0 (0; 0) §	0 (0; 0) §	0 (0; 0) §
BME adjacent to sclerosis	0.8 0 (0;10)	1.7 0 (0; 13)	0.7 0 (0; 3.5)	0 0 (0; 0.5) ‡	0.2 0 (0; 3.5) †	0 0 (0; 0.5)†	0 0 (0; 1) ‡
BME adjacent to erosion	1.6 0.5 (0; 14)	0.2 0 (0; 6.5) §	0 0 (0; 0) ‡	0 0 (0; 0) §	0 0 (0; 0) §	0.1 0 (0; 1.5) §	0 0 (0; 0) §
BME adjacent to ankylosis	0.1 0 (0; 1)	0 0 (0; 0)	0 0 (0; 0)	0 0 (0; 0)	0 0 (0; 0)	0 0 (0; 0)	0 0 (0; 0)
BME adjacent to joint space	≥ 1 26 (63) ≥ 3 23 (56) ≥ 5 19 (46) ≥ 10 7 (17)	20 (44) 13 (28) 4 (9) 1 (2)	3 (21) 1 (7) 1 (7) 0	2 (8) 0 0 0	2 (8) 0 0 0	0 0 0 0	1 (3) 0 0 0
BME adjacent to fat	≥ 1 7 (17) ≥ 3 2 (5) ≥ 5 2 (5)	1 (2) 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0
BME adjacent to sclerosis	≥ 1 7 (17) ≥ 3 2 (5) ≥ 5 1 (2)	13 (28) 6 (13) 6 (13)	2 (14) 1 (7) 0	0 0 0	1 (4) 1 (4) 0	0 0 0	0 0 0
BME adjacent to erosion	≥ 1 11 (27) ≥ 3 7 (17) ≥ 5 4 (10) ≥ 10 1 (2)	2 (4) 1 (2) 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0
BME adjacent to ankylosis	≥ 1 1 (2)	0	0	0	0	0	0

In cells with 1 row, values are N (%). In cells with 2 rows, values are mean (upper row) and median (min; max) (lower row).

Mann-Whitney test, compared with patients with axSpA. §: p<0.001; ‡: p<0.01; †: p<0.05 CRP: C-Reactive Protein; HLA-B27: Human Leucocyte Antigen B27; VAS: Visual Analogue Scale; BME: Bone marrow edema.

Disclosure: S. Seven, None; P. Hededal, None; M. Østergaard, None; L. Morsel-Carlsen, None; I. Juul Sørensen, None; B. Bonde, None; G. Thamborg, None; O. Hendricks, None; N. R. Jørgensen, None; S. J. Pedersen, None.

Abstract Number: 865

Structural and Microstructural Intraarticular Bone Changes at the Metacarpal Heads in Patients with Psoriatic Arthritis Compared to Controls: A HR-pQCT Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Imaging of Rheumatic Diseases I: MRI and CT

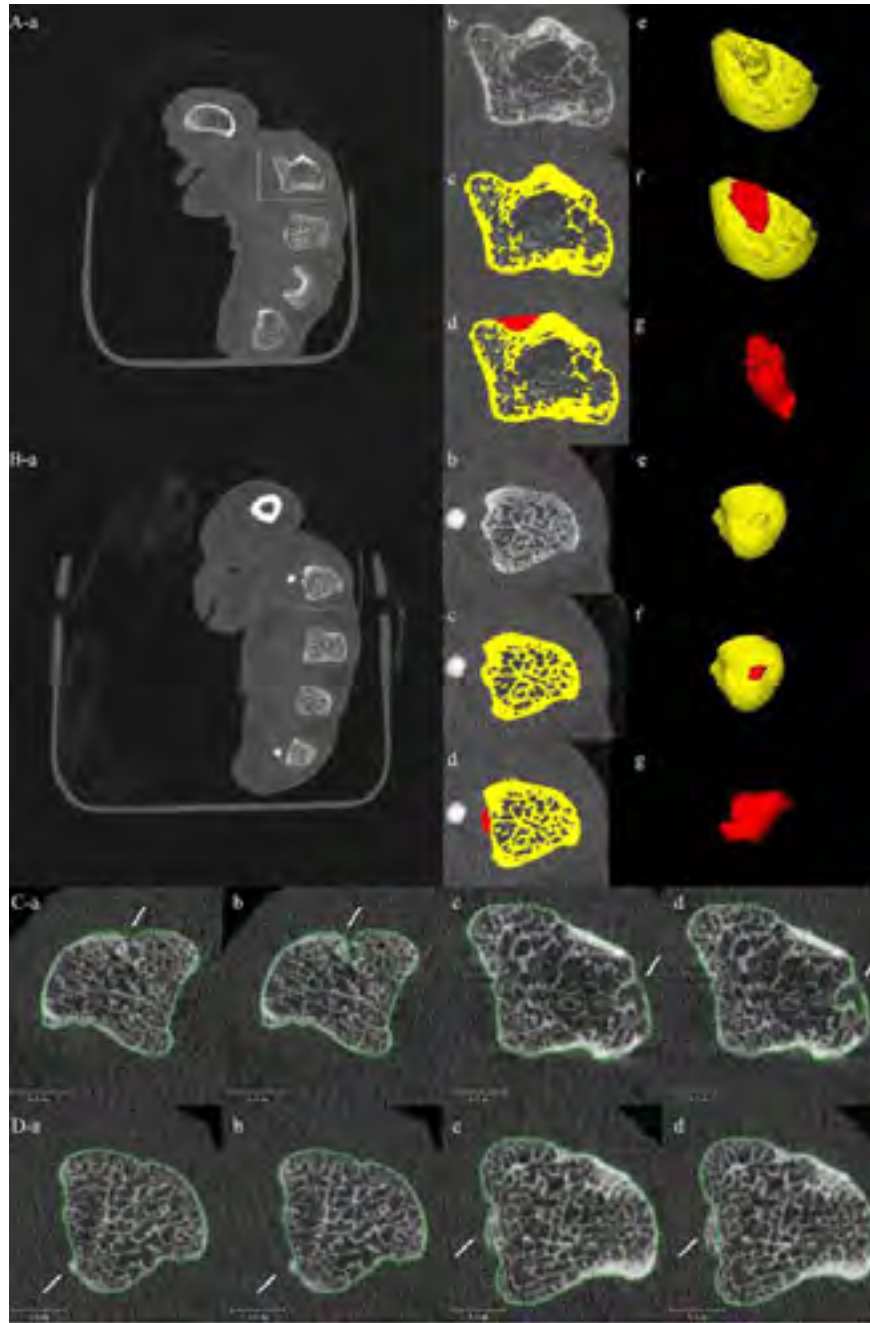
Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Metacarpal head directly exposed to intra-articular inflammatory milieu, therefore may lead to abnormal bone remodeling (bone loss and new bone formation).

The aims of this study are to investigate the structural (bone erosion and enthesiophyte) and microstructural bone changes in patients with PsA at the second and third metacarpal head (MCH2&3) compared with controls.

Methods: 139 subjects (77 PsA, 62 control) underwent high-resolution peripheral quantitative computed tomography (HR-pQCT) scanning at the MCH 2 and 3 and distal radius. Structural and microstructural bone changes at the MCH 2 and 3 were calculated (Figure 1) and compared between PsA patients and healthy controls.



Results: 15 patients with joint destruction were excluded from further analysis. 62 patients with PsA and controls were comparable in age, gender and body mass index (BMI). PsA patients had a significantly increased number (2.4 ± 1.4 vs 1.3 ± 1.1 , $p < 0.001$) and total enthesiophytes volume per person (8.75 ± 6.92 vs 4.36 ± 4.90 mm³, $p < 0.001$) compared to controls. Erosion number (2.9 ± 1.2 vs 2.7 ± 1.4 , $p = 0.408$) and total erosion volume per person (11.88 ± 7.82 vs 9.64 ± 5.96 mm³, $p = 0.076$) were similar in PsA patients compared with control. Regarding microstructure, PsA patients had a significantly decreased total volumetric bone mineral density (vBMD), cortical vBMD and cortical thickness at the distal radius; while a preferential bone loss at the trabecular compartment at the MCH was noticed compared to control. Regression model in PsA showed that advancing age, a higher BMI and C-reactive protein level were independent explanatory variables associated with a larger erosion volume. In contrast, older age and swollen joint count were independent explanatory variable associated with an increase in enthesiophyte volume.

Conclusion: Intra-articular trabecular bone loss and enthesal new bone formation was more prevalent in the MCH of patients with PsA.

Disclosures: This study has been partly presented at EULAR 2018.

Disclosure: D. Wu, None; J. E. Griffith, None; S. H. M. Lam, None; J. Yue, None; P. Wong, None; L. Shi, None; E. Li, None; I. T. Cheng, None; T. K. Li, None; T. Y. Zhu, None; V. W. Hung, None; L. Qin, None; L. S. Tam, None.

Abstract Number: 866

Patterns of Monosodium Urate Deposition on Dual-Energy CT in Gout Patients on Urate-Lowering Therapy

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Imaging of Rheumatic Diseases I: MRI and CT

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Gout is typically characterized as an acute monoarthritis involving the joints of the foot. However, polyarticular involvement develops, especially in advanced disease. Patterns of involvement of monosodium urate (MSU) crystal deposition such as symmetry and clustering in patients with gout has never been described. The aim of this study was to evaluate patterns of MSU deposition using dual-energy CT (DECT) among gout patients on urate-lowering therapy (ULT).

Methods: Using standardized acquisition protocols, DECT scans of the feet/ankles, knees, and hands/wrists were prospectively obtained in 153 patients with a known diagnosis of gout (all meeting 1977 ARA gout classification criteria) and on allopurinol at a dose of at least 300 mg daily for at least 3 months. MSU deposition was evaluated by 2 DECT radiologists at 12 sub-sites in the feet/ankles, 4 sub-sites in the knees, and 15 sub-sites in the hands/wrists. We calculated the number of subjects who would have 0, 1, 2, 3, 4, or 5+ joints with MSU deposition, assuming that its presence in different joints in a subject is independent. Clustering of MSU deposition in the 3 regions was assessed using a χ^2 -test. We then evaluated the patterns of MSU deposition at different joints with generalized estimating equations while adjusting for age, sex, and race.

Results: Our analysis included 153 patients (92% male) with gout (mean disease duration, 15 years) on allopurinol (mean duration of therapy, 5 years; mean daily dose, 333mg). MSU deposition was observed in a clustered manner at multiple joints of the hands/wrists, feet/ankles, and knees more frequently than would be expected by chance ($p < 0.001$ for all 3 regions). Presence of MSU deposition at a given joint was strongly associated with MSU deposition at the same joint of the opposite extremity (i.e., symmetric involvement), followed by other joints in the same ray of the hand or foot (i.e., multiple joints of one digit), followed by other joints in the same row of the hand or foot (i.e., same joint across multiple digits).

Conclusion: MSU deposition often affects multiple joints of the feet/ankles, knees, and hands/wrists in a clustered manner. MSU deposition tends to occur in a highly symmetric pattern in all three regions evaluated. In the hands and feet, MSU deposition is more likely to cluster by ray (i.e., multiple joints of one digit) than by row (i.e., same joint across multiple digits). These findings may shed light on pathophysiologic factors that lead to MSU deposition and may inform clinicians' decisions to obtain bilateral vs unilateral imaging of a target joint.

Table 1 – Pattern of MSU Deposition in Treated Patients with Gout

	Adjusted Odds Ratio* (95% CI)
Hand	
Same joint, other side	26.1 (2.6, 263.6)
Same ray, same side	15.0 (2.1, 107.8)
Same row, same side	14.9 (1.9, 114.3)
Foot	
Same joint, other side	46.9 (23.9, 92.2)
Same ray, same side	4.6 (2.0, 10.6)
Same row, same side	1.5 (0.7, 3.1)
Knee	
Same joint, other side	9.9 (5.9, 16.5)
Same row, same side	4.2 (2.5, 7.2)

Disclosure: C. Yokose, None; Y. Zhang, None; N. Dalbeth, Horizon, 5, Kowa, 5, Amgen Inc., 2, AstraZeneca/Ironwood, 2, AbbVie Inc., 8, Pfizer, Inc., 8, Janssen, 8; J. Wei, None; S. Nicolaou, Siemens, 9; S. Baumgartner, Ardea Biosciences, 3; J. Hu, Heron Therapeutics, 3; M. Fung, Ardea Biosciences, 3; H. K. Choi, Takeda, Selecta, Kowa, and Horizon, 5, Selecta and Horizon, 2.

Abstract Number: 867

An MRI Guided Treat-to-Target Strategy in Rheumatoid Arthritis Patients in Clinical Remission Improved MRI Inflammation but Not Damage Progression – Results from the Imagine-RA Randomized Controlled Trial

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Imaging of Rheumatic Diseases I: MRI and CT

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Magnetic Resonance Imaging (MRI) bone marrow edema (BME)/osteitis and MRI synovitis have been identified as predictors of structural damage progression in rheumatoid arthritis RA^{1,2}. Targeting MRI remission may reduce inflammation and halt damage progression.

The purpose was to investigate whether a 2-year treat-to-target (T2T) strategy targeting MRI remission (defined as absence of BME) suppresses MRI-determined measures of disease activity and structural joint damage in RA patients in clinical remission.

Methods: In the two year investigator initiated, randomized, open label multicentre IMAGINE-RA study, 200 RA patients in clinical remission (defined as DAS28-CRP<3.2 and no swollen joints) receiving conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) were randomized 1:1 to a conventional DAS28-CRP guided T2T treatment strategy targeting DAS28<3.2 and no swollen joints or an MRI guided T2T treatment strategy applying the same clinical T2T strategy and in addition targeting absence of MRI BME. Patients were followed every 4 months over a 2-year follow-up period. In all patients contrast-enhanced MRIs of the 2nd-5th metacarpophalangeal (MCP) joints and wrist of the dominant hand were performed at baseline, 12 and 24 months. In the MRI T2T arm MRI was performed every 4 months ahead of the clinical visit and assessed for presence/absence of BME by one blinded evaluator so the result was available for the

investigator at the visit. In the conventional T2T arm MRI findings were blinded to the investigator. If treatment target was not met treatment was escalated according to a predefined treatment algorithm starting with increment in csDMARD and then adding biologic DMARDs. MRIs (0,12 and 24 months) were evaluated according to the RAMRIS scoring system, with known chronology by one blinded experienced reader. Pearson's chi-square statistics and repeated-measures logistic regression models were used to assess outcomes.

Results: MRI outcomes of inflammation and damage at 24 months are presented in the table. The MRI T2T arm showed statistically significant reductions at 24 months in all inflammatory endpoints (osteitis, tenosynovitis and total inflammation score, $p<0.018$), except synovitis, ($p=0.074$), compared to the conventional T2T arm. No differences between treatment strategies were seen in damage progression.

MRI outcomes at 24 months

	MRI T2T	Conventional T2T	Difference between groups (95% CI)	P value*
MRI				
Inflammation				
Change in osteitis (RAMRIS) score	-1.8 (0.6)	-0.1 (0.5)	-1.8 (-3.2 to -0.3)	0.018
Change in synovitis (RAMRIS) score	-0.5(0.3)	0.3 (0.3)	-0.8 (-1.8 to 0.1)	0.074
Change in tenosynovitis (RAMRIS) score	-0.9 (0.3)	0.3 (0.3)	-1.2 (-2.1 to -0.3)	0.007
Change in total inflammation (RAMRIS) score	-2.9 (1.0)	0.7 (1.0)	-3.6 (-6.4 to -0.8)	0.013
Damage				
Change in erosion (RAMRIS) score	0.5 (0.2)	0.6 (0.2)	-0.1 (-0.6 to 0.4)	0.663
Change in JSN (RAMRIS) score	0.1 (0.2)	0.4 (0.1)	-0.3 (-0.7 to 0.2)	0.236
Change in total damage (RAMRIS) score	0.6 (0.3)	1.0 (0.3)	-0.3 (-1.2 to 0.5)	0.395
No progression in erosion (RAMRIS), n (%)	59 (79.7%)	70 (75.3%)	OR, 1.06 (0.02 to 66.59)	0.976

95% CI, 95% confidence interval; JSN=joint space narrowing; MRI=Magnetic Resonance Imaging; RAMRIS=RA magnetic resonance imaging scoring system; T2T=treat-to-target; total damage score=sum score of MRI erosion and JSN; total inflammation score=sum score of MRI synovitis, osteitis and tenosynovitis. Data are presented as least square means (SE) unless otherwise stated. Analyses are based on full analysis set (patients having a baseline visit and at least one follow-up visit) with no data imputation to replace missing data. *P values are based on repeated-measures logistic regression models. For some of the variables, fewer patients were included in the analyses due to missing data in the MRI T2T arm (range 85-89) and in the conventional T2T arm (range 90-95).

Conclusion: An MRI T2T strategy, aiming to eliminate MRI BME, was more effective than a conventional T2T strategy in reducing MRI inflammation but not MRI damage progression. The reduced inflammatory load caused by the MRI T2T strategy may reduce long-term structural joint damage and improve patient-reported outcomes, but more than two years follow-up data are needed to clarify this.

Clinicaltrials.gov Identifier: NCT01656278

References:

1. Hetland et al, Ann Rheum Dis 2009;**68**(3) 2. Boyesen et al, Ann Rheum Dis 2011;**70**(3)

Disclosure: S. Møller-Bisgaard, None; K. Hørslev-Petersen, None; B. J. Ejbjerg, None; D. Glinatsi, None; M. L. Hetland, None; L. Ørnbjerg, None; J. M. Møller, None; M. Boesen, None; R. Christensen, None; K. Stengaard-Pedersen, None; O. Rintek Madsen, None; B. Jensen, None; J. A. Villadsen, None; E. M. Hauge, None; P. Bennett, None; O. Hendricks, None; K. Asmussen, None; M. Ryszard Kowalski, None; H. Lindegaard, None; S. M. Nielsen, None; H. Bliddal, None; N. S. Krogh, None; T. Ellingsen, None; A. Nielsen, None; L. Balding, None; A. G. Jurik, None; H. S. Thomsen, None; M. Østergaard, None.

Abstract Number: 868

International Multi-Reader Validation of the Outcome Measures in Rheumatology Hip MRI Scoring System (OMERACT HIMRISS) for Bone Marrow Lesions in Osteoarthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Imaging of Rheumatic Diseases I: MRI and CT

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Bone marrow lesion (BML) in hip osteoarthritis (OA) may be a determinant of prognosis and a target for emerging anti-inflammatory therapies. We developed the OMERACT Hip MRI Scoring System (HIMRISS) to maximize reliability & sensitivity to change. Innovations include electronic overlays (touch or mouse-click a region to identify BML), a web-based online interface, and real-time iterative calibration (RETIC) in which new readers perform a scoring exercise online, learning by observing their ICC vs. expert consensus displayed in real-time. Pre-specified minimum ICC must be achieved before becoming eligible to proceed with formal scoring. We tested feasibility, reliability, and responsiveness of HIMRISS for scoring BML in a large prospective cohort.

Methods: In HIMRISS, BML is scored as 0/1 (absent/present) in 100 regions on a web-based grid overlay slice-by-slice in coronal hip MRI. In the Edmonton Steroid Injection in Hip OA (STIHO) cohort, we had n=90 patients x 2 hips x 2 MRI: at baseline presenting for hip steroid injection, and at 8 weeks post injection. Coronal T1/STIR sequences were provided, blinded to time point, to 8 readers: 2 radiology fellows, 3 rheumatologists, 3 musculoskeletal radiologists. Each reader prepared by reviewing a comprehensive HIMRISS methodology module, then had to pass an online RETIC training module with proficiency (ICC 0.80 vs. experts) prior to formal scoring. Readers each scored HIMRISS BML in all 360 hips.

Results: Subjects were 56% male, age 59 ± 13 (mean \pm SD) years, symptom duration 4.4 ± 4.5 years, K-L OA grade 1/2/3/4 in 20%/28%/34%/18%. Reliability (ICC single measure, absolute agreement, 2 way model) was high for baseline BML status for all readers (0.83) and for 2 experts (0.88-0.92). Change was small, mean (SD) $2.1 \pm 10.0/100$. Despite this, ICC for change was (0.42-0.76) for all readers, (0.56-0.81) for experts.

Conclusion: HIMRISS reliably quantifies BML in hip OA at a single time point and can responsively discriminate small changes in BML. Novice readers trained via an online RETIC system achieved reliability close to that of experts. Future studies will assess performance of HIMRISS assessing inflammation in other arthropathies.

Reliability of HIMRISS BML Measurements	Baseline Status		Change	
ICC for BML	All readers	Experts	All readers	Experts
Femoral head	0.83 (0.65-0.91)	0.91 (0.87-0.94)	0.76 (0.65-0.83)	0.81 (0.72-0.87)
Acetabulum	0.83 (0.74-0.89)	0.88 (0.82-0.92)	0.42 (0.23-0.57)	0.56 (0.40-0.68)
Total	0.83 (0.55-0.92)	0.92 (0.88-0.95)	0.72 (0.60-0.81)	0.78 (0.68-0.85)

Change in BML, and HIMRISS Responsiveness	Scoring range	Change observed 0-8 wks; mean(SD)	Smallest detectable change SDC	Hips with change >SDC
Femoral head	0-65	2.2(9.2)	3.6	45%
Acetabulum	0-35	-0.1(2.3)	1.9	33%
Total	0-100	2.1(10.0)	4.6	36%

Disclosure: J. L. Jaremkow, None; R. G. Lambert, None; S. J. Pedersen, None; U. Weber, None; D. Lindsay, None; Z. Al-Ani, None; M. Pianta, None; S. Wichuk, None; K. Steer, None; J. Paschke, None; W. P. Maksymowych, CaRE rthritis, 9.

Abstract Number: 869

Failure to Reach Serum Urate Target Is Associated with Elevated Mortality in Gout

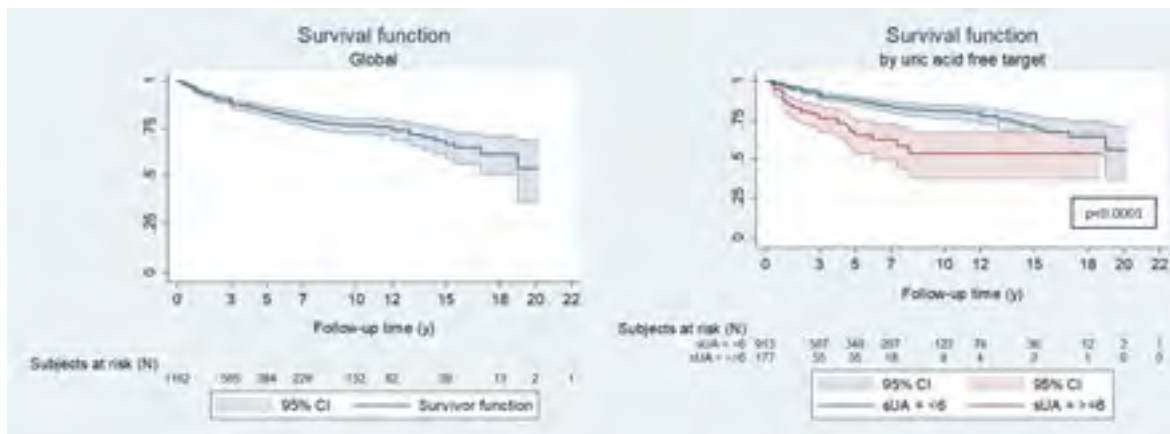
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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Metabolic and Crystal Arthropathies: Comorbidities and Outcomes

Session Type: ACR Concurrent Abstract Session



Session Time: 2:30PM-4:00PM

Background/Purpose: Gout is associated with an increased risk of cardiovascular events and death. It has been shown that both overall and risk of death are associated with increasing gout severity, as reflected by the number of tophi. It remains to be proven whether better control of gout through lowering of serum uric acid (sUA) confers a survival advantage. To determine the impact of achieving sUA less than 6 mg/dl (vs greater) on mortality risk among gout patients.

Methods: Analysis of data from a prospective follow-up cohort (1992 to 2017) of patients attending a gout clinic (85% of patients with microscope or ultrasound diagnosis) and with at least one follow-up visit. Mortality was confirmed from medical records, patients' families, or local death registries if needed. sUA levels were monitored during follow-up and the average sUA until sUA was stable was used as the primary exposure dichotomized as < 6 mg/dl (versus ≥ 6 mg/dl). Descriptive variables and potential confounders included: age, gender, body mass index, previous treatment with urate-lowering drugs (ULDs), number of joints affected at entry, presence of subcutaneous tophi, radiographic evidence of articular damage, number of gout flares in the year preceding evaluation, previous diagnosis of cardiovascular (CV) disease, loop diuretic use, alcohol intake, diabetes, hypertension, hyperlipidemia, and renal function impairment. In addition, the Kaiser Permanente stratification of comorbidity was further used to risk stratify patients from low to high risk of death. Univariate and multivariate Cox proportional hazards models were used to determine mortality risks expressed as hazard ratios (HR) and 95% Confidence Intervals (CI).

Results: The study cohort included 1,193 patients (92% men, mean age 60, 6.8 years disease duration, with an average of 3 to 4 flares in the previous year). Mean follow-up was 48 (median 30, IQR 12-66), with 4,830 patient-year observation. Mean sUA at baseline was 9.1 mg/dl and 16.3% of the patients maintained sUA levels ≥ 6 mg/dl despite treatment. A total of 158 deaths occurred (13% overall mortality), with loss to follow-up in 286 cases (24%). Overall crude mortality rate was 32.7 per 1,000 patient-years (95% CI: 28.0-38.2) and was significantly higher for patients with sUA ≥ 6 mg/dl, 80.9 per 1,000 person-years (95% CI 59.4-110.3) compared to patients with sUA < 6 mg/dl, 25.7 per 1,000 person-years (95% CI: 21.3-30.9). With adjustment for age, sex, previous CV events, and baseline sUA concentration, a sUA ≥ 6 mg/dl was associated with a HR of 2.39 (1.64- 3.50).

Conclusion: Failure to reach a target sUA level of 6 mg/dl is an independent predictor of mortality in gout patients. Control of gout with achievement of sUA target < 6 mg/dl should be considered in order to improve patient survival.

Disclosure: F. Perez-Ruiz, Amgen Inc., 5, 8, Grünenthal, 5, 8, Menarini, 5, 8, Asociación de Reumatólogos de Cruces, 2; P. Richette, Menarini, 5, Grünenthal, 5; A. Stack, Health Research Board, 2, Midwest Research and Education Foundation, 2, Menarini International Operation Luxemburg, 2, 5, Grünenthal, 5, Astellas, 5; R. Karra Gurunath, Grünenthal, 3; M. J. GARCIA DE YEBENES Y PROUS, None; L. Carmona, None.

Abstract Number: 870

Patient-Reported Burden of Gout in 2017 from the United States

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Metabolic and Crystal Arthropathies: Comorbidities and Outcomes

Total Flare Burden

- The total flare burden for US adults with gout is 6.5 flares per year
- 69.2% of flares are pretreated/prevented or suffered and not reported to doctors



Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Gout is reported to impact 3.9% of the US adult population (Zhu. Arthritis Rheum 2011;63:3136-41). Treatment encompasses controlling acute attacks (flares) and, dependent on the degree of severity of joint involvement, long-term efforts to reduce urate levels and dissolve existing urate deposits, while preventing new crystal formation. Gout flares are often self-treated by patients, so it is hypothesized that the number of gout flares experienced is underreported to health care providers, leading to underestimation of the burden of gout. The aim of this study was to describe gout flares experienced and reported, unreported, and prevented per year by patients with gout in the United States.

Methods: A 2017 cross-sectional survey of US adults assessed health conditions, impact on health-related quality of life, and health care resource utilization. Participants aged ≥ 18 years were recruited using a random stratified sampling framework to ensure demographic composition representative of the US population. Participants with self-reported gout were asked to estimate the annual number of flares they experienced and reported to their physician, flares experienced and not reported, and flares prevented. Population level characteristics and outcomes are summarized using descriptive statistics.

Results: In 2017, 3.1% ($n=372$) of a representative sample of US adults ($n=12,146$) reported having gout. Patients with gout reported significantly lower physical health as measured with the Rand VR-12 Physical Component Subscale (41.1 vs 46.5; $P<0.05$). The total flare burden was 6.5 flares per year; 69.2% of flares were pretreated/prevented or suffered and not reported to any physician (Figure). On average, patients with gout told their physician they experienced 2 flares over the last 12 months. They reported another 1.3 flares experienced per year that they did not report to their physician and 3.2 flares per year that were alleviated with treatment of initial flare signs (eg, joint warmth and redness). Females were less likely to report all of their flares to their physician (32.4% of females vs 51.8% of males reported all flares; $P<0.05$). Younger patients were more likely to report all gout attacks to a physician (mean age 55.5 reporting all flares vs 63.1 years not reporting all flares; $P<0.01$). There was no difference in reporting flares by the number of comorbidities or use of a urate-lowering therapy.

Conclusion: Patients report only a third of their flares to physicians, resulting in suboptimal treatment of gout. Likewise, age and gender disparity in underreporting also reveals a missed window of opportunity that is essential to ensure optimal management in a large proportion of patients. Reliance on clinical documentation of physician-reported flares is insufficient to assess the true patient burden of gout.

Disclosure: P. P. Khanna, None; D. C. A. Taylor, Ironwood Pharmaceuticals, Inc., 1, 3; A. C. Fu, Ironwood Pharmaceuticals, Inc., 1, 3; R. Morlock, Ironwood Pharmaceuticals, Inc., 5, Astellas, 5, Heron, 5, CeQur, 5.

Abstract Number: 871

Estimates of Diet Quality Explain Less Variability in Serum Urate Levels Than Genetic Factors

Tanya J. Major¹, Ruth Topless¹, Nicola Dalbeth² and Tony R. Merriman¹, ¹University of Otago, Dunedin, New Zealand, ²University of Auckland, Auckland, New Zealand

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Metabolic and Crystal Arthropathies: Comorbidities and Outcomes

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Hyperuricaemia (elevated serum urate) is a central risk factor for gout, an acute inflammatory form of arthritis. The balance between the hepatic production of urate and the intestinal / renal urate excretion pathways determines an individual's serum urate levels and this balance can be modified by both genetic and environmental factors. This study aimed to evaluate the relative contributions of estimates of diet quality and inherited genetic variants in determining serum urate levels.

Methods: 16,760 American European individuals (8,414 men, 8,346 women) were used to test for associations between serum urate ($\mu\text{mol/L}$) and four composite dietary scores or a genetic risk score, adjusting for sex, age, body mass index, average daily calorie intake, years of education, exercise levels, smoking status, menopausal status, and genome-wide principal component vectors. Genetic heritability of serum urate in these individuals was also assessed.

Results: Three diet quality scores, constructed based on healthy diet guidelines (Healthy-Eating Pyramid, DASH Diet, and Mediterranean Diet), were inversely associated with serum urate (β (in $\mu\text{mol/L}$) = -0.72 , $P = 1.12 \times 10^{-6}$; $\beta = -0.73$, $P = 3.1 \times 10^{-10}$; $\beta = -0.38$, $P = 2.9 \times 10^{-4}$, respectively) and a fourth, data-driven diet quality score associated with raised serum urate ($\beta = 0.59$, $P = 2.3 \times 10^{-8}$). However, each explained $\leq 0.28\%$ of the cohort variance in serum urate. In comparison, a weighted serum urate genetic risk score, constructed from 30 variants previously associated with serum urate in Europeans (Köttgen *et al.* 2013), associated with raised serum urate ($\beta = 0.99$, $P = 2.2 \times 10^{-231}$) and explained 7.9% of the serum urate variance within the cohort. A genome-wide estimate of serum urate heritability explained 23.9% ($P < 1.0 \times 10^{-16}$) of the cohort variance in serum urate.

Conclusion: This study has identified an association between estimates of healthier dietary habits and reduced urate in people of European ancestry and suggests, in contrast to genetic contributions, diet explains very little variation in serum urate levels. Our results are important in demonstrating the relative contributions of overall diet and inherited genetic factors to the population variance of serum urate levels and challenge widely held community perceptions that hyperuricaemia is primarily caused by diet. This study directly shows, for the first time, that genetic variants have a much greater contribution to population-wide variance in hyperuricaemia than dietary habits.

Disclosure: T. J. Major, None; R. Topless, None; N. Dalbeth, Horizon, 5, Kowa, 5, Amgen Inc., 2, AstraZeneca/Ironwood, 2, AbbVie Inc., 8, Pfizer, Inc., 8, Janssen, 8; T. R. Merriman, None.

Abstract Number: 872

Is the Serum Uric Acid Therapeutic Target Protective of Chronic Kidney Disease, Cardiovascular Disease, and Mortality for Patients with Gout? a Longitudinal Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Metabolic and Crystal Arthropathies: Comorbidities and Outcomes

Session Type: ACR Concurrent Abstract Session

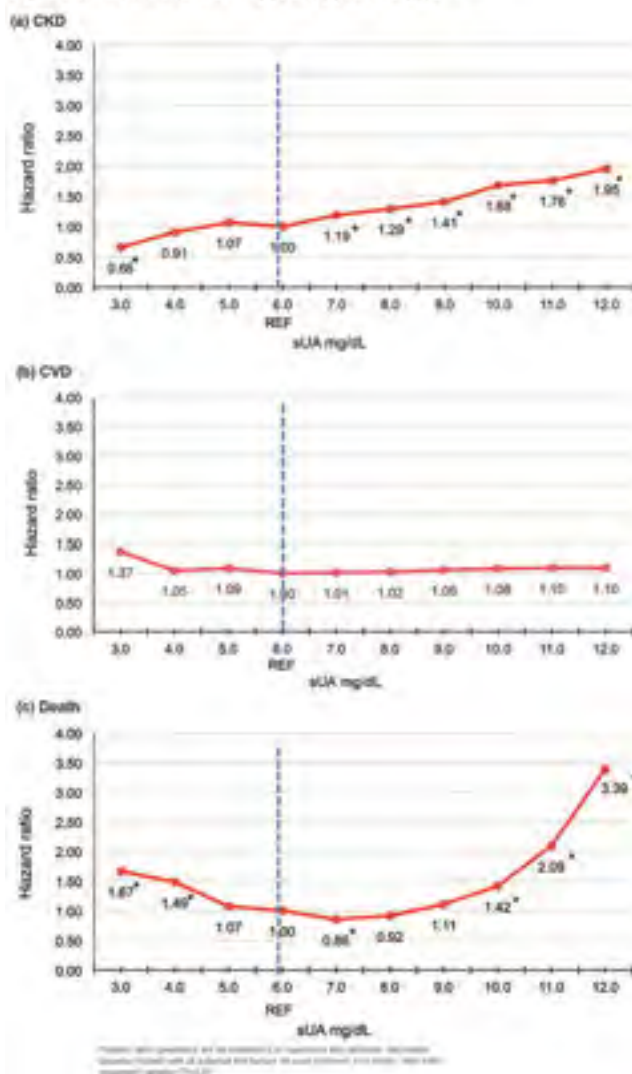
Session Time: 2:30PM-4:00PM

Background/Purpose: Many studies have found that serum uric acid (sUA) levels are associated with the incidence of chronic kidney disease (CKD), cardiovascular disease (CVD), and mortality; however, these associations have not been studied among gout patients. As lowering urate is the mainstay of gout care, these associations would have implications for gout care and future research.

Methods: We conducted a cohort study using data from Clalit Health Services (Israel, January 2006–December 2015). Incident cases of gout were included from 1/2006 to 12/2009 among members aged ≥ 25 years and with continuous enrollment for ≥ 1 year prior to and ≥ 5 years after the first qualified gout diagnosis (the index date). Gout cases were identified based on the following criteria: a) 1 diagnosis of gout from a hospital or specialist visit; or b) ≥ 2 diagnoses of gout from 2 different general practitioner visits and either an elevated sUA (>6 mg/dL) or dispensation of colchicine or allopurinol. Exposure was assessed during the follow-up as: (1) the mean sUA; and (2) a summary measure of sUA above the threshold of 6 mg/dL, and then categorized as either no exposure (sUA-T0) versus quartiles of exposure (sUA-T1 to sUA-T4). We examined the association between time-updated prior sUA levels using either exposure measure and the risk of CKD, CVD, and mortality using extended Cox proportional hazard regression models adjusted for risk factors. Hazard ratios (HRs) were calculated relative to the reference group inclusive of 6 mg/dL.

Results: A total of 12,234 gout patients (mean age at diagnosis=64 years; 76.1% male) were followed for an average of 6.9 years. The mean sUA during the follow-up period was 7.4 mg/dL with sUA category-specific means of sUA-T0=4.4, sUA-T1=6.2, sUA-T2=7.2, sUA-T3=7.8, and sUA-T4=8.7 mg/dL. For CKD endpoints, risks increased with greater UA exposure relative to a mean sUA of 6 mg/dL (Fig1a) and for threshold categories versus sUA-T1 ($HR_{sUA-T2}=1.23$, $HR_{sUA-T3}=1.34$, $HR_{sUA-T4}=1.93$; all $P<0.001$). For CVD endpoints, risks did not differ relative to mean sUA levels of 6 mg/dL (Fig 1b) or versus the thresholds UA-T1 (all $P>0.05$). For mortality, a U-shaped curve was observed for mean sUA exposure (Fig 1c) and for the low and high threshold categories versus sUA-T1 ($HR_{sUA-T0}=1.33$, $HR_{sUA-T4}=2.08$; all $P<0.001$).

Figure 1: Hazard ratio for sUA and (a) CKD, (b) CVD, or (c) Death*



Conclusion: These findings suggest a positive association between cumulative sUA burden above the target level of 6 mg/dL and CKD risk among gout patients. To that end, the sUA target of <6 mg/dL may provide reno-protective benefits among gout patients. Further, gout patients with extreme sUA levels are at risk for increased mortality.

¹Richette et al. Ann Rheum Dis. 2017;76:29-42.

²Khanna, et al. Arthritis Care Res. 2012;64:1431-46.

Disclosure: D. C. A. Taylor, Ironwood Pharmaceuticals, Inc., 1, 3; D. Jaffe, Kantar Health, 3, Ironwood Pharmaceuticals, Inc., 5; M. Hoshen, None; G. Shefer, Clalit Research Institute, 3; A. Bachrach, Clalit Research Institute, 3; B. Feldman, Clalit Research Institute, 3; A. C. Fu, Ironwood Pharmaceuticals, Inc., 1, 3; H. K. Choi, Takeda, Selecta, Kowa, and Horizon, 5, Selecta and Horizon, 2.

Abstract Number: 873

General Safety of Febuxostat and Allopurinol in a Cardiovascular Outcomes Study in Patients with Gout

Kenneth Saag¹, Michael A. Becker², William B. White³, Andrew Whelton⁴, Jeffrey Borer⁵, Philip Gorelick⁶, Barbara Hunt⁷, Majin Castillo⁷ and Lhanoo Gunawardhana⁷, ¹University of Alabama at Birmingham, Birmingham, AL, ²University of Chicago Pritzker School of Medicine, Chicago, IL, ³Cardiology, University of Connecticut School of Medicine, Farmington, CT, ⁴Johns Hopkins University School of Medicine, Hunt Valley, MD, ⁵State University of New York Downstate Medical Center, Brooklyn, NY, ⁶Michigan State University College of Human Medicine, Grand Rapids, MI, ⁷Takeda Pharmaceuticals International, Deerfield, IL

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

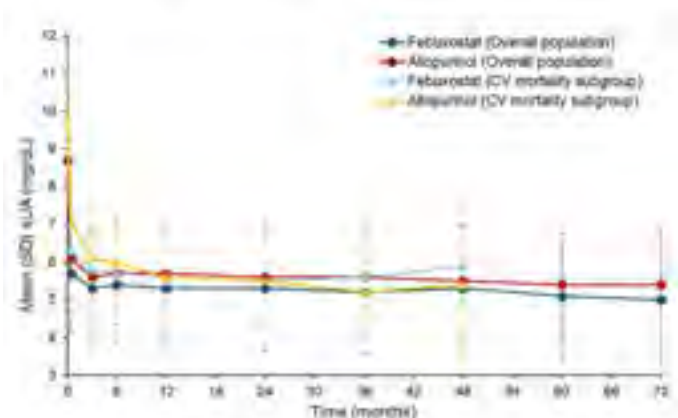
Session Title: Metabolic and Crystal Arthropathies: Comorbidities and Outcomes

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The cardiovascular (CV) safety study CARES has the longest study duration of any randomized controlled trial in patients (pts) with gout and CV disease. In CARES, the proportion of pts with the primary endpoint (composite of CV death, nonfatal myocardial infarction, nonfatal stroke, and unstable angina with urgent revascularization) was non inferior between febuxostat (feb) and allopurinol (allo), but there was an imbalance in rates of CV mortality (4.3% and 3.2%, respectively).¹ We evaluated the general safety of feb and allo in CARES and the relationship between CV mortality and serum urate levels (sUA) or gout flares.

Figure 1. Change in mean sUA with febuxostat and allopurinol in the overall mITT population and CV mortality subgroups during the CARES study⁴

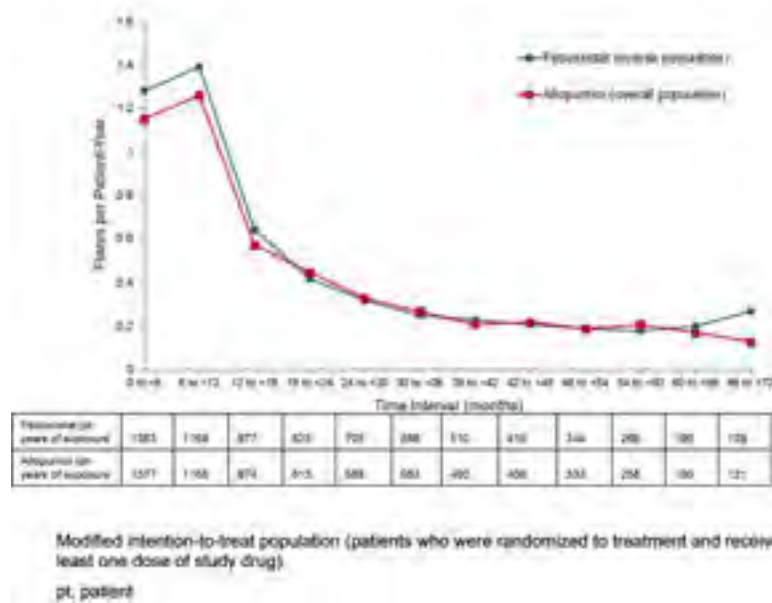


Modified intention-to-treat population (patients who were randomized to treatment and received at least one dose of study drug). At baseline, patient numbers for overall population were: feb n=3098, allo n=3092; CV mortality subgroup: feb n=134, allo n=100

*Number of patients in CV mortality groups with sUA data at Months 60 and 72 were too low (n<5) to allow meaningful interpretation of sUA at these timepoints

CV, cardiovascular; SD, standard deviation; sUA, serum urate levels

Figure 2. Gout flares requiring treatment (per patient-year of exposure) with febuxostat and allopurinol over 5-month intervals during the CARES study (<72 months)



Methods: Pts were randomly assigned to once-daily feb (40 or 80 mg, based on sUA at Week 2) or allo (dose titrated in 100 mg increments from 200–400 mg or 300–600mg, based on kidney function). The modified intention-to-treat population (mITT) comprised pts who were randomized and received treatment. Safety endpoints included treatment-emergent adverse events (TEAEs); key efficacy parameters were changes from baseline in sUA and gout flares. The sUA and flares (while on study drug) were evaluated in those pts with CV mortality versus those in the overall mITT.

Results: Randomized pts were treated with feb (n=3098) or allo (n=3092) over a median follow-up of 32 months (max 85 months); 57.3% and 55.9% of patients randomized to feb and allo, respectively, discontinued treatment early. In the feb and allo treatment groups (mITT), similar proportions of pts had TEAEs (83% vs 82%, respectively) or serious TEAEs (34% vs 32%); most common TEAEs were diarrhea (10% vs 9%) and arthralgia (8% vs 10%). Total incidences of rashes, eruptions, or exanthemas for feb and allo were 4% and 5%, respectively. A total of 13% pts in each group discontinued study drug due to TEAEs. Baseline sUA were higher in pts with CV mortality (feb: 9.3 mg/dL [n=134]; allo: 9.8 mg/dL [n=100]) versus the overall mITT (8.7 mg/dL with feb and allo), but comparable between treatment groups. In the overall mITT, sUA with feb were lower than with allo at Week 2 and Months 3, 6, 12, 24, 36, 48, 60 and 72; however, sUA were not consistently lower with feb in the CV mortality cohort (Figure 1). Gout flare rates were similar with feb and allo and decreased across the study period (Figure 2); flare rates within 3 months of CV mortality were low in both the feb (6%) and allo (2%) groups.

Conclusion: Feb and allo treatments had comparable safety and tolerability findings in pts with gout and CV disease. There were no distinct relationships between CV mortality and sUA or gout flares.

1. White WB et al. *N Engl J Med* 2018;378:1200–10

Disclosure: K. Saag, AstraZeneca, Horizon, SOBI, Takeda, 5; AstraZeneca, Horizon, SOBI, Takeda, 2; M. A. Becker, Takeda Pharmaceuticals, 2, 5; Horizon, 2, 5; Savient, 2, 5; Ardea/AstraZeneca, 2, 5; Ironwood Pharmaceuticals, 2, 5; CymaBay Therapeutics, 5; Kowa Pharmaceuticals, 5; UpToDate Inc., 7; W. B. White, Takeda Pharmaceuticals, 5; A. Whelton, Takeda Pharmaceuticals, 5; J. Borer, Servier, 5; Amgen Inc., 5; AstraZeneca, 5; General Electric, 5; Novartis, 5; Pfizer, Inc., 5; Takeda Pharmaceuticals, 5; SK Biopharmaceuticals, 5; BioMarin Pharmaceutical, 1; P. Gorelick, Takeda Pharmaceuticals, 5; B. Hunt, Takeda Pharmaceuticals, 3; M. Castillo, Takeda Pharmaceuticals, 3; L. Gunawardhana, Takeda Pharmaceuticals, 1, 3.

Preventing a Large Majority of Incident Gout Cases By Modifying Key Risk Factors: Findings from a Prospective Cohort of 44,629 Men over 26 Years

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Metabolic and Crystal Arthropathies: Comorbidities and Outcomes

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Many modifiable risk factors have been found to be independently associated with the risk of developing gout, including dietary factors (e.g., intakes of red meat and fructose), adiposity, alcohol intake, and diuretic use. Conversely, healthy dietary patterns (e.g., the Dietary Approaches to Stop Hypertension [DASH]) and a high intake of vitamin C have been shown to be independently associated with lower gout risk. However, the potential combined impact of these factors on the risk of developing gout is unknown. We aimed to estimate the proportion of incident gout cases that could theoretically be avoided through the simultaneous adoption of multiple low-risk behaviors, including low body mass index (BMI), consumption of a DASH-style eating pattern, no alcohol intake, vitamin C supplementation, and no diuretic use.

Methods: From 1986 to 2012, we prospectively followed 44,629 men free from gout at baseline in the Health Professionals Follow-up Study. Lifestyle, anthropometric, and medical information was collected at baseline and updated biennially. Dietary data were obtained using validated food frequency questionnaires at baseline and approximately every 4 years during follow-up. We ascertained incident cases of gout using the American College of Rheumatology survey criteria for gout. We defined low-risk groups according to combinations of the following five factors: a low BMI ($<25\text{kg/m}^2$), adherence to a DASH-style diet, no alcohol intake, vitamin C supplementation ($\geq 1500\text{mg}$), and no diuretic use. Cox proportional hazard regression models were used to estimate the association of each risk factor with the development of gout and calculate the population attributable risk percent (PAR%).

Results: During 950,086 person-years of follow-up, incident gout developed in 1,687 participants. All five modifiable risk factors were independently associated with incident gout. Obesity was the single most important predictor of gout; all other risk factors were also associated with a statistically significant increased risk of gout, even after adjustment for BMI. As compared with the rest of the cohort, men in the low-risk group (comprised of all five low-risk factors; 4.4% of men) had a relative risk of gout of 0.30 (95% confidence interval [CI], 0.12 to 0.72) (Table). Accordingly, the PAR% for all five risk factors combined was 70% (Table). The PAR% for four and three risk factors was 64% and 50%, respectively (Table).

Conclusion: Five modifiable risk factors accounted for 70% of incident gout cases in this large prospective cohort of male health professionals. Assuming a causal relation, our findings support the hypothesis that the vast majority of cases of gout could be prevented by modifying key risk factors.

Table. Relative and Population Attributable Risks of Gout for Groups Defined by Combinations of Modifiable Risk Factors

	Percentage of Men (%)	Number of Gout Cases	Relative Risk (95% CI)	PAR%
3 factors in low-risk category a	11.0	24	0.49 (0.33, 0.74)	50
4 factors in low-risk category b	10.3	15	0.35 (0.21, 0.59)	64
5 factors in low-risk category c	4.4	5	0.30 (0.12, 0.72)	70

Abbreviations: BMI, body mass index. CI, confidence interval. DASH, Dietary Approaches to Stop Hypertension. PAR%, Population attributable risk percent.

Relative risks were adjusted for total energy intake, coffee intake, and histories of renal failure and hypertension.

^a Low BMI, highest quintile of DASH diet score, and no alcohol intake.

^b Low BMI, highest quintile of DASH diet score, no alcohol intake, and no diuretic use.

^c Low BMI, highest quintile of DASH diet score, no alcohol intake, no diuretic use, and vitamin C supplementation.

Disclosure: S. K. Rai, None; N. Lu, None; C. Yokose, None; H. K. Choi, Takeda, Selecta, Kowa, and Horizon, 5, Selecta and Horizon, 2.

Anti-Calreticulin Antibody – a Novel Antibody in Patients with Idiopathic Inflammatory Myopathies and Its Association with Malignancy

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Muscle Biology, Myositis and Myopathies I: Biomarkers

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: To investigate the occurrence of anti-calreticulin antibodies (anti-CRT Abs) and evaluate its association with malignancy in patients with idiopathic inflammatory myopathies (IIM).

Methods: In total, 211 patients with IIM were enrolled in our study and patients complicated with malignancy were separated into a single category. The levels of anti-CRT Abs were measured in serum samples from 106 with dermatomyositis (DM), 21 with polymyositis (PM), 34 with immune-mediated necrotizing myositis (IMNM), 50 IIM with malignancy and 40 healthy controls (HC) by an in-house enzyme-linked immunosorbent assay (ELISA) using recombinant full-length CALR. The clinical and laboratorial data were collected and compared between anti-CRT Abs positive and negative patients. Then 8 IIM patients were followed longitudinally whose changes in concentrations of anti-CRT Ab were assessed and variations in disease activity were measured by myositis disease activity assessment visual analog scales (MYOACT) scores. Receiver operating characteristic (ROC) curve analysis was performed to determine the value of anti-CRT Abs in distinguishing IIM with malignancy from those without malignancy.

Results: Serum levels of anti-CRT Abs were significantly higher in IIM [median 5.3 AU (IQR 2.5-11.6)] than in HC [median 3.8 AU (IQR 1.8-6.4), $P = 0.003$] and anti-CRT Abs were judged to be positive in 48 of 211 IIM patients (22.7%). Among the IIM subgroups, 17/106 (16.1%) DM, 2/21 (9.5%) PM, 7/34 (20.6%) IMNM and 22/50 (44%) IIM with malignancy were seropositive for anti-CRT Abs. Higher frequency of malignancy, heliotrope rash and gottron papules as well as elevated concentrations of immunoglobulin G (IgG) and anti-nuclear Abs (ANA) were present in IIM patients with positive anti-CRT Abs than in those negative. A positive correlation between serum anti-CRT Abs concentrations and MYOACT scores was shown by longitudinal study. ROC curve analysis revealed that the anti-CRT Abs had diagnostic value in distinguishing IIM with malignancy from those without malignancy, with an area under curve (AUC) value of 0.65 (95% CI 0.56 – 0.74, $P = 0.001$).

Conclusion: This is the first report to discover that anti-CRT Abs could be a novel autoantibody detected in IIM. The levels of anti-CRT Abs increased significantly and markedly high anti-CRT Abs levels could be a possible serological marker of malignancies in IIM patients.

Disclosure: H. Chen, None; G. Wang, None; X. Lu, None.

Dermatomyositis Skin Shares Type I Interferon Overlap with Cutaneous Lupus but Displays Many Unique Expression Changes That May Serve As Biomarkers for Skin Disease

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Muscle Biology, Myositis and Myopathies I: Biomarkers

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Dermatomyositis (DM) is a rare disease with both cutaneous and muscle pathophysiology. In the skin of DM patients, very little is known about the drivers of inflammation. In addition, the pathologic diagnosis of cutaneous DM is complicated by its morphologic overlap with cutaneous lupus erythematosus (CLE). Thus, it can be difficult to differentiate DM from CLE patients based on skin biopsy alone. We thus undertook this study to evaluate the gene expression changes in DM skin to understand the dysregulated genes in this disorder and to compare DM skin expression changes to our database of expression changes in CLE to determine unique and overlapping changes between the two diseases.

Methods: Thirty-six patient samples of DM skin biopsies were obtained through the University of Michigan Pathology Archives under IRB HUM72843. Validation of dermatomyositis was made via chart review for documented muscle disease, classic rash features such as Gottron's papules, and autoantibodies. RNA was isolated from formalin-fixed, paraffin-embedded tissue and subjected to microarray analysis via Affymetrix ST 2.1 chip. Differentially expressed genes in dermatomyositis were identified via linear model (*limma*). DM skin biopsies were stained for interferon (IFN) α , β , and κ via immunohistochemistry.

Results: For patients included in the DM cohort, the mean age was 55.5 (SD 16.7); 9 were male, and 27 were female. Race and ethnic distribution was as follows: 28 were Caucasian, 3 were African American, 2 were Hispanic, and 3 were unspecified. Thirteen had skin-only involvement, 22 patients had both muscle and skin involved. Principal component analysis demonstrated substantial differences between DM and healthy control skin. A total of 6,382 differentially expressed genes (DEGs; FDR \leq 10% and fold change (FC) \geq 2) were identified in DM skin. There was a strong correlation between SCLE and DM DEGs; however, DM patients had 4,550 unique DEG that showed limited dysregulation in SCLE. Of the genes in common between DM and SCLE, we identified a significant type I IFN signature, including *MX1*, *OASL*, and *IFIT1*. Interestingly, similar to our data from CLE skin, we identified IFN κ as the most significantly upregulated type I IFN in DM skin (FC=2, q=7.2E-06). IFN ϵ was the only other type I IFN upregulated by our array (FC=1.4; q=3.05E-02). Upregulation of IFN κ expression was confirmed by immunohistochemistry and displayed expression in the basal keratinocyte layer and in the dermis. Minimal IFN α and IFN β staining was seen. When genes unique to DM were subjected to GO analysis, functional enrichment in pathways involving vesicle transport (q= 2.03E-05), RNA splicing (q= 2.11E-05), and neutrophil degranulation (q= 5.18E-05) were noted.

Conclusion: DM skin displays a strong type I IFN signature and upregulation of IFN κ , similar to CLE, but there are distinct regulatory pathways that separate DM from CLE that may be useful biomarkers for early identification of DM. In addition, our data suggest that targeting type I IFN pathways in DM patients may be of benefit to skin lesions.

Disclosure: T. Nault, None; A. Tsoi, None; T. J. Reed, None; M. Gharraee-Kermani, None; L. Lowe, None; J. Gudjonsson, None; M. Kahlenberg, None.

Abstract Number: 877

Serum Krebs Von Den Lungen-6 Is a Useful Biomarker for Assessing Activity of Myositis-Associated Interstitial Lung Disease

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Muscle Biology, Myositis and Myopathies I: Biomarkers

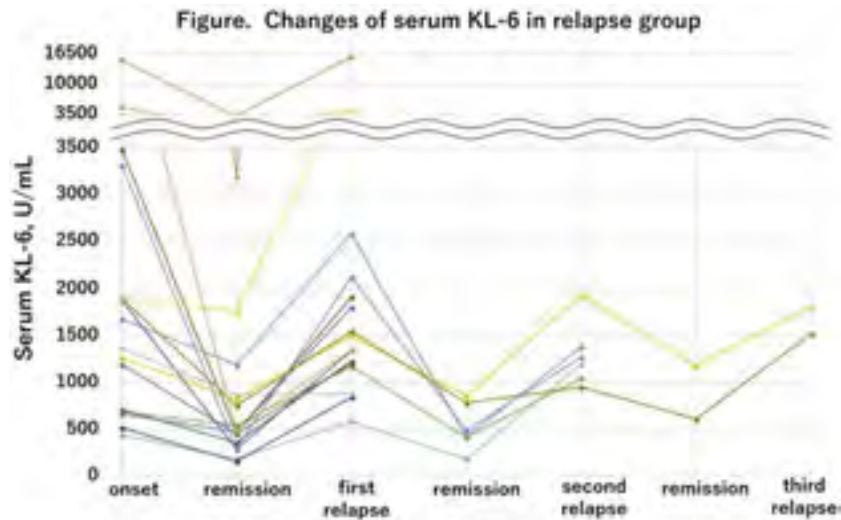
Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Interstitial lung disease (ILD) is one of serious organ involvements in idiopathic inflammatory myositis. Krebs von den Lungen-6 (KL-6) is an antigen produced primarily by regenerating type II pneumocytes and has been known as a biomarker in ILD, although whether it can be used to assess myopathy-associated ILD is unclear. The aim of this study is to elucidate the usefulness of KL-6 in myositis-associated ILD.

Methods: We reviewed consecutive patients with myositis-associated ILD in our institution between 2002 and 2017 and enrolled those with serum KL-6 at diagnosis available. We divided the patients into two groups who relapsed and did not (relapse group and non-relapse group), and compared serum KL-6 levels and its time-course changes during the observation period between 2 groups.

Results: Fifty-eight patients with myositis-associated ILD were included in the analysis. Median age at diagnosis was 51 years old, and female was 60%. Diagnosis consisted with 13 (22%) with polymyositis, 22 (38%) with dermatomyositis and



23 (40%) with clinically amyopathic dermatomyositis. Of those patients, 21 (36%) relapsed and 37 (64%) did not. Median period from diagnosis to the last visit in the non-relapse group was 27 months, and from diagnosis to the relapse in the relapse group was 26 months. Median KL-6 levels at diagnosis were significantly higher in the relapse group than the non-relapse group (1870 vs 935 U/mL, $p = 0.003$). A receiver operating characteristic curve identified baseline KL-6 of 1359 U/mL as a significant indicative level for futuristic relapse. When we followed the relapse group until the last visit (median period was 82 months), 6 patients experienced second or third relapse. The time-course change in serum KL-6 in the relapse group showed remarkable decrease at remission and increase at relapse in each time (Figure). The range of fluctuation of KL-6 levels was significantly wider in the relapse group than in the non-relapse group (866 vs 259 U/mL, $p < 0.001$), suggesting KL-6 levels in the non-relapse group was stable. The increase in KL-6 levels of 625 U/mL could be a cut-off level for relapse by receiver operating characteristic analysis.

Conclusion: Serum KL-6 is a useful biomarker for assessing activity of myositis-associated interstitial lung disease.

Disclosure: S. Takanashi, None; N. Nishina, None; M. Nakazawa, None; Y. Kaneko, None; T. Takeuchi, None.

Abstract Number: 878

IFN Level Assessed By Ultrasensitive Detection Technology in Myositis Patient: A Promising Biomarker of Disease Activity in Dermatomyositis and Anti-Synthetase Syndrome

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Muscle Biology, Myositis and Myopathies I: Biomarkers

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Inflammatory idiopathic myopathies (IIM) is a heterogeneous group of disorders ranging from muscle specific auto-immune diseases to systemic ones (dermatomyositis (DM), anti-synthetase syndrome (ASS), immune-mediated necrotizing myopathy (IMNM) and inclusion body myositis (IBM)). Recent insight into DM pathogenesis highlighted the role of type I interferon (IFN) and the level of IFN-pathway activity is linked to those of the disease. The aim of this study was to measure IFN- α seric level in the different groups of myositis using an ultrasensitive detection technology to evaluate IFN- α as disease activity biomarker.

Methods: IIM patients were enrolled in a monocentric prospective cohort. Clinical and biological data were prospectively collected as well as sera and peripheral blood mononuclear cells. Disease activity was assessed by calculating the Physician Global Activity (PGA) for each patient. To measure IFN- α level, sera were analyzed by single molecule array technology (SIMOA). The expression of IFN-stimulated genes (ISG) was detected by quantitative RT-PCR assays, and IFN scores were assessed by the median gene expression of the 5(ISG).

Results: One hundred and sixty-four patients (57 DM, 48 ASS, 35 IMNM and 24 IBM) and 35 age- and sex-matched healthy controls were included. Patient's characteristics were similar in all groups, but IBM patients were older (67.5 [63.5-78]) with a more severe weakness (Manual muscle testing 8 score was 120 ± 19) compared to DM (142 ± 7.6 , $p=0.001$) and to ASS patients (148 ± 12.4 , $p<0.001$).

IFN- α levels were higher in DM (0.05 ± 1.3 pg/ml, $p=0.005$) and ASS groups (0.06 ± 0.2 pg/ml, $p=0.005$) compared to controls (0.02 ± 0.06 pg/ml). IFN- α levels were similar in IMNM (0.03 ± 0.11 pg/ml), IBM (0.02 ± 0.07 pg/ml) and controls groups. As expected, anti-Jo1 antibody was associated with higher IFN- α level ($p=0.05$). IFN- α levels were correlated to disease activity in DM ($r=0.72$, $p<0.0001$) and ASS groups ($r=0.47$, $p=0.0009$).

Active (PGA >5) DM patients had a higher level of IFN- α (0.28 ± 1.9 pg/ml) compared to non-active patients (0.03 ± 0.05 pg/ml, $p<0.001$) and controls (0.02 ± 0.06 pg/ml; $p<0.001$). The accuracy of IFN- α level to discriminate active and non-active disease was excellent attested by an area of 0.92 under the ROC-curve (AUC). For an IFN- α level above 0.15 pg/ml, the sensitivity was 72.7% and specificity was 96.4%. Active ASS patients had also higher IFN- α level (0.16 ± 0.26 pg/ml) compared to non-active patients (0.04 ± 0.1 pg/ml, $p=0.003$) and controls ($p<0.001$). In ASS group, the accuracy of the test was also good (AUC=0.80) but the sensitivity and specificity were lower (52% and 87% respectively) for an IFN- α level cut-off at 0.29 pg/ml.

In naïve DM and ASS patients ($n=12$), IFN scores, considered as the gold standard to measure IFN activation, were assessed. The correlation between IFN score and IFN- α levels was very good ($r=0.76$, $p=0.005$).

Conclusion: IIM IFN- α level (assessed by SIMOA) is increased not only in DM but also in ASS patients. It is strongly correlated with disease activity especially in DM patients showing that it can be considered as biomarker of disease activity.

Disclosure: L. BOLKO, None; S. Toquet, None; O. Landon-Cardinal, None; K. DORGHAM, None; C. Anquetil, None; D. Duffy, None; N. WESNER, None; D. Amelin, None; G. DZANGUE TCHOUPOU, None; P. Guillaume, None; A. Rigolet, None; B. Hervier, None; M. Vautier, None; N. Champtiaux, None; G. Gorochoy, None; J. H. Salmon, Novartis, 5, Janssen, 5; O. Benveniste, None; Y. Allenbach, None.

Abstract Number: 879

IL-31 Protein Expression in Lesional Skin Correlates with Itch in Dermatomyositis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Muscle Biology, Myositis and Myopathies I: Biomarkers

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Dermatomyositis (DM) is an inflammatory myopathy where itch is a major contributor to impaired quality of life. Previously, we have shown that a cytokine responsible for itch in other diseases, interleukin (IL)-31, is elevated in lesional skin of DM patients. We aim to i) demonstrate the correlation between IL-31 protein expression in lesional skin and clinical assessment tools of itch severity and disease activity; ii) investigate the relationship between IL-31

protein expression in DM responders vs. non-responders in terms of itch and disease activity; iii) identify the cellular source of IL-31 in DM.

Methods: IL-31 protein expression in skin was quantified using immunohistochemistry (IHC) analysis of lesional skin samples of 12 DM patients at two separate time points. The visual analog scale (VAS), and SKINDEX-29 Symptoms Score clinical assessment tools, and Cutaneous Disease and Activity Severity Index (CDASI) were used to evaluate itch and disease activity. IHC co-localization of CD4, IL-31, and either IFN-gamma (Th1) or IL-4 (Th2) was performed on baseline lesional skin samples from 5 DM patients to identify the cellular source of IL-31.

Results: IL-31 expression with respect to mean cell intensity in lesional skin was highly correlated with SKINDEX-29 Symptoms Score, SKINDEX-29 question 10, and VAS itch score ($r=0.85$, $p<0.001$; $r=0.77$, $p<0.01$; $r=0.68$, $p<0.05$ respectively). IL-31 expression with respect to area stained was highly correlated with CDASI ($r=0.78$, $p<0.01$). These correlations were maintained at visit 6 ($r=0.65$, $p<0.05$; $r=0.64$, $p<0.05$; $r=0.60$, $p<0.05$; $r=0.74$, $p<0.01$). Itch responders had a greater reduction of IL-31 relative to non-responders with respect to mean cell intensity ($p<0.05$). Disease responders had a greater reduction in IL-31 staining area relative to non-responders ($p<0.05$). IHC co-staining of IL-31 with Th1 and Th2 markers demonstrated strong co-localization of IL-31 with Th1 T-cells and relatively little Th2 production of IL-31.

Conclusion: IL-31 cell intensity in lesional skin correlates strongly with itch severity while IL-31 staining area is highly correlated with disease activity. The source of IL-31 in DM is likely to be from Th1 cells rather than Th2 cells.

Disclosure: N. Reddy, None; M. Zeidi, None; V. P. Werth, CLASI, 4.

Abstract Number: 880

Serum Cytokine and Chemokine Concentrations Predict Incident Cancer in US Veterans with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes I: Other Co-Morbidities

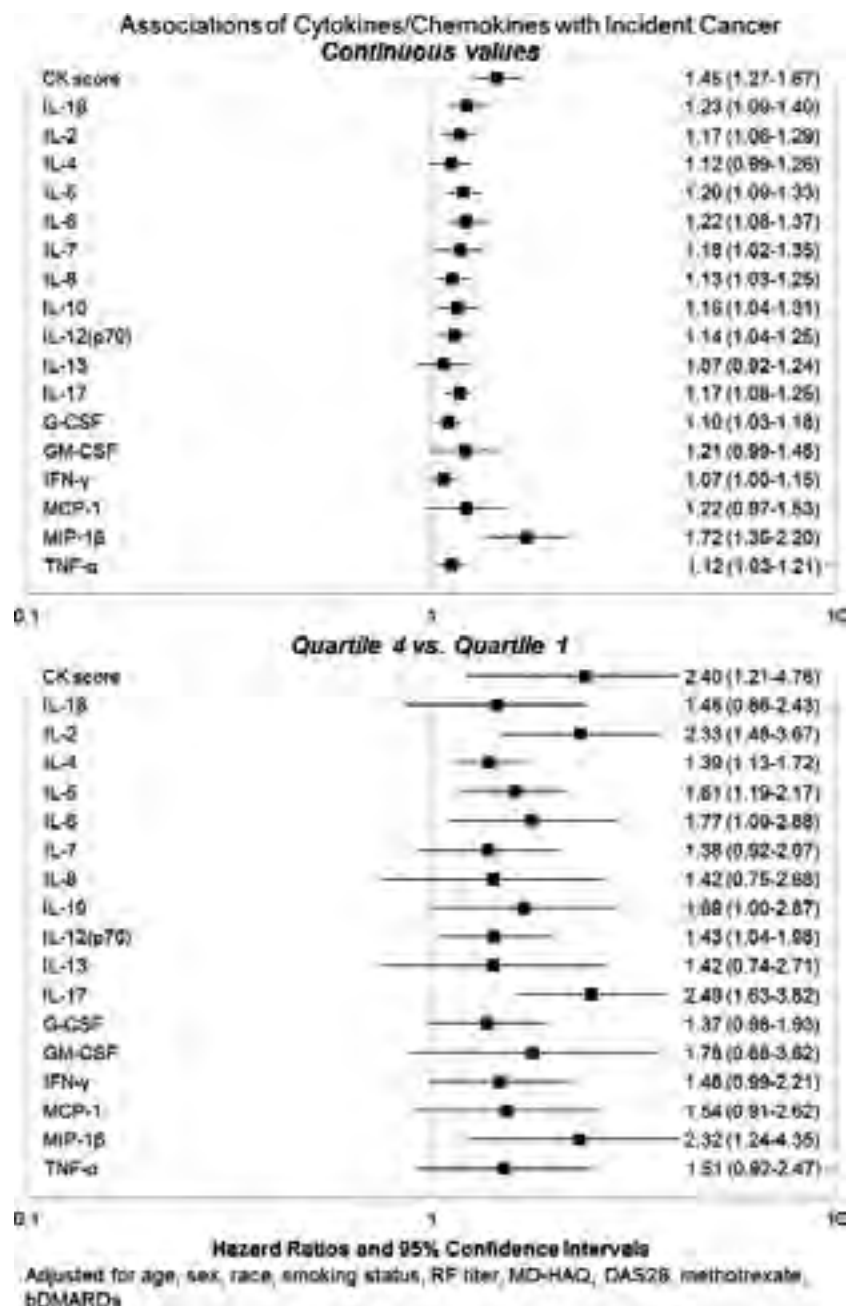
Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The immune system plays a critical protective role in cancer (CA) development. Perturbations in immune signaling, including cytokine dysregulation, may disrupt this homeostatic balance. Recently, IL-1 β inhibition reduced lung cancer incidence and mortality in a large RCT. We have previously shown serum cytokines are predictive of CA mortality in RA. The goal of the current study was to examine whether circulating cytokines are associated with CA incidence.

Methods: We linked the Veterans Affairs Rheumatoid Arthritis (VARA) registry with the VA Central Cancer Registry (VACCR) and the National Death Index (NDI). VACCR captures >90% of CAs occurring in US Veterans. VARA participants with available cytokine data and without a history of CA prior to VARA enrollment were included in analyses. Serum cytokines and chemokines (CKs) were measured with a 17-plex bead based assay using banked serum collected at VARA enrollment. CK score, an overall measure of CK concentrations, was calculated from individual analytes. Associations of CK with incident CA (identified in VACCR and NDI) were assessed using multivariable Cox regression models adjusting for age, sex, race, smoking status, DAS28, MD-HAQ, RF titer, methotrexate, and biologic use. CK score and individual analytes were analyzed as log-transformed continuous values and in quartiles. Additional analyses were stratified by smoking status (current vs. former/never).

Results: We studied 1,216 US Veterans with RA (mean age 63 yrs, 89% male, 78% anti-CCP positive) with available CK data, all without a pre-enrollment history of cancer. During 10,034 pt-yrs of follow-up, 159 incident CAs occurred with a median time to cancer of 4.7 yrs (IQR 2.7-6.9). Lung CA was the most frequent site ($n=41$), followed by prostate ($n=26$),



lymphoproliferative (n=23), and skin (n=15). Log-transformed CK score was associated with an increased risk of incident CA (aHR 1.45, 95% CI 1.27-1.67). Higher concentrations of 13 analytes were associated with increased CA risk (Figure). The highest quartile of CK score was associated with a >2-fold increased risk of CA (aHR 2.40; 95% CI 1.21-4.76). The highest quartiles of 8 analytes were significantly associated with CA risk, with the strongest effect sizes for IL-2 (aHR 2.33; 95% CI 1.48-3.67), IL-17 (aHR 2.49; 95% CI 1.63-3.82), and MIP-1 β (aHR 2.32; 95% CI 1.24-4.35). In stratified analyses, CK score was significantly associated with incident CA in both current and former/never smokers, though greater in current smokers.

Conclusion: Serum CK concentrations are predictive of future CA in RA patients, even after adjustment for RA disease activity and smoking. In addition to suggesting a potential role of CK profiling in modeling CA risk in RA, these results suggest that disease control and “normalization” of systemic CK disturbances could be important strategies in CA prevention in RA.

Disclosure: B. R. England, None; H. Sayles, None; P. Roul, None; A. Ganti, None; J. Sokolove, AbbVie Inc., 3; W. H. Robinson, None; G. W. Cannon, Amgen Inc., 2; B. Sauer, None; J. F. Baker, Corrona, Bristol Myers Squibb, 5; G. M. Thiele, None; T. R. Mikuls, BMS, Ironwood, Horizon, 2, Pfizer, Inc., 5.

Association of Comorbidities with DAS28 Disease Status and Remission in Race/Ethnic Groups with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes I: Other Co-Morbidities

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Racial/ethnic disparities in comorbidity (CM) in rheumatoid arthritis (RA) may confound treatment and outcomes. Rheumatic Disease Comorbidity Index (RDCI) is a validated tool predicting disability and mortality in RA patients. We evaluated the association between RDCI and clinical outcomes within racial/ethnic subsets of RA patients

Methods: Patients enrolled in the Ethnic Minority RA Consortium (EMRAC), with at least one follow-up (FU) visit were analysed. RDCI was compiled from enrolment data. Clinical outcomes: tender joint count (TJC), swollen joint count (SJC), RAPID 3 and DAS28; medication use (recorded and aggregated as prednisone methotrexate, other DMARD, and biologic use), were recorded. Analysis of variance or chi-square tests were used to estimate enrolment differences between racial/ethnic groups. Generalized estimating equations and mixed model regression accounting for repeated measurements were used to estimate any differences between racial/ethnic groups during FU, and explore associations of RDCI on clinical outcomes and remission (DAS28<2.6), adjusting for enrolment age, gender, education, race/ethnicity and medication use.

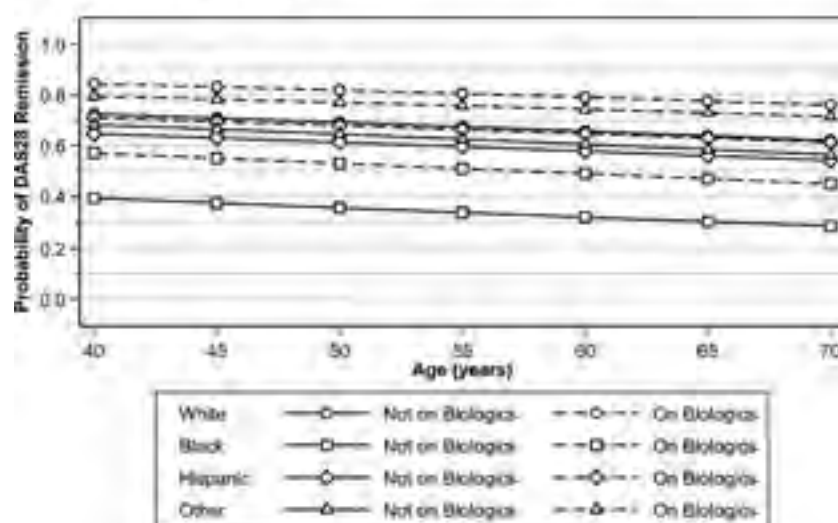
Results: 1066 subjects with 3719 FU visits over 58 weeks were evaluated. Racial/ethnic disparities were seen in formal education, RAPID3, DAS28, TJC, SJC as well as CM. Additionally, racial/ethnic disparities were seen in length of FU and medication use (**Table**). Increased RDCI scores were significantly associated with increased enrolment RAPID3 (P=0.022) and DAS28 (P<0.001), adjusting for age, education, gender and race/ethnicity. Enrolment DAS28 was also significantly higher in Blacks (0.49, 95% CI [0.21, 0.78], P=0.001) and Hispanics (0.70, 95% CI [0.37, 1.03], P=0.001) compared to Whites. While increased RDCI significantly reduced improvement in both RAPID3 (P<0.001) and DAS28 (P<0.001), RDCI was not significantly associated with reducing odds of DAS28 remission. Blacks, however, were significantly less likely to have DAS28 remission than all other race groups (**Figure**). Additionally, biologic use increased odds of DAS28 remission (OR=1.53, 95% CI [1.01, 2.33], P=0.45), but was less with advanced age (OR=0.80, 95% CI [0.68, 0.95], P=0.009).

Conclusion: CM was associated with higher disease activity regardless of race/ethnicity or medication, with black patients having more CM and less odds of remission. Early access to care for management of comorbidities and disease in Black RA patients is necessary to improve outcomes

Table. Enrolment and Follow-up Data by Racial / Ethnicity Groups

	White	Black	Hispanic	Other	Total	P
N	380	258	161	267	1066	
Enrolment						
Age (years)	55.53 (15.62)	56.66 (14.45)	54.48 (13.48)	54.01 (16.32)	55.27 (15.23)	0.214
Education (years)	15.07 (3.12)	13.42 (3.22)	12.61 (4.44)	15.23 (3.47)	14.25 (3.59)	<0.001
Female [N(%)]	296 (78.1%)	213 (82.6%)	129 (80.1%)	221 (86.0%)	859 (81.4%)	0.082
Tender Joints [0-28]	1.05 (3.62)	2.51 (5.02)	2.32 (4.91)	0.50 (2.37)	1.46 (4.06)	<0.001
Swollen Joints [0-28]	0.49 (2.04)	2.00 (3.82)	1.68 (3.85)	0.33 (1.76)	1.00 (2.92)	<0.001
RAPID3 [0-30]	11.33 (7.21)	13.07 (7.10)	12.68 (7.65)	10.83 (7.50)	11.95 (7.34)	<0.001
DAS28 [0-10]	2.32 (1.28)	3.11 (1.26)	3.09 (1.52)	2.41 (1.16)	2.28 (1.10)	<0.001
RDCI > 0 [N(%)]	95 (25.0%)	116 (45.0%)	48 (29.8%)	63 (23.6%)	322 (30.2%)	<0.001
Follow-up*						
Number of Visits	1368	1033	514	804	3719	
Length (weeks)	49.34 (46.59)	84.57 (71.77)	43.07 (46.58)	48.04 (50.25)	57.98 (57.87)	<0.001
Change RAPID3	1.54 (6.56)	0.71 (6.23)	2.37 (6.51)	1.06 (7.12)	1.29 (6.54)	<0.001
Change DAS28	0.34 (1.18)	0.03 (1.09)	0.80 (1.18)	0.37 (1.09)	0.34 (1.09)	<0.001
Prednisone Use [N(%)]	312 (22.8%)	216 (20.9%)	187 (36.4%)	225 (28.0%)	940 (25.3%)	0.030
Methotrexate Use [N(%)]	641 (46.9%)	342 (33.1%)	254 (49.4%)	456 (56.7%)	1693 (45.5%)	<0.001
Other DMARD Use [N(%)]	298 (21.8%)	213 (20.6%)	135 (26.3%)	215 (26.7%)	861 (23.2%)	<0.001
Biologic Use [N(%)]	572 (41.8%)	188 (18.2%)	136 (26.5%)	265 (33.0%)	1161 (31.2%)	<0.001

Figure. Probability of DAS28 Remission by Race / Ethnicity and Biologic Use over Age



* All follow-up visit differences between racial/ethnic groups were estimated using generalized estimating equations.

Disclosure: S. Dowell, BMS, 2, Pfizer, Inc., 2, Genetech, 2, Horizon Pharma, 8, BMS, 2, Genetech, 2; R. Perez-Alamino, None; C. J. Swearingen, None; G. S. Kerr, Novartis, 2; Y. Yazici, Celgene Corporation, 2.

Abstract Number: 882

Predictors of Chronic Kidney Disease in US Veterans with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes I: Other Co-Morbidities

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Chronic kidney disease (CKD) is a comorbidity that may affect patients with rheumatoid arthritis (RA). CKD restricts the use of disease modifying anti-rheumatic drugs (DMARDs) e.g. methotrexate, limiting the ability to control disease activity. We utilized the Veterans Affairs Rheumatoid Arthritis Registry (VARA), an observational chronic disease cohort at 11 Veterans Affairs (VA) medical centers where RA disease activity measures are recorded longitudinally to examine the frequency and progression of CKD in patients with RA..

Methods: VA patients enrolled in the VARA registry were eligible for analysis. This database was used to extract patient demographics and measures of RA disease activity and severity. Administrative data obtained from the VA corporate data warehouse (CDW) was collected for serum creatinine, weight, select comorbidities including ischemic heart disease (IHD), diabetes mellitus (DM) and hyperlipidemia. Creatinine clearance (CrCl) was calculated for each patient using the CKD-EPI creatinine equation and severity of CKD staged. Chi square and analysis of variance were used to compare categorical and continuous variables respectively between the stages of CKD. Longitudinal data from VARA and CDW were collected to examine the progression of CKD from stage II or better to Stage 3 or worse. A cox regression analysis was used to examine the effect of patient demographics and RA characteristics on the progression of CKD.

Results: There were 1577 RA patients available for study, 473 (30.1%) had CKD stages III to V, most, 399 (25.1%) had stage III. CKD was associated with male gender, older age and African American (AA) race (Table 1). There were no differences in the presence of RF, anti-CCP antibodies, radiographic changes or the use of DMARDs, however patients

with CKD were more likely to have subcutaneous (SC) nodules. Greater disease activity 28- C-reactive protein (DAS28-CRP) scores were reported in patients with stage IV and V CKD [4.0 (1.0) and 4.7 (1.4) respectively] compared with stage I and II [3.8 (1.2) and 3.6 (1.3) respectively] $p < 0.0001$. Comorbidities, DM, IHD and hyperlipidemia were independently associated with CKD ($p < 0.0001$). Predictors of progression of CKD included AA race HR= 2.0; CI = 1.48, 2.69, physician global assessment (PGA) HR = 1.36 (CI = 1.03, 1.80), DAS28-CRP, HR = 1.45 (CI = 1.10, 1.91) and IHD, HR = 1.63 (CI = 1.24, 2.16). Age, radiographic erosions, SC nodules and multi-dimensional health assessment questionnaire (MD-HAQ) were not associated with progression of CKD

Conclusion: CKD was not infrequent in US veterans with RA and was associated with older age, AA race, smoking, IHD, rheumatoid nodules and greater disability and disease activity. The predictors for the progression of CKD included AA race, PGA, DAS28-CRP and IHD. RA patients with early CKD should be monitored for disease progression and treatment of both CKD and RA optimized.

Table 1. Association of Patient and RA Characteristics with CKD* Stage

Characteristic	All (n = 1577)	Stage 1 (n = 414)	Stage 2 (n = 690)	Stage 3 (n = 399)	Stage 4 (n = 50)	Stage 5 (n = 24)	P Value
Age (SD)	65.9 (10.9)	58.6 (10.3)	66.3 (9.7)	71.9 (8.9)	72.3 (9.7)	67.3 (11.7)	< 0.0001
Female (%)	143 (9.1)	56 (13.5)	60 (8.7)	22 (5.5)	4 (8.0)	1 (4.2)	0.002
Race							<0.0001
Caucasian (%)	1219 (77.4)	290 (70.2)	548 (79.4)	331 (83.0)	33 (66.0)	17 (70.8)	
African American (%)	260 (16.5)	92 (22.3)	95 (13.8)	50 (12.5)	16 (32.0)	7 (29.2)	
Hispanic (%)	70 (4.4)	19 (4.6)	35 (5.1)	16 (4.0)	0 (0)	0 (0)	
Other (%)	28 (1.7)	12 (2.9)	12 (1.7)	2 (0.5)	1 (2.0)	0 (0)	
RF# (%)	1330 (85.5)	348 (85.3)	572 (84.2)	344 (86.9)	45 (91.8)	21 (87.5)	0.53
Anti-CCP£ (%)	1119 (71.9)	297 (72.8)	492 (72.5)	272 (68.7)	41 (83.7)	17 (70.8)	0.23
Radiographic Erosions (%)	1020 (65.6)	265 (65.0)	440 (64.8)	262 (66.2)	36 (73.5)	17 (70.8)	0.74
MD HAQ+ (SD)	0.94 (0.5)	0.97 (0.5)	0.89 (0.5)	0.96 (0.5)	1.03 (0.5)	1.28 (0.5)	< 0.0001
DAS28-CRP\$ (SD)	3.7 (1.2)	3.8 (1.2)	3.6 (1.3)	3.8 (1.2)	4.0 (1.0)	4.7 (1.4)	< 0.0001

*CKD = chronic kidney disease; # = rheumatoid factor; £ = anti-cyclic citrullinated peptide; + = multi-dimensional health assessment questionnaire; \$ = disease activity score 28 -c-reactive protein

Disclosure: J. S. Richards, None; R. Amdur, None; G. W. Cannon, Amgen Inc., 2; G. S. Kerr, Novartis, 2.

Abstract Number: 883

Evaluation of Fracture Risk and Osteoporosis in Males with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes I: Other Co-Morbidities

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Osteoporosis is an asymptomatic disease complicated by fractures and is associated with increased morbidity and mortality. Rheumatoid arthritis (RA) has been found to be a secondary cause for osteoporosis and it occurs more frequently in the RA population compared to the healthy population. There is a generalized consensus concerning osteoporosis screening in women, however, no such consensus exists for men due to insufficient available data. Current recommendations are to screen men ages 50-69 with increased risk and all men >70. However, with limited data available on appropriate screening guidelines, many with increased risk of osteoporosis are not being screened.

Objectives: The aims of this retrospective study were to assess if dual-energy x-ray absorptiometry (DEXA) scans are being obtained for males between the ages of 50-69, if these patients have decreased bone mineralization and if there is an increased risk of fractures in male patients with RA between the ages of 50-69.

Methods: A total of 1,970 male RA patients ages 50-69 were identified who were seen in an outpatient setting between the years of 2010-2017. Outpatient clinic notes, DEXA scans, radiology reports, laboratory results for rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP), along with hospital medical record discharge abstracts for all patients were retrieved. Outcomes included DEXA scan results and frequency of fractures.

Results: 488 DEXA scan results were obtained with osteopenia reported in 231 patients and osteoporosis reported in 67 patients. Of the overall results, 61% had decreased bone mineralization. Serologies for RF and CCP were compared with DEXA scan results and fractures. Osteoporosis was seen significantly more in the RF positive group compared to the RF negative group (30 and 9 respectively, chi-square 0.0076). Osteoporosis was also seen significantly more in the CCP positive group compared to the negative group (18 and 7 respectively, chi-square 0.027).

Conclusion: Our preliminary data show that in men <70 years of age there is evidence of osteopenia and osteoporosis on DEXA scans, especially in those who are RF and CCP positive. DEXA scans are not being utilized enough in males with RA <70 years of age. Increased screening can help recognize those with decreased bone mineralization who may need treatment to help prevent future fractures.

Disclosure: K. Herath, None; M. Saul, None; L. Zhu, None; L. W. Moreland, None.

Abstract Number: 884

Rheumatoid Arthritis Disease Activity Predicting Incident Clinically-Apparent Interstitial Lung Disease: A Prospective Cohort Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes I: Other Co-Morbidities

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Determining modifiable risk factors for interstitial lung disease (ILD) is crucial given its substantial morbidity/mortality. Treatment to target of remission/low disease activity improves articular RA outcomes, but the association with ILD is unclear. Prior studies correlated active RA with ILD, but were limited by cross-sectional designs with prevalent ILD. Therefore, we aimed to investigate RA disease activity and incident ILD risk.

Methods: We studied RA disease activity and incident ILD in a prospective cohort study at a single center (2003-2016). All subjects had RA according to ACR criteria. Disease activity score with 28 joints and C-reactive protein (DAS28-CRP3) and covariates were measured annually. Two pulmonologists and one radiologist adjudicated every clinically-indicated chest computed tomography (CT) scan. Cases were defined as consensus agreement with ILD diagnosis. We analyzed subjects with no clinically apparent ILD at baseline. We used Cox regression to estimate HRs and 95% CIs for ILD by DAS28-CRP3, adjusting for known ILD risk factors (age, sex, smoking, RA duration, and serostatus). We investigated DAS28-

Table: Hazard ratios for incident ILD among patients with RA according to category of DAS28-CRP3 (n=1,281).

	DAS28-CRP3 category				p for trend
	Remission (<2.6) HR (95%CI)	Low (2.6 to 3.2) HR (95%CI)	Moderate (>3.2 to 5.1) HR (95%CI)	High (>5.1) HR (95%CI)	
(Baseline)					
Unadjusted	1.00 (Ref)	0.92 (0.31-2.68)	2.57 (1.28-5.14)	3.09 (1.51-6.33)	0.0003
Multivariable*	1.00 (Ref)	0.87 (0.30-2.54)	2.31 (1.15-4.66)	2.27 (1.09-4.73)	0.001
Cumulative average updated					
Unadjusted	1.00 (Ref)	1.66 (0.71-3.92)	2.54 (1.28-5.02)	2.50 (1.05-5.92)	0.004
Multivariable*	1.00 (Ref)	1.50 (0.63-3.54)	1.97 (0.99-3.93)	1.59 (0.66-3.82)	0.09

There were 66 incident ILD outcomes during 13,141 person-years of follow-up in the baseline analysis. There were 65 incident ILD outcomes during 8,736 in the cumulative average updated analysis.

The cumulative average updated analysis accounted for all previous and current annual DAS28-CRP3 measures for each cycle predicting ILD risk in the subsequent year.

*Adjusted for age, sex, smoking pack-years, RA duration, and serostatus (+CCP and/or RF vs -CCP and/or RF).

CCP, cyclic citrullinated peptide; CI, confidence interval; DAS28-CRP3, disease activity score with 28 joints and C-reactive protein; ILD, interstitial lung disease; HR, hazard ratio; RA, rheumatoid arthritis; RF, rheumatoid factor.

CRP3 categories at baseline in the primary analysis. As a secondary analysis, we used cumulative average updated DAS28-CRP3, which took into account all previous disease activity measures to predict incident ILD in the subsequent year.

Results: Among 1,281 subjects at baseline, mean age was 56.0 years (SD 14.1), 82.1% were female, 69.6% were seropositive, median RA duration was 9 years, and 58.3% had high/moderate disease activity. During 13,141 patient-years (median follow-up 8 years), we identified 86 cases of incident clinically-apparent ILD. ILD risk significantly increased across baseline DAS28-CRP3 categories. The multivariable HR (95% CI) for ILD by DAS28-CRP3 categories were: 1.00 (reference) for remission, 0.87(0.30-2.54) for low, 2.31 (1.15-4.46) for moderate, and 2.27 (1.09-4.73) for high; *p* for trend=0.001). Compared to low/remission, moderate/high disease activity had HR for ILD of 2.41 (95% CI 1.37-4.25). When analyzing cumulative average updated DAS28-CRP3 with fewer ILD outcomes and shorter follow-up, there was a trend towards significance of active RA increasing ILD risk (*p*=0.09). Seropositivity was strongly associated with ILD risk (HR 2.69, 95% CI 1.38-5.27).

Conclusion: In this large prospective cohort using adjudicated ILD outcomes, active RA was associated with increased risk for clinically-apparent ILD. Replication studies in other prospective cohorts and clinical trials are needed to firmly establish the role of RA treat-to-target approaches and ILD risk, particularly for patients with seropositive RA.

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Abstract Number: 885

Herpes Zoster in Tofacitinib Users with and without Concomitant Methotrexate and Glucocorticoids

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes I: Other Co-Morbidities

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: An increased incidence of herpeszoster (HZ) has been observed with Janus kinase inhibitors such as tofacitinib(TOF). However, among TOF users, a potentially additive or multiplicative risk of HZ associated with concomitant methotrexate (MTX) and glucocorticoid (GC) use is not clear. We evaluated HZ risk in TOF users with and without MTX and GC, to evaluate potential interactions.

Methods: Market Scan and Medicare data (2011-2016) was used to identify all rheumatologist-diagnosed RA patients initiating TOF (indexdate); demographics and covariates were evaluated in the 12 prior months(baseline); pts with HIV, malignancy or prior HZ (or anti-viral commonly used for HZ) in baseline were excluded. All 3 main drug exposures were time-varying with a 30 day extension. HZ was ascertained using ICD9/10 codes with anti-viral drug use (+/-7 days). Multivariable (MV) Cox regression was used to evaluate hazard ratios (HRs) for HZ in TOF users with and without MTX and GC, controlling for baseline covariates.

Results: A total of 8,030 new TOF users meteligibility criteria for analysis. Mean (SD) age was 60.3 (12.6) years, 83.3% women. The crude HZ incidence with TOF use was numerically lowest in the absence of GC (e.g. 3.4/100py with MTX and 3.7/100py without MTX, Table). An approximately two-fold increased crude incidence of HZ was observed for TOF users receiving either GCs alone (6.0/100 py) or both MTX and GCs (6.5/100py).After MV adjustment, the HR for HZ associated with TOF was unchanged when given with MTX but approximately double when TOF was given with GC. Based on the non-significant interaction *p* value, there was no indication of an interaction between MTX and GC. Among various covariates, older age was a significant albeit weak risk factor for HZ (adjusted HR = 1.05, 95% CI 1.03-1.18, per 5 year increment).

Conclusion: These analyses suggest that HZ risk in TOF users is doubled with GC exposure. Concomitant MTX did not confer increased risk.

Table: Herpes Zoster Risk Associated with Tofacitinib according to Concomitant Use of Methotrexate and Glucocorticoids

Concomitant Medications with TOF	Events	Incidence Rate per 100PY	Adjusted Hazard Ratio
No MTX; no GC	73/1986	3.7 (2.9-4.6)	1.0 (ref)
With MTX; no GC	27/791	3.4 (2.3-5.0)	1.00 (0.64, 1.55)
No MTX; with GC	82/1356	6.0 (4.9-7.5)	2.03 (1.42, 2.91)
With MTX; with GC	40/617	6.5 (4.8-8.8)	2.24 (1.47, 3.43)

PY = Patient-years; MTX = methotrexate; GC = glucocorticoid

Disclosure: J. R. Curtis, AbbVie, Amgen, Bristol-Myers Squibb, Corrona, Janssen, Lilly, Myriad, Pfizer, Radius, Roche/Genentech, UCB, 2, AbbVie, Amgen, Bristol-Myers Squibb, Corrona, Janssen, Lilly, Myriad, Pfizer, Radius, Roche/Genentech, UCB, 5; F. Xie, None; S. Bernatsky, None; S. Yang, None; L. Chen, None; H. Yun, Bristol Myers Squibb, 2; K. Winthrop, Pfizer, Inc., 5, Lilly, 5, AbbVie Inc., 5, Galapagos, 5.

Abstract Number: 886

Efficacy and Safety of Switching from Adalimumab to Baricitinib: Long-Term Data from Phase 3 Extension Study in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments I: JAK Inhibitors

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Baricitinib (bari) is an oral JAK1/JAK2 inhibitor approved for the treatment of moderately to severely active RA in adults in over 40 countries, including European countries, the United States, and Japan. In the 52-week Phase 3 RA-BEAM study, bari 4-mg once daily (QD) showed clinical improvements compared with placebo (PBO) and with adalimumab (ADA) in MTX-inadequate-responder (IR) patients (pts).¹ The objective of this analysis was to evaluate efficacy, patient-reported outcomes (PRO), and safety in pts from RA-BEAM who switched treatment from ADA to bari after entering a long-term extension (LTE) study (RA-BEYOND).

Methods: In RA-BEAM (completed September 2015), 1305 pts were randomized 3:3:2 to PBO, bari 4-mg QD, or ADA 40-mg every 2 weeks (wks). At wk 52, pts could enter the LTE, where all pts received open-label bari 4-mg but remained blinded to randomized treatment in RA-BEAM. No ADA washout period was applied. Efficacy, PROs, and safety were evaluated in pts who were not rescued in RA-BEAM and entered the LTE ≥ 48 wks before the data cutoff of April 1, 2017.

Results: Among pts who completed RA-BEAM without rescue, 381/394 (97%) bari (continued bari), and 238/241 (99%) ADA (switched to bari) pts entered the LTE ≥ 48 wks before the cutoff date and were included in the analysis. Pts who switched from ADA to bari showed improvements in disease control through 24 wks post-switch in the LTE without evidence of worsening through the following 24 wks (Table 1) and showed further small improvements in PRO assessment of pain and physical function (HAQ-DI) through wk 48 (Figure 1). Of pts who were non responders (CDAI > 10) at the time of switch (107 and 74 in bari and ADA groups, respectively) approximately half reached low disease activity (CDAI ≤ 10) by wk 48 (54% and 50%, respectively). Exposure-adjusted incidence rates for treatment-emergent adverse events (TEAEs) and infections, including serious AEs, were similar for pts who switched from ADA to bari and those who continued bari (Table 2).

Conclusion: Switching from ADA to bari without ADA washout was associated with maintenance of disease control through 48 wks post-switch, with some non responders being able to achieve LDA as well. There was no increase in TEAEs or serious AEs or infections.

Reference: ¹ Taylor PC et al. *NEJM*, 2017;376:652-62



Table 1. Percent of patients who reached low disease activity and remission at weeks 24 and 48 after entering the LTE RA-BEYOND study for patients switched to baricitinib

	Baricitinib to Baricitinib			Adalimumab to Baricitinib		
	Week 0	Week 24	Week 48	Week 0	Week 24	Week 48
CDAI						
≤10	273 (71.8)	292 (76.8)	297 (78.2)	164 (68.9)	176 (73.9)	175 (73.5)
≤2.8	104 (27.4)	117 (30.8)	120 (31.6)	58 (24.4)	72 (30.3)	67 (28.2)
SDAI						
≤11	273 (71.8)	296 (77.9)	300 (78.9)	164 (68.9)	181 (76.1)	172 (72.3)
≤3.3	108 (28.4)	125 (32.9)	127 (33.4)	59 (24.8)	73 (30.7)	68 (28.6)
DAS28-ESR						
≤3.2	188 (49.5)	181 (47.6)	203 (53.4)	120 (50.4)	138 (58.0)	120 (50.4)
<2.6	111 (29.2)	102 (26.8)	128 (33.7)	71 (29.8)	80 (33.6)	71 (29.8)

CDAI, Clinical Disease Activity Index; DAS28-ESR, Disease Activity Score 28-joint count erythrocyte sedimentation rate; LTE, long-term extension; SDAI, Simple Disease Activity Index. Baricitinib to Baricitinib = Patients completing RA-BEAM (Week 52) on baricitinib who continued baricitinib in RA-BEYOND. Adalimumab to Baricitinib = Patients completing RA-BEAM on adalimumab who transitioned to baricitinib (week 52) upon entering the LTE. Week 0 = Baseline of LTE. Data are n (%) using non-responder imputation for missing data

Table 2. Safety through 48 weeks after switch to baricitinib upon entry to RA-BEYOND

	Baricitinib to Baricitinib (n = 381; PYE = 262.0)	Adalimumab to Baricitinib (n = 238; PYE = 224.0)
Patients with ≥1 TEAE	211 (55.4) [80.5]	162 (68.1) [72.3]
Infections	104 (27.3) [39.7]	87 (36.6) [38.8]
Herpes zoster	6 (1.6) [2.3]	5 (2.1) [2.2]
Gastrointestinal disorders	41 (10.8) [15.6]	29 (12.2) [12.9]
AEs that led to permanent study drug discontinuation	7 (1.8) [2.7]	6 (2.5) [2.7]
Patients with ≥1 SAE	32 (8.4) [12.2]	18 (7.6) [8.0]
Serious infections	10 (2.6) [3.8]	5 (2.1) [2.2]

AE, adverse event; EAIR, exposure-adjusted incidence rate; PYE, patient-years of exposure; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Data are n (%) [EAIR].

Disclosure: M. E. Weinblatt, Amgen, BMS, Crescendo Bioscience, Sanofi/Regeneron, 2, Abbvie, Amgen, BMS, Crescendo Bioscience, Corrono, GSK, Gilead, Eli Lilly and Company, Lycera, Merck, Novartis, Pfizer, Roche, Samsung, Set Point, UCB, 5, Lycero, Can-fite, Scipher, Vorso, Inmedix, 1; P. C. Taylor, Celgene, Eli Lilly and Company, Galapagos, UCB, 2, AbbVie, Eli Lilly and Company, Galapagos, GlaxoSmithKline, Pfizer, UCB, Biogen, Sandoz, Novartis, Janssen, 5; E. C. Keystone, AbbVie, Amgen, Bristol-Myers Squibb, F. Hoffmann-La Roche Inc, Gilead, Janssen Inc, Eli Lilly and Company, Pfizer Pharmaceuticals, Sanofi-Aventis, 2, AbbVie, Amgen, AstraZeneca Pharma, Biotest, Bristol-Myers Squibb Company, Celltrion, Crescendo Bioscience, F. Hoffmann-La Roche Inc, Genentech Inc, Gilead, Janssen Inc, Eli Lilly and Company, Merck, Pfizer Pharmaceuticals, Sandoz, UCB, 5, 9, Amgen, AbbVie, Bristol-Myers Squibb Canada, F. Hoffmann-La Roche Inc., Janssen Inc., Merck, Pfizer Pharmaceuticals, Sanofi Genzyme, UCB, 8; R. A. Ortmann, Eli Lilly and Company, 1, 3; M. Issa, Eli Lilly and Company, 1, 3; L. Xie, Eli Lilly and Company, 1, 3; S. de Bono, Eli Lilly and Company, 1, 3; Y. Tanaka, Mitsubishi-Tanabe, Bristol-Myers, Eisai, Chugai, Takeda, Abbvie, Astellas, Daiichi-Sankyo, Ono, MSD, Taisho-Toyama, 2, Daiichi-Sankyo, Astellas, Eli Lilly, Chugai, Sanofi, Abbvie, Pfizer, YL Biologics, Bristol-Myers, Glaxo-Smithkline, UCB, Mitsubishi-Tanabe, Novartis, Eisai, Takeda, Janssen, Asahi-kasei, 5.

Efficacy and Safety of the Novel Oral Janus Kinase (JAK) Inhibitor, Peficitinib (ASP015K), in a Phase 3, Double-Blind, Placebo-Controlled, Randomized Study of Patients with RA Who Had an Inadequate Response to Dmards

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments I: JAK Inhibitors

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Peficitinib (ASP015K), a novel oral JAK inhibitor, demonstrated efficacy as once-daily monotherapy in patients with moderate to severe RA in a phase 2b study (NCT01649999). In this phase 3 study (NCT02308163), we report efficacy and safety data for peficitinib alone or in combination with DMARDs in patients with RA who had an inadequate response to DMARDs.

Methods: This multicenter, randomized, double-blind, parallel-group, placebo (PBO)-controlled study was conducted in Japan, Korea, and Taiwan. All patients had RA diagnosed according to 1987 ACR or 2010 ACR/EULAR criteria. Patients

Table 1: Primary and selected secondary efficacy endpoints at week 12/ET

Result at 12 weeks/ET	PBO	Peficitinib 100 mg/day	Peficitinib 150 mg/day	Etanercept 50mg/week (open-label arm)
ACR20 ^a , n/N (%)	81/101 (80.7)	60/104 (57.7)***	76/102 (74.5)***	167/200 (83.5)
ACR50 ^a , n/N (%)	9/101 (8.9)	32/104 (30.8)***	43/102 (42.2)***	105/200 (52.5)
ACR70 ^a , n/N (%)	1/101 (1.0)	14/104 (13.5) ^{b,1}	28/102 (27.5)***	61/200 (30.5)
Mean (SD) CRP change from baseline, mg/dL	0.022 (1.498)	-1.056 (1.908)***	-1.734 (1.906)***	-1.207 (2.694)
Mean (SD) ESR change from baseline, mm/h	-1.96 (17.82)	-12.96 (21.51)***	-23.92 (21.26)***	-20.92 (21.66)
DAS28-CRP <2.6 ² , n/N (%)	5/100 (5.0)	25/102 (24.5)***	35/101 (34.7)***	91/200 (45.5)
Mean (SD) DAS28-CRP change from baseline, n	-0.64 (1.20)	-1.63 (1.41)***	-2.17 (1.14)***	-2.42 (1.11)
Mean (SD) change from baseline in patient's assessment of pain, 100 mm VAS	-6.64 (24.61)	-23.78 (30.75)***	-30.85 (27.91)***	-30.82 (27.88)
SDAI remission (SDAI score ≤3.3) ³ , n/N (%)	0/100	9/102 (8.8) ²	9/101 (8.9) ²	37/200 (18.5)

Last Observation Carried Forward imputation method was used. Statistical testing was performed for ASP015K 100 mg and 150 mg, compared with PBO. ***p<0.001 vs PBO according to Wald's chi-square test for ACR20, ACR50, ACR70, DAS28-CRP <2.6, and SDAI remission, and analysis of covariance for CRP, ESR, DAS28-CRP and patient's assessment of pain. Closed testing procedure was used for multiplicity adjustment in the primary analysis.

^aBased on logistic regression model: Response (responder, non-responder) = treatment + the prior biologics (DMARD-10) (no, yes) + concomitant DMARD use (no, yes) + study region (Japan, Korea, and Taiwan).

^bNot estimable owing to the small number of responses.

¹In a post-hoc analysis, based on the logistic regression model in which the only independent variable was treatment, the odds ratio between PBO and peficitinib 100 mg for ACR70 was estimated and p=0.009.

SD=standard deviation; SDAI=simplified disease activity index; VAS=visual analog scale.

Table 2: Treatment-emergent adverse events

	PBO (N=101)	Peficitinib 100 mg/day (N=104)	Peficitinib 150 mg/day (N=102)	Peficitinib 100 mg/day + 150 mg/day (N=206)	Etanercept 50mg/week (open-label arm) (N=200)
Event, n (%), Week 0–12					
Any AE	54 (53.3)	59 (56.7)	55 (53.5)	114 (55.3)	119 (59.5)
Drug-related AE ¹	29 (28.7)	33 (31.7)	38 (37.3)	71 (34.5)	75 (37.5)
Death	0	0	0	0	0
SAE	4 (4.0)	9 (2.9)	2 (2.0)	9 (2.4)	4 (2.0)
Drug-related SAE ¹	3 (3.0)	2 (1.9)	1 (1.0)	3 (1.3)	4 (2.0)
Grade ≥3 AE ²	8 (7.9)	6 (5.8)	3 (2.9)	9 (4.4)	6 (3.0)
AE leading to permanent discontinuation of study drug	4 (4.0)	6 (5.8)	3 (2.9)	9 (4.4)	5 (2.5)
Serious infection	0	0	1 (1.0)	1 (0.5)	1 (0.5)
Herpes zoster-related disease	0	1 (1.0)	0	1 (0.5)	2 (1.0)
Malignancy	0	0	0	0	0
Incidence rate per 100 patient- years (95% confidence interval), overall study period ³	PBO (N=101)	Peficitinib 100 mg/day (N=104)	Peficitinib 150 mg/day (N=102)	Peficitinib total (N=296) ⁴	Etanercept 50mg/week (open-label arm) (N=200)
Serious infection ⁵	0.0	1.1 (0.2, 8.1)	2.2 (0.5, 8.7)	2.0 (0.8, 4.9)	2.0 (0.8, 5.5)
Herpes zoster-related disease	0.0	5.8 (2.4, 13.8)	4.4 (1.7, 11.7)	5.8 (3.4, 9.8)	2.6 (1.1, 6.2)
Malignancy	0.0	2.3 (0.6, 9.1)	0.0	1.2 (0.4, 3.8)	0.5 (0.1, 3.6)

¹Severity or probability related to study drug, as assessed by risk investigator, or events where causation is obvious.

²Based on NCI-CTCAE grade 3–severe or medically significant, grade 4–life threatening, grade 5–death related to AE.

³Median years event from initial dose up to first occurrence of AE for patients who had at least one event; otherwise, the duration of the patient's last event is used.

⁴Includes AEs that occurred after initial peficitinib dosing, and after switching from PBO to peficitinib 100 mg/day or 150 mg/day.

⁵Defined as an AE belonging to the System organ class of "infections and infestations" and regarded as serious.

AE=adverse event; SAE=serious adverse event.

with active RA (defined as ≥ 6 tender and painful joints and ≥ 6 swollen joints, using 68 and 66-joint assessment respectively, and CRP >0.50 mg/dL) and inadequate response to DMARDs (administered for ≥ 90 days) were randomized in a 1:1:1:2 ratio to 52 weeks' treatment with PBO, peficitinib 100 mg/day, peficitinib 150 mg/day or etanercept 50 mg/week (open-label reference arm). At week 12, patients initially assigned to PBO were switched (under blinded conditions) to either peficitinib 100 mg/day or peficitinib 150 mg/day until end of treatment. Concomitant stable dose of DMARDs was permitted. The primary efficacy variable was ACR20 response rate at week 12/early termination (ET).

Results: In total, 507 patients were randomized and treated: PBO (n=101), peficitinib 100 mg/day (n=104), peficitinib 150 mg/day (n=102) and etanercept (n=200). Regarding efficacy at week 12/ET, significant differences were observed with peficitinib 100 mg/150 mg vs PBO ($p<0.001$) in the proportion of patients achieving ACR20, ACR50, ACR70 (150 mg/day dose only) and DAS28-CRP <2.6 , and for change from baseline to week 12/ET in DAS28-CRP (**Table 1**). Week 0–12 safety results were similar between treatment groups, while serious adverse events were more common with PBO than other study treatments (**Table 2**). For the overall study period, the incidence rate of serious infections per 100 patient-years was higher with peficitinib 100 mg/150 mg than PBO (**Table 2**). There were no deaths during the study.

Conclusion: In patients with RA who had an inadequate response to DMARDs, 100 mg/day and 150 mg/day peficitinib doses significantly reduced RA symptoms according to clinical and patient assessment scores. The proportion of patients achieving the primary efficacy variable (ACR20 at week 12/ET) was significantly greater for both peficitinib doses versus PBO. Peficitinib 100 mg/day and 150 mg/day showed acceptable safety and tolerability, with no new safety signals detected compared with other JAK inhibitors.

Disclosure: Y. Tanaka, Astellas Pharma, Inc., 2, 5, 9; T. Takeuchi, Astellas Pharma, Inc., 2, 5, 9; S. Tanaka, Astellas Pharma, Inc., 2, 9; A. Kawakami, Astellas Pharma, Inc., 2, 5, 8, 9; M. Iwasaki, Astellas Pharma, Inc., 9; Y. W. Song, Astellas Pharma, Inc., 9; Y. H. Chen, Astellas Pharma, Inc., 9; M. Rokuda, Astellas Pharma, Inc., 3, 9; H. Izutsu, Astellas Pharma, Inc., 3, 9; S. Ushijima, Astellas Pharma, Inc., 3, 9; Y. Kaneko, Astellas Pharma, Inc., 3, 9; T. Shiomi, Astellas Pharma, Inc., 3, 9; E. Yamada, Astellas Pharma, Inc., 3, 9.

Efficacy and Safety of the Novel Oral Janus Kinase (JAK) Inhibitor, Peficitinib (ASP015K), in a Phase 3, Double-Blind, Placebo-Controlled, Randomized Study of Patients with RA Who Had an Inadequate Response to Methotrexate

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments I: JAK Inhibitors

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Peficitinib (ASP015K), a novel oral JAK inhibitor, demonstrated efficacy as once-daily monotherapy in patients with moderate-to-severe RA in a phase 2b study (NCT01649999)¹. We report phase 3 efficacy and safety data for peficitinib–methotrexate (MTX) combination in patients with RA who had an inadequate response to MTX (NCT02305849).

Table 1: Primary and selected secondary efficacy endpoints at week 12/ET

Result	Week 12/ET			Week 28/ET		
	PBO	Peficitinib 100 mg/day	Peficitinib 150 mg/day	PBO	Peficitinib 100 mg/day	Peficitinib 150 mg/day
ACR20, n/N (%)	37/170 (21.8)	102/174 (58.6)***	112/174 (64.4)***	50/170 (29.4)	129/174 (74.1)***	137/174 (78.7)***
ACR50, n/N (%)	13/170 (7.6)	52/174 (29.9)***	80/174 (46.0)***	19/170 (11.2)	88/174 (50.6)***	103/174 (59.2)***
ACR70, n/N (%)	4/170 (2.4)	21/174 (12.1)***	41/174 (23.6)***	10/170 (5.9)	47/174 (27.0)***	70/174 (40.2)***
Mean (SD) CRP change from baseline, mg/dL	-0.001 (2.038)	-1.499 (1.855)***	-1.421 (2.182)***	-0.041 (2.399)	-1.649 (2.165)***	-1.625 (2.236)***
Mean (SD) ESR change from baseline, mm/h	-2.42 (19.71)	-18.90 (19.85)***	-22.17 (22.79)***	-3.26 (22.68)	-24.51 (23.67)***	-26.21 (24.58)***
DAS28-CRP <2.6, n/N (%)	13/169 (7.7)	54/172 (31.4)***	60/171 (35.1)***	20/169 (11.8)	86/172 (50.0)***	86/171 (50.3)***
Mean (SD) DAS28-CRP change from baseline, n	-0.51 (1.10)	-1.70 (1.20)***	-2.09 (1.33)***	-0.64 (1.33)	-2.27 (1.31)***	-2.56 (1.38)***
Mean (SD) change from baseline in patient's assessment of pain, 100 mm VAS	-6.64 (25.22)	-21.09 (27.04)***	-26.87 (26.65)***	-7.61 (27.81)	-26.33 (28.22)***	-32.23 (27.59)***
SDAI remission (SDAI score ≤3.3), n/N (%)	1/169 (0.6)	12/172 (7.0)**	24/171 (14.0)***	6/169 (3.6)	36/172 (20.9)***	37/171 (21.6)***
	Week 28/ET			Week 52/ET		
	PBO	Peficitinib 100 mg/day	Peficitinib 150 mg/day	PBO	Peficitinib 100 mg/day	Peficitinib 150 mg/day
Mean (SD) mTSS change from baseline ¹	3.37 (5.46)	1.62 (4.23)***	1.03 (2.86)***	6.27 (10.18)	2.12 (5.83)***	1.54 (4.11)***
Patients achieving mean mTSS change from baseline ≤0.5 ¹ , n/N (%)	70/153 (45.8)	110/164 (67.1)***	119/164 (72.6)***	65/153 (42.5)	105/164 (64.0)***	113/164 (68.9)***

Last Observation Carried Forward imputation method was used, except for mTSS. Statistical testing was performed for peficitinib 100 mg, and 150 mg, compared with PBO.

p<0.01 vs PBO; *p<0.001 vs PBO, according to Fisher's Exact test for ACR20, ACR50, ACR70, DAS28-CRP <2.6, SDAI remission, and mTSS change from baseline ≤0.5; analysis of covariance for CRP, ESR, DAS28-CRP, and patient's assessment of pain; and rank analysis of covariance for mTSS change from baseline. Closed testing procedure was used for multiplicity adjustment in the primary analysis.

¹For the calculation of mTSS, patients who discontinued at or before week 28 or were switched from PBO to peficitinib at week 12 due to lack of efficacy, week 28/ET mTSS was extrapolated using linear extrapolation method based on the mTSS at baseline and early termination or week 12 (day 85) (before switching). For patients who discontinued at or before Week 52 or switched to receive peficitinib instead of placebo at Week 12 or Week 28, mTSS at Week 52/ET was extrapolated using a linear extrapolation method based on mTSS at baseline and early termination, Week 12 (Day 85) or Week 28 (Day 197) (before switching).

mTSS=modified Total Sharp score; SD=standard deviation; SDAI=simplified disease activity index; VAS=visual analog scale.

Table 2: Treatment-emergent adverse events

	PBO (N=170)	Peficitinib 100 mg/day (N=174)	Peficitinib 150 mg/day (N=174)	Peficitinib 100 mg/day + 150 mg/day (N=348)
Event, n (%), Week 0–12				
Any AE	84 (49.4)	89 (51.1)	104 (59.8)	193 (55.5)
Drug-related AE ¹	47 (27.6)	57 (32.8)	80 (46.0)	137 (39.4)
Death	0	0	0	0
SAE	4 (2.4)	5 (2.9)	8 (4.7)	8 (2.3)
Drug-related SAE ¹	2 (1.2)	3 (1.7)	3 (1.7)	5 (1.4)
Grade ≥3 AE ¹	5 (2.9)	9 (5.2)	16 (9.2)	25 (7.2)
AE leading to permanent discontinuation of study drug	7 (4.1)	5 (2.9)	5 (2.9)	10 (2.9)
Serious infection	0	3 (1.7)	3 (1.7)	4 (1.1)
Herpes zoster-related disease	0	2 (1.1)	3 (1.7)	5 (1.4)
Malignancy	0	0	0	0
Incidence rate per 100 patient-years (95% confidence interval), overall study period ²	PBO (N=170)	Peficitinib 100 mg/day (N=174)	Peficitinib 150 mg/day (N=174)	Peficitinib total (N=348) ³
Serious infection ²	0.0	3.8 (1.7, 8.4)	3.7 (1.7, 8.3)	3.4 (2.0, 5.5)
Herpes zoster-related disease	0.0 (0.0, 2.8)	8.1 (4.8, 14.3)	3.8 (1.7, 8.4)	5.7 (3.6, 9.4)
Malignancy	0.0 (0.0, 1.1)	0.0 (0.0, 4.4)	0.0	0.0 (0.0, 3.7)

¹Previously or potentially related to study drug, or caused by the intervention, or events which necessitate a report.

²Based on FDA CTCAE global grade 1 events or specifically specified grade 4–5 events occurring at the 5-week point for AE.

³Percentages of serious infections shown up to 12 of patients with RA for whom serious infection was reported at least one event; otherwise, the denominator for the denominator is the number of patients who were included in the study (N=348).

⁴Includes AE that occurred after initial enrollment, and after switching from PBO to peficitinib 100 mg/day or 150 mg/day.

⁵Based on the incidence rate per 100 patient-years of serious infections, and reported as events.

AE=adverse event; SAE=serious adverse event.

Methods: This multicenter, randomized, double-blind, parallel-group, placebo (PBO)-controlled study was conducted in Japan. Patients had RA diagnosed within the past 10 years (1987ACR or 2010 ACR/EULAR criteria), active disease (≥ 6 tender and painful joints and ≥ 6 swollen joints, using 68 and 66-joint assessment respectively; CRP ≥ 1.0 mg/dL; bone erosion; and ACPA or RF positivity) and inadequate response to MTX (administered for ≥ 90 days; ≥ 8 mg/week for ≥ 28 days prior to baseline). Patients were randomized 1:1:1 to 52-week MTX plus PBO, peficitinib 100 mg/day or peficitinib 150 mg/day. At week 12, inadequate responders in the PBO group ($<20\%$ improvement from baseline in tender and swollen joint counts) were switched (under blinded conditions) to peficitinib 100/150 mg until end of treatment. Remaining patients in the PBO group were switched (under blinded conditions) to peficitinib at week 28. Concomitant stable MTX dose (≤ 16 mg/week) was mandatory. Primary efficacy variables were ACR20 response rate at week 12/early termination (ET) and change from baseline in modified Total Sharp score (mTSS) at week 28/ET.

Results: 519 patients were treated: PBO (n=170), peficitinib 100 mg (n=175) and peficitinib 150 mg (n=174). At week 12, 75 PBO-treated patients were switched to peficitinib 100 mg (n=37) and 150 mg (n=38) due to inadequate response. At week 12/ET, peficitinib showed superior efficacy vs PBO with respect to symptoms and inflammatory markers (**Table 1**). At weeks 28 and 52, peficitinib significantly reduced the mean mTSS change from baseline vs PBO (**Table 1**). Week 0–12 safety results were similar for PBO and peficitinib (**Table 2**). For the overall study period, incidence rate of serious infections per 100 patient-years was higher with peficitinib 100 mg/150 mg than PBO (**Table 2**).

Conclusion: In patients with RA who had an inadequate response to MTX, peficitinib 100 mg/day and 150 mg/day demonstrated significant superiority vs PBO in reducing RA symptoms and suppressing joint destruction, according to primary efficacy variables (ACR response and change in mTSS). Peficitinib 100 mg and 150 mg showed acceptable safety and tolerability, with no new safety signals compared with other JAK inhibitors.

1. Takeuchi T, et al. Ann Rheum Dis 2016;75: 1057–64

Disclosure: T. Takeuchi, Astellas Pharma, Inc., 2, 5, 9; Y. Tanaka, Astellas Pharma, Inc., 2, 5, 9; S. Tanaka, Astellas Pharma, Inc., 2, 5, 9; A. Kawakami, Astellas Pharma, Inc., 2, 5, 8, 9; M. Iwasaki, Astellas Pharma, Inc., 9; M. Rokuda, Astellas Pharma, Inc., 3, 9; H. Izutsu, Astellas Pharma, Inc., 3, 9; S. Ushijima, Astellas Pharma, Inc., 3, 9; Y. Kaneko, Astellas Pharma, Inc., 3, 9; T. Shiomi, Astellas Pharma, Inc., 3, 9; E. Yamada, Astellas Pharma, Inc., 3, 9.

Upadacitinib As Monotherapy: A Phase 3 Randomized Controlled Double-Blind Study in Patients with Active Rheumatoid Arthritis and Inadequate Response to Methotrexate

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments I: JAK Inhibitors

EFFICACY ENDPOINTS AT WEEK 14*			
	cMTX N=216	UPA 15 MG N=217	UPA 30 MG N=215
ACR20 (%)	41.2%	67.7% ***	71.2% ***
DAS28-CRP≤3.2 (%)	19.4%	44.7% ***	53.0% ***
ACR50 (%)	15.3%	41.9% ***	52.1% ***
ACR70 (%)	2.8%	22.8% ***	33.0% ***
DAS28-CRP<2.6 (%)	8.3%	28.1% ***	40.5% ***
CDAI≤10 (%)	24.5%	34.5%*	46.5% ***
ΔDAS28-CRP (LSM)	-1.20	-2.29 ***	-2.61 ***
ΔHAQ-DI (LSM)	-0.32	-0.65 ***	-0.73 ***
ΔSF-36 PCS (LSM)	4.32	8.28 ***	10.19 ***
ΔMorning (AM) Stiffness Duration (min.) (LSM)	-53.0	-94.6 **	-102.3 ***
ADVERSE EVENT SUMMARY			
n (%)	cMTX N=216	UPA 15 MG N=217	UPA 30 MG N=215
Any Adverse Event (AE)	102 (47.2)	103 (47.5)	105 (48.8)
Serious AE	6 (2.8)	11 (5.1)	6 (2.8)
AE Leading To Discontinuation Of Study Drug	6 (2.8)	8 (3.7)	6 (2.8)
Infection	57 (26.4)	42 (19.4)	54 (25.1)
-Serious Infection [†]	1 (0.5)	1 (0.5)	0
-Opportunistic Infection [‡]	1 (0.5)	0	3 (1.4)
-Herpes Zoster	1 (0.5)	3 (1.4)	6 (2.8)
Hepatic disorder [§]	4 (1.9)	4 (1.8)	5 (2.3)
Any Malignancy (including NMSC) [¶]	1 (0.5)	2 (0.9)	0
-NMSC	1 (0.5)	0	0
MACE (adjudicated) ^{**}	0	1 (0.5)	2 (0.9)
Venous Thromboembolism (adjudicated)	0	1 (0.5) [†]	0
Death	0	1 (0.5)	0

cMTX, Continuing MTX as a blinded study drug; LSM, least square means; Δ, Change from baseline; CRP, creatine phosphokinase; NMSC, non-melanoma skin cancer; MACE, major adverse cardiovascular event (cardiovascular death, non-fatal MI, non-fatal stroke)

*Results for binary endpoints are based on NRI. Results for DAS28-CRP and HAQ-DI are based on Multiple Imputation. Results for other endpoints are based on Mixed Effect Model Repeat Measurement.

*, **, *** p < .05, < .01 and .001 respectively

[†]Serious Infection events: cMTX: urosepsis; UPA 15: abscess limb

[‡]Opportunistic infection events: cMTX: fungal oesophagitis; UPA 30: 2 oral candidiasis, 1 oropharyngeal candidiasis

[§]Hepatic disorders: Except for 1 case of mild hepatic cyst, all due to liver enzyme elevation

[¶]Malignancies: cMTX: basal cell carcinoma; UPA 15: 1 non-Hodgkins' lymphoma, 1 breast cancer

^{**}MACE (adjudicated): UPA 15: 1 hemorrhagic stroke due to ruptured aneurysm (fatal), investigator deemed as unrelated to study drug; UPA 30: 1 myocardial infarction, 1 stroke; investigators reported both events as unrelated to study drug

[†]VTE: Pulmonary embolism (BMI 36, estrogen hormone therapy); investigator deemed as unrelated to study drug

References:

1. Burmester et al; 2017, Arth Rheum;69 S10
2. Genovese et al; 2017, Arth Rheum;69 S10

Background/Purpose: Upadacitinib (UPA), an oral JAK inhibitor, showed efficacy in rheumatoid arthritis (RA) patients (pts) with an inadequate response to csDMARDs or bDMARDs on continuing stable csDMARD(s)^{1,2}. We assessed the safety and efficacy of switching to UPA 15 or 30mg monotherapy vs continuing methotrexate (MTX) as a blinded study drug was evaluated in pts with inadequate response to MTX (MTX-IR).

Methods: Pts with active RA (TJC \geq 6, SJC \geq 6, hsCRP \geq 3 mg/L) on stable MTX were enrolled and randomized 1:1:1 in a double-blind manner to once-daily (QD) UPA 15mg or 30mg monotherapy or to continue MTX (cMTX) at their prior stable dose. At BL, all pts discontinued prior MTX without washout and received PBO (for pts on UPA) or MTX at prior dose (cMTX) as blinded study drug. The primary endpoints at Week (Wk) 14 were the proportion of pts achieving ACR20, and the proportion achieving DAS28-CRP \leq 3.2 (NRI).

Results: 648 pts were randomized, all received study drug; 598 (92.3%) completed 14 wks. BL demographics and disease characteristics were generally similar across arms. Both primary endpoints were met ($p < .001$); at Wk 14, a significantly greater proportion of pts receiving UPA monotherapy (15mg and 30mg) vs cMTX achieved ACR20 (67.7% and 71.2% vs 41.2%), and DAS28-CRP \leq 3.2 (44.7% and 53.0% vs 19.4%) (**Table**). All key secondary endpoints also showed UPA 15 and UPA 30 monotherapy to be superior to cMTX, including ACR50 (41.9% and 52.1% vs 15.3%), ACR70 (22.6% and 33.0% vs 2.8%), DAS28-CRP \leq 2.6 (28.1% and 40.5% vs 8.3%), Δ HAQ-DI (-0.65 and -0.73 vs -0.32). Δ SF-36PCS and Δ Morning Stiffness data are also shown (**Table**). The proportion of pts achieving CDAI \leq 10 was significantly greater with UPA 15 and 30 vs cMTX (34.6% and 46.5% vs 24.5%).

Adverse events (AEs) were reported at similar frequencies across arms; serious AEs were numerically higher in UPA 15 but similar between cMTX and UPA 30 (**Table**). Numerically more infections were reported in cMTX and UPA 30 vs UPA 15. One serious infection each was reported in UPA 15 and cMTX, and none in UPA 30. Herpes zoster was more frequent in UPA 30 vs UPA 15 or cMTX. 3 malignancies (1 in cMTX and 2 in UPA 15) and 3 adjudicated MACE (1 in UPA 15 and 2 in UPA 30) were reported. One adjudicated pulmonary embolism was reported (UPA 15) in a pt with known risk factors (BMI 36; on estrogen therapy). One death (hemorrhagic stroke due to ruptured aneurysm) was reported in UPA 15. No TB, renal dysfunction or GI perforation was reported. Rates and types of laboratory abnormalities were consistent with prior UPA RA studies to date.

Conclusion: In this MTX-IR study population, switching to UPA as monotherapy at 15mg and 30mg QD showed significant improvements in RA signs and symptoms vs continuing MTX. Numerically higher responses were observed for UPA 30mg vs 15mg, particularly for more stringent efficacy criteria. Safety observations were similar to those in prior UPA studies.

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Abstract Number: 890

A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib to Placebo and to Adalimumab, in Patients with Active Rheumatoid Arthritis with Inadequate Response to Methotrexate

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments I: JAK Inhibitors

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Endpoint	WEEK 12			WEEK 26		
	PBO N=651	UPA 15MG QD N=651	ADA 40MG EQW N=327	PBO N=651	UPA 15MG QD N=651	ADA 40MG EQW N=327
ACR20, %	36.4	70.5*** ^Δ	63.0	35.6	67.4*** ^Δ	57.2
ACR50, %	14.9	45.2*** ^Δ	29.1	20.9	53.9*** ^Δ	41.9
ACR70, %	4.9	24.9*** ^Δ	13.5	9.5	34.7*** ^Δ	22.9
DAS28CRP ≤3.2, %	13.6	45.0*** ^Δ	28.7	18.0	54.7*** ^Δ	38.5
DAS28CRP ≤2.6, %	6.1	28.7*** ^Δ	18.0	9.2	40.9*** ^Δ	26.9
CDAI ≤10 (LDA), %	16.3	46.4*** ^Δ	30.0	22.1	52.7*** ^Δ	38.2
CDAI ≤2.8 (CR), %	3.1	13.4*** ^Δ	7.6	5.5	23.0*** ^Δ	13.8
SDAI ≤11.0 (LDA), %	15.2	40.4*** ^Δ	30.0	22.1	53.9*** ^Δ	38.6
SDAI ≤3.3 (CR), %	2.8	12.1*** ^Δ	7.3	4.8	24.3*** ^Δ	13.8
Bodily remission, %	2.0	9.6*** ^Δ	4.0	3.8	18.1*** ^Δ	9.8
ΔPain	-15.69	-32.10*** ^Δ	-25.61	-16.90	-36.75*** ^Δ	-31.66
ΔHAQ-DI	-0.28	-0.60*** ^Δ	-0.49	-0.33	-0.69*** ^Δ	-0.57
ΔmTSS Wk 26	NA	NA	NA	0.92	0.24***	0.10
ΔJE	NA	NA	NA	0.44	0.02***	0.02
ΔJSN	NA	NA	NA	0.58	0.22***	0.14
No Radiographic Progression Wk 26, %	NA	NA	NA	76.0	83.5**	86.8

Values are LS mean unless specified. Δ, Change from baseline; QD, once daily; ACR20/50/70, 20/50 or 70% improvement in ACR criteria; CR, Clinical remission; DAS28-CRP, 28-joint disease activity score using C-reactive protein; HAQ-DI, health assessment questionnaire disability index; JE, joint erosion; JSN, joint space narrowing; LDA, low disease activity; mTSS, modified total Sharp score; SF-36 PCS, short form 36-physical component score. Results are based on following analyses: binary endpoints, NRI; mTSS, ANCOVA with linear extrapolation; other continuous endpoints, ANCOVA with rescue handling via LOCF. *** p<.01 and .001 for UPA vs PBO. Δ, ** p<.05, .01 and .001 for UPA vs ADA. Black symbols indicate comparisons that were pre-specified for multiplicity control; lighter gray symbols indicate comparisons that were not pre-specified for multiplicity control.

Background/Purpose: To assess efficacy, including inhibition of radiographic progression, and safety with up adacitinib (UPA), aJAK1- selective inhibitor, vs placebo (PBO) and active comparator, originator adalimumab (ADA), in patients (pts) with active rheumatoid arthritis (RA) continuing on prior methotrexate (MTX).

Methods: In SELECT-COMPARE, pts with active RA despite MTX were randomized 2:2:1 to once-daily (QD) UPA 15mg, PBO, or ADA 40mg every other week (wk) in a double-blind manner, while continuing stable background MTX. Primary endpoints were ACR20 and the proportion of pts achieving DAS28CRP≤2.6(NRI) at Wk12. Key secondary endpoints included non-inferiority (and superiority) of UPA vs ADA at Wk12 (for ACR50, DAS28CRP≤3.2, change from BL (Δ) in Pain, and ΔHAQ-DI), and radiographic inhibition(ΔmTSS) for UPA vs PBO at Wk26. Pts with <20% improvement in TJC and SJC were rescued between Wks14- 26 (from PBO to UPA, UPA to ADA, or ADA to UPA).

Results: Of 1629 randomized pts, 91% completed Wk26 (including rescued pts). BL characteristics were similar across arms. All primary and key secondary endpoints were met. At Wk12, significantly more pts on UPA vs PBO achieved ACR20 (70.5% vs 36.4%) and DAS28CRP<2.6 (28.7% vs 6.1%) (**Table 1**). Superiority was met for UPA vs ADA at Wk12 for ACR50 (45.2% vs 29.1%), DAS28CRP≤3.2 (45.0% vs 28.7%), ΔPain (-31.76 vs -25.31) and ΔHAQ-DI (-0.60 vs -0.49). These differences were maintained through Wk26. At Wk26, pts on UPA vs PBO had significantly less radiographic progression (ΔmTSS, 0.24 vs 0.92), and significantly more pts had no radiographic progression (ΔmTSS ≤0)(83.5% vs. 76.0%). At Wk26, more pts on UPA vs PBO or ADA achieved low disease activity or remission by various criteria (nominal p<.001). Up to Wk26, the proportion of pts with adverse events (AEs) and serious infections, censored at rescue, was higher for UPA vs PBO but similar vs ADA (**Table 2**). The proportion of pts with SAEs and AEs leading to discontinuation for UPA was numerically higher vs PBO and lower vs ADA. Herpes Zoster was numerically higher in UPA vs ADA and PBO. Three malignancies, 5 major adverse cardiovascular events, and 4 deaths were reported, none on UPA. Six venous thromboembolic events (VTEs) were reported (1 on PBO, 2 on UPA and 3 on ADA). For pts who were rescued, no deaths, adjudicated MACE, or adjudicated VTE were observed between rescue and Wk26.

Table 2. Adverse Events Summary Through Week 26, n (%) (censored at treatment switch)

	PBO N=652	UPA 15MG QD N=650 ^a	ADA 40MG EOW N=327
Any Adverse Event (AE)	347 (53.2)	417 (64.2)	197 (60.2)
Serious AE	19 (2.9)	24 (3.7)	14 (4.3)
AE Leading To Discontinuation Of Study Drug	15 (2.3)	23 (3.5)	20 (6.1)
Deaths ^b	2 (0.3)	0	2 (0.6)
Infection	154 (23.6)	226 (34.8)	95 (29.1)
-Serious Infection	5 (0.8)	12 (1.8)	5 (1.5)
-Opportunistic Infection	4 (0.6)	4 (0.6)	1 (0.3)
-Herpes Zoster	3 (0.5)	5 (0.8)	1 (0.3)
Hepatic disorder	32 (4.9)	43 (6.6)	12 (3.7)
Gastrointestinal perforation ^c	0	2 (0.3)	0
Malignancy (including NMSC) ^d	2 (0.3)	0	1 (0.3)
MACE (adjudicated) ^e	3 (0.5)	0	2 (0.6)
VTE (adjudicated)	1 (0.2)	2 (0.3)	3 (0.9)
-PE	1 (0.2)	1 (0.2)	3 (0.9)
-DVT	0	1 (0.2)	0

AE, adverse event; NMSC, non-melanoma skin cancer; VTE, venous thromboembolic events; PE, pulmonary embolism; DVT, deep vein thrombosis.

^aOne patient (patient 1) in UPA received only PBO injection before discontinuing and is included in PBO group for safety assessments.

^bDeaths: PBO: 1 cardiovascular (CV) death and 1 death due to Pneumocystis (jirovecii) pneumonia; ADA: 1 death due to cranio-cervical injury and 1 CV death.

^cGastrointestinal perforation (identified using GI perforation MedDRA SMQ): not spontaneous perforations but 1 perforitis, and 1 anal abscess.

^dMalignancies: PBO: 1 cervical carcinoma, 1 basal cell carcinoma; ADA: 1 basal cell carcinoma.

^eMACE, major adverse cardiovascular events (adjudicated). PBO: 2 non-fatal myocardial infarctions and 1 CV death; ADA: 1 non-fatal stroke and 1 CV death.

Conclusion: UPA 15mg QD showed superiority on improvement in RA signs & symptoms vs PBO and ADA in this MTX-IR population. Radiographic progression was significantly lower with UPA vs PBO. Safety events were consistent with Ph 2 and 3 studies in RA to date.

Disclosure: R. Fleischmann, AbbVie, Lilly, Pfizer, Gilead, 2; AbbVie, Lilly, Pfizer, Gilead, 5; A. L. Pangan, AbbVie Inc., 1, AbbVie Inc., 3; E. Mysler, AbbVie, Lilly, Pfizer, Roche, BMS, Sandoz, 2; AbbVie, Lilly, Pfizer, Roche, BMS, Sandoz, 5; L. Bessette, Amgen, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Lilly, Novartis, 2, 5, 8; C. Peterfy, Spire Sciences, Inc, 3, Spire Sciences, Inc, 1, Amgen, Bristol-Myers Squibb; consultant: Centrexion, Crescendo Bioscience, Daiichi Sankyo, EMD Serono, Five Prime, Flexion Therapeutics, Genentech, Gilead, GlaxoSmithKline, Pfizer, Plexikon, Regeneron, Roche, SetPoint., 8; P. Durez, BMS, Lilly, Sanofi, Pfizer, 8; A. Ostor, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Sanofi, Eli Lilly, Novartis, 2, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Sanofi, Eli Lilly, Novartis, 5, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Sanofi, Eli Lilly, Novartis, 8; Y. Li, AbbVie Inc., 1, AbbVie Inc., 3; Y. Zhou, AbbVie Inc., 1, AbbVie Inc., 3; A. A. Othman, AbbVie Inc., 1, AbbVie Inc., 3; I. H. Song, AbbVie, Inc., 1, AbbVie, Inc., 3; M. C. Genovese, AbbVie, Lilly, Pfizer, Galapagos, Gilead, 5, AbbVie, Lilly, Pfizer, Galapagos, Gilead, 2.

Abstract Number: 891

A Phase 3, Randomized, Controlled Trial Comparing Upadacitinib Monotherapy to MTX Monotherapy in MTX-Naïve Patients with Active Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments I: JAK Inhibitors

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: To compare the clinical efficacy, including inhibition of structural damage, and safety of upadacitinib (UPA), a JAK1-selective inhibitor, as monotherapy, vs methotrexate (MTX) monotherapy, in MTX-naïve patients (pts) with moderate to severely active rheumatoid arthritis (RA).

Methods: In SELECT-EARLY, MTX-naïve pts with active RA who were positive for both RF and ACPA and/or had ≥ 1 joint erosion were randomized 1:1:1 to once-daily (QD) UPA at 15mg or 30mg, or weekly MTX (titrated by Wk8). Separate primary endpoints were ACR50 at Wk12 (FDA), or the proportion of pts achieving DAS28CRP < 2.6 at Wk24 (EMA). Secondary endpoints included mean changes from baseline (Δ BL) in modified Total Sharp Score (mTSS) and proportion of pts with no radiographic progression (mTSS ≤ 0) at Wk24.

Results: Of 947 randomized pts, 945 received study drug; 840 (88.7%) completed Wk24. ~50% had an RA diagnosis of < 6 months and RA symptoms < 2 years; Of the 945 pts, 874 (92.5%) had no prior MTX exposure; 706 (74.7%) had no prior csDMARD exposure. Both primary endpoints were met. Significantly more patients receiving UPA 15 and 30mg vs MTX achieved ACR50 responses at Wk12 (52.1% and 56.4% vs 28.3%) and DAS28CRP < 2.6 at Wk24 (48.3% and 50.0% vs 18.5%) (**Table 1**). All ranked secondary endpoints were met: ACR50 at Wk24, improvements in DAS28CRP, HAQ-DI, SF36-PCS, and the proportion of pts achieving DAS28CRP ≤ 3.2 at Wks12 and 24. At Wk24, mean Δ mTSS were 0.14 and 0.07 vs 0.67; significantly more pts had no radiographic progression on UPA 15 and 30mg vs MTX. LDA and remission by various criteria at Wks 12 and 24 were achieved in more pts on UPA vs MTX (nominal $p < .001$ for all).

Up to Wk24, treatment-emergent adverse events (AEs) and serious AEs were similar in the UPA 15mg and MTX arms, and slightly higher in the UPA 30mg arm (**Table 2**). AEs leading to discontinuation were similar across arms. A numerically higher proportion of pts on UPA 30mg reported serious infections vs MTX and UPA 15mg, and there were more cases of herpes zoster in the UPA vs MTX arms. Four malignancies, 4 major adverse cardiovascular events (MACE),

Table 1. Efficacy at Weeks 12 and 24.

	WEEK 12			WEEK 24		
	MTX N=314	UPA 15 MG QD N=317	UPA 30 MG QD N=314	MTX N=314	UPA 15 MG QD N=317	UPA 30 MG QD N=314
ACR20, %	54.1	75.7***	77.1***	58.6	78.9***	78.0***
ACR50, %	28.3	52.1***	56.4***	33.4	60.3***	65.6***
ACR70, %	14.0	32.5***	36.9***	18.5	44.5***	49.7***
DAS28CRP < 2.6 , %	10.7	35.6***	40.8***	18.5	48.3***	50.0***
DAS28CRP ≤ 3.2 , %	28.0	53.9***	54.8***	32.2	56.9***	65.0***
Δ DAS28CRP	-1.85	-2.75***	-2.85***	-2.15	-3.07***	-3.34***
Δ HAQ-DI	-0.48	-0.83***	-0.86***	-0.69	-0.87***	-0.91***
Δ SF-36 PCS	-5.74	8.66***	10.08***	-6.97	10.70***	11.32***
Δ mTSS	NA	NA	NA	0.67	0.14**	0.07**
No radiographic progression, %	NA	NA	NA	77.7	87.5**	89.3***
CDAI10 (LDA), %	29.6	46.4***	49.0***	38.2	56.2***	60.5***
CDAI2.6 (REM), %	6.4	16.1***	21.3***	10.5	28.4***	29.3***
Boolean REM, %	6.4	12.9**	15.3***	7.0	24.3***	24.8***

Values are LS mean (unless otherwise specified). Δ , Change from baseline; QD, once daily; ACR20/50/70, 20/50 or 70% improvement in ACR criteria; CDAI, clinical disease activity index; DAS28CRP, 28-joint disease activity score using C-reactive protein; HAQ-DI, health assessment questionnaire disability index; LDA, low disease activity; mTSS, modified total Sharp score; SF-36 PCS, short form 36-physical component score; REM, remission. Results are based on following analyses: binary endpoints, MFI; DAS28CRP and HAQ-DI, ANCOVA with Multiple Imputation; mTSS, ANCOVA with linear extrapolation. *** $p < .001$, ** $p < .01$ for UPA vs MTX.

	MTX	UPA	UPA
		15 MG QD	30 MG QD
	N=314	N= 317	N=314
Any Adverse Event (AE)	205 (65.3)	203 (64.0)	224 (71.3)
Serious AE	13 (4.1)	15 (4.7)	20 (6.4)
AE Leading To Discontinuation Of Study Drug	16 (5.1)	14 (4.4)	12 (3.8)
Deaths*	1 (0.3)	2 (0.6)	3 (1.0)
Infection	103 (32.8)	104 (32.8)	115 (36.6)
-Serious infection	4 (1.3)	5 (1.6)	8 (2.5)
-Opportunistic infection	0	1 (0.3)	1 (0.3)
-Herpes Zoster [†]	1 (0.3)	7 (2.2)	7 (2.2)
Hepatic disorder	17 (5.4)	19 (6.0)	14 (4.5)
Gastrointestinal perforation [‡]	0	0	2 (0.6)
Malignancy (including NMSC) [§]	1 (0.3)	3 (0.9)	0
MACE (adjudicated)	1 (0.3)	1 (0.3)	2 (0.6)
VTE (adjudicated)	1 (0.3)	0	1 (0.3)
-PE	1 (0.3)	0	0
-DVT	0	0	1 (0.3)

AE: adverse event; NMSC: non-melanoma skin cancer; VTE: venous thromboembolic events; PE: pulmonary embolism; DVT: deep vein thrombosis

*Deaths: MTX: 1 sudden cardiovascular (CV) death; UPA 15: 1 CV death, 1 death due to metastatic malignant melanoma; UPA 30: 1 CV death, 1 death due to pneumonia and sepsis, 1 death due to perforative (also counted under GI perforation)

[†]Herpes zoster: All non serious; 12 were single dermatomes

[‡]Gastrointestinal perforation UPA 30: 1 pt with large intestinal perforation; 1 pt with peritonitis

[§]Malignancies: MTX: 1 case of ovarian cancer; UPA 15: 1 metastatic malignant melanoma; 1 squamous cell carcinoma of the lung; 1 uterine carcinoma in situ

^{||}MACE: major adverse cardiovascular events (adjudicated): MTX: 1 CV death; UPA 15: 1 non-fatal myocardial infarction (MI); CV death due to other CV causes; UPA30: 1 non-fatal MI and 1 CV death (sudden)

and 6 deaths were reported (**Table 2**). Two venous thromboembolic events were reported (1 pulmonary embolism on MTX, 1 deep vein thrombosis on UPA 30mg, none on UPA 15mg). Laboratory abnormalities were consistent with other Phase 2 and 3 studies with UPA.

Conclusion: In MTX-naïve pts, UPA 15 and 30mg QD demonstrated significant and clinically meaningful improvements in RA signs& symptoms vs MTX. Radiographic progression was significantly less with UPA vs MTX. Safety events were consistent with Phase 2 and 3 studies with UPA in RA to date.

Disclosure: **R. van Vollenhoven**, AbbVie, Arthrogen, BMS, GSK, Lilly, Pfizer, UCB, 2, AbbVie, AstraZeneca, Biotest, BMS, Celgene, GSK, Janssen, Lilly, Medac, Merck, Novartis, Pfizer, Roche, UCB, 9; **T. Takeuchi**, Mitsubishi-Tanabe Pharma Corporation, Janssen Pharmaceutical KK, Chugai Pharmaceutical Co Ltd, Astellas Pharma Inc., AbbVie GK, Eisai Co., Ltd, Bristol-Myers Squibb Company, Daiichi Sankyo Company Ltd, Eli Lilly Japan KK, Pfizer Japan Inc., 9, Astellas Pharma Inc., 9, Chugai Pharmaceutical Co Ltd, Mitsubishi-Tanabe Pharma Corporation; Grants; Pfizer Japan Inc., Eisai Co., Ltd, Astellas Pharma Inc., AbbVie GK, Asahi Kasei Pharma Corporation, Nippon Kayaku Co., Ltd, Taisho Toyama Pharmaceutical Co., Ltd., Takeda Pharmace, 9, Astellas Pharma Inc., AbbVie GK, Eisai Co., Mitsubishi-Tanabe Pharma Corporation, Chugai Pharmaceutical Co Ltd, Bristol-Myers Squibb Company, UCB Japan Co., Ltd, 9; **A. L. Pangan**, AbbVie Inc., 1, AbbVie Inc., 3; **A. Friedman**, AbbVie Inc., 1, AbbVie Inc., 3; **M. E. Mohamed**, AbbVie Inc., 1, AbbVie Inc., 3; **S. Chen**, AbbVie Inc., 1, AbbVie Inc., 3; **M. Rischmueller**, Abbvie, Bristol-Meyer-Squibb, Celgene, Glaxo Smith Kline, Hospira, Janssen Cilag, MSD, Novartis, Pfizer, Roche, Sanofi, UCB, 5; **R. Blanco**, AbbVie, MSD, and Roche, 2, AbbVie, Pfizer, Roche, Bristol-Myers, Janssen, and MSD, 2, 8; **R. M. Xavier**, Abbvie, Pfizer, Novartis, Janssen, Lilly, Roche., 5; **V. Strand**, AbbVie, Amgen, Bayer, BMS, Boehringer Ingelheim, Celgene, Celltrion, CORRONA, Crescendo, EMD Serono, Genentech/Roche, GSK, Horizon, Inmedix, Janssen, Kezar, Lilly, Merck, Novartis, Pfizer, Regeneron, Samsung, Sandoz, Sanofi, Servier, UCB., 5.

Establishing the Minimal Clinically Important Difference (MCID) for the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL)

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical I: Axial SpA Epidemiology

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The Ankylosing Spondylitis Quality of Life (ASQoL) is a readable and simple to complete questionnaire relating to health-related quality of life (HRQoL) in subjects with axial spondyloarthritis (axSpA). Although this tool has previously been used in various research settings over the last decade, the minimal clinically important difference (MCID) remains to be defined.

Methods: All subjects seen at the Spondylitis Clinic of the Toronto Western Hospital between July 2003 and January 2018 with a diagnosis of axSpA were included in this study. The ASQoL comprises 18 questions and answers are dichotomized into yes/no. The weighted score for each item is 1 and poorer HRQoL is associated with higher scores. The MCID for

Receiver operating characteristics curve (ROC) method to estimate MCID for ASQoL

	Anchor (AUC)	Δ ASQoL	Sensitivity	Specificity	PPV	NPV	Youden index
MCID for Improvement		-1	0.53	0.71	0.52	0.72	0.24
		-2	0.40	0.84	0.60	0.70	0.24
		-3	0.30	0.90	0.65	0.68	0.20
	HTI (0.654)	-4	0.22	0.93	0.67	0.67	0.15
		-5	0.18	0.96	0.71	0.66	0.13
		-6	0.14	0.97	0.72	0.65	0.11
		-7	0.12	0.97	0.73	0.65	0.09
		-8	0.10	0.98	0.73	0.64	0.08
		-1	0.55	0.67	0.36	0.81	0.21
		-2	0.43	0.79	0.41	0.80	0.22
	Change in GSRH (0.653)	-3	0.36	0.87	0.48	0.80	0.23
		-4	0.28	0.91	0.51	0.79	0.19
		-5	0.22	0.94	0.55	0.78	0.16
		-6	0.18	0.95	0.56	0.78	0.13
		-7	0.16	0.96	0.59	0.77	0.12
		-8	0.13	0.97	0.60	0.77	0.10
MCID for worsening		1	0.51	0.75	0.36	0.85	0.26
		2	0.37	0.85	0.41	0.83	0.22
		3	0.28	0.91	0.47	0.82	0.19
	HTI (0.654)	4	0.22	0.94	0.51	0.81	0.16
		5	0.20	0.96	0.57	0.81	0.15
		6	0.14	0.97	0.52	0.80	0.10
		7	0.12	0.97	0.52	0.80	0.09
		8	0.09	0.98	0.52	0.79	0.07
		1	0.46	0.72	0.32	0.83	0.19
		2	0.35	0.83	0.36	0.82	0.18
		3	0.29	0.90	0.44	0.82	0.18
	Change in GSRH (0.653)	4	0.24	0.94	0.51	0.81	0.17
		5	0.20	0.95	0.53	0.81	0.15
		6	0.16	0.96	0.53	0.80	0.12
		7	0.14	0.97	0.54	0.80	0.11
		8	0.11	0.98	0.57	0.80	0.09

MCID: Minimal clinically important change; AUC: Area under the receiver operating characteristic curve; ASQoL: Ankylosing spondylitis quality of life; PPV: Positive predictive value; NPV: Negative predictive value; HTI: Health transition index; GSRH: global self-rated health

ASQoL was determined by anchor-based methods using two instruments to anchor the change on the ASQoL. The first anchor was the Health Transition Index (HTI) of the Short Form 36 (SF-36): “compared to one year ago, how would you rate your health in general now?”. The answers to this question at the yearly follow-up visit were incorporated in a 5-point Likert scale: “much worse” (-2), “somewhat worse” (-1), “about the same” (0), “somewhat better” (+1) or “much better” (+2). The second anchor was the change in the global self-rated health (GSRH) question of the SF-36 : “In general, would you say your health is [...]”. The answers to this question are: “1- excellent”, “2- very good”, “3- good”, “4- fair” and “5- poor”. The level of change in GSRH between two consecutive visits was considered. A minimal change on the HTI was considered as anyone reporting better (+2 or +1) or worse (-2 or -1), and a minimal change on the GSRH was considered has those who had 1 level of improvement or worsening. The MCID for ASQoL was determined by plotting on receiver operating characteristic (ROC) curves the change in ASQoL that most accurately classified subjects based on optimal sensitivity/specificity ratio (improvement or worsening).

Results: The study consisted of a total of 1328 subjects with longitudinal data cumulated over 5607 visits. Based on ROC curve analyses (image), the MCID for improvement is -2: this had a sensitivity of 40% and specificity of 84% anchored on the HTI, and sensitivity of 43% and specificity of 79% anchored on the GSRH. The MCID for worsening is 1, having a sensitivity/specificity of 40%/84% anchored on the HTI and 43%/79% anchored on the GSRH. Larger cut-off values for ASQoL resulted in a linear increase in the positive predictive value (PPV) up to thresholds of -5 for improvement (PPV=71% anchored on the HTI and PPV=55% anchored on the GSRH) and 5 for worsening (PPV=57% anchored on the HTI and PPV=53% anchored on the GSRH).

Conclusion: This study gives values for MCID and further suggests that larger threshold values in ASQoL change may be applied to better classify subjects according to improvement or worsening in HRQoL. Defining cut-off values will enhance the utility of ASQoL in clinical and research settings.

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Abstract Number: 893

Identification of Axial Spondyloarthritis Patients in a Large Dataset: The Development and Validation of Novel Methods

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical I: Axial SpA Epidemiology

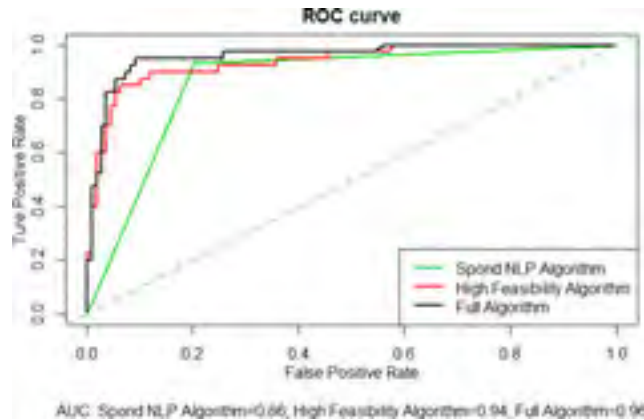
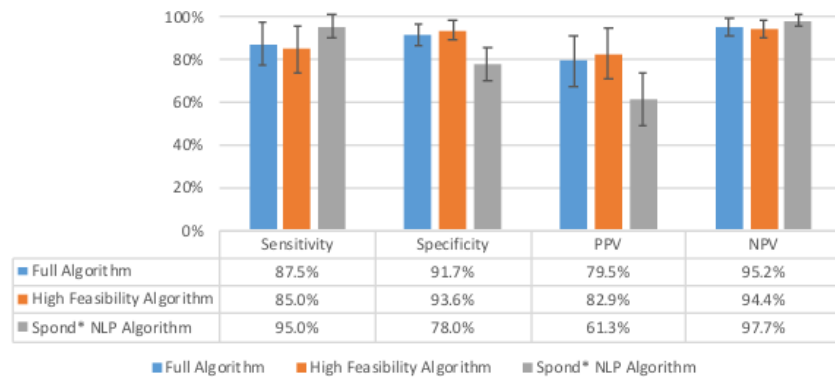
Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Big data research in axial spondyloarthritis (axSpA) is limited by a lack of adequate methods for identifying axSpA patients, since there are no billing codes for most subtypes of axSpA. The objective of this study was to develop accurate axSpA identification methods to enable previously impractical observational research in axSpA.

Methods: The population included 600 Veterans with risk factors for axSpA in the Veteran Health Administration (January 1, 2005 through June 30, 2015). Clinical experts reviewed medical records to determine axSpA status. axSpA identification algorithms were developed in a subset of 451 patients (training set) and tested in the remaining 149 patients (testing set). Forty-nine variables anticipated by clinical experts to be predictive of an axSpA diagnosis were selected for algorithm development. The variables included demographics, billing codes, provider utilization patterns, medication dispensations, laboratory results, and affirmative language for key disease features (spondyloarthritis, sacroiliitis, and HLA-B27 positivity) that was extracted from the free text of documents with natural language processing (NLP). Three algorithms were developed: the Spond NLP Algorithm (NLP algorithm as a single variable), High Feasibility Algorithm (16 coded variables), and Full Algorithm (all coded and NLP variables). Random Forest, 5-fold cross validation, and Random Forest Gini Scores were used for algorithm development, testing, and variable prioritization.

Results: In the testing set, the sensitivity of the Spond NLP Algorithm was 95.0% and the specificity was 78.0%. For the High Feasibility Algorithm, the sensitivity was 85.0% and the specificity was 93.6%. For the Full Algorithm, the sensitivity was 87.5%, and the specificity was 91.7% (Figure 1). The areas under the curve with the receiver operating characteristic



analysis for the testing set were 0.86 for the Spond NLP Algorithm, 0.94 for the High Feasibility Algorithm, and 0.96 for the Full Algorithm (Figure 2).

Conclusion: Sensitive and specific algorithms were developed for identifying axSpA patients for big data research. These algorithms offer a range of performance and feasibility attributes that may be appropriate for a broad array of axSpA research.

Figure1. Sensitivity, specificity, PPV, and NPV of axSpA identification algorithms(n=149)

PPV= positive predictive value, NPV = negative predictive value

Figure 2. Receiver operating characteristic curves (testing set, n=149)

Disclosure: R. S. Overbury, None; S. Pei, None; G. Penmettsa, None; G. W. Cannon, None; D. O. Clegg, None; B. Sauer, None; J. Walsh, None.

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Cancer Risk in Ankylosing Spondylitis in United States Medicare Beneficiaries: Detection of a Chronic Non Steroidal Anti-Inflammatory Drug Use Signature

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical I: Axial SpA Epidemiology

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Few studies have examined risk of cancer in ankylosing spondylitis (AS) since the end of the radiation therapy era. With greater use of biologics, establishing the baseline risk has become more important. The objective of this study was to assess the risk of organ specific cancer in a population-based sample of elderly patients with AS.

Table 1. Organ-Specific Cancer Incidence, Standardized Incidence Ratio

Site	Cancer Events		Standardized Incidence (95% CI) (per 100,000)		SIR (95% CI)
	AS	Control	AS	Control	
Upper Airways	150	3753	119.5	114.0	0.95 (0.80-1.11)
Esophagus	26	18604	19.3	19.3	0.58 (0.36-0.81)
Stomach	22	17195	17.0	30.4	0.55 (0.32-0.79)
Small Intestine	16	3707	12.2	6.5	1.87 (0.95-2.78)
Colorectal	248	132078	190.6	233.7	0.81 (0.71-0.91)
Liver, Gallbladder	18	25807	38.5	45.6	0.84 (0.61-1.07)
Pancreas	68	26932	51.3	47.6	1.07 (0.82-1.33)
Lung	262	168067	213.2	293.8	0.72 (0.64-0.81)
Female Breast	258	102472	569.4	517.6	1.10 (0.96-1.23)
Uterus	49	25044	108.5	126.5	0.85 (0.61-1.09)
Prostate	929	305498	1116.4	831.9	1.34 (1.25-1.42)

Continued: Table 1. Organ-Specific Cancer Incidence, Standardized Incidence Ratio

Site	Cancer Events		Standardized Incidence (95% CI) (per 100,000)		SIR (95% CI)
	AS	Control	AS	Control	
Kidney	160	46593	135.5	85.9	1.57 (1.34-1.80)
Bladder	208	74664	151.2	132.1	1.14 (0.98-1.30)
Thyroid	48	13586	34.5	24.0	1.43 (1.02-1.85)
Connective tissue, Bone	59	19218	44.1	40.2	1.29 (0.96-1.63)
Melanoma	179	48158	127.6	85.2	1.49 (1.27-1.71)
Brain, Eye, Nervous System	62	21491	46.3	38.0	1.21 (0.91-1.52)
Multiple Myeloma	66	22040	51.8	38.9	1.32 (1.01-1.64)
Non-Hodgkin's Lymphoma	251	76365	184.9	135.1	1.36 (1.19-1.53)
Hodgkin's disease	16	5263	12	9.3	1.29 (0.66-1.92)
Leukemia	189	54565	139.8	96.5	1.44 (1.24-1.65)

Methods: We reviewed Medicare databases from 1999 to 2013 for all beneficiaries 65 or older with a diagnosis of AS, excluding those with concomitant diagnosis of other rheumatic diseases. The reference population was a 30% stratified random sample of beneficiaries without a diagnosis of AS, matched on age and sex. New cancer diagnoses were identified in the AS and reference population when there were two identical International Classification of Disease-9 codes in visits at least thirty days apart. Those who developed cancer within the first year of observation were excluded. Patients were followed until 2015. Standardized incidence ratio (SIR) was defined as the ratio of observed to expected number of cancers in AS compared to the reference group, accounting for person-years at risk.

Results: A total of 13,305 AS (66% male, 91% white, median follow up 10 years) and 6,749,053 beneficiaries without AS (66% male, 85% white, median follow up 8 years) were included. AS patients contributed 130,841 person-years and beneficiaries without AS contributed 56,515,489 person-years of follow up. A total of 3322 cancers occurred in AS and 1,211,126 cancers occurred in beneficiaries without AS. SIR (95% confidence interval) for six sites were higher in AS: kidney cancer 1.57(1.34-1.80) melanoma 1.49 (1.27-1.71) thyroid cancer 1.43 (1.02-1.85) leukemia 1.44(1.24-1.65) non-Hodgkin's lymphoma 1.36 (1.19-1.53) and prostate cancer 1.34 (1.25-1.42). SIR for four sites were lower in AS: esophagus 0.58 (0.36-0.81) stomach 0.55 (0.32-0.79) colorectal 0.81 (0.71-0.91) and lung cancer 0.72 (0.64-0.81). (table 1)

Conclusion: Elderly patients with AS are at increased risk of hematological malignancies and kidney cancer but have lower risk of gastrointestinal and lung cancer. The relative protection from gastrointestinal and lung cancer and increased risk of kidney cancer is consistent with the pattern seen with chronic use of nonsteroidal anti-inflammatory drugs. Further study is required to distinguish disease from treatment related cancer risk in AS.

Disclosure: S. Alehashemi, None; M. Ward, None.

Abstract Number: 895

Associations of Statin Usage with Disease Activity in Ankylosing Spondylitis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical I: Axial SpA Epidemiology

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Recent studies have shown possible anti-inflammatory effects and a survival benefit with statin usage in ankylosing spondylitis (AS). The purpose of this study was to assess whether statin usage is associated with lower disease activity in a longitudinal cohort of patients with AS.

Methods: AS patients meeting modified New York Criteria with at least one year of clinical follow-up with statin usage were included in the analysis. Patients on statins were classified into high, moderate, and low intensity statins based on 2013 American Heart Association/American College of Cardiology Treatment of Cholesterol Guidelines [1]. We used a longitudinal negative binomial regression model to evaluate the effect of statin usage on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) using generalized estimating equations controlling for age, sex, ethnicity, education, smoking status, cardiovascular comorbidities, CRP, exercise, antihypertensive, nonsteroidal anti-inflammatory drugs (NSAID) and TNFi usage. We further tested interactions to see whether NSAID usage modified the longitudinal association between BASDAI scores and statin usage.

Results: 814 AS patients, with at least one year of follow-up, were studied. 86 of these patients were on a statin at baseline. 10 patients, 65 patients, and 11 patients were on a low, moderate, and high intensity statin respectively. Follow-up median was 4.8 years, IQR of (2.3,7.1). Statin usage alone was not significantly associated with BASDAI when it was tested in additive models ($p=0.4$). NSAID usage alone was significantly associated with higher BASDAI score ($p<0.01$). In the interactive model, when the interaction effect between statin and NSAID usage in relation to BASDAI was assessed, of patients with an NSAID index $\geq 50\%$, BASDAI score was 32% lower for low intensity statin compared to no statin use ($p<0.001$) and 18% lower for high intensity statin compared to no statin use ($p=0.004$) (Table 1). ESR was collinear with CRP. When interactions of statin and TNFi usage were tested (data not shown), of the patients taking TNFi, statins were not significantly associated with lower BASDAI score. Of the patients not taking TNFi, statins were significantly associated with lower BASDAI scores for high intensity statins compared to no statin use ($p<0.01$).

Table 1: Effect of Statin Usage on BASDAI based on Multivariable Longitudinal Model

	Adjusted Rate Ratio (95% CI)	P-value
<u>Effect of Statin Usage on BASDAI per NSAID index group</u>		0.150
<i>(interaction between Statin and NSAID usage in relation to BASDAI)</i>		
when NSAID index \geq 50%:		
Statin Low Intensity vs no use	0.68 (0.57, 0.81)	<0.001
Statin Moderate Intensity vs no use	0.98 (0.89, 1.09)	0.703
Statin High Intensity vs no use	0.82 (0.72, 0.94)	0.004
Statin High Intensity vs Moderate Intensity	0.84 (0.73, 0.96)	0.009
when NSAID index < 50%:		
Statin Low Intensity vs no use	1.01 (0.88, 1.17)	0.848
Statin Moderate Intensity vs no use	0.94 (0.83, 1.05)	0.286
Statin High Intensity vs no use	1.01 (0.74, 1.38)	0.939
Statin High Intensity vs Moderate Intensity	1.08 (0.80, 1.45)	0.616
when NSAID not used:		
Statin Low Intensity vs no use	1.11 (0.92, 1.35)	0.275
Statin Moderate Intensity vs no use	1.00 (0.92, 1.08)	0.906
Statin High Intensity vs no use	0.94 (0.82, 1.08)	0.389
Statin High Intensity vs Moderate Intensity	0.94 (0.82, 1.09)	0.443
Education Level (college or higher) vs. other	0.78 (0.70, 0.87)	<0.001
White vs. other	0.93 (0.85, 1.03)	0.176
Male vs. female	0.87 (0.80, 0.94)	0.001
AGE \geq 40 years vs. < 40 years	1.12 (1.04, 1.22)	0.005
Ever Smoker vs. Nonsmoker	1.15 (1.06, 1.24)	0.001
Abnormal CRP vs. normal	1.16 (1.12, 1.21)	<0.001
Cardiovascular Diseases* (hypertension excluded) vs. other comorbidities	1.10 (0.96, 1.27)	0.171
Diabetes vs. other	1.23 (1.05, 1.44)	0.012
Exercise \geq 120 mins vs. < 120 mins	0.92 (0.89, 0.95)	<0.001
TNFi use	0.88 (0.83, 0.93)	<0.001
Antihypertensive Medication use	1.07 (1.01, 1.14)	0.031

* cardiac bypass surgery, angioplasty (percutaneous intervention), coronary artery disease, myocardial infarction, angina, valvular heart disease, or heart valve replacement.

Conclusion: Statins when taken with NSAIDs at anti-inflammatory doses were associated with a significant reduction in AS disease activity. TNFi may mask the anti-inflammatory effect of statins. Future studies will require more patients to confirm the effect.

[1] Stone NJ, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. *Circulation*. **129**, S1-S45 (2013).

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Abstract Number: 896

Pharmacogenomics Study of Predicting Response of TNF Blocker and Medical Image Progression in Chinese Han Ankylosing Spondylitis Population

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical I: Axial SpA Epidemiology

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: TNF blockers, have been widely used in immune-mediated diseases and many genetic variations predicting treatment response have been described. We applied previously published genetic variations relevant in response of TNF blockers of rheumatoid arthritis (RA) and spondyloarthritis (SpA) to predict treatment response and radiographic progression of ankylosing spondylitis (AS) patients.

Methods: We recruited 142 AS patients from three medical centers (Guanghua, Changhai and Zhongshan hospital in China). All patients have stopped treatment for more than 6 months before we recruited them or never been treated with TNF blockers. The response to etanercept or adalimumab was evaluated at 3-month and 6-month followup visits by different criteria (BASDAI 50, ASAS20, ASAS 40, ASAS5/6, partial remission and difference of ASDAS) and 62 of AS patients were evaluated for disease activity or progression with MRI (SPARCC) and radiographic imaging. Sixty-two genetic variations were collected by searching in PUBMED. Statistical analyses included Fisher's exact test and logistic regression analysis.

Results: Most of key loci identified belonged to genes in the Toll-like receptor signaling pathway and other immune-relevant loci. The results showed important differences between etanercept and adalimumab when associations between genetic polymorphisms and treatment response were examined. Genetic variations in *ARFGAP2* alleles showed significantly difference between responders and non-responders, especially in patients treated with etanercept (OR = 0.21, P-value = 0.0004). When ASDAS was performed as the response criterion, a *SLCO1C1* allele was highly associated with treatment response (OR = 12.72, P-value = 0.0004), and in the etanercept subgroup, none of the non-responders carried it (P-value = 0.008). In addition, genetic loci in *LRPAP1* had strong linkage with the variation of fat metaplasia and erosion. It was associated with the variation of erosion both in 3-month follow-up and 6-month follow-up. Genetic loci in *MYOM2* was associated with the variation of backfill after 6-month treatment. *IL10* were associated with ankyloses at baseline. *ACE* and *S100A8* are significantly associated with mSASSS score of sacroiliac and spine at baseline, respectively (Table 1).

Conclusion: Several genetic loci showed significantly differences between responders and non-responders to anti-TNF agents in AS and may also predict the MRI/radiographic inflammation and disease progression. This suggests an important role of pharmacogenomics profiling in predicting treatment response and disease progression.

Table 1 Genetic loci associated with Image progression

	Gene	β	P-value
MRI (N=65)			
sacroiliac joint inflammation	ARFGAP2	8	0.02
spine inflammation	TNF	-7.6	0.02
fat metaplasia	LRPAP1	-1.8	0.004
erosion	LRPAP1	1.1	0.006
backfill	MYOM2	-1.6	0.003
ankylosis	IL10	8.1	0.003
mSASSS (N=65)			
sacroiliac	ACE	0.66	0.04
spine	S100A8	11.2	0.01

Disclosure: J. Liu, None; W. Pu, None; Q. Zhu, None; H. Fan, None; W. Wan, None; H. Zou, None; X. Zhou, None; J. D. Reveille, None; D. He, None; J. Wang, None.

Abstract Number: 897

Prevalence of Inflammatory and Chronic Changes Suggestive of Axial Spondyloarthritis in Magnetic Resonance Images of the Axial Skeleton in Individuals < 45 Years in the General Population as Part of a Large Community Study (SHIP)

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical I: Axial SpA Epidemiology

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Magnetic resonance imaging (MRI) is crucial for classification and diagnosis of axial spondyloarthritis (axSpA). Characteristic MRI lesions of axSpA are bone marrow edema (BME) or structural fatty lesions

(FL) of the sacroiliac joints (SIJ) and spine. However, the specificity of these lesions has been questioned, since patients with chronic back pain but no axSpA may also have a positive MRI, as shown in recent cohort studies. In this study we investigate the prevalence of BME and FL on MRI of the spine and the SIJ in the general population.

Methods: Volunteers <45 years of the population based Study of Health in Pomerania (SHIP)^{1,2} underwent MRI examinations of the spine (sagittal orientation, T1 and T2 MRI sequences) and the SIJ (coronal orientation, STIR sequences), independently of clinical symptoms. Two trained readers blinded for age and gender of the examined persons evaluated the prevalence of BME (SIJ and spine) and FL (spine) suggestive of axSpA using the ASAS definitions: a lesion in the SIJ was considered positive if located periarticularly and in the middle part of the joint and a lesion in the spine was considered positive if detected at the edge of the vertebral body). Clearly degenerative lesions involving the vertebral endplate or being accompanied by abnormalities of the intervertebral disc (protrusion or prolapse) were not counted.

Results: A total of 802 complete MRI sets (spine and SIJ) of 394 male (49.1%) and 408 female volunteers (50.9%) was evaluated. The mean age of all patients was 37.5±6.2 years. BME in the SIJ suggestive of axSpA were found in 144 individuals (18%), with an equal distribution between males (n=74, 18.8%) and females (n=70, 17.2%). A similar pattern of BME was found in the spine, again with no differences between males and females. However, the location of the lesions was different: 9.5% had ≥1 lesion in the cervical, 18.6% in the thoracic and 7.4% in the lumbar spine. Overall, 88.6% male and 84.6% female volunteers were found to have ≥1 and 54.6% male and 46.1% female volunteers were found to have at ≥3 positive spinal lesions in any spinal region. In comparison, the prevalence of FL was higher (36.7% volunteers in the cervical, 72.4% in the thoracic and 52.7% in the lumbar spine). Overall, 86.5% volunteers were found to have ≥1 and 50.2% volunteers were found to have ≥3 positive spinal lesions in any spinal segment. Logistic regression analysis showed that age was the only demographic characteristic that independently contributed to the occurrence of both BME (RR=1.22, 95%CI 1.03-1.46, p<0.025) or FL ((RR=1.12, 95%CI 1.07-1.19, p<0.001).

Conclusion: In this large population-based study with healthy volunteers a relatively high prevalence of inflammatory and structural MRI lesions was found. Whether these lesions are to be explained by mechanical stress needs to be further studied. The high prevalence of BME and FL in the axial skeleton in the general population indicates a limited diagnostic value of these MRI findings. Thus, those should be interpreted with caution in relation to diagnosis, classification and assessment of disease activity.

(1) Bundesgesundheitsbl 2012, (2) Völzke H et al. Int J Epidemiol 2011

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Abstract Number: 898

Efficacy and Safety of Tocilizumab for the Treatment of Systemic Sclerosis: Results from a Phase 3 Randomized Controlled Trial

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical I: Clinical Trial Results & Insights

Session Type: ACR Concurrent Abstract Session

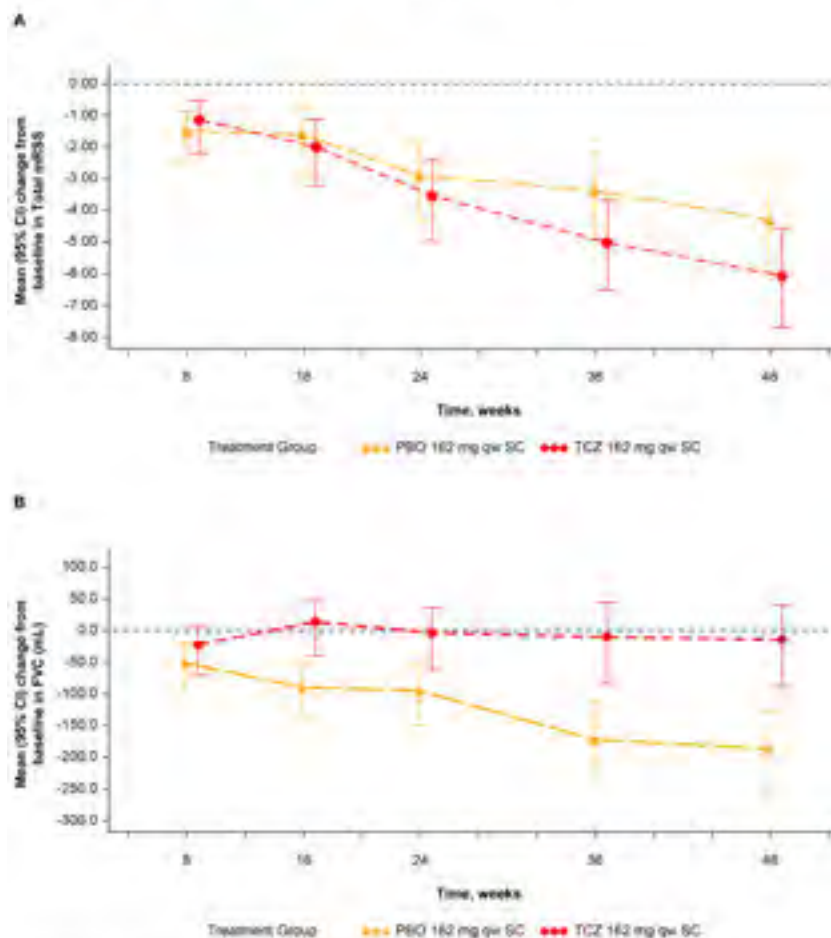
Session Time: 2:30PM-4:00PM

Background/Purpose: The anti-interleukin-6 (IL-6) receptor- α antibody tocilizumab (TCZ) demonstrated numeric improvement in skin thickening (modified Rodnan skin score [mRSS]) and clinically meaningful lung function preservation (forced vital capacity [FVC]) in patients with systemic sclerosis (SSc) in a phase 2 randomized controlled trial.^{1,2} Efficacy and safety of TCZ vs placebo (PBO) in patients with SSc are now reported from the double-blind period of a phase 3 trial (NCT02453256).

Methods: Patients with SSc were randomly assigned 1:1 to receive weekly double-blind injections of subcutaneous TCZ 162mg or PBO for 48 weeks. Patients could receive escape therapy from week 16 if they experienced declines in FVC or from week 24 if they experienced worsened mRSS or worsened SSc complications. The primary end point was difference in mean change in mRSS from baseline to week 48 for TCZ vs PBO. Key secondary end points were change from baseline in percent predicted FVC at week 48 and time to treatment failure (time from first study treatment to first occurrence of death, decline in FVC >10%, increase in mRSS >20% and mRSS \geq 5, or occurrence of predefined SSc-related complications).

Results: Among 212 randomly assigned patients, 81% were women; baseline mean values were age 48 years, SSc duration 23 months, mRSS 20.4, and percent predicted FVC 82.1% (210 patients were treated [PBO, 106; TCZ, 104]). At week 48, the primary end point (change in mRSS) was not met but improved numerically (PBO, -4.41; TCZ, -6.14; adjusted difference in least squares mean, -1.73 [95% CI: -3.78, 0.32]; $p = 0.098$) (Figure). Therefore, all other p values were considered nominal. The cumulative distribution of change from baseline to week 48 in percent predicted FVC favored TCZ over PBO (median [IQR]: PBO, -3.9 [-7.2, 0.6] vs TCZ, -0.6 [-5.3, 3.9]; van Elteren $p = 0.0015$). The difference in mean change from baseline in FVC at week 48 was 167 mL (95% CI: 83, 250) in favor of TCZ. Preservation of lung function with TCZ was shown by change from baseline in FVC over time (Figure). The hazard ratio (95% CI) for the time to treatment failure end point was 0.63 (0.37, 1.06) in favor of TCZ (Cox proportional hazards model; $p = 0.082$). Safety was consistent with known complications of SSc and with the safety profile of TCZ; serious adverse events were reported by 17% of PBO patients and 13% of TCZ patients; serious infections were reported by 7% and 2% of patients, respectively.

Figure. Change from baseline in mRSS (A) and FVC (B)



A mixed model for repeated measures analysis was implemented. The analysis included the fixed, categorical effects of treatment, visit, the stratification factor IL-6 level (<10; \geq 10 pg/mL) at screening, IL-6 level at screening-by-visit interaction, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Conclusion: The primary end point was not met; however, clinically meaningful and consistent differences in FVC were shown in 2 randomized controlled trials. Time to treatment failure is supportive of a clinical benefit of TCZ in SSc.
References: 1. Khanna D et al. *Lancet*. 2016;387:2630-2640. 2. Khanna D et al. *Ann Rheum Dis*. 2018;77:212-220. Medical writing: Sara Duggan, PhD, funded by F. Hoffmann-La Roche Ltd.

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Abstract Number: 899

Changes in the Systemic Sclerosis Molecular Signatures after Myeloablation Followed By Autologous Hematopoietic Stem Cell Transplantation and Their Clinical Correlates

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical I: Clinical Trial Results & Insights

Session Type: ACR Concurrent Abstract Session

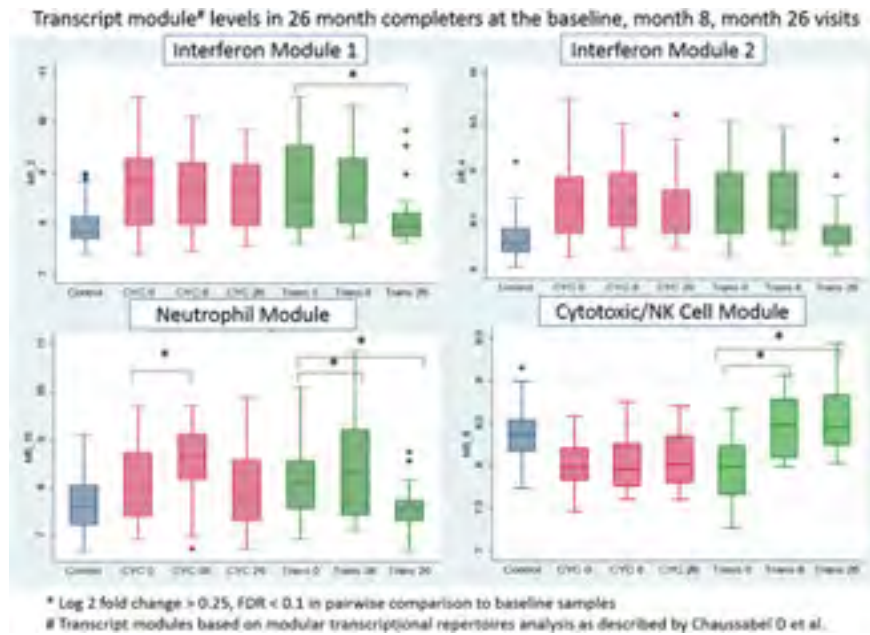
Session Time: 2:30PM-4:00PM

Background/Purpose: Myeloablation followed by autologous hematopoietic stem cell transplantation (HSCT) led to improved clinical outcomes compared to 12 monthly infusions of cyclophosphamide (CYC) in patients with severe diffuse systemic sclerosis (SSc) in SCOT trial¹. Global molecular studies in SSc patients undergoing HSCT have not been reported. Herein, we suggest that HSCT leads to changes in SSc related immune signatures after immune recovery at 26 month visit at the whole blood RNA and serum protein levels.

Methods: Sixty-two SCOT participants (HSCT= 27, CYC = 35) and 62-matched controls were investigated. Whole blood global transcript profiling and determination of 102 serum proteins in concomitantly collected serum samples were performed. All available samples at pretreatment baseline (n=62), 8 months (n=46), and 26 months (n=35) post-randomization were included.

Results: This subset of SCOT participants had a mean disease duration of 2.2 years and 93.5% of them had interstitial lung disease.

At the baseline visit, two interferon (IFN) and one neutrophil transcript modules were upregulated and the cytotoxic/NK module was down-regulated in comparison to controls. A paired comparison of the 26-month to the baseline samples revealed a significant decrease of the IFN and neutrophil modules and significant increase in the cytotoxic/NK module after HSCT but no significant change compared to baseline in the CYC recipients (Figure). Moreover, comparison of 26-month samples in the HSCT arm to healthy controls no longer showed upregulation of IFN or neutrophil modules or



downregulation of cytotoxic/NK module. A decline in the IFN and neutrophil modules was associated with an improvement in lung volumes and an increase in the cytotoxic/NK module correlated with improvement in the skin score at 26-month (Table).

Serum proteins correlating with the IFN and neutrophil transcript modules were identified. The serum protein IFN and neutrophil composite scores also decreased significantly at 26 months after HSCT (fold change (FC)=0.8, $p<0.001$; FC=0.85, $p=0.003$) while similar changes were not observed in the CYC arm at 8 or 26 months, confirming the gene expression level findings at the protein level.

Conclusion: In this first multilevel, global molecular study of HSCT in SSc, HSCT recipients contrary to CYC recipients had significant changes in SSc molecular signatures at both the RNA and serum protein levels at Month 26. The results at Month 26 provide an interim look, but need to be validated at the Month 54 primary endpoint.

1. SullivanKM et al. NEJM 2018; 378:35-47

Table: Correlation of percent change in transcript modules with percent change in clinical outcome

Transcript module	FVC%		mRSS	
	r	p	r	p
M1.2 (IFN)	-0.43	0.012	0.12	0.5
M3.4 (IFN)	-0.39	0.023	0.06	0.745
M5.15 (neutrophil)	-0.37	0.035	0.03	0.853
M3.6 (Cytotoxic/NK cell)	0.14*	0.4334*	-0.53*	0.0014*

Abbreviations: FVC%: Forced vital capacity% predicted; mRSS: Modified Rodnan Skin Score

* Spearman's Rho was used for this analysis

Disclosure: S. Assassi, Bayer, 2, Biogen Idec, 2, Boehringer Ingelheim, 2, 5, Momenta, 2; X. Wang, None; J. Ying, None; L. Keyes-Elstein, None; E. Goldmuntz, None; J. Turner, None; W. Zheng, None; G. Chen, None; M. V. Pascual, None; J. Varga, BSM, 2, Pfizer, Inc., 2, Boehringer, 5, Mitsubishi, 5, Corbus, 5, Scleroderma Foundation, 6; M. Hinchcliff, None; C. Bellocchi, None; P. McSweeney, None; D. E. Furst, no stocks, 2, 5, 6, 7; R. Nash, None; L. Crofford, None; B. Welch, None; A. Pinckney, None; M. D. Mayes, Boehringer-Ingelheim, 2, 5, Corbus, 2, Reata, 2, Sanofi, 2, Mitsubishi-Tanabe, 5, Roche-Genentech, 2; K. Sullivan, None.

Abatacept Vs. Placebo in Early Diffuse Cutaneous Systemic Sclerosis— Results of a Phase 2 Investigator Initiated, Double-Blind, Placebo- Controlled, Multicenter, Randomized Controlled Trial Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical I: Clinical Trial Results & Insights

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Abatacept (ABA) is a recombinant fusion protein including extracellular domain of human CTLA4 and hinge-CH2-CH3 of the Fc domain of human IgG. This phase 2 trial assessed the safety and efficacy of ABA 125 mg subcutaneous (SC) versus placebo SC given every week on skin fibrosis using the modified Rodnan skin score (mRSS) in diffuse cutaneous SSc (dcSSc; clinicaltrials.gov NCT02161406).

Methods: A 12-month, investigator-initiated, double-blind, randomized placebo-controlled trial was conducted between 2014 to 2018 at 27 US, Canadian and UK sites. Eligible subjects were randomized in a 1:1 ratio to either ABA or matching placebo, stratified by duration of dcSSc (≤ 18 vs >18 to ≤ 36 months). Key inclusion criteria included dcSSc with disease duration of ≤ 36 months (defined as first non-Raynaud phenomenon) and mRSS ≥ 10 and ≤ 35 units for disease duration of ≤ 18 months and mRSS ≥ 15 and ≤ 45 units with evidence of active disease for disease duration of >18 -36 months. Escape therapy was allowed at 6 months for worsening SSc. Primary outcomes included safety and change in mRSS over 12 months (Δ mRSS). Secondary endpoints included Δ FVC%, Δ HAQ-DI, Δ patient and Δ physician global assessment, and ACR CRIS (composite measure in dcSSc). The primary endpoint of Δ mRSS was assessed using a linear mixed model with primary end point data censored after initiation of escape therapy.

Results: 88 subjects were randomized (44/group) and formed the mITT group; 34 (77%) and 35 (80%) completed the 12-month double-blind treatment period in ABA and placebo groups, respectively. At baseline, the mean age was 49 years, 75% were female, mean disease duration was 1.59 years, 60% had disease duration ≤ 18 months, mRSS was 22.4, mean FVC% was 85.3%, and mean HAQ-DI was 1.0. Compliance with both drugs was $>98\%$. ABA was well tolerated with comparable adverse events (AEs), serious AEs, and AEs of special interest (e.g., infections and malignancies) between treatments. There were 3 deaths during the treatment—2 in ABA (both scleroderma renal crisis-days 11 and 46) and 1 in placebo (sudden cardiac arrest- day 310). The primary endpoint showed an adjusted mean decrease of mRSS of -6.24 in ABA vs. -4.49 in placebo, $p=0.28$ (Table). The secondary outcome measures were statistically significant (HAQ-DI,

physician global assessment, and ACR CRISS) or showed numerical results favoring ABA (Table). A larger proportion of placebo subjects required escape immunosuppressive therapy vs. ABA (36% vs. 16%, $p=0.03$).

Conclusion: In patients with early dcSSc, ABA was well tolerated, but Δ mRSS was not statistically significant. Secondary outcome measures showed evidence in favor of ABA, including greater requirement of escape therapy in the placebo group. mRSS showed large variability, despite recruiting an early dcSSc population.

Outcome at Month 12	Abatacept N=44	Placebo N=44	Difference (ABA - Placebo)	P-value
Δ mRSS	-6.24	-4.49	-1.75	0.28
Δ Patient Global Assessment	-0.31	-0.09	-0.22	0.73
Δ Physician Global Assessment	-1.30	-0.35	-0.95	0.03
Δ FVC% predicted	-1.34	-4.13	2.79	0.11
Δ HAQ-DI	-0.17	0.11	-0.28	0.005
ACR CRISS index, Median (IQR)	0.68 (1.00)	0.01 (0.86)		0.03

Estimates are from a linear mixed model with treatment group, month (3, 6, and 12), treatment x month interaction, duration of dcSSc (≤ 18 vs >18 to ≤ 36 months), and baseline outcome measure as fixed effects and participant as a random effect (except for ACR CRISS). For ACR CRISS, the treatment differences, adjusted for duration of dcSSc, were assessed by the non-parametric Van Elteren test. Multiple imputation was used for CRISS analysis.

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Abstract Number: 901

Changes in Quantitative Scleroderma Lung CT Measures in Patients Treated with Cyclophosphamide or Transplantation

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical I: Clinical Trial Results & Insights

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Scleroderma related interstitial lung disease (SLD) is a major cause of morbidity and mortality in severe systemic sclerosis (SSc). The Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial) demonstrated that myeloablation followed by autologous hematopoietic stem cell transplant (HSCT) significantly improved event-free and overall survival of SSc patients at 54 months compared with 12 monthly treatments with intravenous cyclophosphamide (CYC) (Sullivan KM, *et al*, N Engl J Med 2018;378:35-47). The aim of the present study was to follow the changes in lung parenchymal abnormalities between baseline and serial follow-up high-resolution CT (HRCT) scans performed in SCOT participants at least yearly for up to 5 years.

Methods: Quantitative scores of SLD were measured using computer based quantitative image analysis of standardized non-contrast volumetric thin section thoracic HRCT. The same CT machine was used for all time points (except for one subject) with careful attention to breath hold reproducibility and image quality. Quantitative CT texture-based scores of disease-extent including Quantitative interstitial lung disease (QILD) and quantitative lung fibrosis (QLF) were derived from a previously described supervised texture classification model (Kim et al Clin Exp Rheumatol, 28 (5 Suppl 62) (2010), S26–S35). Mixed effect models with an interaction between treatment arms and duration were used to compare the changes from the baseline in QLF and QILD scores in whole lung (WL) and the most severe lobe (MSL). Spearman rank correlations were used to test the association between the changes in QLF and QILD versus pulmonary function tests (PFT) in the overall study population

Results: All 75 randomized subjects had baseline lung CT studies. Quantitative scores were calculated for subjects with available follow-up HRCT scans at 14, 26, 48, and 54 months. Baseline characteristics were not different between the two groups. WL QILD scores decreased significantly for the HSCT vs no change in CYC groups ($p=0.024$). There was a significant difference in WL increasing QLF in CYC vs stability in the HSCT arm ($p=0.047$). Changes in means (\pm SE) at 54 months in treatment completers were $-7\%(\pm 2)$ for HSCT and $0\%(\pm 5)$ for CYC in QILD, and $-1\%(\pm 1)$ for HSCT and $+3\%(\pm 3)$ for CYC in QLF. Similarly, significant differences in treatments were also found in MSL ($p=0.004$ in QILD and $p=0.002$ in QLF). The direction of change in structural measures of QILD and QLF for both WL and MSL tracked with physiologic PFT measures in the overall study population as shown in the table

Conclusion: Changes in quantitative lung CT scores of SLD provide independent validation of benefit of HSCT compared to CYC in severe SSc. Imaging improvements after HSCT continue for up to 54 months after randomization providing radiologic confirmation of long-term benefit.

Disclosure: J. Goldin, None; L. Keyes-Elstein, None; L. Crofford, None; D. E. Furst, None; E. Goldmuntz, None; M. D. Mayes, None; P. McSweeney, None; R. Nash, None; H. J. G. Kim, None; M. Brown, None; K. Sullivan, None.

Abstract Number: 902

Longitudinal Trends in Clinical Disease Features after Myeloablative Autologous Stem-Cell Transplantation or Cyclophosphamide in Severe Scleroderma

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical I: Clinical Trial Results & Insights

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The Scleroderma: Cyclophosphamide or Transplantation (SCOT) study established the long-term superiority of hematopoietic stem cell transplant (HSCT) over cyclophosphamide (CYC) [Sullivan KM, et al. N Engl J Med.378:35-47]. The primary endpoint, a global rank composite score (GRCS) at 54months, integrated multiple disease features, but is not a clinical score. Longitudinal trends in the GRCS components can identify changes in clinical progression. Because dropouts, death, or organ failure lead to early loss of subjects, analysis methods must account for data that are not “missing completely at random.”

Methods: Data are from 33 HSCT recipients and 34 who completed ≥ 9 CYC doses. Diffusing capacity of carbon monoxide (DLCO), forced vital capacity (FVC), the Disability Index of the Health Assessment Questionnaire (HAQ-DI), and the modified Rodnanskin score (mRSS) were evaluated regularly up to month 72. For each, trends are compared using a mixed model (MX) that assumes data for subjects lost prematurely continue on their observed trajectories. Joint longitudinal/survival shared-parameter (SP) models that assume missingness is not “ignorable” are used for sensitivity. Figures display trends for observed means and model based fixed effects.

Results: In both arms, observed means for FVC increase over time; as those with poor FVCs are lost, the means for “survivors” go up (Figure1, dotted line). After accounting for subject loss, trends differ between the treatments. For HSCT, after an expected initial fall, the mean increase per year after month 14 was 0.53 percentage points compared to -

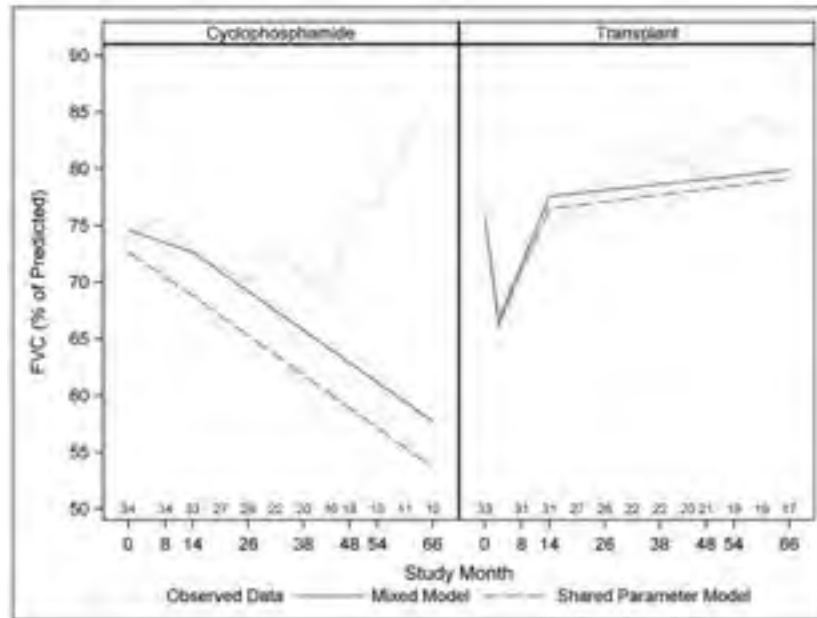


Figure 1. Estimate trends for forced vital capacity by treatment arm
The x-axis indicates times for scheduled assessments; subjects available over time are above the axis. Dotted lines connect means for the observed data over fixed intervals among subjects with available data.

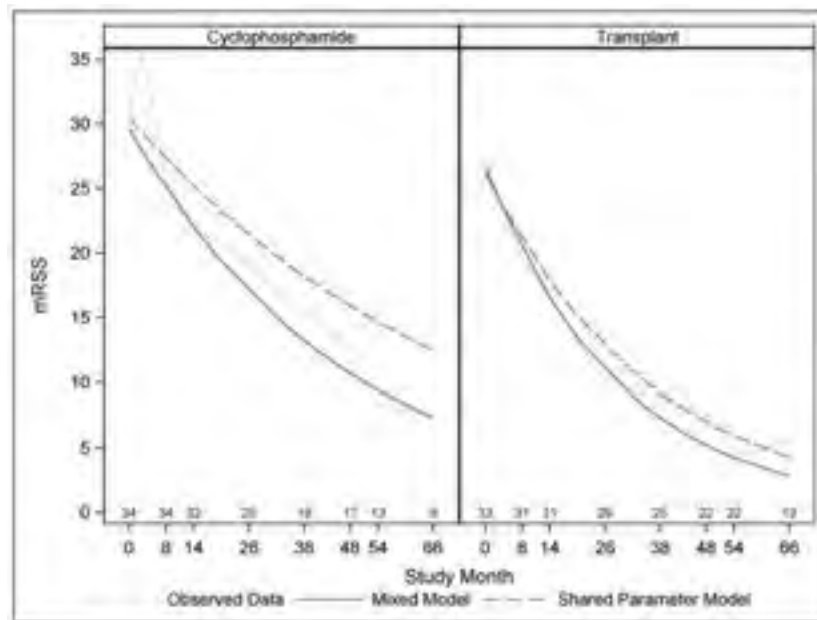


Figure 2. Estimate trends for modified Rodnan skin score by treatment arm
The x-axis indicates times for scheduled assessments; subjects available over time are above the axis. Dotted lines connect means for the observed data over fixed intervals among subjects with available data.

3.44 for CYC ($p=0.005$, MX). Trends for MX and SP models are similar for HSCT, but the SP model suggests an even greater fall for CYC.

mRSS declined exponentially over time in both arms. The yearly decay rate was 0.41 for HSCT and 0.26 for CYC ($p=0.05$, MX). In both arms, MX and observed trends track closely suggesting that trajectories are similar for those lost early and those completing follow up. Trends for SP models are similar with slower decay rates. (Figure 2)

DLCO and HAQ-DI trends are summarized in Table 1. :

Conclusion: Failure to account for early loss of longitudinal data may distort estimates of trends over time. Using two models, these analyses demonstrate the clinical superiority of HSCT over CYC for all components of GRCS even though mRSS improved in both arms.

Table 1. Model-based estimates for trend parameters

	Trend parameter [2]	Mixed Model (MM)			Shared Parameter Model (SP) [1]		
		HSCT	CYC	p-value	HSCT	CYC	p-value
FVC	change per month after month 14 (95% CI)	0.53 (-0.15, 1.21)	-1.44 (-5.98, -0.90)	0.006	0.61 (-0.25, 1.48)	-1.50 (-5.49, 1.49)	0.109
DLCO	change per month after month 14 (95% CI)	0.61 (-0.17, 1.21)	-1.25 (-3.55, -0.95)	0.001	0.43 (-0.35, 1.25)	-2.57 (-6.88, 1.74)	0.125
HAQ-DI	change per month after month 14 (95% CI)	-0.086 (-0.111, -0.032)	0.124 (-0.041, 0.287)	<0.001	-0.087 (-0.173, -0.011)	0.142 (-0.037, 0.237)	0.002
mRSS	decay rate per year (95% CI)	0.41 (0.29, 0.53)	0.29 (0.16, 0.35)	0.048	0.33 (0.21, 0.45)	0.16 (-0.07, 0.38)	0.022

Abbreviations: CI, confidence interval; DLCO, Diffusion Capacity Lung for Carbon Monoxide (% of predicted); FVC, Forced Vital Capacity (% of predicted); HAQ-DI, Health Assessment Questionnaire-Disability Index; mRSS, modified Rodnan skin score.

[1] Estimates from SP models tend to have less precision than MM models, because more parameters are being estimated, which reduces available degrees of freedom.

[2] For all endpoints, model-based means at month 54 favored HSCT, but all p-values for treatment comparisons were >0.05 except for mRSS (p-value=0.023).

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Abstract Number: 903

Riociguat in Patients with Early Diffuse Cutaneous Systemic Sclerosis: A Randomized, Double-Blind, Placebo-Controlled Phase IIb Study (RISE-SSc)

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SESSION INFORMATION

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Background/Purpose: There are few disease-modifying therapies for the treatment of systemic sclerosis (SSc), particularly the more severe diffuse cutaneous form (dcSSc). The soluble guanylate cyclase stimulator riociguat showed antifibrotic effects in animal models and efficacy in patients with pulmonary arterial hypertension associated with connective tissue disease. It was therefore hypothesized that patients with dcSSc might benefit from riociguat therapy. We present results from the Phase IIb, multicenter, randomized, double-blind, placebo-controlled RISE-SSc study (NCT02283762), which investigated the efficacy and safety of riociguat in patients with early dcSSc.

Methods: Inclusion criteria were a diagnosis of SSc (fulfilling 2013 ACR/EULAR criteria) with diffuse cutaneous involvement (based on LeRoy criteria), disease duration ≤18 months, modified Rodnan skin score (mRSS) ≥10 and ≤22 units, forced vital capacity (FVC) ≥45% of predicted, and diffusion capacity of the lung for carbon monoxide ≥40% of predicted at screening. Patients were randomized to either placebo or riociguat individually adjusted from 0.5 mg up to 2.5 mg 3 times daily. The primary endpoint was change in mRSS from baseline to Week 52. Secondary endpoints included ACR Combined Response Index for Systemic Sclerosis (CRISS), Health Assessment Questionnaire-Disability Index (HAQ-DI), and change in FVC % predicted. A prespecified exploratory analysis investigating mRSS progression rate (increase in mRSS >5 units and ≥25% from baseline) and a post hoc analysis on prevention of lung function decline (FVC % predicted decline ≥10% absolute) were also performed. The primary endpoint was analyzed using mixed-model repeated measures including all mRSS assessments from baseline up to Week 52.

Results: In total, 121 patients (riociguat n=60, placebo n=61) were randomized (mean±SD age 51±12 years; 76% female). Baseline mRSS was comparable in riociguat and placebo groups (mean±SD 16.88±3.38 and 16.71±4.06, respectively). At Week 52, mean±SD mRSS was 14.63±6.56 for riociguat vs 15.73±10.48 for placebo (least squares mean treatment difference -2.34 [95% CI -4.99, 0.30; p=0.08]). The difference in mRSS progression rate showed significant effects favoring riociguat (riociguat - placebo: -18% [95% CI -33.57, -2.40; p=0.02, Mantel-Haenszel method]). The proportion of patients with ACR CRISP probability ≥0.60 (considered improved) at Week 52 was the same in both treatment arms (18%). Mean±SD change from baseline to Week 52 in other secondary endpoints for riociguat vs placebo: FVC % predicted, -2.38±7.52 vs -2.95±9.73; HAQ-DI, +0.05±0.38 vs +0.13±0.42, respectively. At Week 52, prevention of lung function decline was observed in 89% of riociguat patients vs 80% with placebo. Fewer serious adverse events occurred with riociguat vs placebo (15% vs 25%, respectively) and no new safety signals were observed.

Conclusion: The primary efficacy endpoint of mean change in mRSS did not reach statistical significance. Exploratory data suggest prevention of disease progression with riociguat in this early dcSSc population. Medical writing support was provided by Adelphi Communications Ltd, Bollington, UK.

Disclosure: O. Distler, Actelion, Bayer, Boehringer Ingelheim, Mitsubishi Tanabe Pharma, Roche, 2, Actelion, AnaMar, Bayer, Boehringer Ingelheim, ChemolmAb, espeRare foundation, Genentech/Roche, GSK, Inventiva, Italfarmaco, Lilly, medac, MedImmune, Mitsubishi Tanabe Pharma, Novartis, Pfizer, Sanofi, Sinoxa, UCB, 5, Patent mir-29 for the treatment of systemic sclerosis licensed, 9; Y. Allano, Actelion, Boehringer, Roche, Sanofi, Inventiva, Medac, Bayer, BMS, Pfizer, 2, Actelion, Boehringer, Roche, Sanofi, Inventiva, Medac, Bayer, BMS, Pfizer, 5; C. P. Denton, Roche, Actelion, GlaxoSmithKline, Sanofi-Aventis, Inventiva, SCL Behring, Boehringer-Ingelheim, Bayer., 5; M. Kuwana, Ono Pharmaceuticals, AbbVie, Astellas, Chugai, Eisai, Mitsubishi-Tanabe, Pfizer, Ayumi, 2, 8; M. Matucci-Cerinic, None; J. E. Pope, Amgen Inc., 5, 9, Pfizer, Inc., 5, 9, UCB, Inc., 5, 9, AbbVie Inc., 5, Bristol-Myers Squibb, 5, 9, Actelion, 5, Eli Lilly and Co., 5, Merck & Co., 5, 9, Bayer, 5, 9, Roche, 5, 9, Novartis, 5, Sanofi, 5, Celtrion, 5, Seagen, 9, Genzyme, 5; J. Pena, Bayer AG, 3; K. Laapas, None; Z. Yao, Bayer Healthcare Co. Ltd., 3; D. Khanna, Eicos Sciences, 1, Pfizer, Inc., 2, Horizon, 2, BMS, 2, Actelion, 5, Bayer, 5, Bayer, 2, Corbus, 5, Cytos, 5, EMD Serono, 5, Genentech, Inc., 5, Sanofi-Aventis, 5, GSK, 5, Boehringer Ingelheim, 5.

Abstract Number: 904

Long-Term Safety of Rituximab in Granulomatosis with Polyangiitis or Microscopic Polyangiitis: Results of the Four-Year Study of Rituximab in ANCA-Associated Vasculitis Registry

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SESSION INFORMATION

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Background/Purpose: Potential therapy-related toxicities are important causes of morbidity in patients with the ANCA-associated vasculitides granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA). Long-term safety studies of rituximab in GPA/MPA are limited. This study characterized the safety of rituximab in a 4-yr observational registry of patients with GPA or MPA.

Methods: Analysis of RaVeR (NCT01613599), an open-label real-world study of adult patients with GPA or MPA receiving rituximab (dosing regimen determined by treating physician according to standard practice and discretion), was conducted after ≤ 4 yrs of observation or until withdrawal of consent, loss to follow-up or death. Adverse events (AEs) of interest included serious AEs (SAEs), serious infection events (SIEs), infusion-related reactions (IRR), serious cardiac or vascular events, and malignancies. Crude incidence rates and 95% CI were calculated.

Results: A total of 97 patients (338 patient-yrs [PYs]; median age 56.3 yrs; mean [SD] baseline VDI 2.0 [2.7]) received rituximab (mean of 8 infusions [range 1-28]). Median duration on study was 3.94 (range 0.05-4.32) yrs. 74% of patients completed the study. 91% of patients were ANCA-positive and 74% had GPA. 20% were receiving rituximab plus cyclophosphamide at baseline. During the study, 38 patients had 94 SAEs, 14 had 24 SIEs, and 10 had 17 serious cardiac events, most of which were arrhythmias (described in the existing label for rituximab; **Table 1**). Six patients had 8 serious

vascular events and 3 patients had malignancy-related events. There were no serious IRRs or SAEs within 24 hours of rituximab infusion. There were 9 deaths; none were considered by the treating physician to be related to rituximab. Causes of death included septic shock, interstitial lung disease, congestive heart failure, cardio-respiratory arrest, lung adenocarcinoma and 4 of unknown etiology. The severe disease flare (worsening disease activity prompting treatment) rate was 4.44/100 PYs (95% CI: 2.49-7.33). Among patients who received rituximab repeat treatment, the rates of SAEs (23.90/100 PYs) and SIEs (6.07/100 PYs) were not increased compared with the overall cohort.

Conclusion: In this cohort study there were no new safety findings related to the use of rituximab for GPA/MPA, and rates for any AE including SIEs, cardiovascular events, malignancies or fatal AEs did not increase over time with repeated rituximab infusions. These results are consistent with the known safety profile of rituximab in GPA/MPA and other autoimmune diseases in which rituximab is approved and provides clinicians with long-term, practice-level safety data.

Table 1 Observed Adverse Events of Interest Among Patients With GPA or MPA Receiving Rituximab

	Number of events	IR per 100 PY (95% CI)
All SAEs	94 in 38 pts (39%)	27.84 (22.50 to 34.07)
Serious infections	24 in 14 pts (14%)	7.11 (4.55 to 10.58)
Serious cardiac events	17 in 10 pts (10%)	5.03 (2.93 to 8.06)
Deaths	9 in 9 pts (9%)	2.67 (1.22 to 5.06)
Serious vascular events	8 in 6 pts (6%)	2.37 (1.02 to 5.96)
Malignancies	3 in 3 pts (3%)	0.89 (0.11 to 3.30)

GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; IR = incidence rate; PY = patient year; CI = confidence interval; SAE = serious adverse event

Disclosure: J. L. Niles, None; P. A. Merkel, Bristol-Myers Squibb, 2, ChemoCentryx, 2, 5, Genentech, Inc., 2, 5, InnfaRx, 5, Inmed, 5, AbbVie Inc., 5, CaridianBCT, 2, 5, GlaxoSmithKline, 2, 5, Kypha, 2, Kiniksa, 5, Boehringer-Ingelheim, 2, 5; L. Mertz, None; P. B. Lehane, Roche Products, Ltd., 3; P. Pordeli, F. Hoffmann-La Roche Ltd., 3; F. Erblang, F. Hoffmann-La Roche, 3.

Abstract Number: 905

Serum Interleukin-6 Levels in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

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SESSION INFORMATION

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Background/Purpose: The deregulated overproduction of interleukin (IL)-6 has been implicated in several inflammatory and antibody-mediated autoimmune diseases. We aimed to investigate serum IL-6 levels (sIL-6) during active disease, remission, and relapse in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), and to explore the association of changes in sIL-6 with repopulation of blood B cells and disease relapse.

Methods: sIL-6 levels were measured longitudinally over 18 months in 78 patients with AAV enrolled in a prospective, double-blinded, randomized, control trial comparing treatment with rituximab (RTX) (n=45) or cyclophosphamide (CYC)/azathioprine (AZA) (n=33). Outcome variables included baseline clinical features, ANCA type and titers, disease activity (status of active disease versus complete remission (CR)), time to B cell repopulation, relapse and severe relapse.

Results: Baseline sIL6 levels were detectable ($>0.49\text{pg/ml}$) in 81% of patients. At baseline, sIL-6 positively correlated with levels of proteinase (PR3)-ANCA ($r_s=0.36$, $p<0.01$), but not with levels of myeloperoxidase (MPO)-ANCA levels ($r_s=-0.17$, $p=0.47$). Higher baseline sIL-6 levels were associated with the presence of fever, pulmonary nodules/cavities, PR3-ANCA, conductive deafness and absence of urinary red blood cell casts ($p<0.05$ for all comparisons).

The median sIL-6 level was higher at baseline and promptly declined with induction therapy at following time-points (baseline, median [25%-75% IQR], 2.66 [0.76-20.98]; month 6th, 0.49 [0.49-1.16]; $p<0.01$) in a similar fashion in both treatment arms.

An increase in sIL-6, but not CRP, during clinical remission was a predictor for subsequent severe relapse in RTX-treated patients (Hazard Ratio (HR) 7.24, $p=0.01$), but not in CYC/AZA-treated patients (HR 0.62, $p=0.50$). In RTX-treated B cell depleted patients (CD19+ B cell/microliter <10), the rise of sIL-6 levels did not precede B cell reappearance, regardless of whether a cut-off of ≥ 10 CD19+B cell/microliter (HR=0.97; $p=0.97$) or of ≥ 69 CD19+B cell/microliter (HR=1.50; $p=0.41$) was considered.

Eighty percent of the patients who subsequently had a severe relapse in the RTX arm had B cell redetection before or at the time of the IL-6 increase, whereas, of the RTX-treated patients who did not have a severe relapse, 79% had B cell redetection but only 21% of those had B cell redetection before or at the same time of the sIL6 increase.

Conclusion: At baseline, sIL-6 correlates with PR3-ANCA titers and associates with specific clinical manifestations of AAV. A rise in sIL-6 levels, but not CRP levels, after complete remission is associated with subsequent severe relapse in RTX-treated patients. The observed discrepancies between treatments deserve confirmation and further study.

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Abstract Number: 906

Defining the Gut Microbiome in Patients with ANCA-Associated Vasculitis

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SESSION INFORMATION

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Session Title: Vasculitis – ANCA-Associated

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Background/Purpose: Although a link between gut microbiome and autoimmune diseases has been suggested, there is a gap in the understanding of the gut microbiome in ANCA-associated vasculitis (AAV). This study evaluated the gut microbiome in AAV (granulomatosis with polyangiitis (GPA), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis) compared to healthy controls.

Methods: Using cross-sectional and longitudinal designs, the gut microbiome was compared among patients with i) newly-diagnosed AAV (active and remission); ii) chronic AAV (active and remission), and iii) healthy controls. Fecal samples were collected using standardized methods and analyzed by sequencing the bacterial 16S rRNA gene (V1-V2 region). Taxa with mean abundance $>1\%$ were compared using Wilcoxon rank sum test, correcting for multiple comparisons. Disease severity was assessed with the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG). Effects of medications were studied using mixed effects models.

Results: 63 fecal samples were studied: 29 active AAV (15 new diagnosis/14 chronic), 20 in remission, and 14 healthy controls. Compared to controls, patients with active AAV had a different microbial composition ($p=0.01$). There was no statistical difference between the gut microbial composition of controls and patients in remission ($p=0.16$). The relative abundance of the taxa *Dialister* and *Prevotella* were different between active and remission AAV. The relative abundance of the genera *Faecalibacterium* and *Sutterella* were different between active and remission newly-diagnosed AAV (Figure 1A). The relative abundance of *Dialister* was significant in patients with high BVAS/WG compared to patients with low BVAS/WG ($p<0.01$) (Figure 1B). High BVAS/WG was associated with greater dysbiosis (Figure 2); similar results were

found in a multivariate linear model ($p=0.02$). The gut microbiome in patients with GPA on immunosuppressive agents was similar to controls ($p=0.54$), whereas the gut microbiome of patients with GPA not on these therapies was significantly different from controls; similar results were found with glucocorticoids and antibiotics use.

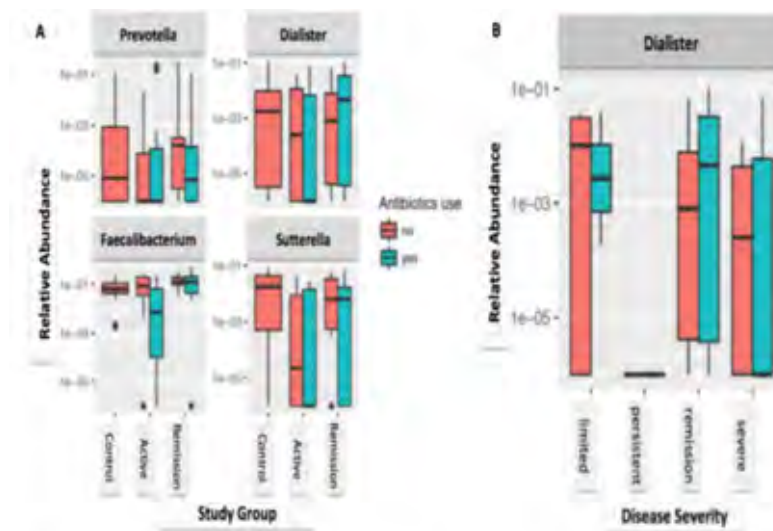


Figure 1. Bacteria with Differential Abundance Between Various Subgroups of Patients with ANCA-Associated Vasculitis (AAV). (A) Compared to patients with AAV in remission, patients with active AAV had a lower proportion of the taxa *Dialister* and *Prevotella* ($p=0.02$ and $p=0.03$, respectively and corrected for false discovery rate). Compared to patients with a new diagnosis of AAV in clinical remission, patients with a new diagnosis of active AAV had a lower proportion of the genera *Faecalibacterium* and *Sutterella* ($p=0.02$ and $p=0.05$, respectively, corrected for false discovery rate). (B) Compared to patients with less disease activity, patients with severe disease had a lower proportion of *Dialister* ($p<0.01$, corrected for false discovery rate).

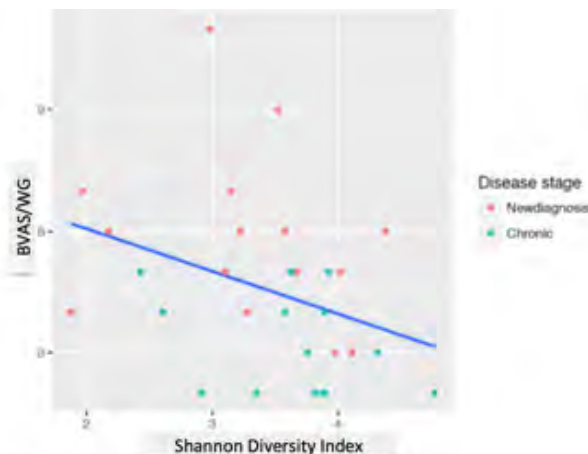


Figure 2. Scatter Plot of BVAS/WG by Shannon Diversity Index in Patients with Active AAV. High BVAS/WG correlated with a greater gut microbiome dysbiosis (lower Shannon diversity index) in patients with active AAV (Pearson coefficient=-0.35; $p<0.01$).

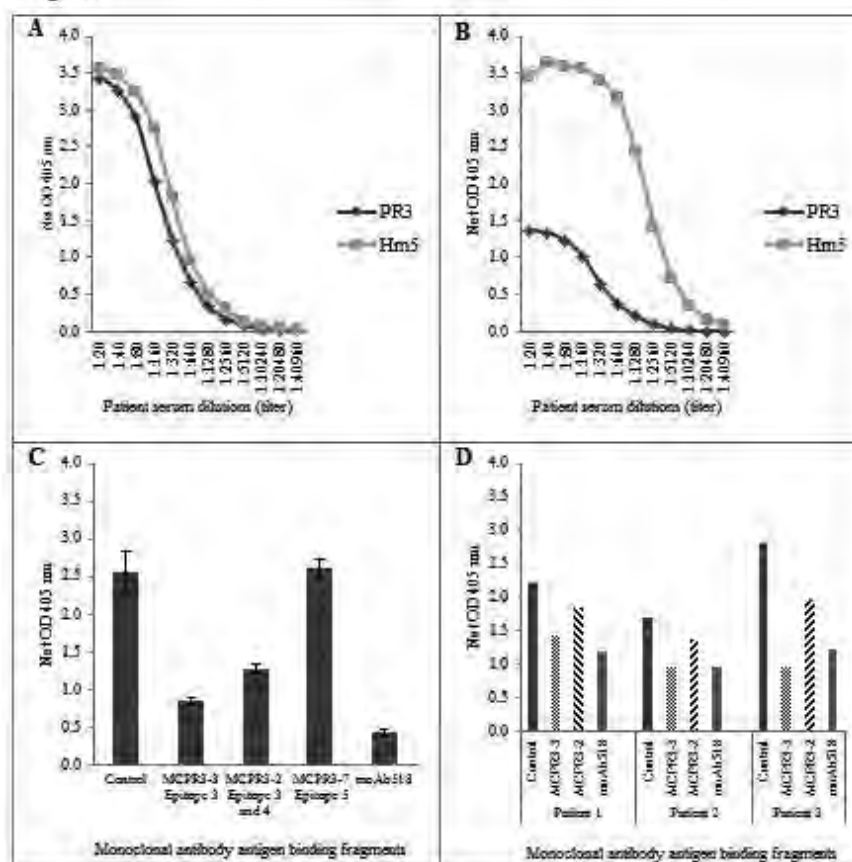
Conclusion: Active AAV is associated with an altered gut microbial composition. Patients in clinical remission have microbial composition similar to healthy controls. Immunosuppressive agents, glucocorticoids, and antibiotics may re-establish a healthy gut microbiome. Severe disease activity is associated with worsening gut dysbiosis suggesting a potential role of gut bacteria in the pathogenesis of AAV.

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Characterization of Preferential Recognition of a Chimeric Recombinant Proteinase 3 Variant By Anti-Neutrophil Cytoplasmic Antibodies

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Figure 1



Representative results from two patients with ANCA-associated vasculitis and antibodies to PR3-ANCA with equal (A) and higher (B) reactivity with Hm5 compared to PR3. (1C) Reduction in moAb518 binding to Hm5 after incubation with Fabs of moAbs that bind Epitope 3 and self. (1D) Similar reduction in PR3-ANCA binding to Hm5 after incubation with Fab that binds Epitope 3 and moAb518.

Fab epitope specificity as follows; MCP3-3 epitope 3, MCP3-2 epitope 4 with some epitope 3 overlap, MCP3-7 epitope 5. Control incubated with TBS with 0.5% BSA.

Abbreviations: optical density (OD), nanometers (nm), monoclonal antibody (moAb), antigen binding fragment (Fab)

SESSION INFORMATION

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Background/Purpose: Human-murine chimeric variants have been used to study specific epitope recognition by anti-neutrophil cytoplasmic antibodies (ANCAs) targeting proteinase 3 (PR3) in patients with ANCA-associated vasculitis. In prior work, a human-murine chimeric PR3 variant (Hm5) was generated by substituting the three human hydrophobic amino acids in Epitope 5 of PR3 by their murine hydrophilic counter parts.¹ Rather than loss of binding of PR3-ANCA to Hm5¹ we observed more avid binding of Hm5 by PR3-ANCAs compared with the mature conformation of PR3. Further studies were completed to better characterize this phenomenon.

Methods: Recombinant target antigens carrying C-terminal poly-HIS tags (PR3, Hm5, myeloperoxidase [MPO], human neutrophil elastase [HNE]) were anchored to nickel-coated plates and used for PR3- and MPO-ANCA detection. Serum samples were obtained from participants in the Wegener's Granulomatosis Etanercept (WGET) and in Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis (RAVE) trials. DNA barcode-enabled sequencing of the antibody repertoire of plasmablasts from 5 participants in the RAVE trial was performed, and 25 human monoclonal antibodies (moAb) were selected for recombinant expression and tested for reactivity with PR3, Hm5, MPO and HNE. Antigen-binding fragments (Fab) of anti-PR3 moAbs were used for inhibition.

Results: All PR3-ANCA positive samples reacted equally with or had increased recognition of Hm5 compared to PR3 (Figure 1A and 1B). In 2 of 52 serum samples from MPO-AAV patients included in RAVE, ANCA binding was detected when using Hm5 as antigen, but not when using PR3; all other samples were unreactive with either PR3 variant. All 25 human moAb derived from patient plasmablasts tested negative for reactivity with PR3, MPO and HNE, but one of these (moAb518) had strong selective reactivity with Hm5. The binding of moAb518 could be inhibited by Fabs from moAbs specific for Epitope 3, but not those specific for Epitope 5 where the 3 mutated residues of Hm5 are located (Figure 1C). The preferred binding of PR3-ANCA from patients to Hm5 could be reduced by inhibition with Epitope-3 specific Fabs in the same way as inhibition with moAb518 (Figure 1D).

Conclusion: (1) Hm5 can serve as an antigen for high sensitivity PR3-ANCA immunoassays. (2) The plasmablast-derived human moAb518 binds selectively to Epitope 3 on Hm5, indicating an unexpected mutational effect on Epitope 3 that is located on the opposite side of Epitope 5. (3) New studies are needed to explain how mutational effects of distal residues can affect conformational epitopes of an antigen.

Reference : 1. Silva F, Hummel AM, Jenne DE, Specks U. Discrimination and variable impact of ANCA binding to different surface epitopes on proteinase 3, the Wegener's autoantigen. *Journal of autoimmunity*. 2010;35(4):299-308.

Disclosure: G. Thompson, None; M. Casal Moura, None; D. Nelson, None; A. Hummel, None; D. E. Jenne, None; F. Fervenza, None; G. S. Hoffman, None; C. G. M. Kallenberg, None; C. Langford, Bristol-Myers Squibb, 2, GlaxoSmithKline, 2, ChemoCentryx, 2, Genentech, Inc., 2, Bristol-Myers Squibb, 9, AbbVie Inc., 9; J. W. McCune, None; P. A. Merkel, None; P. A. Monach, None; P. Seo, None; R. F. Spiera, Roche-genentech, 2, Corbus, 2, chemocentryx, 2, GSK, 2, BMS, 2, Boehringer Ingelheim, 2, GSK, 5, Sanofi, 5, CSL Behring, 5; E. W. St. Clair, None; S. R. Ytterberg, None; J. H. Stone, None; W. H. Robinson, None; Y. P. Pang, None; U. Specks, None.

Abstract Number: 908

Early Prediction of Long-Term Evolutionary Profiles of Eosinophilic Granulomatosis with Polyangiitis (Churg–Strauss) Based on Baseline and Follow-up Characteristics

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Background/Purpose: Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss) is a small-vessel necrotizing vasculitis characterized by blood and tissue eosinophilia and asthma. Glucocorticoids (GCs) effectively control the disease, but relapses and/or GC-dependence are frequent. Recently, efforts were made to improve nosology of EGPA patients. Evolving concepts tend to distinguish vasculitis-related symptoms from asthma and/or ENT manifestations. That distinction has become even more important, since the development of new targeted biotherapies. This study aimed to describe and identify characteristics predicting long-term EGPA outcomes.

Methods: We created a multicenter European collaborative initiative that included 257 EGPA patients from tertiary referral centers. Based on recent consensus, we distinguished 4 EGPA-evolutionary profiles: GC-dependent asthma and/or ENT manifestations (requiring prednisone >7.5 mg/d), at least 1 vasculitis relapse (excluding asthma and/or ENT manifestations), both phenotypes, and prolonged remission (no GC-dependent asthma/ENT signs and no vasculitis relapse). Baseline and follow-up characteristics predicting those outcomes were analyzed.

Results: After median follow-up of 60 months, 24% had GC-dependent asthma and/or ENT manifestations, 18% had at least 1 vasculitis relapse, 8% had both phenotypes, and 50% were in prolonged remission (Table). Patients with GC-dependent asthma/ENT manifestations were younger at diagnosis, had more frequent asthma requiring GCs before overt EGPA and pulmonary infiltrates, less frequent general symptoms and ANCA-positivity, and tended to have lower eosinophil counts. Their daily GC dose and eosinophil counts were higher at every time point; at last follow-up, they had more active asthma and less frequent neurological sequelae. In contrast, patients with only vasculitis relapse(s) had more frequent general symptoms at diagnosis, ANCA-positivity and higher BVAS, and less frequent pulmonary infiltrates. Median diagnosis-to-1st-vasculitis-relapse interval was 15 (9–42) months. During follow-up, their daily GC dose was lower than for those with GC-dependent asthma and/or ENT manifestations but similar to that of those in prolonged remission. At last follow-up, neurological sequelae were more frequent but active asthma less common. Finally, patients in prolonged remission were older, had less frequent asthma requiring GCs before EGPA, and lower daily GC dose and eosinophil counts during follow-up and less frequent sequelae.

Conclusion: Distinct baseline and follow-up characteristics defined 4 evolutionary EGPA profiles predicting patients' long-term outcomes. Each evolutionary pattern was identifiable soon after diagnosis, which would allow early choices of the best therapeutic option in the future.

Table

Characteristic	Evolutionary profile				P
	Prolonged remission (n=129)	GC-dependent asthma/ENT (n=62)	Vasculitis relapse (n=45)	GC-dependent asthma/ENT & vasculitis relapse (n=21)	
Age at diagnosis, yr	57 (44–67)	47 (36–58.2)	52 (44.5–66.5)	43 (31.5–52.2)	<0.0001
Asthma before EGPA	109/129 (84.5)	55/59 (93.2)	36/45 (80)	21/21 (100)	0.0498
Asthma duration, yr	5 (2.1–15.4)	5 (2–14.7)	3 (1–10.3)	2 (1–4.3)	0.02
General symptoms	102/129 (79.1)	41/62 (66.1)	39/45 (86.7)	13/21 (61.9)	0.03
Manifestation					
Cutaneous	45/129 (34.9)	24/62 (38.7)	22/45 (48.9)	8/21 (38.1)	0.43
ENT	91/129 (70.5)	48/62 (77.4)	35/45 (77.8)	15/21 (71.4)	0.67
Pulmonary	123/129 (95.3)	61/62 (98.4)	44/45 (97.8)	21/21 (100)	0.52
Infiltrates	74/129 (57.4)	38/62 (61.2)	19/45 (42.2)	17/21 (81)	0.024
Cardiac	39/129 (30.2)	25/62 (40.3)	16/45 (35.6)	7/21 (33.3)	0.57
Gastrointestinal	30/129 (23.3)	10/62 (16.1)	9/45 (20)	3/21 (14.3)	0.81
Renal	23/129 (17.8)	7/62 (11.3)	8/45 (17.8)	3/21 (14.3)	0.68
Neurological	87/129 (67.4)	34/62 (54.8)	35/45 (77.8)	15/21 (71.4)	0.084
ANCA+	52/129 (40.3)	14/61 (23)	22/45 (48.9)	9/21 (42.9)	0.034
Anti-MPO+	40/106 (37.7)	7/39 (17.9)	18/39 (46.2)	8/16 (50.0)	0.026
CRP, mg/L	35 (13–75)	35 (15–84.2)	59 (29–91)	11 (3.5–49)	0.055
Eosinophils, /mm ³	6680 (3000–11300)	4000 (2185–9125)	4500 (1808–10093)	3900 (1940–6187)	0.055
BVAS	16 (9–21)	10.5 (6–20)	17 (11–23.5)	15 (8–24)	0.038
Deaths	10/119 (8.4)	3/62 (4.8)	2/45 (4.4)	1/21 (4.8)	0.7
GC dose, mg/d					
At 6 months	10 (7–12.8)	14.5 (10–20)	8 (6–20)	16.2 (10–20)	0.0007
A 24 months	5 (5–7)	10 (6–15)	8.2 (5–10.5)	21 (10–40)	<0.0001
Eosinophils, /mm ³					
At 6 months	300 (100–540)	490 (104–980)	628 (142–1422)	610 (288–3300)	0.046

Table . (Cont'd)

Characteristic	Evolutionary profile				P
	Prolonged remission (n=129)	GC-dependent asthma/ENT (n=62)	Vasculitis relapse (n=45)	GC-dependent asthma/ENT & vasculitis relapse (n=21)	
At 60 months	472 (300–847)	900 (400–1200)	568 (409–2235)	1220 (825–6250)	0.065
At last follow-up					
GC dose, mg/d	5 (3–7)	10 (6.7–12.5)	5 (4–10)	10 (7.5–23)	<0.0001
No GCs	25/123 (20.3)	2/61 (3.3)	6/44 (13.6)	0/21 (0)	0.0031
EGPA sequelae	48/84 (57.1)	54/58 (93.1)	13/21 (61.9)	17/20 (85)	0.0007

Values are expressed as n (%) or median [IQR], with respective P values computed with χ^2 or Kruskal–Wallis test.

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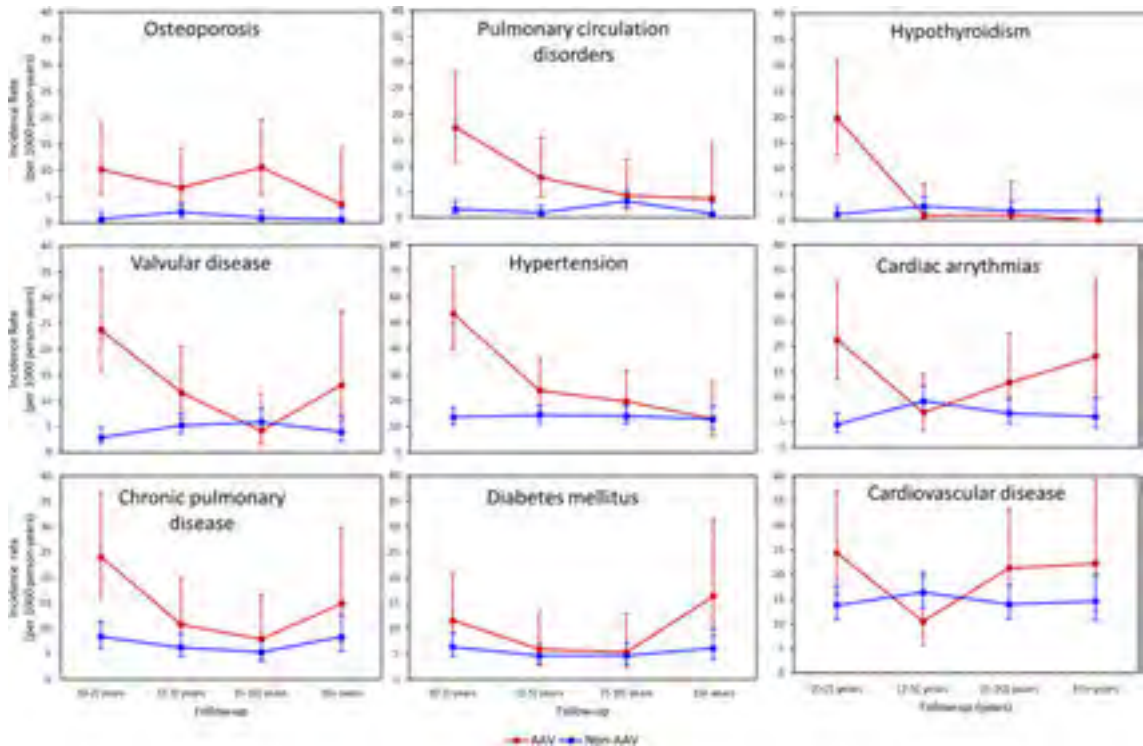
Abstract Number: 909

Temporal Trends of ANCA-Associated Vasculitis Comorbidities: Results from a National, Longitudinal, Matched-Cohort Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018
Session Title: Vasculitis – ANCA-Associated
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM



Background/Purpose: Comorbidity is common in patients with ANCA-associated vasculitis (AAV). However, this comorbidity and its burden over time remains unexplored. In this large multicenter study, we aimed to compare the risk of a broad set of comorbid diseases in AAV patients with the general population and identify potential temporal changes in the risk of their occurrence.

Methods: AAV patients fulfilling European Medicines Agency criteria were identified at seven hospitals in Scotland. Each was matched with up to five controls in the general population by age (± 2 years), sex and geography. Diagnoses of selected comorbidities were retrieved from the Inpatient or Day Case Hospitalisations Database using International Classification of Disease codes. Cohorts were followed from the date of AAV diagnosis until death or 02/28/2017, whichever came first. Comorbidity incidence was assessed using modified Poisson regression. Temporal patterns in comorbidity incidence were assessed using discrete regression analysis at the following intervals: 2-<5 years, 5-<10 years and 10+ years after follow-up.

Results: A total of 543 AAV (53.5% male) patients were matched with 2672 general population controls. The median (interquartile range) follow-up time was 5.1 (2.5 to 9.4) years. Overall, after AAV diagnosis, these patients were at a higher risk of developing the following comorbid diseases compared to the general population (Incidence Rate Ratio; 95% Confidence Interval): osteoporosis (8.0; 4.6-14.2), pulmonary circulation disorders (5.5; 3.3-9.1), hypothyroidism (3.4; 2.0-6.0), valvular disease (3.0; 2.1-4.4), hypertension (2.4; 1.8-3.1), cardiac arrhythmias (2.2; 1.5-3.1), chronic pulmonary disease (2.2; 1.6-3.1), diabetes mellitus (2.1; 1.4-3.0), and major cardiovascular events (1.4; 1.1-1.9). Temporal analyses showed that differences in risk were most apparent in the first two years following diagnosis, and they tended to reduce, if not disappear, for many comorbidities over time (See Figure 1).

Conclusion: To our knowledge, this is the first study to comprehensively examine the breadth and timing of comorbidity risk in AAV. Our findings showed that AAV patients face an increased risk of comorbidity, especially within the first two years of diagnosis. These data should help inform the management of these patients. Further analysis incorporating prescription data might help explain the reduction of risk over time.

Figure 1. Incidence of comorbid diseases in AAV compared with that in the general population

Disclosure: S. Sarica, None; N. Dhaun, None; J. Sznajd, None; J. Harvie, None; N. Joss, None; J. McLaren, None; L. McGeoch, None; N. Amft, None; V. Kumar, None; A. Marks, None; C. Black, None; N. Basu, None.

Abstract Number: 910

In Diagnostic Prevalence and Treatment Patterns of Male and Female Ankylosing Spondylitis Patients in the United States, 2006-2016

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health – ACR/ARHP

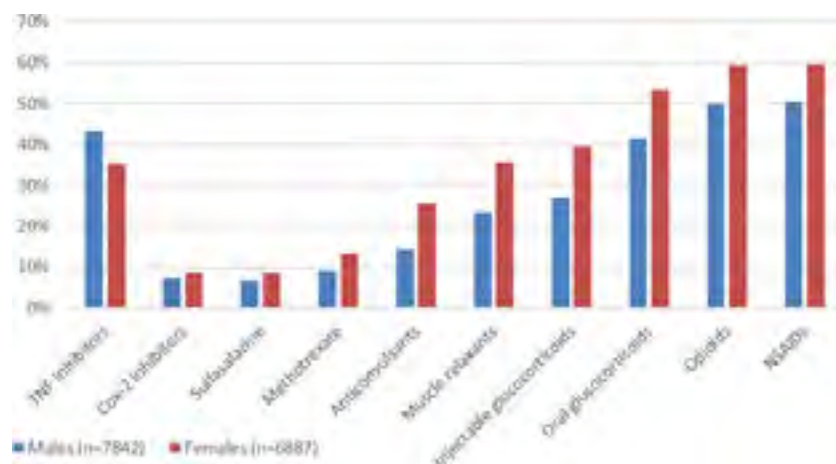
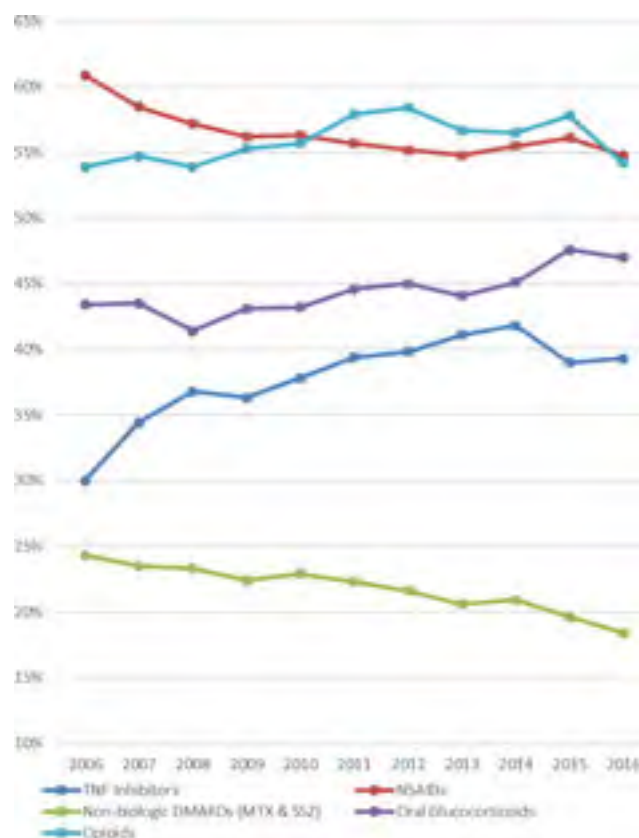
Session Type: ACR/ARHP Combined Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: This study aimed to analyze the prevalence rates and treatment patterns of male and female ankylosing spondylitis (AS) patients in the United States (US) adult insured population from 2006 to 2016.

Methods: Trends in AS prevalence were calculated for the 10-year period covering January 1, 2006 to December 31, 2016. Adult (18+ years old) AS patients were included in this retrospective analysis of medical and pharmacy claims data from the Truven Marketscan Commercial, Medicaid and Medicare-Supplemental Claims database. Prevalence was determined using two AS definitions; A) ≥ 2 AS diagnostic codes (ICD-9:720.0; ICD-10:M45.x), or B) ≥ 1 AS diagnostic code by a rheumatologist. Trends in treatment patterns were also analyzed and stratified by gender.

Results: The AS prevalence ranged from 0.04% to 0.09% from 2006 to 2016. The mean age between 2006 and 2016 ranged from 49.52 -50.00 years. In 2006, approximately 40% of AS patients were female, while in 2016 over 47% of AS patients were female. Rates of use of TNF inhibitors (TNFi) and oral glucocorticoids increased, while NSAIDs and non-biologic DMARDs (sulfasalazine & methotrexate) rates decreased. Opioid use rates were stable (Figure 1). In 2016, males were more likely to be prescribed TNFi, while females were more likely to be prescribed methotrexate, sulfasalazine, NSAIDs, muscle relaxants, anticonvulsants, opioids, and glucocorticoids (Table 2).



Conclusion: The prevalence of AS diagnosis codes more than doubled between 2006 and 2016, but the very low prevalence suggests that AS continues to be under diagnosed and under-addressed in routine clinical practice. Despite the increase in female AS patients, females were less likely to be prescribed TNF inhibitors compared to male AS patients.

Figure 1. Trends in Treatment Patterns among AS Patients, 2006-2016

Figure 2. Medication Use among Male and Female AS Patients in 2016

Disclosure: J. Walsh, Eli Lilly and Company, 5; T. Hunter, Eli Lilly and Company, 1, 3; R. Bolce, Eli Lilly and Company, 1, 3; D. S. Calderon, Eli Lilly and Company, 1, 3; K. Schroeder, Eli Lilly and Company, 1, 3.

Demographic and Clinical Characteristics Reflect Differences in Osteoarthritis Phenotypes of the Lumbar Spine: The Johnston County Osteoarthritis Project

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Spine osteoarthritis (OA) has been defined by the presence of: 1) disc space narrowing (DSN) and vertebral osteophytes (OST), or 2) facet joint OA (FOA). However, anatomical differences of these structures used in these two definitions suggest they may have different etiologies. Our aim was to determine if differences in associations exist between demographic (age, race, sex) and clinical characteristics (body mass index [BMI]), coincident knee, hip or hand OA, and low back symptoms) and OA involvement in the lumbar spine, defined as 1) FOA only and 2) Spine OA only (DSN plus vertebral OST) or 3) FOA and Spine OA, when compared to those with neither Spine OA nor FOA.

Methods: Data were collected from 2003-2010 in the Johnston County OA Project. Each lumbar spine level was graded for OST and DSN in a semi-quantitative fashion (0-3) while FOA was graded as present or absent, according to the Burnett Atlas. Spine OA was defined as the presence of DSN and OST grade ≥ 1 at the same lumbar level. Participants reported the presence of low back symptoms (pain, aching, and/or stiffness) on most days of any one month in the last 6 months and their history of back injury (yes/no). Knee OA and hip OA were both defined by a Kellgren-Lawrence score (K-L) of 2-4. Hand OA was defined as K-L 2-4 in a minimum of one distal interphalangeal (IP) joint and 2 other joints (IP or carpometacarpal). Age, race and sex were collected by self-report and BMI measured at clinical examination. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated with multinomial logistic regression.

Results: Complete data were available for 1,874 participants. The table presents the counts and percentages for spine OA groups, demographics and clinical characteristics.

Table 1a presents demographic adjusted associations. All age categories were strongly associated age categories compared to none with the strength of association increasing with greater age. African Americans were 32% less likely to have FOA only and 49% less likely to have both FOA and Spine OA. Women were 64% more likely to have FOA alone.

Table 1b presents clinical characteristic adjusted associations. Those with FOA only were 74% more likely to have BMI ≥ 30 kg/m². Similar associations were found between knee OA and both FOA only and Spine OA only, though stronger with both FOA and Spine OA. Back injury was strongly associated with Spine OA only. Symptoms, hip OA, and hand OA were not significantly associated with any spine OA involvement.

Conclusion: The differences in demographic characteristics (race and sex) and clinical characteristics (BMI and back injury) suggest pathophysiologic processes may vary for these definitions lumbar spine OA involvement. Increasing associations across categories of age suggests changes over time, however longitudinal studies may elucidate whether those with FOA only or Spine OA only remain an isolated lumbar spine OA phenotype over time.

Variable	FOA only* (n=424, 22.6%)	Spine OA Only* (n=244, 13.0%)	FOA and Spine OA* (n=861, 45.9%)
A. Demographic			
Age ≥ 55 -<65 (n=659, 32.8%) vs. <55 (n=309, 15.4%)	1.90 (1.26-2.86)	2.04 (1.26-3.30)	3.04 (1.99-4.64)
Age ≥ 65 -<75 (n=610, 30.4%) vs. <55	3.00 (1.85-4.88)	3.38 (1.94-5.89)	7.07 (4.37-11.4)
Age ≥ 75 (n=429, 21.4%) vs. <55	4.16 (2.20-7.88)	3.28 (1.57-6.85)	12.80 (6.93-23.5)
African American (n=654, 32.6%) vs. Caucasian	0.68 (0.50-0.94)	0.92 (0.64-1.31)	0.51 (0.38-0.69)
Women (n=1319, 65.7%) vs. Men	1.64 (1.19-2.25)	1.10 (0.77-1.55)	1.16 (0.86-1.55)
B. Clinical Characteristics			
BMI ≥ 30 kg/m ² (n=1000, 49.8%) vs. BMI <30 kg/m ²	1.74 (1.28-2.38)	1.24 (0.87-1.76)	1.86 (1.39-2.49)
Mild Back Symptoms (n=252, 12.6%) vs. None (n=1,172, 58.4%)	0.78 (0.47-1.27)	1.39 (0.84-2.31)	1.30 (0.84-2.02)
Moderate / Severe Back Symptoms (n=600, 29.9%) vs. None	1.10 (0.77-1.57)	1.29 (0.86-1.93)	1.33 (0.95-1.86)

Table . (Cont'd)

Variable	FOA only* (n=424, 22.6%)	Spine OA Only* (n=244, 13.0%)	FOA and Spine OA* (n=861, 45.9%)
Back Injury (n=45, 2.2%) vs. None	1.45 (0.47-4.40)	3.02 (1.06-8.60)	1.53 (0.54-4.31)
Knee OA (n=762, 38.0%) vs. None	1.66 (1.17-2.38)	1.66 (1.11-2.47)	2.45 (1.76-3.40)
Hip OA (n=652, 32.5%) vs. None	0.75 (0.53-1.05)	0.80 (0.54-1.18)	0.80 (0.58-1.10)
Hand OA (617, 30.7%) vs. None	1.22 (0.80-1.85)	1.14 (0.71-1.83)	1.43 (0.97-2.11)

* Versus neither FOA nor Spine OA (n=345, 18.4%)

Adjusted for all other factors in this table

Disclosure: A. P. Goode, None; B. Cleveland, None; T. Schwartz, None; S. Z. George, None; V. B. Kraus, None; R. Gracely, None; J. Chen, None; J. M. Jordan, None; Y. M. Golightly, None.

Abstract Number: 912

Association of Adiposity Measures in Childhood and Adulthood with Knee Cartilage Thickness, Volume and Bone Area in Young Adults

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Adiposity is associated with increased risk of knee osteoarthritis; cartilage thickness, cartilage volume and subchondral bone area are established biomarkers in knee osteoarthritis. We aimed to describe the longitudinal associations of childhood and adulthood adiposity measures with knee cartilage thickness, volume and bone area in young adults.

Methods: Childhood and adulthood adiposity measures (weight, height, waist circumference and hip circumference) of 186 participants were collected in 1985 (aged 7-15 years) and during 2004-2006 (aged 26-36 years). Knee magnetic resonance imaging was conducted during 2008-2010 (aged 31-41 years), and cartilage thickness, volume and bone area were measured using a quantitative approach (Chondrometrics, Germany). Linear regressions were used to examine the above associations.

Results: The prevalence of overweight was 7.6% in childhood and 42.1% in adulthood. Childhood weight was negatively associated with adult patellar bone area ($\beta = -6.24$, 95% confidence interval (CI) -10.25 to -2.22 mm²/kg), while adult weight

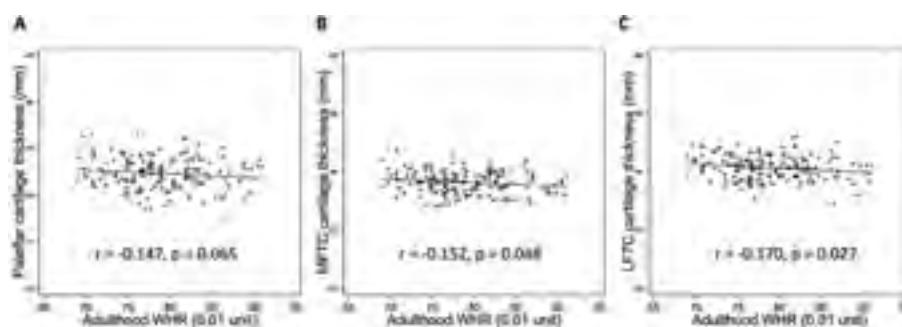


Figure. Scatter plots and linear regression lines for associations between adulthood WHR and knee cartilage thickness (A: patella; B: MFTC; C: LFTC). Linear regression lines are from models adjusted for adulthood age, duration of follow-up, gender and adulthood knee injury. WHR, waist-hip ratio; MFTC, medial femoral tibial compartment; LFTC, lateral femoral tibial compartment.

Table 1. Associations between adulthood adiposity measures and knee cartilage thickness, cartilage volume and subchondral bone area

	Cartilage thickness (mm) β (95% CI)	Cartilage volume (mm ³) β (95% CI)	Bone area (mm ²) β (95% CI)
Patella			
Weight, kg	0.001 (-0.004 to 0.001)	3.14 (-2.88 to 7.94)	-0.28 (-1.68 to 1.12)
BMI, kg/m ²	-0.002 (-0.006 to 0.011)	-8.12 (-31.82 to 12.58)	-0.88 (-6.58 to 4.82)
Overweight, yes	0.043 (-0.664 to 0.134)	-18.37 (-200.22 to 171.48)	-53.90 (-75.08 to 7.30)
WHR, 0.01 unit	0.009 (-0.019 to 0.001) ^a	-21.85 (-37.77 to -5.93)	-4.69 (-8.26 to -1.12)
MFTC			
Weight, kg	0.002 (-0.005 to 0.001)	8.89 (-1.72 to 14.28)	3.89 (-1.44 to 4.74)
BMI, kg/m ²	-0.002 (-0.013 to 0.011)	12.14 (-8.92 to 33.21)	4.89 (-1.82 to 11.38)
Overweight, yes	0.062 (-0.064 to 0.188)	83.88 (-41.37 to 712.67)	70.99 (-22.35 to 264.33)
WHR, 0.01 unit	-0.011 (-0.022 to 0.000)	-34.17 (-28.53 to 1.39) ^a	-2.22 (-6.87 to 2.43)
LFTC			
Weight, kg	0.001 (-0.000 to 0.000)	8.38 (-1.28 to 11.64)	1.85 (-0.19 to 3.51)
BMI, kg/m ²	0.000 (-0.006 to 0.016)	-6.36 (-28.00 to 24.88)	0.90 (-2.58 to 7.79)
Overweight, yes	0.03 (-0.105 to 0.163)	28.87 (-64.89 to 244.34)	2.88 (-21.80 to 27.55)
WHR, 0.01 unit	-0.018 (-0.025 to -0.003)	-23.87 (-42.18 to -5.57)	-4.76 (-9.47 to -0.06)

^a Bold denotes statistical significance, $p < 0.05$.Adjusted for adulthood age, duration of follow-up, gender, adulthood knee injury, height (^a weight was the predictor).

CI, confidence interval; BMI, body mass index; WHR, waist-hip ratio; MFTC, medial femorotibial compartment; LFTC, lateral femorotibial compartment.

^a $p = 0.065$; ^b $p = 0.030$.

Table 2. Associations of the change of adiposity measures from childhood to adulthood with knee cartilage thickness, cartilage volume and subchondral bone area

	Cartilage thickness (mm) β (95% CI)	Cartilage volume (mm ³) β (95% CI)	Bone area (mm ²) β (95% CI)
Patella			
Weight z-score change	-0.047 (-0.114 to 0.019)	-22.13 (-125.77 to 81.53)	0.81 (-20.44 to 22.27)
BMI z-score change	-0.037 (-0.095 to 0.021)	-9.71 (-84.07 to 108.49)	10.02 (-12.13 to 32.17)
WHR z-score change	-0.021 (-0.070 to 0.027)	-83.28 (-162.97 to -3.23)	-21.35 (-39.88 to -3.60)
MFTC			
Weight z-score change	0.034 (-0.11 to 0.062)	-3.66 (-102.32 to 99.01)	8.19 (-18.32 to 34.70)
BMI z-score change	-0.033 (-0.100 to 0.033)	-0.20 (-95.89 to 95.36)	11.34 (-7.72 to 40.00)
WHR z-score change	-0.054 (-0.109 to -0.003)	-83.84 (-158.87 to -8.80)	-13.50 (-36.32 to 9.33)
LFTC			
Weight z-score change	-0.048 (-0.129 to 0.033)	-89.69 (-203.75 to 24.38)	-18.79 (-43.83 to 5.47)
BMI z-score change	-0.093 (-0.118 to 0.055)	-64.10 (-177.37 to 49.58)	-13.75 (-43.82 to 15.30)
WHR z-score change	-0.039 (-0.090 to 0.012)	-100.55 (-190.28 to -10.81)	-24.47 (-47.36 to -1.58)

^a Bold denotes statistical significance, $p < 0.05$.

Adjusted for childhood and adulthood age, gender, childhood and adulthood knee injury, childhood and adulthood height (if weight z-score change is the predictor).

CI, confidence interval; BMI, body mass index; WHR, waist-hip ratio; MFTC, medial femorotibial compartment; LFTC, lateral femorotibial compartment.

was positively associated with bone area in medial femorotibial compartment (MFTC) ($\beta=3.09$, 1.44 to 4.74 mm²/kg) and lateral femorotibial compartment (LFTC) ($\beta=1.85$, 0.19 to 3.51 mm²/kg). Adult waist-hip ratio (WHR) was negatively associated with cartilage thickness (MFTC: $\beta=-0.011$, -0.022 to 0.000; LFTC: $\beta=-0.013$, -0.025 to -0.002 mm/0.01 unit), volume (Patella: $\beta=-21.85$, -37.77 to -5.93; LFTC: $\beta=-23.87$, -42.18 to -5.57 mm³/0.01 unit) and bone area (Patella: $\beta=-4.69$, -8.26 to -1.12; LFTC: $\beta=-4.76$, -9.47 to -0.06 mm²/0.01 unit). The change in WHR z-scores from childhood to adulthood was negatively associated with cartilage thickness (MFTC: $\beta=-0.056$, -0.109 to -0.003 mm), volume (patella: -83.10, -162.97 to -3.23; MFTC: -83.04, -158.07 to -8.00; LFTC: -100.55, -190.28 to -10.81 mm³) and bone area (patella: -21.35, -39.00 to -3.69; LFTC: -24.47, -47.36 to -1.58 mm²).

Conclusion: Childhood weight was negatively but adult weight was positively associated with adult bone area. Adult WHR and the change in WHR from childhood to adulthood were negatively associated with cartilage thickness, volume and bone area. These suggest early life adiposity measures may affect knee structures in young adults.

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Abstract Number: 913

Risk Factors for Knee Pain Exacerbation on Walking: A within-Person Knee-Matched Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health – ACR/ARHP

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Session Time: 2:30PM-4:00PM

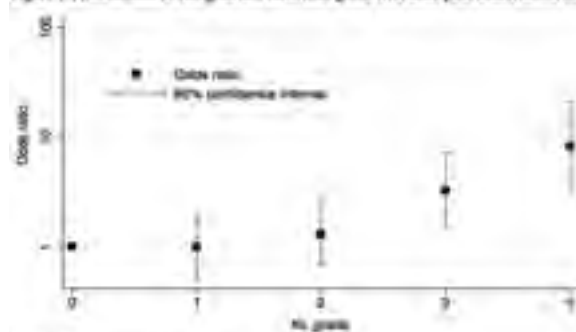
Background/Purpose: Pain exacerbation on walking is common among patients with knee osteoarthritis and often lead to activity avoidance. To date, few risk factors for pain flares have been identified, limiting the development of target prevention and treatment approach. We examined several knee-specific risk factors for this disabling pain experience.

Methods: Participants in the Osteoarthritis Initiative underwent a 20-meter walking test at the 24-month visit. We defined a knee as experiencing pain exacerbation on walking if its pain severity increased by ≥ 1 point from before participating to that during the walking test on a numeric rated scale (0-10). Among subjects who had unilateral knee pain exacerbation on walking, we conducted a within-person between-knee matched case-control study to examine the relation of recent knee injury (i.e., knee injury occurred in the past 12 months that was bad enough to limit the ability to walk for at least two days), Kellgren and Lawrence (KL) grade and isometric extensor muscle strength (IEMS) to unilateral knee pain exacerbation on walking using conditional logistic regression adjusting for each other. We consider a difference in IEMS $\geq 4\%$ as meaningful difference. We depicted the dose-response relationship between IEMS and the risk of knee pain exacerbation on walking using restrictive cubic spline curve.

Results: Among 277 people who experienced unilateral knee pain exacerbation during the walking test, 63.9% were women, mean age = 63.6 years, and the mean body mass index = 29.2 kg/m^2 . Recent knee injury was associated with pain exacerbation on walking with an odds ratio (OR) of 3.4 (95% confidence interval (CI): 1.3, 9.2). Compared with knees with KL=0, the ORs of pain exacerbation on walking were 1.3 (95% CI: 0.7, 2.7), 3.3 (95% CI: 1.5, 7.1), and 8.1 (95% CI: 3.1, 21.1) for knees with KL=2, 3 and 4, respectively. Knees that had 4% lower IEMS than their contralateral knees were at 1.4 (95% CI: 1.0-1.9) higher risk of pain exacerbation on walking.

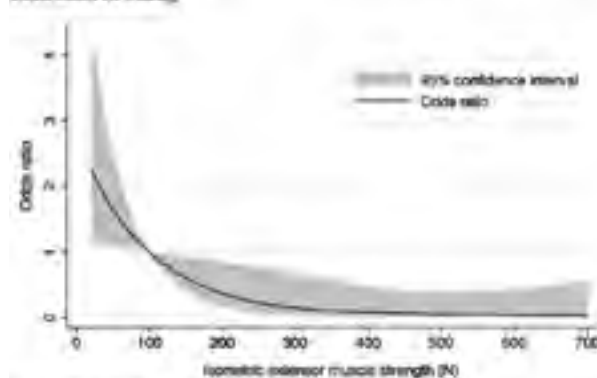
Conclusion: Recent knee injury, KL grade and IEMS were associated with knee pain exacerbation on walking. Our findings reinforce the vital role of pain management in the early stage of radiographic knee OA in preventing pain-related

Figure 1. Associations of Kellgren and Lawrence grade with knee pain exacerbation on walking*



* Adjusting for recent knee injury

Figure 2. Dose-response curve of isometric extensor muscle strength on the risk of knee pain exacerbation on walking*



* Adjusting for Kellgren and Lawrence grade and recent knee injury

disability and also suggest preventing injury and strengthening extensor muscle may reduce the risk of knee pain on walking.

Table 1 Difference in isometric extensor muscle strength (IEMS) within pairs of knees discordant for pain exacerbation on walking

IEMS difference between matched knees	No. matched sets	OR (95% CI) *	P value
IEMS lower $\geq 4\%$ in case knee	57	1.0 (reference)	0.045
IEMS lower $\geq 4\%$ in control knee	79	1.4 (1.0, 1.9)	
Absolute difference $< 4\%$	18	-	

OR = Odds ratio, CI = Confidence interval.

* Adjusting for recent knee injury and Kellgren and Lawrence grade.

Disclosure: Q. Liu, None; D. J. Hunter, None; M. Ferreira, None; B. L. Wise, None; K. Tao, None; Y. Zhang, None; J. Lin, None.

Abstract Number: 914

Increased Adverse Childhood Experiences in Children with Arthritis: An Analysis of the National Survey of Children's Health

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SESSION INFORMATION

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Session Title: Epidemiology and Public Health – ACR/ARHP

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Background/Purpose: Adverse Childhood Experiences (ACEs) are associated with increased risk of chronic disease and poorer health in children and adults. Emerging data suggest an association between exposure to ACEs and autoimmune diseases in adults, but the relationship between ACEs and childhood-onset rheumatologic diseases has not been examined. Our objective was to investigate the relationship between ACEs and arthritis, the most common manifestation of childhood-onset rheumatologic disease, and to examine the relationship between ACEs and health-related outcomes in children with arthritis.

Methods: We examined data from the 2016 National Survey of Children's Health (NSCH) to describe the distribution of ACEs among children with current arthritis compared to 1) children with other chronic acquired physical conditions (CAPC)* and 2) all other children. The NSCH is a survey of sampled households with children < 18 years conducted by the US Census Bureau. We performed bivariate and multivariable logistic regression to determine associations between arthritis and cumulative ACE scores, measured as a categorical variable (0 ACEs, 1 ACE, 2-3 ACEs, ≥ 4 ACEs). Chi-square tests and non-parametric tests for linear trends were used to assess associations between cumulative ACE scores and health-related outcomes.

Results: Among 138 children with current arthritis, 123 had complete ACE data and were included in the analysis. Sixty-five percent of children with arthritis were reported to have at least one ACE, while 40% ($p < 0.001$) of children without arthritis and 53% ($p < 0.001$) of children with other CAPC were exposed to ACEs. Children with a high exposure (≥ 4 ACEs) were more likely to have arthritis compared to those without ACE exposure, odds ratio (OR=5.4, 95% confidence interval (CI) (3.2, 9.2) ($p < 0.001$)). High ACE exposure compared to none was associated with higher likelihood of having arthritis versus having other CAPC, OR=3.4, 95% CI (2, 5.8) ($p < 0.001$). A graded relationship was observed between ACE scores and arthritis in logistic regression models for both children with CAPC and all children (Table 1). Among children with arthritis, children with high ACE exposure had the highest proportion of physical impairment (95%) and comorbid depression/anxiety (68%) with significant linear trends of increasing proportions of affected children for both outcomes across increasing ACE scores, ($p = 0.001$, $p < 0.001$)

Conclusion: A markedly high prevalence of ACEs is reported among youth with arthritis from a large national survey. Higher ACE scores were associated with increased odds of arthritis and among children with arthritis, increased proportions of mental illness and physical impairment. Future investigations should examine how adversity may play a role in arthritis development, disease severity, and physical and mental health outcomes.

Table 1: Odds Ratios (OR) for Arthritis by Adverse Childhood Experience (ACE) Exposure

Number of ACEs	Arthritis among all children** (N = 46,599)			Arthritis among children with CAPC** (N = 12,225)		
	OR	Confidence Interval	p value	OR	Confidence Interval	p value
0 ACEs	1	---	---	1	---	---
1	1.5	0.8 - 2.4	0.14	1.2	0.7 - 2	0.5
2-3	3.4	2.2 - 5.4	<0.001	2.4	1.5 - 3.8	<0.001
≥4	5.4	3.2 - 9.2	<0.001	3.4	2 - 5.8	<0.001

Adjusted models ^						
	OR ^	Confidence Interval	p value	OR ^	Confidence Interval	p value
0 ACEs	1	---	---	1	---	---
1	1.2	0.7 - 2	0.43	1	0.7 - 1.8	0.7
2-3	2.4	1.5 - 3.9	<0.001	2	1.3 - 3.2	0.003
≥4	3.5	2 - 6	<0.001	2.5	1.5 - 4.5	0.001

* Children with a history of arthritis, but no current arthritis, were censored from this analysis.

** CAPC = Chronic acquired physical conditions: allergies, asthma, arthritis, diabetes, and epilepsy.

*Children with a history of arthritis, but no current arthritis, were censored from this analysis.

^ Adjusted for age, sex, minority race/ethnicity, and poverty status.

Disclosure: T. Rubinstein, None; D. R. Bullock, None; K. Ardalán, None; W. B. Mowrey, None; N. Brown, None; R. E. K. Stein, None.

Abstract Number: 915

The Association between Structural and Symptomatic Progression in Knee Osteoarthritis

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SESSION INFORMATION

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Background/Purpose: The link between progression of structure and symptoms in knee osteoarthritis (OA) is not well understood. This uncertainty hinders the effort to develop therapies to treat OA symptoms because it is unclear how treating structure or halting structural progression might alleviate symptoms.

Methods: We used data from the Osteoarthritis Initiative (OAI), a multicenter, longitudinal, observational study of knee OA. We selected patients with baseline (BL) Kellgren-Lawrence (KL) grade 1 – 3 and knee pain. Medial minimum joint space width (JSW) was assessed with a fixed-flexion knee radiograph annually through year 4 and then at years 6 and 8. WOMAC pain was assessed annually. We censored subjects at the time of any reported TKR. We used latent class growth analysis (LCGA) to identify distinct subgroups of JSW progression and pain progression. We included random effects to allow for within-subject variability. We analyzed data from years 1 to 8. We used logistic regression to evaluate the association between JSW and pain trajectories identified in LCGA analysis.

Results: We used data from 1,909 OAI study participants. BL radiographic severity was KL1 in 16%, KL2 in 52%, and KL3 in 32%. The mean (SD) JSW was 4.0mm (1.3). LCGA identified 2 distinct JSW trajectories: most patients (89%) had stable JSW over 8 years of follow-up, while a subgroup of patients (11%) experienced rapid disease progression [Figure 1]. We found 4 distinct pain trajectories. Most patients (75%) had stable low pain. There were also distinct trajectories of decreasing (5%), increasing (10%) and high stable (11%) pain [Figure 2]. The probability of being a rapid JSW progressor in each pain trajectory was 14% (high), 14% (increasing), 16% (decreasing), and 9% (low). This translates to an increased odds of being in the JSW progressor group in the high stable pain (OR: 1.6; 95%CI: 1.0, 2.4); increasing pain (OR 1.5; 95%CI: 0.98, 2.4) and decreasing pain (OR: 1.9; 95%CI: 1.0, 3.4)) groups compared to low stable pain group.

Conclusion: We found distinct subgroups of both JSW and pain progression. While subjects in the low stable pain trajectory had a slightly decreased odds of JSW progression, we did not find differences in the risk of being a rapid JSW

Figure 1. JSW Progression: JSW over time with 95% confidence intervals by trajectory group.

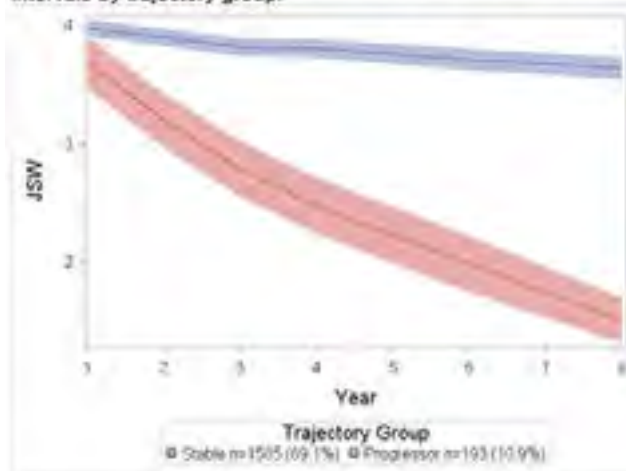
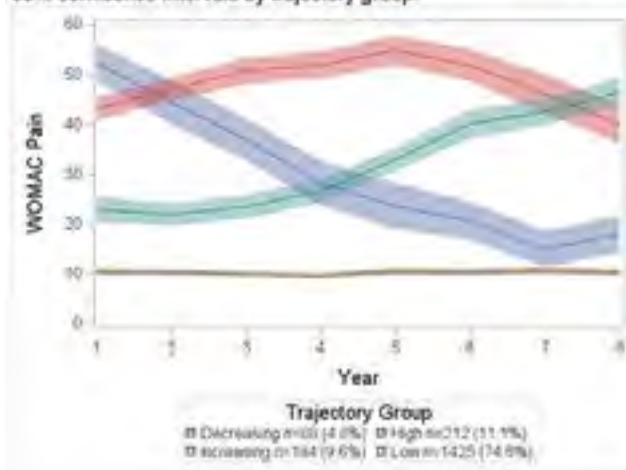


Figure 2. WOMAC Pain Progression. WOMAC Pain over time with 95% confidence intervals by trajectory group.



progressor between the increasing, decreasing, and high pain groups. Future work should consider whether additional joint features as visualized on MRI, such as cartilage, osteophytes, bone marrow lesions, and synovitis, may help to elucidate the link between structural and symptomatic progression.

Disclosure: J. E. Collins, None; S. Shrestha, None; E. Losina, Samumed, LLC, 5, Journal of Bone and Joint Surgery, 9.

Abstract Number: 916

Integrative Analysis of Multi-Omics Data in an Ethnically Diverse Lupus Cohort Identifies Distinct Molecular Subtypes of SLE

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Genetics, Genomics and Proteomics: Precision Medicine

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease with heterogeneous disease manifestations and outcomes. We aimed to define how molecular differences underlie this clinical heterogeneity through an integrative approach leveraging methylation, genetic, and phenotypic data from a well characterized multiethnic cohort of SLE patients.

Methods: 274 participants from diverse ethnic backgrounds were recruited as part of this study. 272 met 4 SLE ACR criteria, the rest had a diagnosis of lupus nephritis or met 3 ACR criteria and had a rheumatologist's diagnosis. In addition to clinical characterization, molecular measurements were collected on the individuals. DNA extracted from blood was analyzed on the illumina EPIC Beadchip. Single nucleotide polymorphism (SNP) genotype data was generated on the Affymetrix LAT1 World Array. First, we defined the phenotypic patient subgroups by clustering analysis - we performed principal component analysis on the ACR clinical criteria and used the top 2 eigenvectors as input for K-means clustering. We identified three stable clusters based on a stability score >0.8 determined by a bootstrap re-sampling method. Second, we applied a multivariate linear regression model adjusting for population stratification, cell composition, sex, smoking history, and age to identify differentially methylated CpGs across the phenotypic clusters. Lastly, we investigated whether the differentially methylated CpG were under genetic control in a methylation quantitative trait loci analyses (cis-meQTLs).

Results: We identified three stable clusters based on ACR criteria: cluster 1 was characterized by a higher proportion of participants of white ethnicity with malar rash, photosensitivity, serositis, arthritis, oral ulcers and fewer subserologies; cluster 2 was characterized by a higher proportion of lupus nephritis and anti-dsDNA antibodies; cluster 3 was characterized by higher proportion of hematologic manifestations, lupus nephritis, anti-dsDNA and anti-Sm antibodies. We identified 196 CpGs in 107 genomic regions that were differentially methylated between the clusters (FDR<0.05). Of these, pathway analysis revealed significant enrichment of genes relating to Type 1 interferon signaling and IFN-gamma (adjusted $p < 1E-08$). Overall, Interferon-alpha responsive genes were hypomethylated in cluster 3, hypermethylated in cluster 1, with cluster 2 presenting an intermediate signature. We then investigated whether the differentially methylated CpG were under genetic control in a *cis*-meQTLs analysis, which identified 542 *cis*-meQTL pairs (FDR<0.01) with 97 CpGs under proximal genetic control, which were enriched for IFN-alpha and IFN-gamma responsive genes (hypergeometric $p < 0.01$).

Conclusion: Overall, we identified three clinically relevant clusters of patients in our multiethnic SLE cohort. The three clusters could be differentiated by 196 CpGs of which 97 were under genetic control and enriched for IFN-gamma and IFN-alpha responsive genes. In this work, we were successful in applying integrative computational methods to elucidate the epigenetic and genetic mechanism behind the role of Type 1 interferon in SLE pathology.

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Abstract Number: 917

Type 1 Interferon Levels Correlates with Age of Diagnosis and Ethnicity in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Genetics, Genomics and Proteomics: Precision Medicine

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Low cost, patient-administered, "from home" genomic tests for monitoring disease activity and therapy response could revolutionize treatment and management of Systemic Lupus Erythematosus (SLE) patients by minimizing the use of ineffective therapies and detecting changes in disease activity before a flare occurs. Here we demonstrate the ability to test gene expression levels associated with Type 1 Interferon (IFN), plasmablast, T-cell

exhaustion and other SLE disease pathways using a multi-module gene expression assay in a large “from home” cohort of self-reported SLE and MS patients.

Methods: 1,278 patients with SLE or multiple sclerosis (MS) were recruited under an IRB-approved, Direct-to-Patient observational study in which participants provided self-collected blood samples. The study included 832 SLE patients, 446 MS patients, 269 demographic normal donors and 189 participants with known common medical conditions. SLE patients provided longitudinal samples resulting in the 2,129 samples for SLE. Testing was performed using a 47-gene, multi-module gene expression assay based on chemical ligation dependent probe amplification (CLPA) which enables direct from stabilized blood testing with no RNA isolation steps.

Results: 13.8% of the normal patients were found to be IFN high while SLE patients were 36.8% IFN High and MS patients were 20% IFN High. The difference in IFN activity between SLE and MS was statistically significant ($p < 0.001$). In the 17 common disease sub-cohort, immunocompromised patients ($n=28$, 32.1%), heart disease ($n=11$, 27.3%) and participants with influenza ($n=12$, 91.7%) displayed above normal IFN levels.

High IFN was associated with ethnicity and age at time of diagnosis in the SLE cohort. Caucasian samples ($n=1,721$) were IFN high 31% of the time, while African American ($n=204$, High IFN 68.1%) and Asian patients ($n=32$, High IFN 90.6%) showed a higher prevalence. IFN activity in SLE participants correlated with age of diagnosis with samples from participants diagnosed under 18 being IFN high 70.4% ($n=115$), 18 to 30 IFN high 45.4% ($n=610$), and over 30 ($n=942$) IFN high 27.3%.

Conclusion: A significant percentage of SLE and MS patients display elevated IFN levels, especially in younger SLE patients, as well as African Americans and Asians. Testing for IFN activity in suspected autoimmune disease patients may improve SLE diagnosis resulting in improved patient care and a reduced cost to the healthcare system.

Sample Set	Sample Count	IFN High Count	IFN Low Count	% IFN High	% IFN Low
Normal	269	11	258	13.8	86.2
SLE	2129	643	1486	36.8	63.2
MS	446	55	391	20.0	80.0
Confounders All	189	25	164	20.1	79.9
Influenza	12	11	1	91.7	8.3
Immunocompromised	28	9	19	32.1	67.9
High BMI	18	0	18	0	100
Heart Disease	11	3	8	27.3	72.7
Allergy	7	1	6	14.3	85.7
Asthma	8	2	6	25	75

Disclosure: M. Abedi, DxTerity, 3; L. Borisov, DxTerity, 1, 3; A. Doyle, DxTerity, 3; F. Flores, DxTerity, 3; J. Fujimoto, DxTerity, 1, 3; A. Jacobs, DxTerity, 3; P. Naranatt, DxTerity, 3; L. Pan, DxTerity, 3; W. Ricketts, DxTerity, 3; J. Spangler, DxTerity, 3; K. Warren, DxTerity, 1, 3; R. Terbrugge, DxTerity, 1, 3, 4.

Abstract Number: 918

A Novel Familial RELA Truncation Is Associated with Behcet's-like Mucocutaneous Ulceration Syndrome

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SESSION INFORMATION

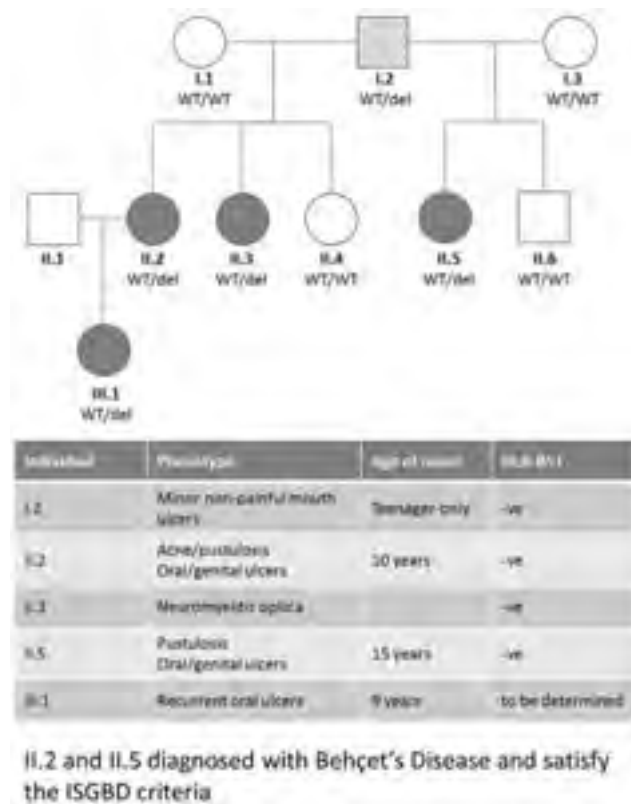
Session Date: Sunday, October 21, 2018

Session Title: Genetics, Genomics and Proteomics: Precision Medicine

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Session Time: 4:30PM-6:00PM

Background/Purpose: Behcet's disease (BD) is a heterogeneous multifactorial auto-inflammatory condition characterized by recurrent episodes of oral and genital ulceration, uveitis and skin lesions, with less frequent involvement of the gastrointestinal tract, large blood vessels and central nervous system. The NF- κ B pathway is a 'master-regulator' of immune and inflammatory signaling, with the ability to control the expression of key inflammatory genes and genes associated with apoptosis and proliferation.



Methods: This study involved a 3-generation family with Behcet's-like mucocutaneous ulceration syndrome; primarily involving childhood-onset chronic oral and genital ulcers (figure 1). ISGBD criteria were used to diagnose Behcet's Disease (BD). DNA was isolated from PBMCs from affected patients and non-affected familial controls. DNA sequencing identified a cysteine deletion at position 1459 in *RELA* which segregated with the condition. Immunoblot analysis of *RELA* confirmed protein truncation. PBMCs were stimulated with TNF and NFκB phosphorylation was measured relative to unstimulated controls.

Results: A heterozygous cysteine deletion at position 1459 in *RELA* was detected in affected individuals. This mutation is coding, inducing a frameshift His487ThrfsTer7, predicted to produce a truncated protein of 492 amino acids which would result in a ~6kDa smaller protein. This truncation was confirmed by immunoblot, with the affected individuals producing two bands: the wild-type and truncated protein whereas unaffected controls produced only the wildtype protein. Preliminary data indicates RelAHis487ThrfsTer7 heterozygotes have different kinetics in response to TNF, as measured by phosphorylation of *RELA*.

Conclusion: This study gives novel information on both the genetic basis and biological mechanisms of BD in individual families. Familial mutations that induce haploinsufficiency of *RELA* have recently been associated with BD. However, the His487ThrfsTer7 results in protein truncation rather than haploinsufficiency. Crucially, the His487ThrfsTer7 mutation interrupts the two C-terminal *RELA* transactivating domains. Our study supports several recently published studies that loss-of-function mutations in the NF-κB pathway are linked with the development of familial early-onset BD-like syndromes. Understanding both the genetic basis and biological mechanisms facilitates personalized medicines approaches that target the primary disease mediators, which result in earlier disease control and reduced tissue damage.

Disclosure: E. Dorris, None; E. Adeeb, None; E. Cummins, None; S. Savic, None; S. Fraser, None; A. G. Wilson, None.

Abstract Number: 919

A Machine Learning Classifier for Assigning Individual Patients with Systemic Sclerosis to Intrinsic Molecular Subsets

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SESSION INFORMATION

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Background/Purpose: High-throughput gene expression profiling of skin biopsies from patients with systemic sclerosis (SSc) has identified four “intrinsic” gene expression subsets conserved across multiple cohorts and tissues. These are the inflammatory, fibro proliferative, normal-like, and limited subsets. In order to classify patients in clinical trials or for diagnostic purposes, supervised methods that can assign a single sample to a molecular subset are required. Here, we introduce a novel machine learning classifier which is a robust predictor of intrinsic subset and test it on multiple independent patient cohorts.

Methods: Three independent gene expression cohorts were curated and merged to create a training dataset covering 297 skin biopsies from 102 SSc patients and controls to train a classifier. Supervised machine learning algorithms were rigorously trained and evaluated using repeated three-fold cross-validation. We performed external validation using three SSc cohorts (GSE66321, GSE65405, GSE58095), including a gene expression dataset generated by an independent laboratory on a different microarray platform. In total, 427 skin biopsies from 213 individuals were analyzed in the training and test cohorts. We used weighted gene co-expression network analysis and g: Profiler to identify and functionally characterize gene modules associated with the intrinsic subsets.

Results: Repeated cross-fold validation identified consistent and discriminative gene expression biomarkers using multinomial elastic net, which performed with an average classification accuracy of 88.1%. All molecular subsets were classified with high sensitivity and specificity (Fig. 1A). In external validation, the classifier achieves an average accuracy of 85.4% (Fig.1B). In a re-analysis of gene expression data from GSE58095, the classifier identified subsets of patients that represent the canonical inflammatory, fibroproliferative, and normal-like subsets (Fig. 1C). The inflammatory subset showed upregulated gene modules significantly enriched in biological processes such as inflammatory response, lymphocyte activation, and stress response. Similarly, gene modules enriched for cell cycle processes were increased in the fibroproliferative subset.

Conclusion: We developed a highly accurate and reliable classifier for SSc molecular subsets for single samples analyzed on multiple gene expression platforms. Prior methods relied on agglomerative methods that could not be applied to single samples. These analyses show that the intrinsic gene expression subsets are a common feature of SSc found across multiple

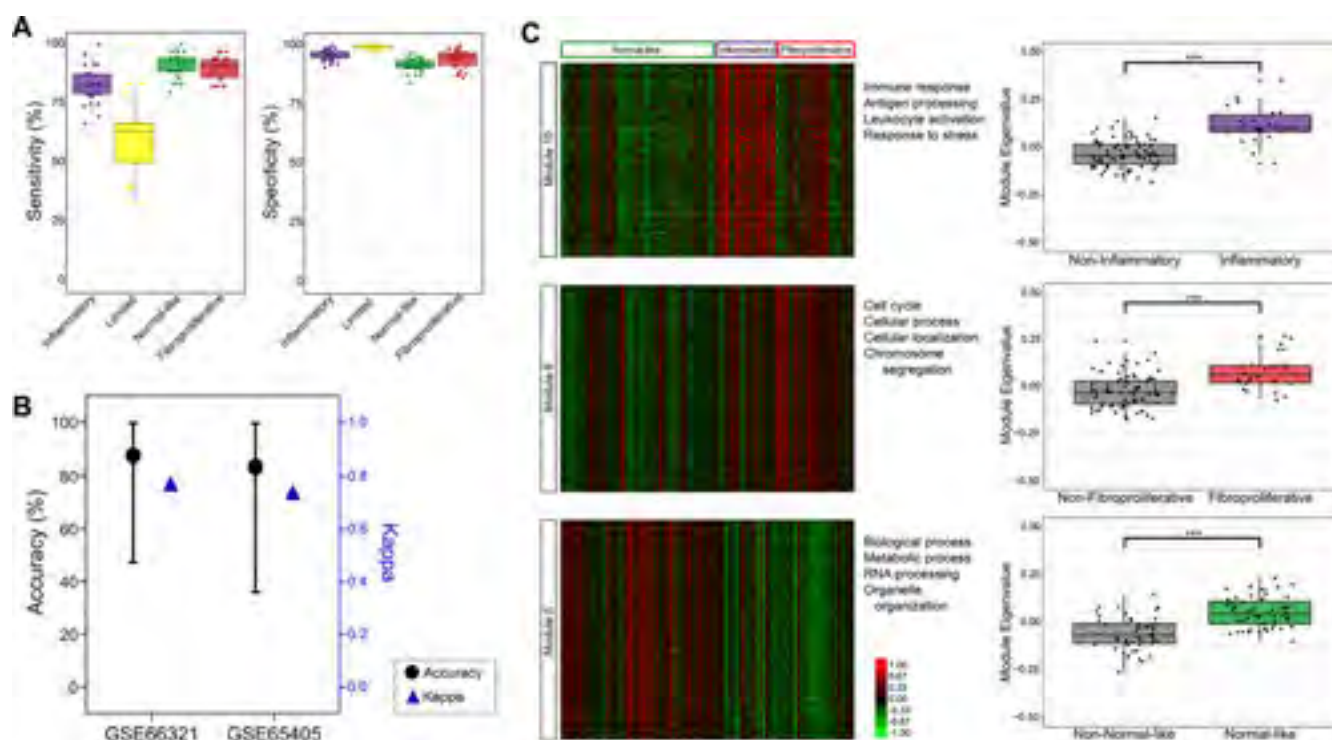


Figure 1: (A) Sensitivity and specificity for all four intrinsic SSc subsets are plotted from repeated cross-fold validation for the final model, (B) in external validations, accuracy of intrinsic subset assignment is plotted in black and Cohen's Kappa in blue. (C) Expression values are shown for gene annotated to modules 10, 6, and 5. The module eigenvalues were further compared for the inflammatory samples vs all others, fibroproliferative samples vs all others, and normal-like samples vs all others using Wilcoxon Rank Sum Test (***) $p < 0.0005$.

validation cohorts. Machine learning methods provide a robust and accurate mechanism for stratifying intrinsic gene expression subsets and can be used to aid clinical decision-making and interpretation for SSc patients and in clinical trials.

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Abstract Number: 920

Rheumatoid Arthritis Patient-Specific Therapeutic Target Identification Using Integrative Epigenetic Profiling

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Genetics, Genomics and Proteomics: Precision Medicine

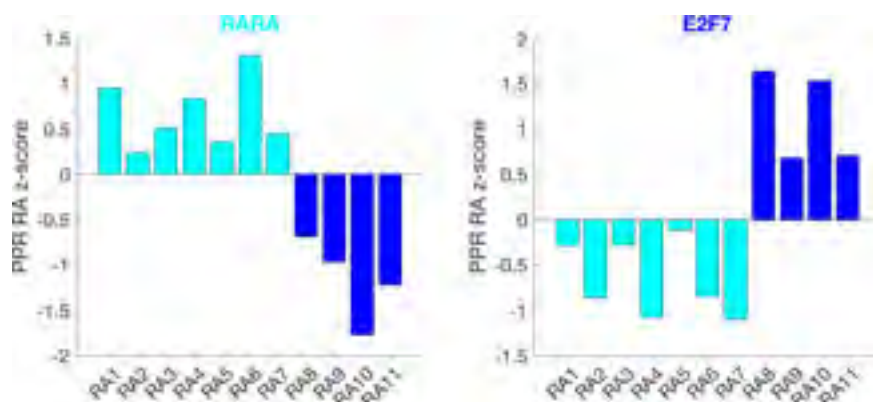
Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: To explain the complex regulatory changes associated with RA synovitis and the diversity of responses to targeted therapies, we developed and applied a novel integrative epigenetic profiling method. This method, known as Taiji, focuses on differences between patients with RA in addition to the traditional RA vs. non-RA methodology. Using Taiji, we identified transcription factors (TFs) central to regulatory patterns in fibroblast-like synoviocytes (FLS) that vary between RA patients that could contribute to variable responses to targeted therapies.

Methods: Whole genome ATAC-seq data from 11 RA and 11 osteoarthritis [OA] FLS lines) were evaluated for overlaps between ATAC-seq peaks and known gene promoter regions (4Kb upstream and 1kb downstream from the TSS). Peaks not assigned to promoters were linked with the nearest gene. 745 TFs, with binding motifs curated from the CIS-BP database, had binding sites within 150-bp of ATAC-seq peaks. 22 network topologies were constructed by forming directed edges between any parent node TF and child node gene or child node TF. Via the integration of our whole genome RNA-seq expression data, edge weights were assigned according to the pooled ATAC-seq peak intensity and the expression of the TF parent node. For each sample, the Personalized Page Rank (PPR) algorithm was run to measure the global influence of each node and variability between RA patients.

Results: Analysis focused on differences between RA patients. We first clustered the patient using the log₂ transcripts per million expression for all genes resulting in two clusters of 7 and 4 RA patients. The mean PPR z-score was calculated for all TFs from each cluster of patients and the absolute difference between the two clusters (DPPR) was calculated. Analysis of the PPR z-score of TF regulatees was conducted to gain statistical power. Ranking TFs by DPPR, the top 200 were intersected with the 310 TFs that have significantly different regulatee PPR z-score values ($p < 0.003$) yielding 80 RA patient-specific TFs that distinguished patients from each other (see Figure showing inter-patient differences in the clusters). High DPPR TFs identified in the two RA clusters included the retinoic acid receptor alpha (RARA) and E2F7 ($p = 0.003$ and $p = 0.010$). RARs play a role in the immuno modulation of synovial inflammation in RA. The E2F TF family member E2F7, plays a role in angiogenesis.



Conclusion: Our novel epigenetic profiling approach defines patient-specific TFs that could contribute to RA patient-to-patient differences. This unique computational approach helps elucidate the mechanism of differential responses to highly targeted agents in RA. Key transcription factors, including genes such as RARA and E2F7, emerge as potential patient-specific TF targets from this *in silico* method to individualize treatment.

Disclosure: R. Ainsworth, None; K. Zhang, None; L. Zheng, None; G. S. Firestein, None; W. Wang, None.

Abstract Number: 921

Multi-Omics Analysis Identifies a Gene Signature Associated with the Clinical Response to Anti-TNF Therapy in Rheumatoid Arthritis

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SESSION INFORMATION

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Session Title: Genetics, Genomics and Proteomics: Precision Medicine

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Rheumatoid arthritis (RA) is the most common inflammatory arthritis affecting up to 1% of the population. Tumor Necrosis Factor (TNF) inhibitors have significantly improved the management of many RA patients. However, ~30% of anti-TNF treated patients do not show a significant clinical improvement. To date, little is known on the biological mechanisms that underlie the differential response to anti-TNF agents. The objective of this study was to identify genetic variation associated with the clinical response to anti-TNF therapy in RA using a sequential multi-omics approach.

Methods: We performed a genome-wide multi-omics analysis integrating multiple sources of molecular information. First, we aimed to identify the gene expression modules associated with anti-TNF response. For this objective, we extracted the RNA from synovial biopsies of 11 RA patients starting anti-TNF therapy and determined the gene expression profiles using Illumina microarrays. Modules of coexpressed genes were subsequently identified using the WGCNA approach. The association between the synovial gene coexpression modules and anti-TNF response was then performed using the first principal component of variation from each module. Clinical response was determined at week 14 using the EULAR criteria. To analyze the association between the transcriptomic modules and the anti-TNF response at the genetic level, we used a cohort of 348 anti-TNF treated RA patients from Spain recruited by the *IMID Consortium*. The statistical association analysis was performed using genome-wide data from the Spain cohort ($N=1,387,382$ SNPs) and the set-based test implemented in PLINK. The gene modules that were significantly associated with the anti-TNF response were subsequently tested for validation in an independent GWAS cohort of 2,706 anti-TNF treated RA patients available from the Synapse public repository. The functional implication of the validated modules was evaluated via pathway and cell type epigenetic enrichment analyses.

Results: The genome-wide coexpression analysis in RA synovial biopsies identified a total of 148 gene coexpression modules. From these, 15 transcriptomic modules were found to be associated with the clinical response to anti-TNF therapy ($P<0.05$). At the genetic level, we detected two of the 15 gene modules to be significantly associated with the response to adalimumab ($P=0.015$) and infliximab ($P=0.021$) in the Spain cohort. Using the independent cohort of RA patients, we replicated the association of the gene coexpression module associated with the response to adalimumab

($P=0.0019$). The validated module was found to be significantly enriched in genes that are involved in the metabolism of nucleotides ($P=2.41e-05$). The epigenetic analysis revealed a significant enrichment of the adalimumab-associated variants in key epigenetic marks from different immune cell types including Tregs ($P=0.04$).

Conclusion: These findings show the existence of a genetic basis for the clinical response to anti-TNF therapy. Our results also suggest that the genetic variation affecting clinical response is treatment-specific and, therefore, biomarker development in RA should take into account this diversity at the molecular level.

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Abstract Number: 922

Anakinra Treatment Prevents Myocardial Mechanical Dysfunction and Inhibits Histologic Evidence of Myocardial Inflammation in the Mouse Model of Kawasaki Disease

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SESSION INFORMATION

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Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Kawasaki disease (KD) is an acute, febrile illness of childhood with sequelae of coronary artery aneurysms and cardiac fibrosis, and is the most common cause of acquired heart disease among children in the developed world. Acutely, a subset of patients with KD will demonstrate echocardiographic evidence of impaired myocardial function, as well as increased left ventricular mass presumed to be due to myocardial edema and inflammation. Further, some patients will develop profound cardiac dysfunction known as Kawasaki Shock Syndrome. Here, we investigated whether inhibition of interleukin-1 activity via anakinra would correct development of the myocardial mechanical dysfunction and myocardial inflammation seen in KD.

Methods: KD was induced via the established model of lactobacillus casei cell wall extract (LCWE) injection in 4-6 week old male mice. For echocardiography and MRI, groups of mice either injected with LCWE alone, LCWE and anakinra, or normal controls were compared. Myocardial inflammation was scored by a blinded pathologist.

Results: Both imaging modalities demonstrated normalized left ventricular function in anakinra treated KD mice via measurements of ejection fraction, fractional shortening (echo) and end diastolic and systolic volumes (MRI). These were significantly ($p<0.05$) normalized as compared to untreated diseased KD mice. Additionally, while KD mice demonstrated increased left ventricular mass index, this was markedly attenuated ($p<0.01$) in anakinra treated mice. Myocardial inflammation scores were significantly ($p<0.05$) lower in anakinra treated vs. untreated mice.

Conclusion: Anti-interleukin-1 therapy in the mouse model of KD prevents the development of myocardial mechanical dysfunction and left ventricular mass enlargement as well as myocardial inflammatory changes. This demonstrates functional efficacy of this therapy in the treatment of children with KD, and also raises the clinical implication of anakinra treatment in patients with severe cardiac dysfunction of Kawasaki Shock Syndrome. Additionally, the demonstration of these findings in the mouse model of KD greatly bolsters the applicability of this model for human KD.

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Neutrophils from Children with Systemic JIA Exhibit Persistent Proinflammatory Activation Despite Long-Standing Clinically Inactive Disease

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Background/Purpose: Systemic juvenile idiopathic arthritis (SJIA) is a chronic childhood arthropathy with features of autoinflammation. New-onset SJIA is associated with expansion and activation of neutrophils with a sepsis-like phenotype, but neutrophil phenotypes in longstanding and clinically inactive disease (CID) is unknown. The objective of this study was to examine activated neutrophil subsets, S100 alarmin release, and gene expression signatures in children with a spectrum of SJIA disease activity.

Methods: This protocol was approved by the Institutional Review Board, and informed consent was obtained from all patients and/or their legal guardians. Highly-purified neutrophils were isolated using a two-step procedure of density-gradient centrifugation followed by magnetic-bead based negative selection using the MACSexpress kit. Neutrophils were then stained for imaging flow cytometry, or RNA isolated using MagMax Total RNA Isolation Kit. Alternatively, neutrophils were cultured for 4hr with or without PMA to quantify S100 protein release. Gene expression analysis was performed with the Ampliseq Transcriptome kit using the Ion Torrent platform.

Results: Patients with SJIA and active systemic features demonstrated a higher number of the immunosuppressive subset CD16⁺CD62L^{lo} neutrophils compared to controls. This neutrophil subset was not seen in patients with inactive disease or those with active arthritis only without systemic features. Using imaging flow cytometry, CD16⁺CD62L^{lo} neutrophils from patients with active SJIA had mildly increased nuclear hypersegmentation compared to CD16⁺CD62L⁺ neutrophils. Serum levels of S100A8/A9 and S100A12 were strongly correlated with peripheral blood neutrophil count (R=0.53 and R=0.64, respectively; p<0.001). Neutrophils from active SJIA patients cultured *in vitro* did not show enhanced resting S100 protein release compared to inactive disease or control neutrophils. However, regardless of disease activity, neutrophils from SJIA patients did show enhanced S100A8/A9 release upon PMA stimulation compared to control neutrophils (P<0.05). Whole transcriptome analysis of highly purified neutrophils from children with active SJIA identified 214 differentially expressed genes compared to control neutrophils (fold change >2.0, p<0.05). The most significantly upregulated gene pathway was Immune System Process (adjusted p=3.4x10⁻¹⁶) including *AIM2*, *IL18RAP*, *NLRC4*, *TLR2*, *TLR5*, and *TNFAIP3*. Interestingly, this gene set showed intermediate levels of expression in neutrophils from patients with long-standing inactive disease but persistent serum IL-18 elevation. Indeed, all patient samples regardless of disease activity demonstrated elevated inflammatory gene expression, including inflammasome components and *S100A8*.

Conclusion: We identify features of neutrophil activation in SJIA, including a proinflammatory gene expression signature in patients with longstanding CID but elevated serum IL-18, reflecting persistent innate immune activation. Taken together, these studies expand understanding of neutrophil function in chronic autoinflammatory disorders such as SJIA.

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10X Genomics-Based Single-Cell RNA-Seq and Low Input RNA-Seq Identify a Transcriptional Landscape Supporting Interferon in the Pathogenesis of Autoimmune-Associated Congenital Heart Block

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – Basic Science

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Towards understanding the molecular mechanisms that link maternal anti-Ro antibodies to the development of conduction system disease in a second trimester fetus, single cell (scRNA-seq) and bulk RNA-seq were applied to a fetal heart dying with complete congenital heart block (CHB) and a gestational age-matched healthy heart from an elective termination.

Methods: The CHB heart was obtained from a 20-week fetus identified to have complete block at 19 weeks. The mother (35 y/o Asian with SS on no hydroxychloroquine) declined dexamethasone or IVIG and elected to terminate, thus no exposure to maternal medications confounded interpretation of findings. Both hearts were obtained under identical conditions. Freshly collected single-cell suspensions were generated using a Langendorff preparation with cannulation and perfusion of the aorta with collagenase and trypsin enzymes. Two approaches were taken to mine the transcriptome in the resulting cell suspensions: agnostic evaluation applying 10X Genomics platform-based scRNA-seq and low input RNA-seq of flow sorted cells upon leukocytes (DAPI negative, CD45+) and fibroblasts (DAPI negative, CD45-, podoplanin-positive).

Results: For scRNA-seq, we obtained 2,693 and 5,408 high-quality scRNA-seq profiles from the control and CHB hearts, respectively. We applied a graph-based clustering method and identified 13 and 14 major clusters of cells from the control and CHB hearts, respectively, as visualized by *t-distributed stochastic neighbor embedding* (*t-SNE*). Differential gene expression analysis guided by established lineage markers revealed four cardiomyocyte clusters (CM1-CM4), three fibroblast clusters (FB1-FB3), endothelial cells (EC), erythroblasts (EB), macrophages (MAC), dendritic cells (DC), T cells (TC) and B cells (BC). Ranked by abundance, the control heart exhibited CM>FB>EC>MAC>DC>EB, BC, TC; the CHB heart exhibited CM>FB>EC, MAC>TC, BC, EB. The CHB heart also contained natural killer cells (NK) and mast cells (MC, lowest abundance). Given the high abundance of MACs among the immune cells (control:108;CHB:606) and the consistent identification of MACs on histologic analysis of CHB hearts, differential expression analysis demonstrated overexpression of interferon-induced genes (4-fold or greater, i.e. $\log_2(\text{CHB-control}) > 2$) in CHB MACs. In CHB, most cell types expressed high levels of ISG1, IFITM1 and IFITM3, whereas in the control only IFITM3 showed widespread expression. For SIGLEC1, expression was restricted to MACs and was expressed by 18% of CHB MACs and only 6% of control MACs. While the transcriptome using low input RNA-seq of anti-CD45 flow-sorted CHB leukocytes did not allow granular analysis of leukocyte subpopulations, expression of SIGLEC1 and interferon-related genes were increased in CHB versus control. Applying 10X Genomics, proliferating fibroblasts expressed MKI67 and TOP2A in CHB but not control fibroblasts.

Conclusion: This unprecedented opportunity to obtain CHB tissue absent any exposure to maternal medications support scRNA-seq's utility to survey landscape and heterogeneity not possible with low input RNA-seq of flow-sorted cells. IFN- and SIGLEC1-positive macrophages may contribute to fibrosis.

Disclosure: H. Suryawanshi, None; J. P. Buyon, Exagen, 2; M. Chang, None; T. Tuschl, None; R. M. Clancy, None.

Abortive Viral Infection Becomes Macrophage Activation Syndrome in Mice with Chronically Elevated Interleukin-18: Evidence for Synergy with Cytotoxic Impairment

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SESSION INFORMATION

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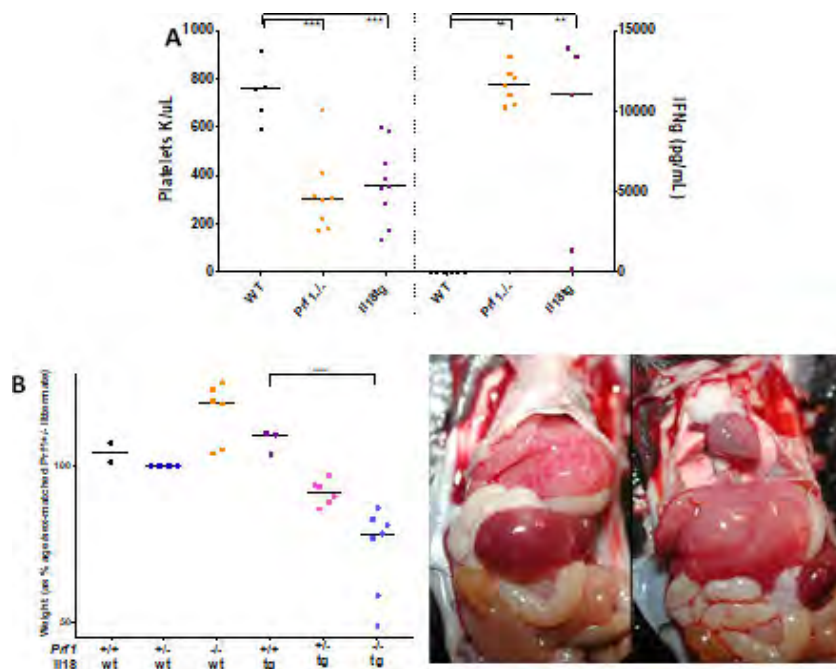
Session Type: ACR Concurrent Abstract Session

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Background/Purpose: Macrophage Activation Syndrome (MAS) and Hemophagocytic lympho histiocytosis (HLH) are clinically similar life-threatening hyperinflammatory syndromes, often triggered by viral infection. HLH is associated with cytotoxic impairment (e.g. Perforin deficiency). The causes of MAS remain unknown, but both cytotoxic impairment and elevated Interleukin (IL)-18 may contribute.

Methods: Mice were infected with the typically self-limiting LCMV-Armstrong virus, and assessed for systemic inflammation, serum cytokines, antigen-specific responses, and viral clearance.

Results: Whereas LCMV-infected WT mice developed no outward inflammation, Il18tg mice developed features of MAS (weight loss, splenomegaly, cytopenias, transaminitis, cytokinemia) nearly as severe as *Prf1*^{-/-} (Fig 1A). Unlike *Prf1*^{-/-}, Il18tg mice had no appreciable impairment in viral clearance and showed normal upregulation of cytotoxic proteins. Consistent with their systemic hyperinflammatory phenotype, Il18tg mice had a larger effector CD8 T-cells response than WT. Unexpectedly, mice with both hyperinflammatory susceptibility factors (*Prf1*^{-/-};Il18tg mice) were born in Mendelian ratios but quickly developed a spontaneous inflammatory phenotype characterized by weight loss, cytopenias, cytokinemia and hepato splenomegaly (Fig 1B). *Prf1*^{-/-};Il18tg mice have a concomitant increase in splenic myeloid and activated CD-8 T cells, all consistent with a spontaneous MAS-like phenotype.



Conclusion: Chronic IL-18 promotes systemic hyperinflammation despite apparently normal viral clearance during LCMV infection, consistent with MAS. Spontaneous MAS in *Prf1*^{-/-}; Il18tg demonstrates the complementary and non-redundant nature of these mechanisms. It also indicates a homeostatic immunoregulatory function for Perforin. Our data suggest clinical assessment of both pathways could improve targeted treatment in these life-threatening hyperinflammatory disorders.

Disclosure: P. Tsoukas, None; C. Schneider, None; L. Van Der Kraak, None; S. Canna, AB2 Bio, Ltd, 5.

Truncating Mutations in SAMD9L Cause an Early-Onset Immune-Dysregulatory Syndrome of Neutrophilic Panniculitis, Interstitial Lung Disease and Cytopenias

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Session Time: 4:30PM-6:00PM

Background/Purpose: The Sterile Alpha Motif Domain Containing 9 Like protein that is encoded by *SAMD9L* plays a role in endosome fusion, and deletions (haploinsufficiency) of *SAMD9L* including loss of the chromosome 7 where *SAMD9L* is located (monosomy 7) have been associated with myelodysplasia in humans and mice. Recently missense mutations in *SAMD9L* were described in patients presenting with ataxia-pancytopenia syndrome. Here we describe 6 patients with *de novo* frameshift mutations in *SAMD9L* who present with early-onset systemic inflammation, variable interstitial lung disease and cytopenias.

Methods: Whole exome/genome sequencing (WES/WGS) on trios using Illumina HiSeq 2000 platform were performed. An interferon-response-gene score was assessed using a customized Nanostring assay. Toll-like receptor (TLR) stimulation assays, STAT phosphorylation assay and immunofluorescence staining were performed in patients and healthy controls (HCs), PBMCs, monocytes and T cells, and fibroblasts, respectively.

Results: We identified 6 patients with 4 *de novo* frameshift variants in *SAMD9L*. All 6 patients had disease onset between 1 and 7 days of life with generalized nodular skin rashes, fever and increased inflammatory markers (ESR and CRP). Skin biopsies from all 6 patients revealed a neutrophilic panniculitis. Four patients (67%) had developed severe interstitial lung disease (ILD) in infancy, all 4 developed pancytopenia, low B-cell count and hypogammaglobulinemia, and two of those underwent bone marrow transplant. The other 2 patients developed leukopenia, a low B cell count, hypogammaglobulinemia and recurrent pulmonary infiltrates at the age of 3 and 5 years, respectively. Additionally, brain imaging revealed basal ganglia calcifications and/or demyelinating changes in 4 out of the 6 patients. Tertiary structure modelling of *SAMD9L* protein predicted that the 4 variants lie in the p-loop containing the hydrolase domain (amino acids 692-946) of the molecule. qRT-PCR of healthy control cell subsets and tissues showed that *SAMD9L* mRNA relative expression is high in B and NK lymphocytes, moderate in T cells, monocytes, neutrophils, lung and muscle, and low in skin, liver, heart and kidney tissues. Analysis of each individual gene expression level by nanostring in comparison with healthy controls demonstrated significantly higher levels of the following IRGs: *DDX60*, *EPSTI1*, *GBP1*, *IFI6*, *ISG15*, *LY6E*, *OAS1*, *OAS2*, *OAS3*, *RSAD2*, *RTP4* and *SOC1*. Stimulation of PBMCs with the TLR ligands poly I:C, ODN, and LPS induced a 200-fold increase in *IFI27* and a 30-fold increase in *IFNA1* and *IFNB1* transcription compared to baseline. IF staining of patient fibroblasts showed a 1.5-fold increase in EEA1 early endosome formation and a 2.5-fold decrease in RAB5 late endosome formation compared to healthy fibroblasts. Patient had constitutive upregulation of STAT1 and STAT6 in monocytes and of STAT1 and STAT3 in T cells.

Conclusion: We describe a novel immunedysregulatory disease caused by *de novo* truncating variants in *SAMD9L* that presents similar to CANDLE with neutrophilic panniculitis and points to an important role of *SAMD9L* on regulation of adaptive and innate immune responses.

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Abstract Number: 927

The Reprogramming of Regulatory T Cells to a Th17 Phenotype in Systemic Juvenile Idiopathic Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – Basic Science

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Systemic juvenile idiopathic arthritis (sJIA) is characterized by fever and rash at disease onset, which are mediated in part by IL-1 β and IL-6. In 40-50% of patients, the disease resolves while in others a chronic inflammatory arthritis develops. The mechanisms that drive the establishment of chronic arthritis are unknown. IL-1 β and IL-6 promote Th17 differentiation and impair regulatory T (Treg) cell function. We aimed to characterize Treg cells in sJIA to determine if these inflammatory cytokines polarize Treg cells to a Th17 fate, potentially contributing to the development of arthritis in this disease.

Methods: Peripheral blood (PB) and/or synovial fluid (SF) samples were collected from acute sJIA (disease duration < 4 months), chronic sJIA (disease duration > 4 months with persistent arthritis), and control subjects. For flow cytometry, PBMCs were stimulated, stained for cell surface markers, fixed, and permeabilized for intracellular staining. For mass cytometry, PBMC/SFMCs were stained for cell surface markers, barcoded, fixed, permeabilized, and then samples were randomized to 1 of 2 mass cytometry runs. RNA was extracted from sorted PB and SF Treg (CD4⁺CD25⁺CD127^{lo}) and effector T (CD4⁺CD25⁻) cells. The Smart-Seq2 platform was used for RNA sequencing. Data analysis was done with GraphPad Prism, FlowJo, Cytobank, and Gene Set Enrichment Analysis.

Results: 10 acute sJIA, 15 chronic sJIA, 5 pediatric control, and 5 adult control subjects were studied. viSNE plots of mass cytometry of SF samples from sJIA patients showed a distinct population of activated Treg cells in the arthritic joints that expressed high levels of CD45RO, HLADR, PD1, Ki67, ICOS, and CD39. A similar population of Treg was also identified in PB of acute and chronic sJIA patients but not adult or pediatric controls. By flow cytometry, acute sJIA patients had a significantly higher frequency of Helios^{hi} Treg cells (78.8 \pm SD 8.4%) than chronic sJIA patients (62.3 \pm 12.3%) and pediatric controls (57.5 \pm 10.6%) (p=0.004). In addition, the percentage of Treg cells from acute sJIA patients expressing IL-17 (5.8 \pm SD 3.2%) was significantly higher than chronic sJIA patients (1.2 \pm 1.1%), pediatric controls (0.45 \pm 0.3%), and adult controls (1.4 \pm 1.0%) (p<0.0001). There was a trend towards increased IL-17⁺ and CCR6⁺ CD4⁺ memory T cells in chronic sJIA patients vs adult controls. Compared to pediatric controls, acute sJIA PB Treg cells upregulated Th17 pathway and downregulated Treg signature genes. Similarly, sJIA SF Treg cells overexpressed IL6/JAK/STAT3 and Th17 pathway genes.

Conclusion: Our data demonstrate an evolving Th17 immune response in sJIA. Treg cells in acute and chronic sJIA express high levels of activation markers, which are not seen in controls. In acute sJIA, Treg cells are subverted to a Th17 phenotype and the generation of peripherally induced Treg cells (Helios^{lo} Tregs) is impaired. In patients with chronic arthritis, there is a trend towards increased Th17 cells in the PB and sJIA SF Treg cells up regulate Th17 related genes. These data suggest that IL-1 β and IL-6 may be reprogramming Treg cells into Th17 cells in sJIA.

Disclosure: L. A. Henderson, None; K. Hoyt, None; J. P. Nguyen, None; P. Lee, None; D. Rao, None; A. H. Jonsson, None; E. Janssen, None; F. Dedeoglu, Novartis, 9; M. M. Hazen, None; M. S. Lo, None; E. Meidan, None; M. B. Son, None; R. Sundel, None; M. L. Stoll, Novartis, 5; C. Nusbaum, None; J. A. Lederer, None; T. A. Chatila, None; P. A. Nigrovic, Sobi, 2.

Abstract Number: 928

Single Cell RNA-Sequencing of Rheumatoid Synovial Fibroblasts Reveals a Disease-Associated Spatial Gradient Modulated By Inductive Notch Signaling

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis I

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: In rheumatoid arthritis (RA), tissue resident fibroblasts orchestrate chronic inflammation and regulate pathologic bone and cartilage remodeling that causes irreversible joint damage. Recently, we and others have identified the selective expansion of CD90+ sublining fibroblasts in RA patients with active, leukocyte-rich synovial histological features. Here, we leveraged droplet-based single cell RNA-sequencing (scRNA-seq), confocal microscopy, and ex vivo tissue organoid cultures to elucidate molecular pathways that govern the expansion of pathologic synovial fibroblasts in RA.

Methods: Single cell RNA-seq. Synovial stromal and endothelial cells from RA and OA synovial tissues were isolated and subjected to droplet-based single cell RNA-sequencing. Gene mapping, read alignment, pseudotime and trajectory analyses were performed.

Confocal Microscopy. RA and OA synovial tissue sections were stained with antibodies against (PRG4)/Lubricin, CD90, MCAM (CD146), VWF, and NOTCH3.

3-D synovial organoids. Synovial organoids comprised of fibroblasts and endothelial cells were reconstituted using an *in vitro* micromass culture system.

Results: ScRNA-seq of 32,000 single synovial stromal cells identified lining (*PRG4+*) fibroblasts, sublining (*CD90+*) fibroblasts, pericytes (*ACTA2+*), and endothelial cells (*VWF+*) as the major tissue resident cells in the synovium. Pseudotime and trajectory analysis revealed unexpected fibroblast transcriptional programs that follow anatomical spatial localization. Confocal microscopy visualization of fibroblast markers CD90, Lubricin and MCAM confirmed a spatial gradient along a perivascular to synovial lining axis. Isolation of spatially-restricted fibroblasts followed by serial passages and parallel transcriptomic profiling revealed spatial transcriptomic signatures diminish after serial passages, suggesting spatial gradients is maintained by local signals derived in situ in the synovial microenvironment. Receptor-ligand analysis followed by an *in vitro* ligand screen identified endothelial-derived Notch signaling as a key driver in establishing the spatial gradient between that perivascular and lining layer fibroblasts. Direct fibroblast-endothelial cell contact using a novel 3-D organoid system recapitulates the in vivo fibroblast-endothelial structure in a Notch-dependent manner. Inhibition of Notch signaling by small molecules and siRNA-mediated silencing of Notch3 abolishes sub-lining formation *in vitro*. In RA, synovial fibroblasts were overrepresented in the perivascular zone characterized by marked increase in Notch signaling, suggesting Notch regulates pathologic synovial remodeling in RA.

Conclusion: Using scRNA-seq, we identified a spatial gradient in synovial fibroblasts regulated by endothelium-derived Notch signaling. In RA, Notch signaling drives expansion of sublining (*CD90+*) synovial fibroblasts. Inhibition of Notch3 signaling prevents *CD90+* synovial sublining expansion, highlighting fibroblast Notch3 signaling as a novel therapeutic target in RA.

Disclosure: K. Wei, Roche, 2; I. Korsunsky, None; J. Marshall, None; G. Watts, None; A. Gao, None; P. Blazar, None; J. Lange, None; T. Thornhill, None; C. Buckley, None; S. Raychaudhuri, None; M. Brenner, Roche, 2.

Abstract Number: 929

Transcriptional Profiling of the Subcutaneous Rheumatoid Nodule: An Insight into Pathogenic Mechanisms and Cellular Content

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis I

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Rheumatoid nodules are the most common cutaneous manifestation in patients with RA, often associated with longstanding and a more severe disease course. Paradoxically, therapy including methotrexate (MTX) and TNF-antagonists, which is effective for synovial inflammation, has been linked to the development of subcutaneous nodules. We employed RNAseq to generate a transcriptome profile of rheumatoid subcutaneous nodules with the aim of identifying pathogenic mechanisms and genes differentially expressed in association with methotrexate therapy.

Methods: Eight subcutaneous nodules were obtained from 8 separate patients with rheumatoid arthritis as defined by ACR criteria, undergoing elective surgery for nodule removal. The patient cohort included 4 patients (3 females) grouped as never/previously (discontinued ≥ 25 months prior) receiving MTX therapy, and 4 patients (3 females) taking MTX (7.5 -20 mg/week) at the time of nodule removal. RNA was extracted using an RNeasy mini kit (Qiagen), including DNase digestion. All nodule RNA passed stringent criteria for purity and integrity (RIN >5.2). Libraries were prepared using a TruSeq RNA library preparation kit (Illumina) and sequenced as 125-bp paired end reads on a HiSeq2000 platform. RNAseq read quality was assessed using FastQC, reads were aligned using STAR aligner, and gene count tables and FPKM values obtained using packages within StringTie. To better characterise the cell types responsible for gene expression differences in nodule tissues, we applied CIBERSORT to estimate cell type composition

Results: Immune genes expressed within nodules were identified using the Immunome database as reference. Immune gene set enrichment analysis highlighted cytokine signalling, neutrophil degranulation and IFN γ -signalling pathways as potential candidates for driving inflammation within nodules. Complement and its regulation and IL-4/IL-13 signalling also feature. RNAseq data further identified 10 genes differentially expressed in nodules (FDR < 0.05), associated with MTX therapy. The expression of two genes (ABI3 and EMCN) was validated using digital PCR; both show expression that is down-regulated (~ 2.3 -fold and ~ 3.9 -fold respectively) in association with MTX therapy. CIBERSORT application to estimate cell type composition within nodules was consistent with a macrophage-dominated granuloma, characterised by an inferred large fraction of M2 macrophages as well as M1 macrophages and monocytes. Nodules exposed to MTX harboured an inferred fraction of M0 macrophages (5-26% of leucocytes) that was absent from nodules lacking MTX exposure.

Conclusion: Cytokine signalling, particularly from IFN γ and IL-4/IL-13, are key to inflammatory pathways operating within nodule tissue. Genes differentially expressed within nodules in association with MTX therapy for RA are not directly part of immune/inflammatory mechanisms, implicating diverse pathogenic mechanisms. Nodules from patients with RA receiving MTX contain M0 macrophages suggesting macrophage depolarisation and/or local proliferation associated with MTX therapy.

Disclosure: J. Marsman, None; M. J. Millier, None; J. Highton, None; L. K. Stamp, Amgen Inc., 8; P. A. Hessian, None.

Joint Location-Specific IL6 and JAK-STAT Signaling in Rheumatoid Arthritis (RA) Fibroblast-like Synoviocytes (FLS)

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis I

Session Type: ACR Concurrent Abstract Session

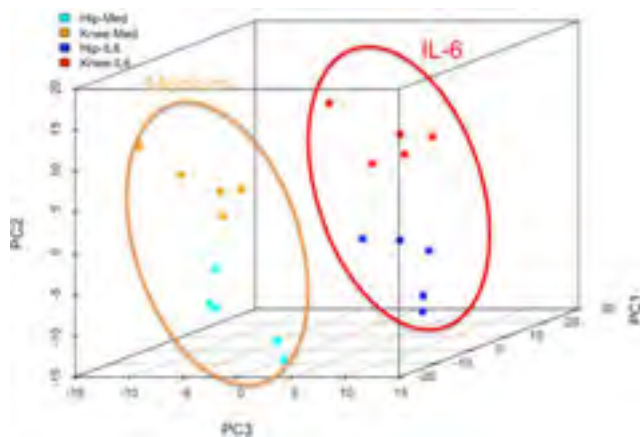
Session Time: 4:30PM-6:00PM

Background/Purpose: Recent studies suggest that epigenetic marks distinguish FLS isolated from different joints in RA. Hip and knee joint-derived FLS, in particular, have distinctive DNA methylation and transcriptome patterns that implicate the “IL-6 signaling pathway” and the “JAK-STAT pathway”. In this study, we determined how hip and knee FLS in RA differ in terms of the response to IL-6 to define the functional sequelae of joint-specific epigenetic imprinting.

Methods: RA FLS lines from hip and knee arthroplasties were used from passage 5-7 (5 each). FLS were serum starved and then stimulated with IL-6 or medium for 2h and RNA-seq was performed. Differential gene expression was determined using edgeR. Gene set enrichment analysis was performed using MSigDB curated gene sets. Differentially modified epigenetic regions (DMERs) between hip and knee FLS were analyzed from published ATAC-seq and histone ChIP-seq using DiffBind (FDR<0.05). Published whole genome bisulfite sequencing (WGBS) datasets were analyzed using DSS. Western blot analysis and/or solid phase immunoassay were performed using antibodies to P-STAT3, STAT3, JAK1 and GAPDH.

Results: RNA-seq data were normalized and principal component analysis was performed (Fig 1). Unstimulated hip and knee FLS transcriptomes segregate, consistent with previous studies. The hip and knee FLS also segregated after IL6 treatment, indicating that joint-specific differences are maintained after IL6 treatment and do not converge. Differentially expressed genes (DEGs) were identified and we focused on hip vs knee differences present in both medium and IL6-treated FLS. Gene Set Enrichment Analysis indicated that the knee was enriched in genes in “Cell adhesion molecules” and “Integrin pathway”, while the hip was enriched in “p38_alpha downstream pathway”. Next, ATAC-seq, histone ChIP-seq and WGBS datasets from RA FLS were explored to identify additional epigenomic differences between the hip and knee in IL6-signaling. In unstimulated FLS, WGBS data showed 4 differentially methylated sites associated with JAK1 and 5 sites associated with gp130. ATAC-seq showed differences in chromatin accessibility in the IL6 receptor and JAK1. The histone H3K27ac was differentially marked for the STAT3 gene. To understand the mechanism of differential IL6 responses, we evaluated hip and knee RA FLS after IL6 stimulation. P-STAT3 levels peaked after 30min and returned to baseline at 4h. Knee FLS had significantly higher P-STAT3 than hip FLS at 30 minutes (1.2 ± 0.4 vs 0.5 ± 0.2 , $p < 0.05$), indicating that enhanced STAT activation accounts for some transcriptome differences between RA hip and knee FLS.

Conclusion: RA hip and knee FLS have distinct transcriptomes, epigenetic marks, and STAT3 activation patterns in the IL6 pathway. These differences could contribute to joint-location responses to targeted therapies such as JAK inhibitors.



Disclosure: D. Hammaker, None; G. Nygaard, None; A. Kuhs, None; R. Ai, None; D. L. Boyle, None; W. Wang, None; G. S. Firestein, Janssen Pharmaceuticals, 2, 5.

Abstract Number: 931

Patients with Seropositive Rheumatoid Arthritis Who Do Not Mount a CRP Response When They Have Synovitis Are Immunologically Distinct and Are Poorly Served By Current Management Strategies

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis I

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: An atypical subgroup of patients with seropositive rheumatoid arthritis (RA) has been identified with confirmed synovitis but normal levels of the acute phase protein C-reactive protein (CRP), often considered an accurate marker of disease activity. We questioned whether this presentation was associated with delayed diagnosis and/or relative under treatment, risking worse disease outcome, and whether there were distinct immunological features.

Methods: 48 RA patients with active synovitis confirmed on Power Doppler ultrasound were recruited; 30 had normal (n)CRP ($\leq 5\text{mg/L}$) and 18 had high (h)CRP ($>5\text{mg/L}$) levels. In all other measures, disease activity was equivalent between the two groups.

Results: Time to diagnosis and time to first disease modifying anti-rheumatic drug (DMARD), were both significantly longer in the nCRP cohort. One and two year follow-up revealed that nCRP patients needed escalation to biologics significantly earlier in their disease. Serum Interleukin (IL)-6, IL-1 β , and tumour necrosis factor (TNF)- α , were appropriately elevated in both patient groups compared to healthy donors (HCs), but while IL-6 expression was positively correlated with other pro-inflammatory cytokines and acute phase reactants in hCRP patients, this synergy was lost in nCRP patients. Moreover, nCRP patients had an anti-inflammatory immune cell phenotype with significantly increased regulatory T-cell (Treg) frequencies and elevated Treg IL-10 production compared to hCRP patients. Proteomics identified differential expression of complement components in serum from hCRP compared to nCRP patients; specifically a significant upregulation of alternative complement pathway factors (eg Factors I, H and B) was seen in hCRP patients and an upregulation of kallistatin, an inhibitor of the alternative pathway in nCRP patients. Complement activation measured by serum C3 cleavage product was similarly elevated in both patient groups compared to HCs ($P<0.01$ HC vs nCRP, $p<0.05$ HC vs hCRP). However, a strong positive correlation was observed between C3 cleavage product and levels of anti-CCP antibodies ($R^2=0.53$, $p<0.05$) in nCRP patients but not hCRP patients. Finally, analysis of complement activation pathways revealed that nCRP patients preferentially activated complement via Classical and Mannose Lectin pathways compared to hCRP patients suggesting that nCRP and hCRP patients have an altered disease pathogenesis.

Conclusion: Patients with normal CRP during flares of RA had an altered immunological profile and altered activation of complement pathways compared to hCRP patients, experienced diagnostic delays and appeared to respond less well to conventional treatment.

Disclosure: T. McDonnell, None; C. Bradford, None; D. Raj, None; C. Ciurtin, None; E. Jury, None; J. Manson, None.

Abstract Number: 932

Fibroblasts Senescence Is Observed in Rheumatoid and Osteoarthritic Synovial Tissues and Triggers a Pro-Inflammatory Program Ex Vivo

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis I

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Inflammation is an important component of most age-related disorders. Cellular changes associated to aging are tightly connected with pro-inflammatory mechanisms. The purpose of this study is to analyze cellular senescence in synovial fibroblasts and its potential influence in the pathogenesis of chronic arthritis, including rheumatoid arthritis (RA) and osteoarthritis (OA).

Methods: The expression of senescence associated markers p16INK4 (p16) and Nanog was analyzed by immunohistochemistry (IHC) and immunofluorescence (IF) in synovial tissues from RA (n=43), OA (n=18), and non-inflammatory synovial tissues (n=15). Senescent synovial fibroblasts (SF) were quantified in cultures by senescence-associated beta-galactosidase (SA- β -gal) staining. For a model of stress-induced senescence, SF were cultured for 14 days after a short course of oxidative stress with H₂O₂ (200 mM for 1h on day 5) or exposure to TNF α (100 ng/ml for 72h on day 2). At 14 days, senescence and further response to stimulation with TNF α 20 ng/ml for 24h were analyzed. RNA was extracted to quantify IL-6, IL-8, MMP-3, MCP-1, p16 and p21 mRNA expression by qRT-PCR and culture supernatants were analyzed for IL-6 and IL-8 production by ELISA. Quantitative data were statistically analyzed by Pearson or Spearman correlation coefficient or Mann-Whitney test where appropriate.

Results: Synovial tissue expression of both p16 and Nanog was detected by IHC and correlated positively with the age of the donors regardless of their origin (p16: p=0.008/r=0.307; Nanog: p=0.001/r=0.413). p16(+) cell density was significantly higher in OA tissues (p=0.01) and Nanog(+) was higher in both RA (p=0.0006) or OA (p<0.0001) tissues compared to controls. p16(+) and Nanog(+) cell density were higher in young (age <40 y/o) RA patients compared to the same group of age in non-inflammatory donors (p= 0.04 and p=0.02 respectively). Double p16 and hsp47 IF labelling confirmed that both hsp47(+) SF and hsp47(-) non-fibroblastic cell fractions contained p16(+) senescent cells. The percentage of SA- β -gal(+) in non-inflammatory control SF after 14 days in culture was positively correlated with age (p=0.008/r=0.75). This fraction was higher in RA (p=0.03) compared to healthy control SF, and increased upon SF exposure to H₂O₂ or TNF α (p=0.004 for both). Stress-induced senescence enhanced the senescence associated secretory phenotype (SASP) in SF, up-regulating the mRNA expression of pro-inflammatory factors such as IL-6, IL-8, MCP-1, and MMP-3. Consistently, senescent SF released more IL-6 and IL-8 than non-senescent SF. Finally, further stimulation with TNF α induced a higher increase in IL-6, IL-8 and MMP-3 mRNA expression in senescent SF compared to non-senescent SF.

Conclusion: Synovial tissues from patients with RA and OA shows an increased proportion of senescent SF. Stress-induced senescence in SF increases the production of pro-inflammatory mediators, and gives rise to an activation state that enhances the responsiveness to TNF α . Our data suggest that SF senescence is linked to the activation of a pro-inflammatory phenotype that may contribute to the pathogenesis of chronic arthritis.

Disclosure: M. J. Del Rey, None; A. Valin, None; A. Usategui, None; S. Ergueta, None; V. Miranda, None; J. Fernández-Felipe, None; J. D. Cañete, None; F. J. Blanco, None; G. Criado, None; J. L. Pablos, None.

Abstract Number: 933

Inflammation in the Hippocampus Affects Insulin-like Growth Factor-1 Receptor Signaling and Contributes to Neurological Sequelae in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis I

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: The central nervous system is not the primary target in rheumatoid arthritis(RA). However, neuropsychiatric symptoms including pain, depression and anxiety are common and may be critical for patients' quality of life. The aim of the present study was to investigate how insulin-like growth factor receptor (IGF1R) signaling in RA associates with morphometric changes of the brain, and ultimately impairment of their functional ability.

Methods: Arthritis was induced in DBA/1 mice by collagen II and the RA-mice were filmed to evaluate behavioral changes. IGF1R was inhibited with short hairpin RNA. At termination, brains were analyzed by quantitative PCR and immunohistochemistry. 15 RA patients, all of them satisfying ACR classification criteria, underwent magnetic resonance imaging (MRI) for volumetric analysis of hippocampus at 3Tesla and processed with brain morphometry software (MAPER). Physical functioning was assessed by the Health Assessment Questionnaire (HAQ). Pain threshold was measured by algometer. Statistical analysis included the Mann-Whitney U-test and Spearman's rank correlation coefficient.

Results: Evaluation of MRI and physical functioning in RA patients revealed that smaller hippocampus volume was linked with exaggerated response of induced pain ($p=0.0006$), higher functional disability (HAQ, $p=0.009$), and lower serum levels of IGF1 ($p=0.05$). RA-mice had signs of inflammation in the hippocampus, presented by higher density of IBA1⁺ microglia and higher transcription of microglia activation marker CD68 ($p=0.0006$) and interleukin-1 β ($p=0.002$). Enrichment of microglia was observed in the pyramidal layer of cornu ammoni (CAsp, $p=0.02$) and the molecular layer of the dentate gyrus (DGmo, $p=0.02$). This coincided with inhibitory phosphorylation of insulin receptor substrate-1 (IRS1) in the subgranular layer of DG (DGsg, $p=0.03$) and CAsp ($p=0.05$), and up-regulation of IGF1R in the CAsp ($p=0.03$). These changes reproduce the molecular signature of IGF1/insulin resistance. DGsg, the site of life-long neurogenesis, became thinner ($p=0.03$) and the reduced thickness correlated with a smaller number of DCX⁺ developing neurons in this area ($r=0.7$, $p=0.005$). There was also a reduction in the total hippocampus area of RA-mice ($p=0.02$). Inhibition of IGF1R in RA-mice led to reduced inhibitory phosphorylation of IRS1 ($p=0.004$) and partial improvement of neurogenesis, seen as an increased number of GFAP⁺ neuronal stem cells in DGsg ($p=0.02$).

Conclusion: We offer a mechanistic link between pain perception in RA and reduced hippocampal volume. Our experimental study demonstrates that inflammation reproduces the molecular signature of IGF1/insulin resistance, which leads to inadequate maintenance of hippocampal neurons and consequently reduced hippocampal volume.

Disclosure: K. Andersson, None; C. Wasén, None; L. Juzokaite, None; M. C. Erlandsson, None; A. Stokowska, None; L. Leifsdottir, None; M. Pekna, None; M. Pekny, None; K. Olmarker, None; R. Heckemann, None; M. Kalm, None; M. I. Bokarewa, None.

Abstract Number: 934

HIV Protease Inhibitors Cure Lupus-Prone Mice and Prevent T Helper 17 Cell-Driven Inflammation By Inhibiting CD95-Non-Apoptotic Signaling Pathway

Manon Charrier¹, Amanda Poissonnier², Daniel Best², Jean-Philippe Guégan², Nicolas Levoine³, Raphael Pineau², Florence Jouan², Ha Thanh Nguyen², Lucie Morere², Sophie Martin², Melissa Thomas², Estibaliz Lazaro¹, Christophe Richez¹, Isabelle Douchet¹, Thomas Ducret⁴, Pierre Van de Weghe², Patrick Blanco¹, Mickael Jean², Pierre Vacher⁵ and Patrick Legembre², ¹UMR CNRS 5164 - Immunoconcept, Bordeaux, France, ²Chemistry Oncogenesis Stress Signaling, INSERM UMR 1242 Rennes University, Rennes, France, ³Bioprojet Biotech, Saint-Grégoire, France, ⁴INSERM U1218, Bordeaux University, Bordeaux, France, ⁵Actions for onCogenesis understanding and Target Identification in ONcology, INSERM U1218, Bordeaux University, Bordeaux, France

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Animal Models

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by loss of tolerance to nuclear components; this results in production of autoantibodies, immune complex formation, and tissue damages. Because SLE is a multifactorial disease with an underlying pathogenic mechanism that is poorly understood, few effective treatments are available. Human and mouse studies indicate a role for Th17 in progression of SLE. Renal damage, which occurs in about half of patients with SLE, is the leading cause of morbidity and mortality. We recently showed that serum concentrations of s-CD95L (also known as FasL) in SLE patients are higher than those in healthy subjects and are associated with disease severity via promotion of Th17 trafficking to inflamed kidneys (*Immunity*, 2016). CD95L is a transmembrane ligand that is cleaved by metalloproteases to release a soluble ligand (s-CD95L). Both s-CD95L and its transmembrane counterpart (m-CD95L) bind CD95. In the presence of m-CD95L, the death domain (DD) of CD95 recruits FADD, which in turn aggregates caspase-8 to trigger apoptosis. By contrast, interaction between s-CD95L and CD95 fails to recruit caspase-8 and FADD but instead induces a Ca^{2+} response via docking of PLCg1 to a novel domain within CD95, called the calcium-inducing domain (CID). In patients with SLE, this pathway induces accumulation of inflammatory Th17 cells in damaged organs, thereby aggravating disease pathology.

Methods: Here, we developed a protein-fragment complementation assay (PCA) and performed a high-throughput screening (HTS) to identify drugs that disrupted the CD95/PLCg1 interaction without affecting CD95/FADD binding. In parallel, a structure-activity relationship approach was performed to synthesize CID peptidomimetics that abrogated both the CD95-driven Ca^{2+} response and transmigration of CD4^{+} Th17 cells. Finally, we established the in vivo therapeutic effects of both the peptidomimetic and the best lead identified from the HTS assay in lupus-prone mice (MRL^{lpr/+}).

Results: HTS identified the HIV protease inhibitor *ritonavir* as a potent disruptor of the CD95/PLCg1 interaction. Lymphocytes from HIV patients treated with *ritonavir* or its structural derivatives failed to respond to the inflammatory cytokine s-CD95L. The second structure-activity approach revealed that *ritonavir* is a peptidomimetic that shares structural characteristics with both human and mouse CID with respect to docking to the SH3 domain of PLCg1. Administration of lupus mice with either ritonavir or a peptidomimetic designated DB550 led to: 1/ a significant reduction in the mesangial proliferation and in the adhesion of the Bowman's capsule; 2/ a significant reduction of inflammatory infiltrates (especially of Th17 cells) and the normalization of kidney architecture; 3/ a reduced C3 deposition and dsDNA antibody levels, as well as an improvement of blood filtration of creatinine.

Conclusion: Overall, this study establishes that HIV protease inhibitors and the peptidomimetic DB550 represent novel and attractive drugs that can be used in the treatment of human lupus.

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Abstract Number: 935

Neuropsychiatric Systemic Lupus Erythematosus Is Dependent on Lipocalin-2

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Animal Models

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Although the pathogenesis of neuropsychiatric lupus (NPSLE) is not fully understood, neuroinflammation plays a major role in disease. Lipocalin-2, an acute phase reactant protein upregulated in SLE, promotes neuroinflammation through inducing brain barrier disruption, glial activation, and neurotoxicity. In this study, we

examined the effects of LCN2 deficiency on the development of neurobehavioral deficits in the lupus-prone B6.Sle1.Sle3 (Sle1,3) mouse strain.

Methods: Sle1,3, Sle1,3-LCN2 knockout (KO), B6.LCN2KO, and B6 mice were evaluated for cognitive dysfunction and depression-like behavior at 7-10 months of age (n=5-10/group). Brains were either paraffin-embedded for immunofluorescence staining, or cortex and hippocampal samples were snap frozen for analysis of gene expression. Indicators of systemic disease, including serum IgG anti-dsDNA titers, spleen weight, and renal pathology were assessed. Brains from a separate cohort of age-matched mice were analyzed by flow cytometry, and CD11b+CD64+CD45-low microglia were sorted for RNA sequencing.

Results: Sle1,3 mice exhibited significant impairment in spatial and recognition memory when compared with B6 mice, and these deficits were significantly attenuated in Sle1,3-LCN2KO mice. Sle1,3 mice also demonstrated anhedonia (abnormal pleasure seeking behavior), and this depression-like behavior was significantly reduced with LCN2 deficiency. Flow cytometry showed a significant increase in brain infiltrating cells, including CD4+ and CD8+ T cells, that was not reduced with LCN2 deficiency. When compared with B6 mice, Sle1,3 mice exhibited increased anti-dsDNA titers, splenomegaly, and glomerular and tubular pathology, but these findings were not attenuated with LCN2 deficiency. In the hippocampus, there was a significant increase in TUNEL-positive cells in Sle1,3 compared with B6 mice, while apoptosis was reduced in the Sle1,3-LCN2KO mice when compared with Sle1,3 brains. Moreover, Iba-1 staining revealed amoeboid (activated) microglial morphology in Sle1,3 hippocampi but a more ramified (resting) morphology in Sle1,3-LCN2KO mice. RNA sequencing of sorted microglia showed that several genes, upregulated in Sle1,3 mice and involved in inflammation and memory (e.g. *Plp1*, *Mal*, and *Apod*), were normalized in Sle1,3-LCN2KO mice. Additionally, in two large independent human cohorts, patients with NPSLE displayed high cerebrospinal fluid levels of LCN2 compared to healthy controls.

Conclusion: Our findings demonstrate that LCN2 deficiency significantly attenuates neurobehavioral deficits, reduces apoptosis in the brain, and modulates microglia morphology in the Sle1,3 lupus-prone strain. Moreover, LCN2 regulates microglial expression of genes essential to NPSLE development, suggesting LCN2 as a novel therapeutic target.

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Abstract Number: 936

Selective Deficiency of Serine Arginine-Rich Splicing Factor 1 (SRSF1) in T Lymphocytes Leads to mTORC1 Activation, Treg Dysfunction and Systemic Autoimmune Disease

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Animal Models

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: T cells from patients with systemic lupus erythematosus (SLE) exhibit defects in signaling and cytokine production, and aberrant numbers and/or function of regulatory T cells (Treg). By discovery approaches we previously identified the serine arginine-rich splicing factor 1 (SRSF1) in human T cells. We showed that SRSF1 promotes normal expression of the CD3 zeta signaling chain, and upregulates IL-2 production in human T cells. SRSF1 expression levels are decreased in SLE T cells, and associate with worse disease. Force expression of SRSF1 into SLE T cells rescued IL-2 production. These results indicate that the SRSF1 deficiency is important in SLE T cell dysfunction. However, it is unknown how SRSF1 deficiency contributes to immune-mediated disease. To this end, we have generated mice with a T cell-restricted deletion of SRSF1, and our goal is to evaluate the mechanistic role of SRSF1 in T cell dysfunction and the development of immune-mediated disease *in vivo*.

Methods: *Srsf1*-conditional knockout (*Srsf1*-cko) mice were generated by crossing *Srsf1*-flox mice with d.*Lck.Cre* mice to delete SRSF1 in mature T cells. Peripheral lymphoid organs were analyzed for immune cell phenotype and function by flow cytometry. T cells were stimulated with anti-CD3, anti-CD28 and PMA plus Ionomycin. Serum and urine were

collected at monthly intervals to assess autoantibodies and proteinuria. Tissues (lung, liver, kidney) were fixed and processed for histopathology. Suppressive function of Tregs was assessed in vitro by Treg-Teffector co-culture assays, and in vivo by adoptive transfer of Tregs followed by induction of dextran sodium sulfate (DSS)-induced colitis in B6 mice. Activity of the mammalian target of rapamycin complex (mTORC) 1 pathway was analyzed after T cell stimulation by western blot and phospho-flow cytometry. Phosphatase tensin homolog (PTEN) expression levels were analyzed by qPCR and western blot.

Results: *Srsf1*-cko mice develop a systemic autoimmune disease phenotype with elevated autoantibodies and systemic inflammation in peripheral organs including lungs, liver, kidneys and increased proteinuria. Kidney histopathology shows glomerular hyperproliferation, glomerular capillary hyperplasia, and interstitial infiltration of mononuclear cells suggestive of lupus-like nephritis. CD4 T cells exhibit an activated phenotype with increased frequencies of IFN- γ and IL-17 producers but lower amounts of IL-2 upon ex vivo stimulation. Tregs from *Srsf1*-cko mice are dysfunctional in vitro, and are unable to suppress DSS-colitis in vivo. Tregs exhibit an inflammatory phenotype with increased IFN- γ and IL-17 production upon ex vivo stimulation. Increased activity of the mTORC1 pathway is observed in Tregs from the *Srsf1*-cko mice, and expression levels of PTEN, an inhibitor of the mTORC1 pathway, are decreased.

Conclusion: SRSF1 is a novel regulator of Treg function, and its deficiency in T cells leads to autoimmunity and lupus-like nephritis. Therefore, deficiency of SRSF1 in T cells may represent a molecular defect that contributes to the pathogenesis of systemic autoimmune disease.

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Abstract Number: 937

Evidence of a Common Microglial Signature in Models of ‘Neuropsychiatric Symptoms of Systemic Lupus Erythematosus’

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Animal Models

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune syndrome affecting multiple organs, including the brain. More than 60% of patients experience neuropsychiatric symptoms of SLE (NPSLE) that often occur early in disease and go undiagnosed. Despite the devastating impact of NPSLE on health-related quality of life, the underlying disease mechanisms are unknown. Microglia are the resident innate immune cells in the brain, and accumulating evidence points to microglia as a source of neurotoxic factors that drive neurodegenerative disease. However, very few studies have examined microglia in the context of NPSLE. Here, microglia isolated from two lupus-prone mouse strains with NPSLE-like disease were evaluated at the transcriptional level to ascertain the existence of a common gene signature.

Methods: Mice with caspase 8 flanked by *loxP* sites (*Casp8^{fl/fl}*) were bred to mice expressing Cre under control of the CD11c gene promoter (*Cre^{CD11c}*) to generate *Cre^{CD11c}Casp8^{fl/fl}* mice. The bicongenic B6.Sle1.Sle3 (Sle1,3) strain was derived from the introgression of 2 lupus susceptibility loci from the NZM2410 spontaneous SLE model onto non-autoimmune C57BL/6 (B6) mice. *Casp8^{fl/fl}*, *Cre^{CD11c}Casp8^{fl/fl}*, B6 and Sle1.3 mice were evaluated for behavioral deficits at 8-10 months of age (n=4/group). Cellular infiltration into the brain was assessed using 10-color flow cytometric analysis. Microglia were sorted for RNA-seq analysis.

Results: We have shown that CD11c-specific deletion of caspase 8, an enzyme in the Fas pathway classically linked to apoptosis initiation and necroptosis suppression, induces an inflammatory disease reminiscent of both human and classic murine models of SLE. *Cre^{CD11c}Casp8^{fl/fl}* mice also exhibit significant impairment in coordination/balance and working memory/learning behaviors similar to patients with SLE. Likewise, the lupus-prone Sle1,3 mouse strain exhibits depression-like behavior and significant impairment in spatial and recognition memory, symptoms detected in SLE patients. In both lupus-prone strains, behavioral deficits correlate with increased leukocyte infiltration including T cells and macrophages. Of the significantly upregulated genes (p<0.05, fold change in expression>1.5) observed in *Cre^{CD11c}Casp8^{fl/fl}* (276) and Sle1,3

(246) microglia compared to their respective controls, 22 genes are shared ($p=3.23 \times 10^{-5}$, hypergeometric distribution). These shared genes are involved in 'cell chemotaxis' ($p=7.99 \times 10^{-4}$; *Vcam1*, *Slamf8*, *Cxcl16*), 'scavenger receptor activity' ($p=1.27 \times 10^{-4}$; *Cxcl16*, *Lgals3bp*), 'negative regulation of inflammatory response' ($p=1.83 \times 10^{-4}$; *ApoE*, *ApoD*, *Slamf8*), 'negative regulation of lipid metabolic process' ($p=1.38 \times 10^{-4}$; *ApoE*, *ApoD*, *Niacr1*) and 'response to external stimulus' ($p=1.31 \times 10^{-4}$; *Igax*, *Slfn2*, *ApoE*, *Axl*, *Pkd2*, *Cxcl16*, *Slamf8*).

Conclusion: These data substantiate a common microglial transcriptional signature associated with NPSLE-like disease suggestive of a more regulatory role. In future studies, through examination of other NPSLE models, we will assess the penetrance of this common signature to further interrogate how defective microglial function may incite NPSLE.

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Abstract Number: 938

Dermal Lymphatic Dysfunction and Photosensitivity in the MRL/Lpr Lupus Model

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Animal Models

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Proper function of lymphatic vessels is needed to limit the magnitude and duration of tissue inflammation. Chronic inflammatory states such as obesity and psoriasis are associated with lymphatic dysfunction, but lymphatics in lupus models have not been well characterized. SLE patients are photosensitive, developing inflammatory skin lesions upon exposure to even ambient ultraviolet radiation (UVR). We hypothesized that lymphatic dysfunction may contribute to photosensitivity in lupus.

Methods: 8-10 week old MRL/MpJ-*Fas*^{lpr/lpr} (*lpr*) mice and age-/sex-matched MRL controls were evaluated at baseline, and after exposure to UVR. The source of UVR was a set of 4 FS40T12 sunlamps emitting UVA and UVB at 40:60 ratio. The overall dose of the total radiation ranged from 2000-2500 J/m². Lymphatic function was assessed with an intradermal injection of 1μL of 2% Evans blue (EB) to the ear, followed by measurement of EB concentration in the draining auricular lymph node (LN). Flow cytometry of ears and auricular LN allowed quantification of resident cell populations, and local mRNA expression of vascular endothelial growth factor-C (VEGF-C) was evaluated by real-time PCR. Mann-Whitney *U* test was used to compare the groups; data is presented as mean ± SE, with a two-tailed *p*-value of <0.05 considered significant.

Results: At baseline, auricular LNs of *lpr* mice are bigger and are about 10-fold more cellular than controls (21523860 ± 3861631 cells vs. 2184360 ± 464267 cells, respectively; $p=0.008$), but there is no compensatory increase in dermal lymphatic endothelial cells (LEC) to allow for an increase in local lymphatic transit to the LN (8918 ± 2142 LEC in *lpr* vs. 6106 ± 1023 LEC in controls; $p=0.421$). Accordingly, already at baseline, the effective flow of EB from the ear to the LN in *lpr* mice is only 44% that of controls, when accounting for the weight of the LN. Importantly, post-UVR, EB drainage in *lpr* mice is reduced to only 10% that of controls, and this value persists both 1 week after UVR and 1 month later. Interestingly, we have observed that at the peak of local inflammation that occurs at around 7 days post-UVR, VEGF-C mRNA levels are suppressed in both *lpr* and MRL strains, compared with non-UV exposed controls.

Conclusion: Dermal lymphatic network of lupus models have never been characterized, despite evidence for a major role of lymphatics in the regulation of chronic inflammation. Here we provide indications to impaired local lymphatic drainage in the *lpr* lupus strain, which can lead to reduced inhibitory signals arriving at the overactive lymph node from the lymphatic circulation, contributing to the unchecked inflammation known to occur in SLE. UVR is shown to further impair local lymphatics, particularly in the lupus strain, possibly through suppression of VEGF-C production.

Disclosure: N. Schwartz, None; S. Chyou, None; T. Li, None; W. D. Shipman, None; T. T. Lu, None.

Rab4A Protects from Lupus Nephritis By Limiting Germinal Center Formation and Pro-Inflammatory Expression of GLUT1 and Integrin By Renal Epithelial Cells

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Animal Models

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Lupus nephritis is most common cause of mortality and morbidity in systemic lupus erythematosus (SLE) patients and 60% of SLE patients develops lupus nephritis. HRES-1/RAB4 genomic locus has been associated with disease manifestations in SLE patients (Arthritis Rheum. 58:532-520). Inhibition of Rab geranylgeranyl transferase prevented nephritis in lupus-prone mice (Ann. Rheum. Dis. 73:1887-1897). To investigate the role of Rab4A in lupus pathogenesis, we developed a mouse model Rab4A-KO^{CD4Cre} (Rab4A^{KO}; mice lacking expression of Rab4A in T cells relative to C57Bl/6 wild-type (WT) and floxed Rab4A^{Q72L} knock-in (Rab4A^{Q72L}) as a control. Previously we showed that Rab4A^{Q72L} knock-in prevents ANA production, immunoglobulin and C3 depositions in glomeruli and lymphocytic infiltration in kidneys relative to Rab4A^{KO} mice. These preliminary results provided rationale for testing our hypothesis that HRES-1/Rab4 plays a crucial role in SLE, including the pathogenesis of lupus nephritis.

Methods: Age and gender matched WT, Rab4A^{Q72L} and Rab4A^{KO} female mice were injected with 0.5 mL pristane per 20 g of body weight, intraperitoneally. 14 days post pristane injection, kidneys were fixed in formalin for H&E and PAS staining or snap freeze in OCT for confocal microscopy. To assess the podocyte injury, 8 µm frozen kidney sections were analyzed anti-podocin and anti-CD51 (Integrin αV). Frozen kidney sections were further analyzed using anti-CCR6 and anti-IL17. To study the effect of Rab4A on GLUT1 glucose transporter, Kidney sections were stained with anti-GLUT1. Splenic germinal centers were investigated using 6 µm frozen spleen sections stained with anti-B220, anti-F4/80, anti-CD3 and anti-CD138. Kidney histology was blindly evaluated by an expert pathologist.

Results: Kidney histology revealed accelerated glomerulonephritis (GN) (3-fold; $p=7.6 \times 10^{-4}$), glomerulosclerosis (GS) (8-fold; $p=0.0106$) in Rab4A^{KO} mice relative to Rab4A^{Q72L} mice. Further, we found 1.7-fold reduction in podocin and 1.9-fold reduction in CD51 expression in kidneys of Rab4A^{KO} relative to WT mice (podocin, $p=0.0027$; CD51, $p=0.0002$) or Rab4A^{Q72L} mice (podocin, $p=0.03$; CD51, $p<0.0001$), suggesting podocyte injury in Rab4A^{KO} animals. In addition, CCR6 and IL-17 expression by kidney-infiltrating lymphocytes was significantly higher in Rab4A^{KO} as compared to WT and Rab4A^{Q72L} mice. GLUT1 expression was elevated 4-fold and confined to the kidney medulla of Rab4A^{KO} mice relative to Rab4A^{Q72L} ($p=0.004$) and WT controls ($p=0.0001$). Relative to WT controls, splenic germinal centers exhibited 1.3-fold increased size in Rab4A^{KO} mice ($p=0.0452$) with 3-fold expansion of T cell zones ($p<0.0001$) and 2-fold accumulation of plasma cells ($p=0.0197$). Interestingly, spleen sections from Rab4A^{Q72L} mice had smaller splenic germinal centers with fewer CD138⁺ plasma cells in comparison to WT ($p=0.0002$; $p=0.0427$) and Rab4A^{KO} mice ($p=0.0083$).

Conclusion: The results suggest that Rab4A protects from nephritis in the pristane-induced model of SLE by limiting the germinal center formation and pro-inflammatory expression of GLUT1 and Integrin αV by renal epithelial cells.

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Inactivated Influenza Vaccine Prevents Respiratory Infections and Improves All-Cause and Cause-Specific Mortality in Immunosuppressed People with Autoimmune Rheumatic Diseases: Propensity Score Adjusted Cohort Study Using Data from Clinical Practice Research Datalink

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health I: Morbidity and Mortality

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: To assess the effectiveness of inactivated influenza vaccine (IIV) in preventing influenza like illness (ILI), lower respiratory tract infection (LRTI), pneumonia, chronic obstructive pulmonary disease (COPD) exacerbation and death in adults with autoimmune rheumatic diseases (AIRDs).

Methods: Adults with AIRDs e.g. RA, Spondyloarthritis, SLE etc., and treated with immunosuppressive drugs in the 3 month period before the 1st September of each year, 2006-2009, and 2010-2015 were identified in the Clinical Practice Research Datalink (CPRD). CPRD is a longitudinal anonymised electronic database containing health records of over 13 million people, registered with >680 general practice surgeries in the UK. It contains details of all diagnoses, prescriptions, immunisations etc. recorded as part of usual medical care. Data for this study were extracted from the CPRD, and from linked Hospital Episode Statistics and Office for National Statistics databases. The 2009-2010 influenza pandemic period was excluded due to co-vaccination with pandemic vaccine and predominance of pandemic virus in community. Propensity score (PS) for vaccination on the 1st September of each year was calculated using previously published and validated methods. Cox-proportional hazard ratio (HR) and 95% confidence intervals (CIs) were calculated to examine association between vaccination and first occurrence of each outcome of interest upto 31st August of the next year. Vaccination was regarded as a time-varying covariate, and the protected period began 14 days from the date of vaccination. Sensitivity analysis restricting to the period in which the flu virus was in circulation in the community was performed. The exposure and outcome variables reverted to unexposed and no-outcome on the 1st September of each year. The association was adjusted for PS for vaccination, year, and included a clustering term to account for data from same participant in multiple years. Stata v14 was used for data analyses.

Results: Data for 30,788 participants (66% female), 76% with RA, 61% treated with methotrexate, and contributing 125,034 person-seasons were included. PS for vaccination predicted vaccination status (area under the curve 0.87). Vaccination reduced the risk of hospitalization for pneumonia, hospitalization for COPD exacerbation, all-cause mortality and death due to pneumonia in that flu season (aHR (95%CI) 0.59(0.51-0.69), 0.59(0.44-0.80), 0.52(0.47-0.59), 0.47(0.35-0.63) respectively). Vaccination also reduced the risk of primary care consultation for ILI (aHR (95%CI) 0.75 (0.60-0.95)) when the analysis period was restricted to the time when influenza viruses circulated. Other protective effects also remained statistically significant in this restricted analysis. These associations did not change when seasons with exposure to sulfasalazine alone were excluded. IIV did not reduce the risk of primary care consultations for LRTI and COPD exacerbations.

Conclusion: This is the first study to demonstrate and quantify the effectiveness of IIV in people with AIRDs. The results provide justification to educate health professionals and actively promote flu vaccination to the immunosuppressed people with AIRDs.

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Causal Inference Methods for the Effect of Rheumatoid Arthritis on Mortality Independent of Lifestyle and Clinical Factors before and after RA Diagnosis

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SESSION INFORMATION

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Session Time: 4:30PM-6:00PM

Background/Purpose: RA is associated with increased total, cardiovascular, and respiratory mortality compared to the general population. This excess RA mortality may be mediated through lifestyle, clinical, or RA-specific factors occurring

Table: Hazard ratios for total and cause-specific mortality for women with RA (reference: matched comparators), adjusted for time-varying covariates before and after the index date of RA diagnosis using marginal structural modeling.

Model and covariates	Total mortality HR (95% CI)	Cardiovascular mortality HR (95% CI)	Respiratory mortality HR (95% CI)
All RA			
(1) Baseline confounder model	1.42 (1.27-1.58)	1.25 (0.97-1.62)	3.79 (2.87-5.40)
(2) Baseline confounder + Time-updated lifestyle factors model	1.52 (1.35-1.71)	1.42 (1.10-1.84)	2.64 (1.95-3.56)
(3) Baseline confounder + Time-updated lifestyle/multimorbidity factors model	1.06 (0.97-1.21)	0.97 (0.75-1.24)	1.64 (1.15-2.06)
Seropositive RA			
(1) Baseline confounder model	1.84 (1.33-1.77)	1.35 (0.97-1.88)	4.85 (3.23-7.29)
(2) Baseline confounder + Time-updated lifestyle factors model	1.67 (1.45-1.92)	1.49 (1.00-1.97)	3.22 (2.29-4.51)
(3) Baseline confounder + Time-updated lifestyle/multimorbidity factors model	1.25 (1.09-1.44)	1.03 (0.78-1.47)	2.13 (1.54-2.94)
Seronegative RA			
(1) Baseline confounder model	1.24 (1.03-1.50)	1.12 (0.75-1.68)	1.95 (0.81-4.24)
(2) Baseline confounder + Time-updated lifestyle factors model	1.18 (1.14-1.67)	1.46 (0.98-2.18)	1.43 (0.71-2.89)
(3) Baseline confounder + Time-updated lifestyle/multimorbidity factors model	0.97 (0.80-1.16)	0.90 (0.61-1.32)	0.72 (0.34-1.51)

Comparator status is the reference in all models.

The all RA analyses included 998 women with all RA and 9,921 matched comparators. The seropositive RA analyses included 617 women with seropositive RA and 6,144 matched comparators. The seronegative RA analyses included 379 women with seronegative RA and 3,777 matched comparators.

Among women with RA, there were 410 (41.2%) total, 75 (18.3%) cardiovascular, and 50 (12.2%) respiratory deaths. Among comparators, there were 2,799 (28.1%) total, 524 (18.9%) cardiovascular, and 195 (7.0%) respiratory deaths.

(1) Baseline confounder model: Adjusted for matching factors (age and calendar year) at index date of rheumatoid arthritis diagnosis as well as baseline factors assessed prior to index date: annual family income, pre-index smoking, body mass index, Alternate Healthy Eating Index, menopausal status and postmenopausal hormone use, physical activity, aspirin use, and Multimorbidity Weighted index.

(2) Baseline confounder + Time-updated lifestyle factors model: Adjusted for variables in (1) as well as time-updated lifestyle factors assessed after index date. Adjustment through inverse probability weighting.

(3) Baseline confounder + Time-updated lifestyle/multimorbidity factors model: Adjusted for variables in (2) as well as time-updated Multimorbidity Weighted Index after index date. Adjustment through inverse probability weighting.

after diagnosis. Causal inference methods, such as marginal structural models, can adjust for both confounders as well as mediators on the causal pathway between RA diagnosis and mortality. We aimed to decipher the mechanism through which RA increases total and cause-specific mortality accounting for potential mediators after RA diagnosis using causal inference methods.

Methods: We used a prospective cohort study, the Nurses' Health Study (n=121,700), to investigate RA and mortality, accounting for lifestyle/clinical covariates before/after RA diagnosis. We identified incident RA meeting ACR criteria during follow-up. We matched each RA case to 10 comparators by age and year at RA diagnosis (index date). We considered lifestyle/clinical factors assessed by biennial surveys as baseline confounders (before index date) or mediators (after index date). Lifestyle factors included smoking, BMI, diet, and physical activity. We used the validated Multimorbidity Weighted Index, composed of 64 prevalent/serious health conditions (interstitial lung disease [ILD] was unmeasured). We used inverse probability weights to adjust for the confounding/mediating effects of covariates on mortality risk for RA vs. comparators. We compared RA effect estimates for mortality in models composed of baseline confounders and time-updated mediators.

Results: At index date, mean age was 60.1 years (SD 10.2). Among 996 women with incident RA, 410 (41.2%) died during mean follow-up of 19.8 years (SD 9.1). Among 9,921 matched comparators, 2,789 (28.1%) died during mean follow-up of 19.5 years (SD 9.7). Adjusting for baseline factors and time-updated lifestyle factors after index date, RA was associated with excess total (HR 1.52, 95%CI 1.35-1.71), cardiovascular (HR 1.42, 95%CI 1.10-1.84), and respiratory (HR 2.64, 95%CI 1.95-3.56) mortality. When accounting for incident multimorbidities after index date, RA was no longer associated with total (HR 1.08, 95%CI 0.96-1.20) or cardiovascular (HR 0.98, 95%CI 0.77-1.25) mortality, but excess respiratory mortality remained (HR 1.54, 95%CI 1.15-2.08). Seropositive RA remained associated with respiratory mortality before (HR 4.85, 95%CI 3.23-7.29) and after adjustment for all covariates (HR 2.13, 95%CI 1.54-2.94).

Conclusion: In this large prospective study using causal inference methods, excess total and cardiovascular RA mortality was explained by incident multimorbidities after diagnosis. For seropositive RA, excess respiratory mortality remained after accounting for measured lifestyle/clinical factors, emphasizing the importance of monitoring other factors (such as ILD, infections, or medications), that may mediate the RA respiratory mortality burden.

Disclosure: J. A. Sparks, None; K. Yoshida, None; T. C. Lin, Amgen Inc., 3; C. Camargo, None; B. Raby, None; H. K. Choi, Takeda, Selecta, Kowa, and Horizon, 5; Selecta and Horizon, 2; M. Barbhuiya, RRF, 2; S. K. Tedeschi, None; B. Lu, None; K. Costenbader, None; E. Karlson, None.

Abstract Number: 942

Risk of Serious Infections in Tocilizumab Versus TNF Inhibitor Initiators in Patients with RA: A Multi-Database Cohort Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health I: Morbidity and Mortality

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: While biologics are known to be associated with risk of serious infections, data on head-to-head comparison of different biologic drugs for the risk of infection are limited. We aimed to investigate the rate of incident serious bacterial, viral or opportunistic infection in rheumatoid arthritis (RA) patients starting tocilizumab (TCZ) versus TNF inhibitor (TNFi).

Methods: We conducted a cohort study using data from 3 U.S. healthcare claims databases: Medicare (2010-2015), 'IMS' PharMetrics Plus (2011-2015) and 'Truven' MarketScan (2011-2015). We identified patients with RA aged ≥18 years who initiated TCZ or a TNFi with prior use of at least one different TNFi, abatacept or tofacitinib. Patients with recent infection, malignancy or rituximab use were excluded. The primary endpoint was incident composite serious infection including bacterial, viral or opportunistic infection with ≥1 inpatient principal diagnosis code. Secondary outcomes were specific subtypes of serious infection (**Table**). To control for >70 potential confounders including demographics, prior DMARD and antibiotic use, comorbidities, medications, and healthcare utilization in each database, TCZ initiators were

Table. Risk of incident serious infection associated with initiating tocilizumab versus TNF inhibitors: a 1:3 variable ratio propensity score matched as-treated analysis

Outcome	Tocilizumab (n=16,074)		TNF inhibitors (n=33,109)	
	IR per 100 PY (95% CI)	HR (95% CI)	IR per 100 PY (95% CI)	HR (95% CI)
Primary				
Serious infection	4.68 (4.31-5.05)	1.05 (0.95-1.16)	3.69 (3.28-4.22)	REFERENCE
Secondary				
Serious bacterial infection	3.95 (3.61-4.29)	1.19 (1.07-1.33)	3.97 (3.27-3.17)	REFERENCE
Herpes zoster	0.11 (0.08-0.17)	0.80 (0.48-1.08)	0.13 (0.07-0.15)	REFERENCE
Opportunistic infection	0.13 (0.07-0.20)	0.99 (0.55-1.79)	0.13 (0.08-0.17)	REFERENCE
Pyelonephritis/UTI	0.49 (0.37-0.69)	0.77 (0.56-1.04)	0.54 (0.40-0.63)	REFERENCE
Skin/soft tissue infection	0.28 (0.19-0.39)	2.38 (1.47-3.86)	0.12 (0.08-0.15)	REFERENCE
Diverticulitis	0.52 (0.40-0.64)	2.34 (1.64-3.34)	0.21 (0.16-0.26)	REFERENCE
Pneumonia/upper resp. tract infection	1.19 (1.10-1.59)	0.82 (0.77-1.10)	1.34 (1.21-1.48)	REFERENCE
Septicemia/bacteremia	1.72 (1.50-1.96)	1.04 (0.98-1.22)	1.51 (1.37-1.65)	REFERENCE

Notes: 1. For the primary as-treated analysis, follow-up time started the day after cohort entry (and ended on treatment discontinuation, outcome occurrence, disenrollment, death, or the end of study period).

2. Hazard ratios for tuberculosis and viral hepatitis (secondary outcomes) are not reported since no events occurred for these endpoints in either TCZ or TNFi group.

3. Hazard ratios (HR) from the 3 PS-matched cohorts were combined by an inverse variance-weighted, fixed-effects model.

propensity score (PS)-matched to TNFi initiators with a variable ratio of 1:3 within each database. We then calculated incidence rates (IR) and hazard ratios (HR) of the primary and secondary outcomes.

Results: A total of 16,074 TCZ initiators were PS-matched to 33,109 TNFi initiators. Mean age was 72 years in Medicare, 51 in IMS and 53 in Truven. At baseline, 69-73% patients used methotrexate and 70-79% used corticosteroids. In the as-treated analysis, the median follow-up time (days) ranged from 181 (MarketScan) to 213 (IMS) in the TCZ group and 198 (Medicare) to 235 (IMS) in the TNFi group. A total of 618 serious infections occurred in TCZ and 1,155 in TNFi group across the 3 databases. In the TCZ group, the IR for serious infections per 100 person-years ranged from 3.07 (Truven) to 7.05 (Medicare), and in the TNFi group, it ranged from 2.47 (Truven) to 7.05 (Medicare). The risk of incident composite serious infections was similar in TCZ versus TNFi initiators with a combined HR of 1.05 (95% CI 0.95-1.16) across all 3 databases. However, TCZ was associated with an increased risk of serious bacterial infection (HR 1.19, 95% CI 1.07-1.33), skin and soft tissue infections (HR 2.38, 95% CI 1.47-3.86) and diverticulitis (HR 2.34, 95% CI 1.64-3.34) compared to TNFi initiators. Secondary and subgroup analyses showed similar results.

Conclusion: This large multi-database cohort study found a similar risk for the composite primary endpoint of serious infection requiring hospitalization in RA patients who initiated TCZ versus TNFi after failing ≥ 1 biologic drug or tofacitinib. However, the risk of serious bacterial infection, skin and soft tissue infections, and diverticulitis was higher in TCZ initiators versus TNFi.

Disclosure: A. Pawar, None; R. J. Desai, None; D. Solomon, Eli Lilly and Co., 2, Pfizer, Inc., 2, AstraZeneca, 2, Genentech, Inc., 2, Amgen Inc., 2, Corrona, LLC, 2; S. Gale, Genentech, Inc., 3; M. Bao, Genentech, Inc., 3; K. Sarsour, Genentech, Inc., 3; S. Schneeweiss, Genentech, 2, Boehringer Ingelheim, 2, WHISCON, LLC, 5, Aetion, Inc., 1, 5; S. C. Kim, Bristol-Myers Squibb, 2, Pfizer, 2, Roche, 2.

Abstract Number: 943

Risk of Prostate Cancer in US Veterans with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health I: Morbidity and Mortality

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Patients with rheumatoid arthritis (RA) are at a small, but significantly increased risk of cancer compared with the general population. This risk varies by cancer type, with highest risk observed in lymphoma and lung cancer. Findings relative to prostate cancer are conflicted (standardized incidence ratio [SIR] 1.15, 95% CI 0.98-1.34, in recent meta-analysis). Recognizing the male predominance and large number of cases available in the Veterans Health System, we estimated the risk of prostate cancer in a national population of male US Veterans with RA.

Methods: We identified male patients with RA using an algorithm that required ≥ 2 diagnostic codes ≥ 30 days apart, rheumatologist diagnosis, and either a DMARD prescription or positive RF or anti-CCP within the VA Corporate Data Warehouse (1/2000-4/2018). We excluded individuals with diagnostic codes for psoriatic arthritis or ankylosing spondylitis, and those with prostate cancer or prostatectomy prior to the index date. Prostate cancer and prostate cancer death were identified from the VA Central Cancer Registry (VACCR; captures up to 90% of cancers in the VA) and the National Death Index. Prostate cancer incidence rates (IR; per 1,000 pt-yrs) and 95% CIs were calculated from the index date (first date RA diagnosis by algorithm). SIR and 95% CI were calculated from age- and race-matched rates in the Surveillance, Epidemiology, and End Results Program (SEER). Multivariable Cox regression models assessed the association of seropositivity (RF or anti-CCP positive) with prostate cancer risk adjusting for age, race, smoking status, and Agent Orange exposure (reported risk factor for prostate cancer).

Results: RA patients included in analyses (n=50,870) had a mean (SD) age of 64 (11) years, 74% were white, 11% were black, 75% were ever smokers, and most were positive for either RF (67%) or anti-CCP (66%). Over 361,419 pt-yrs of follow-up, there were 1,243 incident prostate cancers (IR 3.4; 95% CI 3.3-3.6 per 1,000 pt-yrs). Similar rates were observed in seropositive (IR 3.5, 95% CI 3.3-3.7) and seronegative (IR 3.2, 95% CI 2.8-3.6) RA patients. Relative to SEER rates, SIR of prostate cancer was 0.89 (95% CI 0.85-0.95). Stratified by seropositivity, prostate rates were lower than those in SEER for seronegative patients (SIR 0.81, 95% CI 0.71-0.92) but similar for seropositive patients (SIR 0.94, 95% CI 0.88-1.01). In multivariable models, age, black race, and Agent Orange were independently associated with prostate cancer risk, while seropositivity was marginally associated (HR 1.15, 95% CI 0.97-1.36).

Conclusion: In one of the largest studies of its kind to date, we estimated prostate cancer rates to be slightly lower in RA than in the general population. However, this small difference may be accounted for by cases not captured within VACCR (estimated to approach 10%). Autoantibody status does not appear to portend substantial risk, however, additional investigation will be needed to identify whether other disease-related factors are associated with prostate cancer risk in this population.

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Abstract Number: 944

Gout: A Potential Risk Factor for Uveitis in the Older Adults?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health I: Morbidity and Mortality

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Elevated intraocular levels of these pro-inflammatory cytokines and systemic levels of C-reactive protein are seen in uveitis, which leads to 30,000 new cases of legal blindness annually in the U.S. Limited epidemiological information is available for risk factors for uveitis. Our objective was to assess whether gout in the elderly is associated with a risk of incident uveitis.

Methods: We used the 5% Medicare claims data from 2006-2012 for this cohort study. Gout was identified by the presence of two claims for gout at least 4 weeks apart, with International Classification of Diseases, ninth revision, common modification (ICD-9-CM) code of 274.xx. Study outcome was incident uveitis, identified by two claims for uveitis with an ICD-9-CM code of 364.xx, at least 4 weeks apart and an absence of uveitis claims in the baseline 365-day period, a valid approach. We used multivariable-adjusted Cox proportional hazard models to assess the association of gout with incident uveitis, adjusting for potential confounders/covariates including demographics (age, race, gender), comorbidities (Charlson-Romano comorbidity index), and medications commonly used for cardiac diseases (statins, beta-blockers, diuretics, and angiotensin converting enzyme (ACE)-inhibitors) and gout (allopurinol and febuxostat; Model1).

Results: We found 8,459 incident uveitis cases in our cohort of 1,240,681 Medicare recipients, 464 in people with and 7,995 in people without gout, leading to respective incidence rates of 179 and 93 per 100,000 person-years. The mean [standard deviation (SD)] time from gout diagnosis to the new diagnosis of uveitis was 804 days [SD, 572] (median, 694 days; interquartile range, 329, 1190 days). Compared to people without incident uveitis, people with uveitis were significantly more likely to be older, female, Black and have higher medical comorbidity. After multivariable-adjustment (model 1), gout was associated with 1.53-fold higher hazard of uveitis (95% confidence interval (CI), 1.39, 1.69; $p < 0.0001$) (**Table 1**), as were older age, female gender, Black or other race/ethnicity, and comorbidities including diabetes, chronic pulmonary disease, connective tissue disease or any tumor/leukemia/lymphoma (**Table 1**). Sensitivity analysis that replaced continuous Charlson-Romano index with categorized scale (Model 2) or individual comorbidities plus hyperlipidemia, coronary artery disease and hypertension (Model 3) confirmed the findings from the main analyses with minimal attenuation of hazard ratios.

Conclusion: Gout was independently associated with 1.5-fold higher risk of uveitis in the older individuals after adjustment for demographics, comorbidity and medications, and the risk could be between 1.4 to 1.9-fold higher risk. Future studies need to confirm this finding and evaluate the underlying mechanism of this novel association.

Table 1. Multivariable-adjusted association of gout and other risk factors with incident uveitis

	Multivariable-adjusted (Model 1) *		Multivariable-adjusted (Model 2) *		Multivariable-adjusted (Model 3) *	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (in years)						
65 - <75	Ref		Ref		Ref	
75 - <85	1.21 (1.16, 1.27)	<0.0001	1.19 (1.14, 1.25)	<0.0001	1.19 (1.13, 1.24)	<0.0001
≥85	1.16 (1.06, 1.27)	0.001	1.14 (1.05, 1.24)	0.003	1.20 (1.10, 1.31)	<0.0001
Gender						
Male	Ref		Ref		Ref	
Female	1.16 (1.11, 1.21)	<0.0001	1.15 (1.10, 1.21)	<0.0001	1.12 (1.07, 1.18)	<0.0001
Race						
White	Ref		Ref		Ref	
Black	2.05 (1.93, 2.17)	<0.0001	2.07 (1.95, 2.20)	<0.0001	2.05 (1.93, 2.18)	<0.0001
Other	1.35 (1.24, 1.46)	<0.0001	1.38 (1.27, 1.49)	<0.0001	1.37 (1.27, 1.49)	<0.0001
Charlson-Romano score, per unit change	1.11 (1.11, 1.12)	<0.0001	N/A		N/A	
Charlson-Romano score						
0	N/A		Ref		N/A	
1			1.69 (1.58, 1.80)	<0.0001		
≥2			1.93 (1.84, 2.02)	<0.0001		
Gout	1.53 (1.39, 1.69)	<0.0001	1.51 (1.37, 1.66)	<0.0001	1.39 (1.26, 1.54)	<0.0001

* Model 1 included Charlson-Romano score as a continuous variable; Model 2 replaced it with categorized Charlson-Romano score; and Model 3 replaced it with each of the 17 Charlson-Romano comorbidities. All models were also adjusted for medications for cardiovascular diseases (statins, beta-blockers, diuretics, ACE-inhibitors) and for urate-lowering therapies for gout (allopurinol, febuxostat).

N/A, not applicable; HR, Hazard ratio; CI, confidence interval; Ref, referent category

Bold represents statistical significance, with a P-value <0.05

Disclosure: J. A. Singh, Takeda, Savient, 2,Savient, Takeda, Regeneron, Merz, Iroko, Bioiberica, Crealta/Horizon and Allergan pharmaceuticals, WebMD, UBM LLC, Medscape , Fidia pharmaceuticals and the American College of Rheumatology, 5; J. Cleveland, None.

Abstract Number: 945

Pain, Functional Limitations and Physical Activity Participation Trajectories in Patients with Symptomatic Knee and Hip Osteoarthritis: A Multi-Trajectory Analysis

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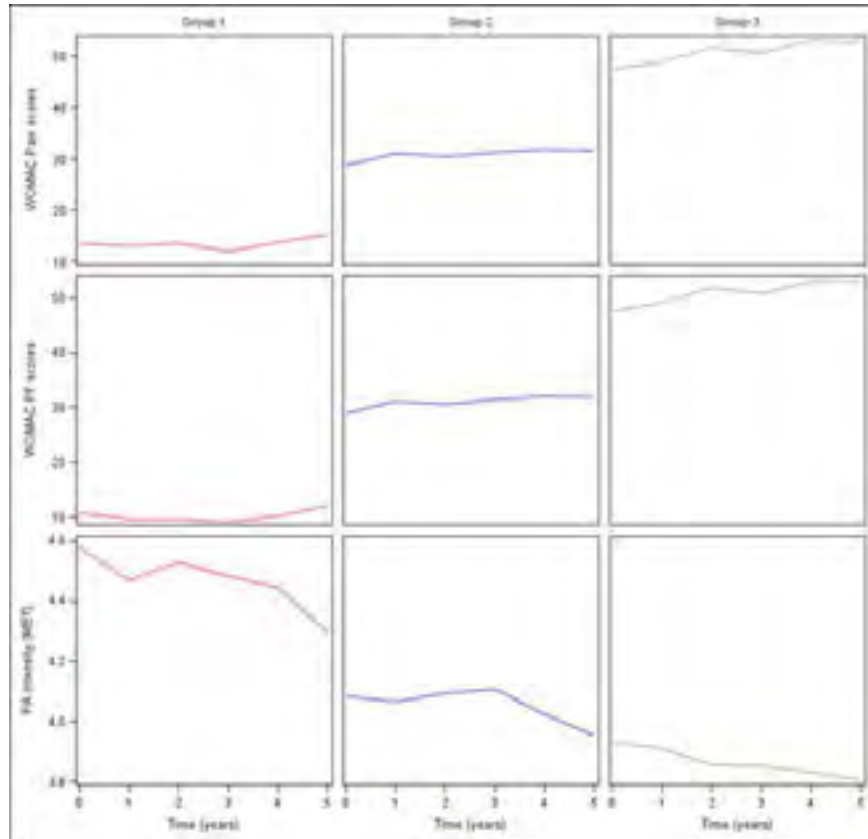
SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Epidemiology and Public Health I: Morbidity and Mortality

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM



Background/Purpose: The aims of this study were to identify homogeneous subgroups of knee and/or hip osteoarthritis (OA) patients with distinct trajectories of the combination of pain, physical function (PF) and physical activity (PA) intensity and to identify the baseline predictive factors associated with these trajectories.

Methods: The KHOALA cohort is a French population-based multicenter cohort of 878 patients with symptomatic knee and/or hip OA (ACR criteria), aged between 40 and 75 years old. Three outcomes assessed annually over 5 years were modeled in a multi-trajectory model. Pain and PF were measured with the WOMAC questionnaire while PA intensity (in Metabolic Equivalent of Task, MET) was assessed by the Modifiable Activity Questionnaire. First, trajectory models were estimated with varying number of groups for each of the outcomes separately and then, included in the multi-trajectory model. The selection of the optimal models was based on maximization of the Bayesian information criterion, the proportion of patients in each group (>5%) and the statistical significance of the equation modeled. Multinomial logistic regressions were performed to identify the predictive baseline characteristics associated with each group and were adjusted for sociodemographic and clinical factors.

Results: Comparison of separate trajectories of pain and PF showed that 2/3 of patients (66.7%) included in the trajectory of severe functional limitations (FL) also belonged to the more severe pain trajectory (Cramer V statistic = 0.59). Group-based multi-trajectory modeling revealed 3 distinct trajectories of pain, PF and PA intensity (Figure 1). The first (N=199, 32.1%) included patients with low pain levels, no FL and who practiced intense PA. The second (N=259, 41.8%) included patients with moderate levels of pain and FL; who practiced a less intense PA. Patients included in the third group (N=162, 26.1%) had severe pain, severe FL and a low-intensity practice. Overall, a decrease in PA intensity was observed in all groups over 5 years, even in the first group. In multivariate analyses, female sex (Odds ratio [OR]=2.93, 95% confidence interval [CI]=1.63-5.27), an increasing age (OR=1.04, 95%CI=1.01-1.08), a primary education level (OR=2.91, 95%CI=1.30-6.54), a high number of comorbidities (OR=1.50, 95%CI=1.23-1.83), a low vitality score (reflecting a high level of fatigue; OR=0.93, 95%CI=0.91-0.95) and a high Kellgren grade (reflecting a high radiological severity; OR=4.07, 95%CI=1.87-8.84) were associated with the third group membership.

Conclusion: Over 5 years, we identified 3 distinct trajectories combining pain, PF and PA intensity. The management of comorbidities and fatigue and slowing radiological progression seem important to maintain PF, limit pain and maintain intensity of PA practice in patients with symptomatic knee and/or hip OA.

Disclosure: M. Wiecek, None; C. Rotonda, None; F. Guillemin, None; A. C. Rat, None.

Short-Term Safety of Fractional-Dose Yellow Fever Vaccination in Autoimmune Rheumatic Diseases and Kinetics of White Blood Cells

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Infection-related Rheumatic Disease

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

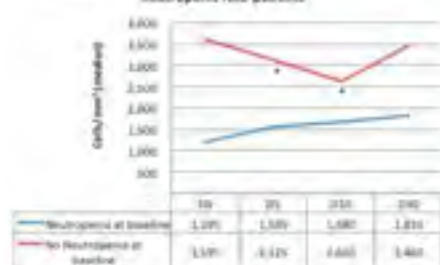
Background/Purpose: Brazil faced a new yellow fever (YFV) outbreak that reached the state of São Paulo in December 2016. The fractional dose was used in this campaign to extend vaccine supplies. Due to the YFV high risk of fatality, the vaccination may be also indicated for autoimmune rheumatic disease (ARD) patients under low immunosuppression. There is, however, no prospective evaluation of YFV safety in these patients. The aim of this study was to evaluate the short-term safety of immunization with the fractional YFV in patients with ARDs.

Methods: One hundred and sixty adult ARD patients [65 systemic lupus erythematosus, 11 rheumatoid arthritis, 8 ankylosing spondylitis, 16 systemic sclerosis, 2 psoriatic arthritis, 8 Behçet's disease, 4 mixed connective tissue disease, 13 primary antiphospholipid syndrome, 7 dermatomyositis/polymyositis, 11 primary Sjögren's syndrome, 3 Takayasu's arteritis, and 2 granulomatosis with polyangiitis, 10 juvenile idiopathic arthritis] and 160 age and gender-matched healthy controls

Figure 1A. Neutrophils and lymphocytes in Control and ARD Patients groups at the day and after fractional YFV

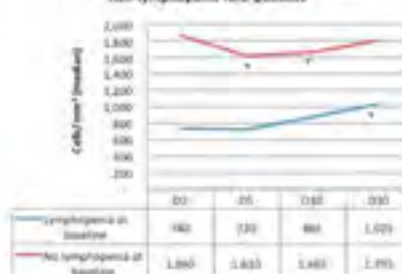


Figure 1B. Neutrophils kinetics in neutropenic and non-neutropenic ARD patients



* P<0.05 - ANOVA (longitudinal analysis - D0 as reference)

Figure 1C. Lymphocytes kinetics in lymphopenic and non-lymphopenic ARD patients



were vaccinated with a 5-fold fractional-dose (0.1mL, subcutaneous route) of the 17DD YFV. All participants were evaluated at entry (D0), 5 days (D5), 10 days (D10) and 30 days (D30) post-vaccination for clinical and laboratory parameters (AST, ALT, complete blood count, CRP) and disease activity according to specific tools for each ARD. Participants were instructed to seek medical attention, if necessary, and a rigorous follow-up of adverse events was performed during the first 30 days after vaccination. Serious adverse events were defined as those resulting in hospitalization or death. ANOVA was performed for longitudinal analysis of laboratory exams.

Results: All disease activity parameters of ARD patients (SLEDAI-2K, DAS28, BASDAI, ASDAS, BR-BDCAF, MMT, ESSDAI, BVAS, ESR and CRP) remained stable 30 days after YFV ($P < 0.05$). ARD patients had higher frequencies of fever, muscle pain, abdominal pain, arthralgia and diarrhea compared to controls ($p < 0.05$). Kinetics of neutrophils and lymphocytes in patients and controls had a similar pattern ($r = +0.99$ and $r = +0.81$) characterized by a significant transient decrease in neutrophils (D10) and lymphocytes (D5) and a full recovery to baseline levels for both in D30 (Figure 1A). In contrast, kinetics of ARD patients with neutropenia/lymphopenia at baseline had a distinct pattern with stable/increase in levels of these cells (Figures 1B and 1C). No serious adverse effect was reported neither mild abnormalities in liver enzymes or renal function.

Conclusion: The 17DD YFV was safe and did not induce flares in ARD patients with low immunosuppression and may be indicated in yellow fever outbreak situations. Further studies are necessary to determine if the observed distinct immune microenvironment kinetics will be relevant for YFV viremia and/or vaccine seroconversion (ClinicalTrials.gov, NCT03430388)

Disclosure: A. C. Tonacio, None; T. N. Pedrosa, None; J. C. Ferreira Filho, None; M. M. Sampaio-Barros, None; R. Fuller, None; M. Lopes, None; E. F. Borba, None; S. G. Pasoto, None, 2; E. Neves, None; C. A. Silva, Fundação de Amparo à Pesquisa do Estado de São Paulo, 2; R. M. R. Pereira, None, 2; P. Sampaio-Barros, None; D. Andrade, None; A. C. Ribeiro, None; J. C. Moraes, None; S. K. Shinjo, None; R. Miossi, None; H. Higashino, None; S. Costa, None; A. Duarte, None; E. P. Leon, None; M. Lopes, None; N. E. Aikawa, None, 2; E. Bonfa, Fundação de Amparo à Pesquisa do Estado de São Paulo, 2, Conselho Nacional de Desenvolvimento Científico e Tecnológico, 2.

Abstract Number: 947

Clinical Characteristics and Outcome after Treatment of a National Cohort of PCR-Positive Lyme Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Infection-related Rheumatic Disease

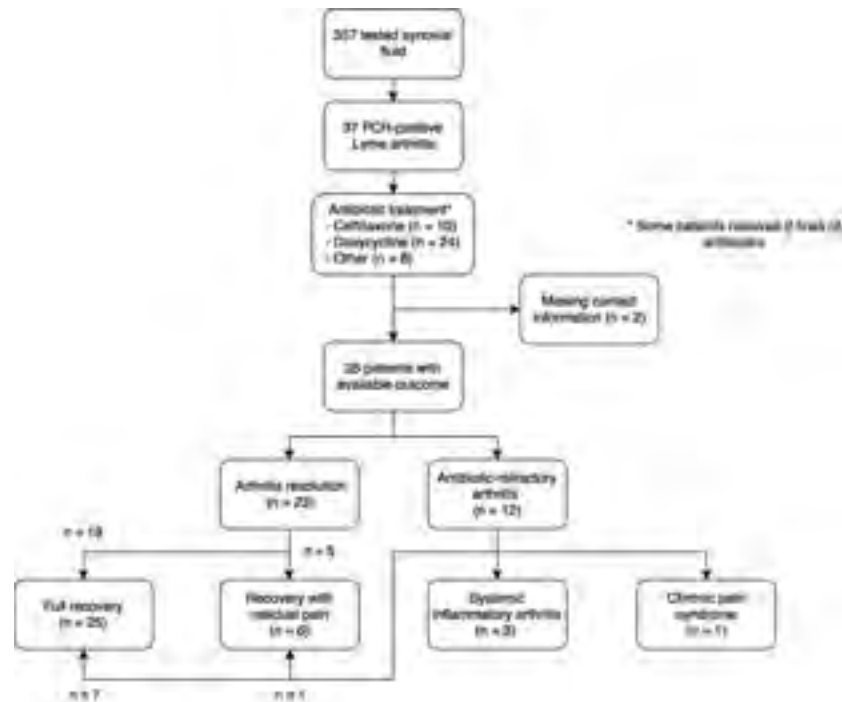
Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Lyme arthritis (LA) is a disseminated *Borrelia* infection whose prevalence is lower in Europe than in the USA, probably because of difference in *Borrelia* species ecology. Few data concerning treatment efficacy and long-term outcome of LA in Europe are available. The aim of our study was to describe clinical characteristics and treatment outcomes of a national cohort of patients with LA confirmed with synovial fluid PCR.

Methods: We conducted a retrospective observational study using the French *Borrelia* reference centre database. Patients presenting with a PCR positive for *Borrelia* DNA in their synovial fluid between 2011 and 2016 were included. PCR-positive patients were offered by their referring physician to participate to a standardized telephonic interview. Patients' medical files were also retrieved. The main objectives were to describe patient characteristics, disease presentation and outcomes after antibiotic treatment.

Results: Between 2011 and 2016, among 358 synovial fluids tested at the national reference center, 37 were positive for *Borrelia* DNA. Among these patients, 35 were contacted (2 missing contact information). Median age was 36 years with 31% minors and 63% men. Tick exposure was reported by 88% patients whereas tick bite and erythema migrans were only reported in 40% (10/25) and 14% (3/21), respectively. The presentation was monoarticular in 91% (32/35) cases and oligoarticular in others. The knee was involved in 97% (34/35) cases and 21% presented fever. The diagnosis was often delayed with a median time from symptom onset to diagnosis of 3 months (range 1 to 112, figure 1). The serology performed before or at the time of the PCR testing was IgG-positive in all cases but only IgM-positive in 40%. All but one positive IgG serologies were also positive with Western-Blot. In the synovial fluid, the identified species of *Borrelia* were *B. burgdorferi sensu stricto*, *B. garinii* and *B. afzelii* in 54%,



29% et 17% of cases, respectively. Antibiotics prescribed were mostly doxycycline and ceftriaxone in 17 and 9 patients, respectively, sometime in combination. Follow-up data were available for 35 patients with a median follow-up time of 27 months (range 1-73). Although proper antibiotic treatment, 34% (12/35) of patients had persistent synovitis lasting at least 2 month justifying intra-articular glucocorticoid use in 75%, with good efficacy. Three patients developed chronic inflammatory arthritis leading to the introduction of DMARDs with good outcomes.

Conclusion: Our study present the biggest European cohort of PCR-positive Lyme arthritis. Although proper antibiotic treatment, one third of patients developed persistent synovitis of the affected joint necessitating anti-inflammatory medication and a small proportion of patients developed inflammatory oligo or polyarthritis justifying DMARD introduction.

Disclosure: M. Scherlinger, None; A. Grillon, None; J. Sibilia, None; B. Jaulhac, None; L. Arnaud, None.

Abstract Number: 948

Effects of Antiretroviral Therapy with Tenofovir and Other Antiretroviral Drugs on the Inflammatory State and Bone Remodeling on Newly Diagnosed HIV-Patients at Basal and 3 Months after Starting Treatment

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Infection-related Rheumatic Disease

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Bone alterations have been observed in the course of HIV infection, with a notable decreases in bone mineral density (BMD) and fractures due to fragility. Anti-retroviral drugs may have a direct or indirect effect on

bone cells, via alterations in RANK/RANKL, cytokines profile, mitochondrial function and changes in phosphate/Vitamin D metabolism. The aim of this study was to evaluate the deleterious effects in bone metabolism and systemic inflammation, produced by Tenofovir vs. other HIV treatment in naïve patients.

Methods: A cohort of 114 HIV-naïve patients were included in the study. Patients were separated by treatment: 1) Tenofovir Disoproxil Fumarate (TDF) (n=23), 2) Tenofovir Alafenamide (TAF) (n=22), 3) Abacavir/Dolutegravir/Lamivudin combo (ADL) (n=39), 4) Protease Inhibitors (PI) (n=12), and 5) patients who changed treatment during the study (n=18). Epidemiological, immunological, and metabolic parameters, as well as BMD were evaluated. Bone markers, proinflammatory and anti-inflammatory cytokines were analyzed in serum at basal and 3 months post-treatment by MILLIPLEX® MAP Luminex® Technology. The diagnosis of osteopenia/osteoporosis was made according to the WHO criteria.

Results: The mean age was 34.7 years (range 19-50 years). 91% was on CDC stage A. The median CD4 was 481 cell/ μ L (IQR=339.5), 10% had CD4 under 200 cell/ μ L, and 42% had CD4/CD8 under 0.4. 71% (71/143 p) had low Vitamin D levels, 4% low BMI (<18.5). Osteopenia (op) or osteoporosis (OP) was found in 53% and 11% respectively. In the serum we found differences at molecular level among different treatments (Tables 1 and 2). We observed that both TDF and TAF presented an osteoclastic profile but not the other treatments. All treatments reduce proinflammatory cytokines 3 months after treatment but no differences among treatments were found.

Treatment	BONE MARKERS (pg/ml)									
	OPN		OPG		RANKL		DKK1		SOST	
	Basal	3 m	Basal	3 m	Basal	3 m	Basal	3 m	Basal	3 m
TDF (n=23)	11811±10179	13441±9716	239.2±133.7	156.9±107.1	77.33±50.6	98.18±60.60	536.47±377.9	378.28±284.7	1916±1126	1677±1147
TAF (n=22)	12110±6251	14832±7098	236.8±127.7	173.2±78.57	123.9±131.7	96.18±139	436.3±284.5	324.2±198.7	1428±893.9	1081±538.1
ADL (n=39)	14632±8955	14835±10371	282.2±177.3	249.3±256.5	89.89±100.2	51.60±50.19	622.7±562.4	427±366.9	2108±1509	1967±1656
PI (n=12)	16725±5928	16342±7284	216.9±67.57	256.7±132.6	87.73±103.9	85.44±113.5	421.4±140.6	403.1±169.6	1166±614.7	1618±603
Change of treatment (n=18)	17080±7111	17014±6026	262.1±121.5	211.3±81.14	67.8±108.1	16.09±26.86	489.8±227.3	354.5±165.2	1336±443.4	1115±440.4

Treatment	CYTOKINES (pg/ml)									
	IL2		INFg		IL4		IL10		IL1-b	
	Basal	3 m	Basal	3 m	Basal	3 m	Basal	3 m	Basal	3 m
TDF (n=23)	2.3±1.9	2.24±1.62	32±44	27.80±373.14	48.47±50.21	37.34±29.03	28.10±30.04	27±29.4	1±1.1	1.14±1.12
TAF (n=22)	1.53±0.76	1.9±1.1	5.71±3.46	6.77±3.83	31.44±16.34	33.48±15.78	11.36±11.47	13.83±10.32	0.54±0.37	0.62±0.35
ADL (n=39)	2.5±2	2.1±1.4	35.6±59.2	19.83±30.63	51.13±51.67	38.73±28.96	32.95±40.49	19.20±17.96	1.24±1.44	0.91±0.78
PI (n=12)	2.11±0.73	1.94±1	5.5±2.6	5.69±2.56	41.71±24.26	42.97±23.06	17.46±9.69	15.58±13.31	0.59±0.27	0.72±0.42
Change of treatment (n=18)	1.91±0.78	2.14±0.93	7±3	7.5±3.5	38.34±13.77	43.89±15.24	18.94±13.48	19.74±0.30	0.67±0.31	0.73±0.35

Conclusion: HIV-naïve patients under 50 years have a high prevalence of osteopenia/osteoporosis, and patients treated with Tenofovir had greater bone deterioration than other patients.

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Abstract Number: 949

Long-Term Rheumatic and Musculoskeletal Disorders Associated to Ebola Virus Infection

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Infection-related Rheumatic Disease

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Between December 2013 and April 2016, the largest epidemic of Ebola virus disease (EVD) to date generated more than 28,000 cases and more than 11,000 deaths in the large, mobile populations of Guinea, Liberia, and Sierra Leone. However, based on the small size of past outbreaks in remote and resource-poor locations that hinder systematic study, there is little knowledge of the frequency of various sequelae post-EVD, their pathogenesis, and optimum treatment. Some short-term and long-term health problems have been reported such as arthralgia and/or myalgia¹.

Methods: The Postebogui study is a prospective multicenter cohort aiming to evaluate the long-term clinical, psychological and socio-behavioral outcomes of EVD survivors infected during the 2014-2015 outbreaks². Nearly 80% of survivors in Guinea were included in the Postebogui cohort. We organized the systematic rheumatic screening of all patients included in the Postebogui cohort (Conakry) regardless of the disease status. A musculoskeletal (MS) Doppler ultrasound (DUS) assessment was performed (Esaote MyLab). Data were collected using a standardized questionnaire and entered into an electronic database.

Results: Of the 382 participants included in the Postebogui cohort in Conakry, 313 patients underwent a complete interview by a rheumatologist nearly 3-year after viral infection: 36 patients never presented joint or muscle pain, 61 patients had experienced previous pain and 216 patients still reported chronic MS pain (69%). No demographic differences were found between both groups except that children significantly reported less chronic MS pain. In the painful group, 58% were female; median age was 29.1 years; median time from Ebola Treatment Center (ETC) discharge to rheumatologic examination was 36 months. Pain manifestations started before EVD for 41 patients (19%). Morning stiffness was present in 46% of patients. Patients had mechanical pain (48%), inflammatory pain (18%) or both (34%). Axial and peripheral were largely involved (84%). Large joints were most frequently affected (89%). Polyarticular presentations were predominant with a symmetrical pain distribution. Furthermore, 91% had at least one painful enthesitis. DUS showed 5 patients with tenosynovitis and 4 patients with synovitis but without hyperemia. One patient suffered with Pes anserine tendonitis. Diagnoses were mainly non-specific MS disorders (67%) and low back pain (39%). No rheumatoid arthritis was retained but axial spondyloarthritis with enthesitis was suspected in few cases (2%).

Conclusion: Our study provides the largest accurate description of MS disorders in the Post-Ebola syndrome with a long-term follow-up (3 year after Ebola infection). Rheumatic sequelae are frequent and pathophysiological mechanisms need to be explored in the future.

References: ¹Pers YM et al. Rheumatology 2017

²Etard JF et al. Lancet Infectious Diseases 2017

Disclosure: Y. M. PERS, None; A. DUBOIS, None; A. BARRY, None; M. SALL, None; M. SALIOU SOW, None; B. TAVERNE, None; L. MARCH, None; J. F. ETARD, None; M. BARRY, None; A. TOURE, None; E. DELAPORTE, None.

Abstract Number: 950

Ultrasonographic Examinations Show Highly Prevalent Abnormalities of Hamstring Tendons in Lyme Arthritis Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Infection-related Rheumatic Disease

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Lyme arthritis (LA), the most common late manifestation of Lyme disease, usually occurs months to up to 2 years after the initial infection. Joint involvement is characterized by proliferative synovitis predominantly affecting the knees. Most patients respond to antibiotic treatment, but a subset have persistent inflammatory arthritis despite resolution of the infection and others may have continued pain despite resolution of synovitis on examination. It is unclear why arthritis onset is delayed after initial spirochetal infection and hematogenous dissemination. It has been postulated that prior to clinical synovitis, less well-vascularized tissues such as tendons or ligaments may harbor spirochetes. Imaging

studies, such as ultrasound (US) may offer further insights, however information is limited about US characteristics of Lyme arthritis.

Methods: We retrospectively reviewed images and clinical characteristics of adult LA patients who underwent musculoskeletal US examinations of the knee joints in the Rheumatology Clinic at Massachusetts General Hospital. Examinations were included when complete diagnostic examination was performed (including longitudinal and transverse suprapatellar views, medial and lateral longitudinal views, posterior transverse and longitudinal views). All LA patients met the diagnostic criteria of the Centers for Disease Control and Prevention (CDC) for Lyme disease. Images from control subjects with osteoarthritis were reviewed as a comparison group. All images were reviewed by 2 ultrasound-trained rheumatologists with inter-reader agreement.

Results: Forty-nine knee examinations were reviewed in 31 individual LA patients. The median age of the patients was 52, and 18 of the 31 patients (58%) were male. Of the LA patients, the majority, 24, had arthritis which was refractory to oral and IV antibiotic treatment, while 7 had arthritis which was responsive to oral or IV antibiotic treatment. The median semi-quantitative synovitis score was 2 (range 0 to 3). Effusion was seen in 67% of examinations and presence of a Baker's cyst was observed in one-quarter of examinations. Presence of radiographic erosion was observed in only one patient. Of the 31 patients, 28 (90%) were found to have abnormalities in posterior knee tendons, most commonly the semimembranosus, and less frequently the semitendinosus, tendons. These abnormalities included hyperechoic deposits with tendinopathy and tenosynovitis. Abnormalities were rarely seen in other tendons and were not seen in control subjects. In several patients who had serial examinations, the tendon abnormalities persisted although synovitis measures improved.

Conclusion: It has not been previously recognized that hamstring tendons are commonly affected in LA. Calcific tendinitis and tendinopathy may contribute to the persistence of knee pain in some LA patients despite resolution of synovial inflammation. Further, evidence of calcification suggests that tendons may be a prior site of *B. burgdorferi* infection. As a privileged site, tendons may initially allow protection of spirochetes from the immune system and may contribute to seeding of synovium later in the disease.

Disclosure: S. Arvikar, None; M. Kohler, Springer publishing, 7; A. Oza, None; A. C. Steere, None.

Abstract Number: 951

IFN-Gamma Production in Lyme Arthritis Synovial Tissue Promotes Differentiation of Fibroblast-like Synoviocytes into Inflammatory Effector Cells

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Infection-related Rheumatic Disease

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Lyme arthritis (LA), a late-disease manifestation of *Borrelia burgdorferi* infection, usually responds to antibiotic therapy. However, some patients may develop a proliferative synovitis lasting months to several years after spirochetal killing, called post-infectious LA. Their synovial lesion is associated with robust expression of interferon (IFN)-responsive genes and suppressed expression of genes associated wound healing. However, it is not yet clear which cell populations contribute to these LA-associated gene signatures.

Methods: Hematopoietic and stromal cell populations in the post-infectious LA synovial lesion were analyzed at the cellular level by flow cytometric analysis and immunofluorescence microscopy. Observations in human patients were validated *in vitro* using primary human fibroblast-like synoviocytes (FLS) derived from post-infectious LA synovial tissue, and *ex vivo* using murine LA models.

Results: T cells and NK cells were highly abundant in synovial tissue and were IFN γ -positive by intracellular cytokine staining. HLA-DR+ FLS were present throughout the synovial lesion, particularly in areas of inflammation. Primary human FLS stimulated with IFN γ expressed HLA-DR molecules and a large number of genes associated with autoimmune/autoinflammatory inflammatory responses, similar to *ex vivo* findings. Co-stimulation of FLS with *B. burgdorferi* and IFN γ potentiated a significantly greater inflammatory cytokine and chemokine response than either *B. burgdorferi* or IFN γ stimulation alone. Tissue from joints of *B. burgdorferi*-infected C57BL/6 mice, which develop mildly inflammatory LA, had a wound-healing myofibroblast phenotype, whereas tissue from severely arthritogenic C3H/HeN and Il10^{-/-} (B6) mice had a pro-inflammatory phenotype, dominated by excessive IFN responses, similar to human findings.

Conclusion: These results suggest that post-infectious LA may be initiated during infection if accompanied by dysregulated IFN γ responses. Under these conditions, *B. burgdorferi* infection may lead to differentiation of FLS into a highly inflammatory phenotype that may persist if IFN γ -producing lymphocytes are chronically activated within the synovial lesion after the infection is cleared, resulting in excessive inflammation and tissue damage.

Disclosure: R. Lochhead, None; D. Ordonez-Del Valle, None; S. Arvikar, None; A. C. Steere, None; K. Strle, None.

Abstract Number: 952

Effusion-Synovitis and Infrapatellar Fat Pad Edema Differentiate Accelerated Knee Osteoarthritis: Data from the Osteoarthritis Initiative

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Accelerated kneeosteoarthritis (AKOA) is a unique endotype of knee osteoarthritis (KOA) that is characterized by a sudden onset of advance-stage disease and greater prodromal knee symptoms than those who develop a more gradual onset of KOA. Effusion-synovitis and infrapatellar fat pad (IFP) edema, may be potential early markers of AKOA because both are associated with pain and predict KOA incidence or progression. We aimed to determine whether greater effusion-synovitis and IFP edema on MRI differentiate incident AKOA from a gradual onset of KOA or no KOA.

Methods: We classified 3sex-matched groups of participants in the Osteoarthritis Initiative who had a knee without radiographic KOA at baseline (Kellgren-Lawrence [KL]<2;n=125/group): 1) AKOA: ≥ 1 knee progressed to KL grade ≥ 3 within 48 months, 2) common KOA: ≥ 1 knee increased in radiographic scoring within 48 months without meeting AKOA criteria, 3) no KOA: both knees had the same KL grade at baseline and 48-months. Observation period included up to 2 years before and after an index visit, which was when the AKOA or common KOA criteria were met (no KOA index visit was matched to AKOA). Two musculoskeletal radiologists reported presence of IFP edema using the MOAKS grading system. Independent readers used a semi-automated method to segment intermediate-weighted fat-suppressed MRIs for effusion-synovitis volume and measurements were finalized by the senior reader. We used generalized linear mixed models with group and time as independent variables, as well as tested a group-by-time interaction.

Results: Table 1 provides descriptive characteristics of each group. Starting at 2 years before disease onset and continuing to up to 2 years after onset, adults who developed AKOA had greater effusion-synovitis volume compared to adults with common or no KOA ($p=0.015, p=0.003$; Figure 1). Individuals who developed AKOA have at least two times the odds of having IFP edema compared to those with no KOA starting at 2 years prior to disease onset, and those with common KOA starting at 1 year prior to disease onset (Table 2, Figure 1).

Conclusion: As early as 2 years prior to disease onset AKOA is characterized by IFP edema and/or greater effusion-synovitis. Clinicians should be aware that people with greater effusion-synovitis and/or IFP edema in the absence of radiographic KOA may be at high risk for AKOA.

Figure 1. Effusion-Synovitis Volume and Infrapatellar Fat Pad (IFP) Edema Among Those with Accelerated Knee Osteoarthritis (AKOA), Common Knee Osteoarthritis (KOA), and No KOA.

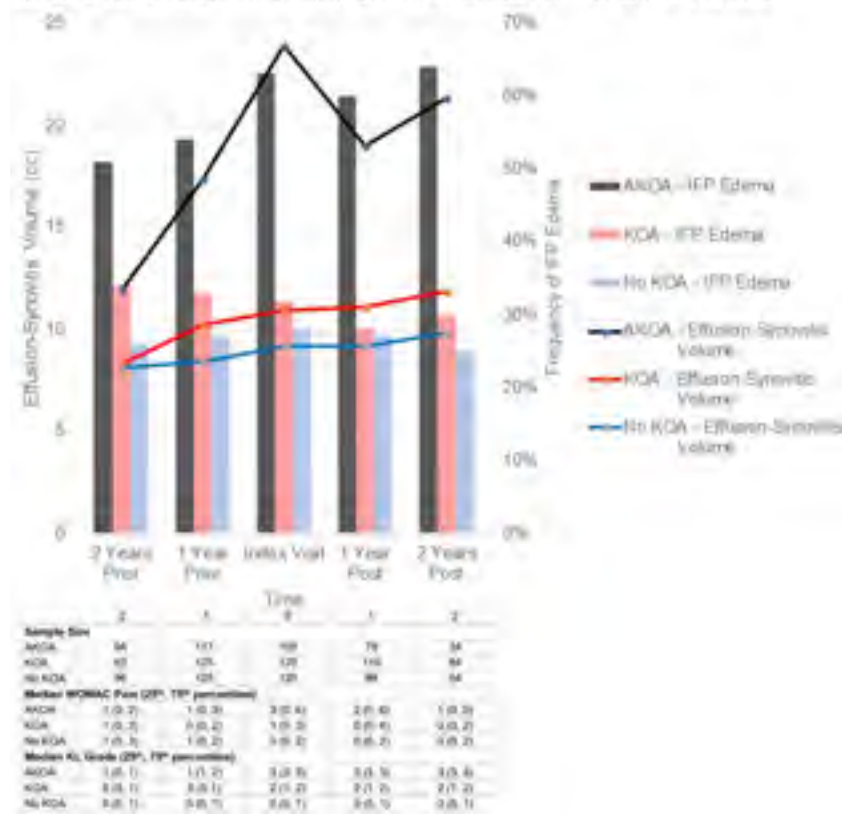


Table 1 Descriptive Characteristics of those with Accelerated Knee Osteoarthritis (AKOA), Common Knee Osteoarthritis (KOA), and No KOA at Osteoarthritis Initiative Baseline

Variables (means, SD; except where noted)	AKOA (n=125)	Common KOA (n=125)	No KOA (n=125)
Females (n, %)	79 (63%)	79 (63%)	79 (63%)
Index knee KL Grade=0 (n, %)	42 (34%)	71 (57%)	92 (74%)
Patellofemoral Osteoarthritis (MR-based) (n, %)	88 (75%)	84 (69%)	80 (66%)
Frequent knee pain in past 12 months (n, %)	44 (35%)	49 (39%)	30 (24%)
Age (years)	62.5 (8.5)	58.4 (8.4)	57.3 (8.2)
Body mass index (kg/m ²)	29.7 (4.6)	28.1 (4.4)	26.9 (4.4)
Global impact rating (0 to 10; higher score=greater impact)	1.7 (1.9)	1.1 (1.5)	0.8 (1.1)
How many days limited activities in past 30 days (0 to 30)?	3.2 (7.3)	1.7 (4.8)	1.4 (4.3)
WOMAC pain (0 to 20; higher score=more pain)	2.3 (3.1)	1.8 (2.3)	1.6 (2.4)

Notes: SD = standard deviation, KL = Kellgren-Lawrence, MR = magnetic resonanceTable 2 Adults with Accelerated Knee Osteoarthritis (AKOA) Have Twice the Odds of Having Infrapatellar Fat Pad Edema Than those with Common Knee Osteoarthritis (KOA), and No KOA (n = 125/group)

Outcome	Visit	AKOA vs No KOA (REF)	Common KOA vs No KOA (REF)	AKOA vs Common KOA (REF)
Infrapatellar Fat Pad Edema (OR [95% CI])				
	-2	2.07 (1.14, 3.78)	1.67 (0.90, 3.08)	1.24 (0.69, 2.25)
	-1	3.06 (1.71, 5.48)	1.46 (0.82, 2.60)	2.10 (1.19, 3.69)
	Index	3.68 (2.07, 6.57)	1.18 (0.68, 2.06)	3.12 (1.79, 5.44)
	1	3.66 (2.04, 6.57)	1.05 (0.60, 1.85)	3.48 (1.97, 6.16)
	2	3.95 (2.09, 7.46)	1.06 (0.59, 1.92)	3.72 (2.01, 6.87)

Notes: OR=Odds Ratio. CI=Confidence Interval. REF= reference group. Group-by-time interaction: p<0.001). Infrapatellar fat pad edema was assessed on intermediate-weighted fat-suppressed magnetic resonance images.

Disclosure: J. Davis, None; R. J. Ward, None; J. MacKay, None; B. Lu, None; L. L. Price, None; T. E. McAlindon, None; C. B. Eaton, None; M. Barbe, None; G. H. Lo, None; M. Harkey, None; J. B. Driban, None.

Evaluating MRI-Detected Knee Inflammation Prior to Total Knee Replacement As a Predictive Biomarker of Clinically Important Pain Reduction Two Years Later

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical

Session Type: ACR Concurrent Abstract Session

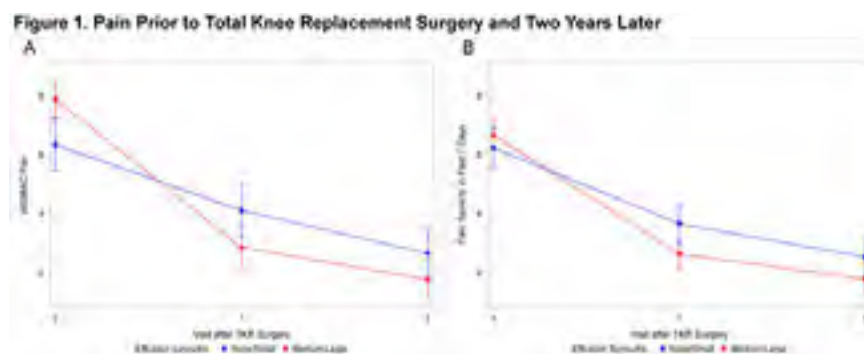
Session Time: 4:30PM-6:00PM

Background/Purpose: Some patients do not experience clinical improvement after total knee replacement (TKR). Presence of structural abnormalities on MRI before surgery may inform pain prognosis following TKR. Our objective was to evaluate MRI-detected knee inflammation before TKR as a risk factor for failure to experience clinically important pain reduction two years later.

Methods: Osteoarthritis Initiative participants with MRI assessment at the clinic visit before TKR and 2 year follow-up post-TKR, were selected. Effusion-synovitis (ES) and Hoffa synovitis (HS) on 3T MRI were scored using the MRI Osteoarthritis Knee Score (MOAKS). Pain was assessed at the clinic visit before TKR as well as 2 years later, with WOMAC pain (0-20) and knee pain severity in the past 7 days (0-10). Mean WOMAC pain and knee pain severity before TKR and 2 years later were estimated using a mixed model for repeated measures. Clinically important reduction in WOMAC pain (-1.5) and pain severity on NRS (-1.7) were defined based on previous literature. Participants with no/small ES/HS and those with medium/large ES/HS were compared based on the proportion reporting no clinically important pain reduction; odds ratios were estimated with logistic regression, adjusted for age, sex, race, and BMI.

Results: Participants (n=156) were predominately white(87%), women (60%), with mean age 66.2 years (SD 8.6) and mean BMI of 29.9 kg/m²(SD 5.1). Before TKR, 62% of the knees had medium/large ES, with higher mean WOMAC pain score compared to those with no/small ES (7.9 [95%CI: 7.1, 8.6] vs. 6.3 [95%CI:5.3, 7.3]). Two years following TKR, the mean WOMAC pain was modestly higher for knees that had no/small ES before TKR (1.8 [95%CI: 1.2, 2.4] vs 2.7 [95%CI:1.9, 3.4]). Knees with medium/large ES prior to TKR had greater pain reduction compared to those with no/small ES (6.7 [95%CI: 5.5, 7.9] vs 4.0 [95%CI: 2.8, 5.3]), a significant difference in mean pain reduction of 2.7 [95%CI: 1.3, 4.1] p=0.002 (Figure 1A). Participants with no/small pre-operative ES had an increased odds of reporting no clinically important pain reduction compared to participants with medium/large ES (29% vs 13%; OR=2.98, 95%CI: 1.26, 7.04). Similarly, knees with no/small ES had less mean pain severity reduction (p=0.006; Figure 1B), and with increased odds of no clinically important pain reduction (27% vs 10%; OR=4.35, 95%CI: 1.69, 11.23). We observed a similar trend for HS, detected in 37% of knees, though pain reduction was not significantly different between the groups (p=0.07).

Conclusion: Participants with no/small ES on MRI before TKR reported less pain reduction 2 years later compared to those with medium/large ES, and had significantly greater odds of no clinically important pain reduction following TKR.



Pre-operative ES, potentially in combination with other features of MRI-detected structural abnormalities, may serve as predictive biomarkers of pain reduction following TKR.

Disclosure: M. Kaur, None; L. Zhou, None; E. L. Ashbeck, None; E. Vina, Astra Zeneca, 5; F. Roemer, BICL, 4; A. Guermazi, MerckSerono, 5, Genzyme, 5, AstraZeneca, 5, TissueGene, 5, OrthoTrophix, 5, Boston Imaging Core Lab (BICL), LLC, 9; D. J. Hunter, None; C. K. Kwok, None.

Abstract Number: 954

A New Way to Think about Composite Magnetic Resonance Imaging Scores to Measure Osteoarthritis Severity and Progression

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical

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Session Time: 4:30PM-6:00PM

Background/Purpose: For some rheumatologic diseases (e.g. lupus), separate scores evaluate cumulative damage and disease activity. No such strategy exists for osteoarthritis (OA). The prevailing approach to evaluate OA focuses on individual structural features or developing composite scores. Our group aimed to define an MRI composite score that accounted common features of knee OA: articular cartilage damage, bone marrow lesions (BMLs), and effusion-synovitis volume. However, we struggled to find such a composite score. We had greater success when we considered OA from the perspective of measuring a cumulative damage score and a disease activity score. The cumulative damage score – based on articular cartilage – measures damage over time and does not wax and wane. In contrast, the disease activity score – based on BMLs and effusion-synovitis – fluctuates over days or weeks. We aimed to evaluate the construct validity of these two scores.

Methods: A convenience sample of 197 participants in the Osteoarthritis Initiative with complete clinical, radiographic, and MRI data at baseline and 24-months was selected. We generated quantitative measures of articular cartilage using the Double-Echo Steady State sequence, and BML and effusion-synovitis volumes using the Intermediate Weighted Fat Suppressed sequences. We assessed BMLs and cartilage damage index at the medial and lateral patella, tibia, and femur. A single effusion-synovitis volume was assessed. All MRI measures were standardized to bone width, and the 2-year difference was standardized so all measurements were on the same scale. The cumulative damage score was calculated by summing the change for each of the 6 locations with cartilage measures. Similarly, a disease activity score was calculated by summing the change in effusion-synovitis volume and the BML volumes for 6 regions. To evaluate construct validity we used logistic regression to estimate odds ratios (OR) for the outcomes of Kellgren Lawrence (KL) progression, joint-space width (JSW) progression (change > the median change) and worsening in WOMAC pain.

Results: Our sample was 54% female, 93% with KL grade 2 or 3, mean age of 61 years and mean body mass index of 30.1 kg/m². Mean WOMAC pain at baseline was 5.0. Worsening cumulative damage score was associated with KL progression (OR=1.52, 95% CI=1.11 to 2.08) and JSW progression (OR=1.67, 95% CI= 1.22 to 2.33), but not with WOMAC pain progression (Table). Conversely, the disease activity score was associated with WOMAC pain (OR=1.67, 95% CI= 1.14 to 2.45), but not KL or JSW progression.

Conclusion: The cumulative damage score (based on cartilage damage) had good construct validity for structural outcomes, while the disease activity score (based on BML and effusion-synovitis volumes) was associated with pain. This suggests that separate scores for cumulative damage and disease activity may have important utility in studying OA and provide critical insights into the disease.

Table 1 A Cumulative Damage Score was Associated with Structural Progression While a Disease Activity Score was Associated with Worsening Knee Pain.

Outcome	Knee Score	Odds Ratio (95% Confidence Interval)
KL Progression (any worsening in KL score)	Cumulative Damage Score	1.52 (1.11, 2.08)
	Disease Activity Score	1.17 (0.85,1.61)
JSW Progression (change greater than the median change)	Cumulative Damage Score	1.67 (1.22, 2.33)
	Disease Activity Score	1.02 (0.77, 1.35)
WOMAC pain worsening by at least 3 points	Cumulative Damage Score	1.27 (0.88, 1.82)
	Disease Activity Score	1.67 (1.14, 2.45)

The cartilage damage score was calculated by summing the change over 2 years for each of the 6 surfaces (standardized so that higher is worse). Similarly, the BML - effusion score was calculated by summing the change in effusion and the same in BMLs for each of the 6 surfaces (higher is worse).

KL = Kellgren-Lawrence, JSW = joint space width

Disclosure: L. L. Price, None; J. B. Driban, None; G. H. Lo, None; M. Zhang, None; M. P. LaValley, None; T. E. McAlindon, None.

Abstract Number: 955

Lower Limb Muscle Strength and Protection Against Functional Decline and Structural Worsening in Knee Osteoarthritis

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SESSION INFORMATION

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Background/Purpose: Lower limb muscle weakness has been proposed as a factor contributing to functional decline and structural progression. Hip abductor strengthening, in addition to quadriceps strengthening, has been advocated in exercise regimes for persons with knee OA. Individuals with hip weakness are likely to have concomitant quadriceps weakness. It is unknown if strong hip muscles confer additional benefits in the context of strong quadriceps. We examined associations of baseline hip abductor strength with functional decline 5 years later and cartilage damage worsening 2 years later, stratified by baseline quadriceps strength.

Methods: Participants all had knee OA (K/L ≥ 2) in at least one knee. Isometric hip abductor and knee extensor strength were measured at baseline, using a Biodex Dynamometer. Peak torques were averaged from 3 trials and normalized to body weight. LLFDI (Late-Life Function and Disability Instrument) and chair stand rate were recorded at baseline and 5-year follow-up; scores were analyzed using quintiles. Poor outcomes were defined as remaining in the same low-function quintiles (worst 2 quintiles) or moving into a worse quintile over 5-year follow-up. Participants underwent 3.0T MRI of both knees at baseline and 2 years later. Baseline-to-2-year cartilage damage progression, defined as any worsening of WOMS cartilage damage score, was assessed at each TF and PF articular surface. Knees graded K/L 4 or with severe PF narrowing at baseline were excluded. We assessed associations of baseline hip abductor strength with functional decline and cartilage damage worsening, using logistic regression with generalized estimating equations, adjusting for age, sex, pain, and K/L grade, stratified by strong vs. weak baseline quadriceps strength and by sex.

Results: 187 persons comprised the function outcome sample and 275 knees from 164 persons the structural outcome sample. In persons with stronger knees, greater hip abductor strength was associated with a reduced risk of poor function outcomes, especially in the chair stand rate and LLFDI disability frequency of participation (Table 1). Among stronger knees, greater hip abductor strength was associated with a reduced risk of cartilage damage worsening in the TF compartments (Table 2). For both outcomes, women-only analyses showed similar findings.

Conclusion: In the setting of strong quadriceps, greater hip abductor strength appeared to confer additional beneficial effects on both joint health and long-term function and disability, suggesting an important role for hip abductor strengthening in persons with knee OA.

Table 1 Person-based subgroup analyses stratified by baseline knee extensor strength and sex: Associations of baseline BW-normalized hip abductor strength (per 0.1 Nm/kg) with baseline-to-5-year poor outcomes by chair stand rate and LLFDI function and disability scores

[Odds Ratio (95% CI)]							
Hip Abductor Strength (Nm/kg)	Chair Stand Rate	LLFDI Total Function	LLFDI Basic Lower Extremity Function	LLFDI Advanced Lower Extremity Function	LLFDI Disability Frequency of Participation	LLFDI Disability Limitation	LLFDI Disability Instrumental Role Limitation
In persons with stronger knees (\geq median) (n = 94 persons)							
Percent with poor outcome	36.7%	50.0%	45.7%	56.4%	47.9%	37.2%	37.2%
Adjusted ^a	0.75** (0.59, 0.95)	0.90 (0.73, 1.11)	0.86 (0.70, 1.06)	0.93 (0.75, 1.14)	0.68** (0.53, 0.87)	0.83* (0.66, 1.03)	0.83* (0.66, 1.03)
In persons with weaker knees (< median) (n = 93 persons)							
Percent with poor outcome	44.7%	68.8%	68.8%	74.2%	49.5%	53.8%	54.8%
Adjusted ^a	0.92 (0.73, 1.16)	0.97 (0.75, 1.24)	0.97 (0.77, 1.23)	0.83 (0.64, 1.08)	1.02 (0.82, 1.27)	0.98 (0.79, 1.23)	1.16 (0.91, 1.47)
In women with stronger knees (\geq median in women) (n = 74 women§)							
Percent with poor outcome	34.7%	41.9%	40.5%	48.6%	39.2%	37.8%	37.8%
Adjusted ^b	0.83 (0.65, 1.06)	0.89 (0.71, 1.12)	0.94 (0.75, 1.18)	0.93 (0.75, 1.16)	0.71** (0.55, 0.93)	0.80* (0.62, 1.04)	0.80* (0.62, 1.04)
In women with weaker knees (< median in women) (n = 73 women§)							
Percent with poor outcome	43.1%	68.5%	68.5%	74.0%	49.3%	50.7%	52.1%
Adjusted ^b	0.84 (0.64, 1.10)	0.95 (0.72, 1.26)	0.90 (0.70, 1.17)	0.80 (0.60, 1.06)	1.07 (0.84, 1.36)	0.93 (0.72, 1.18)	1.06 (0.83, 1.35)

Abbreviations: LLFDI, Late Life Function Disability Instrument; CI, confidence interval; BW, body weight, BMI, body mass index; K/L, Kellgren/Lawrence

a Adjusted for age, sex, hip pain during strength testing, and K/L grade of the knee with worse baseline hip abductor strength

b Adjusted for age, hip pain during strength testing, and K/L grade of the knee with worse baseline hip abductor strength

§ A total of 147 women

** odds ratio (OR) with associated 95% CI that excludes 1.0 is considered statistically significant

* p<0.10

Table 2 Knee-based subgroup analyses stratified by baseline knee extensor strength and sex: Associations of baseline BW-normalized hip abductor strength (per 0.1 Nm/kg) with baseline-to-2-year tibiofemoral and patellofemoral cartilage damage worsening outcomes

[Odds Ratio (95% CI)]						
Baseline Hip Abductor Strength (Nm/kg)	Any TF	Medial TF	Lateral TF	Any PF	Medial PF	Lateral PF
In stronger knees (\geq median) (n = 138 knees from 99 persons)						
Percent with poor outcome	22.5%	11.6%	12.3%	17.4%	8.0%	10.1%
Adjusted ^a	0.73** (0.57, 0.93)	0.77* (0.57, 1.05)	0.72* (0.52, 1.02)	0.89 (0.66, 1.21)	0.86 (0.60, 1.23)	0.93 (0.67, 1.29)
In weaker knees (< median) (n = 137 knees from 96 persons)						
Percent with poor outcome	24.8%	16.1%	9.5%	16.1%	11.7%	6.6%
Adjusted ^a	1.06 (0.86, 1.32)	1.19 (0.90, 1.58)	N/A#	N/A#	N/A#	N/A#
In stronger knees (\geq median in women) among women (n = 112 knees§ from 74 women)						
Percent with poor outcome	21.4%	12.5%	9.8%	21.4%	12.5%	10.7%
Adjusted ^b	0.83* (0.67, 1.03)	0.76** (0.58, 0.99)	0.97 (0.67, 1.39)	0.72 (0.46, 1.14)	0.66* (0.42, 1.02)	0.80 (0.48, 1.33)
In weaker knees (< median in women) among women (n = 111 knees§ from 75 women)						
Percent with poor outcome	25.2%	14.4%	11.7%	15.3%	9.9%	7.2%
Adjusted ^b	1.03 (0.82, 1.31)	1.14 (0.82, 1.60)	0.87 (0.64, 1.18)	0.80** (0.65, 0.98)	0.80 (0.61, 1.05)	0.73** (0.56, 0.94)

Abbreviations: BW, body weight; CI, confidence interval; TF, tibiofemoral; PF, patellofemoral; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; K/L, Kellgren/Lawrence

a Adjusted for age, sex, WOMAC pain, and K/L grade

b Adjusted for age, WOMAC pain, and K/L grade

No men had structural progression in this compartment

§ A total of 223 knees from women

**odds ratio (OR) with associated 95% CI that excludes 1.0 is considered statistically significant

*p<0.10

Disclosure: A. H. Chang, None; J. S. Chmiel, None; O. Almagor, None; K. W. Hayes, None; A. Guermazi, MerckSerono, 5, Genzyme, 5, AstraZeneca, 5, TissueGene, 5, OrthoTrophix, 5, Boston Imaging Core Lab (BICL), LLC, 9; P. Pottumarthi, None; K. C. Moio, None; Y. Zhang, None; J. Szymaszek, None; L. Sharma, None.

Bone Mineral Density Is a Causal Risk Factor for Knee and Hip Osteoarthritis: A Population-Based and Mendelian Randomization Study in the UK Biobank

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Osteoarthritis (OA) involves the whole joint, with alterations of cartilage, synovium and bone. Whether bone changes are a cause or consequence of the disease remains controversial. As there is no curative treatment for OA, identifying causal factors is of major importance. Thus, our aim was to compare observational and causal associations between BMD and different OA phenotypes.

Methods: Individual level clinical and genetic data on 384 838 unrelated participants of European ancestry from the UK Biobank were analysed. As DXA was only available for 1% of the participants, we first tested estimated BMD of the heel (eBMD) as a risk factor for OA at all sites (n= 48 431 cases), at the knee (n= 19 727) or at the hip (n= 11 875), respectively, using hospital diagnoses. The analyses were replicated using knee and hip joint replacement therapy as definitions for severe OA. To assess causality, mendelian randomization (MR) analyses were performed using genetic instruments as proxies for femoral neck (FN) BMD and lumbar spine (LS) BMD. As they are randomly assigned at birth, they are not affected by confounders. Four MR methods were performed with sensitivity analyses excluding genetic instruments associated with body mass index (BMI), to preclude pleiotropy with a known causal confounder. The level of significance after Bonferroni correction was set at 0.05/6 : $P < 0.0083$. All participants gave their written consent to take part in the UK Biobank settings. This project was approved by the UK Biobank committee and has ethical permission.

Results: Linear regression models adjusted for age, sex and BMI revealed that an increase in eBMD by 1 SD was associated with increased risk of all OA (OR= 1.03 [95% CI 1.02 to 1.04]), knee OA (OR= 1.07 [95% CI 1.05 to 1.09]) and hip OA (OR= 1.09 [95% CI 1.07 to 1.11]). Results were similar when considering only incident OA cases or severe OA.

MR analyses by the inverse-variance weighted method demonstrated a causal effect of genetically determined FN BMD, that was associated with all OA (per 1 SD increase, OR=1.15 [95% CI: 1.06 to 1.25]) and both knee (OR=1.20 [95% CI: 1.05 to 1.37]) and hip OA (OR=1.23 [95% CI: 1.12 to 1.36]). Similar findings were demonstrated with joint replacement therapy definitions. The weighted median, the penalized weighted median and Egger's regression method provided similar results. LS BMD was only causally associated with knee OA.

Conclusion: This study demonstrates that high BMD is a risk factor for knee and hip OA and for severe OA, independently of age, sex and BMI. To our knowledge, this is the first evidence of a causal effect of FN BMD. Increasing BMD may not be beneficial for the prevention or the treatment of OA.

Disclosure: T. Funck-Brentano, None; M. Nethander, None; S. Moverare Skrtic, None; P. Richette, None; C. Ohlsson, None.

Biomechanical Therapy for Osteoarthritis of the Knee: A Randomized Controlled Trial

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Osteoarthritis – Clinical

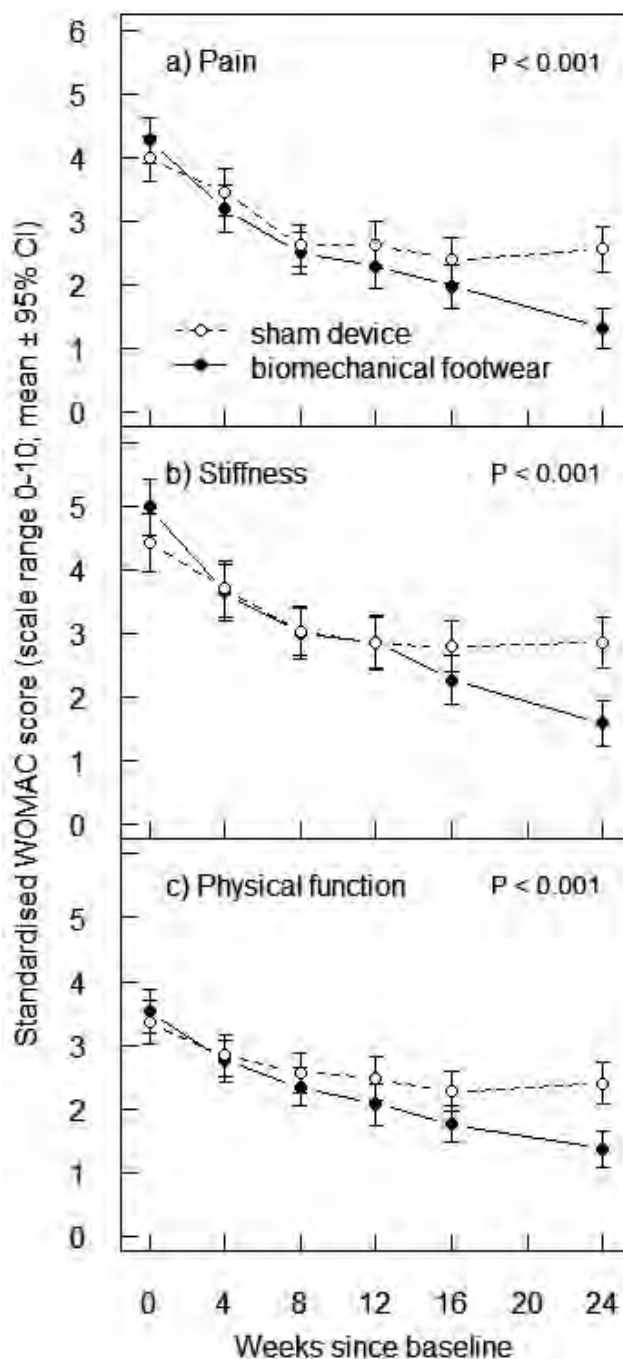
Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Biomechanics plays an important role in knee osteoarthritis (OA). A new biomechanical footwear system aims at altering knee loading patterns and retraining neuromuscular control of the lower extremities. It consists of shoes with two adjustable convex pods at the soles, which are adjusted based on gait analysis, with the hypothesis that adjustments of the location of the pods will alter limb biomechanics so as to unload diseased compartments of the knee and that walking on the convex pods will facilitate muscular retraining.

The aim was to compare the efficacy and safety of the new biomechanical footwear with an identical appearing shoe with flat pods (the sham device) in relieving pain and improving physical function in patients with knee OA.

Methods: In this randomized sham-controlled trial, patients with radiological knee OA (K/L grade ≥ 2) and moderate pain on the WOMAC pain subscale (≥ 3 on a standardized scale from 0 to 10) were randomly assigned 1:1 to the biomechanical footwear or the sham device. The same shoe was provided for bilateral use. Patients in both groups were instructed to use



the footwear for 30 minutes/day during the first week, and to increase use by 10 minutes/day each week to a maximum of 5 hours/day at 24 weeks. After 4, 8, 12, and 16 weeks, each patient's footwear was re-calibrated by technicians. Because the sham device had no adjustable pods on the soles, technicians pretended to make appropriate changes. The primary endpoint was knee pain at 24 weeks in the knee with more pain at screening, assessed with the WOMAC pain subscale. Secondary outcomes were WOMAC physical function and stiffness subscales. These outcomes were analyzed using linear models adjusted for baseline values and the two stratification factors uni- vs. bilateral, and medial vs. lateral osteoarthritis at randomization, using multiple imputation.

Results: Of 697 patients assessed for eligibility, 220 were randomized: 111 to the experimental footwear and 109 to the sham device. The mean age was 65.2 years (SD 9.2) and the mean body mass index was 28.0 (SD 4.6). Overall, 47.3% were women and 88.2% had medial knee OA in the index knee. The mean WOMAC pain score at baseline was 4.1 (SD 1.9). Seven patients in the experimental group and 13 in the sham group dropped out. At the end of the trial, the adjusted mean difference for WOMAC pain was 1.34 (95% CI 0.92 to 1.77) in favor of the experimental footwear. The adjusted mean difference was 1.42 (0.93 to 1.91) for WOMAC stiffness and 1.12 (0.73 to 1.50) for WOMAC physical function (Figure 1). Three serious adverse events occurred in the experimental group, compared with 9 in the sham group; none were treatment-related. Thirty adverse events occurred in the experimental group, compared with 36 in the sham group; 18 and 17 of these, respectively, were possibly treatment-related.

Conclusion: This trial suggests that the new biomechanical footwear system is both efficacious and safe in relieving knee pain in patients with knee OA.

Disclosure: S. Reichenbach, None; S. Heldner, None; A. Lenz, None; D. T. Felson, None; P. Jüni, None.

Abstract Number: 958

Tocilizumab and the Risk for Cardiovascular Disease Events Among Rheumatoid Arthritis Patients: A Direct Comparison in Real World Setting

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments II: Safety

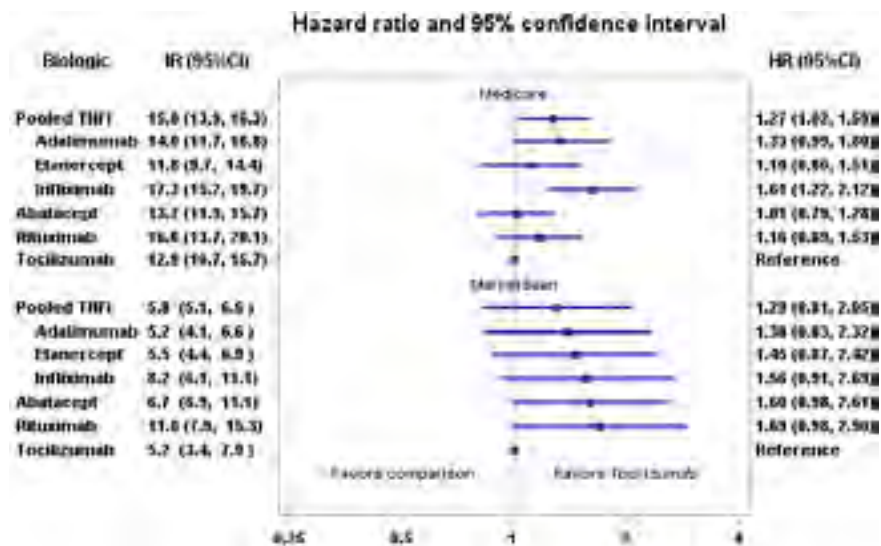
Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Multiple studies have observed unfavorable changes in lipid profile associated with tocilizumab (TCZ, anti-IL6 receptor antagonists) and some other rheumatoid arthritis (RA) therapies. The real-world cardiovascular disease (CVD) risk associated with the first anti IL-6R medication for RA, TCZ, remains uncertain. Our objective was to assess the CVD risk associated with TCZ compared to individual tumor necrosis inhibitor (TNFi) therapies, as well as to other biologics used for RA (e.g. rituximab, abatacept).

Methods: Using 2006-2015 Medicare and MarketScan claims data, we conducted a retrospective cohort study among RA patients who initiated biologic disease-modifying antirheumatic drugs (bDMARDs) after January 1, 2010 and had at least 365 days medical and pharmacy coverage before initiation. The primary outcome was a composite of myocardial infarction (MI), stroke, and fatal CVD assessed using a validated method. Subgroups analyses were done for RA patients experienced to other bDMARDs before initiation and by stratifying patients with respect to key CVD risk factors to identify both higher and lower CVD risk patients. Incidence rates and 95% confidence intervals were calculated using Poisson regression. COX regression was used to generate unadjusted and adjusted hazard ratio.

Results: We identified 354,486 RA patients and 463,446 initiations of bDMARDs. After applying inclusion and exclusion criteria, the final cohort contained 88,463 RA patients and 117,493 episodes. The mean (SD) age was 64.7 in Medicare and 52.2 in Market Scan. The majority were female (83.9% Medicare; 80.5% Market Scan), and 68.6% were non-Hispanic White in Medicare. TCZ users were similar to abatacept and rituximab users except that TCZ users were less likely to be naïve to bDMARDs. Compared to TNFi users, TCZ users were likely to be white, have a history of CVD (other than MI or stroke), heart failure, atrial fibrillation, hospitalization, and more physician visits in baseline. TCZ users were less likely to be diabetic, use methotrexate in baseline, and naïve to bDMARDs. The crude incidence rate (IR) per 1000 patient-years for composite CVD among Medicare patients ranged from 13.3 (95% CI: 11.1-16.0) for etanercept to 19.4 (95% CI: 16.3-20.9) for rituximab users. The crude incidence rate for pooled TNFi users was 16.4 (15.2-17.7). Compared to TCZ, the adjusted hazard ratios were 1.03 (0.82-1.29) for abatacept, 1.25 (0.96-1.61) for rituximab, 1.13 (0.84-1.52) for etanercept, 1.33 (0.99-1.80) for adalimumab, and 1.57 (1.21-2.05) for infliximab.



(Figure). There were no significant differences in CVD risk between tocilizumab and any other biologic using Market Scan data.

Conclusion: Consistent with findings of a recently completed safety trial in RA, tocilizumab was associated with a comparable CVD risk compared to etanercept, as well as a number of other RAbiologics, in two large data sources.

Disclosure: F. Xie, None; H. Yun, Bristol Myers Squibb, 2; E. Levitan, Amgen Inc., 2, 5, Novartis, 5; P. M. Muntner, None; J. R. Curtis, Amgen Inc., 2, 5, AbbVie Inc., 2, 5, BMS, 2, 5, Corrona, LLC, 2, 5, Janssen, 2, 5, Eli Lilly, 2, 5, Myriad, 2, 5, Pfizer, Inc., 2, 5, Roche/Genentech, 2, 5, Radius, 2, 5, UCB, Inc., 2, 5.

Abstract Number: 959

The Prevalence of Methotrexate Associated Hepatotoxicity in a Multi-Hospital Health System

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Rheumatoid Arthritis – Treatments II: Safety

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Session Time: 4:30PM-6:00PM

Background/Purpose: MTX has become the cornerstone in treatment of many rheumatologic disorders including rheumatoid arthritis and psoriasis. Although MTX can have a profound impact on disease management, and is generally continued as lifelong therapy, the feared potential for hepatotoxicity can result in early discontinuation of the drug. Unfortunately, liver function tests demonstrate a low diagnostic accuracy for detection of fibrosis with only a 38%. The purpose of our study is to establish the prevalence of liver toxicity in patients on MTX therapy at our large tertiary hospital setting and to identify characteristics of patients who are more susceptible for hepatotoxicity while on MTX therapy.

Methods: Retrospective cohort of all patients on MTX therapy for any rheumatologic disease including rheumatoid arthritis and psoriatic arthritis, in the in-patient and out-patient settings at NorthShore University Health System, a large tertiary health system, were taken into analysis between January 1, 2006 and December 31, 2016. Out of these approximately 5,000 patients, we screened for patients who had a liver biopsy and/or transient elastography testing done. Variables we looked at included age, gender, liver function tests, cumulative dose of MTX, CKD, history of hepatitis B or C, triglyceride levels, diabetes mellitus, and alcohol use.

Results: Out of the large number of patients who have been on methotrexate therapy (~5,000 patients over ten years of treatment), only 1% underwent further work-up for suspected liver disease by performing a liver biopsy and/or transient

elastography (Fibro Scan). From these 48 patients with suspected liver disease, liver biopsy and/or Fibro Scan revealed 26% had steatosis, 14.4% had fibrosis, 13% had NASH cirrhosis, 34% were normal findings with no liver disease, 5% had acute hepatitis, 2.6% chronic hepatitis, and only 5% had methotrexate associated cirrhosis.

Conclusion: Our findings demonstrate a very low prevalence of MTX associated hepatotoxicity in the rheumatologic patients. Less than 3% of patients had persistent transaminitis on MTX therapy, and even a smaller percentage underwent follow-up imaging with a liver biopsy or FibroScan. Based on our results, the likelihood of developing liver damage on MTX treatment is extremely low, and careful consideration needs to be made before potentially prematurely discontinuing this treatment for elevated liver function tests. Patients more susceptible to liver disease included increased BMI, diabetes mellitus, and elevated triglyceride levels, all at increased risk of fatty liver disease and NASH cirrhosis, consistent with the literature.

Disclosure: E. Pahomov, None; Y. Belopolsky, None; A. Ali, None; R. Woodrick, None.

Abstract Number: 960

The Risk of Gastrointestinal Perforations Associated with Biologic Disease-Modifying Anti-Rheumatic Drugs Used in Rheumatoid Arthritis: A Nationwide Swedish Cohort Study

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SESSION INFORMATION

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Background/Purpose: Gastrointestinal (GI) perforations occur more often than expected in patients with RA. Reports indicate that tocilizumab may be associated with an increased risk of GI perforations compared to synthetic DMARDs (1) or to TNF inhibitors (TNFi) (2). Replications are needed, and there is little data on other biologic DMARDs. In this analysis, we compare GI perforation rates among RA patients exposed to rituximab, abatacept, tocilizumab, or TNFi.

Methods: In this register-based cohort study we included all Swedish RA patients, with follow-up from 2010 to 2016. All initiations of treatment with TNFi, rituximab, abatacept, or tocilizumab were extracted from the Swedish rheumatology register (SRQ); each patient could contribute to several exposure cohorts. Follow-up under each exposure episode ended with a GI perforation event or at censoring by emigration, death, treatment switch or discontinuation, or end of study period. GI perforations were identified in the Swedish National Patient Register as any inpatient or outpatient diagnosis with an International Statistical Classification of Diseases and Related Health Problems (ICD) 10 code from a predefined list. Crude incidence rates were tabulated for each treatment cohort and relative effects were estimated as adjusted hazard ratios (HR) in multivariable Cox regressions, conditioning on baseline characteristics measured at the start of each episode (demographic, disease activity, co-medication, disease history).

Results: We found some evidence for outcome relevant channeling, with patients starting abatacept or rituximab more often having a history of diverticular disease or GI perforation, and some differences in age and co-medication (Table 1). Table 2 presents observed person-time, number of events (95% of which were lower GI perforations), crude rates and adjusted comparisons. The crude GI perforation rate was lowest in the TNFi, and highest in the abatacept cohort. None of the adjusted comparisons of each non-TNFi biologic with TNFi biologics yielded hazard ratios significantly different from 1.

Conclusion: We could not replicate an increased rate of GI perforations for tocilizumab. Taking measured channeling of treatment into account, none of the non-TNFi biologics showed an increased risk compared to TNFi biologics. Effects of residual or unmeasured factors cannot be excluded.

References: 1. Strangfeld A, et al. *Ann Rheum Dis* 2017;76:504–510.
2. Xie F, et al. *Arthritis Rheumatol* 2016;68:2612–2617.

Table 1 Baseline characteristics of each exposure cohort

Characteristic	TNFi	Rituximab	Abatacept	Tocilizumab
Treatment episodes (N)	14536	2965	2188	2041
Mean age (years)	56.65	62.33	59.41	57.21
Females (%)	76.20	75.95	80.80	79.47
Mean DAS28	4.58	4.94	4.88	5.12
Mean disease duration	12.02	15.34	14.61	13.16
Synthetic DMARD1 (%)	73.21	68.19	63.57	57.77
NSAIDs1 (%)	33.93	34.07	36.61	39.81
Steroids1 (%)	47.38	57.91	58.89	57.13
Diverticular Disease2 (%)	2.90	4.65	5.12	3.43
GI perforation3 (%)	0.16	0.34	0.73	0.20

1 Use of conventional synthetic DMARDs, NSAIDs or steroids within 31 days around the start of the episode (Yes/No).

2 Any diagnosis within 5 years before the start of the episode (Yes/No).

3 Any diagnosis within 1 year before the start of the episode (Yes/No).

Table 2 Crude incidence rates (per 1000 person-years) and adjusted Hazard Ratios.

Cohort	No. events	Follow-up (person years - py)	Crude Incidence Rate (/1000 py)	Hazard Ratio1 (95% Confidence Interval)
TNFi	40	26108.27	1.53	Reference
Rituximab	17	7305.85	2.33	0.75 (0.41 to 1.37)
Abatacept	15	3637.22	4.12	1.49 (0.79 to 2.79)
Tocilizumab	11	3898.77	2.82	1.15 (0.57 to 2.35)

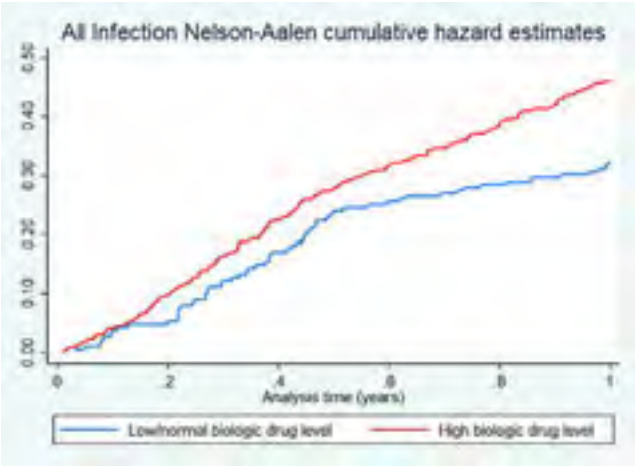
1 Adjusted for: sex, age, education, line of biologic therapy, disease parameters (rheumatoid factor, duration, HAQ, DAS28), co-medication (synthetic DMARDs, NSAIDs, steroids), disease history (cancer, COPD, diabetes, diverticular disease, IBD, GI-perforation) and start of treatment year.

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Abstract Number: 961

The Association of Biologic Drug-Levels with Infection Risk: Results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis

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SESSION INFORMATION

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Background/Purpose: High dose tumour necrosis factor inhibitor (TNFi) drugs are associated with an increased serious infection (SI) risk [1]. It is feasible that high biologic levels predict dose-dependent adverse events such as SI. No registries have systematically evaluated the effect of drug levels on infection risk. The objective was to assess the effect of biologic drug levels in rheumatoid arthritis (RA) patients on (i) all infections (AI) (ii) SI(infections requiring hospitalization, IV antibiotics or lead to death) **Methods:**

Patients recruited to both the British Society for Rheumatology Biologics Register-RA (safety data) and the Biologics in RA Genetics & Genomics Syndicate (serological samples) were included. Both are large national prospective RA cohorts. Biologic drug levels were measured at 3/6/12 months after biologic initiation and stratified as low/normal or high drug levels (HL) as per thresholds defined using concentration-effect curves for each drug. The risk of first and total infections within the first year was analysed. Events occurring on drug or within 90 days of last dose were included. The risk of an event was compared between low/normal vs. HL groups using Cox proportional-hazard models. Factors affecting both drug levels and infection risk were adjusted for in the models. **Results:**

703 patients (286 etanercept, 179adalimumab, 120 certolizumab, 104 tocilizumab and 14 infliximab) had clinical data and serological samples. 74% were women, mean (SD) age 58 (12) years, on a first biologic (89%). The crude rate/1000 pyrs was 314 and 464 for AI; 54 and 76 for SI in the low/normal and HL groups respectively. The adjusted hazard ratio for AI within the first year differed significantly between the two groups with the HL group having 50 percent higher risk of AI (HR: 1.51; 95% CI:1.14, 2.01) (table). The most common types of AI in the HL group were lower(34%) and upper (16%) respiratory tract infections, urinary tract infections(15%), skin infections including shingles (8%).

	Low/ normal drug level (n=241)	High drug levels (n=462)
All events with follow up censored at 1 year (95% CI)		
All infections (n)	63	232
Crude rate (/1000 pyrs)	314 (245, 401)	464 (408, 528)
Unadjusted HR	Ref	1.44 (1.09, 1.91)*
Adjusted HR †	Ref	1.51 (1.14, 2.01)*
Serious infections (n)	11	38
Crude rate (/1000 pyrs)	54 (30, 98)	76 (55, 104)
Unadjusted HR	Ref	1.36 (0.70, 2.67)
Adjusted HR†	Ref	1.17 (0.58, 2.30)
First event within 1st year (95% CI)		
All infections (n)	46	150
Crude rate (1000 pyrs)	229 (172, 256)	300 (256, 352)
Unadjusted HR	Ref	1.24 (0.89, 1.73)
Adjusted HR †	Ref	1.26 (0.91, 1.78)
Serious infections (n)	6	22
Crude rate (/1000 pyrs)	29 (13, 67)	44 (28, 67)
Unadjusted HR	Ref	1.39 (0.56, 3.44)
Adjusted HR†	Ref	1.26 (0.50, 3.16)

* p<0.05†Adjusted for age, gender, DAS score, methotrexate use

Image/graph: :

Conclusion: RA patients with high biologic drug levels have a higher risk of infection. Monitoring drug levels may be helpful in prediction of infection. In disease remission patients with high drug levels, biologic dose tapering may lower infection risk.

References: (1)Singh JA, Cameron C et al. Lancet 2015;368:258-265

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Safety Profile of Baricitinib for the Treatment of Rheumatoid Arthritis up to 6 Years: An Updated Integrated Safety Analysis

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Background/Purpose: Baricitinib (bari), an oral, selective inhibitor of Janus kinase (JAK) 1 and JAK 2, is approved for the treatment of moderately to severely active RA in adults in over 40 countries including European countries, US and Japan. We further describe the drug's safety profile with updated data from an ongoing long-term extension (LTE) study.

	PBO-bari 4 mg ^a (6 study, to Week 24)		Bari 2 mg-4mg-extended ^b (4 study, including LTE)		ALL-bari-RA 01-April-2017	ALL-bari-RA 01-Sept-2016 ^c
	PBO	Bari 4 mg	Bari 2 mg	Bari 4 mg	ALL Bari RA	ALL Bari RA
Exposure						
n of patients	1070	1097	479	479	1402	1092
Patient-years of exposure	101.3	109.4	104.9	145.9	77.00	100.70
Median, days	166	169	257.0	342	341 (2.5 yrs)	760 (2.1 yrs)
Longest exposure, days	135	131	1467	2202	2202 (6.1 yrs)	2109 (5.5 yrs)
Persistent DC due to AE, n (%)	35 (3.3)	47 (4.3)	11 (2.3)	47 (7.3)	455 (3.3)	393 (3.6)
Mortality, n (IR), [95% CI]						
	2 (0.3) [0.1, 1.8]	3 (0.7) [0.1, 2.1]	1 (0.16) [0.0, 0.9]	1 (0.46) [0.1, 1.3]	28 (0.35) [0.23, 0.51]	22 (0.33) [0.2, 0.5]
Malignancy, n (IR), [95% CI]						
Malignancy excluding NMSC	1 (0.5) [0.1, 1.8]	1 (0.5) [0.1, 1.7]	1 (0.5) [0.1, 1.4]	1 (0.7) [0.1, 2.4]	64 (0.8) [0.6, 1.0]	52 (0.8) [0.6, 1.0]
			10 (0.4) ^{***} [0.4, 1.3]	10 (0.4) ^{***} [0.4, 1.3]		
Lymphoma	0	0	0	1 (0.7) [0.004, 0.66]	6 (0.08) [0.0, 0.18]	6 (0.09) [0.0, 0.19]
NMSC	1 (0.3) [0.0, 1.4]	1 (0.7) [0.1, 2.1]	1 (0.3) [0.04, 1.1]	1 (1.3) [0.4, 2.2]	80 (0.6) [0.3, 0.9]	38 (0.4) [0.2, 0.5]
Infections, n (IR), [95% CI]						
Serious Infection	17 (4.2) [2.5, 6.8]	16 (3.8) [2.2, 6.2]	20 (3.3) [2.0, 5.2]	31 (4.8) [3.3, 6.9]	231 (3.0) [3.3, 6.9]	194 (2.9) [2.5, 3.4]
Herpes Zoster	4 (1.0) [0.3, 2.5]	18 (4.3) [*] [2.6, 6.8]	17 (2.8) [1.6, 4.5]	25 (3.9) [2.5, 5.3]	258 (3.3) [2.9, 3.8]	212 (3.2) [2.8, 3.7]
TB	0	1 (0.2) [0.01, 1.33]	0	6 (0.50) [0.18, 1.08]	11 (0.14) [0.07, 0.25]	10 (0.15) [0.07, 0.27]
MAACE, n (IR), [95% CI]						
	1 (0.5) [0.1, 2.0]	1 (0.8) [0.2, 2.2]	1 (0.2) [0.0, 0.9]	1 (0.4) [0.04, 1.3]	38 (0.5) [0.34, 0.68]	31 (0.5) [0.4, 0.7]
GI Perforation, n (IR), [95% CI]						
	0	0	0	1 (0.20) [0.0, 0.9]	3 (0.04) [0.01, 0.11]	3 (0.05) [0.01, 0.13]

95% CI for IR are based on Poisson distribution.

^aData from treatment period up to Week 24, with data up to rescue / treatment switch.

^bAll analysis based on an as-treated method (data censored at rescue or dose change) unless otherwise specified.

^cOn the "as-randomized" analysis for malignancy excluding NMSC, all data were attributed to the initial randomized treatment group & not reporting rescue or dose changes. The patient-years of observation time with the as-randomized analysis were 1208 and 1214 years for 2mg and 4mg groups, respectively.

^dPotential cardiovascular (CV) adverse events from the Pbo 3 study and LTE, identified by investigators or according to a predefined list of event terms, were adjudicated by an independent, external Clinical Endpoint Committee who remained blinded to treatment assignments; includes follow up period.

^e*P<0.01 for bari 4 mg vs placebo based on the proportion of patients with the event.

AE, adverse event; Bari, baricitinib; CI, confidence interval; DC, discontinuation; EIR, exposure-adjusted incidence rates per 100 patient years (exposure time not censored at event); IR, incident rate per 100 patient years (observation time censored at event); GI, gastrointestinal; MAACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; n, number of patients in a specified category; PBO, placebo; TB, tuberculosis; yrs, years.

Methods: Long-term safety of once-daily bari was evaluated in the “all-bari-RA” dataset, which includes all patients (pts) with active RA exposed to any bari dose from 8 randomized trials (4 Phase 3, 3 Phase 2, 1 Phase 1b) and 1 LTE study (data up to 01-April-2017). Previous all-bari-RA analyses¹ are provided for comparison (data up to 10-Aug-2015 and 01-Sept-2016).² Dose responses were evaluated based on the 4 Phase 2/3 trials in which pts were randomized to 2 or 4mg including data from the LTE (the “2mg-4mg-extended” dataset). Data were censored at rescue or dose change (as-treated analysis). Because of the latent period for malignancy, 2mg-4mg-extended was also analyzed without censoring for rescue or dose change (as-randomized analysis). Incidence rates (IR) per 100 patient-years (PY) were calculated.

Results: In the current analysis, 3492 pts received bari for 7860 total PY of exposure (an increase in over 1200 PY; 18% from 01-Sept-2016) for up to 6 years (Table 1). Of these, 2723 (78.0%) were treated for at least 52 weeks and 1788 (51.2%) were treated for at least 130 weeks. Adverse events (AEs) IRs did not increase with prolonged exposure (Table 1). Malignancy (excluding non-melanoma skin cancer (NMSC)) IR were 0.5 and 1.2 for 2mg and 4mg, respectively, with as-treated analysis and 0.8 and 0.8 with as-randomized analysis. For the above events, the current IRs in all-bari-RA are similar to those previously reported (Table 1). The following IRs were observed in the current all-bari-RA: gastrointestinal (GI) perforation (0.04), and tuberculosis (TB) (0.14). Fewer than 1% of pts discontinued due to abnormal lab results.

Conclusion: In this updated integrated analysis of patients with moderately to severely active RA, including patients exposed for up to 6 years, baricitinib maintained a safety profile that was similar to that previously reported^{1,2} acceptable in the context of demonstrated efficacy.^{3,4}

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Abstract Number: 963

Long-Term Safety of Tofacitinib up to 9.5 Years: A Comprehensive Integrated Analysis of the RA Clinical Development Program

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Here, we report the largest integrated safety analysis of tofacitinib to date using data from Phase (P)1, P2, P3, P3b/4, and open-label long-term extension (LTE) studies in adult patients (pts) with RA.

Methods: Data were pooled for pts who received ≥ 1 tofacitinib dose, as monotherapy or with background conventional synthetic DMARDs (csDMARDs), integrated across 2 P1, 10 P2, 6 P3, 1 P3b/4, and 2 LTE studies (ORAL Sequel LTE main study database locked at time of analysis: March 2017). Incidence rates (IR; pts with events per 100 patient-years [PY]) and 95% confidence intervals were obtained for safety events of special interest. Additionally, IRs for deep vein

thrombosis(DVT) and pulmonary embolism (PE) are reported. IRs were based on the number of pts with incident events during the time between the first and last dose plus 28days, which was the clinical trial observation period (previous analyses included events outside of the observation period).

Results: This analysis included 7061 pts, representing 22,875 PY of tofacitinib exposure, with a median exposure of 3.1 years, and 30% of pts had >5years of exposure. A total of 1634 (23.1%) pts discontinued due to adverse events (AEs; IR: 7.1[6.8, 7.5]). The most common treatment-emergent AEs by MedDRA v20.0 preferred term were viral upper respiratory tract infection (17.3%), upper respiratory tract infection (17.2%), and urinary tract infection (11.8%). The IR for serious AEs was 9.0 (8.6, 9.4), of which infections were the most common. Serious infections occurred in 576 pts (8.2%; IR: 2.5 [2.3, 2.7]), and pneumonia was the most frequently reported serious infection (124 pts [22% of all pts with serious infections]). Overall, 782 pts (11.1%) developed herpes zoster (HZ; IR: 3.6 [3.4, 3.9]); in most pts HZ involved a single dermatome (90.2%). Serious HZ was reported in 57 pts (7.3% of all pts with HZ). Opportunistic infections (excluding tuberculosis [TB]) were reported in 90 pts (1.3%; IR: 0.4 [0.3, 0.5]) and TB was reported in 38 pts (0.5%; IR: 0.2 [0.1, 0.2]). Malignancies (excluding non-melanoma skin cancer [NMSC]) occurred in 177 pts (2.5%; IR: 0.8 [0.7, 0.9]), NMSC in 129 pts (1.8%; IR: 0.6 [0.5, 0.7]) and lymphomas in 12 pts (0.2%; IR: 0.1 [0.0, 0.1]). Gastrointestinal perforations were reported in 28 pts (0.4%; IR: 0.1 [0.1, 0.2]) and major adverse cardiovascular events in 85 pts (1.3%; IR: 0.4 [0.3, 0.5]). DVT was reported in 27 pts (0.4%; IR: 0.12 [0.08, 0.17]) and PE in 28 pts (0.4%; IR: 0.12 [0.08, 0.17]). There were 59 deaths (0.8%; IR: 0.3 [0.2, 0.3]). IRs for AEs of interest were stable across 6-month intervals.

Conclusion: This long-term integrated safety analysis with up to 9.5years of follow-up and 22,875PY of tofacitinib exposure represents one of the largest clinical datasets to date for an advanced RA treatment. The safety profile of tofacitinib remained consistent with those of previous randomized controlled trials in the RA clinical development program.

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Abstract Number: 964

Psoriatic Arthritis Impact of Disease (PsAID12) Was Provisionally Endorsed at Omeract 2018 As Core Instrument to Measure Psoriatic Arthritis-Specific Health-Related Quality of Life in Randomized Controlled Trials and Longitudinal Observational Studies

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Methods: We used a multi-step process (Fig1). PsAID12 psychometric evidence to fulfill Filter 2.1 was gathered in a systematic literature review (SLR) of patient reported outcomes (PROM) in PsA³, and additional analyses conducted in an LOS. Analyses that not been published were independently reviewed by the OMERACT technical advisory group. Data were presented to stakeholders [WG, patient research partners (PRP), workshop at the GRAPPA 2017 annual meeting⁴] followed by a survey to vote on domain match and feasibility. All data were summarized as PsAID12 OMERACT pre-conference reading material. Data and process were presented, discussed in 8 breakout groups, and voted on, at the OMERACT 2018 conference (Terrigal, Australia, May 2018).

Results: An excerpt of the PsAID12 evidence presented at OMERACT 2018 is represented in Fig2. PsAID12 fulfilled with green (good to go) domain match, feasibility, reliability, and construct/longitudinal construct validity. Discrimination was assessed in an LOS within change groups. Minimal clinically important improvement in 2 LOS^{2,5} were 3 and 1.4. PsAID12 fulfilled with amber (provisional endorsement) discrimination and thresholds of meaning. The overall WG recommendation was formulated: **amber/provisional endorsement of PsAID12 for measuring PsA specific-HRQoL in RCTs and LOS**. Of 113 participants at the PsA OMERACT workshop 87% (97) voted “yes” endorsing this recommendation. 17 were PRPs and 93% voted “yes”. The WG set a research agenda to fully endorse PsAID12.

Conclusion: At OMERACT 2018, PsAID12 was the first PROM provisionally endorsed as core instrument to measure PsA-specific HRQoL in RCTs. PsAID12 discrimination and improvement thresholds will be studied in RCTs.

Refs: 1 OMERACT handbook, 2 Gossec 2014, 3 Højgaard 2017, 4 Holland 2018, 5 Holland 2017

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Abstract Number: 965

Defining Cutoffs Corresponding to Low Levels of Disease Activity in Psoriatic Arthritis, Using the Patient-Reported Psoriatic Arthritis Impact of Disease Questionnaire (PsAID12). an Analysis of 436 Patients

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical II: PsA Epidemiology

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: The Psoriatic Arthritis (PsA) Impact of Disease questionnaire (PsAID12) score allows an assessment of patient-important symptoms and life impact in PsA. It is provisionally recommended as core outcome measure

Table 1. Cutoffs for PsAID12-defined disease activity states using different external anchors.

	Remission		Low disease activity		Moderate disease activity	
	ROC (AUC)	75th	ROC (AUC)	75th	ROC (AUC)	75th
DAPSA	1.7 (0.94)	1.4	3.1 (0.89)	3.1	4.8 (0.85)	4.5
VLDA / MDA	1.4 (0.94)	0.8	2.0 (0.91)	1.9		
Patient's question	1.7 (0.77)	2.4	3.7 (0.83)	3.7		
Physician's question	1.8 (0.75)	3.0	4.2 (0.77)	4.1		
Mean value for all external anchors	1.7	1.9	3.2	3.2	4.6	4.6

PsAID12: Psoriasis Activity Index (PsA) Impact of Disease questionnaire; ROC: Receiver Operating Characteristic; AUC: area under curve; DAPSA: Disease Activity Index for Psoriatic Arthritis; VLDA: Very Low Disease Activity; MDA: minimal disease activity.

byOMERACT (ref). To date, no cutoffs have been established to help clinicians interpret its results. The objective was to develop such cutoffs for PsAID12 corresponding to disease activity states (i.e. remission (REM), low disease activity (LDA) or moderate disease activity).

Methods: ReFlap (NCT03119805) is an ongoing cross-sectional study in 14 countries of consecutive adult patients with definite PsA and more than 2 years of disease duration. The PsAID12 (0-10 score where 0 is no impact) was collected. Disease activity was defined using the following external anchors: (a) Disease Activity in Psoriatic Arthritis (DAPSA) score (cutoffs of ≤ 4 , ≤ 14 , ≤ 28 for REM, LDA and moderate disease activity, respectively) (b) Very Low Disease Activity (VLDA) / Minimal Disease Activity (MDA) scores (cutoffs of 7/7 and 5/7 criteria met for REM and LDA, respectively) (c) single questions for patient and physician-defined REM and LDA. For each level of disease activity and for each external anchor, cutoffs of PsAID12 were calculated using Youden's index on Receiver Operating Characteristic (ROC) curve analyses and the 75th percentile method. Finally, author consensus was sought on final proposed cutoffs.

Results: Of 466 patients, 436 were analyzed: 218 (50.8%) were men, mean age (standard deviation) was 53.6 (12.7) years, mean disease duration was 11.3 (8.3) years, 62.3% were taking conventional synthetic DMARDs and 60.1% a biologic. Mean PsAID12 was 3.4 (2.5). The frequency of REM varied from 12.8% (VLDA) to 38.5% (Physician REM question) and of LDA from 25.5% (MDA) to 43.1% (Patient LDA question). PsAID functioned well against the external anchors as indicated by high areas under the ROC curves (range, 0.75-0.94). The VLDA and MDA criteria were more difficult to reach than the DAPSA REM and LDA cutoffs, reflected by much lower cutoffs for the PsAID12 score (Table 1). PsAID12 cutoffs varied between 1.7-1.9, 3.2-3.3 and 4.5-4.8 for REM, LDA and moderate disease activity, respectively (Table 1). Proposed final cutoffs of PsAID12 are < 2 for REM, ≤ 3 for LDA and < 5 for moderate disease activity.

Conclusion: It was possible to define cutoffs for PsAID12 corresponding to PsA disease activity states with good known groups validity. This indicates patients' assessment reflects the disease process in PsA. One strength of our study is the use as external anchors to define disease activity based on both composite scores and the patient's opinion. Proposed cutoff values for PsAID12 will be useful when defining treatment targets for PsA. Further validation is needed.

Reference: Pil Højgaard *et al.* Seminars in Arthritis and Rheumatism, 2017.

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Central Triage Clinic for Psoriatic Arthritis – Performance of Triage Methods

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical II: PsA Epidemiology

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Accurate triage methods for patients with psoriasis who have musculoskeletal symptoms could lead to earlier access to rheumatology care for patients with psoriatic arthritis (PsA). We aimed to describe a novel model of care involving a central triage clinic for psoriasis patients with musculoskeletal (MSK) symptoms and to compare the efficacy of several triage methods for PsA.

Methods: Patients with a physician-confirmed diagnosis of psoriasis who experienced musculoskeletal symptoms and did not have a prior diagnosis of PsA were evaluated. Patients could access the triage clinic by self-referral or following referral by their family physician or dermatologist. Participants were assessed in the central triage clinic to determine their likelihood of having PsA. The following triage methods were used: 1) three PsA screening questionnaires (TOPAS-2, PEST, PASE); 2) MSK ultrasound assessment of 14 pre-specified enthesal sites and 8 joint sites in addition to symptomatic joints and entheses; 3) clinical assessment by an advanced practice physiotherapist; 4) levels of CRP and ESR and 5) The presence of *HLA-B*27* allele. Each patient was then assessed by a rheumatologist to determine whether they have PsA. Patients were classified by the rheumatologist to “Not PsA”, “Possible PsA” or “PsA”. The rheumatologist was blinded to the results of the triage methods. The performance of each triage method to identify PsA was assessed by calculating its sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Results: Of the 203 psoriasis patients assessed in the triage clinic, 137 (67.5%) did not have PsA, 48 (23.5%) had possible PsA, and 18 (9%) had PsA. The performance of triage methods is presented in Table 1. The advanced practice physiotherapist's assessment in detecting clinical PsA was highly sensitive (89%) with moderate specificity (58%). The screening questionnaires varied by their sensitivity and specificity with PEST showing highest sensitivity (76%) and PASE with highest specificity (79%). The prevalence of positive MSK inflammation by ultrasound (at least 1 joint or enthesis with positive power Doppler signal) was 50.7%. The sensitivity of positive MSK ultrasound was high (83%) but its specificity was moderate (52%). 43.3% of the study participants who had positive MSK ultrasound findings were not classified by the rheumatologist as having PsA. The performance of CRP, ESR and HLA-B27 as triage methods was poor.

Conclusion: MSK ultrasound and advanced practice physiotherapist were highly sensitive in identifying patients with PsA among psoriasis patients with MSK symptoms. A significant proportion of patients with positive MSK inflammation by ultrasound were not identified as having PsA by the rheumatologist.

Table 1 Properties of various triage methods in detecting clinical PsA among patients with psoriasis and musculoskeletal symptoms (N=203)

Triage Method	Sensitivity	Specificity	PPV	NPV
Positive MSK ultrasound (Definition 1) at least 1 joint or enthesal sites with positive power Doppler signal	83%	52%	15%	97%
Positive MSK ultrasound (Definition 2) at least 2 joint or enthesal sites with positive power Doppler signal	67%	76%	21%	96%
Advanced Practice Physiotherapist: Positive assessment	89%	58%	17%	98%
Positive TOPAS-2 questionnaire	72%	72%	21%	96%
Positive PEST questionnaire	76%	70%	15%	93%
Positive PASE questionnaire	61%	79%	23%	95%
Elevated CRP (>5 mg/dL)	44%	79%	19%	94%
Elevated ESR (Men: >15 mm/hr, Women: >20 mm/hr)	63%	78%	21%	96%
HLA-B*27 allele	6%	92%	7%	91%

MSK – Musculoskeletal, TOPAS – Toronto Psoriatic Arthritis Screening, PEST – Psoriasis Epidemiology Screening Tool, PASE – Psoriatic Arthritis Screening and Evaluation, CRP – C-Reactive Protein, ESR – Erythrocyte Sedimentation Rate

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Health Care Utilization for Musculoskeletal Issues during the Pre-Diagnosis Period in Psoriatic Arthritis – a Population-Based Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical II: PsA Epidemiology

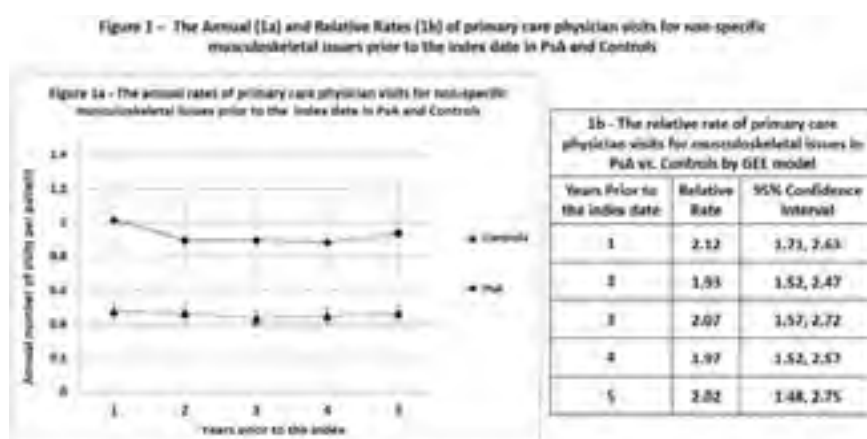
Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Numerous studies have shown delays in diagnosis of psoriatic arthritis (PsA) among patients with psoriasis. The heterogeneous nature and frequently insidious onset of PsA may contribute to the delayed diagnosis. There are limited data about the pre-diagnosis phases of PsA. We aimed to assess health care utilization in a primary care setting during a 5-year period prior to the diagnosis of PsA in comparison to the general population.

Methods: We conducted a matched cohort study using the primary care Electronic Medical Record Administrative data Linked Database (EMRALD) in Ontario, Canada (comprised of >350 primary care physicians and >400,000 patients). EMRALD data were linked with provincial administrative data to obtain information about health care services utilization. Patients with PsA were identified using a validated algorithm (PPV85%). The date of PsA diagnosis (index date) was defined as the first date an inflammatory arthritis billing code was administered by a rheumatologist. Five age- and sex-matched controls from the same family practice clinic were matched for each PsA case. The controls were assigned the same index date as their corresponding case. The primary outcome was visits to primary care physicians for non-specific musculoskeletal (MSK) issues during the 5-year period prior to the index date. We compared the rates of visits and the proportion of patients visiting primary care physicians between PsA and controls using GEE models with negative binomial distribution (for rates) and binary distribution (for probabilities).

Results: We studied 462 PsA patients and 2310 matched controls with a mean (SD) age of 54.2±13.8 (55.6% females). Relative rates and odds of visits were higher in each of the 5 years prior to the index dates for PsA patients vs. controls (Figure 1 and Table 1). The odds ratios (OR) related to visiting a primary care physician for nonspecific MSK issues in patients with PsA vs. controls was 2.14 (95% CI 1.74, 2.63) in the first year prior to the index date and was similarly elevated up to 5 years prior (Table 1). Additionally, the Relative Rates (RR) for MSK-related visits prior to the index date were higher in PsA patients compared to controls (RR ranging from 1.93 to 2.12; Figure 1).



Conclusion: We identified the presence of a prolonged period of non-specific MSK symptoms occurring prior to the diagnosis of PsA, which is greater than the control group. Our findings suggest that there may be a pre-clinical phase of the disease characterized by non-specific MSK symptoms, which may lead to delays in diagnosis of PsA in the primary care setting.

Table 1 - Odds ratios for at least one visit to a primary care physician for non-specific musculoskeletal issues in individuals ultimately developing PsA vs. Controls

Years prior to the index date	Odds Ratio	95% Confidence Interval
1	2.14	1.74, 2.63
2	1.88	1.53, 2.32
3	1.73	1.40, 2.14
4	1.74	1.40, 2.15
5	1.77	1.43, 2.19

Disclosure: L. Eder, None; K. Tu, None; C. F. Rosen, None; R. Alhusayen, None; S. Cheng, None; J. Young, None; W. Campbell, None; S. Bernatsky, None; D. D. Gladman, None; R. J. Cook, None; M. Paterson, None; J. Widdifield, None.

Abstract Number: 968

What Is the Impact of Imaging on Diagnostic Ascertainment of Patients Presenting with Undiagnosed Back Pain in Routine Practice and the Impact of Central Reading? Data from the Screening in Axial Spondyloarthritis in Psoriasis, Iritis, and Colitis Cohort

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical II: PsA Epidemiology

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Session Time: 4:30PM-6:00PM

Background/Purpose: Although MRI of the sacroiliac joints (SIJ) is the most sensitive imaging modality for early diagnosis of axial spondyloarthritis (axSpA) it is costly and not readily available. Therefore, clinicians still rely primarily on radiography. The relative degree to which radiography and MRI changes diagnostic ascertainment of axSpA in patients presenting with undiagnosed back pain has not been formally studied. We aimed to assess the relative impact of radiography and MRI evaluation on diagnostic ascertainment of axial SpA in patients presenting with undiagnosed back pain to rheumatologists, and the impact of central reading on diagnostic ascertainment.

Methods: The multicenter Screening for Axial Spondyloarthritis in Psoriasis, Iritis, and Colitis (SASPIC) Study is aimed at early detection of axial SpA in consecutive patients presenting with undiagnosed back pain. Consecutive patients ≤ 45 years of age with ≥ 3 months undiagnosed back pain with any one of psoriasis, acute anterior uveitis (AAU), or colitis undergo routine clinical evaluation by a rheumatologist for axial SpA and MRI evaluation is ordered per rheumatologist decision. The rheumatologist determines the presence or absence of axial SpA and the degree of confidence in the diagnosis (-10 (definitely not SpA) to +10 (definite SpA) on a numerical rating scale) at 3 consecutive stages: 1. after the clinical evaluation; 2. after the results of labs (B27, CRP) and radiography; 3. After the results of MRI evaluation. We assessed diagnostic ascertainment at each step at the categorical level (axial SpA yes/no) and also according to the degree of confidence (mean (SD) confidence). Two central readers assessed radiographs and MRI scans.

Results: 234 patients (51.3% male, mean age 34.6 years, mean symptom duration 7.0 years, mean back pain duration 7.1 years, B27+36.3%) were referred with AAU (29.9%), psoriasis (18.8%), Crohn's colitis (32.1%), and ulcerative colitis (19.2%). The number of patients diagnosed clinically with axSpA decreased after radiography and then decreased further after MRI while confidence in the diagnosis progressively increased (Table 1). After central reader assessment of imaging, the number of patients diagnosed with axSpA decreased substantially compared to assessment by local readers (Table 2).

Conclusion: In a setting of undiagnosed back pain and higher risk for axial SpA, imaging is primarily helpful in ruling out SpA and reducing false positives. Despite this, central reading of imaging raises concerns regarding ascertainment of false positive SpA in routine practice.

Table 1

Stage of global assessment	Data source	axSpA YES, number (%), plus mean (SD) confidence	axSpA YES with confidence >7 number (%), plus mean (SD) confidence	axSpA NO, number (%), plus mean (SD) confidence	axSpA NO with confidence <-4 number (%), plus mean (SD) confidence
1. N =234	Clinical	157 (67.1%) 5.9 (2.5)	49 (20.9%) 8.8 (0.8)	77 (32.9%) -4.4 (3.2)	39 (16.7%) -7.1 (1.3)
2. N =234	Clinical plus radiography	132 (56.4%) 6.6 (3.0)	63 (26.9%) 9.1 (0.9)	102 (43.6%) -6.2 (3.5)	74 (31.6%) -7.9 (1.9)
1. N =147	Clinical	105 (71.4%) 3.5 (5.4)	25(17.0%) 7.4 (4.0)	42 (28.6%) -2.7 (5.5)	18 (12.2%) -4.6 (4.1)
2. N =147	Clinical plus radiography	92 (62.6%) 5.7 (3.0)	32 (21.8%) 8.8 (0.8)	55 (37.4%) -4.9 (3.5)	35 (23.8%) -6.9 (1.8)
3. N =147	Clinical plus radiography plus MRI	71 (48.3%) 7.4 (3.0)	44 (29.9%) 9.3 (0.8)	76 (51.7%) -7.4 (2.6)	68 (46.3%) -8.1 (1.6)

Table 2

Stage of global assessment	Data source	axSpA YES, number (%)	axSpA NO, number (%)
2. N =212	Clinical plus radiography	120 (56.6%)	92 (43.4%)
2. N = 212	Clinical plus radiography after central reader assessment	66 (31.1%)	146 (68.9%)
3. N =128	Clinical plus radiography plus MRI	62 (48.4%)	66 (51.6%)
3. N = 128	Clinical plus radiography plus MRI after central reader assessment	39 (30.5%)	89 (69.5%)

Disclosure: W. P. Maksymowych, CaRE rthritis, 9; R. Carmona, None; J. Chan, AbbVie Inc., 5,Novartis, 2, 5,Pfizer, Inc., 5,UCB, Inc., 2, 5,Eli Lilly and Co., 5,Janssen, 5,Amgen Inc., 5,Celgene Corporation, 5; J. Yeung, None; D. P. Mosher, None; S. Z. Aydın, None; L. Martin, None; A. Masetto, None; S. Keeling, None; O. Ziouzina, None; S. Rohekar, Abbvie, Amgen, Eli-Lily, Janssen, Merck, Novartis, Pfizer, Roche, UCB, 5,Eli-Lily, 8; J. Paschke, None; A. Carapellucci, None; R. G. Lambert, None.

Abstract Number: 969

Obstetric Outcomes in Women with Psoriatic Arthritis: Results from Nationwide Inpatient Sample Database 2003-2011

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical II: PsA Epidemiology

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Outcomes of pregnancy are well studied in a number of rheumatic diseases such as Rheumatoid Arthritis (RA) and systemic lupus erythematosus. However, there is very limited data in pregnancy outcomes in patients with psoriasis and psoriatic arthritis (PsA). This study was undertaken to determine the frequency of complications occurring during pregnancy for women with psoriasis and/or PsA and to compare these outcomes with the general obstetric population by using the largest inpatient care database.

Methods: By using the 2003-2011 Nationwide Inpatient Sample of Healthcare Cost and Utilization Project, we estimated the number of obstetric hospitalization, deliveries and caesarean deliveries in women between the age group 18-50 years. Patients hospitalized with psoriasis and/or PsA were identified. Demographic characteristics and in-hospital outcomes were recorded for both psoriasis and/or PsA as well as control group. Subsequently, obstetric complications for all pregnancy-related admissions for women with and without psoriasis and/or PsA were compared. Multivariate logistic regression analysis was used to obtain adjusted odds ratio (OR).

Results: The total number of obstetric hospitalization was 42.32 million, of which 11204 were women with diagnosis of psoriasis and/or PsA. The mean maternal age of this population was higher (30.32 years) than the control group (27.32 years) { $p < 0.001$ }. After adjusting for potential confounders, the results suggest that maternal Psoriasis/PsA population had no significant increase in inpatient mortality or fetal death. Prevalence of preterm delivery, premature rupture of membranes, postpartum hemorrhage and cesarean delivery was also similar among the two groups. Interestingly, the odds of hypertensive diseases in psoriasis/PsA patients was significantly lower. The results do suggest that psoriasis/PsA patients may have a higher risk of intrauterine growth retardation. The frequencies of the above outcomes along with Odds Ratio are provided in Table 1.

Conclusion: Based on our study of national cohort, we conclude that pregnancies in women with psoriasis and PsA are relatively safe without any increase in maternal or fetal mortality despite having a higher maternal age. These data are reassuring that these women also do not have higher risk of adverse outcomes of pregnancy than women without psoriasis and PsA. In contrast, RA patients have worse outcomes based on the same analysis. These findings highlight that psoriasis and PsA patients may have a positive/normal physiologic response to pregnancy than RA patients. We suggest that continued close antenatal and post-delivery monitoring pregnancy be performed until these results are further clarified.

Table 1. Obstetric Outcomes for Pregnancy Related Hospitalizations in Psoriasis and Psoriatic Arthritis

	Total	Psoriasis/PsA	Controls	OR	p-value
Number of Pregnancies	42317648	11204	42306444	N/A	N/A
Mean Age		30.34	27.32		<0.001
Fetal Death	259227	60(0.5%)	259167(0.6%)	0.863	0.301
Inpatient Mortality	9628	9(0.1%)	9619(0%)	N/A	0.967
Pre-term delivery	2798719	835(7.5%)	2797884(6.6%)	1.018	0.657
PROM	1456335	93(3.7%)	1456242(3.4%)	1.016	0.769
Cesarean-delivery	11857999	3510(31.3%)	11854489(28%)	0.958	0.063
PPH	1106419	262(2.3%)	1106157(2.6%)	0.948	0.426
APH	863232	216(1.9%)	863016(2%)	0.863	0.160
Hypertensive Diseases	3757992	1526(13.6%)	3756466(8.9%)	0.835	0.000
IUGR	774439	294(2.6%)	774145(1.8%)	1.446	0.000

Abbreviations: AS: Ankylosing Spondylitis, OR: Odds Ratio, N/A: Not applicable, IUGR: Intra-uterine Growth Retardation, PROM: Premature Rupture of Membranes, APH: Ante-partum Hemorrhage, PPH: Post-partum Hemorrhage

Disclosure: S. Boddeda, None; N. Harrison, None; S. Kishore, None; V. Majithia, None.

Abstract Number: 970

Baricitinib in Patients with Systemic Lupus Erythematosus: Results from a Phase 2, Randomized, Double-Blind, Placebo-Controlled Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical I: Clinical Trials

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Baricitinib (Bari), an oral selective inhibitor of Janus kinase (JAK)1 and JAK2, has been approved for the treatment of RA in the Europe and Japan. The purpose was to report results from a 24-week(wk) global, Phase 2, double-blind, placebo (PBO)-controlled study of Bari in patients with SLE receiving standard therapy.

	PBO (N=105)	Bari 2-mg (N=105)	Bari 4-mg (N=104)
Efficacy measure	Week 24		
Resolution of arthritis or rash (SLEDAI-2K)	56 (53.3)	61 (58.1)	70 (67.3)*
SRI-4	50 (47.6)	54 (51.4)	67 (64.4)*
Flare (SFI, any severity)	54 (51.4)	45 (42.9)	34 (32.7)*
Flare (SFI, severe)	12 (11.4)	10 (9.5)	6 (5.8)
LLDAS	27 (25.7)	35 (33.3)	40 (38.5)*
ΔTJC	-5.56	-6.50	-6.80*
ΔSJC	-4.60	-4.12	-4.76
ACLA3 activity score	-2.80	-1.60	-2.27
ΔWorst pain	-0.50	-1.17	-1.31*
ΔWorst fatigue	-1.10	-1.13	-1.52*
Safety measure	Weeks 0-24†		
TEAEs	80 (54.8)	75 (71.4)	76 (73.1)
SAEs	5 (4.8)	11 (10.5)	10 (9.6)
Serious infections	1 (1.0)	2 (1.9)	6 (5.8)
Deep vein thrombosis	0	0	1 (1.0)

Data are n (%) patients, unless otherwise indicated. *least squares mean change from baseline. †includes up to 36 days post treatment. ACLA3=Cutaneous Lupus Erythematosus Disease Area and Severity Index; N=number of patients in the analysis population; n=number of patients in the specified category; TEAE=treatment-emergent adverse event. *p<0.05.

Methods: Patients with SLE (positive ANA or anti-dsDNA, clinical SLEDAI-2K ≥4, arthritis or rash required) receiving stable background SLE therapy were randomized 1:1:1 to PBO, or Bari (2- or 4-mg) once daily. The primary endpoint was resolution of SLEDAI-2K arthritis or rash at Wk24.

Results: Of 314 patients randomized, 79%, 82%, and 83% completed 24 wks of treatment in PBO, Bari 2-mg, and Bari 4-mg groups, respectively. At Wk24, a significantly greater proportion of patients in Bari 4-mg group compared to PBO achieved resolution of SLEDAI-2K arthritis or rash (67% vs 53%, p<0.05); and SLE Responder Index (SRI)-4 response (64% vs 48%, p<0.05). At Wk24, the proportion of patients achieving flare reduction (SELENA-SLEDAI Flare Index [SFI]), Lupus Low Disease Activity State (LLDAS), and tender joint count (TJC) change from baseline were also significantly improved for Bari 4-mg compared to PBO (Table). No statistically significant differences were observed between Bari 2-mg and PBO in any of the above endpoints. Rates of adverse events leading to treatment discontinuation and serious adverse events (SAEs) were higher for both Bari dose groups compared to PBO. There were no deaths, malignancies, major adverse cardiovascular events, tuberculosis, or serious herpes zoster infections; 1 SAE of deep vein thrombosis was reported in a patient with risk factors (Bari 4-mg group).

Conclusion: In patients with SLE receiving standard background therapy, once-daily oral Bari 4-mg was associated with significant clinical improvements compared to PBO and an acceptable benefit/risk profile. These findings support further study of Bari 4-mg as a potential therapy for patients with SLE.

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Abstract Number: 971

A Phase III Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Abatacept or Placebo on Standard of Care in Patients with Active Class III or IV Lupus Nephritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018
Session Title: Systemic Lupus Erythematosus – Clinical I: Clinical Trials
Session Type: ACR Concurrent Abstract Session
Session Time: 4:30PM-6:00PM

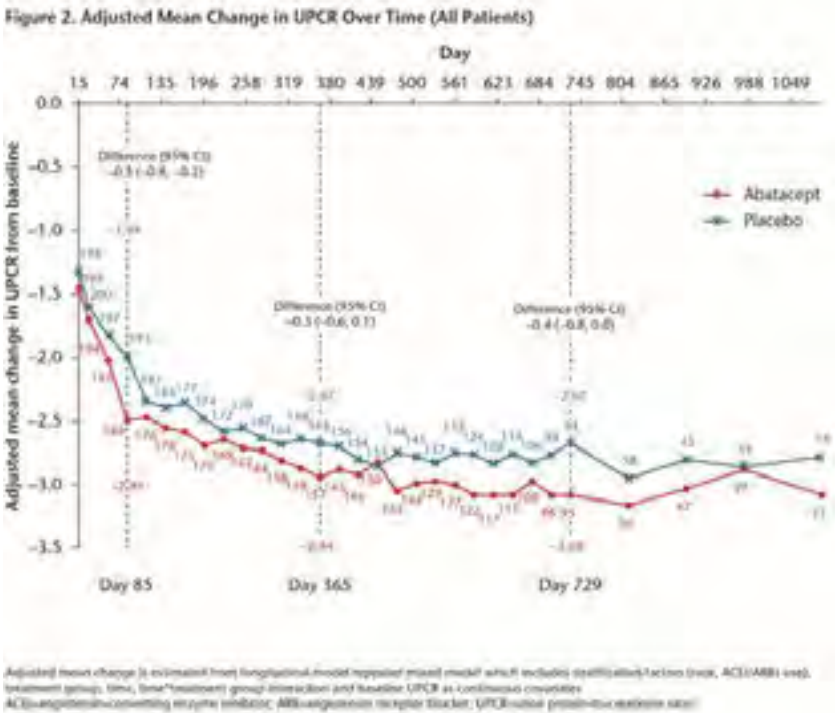
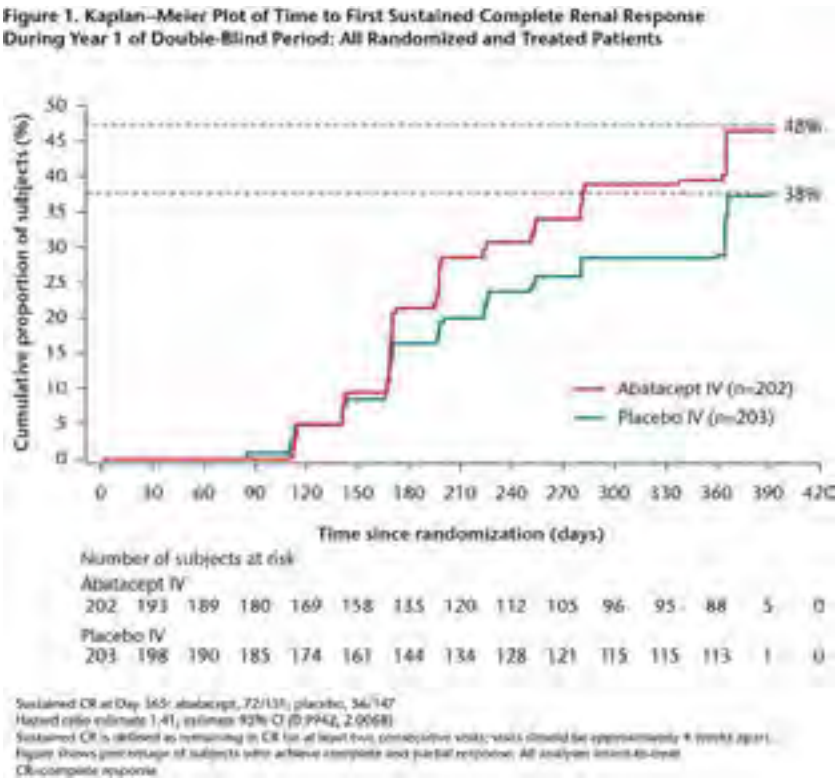
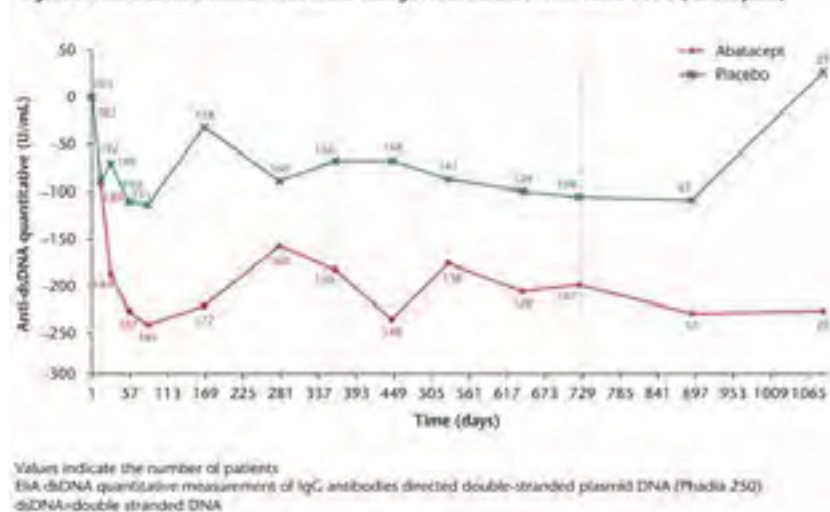


Figure 3. Anti-Double Stranded DNA Mean Change From Baseline From Years 1 to 3 (All Subjects)



Background/Purpose: The tenets of novel treatment (tx) strategies for active class III/IVlupus nephritis (LN) aim to improve renal response rates, decrease extra-renalSLE disease activity and provide an acceptable tx-related safety profile. The study compared efficacy and safety of IV abatacept (ABA) vs placebo (pbo) on background therapy for active proliferative LN.

Methods: This was a 24-month (M), randomized, Phase III, multicenter, double-blind study with a blinded long-term extension. Patients (pts) were randomized 1:1 to pbo or IV ABA 30mg/kg for 3M, followed by ABA ~10 mg/kg every 4 wks on a background ofmycophenolate + corticosteroids (CS). Primary endpoint, complete renal response (CR) at 1 yr, was a composite measure requiring maintenance of glomerularfiltration rate (GFR), urine protein-to-creatinine ratio (UPCR) ≤ 0.5 , absence of urinary cellular casts and CS ≤ 10 mg/day. We report all blinded data up to 3 yrs of tx (as-observed analysis).**Results:** 405pts were randomized (ABA n=202, pbo n=203). At baseline mean age=33 yrs, meanUPCR=3.78, mean eGFR=95 mL/min. Yr 1 study completion rates: ABA 77%, pbo 79%;fewer ABA pts discontinued in Yr 2 (ABA 14%, pbo 22%) and beyond. There were nosignificant differences between tx arms in proportion of pts with CR after 52wks of tx (ABA 35.1%, pbo 33.5%, $p=0.73$). Sustained CR (2 successive visits) occurred earlier and more frequently in ABA-treated pts (Fig 1). Renal response rates were higher and non-response rates were lower in ABA arm in Yr 2 and 3. These benefits were driven by improvement in proteinuria seen as early as 3M and sustained up to 3 yrs (Fig 2).There was no between-group difference in eGFR over 3 yrs. Few non-renal adjudicated BILAG A or B events occurred in Yr 1 and over 3 yrs; BILAG scores were lower in ABA arm. Safety in Yr 1 was consistent with known profile of ABA(serious AE [SAE] rate: ABA 24%, pbo 19%). SAE rates after Yr 1 improved (ABA6%, pbo 13%). Deaths over 3 yrs were equal (7 each). Greater improvements inSLE-related biomarkers (C3, C4, anti-dsDNA autoantibodies) were sustained inABA-treated pts over 3 yrs (Fig 3).

Conclusion: The study failed to meet its primary endpoint of higher CR rate in pts with active LN after 1 yrof abatacept tx. Abatacept-treated pts had more rapid improvement inproteinuria, which led to more sustained CR up to 3 yrs. There were favorable efficacyand safety profiles in Yr 2 and 3 of abatacept tx.

Disclosure: M. A. Dooley, None; G. B. Appel, Bristol-Myers Squibb, 2; R. Furie, Bristol-Myers Squibb, 2, 5; D. Wofsy, GSK, Novartis, Takeda and Celgene, 5; T. Takeuchi, Astellas Pharma Inc, Bristol-Myers K.K., Chugai Pharmaceutical Co, Ltd., Daiichi Sankyo Co., Ltd., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Ltd., AbbVie GK, Asahikasei Pharma Corp., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., 2,Astra Zeneca K.K., Eli Lilly Japan K.K., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Co., Abbvie GK, Nipponkayaku Co.Ltd, Janssen Pharmaceutical K.K., Astellas Pharma Inc., Taiho Pharmaceutical Co., Ltd., 5,AbbVie GK., Bristol-Myers K.K., Chugai Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., and Astellas Pharma Inc, and Diaichi Sankyo Co.,Ltd., 8,Taisho Toyama Pharmaceutical Co., Ltd., Eisai Co., Ltd., AYUMI Pharmaceutical Corporation, Nipponkayaku Co.Ltd, 2; A. Malvar, None; A. Doria, AstraZeneca, Baxalta, Bristol-Myers Squibb, Celgene, Eli Lilly, GSK, 5,Bristol-Myers Squibb, GSK, Eli Lilly, 8; J. Romero-Díaz, None; T. M. Chan, Astellas, Novartis, Boehringer Ingelheim, 5,Astellas, 2; A. Elegbe, Bristol-Myers Squibb, 3; D. Jayne, GSK, Roche, Sanofi, 2,Aurinia, Boehringer Ingelheim, Chemocentryx, CSL, GSK, Influx, Medimmune, Takeda, Sanofi, 5; M. A. Maldonado, Bristol-Myers Squibb, 1, 3.

An Anti-CD28 Domain Antibody, Lulizumab, in Systemic Lupus Erythematosus: Results of a Phase II Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical I: Clinical Trials

Session Type: ACR Concurrent Abstract Session

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Background/Purpose: The T cell costimulatory molecule, CD28, is critical for the activation of pathogenic T cells in autoimmune diseases.^{1,2} An anti-CD28 domain antagonist antibody, lulizumab pegol (lulizumab), was evaluated in a Phase 2 study in subjects with active systemic lupus erythematosus (SLE).

Methods: In a 24-week randomized, multicenter, double-blind study of subjects meeting the American College of Rheumatology criteria for SLE^{3,4}, lulizumab was administered SC at doses of 1.25 mg every other week (EOW), 5 mg EOW, 12.5 mg EOW, or 12.5 mg weekly, or placebo (PBO) SC, on a background of standard of care (SOC) medications. Subjects were required to have elevated serum antinuclear antibodies, as well as BILAG “A” (severe) or “B” (moderate) arthritis and/or cutaneous manifestations, and SLEDAI ≥ 6 (at least 4 from clinical features). The maximum dose of corticosteroids could not exceed 30 mg/day of prednisone or equivalent at screening and no more than 10 mg/day at Day 1. The primary endpoint was the proportion of responders using the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) at Day 169 (Week 24).

Results: 349 subjects with SLE were randomized in five treatment arms (N=68-71/arm). There were no differences in the BICLA response rate at Day 169 (PBO = 59.2%, 1.25 mg EOW = 58.6%, 5 mg EOW = 57.4%, 12.5 mg EOW= 63.2% and 12.5 mg weekly=59.4%). Additional efficacy outcome measures (e.g. SRI-4, SRI-6, SRI-8, SLEDAI change from baseline, CLASI change from baseline, CLASI20 and CLASI50) also did not reveal significant differences between groups. Dose-dependent CD28 receptor occupancy correlated with drug exposure. Lulizumab treatment resulted in effects on T and B cell subsets and on markers consistent with the proposed CD28 mechanism of action. Lulizumab appeared to be well-tolerated overall (Table 1).

Table 1. Summary of safety over 24 weeks

	PBO (N=71)	1.25 mg EOW (N=70)	5 mg EOW (N=68)	12.5 mg EOW (N=68)	12.5mg W (N=69)
Deaths, n (%)	0	2 (2.9)	0	0	0
SAEs, n (%)	6 (8.5)	8 (11.4)	9 (13.2)	4 (5.9)	5 (7.2)
Related SAEs, n (%)	1 (1.4)	0	5 (7.4)	3 (4.4)	3 (4.3)
Discontinued due to SAEs, n (%)	1 (1.4)	5 (7.1)	4 (5.9)	2 (2.9)	3 (4.3)
Total subjects with AEs, n (%)	61 (85.9)	59 (84.3)	60 (88.2)	56 (82.4)	59 (85.5)
Discontinued due to AEs, n (%)	3 (4.2)	9 (12.9)	9 (13.2)	5 (7.4)	8 (11.6)

• 2 deaths in 1.25 mg EOW group were due to cerebral haemorrhage and SLE

Conclusion: There was no significant difference between lulizumab and placebo for the primary (BICLA response rate) or secondary endpoints at Week 24, although PD activity was observed. Lulizumab had a favorable safety profile.

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Disclosure: J. T. Merrill, BMS, GSK, 2,BMS, GSK, UCB, Questcor, EMD Serono, Amgen, Celgene, Pfizer, RemeGen, Exagen, MedImmune, Lilly, Janssen, Xencor, Sanofi, Neovacs, Immupharma, Astellas, Glenmark, ILToo, 5,Have given talks for BMS but not for Speaker’s bureau, 9; D. E. Shevell, Bristol-Myers Squibb, 1, 3,Merck & Co., Inc., 1; D. Duchesne, Bristol-Myers Squibb, 1, 3; M. Nowak, Bristol-Myers Squibb, 1, 3; S. Kundu, Bristol-Myers Squibb, 3; I. G.

Girgis, Bristol-Myers Squibb, 1, 3; Y. S. Hu, Bristol-Myers Squibb, 1, 3; S. G. Nadler, Bristol-Myers Squibb, 1, 3; S. Banerjee, Bristol-Myers Squibb, 1, 3; J. Throup, Bristol-Myers Squibb, 1, 3.

Abstract Number: 973

Low-Dose IL-2 Combined with Rapamycin Efficiently Promoted Disease Remission and Recovered the Balance of Th17/Regulatory T Cells in Patients with Refractory Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

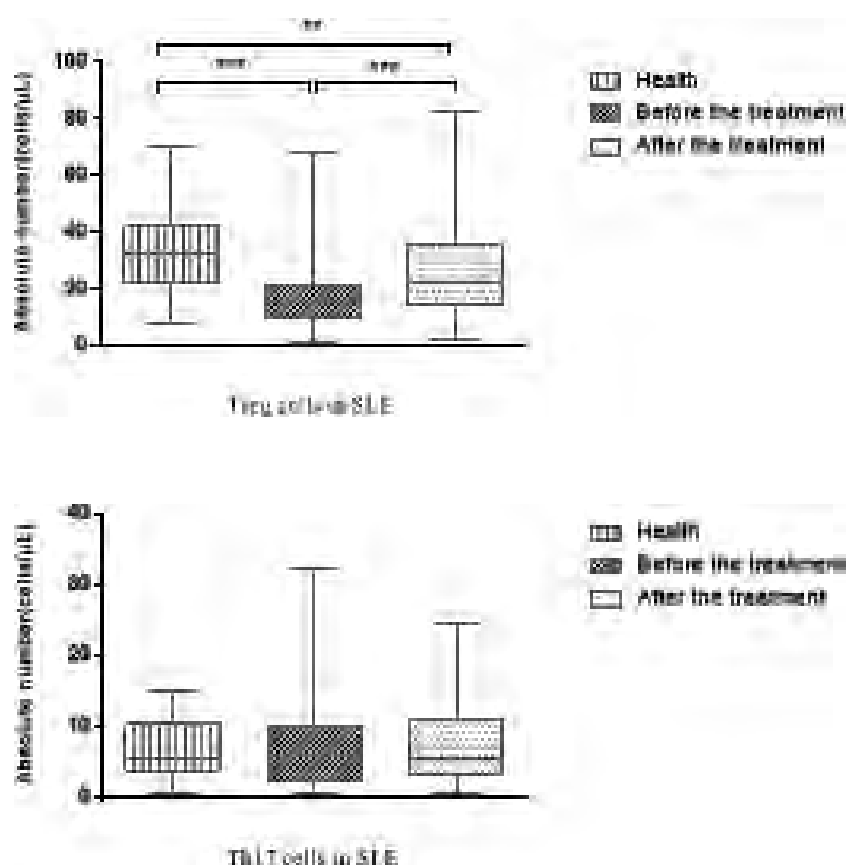
Session Title: Systemic Lupus Erythematosus – Clinical I: Clinical Trials

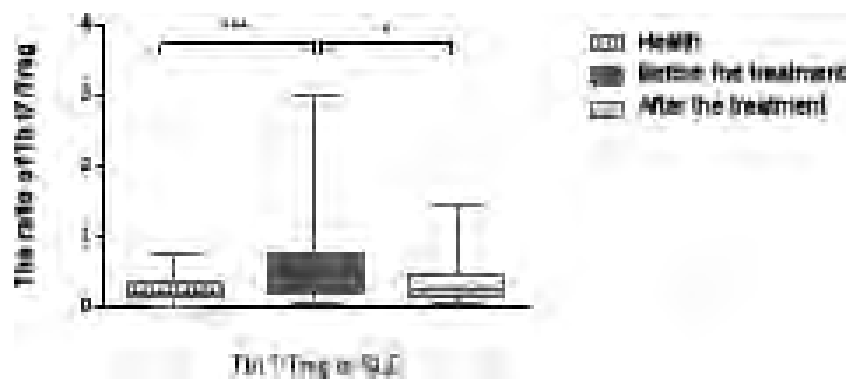
Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: To observe the clinical effect of low-dose IL-2 combined with rapamycin on the balance of Th17/Treg cells and on remission of patients with refractory SLE.

Methods: Ninety refractory SLE patients (96.7% women; mean age 35.85 ± 12.41 years; mean duration 76.98 ± 47.24 months) were enrolled. They were in line with the standard of ACR in 1997 and did not achieve remission by the treatment of glucocorticoid and immunosuppressant for more than one year. Low-dose IL-2 was used among these patients at a dosage of 50 WIU every day for five days and rapamycin (0.5mg each time, twice per week). At baseline, 6, 12, and 24 weeks, respectively, after the therapy combined with conventional drugs, absolute numbers of Th17 and Treg cells were assayed by flow cytometry and other clinical and laboratory data, including the dosage of corticosteroids and immunosuppressant, were collected.





Results: After 24 weeks, administration of low doses of IL-2 and rapamycin promoted 26.2% of patients with refractory SLE to achieve remission, leading to an increase in the absolute number of Treg cells from a median of 14.17 cells/ μ l (at week 0) to 21.66 cells/ μ l (at week 24) ($P=0.001$). The ratio of Th17/Treg cells showed a reduction from a median of 0.44 at week 0 to 0.29 at week 24 ($P=0.029$), indicating a restored balance of them. No significant differences were observed in the absolute number of Th17 cells before and after the combined treatment. At week 24, the mean dosage of prednisone, which refractory SLE patients were receiving, decreased from 18.64 mg/d to 8.80 mg/d. And the categories of DMARDs used were also reduced ($P<0.001$).

Conclusion: Our results suggest that refractory SLE is mainly associated with the decreased number of peripheral Treg cells but not increase in that of Th17 cells. Low-dose IL-2 combined with rapamycin treatment promoted patients with refractory SLE to achieve remission and recovered the balance The Th17 and Treg cells due to an increase in the number of Treg cells. This treatment also reduced the usage of glucocorticoid and DMARDs.

Disclosure: X. Jing, None; C. Gao, None; L. Hao, None; M. Hao, None; Z. Liang, None; X. F. Li, None; J. Chen, None.

Abstract Number: 974

Leflunomide Versus Azathioprine for Maintenance Therapy of Lupus Nephritis: A Prospective, Multicenter, Randomized, Open-Label Clinical Trial

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical I: Clinical Trials

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Previous studies have compared mycophenolate mofetil (MMF) and azathioprine (AZA) as maintenance therapy of lupus nephritis(LN). Leflunomide(LEF) is an immunosuppressive agent widely used in the treatment of rheumatoid arthritis. In 2009, China Food and Drug Administration approved leflunomide for the treatment of LN. However, a randomized controlled trial of LEF for the maintenance treatment in patients with LN has not been reported. The aim of the investigator-initiated study was to compare the efficacy and safety of LEF versus AZA as maintenance therapy for LN.

Methods: 270 adult patients with biopsy-confirmed active LN (class III/IV/V) were enrolled in 7 Chinese rheumatology centers from 2010 to 2015. All patients received induction therapy with six monthly intravenous cyclophosphamide (0.5 g per square meter of body-surface area) plus steroids (starting from 1mg/kg/d and tapering according to protocol). The patients who achieved remission (complete or partial remission ,CR or PR) were randomized to receive prednisone (10mg/

d) in combination with either oral LEF (20mg/d) or oral AZA (initial dose 50mg/d, and after one month increased to 100mg/d) as maintenance therapy for 24 months.

The primary efficacy end point was the rate of renal flare in 24 months. Secondary outcomes included clinical parameters, extrarenal flare and adverse effects. The clinical and laboratory parameters were compared during follow-up by using nonparametric statistical tests. Time to event analysis was performed by the Kaplan-Meier method. This study has been registered on ClinicalTrials.gov (NCT 01172002).

Results: A total of 215 patients who had achieved CR or PR were randomly allocated to LEF group (n=108) and AZA group (n=107). The baseline clinical, biological and pathological characteristics of patients in two groups did not differ. Renal flares were observed in 12 (11.1%) LEF-treated and 15 (14.0%) AZA-treated patients (p=0.520). Time to renal flare did not statistically differ (LEF 9.83 months vs. AZA 10.93 months, p=0.241). For LN patients who achieved CR in induction phase, lower risk of renal flare was observed in LEF group than in AZA group (6.7% vs. 14.3 %, p=0.116). The CR rate in both groups continued to increase with time (LEF: from 60.2% to 87.7% after 24 months, and AZA: 71.9% to 88.7%). Over a 2-year period, 24h proteinuria, serum creatinine, serum albumin, serum C3 and serum C4 improved similarly in both groups. Sustained doubling of serum creatinine or end-stage renal failure was not observed in both groups. Extrarenal flare occurred in 2 patients from AZA group and 1 patient from LEF group. The incidence of adverse events during the 2-year treatment was similar in the two groups: LEF (43.5%, 47/108) and AZA (42.1%, 45/107), respectively. There was no significant difference in the incidence of leukopenia (28.7% and 28.97%), abnormal elevation of liver enzyme (21.3% and 20.56%), and anaemia (12.0% and 12.2%) between groups.

Conclusion: LEF is non-inferior to AZA for maintenance therapy of LN in terms of efficacy and safety profile. With maintenance therapy for 2 years, a trend of lower rate of relapse and higher CR rate was observed in the LEF group. LEF may become a new candidate medicine for maintenance therapy of LN.

Disclosure: Q. Fu, None; L. Lu, None; J. Xu, None; L. Dai, None; L. Zhijun, None; L. He, None; X. Zhu, None; L. Sun, None; C. Bao, None.

Abstract Number: 975

Alteration of Vascular Inflammatory Markers in SLE By Anifrolumab in the Phase IIb Muse Study

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Systemic Lupus Erythematosus – Clinical I: Clinical Trials

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Cardiovascular disease is a leading cause of death for patients with systemic lupus erythematosus (SLE), and the disease is widely known to feature premature atherosclerosis promoted by immune dysregulation. Neutrophil extracellular traps (NETs) can induce endothelial dysfunction and promote inflammatory events. Furthermore, sources of reactive oxygen species released during NET formation promote oxidized high-density lipoprotein, leading to deficient cholesterol efflux capacity (CEC). Type I interferons (IFNs) stimulate NET formation and inhibit vascular repair. Anifrolumab is a fully human, IgG1 κ monoclonal antibody that binds to IFNAR1 and blocks signaling of all type I IFNs. Thus, anifrolumab may decrease mechanisms of vascular damage in SLE. We evaluated the ability of anifrolumab to reduce *in-vivo* NET formation and improve CEC relative to standard of care (SOC) in MUSE.¹

Methods: Baseline IFN gene signature (IFNGS) test status (high/low) of MUSE patients was determined as described.¹ All patients satisfied the ACR classification criteria for lupus.¹ Plasma samples from fasting patients (n=190) were obtained at days 1 and 365 of the MUSE study. Plasma MPO-, HNE- and CitH3-DNA NET complexes were quantified by ELISAs in the MUSE and healthy donor (HD) samples (n=20) as described.² Wilcoxon rank-sum test assessed differences between groups. Post-treatment samples from the 300 mg anifrolumab (n=73) and placebo (n=52) groups were compared with baseline samples. Significance of change from baseline was determined using Wilcoxon signed-rank test. CEC was tested as described.³ Reproducibility of the CEC assay was assessed using percent coefficient of variation (CV) from the analysis of variance (ANOVA). SLE patients with defective baseline CEC were identified as those with CEC < (the HD mean value - 2 standard deviations) in the same testing run.

Results: All 3 neutrophil NET complexes (NNCs) were elevated in SLE patients ($p<0.01$) and were significantly enriched in IFN test-high patients ($p<0.05$). Anifrolumab significantly decreased all 3 NNCs at Day 365 vs. Day 1 ($p\leq 0.05$), whereas in the placebo group, complexes did not change or increased. The repeatability of the CEC assay was 7.5% across 2 days of testing for a subset of 26 baseline samples, and longitudinal changes in steroid dosage for the placebo group did not affect CEC. Greater baseline NET complex levels significantly correlated with poor baseline CEC ($p<0.05$). Anifrolumab significantly increased CEC in IFNGS test-high patients with defective CEC at baseline ($p<0.001$), whereas no significant changes occurred in the placebo group.

Conclusion: Circulating NNCs were significantly elevated in patients with moderate to severe SLE compared with HDs. Anifrolumab decreased circulating NNCs. Although changes in steroid dosages during MUSE did not affect CEC, anifrolumab significantly improved CEC. This work supports continued assessment of anifrolumab effects on vascular diseases and endothelial damage in SLE.

¹Furie R, et al. *Arthritis Rheumatol.* 2017;69:376–86.

²Demoruelle MK, et al. *Arthritis Rheumatol.* 2017;69:1165–75.

³Salahuddin T, et al. *Eur Heart J.* 2015;36:2662–5.

Disclosure: K. Casey, AstraZeneca, 1, MedImmune, 3; W. White, AstraZeneca, 1, MedImmune, 3; N. L. Seto, None; M. Playford, None; M. Smith, AstraZeneca, 1, MedImmune, 3; P. Carlucci, None; B. Yu, AstraZeneca, 1, MedImmune, 3; L. Wang, AstraZeneca, 1, MedImmune, 3; G. Illei, AstraZeneca, 1, MedImmune, 5; N. Mehta, AbbVie, Novartis, Janssen, and Celgene, 2; M. J. Kaplan, MedImmune, 2.

Abstract Number: 976

Transitioning from Paediatric to Adult Health Services: Development of an Integrated Programme Incorporating Patient and Provider Values

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²Rheumatology, Bone and Joint Institute, John Hunter Hospital, Newcastle, Australia, ³University of Newcastle, Newcastle, Australia, Newcastle, Australia, ⁴HNEkidshealth, Hunter New England Local Health District, Newcastle, Australia, ⁵Transition Care Network, Agency for Clinical Innovation, Sydney, Australia, ⁶Paediatric Rheumatology, John Hunter Hospital, Newcastle, Australia, ⁷Rheumatology, Sydney Children's Hospital Network, Randwick and Westmead, Australia

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: The transfer from the supportive and guided environment of paediatric to adult care with its increased emphasis on autonomy and self reliance poses challenges for patients and clinicians. Challenges, which if not recognised, and adequately met, can lead to poor health outcomes.

We sought to develop an integrated programme incorporating patient and carer perception of important issues and information from published models of transition.

Project Aims :

1. To develop a disease relevant, location and community appropriate value transition pathway and package
2. To set up a dedicated clinic for adolescents and young adults with rheumatic disease (AYARD)

Methods: Programme Development

Stage 1: Review of existing programmes

- literature search and personal contact with other institutions and local transition services

Stage 2: Determination of patient and carer perspectives

- Systematic qualitative study of patient attitudes and experiences (Kelly A, Niddrie F, Tunnicliffe D, Hanson C, Major G, Singh-Grewal D, Tong A. Patients' attitudes and experiences of transitional care in paediatric rheumatology: A systematic review of qualitative studies, *Arthritis Rheumatol.* 2017; 69(S10):1-4481)
- Survey by anonymous questionnaire of local >13 year old clinic patients and parents/carers, inviting feedback on the need for an AYARD clinic

Stage 3: Pathway development

- Focus meetings of key personnel (paediatric, adult and adolescent medical, nursing specialists and administrative staff)

- Utilise findings from stage 1 and 2

Results:

1. Identified key components for effective transition
 - Literature review
 - Written transition protocol
 - Dedicated coordinator
 - Age and skill appropriate progression
 - Flexibility in timing
 - Shared care between paediatric and adult team
 - Programme evaluation
 - Systematic qualitative study of patient/carer perspectives
 - Building trust in familiarity
 - Creating a sense of belonging
 - Facilitating the quest for autonomy
2. Patient and Parent/carer attitude to transition.
 - Questionnaire response with 92% strongly supportive of AYARD clinic
3. Programme development
 - Dedicated local coordinator appointed
 - Orientation visit and guided tour for new patients
 - 3 stage transition based on individual needs and skill development
 - Package of documents, including transition pathway, information booklet, skills assessments, clinician checklists, transition plans, transfer document
 - Annual combined paediatric and adult consultations
4. Effectiveness assessment
 - An evaluation tool focused on key programme objectives and incorporating patient reported outcomes is being developed

Conclusion: Paediatric and adult rheumatology services at one location allows a collaborative and coordinated approach to transition. A dedicated clinic, designated coordinator, formal transition pathway, and service specific resources, is anticipated to improve outcomes for patients transitioning from paediatric to adult rheumatology services. Evaluation is required to demonstrate effectiveness.

Disclosure: F. Niddrie, None; G. Major, None; A. Myles, None; D. Singh-Grewal, None; J. Chaitow, None.

Abstract Number: 977

Nurse Led Safe Switching from Original Reference Product Infliximab to Biosimilar in Patients with Juvenile Idiopathic Arthritis and Uveitis – a Single Centre Experience Including Baseline and Post Switch Infliximab Levels and Antibodies

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Original Reference Product (ORP) Infliximab lost market exclusivity in Europe in early 2015. The Scottish National Health service (SNHS), runs a national procurement system called the Clinical Advisory Panel (CAP). CAP recommended all patients new to Infliximab were commenced on biosimilar Infliximab (BIFX). To encourage

switching a project run by NHS Healthcare Improvement Scotland, produced targets for biosimilar uptake and advised the setting up of local drug efficiencies committees. In early 2017 we had a cohort of young people remaining on ORP that we are asked to consider their infliximab preparation.

Methods: The Royal Hospital for Children in Glasgow (RHCG) had a cohort of children principally with Juvenile Idiopathic Arthritis (JIA) and uveitis remaining on ORP infliximab. This use is off market label both with the European Medicine Agency and the Federal drug administration. After a review of evidence the RHCG Rheumatology team regarding the safety of switching elected to create a patient evaluation protocol for switching and patient information. Patients were identified from the Health-board wide IT system. Within the same time period a trial project for measuring trough drug levels and antibodies was introduced in Scotland using the Grifols promonitor system. It was decided to monitor these variables whilst switching. A drug and antibody level was to be taken immediately preceding the planned dose of Biosimilar Infliximab, then again 3 to 4 doses after switching or not. All patients and families were sent out information regarding the possible swap and met individually by a member of the nursing team to discuss the possible change of preparation. At point of switch offer, 12 young people were identified on ORP; 8 with JIA + Uveitis, 2 with idiopathic Uveitis, 1 with sympathetic Uveitis, 1 with JIA. All had clinically inactive disease, from last clinical review.

Results: Of the young people; 6 completed the switch, however 1 was found clinically flaring with active uveitis 4 days after switching. Their pre switch drug levels were low with high antibodies causing a change of therapy and are now in clinical remission. The five who completed the switch remain in clinical remission, this group is too small for any statistical interpretation but drug levels and antibodies are comparable pre and post switch. The 6 who did not swap at original offer to BIFX; 1 did not qualify for switching to biosimilar, 1 elected not to switch, 1 stopped, 1 changed therapy due to geography, 2 changed therapy due to personal choice. Within this group of 6, 3 maintained no active disease, 2 remaining on ORP and one swapped to Adalimumab. 3 developed active disease, 1 has commenced Adalimumab, 2 have attempted multiple biologics and have returned recently to IFX one on ORP and one BIFX. Both are returning to low disease activity. Of the initial group of 12, 4 are on ORP, 5 on BIFX, 3 are on Adalimumab. Pre and post switch period Infliximab levels and antibodies are available for 8 young people. They are comparable regardless of switch. **Conclusion:** Switching was not associated with any adverse events. Disease activity measures for those remaining on IFX were unchanged on either ORP or Biosimilar. Stopping Infliximab was associated with disease flare.

Disclosure: A. Fell, AbbVie Inc., 8; E. Carson, None; G. Coyle, None; N. Martin, None; J. Walsh, None; J. Gardner-Medwin, None.

Abstract Number: 978

Treat-to-Target Study for Improved Outcome in Polyarticular Juvenile Idiopathic Arthritis

Gerd Horneff¹, Ivan Foeldvari², Ralf Trauzeddel³, Toni Hospach⁴, Kirsten Minden⁵, Hans-Iko Huppertz^{6,7} and Ariane Klein⁸, ¹Asklepios Klinik Zentrum für Allgemeine Paediatric und Neonatologie, Sankt Augustin, Germany, ²Hamburger Zentrum für Kinder- und Jugendrheumatologie, Hamburg, Germany, ³Helios Clinics, Berlin, Germany, ⁴Pediatrics, Olgahospital, Klinikum Stuttgart, Stuttgart, Germany, ⁵Charité-Universitätsmedizin Berlin, Berlin, Germany, ⁶Prof Hess Clinic, Bremen, Germany, ⁷Prof. Hess Childrens Hospital, Bremen, Germany, ⁸Center of Pediatrics and Neonatology, Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Juvenile idiopathic arthritis (JIA) is one of the most prevalent chronic diseases of childhood and adolescence. Evidence suggests that early effective treatment is important to minimize the burden of disease during childhood and in further life. We hypothesize that a guided treat to target (T2T) approach as recommended by the German Society for Pediatric Rheumatology (1) is superior to routine care in polyarticular JIA (pJIA) in terms of reaching a clinical state of remission after 12 months of treatment.

Methods: After informed consent, patients with early (disease duration ≤ 12 months) and active (JADAS10 ≥ 5.4) pJIA were enrolled. Targets for treatment were defined by the level of improvement and are progressively more rigorous with ongoing treatment. Failure to meet a defined target required modification of treatment at specified intervals. Initially, all patients received methotrexate (MTX). The choice of biologic was made by shared decision between the investigator and the patient/parent and not influenced by the protocol. Minimal treatment target defined as recognizable improvement of

disease activity (2) was demanded after 3 months of treatment. Until month 6, a JADAS acceptable disease status, until month 9 JADAS MDA and at month 12 JADAS-remission should be reached.

Results: Altogether 58 patient with non-systemic JIA (44/7 RF negative/RF positive polyarthritis, 3 extended Oligoarthritis, 1 ERA, 1PsA) were included (mean age 9.2+/-4.9 years, disease duration 0.4+/-0.6 years). At month 3; 37/51 (72.5%) of patients showed JADAS improvement. In 13 (25.5%) treatment with a biologic was started. At month 6, 32/41 (78%) had JADAS improvement and 30/41 (73.2%) reached JADAS acceptable disease. In 6 (14.6%) a biologic agent was started. At month 9, 34/37 (92%) showed JADAS improvement, 28/37 (76%) reached JADAS acceptable disease and 23/37 (62%) reached JADAS-MDA. In 4 (10.8%) a biologic was started and one patient switched biologics. So far, 30 patients completed 12 months of observation. JADAS MDA was reached by 22 (76%) and JADAS remission was reached by 13 (45%). In total 24 patients were treated with a biologic agent, 12 (41%) of those were followed until month 12 with 3 patients (25%) reaching JADAS remission and 7 (58%) JADAS MDA. 17 patients were treated with MTX only over 12 months of whom 10 (59%) reached JADAS remission and 15 (88%) JADAS MDA.

N	Baseline n=58	Month 3 n=51	Month 6 n=41	Month 9 n=37	Month 12 n=30
JADAS- minimal response	n.a.	72,5%	78,0%	91,9%	96,5%
JADAS acceptable disease (≤ 5.4)	0,0%	43,1%	73,2%	75,7%	79,3%
JADAS MDA (≤ 3.8)	0,0%	33,3%	61,0%	62,2%	75,8%
JADAS Remission (≤ 1)	0,0%	19,6%	31,7%	43,2%	44,8%
NSAIDs	41,4%	25,5%	12,2%	5,4%	0,0%
Steroids	36,2%	31,4%	12,2%	5,4%	3,3%
MTX	100,0%	88,2%	100,0%	83,8%	76,7%
Biologics	0,0%	25,5%	36,6%	40,5%	41,4%
2nd biologic	0,0%	0,0%	0,0%	2,7%	3,3%

Conclusion: These preliminary data indicate that a T2T concept is feasible. A high rate of patients reached JADAS MDA and JADAS remission after 12 months of treatment. Interestingly, about 60% of patients did not need to be treated with a biologic to reach predefined T2T (2). Thus, the early response seems advantageous indicating a window of opportunity to successfully treat polyarticular JIA.

1. Horneff G et al *Pediatr Rheumatol Online J.* 2017; 15:78

2. Horneff G et Becker I. *Rheumatology.* 2014;53:1229-34.

Disclosure: G. Horneff, None; I. Foeldvari, None; R. Trauzeddel, None; T. Hospach, None; K. Minden, None; H. I. Huppertz, None; A. Klein, None.

Abstract Number: 979

Stopping Medicines for Inactive Juvenile Idiopathic Arthritis: What Do Patients and Families Consider?

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

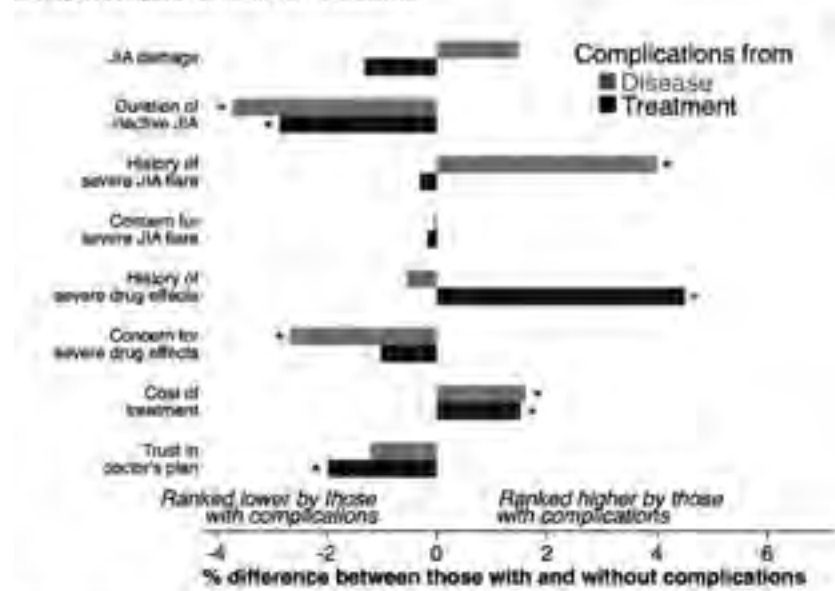
Session Title: Pediatric Rheumatology – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Prior research has focused on factors important to clinicians in decisions about withdrawing JIA therapy. Based on recent interviews with patients and caregivers about stopping JIA therapy, we conducted an online survey to study the trade-offs patients and caregivers consider when deciding to stop treatments.

Figure: Comparison of considerations for decision-making between those who reported and did not report complications from JIA or treatment



Numbers reflect differences in percentage of ranks for each consideration between those with and those without complications of JIA (grey) or treatment (black). * $P < 0.01$

Table: Most highly ranked considerations when deciding to stop treatment

Caregivers	Adults with JIA	Adolescents with JIA
1. Damage from JIA	1. Damage from JIA	1. Damage from JIA
2. Concern for future treatment effects	2. Experience of severe treatment effects	2. Duration of disease inactivity
3. Trust in physician's treatment plan	3. Concern for future treatment effects	3. Trust in physician's treatment plan
4. Experience of severe treatment effects	4. Cost of treatment	4. Concern for future JIA flare
5. Duration of disease inactivity	5. Duration of disease inactivity	5. Concern for future treatment effects
6. Concern for future JIA flare	6. Concern for future JIA flare	6. Ability to skip medicines without problems

Methods: From June 2017 to February 2018, we conducted an anonymous online survey in English and Spanish using REDCap software. We recruited volunteer participants via social media, email, and flyers in pediatric rheumatology clinics in the US and Canada. Eligible participants were (1) adolescents with JIA (13-17y), (2) adults with JIA ($\geq 18y$), or (3) caregivers of children with JIA. Survey questions focused on factors that might influence decisions about stopping JIA treatment. Questions were based on findings from prior interviews and refined via pilot testing. We analyzed responses using descriptive statistics.

Results: 1456 individuals opened the survey and 839 (58%) completed it, including 782 eligible participants (40 adolescents, 120 young adults, and 622 caregivers). A majority of the participants were from the US, had a history of severe JIA flares, and used systemic anti-rheumatic medicines. Overall, adult patients were more likely than caregivers or adolescents to report having more severe disease and more complications from JIA and treatment. Among all groups, damage from JIA was the most highly ranked consideration in deciding whether to stop treatment (Table). Those with prior disease complications (e.g., severe flare, disability) were more likely to prioritize risk of flares in decision-making and generally less concerned about future drug effects (Figure). In contrast, those with prior treatment complications were more likely to prioritize risk of drug side effects (Figure). Trust in physicians was especially important for caregivers and adolescents (Table). Those reporting greater trust in physicians were more willing to accept physicians' recommendations to continue or stop treatment ($P < 0.01$).

Conclusion: Among survey respondents, JIA-related damage was the top consideration in deciding whether to stop treatments for well-controlled JIA. Past complications from JIA or from treatment influenced the ranking of other considerations. Greater trust in physicians increased willingness to accept physicians' recommendations. These findings can help inform shared decision-making when considering whether to stop medicines for well-controlled JIA.

Disclosure: D. B. Horton, Bristol-Myers Squibb, 2; J. Salas, None; A. Wee, None; T. Beukelman, UCB, Inc., 5; Novartis, 5; Sobi, 5; Bristol-Myers Squibb, 5; A. Boneparth, None; J. Guzman, None; K. Haverkamp, None; M. Kohlheim, None; M. L. Mannion, None; N. Moorthy, None; E. Stringer, None; L. Tucker, None; S. Ringold, None; M. Rosenthal, None.

Abstract Number: 980

Long-Term Outcome of Temporomandibular Joint Arthritis in Juvenile Idiopathic Arthritis: Results of 18-Year Follow-up in the Population-Based Nordic JIA Cohort

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Involvement of the temporomandibular joint (TMJ) is a common finding in patients with juvenile idiopathic arthritis (JIA), but the long-term outcome in a non-selected cohort remains unknown. The aims of the study were to assess the symptoms and dysfunction related to TMJ involvement in JIA compared to healthy controls and to describe the frequency of radiological TMJ abnormalities more than 17 years after disease onset.

Methods: From a Nordic, prospective, close to population-based, JIA cohort of 510 consecutive cases with disease onset between 1997 and 2000, 420 were eligible for orofacial evaluation of TMJ involvement.

The follow-up visit included demographic data and a standardized, clinical orofacial examination according to the consensus-based international recommendations¹ and a cone-beam computed tomography (CBCT). Two hundred age-matched healthy, Danish controls were used for comparison. IRB approval was granted.

Results: Out of 420 eligible JIA participants 265 (63%) participants were included (mean age 23.5 (±4.2) years). Of the 265 participants completing the clinical orofacial examination 245 had a full-face CBCT performed. The distribution of the JIA categories was as follows: 4% systemic, 21% persistent oligo articular, 22% extended oligo articular, 20% polyarticular RF negative, 2% polyarticular RF positive, 5% psoriatic, 10% enthesitis-related arthritis (ERA) and 17% undifferentiated JIA.

Orofacial symptoms: In 89/265 (33%) of the participants jaw or facial pain was reported within the last two weeks; of these 53% reported pain less than once a week and 27% reported several times per day or all the time. Compared to the controls, the participants with JIA had significantly more frequent orofacial pain (p=0.027). Of the 265 participants 87

(33%) reported at least one TMJ symptom including TMJ chewing pain, reduced chewing function, TMJ morning stiffness or locking of the TMJ within the last two weeks.

Orofacial dysfunction: Mean maximal incisal opening was significantly reduced in the JIA group (47.2 mm (± 7.7)) when compared to the controls (56.5 mm (± 6.8)) ($p < 0.001$). An asymmetric mouth opening was found in 29/265 cases (11%).

Radiologic TMJ appearance: At least one abnormal radiologic appearance was found in 254/490 (52%) TMJs in 150 participants. Only 95/245 (39%) of the cases demonstrated normal bilateral CBCT findings (Table 1).

Conclusion: To our knowledge, this is the first study on the long-term consequences of TMJ arthritis in a population-based JIA cohort.

1. The participants had significantly more often orofacial pain compared to controls.

2. Maximal incisal opening was significantly lower in the JIA participants.

3. 52% of the TMJs showed abnormal radiological appearance. Only 39% of the participants were without any TMJ abnormalities.

¹ Stoustrup et al. J Rheumatol. 2017 Mar;44(3):326-333.

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Abstract Number: 981

New Consensus on an Updated Core Domain Set for Clinical Trials in Juvenile Idiopathic Arthritis

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SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Pediatric Rheumatology – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: The current JIA Core Set (ACR Pediatric 30) to assess efficacy of medications in randomized controlled trials (RCTs) was published in 1997 and developed without input from patients or caregivers. The current core set includes 6 variables: physician global assessment, parent/patient global assessment of overall wellbeing, physical functional ability, count of joints with active arthritis, count of joints with restricted motion, an acute phase reactant and - for systemic JIA - fever in past week. Outcome Measures in Rheumatology (OMERACT) recommends four core areas to include in RCTs and longitudinal observational studies (LOS) – 1) life impact, 2) pathophysiologic manifestations, 3) resource use, 4) adverse events – and conceptualizes domains along three levels of requirements for inclusion: inner circle – mandatory for all RCTs and LOS; middle circle - important, but optional; outer circle – research agenda. Since 2015, the OMERACT JIA Core Set working group has obtained global stakeholder input from JIA patients, caregivers, health care providers and researchers to update the JIA core domain set. At the OMERACT 2016 meeting, a special interest group voted to reconsider the entire core set. This abstract reports subsequent work.

Methods: Online discussion boards (ODBs) were held with JIA patients and parents in Australia and Italy, and results compared to USA ODBs to generate candidate domains. Three rounds of a Delphi process to prioritize these domains

were held with stakeholders identified by patient advocacy groups, pediatric rheumatology clinical trials organizations and regulators. In the final Delphi round, domains were rated for inclusion in inner, middle or outer circles. Results were presented at the OMERACT conference in May 2018 for consensus among participants, with level of consensus set at $\geq 70\%$.

Results: 53 JIA patients (ages 15-24) and 55 parents participated in ODBs. Three rounds of Delphi considering 27 domains were completed by 196 (response rate 80%), 201 (81%) and 182 (77%) stakeholders, respectively, from 42 countries. Result of the final voting at the OMERACT 2018 conference approved the following core domains for JIA RCTs and LOS with 83% endorsement. Inner circle: pain, activity limitation/physical function, joint inflammatory signs (active joints), patient global assessment, adverse events. Middle circle: extra-articular inflammation (including uveitis), joint damage, labs, physician global assessment, stiffness, growth/maturation, participation restriction, imaging signs of inflammation, fatigue, impact on emotional function/mood/cognition, physical activity. Outer circle: coping with illness, healthcare utilization, sleep, social relationships, personal factors.

Conclusion: We have developed an updated JIA Core Domain Set following OMERACT methodology with qualitative input from patients/parents and broad stakeholders through a Delphi process and consensus voting. A notable change is pain is now recommended as a core domain for all JIA RCTs, LOS. Multiple patient reported domains were also voted as important to consider for inclusion in JIA trials, including fatigue, emotional function, and participation restriction.

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Abstract Number: 982

In the Presence of IL-18, IL-10 but Not IL-6 Induces IFN- γ Production and the Surface Expression of TRAIL on NK Cells

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Cytokines and Cell Trafficking Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Adult-onset Still's disease (AOSD) is a systemic inflammatory disease, the cause of which is largely unknown. AOSD has been recently classified as one of the auto inflammatory diseases in which innate rather than acquired immunity plays an important role in the pathogenesis. Serum IL-18 has been shown to be high in AOSD patients. In this study, we first quantified the levels of multiple cytokines in the serum of AOSD patients and then compared the cytokine profile with that of healthy controls. We next evaluated the effects of the cytokines detectable in the AOSD serum on natural killer (NK) cells, since NK cells are cells of innate immunity and IL-18 has been shown to enhance their cytotoxicity.

Methods: Our patients fulfilled Yamaguchi's criteria for the diagnosis of AOSD. We quantified the serum levels of 10 cytokines (IFN- α , IFN- γ , IL-1 β , IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-17A and TNF- α) using multiplex bead array assays and IL-18 using ELISA. We next sorted NK cells from peripheral blood mononuclear cells of healthy controls and stimulated them *in vitro* in the presence of cytokines that were detected in the AOSD serum. We quantified the level of IFN- γ in the culture supernatant by ELISA and assessed the surface expression level of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) on NK cells by flow cytometry.

Results: The level of IL-18 was high in all of the AOSD samples. IL-6 was detectable in 8 out of 16 patients and IL-10 in 3 out of 16. In contrast, serum IFN- γ was not detected in any sample. When NK cells were stimulated *in vitro* with IL-18 alone, IFN- γ was undetectable in the culture supernatant. The combination of IL-10 and IL-18, but not IL-6 and IL-18, induced IFN- γ . We evaluated the expression of the receptors for IL-6 and IL-10 on NK cells and found that IL-10R and

IL-10RB were present, while IL-6R and gp130 were absent. The combination of IL-10 and IL-18 also induced TRAIL expression on NK cells.

Conclusion: Since IL-18 was originally identified as an inducer of IFN- γ , it was surprising that IFN- γ was not detected in the serum despite the high level of IL-18. Indeed, IL-18 alone did not induce the production of IFN- γ from NK cells *in vitro*. The combination of IL-10 and IL-18, but not IL-6 and IL-18, induced the production of IFN- γ and surface expression of TRAIL on NK cells. As IL-6 is a classic pro-inflammatory cytokine and IL-10 is considered anti-inflammatory, this result was also rather unexpected. The unresponsiveness to IL-6 may be explained by the absence of IL-6 receptor on NK cells. Locally-produced IFN- γ can be detrimental to the body by activating macrophages. As the liver is rich in NK cells and TRAIL has been reported to cause liver injury, TRAIL on NK cells may be responsible for one of the characteristics of AOSD, liver dysfunction. Although IL-10 may be produced to prevent excessive inflammation, in the presence of IL-18, it can exert the opposite effect.

Disclosure: K. Sato, None; Y. Aizaki, None; H. Yazawa, None; T. Mimura, None.

Abstract Number: 983

A MAPK Activated Kinase 2 Inhibitor Attenuates Inflammatory and Destructive Arthritis in Human Ex Vivo Models

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Cytokines and Cell Trafficking Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Targeting intracellular pathways with oral small molecules is an attractive therapeutic approach for treating immune mediated inflammatory diseases. The mitogen-activated protein kinase (MAPK) pathway is activated by environmental stressors, growth factors and inflammatory cytokines. However, the inhibition of central MAPK proteins has so far had undesirable side effects. The MAPK-activated protein kinase 2 (MK2) is a downstream mediator in the MAPK signaling pathway and could therefore be inhibited without the same side effects. The objective of this study was to study the effects of a small molecule inhibiting MK2 on inflammation and structural changes in ex vivo models of immune mediated inflammatory arthritis.

Methods: Synovial fluid mononuclear cells (SFMCs), fibroblast like synovial cells (FLSs) and peripheral blood mononuclear cells (PBMCs) were obtained from a study population consisting of patients with active RA or peripheral SpA with at least one swollen joint (for obtaining synovial fluid) (n=14). SFMCs were cultured for 48 hours with and without addition of a MK2 inhibitor (Celgene) at 1000 nM, 333 nM and 111 nM and supernatants were analyzed by the Olink proseek multiplex interferon panel and commercially available ELISA assays. Because FLSs are only found in small amounts among SFMCs, autologous co-cultures of FLS and PBMCs and SFMCs were also used. SFMCs cultured for 21 days were used to study inflammatory macrophage differentiation and osteoclastogenesis.

Results: In SFMCs cultured for 48 hours, the MK2 inhibitor decreased the production of CXCL9 (P<0.001), CXCL10 (P<0.01), HGF (P<0.01), CXCL11 (P<0.01), TWEAK (P<0.05), and IL-12B (P<0.05) and increased the production of CXCL5 (P<0.0001), CXCL1 (P<0.0001), CXCL6 (P<0.001), TGF α (P=0.01), MCP-3 (P<0.01), LAP TGF β (P<0.05) dose-dependently after Bonferroni correction (all corrected P values). At the highest concentration, the MK2 inhibitor also decreased MCP-1 production (P<0.05). In FLS-SFMC co-cultures, the MK2 inhibitor decreased MCP-1 production (P<0.05) but did not change the production of DKK1 and MMP3. In FLS-PBMC co-cultures, the MK2 inhibitor decreased the production of MCP-1 (P<0.0001), increased MMP3 production (P<0.05) but did not change DKK1 production. In SFMCs cultured for 21 days as a model of inflammatory macrophage differentiation and osteoclastogenesis, the MK2 inhibitor decreased the production of MCP-1 (P<0.05) and tartrate-resistant acid phosphatase (TRAP) (P<0.05) but did not change the production of IL-10.

Conclusion: This study reveals the effects of a MK2 inhibitor in ex vivo models of immune mediated inflammatory arthritis. The MK2 inhibitor changed the secretory profile of SFMCs and decreased inflammatory osteoclastogenesis. Taken together, this points to a role of this MK2 inhibitor in attenuating inflammatory and destructive arthritis.

Disclosure: T. W. Kragstrup, None; A. Mellemkjaer, None; M. A. Nielsen, None; L. D. Heftdal, None; M. Iversen, None; P. Schafer, Investigational drug candidate, 1, 3; B. Deleuran, None.

Abstract Number: 984

Reduced Expression of CX3CR1 in Peripheral CD14⁺⁺CD16⁺monocytes Is a Novel Feature of Patients with Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Cytokines and Cell Trafficking Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Fractalkine (FKN, CX3CL1) and its receptor, CX3CR1, play an important role in chemotaxis of immune cells, such as cell adhesion, migration and infiltration into the organs. Several lines of evidence indicated that serum level of FKN was elevated and correlated with disease activity in patients with rheumatoid arthritis (RA) and the expression of CX3CR1 is upregulated especially in peripheral intermediate monocytes, CD14⁺⁺CD16⁺ in RA patients as compared to healthy controls (HC). On the other hand, it has been reported that elevated expression CX3CR1⁺ macrophages were infiltrated in the kidney of lupus patients and CD16⁺ monocytes within the glomerular blood vessels of the patients corresponds to the high CX3CR1⁺ expressing monocytes. In this study, we investigated the expression level of CX3CR1 in peripheral monocytes and T cells from patients with systemic lupus erythematosus (SLE) and HC to elucidate the possible involvement of CX3CR1 in immunological features of SLE.

Methods: The expression level of CX3CR1 in peripheral monocytes (classical monocytes: CD14⁺⁺CD16⁻, intermediate monocytes: CD14⁺⁺CD16⁺, non-classical monocytes: CD14⁺CD16⁺⁺), CD4 and CD8 T cells was analyzed by FACS with whole blood samples from patients with SLE active (SLEDAI : >10, n = 22), inactive (SLEDAI: <4, n = 22) and HC (n = 34). Differences between the groups were examined for statistical significance using the t test for single comparisons. Correlation analysis was employed for evaluation of the linear relationship between two continuous variables.

Results: FACS analysis revealed that the proportion of CD14⁺⁺CD16⁺ monocytes among CD14⁺ cells was significantly elevated in SLE active (p = 0.0017) and SLE inactive (p = 0.0002) patients as compared to HC, whereas no significant difference was observed in that proportion between SLE active and inactive patients. Notably, the proportion of CX3CR1 positive cells in CD14⁺⁺CD16⁺ monocytes was significantly lower in SLE active patients than patients with SLE inactive (p = 0.014) and HC (p = 0.002), whereas that proportion was not significantly different between SLE inactive and HC. In addition, the proportion of CX3CR1 positive cells in CD4 and CD8 T cells was not significantly different among the groups.

Conclusion: These results give the possibility that FKN binds its receptor, CX3CR1, expressed on CD14⁺⁺CD16⁺ monocytes in SLE, and the cells consequently migrate into the organs through peripheral blood. Our data suggest that targeting FKN signaling may be effective for suppressing inflammatory monocyte recruitment to the organs in SLE.

Disclosure: K. Yoshimoto, None; K. Suzuki, None; S. Saito, None; J. Kikuchi, None; T. Takeuchi, None.

Abstract Number: 985

IL-6 and TNF-α Cooperate to Modulate Cell Cycle of RA-FLS Via Cyclin Dependent Kinase 6

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Cytokines and Cell Trafficking Poster

Session Type: ACR Poster Session B

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

Background/Purpose:

Rheumatoid Arthritis (RA) is a chronic inflammatory disease characterized by a tumor-like synovial overgrowth leading to joint destructions. IL-6 and TNF- α play an important role in the pathogenesis of RA, and the proliferation of RA-synoviocytes (FLS) is controlled by cell cycle regulators including Cyclins, Cyclin dependent kinases (CDK), CDK inhibitors (CKDIs) and retinoblastoma protein (RB).

To reveal actions of proinflammatory cytokines on the cell cycle of RA-FLS, we examined the expressions of the cell cycle regulators and the cellular viability under stimulations of IL-6 and TNF- α .

Methods: RA-FLS were treated with or without IL-6/soluble IL-6 receptor (sIL-6R) (100ng/ml) or TNF- α (10ng/ml). The expressions of CDK4/6 CDKIs (*p16^{INK4a}*, *p21^{Cip1}*, *p27^{Kip1}*) and *Cyclin E1/2* mRNA were measured by Real-time PCR, the protein expression of CYCLIN D, CYCLIN E, RB and the phosphorylation of RB were measured by Western blot, the expression of CYCLIN D and the phosphorylation of RB were observed by immunofluorescence, and the cellular viabilities were measured by WST-8 and BrdU assay. In addition, siRNA/CDK6 was introduced into RA-FLS to measure the cellular viabilities, under stimulations with or without IL-6/sIL-6R or TNF- α .

Results: IL-6/sIL-6R decreased the mRNA expression of *p16^{INK4a}*, whereas increased the protein expression of CYCLIN D and RB. TNF- α decreased the mRNA expressions of *CDK4*, whereas increased the mRNA expressions of *p27^{Kip1}*, *CDK6*, *Cyclin E1/2* mRNA, the protein expression of CYCLIN D, RB and the phosphorylation of RB. The protein expression of CYCLIN D and the phosphorylation of RB were synergistically increased by IL-6 and TNF- α . The cellular viabilities were increased by IL-6 and TNF- α , which were suppressed by siRNA/CDK6.

Conclusion: Results indicate that IL-6 and TNF- α interact with each other in regulating the cell cycle of RA-FLS, and TNF- α dominantly increases the cellular viability *via* CDK6.

Disclosure: K. Kaneshiro, None; K. Yoshida, None; K. Uchida, None; A. Yækura, None; I. Okumura, None; K. Tateishi, None; Y. Terashima, None; N. Shibamura, None; Y. Sakai, None; A. Hashiramoto, None.

Abstract Number: 986

Fucosylated Tumor Necrosis Factor α Is Expressed in Rheumatoid Arthritis Synovial Tissues and Is Involved in Monocyte Adhesion

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Cytokines and Cell Trafficking Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Glycosylation has been reported to associate with tumor invasion and metastasis. Fucosylation is involved in the biological functions of adhesion molecules and growth factor receptors. In regards to arthritis, we have previously reported that glycan in rheumatoid arthritis (RA) serum was higher than that in normal subjects serum. However, a direct role for fucosylated cytokines in RA has not been demonstrated. Here, we examined fucosylated tumor necrosis factor (TNF)- α was expressed in RA synovial tissues, as TNF- α is a central cytokine in RA pathology and the role it plays in monocyte adhesion.

Methods: To determine if the fucosylated TNF- α was expressed in RA and osteoarthritis (OA) synovial tissues, we performed immunofluorescence. In order to indicate that the expression of fucosylated TNF- α was in RA synovial fluids, immunoprecipitation and lectin blotting were performed. 2-deoxy-D-galactose (2-dGal) is an analog of hexose that inhibits fucosylation. In addition, to clarify the mechanism of fucosylation in monocyte adhesion, human umbilical vein endothelial cells (HUVECs) were treated with 2-dGal (15 mM) for 5 days. THP-1 (human acute monocyte leukemia cell line) adhesion to 2-dGal treated or nontreated HUVEC was measured. Finally, to confirm which adhesion molecules were involved in fucosylation, cell surface ELISA was performed.

Results: Fucosylated TNF- α was expressed in RA synovial tissues. Hence, fucosylated TNF- α in RA synovial tissues was significantly highly expressed compared with that in OA synovial tissues. Fucosylated TNF- α in RA synovial fluids was also significantly higher compared with in OA synovial fluids. Fucosylated proteins in 2-dGal treated HUVECs were decreased compared with these in nontreated HUVECs. Adhesion of THP-1 cells to 2-dGal treated HUVECs in response to TNF- α was significantly decreased compared with nontreated HUVECs (adhesion index of THP-1 to HUVECs \pm SEM; 1.2 ± 0.1 and 1.4 ± 0.1 , $p < 0.05$, respectively). In addition, intercellular adhesion molecule 1 (ICAM-1) on TNF- α stimulated 2-dGal treated HUVECs were decreased compared to nontreated HUVECs (fold change of ICAM-1 expressed \pm SEM; 5.5 ± 0.2 and 9.0 ± 0.2 , $p < 0.05$, respectively).

Conclusion: Fucosylated TNF- α was expressed in RA synovium, and inhibition of fucosylation in ECs had less monocyte adhesion. These data indicate that cytokine fucosylation is involved with RA and plays a role in inflammation, suggest that targeting fucosylation may provide a method by which to decrease inflammation.

Disclosure: T. Isozaki, None; S. Nishimi, None; T. Kasama, None.

Abstract Number: 987

CCL11 Is Involved in Cell Migration in Rheumatoid Arthritis

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SESSION INFORMATION

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Session Type: ACR Poster Session B

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

Background/Purpose: Chemokine C-C motif ligand 11 (CCL11) also known as eotaxin-1 is produced by a variety of cell types. By interacting with C-C chemokine receptor 3 (CCR3), CCL11 stimulates the migration of several types of cells. High levels of CCL11 and CCR3 have described in rheumatoid arthritis (RA). Previously, we reported that the expression of CCL11 was increased by tumor necrosis factor (TNF) - α stimulation in RA fibroblast-like synoviocytes (FLS). A recent study reported that receptor activator of nuclear factor kappa-B ligand stimulated CCR3 expression in osteoclasts and the addition of CCL11 caused an increased migration of pre-osteoclast and an increase in osteoclastic bone resorption. The aim of this study is to investigate the expression and the function of CCL11 in RA.

Methods: The levels of CCL11 were determined in serum from healthy control (HC) and RA patients in onset using enzyme-linked immunosorbent assay (ELISA). We also measured the levels of CCL11, TNF- α and MCP-1 in synovial fluids (SFs) from the patients with RA and osteoarthritis (OA). To investigate the expression of CCL11 or CCR3 in RA FLS, cells were left unstimulated or were stimulated with recombinant TNF- α or CCL11. After stimulation, the protein expression levels in the culture medium were measured by ELISA and the messenger (mRNA) expression levels were measured by quantitative polymerase chain reaction analysis. The expression of CCL11 or CCR3 on RA FLS were also demonstrated by immunohistochemistry. To confirm the role of CCL11 in cell migration, RA FLS were stimulated with recombinant CCL11 and were allowed to migrate through uncoated transwell chambers. Finally, to block the expression of CCL11, RA FLS were transfected with small interfering RNA (siRNA) against CCL11, and proinflammatory cytokines in TNF- α stimulated RA FLS conditioned medium were measured using ELISA.

Results: The levels of CCL11 in the serum from RA ($n=26$) were higher than those in the serum from HC ($n=28$) (median [IQR]; $78.3 [62.7-114.1]$ pg/mL and $46.8 [30.9-67.7]$ pg/mL, $p < 0.05$, respectively). The levels of CCL11 in SFs from the patients with RA ($n=15$) were higher than those in SFs from the patients with OA ($n=16$) ($20.3 [5.3-26.3]$ pg/mL and $4.1 [0.2-9.0]$ pg/mL, $p < 0.05$, respectively) and were positively correlated with the levels of TNF- α ($r=0.74$, $p < 0.05$) and MCP-1 ($r=0.64$, $p < 0.05$). The mRNA expression of CCL11 and CCR3 in RA FLS were increased by TNF- α stimulation ($p < 0.05$). In addition, we confirmed that the expression of CCL11 and CCR3 were increased with TNF- α stimulation using immunohistochemistry. Furthermore, the expression of CCR3 mRNA were increased by CCL11 stimulation ($p < 0.05$). CCL11 stimulated cells were significantly higher efficient at migration than unstimulated cells ($p < 0.05$). CCL11 siRNA treatment decreased the expression of MCP-1 in TNF- α treated RA FLS conditioned medium ($p < 0.05$).

Conclusion: These data show that CCL11 and CCR3 are increased by TNF- α stimulation in RA FLS and CCL11 is associated with RA FLS migration and the secretion of MCP-1. CCL11 may play an important role of inflammation in RA.

Disclosure: K. Wakabayashi, None; T. Isozaki, None; S. Nishimi, None; T. Kasama, None.

Abstract Number: 988

Regulatory T Cells with Skewed Responses and Propionate-Producing Gut Bacteria Increased Simultaneously in Patients with Relapsing Polychondritis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Cytokines and Cell Trafficking Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Several intestinal bacteria produce short-chain fatty acids (SCFA) by the fermentation of dietary fibers. SCFA in the intestine differentiate regulatory T (Treg) cells by stabilizing the expression of the master gene, Foxp3. We have reported that SCFA-producing bacteria increased significantly in patients with relapsing polychondritis (RP) (Arthritis Rheumatol. 2017; 69 Suppl 10: 2477–2478.). Here, adding to the metagenomic analysis with newly recruited samples, we evaluated T cell cytokine gene expression titers of peripheral blood mononuclear cells (PBMC) in RP patients and compared the data with those in normal individuals.

Methods: We explored fecal microbiota of 25 patients with RP and 27 normal individuals by sequencing of 16S rRNA gene. The effect size of each bacterium in the two groups were estimated by LEfSe software. We cultured PBMC of 22 RP patients and 11 normal individuals with and without mitogen stimulation and measured T cell cytokine gene expressions of the cells. We measured serum matrix metalloproteinase protein (MMP3) concentrations, an RP-related biomarker, in RP patients using an Elisa assay kit.

Results: We found that annotated species numbers were significantly higher in the intestine of RP patients than those of normal individuals. In the RP gut microbiota, we observed several predominant species which were reported to associate with propionate production in human intestine. Propionate was reported to induce IL-10-producing Treg cells in the intestine and we measured IL-10 gene expressions in PBMC of RP patients and normal individuals. We found that IL-10 gene expressions were significantly higher in freshly isolated PBMC of RP patients than those of normal individuals ($P < 0.0001$). In contrast, 6 hours after the initiation of the PBMC culture, IL-10 gene expressions of RP patients were significantly lower than those of normal individuals, regardless of the presence and absence of the mitogen stimulation ($P = 0.0011$ and $P < 0.0001$, respectively). Serum MMP3 concentrations were significantly higher in RP patients than those in normal individuals and correlated well with IL-10 gene expression levels in freshly isolated PBMC of the RP patients ($P < 0.0001$).

Conclusion: We suggest that propionate continuously stimulates intestinal Treg cells and induce hypo-responsiveness of the cells to antigenic stimulation in RP patients. Treg skewed cells may play a role in the chondritis of RP patients through inappropriate chondrocyte secretion of MMP3.

Disclosure: J. Shimizu, None; T. Kubota, None; N. Suzuki, None.

Abstract Number: 989

Reduction of Serum IL17F and IL22 By IL23p19 Blockade with Guselkumab Is Associated with Improvement in Joint Symptoms in Psoriatic Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Cytokines and Cell Trafficking Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Guselkumab (GUS) is a fully human monoclonal antibody that binds to the p19 subunit of IL23. In a recent Phase 2 study, GUS demonstrated clinical reduction of signs and symptoms of arthritis and improvement of psoriatic lesions in patients with active psoriatic arthritis (PsA). Longitudinal analysis on serum proteins was performed to evaluate the impact of IL23 blockade on effector cytokines associated with the IL23/Th17 axis and biomarkers that may be impacted by treatment or associated with clinical response to GUS over 16 weeks.

Methods: In a double-blind, placebo-controlled, multicenter study (CTA:2014-003697-17), patients with active PsA and $\geq 3\%$ body surface area (BSA) of plaque psoriasis despite current or previous treatment with standard of care therapies, including those previously exposed to anti-TNF α agents, were randomized 2:1 to receive GUS 100 mg subcutaneously (SC) (n=97) or placebo (PBO) (n=45) at weeks 0, 4, and every 8 weeks (q8w) thereafter through week 44. The study included 149 patients fulfilling the American College of Rheumatology 2012 criteria for the classification of PsA. Serum samples were collected at week 0, week 4, and week 16. Acute phase (C-reactive protein (CRP), serum amyloid A (SAA), soluble cell adhesion molecules (sICAM1, sVCAM1)) (Meso Scale Discovery Platform) and Th17 effector cytokines (IL17A, IL17F, and IL22) (SMC Immunoassay platform) were measured in the serum samples. Baseline protein levels were fitted in Generalized linear model (anti-TNF usage as covariate) to test for association with treatment group, baseline demographic and clinical phenotypes of PsA, PsA medicine history, and clinical response for major study endpoints. Within-subject change from baseline levels were used to test the pharmacodynamic effect of GUS and association with clinical response.

Results: Acute phase proteins (CRP, SAA, sICAM, sVCAM) and Th17 effector cytokines (IL17A, IL17F, and IL22) were elevated at baseline in patients with PsA compared to healthy (Mean levels $\geq 50\%$ higher than healthy, $P < 0.05$). Baseline IL17A, IL17F and IL22 levels were positively correlated with BSA ($R > 0.4$ and $P < 0.05$). No correlation was identified with other demographics and ACR component measures evaluated. GUS treatment significantly decreased all 7 analytes at week 16 ($P < 0.05$), with significant down-modulation of IL17A, IL17F, IL22, and SAA already observed by week 4, which is consistent with clinical observations. Week 24 ACR20 responders to GUS had a significantly larger down-modulation of IL17F, IL22, and CRP compared to non-responders ($P < 0.05$). Week 24 PASI75 responders to GUS had a significantly larger down-modulation of sVCAM1 and IL17A compared to non-responders ($P < 0.05$).

Conclusion: In patients with active PsA in this study, GUS significantly decreased the levels of acute phase inflammation proteins and Th17 effector cytokines. These decreases were significant by the week 4 visit, suggesting a rapid pharmacodynamic effect of GUS. Down-modulation of IL17F, IL22, and CRP was associated with benefit to joint symptoms, while down-modulation of IL17A and sVCAM1 was associated with improvement in plaque psoriasis activity.

Disclosure: Q. Song, Janssen Research and Development, LLC, 3; M. Loza, Janssen Research and Development, LLC, 3; K. Leander, Janssen Research and Development, LLC, 3; B. Scott, Janssen Research and Development, LLC, 2; P. Branigan, Janssen Research and Development, LLC, 3; K. Sweet, Janssen Research and Development, LLC, 3.

Abstract Number: 990

Guanylate Binding Protein 5 (GBP5) Inhibits Rheumatoid Arthritis Synovial Fibroblast Mediated Inflammation and Tissue Destruction

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Cytokines and Cell Trafficking Poster

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

Background/Purpose: Guanylate binding protein 5 (GBP5), an interferon gamma (IFN- γ) inducible protein, helps to defend against invading pathogens. However, its role and properties beyond anti-viral or anti-bacterial action remains unknown. In the present study, we evaluated the role of GBP5 and its corroboration with IFN- γ in regulating rheumatoid arthritis synovial fibroblast (RASf) mediated inflammation and tissue destruction.

Methods: Cell lysates from RASfs and non-diseased SFs (NLSFs) were prepared to evaluate the expression levels of GBP5 using Western immunoblotting and qRT-PCR methods. siRNA mediated knockdown of GBP5 was conducted to study its effect on IFN- γ (10 ng/ml), IL-1 β (10 ng/ml) and/or TNF- α (20 ng/ml)-induced downstream signaling pathway in RASfs. Conditioned media was used to quantitate IL-6, IL-8, matrix metalloproteinase-1 (MMP-1), and CXCL5

production by ELISA. The lentiviral delivery method was used to overexpress GBP5 to evaluate its potential regulatory effects in RASFs.

Results: Our Western blot analysis showed that the expression of GBP5 is significantly reduced in RASFs compared to NLSFs ($p < 0.05$; $n = 6$). We observed a higher expression of GBP5 upon IFN- γ stimulation and the expression was further augmented with IL-1 β stimulation ($p < 0.05$; $n = 6$). Co-treatment of RASFs with IFN- γ significantly downregulated IL-1 β -induced IL-6, IL-8, and MMP-1 production in RASFs ($p < 0.05$; $n = 3$). To our surprise, siRNA-mediated knockdown of GBP5 reduced the inhibitory potential of IFN- γ and resulted in further upregulation of IL-1 β -induced IL-6, IL-8, MMP-1, and CXCL5 production by 84%, 66%, 8-fold, and 72%, respectively ($p < 0.05$; $n = 3$). Evaluating the impact of GBP5 knockdown on the RASF signaling pathways, we observed that GBP5 knockdown in human RASFs selectively amplified the constitutive as well as IL-1 β -induced phosphorylation of ERK1/2 and JNK mitogen-activated protein kinases, which are important mediators of inflammation and tissue destruction in RA. Intriguingly, lentivirus-mediated restoration of GBP5 abrogated IL-1 β -induced proinflammatory cytokine production, suggesting that GBP5 plays an anti-inflammatory role by inhibiting RASF mediated inflammation.

Conclusion: Our findings suggest that the lack of GBP5 contributes to synovial inflammation, and its restoration suppresses RASF-mediated inflammation and tissue destruction.

Disclosure: M. Haque, None; A. K. Singh, None; S. Ahmed, None.

Abstract Number: 991

Critical Role of Interleukin-1 α (IL-1 α) in IL-1 β -Induced Inflammatory Responses: Cooperation with NF- κ Bp65 in Transcriptional Regulation

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Background/Purpose: Interleukin-1 β (IL-1 β) and IL-1 α are cytokines of IL-1 family that orchestrate acute and chronic inflammatory diseases. However, their distinct role or the extent of overlap in the inflammatory processes remains poorly understood. This prompted us to explore the role of IL-1 α in IL-1 β -activated signaling pathways causing synovial inflammation in rheumatoid arthritis (RA).

Methods: Normal and RA synovial tissues were obtained from total joint replacement surgery or synovectomy under an Institutional Review Board approved protocol in compliance with the Helsinki Declaration. RNA isolated from these tissues were subjected to RNA sequencing using Illumina platform. Synovial fibroblasts from RA tissues (RASFs) were treated with various IL-1 β , tumor necrosis factor- α (TNF- α), or lipopolysaccharide (LPS) to study the expression of IL-1 α using Western blotting, immunofluorescence (IF), and qRT-PCR methods. Native immunoprecipitation (IP) and chromatin IP (ChIP) methods were used to study protein-protein interactions and chromatin remodeling function of IL-1 α . Small interfering RNA (siRNA) method was used to study the role of IL-1 α in IL-1 β signaling pathway. Molecular dynamics (MD) simulation were performed to assess binding patterns of IL-1 α or IL-1 β as ligand on IL-1 receptor (IL-1R) crystal structure to identify functional differences in activating phosphorylation of key IL-1 signaling proteins.

Results: IL-1 β selectively induced the expression of IL-1 α transcript ($p < 0.01$; $n = 4$), which reached to >1,000-fold within 6 hours stimulation. Evaluation of the signaling inhibitors showed that IL-1 β significantly stimulated IL-1 α expression, which was selectively inhibited by blocking NF- κ B pathway, whereas further exacerbated by p38-MAPK inhibition. Interestingly, knockdown of IL-1 α using siRNA abolished IL-1 β -induced pro-IL-1 α and pro-IL-1 β expression and suppressed inflammation ($p < 0.05$; $n = 3$). IF results showed that IL-1 α primarily resides in nuclear and chromatin bound fractions of RASF and interacts with p65 subunit of NF- κ B protein upon IL-1 β stimulation. Native IP and ChIP studies showed that IL-1 α cooperates in NF- κ Bp65 binding to the distal region of IL-1 α promoter and to the proximal region of IL-1 β promoter upstream of the transcription start site to stabilize their gene transcription. Furthermore, MD simulation of IL-1 α or IL-1 β binding to IL-1R crystal structure showed distinct interaction sites for each cytokine, where more π - π interactions were observed with IL-1 β over IL-1 α with IL-1R indicating stable complex formation. These results corroborate with the ability of IL-1 α to differentially activate phosphorylation of signaling proteins compared to IL-1 β ,

where phosphorylation of proteins such as IRAK1^{Ser387}, IRAK4^{Ser345}, TAK1^{Thr184/187/412} and the degradation of IRAK1 were more rapid in IL-1 β stimulated RASFs compared to IL-1 α stimulation.

Conclusion: These results suggest that IL-1 β relies on IL-1 α to stabilize its expression and propagate inflammation. It may be postulated that IL-1 α targeted therapies may have some benefit over IL-1R antagonists in regulating inflammation.

Disclosure: A. K. Singh, None; S. Fechtner, None; M. Chourasia, None; J. Sicalo, None; S. Ahmed, None.

Abstract Number: 992

Epigallocatechin-3-Gallate (EGCG) Suppresses Systemic Inflammation By Inhibiting IL-6-Induced STAT3 Activation in Cultured Hepatocytes and in Liver Tissue of Adjuvant-Induced Arthritis (AIA) Rats

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Background/Purpose: In rheumatoid arthritis (RA), the pro-inflammatory cytokine interleukin-6 (IL-6) induces systemic inflammation by activating hepatocytes through IL-6 receptor (IL-6R)- mediated JAK/STAT3 signaling pathway. The present study was undertaken to determine the role of epigallocatechin 3-gallate (EGCG), an active compound found in green tea, in regulating IL-6-induced JAK/STAT3 pathway in Hep3B cells and in a rat adjuvant-induced arthritis (AIA) model.

Methods: Hep3B cells were starved, pretreated overnight with EGCG (5-20 μ M), and then stimulated with IL-6 (50 ng/ml). Cells were harvested after 30 minutes to evaluate the effect on different phosphorylation sites on JAK/STAT3 using Western immunoblotting, or after 24 hours of IL-6 stimulation for C-reactive protein (CRP) expression using Western blotting and qRT-PCR methods. Nuclear and cytoplasmic extracts were prepared to study nuclear translocation and DNA binding activity using ELISA kit. Liver homogenates and nuclear extracts were prepared from naïve, AIA, and AIA+EGCG (50 mg/kg, i.p.) treated rats. A molecular docking study of EGCG to STAT3 was performed using an X-ray crystal model of mouse STAT3 (PDB ID: 1BG1) as a template and EGCG as a ligand.

Results: Pretreatment of Hep3B cells with EGCG inhibited IL-6-induced STAT3^{Ser727} and STAT3^{Tyr705} activation in a dose-dependent manner, which may partially be attributed to the inhibition of pJAK1^{Tyr1022/1023} and pJAK2^{Tyr1007/1008} expression by roughly 37% and 27%, respectively ($p < 0.05$). Inhibition of pSTAT3^{Ser727} was more prominent than pSTAT3^{Tyr705} inhibition with EGCG pretreatment. Evaluation of the nuclear fractions from the treated Hep3B cells showed that EGCG significantly inhibited the nuclear translocation of IL-6-induced STAT3 ($p < 0.05$). This resulted in ~25% decrease in STAT3 DNA binding activity by EGCG treatment and a dose-dependent decrease in CRP expression ($p < 0.05$). Surprisingly, EGCG exhibited no effect on the endogenous STAT3 regulator, SOCS3. Administration of EGCG (50 mg/kg, i.p.) daily for 10 days significantly reduced the severity and incidence of arthritis compared to the untreated rats ($p < 0.05$; $n = 6/\text{group}$). Evaluation of the liver homogenates from these rats showed that EGCG inhibited pSTAT3^{Ser727} by ~70% and reduced its nuclear translocation. Molecular docking studies showed that EGCG can bind to R382, R417, R423, S465, and N469 residues on STAT3, which may potentially inhibit the DNA binding activity of STAT3.

Conclusion: Our results suggest that the EGCG may elicit its beneficial effects in part through the suppression of IL-6-induced systemic inflammation.

Disclosure: A. K. Singh, None; S. Fechtner, None; D. Wang, None; M. Chourasia, None; S. Ahmed, None.

Elucidating the Role of the Lymphatic System in the Pathogenesis of Psoriasis and Psoriatic Arthritis

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Session Title: Cytokines and Cell Trafficking Poster

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Background/Purpose: Psoriasis is a common T-cell driven inflammatory skin disorder that is featured by immune cell infiltration, and vasculopathy of both blood and lymphatic vasculature. Psoriatic arthritis (PsA) is a destructive joint disease that occurs in up to 30% of psoriasis patients, but how the disease progresses from only skin inflammation to also synovial membrane involvement of the joints and entheses is unclear. The T helper 17 (Th17) subpopulation has been put forward as the main driver of the disease manifestations in psoriasis and PsA. Recently, our group showed that lymphatic endothelial cells (LEC) lining the interior surface of the lymphatic vasculature, have the capacity to suppress Th17 differentiation and alter the chemokine receptor profile that controls their specific tissue homing. We hypothesize that the LECs in the skin of PsA patients are dysregulated and allow pathogenic Th17 cells to migrate to extracutaneous sites. To get a better understanding of how these regulatory mechanisms affect Th17 migration from skin to synovial joints in PsA, we investigated LEC derived from different sources, and compared LEC with another disease-relevant stromal cells.

Methods: Human dermal LEC and dermal fibroblasts (DF) were cell-sorted from skin discarded from healthy individuals undergoing elective skin surgery. Also, LECs were cell-sorted from human lymph nodes derived from patients undergoing vascular surgery without a medical history of chronic inflammatory disorders. We determined the expression of immunomodulatory and co-stimulatory molecules across LEC populations in skin and lymph node, and in DF using flow cytometry and real-time quantitative PCR (qPCR). Subsequently, we assessed the inflammatory responses of dermal LEC and DF by qPCR during a 24 h culture with the cytokines IL-17A, IL-22, TNF α , and IL-1 β .

Results: Flow cytometric analysis demonstrated that both lymph node LEC and dermal LEC, but not DF, expressed the MHC class II molecule HLA-DR. In line, qPCR analysis revealed that both lymph node LEC and dermal LEC, but not DF, expressed fundamental immunomodulatory molecules that affect T-cell activation and polarization including programmed death-ligand 1 and 2 (PD-L1/2), galectin 1,3 and 9, glucocorticoid-induced TNFR-related ligand (GITRL), OX40 ligand, and inducible T Cell Costimulator Ligand (ICOS-L). Secondly, a 24 h culture with IL-17A, IL-22 and TNF α , strongly induced ICOS-L and the chemokine ligand 20 (CCL20) in dermal LEC, whereas DF showed no effect upon cytokine stimulation.

Conclusion: We found that human LEC populations in both skin and lymph nodes, as compared to DF, are endowed with immunomodulatory properties underscoring the essential role for LECs in shaping peripheral T-cell responses. Under inflammatory conditions, particularly dermal LECs, but not DF, seem to be important in regulating T-cell activation and recruitment of CCR6-expressing T-cell subpopulations responding to CCL-20. Further studies on LEC populations that originate from skin, lymph node and synovial joints from patients with psoriasis and PsA to validate and expand on the abovementioned results are underway.

Disclosure: H. den Braanker, None; A. Otten-Mus, None; P. Asmawidjaja, None; N. Davelaar, None; A. A. E. A. de Smet, None; G. P. Akkersdijk, None; B. Fioole, None; J. B. Jaquet, None; A. Hofman, None; O. P. Schuitema, None; S. W. Tas, None; R. Mebius, None; E. Lubberts, None; M. R. Kok, None; R. J. Bisoendial, None.

Platelet Derived Growth Factor Receptors (PDGFRs) and Their Implication in Inflammatory Arthritis

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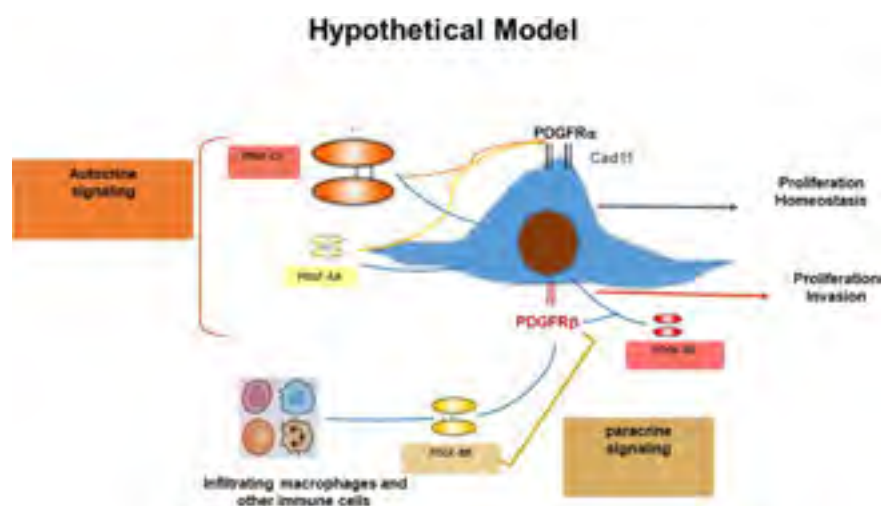
Background/Purpose: Rheumatoid arthritis(RA) is inflammatory joint disease characterized by immune infiltration and synovial hyperplasia. Hyperplastic synovium contains increased numbers of activated synovial fibroblasts, which amplify inflammation and directly invade cartilage. Fibroblast proliferation and invasion is stimulated *in vitro* by platelet-derived growth factor receptor (PDGFR) ligands. PDGFR and ligand expression are upregulated in RA, suggesting a pathogenic role. However, PDGFR signaling is complex, involving differential activation of PDGFR- α (PDGFR α) and PDGFR- β (PDGFR β) homo- and heterodimers by five ligands. Our hypothesis is that PDGFR α and PDGFR β function differently in RA, with PDGFR α having a more homeostatic role while PDGFR β promotes a more invasive phenotype.

Methods: Human synovial fibroblast PDGFR expression was determined by quantitative reverse transcription-polymerase chain reaction (qRT-PCR), western blot, and flow cytometry. PDGF ligand expression was determined by qRT-PCR. Fibroblast proliferation and appearance was determined after activation with PDGFR α - or PDGFR β -specific ligands. Cadherin-11 signaling was induced with cadherin-11 extracellular binding domains linked to human Fc domains.

Results: Synovial fibroblasts expressed significantly higher levels of PDGFR α compared to PDGFR β . In addition, they expressed high levels of the PDGFR α -specific ligands, PDGF-CC and PDGF-AA. In contrast, fibroblasts expressed less PDGFR β -specific ligands, with low PDGF-DD and undetectable PDGF-BB levels. Both PDGFR α and PDGFR β ligands increased fibroblast proliferation. However, only PDGFR α interacted with the fibroblast cell adhesion molecule cadherin-11 to induce proliferation. Conversely, only stimulation with PDGFR β -activating ligands (PDGF-BB and -DD) induced a rounded, more migratory cell phenotype.

Conclusion: After evaluating PDGF ligand expression and the effects of PDGFR α versus PDGFR β activation, our hypothesis is that PDGFR α and PDGFR β have functionally distinct roles in inflammatory arthritis. Our model is that PDGFR α ligands, especially highly expressed PDGF-CC, maintain fibroblast proliferation in autocrine fashion. In contrast, release of PDGFR β ligands by infiltrating macrophages promotes fibroblast migration and invasion, contributing to RA cartilage damage. Better understanding of how PDGFR α and PDGFR β function to promote inflammatory arthritis will help to target activated synovial fibroblasts in RA treatment.

Disclosure: B. Madarampalli, None; J. Kyung Kim, None; P. Panipinto, None; H. Labinsky, None; V. Mahajan, None.



Anti-Fractalkine Monoclonal Antibody Inhibits Joint Destruction through Suppression of Osteoclast Precursor Migration and Induces Synovial Cell Death in Collagen-Induced Arthritis Model Mice

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Background/Purpose: In the Phase 1/2 clinical study, E6011, a novel humanized anti-fractalkine (FKN) mAb demonstrated a promising efficacy in active RA patients who were inadequately controlled by MTX and/or TNF- α inhibitors. FKN is expressed on endothelial cells and fibroblast-like synoviocytes in synovium and also expressed on osteoblasts. CX3CR1, the receptor for FKN, is expressed on monocytes/macrophages and osteoclast precursors (OCPs). Therefore, the FKN-CX3CR1 interaction might play pivotal roles in these cells function. To elucidate the precise roles of the FKN-CX3CR1 pathway in joint destruction, we examined the effect of treatment with anti-mouse FKN (mFKN) mAb, using the CIA model mice.

Methods: For the induction of CIA, mice were immunized with bovine type II collagen. Anti-mFKN mAb was injected twice a week. The clinical arthritis score was monitored, and joint destruction was evaluated by soft X-ray and histology. The mRNA expression levels were assessed by quantitative RT-PCR. Blood parameters were measured using ELISA. In *in vitro*, effect of immobilized FKN on RANK ligand (RANKL)-induced osteoclast differentiation was examined. In *in vivo*, bone marrow-derived OCPs were fluorescein-labeled and transferred to CIA mice to evaluate the migration of OCPs into synovium. Inhibitory effect of anti-mFKN mAb, etanercept or tofacitinib against OCP migration was assessed. To examine the effect of anti-mFKN mAb against CIA synovium, propidium iodide (PI) was injected to anti-mFKN mAb-treated CIA mice to detect the synovial cell death.

Results: Anti-mFKN mAb significantly reduced the arthritis and soft X-ray scores in both prophylactic and therapeutic treatment. Anti-mFKN mAb histologically improved synovitis, cartilage destruction and bone damage, with marked reduction of osteoclast numbers. Plasma levels of COMP and were also decreased, while those of serum amyloid A, TNF- α and IL-6 were unaffected after the anti-mFKN mAb treatment. Interestingly, anti-mFKN mAb significantly suppressed Tnf and Il6 mRNA expression in the affected joints. In *in vitro*, RANKL-induced osteoclast differentiation was enhanced by immobilized FKN, and anti-mFKN mAb suppressed FKN-dependent osteoclast formation. In *in vivo*, anti-mFKN mAb

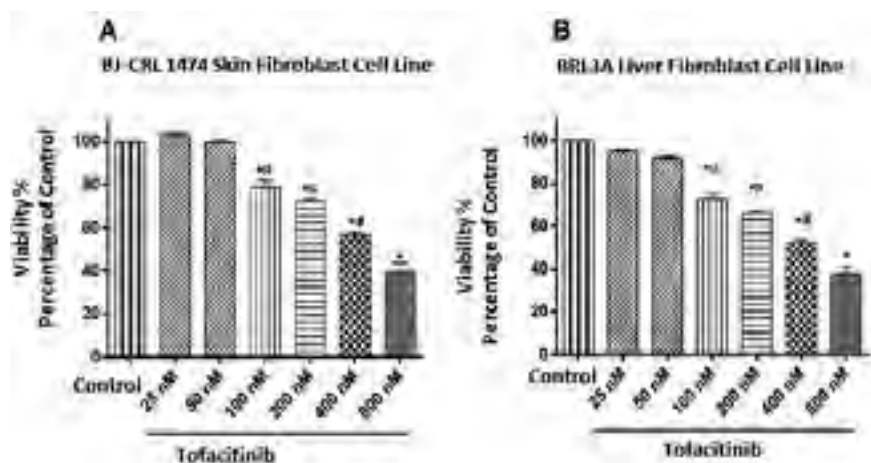


Figure1: The effects of tofacitinib in cell culture by concentration A: Skin Fibroblast cell line B: Liver Fibroblast cell line

strongly inhibited the migration of OCPs into the CIA synovium, whereas etanercept or tofacitinib had no effect. Importantly, synovial cell death was abundantly found in CIA synovium after the anti-mFKN mAb treatment.

Conclusion: In CIA model mice, anti-mFKN mAb suppressed local inflammatory cytokine expression in the inflamed joints, without affecting systemic inflammatory parameters. Anti-mFKN mAb remarkably ameliorated the joint destruction with the reduction of osteoclasts by the inhibition of both OCP migration and osteoclast formation in inflamed joint. In addition, anti-mFKN mAb immediately induced synovial cell death in the synovium, suggesting the direct inhibitory effect in the synovitis. These results indicate that inhibition of FKN-CX3CR1 axis by a humanized anti-FKN mAb, E6011, could be an attractive and affected joints-selective therapeutic option for the treatment of both inflammatory synovitis and joint destruction in RA patients.

Disclosure: K. Hoshino-Negishi, KAN Research Institute, Inc., 3; M. Ohkuro, EA Pharma Co., Ltd., 3; T. Nakatani, KAN Research Institute, Inc., 3; W. Ikeda, KAN Research Institute, Inc., 3; Y. Kuboi, KAN Research Institute, Inc., 3; N. Ishii, KAN Research Institute, Inc., 3; N. Yasuda, KAN Research Institute, Inc., 3; T. Imai, KAN Research Institute, Inc., 3.

Abstract Number: 996

Neutralizing Effect of Anti-Infliximab Antibodies on Infliximab-Stimulated Human Coronary Artery Endothelial Cells

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Cytokines and Cell Trafficking Poster

Session Type: ACR Poster Session B

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

Background/Purpose: As a consequence of endothelial dysfunction, patients with rheumatoid arthritis (RA) have an increased risk of atherosclerosis and early development of cardiovascular disease. Serum amyloid A (SAA), tumour necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) up-regulated in the sera of RA patients were previously reported to activate human coronary artery endothelial cells (HCAEC), however their combined effects are unclear. Furthermore, the effect of anti-TNF- α drugs, such as infliximab, in the presence and absence of their anti-infliximab antibodies, has not yet been elucidated.

In our study, we aimed to investigate the combined effects of TNF- α , IL-1 β , SAA, infliximab and anti-infliximab antibodies on IL-6 released levels in HCAEC.

Methods: Primary HCAEC (Lonza), passage 5, were grown to confluency in 5% FBS/EGM-2M medium, serum starved for 2 hours and incubated with human recombinant cytokines (SAA1/2 (Peprotech, 500nM), TNF- α (Thermo Fisher Scientific, 2.5 ng/mL) and IL-1 β (Thermo Fisher Scientific, 1 ng/mL)), infliximab, anti-infliximab antibodies and their combinations. After 24 hours, supernatants were collected, centrifuged, aliquoted and frozen at -20°C.

Infliximab was used at a final concentration of 10 μ g/mL, in combination with the cytokines. For the neutralizing effect of anti-infliximab antibodies (final concentration 0.55 μ g/mL) on infliximab (final concentration 0.1 μ g/mL), polyclonal anti-infliximab antibodies were purified by affinity chromatography from sera samples of 2 patients with chronic rheumatic diseases, who exhibited positive levels of anti-infliximab antibodies, as previously determined by an *in-house* competitive and bridging ELISA. IL-6 was measured by ELISA (Invitrogen). One-way ANOVA was used for statistical analysis.

Results: Triple stimulation of HCAEC with TNF- α /IL-1 β /SAA significantly and synergistically elevated the release of IL-6 levels in cell supernatants (3-fold above IL-1 β alone). Double stimulation with IL-1 β /SAA, TNF- α /SAA, as well as TNF- α /IL-1 β and IL-1 β alone, also led to significantly higher levels of IL-6, while TNF- α alone did not increase IL-6 levels. Infliximab was effective in lowering released IL-6 levels in the TNF- α /IL-1 β double treatment, however the strongest inhibition was observed in TNF- α /IL-1 β /SAA triple-stimulated HCAEC, where it significantly reduced IL-6 released levels by around 50%.

Anti-infliximab antibodies significantly restored IL-6 released levels from HCAEC treated with infliximab and TNF- α /IL-1 β /SAA (complete neutralization of the infliximab inhibition).

Conclusion: TNF- α , IL-1 β and SAA synergistically elevated IL-6 release in supernatants of HCAEC, with infliximab substantially inhibiting its levels. Isolated polyclonal anti-infliximab antibodies were capable of neutralizing infliximab, in the presence of TNF- α /IL-1 β /SAA, thereby promoting chronic inflammation in HCAEC.

Disclosure: M. Ogrić, None; K. Mrak Poljšak, None; K. Lakota, None; P. Žigon, None; S. Praprotnik, None; S. Čučnik, None; S. Sodin Semrl, None.

Abstract Number: 997

The Effects of the Jak-Stat Signal Pathway Inhibition on Collagen Biosynthesis in Fibroblast Cell Culture

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Cytokines and Cell Trafficking Poster

Session Type: ACR Poster Session B

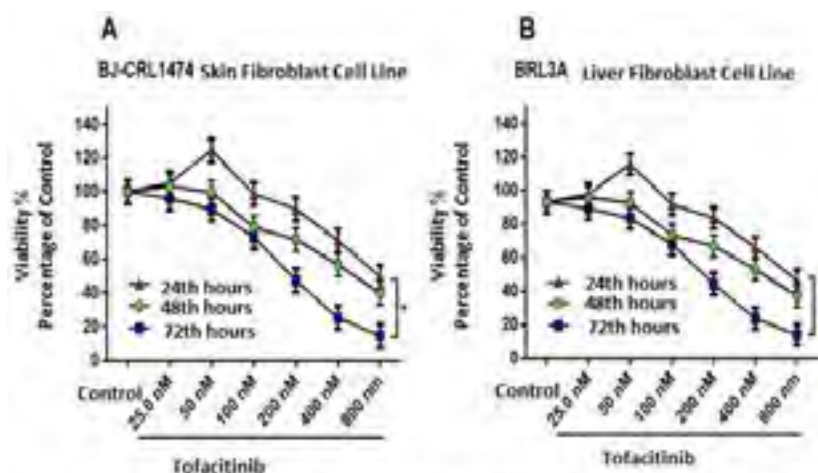
Session Time: 9:00AM-11:00AM

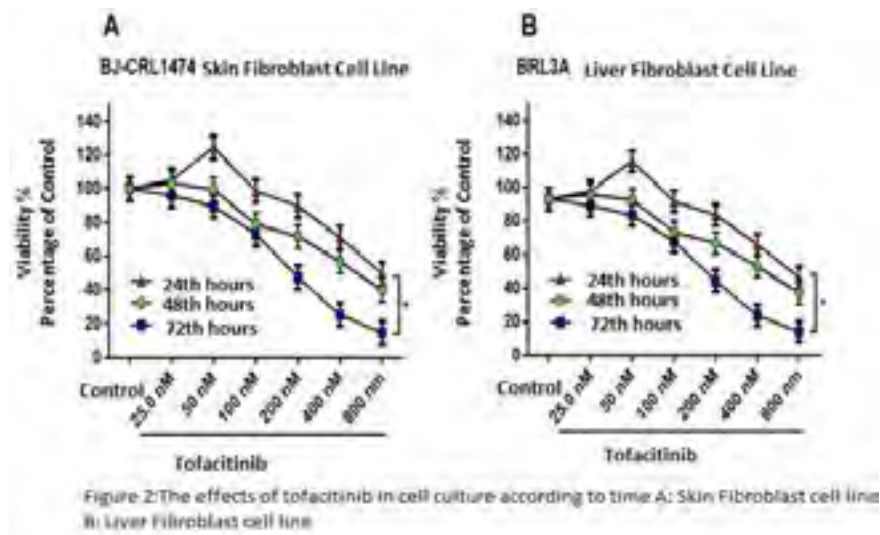
Background/Purpose: Uncontrolled collagen synthesis and deposition occur in various diseases such as hepatic fibrosis, scleroderma. Tofacitinib is a selective JAK-kinase (1/3) inhibitor. Currently it is used in the treatment of rheumatoid arthritis. The aim of the study is to investigate the effect of JAK-STAT signal pathway inhibition on collagen biosynthesis in fibroblast cell-culture.

Methods: BJ-CRL1474[®] (skin) and BRL3A[®] (hepatic) fibroblast cell cultures were proliferated in the appropriate medium. Tofacitinib was administered to fibroblast cells proliferating on 96-well flasks at concentrations of 25 nM, 50 nM, 100 nM, 200 nM, 400 nM and 800 nM, respectively. Cell viability and quantity were read by spectrophotometer. Tissue metalloproteinase inhibitor (TIMP-1), matrix metalloproteinase-3 (MMP-3), transforming growth factor (TGF-1 β) and hydroxyproline levels were measured by ELISA method.

Results: The cytotoxic effect of tofacitinib started at 100 nM concentration ($p < 0.05$). The highest effect was obtained at 800 nM. The cytotoxic effect at concentrations of 400 nM and 800 nM was higher than at 100 nM and 200 nM concentrations ($p < 0.05$) (Figure 1). The time-dependent cytotoxic effect of tofacitinib was significantly higher at 72th hours than at 24th and 48th hours at all concentrations ($p < 0.05$) (Figure 1). TGF-1 β , the major stimulus of collagen synthesis, was found to be significantly low even at 25 nM concentration ($p < 0.05$). The lowest concentration was reached at 800 nM ($p < 0.05$). There was a significant decrease in MMP-3, TIMP-1 and hydroxyproline levels respectively ($p < 0.05$). The decline in all three biomarkers started at a concentration of 100 nM. The maximum decrease in the levels of four biomarkers was observed at a concentration of 800 nM (Figure). The results in both cell cultures were similar and not statistically significant ($p > 0.05$).

Conclusion: Tofacitinib was shown to reduce fibroblast proliferation and viability in fibroblast cell culture. The decrease in the levels of TGF- β , which is also the main stimulus of collagen synthesis and is also released from fibroblasts, may be due to reduced release of TGF- β . The level of hydroxyproline in the collagen structure is expected to decrease. We found that the level of MMP-3 was also reduced. MMP-3 was not needed in conditions such as collagen synthesis decreased and





in vitro. We found a decrease in TIMP-1, an inhibitor of MMP-3. JAKkinase inhibitor, tofacitinib inhibited fibroblast cell proliferation in fibroblast cell culture by time and concentration.

Table-1: Effect of Tofacitinib on levels of TGF-1 β , MMP-3, TIMP-1 and hydroxyproline.

Tofacitinib	TGF-1 β (pg/mg)	MMP-3	TIMP-1 (pg/ml)	Hydroxyproline (Ratio of control)
Control	23,4 \pm 2,6	12,9 \pm 2,6	860,5 \pm 23,3	1
25 nM	18,6 \pm 3,5*	11,3 \pm 2,8	840,2 \pm 21,9	0,91 \pm 0,13
50 nM	17,2 \pm 1,9*	10,8 \pm 1,9	800,0 \pm 20,3	0,85 \pm 0,08
100 nM	11,3 \pm 2,1**	4,2 \pm 1,1*	621,3 \pm 25,6*	0,61 \pm 0,07*
200 nM	10,6 \pm 1,8**	3,8 \pm 0,9*	324,3 \pm 17,5**	0,52 \pm 0,05*
400 nM	3,6 \pm 0,9#	3,6 \pm 0,6*	321,9 \pm 16,2**	0,48 \pm 0,03*
800 nM	2,1 \pm 0,7#	1,2 \pm 0,4**	310,2 \pm 18,8**	0,12 \pm 0,02**

*p<0.05, **p<0.05, #p<0.005

Disclosure: M. SAHİN, None; H. AYDIN, None; A. ALTUN, None; M. E. DERİN, None; A. Sahin, None.

Abstract Number: 998

Transcription Factor Fli-1 Impacts Renal IL-17 Expression in Adult MRL/Lpr Mouse Despite Similar Interstitial Immune Cell Infiltration into the Kidney

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SESSION INFORMATION

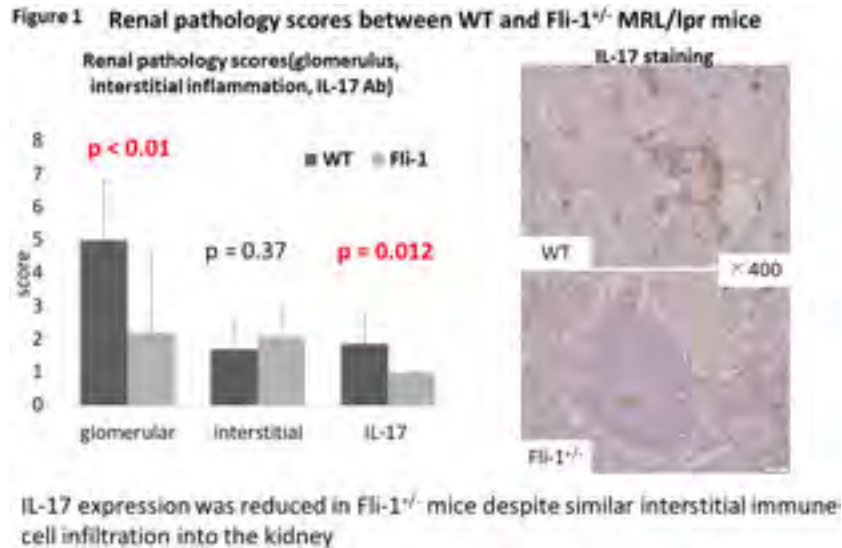
Session Date: Monday, October 22, 2018

Session Title: Cytokines and Cell Trafficking Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Fli-1 is a member of Ets transcription factor and plays an important role in lupus nephritis development. Reduced Fli-1 expression (heterozygote Fli-1: Fli-1^{+/-}) results in improvement of kidney inflammation and prolongs overall survival in lupus model mouse. Previously, we have reported that Fli-1 directly regulates cytokine/chemokine expression (MCP-1, RANTES, CXCL2, IL-6, and G-CSF) and impacts lupus nephritis development in lupus model mouse. IL-17 is a cytokine with powerful inflammatory properties. Past reports indicate that IL-17 is associated with disease activity in patients with lupus nephritis. The relationship between Fli-1 and IL-17 is unknown. The aim of this study is to elucidate whether reduced Fli-1 expression affects IL-17 production and impacts lupus nephritis development into the kidney.



Methods: Serum IL-17 concentrations of adult (4-months-old or older) Wild-type (WT) and Fli-1^{+/-} MRL/lpr mice were measured by ELISA and compared between the two groups. Kidneys were removed from these mice and evaluated using pathology scoring system (glomerular and interstitial lesions). Immunostaining of IL-17 in the kidney was also performed and compared between the two groups. Expression of mRNA of IL-17, IL-18 and IL-1 β in the kidney tissue were also compared.

Results: Serum IL-17 concentrations were relatively decreased but not significant in Fli-1^{+/-} MRL/lpr mice (WT: 55.7 vs Fli-1^{+/-}: 3.12 pg/mL, respectively, p=0.35). Relative mRNA expression of IL-17 in the kidney was decreased (19.7%) in Fli-1^{+/-} MRL/lpr mice compared to WT MRL/lpr mice. Relative expression of IL-18 and IL-1 β mRNA in the kidney were significantly decreased in Fli-1^{+/-} MRL/lpr mice (p=0.02). In histological examination, glomerular inflammation was significantly decreased in Fli-1^{+/-} MRL/lpr mice. However, interstitial inflammation was similar between the two groups. In contrast, immunostaining of IL-17 showed significantly decreased IL-17 positive immune cells in the kidney of Fli-1^{+/-} MRL/lpr mice (Figure 1).

Conclusion: Fli-1 impacts lupus nephritis progression through affecting the reduction of IL-17-positive immune cell infiltration into the kidney. Reduced expression of IL-1 β and IL-18 in the kidney can also affect IL-17 expression in Fli-1^{+/-} MRL/lpr mice.

Disclosure: S. Sato, None; X. Zhang, None; Y. Fujita, None; M. Yashiro, None; T. Asano, None; H. Kobayashi, None; H. Watanabe, None; K. Migita, None.

Abstract Number: 999

Development of an Affimab Engineered to Simultaneously Target IL-6 and Tnf α for Therapeutic Use in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Cytokines and Cell Trafficking Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Antibodies may be functionalized using Affibody® molecules to create bispecific AffiMabs. We used protein engineering to develop single-construct biologics suitable for blocking inflammation driven by a combination of cytokines. AM201 is an AffiMab simultaneously targeting interleukin 6 (IL-6) and the tumor necrosis factor alpha (TNF α).

Methods: A set of affinity matured Affibody molecules binding to IL-6 were fused to either the N- or C-terminus of both the heavy and light chains of an anti-TNF monoclonal antibody based on adalimumab to produce bi-specific AffiMabs.

Among these bi-specific antibodies, AM201 was determined on the basis of internal selection criteria including the efficacy and stability.

Results: AM201 blocks the interaction between complexes of the soluble IL-6 receptor (sIL-6Ra) and IL-6 and the co-receptor gp130 (IL-6 trans-signaling pathways) whilst it blocks IL-6 cis-signaling less potently. AM201 neutralize both TNF α and IL-6 simultaneously *in vitro*. AM201 was subsequently evaluated in an acute serum amyloid alpha (SAA) model in mice for *in vivo* activity. AM201 efficiently blocks combined IL-6 and TNF-triggered SAA secretion *in vivo*. We confirmed that AM201 potentially reduce arthritic score in Tg197, human TNF α transgenic mouse. The quantitative PCR using human samples showed that AM201 efficiently block the gene expressions associated with bone removal including RANK, MMP9 and RANKL. We pursue efficacy test against non-human primate collagen-induced arthritis model and a drug development process with the aim to develop an innovative bi-specific AM201 simultaneously targeting TNF α and IL-6.

Conclusion: AM201 can be a novel potent therapeutic option for the treatment of rheumatoid arthritis patients who commonly develop aberrant expression of both TNF α and IL-6.

Disclosure: K. T. Kim, None; J. S. Lee, None; B. K. Ko, None.

Abstract Number: 1000

Surface Adenosine Monophosphate Deaminase 2 As a Novel Regulator Modifying Ectonucleotidase-Driven Generation of Anti-Inflammatory Extracellular Adenosine

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Cytokines and Cell Trafficking Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Extracellular ATP and adenosine are potent immunomodulatory molecules that accumulate in states of inflammation. ATP/ADP are released from damaged or stressed cells and sequentially catabolized to AMP which is then catabolized to adenosine by the action of the ecto nucleotidases CD39 and CD73, which promotes a shift from an ATP-driven pro-inflammatory environment to an anti-inflammatory milieu induced by adenosine. AMPD2 encodes one of three known AMP deaminase homologs. Intracellularly, it executes AMP deamination to IMP thereby reducing adenosine formation. Here, we postulate that this mode of action is also present on the cell surface of immune cells, which may lead to an increased state of inflammation such as found in chronic inflammatory diseases (**Fig. 1**).

Therefore, we analyzed surface AMPD2 expression and its modulation on distinct cell lines and primary immune cells.

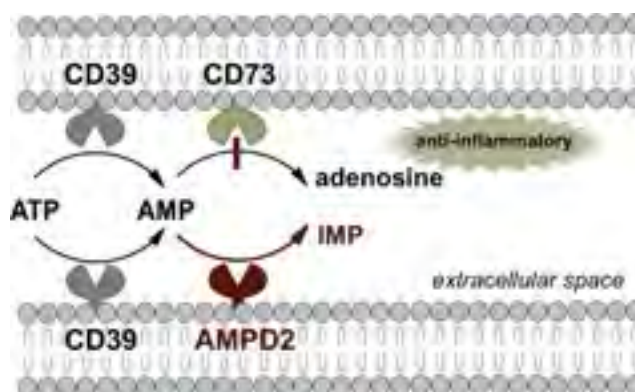


Figure 1: Model: possible role of surface AMPD2

Methods: To this end, surface AMPD2 expression was evaluated on cell lines (THP1, Jurkat, HMEC1, and HEK293), human PBMCs and isolated monocytes by flow cytometry. Moreover, co-expression of surface AMPD2, CD73 and CD39 was analyzed on PBMCs and isolated monocytes. Association of surface AMPD2 and cell death was visualized using annexin V and 7-AAD staining and examined by flow cytometry. In addition, expression of AMPD2 was analyzed by immunoblot of precipitated AMPD2 from membrane fractions and by mass spectrometry after precipitation from membrane fractions and from biotinylated surface-molecules using the surface AMPD2-positive cell lines HEK293 and HMEC1.

Results: Here, we show that (i) surface AMPD2 is present on T cells and monocytes in PBMCs from healthy donors, (ii) LPS enhances surface expression of AMPD2 in monocytes after 24h whereas AMPD2 surface expression is reduced in T cells treated with LPS and PHA, respectively, (iii) LPS significantly decreases CD73 expression on monocytes in PBMC co-culture, and (iv) all cell lines analyzed are capable of expressing surface AMPD2. Surface AMPD2 expression was significantly reduced after Golgi transport inhibition in both PBMCs and HEK293. AMPD2 surface expression was not accompanied by enhanced cell death. AMPD2, CD39 and CD73 co-staining revealed an opposing expression pattern on lymphocytes and monocytes in PBMC co-culture. Expression of AMPD2 could be confirmed in membrane fractions of HEK293 and HMEC1 using immunoblot of precipitated AMPD2 and mass spectrometry, respectively.

Conclusion: We demonstrate for the first time surface expression of AMPD2 on immune cells enabling these cells to extracellularly convert AMP into IMP constituting a shunt-like mechanism to control the levels of adenosine and extracellular ATP formed from adenine nucleotides thereby controlling immunomodulation.

Disclosure: L. Ehlers, None; A. Kuppe, None; A. Damerau, None; Y. Chen, None; C. Strehl, None; M. Kirchner, None; F. Buttgerit, Amgen, Roche/Chugai, GSK, BMS, Pfizer, Medac, Horizon, Mundipharma, 2, Medac, Mundipharma, Celgene, Horizon, 2, Sanofi, Pfizer, BMS, 5, Lilly, Abbvie, Pfizer, UCB, Roche, 8; T. Gaber, None.

Anti-Fractalkine Monoclonal Antibody Dislodges Intravascular Monocytes Involved in Exacerbation of Synovial Inflammation in Collagen-Induced Arthritis Model

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Cytokines and Cell Trafficking Poster

Session Type: ACR Poster Session B

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

Background/Purpose: In the Phase 1/2 clinical study, E6011, a novel humanized anti-fractalkine (FKN) mAb demonstrated a promising efficacy in active RA patients who were inadequately controlled by MTX and/or TNF- α inhibitors. In preclinical study, anti-FKN mAb significantly lowered arthritis score of CIA model, and reduced infiltration of inflammatory cells and bone erosion in the synovium (Nanki et al., J Immunol 2004). Furthermore, anti-FKN mAb reduced the migration of adoptively transferred splenic monocytes/macrophages into the inflamed synovium. FKN is expressed on endothelial cells and fibroblast-like synoviocytes and also expressed on osteoblasts. CX3CR1, the receptor for FKN, is expressed on monocytes/macrophages and osteoclast precursors. Moreover, intravascular monocytes contribute vascular inflammation. However, the roles of FKN and CX3CR1 in the pathogenesis of RA, especially the behavior of intravascular monocytes, remain unclear. In this study, we evaluated the role of FKN-CX3CR1 axis on intravascular monocyte behavior in synovium of CIA model by intravital imaging and tissue-clearing techniques.

Methods: For the induction of CIA, mice were immunized with bovine type II collagen. The effect of anti-FKN mAb on synovium of MCP joint was examined by intravital imaging and three-dimensional (3D) tissue analysis with tissue-clearing technique. In intravital imaging, we established a system for MCP joint observation by two-photon laser scanning microscope (TPLSM), and the behavior of intravascular monocytes visualized by anti-CD115 mAb were compared in the presence or absence of anti-FKN mAb or control IgG. 3D tissue analysis was performed by tissue-clearing reagent LUCID (WO 2014115206 A1) and TPLSM. One hour after anti-FKN mAb or control IgG administration, the mice underwent to low-speed perfusion fixation so that the cells attached to the blood vessels did not detach. Before fixation, intravascular monocytes and blood vessels were visualized by anti-CD115 mAb and RCA-1, respectively. The number of intravascular monocytes were quantified. In order to clarify the difference of point of action with other biologics, the same experiment was carried out with TNF- α inhibitor or CTLA4-Ig administration.

Results: In intravital imaging, angiogenesis in the synovium of CIA occurred actively, and adhered and/or slow-paced monocytes appeared in the vasculature. At thirty minutes after anti-FKN mAb administration, the intravascular monocytes were reduced, but control IgG did not change compared to before administration. In tissue transparency analysis, the number of intravascular monocytes was markedly reduced by anti-FKN mAb as compared with control IgG. When the same experiments were performed with TNF- α inhibitor or CTLA4-Ig, intravascular monocytes were not reduced.

Conclusion: Intravital imaging and tissue-clearing techniques revealed that anti-FKN mAb dislodges intravascular monocytes in inflamed synovium. These results suggest that the FKN-CX3CR1 axis regulates intravascular monocyte behavior in inflamed synovium, such as enhancement of vascular inflammation and infiltration of osteoclast precursors. FKN-CX3CR1 blockade may be a novel attractive strategy for the treatment of RA.

Disclosure: W. Ikeda, KAN Research Institute, Inc., 3; K. Hoshino-Negishi, KAN Research Institute, Inc., 3; E. Fusaoka-Nishioka, KAN Research Institute, Inc., 3; T. Nakatani, KAN Research Institute, Inc., 3; Y. Kuboi, KAN Research Institute, Inc., 3; N. Ishii, KAN Research Institute, Inc., 3; N. Yasuda, KAN Research Institute, Inc., 3; T. Imai, KAN Research Institute, Inc., 3.

Abstract Number: 1002

Pkca Deficiency Protected Mice from UVB Induced-Skin Inflammation through Attenuation of Neutrophil Netosis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Innate Immunity Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Neutrophil NETosis is a form of cell death characterized by nuclear envelope rupture, nuclear chromatin release, and neutrophil extracellular trap formation. NETosis is important in various human diseases, including autoimmune diseases. We recently found involvement of neutrophil NETosis in UVB-induced murine skin inflammation. UVB is known to induce multiple agents including the lipid mediator Platelet activating factor (PAF). We also found that PKC α may mediate neutrophil NET release through regulation of nuclear envelope rupture. The goal of our study is to explore the causal role of PAF Receptor (PAFR) signaling and PKC α in neutrophil NETosis and its effect on skin inflammation.

Methods: Peritoneal- and bone marrow-derived neutrophils were isolated from wildtype, PAFR KO mice, or PKC α deficient mice and purified by anti-Ly-6G micro bead kit. To study NETosis, neutrophils were stimulated with or without PAF for 3 hours, then fixed with 2% PFA, stained by Sytox Green, and assayed for NET formation, finally confirmed by fluorescent microscopy. For UVB-irradiation, PKC α deficiency mice and their litter wildtype mice were exposed with/without 150 mJ/cm²/day under anesthesia for consecutive 5 days. Dorsal skin tissues were harvested. H&E and IHC staining were conducted.

Results: We found that PAF can induce NETosis in neutrophils from human and WT mice, while depletion of PAF receptor (PAFR) attenuated NETosis in neutrophils from PAFR KO mice, suggesting the role of PAF in neutrophil NETosis was mediated by PAFR. To study the role of PKC α , we found PAF increased PKC α phosphorylation in a time-dependent manner in parallel to the induction of neutrophil NETosis. Moreover, pharmacologic inhibition of conventional PKC with Go6976 decreased PKC α phosphorylation, nuclear envelope rupture and neutrophil NETosis. Furthermore, PKC α deficiency significantly impaired PAF-induced NETosis in neutrophils from PKC α deficient mice. Importantly, PKC α deficiency attenuated UVB-induced skin inflammation with decreased neutrophil NETosis and decreased proinflammatory cytokines (TNF α and IL-17A) in the inflamed skin of PKC α deficient mice as compared to those of the wildtype mice under UVB exposure.

Conclusion: These findings suggested that PAF might be a potential mediator of neutrophil NETosis in the skin of the UVB irradiated mice. PKC α appears to play vital roles in neutrophil NETosis in UVB-induced skin inflammation. The PAFR and PKC α might be potential therapeutic targets in human diseases related to UVB-induced skin inflammation.

Disclosure: Y. Li, None; J. B. Travers, None; V. P. Werth, None; M. L. Liu, None.

Abstract Number: 1003

Neutrophil Response to Ultraviolet Light in Normal and Lupus Conditions

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SESSION INFORMATION

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Session Title: Innate Immunity Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Two-thirds of systemic lupus erythematosus (SLE) patients are sensitive to sunlight and artificial light. Ultraviolet (UV) B light induces sterile inflammation in the skin and results in both localized cutaneous and systemic disease, including lupus nephritis. The precise mechanisms of photosensitivity-triggered systemic reactions in SLE are unknown.

Methods: Mice (C57BL/6J, 3-4mo female and male) were exposed to a single dose of UVB (500mJ/cm²). Individual mice were euthanized on 1, 2, or 6 days after UVB and perfused with saline; non-irradiated age and sex matched mice were used as controls. Immune cells isolated from the skin, bone marrow (BM), blood, spleen, lung, and kidney were profiled and neutrophil phenotype characterized by flow cytometry (FC). Cytokine and chemokine gene expression in skin was evaluated by QPCR. Tissue apoptotic cells and IgG were examined by immunofluorescence and kidney pathology evaluated by PAS staining.

Results: Following skin UVB exposure, the decline in the number of BM neutrophils associated with an increase in blood and skin neutrophil numbers at days 1-2 (d1-2). Of considerable interest, neutrophil numbers also increased in the lung, spleen, and kidney, with a peak on d6 post-UVB. While a similar migration pattern was seen in both male (M) and female (F) mice, the dynamic of the immune response was sex-dependent. Neutrophils in F mice infiltrated the irradiated skin more rapidly (d1 in F vs. d2 in M), a response reflected by faster gene induction of neutrophil chemoattractants (G-CSF, KC, LIX) and inflammatory cytokines (IL1b, IL6, IL33) in the F mice. Significantly higher levels of circulating neutrophils were found on d6 following UVB in F, relative to their M counterparts. In both M and F mice, immediately following UVB, circulating neutrophils expressed increased CXCR2, while later on (d6) CXCR4^{hi} neutrophils were detected in the kidney and the BM and ICAM1^{hi}CXCR1^{lo} neutrophils were found in the kidney, lung, BM, and blood. To investigate the effects of UV exposure in a lupus prone model we studied *Sle1.Mfge8-/-C3-/-* mice. These mice were particularly sensitive to UVB, with persistent skin lesions and increased accumulation of apoptotic debris and IgG in the skin. UV exposure in this lupus model led to nephritis and premature death. Preliminary data indicate that UVB exposure resulted in glomerular antibody deposition associated with CXCR4^{hi} and ICAM1^{hi}CXCR1^{lo} neutrophil infiltration.

Conclusion: Our findings provide several novel insights into the neutrophil response to UVB exposure: i) localized skin sterile injury triggers neutrophil migration to peripheral organs, including the kidney, ii) the dynamics of neutrophil infiltration into the skin are sex-dependent, and iii) presence of CXCR4^{hi} and ICAM1^{hi}CXCR1^{lo} neutrophil populations in peripheral organs suggests that a subset of activated skin-infiltrating neutrophils has migrated to distal organs, possibly via reverse transmigration. Evidence of a similar neutrophil population in a UV-sensitive lupus model associated with kidney injury strongly suggests neutrophil involvement in UV-triggered systemic pathology in SLE.

Disclosure: S. Skopelja-Gardner, None; X. Sun, None; J. Tai, None; L. Colonna, None; L. Tanaka, None; K. B. Elkon, Amdax Therapeutics, 2, 6.

Abstract Number: 1004

Reevaluating Citrullination and Peptidylarginine Deiminases in Neutrophil Extracellular Trap-like Structures

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Innate Immunity Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Neutrophil extracellular traps (NETs) are webs of chromatin and proteins extruded from neutrophils during NETosis. NETs are increased and display citrullinated proteins that are targeted by autoantibodies in rheumatoid arthritis. Citrullination, the posttranslational deimination of arginines to citrullines, is catalyzed by the peptidylarginine deiminases (PADs). Thus, NETs and PADs are thought to be important in the pathophysiology of rheumatoid arthritis. However, not all stimuli induce NETs with citrullinated proteins and, further, it has been suggested that different stimuli may induce different types of NET-like structures defined in part by the presence or absence of citrullination. Also, the requirement for PAD2 and PAD4, the main PADs expressed in neutrophils, in the formation of different NET-like structures has not been clearly defined, in part because many studies assess only citrullinated NETs. Here, we determine if

specific stimulants induce citrullinated and/or uncitrullinated NET-like structures in humans and mice and if those structures require PAD2 or PAD4.

Methods: Neutrophils were isolated from human peripheral blood or the bone marrow of wild type, PAD4^{-/-}, and PAD2^{-/-} mice and were treated for 4 hours with no stimulant, ionomycin, monosodium urate (MSU) crystals, phorbol myristate acetate (PMA), or *Candida albicans*. Cells were fixed, stained with 4'6-diamidino-2-phenylindole (DAPI) and an anti-citrulline antibody (F95) and imaged at preset locations at 400x. NET-like structures, defined as highly decondensed DNA, were quantified in a blinded manner. A t-test was used to analyze results with p<0.05 considered significant.

Results: PMA, MSU, and *C. albicans* were strong activators of NET-like structures in human neutrophils with MSU and *C. albicans* inducing primarily citrullinated NET-like structures and PMA primarily uncitrullinated. Ionomycin was a weak inducer of NET-like structures, about a third of which were citrullinated. In contrast, ionomycin and *C. albicans* were strong inducers of NET-like structures in murine neutrophils with ionomycin-induced NETs mostly citrullinated. MSU variably induced NET-like structures and PMA induced very few NET-like structures in mice, which were almost all uncitrullinated. Murine *C. albicans*- and MSU-induced NET-like structures were a mix of citrullinated and uncitrullinated. PAD4^{-/-} neutrophils generated almost no citrullinated NET-like structures, with similar numbers of uncitrullinated NET-like structures to PAD4^{+/+} neutrophils. PAD2^{-/-} neutrophils demonstrated no defects in any NET-like structures.

Conclusion: Different stimuli induce varying proportions of citrullinated and uncitrullinated NET-like structures in mice and humans making it difficult to define NET subsets by citrullination status and stimulant. PAD4 is required for the generation of citrullinated NET-like structures only, whereas PAD2 is dispensable for any murine NET-like structure. These findings critically inform the design and interpretation of studies evaluating the role of citrullination, PADs, and NET-like structures in rheumatoid arthritis.

Disclosure: C. L. Holmes, None; D. Shim, None; J. Kernien, None; C. J. Johnson, None; J. E. Nett, None; M. A. Shelef, None.

Abstract Number: 1005

Regulation of Neutrophil Activation in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Innate Immunity Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease characterized by immune dysfunction and autoantibody production. In addition to the adaptive immune system, neutrophils likely also play an important role in SLE pathogenesis. Neutrophils are terminally differentiated cells and are highly sensitive to environmental cues, including infections, sterile inflammation and medication. This study examined whether the increased levels of inflammatory cytokines in SLE induce neutrophil activation and whether the regulation of neutrophil function differs in SLE patients compared to controls.

Methods: Neutrophils from 19 SLE patients with varying disease activity and 11 controls were enriched by dextran sedimentation and density gradient centrifugation. Basal and stimulated levels of activation marker L-selectin (CD62L) and exocytosis marker CD66b were measured by flow cytometry. Percentage of cells with neutrophil extracellular traps (NET) were determined by microscopy. Plasma cytokines were measured by xMAP assays. Expression of mRNA and microRNA were determined by quantitative PCRs.

Results: Basal levels of CD62L were not different between SLE patients and controls; however, upon stimulation with TLR7/8 ligand, SLE patients showed reduced activation compared to controls ($p < 0.0001$). The CD62L levels negatively correlated with inflammatory cytokines IL1 β ($r = -0.7866$, $p = 0.0094$), IL23 ($r = -0.845$, $p = 0.0033$), IL6 ($r = -0.75$, $p = 0.0159$), MIP1 α ($r = -0.8424$, $p = 0.0037$), TNF β ($r = -0.7091$, $p = 0.0268$) in controls, suggesting increased downregulation of CD62L or increased activation of neutrophils due to exposure to inflammatory mediators. No correlation between these cytokines and CD62L levels were observed in SLE. CD66b levels were significantly lower in SLE patients compared to controls ($p = 0.0030$). In this small cohort, no significant differences between basal levels of NET forming cells between

SLE and controls were found. However, CD66b levels in SLE patients, but not in controls, positively correlated with the percentage of netting neutrophils ($r = 0.5858$, $p = 0.015$), suggesting a role for reactive oxygen species in NET formation in SLE. CD66b levels in SLE patients negatively correlated with BAFF ($r = -0.4848$, $p = 0.0354$), while the levels in controls did not correlate with plasma cytokines. Fold changes in surface markers upon stimulation with formyl peptide were similar between SLE and controls. The levels of surface markers on SLE neutrophils were not influenced by prednisone or hydroxychloroquine use. SLE neutrophils had significantly higher levels of genes involved in NF κ B signaling and lower levels of micro RNA miR223 and miR27a, suggesting hypersensitivity to infectious stimuli and reduced apoptosis.

Conclusion: SLE neutrophils had higher activation thresholds for mediators of sterile inflammation. Our data suggest that the regulation of neutrophil responses in SLE may be through pathways distinct from those in unaffected individuals, although the neutrophils maintain their ability to respond to external stimuli.

Disclosure: N. R. Jog, None; T. Aberle, None; E. Chakravarty, None; C. Arriens, Exagen Diagnostics, Inc, 2; J. M. Guthridge, None; M. E. Munroe, Progentec Diagnostics, Inc., 2; J. A. James, None.

Abstract Number: 1006

Physical Activity at Lower Intensities Reduces Localized IL-1 β in a Murine Model of Gout By Systemically Down-Regulating TLR2 Expression on Circulating Neutrophils and Suppressing CXCL1 Expression

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Innate Immunity Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Exercise was originally believed to exacerbate inflammation in rheumatic disease, however, recent studies have shown that regular physical activity is anti-inflammatory. In gout, there have been only a few pilot studies examining the effects of exercise on inflammation. Consequently, there are no exercise recommendations for gout patients in the clinical practice recommendations by the American College of Rheumatology (2012) and the American College of Physicians (2016). The objective of this study was to immunologically and mechanistically characterize the effects of different exercise intensities in a murine model of acute gout.

Methods: Using a model of acute gout we previously developed using transgenic mice harboring an NF κ B-luciferase reporter, we examined the effects of regular exercise at varying intensities on inflammation. Mice were exercised daily by treadmill walking (45 min/day for 2 weeks) at low intensity, moderate intensity, and high intensity and were subsequently injected with monosodium urate (MSU) crystals (0.5mg) into the tibio-tarsal joint (ankle). Localized NF κ B activity was measured 16 hours later in the injected ankle via bioluminescent imaging and tissue was collected and processed for immunohistochemical (IHC) and immunofluorescent (IF) analysis. Expression of Toll-like receptor (TLR) 2/4 and chemokine receptors on peripheral monocytes and neutrophils was determined using flow cytometry. Serum was collected for systemic chemokine expression.

Results: Mice in the low/moderate intensity exercise groups had measurably less swelling and significantly less NF κ B activity at the site of MSU crystal injection compared to the high-intensity group and non-exercised controls. Similarly, IHC of the synovial space of low/moderate intensity groups had decreased F4/80+ macrophages and MPO+ neutrophils relative to both high-intensity or non-exercised controls. Analysis by IF confirmed that both neutrophils and macrophages were secreting IL-1 β in the ankle joints. Considering that MSU crystals, at least in part, induce their inflammatory response with activation of TLR2, surface expression was measured by flow cytometry on peripheral neutrophils and demonstrated a decrease of 17% in the low-intensity and 48% in the moderate-intensity groups. In concordance, localized IL-1 β expression via IHC was reduced in low/moderate intensity exercise conditions. While there was little difference in chemokine receptor expression (CCR1, CCR2, CCR4, and CXCR2) on peripheral monocytes/neutrophils, the peripheral chemokine CXCL1 was significantly reduced with low and moderate exercise.

Conclusion: We hereby report that regular low/moderate intensity exercise regimens can reduce localized MSU crystal-induced inflammation, while high intensity training negates this response. An exercise-mediated suppression of NF κ B activity and IL-1 β expression locally can be explained, at least in part, by a reduction of TLR2 expression on peripheral neutrophils recruited to the site of inflammation and a down-regulation of CXCL1 expression.

Disclosure: K. Jablonski, None; N. A. Young, None; B. Sandoval, None; I. Okafor, None; E. Schwarz, None; C. Henry, None; P. Harb, None; A. Kalyanasundaram, None; W. Jarjour, None; N. Schlesinger, Astra Zeneca, 2, Novartis, Horizon, 5.

Abstract Number: 1007

Macrophage Mediators of Autoimmune Valvular Carditis and Fibrosis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Innate Immunity Poster

Session Type: ACR Poster Session B

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

Background/Purpose: K/B.g7 TCR transgenic mice spontaneously develop both autoimmune arthritis and valvular carditis. We utilize this model to define mediators of rheumatic disease-associated cardiovascular inflammation and fibrosis. We recently demonstrated that CX3CR1- and CD301b-expressing macrophages are critical drivers of valvular carditis in this system. Here we investigated the molecules that these macrophages use to promote cardiovascular inflammation.

Methods: We evaluated specific macrophage activation pathways using whole-animal and macrophage-specific (CX3CR1) conditional gene deletion, as well as in vivo antibody-blocking studies. We focused on prototypic M1 macrophage-associated molecules (IFN γ , TLR4, iNOS, IRF5) and on M2 macrophage-associated molecules (IL-4, IL-13, IL-4R α). We used immunofluorescent staining and flow cytometry to identify key cell types in the inflamed mitral valves of K/B.g7 mice as well in valve specimens from patients with rheumatic heart disease (RHD).

Results: Arthritis and valvular carditis develop normally in K/B.g7 mice lacking the M1-associated genes *Ifng*, *Tlr4*, or *Nos2* and or with macrophage-specific deletion of the M1 transcription factor IRF5. In contrast, macrophage-specific deletion of IL-4R α appears to protect K/B.g7 mice from valvular carditis without influencing the development of arthritis. IL-4R α and IL-13R α 1 are highly expressed in the inflamed valves of K/B.g7 mice and in human patients with RHD. Blockade of IL-13 but not IL-4 reduces valve inflammation.

Conclusion: Valvular carditis in K/B.g7 mice depends on CD301b- and IL-4R α -expressing macrophages but not on canonical M1 macrophage-associated molecules. IL-13 is a critical driver of disease in this model and may also be involved in human RHD. We speculate that targeting this pathway could reduce rheumatic disease-related cardiovascular disease.

Disclosure: L. Meier, None; M. Gonzalez-Torres, None; J. L. Auger, None; A. Marath, None; B. A. Binstadt, None.

Abstract Number: 1008

Presence of a Specific Defect in M2 Polarization of Blood Monocytes from Patients with Rheumatoid Arthritis, Associated with Increased microRNA-155

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Innate Immunity Poster

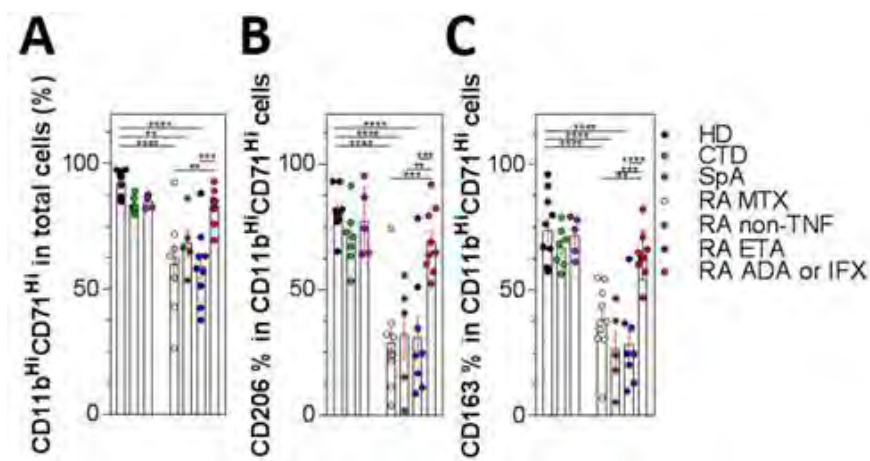
Session Type: ACR Poster Session B

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

Background/Purpose: Macrophages contribute in situ to the RA pathogenesis. Two distinct states of polarization for macrophages have been recognized: the **classically activated macrophage phenotype** (M1), considered to be pro-inflammatory and the **alternatively activated macrophage phenotype** (M2) considered to be regulatory. miRNAs are recently discovered class of post-transcriptional regulators. miR-155 is upregulated in RA synovial monocytes, macrophages and fibroblasts, but also in blood CD14⁺ monocytes. Here, we assessed monocytes capacity of differentiation into M2 macrophages and implication of miR-155 in RA patients or controls (healthy donor (HD), connective tissue disease (CTD) or spondylarthritis (SpA)).

Methods: CD14-CD16 monocytes were isolated from PBMCs by negative selection. To generate monocyte-derived macrophages(MDM), monocytes were incubated 6 days in the presence of M-CSF (M2) or GM-CSF(M1). Expressions of total macrophages markers (**CD11b** and **CD71**), M2 macrophage polarization markers (**CD163**, **CD206**, **IL-10** and **Arginase**) and M1 macrophage polarization markers (**INOS**, **IFR5** and **IL1 β**) were evaluated. The microRNA transfections were performed using **AMAXA technology**.

Results: We observed a significant decrease of macrophages induction by M-CSF in RA patients as shown by a decreased expression of **CD11b-CD71**. We have found a specific decreased level of M2 markers (**IL-10** Mean **26.4** HD versus **2.5** pg/mL RA-**Arginase** Mean **86.8** HD versus **26.9** RA **Fig1 A-C**). Moreover, we found that Adalimumab but not Etanercept is able to partially correct this defect (IL-10 **17.6** pg/mL and Arginase **69.9**%). We confirmed that under M-CSF treatment, RA monocytes have a propensity for preferential maturation towards M1 phenotype (**INOS** Mean **0.8** HD versus **25**% RA - **IFR5** expression Mean **1.35** HD versus **3.2** $\Delta\Delta$ Ct RA and **IL-1 β** secretion Mean **3.4** HD versus **20.9** pg/mL RA). We have hypothesized the involvement of **miR-155** on this defect. In M1 macrophages, the level of miR-155 was the same in controls and RA, whereas it was increased in M2 RA macrophages (Mean **0.6** HD versus **2.3** $\Delta\Delta$ CtRA). Subsequently preliminary experiments of transfected monocytes from healthy donors with **miR-155 mimic** leads to decrease M2 differentiation, conversely on RA monocytes transfection with amiR-155 inhibitor allowed the restoration of M2 polarization.



Conclusion: RA patients have a specific impaired maturation of monocytes to M2 while the differentiation to M1 phenotype is maintained. The use of monoclonal anti-TNF restores M2 polarization while Etanercept or non- anti-TNF drugs do not restore M2 polarization. This lack is associated with miR-155 increase that leads to IFR5 INOS and IL-1 β increase. Preliminary experiments showed that transfection of RA monocytes with an antagomiR may correct this lack, justifying the proof of concept trial of monocytes-targeted nanoparticles containing microRNA in mouse models of RA.

Disclosure: A. Paoletti, None; J. Rohmer, None; J. Pascaud, None; B. Oumouly, None; E. Rivière, Arthritis Fondation PhD fellowship, 2; S. Bitoun, None; G. Nocturne, None; X. Mariette, None.

Monocytes Membrane TNF Expression and Anti-TNF Treatment in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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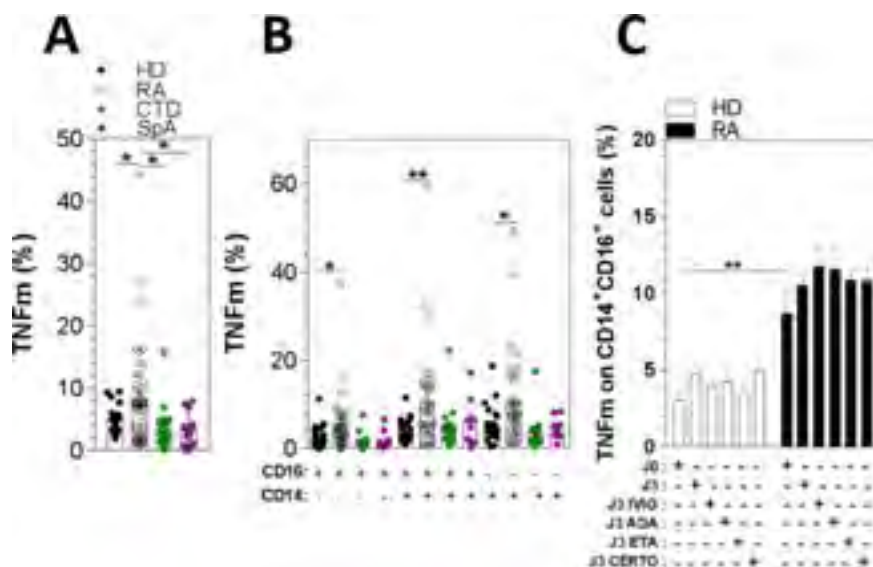
Session Time: 9:00AM-11:00AM

Background/Purpose: Three monocyte subsets have been described based on their CD14 and CD16 expression profiles. The subpopulation CD14⁺CD16⁺ being expanded in rheumatoid arthritis (RA) patient. Monocytes are one of the blood cellular populations expressing the most membrane TNF. TNF antagonist is the most popular biological drug in RA but after 20 years of use, we do not have any biomarker for predicting the response to this class of drug. Some studies suggested that serum soluble TNF and expression of TNF in the synovium could be predictive of response to anti-TNF but, curiously, possibly because of technical issues, no study addressed the level of expression of membrane TNF on blood monocytes and subtypes of monocytes in RA patients. Here, we assessed monocytes subsets and their mTNF expression in RA patients (treated or not with classical DMARDs or biologics) or controls (healthy donor (HD), connective tissue disease (CTD) or spondylarthritis (SpA) patients)

Methods: PBMCs were isolated and we first determined monocytes subpopulations and looked at expression of mTNF by flow cytometry. CD14CD16 monocytes were isolated by negative selection, and culture in RPMI with or without anti-TNF (Etanercept, Adalimumab or Certolizumab) during 3 days at 10 µg/ml corresponding to a mean serum concentration in treated patients.

Results: We have confirmed that the CD14⁺CD16⁺ monocyte subset was expanded in RA patients. For the first time, we have demonstrated *ex vivo* that mTNF expression was significantly increased only in monocytes in RA patients. Furthermore, mTNF is significantly increased in the three populations of monocytes in RA patients (**Fig1 A,B**). Very interestingly, mTNF expression on monocytes correlated with the activity of the disease assessed by DAS28 CRP (Spearman r **0.48** p-value **0.05**).

We wanted to look at *ex vivo* impact of anti-TNF on mTNF expression. We demonstrated that mTNF expression is equal between RA monocytes and RA anti-TNF treated monocytes in patients with a DAS28 ≤ 4 (Mean **7.42%** RA versus **7.26%**



in RA treated). To go further, we have tested *in vitro* monocytes treatment by anti-TNF from healthy donors or RA patients, but unfortunately, we have found no impact of anti-TNF on mTNF expression (**Fig1 C**).

Conclusion: Increased expression of mTNF on blood monocytes is a specific biomarker of RA not present in healthy controls or in patients with other inflammatory diseases like CTD or SpA. This increase in mTNF is linked to disease activity and is not influenced by the treatment *in vivo* or *in vitro*. Conversely to a recent publication (Ehrenstein et al) we did not observe an increase in monocytes mTNF with treatment with adalimumab. The possible link between the increased monocytes mTNF expression and macrophages abnormalities seen in RA, as well as the predictive value of monocytes mTNF expression for response to anti-TNF or to other treatments of RA remain to be evaluate.

Disclosure: A. Paoletti, None; J. Rohmer, None; J. Pascaud, None; B. Oumouly, None; E. Rivière, Arthritis Fondation PhD fellowship, 2; S. Bitoun, None; G. Nocturne, None; X. Mariette, None.

Abstract Number: 1010

Inhibition of Bruton's Tyrosine Kinase (BTK) Prevents Inflammatory Macrophage Differentiation: A Potential Role in RA and SLE

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Innate Immunity Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Bruton's Tyrosine Kinase (BTK) mediates B cell receptor (BCR) and Fc receptor (FcR) signalling in several hematopoietic cell lineages, including B cells, macrophages and neutrophils. The BTK inhibitor evobrutinib silences B cells and prevents innate immune activation via FcR and is efficacious in preclinical models for rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Macrophages can have pro-inflammatory and anti-inflammatory properties and thus they play a crucial role in exacerbation versus control of autoimmune disease. BTK function has been implied downstream of certain cytokine receptors that control macrophage differentiation. The aim of this preclinical study was to investigate the effect of BTK inhibition on the differentiation and activation of monocytes and macrophages.

Methods: Monocytes were isolated from the peripheral blood of healthy volunteers. BTK activation was analyzed by Western blot following a 30-minute BTK inhibitor treatment and a subsequent granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulation time course. Survival of GM-CSF differentiated M1 cells was analyzed by flow cytometry following AnnexinV/PI staining. Expression levels of IL-1 β and IL-10 were determined by qPCR following 48 hours of GM-CSF stimulation and BTK inhibitor treatment. TNF- α levels in cell culture supernatants were measured by ELISA following overnight LPS stimulation and BTK inhibitor treatment. The uptake of apoptotic cells by M2 macrophages was analyzed by flow cytometry.

Results: BTK was activated downstream of the GM-CSF receptor. In line with this finding, *in vitro* GM-CSF differentiated M1 macrophages underwent apoptosis upon BTK inhibition using evobrutinib. Monocytes treated with GM-CSF in the presence of BTK inhibitor secreted less TNF- α and expressed less IL-1 β , and the expression of anti-inflammatory genes, such as IL-10, was upregulated. Furthermore, treatment with BTK inhibitor increased the rate of phagocytosis by anti-inflammatory M2 macrophages *in vitro*.

Conclusion: Our findings show that BTK inhibition hinders M1 macrophage differentiation and skews monocytes towards an anti-inflammatory M2 phenotype, while enhancing apoptotic cell uptake by M2 cells. Therefore, BTK inhibition could have additional benefits in the treatment of autoimmune diseases such as RA and SLE, by targeting both B cells and myeloid cells simultaneously.

Disclosure: Y. Beguem Alankus, Merck KGaA, 3; R. Grenningloh, EMD Serono, 3; P. Haselmayer, Merck KGaA, Darmstadt, Germany, 3; A. Bender, EMD Serono, 3; J. Bruttger, Merck KGaA, 3.

Tissue Resident Macrophages Establish a Niche That Limits Monocyte to Macrophage Differentiation in Synovial Tissue during Homeostasis

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Session Title: Innate Immunity Poster

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

Background/Purpose: Monocytes and Macrophages play critical roles in immune homeostasis and host defense. Recent studies identified that macrophages are highly heterogeneous in terms of location, origin and function. However, the sources of macrophages in the synovium and their functions are not yet clear. We performed BrdU incorporation and RNAseq profiling of blood monocytes and synovial macrophages from normal C57BL/6 mice under homeostatic conditions to identify functional differences.

Methods: Five distinct macrophage populations in synovium were determined by flow cytometry, based on subsetting CD45⁺CD64⁺CD11b⁺ cells by their expressions of Ly6C, MHCII and F4/80. Three F4/80^{int} (FI) subsets defined as Ly6C⁺MHCII⁻ (FI1), Ly6C⁺MHCII⁺ (FI2) and Ly6C⁻MHCII⁺ (FI3); and 2 subsets of F4/80^{hi} (FH) cells defined as MHCII⁻ (FH1) and MHCII⁺ (FH2) were identified. BrdU was used to identify proliferating cells. Populations of synovial macrophages and classical (CM) and non-classical (NCM) circulating monocytes were sorted by flow cytometry. High quality mRNAs from each of the cell populations was processed for RNAseq. The gene expression profiles and pathways were analyzed by Gene software and GOrilla database.

Results: BrdU⁺ CM and FI1 and FI2 macrophages that originated from bone marrow monocyte progenitors were detected within 24 hours. NCM and FI3 macrophages were BrdU⁺ on day 3. The FH1 and FH2 subsets were not renewed by circulating monocytes over 5 days, but were slowly proliferating. The distinct gene expression patterns were identified for each cell type by principal component analysis and pairwise correlation among cell groups. Genes that were highly expressed in CM were enriched in immune system processes, leukocyte activation, and signal transduction pathways such as Irf8, Stat1, Syk and Lyn. The majority of genes (65%) expressed in FH1 macrophages were maintained compared with CMs. This ratio of maintained genes gradually decreased going from the FI3, FH2 to FH1 subsets (60-54%). Further, comparing each macrophage subset to CMs, the ratio of differentially expressed genes (DEGs) increased from 14% (FI1), 23% (FI3), 27% (FH2) to 30% in FH1 macrophages. Of interest, host defense genes were highly represented in the FI1 macrophages compared with CMs. Expression of genes in the FH1 subset was highly correlated with those expressed in microglia and alveolar macrophages.

Conclusion: CM rapidly enter synovial tissue under homeostatic conditions but differentiate no further the FI3 population. FH macrophages are long-lived tissue resident macrophages of the joints. These observations suggest that under homeostatic conditions the FH1 subset provides a niche that prevents the further differentiation of FI1 macrophages to tissue resident macrophages. Further studies will address the mechanisms contributing to this niche.

Disclosure: Q. Q. Huang, None; R. E. Doyle, None; A. Misharin, None; S. Y. Chen, None; D. R. Winter, None; R. M. Pope, None.

Inhibition of Inflammation and Oxidative Stress in Systemic Sclerosis (SSc) Macrophages

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SESSION INFORMATION

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Session Title: Innate Immunity Poster

Session Type: ACR Poster Session B

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Background/Purpose: Systemic sclerosis (SSc) is a chronic autoimmune disease of unknown etiology that is characterized by vasculopathy, fibrosis, and inflammation. Our work and that of others have implicated MØs in SSc pathogenesis and thus targeting MØs may have significant therapeutic benefit. We have shown that MØs are aberrantly activated in SSc, releasing inflammatory mediators and inducing activation of fibroblasts. We now show that the synthetic oleanane triterpenoid CDDO-methyl ester (CDDO-Me) inhibits immune activation and oxidative stress in SSc MØs, resulting in inhibited expression of TGF- β , CCL2, and IL-6 and enhanced activation of Nrf2 signaling.

Methods: Plasma and PBMCs were obtained from whole blood of 7 SSc patients or 5 healthy age and gender-matched control subjects following informed written consent. CD14⁺ monocytes were isolated from PBMCs using magnetic bead selection, and were cultured with either autologous or allogeneic plasma for 7 days to differentiate the cells into MØs. Immune activation studies were performed using 10 ng/ml LPS. RNA expression in MØs was analyzed using qRT-PCR, and protein expression and secretion were monitored using flow cytometry and by ELISA.

Results: CDDO-Me markedly inhibits basal mRNA and protein expression of TGF- β , CCL2, and IL-6 in SSc MØs, and attenuates surface expression of CD163 and CD206, which are upregulated on pro-fibrotic SSc MØs. We further demonstrate that CDDO-Me upregulates targets of Nrf2 activation in SSc MØs, suggesting CDDO-Me attenuates oxidative stress in these cells. CDDO-Me treatment does not impair SSc MØ viability.

Conclusion: Our data suggest that CDDO-Me attenuates inflammatory activation and induces anti-oxidant activity in SSc MØs. For the first time, we have shown that CDDO-Me treatment attenuates the pro-fibrotic activation profile of SSc MØs. For the first time, we have also shown that CDDO-Me inhibits expression of surface markers and cytokines associated with SSc inflammation and pathogenesis. In addition to regulating these factors, CDDO-Me also induces Nrf2 activation in SSc MØs. As CDDO-Me is currently undergoing Phase III clinical trial testing in patients with pulmonary arterial hypertension, a frequent complication and leading cause of death in SSc, potential repositioning of this drug to treat SSc is especially exciting. Because there are still no FDA-approved disease-modifying therapies that target innate immune activation in SSc, CDDO-Me may be a potentially important drug in our arsenal of therapeutics to combat MØ activation in this disease.

Disclosure: R. Bhandari, None; M. Ball, None; S. Han, None; K. Aren, None; M. A. Carns, None; M. Hinchcliff, None; M. L. Whitfield, None; K. Liby, None; P. A. Pioli, None.

Abstract Number: 1013

Circulating Hybrid M1/M2 Monocytes/Macrophages in Systemic Sclerosis Patients with Lung Involvement

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Background/Purpose: Systemic sclerosis (SSc) is an autoimmune disease characterized by immune system alterations, vasculopathy and fibrosis [1]. SSc-related interstitial lung disease (ILD) represents a common and early complication of SSc, being the leading cause of mortality [2]. Monocytes/macrophages seem to have a key role in SSc-related ILD. Interestingly, the classically (M1) and alternatively (M2) activated monocyte/macrophage phenotype categorization is currently under revision [3]. Our aim was to evaluate if circulating monocyte/macrophage phenotype could be hypothesized as a pathogenic factor and/or used as biomarker for SSc-related ILD. To this purpose we developed a wide phenotype characterization of circulating monocyte/macrophage subsets in SSc patients and evaluated relations with lung involvement parameters.

Methods: A single centre, cross-sectional study was performed, in fifty-five consecutive SSc patients (50 females/5 males, mean age of 63 ± 13 years, 36 with a diffused cutaneous disease form and 19 with a limited cutaneous disease). All clinical and instrumental tests requested for SSc follow up and in particular: lung computed tomography (CT) scan, pulmonary function tests (PFTs), Doppler echocardiography with systolic pulmonary artery pressure (sPAP) measurement, blood pro-hormone of brain natriuretic peptide evaluation, were performed in each patient. Flow-cytometry characterization of circulating monocytes/macrophages was performed using surface markers attributed both to M1 and M2 cell subsets. Non-parametric tests were used for statistical analysis and any p-value lower than 0.05 was considered as statistically significant.

Results: Several mixed M1/M2 monocyte/macrophage subsets showed higher percentages in patients positive for anti-topoisomerase antibody, a well-known lung involvement predictor. A higher percentage of circulating cells positive for both CD204, CD163, CD206 (M2 markers) and TLR4, CD80, CD86 (M1 markers), was identified to characterize patients affected by SSc-related ILD and higher systolic pulmonary artery pressure. Higher percentages of circulating M1/M2 subsets showed a linear negative correlation with diffusion lung capacity of carbon monoxide (DLCO)%. A FVC/DLCO ratio higher than 1.5 correlated with higher circulating M1/M2 percentages.

Conclusion: The present study shows for the first time, through a wide flow cytometry surface marker analysis, that higher circulating mixed M1/M2 monocyte/macrophage cell percentage significantly correlated with anti-topoisomerase antibody positivity, ILD and sPAP in SSc, opening the path for research on their possible role as pathogenic or biomarker elements for SSc lung involvement. **References.**[1] Cutolo M, et al. Nat Rev Rheumatol 2015; 11:569-71. [2] Steen VD, et al. Ann Rheum Dis 2007;66:940-4. [3] Christmann RB, et al. Arthritis Rheumatol. 2014;66:714-25.

Disclosure: M. Cutolo, Bristol Myers Squibb, 2; A. C. Trombetta, None; V. Tomatis, None; S. Paolino, None; C. Pizzorni, None; V. Smith, None; P. Contini, None; P. Montagna, None; R. Brizzolara, None; S. Soldano, None.

Abstract Number: 1014

Distinct Macrophage Phenotype and Bioenergetic Profiles in Rheumatoid Arthritis

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SESSION INFORMATION

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

Background/Purpose: Synovial macrophages play a key role in RA disease progression, yet the diversity of macrophage subsets within the joint remains unknown. The concept of macrophage polarization into M1 inflammatory macrophages and M2 tissue-resolving macrophages, paralleled by changes in the bioenergetic cell profile, has received much attention. However the diversity and plasticity of macrophage subsets and their metabolic profile within the joint has yet to be elucidated.

Methods: Synovial tissue biopsies from Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA) and Osteoarthritis (OA) were obtained through key-hole arthroscopy. To phenotype distinct macrophage subtypes in the RA joint, synovial tissue biopsies (~10-15) were enzymatically and physically digested using an enzymatic cocktail and the GentleMACs dissociation system to yield a synovial single cell suspension. RA, PsA and OA synovial cell suspensions along with synovial fluid mononuclear cells were stained using a specific antibody panel (CD40, CD45, CD64, CD68, CD163, CD206, CD253) and analysed by advanced-multicolour flow cytometry analysis. Blood was also obtained from healthy and RA donors, CD14⁺ cells sorted and differentiated into macrophages for 8 days and polarised to either M1 (LPS/IFN γ) or M2 (IL-4) macrophages.

Inflammatory and metabolic genes were measured by RT-PCR. The two major energy-using pathways, glycolysis (ECAR) and oxidative phosphorylation (OCR) were measured by Seahorse XFE technology.

Results: M1 cells displayed higher expression of pro-inflammatory genes and demonstrated a pro-glycolytic phenotype with significant increases in HIF1 α , HK2, LDHA and PFKFB3, compared to M2, this effect was then further exacerbated in RA macrophages compared to healthy control. Using seahorse technology we demonstrate that in RA, both M1 and M2 macrophages display higher ECAR and OCR profiles compared to HC indicating that RA macrophages are more metabolically active compared to HC. Furthermore we note increased ECAR:OCR profiles in RA vs HC, thus RA macrophages utilise glycolysis more readily than HC. Flow cytometry analysis of RA synovial tissue and fluid revealed that CD68+ macrophages display markers typical of both M1 (CD40+CD253+) and M2 (CD206+CD163+). A significant increase in the frequency of CD68+ and CD64+ macrophages in the synovial tissue compared to fluid was observed, along with significant increases in marker expression of CD40, CD163 and CD206. Further analysis revealed a spectrum of macrophage subtypes exists within the inflamed joint, with a dominant macrophage subtype consisting of double positive CD206+ CD163+ identified, which is enriched in the synovial tissue compared to synovial fluid. Furthermore, we demonstrate that the frequency of this enriched population is significantly increased in RA synovial tissue compared to that of PsA and OA synovial tissue.

Conclusion: This study demonstrates distinct metabolic profiles in M1/M2 RA macrophages; associated with differences in key inflammatory mediators. Furthermore, we have identified, for the first time, a dominant subtype of RA tissue-specific macrophages, suggesting that these cells remain plastic and their function dependent on their microenvironment.

Disclosure: M. M. Hanlon, None; M. Canavan, None; T. McGarry, None; C. Low, None; S. C. Wade, None; D. J. Veale, None; U. Fearon, None.

Abstract Number: 1015

Rheumatoid Arthritis Peripheral CD14+ Monocytes Are Hyper-Inflammatory, Hyper-Glycolytic and Retain a Memory Bias Toward M1 Macrophages

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SESSION INFORMATION

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Background/Purpose: Myeloid cells with a monocyte/macrophages phenotype are present in large numbers in the rheumatoid arthritis (RA) joint, significantly contributing to disease. This study aimed to assess whether peripheral monocytes in RA are pre-programmed to become M1 pro-inflammatory macrophages.

Methods: Blood was collected from healthy donors, at-risk individuals (Those with arthralgia, ACPA+/RF+, normal CRP and no evidence of synovitis) and established RA patients. CD14+ monocytes were isolated from peripheral blood mononuclear cells using a CD14 magnetic bead separation kit. Cells were stimulated with LPS (100ng/ml) for 3-24 hours and to assess the effects of STAT3 inhibition, cells were pre-treated with STAT3i (10 μ M) for 30mins. A Human Cytokine and Chemokine PCR array was carried out and those genes most differentially expression were further validated in a larger cohort of patients using RT-PCR. The metabolic profile of cells was analysed using Seahorse XFE Technology, which concomitantly analysis glycolysis and mitochondrial respiration in real-time. Gene and protein expression of key inflammatory and glycolytic markers was also carried out by RT-PCR, western blotting and ELISA.

Results: CD14+ RA monocytes are hyper-inflammatory upon stimulation, with significantly higher expression of IL-1 β , TNF α , IL-6, IL-27, CXCL10 and CXCL11 compared to healthy controls, which is indicative of a M1-like pro-inflammatory phenotype. These hyper-inflammatory cells are highly glycolytic, with increased expression of HIF1 α and PFKFB3, a key glycolytic enzyme. Both baseline glycolysis and the maximal glycolytic capacity are increased in RA CD14+ monocytes, with no changes observed in mitochondrial respiration. This hyper-inflammatory, hyper-glycolytic phenotype is mediated by STAT3, as selective STAT3 inhibition can significantly decrease M1-like cytokines and PFKFB3 expression.

Finally, this pro-inflammatory phenotype is evident in CD14⁺ monocytes from arthralgia ACPA⁺/RF⁺ people at risk of developing disease, demonstrating that these processes may precede clinical manifestations in RA.

Conclusion: This study demonstrates the unique inflammatory and metabolic phenotype of RA monocytes, suggesting that peripheral CD14⁺ monocytes may be pre-programmed to become M1-like pro-inflammatory macrophages. In addition, the observation of this phenotype in at-risk individuals indicates that these features may precede clinical manifestations of RA and therefore could be useful as a biomarker for early diagnosis.

Disclosure: T. McGarry, None; M. M. Hanlon, None; C. C. Cunningham, None; D. J. Veale, None; U. Fearon, None.

Abstract Number: 1016

The Distinct Profile of Ly6c^{lo} Monocytes in the Murine Joint Compared with Those in Circulation Suggests a Unique Role in Inflammatory Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Innate Immunity Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Populations of monocytes in mice are distinguishable by expression of Ly6c. Ly6c^{hi} monocytes are associated with pro-inflammatory responses, while Ly6c^{lo} are involved in lining and patrolling endothelial membranes. Both Ly6c^{hi} and Ly6c^{lo} monocytes can differentiate into macrophages and have been implicated in inflammatory arthritis and we have previously shown Ly6c^{lo} monocytes are essential for development of serum transfer induced arthritis (STIA). In the present study we show that NR4A1-deficient mice, which have a marked reduction of circulating Ly6c^{lo} monocytes but retain Ly6c^{lo} monocytes attached to endothelial vessels, also develop arthritis. Thus, we postulate that Ly6c^{lo} monocytes may be a heterogeneous population with distinct functions (circulating vs patrolling).

Methods: Female NR4A1^{-/-} and C57Bl/6 mice were bred in house to 8-10 weeks old. STIA was induced by intravenous (IV) administration of KBxN sera at 85µl/20g. Arthritis was measured using clinical score, and mean clinical scores of N=4 per group were calculated. Monocytes were depleted using IV administration of clodronate-loaded liposomes (Clo-Lip). PBS-loaded liposomes were used as a negative control. Mice were euthanized by CO₂. Blood was collected by cardiac puncture and distal joints were collected following perfusion with PBS. Blood and joint monocytes were isolated by FACS and characterized by flow cytometry and RNA-sequencing (RNA-seq). Statistical analysis of disease and flow cytometry was carried out in GraphPad Prism. Statistical significance was considered at $P \leq 0.05$.

Results: NR4A1^{-/-} mice displayed a significant reduction in Ly6c^{lo} monocytes in the blood compared to C57Bl/6 controls, although joint Ly6c^{lo} monocytes in the joint were not significantly reduced. No significant differences were observed between arthritis severity between genotypes. In C57Bl/6 mice, Clo-lip administration resulted in over 90% depletion of CD115⁺ blood monocytes, however over 35% of synovial monocytes remained, suggesting they are not in the circulation. Of these, Ly6c^{hi} and Ly6c^{int} populations were significantly reduced ($P < 0.05$), while Ly6c^{lo} monocyte numbers were unaffected. Further, flow cytometric analysis of blood and synovial macrophages identified a population of Ly6c^{lo} monocytes in the joint of C57Bl/6 mice which express endothelial cell surface marker CD105. 60% of Ly6c^{lo} monocytes in the joint were CD105⁺ compared to 14% and 16% of Ly6c^{hi} and Ly6c^{int} respectively. Finally, transcriptional profiling of Ly6c^{lo} monocytes reveals upregulated genes in blood Ly6c^{lo} cells are enriched for processes such as monocyte activation and differentiation processes, compared to processes involved in cell migration and localization enriched in Ly6c^{lo} cells isolated from the joint.

Conclusion: These findings suggest a population of Ly6c^{lo} monocytes reside in the murine joint and have a distinct phenotype from blood Ly6c^{lo} monocytes measured by cell surface markers and transcriptional profile. Combined with the finding that NR4A1^{-/-} mice are susceptible to KBxN arthritis, this sub-population of Ly6c^{lo} monocytes is likely to have unique pro-inflammatory capabilities.

Disclosure: A. B. Montgomery, None; P. J. Homan, None; D. R. Winter, None; H. Perlman, None.

Abstract Number: 1017

Autoantigen Pentraxin-3 Is an Inflammatory Cytokine Storms Suppressor By Switching Monocytes Pyroptosis to Apoptosis in a Complement-Dependent Manner in Rheumatoid Arthritis

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SESSION INFORMATION

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Background/Purpose: A delayed diagnosis and therapy of ACPA (Anti cyclic citrullinated peptide antibody)-negative RA patients might be associated with effective serum biomarkers in clinic.

Methods: In the present study, we performed protein chip analysis in 30 HC, 60 patients with RA (including 30 ACPA-positive and 30 ACPA-negative), and 30 with other Autoimmune diseases.

Results: We found that anti-pentraxin 3 autoantibodies were significantly up-regulated in both ACPA negative and positive RA patients compared with healthy controls and other AIDs with high sensitivity and specificity. Enlarged samples of small protein chip confirmed the up-regulated anti-PTX3 level in ACPA negative RA patients. Further ELISA analysis of anti-PTX3 and its autoantigen pentraxin 3 in serum and synovial fluid showed that both anti-PTX3 and PTX3 was significantly up-regulated in ACPA positive and negative RA patients and positively correlated with clinical manifestations of DAS28 and RF as well as serum inflammatory cytokines, IL-1 β , IL-6 and TNF- α . We also showed that increased PTX3 secretion was derived from CD19⁺ B cells and preferentially bound to CD14⁺ monocytes in a C1q-dependent manner. Serum C1q level was higher in RA patients compared with HC and AIDs and positively correlated with PTX3 expression in RA patients. Moreover, PTX3 treatment of CD14⁺ monocytes combined with C1q in vitro could significantly up-regulate the activation marker CD40 expression and increased 7-AAD⁺Annexin V⁺ double positive late apoptotic cells in some RA patients. The induction of CD14⁺ monocytes apoptosis strongly inhibited RA-related inflammatory cytokine IL-1 β , IL-6 and TNF- α secretion after LPS stimulation in vitro. LDH release and the cleaved GSDMD and caspase-1 was significantly down-regulated while cleaved caspase-3 and Bcl-2 was significantly up-regulated after C1q and PTX3 combined treatment.

Conclusion: Our results demonstrated a detection of Anti-Pentraxin-3 autoantibodies in ACPA-negative RA Patients and autoantigen PTX3 combined with C1q could effectively inhibit GSDMD mediated pyroptosis and inflammatory cytokine release.

Disclosure: X. Zhang, None; X. Wu, None.

Abstract Number: 1018

Tofacitinib Impairs Monocyte-Derived Dendritic Cell Differentiation in Rheumatoid Arthritis and Psoriatic Arthritis.

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Background/Purpose: Tofacitinib (Pfizer) is an oral Janus kinase inhibitor, recently approved for the treatment of rheumatoid arthritis (RA) and psoriatic arthritis (PsA). Although its mechanism of action has been explored in circulating

cells, in particular neutrophils and lymphocyte, its effect on dendritic cells development and function remains still to be elucidated.

Monocyte-derived dendritic cells are a subset of inflammatory DC derived from circulating monocytes and have a key role in inflammation and infection. The aim of this project is to evaluate the effect of Tofacitinib on inflammatory monocyte-derived dendritic cells (Mo-DC) from RA and PsA patients, and in particular on the ability of monocyte to differentiate into dendritic cells, an important step in innate immunity.

Methods: Monocytes were isolated from blood of healthy donor (HC), RA and PsA patients by magnetic separation and plated in presence/absence of GM-CSF/IL-4 cocktail for 7 days, to acquire immature dendritic cells (DC) phenotype. To evaluate the effect of Tofacitinib on Mo-DC differentiation, monocyte were treated with 1 μ M Tofacitinib (or DMSO as control) for 15 minute prior to cytokine stimulation. CD209 (immature DC marker) and CD14 (monocyte marker) were evaluated by flow cytometry in the CD11c positive population. Non-specific macropinocytosis (using Lucifer Yellow) and receptor-mediated endocytosis (using DQTM Ovalbumin) were investigated by flow cytometry. Western blot analysis was utilized for analysis of the effect of Tofacitinib on NADPH oxidases (NOX) 5 and 2, known player in Mo-DC differentiation. Finally, the frequency of CD209 cells was evaluated by flow cytometry in both peripheral blood (PBMC) and synovial fluid (SFMC) mononuclear cells from RA and PsA patients.

Results: Pre-treatment of Mo-DC with Tofacitinib inhibited Mo-DC differentiation in RA and PsA patients, as shown by reduced CD209 marker expression, paralleled by an increase of CD14 marker expression. The decreased ability of monocytes to differentiate into DC in the presence of Tofacitinib was translated into a function impairment of phagocytic ability, in particular in PsA patients, as observed by the decreased uptake of both DQTM Ovalbumin (receptor-mediated endocytosis) and Lucifer Yellow (micropinocytosis).

When comparing the ability of monocyte to differentiate into DC, we observed that RA monocytes differentiated faster than HC and PsA, expressing CD209 marker already at day 1.

NOX5 has previously been shown to play a key role in Mo-DC differentiation, therefore we sought to investigate whether the effect of Tofacitinib on Mo-DC differentiation is mediated through modulating NOX5. Interestingly, Tofacitinib decreased NOX5 and increased NOX2 protein expression in Mo-DC in both PsA and RA Mo-DC. Finally, we identified the CD209 population in PBMC cells from RA and PsA patients, and we observed an increased frequency of this population at the site of inflammation in SFMC cells from PsA and RA patients.

Conclusion: Together, these observations suggest a novel mechanism of action of Tofacitinib in RA and PsA, by inhibiting Mo-DC development, which may alter migration of DC to the joint and subsequent activation of the immune response.

Disclosure: V. Marzaioli, Pfizer, Inc., 2; M. Canavan, None; A. Floudas, None; S. C. Wade, None; C. Low, None; D. J. Veale, Pfizer, Inc., 2; U. Fearon, Pfizer, Inc., 2.

Abstract Number: 1019

Involvement of Mast Cells in the Pathogenesis of Sjögren's Syndrome By Induction of Tissue Fibrosis Via Fibroblast Collagen Synthesis

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Background/Purpose: There is an emerging view that mast cells may play a pivotal role in several inflammatory and autoimmune diseases. However, the role of mast cells in Sjögren's syndrome remains unclear. We examined whether mast cells play a critical role in immune-mediated inflammation and fibrosis in patients with Sjögren's syndrome.

Methods: Labial salivary gland samples were collected from 22 individuals with primary Sjögren's syndrome and 10 with sicca syndrome (controls) and were examined using histological and immunohistochemical methods. Saliva production was evaluated by Saxon's test. Mast cell density in the minor salivary glands was calculated at x400 magnification. Five fields

were counted in all cases. The lymphocyte focus score was evaluated based on the number of inflammatory cell aggregates containing >50 lymphocytes per 4 mm². The degree of fibrosis in the minor labial salivary glands was graded on a quantitative scale as previously reported (Clin Exp Rheumatol.1998;16:63-65). We used immunohistochemistry to identify and quantify tryptase-positive mast cells and vimentin-positive fibroblasts. Fibrous tissue was identified using elastic Van Gieson (EVG) staining. Human mast cell line 1 (HMC-1) cells were cocultured with pulmonary fibroblasts for 7 days using a transwell system, and type I collagen synthesis in fibroblasts was evaluated by quantitative RT-PCR.

Results: We found that the number of mast cells in the labial salivary glands of patients with primary Sjögren's syndrome was significantly increased compared to that in control subjects ($p<0.0001$). There was a significant negative correlation between the Saxon's test results and the number of mast cells ($r=-0.6742$, $p=0.006$), suggesting the involvement of mast cells in the decreased salivary secretion. There was no significant correlation between the intensity of lymphoid infiltration assessed by the focus score and the mast cell density ($r=0.01545$, $p=0.58$). In contrast, a significant correlation between the number of mast cells and the degree of fibrosis was observed ($r=0.5911$, $p=0.0038$). Consistent with these findings, histochemical analysis revealed that mast cells were usually present in close proximity to EVG-stained fibrous tissue in the labial salivary glands. Furthermore, double immunostaining revealed that the mast cells were located proximal to vimentin-positive fibroblasts. We hypothesized that mast cells were involved in the development of tissue fibrosis via modulation of fibroblast immune function in sialadenitis and conducted an in vitro co-culture of HMC-1 cells and pulmonary fibroblasts. Significant up-regulation of Col1a mRNA was observed in fibroblasts co-cultured with HMC-1 cells compared to that in fibroblast monocultures ($p=0.02$).

Conclusion: These results suggest a novel role for mast cells in the development of sialadenitis in patients with primary Sjögren's syndrome by induction of tissue fibrosis via fibroblast collagen synthesis.

Disclosure: S. Kaieda, None; K. Fujimoto, None; M. Tominaga, None; M. Okamoto, None; T. Hoshino, None; H. Ida, None.

Abstract Number: 1020

Involvement of Toll-like-Receptor-9 Pathway on Natural Killer Cells in Systemic Lupus Erythematosus

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SESSION INFORMATION

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Background/Purpose: Natural killer (NK) cells participate in systemic lupus erythematosus (SLE) pathogenesis by promoting dendritic cell (DC) activation and/or interferon (IFN) γ over-production. NK cell activation pathways remain unknown. One mechanism leading to plasmacytoid DC activation in SLE is the binding of auto-antigens (nucleic acids) with their cognate intracellular toll-like receptors (TLR), which includes TLR-9. Using synthetic CpG-ODN-A-2216 as TLR-9 ligand, the aim of this study was to determine if this pathway is similarly involved in NK cell activation and if hydroxychloroquine (HCQ) has an effect on this pathway.

Methods: From 2013-2018, 41 HCQ-free and 8 HCQ-treated SLE patients were compared to 29 controls. SLEDAI ≥ 6 defined active patients. Fresh CD3⁺CD56⁺ NK cells were stained with anti-CD69-ECD and TLR-9-PE after permeabilization. Polyfunctionality assays detected both degranulation (anti-CD107a-FITC) and intracellular IFN γ (anti-IFN γ -AF700) after a 5-hour-co-culture of either PBMCs or purified NK cells with K562 target cells to a 1:1 ratio. CpG-ODN-A-2216 was added overnight to 10⁶ cells/ml cultures at 12.5 mM/ml. When added, soluble HCQ was used at 0.1, 0.5, 1, or 5 mg/ml.

Results: In HCQ-free SLE patients, % of TLR9⁺-NK cells was increased in active patients as compared to inactive patients: 31 ± 17% vs. 13 ± 15%. TLR-9 expression correlated with the % of CD69⁺-activated NK cells ($r^2=0.68$; $p=0.004$). Overnight stimulation of PBMCs by CpG-ODN-A-2216 led to activation of NK cells (CD69 increasing from 31 ± 18% to 70 ± 18%, $p<0.001$) and resulted in degranulation and slight production of IFN γ with similar effects in patients and controls: 50 ± 14% vs. 49 ± 16% and 7 ± 6% vs. 8 ± 6%, $p<0.001$, respectively. CpG-ODN-A-2216 had a direct effect in purified-NK cell activation: % CD69 increasing from 25 ± 15% to 39 ± 19%, $p=0.008$. However, it was not sufficient to induce both their degranulation and IFN γ production in patients vs. controls. Adding HCQ prior to the PBMCs stimulation inhibits CpG-ODN-A-2216, with a dose effect *in vitro*. Interestingly, the significant effect started at the *in vivo*-target dose of 1 mg/ml: % CD69 decreasing from 70 ± 24% to 38 ± 31%, $p=0.036$. Furthermore, CpG-ODN-A-2216 stimulation of both PBMCs and purified NK cells from patients treated with HCQ (concentration > 0.77 mg/ml) did not show any effect: CD69 remaining stable at 24 ± 20% vs. 34 ± 24%, $p=0.5$ and 16.5 ± 10% vs. 16 ± 11%, $p=1$, respectively.

Conclusion: Although CpG-ODN-A-2216 had only a partial direct effect on NK cell polyfunctionality, these results indicate that TLR-9 pathway is involved in NK cell activation in SLE. Further investigations are needed to determine if the “physiological” auto-antigens act like the CpG-ODN-A-2216.

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Abstract Number: 1021

Impact of TLR7 Ligation in RA Pathology

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SESSION INFORMATION

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Background/Purpose: Expression of Toll-like receptor 7 (TLR-7) is highly elevated in rheumatoid arthritis (RA) and osteoarthritis (OA) compared to normal (NL) synovial tissue lining and sublining macrophages. Interestingly in RA blood monocytes, TLR7 expression closely correlates with disease activity score (DAS28) and TNF- α transcription levels. We recently uncovered a novel endogenous TLR7 ligand; miR-Let7b, that is predominately packaged in RA synovial fluid macrophages. To document the impact of miR-Let7b ligation to TLR7 in RA pathogenesis, studies were performed using RA cells and preclinical models.

Methods: To understand the mechanism by which synovial fluid miR-Let7b promotes RA pathology, ligation of TLR7 was investigated on inflammatory response provoked by myeloid and T cells. Next, the impact of ectopic expression of miR-Let7b was examined in naïve mice and collagen induced arthritis (CIA) preclinical models.

Results: We found that TLR7 endogenous ligands, single strand (ss)RNAs, were undetectable in NL and RA plasma while these ligands were highly expressed in RA synovial fluid (SF). Consistent with the distribution of RA SF ssRNA, we show that miR-Let7b is markedly elevated in RA SF compared to OA SF (14 fold lower), RA (260 fold lower) and NL plasma (450 fold lower). We reveal that exosomes released from RA SF macrophages are an important source of miR-Let7b storage (78 copies; shown as 1 fold) and that cell death mediated by apoptosis (660 copies, 8 fold) or necrosis (74820 copies, 950 fold) can further potentiate the discharge of exosomal miR-Let7b into RA SF. Moreover, we determined that stimulation with miR-Let7b or TLR7 agonist can markedly accentuate TNF- α and IL-6 transcription and production (50-100 fold increase respectively) in RA peripheral blood (PB) *in vitro* differentiated macrophages. In contrast, neither TLR7 agonist nor miR-Let7b stimulation had any effect on IL-10 transcription. We also found that in PB mononuclear cells (T cells plus myeloid cells), TH-17 cells are strongly polarized by TLR7 ligation, in part due to secretion of IL-6 and IL-1 β from RA myeloid cells. We next show that ligation of TLR7 by local injection of miR-Let7b, results in significantly elevated joint inflammation. Consistently, when CIA mice were ectopically treated with miR-Let7b, joint swelling was markedly potentiated, while the control ankle circumference remained at a plateau phase. We uncovered that levels of monokines secreted from CIA ankle joints, including TNF- α , CCL2, CCL5 and IL-1 β were exacerbated by local administration of miR-Let7b in comparison to the control mice. Extending our observations in RA cells, we document that miR-Let7b treatment in CIA mice can amplify joint TH-17 cells/IL-17 differentiation. Our results indicate that RA disease activity is augmented by miR-Let7b ligation to TLR7 which activates effector myeloid and T cells function in these patients.

Conclusion: Overall our findings suggest that ligation of miR-Let7b to TLR7 perpetuates RA inflammation and blockade of this pathway may be an attractive target for RA therapy.

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TNF- α Regulates Plasmacytoid Dendritic Cells By Suppressing IFN- α Production and Enhancing Th1 and Th17 Cell Differentiation

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Background/Purpose: Human plasmacytoid dendritic cells (pDCs) play a vital role in modulating immune responses. pDCs can produce massive amounts of type I IFNs in response to nucleic acids via toll-like receptors (TLRs) and they are known to possess weak antigen-presenting properties inducing CD4⁺ T cell activation. Previous data showed a cross-regulation between TNF- α and IFN- α but the effect of TNF- α on pDCs remains unclear. The aim of this study was to investigate how TNF- α regulates the immune function of human pDCs.

Methods: Freshly isolated peripheral blood mononuclear cells were treated with TNF- α , TLR7 and TLR9 synthetic agonists. pDCs were immunophenotyped using flow cytometry. RNA from sorted pDCs was extracted and sequenced using Smart-seq2 for sensitive full-length transcriptome profiling. For pDC/T cell co-culture, fresh or TNF- α -treated pDCs were cultured with naïve CD4⁺ T cells for 5 days. The production of cytokines was measured by intracellular staining and ELISA.

Results: Upon stimulation with TLR7 and TLR9 agonists, there were three main pDC populations: non-producers, TNF- α -producers, TNF- α /IFN- α -producers. Exogenous TNF- α significantly reduced the production of both IFN- α and TNF- α in TLR9-stimulated pDCs but only IFN- α in TLR7-stimulated pDCs. Neutralization of autologous TNF- α with anti-TNF antibody partially sustained IFN- α secretion by TLR9-stimulated pDCs after 24 hours. Exogenous TNF- α significantly promoted pDC maturation by upregulation of costimulatory molecules and chemokine receptors such as CD80, CD86, HLA-DR, and CCR7. RNA-sequencing data analysis suggested that TNF- α inhibits IFN- α production by interfering with the IRF7 and NF κ B pathways but promotes antigen processing and presentation pathways as well as T cell activation and differentiation. Indeed, the *in vitro* co-culture showed that TNF- α -treated pDCs induced higher CD4⁺ T cell proliferation and favoured Th1/Th17 polarization.

Conclusion: Although pDCs possess weak antigen-presenting properties, TNF- α can enhance pDC maturation by switching their main role as IFN- α -producing cells to a more conventional DC phenotype. The functional status of pDCs might be strongly influenced by overall inflammatory environment and TNF- α might regulate IFN- α -mediated aspects of a range of autoimmune and inflammatory diseases.

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Plasmacytoid Dendritic Cells That Infiltrate the Lungs Produce Profibrotic Cytokines and Chemokines in Bleomycin-Induced Model of Systemic Sclerosis

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Background/Purpose: In bleomycin-induced model of systemic fibrosis and patients with systemic sclerosis, plasmacytoid DC (pDC) are unaffected or reduced systemically (spleen/peripheral blood) but they increase in the lungs (Kafaja S, et al, JCI Insight 2018). Depletion of pDCs ameliorated fibrosis in the bleomycin model and altered the expression levels of proteins and genes implicated in chemotaxis, inflammation, and fibrosis in the lungs. In resonance with animal findings, the frequency of pDCs in the lungs of patients with SSc correlated with the severity of lung disease. Treatment with a tyrosine kinase inhibitor imatinib that has been reported to reduce and/or prevent deterioration of skin and lung fibrosis profoundly reduced pDCs in lungs but not in peripheral blood of patients with systemic sclerosis. In patients with systemic sclerosis, the frequency of pDCs also correlated with levels of proteins implicated in inflammation, vasculopathy and fibrosis. It is unclear if pDCs directly contribute to inflammatory and profibrotic milieu in the development of systemic fibrosis. Here, we asked if pDCs as compared to other immune cells contribute to proteins that are differentially expressed in the lungs after bleomycin exposure.

Methods: Female C57Bl/6 mice were injected with bleomycin (4 U/kg body weight) subcutaneously daily for 2 weeks. Lungs were harvested from bleomycin or control PBS injected animals on day 28. Lung extracts were analyzed for proteins by Western blot and ELISA, and freshly isolated single cells were analyzed for the expression of proteins on pDCs, myeloid dendritic cells (CD11c⁺CD11b⁺; mDC), other myeloid cells (CD11b⁺CD11c⁻, monocyte/macrophages and neutrophils), B cells, and T cells by multiparameter flow cytometry. Relative expression of proteins was expressed as the ratio of the mean fluorescent intensity of cells stained with respective antibodies and isotype controls.

Results: Scavenger receptor CD36 that is implicated in platelet-collagen adhesion, oxidative stress and inflammation was significantly increased on pDCs ($p < 0.01$) but not on mDCs, other myeloid cells, B cells and T cells in the lungs of bleomycin-injected animals as compared to control animals. TLR7 was also increased more on pDCs than on all other immune cells examined, whereas TLR2 was increased more on mDCs and other myeloid cells but not significantly on pDCs and B cells in the lungs of bleomycin-injected animals as compared to control animals. TGF β latent peptide was higher on the surface of all immune cells examined in the lungs of bleomycin-injected animals than in control lungs. Among chemokine receptors examined, CCR2, CCR3, CCR6, CCR9 and CXCR4 were higher on pDCs than most other cells examined. CCR2 and CCR9 were also higher on mDCs, and CXCR4 was higher on B cells and mDCs in the lungs of bleomycin-injected animals as compared to control animals.

Conclusion: Our data suggest an important role of pDCs in eliciting pro-inflammatory and profibrotic milieu in the development of systemic fibrosis. These observations along with recently published studies identify the increased trafficking of pDCs to the affected organs as a potential therapeutic target in systemic sclerosis and other fibrotic diseases.

Disclosure: I. Valera, None; R. R. Singh, None.

Unique Pattern of Lectin Pathway Complement Protein Levels in Axial Spondyloarthritis

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Background/Purpose: Spondyloarthritis (SpA) represents a group of immune-mediated inflammatory diseases that exhibit overlapping clinical features, genetic predisposition and a not fully understood pathogenesis. Inflammation and structural damage of target tissue are clinical characteristics. Growing evidence indicates that parts of the pro-inflammatory profile in SpA is caused by abnormal innate immune responses. In SpA it is believed that immune system failures result in insufficient removal of dead cells from the body, leading to an increased or abnormal pressure on the immune system. This may lead to activation of the Lectin Pathway (LP) of the complement system. The LP of the complement system plays a role in the clearance of apoptotic and necrotic cells. We hypothesize that a characterization of the lectin pathway proteins in SpA patients compared to controls may provide new insight into the pathogenesis of SpA.

Methods: Prospectively, blood samples (EDTA plasma) and disease activity scores (ASDAS, BASDAI and BASMI) were collected in a well-defined cross sectional SpA cohort of 120 patients (median age 36.5 years, range 18-72; 85% HLA-B27 positive, 61% male; 45% bDMARD treated) fulfilling the ASA 2009 criteria and of 120 controls. Ten proteins of the LP were measured in plasma using in-house developed assays. As indicators of complement consumption and activation the complement proteins C3 and C3dg were assessed.

Results: Concentrations of the LP proteins were altered in a specific pattern in this cross-sectional SpA cohort compared with healthy controls. High concentrations in plasma of H-ficolin, MAP44 and M-ficolin and low concentrations of CL-L1 were observed for patients with SpA compared to healthy individuals (p-values all <0.001). The differences in LP proteins observed between patients and controls were not significantly associated with complement activation or disease activity (ASDAS, BASDAI). Using the 75-percentile in healthy controls as cut-off for an elevated concentration of H-ficolin, MAP44, and M-ficolin and the 25-percentile as cut-off for a reduced concentration in CL-L1, we then used resulting elevated or reduced values as disease biomarkers. Using the cumulative presence of the four altered LP concentrations in patients and controls, we could to a high degree separate SpA patients from healthy controls. Among controls with LP concentrations within the normal range a negative predictive value of 0.90 was found and among SpA patients with three altered LP concentrations a positive predictive value of 0.87 was found.

Conclusion: In this cross-sectional SpA cohort we observed specific changes in 4 of 10 LP proteins. The specific pattern (high H-ficolin, L-ficolin, MAP44 and low CL-L1) clearly differentiated to a high degree SpA patients from healthy individuals. Potentially, this could improve the diagnosis of SpA. These novel findings may substantiate the involvement of LP proteins in the pathogenesis of SpA.

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MiR-146a a Key Player in Bone Metabolism

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Background/Purpose: Micro RNAs (miRNAs) play a crucial role in the regulation of bone metabolism. MiR-146a, an important anti-inflammatory miRNA, was found to negatively impact osteogenesis and bone regeneration *in vitro*, by controlling the differentiation of mesenchymal stem cells. But to date the role of miR-146a in bone remodelling, its influence on bone stability and development of osteoporosis is not known.

Methods: Systemic bone, tibiae and femur, of wt and miR-146a deficient animals was assessed histologically and via μ CT analysis, over a period of 3 to 18 months of age. Serum cytokine levels were analysed by Elisa. mRNA expression levels in bone were analysed by qPCR. To induce osteoporosis, ovariectomy (OVX) induced bone loss was performed.

Results: When we analysed bone volume of long bones histologically as well as with μ CT analysis we detected significantly increased trabecular bone mass in miR-146a deficient compared to wt animals, starting at an age of 6 months. However, cortical thickness of systemic bones from miR-146a knock out animals was significantly reduced compared to control mice. Analysis of serum in aged miR-146a deficient animals displayed elevated activity of bone resorbing osteoclasts as amounts of CTX I in miR-146a^{-/-} mice were significantly increased compared to wt animals. Q-PCR analysis of important osteoclast as well as osteoblast marker genes in bones *ex vivo* displayed elevated expression of signature molecules of both cell types in aged miR-146a deficient mice, suggesting a regulatory role of miR-146a in both osteoclasts as well as osteoblasts. When we induced osteoporosis using the OVX disease model, histological analysis of long bones showed significant trabecular bone loss in ovariectomized wt mice. In contrast, we detected no trabecular bone loss in ovariectomized miR-146a knock out animals, suggesting that loss of miR-146a deficiency protects bone loss induced by estrogen deficiency.

Conclusion: MiR-146a seems to control bone turnover and miR-146a deficient mice accrue bone over time. Moreover this miRNA has a negative influence on bone loss occurring during oestrogen loss induced osteoporosis. Therefore miR-146a could be possibly used as a therapeutic target in the treatment of osteoporosis.

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Autoinflammatory Diseases, Particularly SAVI and Candle, Are Driven By Chronically Active Type I Interferons

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Background/Purpose: STING Associated Vasculopathy with onset in Infancy (SAVI) is caused by gain-of-function mutations in *TMEM173*/STING and Chronic Atypical Neutrophilic Dermatitis with Lipodystrophy and Elevated Temperature (CANDLE) by loss-of-function mutations in proteasome subunits. Both are IFN-mediated disease but the origin of the IFN production has not been systematically evaluated in patients. The purpose of our study was to determine the cellular origin of IFNs, from SAVI and CANDLE patients (PTs) compared to healthy controls (HC).

Methods: We evaluated sorted PBMCs (n=5 HC, PTs) and lesional skin biopsies (n=2-3 HC, PTs) for detection of IFN production by qRT-PCR.

Results: In both diseases, pan-interferon (IFN)- α serum levels are 8 and 25-fold increased, respectively. PTs had a mean of 12-fold increase in IFN-response-gene (IRG) signatures compared to HC. SAVI pts. constitutively expressed elevated IFN-transcript levels and qPCR results showed a 450-fold and 280-fold increase in *IFNB1* [IQR 0.5-61, 60.6], and 3.5-fold and 4.4-fold increase in *IFNA17* [IQR 0-2.93, 2.93] transcription in monocytes (n=5) and dendritic cells (n=3) respectively, compared to CANDLE and HC. During disease flares but not at rest, CANDLE monocytes increased *IFNB1* production 4.6 and 184-fold and *IFNA72.5* to 110-fold (n=2). In contrast to CANDLE and HC monocytes, SAVI monocytes cannot be differentiated into macrophage and 82% \pm 14 SD died in culture within 24-hours. SAVI monocytes expressed 24-fold increase of actively cleaved caspase-1 in the supernatant from the immunoblot analysis compared to HC and did not show active form of caspase-3. ELISA demonstrated low expression of IL-1 β in the supernatant and immunofluorescence showed elevated intracellular staining of gasdermin-D and NLRP3, suggesting cell death occurs through pyroptosis.

Conclusion: The cellular sources of IFN production vary in CANDLE and SAVI; Type I IFN transcription in SAVI patients occurs mainly in monocytes and in dendritic cells, in contrast, in CANDLE patients, Type I IFNs are only expressed in monocytes prior to JAK inhibitor treatment during a disease flare (Tx). However interferon-response genes

are expressed in all cell types. Constitutively active STING from SAVI monocytes undergo rapid cell death in culture, which may indicate rapid cell turnover in the blood. Studies evaluating the mechanism that leads to monocyte death is ongoing. Understanding the signaling pathways in autoinflammatory diseases associated with high IFN signatures is important in our ability to identify and interpret biomarkers that will aid in the diagnosis and the design of targeted treatments.

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Abstract Number: 1027

A Novel IL-1 Mediated Autoinflammatory Disease Caused By a Specific Gain-of-Function Mutation in Dysferlin

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Background/Purpose: Genetically defined IL-1 mediated autoinflammatory diseases are caused by monogenic defects that regulate inflammasome activity. By whole exome sequencing (WES) analysis we identified one *de novo* mutation in *DYSF* encoding dysferlin, in 2 unrelated patients (pts.) with systemic inflammation and sterile pulmonary abscesses. Unlike dysferlin mutations that cause muscular dystrophies, the patients have no muscle disease. A robust clinical response to IL-1 blockade suggested a link to overproduction of IL-1. We studied monocytes and neutrophils to assess the mechanism of the IL-1 dependent inflammation. The aim of our study is to understand the role of *DYSF* on the upregulation of IL-1 production and the development of lung abscesses.

Methods: Flowcytometry, ELISA, cytokine array, survival assay and immunofluorescence techniques were used to study monocyte and neutrophil function in patients and controls.

Results: Lipopolysaccharides (LPS) and ATP-stimulated IL-1 production in monocyte and monocyte-derived macrophages (MDM) was significantly higher in the *DYSF* pts. compared to IL-1 production in NOMID pts. ($p=0.029$) and healthy controls (HC) ($p=0.038$). Dysferlin colocalizes with NLRP3 and expression of Asc, and caspase-1 were increased in the *DYSF* pts. compared to healthy controls, which is linked to higher IL-1 β production. Our data confirmed NLRP3 and Caspase-1 co-localization in patient monocytes as well. The development of sterile neutrophilic abscesses in the lung raised questions of the role of dysferlin in neutrophil activation and clearance. In contrast to MDMs, IL-1 was not upregulated in patient neutrophils, however MIF (5 fold) and IL-16 (2-3 fold) were significantly upregulated compare to HC and NOMID but not in monocytes or macrophages. Neutrophils had a higher survival rate and lower LDH release compared to healthy controls upon stimulation with LPS and ATP. Elevated MIF and IL-16 release may prevent neutrophil apoptosis and enhance persistence of sterile neutrophils in the lung. Mechanistic studies to explore these pathways are ongoing.

Conclusion: Consistent with clinical responses of IL-1 blocking treatment, our *in vitro* results confirm mutant monocytes and MDMs as the source for the high IL-1 production in two patient with a *de novo* mutation in dysferlin. Moreover, the upregulation of MIF and IL-16 in neutrophils from dysferlin patients but not NOMID patients or healthy controls and the impairment of neutrophil apoptosis may provide a mechanism to explain the development of sterile abscesses in the patients' lungs. This is the first report that links dysferlin to the regulation of the NLRP3 inflammasome and to neutrophil survival and adds to a number of intracellular pathways that control inflammasome activation and suggest novel targets for treatment.

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An Enthesal Innate Immune Cell Biological Basis for Differential Efficacy of PDE4 and IL-23 Pathway Blockade between Psoriatic Disease and Rheumatoid Arthritis

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Background/Purpose: Both IL-23 and phosphodiesterase (PDE) 4 inhibition are ineffective in RA but show efficacy in PsA-related synovitis despite similar cytokine and molecular profiles between synovitis in both disease settings. We hypothesised that enthesitis resident innate immune cells, especially myeloid cells, might be capable of IL-23 production that could be modulated by blockade of PDE4, which controls intracellular cyclic AMP (cAMP) levels.

Methods: Human entheses (n=6) were digested and myeloid cells (CD14+) sorted from both the adjacent bone (EB) and soft tissue (ST) fractions. Both CD14+ sorted and CD14- unsorted cells were stimulated with bacterial and fungal adjuvants (TLR and CLR agonists) in the presence and absence of a PDE4 inhibitor and analysed by ELISA and flow cytometry for production of disease-relevant mediators (IL-23, TNF α , and CCL20). Corresponding peripheral blood populations were also stimulated with and without a PDE4 inhibitor and other cAMP-elevating agents to assess the role of cAMP in regulating IL-23 associated inflammation.

Results: A CD45+/CD14+ myeloid cell population could be isolated from the normal enthesitis in both the ST and EB fractions but with a much higher abundance in EB. This purified population from both ST and EB produced IL-23, TNF α and CCL20 following TLR/CLR receptor stimulation. IL-23 and TNF α production was negligible in the CD14- fraction. Moreover, IL-23 and TNF induction was inhibited by the PDE4-selective inhibitor rolipram. In blood derived myeloid cells, rolipram and other cAMP-elevating agents (histamine and 8-bromo-cAMP), also inhibited IL-23 release.

Conclusion: These findings demonstrate that the human enthesitis harbours an IL-23-producing myeloid cell population which can be modulated by cAMP elevation and PDE4 inhibition. These findings support the idea of the IL-23/17 pathway genetic architecture of SpA in the context of enthesal biology and offer a "reverse translation" explanation for divergent therapeutic pathways between SpA and RA.

Disclosure: C. Bridgewood, None; R. Cuthbert, None; A. Watad, None; T. Russell, None; T. Palmer, None; R. Dunsmuir, None; A. Khan, None; A. Rao, None; M. Wittmann, Novartis, 5, Janssen, 5, AbbVie Inc., 5, Celgene Corporation, 5; D. McGonagle, Novartis, Janssen, Pfizer, AbbVie, 2, Novartis, Janssen, Pfizer, AbbVie, 8.

Fibroblast-like Synoviocytes As Immune Effectors in the Pathogenesis of Synovial Lesion in Antibiotic-Refractory Lyme Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Innate Immunity Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Antibiotic-refractory Lyme arthritis (LA) is characterized by marked proliferative synovitis that persists for months-to-years after oral and IV antibiotic therapy for *Borrelia burgdorferi*. Although the infection serves as the initial trigger for LA, the processes that shape the post-antibiotic phase of refractory LA are incompletely understood. Herein we assessed the role of fibroblast-like synoviocytes (FLS), the predominant cell type in synovial lesion, in modulating the responses to infection with highly virulent *B. burgdorferi* RST1 strain and the prototypical Th1 effector cytokine, IFN γ ; the key microbial and immune factors in antibiotic-refractory LA.

Methods: FLS were derived from synovia of antibiotic-refractory LA patients undergoing arthroscopic synovectomies. Low passage FLS were stimulated with *B. burgdorferi*, IFN γ , or a combination for 16h. After stimulation, genome-wide transcriptome profiles were assessed using RNASeq and protein levels of inflammatory mediators were measured using Luminex.

Results: FLS sense and respond to *B. burgdorferi* by upregulating the expression of 68 genes associated primarily with pathogen sensing and innate immune responses, such as TLR2, NOD2, IL-1 β , and IL-6. In contrast, stimulation with IFN γ leads to marked upregulation >2000 genes involved in pathways associated with immune dysregulation, cancer, and autoimmunity. These responses were amplified in FLS costimulated with *B. burgdorferi* and IFN γ which acted in synergistic fashion to induce a unique signature of differentially expressed genes that most closely resembled the transcriptome profiles in patients' synovial tissue, including high upregulation of antigen-presenting molecules (HLA-DR, CIITA, CD40, and PD-L1; $P < 1 \times 10^{-12}$). Moreover, cytokine and chemokine protein profiles secreted by FLS in response to costimulation, mimicked those in synovial fluid and tissue from patients with antibiotic-refractory LA, linking FLS to excessive inflammation in the joint.

Conclusion: FLS play an important role in arthritis pathogenesis by initially shaping the immune responses to *B. burgdorferi* infection, and later by perpetuating dysregulated inflammatory responses in patients with antibiotic-refractory LA by responding to inflammatory milieu in the joint. The highly-activated state of FLS, including antigen-presentation, suggests an immune effector function of these cells even in the post-infectious period. These findings help explain how the initial host-pathogen interactions such as infection with an RST1 strain in patients with a TLR1-1805GG SNP, which lead to excessive IFN γ responses, may contribute to synovial hypertrophy and dysregulated immunity in the post-antibiotic period when few if any intact spirochetes remain.

Disclosure: K. Strle, None; R. Lochhead, None; R. Sadreyev, None; A. C. Steere, None; J. Aversa, None.

Abstract Number: 1030

Parenteral Injection of Human Adipose-Derived Mesenchymal Stem Cells Attenuates Inflammation in an Acute Model of Gouty Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Innate Immunity Poster

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

Background/Purpose: The regenerative and immunomodulatory properties of Adipose-Derived Mesenchymal Stem Cells (ASCs) make them a potential therapeutic approach for the treatment of chronic inflammatory diseases, such as osteoarthritis and rheumatoid arthritis. However, their effect in the treatment of acute joint inflammation, where the activation mostly depends on innate immunity, remains elusive. Gouty arthritis is characterized by the deposition of monosodium urate (MSU) crystals in the joints, associated with acute flares. Frustrated phagocytosis of MSU crystals by resident leukocytes leads to NLRP3 inflammasome activation and subsequent amplification of the inflammatory response. Our aim was to study the effect of ASCs administration in the clinical inflammatory response, and the molecular mechanisms involved.

Methods: Acute gout flare was induced in 15 rabbits by intra-articular injection of MSU crystals in both knees. A single dose of 2.5×10^6 ASCs/kg was administered to 7 of these rabbits through the right femoral artery 1h after MSU injection (MSU+ASC), whereas 8 animals were not treated (MSU). This route of administration allowed to study the effect of a direct ASC administration in the right knee synovial membrane (SM) and the contralateral knee, which received the cells after their distribution through the organism. Four rabbits were used as healthy (H) controls. Inflammation was followed up measuring knee swelling and serum CRP. Animals were sacrificed 72h after MSU injections, and SM were collected for further studies.

Results: ASCs ameliorated joint swelling in both knees 24h after MSU injections, and a significant decrease in serum CRP was observed (H: 73 ± 51 ; MSU: $818 \pm 238^*$; MSU+ASCs: 270 ± 241 mg/ml*#; $p < 0.05$ *vs. H; # vs. MSU). Histopathological analysis showed that ASCs significantly diminished SM inflammation 72h after MSU injection (Krenn Score: H: 0.2 ± 0.4 ; MSU: $5.6 \pm 2.3^*$; MSU+ASC: $3.4 \pm 1.2^{* \#}$). SM vascularization was also reduced in treated animals (%CD31+ staining: H 0.5 ± 0.2 ; MSU $0.8 \pm 0.2^*$; MSU+ASC $0.6 \pm 0.2^{\#}$). ASCs treatment evoked a reduction of the inflammasome components in the SM: pro-IL1 β (H: 0.9 ± 0.2 ; MSU: $1.5 \pm 0.5^*$; MSU+ASC: $1.1 \pm 0.2^{* \#}$), pro-caspase-1 (H: 1 ± 0.6 ; MSU: $3.5 \pm 3.1^*$; MSU+ASC: $1.4 \pm 0.5^{* \#}$), NALP3 (H: 1 ± 0.3 ; MSU: $2.9 \pm 2.1^*$; MSU+ASC: $1.4 \pm 0.7^{* \#}$), and NF κ B activity was attenuated (H: 0.12 ± 0.01 ; MSU: $0.22 \pm 0.07^*$; MSU+ASC: $0.16 \pm 0.03^{* \#}$). Synthesis of pro-inflammatory cytokines COX-2 (H 0.9 ± 0.1 ; MSU $4.2 \pm 3.3^*$; MSU+ASC $2.1 \pm 1.4^{* \#}$) and TNF α (H: 0.9 ± 0.3 ; MSU: $1.3 \pm 0.3^*$; MSU+ASC: $0.9 \pm 0.2^{* \#}$) were also reduced in the MSU+ASC animals, while TGF β (H: 0.9 ± 0.2 ; MSU: $0.7 \pm 0.2^*$; MSU+ASC: $1.3 \pm 0.3^{* \#}$) and IL10 (H: 1.1 ± 0.5 ; MSU: $1.1 \pm 0.7^*$; MSU+ASC: $1.8 \pm 0.5^{* \#}$) were increased in comparison to MSU group. No differences between the direct and the indirect treatment were found, since both right and left SMs were equally damaged.

Conclusion: Our data showed that a single parenteral dose of ASCs is able to decrease the inflammatory response in an acute gouty arthritis model in rabbits by inhibiting NALP3 inflammasome activation. Therefore, this therapeutic approach may be considered for treating gouty flares, as a pharmacological alternative in patients with comorbidities that preclude conventional treatment.

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Abstract Number: 1031

Orally Administered Cherry Juice Inhibits Localized Nfkb Activity and Histopathological Infiltrates in a Murine Model of Gout

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Innate Immunity Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Gout is caused by the inflammation induced from the precipitation of monosodium urate (MSU) crystals in joints and is the most common inflammatory arthritis in the United States, occurring mostly in males and in up to 4% of the population. Since high levels of systemic uric acid and inflammation are both contributors to this chronic inflammatory condition, the pharmacological armamentarium includes both urate-lowering and anti-inflammatory therapeutic regimens. In adjunct to drugs to reduce inflammation, natural methods including dietary modifications and supplementation with nutraceutical compounds known to reduce inflammation have demonstrated some success in previous studies. In agreement, we have previously shown that cherry juice can reduce the incidence of flares in gout patients and significantly suppress IL-1 β secretion in vitro in human cells. The objective of this study was to establish the anti-inflammatory influence of cherry juice in a murine model of gout to create a model experimental platform to use in future work investigating the molecular mechanism suppressing inflammation.

Methods: Cherry juice concentrate was administered daily by oral gavage (240 μ L/kg) to commercially available BALB/C-Tg (NF κ B-RE-luc)-Xen mice that harbor a firefly luciferase cDNA reporter under the regulation of 3 NF κ B responsive elements. After 14 days, gouty inflammation was induced by intra-articular injection of monosodium urate (MSU) crystals

(0.5 mg) into the tibio-tarsal joint (ankle) under anesthesia. NFκB activity was measured locally in the injected ankle using the Xenogen *in vivo* imaging system (IVIS 200) and decalcified feet/ankles were paraffin-embedded and stained by H&E for histopathological analysis.

Results: Oral administration of cherry juice concentrate significantly reduced NFκB activity in mouse feet/ankles by IVIS analysis relative to control mice treated with PBS. Bioluminescent imaging signals correlating to NFκB activation and measured by total photon counts were inhibited almost 2-fold with the entire foot used as the region of interest in the analysis. Furthermore, histopathology by H&E showed a suppression of infiltrates into the space of the tibio-tarsal joint in mice receiving cherry juice concentrate when compared to PBS-treated control counterparts.

Conclusion: The results of this study demonstrate a significant inhibition of inflammation, as measured by histology and NFκB activity, in the joint space of mice injected with MSU to induce gout; thereby recapitulating the conclusions of our previous work in human cells and gout patients and establishing a viable mouse model to use in future experiments delineating the molecular mechanism of this immunosuppressive response. Near future experiments include a comprehensive analysis of proinflammatory cytokines in the serum of these mice and long-term work will include *in vitro* assays investigating the effects of cherry juice concentrate on oxidative burst and IL-1β secretion following inflammasome activation.

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Abstract Number: 1032

Aberrant Sarcoplasmic Expression of the Alarmin ‘High Mobility Group Box Protein 1’ (HMGB1) in Patients with Idiopathic Inflammatory Myopathy

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Innate Immunity Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Components of the innate immune system, such as High Mobility Group Box Protein 1 (HMGB1), may contribute to the initiation, perpetuation and resolution of the idiopathic inflammatory myopathies (IIMs). HMGB1 is a ubiquitous nuclear DNA-binding protein that can translocate to the cytoplasm and extracellular space, where it exerts pro-inflammatory or pro-repair effects depending on its molecular state and the surrounding cytokine milieu. Given HMGB1 undergoes rapid, passive release from necrotic cells, we postulate a key role for this protein in the aetiopathogenesis of necrotising myopathy (NM). Herein, we evaluate sarcoplasmic expression of HMGB1 in different forms of IIM and correlate it with clinical, serological and histological parameters.

Methods: Consecutive muscle sections were stained for HMGB1, CD68 (macrophages), CD45 (lymphocytes), neonatal myosin heavy chain (nMHC, regenerating myofibres) and LC3 (an autophagic protein) using immunohistochemistry. Standard H&E stains were performed to assess the degree of necrosis. Slides were independently graded by a muscle pathologist. Clinical and demographic data were prospectively collected. Dermatomyositis (DM) and polymyositis (PM) patients satisfied EULAR/ACR criteria. Inclusion Body Myositis (IBM) patients satisfied European Neuromuscular Centre Criteria. The diagnosis of necrotising myopathy (NM) was made where necrotic muscle fibres were the predominant abnormal histological feature and macrophage infiltration exceeded lymphocyte infiltration.

Results: Samples from 132 IIM patients with NM (n = 59), DM (n = 17), PM (n = 19), IBM (n = 22) and non-specific IIM (NSIIM, n = 15) were analysed, in addition to 18 control samples. Sarcoplasmic HMGB1 was significantly elevated in all IIM subtypes compared with controls (p < 0.001). Levels correlated positively with creatine kinase (Rs 0.31, p = 0.002) and physician's global assessments of disease activity (Rs 0.89, p = 0.001), negatively with manual assessments of muscle strength (MMT8, Rs -0.77, p = 0.009) and negatively with cumulative prednisolone dose (Rs -0.24, p = 0.03). Patients with NM and IBM had significantly increased sarcoplasmic HMGB1 compared with DM, PM and NSIIM. In NM patients,

HMGB1 grades were highly correlated with the degree of necrosis (R_s 0.74, $p < 0.001$) and inflammatory infiltration (CD68: R_s 0.66, $p < 0.001$; CD45: R_s 0.62, $p < 0.001$). In IBM, HMGB1 grades were highly correlated with regenerating myofibers (R_s 0.81, $p < 0.001$) and autophagic proteins (R_s 0.85, $p = 0.002$).

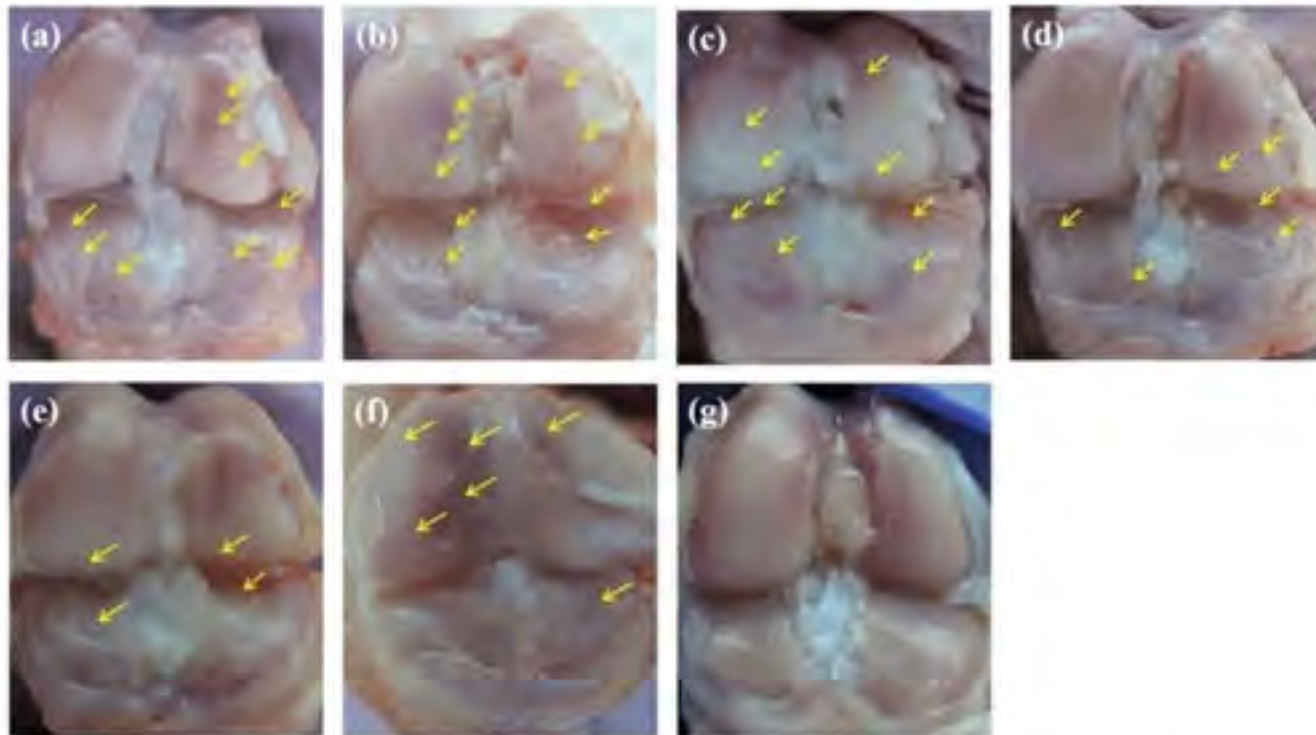
Conclusion: Sarcoplasmic levels of HMGB1 are significantly elevated in NM and IBM compared with other IIM subtypes. The mechanisms underpinning aberrant sarcoplasmic expression in these subtypes are likely to be distinct and may reflect differing roles for this protein in these particular subtypes. Our finding of a negative association with cumulative prednisolone exposure supports earlier work demonstrating a reduction in tissue HMGB1 with treatment. Understanding the role of HMGB1 in the pathogenesis of these complex conditions may lead to novel diagnostic paradigms and therapeutic interventions.

Disclosure: J. Day, None; S. Otto, None; K. Cash, None; P. Eldi, None; P. Hissaria, None; S. Proudman, None; J. Hayball, None; V. Limaye, None.

Abstract Number: 1033

Comparison of Oral Administration of Diacerein, Intra-Articular Injection of Diacerein Solution, and Intra-Articular Injection of Diacerein-Loaded Nanoparticle in Osteoarthritis Rat Model

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Gross morphology of the rat knee joint at the 9th week of MIA injection (8th week of DIA treatment). The treated groups were divided as follows: (a) MIA, (b) MIA+NPs, (c) MIA+DIA solution, (d) MIA+1%DIA/NPs, (e) MIA+5%DIA/NPs, (f) MIA+oral DIA, and (g) control. Yellow arrows indicate erosions.

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

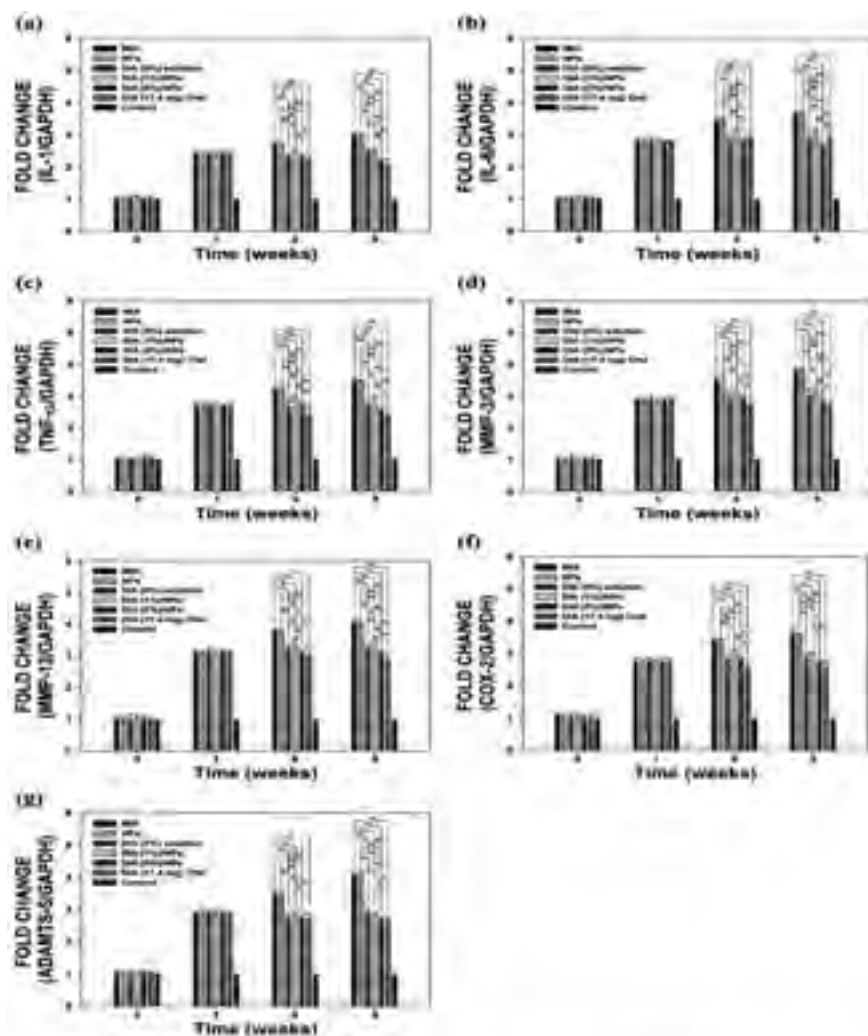
Session Type: ACR Poster Session B

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

Background/Purpose: Osteoarthritis(OA) treatment is typically administered to control symptoms. Diacerein (DIA) reduces interleukin (IL)-1receptor on chondrocytes and prevents structural degradation of joint tissue. Direct injection of DIA into joint is preferred to increase its bioavailability and reduce systemic side effects. We investigated whether poly(d,l-lactide-co-glycolide) (PLGA)nanoparticles (NPs) could effectively deliver DIA and inhibit the inflammatory reaction.

Methods: Monosodiumiodoacetate (MIA)-induced OA rats were divided into seven groups with injection of MIA alone (group 1) and with, NPs (2), 5% DIA (3), 1% DIA/NPs (4) or 5% DIA/NPs (5), oral DIA (6), and non-treated healthy control rats (7). The mRNA expression of pro-inflammatory cytokines and derived enzymes were investigated, including interleukin (IL)-1, IL-6, tumor necrosis factor-alpha (TNF- α), matrix metalloproteinase (MMP)-3, MMP-13, cyclooxygenase (COX)-2, and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-5. Macroscopic, radiographic, and histologic evaluations of the joints were done at 8 weeks of DIA treatment.

Results: In group 5, the mRNA expression of inflammatory cytokines and derived enzymes decreased gradually and significantly compared with groups 1–4. Group 3 levels of mRNA expression were decreased at 5 weeks similar to that of group 5, but increased at 9 weeks. Group 6 displayed the lowest mRNA levels of inflammatory cytokines and derived enzymes, except for IL-6, which was lowest in group 5. Macroscopic erosions were fewest in group 5, followed in order by



The mRNA expression of pro-inflammatory cytokines and derived enzymes and anti-inflammatory cytokines, (a) IL-1, (b) IL-6, (c) TNF- α , (d) MMP-3, (e) MMP-13, (f) COX-2, and (g) ADAMTS-5 in the whole blood at baseline, and at the 1st, 5th, and 9th week of MIA injection.

groups 6, 4, and 3. Micro-computed tomography revealed only slight irregularity of the joint surface and minimal erosion of articular cartilage in group 5 and 6.

Conclusion: Intra-articular injection of DIA/NPs inhibited the inflammatory reaction and progression in OA, with histologically less cartilage damage detected than induced by oral DIA. The 5% DIA/NPs dose produced significant reductions of the serum IL-6 levels compared with oral administration, and is a candidate treatment for the inhibition of inflammation and protection of the cartilage in OA.

Disclosure: J. H. Jung, None; S. J. Choi, None; G. G. Song, None; S. E. Kim, None; H. J. Kim, None.

Abstract Number: 1034

A Conplastic Mice Model of Aging Reveals That Mitochondrial DNA Variation Influences the Process of Joint Deterioration

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Different studies showed interesting genetic associations between mtDNA haplogroups and OA-related features, including prevalence, incidence and progression of the disease. The aim of this work is to study the influence of mtDNA variation in the degree of joint deterioration of knees from a conplastic mouse model of aging

Methods: For this purpose, mtDNAs from C57BL/6 and NZB/OlaHsd mice were used. These mtDNAs differ by 12 missense mutations, 10 non-coding-region mutations, 8 ribosomal RNA mutations and 4 transfer RNA mutations. A conplastic mice strain was developed with the C57BL/6 nuclear genome and the NZB/OlaHsd mtDNA (named BL/6^{NZB}) to compare with the original C57BL/6 strain (named BL/6^{C57}) in animals of 25 and 75 weeks (25w and 75w). A total of 38 limbs from 19 mice were processed to perform different histologic analysis: 8 BL/6^{NZB} 25w, 10 BL/6^{NZB} 75w, 10 BL/6^{C57} 25w and 10 BL/6^{C57} 75w. Appropriate non-parametric statistical procedures were applied using SPSSv24

Results: Cartilage and epiphyseal plate were the joint tissues with the most relevant findings. Mankin score data showed significantly increased values in all knees from both animal models at 75 weeks compared with 25 weeks (p<0,001), confirming the aging of the joint. When 75-week mice were selected (table 1), the BL/6^{C57} strain showed a significantly increased score in whole joint (p=0.038), medial femoral condyle (p=0,015) and femoral condyle (p=0,021) than BL/6^{NZB} strain. Safranin-O/Fast-green ratio value at 75w was higher in the medial compartment (both tibial plateau and femoral condyle) of BL/6^{NZB} compared with BL/6^{C57}; however, only the differences detected in the medial compartment of the tibial plateau reached the statistical significance (p<0,001), whilst the differences detected in the femoral condyle borderline the statistical significance (p=0,091).

The width of the epiphyseal plate was analyzed in both femur and tibia bones. The results showed significantly decreased values in BL/6^{C57} 75w compared with the same strain at 25 weeks in femoral condyle (p=0,049) and tibial plateau

Table 1. Mankin score grading of cartilage destruction in conplastic mice BL 6^{C57} and BL 6^{NZB} at 75w

	LTP	LFC	MTP	MFC	TP	FC	Med comp	Lat comp	Whole joint
BL 6 ^{C57}	5,80±1,81	4,40±1,07	4,67±2,06	6,00±1,07	10,44±3,43	10,37±1,85	10,14±3,02	10,20±2,39	19,71±4,57
BL 6 ^{NZB}	5,00±2,11	4,38±0,92	4,40±2,12	4,44±1,24*	9,40±1,78	8,71±1,70*	8,44±2,60	9,13±1,55	17,43±1,72*

LTP: lateral tibial plateau; LFC: lateral femoral condyle; MTP: medial tibial plateau; MFC: medial femoral condyle; TP: tibial plateau; FC: femoral condyle; Med comp: medial compartment; Lat comp: lateral compartment; *p<0,05 with respect to BL 6^{C57}

($p < 0.001$); however, these differences were not observed in animals belonging to BL/6^{NZB} strain. In addition, the BL/6^{C57} 75wstrain also showed significantly lower values in tibial plateau than BL/6^{NZB} strain at the same age ($p = 0.032$).

Conclusion: mtDNA variation plays an important role in the process of joint deterioration associated to age, leading to consider both mitochondria and mtDNA as potential therapeutic targets and complementary biomarker, respectively, for the age-associated phenotype of OA

Disclosure: I. Rego-Pérez, None; A. V. Lechuga-Vieco, None; M. Scotece, None; P. Filgueira-Fernández, None; S. Pertega, None; J. A. Enríquez, None; F. J. Blanco, None.

Abstract Number: 1035

Different Cartilage-Bone Unit in Patients with Primary Osteoarthritis and Secondary Osteoarthritis Caused By Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Despite distinct aetiologies of joint diseases, the osteoarthritic end-stage of primary osteoarthritis (OA) and rheumatoid arthritis (RA) are described using similar radiological features. However, primary and secondary osteoarthritis may be different at the cartilage-bone unit depending on the pathogenesis. Therefore, the main purpose was to investigate the histological differences in the cartilage-bone unit of the hip joint in patients with primary OA and patients with secondary OA due to RA.

Methods: Femoral heads were obtained during arthroplasty from twelve patients with primary OA and six patients with secondary OA due to RA. The primary OA patients mean(SD) age was 62(5) years and consisted of six males and six females. The RA patients had a mean age of 63(3) years and consisted of three males and three females. The entire femoral heads were investigated, using design-based stereology methods that utilise random, systematic sampling to provide unbiased and quantitative data. The volume and thickness of the articular cartilage, calcified cartilage and subchondral bone plate were obtained. Osteophytes were, however, studied based on simple area measurements. Data were normalised if not normally distributed, and statistical significance was tested using Student's t-test.

Results:

	Units	Osteoarthritis (n = 12)	Rheumatoid arthritis (n = 6)	P-value
Femoral head Volume#	cm ³	21.8 [18.6-25.0]	20.6 [16.8-24.4]	0.60
Articular Cartilage Volume*	cm ³	2.4 [2.0-3.0]	1.3 [0.8-2.3]	0.04
Articular Cartilage Thickness#	µm	1134.1 [930.7-1337.6]	721.4 [403.3-1039.5]	0.02
Subchondral bone thickness	µm	406.2 [285.3-527.1]	408.6 [185.8-631.5]	0.98
Calcified cartilage thickness*	µm	119.3 [94.1-151.3]	56.6 [25.3-126.5]	0.01
Osteophyte area*	mm ²	70.9 [41.4-121]	49.2 [4.7-513]	0.66

*Data are presented as geometric mean and [95% confidence interval]. #Data are presented as mean and [95% confidence interval]. The results were considered significant at $P < 0.05$.

Conclusion: Patients with RA had thinner articular and calcified cartilage but were otherwise not significantly different compared with OA patients. Thus, the inflammatory joint in RA was associated with a more pronounced loss of cartilage than the degenerative joint disease in primary osteoarthritis. The increased thickness of calcified cartilage in primary osteoarthritis has been attributed to endochondral ossification, which does not seem to be the case in RA.

Disclosure: R. Klose-Jensen, None; A. F. Christensen, None; K. K. Keller, Pfizer, Inc., 9; E. M. Hauge, AbbVie Inc., 5, UCB, Inc., 5, Roche, 2, 9, Novartis, Inc, 2, MSD, 5, 9, Sobi, 2, 9, Pfizer, Inc., 9, Celgene Corporation, 9.

Effects of Three Potential Anabolic Disease-Modifying Osteoarthritis Drugs – Sprifermin, Insulin-like Growth Factor 1 and Bone Morphogenetic Protein 7 – on Matrix Production and the Phenotype of Articular Chondrocytes

Sylvia Muller, Martin Michaelis, Sven Lindemann and Anne Gigout, Merck KGaA, Darmstadt, Germany

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Disease-modifying osteoarthritis drugs with an anabolic mode of action should stimulate the growth of new hyaline cartilage. For instance, recombinant human fibroblast growth factor 18 (FGF18; sprifermin) has been shown to increase cartilage volume in knee OA patients. *In vitro* studies have also shown that sprifermin stimulates proliferation and the production of hyaline cartilage matrix molecules in articular chondrocytes. Other growth factors, such as insulin-like growth factor 1 (IGF1) and bone morphogenetic protein 7 (BMP7), also exert an anabolic effect on cartilage or cartilage cells *in vitro* and *in vivo*. How these three growth factors compare with each other is unknown. The aim of this study was to differentiate the effects of sprifermin, IGF1 and BMP7 on matrix production and cell phenotype in articular chondrocytes.

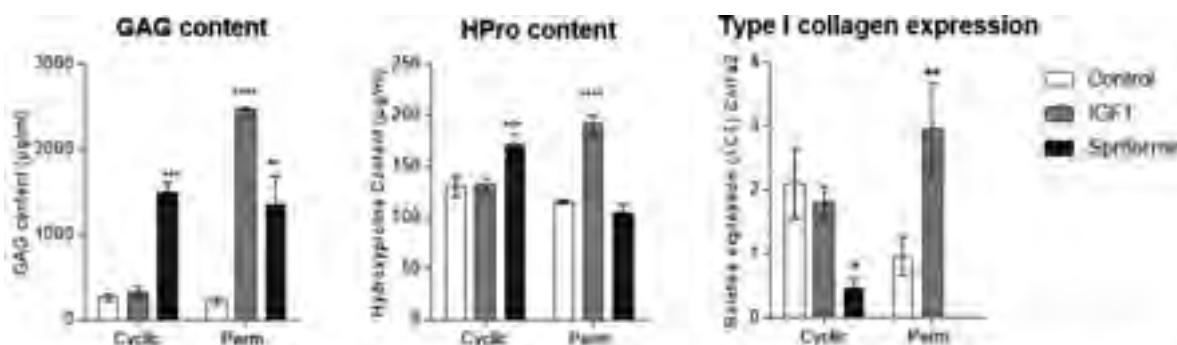


Figure 1: Comparison of IGF1 and sprifermin. Biochemical analysis (GAG and HPro) and gene expression analysis (type I collagen) of the 3D constructs. The mean and standard error of the mean (SEM) are presented. Statistical analysis consists of a two-way ANOVA corrected for multiple comparison with a Dunnett test. **, *** and **** mean difference from control for the same exposure with $p < 0.01$, 0.001 or 0.0001 , respectively.

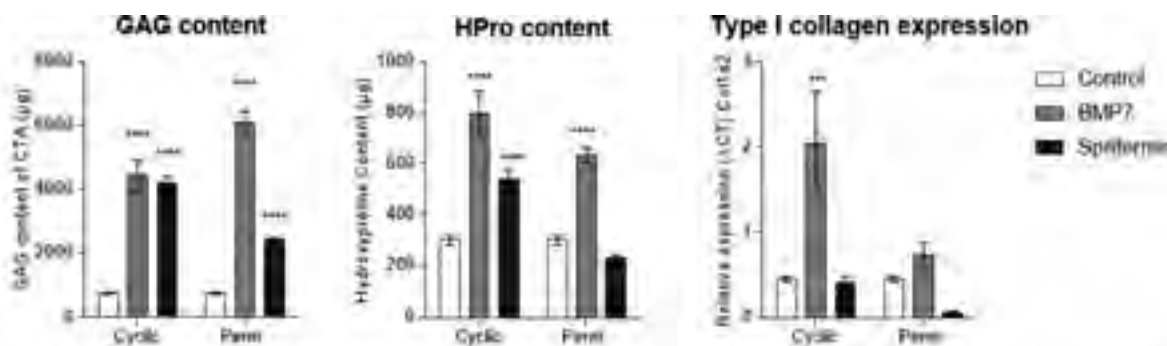


Figure 2: Comparison of BMP7 and sprifermin. Biochemical analysis (GAG and HPro) and gene expression analysis (type I collagen) of the 3D constructs. The mean and standard error of the mean (SEM) are presented. Statistical analysis consists of a two-way ANOVA corrected for multiple comparison with a Dunnett test. *** and **** mean difference from control for the same exposure with $p < 0.001$ or 0.0001 , respectively.

Methods: Primary bovine chondrocytes were cultured as 3D scaffold-free constructs for 4 weeks with sprifermin 100 ng/mL, IGF1 100 ng/mL or BMP7 300 ng/mL with permanent or cyclic exposure (24h at the beginning of each week) or left untreated (control). Two experiments were made: sprifermin versus IGF1 and sprifermin versus BMP7. At the end of the culture, the 3D constructs were harvested for biochemical (glycosaminoglycan or GAG and hydroxyproline or HPro) and gene expression analysis (N=3-4).

Results: As previously shown, cyclic exposure to sprifermin increased the GAG and HPro content of the 3D constructs while permanent exposure had a lower effect on GAG production and no effect on HPro (Figs. 1 and 2). Similarly, expression of *col2a1* (type II collagen) and *acan* (aggrecan) increased with cyclic exposure. Furthermore, sprifermin reduced *colla2* (type I collagen) expression and had no effect on hypertrophy markers. IGF1 increased extracellular matrix (ECM) production (GAG and HPro content, Fig. 1) as well as expression of *col2a1* and *acan*, but only with permanent exposure. *Colla2* expression was increased with permanent exposure. Similarly, BMP7 increased ECM production but also increased *colla2* expression (with cyclic exposure) and hypertrophy marker expression.

Conclusion: A similar stimulation of cartilage ECM molecule expression in chondrocytes was obtained with permanent exposure to IGF1, permanent or cyclic exposure to BMP7 and cyclic exposure to sprifermin. However, sprifermin was the only growth factor that both influenced the chondrocytes towards the production of hyaline cartilage and prevented two unwanted phenomena: production of fibrous cartilage (containing type I collagen) and cartilage hypertrophy.

Disclosure: S. Muller, Merck KGaA, 3; M. Michaelis, Merck KGaA, 3; S. Lindemann, Merck KGaA, 3; A. Gigout, Merck KGaA, 3.

Abstract Number: 1037

Develop an in Vitro Model to Test the Different Behavior of mtDNA in OA and Healthy Patients, Based on Mitochondrial Activity and Metabolic Response

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Mitochondrial dysfunction is well documented in OA and has the capacity to alter chondrocyte function and viability, contributing to cartilage degeneration. Several studies have showed that chondrocytes from OA patients have mitochondrial alterations. With this background, it is important to evaluate the influence of mitochondria in the pathogenesis of OA using an in vitro model to explain the functional consequences of this association and help us to identify potential diagnostic biomarkers and/or therapeutic targets. Trans-mitochondrial cybrids are a useful cellular model to study the mitochondrial role in the cellular behavior, since they carry different mitochondrial variants with the same nuclear background. The aim of this work is to use an *in vitro* model based in cybrids with mtDNA from healthy and OA donors and characterize them. Comparing the data with data obtained from human articular chondrocytes.

Methods: mtDNA Cybrids were developed using 143B.TK⁺Rho⁻ cell as nuclear donor, and platelets from patients N and OA. Human articular chondrocytes were obtained from patients with hip replacement. The mtDNA copy number was measured by real-time PCR method. The O₂⁻ production was evaluated using flow cytometry. The glucose oxidation assay was measured using D-[¹⁴C(U)]glucose during 4 h CO₂ trapping. The glycolytic activity was measured after addition of

glucose, oligomycin and 2-dioxyglucose using Seahorse XFp (ECAR). The OXPHOS function was evaluated by SeaHorse XFp (OCR) after addition of oligomycin, FCCP and Rotenone/Antimycin. Appropriate statistical analyses were performed with GraphPad Prism v6.

Results: mtDNA copy number showed that OA have higher levels than N in cybrids and human chondrocytes showed the same results. The analysis of O_2^- production showed that OA had higher levels than N in both types of cells. The metabolic status analyzing glucose oxidation and total glucose cellular uptake reflected higher values in OA cybrids than N cybrids. But the analysis of glycolysis showed lower values in OA than N cybrids. The analysis of OXPHOS function showed that OA had lower basal respiration and maximal respiratory capacity than N in both types of cells.

Conclusion: In this study, we showed that OA cybrids behave differently from cybrids from healthy (N) donors, while they have a similar behavior to OA and N articular chondrocytes. This information enhances our understanding of the role of mitochondria in OA and suggests that cybrids are a possible model for the study of OA pathogenesis. All these data support that N cybrids and chondrocytes use mitochondria with more efficiency.

Disclosure: M. Fernandez Moreno, None; A. Dalamao-Fernandez, None; T. Hermida-Gómez, None; J. Lund, None; A. Rustan, None; M. E. Vazquez Mosquera, None; S. Relano-Fernandez, None; I. Rego-Pérez, None; F. J. Blanco, None.

Abstract Number: 1038

Tenofovir, a Nucleoside Analog Reverse Transcriptase Inhibitor for Treatment of HIV, Promotes Osteoclast Differentiation and Decreases Osteoblast Formation By a Mechanism Depending on ATP Release and Adenosine

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Human Immunodeficiency Virus (HIV) infection devastates the immune system but also affects tissues and organs such as kidney, liver, central nervous system, heart and bone. Bone alterations have been observed in HIV disease for nearly two decades, in particular a higher risk of low bone mineral density (BMD) and fragility fractures. Treatment of patients with Tenofovir alone or in combination (as part of HAART), leads to further changes in bone catabolism markers and significant reductions in BMD in children and young adults. Tenofovir is taken up by cells and phosphorylated; tenofovir-phosphate inhibits HIV-reverse transcriptase by mimicking AMP. We have recently found that Tenofovir inhibits Pannexin-1/Connexin-43-mediated ATP release from cells and decreases extracellular adenosine levels and fibrosis in murine models. As adenosine and ATP are key regulators of bone homeostasis, we determined whether Tenofovir directly affects bone by an adenosine- or ATP-dependent mechanism.

Methods: M-CSF/RANKL-induced osteoclast (OC) and stimulated osteoblast (OB) differentiation were studied in primary murine bone marrow culture as the number of TRAP-positive or Alizarin Red-positive cells, respectively, after challenge with Tenofovir (1nM-100µM) alone or in combination with Dipyrindamole (1nM-100µM), an agent that increases extracellular adenosine by blocking cellular adenosine uptake. Pannexin-1 and Connexin-43 expression were permanently knocked down in RAW264.7 cells by lentiviral infection with appropriate shRNA or scrambled shRNA and these cells were induced to differentiate into OC by RANKL. OC/OB differentiation markers were study by RT-PCR, and intracellular pathways by Western Blot.

Results: Tenofovir produced a dose-dependent increase in OC differentiation (EC₅₀=44.5nM) that was reversed by Dipyrindamole (IC₅₀=0.3µM). Tenofovir increases Cathepsin K and NFATc1 mRNA levels during OC differentiation, and the effect was reversed by Dipyrindamole. When both Pannexin-1 and Connexin-43 were absent, Tenofovir did not increase OC number. Dipyrindamole reversed the effect of Tenofovir on pERK1/2, pp38 and NFκB nuclear translocation. Tenofovir inhibits OB differentiation in a dose-dependent manner (IC₅₀=0.4µM) and treatment with Dipyrindamole reversed this

effect ($EC_{50}=10nM$). Tenofovir increases RANKL mRNA expression and decreases OPG mRNA expression during OB differentiation; these effects are reversed by Dipyridamole. We have also found alterations in beta catenin signaling pathway due to Tenofovir treatment.

Conclusion: Tenofovir enhances osteoclast differentiation and inhibits osteoblast differentiation by an adenosine-dependent mechanism, a finding that suggests that treatment with agents that increase local adenosine concentrations, like Dipyridamole, might prevent bone loss due to Tenofovir treatment.

Disclosure: F. M. Conesa-Buendia, None; P. Llamas, None; R. Largo, None; G. Herrero-Beaumont, None; B. N. Cronstein, Cantic Biopharma, Regenosine, 1,NIH Arthritis foundation, Astrazeneca, 2,Horizon Pharmaceuticals, Regenosine, 5,Patent issued and pending, 9; A. Mediero, CP15/00053 PI16/0991, 2, 9.

Abstract Number: 1039

Tenofovir Induces Osteopenia and Dipyridamole, an Inhibitor of the Ent-1 Nucleoside Transporter, Reverses the Osteopenic Effect of Tenofovir In Vivo

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Osteopenia and fragility fractures have been associated with HIV infection. Tenofovir, one of the most commonly used antivirals in HIV, also leads to increases in bone catabolism markers and decreased bone mineral density (BMD) in children and young adults. In murine models and human cell lines, Tenofovir inhibits ATP release and decreases extracellular adenosine levels. Adenosine, acting at its adenosine A2A and A2B receptors, inhibits osteoclast formation, and increasing local adenosine concentration with Dipyridamole, an agent that blocks adenosine cellular uptake, stimulates new bone formation as well as rhBMP-2 by an A2A receptor-dependent effect. We hypothesized that Tenofovir regulates bone resorption by diminishing endogenous adenosine levels and determined whether Dipyridamole could counteract the deleterious effects of Tenofovir on bone.

Methods: Male C57Bl/6 mice were treated as follows: IP injection of saline (control), Tenofovir 75mg/Kg/day, Dipyridamole 25mg/Kg/day, combination Tenofovir/Dipyridamole (n=10, 4 weeks). Female C57Bl/6 mice were ovariectomized and treated as follow: sham (no surgery), saline (control), Tenofovir 75mg/Kg/day, Dipyridamole 25mg/Kg/day, combination Tenofovir/Dipyridamole (n=10, 5 weeks). Weekly weight was annotated. DXA scanning was performed before sacrifice. Calcein/AlizarinRed-labelling of newly formed bone was used, and long bones were prepared for microCT/histology.

Results: Male mice treated with Tenofovir lost nearly 10% of body weight ($p<0.001$). DXA scanning showed a decrease in BMD in mice treated with Tenofovir that was reversed with Dipyridamole. microCT revealed decreased BMD and diminished trabecular bone in Tenofovir-treated mice and reversal by Dipyridamole treatment. TRAP-staining showed increased osteoclasts in Tenofovir-treated mice ($p<0.005$) an effect reversed by Dipyridamole. Similar results were obtained for Cathepsin K and CD68. RANKL-positive-cells were increased in Tenofovir-treated mice whereas OPG-positive-cells decreased, and both effects were reversed by Dipyridamole. In the case of female OVX mice, Tenofovir treatment also produced a decreased in body weight ($p<0.05$) that was reversed with Dipyridamole. DXA scanning showed decreased BMD in Tenofovir-treated mice and microCT revealed diminished trabecular bone, similar to findings in male mice. Similar results were found for Cathepsin K, CD68, RANKL and OPG-positive-cells.

Conclusion: These results suggest that treatment with agents that increase local adenosine concentrations, like Dipyridamole, might prevent bone loss following Tenofovir treatment.

Disclosure: F. M. Conesa-Buendia, None; P. Llamas, None; T. Wilder, None; R. Largo, None; G. Herrero-Baumont, None; B. N. Cronstein, Cantic Biopharma, Regenosine, 1, NIH Arthritis foundation, Astrazeneca, 2, Horizon Pharmaceuticals, Regenosine, 5, Patent issued and pending, 9; A. Mediero, CP15/00053 PI16/0991, 2, 9.

Abstract Number: 1040

The Potential Role of Choline Kinase Alpha in Osteoarthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Osteoarthritis (OA) is the most common joint disease and a leading cause of disability. Cartilage degeneration is the central characteristic of OA, and low-grade synovitis can promote OA progression. In OA, both chondrocytes and synoviocytes undergo metabolic alterations and shift from a resting regulatory state to a highly metabolically active state. Choline kinase (ChoK) is an enzyme that catalyzes the conversion of choline to phosphocholine, which serves as a precursor for the production of phosphatidylcholine (PtdCho). PtdCho is the major phospholipid constituent of membranes and substrate for the synthesis of lipid signaling molecules such as lysophosphatidic acid (LPA) and phosphatidic acid (PA). Here, we determined whether ChoK is a key regulator of OA synoviocytes and chondrocytes phenotype.

Methods: ChoK expression in OA synovial and cartilage tissues was evaluated by immunohistochemistry (IHC). Human fibroblast-like synoviocytes (FLS), mouse macrophages (tioglycollate-elicited), human knee chondrocytes, synovial and cartilage explants were stimulated with proinflammatory mediators (IL-1b (2ng/ml), TNFa (10ng/ml) and LPS (100ng/ml)) in the presence or absence of MN58b (5mM), an inhibitor of ChoKa. Release of IL-1 β , IL-6 and MMP3 was quantified from conditioned media by ELISAs. Phosphorylation of AMPK in FLS and chondrocytes was examined by Western Blot analysis. Expression of fibrosis-related genes including collagen (COL) 1 α 1, COL2 α 1, COL10 α 1, α smooth muscle actin (α SMA) and procollagen-lysin,2-oxoglutarate 5-dioxygenase 2 (PLOD2) was quantified in FLS treated with TGFb (10ng/ml) by quantitative RT-PCR.

Results: IHC studies demonstrated that ChoK expression was upregulated in human knee OA cartilage and synovium, and in normal cartilage with aging *in situ*. In addition, ChoK activity was increased in human OA FLS, and was significantly enhanced by inflammatory mediators in synoviocytes and chondrocytes. Moreover, pharmacological inhibition of ChoK activity by MN58b significantly decreased IL-1 β -induced nitric oxide (NO) secretion from $8.3 \pm 4 \mu\text{M}$ to $0.72 \pm 0.3 \mu\text{M}$ ($p = 0.0004$, 3 donors) in OA chondrocytes, and MMP-13 release in chondrocytes and cartilage explants. At the same time, it attenuated IL-6 secretion from $31.4 \pm 4.85 \text{ ng/ml}$ to $26.6 \pm 6.3 \text{ ng/ml}$ ($p = 0.02$) in OA synovium explants. MN58b also impaired IL-1 β secretion in macrophages and synovium explants (from $0.46 \pm 0.09 \text{ ng/ml}$ to $0.015 \pm 0.009 \text{ ng/ml}$; $p = 2.64 \times 10^{-5}$, 3 donors) in response to LPS+ATP stimulation. These were associated with increased phosphorylation of AMPK in chondrocytes, FLS and in synovium explants. Furthermore, MN58b suppressed by $>50\%$ ($p < 0.05$) the expression of fibrosis related genes, COL1 α 1, COL2 α 1, COL10 α 1, α SMA and PLOD2 in OA FLS in response to TGF β 1.

Conclusion: Dysregulation of ChoK is likely involved in OA pathogenesis, and ChoK could potentially be a novel target for OA. Further translational and mechanistic studies of pharmacologic inhibition of ChoK on OA progression are warranted.

Disclosure: R. Coras, None; L. Y. Chen, None; E. Sanchez-Lopez, None; M. Lotz, None; R. Liu-Bryan, None; M. Guma, None.

The Anti-Adams-5 Nanobody®, M6495, Protects Against Cartilage Breakdown in Cartilage and Synovial Joint Tissue Explant Models

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

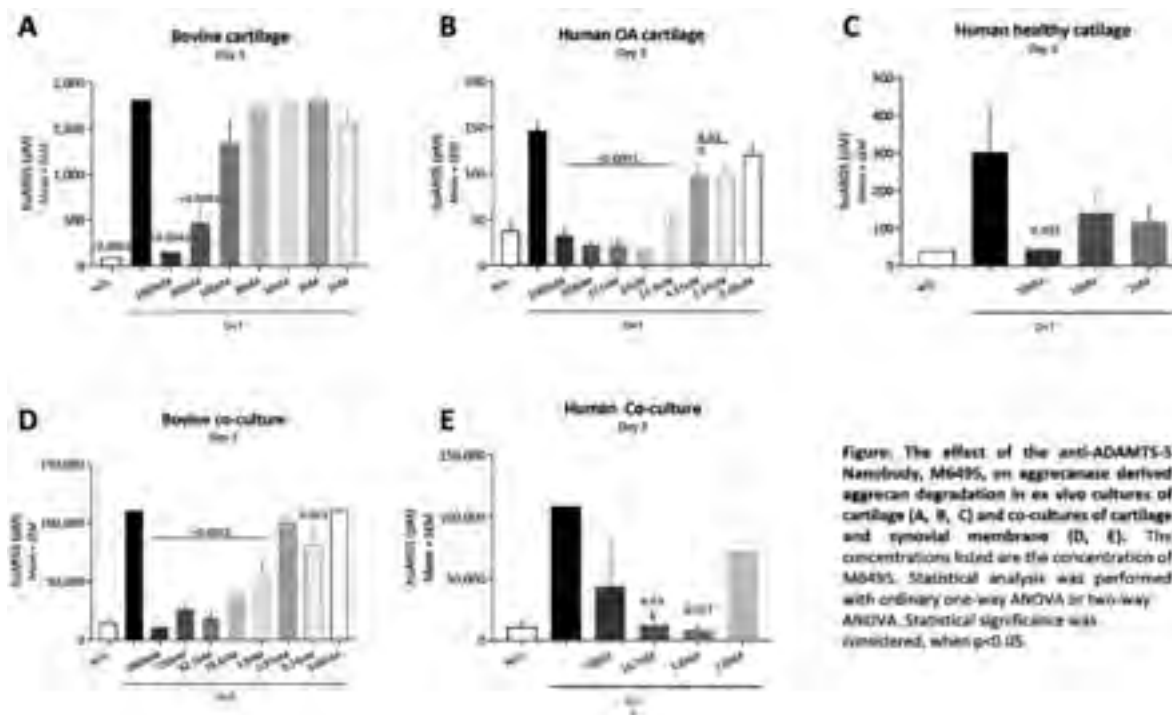
Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Osteoarthritis (OA) is associated with cartilage breakdown, where degradation of aggrecan by ADAMTS-5 (a disintegrin and metalloproteinase with thrombospondin motifs5) is thought to be an early event of the breakdown. Animal studies have suggested that inhibition of aggrecan degradation inhibits cartilage breakdown, whereas inhibition of the later collagen degradation has limited effect on cartilage preservation. We investigated the effect of M6495, an anti-ADAMTS-5 inhibiting Nanobody®, on cartilage turnover in explant cultures.

Methods: Bovine cartilage explants (BEX, N=4), human OA cartilage explants from replaced knee joints (HEX, N=8), and from 1 healthy human knee joint (hHEX) were cultured for 21 days in medium alone (w/o), in pro-inflammatory cytokines (on costatin M [10 ng/mL] + TNF α [20 ng/mL] (O+T)) or O+T with M6495 [1 μ M–1 nM]. Cartilage and synovium from cows (bCC) and OA human knee joints (hCC, N=4) were co-cultured for 28 days in w/o, with O+T or O+T plus M6495 [1 μ M–0.6 nM]. Metabolic activity was assessed by Alamar Blue. Cartilage tissue turnover was assessed by ELISA (huARGS, AGNxI, C2M and ProC2) in conditioned medium, which are measurement of type II collagen and aggrecan degradation and type II collagen formation. Data was analyzed by 1-way and 2-way ANOVA.



Results: Metabolic activity of BEX, HEX, and bCC was stable throughout the culture period, whereas the metabolic activity in hCC and hHEX dropped markedly from day 14 in O+T treated conditions compared to w/o. In cultures stimulated with O+T, metabolites of ADAMTS-5 degraded aggrecan peaked within the first week of the culture, except for hHEX in which huARGS and exAGNxI increased slightly later. Type II collagen degradation, C2M, by O+T peaked after day 19. Type II collagen formation, ProC2, remained relatively stable throughout the cultures, compared to the w/o control. In BEX, treatment with M6495 in combination with O+T decreased huARGS with the highest doses on day 5 (8% of O+T); in HEX (40% of O+T), bCC (10% of O+T), hCC (40% of O+T), and hHEX (24% of O+T) (Fig.). The effect of

M6495 on exAGNxl was similar to huARGS in the cultures tested. M6495 also reduced C2M (marker for type II collagen degradation) significantly, albeit the effect was less than for aggrecan degradation markers. M6495 had no effect on ProC2.

Conclusion: Here, we have shown that the Nanobody® M6495 has cartilage protective effects due to its inhibition of ADAMTS-5-mediated aggrecan degradation and MMP-mediated type II collagen degradation in pro-inflammatory conditions of bovine and human cartilage cultures and in co-cultures of cartilage and synovium.

Disclosure: A. S. Siebuhr, Nordic Bioscience, 3; A. C. Bay-Jensen, Nordic Bioscience, 1, 3, IMI APPROACH, 2; C. S. Thudium, Nordic Bioscience, 3; M. A. Karsdal, Nordic Bioscience, 1, 3; B. Serruys, Ablynx, 3; D. Werkmann, Merck KGaA, 3; M. Michaelis, Merck KGaA, 3; C. Ladell, Merck KGaA, 3; S. Lindemann, Merck KGaA, 3.

Abstract Number: 1042

Development of a Neo-Epitope Specific Assay for Serological Assessment of Type X Collagen Degradation and Its Potential Diagnostic Value for Knee Osteoarthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

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

Background/Purpose: Phenotypic changes of chondrocytes toward hyper trophy might be fundamental in the pathogenesis of OA, of which type X collagen is a well-known marker. The purpose was to develop a specific immunoassay for quantification of a newly identified neo-epitope of type X collagen to assess its diagnostic value for radiographic knee osteoarthritis (OA).

Methods: A neo-epitope of type X collagen was identified in human urine from OA patients by liquid chromatography-mass spectrometry (LC-MS/MS). A monoclonal antibody against the neo-epitope was produced. To identify the enzyme responsible for the cleavage of Col10, articular cartilage isolated from patients who underwent total knee replacement (TKR) was cleaved by numerous proteases *in vitro* and *immuno detected*. Immunohistochemical detection of this neo-epitope was performed on human OA cartilage from femoral condyle. A specific enzyme-linked immunoassay was developed by employing the neo-epitope antibody and quantified in plasma samples of two clinical studies: the C4Pain-003 and the NYU OA progression study. ROC curve analysis was carried out to evaluate the discriminative power of Col10neo between OA and RA.

Results: A mAb 2F4 targeting Cathepsin K- generated ⁴⁷⁹GIATKG neo-epitope was produced. In knee cartilage sections with mild or moderate cartilage degradation stained with Safranin O/Fast green, GIATKG neo-epitope was localized to the pericellular matrix of chondrocytes, while specimen with advanced cartilage degradation, its presence was extended to the territorial matrix of chondrocyte clusters and more prominent in superficial fibrillation. In the C4Pain study, there was a trend toward a higher level of Col10neo in subjects with greater KL. The greatest percent of subjects with KL3-4 was in the group of the highest tertile of Col10neo. In the NYU study, Col10neo was statistically higher in OA than control or RA. No significant difference was seen between control and RA (Figure 1). When adjusted for age, gender, and BMI, Col10neo remains significantly higher in OA compared to control and RA (Figure 2A). ROC curve analysis revealed area under the curve (AUC) was 0.88 (95% CI 0.81-0.94) (Figure 2B).

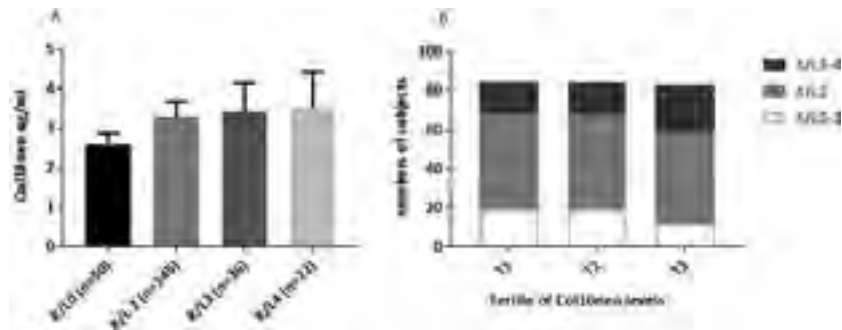


Fig. 1

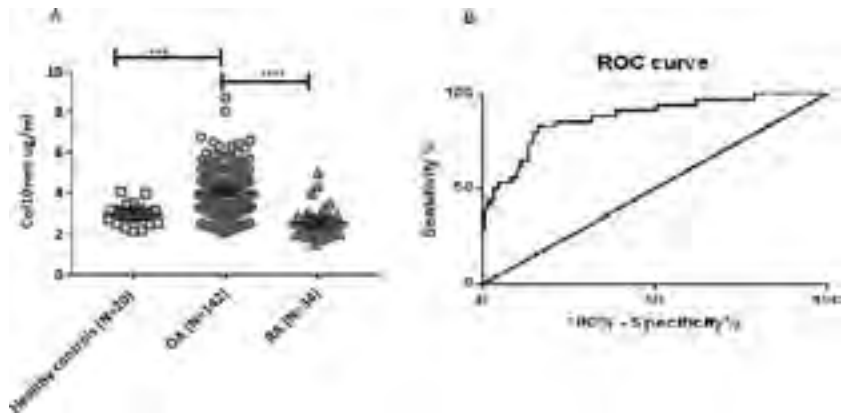


Fig.2

Conclusion: Our findings indicate that Col10neo could be used as a diagnostic biochemical marker for knee OA.

Disclosure: Y. He, Nordic Bioscience, 3; T. Manon-Jensen, Nordic Bioscience, 3; L. Arendt-Nielsen, None; K. Petersen, None; T. Gantzel, None; J. Samuels, None; S. B. Abramson, None; M. A. Karsdal, Nordic Bioscience, 1, 3; M. Attur, None; A. C. Bay-Jensen, Nordic Bioscience, 1, 3.

Abstract Number: 1043

Computational Analysis of Potential Self-Antigens in Osteoarthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Recent work in a subpopulation of individuals with osteoarthritis (OA) suggests that T cells are (1) responding to auto-antigenic stimuli (e.g. peptidoglycan epitopes), (2) not being effectively quieted by peripheral tolerance mechanisms, and (3) driving local inflammation. In this study, we assessed the possibility that in OA, T cells are responding to self-antigen peptides (SAP) bound more tightly to HLA by measuring OA-HLA associations and SAP-HLA binding distributions in a large community-based cohort, the Johnston County (JoCo) OA Project.

Methods: We included 1477 JoCoOA participants of European Ancestry (EA) and defined hip or knee OA as having both symptoms and a Kellgren-Lawrence grade of 2 or more in a given joint. We imputed HLA from SNP data using SNP2HLA and verified imputation accuracy using 1000 Genomes Project data. To evaluate the effect of cumulative potential SAP-HLA binding, we used NetMHC pan to predict binding of the reference peptidome to each sample HLA for coding transcripts from the top 100 genes and nonsense mediated decay (NMD) transcripts from the top 1000 genes expressed in synovium. Chi-square tests for HLA with allele frequency >2% were used to discover individual HLA

Figure 1. Kernel Density for Potential Self-Antigens in a Population of European Ancestry with and without Knee Osteoarthritis.

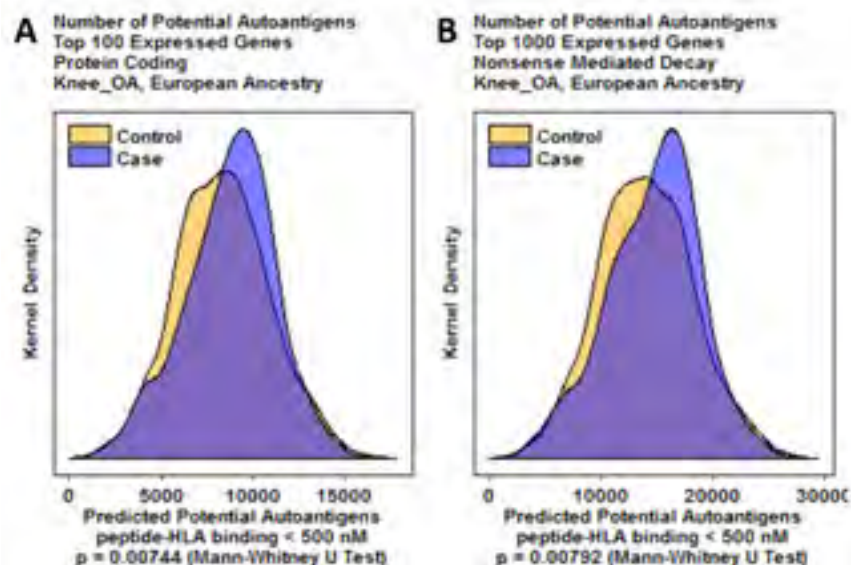


Table 1. Contingency Table Analysis for HLA-B Alleles in a Population of European Ancestry with and without Knee Osteoarthritis.

HLA	Carrier Freq	OA carrier	OA noncarrier	nonOA carrier	nonOA noncarrier	p-value	Rank	(I/m)Q
B*3501	9.6%	7	202	134	1133	1.5E-03	1	2.8E-03
B*5101	9.1%	28	181	106	1161	2.7E-02	2	5.6E-03
B*1302	5.8%	19	190	67	1200	4.4E-02	3	8.3E-03
B*1501	13.3%	35	174	161	1106	1.4E-01	4	1.1E-02
B*0801	21.7%	37	172	283	984	1.6E-01	5	1.4E-02
B*3801	2.8%	9	200	33	1234	2.5E-01	6	1.7E-02
B*4403	9.8%	25	184	119	1148	3.0E-01	7	1.9E-02
B*2705	8.7%	22	187	107	1160	3.9E-01	8	2.2E-02
B*5501	4.9%	8	201	64	1203	5.6E-01	9	2.5E-02
B*4402	18.8%	36	173	241	1026	6.0E-01	10	2.8E-02
B*5701	7.2%	13	196	94	1173	6.3E-01	11	3.1E-02
B*1801	8.6%	16	193	111	1156	6.9E-01	12	3.3E-02
B*3503	2.5%	6	203	31	1236	9.0E-01	13	3.6E-02
B*0702	24.8%	53	156	313	954	9.1E-01	14	3.9E-02
B*1402	4.9%	11	198	61	1206	9.2E-01	15	4.2E-02
B*4001	13.7%	28	181	174	1093	9.8E-01	16	4.4E-02
B*4901	4.3%	9	200	54	1213	1.0E+00	17	4.7E-02
B*4002	3.3%	7	202	42	1225	1.0E+00	18	5.0E-02

association with knee and hip OA, accounting for multiple comparisons with Bonferroni and Benjamini-Hochberg FDR adjustment. Mann-Whitney U tests were used to compare cumulative potential SAP-HLA binding distributions for participants with and without OA.

Results: HLA imputation identified 94% of 2-digit HLA types and 87% of 4-digit subtypes in the European1000 Genomes Super-Population. HLA-B*35:01 associated with knee OA from within the group of B alleles after adjustment (**Table 1**). Cumulative potential SAP-HLA binding for both protein coding transcripts and NMD transcripts also associated with knee OA (**Figure 1**).

Conclusion: An individual's HLA type affects the potential space of SAP which can bind tightly and be presented to T cells. HLA-B*35:01 was weakly associated with knee OA in the EA JoCo subset. We hypothesize that it is the cumulative propensity for highly expressed synovial peptides to bind to an individual's HLA that determines a baseline level of knee OA risk, which is then augmented by joint injury, obesity, aging, or other factors that increase local inflammation and/or expose a higher burden of synovial SAP to T cells.

Disclosure: J. Lansford, None; L. Arbeeva, None; B. Vincent, None; J. M. Jordan, None; R. Loeser, None; A. Nelson, None.

Abstract Number: 1044

Alendronate-CGS21680 Conjugates Prevent Bone Erosion in a Murine Osteolysis Model

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: The most common cause of total joint replacement revision surgeries is loosening of the implant due to loss of bone around the prosthesis. Wear particles shed from the prosthesis plays a critical role by increasing local inflammation and osteoclast number and activity, ultimately causing osteolysis. We have previously reported that an A_{2A} adenosine receptor selective agonist (CGS21680, CGS) prevents osteolysis in wear particle-induced osteolysis model in mice. Frequent administration requirements and potential toxicity make it a less than optimal treatment for inflammatory osteolysis. We therefore generated and tested a novel alendronate-CGS conjugate (MRS7216) that specifically localizes to bone targeting the agonist to the site of tissue injury and thereby diminishing the frequency of administration and curtailing systemic side effects.

Methods: The conjugate was synthesized from CGS by sequential activation of the carboxylic acid moiety and reacting with the appropriate amino acid under basic conditions. A PEG₆ linker was incorporated to alendronic acid by direct coupling. Osteolysis in 6–8-week-old C57BL/6J mice was induced by surgical implantation of 3mg of ultrahigh-molecular-weight-polyethylene particles over the calvaria. Mice received a weekly 10mg/kg intraperitoneal dose of MRS7216 conjugate, starting at the time of surgery. Other groups of mice were treated with equivalent weekly doses of alendronate-PEG₆ (AlenP) or saline respectively. An additional control group underwent sham surgery. After 2 weeks, animals were sacrificed and microCT and histology analyses were performed. The studies were approved by the Institutional Animal Care and Use Committee of NYU School of Medicine.

Results: Receptor binding studies demonstrate that the K_i for CGS, 7216 conjugates and the control AlenP molecules were 21.5 nM, 69.2 nM and >10,000 nM respectively, indicating that MRS7216 efficiently binds the A_{2A} adenosine receptor. MicroCT studies showed that mice treated with weekly doses of 7216 had a significant reduction in bone damage of 40% (p=0.04) compared to saline treated mice. In contrast, AlenP molecules did not prevent bone erosion. Histological analysis of TRAP stained samples showed a significant decrease of osteoclast number/high-power field (HPF) of 55% (p=0.03) in AlenP treated mice compared to the saline treated group. The osteoclast depletion was more dramatic in MRS7216 treated group with an 81% reduction of osteoclasts number/HPF (p= 0.002). Additionally alkaline phosphatase staining in MRS7216 treated group, showed a significant increase in osteoblast number/HPF compared to saline (55%, p=0.01) and to AlenP group (45%, p=0.03).

Conclusion: Alendronate-CGS conjugates represent a novel therapeutic approach to prevent osteolysis and prosthetic failure in patients with prosthetic joints.

Disclosure: A. Larrañaga Vera, None; K. Toti, None; E. Warnick, None; H. Rao, None; Z. G. Gao, None; A. Gadiano, None; A. Mediero, CP15/00053 PI16/0991, 2, 9; K. A. Jacobson, None; B. N. Cronstein, Cantic Biopharma, Regenosine, 1, NIH Arthritis foundation, Astrazeneca, 2, Horizon Pharmaceuticals, Regenosine, 5, Patent issued and pending, 9.

Abstract Number: 1045

The Coll2-1 Peptide of Collagen Type II: A New Actor of Synovitis in Osteoarthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: We evaluated the inflammatory effect of Coll2-1 peptide in osteoarthritic synoviocytes and rats by comparing peptide-induced inflammatory reaction with the one induced by bovine type II collagen or streptococcal cell wall.

Methods: Human synoviocytes from knee OA patients (n=10) were pre-treated with AS0619 or CLI-095 (500nM, 1 and 2.5μM) before a 24 hours treatment with Coll2-1 peptide (¹⁰⁸HRGYPGLDG¹¹⁶; 0.45 or 4.5nmol). Expression of Interleukin (IL)-8, Vascular Endothelium Growth Factor (VEGF) and phosphorylation of the IκB-α and p65 were evaluated. Either Coll2-1 peptide, bovine type II collagen (CIA), streptococcal cell wall (SCW) or saline solution (100μl SC or 50μl IA) were injected into Lewis rats (n = 108). The Coll2-1 peptide was injected subcutaneously (SC; 20 and 200μg/100μl/animal) or intra-articular (IA; 0.5 and 5μg/50μl/animal). The bovine type II collagen was SC injected (200μg/100μl/animal), streptococcal cell wall in IA (5μg/50μl/animal). The animals were injected on day 10 and monitored for 21 or 28 days. Visual evaluation of the severity of arthritis and histological lesions were performed.

Results: Coll2-1 at 0.45 nmol (**P<0.01) and 4.5 nmol (*P<0.05) significantly increased IL-8 gene expression and tended to increase VEGF expression by synoviocytes. With AS0619, a specific antiserum for Coll2-1 peptide, IL-8 expression significantly decreased (*P<0.05). Coll2-1 also induced both translocation of p65 and IκBα degradation. The latter being reduced with oxidative stress inhibitors. With CLI-095, we observed a decrease of IL-8 expression. *In vivo*, bovine type II collagen injection and Coll2-1 peptide injection resulted in an increase in visual arthritis score from D7. The global histological score was also increased by bovine type II collagen on D21 (p=0.0005) and on D28 (p<0.0001) and by the peptide Coll2-1 on D21 at the concentration of 200μg (p=0.0252) and on D28 at the concentration of 20μg (p=0.0025). Compared to control, all the components of the histological score were similarly modified by bovine type II collagen and the peptide Coll2-1 at both on D21 and on D28: increase in the inflammatory parameter (D21 200μg p=0.0217 and D28 20μg p=0.0021), reduction of proteoglycan contents (D28 200μg p=0.0072 and 20μg p=0.0024), increased cartilage degradation (J28 200μg p=0.0070 and 20μg p=0.0024) and modification of the subchondral bone (D21 200μg p=0.0025 and D28 20μg p=0.0065). Similarly, both the injection of SCW and that of Coll2-1 peptide induced an increase in the visual score from D10. The effect of Coll2-1 peptide on this score was identical to that of the SCW. Compared to control, SCW and Coll2-1 peptide increased the global histological score (D21 p=0.0119 and D28 p=0.0045). Like SCW, the injection of Coll2-1 peptide caused both inflammatory reaction, loss of proteoglycan, appearance of cartilage structural lesions (D28 0.5μg p=0.0201) and subchondral bone modification.

Conclusion: Coll2-1 peptide is able to induce an inflammatory reaction and structural changes. Coll2-1 may initiate nonspecific natural immunity and therefore be a therapeutic target for biotherapy.

Disclosure: C. Lambert, None; D. Borderie, None; J. E. Dubuc, None; F. Rannou, None; Y. Henrotin, Fidia -Artialis, 1, 5, 8.

Abstract Number: 1046

Distinct Balance of TNF-α/IL-10 in Circulating and Infiltrating CD163+ Macrophages between Rapidly and Slowly Progressive Symptomatic Knee Osteoarthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: There is a subtype of osteoarthritis (OA), which shows higher level of inflammation and higher risk of disease progression. In the current study, we analyzed the TNF- α and IL-10 level in circulating and infiltrating macrophages, and correlation of CRP and BMI between rapidly and slowly progressive patients.

Methods: We categorized 41 patients (32 female and 9 male) with symptomatic knee osteoarthritis for primary total knee arthroplasty (TKA) into rapidly progressive group (ROA, n=20) and slowly progressive group (SOA, n=22), based on disease duration less than 5 years, or more than 5 years. The average disease duration of ROA was 3.3 ± 2.105 years, and the SOA was 12 ± 5.385 years. 5 patients (3 female and 2 male) with knee joint fracture fixation were selected as control (FX). Circulating macrophages were separated from patients' peripheral blood. Infiltrating macrophages were separated from knee synovial tissue from TKA. The expression of IL-10 and TNF- α in the CD163+ macrophages in the synovial membrane and peripheral blood were detected by flow cytometry. The difference of the correlation of CRP and BMI between the ROA and the SOA were analyzed.

Results: ROA patients showed significantly increased CD163+ macrophages in peripheral blood (ROA $12.53 \pm 4.56\%$, SOA $3.59 \pm 3.92\%$, FX $0.52 \pm 0.57\%$, $p < 0.05$), and even more in synovium (ROA $41.06 \pm 10.02\%$, SOA $20.06 \pm 3.96\%$, FX $0.594 \pm 0.50\%$, $p < 0.05$). CD16+ macrophages from ROA patients showed trends to TNF- α in both peripheral blood (ROA *VS* SOA: $42.32 \pm 6.91\%$ *VS* 26.01 ± 5.28 , $p < 0.05$), and synovium (ROA *VS* SOA: $36.6 \pm 5.7\%$ *VS* $23.33 \pm 4.14\%$, $p < 0.05$). However, CD16+ macrophages from SOA patients showed advantage in IL-10 (peripheral blood ROA *VS* SOA: $2.11 \pm 2.17\%$ *VS* $4.71 \pm 3.46\%$, $p < 0.05$; synovium ROA *VS* SOA $1.96 \pm 1.44\%$ *VS* $3.80 \pm 2.33\%$, $p < 0.05$). In ROA group, CRP was positively correlated with BMI ($r = 0.680$, $P < 0.05$); but in SOA group, CRP was not related to BMI.

Conclusion: Both circulating and infiltrating macrophages from patients with ROA and SOA display distinct inflammatory characters.

Disclosure: L. Wang, None; W. Wang, None; H. Chu, None; X. Shang, None; X. Li, None.

Abstract Number: 1047

Signaling at Adenosine A2A Receptor (A2aR) in Osteoblasts; Crosstalk with Wnt/ β -Catenin Signaling Pathway

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: The Wnt/ β -catenin signaling pathway plays a key role in regulating bone formation and maintaining bone hemostasis. Wnt activates a pathway that leads to stabilization of β -catenin and its translocation to the nucleus. Osteoblast differentiation and proliferation are also regulated by adenosine receptors, among other signals. We recently reported that A2aR signaling promotes Wnt/ β -catenin signaling in fibroblasts via activation of Akt and p38MAPK. In the present study we sought to determine whether there is a similar interaction between these pathways in osteoblasts.

Methods: We studied murine osteoblast cell line (MC3T3-E1) and primary osteoblasts derived from bone marrow-derived mesenchymal stem cells of mice. The cells were treated with CGS21680, a selective A2aR agonist, at doses ranging from 0 to $10 \mu\text{M}$, and for varying incubation periods up to 240 minutes. Levels of phosphorylated β -catenin at Ser552 (p-Ser552), a β -catenin isoform with enhanced transcriptional activity, were measured by Western Blot assays before and after A2aR activation. We also analyzed nuclear translocation of p-Ser552 β -catenin in the osteoblastoid cell line and primary cell cultures using immunofluorescence (IF) staining. Cellular levels of activated AKT were measured by immunoblotting assays before and following administration of CGS21680.

Results: We observed a significant increase in p-Ser552 β -catenin levels in the osteoblastoid cells treated with $1 \mu\text{M}$ CGS21680 compared to the control, starting at 15 minutes following A2aR activation ($253 \pm 122\%$, $p < 0.05$, $n = 5$). Western blot analysis showed a significant increase in nuclear translocation of p-Ser552 β -catenin at 15 minutes after treatment with A2aR agonist in MC3T3-E1 cells ($153 \pm 37\%$, $p < 0.05$, $n = 4$), and primary osteoblasts ($148 \pm 31\%$, $p < 0.05$, $n = 4$). Similarly, immunofluorescence revealed approximately a 40% increase in nuclear accumulation of p-Ser552 β -catenin in CGS21680-

treated MC3T3-E1 cells as well as in primary osteoblasts. We also found a significant increase in the levels of phosphorylated AKT at Ser473 among osteoblastoid cells following A2aR stimulation ($203 \pm 47\%$, $p < 0.05$, $n = 4$).

Conclusion: These findings demonstrate cross-talk between A2aR and Wnt/ β -catenin signaling pathways in osteoblasts. Moreover, our results suggest that A2aR activation can bypass blockade of Wnt ligands at the cell surface and thereby maintain bone homeostasis.

Disclosure: S. Borhani, None; C. Corciulo, Regenosine, 1,Intellectual property, 9; A. Larrañaga Vera, None; B. N. Cronstein, Cantic Biopharma, Regenosine, 1,NIH Arthritis foundation, Astrazeneca, 2,Horizon Pharmaceuticals, Regenosine, 5,Patent issued and pending, 9.

Abstract Number: 1048

Identification of Novel Molecules with Senolytic and Autophagy Activity As Osteoarthritis Therapeutics

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SESSION INFORMATION

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Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Disease-modifying treatments for Osteoarthritis (OA) are not available. Aging-related features such as failure of homeostasis mechanisms, including autophagy, cause extracellular matrix damage, chondrocyte senescence and death, which leads to articular cartilage degeneration and joint dysfunction. *The objective of this study was to identify Senolytic and Pro-Autophagy molecules to prevent cartilage degeneration and OA.*

Methods: Cellular senescence and defective autophagy was induced in immortalized human chondrocytes (T/C28-a2) with IL-6, a SASP factor, at 20ng/ml for 72 or 18 hours, respectively. Then, chondrocytes were incubated with Prestwick Chemical Library at 10 μ M for 72 hours. To identify senolytics, SA- β -gal activity was determined by Imagene Green C12FDG substrate reporter. To identify molecules activating autophagy flux, pBABE-mCherry-EGFP-LC3 reporter was used to generate stable expression in chondrocytes by retrovirus transfection. Imaging was done by using Operetta® High Content Screening system. Confirmatory assays with readouts for senescence, autophagy, inflammation and apoptosis were performed in primary human chondrocytes. The anabolic effect was evaluated by Safranin O staining and Nitric Oxide production in human cartilage. To establish the senomorphic or senolytic nature of the candidate, senescent cells and total cells were counted with Cell Analyzer 6000 Confocal Imaging System. Navitoclax 2,5 μ M and Rapamycin 10 μ M were used as controls for senolytic and senomorphic activity, respectively. The functional consequence of treatment with the candidate was evaluated in blood, chondrocytes and cartilage from non-OA and knee OA patients.

Results: Primary screen yielded 279 senolytic compounds. Secondary screen identified 37 compounds with both senolytic and pro-autophagy activity. Fenofibrate (FN), a PPAR α agonist approved for dyslipidemia was selected as candidate. FN reduced senescence ($p < 0.001$) and increased autophagic flux ($p < 0.0001$), protecting against defective autophagy and inflammation in response to IL-6 and IL-1 β . This protection was confirmed in articular cartilage explants by a reduction of proteoglycans loss ($p < 0.05$) and in primary human chondrocytes by a reduction of NO production and death by apoptosis ($p < 0.0001$). Moreover, a senolytic effect was observed in human chondrocytes ($p < 0.05$) by selective reduction the number of senescent cells by apoptosis. Furthermore, FN upregulated PPAR α target genes and FoxO1 expression. These effects were also observed for structurally distinct PPAR α agonists, suggesting that pharmacological modulation of PPAR α may provide therapeutic benefits in OA. Remarkably, PPAR α expression was reduced in blood and cartilage from knee OA patients.

Conclusion: Our cell-based imaging assay provides a unique opportunity to identify novel drugs and mechanisms to prevent cartilage pathology. Dual senolytic and pro-autophagy effects may provide benefits in cartilage degeneration associated to aging and inflammation. A positive outcome of ongoing efficacy studies focused on PPAR α might provide the basis to propose proof-of-concept studies in patients with OA.

Disclosure: U. Nogueira-Recalde, None; F. J. Blanco, None; M. I. Loza, None; D. Grassi, None; P. Robbins, None; E. Dominguez, None; B. Carames, None.

Abstract Number: 1049

Optical Biomarkers for the Early Diagnosis of Osteoarthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

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Background/Purpose: Osteoarthritis (OA) is a rheumatic disease characterized by articular cartilage degradation. On its early stages, OA is asymptomatic and its current gold-standard diagnosis (X-Rays), focused on changes on the adjacent tissue – bone – presents a limitation to the early diagnosis of this disease. Raman spectroscopy (RS) has been recently described as a non-invasive tool to detect molecular changes in biological tissues, producing a unique fingerprint. For this reason, its application for the diagnosis of different diseases offers high potential. Beyond its clinical application, RS offers

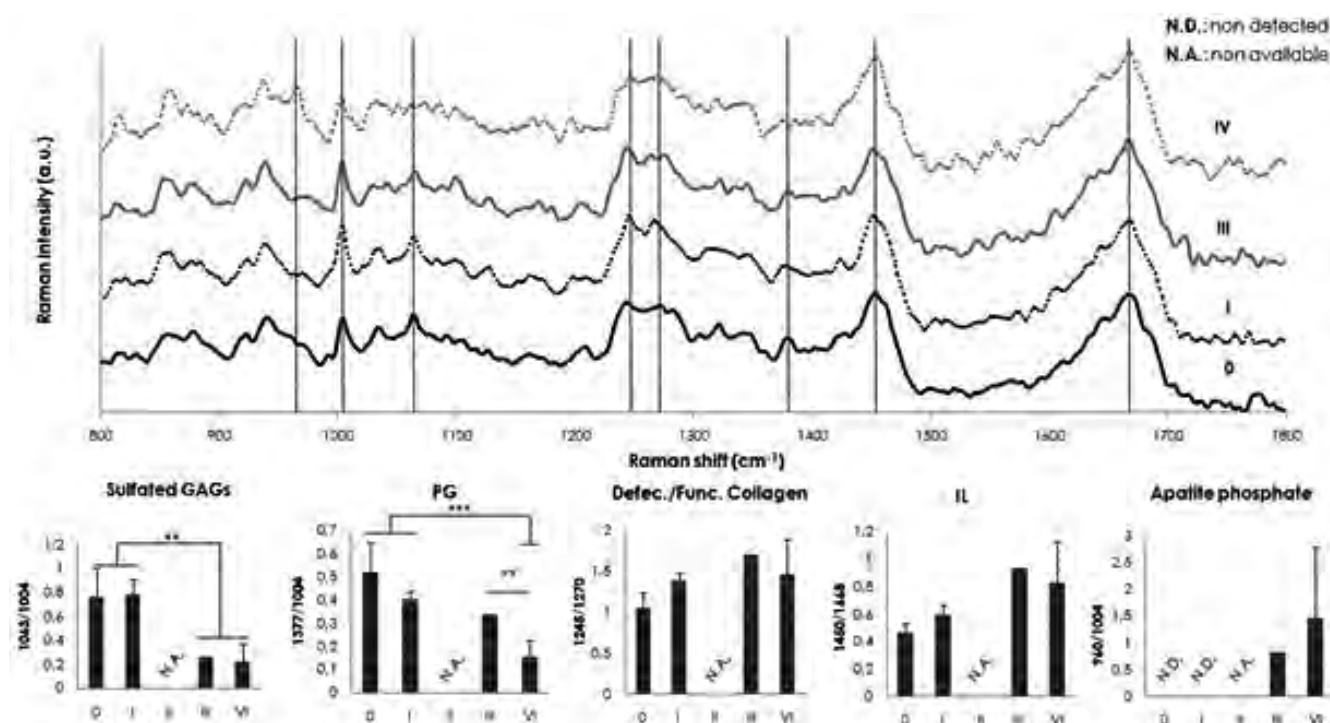


Fig.1. A. Raman spectra for H and OA cartilage (K-L: 0 to IV) and assigned peaks. **B.** Quantitative analysis of the main components found: glycosaminoglycans (GAGs), proteoglycans (PG), Defective/Functional Collagen, lipid index (LI) and phosphate apatite. Significant differences are represented as **p<0.01 or ***p<0.001.

value as a molecular quantification technique for tissue engineered cartilage characterization. The aim of this work was to evaluate the potential of RS for the early diagnosis of OA.

Methods: Human hip cartilage explants (n=14), from healthy (H) and OA donors, with Kellgren-Lawrence (K-L) radiological grades from 0 to IV, were obtained after informed consent. Raman analysis was performed on fresh tissue, using a Bruker RFS100 Spectrometer with a Nd:YAG laser ($\lambda=1064$). Main peaks were assigned according to literature³, following their area's measurement after a normalization process. One-way ANOVA statistical analysis was performed and differences considered significant for $p<0.05$. We further analyzed correlations (Pearson's coefficient) between peaks and K-L grade.

Results: RS cartilage spectra (Fig.1A) revealed the following assignments: 1245-1270 cm^{-1} amide III doublet (random coil and α -helix collagen), 1063 cm^{-1} (sulfated glycosaminoglycans, GAGs), 1377 cm^{-1} (proteoglycans, PG), 1450 cm^{-1} (nonspecific signal of lipids and proteins) and 1668 cm^{-1} (carbonyl group in proteins). For higher K-L grades, a peak appeared at 960 cm^{-1} (apatite phosphate), related to tissue mineralization. After quantitative analysis (Fig.1B) we observed the main molecular changes: GAGs and PG peaks showed a significant decrease with OA severity ($p<0.01$), supported by high correlation coefficients ($R^2=0.7361$ and $R^2=0.7999$, respectively), related to GAGs' degradation; an increase in 1245/1270 ratio (defective/functional collagen) could reveal collagen arrangement loss, although there was a low correlation vs K-L ($R^2=0.3764$); an indirect lipid index (IL), calculated as A1450/A1668, showed an increase of lipids in OA tissues.

Conclusion: RS analysis revealed a hip cartilage molecular fingerprint. Variations found between H and OA tissue are representative of the molecular changes during OA progression. A set of parameters is suggested as an optical biomarker panel: defective/functional collagen (1245-1270 cm^{-1}), GAGs (1063 cm^{-1}), PG (1377 cm^{-1}) and IL (1450/1668).

Disclosure: P. Casal Beiroa, None; E. F. Burguera, None; T. Hermida-Gómez, None; N. Goyanes, None; N. Oreiro, None; P. González, None; F. J. Blanco, None; J. Magalhaes, None.

Abstract Number: 1050

Pharmacokinetic and pharmacodynamic modelling of the novel anti-ADAMTS-5 nanobody M6495 using the neo-epitope ARGS as a biomarker

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

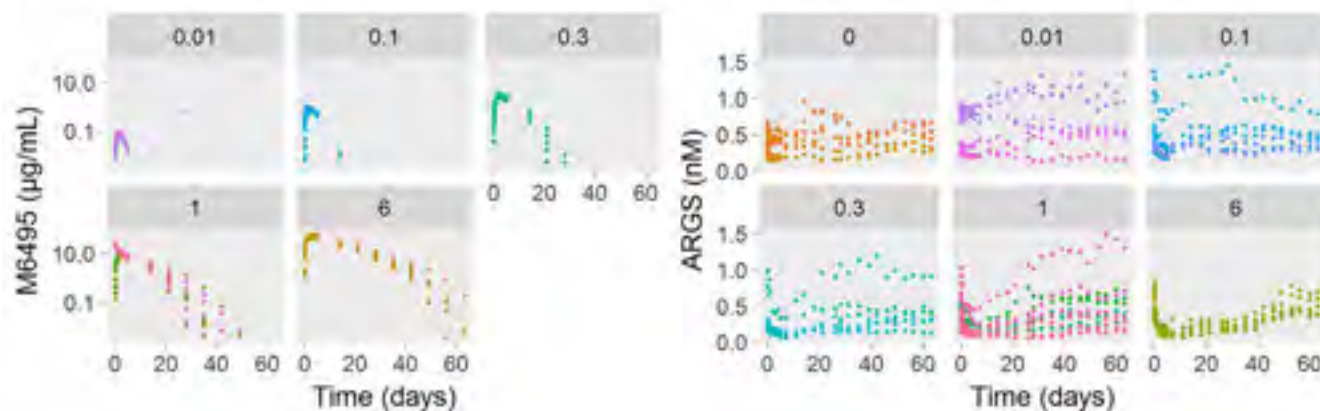
Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: The anti-ADAMTS-5 Nanobody®, M6495, is a first-in-class, highly selective, bifunctional Nanobody® and apotent inhibitor of ADAMTS-5, with the potential to be the first self-administered disease modifying osteoarthritis drug (DMOAD). A model-based approach was used to explore the relationship between plasma concentrations of M6495

Pharmacokinetics and Pharmacodynamics of M6495 after a single dose (mg/kg) in cynomolgus monkeys



and the reduction of serum concentrations of the target engagement biomarker, the ADAMTS-5 generated neo-epitope of aggrecan (ARGS), in cynomolgus monkeys.

Methods: A dedicated single dose pharmacokinetics and pharmacodynamics (PK/PD) study was conducted in cynomolgus monkeys receiving subcutaneous (SC) M6495 at doses ranging from 0.01 to 6 mg/kg or vehicle. An additional group received intravenous M6495 which allowed the estimation of bioavailability. Both M6495 and ARGS concentrations were measured over time. The data were then pooled with PK/PD data collected in a separate multiple-dose study in cynomolgus monkeys that received weekly M6495 at doses up to 150 mg/kg. Plasma concentrations of M6495 and decrease in ARGS serum concentrations upon drug administration were modelled with a non-linear mixed effects PK/PD model.

Results: A 2-compartment model including linear and non-linear elimination from the central compartment and first order absorption upon SC administration, adequately described the drug concentration-time profiles of M6495. The non-linear PK indicated a mechanism of target-mediated drug disposition which can be saturated at higher serum concentrations of M6495. ARGS levels decreased upon drug administration, with higher decrease demonstrable at higher doses (see Figure), reaching levels below the lower limit of quantification (LLOQ) for M6495 doses of 6 mg/kg and higher, indicating a strong inhibition of ADAMTS-5 (higher than 70%). Furthermore, the bioavailability after SC injection was estimated to be close to 100%. A marked decrease in serum ARGS levels, lasting several weeks, could already be observed after a single dose of M6495. The decrease in ARGS serum concentrations was delayed in relation to the exposure, and could be described with an indirect response model.

Conclusion: A single injection of the anti-ADAMTS-5 Nanobody®, M6495, in cynomolgus monkeys lead to a long-lasting decrease in ARGS at the highest dose tested, indicating a long-term inhibition of ADAMTS-5. This PK/PD model can be used to explore the exposure/pharmacodynamic response relationship between M6495 serum concentrations and the ARGS serum biomarker.

Disclosure: J. Pereira, Merck KGaA, 3; I. Ottevaere, Ablynx NV, Belgium, 3; B. Serruys, Ablynx, 3; E. Dejonckheere, Ablynx NV, Belgium, 3; A. C. Bay-Jensen, Nordic Bioscience, 1, 3, IMI APPROACH, 2; A. S. Siebuhr, Nordic Bioscience, 3; S. El Bawab, Merck KGaA, 3; C. Ladel, Merck KGaA, 3; S. Lindemann, Merck KGaA, 3.

Abstract Number: 1051

Hoxd Genes Regulate Arthritis-Relevant Pathways

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Gene expression and functions of synovial fibroblasts (SF) differ profoundly between distinct joints. This might lead to site-specific activation of arthritis-relevant pathways with implications for arthritis pathogenesis and drug targeting¹. Homeobox (HOX) transcription factors guide the proper morphogenesis of limb structural elements and appear to influence site-specific development of various diseases. Here we analyzed the expression and epigenetic regulation of HOXD genes in SF from different joints of the hand and identified their target genes and functional effects.

Methods: The expression of HOXD in SF was analyzed by RNA sequencing (n=21), quantitative Real-time PCR (qPCR; n=14) and Western blotting (n=10). The histone marks H3K4me1 (enhancers), H3K4me3 (promoters), H3K27me3 (repressed chromatin) and H3K27ac (active chromatin) were analyzed by Chromatin Immuno precipitation DNA sequencing (ChIPseq) in SF from one RA (finger II) and one osteoarthritis (OA; thumb) patient. HOXD10, HOXD11 and HOXD13 were silenced using antisense LNATM GapmeRs in finger II-IV SF (n=4). The expression of potential target genes was analyzed by qPCR in joints of the hand (n=7). Growth of transfected SF (n=3) was analyzed using an impedance-based system (xCELLigence).

Results: Among the genes in the HOX cluster, HOXD10, HOXD11 and HOXD13 transcripts and proteins were significantly increased in SF in digits II-IV (MCP, PIP) and wrists compared to SF from the thumb (CM I, MP I). This signature was independent of disease and recapitulated the embryonic HOXD expression pattern in the developing hand. ChIPseq showed an increase of H3K27ac and H3K4me3 marks in the genomic region between HOXD9 and HOXD13 in

SF from an RA finger II compared to SF from an OA thumb. This was paralleled by a loss of the repressive histone mark H3K27me3 in this region in RA finger II. Similar to the low expression of HOXD10-13 in thumbs, the expression of thrombospondin 2 (THBS2; $p<0.05$), receptor tyrosine kinase like orphan receptor 2 (ROR2; $p<0.05$), collagen type XI alpha 1 chain (COL11A1; $p<0.01$) and ATP binding cassette subfamily C member 9 (ABCC9; $p<0.05$) was decreased in joints of the thumb compared to joints of digits II-IV as measured by RNAseq and qPCR. Accordingly, silencing of HOXD13 decreased the expression of THBS2 ($p<0.001$), ROR2 ($p<0.001$) and COL11A1 ($p<0.01$), whereas ABCC9 ($p<0.01$) was decreased by silencing of HOXD10 ($p<0.01$) and HOXD13 ($p<0.01$). Silencing of HOXD13 but not HOXD10 and HOXD11 reduced the proliferation of SF by 83,7% ($p<0.01$).

Conclusion: HOXD10-13 exhibit an epigenetically regulated, increased expression in fingers II-IV compared to thumb that determines the site-specific signature of downstream target genes and the proliferative capacity of SF. This might influence the differential activation of arthritis-relevant pathways and patterns of OA and RA in the small joints of the fingers II-IV versus the thumb.

References:

¹Frank-Bertoncelj et al., *Nat Commun*, 2017.

Disclosure: K. Klein, None; M. Frank Bertoncelj, None; M. Krošelj, None; M. Tomšič, None; C. Kolling, None; O. Distler, Actelion, Bayer, Boehringer Ingelheim, Mitsubishi Tanabe Pharma, Roche, 2, Actelion, AnaMar, Bayer, Boehringer Ingelheim, ChemomAb, espeRare foundations, Genentech/Roche, GSK, Inventiva, Italfarmaco, Lilly, medac, MedImmune, Mitsubishi Tanabe Pharma, Novartis, Pfizer, Sanofi, Sinova, UCB, 5, mir-29 for the treatment of systemic sclerosis licensed, 9; C. Ospelt, None.

Abstract Number: 1052

Detection of Precursors of RANK- Osteoclast-like Cells (Olcs) in Peripheral Blood and Olcs in Bone Tissue from Rheumatoid Arthritis Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Proinflammatory cytokines play an important role in bone destruction in rheumatoid arthritis (RA), as inferred by the efficacy of biologics. Previously, we reported that novel osteoclast-like cells (OLCs) were induced, both *in vitro* and *in vivo*, from mouse bone marrow-derived macrophages by a combination of TNF α and IL-6 (Yokota K *et al.*, *Arthritis Rheumatol* 2014, 66:121-129). Herein, we aimed to examine the differentiation of OLCs, which were induced by a combination of TNF α and IL-6 from human peripheral blood mononuclear cells (PBMCs) and CD14⁺ monocytes and to identify differences in molecular expression patterns between OLCs and conventional osteoclasts. Furthermore, we identified OLCs and osteoclasts on the bone tissue of the joint in patients with RA.

Methods: PBMCs and CD14⁺ monocytes from healthy volunteers and/or RA patients were stimulated with TNF α and IL-6 or RANKL. Quantitative RT-PCR was used to measure mRNA expression levels of osteoclastogenesis-related genes. Prepared undecalcified tibial bone from 6 RA or osteoarthritis (OA) patients undergoing joint surgery were stained by tartrate-resistant acid phosphatase (TRAP) staining and immunohistochemistry with anti-RANK antibody, expression of which were analyzed. Osteoclasts and OLCs were identified as multinucleated TRAP⁺/RANK⁺ cells and TRAP⁺/RANK⁻ cells, respectively, adherent to the bone surface.

Results: The number of osteoclasts treated with RANKL and OLCs treated with a combination of TNF α and IL-6 from PBMCs or CD14⁺ monocytes in RA patients was significantly increased compared to that in healthy volunteers. Expression levels of *TRAP* mRNA was clearly up-regulated in osteoclasts and OLCs compared to that in osteoclast precursors. On the other hand, expression levels of *RANK* mRNA was obviously up-regulated in osteoclasts, and was down-regulated in OLCs. In cancellous bone, the number of TRAP⁺/RANK⁺ osteoclasts and TRAP⁺/RANK⁻ OLCs was significantly increased in RA patients compared to that in OA patients. Interestingly, numerous TRAP⁺/RANK⁻ OLCs were present in the cancellous bone of RA patients, while almost none were observed in the cancellous bone of OA patients.

Conclusion: The combination of TNF α and IL-6 strongly induced the differentiation of OLCs from PBMCs or CD14⁺ monocytes in RA patients. OLCs was characterized with TRAP⁺/RANK⁻ multinucleated cells, which can be distinguished from conventional TRAP⁺/RANK⁺ multinucleated osteoclasts. TRAP⁺/RANK⁻ OLCs also were present in the bone tissue of RA patients. These results suggest that conventional osteoclasts and novel OLCs could be involved in the pathogenic mechanisms of inflammatory bone destruction such as RA.

Disclosure: K. Yokota, None; S. Tanaka, None; M. Sekikawa, None; Y. Aizaki, None; K. Sato, None; H. Oda, None; T. Mimura, None.

Abstract Number: 1053

Synovial Inflammation Identifies Patients Clusters in Osteoarthritis

Hannah Labinsky¹, Paul Panipinto¹, Kaytlyn Ly², Deric Khuat², Bhanupriya Madarampalli³, Vineet Mahajan¹, Jonathan Clabeaux⁴, Kevin MacDonald⁴, Peter Verdin⁴, Jane H. Buckner² and Erika H. Noss³, ¹Medicine, Division of Rheumatology, University of Washington, Seattle, WA, ²Benaroya Research Institute at Virginia Mason, Seattle, WA, ³Rheumatology, University of Washington, Seattle, WA, ⁴Orthopedics, Virginia Mason Hospital, Seattle, WA

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Synovial membrane inflammation is common in osteoarthritis (OA). Inflammation may be present at all disease stages, increases the risk of cartilage injury, and is heterogeneous histologically, with variable synovial hyperplasia, inflammatory infiltrates, and angiogenesis. Our objective in this study was to develop an approach to characterize this variability in inflammation using flow cytometry and multiplex assays. We focused particularly on IL-6, as this inflammatory cytokine independently associates with poor OA outcomes.

Methods: Cell composition and soluble protein release was measured in synovium collected from thirty-five knee OA patients undergoing joint replacement surgery. Correlation-based clustering identified patient-specific inflammatory networks.

Results: We first measured release of thirteen inflammatory cytokines and adipokines by intact synovium. These proteins separated into at least two expression groups: (1) strong correlation between IL-6 and IL-8, linked through IL-8 to correlations with adipsin, CCL2, CXCL10, and adiponectin (potential fibroblast/macrophage pattern); and (2) correlations between IL-10, IFN- γ , resistin, TNF α and IL-1 β (potential T cell pattern). We next enzymatically disaggregated synovium and found that identifying mesenchymal and hematopoietic cell populations required different digestion conditions. Collagenase with higher dispase concentrations markedly improved total cell yield and mesenchymal marker staining. However, it negatively impacted T and natural killer (NK) cell staining. Intracellular IL-6 expression was detected in many cells, but was highest in mesenchymal cells, especially those expressing both CD90 and CD34. IL-6⁺ synovial cell numbers correlated strongly with IL-6 tissue release, validating our flow cytometry assay. IL-6 release did not correlate with leptin or body mass index, suggesting adipocytes produce little IL-6. OA synovial T cell infiltration was highly variable, with increased percentage of T cells correlating with CD8⁺ cytotoxic T cell influx. CD8⁺ T cells showed variable CD45RA and CD45RO expression and their presence correlated positively the soluble T cell pattern above. Finally, combining flow cytometric and multiplex data identified at least five possible OA synovial inflammation patterns, expanding on the networks identified by soluble protein analysis alone.

Conclusion: We have developed a novel approach to analyze OA inflammation that has identified patient-specific inflammatory clusters, including an unexpected involvement of CD8⁺ T cells. This study argues that identifying synovial inflammatory will provide new insights into OA patient heterogeneity and biomarker development.

Disclosure: H. Labinsky, None; P. Panipinto, None; K. Ly, None; D. Khuat, None; B. Madarampalli, None; V. Mahajan, None; J. Clabeaux, None; K. MacDonald, None; P. Verdin, None; J. H. Buckner, None; E. H. Noss, None.

Study of the Metabolic Effect of MSCs on Their Chondroprotective and Regenerative Properties: Modulating Their Metabolism to Improve Their Therapeutic Potential for the Treatment of Osteoarthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Mesenchymal Stem Cells (MSCs) are stromal multipotent cells with wide regenerative and immunomodulatory properties and have been proposed as a powerful therapeutic tool. Among the mechanisms associated with their regenerative potential are their ability to differentiate into several cell lineages, as well as the production of paracrine factors, which promote the survival and proliferation of cells in damaged tissues. On the other hand, their ability to regulate the immune response, allows them to inhibit the inflammation associated with tissue damage, promoting efficient and coordinated tissue regeneration. More recently, it has been described that some biological functions of MSCs, such as their differentiation potential are regulated by their metabolic activity, suggesting that changes in their metabolic state could also be regulating their therapeutic potential. For example, for chondrogenesis, cells need maintain a glycolytic-dependent metabolism during their differentiation process². Therefore, the hypothesis of the present study is that the induction of a glycolytic state on MSCs will promote their chondrogenic differentiation, as well as their chondroprotective and immunosuppressive properties.

²Pattappa, G., Heywood, H.K, de Bruijn, J. D., & Lee, D. A. (2011) The metabolism of human mesenchymal stem cells during proliferation and differentiation. *Journal of Cellular Physiology*, 226(10), 2562-2570. <https://doi.org/10.1002/jcp.22605>

Methods: MSCs were pretreated with either an inhibitor of glycolysis or mitochondrial metabolism during 24 hours. After that, cells were cultured in presence of a chondrogenic differentiation media. Chondrogenesis was evaluated by staining with safranin O and qRT-PCR for the chondrogenic genes aggrecan and collagen II. Separately, pretreated MSCs were co-cultured with chondrocytes (HC-a) and HC-a proliferation was measured with WST1 kit assay. Statistical analysis was performed with the Kruskal-Wallis test for the comparison of medians and Mann-Whitney as a post-hoc test.

Results: MSCs pretreated with an inhibitor of mitochondrial metabolism (glycolytic-MSCs), have a higher level of expression of chondrogenic genes after 11 days of differentiation compared to control MSCs. Moreover, MSCs pretreated with a glycolysis inhibitor (OXPHOS-MSCs) significantly reduced their chondrogenic potential. Interestingly, it was observed that glycolytic-MSCs were able to differentiate into chondrocytes without the need of differentiation medium. Additionally, glycolytic-MSCs significantly increase the proliferation of HC-a when they are incubated in co-culture without cell contact.

Conclusion: The inhibition of mitochondrial metabolism was able to induce chondrogenesis without the needed of a specific differentiation media. Our results suggest that the potentiation of a glycolytic state on MSCs to favor the proliferation of chondrocytes is associated to a mechanism dependent of soluble factors. These results present a new method to increase the therapeutic effect of MSCs in osteoarthritis, where the etiology of the disease is associated with inflammation and tissue destruction of the joint.

Disclosure: L. Martinez-Viola, None; P. Luz-Crawford, None; R. A. Contreras, None.

The TLR-4 Inhibitor 6-Shogaol As a Treatment in Osteoarthritis Trough the Modulation of Chondrocyte Hypertrophy and Matrix Calcification

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Osteoarthritis (OA) is a complex joint disease characterized by a progressive loss of articular cartilage (AC) and synovial inflammation. The latest theories of OA pathogenesis implicate the interplay between mechanical damage and chronic inflammation that has been associated to the activation of the innate immune system, intricately involved in the development of this low-grade inflammation. During the course of OA, Toll-like receptor (TLR) activation has been related to the release of cytokines and inflammatory mediators, which further aggravates synovitis and AC damage. In this scenario, hyaline chondrocytes seem to acquire a hypertrophic-like phenotype associated to AC degradation. 6-shogaol (6S), an effective anti-inflammatory ginger derivative, is able to inhibit TLR4-mediated innate immune responses. Our aim was to study the therapeutic benefit of 6-shogaol treatment in an OA mice model and its effect in the modulation of hypertrophic markers in chondrocyte cultures.

Methods: C57BL/6 male mice were randomly assigned to two groups: control (n=7) and OA (n=17). OA was induced by transection of the medial menisco-tibial ligament. Nine OA mice started receiving 6S (15mg/kg/day; OA+6S) since surgery. After 8 weeks, animals were euthanized and joints were collected. Chondrogenic differentiation was induced *in vitro* in the pre-chondrogenic cell line ATDC5 by ITS (insulin-transferrin-selenium) in presence or absence of 5×10^{-6} M 6S. Gene expression of hypertrophic markers as well as mineralization and proteoglycan synthesis were determined.

Results: Both synovial inflammation and AC damage were more severe in OA animals (Control: 0.1 ± 0.1 ; OA: 3.0 ± 0 ; $p < 0.05$, and Control: 0.5 ± 0.2 , OA: 5.4 ± 0.6 ; $p < 0.05$, respectively) with a significant reduction in OA+6S animals (2.4 ± 0.2 ; $p < 0.05$ and 2.6 ± 0.5 $p < 0.05$ vs. OA, respectively). Type X Collagen X (Col X) and MMP13 immunohistochemistry showed an increase in the AC of OA and OA-6S mice vs control animals (ColX: Control: 0.13 ± 0.03 , OA: 0.93 ± 0.10 ; OA-6S: 0.43 ± 0.10 ; $p < 0.05$ vs Control and MMP13: Control: 0.35 ± 0.10 , OA: 0.68 ± 0.10 , OA-6S: 0.28 ± 0.07 , $p < 0.05$ vs Control), while a significant reduction was found in 6S-treated mice ($p < 0.05$ vs OA). Similar results were found in the synovium and meniscus for MMP13 and in meniscus for Col X. In addition, 6S was able to significantly inhibit the expression of Collagen X, Ihh and MMP13 in ITS-stimulated cells after 14 and 21 days of culture. Furthermore, 6S prevented the increase in mineralization and proteoglycan synthesis in ITS-stimulated ATDC5 cells after 14 days of culture ($p < 0.05$ ITS vs basal, and $p < 0.05$ ITS-stimulated vs ITS), assessed by Alizarin red and Alcian blue staining, respectively.

Conclusion: Our results showed that 6S significantly prevented cartilage degradation and synovial inflammation, in parallel to a reduction of the presence of hypertrophic markers in the cartilage of OA mice. *In vitro*, 6S inhibited the chondrogenic differentiation of ATDC5 cells. These results suggest that 6S could work as a good treatment in OA both inhibiting hypertrophic differentiation markers and reducing the severity of joint damage in an OA murine model.

Disclosure: P. Gratal, None; A. Mediero, CP15/00053 PI16/0991, 2, 9; A. Lamuedra, None; R. Largo, None; G. Herrero-Beaumont, None.

Abstract Number: 1056

Association of Paraoxonase 1 Gene Polymorphisms and Enzyme Activity with Progression of Carotid Atherosclerosis in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Paraoxonase 1 (PON1) is a high density lipoprotein (HDL) associated enzyme, which promotes the anti-oxidant and anti-inflammatory properties of HDL. PON1 polymorphisms and enzyme activity have previously been associated with cardiovascular (CV) events in the general population. The current work investigated the relationship of

genetic and biochemical determinants of PON1 activity with progression of carotid atherosclerosis (ATH) in a longitudinal cohort of patients with rheumatoid arthritis (RA).

Methods: Carotid ultrasounds were performed at 2 time points separated by a mean \pm SD of 5.6 ± 1.2 years on a longitudinal cohort of 149 RA patients at a single academic center. The number and type of carotid plaques were assessed and an ATH score provided by the same radiologist for all scans. Fasting blood was collected for lipoprotein analysis and inflammatory markers done by standard assays, and PON1 activity was measured using paraoxon as the substrate. Genotyping for the PON1 Q192R polymorphism (SNP rs662) was done for all patients as described previously (Arthritis Rheum. 2013 Nov;65(11):2765-72). Traditional cardiovascular risk factors, medication use, and RA disease characteristics were assessed for all patients at baseline and follow-up visits.

Results: The PON1 genotype demonstrated a significant dose dependent association with PON1 activity (RR192 > QR192 > QQ192) ($p \leq 0.003$) at baseline and follow-up visits. Compared to patients with either the PON1 RR192 or QR192 genotype, patients with the QQ192 genotype demonstrated increased risk of carotid plaque progression measured by \geq one unit increase in carotid ATH score in multivariate analysis controlling for significant traditional CV risk factors, RA disease characteristics, medication use, and the presence of carotid plaque on baseline ultrasound ($p < 0.05$). Similar results were noted when defining ATH progression by \geq one new carotid plaque from the baseline scan. Separate multivariate logistic regression analysis controlling for the same significant RA and traditional CV risk factors also revealed a significant association of mean plasma PON1 activity with carotid ATH progression in RA patients. Lower mean plasma PON1 activity was associated with increased risk of carotid ATH progression as assessed both by \geq one unit increase in carotid ATH score, or by \geq one new carotid plaque from the baseline study in individual multivariate models ($p < 0.05$). Mean total, LDL, and HDL cholesterol levels were not associated with carotid ATH progression in this cohort.

Conclusion: The current work suggests a relationship between the genetic determinants and activity of PON1 with cardiovascular risk in RA patients as assessed by the progression of carotid ATH over 5 year longitudinal follow-up. Further CV outcome studies may be warranted to determine if PON1 is a useful biomarker of CV risk in patients with RA.

Disclosure: C. Charles-Schoeman, Bristol Myers Squibb, AbbVie, Octapharma, and Pfizer, 2, Regeneron-Sanofi, Pfizer, Octapharma, Amgen, and Gilead, 5; J. Wang, None; A. Shahbazian, None; J. Moriarty, None; T. Dowd, None; B. Oganessian, None; I. Golub, None; J. Fitzgerald, None; V. K. Ranganath, Genentech, Inc., 2, Pfizer, Inc., 2, Mallinckrodt, 2, Amgen Inc., 5; M. Taylor, Celgene Corporation, 8, AbbVie Inc., 8; M. A. McMahon, None; G. Alan, None; S. T. Reddy, None.

Abstract Number: 1057

Autophagy Promotes Citrullination of Vimentin and Its Interaction with Major Histocompatibility Complex Class II in Synovial Fibroblasts

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Citrullinated vimentin (cVIM) is one of the major autoantigens in patients with rheumatoid arthritis (RA), recognized by anti-citrullinated peptide antibodies. Autophagy is a self-cannibalism system to adapt to starvation but also regulates various cellular functions. Since autophagy is involved in antigen presentation with major histocompatibility complex (MHC) class II and accelerates peptidylarginine deiminase activity, we hypothesized that activation of autophagy causes citrullination of vimentin and its interaction with MHC class II in synovial fibroblasts (SF), one of the effector cells in RA.

Methods: SF were derived from synovial tissue specimens obtained from RA patients during joint replacement surgery. To evaluate antigen presenting capacity of SF, the cell surface expression of MHC class II and B7 molecules were analyzed by flow cytometry after 72h treatment with IFN- γ . Anti-cVIM antibodies were measured in RA patients' sera using enzyme-linked immunosorbent assay. Intracellular citrullinated autoantigens in SF were analyzed by western blotting using anti-cVIM antibody positive patient's serum as a primary antibody. To induce autophagy, SF were incubated in serum-free medium for 2h or treated with 10 μ M of the proteasome inhibitor MG132 for 24h. To inhibit autophagy, SF were treated with 5 mM of 3-methyladenine. Intracellular cVIM was evaluated by western blotting and immunocytochemistry using anti-vimentin and -citrulline antibodies. To evaluate the interaction between MHC class II and cVIM, lysates of IFN- γ treated SF were immunoprecipitated by anti-HLA-DR antibody, followed by western blotting for vimentin and citrulline. In addition, proximity ligation assay was performed using anti-HLA-DR, -vimentin, and -citrulline antibodies.

Results: MHC class II, B7-H1, and B7-DC were expressed on SF following treatment with IFN- γ , while B7-H3 was expressed on SF regardless of the presence of IFN- γ . Anti-cVIM positive RA patients' sera recognized 54 kDa protein in SF. By co-immunoprecipitation using anti-vimentin and -citrulline antibodies, the 54 kDa protein recognized by RA sera was revealed to be citrullinated vimentin. Following induction of autophagy by serum-free starvation or proteasome inhibition, intracellular cVIM was increased in SF but the effect was cancelled by the autophagy inhibitor 3-methyladenine. The interaction between MHC class II and cVIM was demonstrated by co-immunoprecipitation. Furthermore, proximity ligation assay revealed that the MHC class II-cVIM interaction significantly increased following induction of autophagy.

Conclusion: Our current data indicate that SF contribute to the autoimmunity in RA through citrullination of vimentin and its interaction with MHC class II promoted by autophagy.

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Abstract Number: 1058

Doxycycline Directly Scavenges Reactive Oxygen Species and Inhibits the Formation of Malondialdehyde-Acetaldehyde-Protein Adducts – a Novel Mechanism of Action for an Old Drug

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Background/Purpose: Oxidative stress plays a role in the progression of inflammatory diseases such as Rheumatoid Arthritis (RA) due to the imbalance between levels of reactive oxygen species (ROS) and endogenous antioxidant defense mechanisms. Resulting from oxidative stress, Malondialdehyde-Acetaldehyde-protein adduct (MAA) formation is increased in RA joint tissues where these co-localize with citrullinated proteins, acting as potent immune adjuvants. Doxycycline (DOX) and other tetracycline derivatives demonstrate efficacy in the treatment of RA. Interestingly, this clinical benefit does not appear to stem from their antibacterial properties, and the anti-inflammatory properties of DOX are currently unknown. Therefore, we tested the hypothesis that DOX directly scavenges ROS and inhibits the formation of redox-mediated MAA-adduct formation.

Methods: To test whether DOX inhibits the formation of MAA-Albumin, a cell-free system was used by adding DOX to human serum albumin (ALB) in the presence of 2mM malondialdehyde (MDA) and 1mM acetaldehyde (AA). MAA-

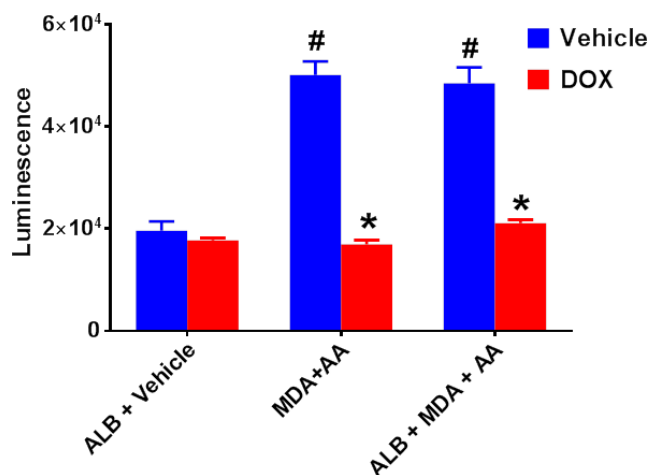


Figure 1.

ALB formation was monitored by autofluorescence at 498 nm. Electron paramagnetic resonance(EPR) was used to quantify free radical production and superoxide scavenging in the presence/absence of DOX. HEK 293cells transfected with the nuclear factor erythroid 2-relatedfactor/antioxidant response element (Nrf2/ARE) were used to determine whether DOX alters intracellular redox signaling pathways activated by MAA-adduct generation. Nrf2 activation was quantified by measuring the amount of luciferase via cellular luminescence.

Results: Cell-free studies showed that DOX reduced MAA-adduct formation at all time points investigated ($p < 0.0001$). EPR revealed that DOX significantly inhibited free radical production related to MAA-adduct formation and scavenged superoxide($p < 0.0001$ vs. sham). Finally, incubation of AA, MDA and/or ALB increased Nrf2 activation (Figure 1), an effect that was significantly reduced($p < 0.001$) in the presence of DOX.

Conclusion: DOX, a drug used sparingly in the management of RA and other chronic inflammatory diseases, scavenges ROS produced in the process of MAA-adduct formation. Additionally, DOX inhibits MAA-induced Nrf2 activation, a redox-sensitive transcription factor, thus demonstrating its ability to alter intracellular redox signaling. Together, these data strongly indicate a novel antioxidant property of DOX that could explain its clinical benefit in the context of select chronic inflammatory conditions that are characterized by oxidative stress.

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Abstract Number: 1059

Differentially-Utilized Transcription Factors and Enhancers in Rheumatoid Arthritis (RA) Fibroblast-like Synoviocytes

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Background/Purpose: RA fibroblast-like synoviocytes (FLS) display a unique aggressive phenotype with a distinct epigenetic profile marked by altered chromatin accessibility. We hypothesized that differentially utilized transcription factors (TFs) and/or promoters correlating with open chromatin regions may contribute to RA FLS behavior. We utilized ATAC-sequencing data to compare regions of open chromatin in RA FLS that are the most different when compared to OA. This filter allowed us to identify DNA sequence motifs of TFs most likely to account for RA-specific cell functions.

Methods: ATAC-seq data from the FLS derived from RA and OA arthroplasty samples and differences corresponding to chromatin accessibility were identified using DiffBind. Loci were filtered for those present in all 11 RA samples but $\leq 5/10$ OA samples or loci present in ≥ 5 RA samples but in ≤ 1 OA sample (and vice versa) to identify the extremes of RA-OA differences. These loci were then analyzed for DNA sequence biases using MEME (Multiple EM for Motif Elicitation). Identified motifs were compared to known TFs found in multiple databases using Tomtom. Motifs were identified with high confidence if they corresponded with known patterns in all databases and expressed in FLS.

Results: Multiple relevant TFs motifs were associated with the extremes of RA-OA chromatin accessibility differences. Motifs for KLF4 and the E2F family of TFs were identified and among the most highly significant. The motif for the E2F family of TFs was identified in 159/575 total sites where chromatin was more open in the RA vs OA samples (MEME $e = 1.2e-64$, HOCOMOCO $q = 2.2e-2$). There were 84 genes found within 1000 kb of these 159 sites, and of these, 9 sites were found within gene bodies. RNA-seq was then utilized to identify which genes associated with E2F family binding sites in open chromatin are differentially expressed. Seven of these genes were associated with significant differential expression (CRYBG3, Metazoa_SRP, ANGPTL2, ITGB3, PMP22, GLS and U4; $q < 0.05$). The motif for the KLF family of TFs was identified in 18/1156 total sites where chromatin was more open in the OA vs RA samples (MEME $e = 3.4e-2$, TFBSshape $q = 0.19$). There were 18 genes identified within 1000 kb of these 1156 sites, and of these, 7 sites were found within gene bodies. None of these were differentially expressed.

Conclusion: Using differences in chromatin access we identified TFs that are associated with neighboring genes with differential expression that distinguish RA from OA. Protein coding genes identified by this approach include proteins involved with cell adhesion that could participate in the pathogenesis of RA.

Disclosure: J. Mills, None; G. S. Firestein, Janssen Pharmaceuticals, 2, 5; B. Pedersen, None.

Abstract Number: 1060

Variation in the Synovial Fluid Metabolome According to Disease Activity in Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic, inflammatory disease characterized by persistent inflammation and joint damage with a heterogeneous course and different pathogenic mechanisms. Metabolomics, defined as the comprehensive analysis of the small-molecule metabolites in a biological system, is a rapidly developing biomedical research area. This study was to investigate metabolic perturbation in the synovial fluid (SF) of RA patients according to the degree of disease activity using gas chromatography/time-of-flight-mass spectrometry (GC/TOF-MS) to gain more insight into the pathologic metabolic alterations in RA.

Methods: We included 47 patients with diagnosed active RA (15 male, 32 female). Disease activity was assessed using DAS28-ESR. SF metabolomic profiling was performed using GC/TOF MS, in conjunction with multivariate statistical analyses and pathway analyses such as metabolite set enrichment analysis (MSEA).

Results: A total of 125 metabolites were identified from SF of RA, which were classified into various chemical classes, such as amino acids (21% of identified metabolites), organic acids (21%), sugar and sugar alcohols (18%), fatty acids (14%), amines (9%), and phosphates (5%).

We indicated statistical significant correlation between DAS28-ESR value and the intensities of 12 metabolites (β -alanine, asparagine, citrate, cyano-L-alanine, indol-3-lactate, leucine, nicotinamide, citrulline, methionine, oxoproline, salicylaldehyde, and glycocyamine). The intensities of glycocyamine and indol-3-lactate positively correlated with DAS28-ESR value ($\rho = 0.311$, $p = 0.017$; $\rho = 0.345$, $p = 0.033$). On the other hand, β -alanine, asparagine, citrate, cyano-L-alanine, leucine, nicotinamide, citrulline, methionine, oxoproline, and salicylaldehyde negatively correlated with DAS28-ESR.

To investigate whether metabolism is affected by disease activity in RA, we have performed MSEA and metabolic pathway analysis by using MetaboAnalyst. We found that the higher the disease activity, the more amino acid metabolic processes were affected. In MSEA, we found six unique pathways, namely, fructose and mannose degradation, phenylalanine and tyrosine metabolism, citric acid cycle, galactose metabolism, tryptophan metabolism and pyrimidine metabolism that were significantly associated with disease activity in RA.

Conclusion: Synovial metabolite perturbations, especially perturbation in amino acid metabolism, are suggested to be correlated with disease activity of RA. SF metabolomic approaches based on GC/TOF-MS can provide important information relating to monitor disease activity in RA and be important approach to understanding the altered metabolism and pathophysiology of RA.

Disclosure: J. K. Ahn, None; J. Hwang, None; J. Lee, None; E. M. Koh, None; H. S. Cha, None.

Serum Metabolomic Profiling Predicts Synovial Gene Expression in Rheumatoid Arthritis

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Background/Purpose: Metabolomics is an emerging field of biomedical research that may offer a better understanding of mechanisms underlying conditions that could include inflammatory arthritides. Perturbations caused by inflamed synovial tissue can lead to correlated changes in concentration of certain metabolites in the synovium and thereby function as potential biomarkers in blood. Here, we explore the hypothesis of whether characterization of patients' metabolomic profiles in blood, utilizing ¹H-nuclear magnetic resonance (NMR), predicts synovial cytokine profiling in rheumatoid arthritis (RA).

Methods: Nineteen active seropositive RA patients on concomitant methotrexate were studied. One of the involved joints was a knee or a wrist appropriate for arthroscopy. A Bruker Avance 700 MHz spectrometer was used to acquire NMR spectra of serum samples. Gene expression in synovial tissue obtained by arthroscopy was analyzed by real-time PCR. Data processing and statistical analysis were performed in Python and SPSS.

Results: Analysis of the relationships between each synovial cytokine-serum metabolite pair, using linear regression and controlling for age and gender, revealed significant clustering structure in these data. We observed an association of serine/glycine/phenylalanine metabolism and aminoacyl-tRNA biosynthesis with lymphoid cell gene signature. Alanine/aspartate/glutamate metabolism and choline derived metabolites correlated with TNF- α synovial expression. Circulating ketone bodies were associated with gene expression of synovial metalloproteinases. Discriminant analysis identified serum metabolites that classified patients according to their synovial cytokine levels.

Conclusion: The relationship between serum metabolite profiles and synovial biomarker profiling suggests that NMR may be a promising tool for predicting specific pathogenic pathways in the inflamed synovium of RA patients.

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Linking Systemic Angiogenic Markers to Synovial Vascularization in Rheumatoid Arthritis

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Background/Purpose: Neoangiogenesis is a crucial event to promote the development of the hyperplastic proliferative pathologic synovium in Rheumatoid arthritis (RA). Ultrasound (US) is sensitive for detection of power Doppler (PD) vascularization. Our aim was to explore the associations between a set of complementary circulating angiogenic markers reflecting different angiogenic processes and a comprehensive US assessment in patients with RA.

Methods: Serum levels of eight angiogenic markers (Vascular Endothelial Growth Factor (VEGF), Placenta Growth Factor (PlGF), Tie-2, Angiopoietin-1, soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1), Interleukin-8 (IL-8, CXCL8), CYR61 (CCN1) and Angiostatin), reflecting endothelial cell activation, proliferation, survival, growth and migration, as well as vessel maturation and stabilization, were measured by quantitative ELISAs in a total of 125 patients with RA, who were all systematically assessed in parallel by PDUS, performed on 32 joints.

Results: Synovitis was detected in 84 patients with RA (67.2%). Among these patients, 53 patients (42.4%) had positive Doppler signal, including 31 with moderate to marked hyperemia. Serum levels of soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1) (808 ± 293 ng/mL vs. 697 ± 240 ng/mL, $P=0.022$) and Tie-2 (16.2 ± 7.5 ng/mL vs. 13.8 ± 4.9 ng/mL, $P=0.038$), were more likely to be increased in patients with synovial hyperemia detected on at least one joint (Power Doppler grade ≥ 1). sVCAM-1, Tie-2 and Angiostatin concentrations gradually increased together with the grade of the semiquantitative PDUS scale and concentrations of these three markers were markedly increased in patients with moderate to marked hyperemia (Power Doppler grade 2 and 3). Levels of sVCAM-1 ($r=0.20$, $P=0.028$), Tie-2 ($r=0.28$, $P=0.001$), and Angiostatin ($r=0.25$, $P=0.006$) correlated with a global arthritis sum score, defined by the sum of the semiquantitative PDUS scores for all joints examined.

Among the 81 patients with a DAS28-CRP ≤ 3.2 , 22 patients had synovial hyperemia detected on at least one joint (Power Doppler grade 1 in 13 patients, grade 2 in 6 patients and grade 3 in 3 patients). Patients with synovial hyperemia on at least one joint were more likely to have significantly increased levels of PlGF (18.9 ± 11.2 pg/mL vs. 13.1 ± 9.5 pg/mL, $P=0.022$) and Tie-2 (15.7 ± 5.8 ng/mL vs. 12.6 ± 3.4 ng/mL, $P=0.004$) than patients with absence of synovial hyperemia.

Conclusion: Serum levels of the angiogenic markers Tie-2, sVCAM-1 and Angiostatin were strongly associated with synovial vascularization and inflammation assessed by PDUS among patients with established RA. Moreover, Tie-2 and PlGF were associated with persistent disease activity in RA patients in low disease activity. These findings suggest that it may be possible to find surrogate serum angiogenic biomarkers of active synovitis that might replace PDUS examination, in case of further confirmation of their pertinence.

Disclosure: A. Leblond, None; S. Pezet, None; A. P. Trouvin, None; M. Elhai, None; V. Gonzalez, None; Y. Allanore, None; J. Avouac, None.

Abstract Number: 1063

Role of Mitochondrial-Bound HK2 in Rheumatoid Arthritis Fibroblast-like Synoviocytes

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Background/Purpose: Hexokinases (HKs) catalyze the first step in glucose metabolism. HK2 constitutes the principal inducible isoform with a restricted distribution in normal adult tissues. Fibroblast-like synoviocytes (FLS) are a key component of rheumatoid arthritis (RA) invasive synovium, and display unique aggressive features, including increased migration and invasion. We have recently showed a critical role of glucose metabolism and specifically of HK2 in RA FLS phenotype. Of interest, HK2 localizes not only in the cytosol but also at mitochondria and protects mitochondria against apoptosis. We hypothesize that mitochondrial-bound HK2 is key regulator of RA FLS phenotype.

Methods: HK2 localization at baseline and after RA FLS activation with platelet derived growth factor (PDGF, 10ng/ml) was evaluated by cell fractionation and western blot (WB), and confocal microscopy. RA FLS were infected with GFP, full-

length (FL)-HK2 or HK2 lacking its mitochondrial binding motif (HK2ΔN) expressing adenovirus (ad). RA FLS were also incubated with methyljasmonate (MJ, 2.5mM), which dissociates HK2 from mitochondria. FLS function in medium and PDGF stimulated cells was evaluated by measuring 1) migration of cultured FLS monolayers (scratch assay); 2) in vitro invasion assay using matrigel. For arthritis experiments, mice were injected with K/BxN sera on day 0. MJ (25mg/kg) was injected daily i.p. beginning on day 0 after serum administration or starting at the peak of arthritis (from day 5). Clinical arthritis scores were serially assessed. Joint histology was evaluated using a semiquantitative scoring system.

Results: 30 minutes after PDGF stimulation, cell fractionation and confocal microscopy revealed that PDGF induced the translocation of HK2 to the mitochondrial fraction. Overexpression of the HK2 mutant reversed the invasive phenotype induced by full-length HK2 after PDGF stimulation, and also FLS migration rate, GFP-ad: 101.2 ± 12.69 ; FL-HK2-ad: 135.7 ± 38.88 ; HK2ΔN-ad 112.6 ± 35.72 (FL-HK2-ad vs. HK2ΔN-ad: $p < 0.01$). MJ treatment also significantly reduced RA FLS invasion from 46.79 ± 8.961 to 22.45 ± 7.48 ($p < 0.001$) and migration rate from 253 ± 14 to 152 ± 6 ($p < 0.001$) after PDGF stimulation. Finally, MJ treatment significantly decreased arthritis severity. Day 10 scores were 4.8 ± 0.9 and 1.2 ± 0.58 ($P < 0.01$) for vehicle and MJ-treated mice respectively, when mice were treated from day 0 after serum administration, and 12.5 ± 0.5 and 9.2 ± 0.663 ($p < 0.05$) for vehicle and MJ-treated mice when mice were treated from day 5. Joint histology scores for vehicle and MJ-treated mice from day 0 were: for inflammation 0.9 ± 0.821 and 0.4 ± 0.42 ($p < 0.05$), bone erosion scores were 1.5 ± 0.61 and 0.3 ± 0.45 ($p < 0.01$), and cartilage damage scores were 1.9 ± 0.42 and 0.3 ± 0.45 ($p < 0.01$), respectively.

Conclusion: Our results suggest that mitochondrial HK2 is key regulator of aggressive FLS phenotype, which contributes to joint destruction in RA. Targeting HK2, as an isoform-specific contributor to RA FLS phenotype, offers a safer approach than global glycolysis inhibition. Other possible strategy to improve selectivity would be to target HK2 binding to the mitochondria.

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Identification of a Panel of Circulating Proteins Associated to Synovial Pathotypes in Early Rheumatoid Arthritis Patients

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Background/Purpose: Rheumatoid arthritis (RA) is characterized by high clinical variability and an underlying cellular and molecular heterogeneity. Efforts to find tools for the classification of disease phenotypes and patient stratification are key to develop tailored therapies and improve RA management. According to this, specific pathological phenotypes of synovial tissue (pathotypes) have arisen as possibly associated to diverse clinical evolution and response to therapy (Humby et al., 2017). In the present work, we aimed to identify signatures of circulating proteins that correlate with the synovial pathotype in patients with RA.

Methods: A proteomic analysis was carried out on samples from patients enrolled in the Pathobiology of Early Arthritis Cohort (PEAC). Ultrasound-guided synovial biopsies allowed their classification into three groups according to the phenotype of the synovial tissue (lymphoid, myeloid or fibroid), as described previously (Pitzalis et al., 2013). The study was performed using 54 serum samples at baseline: 22 of lymphoid phenotype (L), 18 myeloid (M), and 14 fibroid (F). Sera were depleted from the most abundant proteins by affinity chromatography to remove background, and analysed by reversed-phase nanoliquid chromatography coupled to mass spectrometry using a SWATH strategy and a triple TOF MS (Sciex). The quantitative data were processed using the ProteinPilot 5.0.1 and PeakView 2.1 software (Sciex). A two-stage support vector machine (TSSVM) with RBF kernel and 10 cross-fold validation was applied using the Classyfire, e1071 and caret R packages.

Results: The proteomic analysis led to the identification and quantification of 229 proteins. The screening analysis was performed on the data obtained from a first group of 30 samples (Train set: 10 L, 10 M and 10 F). Data were pre-

processed by PCA for dimension reduction. Then, application of machine learning tools led to the identification of a panel of 11 proteins whose different abundance is associated with a specific phenotype of the synovial tissue (either Lymphoid, Myeloid or Fibroid) in rheumatoid arthritis patients. Table 1 shows the most relevant metrics obtained with this analysis. A very high accuracy and Kappa coefficient were achieved using this classification tool. The results were then confirmed on an independent validation set of 24 samples (12 L, 8 M and 4 F) with also good performance. This protein signature allowed the correct classification of the samples into the three pathotypes with very high sensitivity and specificity.

Table 1. Metrics of the performance of the 11-protein panel to classify the synovial pathotype of the patient. Cut-off for significance was p-value < 0.05.

Train set				Classes in the train set			
Accuracy	0.9667	95% CI	(0.8278 - 0.9992)	Sensitivity/ Specificity	Fibroid	Lymphoid	Myeloid
					1.000/1.000	1.000/ 0.9524	0.9091/ 1.000
Kappa	0.95	P-Value	4.48E-09	Pos/Neg Pred Value	1.000/ 1.000	0.9000/ 1.000	1.000/ 0.9500
					Classes in the validation set		
Accuracy	0.875	95% CI	(0.6764 - 0.9734)	Sensitivity/ Specificity	Fibroid	Lymphoid	Myeloid
					1.000/ 0.9524	0.8462/ 0.9091	0.8750/ 0.9375
Kappa	0.7907	P-Value	0.0005881	Pos/Neg Pred Value	0.7500/ 1.000	0.9167/0.8333	0.8758/0.9375

Conclusion: We have identified a signature of 11 circulating proteins associated with synovial pathotypes in RA patients. The putative correlation of this protein profile with the clinical evolution and/or response to therapy of the patients remains to be elucidated.

Disclosure: C. Ruiz-Romero, None; F. Picchi, None; P. Fernández, None; L. González, None; R. Hands, None; V. Calamia, None; M. Camacho, None; C. Bessant, None; C. Pitzalis, None; F. J. Blanco, None.

Abstract Number: 1065

Artesunate Can Synergize with Methotrexate on Inhibiting Migration and Invasion of Fibroblast-like Synoviocytes from Patients with Rheumatoid Arthritis

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Background/Purpose: Fibroblast-like synoviocytes (FLS) play important roles on joint destruction in rheumatoid arthritis (RA). Recent reports showed that antimalaria drug artesunate presents anti-cancer potential by suppressing cancer cells invasion and metastasis. We have found that artesunate could inhibit migration and invasion of RA-FLS as well as MMP-2/9 expression. Methotrexate (MTX) is the anchor drug for RA treatment. Here we aimed to investigate the synergistic effect of artesunate with MTX on inhibiting aggressive ability of RA-FLS.

Methods: Synovial tissues were obtained by closed needle biopsy from 6 active RA patients and FLS were isolated. Primary RA-FLS were cultured in vitro and pretreated with 60 μ M artesunate, 10nM MTX, or combination of 60 μ M artesunate and 2.5nM~10nM MTX respectively for indicated times. Their effects on cell viability and proliferation were measured by CCK-8 assay, while effects on migration and invasion capacity of RA-FLS were detected by wound healing and transwell assays. Differential expression of MMP-2/9 and tissue inhibitors of metalloproteinases (TIMP) -1/2 were detected by quantitative real-time PCR, western blot and ELISA.

Results: (1) Compared with untreated group, 60 μ M artesunate, 10nM MTX or combination of 60 μ M artesunate and 2.5nM~10nM MTX showed no significant effect on cell viability and proliferation of RA-FLS for 72 hours (Fig 1A). (2) Both 60 μ M artesunate and 10nM MTX alone significantly inhibited migration and invasion of RA-FLS. The combination of 60 μ M artesunate and 7.5nM MTX had stronger inhibitory effect on migration and invasion than 60 μ M artesunate or 10nM

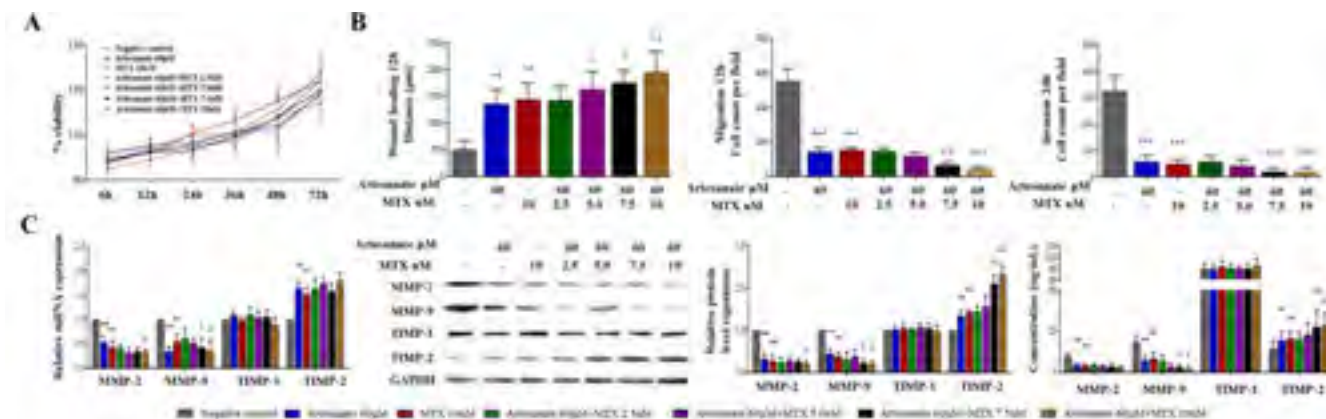


Figure 1 Effects of artesunate and MTX on primary RA-FLS. **A** Effects of 60μM artesunate, 10nM MTX or combined of 60μM artesunate and 2.5nM–10nM MTX on viability and proliferation of primary RA-FLS was measured by CCK-8 assays at 6, 12, 24, 36, 48 and 72 hours. **B** Effects of combined treatment with artesunate and MTX on migration and invasion capacity of primary RA-FLS was measured by wound healing and transwell assays. **C** Effects of combined treatment with artesunate and MTX on the expression of MMP-2, MMP-9, TIMP-1 and TIMP-2 in primary RA-FLS were measured by quantitative real-time PCR, western blot and ELISA. Bar are representative as means ± SD from six RA patients. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, compared with RA-FLS without any treatment. $\Delta P < 0.05$, $\Delta\Delta P < 0.01$, compared with RA-FLS treatment with 10nM MTX.

MTX alone (Fig 1B). (3) Both 60μM artesunate and 10nM MTX alone significantly inhibited MMP-2/9 expression but promoted the expression of TIMP-2. The combination of 60μM artesunate and 7.5nM MTX had stronger effect on regulating MMP-9 and TIMP-2 than 60μM artesunate or 10nM MTX alone (Fig 1C).

Conclusion: Artesunate can synergize with MTX on inhibiting migration and invasion of primary RA-FLS by inhibiting MMP-9 and promoting TIMP-2 expression, which implies the potential of combination therapy of artesunate and MTX for RA.

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Abstract Number: 1066

Tocilizumab Effect on Serum Angiogenic Factors in Rheumatoid Arthritis Patients

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SESSION INFORMATION

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Background/Purpose: Several inducers of angiogenesis have been shown to play a central role in rheumatoid arthritis (RA) pathogenesis: VEGF (Vascular Endothelial Growth Factor), EMMPRIN (Extracellular Matrix Metalloproteinase Inducer), a transmembrane immunoglobulin which stimulates secretion of MMPs (Matrix Metalloproteinases); and NGAL (Neutrophil Gelatinase-Associated Lipocalin), a pro-inflammatory adipokine which binds MMP9 and inhibits its degradation, but which has also anti-inflammatory properties. IL-6 blockade by Tocilizumab (TCZ), an effective treatment for RA, may inhibit angiogenesis.

Aim: To explore the effect of TCZ treatment on serum levels of the above pro-angiogenic factors in RA patients compared to healthy controls (HC).

Methods: Clinical data and blood samples were collected from 40 active RA patients and 40 age and sex-matched HC. Serum levels were analyzed for high sensitivity C-Reactive Protein (hsCRP), VEGF, EMMPRIN, MMP-9 and NGAL by Enzyme-Linked Immunosorbent Assay (ELISA) before initiation of TCZ treatment and 4 months following treatment in the RA group compared to HC. Student's t-test was used for analysis of EMMPRIN, MMP-9, and NGAL levels and Mann-Whitney Test and Pearson Chi-square Test were used for analysis of VEGF levels. Results were considered statistically significant for p values ≤ 0.05 .

Results: The majority of the patients responded to TCZ treatment and reduced their disease activity scores (DAS) from DAS28 score of 5.45 ± 1.06 to 3.46 ± 1.37 ($p < 0.0001$). The levels of hsCRP were higher in RA patients than in HC and decreased 4 months after initiation of TCZ treatment (3.37 ± 2.0 , 0.74 ± 1.36 mg/dl, $p < 0.001$). EMMPRIN levels were higher in RA patients than HC (43.55 ± 10.77 ng/ml, 34.44 ± 10.00 ng/ml respectively, $p < 0.0002$) and were reduced significantly following initiation of treatment (40.01 ± 8.43 ng/ml, $p < 0.006$). VEGF levels were very low, and therefore separated into two groups (equal to 0, above 0 pg/ml), 15% of RA patients had detectable levels as compared to 41% of HC ($P < 0.01$) and it did not change significantly following 4 months of treatment. Interestingly, serum NGAL levels were higher in HC than RA patients (91.78 ± 31.44 ng/ml, 73.21 ± 20.80 ng/ml, respectively $p < 0.003$), and increased in the RA group following TCZ treatment (85.27 ± 28.9 ng/ml, $p < 0.001$). Similarly, MMP-9 levels were higher in the serum of HC than RA patients (119.76 ± 45.49 ng/ml, 75.85 ± 47.47 ng/ml, respectively, $p < 0.0001$) but were not affected by TCZ (75.89 ± 44.91 ng/ml, $p < 0.84$).

Conclusion: Our results demonstrate that IL-6 pathway blockade using TCZ was effective in reducing the serum level of EMMPRIN in RA patients, implying its clinicopathologic role in the disease pathogenesis. Our results suggest that IL-6 blockade did not affect serum VEGF, NGAL and MMP-9 levels, either because they are active at the joint level and not peripherally, or because NGAL may play an anti-inflammatory role in RA, so that IL-6 blockade increased its levels. Future studies may help elucidate the site of action and mechanism of action of the various pro-angiogenic factors in RA pathogenesis.

Disclosure: M. Elias, None; M. A. Rahat, None; J. Feld, None; I. Rosner, None; L. Kaly, None; I. Lavi, None; T. Gazitt, None; D. Zisman, None.

Abstract Number: 1067

Simulating the Pathogenesis of Arthritis in Vitro By Developing a Human-Based Multicomponent 3D Joint Model

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Background/Purpose: Although arthritis is a matter of research since more than 140 years, there is currently no valid 3D model available, which is able to mimic an inflamed joint. Thus, our ultimate goal is to develop a valid human *in vitro* 3D joint model in order to simulate arthritis. The model will contain all involved tissue components and cell types enabling the interactions between cells by cell contacts, signaling molecules and metabolites. As an alternative experimental setup for traditional animal models, our *in vitro* model will enable us to study the influence and efficacy of drug treatment. To this end, we firstly developed all single components of the joint, namely the (1) osteogenic and (2) chondrogenic part, (3) the joint space with synovial fluid and (4) the synovial membrane, separately.

Methods: The osteogenic component was synthesized by seeding human bone marrow-derived mesenchymal stromal cells (hMSC) on β -tricalcium phosphate (TCP) coated with an additional hMSC monolayer cell-sheet and cultured for a total of 6 weeks. Survival, adhesion and structural integrity of the cells were evaluated by Scanning Electron Microscopy (SEM), LIVE/DEAD staining and cellular release of LDH. Osteogenic differentiation was analyzed both by μ CT for mineralization and on gene expression level using qPCR. To mimic the chondrogenic part, a scaffold-free 3D cartilage construct was generated by chondrogenic differentiation of hMSC with intermittent mechanical stimulation. Constructs were analyzed by histology and qPCR. Non-animal stabilized hyaluronic acid was used to simulate the synovial fluid component. In order to model the synovial membrane, hMSC were differentiated towards the fibroblast lineage and then a confluent layer was formed on a polycarbonate membrane, which was visualized by histology.

Results: We developed an *in vitro* 3D osteogenic model by successfully seeding hMSC on a β -TCP scaffold. Cells consistently adhere onto the scaffold for up to 6 weeks as observed by SEM. The analysis of cell viability via LDH detection and LIVE/DEAD staining showed no toxic effects on the cells as compared to the corresponding control. Osteogenic differentiation of

hMSC grown in 3D was verified demonstrating an increase in mineralized bone volume and the induction of bone-related gene expression (*RUNX2*, *SPPI* and *COL1A1*) as compared to the corresponding control. Chondrogenic phenotype was verified by HE and Alcian Blue staining as well as by the reduced expression of *COL1A1* and an abundant expression of *COL2A1*. Interestingly, co-cultivation of the osteogenic and chondrogenic part for up to 3 weeks demonstrated successful colonization, connectivity and initial calcification implying a functional transitional bridging area. Modelling the synovial membrane, we successfully and reproducibly created a confluent monolayer of hMSC, which is easily transferable to the model.

Conclusion: In summary, we confirmed and validated in a standardized manner phenotypic integrity and stability of each single component. To finalize the development of healthy joint model we will combine the established parts to provide suitable 3D joint model that enables us to study the efficacy of drug treatment *in vitro*.

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Abstract Number: 1068

Characterization of the Role of Endocannabinoid System Using Jwh-133, a Selective Cannabinoid CB2 Receptor Agonist, in IL-1 β -Induced Inflammation in Human Rheumatoid Arthritis Synovial Fibroblasts

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SESSION INFORMATION

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Background/Purpose: The endocannabinoid system (ECS) is comprised of two evolutionary conserved cannabinoid receptors 1 and 2 (CB1 and CB2) which participate in pain management through G_{ai/o} mediated signaling. Recent studies show that the expression of CB2, not CB1, is upregulated at both the mRNA and protein levels in rheumatoid arthritis synovial fibroblasts (RASFs) as compared to normal synovial fibroblasts, however, the role the ECS receptors in pro-inflammatory cytokine signaling in RASFs remains poorly understood. In the present study, we used a selective agonist of CB2 (JWH-133) to characterize the role of CB2 activation in interleukin-1 β (IL-1 β)-induced inflammation in human RASFs.

Methods: Human RASFs were obtained from patients diagnosed with RA according to the ACR guidelines (8 female, 2 male, average age 47.7 \pm 5.7 years). Human RASFs were pre-treated with JWH-133 (10-20 μ M) for 10 minutes prior to the addition of IL-1 β (10 ng/mL) stimulation for 30 minutes for signaling studies or for 24 hours to evaluate the inflammatory mediators. The role of CB2 in IL-1 β signaling was examined by employing a small interfering RNA (siRNA) method or using overexpression plasmid specific for CB2. Conditioned media was used for the quantification of IL-6 and IL-8 by ELISA and cell lysates were prepared for the analysis of IL-1 β signaling proteins and nuclear translocation of transcription factors NF- κ Bp65 or AP-1 using Western immunoblotting. To study protein-protein interactions, RASFs treated with JWH-133 or IL-1 β were incubated with TAK-TAB_V5 protein. Associated partners were pulled down by immunoprecipitation of V5 beads and analyzed using a Western blotting method.

Results: Pretreatment of JWH-133 exacerbated IL-1 β -induced IL-6 and IL-8 production by 21% and 12%, respectively, in human RASFs (p<0.05; n=3). Furthermore, we observed that JWH-133 selectively increased the expression of IL-1 β -induced Cox-2 by >2-fold (p<0.05; n=3), suggesting a proinflammatory role of CB2 in IL-1 β signaling in human RASFs. Knockdown of CB2 using siRNA inhibited IL-1 β -induced IL-6 and IL-8 production by more than 50% and completely abrogated Cox-2 expression in RASFs (p<0.05; n=3). In contrast, the overexpression of CB2 further increased IL-1 β -induced IL-6 and IL-8 by approximately 3-fold and 4-fold, respectively (p<0.05; n=3), confirming its proinflammatory role in RASF mediated pain and inflammation. Analysis of immunoprecipitation studies revealed that CB2 associates with active TAK1 upon JWH-133 stimulation to coordinate with IL-1 β signaling pathways as observed with an increased nuclear translocation of NF- κ Bp65 and AP-1.

Conclusion: Our study provides novel evidence that CB2 elicits proinflammatory role in IL-1 β signaling in RASFs and suggests CB2 as a potential therapeutic target in the management of pain and inflammation in RA.

Disclosure: S. Fechtner, None; A. K. Singh, None; S. Ahmed, None.

Non-Receptor Protein Tyrosine Phosphatase 14 (PTPN14) Promotes YAP-Dependent Tgfbeta Signaling in RA FLS

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Background/Purpose: Non-Receptor Protein Tyrosine Phosphatase 14 (PTPN14) was identified in a phosphatase expression profile survey to be highly expressed in synovial fibroblasts derived from patients with rheumatoid arthritis (RA FLS). PTPN14 is a negative regulator of transcriptional co-activator YAP -a key Hippo pathway player- in cancer cells. Here we aimed to investigate the role of PTPN14 in RA FLS.

Methods: Gene expression level in RA FLS and FLS from osteoarthritis patients (OA FLS) was measured by qPCR. Specific gene knockdown was achieved using antisense oligonucleotides. PTPN14, YAP and SMAD3 protein expression levels were visualized in Western blotting and immunofluorescence. Immunoprecipitation was used to detect protein-protein interaction. The passive K/BxN arthritis and RA FLS/cartilage co-implantation models were used to assess effects of chemical inhibition of YAP.

Results: RA FLS displayed TGFbeta-dependent overexpression of PTPN14 compared to OA FLS ($p < 0.01$). PTPN14 knockdown in RA FLS impaired TGFbeta-dependent expression of matrix metalloproteinase 13 ($p < 0.05$) and potentiation of inflammatory cytokine signaling. In RA FLS, PTPN14 forms a complex with YAP, promoting TGFbeta-dependent YAP and SMAD3 nuclear localizations. Chemical inhibition of YAP inhibited RA FLS pathogenic behavior and ameliorated arthritis severity *in vivo* ($p < 0.0001$).

Conclusion: In RA FLS, TGFbeta-dependent PTPN14 overexpression acts as a positive feedback TGFbeta-signaling regulator. Surprisingly, in RA FLS PTPN14 enhances nuclear YAP-mediated promotion of SMAD signaling. YAP promotes a wide range of RA FLS pathogenic behaviors, pointing to the Hippo pathway as a potential important regulator of RA FLS and a player in RA pathogenesis.

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Seroreactivity Against Recombinant Citrullinated Myosin Is Associated with Measures of Diastolic Dysfunction in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

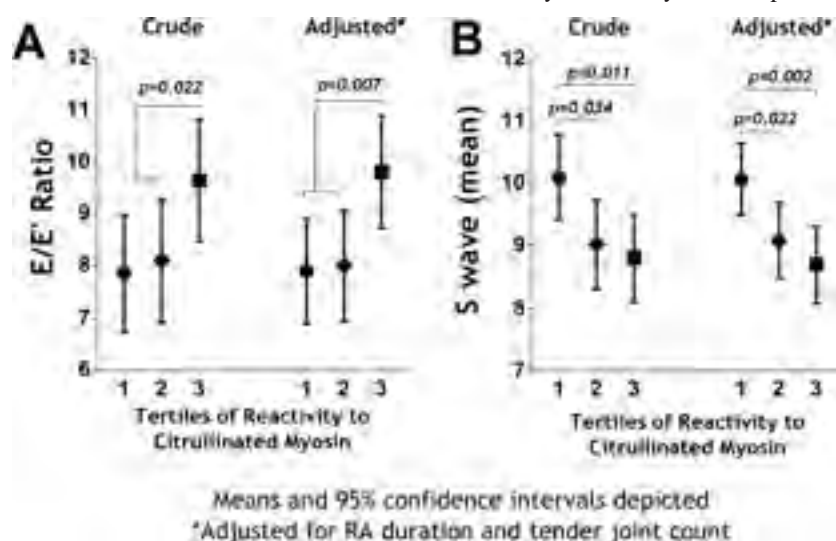
Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster II

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

Background/Purpose: Diastolic dysfunction and heart failure with preserved EF are more prevalent in RA. We have previously shown increased staining for citrullinated substrates in necropsied hearts of RA patients. We hypothesized that individuals with RA may generate antibodies against citrullinated myocardial proteins and that such antibodies may be associated with left ventricular (LV) dysfunction.

Methods: 59 sera from RA patients enrolled in a cohort study were incubated with uncitrullinated or citrullinated (exposed topeptidyl-arginine-deiminase-2 [PAD-2]) myocardial proteins (actin, myosin, tropomyosin, and troponin). Fluorescent anti-human IgG Fc antibody was added, rinsed, and mean fluorescence intensities (MFI) were recorded. Demographics, RA characteristics, and measures of LV function were compared between highest and lowest MFI tertiles for each protein in both citrullinated and uncitrullinated forms. The associations of anti-myocardial antibodies with measures of cardiac function, assessed by 3D echocardiography, were modeled using generalized linear models, adjusting for relevant confounders (variables associated with both LV function and seroreactivity to anti-myocardial proteins).



Results: Patients era with the highest tertile of seroreactivity against citrullinated (but not uncitrullinated) myosin showed multiple differences ($p < 0.05$) in measures of diastolic function: E/A ratio (0.95 vs 1.05), mean S wave (8.80 vs 10.09) and E/E' ratio (9.64 vs 7.86) all indicated better diastolic function for patients in the lowest tertile. Systolic function between the seroreactivity tertiles was not different. Levels of other myocardial protein antibodies were not associated with diastolic function with the exception of S wave for citrullinated tropomyosin ($p = 0.021$). Multivariable analyses showed that the diastolic parameters E/E' ratio and S wave (mean) remained significantly associated after controlling for RA duration and Tender Joint Count, previously identified potential confounders (Fig. 1).

Conclusion: These data suggest that RA patients may generate antibodies against citrullinated myosin and that this may contribute to myocardial dysfunction in RA. Analyses of additional patient sera and ultimately verifying this observation in human myocardial tissue are needed.

Fig. 1: E/E' ratio and S wave (mean) by tertiles of reactivity to citrullinated myosin.

E/E' ratio and S wave (mean) are echocardiographic parameters that are increased (E/E' ratio) and decreased (S wave [mean]) in diastolic dysfunction

Disclosure: C. Geier, None; J. Fert-Bober, None; J. T. Giles, None; C. Russo, None; S. Bokhari, None; A. Tugcu, None; J. Van Eyk, None; J. Bathon, None.

Protective Role of the Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Rs2495477 Polymorphism in Patients with Rheumatoid Arthritis

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Background/Purpose: RA is associated with the development of cardiovascular (CV) disease and subclinical atherosclerosis, which leads to an increased risk of CV mortality in RA patients¹. The presence of carotid plaques assessed by ultrasonography studies is a surrogate marker for subclinical atherosclerosis². Proprotein convertase subtilisin/kexin type 9 (PCSK9) is involved in homeostasis of cholesterol, a traditional CV risk factor related to RA and atherosclerosis^{1,3}. *PCSK9* polymorphisms can both increase and decrease the risk of CV disease in patients with atherosclerosis³. However, there are no information on *PCSK9* polymorphisms in RA. In the present study, we assess the role of several *PCSK9* polymorphisms in RA as well as determine if these ones may influence on *PCSK9* protein levels.

Methods: *PCSK9* rs562556, rs505151, rs2495477, rs2483205, rs2495482, rs2479409, rs11591147 and rs11583680 polymorphisms were genotyped in 1,170 Spanish RA patients, who met the 1987 ACR and the 2010 ACR/EULAR criteria for RA^{4,5}, and 528 healthy controls. Hardy-Weinberg equilibrium and allelic frequencies for each *PCSK9* polymorphism was checked and compared by X² test. Associations were estimated using odds ratios (OR) and 95% confidence intervals (CI). The potential association between significant *PCSK9* polymorphisms and carotid plaques was evaluated by logistic regression. In addition, *PCSK9* serum levels were determined by ELISA. All the results were adjusted by sex, age and traditional CV risk factors.

Results: Significant differences in the allele frequencies of rs2495477 between RA patients and controls were found (risk allele: p=0.014, OR=0.55, CI=0.34-0.89). A significant association between risk allele of rs2495477 and carotid plaques was also disclosed in RA patients (p=0.023, OR=0.76, CI=0.59-0.96). *PCSK9* protein levels were significant decreased in RA patients carrying rs2495477 risk allele compared to controls (p=0.0001).

Conclusion: Our study shows for the first time a protective role of *PCSK9* rs2495477 in a large cohort of RA patients, suggesting this polymorphism as a marker of RA. Furthermore, the risk allele of rs2495477 revealed a protective effect against the development of subclinical atherosclerosis in RA patients. Finally, rs2495477 decrease *PCSK9* levels in patients that may be crucial to control RA.

[1] Autoimmun Rev.2016;15:1013-30; [2] Ann Rheum Dis.2014;73:722-7; [3] J Am Coll Cardiol. 2005;45:1611-9; [4] Arthritis Rheum.1988;31:315-24; [5] Arthritis Rheum.2010;62:2569-81.

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Fibrin-Triggered Chondrosynovial Adhesion As a Novel Mechanism of Cartilage Damage in Rheumatoid Arthritis

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

Background/Purpose: Pannus infiltration and inflammatory cytokines are the main responsible factors for cartilage damage in rheumatoid arthritis (RA). Moreover, the crosstalk between inflammation and coagulation amplifies and maintains chronic inflammation. Whilst extravascular fibrin deposits in synovial fluid and synovial membrane being hallmarks of RA, there are no reports on direct fibrin deposition and its relation to cartilage damage in RA so far. The first aim is to investigate if fibrin deposition occurs in murine and human RA cartilage, and if there is a direct relation with cartilage degradation. Moreover, we want to determine the possible mechanism by which fibrin could play a role in the pathogenesis of RA.

Methods: Full-thickness cartilage explants were obtained from RA patients undergoing total knee replacement. Immunohistochemistry was performed on paraffin sections to study fibrin deposition, while Safranin-O staining was used to investigate cartilage damage. An *in vitro* model of chondrosynovial adhesion was established using primary human RA synoviocytes seeded on human RA cartilage explants. Adherent synoviocytes to cartilage were evaluated on H&E-stained histological sections and fibrin immunohistochemistry was performed on consecutive sections. An experimental RA model (antigen induced arthritis -AIA-) was applied in wild-type (WT) and fibrinogen knock-out mice and paraffin sections of knee joints assessed for fibrin deposition, cartilage damage, and chondrosynovial adhesion.

Results: In human RA cartilage, the amount of fibrin deposits positively correlated with the degree of cartilage degradation. In knees from WT mice fibrin deposition was preferentially found on damaged cartilage and on cartilage areas in direct contact with synovial membrane (i.e chondrosynovial adhesions). In contrast, cartilage degradation and chondrosynovial adhesion were significantly lower in fibrin deficient mice. Mechanical stripping of superficial cartilage layers by fibrin was observed in regions of chondrosynovial adhesion, indicating waxing properties of fibrin. Finally, fibrin-mediated chondrosynovial adhesion was confirmed in the *in vitro* model, where synoviocytes were found to adhere to human OA cartilage especially in severely damaged and fibrin-rich areas.

Conclusion: Our results demonstrate that fibrin deposition on cartilage is highly associated with chondrosynovial adhesion and subsequent cartilage damage in RA. We hypothesize that fibrin mediates chondrosynovial adhesion especially during joint resting periods (i.e night-time), leading to mechanical stripping of superficial cartilage layers following motion.

Disclosure: S. Nasi, None; J. Degen, None; N. Busso, None; A. So, None; T. Hügle, None.

Connective Tissue Growth Factor Associates with Angiogenesis through Notch-1 Activation in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Aberrant angiogenesis has been considered as one of important factors for pathogenesis of rheumatoid arthritis (RA). Several angiogenetic mediators are reported to be massively expressed in synovial tissues of RA patients. Among the mediators, Notch-1 has been reported as one of important angiogenetic mediators in RA. A series of our previous studies have demonstrated that connective tissue growth factor (CTGF) was highly expressed in synovial tissue of RA. CTGF is a multifunctional cytokine and well known as strong mediator for fibrosis. Although we found that CTGF played an important role for the disease progression of RA by multiple mechanisms such as osteoclastogenesis, CTGF interestingly has also been reported as a potent angiogenetic mediator in other diseases. Therefore, this study was conducted to clarify whether CTGF associates with angiogenesis of RA, especially in terms of relation to Notch-1. Furthermore, the therapeutic efficacy of CTGF blockade for prevention of aberrant angiogenesis was also evaluated in animal model of RA.

Methods: Synovial tissue samples of RA patients were used for immunohistochemical analysis. CTGF association for angiogenesis was evaluated by tube formation assay and Boyden chamber assay using human umbilical vein endothelial cells (HUVECs) *in vitro*. CTGF-mediated Notch-1 activation were evaluated by immunofluorescence, immunoblotting, and quantitative RT-PCR analysis in HUVECs. Therapeutic efficacy of CTGF blockade for prevention of increased angiogenesis was evaluated in collagen induced arthritis (CIA) mice by administration of the neutralizing anti-CTGF antibodies.

Results: Synovial tissues of RA patients showed upregulation of Notch-1 pathway indicated by strong expression of Notch-1, Notch-1 transmembrane domain (NICD), and DLL-4. CTGF functioned as angiogenetic mediator and was able to activate Notch-1 signaling pathway *in vitro*. Administration of neutralizing anti-CTGF antibodies prevented the development of angiogenesis through inhibition of Notch-1 expression in CIA mice.

Conclusion: CTGF is able to mediate activation signal against Notch-1 which has been recently postulated as important factor of angiogenesis in RA. CTGF was considered to play an important role for aberrant angiogenesis of RA in combination with Notch-1. CTGF may become a novel target molecule for treatment of RA as CTGF blockade may ameliorate RA by multiple therapeutic mechanisms including suppression of aberrant angiogenesis.

Disclosure: K. Nozawa, None; T. Hirai, None; H. Tsushima, None; K. Yamaji, None; N. Tamura, None; I. Sekigawa, None.

Abstract Number: 1074

Distinct Metabolic Profile in the Urine of Rheumatoid Arthritis Patients:a Possible Link to Arthritis Phenotypes

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster II

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Background/Purpose: A great deal of recent attention has been directed at a possible link between intestinal microbial metabolism and inflammation. Metabolites represent the intermediate products of physiological processes that are influenced by the mechanisms of disease, environment, microbiota, and the digestion and biotransformation of foods and their constituents. Metabolomics captures the global metabolic status of individuals by assaying an extensive set of metabolites simultaneously. This study was undertaken to investigate discriminant metabolites in urine from patients with established rheumatoid arthritis (RA) from healthy individuals and patients with systemic lupus erythematosus (SLE). We further identified the *in vivo* role of metabolites in the animal arthritis model and human clinical data.

Methods: Urine samples were collected from 148 established RA patients, 41 SLE patients and 104 healthy participants. Urinary metabolomic profiles were assessed using ¹H-NMR spectroscopy. The relationships between discriminant metabolites and clinical variables were assessed in a large clinical cohort. Collagen-induced arthritis was induced in mice to determine if a choline-rich diet reduces arthritis progression.

Results: The urinary metabolic fingerprint of patients with established RA differs from that of healthy controls and SLE patients. Metabolites of gut microbiota and diet (trimethylamine-N-oxide; TMAO), and oxidative stress (dimethylamine) were upregulated in patients with RA. Metabolites of mitochondrial dysfunction (citrate and succinate) and metabolic waste products (p-cresol sulfate; p-CS) were downregulated. Urine metabolites were associated with RA disease activity. Particularly, urine levels of TMAO were negatively associated with serum inflammatory markers in patients with RA. Moreover, a more rapid radiographic progression over two years was observed in patients with lower p-CS levels. The *in vivo* functional study demonstrated that mice fed with 1% choline, a source of TMAO, showed a less severe form of collagen-induced arthritis than those fed with normal diet.

Conclusion: Patients with RA showed a distinct urinary metabolomics pattern. Urinary TMAO and p-CS can serve an indicative of inflammation or accelerated radiographic progression of RA. A choline-rich diet reduces experimentally-induced arthritis, suggesting that interaction of diet with intestinal microbiota contributes to the phenotype of RA.

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Disclosure: J. Koh, None; Y. J. Park, None; H. K. Min, None; M. Y. Kim, None; S. A. Yoo, None; C. S. Cho, None; W. U. Kim, None.

Abstract Number: 1075

Automated Multiparameter Microscopy and Image Analysis: Next Generation Synovial Tissue Histology

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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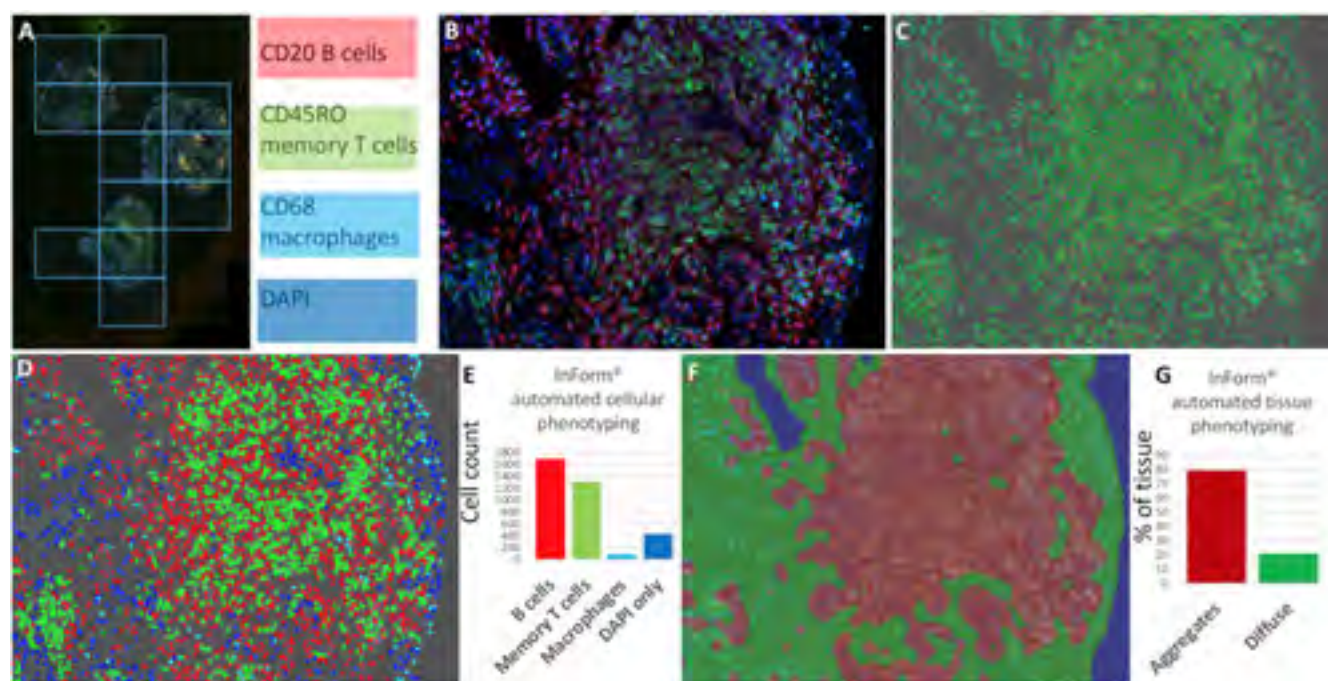


Figure 1. Automated multiparameter imaging and analysis of RA ST. A, whole slide scanning. B, high-resolution multiparameter microscopy for CD20 (red), CD45RO (green) and CD68 (cyan). C, cell segmentation map. D, cellular phenotyping and E, automated cellular counting. F, tissue phenotyping and G, automated phenotype assessment.

Background/Purpose: Currently, histological assessment of synovial tissue (ST) in Rheumatoid Arthritis (RA) is hampered by 3 main factors: 1) tissue is a finite resource, 2) sequential sections of single conventional immunohistochemistry stains do not adequately preserve architectural and co-staining data, and, 3) image analysis and quantification is open to interpretation and human error. Furthermore, in RA, growing evidence implicates heterogeneous histopathological phenotypes with different disease outcomes and treatment responses, critical, as 30-40% of patients do not respond to current therapies and long-term drug-remission is rare, reflecting differential recruitment of inflammatory pathways and cell types. Thus, there is an unmet need for tools that can perform automated multi-parameter cellular identification and phenotype analysis on tissue sections, enabling translational research to assist in the development of personalised medicine.

Methods: Sequential 4µm thick RA ST sections were prepared for Opal multispectral imaging. In brief, for Opal; primary antibodies identifying memory T (CD45RO), B (CD20) and macrophage cell (CD68) are stained in turn, each followed by specific Opal reactive fluorophores. Primary antibody stripping prepares the section for the next primary antibody ready to repeat the process. Once all Opal targets have been developed, DAPI nuclear staining is performed prior to whole slide scanning (Figure 1A) and high-resolution (x20 magnification) image acquisition for CD45RO (green), CD20 (red), CD68 (cyan) and DAPI nuclear stain (blue) (Figure 1B) on the Perkin Elmer Vectra 3.0 automated imaging system.

Results: The image analysis and machine learning software package, in Form® was used to segment individual cells (Figure 1C), identify and quantify cellular phenotype (Figure 1D&E) and distinguish regions with “follicular” and “diffuse” staining patterns (Figure 1F&G).

Conclusion: Due to the recent surge in interest in ST biology, in particular in clinical trials investigating biologic therapies, there is a need for effective, reproducible and high-throughput technologies for immune-histological examination. Thus, a tool such as Opal can be utilised for whole slide scanning and automated analysis of ST infiltrates and tissue phenotype analysis. ST phenotype is thought to influence treatment outcomes in patients, therefore, comprehensive analysis of ST histology will result in more personalised and stratified medicine regimes for patients.

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Abstract Number: 1076

Phospholipase C-eta2, As a C2 Domain-Containing Protein, Regulate Aggressiveness of Fibroblast-like Synoviocytes and Ameliorate Arthritis in Experimental Animal Models of Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster II

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

Background/Purpose: The C2 domain is a Ca²⁺-dependent membrane-targeting motif found in many cellular proteins involved in signal transduction or inflammatory pathway. However, the effects of C2 domain-containing proteins in the pathogenesis of rheumatoid arthritis (RA) have not yet been elucidated. This study aims at screening the novel C2 domain-containing proteins related to the aggressiveness of RA fibroblast-like synoviocyte (RA-FLS) and confirm its precise roles in RA.

Methods: A recombinant adenovirus library expressing 145 kinds of C2 domains was transduced into RA-FLS to check the effects on the proliferation and NF-κB activation. Phospholipase C-eta2 (PLCH2) was selected as a target for C2 domain-containing protein. Recombinant adenovirus expressing PLCH2 (Adv-PLCH2) or C2 domain of PLCH2 (Adv-PLCH2_C2) were used for *in vitro* experiments using RA-FLS and MH7A cell line. The effect on the cell death of PLCH2 was assessed *in vivo* using a mouse Matrigel-plug model. Collagen-induced arthritis (CIA) model is also used to investigate the anti-arthritic effects of Adv-PLCH2, Adv-PLCH2_C2, and m-3M3FBS (PLC activator).

Results: PLCH2 levels were decreased in the RA-synovium and RA-FLS compared to osteoarthritis (OA), and further reduced after stimulation of LPS. Adv-PLCH2 and Adv-PLCH2_C2 suppressed proliferation, migration, invasion, NF-κB activation, cytokines/proteases production of RA-FLS and MH7A cell line. Adv-PLCH2 and Adv-PLCH2_C2 sensitized RA-FLS to apoptosis *in vitro* and *in vivo* model. Adv-PLCH2 or Adv-PLCH2_C2, as an intra-articular delivery, and m-3M3FBS, as systemic delivery of PLC activator, ameliorated inflammation and bone destruction in CIA mice.

Conclusion: Our data identify that PLCH2 and its activation efficiently suppress the aggressiveness of RA-FLS and inflammatory arthritis of CIA and suggest that PLCH2 may be an intriguing therapeutic target in RA.

Disclosure: M. Kim, None; H. M. Jeon, None; H. S. Noh, None; S. M. Yi, None; S. I. Lee, None.

Abstract Number: 1077

Identification of Biomarkers Involved in the Resolution Phase of Inflammation: Specialized Pro-Resolving Mediator Receptors Expression in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster II

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

Background/Purpose: Inflammation is part of the complex biological response of body tissues to harmful stimuli, involving immune cells, blood vessels, and molecular mediators. At the initial phase, characterized by an increase in pro-inflammatory cytokines aiming to neutralize the tissue injury, the resolution process must follow to down-regulate the inflammation and to promote tissue repair. That latter phase is driven by the so called Specialized Pro-Resolving Mediators (SPMs), such as Resolvin (RvD and RvE), Protectins, Maresins and Lipoxin A4 (LXA4), bioactive metabolites of omega-3 fatty acids that act by interacting with specific cellular receptors: CMKLR1, FPR2 and GPR32. In rheumatoid arthritis (RA) the reactive inflammation becomes persistent and the innate immune response turns into the adaptive immune activation. Nowadays there is no evidence whether SPMs are involved in RA pathogenesis. Purpose of this study was to evaluate the expression of CMKLR1, FPR2 and BLT1 in RA patients and to correlate it to the disease activity.

Methods: Patients affected with RA, according to the 2010 EULAR/ACR classification criteria, were enrolled in this study. Exclusion criteria were: minority age, status of pregnancy or breastfeeding, concomitant any other autoimmune disease. At entry, ESR, CRP, DAS28-ESR, CDAI, Health Assessment Questionnaire Disability Index (HAQ) and peripheral venous blood sample were collected. Based on DAS28-ESR, patients were divided into high-moderate (H-Mo/RA if DAS28-ESR ≥ 3.2) and low-remission (L-Rem/RA if DAS28 < 3.2) disease activity group. The expression of CMKLR1, FPR2 and BLT1 in peripheral T cells (CD3) and B cells (CD19), monocytes (CD14) and granulocytes (gated by high side scatter), was evaluated by flow-cytometry assay. Differences for continuous variables were evaluated using the Mann-Whitney test, while for categorical data the Fisher's probability test. Correlations were assessed using the Spearman test.

Results: Thirty RA patients, 21 H-Mo/RA and 9 L-Rem/RA, and 6 healthy control (HC) were studied. While no difference in the expression of CMKLR1, FPR2 and BLT1 in RA vs HC was found, SPMs receptors were differently expressed on CD14-monocytes: BLT1⁺CD14⁺ cells were significantly higher in L-Rem/RA (90,96%) than in H-Mo/RA / RA (56,70%) (p: 0.0001). Likewise, FPR2⁺CD14⁺ cells were significantly higher in L-Rem/RA (92,29%) than in H-Mo/RA / RA (79,94%) (p: 0.01). We also demonstrated an inverse correlation between BLT1 level in monocytes and ESR (p: 0.01), CRP levels (p: 0.008), DAS28-ESR (p: 0.03), CDAI (p: 0,0076) and HAQ (p: 0,0138) and a weak correlation between FPR2 expression and HAQ (p: 0.05).

Conclusion: In this study, FPR2 and BLT1 expression seem to be regulated by the activity of RA disease. As FPR2 and BLT1 should be involved in down-regulating inflammation by monocytes, it might be hypothesized that a defective signalling through these SPMs receptors may contribute to prevent the beginning of resolution phase, perpetuating chronic inflammation in active RA. However, further studies are needed to explore the intrigue mechanisms beyond inflammation and its resolution.

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Standardization of Synovial Biopsies Procedures across Centers: A Consensus Initiative Using a Delphi Survey

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SESSION INFORMATION

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

Background/Purpose: Synovial biopsies are increasingly performed in both clinical setting and translational research. Synovial tissue analysis role in prediction of response to treatment is to be yet considered and regarding that most studies involve multicentric participation, an unmet need is the standardization of synovial biopsies procedures. The aim of this collaborative work was to create a consensual set of items for handling and analysis of synovial biopsies in clinical practice and translational research.

Methods: EULAR Synovitis Study Group (ESSG) and Synovial Tissue Special Interest Group (SIG) members were consulted through a Delphi survey. 3 sequential rounds occurred between June 2016 and June 2017. The items were identified and formulated based on a comprehensive literature review. Members were sent a written questionnaire containing items divided in 2 parts. The first part of the questionnaire referred to clinical practice containing 5 subsections: biopsy sampling, biopsy handling, histological analysis, staining and immunohistochemistry (IHC), biopsy analysis and pathologist's report. The second part referred to translational research and contained 6 subsections (same 5 plus RNA analysis).

Every participant was asked to score each item with a 5 points Likert (0: strongly disagree, 5: strongly agree), comments were allowed for each item. Items with a median score above 3.5 on 5 and a percentage of agreement above 70% were for the next round. Items with lower score were either suppressed or modified according to participants' comments. Anonymized detailed results were circulating through participants between each round. Last round occurred orally at ESSG meeting in June 2017.

Results: 27 ESSG members from 19 centers were contacted by email. 20 participants from 17 centers answered (response rate of 74%). Response rates for next rounds were 100%. First questionnaire contained 44 items for Part 1 Clinical practice and 43 items for the second part about translational research. The flow chart is described in Figure 1. Third oral round allowed to obtain a final set of items unanimously (Figure 2).

Figure 1. Delphi Flow Chart



Figure 2. Final list of items

CLINICAL PRACTICE

1. Biopsy sampling

- A minimum of 4 synovial biopsies needs to be retrieved in small joints.
- Biopsies shall be retrieved in different areas of the joint, if possible.
- If it is clinically relevant, bacteriological, fungal and mycobacteriological assessment should be performed.
- Polymerase chain reaction analysis for AIN (ES) should be performed if clinically relevant, especially if empiric antibiotic course has been started.
- If it is clinically relevant, Polymerase chain reaction analysis for Lyme and Whipple diseases should be performed.

2. Biopsy processing

- The biopsies should spend 24 hours in formalin 4%.
- At least 2 biopsies should be formalin-fixed and paraffin-embedded.

3. Histological criteria

- Synovial biopsy surface should be more than 2.5mm².
- A lining layer should be seen.
- Morphology of the synovial tissue should be preserved.

4. Staining and immunohistochemistry (IHC)

- H&E staining should always be performed.
- CD68 staining should be performed.
- In particular clinically relevant cases, additional staining should be performed (CD3, CD20, CD138, CD31 or FvII).
- If performed, IHC results can be given using a semi-quantitative score.

5. Biopsies interpretation and Pathologist's report

- A synovitis score should be performed, analyzing: lining layer hyperplasia, inflammatory infiltrate and resident cell activation (Kern, other).
- Lining layer hyperplasia should be scored.
- Synovial pathology should be described.
- Presence or absence of lymphoid follicles within the membrane should be described.
- Analysis can be semi-quantitative or quantitative depending on the question.
- If a semi-quantitative or quantitative analysis is performed for multiple biopsies, an average score should be calculated and given for the analysis of inflammation and vascularization.
- The pathologist should mention the presence of granulomas.

TRANSLATIONAL RESEARCH

1. Biopsy sampling

- A minimum of 6 synovial biopsies needs to be retrieved in large joints.
- A minimum of 4 synovial biopsies needs to be retrieved in small joints.
- Biopsies shall be retrieved in different areas of the joint, if possible.

2. Biopsy processing

- The biopsies should spend 24 hours in formalin 4%.

3. Histological criteria

- Synovial biopsy surface should be more than 2.5mm².
- A lining layer should be seen.
- Morphology of the synovial tissue should be preserved.

4. Staining and immunohistochemistry (IHC)

- H&E staining should always be performed.
- CD68 staining should be performed.
- CD3, CD19 or CD20 staining should be performed.
- Additional CD 31 or FvII, CD4, CD8, CD138 staining might be performed depending on the question.

5. Biopsies interpretation and Pathologist's report

- A synovitis score should be performed, analyzing: lining layer hyperplasia, inflammatory infiltrate and resident cell activation (Kern, other).
- Lining layer hyperplasia should be scored.
- Synovial pathology should be described.
- Presence or absence of lymphoid follicles within the membrane should be described.
- Analysis can be semi-quantitative or quantitative depending on the question.
- If a semi-quantitative or quantitative analysis is performed for a single biopsy, at least 3 area of the biopsy should be assessed.

6. RNA Analysis

- Biopsies of one patient can be pooled for RNA extraction if needed.

Conclusion: We hereby propose a set of consensual points to consider on analysis of synovial biopsies in clinical practice and translational research to be further used in multicentric clinical trials and therefore ensure reliability.

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Abstract Number: 1079

Plasma Metabolomic Analysis Combined with Transcriptome Data Has Revealed the Importance of Amino Acids Homeostasis in SLE Pathogenesis

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

Background/Purpose: Recently, many reports on immune metabolism have been accumulated and metabolic changes are now considered to be a key factor for controlling immune cell differentiation, proliferation and function. Although precise mechanism of tuning metabolic status in immune cells has been clarified, these results have mainly come from the mice experiments and metabolomics analysis on human autoimmune diseases gets underway. The aim of this study is to get some insights on metabolomic regulation in SLE by comprehensively measuring plasma metabolites.

Methods: We collected plasma samples from patients with SLE (n=41) who met the 1997 American College of Rheumatology criteria for SLE and had the history of lupus nephritis. Gender- and age-matched healthy controls (HCs) (n=30) were recruited. For comparison, plasma from 19 rheumatoid arthritis (RA) patients were also collected. Metabolic profiles were analyzed with capillary electrophoresis (CE)- and liquid chromatography (LC)- time of flight mass spectrometry (TOFMS) in conjunction with multivariate statistical analysis. Transcriptome data of SLE patients were obtained from our RNA-sequencing data of each immune cell subset (total 20 subsets).

Results: About 180 peaks were detected from CE-TOFMS including absolutely quantified 110 metabolites and about 160 peaks were detected from LC-TOFMS. Random Forest, one of the machine learning algorithms, revealed the importance of histidine (His) to classify SLE patients from HCs. Partial least squares discriminant analysis (PLS-DA) also showed the significance of His, whose plasma level was lower in SLE patients. In addition, we divided SLE patients into two groups by using transcriptome data; interferon (IFN)-signature high and low. Interestingly, we found some amino acids were associated with IFN-signature level. In addition, inverse correlation between His level and titer of ds-DNA was detected. His level was also decreased in RA patients compared to HCs and was inversely correlated with DAS28-ESR and CRP in RA. Weighted gene co-expression network analysis (WGCNA), one of network analysis, showed positive correlation between mitochondria-related module and plasma His level in B cells.

Conclusion: Plasma metabolic changes in autoimmune diseases might not only reflect the chronic activated immune-status but also associate with their pathogenesis themselves. His may be an important factor for SLE pathogenesis especially in B cells independently from IFN signal. SLC15A4, a transporter of His on lysosome, is one of the SLE GWAS SNPs and has been reported to play an important role in IFN production in B cells through regulation of TLR7/9 activation. Low plasma level of His could be a useful marker of SLE activity and maintenance of His homeostasis could become a novel treatment target for SLE.

Disclosure: Y. Iwasaki, None; Y. Takeshima, None; M. Ota, None; Y. Nagafuchi, None; S. Sumitomo, None; A. Suzuki, None; Y. Kochi, None; T. Okamura, None; I. Miki, None; K. Sakurada, None; S. Koyasu, None; K. Yamamoto, Astellas, BMS, MitsubishiTanabe, Pfizer, Ayumi, Takeda, Chugai, Eisai, Taisho Toyama, UCB, and ImmunoFuture, 2; K. Fujio, Astellas, BMS, MitsubishiTanabe, Pfizer, Ayumi, Takeda, Chugai, Eisai, Taisho Toyama, Eli Lilly, Sanofi, and UCB, 2.

Abstract Number: 1080

Hypomethylation of STAT1 and HLA-DRB1 in CD8+ T Cells Is Associated with Type-I Interferon-Dependent HLA-DRB1 Overexpression and Activation of Autologous CD4+ T Cells in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Systemic lupus erythematosus is a chronic autoimmune disease characterized by epigenetic dysregulation, and increased autoantibody and type-I interferon (IFN) production. The goal of this study was to explore possible pathogenic roles of CD8+ T cells in lupus through characterizing DNA methylation changes.

Methods: Genome-wide DNA methylation of lupus and age, sex and ethnicity-matched control CD8+ T cells was measured using the Infinium MethylationEPIC arrays. Data preprocessing and statistical analysis of differentially methylated CpG sites was performed using GenomeStudio (Illumina). Gene ontology analysis of differentially methylated sites was performed with DAVID. Measurement of HLA-DRB1 expression on the surface of lupus and control CD8+ T cells with and without interferon alpha (IFN α) was performed by flow cytometry. Co-incubation of IFN α -treated CD8+ T cells from lupus patients and controls with autologous naïve CD4+ T cells to assess effects on CD4+ T cell stimulation were performed. CD8+ T cell mRNA levels normalized to β -actin were quantified by qPCR.

Results: Lupus CD8+ T cells had 188 hypomethylated CpG sites compared to healthy matched controls. Among the most demethylated were sites associated with *HLA-DRB1* (Db = -0.33) and *STAT1* (Db = -0.15). The proportion of CD8+ T cells expressing HLA-DRB1 was significantly higher in lupus compared to controls. IFN α treatment upregulated cell surface expression of HLA-DRB1 on CD8+ T cells of lupus patients but not healthy controls. Co-incubation of naïve CD4+ T cells with IFN α -treated autologous CD8+ T cells led to increased expression of the stimulation marker CD69 on CD4+ T cells in lupus patients, but not in healthy controls. This effect can be abrogated using HLA-DR blocking antibodies. Lupus and control CD8+ T cells significantly increased STAT1 mRNA levels after treatment with IFN α . The expression of CIITA, a key interferon/STAT1 dependent MHC-class II regulator, is induced by IFN α in lupus CD8+ T cells, but not healthy controls.

Conclusion: *HLA-DRB1* and *STAT1* loci are hypomethylated and epigenetically poised for overexpression in lupus CD8+ T cells in the presence of type-I interferon. IFN α -treated lupus CD8+ T cells stimulate autologous CD4+ T cells *in vitro* and blocking of HLA-DR on CD8+ T cells can abrogate this effect. These data suggest a possible pathogenic role for CD8+ T cells in lupus that is dependent upon a high type-I interferon environment and epigenetic priming.

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Abstract Number: 1081

Associations between Daily Alcohol Intake and SLE-Related Cytokines and Chemokines U.S. Female Nurses without SLE

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster II

Background/Purpose: Low or no alcohol intake (0-5gm/day or <0.5 drinks/day) has been associated with increased SLE risk among women. Several cytokines and chemokines are involved in disease pathogenesis and are upregulated prior to SLE onset. We investigated whether alcohol intake was associated with B-lymphocyte stimulator (BLyS), stem cell factor (SCF), interferon alpha (IFN- α) and interferon-gamma induced protein (IP-10) concentrations in a large cross-sectional study of women.

Methods: The Nurses' Health Study (NHS, n=121,700 and NHSII n=116,429) cohorts began in 1976 and 1989, collecting exposure and outcome data on detailed biennial questionnaires. In 1988-1989, ~25% participants donated a blood sample. Cumulative average intake of beer, wine or liquor in drinks per day was assessed prior to the blood draw. We identified 1177 women without SLE prior to blood draw with banked plasma samples and alcohol data. Samples were tested by ELISA assays for BLyS, SCF, IFN- α and IP-10 (each passed quality control [QC] using blinded split samples). We adjusted for inter-batch variation using common QC samples and natural log-transformed all biomarkers to improve normality. ANA (hep2 IF) and ELISAs for anti-dsDNA and extractable nuclear antigens (ENAs; anti-Ro, anti-La, anti-Sm and anti-RNP) were tested. We assessed relationships between alcohol intake (0-5 [low] vs. >5 [high] grams/day) and biomarker concentrations overall and among women with SLE autoantibody positivity in age-adjusted and then multivariable models adjusting for age, race, body mass index, smoking status, and history of depression. SCF and BLyS were assessed using general linear regression, and IP-10 and IFN- α were assessed using Tobit regression due to the high proportion below threshold (IP-10 undetectable=165 [14%] and IFN- α undetectable=754 [64%]).

Results: Mean age at blood draw was 56 years (SD 10). Low alcohol intake was associated with increased circulating SCF concentration among all women (β [SE]= 0.10 [0.02], $p<0.0001$) and among the 295 ANA, dsDNA or ENA positive women (β [SE]=0.11[0.04], $p=0.05$). (Table) In age-adjusted models, BLyS and IP-10 were higher (BLyS β [SE]= 0.05[0.02], $p=0.03$; IP-10 β [SE]=2.04 [0.51], $p<0.0001$) among women with low alcohol intake, while IFN- α concentration was lower (β [SE]=-5.9 [2.3]; $p=0.01$).

Conclusion: Low or no alcohol intake was associated with increased SCF concentrations, but not with other SLE-related cytokine/chemokine concentrations in this cross-sectional sample of women without SLE in the NHS and NHSII cohorts. Stem cell factor (SCF) plays a role in T-cell differentiation and hematopoiesis. It is thought to be upregulated prior to SLE diagnosis. Decreased SLE risk among women with moderate alcohol intake may be related to inhibition of SCF.

Table. A: Mean Daily Alcohol Intake (≤ 5 gm vs. >5 gm) and Continuous Log Concentrations of BLyS and SCF-1 within a cross-sectional sample of women in the Nurses' Health Study Cohorts

	Log BLyS				Log SCF			
	Age-adjusted Models		Multi-variable Models		Age-adjusted Models		Multi-variable Models	
≤ 5 gm vs. >5 gm per day Alcohol Intake	β (SE)	P	β (SE)	P*	β (SE)	p	β (SE)	P*
Among all women (n=1177)	0.05 (0.02)	0.03	0.04 (0.02)	0.07	0.10 (0.02)	<0.0001	0.08 (0.02)	0.0001
Among ANA/dsDNA/ENA+ women (n=295)	0.01 (0.05)	0.76	0.03 (0.05)	0.50	0.11 (0.04)	0.005	0.08 (0.04)	0.05

Table. B: Mean Daily Alcohol Intake (≤ 5 gm vs. >5 gm) and Continuous Log Concentrations of IP-10 and IFN- α within a cross-sectional sample of women in the Nurses' Health Study Cohorts

	Log IP-10**				Log IFN- α **			
	Age-adjusted Models		Multi-variable Models		Age-adjusted Models		Multi-variable Models	
≤ 5 gm vs. >5 gm per day Alcohol Intake	β (SE)	P	β (SE)	P*	β (SE)	p	β (SE)	P*
Among all women (n=1177)	0.03 (0.11)	0.82	0.08 (0.11)	0.47	-0.42 (0.45)	0.35	-0.22 (0.46)	0.62
Among ANA/dsDNA/ENA+ women (n=295)	2.04 (0.51)	<0.0001	0.32 (0.22)	0.14	-5.9 (2.3)	0.01	-0.22 (0.95)	0.82

* Multivariable general linear regression and Tobit models, adjusted for age (continuous), race (Black vs. other), smoking (current/recent quit vs. never or remote quit), body mass index (continuous), history of depression (present vs not)

** Tobit analysis is utilized for maximum usage of cytokines/chemokines if there are many undetectable values.

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Peripheral Blood CD11c+ CD21- Age-Associated B Cells (ABCs) in Human Systemic Lupus Erythematosus Are Associated with Innate Type III Interferon and Disease Activity

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by an interferon-stimulated gene (ISG) signature typically attributed to interferon (IFN)- α . However, ISGs can be induced by other innate type I interferons (such as β) as well as type III IFN (λ). Type I IFNs may contribute to disease pathogenesis through immune dysregulation, including activation of the B cell compartment. One recently described B cell abnormality associated with lupus in mouse models is the presence of age-associated B cells (ABCs), a population expanded by self-antigen and type II adaptive IFNs (γ), enriched for autoreactivity, and poised for plasma cells differentiation. ABCs have been characterized as CD11c+, CD21- and T-bet+ B cells. The precise frequency and triggers of ABCs in human lupus remain unclear. The purpose of this study was to characterize the ABC population in SLE patients and relationship with disease activity and innate IFN serum levels.

Methods: Peripheral blood leukocytes from 26 lupus patients with a range of disease activity as well as 6 normal healthy donors (ND) were analyzed by flow cytometry using a panel which included CD3, CD11c, CD19, CD20, CD21, CD24, CD27, CD38, CD95, CXCR3, IgD, and T-bet. All lupus patients met ACR criteria. Lupus patients were divided into groups based upon SLEDAI score. IFN- α , IFN- β , and IFN- λ 1 (IL-29) levels were quantitated by ELISA from sera drawn on the same day.

Results: CD11c+ CD21- identified a distinct B cell population. The majority of these putative ABCs (CD3- CD19+ CD11c+ CD21-) were distributed in the IgD- CD27- double negative B cell compartment (mean \pm SEM% of ABC; 61.5 \pm 2.8 in SLE, 66.8 \pm 4.3% ND) followed by IgD+CD27- total naive (23.0 \pm 3.0% SLE, 17.9 \pm 3.4% ND), then switched memory IgD-CD27+ (12.2 \pm 1.4% SLE, 11.0 \pm 1.2% ND). ABC were primarily CD24- (84.4 \pm 1.9% SLE, 78.3 \pm 8.3% ND). Thus, activated naive represented the majority ABC in the total naive compartment. Putative ABCs comprised a greater percentage of total B cells in lupus patients (4.7 \pm 1.1%) compared to ND (0.99 \pm 0.1%, unpaired T test with Welch's correction p-value = 0.0026 with significant difference in variances). Within this CD11c+CD21- B cell population, a subset of cells expressed T-bet (46.2 \pm 4.3% SLE, 58.1 \pm 5.4% ND). IFN- λ 1 serum level positively correlated with CD11c+CD21- (Spearman r =+0.415, p =0.018), double negative IgD-CD27-CD24-CD21- (Spearman r =+0.454, p =0.009) and T bet+ (Spearman r =+0.304, p =0.09) expressing B cells. IFN- β serum level positively correlated with the percentage of transitional B cells (Spearman r =+0.428, p =0.015). ABCs made up a statistically significant greater percentage of total B cells in patients with a SLEDAI >8 compared to patients grouped by lower disease activity scores (p =0.01, 2-tailed unpaired T test). No correlation between B cell subsets or SLEDAI was found with serum IFN- α level as measured by an all alpha subtype ELISA.

Conclusion: Our data highlights the importance of innate IFNs other than IFN- α (such as IFN- λ 1 and IFN- β) in B cell abnormalities in SLE, including the expansion of ABCs and transitional B cells. Functional characterization of the ABC subset is needed to better understand how it contributes to disease pathogenesis and further define therapeutic target potential.

Disclosure: J. L. Barnas, Rheumatology Research Foundation, 2; L. Gao, None; M. O'Connell, None; J. Albrecht, None; N. Meednu, None; R. J. Looney, AstraZeneca, 5; J. Anolik, None.

Changes of Innate Lymphoid Cells in Peripheral Blood of Patients with Systemic Lupus Erythematosus and Its Correlations with Clinical Markers

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster II

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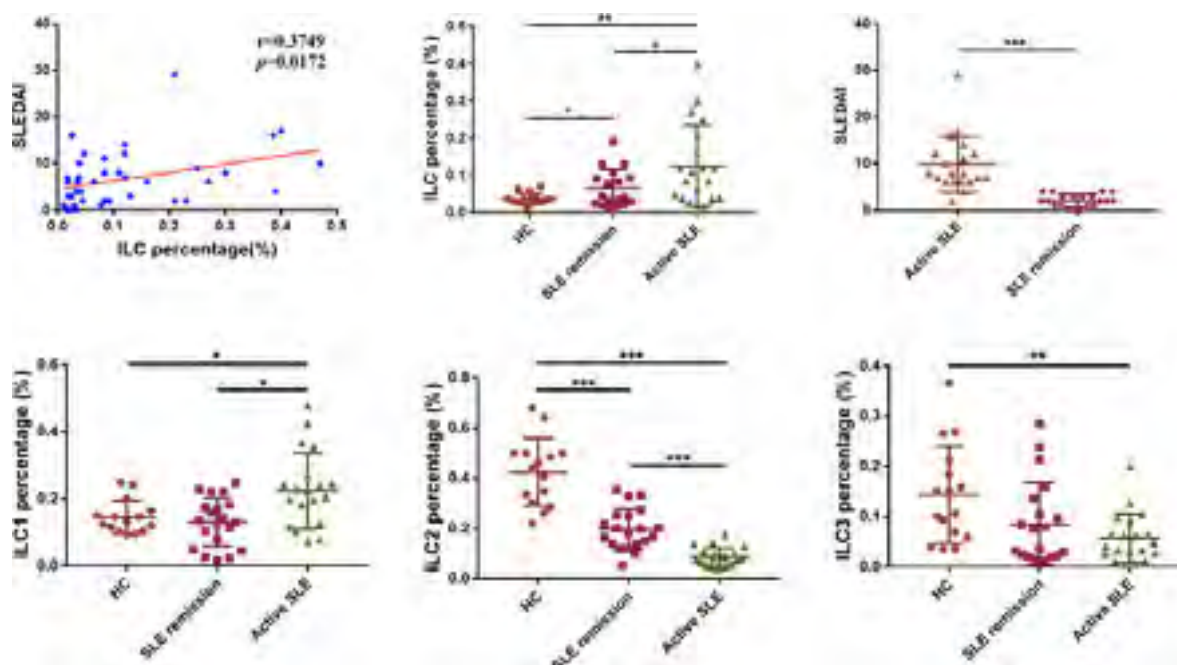
Session Time: 9:00AM-11:00AM

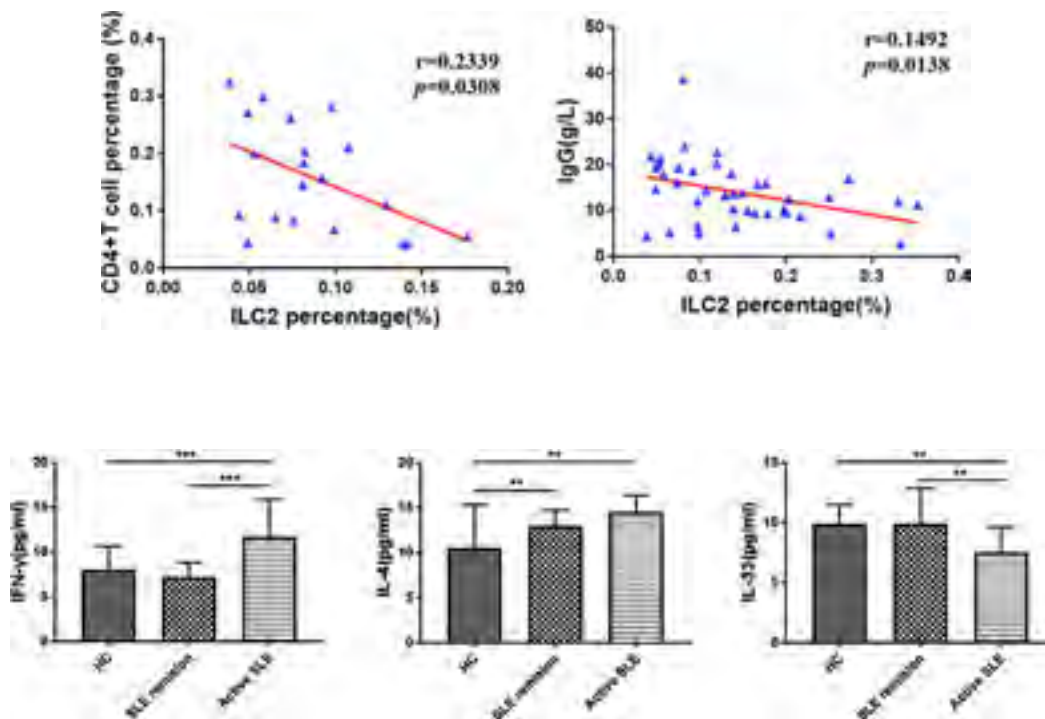
Background/Purpose: Innate Lymphoid Cells (ILCs) are a novel group of innate immune cells, according to the cytokine profile, they were divided into three major subsets: ILC1(Lin⁻CIL7R+NKp46+ILCs), ILC2(Lin⁻CIL7R+CRTH2+ILCs) and ILC3(Lin⁻CIL7R+CRTH2⁻CCD117+ILCs). Little research on ILC in the pathogenesis of systemic lupus erythematosus. Our purpose is to explore the function and role of innate lymphoid cells(ILCs) in the pathogenesis of systemic lupus erythematosus at different disease activity levels.

Methods: 40 patients with SLE were included, according to the SLEDAI-2K, patients were divided into active group(n=20) and remission group(n=20), 15 age-matched healthy non-immune-related diseases controls. The frequency of ILCs, B cells, CD4+T and CD8+T cells from PBMCs was detected by flow cytometry. Analysis the subsets of ILCs in each group which compared with B cells and T cell subsets respectively and correlated with clinical serologic markers. Analyze the level of IL-4, IL-33 and IFN- γ in each group by ELISA.

Results: Compared with the control group, ILC1 percentage was significantly increased in SLE active group(P=0.0181); ILC2 was decreased significantly in both remission(P<0.0001) and active groups(P<0.0001); ILC3 was decreased significantly in active group(P=0.0013). The frequency of ILCs in all patients positively correlated with SLEDAI score(P=0.0172). The frequency of ILCs in the remission(P=0.0462) and activity group (P=0.0037) are both increased significantly (**Figure1**). Moreover, the frequency of ILC2 in active group was negatively correlated with CD4+T cells(P=0.0308), and the serum IgG inpatients was negatively correlated with ILC2 of all patients (P=0.0138)(**Figure2**). Compared with either control group or the remission group, the levels of IFN- γ (P=0.0001) and IL-4 (P=0.0047) in active group were remarkable higher. However, IL-33 was significantly reduced in active group(P=0.0027)(**Figure3**). (*,p<0.05; **,p<0.01; ***,p<0.001).

Conclusion: The frequency of ILCs is related to disease activity, and ILCs play a “double-edged” role in the pathogenesis of SLE. Its function and mechanism are worth further exploration.





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Abstract Number: 1084

Dysfunction of the DNASE1L3 Pathway and Antigen Accumulation in Lupus Nephritis

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: DNASE1L3 is a unique secreted DNase that is capable of degrading DNA complexed with proteins and/or encapsulated in membranes, such as chromatin within microparticles from apoptotic cells. The role of DNASE1L3 in the pathogenesis of SLE is supported by the nearly universal association of DNASE1L3 null mutations with familial SLE, the linkage of a hypomorphic variant to sporadic SLE, and the development of anti-DNA response and SLE-like disease in DNASE1L3-deficient mice. Accordingly, this study was initiated to delineate the role of microparticle-associated antigens sensitive to DNASE1L3 digestion as targets of antibody reactivity in human SLE.

Methods: Antibodies to DNA on microparticles were measured using an in vitro assay. Jurkat human T cells were treated with staurosporine to induce apoptosis, and microparticles were isolated. After mock-treatment or treatment with recombinant DNASE1L3, the microparticles were subsequently incubated with sera, washed, and stained with fluorescently labeled anti-human IgG prior to evaluation using flow cytometry. The ratio of binding values with or without DNASE1L3 pre-treatment indicates the binding to DNASE1L3-sensitive antigens (including DNA and/or DNA-associated proteins) versus other antigens exposed on microparticles.

Results: Evaluation of sera (76 from 66 SLE patients, 19 controls, 34 anti-Ro positive neonatal lupus mothers) revealed three types of reactivity to microparticles: i) no binding; ii) binding insensitive to DNASE1L3; and iii) binding that is

sensitive to DNASE1L3. Notably, the only two patients heterozygous for the DNASE1L3 (R206C) hypomorphic variant belonged to this latter group. Samples from 30 (45%) of the SLE patients showed DNASE1L3-sensitive binding while this reactivity was absent in all controls. Although hypomorphic allelic variants are restricted to European ancestry, sensitive binding was observed in all ethnic/racial groups. SLE patients with sensitive vs insensitive binding had a significantly higher frequency of past/present renal disease (87% vs 44%, $p=0.0007$). Moreover, at the time of blood sampling, sensitive binding was associated with the presence of >0.5 uPCR (61% vs 30%, $p=0.012$) and low complement levels (78% vs 53%, $p=0.031$). Overall, sensitive binders were more active with SLEDAI score ≥ 8 in 47% vs 21% ($p=0.007$). Supporting that DNASE1L3 can disrupt pre-formed complexes of IgG with antigen on microparticles, binding to the native microparticles could be abrogated by subsequent addition of the enzyme. Several subjects within the group of high titer anti-Ro positive mothers (asymptomatic, UAS, SS, SLE but no history of nephritis) showed strong binding to native microparticles, but this binding was not DNASE1L3-sensitive.

Conclusion: These data support that reactivity to physiological DNA-associated antigens from apoptotic cells is relevant in lupus nephritis and suggest DNASE1L3 as a novel pharmacological approach to forestall organ injury.

Disclosure: J. Hartl, None; R. M. Clancy, None; P. M. Izmirly, None; H. M. Belmont, Exagen, 2; N. Kaiden, Exagen, 2; N. Bornkamp, None; V. Sisirak, None; B. Sally, None; J. P. Buyon, Exagen, 2; B. Reizis, None.

Abstract Number: 1085

Natural Gingerols Inhibit Neutrophil Extracellular Trap Release Elicited By Lupus Autoantibodies

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Recent studies have revealed a role for neutrophils in the pathogenesis of lupus and antiphospholipid syndrome (APS). Indeed, neutrophils are activated by various disease-relevant stimuli including ribonucleoprotein (RNP)/anti-RNP complexes and antiphospholipid antibodies (aPL) to release tangles of DNA and protein known as neutrophil extracellular traps (NETs). Ginger is known to have anti-inflammatory and anti-oxidative effects, and has traditionally been used as an herbal supplement in the treatment of inflammatory diseases. Here, we hypothesized that compounds isolated from ginger might mitigate NET release (NETosis) in response to lupus- and APS-relevant stimuli.

Methods: Control human neutrophils were prepared from healthy volunteers and stimulated with phorbol 12-myristate 13-acetate (PMA); *E. coli* lipopolysaccharide (LPS); total IgG fractions prepared from primary APS patients (aPL); or RNP/anti-RNP complexes prepared from lupus patients. Stimulation was in the presence of various bioactive compounds derived from ginger root. NETosis was quantified via chromogenic measurement of the enzymatic activity of NET-associated myeloperoxidase.

Results: So-called “gingerols” are the major bioactive compounds of ginger root. We first tested the efficacy of three related compounds, 6-gingerol, 8-gingerol, and 10-gingerol, for their ability to suppress NETosis by control neutrophils (of these compounds, 6-gingerol is the most abundant in ginger root). At doses ranging from 1 to 10 micromolar, both 6- and 8-gingerol completely neutralized aPL- and LPS-triggered NETosis, while 10-gingerol reduced NETosis by about 75%. 6-gingerol also effectively suppressed RNP/anti-RNP-induced NETosis at low micromolar concentrations. Interestingly, none of the compounds were efficacious against PMA-induced NETosis. Mechanistically, we reasoned that gingerols might suppress NETosis by preventing the neutrophil oxidative burst, as reactive oxygen species (ROS) are required for most forms of NETosis. Interestingly, aPL, LPS, and PMA all triggered significant hydrogen peroxide production by neutrophils, but gingerols only neutralized peroxide elicited by aPL and LPS.

Conclusion: We demonstrate for the first time that various natural gingerols found in ginger root can attenuate NET release and ROS production in response to various lupus-relevant stimuli (but not PMA) *in vitro*. Studies are underway to determine the extent to which these natural compounds may mitigate NET release, endothelial dysfunction, and venous thrombosis in mouse models of lupus and APS.

Disclosure: R. A. Ali, None; J. S. Knight, None.

Abstract Number: 1086

Low-Dose IL-2 Combined with Rapamycin Efficiently Promotes Remission of Refractory Systemic Lupus Erythematosus

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SESSION INFORMATION

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

Background/Purpose: Systemic lupus erythematosus (SLE) is a potentially fatal autoimmune disease. Regulatory T (Treg) cells and T helper type 17 (Th17) cells play opposite roles in immune tolerance and autoimmune diseases. It was reported previously that elevated Th17 and/or decreased Treg cells caused an imbalance of Treg/Th17 in SLE. Since low-dose IL-2 can selectively stimulate the differentiation of CD4⁺Treg cells and rapamycin can promote the proliferation of Treg cells and inhibits differentiation of Th17 cells, the combined treatment of the low-dose IL-2 and rapamycin may increase the remission rate of SLE.

Methods: Sixty-six refractory SLE patients (53 women and 3 men), with an average course of 74.22±40.91 months and average age of 33.10±11.72 years, were enrolled. They fulfilled the 1997 ACR criteria and had been treating with glucocorticoid and immunosuppressant for more than one year, but had not yet reached the disease remission. The standard for remission is defined as meeting all the following conditions: sustained remission of clinical symptoms, no organ damage indication, normal inflammatory index and normal immune function. The eligible patients were given IL-2 and rapamycin in combination with conventional therapy. At 0, 6, 12, 24 week respectively after medication, the absolute numbers of Th17 cells and Treg cells in blood were examined by flow cytometry. Also, the clinical symptoms, blood routine, urine routine, ESR, the dosage of corticosteroids and immunosuppressant, or the remission rate was registered respectively.

Results: As compared with healthy controls, the absolute number of Treg cells in the patients with refractory SLE significantly decreased, whereas that of Th17 cells did not increase clearly. At 24 week after treatment with low-dose IL-2 combined with rapamycin, 36.0% of patients with refractory SLE achieved remission, accompanying increase in the absolute numbers of peripheral Treg cells from a median of 17.08 cells/μl (at week 0) to 28.16 cells/μl (at week 24) (P=0.002). Accordingly, the ratio of Th17/Treg cells showed a reduction from a median of 0.87 at week 0 to 0.31 at week 24 (P=0.019), indicating a restored balance of them. No significant difference was observed in the absolute numbers of Th17 after combined treatment. At week 24, the mean dosage of prednisone used in refractory SLE patients was decreased from 17.19 mg/d to 9.11 mg/d. And the categories of immunosuppressant used were also reduced (P<0.05).

Conclusion: Our findings indicate that refractory SLE is associated with the decreased absolute number of Treg cells but not increased Th17 cells in blood. Low-dose IL-2 combined with rapamycin treatment can restore the balance of Th17 and Treg cells in refractory SLE due to the significant increase in Treg cells. This therapy can induce higher remission rate of the patients after 24-week treatment and reduce the usage of glucocorticoid and immunosuppressant.

Disclosure: Z. Liang, None; X. Jing, None; M. Hao, None; C. Gao, None; X. F. Li, None; J. Chen, None.

Abstract Number: 1087

Association between Cigarette Smoking and Systemic Lupus Erythematosus – a Bayesian Multivariate Meta-Analysis of Case-Control and Cohort Studies

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: The association between cigarette smoking and the occurrence of SLE has been studied over the past two decades but results are conflicting. The global increase in women smokers and the availability of prospective data addressing the risk of the development of SLE and cigarette smoking warrant an update on the evidence of the relationship between cigarette smoking and the occurrence of SLE. This study aims to refine the association between cigarette smoking and the odds of SLE occurrence by Bayesian multivariate meta-analysis of case-control and cohort studies.

Methods: An extensive literature search using the relevant keywords including “systemic lupus erythematosus”; “lupus”; “smoking”; “cigarette smoking”; “environmental”; “autoimmune disease” and “connective tissue disease” in various combinations was performed in order to identify case-control and cohort studies addressing the relationship between cigarette smoking and SLE published in English in computerized databases including PubMed (from 1966 to Jan 2018), Embase (1980 to Jan 2018) and Cochrane Central Register of Control Trials (last quarter of 2017). A Bayesian multivariate meta-analysis was conducted by computing the log odds ratios (ORs) between current and never smokers, and between ex-smokers and never smokers. Following which, the sampling covariances of the effect sizes were calculated and heterogeneity variances of the case-control and cohort studies were assumed to be the same. The average log ORs, the heterogeneity (SDs) and their corresponding 95% credible intervals (CIs) of the posterior distributions were then reported.

Results: Twelve relevant studies (10 retrospective case-control and 2 cohort) were eligible for the meta-analysis. Data were aggregated based on smoking statuses comprising current, ever and never smoking. Bayesian analysis of combination of the case-control and cohort studies revealed significant relationship between the occurrence of SLE and current smoking (log OR 0.43, 95% CI [0.07, 0.81]), and a smaller and insignificant association between SLE and ever smoking (log OR 0.33, 95% CI [-0.05; 0.74]). The year of publication, patients’ mean age and the proportion of female subjects in the studies were not mediators for the aggregated effect sizes.

Conclusion: Current smoking is associated with the occurrence of SLE based on the Bayesian aggregation of effect sizes from case-control and cohort studies. The higher risk of development of SLE in current but not among ex-smokers compared to never smokers warrants further mechanistic studies to unravel the actual immunologic impact of cigarette smoke on SLE development in different subsets of SLE patients, and highlights the importance of smoking cessation.

Disclosure: M. H. Y. Chua, None; I. A. T. Ng, None; M. W. L. Cheung, None; A. Mak, None.

Abstract Number: 1088

Pro-Inflammatory and Regulatory Soluble Mediator Pathways Vary between African American and European American SLE Patients

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Background/Purpose: Systemic lupus erythematosus(SLE) is an autoimmune disease that primarily affects women, and is associated with periods of elevated and suppressed clinical symptoms. SLE prevalence varies between ethnic groups, with African American women having higher rates and increased disease severity. Understanding how dysregulated immune pathways associate with disease activity within different ethnic groups is critical for optimizing effective and personalized treatment options for SLE.

Methods: Plasma cytokine levels of European or African American healthy controls (n=18) and SLE patients with either higher(SLEDAI≥4) (n=20) or lower (SLEDAI<4) (n=20) disease activity were assessed by 37-plex xMAP assays and ELISAs. Further, peripheral whole blood samples collected from subjects were stimulated for 24 hours with either PMA

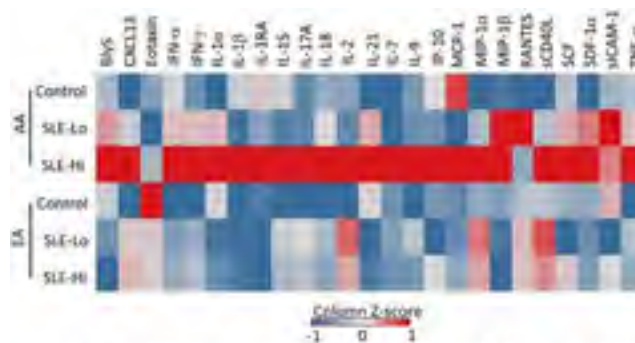


Figure 1. Pro-inflammatory cytokines are elevated in SLE patients, most significantly in patients of African American descent. Pro-inflammatory soluble mediators were measured by multiplex or ELISA. Overall trends in relative plasma soluble mediator levels are depicted by heatmap using Z-scores.

and ionomycin, PHA and ionomycin or Toll-like receptor (TLR) ligands TLR4, TLR7/8 and TLR9 for cytokine analysis of cell culture supernatants. All SLE patients met ACR classification criteria.

Results: Plasma levels of SCF ($p=0.0051$), sICAM-1 ($p=0.0097$), TNF α ($p=0.0302$), BlyS ($p=0.0312$), and IL-1RA ($p=0.0422$) were higher in African American SLE patients compared to European American SLE patients, whereas eotaxin ($p=0.0055$) was only higher in European American patients (Figure 1). In European American SLE patients with higher disease activity, SCF and sICAM-1 ($p<0.05$) were elevated compared to SLE patients with lower disease activity. African American SLE patients with higher disease activity were distinguished from lower disease activity patients by elevated levels of MCP-1 ($p=0.0048$), eotaxin ($p=0.029$), IL-7 ($p=0.03$), IL-9 ($p=0.041$) and CXCL13 ($p=0.032$). Following TLR stimulation, SLE patients with higher disease activity had a reduced fold change in most soluble mediators compared to SLE patients with lower disease activity and healthy controls, specifically with Type I and II IFN and IFN associated cytokines ($p<0.05$). This is likely due to the cell pathways being previously activated before stimulation. In addition, European American higher disease activity patients were distinguished from African American SLE patients by a higher fold change in IL-10 ($p=0.0068$) and IL-1RA ($p=0.045$) following TLR stimulation. African American patients were characterized by a higher fold change in most soluble mediators following PMA and ionomycin stimulation, whereas only the fold change in IL-10 ($p=0.023$) was higher in European American controls compared to patients.

Conclusion: Elevated soluble mediators contribute to heightened disease activity that is influenced by race with African American SLE patients having higher levels of pro-inflammatory cytokines and less involvement of regulatory pathways compared to European American patients.

Disclosure: S. Slight-Webb, None; M. C. Smith, None; H. T. Maecker, None; P. J. Utz, None; J. M. Guthridge, None; J. A. James, None.

Abstract Number: 1089

Commensal Gut Bacteria of Anti-Ro Positive Mothers of Children with Neonatal Lupus in Aggregate Resemble Healthy Subjects without Overt Dysbiosis of Abundance of Microorganisms

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Session Type: ACR Poster Session B

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Background/Purpose: Anti-Ro60 autoantibodies are present in asymptomatic individuals years before onset of disease. We hypothesize that differences in autoreactivity-inducing commensal abundances may drive progression to autoimmune diseases such as SLE. This study tests whether gut pathobionts associate with disease outcome in high titer anti-Ro⁺ women of children with neonatal lupus.

Methods: The study included 25 healthy controls and 85 anti-Ro⁺ mothers recruited from the Research Registry for Neonatal Lupus (RRNL); the RRNL consisted of 27 asymptomatic or undifferentiated autoimmune syndrome (UAS) (incomplete) and 58 Sjögren's Syndrome and/or ACR/SLICC SLE (complete), and 77 SLE patients (non-RRNL, recruited from NYU Specimen and Matched Phenotype Linked Evaluation (SAMPLE)). The rheumatologic diagnoses of the RRNL women were independently determined by two rheumatologists via questionnaire, telephone, and/or in-person history/physical exam, and review of medical records. After extraction of host and non-host genomic DNA from stool, the microbiome was assessed using 16S rRNA gene amplification using standard protocols (mean of 20k sequences per sample). Operational taxonomic units (OTUs) were identified by closed-reference OTU-picking using Green Genes as reference. Shannon's index (H') and relative abundance were tested for differences using the Kruskal-Wallis tests. To adjust for multiple comparisons, tests of lower taxa required significance at all higher taxonomic levels, similar to a Fisher's protected least significant multiple comparisons procedure.

Results: H' was different for phylum (p=0.0023), class (p<0.0001) and order (p<0.0001), but not family (p=0.62), between controls, RRNL and SLE (non-RRNL). For these three taxonomic levels, the non-RRNL SLE cases had greater diversity than either the controls or RRNL subjects. The strongest differences in relative abundance were for multiple subtaxa of the phylum *Firmicutes* (p=5.9x10E-4). Within *Firmicutes*, class *Clostridia* (p=9.3x10E-6), order *Clostridiales* (p=9.3x10E-6) show the strongest differences in mean abundance (controls 0.727, RRNL 0.717, SLE (non-RRNL) 0.620). Multiple families within *Clostridiales* showed significant differences (p<0.01) with *Peptostreptococcaceae* exhibiting the strongest statistical evidence (mean abundance controls 0.0248, RRNL 0.0303, SLE (non-RRNL) 0.0117; p=3.2E-07). Within RRNL, the complete and incomplete groups had comparable abundances at the order level (complete 0.7156, incomplete 0.7158), suggesting the primary distinction is with non-RRNL SLE cases.

Conclusion: Non-RRNL SLE showed significant increases in fecal diversity and significant reduction in relative abundance at multiple taxa compared to high titer anti-Ro RRNL subjects who in aggregate more closely resemble healthy subjects. Fecal microbiome differences between preclinical and established disease may provide insight regarding anti-Ro positivity and the progression to complete SLE.

Disclosure: R. M. Clancy, None; C. Langefeld, None; H. C. Ainsworth, None; H. M. Belmont, Exagen, 2; M. Blaser, None; P. M. Izmirly, None; C. Lacher, None; M. C. Marion, None; M. Masson, None; G. Silverman, None; J. P. Buyon, Exagen, 2.

Abstract Number: 1090

Cell-Free Mitochondrial DNA As a Novel Biomarker in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: We recently described a fundamental role for mitochondrial (mt)-mediated inflammation in systemic lupus erythematosus (SLE). Briefly, mtROS promoted formation of neutrophil extracellular traps (NETs), and extrusion of cell-free mitochondria and highly oxidized interferogenic mtDNA propagating disease in lupus-prone mice. However, though our data clearly demonstrate a role of mtDNA in vitro as well as in animal models, the clinical utility of cell-free mtDNA in human SLE was not known. Thus, the aim of the current study was to investigate the clinical utility of cell-free mtDNA as a non-invasive biomarker in SLE patients.

Methods: DNA isolated from plasma samples of healthy individuals (HC, n=20) and SLE patients (n=39) was analyzed for mtDNA (Cytochrome C Oxidase Subunit II) and nuclear (nu) DNA (Ribosomal Protein Lateral Stalk Subunit P0) using qPCR. NETs were analyzed by an in-house MPO-DNA ELISA. Anti-mitochondrial antibodies (anti-cardiolipin antibodies, aCL) were analyzed by ELISA. Patients were stratified based on mtDNA, aCL and NET levels using classification and regression tree (CART) analysis.

Results: SLE patients had significantly elevated levels of mtDNA as compared to HC ($p<0.0001$, 166576 vs. 36781 copies/ml of plasma). Surprisingly, in contrast to the elevated mtDNA levels, SLE patients had significantly lowered nuDNA compared to HC ($p<0.001$, 6799 vs. 15551 copies/ml of plasma), resulting in a skewed mtDNA/nuDNA ratio ($p<0.0001$, 30.82 vs. 2.602). Consistent with our hypothesis, mtDNA levels were particularly elevated in patients with evidence of NETosis as compared to patients with no NETs ($p<0.01$, 227404 vs. 124422 copies/ml of plasma). Further, mtDNA levels were associated with markers of inflammation and disease activity: erythrocyte sedimentation rate ($r=0.49$, $p<0.01$), hemoglobin ($r=-0.59$, $p<0.01$) and complement consumption ($p<0.05$). In addition to mtDNA, mitochondrial-specific autoantibodies are also indicative of mitochondrial extrusion. Accordingly, we found a significant correlation between mtDNA levels and autoantibodies specific for cardiolipin, an important mitochondrial phospholipid ($r=0.38$, $p<0.05$). A subgroup analysis revealed that aCL-positive patients had elevated mtDNA levels compared to aCL-negative patients ($p<0.05$, 183291 vs. 128096 copies/ml of plasma). In CART analysis, aCL levels, mtDNA copies/mL and NETs were identified as major predictors to stratify patients into non-active (SLEDAI 0-5) and active disease groups (SLEDAI ≥ 6 to 18) with a sensitivity and specificity of 79% and 71% respectively.

Conclusion: SLE patients have evidence of markedly elevated levels of mtDNA associated with mitochondrial autoimmunity and disease activity, indicating exaggerated mitochondrial extrusion and impaired mitochondrial clearance partaking in the lupus pathogenesis. Though a limited number of patients, the ability to stratify patients into active and inactive disease suggest that mtDNA may be a promising novel biomarker in SLE. Thus, therapies targeting mitochondrial extrusion are expected to reduce inflammation, as well as long-term morbidities, including cardiovascular disease.

Disclosure: B. Duvvuri, None; R. Moore, None; C. Lood, None.

Abstract Number: 1091

Serine Arginine-Rich Splicing Factor 1 (SRSF1) Is Essential for T Lymphocyte Homeostasis and Decreased Levels of SRSF1 Correlate with Lymphopenia in SLE Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Lymphopenia is one of the most common clinical features in patients with systemic lupus erythematosus (SLE), and associates with severe disease and comorbidities such as infections. However, the mechanisms of lymphopenia in SLE are still unclear. T cells from SLE patients exhibit numerous defects in gene expression, including altered expression the Bcl-2 family genes, which have pro- and anti-apoptotic alternative splice isoforms. By discovery approaches we previously identified the serine arginine-rich splicing factor 1 (SRSF1) in human T cells and showed that it is an important regulator of signaling and cytokine genes. SRSF1 expression levels are decreased in T cells from SLE patients, and this decrease associates with severe disease. Because SRSF1 is an important survival factor known to regulate alternative splicing of Bcl-2 genes, we evaluated the role of SRSF1 in T cell homeostasis and correlation with lymphopenia in patients with SLE.

Methods: To delete *Srsf1* selectively in T cells, we crossed *Srsf1*-flox mice with *d.Lck*.Cre transgenic mice to generate *Srsf1*conditional knockout (*Srsf1*-cko) mice, and analyzed lymphoid tissues (spleen and lymph nodes). Apoptosis was assessed in splenocytes ex vivo or after crosslinking with anti-CD95 (Fas), and flow cytometry staining for 7AAD and Annexin V. Apoptosis associated genes were analyzed by RT-qPCR. Naïve CD4 T cells from *Srsf1*-wt and -cko mice were stimulated with anti-CD3 and anti-CD28 antibodies for 72hrs, and total RNA was subjected to RNA-sequencing. Peripheral blood was collected from 42 SLE patients, and age-, race- and gender-matched healthy individuals. T cells were isolated by negative selection, and SRSF1 protein levels assessed by western blots. Clinical and lab tests for all patients were recorded. SLE patients were divided into lymphopenic ($<1000/\mu\text{L}$) and non-lymphopenic groups, and correlations were assessed with relative SRSF1 expression levels.

Results: Peripheral T cell lymphopenia was observed in the *Srsf1*-ckomice. Lymphopenia was evident in young mice compared with aged mice, and was more profound in CD8 than CD4 T cells. Crosslinking with anti-CD95 (Fas) antibody led to increased apoptosis in T cells from *Srsf1*-cko mice. Gene set enrichment analysis (GSEA) of RNA-sequencing data from effector CD4 T cells of *Srsf1*-cko mice showed aberrant expression of genes in the apoptosis and cell cycle pathways.

We validated expression levels of the Bcl-x gene and found that its anti-apoptotic long (L) isoform was decreased in spleen cells from *Srsf1*-cko mice. In parallel, examination of SRSF1 levels in T cells from SLE patients revealed that reduced SRSF1 protein levels correlated positively with lymphopenia in SLE patients.

Conclusion: These results suggest that SRSF1 controls expression of survival/apoptosis-related genes in T cells and is a vital regulator of T lymphocyte homeostasis *in vivo*, and its reduced expression levels associate with lymphopenia in SLE patients. Therefore, the deficiency of SRSF1 may represent a molecular defect that contributes to the pathophysiology of autoimmune disease.

Disclosure: T. Katsuyama, None; K. Iida, None; V. R. Moulton, None.

Abstract Number: 1092

Immune Complex-Driven Neutrophil Activation and BAFF Production Promote B Cell Activation and Autoantibody Production in Human SLE

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: The production of anti-nuclear auto-antibodies (Ab) and the formation of immune complexes (IC) are hallmarks of Systemic Lupus Erythematosus (SLE). Enhanced neutrophil (PMN) activation and formation of neutrophil extracellular traps (NETs), through engulfment of nucleic acid-containing ICs, have been implicated in disease pathogenesis, particularly in the acceleration of tissue inflammation, end-organ and vascular damage. Upon activation, PMNs may contribute to B cell activation and auto-Ab production by three main mechanisms: indirectly by NETs-stimulated interferon production, or directly, by releasing B cell activating factor (BAFF) and extruding autoantigens, such as mitochondria, during NETosis. Still, little is known about the link between the PMN activation and B cell immune responses in human SLE. This study was undertaken to test whether IC-driven PMN activation and NET formation contribute to BAFF increase, auto-Ab production and B cell activation in SLE patients.

Methods: BAFF levels were analyzed in serum samples from 60 SLE patients and 20 healthy controls (HC) by ELISA. Markers of neutrophil activation and NETosis (S100A8/A9, MPO-DNA complexes, cell-free oxidized (8-OHdG) DNA and mitochondrial (mt) DNA levels) were analyzed by ELISA, fluorimetric assays, and qPCR. FcγRIIA internalization, a bioassay for IC quantification, was analyzed by flow cytometry. Anti-DNA IgG titers, anti-cardiolipin (CP) IgM and IgG, C3 and C4 complement and CRP levels were obtained from clinical records. PMNs from healthy donors were stimulated with RNP-containing ICs and PMN activation, BAFF production, and B cell activation were studied *in vitro*.

Results: Levels of BAFF were markedly elevated in SLE as compared to HC serum samples ($p < 0.0001$). Consistent with our hypothesis of neutrophil-driven BAFF release in SLE, levels of BAFF correlated with markers of PMN activation (S100A8/A9) and NET-derived components, including mtDNA and cell-free 8-OHdG DNA ($r = 0.34-0.38$, $p < 0.05$ for both analyses). Increased BAFF levels associated significantly with decreased serum C3 and C4 levels, suggesting an association with ongoing IC-driven disease. Furthermore, levels of serum ICs correlated with an increase in BAFF levels ($r = 0.38$, $p = 0.02$) as determined by a flow cytometry-based bioassay. Auto-Ab analysis showed positive correlations between anti-DNA and anti-CL Ab titers, BAFF levels and markers of NETosis, including 8-OHdG DNA and S100A8/A9 levels. Stimulation of PMNs with ICs *in vitro* induced PMN activation, NET formation, and a significant increase in BAFF release three-to-six hours post-stimulation. PMN-B cell co-culture experiments showed increased B cell activation in response to IC-induced PMN activation.

Conclusion: Our results support the hypothesis that PMNs, through IC-mediated activation, release BAFF and auto-Ags, including DNA and mitochondrial components, which may contribute to B cell activation and production of pathogenic auto-Abs. These findings bring new insight into the mechanisms of PMN-B cell interactions involved in the pathogenesis of SLE.

Disclosure: A. Vasconcellos, None; J. Marken, None; S. Skopelja-Gardner, None; C. Lood, None; N. V. Giltiay, None.

Serologic Evidence Linking Epstein Barr Virus Reactivation, Heightened Interferon Pathway Activation and Increased Disease Activity in Patients with Systemic Lupus Erythematosus

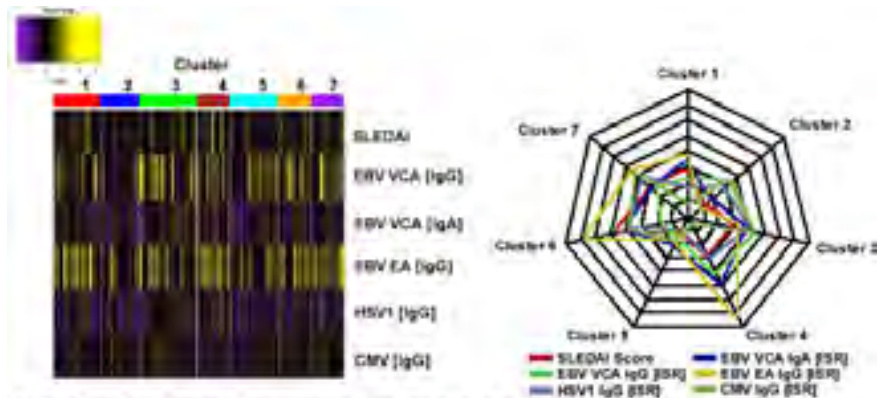
Rebecca Wood¹, Lauren Guthridge¹, Carla J. Guthridge², Rebecka L. Bourn¹, Hua Chen¹, Wade DeJager¹, Susan R. Macwana¹, Stan Kamp¹, Rufe Lu^{1,3}, Cristina Arriens¹, Eliza Chakravarty¹, Katherine Thanou¹, Joan T. Merrill¹, Joel M. Guthridge^{1,4} and **Judith A. James**^{4,5}, ¹Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, ²Arthritis & Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, ³Medicine and Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, ⁴University of Oklahoma Health Sciences Center, Oklahoma City, OK, ⁵Arthritis and Clinical Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK

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Session Date: Monday, October 22, 2018
Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster II
Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: SLE is a clinically heterogeneous disease oftentimes characterized by a waxing and waning course. Mechanisms of SLE flare remain elusive. This study examined relationships between SLE disease activity, immune pathways and serologic evidence of viral exposures and reactivation in molecular subsets of SLE patients.

Methods: Serial or single samples of plasma and RNA (n=290) were collected from 184 adult SLE patients who met ACR classification and cohort matched controls (n=49). Disease activity was assessed by the SELENA- modified SLEDAI. Immune pathways were evaluated by modular transcriptional analysis of gene expression data (Illumina Beadchip) and by soluble mediators (n=32; multiplex bead-based assay and ELISAs). These data were used in random forest modeling to group patients into seven molecular defined subsets. Viral seropositivity and antibody concentrations were detected by



International Standardized Ratio of Viral Antibodies in SLE Patients with High and Low Disease Activity, and Controls						
	Higher Disease Activity (n=126) ¹	Lower Disease Activity (n=166) ²	Control	Higher vs Control P-value	Lower vs Control P-value	Higher vs Lower P-value
EBV-VCA IgG	4.44 (3.42, 5.15)	4.38 (3.47, 5.19)	3.52 (2.75, 4.65)	0.0045	0.0037	1
EBV VCA IgA	0.714 (0.304, 1.39)	0.713 (0.313, 1.55)	0.524 (0.225, 0.899)	0.031	0.033	0.85
EBV EA IgG	0.822 (0.324, 2.23)	0.540 (0.242, 1.46)	0.045 (0.206, 0.630)	9 X 10⁻⁵	0.013	0.033
CMV IgG	3.58 (0.485, 5.10)	2.86 (0.298, 4.79)	1.97 (0.977, 3.00)	0.0056	0.098	0.1
HSV-1 IgG	3.42 (1.60, 4.40)	3.35 (1.44, 4.22)	3.37 (1.71, 3.76)	0.14	0.45	0.33

¹SLEDAI-high, ²SLEDAI-low

ELISA for antibodies against Epstein Barr virus (EBV)-Viral Capsid Antigen (VCA; IgG and IgA), EBV-Early Antigen (EA; IgG), Cytomegalovirus (CMV; IgG), and Herpes Simplex Virus (HSV1; IgG).

Results: Serologic evidence of EBV reactivation was more common in SLE patients versus controls as measured by antibodies against EBV-EA (IgG; 40% vs 13%; OR=4.57, $p=0.0006$) or EBV-VCA (IgA; 36% vs 17%; OR=2.70, $p=0.019$). CMV1 and HSV1 seropositivity rates showed no differences between patients and controls. IgG responses against EBV-VCA were nearly universal in these adult patients and controls, but concentrations of EBV-VCA (IgG and IgA) and EBV-EA (IgG) were higher in SLE patients (Table). In cross sectional analysis SLE patients with higher disease activity had higher concentrations of EBV-EA IgG than those with lower disease activity (Table). SLE patients with serologic evidence of EBV reactivation by EA IgG responses had higher levels of interferon (IFN) associated molecules IP10 ($p=3.4 \times 10^{-14}$), BLYS (5.5×10^{-5}), and IL10 ($p=0.00013$). HSV1 IgG positive SLE patients also showed higher levels of IP10 (2.2×10^{-7}). EBV-EA IgG responses were enriched in molecularly defined patient clusters with higher expression of IFN and inflammatory modules and soluble mediators (Figure). Patients in these clusters were also more likely to have major organ involvement, such as renal or neurologic disease.

Conclusion: Serologic evidence of EBV reactivation is more common in SLE patients compared to healthy controls. EBV-EA IgG is elevated in SLE patients with active disease and corresponds with increases in IFN-associated mediators. This study provides serologic evidence suggesting a possible role for viral reactivation in SLE disease activity.

Disclosure: R. Wood, None; L. Guthridge, None; C. J. Guthridge, None; R. L. Bourn, None; H. Chen, None; W. DeJager, None; S. R. Macwana, None; S. Kamp, None; R. Lu, None; C. Arriens, Exagen Diagnostics, Inc, 2; E. Chakravarty, None; K. Thanou, None; J. T. Merrill, BMS, GSK, 2, BMS, GSK, UCB, Questcor, EMD Serono, Amgen, Celgene, Pfizer, RemeGen, Exagen, MedImmune, Lilly, Janssen, Xencor, Sanofi, Neovacs, Immupharma, Astellas, Glenmark, ILTo, 5, Have given talks for BMS but not for Speaker's bureau, 9; J. M. Guthridge, None; J. A. James, None.

Abstract Number: 1094

Endogenous $\text{IFN}\beta$ Production Is Required for Efficient BCR Crosslinking and Survival of SLE B Cells

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Session Date: Monday, October 22, 2018

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Background/Purpose: Increased type I interferon (IFN) has been shown to affect survival and activation of B cells in SLE. This study investigated novel mechanisms of endogenous production and autocrine activity of $\text{IFN}\beta$ in SLE B cells at the single-cell level.

Methods: $\text{IFN}\beta$ in B cells from SLE patients was analyzed using t-SNE platform based high dimensional flow cytometry. Intracellular $\text{IFN}\beta$ expression was visualized and analyzed by super-resolution confocal imaging and ImageStream analysis. Single cell gene expression analysis was carried out using the Fluidigm/BioMark system for targeted expression of low abundance genes, and the 10x Chromium platform for unbiased transcriptome analysis of up to 4,000 B cells per subject. Functional production of type I IFNs by B cells was analyzed using a human type I IFNs SEAP reporter HEK293 cell line.

Results: High dimension flow cytometry analysis identified intracellular $\text{IFN}\beta$ expression in pDCs, B cells, and CD4 T cells. There was increased expression of $\text{IFN}\beta$ in B cells from PBMCs of African American SLE patients compared to European SLE patients and healthy controls. B-cell intracellular $\text{IFN}\beta$ was associated with serum positivity of ANA and renal disease. Using a Fluidigm targeted-gene approach, B cells could be divided into three subpopulations, namely $\text{IFN}\beta$ +, $\text{IFN}\alpha$ +, and ISG + subpopulations, suggesting B cells not only respond to type I IFNs but also express type I IFNs including $\text{IFN}\beta$ and different $\text{IFN}\alpha$ genes. TLR7 and TLR3 were mainly expressed by $\text{IFN}\beta$ + and $\text{IFN}\alpha$ + cells, respectively. The production of functional $\text{IFN}\beta$ and $\text{IFN}\alpha$ protein by single B cells from SLE subjects and was verified using a novel AP live staining of HEK-blue reporter cells. There was enhanced IFNAR signaling by reporter cells in direct

contact with SLE B cells which was blocked by anti-IFN β and anti-IFN α . Unbiased single cells transcriptome analysis of SLE B cells using the 5' 10X Chromium platform and Loupe™ V(D)J Browser indicated that gene clusters in type I IFN expressing or responding SLE B cells exhibited unique heavy- and light-chain gene expression repertoires.

Conclusion: (i) B cells are an important source of type I IFNs in modulating TLR and BCR responses in SLE; (ii) well-orchestrated and distinct programs in type I expression and responses genes in subsets of B cells, and (iii) distinct pathways of B cell survival and activation based on combined signaling through TLR, BCR and IFNAR with a distinct BCR heavy- and light-chain repertoire.

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Abstract Number: 1095

IFN Gene Expression Correlates with Frequency of Circulating Switched Memory B-Cells in Patients with Incomplete Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

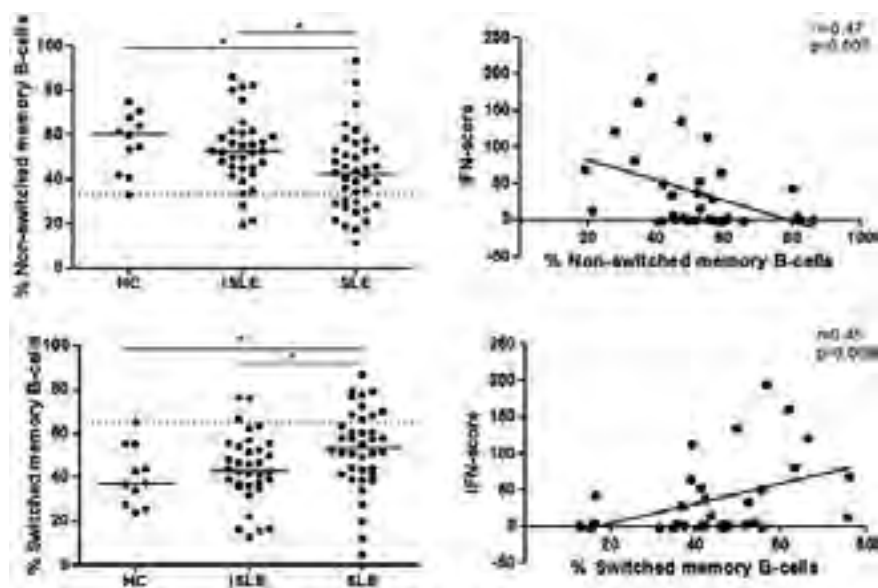
Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Incomplete systemic lupus erythematosus (iSLE) includes patients with typical features of SLE, who do not meet classification criteria. Still, up to 50% will develop SLE in the future. Follow-up of these iSLE patients can potentially unravel the pathogenesis of SLE. Interferon (IFN) type-I is an important early mediator in SLE. Furthermore, B cells are considered to be the main culprits in SLE pathogenesis, owing to their production of autoantibodies. The purpose of this research is assessing whether IFN gene upregulation is associated with alteration in B-cell subset distribution in iSLE patients.

Methods: Thirty-four iSLE patients (ANA titer $\geq 1:80$, ≥ 1 ACR clinical feature), 38 SLE patients with quiescent disease (SLEDAI ≤ 4) and 11 HC were included. B-cell subsets were determined in peripheral blood mononuclear cells (PBMC) by flow cytometry based on surface markers and were subdivided into naïve B-cells (CD27⁺CD38^{low}), transitional B-cells



(CD27⁺CD38^{High}), plasma cells (CD27^{High}CD38^{High}), and memory cells (CD27⁺), of which the latter were subdivided into switched (IgD⁻IgM⁺) and non-switched (IgD⁺IgM⁺) memory B cells. Simultaneously, RNA was isolated from whole blood using PAX gene tubes and reversely transcribed to cDNA and quantitatively analyzed by RT-PCR. IFN score was calculated based on cumulative expression of 3 IFN-related transcripts (IFI44L, LY6E, MX1).

Results: Baseline characteristics are shown in Table 1. SLE patients had decreased non-switched memory cells and increased switched memory cells in comparison with iSLE patients and HC (figure 1). Other subsets were statistically comparable between the groups. The IFN score was increased in 17/32 iSLE patients (53%) and 24/38 SLE patients (63%). Remarkably, in iSLE patients, IFN score correlated positively with percentages of switched memory cells (figure 2, $r=0.45$, $p=0.009$), plasma cells ($r=0.42$, $p=0.01$), transitional B-cells ($r=0.47$, $p=0.006$) and negatively with non-switched memory cells ($r=-0.47$, $p=0.007$). In SLE, IFN score correlated with transitional B-cells ($r=0.47$, $p=0.003$), naïve B-cells ($r=0.47$, $p=0.003$) and negatively with total memory B-cells ($r=-0.41$, $p=0.01$), but not with switched or non-switched memory cells.

Conclusion: Although lower proportions of circulating switched memory B cells were seen in iSLE compared to SLE patients, IFN score in iSLE patients correlates strongly with switched memory cells. This could imply that IFN expression triggers progression to SLE by stimulating isotype switching of B-cells.

	HC (n=11)	iSLE (n=34)	SLE (n=38)
Female gender, n (%)	9 (82)	27 (79)	32 (84)
Age, median (range)	34 (26-64)	46 (18-84)	42 (19-74)
Disease duration, years, median (range)		1.2 (0.1-4.6)	3.1 (0.5-6.8)
ACR criteria, median (range)		3 (1-3)	5 (2-9)
SLICC criteria, median (range)		3 (1-4*)	5 (4-9)
SLEDAI median (range)		0 (0-6)	2 (0-4)
Hydroxychloroquine use, n (%)		10 (30)	31 (82)
Immunologic features, n (%)			
ANA or SSA-pattern pos (%)		34 (100)	39 (100)
Anti-dsDNA pos (%)		9 (26)	32 (84)
Anti-SSA pos (%)		15 (44)	13 (34)
Anti-Sm pos (%)		2 (6)	7 (18)
Decreased complement pos (%)		5 (19)	23 (62)

Disclosure: W. Lambers, None; G. Lanting, None; W. H. Abdulahad, None; H. Bootsma, None; J. Westra, None; K. de Leeuw, None.

Abstract Number: 1096

Unexpected Association between Health-Related Quality of Life and the Blood Interferon Modular Transcriptional Signatures in Patients with Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: SLE has important effects on health-related quality of life (HRQOL) and is not well correlated to disease activity. As most SLE patients in remission have a consistent interferon (IFN) signature, it is assumed that persistent fatigue and/or impaired HRQOL is mediated by insufficiently controlled IFN response. The objective of the study was to test whether blood transcriptomic IFN signatures were associated with HRQOL.

Methods: Patients fulfilling the ACR revised criteria for SLE were included at a referral center for autoimmune diseases and followed up prospectively. Each assessment included demographic, clinical and laboratory evaluations, as well as whole blood transcriptomic data (Illumina beadchips). Disease activity was evaluated by the SELENA-SLEDAI score. HRQOL was assessed at each visit by the self-administrated SF-36 questionnaire, which includes two summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS), and eight domains: physical function (PF), role

physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). SF-36 scores ranged from 0 to 100, with higher scores reflecting better HRQOL. Transcriptomic analyses were performed using the second generation of a modular framework. Three IFN modules defined the modular IFN score: M1.2, M3.4 and M5.12.

Results: 57 SLE patients were evaluated. Median age was 38 years (18-70), 86% were women and 88% were caucasian. Median SLEDAI was 4 (0-22). At inclusion, SLE was clinically quiescent in 27 (47%) patients, while 30 (53%) were experiencing a flare, with active lupus nephritis in 19 (33%). Compared to the French general population (n=18754, mean age of 42 years), SLE patients had a marked reduction of HRQOL in all SF-36 domains and summary scores ($p<0.0001$), with delta of SF-36 scores ranging from 6 (MCS) to 27 (RP). In univariate analysis, the 3 IFN modules showed no significant correlation with any of the SF36 domains except for SF ($r=0.44$, $p<0.01$; $r=0.33$, $p<0.05$; $r=0.28$, $p<0.05$ for M1.2, M3.4 and M5.12 respectively), revealing unexpectedly that the higher the IFN signature, the better SF score. In multivariate analysis, taking into account other parameters associated with HRQOL such as flares, age, ethnicity, smoking and renal severity (nephrotic syndrome), SF was independently associated with the IFN score ($p = 0.027$). Analyses restrained to only quiescent patients ($n=27$, defined as clinically quiescent patients with or without immunological activity) yielded greater association between IFN score and SF (for the 3 modules) as well as MH (for M3.4). Additional analysis on all samples from quiescent visits ($n=51$) confirmed the association between the 3 IFN modules activity and SF, as well as MH and BP.

Conclusion: Far from confirming our hypothesis, this study demonstrates an unexpected positive association between IFN signature and HRQOL in SLE patients. These findings, consistent with the absence of impact on fatigue or HRQOL of recently tested IFN-blockade strategies, needs to be confirmed by other studies.

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Abstract Number: 1097

Spatial-Time Cluster Analysis of SLE Disease Activity

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Cluster detection is an essential tool in the public health domain with the goal of detecting anomalous clusters of disease cases. We performed a spatial-time cluster analysis of the Hopkins Lupus cohort with the goal of identifying potential spatial-time clusters of SLE organ specific disease activity.

Methods: 1844 patients who fulfilled ACR or SLICC classification criteria for SLE and who had recorded home addresses were included in the analysis. Cluster detection analysis in both space and time of disease activity expressed as Physician Global Estimate (PGA) was performed. The area utilized in this analysis was a 350 kilometer radial buffer around the Hopkins Lupus Center, and included all of Maryland, Delaware, and District of Columbia, as well as parts of Pennsylvania, New Jersey, Virginia, and West Virginia. This area was considered due to the high and consistent density of study participants. The data ranged from 1987 to 2017, with the spring, summer, fall, and winter seasons serving as time units for the temporal based analyses.

Results: CNS, renal, and joint flares have both seasonal patterns as well as large-scale multi-year trends. CNS flares clustered between Annapolis, MD and Frederick, MD between 1987 and 2000, renal flares clustered in central Maryland and northern Virginia between 2002 and 2006, and a joint flares cluster included Delaware, Delaware Bay area, and Chesapeake Bay area between 2003 and 2014. Maps were generated highlighting the study area, flares, and identified clusters from all analyses.

Conclusion: We describe the first space-time clusters of lupus organ-specific disease activity, strongly supporting the role of environmental factors as drivers of lupus activity.

Disclosure: G. Stojan, None; A. Kvit, None; F. Curriero, None; M. Petri, None.

Comparative Analysis of the Total Proteome of the Skin Lesions from Cutaneous Lupus Erythematosus (CLE) and Dermatomyositis (DM)

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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

Background/Purpose: Cutaneous lupus erythematosus (CLE) and dermatomyositis (DM) are autoimmune diseases. The histopathological pattern of skin involvement can be similar, i.e. interface dermatitis, but the systemic manifestations are very different. While dermatomyositis commonly affect muscles, lupus erythematosus may affect any organ system. Autoantibodies against intracellular targets are common in both conditions, but the specific targets of the autoantibodies differ between the two conditions.

Our aim was to investigate a whole proteome of inflammatory foci of the CLE and DM lesions in a comparator manner and identify disease unique mechanisms of inflammation.

Methods: Patients with CLE (n=6), DM (n=5) and controls (n=6) were included and biopsied at diagnosis or disease exacerbation. Skin biopsies were examined by a pathologist, and selected inflammatory foci were laser microdissected. The total protein content of the microdissected tissue was then analyzed using mass-spectrometry.

Results: In DM, there were 25 highly upregulated proteins, while CLE infiltrates were more protein rich and there were 88 proteins with up to 9-fold upregulation. Protein expression comparison between CLE and DM identified 22 differentially upregulated proteins, and all had higher abundance in CLE than in DM. A protein network analysis was performed by STRING platform (string-db.org). The network of interferon (IFN)-regulated proteins was abundant in both CLE and DM, including: IFIT, MX, OAS, STAT gene families and also EIF2AK2. Also, proteins involved in oxidative stress and antigen processing: IL4I1, TAP1 and TAP2 were highly upregulated in both CLE and DM. Proteins expressed differentially in CLE covered complement proteins (C1b), including membrane attack complex (C5, C6, C7, C8A and B) and complement regulators (CFHR1, CFHR2, CFHR5). Also, regulators of coagulation: thrombospondin 2 (THBS2), thrombin (F2) and annexin A3 (ANXA3) were highly abundant in CLE.

Conclusion: Inflammatory foci in the interface dermatitis in CLE and DM contain high abundance of IFN-regulated proteins, as well as regulators of oxidative stress and antigen processing. The proteomics technique allowed identification of pathways differentially activated in CLE, including complement activation products and regulators of coagulation. Our study identified multiple pathways activated at the site of inflammation which will be of interest in further search of new therapeutic targets.

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Ongoing DNA Damage, Chromatin Deregulation and Defective DNA Damage Response in Systemic Autoimmune Rheumatic Diseases

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Recent data highlight that patients with Systemic Lupus Erythematosus (SLE) have defects in two main DNA repair pathways, namely nucleotide excision repair (NER) and DNA double-strand break repair and that increased apoptosis observed in SLE may be partly attributed to the deregulated DNA damage response (DDR) network. Herein, we tested the hypothesis that ongoing DNA damage is present in patients with systemic autoimmune rheumatic diseases.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from patients with SLE (n=14), Rheumatoid Arthritis (RA) (n=23), Systemic Sclerosis (SSc) (n=8) and 34 healthy controls (HC). Endogenous DNA damage levels were assessed using single-cell gel electrophoresis (comet assay) of untreated PBMCs. Repairing capacity of the two sub pathways of NER, i.e. global genome repair (GGR) and transcription-coupled repair (TCR), as well as interstrand cross-links (ICL) repair were assessed after *ex vivo* treatment of PBMCs with genotoxic agents. Chromatin organization and expression of critical DNA repair-associated genes were also examined.

Results: Higher levels of endogenous DNA damage were present in patients compared to HC [Olive Tail Moment units of HC: 4.0 (1.5-9.9), SLE: 9.0 (2.4-23.0), RA: 11.5 (3.4-35.6) and SSc: 12.1 (5.4-29.3, all $p < 0.01$]. SLE patients and HC displayed similar DNA repair efficiencies of the transcribed strand of the active N-ras gene (repaired by TCR), but in SLE the repair in the non-transcribed strand of the active N-ras gene was slower, as well as in both strands of a non-coding DNA region located outside the N-ras gene (repaired by GGR, all $p < 0.001$), showing that the previously observed deficiency of NER in SLE patients may be specifically attributed to reduced GGR capacity while TCR is preserved. Of interest, we found that the repair efficiency of GGR in different genomic loci was inversely correlated with the local chromatin condensation, with autoimmune disease patients exhibiting more condensed chromatin structures. Moreover, critical molecular components of NER [such as DDB1 and XPC genes (associated with the GGR sub pathway) and XPA, LIG1, RPA1, ERCC2 genes (associated with both NER sub pathways)] were significantly down-regulated in SLE, RA and SSc patients versus HC. Finally, although the repairing capacity of cytotoxic ICL-lesions was similar in both HC and autoimmune disease patients, higher accumulation of these lesions was observed in patients' PBMCs, possibly due to the higher burden of unrepaired NER lesions (precursors of ICLs). Interestingly, individual ICL repair efficiencies were inversely correlated with apoptosis rates in the same cells, underlying the cytotoxic character of this lesion.

Conclusion: Our study demonstrates that increased ongoing, spontaneous DNA damage is present in SLE, RA and SSc, possibly due to epigenetically regulated defective DNA repair mechanisms. Further studies to uncover a potentially crucial role of these mechanisms in the pathogenesis of systemic autoimmunity are underway.

Disclosure: M. Pappa, None; N. I. Vlachogiannis, None; A. Argyriou, None; V. L. Souliotis, None; P. Sfikakis, None.

Abstract Number: 1100

The Frequencies and Molecular Profiles of CD16+ Monocyte Subsets in Patients with Systemic Lupus Erythematosus, Primary Antiphospholipid Syndrome, and Antiphospholipid Syndrome with Lupus, Identify Specific Clinical Features of These Diseases

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster II

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Background/Purpose: This study, developed within the IMI-JU project PRECISESADS framework, aimed to determine the enrichment on CD14+ and CD16+ monocyte subpopulations in SLE, APS and APS+SLE patients, and to investigate their profiles and role in the pathogenesis of these diseases.

Methods: The frequencies of monocyte subpopulations in the peripheral blood of 146 healthy donors and 140 SLE patients included in the PRECISESADS study were determined by flow cytometry. Two additional cohorts of 21 APS+SLE and 19 APS patients were also evaluated. Clinical features, proinflammatory circulating mediators, as well as the prothrombotic/proinflammatory/pro-oxidative profiles of monocytes subsets -at both gene and protein levels- were analyzed.

Results: The frequencies of CD14+CD16++ (non-classical) monocytes were reduced in SLE patients, while CD14+CD16+ (intermediate) monocytes were increased. The reduced frequencies of CD16+ monocytes were negatively associated with the positivity for anti-dsDNA autoantibodies, as well as with renal involvement -demonstrated by biopsy-confirmed nephritis, proteinuria, and presence of macrophages in urine samples-, all of which might reflect a recruitment process of this subset in renal tissues. Correlation studies indicated a link between the reduced frequency of non-classical monocytes and increased levels of circulating inflammatory mediators. Conversely, in SLE patients with augmented cardiovascular risk, increased frequencies of CD14+CD16+ monocytes were observed. These results prompted us to evaluate the proportion and profile of this inflammatory subtype in parallel cohorts of SLE+APS and APS patients, on which thrombosis is the main clinical disorder.

SLE+APS patients showed enrichment in both CD16+ subsets of monocytes, associated with the positivity for anti-dsDNA antibodies and the presence of atheroma plaques. Correlations among the frequency of those monocyte subsets and circulating inflammatory mediators were also demonstrated. Moreover, these subsets displayed an increased inflammatory and prothrombotic profile when compared with classical CD14+ monocytes.

In APS patients we also saw enrichment of the CD16+ inflammatory subsets, associated to recurrent thrombotic events and pathologic carotid intima-media thickness. The scores of various markers related to autoimmunity, oxidative stress and prothrombotic molecules correlated with the proportions of CD16+ monocytes, which showed an activated profile similar to that observed in SLE+APS patients.

Conclusion: Circulating CD16+ monocytes might constitute a subpopulation of proinflammatory cells whose frequency and molecular profiles might identify APS, APS+SLE and SLE patients suffering thrombosis, atherosclerosis and organ involvement.

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Abstract Number: 1101

Extracellular Vesicle-Mediated Delivery of EBV SMALL RNA (EBER1) Activates LUPUS Nephritis Related Antiviral Immunity in Tubular Epithelial CELLS VIA TLR3

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: In lupus nephritis (LN), genetic and environmental factors drive the chronic activation of antiviral defenses leading to immune complex-mediated glomerular and tubular damage. Increasing evidence suggests the involvement of extracellular vesicles (EVs) in autoimmune disease. Currently a role for EVs in the pathogenesis of lupus nephritis has not been proposed. Objectives: To investigate the role of EVs in the pathogenesis of LN.

Methods: To determine the presence of EVs in kidneys, biopsies from LN patients and IgA- nephropathy and Focal Segmental Glomerulosclerosis control patients were used. Serum samples from SLE patients and from RA patients as controls were used to determine the presence of circulating EVs. Primary renal tubular epithelial cells (TEC) were cultured, and Kidney injury molecule-1 (KIM1) expression was assessed by FACS. Exosomes were analyzed by electron microscopy and western blot. mRNA analysis was performed by qPCR. TLR3 inhibition was performed with TLR3/dsRNA complex inhibitor and with hydroxychloroquine.

Results: We show that EVs deliver virus-derived small RNA and activate TEC via toll-like receptor 3 (TLR3). Highly specific stem-loop RT-PCRs revealed Epstein Barr Virus (EBV)-encoded small RNAs in LN biopsies while quantitative EBV-DNA PCR, sensitive to a single copy was negative. In situ hybridization failed to detect nuclear EBV-EBER1 (i.e. EBV-infected cells) in LN biopsies. However, we observed atypical EBER signal in the cytoplasm of TECs in LN but not in disease control biopsies, suggestive of uptake of extra-renal EBER. Consistent with this, we detected EBER1 in circulating EVs of SLE sera. The LN tissues express strongly elevated levels of TLR3, Interferon induced transmembrane-1 and -3, and TNF α . Primary TEC cultured in vitro endocytose EBER1-EVs secreted by EBV-infected B cells via phosphatidylserine receptors such as KIM-1. Importantly, EV-EBER1 uptake by TEC triggers antiviral immunity and pro-inflammatory cytokine secretion in a Toll-like receptor 3 (TLR3)-dependent manner. Treatment with hydroxychloroquine (HCQ) or a small molecule inhibitor that blocks TLR3-RNA interactions strongly reduced the pro-inflammatory effects of EBER1.

Conclusion: We propose that small RNA-loaded EVs exacerbate pre-existing autoimmunity in SLE patients by engaging tubular epithelial TLR3, supporting the rationale for TLR3-blockade as therapeutic strategy in the treatment of lupus nephritis.

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Abstract Number: 1102

Multi-Organ RNA-Sequencing of Patients with Systemic Sclerosis (SSc) Finds That Intrinsic Subsets Are Conserved across Organ Systems

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SESSION INFORMATION

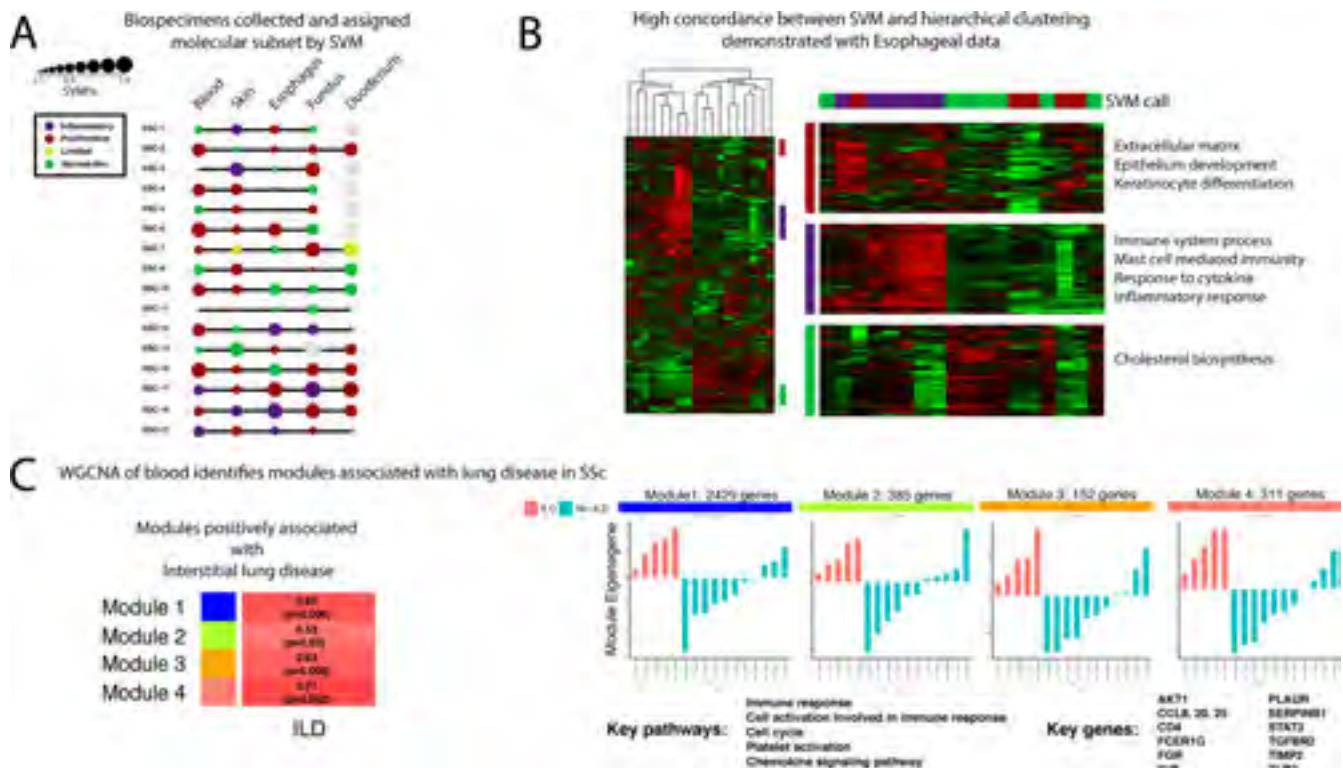
Session Date: Monday, October 22, 2018

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Session Type: ACR Poster Session B

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

Background/Purpose: Internal organ involvement is the primary cause of morbidity and mortality in systemic sclerosis (SSc). Here we tested the hypothesis generated from a meta-analysis of ten different SSc datasets, that any single patient



with SSc would have the same deregulated molecular signatures across multiple organ systems, consistent with the systemic nature of the disease.

Methods: RNA sequencing (RNA-seq) was performed on at least four organ biospecimens (skin, esophagus, fundus, duodenum, and blood) from 16 patients who met 2013 ACR/EULAR criteria for SSc. RNA was sequenced by 75bp paired-end RNA-seq at >80 million reads per sample and aligned to the reference genome (hg19). DESeq2 was used to identify differentially expressed genes across the various tissue pairs. Each sample was assigned to an intrinsic gene expression subset (inflammatory, proliferative, limited, or normal-like) using a Support Vector Machine (SVM) classifier and unsupervised hierarchical clustering with profiles of normalized Reads Per Kilobase of transcript per Million mapped reads (RPKM) values. Weighted Gene Co-Expression Analysis (WGCNA) was used to identify modules across tissues.

Results: Hierarchical clustering shows that biospecimens from the same tissue type cluster together regardless of whether a patient has SSc. We normalized each tissue specific dataset to allow comparative analyses of SSc biology across the tissues. We recapitulated the intrinsic subsets previously identified in the skin and esophagus of SSc patients. SVM classification further identified intrinsic subsets in the duodenum, fundus, and blood of patients with SSc. The majority of our patients (9/16) exhibit >60% concordance of intrinsic subset assignment across tissues. Importantly, all five organs were represented in the SVM calls of inflammatory, proliferative, and normal-like intrinsic subsets. WGCNA identifies modules of genes in blood of patients with SSc that are significantly associated with clinical variables. Most notably, four modules positively associated with interstitial lung disease in patients contain genes (STAT3, IL1B, TGFBR2) and are enriched in pathways (Immune response, cell cycle, chemokine signaling) that have been implicated in SSc pathogenesis.

Conclusion: We have completed collection of >4 biospecimens from 16 individuals with SSc. Our data shows that the intrinsic gene expression subsets, first identified in skin, exist systemically in patients with SSc. These molecular profiles are more consistent than chance within single individuals and are thus, a common feature in end-organ pathology in SSc. We have identified modules of genes in easily accessible tissues that can be used to assess interstitial lung disease (ILD) in patients. Modules associated with additional clinical variables (antibody status, esophageal pathology, and treatment) are currently being evaluated.

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Systemic Sclerosis Has a Distinct Serum Protein Profile That Correlates with Its Clinical Manifestations

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Proteomic studies with an extensive panel of measured proteins are still scarce in systemic sclerosis (SSc). The Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial showed improved clinical outcomes in participants randomized to myeloablation followed by autologous hematopoietic stem cell transplantation compared to monthly cyclophosphamide (1). In the present study, we performed a proteomic analysis of baseline serum samples collected in the SCOT trial to investigate clinical correlates of serum protein dysregulation at baseline in early diffuse cutaneous SSc (dcSSc).

Methods: A panel of 232 baseline serum proteins in 66 SCOT participants (mean disease duration=2.2 years) compared to 66 age and gender matched controls was analyzed by RBM Human Discovery Multi-Analyte Profiling multiplexed assays. Proteins with levels below the lower limit of detection in more than 50% of SCOT participants, were excluded. Proteins were considered differentially expressed with false discovery rate (FDR) of <5%.

Results: Ninety proteins were differentially expressed in dcSSc versus controls (FDR<0.05). Sixty-five proteins were upregulated, of which 42% (27 molecules) were Type I IFN inducible accordingly to the Interferome database. The ten most up- and down-regulated proteins are presented in Table 1. Serum protein correlates of modified Rodnan Skin Score (mRSS) are shown in Table 2. Carcinoma Antigen 15.3 (CA 15.3) and Epithelial Derived Neutrophil Activating Protein 78 (CXCL5) were inversely correlated with forced vital capacity (FVC) ($r=-0.33$, $p<0.006$; $r=-0.34$, $p<0.06$ respectively) and positively correlated with HRCT fibrosis score ($r=0.28$, $p<0.023$; $r=0.28$, $p<0.025$) showing an association with lung fibrosis. The Ingenuity Pathway Analysis (IPA) revealed hepatic fibrosis, granulocyte adhesion and diapedesis and agranulocyte adhesion and diapedesis as the top three over-represented pathways, indicating that the serum protein profile of SSc reflects fibrotic as well as immunological dysregulations in SSc.

Conclusion: SSc has a distinct serum protein profile including a prominent upregulation of IFN inducible proteins. The IPA pathway analysis showed top over-represented pathways in SSc serum proteomic analysis parallels those found to be dysregulated in SSc skin global gene expression studies. (2). Finally, we identified several serum proteins that correlate with the extent of skin and lung fibrosis in SSc.

(1). Sullivan KM, et al. N Engl J Med. 2018 Jan 4;378(1):35-47

(2). Assassi S, et al. Arthritis Rheum. 2015 Nov;67(11):3016-26

Table 1: Top up-/ down-regulated serum proteins in SSc vs. control comparison

Protein name	Gene name	Fold Change	P raw	P FDR	Direction
Growth Hormone	GH1*	3.69	<0.001	<0.001	Up-regulated
Ferritin	FTH1	3.04	<0.001	<0.001	Up-regulated
C-Reactive Protein	CRP	2.98	<0.001	<0.001	Up-regulated
Chromogranin-A	CHGA	2.77	<0.001	<0.001	Up-regulated
Macrophage inflammatory protein 3 beta	CCL19*	2.48	<0.001	<0.001	Up-regulated
Monocyte Chemotactic Protein 1	CCL2*	2.48	<0.001	<0.001	Up-regulated

Table . (Cont'd)

Protein name	Gene name	Fold Change	P raw	P _{FDR}	Direction
Myoglobin	MB	2.38	<0.001	<0.001	Up-regulated
Monokine Induced by Gamma Interferon	CXCL9*	2.30	<0.001	<0.001	Up-regulated
B Lymphocyte Chemoattractant	CXCL13	2.19	<0.001	<0.001	Up-regulated
Prolactin	PRL	2.08	<0.001	<0.001	Up-regulated
Lactoylglutathione lyase	GLO1	0.49	<0.001	<0.001	Down-regulated
Neuron-Specific Enolase	ENO2	0.56	0.002	0.007	Down-regulated
Vitamin K-Dependent Protein S	PROS1	0.56	0.005	0.013	Down-regulated
Superoxide Dismutase 1	SOD1	0.65	<0.001	<0.001	Down-regulated
Protein S100-A6	S100A6	0.69	0.002	0.006	Down-regulated
Macrophage Migration Inhibitory Factor	MIF	0.71	0.023	0.046	Down-regulated
Adiponectin	ADIPOQ	0.72	<0.001	<0.001	Down-regulated
Kallikrein-7	KLK7	0.73	<0.001	<0.001	Down-regulated
Insulin like Growth Factor Binding Protein 6	IGFBP6	0.73	<0.001	<0.001	Down-regulated
Tetranectin	CLEC3B	0.75	<0.001	<0.001	Down-regulated

* : type I IFN related protein according to <http://interferome.its.monash.edu.au/interferome/>

Table 2: Serum proteins correlating significantly with mRSS

Protein name	Gene name	Correlation		Adjusted for age, gender	
		r	P ^u	b (CI)	P ^m
Alpha 1 Antichymotrypsin	SERPINA3	0.42	0.001	9.07 (4.04, 14.12)	0.001
NT proBNP	NPPB	0.38	0.002	3.11 (1.18, 5.04)	0.002
Endostatin	COL18A1	0.37	0.002	12.56 (4.81, 20.31)	0.002
Osteopontin	SPPI	0.34	0.006	7.08 (2.61, 11.56)	0.002
Angiopoietin 2	ANGPT2	0.33	0.005	5.43 (1.51, 9.36)	0.007
Serum Amyloid P Component	APCS	0.32	0.008	9.55 (2.38, 16.72)	0.010
Tenascin C	TNC	0.31	0.011	5.53 (1.36, 9.70)	0.010
Alpha 1 Microglobulin	AMBP	0.31	0.011	8.85 (2.02, 15.69)	0.012
Insulin like Growth Factor Binding Protein 4	IGFBP4	0.30	0.018	5.36 (1.41, 9.31)	0.009
Interleukin 22	IL22	-0.30	0.016	-8.20 (-15.08, -1.32)	0.020
Hepatocyte Growth Factor receptor	MET	-0.30	0.016	-9.63 (-17.08, -2.18)	0.012
Tetranectin	CLEC3B	-0.31	0.011	-11.99 (-20.57, -3.41)	0.007
Kallikrein 5	KLK5	-0.33	0.007	-6.35 (-10.95, -1.77)	0.007
Urokinase type Plasminogen Activator	PLAU	-0.34	0.005	-6.83 (-11.55, -2.12)	0.005
Thymus and activation regulated chemokine	CCL17	-0.35	0.003	-4.10 (-6.80, -1.41)	0.003
Tamm Horsfall Urinary Glycoprotein	UMOD	-0.40	0.001	-7.55 (-11.75, -3.35)	0.001
Macrophage Derived Chemokine	CCL22	-0.43	<0.001	-11.14 (-16.96, -5.31)	<0.001
Epidermal Growth Factor Receptor	EGFR	-0.43	<0.001	-11.61 (-18.02, -5.32)	0.001

r: Pearson correlation coefficient; P^u: p value from univariable model; b: Mean difference in the cytokine per unit of mRSS in the multivariable model; CI: confidence interval; P^m: p value from multivariable model after adjustment for age and gender

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Abstract Number: 1104

Mass Cytometry Analysis Detects Dysregulated T Cell Complement Responses in Diffuse Cutaneous Systemic Sclerosis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Aberrant CD4⁺ T cell activation is implicated in disease progression in systemic sclerosis (SSc). Activated T cells release various cytokines that may drive inflammation, microvasculopathy and fibrosis. Emerging evidence indicates the critical role of complement dysregulation of CD4⁺ T cell responses in autoimmunity. The aim of this study was to further characterise complement signature on CD4⁺ T cells in SSc.

Methods: We developed a method that could provide a rapid and comprehensive exploration of T cell-complement axis in patients. We therefore employed mass cytometry (CyTOF) technology. We first generated a 35member antibody-conjugate panel designed to delineate CD4⁺T sub-populations, recognize cytokines and transcription factors indicative of population expansion or contraction, and quantify 18 complement intracellular and surface proteins. Using the panel and a combinatorial pipeline for data analysis (t-SNE/viSNE followed by SPADE and Marker Enrichment Modeling), we examined T cells from healthy donors, fully recapitulating at single-cell resolution all published data assessed via 'classical' FACS, confocal microscopy and Western blot analyses. Pharmacological intervention with selective antagonists and agonists were used to explore the autocrine C3/C5 system in activated CD4⁺T cells. Cytokine profiles in cell supernatants were assessed following T cell activation by ELISA.

Results: 23 patients (18 females, age(mean±SEM), 49.6±2.2 years) with early diffuse SSc (mean disease duration 11.6±2.4 months) and mean baseline modified Rodnan skin score 21±2 were recruited for this study. Compared with healthy donors, circulating T cells from SSc patients displayed an aberrant complement signature and hyperactive phenotype. *Invitro* stimulation with immobilized antibodies to the T cell receptor CD3, together with antibodies to CD46, further increased complement dysregulation (in particular, increased C3 and C5 activation fragment generation and C5aR1 expression) and IFN-γ and IL-17 secretion with increased IFN-γ/IL-10 ratio (p<0.05, **Figure 1**). Furthermore, reducing activity of the autocrine 'C5 system' with a C5aR2 agonist corrected this deregulated phenotype with normalization of T cell activity.

Conclusion: By combining multidimensional mass cytometry with an unbiased data-driven analysis pipeline, we demonstrated, for the first time, biological coupling of dysregulated complement with aberrant T cell responses in SSc. Altered cytokine secretomes and intracellular complement activation involving C5 are critical features of T cell activation in SSc. This technique may potentially be useful for early detection of T cell dysregulation and this distinct complement signature may represent a novel biomarker in this subset of SSc patients.

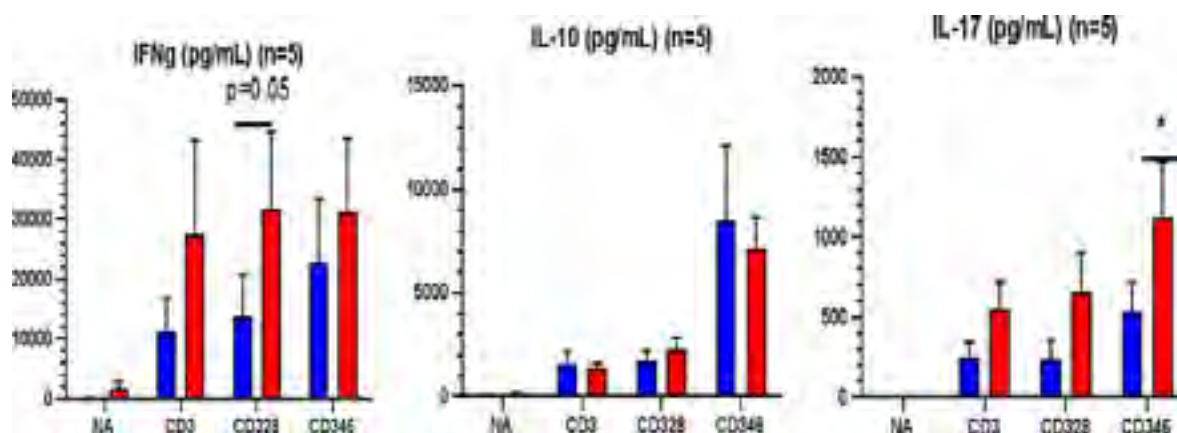


Figure 1: Circulating CD4⁺T cells from SSc patients have reduced capacity for Th1 contraction (*p<0.05, blue: healthy donors, red: patients)

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Abstract Number: 1105

Abatacept Is Effective in Experimental Digestive and Lung Tissue Fibrosis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: A previous report showed that abatacept (IgG-CTLA-4) prevented and induced regression of inflammation-driven dermal fibrosis in two different mouse models of systemic sclerosis (SSc) (1). We aimed to investigate the efficacy of abatacept in preclinical mouse models of digestive involvement, pulmonary fibrosis and related pulmonary hypertension (PH), mimicking internal organ involvements of SSc.

Methods: Abatacept has been evaluated in the chronic graft-versus-host disease (cGvHD) mouse model (abatacept 1 mg/mL for 6 weeks), characterized by liver and intestinal fibrosis and in the Fra-2 mouse model (1 mg/mL or 10 mg/mL for 4 weeks), characterized by interstitial lung disease (ILD) and pulmonary vascular remodeling leading to PH.

Results: Treatment with abatacept was well tolerated in all mouse models. In the cGvHD model, treatment of allogeneically transplanted mice with abatacept led to a significant reduction of alanine aminotransferase (24%, $P=0.014$) and aspartate aminotransferase levels (61%, $P<0.001$). Pathological analysis of colon revealed decreased inflammatory infiltrates and destruction of crypts in allogeneically mice receiving abatacept. When assessed by chest micro-CT imaging, Fra-2 transgenic mice treated with abatacept displayed a significant 12% decrease in lung density (10 mg/ml, $P=0.037$) as well as a marked increase in functional residual capacity as compared to IgG1-treated mice (16% for 1 mg/ml, $P=0.001$ and 14% for 10 mg/ml, $P=0.005$). Consistent with these results, abatacept 10mg/L decreased histological fibrosis score (Ashcroft score) as well as hydroxyproline content by 79% ($P=0.009$) and 31% ($P=0.044$) respectively, as compared to IgG1-treated mice. Treatment with abatacept 10mg/mL markedly reduced protein levels in the lesional lungs of Fra-2 transgenic mice of the fibrogenic markers MCP1 by 79% ($P=0.043$) and osteopontin by 87% ($P=0.039$). Levels of TGF- β were also reduced with abatacept (61% for 1mg/mL, $P=0.037$ and 69% for 10mg/mL, $P=0.013$). Further, abatacept dramatically decreased M1 and M2 macrophages infiltration as well as T-cell proliferation in the lesional lungs of Fra-2 mice. Upon treatment with abatacept a substantial reduction of right ventricular systolic pressure (28.1 ± 1.5 mmHg vs. 36.0 ± 5.1 mmHg, $P=0.037$ for 10mg/mL) and right ventricular hypertrophy (0.29 ± 0.01 vs. 0.33 ± 0.010 , $P=0.037$ and $29\pm0.01\%$ vs. $0.33\pm0.01\%$ for 10mg/mL, $P=0.037$) was observed compared to IgG1-treated mice. Consistent with these findings, abatacept 10mg/mL was associated with significant decrease in percent medial wall thickness and numbers of muscularized distal pulmonary arteries.

Conclusion: Abatacept improves digestive involvement, prevents lung fibrosis and attenuates PH. These findings suggest that abatacept might be an appealing therapeutic approach beyond skin fibrosis for organ involvement in SSc.

References:

(1) Ponsoye M et al. Ann Rheum Dis. 2016 Dec;75(12):2142–9

Disclosure: G. Boleto, None; C. Guignabert, None; S. Pezet, None; A. Cauvet, None; J. Sadoine, None; L. Tu, None; C. Nicco, None; C. Gobeaux, None; F. Batteux, None; Y. Allano, Actelion, Bayer, Biogen Idec, Bristol-Myers Squibb, Genentech/ Roche, Inventiva, Medac, Pfizer, Sanofi/Genzyme, Servier and UCB., 2, 5; J. Avouac, Actelion, Roche, Pfizer and Bristol-Myers Squibb., 2.

Abstract Number: 1106

Signal Transducer and Activator of Transcription 3 (STAT3) Activation in Peripheral Blood Mononuclear Cells of Systemic Sclerosis Patients: Correlation with Disease Specific Manifestations

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster II

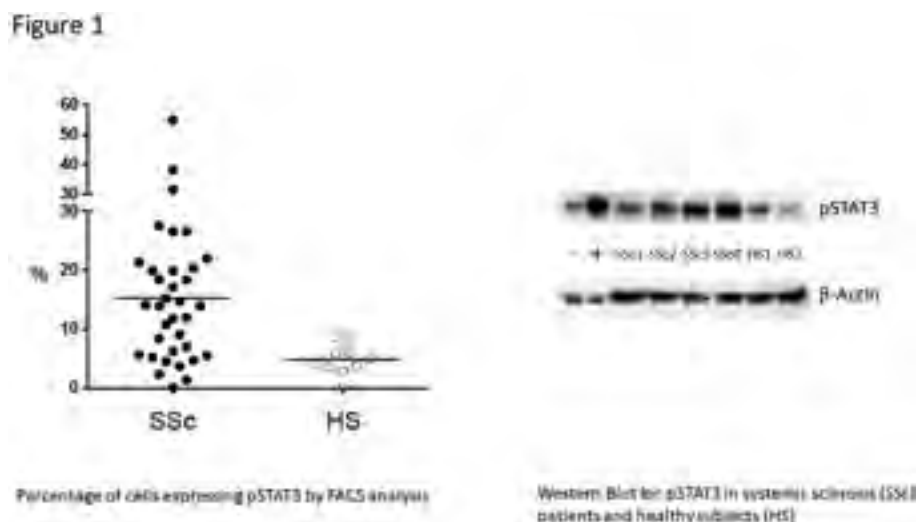
Session Type: ACR Poster Session B

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

Background/Purpose: Signaltransducer and activator of transcription 3 (STAT3) is a transcription factorregulated by phosphorylation of key tyrosine residues that regulates pivotal cell processes such as growth and proliferation, apoptosis, and immune responses[1]. STAT3 pathway has been evaluated in different inflammatory rheumatic diseases, and findings from ex vivo and animal experimental model proposed theSTAT3 pathway as a novel core mediator of fibrosis in systemic sclerosis (SSc)[2]. We evaluated the phosphorylated (p) STAT3 in peripheral blood mononuclear cells (PBMCs) from SSc patients.

Methods: Intracellular expression of phosphorylated and thus activated STAT3 was analysed in 35 SScpatients (female 30; 82% - median disease duration 96 months; 95%-CI 87-172), diagnosed according to the 2013 ACR/EULAR classification criteria, and 10 healthy matched subjects (HS) by FACS analysis and Western Blot. The level of STAT3 gene was studied by qPCR. pSTAT3 was correlated to demographic, clinical, laboratory and instrumental findings of SSc patients.

Results: pSTAT3 was found significantly higher in SSc patients compared to HS (3-folds higher;P=0.007) [Figure 1], and specifically with higher expression in CD14+ cells, while no difference in the expression of STAT3 levels was found. Patients with disease duration longer than 2 years showed higher pSTAT3 (P=0.01) and a direct correlation was found between months from diagnosis and pSTAT3 (r 0.38;P=0.01). We observed an inverse correlation between pSTAT3 and the modifiedRodnan Skin Score (mRSS) (r -0.37; P=0.02). Significantly lower pSTAT3 activity was detected in patients with interstitial lung disease (ILD) compared to patients without ILD (P=0.006). Furthermore, we observed an inverse significant correlation between pSTAT3 and body mass index (BMI) (r -0.34; P=0.02). No correlations with markers of inflammation and specific auto antibodies were detected. Moreover, no differences in diffuse vs limited cutaneous subsets of the disease, pulmonary hypertension, or gastrointestinal involvement, steroid or immunosuppressive cumulative dose or ongoing treatment were found.



Conclusion: We have preliminary demonstrated higher pSTAT3 in SSc PBMCs with a specific expression in CD14+ cells without any modification of STAT3 expression. Patients with longer disease duration, lower mRSS and BMI, and no ILD presented an increasedpSTAT3 activation. The changes in metabolic pathways related to disease duration may explain our findings [3]. Further studies could explain our intriguing results.

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Disclosure: F. Cacciapaglia, None; S. Perniola, None; L. Urso, None; E. Praino, None; R. Bizzoca, None; D. Natuzzi, None; N. Lacarpia, None; F. Iannone, None.

Abstract Number: 1107

Expression Quantitative Trait Loci -eQTL- Analysis in Systemic Sclerosis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Systemic Sclerosis (SSc) is a complex systemic autoimmune disorder characterized by fibrosis of the skin and internal organs. Genetics and environmental factors contribute both to the etiology of the disease. Most variants discovered by GWAS locate in non-coding regions, which impedes immediate interpretation. Expression quantitative trait locus (eQTL) mapping is one tool to discover the molecular mechanisms by which SSc- genetic variants exert their risk.

Methods: In this study, we performed genome-wide eQTL analysis using GWAS and RNA-Seq data derived from whole blood samples of 220 SSc patients and 325 healthy control subjects. All samples analyzed are of European ancestry and form part of the PRECISESADS project dataset. We used matrixEQTL with 8 cofactors to condition on batch, RIN, age, sex, medication, fever, genetic background and blood cell composition.

Results: We show that SSc-associated variants have widespread effects on genome-wide DNA expression levels. By means of stratified and interaction analyses we further show the gender and disease-specific context of SSc-eQTL variants. Interestingly, in SSc patients we found two independent variants, which affect expression levels of the SPARC gene an effect not seen in control subjects. SPARC is overexpressed in SSc and related to the profibrotic effect of TGFbeta. We modeled the expression of SPARC using both variants and assessed the variance explained.

Conclusion: Our results will show how SSc context-specificity works at the molecular level and serve to illustrate the possible regulatory downstream effects of risk variants. This will ultimately inspire the generation of new hypotheses needed to increase our understanding of the biology of SSc and autoimmunity.

Disclosure: M. Kerick, None; D. Gonzalez Serna, None; M. Teruel, None; S. Babaei, Bayer, 3; M. Acosta-Herrera, None; E. Carnero-Montoro, None; Z. Makowska, Bayer, 3; A. Buttgerit, Bayer, 3; G. Barturen, None; S. Hayat, Bayer, 3; J. Kageyama, Bayer, 3; M. Martínez-Bueno, None; P. Clinical Consortium, None; R. Lesche, Bayer, 3; M. Alarcón-Riquelme, Sanofi, Bayer, UCB, Eli Lilly and Servier, 2; J. Martín, None.

Abstract Number: 1108

Antibody Repertoire Dynamics in Systemic Sclerosis after Myeloablative Autologous Hematopoietic Stem-Cell Transplantation or Cyclophosphamide Treatment

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SESSION INFORMATION

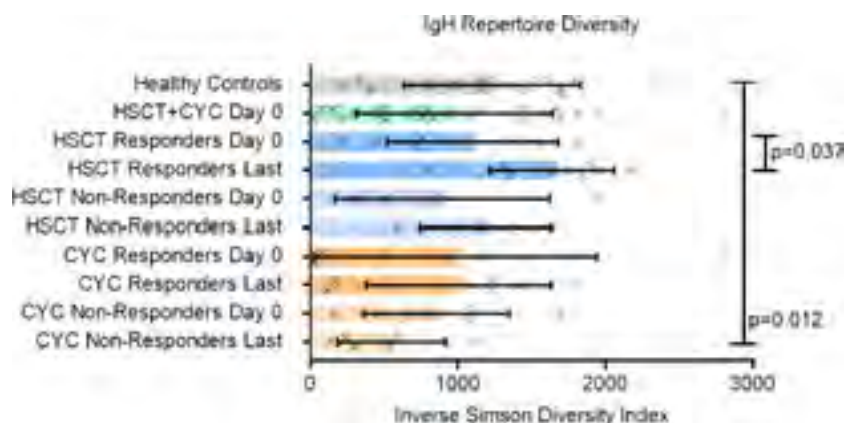
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Background/Purpose: Myeloablative autologous hematopoietic stem-cell transplantation (HSCT) was recently demonstrated to provide benefit over monthly cyclophosphamide (CYC) in the treatment of diffuse cutaneous systemic sclerosis (dcSSc) (1). As the dysregulation of the B cell compartment is implicated in the pathogenesis of SSc (2), we used antibody repertoire sequencing to characterize B cell repertoire dynamics over the course of HSCT and CYC treatment with the goal of identifying characteristics that differentiate responders from non-responders.

Methods: Immunoglobulin heavy-chain (IGH) sequencing from peripheral blood RNA was performed on HiSeq2500 using an approach adapted from previously described methods (3). Fastq files de-multiplexed by sample were processed with MIGEC and MIXCR software to establish consensus sequences and identify unique clonotypes within each patient's repertoire. Further analysis was performed using VDJtools, Immcantation, and IMGT-HiVQuest software. Samples yielding fewer than 3,500 sequences aligned to IGH genes were excluded from analysis. Event-free survival (EFS) at 54 months post treatment, characterized by no significant organ damage, was used to define treatment responders. The cohort included 13 HSCT recipients (8 responders), 14 CYC treated patients (7 responders) and 15 healthy controls. Responders were assessed at 3-4 time points (baseline and at 26 and/or 36 and/or 48 months post-treatment), non-responders at 2-3 time points (baseline and any time points leading up to and including EFS failure) and healthy controls at a single time point.

Results: Mean IGH repertoire diversity as assessed by the Inverse Simpson Diversity Index was equivalent in both dcSSc treatment groups and healthy controls at baseline (HSCT 1037 ± 604.7 , CYC 919 ± 735.5 , and healthy controls 1232 ± 600.6). At last study time point, HSCT recipient responders exhibit an increase in mean IGH repertoire diversity compared to baseline (1100 ± 578.9 vs. 1638 ± 420.5 , $p=0.037$, paired t-test) which was not observed in HSCT non-responders. Although in comparing last study point to baseline, there was no difference observed in CYC treated patients, CYC treated non-responders exhibit lower mean IGH repertoire diversity at last study time point than healthy controls (1232 ± 600.6 vs. 551.2 ± 365 , $p=0.012$, unpaired t-test).



Conclusion: Increased mean IGH repertoire diversity from baseline is seen in HSCT responders. CYC treated non-responders have decreased mean IGH repertoire diversity as compared to healthy controls.

References:

(1) Sullivan KM et al. N Engl J Med 2018;378:35-47. (2) Yoshizaki A. Immunol Lett 2018;195:76-82. (3) Turchaninova MA et al. Nat Prot 2016;11:1599-1616.

Disclosure: J. Z. Adamska, None; L. Crofford, None; D. E. Furst, None; E. Goldmuntz, None; L. Keyes-Elstein, None; M. D. Mayes, None; P. McSweeney, None; R. Nash, None; A. Pinckney, None; B. Welch, None; K. Sullivan, None; W. H. Robinson, None.

Abstract Number: 1109

Gene Expressions of TMEM176A and TMEM176B Were Prominent at the Stage of Subclinical Pulmonary Vascular Disease in Systemic Sclerosis

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Background/Purpose: Pulmonary arterial hypertension (PAH) is prominent as a vascular involvement of systemic sclerosis (SSc), which remains a leading cause of death in spite of current best treatments. As the pulmonary vascular disease (PVD) can be well compensated for, more than a half of the pulmonary circulation is impaired before PAH is detected. So far, the underlying molecular mechanisms have not been fully elucidated, especially at the early stage of SSc. In this study, we focused on the stage of subclinical PVD, and try to detect candidate genes involved in the pathogenesis of exercise-induced pulmonary hypertension (exPH) at the early stage of SSc.

Methods: Total of 88 patients who had not met PAH criteria with Raynaud phenomenon (n=75), skin sclerosis (n=58) or SSc-related autoantibody (n=59) was enrolled. To detect the early PVD, exercise Doppler echocardiography was carried out. The exPH group was segregated from normal response group (exN) with using the reported definition.¹ For gene expression analysis, total RNAs from whole peripheral blood cells were extracted by PAXgene system and multiplex sequencing was done. To identify changes of transcriptomes for developing exPH, hierarchical clustering, weighted gene co-expression network analysis (WGCNA), pathway enrichment analysis (PathVisio) and volcano plots were performed with using differentially expressed genes (DEGs) between exPH and exN group.

Results: After applying 1204 DEGs to hierarchical clustering analysis, 5 major clusters were identified and 93% of exPH samples were segregated into 2nd cluster. WGCNA and pathway analysis revealed 6 co-expression modules and they were significantly enriched with genes of several pathways, such as Wnt, endothelin, IL-1, TNF-alpha, prostaglandin, toll-like receptor, EGF, VEGF-A, type3 interferon and integrin-mediated cell adhesion. Volcano plots were scatter plots calculated to visualize fold-changes and p-values of DEGs. It indicated that expressions of TMEM176A and TMEM176B (\log_2 fold-change >1.25 and $-\log_{10}$ p-value >3.5) were prominent in exPH patients. We also found that the expressions of these genes were highly correlated with each other ($R^2=0.9724$, $p<0.01$).

Conclusion: The paradigm of SSc-PAH management should ideally be aimed at starting treatment before development of PAH. Although elucidating the mechanisms for progression of PVD in the early stage of SSc remains a major challenge, (1) we found exPH patients were segregated from exN group by gene expression profiles of peripheral blood; (2) DEGs were enriched with genes of several important pathways for pathogenesis of SSc, which reported previously; (3) up-regulation of TMEM176A and TMEM176B were prominent in exPH group. The trans-membrane protein TMEM176A and TMEM176B were found initially to be a regulator for DC maturation in mice², but functions of human ortholog of these genes remain still unclear. As our findings revealed active changes of transcriptomes in peripheral blood prior to fulfilling PAH criteria in SSc patients, it will encourage the therapeutic intervention at early stage of SSc to prevent PVD.

References:

¹R. Naeije *et al.*, *Am J resp and critical care med* **187**, 576-583 (2013). ²Condamine, T. *et al.*, *J of leuko biol* **88**, 507-515 (2010).

Disclosure: Y. Koyama, None; S. Fuke, None; T. Ohno, None; Y. Sato, None; T. Higuchi, None.

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Characterization of CD20+ T Cells in Patients with Systemic Sclerosis

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Background/Purpose: Recently, it has been demonstrated that a subset of T cells expresses the B-cell marker CD20. It has been postulated that in rheumatoid arthritis (RA) and multiple sclerosis (MS) the effect of rituximab (RTX), an antibody against this molecule, is partly due to the depletion of this T cell subset. Interestingly, nothing is known about CD20⁺ T cells in another autoimmune disease that is effectively treated by RTX, viz. systemic sclerosis (SSc). The aim of our study was to determine the frequency of CD20⁺ T cells and further characterize this specific subpopulation in SSc.

Methods: Peripheral blood mononuclear cells from healthy controls (HC; n=10), SSc patients treated with RTX (SSc⁺^R; 500mg for 2x, every 3 month; n=16) or not treated with RTX (SSc⁻^R; n=11) were characterized by flow cytometry for the surface expression of T cell specific markers as well as the production of different cytokines, i.e. TNF α , IFN γ , IL-17, after stimulation with PMA and ionomycin. In addition, apoptosis was analyzed before and after heat induction (65 °C for 5 min).

Results: SSc patients had significantly less CD20⁺ T cells compared to HC, independent of RTX-therapy. Thus, in SSc⁻^R the frequency of CD20⁺ T cells was $1.63 \pm 0.32\%$ (mean \pm SE), in SSc⁺^R $0.11\% \pm 0.09\%$ and in HC $2.89\% \pm 1.5\%$ ($p < 0.023$ and $p < 0.001$; respectively).

RTX therapy predominantly eliminated the CD8⁺CD20⁺ T cells. The ratio of CD4/8 in CD20⁺ T cells of SSc before RTX was 0.6 similar to HC and increased during RTX to 2.1 ($p < 0.001$).

In SSc patients, as well as in HC, the CD20⁺ T cell helper (Th) population is dominated by the Th1-subset ($42.7 \pm 15.0\%$ and $42.9 \pm 11.6\%$; respectively). In contrast, in CD20⁺ T cells, the Th17 population was most often found ($34.6 \pm 19.3\%$ and $38.0 \pm 14.0\%$; respectively). CD20⁺ T cell of SSc⁻^R produced more IFN γ , TNF α and IL-2 compared to HC. During RTX therapy these cells were less capable to produce the cytokines.

In SSc⁻^R a higher frequency of CD20⁺ T cells, were already in the early apoptotic phase compared to HC ($32.17 \pm 13.66\%$ vs. $7.5 \pm 13.49\%$) and after heat exposure significantly more of these cells were found in the late apoptotic phase (LAP). Thus, in SSc patients $28.00 \pm 24.88\%$ were found in the LAP compared to $5.29 \pm 4.30\%$ in HC. This effect on apoptosis seemed to be restricted to CD20⁺ T cells, since it was not found in B cells of HC or SSc.

Conclusion: SSc patients have a lower percentage of CD20⁺ T cells compared to HC and to the reported frequency in RA or MS. Whether patients with SSc have per se a lower number of this cell subset in general or these cells might localize into tissue has to be determined. Furthermore, the cytotoxic T cell population of SSc is enriched in CD20⁺ cells that produce a higher number of pro-inflammatory cytokines. The role of IFN γ -production by these cells in the fibrotic process in SSc is still unclear since there are reports, that indicate pro- as well as anti-fibrotic effects of this cytokine. Similar to previous reports the CD20⁺ T cell population is prone to apoptosis. Whether the therapeutic effect of RTX is related to the preferential elimination of CD20⁺CD8⁺ T cells needs further investigation.

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CBS004, a Novel Monoclonal Antibody Against Bcl-2 Inhibits TLR-Induced Activation of Human pDC in Vitro and In Vivo. a Novel Therapeutic Target for Systemic Sclerosis

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Background/Purpose: Human plasmacytoid dendritic cells (pDCs) have been implicated in the pathogenesis of Systemic Sclerosis (SSc) through their ability to infiltrate the skin and secrete interferons (IFN), interleukin-6 (IL-6) and other proinflammatory chemokines directly, or through type-I IFN response of resident cells. Blood dendritic cell antigen 2 (BDCA-2) is a human-specific pDC-type II C-type lectin that potentially inhibits IFN secretion. Here we determined the effects of CBS004, a novel monoclonal antibody against BDCA-2, on Toll-like receptor (TLR)-induced transcriptome and

IFN secretion in pDCs from healthy volunteers (HV) or patients with SSc *in vitro*, and developed a xeno-transplant mouse model of human pDC activation.

Methods: Peripheral blood mononuclear cells (PBMCs) were collected from 16 SSc patients and 12 HV. IFN and CXCL-4 secretion were evaluated by ELISA. TLR7-9 stimulation was induced by Imiquimod or CpG-oligodeoxynucleotides. pDCs were isolated by magnetic cell sorting. Full transcriptome was analysed by RNA-sequencing. For the xeno-transplant model, NOD/SCID mice were injected in the tail vein with 25×10^4 human pDCs, 12 h after topical application of Imiquimod with or without intra-peritoneal (IP) injection of CBS004 (5 mg/kg). Harvested skin was analysed by FACS for human pDC infiltration and by real-time PCR using a mouse type-I IFN response array (Qiagen).

Results: PBMCs from SSc patients spontaneously produced higher levels of IFN-I and CXCL-4 compared to HV *ex vivo* (206.7 ± 23.4 vs. 43.4 ± 6.8 pg/ml, $P < 0.0001$ and 216.6 ± 36.6 vs. 8.6 ± 0.3 ng/ml, $P < 0.05$, respectively). CBS004 significantly inhibited basal levels of IFN-I in 83% of SSc samples. TLR7 or 9 stimulation showed only modest induction of CXCL-4 in both HV and SSc PBMC. TLR9 stimulation of SSc PBMCs induced >30-fold increase in IFN-I secretion (7167 ± 4377 pg/ml), which was completely abrogated by treatment with CBS004 (209 ± 40.5 pg/ml, $P < 0.001$). RNA-seq analysis of human pDCs (Lineage⁻HLA-DR⁺CD123⁺CD304⁺) stimulated with TLR-9 agonist revealed 168 Differentially Expressed Genes (DEGs, FDR <1%) mapping to IFN, JAK/STAT, IL-6, NF- κ B and angiogenesis pathways. Pre-treatment with CBS004 prevented upregulation of most DEGs, which drove an expression profile similar to non-stimulated pDCs. In the xeno-transplant model, Tail vein injection of pDC resulted in detection of human CD123⁺CD304⁺ cells in the skin (0.3%) with at least 2-fold upregulation of 35/74 mouse type-I IFN response genes including Ccl2, 4, 5 and Cxcl10, Ifit1, 2 and 3, Mx1 and 2, Oas1, Tlr7, 8 and 9 compared to imiquimod treatment alone ($P < 0.005$). Mice receiving IP injection of CBS004 had a 3-fold reduction in infiltrating pDCs (0.1%) and suppression of 85% of the type-I IFN response genes upregulated by pDC injection and Imiquimod treatment (Anova $P < 0.01$).

Conclusion: Our study demonstrates that pDCs from SSc patients are in active status in the blood and can be functionally inhibited by BDCA-2 targeting with CBS004 mAb. Further, we show for the first time that TLR stimulation and BDCA-2 inhibitory effects go beyond IFN secretion including proinflammatory and proangiogenic response and we develop a novel xeno-transplant mouse model for studying human pDC function *in vivo*.

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Abstract Number: 1112

Downregulated Expression of Interferon Regulatory Factor 8 in Circulating Monocytes Exhibits Pro-Fibrotic Phenotype in Patients with Systemic Sclerosis

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Background/Purpose: Systemic sclerosis (SSc) is a multisystem connective tissue disease characterized by autoimmunity, vasculopathy, and excessive organ fibrosis. Although the etiology of the disease is still unknown, several lines of evidences suggest the monocytes/macrophages involvement in the pathogenic process of SSc. Interferon regulatory factor 8 (IRF8), a member of IRF family, is a transcriptional regulator that plays essential roles in the differentiation and function of monocytes and macrophages. Genetic association of IRF8 with SSc was reported by genome-wide association study, however, its detailed function is yet to be discovered. In this study, we determined the expression level of IRF8 in circulating monocytes of SSc patients and further analyzed those phenotypic function.

Methods: IRF8 expression levels in peripheral blood mononuclear cells (PBMCs) and circulating monocytes were evaluated by quantitative PCR in 33 patients with SSc (diffuse cutaneous SSc (dcSSc); n=13, limited cutaneous SSc (lcSSc); n=20) and 15 healthy controls in association with clinical characteristics. IRF8 in circulating human monocytes was silenced by RNA interference, then those monocytes were differentiated into macrophages. Cell surface markers, cytokine/

chemokine profiles, and expressions of pro-fibrotic factors and extracellular matrix were assessed by flow cytometry and quantitative PCR.

Results: Although no significant difference was observed on IRF8 levels of PBMCs between total SSc patients and healthy controls, dcSSc patients had significantly lower levels of IRF8 compared with healthy controls and lcSSc patients. In addition, that particular downregulation of IRF8 was observed in circulating monocytes from patients with dcSSc. Differentiated macrophages from IRF8-silenced human monocytes tended to exhibit M2 phenotype. Furthermore, mRNA expression levels of tissue growth factor- β , early growth response-1, α -smooth muscle actin, and monocyte chemoattractant protein-1 were significantly upregulated in macrophages from IRF8-silenced monocytes than that in control macrophages. There was also a trend toward increased levels of IL-6 and tumor necrosis factor- α in those macrophages compared to that in controls.

Conclusion: IRF8 was significantly downregulated in circulating monocytes from dcSSc patients and pro-fibrotic phenotype was observed in macrophages differentiated from IRF8-silenced monocytes. IRF8 may play an important role as a key regulator in the pathogenic process of SSc.

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Abstract Number: 1113

Distinct Pathways in Anti-RNP-Associated Pulmonary Hypertension and Anti-RNP-Associated Raynaud's Phenomenon

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Background/Purpose: Anti-RNP Autoimmunity is associated with multiple manifestations of vasculopathy, including Raynaud's Phenomenon (RP) and Pulmonary Hypertension (PH). We have previously linked anti-K10 antibodies to RP. However, since RP typically presents early in disease whereas PH is typically a late manifestation of disease, we hypothesize that they are mediated by differing factors.

Methods: Using IRB-approved studies on a human cohort of anti-RNP autoimmunity, as well as IACUC-approved protocols to study murine models of anti-RNP-associated autoimmunity, we performed studies to assess the contribution of autoantibodies, T cell-mediated autoimmunity, and cellular components of the innate immune system to the development and persistence of anti-RNP-associated RP and PH.

Results: In a cohort of 130 patients with anti-RNP autoimmunity, 19 patients (15%) had PH (by criteria and/or clinical diagnosis). RP was present in 79/111 patients without PH (71%), but only in 10/19 patients with PH (53%, Fisher's $p = 0.12$). Anti-K10 antibodies were present in 7/19 PH patients (37%) but in 67/111 not PH patients (60%, $p = 0.08$). Thus, trends disfavored associations between PH and either RP+ or anti-K10+ status.

Spontaneously autoimmune Trex1-deficient mice developed anti-K10 antibodies only concurrent with or after the development of anti-RNP antibodies (12/38 RNP+ vs 0/13 RNP- mice, $p = 0.02$). Spontaneous ischemic thermoregulatory tissue loss was observed infrequently (2/12), but only in the subset of mice that developed anti-K10 antibodies. However, up to 18 weeks after the development of anti-RNP antibodies, there were no differences in (normal) BNP levels observed in mice with versus without anti-K10 antibodies.

In contrast, study mice that received CD11c+ spleen cells from RNP+ syngeneic donors uniformly developed RNP+ status with increased serum BNP levels and increased right heart pressures by direct catheter measurements, but without clinical evidence of RP. Treatment with a small molecule antigen presenting cell toxin targeted to CD11b+ cells rapidly reversed established pulmonary hypertension in 4/5 (80%) mice (vs 0/6 controls, $p = 0.02$). Likewise, an RNP antigen-specific T cell vaccination induced reductions in BNP levels in 6/9 treated mice with induced anti-RNP lung disease, with substantially lower BNP values than in mock-treated controls (Mann-Whitney $p = 0.007$) while causing no changes in anti-RNP antibody levels.

Conclusion: While anti-K10 antibodies may be sufficient to induce RP in anti-RNP autoimmunity, anti-RNP-associated PH shows trends toward a negative association with anti-K10 and instead may be mediated by T cells and cellular innate immune constituents.

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Abstract Number: 1114

Proteomic Aptamer Analysis Reveals a Distinct Profile of Very Early Systemic Sclerosis (SSc) Patients at Risk for Progression Toward Definite SSc

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Background/Purpose: To determine via SOMAscan aptamer proteomic analysis(>1200 proteins analyzed) the factors associated with disease transition from very early systemic sclerosis (EaSSc) to definite SSc.

Methods: Serum samples from 13 EaSSc, defined according to LeRoy and Medsger criteria (Raynaud phenomenon plus a positive nailfold capillaroscopy and SSc-specific auto-antibodies without any other sign of definite disease) [1] and 8 age-, sex-, matched healthy controls (HCs) were analyzed via SOMAscan aptamer assay [2]. Prospective data were available up to 4.9 years from sampling (median=4.1, IQR=3.5-4.5 yrs) to determine the progression to definite SSc according to the EULAR/ACR 2013 criteria [3]. Relevant proteins were selected among those with relative fluorescence units (RFU) >1.5-fold HCs via predictive modeling (bagging). Gene Ontologies (GO terms) of proteins with corrected p<0.05 after 10,000-fold permutation testing, were aggregated to determine the relevance of biological processes in patients at risk of evolution.

Results: Seven patients (54%) did evolve into definite SSc, while 6 did not progress. Nonprogressors and progressors were similar regarding baseline characteristics (ACA+, 66% vs 57%; FVC, 105[97-102] vs 110 [109-115]; DLco, 92 [87-105] vs 85[82-101]). Ten proteins were significantly associated with evolution (Table); the relative RFUs are represented via heatmaps in Figure, left panel. GO term analysis revealed that patients at risk for progression shared several biological processes (Figure, right panel) related to fibrosis, vascular function and angiogenesis and that these were upregulated compared to non-progressors.

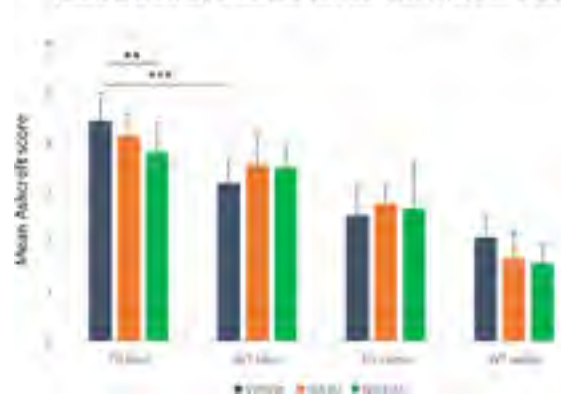
Conclusion: Increased expression of proteins and pathways related to angiogenesis, extracellular matrix remodeling and fibrosis distinguish EaSSc at risk of progression from those with stable disease up to 5 years from referral. This is the very first proteomic study to determine the baseline factors associated with disease evolution in very early SSc patients. Our findings may have relevance for early therapeutic intervention and disease interception.

Table: Selected proteins

Target	Gene	RFU* Non-progressors (n=6)	RFU* Progressors (n=7)	Risk threshold*	Accuracy**	Perm P**
MEP2B	NCR3	458.9 (439.7 - 483)	909.8 (541.4 - 1749.8)	≥ 812.434	0.835	0.0373
COL6A2	COL6A2	22529.7 (20469.5 - 25445.5)	30689 (28044.7 - 33112.1)	≥ 27514.38	0.835	0.0075
FGF2	FGF2	1960.3 (1311.6 - 2574.5)	6801.4 (3050.6 - 13495.8)	≥ 2791.214	0.83	0.0375
ECM1	ECM1	5892.1 (3317.5 - 8555.2)	6891.8 (7329 - 10011.8)	≥ 7222.982	0.766	0.0348
FGF18	FGF18	344.6 (327.1 - 367)	796.2 (393.1 - 1579.8)	≥ 359.588	0.753	0.0324
PH	PH	668.5 (547 - 877.2)	390 (348.2 - 449.8)	≤ 489.331	0.749	0.0345
Vimentin 1.3 (FN1.3)	FN1	1510.8 (1264.8 - 1790.1)	2543.9 (1318.1 - 2949.8)	≥ 1921.266	0.740	0.0402
Uspapin-1	BPS27A	3467.7 (2805.1 - 6077.7)	1947.5 (1607.1 - 2388.8)	≤ 2465.237	0.740	0.0402
F4/40 cytokeratin (FABP)	FABP4 (FABP)	2692.8 (2344.8 - 4014.2)	4751.2 (4114.8 - 5588.7)	≥ 4101.777	0.734	0.0459
FABP	FABP1	3679.5 (2870.6 - 4466.3)	5280.5 (4731.8 - 6006.1)	≥ 4679.742	0.732	0.0467

*Mean of values after 100 resampling with replacement (median, interquartile range)
**Accuracy of resampled threshold in out-of-bag samples (bagging accuracy); Family-wise corrected p-values after 10,000 permutations

Figure 1: Amelioration of the fibrotic response to bleomycin and unbuffered saline in TgTGF- β and wildtype Blomale mice using pan-PPAR agonist lanifibranor.



Results: As expected, TG mice demonstrated an exaggerated fibrotic response to or pharyngeal aspiration of bleomycin compared to WT, and to unbuffered saline compared to WT animals (figure 1); demonstrating similar impact when compared with the more invasive intra-tracheal administration published previously.

TG mice treated with higher dose lanifibranor demonstrated significantly greater protection from lung fibrosis than those treated with vehicle or lower dose lanifibranor, for instance: mean Ashcroft score TG-bleo IVA100 3.8 ± 0.58 ; TG-bleo vehicle 4.4 ± 0.58 ; $p < 0.01$. Treatment with lanifibranor in WT animals was less effective at preventing fibrosis (WT-bleo IVA100 3.5 ± 0.46 ; WT-bleo vehicle 3.2 ± 0.5 ; not significant), suggesting that the pro-fibrotic phenotype due to TGF- β upregulation in this model is substantially ameliorated by lanifibranor.

In this study, administration of bleomycin to a transgenic mouse resulted in an Ashcroft score 65% higher compared to saline administration in WT mice. This excessive fibrosis was then reduced by 15% with the use of lanifibranor at 100mg/kg.

Conclusion: Treatment with 100 mg/kg lanifibranor ameliorates lung fibrosis in the TgTGF- β mouse model of scleroderma. This model, which demonstrates severe and persistent fibrosis compared to WT mice, provides mechanistic support for trials of lanifibranor in scleroderma including cases with pulmonary involvement.

References:

1. Hoyles RK et al; Arthritis Rheum. 2008;58:1175-88.
2. Avouac J et al; Ann Rheum Dis. 2017;76:1931-1940.

Disclosure: E. C. Derrett-Smith, None; S. Xu, None; D. Abraham, None; O. Lacombe, Inventiva, 3; P. Broqua, Inventiva, 3; J. L. Junien, Inventiva, 3; I. Konstantinova, Inventiva, 3; C. P. Denton, Roche, Actelion, GlaxoSmithKline, Sanofi-Aventis, Inventiva, SCL Behring, Boehringer-Ingelheim, Bayer., 5.

Abstract Number: 1116

Risk of Systemic Sclerosis According to Charge of the HLA-DR β 1 Third Hypervariable Region

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis of skin and internal organs and has a predilection for women. The strongest genetic contribution to SSc is from the Human Leukocyte Antigen (HLA) class II region. Previous studies have reported increased *DRB1**11, especially *DRB1**1101 and *1104, and decreased *DRB1**07 and *DRB1**15 in Caucasian women with SSc.(1) The third hypervariable region (HV3), corresponding to amino acid sequences from positions 67 to 74 of the DR β 1 molecule, forms the primary T-cell recognition site.(2)

Peptide and T-cell interactions are influenced by charge and SSc risk evaluation according to HV3 charge could provide insight into the immunological basis of HLA associations with SSc. We therefore asked whether SSc patients differ from healthy individuals for HV3 amino-acid charge.

Methods: High resolution *HLA-DRB1* genotyping was conducted for 420 adult females, 157 SSc and 263 healthy controls. Alleles were classified into 4 groups based on the 67–74 amino acid sequence charge: –2, 0, +1, and +2 (no individual had a –1 charge). Odds Ratios (OR) were calculated for 9 of 10 possible genotypic combinations accounting for 99% of subjects. P-values were calculated by Fisher Exact test.

Results: In 9 comparisons, the genotypic OR of SSc risk according to HV3 charge ranged from 0.42 to 2.14. Risk was statistically significant when both alleles encoded for HV3 with a charge of 0, OR [and 95% confidence interval] 2.14 [1.33–3.37], 30/157 SSc vs. 77/263 controls; $p = 0.0016$, $p = 0.014$ after correcting for 9 comparisons. Protection from SSc was significant for the combination of 0 charge encoded by one allele and +1 charge by the other allele, OR 0.57 [0.35–0.92], 49/157 in SSc vs. 46/263 in controls; $p = 0.028$, however this was not significant after correcting for 9 comparisons $p = 0.25$. The most frequent alleles with a 0 charge in our population were *DRB1**07:01 (23% of cases and 25% of controls), *DRB1**15:01 (18% of cases and 25% of controls), and *DRB1**11:01/4 (31% of cases and 13% of controls); the latter was significantly increased in cases ($p < 0.0001$; OR 2.88 [1.75–4.67]) as expected, consistent with previous studies. Homozygosity for these 3 alleles (5/157 SSc and 10/263 controls) did not explain the observation of SSc risk when both alleles encode 0 charge HV3. Furthermore, having a single “dose” of 0 charge did not differ in cases vs. controls (71% vs. 70%, respectively).

Conclusion: SSc risk is associated with inheritance of a 0 charge DRβ1 molecule for positions 67–74 encoded by both parental haplotypes, independent of the allelic identity of the *DRB1* gene. Inheritance of one allele encoding a 0 charge and the other a +1 charge was associated with protection but was not significant after correction for multiple comparisons. The amino-acid sequence of the HV3 is thought to be particularly important in the HLA-peptide-Tcell interaction. The current observation regarding HV3 charge on both haplotypes points to an aspect of that interaction that may help elucidate the role of HLA molecules in SSc pathogenesis.

1. F. Arnett et al., *Annals of the Rheumatic Diseases*, in press, <https://doi.org/10.1136/ard.2009.111906>.
2. C. Gentil et al., *Arthritis Research & Therapy*. 19 (2017), <https://doi.org/10.1186/s13075-017-1253-9>.

Disclosure: O. Sensoy, None; S. B. Kanaan, None; J. L. Nelson, None.

Abstract Number: 1117

Characterization of the Esophageal Microbiome in Patients with Systemic Sclerosis (SSc)

Monica Espinoza¹, Bhaven K. Mehta¹, Yue Wang¹, Aileen Hoffmann², Mary A. Carns³, Noelle Kosarek¹, Tammara A. Wood⁴, Monique Hinchcliff⁵ and Michael L. Whitfield⁶, ¹Molecular and Systems Biology, Geisel School of Medicine at Dartmouth, Hanover, NH, ²Department of Medicine, Division of Rheumatology, Northwestern University Feinberg School of Medicine, Northwestern University, Chicago, IL, ³Northwestern University, Feinberg School of Medicine Scleroderma Program, Chicago, IL, ⁴Department of Molecular and Systems Biology, Geisel School of Medicine at Dartmouth, Hanover, NH, ⁵Rheumatology, Northwestern University, Chicago, IL, ⁶Biomedical Data Science, Geisel School of Medicine at Dartmouth, Hanover, NH

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM–11:00AM

Background/Purpose: Systemic Sclerosis (SSc) is an autoimmune disease characterized by fibrosis and inflammation. Multiple organ systems are affected including the skin, gastrointestinal tract, vasculature, and lungs (Katsumoto, Whitfield, & Connolly, 2011). It is a heterogeneous disease but gene expression analyses have defined four distinct molecular subtypes (inflammatory, fibroproliferative, normal-like, and limited). Prior studies have implicated microbial dysbiosis in SSc (Arron et al., 2014; Volkmann, 2017), but have not assessed the relationship between host immune processes/molecular subtype and microbial community characteristics. In this study we characterize the esophageal microbiome of patients with SSc and explore its relationship to host gene expression.

Methods: RNA-sequencing was performed on 19 patient and 4 healthy control (paired upper and lower) esophageal biopsies. Raw reads were aligned to hg19 via STAR and normalized to reads per kilobase million (RPKM). Intrinsic Gene

Conclusion: SSc esophageal tissues recapitulate SSc processes and show an increase in abundance of potentially pathogenic commensal microbes when compared to healthy controls. Microbes do not hierarchically cluster samples by site, implicating a disease driven difference in microbial communities potentially also divided by SSc subtype.

Disclosure: M. Espinoza, None; B. K. Mehta, None; Y. Wang, None; A. Hoffmann, None; M. A. Carns, None; N. Kosarek, None; T. A. Wood, None; M. Hinchcliff, None; M. L. Whitfield, None.

Abstract Number: 1118

Identification of Transcriptional Regulatory Networks in Systemic Sclerosis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster II

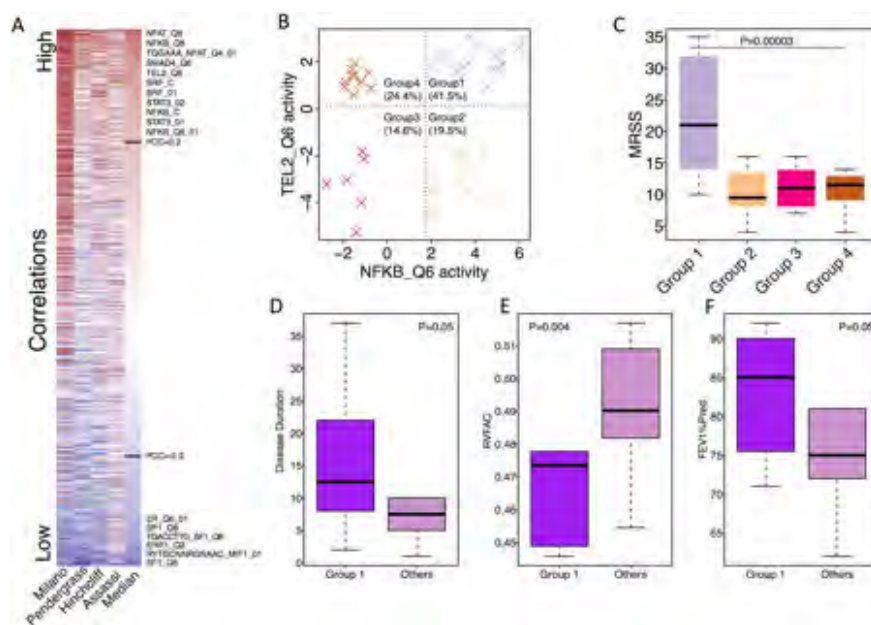
Session Type: ACR Poster Session B

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

Background/Purpose: Systemic sclerosis (SSc) is a heterogeneous autoimmune disorder with poor outcomes and no FDA-approved therapies. Prior work has shown gene expression patterns associated with inflammation and innate immune system activation in multiple affected organ systems. Networks of activating transcription factors (TF) and miRNAs that underlie SSc molecular subsets and clinical co-variates have not been characterized in detail. We analyzed transcriptional regulatory networks underlying the inflammatory intrinsic gene expression subset of SSc and associated clinical covariates.

Methods: Gene expression profiles were downloaded from Milano et al (GSE9285; 75 samples), Pendergrass et al (GSE32413; 89 samples), Hinchcliff et al (GSE59787; 165 samples) and Assassi et al (GSE58095; 102 samples). In total 431 samples from 244 patients were analyzed. The C3 target gene set (836 regulators) was downloaded from the MSigDB. Gene expression and target gene profiles were integrated using the BASE algorithm to calculate sample-specific regulator activity scores. TF activity scores were positively correlated and miRNAs activity scores were negatively correlated with gene expression. Correlations were calculated between activity scores and samples MRSS. Regulators were selected from those that had correlations greater than 0.15 or lesser than -0.15 in at least 3 cohorts. A transcriptional interaction network was created by Cytoscape.

Results: We identified 60 regulators whose activity scores were consistently, positively correlated with MRSS in inflammatory patients in all datasets. Examples include core binding factors, innate immune-related pathways, and telomere maintenance (NFAT, NFkB, STAT3, TEL2; Fig. 1A). We also found that using the activities of NFkB and TEL2, inflammatory samples were clustered into 4 subtypes (Fig. 1B). Doublehigh samples in group 1 had much worse skin



disease (Fig. 1C, $P=0.00003$) with longer disease duration (Fig. 1D, $P=0.05$) compared to other samples. Group 1 samples tended to have worse pulmonary hypertension (Fig. 1E, $P=0.004$) and were less likely to have pulmonary fibrosis (Fig. 1F, $P=0.05$) than the remainder of samples. Lastly, a regulator interaction network was created to provide novel insights for SSc and visualize the connectivity between different components of the regulator network.

Conclusion: We have identified a subtype of samples classified as the inflammatory gene expression subset that show increased expression of innate immune pathways NFAT, NFkB and STAT3. Patients with high expression of two of these pathways, which we have termed “double high”, had evidence of increased disease severity. This further highlights the role of innate immune transcriptional activators in SSc pathogenesis. The framework can be easily applied to any samples with molecular gene expression data to develop transcriptional activity networks.

Disclosure: Y. Wang, None; J. Franks, None; M. L. Whitfield, Celdara LLC, 4.

Abstract Number: 1119

Genetic Signatures from RNA Sequencing of Pediatric Localized Scleroderma (LS) Skin

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SESSION INFORMATION

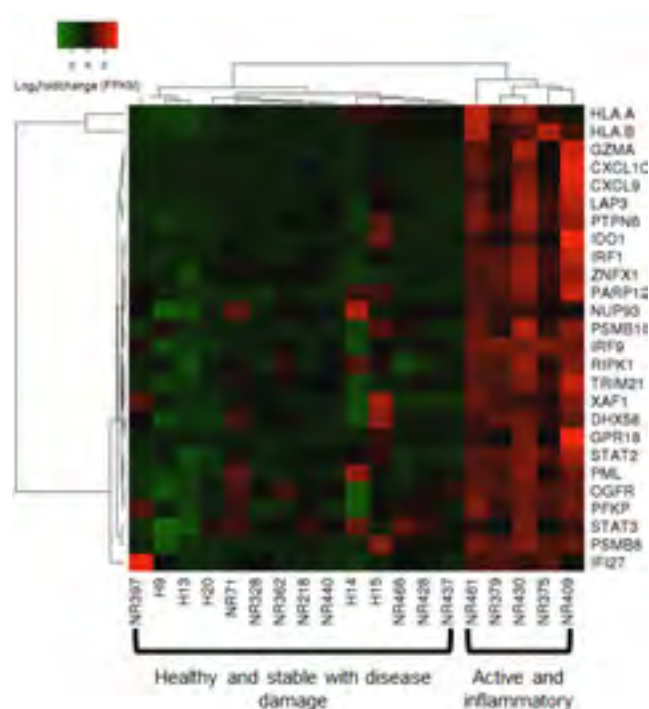
Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Localized scleroderma (LS) is a progressive disease of the skin and underlying tissue that causes significant functional disability and disfigurement, especially in developing children. During the active inflammatory stage of the disease, systemic immunosuppressive therapy intervention can halt disease progression and ameliorate disease features such as joint contractures. The existing clinical process for determining when LS is active and susceptible to intervention and when to gradually stop intervention is often convoluted. Commercially available inflammatory serologic markers currently have limited utility in the clinical assessment of active disease. RNA sequencing (RNAseq) technology allows for improved understanding of relevant cellular expression through transcriptome analysis of specific time points



during LS disease progression. It also permits the use of RNA extracted from existing paraffin-embedded skin tissue increasing the availability of samples.

Methods: RNAseq was performed on paraffin-embedded skin (n=15 LS, n=5 pediatric healthy) and RNAlater preserved skin specimens (n=2 LS, n=4 healthy) using the Illumina HTS using TrueSeq Access library preparation and collected through IRB#PRO11060222. Paired end RNA sequencing data was aligned using STAR and analyzed for differential gene expression (DEGs) using DESeq2. Genes were reanalyzed using DEG cutoffs of log₂fold change > ±2.5, adjusted p<0.05, and a false discovery rate (FDR) cutoff of <0.01 for enrichment software (GSEA®). PCA and hierarchical clustering was performed using Cluster3.0 and Partek® softwares. Clinical subtype data (active/inflammatory vs. stable/disease damage) was applied to these clustering techniques.

Results: A strong correlation ($r_s=0.90$, $p=0.0001$) was observed between the comparison of genes expressed between fresh (RNAlater) and paraffinized skin in healthy and LS subjects. When compared to healthy controls, we observed distinct expression of an inflammatory response gene signature (IRGS) composed of IFN γ , IFN α and TNF α associated genes. GSEA® enrichment analysis showed the IRGS, including interferon inducible chemokines such as CXCL9, CXCL10, CXCL11 and IFN γ itself, was more highly expressed in LS patients with more inflammatory lesions (see Figure).

Conclusion: The use of paraffinized skin for sequencing was proven to be an effective substitute for fresh skin by comparing gene expression profiles. The prevalence of the IFN γ signature in the lesion biopsies of active LS patients indicates these genes are reflecting clinical parameters and provide insight into disease propagation, possibly a Type 1 monocyte or T-cell response, which will be further investigated in regard to disease propagation.

Disclosure: E. Mirizio, None; R. Mandal, None; Q. Yan, None; W. Horne, None; K. Schollaert-Fitch, None; K. S. Torok, None.

Abstract Number: 1120

Strong HLA and Novel Non-HLA Associations Identified By Auto-Antibody Subset Analysis of African Americans with Scleroderma from the Genome Research in African American Scleroderma Patients Cohort

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Anti-fibrillarin (nucleolar, AFA) and anti-topoisomeraseI (ATA) autoantibodies are specific to systemic sclerosis (SSc) and are common in African Americans (AA). These auto antibodies define clinically distinct phenotypes but the genetic risk factors contributing towards them are largely unknown.

Methods: Data from the genome-wide association study (GWAS) of AA SSc collected under the Genome Research in African American Scleroderma Patients (GRASP) cohort were utilized. 207 AFA and 245 ATA positive patients were compared to 946 controls. After quality control filtering, SNP imputation was performed using Beagle and classical *HLA* types were imputed using HLA*IMP:03 web server. Odds ratios for *HLA* alleles and amino acid residues were calculated using a dominant model.

Results: In the GRASP cohort, 22.2% of patients had nucleolar ANA pattern (AFA) after removing other nucleolar staining, SSc specific auto antibodies. In the AFA+ subset, *HLA-DRB1*08:04* demonstrated the strongest association with $P=4.2 \times 10^{-27}$, OR=5.98 (95% CI 4.2-8.5) (Figure 1A). *HLA-DRB1*08:04* is a predominantly African ancestry allele and its leucine 74 residue in the peptide binding groove was strongly associated with AFA+ SSc with OR=5.12 (95% CI 3.7-7.1). The top SNP in the *HLA* region was rs573310147 with $P=1.3 \times 10^{-19}$. ATA positivity was seen in 26.2% of patients in the GRASP cohort. In the ATA+ subset, rs28667353 was the top SNP with $P=1.4 \times 10^{-19}$ (Figure 1B). *HLA-DPB1*13:01* was

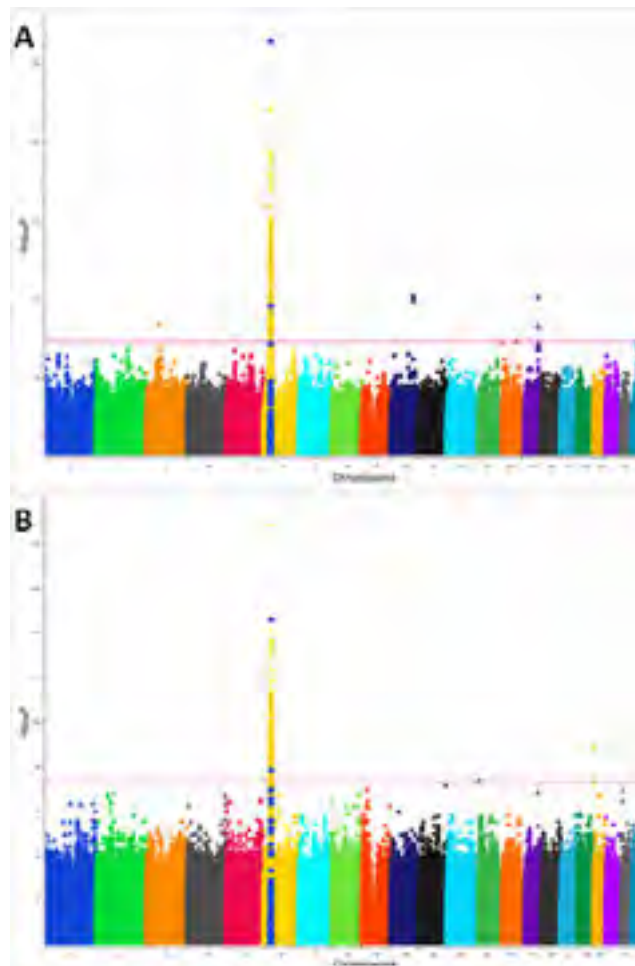


Figure 1. GWAS of Illumina MEGA array with imputed SNPs (triangles) and classical *HLA* types (blue squares). A: 207 AFA+ SSc and 946 controls; B: 245 ATA+ SSc and 946 controls. Pink line denotes p-value for genome-wide significance ($P=5 \times 10^{-8}$).

seen in 15.8% of ATA+ SSc as compared to 6.2% in ATA- SSc and 5.1% in controls. *HLA-DPB1*13:01* demonstrated the strongest association with $P=1.1 \times 10^{-16}$, OR=4.1 (95% CI 2.9-5.8) in the ATA+ subset. *HLA-DPB1*13:01* has been reported as a risk loci in ATA+ subset in SSc patients from several different ancestries. Meta-analysis with the European ancestry SSc yielded a highly significant $P=2.18 \times 10^{-61}$. On examining the amino acid residues, isoleucine 76 in the peptide binding groove of HLA-DPB1 increased risk for SSc with OR=2.8 (95% CI 2.1-3.8). Six other previously unreported, non-*HLA* loci were identified in the AFA+ subset and two in the ATA+ subset at genome-wide significance with the top one being *FSD2* (Fibronectin type III and SPRY domain containing 2).

Conclusion: *HLA-DRB1*08:04* is a predominantly African ancestry allele that increases SSc risk 6-fold in AFA subset which is primarily observed in AAs with SSc. This may help explain the increased prevalence and severity of SSc in AAs. *HLA-DPB1*13:01* increases risk of SSc in not only AAs but all ancestral populations. Also, *HLA-DPB1*13:01* control frequency in a population correlates with the prevalence of SSc in that ancestral population. Functional roles of these novel non-*HLA* loci need to be experimentally evaluated. Understanding the mechanism of peptide presentation by these two *HLA* alleles will lead to a better recognition of the trigger that leads to autoimmunity in SSc.

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Abstract Number: 1121

Characterizing the T Cell Receptor Repertoire in Patients with Systemic Sclerosis

Jennifer Franks¹, Yue Wang², Rajan Bhandari³, Diana M. Toledo⁴, Bhaven K. Mehta², Tammara A. Wood⁵, Noelle Kosarek², Monique Hinchcliff⁶, Chris Bailey-Kellogg⁷, Patricia A. Pioli⁸ and Michael L. Whitfield⁹, ¹Geisel School of Medicine at Dartmouth, Hanover, NH, ²Molecular and Systems Biology, Geisel School of Medicine at Dartmouth, Hanover, NH, ³Geisel School of Medicine at Dartmouth, Lebanon, NH, ⁴Department of Molecular & Systems Biology, Geisel School of Medicine at Dartmouth, Hanover, NH, ⁵Department of Molecular and Systems Biology, Geisel School of Medicine at Dartmouth, Hanover, NH, ⁶Rheumatology, Northwestern University, Chicago, IL, ⁷Computer Science, Dartmouth College, Hanover, NH, ⁸Microbiology and Immunology, Geisel School of Medicine at Dartmouth, Hanover, NH, ⁹Biomedical Data Science, Geisel School of Medicine at Dartmouth, Hanover, NH

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: T cell receptors (TCRs) are a vital component of the adaptive immune system and TCR repertoire diversity is considered a measure of the immune system's strength and competency. T cells have been implicated in the progression of systemic sclerosis (SSc), yet the TCR repertoire in SSc remains understudied. Here, we present findings from TCR sequencing in SSc patients to characterize their TCR repertoire.

Methods: Peripheral blood mononuclear cells (PBMCs) were collected from 11 patients with SSc and 7 controls, matched for age, gender, and race. We performed TCR sequencing on genomic DNA isolated from CD14⁺ lymphocytes. RNA-seq was also performed on RNA isolated from these cell populations. We used various metrics including CHAO1, Shannon Index, and Inverse-Simpson to quantify diversity of the TCR repertoire in each sample. Pearson correlation and Wilcoxon Rank Sum Test were used to relate clinical covariates to TCR repertoire diversity in SSc patients and controls. We used edgeR (Bonferroni-Holmes corrected $p < 0.05$) to identify differentially expressed genes from RNA-seq data and identified significantly enriched Gene Ontology biological pathways using g:Profiler (g:SCS corrected $p < 0.05$).

Results: We quantified measures of TCR repertoire diversity for each individual sample and correlated these measures with clinical variables. Reduced TCR repertoire diversity was associated with increased age in both SSc and controls, as

previously reported ($R=-0.44$, $p=0.06$). There was a statistically significant reduction in TCR diversity in SSc patients compared to controls ($p=0.0154$). Reduction in TCR diversity was most notable for patients with limited cutaneous SSc, though this did not reach statistical significance in our small sample size. There were no statistically significant relationships between TCR repertoire diversity and FVC, DLCO, or disease duration. We identified a total of 5735 differentially expressed genes (2651 up-regulated, 3084 down-regulated) in SSc samples compared to healthy control samples. Upregulated biological processes for SSc lymphocytes included *CD4+*, *alpha beta activation*, *Type I interferon production*, *T cell differentiation*, *mRNA processing*, and *cell cycle* ($p<0.05$). Upregulated biological processes for control samples included *leukocyte degranulation*, *lipid oxidation*, and *translational termination*.

Conclusion: We find a reduced diversity of TCR repertoire in patients with SSc relative to healthy controls. Gene expression analyses indicate that circulating T cells of SSc patients may be different from healthy controls, favoring suppression of effector Th1 generation, consistent with the development of autoimmunity.

Disclosure: J. Franks, None; Y. Wang, None; R. Bhandari, None; D. M. Toledo, None; B. K. Mehta, None; T. A. Wood, None; N. Kosarek, None; M. Hinchcliff, None; C. Bailey-Kellogg, None; P. A. Pioli, None; M. L. Whitfield, None.

Abstract Number: 1122

Lymphocyte Immunophenotypes at Randomization on the Scleroderma: Cyclophosphamide or Transplantation Trial: Comparison of Treatment Naïve and DMARD Treated Participants with Healthy Controls

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Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: The Scleroderma: Cyclophosphamide or Transplantation Trial (SCOT) study compared stem cell transplant to monthly cyclophosphamide (CYC) in patients with scleroderma (SSc). We studied baseline lymphocyte subsets comparing age and gender matched controls with SCOT participants who were previously treated in the prior 12 months and those who received no treatment during this period.

Methods: Lymphocytes from 123 controls and 72 SCOT participants at baseline were analyzed by flow cytometry. For each lymphocyte subset count, the significance of difference was determined using the Mann-Whitney-Wilcoxon on rank sum test.

Results: Compared to controls, those with SSc showed significant reductions in central memory CD8 T cells, memory B cells, myeloid and plasmacytoid dendritic cells, and in FOXP3+CD25+ T regulatory (Treg) cells (Table 1). Conversely, participants had increases in naïve CD4 cells and effector CD8 T cells. No significant differences in any lymphocyte subset were observed between those previously treated ($n=57$) and untreated ($n=15$). Additionally, no differences were observed between participants previously treated with CYC ($n=23$) and those that were not ($n=49$). All participants had an increased Th2/Th1 CD4 cell ratio compared to controls.

Conclusion: We found a number of differences between healthy controls and participants in terms of T cell subsets (including Tregs) and B cells attesting to the profound immune dysregulation in severe early diffuse SSc. Increased numbers of induced Th2 CD4 T cells supports the theory that Th2 (rather than Th1) cell play a role in the pathogenesis. Furthermore, the decreased numbers of Tregs may transformation to pathogenic effector T cells of Th17 or Th2 lineages with respective pro-inflammatory or pro-fibrotic activity. The role of memory B cells is unclear, although reduced numbers may represent trafficking to sites of inflammation or disease activity. The counts of abnormal cell subsets were similar in the treated and untreated patients suggesting that even in the treated patients the subset counts were abnormal primarily due to scleroderma itself rather than immune modulatory treatment. Even treatment with cyclophosphamide resulted in a baseline lymphocyte profile that was not significantly different from those patients treated with other agents. In other words, our data suggests severe disease was more influential than drug immunosuppression in producing the

immunophenotype abnormalities. The hypothesis that correction of lymphocyte aberration will affect clinical disease progression needs to be studied in a prospective trial.

Table 1: Lymphocyte subset counts (per microliter of blood) in patients with SSc and healthy controls.

Lymphocyte subset	Healthy Controls (n=123) Median (10 th -90 th percentile)	Untreated Patients (n=15) Median (10 th -90 th percentile)	Treated Patients (n=57) Median (10 th -90 th percentile)	Treated vs. untreated patients (p-value)	Healthy controls vs. all SSc patients (p-value)
T cells	1447 (799-2247)	1181 (719-2504)	1226 (452-2386)	Not signif.	Not signif.
CD4 T cells	935 (503-1544)	731 (444-1924)	843 (334-1806)	Not signif.	Not signif.
CD8 T cells	395 (199-735)	347 (232-556)	247 (99-721)	Not signif.	<0.001
Naïve CD4 T cells	88 (26-273)	231 (38-375)	173 (24-467)	Not signif.	<0.001
Central memory CD4 T cells	376 (199-683)	227 (66-717)	252 (82-518)	Not signif.	<0.001
Effector memory CD4 Cells	16 (6-42)	31 (4-94)	20 (9-91)	Not signif.	0.003
Naïve CD8 T cells	35 (7-119)	81 (6-127)	27 (4-119)	Not signif.	Not signif.
Central memory CD8 T cells	108 (49-246)	13 (4-49)	15 (2-70)	Not signif.	<0.001
Effector memory CD8 T Cells	12 (2-42)	19 (4-44)	8 (1-119)	Not signif.	Not signif.
Effector CD8 T cells	5 (1-19)	29 (9-106)	24 (6-90)	Not signif.	<0.001
Activated T cells	99 (40-256)	57 (13-402)	25 (6-259)	Not signif.	<0.001
Activated CD4 T cells	53 (20-138)	16 (4-296)	9 (2-139)	Not signif.	<0.001
Recent Thymic CD4 emigrants	63 (21-181)	114 (19-208)	84 (10-191)	Not signif.	Not signif.
Gamma/delta T cells	39 (13-97)	41 (4-94)	20 (5-63)	Not signif.	<0.001
Induced Th1 CD4 T cells	205 (64-543)	269 (24-1071)	217 (28-568)	Not signif.	Not signif.
Induced Th2 CD4 T cells	13 (2-49)	31 (0-131)	36 (6-95)	Not signif.	<0.001
Th2/Th1 CD4 cells ratio	0.051 (0.018-0.150)	0.146 (0.000-0.209)	0.153 (0.035 – 0.746)	Not signif.	<0.001
Induced Th1 CD8 T cells	249 (79 -585)	268 (22-633)	182 (47-702)	Not signif.	Not signif.
Induced Th2 CD8 T cells	2 (1-13)	4 (0-10)	4 (1-25)	Not signif.	0.012
Th2/Th1 CD8 cells ratio	0.010 (0.002-0.056)	0.015 (0.000-0.108)	0.021 (0.004-0.254)	Not signif.	<0.001
NK cells	176 (76-404)	205 (104-326)	198 (91-355)	Not signif.	Not signif.
B cells	197 (87-449)	208 (84-320)	159 (39-458)	Not signif.	Not signif.
Naïve B cells	151 (62-351)	183 (54-291)	141 (33-425)	Not signif.	Not signif.
Non-switched memory B cells	13 (5-29)	7 (1-18)	6 (1-22)	Not signif.	<0.001
Switched memory B cells	25 (9-57)	10 (4-17)	5 (2-22)	Not signif.	<0.001
Myeloid DCs/precursors	43 (24-88)	17 (9-70)	19 (8-42)	Not signif.	<0.001
Plasmacytoid DCs/precursors	5 (2-9)	2 (0-6)	3 (0-9)	Not signif.	<0.001
CD3+CD4+CD25+Fox P3+	37 (7-134)	4 (0-13)	2 (0-17)	Not signif.	<0.001
CD3+CD4+CD25+Fox P3+CD127-	34 (6-125)	4 (0-10)	2 (0-15)	Not signif.	<0.001

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Abstract Number: 1123

Plasmacytoid Dendritic Cells in Bronchoalveolar Lavage Correlate with Pulmonary Artery Diameter and Infiltrate Perivascular Areas in the Lungs from Patients with Systemic Sclerosis Associated Pulmonary Hypertension

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: In patients with systemic sclerosis (SSc), plasmacytoid dendritic cells (pDCs) increase in the bronchoalveolar lavage (BAL) and lung tissues (Kafaja S, et al, JCI Insight 2018). Importantly, the frequency of pDCs in the lungs of patients with SSc correlated with the severity of interstitial lung disease, and with the frequency of CD4⁺ and IL-4⁺ T-cells in the lung. A pivotal role of pDCs was shown in animal studies, where the depletion of pDCs ameliorated fibrosis in the bleomycin model. These data suggest a role of pDCs in the pathogenesis of fibrosis. Fibroblast proliferation and accumulation around pulmonary vessels is also an early and important event during the development of pulmonary arterial hypertension (PAH). Here, we explore a possible relationship between pDCs and pulmonary hypertension.

Methods: Previous studies have suggested the utility of HRCT-determined pulmonary artery diameters in predicting pulmonary hypertension. In one study, right pulmonary artery diameter of more than 18.7 ± 2.8 mm was considered abnormal, and main pulmonary artery diameter of >29 mm was predictive of pulmonary hypertension. Hence, to begin to investigate a relation between immune cell subsets and subclinical pulmonary arterial hypertension, we analyzed correlation between diameters (mm) of main or right pulmonary arteries and frequencies (% of total) of cell types in BAL. Frequencies of cellular subsets from RML and RLL were averaged. Next, we stained lung tissue slides from patients with SSc-PAH using markers for pDCs and blood vessels (alpha-smooth muscle cells and endothelial cells).

Results: The frequencies of pDCs correlated with the diameters of both main ($r = 0.45$) and right pulmonary arteries ($r = 0.57$). There was no correlation between the frequencies of T-cells ($CD4^+$, $CD8^+$, Th2 and Tc2) and pulmonary artery diameters. We further found increased pDCs around blood vessels and other areas of lungs from patients with SSc-PAH as compared to control lungs.

Conclusion: These data argue for a possible role of pDCs in SSc-associated pulmonary vascular disease.

Disclosure: I. Valera, None; A. Divekar, None; D. Khanna, None; F. Abtin, None; R. Saggat, None; R. R. Singh, None.

Abstract Number: 1124

Epidemiological Characteristics of Inpatient Admissions for Acute Inflammatory Gout Arthropathy and Factors Affecting Length of Stay: A National Level Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II: Gout, Ankylosing Spondylitis, Osteoarthritis, Osteoporosis, Pain, and Function

Session Type: ACR Poster Session B

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

Background/Purpose: Gout is a common cause of inflammatory arthritis due to accumulation of monosodium urate crystals in joints, bones and soft tissues. The aim of the study will be to understand the epidemiological characteristics of acute gout (ICD 9 code: 274.01) as a primary diagnosis in hospital discharges in the year 2014 using the National Inpatient Sample (NIS).

Methods: The NIS is a nationally representative sample of 20% of all non-federal hospitals in the USA with information from approximately 1000 hospitals pertaining to records from 7 million inpatient hospital admissions. The epidemiological characteristics we studied were age, gender, race, payer (Medicare/Medicaid/private insurance/uninsured), patient residence (large central metro, suburbs, medium and small metro and rural areas) and region (northeast, mid-west, southern and west) and associated co-morbidities: hypertension, diabetes, heart failure, chronic kidney disease, osteoarthritis & heart failure. Multiple linear regression was used to analyze factors that were associated with an increased length of stay.

Results: For 2014, from a total of nearly 7 million records (7,071,762), there were 11,415 admissions for acute gout as the primary diagnosis (0.16%) which translated to 3.6 admissions per 100,000 persons. The majority of admissions were in the age group of 65 – 84 years (46.1 %) followed by 45-64 age group (34.3%). A majority of the admissions were males (67.3%) compared to females (32.3%). Gout was most prevalent among Caucasians (65.8%). African Americans represented 14.8% of all admissions followed by Hispanics at 12.1%. Asian or pacific islanders were 2.8% whereas Native Americans represented 0.6%. The total aggregate costs were \$76,249,619 for 2014 amounting to a mean of \$6,654 per admission. Medicare remained the highest payer (62.8%) followed by private insurance (17.7%) and finally Medicaid (12.9%). Uninsured patients accounted for 5.2% of all admissions. Patients from a large central metro were the majority of inpatient admissions (39.1%) followed medium and small sized metro (25.1%). 24.1% of patients were from the suburbs and whereas only 11% were from a rural area. The southern region accounted for majority of admissions (33.2%) followed by northeast region (26.9%). 23.8% were from Midwest and Western region had only 15.9% of all admissions. The mean length of stay (LOS) was 3.9 ± 0.06 days. CKD was present in 47.8%, hypertension in 37.5%, CAD in 35.5%, heart failure in 35.1%, diabetes in 28.4% and osteoarthritis in 16% of patients. Using multivariate analysis the only factors significantly affecting LOS were female gender and presence of heart failure. Female gender was inversely related to LOS ($p < 0.001$) whereas heart failure exacerbation resulted in an increased LOS ($p < 0.001$).

Conclusion: Acute gout places a significant burden on in-hospital resources. Although CKD was present in nearly half of patients, only gender & heart failure resulted in significantly affecting LOS.

Disclosure: V. Murugesan, None; J. Tran, None.

Abstract Number: 1125

Association between Hyperuricemia and Metabolic Syndrome with or without Obesity: Results from the 2016 Korea National Health and Nutrition Examination Survey

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II: Gout, Ankylosing Spondylitis, Osteoarthritis, Osteoporosis, Pain, and Function

Session Type: ACR Poster Session B

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

Background/Purpose: Hyperuricemia is increasing worldwide, and is emerging as a potential biomarker and predictor for metabolic syndrome and related complications. We aimed this study to investigate the association between hyperuricemia and metabolic syndrome with or without obesity.

Methods: We performed multivariate logistic regression analyses using the 2016 Korea National Health and Nutrition Examination Survey (KNHANES) data collected in a representative sample of Korean adults (defined by age ≥ 20 years). Hyperuricemia was defined by serum uric acid level ≥ 7.0 mg/dl for men and ≥ 6.0 mg/dl for women. Obesity was based on body mass index (BMI) ≥ 25 kg/m².

Results: Among a total of 5,591 Korean adult participants, 685 (12.3%) individuals were classified as having hyperuricemia. Hyperuricemia was significantly associated with metabolic syndrome in both men (Odd ratio (OR) = 1.74, 95% CI: 1.29-2.34) and women (OR = 2.47, 95% CI: 1.55-3.93) after adjustments for age, sex, smoking, alcohol, exercise, BMI and estimated glomerular filtration rate (eGFR). Obesity was also independently related to hyperuricemia in both sex (OR = 1.70, 95% CI: 1.31-2.19 in men, OR = 3.73, 95% CI: 2.57-5.41 in women). Among the components of metabolic syndrome, elevated blood pressure, elevated triglyceride and reduced high-density lipoprotein (HDL)-cholesterol in men, and increased waist circumference, hyperglycemia, elevated triglyceride in women were risk factors for hyperuricemia. In subgroup analyses, individuals who had metabolic syndrome with obesity were at the highest risk of hyperuricemia, followed by those with metabolic syndrome without obesity in overall population (OR = 3.91, 95% CI: 3.00-5.09, OR = 3.21, 95% CI: 2.28-4.52, respectively). In population with metabolic syndrome, the presence of obesity posed higher risk for hyperuricemia in women compared with men (OR = 7.24, 95% CI: 4.56-11.50 versus OR = 2.90, 95% CI: 2.12-3.96).

Conclusion: Our results indicate that hyperuricemia is independently associated with metabolic syndrome and obesity in both sex. The effect of obesity in increasing the risk of hyperuricemia was more pronounced in women compared to men.

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Abstract Number: 1126

Gout and Chronic Pain in Older Adults: A Medicare Claims Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II: Gout, Ankylosing Spondylitis, Osteoarthritis, Osteoporosis, Pain, and Function

Session Type: ACR Poster Session B

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

Background/Purpose: To assess if gout is associated with a higher risk of incident chronic pain in older adults, 65 years or older.

Methods: This study used the 2006-2012 Medicare claims data. We used multivariable-adjusted Cox regression analyses to examine the association of pre-existing diagnosis of gout with incident (new) diagnosis of chronic pain, adjusting for demographics, medical comorbidity and use of common medications for cardiovascular disease and gout. Sensitivity analyses substituted Charlson-Romano score with acategorical variable or each Charlson-Romano comorbidity. Gout was identified by the presence of two claims for gout at least 4 weeks apart, with International Classification of Diseases, ninth revision, common modification (ICD-9-CM) code of 274.xx. Study outcome was incident (new) chronic pain, with an absence of this diagnosis in the baseline period of 1 year, that occurred in patients with or without pre-existing gout diagnosis that preceded the diagnosis of chronic pain. We identified chronic pain by the occurrence of at least two claims 4-weeks apart containing any of the following ICD-9-CM codes [12]. 307.80, 307.89, 338.0, 338.2, 338.4, 719.41, 719.45 - 719.47, 719.49, 720.0, 720.2, 720.9, 721.0 - 721.4, 721.6, 721.8, 721.9, 722, 723.0, 723.1, 723.3 - 723.9, 724.0 - 724.6, 724.70, 724.79, 724.8, 724.9, 729.0 - 729.2, 729.4, 729.5. This approach has been shown to be valid, with positive predictive value of 95%, sensitivity of 70% and specificity of 99%. We used multivariable-adjusted Cox proportional hazard models to assess the association of gout with incident GCA, adjusting for potential confounders/covariates including demographics (age, race, gender), comorbidities (Charlson-Romano comorbidity index), and medications commonly used for cardiac diseases (statins, beta-blockers, diuretics, and angiotensin converting enzyme (ACE)-inhibitors) and gout (allopurinol and febuxostat; Model 1).

Results: There were 1,321,521 eligible people, of whom 424,518 developed incident chronic pain. Crude incidence rates of chronic pain were as follows: gout, 158.1 per 1,000 person-years and no gout, 64.5 per 1,000 person-years. In multivariable-adjusted Cox regression analyses, gout was associated with higher hazard ratio of chronic pain, 2.02 (95% CI, 1.98, 2.05), confirmed in sensitivity analyses 1.96 (95% CI, 1.93, 1.99) (model 2) and 1.77 (95% CI, 1.74, 1.80) (model 3). No meaningful differences were found by gender and race in subgroup analyses; slightly lower hazard of gout with chronic pain was seen in oldest people (Table 1).

Conclusion: Gout was associated with a doubling of the risk of chronic pain. Efforts must be made to optimize gout control and gout inflammation, so that long-term sequelae of gout, including chronic pain can be avoided and when present, treated early and appropriately.

Table 1. Association of gout with chronic pain, in pre-defined subgroup analyses, by age, gender, and race

	Multivariable-adjusted (Model 1)		Multivariable-adjusted (Model 1)		Multivariable-adjusted (Model 1)	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Gout	Black 2.27 (2.17, 2.38)	<0.0001	White 1.97 (1.94, 2.01)	<0.0001	Other race 2.19 (2.04, 2.34)	<0.0001
Gout	Female 1.95 (1.90, 2.00)	<0.0001	Male 2.04 (2.00, 2.08)	<0.0001		
Gout	65-75 years 2.20 (2.15, 2.25)	<0.0001	75-85 years 1.86 (1.81, 1.91)	<0.0001	>85 years 1.75 (1.67, 1.85)	<0.0001

Race*Gout p-value <0.0001;

Sex*gout p-value <0.0001;

Age*gout p-value <0.0001;

HR, Hazard ratio; CI, confidence interval;

Hazard ratios that are significant with p-value <0.05 are in bold

Disclosure: J. A. Singh, Takeda, Savient, 2, Savient, Takeda, Regeneron, Merz, Iroko, Bioiberica, Crealta/Horizon and Allergan pharmaceuticals, WebMD, UBM LLC, Medscape, Fidia pharmaceuticals and the American College of Rheumatology, 5; J. Cleveland, None.

Risk of Stroke Among Patients with Gout in Taiwan: A Nationwide Population Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II: Gout, Ankylosing Spondylitis, Osteoarthritis, Osteoporosis, Pain, and Function

Session Type: ACR Poster Session B

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

Background/Purpose: To determine whether the Taiwanese patients with gout have a higher risk of stroke.

Methods: Using the National Health Insurance database, we identified a cohort of new-onset gout patients in Taiwan between 2000 and 2005, follow up till 2015. The gout cohort was frequency-matched according to birth year and gender with patients without gout (control cohort). Cumulative probability and multivariable hazard ratio (HR) adjusted by age, sex, Charlson comorbidity index and co-medication was performed to evaluated the risk of stroke, including ischemic and hemorrhage stroke.

Results: In this study, we identified 646,983 incident patients with 1:1 matched of control group without gout. The incidence (100 person-years) of ischemic stroke and hemorrhagic stroke were both higher in gout group [7.26 (95% CI, 7.19-7.33); 2.47 (95% CI, 2.42 - 2.51) respectively] than control group [5.95 (95% CI, 5.88- 6.01); 2.04 (95% CI, 2-2.07), respectively]. Both risk of ischemic stroke and hemorrhage stroke were higher in gout group (HR 1.15, 95% CI 1.14-1.17; HR1.17, 95% CI 1.14-1.20, respectively) (**Table**).

Conclusion: Patients in Taiwan with gout have a higher risk of stroke, including ischemic stroke and hemorrhagic stroke. The incidence of ischemic stroke was three-fold than hemorrhagic stroke in gout patient.

Table: Clinical characteristics of patients and Hazard ratios for incidence of stroke.

	Gout (n= 646,983)	No Gout (n= 646,983)	P Value
Sex, No. (%)			
Male	473362(73.16)	473362(73.16)	1.0000
Female	173611(26.83)	173611(26.83)	
Age, mean (SD), y	49.63 (17.18)	49.62 (17.18)	0.9476
Hypertension	165148(25.53)	107091(16.55)	<.0001
Ischemic stroke			
Incidence/100 person-years(95%CI)	7.26(7.19-7.33)	5.95(5.88-6.01)	
No. of case, (%)	39812(6.15)	32619(5.04)	
Age and sex adjusted Hazard Ratio(95%CI)	1.26(1.24-1.28)*	1.0	
Multivariable Hazard Ratio# (95% CI)	1.16(1.14-1.18)*	1.0	
Multivariable Hazard Ratio† (95% CI)	1.15(1.14-1.17)*	1.0	
Hemorrhagic stroke			
Incidence/100 person-years(95%CI)	2.47(2.42-2.51)	2.04(2-2.07)	
No. of case, (%)	13703(2.12)	11289(1.74)	
Age and sex adjusted Hazard Ratio(95%CI)	1.23(1.20-1.26)*	1.0	
Multivariable Hazard Ratio# (95% CI)	1.16(1.13-1.19)*	1.0	
Multivariable Hazard Ratio† (95% CI)	1.17(1.14-1.20)*	1.0	

* adjusted for age, sex and charlson comorbidity index (myocardial infarction, congestive heart disease, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, Renal failure, peptic ulcer disease, mild liver disease, moderate or severe liver disease, diabetes and diabetes with complications, hemiplegia and paraplegia, any malignancy including leukaemia and lymphoma, metastatic tumour, human immunodeficiency virus [HIV] infection and hypertension).

† adjusted for age, sex, charlson comorbidity index (myocardial infarction, congestive heart disease, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, Renal failure, peptic ulcer disease, mild liver disease, moderate or severe liver disease, diabetes and diabetes with complications, hemiplegia and paraplegia, any malignancy including leukaemia and lymphoma, metastatic tumour, human immunodeficiency virus [HIV] infection and hypertension), NSAID, Colchicine, Prednisolone, PPI, Vitamin D, Bisphosphonates, Glucocorticoids, insulin, glucose, antihypertensives, nitrates, lipid, anticonvulsants, anticoagulants and DMARD.

Disclosure: P. H. Tsai, None; C. F. Kuo, None.

Impact of Urate-Lowering Therapy on the Risk of Cardiovascular Events and All-Cause Mortality Among Individuals with Gout

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II: Gout, Ankylosing Spondylitis, Osteoarthritis, Osteoporosis, Pain, and Function

Session Type: ACR Poster Session B

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

Background/Purpose: Gout results from an increased body pool of urate that occurs with hyperuricemia. Although urate-lowering therapy (ULT) is beneficial to prevent gout attack, current recommendations do not advise every patient with gout to receive a ULT. In this study, we evaluated the impact of ULT on the risk of major cardiovascular (CV) events and all-cause mortality among individuals with gout.

Methods: We conducted an incident user cohort study with 1:1 propensity score matching by using the National Health Insurance Service-National Sample Cohort (NHIS-NSC), a Korean population-based cohort of individuals who submitted medical care claims between 2002 and 2013, linked with the results of the National Health Checkup Service in Korea. Incident gout cases were defined as newly used *International Classification of Diseases (ICD)* code M10 from 2003 to 2013, excluding patients who had an M10 code in 2002. For propensity score matching, age, sex, income, presence of diabetes mellitus, hypertension, hyperlipidemia and atrial fibrillation, smoking, alcohol consumption, body mass index, and Charlson comorbidity index scores were considered. Major CV events were defined as acute myocardial infarction (*ICD* codes I21 and I22) and stroke (I63).

Results: In the NHIS-NSC cohort, 37730 incident gout cases were identified between 2003 and 2013. Among the cases, 9387 were treated with allopurinol, febuxostat, or benzbromarone more than twice (ULT initiators) and the other 28333 were not (comparators). Of the 9387 and 28333 patients, 948 (10.1%) and 2117 (7.5%), respectively, developed major cardiovascular events in the first 10 years of the disease (mean follow-up: 4.1 years), and 714 (7.6%) and 962 (3.4%), respectively, died in the first 10 years of the disease (mean follow-up: 4.4 years). After propensity score matching, 4034 ULT initiators and 4034 matched comparators were compared. Among the initiators and comparators, 349 and 288, respectively, had new major CV events in the first 10 years of the disease (mean follow-up: 4.1 years), and 23 and 16, respectively, died in the first 10 years of the disease (mean follow-up: 4.3 years). ULT initiation was associated with a higher risk of CV events (matched HR, 1.196; 95% confidence interval [CI], 1.022–1.399) and all-cause mortality (matched HR, 1.355; 95% CI, 1.078–1.702).

Conclusion: The current population-based matched-cohort study does not support the beneficial effects of ULT initiation on the cardiovascular outcomes or all-cause mortality in patients with gout during the first 10 years of the disease. Further study regarding the effects of steady ULT maintenance in the whole population cohort would be needed.

Disclosure: I. A. Choi, None; H. Jang, None; G. W. Kang, None.

Prevalence, Incidence, Determinants, and Impacts of Depression and Anxiety in Gout: A Systematic Review

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Background/Purpose: A previously synthesized positive association between gout and depression has combined studies of both prevalent and incident depression. To disentangle these data and provide a comprehensive understanding of the burden, risk, impacts, and determinants of psychiatric complications in gout, our objective was to conduct a systematic review of observational studies of depression as well as anxiety among patients with gout.

Methods: We conducted a mapped search of Medline, Embase, and Cochrane Database of Systematic Reviews on the Ovid platform, and CINAHL Complete and PsycINFO on Ebscohost to identify full-length articles published in English meeting the following inclusion criteria: 1) observational design; 2) study sample including gout patients with or without a comparator group; 3) depression and/or anxiety evaluated as a comorbidity, outcome, or predictor of a health outcome and assessed using routinely reported measures; and 4) reporting of relevant estimates (e.g. prevalence proportion, odds ratio [OR], hazard ratio [HR]) or sufficient data to allow calculation. We extracted information on study setting and design, patient population and sample size, gout ascertainment, and methods of assessing depression and anxiety. Where relevant and sufficient data permitted, we pooled estimates using random effects models.

Results: From 771 articles identified with our search strategy, we included 16 studies with 9 assessing both depression and anxiety and 7 assessing depression alone. With respect to depression, the pooled prevalence proportion based on 8 studies and a total of 57,103 gout patients was 10% (95% confidence interval [CI], 8% to 12%) and pooled OR was 1.19 (95% CI, 1.03 to 1.35). The incidence of depression in gout patients as compared to the general population was reported in 3 studies and meta-analysis yielded a pooled adjusted (a)HR of 1.09 (95% CI, 0.93 to 1.26). With respect to anxiety, pooled prevalence proportion based on 5 studies and a total of 36,708 gout patients was 6% (95% CI, 3% to 10%) and pooled OR was 1.54 (95% CI, 1.43 to 1.65). Only 1 study assessed the incidence of anxiety among gout patients (aHR, 1.01; 95% CI, 0.87 to 1.16). Determinants of psychiatric complications include a higher frequency of gout attacks, having oligo/polyarticular gout, greater number of tophi, disability, quality of life, and education level (anxiety only). Finally, both depression and anxiety in gout significantly impact patients' health-related quality of life.

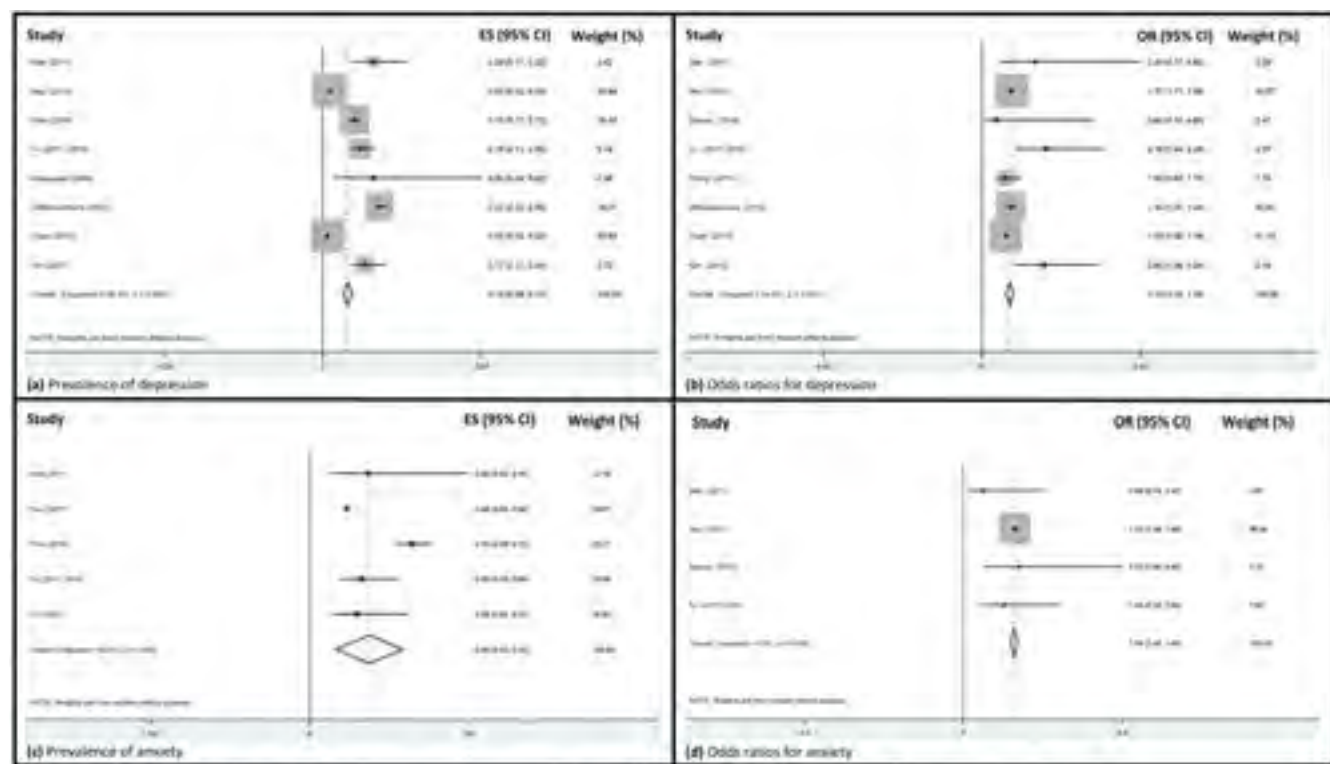


Figure 1. Pooled prevalence estimates (ES) and odds ratios (OR) for depression (a-b) and anxiety (c-d) in gout.
Abb: CI = confidence interval

Conclusion: Our findings establish a substantial prevalence of both depression and anxiety among gout patients. This highlights the need for further research to better understand the onset (incidence) of psychiatric complications after gout diagnosis as well as identify potential targets for intervention.

Chronic Risk Factors for Recurrent Gout Flares Among Established Gout Patients: A Prospective Cohort Analysis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II: Gout, Ankylosing Spondylitis, Osteoarthritis, Osteoporosis, Pain, and Function

Session Type: ACR Poster Session B

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

Background/Purpose: Understanding the risk factors for recurrent flares among established gout patients is directly relevant to clinical care; however, relevant data are scarce. A previous prospective study of 197 gout patients found that chronic risk factors such as age, sex, education level, obesity, gout disease duration, and the presence of hypertension, diabetes, renal disease, or congestive heart failure (CHF) were not significantly associated with the risk of recurrent gout, although some point estimates were suggestive of an association. We re-examined the same risk factors among 997 gout patients in an expanded follow-up study.

Methods: We conducted a cohort analysis of a prospective study designed to examine the associations of putative risk factors with recurrent gout attacks. Individuals with gout were recruited and followed up online for one year. Participants were asked to provide the following information regarding their gout attacks: date of gout attack onset, symptoms and signs, medications (including anti-gout medications), and exposure to potential risk factors at baseline and during the follow-up in relation to gout flares. We used Cox proportional hazard models to calculate hazard ratios for the risk of recurrent gout attacks related to age, sex, education level, body mass index, gout disease duration, and the presence of hypertension, diabetes, renal disease, and CHF at baseline.

Results: Among 997 gout patients (mean age, 53.6 years; 78.4% male), we documented 361 gout flares during a mean follow-up of 0.49 years. Overall, the annual incidence rate was 75 per 100 person-years (**Table**). Younger age (<60 years), disease duration (>1 year), and the presence of CHF were independently associated with a 45%, 71%, and 57% higher risk of gout flares, respectively (**Table**). Female sex, obesity, and diabetes tended to be associated with a higher risk of gout flares (**Table**), although not statistically significant.

Conclusion: This large prospective gout cohort study suggests that younger age, longer disease duration, and having CHF all confer a higher risk of gout flares, independent of other risk factors. While these associations may be due to higher serum urate levels and pools associated with these factors even among gout patients, it remains conceivable that these factors may contribute to the risk of flares independent of their urate level impact. Regardless, these data suggest a potential need for more aggressive therapy among patients with these risk factors.

Risk Factor	No. of Gout Flares	Incidence Rate (per 100 person-years)	Age-, Sex-Adjusted RR (95% CI)	Multivariable RR (95% CI)*
All	361	74.6	-	-
Age				
≥60 years	113	61.8	1.0	1.0
<60 years	248	82.4	1.39 (1.11, 1.74)	1.45 (1.14, 1.85)
Sex				
Female	86	86.1	1.0	1.0
Male	275	71.6	0.80 (0.62, 1.02)	0.78 (0.61, 1.01)
Education				
<College graduate	161	82.9	1.0	1.0
College graduate	200	69.4	0.86 (0.70, 1.06)	0.94 (0.76, 1.17)
Body Mass Index (kg/m ²)				
<25	31	56.6	1.0	1.0
25-29.9	124	67.7	1.21 (0.81, 1.79)	1.23 (0.83, 1.82)
≥30	206	83.9	1.46 (1.00, 2.13)	1.40 (0.96, 2.05)
Disease Duration				
<1 year	47	48.8	1.0	1.0
≥1 year	314	81.0	1.73 (1.26, 2.36)	1.71 (1.25, 2.33)

Table . (Cont'd)

Risk Factor	No. of Gout Flares	Incidence Rate (per 100 person-years)	Age-, Sex-Adjusted RR (95% CI)	Multivariable RR (95% CI)*
Presence of DM				
No	305	71.4	1.0	1.0
Yes	56	99.5	1.53 (1.15, 2.05)	1.32 (0.97, 1.80)
Presence of CHF				
No	333	72.4	1.0	1.0
Yes	28	117.2	1.86 (1.26, 2.75)	1.57 (1.05, 2.36)
Presence of CKD				
No	306	73.5	1.0	1.0
Yes	55	81.9	1.19 (0.89, 1.60)	1.14 (0.84, 1.54)
Presence of HTN				
No	223	73.0	1.0	1.0
Yes	138	77.5	1.17 (0.94, 1.47)	1.05 (0.83, 1.33)

CHF = congestive heart failure, CKD = chronic kidney disease, DM = diabetes mellitus, HTN = hypertension.

* Mutually adjusted for the variables in this table.

Disclosure: Y. Zhang, None; J. Wei, None; C. Yokose, None; S. K. Rai, None; H. K. Choi, Takeda, Selecta, Kowa, and Horizon, 5, Selecta and Horizon, 2.

Abstract Number: 1131

The Prevalence and Incidence of Gout, Its Associated Comorbidities and Treatment Pattern: An Epidemiological Study from Germany

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II: Gout, Ankylosing Spondylitis, Osteoarthritis, Osteoporosis, Pain, and Function

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Background/Purpose: The most common type of inflammatory arthritis in Germany is gout, however the last epidemiological study was done a decade ago (Annemanns, 2007). This study aimed to provide an up-to-date analysis on the prevalence and incidence of gout, associated comorbidities, and current treatment patterns.

Methods: The InGef research database, comprising a sample of ~4 million healthcare claims, was used for the analyses. Patients were included based on hospital discharge or ambulatory diagnoses of gout (ICD10M10) or hyperuricemia (E79.0) in combination with uric acid tests, prescription of urate lowering therapy (ULT), and treatment of gout flare. Prevalent gout cases were analysed according to comorbidities and pharmacological treatment. Additionally, a comparison to an age- and sex-matched control group without gout was performed.

Results: The study included 62,425 gout claims. Prevalence was 1.63% (standardized), corresponding to 1.325 million gout patients in Germany. Incidence was 0.45% (standardized). Male-to-female ratio was 3.2 for prevalence and 2.7 for incidence. The mean age of diagnosis was 66 years. Gout patients suffered significantly more from comorbidities than patients without gout (Table 1). The most common comorbidities were hypertension (80%), hyperlipidemia (58%), diabetes (38%), and obesity (32%). About 70% of gout patients received ULT (63% Allopurinol, 6% Febuxostat, 0.6% Benzbromarone). Overall, gout patients received an average of 8.7 (SD: 5.5) medications; 44% took ≥9 different medications in comparison to 20% of patients without gout (Table 2). Most common medications were NSAIDs (49%) and beta blocking agents (49%), lipid lowering drugs (35%), and antidiabetic drugs (23%). Accordingly, mean costs for drug treatment were substantially higher (1,148€ vs. 815€). About 29% of gout patients had ≥1 hospital visits in 2016 compared to only 21% of patients without gout (p<0.001).

Conclusion: The prevalence of gout (1.63%) was slightly higher compared to a previous analysis of German claims data (1.4%; Annemanns, 2007). This study confirms that gout patients suffer from more comorbidities with a high need for multiple medications, resulting in significantly greater mean drug costs compared to patients without gout.

Table 1: Comorbidities of patients with gout and without gout

Comorbidities	Prevalent gout cases (n,%)		Control group without gout (n,%)		p-value (Fisher's exact test)
Alcohol intake	3,508	5.62	1,744	2.79	<0.001
Chronic kidney disease	14,222	22.78	4,942	7.92	<0.001
Diabetes mellitus	23,437	37.54	13,322	21.34	<0.001
Heart failure	12,281	19.67	6,053	9.70	<0.001
Hyperlipidemia	35,956	57.60	25,325	40.57	<0.001
Hypertension	49,801	79.78	35,701	57.19	<0.001
Hyperuricemia	31,899	51.10	4,727	7.57	<0.001
Obesity	19,910	31.89	8,529	13.66	<0.001
Osteoarthritis	5,034	8.06	2,898	4.64	<0.001

Table 2: Comedications of patients with gout and without gout

Comedications	Prevalent gout cases (n,%)		Control group without gout (n,%)		p-value (Fisher's exact test)
Acetylsalicylic acid	7,311	11.71	5,476	8.77	<0.001
Antidiabetic drugs (incl. insulin)	14,298	22.90	8,190	13.12	<0.001
Beta blocking agents	30,656	49.11	18,806	30.13	<0.001
Glucocorticoids	9,906	15.87	4,936	7.91	<0.001
Lipid lowering drugs	21,827	34.97	14,472	23.18	<0.001
NSAIDs	30,823	49.38	16,977	27.20	<0.001
Opioids	9,089	14.56	5,790	9.28	<0.001
Other analgesics	15,942	25.54	10,104	16.19	<0.001
Other antihypertensive agents	45,858	73.46	30,703	49.18	<0.001
Thiazide and loop diuretics	7,437	11.91	3,805	6.10	<0.001

Disclosure: U. Kiltz, Grünenthal GmbH, 2, 5, AbbVie Inc., 2, 5, Chugai, 2, 5, Novartis, 2, 5, Eli Lilly and Co., 2, 5, Janssen, 2, 5, MSD, 2, 5, Roche, 2, 5, Roche, 2, 5; F. Perez-Ruiz, Grünenthal GmbH, 5, Menarini, 5, Cruces Hospital Rheumatology Association, 2; T. Uhlig, Grünenthal GmbH, 2, 5, AbbVie Inc., 2, 5, UCB, Inc., 2, 5, Ardea, 5, Astra Zeneca, 5, BMS, 5, Eli Lilly and Co., 5, Janssen, 5, Novartis, 5, Pfizer, Inc., 5, Roche, 5, Sandoz, 5, Menarini, 5; T. L. Jansen, Grünenthal GmbH, 5, Novartis, 5; R. Karra Gurunath, Grünenthal, 3; N. Schmedt, None; W. Galetzka, None; G. Petersen, Grünenthal GmbH, 3; T. Schoenfelder, Grünenthal GmbH, 2; A. K. Tausche, Berlin Chemie, 8, Menarini, 8, Ipsen, 8, Sobi, 8, Novartis, 8, Ardea Biosciences, 8, Ardea Biosciences/Astra Zeneca, 2, 8.

Abstract Number: 1132

Diet Modification for Gout Patients: Effects on Gout Attacks and Risk Factors for Metabolic Syndrome

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SESSION INFORMATION

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Session Title: Epidemiology and Public Health Poster II: Gout, Ankylosing Spondylitis, Osteoarthritis, Osteoporosis, Pain, and Function

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

Background/Purpose: Gout affects 8 million individuals in the US and is prevalent among patients with metabolic syndrome. Although there are many medications to control gout attacks and to lower serum uric acid (sUA), they come with potential side effects, and many patients are refractory to pharmacological treatment. Less emphasis has been placed on dietary counseling, which may provide a cost-effective benefit in controlling gout and as a supplement to medications. The aim of this study is to investigate if counseling gout patients on diet and lifestyle modifications will decrease the number of gout flares and further improve their risk factors for metabolic syndrome.

Methods: A retrospective study involving Long Beach Veteran Hospital patients was performed (N= 159). Gout patients were identified by their International Classification of Disease version ICD 9 or 10 from 2013 to 2016, and were grouped into those that received 1) no diet counseling (n=42), 2) diet counseling since their gout diagnosis (n=92) and 3) diet counseling 2 years after initial gout flare (n=25). Extensive electronic medical record review was performed for a 24-month period to evaluate the effectiveness of diet counseling in gout management based on the change in frequency of gout flares, renal function (eGFR) and sUA. Risk factors for metabolic syndrome, including blood pressure, BMI, lipid profile and HgA1c levels were obtained as outcome measures of diet modification that are associated with gout attacks.

Results: Patients who received diet counseling had fewer accumulative gout attacks (2.68 vs. 1.3 p=0.002) and more pronounced decrease in sUA (28.7% vs 3.1%, p =0.01) when compared to those without counseling over the 24-month period. With diet counseling, the patients' HDL increased (10.1% p <0.05) and LDL decreased (7.5%, p<0.01) but their BMI and blood pressure were comparable irrespective to diet counseling.

Conclusion: Gout patients who underwent diet counseling had fewer gout attacks afterwards. Patients who received documented diet counseling by their primary care physicians or rheumatologists had more effective reduction in serum uric acid and cholesterol levels over 24 months. Diet counseling may further benefit gout patients by decreasing risk factors that contribute to metabolic syndrome to provide better control of gout flares long term. A larger study over a longer period of time is needed to elucidate the impact of the risk factors for metabolic disorders in relation to gout management.

Disclosure: M. DiFiore, None; M. Wong, None; J. Chang, None.

Abstract Number: 1133

Factors for Opioids Use in the Early Treatment Options for the Knee Osteoarthritis Patients

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Background/Purpose: Current guidelines for osteoarthritis (OA) treatment recommend a range of nonpharmacological and pharmacological interventions to alleviate pain, improve function and quality of life. Most guidelines do not recommend opioids for OA treatment as an early treatment option, but some guidelines suggest using opioids on a restricted basis for short-term use in select patients with refractory symptoms. Although opioids can emerge as a treatment option that may provide effective pain relief with less risk than NSAIDs, they have the potential to cause harm. Until now, the current burden of opioid use for knee OA in Korea is not well understood. We investigated how many prescriptions of opioids for early knee OA treatment are given in Korea, and examined the factors related with opioid use in the early treatment options for knee OA.

Methods: Using the Korean nationwide claims database, all knee OA patients during 2013-2015 were identified by our validated operational definition. Among them, we extracted incident cases to identify opioid use in the early treatment options for knee OA patients. Opioids included tramadol as a weak opioid, and the utilization of opioids was analyzed by dividing strong opioids and weak opioids. A multivariable model was constructed to examine the factors related with opioids use.

Results: Among a total of 2,857,999 incident knee OA patients, 12.2% (n=348,516) were treated with opioids in their first year after diagnosis. However, strong opioid use (not including tramadol) was only 0.07% among the knee OA patients (n=1,972). Opioid users were slightly older (64.2 vs. 64.0 years old, $p<0.01$) and more likely to be male (44.0% vs. 37.8%, $p<0.01$) than opioid non users. Most of the opioids (88.6%) were prescribed in community hospitals and clinics. The frequency of opioid prescription was highest in the department of orthopedic surgery (70.1%), followed by internists (9.7%). Elixhauser comorbidity index score was higher in opioid users (4.51 ± 6.36 vs. 4.43 ± 6.23 , $p<0.01$). Related factors with early opioid use were older age (≥ 70 years old: odds ratio [OR], 1.02; 95% confidence interval [CI], 1.01-1.03, reference 50-59 years old), male (OR 1.29; 95% CI, 1.28-1.30), and medical aid patients (OR 1.13; 95% CI, 1.12-1.15). In terms of comorbidities present, there were peptic ulcer disease (PUD) (OR 1.03; 95% CI, 1.02-1.04), depression (OR 1.05, 95% CI, 1.04-1.06), and musculoskeletal diseases (low back pain: OR 1.12; 95% CI, 1.12-1.13, intervertebral disc: OR 1.11, 95% CI, 1.10-1.13, spinal stenosis: OR 1.27, 95% CI, 1.26-1.29, fibromyalgia: OR 1.14, 95% CI, 1.11-1.17), while diabetes (OR 0.98, 95% CI, 0.97-0.99) and malignancy (OR 0.89, 95% CI, 0.88-0.90) were protective.

Conclusion: In Korea, strong opioid use is not common as a treatment option for early knee OA treatment, but tramadol use is common. Being elderly, male, having comorbidities such as PUD and musculoskeletal diseases, and medical aid patients were more likely to be treated with strong opioids or tramadol.

Disclosure: S. K. Cho, None; S. Choi, None; S. G. Im, None; H. Kim, None; S. Y. Jung, None; E. J. Jang, None; Y. K. Sung, None.

Abstract Number: 1134

Some Is Better Than None: Minimum Physical Activity Threshold to Prevent Disability in Older Adults with Lower Extremity Joint Symptoms

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SESSION INFORMATION

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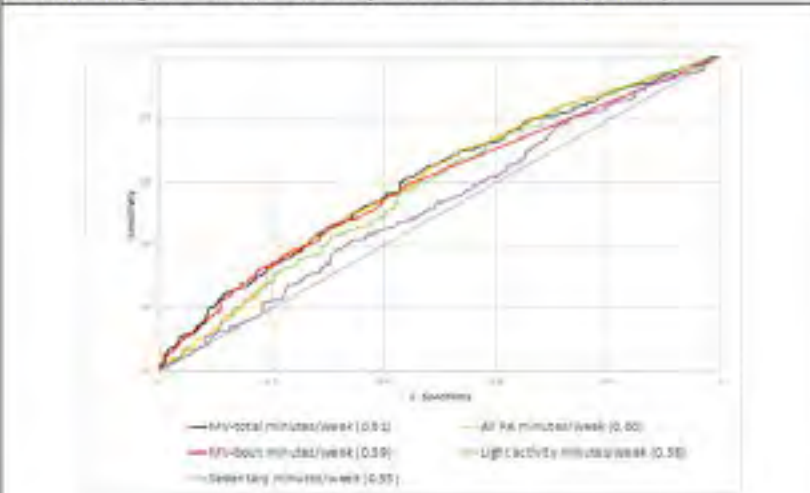
Background/Purpose: This study evaluated physical activity and sedentary times to identify a evidence-based threshold related to remaining free of disability over 4 years among adults with lower extremity joint symptoms.

Methods: Remaining free of disability over 4 years (i.e., no disability onset) was assessed from self-report of no limitations in activities of daily living (ADL-disability free) and objective gait speed ≥ 1 meter/second (mobility-disability free). Adults with symptomatic lower extremity (hip, knee, ankle, foot) joint pain/aching/stiffness who participated in an accelerometer substudy of the Osteoarthritis Initiative (OAI) included n=1564 ADL-disability free (n=1460) or mobility-disability free (n=1370) persons at baseline (OAI 48-month clinic visit). Optimal thresholds predicting 4-year disability-free status were assessed by maximum area under the receiver operating characteristic curve (AUC) and classification tree analysis.

Results: Over four years 84% (1222/1460) participants remained free of ADL-disability and 89% (1223/1370) remained free of mobility-disability. Figure 1 shows total MV activity per week was the strongest predictor of all Table 1 candidate measures based on the greatest AUC of remaining free of ADL-disability (AUC=0.61) and free of mobility-disability (AUC=0.80). Classification tree analyses selected total MV > 55 minutes/week over all possible activity/sedentary candidate thresholds as the best discriminator between remaining free of versus developing ADL-disability and mobility-disability. Observed disability onset rates over four years were almost double (23% versus 12%) for developing ADL-disability and 8 times greater (24% versus 3%) for mobility-disability among persons below compared to those above this threshold.

Figure 1. Receiver Operating Characteristic (ROC) Curves for Remaining Free of Disability over 4 Years by Physical Activity Measures among Adults with Lower Extremity Joint Symptoms

A. Remaining Free of ADL-Disability over 4 Years ROCs (n=1460)



B. Remaining Free of Mobility-Disability over 4 years ROCs (n= 1370)

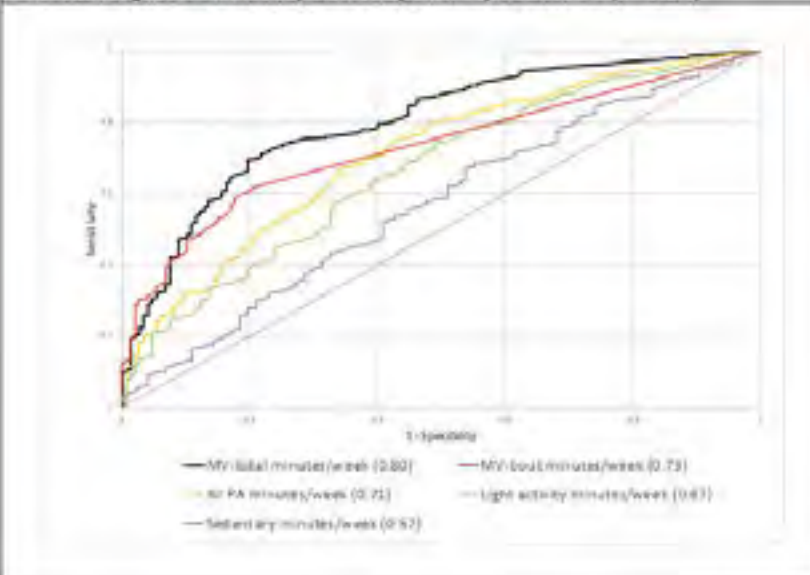


Table 1. Baseline Candidate Physical Activity/Sedentary Measures in adults with lower extremity joint symptoms free of baseline ADL and/or mobility disability			
Baseline Candidate Physical Activity/Sedentary Measures in minutes/week	Overall (n=1564*) Mean±SD	Men (n=895) Mean±SD	Women (n=669) Mean±SD
Total physical activity time	2122.2 ± 583.9	2096.4 ± 588.4	2197.3 ± 578.8
Total moderate-vigorous (MV) time	129.2 ± 134.9	154.7 ± 154.0	100.5 ± 109.2
MV-bout time*** (Legacy measure)	58.1 ± 98.0	75.0 ± 113.1	44.6 ± 81.3
Light activity time	1993.0 ± 538.1	1901.7 ± 527.2	2098.7 ± 537.5
Sedentary time	4128.5 ± 818.7	4231.5 ± 860.6	4020.4 ± 820.7

*Free of ADL-disability (n=1460) or free of mobility disability (n=1370) at baseline and followed over four years
 ** Total (light+MV) physical activity
 *** MV activity accrued in bouts lasting 10 minutes or more, the legacy metric used in federal recommendations

Meeting the 55total MV minute/week threshold significantly increased the odds for remaining free of ADL-disability (odds ratio [OR]: 2.0, 95% CI: 1.5 to 2.7) and free of mobility disability (OR 8.6, 95% CI: 5.7 to 13.1). Thresholds were consistent acrosssex, BMI, age, and radiographic knee OA status.

Conclusion: Meeting an evidence-based threshold of at least 55 total MV minutes/week increased the likelihood of remaining free of both ADL-disability and mobility-disability over 4 years among adults with lower extremity joint

symptoms. This evidence-based threshold supports future disability-free status and may help motivate sedentary adults with joint conditions to begin their path towards attaining the federal recommendation which promotes a wide range of health benefits.

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Abstract Number: 1135

Genome-Wide Meta-Analysis Identified Two Novel Variants Associated with Hallux Valgus

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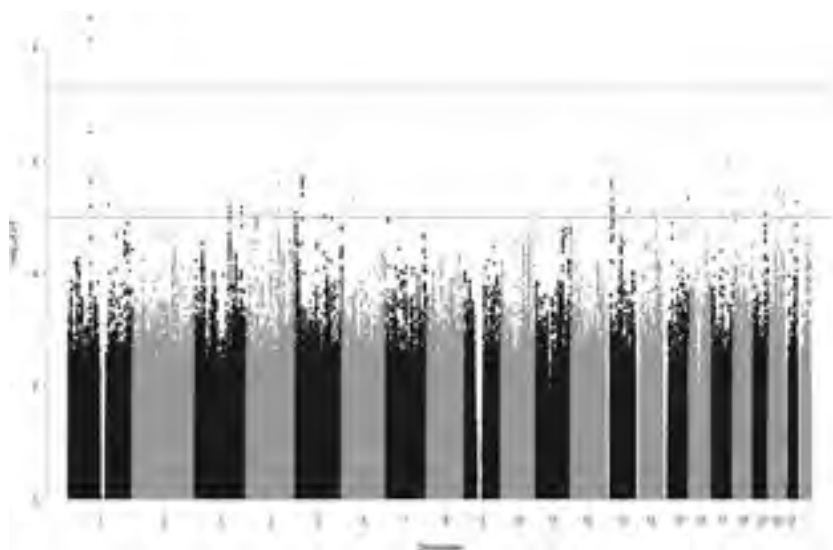
Session Title: Epidemiology and Public Health Poster II: Gout, Ankylosing Spondylitis, Osteoarthritis, Osteoporosis, Pain, and Function

Session Type: ACR Poster Session B

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

Background/Purpose: Hallux valgus(HV) is a common foot disorder that is highly heritable. A genome-wide association study (GWAS) conducted in 4,409 Caucasians from the Framingham Heart Study(FHS), the Genetics of Generalized Osteoarthritis (GOGO) Study, and the JohnstonCounty Osteoarthritis (JoCoOA) Project did not find genome-wide significant(GWS) associations with HV in both gender-specific and sex-combined GWASmeta-analyses. In this analysis, we expand the sample by including data from Caucasians enrolled in the Osteoarthritis Initiative (OAI), and impute genotypes to the most current Haplotype Reference Consortium (HRC) reference panel. Our objective was to identify novel genetic variants associated with HV in this expanded sample of Caucasian adults with deeper imputation.

Methods: We included 5,925 participants of European Ancestry (EA) from four cohorts: FHS,GOGO, JoCoOA and OAI. HV was considered present if determinedby trained examiners using validated protocol (FHS, GOGO, JoCoOA),or the participant reported a bunionectomy or Manchester grade (MG) was 3 or 4in one or both feet (OAI). Controls included those without surgery and MG of one in both feet and those who did not meet examiner's criterion. Genotyping was performed using commercially available arrays with imputation to the HRCreference panel. In OAI and JoCoOA, GWAS was performed using logistic regression models with additive genetic effects to examine association betweenSNPs and HV.



For FHS and GOGO, GEE models were used to account for the within-family correlations. All models were adjusted for age, gender, body mass index and study specific covariates. After harmonization and quality control of WAS results, fixed-effect inverse-variance weighted meta-analysis was conducted for the total sample and for men and women, separately. The genome-wide significance (GWS) level was set at $p < 5 \times 10^{-8}$.

Results: Two intronic variants in the gene CLCA2 on chromosome 1 were GWS for HV: rs55807512 (OR=0.48, $p=2.96 \times 10^{-9}$, MAF=0.04) and rs12124247 (OR=2.20, $p=7.38 \times 10^{-9}$, MAF=0.03). The SNPs were in weak LD ($r^2=0.46$). No other loci reached GWS although four variants of suggestive significance were located near the MIR2054 gene on chromosome 4. The association signals diminished in gender-specific analyses.

Conclusion: We identified two novel variants in the gene CLCA2 associated with HV. This gene encodes a member of the calcium-activated chloride channel regulator family of proteins. CLCA2 plays a role in modulating chloride current across the plasma membrane in a calcium-dependent manner, and cell adhesion. These findings require replication.

Disclosure: L. Arbeeve, None; B. Mitchell, None; R. D. Jackson, None; M. S. Yau, None; K. Ryan, None; Y. M. Golightly, None; M. T. Hannan, None; A. Nelson, GlaxoSmithKline, 5, Health press limited, 7; J. M. Jordan, None; M. C. Hochberg, None.

Abstract Number: 1136

Association of Mitochondrial DNA Haplotypes with Symptomatic Hand and Thumb Based Osteoarthritis and Hand OA Progression

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II: Gout, Ankylosing Spondylitis, Osteoarthritis, Osteoporosis, Pain, and Function

Session Type: ACR Poster Session B

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

Background/Purpose: Hand osteoarthritis (OA) can be a painful, disabling condition, with an increased prevalence in women, the elderly, and has a strong genetic component (heritability index= 60%). Mitochondrial DNA haplotypes (mDNA haplotypes) track maternal genetic inheritance and have been used in understanding population genetics. Recently mDNA haplotypes have been associated with knee OA in the OAI and CHECK cohorts. Basic science studies of mDNA haplotypes have demonstrated that mDNA haplotypes modulate critical cell functions including ATP production, oxygen consumption, generation of oxidative species, mitochondrial and nuclear gene expression which impact bioenergetics, inflammatory responses, apoptosis, aging-related responses, and calcium metabolism. We explored, given the strong gender and genetic associations with Hand OA, whether mDNA haplotypes were associated with prevalent hand OA, symptomatic hand OA, thumb-base OA, symptomatic thumb OA in cross-sectional analyses, and incident hand OA, symptomatic hand OA, thumb-base OA, symptomatic thumb-base OA and hand OA progression in prospective analyses.

Methods: 3558 Caucasian participants in the Osteoarthritis Initiative (OAI) had hand xrays in the dominant hand read for radiographic severity (Kellgren-Lawrence [KL] grade) at baseline and year 4, and had mDNA haplotypes assessed at baseline. Eleven mDNA haplotypes were categorized into 5 groups (H, UK, T, J, other) with 103 samples excluded due to technical and sampling errors. Age and sex adjusted odds ratios were calculated comparing all mDNA haplotypes to the H haplotypes. Hand OA was defined as two joints on different rays with $KL \geq 2$ excluding the thumb-base joints, thumb OA as $KL \geq 2$ in CMC or ST-T joints. Symptomatic hand OA was defined as either new interphalangeal joint (IPJ) OA at year 4 in a previous symptomatic individual, new symptoms in a participant with previous hand OA, or both new symptoms and meeting the hand OA definition. Hand OA progression was defined the mean change in number of joints with a new KL grade over the four-year period.

Results: For Incident disease, mDNA haplotypes of UK (OR=0.70, 95%CI 0.53,0.92) and T (OR=0.57, 95% CI 0.38,0.86) were associated with protective effects compared to H for symptomatic hand OA and symptomatic thumb-base OA of UK (OR=0.68, 95%CI 0.52,0.89) and T (OR=0.49, 95% CI 0.32,0.79). False Discovery Rate (FDR) $p < 0.05$. Evaluating hand OA progression, the T group compared to the H group had a reduced mean rate of progression of -0.11, $p < 0.01$. FDR $p < 0.08$. No association was found for prevalent OA or incident radiographic hand or thumb OA.

Conclusion: In a sample of Caucasian participants in the OAI, the mDNA haplotype T and Uk appear to be inversely associated with incident symptomatic hand and thumb OA and T with hand OA progression. This differs from the findings of an inverse association with knee OA incidence and progression with mDNA haplotype J compared to H previously reported in this same OAI sample. Given multiple comparisons, caution should be used in interpreting our results and our findings need to be replicated in other cohorts.

Disclosure: C. Eaton, None; M. Roberts, None; J. B. Driban, None; I. K. Haugen, None; L. F. Schaefer, None; B. Lu, None; R. D. Jackson, None; M. C. Hochberg, None; C. K. Kwoh, None; F. J. Blanco, None; T. E. McAlindon, None.

Abstract Number: 1137

Prediction Models for Poor Function Outcomes over 10 Years in Persons at High Risk for Knee Osteoarthritis

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SESSION INFORMATION

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Background/Purpose: Among persons at high risk for knee osteoarthritis (OA), identifying those who will have function decline is important; instituting prevention strategies in all at high risk is impractical and costly. Our focus is a cohort at high risk but without knee OA, at the same stage, before disease contaminates risk factors, and when prevention strategies

Table 1. Comparisons of Proportional Hazards (PH) Regression Models for Prediction of Slow Gait Speed, Using Likelihood Ratio (LR) Tests and Schwarz Bayesian Information Criterion (SBC) (1197 persons)

Baseline predictor added to base model (Each row is a separate model)	Adjusted HR (95% CI)	LR test statistic (p-value)	SBC for base model + measure
Prevalent knee pain (knee osteoarthritis)	1.11 (1.01, 1.22)	4.23 (p = 0.04)	-2122.62
WOMAC Pain ¹	1.08 (1.02, 1.14)	7.04 (p = 0.008)	-2119.80
WOMAC Stiffness ¹	1.14 (1.02, 1.27)	4.48 (p = 0.03)	-2121.80
WOMAC Function ¹	1.03 (1.02, 1.05)	15.68 (p = 0.0001)	-2111.20
KOOS Pain ²	0.89 (0.87, 0.90)	8.87 (p = 0.018)	-2108.87
KOOS Stiffness ²	0.98 (0.97, 0.99)	4.29 (p = 0.036)	-2122.40
KOOS QOL ²	0.98 (0.98, 0.99)	13.48 (p = 0.0002)	-2113.37
KOOS QOL, Sex = female (vs. male) (reference)	1.11 (0.87, 1.27)	3.12 (p = 0.07)	-2124.70
KOOS QOL, Sex = married (vs. not married) (reference)	1.32 (1.14, 1.53)	12.11 (p = 0.0005)	-2114.73
KOOS QOL, Sex = low income (vs. high income) (reference)	1.25 (1.14, 1.37)	10.83 (p = 0.001)	-2116.02
KOOS QOL, Sex = in general, how much difficulty with knees	1.81 (1.22, 2.68)	13.60 (p = 0.0002)	-2113.34

BASE MODEL: includes age, gender, BMI, race, education, health care coverage, marital status, number living in household, walking & running for activities, medication use, hand OA, back pain, hip pain, ankle pain, depressive symptoms, comorbidity, previous knee replacement, fall. Smoking (SBC for base model = -2121.77).

¹ Higher is worse.

² Higher is better.

Among 1197 persons, 181 (15.1%) experienced the outcome. Each row represents a separate model and shows results (LR test) comparing the adjusted hazard ratio for slow gait speed, after adding the specific questionnaire or item score to the base model. Higher LR test statistic and lower SBC indicate model improvement for specified row model compared to base model. (HR = hazard ratio)

Table 2. Comparisons of Proportional Hazards (PH) Regression Models for Prediction of Inability to Complete Sit-to-Stand without Arms, using Likelihood Ratio (LR) Tests and Schwarz Bayesian Information Criterion (SBC) (1197 persons)

Baseline predictor added to base model ¹ (Each row is a separate model)	Adjusted HR (95% CI)	LR test statistic (p value)	SBC for base model ² = reference
Forward knee joint velocity (normal-walk)	1.15 (1.03, 1.28)	3.95 (p = 0.08)	1339.64
WOMAC Pain ³	1.11 (1.05, 1.18)	3.86 (p = 0.002)	1323.13
WOMAC Function ³	1.19 (1.04, 1.36)	6.45 (p = 0.01)	1298.64
KOOS Symptom ³	1.04 (1.02, 1.06)	11.02 (p = 0.0009)	1293.07
KOOS QOL ³	0.98 (0.97, 1.00)	3.44 (p = 0.06)	1359.65
KOOS QOL item ³	0.97 (0.96, 0.99)	6.39 (p = 0.02)	1307.77
KOOS QOL item + how often unable to perform with knee ³	1.27 (1.07, 1.52)	7.04 (p = 0.008)	1316.03
KOOS QOL item + modified lifestyle to avoid potentially damaging activities to knees ³	1.49 (1.24, 1.80)	18.08 (p = 0.0001)	1347.12
KOOS QOL item + how much trouble with lack of confidence in knees ³	1.47 (1.18, 1.84)	16.78 (p = 0.001)	1350.93
KOOS QOL item + in general, how much difficulty with knees ³	1.88 (1.18, 3.02)	3.07 (p = 0.002)	1360.81

¹**BASE MODEL** includes age, gender, BMI, knee osteoarthritis, history of knee surgery, number living in household, walking & standing for arthritis, medication use, hand OA, back pain, hip pain, ankle pain, deep knee symptoms, community activities, comorbidity, education, self-reported health, existing SBC for base model = 1359.65.

²Higher is worse.

³Higher is better.

Among 1197 persons, 95 (8.3%) experienced the outcome. Each row represents a separate model and shows results (LR test) comparing the adjusted hazard ratio for slow gait speed, after adding the specific questionnaire or item score to the base model. Higher LR test statistic and lower SBC indicate model improvement for specified row (model compared to base model). (HR = hazard ratio)

are likely to be effective. Our objectives were: 1) develop prediction models for poor function outcomes, and 2) test if adjusting for variables linked to behavior change, modified lifestyle to avoid damaging activities to knees, or lack of knee confidence, improves prediction.

Methods: In 1197 OAI participants KL0 in both knees, baseline predictors analyzed included: demographic, socioeconomic, psychological, comorbidity; WOMAC Pain (P), WOMAC Function (F), KOOS Symptoms (Sx), KOOS QOL (higher worse); KOOS QOL items (higher better). Proportional hazards (PH) regression models were used to develop prediction models for each outcome, unable to complete sit-to-stand without arms, and slow gait speed (< 1m/sec), over up to 10 years follow-up. For each outcome, a base model included predictors with univariate hazard ratio $p \leq 0.20$; separate models also included P, F, Sx, and QOL. Comparisons of nested PH models used a likelihood ratio (LR) chi-square test and Schwarz Bayesian Information Criterion (SBC). We calculated the AUC of the ROC for logistic regression models including variables that improved prediction in the corresponding PH model. Hosmer-Lemeshow X^2 statistics (H-L) tested goodness-of-fit; large H-L p-values and high AUC indicate good calibration and discrimination, respectively.

Results: For *gait speed outcome*, the expanded prediction model vs. base model was significantly improved by including WOMAC and KOOS variables, particularly WOMAC-F, KOOS-QOL, and KOOS-QOL items (Table 1, LR tests). For *sit-to-stand outcome*, prediction was significantly improved by KOOS-QOL and KOOS-QOL items (Table 2). For both outcomes, among the models, performance was best with base model + modified lifestyle to avoid potentially damaging activities to knees: for slow gait speed, AUC 0.80 (95% CI 0.76, 0.84), H-L $p = 0.55$; and for sit-to-stand, AUC 0.78 (95% CI 0.74, 0.82), H-L $p = 0.56$.

Conclusion: In persons at high risk for knee OA, improved prediction and best performance for poor function outcome was achieved by including modified lifestyle to avoid potentially damaging activities to knees. Such a model, achieving excellent AUCs using easily assessed variables, may help early-stage identification of persons at high risk for poor outcome and inform focus of prevention strategies.

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Public Health Impact of Physical Inactivity in the Knee OA Population in the US

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SESSION INFORMATION

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

Background/Purpose: The benefits of physical activity (PA) in persons with OA are well-documented: PA reduces OA pain, improves mental health, and reduces the risk of cardiovascular disease (CVD), diabetes mellitus (DM), and some cancers. Despite this, the majority of knee OA patients are physically inactive. The public health impact of low uptake of PA in this population has not been evaluated.

Methods: We used data from the Osteoarthritis Initiative and Centers for Disease Control to estimate the proportion of the US knee OA population that is inactive, insufficiently active, and active, defined as 0-10, 10-149, and 150+ minutes of moderate-to-vigorous PA per week. Using the Osteoarthritis Policy Model (OAPol), a widely published and validated micro simulation of knee OA, we estimated survival and quality-adjusted survival losses among cohorts of individuals with knee OA and different levels of PA. We calculated the per person quality-adjusted years of life (QALYs) lost among those who are inactive or insufficiently active compared to those who are active. We estimated the negative public health impact by multiplying the per-person QALYs lost due to physical inactivity or insufficient activity by the number of persons with knee OA in each of those activity groups. We also calculated the positive public health impact of increasing PA levels among knee OA patients (assuming interventions that could lead 5% or 10% of the population at lower PA levels to increase their activity) by calculating QALYs saved and cases of CVD, DM, and cancer prevented due to such interventions. OAPol data inputs were derived from national and multicenter cohorts and included: 1) background mortality rates; 2) prevalence of and mortality attributable to CVD, DM, and cancers; 3) reduction in quality of life due to physical inactivity and major comorbidities; 4) increased risk of comorbidities due to physical inactivity.

Results: Currently, of 11.7 million persons in the US with knee OA, 47% are inactive and 41% are insufficiently active, resulting in 6.7 million QALYs lost over their remaining lifespan. Table 1 presents the positive public health impact of PA interventions. If an intervention could simultaneously lead 10% of inactive persons to become insufficiently active and 5% of insufficiently active persons to become active over their remaining life spans, 316,181 QALYs would be saved (191,718 + 124,463, Table 1, QALYs row, shaded cells). This would also prevent 80,379 (63,817 + 16,562, Table 1, CVD row, shaded cells) cases of CVD and 85,425 (71,768 + 13,657, Table 1, DM row, shaded cells) cases of DM.

Conclusion: These results suggest that even modestly effective programs focused on increasing PA among knee OA patients could have a tremendous public health impact. Our projections of improvements in morbidity and mortality could be useful in setting realistic goals for activity promotion among knee OA patients.

	% Inactive Becoming Active		% Inactive Becoming Insufficiently Active		% Insufficiently Active Becoming Active	
	5%	10%	5%	10%	5%	10%
QALYs Saved	209,171	418,343	95,859	191,718	124,463	248,926
CVD Cases Averted	51,807	103,614	31,908	63,817	16,562	33,124
DM Cases Averted	51,528	103,040	35,884	71,768	13,657	27,313
Cancer Cases Averted	24,847	49,695	23,599	47,199	1,021	2,042

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Abstract Number: 1139

Can Body Composition Explain the Sex Disparity in Risk of Osteoarthritis?

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Background/Purpose: Obesity is a major risk factor for knee osteoarthritis (OA), but the mechanisms by which obesity confers OA risk remains unclear. There is a recognized sex disparity in knee OA prevalence, and also a recognized distinct sex-specific distribution of fat depots especially after menopause in women. Visceral fat which accumulates after menopause is a major source of adipokines and other cytokines and its accumulation is associated with an increased heart disease risk. How these same metabolic products may affect OA risk is not clear. Given the recognized sex disparity in the occurrence of knee OA, whether body composition contributes to this disparity merits evaluation.

Methods: We used data from participants free of OA at baseline in the Multicenter Osteoarthritis Study (MOST), a NIH-funded longitudinal cohort of persons with or at risk of knee OA. Incident radiographic OA (ROA) was defined as those who developed either radiographic knee OA (Kellgren-Lawrence (KL) ≥ 2) (irrespective of symptoms) or had a knee replacement (KR) during follow-up. We defined incident symptomatic OA (SOA) as those who developed radiographic knee OA (KL grade ≥ 2) with frequent knee pain, or a KR during follow-up over 5 years. Body composition was assessed at baseline using whole body dual-energy x-ray absorptiometry and analyzed using Hologic software to delineate visceral and subcutaneous fat, total fat mass, gynoid fat mass, android fat mass, and gynoid:android ratio. We evaluated the relation of sex-specific body composition parameters, categorized as quintiles, to risk of incident ROA and SOA using Cox proportional hazards model, adjusted for potential confounders.

Results: We identified 514 participants with incident ROA (331 women and 183 men) and 433 with incident SOA (273 women and 160 men). The adjusted hazard ratio for risk of incident ROA in women compared with men was 1.24 (95% CI: 1.01-1.51) and was 1.14 (95%CI: 0.92-1.41) for incident SOA. Other measures of adiposity assessed were not associated with either OA outcome. Gynoid mass and gynoid-to-android ratio were associated with elevated risk of incident ROA and SOA, while total fat mass was only associated with incident ROA (**Table**).

Conclusion: Our study indicates that differences in body composition related to total fat mass as well as the anatomic distribution of the fat mass, particularly a high gynoid-to-android ratio, were associated with elevated risk of OA and may explain the sex disparity in risk of OA. In contrast, the purported metabolic differences between visceral and subcutaneous fat did not impact OA risk.

Association between body composition and risk of incident OA

	Radiographic OA		Symptomatic OA	
	Q5 vs. Q1	P trend	Q5 vs. Q1	P trend
Total body fat mass, %	1.01 (0.75-1.36)	0.005	1.06 (0.77-1.46)	0.23
Visceral fat, %	1.24 (0.93-1.64)	0.09	1.08 (0.80-1.44)	0.73
Subcutaneous fat, %	1.00 (0.80-1.24)	0.02	1.08 (0.85-1.37)	0.02
Ratio of Gynoid vs. Android fat mass	1.67 (1.31-2.13)	0.002	1.48 (1.13-1.92)	0.002
Android fat, %	0.60 (0.47-0.77)	<0.001	0.68 (0.52-0.88)	0.001
Gynoid fat,%	1.69 (1.32-2.16)	<0.001	1.47 (1.13-1.92)	0.002

Q: Quintile

HR and 95%CI were comparing Q5 vs. Q1

Multivariable model adjusted for age, sex, race, education level, physical activity, smoking, and BMI.

Disclosure: S. Li, None; T. Neogi, None; D. Misra, None; A. Schwartz, None; M. C. Nevitt, None; C. E. Lewis, None; J. Turner, None; D. T. Felson, None.

Abstract Number: 1140

Cause-Specific Mortality in Knee, Hip and Hand Osteoarthritis

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SESSION INFORMATION

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Background/Purpose: All-cause mortality in osteoarthritis (OA) is reported to be increased. However, the knowledge about cause-specific mortality in OA is still very limited. Thus, our purpose was to estimate cause-specific mortality in osteoarthritis compared to the general population.

Methods: We identified all residents in southern Sweden aged 45 to 84 years in 2003. Through the Skane Healthcare Register we identified those diagnosed with osteoarthritis (OA) in peripheral joints between 1998 and 2003. We followed all residents from 2004 until relocation outside of the region, death, or end of 2014. We classified the underlying cause of death from death certificates into: cardiovascular, neoplasms, diabetes, infections, dementia, digestive, or other causes. For estimation, we used multi-state adjusted Cox proportional hazards models.

Results: We identified 15 901 patients (mean age [SD] 67 years [10], 41% men) with prevalent doctor-diagnosed OA in knee, 9347 in hip, 4004 in hand and 5447 with diagnosed OA in other peripheral joints among 469 177 residents. For most causes of death in OA patients, we found no increased mortality, with hazard ratios (HR) close to 1. However, for knee and hip OA and cardiovascular death, HRs were non proportional and increased to 1.19 (95%CI 1.10, 1.28) and 1.13 (1.03, 1.24) during 9 to 11 years of follow-up, mostly due to excess mortality from chronic ischemic heart diseases and heart failure in patients with OA (Figure 1 and 2).

Conclusion: The risk of cardiovascular excess death increases with duration of knee and hip OA. The major contributors are chronic ischemic heart diseases and heart failure. Our results call for improved implementation of guidelines in OA treatment, with major focus on maintaining physical activity and weight-management as well as other preventative measures to reduce cardiovascular deaths.

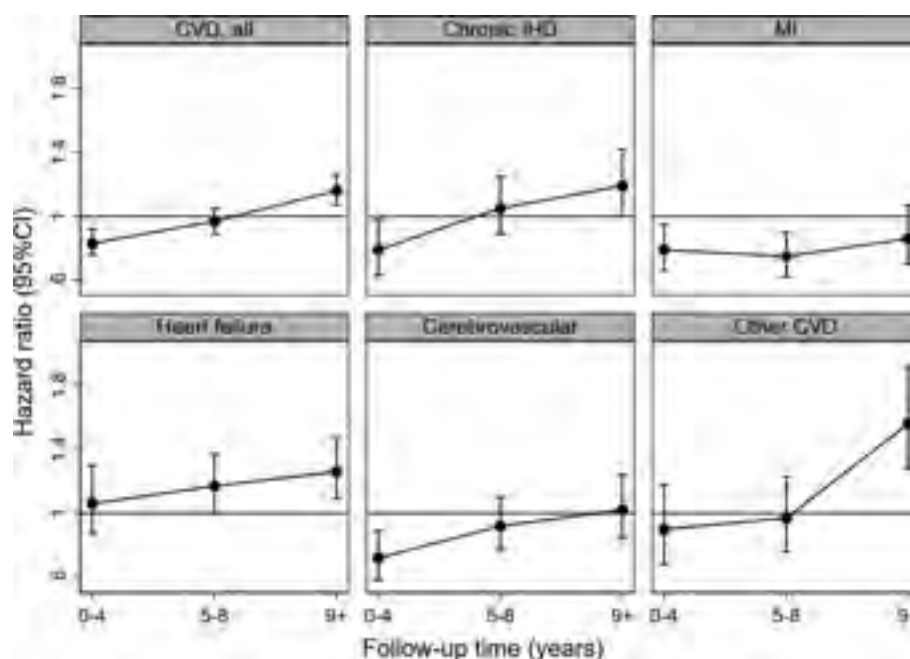


Figure 1. Cardiovascular mortality in patients with *knee OA* as compared to the general population - adjusted hazard ratios with 95%CI from Cox regression model during 3 periods of the follow-up time.

*CVD – cardiovascular diseases, IHD – ischemic heart diseases, MI – myocardial infarction

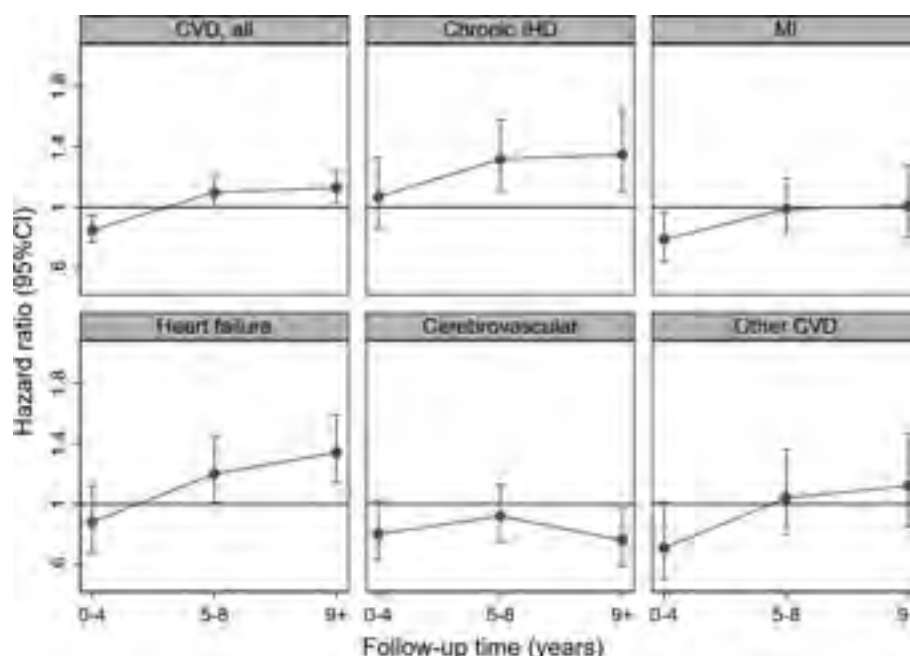


Figure 2. Cardiovascular mortality inpatients with *hip OA* as compared to the general population - adjusted hazard ratios with 95%CI from Cox regression model during 3 periods of the follow-up time.

*CVD – cardiovascular diseases, IHD – ischemic heart diseases, MI – myocardial infarction

Disclosure: A. Turkiewicz, None; A. Kiadaliri, None; M. Englund, None.

Abstract Number: 1141

Trajectories of Extensive Sitting and Associated Predictors in Persons at High Risk for Knee Osteoarthritis

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Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II: Gout, Ankylosing Spondylitis, Osteoarthritis, Osteoporosis, Pain, and Function

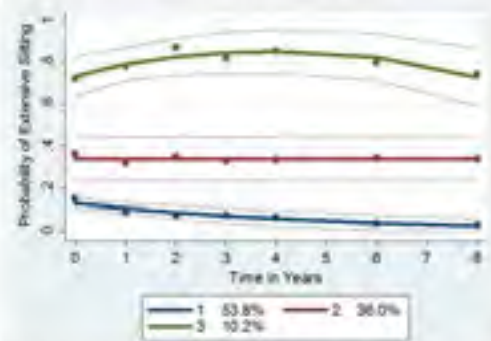
Session Type: ACR Poster Session B

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

Background/Purpose: Too much sitting has been recognized as a major public health issue. However, it is unknown if distinctive patterns of extensive sitting over time exists among unique groups of persons at high risk for osteoarthritis(OA) or if sitting behavior changes over time. The purpose of this study was to examine whether there are distinct extensive sitting trajectories over up to 8years of follow-up, then to identify baseline demographic or clinical predictors for membership in specific sitting trajectories.

Methods: Prospective cohort data from 1194 OAI participants without OA in either knee (bilateral KL 0 on baseline x-rays) were collected at 4 US sites through 8 years of follow-up. Extensive sitting was defined as a self-report of 5 or more days of sitting activities over the past week and more than 4hours per day during those days using PASE sitting items. Latent mixture modeling was used to identify trajectories in extensive sitting (yes vs. no) over time. Baseline demographic and clinical predictors were examined using multinomial logistic regression to identify predictors for membership in extensive sitting trajectories.

Figure 1. Trajectories of extensive sitting over 8 years among persons at high risk of knee OA (n=1194)



Extensive sitting defined by sitting often (5-7 days per week) for greater than 4 hours per day. Actual (dot) and estimated (solid line) proportion of extensive sitting and their 95% confidence intervals (dotted line) by extensive sitting trajectory groups: 1 (blue): low frequency of extensive sitting, 2 (red): moderate frequency of extensive sitting, 3 (green): high frequency of extensive sitting.

Table 1. Association of Baseline Predictors with Each Extensive Sitting-Time Trajectory Membership (n=1107)

Baseline Predictors	Moderate vs. low frequency of extensive sitting groups	High vs. low frequency of extensive sitting groups
	RRR ^a (95% CI)	RRR ^a (95% CI)
Age per 5 years	1.14 (1.06, 1.23)	1.26 (1.12, 1.43)
Female vs. Male	0.66 (0.49, 0.94)	0.61 (0.37, 1.02)
BMI per 5 kg/m ²	1.18 (1.01, 1.37)	1.48 (1.17, 1.87)
Depressive Symptoms per 5 units	1.09 (0.98, 1.21)	1.22 (1.05, 1.42)
Comorbidity	1.25 (1.05, 1.51)	1.32 (1.05, 1.66)
WOMAC ^b Knee Pain per 3 units	1.00 (0.88, 1.16)	1.17 (0.95, 1.44)
Knee Extensor Strength per 60 Newton	0.94 (0.84, 1.00)	0.89 (0.79, 1.00)

^a Relative risk ratio; ^b Western Ontario & McMaster Universities Osteoarthritis Index

Results: Three distinct extensive sitting trajectories were identified from the 1194 participants (mean age 58.4 years [SD 8.9], 58.4%female, mean BMI 26.8 kg/m² [SD 4.5]): low frequency of extensive sitting (54%), moderate frequency of extensive sitting (36%), and high frequency of extensive sitting (10%) (Figure 1). All trajectories were fairly stable over time. Compared to the low-frequency of extensive sitting group, persons in high-frequency were significantly more likely to be older (relative risk ratio [RRR]=1.26 per 5 years increase; 95% confidence interval (CI)=1.12,1.43), have higher BMI (RRR=1.48 per 5 kg/m² increase; 95% CI=1.17,1.87), report higher depressive symptoms (RRR=1.22; 95% CI=1.05, 1.42), and more comorbidities (RRR=1.32, 95% CI=1.05, 1.66 per 3 unit increase) after adjusting for confounders (Table 1); persons in moderate-frequency of extensive sitting had similar findings, but depressive symptoms was not statistically significant (RRR=1.09 per 3 unit increase, 95% CI=0.98, 1.21).

Conclusion: We identified three distinct extensive sitting trajectories among persons at high risk of knee OA. Baseline factors including depressive symptoms and comorbidity independently predicted trajectory membership in high vs. low frequency of extensive sitting. These factors could be considered in future interventions to reduce extensive sitting in persons at high risk of knee OA.

Disclosure: J. Lee, None; A. H. Chang, None; O. Almagor, None; J. S. Chmiel, None; K. W. Hayes, None; C. K. Kwok, None; L. Sharma, None.

Trend of Lymphoma Incidence in US Veterans with Rheumatoid Arthritis Vs Osteoarthritis: 2002-2017

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II: Gout, Ankylosing Spondylitis, Osteoarthritis, Osteoporosis, Pain, and Function

Session Type: ACR Poster Session B

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

Background/Purpose: Past epidemiologic studies have consistently demonstrated a link between Rheumatoid Arthritis (RA) and lymphomas and have posited that high systemic inflammatory activity is a major risk determinant for lymphomagenesis. In 2010, RA treatment guidelines recommended a treat to target (T2T) approach, but the impact of this approach on lymphoma incidence remains poorly understood. This study examined and compared temporal trends in lymphoma incidence in US veterans with RA versus veterans with osteoarthritis (OA), who are not expected to be impacted by T2T implementation.

Methods: Patients with RA or OA were identified in the Veteran Affairs (VA) Corporate Data Warehouse. The RA cohort included patients with 2 or more RA diagnostic codes at least 6 months apart during 2002-2017, with at least one visit in a rheumatology clinic. We used a similar algorithm to identify OA patients. Patients with other autoimmune diseases like lupus, celiac disease, inflammatory bowel disease were excluded. Lymphoma incidence was identified from the VA Central Cancer Registry. We used proportional hazards regression to compare the relative hazard of lymphoma for patients diagnosed with RA or OA during 2002-2005, 2006-2009, 2010-2013, and 2014-2017, while controlling for age, sex, and race. Censoring events included death or end of follow-up, with a maximum follow-up period of 5 years for each patient.

Results: We identified 105,297 patients diagnosed with OA and 50,298 diagnosed with RA. We observed 356 RA patients and 558 OA patients with lymphoma onset within 5 years of initial fulfillment of RA or OA algorithm. The hazard of lymphoma decreased significantly for patients diagnosed with RA during 2014-2017 relative to patients diagnosed in 2002-2005 (Hazard Ratio [HR] = 0.63; p=0.02) (Figure 1). Among OA patients, the hazard of lymphoma also decreased, although the decrease was not statistically significant (HR=0.74; p=0.09). There was no significant difference in trends between the OA and RA patients (p=0.55).

Conclusion: We observed a decline in lymphoma incidence in RA patients after adjusting for race, age, and sex, although the decline was not significantly different between OA and RA veterans.

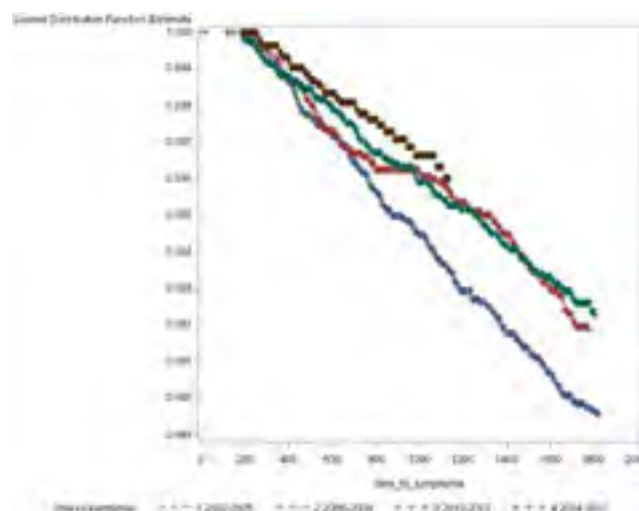


Figure 1. Kaplan-Meier curves showing time to lymphoma for RA patients stratified by the year of diagnosis.

Disclosure: N. Singh, None; Y. Gao, None; B. Beck, None; B. R. England, None; G. W. Cannon, Amgen Inc., 2; T. R. Mikuls, BMS, Ironwood, Horizon, 2, Pfizer, Inc., 5; J. R. Curtis, AbbVie, Amgen, Bristol-Myers Squibb, Corrona, Janssen, Lilly, Myriad, Pfizer, Radius, Roche/Genentech, UCB, 2, 5; B. Link, None; C. Lynch, None; E. Field, None; M. Vaughan-Sarrazin, None.

Abstract Number: 1143

Periodontal Disease Is Associated with an Increased Risk of Ankylosing Spondylitis: A Systematic Review and Meta-Analysis

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Abstract:

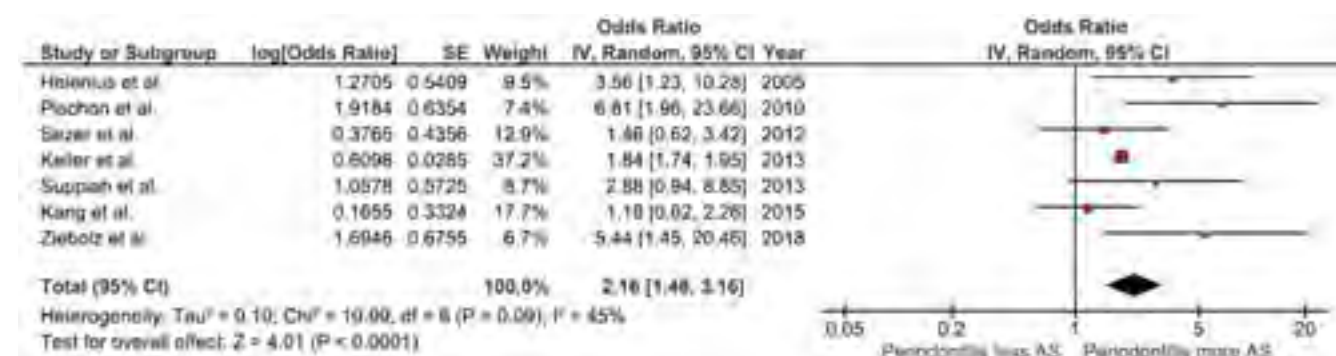
Background/Purpose: The association between periodontal disease and rheumatoid arthritis is well-recognized. Recent studies have suggested a similar association between periodontal disease and ankylosing spondylitis although the data are still limited. The current systematic review and meta-analysis was conducted with the aims to identify all available studies on this association and summarize their results together.

Methods: Two investigators independently searched for published studies indexed in MEDLINE and EMBASE database from inception to April 2018 using the search strategy that included the terms for periodontal disease and ankylosing spondylitis. Studies were included if they fulfilled all the following criteria: (1) Case-control or cohort studies comparing the risk of ankylosing spondylitis in individuals with and without periodontal disease (2) Individuals without periodontal disease were used as comparators in cohort studies while individuals without ankylosing spondylitis were used as controls in case-control studies and (3) Effect estimates and 95% confidence intervals (CI) of the association were provided. Point estimates and standard errors from each study were extracted and combined together using the random effect, generic inverse variance technique of DerSimonian and Laird.

Results: Of 524 retrieved articles, a total of 7 case-control studies comprising of 41,575 participants met the inclusion criteria and were included in this meta-analysis. The risk of ankylosing spondylitis among patients with periodontal disease was significantly higher than individuals without periodontal disease with the pooled odds ratio of 2.16 (95% CI, 1.48–3.16). The statistical heterogeneity was low with an I^2 of 45%. The forest plot of this meta-analysis is shown as figure 1.

Conclusion: A significantly increased risk of ankylosing spondylitis among patients with periodontal disease was observed in this study.

Figure 1: Forest plot of this meta-analysis



Disclosure: P. Ungprasert, None; K. Wijarnpreecha, None; W. Cheungpasitporn, None.

Abstract Number: 1144

Risk of Osteoporotic Fractures in Patients with Rheumatoid Arthritis and End Stage Renal Disease. Findings from the Usrds Database

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SESSION INFORMATION

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Background/Purpose: Rheumatoid arthritis (RA) and End Stage Renal Disease (ESRD) are independent risk factors for osteoporotic fractures. Approximately one percent of persons with ESRD have RA. To our knowledge, there are no reports of whether persons with RA and ESRD are at greater risk for osteoporotic fracture than the general ESRD population. The purpose of this study was to determine whether RA is a risk factor for fractures in patients with ESRD and to characterize risk factors for these fractures.

Methods: A cohort study of ESRD patients with and without RA within the United States Renal Data System (USRDS) from 2006-2008 followed through 2011. The International Classification of Diseases, ninth revision (ICD-9) codes 714.0, 714.1, 714.2, 714.81 were utilized to identify those with a history of RA using the hospital claims data occurring on or before their dialysis start date. Fractures were identified using ICD-9 codes for fracture of the vertebrae (805.xx-806xx), upper (812.xx-817.xx), hip (820.xx-822.xx), lower extremity (823.xx-825.xx), pathological fracture (733.0, 733.1, 733.11, 733.12, 733.13, 733.14, 733.15, 733.16, 733.19) and stress fracture (733.93-733.98).

Results: There were 10,706 persons with ESRD and no history of RA in the analysis data set of whom 1570 (14.5%) had an incident fracture and 1040 persons with RA of whom 14.5% (266 persons) had an incident fracture. In multivariable adjusted models including age, gender, race, ethnicity, BMI, type of dialysis, smoking, alcohol use, vitamin D deficiency, hyperparathyroidism, secondary osteoporosis (of renal origin), hypogonadism, hyperthyroidism and prevalent fractures (within 5 years prior to start of dialysis), RA was a significant risk factor for any incident fracture (RR 1.83 (95% CI 1.59-2.11)) and incident hip fractures (RR 1.86 (95% CI 1.50-2.30)). Prevalent fractures (in the five years prior to initiation of dialysis) were significantly associated with all and hip fractures ($p < 0.01$) and Black and Other race and BMI were significantly inversely associated with all and hip fractures.

Conclusion: In patients with RA and ESRD, the risk of osteoporotic fractures including hip and spine fractures is almost twofold greater than that of the general ESRD population. Risk factors for fractures in patients with RA and ESRD are similar to that of the general population. Attention to osteoporosis prevention is important in patients with RA and renal disease.

Disclosure: R. Peterkin-McCalman, None; J. Waller, None; B. Le, None; A. Oliver, None; E. Manning, None; S. Nahman, None; L. Carbone, None.

Abstract Number: 1145

Association of Niacin Intake with Osteoporosis. the Cardiovascular Health Study

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Background/Purpose: Interest in niacin has increased in the setting of reports suggesting that niacin plays a role in diseases of aging, including Parkinson's disease and nonmelanomatous skin cancers. Because niacin regulates NAD-dependent deacetylase Sirtuin 1 expression and decreases inflammation, it plausibly may improve skeletal health. However, experimental studies in chicks suggest that higher niacin intake may result in impaired bone strength. No study to date has examined the association of dietary niacin intake with multiple skeletal health parameters including bone mineral density (BMD), hip fractures, and body composition, and none have included both African-American and Caucasian men and women.

Methods: Participants included 5187 men and women ≥ 65 y from the Cardiovascular Health Study (CHS) who had complete dietary information by FFQ on niacin intake in 1989-1990 and had data collected on incident hip fractures (ascertained from hospital discharge ICD-9 codes 820.xx) from their 1989-90 study visit through June 30, 2013. A subset (n=1336) also underwent Dual Energy X-ray absorptiometry (DXA) measurements of the hip and total body and body composition assessments in 1994-1995. Risk of incident hip fracture per 10 mg increment of daily dietary niacin intake was estimated using Cox regression.

Results: Mean daily dietary niacin intake was 32.6 mg, with quartiles 1 through 4 defined as 3.6-21.8 mg/day, 21.9-30.2 mg/day, 30.3-40.9 mg/day and 41.0-102.4 mg/day, respectively. During a median follow-up of 13 years, 725 participants had an incident hip fracture. The overall incidence rate for hip fractures was 1.08 per 100 person-years (95% CI: 0.91, 1.3). In multivariable-adjusted models adjusted for age, gender, race, clinic site, BMI, cystatin C, diabetes, education, calcium and vitamin D intake, medications associated with osteoporosis, smoking, alcohol, frailty, total energy (kcal/day) and protein intake, higher niacin intake was significantly associated with hip fractures (hazard ratio (HR) 1.12 (95% CI: 1.01, 1.24). In multivariable-adjusted models both the lowest (HR, 1.31; 95% CI, 1.04-1.66) and highest (HR, 1.53; 95% CI, 1.20-1.95) quartiles of niacin intake were associated with an increased risk of incident hip fracture versus quartiles 2 and 3. In multivariable adjusted linear regression models, there was a trend for a significant inverse association of niacin intake with hip BMD (p=0.06). There was no significant association of niacin intake with total body BMD or any measures of body composition.

Conclusion: In this cohort of elderly, community-dwelling African American and Caucasian men and women, both high and low dietary niacin intakes were associated with a significantly increased risk of subsequent hip fracture, suggesting a possible U-shaped association. By comparison, dietary niacin may have an inverse linear association with hip BMD. There may be an optimum intake of dietary niacin (approximately 22-41 mg/day) which does not impair skeletal health.

Disclosure: B. Le, None; P. Bužková, None; H. Fink, None; J. Robbins, None; M. Raiford, None; C. Isales, None; J. Shikany, None; S. Coughlin, None; L. Carbone, None.

Abstract Number: 1146

The Association of Raas Inhibitor Use with Osteoporosis. Findings from the Women's Health Initiative

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Background/Purpose: Experimental studies have implicated a role for the Renin Angiotensin Aldosterone System (RAAS) in osteoporosis. However, the relationship of pharmacological inhibition of the RAAS to skeletal health is controversial. Therefore, the purpose of this study was to determine the relationship of use of RAAS Inhibitors (Angiotensin Receptor Blockers (ARBs), Angiotensin Converting Enzyme Inhibitors (ACE), Direct Renin Inhibitors, Selective Aldosterone Receptor Blockers and RAAS inhibitors in combination with other antihypertensive medications) to incident fractures, changes in bone mineral density (BMD) and body composition measurements in postmenopausal women.

Methods: 155,565 women from the WHI Observational study (OS) and Clinical Trials (CT) were included. The BMD and body composition analyses included the 11,437 women with a Dual Energy X-ray Absorptiometry measurement. Change in BMD and body composition were modeled using linear regression. Cox proportional hazards models were fit for each fracture outcome. Change in RAAS inhibitor use over time was evaluated by entering use as a time dependent exposure variable. Unadjusted and models adjusted for demographic and clinical covariates and medication use associated with osteoporosis and a final multivariable model adjusted for all covariates plus BMD were determined.

Results: There were 13,749 (9%) users and 141,816 (91%) nonusers of RAAS inhibitors at the baseline visit of WHI. In 16.8 years of follow-up there were 34,276 total fractures, 2,912 (annualized percentage 2.20%) in the baseline users of RAAS inhibitors, 31,364 (annualized percentage 2.16%) in baseline nonusers. In unadjusted models with time-dependent covariate defined as any prior use of RAAS inhibitors, there was a significant positive association of RAAS inhibitor use with all (HR 1.05 (95% CI 1.01, 1.09)), other (HR 1.11. (1.06-1.16)) and composite fragility fractures (HR 1.11 (95% CI 1.03, 1.20)) and a significant negative association with forearm fractures (HR 0.89 (0.82, 0.97)). In final multivariable models including baseline BMD, there was no significant association of use of RAAS inhibitors with all fractures or any fracture site (clinical vertebral, forearm, hip or composite fractures (hip, humerus, clavicle, scapula)), ($p \geq 0.13$ for all) or with change in BMD of the total hip, femoral neck or lumbar spine from baseline to three ($p \geq 0.20$ for all) or six years ($p \geq 0.70$ for all). There was no significant association of RAAS inhibitor use with changes in total body, lean body mass or fat mass from baseline to three ($p=0.06$, $p=0.24$, $p=0.09$ respectively) or six years ($p=0.41$, $p=0.08$ and $p=0.95$ respectively).

Conclusion: In postmenopausal women, use of RAAS inhibitors does not appear to be importantly related to osteoporosis endpoints. However, there may be differences among individual classes of RAAS inhibitors and their relationship to skeletal health, which deserve further exploration.

Disclosure: L. Carbone, None; S. Vassan, None; R. Prentice, None; G. Harshfield, None; B. Haring, None; J. A. Cauley, None; K. Johnson, None.

Abstract Number: 1147

Golimumab Improves Work Productivity and Activity Impairment in Patients with Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS) and Psoriatic Arthritis (PsA): 1-Year Results from a Non- Interventional Trial in Germany

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Background/Purpose: Non-interventional studies (NIS) are essential instruments in pharmaceutical research not only for pharmaceutical companies but also for regulatory authorities or reimbursement bodies in Germany. Aside from direct costs caused by a disease, German sick funds as well as health authorities have a keen interest in indirect costs, such as costs derived from loss of work productivity.

Methods: As primary endpoint, the change of work productivity impairment and ability for daily activities in month 3 (V1) vs baseline visit (V0) was evaluated.

All 4 subscores of the WPAI were analysed: disease related absence from work (absenteeism), working while sick (presenteeism), total work productivity impairment (TWPI) and activity impairment with TWPI as primary score. In addition, an evaluation of the activity impairment in the mITT population (**modified-Intention-To-Treat**) was performed. For the secondary analysis of the primary endpoint, the change in work productivity/activity impairment after 6 months and 12 months vs baseline as measured by WPAI for PsA, RA and AS pts treated with Golimumab (GLM) in German clinical practice was evaluated.

Results: Of 748 pts (100%) who started treatment with GLM at V0 (baseline), 666 (89.0%), 634 (84.8%) and 552 pts (73.8%) continued treatment until V1 (Mo 3), V2 (Mo 6), and V3 (Mo 12/end of observation period), respectively. Efficacy analyses were performed on the mITT population which included 700 pts (RA=237, PsA=235, AS=228) who had at least 2 documented visits.

The primary efficacy endpoint was analyzed in the mITT subset of 493 pts (RA=158, PsA=157, AS=178) with full-time or

part-time **employment** at baseline (mITTe).

The statistically significant improvements in the mean WPAI domain scores were maintained over the 12-month observation period in all 3 indications with a higher treatment effect regarding “activity impairment” and “presenteeism” than with “absenteeism” (Table 1). The magnitude of improvements in the 4 WPAI domains and the time course of improvements varied between the underlying disease (RA, PsA, AS).

In general, the improvements in the 4 WPAI domains were greater in pts with AS and PsA compared to RA. A continuous improvement over time was seen in AS pts regarding the domain “activity impairment” (Table 1). A positive effect of pre-treatment with biologics (i.e. better improvement in WPAI) was seen in RA pts for 3 domains (TWPI, absenteeism, presenteeism), and in PsA pts for 2 domains (absenteeism, activity impairment).

Conclusion: GLM s. c. 1 x monthly is an effective treatment in pts with RA, AS and PsA.

All scores of the WPAI showed a significant ($p < 0.05$) reduction in mean score values in each indication.

GLM leads to an improvement of work productivity and daily activities in all pts already within the first 3 months of treatment and provided sustained improvement in WPAI in pts with RA, PsA and AS.

Table 1: WPAI - Changes in the 4 domain scores from baseline to Months 3, 6 and 12 (mITTe)

Disclosure: K. Krüger, None; S. Remstedt, None; A. Thiele, None; I. Klaudius, None.

Timepoint	Statistics	Total work productivity impairment	Absenteeism	Presenteeism	Activity impairment
RA patients (mITTe: N=158)					
V0 (baseline)	N	106	130	113	154
	Mean	-8.8	11.9	48.0	50.9
	SD	27.00	30.80	27.70	28.30
Change in scores					
V0 - V1 (Month 3)	N	78	110	83	133
(primary endpoint)	Mean	-11.3	-5.8	-12.5	-13.0
	SD	23.77	28.37	23.00	26.77
	p-value	<0.0001 ^a	0.0429 ^b	<0.0001 ^a	<0.0001 ^a
V0 - V2 (Month 6)	N	76	106	87	127
	Mean	-8.7	-2.1	-10.2	-12.3
	SD	30.74	30.42	27.58	28.73
	p-value	0.0001 ^a	0.5049 ^b	0.0012 ^a	<0.0001 ^a
V0 - V3 (Month 12)	N	67	89	75	114
	Mean	-13.2	-8.8	-12.7	-15.2
	SD	23.40	35.51	22.06	24.23
	p-value	<0.0001 ^a	0.0128 ^b	<0.0001 ^a	<0.0001 ^a
PsA patients (mITTe: N=157)					
V0 (baseline)	N	114	137	115	153
	Mean	-5.0	12.9	33.4	43.2
	SD	27.77	30.87	26.42	28.45
Change in scores					
V0 - V1 (Month 3)	N	81	109	85	128
(primary endpoint)	Mean	-13.8	-4.9	-15.4	-17.4
	SD	25.02	28.33	25.98	30.44
	p-value	<0.0001 ^a	0.0448 ^b	<0.0001 ^a	<0.0001 ^a
V0 - V2 (Month 6)	N	80	103	88	128
	Mean	-16.8	-0.7	-16.8	-18.5
	SD	29.20	29.45	26.20	30.85
	p-value	<0.0001 ^a	0.0202 ^b	<0.0001 ^a	<0.0001 ^a
V0 - V3 (Month 12)	N	77	99	80	118
	Mean	-10.6	-4.6	-12.7	-16.3
	SD	30.40	30.62	27.82	30.28
	p-value	0.0001 ^a	0.2028 ^b	0.0001 ^a	<0.0001 ^a
AS patients (mITTe: N=178)					
V0 (baseline)	N	156	160	142	177
	Mean	-8.2	14.8	45.9	52.1
	SD	28.08	29.55	26.74	25.87
Change in scores					
V0 - V1 (Month 3)	N	154	155	111	162
(primary endpoint)	Mean	-18.0	8.9	-15.8	-18.3
	SD	26.62	30.73	24.06	26.43
	p-value	<0.0001 ^a	0.0001 ^b	<0.0001 ^a	<0.0001 ^a
V0 - V2 (Month 6)	N	151	127	113	144
	Mean	-14.3	-9.0	-12.5	-19.7
	SD	32.62	32.43	29.36	25.85
	p-value	<0.0001 ^a	0.0001 ^b	<0.0001 ^a	<0.0001 ^a
V0 - V3 (Month 12)	N	93	120	100	130
	Mean	-16.8	-6.1	-16.1	-22.8
	SD	31.92	31.46	30.45	28.77
	p-value	<0.0001 ^a	0.0141 ^b	<0.0001 ^a	<0.0001 ^a

a: Fisher's D; b: Wilcoxon Signed rank test.

The Effects of Physical Activity on Bone Density of High School Girls: A Prospective Study

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Session Type: ACR Poster Session B

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

Background/Purpose: More than 50% of peak bone mass (PBM) is gained during adolescence and high impact exercise has been shown to impact bone accrual. We evaluated bone mass in age and gender matched teenagers who were more or less physically active using calcaneal ultrasound.

Methods: Forty-six consecutive high school girls (14-18 years) were prospectively recruited between February-April 2018 after obtaining written informed parental consent. Subjects were divided into two groups, athletes (who reported ≥ 4 hours of aerobic physical activity/week) and non-athletes with < 1 hour. No subject had any orthopedic injuries or metabolic bone disorders. Each study participant self-reported their a) use of calcium (with or without vitamin D) supplementation and b) weekly servings of 8 oz. dairy products. BMD (bone mineral density) was measured (g/cm²) using a Sahara, Hologic Clinical Bone Sonometer). Continuous variables are reported as mean \pm standard deviation and compared using Student's

Figure 1a: Baseline data of the study sample (n=46)

Variable	Total (n=46)	Athletes (n=23)	Nonathletes (n=23)	P-value
Age (years)	16 \pm 1	15 \pm 1	16 \pm 1	0.32
Height (cm)	163 \pm 10	163 \pm 8	163 \pm 10	0.62
Vitamin D and calcium supplementation				
None	29 (63%)	14 (61%)	15 (65%)	
Vitamin D or calcium supplementation	7 (15%)	4 (17%)	3 (13%)	0.62
Vitamin D and calcium supplementation	10 (22%)	5 (22%)	5 (22%)	
Number of 8 oz. dairy servings/week	8 \pm 0	7 \pm 5	9 \pm 6	0.22

Figure 1b: Box and whisker plot demonstrating the significant differences in BMD between athletes and nonathletes

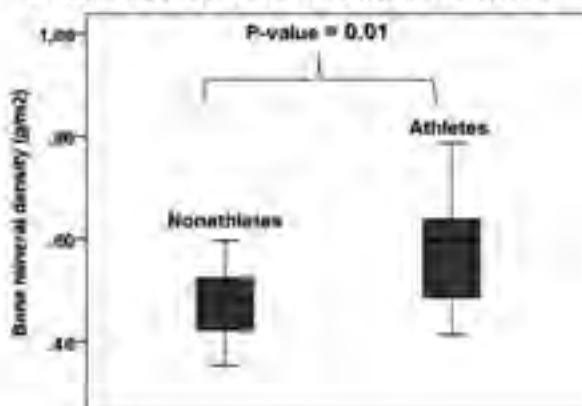


Figure 1c: Univariable linear regression analysis between bone mineral densities and various potential impacting factors in the study sample

	Standardized Beta	P-value
Age	0.09	0.57
Height	-0.03	0.83
Amount of weekly dairy intake	0.08	0.58
Calcium/vitamin supplementation vs. none	0.12	0.21
Athletes vs. nonathletes	0.41	0.009

t-testing, while categorical variables are reported as percentage of total and compared using Chi-square. Linear regression analysis was also performed to test the association between BMD and various predictors. A p-value < 0.05 was considered significant.

Results: The baseline data are shown in Figure 1a. Mean BMD was significantly higher in athletes vs. nonathletes (0.58 ± 0.1 vs. 0.49 ± 0.1 g/cm², $p=0.01$, Figure 1b). The association between BMD and various potential factors, using linear regression analysis, is shown in Figure 1c. The groups were well matched for age, height, and dairy intake with nonsignificant differences.

Conclusion: In high school girls who had heel BMD testing, participants who were physically active had higher BMD vs. those who were not. The findings were independent of age, dietary dairy intake as well as calcium/vitamin D supplementation. This study shows the importance of exercise in adolescent girls for accruing bone and attaining a higher PBM which will have a significant effect on bone mass later in life, potentially resulting in a lower lifetime risk for fracture. These findings need to be validated in a larger sample.

Disclosure: R. Desai, None; B. Carpenter, None; M. Kennedy, None; M. Desai, None; L. Damour, None; C. Deal, None.

Abstract Number: 1149

Contemporary Prevalence of Gout and Hyperuricemia in the United States (National Health and Nutrition Examination Survey [NHANES] 2015-2016) and Decadal Trends (NHANES 2007-2016)

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II: Gout, Ankylosing Spondylitis, Osteoarthritis, Osteoporosis, Pain, and Function

Session Type: ACR Poster Session B

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

Background/Purpose: The prevalences of gout and hyperuricemia from the National Health and Nutrition Examination Survey (NHANES) 2007-2008 were 3.9% (8.3 million) and 21.4% (43.3 million individuals), respectively, representing increases of 44% and 18% from a decade earlier (Zhu et al., *Arthr Rheum.* Oct 2011, pp 3136-3141). Our objective was to determine the latest national prevalence estimates (NHANES 2015-2016) of gout and hyperuricemia and their decadal trends from NHANES 2007-2016.

Methods: Using data from 5,467 participants in the NHANES 2015-2016, we estimated the prevalence of gout and hyperuricemia. During the home interview in each NHANES survey cycle, all participants were asked about a history of health professional- or physician-diagnosed gout. Our definition of hyperuricemia was a serum urate level (SUL) >7.0mg/dL in men and >5.7mg/dL in women. We explored potential secular trends in these estimates and their possible explanations by comparing the latest estimates with those from 22,654 participants from NHANES 2007-2014. All statistical analyses were conducted using survey commands of Stata (Version 15.1, Stata Corporation, College Station, Texas) to adjust for clusters and strata of the complex sample design as well as incorporate sample weights to generate estimates for the total civilian, non-institutionalized population of the US. Population estimates (in millions) were calculated as per the NHANES analytic guidelines.

Results: The prevalence of gout was 3.9% (9.2 million) among US adults in 2015-2016 (5.2% [5.9 million] among men and 2.7% [3.3 million] among women) (**Table**). The mean SULs were 6.0mg/dL among men and 4.8mg/dL among women, which corresponds to hyperuricemia prevalences of 20.2% and 20.0%, respectively. The prevalence of gout and hyperuricemia among US adults was stable over the past decade (P-value for trend= 0.69 and 0.24 for men and women, respectively). The decadal trends for gout remained stable when stratified by sex, hypertension, chronic kidney disease (CKD) and obesity (all P-values for trend> 0.05).

Conclusion: These findings from this nationally-representative sample of US adults suggest that the prevalences of gout and hyperuricemia remain substantial (9.2 and 47.1 million adults, respectively), although they appeared to have plateaued over the past decade. This may be related to plateauing frequency of CKD (Murphy et al., *Ann Intern Med.* Oct 2016, pp 473-481), and hypertension (Fryar et al., *NCHS data brief*, no., 289. Oct 2017).

Table. Prevalence of Gout and Hyperuricemia and Number of Affected Adults in the US, NHANES 2015-2016*

	Gout		Hyperuricemia	
	Prevalence, % (95% CI)	N of US adults, millions	Prevalence % (95% CI)	N of US adults, millions
All	3.9 (3.3, 4.7)	9.18	20.1 (17.8, 22.4)	47.13
Sex				
Male	5.2 (4.4, 6.2)	5.86	20.2 (16.6, 24.3)	22.76
Female	2.7 (2.0, 3.8)	3.33	20.0 (17.8, 22.4)	24.37
Age				
20-39	0.7 (0.3, 1.5)	0.56	16.6 (13.6, 20.1)	14.07
40-59	3.4 (2.2, 5.3)	2.89	18.7 (15.1, 22.9)	15.71
60-79	8.8 (7.2, 10.7)	4.77	26.1 (22.7, 29.8)	14.20
≥ 80	8.7 (5.8, 12.7)	0.97	27.8 (21.0, 35.8)	3.10
Race/ethnicity				
Non-Hispanic White	4.0 (3.1, 5.3)	6.13	21.4 (18.1, 25.1)	32.59
Non-Hispanic Black	4.8 (3.8, 6.0)	1.31	22.6 (20.9, 24.3)	6.15
Hispanic	2.0 (1.4, 2.9)	0.73	14.9 (12.6, 17.5)	5.33
Other	5.2 (3.4, 7.9)	0.99	17.0 (13.8, 20.7)	3.23

* The data were adjusted for clusters and strata of the complex sample design of the National Health and Nutrition Examination Survey (NHANES) 2015–2016, with incorporation of sample weights. 95% CI = 95% confidence interval

Disclosure: M. Chen-Xu, None; C. Yokose, None; M. Pillinger, Horizon Pharmaceuticals, 5,Ironwood, 5,SOBI, 5; H. K. Choi, Takeda, Selecta, Kowa, and Horizon, 5,Selecta and Horizon, 2.

Abstract Number: 1150

The Potential Uses of an Infodemiology Approach for Health-Care Services in Rheumatology

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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

Background/Purpose: Infodemiology can help achieve the patient-centered care model. It is the science of determinants and distribution of information on electronic media. It can provide data to develop, collect, and evaluate metrics and indicators for information and communication patterns that are related to epidemiologic data or are useful for public health, policy making or even clinical practice. Google Trends (GTr) and Google AdWords (GAd) are two useful tools to assess demand-based infodemiology indicators. Its use is scanty in rheumatology.

To illustrate the potential use of GTr and GAd, we present three case-studies: A) What search terms related to rheumatology are typed by people in Mexico (MX), the United States of America (USA), and Canada (CAN)? B) What is the search volume for specific DMARDs typed by people in MX, USA, and CAN?, and C) What is the positioning of the search term “arthritis” compared with two non-rheumatic diseases (“hepatitis C”, “breast cancer”) among MX, USA, and CAN?

Methods: GTr output is a relative search volume (the biggest volume is transformed to 100 and the rest are given as a proportion of it) and GAd output is the average number of searches per unit of time. We ran 3 different queries (MX, USA, CAN) for each case-study using GTr and GAd for years 2015-2017. Results were exported to a database for further analysis. Search volumes were adjusted per country’s population and expressed as crude rates (searches per million; spm) when appropriate.

Results: To look for information on “rheumatology” people used 298 (MX), 654 (USA), and 637 (CAN) associated terms. “Arthritis” had 656, 550, and 548 associated terms in MX, USA, and CAN, respectively. For “arthritis treatment” there were 635, 569, and 569 associated terms in MX, USA, and CAN, respectively. Regarding DMARDs, there were 1,053 million searches during this period: methotrexate (28.5%), adalimumab (15.6%), rituximab (10.4%), and infliximab and etanercept (8.6% each). However, for every b- or tsDMARD search, there were fourteen (USA, CAN) to fifty-eight (MX) “turmeric” searches for the “treatment of arthritis”. In 2015, search volume for “arthritis” was 120, 638, and 668 spm in

MX, USA, and CAN, respectively. For 2016 and 2017, figures remained similar for MX and CAN, but showed a 12% increase for the USA. In MX, “hepatitis C” had 114 spm in 2015, with a 32% increase by 2017. The USA and CAN had 1,131 and 648 spm in 2015, with a 5% increase and an 8% decrease by 2017, respectively. For “breast cancer”, search rates were 4 times higher than for “arthritis” for the three years in MX, with an average increase of 250% each October, concurrent with public awareness campaigns. In the USA and CAN, search volume was 36% and 56% less than that for “arthritis”, with a 57% and 33% increase each October, respectively.

Conclusion: Infodemiology can have an added value to traditional research designs. It can serve for diverse purposes, such as assessing the penetration and impact of public awareness campaigns, patients’ perceived needs, the appearance of new remedies, the positioning of diseases, disease-related cultural differences in ethnic groups, people perceptions on specific health-care systems, etc.

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Abstract Number: 1151

Comparison of Methodologic Approaches to Maximize the Validity of Fitbit Device Data for Arthritis-Related Research Purposes

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SESSION INFORMATION

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Background/Purpose: Health activity tracker devices(e.g. Fitbit) are increasingly used component of medical evaluation. However, the validity and suitability of the data from such devices for research is not clear, specifically, methods are lacking to ascertain whether patients are consistently wearing the device and if the data is complete. We compared various methodologic approaches to describe the completeness of data capture in the context of a pilot study of patients with inflammatory arthritis.

Methods: We evaluated active & passively collected data from a trial of patients with gout who had a recent flare. All patients were given a Fit bit Charge HR2. Fit bit data (step count, sleep, heart rate [HR]) was evaluated in 1-minute increments. Minute-level HR data was compared with a gold standard for ‘Complete Wear’ as composite of step count, sleep, and HR, with imputation to 60-minute increments. Imputation of wear was performed for shorter intervals (1, 15, 30-minutes). Definitions for Complete of wear at a person-day level were evaluated using various parameters (e.g. ≥ 1200 minutes, or ≥ 800 minutes for days without sleep data). Variability in step count data was decomposed as between-person; within-person, between-day; and within-person, within-day (including error) based upon comparing sums of squares to total variance.

Results: At time of evaluation, 36 people contributed 4,534 person-days of observation. A total of 60% of person-days were considered Complete data with sleep, 14% as Complete data without sleep, and 26% with Partial Data. On days with Complete wear with sleep (gold standard), 13% of person-minutes were misclassified if only minute-level HR data was used, and step count & sleep data were ignored, while 8% were misclassified if only HR data was used, with imputation. Adding sleep and step count data, 12% of person-minutes were misclassified if minute-level data without imputation was used; 6% of person-minutes were misclassified if imputation to 60-minutes was applied, but the 1200/800 minute thresholds for Complete wear over a day were not required.

Imputation at 60-minute intervals yielded similar results to imputation at 1, 15, and 30-minute increments. There were intervals as long as 3+ hours where patients were wearing the device (based on gold standard) yet had no HR data. Among Complete wear days, variance in the step count data was much more related to between-person variability (36%) rather than within-person, between-day variability (<1%). With imputation at 60-minute increments, wear patterns are shown in the heat map (Figure).

Conclusion: Fit bit and other health tracker data appear useful as part of arthritis research, but several methodologic issues must be considered to maximize validity and interpretation.

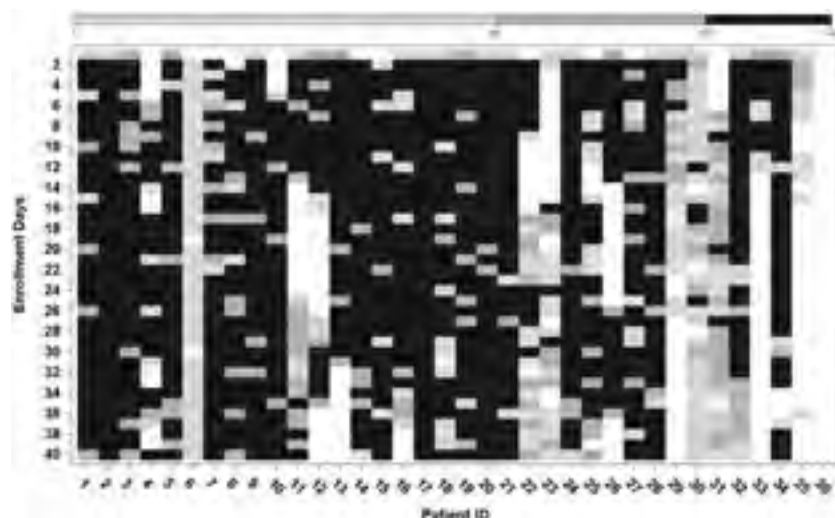


Figure: Heat Map - Data of Complete Wear with Sleep(>1200 minutes) [Black], Complete Wear without Sleep [Dark Gray], and Incomplete Wear [Light Gray]

Disclosure: J. R. Curtis, Amgen Inc., 2, 5, AbbVie Inc., 2, 5, BMS, 2, 5, Corrona, LLC, 2, 5, Janssen, 2, 5, Eli Lilly, 2, 5, Myriad, 2, 5, Pfizer, Inc., 2, 5, Roche/Genentech, 2, 5, Radius, 2, 5, UCB, Inc., 2, 5; S. Yang, None; L. Chen, None; N. Elmagboul, None; D. T. Redden, None; A. S. Mudano, None; P. J. Foster, None; F. Cooper, None; T. R. Mikuls, None; J. K. Owensby, None; K. Saag, Amgen Inc., 2, 5, Merck & Co., 2, 5, Lilly, 5, Radius, 5.

Abstract Number: 1152

“Doctor, a Storm Is Coming and My Joints Hurt”: Evaluating Associations between Weather Changes and Arthritis Symptoms

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SESSION INFORMATION

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Background/Purpose: Arthritis symptoms reported by patients have been anecdotally associated with weather changes, but large-scale, systemic evaluations are few in number. A variety of parameters associated with weather that might underlie arthritis-related pain and related symptoms have been inconsistently reported.

Methods: Patients participating in the ArthritisPower registry and contributing data via a Smartphone or computer App from the continental U.S. were eligible for analysis. Geolocation (latitude/longitude) was extracted from the Smartphone's physical location or computer IP address. Various weather parameters (e.g. temperature, humidity, wind speed/direction, barometric pressure) were obtained from the nearest National Oceanic and Atmospheric Administration (NOAA) weather station based on patient's geolocation. Various restrictions in the maximal allowable distance to the nearest weather station (e.g. <25 miles) were evaluated. Patient disease activity by the RAPID3, and patient reported outcomes (PROs) including pain interference, fatigue and physical function measured by the NIH PROMIS instruments (using computer adaptive testing) were obtained from the registry, and associated with NOAA weather data at that same time (to the nearest hour) and location, and at the same location 24 hours before and after each patient observation. Cross-sectional correlation between various weather parameters and PROs were quantified as r values using Pearson correlation coefficients. A “cold front” definition was proposed based on the confluence of longitudinal change over 3 days in relative humidity, wind direction, barometric pressure, and dew point.

Results: At the time of this analysis, 1334 unique patients contributed 2425 PRO observations with linkable NOAA weather data. Mean(SD) age was 53.9(10.3) years, 91% women, 90% white. In terms of various arthritis conditions represented in Arthritis Power, 45% had rheumatoid arthritis, 10% psoriatic arthritis, 9% ankylosing spondylitis, and 62% osteoarthritis (with or without a concomitant inflammatory arthritis). Many of the correlations between various weather parameters and PROs were statistically significant ($p < 0.001$) albeit numerically weak (all r values < 0.2). For patients contributing any PRO data at the time of an evolving cold front using the proposed definition, patient symptoms were not different as measured by various PROs (Table).

Conclusion: Weather is quantitatively related to patient's arthritis symptoms. Additional work is ongoing to refine specific weather parameters and their associations with PROs in order to provide potentially actionable information to patients and their healthcare providers.

Table: Association between Patient Symptoms and the Presence of a Cold Front based on Geolocation and Linked Weather Data (n=2425)

	Cold Front	No Cold Front
RAPID3 (0-30)	15.0 (9.0, 20.0)	17.0 (13.0, 21.0)
PROMIS Pain Interference (1-100)	63 (55, 67)	66 (62, 70)
PROMIS Fatigue (1-100)	60 (51, 64)	64 (59, 71)
PROMIS Physical Function (1-100)	63 (55, 67)	66 (62, 70)

Disclosure: J. R. Curtis, AbbVie, Amgen, BMS, Eli Lilly and Company, Janssen, Pfizer, Roche/Genentech, Corrona, UCB, Myriad, 2, 5; S. Yang, None; C. Clinton, None; L. Chen, None; W. B. Nowell, GlaxoSmithKline, 1, Merck & Co., 1, Pfizer, Inc., 1, 2, AbbVie Inc., 1, Bristol-Myers Squibb, 1, 2, Eli Lilly and Co., 1, 2, Janssen, 1, Novartis, 2; H. Yun, Pfizer, Bristol-Myers Squibb, 2; D. Curtis, None.

Abstract Number: 1153

EULAR 'Points to Consider' for the Conduction of Workforce Requirement Studies in Rheumatology

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SESSION INFORMATION

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Background/Purpose: Recommendations and strategies have been developed for early referral, diagnosis and treatment of rheumatic diseases. These strategies, however, can only be implemented if sufficient manpower is available. An estimation of how many rheumatologists are needed to meet current and future population needs must be provided in order to counsel health care planners and decision makers. Current methods used for forecasting manpower are disparate, as are the variables incorporated into workforce projection models. Consequently, projections for the need of rheumatologists

may vary by a factor of five between studies. The objective of these EULAR points to consider (PTC) was to guide future workforce studies in adult rheumatology in order to produce valid and reliable manpower estimates.

Methods: The EULAR Standardised Operating Procedures were followed. A multidisciplinary task force with experts including patients with rheumatic diseases from 11 EULAR countries and the USA was assembled. A systematic literature review (SLR) was conducted to retrieve workforce models in rheumatology and other medical fields. PTC were based on expert opinion informed by the SLR, followed by group discussions with consensus obtained through informal voting. The level of agreement with the PTC was voted anonymously.

Results: A total of 10 PTC were formulated (Table). The task force recommends models integrating supply (= workforce available to rheumatology), demand (= health services requested by the population) and need (= health services that are considered appropriate to serve the population). Projections of workforce requirement should consider all factors relevant for current and future workload in and outside direct patient care. Forecasts of workforce supply should consider demography and attrition of rheumatologists, as well as the effects of new developments in health care.

Conclusion: These EULAR endorsed PTC will provide guidance on the methodology and the parameters to be applied in future national and international workforce requirement studies in rheumatology.

Table 1. EULAR points to consider for the conduction of workforce requirement studies in rheumatology

No	Point to consider	LoA	LoE
1	Workforce models should integrate supply, demand and need of the respective geopolitical entity (e.g. municipality, region, state, country), and should express results as full time equivalents and as number of rheumatologists.	9.5 (0.9) 95% \geq 8	5
2	Workforce models should provide projections over a period of 5-15 years.	9.1 (1.1) 90% \geq 8	5
3	Workforce models should not assume a current balance between supply and need.	9.6 (0.7) 100% \geq 8	5
4	Workforce models should, where possible, rely on several data sources and include uncertainty analyses.	9.8 (0.4) 100% \geq 8	5
5	Workforce models should be regularly updated; updates should include an analysis of the actual performance (i.e. prediction validity) of the previous model.	9.5 (0.6) 100% \geq 8	5
6	Workforce need for patient care should be based on the prevalence and referral rates of diseases managed by rheumatologists as well as on an estimation of time needed per patient.	9.7 (0.7) 100% \geq 8	5
7	Workforce need for patient care should consider current and future demographics, sociocultural characteristics of the population and disease patterns.	9.5 (0.9) 95% \geq 8	5
8	Workforce need and supply should consider work outside rheumatology patient care (e.g. administrative tasks, research, teaching, non-rheumatologic disease management), as well as patient care performed by other health professionals in rheumatology.	9.4 (0.9) 95% \geq 8	5
9	Workforce supply should account for demographic composition of rheumatologists, the number of rheumatologists entering and leaving the workforce, and generational attitudes of rheumatologists towards scope of practice and work-life balance.	9.1 (2.3) 85% \geq 8	5
10	Workforce models should consider the effects of medical developments, including new technologies, medications, artificial intelligence and e-health, on demand and supply.	9.4 (1.1) 85% \geq 8	5

Numbers in column 'LoA' indicate the mean and SD (in parentheses) of the LoA, as well as the percentage of task force members with an agreement \geq 8. None of the studies identified corresponded to any of the categories of Oxford Centre for Evidence-Based Medicine (OCEBM). Evidence level was therefore set as "5", which is the lowest level of evidence. LoA, Level of Agreement; LoE, Level of Evidence according to OCEBM 2011 levels of evidence.

Disclosure: C. Dejaco, None; P. Putrik, None; J. Unger, None; D. Aletaha, None; G. Bianchi, None; J. W. J. Bijlsma, None; A. Boonen, None; N. Cikes, None; A. Finckh, None; L. Gossec, None; T. Kvien, None; J. Madruga Dias, None; E. L. Matteson, None; F. Sivera, None; T. Stamm, None; Z. Szekanecz, None; D. Wiek, None; A. Zink, None; S. Ramiro, None; F. Buttgeriet, None.

Abstract Number: 1154

Patterns of Opioid Use and Patient Characteristics before Total Hip and Knee Replacement

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SESSION INFORMATION

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

Background/Purpose: Patients with moderate-to-severe hip or knee arthritis often use opioids before undergoing total joint replacement (TJR). Preoperative opioid use may lead to persistent opioid use and poor clinical outcomes after TJR. We aimed to describe patterns of opioid use before TJR.

Methods: Using Medicare (Parts A/B/D, 2010-2014) data, we conducted a cohort study among patients aged ≥ 65 who underwent incident total hip replacement (THR) or total knee replacement (TKR). Index date was the incident TJR date. Eligible patients were required to have continuous enrollment in Part A/B/D for at least 360 days before the index date. We excluded patients with: 1) no medical and/or pharmacy claims in the 360-days before the index date, and 2) both THR and TKR on the same date. Any opioid use was defined as having ≥ 1 opioid dispensing during the 12-month period; continuous opioid use was characterized as having ≥ 1 opioid dispensing in each of 12 months during the before the index date. We calculated mean morphine milligram equivalent (MME) per day and proportion of days covered (PDC) in each month. 50 MME is equivalent to 50 mg hydrocodone. We assessed variables potentially associated with opioid use, such as demographics, pain/fractures, other comorbidities, medication use, and healthcare use in 360 days prior to the surgery. A multivariable logistic regression model estimated the associations between patient characteristics and preoperative opioid use patterns.

Results: We identified a total of 473,781 patients who underwent TJR: 155,516 THR and 318,265 TKR. Mean (SD) age was 75 (7) years for THR and 74 (6) for TKR patients. 67.4% were female and 91.5% were White. Back pain was a common comorbidity in both THR (62%) and TKR (46.8) patients. 60.2% patients had any use of opioids before the surgery. Of those, 12.4% used opioids at least once a month continuously over the 12-month preoperative period. Hydrocodone was most commonly used agent, followed by tramadol and oxycodone. Among any users of opioids, MME per day and PDC both increased toward the TJR date. Continuous opioid users had over 90% PDC in the month before TJR and used higher MME dose of opioids per day (58mg in THR, 51mg in TKR) compared to any users (16mg in THR, 12mg in TKR) (p -values < 0.0001) (**Figure**). Correlates of continuous opioid use included history of drug abuse (OR=5.19, 95% CI=3.96-6.84) and back pain (OR=2.32, 95% CI=2.24-2.40). African American patients had a 2-fold higher odds of using opioid continuously compared with White Americans (OR=2.14, 95% CI=2.01-2.28).

Conclusion: Among patients in Medicare who underwent TJR, 60.2% had any use of opioids and 7.5% had continuous use of opioids in the year before the surgery. Use of opioids and MME increased gradually toward the index TJR date. History of drug abuse, back pain, and race African American were strongly associated with continuous use of opioids preoperatively.

Disclosure: Y. Jin, None; D. Solomon, None; P. D. Franklin, None; Y. C. Lee, None; J. Lii, None; J. N. Katz, None; S. C. Kim, None.

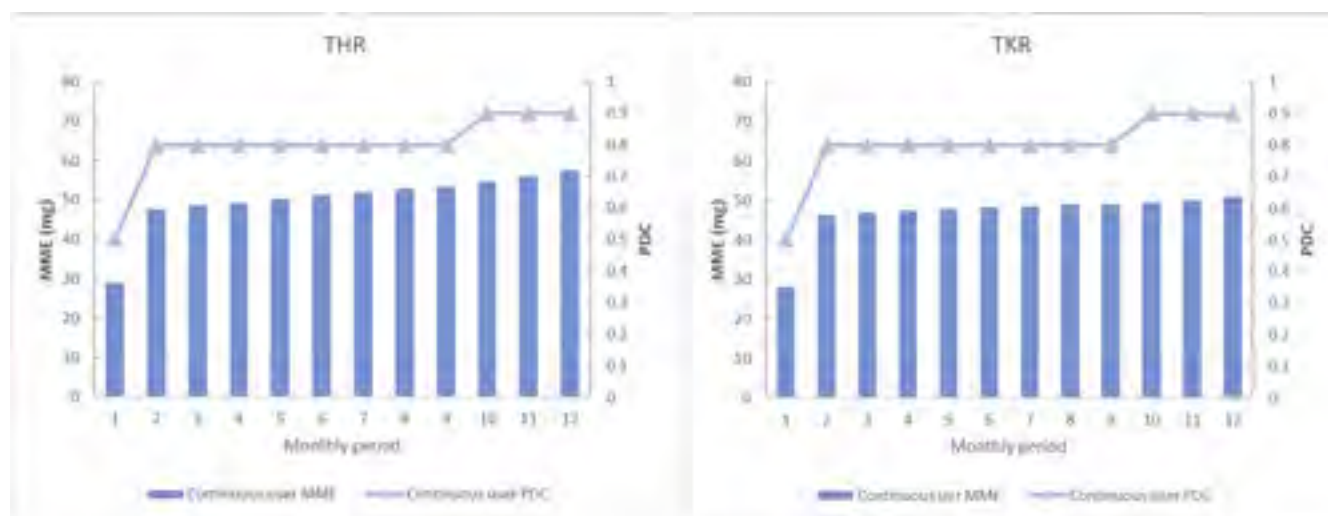


Figure. Mean daily opioid morphine milligram equivalents (MME) and proportion of days covered (PDC) during 360-day preoperative period among continuous users stratified by procedure type (THR or TKR)

A Collaborative Cardio-Rheumatology Clinic for Primary Prevention of Cardiovascular Diseases – a Descriptive Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II: Gout, Ankylosing Spondylitis, Osteoarthritis, Osteoporosis, Pain, and Function

Session Type: ACR Poster Session B

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

Background/Purpose: Patients with inflammatory arthritis are at increased risk for atherosclerotic cardiovascular (CV) disease. This has been under-recognized in clinical practice. Additionally, the current risk stratification methods underestimate risk in this population.

The purpose of our study was to describe the population characteristics of patients attending a Cardio-Rheumatology Clinic, a new collaborative initiative at a large academic medical centre in Canada, which aims to improve CV care of patients with inflammatory arthritis, and to report changes in treatments for CV prevention initiated during their clinic visit.

Methods: This study is a cross sectional analysis of patients assessed in the Cardio-Rheumatology Clinic from July 2017 to May 2018. Patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) with no known CV disease were referred to the clinic. Information about their rheumatic disease, lifestyle habits, medications and co-morbidities was recorded. Each patient was evaluated by a cardiologist focusing on CV risk assessment. All patients underwent blood tests for lipids and cardiac biomarkers, electrocardiogram, coronary artery calcium scoring, stress echocardiography and carotid ultrasound.

Results: 95 patients with RA (49.5%), PsA (38.9%) and AS (11.6%) were evaluated (mean age 59.5 years, 67.4% female). Hypertension was reported in 31.6%, dyslipidemia in 26.3%, diabetes mellitus in 8.4% and family history of premature CVD in 30.1%. History of current smoking was present in 10.2%. Sedentary lifestyle was common; only 20% of patients reported 3 hours or more of vigorous exercise per week and functional capacity was rated as below average for age and sex in 31.8%, and 72.3% were overweight or obese. Table 1 summarizes the CV risk factors and laboratory findings and Table 2 describes key CV abnormalities in imaging. Importantly, 53.8% of patients had a change in pharmacological therapy as a result of evaluation in the clinic, including 39.7% for lipid lowering, 32.1% for antiplatelet, 14% for antihypertensive therapy, 1.3% were retreated for heart failure and 1.3% were placed on lifelong anticoagulation therapy for atrial fibrillation. One patient underwent percutaneous coronary stenting.

Conclusion: A dedicated Cardio-Rheumatology Clinic has led to identification of increased CV risk, early atherosclerosis and optimization of CV care in a large proportion of our clinic population. Further work in this area is needed to help raise awareness of this increased risk and to help develop more accurate tools to assess CV risk in this population.

Table 1. Baseline characteristics of the study population (N=95)

Variable	Mean (SD)/Frequency (%)
Age (years)	59.5 (12)
Sex: Female	64 (67.4%)
Diagnosis	
Rheumatoid Arthritis	47 (49.5%)
Psoriatic Arthritis	37 (38.9%)
Ankylosing Spondylitis	11 (11.6%)
Disease duration (years)	13.4 (13.1)
Current use of NSAIDs	
Daily	24 (25.2%)
As needed	24 (25.2%)
Systemic Corticosteroids	
Current	7 (7.7%)
Past	14 (15.4%)
Use of Non-biologic DMARDs	73 (76.8%)

Table . (Cont'd)

Variable	Mean (SD)/Frequency (%)
Use of Biologic DMARDs	35 (36.8%)
Family history of CVD	28 (30.1%)
Diabetes Mellitus	8 (8.4%)
Patient reported Dyslipidemia	25 (26.3%)
Use of lipid lowering drugs	16 (16.8%)
Patient reported Hypertension	30 (31.6%)
Use of anti-HTN drugs	27 (28.4%)
Clinic Blood pressure measurement	
Systolic	
>140	18 (18.9%)
120-140	63 (66.3%)
<120	32 (33.6%)
Diastolic	
>90	11 (11.6%)
80-90	35 (36.8%)
<80	49 (51.6%)
BMI	
Overweight	35 (37.2%)
Obese	33 (35.1%)
Smoking	
Current	9 (10.2%)
Past	46 (52.7%)
Hs-CRP	
<1 mg/L (low risk)	22 (24.2%)
1-3 mg/L (Moderate risk)	23 (25.3%)
>3 mg/L (High risk)	46 (50.5%)
Total cholesterol	
>5.2 mmol/L	33 (36.3%)
Triglycerides	
<1.7 mmol/L (normal)	60 (65.9%)
1.7-2.25 mmol/L (borderline)	14 (15.4%)
>2.25 mmol/L (high)	17 (18.7%)
HDL	
<1 mmol/L	7 (8%)
LDL	
<2 mmol/L	17 (19.3%)
>3.4 mmol/L	21 (23.9%)
>4.9 mmol/L	2 (2.3%)
Non-HDL-c	
<2.7 mmol/L	22 (24.4%)
>4.2 mmol/L	21 (23.3%)
Troponin T	
Elevated TnT (>15 ng/L)	7 (7.9%)
NT – pro – BNP	
Elevated NT-pro-BNP (>100 pg/ml)	8 (8.9%)

Table 2. Summary of Cardiovascular Imaging Findings

Echocardiogram (N = 77)	
Left ventricular systolic function	
Normal	77 (100%)
Abnormal	0
Increased LV wall thickness/Left ventricle hypertrophy	13 (16.9%)
Diastolic dysfunction	5 (6.7%)
Grade 1	4
Grade 2	1
Dilated left atrium	5 (6.7%)
Aortic regurgitation	9 (11.6%)
Trace	1
Mild	8
Mitral regurgitation	9 (11.6%)
Trace	2
Mild	7
Pulmonary hypertension	0
Dilated aorta	18 (23.3%)
Overall stress echo assessment of ischemia	
Positive	0
Indeterminate	6
Carotid Ultrasound (N = 77)	
Presence of atherosclerotic plaques	
No Plaque	46 (59.7%)
Unilateral Plaque	23 (29.8%)
Bilateral Plaque	8 (10.5%)

Table . (Cont'd)

Intima media thickness	
Intimal Medial Thickness (>900)	7 (9.1%)
Coronary Artery Calcium Scoring (N = 81)	
Total Coronary artery calcification	
0	40 (49.4%)
0 – 100	24 (29.6%)
>100	17 (21%)

Disclosure: S. Akhtari, None; P. Harvey, None; M. Jacobson, None; S. Nagler, None; K. Colaco, None; L. Eder, None.

Abstract Number: 1156

Work Productivity and Activity Impairment in Patients with Rotator Cuff Tendinopathy

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II: Gout, Ankylosing Spondylitis, Osteoarthritis, Osteoporosis, Pain, and Function

Session Type: ACR Poster Session B

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

Background/Purpose: The objective of this study was to evaluate the work productivity and its relationship with the degree of physical work demand in patients with rotator cuff tendinopathy.

Methods: We included consecutive patients over 18 years of age, working actively, with rotator cuff tendinopathy, diagnosed clinically and ultrasonography. Patients with diagnosis of inflammatory arthropathies, fibromyalgia and any other condition that prevents reading or understanding of the questionnaires were excluded. Demographic variables and work characteristics were determined. Work productivity was assessed using the WPAI:GH questionnaire, and the degree of physical work demand through the Pujol scale.

Results: 48 patients were evaluated, 66.6% were women. The mean age was 48 ± 10 years. The median of duration of symptoms was 3 months (RIC 2-6), and the time of occupation was 40 hours per week (RIC 30-50). The most frequent occupations were domestic staff (34.04%), construction workers (12.77%) and nurses (10.64%). The percentage of patients who performed sedentary or mild work was 47.9% (23/48), while 52.1% (25/48) performed jobs with intermediate, heavy or very heavy physical demand. The tendon most frequently affected was the supraspinatus (64.5%). The median of absenteeism was 20% (RIC 0-41.43 - IC 95: 17.53 to 32.44). We observed a reduced on the job effectiveness (Presenteeism) of 75% (RIC 55-100 - IC 95: 61.26 to 78.31) and a work productivity loss of 85.8% (RIC 60-100 - IC 95: 65.15 to 82.32). The impairment in activities of daily living (ADL) was 60% (RIC 50-80 - IC 95: 53.82 to 69.07). No statistically significant differences were found in any of the WPAI variables in terms of sex, the correlation was low and not significant with respect to age. Significant differences were observed regarding the degree of physical work demand (light work vs. intermediate / heavy work), those who performed intermediate / heavy work had greater impairment at work (85% (RIC 60-100) vs 40% (RIC 20-80) $p = 0.008$) and loss of total work productivity (90% (RIC 69-100) vs 45% (RIC 20-81.7) $p = 0.007$).

Conclusion: In patients with rotator cuff tendinopathy an impairment was observed in the four WPAI variables, being more marked in those patients with occupations that require greater physical demand.

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Acknowledged Biostatistical Help and the Quality of Statistical Analyses in Randomized Controlled Trials in Rheumatology

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SESSION INFORMATION

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Background/Purpose: The quality of statistical analysis reporting is wanting even in our most prestigious journals. It stands to reason that active participation of biostatisticians/epidemiologists (b/e) in reporting would improve the situation. We tested the hypothesis that more close cooperation with a b/e would improve the quality of reporting randomized clinical trials (RCTs) in rheumatology. We defined this *close cooperation* as the inclusion of a formal b/e among the co-authors and/or a declaration of formal statistical help in the study reports.

Methods: Two independent observers screened both by reading and electronic scanning, when applicable, the texts of all RCTs in *Annals of the Rheumatic Diseases*, *Arthritis Care and Research*, *Arthritis and Rheumatology*, *Rheumatology Oxford* published in 2015 and 2016. Using a pre-prepared worksheet, the observers specifically tabulated the presence of a b/e among the co-authors and/or formal acknowledgement of statistical help in the methods, the inclusion of effect sizes (the kind, whether they were specifically voiced as effect sizes, whether they could be calculated by the reader from the data presented or not given at all) and the presence of associated confidence intervals for the given effect sizes. Also tabulated were the improper aspects of *p* value reporting, including giving relative ($>p>$) instead of exact ($p=$) *p* values and the erroneous inclusion of *p* values in tables depicting trial entry data in randomized trials, since these tables, by definition, display randomized features (1). An arbiter (HY) decided the final tabulation when there were discrepancies between the 2 observers and there were up to 15 discrepancies in total where more than 1 discrepancy was possible per article.

Results: The total number of RCTs was 134. There were 29 (22%) articles (Group I) in which a formal statistical help was acknowledged. In 26/29 this was a co-authorship and in 3, only a mention in the text. The remaining 105 (78%) of the articles made up Group II. The Table gives the findings. It is seen that the reporting of effect sizes and the desired way of reporting exact *p* values were significantly more common in Group I. On the other hand, reporting of confidence intervals and including *p* values for baseline data after randomization did not show significant differences between the groups.

Conclusion: The inclusion of a b/e, interestingly formally present in only 29/134 (22%) of the analyzed manuscripts, improved the reporting of effect sizes -at least rendering them calculable- and in reporting exact *p* values. The same cannot be said for reporting confidence intervals for effect sizes and giving *p* values for baseline data. A limitation of our work was the relatively small number of manuscripts in Group I.

Table: The differences of the parameters between two groups

	Group I (n=29) with a b/e	Group II (n=105) without a b/e	Differences between the Groups I and II
Effect size reporting, n (%)	26 (90)	61 (58)	32% (95% CI 13.1-43.3), $p=0.001$
Given directly, n (%)	2 (7)	5 (5)	
Can be calculated (given HR, OR, RR, β coefficient), n (%)	24 (83)	56 (53)	30% (95% CI 9.8-42.9), $p=0.004$
NNT and NNH calculated, n (%)	0	2 (1)	
Confidence intervals for effect size reporting, n (%)	16 (55)	43 (41)	14% (95% CI -5.8 -32.9), $p=0.18$
Reporting exact <i>p</i> values, n (%)	25/27 (93)	63/91 (69)	23% (95% CI 5.2-34.7), $p=0.014$
Inclusion of <i>p</i> values for the baseline data, n (%)	3/27 (11)	20/91 (22)	11% (95% CI -7.5-22.8), $p=0.21$

Reference:

1. <http://www.consort-statement.org/checklists/view/32--consort-2010/510-baseline-data> accessed June 4 2018

Disclosure: E. Dincses, None; G. Guzelant, None; G. Hatemi, None; H. Yazici, None.

Privacy-Preserving Linkage between the Arthritis power Registry and Commercial Payer Claims Data to Support Comparative Effectiveness and Outcomes Research

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SESSION INFORMATION

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Background/Purpose: Integration of registry information with administrative claims data may be used to conduct patient-centered outcomes research (PCOR), including comparative effectiveness and safety studies, and to improve the quality of clinical care. While a variety of methods exist to link data, the unique requirements for linking data provided by patients in a research registry to claims data held by health plans and payers may present unique obstacles. These challenges are even greater if 1) no patient identifiers can be directly shared, and 2) no unique identifiers (e.g. social security number) are acceptable for use given privacy concerns. We evaluated results of a method to link data from a patient registry to the clinical outcomes research subsidiary of a large commercial payer under these two constraints.

Methods: A novel, preliminarily validated encryption algorithm using a secure HIPAA-compliant cryptographic one-wayhash function was developed to convert a vector of non-unique patient identifiers (first name, last name, sex, date of birth) into unique hashed identifiers. Both the Arthritis Power registry and HealthCore,Anthem Inc.'s research subsidiary, utilized the hashing algorithm and exchanged only these identifiers; exact match on the hashed identifiers was required. The diagnoses self-reported by patients in the Arthritis Power registry were compared with ICD9/10-based diagnoses in the claims data for the same conditions, and similar autoimmune conditions, varying the amount of health plan coverage available (any, or >5 years), using both a sensitive (≥ 1 outpatient diagnosis) and a more specific (≥ 2 diagnoses from relevant specialist)claims-based definition, and considering whether the condition matched exactlyvs. matched a broader set of inflammatory arthritis diagnosis codes (e.g. RA, PsA, ankylosing spondylitis).

Results: Of 11,343 ArthritisPowerregistry participants enrolled at time of data integration with any health condition, 19.1% (n=2166) were linked to Anthem claims data with no minimum coverage duration requirement; 1600 were commercially insured. Of these, mean (SD) age was 49 (10.7), 93% women, and they resided in the Northeast (12%), Midwest (29%), South (37%) and West (22%). Among patients with more than 5years of coverage and who met the ICD9/10 definition for the computable phenotypes of RA, PsA or psoriasis, confirmation rates varied modestly according to the various parameters permuted (Table).

Conclusion: Information from a patient-ledarthritis research registry where in-person visits are not required can be linked to data from a research subsidiary of a large commercial payer using a hashing algorithm that does not require unique identifiers nor sharing of individual patient information. Ongoing work is underway to maximize the accuracy of linkage and confirmation rates using various approaches.

Table: Confirmation Rates (%) between Patient Self-Reported Health Conditions and Claims-Based Algorithms for RA, PsA, and Psoriasis

Health Condition	Sensitive Definition		Specific Definition	
	Exact condition	Related Conditions	Exact condition	Related Conditions
Rheumatoid Arthritis	67	68	59	61
Psoriatic Arthritis	67	67	47	77
Psoriasis	79	80	47	74

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Abstract Number: 1159

Fat Mass Is Associated with Musculoskeletal Pain in Women : A Three-Year Longitudinal Study

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SESSION INFORMATION

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Background/Purpose: Increase in fat mass is correlated with musculoskeletal pain. The aim of this study was to examine the relationship between fat mass and the musculoskeletal pain prospectively in Korean community residents.

Methods: In the Korean Health and Genome Study, participants (mean age 60.2 years, 56.2% women) completed pain questionnaires and underwent dual x-ray absorptiometry to calculate body composition. Three-year follow-up data on pain was available for 1,325 participants. Pain was categorized according to number of pain regions. At three years of follow-up, participants were classified as follows: 1) no pain both at baseline and at three years (no pain), 2) any pain (one, two or more, or widespread regions) at baseline and no pain at three years (transient pain), 3) no pain at baseline and any pain at three years (new pain) 4) any pain both at baseline and at 3 years (persistent pain). 1) and 2) were grouped as no/transient pain group (no pain) and 3) and 4) as new/persistent pain group (pain).

Results: Female gender and obesity were two significant factors associated with the persistence or development of pain. Total fat mass and fat:muscle mass ratio were associated with pain among female participants only, and the odds ratios for pain were significantly increased in female participants in the highest quartile of total fat mass and fat muscle ratio after adjustment. Among normal weight participants, those without metabolic syndrome were less likely to belong to the pain group, especially among women.

Conclusion: In conclusion, both female gender and obesity were two significant factors associated with pain. Fat mass parameters and pain were significantly associated only among females.

Disclosure: H. A. Kim, None; J. I. Hong, None.

Abstract Number: 1160

Non-Elderly Adults Who Have Never Seen a Health-Care Provider for Chronic Joint Symptoms- Updated Results from National Health Interview Survey 2015

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Background/Purpose: Arthritis and chronic joint symptoms (CJS) are a leading cause of disability among adults in the United States. For some forms of arthritis, early diagnosis and aggressive treatment are essential to limit permanent joint damage and disability, especially in relatively younger population. Approximately 10.3 million adults (21.7% of adults with CJS) never had seen a health-care provider for their joint symptoms in 2001.

Methods: Data were extracted from the population-based National Health Interview Survey 2015. Never Seen a Health-Care Provider for Chronic Joint Symptoms was defined as negative answer to the question: "Have you EVER seen a doctor or other health professional for these joint symptoms?" Respondents were classified as having CJS if they fit two

criteria 1) had any symptoms of pain, aching, or stiffness in or around any joint except for back or neck; 2) the duration of joint symptoms exceed 3 months. Adults aged 18 to 64 years were included. SAS was used to calculate estimations with weighted analyses. Logistic regression was used to produce odds ratios for a full model that adjusted for all variables.

Results: 50 million non-elderly adults (25.5%) were identified with chronic joint symptoms in NHIS 2015. Approximately 12.5 million (27.3%) of them have never seen doctors or other health professionals for their chronic joint symptoms. Never seen doctors or other health professionals for CJS were associated with Male ($p=0.02$), Hispanic ethnicity ($p=0.06$), No insurance ($p<0.001$), No primary care provider ($p<0.001$), and better general physical health ($p<0.001$). Patients with \neq Other Coverage \pm (Disability-related Medicare and Military Care) ($p<0.001$), higher age ($p<0.001$) were significantly more likely to see healthcare professional for their chronic joint pains.

Conclusion: After 14 years, there is still a significantly proportion of non-elderly adults who have never seen a health-care provider for their chronic joint symptoms. It calls for further efforts in patient education and health policy. A large group of underserved patients might benefit from intervention and their potential disabilities from arthritis might be prevented.

Table 1. Estimated Prevalence of Non-Elderly Adults (Aged 18-64 Years) With Chronic Joint Symptoms (CJS) Who Have Never Seen A Health-Care Provider For CJS, By Selected Characteristics- National Health Interview Survey 2015

	Prevalence of Never Seen a Health-Care Provider for CJS			Odds of Never Seen a Health-Care Provider for CJS	
	N	%	(95% CI)	Odds Ratio	(95% CI)
Age					
18-24	1250611	9.0	(7.0 - 11.0)	1.00	
25-44	5673762	40.7	(37.7 - 43.7)	0.83	(0.56 - 1.23)
45-64	7005869	50.3	(47.3 - 53.3)	0.57	(0.39 - 0.84)
Gender					
Male	7627579	54.8	(51.8 - 57.7)	1.32	(1.11 - 1.56)
Female	6302663	45.2	(42.3 - 48.2)	1.00	
Race					
Non-Hispanic white	9526760	68.4	(65.6 - 71.2)	1.00	
Non-Hispanic black	1390646	10.0	(8.5 - 11.5)	0.82	(0.65 - 1.05)
Hispanic	2227306	16.0	(13.9 - 18.1)	1.29	(1.03 - 1.61)
Asian	586086	4.2	(3.1 - 5.3)	1.20	(0.82 - 1.75)
Other	199444	1.4	(0.6 - 2.3)	0.84	(0.33 - 2.11)
Education level					
Less than high school	2197285	15.8	(13.9 - 17.8)	1.00	
High school graduate	3023951	21.8	(19.5 - 24.1)	1.03	(0.77 - 1.37)
Some College or above	8654813	62.4	(59.8 - 64.9)	0.84	(0.65 - 1.08)
Household Income					
\$0 - \$34,999	3983834	30.3	(27.6 - 33.0)	1.00	
\$35,000 - \$74,999	3788164	28.8	(26.2 - 31.5)	0.93	(0.74 - 1.16)
\$75,000 - \$99,999	1719907	13.1	(10.9 - 15.3)	0.94	(0.72 - 1.23)
\$100,000 and over	3651749	27.8	(24.5 - 31.0)	1.07	(0.81 - 1.41)
Insurance					
Private	9340711	67.7	(65.0 - 70.4)	1.00	
Medicaid and other public	1748364	12.7	(10.8 - 14.6)	0.87	(0.68 - 1.12)
Other coverage	492254	3.6	(2.6 - 4.5)	0.54	(0.38 - 0.76)
Uninsured	2208325	16.0	(14.0 - 18.1)	1.67	(1.28 - 2.17)
Living status					
Not married	5139876	36.9	(34.0 - 39.9)	1.00	
Married/living with partner	8775840	63.1	(60.1 - 66.0)	0.87	(0.72 - 1.05)
BMI					
25 or less	4026588	29.6	(27.1 - 32.2)	1.00	
25-30	4663294	34.3	(31.3 - 37.4)	0.90	(0.72 - 1.11)
30 or more	4890799	36.0	(33.1 - 38.9)	0.85	(0.70 - 1.05)
Has primary care provider					
No	5509810	40.1	(37.0 - 43.2)	2.31	(1.93 - 2.76)
Yes	8229597	59.9	(56.8 - 63.0)	1.00	
General physical health					
Fair/poor	1719244	12.3	(10.6 - 14.0)	1.00	
Good	4278202	30.7	(28.2 - 33.2)	1.86	(1.48 - 2.34)
Excellent/very good	7932796	56.9	(54.5 - 59.4)	2.58	(2.07 - 3.22)

Disclosure: C. Jiang, None; Y. Luo, None.

Association of Knee Ligament and/or Meniscal Injury with Radiographic Knee Osteoarthritis in Military Officers

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II: Gout, Ankylosing Spondylitis, Osteoarthritis, Osteoporosis, Pain, and Function

Session Type: ACR Poster Session B

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

Background/Purpose: Traumatic knee injuries, such as injuries to the anterior cruciate ligament and menisci, are associated with the early onset and progression of osteoarthritis (OA). However, our understanding of the pathobiologic processes underlying this association is limited. This study examined the precipitating effect of knee ligament and/or meniscal injury on radiographic OA in military officers, a population at high risk of knee injury that also experiences sustained biomechanical loads on the knee joint.

Methods: Radiographic OA was assessed in military officers with a prior history of knee ligament and/or meniscal injuries (injury group) and comparison participants (injury-free group), both selected from a cohort of 6452 military officers enrolled between 2004 and 2009, when participants matriculated at the U.S. Air Force Academy, U.S. Military Academy, or U.S. Naval Academy. The injury group had knee ligament and/or meniscal injuries prior to, during, or after their 4-year academy career (n=115). The injury-free group was site-matched from the same source cohort but had no history of knee ligament and/or meniscal injuries (n=114). Both groups had bilateral knee radiographs taken by radiographic technicians at military treatment facilities who followed a standardized image acquisition protocol using fixed-flexion knee positioning. All images were digitally transferred to a single, highly-experienced musculoskeletal radiologist reader (JBR). Radiographic OA was defined as Kellgren-Lawrence grade 2 or greater. Injury status was established using a standardized questionnaire (first surveys completed between 08/15/15 and 12/13/17; all injuries were verified by clinical record review).

Results: Mean age was 27.7 years (injured: 27.7 years; non-injured 27.7 years) and 38% were women (injured: 34%; non-injured: 42%). Mean weight was 77.4 kg and body mass index was 25.1 kg/m². Mean time from first knee ligament and/or meniscal injury ("knee injury" hereafter) to radiographic assessment was 8.8 years. Officers with a history of knee injury had a greater prevalence of radiographic OA (16.5%) than injury-free officers (0.0%, $p<0.001$). Officers with knee injury were more likely to have osteophytes (40.9% vs. 7.0%, $p<0.001$) and joint space narrowing (22.6% vs. 0.9%, $p<0.001$). Surprisingly, OA prevalence was only weakly related to timing of injury. Specifically, prevalence differences (PDs, injury-free as reference) were similar for those who sustained their first knee injury at high school age (PD=14%, 95%CI: -2%, 31%), collegiate age (PD=20%, 95%CI: 3%, 36%), and post college graduation (PD=13%, 95%CI: -13%, 38%). Similar PDs were obtained from sub-analyses of the unilateral injury subgroup using non-injured limbs (rather than non-injured people) as the reference category.

Conclusion: Nearly 1 out of every 5 officers with knee injury progresses to radiographic OA before age 30. This progression rate may reflect the physically-demanding nature of their occupation. We observed no relationship to timing of injury, suggesting that these "early-progressors" react quickly to the physical insults of knee trauma and surgery.

Disclosure: Y. M. Golightly, None; M. Nocera, None; A. I. Beutler, None; J. B. Renner, None; A. Guermazi, MerckSerono, 5, Genzyme, 5, AstraZeneca, 5, TissueGene, 5, OrthoTrophix, 5, Boston Imaging Core Lab (BICL), LLC, 9; J. Cantrell, None; D. A. Padua, None; K. L. Cameron, None; S. J. Svoboda, None; J. M. Jordan, None; R. Loeser, None; L. F. Callahan, Lilly, 5; V. B. Kraus, None; L. S. Lohmander, None; S. W. Marshall, None.

Standing Balance and Walking Time Among Older Adults with and without Joint Hypermobility: The Johnston County Osteoarthritis Project

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II – ARHP

Session Type: ACR Poster Session B

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

Background/Purpose: Physical function and balance often decline in older adults, and joint hypermobility, a condition in which joint range of motion is greater than normal, may be related to impaired physical function and balance. This cross-sectional study examined the association of joint hypermobility with measures of lower extremity function (standing balance and walking time) in a community-based cohort of older adults.

Methods: Data were collected during 2003-2010 from Johnston County Osteoarthritis Project participants. The Beighton criteria were used to assess hypermobility at nine body sites: the trunk and bilaterally for the first and fifth fingers, elbows, and knees. General joint hypermobility (GJH) was defined as a Beighton score ≥ 4 (range 0-9). Knee hypermobility was defined as hyperextension of at least one knee, and trunk hypermobility was defined as the ability to place one's palms on floor during forward trunk flexion with knees extended. Physical function outcomes were: 8-foot walk (unable to do or ≥ 3.5 seconds [s] vs. < 3.5 s), standing balance (full tandem unable to do or < 10 s vs. $10+$ s), and functional reach test (< 28.0 cm vs. ≥ 28.0 cm). Separate logistic regression models were used to estimate associations between joint hypermobility and physical function, adjusting for age, body mass index (BMI), sex, race (African American vs. White), self-reported physical activity from standard questionnaire (≥ 150 vs. < 150 minutes moderate physical activity per week), and presence/absence of symptomatic osteoarthritis (sxOA) separately at the knee and hip.

Results: Data were available for 1695 participants (6.5% with GJH, mean age 69 years, mean BMI 31 kg/m^2 , 67% women, 31% African American, 38% achieving ≥ 150 minutes of moderate physical activity per week, 23% knee sxOA, 127% hip sxOA). In unadjusted analyses, presence of GJH was associated with the better-performing groups for tandem stance time and 8-foot walk time, but associations were no longer statistically significant in adjusted models (see Table). Knee hypermobility models, both unadjusted and adjusted, showed no statistically significant differences in physical function measures. Crude models of trunk hypermobility were associated with better functional reach and 8-foot walk time, but results were attenuated and not statistically significant after adjusting for covariates.

Conclusion: While unadjusted models indicated associations of GJH with balance and walk-time, once covariates were taken into account, particularly age, the associations were attenuated. Trunk hypermobility (signifying increased hamstring flexibility) may be a marker of better lower body physical function and balance. Prospective studies may determine how the presence or absence of joint hypermobility relates to physical function and balance over time.

Table. Associations of Physical Function Measure and Joint Hypermobility.

Physical Function Measure	General Joint Hypermobility		Knee Hypermobility		Trunk Hypermobility	
	OR (95% CI)	aOR* (95% CI)	OR (95% CI)	aOR* (95% CI)	OR (95% CI)	aOR* (95% CI)
Functional Reach Test	1.53 (0.94, 2.51)	1.07 (0.63, 1.82)	0.99 (0.53, 1.85)	0.78 (0.40, 1.52)	1.83 (1.00, 3.34)	1.50 (0.78, 2.90)
Tandem Stance time	1.80 (1.13, 2.86)	1.51 (0.90, 2.53)	1.05 (0.60, 1.82)	0.91 (0.50, 1.68)	1.56 (0.96, 2.55)	1.18 (0.67, 2.02)
8-foot walk time	1.62 (1.09, 2.41)	1.36 (0.86, 2.17)	0.88 (0.53, 1.48)	0.76 (0.43, 1.40)	1.73 (1.12, 2.68)	1.43 (0.86, 2.38)

odds ratio = OR (> 1.0 indicates better physical function), adjusted odds ratio = aOR, 95% confidence interval = 95% CI

* adjusted for age, BMI, sex, race, self-reported physical activity, symptomatic knee or hip osteoarthritis

Disclosure: J. Hankins, None; C. Hill, None; M. T. Hannan, None; H. J. Hillstrom, None; A. P. Goode, None; Y. M. Golightly, None.

Patterns of Depressive Symptoms before and after Surgery for Hip, Knee and Lumbar Spine Osteoarthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II – ARHP

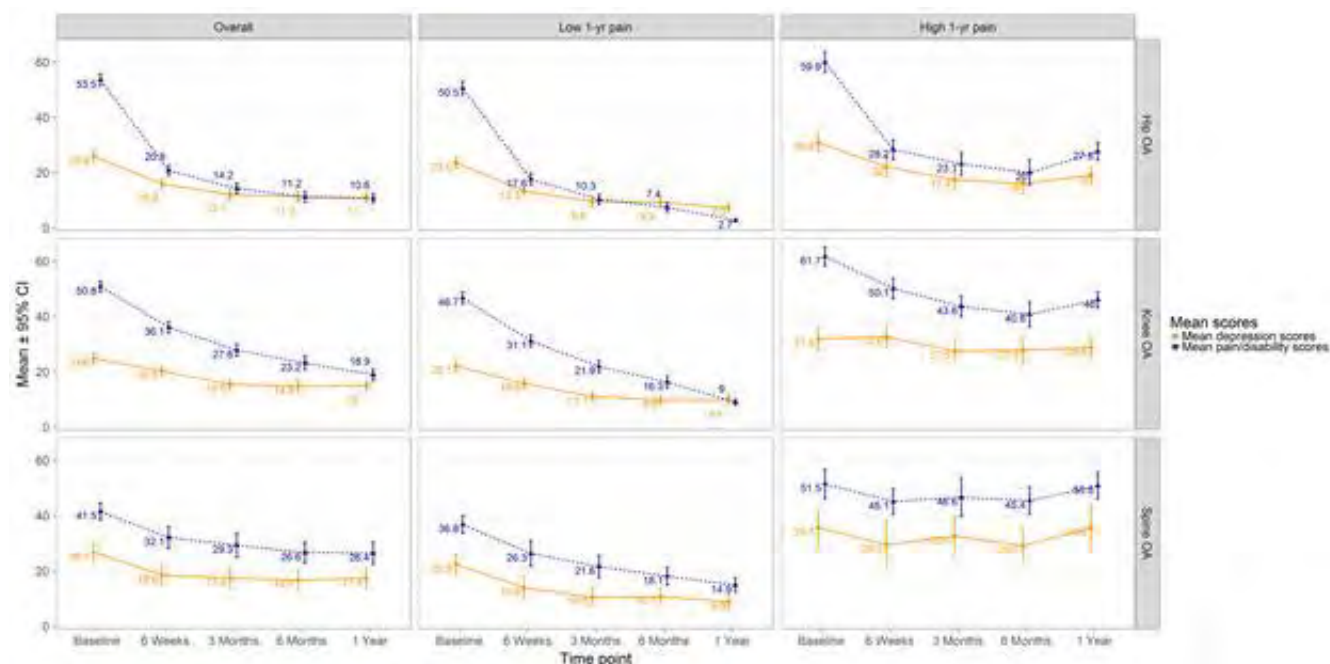
Session Type: ACR Poster Session B

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

Background/Purpose: Although pain and decreased function are the primary symptom targets of OA surgeries, OA is also associated with depression. The impact of surgery on depressive symptoms is not clear. Further, since 20% or more of patients report residual pain post-surgery, and pain and depression are closely linked, the impact of surgery on depression may vary dependent on pain-related outcomes. The objective our study was to examine patterns of depressive symptoms before and over the year following OA surgery, stratified by 1-year post-surgical outcome and surgical joint. We also examined patterns of patient reported depression diagnoses and treatment.

Methods: Participants were 747 patients with hip (n=287), knee (n=360) and lumbar spine (n=100) OAscheduled for joint replacement or decompression surgery +/- fusion. One pre- and 4 post-surgery questionnaires were completed. Depressive symptoms were quantified using the Hospital Anxiety and Depression Scale (HADS). Pain was measured using the WOMAC pain subscale for hip and knee patients. Oswestry Disability Index (ODI) measured disability due to low back pain for spine patients. One-year pain-related outcomes were categorized as 'high' (worse) (top pain/disability tertile) vs. 'low' (2 lower pain/disability tertiles). Based on the 5 study time points, 2 sets of plots were generated stratified by 1-year outcome and surgical joint: 1) mean pain/disability and depressive symptom scores; 2) percentage of patients meeting the HADS cut-off for 'caseness' of depression, reporting depression, and reporting current treatment for depression.

Results: Post-surgical changes in mean depression scores varied by joint and 1-year outcome groups. There were notable decreases in depression scores for patients with better pain outcomes across all joint groups. However, for those with poorer outcomes, decreases were smaller for hip and particularly knee patients, and no change was observed among spine patients (Figure). Among those with poorer outcomes, 25% of spine and knee patients were depression 'cases' pre- and post-surgery; an additional 16% of spine and 10% of knee patients developed new depression 'caseness' post-surgically. The proportion of these knee and spine patients deemed depression 'cases' by symptom score was much higher than the proportion reporting depression diagnosis/treatment.



Conclusion: Although depressive symptoms decrease overall in OA patients post-surgery, patterns and degrees of change vary by joint and surgical outcome. Findings support that greater attention to mental health pre- and post-surgery is warranted, particularly among knee and spine patients. Given the close interrelationship of pain and depression, appropriate assessment and treatment of depression in OA patients may lead to decreases in post-surgical pain and improved surgical outcomes, in addition to better overall quality of life.

Disclosure: J. D. Power, None; P. Kudesia, None; A. Nadeem, None; A. V. Perruccio, None; Y. R. Rampersaud, None; N. Mahomed, None; R. Gandhi, None.

Abstract Number: 1164

Canadians' Views about Using Big Data in Health Research from a National Online Survey: A Partnership of Patient-Consumers and Researchers

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II – ARHP

Session Type: ACR Poster Session B

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

Background/Purpose: Findings from health research using “big data” (large sets of routinely-collected healthcare data) have benefitted individual arthritis patients and society as-a-whole. However, growing public concerns about personal information being accessed for unintended purposes could erode trust in this research and its potential benefits. We conducted this study to elucidate the public's views on the role of big data in health research.

Methods: This was a partnership between researchers at Arthritis Research Canada and consumer-patient leaders from three joint and skin disease patient organizations. We developed an online survey assessing: 1) Perceptions about the role of big data in health research and access and privacy controls, 2) Willingness to participate in projects using big data, 3) Major concerns, and 4) Interest in learning more. Respondents were recruited via the websites, e-mail lists, and social media channels of Canadian health research groups, including the three patient organisations.

Survey: Our three-part, ~20-min. survey was open from Jan-Aug 2017. Part 1 asked about respondents' familiarity and initial perceptions about using big data in health research. In Part 2 they were provided with some background information, and then asked their views on specific topics (i.e. benefits of using big data, data access and privacy). In Part 3 respondents were queried further about their perceptions of big data and ongoing educational needs.

Analysis: For each question, we calculated the percentage of respondents selecting each response option.

Results: 151 individuals completed the survey (117=77% female; 47% aged 50-69 years, 28% aged 30-49 years). 101 (67%) had chronic disease.

At the start of the survey (Part 1), 79% of respondents felt positively about the use of big data for health research and 95% knew the term “electronic health/medical record”, but only 58% knew the terms “administrative data/health database”. In Part 2, respondents felt the ability to study large numbers of people (selected by 73%) and long-term effects and rare events (76%) were the top benefits of using big data; long-term treatment effects and disease complications were the most important research topics (see Table).

59% felt the use of big data should be approved by university research ethics boards, and 67% wanted to learn more about how data stewards grant access to data. De-identifying personal information was the most important privacy measure (selected by 89%).

At the end of the survey (after viewing background information about big data), 93% felt positively about big data (vs. 79% at the start), but only 58% were confident about privacy and security measures in place.

Conclusion: While ethics board approvals and de-identification of healthcare data were highly regarded, more public education, especially about data access and privacy controls, may enhance public trust about using big data in health research.

Table: Percentage of Respondents Selecting Each Feature and Data Access/Privacy Measure Described in Part 2 of the Survey (Most- to Least-Frequently Selected)

Advantages of Using Big Data for Health Research								
Most Important <i>(select up to 3)</i>	1. Long-Term Effects and Rare Events	2. Large Numbers	3. Study Potentially-Harmful Treatments	4. General Population Comparisons	5. More Inclusive			
	75.5%	72.8%	50.3%	46.4%	43.0%			
Want Additional Information About <i>(select up to 3)</i>	1. Study Potentially-Harmful Treatments	2. Long-Term Effects and Rare Events	3. Large Numbers	4. General Population Comparisons	5. More Inclusive			
	64.2%	63.6%	44.4%	41.7%	35.1%			
Health Research Questions to Study Using Big Data								
Most Important <i>(select up to 3)</i>	1. Treatment Benefits	2. Treatment Harms	3. Disease Complications	4. Changes in Policy or Practice	5. Quality of Care	6. Cost-Effectiveness	7. Risk Factors for Disease	8. Disease Incidence and Prevalence
	55.6%	55.0%	52.3%	43.7%	30.5%	27.8%	23.2%	9.9%
Data Access Controls								
Most Important <i>(select up to 2)</i>	1. Must Apply for Data Access	2. Approval from Research Ethics Board	3. Approval from Data Stewards	4. Access Data for Limited Time				
	62.3%	58.9%	51.0%	20.5%				
Want Additional Information About <i>(select up to 2)</i>	1. Approval from Data Stewards	2. Approval from Research Ethics Board	3. Access Data for Limited Time	4. Must Apply for Data Access				
	66.9%	46.4%	29.8%	25.2%				
Privacy and Security Controls								
Most Important <i>(select up to 3)</i>	1. Data are De-Identified	2. Privacy Training and	Confidentiality Agreement	3. Review of Research Outputs	4. Funding Agencies Cannot Access Data	5. No Access Outside Canada		
	89.4%	57.6%	43.7%	35.8%	35.1%			

Expressed as the percentage selecting each response option; as multiple responses could be selected, the sum of percentage-frequencies exceeds 100%

Disclosure: N. McCormick, None; C. Hamilton, None; C. L. Koehn, None; K. English, None; A. Stordy, None; L. Li, None.

Abstract Number: 1165

Restless Sleep Trajectories over 8 Years: Data from the Osteoarthritis Initiative

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II – ARHP

Session Type: ACR Poster Session B

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

Background/Purpose: Sleep disturbance has been recognized as a major public health issue. Evidence has shown that individuals with osteoarthritis (OA) are more likely to have disturbed sleep. However, it is unknown if distinctive patterns of sleep disturbance over time exist among adults with OA. The purpose of this study is to examine trajectories of restless sleep in adults with or at high risk for knee OA and to identify modifiable risk factors associated with these trajectories.

Methods: We analyzed baseline to 8-year data from Osteoarthritis Initiative. Restless sleep was identified annually as self-report of 3 or more nights of restless sleep during the past week. Group-based modeling (PROC TRAJ) was conducted to identify homogeneous clusters of restless sleep trajectories over 8 years. Baseline descriptive (age, sex, race, education, BMI, Kellgren-Lawrence grade, chronic knee symptoms, prior knee injury) and potentially modifiable (cardiovascular disease, high depressive symptoms, pulmonary disease, bodily pain interference, smoking, WOMAC function, gait speed, PASE physical activity) factors were examined using multiple logistic regression to identify predictors for membership in restless sleep trajectories.

Results: Four distinct restless sleep trajectories (Figure) were identified from the 4290 participants (mean age 61.1 years [SD 9.1], 58% women, mean BMI 28.5 kg/m² [SD 4.8]): good - persistently low (11.4%), worsening - low to high (66.4%),

poor - persistently high (9.5%), improving - high to low (12.7%) probabilities of restless sleep. Compared to the good group, individuals with worsening probabilities for restless sleep were more likely to report at baseline high depressive symptoms (odds ratio [OR]=2.04, 95% confidence interval [CI]=1.37, 3.05), pain in non-knee joints (OR=1.63, 95% CI=1.17, 2.26), smoking (OR=1.61, 95% CI=1.05, 2.47), and pulmonary disease (OR=1.46, 95% CI=1.06, 2.02), and were less likely to report physical activity scores above the median (OR=0.77, 95% CI=0.61, 0.96), adjusting for descriptive and other modifiable risk factors. Compared to the poor group, those who improved by reducing restless sleep probabilities were less likely to have baseline high depressive symptoms (OR=0.56, 95% CI=0.39, 0.81).

Conclusion: We identified four distinctive restless sleep trajectories among people with or at high risk of knee OA. Baseline factors including less physical activity, high depressive symptoms, pain in other joints, smoking, and pulmonary disease independently predicted a worsening probability trajectory of restless sleep. Future interventions may want to target these factors to address sleep quality.

Disclosure: J. Song, None; J. Lee, None; Y. C. Lee, Pfizer, Inc., 2, Pfizer, Inc., 2, Eli Lilly and Co., 6, Eli Lilly and Co., 6; A. H. Chang, None; P. Semanik, None; L. S. Ehrlich-Jones, None; R. W. Chang, None; D. D. Dunlop, None.

Abstract Number: 1166

Friend or Foe: Does Walking at Higher Intensities Increase or Decrease the Risk of Total Knee Arthroplasty over Five Years?

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

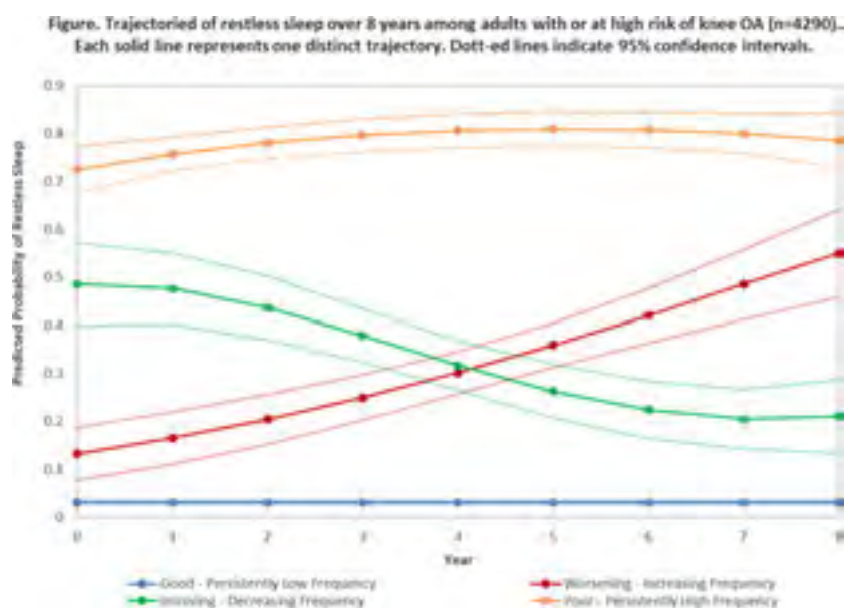
Session Title: Epidemiology and Public Health Poster II – ARHP

Session Type: ACR Poster Session B

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

Background/Purpose: There is contradicting evidence whether walking more is associated with structural worsening and total knee arthroplasty (TKA). One reason for inconsistent findings is that walking can occur at different intensities. However, little is known about the association of walking intensity with the risk of TKA. The purpose of this study was to examine the extent to which walking intensity is associated with the risk of TKA over five years in adults with or at high risk of knee OA.

Methods: Using data from the Osteoarthritis Initiative (OAI), we included participants who did not have TKA at or before the 48-month follow-up visit, which we considered our study baseline. Time spent in different walking intensities was quantified by step cadence recorded by an accelerometer (Actigraph GT1M). We defined <1 step/min as non-walking,



1-49 steps/min as very-light, 50-100 steps/min as light, and >100 steps/min as moderate-to-vigorous intensities of walking. Time to TKA was quantified in months from the baseline visit date to TKA date if received in the subsequent five years, i.e., until the 108-month OAI visit. Participants without TKA at the 108-month OAI visit or lost to follow-up were censored. We examined effects of replacing time not walking with walking at very-light, light, or moderate-to-vigorous intensities with the risk of TKA over five years using temporal substitution within a Cox proportional hazard model. Specifically, we calculated hazard ratios (HR) and 95% confidence interval (CI) adjusted for potential confounders. We repeated analyses restricting our sample to participants with radiographic (ROA) and symptomatic (SxOA) knee OA (see Table).

Results: Of the 1854 participants without TKA at baseline and who wore the accelerometer for ≥ 4 days ([mean \pm sd] age: 65.0 ± 9.1 years, BMI: 28.4 ± 4.8 kg/m², 55% female), 108 (6%) participants received a TKA over five years. Replacing 5 minutes of non-walking time with 5 min of walking at moderate-to-vigorous intensity reduced the risk of TKA by 16% (HR 0.84, 95% CI [0.72, 0.98]). There was no effect for very-light and light intensity. We found similar results for ROA and SxOA only samples (see Table).

Conclusion: Replacing time not walking with walking at moderate-to-vigorous intensity was associated with not more but less risk of TKA over five years. Our findings suggest that small changes in walking behavior could delay the need for TKA in people with or at high risk of knee OA.

Disclosure: H. Master, None; L. Thoma, None; M. Christiansen, None; D. Mathews, None; E. Macri, None; M. Ziegler, None; J. J. Stefanik, None; D. White, None.

Abstract Number: 1167

The Role of Fear-Avoidance Model on Pain and Disability in Knee Osteoarthritis Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II – ARHP

Session Type: ACR Poster Session B

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

Background/Purpose: The model of Fear-Avoidance of pain (anxiety, catastrophization and hypervigilance) appears when the pain has maladaptive interpretations, being associated with greater pain and limitations of the activity. Our purpose was to determine the influence of the Fear-Avoidance model in the levels of pain and disability in knee osteoarthritis patients.

Methods: Patients diagnosed with knee osteoarthritis in the last year of our outpatient clinic who gave their consent completed the evaluation battery and performed the experimental task of hypervigilance. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to assess pain, stiffness and function of the patient. The variable pain anxiety was measured by the Pain Anxiety Symptoms Scale (PASS-20), *catastrophization* by the Pain Catastrophizing Scale (PCS), and hypervigilance with an attention task (dot-probe) using E-Prime Software. Secondary variables as sociodemographic (age, sex, work status), clinical (previous knee surgeries and radiological damage with the Kellgren-Lawrence scale [KL] and treatment (analgesic drugs) were also recorded. Descriptive, bivariate and linear regression models (adjusted by secondary variables) were performed to determine the variables of the Fear-Avoidance model associated with pain and disability.

Results: A total of 33 patients with knee osteoarthritis were included in the study. 70% were women with a mean age of 77.4 ± 10.3 years. 8.5% had previous surgeries. 27.5% were active workers, 44.8% were retired and 25.5% housewives. 82% were on non-opioid drugs, and 11.4% weak opioids. Radiographic disease severity was 51.8% early stage (K/L <2), 48.2% advanced-stage (K/L >2). In bivariate analyses, for global WOMAC, pain anxiety, *catastrophization*, and work status (active worker) were founded as predictors. For the pain subscale, pain anxiety and age result statistical significant. Finally for physical function subscale pain anxiety *catastrophization* and work status (active worker) were founded predictors. Regression models adjusted for secondary variables, included all variables that showed significant differences or trend ($p=0.1$) in the bivariate. In multivariate models, for global WOMAC, the pain anxiety achieved signification ($p=0.005$). For the pain subscale, active work status was founded a predictor ($p=0.04$), with a tendency for pain anxiety ($p=0.06$). For

the physical function subscale, pain anxiety was significant ($p=0.002$).Hypervigilance showed a tendency to increase the stiffness ($p=0.05$) and worsen the physical function ($p=0.1$) and the global WOMAC ($p=0.1$).

Conclusion: Variables that integrate the Fear-Avoidance model were the main predictors of the total WOMAC and its subscale, together with the active work status in the pain scale. Identifying these variables in knee osteoarthritis patients will allow us to explain the high levels of pain or disability in patients, which sometimes do not correlate with their damage or injury, and can complicate the prognosis or evolution.

Disclosure: L. Leon, None; M. Redondo, None; S. Lopez de Felipe, None; D. Garriguez, None; L. A. Alcazar, None; L. Rodriguez-Rodriguez, None.

Abstract Number: 1168

Is a Change in Physical Activity Associated with a Change in Health-Related Quality of Life after Total Knee Replacement?

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II – ARHP

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Background/Purpose: Health-related quality of life (HRQoL) is the impact health status has on quality of life. The ability to maintain or increase physical activity (PA) is important for the physical domain of HRQoL in older adults. However, little is known about this relationship for people after TKR, who often elect to have surgery due to decline in HRQoL. As well, this association may differ for younger vs. older adults since also HRQoL declines with age. Therefore, the purpose of this study was to examine the association of a change PA at least 1-year prior to TKR to 1-year after TKR stratified by older and younger adults with a change in HRQoL after TKR.

Methods: We used data from the Osteoarthritis Initiative (OAI) and included participants who had a TKR after enrolling in the study. The exposure was change in self-reported PA at least 1-year before or after TKR. We quantified PA using established categories from the Physical Activity Scale for the Older (PASE) as Low PA ≤ 94 , Moderate PA 95-146, High PA 147-206, Very High PA ≥ 207 . Next we classified study participants who stayed in the same category or went up one more PA levels as Increased/Maintained PA, and those who went down one level as Decreased PA. We stratified by the median age of 68 to classify older and younger adults. Our primary outcome was a change in HRQoL before TKR to after TKR which was quantified using 12-item Short Form Survey Physical Component Summary (PCS). We dichotomized PCS scores using the minimal clinically important difference of 2; < -2 Decline HRQoL and ≥ -2 Maintained HRQoL. We

	Incident TKA n (%)	Adjusted HR (95%CI) ^a
Overall sample (N=1854)	188 (6)	
Replacing 5 mins not walking with 5 mins walking at:		
very-light intensity		1.00 (0.99, 1.02)
light intensity		1.00 (0.93, 1.10)
moderate-to-vigorous intensity		0.84 (0.72, 0.98)
Sub-sample with ROA^b (N=1129)	101 (9)	
Replacing 5 mins not walking with 5 mins walking at:		
very-light intensity		1.00 (0.99, 1.02)
light intensity		1.01 (0.93, 1.10)
moderate-to-vigorous intensity		0.83 (0.70, 0.97)
Sub-sample with SaOA^c (N=488)	80 (16)	
Replacing 5 mins not walking with 5 mins walking at:		
very-light intensity		0.99 (0.98, 1.01)
light intensity		1.05 (0.96, 1.15)
moderate-to-vigorous intensity		0.86 (0.73, 1.01)

^a Adjusted for age (continuous), sex, race, BMI, and self-reported TKA, osteoarthritis, pain, the presence of OOA, joint, or immobilization, and previous knee surgery.

^b ROA was defined as participants with Kellgren and Lawrence grade ≥ 1 in every knee joint.

^c SaOA was defined as participants with OOA and pain, lasting or affecting at least days of a month during the previous year.

Table: Adjusted odds ratios and 95% confidence intervals for Decline in HRQoL		
	Equivalent Decline in HRQoL, n (%)	*Adjusted OR (95%CI)
< 65 years of age		
Decreased PA (n=35)	7 (21.1)	1.0 (REFERENCE)
Increased/Maintained PA (n=71)	15 (21.1)	0.79 (0.29-2.7)
≥ 65 years of age		
Decreased PA (n=37)	13 (35.1)	1.0 (REFERENCE)
Increased/Maintained PA (n=78)	12 (15.1)	0.28 (0.10-0.82)
*Adjusted for baseline age, BMI, sex (sex=other), race (race=other), education (education=other), income (income=other), marital status (marital status=other), smoking (smoking=other), comorbidity (comorbidity=other), depression (depression=other), knee pain (knee pain=other) and 12-item SF-36 (SF-36=other) (n=4486).		
95% CI = 95% confidence interval.		

calculated odds ratios and 95% confidence intervals (95%CI) to examine the association between change in PA with a change HRQoL in older and younger adults adjusted for age, body mass index (BMI), sex, race, education, income, marital status, smoking status, comorbidity, depression, and knee pain (Table).

Results: Of the 421 participants who had unilateral or bilateral TKR since enrollment, 220 participants had complete PASE and PCS data (61% female, age 64 ± 8 years, BMI 29.9 ± 4.8 kg/m²). Older adults who Increased/Maintained PA after TKR had 71% (0.29-0.82) less risk of a Decline in HRQoL compared to those who Decreased PA after TKR (Table). Change in PA was not associated with HRQoL in younger adults (Table).

Conclusion: Decreasing PA after TKR may be an important risk factor for older adults, who already engage in less PA than younger adults. Increasing and/or maintaining PA after TKR may protect against a decline in HRQoL in older adults.

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Abstract Number: 1169

Association between Depressive Symptom Subtypes and Disease Severity in Knee Osteoarthritis

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SESSION INFORMATION

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Background/Purpose: Latent and modifiable factors, such as depressive symptoms, may affect the course of knee OA. Depression is clinically heterogeneous, and effects on pain and disability may manifest differently by depressive symptom subtypes. This study evaluated trajectories of pain and disability by depressive symptom subtypes among individuals who have or are at risk for knee OA.

Methods: Participants (n=4486) were reenrolled in the Osteoarthritis Initiative. Latent class analysis was applied to the 20-Item Center for Epidemiological Studies Depression Scale measured at baseline and used to assign participants to one of four depressive symptom subtypes identified previously (“No Symptoms”, “Catatonic”, “Anhedonic”, and “Melancholic”). OA disease severity was assessed annually over four years using the pain and disability subscales (rescaled range = 0-100) of the WOMAC. Analyses were stratified by those with (n=1626) and without (n=2860) symptomatic knee OA at baseline, defined as pain on most days of a month in the past 12 months. Propensity score weights were used to balance the four depressive symptom subtypes on baseline confounders: age, sex, race, education, smoking status, alcohol consumption, health insurance, employment status, BMI, Kellgren-Lawrence grade, history of knee injury, analgesic use, and total WOMAC score. Non-response weights were computed with logistic regression and were used to account for missing data. Weighted estimating equations were used to estimate pain and disability trajectories and to evaluate between-group differences in disease severity by baseline depressive symptom subtype during the follow-up period.

Results: Among participants with symptomatic knee OA, the “Melancholic” depressive symptom subtype had more severe pain ($\beta=3.61$; 95% CI: -0.15, 7.39; $P=0.060$) and significantly greater disability ($\beta=5.36$; 95% CI: 1.41, 9.32; $P=0.007$) than the “No Symptoms” subtype (Table 1). In individuals without symptomatic knee OA, the “Anhedonic” subtype had significantly worse pain ($\beta=1.33$; 95% CI: 0.20, 2.47; $P=0.020$) and disability ($\beta=1.34$; 95% CI: 0.27, 2.42; $P=0.014$) compared to the “No Symptoms” subtype (Table 1). Differences in pain and disability between the “Catatonic” and “No Symptoms” subtypes were small and not statistically significant in both participants with and without symptomatic knee OA.

Conclusion: Findings indicate that the effects of depressive symptoms on pain and disability are largest in persons with symptomatic knee OA who exhibit “Melancholic” symptom logy. “Melancholic” depressive symptoms are characterized by the inability to feel pleasure, decreased energy and movement, and somatic complaints; and thus, may be a modifiable risk factor for worsening disease severity and potential target for intervention in patients with symptomatic knee OA.

Table 1. Differences in pain and disability by baseline depressive symptom subtype among Osteoarthritis Initiative participants with (n=1626) and without (n=2860) symptomatic knee OA over four years of follow-up.

Depressive Symptom Subtype	Pain			Disability		
	β	95% CI	P Value	β	95% CI	P Value
Symptomatic OA						
<i>No Symptoms</i>	REF	REF	REF	REF	REF	REF
<i>Catatonic</i>	-0.09	-3.10, 2.91	0.950	0.10	-2.87, 3.07	0.945
<i>Anhedonic</i>	0.19	-2.11, 2.51	0.867	0.42	-1.79, 2.65	0.705
<i>Melancholic</i>	3.61	-0.15, 7.39	0.060	5.36	1.41, 9.32	0.007
Non-symptomatic OA	β	95% CI	P Value	β	95% CI	P Value
<i>No Symptoms</i>	REF	REF	REF	REF	REF	REF
<i>Catatonic</i>	0.76	-0.81, 2.34	0.340	0.11	-1.13, 1.35	0.862
<i>Anhedonic</i>	1.33	0.20, 2.47	0.020	1.34	0.27, 2.42	0.014
<i>Melancholic</i>	1.30	-1.08, 3.69	0.284	1.83	-0.48, 4.15	0.120

Disclosure: A. Rathbun, None; M. Schuler, None; E. Stuart, None; M. Shardell, None; M. S. Yau, None; J. Gallo, None; M. C. Hochberg, Bioberica, 5,EMD Serono, 5,Novartis Pharma AG, 5,Plexxikon, 5,Pfizer, Inc., 5,Proximagen, 5,Regeneron, 5,Samumed, LLC, 5,Theralogix LLC, 5.

Abstract Number: 1170

Sex-Specific Associations between Systemic Inflammatory Cytokines and Osteoarthritis Knee Pain

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health Poster II – ARHP

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Background/Purpose: Significant challenges remain in mitigating OA pain and despite growing evidence of sex differences, including in pain and in response to NSAIDs, sex has received little attention in clinical studies of potential OA drug treatment strategies. In this study, we investigated the association between knee-specific OA pain and systemic markers of inflammation, focusing on whether associations differed by sex.

Methods: Study participants were 231 patients with knee OA scheduled for total joint arthroplasty at a tertiary care hospital in Toronto, Canada. Eligibility: 35+ years of age; English fluency. Exclusions: acute trauma/injury or inflammatory arthritides. Health questionnaires were completed and blood samples drawn in-clinic prior to surgery. Questionnaires collected data on knee pain (WOMAC pain subscale) and sex, age, height and weight (used for BMI calculation), comorbidity, depressive symptoms (HADS depression scale), symptomatic joint count, and pain medication use. Blood cytokine analyses included IL-6, -8, -10, -1 β and TNF- α using Luminex bead-based ELISA assays. A series of linear regression models were estimated with knee pain as the outcome. The final model included sex, age, BMI, comorbidity count, depressive symptom score, symptomatic joint count, log-transformed cytokine concentrations, and interaction terms between sex and any factors found to have sex-specific influences. Sensitivity analyses: final model a) in individuals aged 55+ only (age-based proxy for post-menopausal status) and b) with consideration for medication use.

Results: Participants were of mean age 65 years (range 43-89); women comprised 57.6% of the sample. Women had higher comorbidity and joint counts, and worse depressive symptoms and knee pain scores than men. No sex differences were found in median cytokine concentrations, except for higher TNF- α in men (8.1 vs. 6.9 pg/ml; $p=0.006$). In adjusted linear regression, initially not allowing for sex-specific effects, only 2 cytokines were significantly associated with knee pain scores; higher IL-10 with lower pain ($p=0.002$), and higher TNF- α with worse pain ($p=0.031$). With consideration of potential sex-specific effects, the association between knee pain and IL-10 and TNF- α remained unchanged and was similar for women and men. However, the association between knee pain and IL-8 (interaction term $p<0.001$), IL-6 (interaction term $p=0.023$) and IL-1 β (interaction term $p=0.047$) differed significantly between women and men. In addition, higher BMI for men, and higher depressive symptoms and joint count for both sexes were significantly associated with worse knee pain scores. Findings from sensitivity analyses were consistent with primary analyses.

Conclusion: While cytokine-targeted treatments exist, indiscriminate use in OA populations may limit effectiveness. Our findings provide evidence of sex-specific associations between individual inflammatory cytokines and knee OA pain, and suggest that sex-specific targets of anti-inflammatory treatments for OA need to be considered.

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Abstract Number: 1171

Mortality Among Those with OA: Time-Varying Effects of Socioeconomic Measures

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Background/Purpose: Measures of socioeconomic status (SES) have been shown to be associated with increased OA and disability. However, it is unknown whether changes in SES measures over time can predict death. We therefore examined whether SES measured over time was associated with death among those with radiographic OA (rOA).

Methods: We analyzed data from 2,605 participants in a community-based cohort of African American (AA) and Caucasian men and women aged ≥ 45 years. Participants completed assessments at baseline and up to 3 follow-ups and all had rOA, defined as Kellgren-Lawrence grade ≥ 2 in at least one knee/hip. SES measures were 1) high school (HS) education ($< \text{HS diploma}$ vs. $\geq \text{HS diploma}$), 2) professional occupation (PRO) (non-PRO vs. PRO), and 3) block group poverty (BGP) ($\geq 20\%$ BGP vs. $< 20\%$ BGP). Date of death was assessed through December 31, 2015. Comorbidities and demographic characteristics were considered as covariates (see Table legend). Multiple imputation was used to impute missing values of covariates. Follow-up time was calculated from baseline until death or censoring which took place when a participant was lost to follow-up or reached the end of study period. Cox proportional hazards regression with time-varying covariates (TVC) changing at irregular intervals was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality. In the TVC analysis, SES and covariates were allowed to change from “unexposed” to “exposed” from prior assessments to ensure HRs accurately represent the risk of mortality as one’s SES and covariate status changed. Additional analyses stratified by sex, race and age were carried out.

Results: Mean age at baseline was 65.4 years, with 64.0% women and 34.1% AA. Overall, 37.7% had $< \text{HS}$ education, 41.3% lived in areas with $\geq 20\%$ BGP, and 61.0% had a non-PRO occupation. Through 2015 there were 1,154 deaths (44.0%), and median follow-up time was 10.2 years.

In covariate adjusted models where individual SES measures were considered, we observed an increased risk of all-cause mortality in participants with $< \text{HS}$ education (HR=1.30, 95% CI=1.15-1.48) and non-PRO occupation (HR=1.21, 95% CI=1.06-1.39) (Table). However, when all SES measures were considered simultaneously, only $< \text{HS}$ education remained associated with death (HR=1.25, 95% CI=1.09-1.43). In stratified analyses, the observed association with education was restricted to women. Living in an area with high BGP appeared to be a predictor of mortality among Caucasians only.

Table. Hazard ratios for the association between SES measures and all-cause mortality

	<HS Education HR (95% CI)	Non-professional Occupation HR (95% CI)	Block Group Poverty ≥20% HR (95% CI)
Overall			
Single SES measure‡	1.30 (1.15-1.48)	1.20 (1.04-1.38)	1.13 (0.99-1.28)
All SES measures§	1.25 (1.09-1.43)	1.12 (0.95-1.28)	1.10 (0.97-1.26)
Stratified			
Men§	1.07 (0.86-1.33)	1.25 (0.99-1.58)	1.18 (0.96-1.44)
Women§	1.40 (1.17-1.67)	1.02 (0.84-1.25)	1.09 (0.92-1.29)
African American§	1.33 (1.05-1.69)	1.05 (0.78-1.42)	0.98 (0.79-1.22)
Caucasian§	1.20 (1.02-1.43)	1.13 (0.95-1.35)	1.17 (1.00-1.37)
Age <65 years§	1.39 (1.05-1.84)	1.15 (0.82-1.60)	1.27 (0.97-1.66)
Age ≥65 years§	1.21 (1.03-1.42)	1.10 (0.93-1.30)	1.05 (0.91-1.22)

‡ Adjusted for age, sex, race, birth cohort, enrollment wave, ever alcohol drinker, ever smoker, obesity, physical activity, cancer, liver, CVD, diabetes, high blood pressure, depressive symptoms, NSAIDs

§ Additionally adjusted for other SES measures

Conclusion: As noted in other chronic conditions, we demonstrated increased mortality among individuals with knee or hip OA with low education, particularly among women. Our results were independent of other comorbidities and demographic measures linked to increased mortality. Individuals with OA and lower education may represent a high risk group in need of more focused clinical care and resource allocation.

Disclosure: B. Cleveland, None; T. Schwartz, None; A. Nelson, None; J. B. Renner, None; J. M. Jordan, None; L. F. Callahan, Lilly, 5.

Abstract Number: 1172

Symptoms Compatible with Osteoarthritis and Self-Reported Osteoarthritis in the Population: Findings from the Canadian Longitudinal Study on Aging

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Background/Purpose: To report on the prevalence of self-reported doctor-diagnosed knee, hip and hand osteoarthritis (OA) in the population aged 45-85 years, and the prevalence of knee, hip and hand symptoms compatible with an OA diagnosis.

Methods: Data are from the baseline 'Comprehensive' subsample of the population-based Canadian Longitudinal Study on Aging (CLSA) (n=30,097, ages 45 to 85 years). Respondents were asked whether a doctor had ever told them they had arthritis, including OA in the knee, hip, or hand. All CLSA respondents, irrespective of arthritis diagnosis, were asked about symptoms compatible with OA (Sx-OA). These were pain during the past 4 weeks on most days in the knee, hip (groin or upper inner thigh) or hand (base of thumb or small joints close to fingernails), swelling in the knee, pain in the knee or pain in the hip while walking down stairs or climbing down slopes, and enlargement of the hand joints.

Results: Overall 53% (n= 16,024) of the sample reported either doctor diagnosed OA or Sx-OA in at least one of the 3 sites (knee, hip or hand). Specifically, 26% reported OA and 27% reported Sx-OA but not OA. 80% of those with OA and 37% of those without OA reported Sx-OA. Over 40% of respondents with OA and over 50% of those with Sx-OA but not OA were aged less than 65. Of respondents with OA, 57% reported knee OA, 32% reported hip OA, and 49% reported hand OA, with 30% reporting OA at more than one site. Of individuals with only Sx-OA, 55% reported knee symptoms, 12% reported hip symptoms, and 54% reported hand symptoms, with 20% of respondents reporting Sx-OA at more than one site. The proportion with OA at more than one site increased with age, from 20% for respondents aged 45-54 to 35% for respondents aged 75-85, with the corresponding increase for only Sx-OA from 17% to 23%. The proportion of respondents reporting overall general pain (not specific to arthritis) was 55% for those with OA, 40% for those with only Sx-OA. There was little variability in this proportion by age for both these groups. The proportion needing help with at least one daily living activity was 27% for the OA group, and 17% for the only Sx-OA group with an increase with age for both groups.

Conclusion: Similar proportions of this population-based sample reported having OA (knee, hip or hand) or joint symptoms compatible with OA in these joints. Though overall proportions differed, similar age and multijoint patterns were found between OA and Sx-OA without OA groups. The proportion of Sx-OA without OA reporting general pain or needing help was somewhat lower than those with OA but still substantial. Whether Sx-OA represents as yet undiagnosed OA is unknown until follow-up data from the next cycle of the CLSA are available. The high proportion of people with OA-compatible symptoms represent a potential target for the attention of primary care physicians, arthritis organizations and public health to encourage seeking a diagnosis and to stress the value of participation in physical activity and other arthritis pain management strategies.

Disclosure: E. M. Badley, None; C. Yip, None; A. V. Perruccio, None.

Abstract Number: 1173

Measuring the Advanced Clinician Practitioner in Arthritis Care (ACPAC) Program Trained Extended Role Practitioner (ERP) Workforce in Canada: A Profile of Practice Settings, Roles and Participation in Models of Arthritis Care in Canada

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Health Services Research Poster II – ACR/ARHP

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Background/Purpose: 1. To measure and map the ACPAC ERP workforce in Canada. 2. To present a snapshot of general practice characteristics relating to the ACPAC-trained ERP including the nature of their settings, roles and participation in the workforce as ERPs, and models of arthritis care in which they practise.

Methods: As part of quality assurance measures, graduates of the ACPAC program (www.acpacprogram.ca) were asked to contribute data pertaining to their current practice in the following categories: discipline, geographic location/setting (urban, community, remote/rural), participation in workforce as an ERP (% FTE), nature and percent of practice (orthopaedic, rheumatology) as an ERP, age groups treated, and participation in different models of arthritis care. General practice locations of ACPAC program trained ERPs were geospatially plotted by province across Canada, as well as superimposed upon Ontario-derived LHIN (local health integrated network) based maps representing Rheumatologist distribution in Ontario.

Results: There have been 69 graduates of the ACPAC program with 66 in the current workforce (2 retired, one deceased); base disciplines include Physical Therapists (n=49), Occupational Therapists (n=13) and Registered Nurses (n=7). 9 remain working in traditional roles and 3 are in leadership roles leaving a residual of 54 in active ERP roles. The practice settings of these ERPs are as follows: urban (50%); community (35%); and remote/rural (15%). The nature and percent of practice of these ERP roles are as follows: triage rheumatology 100% FTE (20%) and fractional <100% (46%); triage orthopaedics 100% FTE (6%) and fractional <100% (15%); triage rheumatology and orthopaedics 100% FTE (9 %) and fractional <100% (4%). The patient age-groups treated are adults/seniors (83%), adults and paediatrics (7%), and paediatrics (10%). The ACPAC ERPs currently practise in community-based home care, community-based Rheumatologists' clinics, telehealth/ECHO, family health teams, hospital-based, visiting Rheumatologist and visiting ERP/ fly in models of arthritis care.

Conclusion: It is important to understand the distribution and nature of practice settings of the highly trained advanced clinician practitioners in arthritis care, and recognize their potential to improve capacity in Rheumatology services delivered through different models of arthritis care. Aside from resource planning, this information is a practical step toward achieving improved connectivity between Rheumatologists and a network of ACPAC program trained ERPs which will ultimately benefit access to arthritis care for patients. Next steps include issuing a Pan-Canadian workforce survey which will explore attributes of all identified non-physician arthritis care specialists (Stand Up and Be Counted Too (2).

Disclosure: K. Lundon, None; R. Shupak, None; A. Pullan, None.

Comparative Cost per Response for Four Clinical Outcomes of Tocilizumab Monotherapy Versus Adalimumab Monotherapy in a Head-to-Head Randomized Double-Blind Superiority Trial in Patients with Rheumatoid Arthritis

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Background/Purpose: The cost-effectiveness of different biologic therapies is an important component in guiding treatment decisions for patients with rheumatoid arthritis (RA). The objective of this analysis was to compare drug and adverse event costs and cost per successful clinical response with tocilizumab (TCZ) monotherapy vs adalimumab (ADA) monotherapy in patients with RA.

Methods: Patients in the ADACTA trial were randomized to either TCZ 8 mg/kg intravenously every 4 weeks or ADA 40 mg subcutaneously every 2 weeks as monotherapy for 24 weeks. Drug costs of \$397.71 per 80-mg vial for TCZ (plus \$136 administration cost per infusion) and \$2220.62 per 40 mg for ADA were based on WAC drug prices (July 2017). Outcomes included patient-level drug costs and cost of hospitalization due to adverse events, and cost per response. Cost per response was calculated by dividing the mean drug plus administration cost by the proportion of patients achieving Disease Activity Score-28 joints (DAS28) < 2.6 (remission) or American College of Rheumatology response criteria 20%/50%/70% (ACR20/ACR50/ACR70). The proportions of patients achieving DAS28 < 2.6, ACR 20, ACR50 and ACR70 were 39.9%, 65.0%, 47.2% and 32.5% for TCZ, respectively, and 10.5%, 49.4%, 27.8% and 17.9% for ADA, respectively; $P < 0.0001$, $P = 0.0038$, $P = 0.0002$, $P = 0.0023$ for TCZ vs ADA, respectively. Hospitalization costs were calculated using the daily hospital cost of \$2433 (2017) and number of hospital days.

Results: Among the 163 patients treated with TCZ and 162 with ADA, mean total drug and administration costs per patient over 24 weeks were \$16,674.74 and \$23,357.63, respectively. Mean drug and administration costs were lower per each clinical response achieved with TCZ compared with ADA (DAS28 < 2.6: \$41,791 vs \$222,454; ACR20: \$25,653 vs \$47,283; ACR50: \$35,328 vs \$84,020; ACR70: \$51,307 vs \$130,490). The total hospital days/costs were 32/\$77,856 for TCZ and 43/\$104,619 for ADA.

Conclusion: In this comprehensive comparative assessment, the cost to achieve all four clinical responses was lower for patients receiving TCZ than for ADA.

Disclosure: J. H. Best, Genentech, Inc., 3; J. Pei, Genentech, Inc., 3.

Abstract Number: 1175

Withdrawn

Experiences of Urban First Nations and Métis Patients Accessing and Navigating the Health System for Inflammatory Arthritis Care

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Session Type: ACR/ARHP Combined Abstract Session

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

Background/Purpose: Outcome inequities exist for Indigenous patients in Canada with inflammatory arthritis conditions. Primary health services innovations that better support urban Indigenous patients exist, but these innovations have not been adopted broadly by specialty care systems. To inform specialty care systems and providers so as to better respond to urban Indigenous patient needs, develop care alliances with patients and primary health service providers, and ultimately resolve care gaps, we conducted a qualitative study using novel patient-driven methodology to identify experiences in accessing and navigating the health system for inflammatory arthritis care.

Methods: The Patient and Community Engagement Research Program (PaCER) method is a qualitative research method led by patients using an iterative three phase process: *Set*, *Collect* and *Reflect*. The *Reflect* phase was completed with urban First Nations and Métis patients engaged in a multidisciplinary urban Indigenous primary health service with integrated rheumatology specialty services using an adapted interview guide and referring to the themes identified in a parallel non-First Nations and non-Métis inflammatory arthritis patients study. Experiences and challenges in: 1) Initial access to rheumatology care; 2) Ongoing access to rheumatology care; 3) Information about the disease and resources for those living with arthritis; 4) Fear of the future; and 5) Collaborative and continuous care; were explored. Multiple rounds of coding, theme determination and review were conducted to ensure authentic representation of patient experiences, and full incorporation of Indigenous perspectives in the research.

Results: Eleven First Nations and Métis women with inflammatory arthritis representing a spectrum of recent-onset to established disease, and ranging from 39-70 years of age, consented to be interviewed. Access to care, continuity of care and collaboration were facilitated by a supportive and culturally safe environment that addressed care needs, assisted patients in navigating complex networks of primary and tertiary providers and social services, and that recognized the value in offering traditional approaches to health and wellness. Despite the overall positive experiences reported by participants, there was still tension and discomfort around pharmacotherapy for inflammatory arthritis. Experiences of incomplete effect, occurrence of side effects and fear of addiction were shared.

Conclusion: The results draw attention to the need for specialty care system change to build on culturally responsive models of care that already exist. Initial access and continuity of specialty care can be facilitated with collaboration between primary and specialty care in an urban Indigenous health service model. Enhanced patient education and resource coordination is required, as is support for decisions around pharmacotherapy to optimize inflammatory arthritis management.

Disclosure: C. Barnabe, None; J. Miller, None; S. Teare, None; C. Eaglespeaker, None; B. Roland, None; S. Calling Last, None; N. Eshkakogan, None; L. Crowshoe, None; E. Lopatina, None; D. A. Marshall, None.

Abstract Number: 1177

How Are Patients with Chronic Musculoskeletal Pain Conditions Being Managed Initially in the U.S.?

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Health Services Research Poster II – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

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

Background/Purpose: Chronic musculoskeletal pain (e.g. back and neck pain, pain due to arthritis, leg pain, and arm pain) affects up to 24% of the general population. Various approaches, both pharmacologic and nonpharmacologic, have been developed to manage chronic pain. With respect to pharmacological treatments, the overuse of opioid medications has led to an epidemic, even though many other evidence-based treatments are available and effective. Current guidelines recommend pharmacologic and nonpharmacologic treatments should be optimized before initiating a trial of opioids. The goal of this study was to explore initial clinical management of chronic musculoskeletal pain. We sought 1) to explore what treatments are prescribed at the initial visit with the physician for chronic musculoskeletal pain: i.e. medications, physical therapy, counseling; and 2) to describe factors associated with these prescribed treatments or services: more specifically clinician-related factors and patient-related factors.

Methods: We analyzed data from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey-Out Patient Department (NAMCS) between 2007 and 2015. Visits with a new chronic musculoskeletal pain condition were identified using pre-determined diagnostic criteria. We documented the following treatment prescriptions: opioids, non-opioid pain medication, physical therapy, mental health counseling, stress management, injury prevention, exercise, diet, weight reduction and health education. We used logistic regression to explore associations between patient and provider factors and each of these prescription categories. Data were programmed using SUDAAN and descriptive statistics are presented. Logistic regression models to determine physician and patient-related factors associated with treatment prescription will be calculated.

Results: There were 19,341 *initial visits* over the 9-year period with a diagnosis of chronic musculoskeletal pain in the NAMCS database translating into 528,715,590 weighted *initial visits*. Mean age of patients at these initial visits was 49.4 years (95% confidence interval: 48.7-50.0) and 58.9% were female. The proportions of patients that were prescribed the following medications: NSAIDs, opioids, acetaminophen and muscle relaxants were 27.98, 19.15, 16.8, and 10.19% respectively. The proportion of visits with referral to physical therapy was 9.73%, counseling for mental health 0.3%, stress management 0.92%, injury prevention 5.52%, exercise 10.60%, diet 6.47%, weight reduction 2.66%, and health education 14.03%. Ongoing analyses will elucidate patient and physician related factors associated with these various categories of treatment prescriptions.

Conclusion: There is a high frequency of visits for chronic musculoskeletal pain conditions. The frequency for opioid prescription was nearly double that of physical therapy. This result is troubling in view of the evidence and current guidelines that support non-opioid treatments for chronic musculoskeletal pain conditions.

Disclosure: D. Ehrmann Feldman, None; L. Carlesso, None; R. Nahin, None.

Abstract Number: 1178

Patients' and Healthcare Professionals' Resource Preferences for a Knowledge Translation Toolkit for Hip and Knee Replacement Rehabilitation

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Health Services Research Poster II – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

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

Background/Purpose: Widely varying rehabilitation practices for total joint replacement (TJR) for hip and knee osteoarthritis (OA) contribute to inconsistent patient outcomes and satisfaction. Informed by high quality evidence and expert consensus, quality indicators (QIs) were developed to guide improvements in the quality and consistency of TJR rehabilitation care. This study aimed to identify patients' and healthcare professionals' (HCPs) resource preferences and priorities for knowledge translation toolkits for implementing the QIs into routine clinical practice.

Methods: We conducted online patient (termed 'EQUIP-TJR') and HCP (termed 'QUICK-TJR') surveys in May and November 2017 respectively. Patients were adults on a surgical waitlist for TJR for hip or knee OA OR who had a TJR in past year and HCPs treated or educated patients before or after TJR. Posters, social media, targeted e-mail blasts, and e-newsletters were used for recruitment and a \$100 gift card prize draw was included. Surveys had 4 sections: 1) Rating toolkit resources on 5-point scale; 2) Rating toolkits' impact on rehabilitation care and outcomes on 5-point scale; 3) Toolkit dissemination strategies; and 4) Participant demographics. Surveys took 15 minutes to complete. Descriptive analyses were performed. The UBC Behavioural Research Ethics Board approved the study.

Results: Totals of 137 and 164 individuals completed the EQUIP-TJR and QUICK-TJR surveys respectively. In both surveys, a majority were from the Western Provinces and female. About 80% of EQUIP-TJR respondents were aged 55-74 years, equal proportions were undergoing hip and knee surgery and 68% were post-operative. QUICK-TJR respondents were predominantly physical therapists (77%), of varied age groups, and from public and private practice settings. Patients' five highest rated QI resources were: 1) Education booklets-98%; 2) QI questionnaire-84%; 3) QI checklist-80%; 4) QI passport-72%; and 5) Patient video vignette-71%. The first three of these tools were also among HCPs' top five plus QIs embedded in assessment forms (51%) and QI pocket cards (41%). Patients and HCPs agreed that the toolkit resources would help to improve the rehabilitation care provided (65% and 84%), track quality of care (85% and 68%) and communicate expectations (83% and 78%), respectively. Respondents suggested a wide range of targeted toolkit dissemination strategies including print and electronic formats, traditional and social media for local and national audiences.

Conclusion: There is considerable overlap in patient and HCP preferences and perceived value of QI resources. Results will inform development of EQUIP-TJR and QUICK-TJR toolkits and future research of their impact on quality and outcomes of rehabilitation care.

Disclosure: M. Westby, None; C. L. Koehn, None; S. Kerr, None; A. Hoens, None.

Abstract Number: 1179

Achieving Important Improvement in WOMAC Pain and Function By Three Months Post-Surgery Influences Satisfaction 1 Year Following Total Knee Replacement (TKR)

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Session Type: ACR/ARHP Combined Abstract Session

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

Background/Purpose: Understanding the impact of the time of achievement of important improvement (II) in pain and function may further understanding of outcome and inform care pathways for people with TKR. This work evaluated if the

Figure 1: Predictors of satisfaction following TKR



time to achieve II in WOMAC pain and function and Late Life Disability (LLDI) higher demand function was associated with satisfaction.

Methods: We followed 354 patients to 1-year post-TKR. Demographic and health information, WOMAC pain and function and LLDI limitation subscales and outcome expectations for pain, other symptoms, mobility/activities of daily living (ADL), and participation in social roles/instrumental activities of daily living (IADL) were completed pre-surgery. WOMAC and LLDI also were completed 3, 6, and 12 months post-surgery. Satisfaction was completed at 12 months. All were scored 0-100 with higher scores indicating better outcome. We derived an ordinal variable of achieved II by 3, 6 or 12 months post-surgery or not achieved for each outcome. We categorized those with baseline scores precluding II achievement who reached the measure ceiling as achieving II. We used a Bayesian path model with non-informative priors to evaluate if time to II achievement was associated with satisfaction, adjusting for age, sex, education, obesity, depression, comorbidity count and self-rated health. Expectations were modeled as individual predictors. The Bayesian model (model 1) provided a single estimator for ordinal II variables, so we fit a generalized linear model to understand which time of II achievement was associated with satisfaction (model 2).

Results: Mean age 65 years; 65% female. Mean pre-surgery pain, function and high demand activities scores were 47.8 (sd=17.8), 50.3 (sd=18.5) and 59.2 (sd=11.0). Mean satisfaction was 80.7 (sd=21.9). Those with II in pain, function and high demand activities by 3 months had higher satisfaction scores (range 87.8-89.3 vs 64.7-69.8). Fifty-seven, 47, 57 and 15% expected improvement in pain, other symptoms, mobility/ADL and social roles/IADL. In model 1 (Figure 1), earlier II achievement in pain (estimate -0.191) and function (estimate -0.389) was directly associated with more satisfaction and higher expectation for mobility/ADL improvements (-0.106) was directly associated with less satisfaction. Earlier achievement of II in function was associated with higher demand II achievement (0.628); II in higher demand activities was not associated with satisfaction. Other significant effects were indirect. Achievement of II in pain, function and high demand activities by 3 months was significantly associated with higher satisfaction as compared to achievement by 6 or 12 months (2-5 fold impact) or not achieving II (12-17 fold impact) (model 2).

Conclusion: Efforts to minimize recovery time post TKR should be tested to determine if more people recover more quickly and are satisfied with their outcomes.

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The Economic Burden of Systemic Lupus Erythematosus (SLE) within a Commercially-Insured Population in the United States Stratified By Disease Severity

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SESSION INFORMATION

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

Background/Purpose: Most currently available estimates of the economic burden of SLE in the US do not consider disease severity. The purpose of this study is to compare the economic burden between patients receiving treatment indicative of mild versus moderate-to-severe SLE.

Methods: Individuals ages 18-64 years, with an SLE ICD-9-CM code, treated with antimalarials, biologics (abatacept, belimumab, and rituximab), immunosuppressants, or systemic glucocorticoids from 1/1/2010 through 12/31/2014 were identified in a large administrative claims database. The first prescription fill date was the index date. Patients were required to have ≥ 1 inpatient claim or 2 non-diagnostic outpatient claims >30 days apart for SLE in the 12 months prior to index. If the patient had only outpatient claims, ≥ 1 SLE diagnoses must have been made by a rheumatologist or nephrologist. Patients were categorized according to SLE treatment during a 6-month exposure period after the index as: 1) mild SLE: either antimalarial or low-dose oral glucocorticoid (≤ 5 mg/day) monotherapy or 2) moderate-to-severe SLE: any immunosuppressive or combinations of SLE medications other than either antimalarial or low-dose oral glucocorticoid monotherapy. All-cause healthcare utilization and costs were evaluated during the 12 months following the initial exposure period (in 2016 US dollars). Generalized linear modeling with log link and gamma error distribution estimated: 1) total costs and 2) total costs excluding outpatient pharmacy costs during follow-up, adjusting for demographic and clinical characteristics.

Results: 8,231 treated SLE patients were identified; based on treatment during the exposure period, 32.6% were classified as having mild SLE (mean age [SD]: 47.7 years [10.2]; 92.2% female) and 67.4% as having moderate-to-severe SLE (mean

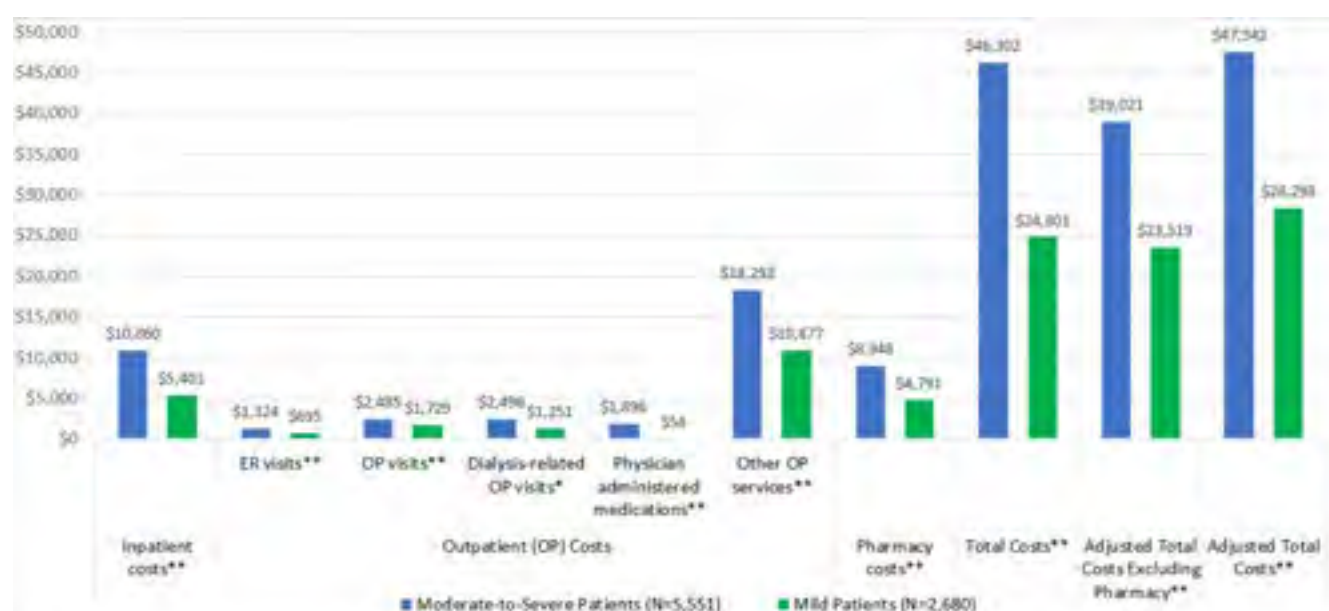


Figure 1: Mean unadjusted total costs, total and by type of service, and multivariable-adjusted total costs during 12-month follow-up period compared between commercially-insured moderate-to-severe and mild SLE patients. Generalized linear modeling with log link and gamma error distribution estimated total healthcare costs adjusting for differences in age, sex, urbanicity of residence, health plan type, and mean Charlson Comorbidity Index (CCI). *p-value < 0.05 **p-value < 0.001

age [SD]: 46.6 years [10.6];90.2% female). Patients receiving treatment indicative of moderate-to-severe SLE had significantly ($p<0.001$) more lupus nephritis (20.2% vs. 8.1%), and more comorbidities including cardiovascular disease (13.3% vs. 10.3%), type 2 diabetes (10.3% vs. 6.9%), and hypertension (41.9% vs. 34.0%). Mean unadjusted total costs and by type of service and multivariable adjusted total costs are shown in Figure 1. The mean multivariable-adjusted total costs and total costs excluding pharmacy costs, respectively, were \$47,542 and \$39,021 among moderate-to-severe patients and \$28,298 and \$23,519 among those with mild SLE ($p<0.0001$ for both).

Conclusion: The mean 12-month adjusted total costs for patients with moderate-to-severe SLE were 68% higher than those of patients with mild SLE. These differential costs are important to consider in future studies examining cost-effectiveness and in designing interventions to improve health and reduce health spending for SLE.

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Abstract Number: 1181

Hydroxychloroquine: Do We All See Eye to Eye? a Single-Site Analysis of Hydroxychloroquine Dosing Compared to 2016 American Academy of Ophthalmology Guidelines

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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

Background/Purpose: Hydroxychloroquine is universally recommended to treat patients with SLE, stressing the importance of appropriate dosing. The 2016 American Academy of Ophthalmology (AAO) guidelines recommend a maximum dose of hydroxychloroquine $\leq 5\text{mg/kg/day}$ actual body weight (ABW),¹ which correlates more with retinal toxicity risks than using ideal body weight to calculate dosage. We evaluated the extent of adherence to dosing guidelines by SLE providers to encourage further prospective analysis and intervention to prevent retinal toxicity.

Methods: Data collected from the Southern California Lupus Registry (SCOLR), an academic single-center cohort of 162 SLE patients, was analyzed. Patients were identified to have SLE by either ACR or 2012 SLICC criteria.^{2,3} Chart review identified patients prescribed hydroxychloroquine, dose prescribed, if this dosing was aligned with AAO guidelines, and, if dosed in excess, the amount (in mg) of excess daily hydroxychloroquine.

Results: Of 162 patients with SLE, 136 received hydroxychloroquine. Fifty-six (41%) of those patients on hydroxychloroquine were on doses exceeding 5mg/kg ABW and eighty (58%) were in line with AAO recommendations. The remaining 26 patients were not on hydroxychloroquine; reasons included adverse reactions or underlying or consequential retinal disease.

Among patients on excessive doses of hydroxychloroquine, the prescribed dose was in excess of recommended dosing by 1.1mg/kg on average (absolute dose 6.1mg/kg). 23 of these patients were dosed greater than 6mg/kg and 6 were receiving doses higher than 7mg/kg.

Conclusion: Recent uptick in retinopathy in patients on hydroxychloroquine for 5 years or more has reiterated that daily dosing of hydroxychloroquine is the most critical determinant of retinal toxicity risk. This, combined with our findings, implicates the dire need for physicians to appropriately dose hydroxychloroquine in SLE management. We found patients in our cohort dosed in excess as per both 2011 and 2016 American Academy of Ophthalmology Guidelines. This data underscores the importance of reviewing or adjusting hydroxychloroquine doses on regular clinic visits. Further, while use of weight-based dosing of hydroxychloroquine has demonstrated reduced risk of retinopathy, feasibility of dose adjustments as low as 50 milligrams warrants review of available doses of this medication. Perhaps the availability of 50-100mg dosing will be beneficial in avoiding long term adverse events.

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Disclosure: V. K. Sandhu, None; N. Goel, None; J. Hanna, None.

Abstract Number: 1182

The Disproportionate High Risk of Re-Fracture after Osteoporotic Treatment in Patients with Autoimmune Diseases

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Session Type: ACR/ARHP Combined Abstract Session

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

Background/Purpose: Patients with autoimmune diseases are associated with an increased risk of osteoporotic fracture. Anti-osteoporotic treatment could diminish re-fracture rates in post-menopause women. However, treatment failure of anti-osteoporotic medication in patients with autoimmune diseases remained unknown. The aim of study is to investigate the outcome of anti-osteoporotic treatment in patients with autoimmune rheumatic diseases.

Methods: We conducted a retrospective case-control study analyzing hospital database of a tertiary referral center in Taiwan. From January, 2002 to December 2016, subjects with osteoporotic fracture and anti-osteoporotic treatment were enrolled. Diagnosis of rheumatoid arthritis, systemic lupus erythematosus and primary Sjogren's syndrome were identified using ICD-9-CM and ICD-10-CM codes. Cases with re-fracture were compared with age-, gender-matched controls (1:4) without re-fracture. Re-fracture incidences were compared among anti-osteoporotic drugs and autoimmune diseases.

Results: In total, 9,384 fracture patients with anti-osteoporotic drugs were identified; 1,829 patients with autoimmune diseases. Patients receiving teriparatide were older and had lower bone density compared with those receiving bisphosphonates, raloxifene and denosumab, respectively. Participants with previous hip fractures had higher chance of re-fracture compared with their counterparts of previous spine fractures or other fractures. Patients with autoimmune diseases were at higher risk of recurrent fractures (19.3% vs. 10.6%, $p < 0.001$). Moreover, bisphosphonates-treated patients also had higher re-fracture rates compared with those treated with raloxifene, denosumab and teriparatide.

Conclusion: Our results indicated that rheumatic patients were at increased risk of treatment failure in osteoporosis. Adherence of anti-osteoporotic drugs and fall prevention are essential to prevent re-fracture in patients with autoimmune diseases.

Table 1. Demographic data and baseline bone mineral density in patients receiving anti-osteoporotic treatment

	Bisphosphonate (n=5853)		Teriparatide (n=916)		Denosumab (n=1058)		Raloxifene (n=1557)		Total (n=9384)		p value
	n	%	n	%	n	%	n	%	n	%	
Age	72.0	71.2	76.4	83.5	73.3	70.5	71.0	70.3	72.4	70.9	<0.001**
Gender											<0.001**
Female	4260	(72.8%)	760	(83.0%)	902	(85.3%)	1554	(99.8%)	7476	(79.7%)	
Male	1593	(27.2%)	156	(17.0%)	156	(14.7%)	3	(0.2%)	1908	(20.3%)	
First fracture											<0.001**
Osteoporotic fracture	2560	(43.7%)	226	(24.7%)	347	(32.8%)	711	(45.7%)	3844	(41.0%)	

Table . (Cont'd)

i@	Bisphosphonate (n=5853)		Teriparatide (n=916)		Denosumab (n=1058)		Raloxifene (n=1557)		Total (n=9384)		p value
	n	%	n	%	n	%	n	%	n	%	
Spine fracture	2555	(43.7%)	603	(65.8%)	513	(48.5%)	644	(41.4%)	4315	(46.0%)	
Hip fracture	510	(8.7%)	63	(6.9%)	120	(11.3%)	140	(9.0%)	833	(8.9%)	
Others	228	(3.9%)	24	(2.6%)	78	(7.4%)	62	(4.0%)	392	(4.2%)	
RA	445	(7.6%)	40	(4.4%)	52	(4.9%)	60	(3.9%)	597	(6.4%)	<0.001**
SLE	309	(5.3%)	31	(3.4%)	31	(2.9%)	44	(2.8%)	415	(4.4%)	<0.001**
pSS	615	(10.5%)	56	(6.1%)	63	(6.0%)	83	(5.3%)	817	(8.7%)	<0.001**
Subspecialties											<0.001**
Orthopedics	2972	(50.8%)	416	(45.4%)	564	(53.3%)	1022	(65.6%)	4974	(53.0%)	
Neurosurgery	1275	(21.8%)	367	(40.1%)	200	(18.9%)	308	(19.8%)	2150	(22.9%)	
Rheumatology	862	(14.7%)	90	(9.8%)	106	(10.0%)	85	(5.5%)	1143	(12.2%)	
Others	744	(12.7%)	43	(4.7%)	188	(17.8%)	142	(9.1%)	1117	(11.9%)	
Baseline											
Femoral neck BMD (g/cm ²)	0.6	̄0.1	0.6	̄0.1	0.6	̄0.1	0.6	̄0.1	0.6	̄0.1	<0.001**
Lumbar spine BMD (g/cm ²)	0.9	̄0.2	0.8	̄0.2	0.9	̄0.2	0.8	̄0.2	0.9	̄0.2	<0.001**
T-score	-2.8	̄0.9	-3.4	̄0.9	-2.8	̄0.8	-2.8	̄0.9	-2.9	̄0.9	<0.001**

Chi-Square test. Kruskal Wallis test. * $p<0.05$, ** $p<0.01$.

Continuous data were expressed mean̄SD.

Categorical data were expressed number and percentage.

Table 2. Comparisons of demographic data, concomitant autoimmune diseases and anti-osteoporotic treatment in patients with and without re-fracture

i@	Without re-fracture (n=3256)		With re-fracture (n=814)		Total (n=4070)		p value
Age	74.1	̄10.0	73.7	̄10.2	74.0	̄10.0	0.628
Gender							1.000
Female	2564	(78.7%)	641	(78.7%)	3205	(78.7%)	
Male	692	(21.3%)	173	(21.3%)	865	(21.3%)	
First fracture							0.008**
Osteoporotic fracture	1466	(45.0%)	386	(47.4%)	1852	(45.5%)	
Spine fracture	1348	(41.4%)	290	(35.6%)	1638	(40.2%)	
Hip fracture	284	(8.7%)	92	(11.3%)	376	(9.2%)	
Others	158	(4.9%)	46	(5.7%)	204	(5.0%)	
Autoimmune disease	345	(10.6%)	157	(19.3%)	502	(12.3%)	<0.001**
RA	194	(6.0%)	102	(12.5%)	296	(7.3%)	<0.001**
SLE	123	(3.8%)	78	(9.6%)	201	(4.9%)	<0.001**
pSS	274	(8.4%)	124	(15.2%)	398	(9.8%)	<0.001**
Anti-osteoporotic treatment							<0.001**
Bisphosphonate	2045	(62.8%)	578	(71.0%)	2623	(64.4%)	
Teriparatide	305	(9.4%)	47	(5.8%)	352	(8.6%)	
Denosumab	385	(11.8%)	46	(5.7%)	431	(10.6%)	
Raloxifene	521	(16.0%)	143	(17.6%)	664	(16.3%)	
Subspecialties							0.001**
Orthopedics	1803	(55.4%)	431	(52.9%)	2234	(54.9%)	
Neurosurgery	650	(20.0%)	141	(17.3%)	791	(19.4%)	
Rheumatology	384	(11.8%)	139	(17.1%)	523	(12.9%)	
Others	419	(12.9%)	103	(12.7%)	522	(12.8%)	
Baseline lab data							
Creatinine	1.1	̄0.8	1.1	̄0.9	1.1	̄0.9	0.008**
ALT	23.5	̄26.3	24.1	̄22.9	23.6	̄25.7	0.083
Hgb (n=2536)	12.1	̄1.7	11.9	̄1.9	12.1	̄1.7	0.006**
Femoral neck BMD (g/cm ²)	0.6	̄0.1	0.6	̄0.1	0.6	̄0.1	0.017*
Lumbar spine BMD (g/cm ²)	0.9	̄0.2	0.9	̄0.2	0.9	̄0.2	0.438
T-score	-2.8	̄0.9	-2.9	̄1.0	-2.8	̄0.9	0.227

Chi-Square test. Kruskal Wallis test. * $p<0.05$, ** $p<0.01$.

Continuous data were expressed mean̄SD.

Categorical data were expressed number and percentage.

Disclosure: W. N. Huang, None; Y. M. Chen, None; W. T. Hung, None; Y. W. Liao, None; Y. H. Chen, None.

The Distribution of Insurance in a Population-Based Cohort of SLE: Georgians Organized Against Lupus Cohort, 2012-2016

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Health Services Research Poster II – ACR/ARHP

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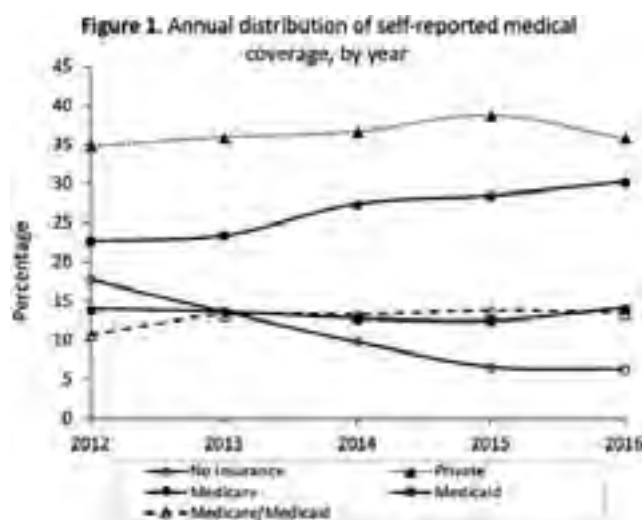
Session Time: 9:00AM-11:00AM

Background/Purpose: Having health insurance coverage is important for people with chronic conditions. Those with systemic lupus erythematosus (SLE) are particularly vulnerable given the disproportionate impact on young minorities and women. This is the first description of health insurance changes over time overall and by sociodemographic groups on a population level.

Methods: The Georgians Organized against Lupus (GOAL) is a cohort of validated patients with SLE living in Atlanta, predominantly derived from the population-based and Centers for Disease Control and Prevention (CDC) funded Georgia Lupus Registry. Participants have been surveyed annually, including sociodemographics, health insurance, disease activity (Systemic Lupus Activity Questionnaire), and damage (Self-Administered Brief Index of Lupus Damage). Self-reported health insurance was categorized into no insurance, private, Medicare, Medicaid, and Medicare/Medicaid. Those reported being in a different category the year before were classified as having changed insurance.

Results: An average of 642 individuals were surveyed annually from 2012 to 2016. At 2012 baseline, the average age was 46.4 ± 13.4 and disease duration was 13.6 ± 9.2 years. 93.6% were female and 78.5% black. 35.1% had a high school education level or less, 45.8% were at or below the Federal poverty level, 34.6% were married or with a partner, and 35% were employed. Figure 1 shows the distribution of insurance categories from 2012 through 2016. Compared to the year before, 23.8% changed insurance in 2013, 22.2% in 2014, 24.1% in 2015, and 26.8% in 2016. Those who changed insurance were more likely to be black, lower in educational attainment, poorer, unemployed, and have greater disease activity and damage.

Conclusion: In a population-based cohort in Georgia, the majority (~60%) with SLE have private insurance and Medicare, which has grown over time while those uninsured have dropped. The decrease in the uninsured mirrors national trends as the Affordable Care Act expanded coverage through Medicaid expansion and insurance exchanges. Georgia is one of the states that has not expanded Medicaid, the impact of which is not entirely clear in the SLE population and deserves further exploration. There also appears to be a slight increase in those who switch insurance categories. It is important to learn how types of and changes in insurance coverage affect healthcare utilization, disease treatment and outcomes, self-reported health, and mortality in SLE, particularly given the disproportionate impact on socially vulnerable groups. Studies



utilizing administrative data should also be aware of insurance coverage distributions and regional variations in policy that impact these distributions.

Disclosure: S. S. Lim, None; C. G. Helmick, None; G. Bao, None; C. Gordon, None; J. M. Hootman, None; C. Drenkard, None.

Abstract Number: 1184

Withdrawn

Abstract Number: 1185

Cause and Rate of Hospitalization of Lupus Patients

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SESSION INFORMATION

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Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic multiorgan disease that is associated with significant morbidity and mortality. Literature suggests improvement in the survival rates among SLE patients over the last decades. However, economic burden of SLE including health care and hospitalization is significantly high. The aim of this study is to evaluate the burden of hospitalization among SLE patients and assess the risk factors of hospitalization among SLE patients.

Methods: All patients who are followed in rheumatology clinics (Tawam hospital) and fulfilled the American college of Rheumatology (ACR) SLE criteria were identified. Retrospective chart reviews for previous admissions in this hospital or any other Abu Dhabi Health Services Company (SEHA) hospitals were performed using electronic health records (available since 2009). Demographic data, reason for hospitalization, duration of hospitalization, ICU admission, and SLE features at time of admission were collected. Hospitalization rate was calculated as number of hospitalization divided by disease duration. Regression analysis for factors associated with hospitalization and with duration of hospitalization were performed.

Results: Ninety one patients (88, 97%, females) were identified who fulfil ACR criteria with mean disease duration of 10.16 (SD \pm 5.5) years. Mean number of criteria of those patients are 5.6. Sixty six (72.5%) of these patients were admitted at least once to the hospital with a total of 222 admissions over the years and with the mean annual rate of hospitalization calculated at 27.5 %. Mean hospitalization duration was 5.9 days (SD \pm 5.98). In 41 admissions, there were 2 reasons for admission. In total, 32.4% admitted for SLE disease activity, 25.2% for infection, 30.2% for pregnancy and related conditions, 2.3% for medication side effects and 27.5% for other medical and surgical causes. SLE features during SLE activity admissions include lupus nephritis (50%), hematological manifestation (34.6%), arthritis (21.2%) and Neuropsychiatric lupus (19.2%). In 6% of hospital admissions, patients needed an intensive care (ICU) admission. In multivariable regression, the number of hospitalization was significantly associated with younger age at diagnosis ($P=.02$), and ever lupus nephritis ($P=.003$). In another multivariable analysis, increased duration of hospitalization was significantly associated with being admitted for SLE disease activity ($p=.009$), presence of DsDNA antibodies ($P<.001$), and admission to ICU ($P<.001$).

Conclusion: Significant proportions of SLE patients were hospitalized during their disease course, with one third of hospitalizations due to active disease. Hospitalization of SLE patients carries a substantial economic burden on the healthcare system.

Disclosure: R. Aldarmaki, None; H. Khogali, None; A. AIDhanhani, None.

Comparison of Biologic Discontinuation in Patients with Elderly-Onset Vs Younger-Onset Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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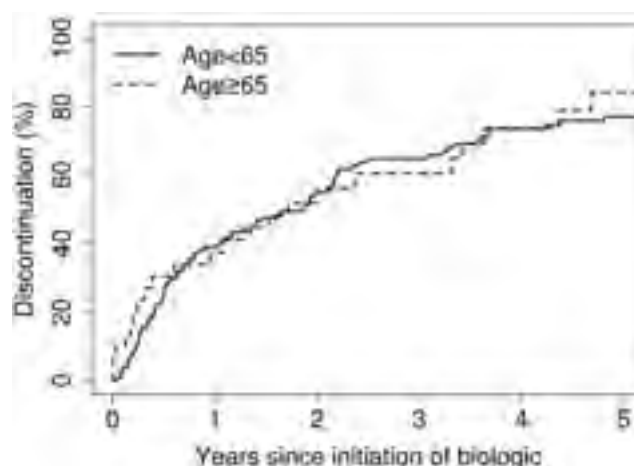
Session Time: 9:00AM-11:00AM

Background/Purpose: Several studies have suggested that patients with elderly-onset rheumatoid arthritis (EORA) receive biologic treatments less frequently than patients with younger-onset RA (YORA). This has been demonstrated even in patients with comparable disease activity. Risk of treatment complications and financial challenges associated with Medicare reimbursement may also contribute to this disparity. Our objective was to compare biologic drug discontinuation rates for older vs. younger onset RA, as this is a key outcome measure that could impact prescribing practices.

Methods: A retrospective medical record review was performed of all patients who fulfilled the 1987 ACR criteria for adult-onset RA in 1980-2013 among residents of a geographically defined area with follow up until death, migration or July 1, 2016. EORA was defined as RA diagnosis at age ≥ 65 years and YORA was defined as age 18-64 years. Discontinuation rates were estimated using cumulative incidence adjusted for the competing risk of death. Risk factors were examined using Cox models adjusted for age, sex and calendar year of RA incidence.

Results: 171 cases of EORA and 435 cases of YORA were identified (67% and 71% female respectively, $p=0.33$). EORA patients had a lower rate smoking at time of RA diagnosis (8% vs. 18%, $p=0.002$), though ever smoking was not a significant risk factor for starting a biologic ($p=0.42$). There were no significant differences in rheumatoid factor (RF) or anti-cyclic citrullinated peptide antibody (CCP) positivity ($p=0.26$) or body mass index (BMI) ($p=0.23$) at time of diagnosis. Cumulative incidence of biologic initiation was lower among EORA compared with YORA (11% vs 19% at 2 year after RA diagnosis, respectively, $p<0.001$). Among those treated with a biologic, years from RA diagnosis to first biologic was not significantly different between the two groups ($p=0.17$). Cumulative incidence of first biologic discontinuation was 38% at 1 year (95% confidence interval [CI], 23-61%) and 56% at 2 years (95% CI, 40-79%) for EORA compared with 39% at 1 year (95% CI, 31-49%) and 55% at 2 years (95% CI, 46-65%) for YORA ($p=0.61$). Concurrent glucocorticoid use at initiation of first biologic was statistically significantly associated with a lower risk for discontinuation in EORA (hazard ratio: 0.19; 95% confidence interval: 0.06-0.59), but not in YORA (interaction $p=0.06$). There were no significant predictive factors for discontinuation in YORA.

Conclusion: Discontinuation rates of biologic medications did not differ significantly between patients with EORA and YORA.



Disclosure: M. Richter, None; E. L. Matteson, None; J. M. Davis III, None; S. J. Achenbach, None; C. S. Crowson, None.

Abstract Number: 1187

Impact of a Nurse-Led Program of Patient Self-Assessment and Self-Management Axial Spondyloarthritis: Results of a Prospective, Multicentre, Randomized, Controlled Trial

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SESSION INFORMATION

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Session Type: ACR/ARHP Combined Abstract Session

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

Background/Purpose: The objective of this study was to evaluate the impact of a nurse-led program of self-management and self-assessment for disease activity program in axSpA

Methods: Study design: Prospective, randomized, controlled, open, 12-month trial (NCT02374749). **Participants** 1/Patients: consecutive Axial SpA patients (according to rheumatologist) attending a clinic of the participating centers were invited. 2/Nurses: all participated at a 1 day meeting prior the start of the study.

Study treatment: a program including: 1) Self-management = a) a video explaining the disease, the interest of smoking cessation in axial SpA, the role of NSAIDs as cornerstone treatment in axSpA in the absence of contra-indications, the interest of physical activity and exercise, followed by a discussion with the nurse; b) physical examination by the nurse to check for the presence of spinal deformities suggesting a severe disease, and depending on the absence/presence of such deformities projection of a specific video of home-based exercises examples for patients with severe/not severe disease. 2) Self-assessment: Video presentation of the rationale of the use of a composite index such as ASDAS and BASDAI, followed by discussion with the nurse. Explanation by the nurse of the collection, calculation of BASDAI and ASDAS (via a calculator provided to the patient) and reports of the results on a sheet form. Monthly evaluation at home recommended by the nurse. **Treatment allocation:** after written informed consent, the treatment was allocated randomly via an electronic system (e.g. either this above program or an evaluation of potential co-morbidities (not reported here). **Outcome variables:** Primary: The level of coping (0-10, where 0= very well) after 12 months. Other variables: Successful smoking cessation, NSAID intake, Number of home-based or supervised exercise, international physical activity questionnaire (IPAQ)

Results: There was no difference in the baseline characteristics of the 502 recruited patients (250 and 252 in the active and control groups, respectively): Age: 46.7±12.2 years, male gender: 62.7%, disease duration: 13.7±11.0y, Xray sacroiliitis 62.8%, MRI sacroiliitis 65.7%, current biologic treatment: 78.3%, ASDAS-CRP: 1.9 ± 0.8, BASFI: 25.6±22.3. After the 1year follow-up period, the coping level was lower in the active group, but this difference was not significant (2.8±2.0 vs. 3.0±2.1, p=0.3). However, there was a significant decrease in the BASDAI in the active group (- 1.2 ± 15.8 vs. +1.4 ± 15.7, p=0.03), a significant increase in the number (6.1± 28.8 vs. -0.4±26.9, p=0.03) and duration (4.3±20.1 vs. -1.7±20.7, p<0.01) of the home-exercises in the active group, and a greater IPAQ score in the active group at the end of follow-up (138.4±227 vs. 95.6±173, p=0.02). Neither smoking cessations nor NSAID intake were different after one year in both groups.

Conclusion: This study highly suggests a short-term benefit of a nurse led program on the self-management and self-assessment for disease activity in a young axSpA population in particular with regard to the frequency and the duration of home exercises

Disclosure: A. Molto, None; A. Etcheto, None; S. Poiraudreau, None; L. Gossec, Lilly France, BMs France, Pfizer France, Orange IMT, 2; P. Claudepierre, None; M. Soubrier, None; F. Fayet, None; D. Wendling, None; P. Gaudin, None; E. Dernis, None; S. Guis, None; S. Pouplin, None; A. Ruysen-Witrand, None; M. Dougados, Abbvie, Pfizer, Eli Lilly and Company, Novartis, UCB, Merck, Roche, BMS, UCB, 2, 5.

Abstract Number: 1188

Are Residents Choosing Wisely? Analysis of Adherence to Recommendations of Ordering Anti-Nuclear Antibody Testing in an Internal Medicine Residency Primary Care Clinic

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Session Date: Monday, October 22, 2018

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Background/Purpose: A positive anti-nuclear antibody (ANA) is considered very useful for the diagnosis of SLE and systemic sclerosis, and somewhat useful for the diagnosis of Sjögren's syndrome and polymyositis/dermatomyositis. Higher the prior probability that a patient has a systemic autoimmune disease, the more likely the results of an ANA test will assist in establishing the diagnosis. However, ANA testing is ordered indiscriminately leading to high false positive results, increased unnecessary downstream testing and referral to rheumatology. ACR Choosing Wisely campaign in 2013 recommended not to test ANA sub-serologies without a positive ANA and clinical suspicion of immune-mediated disease. Our study aimed to study the adherence to these recommendations by residents in their outpatient primary care clinic of a community teaching hospital.

Methods: Retrospective analysis of electronic medical records of patients seen by internal medicine residents in the primary care clinic during the duration of January 1, 2012 to December 31, 2016 was performed. The method of ANA testing used was EIA (Enzyme immunoassay). If positive ($> 1:80$), reflex EIA for individual ANA sub serologies were performed. We analyzed the frequency of ANA ordering, reasons for ANA ordering and adherence to current ACR recommendations for subserology testing.

Results: 57 patients (out of total 757) had ANA tested during this period. Only 38/57(66%) had a documentation of strong clinical suspicion of an autoimmune disorder. 54 tests were complete at the time of data collection, two results were pending and one screen never completed. Of the 54 completed tests, 44/54 (81.5%) were negative and 10/54 (18.5%) were positive. The most common symptom for which ANA was ordered was joint pain 18/52 (34.6%) of which 5/18 patients had knee pain. In 9/54 patients (16.6%), ANA was ordered more than once (twice in 7 patients and thrice in 2 patients). Most common antibodies tested positive following a positive ANA were anti-double stranded DNA (anti-Ds DNA) in 5/10(50%) followed by anti-Jo1 antibody (antibody against anti-histidyl t RNA synthetase) 4/10(40%). Other antibodies positive were anti-c ANCA (1/10, 10%) and anti-SSA antibodies (1/10,10%). Most common diagnoses among the patients tested for ANA was osteoarthritis 7/54 (12.9%) followed by fibromyalgia (3/54,5.5%). 16/54 (29.6%) had no diagnosis. Among the 44 patients who were tested negative for ANA, 13/44 (29.5%) had other autoantibodies ordered.

Conclusion: ANA testing was ordered without a strong clinical suspicion for a rheumatic/autoimmune disorder in 33% of patients. ANA was ordered more than once in 16.6% of the patients. Additional antibody testing was in 29.5% of patients with negative ANA in whom there was no clinical suspicion of a rheumatic/autoimmune disorder, which is against the "ACR Choosing Wisely recommendations". Our study demonstrates that non-adherence to ACR recommendations for ordering ANA and ANA subserology testing is prevalent among trainees in the outpatient primary care setting. Educational and electronic medical record based interventions could be instituted to check this practice.

Disclosure: A. Das, None; R. Panneerselvan, None; A. Faisal, None; J. Rind, None; R. Shah, None.

Secukinumab Versus Adalimumab for the Treatment of Ankylosing Spondylitis: A Cost per Responder Analysis from Korean Perspective

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Background/Purpose: Various kinds of biologic agents are available for treating ankylosing spondylitis (AS). However, there is considerable economic burden for patients and society. This study was performed to estimate the response rate of secukinumab (fully human anti-interleukin 17A) and adalimumab in AS patients, and to compare the cost-effectiveness between secukinumab and adalimumab from Korean perspective.

Methods: A systematic literature search was performed via PubMed for relevant randomized controlled trials (RCTs) for response rate. The cost per responder for each treatment was estimated by dividing drug acquisition cost for the treatment course with its response rate of Assessment of Spondyloarthritis International Society (ASAS) outcomes. Response rates in anti-TNF-naïve subjects were extracted from RCTs of secukinumab and adalimumab, respectively. All analyses were calculated in case of both with or without loading condition of secukinumab. Cost was expressed with US dollars (USD) (1USD = 1,082 Korean Won).

Results: Of the 295 articles retrieved, five RCTs were identified including long-term response data. The ASAS 20 and 40 response rates from selected studies were comparable between secukinumab and adalimumab. The cost per ASAS 20 responder were lower by 40% in secukinumab compared with adalimumab: USD 9,637 vs. USD 16,129 at 52 weeks and USD 20,051 vs. USD 32,699 at 104 weeks for secukinumab vs. adalimumab (in case of maintenance condition), respectively. In addition, the cost per ASAS 40 responder were also lower by about 40% in secukinumab: USD 12,179 vs. USD 22,395 at 52 weeks and USD 27,338 vs. USD 41,655 for secukinumab vs. adalimumab, respectively. Even in case of loading condition with secukinumab at 52 and 104 weeks, secukinumab showed lower cost per responder by approximately 25% than adalimumab.

Conclusion: The response rates of secukinumab and adalimumab were comparable. The costs per responder for ASAS 20 and 40 were consistently lower for secukinumab compared with adalimumab. The treatment with secukinumab for biologic-naïve AS patients could be the cost-effective treatment option in Korea with a given budget.

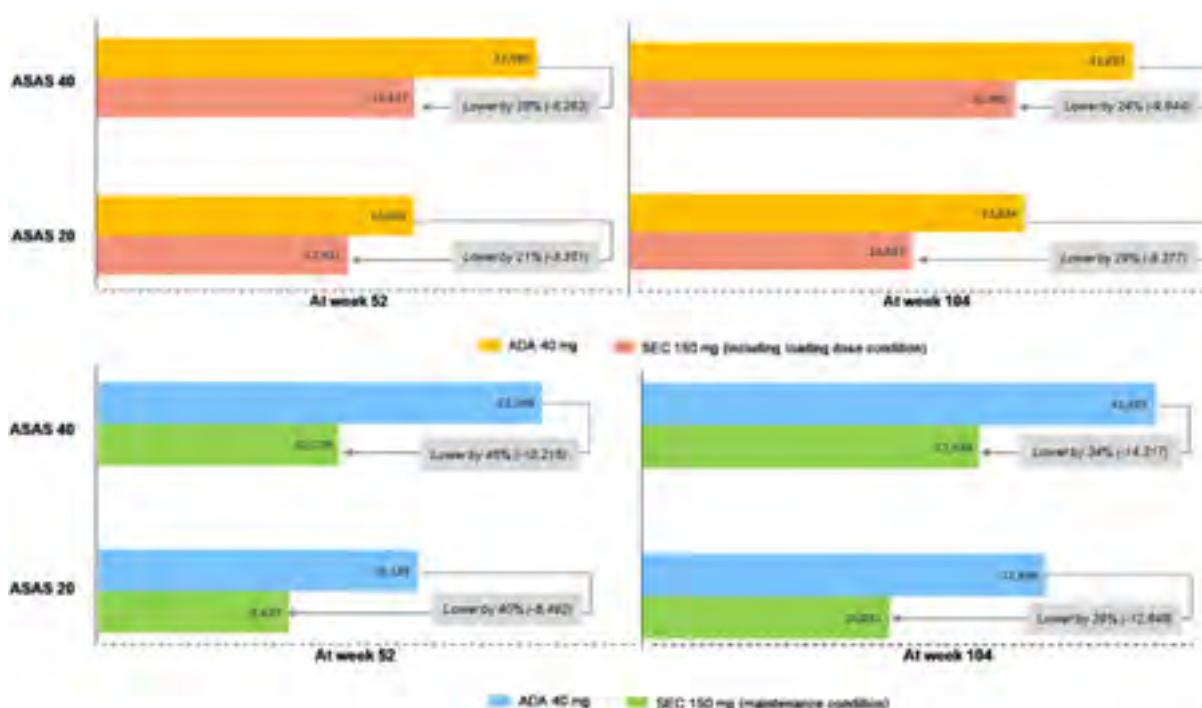


Figure 1. Cost per response of ASAS 40 and 20 for secukinumab (SEC) vs. adalimumab (ADA) for the treatment of AS at week 52 and 104 (upper: with SEC loading condition, bottom: with SEC maintenance condition)(unit: USD)

Disclosure: D. Kim, Novartis Korea, 2; H. Kim, Novartis Korea, 3; S. Cho, Novartis Korea, 3; M. C. Park, Novartis Korea, 2.

Abstract Number: 1190

Use of Biologic Drugs and Adverse Events in Patients with Rheumatic Disease: DATA from the Mexican Biologics Registry

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Background/Purpose: National registries of biologic drugs have proven to be valuable tools in following patients with rheumatic disease and some outcomes in real-life situations. The objective of this study was to describe Mexican Rheumatologists' preferences when treating patients with biologic drugs and to analyze factors associated to the use of this therapy.

Methods: Data from patients undergoing biologic treatment in Mexico is gathered into the BIOBADAMEX online database, which is part of the BIOBADAMERICA initiative and based on the BIOBADASER Phase 3 platform. Phase 3 in Mexico started gathering patient data in April 2016 and to date has information on 283 patients. The database collects information such as gender, age, diagnosis, disease duration, biologic treatment, DMARD treatment, concomitant therapy, motives for discontinuation of biologics, comorbidities, adverse event (AE) severity, infection site and germ involved. Descriptive statistics were applied on the data collected from April 2016 to April 2018.

Results: We analyzed data on the use of 267 biologic treatments in 289 patients. Most of them receive biologic therapy through socialized medical insurance programs which may have led to bias. 82% of patients were female, mean age 49 ± 15.2 (4-85) years, 42.5% belonging to the <50 group. 70.9% of patients in the registry have RA, 15.9% AS and 5.1% PsA. Mean disease duration is 11 ± 8.9 (0-58) years. The most commonly used biologic overall is Abatacept (15.3%), followed by Adalimumab (13.8%), Tocilizumab (11.2%), Certolizumab (10.1%), Golimumab (8.6%), Rituximab (8.2%), and Etanercept biosimilar (7.4%), Etanercept (6.3%), Infliximab (4.1%) and Benlystia (1.1%). All others, including JAK inhibitors, are used in <1% of patients. The preference for first biologic drug was Etanercept (32.4%), followed by Adalimumab (12%), Infliximab (8.3%), Rituximab and Tocilizumab (5.5% each) and Abatacept (2.7%). The most commonly used second-line biologics were golimumab, the etanercept biosimilar and abatacept. Most treatments were stopped due to lack of efficacy (60.4%), disease remission (7.4%), other causes (20.1%), AE (4.4%), with the rest of the causes each affecting <5% of patients. 18.5% of AE were considered severe. Comorbidities were present in 87 patients (40%), the most common being Hypertension (13.4%), Diabetes (7.8%) and Dyslipidemia (6.9%). Non-lymphoma neoplasms were reported in 1.3%. 25% of AE were considered serious but most (70%) were mild. Only 6 patients reported infections with the most common sites being the skin (33.3%), urinary tract (16.6%) and middle-ear (16.6%). The causal germ was undetermined in half of the cases of infection.

Conclusion: When using biologic drugs, TNF inhibitors are the most commonly used initial mechanism of action for the treatment of rheumatic diseases in the BIOBADAMEX registry. Upon treatment failure, patients often undergo a switch to another mechanism of action, mainly using Abatacept. Adverse events and infections related to the use of biologics are infrequent, but 40% of patients present chronic comorbidities.

Disclosure: D. Xibille-Friedmann, None; S. M. Carrillo -Vazquez, None; S. Sicsik Ayala, None; F. Irazoque-Palazuelos, None; A. Ramos-Sanchez, None; S. Duran-Barragan, None; M. A. Saavedra, None; L. Barile, None; G. Olvera, None.

The Importance of Quantitative Assessment of Joint/Organ Damage and Patient Distress in Addition to Inflammatory Activity in Routine Clinical Care

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Background/Purpose: Quantitative measures such as laboratory tests and pooled indices have advanced clinical rheumatology care far beyond narrative decisions. These measures generally are directed to assess inflammatory activity, based on the primary concern of rheumatologists to control inflammation in order to prevent damage to joints and other organs. However, structural damage and patient distress, seen as fibromyalgia, depression, etc., are important clinical problems in many patients, in addition to active inflammation, but are not assessed quantitatively in routine clinical care, or even much clinical research concerning inflammatory rheumatic diseases. We introduced quantitative assessment of inflammation, damage, and distress in care of individual rheumatology patients, and hypothesized that structural damage and distress would be at least as important in current practice as inflammation. Here, we assess the relative contribution of each to physician global assessment.

Methods: As part of routine care, rheumatologists at one academic site complete a 0-10 physician global assessment (DOCGL) VAS, as well as 3 further 0-10 VAS to assess inflammation (reversible disease) (DOCINF), joint and other organ damage (irreversible disease) (DOCDAM), and patient distress (fibromyalgia, depression), etc. (DOCSTR). The proportion of DOCGL attributed to inflammation, damage, and distress (total=100%) also is estimated. Mean values were analyzed in a cross-sectional study of 570 patients, and compared in subgroups of 98 with rheumatoid arthritis (RA), 131 with osteoarthritis (OA) and 89 with fibromyalgia (FM), using t tests and analysis of variance (ANOVA).

Results: Mean 0-10 DOCGL scores were 4.4 in all patients, 4.4 in OA, 4.6 in RA, and 5.2 in FM (Table) ($p=0.04$). Highest mean scores were seen for DOCINF in RA, DOCDAM in OA, and DOCSTR in FM, and differing significantly in each diagnosis (Table), confirming face validity. Importantly, damage VAS scores (DOCDAM) were higher than inflammation (DOCINF) scores in all groups, including in RA, and mean estimates of the proportion of DOCGL attributed primarily to damage were greater than to inflammation in all conditions (Table). Scores for DOCSTR were higher than for DOCINF in all patients and subgroups, other than in RA.

Mean VAS Scores and % of physician global assessment (DOCGL) attributed to inflammation (DOCINF), damage (DOCDAM), and distress (DOCSTR) in patients with rheumatic diseases

	ALL	RA	OA	FM	P*
N	570	98	131	89	
Mean VAS Scores					
VAS DOCGL	4.4 (1.6)	4.6 (1.8)	4.4 (1.5)	5.2 (1.6)	0.04
VAS DOCINF	1.8 (2.0)	2.8 (2.4)	0.7 (1.1)	0.8 (1.3)	<0.001
VAS DOCDAM	3.1 (2.2)	3.8 (2.3)	4.4 (1.8)	1.7 (1.9)	<0.001
VAS DOCSTR	2.1 (2.9)	1.2 (2.2)	1.5 (2.5)	6.0 (2.5)	<0.001
P (DOCINF vs DOCDAM)	0.001	0.01	<0.001	<0.001	
P (DOCINF vs DOCSTR)	0.11	<0.001†	<0.001	<0.001	
Mean % of clinical management decision attributed to...					
%inflammation	29 (31)	39 (29)	12 (19)	6 (11)	<0.001
%damage	48 (35)	52 (30)	73 (31)	18 (23)	<0.001
%distress	22 (34)	9 (20)	15 (27)	76 (27)	<0.001

*ANOVA - RA vs OA vs FM † -only comparison in which DOCINF higher than DOCSTR

Conclusion: Physician VAS scores and DOGCL sub-scores attributed to damage and distress in individual patients were higher than for inflammation in all diagnosis groups, even in RA patients as a group. Control of inflammation remains the primary concern for rheumatologists, but modern therapeutics have been largely effective, leaving structural damage and patient distress as more prominent issues among individual patients in routine patient care and Systematic quantitation may be critical to understand the effects of these problems on patient well being and limited responses to anti-inflammatory therapies.

Disclosure: T. Pincus, Medical History Services, LLC., 7, 9; I. Castrejón, None; J. A. Block, Gilead, 1, Novartis, 2, Pfizer, Inc., 2, Janssen, 2, GlaxoSmithKline, 5, Zynerva Pharmaceuticals, 5, Agios, Inc, 7, Daiichi Sankyo, Inc., 7, Omeros, Inc., 7.

Abstract Number: 1192

The Impact of Participation in an Adalimumab (Humira) Patient Support Program on the Onset and Management of Disease Flares

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Health Services Research Poster II – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

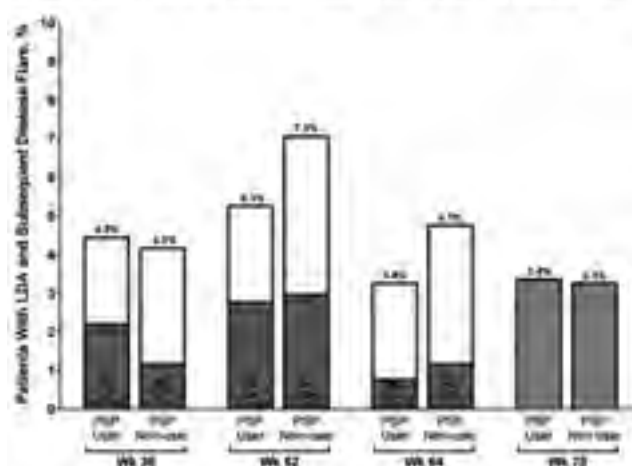
Session Time: 9:00AM-11:00AM

Background/Purpose: The AbbVie patient (pt) support program (PSP) is offered to pts prescribed adalimumab for RA and other indications. The purpose of this analysis was to evaluate the incidence of disease flare and the regain of disease control after flare among pts treated with adalimumab in the PASSION study according to PSP participation.

Methods: Pts with moderate to severe RA were enrolled in a 78-wk post marketing, global, observational study (PASSION) and received adalimumab in routine clinical care. Pts achieving low disease activity (LDA), defined as a 28-joint Disease Activity Score using C-reactive protein (DAS28[CRP]) ≤ 3.2 , were evaluated for the incidence of disease flare and recovery of LDA through wk 78. Disease flare was defined as an increase in DAS28(CRP) ≥ 0.6 at 2 consecutive visits (current and previous visits) and DAS28(CRP) > 3.2 at either visit if pts had achieved DAS28(CRP) LDA or better at or before the previous visit. The proportion of PSP users and PSP non-users with LDA experiencing disease flare and the proportion who re-established LDA following disease flare were summarized by visit. Differences between PSP users and PSP non-users were evaluated using a Chi-square test.

Results: Of the 1025 pts enrolled in PASSION, 695 pts achieved LDA through wk 78 (357/499 [72%] PSP users; 338/526 [64%] PSP non-users); 124 (18%) of whom experienced disease flare at ≥ 1 time point (59/357 [17%] PSP users; 65/338 [19%] PSP non-users). Of pts who experienced a flare, similar proportions of PSP users and PSP non-users were female (46/59 [78%] PSP users; 55/65 [85%] PSP non-users) and < 65 years (48/59 [81%] PSP users; 46/65 [71%] PSP non-users); however, significant differences ($P < 0.001$) were observed for race (white; 44/59 [75%] PSP users; 64/65 [99%] PSP non-

Figure: Proportion of Patients With LDA Experiencing Disease Flare And Regaining LDA



users), ethnicity (Hispanic/Latino; 17/59 [29%] PSP users; 3/65 [5%] PSP non-users), and prior biologic DMARD use (4/59 [7%] PSP users; 22/65 [34%] PSP non-users). Flares occurred in similar proportions of PSP users (3.4%–5.3%) and PSP non-users (3.3%–7.1%) with LDA at assessed time points (**Figure**). Greater portions of PSP users (50%–53%) vs PSP non-users (29%–42%) regained LDA after flare through wk 52; 12 PSP users and 11 PSP non-users experienced disease flare at wk 78 and were unable to be assessed for LDA achievement following flare.

Conclusion: Flares occurred in <20% of pts receiving adalimumab and achieving LDA in the 78-wk PASSION study. Greater proportions of PSP users than PSP non-users regained disease control after flare through study wk 52.

Acknowledgment: AbbVie funded the study, contributed to the design, collection, analysis, and interpretation of the data, and in the writing, review, and approval of the abstract. Medical writing support was provided by Catherine DeBrosse, PhD, and Janet Matsuura, PhD, of Complete Publication Solutions, LLC (North Wales, PA) and was funded by AbbVie.

Disclosure: F. van Den Bosch, AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Lilly, Merck, Novartis, Pfizer, and UCB, 2, AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Lilly, Merck, Novartis, Pfizer, and UCB, 5, AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Lilly, Merck, Novartis, Pfizer, and UCB, 8; S. Wassenberg, AbbVie, Celgene, Janssen, Chugai, Lilly, Novartis, Pfizer, MSD, and UCB, 8, AbbVie, Celgene, Janssen, Chugai, Lilly, Novartis, Pfizer, MSD, and UCB, 5, AbbVie, BMS, Fuji, Gilead, Novartis, Pfizer, Roche, Sandoz, and UCB, 9; B. Haraoui, Amgen Inc., 5, AbbVie, Amgen, BMS, Janssen, Pfizer, Roche, and UCB, 8, AbbVie, Amgen, BMS, Janssen, Pfizer, Roche, and UCB, 2, AbbVie, Amgen, BMS, Eli Lilly, Janssen, Pfizer, Roche, and UCB, 6; P. Zueger, AbbVie Inc., 3, AbbVie Inc., 1; M. Wu, AbbVie Inc., 3, AbbVie Inc., 1; I. Lagunes Galindo, AbbVie Inc., 3, AbbVie Inc., 1; A. Ostor, Lilly, Roche, MSD, AbbVie, Pfizer, Novartis, Janssen, and Bristol-Myers Squibb, 9, Lilly, Roche, MSD, AbbVie, Pfizer, Novartis, Janssen, and Bristol-Myers Squibb, 9, Lilly, Roche, MSD, AbbVie, Pfizer, Novartis, Janssen, and Bristol-Myers Squibb, 5.

Abstract Number: 1193

Consensus Statements on Scanning Conventions and Documentation in Musculoskeletal Ultrasound

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Imaging of Rheumatic Diseases Poster II: Ultrasound

Session Type: ACR Poster Session B

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

Background/Purpose: Point-of-care (POC) musculoskeletal ultrasound (MSUS) over the past decade has increasingly been adopted to evaluate patients with rheumatic diseases. In 2011, a group of rheumatology MSUS experts developed a document on documentation, scanning conventions, and tiered-mastery designation for anatomic region views. This study aims to update consensus reflective of the current usage MSUS in rheumatology. This consensus statement will guide development of a Rheumatology MSUS fellowship curriculum and professional training in the United States.

Methods: A 3-round Delphi method study was done utilizing a 96-item questionnaire. Agreement/disagreement on documentation and scanning conventions covered 5 items each; other items included demographics; and tier designations for anatomic-regions. Comments were solicited for each question. Dissemination was done via Qualtrics[®] to 101 respondents, with a target participant number of 38. Respondent selection was based on: identified lead MSUS academic faculty, course instruction, certification by ACR (RhMSUS), and publication. Informed consent process was done. Questionnaire initiation and completion indicated consent. We used McNemar's chi-square to test agreement in the paired responses for scanning and documentation. High agreement was defined as agreement of $\geq 85\%$. Comments were reviewed for content analysis. This study was approved by the Institutional Review Board of Loma Linda University Medical Center.

Results: 46 respondents completed all three rounds. 73% were full time academic faculty. 73% had RhMSUS certification. Table 1 shows results of levels of agreement/disagreement with the original consensus statements and with proposed alternative statements. . 4 (80%) of the documentation and 5 (100%) of the scanning convention statements reached or maintained high consensus. For the documentation statement that did not reach consensus ("A dynamic scan should be saved as a clip"), 9 out of the 39 who agreed with this statement in Round 1, disagreed with it at Round 3 and this change was statistically significant ($p=0.021$). Commentary analysis showed three main themes: 1) the need for a more clinically

realistic and rheumatology-specific “complete” vs “limited” scan, possibly applying these terms towards disease-specific (eg. rheumatoid arthritis) evaluation as opposed to utilizing anatomic region-based descriptions determined largely by radiologists; 2) current coding and billing constrain the “complete scan” definition.

Conclusion: Many scanning conventions from 2011 remain relevant in current practice. Documentation standards from 2011 may need revision. Current definitions of “complete” and “limited” scans may not accurately reflect relevant usage of MSUS in current rheumatology practice, and descriptions based on disease-based evaluations should instead be considered.

Table 1. Scanning Conventions and Documentation: Levels of Agreement and Disagreement with 2011 Consensus Statement, Delphi rounds 1-3, N=46

2011 Consensus Statements	Agreement vs. Disagreement	Proposed Alternative statement
Scanning Conventions		
The radiologic anatomic position is used as a reference with palms facing forward, hence the left side of the ultrasound monitor screen is medial, cranial, ulnar or tibial. (SC1)	44 (95.7%) vs. 2 (4.3%)	The radiologic anatomic position can be used as a reference with palms facing forward, hence the left side of the ultrasound monitor screen is medial, cranial, ulnar or tibial or individual sonographer consistent orientation is maintained. Agreement with alternative: 14 (30.4%) Disagreement with alternative: 32 (69.6%)
The left side of the ultrasound monitor screen is designated anterior when a choice exists to scan posterior or anterior in the sagittal plane (for example: lateral hip). (SC2)	40 (87%) vs. 6 (13%)	When a choice exists to orient the probe anterior or posterior for lateral examinations, individual sonographer consistent orientation is maintained. Agreement with alternative: 8 (17.4%) Disagreement with alternative: 32 (82.6%)
“Longitudinal” scans imply alignment of the probe in the longitudinal axis of the structure under examination. (SC3)	45 (97.8%) vs. 1 (2.2%)	-
“Transverse” scans imply alignment of the probe transverse to the structure under examination. (SC4)	44 (95.7%) vs. 2 (4.3%)	-
“Orthogonal” scans imply that longitudinal and transverse scans have been done. (SC5)	44 (95.7%) vs. 2 (4.3%)	“Orthogonal” scans imply that longitudinal and transverse scans have been done to document pathology in two perpendicular planes. Agreement vs. Disagreement with alternative: 24 (52.2%) Vs. 22 (47.8%)
Documentation		
All static normal scans should be documented. (D1)	43 (93.5%) vs. 3 (6.5%)	-
All abnormal scans should be documented. (D2)	44 (95.7%) vs. 2 (4.3%)	-
A dynamic scan should be saved as a clip. (D3)	31 (67.4%) vs. 15 (32.6%)	A dynamic scan can be saved as a clip or as static images of abnormal findings or as images of accurate procedure performance. Agreement vs. Disagreement with alternative: 33 (71.7%) vs. 13 (28.3%)
A complete musculoskeletal ultrasound examination of an extremity consists of real time scans of a specific joint that includes examination of the muscles, tendons, joint, other soft tissue structures, and any identifiable abnormality. (D4)	42 (91.3%) vs. 4 (8.7%)	A comprehensive rheumatology musculoskeletal ultrasound examination consists of real time scans of a specific region that can include examination of the muscles, tendons, joints, other soft tissue structures, and any identifiable abnormality relevant to a rheumatic differential diagnosis or a multi structure rheumatic disease assessment tool. Agreement vs. Disagreement with alternative: 30 (65.2%) vs. 16 (34.8%)
A limited musculoskeletal examination of an extremity looks at a specific anatomic structure in the extremity region. (D5)	46 (100%) vs 0	A limited or focused musculoskeletal examination of an extremity looks at a specific anatomic structure in an extremity region. Agreement vs Disagreement with alternative: 29 (63%) vs 17 (37%)

Disclosure: K. Torralba, None; M. J. Nishio, None; R. G. Thiele, AbbVie Inc., 8, Amgen Inc., 8; R. Fairchild, None; K. Choi, None; L. Salto, None; A. C. Cannella, None; E. Kissin, None.

Abstract Number: 1194

The Physiological Changes of the Enthesis in Response to Age, Body Mass Index and Physical Activity: An Ultrasound Study in Healthy People

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Imaging of Rheumatic Diseases Poster II: Ultrasound

Session Type: ACR Poster Session B

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

Background/Purpose: Entheses are exposed to biomechanical stress throughout life and sonographic enthesal abnormalities may not reflect an underlying inflammatory arthritis in all cases. In this study, we aimed to determine the prevalence of enthesal abnormalities in healthy subjects and explore factors that are contributing for the occurrence and severity of these findings.

Methods: Eighty healthy subjects who had no joint pain, recent joint trauma or surgery had ultrasound (US) scans for the insertions of the triceps, quadriceps, Achilles tendons and plantar fascia and the origins and insertions of the patellar tendons. The enthesis were scored for hypoechogenicity, thickening, Doppler signals, enthesophytes, erosions and calcifications, semi quantitatively between 0-3, calculating the total enthesitis score. The correlation between the total enthesitis score and various demographic and lifestyle factors was evaluated. A multiple linear regression was calculated to predict total US score based on age, sex, smoking status, BMI, and physical activity.

Results: Doppler signals and erosions were detected in 10% and 6.25% of the participants, respectively. Thickening was the most frequent sonographic enthesal lesion that could also be seen in the absence of hypoechogenicity (70% of the proximal patellar tendon origin). Enthesophytes were common at the Achilles tendon insertion seen in 78.7% of the participants. The total US scores correlated with age ($r:0.561$, $p<0.001$) and body mass index ($r:0.344$, $p:0.022$). Smokers had higher scores (14.0 ± 10.6 vs 9.02 ± 9.6 , $p:0.010$), similar to participants who were exercising more (13.53 ± 11.1 vs 7.94 ± 8.4 , $p:0.005$). In addition, men had higher scores than women (15.73 ± 11.6 vs 8.06 ± 8.2 , $p:0.001$) (Figure 1). In linear regression model age, gender, BMI and physical activity independently predicted to total US score (Table 1).

Figure 1: Differences within US scores and gender, BMI, smoking status and physical activity.

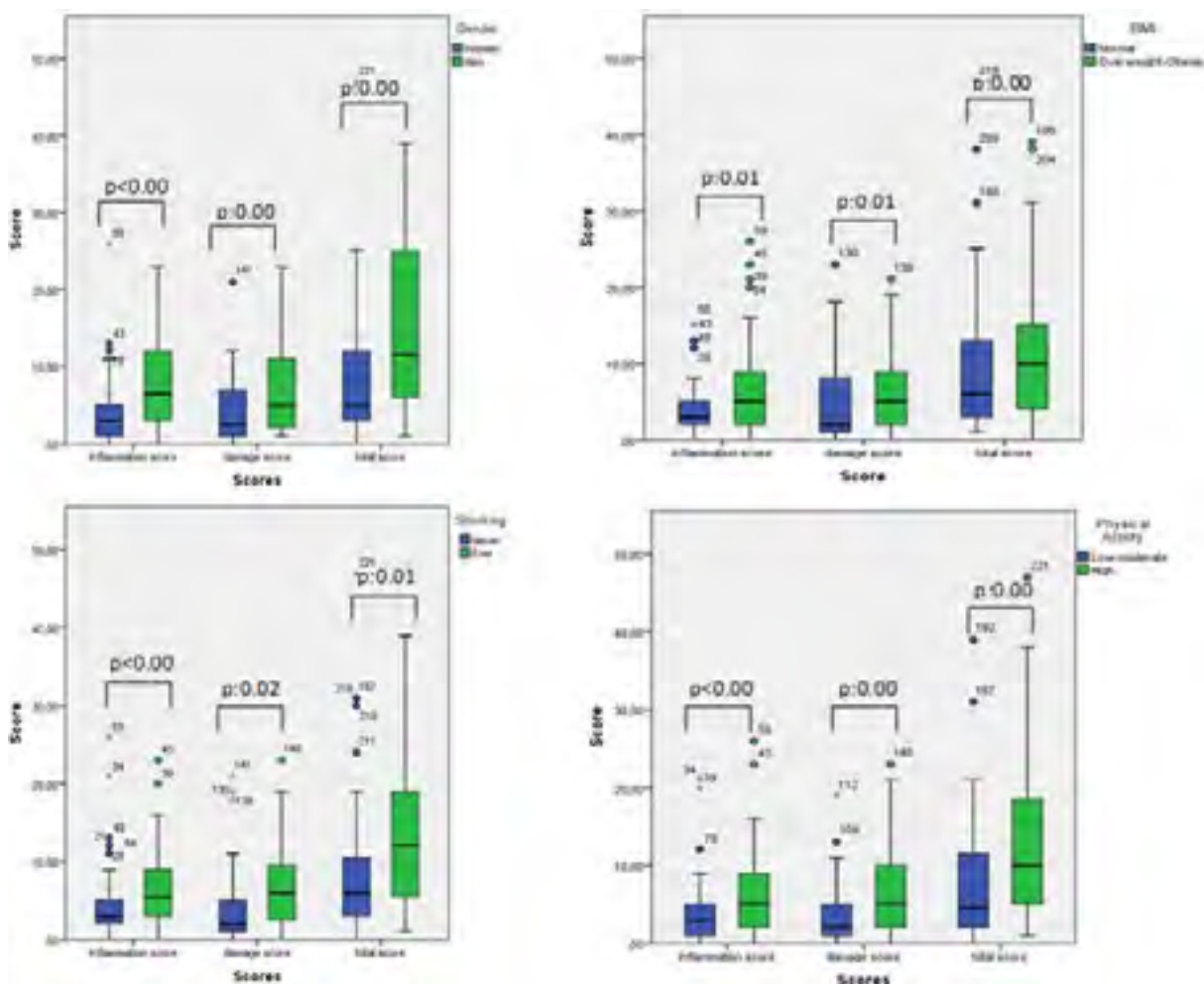


Table 1. Linear regression results of the factors affecting total US score

	Coefficients (B)	95 % CI	P
Age	0.358	0.253-0.463	<0.001
Gender	5.053	1.820-8.287	0.003
Smoking status	-0.146	-3.461-3.168	0.930
BMI	0.613	0.248-0.978	0.001
Physical activity	4.418	1.253-7.583	0.007

Conclusion: There are physiological changes within the enthesis that are associated with older age, higher BMI and physical activity. The enthesal abnormalities observed in the healthy enthesissupport the impact of biomechanical forces on the enthesis, not necessarily reflecting a pathology leading to any symptoms. Men and smokers, both of which are risk factors for radiographic severity in AS, have higher enthesal scores on ultrasound and the effect of these factors on the enthesis may be an explanation for the severe abnormal response on the spine in AS.

Disclosure: D. Solmaz, None; S. Bakirci, None; W. Stephenson, None; L. Eder, None; J. Roth, None; S. Z. Aydın, None.

Abstract Number: 1195

The Evaluation of the Small Enthesis of the Hands By Ultrasound: A Study on Healthy Subjects

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Imaging of Rheumatic Diseases Poster II: Ultrasound

Session Type: ACR Poster Session B

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

Background/Purpose: The literature on sonographic enthesitis is primarily based on the large enthesis, ignoring the involvement of the small enthesis such as the hands. In this study, we aimed to determine the prevalence of enthesal abnormalities in small enthesis of the hands in healthy subjects and explore factors that are contributing to the occurrence of these findings.

Methods: Healthy subjects who had no joint pain, recent joint trauma or surgery had US scans of the flexor and extensor tendon insertions to the DIP and extensor tendon insertions to the middle phalanx at the level of the PIP, on the 3rd digits, on both hands. The enthesis were scored as present or absent for elementary lesions of enthesitis (hypoechoogenicity, thickening, Doppler signals, enthesophytes, erosions and calcifications) and osteophytes were also recorded.

Results: Within 80 healthy subjects (mean age: 45.0 ± 16.1; 62.5% female) 8 had OA. The enthesophytes were the most frequent elementary lesion of enthesitis that could also be seen in the absence of other lesions and were detected in 15% of the DIP extensor tendon insertions, 3.75% of the DIP flexor tendon insertions and 3.75% of the PIP extensor tendon insertions (Figures 1 and 2). 41% of the patients with enthesophytes at the DIP extensor tendon insertion also had osteophytes at the same site, which was significant higher than people without any enthesophytes (5/12 vs 1/68 p<0.001). Patients with enthesophytes were older (67.5 ± 12.6 vs 41.3 ± 13.3; p<0.001) and more frequently men (8/12 vs 22/68; p:0.048). The other elementary lesions were seen in the minority of the digits (Figure 1).

Conclusion: Enthesophytes of the small enthesis are frequent in healthy people and these lesions can be seen in the absence of other elementary lesions. It can be challenging to differentiate enthesophytes from osteophytes at the level of the DIP joints. Therefore the definition of enthesitis for the small enthesis may exclude enthesophytes not to overall patients with enthesitis. The other features of enthesitis were not common in healthy people, suggesting a good specificity to reflect pathology when detected, however studies on disease groups are needed to clarify.

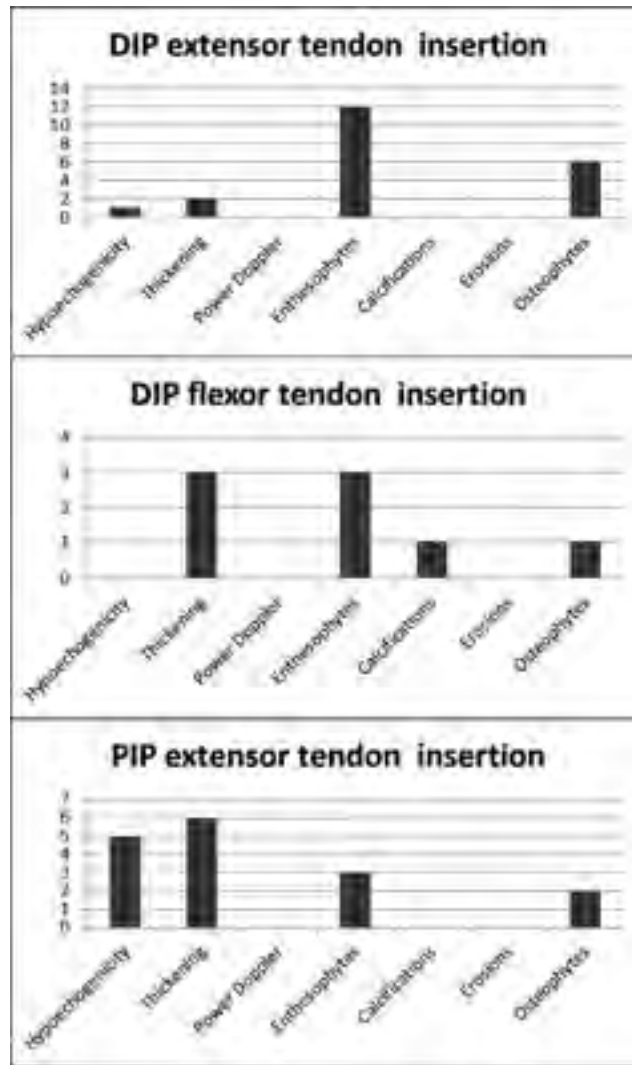


Figure 1. Elementary lesions of enthesitis on extensor and flexor tendon insertions at the DIP joint and flexor tendon insertion at the PIP joint level.

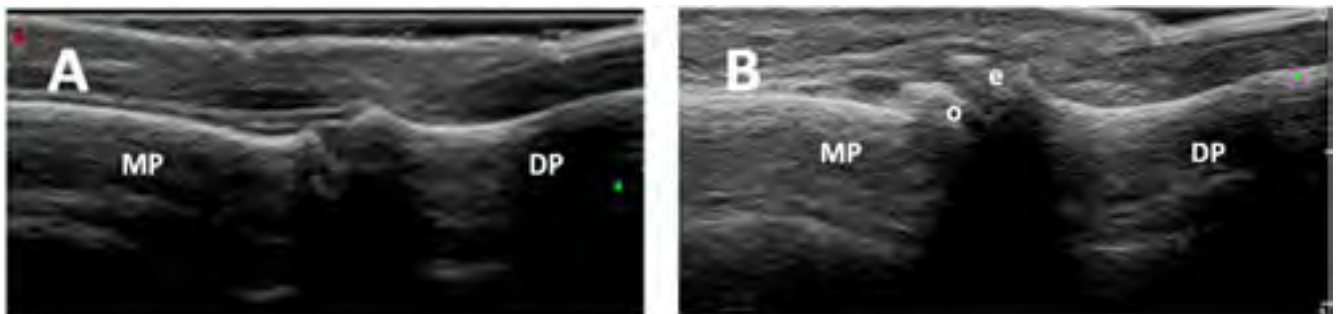


Figure 2. Longitudinal scans of the extensor tendon insertion to the distal phalanx. A: A healthy enthesis B: Thickening and hypoechoogenicity with enthesophyte as well as an osteophyte. MP: Middle Phalanx; DP: Distal Phalanx; o: osteophyte; e: enthesophyte

Disclosure: S. Bakirci, None; D. Solmaz, None; W. Stephenson, None; L. Eder, None; J. Roth, None; S. Z. Aydın, None.

Enthesal Involvement in Asymptomatic Healthy Subjects: Prevalence and Distribution of the Ultrasound Elementary Lesions of Enthesitis, with a Particular Focus on Those Indicating “Active” Inflammation

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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

Background/Purpose: According to the OMERACT definitions, thickening, hypoechogenicity and power Doppler (PD) signal represent the US findings indicative of enthesal “active” inflammation. However, these US elementary findings can be detected also in healthy subjects as shown in other studies, and a variable prevalence has been reported. Despite an experts agreement has been obtained, further investigation is still required to gather more data especially regarding entheses in healthy subjects. To explore the prevalence and distribution of the US findings indicative of enthesitis, defined according to the OMERACT definitions, in a group of asymptomatic healthy subjects.

Methods: US and clinical assessment of quadriceps, patellar and Achilles tendons, and plantar fascia entheses were performed on 82 healthy volunteer subjects. Exclusion criteria: previous surgery or procedural interventions in the knees and/or ankles, clinical enthesitis on the physical examination, history of enthesal pain in the 3 months preceding the evaluation, previous diagnosis of rheumatic disease, family history of psoriasis or inflammatory bowel disease. The US examination was carried out with a My Lab Twice (Esote S.p.A. Genoa, Italy), working with a high frequency linear probe (6-18 MHz) and at a Doppler frequency of 9.1-11.3 MHz. The US enthesal abnormalities of “structural damage” (enthesophyte, bone erosion and calcification) and “active enthesitis” (thickening, hypoechogenicity and PD signal) were identified according to the OMERACT definitions. Moreover, a semiquantitative score for the PD signal was used (0-3).

Results: Eight hundred and twenty entheses were evaluated in 82 subjects [age (mean \pm SD) 44.0 \pm 14.8, 59.8% females]. The prevalence and distribution of the US findings indicative of enthesitis are reported in Table.1. One or more US finding indicative of “active” inflammation were found in at least one entheses in 30 out of 82 healthy subjects (34.1%), in 69 out of 820 entheses (8.4%). US findings of “active” inflammation were found as isolated in 61 out of these 69 entheses, (38 thickening, 12 hypoechogenicity, 11 PD signal) and in combination in the remaining 8 entheses (thickening + hypoechogenicity).

Table 1. Prevalence and distribution of the US abnormalities at the lower limb entheses in healthy subjects

Ultrasound findings	Healthy subjects		Entheses of the lower limbs							Total		
			Quadriceps tendon	Patellar tendon proximal insertion	Patellar tendon distal insertion	Achilles tendon	Plantar fascia					
Thickening	22	26.8%	07	8.1%	5	3.7%	17	8.1%	15	7.0%	44	5.4%
Hypoechogenicity	11	13.4%	4	2.4%	0	0.0%	3	1.8%	8	4.0%	4	2.4%
PD signal ≥ 1	7	8.1%	3	2.4%	1	0.6%	4	2.0%	0	0.0%	8	1.0%
PD signal > 1	1	1.2%	1	0.1%	0	0.0%	0	0.0%	0	0.0%	1	0.1%
Entesophyte	20	24.4%	18	8.5%	2	0.2%	1	0.2%	14	6.3%	4	2.4%
Bone erosion	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Calcification	21	25.0%	11	6.7%	0	0.0%	12	5.3%	10	5.1%	0	0.0%

Percentages refer to the total number of patients (n=82) and entheses (n=820), respectively. Legend: PD: power Doppler

Conclusion: The prevalence of the US findings of “active” inflammation, defined according to the OMERACT definitions, in a group of asymptomatic healthy subjects was low in relation to the total number of entheses but remarkable at subject-level. Combining US elementary lesions of “active” inflammation (i.e. PD signal ≥ 1 + enthesal thickening and/or hypoechogenicity) or considering as pathological only PD scores > 1 may increase the diagnostic accuracy of the US findings.

Reference:

- Terslev L et al. Defining enthesitis in spondyloarthritis by ultrasound: results of a Delphi process and of a reliability reading exercise. Arthritis Care Res (Hoboken).2014 May;66(5):741-8.

Disclosure: A. Di Matteo, None; E. Filippucci, None; E. Cipolletta, None; M. V. Martire, None; D. Jesus, None; M. Isidori, None; D. Corradini, None; W. Grassi, None.

Abstract Number: 1197

The Characteristics of the Distribution of Normal Feeding Vessels between Young and Elderly Adults in Wrist Joints of Healthy Volunteers Depicted By Ultrasound (MSKUS)

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Session Date: Monday, October 22, 2018

Session Title: Imaging of Rheumatic Diseases Poster II: Ultrasound

Session Type: ACR Poster Session B

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

Background/Purpose: Synovial vascularity as measured by power Doppler (PD) of MSKUS is correlated to rheumatoid arthritis disease activity, and PD signal reveals the prevalence of subclinical synovitis overlooked on physical examination. It is frequently difficult to distinguish bone erosion from normal concave surface of the bone. It is necessary for us to know these normal structures well in evaluating disease activity by using MSKUS. Here we examine the age-specific differences of normal feeding vessels and bone surface irregularity between in wrist joints. To elucidate the differences of distribution of feeding vessels and bone surface irregularity in wrist joints both young and older adults of healthy volunteers.

Methods: The dorsal side of wrist joints was scanned with 2D-probe in healthy volunteers (young <50 y.o., elder ≥50 y.o.). The distribution of feeding vessels in the capsule and the extensor (E.) tendon sheath (TS), and the evaluation of bone surface irregularity at lunate (Lu) were examined. The comparative review between young and elderly adults was validated.

Results: The distribution of feeding vessels in younger healthy volunteers (n=30; mean age 32.2±8.0) vs elderly healthy volunteers (n=21; mean age 66.0±7.2) were near-Trapezoid (Rt100.0%vs100.0%, Lt100.0%vs100.0%; p=1.00), E. digitorum TS (Rt86.7%vs81.0%; p=0.59, Lt66.7%vs76.2%; p=0.47), E. digiti minimi TS (Rt30.0%vs52.4%; p=0.11, Lt30.0%vs66.7%; p=0.0089), near-Capitate (Rt23.3%vs42.9%; p=0.14, Lt30.0%vs47.6%; p=0.21), near-TFCC (Rt16.7%vs19.0%; p=0.83, Lt30.0%vs38.1%; p=0.56), distal radial side of radiocarpal joint (Rt20.0%vs42.9%; p=0.08, Lt23.3%vs28.6%; p=0.68), distal end of Ulna (Rt10.0%vs42.9%; p=0.006, Lt16.7%vs28.6%; p=0.31). Feeding vessels from vascular channels were depicted at Lu (Rt53.3%vs52.4%; p=0.95, Lt46.7%vs66.7%; p=0.16), Radius (Rt20.0%vs33.3%; p=0.29, Lt16.7%vs23.8%; p=0.54), Triquetrum (Rt10.0%vs42.9%; p=0.0057, Lt16.7%vs33.3%; p=0.17) and Capitate (Rt6.7%vs33.3%; p=0.013, Lt10%vs33.3%; p=0.0395). The bone surface irregularity as a transverse diameter (Mean±S.D.) at Lu of dominant hand in both groups were 1.26±0.33vs1.14±0.2mm; p=0.21, respectively.

Conclusion: The frequency of feeding vessel's distributions in elderly adults were significantly higher at E. digiti minimi TS, distal end of Ulna and Triquetrum/ Capitate vascular channels compared to those of younger adults. It is suggested that these differences are crucial to evaluate the age-specific synovitis by ultrasound.

Disclosure: K. Misaki, None; K. Ikeda, None; K. Inoue, None; M. Miyazaki, None; N. Dobashi, None; Y. Imaizumi, None.

Abstract Number: 1198

Ultrasound-Detected Joint Erosions in Rheumatoid Arthritis: What Every Sonographer Should Know

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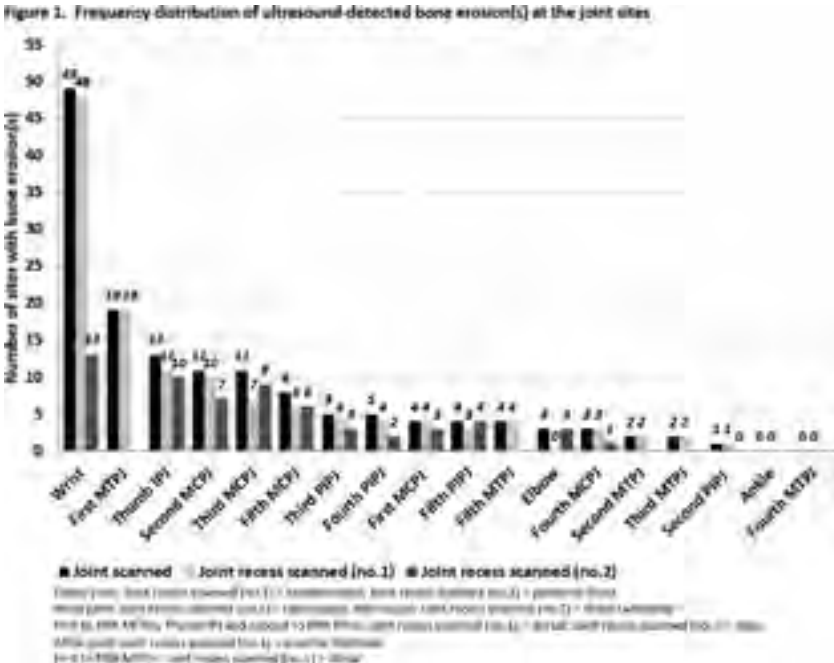
SESSION INFORMATION

Session Date: Monday, October 22, 2018
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Background/Purpose: Previous work in rheumatoid arthritis (RA) on bone erosion(s) using ultrasound (US) focused mostly on small joints of the fingers and toes. We aim to gain further insight into US-detected bone erosion(s) by including a larger number of joints and studying them in relation to US inflammatory joint findings.

Methods: 36 joints and 60 joint recesses were scanned per patient (table 1). At each joint recess scanned, US power Doppler (PD) and grey-scale (GS) joint inflammation were graded semi-quantitatively (0-3) and these scores were summed to obtain a combined US (CUS) score, while bone erosion(s) was scored dichotomously (1=yes/0=no). As US findings for different joints in the same patient may not be independent, Generalized Estimating Equations (GEE) analysis was used to compare mean PD, GS and CUS scores between (a) joint recesses scanned with bone erosion(s) detected and (b) joint recesses scanned without bone erosion(s) detected. Means and 95% CIs were estimated using GEE with robust Huber-White variance estimates.

Results: 1080 joints and 1800 joint recesses were scanned in 30 RA patients all of whom fulfilled the 1987 and/or 2010RA classification criteria. The patients' baseline characteristics were: mean age, 61.7 years; 93.3% female; 76.7% Chinese; mean (SD) disease duration, 70.3(61.2) months; mean (SD) DAS28, 3.58 (1.20). 144/1080 (13.3%) joints and 189/1800(10.5%) joint recesses scanned exhibited bone erosion(s), respectively. Figure 1 shows the frequency distribution of US-detected bone erosion(s) at the jointsites. Of the 144 joints with bone erosion(s), the 5 joints most frequently encountered were: wrist, n=49 (34.0%); first MTPJ, n=19 (13.2%); thumb IPJ, n=13 (9.0%); second MCPJ, n=11 (7.6%) and third MCPJ, n=11 (7.6%). Comparing joint recesses scanned with bone erosion(s) detected versus those scanned with no bone erosion (s) detected, mean (95% CI) PD, GS and CUS scores were 0.36 (0.21, 0.50) vs. 0.013 (0.002, 0.024), 1.77 (1.54, 2.00) vs. 0.47 (0.40, 0.55), and 2.13 (1.78, 2.47) vs. 0.49 (0.41, 0.57), respectively. P-values were all <0.001.



Conclusion: From the literature, second and fifth MCPJ and fifth MTPJ were recommended US target joints in RA. In our study cohort, other than the second MCPJ, the wrist, first MTPJ, thumb IPJ and third MCPJ were among the 5 joints most commonly affected by bone erosion(s). Joint sites with bone erosion(s) were more likely to exhibit greater joint inflammation severity seen on both PD and GS US. Sonographers assessing structural joint damage should pay particular attention to these joints when scanning for bone erosions in RA.

Table 1. Joints and joint recesses scanned

	Bilateral elbow joints	Bilateral wrist joints	Bilateral first to fifth MCPJs, thumb IPJs, second to fifth PIPJs	Bilateral ankle joints	Bilateral first to fifth MTPJs
Joint recesses scanned	1). Humeroradial 2). Posterior fossa	1). Radiocarpal, intercarpal (dorsal) 2). Distal radioulnar (dorsal)	1). Dorsal 2). Volar	1). Anterior tibiotalar	1). Dorsal

Disclosure: Y. K. Tan, None; H. Li, None; J. C. Allen Jr, None; J. Thumboo, None.

The Use of Musculoskeletal Ultrasound to Assess Remission in Patients with Rheumatoid Arthritis

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Background/Purpose: Patients with rheumatoid arthritis (RA) should achieve remission rapidly to avoid irreversible joint sequela. Studies have shown that patients with apparent clinical remission have positive power Doppler on ultrasound examination, suggestive of ongoing inflammatory disease activity. The purpose of this study was to retrospectively determine the flare rate at 12 months in patients with RA, who had a diagnosis of clinical remission and ultrasound remission compared with patients who had only a diagnosis of clinical remission.

Methods: In this retrospective study, we used medical charts to identify patients with RA and a diagnosis of remission made between January 2012 and January 2017. Patient demographics and information on treatment and outcome were retrieved from the medical charts (Table 1). Patients were defined to be in remission when they had ≤ 1 swollen joint and diagnosis of remission by clinician. We then separated patients in 2 groups based on whether the patient had undergone ultrasound. We retrospectively compared the flare rate at 12 months, in patients who had a clinical diagnosis of remission and an ultrasound diagnosis of remission versus patients who had a clinical diagnosis of remission. Flare during follow-up was defined by clinician diagnosis and >1 swollen joint and/or need to change the medication regimen for RA. We also calculated the time between diagnosis of remission and flare.

Results: A total of 121 patients were included, 108 females and 13 males. Clinical and ultrasound remission was diagnosed in 34 patients while 87 patients were diagnosed with clinical remission. Baseline characteristics in 2 groups were similar, except for longer duration of disease, more biologic therapy received in the past and more smokers in the group without ultrasound (Table 1). Of the patients who had a diagnosis of remission with ultrasound, 7 (20.6%) flared during follow-up compared to 37 (42.5%) who did not have an ultrasound. After accounting for smoking as a covariate, this difference in flare rates was statistically significant ($p=0.047$). The time to first flare appeared longer in the ultrasound group compared to the clinical group, although this difference was not significant ($p=0.105$).

Conclusion: This retrospective study demonstrated a smaller incidence of RA flare at 12 months in patients who had a clinical diagnosis of remission with ultrasound compared to patients who had a diagnosis of remission without ultrasound. Further prospective studies comparing the clinical approach with combined approach are needed to identify the real value of ultrasound for RA remission diagnosis

	All (n= 121)	Ultrasound (n=34)	Clinical (n=87)
Age (years) at remission, mean (SD)	61.72	57.09	63.54
Female Gender, n (%)	108 (85.1)	28 (82.4)	75 (86.2)
Years since diagnosis, mean (SD)	8.1	4.2	11.2
Smoking when remission diagnosed, n (%)	19 (15.7)	3 (9.4)	16 (18.6)
Biologic DMARDs in the past n (%)	49 (40.5)	7 (21.2)	42 (48.3)
CDAI when remission diagnosed, mean (SD)	6.3	8.3	5.6
HAQ when remission diagnosed, mean (SD)	1.56	1.00	1.74
Swollen joint when remission diagnosed, (n) mean (SD)	0.29	0.24	.31
Positive Rheumatoid factor, n (%)	58 (47.9)	17 (50)	41 (55.8)
Rheumatoid factor value (if positive), mean (SD) IU/ml	325.49	711.80	164.53
Positive anti-CCP, n (%)	62 (52.2)	16 (46.4)	46 (52.4)
Anti-CCP value if positive, mean (SD) U/L	157.25	133.23	168.81
CRP when remission diagnosed, mean (SD) mg/L	4.27	3.093	4.750
ESR exact value, mean (SD) mm/hour	15.11	11.76	16.46
CDAI at time of flare diagnosis, mean (SD)	20.59	16.20	21.88
HAQ at time of flare diagnosis, mean (SD)	2.83	1.3300	3.0471
Patients on synthetic DMARDs at remission diagnosis, n (%)	96 (79%)	29 (85%)	67 (77%)
Patients on biologic DMARDs at remission diagnosis, n (%)	39 (32%)	5 (15%)	34 (39%)

Disclosure: M. Allen, None; M. Larche, None; K. A. Beattie, None.

Abstract Number: 1200

Unilateral Ultrasound Scoring Methods for Synovitis in Rheumatoid Arthritis: An Agreement Study Exploring the Most Inflammatory Active Side

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SESSION INFORMATION

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Background/Purpose: Several unilateral scoring systems have been proposed to increase the feasibility of ultrasound (US) for joint evaluation in rheumatoid arthritis (RA) patients. Both the clinically most affected side and the dominant hand have been proposed as the default monitoring approach during treatment, however, no consensus exists on which side to choose. The aim is to evaluate if the dominant hand or the hand with more clinically swollen joints is per default the more inflammatory active side, as judged by US, to be chosen for unilateral scoring systems in RA patients.

Methods: We performed an agreement study exploring the impact on US scoring methods in a cross-sectional study of an early RA (ARCTIC trial, n=230) and established RA cohort (ULRABIT trial, n=212) with patients initiating conventional and biological Disease Modifying Anti-Rheumatic Drugs, respectively. Tender and swollen joint count for 28 joints (TJC28 and SJC28) and C-reactive protein (CRP mg/L) were obtained. Using the hands as model, bilateral MCP 1-5, PIP 2+3 and wrists were evaluated by US using a 0-3 scoring system for both grey-scale (GS) and power Doppler (PD) US according to the atlas by Hammer et al. A GS sum score, a PD sum score and a global synovitis score (GLOSS) were calculated for each hand (0-30). According to our prespecified protocol a reasonable equivalence margin in this study (agreement between groups) was defined to correspond to a 95% Confidence Interval around the observed paired mean difference: -2.99 to +2.99; a difference of at least 3 in sum score defined a clinical significant difference defining which hand was more inflammatory active.

Results: In total, 442 RA patients were included; 71% women, 79% anti-CCP pos, 71% RF pos, median(IQR) age 54(42-62) years, CRP 7(3-16), SJC28 5(3-26) and TJC28 6(2-28). The median(IQR) PD sum score was 3(0-7) for right hand and 2(0-5) for left hand, GS sum score was 5(2-9) for both hands, and GLOSS was 5(2-10) for right hand and 5(2-9) for left hand.

The dominant hand was not more inflammatory active than the non-dominant (mean difference, 95%CI) for PD sum score -0.58(-1.35 to 0.2), GS sum score -0.69(-1.61 to 0.24) and GLOSS -0.79(-1.76 – 0.18). This was in clear contrast to analyses of the hand with more swollen joints which was statistically significantly more inflammatory active (p<0.0001): for PD sum score 1.70(0.94 to 2.47), GS sum score 2.21(1.30 to 3.12) and GLOSS 2.31(1.36 to 3.26) – see table.

Table Ultrasound inflammatory activity in the dominant hand versus non-dominant hand and in the hand with clinically more swollen joints versus less swollen joints using different unilateral scoring systems			
	Doppler sum score (0-30)	GS (0-30)	GLOSS (0-30)
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
*Dominant hand			
Dominant	4.3 (4.1 – 4.4)	7.3 (7.1 – 8.4)	6.3 (7.4 – 8.8)
Non-Dominant	4.3 (3.3 – 4.8)	7.1 (6.4 – 7.7)	7.8 (8.6 – 8.2)
Difference	-0.58 (-1.15 – 0.10)	-0.69 (-1.61 – 0.24)	-0.79 (-1.6 – 0.18)
P-value	0.14	0.15	0.17
*Clinical assessment			
Hand with more clinically swollen joints	5.37 (4.8 – 5.9)	8.5 (7.9 – 9.16)	8.8 (8.2 – 9.5)
Hand with less clinically swollen joints	3.64 (3.1 – 4.2)	8.3 (6.7 – 8.9)	6.5 (5.8 – 7.2)
Difference	1.73 (1.24 – 2.47)	0.2 (1.32 – 1.85)	2.31 (1.63 – 3.4)
P-value	<0.0001	<0.0001	<0.0001

*Analysed using a t-test for the specific analysis and test (ARCTIC and ULRABIT, respectively) as a main effect, and the patient ID was included as a random effect

Conclusion: Based on this study, the dominant hand is not significantly more affected than the non-dominant hand regarding inflammatory activity evaluated by US. As the hand with clinically more swollen joints are more inflammatory active by PD sum score, GS sum score and GLOSS, the hand with most swollen joints is suggested to be chosen as basis for unilateral scoring systems.

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Finger Extensor Tendon Involvement Is Frequent in Early Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Background/Purpose: Finger extensor involvement (FET) at ultrasound examination (US) was previously described in patients suffering from early psoriatic arthritis. Contradictory results were published in patients suffering from rheumatoid arthritis. We aimed to assess the involvement of FET in early rheumatoid arthritis (ERA) patients and in asymptomatic subjects (CTR)

Methods: Inclusion criteria for ERA patients were: less than 6 months since the ERA diagnosis; age >18 years; without DMARD treatment or oral glucorticoids at US examination. Inclusion criteria for CTRL subjects were : age >18 years; no pain in hands and fingers (VAS pain =0/100); no known rheumatic disease such a systemic diseases, rheumatoid, psoriatic arthritis, spondyloarthritis, hand osteoarthritis, gout, chondrocalcinosis; no psoriasis, no inflammatory bowel diseases. US assessments were performed blindly to the clinical and laboratory data. FET were assessed in longitudinal and in transverse view at the metacarpo phalangeal joint (MCP) and proximal phalangeal joint (PIP) level both in grey-scale (GS), power Doppler (PD) and in color Doppler (CD) mode. In addition the following joints were assessed for the presence and grade (0-3) of GS/PD synovitis

Results: Sixty-two consecutive ERA patients and 34 CTR were included in this study. Mean age and gender distribution were comparable between ERA and CTR (47,3±14,5 vs. 43,4±12,5). ACPA were present in 61%, rheumatoid factor in 54% and bone erosions in 27% of ERA patients. 57% of ERA patients presented with FET and 0% of CTR (p<0.001). The delay between the first symptom and diagnosis, the DAS28CRP, SDAI, CDAI, CRP level, 44TJC, 44SJC, HAQ did not differ significantly between patients with FET involvement and those without. In univariate analysis, the presence of FET involvement was significantly associated with the presence of bone erosions (p=0.02), ACPA (p=0.002), rheumatoid factor (RF) (p=0.02) and tobacco use (p=0.02). In multivariate analysis, the presence of FET involvement was significantly associated with the presence of bone erosions (p=0.01), ACPA (p=0.001) and RF (p<0.01).

Conclusion: FET is relatively frequent in ERA patients and it is not present in asymptomatic subjects. Our results show that FET involvement is associated with the presence of ACPA, rheumatoid factor and bone erosions, thus identifying patients with possibly more aggressive or severe disease at baseline.

Disclosure: M. Maruseac, None; P. Durez, None; A. Nzeusseu Toukap, None; M. Stoenoiu, None.

Tenosynovial Aspiration By Ultrasound Guidance: Even Small Volumes Can Have a Big Impact

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SESSION INFORMATION

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Background/Purpose: Rheumatologists commonly use synovial fluid analysis to help establish a diagnosis in patients with joint effusions. Although tenosynovial (TS) effusions are common in rheumatic conditions, there is no guide to inform the interpretation of fluid aspirated from tendon sheaths. Musculoskeletal ultrasound (MSUS) has allowed for routine aspiration of TS effusions. To better characterize TS fluid and MSUS findings in rheumatic diseases, we organized a multi-center collaboration to prospectively analyze TS findings on patient aspirations. This is an interim report of the first eight months of the study.

Methods: Patients with TS aspiration planned as part of routine care were included. We are collecting information on patient demographics, underlying rheumatic disease, involved tendon location, duration of TS symptoms, TS fluid characteristics, MSUS appearance and tendon specific diagnosis. Specific TS fluid data collected includes volume (hemocytometer used if fluid volume below clinical laboratory threshold), gross appearance, leukocyte count, and crystal identification. This interim descriptive analysis reports on the patient and disease characteristics of subjects enrolled to date.

Results: 59 of 100 subjects have been enrolled at 10 participating sites. Table 1 reports the patient characteristics, involved tendons and volume of TS fluid aspirated. Four patients presented after trauma to the involved tendon. 78% of all TS aspirations were derived from 5 locations: 4th extensor compartment, bicipital tendon, extensor carpi ulnaris, posterior tibial and peroneal tendons. 14 (24%) of the aspirations had a fluid volume of <0.5mL. Table 2 shows the established rheumatologic diagnosis, and diagnosed cause of TS effusion after the aspiration. Of note, only 4 aspirations were from patients known to have a crystalline diagnosis, but a total of 12 were diagnosed after aspiration. Rheumatoid arthritis was the most common patient diagnosis to require a TS aspiration. Only one case of infection - coccidioidomycosis was diagnosed so far.

Table 1. General patient characteristics

Characteristics	Results N=59
Age (years)	60 (21-95)
Mean (range)	
Gender, N (%)	
Males	20 (33.9)
Females	39 (66.1)
Duration of tendon disease	
< 1 week	2 (3.4)
>1 week to <1 month	8 (13.6)
>1 month to <1 year	34 (57.6)
>1 year	15 (25.4)
Involved tendon N (%)*	
Wrist extensor compartment 4	18 (30.5)
Bicipital tendon	9 (15.3)
Posterior tibial tendon	7 (11.9)
Wrist extensor compartment 6 / ECU	7 (11.9)
Peroneal tendon	5 (8.5)

Table . (Cont'd)

Characteristics	Results N=59
Extensor digitorum longus, lower limb	4 (6.8)
Wrist extensor compartment 1	3 (5.1)
Anterior tibial tendon	2 (3.4)
Wrist extensor compartment 2	1 (1.7)
Wrist extensor compartment 3	1 (1.7)
Wrist flexor tendon	1 (1.7)
Finger flexor tendon, second digit	1 (1.7)
Aspirated fluid volume, mL	1.3 (0.03 – 5.0)
Mean (Range)	
Aspirated fluid volume below 0.5 mL, N (%)	14 (23.7)

N: number; %: percentage; ECU: extensor carpi ulnaris; mL: milliliters; *percentages do not add up to 100 due to rounding to one decimal place.

Table 2. Patient level diagnosis pre-aspirations, and tenosynovial level diagnosis post-aspiration

Pre-existing Rheumatic Diagnosis at Presentation	Patients, N	Tenosynovial Diagnosis Post-aspiration, N
Uncertain/No diagnosis	25	9
Rheumatoid arthritis	11	11
Seronegative inflammatory arthritis	10	10
CPPD	3	9
Mechanical	0	9
Gout	1	3
Vasculitis	2	0
Polymyalgia rheumatica	0	3
Tendonitis	3	0
Drug-induced	0	2
Systemic lupus erythematosus	2	1
Infection	1	1
Osteoarthritis	1	0
IRIS	0	1

CPPD: calcium pyrophosphate deposition; IRIS: immune reconstitution inflammatory syndrome; N: number.

Conclusion: TS pathology occurs in a variety of inflammatory and non-inflammatory diseases commonly seen in rheumatology. MSUS guidance allows aspiration of very small volumes of TS fluid. Automated cell counts may not be possible on the small volumes obtained, but can be determined using a manual hemocytometer. TS aspirates can be used to establish a diagnosis, particularly crystalline forms of arthritis. The distribution of TS effusions could be used to focus teaching and performance of MSUS to the most frequently affected areas.

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Abstract Number: 1203

Tenosynovitis Detected By Ultrasound Predicts Arthritis Onset in Individuals at Risk of Developing Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Imaging of Rheumatic Diseases Poster II: Ultrasound

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Background/Purpose: The urgent need for identifying imaging and serological markers that early predicts rheumatoid arthritis (RA) is clinically important. We aim to identify ultrasound findings that precedes arthritis onset in Anti-Citrullinated Protein Antibody (ACPA) positive subjects at risk for developing RA.

Methods: Patients with musculoskeletal complaints and a positive ACPA test were referred from primary-care units to the rheumatology department for specialized care. Those lacking arthritis by clinical and ultrasound (US) examination were included in the prospective Risk-RA program, and monitored by a multidisciplinary team. Hand (Wrists, MCP's, PIP's, DIP's) and feet (symptomatic joints included), were US-assessed for synovial hypertrophy and Doppler activity according to the EULAR-OMERACT definitions. Hand tendons [extensor wrist tendon compartments (1-6) and flexor finger tendons (2-5)] were examined for signs of tenosynovitis (tendon sheath thickening and/or fluid, with/without Doppler activity). Serum samples from inclusion were analysed on a multiplex immunoassay.

Results: At inclusion, 66 Risk-RA patients [85% female, median(range) age 50(22-82)yrs] were US-evaluated, and followed until arthritis onset. Within 2½ yrs [median 8(1-27) months] from recruitment, 27 patients [41%, 86% female, median age 52(22-74) yrs] developed an arthritis diagnosis. Of these 27 patients, 7 had tenosynovitis detected by US at inclusion, and 7 more developed tenosynovitis at follow-up visits (n=14). At the time of diagnosis, 20 out of 27 patients presented with both tenosynovitis and synovitis.

Majority of patients with tenosynovitis (12 out of 14, 86%) and a minority without tenosynovitis (15 out of 52, 29%) developed arthritis, resulting in an increased relative risk of 3.0 (95% CI 1.8-4.8) to develop arthritis for those presenting with tenosynovitis at baseline or follow-up visits (p=0.001). The extensor-carpi-ulnaris wrist tendons (7 of 12 patients) and 2nd finger flexor-tendons (5 of 12 patients) were commonly affected.

Concentrations of the ACPA specific antibodies tended to be higher in tenosynovitis patients developing arthritis [n=12, median of 70(2-175) AU/ml for anti-CCP, median of 68(0-673) AU/ml for anti-CEP, median of 53(0-644) for anti-vimentin] as compared to those without tenosynovitis developing arthritis [n=15, median of 35(1-100) AU/ml for anti CCP, median of 12(0-1179) for anti-CEP, median of 29(0-332) for anti-vimentin]. Same trend was noted in tenosynovitis patients developing arthritis vs those without-tenosynovitis not-developing arthritis. The 2 tenosynovitis patients' not developing arthritis had lower levels of the antibodies compared to the tenosynovitis patients that developed arthritis.

No significant differences were noted in other patient baseline characteristics in those with tenosynovitis versus those without tenosynovitis [86 vs 85 % female, median age 54(29-71)yrs vs 50(22-82)yrs, mean visual analogue scale pain 34 vs 31, mean CRP 2.7 vs 3.2; and tender joint count 1.2 vs 0.7].

Conclusion: Tenosynovitis detected by ultrasound is highly predictive of rapid arthritis onset in ACPA positive subjects at risk for developing arthritis.

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Abstract Number: 1204

Experience Matters in Ultrasound Assessment of Gout

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Imaging of Rheumatic Diseases Poster II: Ultrasound

Session Type: ACR Poster Session B

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

Background/Purpose: Ultrasound has emerged in the field of rheumatology as a diagnostic aid for gout and other similar forms of arthritis. While a number of studies have looked into the test characteristics of ultrasound in diagnosing gout, only a few studies have examined the correlation between user experience with soft tissue ultrasound and diagnostic precision. Our study seeks to examine the correlation between the diagnostic accuracy of clinicians for gout using ultrasound and factors pertaining to experience and training.

Methods: Graduates of a MSUS (musculoskeletal ultrasound) training program were asked to anonymously complete a set of multiple-choice questions (single best answer type) asking for the most likely patient diagnosis based on de-identified ultrasound images of bilateral knee and 1st metatarsophalangeal joints from patients with non-tophaceous, crystal proven gout (n=6), crystal proven calcium pyrophosphate arthropathy (n=5), or synovial fluid and radiograph supported osteoarthritis (n=2). No normal images were included in the questionnaires. They were also asked information regarding the use of MSUS within the participant's practice/fellowship, years in practice, MSUS CME (Continuing Medical Education) scores. Participants were categorized into quartile groups based upon prior final exam scores. We used Wilcoxon Signed Rank Test and Spearman's Rank Correlation Co-efficient methods for the statistical analysis.

Results: Survey was sent to 240 clinicians, 32 graduates responded to the survey, 10 of which did not answer demographic questions. Clinicians with 5 or more years of practice had more correct answers in gout questions than the ones who practice less than 5 years (76% accurate answers in gout questions vs 54%, $p<0.05$; $r=0.54$). They also had more correct answers in overall questions including gout, pseudo-gout and OA compared to the clinicians who practice for less than 5 years, however this was not clinically significant (64% accurate answers in overall questions vs 52%, $p=0.08$; $r=0.32$). Differences in gout diagnosis accuracy based on CME credits was not statistically significant ($p=0.2$). There was no correlation found between general MSUS training exam scores and accuracy in diagnosing gout.

Conclusion: This is the first study which shows how the length of time in practice affects the accuracy in diagnosing gout, and that this effect is more significant than extent of CME hours or MSUS training exam performance. However, it should be noted that the training exam performance was not specific to gout.

Disclosure: B. Elkiran, None; E. Y. Kissin, None.

Abstract Number: 1205

Musculoskeletal Ultrasound and Conventional Radiography Evaluation of the Hip in Patients with Calcium Pyrophosphate Deposition Disease

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Background/Purpose: Conventional radiography (CR) and, more recently, US play a key role in the diagnosis of CPPD. To date, only a very few studies have investigated the diagnostic ability of US and CR in the assessment of hip joint in CPPD patients. To the best of our knowledge, there is no study that has compared the diagnostic accuracy of these two imaging techniques in the detection of calcium pyrophosphate (CPP) crystal deposits at the hip in patients with CPPD.

The aims of this study are to investigate the prevalence of the US findings indicative of CPP crystal deposits at the hip in patients with CPPD and to evaluate the diagnostic performance of US and CR and the agreement between these two imaging techniques in the evaluation of CPP crystal deposits at the hip in patients with CPPD.

Methods: Consecutive patients with “definite” CPPD, diagnosed according to the Ryan and McCarty criteria, and age/sex/body mass index-matched disease controls were enrolled. Inclusion criteria: knees and hips CR performed within the previous 6 months and synovial fluid analysis. Exclusion criteria: prior remarkable hip injuries, surgery procedures or severe osteoarthritis.

A rheumatologist, blinded to clinical data, performed bilateral US examinations of the hip in all patients, assessing the presence of CCP crystal deposits both at the acetabular fibrocartilage and at the hyaline cartilage of the femoral head. The OMERACT definition for the identification of CPPD by US were used. The US examination was carried out using a My Lab Twice US machine (Esaote S.p.A. Genoa, Italy), working with a linear (3-13 MHz) and, when necessary, a convex probe (2-7 MHz).

Two independent radiologists, blinded to the clinical and US findings, evaluated the presence/absence of CR calcifications at hip joints in both groups.

Results: Forty-three patients with CPPD [age (mean±standard deviation) 72.0±9.2; 24 females] and 40 controls were included in the study.

US findings indicative of CPP crystal deposits were found in at least one hip in 39 out of 43 (90.7%) patients with CPPD, in 62 out of 86 (72.1%) hips. US and CR sensitivity was 91% and 86%, respectively, whereas US and CR specificity was 85% and 90%, respectively. Sixty-nine patients were assessed using a linear probe (34 patients with CPPD, 35 controls) whereas the remaining 14 patients were studied using a convex probe (9 patients with CPPD, 5 controls).

The inter-reader agreement between the two radiologists which evaluated the CR images was $k=0.77$ (95%CI 0.67-0.87).

The agreement between the US and CR finding was $k=0.76$ (95%CI 0.67-0.87).

Conclusion: Our results show a high prevalence of CPP crystal deposits at the hip in patients with CPPD. This study supports the role of US as a first-line safe and more sensitive imaging technique compared to CR.

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Rensick D et al. Clinical, radiographic and pathologic abnormalities in calcium pyrophosphate deposition disease (CPPD): pseudogout. *Radiology* 1977 Jan;122(1):1-15.

Disclosure: A. Di Matteo, None; E. Filippucci, None; E. Cipolletta, None; A. Musca, None; M. Carotti, None; R. Mashadi Miza, None; D. Jesus, None; M. Di Carlo, None; F. Salaffi, None; W. Grassi, None.

Abstract Number: 1206

Ultrasonographic Involvement of the Anterior Chest Wall, a Five Years Follow up

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SESSION INFORMATION

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Background/Purpose: Spondyloarthritis is characterized by inflammatory back pain. Anterior chest wall (ACW) pain is common and a previous study reported a prevalence à 35.5 % of ultrasonographic lesions of this anatomical region [1]. The objective of this study is to evaluate the prevalence of ACW ultrasonographic lesions after a follow up of 5 years and to identify factors associated with the development of new lesions.

Methods: This a monocentric and prospective study including patients with Spondyloarthritis meeting the ASAS 2009 criteria. Patients were followed during five years. ultrasound B mode and power Doppler examination of the two sternoclavicular joint and the manubrio-sternal joint were performed by the same two examiners at baseline and five years later. The presence of erosion, synovitis, ankylosis, power Doppler signal, joint effusion and bone margin narrowing were assessed. Clinical characteristics and disease activity were evaluated at 5 years.

Results: In the 136 patients at baseline, 30 patients were evaluated 5 years later. The mean age was 48 +/- 10 years old, with 80% of male and 85 % of HLA B27. 53,5 % of these patients had a history of pain of the ACW. The prevalence of ultrasonographic involvement of the ACW was 36,7 % at baseline and 63 % five years later. The most frequent lesions were erosions of the sternoclavicular joint (36,5 %) and ankylosis of the manubriosternal joint (33,5%). At 5 years, patients with lesions of the ACW are older but not significantly (49,9 +/- 9,9 VS 44,6 +/- 10,1, p=0,15) and use statistically more anti TNF (p= 0,047). There were no differences concerning the presence of HLA B27 and the presence of a radiographic sacroilitis or syndesmophytes. Among these 30 patients, 14 developed a new lesion of the ACW. There is a trend on an association between a higher ASDAS CRP and new lesions of the ACW (1,97 +/- 1,14 VS 2,7 +/- 0,768, p = 0,07) and with the level of CRP (6,33 +/- 9,63 VS 15 +/- 20,9, p = 0,13). Nevertheless, the ASDAS CRP at baseline is not predictive of the occurrence of new lesions of the ACW.

Conclusion: The prevalence of ultrasonographic lesions of the ACW increased after 5 years of follow up. The use of anti TNF is associated with more lesions and patients with new lesions had a trend of a more active disease. These data must be completed with a higher number of patients.

Reference:

Verhoeven F. et al. Ultrasonographic evaluation of the anterior chest wall in spondyloarthritis: a prospective and controlled study. *J Rheumatol*. 2015;42:87-92.

Disclosure: F. Verhoeven, None; M. Sondag, None; M. Chouk, None; C. Prati, None; D. Wendling, None.

Abstract Number: 1207

Clinical Evaluation Correlates Poorly with Ultrasound and Magnetic Resonance Imaging of Joints and Entheses in Early Peripheral Spondyloarthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Imaging of Rheumatic Diseases Poster II: Ultrasound

Session Type: ACR Poster Session B

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Background/Purpose: Enthesitis is a hallmark of spondyloarthritis (SpA), which occurs in 30 to 50% of psoriatic arthritis patients [1]. Evaluation of tenderness at the site of an enthesitis with a standard palpation approach remains the gold standard for detection of enthesitis. However, inter- and intra-observer variability is rather high. All existing clinical enthesitis scoring systems lack validity. Imaging could avoid these drawbacks. The objective of this study is to compare the performance of ultrasound (US) and magnetic resonance imaging (MRI) with clinical examination (CE) of joints and entheses in peripheral (p)SpA.

Methods: Clinical REmission in peripheral SPondyloArthritis (CRESPA) is a placebo-controlled trial of golimumab treatment in 60 early (symptom duration < 12 weeks) pSpA patients. CE included tender and swollen joint count, dactylitis and enthesitis (evaluation of palpation tenderness) count. All patients underwent Power Doppler (PD) US of entheses and knee, talocrural (TC) and subtalar (ST) joints. Synovitis was scored according to the OMERACT-EULAR-US composite PDUS scale, giving a score of 0-3 for each joint. Enteseal sites were evaluated for hypoechogenicity and intraenthesitis Doppler signal and were scored on a scale of 0 –3. Modified whole-body MRI was performed at baseline. Bone marrow edema (BME), synovitis and soft tissue inflammation (STI) were scored (scale 0-3) by 3 readers at several anatomical sites of pelvis and lower limbs. For each site a mean of the scores of the 3 readers was calculated.

Results:

Table 1. Prevalence of synovitis and enthesitis on CE, US and MRI

Joints/entheses	CE	US	MRI
Hip joint	3/60 (0)	-	4/60 (1)
Knee joint	21/60 (6)	25/60 (8)	24/60 (7)
Talocrural joint	14/60 (1)	9/60 (1)	24/60 (13)
Subtalar joint	7/60 (2)	10/60 (12)	15/60 (0)
Quadriceps tendon	10/60 (2)	9/60 (1)	4/60 (0)
Superior patellar ligament	8/60 (2)	8/60 (1)	7/60 (3)
Inferior patellar ligament			6/60 (1)
Achilles tendon	14/60 (2)	11/60 (2)	17/60 (4)
Plantar fascia	15/60 (4)	7/60 (1)	17/60 (9)

Prevalence of bilateral involvement is indicated between brackets.

Synovitis detected by US and MRI was most prevalent at knee joints (Table 1). A discrepancy was noted between TC synovitis detected by CE, US and MRI. Enthesitis was most prevalent at Achilles tendon and plantar fascia. Regarding enthesitis, agreement between CE and US ranged from no (kappa -0.082) to moderate agreement (kappa 0.562). The highest agreement was observed at the enteseal sites of Achilles tendon (left 0.511, right 0.350) and plantar fascia (left 0.321, right 0.507). MRI did not correlate better with CE than US (kappa from -0.077 to 0.446). The correlation between MRI and US was overall poor and only in the Achilles tendon moderate (range -0.106 to 0.656).

Conclusion: There was a weak agreement between CE and imaging in detecting enthesitis. In general, US detects less enthesitis compared to CE, while MRI detects more.

References:

1. Gladmann DD, Chadrin V. Observational cohort studies: lessons learnt from the university of Toronto Psoriatic Arthritis Program. *Rheumatology* 2011;50(1):25-31.

Disclosure: T. Renson, None; A. S. De Craemer, None; P. Carron, None; S. Krabbe, None; L. Jans, None; M. de Hooge, None; P. Jacques, None; M. Østergaard, None; D. Elewaut, None; F. van Den Bosch, None.

Abstract Number: 1208

Indicators for Active Musculoskeletal Ultrasound Findings of Psoriatic Arthritis Vary on Each Body Part

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SESSION INFORMATION

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Background/Purpose: Although some global composite measures (DAPSA, DAS28) reflect musculoskeletal ultrasound (MSUS) findings of psoriatic arthritis (PsA), there is little knowledge on how to predict whether certain joints have US active findings. We examined the relationship between composite measure score of PsA and MSUS findings for each body part, and searched for useful indicators for active MSUS findings.

Methods: Total 98 PsA consecutive cases who fulfilled CASPAR criteria were evaluated. PASDAS, DAPSA, PASI, DAS28-CRP, DAS28-ESR, BASDAI, SDAI, CDAI, CPDAI were calculated using clinical examinations of 68 tender joints, 66 swelling joints, 6 enthesitis and 20 dactylitis. 5 body parts (hand, elbow, shoulder, knee, foot) specific PASDAS, DAPSA were also calculated. MSUS evaluated 60 joints, 16 entheses and 24 tendons. Enthesitis was assessed according to the MASEI investigating the inflammatory scores (entheseal thickening, structural changes, bursitis and vascularization) and chronic damage scores (calcifications, enthesophytes, and erosions). US findings were grouped into 7 body parts (finger, wrist, elbow, shoulder, knee, ankle, toe), and the relationship between composite measure score of PsA and MSUS findings we reanalyzed using Receiver Operating Characteristic (ROC) curve analysis.

Results: MSUS PD \geq 1 in joints were frequent in wrist (13.9 % 3.4%), knee (7.65 % 6.5%) and elbow (13.9 % 3.4%). MSUS enthesitis were frequent in Achilles tendon (inflammatory 18.9%, chronic 29.5%) and knee quadriceps (inflammatory 11.5%, chronic 32.8%). Composite measures predicting active MSUS findings (PD \geq 1 in joint or tendon, or positive for inflammatory scores of enthesitis) were different among body parts (Table 1). In fingers, DAS28-CRP, SDAI, CDAI predictive MSUS findings with moderate accuracy. In wrist, ankle and toe, hand-specific PASDAS, foot-specific PASDAS or foot-specific DAPSA predictive MSUS findings than global PASDAS and DAPSA. On the other hand, in elbow, shoulder and knee, BASDAI predict active MSUS findings with the highest accuracy.

Conclusion: Composite measures predicting active MSUS findings were different according to body parts. Parts-specific composite measure improved predicting wrist or ankle MSUS findings. Since there is laterality of arthritis or enthesitis of PsA, location specificity is considered to be important than global composite measures. BASDAI is important when

considering elbow, shoulder and knee, which is presumably related to the importance of the element of enthesitis in these parts. Careful evaluation according to each part is considered important for prediction of MSUS.

Table 1: Relationship between activeMSUS findings in body parts and composite measures (value = AUC).

	PASDAS	DAPSA	Part PASDAS	Part DAPSA	PASI	DAS28- CRP	BASDAI	SDAI	CDAI	CPDAI
Finger	0.7983	0.7841	0.7747	0.7680	0.5298	0.8452	0.7124	0.8267	0.8366	0.7287
Wrist	0.6574	0.6984	0.7588	0.7174	0.4788	0.7196	0.5438	0.7110	0.7209	0.6772
Elbow	0.5816	0.5373	0.6258	0.5593	0.5104	0.5868	0.6748	0.6093	0.6024	0.6814
Shoulder	0.7139	0.7380	0.4957	0.4957	0.4760	0.6827	0.7863	0.7348	0.7524	0.5420
Knee	0.8162	0.5818	0.4998	0.5641	0.4433	0.5428	0.7085	0.5912	0.6062	0.6123
Ankle	0.5189	0.5897	0.6725	0.6489	0.4720	0.6011	0.5539	0.5789	0.5594	0.5349
Toe	0.7837	0.7548	0.7795	0.8278	0.5493	0.6274	0.6589	0.7019	0.7200	0.6569

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Abstract Number: 1209

Peritenon Extensor Tendon Inflammation, Synovitis and Enthesopathy in Psoriatic Arthritis: What Is the Connection?

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SESSION INFORMATION

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Background/Purpose: Metacarpophalangeal joint (MCPj) swelling in PsoriaticArthritis (PsA) can be produced both by synovitis (IAS) and peritenonextensor tendon inflammation (PTI), having been this last lesion reported by some authors as an enthesitis-like lesion. Our objective was to explore the association of PTI and IAS with enthesitis in PsA,using the enthesitis US score MASEI (Madrid Sonographic Enthesis Index).

Methods: 27 consecutive non selected PsA patients were included. An expert rheumatologist obtained US images from the dorsal aspect of 2nd to 5th MCPj of both hands evaluating IAS and PTI in grey scale (GS) and power Doppler (PD), and also performed the MASEI examination. In addition to the PD item of MASEI (defined as signal in bone profile or intratendon or bursa at the enthesitis), PDOMERACT was evaluated as present or absent (defined as signal in the enthesitis 2 mm to the bone profile). We used a MyLab 70 XVG machine, Esaote, Genoa, Italy, with a GS 13 MHz probe and 7.1 MHz PD frequency, PRF 750 Hz and 60 Gain. 3-5 seconds videos of each MCPj and enthesitis were obtained in transverse and longitudinal views for further reliability analysis. Reliability of IAS and PTI was performed by 5 readers (true US result was the consensus of at least three) and MASEI«s by 3 readers (true US result was the consensus of at least two). For qualitative reliability analysis, mean Cohen kappa was used for PD, IAS and PTI, and intraclass correlation coefficient (ICC) for MASEI based on a mean-rating of three readers, absolute-agreement, two-way mixed effect model. Statistical association between IAS, PTI and MASEI was analyzed with T student test. SPSS statistical package version 20 (SPSS Inc, Chicago, IL) was used.

Results: Eighteen patients had PTI PD (66,7%) and same value for SIA PD. The inter-reader reliability for PTI and IAS was good with kappa values of 0.685 and 0.680 respectively. The inter-reader reliability for MASEI was excellent with ICC 0,922 (CI 95% 0,846-0,960). The inter-reader reliability for PD MASEI was ICC 0,921(CI 95% 0,855-0,963) and for PD OMERACT ICC 0.895 (CI 95% 0,802-0,949). Table 1 shows the existence of association between PTI and enthesitis

identified by PD. This association was not found with IAS. PTI, both GS and PD, showed a significant relation with IAS PD (p 0.009 and p 0.037, respectively). IAS GS didn't show any relation with PTI both PD (p 0.055) and GS (p 0.334).

Table 1. Relation between IAS and PTI with MASEI and different PD subtypes. Results are expressed as mean \pm standard deviation (SD).

	PTI		p value	IAS		p value
	Present	Absent		Present	Absent	
Mean MASEI \pm SD	32,44 \pm 15,62	27 \pm 9,33	0,270	32 \pm 6,16	27,89 \pm 7,72	0,380
Mean PD MASEI \pm SD	8 \pm 6	3,67 \pm 3,28	0,023	6,83 \pm 6,15	6 \pm 4,5	0,694
Mean PD OMERACT \pm SD	1,61 \pm 1,33	0,56 \pm 1,01	0,033	1,39 \pm 1,46	1 \pm 1	0,426

Conclusion: The present study finds PTI to be associated with enthesitis as opposed to MCPjsynovitis, which may support a functional association between PTI and enthesitis, and reinforces the role of PTI in PsA as an enthesitis-like lesion.

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Abstract Number: 1210

Sonographic Appearance of Inflammatory Myopathies: Increased Muscle Echointensity and Qualitative Changes

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Session Type: ACR Poster Session B

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

Background/Purpose: The use of ultrasound in the assessment of muscle conditions has grown over the years. Various myopathies have shown an increase in echo intensity compared to healthy muscle¹. The objective of this study was to compare muscles affected by myositis with normal controls on the basis of echo intensity, and to assess for differences in subjective appearance among particular forms of myositis.

Methods: : Sixty-two subjects were included in this study, consisting of 9 patient with polymyositis (PM), 7 with dermatomyositis (DM), 18 with inclusion body myositis (IBM), and 28 healthy controls. All patients met the ACR classification criteria for their particular disease. Seven muscle groups were examined bilaterally using ultrasound, including

Figure 1. Mean Heckmatt Score and echo intensity per muscle group

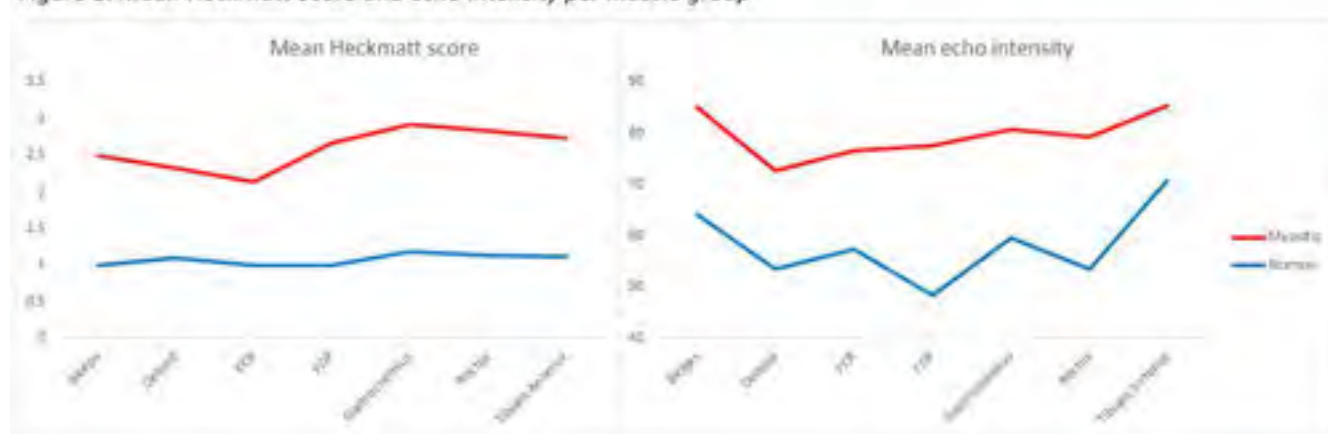




Figure 2. Representative images of the biceps muscle in each subgroup. A: Healthy muscle showing a hypoechoic muscle and subcutaneous fat layer, with a hyperechoic speckled pattern of perimysium. B: An affected muscle from a DM patient showing focal areas of increased echo intensity and increased echo intensity of the fat layer. C: An acute case of PM (necrotizing) showing homogeneously increased echo intensity and loss of perimysial septa. D: An atrophic biceps muscle in IBM with markedly increased echo intensity.

	IBM	PM	DM	Healthy controls
Total #	18	9	7	28
Female : Male	9 : 9	8 : 1	2 : 2	15 : 13
Mean age (years)	54	57	55	48
Age range	32 – 84	28 – 70	35 – 82	21 – 74
Duration of symptoms (months)	118	45	55	Not A.
Average muscle strength (based on MMFT)	64	92	85	18
Blood creatine phosphokinase	578	284	218	864
Antibodies (percentage)	CNLS	100% IL, RNP, Jo-1	PM-S/40, PM-S/L, SAE, PL-7, Jo-1	Not A.

the deltoids, biceps, flexor carpi radialis (FCR), flexor digitorum profundus (FDP), rectus femoris, tibialis anterior and gastrocnemius muscles using a standardized protocol. Echo intensity was measured both subjectively using the Heckmatt scale (1-4)¹ and quantitatively by mean gray-scale analysis using the program ITK-SNAP. Other parameters measured were duration of symptoms, muscle strength and muscle enzyme levels.

Results: Echo intensity was increased in patients with myositis across all muscle groups studied when compared with normal muscles. Although numbers per subgroup were small, some visual patterns could be noted. Subcutaneous edema and increased echo intensity of fat could be seen in active DM. Focal areas of increased echogenicity were also noted within involved muscles, and other stigmata of DM such as calcinosis could be seen. PM, made up mostly of necrotizing myopathies, usually showed a more homogenous distribution of increased echo intensity in involved muscles and preserved fat echo intensity. IBM showed the most severely increased echo intensity and atrophy of the involved muscles.

Conclusion: In the inflammatory myopathies, a higher echo intensity is seen in affected muscles. Additionally, disease specific characteristics may be seen on visual inspection and can make ultrasound a useful tool in the evaluation of muscle involvement in myositis.

1. Heckmatt et al. Detection of pathological change in dystrophic muscle with B-scan ultrasound imaging. *Lancet* **1**, 1389–1390 (1980).

Disclosure: K. Leeuwenberg, None; L. Christopher-Stine, None; C. O. Bingham III, None; J. J. Paik, None; E. Tiniakou, None; S. Billings, None; P. Burlina, None; J. Albayda, None.

Contribution of Ultrasonography Examination in Symptomatic Radiographic Knee OA

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Imaging of Rheumatic Diseases Poster II: Ultrasound

Session Type: ACR Poster Session B

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

Background/Purpose: To evaluate and to compare ultrasonographic (US) features to clinical data and structural damage in symptomatic radiographic (RX) knee osteoarthritis (OA).

Methods: Patients with symptomatic (VAS-pain > 30/100) and RX (Kellgren-Lawrence (KL)≥2) knee OA responding to ACR criteria (1986) were included in a clinical trial N° NCT01544647. Clinical knee effusion, VAS-pain, WOMAC scores and radiographic severity (KL>2) were recorded. On US, effusion (≥ 4 mm), synovitis (depicted in the three subquadricepsal ramps on B- and PD-modes) and Baker's cyst (BC) were assessed according to binary and semi quantitative manners. Total US score (sum of effusion (0 to 6), synovitis scores (0- 15) and presence of BC (0-1)) varied from 0 to 22.

Results: 283 patients were evaluated (67% of women, mean age (SD): 64.1(±9.1) years, BMI: 29.1(±5.7), 58.4% with KL>2). Knee effusion was detected in 82 patients (29.1%) by clinical examination and in 185 patients (65.6%) by US. On US, synovitis was detected in 60.3% on B-mode and 28.0% on PD-mode. BC was observed in 70 patients (24.9%). The mean +/-SD effusion, synovitis and total US scores were 0.8±1.2, 2.5±2.6 and 3.6±3.4 respectively. For an US effusion score >2, more than 50% of knee effusions were clinically detected. Only effusion score was associated with VAS-pain (p=0.01) on univariate analysis. There was a significant association between RX severity and US effusion and synovitis scores (B-mode and DP-mode) in univariate and multivariate analysis (p<0.05).

Conclusion: US detected two times more knee effusion than clinical examination and only US effusion score demonstrated association with pain. US effusion and synovitis were strongly associated to structural damages.

Disclosure: O. BAZIN, None; W. Nguéyon Sime, None; A. Desvignes, None; E. Spitz, None; F. Guillemin, None; A. C. Rat, None; I. Chary-Valckenaere, None; D. Loeuille, None.

Superiority of Musculoskeletal Ultrasound (MSUS) over Clinical Examination Regarding Detection of Arthritis in Patients with Systemic Sclerosis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Imaging of Rheumatic Diseases Poster II: Ultrasound

Session Type: ACR Poster Session B

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

Background/Purpose: Arthralgia is frequent in patients with systemic sclerosis (SSc). However, correct clinical assessment of arthritis remains a challenge especially in patients with severe soft tissue edema and/or scleroderma. This study investigates the frequency of arthritis in SSc using musculoskeletal ultrasound (MSUS) compared to clinical investigation and in SSc.

Methods: Synovitis in B- and PD-mode as well as effusion was assessed in 56 consecutive patients with SSc using MSUS. Wrist, finger, upper and lower ankle joints as well as metatarsophalangeal (MTP) joints were scanned totaling 2016 joints. In all patients carotid intima media thickness (CIMT) as well as prevalence of carotid plaques was assessed by Doppler ultrasound. Arthritis disease activity was evaluated by the health assessment questionnaire (HAQ), and the DAS66/68. Joint pain and patient global health (PGH) were quantified on a visual analogue scale (VAS). Skin involvement was quantified using the modified Rodnan Skin Score (mRSS). CVRF such as smoking, hypertension or positive family history were recorded.

Results: All patients were negative for ACPA and rheumatoid factors. 15/56 patients had elevated CRP-levels. Doppler ultrasound found 12 pathological CIMT in 10 individual patients; 44/112 carotid arteries had at least one plaque. Patients with CIMT and/or carotid plaques were elderly (62.3 years +/- 11.02), long term sick (148.61 +/- 127.58 months), and had at least one cardiovascular risk factor. 8/15 CRP-positive patients had carotid plaques (53.3% vs 4.88% CRP-negative), and had a significantly higher number of CVRF than CRP-positive patients without carotid plaques (median 3.5 [1-5] vs. 1[0-5]). A cutoff diameter of >13mm² was deemed pathologic for median nerves, >11mm² and <13mm² was intermediate. 11/56 patients had either pathologic or intermediate median nerves. 46.43% (n=26) of patients had joint pain, 16.07% (n=9) clinical joint swelling. In MSUS, 167 joints with effusion were detected in 38 patients (I°: n=93 joints, II°: n=74 joints). 36 joints in 17 patients were detected by B-mode synovitis (I°: 13 joints, II°: 23 joints). 12 joints in 5 patients showed PD-synovitis (I°: 4 joints, II°: 8 joints). In 15 patients MSUS could detect effusion where clinical examination could not; none of the clinically suspicious joints had effusion in MSUS. B-mode synovitis was detected in 5 clinically normal patients, in 7 patients with joint pain, and in 5 patients with joint pain and swelling. The overall correlation of MSUS with clinical examination was poor (p>0.05). B-mode synovitis and PD-mode synovitis prevailed the MTPs (69.44%, n=25 and 58.33%, n=7, respectively).

Conclusion: In patients with arthralgia MSUS could detect clinically inapparent arthritis. Especially in joints with soft tissue edema and sclerotic skin MSUS was superior to clinical examination. Interestingly, arthritis was most frequently found in the MTP and wrist joints supporting recent data (Iagnocco 2013). In this small cohort there was no significant correlation between CRP positivity and arthritis. Not surprisingly, carotid plaques were more frequent in elderly, long-term patients with over 1 CVRF.

Disclosure: D. Feldmann, None; R. Voll, None; F. Kollert, None; S. Finzel, None.

Abstract Number: 1213

Simplified Salivary Gland Ultrasonography for Sjögren Syndrome and Sicca Symptoms: Experience from a Single Medical Center in Taiwan

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Imaging of Rheumatic Diseases Poster II: Ultrasound

Session Type: ACR Poster Session B

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

Background/Purpose: Sjögren's syndrome is an autoimmune disease involving multiple organs, especially the lacrimal and salivary glands. Salivary gland ultrasonography (SGUS) provided a rapid and direct method for evaluation the conditions of salivary glands. Several parameters or evaluation protocols were proposed for stratification the severity of salivary glands. In previous published method, bilateral parotid and submandibular glands were scored from 0 to 4, which resulted in a total score of 0-16. The applications of SGUS was still under investigation and with technique-based barriers.

Methods: Total SGUS with 102 patients were retrospectively evaluated. SGUS was conducted by a 10MHz-13MHz linear probe at both parotid and submandibular glands. Each gland was scored from 0 to 4 according to the scoring scale proposed previously. The total maximum score was 16. Simplified SGUS score was conducted through combinations of each two glands from right side and left side.

Results: The average SGUS score of 102 patients was 7.75 (SD 4.769). The correlations between right side and left side was fair (parotid gland, Pearson coefficient 0.889, $p < 0.001$; submandibular gland, Pearson coefficient 0.843, $p < 0.001$). Compared with parotid gland and submandibular gland in the same side, the correlation was also good (right side, Pearson coefficient 0.640, $p < 0.001$; left side, Pearson coefficient 0.570, $p < 0.001$). The average score of parotid gland and submandibular gland were similar (parotid gland: left side 1.84 (SD 1.426), right side 1.74 (SD 1.528); submandibular gland: left side 2.08 (SD 1.208), right side 2.06 (SD 1.201)). The combination of right side two glands and left side two glands revealed good correlations ($p < 0.001$) with similar score (right side 3.79, left side 3.92). Each side of score correlated well with original score of summation of 4 glands. Both side of SGUS correlated with the severity of small salivary gland biopsy (right side $p = 0.008$, left side $p < 0.001$) and sialocintigraphy (both sides $p < 0.001$).

Conclusion: SGUS could be conducted via only one side of parotid and submandibular gland, which correlated well with the severity of small salivary gland biopsy and sialocintigraphy. This may shorten the examination time and more feasible for practice in clinic. However, SGUS was technique-based and should be trained for certification.

Disclosure: Y. P. Tsao, None; M. H. Chen, None; W. S. Chen, None; C. C. Lai, None; C. Y. Tsai, None.

Abstract Number: 1214

Comparison of Ultrasound Features of Major Salivary Glands in Sarcoidosis, Amyloidosis, and Sjögren's Syndrome

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Imaging of Rheumatic Diseases Poster II: Ultrasound

Session Type: ACR Poster Session B

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

Background/Purpose: Salivary gland enlargement occurs in conditions such as Sjögren's syndrome (SS), sarcoidosis (SAR), and AL amyloidosis (AL). Salivary gland ultrasound (US) has been shown to be useful in diagnosing SS. Our purpose is to compare salivary gland ultrasound features in SAR and AL with those in patients with SS, and controls (C) without known salivary gland disease.

Methods: In this 1 year cross-sectional study, we enrolled consecutive adult clinic out patients. Enrollment inclusion criteria include: clinical diagnosis of either primary or secondary SS fulfilling American-European Consensus 2002 classification criteria; clinical diagnosis of SAC or AL with histological confirmation from any tissue; and rheumatology outpatients without these diagnoses or other autoimmune rheumatic disease.

Subjects underwent clinical examination including Schirmer testing, and unstimulated salivary flow measurement, and bilateral parotid and submandibular salivary gland ultrasound by single unblinded investigator, using an ultrasound machine with an 18-6 MHz ultrasound probe. Another investigator, blinded to underlying diagnosis, analyzed ultrasound images for salivary gland ultrasound score (SGUS) per Hoyer protocol (parenchymal echogenicity, homogeneity, hypoechoic areas, hyperechoic foci, border visibility, and color Doppler signals), lymph nodes, and hyperechoic septae. US findings are compared between the groups using T test and Mann Whitney test as appropriate with P -value of < 0.05 as being statistically significant.

Results: Subjects enrolled, with mean age (A), % abnormal Schirmer (Sch), and % abnormal salivary flow (Sf) as follows: 27 SAC (A 55, Sch 65, Sf 4), 22 AL (A 66, Sch 86, Sf 32), 21 SS (A 49, Sch 57, Sf 62), and 16 C (A 58, Sch 38, Sf 25). In the control group, there was no correlation between age and SGUS score. By Shapiro-Wilk test of normality, only the AL group violated the assumption of normality. ANOVA of the mean SGUS showed significant difference among the four groups ($p < 0.00008$). SS SGUS was significantly higher than SAC, AL, and C groups (20 vs. 11, 14, 9 respectively all with $p < 0.05$). AL SGUS was higher than C (14 vs. 9, $p < 0.05$), but SAC was not different from C (11 vs. 9, $p = \text{NS}$). Intraglandular lymph node number, size, shape, and Doppler flow did not differ between the groups ($p = \text{NS}$). Gland septae

score was greater for SS and AL groups than SAC and C groups (0.39 and 0.44 vs. 0.18 and 0.16, $p=0.0040$). Hypoechoic area score was higher for SS and AL than SAC and C groups (1.6 and 1.2 vs. 0.95 and 0.77, $p=0.0039$). There was a trend towards greater difference between groups in the percentage of subjects with hyperechoic area scores for the SS and AL groups than SAC and C groups (0.37 and 0.35 vs. 0.19 and 0.063, $p=0.051$).

Conclusion: While SGUS was highest in SS, US abnormalities of SS were more similar to those of AL than those of SAC. Hyperechoic foci and septae, may be most helpful in distinguishing patients with SS and AL from those with SAC and patients without a systemic disease of the salivary glands.

Disclosure: S. Law, None; P. Govender, None; S. R. Jafarzadeh, None; X. Sun, None; V. Sanchorawala, None; E. Y. Kissin, None.

Abstract Number: 1215

Characterizing Changes in the Median Nerve during Hand Grip Using Dynamic Sonographic Imaging

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Session Information

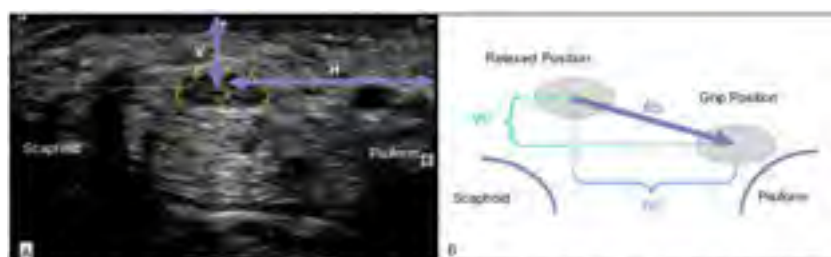
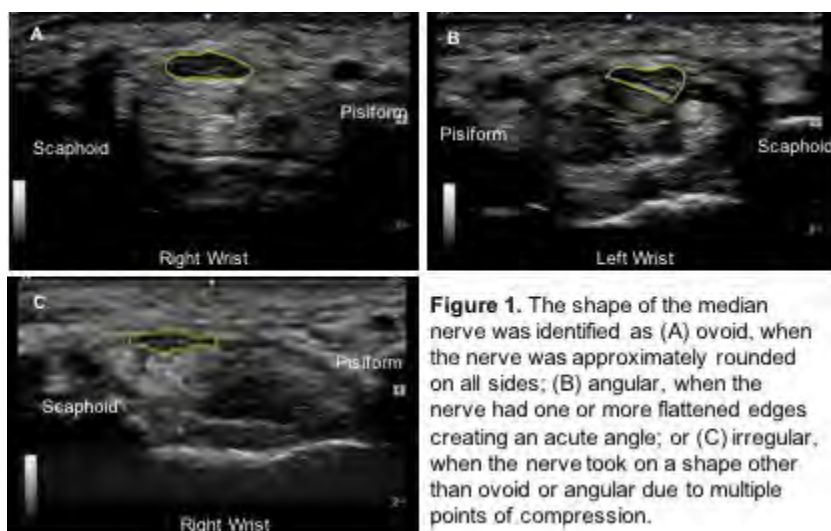
Session Date: Monday, October 22, 2018

Session Title: Imaging of Rheumatic Diseases Poster II – ARHP

Session Type: ACR Poster Session B

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

Background/Purpose: Sonography is used to evaluate inflammation, identify joint changes, and measure morphology; dynamic assessment of tissue movement is an additional benefit. Dynamic sonographic identification of median nerve entrapment at the wrist during finger motion could improve understanding of carpal tunnel syndrome (CTS) etiology, as



well as inform strategies to avert secondary CTS in patients with inflammatory conditions. This study aimed to evaluate a method for identifying and characterizing median nerve entrapment during functional grasp.

Methods: Healthy participants sat with their forearm on a table, palm up, and fingers in a relaxed position. A 12-MHz, linear transducer was placed in cross-section of the wrist at the level of the pisiform. Dynamic videos were obtained while the participant flexed the fingers until the tips touched the palm. Any compression of the median nerve was noted, nerve shape was identified at beginning and end of motion (Fig. 1), and direction and distance of nerve displacement was measured (Fig. 2). Frequencies/averages were calculated and chi-square/t-tests were used to compare right to lefthands.

Results: Participants (N=51) were predominantly right-handed (92.5%) females (88.7%) with an average age of 24.4 years (SD, 3.5). During gripping, 72.5%/68.6% of participants had compression of the nerve in the right/left hands. From rest to grip, the frequency of angular or irregular shapes nearly doubled from 13.7% to 25.4%. Maximum nerve movement (mm) ranged from 0.76-1.08, 2.70-4.02, and 0.06-4.07 for vertical, horizontal, and endpoint displacement respectively; in 20% of hands, essentially no movement occurred. There were no significant differences between left and right, and no direction of movement predominated.

Conclusion: Despite being young and healthy, most participants had nerve compression during finger movement; some with significant entrapment (e.g., angular/irregular shapes). Longitudinal studies are needed to determine if these measures are a CTS predictor or risk factor. These methods can also be translated to clinical practice to inform personalized care for reducing or preventing symptoms in individuals with CTS and other inflammatory conditions.

Disclosure: S. Roll, None; A. Cristino, None; J. Mitchell, None.

Abstract Number: 1216

To Study the Frequency of Persistent Arthritis, in Patients with Chikungunya Fever, in a Tertiary Health Care Center

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Infection-related Rheumatic Disease Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Chikungunya virus is an alphavirus, belonging to the Togaviridae family. It is transmitted by several species of mosquitoes, with *Aedes* species being main culprit. The symptoms generally start 4–7 days after the bite. Acute infection lasts for 1–10 days and is characterized by abrupt onset of fever, headache, fatigue, nausea, vomiting, rash, myalgia, and severe arthralgia. Painful polyarthralgia is the typical symptom causing serious economic and social impacts on both the individuals and the affected communities. This study was meant to look at frequency of patients coming with persistent arthritis and to share our experience in treating it.

Methods: This cross-sectional study was conducted in Liaquat National Hospital, Karachi. It comprised of collected data of patients who presented with arthritis and positive chikungunya serology. Data was collected on a pre-designed proforma. It was analysed by using the Statistical package for social science (SPSS) version 20.0. Response to treatment was characterized according to visual analogue scale (VAS) taken at baseline, 2 weeks and 4 weeks. Stratification was done according to age, gender, duration of fever, number of joints, duration of symptoms, laboratory parameters and co-morbidities. Post stratification Chi square test was applied taking p value ≤ 0.05 as significant.

Results: A total of 112 patients were included in the study, of which 31 (27.7 %) were male and 81 (72.3 %) were female. Symmetrical arthritis was reported in 85 (75.9%) patients, while asymmetrical arthritis was seen in 27 (24.1%) patients. 75 (66.9%) had polyarthralgia involving small, medium and large joints ($P=0.000$). Morning stiffness was reported in 68 (60.7%) of patients ($P=0.000$). ESR was raised in 78 (69.6%) patients ($P=0.000$), while raised CRP was seen in 69 (61.6%) patients ($P=0.001$).

37 (33%) patients were given NSAIDs, 66 (58.9%) received steroids, and other forms of analgesics were prescribed to 9 (8%) patients. In nearly half of the patients, i.e. 62 (55.4%) partial response was seen, 13 (11.6%) showed complete response, while 37 (33%) had persistent arthralgia. Out of 66 patients treated with steroids, 48 (72.7%) showed partial response (VAS score <5), 13 (19.7%) showed complete response (VAS score 0), while 5 (7.57%) patients had persistent arthralgia (VAS score >5) ($P=0.000$).

Out of the 5 patients having persistent arthralgia in the steroid group, 3 patients later after 6 months of follow-up on repeating had anti-CCP positive, while 2 were negative. They were treated as inflammatory arthritis with DMARDS.

Conclusion: This study shows post-chikungunya arthritis to be a great mimicker of inflammatory arthritis. This study brought us to the conclusion that a single dose of methylprednisolone was helpful in successfully treating patients experiencing post-chikungunya arthritis and this did not have a significant impact on patients monetary wise. With all this said further research needs to be conducted on establishing the link between chikungunya virus and development of inflammatory arthritis.

Disclosure: H. Alam, None; T. Perveen, None; L. Nazir, None; I. Khanum, None.

Abstract Number: 1217

Trend of Frequency and Outcome of Reactive Arthritis in Japanese Patients with Bladder Cancer Following Intravesical BCG Therapy over the Last 20 Years

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Infection-related Rheumatic Disease Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Reactive arthritis (ReA) is a sterile arthritis occurring in a genetically predisposed individual, secondary to an extra-articular infection, usually of the gastrointestinal or genitourinary tract. Intravesical instillation of Bacillus Calmette-Guerin (iBCG) is used as an effective immunotherapy of bladder cancer. Despite of the clinical efficacy, ReA could develop as adverse event and the frequencies are known as about 0.5 to 1 % in Western countries. To assess the trend of frequency, HLA phenotype and outcome of iBCG-induced ReA in Japanese patients with bladder cancer following iBCG therapy.

Methods: The clinical findings of Japanese patients who received iBCG ($n = 555$) for bladder cancer from March 1997 to February 2017 were retrospectively assessed, with specific attention to frequency and HLA phenotype of ReA. Because of the change of using iBCG dosage, iBCG-induced ReA patients diagnosed from 1997 to 2007 were also compared with ReA from 2007 to 2017 and the trend of frequency was examined. Furthermore, we assessed outcomes of iBCG-induced ReA patients over the 20 years.

Results: Patients' mean age was 72 ± 10 years and male/female ratio was 438/117. Of the 555 cases, ReA was revealed in 11 (2.0%). 9.1% of 11 ReA patients had HLA-B27. Although the protocol of iBCG therapy was not statistically different over the 20 years, but a half dose of iBCG was used in 2007 to 2017 more than in 1997 to 2007. Despite the increase of half dose using of iBCG in 2007 to 2017, the overall frequency of iBCG-induced ReA was not significantly different between from 1997 to 2007 and from 2007 to 2017 (2.1% and 1.9%, respectively). Finally, as outcomes, all iBCG-induced ReA patients did not progress to chronic peripheral arthritis type and axial SpA, even if with sacroiliitis.

Conclusion: The 2.0% iBCG-induced ReA frequency in Japanese patients exceeds that in Western countries. Despite iBCG dosage was different, the trend of frequency has been stable, which suggested possible dose-independent development. Furthermore, all iBCG-induced ReA, even if revealing sacroiliitis, did not progress to chronic peripheral arthritis type and SpA over the last 20 years.

Disclosure: S. Inotani, None; Y. Taniguchi, None.

Abstract Number: 1218

Synovial Fluid Culture: Comparison of Two Culture Methods

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Infection-related Rheumatic Disease Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Septic arthritis (SA) is one of the emergencies in rheumatology. This pathology is more common due to the increased usage of artificial joints. Culture is the “gold standard” for diagnosis of the disease which in many cases is quite obscure, due to nonspecific clinical symptoms and laboratory results. Optimal treatment of this condition depends on timely and accurate culture report. A major goal is to optimize the essential culture method. Different essays suggested adding Bactec™, a blood culture system (BC), to the basic conventional culture (CC). The original culture is based on an agar plate being a platform for growth of bacteria. The organism is identified and analyzed regarding sensitivity to different antibiotics. The instrumented blood culture systems are based on media that permits screening for microorganisms present in blood allowing growth of microorganisms that may not occur with conventional media. This greater recovery leads to more accurate diagnosis and effective treatment, which can in turn lead to shorter hospital stays, lower patient costs, and greater overall laboratory and institutional efficiency. However the cost is increased and the false positive rate may increase leading to unnecessary antibiotic treatment. The aim of this study is to evaluate cases where both methods were used regarding a possible added value of operating both methods.

Methods: After obtaining ethical permission we assessed consecutive synovial fluid samples submitted to the microbiology laboratory. Samples that had been submitted in both methods i.e. CC and BC were included in the cohort. All cases with a positive result by either method were reviewed for clinical and demographic data. Specimens were defined as contamination when there was an alternative infectious diagnosis, when the white cell count was lower than 50,000 and in most cases of coagulase negative staphylococcus. Data was analyzed regarding sensitivity, specificity, and positive and negative predictive values (PPV, NPV).

Results: 1024 samples were reviewed, 803 of them showed no growth by either method. 221 cultures were positive, 67 by BC method only and 73 on by CC method, and 81 of the samples positive by both methods. All cases were reviewed regarding the clinical diagnosis. Cases were considered as having SA when there were clinical signs of joint infection and no other source of infection was found. Most of these cases had more than 50,000/μl leukocytes in the synovial fluid. 225 cases were defined clinically as septic arthritis. The sensitivity, specificity, positive and negative predictive values are shown in the following table.

	Sensitivity	Specificity	PPV	NPV
Blood Culture (BC)	.50 (.45 - .54)	.95 (.94 - .96)	.76 (.69 - .82)	.87 (.86 - .88)
Conventional Culture (CC)	.42 (.37 - .47)	.92 (.91 - .94)	.62 (.55 - .69)	.85 (.83 - .86)
Both	.60 (.55 - .65)	.89 (.88 - .90)	.62 (.56 - .65)	.89 (.87 - .90)

Conclusion: BC carries better sensitivity, specificity, positive and negative predictive values in comparison to CC. It should be considered as the preferred method for synovial culture in cases when SA is suspected. The added value of co-culture with CC is relatively low.

Disclosure: A. Natsheh, None; D. Cohen, None; E. Ben Chetrit, None; G. Neshet, None; G. S. Breuer, None.

Abstract Number: 1219

Antibiotic Resistance Trends Among Bacteria Causing Septic Arthritis at One Medical Center between 2002-2016

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SESSION INFORMATION

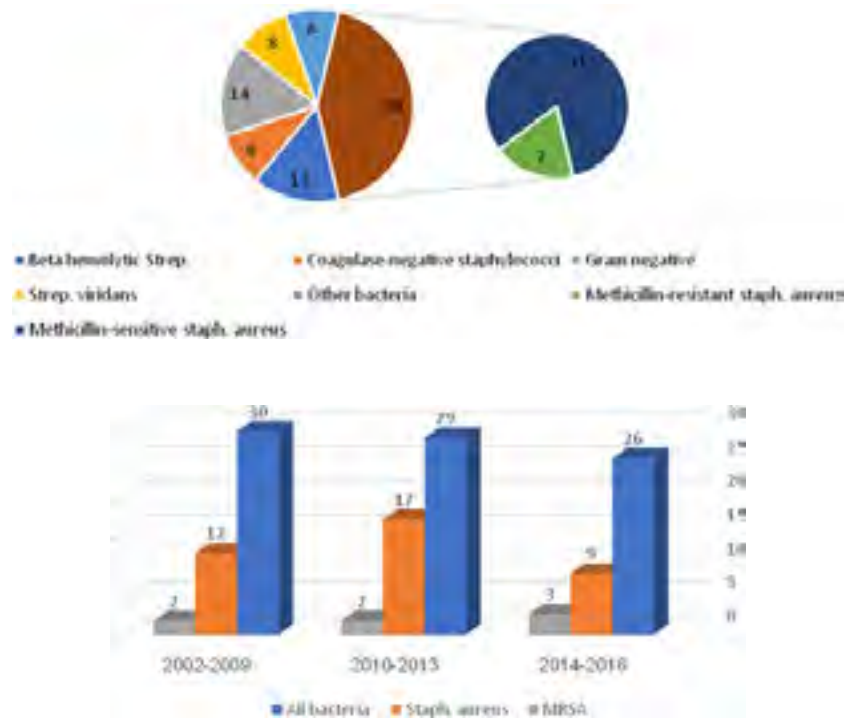
Session Date: Monday, October 22, 2018

Session Title: Infection-related Rheumatic Disease Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Septic arthritis (SA) is caused mainly by Staphylococcus aureus (S. aureus). Methicillin-resistant S. aureus (MRSA) SA is increasing and accounts for 25-50% of all S. aureus SA cases in the US. Most coagulase- negative



staphylococci (CNS) isolated from joints represent a contamination, however after surgical arthroscopy, multiple procedures, and joint replacement these may be true infection. Gram negative pathogens are less common. The purpose of this study is to examine the prevalence of *S. aureus* in comparison to other pathogens and whether there is an increase in the prevalence of antibiotic resistance in adults with natural and prosthetic joints in one medical center over 15 years (2002-2016).

Methods: The study population included patients aged 18 years and older who were diagnosed with culture positive SA between January 2002 and December 2016, based on ICD-9 encoding. Cases were reviewed regarding culture and treatment for septic arthritis. Children under the age of 18, patients in whom a diagnosis of contamination was made and cases with culture negative SA were excluded.

Results: A diagnosis of SA or suspected SA was made in 323 cases of which 85 had proven SA. In 9 cases a diagnosis of culture negative SA was made. Two-thirds of the patients were males. Median age was 74 (23-95) years, and most SA cases were community acquired, and in natural joints. The most common joint involved was the knee and in almost all cases it was monoarthritis. 10% of the patients had evidence of previous infection in a joint in the past year. The median duration of in-hospital treatment was 16 days. Fifteen patients had an infection of a prosthetic joint. In 3 cases the infection occurred in a prosthesis in which a revision was performed during the past year. Polymicrobial growth was found in three cases.

Conclusion: The most common cause of SA is *Staph. aureus*. This finding is consistent with the literature. Our study suggests that there is no evidence of an increase in antibiotic resistance among pathogens that cause SA in prosthetic and natural joints in adults. In addition we did not find increase in the rate of MRSA SA over the course of 15 years.

Figure 1: Pathogens isolated in cases of SA

Beta hemolytic streptococcus: Group A, B and G Streptococci.

Gram negative: *Haemophilus parainfluenzae*, *E. Coli*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis*, *Neisseria* spp, *Salmonella* group and *Stenotrophomonas koreensis*.

Other: *Propionibacterium acnes*, *Leuconostoc* sp., *Enterococcus* sp., *Strep. pneumoniae* and *Listeria monocytogenes*.

Figure 2: *Staph. aureus* cases in comparison to all other bacteria over the years 2002-2016

Disclosure: G. S. Breuer, None; A. Zamir, None; G. Neshet, None; E. Ben Chetrit, None.

The Impact of Gender on the Clinical Presentation, Management and Outcomes of Patients with Native Joint Septic Arthritis

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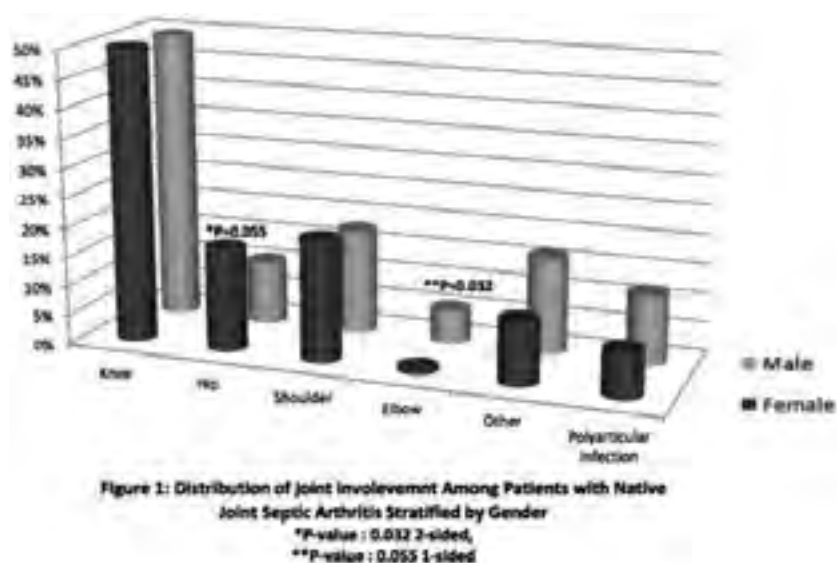
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Background/Purpose: Approximately 20,000 cases of septic arthritis (SA) occur in the United States each year with 2-10 cases per 100,000 person-years in the general population. SA is more common in men while women are three times less likely to have joint replacement surgery. It is currently unknown whether gender-related differences exist in the presentation, intervention and outcomes of patients with native joint septic arthritis (NJSA).

Methods: We conducted a retrospective study that included patients aged 18 and older admitted to a single tertiary care hospital between 1998 and 2015 diagnosed with monoarticular NJSA and treated surgically. We excluded all cases of osteomyelitis, septic bursitis, and prosthetic joint infection. We reviewed the patients' charts and collected specific data including the patients' demographic information, comorbidities, clinical presentations, microbiology, management and outcomes. A comparison was made between men and women with p-values of < 0.05 defined as the threshold for significance.

Results: Of the 324 patients with NJSA, 130 were female (40.1%). Women were significantly older at presentation than their male counterparts (mean age: 63.6 versus 58.3 years; $p = 0.006$). Overall, the frequency of comorbid conditions was similar between groups. Prior joint pathology in the involved joints was more common among female patients, including osteoarthritis (20.8% vs 12.9%; $p = 0.042$) and rheumatoid arthritis (10% vs 3.6%; $p = 0.032$). The knee was the most commonly involved joint (~50% in both groups). A trend towards a higher frequency of hip involvement was observed in women (17.7% vs 10.8% $p = 0.05$). There were no observed differences in the clinical presentation, culture results, management (e.g. antibiotics and surgery), or outcomes between the groups.



Conclusion: Compared to men with NJSA, women with NJSA present at an older age, with more prior joint pathology and a higher frequency of hip involvement. It appears that these differences have no significant impact on the presentation, management, and outcomes.

Disclosure: L. Nissim, None; M. L. Fowler, None; R. Shmerling, None; S. Lieber, None; M. Naffaa, None; Z. Paz, None.

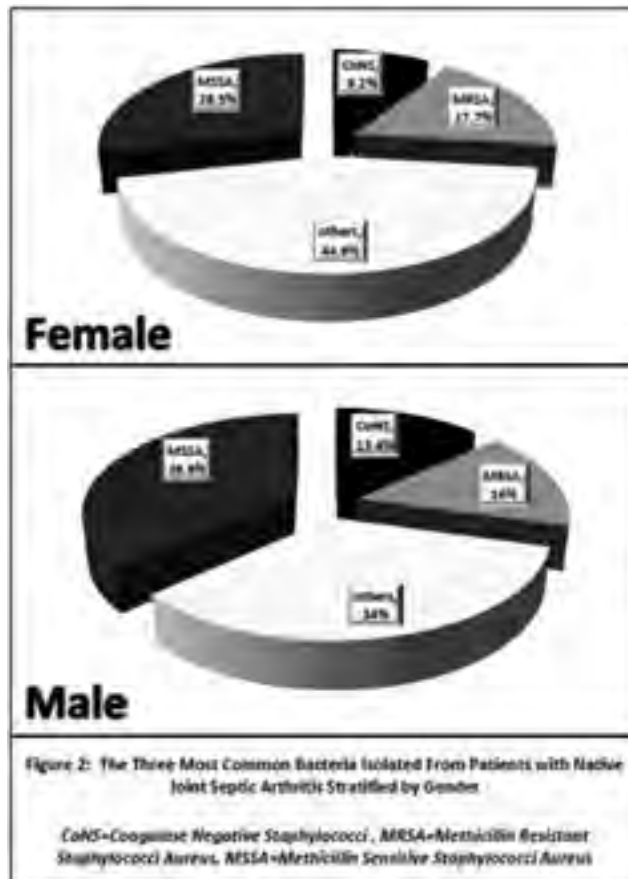


Table 1. Demographic Features and Comorbidities of patients with Native Joint Septic Arthritis stratified by gender.

	Female (n=130)	Male (n=194)	p-value
Age (y), mean (\pm SD)	63.6 (\pm 17.3)	58.3 (\pm 15.7)	0.006
Cancer, N (%)	25 (20.0)	29 (14.9)	0.29
Dementia, N (%)	4 (2.1)	4 (3.1)	0.72
Dialysis, N (%)	8 (6.2)	20 (10.3)	0.23
Diabetes mellitus, N (%)	41 (31.5)	71 (36.6)	0.40
History of endocarditis, N (%)	4 (3.1)	2 (1.0)	0.22
Cirrhosis, N (%)	2 (1.5)	3 (4.6)	0.21
HIV, N (%)	3 (2.3)	6 (3.1)	0.74
HCV, N (%)	13 (10.0)	21 (10.8)	0.85
¹ Immunosuppression, N (%)	25 (19.2)	29 (14.9)	0.36
Intravenous drug use, N (%)	9 (6.9)	14 (7.2)	1.0
History of septic arthritis in the involved joint**, N (%)	21 (16.2)	30 (15.5)	0.88
Joint trauma within 30 days, N (%)	19 (14.6)	37 (19.1)	0.37
Joint procedure within 1 year, N (%)	46 (35.4)	48 (24.7)	0.046
OA, N (%)	27 (20.8)	25 (12.9)	0.042*
Gout, N (%)	3 (2.3)	18 (9.3)	0.19
Rheumatoid arthritis, N (%)	13 (10)	7 (3.6)	0.032

SD: Standard deviation, HIV: Human Immunodeficiency Virus, HCV: Hepatitis C Virus.

OA: Osteoarthritis.

¹ Currently treated with chemotherapy or prednisone dose above 20 mg.

*1 sided p-value.

**Cases of septic arthritis in the index joint within 90 days prior to admission were excluded.

Serologic Screening for Coccidioidomycosis Among Medicare Beneficiaries with Rheumatic Diseases on Biologic Response Modifiers, Corticosteroids, and Dmards

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Background/Purpose: The 2016 Infectious Disease Society of America (IDSA) guidelines recommend serologic screening for coccidioidomycosis (Cocci) prior to initiation of biologic response modifiers (BRMs). Current screening practices for Cocci in endemic communities have not been described. Our objective was to estimate serologic screening rates for Cocci by state, medication class, physician specialty (rheumatologist vs. non-rheumatologist), and by year.

Methods: In a retrospective cohort study using 2011-2015 Medicare claims data (a 5% representative sample), we identified fee-for-service beneficiaries residing in 7 endemic states (Arizona, California, New Mexico, Nevada, Texas, Utah, and Washington), with any of 10 rheumatic/autoimmune diseases (RA, PsA, AS, SLE, ReA, PM/DM, SSc, Psoriasis, BID). We included beneficiaries with at least one prescription for a BRM, DMARD, and/or CS between 2012-2015 with continuous Parts A and B coverage in the 365 days preceding the prescription date in the analysis. Screening was considered current if the beneficiary had undergone serologic screening 365 days prior to the prescription date. Logistic regression was used to estimate the proportion of prescriptions that were current for serologic screening, by state, medication class, physician specialty, and by year, with 95% CIs. A sensitivity analysis was conducted to assess the serologic screening rate for newly initiated BRMs, defined as no supply of BRMs within the past 365 days. Generalized estimating equations were used to account for prescriptions written by the same provider.

Results: Among 296,987 prescriptions for 19,109 beneficiaries filled across the 7 endemic states, 3,004 had current serologic screening. In Arizona, 10.6% (95% CI: 8.6, 12.9) of all prescriptions (n=19,822) were current for serologic screening, compared to less than 1% in the other 6 states, prompting us to focus on Arizona for remaining analyses. Prescriptions for BRMs, CSs, and DMARDs had current screening for 20.6% (95% CI: 15.2, 27.4), 8.8% (95% CI: 7.2, 10.8), and 9.5% (95% CI: 7.6, 11.9), respectively. Screening rates for BRMs increased from 18.7% (95% CI: 11.3, 29.4) in 2012 to 28.5% (95% CI: 20.2, 38.5) in 2015. Rheumatologists and non-rheumatologists screening practices were similar (Table 1). Screening prior to newly initiated BRMs was 27.8% (95% CI: 19.8, 37.6) in a limited sample (n=115).

Table 1: Screening rates for medication classes by physician specialty in Arizona

Physician specialty	Medication class	Number of prescriptions	Current serologic screening, # (%)	(95% CI)
Rheumatologist	DMARD	5,070	528	10.4 % (7.3, 14.7)
Non-rheumatologist	DMARD	4,191	337	8.0 % (6.1, 10.5)
Rheumatologist	BRM	1,589	336	21.2 % (14.0, 30.7)
Non-rheumatologist	BRM	857	147	17.2 % (10.9, 26.1)
Rheumatologist	CS	1,937	285	14.9 % (10.1, 21.5)
Non-rheumatologist	CS	5,517	367	6.7 % (5.3, 8.3)

Conclusion: Serologic screening rates for Cocci among Medicare beneficiaries with rheumatic/autoimmune diseases on BRMs, CSs, and DMARDs was low in the 7 endemic states, with almost no screening outside of Arizona. IDSA guidelines recommend Coccidioides serologic screening prior to initiation of BRMs, though not repeated annual serologic screening. Further, while the IDSA guidelines recognized increased risk of disseminated Cocci with use of CSs, no screening recommendations have been issued.

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Suboptimal Immunization Coverage Among Rheumatology Patients in Routine Clinical Care

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Background/Purpose: Vaccine-preventable infections pose an increased risk of infection and complications in patients with rheumatic diseases. While recommendations highlight the importance of vaccination in this at-risk population, immunization coverage in this population remains largely unknown. We assessed vaccination rates and predictors of vaccination among rheumatology patients in routine clinical care.

Methods: In this cross-sectional study, consecutive patients presenting to a tertiary rheumatology clinic at the McGill University Health Center between May and September 2015 were asked to fill a survey on vaccination. Patients self-identified as having rheumatoid arthritis (RA) (RA, juvenile idiopathic arthritis), systemic autoimmune rheumatic diseases (SARD) (e.g., vasculitis, lupus, systemic sclerosis, myositis), spondyloarthropathies (SpA) (psoriatic arthritis, ankylosing spondylitis), or other non-inflammatory problems (Control). Multivariate logistical regression analyses were performed to evaluate patient and physician factors associated with vaccination (influenza, pneumococcus, hepatitis B virus [HBV], and herpes zoster [HZ]).

Results: 352 patients were included in the analysis (RA: 136, SARD:113, SpA:47, Control:56). Vaccination rates were reported as: (1) influenza: RA 48.5%, SARD 42.0%, SpA 31.9%, Control 88.9%; (2) pneumococcal: RA 42.0%, SARD 37.8%, SpA 29.7%, Control 33.3%; (3) HBV: RA 33.6%, SARD 55.6%, SpA 73.5%, Control 36.8%; and (4) HZ: RA 5.6%, SARD 28.6, SpA 25.0%, Control 16.7%. In multivariate analysis, the association between age and vaccination varied by vaccine (influenza: odds ratio (OR) 1.03, 95% confidence interval (CI) 1.01-1.05; pneumococcus: OR 1.01, 95% CI 0.97-1.04; HBV: OR 0.96, 95% CI 0.94-0.99). Moreover, physician recommendation was the strongest independent predictor of vaccination across all vaccine types (influenza: OR 8.56, 95% CI 2.80-26.2; pneumococcus: OR 314, 95% CI 73.0-1353; HBV: OR 12.8, 95% CI 5.27-31.1). Disease group, disease duration, comorbidities (cancer, diabetes, renal disease), treatment type (disease-modifying anti-rheumatic drugs and/or biologics), and access to a primary care physician were not significantly associated with vaccination.

Conclusion: Despite national guidelines and recommendations for vaccination in this at-risk population, immunization coverage against influenza, pneumococcus, HBV, and HZ is far from optimal among ambulatory rheumatology patients. An important role for both patient and physician education is highlighted from our study, especially as physician recommendation of vaccination was strongly predictive of vaccine uptake. These results can help inform strategies aimed at optimizing vaccination rates in this at-risk population.

Disclosure: T. Qendro, None; M. L. de la Torre, None; P. Panopalis, None; E. Hazel, None; I. Colmegna, None; M. Hudson, None.

Reduced Antibody Titers Against Pertussis in Rheumatoid Arthritis

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Background/Purpose: Patients with rheumatoid arthritis, an autoimmune disease affecting ~1% of the population, have an increased risk of infection. Interestingly, data are mixed for response to vaccination with rheumatoid arthritis patients showing a reduced response to some vaccine antigens, but relatively normal antibody titers in response to others, like the highly efficacious tetanus vaccine. Little is known about the response to pertussis vaccination in rheumatoid arthritis, a concerning omission given the relatively low efficacy of the pertussis vaccine, the rise in pertussis infections in the last 20 years, and the increased susceptibility of rheumatoid arthritis patients to infection. The purpose of this study is to determine if pertussis titers are reduced in vaccinated subjects with rheumatoid arthritis versus controls as well as to determine if clinical factors in rheumatoid arthritis, including the use of immune suppressing medications, correlate with pertussis titers.

Methods: Serum from 98 subjects with seropositive rheumatoid arthritis not using rituximab (a B cell depleting drug) and 77 controls, all vaccinated within 10 years of serum collection with the Tdap (tetanus, diphtheria, and pertussis) vaccine, were selected from our biorepository. Serum was subjected to enzyme-linked immunosorbent assay to detect IgG titers against pertussis and tetanus toxoid. Titers were compared by unpaired t-test and the rates of immunity based on manufacturer cut-offs were compared by a Fisher's exact test. Univariate and multivariate logistic regression was used to identify clinical factors that correlate with pertussis titers. A p value <0.05 was considered significant.

Results: Subjects with rheumatoid arthritis had significantly lower IgG titers against pertussis, but not tetanus, compared to controls and fewer rheumatoid arthritis subjects were immune to pertussis. At less than 5 years post-vaccination, there was no significant difference in pertussis titers between rheumatoid arthritis patients and controls. However, at 5-10 years post-vaccination, rheumatoid arthritis patients had 50% lower titers than controls and fewer rheumatoid arthritis subjects met immune thresholds. Multivariate regression demonstrated that rheumatoid arthritis, female sex, and longer length of time since vaccination correlated with lower than median pertussis titers. Interestingly, the use of leflunomide or methotrexate at the time of serum collection correlated with higher and lower than median pertussis titers, respectively. No correlation was seen between TNF-inhibiting medications and pertussis titer.

Conclusion: Patients with rheumatoid arthritis have lower IgG titers against pertussis, especially 5-10 years post-vaccination. Reduced titers could be due to the relatively low efficacy of the pertussis vaccine, a dysregulated immune system in rheumatoid arthritis, and/or the use of certain medications. Future studies are needed to determine the mechanism for reduced immunity to pertussis, if more frequent vaccination would improve titers against pertussis, and if susceptibility to pertussis infection is increased in patients with rheumatoid arthritis.

Disclosure: C. L. Holmes, None; C. Peyton, None; A. Bier, None; T. Donlon, None; C. M. Bartels, Pfizer, Inc., 2; M. A. Shelef, None.

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High Rates of Conversion and Reversion of Tuberculosis Screening Assays in Rheumatic Patients during Long Term Biologic Treatment

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Background/Purpose: Baseline screening for tuberculosis (TB) with tuberculin skin testing (TST) and/or interferon-gamma release assays (IGRAs) is recommended for all rheumatic patients starting biologic DMARDs (bDMARDs). Spontaneous conversions (from negative to positive) and reversions (from positive to negative) of available tests have questioned the value of re-screening patients during therapy. The aim of this study was to assess the long-term conversion and reversion rates of TB screening tests (TST and one IGRA: T.SPOT-TB) during long term bDMARD treatment.

Methods: Prospective study of rheumatic patients with negative baseline TB screening (TST and T.SPOT-TB, LTBI-1) prior to TNFi initiation who were re-screened for a 2nd (LTBI-2: 1.4 ± 0.6 years) and 3rd time (LTBI-3: 6.9 ± 1.0 years) after the 1st screening. Data regarding patient and disease characteristics, treatment patterns as well as conversion and reversion rates at LTBI-2 and LTBI-3 were recorded.

Results: 50 patients were included in the study; 4 patients who were treated with isoniazid due to a positive testing at LTBI-2 were excluded and thus 46 patients were available for final analysis. Twenty-eight (61%) were women and the mean age at LTBI-3 was 58.9 ± 13.5 years. RA was the most common diagnosis (n=22, 48%), followed by AS (n=13, 28%), PsA (n=9, 20%) and other rheumatic disease (n=2, 4%), with a mean disease duration of 15.6 ± 10 years. Forty-three (93%) patients were still on bDMARDs at LTBI-3 [TNFi: n=24 (56%), non-TNFi: n=19, (44%)] while 35% were on csDMARDs (n=16) and 15% on corticosteroids (n=7, mean daily prednisone dose = 4.5 ± 1 mg). Only one patient reported possible TB exposure during follow-up. Twelve (26%) patients had history of BCG vaccination. During follow-up, 35 patients (76%) remained persistently negative with both tests at the 2 re-screenings (“non-converters”). Among the “converters” (n=11), 4 (9%) had a transient conversion to positivity at LTBI-2 (3 with TST and 1 with T.SPOT-TB) that reversed to negative at the 3rd re-screening (“transient converters”), 5 (11%) had a late conversion to positivity (“late converters”) between the 2nd and 3rd re-screening (4 with TST and 1 with T.SPOT-TB) while only 2 (4%) were “persistent converters” (both with TST). There was no statistically significant difference between “converters” (n=11) and “non-converters” (n=35), with the exception of a higher non-RA diagnosis among “converters” (73%) compared to “non-converters” (46%, p=0.04). Among the 11 conversions/reversions, 9 were observed with TST (20%) and 2 with T.SPOT-TB (4%); none of the patients developed TB during follow-up.

Conclusion: In a low-TB prevalence country, approximately one out of four rheumatic patients with negative TB screening at baseline displayed a positive TB screening test during long term biologic treatment (~7 years); most of the conversions/reversions were seen with TST than with the IGRA test (T.SPOT-TB). These data emphasize the need for large scale studies assessing the value of TB re-screening in this patient population.

Disclosure: K. Thomas, None; A. Makris, None; C. Tsalapaki, None; A. Lazarini, None; K. Klavdianou, None; K. Antonatou, None; C. Koutsianas, None; C. Hatzara, None; E. Hadziyannis, None; D. Vassilopoulos, None.

Abstract Number: 1225

Screening for Acquired Latent Tuberculosis in Patients with Rheumatoid Arthritis(RA) on Anti-Tnf α Therapy (TNF-I) in Southern California

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Background/Purpose: There is increased risk of tuberculosis in patients treated with TNF-I. ACR guidelines recommend annual screening for latent tuberculosis infection (LTBI) in RA patients with risk factors. Few studies in the United States (US) assess risk of sero-conversion to positive TB test in patients on TNF-I. Conversion rates have been found to low, 0.138/100 patient year.¹ Studies in Greece and Argentina (TB incidence 4.4 and 24 per 100,000) show conversion rate of 30% and 9.4% respectively^{2,3}. Incidence of TB in California (5.2/100,000) is twice the national rate of 2.8/100,000 cases, with some Southern California counties with incidence up to 7.1/100,000. This study aims to analyze screening practices at academic centers in Southern California and to assess sero-conversion in RA on TNF-I agents.

Methods: Data was extracted from the electronic health record for 400 adult patients with RA (based on ICD 9 and 10 codes) across 3 academic centers from January 2010- 2017. Inclusion criteria were TNF-I use for ≥ 1 year and negative QuantiFERON Gold status prior to use. Tuberculin skin test was not used at these sites. Demographics, drug type, duration of use and QuantiFERON test results were collected. Risk factors (birth in or travel to endemic areas,

incarceration, homelessness, congregate residency, known exposure to contacts with TB) were assessed. Subjects with exposure to anti-mycobacterial drugs or use of non-TNF-I biologics were excluded. Rates of re-screening, sero-conversion and its association with drug use and other factors were calculated.

Results: A total of 203 subjects were identified. 106 (52.2%) subjects had been rescreened for LTBI at a median time of 28 months post drug initiation. LTBI was diagnosed in 10 (9.4%) of the rescreened subjects: 5 on infliximab, 2 on adalimumab and golimumab each, 1 on etanercept. Median drug intake duration prior to seroconversion was 31 months and none had known risk factors. Testing for association of TNF-I with LTBI showed that 50% of patients in sero-conversion group were on Infliximab vs 27% of those in the negative conversion group. Comparison of risk with ethnicity showed that patients in the sero-conversion group were more likely to be Hispanic (75%) than non-Hispanic whites (25%).

Conclusion: LTBI development was seen in 9.4% of patients with lack of known risk factors or exposure. This seroconversion was considerably higher than previous US-based studies and more in line with results from endemic countries. We conclude that annual screening for LTBI on TNF-I should take into consideration local/state TB prevalence, ethnicity, drug type and duration of drug use. For our local population, annual screening should be strongly considered.

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Disclosure: Disclosure

N. Goel, None; K. Torralba, None; L. Salto, None; C. Downey, None.

Abstract Number: 1226

Effect of New Method for Pre-Administration Assessment of Intravenous Biologics on Infections in Patients with Rheumatoid Arthritis

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Background/Purpose: Biologics are widely used and effective treatments for rheumatoid arthritis (RA), but generally biologics are avoided when patients have active infections on the day of administration.

In Japan, nurses are not authorized to assess whether patients have active infections or not. In our hospital, doctors in charge of the pre-administration assessments conventionally checked patient's status by taking history and physical examinations on the day of intravenous biologics, but it does not seem to be time efficient. We implemented new method in which nurses systematically screen according to pre-determined questionnaires on infections before doctors see patients. Our aim of this study is to reveal effectiveness of this new method of assessments.

Methods: We retrospectively review charts of patients with RA who received intravenous biologics at our hospital in Tokyo, Japan from June 2016 to April 2018. We investigated basic demographics, kinds of biologics and other treatments, underlying diseases, numbers and sites of serious infection (SI), and opportunistic infections. SI was defined as infections

Figure 1. Scheduled administration of intravenous biologics and its decision after assessments

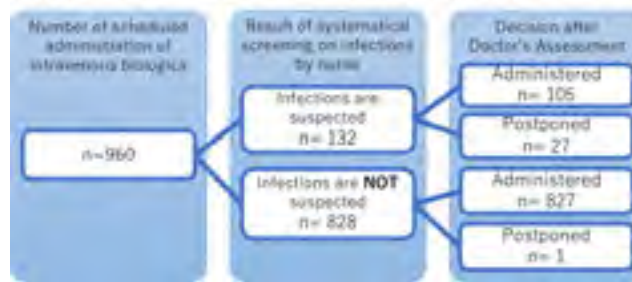


Table 1. Baseline characteristics and univariate analysis

	Overall (n=360)	Conventional method (n=189)	New method (n=171)	p value
Age	58 [18-90]	58 [18-90]	58 [18-89]	0.581
Female (%)	261 (72.5)	136 (72.0)	125 (73.1)	0.814
Seropositive RA(%)	224 (62.2)	117 (61.9)	107 (62.6)	0.914
Biologics				
Infliximab (%)	118 (32.8)	62 (32.8)	56 (32.7)	1
Abatacept (%)	129 (35.8)	70 (37.0)	59 (34.5)	0.66
Tocilizumab (%)	122 (33.9)	61 (32.3)	61 (35.7)	0.506
DMARDs				
MTX (%)	263 (73.1)	138 (73.0)	125 (73.1)	1
SASP (%)	166 (46.1)	88 (46.6)	78 (45.6)	0.916
MZR (%)	87 (24.2)	48 (25.4)	39 (22.8)	0.622
IGU (%)	94 (26.1)	51 (27.0)	43 (25.1)	0.72
BUC (%)	124 (34.4)	66 (34.9)	58 (33.9)	0.912
TAC (%)	24 (6.7)	14 (7.4)	10 (5.8)	0.673
Steroid (%)	272 (75.6)	147 (77.8)	125 (73.1)	0.327
Serious Infection (%)	16 (4.4)	8 (4.2)	8 (4.7)	1
TB (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
PCP (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Candida (%)	9 (2.5)	5 (2.6)	4 (2.3)	1
Zoster (%)	2 (0.6)	2 (1.1)	0 (0.0)	0.5

requiring intravenous antibiotics, hospitalization, or resulting in death. We compared numbers of infections in the new method with those in conventional one. Univariate analysis and Chi-square test were performed.

We also calculated the number of scheduled administrations and evaluated results of screening by nurse and doctor's assessment.

Results: We identified 360 cases in total. There are 189 and 171 patients who received intravenous biologics from June 2016 to May 2017 with conventional assessment and from June 2017 to April 2018 with new-style assessment.

The baseline characteristics are shown in table 1. Though there are no significant differences in the number of SI between new and conventional methods, the rate of SI was 4.4% and lower than that reported in previous studies.

The number of scheduled administration of biologics and its decision after assessments by nurse and doctors are shown in figure 1. There was just 1 case in which doctors postponed biologics even the patient was assessed not to have active infections by nurse.

Conclusion: Systematical screening by nurse with pre-determined questionnaires is very sensitive so that doctors can carefully see cases in which infections are suspected by the screening. Our new-method of pre-administration assessments can contribute to time-efficient practice without any increasing risk of SI.

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Indicator Opportunistic Infections after Biological Treatment in Rheumatoid Arthritis, 10 Years Follow up in Clinical Practice

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SESSION INFORMATION

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Session Type: ACR Poster Session B

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

Background/Purpose: Biologic disease-modifying anti-rheumatic drugs (bDMARDs) may be associated with opportunistic infections. Our purposes were to describe their incidence in Rheumatoid Arthritis (RA) taking bDMARDs, and compare the risk of development between TNF-targeted and non-TNF-targeted biologics.

Methods: Retrospective longitudinal study from 2007 to 2017. We included RA patients, from our outpatient clinic, whom started treatment with a TNF-targeted bDMARD [etanercept (ETN), golimumab (GOLI), certolizumab (CTZ), infliximab (IFX), adalimumab (ADA)], or non-TNF-targeted bDMARD [rituximab (RTX), abatacept (ABA), or tocilizumab (TCZ)]. We consider OI according to microbiologist criteria [An “indicator opportunistic infection after biological (IOIb)” according to consensus recommendations of the presence, or specific presentation, of a pathogen that suggests a greater probability of an alteration in the immunity in a host under treatment with bDMARDs¹]. Independent variable was the type of targeted bDMARD: TNF vs non-TNF. Secondary variables: sociodemographic; clinical and treatments. We used survival techniques to estimate the incidence of IOIb, per 1000 patient-year [CI 95 %]. The exposure time was defined from the start date of each bDMARD to the development of an IOIb, loss of follow up or end of study. We performed a Cox multivariate regression model to compare the risk of IOIb. Results were expressed in Hazard ratio (HR).

Results: 441 RA patients were included, starting 761 different courses of bDMARDs. 81% were women with a mean age at first bDMARD of 57.3±14 years. 71.3% of the courses were TNF-targeted bDMARDs and 28.7% non-TNF-targeted bDMARDs. There were 38 OI [26 Viral infections (18 Herpes Zoster, 2 VHB reactivation, 3 VHC reactivation, 1 Epstein Bar virus, 1 H1N1 flu, 1 CMV reactivation), 6 Fungal infections (5 Invasive-oropharyngeal candidiasis, 1 dermatophytosis by *Trichophyton* spp), 5 Bacterial infections (1 Legionellosis, 1 Salmonellosis and 3 Tuberculosis), 1 parasitic (Leishmaniasis)]. 9 of them required hospitalization and one died. The median time from onset of bDMARD until IOIb was 3.1 years [0.5-4.6]. The global incidence of IOIb was 21.8 [15.9-30]. TNF-targeted bDMARDs had 26 IOIb, incidence 19.8 [13.4-29.1], and non-TNF-targeted bDMARDs had 12 IOIb, incidence 28.1 [16-49.6]. In the multivariate analysis (adjusted by age, sex and calendar-time), we did not find statistical difference between type of targeted bDMARDs (HR 1.37, p=0.4), whereas male sex achieved a significant risk for IOIb (HR 2.18, p=0.04). Age (HR 1.02, p=0.08), concomitant treatment with glucocorticosteroids (HR 6.67, p=0.05) and leukopenia (HR 2.73, p=0.08) showed a tendency to increase the risk of IOIb.

Conclusion: Incidence of IOIb due to bDMARDs was near 22 cases per 1000 patients-year. Crude incidence was higher for non-TNF-targeted bDMARDs compared to TNF-targeted bDMARD, moreover this difference was not maintained in the multivariate analysis. Close monitoring should be taken in those RA patients treated with bDMARDs and glucocorticoids, and those with leukopenia, mainly elderly and male patients.

1. Winthrop et al. Ann Rheum Dis 2015; 74: 2107-2116

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Spine Immobilization and Neurological Complications in Vertebral Osteomyelitis: Results from a Multicenter Prospective Observational Study

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SESSION INFORMATION

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Background/Purpose: In a previous work, we showed that neurological complication can occur in up to 40% of patients with vertebral osteomyelitis (VO). Bed rest and spine immobilization are usually prescribed to prevent those complications. There is currently no consensus about the best immobilization protocol to follow in VO. Objectives of our work were to assess the prescription of spine immobilization for VO and its effect of neurological complications.

Methods: A prospective study was performed in 10 centers. All patients with native VO were included and followed prospectively: neurological complications, imaging findings, type and duration of immobilization were reported and patients were divided in two groups: “Immobilization” or “No Immobilization”, regarding if they had a prescription of spine bracing or not. We present here the data of our study after 6 months of follow-up.

Results: To date, 102 patients were included: 72 in the “Immobilization” group, and 30 in the “No Immobilization” group. Median duration of symptoms before diagnosis was 27 days, IQR (11-40). Thirty-six percent of the patients (n=37) had an abnormal neurological exam at baseline: 23.5% (n=24) had minor neurological signs (sensory loss or radiculopathy), and 12.7% (n=13) had major neurological signs (motor deficit or cauda equine syndrome). During hospital stay, 4 patients developed major neurological signs (median 5 days after diagnosis) and 5 patients developed minor neurological signs (median 6 days after diagnosis). Half of the patients with abnormal neurological exam at baseline had a normal neurological examination at 6 months. Median duration of bed rest was 9 days (IQR 7-18). In the “Immobilization” group (n=72), median duration of spine bracing was 8 weeks, IQR (6-12) and it was rigid bracing in 90% of cases. Main characteristics of the 2 groups are described in Table 1. They were no significant differences in age, associated diseases, or pathogen. Only one patient in the “No Immobilization” Group developed a paraplegia during follow-up, and the reason of the absence of immobilization was unclear. All patients with cervical involvement had a prescription of spine immobilization, whereas only half of the patients with lumbar involvement were immobilized. There were significantly less thoracic spine involvement in the “Immobilization” group. There were no differences in terms of neurological complications during follow-up between the two groups.

	Immobilization n= 72 (%)	No immobilization n=30 (%)	p
Demographical characteristics			
Age, years (standard deviation)	65 (+/- 15)	72 (+/- 14)	NS
Male	51 (70.8)	17 (56.6)	0,18
Diabetes	14 (19.4)	8 (26.6)	0,4
Obesity (BMI>30kg/M2)	17 (23.6)	8 (26.6)	0,7
Level of vertebrae involved			
Multifocal	11 (15.3)	9 (30)	0,09
Lumbar	37 (51.4)	16 (53.3)	0,8
Thoracic	18 (25)	14 (46.6)	0,03
Cervical	13 (18.1)	0	NS
Pathogen			
<i>Staphylococcus aureus</i>	22 (30.5)	12 (40)	0,3
Neurological state			
Major neurological sign at baseline	7 (9.7)	5 (16.6)	0,3
Minor neurological sign at baseline	20 (27.7)	4 (13.3)	0,11
Major neurological sign occurring during follow up	3 (4.2)	1 (3.3)	0,8
Minor neurological sign occurring during follow up	5 (6.9)	0	NS

Conclusion: Neurological complications occurred in 36% of our patients. Interestingly, 30% of our patients were not immobilized. None of them had cervical involvement and neurological outcome was favorable for 95% of “Not Immobilized” patients.

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Abstract Number: 1229

Diagnosing Prosthetic Joint Infections in Patients with Inflammatory Arthritis

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SESSION INFORMATION

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Background/Purpose: Patients with inflammatory arthritis (IA) are at increased risk of prosthetic joint infections, yet differentiating between septic and aseptic failure is a challenge in patients with IA. Synovial fluid biomarkers, may be helpful for detection of PJI. The aim of our systematic review is to evaluate synovial fluid biomarkers and their efficacy at diagnosing PJI in patients with IA.

Methods: A comprehensive literature search was performed in the following databases from inception – January 2018: Ovid MEDLINE, Ovid EMBASE, and The Cochrane Library. Studies retrieved were screened for eligibility against predefined criteria. Searches across the databases retrieved 367 results. After de-duplication, 2 of 5 (SM, CK, SR, JB, SG) independently screened a total of 298 citations. Discrepancies were resolved by a 3rd reviewer. After review of titles and

Marker	Non-inflammatory and Aseptic (n=1435)	Non-inflammatory and Septic (n=426)	Inflammatory and Aseptic (n=64)	Inflammatory and Septic (n=26)	p-value
RBC	27725.00 [5250.00, 185000.0] (n=74)	75000.00 [20000.00, 172500.0] (n=26)	4286.00 [1160.00, 20000.00] (n=6)	30000.00 [3000.00, 100000.0] (n=5)	0.142
CRP, ratio to normal	0.50 [0.13, 0.90] (n=482)	3.44 [0.86, 7.00] (n=150)	0.50 [0.10, 1.00] (n=33)	2.09 [0.75, 4.48] (n=21)	<0.001
ESR, ratio to normal	1.15 [0.60, 2.00] (n=561)	2.70 [1.92, 4.28] (n=148)	1.05 [0.52, 2.40] (n=38)	2.61 [1.99, 4.59] (n=20)	<0.001
Synovial					
%PMN	28.50 [7.00, 63.00] (n=494)	95.00 [89.00, 96.00] (n=110)	59.00 [14.00, 71.00] (n=34)	90.00 [83.00, 95.80] (n=16)	<0.001
WBC	7.22 [0.59, 360.00] (n=833)	79.05 [17.60, 13630.00] (n=292)	580.00 [80.00, 4360.00] (n=27)	35875.00 [11500.00, 60825.00] (n=16)	<0.001
IL-6	330.45 [126.50, 501.00] (n=97)	501.00 [501.00, 8193.20] (n=50)	501.00 [501.00, 501.00] (n=11)	323.85 [5038.00] (n=2)	<0.001
IL-8	501.70 [242.41, 1001.00] (n=97)	1001.00 [850.90, 3817.58] (n=52)	536.00 [257.40, 1001.00] (n=11)	1638.07, 3962.32 (n=2)	<0.001
IL-1b	0.00 [0.00, 2.11] (n=97)	13.24 [1.88, 134.81] (n=52)	0.00 [0.00, 11.25] (n=11)	5.30, 24.86 (n=2)	<0.001
GCSE	2.25 [0.00, 15.00] (n=95)	11.78 [0.33, 113.38] (n=52)	17.08 [0.00, 140.25] (n=11)	2.30, 2.97 (n=2)	0.020
CRP	2.00 [0.50, 9.50] (n=527)	14.20 [6.20, 25.10] (n=220)	13.40 [2.00, 25.10] (n=22)	16.80 [8.50, 30.60] (n=5)	<0.001
INFa	15.80 [6.73, 29.70] (n=95)	21.00 [8.54, 54.50] (n=50)	28.80 [14.39, 54.20] (n=10)	4.80 (n=1)	0.071
IFN gamma	0.00 [0.00, 0.00] (n=42)	13.18 [0.00, 33.62] (n=24)	0.00 [0.00, 0.00] (n=3)	6.85 (n=1)	0.006
IL-12p70	0.00 [0.00, 1.68] (n=44)	0.00 [0.00, 16.25] (n=26)	0.00 [0.00, 5.67] (n=3)	0.00, 21.25 (n=2)	0.305
IL-2	0.00 [0.00, 0.00] (n=42)	1.99 [0.00, 9.26] (n=26)	0.00 [0.00, 0.00] (n=3)	0.00, 6.11 (n=2)	0.025
IL-10	15.05 [11.75, 25.54] (n=41)	38.62 [17.04, 89.78] (n=24)	19.29 [7.15, 20.83] (n=3)	45.07 (n=1)	0.006

For all available patients, biomarkers are summarized with medians [interquartile ranges] and were compared using the Kruskal-Wallis test.

Table 2. Optimal cutpoints for each marker to identify infections

Marker	Cutpoint	Sensitivity	Specificity	Negative predictive value (NPV)	Positive predictive value (PPV)
%PMN	78	0.952	0.850	0.987	0.603
WBC	6.5	0.864	0.484	0.908	0.375
RBC	16,000	0.806	0.413	0.846	0.347
CRP, ratio to normal	1.89	0.629	0.885	0.875	0.462
ESR, ratio to normal	2.05	0.732	0.764	0.911	0.466
Synovial					
IL-6	339.9	0.846	0.589	0.869	0.444
IL-8	954.9	0.759	0.667	0.847	0.532
IL-1b	5.215	0.704	0.833	0.849	0.679
OCSP	34.25	0.389	0.868	0.756	0.606
CRP	5.2	0.791	0.623	0.879	0.462
TfR _h	49.22	0.294	0.867	0.717	0.517
IFN gamma	4.566	0.640	0.870	0.800	0.640
IL-12p70	6.540	0.357	0.956	0.710	0.769
IL-2	1.699	0.536	0.872	0.759	0.714
IL-10	28.121	0.720	0.818	0.837	0.692

Optimal cut points were chosen based on the maximum Youden index value (equal to sensitivity + specificity - 1).

abstracts, full text articles were pulled for further screening and data extraction. 20 articles were included, in this review. Due to methodological differences findings could not be pooled for meta-analysis. 5 studies that specifically investigated PJI in IA patients and non-IA patients were included and used to derive optimal cut points for common synovial tests.

Results: Our final analysis included 1435 non-IA aseptic patients, 426 non-IA septic patients, 64 IA aseptic patients and 26 IA septic patients. There was a significant difference in detection amongst the four groups when using %PMN, WBC, serum CRP and ESR, synovial IL-6, IL-8, IL-1b and CRP (Table 1). Median values of WBC count, IL-6, IL-8, and serum CRP were significantly higher in patients with IA, and although sensitivity was high, specificity was low (Table 2). PMN% had the highest sensitivity (95.2%) and specificity (85.0%) to detect infections with a threshold of optimum sensitivity and specificity of 78%.

Conclusion: Few studies address the diagnosis of PJI in patients with inflammatory arthritis and no synovial biomarker demonstrates high sensitivity and specificity. In contrast to PJI in patients with OA, we did not find synovial WBC count to be sensitive or specific in diagnosing PJI in IA patients. While diagnostic tests for synovial WBC, IL-6, IL8 and serum CRP appear higher in patients with inflammatory arthritis, there is overlap with those who are not infected. Further studies are needed to explore diagnostics tests that will better detect PJI in patients with IA

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Abstract Number: 1230

Invasive Fungal Infection with Cryptococcal Meningitis in Patients with Systemic Lupus Erythematosus

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SESSION INFORMATION

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Session Title: Infection-related Rheumatic Disease Poster

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Background/Purpose: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder with immunodeficiency associated with the disease itself and immunosuppressive treatment. Infections are very frequent events and one of the

main causes of morbidity and mortality. However, fungal infections have a low incidence, being those associated with *Cryptococcus neoformans* (CN) the most frequently described.

The aim of this study was to describe clinical, biochemical and outcomes of the invasive fungal infection (IFI) produced by CN in patients with SLE assisted in our hospital.

Methods: A retrospective and observational study of the IFIs by CN was carried out in adult patients with SLE (ACR82-97), assisted between January 1, 1993 and 1 May 2018.

Detection of capsular antigen in cerebrospinal fluid (CSF), a positive result of the ink test or isolation of the fungus from sterile sites according to EORTC/MSG 2008 criteria (European Organization for Research and Treatment of Cancer / Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group) were defined as IFI tested by CN. Evolution time of SLE at infection diagnosis, time of hospitalization, SLE activity measured by SLEDAI, clinical manifestations and immunosuppressive treatment were analyzed.

Results: Twenty one SLE patients with IFI were identified, and 7 (33%) of them presented CN infection. Rest of IFIs were caused as follows: 7 (33%) by *Candida* spp., *Aspergillus* spp: 2 (14,3%), *H. capsulatum*: 3 (9,52%), *P. jiroveci*: 1 (4,8%), *H. capsulatum* / *Alternaria* spp (mixed infection): 1 (4,8%). Seven cases infected with CN occurred in women with a mean of 40 years \pm 16. Mean evolution time of SLE at fungal infection was 9.7 years (9-180 months). Mean SLEDAI was 10 (0-24). 86% (6/7) of the patients had nephropathy and 57% (4/7) required hemodialysis. 43% (3/7) received treatment with cyclophosphamide but only 2 patients presented neutropenia. 86% (6/7) received corticosteroid therapy with meprednisone at doses greater than 20 mg/day and 29% (2/7) were treated with pulses of methylprednisolone. Other treatments were: Azathioprine, intravenous gammaglobulin, Mycophenolate Mofetil.

All the patients presented symptoms related to meningoencephalitis and Chinese ink test, antigenemia and CSF culture were positive in all cases. In 2 patients, CN was also isolated in the blood culture and in one of them also in sputum (disseminated infections). All were treated with Amphotericin B (liposomal amphotericin B was used in one patient due to renal failure and in another patient associated with fluconazole). Two patients continued with secondary prophylaxis with fluconazole. 5/7 patients died during hospitalization (71.4%), in most cases directly related to the infection.

Conclusion: Invasive fungal disease by *Cryptococcus neoformans* in SLE patients was associated to active disease, renal compromise and immunosuppressive treatment. Meningoencephalitis was the most prevalent clinical manifestation of cryptococcosis and in all cases the germ was isolated in the CSF. Two patients had a disseminated infection (blood cultures and positive sputum). All were treated with amphotericin B. The mortality was 71.4%.

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Abstract Number: 1231

Pyogenic Vertebral Osteomyelitis: Outcome Variables Analysis in a 116 Patients Cohort at a Tertiary Hospital during the Last 8 YEARS

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Background/Purpose: Vertebral Osteomyelitis is an infectious disease of the vertebral body which could involve the intervertebral space (spondylodiscitis). Early diagnosis and treatment are essential in order to achieve the best chance of a good outcome, but these are often delayed because it tends to present nonspecific manifestations. Our purpose was to identify risk factors and outcome variables in our cohort.

Methods: Single center longitudinal retrospective observational study including patients diagnosed of Vertebral Osteomyelitis from January 2010 to March 2018. Demographic, clinical, microbiology and radiological data were compiled.

Long hospital stay, readmission, vertebral destruction, neurological damage and death were chosen as outcome variables. Patients aging under 18 were excluded. The statistical analysis was performed with the software R, version 3.3.2.

Results: 116 patients were included, with a mean age of 62.05 (16.94) years old. Male sex accounted 68.10%. 58.62% had medical history of spine pathology. 18 patients (15.51%) presented immunosuppression (rheumatic or inflammatory bowel disease on treatment, malignancy, HIV or solid organ transplantation). Most frequent symptom was back pain (99.14%), fever was only in 45 patients (38.79%). Acute paraparesis was presented in 21 patients (19.10%) at diagnosis. Mean diagnosis delay was 54.14 days. 14 patients had underlying endocarditis (12.07%). Most of patients (94.83%) showed high CRP levels at diagnosis, with an average value of 103.47 mg/L, which was not related to worse outcome. Mean length of hospital stay was 34.24 (34.3) days and readmission rate was 34.9%. Blood cultures were positive in 46 patients (39.66%). Punction-aspiration was performed in 84 patients (72.10%) and its culture were positive in 48 samples (57.14%). Median delay from suspicion to biopsy was 6 days. Gram positive predominated (73.86%), followed by Gram negative species (12.5%), mycobacteria (10.23%) and fungi (3.41%). No microorganism was identified in 28 patients (24.14%). On imaging, most of the patients (92.24%) had paravertebral or epidural abscess. 63 cases (54.31%) showed vertebral destruction and 39 (33.62%) cord compression. Vertebral destruction was related to epidural abscess ($p=0.006$). 22 patients (18.97%) required further surgical procedures. Age trend to be related to worse outcome with no statistical signification. Diabetes mellitus was associated to greater vertebral destruction ($p=0.01$) and cord compression ($p=0.02$). Longer pain duration correlated with neurological damage ($p=0.02$). Underlying infectious endocarditis patients showed higher vertebral destruction ($p=0.01$). 11 patients (9.48%) died during follow-up.

Conclusion: Delay in diagnosis is still an important issue that is associated to higher complication rates, mainly related to structural damage of the spine. It has been also found that the presence of an epidural vertebral abscess is related to greater vertebral destruction. Elderly, diabetic and immunosuppressed patients had the worse chance of a good outcome, so these patients should be more careful managed (always try to obtain an imaging-guided biopsy, correct antibiotic treatment, and a functional and clinical follow-up).

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Abstract Number: 1232

Synovial Fluid Profile in Neutropenic Patients with Septic Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Infection-related Rheumatic Disease Poster

Session Type: ACR Poster Session B

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

Background/Purpose: In patients with septic arthritis, the white blood cell count in the synovial fluid is classically $>50,000$ cells/ μ L. While a microorganism must be identified in the synovial fluid to make a definitive diagnosis, the clinician often relies on the synovial white cell count to guide management prior to the culture results. There are few studies detailing the synovial fluid profile of patients with acquired neutropenia and septic arthritis. We performed a retrospective study to investigate synovial fluid white cell counts in neutropenic patients with culture positive septic arthritis.

Methods: Using ICD-9 and ICD-10 codes, we identified patients who carried both “septic arthritis” and “neutropenia” diagnoses at the University of Virginia Medical Center between January 2000 – January 2018. Twenty-six patients fulfilled these initial criteria. Charts were then reviewed individually to identify patients with an absolute neutrophil count (ANC) of less than 1000 cells/ μ L and synovial fluid cultures that confirmed septic arthritis.

Results: Three patients met the above criteria. The first patient was a 62 year old male with acute myelogenous leukemia. After induction chemotherapy, he presented with neutropenic fever secondary to *Candida tropicalis* candidemia. His course was complicated by septic arthritis of the right shoulder with synovial fluid cultures growing the same species of *Candida*. Aspiration of the joint revealed a synovial fluid count of 2 WBCs/ μ L. His total peripheral WBC count at the time of the arthrocentesis was 122 cells/ μ L (ANC undetectable). The second case was an 80 year old female with acute myelogenous leukemia. She presented after induction chemotherapy with neutropenic fever secondary to *coagulase-negative*

Staphylococcus bacteremia. She developed septic arthritis of the right knee that grew this bacteria as well. Aspiration of the synovial fluid yielded a cell count of 9 total WBCs/ μ L. Her ANC was 110 cells/ μ L. The final patient was a 64 year old male with multiple myeloma and ESRD. He presented with neutropenic fever secondary to Vancomycin-resistant *Enterococcus faecium* (VRE). He developed septic arthritis of the right knee with synovial fluid cultures also growing VRE. His synovial fluid cell count was 22,125 WBCs/ μ L. His ANC was 730 cells/ μ L at that time of his septic arthritis diagnosis.

Conclusion: In patients with acquired neutropenia and septic arthritis, the degree of peripheral neutropenia correlates with the synovial fluid white blood cell count. Neutropenic patients with a total ANC above 500 cells/ μ L appear to be able to mount a modest inflammatory response in the infected joint, whereas patients with an ANC below 500 cells/ μ L may have normal synovial fluid white cell counts. Clinicians should maintain a high level of suspicion for septic arthritis in neutropenic patients with joint pain and swelling even in the face of a normal synovial fluid white cell count. Synovial fluid cultures are essential in establishing the diagnosis of septic arthritis.

Disclosure: S. Minkin, None; A. Carlson, None.

Abstract Number: 1233

Rituximab Safety in Patients with Rheumatoid Arthritis. an Eleven-Year Follow-up Observational Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Infection-related Rheumatic Disease Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Rituximab (RTX) is a chimeric monoclonal antibody approved for the treatment rheumatoid arthritis (RA) patients who failed to respond to tumornecrosis factor inhibitors. Due to its effect on induction of B cell depletion, the administration of multiple cycles can lead to a decrease in immunoglobulins (Ig) which may increase the risk of infection. We aim to evaluate the long-term safety of RTX in RA patients.

Methods: Retrospective observational study was conducted including RA patients treated in a tertiary hospital between June 2006 and May 2017 who had received at least two RTXcycle. At RTX initiation we analyzed: comorbidities and Charlson score, presence of rheumatoid factor (RF) / anti-citrullinated protein antibodies (APC),previous biological DMARD (bDMARD); concomitant treatment (csDMARD /glucocorticoids (GC)) as well as demographic and clinical features.Serum Ig levels before every RTX cycle, the number ofRTX cycles and adverse events (AE), including serious and opportunistic infections were also analyzed. Non-disseminated Herpes-Zoster (HZ) were not considered opportunistic infection.

Results: 53patients were included (86.8% women, mean age 55.5 ± 13.5 years), 58% had aCharlson score ≥ 3 . Mean disease duration was 16 ± 9.1 years; 84.9% and92.5% were RF and ACPA positive, respectively. Before starting RTX, 81% of patients had received other bDMARD ($58.5\% \geq 2$), 88% received concomitantcsDMARD, (52% methotrexate and 32% leflunomide) and 81% were treated with GC(median dose 10 mg, P25-75 5-10 mg). The median number of RTX cycles received per patient was 5 (P25-75 2-6). 80 AE were reported: 12 infusion reactions, 8cases of neutropenia, 51 infections (18 respiratory, 8 urinary, 4 skin and soft tissues, 8 gastrointestinal, 4 cases of non-disseminated HZ, 1 bacteremia, 2 septic shock and 6 other) of which 19 were serious. 5 malignancies (2melanomas, 2 cervix, and 1 bladder) were also notified. The incidence rate of serious infections was $6.75 / 100$ PY, and its appearance remained stable throughout the follow-up time (Figure.1). No opportunistic infections or HBVreactivations were reported. Ig levels were obtained for 41 subjects: 7,5 and 1 patients had low levels of IgG, IgM and IgA, respectively. Patients who developed infections received a greater number of RTX cycles ($p<0.0002$) and had more frequently low levels of serum IgG during follow-up ($p<0.044$) than those who did not have infections. >0.002) and had more frequently low levels of serum IgG during follow-up ($p<0.044$) than those who did not have infections.

Conclusion: Long-term exposure to RTX showed a good safety profile with a low incidence of serious infectious and no opportunistic infections. Only number of cycles received and low serum levels of IgG at any point during follow-up were associated with the development of infections.

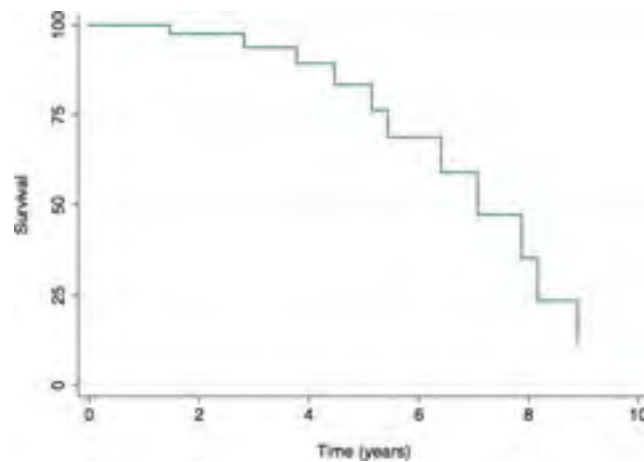


Figure 1. Evolution of Serious Infections Occurrence During Follow-up

Disclosure: R. Castellanos-Moreira Sr., None; S. C. Rodriguez-Garcia, None; M. V. Hernández, None; V. Ruiz-Esquide, None; O. Camacho Sr., None; A. Cuervo, None; J. Ramírez, None; J. Cañete, None; J. Gomez Puerta, None; R. Sanmartí, None.

Abstract Number: 1234

Incidence of Conversion of Screening Tests for M. Tuberculosis (PPD, GIF-release assay) in a Metropolitan Cohort of Patients Treated with TNF- α Inhibitors

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Infection-related Rheumatic Disease Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Tumor necrosis factor alpha (TNF- α) inhibitors are used to reduce the inflammatory process in many autoimmune diseases. Due to the risk of reactivation of latent tuberculosis, screening for latent infection with either purified protein derivative (PPD) skin testing or gamma interferon (GIF) release assay is necessary prior to initiation of treatment. Recommendations for subsequent testing while on TNF- α inhibitors vary, and there is a lack of data regarding the incidence of screening test conversion for patients on TNF- α inhibitors.

Methods: Between March 29, 2010 and October 19, 2016, patients over the age of 18 who had had an encounter with a rheumatologist at one of the University of Rochester Medical Center rheumatology practice clinics were identified through a search of our electronic medical record. Our physicians provide care for an estimated 60% of the patients in the referral catchment population of approximately 1.1 million residents (including 5 suburban and agricultural counties and a medium sized city of 210,000). The charts of those who had been prescribed a TNF- α inhibitor (adalimumab, certolizumab, etanercept, golimumab, or infliximab) and who had been identified by ICD coding for positive PPD or GIF release assay testing, were reviewed.

Results: Of the 2807 rheumatology clinic patients treated with TNF- α inhibitors, 89 cases (2.9%) of latent tuberculosis were identified and verified by chart review to have a confirmed positive PPD reading or GIF release assay. 25 (28.1%) of these cases were identified after the initiation of a TNF- α inhibitor as new converters. The rate of PPD or GIF-release assay conversion with TNF- α inhibitor use amongst our cohort is 0.89% (25 of 2807 patients).

Conclusion: We documented a 0.89% PPD/GIF conversion rate in our patients on TNF- α inhibitors. Our data suggests that continued screening of patients maintained on TNF- α inhibitor therapy will improve identification of these patients unknowingly exposed to mycobacterial infection.

Disclosure: H. Trinh, None; D. Tabechian, None.

Isoniazid Monotherapy As a Prophylaxis for Tuberculosis in Patients with Rheumatic Diseases Exposed to Prolonged, High-Dose Glucocorticoids

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Infection-related Rheumatic Disease Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Although use of glucocorticoid increases the risk of tuberculosis (TB) disease, there has been few studies investigating its incidence and risk/benefit assessment of the prevention in rheumatic disease patients with this treatment. Furthermore, result of tuberculin skin test and interferon gamma release assay (IGRA) could be significantly influenced by steroids itself. In this study, we investigated the efficacy and safety of isoniazid (INH) monotherapy as a prophylaxis of TB disease in rheumatic disease patients receiving prolonged, high-dose steroids.

Methods: This single center cohort study analyzed 1618 treatment episodes with prolonged (4 weeks or more), high-dose (30mg/day or more of prednisone) steroids from 1160 patient's between 2004 and 2016. IGRA was performed in 187 (11.6%) episodes and selection of patients for INH monotherapy and its duration was mainly determined by treating physician. Overall, 152 episodes (INH group) received isoniazid monotherapy with steroid while other 1466 episodes did not receive prophylaxis (control group). Primary outcome was 1-year incidence of TB disease between the two groups, which was compared using Cox regression. Incidence rate of adverse drug reaction (ADR) related to INH was also investigated. Risk-benefit analysis of INH monotherapy was performed by comparing the number needed to be treated (NNT) to prevent 1 case of TB disease vs. the number needed to harm (NNH) due to ADR. As part of a sensitivity analysis, propensity score matching was used to minimize baseline imbalances, and the same analysis was performed in post-matched population (n=147 in each group).

Results: Patients in the INH group were older (45.1 vs. 42.1 years) and more frequently had SLE (56.6% vs. 48.7%) and MPA (5.3% vs. 0.9%) than those in the control group. Median (IQR) steroid dose at initiation was also higher in the INH group (55.0 [30.0] vs. 60 [15.0] mg/day of prednisone). During a 1579.8 person-year, a total of 21 cases of TB disease occurred. Prophylaxis with INH trended toward a reduced 1-year incidence of TB in the multivariable model where SLE, cumulatively used steroid dose and risk factors for TB disease were adjusted (adjusted HR = 0.57 [95% CI 0.13 to 2.52]) (Figure). The sensitivity analysis performed in the post-matched population was consistent with the main results (adjusted

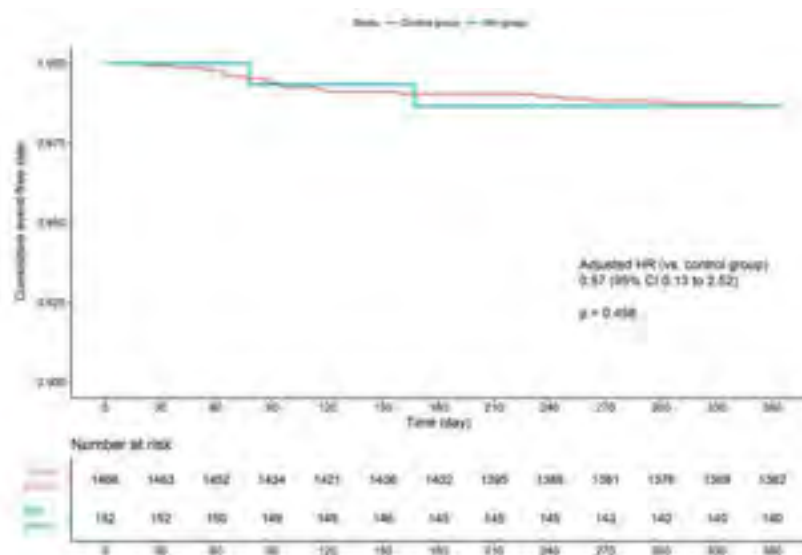


Figure. Kaplan-Meier curve indicating 1-year incidence of tuberculosis disease between the control group and isoniazid (INH) group.

HR = 0.67 [0.10 to 4.38]). In contrast, incidence rate of any ADRs during the INH treatment was 113.0 (90.5 to 139.3)/100 person-year including one case of fulminant hepatitis. Because absolute risk for TB disease was higher in the INH group, NNT was calculated as a negative value whereas NNH for any ADR and serious ADR were 2 (1.6 to 2.1) and 76 (32.0 to 110), respectively.

Conclusion: Isoniazid monotherapy as a prophylaxis for TB in rheumatic disease patients receiving prolonged, high-dose steroids shows partial efficacy, but high incidence of ADR limits its role as a general practice.

Disclosure: J. W. Park, None; J. R. Curtis, None; H. Lee, None; Y. W. Song, None; E. B. Lee, None.

Abstract Number: 1236

Peripheral-Blood B-Cell Subset Disturbances in Whipple's Disease

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Infection-related Rheumatic Disease Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Whipple's disease (WD) is a rare, systemic, disease caused by the intracellular Gram-positive bacterium *Tropheryma whippie* (TW). This ubiquitous commensal organism is transmitted among humans via the oro-fecal route. Chronic WD and the immune system are closely linked. To our knowledge, no studies have evaluated the potential role for B cells in WD. We noticed lymphocyte subset abnormalities similar to those seen in primary Sjögren's syndrome in patients whose symptoms suggested ankylosing spondylitis (inflammatory low back pain) or rheumatoid arthritis (chronic polyarthritis). We then observed the same abnormalities in patients with infectious rheumatic diseases due in particular to *Bartonella* (cat-scratch disease) or TW. We therefore designed the present study with the aim of describing peripheral-blood lymphocyte subsets, with special attention to B cells, in patients with WD. We aimed to assess whether any abnormalities found were sufficiently characteristic to help in diagnosing and monitoring WD.

Methods: Consecutive patients seen between 2010 and 2016 for suspected inflammatory joint disease were identified retrospectively. Results of standardized immunological and serological tests and of peripheral-blood B-cell and T-cell subset analysis by flow cytometry were collected. Patients with criteria suggesting WD underwent PCR testing for *Tropheryma whippie*, and those with diagnosis of WD (cases) were compared to those without diagnosis (controls). We used ROC curve analysis to evaluate the diagnostic value of flow cytometry findings for WD.

Results: Among 2917 patients seen for suspected inflammatory joint disease, 121 had suspected WD, including 9 (9/121, 7.4%) with a positive PCR and a dramatic response to antibiotic therapy for WD. Proportions of T cells and NK cells were similar between cases and controls, whereas cases had a lower proportion of circulating memory B cells (IgD⁺CD38^{low}, 18.0%±9.7% vs. 26.0%±14.2%, $P=0.041$) and higher ratio of activated B cells over memory B cells (4.4±2.0 vs. 2.9±2.2, $P=0.023$). Among peripheral-blood B-cells, the proportion of IgD⁺CD27⁻ naive B cells was higher (66.2%±18.2% vs. 54.6%±18.4%, $P=0.047$) and that of IgD⁺CD27⁺ switched memory B cells lower (13.3%±5.7% vs. 21.4%±11.9%, $P=0.023$), in cases vs. controls. The criterion with the best diagnostic performance was a proportion of IgD⁺CD27⁻ naive B cells above 70.5 %, which had 73% sensitivity and 80% specificity.

Conclusion: Our study provides data on peripheral-blood B-cell disturbances that may have implications for the diagnosis and pathogenetic understanding of WD.

Disclosure: M. Le Goff, None; D. Cornec, None; D. Guellec, None; T. Marhadour, None; V. Devauchelle-Pensec, None; S. Jousse-Joulin, None; M. Herbette, None; J. M. Cauvin, None; C. Le Guillou, None; Y. Renaudineau, EFPIA, 2; J. O. Pers, None; A. Saraux, None.

SESSION INFORMATION

Session Title: Infection-related Rheumatic Disease Poster

Session Type: ACR Poster Session B

Background/Purpose: Synovial biopsies are increasingly performed for research purposes but also in clinical practice. The development of US guided procedure has made this procedure simpler. In addition, both small and large joints as well as tendon sheaths and bursae are accessible. In clinical practice, synovial biopsies are traditionally performed in cases of suspected septic arthritis. The goal of this work was to assess the usefulness of synovial biopsies in a large cohort of synovial biopsies performed in clinical practice.

Results: 153 biopsies were performed between 2007 and 2018. 22 patients were finally diagnosed with septic arthritis. There were 11 females, mean age 63 years old (+/- 18). The biopsy was performed in the knee (n=9); wrist (n=3); shoulder, hip, elbow (n=2 each); ankle, sternoclavicular acromioclavicular and flexor of hand (n=1 each). Biopsy did not retrieve synovial tissue in 2 cases. Pathological analysis was characteristic of septic arthritis in 5 cases, compatible in 9 cases, not suggestive in 5 cases. Characteristics of the patients, synovial fluid and biopsy and blood test results are summarized in table 1. Overall, the bacteria were identified by culture or PCR in 16 cases. *Mycobacterium* sp. was identified in 2 cases with a positive synovial fluid analysis and/or lavage. Slow-growing bacteria were identified in 8 cases: Lyme disease (n=5), Whipple disease (n=2) and *coxiella burnetii* (n=1). In these cases, PCR was positive in the synovial tissue in 4 cases but negative in 4 cases (diagnosis based on blood serology or PCR of other tissues). Pyogenic bacteria were identified in 7 cases: diagnosis was made only on the culture of the synovial biopsy in 4 cases; on serum saline lavage of the joint in 2 cases (negative synovial tissue culture); on the blood culture in one case.

			Species 1 host				Species 2 biology					Host	
patient	Site	Species	Genotyping	Molecular biology	Pathology	PCR	Genotyping	Molecular biology	Pathology	PCR	Genotyping	Micro culture	Pathology
1	Eye	Eye	Yes	Yes		Yes	Yes	Yes			Compatible with rapid culture	Yes	
2	Shoulder	Eye	Yes	Yes			Yes	Yes			Compatible with rapid culture	Yes	
3	Eye	Eye	Yes	Yes			Yes	Yes			Compatible with rapid culture	Yes	
4	Shoulder	Eye	Yes	Yes			Yes	Yes	Yes		Compatible with rapid culture	Yes	
5	Eye	Eye					Yes	Yes	Yes		Compatible with rapid culture		
6	Eye	Shoulder (eye)	Yes	Yes			Yes	Yes			Not suggestive of rapid culture		
7	Eye	Shoulder	Yes	Yes			Yes	Yes			Not suggestive of rapid culture		
8	Eye	Shoulder (eye)	Yes				Yes	Yes	Yes		Compatible with rapid culture		
9	Eye of host	Shoulder (eye)						Yes			Not suggestive of rapid culture		
10	Eye	Shoulder (eye)					Yes	Yes	Yes	Yes	Not suggestive of rapid culture		
11	Eye	Shoulder (eye)	Yes		Yes		Yes				Compatible with rapid culture		
12	Eye	Shoulder (eye)	Yes	Yes			Yes	Yes	Yes	Yes	Compatible with rapid culture		
13	Eye	Shoulder (eye)	Yes					Yes	Yes		Compatible with rapid culture	Yes	
14	Eye	Shoulder (eye)	Yes	Yes			Yes	Yes	Yes		Compatible with rapid culture		
15	Eye	Shoulder (eye)		Yes	Yes		Yes	Yes			Compatible with rapid culture	Yes	
16	Eye	Shoulder (eye)	Yes	Yes			Yes	Yes		Yes	Not suggestive of rapid culture	Yes	
17	Eye	Shoulder (eye)	Yes	Yes				Yes	Yes	Yes	Compatible with rapid culture	Yes	Yes
18	Eye	Shoulder					Yes	Yes		Yes	Not suggestive of rapid culture		
19	Eye	Shoulder (eye)		Yes			Yes	Yes			Not suggestive of rapid culture		
20	Shoulder (eye)	Shoulder (eye)					Yes						
21	Eye	Shoulder (eye)						Yes			Compatible with rapid culture	Yes	
22	Shoulder (eye)	Shoulder (eye)						Yes	Yes		Compatible with rapid culture	Yes	Yes

performed during the biopsies as they could lead to the identification of the bacteria; 2. Pathological analysis of the synovial tissue could be not suggestive of septic arthritis in case of slow growing bacteria; 3. None of these analyses are highly sensitive for the diagnosis that remains based on epidemiological, clinical, bacteriological and histological arguments.

Disclosure: B. Ouvrard, None; G. Bart, None; C. Darrieutort, None; A. Najm, None; B. Le Goff, None.

Abstract Number: 1238

The Effect of Antibiotic Therapy on Positive Culture Results Among Patients with Prosthetic Joint Septic Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Infection-related Rheumatic Disease Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Little is known about the effects of antibiotic therapy on synovial and blood culture results among patients with prosthetic joint septic arthritis (PJSA). In this study we aimed to determine this effect.

Methods: We conducted a retrospective study of patients 18 years and older admitted to a single tertiary care center between 1998 and 2015 with culture-positive PJSA. Only patients with serial blood or synovial fluid cultures who received appropriate antibiotic treatment (i.e. matched to the bacterial antibiogram) and in whom the timing of initiation of antibiotic therapy was documented were included in this study. Time to conversion of cultures from positive to negative was calculated using Kaplan-Meier and Cox regression models. Log Rank (Mantel-Cox) test and Wald test were used to compare survival curves among groups and versus the general tendency. A p-value < 0.05 was considered significant for all tests.

Results: Among patients with culture- positive PJSA serial blood and synovial fluid cultures were obtained in 38 (36.5%) and 66 (63.5%) patients, respectively. Mean number of samples per patient was 10.7 and 2.4 for blood and synovial fluid cultures, respectively. Vancomycin was the most commonly prescribed antibiotic and was administered to 84.5% of the patients. Median time to conversion from positive to negative culture results was significantly longer for synovial fluid cultures compared with blood cultures (147.7 vs 34.9 hours; p-value <0.001). Median time of conversion from positive to negative blood culture results varied significantly for the top 3 pathogens; *Coagulase negative Staphylococcus* (CONS), *methicillin-sensitive Staphylococcus Aureus* (MSSA), *methicillin-resistant Staphylococcus Aureus* (MRSA) (22.9 vs 47.1 vs 37.3 hours, respectively; p= 0.006).

Conclusion: To our knowledge, this is the first study to demonstrate the effect of antibiotic administration on blood and synovial culture positivity over time. Blood cultures appear to be more sensitive than synovial fluid cultures to the effect of antibiotics. We also were able to demonstrate that the effect of antibiotics on blood culture sterility varies between different bacterial pathogens.

Disclosure: E. Gur Rosset, None; M. L. Fowler, None; S. Lieber, None; R. Shmerling, None; Z. Paz, None.

Organisms Associated with Prosthetic Joint Septic Arthritis over the Past Two Decades: Data from a Single Tertiary Medical Center Located in the Northeastern United States

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SESSION INFORMATION

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Session Title: Infection-related Rheumatic Disease Poster

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

Background/Purpose: In recent years, joint replacement surgery (JRS) has become increasingly common. Prosthetic joint septic arthritis (PJSA) may complicate JRS in up to 1% of cases. As is true for other types of infections (e.g. cellulitis, pneumonia), the microbiologic causes of PJSA may change over time. Early, effective therapy of PJSA may be enhanced by improving our knowledge on the major causes of PJSA. In this study we aimed to determine the trends in the organisms associated with PJSA.

Methods: We conducted a retrospective study including all patients 18 and older with surgically-treated, culture-positive PJSA admitted to a single tertiary medical center in Boston between the years of 1997-2015. We excluded cases of culture negative SA, native joint SA, osteomyelitis and septic bursitis. Patients with prosthetic joint arthritis were considered culture-positive if pathogenic bacteria were isolated from synovial fluid, blood cultures or synovial biopsy.

Results: We identified 190 patients with culture- positive PJSA. The most commonly identified organisms over the study period were: *Methicillin sensitive Staphylococcus aureus* (MSSA) (34.2%), *coagulase negative Staphylococci* (CoNS) (18.9%), *methicillin resistant Staphylococcus aureus* (MRSA) (13.2%) and *group B Streptococcus* (GBS) (11.6%). When our cohort of patients was divided into 5 years intervals, a significant change in the rates of MRSA related PJSA was observed: 7.7% in 1997-2002, 28.9% in 2003-2008, 9.7% in 2009-2014, p value = 0.005.

Over the study period 12.6% of the patients presented with early PJSA (JRS≤42 days), 26.8% with delayed PJSA (365>JRS>42 days) and 54.2% with late PJSA (JRS>365 days). A trend toward a significant increase in GBS related late PJSA was observed (early GBS related PJSA= 4.2% delayed GBS related PJSA =5.9% late GBS related PJSA= 17.5%, p value=.060). *Enterococcus*, *Pseudomonas aeruginosa* and *Streptococci Viridins* were not isolated in the early PJSA group.

Conclusion: Similar to other studies we showed that MSSA, CoNS and MRSA are the top three causes of PJSA. The novel observations of our study include the falling incidence of MRSA in recent years, the higher rates of GBS in late PJSA and the absence of *Enterococci* and *Pseudomona Aeruginosa* in early PJSA.

Disclosure: M. M. Arieli, None; M. L. Fowler, None; S. Lieber, None; R. Shmerling, None; M. Naffaa, None; Z. Paz, None.

Foot Osteomyelitis in Inflammatory Rheumatic Diseases: A Retrospective Observational Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Infection-related Rheumatic Disease Poster

Session Type: ACR Poster Session B

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

Background/Purpose: Foot involvement is frequently pointed by patients with chronic inflammatory rheumatic diseases (IRD), such as rheumatoid arthritis (RA), spondyloarthritis (SpA) or psoriatic arthritis (PsA). According to previous studies, IRD patients are at higher risk of developing osteomyelitis (rate ratio 10.63), although incidence rate seems to be low (0,17/100 patients-years)¹. Given the increased infectious risk, especially induced by steroids or immunosuppressive drugs, our aim was to report the occurrence of foot osteomyelitis in the patients suffering from IRD and recruited in our center over the last twenty years.

Methods: We performed a monocentric retrospective observational study that collected MISP (Medicalized Information System Program) data in the Montpellier University Hospital, from August 1996 to May 2016. We included all patients with IRD who presented a clinical suspicion of osteomyelitis (classic inflammation signs, or fever), with confirmation by definite imaging (Magnetic Resonance Imaging, tomography, or radiographic) findings and at least one positive microbiological culture. We excluded patients with isolated soft tissue infection, no microbiological sampling, or no imaging finding, as well as patients with incomplete data about their IRD history (long-term treatments, immunology, erosive status). Two groups were dissociated: the first with foot osteomyelitis patients (FO), the other with osteomyelitis patients not affecting the foot (NFO). In the patient medical file, we collected demographic, clinical, biological and imaging data. The comparison between each group was performed using the Student test for quantitative variables and using a Chi-2 test for qualitative variables.

Results: Among the 235 MISP search findings, we identified 69 bone infections that met the inclusion criteria, of which 41 (59.4%) involving the foot. In the FO group, RA was highly predominant (92.6%), with an advanced (24.6 +/- 13.1 years of evolution) and severe illness (37 cases, 92.5% patients with erosions). Patients were mainly treated by corticosteroids (65.9%), methotrexate (32.1 %) and biologics (28.6%). Diabetes was the most frequent comorbidity (8 cases, 19.5%). Osteomyelitis mainly involved forefoot (75.6%), especially in the first ray (41.1% of infections). *Staphylococcus aureus* was the most involved organism (53.7%). We significantly found fewer systemic complications (sepsis or endocarditis) in the FO group compared to the NFO group (2.4% vs. 28.6%, $p = 0.002$). Furthermore, corticosteroids use was associated to a significant risk in the FO group compared to the NFO group (65.9% vs. 39.3%, $p = 0.03$). No increasing infectious risk was found for biological drugs users in the FO group (31.7% vs 28.6%, $p = 0.78$).

Conclusion: Description of FO is scarce in IRD. Our study reported a significant occurrence, especially in patients with severe RA using steroids. A special attention should be done to identify risk factors and possibly correct them.

References:

1. Doran et al. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum.* 2002 Sep;46(9):2287–93

Disclosure: A. HOMES, None; P. ABOUKRAT, None; C. JORGENSEN, None; Y. M. PERS, None.

Abstract Number: 1241

Pneumococcal Vaccination Quality Improvement Initiative within a Rheumatology Clinic at an Academic Medical Center

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Infection-related Rheumatic Disease Poster – ARHP

Session Type: ACR Poster Session B

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

Background/Purpose: Rheumatology patients are at an increased risk of infection secondary to immunosuppressive medications used for disease management. However, vaccination is underutilized and rates remain low in this population despite guideline recommendation for receipt. Our aim was to improve pneumococcal vaccination rates in patients receiving biologic medications and to identify barriers to vaccination.

Methods: We implemented a multifaceted intervention within an adult rheumatology clinic at an academic medical center. Intervention included pharmacist pre-visit review of vaccination status, flagging charts with recommended vaccine, physician face-to-face discussion, and optional in-clinic nurse administration.

Results: 514 patients were reviewed prior to their visit. 369 were identified as eligible for pneumococcal vaccination. Of patients who were current with pneumococcal vaccination at the time of their visit, 34% had vaccination records located outside of our electronic medical record, primarily found in state immunization registries. Following five months of our intervention, 343 patients are now current with pneumococcal vaccinations, shifting those with an updated status from 28% to 67%. Of those that did not receive vaccination at time of visit, most common documented reasons were, no recommendation was identified within visit note, followed by patient will discuss with primary care physician.

Conclusion: Our intervention significantly improved pneumococcal vaccination rates and highlights the benefit of a multidisciplinary approach to optimize vaccination. Barriers to vaccination identified in our study emphasize confusion surrounding current guideline recommendations and the need for a reliable, transparent immunization record.

Disclosure: A. Goodson, None; B. Libman, None; A. Nevares, None; M. Edwards, None; A. Kennedy, None.

Abstract Number: 1242

Rheumatologists Participating in the RISE Registry Succeeded in the First Year of the Merit-Based Incentive Payment System (MIPS)

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Under the Medicare Access and CHIP Reauthorization Act (MACRA), rheumatologists face financial repercussions through the Merit-Based Incentive Payment System (MIPS) based on performance on quality measures and use of electronic health records (EHRs). For the MIPS 2017 reporting year (Jan. 1, 2017-Dec. 31, 2017), providers were scored across 3 domains: Quality, Improvement Activities (IA), and Advancing Care Information (ACI). In this study, we sought to evaluate MIPS performance for practices that reported through the ACR's Rheumatology Informatics System for Effectiveness (RISE) registry.

Methods: The RISE registry continuously collects data from the EHRs of participating practices, allowing centralized aggregation and automated analysis of quality measures under the quality domain. RISE also allows providers to self-report on the other two domains that were active for 2017, IA and ACI. Using data from RISE, we calculated performance for all providers who reported for MIPS through the registry. We also evaluated the differences in performance on all three domains among providers who reported individually versus as part of a group.

Results: For the 2017 reporting year, 346 providers from 125 practices used the RISE registry to complete a total of 178 MIPS submissions for at least one domain, representing about 10% of MIPS-eligible rheumatology clinicians in the U.S. Most practices were either a group (47%) or solo practice (30%). Others were in some other clinical setting (5%), a health system (1%) or did not have practice setting information (18%). Of all submissions through RISE, 134 (76%) were considered full submissions on all 3 domains (Quality, IA and ACI). All full submissions exceeded the exceptional performance threshold of 70 points out of 100, earning all providers an additional bonus. While all rheumatologists submitting through RISE had high performance, those who submitted as part of a group had a slightly higher overall average performance (95.0 points) than those who submitted individually (92.1 points).

Conclusion: We found that all rheumatologists who completed full submissions through RISE were successful in the first year of MIPS, earning bonuses on their payment reimbursements for 2019. While some aspects of MIPS will be changing in 2018, RISE is continuously updated to track and maximize success in 3 of the 4 2018 MIPS domains. Further research is planned to investigate the workflows of group and solo practices who were top performers, as well as to assess the correlation between providers' MIPS scores and their patients' outcomes.

Disclaimer: This data was supported by the ACR's RISE Registry. However, the views expressed represent those of the authors, not necessarily those of the ACR.

Disclosure: T. Johansson, None; R. Larosa, None; R. Myslinski, None; N. Brown, None; L. Lewis, None; J. Yazdany, Pfizer, Inc., 2.

Abstract Number: 1243

A Quality Improvement Initiative to Increase Adherence to Hydroxychloroquine Dosing Guidelines at an Academic Medical Center

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster II

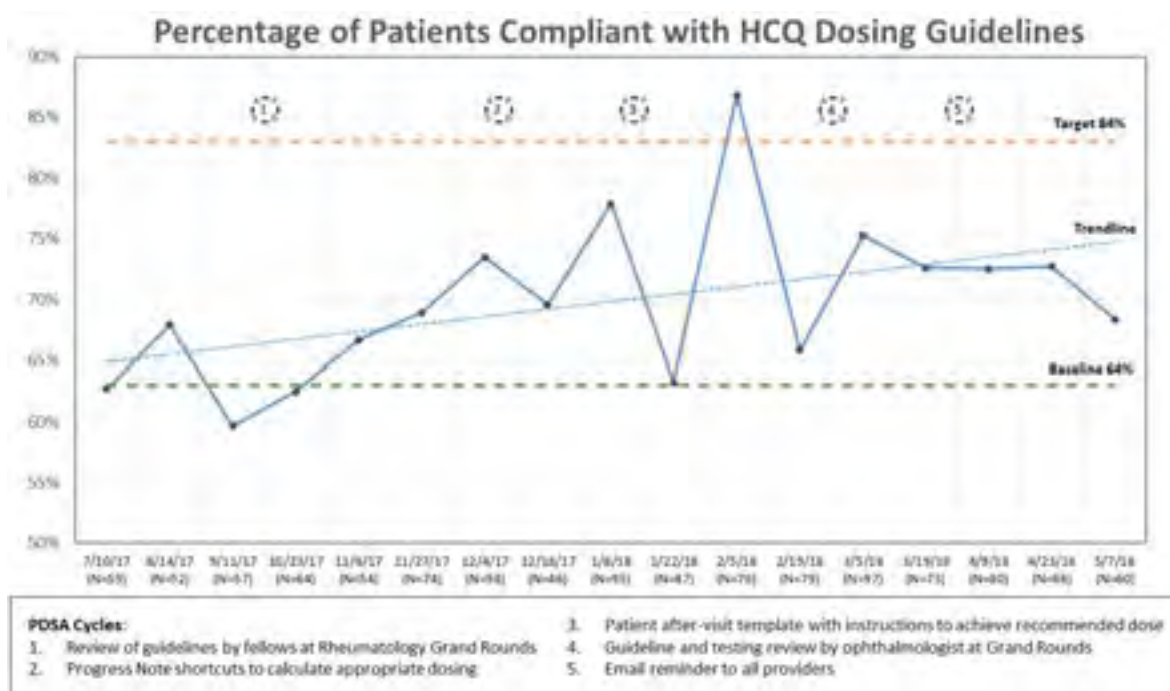
Session Type: ACR Poster Session B

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

Background/Purpose: In 2016, the American Academy of Ophthalmology published revised guidelines on HCQ dosing, recommending a maximum daily dose of 5mg/kg actual body weight as higher doses increase the risk of irreversible retinal toxicity. We conducted a QI initiative to increase provider adherence to these guidelines. We aimed to increase dosing compliance by 20 percentage points.

Methods: HCQ guideline compliance was measured every other week over 10 months by retrospectively reviewing all encounters with non-pregnant patients prescribed HCQ in an adult rheumatology clinic. We recorded date of visit, sex, weight, average daily HCQ dose, any change in dose, and HCQ indication. We used a strict threshold of 5mg/kg in assessing dosing compliance. We also surveyed providers regarding baseline perceptions towards HCQ dosing in clinical practice. Using Plan-Do-Study-Act methodology, we conducted these interventions: grand rounds lectures, modifications of electronic medical record templates, and an email reminder to providers. Charts were analyzed at baseline, between and following interventions.

Results: In the baseline survey (N=16) when asked, "How worried are you that discussing the new guidelines might lead to non-adherence?" 71% reported little or no concern while 29% of providers were "worried." Queried whether changing the



HCQ dose per guidelines has directly led to an adverse clinical outcome, 23% answered at least one occurrence; 15% recalled having at least one patient suffer significant visual impairment from HCQ.

We analyzed 1218 encounters (87% female) where HCQ was prescribed. The average daily dose was 350mg with 400mg daily being most commonly prescribed (65%). The average weight was 81.5kg. The top three indications for HCQ use were SLE (39%), RA (27%), and UCTD (16%). Baseline guideline compliance was 63% (N=169). During interventions, weekly compliance increased to a peak of 87%, with an overall average of 72% (Figure). Compliance was 99% in patients \geq 80kg and 44% in patients <80kg. Dose was decreased in 7% of encounters with a compliance of 62% after reduction. HCQ was started in 10% of encounters with 76% compliance. Dose was increased in 3% of encounters with resultant compliance of 59%. Compliance during interventions was lower among SLE (67%) than other diagnoses (75%).

Conclusion: Our QI initiative increased compliance by 10 percentage points, short of our aim of 20. This result is not surprising as 29% of providers were worried about flares with dose reduction. A dose decrease did not always result in improved adherence. New initiation of HCQ demonstrated improved adherence compared to the baseline. No one specific intervention appeared most effective. Patients with SLE and weight <80kg were less often within dosing guidelines potentially reflecting a focus for future targeted interventions. Additional studies are also needed to determine flare risk with dose reductions.

Disclosure: R. Jessee, None; S. L. Giattino, None; A. Kapila, None; K. Kaufman, None; J. Golenbiewski, None; B. J. Andonian, None; D. Leverenz, None; L. Criscione-Schreiber, GlaxoSmithKline, 2.

Abstract Number: 1244

Hydroxychloroquine Quality Improvement Project at UF Health Jacksonville Rheumatology Clinics

Shameik Brooks, Gurjit Kaeley and Lanh Dang, UF Health Jacksonville, Jacksonville, FL

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Hydroxychloroquine (HCQ) is a treatment option for lupus erythematosus and rheumatoid arthritis. The risk of retinopathy in the first 5 years of therapy is estimated to be less than 1% in patients prescribed doses below 5 mg/kg per day. However, the risk increases to approximately 20% after 20 years of treatment. The American Academy of Ophthalmology (AAO) has identified the following risk factors for retinopathy secondary to HCQ: duration of treatment greater than 5 years, dose greater than 5 mg/kg actual body weight per day, kidney disease, concurrent tamoxifen use and history of macular disease. This study was conducted to identify patients who are at high risk for HCQ-induced retinopathy and to consider dose reduction if possible.

Methods: Data was obtained from the electronic health record (EHR) from July 1, 2016 to July 30, 2017. Clinic practice changed August 1, 2017 to identify patients at high risk for HCQ retinal toxicity and doses were decreased to below 5 mg/kg per day if possible. A repeat assessment was completed using EHR data from August 1 2017 to November 30, 2017 to determine the number of patients who remained at high risk for retinal toxicity, if dose reductions occurred, and if there was any impact on disease control.

Results: The initial assessment included 436 patients. One-hundred and five patients (24.1%) were prescribed HCQ at doses greater than 5 mg/kg per day. Sixty-three of the 105 patients had doses greater than 6 mg/kg per day and of those 63 patients, 20 of them had doses greater than 7 mg/kg per day. One patient was on concurrent tamoxifen therapy and HCQ was decreased to 200 mg per day. Twelve patients were identified to have an eGFR less than 60. There were 151 unique ophthalmology visits during the initial assessment.

The repeat assessment included 145 patients. Twenty-four patients (16.6%) were prescribed HCQ at doses greater than 5 mg/kg per day. Nine of the 24 patients had doses greater than 6 mg/kg per day and of those 9 patients, 3 of them had doses greater than 7 mg/kg per day. Doses did not exceed 8 mg/kg in any of the patients assessed. No patients in the repeat assessment were on concurrent tamoxifen therapy. One patient was identified to have an eGFR less than 60. There were 66 unique ophthalmology visits during the repeat assessment. After the conclusion of the study period, 1 patient with lupus erythematosus experienced increased disease activity since dose reduction from 8 mg/kg per day to 4 mg/kg per day. The HCQ dose was increased back to the previous dose in this patient.

Conclusion: Repeat assessment showed that less patients were prescribed HCQ at doses greater than 5 mg/kg/day compared to the initial assessment. Patient assessment to determine if HCQ dose reduction to less than 5 mg/kg per day is

clinically appropriate. However, it is important to monitor for increased disease activity in these patients. Assessing the number of ophthalmology visits was not fully informative as it does not indicate the number of patients specifically assessed for HCQ retinal toxicity. A more streamlined method to identify HCQ-related ophthalmology visits would be valuable in monitoring these patients.

Disclosure:

S. Brooks, None; **G. Kaeley**, None; **L. Dang**, None. :

Abstract Number: 1245

Methotrexate Quality Improvement Project at UF Health Jacksonville Rheumatology Clinics

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: The diagnosis of interstitial lung disease (ILD) is comprised of a large group of respiratory disorders. ILD can lead to scarring of lung tissue. Factors such as environmental exposure, certain diseases (e.g. rheumatoid arthritis) and medications have been implicated. Methotrexate (MTX) has been identified as one of the medications with potential to cause ILD although the exact incidence of MTX-specific ILD remains unknown. Salliot et al conducted a systematic literature review to assess the long-term implications of MTX therapy. The results of 21 prospective studies (N= 3463) were combined to determine the frequency of adverse events (AEs). Eighty-four patients (2.4%) experienced respiratory-related AEs; The AEs experienced by 15 of those patients were attributed to MTX pneumonitis. Conway et al also conducted a systematic literature review to identify the risk of pulmonary disease in patients prescribed MTX. Seven studies were included in the review (N=1630) and 504 respiratory-related AEs were documented. MTX was not found to be associated with an increased risk of respiratory AEs. Burmester et al conducted a post hoc analysis including data from two studies: CONCERTO (N= 395) and MUSICA (N= 309), chronic dry cough as the only respiratory AE was 0.8% and 0.6% respectively. This study was conducted to determine how many patients prescribed MTX in the UF Health Jacksonville Rheumatology Clinics have completed chest imaging and if any patients were diagnosed with ILD.

Methods: Data was obtained from the electronic health record (EHR) from September 1, 2014 to September 30, 2017. Patients prescribed MTX from UF Health Jacksonville Rheumatology clinics, had chest imaging [chest x-ray, chest CT scan or chest MRI] and a diagnosis of ILD [ICD -10 code J84.9] were included. Patients with the diagnosis of ILD were further evaluated to determine the MTX dose and if MTX discontinuation occurred.

Results: A total of 701 patients were prescribed MTX during the evaluation period. Chest imaging was obtained on 137 patients (19.5%) and of these patients, 80 patients had a chest x-ray. Initially, 7 patients (0.9%) were identified to have the intended ICD-10 code J84.9 for ILD. On further evaluation, it was discovered that an additional ICD-10 code J84.10 for pulmonary fibrosis (PF) was included in the data, which accounted for 3 of the initial 7 ILD patients. Therefore, 4 patients (0.6% of 701 patients) had a diagnosis of ILD. Of the 4 ILD patients, MTX was discontinued in two patients. MTX was discontinued in all 3 patients with PF.

Conclusion: Based on the results of this retrospective study and low incidence of ILD cited in literature, it is difficult to justify routine chest imaging for MTX monitoring. Almost 20% of the patients prescribed MTX also obtained chest imaging during the evaluation period. A chest x-ray was the most common type of imaging performed in all patients prescribed MTX during the evaluation period. Four of 701 patients (0.6%) evaluated had a diagnosis of ILD based on the problem list. A limitations of this study was using only the ILD specific ICD-10 code to identify patients.

Disclosure: **S. Brooks**, None; **G. Kaeley**, None; **L. Dang**, None.

Practices of Hydroxychloroquine Dosing Based on the American Association of Ophthalmology (AAO) 2016 Recommendations: A Single Center Experience

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: In March 2016, the AAO updated antimalarial medication screening recommendations for retinopathy prevention, with a recommended dose of hydroxychloroquine (HCQ) ≤ 5.0 mg/kg total body weight (TBW) as compared to ≤ 6.5 mg/kg ideal body weight (IBW) previously. To assess guideline implementation at the two-year mark, we compared HCQ dosing before the March 2016 update and at March 2018. We also assessed whether there was adherence to screening eye exams and evidence of retinal toxicity.

Methods: We performed a retrospective chart review of patients on HCQ at Albany Medical Center between March 2009 through March 2018. HCQ doses based on TBW and IBW prior to the recommendation updates on March 2016 were compared to TBW-based dosing at March 2018 post-guidelines. We assessed frequency of eye examinations and evidence of retinal toxicity.

Results: Of 248 charts reviewed, 178 were excluded due to insufficient follow-up or insufficient data for paired analysis between 3/2016 and 3/2018. 70 subjects were analyzed; 64 were female. The mean age was 42.9-years-old (95% CI 39.2-46.6). Mean duration of HCQ therapy at 3/2018 was 62.2 months (95% CI 52.4-71.9). TBW did not change between initiation of HCQ (79.5 kg, 95% CI 74.0-85.2), at 3/2016 (83.0 kg, 95% CI 77.2-88.7), or at 3/2018 (82.9 kg, 95% CI 77.0-88.8) ($p=0.64$). TBW-based dosage was significantly less at 3/2018 (3.9 mg/kg, 95% CI 3.6-4.2) than TBW-based at 3/2016 (4.3 mg/kg, 95% CI 4.0-4.7) ($p<0.03$). The TBW-based dosage was significantly less at 3/2018 (3.9 mg/kg, 95% CI 3.6-4.2) than IBW-based dosage at 3/2016 (5.8 mg/kg, 95% CI 5.4-6.2) ($p<0.001$). At 3/2016, 34 subjects (49%) were dosed at >6.5 mg/kg IBW (mean 7.4 mg/kg, 95% CI 7.1-7.6) and 7 subjects (10%) at >6.5 mg/kg TBW (mean 7.6 mg/kg, 95% CI 7.2-8.1). At 3/2018, 6 subjects (9%) were dosed at >5.5 mg/kg TBW (mean 6.2 mg/kg, 95% CI 5.4-6.9). Comparing the overdosed groups, the number of subjects and the TBW dosage of HCQ at 3/2018 were less than the IBW dosage of HCQ prior to 3/2016 ($p<0.001$). 34 of 70 (49%) patients had documented retinal exams either annually or biannually. Of the 34 IBW-overdosed at 3/2016, 30 (88%) were appropriately dosed based on TBW by 3/2018, 13 of 34 (38%) and 4 of 7 (57%) overdosed subjects based on IBW and TBW dose at 3/2016, respectfully, did not have eye exams. 4 of 7 (57%) overdosed based on TBW at 3/2018 did not have eye exams. One incidence of retinal toxicity was found and was overdosed (7.5 mg/kg) based on the IBW at 3/2016.

Conclusion: After the AAO 2016 recommendations, dosing of HCQ decreased based on the change from IBW to TBW. The majority of patients with prior overdosing were re-dosed appropriately by 3/2018. The number of subjects overdosed on HCQ declined at two-year follow-up. Closer retinal exam follow-up is needed to improve screening and prevent toxicity. Overall, the proportion of patients at-risk based on dosage was reduced.

Disclosure: A. Ocon, None; M. Saad Shaukat, None; V. Mehta, None; M. Tageldin, None; D. Morales, None; E. Acosta, None; J. Calderone, None; M. Humantla, None; R. Peredo, None.

Pharmacist-Managed Titration of Urate-Lowering Therapy to Streamline Gout Management

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Session Type: ACR Poster Session B

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

Background/Purpose: The treat-to-target approach for serum uric acid is the recommended model in gout management according to the 2012 American College of Rheumatology (ACR) guidelines. Adherence to an urate-lowering therapy (ULT) can be difficult for patients due to barriers, including medication burden, financial hardship, and lack of medical literacy. Additionally, practice gaps may occur with providers in titration of ULT to targeted serum uric acid. We examined the practice gap in gout management at an academic rheumatology clinic, which cares for a complex county patient population. Our aim was to create a pharmacist-managed referral for the titration of ULT to target serum uric acid levels.

Methods: A clinical database was utilized to query patients seen in rheumatology clinic over a twelve-month period with ICD-10 diagnosis for gout. The inclusion criteria were indications for ULT per 2012 ACR guidelines with the most recent serum uric acid level above target (>6 mg/dL or >5 mg/dL if tophaceous and/or erosive disease).

Rheumatology providers were asked to consider referral for the identified patients to the clinical pharmacy for assistance with titration of ULT (allopurinol or febuxostat) to target serum uric acid levels based on ACR guidelines.

The intervention group consisted of 14 patients who were referred during the five-month study period. The control group consisted of 22 patients who met inclusion criteria and seen within the same time frame but not referred. Referral was based on provider preference. At the end of the study period, the most recent serum uric acid levels were collected to assess effectiveness of pharmacist-managed titration of ULT.

Results: The patients in the intervention group had an average age of 60.5 years, 78.6% were male, and 42.9% had erosive or tophaceous disease. The average serum uric acid was 8.26 mg/dL (SD 1.48) at the time of referral. At the end of the study period, the average serum uric acid was 6.78 mg/dL (SD 1.84), which was a 1.48 mg/dL decrease ($P = 0.03$). 4 out of 14 (28.57%) patients were at goal by the end of the study.

The patients in the control group had an average age of 54.2 years, 86.4% were male, and 45.5% had erosive or tophaceous disease. The average serum uric acid was 8.365 mg/dL (SD 2.037) at the start of the referral period. At the end of the study, the average serum uric acid was 7.645 mg/dL (SD 2.448), which is a decrease of only 0.72 mg/dL ($P = 0.166$). Only 2 out of 22 (9.09%) patients were at goal by the end of the study.

Conclusion: Our institution treats a complex patient population with significant barriers to treatment. This newly instituted pharmacist-managed titration program was able to achieve a significantly lower average serum uric acid than the control group who received standard gout management. Although the program remains novel, reasons for its success likely include more timely up-titration of ULT, more personalized education regarding gout and importance of medication adherence, and closer monitoring of side effects including flares. Pharmacists should be integrated into the rheumatology clinic to help patients reach their serum uric acid goals.

Disclosure: I. Huang, None; J. Liew, None; M. Barnes, None; S. Zuo, None; C. Crawford, None; A. Bays, None.

Abstract Number: 1248

Revisit an Old Question: Should Glucose-6-Phosphate Dehydrogenase Level be Checked in Patients with Rheumatic Diseases Prior to Initiating Certain Drugs?

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Glucose 6 Phosphated hydrogenase (G6PD) deficiency is the most common enzymatic disorder of red blood cells, and its frequency varies among different ethnicities. People with G6PD deficiency may develop hemolytic anemia with certain drugs such as hydroxychloroquine, sulfasalazine and dapsone. Clinically, there is inconsistent practice

intesting G6PD level among rheumatologists before initiating drugs like hydroxychloroquine, and there are no set guidelines on testing the enzyme. G6PD deficiency occurs in 0.5-7% in Americans, and its frequency in patients with rheumatic diseases was not previously reported in America. This study aimed at determining the frequency of G6PD deficiency in the disease population.

Methods: This study is a retrospective chart review and was approved by the Institutional Research Board. Electronic Medical Records (EMRs) were reviewed of patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren Syndrome, and seronegative spondyloarthritis between July 2013 and December 2016. These patients could be tested for G6PD due to concern for anemia from potential use of the above drugs. Patients aged 18 and older were included, and their demographics, rheumatic diseases, the medication use and G6PD testing results were recorded. G6PD deficiency was considered to be present if its value was less than 7.0-20.5 U/g. Descriptive statistics and chi-square/fisher exact tests were used for the data analysis.

Results: Eighty-nine (39%) of 228 patients with rheumatic diseases were screened for G6PD deficiency. In the 89 patients tested, 7 patients (7.9%) including 5 females and 2 males were found to be G6PD deficient. Their mean age was 34.9 years, and there were 5 (71%) Caucasians and 2 (29%) African Americans. Overall, the frequency of G6PD deficiency in patients with rheumatic diseases was close to that in the general American population. Caucasians patients had a frequency of 5.6%, and this may be due to higher Caucasians tested in our study. Demographics and relevant data in patients with G6PD tested and those with G6PD deficiency are shown in Table. The overwhelming majority of the patients tested were treated with hydroxychloroquine. G6PD deficiency is an x-linked disease, mainly affects male, and should be considered in female as well. There was a higher percentage of females with G6PD deficiency than males in this study as the disease population tested consisted of 97% of female patients.

Table 1. Demographics and Relevant Data in Patients with G6PD Tested and Those with Deficiency

N=89	G6PD Deficiency		P-Value
	No (N=82)	Yes (N=7)	
Gender			
Male	2 (2.44)	2 (28.57)	0.0298
Female	80 (97.56)	5 (71.43)	
Age			
Median (IQR)	43.3 (22.3)	34.9 (33.4)	0.9332
Race			
White/Caucasian	45 (55.56)	5 (71.43)	0.7824
Black/African American	16 (19.75)	2 (28.57)	
Hispanic/Latino	8 (9.88)	0 (0.0)	
Other	12 (14.81)	0 (0.0)	
Age at Diagnosis (65 missing)			
Median (IQR)	35 (24)	25 (15)	0.0890
Duration of Disease in Years (65 missing)			
Median (IQR)	4.6 (4.6)	11.1 (21.3)	0.2984
SLE			
No	5 (6.10)	1 (14.29)	0.3974
Yes	77 (93.90)	6 (85.71)	
PsA			
No	81 (98.78)	7 (100.0)	1.0000
Yes	1 (1.22)	0 (0.0)	
AS			
No	81 (98.78)	7 (100.0)	1.0000
Yes	1 (1.22)	0 (0.0)	
IBD Arthropathy			
No	82 (100.0)	7 (100.0)	N.A
Yes	0 (0.0)	0 (0.0)	
RA			
No	71 (86.59)	7 (100.0)	0.5899
Yes	11 (13.41)	0 (0.0)	
Sjögren's Disease			
No	72 (87.80)	6 (85.71)	1.0000
Yes	10 (12.20)	1 (14.29)	
Hydroxychloroquine Use (1 missing)			
No	2 (2.44)	5 (71.43)	<0.0001
Yes	80 (97.56)	2 (28.57)	
Sulfasazine			
No	81 (98.78)	7 (100.0)	1.0000
Yes	1 (1.22)	0 (0.0)	
Dapsone			
No	82 (100.0)	7 (100.0)	N.A
Yes	0 (0.0)	0 (0.0)	
Duration of Drug Use in Years (94 missing)			
Median (IQR)	3.4 (2.6)	4.4 (6.0)	0.9502

Conclusion: This may be the first study to examine the frequency of G6PD deficiency in the American patient population with rheumatic diseases. Such testing might not be cost effective given the low incidence of G6PD deficiency in the patient population. Instead, we recommend to monitor for potential anemia with complete blood counts in the setting of hydroxychloroquine use.

Disclosure: I. Abramova, None; S. Tuladhar, None; K. Park, None; C. Hosny, None; E. Taub, None; A. Patniak, None; Q. Yao, Novartis, 5.

Abstract Number: 1249

Contraception Compliance in Patients with Rheumatological Diseases on Disease Modifying Antirheumatic and Cytotoxic Drugs

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Women of child bearing age with autoimmune diseases are often prescribed teratogenic medications as Methotrexate, Mycophenolate Mofetil, Leflunomide and Cyclophosphamide. Contraceptive compliance in this group of patients has been shown to be low. Patients are required to use reliable methods of birth control to prevent undesirable consequences. Our goal was to improve documentation of variables which help physicians to assess contraception compliance in this group of patients and minimize the deviation from standard of care.

Methods: This study had two retrospective arms, pre and post-implementation of immunosuppressive section to rheumatology clinic note. Subjects are females (50 cases in each arm) aged 21-50 y/o on immunosuppressive medications who are sexually active. Females with hysterectomy, tubal ligation and prisoners were excluded. Variables subjected to review included plan to conceive, contraception use, contraception method, gynecology referral. We applied Chi-squared test to analyze the data.

Results: Documentation of four variables mentioned above was compared between two 50-patient groups (pre-intervention vs post-intervention). There was statistically significant improvement in documentation of all four variables following the intervention as follows: plan to conceive (84% vs 36%)(p=0.000001), contraception used (90% vs 54%)(p=0.00006), type of contraception (76% vs 50%)(p=0.007), gynecology referral (84% vs 38%)(p=0.000002).

Conclusion: Identification of variables which represent patients' compliance is essential and should be addressed in each patient visit. In this study we improved documentation of variables which could help clinician in early recognizing patients who do not follow the guidelines for contraception to consider them for close monitoring or switch to non-teratogenic medications. In this study in light of poor documentation in the first arm we were unable to compare contraception compliance of patients pre and post intervention.

Disclosure: S. Naji Rad, None; P. Pacheco, None; L. Calvo, None; H. H. Maung, None; W. Illyas, None; P. Anand, None.

Abstract Number: 1250

An Evaluation of Utilization Patterns and Appropriateness of Laboratory Tests Among New Referrals to Rheumatologists: Choosing Unwisely!

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster II

Background/Purpose: Laboratory testing comprises the highest volume procedure in medicine and is therefore an important target for improving healthcare spending and efficiency. Unnecessary testing both increases healthcare costs and results in higher false positive rates with associated costly downstream testing and procedures. Additionally, unnecessary testing increases the patient burden and may increase the probability of an adverse health event.

This study aimed to examine the utilization patterns, appropriateness, and associated cost of rheumatologic tests ordered for patients referred to a university rheumatology clinic. A secondary aim of this study was to determine whether demographic factors such as patient sex, reason for referral, and referring practice population size were predictive of inappropriate testing.

Methods: This study consisted of a chart audit of consecutive referrals to three rheumatologists at an academic university rheumatology clinic over one year. All new referrals that had proper documentation, were not transfers of care, and did not have previously established diagnoses were considered. Of referrals that met inclusion criteria (n=631), 398 accepted and 233 rejected referrals were reviewed. Ordering of specific tests (ANA, ENA, anti-dsDNA, RF, and complement levels) and their appropriateness based on clinical presentation were extracted from medical charts. Lab tests ordered within 2 years prior to referral were collected for accepted referrals. Additionally, the reason for referral, diagnosis (accepted referrals), reason for rejection (rejected referrals), patient age and sex, and the population size of the referring practice was collected to identify potential predictors of inappropriate testing.

Results: The number one reason for referral in accepted referrals and rejected referrals was seronegative spondyloarthritis and fibromyalgia respectively. Of the referrals reviewed (n=631), 41% had at least one instance of inappropriate testing. ANA was most frequently ordered inappropriately, with 20% of all referrals having ANA testing with no clinical indication. Additionally, 56% of ANA testing in accepted referrals was repeated testing. Family physicians and nurse practitioners were significantly more likely to order inappropriate tests than specialists ($p = 0.007$). Chi-squared testing found patient age ($p=0.445$), gender ($p=0.051$), and population size ($p=0.855$) were not predictive of inappropriate testing.



Conclusion: The results of this study showed a significant problem with inappropriate testing in referrals made to this institution. Cost estimation of inappropriate testing identified a potential cost reduction of 49%. Future research should focus both on implementing existing guidelines, and on creating interventions tailored to family medicine practice to produce the greatest reduction in cost.

Disclosure: S. Barrett, None; A. Ahrari, None; S. Rohekar, Abbvie, Amgen, Eli-Lily, Janssen, Merck, Novartis, Pfizer, Roche, UCB, 5, Eli-Lily, 8; P. Basharat, None; J. E. Pope, AbbVie Inc., 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Lilly, 5, Merck & Co., 5, Novartis, 5, Pfizer, Inc., 5, Roche, 5, Sanofi, 5, Sandoz, 5, Celltrion, 5, United Chemicals Belgium, 2.

Abstract Number: 1251

Guideline Adherence for Perioperative Use of Immunosuppressive Medications in Patients with Rheumatologic Disease

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Background/Purpose: In response to the lack of clear data to dictate recommendations for use of DMARDs and biologic therapy in the perioperative period, The American College of Rheumatology and American Association of Hip and Knee Surgeons developed guidelines for management of these medications in patients undergoing elective hip or knee arthroplasty. Based on literature review, it is recommended to continue DMARDs through elective hip or knee arthroscopy and to hold biologic therapy during the perioperative period. This QI study examines compliance of a community hospital system with these preoperative guidelines and assesses patient outcomes, specifically infectious complications and rheumatologic disease flare.

Methods: Retrospective data was obtained using the community hospital's electronic medical record based on completion of an elective surgical procedure, use of maintenance DMARDs, biologic agents, and steroids, and ongoing care under the LVHN Rheumatology department for inflammatory arthritis, connective tissue disease, or giant cell arteritis between the dates of 1/1/2016 and 1/1/2018. Post-procedure disease flare was characterized as addition/increase of systemic steroids based on reported symptoms. Post-operative surgical site infection (SSI) was defined as the addition of antibiotic therapy due to concern for surgical site infection.

Results: A total of 54 patient charts met parameters, however 20 of these charts (37%) did not provide adequate data regarding perioperative medication use. From the remaining 34 patient charts, most patients had rheumatoid arthritis (76.5%), were female (76.5%), and had a median age of 58 years old. Orthopedic elective surgeries made up the majority of elective surgical procedures (47.1%). Sixteen out of 34 patients (47%) received correct instruction regarding perioperative medication use, and of these 44% were rheumatology-directed. When direction was identifiable, the patient's rheumatologist or surgeon was responsible for directing medication changes (29.4% and 26.5%, respectively), although 29.4% did not have clear provider ownership of given instructions. There were 2 postoperative SSI's which occurred in patients with inadequate pre-operative medication holding times. There were 4 post-operative flares, 50% associated with inappropriate hold of patient medication.

Conclusion: Although this project is ongoing, results thus far show that clear preoperative patient instruction regarding immunosuppressive medications is lacking. Multiple studies support the correlation between medication error and lack of clear patient instruction regarding medication use. Deviation from typical perioperative medication recommendations was seen in half of patients with unclear contributing factors. Medications dosed less frequently than monthly such as Rituximab and Infliximab tended to correlate with shorter than preferred pre-operative hold times while biologic agents given more frequently were held for a longer duration than recommended. Implementation of formatted written patient instructions as well as provider-directed education sessions with reassessment of guideline compliance are planned next steps for improved patient outcomes.

Disclosure: **G. Berlin**, None; **C. Casey**, None; **S. Kim**, None; **J. Ross**, None.

Abstract Number: 1252

Screening for Tuberculosis before Initiating TNF Inhibitors: How Well Do We Do? a Nationwide Experience

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Background/Purpose: Tumor necrosis factor inhibitors (TNFi) revolutionized treatment of various conditions, however they drastically increase the risk of latent tuberculosis (LTBI) reactivation. Many national medical bodies recommend screening for LTBI prior to initiating TNFi, and this has been incorporated as a Merit-Based Incentive Payment System (MIPS) measure. We determined screening rates for LTBI across the United States, prior to initiating a TNFi.

Methods: We retrospectively analyzed patients in Truven MarketScan from 2011-2015. This dataset contains de-identified inpatient and outpatient claims records on over 100 million patients. We included patients' over 18 years with at least 1 filled prescription for TNFi. To ensure these were new TNFi starts we excluded patients without a 6-month washout period (i.e. during which time they could not receive biologic DMARDs). Continuous enrollment in the database was required during the washout period and 3 months after TNFi initiation. Our primary outcome was the proportion of patients screened for TB during the 6-month washout period, either by interferon gamma release assays (IGRA) or tuberculin skin testing (TST). Sensitivity analysis was performed to extend the eligible screening period to 12 months pre-drug. Descriptive statistics were represented as means and medians for continuous variables and as percentages for categorical variables.

Results: We identified 76,128 patients starting a TNFi. The mean age was 44.7 years, the cohort was 61% female. Adalimumab and Etanercept were the most common TNFi. 50.9% of patients had a rheumatologic diagnosis, 22.4% gastrointestinal, 17.6% dermatologic, and 0.8% ophthalmic. Most patients received specialty care, and a rheumatologist was involved in 40.9% of cases 40,282 (52.9%) were screened for TB in the 6-month washout. By extending the pre-drug washout to 12 months, the proportion of unscreened patients improved mildly to 59.3%. 48.5% were screened by IGRA, 27% by TST, and 24.5% unknown. Steroid and DMARD use, male sex, urban residence, low Charlson comorbidity score and specialty care were associated with increased TB screening rates. Patients cared for by a rheumatologist or dermatologist were more commonly screened than those seeing gastroenterologists. Care by an ophthalmologist was not associated with improved screening.

Conclusion: In the United States, screening for latent TB prior to initiating TNFi therapy was poor, such that only 52.9% received appropriate pre-drug screening. Our study population of over 75,000 patients starting a new TNFi represents nationwide, real world data across various specialties. As clinicians, these results suggest we need to improve compliance with guidelines and quality measures. Care by rheumatologists and dermatologists was associated with improved screening compared to that by gastroenterologists and ophthalmologists.

Table 1. Predictors of TB Screening.

Age	OR	95% CI	p-value
35-44 v. 18-34	1.03	(0.98,1.07)	0.265
45-54 v. 18-34	1.01	(0.97,1.05)	0.665
55-64 v. 18-34	0.99	(0.94,1.03)	0.497
Sex			
Female v. Male	0.88	(0.86,0.91)	<0.001
Geography			
Rural v. Urban	0.81	(0.77,0.84)	<0.001
Provider type			
No Specialist	Ref		
Dermatologist	1.36	(1.28,1.44)	<0.001
Gastroenterologist	1.17	(1.10,1.25)	<0.001
Ophthalmologist	1.10	(0.98,1.25)	0.116
Rheumatologist	1.35	(1.30,1.40)	<0.001
Primary care physician (w/wo specialist)	1.09	(1.06,1.13)	<0.001
Index TNFi Inhibitor			
Adalimumab	Ref		
Etanercept	0.59	(0.55,0.65)	<0.001
Infliximab	0.93	(0.90,0.96)	<0.001
Certolizumab	0.57	(0.52,0.62)	<0.001
Golimumab	0.74	(0.71,0.78)	<0.001
Systemic steroids prescribed	1.22	(1.18,1.26)	<0.001
DMARD prescribed	1.20	(1.17,1.24)	<0.001
High risk factors for TB reactivation	0.70	(0.43,1.13)	0.147
Travel	2.09	(0.95,4.62)	0.069
Charlson Comorbidity Index			
1 v. 0	0.92	(0.89,0.96)	<0.001
2+ v. 0	0.91	(0.85,0.96)	<0.05

Disclosure: K. Ladak, None; T. Pan, None; C. MacLean, None.

Lipid Screening and Treatment Patterns Among Patients with Rheumatic Diseases

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: The importance of lipid management is well recognized in rheumatic diseases. In fact, annual cardiovascular risk assessment is especially recommended for individuals with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. The comorbid traditional cardiovascular risk factors compound the morbidity and mortality risk. Despite an abundance of data supporting that patients with rheumatic diseases have increased rates of major adverse cardiovascular events, patients are inadequately screened and often under treated.

Methods: We conducted a retrospective study between 2013 and 2017 at the two infusion centers affiliated with the University of Arizona Arthritis Center, and identified the patients on biological infusions with comorbid cardiovascular disease, diabetes, hyperlipidemia, hypertension or smoking, and then examined whether these patients had lipid testing done and/or were on statins during this period.

Results: Of the total 253 patients with rheumatologic diagnoses, the mean age was 62 years and 77.5% of the sample was female. 62.5% had rheumatoid arthritis, 8.7% had osteoporosis, 5.5% had systemic lupus erythematosus, 5.1% had psoriatic arthritis, 4.7% had ankylosing spondylitis, 2.8% had mixed connective tissue disease, 2.0% had juvenile idiopathic arthritis, 2.4% had anti-neutrophil cytoplasmic antibodies vasculitis, 1.6% had osteoarthritis, 0.8% had Bechet's disease, 0.8% had dermatomyositis, 0.8% had polymyositis, 0.8% had adult-onset still's disease, 0.4% had giant cell arteritis, 0.4% had inclusion body myositis, 0.4% had fibromyalgia, and 0.4% had gout. Of those with a rheumatologic diagnosis and at least one qualifying co-morbid condition, 38.72% had hypertension, 30.83% had hyperlipidemia, 18.04% had diabetes, 15% were smokers, and 6.39% of patients had known cardiovascular disease. The lipid testing was performed in 40.23% of patients, and only 29.41% were on statin therapy.

Conclusion: The findings of this study suggested that the majority of patients (60%) with rheumatic diseases lacked lipid testing, and subsequently, cardiovascular risk stratification. Given the increased cardiovascular morbidity and mortality in these patients, rheumatologists, in collaboration with primary care physicians, can ameliorate this clinical gap by ensuring that patients receive age- and disease-appropriate risk assessments. Such screening efforts may improve treatment responses and reduce the risk of adverse cardiovascular events.

Disclosure: A. Peck, None; G. Ortega, None; J. Bilal, None; E. Starobinska, None; P. Saligrama, None; D. Sudano, None.

Abstract Number: 1254

QI Project: Inpatient Practices in Ordering Fluorescent Anti-Nuclear Antibodies (F-ANA) and ANA Subserologies in a City Hospital in an Underserved Community

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Session Information

Session Date: Monday, October 22, 2018

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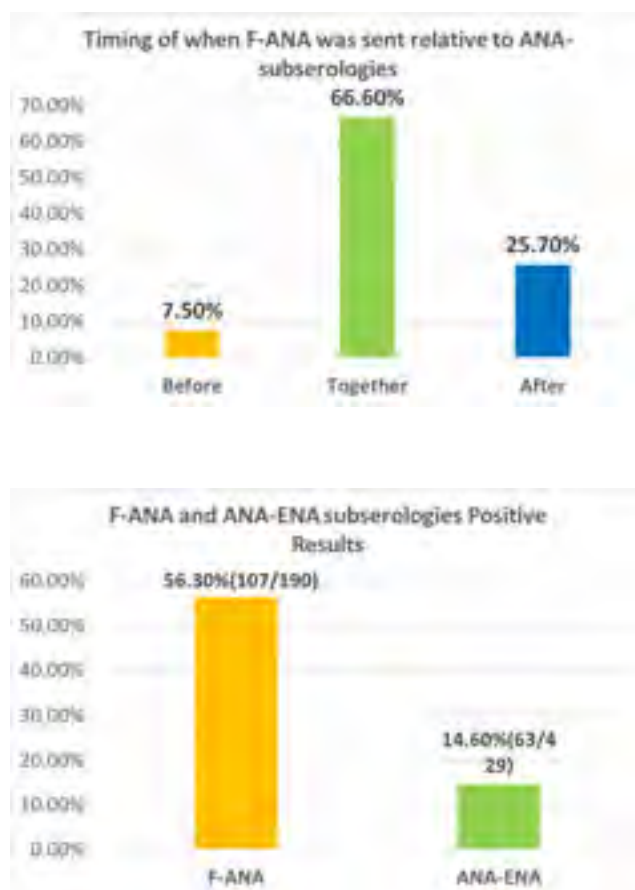
Session Type: ACR Poster Session B

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

Background/Purpose: It is important for internists to know how to appropriately and effectively order subspecialty labs. As part of the choosing wisely campaign in 2013, the American College of Rheumatology (ACR) issued a series of recommendations to improve clinical practice including not to test ANA subserologies without a positive F-ANA.¹ Multiple studies and laboratory guidelines have evaluated this algorithmic approach which begins with the clinical suspicion of a rheumatic disease and then assessment of F-ANA and ANA sub-serologies as indicated.²⁻⁶

Methods: A retrospective review of medical records of patients admitted to our large, urban medical center in an underserved area from June 2016 through June 2017 was performed. 460 patients in whom F-ANA or ANA-ENA panel testing was performed were examined. Case records were analyzed for the number of tests requested, the sequence of the testing, and test results. Indeterminate results in the ANA-ENA panel were not taken into consideration for the analysis. Data was analyzed using Excel 2013.

Results: One hundred ninety F-ANA and 429 ENA panels were ordered. Positive results were found in 56.3% (107/190) of F-ANA and 14.6% (63/429) of the ENA panels. When both F-ANA and ENA panels were requested, F-ANA was performed before the ENA panel as recommended in the minority of patients 7.5% (12/159). The majority had the two tests done at the same time 66.6% (106/159). 25.7% (41/159) had the F-ANA sent after the ENA panels. ENA panels were requested alone the majority of the time 62.9% (270/429). Females represented 57.6% of the patients.



Conclusion: The majority of the time a F-ANA was not ordered before the subserologies as per ACR recommendations. Therefore we conclude that in our hospital population the ACR guidelines are not being followed with the potential for decreased quality of care and missed diagnosis. This may be due to the cost constraints of the hospital where finances are limited and F-ANA costs \$14.81 and ANA-ENA panel costs \$6.09. Additionally, in our ordering system, it is not obvious that the ANA-ENA panel does not include the F-ANA. We suggest further education of the house staff about understanding the difference between the F-ANA and ANA-ENA panel as a point to start toward quality improvement in this area. Also, we feel that these results open the question of whether other hospitals and communities with limited resources are able to follow the ACR guidelines for F-ANA and ENA ordering due to financial constraints. Further study in this area could help further inform guidelines going forward.

Disclosure: I. E. Ramirez de Oleo, None; B. Johnson, None; B. Mendez-Agrusa, None.

Elevated Serum Globulin Gap As a Reliable and Cost-Savings Marker of Inflammation in Patients with Systemic Rheumatic Diseases

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Background/Purpose: In clinical practice, the two most commonly used markers of systemic inflammation are the serum CRP level and ESR. The economic costs of these tests are substantial, with Medicare allowable charges in Los Angeles in 2018 for CRP level and ESR being \$38.04 and \$62.76, respectively. An algorithm that reduces the need for these tests in the care of patients with systemic rheumatic diseases could lead to considerable cost savings without sacrificing the quality of patient care.

Methods: The electronic medical records of two independent cohorts (discovery and validation) of patients with systemic rheumatic diseases seen between May 2015 and June 2017 in the rheumatology clinics at a single academic medical center were retrospectively reviewed. Correlations and receiver operator characteristic (ROC) curves between serum CRP level and ESR vs serum globulin gap (the difference between levels of total protein and albumin) and albumin-to-globulin (A:G) ratio were determined.

Results: The discovery (263 subjects, 446 entries) and validation (438 subjects, 1959 entries) cohorts were predominantly female (89.0% and 82.9%) and Hispanic (93.9% and 87.9%), with median ages of 47.4 and 51.6 years at the time of sample collection and the majority (52.7% and 67.1%) of entries coming from RA or SLE patients. In each of these independent cohorts, the globulin gap and A:G ratio correlated significantly ($p < 0.001$) with CRP level and ESR, with the respective correlation coefficients being greater for ESR (discovery: 0.472 and -0.672; validation: 0.509 and -0.596) than for CRP level (discovery: 0.308 and -0.374; validation: 0.225 and -0.310). ROC curve analyses demonstrated better respective abilities of globulin gap and A:G ratio to discriminate between normal and elevated ESR (discovery area-under-curve [AUC]: 0.726 and 0.823; validation AUC: 0.738 and 0.771) than between normal and elevated CRP level (discovery AUC: 0.681 and 0.726; validation AUC: 0.602 and 0.656). These relationships were independent of sex (female vs male) or ethnicity (Hispanic vs non-Hispanic), and similar results were obtained when only RA or SLE was considered. Elevated globulin gap (≥ 4.0 g/dl) and low A:G ratio (< 0.8) had respective positive predictive values (PPVs) of only ≥ 0.554 and ≥ 0.788 for elevated CRP level, whereas the respective PPVs for elevated ESR were ≥ 0.962 and ≥ 0.960 . When only the first entry for a given patient was considered, the correlations between ESR and globulin gap ($r = 0.531$) and A:G ratio ($r = -0.648$) and the corresponding AUCs (0.742 and 0.795) were similar to those observed for all entries. Moreover, the abilities of elevated globulin gap and low A:G ratio to predict an elevated ESR remained very high, with PPVs of 0.976 and 0.966, respectively. Among patients with high globulin gap, the change in globulin gap over time faithfully reflected changes in ESR.

Conclusion: In patients with systemic rheumatic disease, elevated globulin gap (readily calculable from the routinely-obtained comprehensive metabolic panel) is a highly reliable marker of elevated ESR. Ordering an ESR (or CRP) test in such patients may frequently be unnecessary, resulting in an estimated savings of \$7.56 million per million patients with systemic rheumatic disease.

Disclosure: W. Stohl, None; B. Kenol, None; A. Kelly, None; A. Ananth Correa, None; R. Panush, None.

A Customized Health Information Technology Effectively Identifies and Directs Bone Health Services in Rural Veterans with Osteoporosis Risk Factors

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Background/Purpose: Osteoporosis is under diagnosed and undertreated in the Veterans Health Administration (VHA), especially in rural Veterans. Tools to identify risk factors in Veterans are available. To address this issue, VHA Salt Lake City Rural Bone Health Team (BHT) developed the Enrollment Report, a health information technology (HIT). The Enrollment Report operationalizes evidence-based screening guidelines to capture risk factors. Identified Veterans were contacted to participate in the BHT program, a population health osteoporosis management program. This investigation compared the proportion of Veterans with risk factors receiving bone health services, based on participation in the BHT program.

Methods: This study evaluated the impact of a HIT, Bone Health Team Enrollment Report (BHT-ER), on directing bone health services to at-risk Veterans. Risk factors were captured using the VHA Corporate Data Warehouse, a health data repository. For this study, we included Veterans contacted for enrollment between 10/13/2017 and 02/01/2018. A non-experimental cohort design was used to evaluate for changes in the proportion of Veterans with completed diagnostic imaging, ≥ 1 clinical encounter with an osteoporosis diagnosis and prescribed pharmacotherapy, before and after the index date, defined as the first date BHT contacted the Veteran.

Table. Demographics, identified risk factors and bone health services received pre- and post-index date

	Enrolled		Non-Enrolled		p value
	n (%)	95% CI	n (%)	95% CI	
Veterans Contacted	234 (31.2)		516 (68.8)		
Age (mean)	78.8	(77.64 - 79.86)	78.3	(77.55 - 79.08)	0.527
Male	224 (95.7)	(93.14 - 98.32)	474 (91.9)	(89.50 - 94.22)	0.054
OST Score ^a (mean)	0.53	(0.05 - 1.00)	0.18	(-0.10 - 0.47)	0.197
Osteoporosis Risk Factors					
OST ≤ 1	165 (70.5)	(64.67 - 76.36)	375 (72.7)	(68.83 - 76.52)	0.541
Male ≥ 80	131 (56.0)	(49.62 - 62.34)	259 (50.2)	(45.88 - 54.51)	0.142
Female ≥ 65	8 (3.4)	(1.19 - 5.75)	34 (6.6)	(4.45 - 8.73)	0.080
Chronic Medication Use ^b					
Oral Glucocorticoids ^c	15 (6.4)	(3.27 - 9.55)	32 (6.2)	(4.12 - 8.28)	0.913
Aromatase Inhibitors ^d	0	-	0	-	-
Anti-Androgens ^e	5 (2.1)	(0.28 - 3.99)	11 (2.1)	(0.89 - 3.38)	0.997
Hormone Therapy ^f	8 (3.4)	(1.09 - 5.75)	18 (3.5)	(1.91 - 5.07)	0.962
Pre-Index Date					
DEXA Completed	21 (9.0)	(5.31 - 12.64)	71 (13.8)	(10.79 - 16.73)	0.064
≥ 1 Clinical Encounter with an Osteoporosis Diagnosis	8 (3.4)	(1.09 - 5.75)	49 (9.5)	(6.97 - 12.03)	0.004
Prescribed Anti-Resorptive	10 (4.3)	(1.68 - 6.86)	38 (7.4)	(5.11 - 9.62)	0.109
Post-Index Date					
DEXA Completed	190 (81.2)	(76.19 - 86.20)	17 (3.3)	(1.75 - 4.83)	<0.001
≥ 1 Clinical Encounter with an Osteoporosis Diagnosis	43 (18.4)	(13.41 - 23.24)	11 (2.1)	(0.89 - 3.38)	<0.001
Prescribed Anti-Resorptive	60 (25.6)	(20.05 - 31.24)	16 (3.1)	(1.61 - 4.60)	<0.001

^a OST: Osteoporosis Self-Assessment Tool. Calculated as $0.2 * (\text{weight [kg]} - \text{age})$. ^b Chronic medication use is defined as ≥ 83 continuous days of pharmacotherapy. ^c Oral glucocorticoids consists of hydrocortisone, cortisone, dexamethasone, prednisolone, methylprednisolone, prednisone and budesonide. ^d Aromatase inhibitors consists of anastrozole, exemestane and letrozole. ^e Anti-Androgens consists of abiraterone, bicalutamide, enzalutamide, flutamide and nilutamide. ^f Hormone Therapy consists of degarelix, leuprolide, triptorelin, goserelin and histrelin in male Veterans, and fulvestrant in female Veterans.

Results: Medical and pharmacy records for 81,116 rural Veterans at 4 healthcare systems were queried, with 9,845 (12.1%) Veterans having ≥ 1 risk factor. In the first batch, 750 Veterans have been contacted to participate, 234 (31.2%) have enrolled and 516 (68.8%) have not enrolled. Efforts to enroll the remaining 9,095 Veterans is ongoing. A higher proportion of males have enrolled in the BHT program, with a higher mean Osteoporosis Self-Assessment Tool (OST) score, compared to the Non-Enrolled group. An OST score ≤ 1 was the most commonly identified risk factor in both groups. In the 5 years preceding the index date, a higher proportion of the Non-Enrolled group received bone health services, compared to the Enrolled group. After the index date, a significantly higher proportion of the Enrolled group had a complete DEXA scan, ≥ 1 clinical encounter with an osteoporosis diagnosis and were prescribed anti-resorptive pharmacotherapy, compared to the Non-Enrolled group.

Conclusion: A higher proportion of Veterans received bone health services when enrolled in the BHT program, compared to Veterans who did not enroll. The synergy between the BHT-ER and the BHT program increased the delivery of bone health services to at-risk Veterans. Embedding evidence-based guidelines into HIT effectively identifies risk factors and reduces disparities in bone health care provided to rural Veterans. The BHT program concept and use of HIT can be replicated to increase the delivery of other important clinical services within VHA and medical communities outside VHA.

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Abstract Number: 1257

Simple and Cost-Effective Intervention Doubled the Rate of Osteoporosis Screening in High Risk Rheumatology Patients

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Session Information

Session Date: Monday, October 22, 2018

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Session Type: ACR Poster Session B

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

Background/Purpose: Osteoporosis is a common bone disorder that places patients at risk of pathologic fractures. Osteoporotic fractures can be devastating and associated with significant morbidity, mortality and economic burden. Rheumatologic patients especially those with rheumatoid arthritis (RA) are known to have higher risk of low bone mineral density and osteoporosis. This is more pronounced in patients with active/severe disease and those taking glucocorticoids. Early diagnosis and treatment of osteoporosis can prevent fractures and their grave sequelae. In this study we aim to evaluate the rate of osteoporosis screening using the standard Dual-Energy X-ray Absorptiometry (DEXA) scans in our rheumatology clinic before and after introducing a simple and cost-effective intervention to improve this rate. Our target for screening is women at age of 65 or older, rheumatoid arthritis patients, and/or patients taking prednisone ≥ 7.5 mg daily for more than 3 months.

Methods: Patients seen in our rheumatology clinic during September-November 2016 were identified as baseline pre-intervention group. Intervention period was between January-March 2018. During this period, bright orange cards highlighting the indications for osteoporosis screening were added by clinic staff to every patient's chart at time of check-in. At the end of the intervention period, the data was collected by sorting patient's medical record numbers in descending numerical order and the top 100 patients in each group were analyzed. The following data was collected: age, gender, rheumatologic diagnosis, chronic moderate to high dose steroid use (defined as systemic steroid dose equivalent to prednisone ≥ 7.5 mg daily for more than 3 months), and DEXA scan orders. In each group, the total number of patients who had an indication for osteoporosis screening as defined in our study was determined as well as the total number of DEXA scan ordered for such indications.

Results: Combined analysis of both groups revealed that 84% (169/200) of total patients were women of all ages, 14% (28/200) were women age 65 or older, RA patients were 53% (107/200), and patients on moderate to high dose steroids were 37% (74/200). Separate analysis of each group revealed that 71 out of 100 patients in the pre-intervention group had an indication for osteoporosis screening as defined in our study, of those only 11 patients had a DEXA scan ordered (15%). In the intervention group, 75 out of 100 patients had an indication for screening and out of those 30 DEXA scans were ordered as indicated (40%).

Conclusion: Majority of rheumatologic patients are at high risk for osteoporosis. Analyzing the data from our rheumatology clinic has shown that the rate of osteoporosis screening based on indications mentioned above were low. However, simple cost-effective reminders in the form of cards has more than doubled the rate of screening. Considerable improvement seen with this simple intervention and further improvement can possibly be achieved by incorporating reminders in the electronic medical records. Rheumatologists and primary care physicians are encouraged to closely evaluate rheumatologic patients for osteoporosis screening, prevention and treatment when indicated.

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Abstract Number: 1258

Can Patients Enter Medical History Data By Self-Report Directly into an Electronic Medical Record (EMR)? “Private Medical History” (PMH) Software for Physician Report in EMR Format and Patient Storage to Correct and Update Medical History for Any EMR

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Background/Purpose: The electronic medical record (EMR) promised greater efficiencies in clinical medicine. This goal may be met in part in an ICU, operating room, and other settings in which large amounts of data are exchanged in real time, and a patient medical history contributes little to work-flow. However, in outpatient management of chronic diseases, particularly in rheumatology, in which the patient history contributes importantly to diagnosis and management, the EMR has been associated with serious compromises of doctor-patient communication and inefficient time-management. Many physicians spend considerable periods entering and/or dictating information into an EMR after the patient has left the exam room, and not infrequently during evening hours. Some rheumatologists have suggested that the EMR results in seeing fewer patients per day, leading to a reduction in income despite up coding of visits using EMR documentation. One approach to this problem involves application of a simple principle seen in customers of airlines printing boarding passes and of supermarkets checking out groceries, by having patients complete an electronic self-report history questionnaire that can be uploaded directly into an EMR in a traditional history format, with review by a physician, using software termed “private medical history” (PMH).

Methods: Patients enter medical history data on a structured self-report questionnaire, including all diagnoses, operations, illnesses, hospitalizations, allergies, family history, social history and demographic information, into PMH software. The data can be uploaded in a standard format into an EMR, although interaction with the EMR vendor is required to implement this feature. The PMH software also allows patients keep maintain the data at a password-protected, HIPAA compliant, secure PMH website, which can allow the patient to store the data for any health professional as a paper print out or PDF file, and, as more EMR organizations become compliant with the PMH system, to interact directly with any EMR. The patient web page allows the patient an option to indicate that each section of the history is correct or requires update(s) and/or correction(s).

Results: Preliminary studies indicate at least 80% agreement of patient self-report medical history information with what is reported in the EMR in more than 80% of patients. Some patients require help from family and/or health professionals to provide an accurate history. Most patients appear at least as accurate or more accurate than health professionals. Use of the system saves about 15 minutes for the doctor per new patient.

Conclusion: A large fraction of patients can enter much medical history information directly into an EMR and store the information to update and/or correct, and be available for any health professional or facility with any EMR for future visits. Rheumatologists who would like to implement such a system are encouraged to contact the authors of this abstract.

Disclosure: T. Pincus, Medical History Services, LLC., 7, 9; R. Gomez Lara, None; N. S. Krogh, None.

Driving Performance and Safety in Rheumatoid Arthritis: A Systematic Review

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Background/Purpose: Automobile driving represents an instrumental activity of daily living (IADL). Symptoms accompanying RA, including fatigue, joint pain and stiffness, decreased strength, reduced mobility, and poor sleep quality, have the potential to adversely impact driving ability. In this systematic review, we aimed to identify whether is associated with driving performance and/or the use of assistive devices or modifications to improve driving performance.

Methods: We conducted a systematic literature review following PRISMA guidelines of RA and driving performance/modifications by searching CINAHL, Cochrane library, EMBASE, MEDLINE, PREMEDLINE, PsycINFO, Google Scholar, and Scopus databases from inception to April 2018. We excluded studies that were not in English, had no original or quantitative data, included <5 RA patients, or did not report specifically on RA.

Results: Our search yielded 1935 potential manuscripts, of which 22 fulfilled eligibility criteria. Most studies were cross-sectional (n=14). Studies reporting the prevalence of driving factors among persons with RA are summarized in the Table. Based on weighted means, of total RA patients studied 13% were involved in motor vehicle crashes (MVCs), 26% experienced difficulties with driving, 34% leveraged assistance or modifications to drive, and 26% were unable to drive. In at least one study, Repaints were involved in fewer MVCs than their age-matched controls (23% vs.35%) [Maki et al., 1976]. A separate investigation employing an independent driving assessment determined that 19% (n=37) of RA patients were not fit to drive [Jones et al., 1991].

Conclusion: There is a scarcity of data that quantitatively relates RA to driving performance and or related safety outcomes. Recognizing significant variability among individual reports, available data suggests that driving difficulties and the subsequent use of modifications are prevalent in those with RA. Given its importance as an IADL, further investigation of driving performance and potential driving modifications are needed.

Outcome Examined/References	No. of RA pts.	Frequency with End Point, %	Outcome Examined/References	No. of RA pts.	Frequency with End Point, %
Experiencing MVC			Inability to Drive		
Cranney, 2005	520	7.7	Cranney, 2005	520	7.7
Koepsell, 1994	11	45.5	Dawson, 1995	50	50.0
Maki, 1976	208	23.1	Ekdahl, 1989	26	7.7
<i>Weighted Mean Frequency</i>		13.1	Katz, 2008	547	1.1
Reporting Driving Difficulty			Wollenhaupt, 2013	276	7.2
Ewert, 2004	37	51.4	<i>Weighted Mean Frequency</i>		26.3
Katz, 2008	547	27.1	Difficulty Commuting		
Nordenskiöld, 1998	21	76.2	Ahlstrand, 2015	737	80.3
Thyberg, 2005	276	15.2	Allaire, 1996	469	10.9
Thyberg, 2004	169	17.2	Allaire, 2009	953	4.0
Wollenhaupt, 2013	256	33.6	<i>Weighted Mean Frequency</i>		31.5
<i>Weighted Mean Frequency</i>		26.0	Reduced Transport Mobility		
Use of Driving Assistance			Albers, 1999	186	52.2
Busteed, 2004	30	26.7	Chorus, 2001	720	10.0
Dawson, 1995	25	36.0	<i>Weighted Mean Frequency</i>		18.7
Katz, 2007	458	37.8			
Lapsley, 2002	81	14.8			
<i>Weighted Mean Frequency</i>		34.0			

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Abstract Number: 1260

Predictors of Hospitalization Due to Acute Gout: A Retrospective Cohort Study

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Background/Purpose: Despite effective treatments, hospitalization due to acute gout is increasing and financially burdensome. Prior studies have primarily attributed the increased rate of gout hospitalizations to physicians' gaps in knowledge regarding gout management. However, these studies fail to address patient and systems factors which may be associated with this risk. Our aim was to assess the association between these factors and risk of hospitalization among patients visiting the emergency department (ED) using a statewide healthcare system.

Methods: Lifespan is the largest provider of healthcare in Rhode Island and has 3 EDs across the state. We identified gout patients 18 years of age or older who presented to the ED between 3/30/2015 and 9/30/2017 using ICD9 and ICD10 diagnostic codes. If the patient was seen more than once during this time only the first encounter was included. Outcome of interest was admission from ED to inpatient or observation. We collected information regarding: a) patients factors including demographics, medications and co morbidities assessed at presentation, b) clinical presentation of gout (single versus multiple joint involvement) and severity as assessed by the triage nurse on a 5-point ED severity scale (1 being the worst), and c) systems factors including time of day and time of year at presentation to the ED, and type of insurance (commercial versus state health agencies/governmental insurance). Multivariable logistic regression model was used to identify factors associated with hospitalization.

Results: A total of 458 patients (mean age 58.71 ± 16.36 years, 79.43% males) were included. Of these 458 patients, 51 patients (11.1%) were admitted; 29 (6.4%) to inpatient and 22 (4.8%) to observation. Older age, presence of comorbidities, pattern of joint involvement and severity and time of presentation to the ED were associated with increased odds of admission. In multivariable model, older age [aOR 1.05 (1.01 to 1.08)], having oligo- or polyarticular gout [aOR 8.67 (3.50 to 21.48)], diabetes [aOR 4.74 (1.86 to 12.11)], history of inflammatory arthritis [aOR 5.83 (1.36 to 25.01)] and time of presentation to the ED between 8 AM–4 PM [aOR 5.92 (1.28 to 27.46)] and 4 PM–12 AM [aOR 7.04 (1.35 to 36.66)] continued to remain significant.

Conclusion: Our study demonstrates increased hospitalization rates among older patients, and those with comorbid diabetes or pre-existing inflammatory arthritis. This may be related to fear that these patients are at higher risk of joint infection. The study highlights increased odds of admission in patients presenting between 8 AM and midnight compared to those presenting between midnight and 8 AM. It is likely that decision to admit in case of the latter is made during regular business hours. Hence, highlighting the need to improve systems for after hour care of gout patients.

Table 1. Baseline cohort characteristics

		Discharged from the ED (n=)	Admitted from the ED (n=)
Age (mean \pm SD)*		57.2 \pm 16.02	70.8 \pm 13.87
Gender Ethnicity	Male	328/406 (80.8%)	35/51 (68.6%)
	African American	72/406 (17.7%)	5/51 (9.8%)
	Asian	10/406 (2.5%)	3/51 (5.9%)
	Caucasian	249/406 (61.3%)	38/51 (74.5%)
	Other	75/406 (18.5%)	5/51 (9.8%)
Pattern of joint involvement*	Oligo/polyarticular	50/407 (12.3%)	21/51 (41.2%)
Comorbidities	Diabetes*	97/304 (31.9%)	33/50 (66%)

Table . (Cont'd)

		Discharged from the ED (n=)	Admitted from the ED (n=)
	Hyperlipidemia*	185/304 (60.9%)	41/50 (82%)
	Prior gout history	214/304 (70.4%)	30/50 (60%)
	Alcohol use	39/304 (12.8%)	6/50 (12%)
	Chronic pain	8/304 (2.6%)	0/50 (0%)
	Hypertension*	227/304 (74.7%)	49/50 (98%)
	Coronary artery disease	70/304 (23%)	26/50 (52%)
	Heart failure*	58/304 (19.1%)	20/50 (40%)
	Chronic kidney disease*	65/304 (21.4%)	23/50 (46%)
	Inflammatory arthritis*	13/304 (4.3%)	7/50 (14%)
ED Severity Index*	2/3 (moderate severity)	184/355 (51.9%)	41/48 (85.4%)
	4/5 (least severe)	171/355 (48.1%)	7/48 (14.6%)
Time of day patients presented to the ED*	12 AM – 8 AM	72/355 (20.3%)	3/49 (6.1%)
	8 AM – 4PM	175/355 (49.3%)	29/49 (59.2%)
	4 PM – 12 AM	108/355 (30.4%)	17/49 (34.7%)
Time of the year patients presented to the ED	Jan - March	64/355 (18%)	10/49 (20.4%)
	April - June	122/355 (34.4%)	10/49 (20.4%)
	July - Sept	97/355 (27.3%)	16/49 (32.7%)
	Oct - Dec	72/355 (20.3%)	13/49 (26.5%)
Insurance carrier*	Medicare, Medicaid or other State Health	191/406 (47%)	38/51 (74.5%)
	Commercial	173/406 (42.6%)	13/51 (25.5%)
	Self-pay or Uninsured	42/406 (10.3%)	0/51 (0%)

* Represents statistically significant results (p <0.05).

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Development a Core Domain Set to Assess Shared Decision Making Interventions in Rheumatology: An OMERACT White Paper to Facilitate Endorsement

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Background/Purpose: Shared decision making (SDM) improves decisional outcomes and patient-physician communication and holds great potential for improving the management of various rheumatology conditions. However, the lack of consensus on how to measure the effectiveness of SDM in clinical trials creates a barrier to further evaluation of SDM interventions. Members of the SDM Outcome Measures in Rheumatology (OMERACT) working group (WG) sought to determine a core domain set, distinguishing process and outcome domains, for measuring the effectiveness of SDM interventions in rheumatology clinical trials. The WG followed the OMERACT Filter 2.0 and developed a draft core set of SDM process and outcome domains based on a previous systematic review and a nominal group process conducted at the OMERACT 2014 meeting. In 2016, an international electronic Delphi survey was conducted among patients, caregivers, clinicians and researchers to refine the domains of the OMERACT draft core set. A workshop was held at the OMERACT 2016 meeting in which no agreement was reached on the core set.

Methods: To help address reasons for which consensus was not achieved, a white paper was drafted. The aim of the white paper was to clarify the background and development process of the draft SDM core domain set. Key stakeholders playing a leadership role within OMERACT were identified and contacted to participate in semi-structured interviews by telephone or virtually to determine how to modify the core set and inform the white paper to facilitate its endorsement.

Results: A preliminary sample of nine OMERACT members from North America and Europe participated in interviews, including eight scientists/clinicians and one patient. All participants felt that domains pertaining to the process and the outcomes of SDM are relevant but should be clearly delineated. Some mentioned that, since OMERACT pertains more to outcomes than process, consensus-building efforts should focus on outcome domains rather than process domains. Most felt that all SDM outcome domains were relevant, but suggested minor changes in language and the addition of definitions to clarify domains. Outcomes include: knowledge of the options and their features; accurate risk perceptions; match between values/preferences and chosen option; confidence in decision making; satisfaction with decision making process; and use of the chosen option. The white paper was felt to be helpful in understanding the core set.

Conclusion: Preliminary evidence from the interviews demonstrates a need to focus efforts on clarifying and gaining consensus on the outcome domains rather than on the process domains of SDM interventions. Further interviews will be conducted with all key stakeholders and this feedback will be used to improve the white paper and core set. International consensus-building efforts will also take place to ensure all key stakeholders endorse the core set of outcome domains used to measure in trials of SDM interventions.

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Abstract Number: 1262

The Importance of Standardization of Musculoskeletal Procedures Performed in an Academic Rheumatology Clinic

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

Background/Purpose: Diagnostic and therapeutic arthrocentesis and soft tissue injections are routinely performed by Rheumatologists mostly in the outpatient and some in the inpatient settings. There are variations in technique and the dosing of medications used. Our aim was to assess the procedural variability among rheumatologists at a single academic

medical center in an attempt to standardize the process using evidence-based medicine when applicable, thereby improving clinic workflow and efficiency.

Methods: An anonymous 2 part questionnaire was completed by 12 rheumatology staff physicians and fellows. The 2nd part of the questionnaire covered the procedure clinic workflow using the Likert scale which was completed by 7 rheumatology clinic nurses as well. Review of literature was done using the PubMed. Medication information was referenced using www.lexicomp.com

Results: Part 1 of the questionnaire was notable for preference for lidocaine as local anesthetic of choice (Table 1). There was a wide variability in the dose of methylprednisolone and lidocaine used for the knee and glenohumeral intra-articular (IA) injections, trochanteric bursa and trigger finger injections in our clinic. Part 2 revealed concordance between the physicians and nursing staff regarding delays and inefficiency of the clinic workflow (75% and 86% respectively, were in agreement). 92% of physicians and 86% of nurses agreed that standardization would be beneficial despite 41% physicians and 57% nurses indicating satisfaction with the current clinic workflow.

Review of published literature was notable for the following: Utilization and type of gloves used (sterile vs non-sterile) or sterile vs aseptic techniques varied widely in clinical practice. Chlorhexidine was superior to iodine for skin sterilization. The choice of intraarticular glucocorticoids was largely driven by the training background of physicians, with lack of definitive data to support the use of one over the other. Mepivacaine and Ropivacaine are thought to be less chondrotoxic compared to lidocaine and bupivacaine. Use of directoral anticoagulants and warfarin with INR <2 do not increase the risk for hemarthrosis.

The next step is to implement the standardized procedure practice within the clinic using the information gathered and follow this with a post implementation survey and practice monitoring.

Conclusion: There are no specific consensus or common practice guidelines such as the use of sterile gloves to perform sterile technique vs aseptic technique, iodine use and use of lidocaine for I injections as certain practices are not evidence based and depend on previous training and individual preferences. Standardization may help improve efficiency and staff satisfaction and reduce potential errors. There is an unmet need for development of evidenced-based musculoskeletal procedure guidelines in rheumatology.

Table 1

Questionnaire-PART 1 (n=12)					
Parenthesis indicate number of rheumatologists performing the procedure or utilizing the medication.					
1. Preferred approach for knee IA injection	Superolateral (1) (8.3%)	Inferolateral (4) (33.3%)	Inferomedial (2) (16.7%)	Combination (3) (25%)	N/A(2) (16.7%)
2. Preferred approach for glenohumeral IA injection	Anterior (2) (16.7%)	Posterior (10) (83.3%)			
3. Preferred approach to subdeltoid bursa injections	Anterior (2) (16.7%)	Superior (0)	Lateral (7) (58.3%)	Combination (2) (16.7%)	N/A(1) (8.3%)
4a. Type of skin disinfectant used	Chlorhexidine Qtip (3) (25%)	Chlorhexidine sponge (5) (41.7%)	Iodine/betadine (1) (8.3%)	Combination (3) (25%)	
4b. Duration of skin contact (seconds)	5-120s (8/12) (66.7%)	N/A (4/12) (33.3%)			
5. Type of gloves used	Sterile (6) (50%)	Non-sterile (4) (33.3%)	Combination (2) (16.7%)		
6. Use of a topical anesthetic (ethyl chloride) prior to soft tissue or IA injection	Yes (12) (100%)	No (0)			
7. Use of lidocaine vs mepivacaine for soft tissue injections	Lidocaine (12) (100%)	Mepivacaine (0)			
8. Use of lidocaine vs mepivacaine as a local anesthetic during IA injections	Lidocaine (7) (58.4%)	Mepivacaine (4) (33.3%)	None (1) (8.3%)		
9. Use of lidocaine vs mepivacaine for IA injections in conjunction with steroids	Lidocaine (11) (91.7%)	Mepivacaine (0)	Combination (1) (8.3%)		
10. Medication dose for IA injections	Shoulder joint	Knee joint	Trochanteric bursa	Trigger finger	
a. Methylprednisolone	40-80mg	80-120mg	40-160mg	<10-40mg	
b. Lidocaine	10-40mg	20-60mg	20-60mg	<5-10mg	
	Yes (3) (25%)	No (9) (75%)			

Table . (Cont'd)

Questionnaire-PART 1 (n=12)

11. Routine use of USG for IA injections		
12. Agree with implementation of a standardized approach to the procedure clinic	Yes (10) (83.3%)	No (2) (16.7%)
PART 2 (n=19)	Physicians (n=12)	Nursing staff (n=7)
1. Delays have been encountered in clinic due to medication related questions	Agree (50%) Strongly agree (25%)	Agree (57%) Strongly agree (29%)
2. The current rheumatology procedure work flow is satisfactory	Agree (41%) Disagree (42%) Neither (17%)	Agree (57%) Disagree (43%)
3. Standardization will help improve clinic workflow	Strongly agree (50%) Agree (42%) Neither (8%)	Strongly agree (72%) Agree (14%) Neither (14%)

Disclosure: S. Ifteqar, None; R. Mehta, None; P. Schmidt, None; M. Maz, None.

Abstract Number: 1263

Develop a Master Algorithm for Drug Withdraw Strategy in Reduction of Adverse Events – a Machine Learning Model from the Smart System of Disease Management (SSDM)

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster II

Session Type: ACR Poster Session B

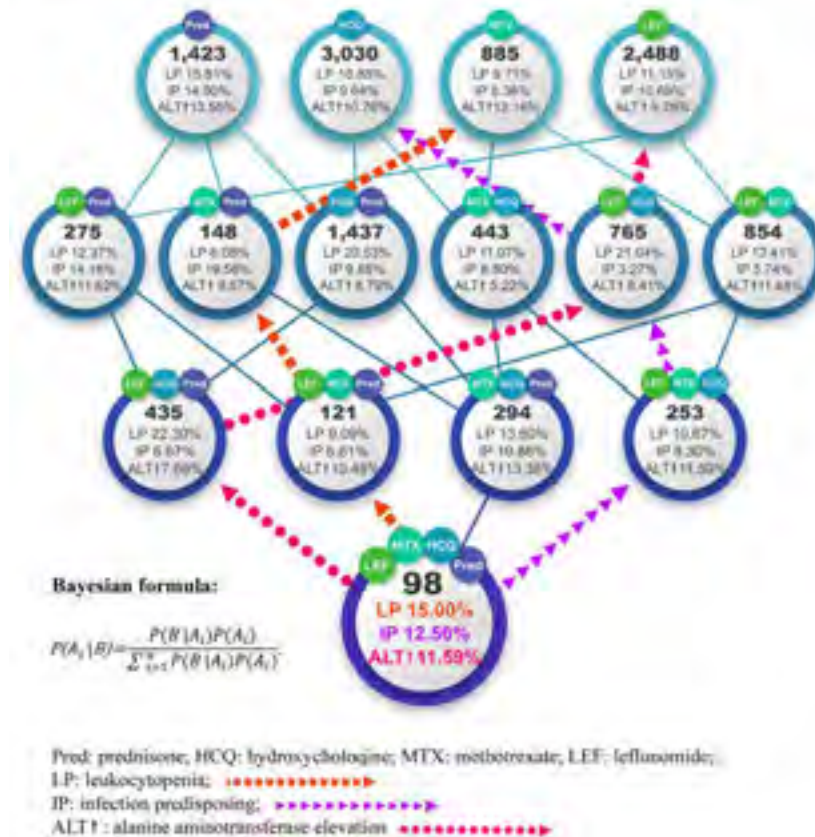
Session Time: 9:00AM-11:00AM

Background/Purpose: Combination therapy with DMARDs for treating RA is considered as standard of care. However, certain rates of adverse events (AEs) are unavoidable. The stigma is which drug should be stopped first once AEs emerge and the following sequence if AEs persist for optimal risk reductions. The decisions made by clinicians a real ways empirically. The purpose of this study is to develop an algorithm for decision-making on drug withdraw sequence in face of adverse events with combination therapy based on data mining and machine learning from the smart system of disease management (SSDM).

Methods: SSDM is an interactive mobile disease management tool, RA patients can input medical records (including medication and laboratory test results) and perform self-evaluation via applications (App). The data synchronizes to the mobiles of authorized rheumatologists through cloud and advices could be delivered.

In order to develop the master algorithm, abnormal white blood cell counts (WBC) and alanine amino transferase (ALT) elevation were targeted. WBC, ALT and medication data was collected, extracted, validated, and then based on Bayesian

Image 1. Bayesian network and data processing: patients' number (black bold as blow showed) and the rate of LP, IP and ALT in 15 regiments.



networks, data mining, modeling, calculating, analyzing were performed. WBC under 4,000/ml is defined as leukocytopenia (LP), over 10,000/ml as infection predisposing (IP), and ALT > 40 U/L as ALT elevation.

Results: From June 2014 to June 2018, 32,130 RA patients from 587 centers registered in SSDM. 7,086 are male and 24,144 are female with mean age of 49.82 year. 129 different drugs and 479 types of combination therapies are identified. Lab test results showed LP happened in 311 and IP 217, ALT 316 in 554 mono or combinational treatment regiments. Among them we selected prednisone (Pred), leflunomide (LEF), MTX, HCQ as an example to develop a master algorithm based on Bayesian networks and learning model. Image 1 shows Bayesian network and data processing, in which, quartet are correlating with 15 different regiments. Drug withdraw sequence for LP is HCQ, then LEF and then Pre, and the risks of LP are reduced by 39%, 33% and 23%, respectively. For IP, withdraw sequence is Pred, then MTX and then HCQ, and the risks of IP are reduced by 47%, 51% and 15%, respectively. For ALT, withdraw sequence is MTX, then Pred and then HCQ, and the risks of ALT are reduced by 51%, 28% and 16%, respectively.

Conclusion: Big data system can be built using SSDM via empowering patient. Through data mining, networking, modeling, and Bayesian calculation, a master algorithm for drug withdraw strategy in reduction of adverse events with combination therapy is developed, which can be applied on the other AEs in SSDM and may be replicated in other diseases. Following the continuing data inputs and machine learning, an artificial intelligent system in assisting clinical decision making may be achieved.

Limitations: This study only focus on rate of AE without considering the efficacy, without stratifying dosing.

Disclosure: Y. Zhao, None; J. Yang, None; J. Huang, None; H. Wei, None; Y. Wang, None; R. Mu, None; X. Zuo, None; H. Wang, None; X. Duan, None; J. Xue, None; H. Sun, None; B. Wu, None; L. Kang, None; F. Wei, None; C. Mi, None; Y. Zhao, None; Y. Li, None; H. Chen, None; Z. Li, None; Q. Meng, None; Y. Jia, None; H. Xiao, None; F. Xiao, None.

Modeling the Costs and Outcomes Associated with Treatment Sequences, with and without Tofacitinib, for Moderately to Severely Active Psoriatic Arthritis in the US

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Measures and Measurement of Healthcare Quality Poster II

Session Type: ACR Poster Session B

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

Background/Purpose: Psoriatic Arthritis (PsA) is a chronic progressive inflammatory condition associated with significant direct and indirect costs. Tofacitinib is an oral Janus kinase inhibitor for the treatment of PsA. Economic evaluations, alongside clinical data, help inform payers and formulary decisions in the USA. To better understand the impact of including tofacitinib on US payer formularies for treatment of patients (pts) with moderately to severely active PsA with a previous inadequate response (IR) to a conventional synthetic disease-modifying ant rheumatic drug (csDMARD), a decision tree model was designed to estimate and compare total costs, clinical responses, and per member per month (PMPM) costs between treatment sequences with and without tofacitinib.

Methods: The decision tree model was designed to estimate costs and outcomes from a third-party US payer perspective. In the base case, it was assumed the payer insured 1,000,000 individuals. The number of insured csDMARD-IR PsA pts was estimated from drug utilization and PsA epidemiology data. The analytical horizon was 2 years, with decision points for continuing/switching treatments occurring quarterly based on efficacy or occurrence of adverse events. The decision tree allowed for the comparison of multiple treatment strategies, each with up to four lines of advanced therapy for PsA. The base case compared a 'tofacitinib treatment sequence' (tofacitinib, adalimumab, etanercept, apremilast) vs a comparator sequence (adalimumab, etanercept, apremilast, secukinumab). Efficacy was measured using ACR20/50/70 and adverse event data were taken from US product information or published randomized clinical trials. The estimated total costs include the costs of treatment, monitoring, administration, and adverse events.

Results: Among 1,000,000 insurants, it was estimated that 274 csDMARD-IR PsA pts would receive an advanced therapy. The 'tofacitinib treatment sequence' was estimated to reduce total costs by \$5,223,990 vs the comparator sequence without tofacitinib, with estimated total 2-year costs of \$31,225,220 and \$36,449,210, respectively; the PMPM cost of the 'tofacitinib treatment sequence' was \$1.30 vs \$1.52 for the comparator sequence. Over 2 years, it was estimated that 261 (95%), 171 (62%), and 81 (30%) patients in the 'tofacitinib treatment sequence' will achieve ACR20/50/70 responses, respectively, vs 252 (92%), 169 (62%), and 81 (30%) patients in the comparator sequence, respectively. Sensitivity analyses on treatment sequences and key parameters including drug cost, efficacy, and switching probability showed the model results to be robust with treatment sequences including tofacitinib consistently being cost-saving sequences excluding tofacitinib.

Conclusion: This model suggests including tofacitinib in treatments for csDMARD-IR PsA pts is a cost-saving alternative to treatment sequences without tofacitinib. The inclusion of tofacitinib on formulary for payer insuring 1,000,000 individuals could reduce payer costs for PsA advanced therapies by more than \$5 million.

Disclosure: G. Bungey, Pfizer Inc, 5; S. Chang-Douglass, Pfizer Inc, 5; M. A. Hsu, Pfizer Inc, 1, Pfizer Inc, 3; J. C. Cappelleri, Pfizer Inc, 1, Pfizer Inc, 3; P. Young, Pfizer Inc, 1, Pfizer Inc, 3; J. Woolcott, Pfizer Inc, 1, Pfizer Inc, 3.

The Challenges of Managing Gout in Primary Care: Results of a Best Practice Audit

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: The majority of gout management occurs in primary care and may be suboptimal. While community based clinical trials have reported improvements whether such improvements can be replicated in routine clinical care is unknown. The aim of this study was to determine the effects of a package of care for (POC) gout in a real life primary care setting.

Methods: A POC was developed reflecting current gout management guidelines including patient education, a structured approach to the management of gout flares and urate lowering therapy (ULT) and screening for co-morbidities. An audit of gout management in a single rural general practice was undertaken before (2012) and after (2015) introduction of the POC.

Results: In 2012 one-hundred and twenty people with gout and in 2015 one-hundred and seventy one people with gout were identified. After the introduction of the POC more people with gout were prescribed ULT (79/120 (65.8%) vs. 127/171 (74.5%); $p=0.12$) and there was a significant increase in the median (IQR) number of prescriptions per individual over the 12 month period (1 (0-4) vs. 3 (0-4) $p<0.001$) (Figure). There was a significant increase in the number of individuals commenced on allopurinol ≤ 100 mg daily and a corresponding decrease in the number commenced on ≥ 200 mg daily ($p<0.001$) (Figure). There was a significant increase in the frequency urate testing between 2012 and 2015 ((median (range) 1 (0-3) vs 2 (0-10) respectively $p<0.001$). Of those individuals who had at least one urate measurement the proportion of individuals who never achieved target rate reduced from 43/67 (64.2%) in 2012 to 52/133 (39.1%) in 2015; $p=0.001$. With the exception of smoking, screening for important co-morbidities improved significantly after introduction of the POC. Of the 67 individuals who had a urate test in 2012 none received a ULT dose increase despite urate being above target in 46 instances. Of the 133 individuals who had a urate tested in 2015, 34 had at least one increase in allopurinol dose and of the 99 who were not dose escalated 28 were at target urate.

Conclusion: A structured POC can improve gout management in primary care although allopurinol dose escalation remains challenging.

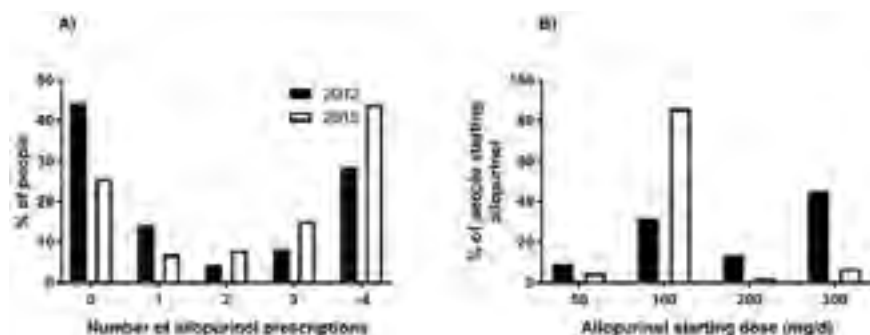


Figure: Differences between 2012 and 2015 with regards to A) number of allopurinol prescriptions and B) allopurinol starting dose

Disclosure: L. K. Stamp, Amgen Inc., 8; P. T. Chapman, None; B. Hudson, None; G. Hamilton, None; A. Judd, None.

Abstract Number: 1266

ABCG2 rs2231142 Q141K and Oxypurinol Concentration in People with Gout Receiving Allopurinol

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Association of *ABCG2* Q141K (p.141Lys) with poor urate-lowering response to allopurinol has been reported although the mechanism is unclear. *ABCG2* has been reported to be an efflux pump for allopurinol and oxypurinol [1] and for oxypurinol alone [2]. Based on data from the HEK293 cell-line it has been suggested that dysfunctional variants of *ABCG2* such as p.141Lys could lead to decreased renal excretion of oxypurinol, higher oxypurinol levels and greater serum urate lowering [2]. To further investigate the apparent inconsistency between ref [2] and association of p.141Lys with poor allopurinol response, we examined the relationship between *ABCG2* p.141Lys and plasma oxypurinol.

Methods: We examined, using linear regression, plasma oxypurinol concentrations using participants from the Long-term Allopurinol Safety Study Evaluating Outcomes in Gout Patients and Genetics of Gout in Aotearoa studies based on the presence of the *ABCG2* p.141Lys.

Results: Of the 688 individuals, 294 (42.7%) were positive for \geq one p.141Lys allele. In a univariate model plasma oxypurinol concentration was significantly lower in these individuals compared to Gln/Gln homozygotes (mean (SEM) 84.8 (3.6) μ mol/l vs. 96.6 (3.1); $p=0.013$) despite higher allopurinol dose (mean (SD) 326 (101.3) vs. 297 (80.5)mg/d; $p<0.001$) and higher eGFR (72.7 (24.8) vs 67.5 (22.6) ml/min/1.73m²; $p=0.004$). Of those in the p.141Lys-positive group, fewer were receiving diuretics compared to the Gln/Gln group (22.4% vs. 31.0%; $p=0.08$). In a multivariate model that included allopurinol dose, eGFR and the use of diuretics, there was no statistically significant difference between plasma oxypurinol concentrations in the p.141Lys-positive and -negative groups, although levels were numerically lower in the p.141Lys-positive group (97.7 (3.5) μ mol/l vs. 104.3 (2.8) μ mol/l $p=0.12$).

Conclusion: Our results suggest that there are unidentified factors that influence plasma oxypurinol and, despite the evidence presented from the HEK293 cell-line model [2], plasma oxypurinol levels are not significantly different in individuals with the *ABCG2* p.141Lys variant. We recommend an individualised dose titration to target serum urate strategy for patients establishing on allopurinol.

1. Wen, C., et al., *Genome-wide association study identifies ABCG2 (BCRP) as an allopurinol transporter and a determinant of drug response*. Clin Pharm Ther, 2015. **97**(5): p. 518-25.
2. Nakamura, M., et al., *Investigation of the transport of xanthine oxidase dehydrogenase inhibitors by the urate transporter ABCG2*. Drug Metabol Pharmacokinet, 2017. <https://doi.org/10.1016/j.dmpk.2017.11.002>.

Disclosure: L. K. Stamp, Amgen Inc., 8; M. Wallace, None; R. Roberts, None; C. Frampton, None; J. Miner, None; T. R. Merriman, None; N. Dalbeth, Horizon, 5, Kowa, 5, Amgen Inc., 2, AstraZeneca/Ironwood, 2, AbbVie Inc., 8, Pfizer, Inc., 8, Janssen, 8.

Abstract Number: 1267

The Association between Clinically Suspect Arthralgia and Adipokines in Obese Patients

Taskin Senturk¹, Reyhan Kose¹, Gokhan Sargin¹, Songul Cildag², Mustafa Unubol³, Burcin İrem Abas⁴ and Cigdem Yenisey⁴, ¹Rheumatology, Adnan Menderes University Medical School, Aydin, Turkey, ²Allergy and Immunology, Adnan Menderes University Medical School, Aydin, Turkey, ³Endocrinology and Metabolism, Adnan Menderes University Medical School, Aydin, Turkey, ⁴Biochemistry, Adnan Menderes University Medical School, Aydin, Turkey

Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Obesity is a moderate low-grade chronic inflammatory condition. Also, it has been reported to be a risk factor for inflammatory rheumatic diseases, seronegative inflammatory polyarthritis, and psoriatic arthritis. The cause of low-grade inflammation in obese patients who have non-specific musculoskeletal symptoms may be the subject of debate in clinical practice. Our aim is to determine whether inflammation is associated with obesity or rheumatic disease, and the association between leptin, chemerin, visfatin and inflammatory markers in obese patients with/without musculoskeletal symptoms.

Methods: In the period between March 2017 and January 2018, seventy-four obese patients (4 male, 70 female, with the mean age of 47.09 \pm 10.7 years) who admitted to our clinic with non-specific musculoskeletal symptoms were enrolled. The control group consisted of 40 obese patients (5 male, 35 female, with the mean age of 44.9 \pm 10 years) who have no rheumatic symptoms. Body mass index (BMI) is calculated in kg/m² with body weight ratio to height squared, and defined obesity BMI 30 or above. Age, gender, sedimentation, CRP, TNF- α , IL-6, IL-1, leptin, chemerin, and visfatin were

evaluated. The relationship between all parameters was assessed by Spearman correlation, Wilcoxon Signed-rank, and paired t-tests.

Results: There were no significant differences for sex, gender, and BMI between obese patients with non-specific musculoskeletal symptoms and control group. The mean TNF- α , IL-1 β , IL-6 concentrations were 60.8, 39.9, and 26.2 in obese patients with non-specific musculoskeletal symptoms respectively and significantly higher than the control group. Sedimentation and CRP levels were higher in those patients compared to control group without statistical difference. There were significant differences for chemerin, visfatin, but not for leptin between both group (Table 1). Also, the significant correlation was found between proinflammatory cytokines and visfatin, chemerin.

Conclusion: Visfatin and chemerin correlated with inflammation may be a useful indicator of undifferentiated inflammatory arthritis in obese patients who have non-specific musculoskeletal symptoms with low-grade inflammation.

Table 1. Demographic characteristics and laboratory values of obese patients with clinically suspect arthralgia and without any rheumatic symptoms

	With clinically suspect arthralgia	Without any rheumatic symptoms	p-value
Obese patients (n)	74	40	-
Age (years)	47.09 \pm 10.7	44.9 \pm 10	NS
Gender (female/male)	70/4	35/5	NS
Body Mass Index (kg/m ²)	37.6 \pm 7.2	36.9 \pm 4.8	NS
Sedimentation (mm/h)	32.9 \pm 15.1	27.5 \pm 16.1	NS
CRP (mg/dL)	8.4 [0.1-35.3]	7.9 [1-54.7]	NS
IL-1 β (pg/ml)	39.9 [4-347.5]	20.4 [0.7-266.1]	0,04*
IL-6	26.2 [3.8-350.9]	13.2 [3-63]	0,001*
TNF- α (pg/ml)	60.8 [11.3-301.6]	36.2 [5.6-243.3]	<0,001*
Visfatin (ng/ml)	4.8 [0.2-48.9]	1.5 [0.1-19.5]	<0,001*
Chemerin (ng/ml)	4.2 [0.1-39.5]	1.3 [0.1-20.4]	<0,001*
Leptin (pg/ml)	3460.8 \pm 510.9	3285.2 \pm 696.6	0,16

NS: not significant, [minimum-maximum], * significant difference.

Disclosure: T. Senturk, None; R. Kose, None; G. Sargin, None; S. Cildag, None; M. Unubol, None; B. İ. Abas, None; C. Yenisey, None.

Abstract Number: 1268

Assessment of the Persistence of Crystals Under Polarised Light Microscopy in Stored Synovial Fluid Samples

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Session Information

Session Date: Monday, October 22, 2018

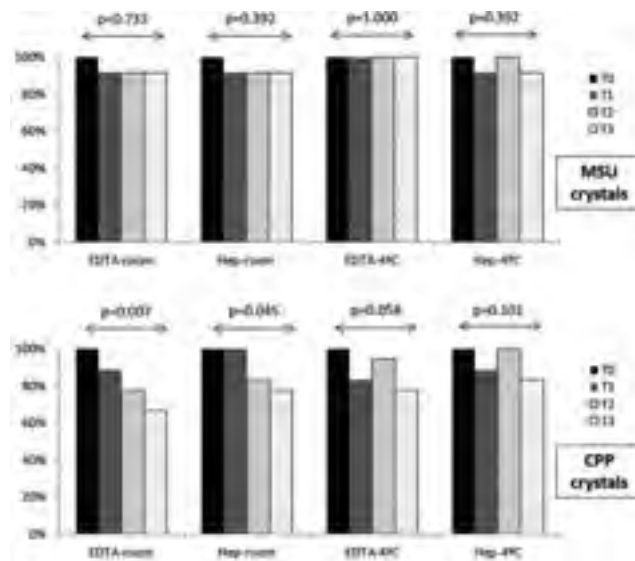
Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Lacking an immediate access to a polarized light microscope is sometimes used to justify the clinical diagnosis of crystal-related arthritis. Some studies have assessed the persistence of crystals in stored synovial fluid samples, with disparities in methodology and results that hamper the extraction of firm conclusions. The aim of this study was to determine the influence of the time from sampling and the method of preservation on the crystal identification in the synovial fluid samples under polarized light microscopy at different time points.

Methods: A prospective, longitudinal, observational study was designed. Synovial fluid samples were obtained in clinical practice (T₀) and a trained rheumatologist identified crystals – monosodium urate (MSU) or calcium pyrophosphate (CPP). Fluids in which both types of crystals were detected, were excluded. On extraction, each fluid was divided into four samples. Two samples were stored in each type of tube - heparin or ethylenediaminetetraacetic acid (EDTA) as preserving agents -, at varying temperatures - room temperature or refrigerated at 4°C (39.2°F). Samples were analysed at around 24h (T₁), 72h (T₂), and 7days (T₃) by simple polarized light microscopy, and the presence of crystals was recorded. A medical student, who underwent training in crystal identification before the study, performed synovial fluid analyses; this training



was repeated after every ten samples. The student was blinded to baseline data, and synovial fluid samples containing no crystals were included to ensure blinding. Differences in the proportion of crystal-containing samples throughout the time-points were assessed using Cochran's Q and McNemar's tests.

Results: Thirty synovial fluid samples were analysed, 12 with MSU and 18 with CPP crystals at baseline. This meant a total of 120 samples at follow-up time points. A total of 360 microscope visualizations were performed, at a mean (SD) of 31.0h (10.3) for T₁, 90.5h (29.3) for T₂, and 7.5 days (0.7) for T₃. The Figure shows the rate of samples containing crystals at different time-points. The identification of crystals within the MSU samples did not modify throughout study, being observed in 11/12 (91.7%) of room temperature samples and in 12/12 (100%) of refrigerated samples at T₃. However, the identification of CPP crystals tended to decrease in all conditions, especially when preserved with EDTA and kept at room temperature (12/18 (66.7%) at T₃).

Conclusion: MSU crystals persisted in stored samples for over a week, but CPP crystals tended to disappear in the same period, especially when kept at room temperature and/or preserved with EDTA. Keeping samples preserved with heparin and refrigerated at 4°C appears to allow a delay microscope analysis for crystals. Foregoing crystal-proven diagnosis, due to immediate unavailability of a microscope, no longer appears justified.

Disclosure: S. Pastor, None; R. Caño, None; S. Gomez-Sabater, None; M. Andrés, None.

Abstract Number: 1269

Influence of Diuretic-Response Sodium Transporter Genes on Renal Uric Acid Handling in Response to Frusemide

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Elevated serum urate and reduced fractional excretion of uric acid (FEUA) are common in people on diuretics. Changes in FEUA in response to frusemide are associated with changes in fractional excretion of sodium (FENa). Variants in renal sodium transporters NCC (encoded by *SLC12A3*) and ENaC (encoded by *SCNN1B* and *SCNN1G* beta and gamma subunits, respectively) have been associated with FENa responses to frusemide (Vormfelde

et al, Clin Pharmacol Ther 2007). The aim of this study was to determine whether variations in these sodium transporters also have an effect on FEUA or serum urate responses to frusemide administration.

Methods: Data were analysed from a short-term study of 100 healthy participants receiving a 40mg oral tablet of frusemide. The following single nucleotide polymorphisms (SNPs) were genotyped: *SCNN1B* rs152745, *SCNN1G* rs13306653 and *SLC12A3* rs1529927. A mixed-model approach to repeated measures (analysis of variance; ANOVA) all adjusted for age, sex, and ethnicity was employed. The key primary endpoint was FEUA and the secondary endpoints were serum urate, FENa, and fractional excretion of potassium (FEK).

Results: Oral intake of 40mg frusemide led to marked diuresis and increase in FENa and FEK throughout the study period (ANOVA $P < 0.0001$ for all). FEUA initially increased and then decreased over the study period ($P < 0.0001$). For *SCNN1B* rs152745, homozygosity for the frusemide response A allele (15% of participants) was associated with a greater increase in FENa (ANOVA $P_{\text{time} \times \text{SNP}} = 0.007$) and FEUA ($P_{\text{time} \times \text{SNP}} = 0.02$). For *SLC12A3* rs1529927, presence of the frusemide response C allele (3% of participants) was associated with a greater increase in FEUA ($P_{\text{time} \times \text{SNP}} = 0.00013$) and a trend to increase in FENa ($P_{\text{time} \times \text{SNP}} = 0.09$) following frusemide intake. No effects on diuretic responses were observed with *SCNN1G* rs13306653, and none of tested SNPs had significant effects on serum urate or FEK over the study period.

Conclusion: Two previously reported diuretic-response sodium transporter genes are associated with an elevated FEUA response to frusemide. These findings suggest that genetic variation in *SLC12A3* and *SCNN1B* influence renal uric acid handling in response to diuretics, perhaps through altered renal sodium handling.

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Abstract Number: 1270

Lack of Association of Comorbidities with Ultrasonographic Urate Deposition in Asymptomatic Hyperuricemia

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Session Information

Session Date: Monday, October 22, 2018

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

Background/Purpose: Hyperuricemia is common, and along with other comorbidities (CM), is increasing in prevalence. Though often asymptomatic, it is associated with subclinical urate deposition detectable by ultrasound (US) imaging. This study aims to evaluate the association of CM with urate deposition in individuals with asymptomatic hyperuricemia (ASU) via US.

Methods: ASU was defined as serum urate (sUA) $> 6\text{mg/dl}$; sUA $< 6\text{mg/dl}$ served as controls. Demographic factors, CM – (hypertension [HTN], hyperlipidemia [HLD], diabetes mellitus [DM], cardiovascular disease [CVD], renal disease [CKD], metabolic composite [presence of any CM, BMI > 30], osteoarthritis [OA]), diuretic use, and dietary data (alcohol [ETOH], red meat, seafood) were collected. US of joints (knee/1st MTP) and tendons (triceps, quadriceps/patella, Achilles) was performed via standard procedure, OMERACT parameters of urate deposition documented, and images read by an Expert ultrasonographer blinded to sUA and CM categories. Correlations between sUA levels and urate deposition with CM, medication and dietary risk factors were analyzed by multivariable logistic regression model.

Results: Of 95 predominantly Black patients (mean age 59.7 yrs, BMI $\sim 32\text{ kg/m}^2$) ASU subjects ($n=71$, median sUA = 8.0 mg/dl) were older men, with more frequent HTN, CVD, CKD, and alcohol ingestion versus controls (Table 1). Presence of

HTN, CVD, CKD and diuretic use were associated with higher sUA (>8 vs 6-7.9 mg/dl). In multivariate analyses adjusting for demographic and clinical characteristics, sUA>6mg/dl and advanced age were positively associated with joint urate deposition, (OR=5.23; 95%CI: 1.18-23.12, OR=1.06; 95%CI: 1.00-1.11, respectively) [Table 2]. There was however, no significant association between individual or composite CM and urate deposition at either joint or tendon, even when adjusting for sUA levels. Urate deposition at tendons was more frequent in men (OR=9.09; 95%CI: 1.08-76.68), but unrelated to sUA (p=0.23).

Conclusion: While ASU and age predict US urate deposition, the presence of comorbid conditions and diuretic use though themselves associated with higher levels of sUA, do not. A larger cohort with other imaging modalities such as DECT, may provide additional information.

Table 1 Cohort Clinical Characteristics and sUA status

Variable	All Cohort (N=95)	Control (n=24)	ASU (SUA>6.0) (n=71)	p-value	SUA: 6-7.9 (n=35)	SUA>=8.0 (n=36)	p-value
Demographic Characteristic							
Male	68(71.6%)	10(41.7%)	58(81.7%)	<.01	26(74.3%)	32(88.9%)	0.13
Age--mean(SD)	59.7(10.9)	54.9(14.2)	61.4(9.1)	0.05	59.3(10.0)	63.5(7.7)	0.06
Race	10 (10.5%)	2(8.3%)	8(11.3%)	0.38	4(11.4%)	4(11.1%)	>.99
--White	76(80.0%)	18(75.0%)	58(81.7%)		29(82.9%)	29(80.6%)	
--Black	9 (9.5%)	4(16.7%)	5(7.0%)		2(5.7%)	3(8.3%)	
--Other/Unk							
BMI--mean(SD)	31.9 (7.4)	31.1(8.8)	32.1(6.9)	0.55	32.0(6.7)	32.3(7.1)	0.87
Co-morbidities							
DM	31 (32.6%)	5(20.8%)	26(36.6%)	0.21	10(28.6%)	16(44.4%)	0.22
HTN	58 (61.1%)	10(41.7%)	48(67.6%)	0.03	17(48.6%)	31(86.1%)	<.01
HLD	44 (46.3%)	10(41.7%)	34(47.9%)	0.64	18(51.4%)	16(44.4%)	0.64
Cancer	8 (8.4%)	1(4.2%)	7(9.9%)	0.67	3(8.6%)	4(11.1%)	>.99
Renal	22 (23.2%)	2(8.3%)	20(28.2%)	0.05	2(5.7%)	18(50.0%)	<.01
OA	45 (47.4%)	16(66.7%)	29(40.8%)	0.03	15(42.9%)	14(38.9%)	0.81
CVD	16(16.8%)	0(0)	16(22.5%)	0.01	3(8.6%)	13(36.1%)	0.01
Dietary							
Red meat>=3x/wk	28 (30.1%)	5(20.8%)	23(33.3%)	0.31	12(34.3%)	11(32.4%)	>.99
Seafood>=3x/wk	21(22.6%)	6(25.0%)	15(21.7%)	0.78	10(28.6%)	5(14.7%)	0.24
Alcohol(Current)	43 (46.7%)	8(34.8%)	35(50.7%)	0.23	19(54.3%)	16(47.1%)	0.63
Medication							
Diuretic	45(48.9%)	7(29.2%)	38(55.9%)	0.03	12(37.5%)	26(72.2%)	<.01

Table 2 Multivariate Logistic Regression Results of US Findings on Potential Predictors

Variable	Any Deposition		Joint Deposition		Tendon Deposition	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR(95%CI)	p-value
ASU (sUA>6mg/dl)	3.47(0.75-15.96)	0.11	5.23(1.18-23.12)	0.03	0.35(0.06-1.92)	0.23
Age	1.01(0.96-1.07)	0.70	1.06(1.00- 1.11)	0.05	0.94(0.88-1.00)	0.06
Male	1.51(0.38-5.99)	0.56	0.74(0.19- 2.91)	0.67	9.09(1.08-76.68)	0.04
African American	1.51(0.35-6.46)	0.58	1.09(0.27-4.49)	0.90	2.38(0.46-12.43)	0.30
CKD	0.31(0.08-1.19)	0.09	0.37(0.10-1.36)	0.13	0.73(0.16-3.39)	0.69
CVD	0.90(0.18-4.47)	0.90	0.82(0.17-4.05)	0.81	3.65(0.67-19.85)	0.13
OA	1.65(0.49-5.54)	0.42	1.44(0.46-4.52)	0.53	1.75(0.50-6.15)	0.39
Metabolic composite	0.13(0.01-1.61)	0.11	0.16(0.02-1.35)	0.09	0.52(0.09-3.05)	0.46
ETOH+ Red meat + Seafood diet	1.38(0.66-2.88)	0.39	1.42(0.70-2.87)	0.33	1.71(0.78-3.73)	0.18
Diuretic medication	0.99(0.27-3.58)	0.98	1.24(0.36-4.29)	0.73	2.42(0.54-10.84)	0.25

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Abstract Number: 1271

Predictive Factors of Increased Vascular Stiffness in Patient with Gout and Hyperuricemia

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose

Background: Gout is the most common form of inflammatory arthritis and its prevalence is increasing in more affluent countries in recent decades. Many studies have reported that gout and hyperuricemia are associated with an increase in all-cause mortality and cardiovascular mortality. Increased arterial stiffness is an independent marker of cardiovascular diseases and risk predictors. Many studies have shown a significant correlation between uric acid levels and arterial stiffness. Augmentation Index (AI) is an indirect measure of arterial stiffness.

Purpose: The aim of this study is to evaluate the predictors of increased arterial stiffness in gout and hyperuricemia patients.

Methods: Between June 2017 and June 2018, AI was measured using SphygmoCor for patients who visited Jeju National University Hospital in South Korea with gout or hyperuricemia. Medical records, laboratory and AI data were retrospectively analyzed and multivariate analysis was performed.

Results: One hundred twenty two patients participated in the study and AI was measured. Most (96.7%) of the patients were male. At the time of the examination, 99 patients (81.1%) were treated with uric acid lowering and the mean duration of the disease was 6.9 years. When the patients were divided into two groups according to the presence or absence of Tophi, the average age (60.2 ± 11.6 vs 53.4 ± 13.2 , $p=0.023$) of the patients with Tophi was significantly higher, duration of disease (13.0 ± 6.5 vs 5.4 ± 5.4 , $p=0.000$) was longer and the AI (28.7 ± 7.8 vs 20.7 ± 10.4 , $p=0.001$) was higher. When univariate regression analysis was performed, tophi was able to predict high AI ($b = 7.99$, 95% CI 3.50-12.49, $p=0.001$). When multivariate regression analysis was performed to exclude the effects of other variables (DM, HTN, hyperlipidemia, age, BMI, total cholesterol, creatinine), tophi was a predictor of high AI ($b = 6.10$, 95% CI 0.43-11.79, $p=0.035$)

Conclusion: This study suggests that the presence of tophi is an independent predictor of increased arterial stiffness in patients with gout and hyperuricemia.

Disclosure: W. Jeong, None; J. Kim, None; J. H. Choi, None; B. Ghang, None.

Abstract Number: 1272

Quality of Gout Management in a Rheumatology Clinic Using a Provider-Pharmacist Team-Based Approach

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Gout is the most common form of inflammatory arthritis.¹ The cornerstone of treatment for gout is urate-lowering therapy (ULT), which in the U.S. includes the xanthine oxidase inhibitors (XOI) allopurinol or febuxostat. Studies have shown poor adherence to quality indicators in gout, such as monitoring serum uric acid (SUA) and achieving goal SUA.^{1,2}

A clinical pharmacist has been a part of the Froedtert & the Medical College of Wisconsin (F&MCW) Rheumatology Clinic since January 2012. A collaborative practice agreement (CPA) for gout management by the pharmacist, reviewed by the rheumatology providers, has been in place since 12/19/14. Under this CPA, providers have had the opportunity to refer patients with gout to the pharmacist. Providers include referral information, such as preferred medications or how to manage flares, or can defer these decisions to the pharmacist. The CPA, updated yearly, guides therapy in relation to ULT including SUA checks every 3 weeks, flare prophylactic therapy, and treatment of acute flares.

The aim of this study is to measure quality of care in subjects with gout co-managed by rheumatology provider(s) and a pharmacist at the F&MCW Rheumatology Clinic.

Methods: This study is a retrospective analysis assessing patients newly starting ULT between January 1, 2015 and November 30, 2017, and followed 6 months after referral. Adults diagnosed with gout by microscopic evaluation or

provider clinical assessment were included. Patients were excluded if any non-XOI ULT was used, SUA was <6mg/dL at the time of ULT initiation, or the patient had an active cancer diagnosis.

Results: Thirty patients were included in the study. At baseline, mean age was 64 years, mean SUA was 9.4mg/dL, and 80% were crystal-proven. At the time of referral, 26 patients were started on allopurinol at a mean dose of 152mg/day, and 4 patients were started on febuxostat at a mean dose of 60mg/day. Twenty-two patients (73%) achieved SUA <6mg/dL during management (primary outcome), 4 patients were non-responsive to outreaches, and 4 patients are still being managed. On average, patients reached goal SUA <6mg/dL at 10 weeks, and SUA decreased by 61% to 5.7mg/dL. The mean ULT doses at the end of the study period were allopurinol 296mg/day and febuxostat 80mg/day. The percentage of patients that were prescribed flare prophylaxis was 100%. During management, the pharmacist had 154 encounters with patients, compared to 51 with providers.

Conclusion: Seventy-three percent of patients co-managed by rheumatology providers and a pharmacist were able to achieve SUA <6mg/dL, occurring at a mean of 10 weeks, and 100% were prescribed flare prophylaxis. Team-based gout management including a pharmacist may provide a method of achieving goals of therapy while reducing time required of providers.

References:

1. Hughes JC, Wallace JL, Bryant CL, Salvig BE, Fourakre TN, Stone WJ. Monitoring of urate-lowering therapy among US veterans following the 2012 American College of Rheumatology guidelines for management of gout. *Ann Pharmacother* 2017;51(4):301-306.
2. Singh JA, Hodges JS, Asch SM. Opportunities for improving medication use and monitoring in gout. *Ann Rheum Dis* 2009;68:1265-1270.

Disclosure: J. Michaud, None; J. Beatty, None.

Abstract Number: 1273

What Did Patients from the US Think about Their Gout in 2017?

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

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Background/Purpose: The impact of chronic gout and acute flares on daily activities is severely limiting. Yet only 40% of gout patients receive urate-lowering therapy (ULT), usually without titration to guideline targets (Doherty. *Ann Rheum Dis* 2012;71:1765-70; Kuo. *Ann Rheum Dis* 2015;74:661-7). Several barriers have been identified leading to suboptimal care. When patients are fully informed about their disease and involved in management decisions, uptake of ULT is higher and subsequent adherence can be improved (Rees. *Ann Rheum Dis* 2013;72:826-3). The aim of this study was to evaluate patient characteristics and key perceptions of gout in the US.

Methods: A 2017 cross-sectional survey of US adults assessed health conditions, health-related quality of life (HRQoL), and health care resource utilization. Participants aged ≥18 years were recruited using a random stratified sampling framework to ensure demographic composition representative of the US population. Participants who reported having gout completed a series of questions about current treatments, serum urate (sUA) laboratory assessments, disease severity, satisfaction with disease control, acute gout attacks (flares), and their own and physicians' level of concern about their gout. Population level characteristics, treatments, sUA testing, and patient descriptions of burden of gout are summarized using descriptive statistics.

Results: A total of 372 (3.1%) of 12,146 participants reported having gout. Patients' characteristics are presented in the Table. Less than half (42.5%) reported currently taking ULT. Of those on ULT, the majority (90.5%) reported taking allopurinol and, of these, most (83.8%) reported taking 300 mg or less/day. A total of 58.2% of those reported taking anti-inflammatory medication for their flares. Less than half (45.1%) had their sUA tested in the last 12 months and only 36.3% knew their test results. Among the tested, only 38.3% reported an sUA <6 mg/dL. Nearly 30% reported their condition as severe to very severe, and 22.7% reported a low concern. Despite the majority of patients failing to achieve target sUA goals, only 20% reported being dissatisfied with their treatment of gout. Patients described their gout pain as a "one of a kind, indescribable pain"; [like a] "broken or bruised bone"; "excruciating pain"; and "unbearable." A summary and classification of patient quotes illustrates the extreme burden experienced by patients with gout.

Table1: Patient Characteristics	
Patient characteristics	With gout
Male, %	75.0
White, %	82.4
Hispanic origin, %	3.1
Married, %	51.4
Age, mean	58.9
Income, median, \$	53,448
Income, mean, \$	65,989
Education, %	
High school or less	22.7
More than high school	77.3
Currently smoke, %	19.3
On a diet, ^a %	19.5
Body mass index, mean	32.1
Obesity, %	56.8
Exercise (including walking), %	
Less than 3 times per week	39.7
3 times or more per week	60.3
Exercise (excluding walking), %	
Less than 3 times per week	65.3
3 times or more per week	34.7
Depression, PHQ-9, %	
No or minimal depression	61.2
Mild to moderate	28.6
Severe depression	10.2
Anxiety, GAD-7, %	
No or minimal	69.0
Mild to moderate	24.5
Severe anxiety	6.4
Health-related quality of life (HRQOL) measures	
Physical Health Composite Score (PCS), ^b mean	41.1
Mental Health Composite Score (MCS), ^b mean	49.4
Health Utility (6D), ^c mean	0.7
^a Refers to any special diet, not specifically a gout-related diet	
^b Norm based scoring where 50=population average score	
^c Utility value derived from the VR-12, captures overall health status where a score of 0 is death and 1 is perfect health.	

Conclusion: In 2017 less than half of the gout patients from the US were being treated with ULT and the majority fell short of treatment goals, despite gout being described as one of the most debilitating painful conditions ever experienced. Improving the care for patients with gout continues to be clear unmet need that can potentially reduce the severity of this disease, thus significantly impact HRQoL.

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Abstract Number: 1274

Atmospheric Temperature and the Incidence of Gout Flare: Data from the Korea Meteorological Association and National Health Insurance Service

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Session Information**Session Date:** Monday, October 22, 2018**Session Title:** Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I**Session Type:** ACR Poster Session B**Session Time:** 9:00AM-11:00AM

Background/Purpose: Gout management is mainly focused on life style modification and proper medications. Of note, seasonal variation of gout flare was also implemented to be a factor to consider. There is yet no study in which investigated the association of climate and gout flare by utilizing big data.

Methods: The operational definition of gout flare was developed and pre-tested in a single institute (BRMC). Patient data (2008-2014) were obtained from the National Health Insurance Service. Ambient and dew point temperature during the same period were acquired from the weather station located in Seoul. Using generalized additive and piecewise linear regression models, we estimated the number of gout flare admissions associated with daily apparent temperature after adjusting relevant covariates. We also compared this model in patients admitted for stroke or acute myocardial infarction.

Results: A total of 71,687 episodes were identified as gout flares in Seoul. The mean daily and dew point temperature were 12.6 °C, 4.4 °C, respectively, and the mean daily apparent temperature was 12.5 °C. Increase in gout flare admissions displayed a nonlinear relationship with the apparent temperature within 2 days of admission, at both low and high ends. Especially, the number of admissions increased by 7.77% (95% confidence interval 6.35, 9.22) per 1 °C decrease in apparent temperature below the -3 °C flexion point. This distinctive nonlinear pattern was not observed in admissions due to hemorrhagic, ischemic stroke or acute myocardial infarction.

Conclusion: Our data indicate that monitoring sudden changes of daily apparent temperature alongside abiding treatment guidelines could add additional benefit to gout patients in their daily lives.

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Abstract Number: 1275

Dual-Energy CT for the Diagnosis of Gout: A Prospective Study in Patients with No Prior History of Gout

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Session Information**Session Date:** Monday, October 22, 2018**Session Title:** Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I**Session Type:** ACR Poster Session B**Session Time:** 9:00AM-11:00AM

Background/Purpose: Gout is associated with joint damage, and increased cardiovascular morbidity, so to diagnose and treat gout early is important. However, joint aspiration and microscopy not always yield the diagnosis. The latest diagnostic technique to visualize monosodium uric acid (MSU) depositions is Dual Energy CT scan (DECT).¹ We purpose to assess the sensitivity and specificity of DECT for diagnosing gout in patients with unclassified arthritis.

Methods: We included 87 consecutive patients with acute mono or oligo arthritis without prior gout diagnosis who presented to the outpatient clinic of the Department of Rheumatology of Meander Medical Centre, Amersfoort, the Netherlands, ClinicalTrials.gov number NCT03038386. Seven patients dropped out, see Figure. Patients underwent aspiration of the arthritic joint for the detection of MSU crystals (see Table) and a DECT scan of hands and wrists, knees, ankles and feet. The synovial fluid result for MSU crystals was the gold standard for gout.

Results: For demographic and clinical characteristics of the patients see Table, and for study data and outcomes see Figure. The sensitivity and specificity of DECT for gout deposition in the index joint were 0.58 (95% CI 0.43-0.72) and 0.75 (95% CI 0.57-0.89), respectively, with an area under the ROC curve of 0.67 (95% CI 0.55-0.79), $p < 0.05$. When

classifying DECT as positive if deposition was observed at the index joint and/or in other locations, sensitivity was higher: 0.77 (95% CI 0.63-0.88), but specificity lower: 0.69 (95% CI 0.48-0.86).



Conclusion: These preliminary data show the diagnostic value of DECT in patients with acute unclassified mono or oligoarthritis. Probably, DECT sensitivity is underestimated by false negative MSU results due to a sampling error, because of incorrect aspiration, or extra-articular locations of the gout, e.g. around tendons.

Table. The demographic and clinical characteristics of the patients (n=80) included in the study

	Patients MSU positive (n=48)	Patients MSU negative (n=32)
Age in years, mean (SD),	59.0 (15.6)	63.1 (13.0)
Sex, N (%)		
Male	41 (85.4)	25 (78.1)
Female	7 (14.6)	7 (21.9)
Arthritic joint aspirated (N, %)		
MTP1	29 (60.4)	6 (18.8)
Other joints	19 (39.6)	26 (81.2)
Period between 1 th arthritis attack and baseline visit in months, median (IQR)*	12 (56)	6 (35.8)
Serum uric acid (µmol/L) mean (SD)	465.72 (120.65)	403.50 (109.71)

* according to patient

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Abstract Number: 1276

Effect of Colchicine on Diabetes Incidence Among Gout Patients in a Veterans' Affairs Population

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

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

Background/Purpose: Previous studies suggest that patients with gout are at increased risk for developing diabetes.¹ One possible explanation for this increased risk is the activation of pathologic pathways common to both diabetes and gout, including IL-1b.² Among its many mechanisms, colchicine has been found to suppress activation of the NLRP3 inflammasome, inhibiting activation of IL-1b. Colchicine may also activate AMPK, a down regulator of inflammation and gluconeogenesis.³ In the present study, we investigated whether chronic colchicine use reduces diabetes incidence among patients with gout.

Methods: We reviewed the Computerized Patient Record System (CPRS) of the New York Harbor Veterans' Affairs Healthcare System to assess the incidence of diabetes between 2000 and 2015 among 140 randomly selected patients with gout who had taken colchicine daily for some or all of the study period. We compared the diabetes incidence among these patients with 115 randomly selected patients with gout who did not take colchicine during the same time period. At study entry, all subjects met a modified version of 1977 ARA gout classification criteria and had no diabetes diagnosis. Patients were excluded if their duration of colchicine use was <60 contiguous days. Incident diabetes was defined as a new hemoglobin A1c value of $\geq 6.5\%$ during the study period.

Results: Among gout patients who had taken colchicine, we observed no difference in diabetes incidence compared to patients not taking colchicine (17.1% versus 17.4%, OR = 0.983, $p = 1.0$). When patients were analyzed by duration of colchicine use, there was no significant difference in diabetes incidence between patients in the longest (36.5 to 114 months) compared to the shortest tertile (2.3 to 14 months) (27.3% versus 9.1%, $p = 0.24$) of colchicine exposure. Among patients in the colchicine group who experienced incident diabetes during the study period ($n = 24$), 50% ($n = 12$) were actively taking colchicine at the time of their diagnosis and 50% ($n = 12$) had discontinued colchicine use prior to their diabetes diagnosis.

Conclusion: We found no significant difference in the 15-year diabetes incidence between patients taking colchicine and those not taking colchicine, suggesting that colchicine is not beneficial to prevent incident diabetes. Larger and prospective studies will be needed to confirm this observation.

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Abstract Number: 1277

A Prospective Study Examining the Prevalence of CT Erosions in the Feet and Ankles of Patients with Gout Treated with Allopurinol

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Gout is characterized by episodes of acute arthritis that are self-limiting. However, patients with gout can also develop tophi, bone erosions, joint deformity and dysfunction in advanced disease. Previous studies based on relatively small sample sizes or exclusively tophaceous gout cases suggested that the prevalence of erosions in gout could be substantial. However, the precise prevalence estimate, particularly among non-tophaceous gout cases remains unclear. The aim of this study was to determine the prevalence of erosions in patients with gout on urate-lowering therapy using dual-energy CT (DECT).

Methods: DECT of the bilateral feet and ankles were prospectively obtained on 153 patients who fulfilled the 1977 ARA gout classification criteria and were on allopurinol ≥ 300 mg daily for at least 3 months. Enrollment was conducted in a monitored fashion to ensure the population included approximately 25% of patients with palpable tophi and approximately 50% of patients with serum uric acid (SUA) < 6 mg/dL. The presence of erosions was evaluated at 12 anatomic sites (1st-5th interphalangeal (IP) joints, 1st-5th MTP joints, tarsals, and Achilles tendon calcaneal insertion) in the feet and ankles by 2 radiologists familiar with interpreting DECT.

Results: Our analysis included 153 patients (92% male) with gout (mean disease duration, 15 years) on allopurinol (mean duration of therapy, 5 years). Mean allopurinol dose was 333mg daily (range 300-750mg daily). Erosions in the feet and ankle were present in 72% of patients. Patients with tophi had significantly higher prevalence of erosions than those without tophi (83% vs 67% respectively, $p = 0.04$). The three sites most commonly affected by erosions overall were the first MTP joint, tarsals, and first IP joint (68%, 38%, and 13%, respectively) (Table). The pattern of erosion involvement in the feet/ankles did not differ significantly based on tophus status.

Conclusion: Among patients with gout on allopurinol, erosions in the feet and ankles are common, with 72% of all subjects demonstrating at least one erosion. The most frequent sites of erosions are the first MTP joint and themed-foot areas, common locations of gouty arthritis. While patients with clinical tophi have a higher prevalence of erosions, 67% of patients without tophi had at least one erosion.

Table. Prevalence of erosions on DECT of feet/ankles.

Site	All Patients N=153 Erosions	Clinical Tophi N=48 Erosions	No Tophi N=105 Erosions
Any site	72%	83%	67%
MTP 1	68%	75%	65%
Tarsals	38%	46%	34%
IP 1	13%	17%	12%
MTP 5	12%	23%	7%
MTP 2	9%	13%	7%
MTP 4	3%	8%	≤1%
IP 2	3%	4%	3%
MTP 3	3%	6%	2%
Achilles	≤ 1%	2%	≤1%
IP 4	2%	2%	2%
IP 3	≤ 1%	0%	≤1%
IP 5	≤ 1%	2%	≤1%

MTP = metatarsophalangeal joint; IP = interphalangeal joint

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Abstract Number: 1278

Evaluating a Causal Role of Mitochondrial Variation in the Development of Gout

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Mitochondria execute roles in diverse cellular pathways. As a danger signal, damaged mitochondria can induce inflammation in response to stress through NLRP3 inflammasome activation, which is central to gout. We recently reported association of reduced mitochondrial DNA (mtDNA) copy number with prevalent gout in New Zealand Māori and Pacific (Polynesian) people¹. However the cause-effect relationship is unknown. This could be evaluated by testing nuclear genetic variants that associate with mtDNA copy number for association with gout. Here the aims were: 1) Perform a genome wide association study (GWAS) to identify nuclear variants associated with mtDNA copy number; 2) test these identified variants for association with gout.

Methods: The mtDNA copy number GWAS comprised 1,340 Eastern Polynesian, 816 Western Polynesian and 4,579 European individuals (New Zealand, Europe) genotyped on the Illumina CoreExome v24 array. The median of the

absolute differences in X and Y probe intensities was used as a measure of mtDNA copy number. This measure was associated with genome-wide genotype calls, adjusted by age, sex and by principal component vectors calculated from the probe intensities of an additional 10,000 randomly selected autosomal SNPs. Nuclear variants identified as being associated with mtDNA copy number were then tested for association with gout, adjusting by age, sex and the first 10 principle component vectors generated from genotype calls for 3,000 independent autosomal SNPs.

Results: As previously reported mtDNA copy number negatively associated with gout in the Polynesian sample sets ($\beta=-2.81$, $P=2.9 \times 10^{-6}$ for East Polynesian and $\beta=-8.11$, $P=3.6 \times 10^{-16}$ for West Polynesian). However there was no evidence for association in the European sample set ($\beta=-0.16$, $P=0.66$). The nuclear variant *MUC17 rs78010183* T-allele associated with increased mitochondrial CN at an experiment-wide level of significant ($P<1 \times 10^{-7}$) in people of Eastern Polynesian ancestry ($\beta=0.07$, $P=4.7 \times 10^{-13}$). There were no other nuclear variants significantly associated with mtDNA copy number in the Western Polynesian or European sample sets. Association of the *MUC17 rs78010183* variant with increased mtDNA copy number replicated in Europeans, with the T-allele increasing copy number ($\beta=0.06$, $P=1 \times 10^{-4}$) but not in Western Polynesian ($\beta=0.09$, $P=0.15$). Testing for association with gout, the *rs78010183* T-allele was not significantly associated in Eastern Polynesian (OR=1.38, $P=0.17$) but was associated in European (OR=15.88, $P=1 \times 10^{-3}$) sample sets, with the mtDNA copy number-increasing allele associated with increased risk of gout.

Conclusion: Genetic variants associated with mtDNA copy number also associate with gout, providing evidence for a direct role of either mtDNA copy number, or another related factor such as mitochondrial dysfunction, in gout. However, the nuclear variant *rs78010183* supports a direct relation of increased mtDNA copy number with gout, conflicting with our previous observational report of association of reduced mtDNA copy number with gout.

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Abstract Number: 1279

Relative Insufficiency of Renal Uric Acid Excretion in Gout Patients with Obesity Leads to High Serum and Glomerular Filtration Load of Uric Acid

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

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Session Time: 9:00AM-11:00AM

Background/Purpose: Gout is usually accompanied by metabolic diseases including obesity, hypertension, diabetes, and dyslipidemia. Obesity has been confirmed as a risk factor for gout. This study aims to explore the clinical and renal uric acid excretion features in gout patients with obesity.

Methods: Primary gout patients hospitalized from 2013 to 2017 were included. The diagnosis of gout fulfilled the 1977 ACR gout classification criteria or the 2015 ACR/EULAR classification criteria. The patients with estimated glomerular filtration rate (eGFR) $<30 \text{ ml/min/1.73m}^2$ and secondary gout were excluded. Baseline characteristics, fasting blood biochemical indexes, incidence of comorbid diseases were collected. The 24h urinary uric acid (UUA) and urinary creatinine excretion (UCr) were evaluated on unrestricted diet, which were used for the calculation of renal uric acid excretion variables. Obesity was defined as body mass index (BMI) $\geq 28 \text{ kg/m}^2$.

Results: ① Among 212 recruited patients, 89.2% were male, the median age of onset was 43 (33, 58) years old and median serum uric acid (sUA) was 545 (454, 663) $\mu\text{mol/L}$, 40 patients (18.9%) had obesity. ② Compared with non-obese group (n=172), the obese group presented a younger onset age [36 (26, 48) years vs. 46 (36, 59) years], significantly higher

Clinical characteristic	All patients (n=212)	Obese group (n=40)	Non-obese group (n=172)	P
Male, n(%)	189(89.2)	37(92.5)	152(88.4)	0.480
Onset age, years	43(33.58)	36(26.46)	46(36.59)	0.002
Duration of gout, years	7.0(3.4,10.9)	6.0(3.0,10.0)	7.5(3.0,12.0)	0.102
Count of affecting joints	6(4.9)	6(4.10)	6(4.39)	0.905
Tophi, n (%)	76(34.9)	15(32.5)	61(35.5)	0.723
Urolithiasis, n (%)	80(37.7)	19(47.5)	61(35.5)	0.205
Chronic kidney disease, n (%)	72(34.0)	11(27.5)	61(35.5)	0.362
Serum uric acid, $\mu\text{mol/L}$	545(434,663)	593(522,697)	531(416,660)	0.013
Serum creatinine, $\mu\text{mol/L}$	103(90,126)	103(86,123)	104(90,128)	0.421
eGFR, ml/min/1.73m^2	70(35.86)	75(58.93)	69(52.85)	0.111
Hypertension, n (%)	95(43.9)	18(45.0)	77(43.6)	1.000
Diabetes mellitus, n (%)	87(41.0)	14(35.0)	73(42.4)	0.476
Hypercholesterolemia, n (%)	46(21.7)	14(35.0)	32(18.6)	0.032
High low-density lipoprotein cholesterol, n (%)	48(22.7)	15(37.5)	33(18.0)	0.010
Low high-density lipoprotein cholesterol, n (%)	101(48.6)	23(62.5)	78(45.3)	0.055
Hypertriglyceridemia, n (%)	60(28.9)	10(25.0)	50(27.4)	0.269
Metabolic syndrome	60(28.3)	18(45.0)	42(24.4)	0.012

Renal uric acid excretion characteristics	All patients (n=212)	Obese group (n=40)	Non-obese group (n=172)	P
24h urine volume, L	1.8(1.3,2.2)	1.7(1.4,2.2)	1.8(1.2,2.2)	0.279
24h UUA, $\mu\text{mol/1.73m}^2$	2523(1879,3427)	2993(2138,4055)	2041(1840,3278)	0.022
24h UICr, $\mu\text{mol/1.73m}^2$	7.8(5.9,9.9)	9.7(6.4,12.7)	7.5(5.7,9.7)	0.065
Uric acid clearance, ml/min/1.73m^2	1.29(0.85,1.72)	1.36(2.49,4.63)	1.26(2.18,4.87)	0.790
Creatinine clearance rate, ml/min/1.73m^2	52(38,69)	60(49,88)	50(34,68)	0.005
Fractional excretion of uric acid, %	6.52(4.73,8.89)	1.53(3.90,7.39)	6.75(5.00,9.48)	0.007
Glomerular uric acid filtered load, mg/min	4.43(3.18,6.27)	5.20(4.08,7.14)	4.12(3.09,5.85)	0.084
UUA/UICr	0.33(0.26,0.42)	0.54(0.23,0.43)	0.32(0.26,0.41)	0.552

level of sUA [593 (522,697) $\mu\text{mol/L}$ vs. 531 (416,660) $\mu\text{mol/L}$], higher incidence of hypercholesterolemia (35.0% vs. 18.6%), high low-density lipoproteinemia (37.5% vs. 18.0%), and metabolic syndrome (45.0% vs. 24.4%, all $P<0.05$). There were no significant difference between two groups in gender, duration of gout, count of affecting joints, levels of serum creatinine and eGFR, and incidence of tophi, urolithiasis, chronic kidney disease, hypertension, diabetes mellitus, low high-density lipoprotein cholesterol and hypertriglyceridemia (all $P>0.05$, Table 1). ③ The glomerular uric acid filtered load [5.20 (4.08, 7.14) mg/min vs 4.12 (3.09, 5.85) mg/min] was significantly higher in the obese group. Although the 24h UUA excretion was significantly higher [2993 (2138, 4055) μmol vs. 2041 (1840, 3278) μmol], the fractional excretion of uric acid in the obese group was significantly lower [5.53 (3.90, 7.39) % vs. 6.75 (5.00, 9.48)%, Table 2].

Conclusion: High uric acid load of serum and glomerular filtration in gout patients with obesity may due to the relative insufficiency of renal uric acid excretion.

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Abstract Number: 1280

Higher Body Fat Percentage in Non-Obese Late-Onset Gout Patients

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Session Information

Session Date: Monday, October 22, 2018

Background/Purpose: There is a trend of younger gout onset related to higher obesity prevalence. BMI is limited to discriminate between fat and lean mass. Body composition (BC) analysis is an alternative tool to assess metabolic status. We aimed to investigate the characteristics of BC in early and late onset gout patients.

Methods: Consecutive gout patients who fulfilled the 2016 ACR/EULAR classification criteria were recruited between June 2017 and May 2018. BC was assessed by bioelectric impedance analysis. General obesity was classified by BMI ≥ 28 kg/m². Central obesity was defined as a waist-hip ratio (WHR) above 0.90 for males and above 0.85 for females. The patients with gout onset before age 30 years were defined as early-onset group while the others were defined as late-onset group.

Results: Among 230 gout patients recruited, mean age was 42.3 with standard deviation 22 years. Mean serum uric acid (sUA) was 9.2 with standard deviation 2.1mg/dl and 40 (17.4%) patients presented tophi. The prevalence of general obesity and central obesity was 23.4% and 64.8%, respectively. There were 91 (39.5%) patients in early-onset group. Late-onset group (n=149) showed lower prevalence of general obesity than early-onset group [25 (16.7%) vs. 29 (31.8%), P=0.017] but higher prevalence of central obesity [99 (71.2%) vs. 50 (54.9%), P=0.016]. Among obese outpatients, late-onset group showed lower estimated glomerular filtration rate (eGFR), higher prevalence of hypertension and diabetes mellitus, WHR without significant difference in other BC indicators compared with early-onset group (Table 1). Among non-obese gout patients, late-onset group presented significantly lower level of sUA and eGFR, higher prevalence of hypertension and metabolic syndrome compared with early-onset group (P<0.05, Table 1). Non-obese late-onset gout patients exhibited higher WHR, central obesity, total fat percentage and trunk fat percentage (P<0.05, Table 1) although there were no significant difference of BMI and prevalence of overweight between the two groups.

Conclusion: There were more BMI defined obese patients in early-onset gout patients but non-obese late-onset gout patients showed more central obesity and fat percentage without difference in BMI compared with on-obese early-onset gout patients.

Table 1 Clinical characteristics and body composition of gout patients

Characteristics	All patients (n=230)	Non-obesity			Obesity		
		Early-onset group(n=62)	Late-onset group (n=114)	P	Early-onset group(n=29)	Late-onset group (n=25)	P
Male, n(%)	218 (94.8)	61 (98.4)	105 (92.1)	0.101	29 (100)	23 (92.0)	0.210
Age, years	42.3±22.1	27.9±6.8	52.6±25.4	<0.001	28.3±6.5	48.0±11.9	0.018
Age of onset, years	37.7±22.0	23.4±5.3	47.9±25.6	<0.001	23.2±4.4	43.1±10.7	0.129
Family history, n (%)	82 (35.7)	24 (38.7)	34 (29.8)	0.244	13 (44.8)	11 (44.0)	1.0
Tophi, n (%)	40 (17.4)	11 (17.7)	20 (17.5)	1.000	4 (13.8)	5 (20.0)	0.718
sUA, mg/dl	9.2±2.1	10.0±2.0	8.7±2.0	<0.001	9.6±1.7	9.0±1.8	0.241
eGFR, ml/min ^{1.73} /1.73m ²	84.0±18.7	90.3±14.2	78.3±18.0	<0.001	94.4±19.2	81.4±21.4	0.022
Hypertension, n (%)	21 (9.1)	8 (12.9)	44 (38.6)	<0.001	7 (24.1)	14 (56.0)	0.023
Diabetes mellitus, n (%)	73 (31.7)	1 (1.6)	16 (14.0)	0.480	0 (0)	5 (20.0)	0.017
Dyslipidemia, n (%)	27 (11.7)	32 (51.6)	72 (63.2)	0.151	24 (82.8)	16 (64.0)	0.134
Metabolic syndrome, n (%)	144 (62.6)	11 (17.7)	48 (42.1)	0.001	19 (65.5)	19 (76.0)	0.590
Body weight, kg	72.5±12.0	67.8±8.7	67.7±7.2	0.906	91.2±11.1	85.3±7.6	0.032
Body height, cm	168.8±6.8	169.9±6.0	167.4±6.9	0.018	172.7±6.3	167.6±6.9	0.008
BMI, kg/m ²	25.4±3.4	23.5±2.8	24.1±2.1	0.129	30.5±2.2	30.4±1.8	0.824
Overweight, n (%)	54 (23.5)	29 (46.8)	61 (53.5)	0.432	29 (100)	25 (100)	1.0
Waist circumference, cm	90.5±9.8	84.3±8.4	88.2±6.7	<0.001	102.1±7.2	102.6±5.6	0.750
Hip circumference, cm	98.3±7.2	95.4±6.6	95.8±4.5	0.610	108.0±5.9	105.5±4.7	0.096
WHR	0.92±0.07	0.88±0.08	0.92±0.06	0.001	0.94±0.04	0.97±0.05	0.040
Central obesity, n (%)	149 (64.8)	24 (38.7)	61 (53.5)	0.001	26 (89.7)	25 (100)	0.240
Total fat mass, kg	19.2±7.1	15.6±5.5	16.6±4.0	0.213	29.5±5.6	28.0±4.3	0.266
Total fat percentage, %	25.9±6.7	22.6±6.3	24.5±5.6	0.038	32.4±4.0	32.9±4.9	0.707
Trunk fat mass, kg	10.2±5.2	8.7±7.6	8.6±2.2	0.851	15.5±2.7	14.8±2.0	0.323
Trunk fat percentage, %	27.3±7.3	23.5±7.2	25.8±6.0	0.026	34.6±3.7	34.8±4.6	0.826
Fat free mass, kg	53.3±7.5	52.2±5.9	51.0±6.3	0.234	61.3±7.8	57.4±7.1	0.062
Total muscle mass, kg	29.8±4.5	29.2±3.6	28.4±3.9	0.216	34.7±4.6	32.4±4.4	0.069
Trunk muscle mass, kg	24.1±3.2	21.4±3.8	23.1±3.8	0.493	27.5±2.9	26.3±3.1	0.151

sUA: serum uric acid; eGFR: estimated glomerular filtration rate; WHR: waist-hip ratio

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Abstract Number: 1281

Association of HFE Genotypes with Clinical Severity in Patients with Definite Calcium Pyrophosphate Arthritis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

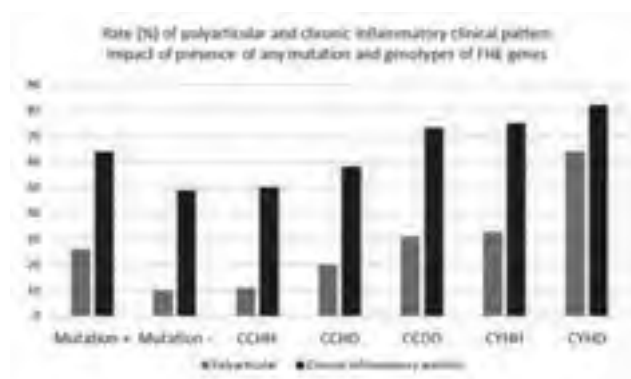
Session Time: 9:00AM-11:00AM

Background/Purpose: Several metabolic disturbances that reduce the activity of pyrophosphatases have been associated with development of pyrophosphate arthritis (PPA), but there is scarce data on their influence of clinical manifestations, as such disease-specific variables are not recorded in most available databases. To evaluate factors associated to severity of clinical joint involvement in patients with definite PPA.

Methods: Transversal study with prospective recruitment of cases (patients con a PPA diagnosis confirmed by microscopy plus presence fox-ray chondrocalcinosis in at least one joint) and controls (patients with synovial effusion shown to have no PP crystals and no chondrocalcinosis in hands and knee X-rays, paired by age and gender). Patients with hemochromatosis or primary hyperparathyroidism were not included. [[Population general variables were included along with plausible metabolic variables (Ca, P, Mg, iPTH, iron saturation [satFe%], ferritin, diuretics and type of diuretic, and HFE genotype), and joint involvement distribution (mono-oligo-polyarticular) and clinical manifestations (acute PPA [A-PPA] and chronic inflammatory PPA [CI-PPA]), as in EULAR recommendations.

Results: 340 patients and 316 controls were recruited, 53% were men, age at inclusion was 67±10 yr (IQ range 62-75), time from onset of symptoms 5.2±5.3 yr (IQ range 1-8). Regarding cases, A-PPA was present in 147(43.2%), CI-PPA in 193 (56.8%), monoarticular joint distribution in 102 (30.0%), oligoarticular in 176 (51.8%), and polyarticular in 62 (18.2%). Patients showed higher serum ferritin levels and lower Mg levels than controls (253mcg/dl and 2.00 mg/dl vs. 204 mcg/dl and 2.08 mg/dl, respectively), along with higher rate of any HFE gene mutations (Odds 2.30, 95% CI 1.66-3.20). Genotypes including heterozygotic mutations for C282Y allele (CY), homozygotic of H63D allele (DD), and double heterozygotic for C282Y and H63D (CYHD) were statistically associated with higher frequency of polyarticular involvement and with CI-PPA (Figure). Nonetheless, only CY genotypes were associated with the most severe phenotypes when time from onset of symptoms was considered in analysis, also showing the highest sat Fe%.

Conclusion: Patients with definite PPA show differences in magnesium and iron parameters compared to controls, and may contribute, along with other factors, to development of PPA. Nevertheless, only presence of some HFE genotypes, especially CY, were associated with more severe pattern of clinical involvement.



Disclosure: F. Perez-Ruiz, Asociacion de reumatologos de cruces, 2,Asociacion de reumatologos de cruces, 2; J. Atxotegi, None.

Abstract Number: 1282

Influence of Renal Function on the Velocity of Tophus Resolution and Achievement of Disease Remission in Patients with Chronic Refractory Gout Treated with Pegloticase

Brian F. Mandell¹, Naomi Schlesinger², N. Lawrence Edwards³, Anthony Yeo⁴ and Peter E. Lipsky⁵, ¹Rheumatology, Cleveland Clinic, Cleveland, OH, ²Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, ³Rheumatology, University of Florida Health Science Center, Gainesville, FL, ⁴Horizon Pharma, Lake Forest, IL, ⁵AMPEL BioSolutions, Charlottesville, VA

Session Information

Session Date: Monday, October 22, 2018

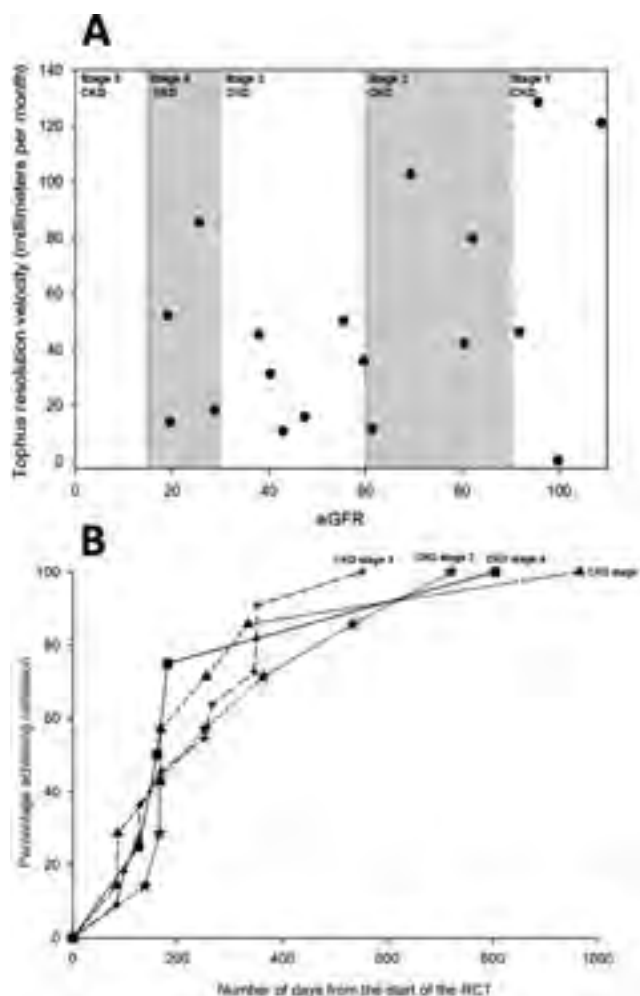
Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

INFLUENCE OF RENAL FUNCTION ON THE VELOCITY OF TOPHUS RESOLUTION AND ACHIEVEMENT OF DISEASE REMISSION IN PATIENTS WITH CHRONIC REFRACTORY GOUT TREATED WITH PEGLOTICASE

Background/Purpose: Impaired kidney function is a recognized comorbidity of gout,¹ but it is not known whether chronic kidney disease (CKD) alters the velocity of resolution of tophi or time required to achieve disease remission in response to pegloticase therapy in subjects with chronic refractory gout.



Methods: This analysis used results from two 6-month randomized controlled trials of pegloticase² in patients with chronic refractory gout to address these issues. Velocity of tophus resolution was determined in 18 subjects with chronic refractory gout and visible tophi who responded to pegloticase (8 mg every 2 weeks) with sustained serum urate reductions (<6 mg/dL) over 6 months. Achievement of remission³ was evaluated in all 34 such subjects who had persistent lowering of serum urate in response to biweekly pegloticase. eGFR was determined at baseline and after 3 and 6 months of treatment. Tophi were photographed and measured at baseline, 3, 4, 5, and 6 months.

Results: At baseline, the mean area of photographed tophi was 585.8 mm². The velocity of tophus resolution for all subjects was 60.1 mm² per month. There was no significant relationship between baseline eGFR and velocity of tophus resolution (P=0.5) (Figure 1A). In addition, there were no significant differences in the velocity of tophus resolution for patients with Stage 1 chronic kidney disease (CKD) vs Stage 2 CKD (P=0.7), Stage 3 CKD (P=0.9), or Stage 4 CKD (P=0.7). The relationship between baseline CKD severity and time to achieve remission is shown in Figure 1B. Here, 29/34 (85.3%) subjects with persistent urate lowering in response to pegloticase achieved remission. There were no significant differences in the achievement of remission in those with various stages of CKD determined by eGFR. Notably, there was no significant change in eGFR in response to pegloticase therapy through the 6-month duration of the study.

Conclusion: The results from this analysis indicate that renal impairment does not compromise the ability of pegloticase to resolve tophi rapidly in patients who respond with sustained reductions in serum urate. They also suggest that severity of renal disease does not influence achievement of remission in pegloticase-treated subjects with chronic refractory gout who have persistent urate lowering.

References: 1. Nyberg F, et al. *Adv Ther.* 2016;33:1180.
2. Sundry JS, et al. *JAMA.* 2011;306:711.
3. de Lautour H, et al. *Arthritis Care Res (Hoboken).* 2016;68:667.

Figure 1. Relationship between baseline eGFR and velocity of tophus reduction (A) and times to remission in the subjects in the different CKD groups (B).

Disclosure: B. F. Mandell, Horizon Pharma, 2, 5; N. Schlesinger, Astra Zeneca, 2, Novartis, Horizon, 5; N. L. Edwards, Horizon Pharma, Ironwood Pharmaceuticals, Astra Zeneca, Selecta, 5; A. Yeo, Horizon Pharma, 3; P. E. Lipsky, None.

Abstract Number: 1283

Calcium Pyrophosphate Crystal Deposition in a Cohort of 48 Patients with Gitelman Syndrome

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Gitelman syndrome (GS) is a rare recessively inherited tubulopathy, caused by inactive mutations in *SLC12A3* gene encoding the thiazide-sensitive-sodium-chloride transporter. It is characterized by an hypokaliemic metabolic alkalosis with hypomagnesemia and hypocalciuria. Calcium pyrophosphate (CPP) crystals deposition is frequently described in cases-report GS but its prevalence and clinical phenotype are unknown.

Aims: to describe clinical, biological and radiological features of CPP in a cohort of patients with genetically proven GS.

Methods: All patients (pts) with genetically proven GS in the French national reference center of rare diseases were proposed to have a consultation with a rheumatologic senior. Demographic data, history of joint pain and flare and biology disorders were recorded. Other causes of CPP disease were systematically ruled out. CPP crystal deposition was assessed by X-Ray (all peripheral joints and cervical spine) and ultrasonography (US) (wrists, knees, ankles and symptomatic joints). Patients with history of cervical pain underwent computed tomography (CT).

Results: Forty-eight GS pts (20 men, mean age 46.6± 12.2 years) have been examined by a rheumatologist. Majority had a mutation on *SLC12A3* gene. Forty pts experienced joint pain, 22 joint flare and 25 cervical pain. X-rays were performed in 40 pts, US in 34 and CT in 21. CPP depositions were observed in 34 (85.0%) pts, 26 (76.5%) and 15 (71.4%) by X-Ray,

US and CT, respectively. They occurred in knees (n=25), wrists (n=19), cervical spine (n=17), shoulders (n=11), feet (n=10) and Achilles' tendon or plantar fascia (n=11). CPP depositions were widespread involving at least 3 joints in 19 (55.9%) pts. In knees, CPP depositions involved meniscus (n=15), hyaline cartilages (n=8) and ligament or joint capsule (n=5). Cervical spine CT demonstrated CPP deposition in vertebral disc (n=12), transverse ligament (n=13), yellow ligament (n=6), vertebral facets (n=3) and temporo-mandibular joint (n=5). Pts with CPP crystal deposition were older (49.8 ± 11.1 vs 34.0 ± 10.0 , $p < 0.01$), more symptomatic and had lower magnesemia at consultation (0.60 ± 0.11 vs 0.75 ± 0.15 mM, $p = 0.029$). CPP crystal deposition remained statistically correlated to serum magnesium level after age-adjustment. It was not associated with potassium level.

Table 1. Patients characteristics depending on the presence of CCP on radiographies

	CCP+ (n=34)	CCP- (n=6)	p value
Male sex, n (%)	14 (41.2)	1 (16.7)	0,381
Age, \pm SD	49.8 ± 11.1	34.0 ± 10.0	$p < 0,01$
SLC12A3 mutation, n (%)			
heterozygous	5 (14.7)	0	0,569
homozygous	23 (67,6)	5 (83.3)	
Clinical features, n (%)			
joint pain	30 (88.2)	3 (50.0)	0,055
joint flare	21 (61.8)	0	$p < 0,01$
cervical pain	20 (58.8)	2 (33.3)	0,381
CCP crystal deposition, n (%)			
shoulder	11 (32.4)		
wrist	19 (55.9)		
symphysis	9 (26.5)		
knee	25 (73.5)		
foot	10 (29.4)		
cervical spine	17 (50)		
≥ 3 sites	19 (55.9)		
Calcemia, \pm SD (mM)	2.4 ± 1.0	2.5 ± 1.4	0,188
Kaliemia at GS diagnosis, \pm SD (mM)	3.2 ± 1.6	3.1 ± 1.7	0,967
Magnesemia, \pm SD (mM)	0.60 ± 0.1	0.75 ± 0.15	0.029

Conclusion: CPP crystal deposition occurred in more than 80% of patients with GS, was widespread and often symptomatic. Most affected sites are wrists, knees and cervical spine. CPP crystal deposition was associated with long-standing GS, older age and low serum magnesium level. Further studies are necessary to understand how GS favors CPP crystal deposition.

Disclosure: E. Chotard, None; A. Blanchard, None; G. Gailly, None; R. Vargas-Poussou, None; H. K. Ea, None.

Abstract Number: 1284

Initial Pegloticase Serum Levels Predict Persistent Responsiveness in Patients with Chronic Refractory Gout

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Pegloticase is a pegylated recombinant mammalian uricase approved for treatment of persons with chronic gout refractory to standard urate lowering therapy¹. Despite an initial profound reduction of serum urate, some patients may lose the urate-lowering effect of pegloticase owing to the development of anti-drug antibodies². The TRIPLE trial was undertaken to determine whether an additional dose of 8 mg of pegloticase 1week after the initial dose and 1 week before the subsequent dose might be sufficient to maintain high serum pegloticase levels and contribute to the development of high-zone tolerance and a more persistent rate lowering effect.

Methods: TRIPLE is a multi-center, open-label trial enrolling subjects with chronic gout whose serum urate was not maintained at ≤ 6 mg/dL. Background urate lowering therapy was discontinued and subjects were treated with 3 weekly

doses of 8 mg pegloticase followed by biweekly administration of 8 mg of pegloticase for a total of 10 doses over 17 weeks. Serum urate was measured immediately before each dose and after the first administration, and continued dosing was only permitted if the serum urate was ≤ 6 mg/dL. Trough serum pegloticase levels were measured before each dose. Standard infusion prophylaxis and gout flare prophylaxis were required. The primary outcome was the maintenance of serum urate at ≤ 6 mg/dL throughout the treatment period.

Results: Results are available for 50 subjects. There were 22 responders (44%), 21 nonresponders (42%) and 7 subjects who dropped out (14%). Responders had significantly higher trough levels of pegloticase than nonresponders 1 week after the initial infusion (Figure) that persisted throughout the trial. Pegloticase levels at 1 week post infusion predicted responsiveness. Fourteen of 19 subjects (73.7%) with trough pegloticase levels >1.22 mg/mL at 1 week were responders to treatment whereas only 6 of 19 patients (31.6%) with trough levels ≤ 1.22 mg/mL at 1 week were responders (Chi-square test with continuity correction, $P=0.023$).

Conclusion: To date, the TRIPLE strategy of adding an additional tolerizing dose of pegloticase between the first and second biweekly administrations showed an overall response rate of 44%. Pegloticase serum levels after the initial dose may predict subsequent persistent responsiveness and provide guidance regarding adjustment/continuation of treatment.

References: 1. Sundy JS, et al. *JAMA*. 2011;306:711.

2. Lipsky PE, et al. *Arth Res Ther*. 2014;16:R60.

Figure.

Disclosure: K. Saag, Ironwood, Astra Zeneca, Horizon, SOBI, Takeda, 2, 5; M. Feinman, None; H. S. B. Baraf, Horizon Pharma, 2, 5, 8; R. Fleischmann, None; A. Kavanaugh, None; P. E. Lipsky, None.

Abstract Number: 1285

Comparison of Urate Burden in Well and Poorly Controlled Gout Patients: A Dual-Energy CT Study

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Session Information

Session Date: Monday, October 22, 2018

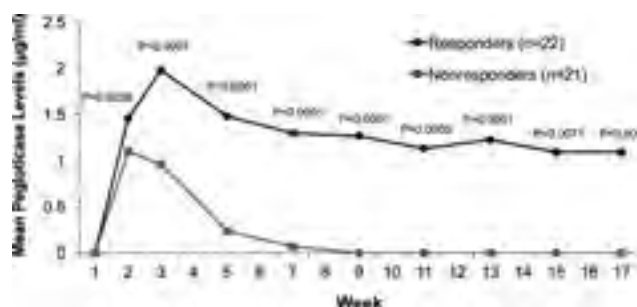
Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Dual-energy computed tomography (DECT) allows sensitive and quantitative detection of monosodium urate (MSU) crystals in patients with gout. Although its usefulness in diagnosing gout is well defined, its role in monitoring changes of MSU depositions after urate lowering therapy (ULT) is unclear. The aim of our study was to investigate the difference in MSU deposition amount and pattern detected by DECT in well and poorly controlled gout patients.

Methods: DECT scans of feet and ankles were performed in 109 gout patients. Sixteen joints of ankles and feet, and achilles tendon insertion sites were evaluated for the presence of MSU deposition. The total volume of MSU deposition was quantified using an automated software program of DECT. Clinical, laboratory, and radiologic features were obtained at the time of DECT evaluation. Patients who maintained serum uric acid (sUA) level < 6.0 mg/dL for more than 6 months prior to DECT evaluation were considered 'well-controlled' and otherwise, 'poorly-controlled'.



Results: Twenty-five (22.9%) well-controlled patients were compared with 84 (77.1%) poorly-controlled. Well-controlled group showed mean sUA of 4.97 ± 0.84 mg/dL while poorly-controlled group showed mean sUA of 8.01 ± 1.78 mg/dL. Well-controlled group had significantly lower mean volume of MSU deposition compared with the poorly-controlled group (0.12 cm^3 vs 0.78 cm^3 , $p=0.001$), and had lower number of MSU deposition (2 vs 4, $p=0.002$). Although volume and number of MSU depositions were significantly decreased, MSU depositions were still detected in the well-controlled group. In well-controlled group, MSU depositions were less frequently detected in MTP and ankle joints compared with the poorly-controlled group, whereas frequency of MSU deposition was not significantly different in the Chopart joint and Achilles tendon sites.

Conclusion: Well-controlled gout patients showed significantly reduced urate burden. However, since MSU deposition does not completely resolve even in well-controlled patients, continuous ULT is recommended for optimal management of the gout patients.

Disclosure: M. K. Chung, None; H. Hyun, None; J. Y. Hwang, None; J. Lee, None.

Abstract Number: 1286

Pretreatment and Coadministration with Methotrexate Improved Durability of Pegloticase (Krystexxa) Response: A Prospective, Proof-of-Concept, Case Series

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Pegloticase is a recombinant DNA-produced porcine-like uricase enzyme which metabolizes relatively insoluble urate to highly soluble allantoin. It is used in the treatment of refractory gout which has failed maximal medical management, typically with xanthine oxidase inhibitors (XOI). Studies have shown a complete responder rate of 42% when defined as repeat serum uric acid levels <6.0 mg/dL for $>80\%$ of the time during months 3 and 6 of treatment. Therefore 58% of patients failed to maintain repeat serum uric acid levels <6.0 mg/dL during this time period. The driving mechanism of this failure has been proposed to be driven by neutralizing antibodies. As is done in treatment of other rheumatologic diseases, coadministration of other medications could potentially temper the development of these neutralizing antibodies. The aim of the current study was to identify and quantify the improvement (as defined by maintenance of response) in patients treated with pegloticase for refractory gouty arthropathy.

Methods: In this prospective, proof-of-concept, case series, 8 patients with refractory tophaceous gouty arthropathy being started on treatment with pegloticase 8mg every 2 weeks were identified. Methotrexate 15mg orally once weekly and folic acid 1mg orally once daily was started one month prior to the initial administration of pegloticase and continued throughout the pegloticase treatment. Serum uric acid was measured every two weeks, prior to each subsequent infusion. At the completion of pegloticase treatment (or end of the observation period, June 1, 2018) the number and percentage of patients able to maintain a serum uric acid at goal <6.0 mg/dL was recorded. The primary objective was to evaluate the response rates in patients coadministered methotrexate vs. published response rates (known to be 42%) in those on pegloticase monotherapy between 3 and 6 months of treatment.

Results: Eight patients were identified, from 3 separate infusion centers. Seventy-three total pegloticase infusions were performed within the observation period, with 7 patients receiving at least 8 infusions (4 months) and 3 patients receiving at least 12 infusions (6 months). Of the 8 patients followed, 100% of patients were responders as defined by $>80\%$ of serum uric acid levels being maintained at goal <6.0 mg/dL during the observation period. Furthermore, there were only 2 patients who each had a single uric acid level above 6.0mg/dL (one following the second infusion and one following the third infusion) and both returned to goal <6.0 mg/dL on all subsequent infusions.

Conclusion: Pretreatment and coadministration with methotrexate 15 mg orally once weekly significantly reduced failure rates in pegloticase treated patients with chronic gouty arthropathy. Although additional studies would be needed to corroborate these results, these data support a potential paradigm shift in treatment of refractory gout with pegloticase.

Disclosure: J. Botson, Horizon Pharma, 5, 8; J. Peterson, Horizon Pharma, 5, 8.

Strong Impact of Dysfunctional Variants of ABCG2 on Hyperuricemia and Gout in Children and Adolescents

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Common dysfunctional variants of ABCG2, a high-capacity urate transporter gene, that result in decreased urate excretion, are major causes of hyperuricemia and gout. However, the association of ABCG2 variants in pediatric-onset hyperuricemia and gout is unknown. In the present study, we analyzed the *ABCG2* gene in a Czech hyperuricemia and gout cohort concentrating on patients with pediatric-onset before 18 years of age.

Methods: In total, 234 Caucasians suffering from hyperuricemia (N = 59) or primary gout (N = 175) were recruited, 31 with pediatric onset of the condition (18 hyperuricemia/13 gout); 115 normouricemic controls were used for comparison. Patients suffering from secondary gout and other purine metabolic disorders associated with pathological concentrations of serum uric acid were excluded. The pediatrics subjects were specifically screened for kidney and metabolic genetic disorders. We amplified, directly sequenced, and analyzed 15 *ABCG2* exons¹. Chi-square goodness-of-fit test was used to compare minor allele frequencies, log-rank test to compare empirical distribution functions.

Results: The analysis of *ABCG2* revealed two common nonsynonymous variants: rs2231137 (p.V12M) and rs2231142 (p.Q141K) and two rare nonsynonymous variants rs750972998 (p.K360del) and rs199854112 (p.T421A) in pediatric-onset subcohort. Seven of the 31 pediatric-onset patients were homozygous for p.Q141K and 11 were heterozygous. This makes the minor allele frequency (MAF) of p.Q141K 38.7 % compared to adult onset MAF = 21.2 % (OR = 2.4, P = 0.005), to normouricemic controls cohort MAF = 8.5 % (OR = 6.8, P < 0.0001) and Caucasian Central Europe population MAF = 9.4 % (OR = 5.7, P < 0.0001). One adolescent patient was compound heterozygous for p.Q141K and a rare variant p.K360del and one other patient was heterozygous for a rare p.T421A variant. Among the 31 pediatric-onset patients we have found 23 (74 %) that had affected family members (in 19 cases, 61 %, there were first degree relatives). This was more than twice than among adult onset individuals (31 %, P < 0.0001). Alternatively, while patients without family history of hyperuricemia/gout had median age of onset 47 years, patients with affected family members had median age of onset 28 years (P < 0.0001).

Conclusion: Our data showed, for the first time, that ABCG2 dysfunction is strong independent risk in pediatric-onset of hyperuricemia and gout where other factors appearing in adulthood, such as alcohol consumption, diuretic use and increase in BMI, may further increase the risk of developing gout. The extremely high frequency of dysfunctional variants of the ABCG2 transporter among the patients with pediatric-onset of hyperuricemia and gout should be kept in mind during differential diagnostic procedures and probably also in therapeutic approach.

References: 1. Stiburkova B, et al. Functional non-synonymous variants of ABCG2 and gout risk. *Rheumatology (Oxford)*. 2017 Nov 1;56(11):1982-1992.

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Disclosure: B. Stiburkova, None; K. Pavelcova, None; M. Pavlikova, None; K. Pavelka, None.

Association between Musculoskeletal Ultrasonography and Bone Remodeling Markers and the Role of Ultrasonography on Monitoring Treatment Responsiveness in Patients with Gout and Hyperuricemia

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Musculoskeletal ultrasonography (US) is an invasive method to identify gout related bone damage, while Dickkopf-1 (DKK-1) and receptor activator of nuclear factor- κ B ligand(RANKL)are bone remodeling factors associated with bone destruction. The association between bone remodeling factors and US is unknown and the role of ultrasonography in the evaluation of response to treatment needs to be further explored.

Methods: To evaluate the association between DKK-1, RANKL and US manifestations in patients with gout and hyperuricemia, and to clarify the role of ultrasonography on disease monitor and treatment responsiveness.

Results: (1) Gout patients were divided into three groups according to US manifestations: normal group, aggregates and/or double contour signs group, tophus and/or bone erosion group. Similarly, patients with hyperuricemia were classified into two groups: normal US group, abnormal US group (at least one of the following manifestations, i.e. aggregate, double contour signs, tophus or bone erosion). Levels of DKK-1 and RANKL of gout patients with US-evidenced aggregates and/or double contour signs was higher than that of normal US group. Gout patients with tophus and/or bone erosion had the highest levels of DKK-1 and RANKL ($P < 0.001$). (2)The levels of DKK-1 and RANKL in hyperuricemia patients with abnormal US were significantly higher than that of normal US hyperuricemia patients. (3) After one year ULT, US abnormalities disappeared in 12 gout patients and 8 hyperuricemia patients. Besides, the diameter of the largest tophus was shortened after treatment in patients with gout ($t=6.092$, $P<0.001$). Moreover, the concentrations of serum DKK-1 and RANKL significantly decreased after treatment for both gout and hyperuricemia patients. The lower the serum urate level was, the higher ratio of the normal US feature was in patients with gout and hyperuricemia. The levels of DKK-1 and RANKL, respectively, were positively correlated with the disease duration in both patients with gout ($r=0.430$, $P<0.001$; $r=0.359$, $P<0.001$) and hyperuricemia ($r=0.446$, $P<0.001$; $r=0.379$, $P<0.001$).

Conclusion: In patients with gout and hyperuricemia, musculoskeletal ultrasonography is remarkably associated with levels of DKK-1, RANKL, and ameliorates after ULT. Thus, US could be a useful tool on reflecting bone remodeling and monitoring disease responsiveness to treatment.

Disclosure: Y. D. Zou, None; Y. N. Fei, None; H. Gao, None; L. F. Xie, None; Y. C. Zhong, None; X. Zhang, None.

Immunosuppressant Use and Gout in the Prevalent Solid Organ Transplant Population

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Gout is a frequent co-morbidity of solid organ transplant (SOT). Cyclosporine (CsA) is often cited as the main cause of gout in SOT, as other immunosuppressant (IS) regimens were associated with lower gout rates (e.g. 1980s studies of azathioprine monotherapy). In most guidelines & institutions, tacrolimus (TAC) has replaced CsA in SOT IS regimens. However, two questions are largely unknown: (1) to what degree is CsA still used among prevalent SOT patients? (2) Can CsA fully explain high rates of gout still seen among SOT patients? This retrospective patient claims data analysis was performed to evaluate IS use and gout in the prevalent SOT population.

Methods: IS regimens and gout prevalence among prevalent SOT patients were assessed via commercial claims data (IQVIA™ Real-World Data Adjudicated Claims – US). Definitions used were – SOT: claim with an SOT procedure code OR any claim with a history of SOT status code; IS: ≥ 1 claim for a given IS drug in the calendar year; Gout: ≥ 1 claim with any gout diagnosis code. IS use at time of transplant for 2016 recipients was obtained from the Organ Procurement and Transplantation Network (OPTN).

Results: The proportion of prevalent SOT patients on CsA declined from 2012 to 2016: heart 22% to 18%, kidney 21% to 17%, lung 16% to 11%, liver 15% to 12% (all $p < 0.01$). TAC use increased: heart 66% to 73%, kidney 67% to 74%, lung 75% to 80%, liver 77% to 82% (all $p < 0.01$). CsA use was higher in prevalent vs. incident SOT populations (e.g. 17% vs. 1.7% kidney 2016, $p < 0.0001$). 2016 gout prevalence was 16% vs. 8% among CsA vs. non-CsA patients. Among all SOT patients with gout, 69% and 26% were on TAC and CsA, respectively.

Conclusion: Despite declining CsA use, gout remains a problem in SOT patients. For one, this study finds that many prevalent SOT patients still receive CsA. Additionally, gout prevalence in the non-CsA population was much higher (8%) than established rates reported in the general population (e.g. 3.9%). This suggests CsA is not the sole driver of gout in SOT. In fact, this analysis finds that post SOT, more than twice as many gout sufferers are on TAC than on CsA. Physicians should be aware that with any transplant IS regimen including calcineurin inhibitors, gout is likely to remain a frequent co-morbidity of SOT.

Disclosure: A. Milgroom, Horizon Pharma, 2; M. O. Lenco, Horizon Pharma, 2; K. Francis, Horizon Pharma, 2; J. D. Kent, Horizon Pharma, 3; B. LaMoreaux, Horizon Pharma, 3; B. F. Mandell, Horizon Pharma, 2, 5.

Abstract Number: 1290

Systemic Inflammation and Atherosclerosis in Patients with Gout. Results from the NOR-Gout Study

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Systemic inflammation and atherosclerosis in patients with gout. Results from the NOR-Gout study

Background/Purpose: The association between gout and cardiovascular disease (CVD) is well-known, whereas mechanisms behind this association are poorly understood. This study aimed to evaluate factors associated with asymptomatic carotid atherosclerosis in patients with gout.

Methods: In this prospective study patients with crystal-proven gout were included after recent disease flare, if the serum urate level was $>360 \mu\text{mol/L}$ ($>6 \text{ mg/dl}$). We analysed baseline data in patients without established CVD who were referred to a CVD risk evaluation, including ultrasound of the carotid arteries, blood pressure measurement and laboratory tests. Carotid atherosclerotic plaques were defined in the longitudinal view as protrusions into the lumen of $\geq 1.5 \text{ mm}$ or at least 2 times the adjacent intima-media thickness according to the Mannheim criteria.

Results: Of the 79 gout patients included, approximately 10% were females, and mean (SD) age was 52.1 ± 13.1 years. 32 (40.5%) had carotid plaques (Table). Only 9.3% were current smokers, while mean (SD) body mass index was high ($29.1 \pm 4.7 \text{ kg/m}^2$). Lipids were in the normal range, with a mean (SD) total cholesterol at $5.3 \pm 1.09 \text{ mmol/L}$ and low density lipoprotein cholesterol $3.12 \pm 0.95 \text{ mmol/L}$. Systolic blood pressure was in the normal range $134.0 \pm 15.1 \text{ mmHg}$, although 29.1% of the patients were treated with antihypertensive agents.

In univariate analyses, higher age, hypertension and higher erythrocyte sedimentation rate (as a marker of systemic inflammation) were significantly associated with the presence of carotid plaques ($p=0.01$ and $p=0.04$, respectively) (Figure). However, there were no statistically significant relations after adjusting for age, a strong predictor for development of atherosclerosis. Serum urate levels or disease duration were not associated with carotid plaques ($p=0.27$ and $p=0.44$, respectively).

Conclusion: Our results indicate an association between systemic inflammation and atherosclerosis in patients with gout. To be able to efficiently prevent CVD in this patient group, prospective studies with larger sample sizes are needed to elucidate the mechanisms behind the increased risk of CVD in gout patients.

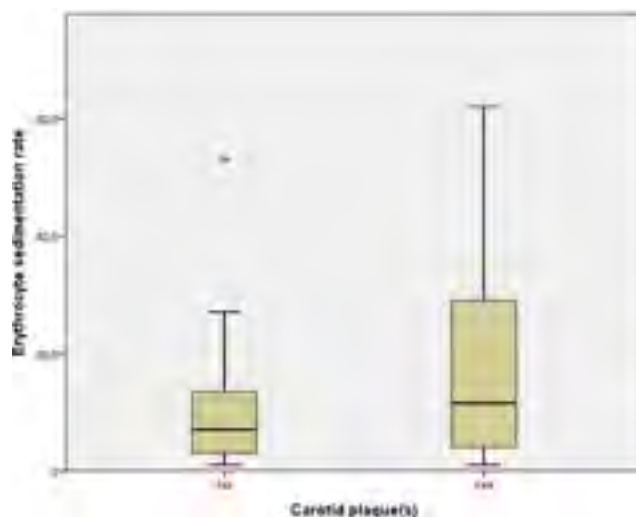


Figure. Association between inflammation and atherosclerosis.

Table. Patients characteristics

	All	+carotid plaque	÷carotid plaque	p-value
Number n (%)	79 (100.0)	32 (40.5)	47 (59.5)	-
Age (years) mean±SD	52.1±13.1	60.0±10.4	46.7±12.1	<0.0001
Sex male/female n (%)	72/7 (91.1)/(8.9)	28/4 (87.5)/(12.5)	44/3 (93.6)/(6.4)	0.43
Disease duration (median IQR)	6.0 (3.0-12.0)	6.0 (3.8-14.3)	5.0 (2.0-10.0)	0.44
<i>V risk factors</i>				
Smoking n (%)	7 (9.3)	2 (2.7)	5 (6.7)	0.69
BMI mean±SD	29.1±4.7	28.5±4.2	29.5±5.0	0.35
TC (mmol/L) mean±SD	5.3±1.09	5.21±1.18	5.39±1.02	0.48
LDL-c (mmol/L) mean±SD	3.12±0.95	3.24±1.07	3.04±0.84	0.41
BP systolic (mm Hg) mean±SD	134.0±15.1	138.0±16.2	131.3±13.9	0.06
BP diastolic (mm Hg) mean±SD	82.8±8.0	83.6±6.9	82.3±8.8	0.46
<i>Co-morbidities n (%)</i>				
Hypertension	36 (45.6)	21 (26.6)	15 (19.0)	0.01
Diabetes	4 (5.1)	3 (3.8)	1 (1.3)	0.30
<i>Biomarkers mean±SD</i>				
S-urate (μmol/L)	495.6±84.0	481.8±97.5	504.9±73.2	0.27
ESR (mm/h)	12.9±13.9	17.3±17.6	9.8±9.7	0.04
CRP (mg/L) median (IQR)	3.5 (2.0-7.8)	5.0 (2.0-13.5)	3.0 (1.0-6.0)	0.09

Disclosure: S. Rollefstad, None; T. Uhlig, Biogen, 5, Bristol-Myers Squibb, 5, Eli Lilly and Co., 5, Janssen, 5, Merck & Co., 5, Novartis, 5, Roche, 5; L. F. Karoliussen, None; H. B. Hammer, None; A. G. Semb, None.

Abstract Number: 1291

Efficacy and Safety of Anakinra in Congestive Heart Failure Patients, Including Lvad, with Acute Gouty Arthritis: A Retrospective Study of 36 Patients at an Academic Medical Center

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Session Information**Session Date:** Monday, October 22, 2018**Session Title:** Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I**Session Type:** ACR Poster Session B**Session Time:** 9:00AM-11:00AM

Background/Purpose: Gout is the most common inflammatory arthritis worldwide and many patients with gout are 'complicated' by multiple comorbidities including metabolic syndrome, renal disease and congestive heart failure (CHF). Treatment of acute gout can be very challenging sometimes, especially in patients with CHF, including those managed with left ventricular assist devices (LVAD), as there are no guidelines or specific recommendations for the treatment of these patients. Due to concerns of LVAD infection, there is often hesitance to administer systemic corticosteroids, and drugs like NSAIDs are often contraindicated in these patients. Recent data has shown that interleukin (IL)-1 antagonism with anakinra is successful in improving acute gout symptoms in critically ill hospitalized patients with comorbid medical conditions. In this study, we aim to evaluate the efficacy and safety of anakinra for the treatment of acute gouty arthritis in a cohort of hospitalized CHF patients including those with LVAD placement.

Methods: We conducted a retrospective chart review of all patients who had a diagnosis of CHF and received inpatient anakinra for acute gouty arthritis over a three year period at an academic medical center. Data collected included demographics, use of LVAD, other medication use, and clinical response of gout to treatment. Patient's records were evaluated for up to a month post anakinra exposure for assessment of gout recurrence and adverse events.

Results: There were 36 hospitalized gouty patients identified, 6 were monoarticular and 30 polyarticular (26 men; mean age 64 ± 17 years, 10 women; mean age 70 ± 13) all of whom carried a CHF diagnosis (median EF 40-45%); 5 patients also had LVAD placement. The mean serum uric acid level was 8.9 (1.9-12.5) and the mean serum creatinine in the non-dialysis patients was 2.1 (0.8-4.8). 2 patients were ESRD and receiving hemodialysis. All patients received anakinra 100mg/d for 3 consecutive days for the management of an acute gouty flare. All patients were also noted to have contraindications to and/or failure of conventional acute gout therapies prior the selection of anakinra. Prior therapies primarily consisted of systemic corticosteroids. Most (35; 97%) patients demonstrated a good response ($>50\%$ improvement in pain as charted by the clinician) to anakinra within 3 days, with only one person who failed to demonstrate improvement in gouty arthritis symptoms. During the 1 month post observation period, 3 patients experienced a recurrence of gout flare. There was one death in a non-LVAD patient which was attributed to severe heart failure. There were no infections noted in the charts over a 1 month period of follow up for any patient who received anakinra.

Conclusion: Anakinra has been shown to be efficacious and safe for the management of acute gouty arthritis, and this study suggests that patients with CHF, including those with LVADs, and acute gout may also be an appropriate candidate population for IL-1 antagonist therapy. As this was a retrospective chart review, a more accurate assessment of safety and efficacy of anakinra in this group of patients warrants a larger prospective study.

Disclosure: A. Hassantoufighi, None; P. Alejandro, None; C. E. Collins, Exagen Diagnostics, Inc, 2; F. Constantinescu, None; J. Bhargava, None.

Abstract Number: 1292

HLA-B*58:01 Genotype and the Risk of Allopurinol-Associated Severe Cutaneous Adverse Reactions in a Predominately Black or African American Population with Advanced Chronic Kidney Disease

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Background/Purpose: Allopurinol is the first line urate lowering drug used for treatment of gout. Its most feared side effect includes development of hypersensitivity drug reactions which may range from mild maculopapular eruption to life threatening severe cutaneous adverse reactions (SCARs) including drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). HLA-B*58:01 is strongly associated with the development of allopurinol-associated SCARs in the Han Chinese, Thai and Korean populations. Interestingly, the association between HLA-B*58:01 and SCARs is not as strong in Japanese, European and Australian populations. This

suggests that this HLA association with allopurinol-induced SCARs varies with ethnicity. Studies in the United States have suggested that Asians and Blacks have substantially increased risk of allopurinol-associated SJS/TEN as compared to Whites and Hispanics which correlates with the allele frequency (7.4%, 4%, 1% and 1%, respectively). This study was conducted to evaluate the frequency of the HLA-B*58:01 allele and its possible relationship of allopurinol-associated SCARs in a predominately Black or African American population with advanced chronic kidney disease (CKD) undergoing evaluation for renal transplantation. Given that CKD is a risk factor for development of gout, this population of patients is at high risk for development of gout and thus for exposure to allopurinol.

Methods: All patients with advanced CKD undergoing evaluation for renal transplantation from 5/1/2012 to 8/2/2017 who were genotyped as part of the transplant evaluation within the inclusion period were included in the study and assessment was made of the presence or absence of the HLA-B58:01 allele. The entire cohort was assessed for the presence of a documented allergy to allopurinol.

Results: From 5/1/2012 to 8/2/2017, 2080 patients were assessed for renal transplantation and genotyped. Of these, 1355 (65%) were Black or African American, 587 (28%) were White, 42 (2%) were Asian. 92 patients were HLA-B*58:01 positive, 77 were HLA-B*58:02 positive and 42 were HLA-B58 positive, but the specific allele was not clear. Of the patients who were HLA-B*58:01 positive, 82 (89%) were Black or African American, 6 (6.5%) were White, 2 (2.2%) were Asian and 2 (2.2%) were another race. The prevalence of HLA-B*58:01 was 6% in this African American or Black population. Only one patient had allopurinol listed as a drug allergy with the reported reaction of DRESS. This patient was HLA-B*58:01 positive and was African American.

Conclusion: In this cohort of predominately African American patients undergoing evaluation for renal transplant, there was a higher frequency of the HLA-B*58:01 allele in the African American or Black population, however overall incidence of allopurinol-associated SCARs was uncommon. This suggests that despite the increased frequency of the HLA-B*58:01 allele in this population and its noted association with allopurinol-associated SCARs in other ethnicities, genetic testing for the HLA-B*58:01 allele prior to initiation of allopurinol therapy for gout is not warranted in the African American or Black population.

Disclosure: S. Ford, None; P. Kimball, None; G. Gupta, None; N. Shah, None.

Abstract Number: 1293

Identification of New and Rare Variants in ABCG2, SLC22A1 and ALDH16A1 Genes in Crystal-Proven Early-Onset Gout

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Session Information

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Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

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Session Time: 9:00AM-11:00AM

Background/Purpose: Early-onset or juvenile gout (EOG) without hypoxanthine-guanine phosphoribosyltransferase enzyme deficiency (*HPRT*, OMIM 300323) and not related to familial juvenile hyperuricemic nephropathy (*UMOD*, OMIM 300323) is a rare gout phenotype characterized by a first flare in adolescence or in young adulthood. While numerous genome wide association studies (GWAS) have been done in classical and late-onset gout, very few studies have been performed in EOG patients. Moreover, until now most genetic studies only assess association between pre-defined single nucleotide polymorphisms (SNP) and gout.

Our aim was to identify the genetic variants of clinically confirmed EOG by screening all exons of gout-associated genes with targeted Next-Generation Sequencing (NGS) approach

Methods: Twenty-six urate crystal-proven gout patients with first flare occurring before the age of 30 years were included. Gout history, comorbidities and patient characteristics were recorded. All participants provided written informed consent to genetic analysis. After DNA extraction from total blood samples, the NGS libraries were prepared with surselectQXT (Agilent) and sequencing was performed with miseq (Illumina).

The multigene panel included 80 genes described in GWAS and genes involved in rare diseases such as *HPRT* and *UMOD*.

Results: Twenty-six patients (24 men, 20 Caucasians, 5 Asians and 1 African) with crystal-proven gout had experienced their first flare at a mean age of 22.8 years [14-29]. Gout duration was 11.5 years [1-46] and clinical tophi observed in 9 patients. Mean age was 37.5 [24-69] years and mean body mass index 27.6 kg/m² [20.1-40.7]. Ten patients were overweight, 5 had obesity, 1 hypertension, 0 diabetes mellitus, 7 dyslipidemia and 10 chronic kidney disease stages 2-4. Mean serum urate level was 527 µmol/L [270-803]. Amongst 26 affected patients, 7 had a molecular anomaly (26.9%). Six patients harbored one rare or novel variant in *ABCG2* (three Caucasian patients), *ALDH16A1* (two Caucasian patients) and *SLC22A11* (one African patient). Two other patients (one Caucasian and one Asian) carried an association of variants in both *ABCG2* and *ALDH16A1*. All variants had a Minor Allele Frequency (MAF) below 0.3% or were never described in public databases. All variant were considered as probably pathogenic according to *in silico* predictive algorithms. Interestingly, the well-known p.Gln141Lys SNP of *ABCG2* was identified in 3 Asian patients (11.5%) at homozygous level.

Conclusion: Our finding of very rare and novel pathogenic variants in *ABCG2*, *ALDH16A1* and *SLC22A11* genes provides better insights of the molecular pathogenesis in early-onset juvenile gout. However, our results also highlight the involvement of yet undetermined genes in this population.

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Abstract Number: 1294

Initial Phase 2 Clinical Data of SEL-212 in Symptomatic Gout Patients: Monthly Dosing of a Pegylated Uricase (Pegadricase) with Svp-Rapamycin Enables Sustained Reduction of Acute Gout Flares

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Session Information

Session Date: Monday, October 22, 2018

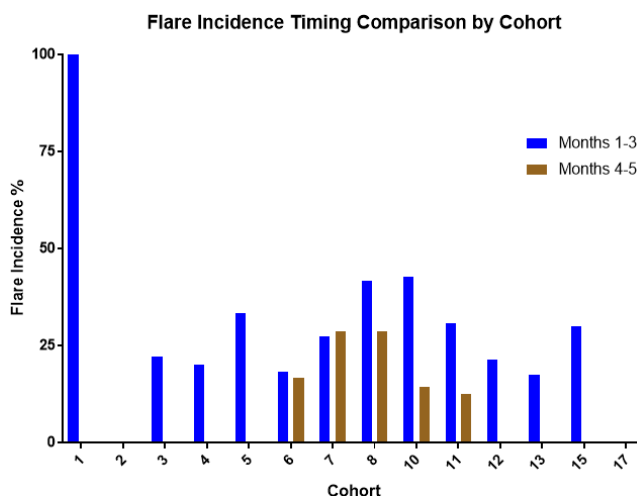
Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Pegylated uricases are therapies for treatment of severe chronic gout, particularly for rapid tophi resolution. However, uricases are limited by induction of anti-drug antibodies (ADA) that can compromise efficacy and safety. SEL-212 is a novel combination product consisting of pegadricase (also known as pegsiticase) co-administered with synthetic vaccine particles encapsulating rapamycin(SVP-R). We report initial data on gout flares from an ongoing Phase 2 study in symptomatic gout patients.

Gout is caused by deposition of monosodium urate (MSU) crystals in joints due to chronic hyperuricemia. Long term treatment focuses on reducing sUA levels, allowing MSU crystals to dissolve. Rapid dissolution of MSU crystals during initial phase of urate lowering therapy (ULT) is associated with an increased frequency of acute gout flares, which can



contribute to poor treatment compliance. During ULT initiation, colchicine, NSAIDs or corticosteroids are used for gout flare prophylaxis.

Methods: Patients with symptomatic gout (≥ 1 tophus, gout flare within 6 months or gouty arthropathy) and elevated serum uric acid (sUA) ≥ 6 mg/dL were treated with fixed doses of pegadricase (0.2 mg/kg or 0.4 mg/kg) alone or in combination with SVP-Rapamycin (0.05 to 0.15 mg/kg). SEL-212 was infused in 28-day cycles x3 doses followed by challenge with pegadricase alone on 28-day cycles x2 doses, or in 28-day cycles x5 combination doses off-Rapamycin and pegadricase. Safety, tolerability, sUA, and ADAs were monitored.

All randomized patients received colchicine (1.2 mg loading dose, 0.6 mg QD for the remainder of their participation in the trial) as premedication for gout flare prevention. If colchicine was contraindicated, patients received ibuprofen 600 mg TID or equivalent dose of aNSAID. If colchicine and NSAIDs were contraindicated, patients did not receive any premedication.

Results: As of 21 May 2018, demographics of the 140 treated patients were 32 - 75 years old (mean 54.9 years), male 90.7%, and white 67.1%. The mean BMI at baseline was 35.0 kg/m². 70.0% of patients were obese with mean duration of established or symptomatic gout as 10.8 years.

Flare incidence was 27.1% (months 1-3) and 10.2% (months 4-5), flare frequency was 0.41 flares/patient (months 1-3) and 0.14 flares/patient (months 4-5). Mean duration of the gout flares was 7.28 days, with majority of the gout flares (93.8%) being categorized as mild/moderate, with 6.1% (n=4 cases) noted as severe in intensity. Adjustments to gout flare prevention medication were not required for 43% of the patients. No gout flares resulted in a patient discontinuation or were reported as a serious adverse event.

Figure 1. Comparison of Gout Flare Incidence.

Conclusion: SEL-212 has been well-tolerated and lowers flares at the initiation of therapy relative to pegylated uricases alone, and the effect persists over the duration of therapy.

Disclosure: R. Azeem, Selecta Biosciences, 1, 3; A. J. Kivitz, Novartis, 1, AbbVie, Boehringer Ingelheim, Flexion, Genzyme, Janssen, Pfizer Inc, Regeneron, Sanofi, Sun Pharma, UCB, 5, Celgene, Flexion, Genentech, Genzyme, Horizon, Ironwood, Merck, Novartis, Pfizer Inc, Regeneron, Sanofi, 8, Altona Center for Clinical Research, 9; E. Sands, Selecta Biosciences, 1, 3; W. DeHaan Ph.D., Selecta Biosciences, 1, 3; L. Johnston, Selecta Biosciences, 1, 3; T. K. Kishimoto, Selecta Biosciences, 1, 3.

Abstract Number: 1295

Anakinra Is More Effective at Reducing Pain from Acute Crystal Induced Arthritis When Compared to Conventional Therapy: A Retrospective Review at a Tertiary Care Center

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Session Information

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Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The management of Acute Crystal-Induced Arthritis (ACIA) relies on NSAIDs, colchicine, and glucocorticoids as conventional therapy. In presence of comorbidities (e.g. renal insufficiency, diabetes mellitus, etc.), conventional treatment may be challenging and may lead to poor hospital outcomes. The IL-1 receptor inhibitor anakinra has effectively treated diseases in which the inflammasome plays a main pathogenic role, including ACIA. We studied inpatients with ACIA receiving anakinra at Albany Medical Center compared to conventional therapy to determine differences in pain scores and length of stay.

Methods: Single center retrospective chart review of ACIA inpatients between January of 2016 and May 2018 was performed. Data collection included demographics, medications, comorbidities, and Visual Analog Pain Scale (VAS-pain). Response to treatment was defined as a decrease in VAS-pain by more than 2 points on a 0-10 scale at 24, 48, and 72 hours. A 1:2 case-control matched pairing (based on demographics, number of joints affected) were selected as controls from the conventional group. A total of 204 patients meeting ACR/EULAR criteria for ACIA were reviewed. Sixteen patients receiving anakinra for ACIA met selection criteria. Thirty-two patients with conventional treatment were matched

with the anakinra group. Repeated measures ANOVA was used to compare each group at each time-point of pain assessment. Tukey-Kramer multiple comparisons test was used for post-hoc comparisons.

Results: All the patients receiving anakinra had a good response, with statistically significant improvement in pain scores compared to the conventional group ($p < 0.001$). Within the anakinra group, pain was significantly improved at 24 hours ($p < 0.05$) and at 48 hours ($p < 0.001$) compared to baseline. The conventional therapy group had significant improvement at 48 hours compared to baseline ($p < 0.05$) but was not significantly improved at 24 hours ($p > 0.05$). Between groups, pain was not different at baseline or at 24 hours ($p > 0.05$) but was at 48 hours ($p < 0.001$). The average length of stay of patients on anakinra was nearly 2 days shorter in comparison to the conventional group. On average, 3.1 doses (95% CI 2.3 – 3.9) of Anakinra 100mg subcutaneously were required for pain relief. There were no significant adverse events noted.

Conclusion: Anakinra is an effective treatment for ACIA with faster resolution of symptoms compared to conventional therapy prompting a shortened length of stay. Anakinra may be a safe alternative for patients with contraindications to conventional treatment or who may be at high risk for complications from conventional treatment. Further evaluation of these findings in a prospective study may provide more information regarding a role of anakinra in management of ACIA.

Table 1. Patient Characteristics and Outcomes by Conventional Group versus Anakinra Group.

Variable	Conventional Group(n=32)	Anakinra Group (n =16)
PATIENT CHARACTERISTICS		
Age, Mean [95% CI]	63.9 [60.1 – 67.6]	69.0 [62.3 – 75.7]
Sex, No. [%]		
Male	18 [56%]	10 [63%]
Female	14 [43%]	6 [37%]
Race, No. [%]		
Caucasian	16 [50%]	12 [75%]
African American	11 [34%]	2 [13%]
Hispanic	3 [6%]	1 [6%]
Unknown	None	1 [6%]
Crystal Type, No. [%]		
Uric Acid	13 [77%]	9 [56%]
CPPD	3 [18%]	1 [6%]
Uric Acid + CPPD	1 [6%]	None
Flare Duration, Days [95% CI]	4.4 [2.9-5.9]	3.3 [2.2 – 4.5]
Diabetes Mellitus, No. [%]	14 [44%]	7 [43%]
CKD Stage 2 or Greater, No. [%]	10 [31%]	9 [56%]
Uric Acid, Mean [SD]	7.2 [2.7]	6.2 [2.2]
Median No. of Joints [Min – Max]	2 [1 – 6]	2 [1 – 5]
Mean ESR [95% CI]	67.1 [55.8 – 78.4]	54.1 [36.2 – 71.9]
Mean CRP [95% CI]	101.1 [71.3 – 131]	146.6 [114 – 179.2]
Renal Function [95% CI]		
Blood Urea Nitrogen mg/dL	28.3 [22.7 – 33.9]	25.4 [19.1 – 31.8]
Serum Creatinine mg/dL	1.57 [1.22 – 1.92]	1.81 [0.97 – 2.65]
Glomerular Filtration Rate mL/min/1.73m ²	45.3 [40.0 – 50.6]	45.9 [37.0 – 54.8]
OUTCOMES		
Mean VAS Pain Score [95% CI]		
Before Treatment	7.8 [7.1 – 8.4]	7.9 [6.9 – 8.9]
24 hours after treatment ^a	7.3 [6.6 – 8.1]	6.3 [5.3 – 7.4]
48 hours after treatment ^{b,c}	6.7 [5.7 – 7.8]	4.0 [2.5 – 5.5]
72 hours after treatment	6.7 [5.7 – 7.6]	3.1 [1.3 – 4.9]
Mean Length of Stay, Days [95% CI]	7.7 [5.6 – 9.8]	5.5 [4.2 – 6.9]
Median doses of Anakinra [Min – Max] ^d	None	3 [1 – 9]
Mean doses of Anakinra [95% CI]	None	3.1 [2.3 – 3.9]

Abbreviations

CI, Confidence Interval; SD, Standard Deviation; Min, Minimum; Max, Maximum; ESR, Erythrocyte Sedimentation Rate; CRP, C-Reactive Protein; No, Number; CKD, Chronic Kidney Disease; VAS, Visual Analog Scale; CPPD, Calcium Pyrophosphate Disease

a, Anakinra group has significantly lower pain scores than the conventional group at 24 hours ($p < 0.05$) and at 48 hours ($p < 0.001$)

b, Conventional group had significantly improved at 48 hours compared to baseline ($p < 0.05$) but was not significantly improved at 24 hours ($p > 0.05$)

c, At 48 hours, pain was significantly less in the anakinra group compared to conventional group ($p < 0.001$)

d, Only patients in the anakinra group received it at 100 mg subcutaneously daily.

Disclosure: S. Singh, None; A. Ocon, None; V. Mehta, None; S. Musa, None; R. Peredo, None.

A Novel Potent and Selective Urate Transporter 1 Inhibitor, NC-2700, with pH-Raising Effect on Low Urinary pH

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

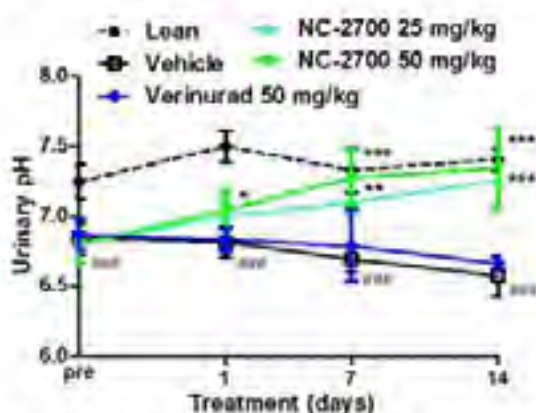
Background/Purpose: In most patients with gout, renal underexcretion of uric acid is the main mechanism for hyperuricemia. However, for the risk of uric acid kidney stone, uricosuric drugs are second-line treatment for hyperuricemia. It is also known that low urinary pH significantly increases the risk of uric acid crystallization and is strongly related with insulin resistance. Patients with gout frequently have metabolic syndrome, closely associated with insulin resistance. In this study, we describe a novel potent urate transporter 1 (URAT1) inhibitor, NC-2700, with pH-raising effect on low urinary pH.

Methods: HEK293 cells stably expressing URAT1 were treated with NC-2700, verinurad or lesinurad, and the inhibitory activity was determined by measuring the uptake of [¹⁴C]uric acid into the cells. To determine the selectivity of NC-2700 to URAT1, the effects on other transporters, including OAT1, OAT3 and ABCG2 were tested. The uricosuric effect and pH-raising effect of NC-2700 on low urinary pH were evaluated following single and/or multiple (once a day) doses in tufted capuchin monkeys and Zucker diabetic fatty rats (ZDF rats, type 2 diabetic model), respectively.

Results: NC-2700 inhibited URAT1 concentration-dependently with Ki value of 31.4 nmol/L. Inhibitory activity of NC-2700 against URAT1 was about 3-fold and roughly 1000-fold stronger than those of verinurad and lesinurad. In addition, NC-2700 showed high selectivity to URAT1 over other transporters. In *in vivo* studies, NC-2700 dose-dependently increased the fractional excretion of urinary uric acid in tufted capuchin monkeys and the effect of NC-2700 was great compared with verinurad. Moreover, unlike verinurad, NC-2700 raised urine pH levels lowered in ZDF rats to normal levels.

Conclusion: NC-2700 is a novel potent and highly selective URAT1 inhibitor, and has not just a great uricosuric effect compared with verinurad in monkeys, but also pH-raising effect on low urinary pH in ZDF rats. NC-2700 is a promising

Figure 1. Effects of NC-2700 and verinurad on low urinary pH in Zucker diabetic fatty rats, a model of type 2 diabetes



Mean ± SD (n=5). ***, $p < 0.001$, vs Lean (Student's or Welch's Test).
^{*} $p < 0.05$, ^{**} $p < 0.01$, ^{***} $p < 0.001$, vs Vehicle (Dunnett's test)
 Drugs were orally administered to seven-week-old ZDF and lean rats once daily for 2 weeks.

candidate for the treatment of patients with gout and hyperuricemia, which could decrease the risk of renal calculus and nephrotoxicity with urate crystals in the urine, the most common issue with uricosuric therapy.

Disclosure: M. Hirano, Nippon Chemiphar Co., Ltd., 3; T. Muto, Nippon Chemiphar Co., Ltd., 3; T. Hirai, Nippon Chemiphar Co., Ltd., 3; P. Jutabha, None; N. Anzai, None; T. Horie, DeThree Res. Lab. Inc., 3; Nippon Chemiphar Co., Ltd., 5; H. Endou, J-Pharma Co., Ltd., 3; Nippon Chemiphar Co., Ltd., 5; T. Yamakawa, Nippon Chemiphar Co., Ltd., 3.

Abstract Number: 1297

Risk of Dementia in Patients with Gout and the Impact of Urate-Lowering Therapies: A Large Population-Based Cohort Study

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Evidence is conflicting concerning dementia risk in gout patients, with hyperuricaemia proposed to exert a neuroprotective effect. Serum urate(sUA) targets guiding urate-lowering therapies (ULT) are poorly evidenced-based and there is a shifting consensus towards a more lenient target to attempt to balance the theoretical harmful effects of hypouricaemia. The aim of this study was two-fold; first, to estimate the risk of dementia among patients with gout, second, to assess the potential impact of ULT.

Methods: Retrospective population-based matched cohort study conducted using the Clinical Practice Research Datalink (CPRD), a large anonymized primary care database. Gout exposure was defined as a first entry of a medical code for gout (previously validated in CPRD with high accuracy (>90%))¹ between April 1998-February 2016. Each gout exposed patient was matched to 4 unexposed controls on age (± 5 years), gender, general practice and follow-up in CPRD (± 3 years). The absolute rate of dementia onset was calculated for gout exposed and unexposed and hazard ratios (HR) were modelled using Cox Proportional Hazards Regression. The analysis was stratified by dementia type (Alzheimer disease (AD), vascular dementia, other dementia types). Finally, among gout cases we assessed the impact of ULT on dementia onset. ULT exposure, defined as at least 6 month prescription, was assessed within 1 and 3 year exposure windows after gout diagnosis.

Results: Our cohort of 79,097 gout exposed and 276,808 unexposed had a median follow-up time of 5 years (interquartile range=6.2), mean age of 62 years (standard deviation=15.2) and 73% male. The absolute incidence rate of all-type dementia per 10,000 years was lower in the gout exposed cohort than the unexposed (35.6 (95% Confidence Interval (CI) 33.8 – 37.4) vs 40.7 (95% CI 39.8 – 41.7)) corresponding to a 17% lower risk (HR=0.83 95% CI 0.78 - 0.87) (Table 1). The incidence of AD and other dementia types was lower in the gout cohort, but nonvascular dementia (Table 1). Within gout cases, ULT exposure within 1 and 3 years after gout diagnosis did not significantly affect dementia risk after adjustment for potential confounders.

Table 1: Incidence rate of all-type dementia, Alzheimer's Disease and vascular dementia per 10,000 years and adjusted hazard ratios (HR) for gout-exposed vs unexposed with 95% confidence intervals (CI)

Variable	Gout Exposed		Unexposed		Adjusted*	
	Rate	95%CI	Rate	95% CI	HR	95% CI
All-type Dementia						
Overall	35.6	33.8, 37.4	40.7	39.8, 41.7	0.83	0.78, 0.87
Male	25.7	24.0, 27.5	30.0	29.0, 31.0	0.81	0.75, 0.87
Female	65.2	60.6, 70.2	72.6	70.0, 75.2	0.85	0.78, 0.93
Alzheimer's Disease						
Overall	9.4	8.5, 10.3	12.6	12.0, 13.1	0.74	0.66, 0.82
Male	6.7	5.9, 7.7	8.8	8.3, 9.4	0.74	0.64, 0.86
Female	17.5	15.1, 20.1	23.6	22.2, 25.1	0.74	0.63, 0.87
Vascular Dementia						
Overall	11.4	10.4, 12.4	11.0	10.5, 11.6	0.91	0.82, 1.00
Male	8.4	7.4, 9.4	8.9	8.4, 9.4	0.83	0.72, 0.95
Female	20.5	18.0, 23.4	17.3	16.1, 18.7	1.04	0.89, 1.21

*Adjusted for age, gender (only in overall analysis), Charlson Comorbidity Index, BMI, smoking and alcohol history

Conclusion: This provides observational evidence supporting the hypothesis that hyperuricaemia has a neuroprotective role, with gout patients having lower dementia risk. This risk was unaffected by ULT, but further studies are required to determine if this differs with longstanding ULT use, dose or magnitude of urate-lowering. This would help devise a more evidence-based sUA target for guiding gout management, which optimally balances a therapeutic target against the possible harmful effect of hypouricaemia.

References:: 1.Meier, C. R. & Jick, H. Omeprazole, other antiulcer drugs and newly diagnosed gout. *Br. J. Clin. Pharmacol.* 44, 175–8 (1997).

Disclosure: L. Crowley, None; A. Abdul Sultan, None; E. Roddy, None; C. Mallen, None; J. Protheroe, None; L. Clarson, None.

Abstract Number: 1298

Gout and the Risk of Parkinson’s Disease in Older Adults: A Study of U.S. Medicare Data

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Session Information

Session Date: Monday, October 22, 2018
Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I
Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: In the presence of limited available data, our objective was to assess the association of gout with the risk of incident Parkinson’s disease (PD) in older adults ≥65 years.

Methods: We used the 5% Medicare claims data from 2006-2012 for this cohort study. Gout was identified by the presence of two claims for gout at least 4 weeks apart, with International Classification of Diseases, ninth revision, common modification (ICD-9-CM) code of 274.xx. Study outcome was incident GCA, identified by two claims for PD with an ICD-9-CM code of 446.5, at least 4 weeks apart and an absence of PD claims in the baseline 365-day period, a valid approach. We used multivariable-adjusted Cox proportional hazard models to assess the association of gout with incident GCA, adjusting for potential confounders/covariates including demographics (age, race, gender), comorbidities (Charlson-Romano comorbidity index), and medications commonly used for cardiac diseases (statins, beta-blockers, diuretics, and angiotensin converting enzyme (ACE)-inhibitors) and gout (allopurinol and febuxostat; Model1).

Results: In a cohort of 1.72 million people, the mean age was 75 years (standard deviation [SD], 7.6), mean Charlson-Romano comorbidity index score was 1.60(SD, 2.39), 58% were female, 86% were White and 37% had Charlson-Romanocomorbidity index score of ≥2. Of these, 22,636 people developed incident PD during the study follow-up, 1,129 with gout and 21,507 without gout, with respective crude incidence rates of incident PD of 3.7 vs. 2.2 per 1,000person-years, respectively. Gout was associated with a higher risk of PD in the main analysis, 1.14 (95% CI, 1.07, 1.21). Sensitivity analyses confirmed main findings. No gender or race differences were noted, but the risk differed slightly by age; ages 65-75, 75-85 and >85 had hazard ratios of incident PD with gout of 1.27 (95% CI, 1.16, 1.39), 1.07 (95% CI, 0.97, 1.16) and 0.97 (95% CI, 0.79, 1.20), respectively (**Table 1**).

Conclusion: Gout was associated with a higher risk of incident PD in older adults. The risk of PD with gout was highest in the age group 65-75 years. Mechanisms of this increased risk need to be evaluated in future studies.

Table 1. Association of gout with Parkinson’s Disease, in pre-defined subgroup analyses, varying by age, gender and race

	Multivariable-adjusted (Model 1)		Multivariable-adjusted (Model 1)		Multivariable-adjusted (Model 1)	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Gout	65- <75 years 1.27 (1.16, 1.39)	<0.0001	75- <85 years 1.07 (0.97, 1.16)	0.17	≥85 years 0.97 (0.79, 1.20)	0.77
Gout	Female 1.17 (1.06, 1.30)	0.003	Male 1.11 (1.03, 1.20)	0.006		
Gout	Black 1.09 (0.87, 1.36)	0.46	White 1.13 (1.06, 1.21)	0.0003	Other race 1.36 (1.05, 1.77)	0.02

Interaction terms: Gout*age p-value <0.0001; Gout*gender p-value = 0.52; Gout*race p-value = 0.65
R, Hazard ratio; CI, confidence interval.
Bold estimates represent those with statistical significance, i.e., p-value <0.05.

Disclosure: J. A. Singh, Takeda, Savient, 2,Savient, Takeda, Regeneron, Merz, Iroko, Bioiberica, Crealta/Horizon and Allergan pharmaceuticals, WebMD, UBM LLC, Medscape , Fidia pharmaceuticals and the American College of Rheumatology, 5; J. Cleveland, None.

Abstract Number: 1299

A Novel Recombinant Oral Urate Oxidase (UrOx) Alln-346 Reduces Severe Hyperuricemia and Normalizes Hyperuricosuria in Nephropathic UroX Knockout (UrOxKO) Mice

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

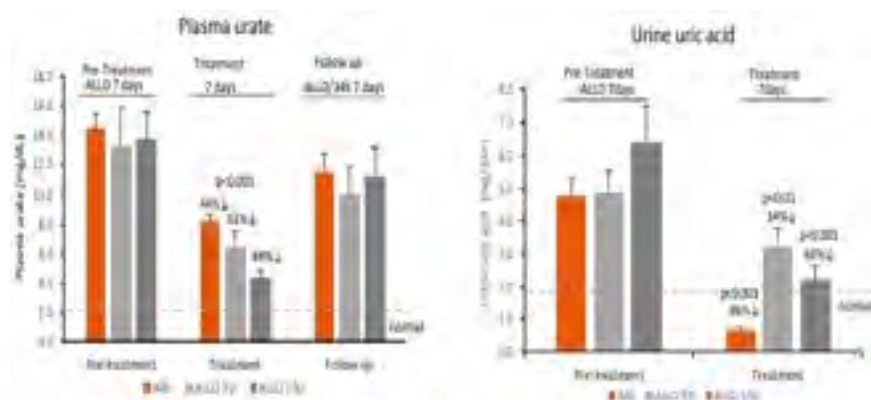
Session Time: 9:00AM-11:00AM

A novel recombinant oral urate oxidase (UrOx) ALLN-346 reduces severe hyperuricemia and normalizes hyperuricosuria in nephropathic UrOx knockout (*UrOxKO*) mice

Background/Purpose: Limitations in efficacy and/or tolerance of oral xanthine oxidase inhibitors, uricosurics, and intravenous uricase agents contribute to refractoriness to urate-lowering therapy (ULT) in gout. Renal excretion is the major route of uric acid elimination, but the gastrointestinal tract (GIT) plays an increasingly recognized role in urate homeostasis, especially in chronic kidney disease (CKD) where urate renal elimination is impaired. Here, we targeted gut elimination of urate *in vivo* with ALLN-346, an orally administered, engineered UrOx optimized for proteolytic stability in the GIT. We tested ALLN-346 in *UrOxKO* mice, with severe hyperuricemia, hyperuricosuria and uric acid crystalline obstructive nephropathy.

Methods: This was a parallel 21-day study of 3 periods (pre-treatment, treatment and follow up, each 7d) and 3 arms, ALLN-346 mixed with food (150 mg/day, n=8) compared to allopurinol (ALLO) doses of 150 mg/L (n=9) and 50 mg/L (n=8) supplemented in water. During the pre-treatment period, the maintenance dose of ALLO (150 mg/L) was removed. Plasma urate was measured in samples collected on the last day of each study period, and uric acid was measured in 24-hour urine samples collected during the last 3 days of pre-treatment and treatment periods (Cormay LiquickCor-UA 30 plus, PL).

Results: Hyperuricemia was reduced significantly ($p < 0.001$) and hyperuricosuria normalized with 7 days ALLN-346 oral therapy (Figure 1). On ALLN-346, mean (SEM) plasma urate decreased by 44% from pre-treatment (14.5 ± 0.9 to 8.1 ± 0.5 mg/dL), similar to 51% in the 50 mg ALLO group (13.2 ± 2.6 to 6.5 ± 1.1 mg/dL); $p = NS$. The highest reduction of 69% was in the ALLO 150 arm (13.8 ± 1.7 to 4.3 ± 0.6 mg/dL). Urine urate excretion normalized (< 2 mg/24h) with ALLN-346, mean (SEM) reduction was 86% (4.7 ± 0.6 to 0.7 ± 0.1 mg/24h); while in ALLO 50 and 150 arms reduction was 34% (4.9 ± 0.4 to 3.2 ± 0.3 mg/24h) and 66% (6.4 ± 0.7 to 2.2 ± 0.3 mg/24h) respectively. Removal of ALLN-346 or ALLO in follow up resulted in hyperuricemia returning to approximately pre-treatment levels. Analysis of chiefdom different GIT segments indicated the urate presence along the whole gut.



Conclusion: Novel targeting of enteric uric acid by oral ALLN-346 therapy successfully lowered serum urate and normalized urinary uric acid in nephropathic *UroXKO* mice. Enhanced elimination of urate via degradation in the GIT could be an effective addition to pharmacologic ULT and supports rationale for testing ALLN-346 in humans without and hyperuricemia, particularly in CKD.

Disclosure: D. Grujic, None; A. Desphande, None; R. Terkeltaub, Ironwood/Ardea-Astra-Zenec, 2, Selecta, Kowa, SOBI, RELBURN, Horizon, 5; N. Mosiichuk, None; K. Goncharva, None; S. Pirzynowski, None.

Abstract Number: 1300

The Relationship between Metabolic Syndrome Severity and the Risk of Mortality in Gout Patients: A Population Based Study

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The metabolic syndrome (MS) is common among gout patients. The metabolic syndrome is diagnosed when a patient has at least 3 of the following 5 conditions: hyperglycemia, hypertension, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, abdominal obesity. Little is known about the relationship between the cumulative effects of all 5 MS conditions and the risk of mortality among adult patients with gout. The MS Severity Score (MSSS) is a validated summary score that accounts for the combined effects of all 5 metabolic features. Our goal was to use the MSSS to examine the overall associations between MS severity and the risk of mortality related to all-causes, cardiovascular disease and diabetes among United States (US) gout patients.

Methods: We analyzed mortality-linked data for 9,747 adults aged 20 to 74 years who participated in the Third National Health and Nutrition Examination Survey (NHANES III). Data from NHANES III were linked to national mortality records for all participants up to time of death or end of study (i.e. 23 years following initial recruitment). All 5 metabolic features were used to calculate gender-race/ethnicity specific MSSS Z-scores in gout patients. The calculated Z-scores are a continuous representation of all MS conditions while accounting for gender-race/ethnicity disparities. Cox proportional hazard models adjusting for age, marital status, gender, income, education, race, smoking, BMI, insurance, physical activity, alcohol intake and diet, were used to test the associations between MS severity and risk of mortality in gout patients. Complex survey methods with sampling weights, clusters and strata were applied to yield nationally representative prevalence and inference estimates.

Results: A total of 2,072 deaths were observed, of which 127 had gout. The prevalence amongst adults was 2.40% (95% CI; 1.93%-2.87%). Moderate to high MS severity was significantly prevalent among gout patients (47.33% vs. 21.16 % no gout; P-value <0.0001). The mean MSSS Z-score for gout patients was significantly higher than those without gout (0.71 vs. -0.04 no gout; P-value <0.0001). Among all patients, a one unit increase in MSSS score was associated with a higher risk of mortality in all adjusted models. For gout patients, a one-unit increase in MSSS score was associated with significant increase in the risk of all-cause mortality Adjusted Hazard Ratio (aHR) 1.46 (95% CI; 1.13, 1.87). In a disease-specific survival model, a one-unit increase in MSSS score was associated with 79% and 124% increases in cardiovascular and diabetes mortality risks, aHR 1.79 (95% CI; 1.20, 2.67) and 2.24 (95% CI; 1.21, 4.16), respectively.

Conclusion: Studies published to date have not accounted for the combined effects of all 5 MS features in gout patients. For gout patients, a one-unit increase in MSSS score was associated with significant increase in the risk of all-cause mortality and 79% and 124% increases in cardiovascular and diabetes mortality risks. The MSSS is a clinically accessible tool for predicting mortality risks in gout patients with the MS.

Disclosure: M. Elsaid, None; V. Rustgi, None; N. Schlesinger, Astra Zeneca, 2, Novartis, Horizon, 5.

Organic Anion Transport Inhibitors Suppress Chondrocyte Pyrophosphate Production

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Session Information

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Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

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Session Time: 9:00AM-11:00AM

Background/Purpose: Calcium pyrophosphate deposition (CPPD) disease results from articular calcium pyrophosphate deposition leading to arthritis. We currently lack specific and effective therapies for this commonly encountered entity. Prior studies have demonstrated excess pyrophosphate (PPi) production in the cartilage of patients with CPPD. Targeting the earliest phases of CPP crystal formation has the potential to reduce future joint damage and avoid inflammatory episodes. Previous studies demonstrated that probenecid reduced PPi production by chondrocytes. Probenecid is an organic anion transport inhibitor. It has some disadvantages in that it is highly insoluble in culture and may not achieve therapeutic levels in synovial fluids. In this project, we tested the ability of other FDA approved drugs that act as organic anion transport (OAT) inhibitors to suppress PPi levels in chondrocyte cultures.

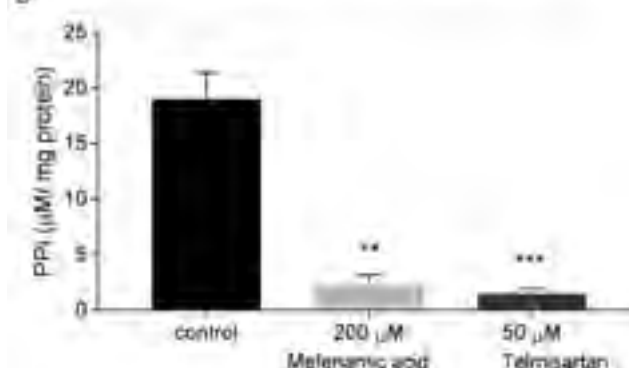
Methods: Normal knee cartilage was obtained from mature pigs. Cartilage was enzymatically digested and chondrocytes were plated in high density serum-free culture conditions shown to preserve the chondrocyte phenotype. Chondrocytes were treated with various OAT inhibitors including diflunisal, ketoprofen, valsartan, telmisartan, and mefenamic acid at three separate concentrations for 72 hours. Media were collected and a luminescent PPi assay was utilized to measure PPi levels. PPi levels were corrected for cell protein and media LDH levels were used to assess for toxicity. Two of the OAT

Figure 1

A

Drug	PPi fold change	LDH (% control)
Diflunisal (500 μ M)	3.36 \pm 2.37	1.09 \pm 0.23
Ketoprofen (500 μ M)	2.46 \pm 1.04	0.68 \pm 0.30
Valsartan (50 μ M)	2.10 \pm 0.85	1.13 \pm 0.25
Telmisartan (50 μ M)	0.08 \pm 0.08	1.18 \pm 0.36
Mefenamic acid (200 μ M)	0.12 \pm 0.14	0.82 \pm 0.19

B



inhibitors, telmisartan and mefenamic acid, were further tested based on the initial results. Significant differences between groups were assessed utilizing a Kruskal-Wallis statistical test.

Results: Figure 1A summarizes average PPI changes and LDH levels in three experiments using the concentration of each drug that had the maximal effect on PPI. Of the 5 drugs tested, mefenamic acid and telmisartan displayed inhibition of PPI levels without causing toxicity. Figure 1B shows statistically significant suppression of PPI by mefenamic acid 200 μ M and telmisartan 50 μ M. (N=12 and $p < .01^{**}$, and $p < .001^{***}$)

Conclusion: We show here that PPI levels were decreased in the presence of two FDA-approved OAT inhibitors, mefenamic acid and telmisartan. These drugs show some promise in their ability to modulate PPI production, a process essential to CPP crystal formation. Further work will be needed to validate the clinical importance of this interesting finding.

Disclosure: M. Faseehuddin, None; C. Gohr, None; E. Mitton-Fitzgerald, None; A. Rosenthal, None.

Abstract Number: 1302

Opioid Analgesic Use in Acute Gout Patients Discharged from the Hospital

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The Health and Human Services has declared the opioid epidemic as a public health emergency. It has been demonstrated that even short exposures to opioids could progress to episodic and ultimately long-term opioid use. Acute gout is among the most painful inflammatory arthritis. However, the burden of opioid use in acute gout has not been previously evaluated. Our aim was to assess the use of prescription opioids among patient discharged from the hospital with acute gout and factors associated with it.

Methods: Lifespan healthcare system, the largest in Rhode Island, comprises of 3 acute-care facilities with emergency departments (ED) and outpatient centers. Adult gout patients (greater than 18 years) discharged from the ED or inpatient facility were identified using ICD-9 and ICD-10 codes from the electronic health records. We included all patients seen between March 2015 and Sept. 2017. If a single patient was seen multiple times, only the first encounter was included. Outcome of interest was prescription opioid given at discharge from ED/inpatient stay. We collected information regarding patient demographics, comorbidities including history of chronic pain and substance abuse, prior to admission opioid use and time of presentation to ED. Information regarding single versus multiple joint involvement and severity of disease as assessed by the triage nurse on ED severity scale (1 being the most severe and 5 being least) was also abstracted. A multivariable logistic regression was used to assess factors associated with the use of prescription opiates at discharge from the hospital.

Results: A total of 456 patients (mean age 58.7 ± 16.4 years, 79% male) were treated for acute gout in the ED of which 11.2% were hospitalized. A total of 129 patients (28.3%) received prescription opioid at discharge. Of these, 102 (79%) patients were not on opioids at admission. In a multivariable model, diabetes [aOR 2.02 (1.13–3.59)], prescription opioid use at admission [aOR 2.1 (1.01–4.34)] and having a polyarticular gout attack [aOR 2.58 (1.33–4.99)] were associated with increased odds of prescription opioid use at discharge.

Conclusion: Despite the availability of effective treatments, opioids are commonly used for management of acute gout, even in patients who are not present on it at admission. Fear of steroid use in diabetics could have led to increased reliance on opioids. Similarly, polyarticular involvement led to increased use of opioids. The study highlights an opportunity to curb the opioid epidemic among acute gout patients.

Table 1. Baseline characteristics of the cohort.

		Opioids not used at discharge (n=327)	Opioids used at discharge (n=129)
Age (years)		59.27 ± 16.6	57.37 ± 15.8
Male (%) [*]		251 (77)	110 (85.3)
Race	African American	51 (15.6)	25 (19.4)
	Asian	8 (2.5)	5 (3.9)
	Caucasian	206 (63.2)	80 (62)
	Other	61 (18.7)	19 (14.7)
	Missing	1	0
Diabetes [*]		79/245 (32.2)	51/107 (47.7)
Hyperlipidemia		149/245 (60.8)	76/107 (71)
Hypertension [*]		185/245 (75.5)	91/107 (85.1)
Coronary artery disease		66/245 (26.9)	30/107 (28.0)
Congestive heart failure		51/245 (20.8)	27/107 (25.2)
Chronic kidney disease		59/245 (24.1)	29/107 (27.1)
Inflammatory arthritis		15/245 (6.1)	5/107 (4.7)
History of gout		168/245 (68.6)	75/107 (70.1)
Alcohol abuse		30/245 (12.2)	15/107 (14.0)
History of substance abuse [*]		17/245 (6.9)	15/107 (14.0)
Chronic pain		5/245 (2.0)	3/107 (2.8)
Prior to admission opioids use [*]		27/327 (8.3)	27/129 (20.9)
ED Severity Scale	Moderate to severe (2 & 3)	163/284 (57.4)	61/117 (52.1)
	Mild to moderate (4 & 5)	121/284 (42.6)	56/117 (47.9)
Time at presentation to the ED	Midnight to 8 AM	55/284 (19.4)	19/118 (16.1)
	8 AM to 4 PM	144/284 (50.7)	60/118 (50.9)
	4 PM to midnight	85/284 (29.9)	39/118 (33.0)
Time of year of presentation	Jan-Mar	52/284 (18.3)	21/118 (17.8)
	Apr-Jun	94/284 (33.1)	37/118 (31.4)
	Jul-Sep	80/284 (28.1)	33/118 (28.0)
	Oct-Dec	58/284 (20.4)	27/118 (22.8)
Admitted patients		33/327 (10.1)	18/129 (14.0)
Joint distribution (polyarticular) [*]		37/327 (11.3)	34/129 (26.4)

^{*} represent p<0.05.

Disclosure: D. Dalal, None; N. Mbuyi, None; I. Shah, None; P. Malhotra, None; S. Reinert, None; R. Hilliard, None.

Abstract Number: 1303

Rituximab Versus Mycophenolate Mofetil in Interstitial Lung Disease Secondary to Connective Tissue Disease

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Interstitial lung disease (ILD) is a major cause of morbidity and mortality in connective tissue diseases (CTD). CTD-related ILD (CTD-ILD) has typically been treated with mycophenolate mofetil (MMF) and cyclophosphamide. B-cell depletion therapy with rituximab is increasingly being used in CTD-ILD based on the concept that B cells play a key role in the inflammatory process. The goal of this study was to compare the effect of rituximab versus MMF on pulmonary function in patients with CTD-ILD.

Methods: The study was conducted at two sites, Stanford and Centre Hospitalier de l'Université de Montreal. Retrospective chart review was performed on 83 subjects; the 15 patients in the treatment group received rituximab ± MMF (10/15 received both), and the 68 patients in the control group received MMF only. All had documented ILD and met validated classification criteria for a specific CTD, including systemic sclerosis (n=26), dermatomyositis/polymyositis (16), rheumatoid arthritis (15), Sjogren's syndrome (12), mixed connective tissue disease (8), and undifferentiated connective tissue disease (6). The difference in predicted forced vital capacity (FVC) and diffusion capacity of carbon

monoxide (DLCO) at baseline and after 6-12 months of therapy was compared between the treatment group and control group by Wilcoxon rank-sum test. Linear mixed models accounting for repeated measures assessed for changes in PFTs over time. Kaplan-Meier estimates compared survival between groups.

Results: There were no significant differences in age, gender, ethnicity, baseline FVC, presence of pulmonary hypertension, or concurrent use of other immunosuppressive medications. However ILD duration prior to treatment initiation was longer in the treatment group at 47 months (range 4-170 months) versus 6.5 months (range 0-164 months) in the control group ($p=0.0003$). Baseline DLCO was numerically lower in the treatment group at 51.5% (range 28-76%) versus 62.0% (range 27-116%, $p=0.058$) in the control group. Wilcoxon rank-sum testing revealed a 3.5% (range -11-21%) decrease in FVC in the treatment group compared to a 2.0% (range -14-25%) increase in the control group ($p=0.029$), and a 3.0% (range -10-12%) decrease in DLCO in the treatment group compared to a 4.5% (range -30-36%) increase in the control group ($p=0.046$).

Mixed model analysis controlling for ILD disease duration at treatment initiation, baseline DLCO, SSc vs. non-SSc, presence of pulmonary hypertension, and use of prednisone showed no significant difference in FVC between groups at 6 months (-1.77 (95% CI -10.25-6.72), $p=0.70$) and 1 year (-3.06 (95% CI -11.59-5.46), $p=0.48$). There was a non-significant decrease in DLCO in the treatment compared to control group at 6 months (-4.58 (95% CI -10.28-1.12), $p=0.11$), and a significant decrease at 1 year (-6.20 (95% CI -11.97--0.43), $p=0.04$). The all-cause mortality rate was 2/15 in the treatment group and 6/68 in the control group, with 1, 2, and 3 year survival rates of 100%, 100%, and 89% vs. 99%, 94%, and 92%, respectively ($p=0.45$).

Conclusion: Rituximab \pm MMF did not improve pulmonary function, but resulted in similar survival compared to MMF alone in a recalcitrant population of CTD-ILD.

Disclosure: L. Zhu, None; S. Li, None; L. Gagne, None; S. Jacobs, None; J. Morisset, None; J. Mooney, None; R. Raj, None; L. Chung, Third Rock Ventures; Incyte, 5.

Abstract Number: 1304

Rituximab in Connective Tissue Disease – Associated Interstitial Lung Disease

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Interstitial lung disease (ILD) is a major cause of morbi-mortality in patients (pts) with CTD. Small studies have recently demonstrated a promising role for rituximab (RTX) in the treatment of CTD-ILD.

Methods: We conducted a retrospective multicenter study including CTD-ILD pts treated with RTX. ILD was based on high resolution CT (HRCT) and/or lung biopsy. Results of HRCT, pulmonary function tests (PFTs) and 6-minute walking test (6MWT) before and after RTX were collected and compared using Wilcoxon matched pair test.

Results: Forty-five pts were included (77.8% female, 62 ± 12.9 years (yrs) old at last follow-up and mean CTD duration of 12.8 ± 6.8 yrs). Eighteen pts (40%) were current/former smokers. Twenty-nine (64.4%) pts had RA, 4 (8.9%) primary SS, 3 (6.7%) SSc, 3 PM, 3 SLE, 1 (2.2%) DM, 1 anti synthetase syndrome and 1 overlap syndrome (SLE/SS). Among RA pts, 24 (82.8%) had positive RF and 28(96.6%) ACPA. ANA were positive in 26/44 pts (57.8%).

ILD was diagnosed after 4yrs [IQR 1-9.5] of CTD. Only 1 pt with overlap SLE/SS had ILD as a prior diagnosis. Non-specific interstitial pneumonia (NSIP) was present in 17 (37.8%) pts, usual interstitial pneumonia in 16 (35.6%),

Table 1

Revaluation	6-24 months	25-48 months	49-72 months
DLCO (n)	23	9	4
≥ 15% from baseline	19 (82.6%)	8 (88.9%)	3 (75%)
< 15% from baseline	4 (17.4%)	1 (11.1%)	1 (25%)
FVC (n)	32	11	5
≥ 10% from baseline	27 (84.4%)	11 (100%)	4 (80%)
< 10% from baseline	5 (15.6%)	0 (0%)	1 (20%)
HRCT (n)	25	9	4
Improvement/stabilization from baseline	22 (88%)	7 (77.8%)	4 (100%)
Worsening from baseline	3 (12%)	2 (22.2%)	0 (0%)

Legend: DLCO – gas transfer; FVC – forced vital capacity; HRCT - high resolution computed tomography

lymphocytic interstitial pneumonia in 2 (4.4%) and endogenous lipoid pneumonia in 1 (2.2%); 9 pts had unspecific ILD pattern in HRCT.

RTX was administered 1g twice, 2 weeks apart, with a median of 2 cycles [IQR 1-4]. Three pts received concomitantly AZA. Four pts were previously treated with CYC and/or MMF and/or AZA in association with steroids. The median interval between ILD diagnosis and first RTX administration was 1yr [IQR 0-4.5]. After 1yr on RTX there was a stabilization in gas transfer (+7.1%, p=0.15) and in forced vital capacity (+3%, p=0.49) in the whole group. At last follow-up (median 3yrs [IQR 1-6] after starting RTX), 30/31 pts (36.8%) had stabilized/improved dyspnea according to New York Heart Association criteria. Data on 6MWT were lacking for proper conclusions. Detailed responses to RTX are shown in table 1.

Thirteen (28.9%) pts stopped RTX, with infection being the main cause (4pts; none had hypogammaglobulinemia; 2 receiving concomitant LFN and 1 AZA). Infusion reaction, uncontrolled joint disease, suspected lung cancer and long-standing stable disease led to RTX suspension in 2 pts each. Five pts died, 2 yrs (IQR 1-5.25] after CTD diagnosis. One pt concomitantly treated with MTX died 1 week after the first RTX cycle due to chest infection; in the other pts the cause was unknown.

Conclusion: Our results reinforce the promising role of RTX in a wide range of CTD-ILD pts and demonstrate an association with long-standing disease stability, particularly in pts with NSIP (7/11 pts with FVC≥10% from baseline after more than 24 months on RTX had NSIP). Four pts suspended RTX and 1 died due to infection, making monitoring and prophylaxis (vaccines) of extreme importance, particularly in pts with underlying ILD.

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Abstract Number: 1305

Risk of Progression of Interstitial Lung Disease with Autoimmune Features to a Systemic Autoimmune Rheumatic Disease

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Session Information

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Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Approximately 15-25% of patients diagnosed with idiopathic interstitial lung disease (ILD) have some features of autoimmunity, yet do not meet classification criteria for a systemic autoimmune rheumatic disease (ARD). In 2015, the American Thoracic Society (ATS) and European Respiratory Society (ERS) proposed the term “interstitial pneumonia with autoimmune features” (IPAF) to describe these patients. The natural history of IPAF with regard to its potential progression to an ARD is largely unknown. The aim of this study was to compare the risk of progression to an ARD between patients with IPAF and those with idiopathic ILD without autoimmune features.

Methods: We performed a retrospective cohort study of patients with ILD who were evaluated at Columbia University Medical Center from 2009-2017. Data were extracted from the electronic medical record. Patients were identified using ICD-9 and ICD-10 codes for ILD. After excluding patients with ILD due to a secondary cause, the remaining patients

were labeled “idiopathic ILD” and were divided into 2 categories based on the ATS/ERS classification criteria for IPAF: (1) those who met IPAF criteria and (2) those who did not meet IPAF criteria at initial ILD diagnosis. We then determined the percentage of patients with idiopathic ILD who were diagnosed with an ARD by a rheumatologist in the follow up period. We performed multiple logistic regression modeling the presence of IPAF at initial ILD diagnosis as the independent binary variable and diagnosis of an ARD in the follow up period as the dependent binary variable, controlling for age, sex, smoking status and immunosuppressive therapy.

Results: Out of 650 patients with ILD who were screened, complete longitudinal data were available for 393 patients. Of these 393 patients, 225 had ILD due to a secondary cause (e.g., hypersensitivity pneumonitis, ARD, sarcoidosis) and 168 had idiopathic ILD at baseline. Of the 168 patients with idiopathic ILD, 48 met IPAF criteria at initial ILD diagnosis and 120 did not. Compared to patients without IPAF, those with IPAF were younger and a greater proportion (1) were female; (2) had positive autoantibodies; (3) had an NSIP pattern on HRCT; and (4) had pulmonary hypertension at initial ILD diagnosis. In the mean follow up period of 5.5 ± 3 years, 17% (8/48) of patients with IPAF were later diagnosed with an ARD compared to 2% (2/120) of patients without IPAF. In a multivariable model adjusted for age, sex, smoking status and immunosuppressive therapy, the odds of progressing to an ARD were 13 times higher in patients with IPAF than in those without IPAF (OR 13.3, 95% CI 1.3-130.5, p-value=0.03).

Conclusion: Among patients with idiopathic ILD, IPAF confers a significantly higher risk of progression to an ARD. Prospective studies are needed to further characterize the natural history of IPAF.

Disclosure: M. Alevizos, None; E. J. Bernstein, Genentech, Inc., 5.

Abstract Number: 1306

Clinical Characteristics and Treatment Patterns in Patients with Interstitial Pneumonia with Autoimmune Features (IPAF)

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Session Information

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Background/Purpose: Interstitial pneumonia with autoimmune features (IPAF) has recently been defined to describe patients with interstitial lung disease (ILD) with certain clinical, serologic, and/or morphologic autoimmune characteristics who do not meet criteria for a specific CTD. It remains unclear, however, whether these patients have similar clinical presentations and prognoses to those with CTD-ILD. Our goal was to compare the characteristics of patients with IPAF to those with CTD-ILD, idiopathic pulmonary fibrosis (IPF), and IPF with positive autoantibodies.

Methods: We conducted a retrospective review of patients with ILD enrolled in a single-center, prospective pulmonary cohort from 2012-2017. All patients had undergone a comprehensive clinical, radiographic, and serologic evaluation with an ILD diagnosis established by a multidisciplinary panel including pulmonologists, a radiologist, and a pathologist. We reviewed medical records to collect additional information regarding patients' rheumatologic history at the time of their initial presentation to our center and identified patients with either: a) IPAF (meeting ≥ 2 of the published clinical, serologic, or morphologic criteria), b) CTD-ILD (meeting established criteria for a CTD) c) IPF without autoantibodies, or d) IPF with autoantibodies (not meeting criteria for IPAF). We compared clinical characteristics, imaging findings, baseline pulmonary function tests (PFTs), and treatment patterns between patients with IPAF and each of the other groups.

Results: We identified 46 patients with IPAF, 117 with CTD (including 33 RA, 31 SSc, 30 DM/PM, and 11 SS), 98 with IPF, and 37 with IPF with autoantibodies. IPAF and CTD-ILD patients were predominantly female and approximately 30% non-white, with similar rates of smoking, family history of autoimmunity, and baseline imaging characteristics (Table). Patients with IPF with or without antibodies were predominantly male and white, more likely to smoke, and less likely to have seen a rheumatologist. Baseline PFTs were similar across the groups. Treatment patterns during follow up were similar in patients with IPAF and CTD-ILD, with >50% receiving glucocorticoids and >30% receiving mycophenolate. A minority of patients with IPF with or without autoantibodies received glucocorticoids during follow-up and >25% of patients in both of these groups received pirfenidone.

Conclusion: Demographic and imaging characteristics were similar among patients with IPAF and CTD-ILD but quite different from those with IPF with or without autoantibodies, supporting the notion of a similar pathophysiology in IPAF and CTD-ILD. IPAF and CTD-ILD patients both commonly received immunosuppression; future work is needed to evaluate whether treatment response is similar in these population and whether immunosuppression can benefit patients with IPF with positive autoantibodies.

Table: Comparison of clinical characteristics, imaging, pulmonary function tests, and treatment patterns in patients with IPAF, CTD-ILD, IPF without autoantibodies, and IPF with autoantibodies

	IPAF N = 46	CTD-ILD N = 117	IPF without antibodies N = 98	IPF with antibodies N = 37
Baseline Clinical Characteristics				
Female	28 (60.9%)	81 (69.2%)	35 (35.7%)*	10 (27%)*
White	33 (71.7%)	81 (69.2%)	84 (85.7%)*	32 (86.5%)
Smoking (current or former)	21 (46.7%)	52 (45.2%)	66 (69.5%)*	22 (59.3%)
Inflammatory arthritis	9 (20.0%)	55 (47.8%)*	2 (2.1%)*	2 (5.4%)
Raynaud's	12 (26.1%)	49 (43.8%)*	1 (1.1%)*	1 (2.7%)*
GERD	19 (41.3%)	45 (38.5%)	37 (37.8%)	15 (40.5%)
Cough	31 (67.4%)	72 (61.5%)	63 (64.3%)	28 (75.7%)
Dyspnea	36 (78.3%)	89 (76.1%)	66 (67.4%)	28 (75.7%)
Family history of IPF	1 (2.2%)	1 (0.9%)	9 (9.2%)	6 (16.2%)*
Family history of autoimmunity	10 (21.7%)	35 (29.9%)	10 (10.2%)	4 (10.8%)
Rheumatologist visit	28 (60.9%)	102 (88.7%)*	3 (3.1%)*	9 (24.3%)*
Baseline CT characteristics				
Reticulation	39 (84.8%)	87 (74.4%)	92 (93.9%)	35 (94.6%)
Honeycombing	12 (26.1%)	39 (33.3%)	67 (68.4%)*	26 (70.3%)*
Traction bronchiectasis	17 (37.0%)	55 (47.0%)	62 (63.3%)*	25 (67.6%)*
Ground glass	26 (56.5%)	57 (48.7%)	30 (30.6%)*	15 (40.5%)
Consolidation	3 (6.5%)	14 (12.0%)	2 (2.0%)	1 (1.0%)
Baseline pulmonary function				
FVC % predicted	65.8 +/- 17.2	69.6 +/- 17.1	71.1 +/- 16.1	70.1 +/- 15.6
FEV1 % predicted	69.9 +/- 20.3	73.4 +/- 17.0	76.7 +/- 17.9*	79.2 +/- 17.3*
FEV1/FVC < 0.7	5 (10.9%)	8 (7.1%)	5 (5.4%)	0 (0.0%)
TLC % predicted	64.0 +/- 16.6	71.7 +/- 16.3*	69.5 +/- 14.8	70.6 +/- 15.9
DLCO % predicted	51.4 +/- 21.8	55.4 +/- 22.6	52.6 +/- 21.1	55.5 +/- 18.9
Immunosuppression at baseline	21 (46.7%)	83 (70.9%)*	26 (26.8%)*	15 (40.5%)
Treatment during follow-up				
Glucocorticoids	25 (54.4%)	70 (59.8%)	21 (21.4%)*	14 (37.8%)
Mycophenolate	14 (30.4%)	45 (38.5%)	4 (4.1%)*	3 (8.1%)*
Azathioprine	3 (6.5%)	11 (9.4%)	3 (3.1%)	1 (2.7%)
Tacrolimus	1 (2.2%)	5 (4.3%)	4 (4.3%)	3 (8.1%)
Cyclophosphamide	1 (2.2%)	3 (2.6%)	0 (0.0%)	0 (0.0%)
Rituximab	0 (0.0%)	12 (10.3%)	0 (0.0%)	0 (0.0%)
Pirfenidone	3 (6.5%)	5 (4.3%)	28 (28.6%)*	10 (27.0%)*
Nintedanib	2 (5.4%)	1 (0.9%)	6 (5.4%)	11 (37.7%)

N (%) and mean +/- standard deviation shown.

* p < 0.05 in pairwise comparison with IPAF, comparing proportions with chi squared or Fisher's exact test and comparing means with Student's t-test.

IPAF = interstitial pneumonitis with autoimmune features, IPF = idiopathic pulmonary fibrosis, GERD = gastroesophageal reflux disease, FVC = forced vital capacity, FEV1 = forced expiratory volume in 1 second, TLC = total lung capacity, DLCO = diffusing capacity for carbon monoxide

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Autoantibodies in Idiopathic Interstitial Lung Disease and Interstitial Pneumonia with Autoimmune Features – a Prospective Study

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Session Information

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Background/Purpose: The detection of autoantibodies plays a vital role in the diagnosis of occult connective tissue disease (CTD) in patients with interstitial lung disease (ILD), with major implications for prognosis and management. However, the prevalence and impact of autoantibodies in idiopathic interstitial pneumonia (IIP) and the newly defined research entity – interstitial pneumonia with autoimmune features (IPAF) whereby there are features suggestive but not diagnostic of an underlying CTD, is unclear.

Aim: Describe the prevalence of CTD autoantibodies in IIP, IPAF and connective tissue disease associated ILD (CTD-ILD).

Methods: Consecutive patients attending the Royal Prince Alfred Hospital ILD clinic (from 18 August 2016) were prospectively identified. Patients with IIP, IPAF and CTD-ILD defined by American Thoracic Society/European Respiratory Society, American College of Rheumatology (ACR), EULAR and complementary rheumatologic criteria were included. Extensive serological testing (ANA, ENA, SSA/Ro-60, Ro52, SSB/La, RNP, Scl70, Sm, centromere, PCNA, Ribosomal-P, SRP and myositis panel (Jo-1, PL-7, PL-12, EJ, OJ, Ku, Mi2, PMScl75, PM-Scl100)) was performed. All diagnoses were confirmed at ILD multidisciplinary meeting and rheumatology assessment if CTD-ILD or IPAF.

Results: 80 ILD patients (mean age 65 ± 10 (SD) years; 43% female; FVC% pred 74 ± 18 (SD); DLCO% pred 54 ± 17 (SD)) were included. 34 (43%) IIP, 22 (28%) CTD-ILD and 24 (48%) IPAF patients were identified. IIP and IPAF patients were older compared with CTD-ILD (mean age 70 and 65 vs. 57 years respectively; $p < 0.0005$ and 0.02). CTD-ILD and IPAF patients were more female predominant compared with IIP (68% and 54% vs. 21%, $p = 0.0006$ and 0.012). There was no difference in lung function parameters between ILD subgroups.

Table 1. Number of patients demonstrating autoantibodies by ILD subgroup

	IIP n=34	CTD-ILD n=22	IPAF n=24	TOTAL n=80
ANA $\geq 1:320$	2 (6)	9 (41) ^a	10 (42) ^a	21 (26)
Any ENA autoantibody	4 (12)	11 (50) ^a	8 (33)	23 (29)
SSA/Ro60/ Ro52	1 (3)	6 (27)	7 (29)	14 (18)
RNP	1 (3)	2 (9)	—	3 (4)
Scl-70	2 (6)	3 (14)	1 (4)	6 (8)
ACA	—	1 (5)	—	2 (3)
Ribosomal-P	1 (3)	—	—	1 (1)
Any myositis autoantibody	7 (21)	3 (14)	11 (46) ^b	21 (26)
Mi-2	1 (4)	—	1 (4)	2 (3)
Ku	2 (6)	1 (5)	1 (4)	4 (5)
PM-Scl100 and 75	3 (9)	1 (5)	5 (21)	9 (11)
Jo-1	2 (6)	—	1 (4)	3 (4)
PL-7 and PL-12	—	1 (5)	5 (21)	6 (8)
Anti-CCP and/or RF	—	3 (14)	3 (13)	6 (8)
dsDNA	—	1 (5)	1 (4)	2 (3)
Any Ab positive	12 (35)	13 (60)	21 (88) ^b	46 (58)

DATA are n(%). within ILD subgroup. ^a $p < 0.05$ compared with IIP. ^b $p < 0.05$ compared with IIP and CTD-ILD

At least one antibody was detectable in 46 (58%) of all patients, and most frequently in IPAF patients (88% vs. 35% IIP and 60% CTD-ILD, $p=0.0001$ and $p=0.04$ respectively). The prevalence of specific autoantibodies in each ILD subgroup is shown in Table 1.

IPAF and CTD-ILD patients were more likely to demonstrate ANA 1 1:320 compared with IIP (42% and 41% vs. 6%, $p=0.002$). CTD-ILD patients were more likely to demonstrate ENA versus IIP (50% vs. 12%, $p=0.004$). Myositis antibodies were most frequently demonstrated in IPAF compared with IIP and CTD-ILD (46% vs. 21% and 14%, $p=0.05$ and 0.026).

Conclusion: Autoimmune autoantibodies, including specific and myositis related, are frequently identified across ILD subtypes, including those without a defined autoimmune disease. Larger prospective studies are urgently required to validate the prevalence of autoantibodies in ILD, and determine the clinical implications for diagnosis, outcomes and management.

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Efficacy of Rituximab for Connective Tissue Disease (CTD) Associated Interstitial Lung Disease (ILD): a Single Center Study of 47 Patients

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

Session Type: ACR Poster Session B

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Background/Purpose: Interstitial lung disease (ILD) is a fatal complication of connective tissue diseases (CTDs). Despite numerous advances in immunosuppressive agents, data on effective treatment for this challenging entity is limited. This study aims to evaluate the efficacy of rituximab (RTX) in patients with CTD-ILD and determine factors correlated with outcomes at 6, 12 and 24 months post-RTX.

Methods: We studied 47 patients with CTD-ILD, who met ACR classification criteria for a specific CTD. ILD was confirmed by high-resolution CT chest (HRCT) and pulmonary function tests with forced vital capacity (FVC) and diffusion capacity of lung for carbon monoxide (DLCO). We compared HRCT chest findings, %FVC and %DLCO at time of diagnosis and at 6, 12 and 24 months post-RTX. At diagnosis HRCT chest findings classified into 3 groups (mild, moderate, severe). At 6, 12 and 24 months after RTX, using the same semi-quantitative scoring system, HRCT chest findings were ranked as worsening, stable or improving.

Multiple patient characteristics (Table 1) were tested for their correlation with each outcome. For some variables, nonparametric statistical methods were used due to a small number of non-missing variables. The Spearman rank correlation and Wilcoxon signed rank test were used to determine % change in FVC and DLCO at 6, 12 and 24 months after RTX treatment.

Table 1.

% Change in	Mean±SD	# Missing	p-value ¹
FVC at 6 months	0.12±11.4%	23	0.66
FVC at 1 year	12.7±23.8%	32	0.08 ²
FVC at 2 years	-0.35±12.7%	32	0.91
DLCO at 6 months	1.5±10.6%	36	0.64
DLCO at 1 year	7.1±15.5%	35	0.18
DLCO at 2 years	6.9±13.8%	38	0.25

Characteristic / Outcome	Number (%) or Mean±SD	Number Missing
Gender:		
Female	39 (83.0)	
Male	8 (17.0)	
Race:		
Black	37 (78.7)	
White	10 (21.3)	
CTD Type Groups:		
RA	17 (36.2)	
Scleroderma	7 (14.9)	
MCTD	8 (17.0)	
DM/PM	8 (17.0)	
Lupus / Other	7 (14.9)	
Active prednisone use	23 (48.9)	
HRCT at diagnosis		
Mild (1)	17 (36.2)	
Moderate (2)	19 (40.4)	
Severe (3)	11 (23.4)	
HRCT at 6 months		20
Worsened	1 (3.7)	
Stabilized	21 (77.8)	
Improved	5 (18.5)	
HRCT at 1 year		28
Worsened (0)	1 (5.3)	
Stabilized (1)	16 (54.2)	
Improved (2)	2 (10.5)	
HRCT at 2 years		26
Worsened	0 (0)	
Stabilized	13 (61.9)	
Improved	8 (38.1)	
Age (years)	55.4±12.7	
CTD duration (years)	4.43±6.01	
ILD duration (years)	2.61±2.99	1
% FVC at diagnosis	64.7±22.9%	8
% FVC at 6 months	64.2±20.5%	20
% FVC at 1 year	71.7±29.3%	31
% FVC at 2 years	64.2±14.4%	25
% DLCO at diagnosis	45.6±14.9%	22
% DLCO at 6 months	48.7±16.8%	31
% DLCO at 1 year	52.2±16.3%	35
% DLCO at 2 years	55.2±19.3%	32
Number of drugs for PI ^a	1.4±1.0	

Results: Table 2.

1. Most patients were female and African American with median age of 60.
2. HRCT Chest findings after RTX showed either improvement or stability at 6, 12, 24 months (96.3%, 94.7%, and 100% respectively).
3. Given multiple missing variables, there was no statistical difference for changes in FVC and DLCO, however observed changes improved with the median %change ranging from 1 to 3.5. The largest changes were observed for FVC and DLCO at 1 year and DLCO at 2 years after treatment (12.7%, 7.1% and 6.9%, respectively) (table 2).
4. CTD duration showed negative correlation with FVC change at 1 year post-RTX with estimated 1.1% decrease in FVC for every year increase in CTD. ILD duration showed negative correlation with DLCO change at 2 years post-RTX with estimated 3.9% decrease in DLCO for every year increase in ILD.

Conclusion: RTX is an effective therapy for CTD-ILD. Our study suggests that using RTX earlier in the disease course may have long-term positive impact. RTX may help fill an unmet therapeutic need for CTD-ILD but larger randomized clinical trials are needed.

Disclosure: M. Tariq, None; S. Patel, None; S. Umer, None; G. Caldito, None; S. Hayat, None.

Interstitial Pneumonia with Autoimmune Features: Is It Frequent?

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Session Information

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Background/Purpose: A particular subset of interstitial pneumonia, associated to one or more clinical and serological features, suggesting a possible underlying autoimmune disorder, has been described and recently named Interstitial Pneumonia with Autoimmune Features (IPAF). Its prevalence and prognosis remains controversial and seems to include a very heterogeneous population. Our objective was to evaluate patients with interstitial lung involvement seen at a university hospital in Latin America in order to determine IPAF frequency and characteristics.

Methods: All electronic medical records of patients seen by pneumonologists during a 1 year at our hospital because of an interstitial lung disease (ILD) were reviewed by a rheumatologist and a pneumonologist in conjunction. Patients were classified in 3 groups: Idiopathic Pulmonary Fibrosis (IPF), IPAF and Interstitial Pneumonia associated with a connective tissue disease (IP-CTD). Demographic and clinical data, images features, lung function tests, and survival were recorded. Patients' characteristics were compared between groups and a multivariate logistic regression analysis was performed in order to identify associations with an autoimmune ILD.

Results: 80 patients were seen in 1 year with ILD: 31 with IFP (38.8%), 3 with IPAF (3.8%) and 46 (57.5%) with IP-CTD. Patients' characteristics are shown in table 1. Rheumatologic diseases with IP-CTD were Lupus in 2 patients, Mixed Connective Tissue Disease in 6, Limited Systemic Sclerosis in 2, Diffuse Systemic Sclerosis in 19 and 1 Inflammatory Myopathy. During a median follow up of 4.8 years (IQR 3.8-6.9) after ILD diagnosis, 5 patients died (6.3%): 3 with IFP and 2 with IP-CTD. Gender, Age and Physiology score (GAP) was associated with mortality as it has been previously described (OR 1.76, 1.02-3.07). In patients with IFP, CT pattern was UIP in 41.9% (CI 25.7-60.1%) and NSIP in 35.5 % (CI 20.5-54.0%). On the other hand, patients with IP-CTD, NSIP was the most frequent pattern in 60.0% (CI 44.8-73.5%), and 24.4% (13.9-39.4%) had an UIP pattern. Although NSIP was more frequent in autoimmune related ILD, it was not independently associated to it. In the multivariable logistic regression analysis female sex (OR 10.5, CI 2.75-40.15) and a younger age (OR 0.94, CI 0.89-0.98) were associated with an autoimmune ILD diagnosis.

Conclusion: When evaluated together by a rheumatologist and a pneumonologist, IPAF diagnosis was very rare (3.8%). An autoimmune ILD disease must be suspected in females and younger patients.

	Idiopathic Pulmonary Fibrosis (n=31)	Interstitial pneumonia with autoimmune features (n=3)	Interstitial Pneumonia associated with a connective tissue disease (n=46)	p
Mean Age at interstitial lung disease diagnosis (ILD), (SD)	68.2 (10.9)	69.2 (3.6)	55.3 (16.6)	0.01
Female, n (%)	14 (45.2)	2 (66.7)	43 (93.5)	<0.01
Median Follow up after interstitial lung disease diagnosis, years, (IQR)	4.5 (3.7-5.7)	6.6 (4.3-7.5)	5.1 (3.8-6.9)	0.50
Death during follow-up, n (%), CI)	3 (9.7, 3.0-26.8)	0	2 (4.3, 1.0-16.3)	0.58
Ever smoker, n (%), CI)	13 (41.9, 25.7-60.1)	3 (100)	14 (30.4, 18.7-45.5)	0.04
Corticosteroid treatment because of ILD, n (%), CI)	23 (74.2, 55.6-86.8)	2 (66.7, 9.2-97.5)	31 (67.4, 52.3-79.6)	0.81
Immunosuppressant treatment because of ILD, n (%), CI)	10 (32.3, 17.9-50.9)	1 (33.3, 2.5-90.8)	23 (50.0, 35.6-64.4)	0.30
First Vital Force Capacity (VFC), %, median (IQR)	73 (63-80)	97 (85-120)	81 (74-97)	0.01
Last Vital Force Capacity (VFC), %, median (IQR)	70 (60-81)	83 (58-94)	77(57-90)	0.45
Decline in VFC >10% during follow- up, n (%), CI)	8 (28.6, 14.6-48.3)	1 (33.3, 24.4-90.9)	10 (25.6, 14.1-41.9)	0.94
	62 (51-70)	64 (48-74)	72 (61-81)	0.01

Table . (Cont'd)

	Idiopathic Pulmonary Fibrosis (n=31)	Interstitial pneumonia with autoimmune features (n=3)	Interstitial Pneumonia associated with a connective tissue disease (n=46)	p
First Diffusing capacity of the lung for carbon monoxide (DLCO), %, median (IQR)				
Last Diffusing capacity of the lung for carbon monoxide (DLCO), %, median (IQR)	52 (44-64)	48 (45-52)	64 (53-70)	0.05
Non-specific interstitial pneumonia at chest CT, n (%; CI)	11 (35.5, 20.5-54.0)	3 (100)	27 (60.0, 44.8-73.5)	0.03
GAP Index for Idiopathic Pulmonary Fibrosis (IPF), median (IQR)	4 (3-5)	3.5 (3-4)	2 (1-3)	<0.001

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Diagnostic Utility of Myositis Antibodies in Patients with Interstitial Lung Disease and Suspected Underlying Connective Tissue Disease

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Session Information

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Background/Purpose: Interstitial Lung Disease (ILD) is a common manifestation of Connective Tissue Diseases (CTD), mainly Systemic sclerosis(SSc), Rheumatoid Arthritis and Idiopathic Inflammatory Myositis (IIM) spectrum diseases. New myositis specific (MSA) and associated (MAA) antibodies have shown to be useful in identifying underlying CTD in patients with ILD of unknown etiology. They have helped identifying diagnosis such as Anti-synthetase Syndrome (AS), MDA-5 associated IIM, overlap syndromes (OS) and Interstitial lung disease with autoimmune features (IPAF). Our purpose is to evaluate the diagnostic utility of the determination of MSA/MAA in a group of patients withheld of unknown etiology and clinical features suggestive of underlying CTD.

Methods: It is a descriptive study. Between January 2017 and March 2018, a commercially available myositis panel (16 antibodies, Immunoblot technique) was performed in 111 patients from a rheumo-pneumological clinic in the Instituto Nacional del Tórax in Santiago, Chile. All patients had confirmed ILD by high resolution chest tomography (HRCT) and clinical features suggestive of underlying CTD.

Results: Among 111 patients, 76 (72%) were female, and the average age was 51,5 +/- 12,9 y/o. All patients had confirmed ILD by high resolution chest tomography (HRCT). There were 56 (50,5%) positive patients for one or more antibodies of the panel; and 55 patients (49,5 %) were negative. Antibodies against Ro-52 were the most frequent (n= 35, 62,5 %), followed by PM/Scl-75 (n= 12, 21,4%); Ku (n=9, 16%) and PL-12 (n=7, 12,5%). AS was the most common final diagnosis (14 patients). Antibodies, final diagnosis and ILD patterns of the positive patients are detailed in Table 1. Final diagnosis of the 55 negative patients are detailed in Table2.

Conclusion: Myositis antibodies are useful in the study of patients with ILD of unknown etiology and clinical features suggestive of an underlying CTD. They can help establish a definite rheumatological diagnosis, and therefore offer the patient a proper treatment. We highlight the importance of Idiopathic inflammatory myopathies in this group of patients, mainly AS and MDA-5 myopathy. Our cohort shows low rate of Jo-1 because this antibody is widely available in our

TABLE 1: MYOSITIS ANTIBODIES, DIAGNOSIS AND ILD PATTERNS IN POSITIVE PATIENTS (N = 56)		
Myositis antibodies	n	%
RO-52	35	62,5
PM/Scl-75	12	21,4
KU	9	16
PL-12	7	12,5
MDA-5	5	8,9
PM/Scl-100	5	8,9
SRP	4	7,1
SAE-1	4	7,1
EJ	3	5,4
Mi-2	3	5,4
Jo-1	2	3,6
PL-7	2	3,6
OJ	1	1,8
NXP-2	1	1,8
TIF1y	0	0
Diagnosis		
IIM	26	46,4
AS	14	26,8
MDA-5 associated IIM	5	8,9
Amyopathic Dermatomyositis	3	5,4
Dermatomyositis (DM)	2	3,6
Polymyositis (PM)	2	3,6
Other	30	53,6
IPAF	12	21,4
SSc	6	10,7
PM-DM/SSc overlap	5	8,9
Primary Sjögren's disease	4	7,1
Systemic Lupus Erythematosus (SLE) /SSc overlap	2	3,6
SLE/ PM-DM overlap	1	1,8
ILD Patterns		
Non-specific interstitial pneumonia (NSIP)	26	46,4
Organizing Pneumonia (OP)	10	17,9
NSIP/OP overlap	13	23,2
Lymphocytic interstitial pneumonia (LIP)	1	1,8
Unclassified pattern	1	1,8

TABLE 2: FINAL DIAGNOSIS IN NEGATIVE PATIENTS (N = 55)		
	n	%
IPAF	21	38,1
Suspected Scleroderma "sine"	6	11
Mixed Connective Tissue Disease (MCTD)	1	1,8
Chronic Hypersensitivity Pneumonia (cHP)	7	12,7
Idiopathic NSIP	7	12,7
Idiopathic Pulmonary Fibrosis (IPF)	5	9,1
Pending final diagnosis (under study)	7	12,7

country, and we didn't perform the myositis panel in patients who had previously positive Jo-1. Finally, we highlight the contribution of MSA/MAA in detecting IPAF patients.

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A Multidisciplinary Cohort of Patients with Interstitial Pneumonia with Autoimmune Features

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Session Information

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Background/Purpose: Interstitial Lung Disease (ILD) remains a significant diagnostic and therapeutic challenge, especially for patients who do not meet criteria for a connective tissue disease (CTD) or idiopathic pulmonary fibrosis. In 2015, the ATS/ERS developed the classification criteria for Interstitial Pneumonia with Autoimmune Features (IPAF) to describe individuals with features of autoimmunity who do not meet classification criteria for a CTD. It is unknown whether these criteria identify patients who could benefit from immunosuppressive therapies, we aim to evaluate this in a prospective cohort of patients.

Methods: IRB approval for the MYSTIC cohort was obtained in 9/2017. Patients were identified in the Vanderbilt University pulmonary and rheumatology clinics; inpatients were referred by their treating providers. Clinical phenotyping was performed by chart abstraction, and biospecimens were banked for future study. Additional data on pulmonary outcomes (radiographic studies, pulmonary function tests, echocardiograms, 6 minute walk test, supplemental oxygen use) will be collected at 6 month intervals.

Table 1: Demographics of Interstitial Pneumonia with Autoimmune Features Cohort (N=29)	
Age	
30-40	2 (6.9)
41-50	5 (17.2)
51-60	8 (27.6)
>61	14 (48.3)
Sex	
Female	15 (51.7)
Race/Ethnicity	
Caucasian	24 (82.7)
Site of Enrollment	
Pulmonary Clinic	9 (31.0)
Rheumatology Clinic	17 (58.6)
Inpatient Pulmonary Service	2 (6.9)
Intensive Care Unit	1 (3.4)
Subspecialty Evaluation	
Pulmonary Clinic Only	2 (10.3)
Rheumatology Clinic Only	0
Both Pulmonary and Rheumatology Clinic	27 (93.1)
Immunosuppression at time of Enrollment	
Prednisone	15 (51.7)
Azathioprine	5 (17.2)
Mycophenolate mofetil	10 (34.5)
Methotrexate	1 (3.4)
Hydroxychloroquine	2 (6.9)
Cyclosporine	0
Rituximab	1 (3.4)
No Treatment	6 (20.1)
Supplemental Oxygen Use	
Yes	17 (58.6)

Table 2: Findings of Interstitial Pneumonia with Autoimmune Features by Criteria (N=29)	
Clinical Criteria n(%)	16 (55.2)
Raynaud's Phenomenon	8 (27.6)
Inflammatory Arthritis	8 (27.6)
Mechanic's Hands	6 (20.7)
Gottroff's Sign	0
Shawl Sign	1 (3.4)
Heliotope Rash	1 (3.4)
Distal Tip Ulceration	0
Telangiectasia	0
Unexplained Digital Edema	0
Serologic Criteria n(%)	29 (100)
ANA	19 (65.6)
Isolated ANA Positivity	11 (37.9)
RF > 2x Normal	4 (13.8)
Isolated RF Positivity	0
Anti-CCP	2 (6.9)
Anti-Ro	8 (27.6)
Other Extractable Nuclear Antigens (dsDNA, Sm, La, RNP)	4 (13.8)
Anti-Scl70	4 (13.8)
Anti-RNA Synthetase	6 (20.7)
Anti-Pm/Scl	2 (6.9)
Anti-MDA5	1 (3.4)
Morphologic Criteria n(%)	28 (96.6)
Radiographic (N=23)	
NSIP on CT	8 (34.8)
Organizing Pneumonia on CT	0
NSIP+ Organizing Pneumonia on CT	0
Inconsistent with UIP on CT	15 (65.2)
LIP	0
Histologic (N=9)	
Fibrosing NSIP	3 (33.3)
Cellular NSIP	2 (22.2)
Organizing Pneumonia	5 (55.6)
LIP	0
Interstitial Lymphoid Aggregates with Germinal Centers	1 (11.1)
Diffuse Lymphoplasmacytic Infiltration	2 (22.2)
Multi-Compartment Involvement	
Pulmonary Hypertension	5 (17.2)
Other	1 (3.4)

Results: 29 patients meeting IPAF criteria were enrolled. The median age was 60, and 51.7% were female. 93% were evaluated by both pulmonologists and rheumatologists (table 1). Clinical criteria were present in 55.2%, serologic criteria in 100%, and morphologic criteria in 96.6% (table 2). The most common clinical features were Raynaud's phenomenon, inflammatory arthritis, and mechanic's hands. The vast majority of patients had a high resolution CT scan read as NSIP or "inconsistent with UIP"; only 3.4% had an HRCT scan consistent with UIP. 37.9% had an isolated positive ANA or rheumatoid factor, while 27.6% had anti-synthetase or anti-PM/Scl antibody.

Conclusion: IPAF undoubtedly encompasses a heterogeneous group of patients. Our cohort contains much less UIP than prior reports and has many patients with myositis associated antibodies. Additional work is needed to ascertain if (1) patients with myositis associated antibodies behave differently from patients with non-specific serologies and (2) whether these criteria identify patients who benefit from immunosuppression.

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Abstract Number: 1312

Interstitial Pneumonia with Autoimmune Features (IPAF)-Nsis: Hurdles to Reclassification of Overlapping Ilds

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Background/Purpose: Interstitial lung disease (ILD) may occur in the presence of autoimmune elements without meeting criteria for a distinctive Connective Tissue Disease.

The European Respiratory Society/ American Thoracic Society proposed a term 'interstitial pneumonia with autoimmune features' (IPAF) to further classify these individuals based on a combination of features from three domains: clinical, serologic and pulmonary morphologic.

We sought to assess the incidence of IPAF previously classified as idiopathic interstitial pneumonia or ILD associated with undifferentiated connective tissue disease (UCTD). Hurdles in the reclassification process were also highlighted.

Methods: Our institution's pathology database was scanned for 10 years of surgical lung biopsy data. Patients with biopsy proven nonspecific interstitial pneumonia (NSIP) were studied. Their clinical and serologic data was collated. Cases with a prior diagnosis of idiopathic NSIP or ILD associated with UCTD were screened by the ERS/ATS criteria for IPAF and reclassified.

Results: 17 of 278 surgical lung biopsies performed from 2006 to 2016 for ILD were reported as NSIP. 41% of these NSIP cases were previously classified as idiopathic, 17.7 % as associated with UCTD and the remaining had established autoimmune etiologies for an ILD.

57% of the prior idiopathic cases were reclassified as IPAF and 100% of the prior UCTD were reclassified as IPAF. All cases met morphologic criteria (NSIP on lung biopsy), 57% had serologic criteria and 71% met clinical criteria. The serologic workup was incomplete in a few patients.

Conclusion: Previous diagnoses of UCTD-ILD and Idiopathic NSIP may be reclassified as IPAF. This will help promote future research to guide management of this unique population. It is important to stress the need for serologic work up of ILD patients, to enable complete assessment and appropriate classification of patients.

Disclosure: A. Odonwodo, None; A. Pande, None.

Abstract Number: 1313

Clinical Features and Timing of Studies in Interstitial Lung Disease with Autoimmune Disease Features: Do Autoantibody Panels Improve Diagnostic Yields and/or Increase Costs?

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Session Time: 9:00AM-11:00AM

Background/Purpose: The entity of interstitial lung disease with autoimmune disease features (ILD-AF) is increasingly gaining traction as condition that is best co-managed by pulmonologists and rheumatologists. In September 2016, our institution initiated a comprehensive ILD auto-antibody panel, including ANA, RF, CCP, Jo-1, PL-7, PL-12, EJ, OJ, SRP, MDA5, NXP2, Ku, PMSCL, U1RNP, and Scl-70 to assist in the diagnosis of ILD-AF. We compared the number of additional diagnostic studies ordered in patients that had an autoantibody panel ordered to determine if autoantibody panels improve diagnostic yields and/or increase costs.

Methods: In patients that had an autoantibody panel, we assessed whether the test resulted in hand radiographs (XR), creatinine kinase (CK), aldolase, electromyogram(EMG), muscle magnetic resonance imaging (MRI), capillaroscopy, age appropriate cancer screening, and whether a CTD or ILD-AF diagnosis was subsequently given by a comprehensive chart review. We compared the number of tests ordered when panel was positive versus negative by frequency (descriptive statistics). This project was IRB approved.

Results: In the course of 18 months, 170 comprehensive autoantibody panels were ordered. Of these, 100 patients (59%) had at least one positive autoantibody test. As expected both groups had the same number of HRCT chest, but the frequency of tests subsequently ordered after a positive vs. negative autoantibody panel are described in Table 1. A diagnosis of CTD or ILD-AF was given in 26% of patients with at least one positive autoantibody test identified on these panels, compared to 3% of patients with negative panels.

Conclusion: In a single center cohort retrospective analysis, positive auto-antibodies identified on ILD-AF panels resulted in more creatine kinase levels, aldolase levels, hand radiographs, and muscle MRIs, but was also more likely to result in a diagnosis of CTD or ILD-AF. In conclusion, a positive auto-antibody panel appears to increase costs by number of tests ordered, but also improves diagnostic yields. The role of capillaroscopy in ILD-AF diagnosis may be important.

Table 1. Tests and diagnostic yield in patients with ILD autoantibody panel.

	CK	Aldolase	Hand XR	Muscle MRI	EMG	Cancer Screening	Capillaroscopy	Diagnosis of CTD or ILD-AF
Positive Panel	0.34	0.24	0.09	0.07	0.12	0.13	0.07	0.26
Negative Panel	0.15	0.07	0.02	0.02	0.18	0.22	0	0.03

Disclosure: J. Wright, None; D. Odrobina, None; M. B. Scholand, None; A. E. Tebo, None; T. M. Frech, None.

Abstract Number: 1314

Autoantibodies and Clinical Outcomes in Pulmonary Arterial Hypertension Associated with Connective Tissue Diseases

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Pulmonary arterial hypertension (PAH) associated with SSc (SSc-PAH) has a substantially worse prognosis as compared to other connective tissue diseases(CTD)-PAH. Although SSc-PAH are generally treated with pulmonary vasodilators, they could be additionally considered with intensive immunosuppressive therapies (IIT), if overlapping inflammatory autoimmune diseases such as SS and SLE. However, it has not been known their outcome. We assessed the detailed autoantibodies and discriminative clinical symptoms and followed up their outcomes.

Methods: This retrospective study included 50 PAH patients associated with SSc (n=17), SLE (n=18), primary SS (n=8), and MCTD (n=7) referred to our hospital between 2000 and 2018. We performed right-heart catheterization and PAH defined as mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg and the pulmonary arterial wedge pressure (PCWP) ≤ 15 mmHg at rest. We obtained their serum and determined autoantibodies against cytoplasmic and cell-nuclear antigens, including centromere, Scl-70, RNA-polymerase III, centriole, NuMA1, RNP, Sm, SSA/Ro, SSA/Ro52, SSB, PM-Scl, fibrillarin, Th/To, Ku, dsDNA, nucleosomes, histones, ribosomal P-proteins. We treated all patients with pulmonary

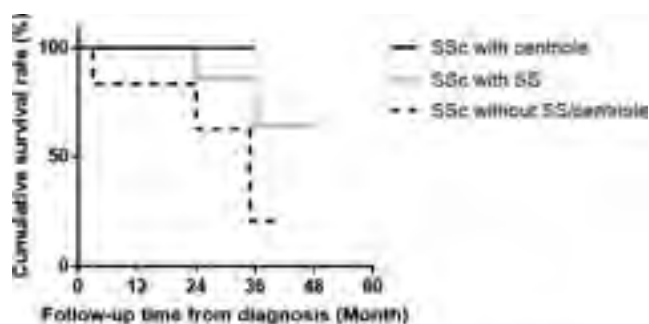


Figure. Cumulative survival rate of SSc-PAH subgroup

vasodilators, and additionally treated with IIT, including cyclophosphamide (IVCY500mg/month x 10 times) and steroid (prednisolone 1mg/kg for 4 weeks and tapered to 5-10mg) for most of SLE, pSS, and MCTD, and some of SSc overlapping inflammatory autoimmune symptoms. Survival analysis was performed using the Kaplan-Meier method, and cumulative survival rates were compared by log-rank tests.

Results: In terms of SSc, we divided into three groups because those were different outcomes, which were (1) overlapping SS diagnosed by ACR criteria (n=7), (2) with centriole antibodies(n=3), or (3) without SS/ centriole antibody(n=7). We treated some severe PAH with SS overlapping SS by IVCY with half dose steroid (0.5mg/kg) and PAH improved. All of centriole-SSc had discriminative digital ulcer. The one of them had quite severe ulcer and IVCY was remarkably effective for both ulcer and PAH, then treated in the same way for others. There was significantly worse cumulative survival rate in SSc than in SLE, pSS. In terms of SSc subgroup, there was a trend towards a better survival rate in centriole and overlapping SS than in other SSc (Figure). Th/To, which was one of the marker of lcSSc, existed in two patients although the one did not have scleroderma. Ribosomal P antibody existed in 4 patients, however, 3 of them did not have any neuro-psychiatric-SLE symptoms.

Conclusion: Although SSc-PAH has a substantially poor prognosis, we found that SSc overlapping SS and centriole type SSc-PAH might have better outcome than other SSc associated PAH and we could consider IIT for them. However, we should consider the risk of renal crisis, digestive symptoms other life-threatening symptoms before utilizing IIT for SSc.

Disclosure: Y. Shiota, None; T. Ishii, None; T. Shirai, None; H. Fujii, None; H. Harigae, None.

Abstract Number: 1315

Japanese Relapsing Polychondritis Patients with Airway Involvement Were Mutually Exclusive with Those with Ear Involvement in the Clinical Characteristics

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

Session Type: ACR Poster Session B

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Background/Purpose: Relapsing polychondritis (RP) is a multisystem disorder of cartilaginous tissues. We previously found that, in a Japanese cohort study, RP patients with airway involvement and RP patients with external ear involvement were mutually exclusive in the clinical characteristics, suggesting an inverse relationship between airway involvement and ear involvement (Arthritis Rheumatol. 2018; 70: 148–9.). Here, we divided the patients into two subgroups by the patterns of clinical manifestations, namely a subgroup of patients with airway involvement (A subgroup) and those with ear involvement (E subgroup) and investigated the clinical and laboratory characteristics of each subgroup.

Methods: After categorizing 239 Japanese patients into two (A and E) subgroups, we compared patients' profiles, clinical features, laboratory findings, medicines, and prognosis using dummy variables and the Student's t-test. The presence and absence of these clinical and laboratory parameters formed dummy variables, 1 and 0, respectively. We measured serum matrix metalloproteinase-3 (MMP3) concentrations and anti-type II collagen antibody titers, disease-related biomarkers, of 26 samples obtained from 22 newly recruited RP patients.

Results: In Japanese RP patients, 47 patients (19.7%) and 118 patients (49.4%) were allocated to the A and E subgroups, respectively. In a comparison of the clinical data between the two subgroups, saddle nose deformity and progressive disease course were observed frequently in the A subgroup. Joint, eye, and CNS involvement were observed frequently in the E subgroup. The remaining RP patients formed the third subgroup (75 patients, 31.4%) and had both airway and ear involvement (termed as B subgroup). Disease duration of the B subgroup (5.70 ± 0.64 years) was significantly longer than that of the E subgroup (4.12 ± 0.45 years). We found that cardiovascular involvement was more predominant in the B subgroup than in the A and E subgroups. High concentrations of serum MMP3 were observed frequently in the B subgroup compared with A and E subgroups. In a new cohort of 26 serum samples, MMP3 concentrations were significantly higher in the B subgroup (n=10) than those in the A subgroup (n=6) and E subgroup (n=10).

Conclusion: RP patients in the A and E subgroups exhibited different characteristics from each other. Progressive disease course and CNS involvement were observed frequently in the A and E subgroups, respectively, in Japanese patients with RP. We did not observed cardiovascular involvement in the A subgroup of the RP patients.

Disclosure: J. Shimizu, None; N. Suzuki, None.

Abstract Number: 1316

Respiratory Involvement in Relapsing Polychondritis – a Single Centre Study

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Relapsing Polychondritis (RP) is a rare immune mediated inflammatory disorder that may result in destruction of cartilaginous tissues. Diagnostic delay is common due to its heterogeneous clinical spectrum and its rarity. RP is most commonly seen in Caucasians. Pulmonary manifestations are common and are associated with significant morbidity and mortality.

Methods: We completed a retrospective data analysis of patients attending the Louise Coote Lupus Unit with a clinical diagnosis of RP, focusing on those with respiratory involvement. We used McAdams classification criteria. All patients had lung function tests, high resolution CT scan imaging and bronchoscopy / laryngoscopy wherever necessary along with inflammatory markers and serology to rule out other diseases such as ANCA vasculitis.

Results: We identified 57 patients with a diagnosis of RP, with respiratory involvement in 23 patients (40%) (14 female and 9 male). 18 patients (78%) were Caucasian, 3 (13%) Afro Caribbean and 2 (9%) Asian. Sixteen (70%) patients presented with respiratory symptoms ranging from asthma like illness to the need for emergency tracheostomy. Median age at the symptom onset varying from 18-70 (median age of 41). There was a mean delay in diagnosis of 82 months. 32/57 patients fulfilled McAdams classification criteria. The other 25 patients had clinical presentations compatible with a diagnosis of RP.

Median ESR was 10 (5-70) mm per hour and CRP was 6 (1- 110)mg/l. : Respiratory complications: 6 patients had tracheomalacia, 5 had tracheal stenosis +/- thickening, 8 had tracheal and bronchial collapse +/-stents and 2 had an emergency tracheostomy.

Most patients were on a combination of oral prednisolone and disease modifying anti-rheumatic drugs.

Four patients received biologics. One received rituximab, two Infliximab and one adalimumab. Two patients did not respond to treatment (rituximab and infliximab). The remaining two patients had a good response.

Five patients required CPAP to maintain airways patency due to respiratory collapse.

Number of other organ involvement: 7/23 eyes 12/23 ears, 7/23 nose, 17/23 airways, 14/23 chest wall/joints

One patient had 5 organ involvement, three had 4 organ involvement, six had 3 organ involvement, nine patients had 2 organ involvement and four patients had only respiratory involvement.

Conclusion: Pulmonary involvement in RP may cause significant morbidity and mortality due to organ damage. All RP patients should be evaluated for pulmonary involvement and early detection may help to prevent the damage. Immunosuppressive agents should be considered as soon as the diagnosis of RP with respiratory involvement is established. The role of biologic therapies in treatment resistant patients is uncertain.

Pulmonary complications in RP.

N= 23	Tracheal Stenosis	Airway Inflammation	Broncho-malacia	Tracheo-Broncho malacia/ Stenosis	ESR	CRP	Prednisolone	DMARDS	Tracheostomy	Death
1	No	Yes	Unknown	Unknown	30	52	Yes	MTX	No	Unknown
2	Yes	Yes	Unknown	Unknown	39	20	Yes	No	No	No
3	Yes	Yes	No	Yes	3	<5	Yes	MMF	No	No
4	No	Yes	No	No	3	<5	Yes	MTX	No	No
5	No	Yes	Unknown	Unknown	22	7	No	No	No	Yes

Table . (Cont'd)

N= 23	Tracheal Stenosis	Airway Inflammation	Broncho-malacia	Tracheo-Broncho malacia/ Stenosis	ESR	CRP	Prednisolone	DMARDS	Tracheostomy	Death
6	No	Yes	No	Yes	61	96	Yes	MTX	Yes	No
7	Yes	Yes	Unknown	Unknown	6	5	Yes	No	No	Yes
8	Yes	Yes	Unknown	Yes	12	43	Yes	MMF	No	No
9	No	No	No	No	10	48	Yes	MMF, Minocycline	No	Unknown
10	Unknown	Unknown	Unknown	Yes	2	<5	Yes	MTX, Dapsone	No	Yes
11	No	Yes	No	Yes	6	<5	Yes	MTX	Yes	Yes
12	No	Yes	No	Yes	64	16	No	AZA	No	No
13	No	Yes	No	Yes	8	5	Yes	No	No	No
14	No	Yes	No	Yes	39	17	Yes	MMF	No	Unknown
15	No	Yes	No	Yes	8	6	Yes	MTX	No	No
16	No	Yes	No	Yes	15	4	Yes	No	No	Unknown
17	Yes	Yes	No	No	70	110	Yes	MTX	Yes	No
18	No	No	No	No	19	29	Yes	HCO, MTX	No	No
19	Yes	Yes	Unknown	Unknown	25	42	Yes	MMF	Yes	Unknown
20	No	Yes	No	Yes	4	1	Yes	AZA	No	No
21	No	Yes	Yes	Yes	7	5	Yes	MTX	No	No
22	Yes	Yes	No	Yes	5	2	No	No	No	No
23	Yes	No	No	No	4	<5	Yes	MTX	No	No

MTX = Methotrexate, MMF = Mycophenolate Mofetil, AZA = Azathioprine, HCO = Hydroxychloroquine.

Disclosure: C. D. Hughes, Lilly, 5; B. Lopez Garcia, None; C. Cheah, None; Y. J. Poh, None; S. Sangle, None; D. D'Cruz, GlaxoSmithKline, 5, 8.

Abstract Number: 1317

Tracheomalacia in Coventry in UK

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Tracheomalacia (TM) is pathological diffuse or segmental narrowing of the tracheal lumen, caused by softening of the supporting cartilage and reduction in stiffness of the walls. If the weakness extends to the right or left main bronchi then it is termed tracheobronchomalacia (TBM). Tracheomalacia can occur due to relapsing polychondritis, other etiologies include mechanical compression due to intubation or goitre. Although there have been a number of descriptions of TBM, it has not been recognised as an entity in itself. We present here a series of patients who have TBM without an alternative diagnosis to explain TBM.

Methods: These patients were identified from the TBM database. Patients were identified from rheumatology or respiratory clinics or from acute admissions with severe breathing difficulties and found to have TBM. The TBM database was set up in 2017, although the first patient was diagnosed in 2013. Patients who were initially labelled as TBM and subsequently found to have RP or another explanation for TBM were excluded from this study.

Results: We found 25 patients who had TBM, of these mechanical causes were found in only 1 patient. The diagnosis was established through inspiratory and expiratory CT scans and/or bronchoscopy in most patients and supported with pulmonary function testing which suggested large airway obstruction (intrathoracic) for the majority of patients. Patients often had symptoms for a number of years prior. A number of patients had previous CT scans which had shown evidence of TBM, this was either missed or ignored. 15 patients were treated with immunosuppression, and most of them had extremely good response to immunosuppression. These have been labelled as 'inflammatory tracheobronchomalacia' as there is no alternative label for these patients. Drugs used in these patients include steroids (IV and oral), Methotrexate, Azathioprine, Mycophenolate and Rituximab. All patients have noticed very significant results with steroids, 9 patients have not been given immunosuppression currently. CPAP has been tried in 7 patients, only 1 patient struggled to tolerate

this. In one patient, tracheobronchomalacia evolved into relapsing polychondritis, suggesting that TBM could be a 'forme fruste' of an inflammatory condition.

Death has occurred in 6 patients who have been treated with immunosuppression and 2 patients who has not been treated with immunosuppression.

Conclusion: Tracheobronchomalacia is a relatively common condition with high mortality, which is not very well characterised. Optimal management strategies are yet to be defined.

This is the first report for 'inflammatory tracheobronchomalacia' suggesting that immunosuppression might have a significant role in management of TBM.

Disclosure: G. Pink, None; S. Dubey, None; A. Ali, None; J. Shakespeare, None; C. Taylor, None; C. Gelder, None.

Abstract Number: 1318

Clinical Utility of Ultrasonography (US) in Diagnosing and Monitoring Disease Activity of Relapsing Polychondritis (RP) and Comparison of Cartilaginous US Findings between RP, Repeated Trauma and Healthy Subjects

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Relapsing polychondritis (RP) is a rare systemic inflammatory disorder, and the diagnosis and treatment evaluation are often difficult. Therefore, the discovery of more convenient imaging modality than contrast-CT, MRI and FDG-PET/CT would be required on diagnosis and treatment. To assess the clinical utility of ultrasonography (US) in diagnosing and monitoring disease activity of relapsing polychondritis (RP).

Methods: Auricular and nasal chondritis of patients with RP (n=6) were initially assessed by US before and after treatments. Secondly, the changes of US findings and serum inflammatory markers were compared in RP. Finally, the auricular and nasal US findings between patients with RP (n=6), repeated trauma (n=6) which finding is similar to RP, and healthy subjects (n=6) were examined comparatively.

Results: In all cases of RP, US finding before treatment showed low-echoic swollen auricular and nasal cartilage with increased power Doppler signals (PDS), corresponding to biopsy findings. After treatment with prednisolone (PSL) combined with methotrexate, the swollen ear and nose completely resolved. Then, swollen cartilage on US also dramatically reduced with the decrease of PDS. When serum inflammatory markers completely improved, but PDS remained in 2 of 6 cases, and these cases showed flare due to early PSL tapering. Finally, the cartilage of RP on US could be apparently differentiated from repeated trauma and healthy subject due to thickness of cartilage, PDS and subperichondrial serous effusion.

Conclusion: Assessment of RP lesions by US possibly facilitates evaluation of cartilaginous lesions and monitoring of disease activity, especially when we consider the treatment response and the timing of drug tapering.

Disclosure: S. Inotani, None; Y. Taniguchi, None.

Familial Mediterranean Fever Related Damage Assessed By Auto-Inflammatory Disease Damage Index (ADDI) and Associated Factors with Damage

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Session Information

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Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

Session Type: ACR Poster Session B

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Background/Purpose: Familial Mediterranean Fever (FMF) is the most frequent auto-inflammatory disease caused by MEFV gene mutations. Although FMF is characterized by intermittent inflammatory attacks some patients exert chronic persistent inflammation that can result in damage of multiple organs. Available reports investigated only specific components of damage such as amyloidosis. All possible organ targets of damage have not been entirely evaluated before. To investigate all components of FMF related damage and associated factors with damage.

Methods: All patients recruited from FMF in Central Anatolia (FiCA) cohort, currently comprising 664 adult subjects (mean age 36±12.1, 63.5% female). All patients fulfilled Tel Hashomer criteria and all were using colchicine for at least 1 year. Demographic data, FMF disease and mutation (if available) characteristics and treatment features were recorded. FMF related damage was evaluated with recently validated auto-inflammatory disease damage index (ADDI). Association between damage and demographic, disease and treatment characteristics were analyzed.

Results: Proportions of FMF manifestations were fever 81.2%, peritonitis 90%, pleuritis 48.8%, arthritis 54.4% and skin rash 29%. Dominant attack types were fever in 7.1%, serositis in 62.7%, musculoskeletal in 16.7% and all attacks were common in rest of patients. MEFV mutations were available in 536 subjects and 77.6% of subjects harboring M694V mutation (28.8% homozygous for M694V). Among all 59.5% patients were well responded to colchicine and 9.2% were non-responders. Median ADDI score was 1 (min 0 max 11). Most common FMF related damages were observed in musculoskeletal, reproductive and kidney domains. Chronic musculoskeletal pain was present in 52.4%, joint deformity in 2.7%, infertility in 11.2%, amenorrhea in 7.1%, proteinuria in 7.8%, amyloidosis in 6.8% and severe renal failure in 4.1%. Age, M694V homozygous mutation, presence of persistent inflammation, dominant musculoskeletal attacks and colchicine nonresponse were found to be the independent predictors of damage.

Conclusion: M694V homozygous mutation, persistent inflammation, colchicine non-response and musculoskeletal dominant attacks are predictors of damage and effective therapeutic interventions must be undertaken to prevent from damage in these patients.

Disclosure: A. Tufan, None; B. Armagan, None; E. Bodakci, None; T. Kasifoglu, None; H. Satis, None; N. Atas, None; A. Sari, None; H. Babaoglu, None; G. Yardimci, None; R. Salman, None; L. Kilic, None; N. S. Yasar Bilge, None; M. A. Ozturk, None.

Activity Tracker Bracelets Captures Familial Mediterranean Fever Attacks and Their Impact on Daily Physical Activities

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Session Information

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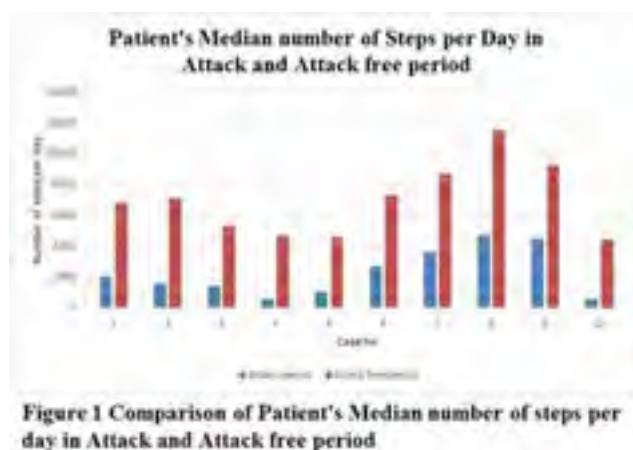
ActivityTracker bracelets captures Familial Mediterranean Fever attacks and their impact on daily physical activities

Background/Purpose: Familial Mediterranean fever (FMF) is a recessively inherited systemic auto-inflammatory disease characterized by recurrent febrile episodes. Typical FMF attacks are mostly devastating and exhausting and results in bed confinement. The objective of this study was to assess the impact of FMF attacks on daily physical activities and detection of FMF attacks by using a connected activity tracker.

Methods: Patients, who had definite diagnosis of FMF according to Tel- Hashomer criteria and agreed to use a validated activity tracker were included in this prospective observational study. Daily physical activities and whether patient wore the device were examined daily via the software of activity tracker. All-patient reported data including occurrence of an attack were collected weekly via mobile phone conversation to avoid memory bias. Median steps per day were calculated each patient. Wilcoxon rank test was used to compare median daily physical activities during attacks and attack free periods. Sensitivity and specificity thresholds for capturing attacks were set to 2/3 step number of median attack free days.

Results: Twelve patients completed the study. Median age of participants was 26 (18-32) and 5(42) of them were female. Median disease duration was 156 (36-300) months. Ten patients harbored homozygous or compound heterozygous, while one patient had single heterozygous exon 10 MEFV mutations.

While the duration of follow up was 514 days, the number of days that patient's wore activity tracker was 452 days (88%). Mean activity tracker use was 37.7 ± 21 days. Ten of the patients reported at least one attack in the observation period. In sum, patients reported 28 separate attacks with a total duration of 45 days (10%). Patients walked a median of 7302 (4500-10300) steps per/day in attack free days, while this number decreased to 1841 (590-4700) steps in attack days. For the assessment of whether activity tracker was capable of capturing an attack, cut off value was determined as two tertile of median steps-day. Activity tracker captured 42 of 45 attack days, 312 of 361 attack free days for each patient. Cut-off value was found 93% sensitive, and 86% specific for capturing attacks.



Conclusion: FMF attacks significantly affect daily physical activity of patients. Activity tracking may also be a reasonable way to capture and document FMF attacks. This might prevent errors due to memory bias and help to identify patients resistant to medical therapy. Thus, daily physical activity tracking maybe a better way of following up the patient aiding more accurate treatment decision for FMF patients who declares frequent attacks.

Disclosure: H. Babaoglu, None; O. Varan, None; N. Atas, None; H. Satis, None; R. Salman, None; M. A. Ozturk, None; B. Goker, None; S. Haznedaroglu, None; A. Tufan, None.

Clinical and Genetic Analysis of the Patients Mimicking Familial Mediterranean Fever

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Session Information

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Clinical and genetic analysis of the patients mimicking familial Mediterranean fever

Background/Purpose: Familial Mediterranean fever (FMF) is an auto-inflammatory disease characterized by recurrent episodes of fever and polyserositis. The differential diagnosis is sometimes difficult because the symptoms of FMF are nonspecific and the disease markers or auto antibody are not existed. We aimed to evaluate the diseases to watch out for differential diagnosis of FMF.

Methods: We analyzed 15 patients initially suspected as having FMF but diagnosed as other disease after the analysis of *MEFV* gene mutation. All patients were fulfilled diagnostic criteria (Livneh criteria). Their clinical symptoms, final diagnosis, effectiveness of colchicine, and genetic mutations were retrospectively investigated.

Results: The diagnosis of these 15 patients were as follows; Behcet's disease (n=4), malignant disease (n=2), infectious disease (n=2), periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) (n=2), and Crohn's disease, adult-onset Still's disease, calcium pyrophosphate dihydrate deposition disease, sarcoidosis, and adrenalism (n=1, each). All patients had recurrent fever. Eight patients (53.3%) had abdominal pain, 6 (40%) had chest pain, and 6 (40%) had arthralgia. Colchicine was prescribed for 10 patients and effective for 5 patients (50%) but ineffective for 4 patients (40%). Most of the colchicine-responsive patients had the colchicine effective disease such as Behcet's disease. Although known *MEFV* gene mutation were identified in 10 patients (66.7%), exon 10 mutations were not found.

Conclusion: Behcet's disease, malignancies, infection, and other auto inflammatory disease would be important differential diagnosis of FMF. The frequency of serositis and the prevalence of pathogenic mutations were lower than typical FMF. Patients not having the pathogenic mutation and refractory to colchicine treatment may be needed to re-examine malignancies and infections. Even if colchicine treatment was effective, we might have to pay attention to existence of specific symptoms of other auto inflammatory disease.

Table 1. *MEFV* mutations of the patients.

No identifiable mutation	5
p.E148Q	3
p.L110P/p.E148Q	2
p.E84K	1
p.R202Q	1
p.G304R	1
p.S503C	1
p.L110P/p.E148Q/p.P369S/p.R408Q	1

Disclosure: D. Kishida, None; Y. Shimojima, None; Y. Sekijima, None.

Comparison of Serum Hecpidin and Calprotectin Levels in Patients with Familial Mediterranean Fever (FMF) and Healthy Subjects

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Familial Mediterranean fever (FMF) is an auto inflammatory disease which has self-limiting inflammatory attacks placing in polyserositis. Hepcidin is a protein in peptide structure and it is synthesized from the liver. Hepcidin plays a role in iron metabolism. Especially hepcidin increased at the during inflammation and it decreases the serum level of iron. IL-6 stimulation increases the level of hepcidin. The cause of anemia in chronic diseases is associated with hepcidin. Calprotectin is a recently defined cytokine released from monocytes and neutrophils in response to tissue trauma and inflammation. To compare the levels of hepcidin and calprotectin in healthy individuals and FMF patients with attack-free period and to show the relation with genetic mutations.

Methods: Between July 2017-December 2017, sixty patients diagnosed with FMF and sixty healthy volunteers enrolled in this study. All of FMF patients were used colchicine (1-1.5mg/day). Clinical findings and PRAS scores of all patients and were recorded. The blood from a peripheral vein using suitable blood tubes was withdrawn to measure serum prolidase and HIF-1 α levels. Bloodtest were examined by Elisa. The study protocol was approved by the local ethics committee.

Results: Laboratory findings and basic characteristics of FMF and healthy control group are shown in Table1. Mean serum hepcidin level was measured as 468.1(210.3-807.8) pg/ml in FMF group and 890.0 (495.0-1716.9) pg/ml in healthy control (HC) group ($p<0.001$). The mean serum levels of calprotectin in the FMF group were measured as 1331.4 (969.3-1584.6) pg/ml and 73.8(45.0-147.9)pg/ml in the HC group ($p<0.001$). According to ROC analysis optimal levels of serum hepcidin (<581.25 pg/ml; sensitivity was 66.7% and specificity was 71.7%, $p<0.05$) and calprotectin (>238 pg/ml; sensitivity was 96.7% and specificity was 100%, $p<0.05$). There was nonsignificant difference between serum hepcidin and calprotectin levels in FMF patients with M694V homozygous and M694V heterozygous ($p>0.05$). There was nonsignificant difference in serum hepcidin levels between FMF patients with and without arthritis, proteinuria and amyloidosis ($p>0.05$). There was nonsignificant correlation between laboratory findings, sex, age, and serum calprotectin and hepcidin levels ($p>0.05$ $r<0.25$).

Conclusion: Serum calprotectin levels in FMF patients with attack-free period were significantly higher than in the healthy control group. Serum hepcidin levels in FMF patients were significantly lower than in the healthy control group. Low levels of hepcidin may be explained that including FMF patients with attack-free period in to the study. Calprotectin may be an important biomarker in FMF. To understand the role of these biomarkers in the diagnosis of FMF are needed to evaluate in more comprehensive studies.

Variable	Group		p
	FMF (n:60)	Control (n:60)	
Age	36.90 \pm 12.53	30.23 \pm 11.76	0.003
Sex			
Female	35(58.3)	40(66.7)	0.451
Male	25(41.7)	20(33.3)	
Neutrophil (%)	63.74 \pm 9.54	59.01 \pm 7.13	0.003
Lymphocyte (%)	28.09 \pm 8.46	32.68 \pm 6.29	0.001
N/L	2.2(1.7-3.0)	1.8(1.4-2.3)	0.003
Hemoglobin (g/dl)	13.38 \pm 1.99	14.27 \pm 1.84	0.013
Platelet (ul)	252.63 \pm 72.89	261.67 \pm 60.63	0.462
Leukocyte(WBC) (fl)	3.9(3.8-3.9)	3.8(3.8-3.9)	0.207
Iron (μ g/dl)	61.30 \pm 24.92	79.37 \pm 42.11	0.014
Creatinine (mg/dl)	0.7(0.6-1.0)	0.7(0.6-0.9)	0.684
ALT (U/L)	17.0(12.0-29.3)	14.0(10.0-20.8)	0.042
AST (U/L)	17.5(14.3-22.8)	16.0(13.0-18.0)	0.027
MPV (fl)	9.5(8.7-10.6)	10.0(9.0-10.5)	0.335
Erythrocyte sedimentation rate (mm/h)	15.5(6.0-35.8)	7.5(5.0-11.3)	<0.001
CRP (mg/l)	4.7(3.2-13.8)	3.7(2.2-6.0)	0.004
Fibrinogen (mg/dl)	359.0(293.5-476.0)	289.0(282.0-387.0)	0.214
Ferritin (ng/ml)	30.8(12.8-63.9)	31.3(15.1-91.5)	0.522

The data are expressed as mean \pm standard deviation, median (1th quarter-3th quarter) and n (%).

Disclosure: G. ASAN, None; M. E. DERİN, None; H. O. DOĞAN, None; M. BAYRAM, None; M. SAHİN, None; A. Sahin, None.

Evaluation of Prolidase and HIF-1 α Levels in Patients with Familial Mediterranean Fever (FMF)

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Familial Mediterranean Fever (FMF) is an auto inflammatory disease characterized by recurrent fever attacks, sterile peritonitis, pleural inflammation, arthritis and / or erysipelas like rash. Prolidase is a specific imidodipeptidase that plays a role in collagen degradation. HIF-1 α is an important protein in the regulation of immunological response, hemostasis, vascularization and anaerobic (oxygen-free) metabolism. Serum prolidase activity in patients with ankylosing spondylitis (AS) was statistically significantly lower than in the control and rheumatoid arthritis (RA) groups. Prolidase activity was not significantly different in patients with RA compared to the control group. In patients with Behcet's disease, prolidase activity was statistically significantly higher than in healthy control group. In FMF patients, the effect of prolidase enzyme is unknown. The aim of the study is to compare serum prolidase and HIF-1 α levels in patients with FMF in attack-free period and healthy control group.

Methods: Between August 2017 and December 2017, sixty patients who diagnosed FMF according to the criteria of the tel- and sixty healthy volunteers were enrolled in the study. All of FMF patients were under treatment of colchicine (1-1.5mg). Clinical findings and PRAS scores of all patients and were recorded. Blood tests were examined by Elisa method. The study protocol was approved by the local ethics committee.

Results: Laboratory findings and basic characteristics of FMF and healthy control group are shown in Table 1. In this study, mean serum prolidase level was measured as 72.1 (25.1-114.9) ng/ml in FMF group and 30.7 (21.3-86.2) ng/ml in healthy control (HC) group (Figure 1). There was statistically significant difference between two groups ($p=0.018$). The mean serum levels of HIF-1 α in the FMF group were measured as 482.0 (292.0-3967.0) pg/ml and 632.0 (362.0-927.0) pg/ml in the HC group. There was no statistically significant difference between the two groups ($p<0.05$). According to ROC analysis, optimal levels of serum prolidase (>54.03 ng/ml; sensitivity was 65% and specificity was 68.3%, $p<0.05$). There was no significant difference between serum prolidase and HIF-1 α levels in the mild, moderate and severe patient groups according to PRAS score ($p>0.05$). There was no significant correlation between laboratory findings, sex, age, and prolidase ($p>0.05$, $r<0.25$).

Conclusion: Serum prolidase enzyme levels in FMF patients with attack-free period were significantly higher than in the healthy control group. There was no significant difference between the two groups at HIF-1 α level. High prolidase enzyme levels may be associated with clinical or subclinical inflammation in FMF patients. However, the role of prolidase and HIF-1 α in the FMF disease needs to be clarified with more extensive and comprehensive studies.

Variable	Group		p
	FMF (n=60)	Healthy control (n=60)	
Age	33.45 \pm 11.91	26.58 \pm 8.67	<0.001
Sex			
Female	33(55.0)	30(50.0)	0.583
Male	27(45.0)	30(50.0)	
Neutrophil (%)	62.27 \pm 10.06	60.31 \pm 7.97	0.238
Lymphocyte (%)	29.26 \pm 9.03	31.49 \pm 6.71	0.127
N/L	2.2(1.5-2.9)	1.9(1.5-2.4)	0.091
Platelet (ul)	260.47 \pm 71.30	273.82 \pm 70.36	0.304
Hemoglobin (g/dl)	13.87 \pm 1.80	14.92 \pm 1.65	0.001
Leukocyte(WBC) (fl)	3.8(3.8-3.9)	3.9(3.8-3.9)	0.431
Creatinine (mg/dl)	0.7(0.6-0.9)	0.8(0.7-0.9)	0.121
ALT(U/L)	17.5(12.0-26.8)	15.5(11.3-21.5)	0.193
AST(U/L)	18.0(15.3-20.0)	16.0(14.0-19.0)	0.060
MPV (fl)	9.5(8.9-10.4)	9.6(8.8-10.5)	0.795

Table . (Cont'd)

Variable	Group		p
	FMF (n=60)	Healthy control (n=60)	
CRP (mg/l)	3.9(2.2-8.9)	3.0(1.9-4.0)	0.011
Fibrinogen (mg/dl)	326.0(266.3-412.3)	284.0(265.0-336.3)	0.227
Erythrocyte sedimentation rate (mm/h)	10,0(5,0-26,5)	7,5(4,0-10,0)	0,003

The data are expressed as mean \pm standard deviation, median (1thquarter-3th quarter) and n(%).

Disclosure: M. BAYRAM, None; M. E. DERİN, None; H. O. DOĞAN, None; G. ASAN, None; M. SAHİN, None; A. Sahin, None.

Abstract Number: 1324

Anakinra Treatment in Refractory Cases of Adult-Onset Still Disease: Case Series

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Despite methotrexate and steroid treatment, in cases of Adult-onset Still's disease (AOSD) it is usually difficult to maintain clinic stability. In refractory cases, Anakinra treatment has been reported to be efficacious (1). In this retrospective review, it is aimed to evaluate the AOSD cases treated with anakinra in our center.

Methods: Fourteen AOSD patients (11 female, 3 male) who were being followed in our outpatient clinic were reviewed retrospectively. The demographic characteristics, pre- and post-treatment clinical findings were reported.

Results: The mean follow-up period of the patient population was 33.5 ± 30.07 months (mean \pm SD). Initial prednisolone dose was 37.3 mg/day. Except for one, all of our patients were exposed to methotrexate before being treated with anakinra. This patient was being treated with cyclosporine instead, since she had concomitant Macrophage Activation Syndrome. The other medications, the patients were previously treated with, were Etanercept (n=2), Tocilizumab (n=3), Infliximab (n=1) and Adalimumab (n=1). All patients were on 100 mgs of Anakinra, daily, except for the one treated with 200 mg/day. The mean duration of Anakinra therapy was 11.4 months. Among 7 patients in whom anakinra therapy was terminated, 1 had drug induced urticaria, 1 was primary irresponsive, 4 were secondary irresponsive and the other had severe pneumonia. Primary irresponsiveness is the lack of response to the therapy since the drug was first introduced, whereas in secondary irresponsiveness the case responds to the medication for a while and starts to flare again after a symptom-free period on the medication. Among 14, 7 of our patients are still on 100 mg/d Anakinra. The mean level of C reactive protein (CRP) measures was reduced from 64.38 ± 61.95 mg/L to 34.3 ± 24.3 mg/L with Anakinra therapy ($p=0.003$). Similarly, mean Erythrocyte Sedimentation Rate (ESR) was dropped to 33 ± 22 mm/h from 59 ± 35 mm/h by the help of the therapy ($p<0.001$). Among patients who primarily responded Anakinra therapy the mean Ferritin measures dropped to 427.25 ng/mL from 910 ng/mL ($p=0.006$). On the other hand, the Ferritin level was not significantly reduced in patients who did not respond Anakinra. The mean Patient reported Global Visual Analogue Scale (PG-VAS) score was also decreased to 3.83 ± 4.7 from 9.5 ± 0.7 following the therapy ($p<0.001$). Unfortunately, one of our 7 patients who were followed in remission under Anakinra died of an unknown etiology.

Conclusion: Adult-onset Still's disease is a challenging disorder, lacking a sufficient long-time clinical control. In order to obtain a full remission, various efforts have been spent so far. One of these approaches is to treat refractory cases with Anakinra, an IL-1 blocking agent. According to our clinical experience we state that, anakinra has a relatively high efficacy in controlling refractory cases.

Disclosure: S. Ugurlu, None; B. Yurttaş, None; G. Guzelant, None; B. Ergezen, None; H. Ozdogan, None.

Canakinumab Treatment in Adult-Onset Still's Disease: Case Series

Serdal Ugurlu¹, Gul Guzelant¹, Berna Yurttas¹, Bilgesu Ergezen¹, Ediz Dalkilic², Timucin Kasifoglu³, Burcu Yagiz⁴ and Huri Ozdogan¹, ¹Istanbul University, Cerrahpasa Medical Faculty, Department of Internal Medicine, Division of Rheumatology, Istanbul, Turkey, ²Department of Internal Medicine, Division of Rheumatology, Uludağ University Faculty of Medicine, Bursa, Turkey, ³Department of Internal Medicine, Division of Rheumatology, Eskisehir Osmangazi University Faculty of Medicine, Eskisehir, Turkey, ⁴Uludag University, Medical Faculty, Department of Internal Medicine, Division of Rheumatology, Bursa, Turkey

Session Information

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: In Adult-onset Still's disease (AOSD), cases refractory to typical DMARDs, Canakinumab (an anti-IL-1 β monoclonal antibody) has been reported to be effective in a limited number of refractory cases (1). The aim of this retrospective study was to represent AOSD patients treated with Canakinumab in 3 centers.

Methods: The follow up data of 10 AOSD patients (8 female, 2 male), who were followed up in outpatient clinics of 3 tertiary centers were reviewed retrospectively. The initial characteristics and follow up findings were reported.

Results: The mean time span between the initial diagnosis and Canakinumab treatment 45.2 ± 29 months (mean \pm SD). Before the onset of Canakinumab therapy, all patients were exposed to methotrexate, 1 to leflunomide, 8 to Tocilizumab and 8 to Anakinra. As for the biologic agents, 3 patients were also treated beforehand with Infliximab, 2 with Adalimumab, 2 with Etanercept and 2 with Rituximab. Canakinumab therapy was initiated in all patients with the indication of refractory disease under other medications, except for the one in whom neutropenia became evident under anakinra. The mean number of Canakinumab injections was 9.3 ± 8 . The mean follow-up period of patients treated with Canakinumab was 43.1 ± 33 months. Seven out of 10 patients are still being treated with Canakinumab of 150 mg/month and one of 150 mg/every 2 months. One patient had a single injection and was fully controlled. The mean ferritin measure of 9 patients was reduced from 1292.3 ± 1530 ng/ml to 354 ± 530.2 ng/ml following the Canakinumab therapy ($p=0.035$). The mean of patient-reported global visual analogue scale (PG-VAS) scores was reduced from 7.4 ± 2.4 to 2.3 ± 2.2 with Canakinumab ($p<0.001$). Mean Erythrocyte sedimentation rate (ESR) was reduced from 44.2 ± 35.1 to 22.7 ± 26.5 with the help of Canakinumab therapy ($p = 0.005$). Six patients are still on prednisolone at a maximum dose of 10 mg/day. The indication of therapy termination in the remaining 1 patient was the diagnosis of tuberculosis at 9th month of the treatment despite isoniazid prophylaxis. The patient was also treated with multiple biological agents before hand, therefore it is not easy to conclude that treatment with Canakinumab induces tuberculosis flares.

Conclusion: Canakinumab treatment seems to be effective in refractory AOSD patients who were previously treated with various agents. We state that an IL-1 blocking agent, Canakinumab is a relatively safe and effective alternative in managing refractory AOSD cases. On the other hand, randomized controlled trials are needed to further investigate the role of Canakinumab in these cases as well as its use as the first choice of biologic agents.

Reference: Kontzias A, Efthimiou P. The use of Canakinumab, a novel IL-1 β long-acting inhibitor, in refractory adult-onset Still's disease. *Semin Arthritis Rheum.* 2012;42(2):201-5.

Disclosure: S. Ugurlu, None; G. Guzelant, None; B. Yurttas, None; B. Ergezen, None; E. Dalkilic, None; T. Kasifoglu, None; B. Yagiz, None; H. Ozdogan, None.

Does Testing for SAA Is More Beneficial Than CRP for the Follow-up of Patients with Familial Mediterranean Fever ?

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: In order to follow subclinical inflammation and adjust the therapy for an optimal disease control, clinicians seek for readily accessible, affordable and reproducible markers. C reactive protein (CRP) is widely used for this purpose. Some suggest that CRP measures are not conclusive in all cases, especially in initial stages of inflammation. It is suggested that Serum Amyloid A (SAA) may be more reliable and sensitive in predicting an ongoing inflammation.

Methods: In order to evaluate and to compare the sensitivity of SAA and CRP, 148 measurements from 33 FMF patients with M694V homozygous mutation were obtained during a mean follow-up of 4 months. For the analysis, the folds of normal CRP and SAA values were used for correlation. Serum levels of the given markers were measured with nephelometric kits (normal CRP levels <5 mg/L and SAA levels <6.8 mg/L).

Results: All patients were on prophylactic colchicine. Among 33 patients 1 patient was being treated with tocilizumab, 2 patients with adalimumab, 19 patients with anti-IL-1 regimens. There were a total of 143 measurements of CRP and SAA from 33 patients. Figure 1 demonstrates the correlation between CRP and SAA results. A similar significant correlation was found when we tested only the values obtained during 128 attack-free occasions ($r=0.743, p<0.001$). Both acute phase reactants were increased in 102 measurements, while in 9 CRP was high but SAA was normal and in 17 SAA was high however CRP was within normal limits. The mean increase in CRP of the population was 2.55 ± 5.26 fold, whereas mean increase in SAA was 6.78 ± 16.39 fold of the normal.



Conclusion: According to these results, serial testing of SAA does not provide any additional advantages over CRP. Readily accessible and affordable bio-marker CRP seems to be sufficient for follow-up of patients with FMF

Disclosure: S. Ugurlu, None; O. Selvi, None; B. Ergezen, None; H. Ozdogan, None.

Abstract Number: 1327

The Effect of Etoposide on Inducing Remission in Refractory Adult-Onset Still's Disease: A Retrospective, Single-Center Study

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

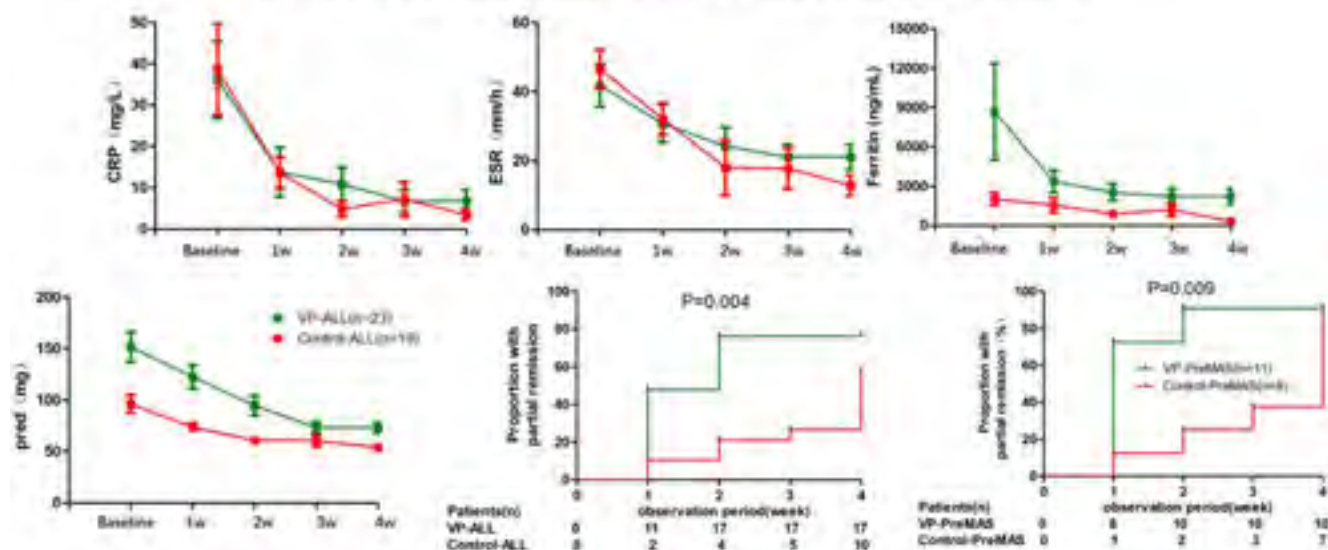
Background/Purpose: Adult onset Still's disease (AOSD) is a rare inflammatory disorder of unknown etiology. Macrophage activation syndrome (MAS) is a life-threatening complication and has been recognized to complicate AOSD. Etoposide (VP-16) has been previously utilized in patients with MAS and induced a favorable and rapid response in cases. In this study, we conducted a single-center, retrospective survey to evaluate the efficacy of etoposide in inducing remission in a series of refractory AOSD patients.

Methods: We included 42 refractory AOSD patients who previously received high dose of steroids (≥ 2 mg/kg/day of prednisone), immunosuppressive drugs and biologic agents. HLH-2004 was used to define AOSD-MAS, and sJIA MAS-2016 was used to exclude those with MAS tendencies (pre-MAS). 23 patients were treated with etoposide (VP-16 group) and 19 patients were treated with methotrexate (MTX) or cyclosporine (CsA) (Control Group). We evaluated disease course, efficacy of treatment and potential adverse effects for at least one year. Efficacy was evaluated as \geq Partial response (PR: clinical improvement without normalization of inflammatory markers, nor $>50\%$ reduction in the dose of prednisone).

Results: The average age was 36 ± 14 years in VP-16 group and 37 ± 13 years in control group. MAS and Pre-MAS of each group were observed in 48% vs. 11% and 47% vs. 42%. At the time of VP-16/Control treatment, the most frequent clinical manifestation was fever (100%/100%), Rash (87%/100%) and Joints involvement (78%/79%). The laboratory parameters such as ferritin, triglycerides and alanine transaminase showed higher level in VP-16 group at baseline. The median dosages of VP-16 were 575mg (IQR 150-1400mg). The median treatment course were 4 weeks (IQR 2 weeks-10 months). The majority of patients showed clinical improvement after VP-16/Control therapy. A dramatic reduction of inflammatory laboratory markers and prednisone dose were achieved. 17 patients responded to VP-16 (PR 74%) and 10 patients responded to CsA or MTX (PR 53%) at 4th week. Besides, in Pre-MAS patients, compared with CsA or MTX, there was rapid increase of PR in VP group (Figure 1).

Adverse events were seen as follows: hemocytopenia ($n=2/n=1$), gastrointestinal effects ($n=3/n=1$), alopecia ($n=1/n=0$), and infections ($n=6/n=5$). 2 patients died (one with shock and one with infection) in VP-16 group and the rest survived. With an average follow-up of 21 ± 11 months/ 24 ± 14 months, a decrease in the dose of steroids and immunosuppressants was possible in all patients [discontinuation: 9%/16%; steroid monotherapy (≤ 15 mg/d): 13%/5%; steroids + DMARDs: 57%/42%].

Figure.1 Improvement following the initiation of VP-16 /Control therapy



Conclusion: Etoposide treatment was associated with rapid and maintained clinical and laboratory improvement in patients with AOSD refractory. It is necessary to carry out large samples and long-term follow-up clinical studies to evaluate its exact effects and safety.

Disclosure: H. Wang, None; X. Wang, None; T. Li, None; S. Ye, None.

Recurrent Pericarditis: A Challenge in Autoinflammatory Disease Clinic and the Role of Anakinra

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Recurrent pericarditis is a common complication following an acute episode of pericarditis affecting about 15-30% of the cases. The etiology of this condition is unknown in most of the patients but it is thought that an auto inflammatory process has an important role in the pathogenesis. Anakinra is an interleukin-1 receptor antagonist that reduces systemic inflammatory responses. The aim of our study was to describe the clinical characteristics and response to anakinra in patients with recurrent pericarditis.

Methods: We retrospectively reviewed patients referred to our clinic with the diagnosis of recurrent pericarditis who were resistant to conventional therapy.

Results: A total of 11 patients were included. The majority were females (7 [64%]) with a median age at presentation of 20 years. Nine patients were diagnosed with recurrent idiopathic pericarditis, one case was found to have familial Mediterranean fever and another patient had a history of systemic lupus erythematosus. Autoimmune workup was negative in all of the cases except in the patient with a history of lupus. Standard doses of nonsteroidal anti-inflammatory drugs, colchicine, and steroids were used in all of the cases. Good response to steroids was noted in all patients (except in the case of lupus) but it was not possible to taper glucocorticoids completely because of recurrence of the pericarditis. Other immunosuppressive medications used were methotrexate, hydroxychloroquine, infliximab, azathioprine, and mycophenolate mofetil. Anakinra, doses between 100-300 mg daily, was associated with clinical response in most of the patients (complete response in 5 patients, partial response in 4 patients, and no response in 1 patient). One patient did not have a follow-up evaluation after anakinra treatment. Anakinra was well tolerated and the main adverse side effect was local reactions.

Conclusion: Anakinra is a safe and effective drug for the management of treatment-resistant recurrent pericarditis.

Disclosure: B. Betancourt, None; A. Ombrello, None; A. Subedi, None; P. M. Hoffmann, None; D. L. Kastner, None.

Combination of Methotrexate and Leflunomide in Refractory Chronic Adult Onset Still's Disease: Case Series and Literature Review

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Session Information

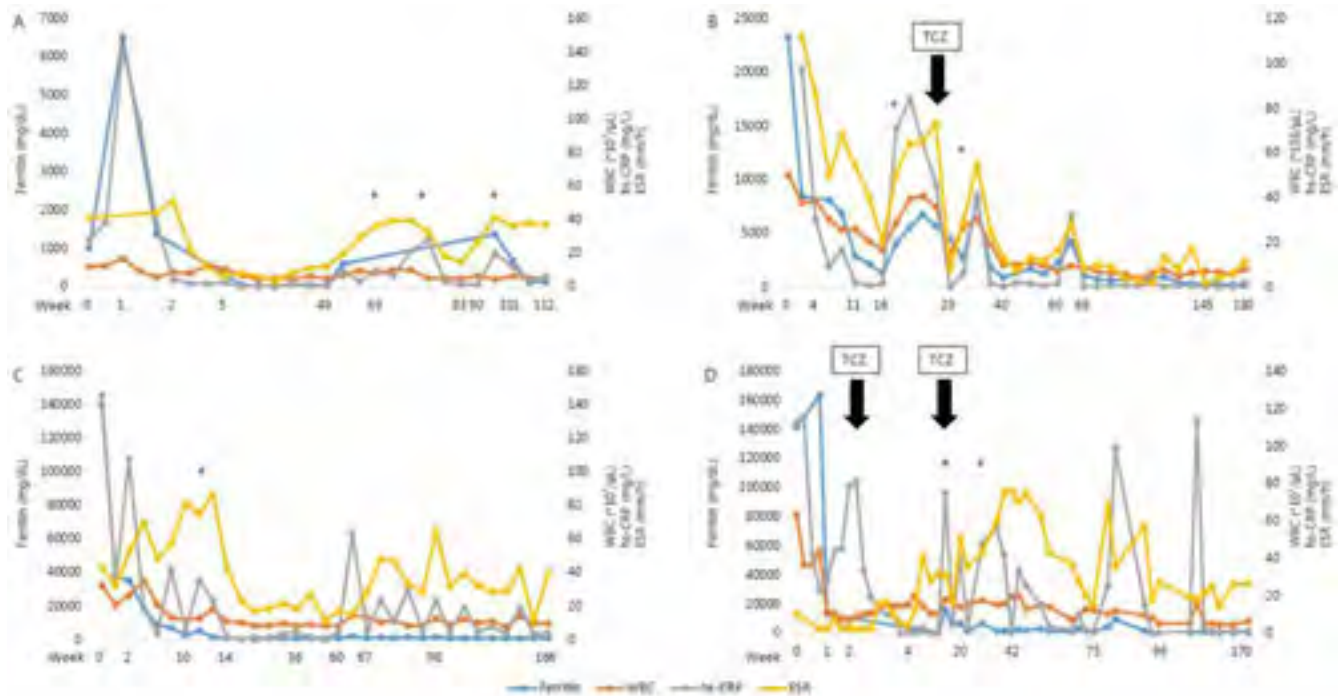
Session Date: Monday, October 22, 2018

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To demonstrate the efficacy of methotrexate (MTX) and leflunomide (LEF) combination therapy in refractory chronic adult onset Still's disease (AOSD).



	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Initial CS dose (PD equivalent) (day)	60 mg	30 mg → 60 mg	156 mg*3 days → 60 mg	60 mg	30 mg
CS dose at flare without MTX (day)	0 mg, 15 mg	NA	NA	7.5 mg	7.5 mg
Duration of remission with CS + MTX	24 weeks	22 weeks	4 weeks	14 weeks	2 weeks
CS dose at flare with CS + MTX (day)	15 mg	7.5 mg	20 mg	7.5 mg	7.5 mg
Duration of remission with MTX + LEF ± CS	13 weeks	147 weeks	154 weeks	106 weeks	46 weeks
Time to CS discontinuation after adding LEF	CS at remission	44 weeks	100 weeks	61 weeks	31 weeks
CS dose at last follow up (day)	3 mg	0 mg	0 mg	0 mg	0 mg
MTX dose (week)	15 mg	15 → 20 → 25 → 15 mg	15 mg	15 → 20 → 5 mg	15 mg
LEF dose (day)	10 mg	10 → 20 mg	10 → 20 mg	10 → 20 → 10 mg	30 mg
The time and reason for TCZ administration	NA	8 mg/kg once for systemic inflammation at 2nd flare	NA	8 mg/kg once for respiratory failure at diagnosis and once at 1st flare	NA
CRP (mg/L), ESR (mm/h), ferritin (ng/mL) at last visit	6.2, 37, 131.0	2.0, 12, 164.5	8.0, 11, 810.3	1.3, 52, 200.0	12.0, 39, 99.1

Methods: This is a retrospective case series of five consecutive patients with AOSD who were treated with MTX and LEF. Medical records were reviewed and laboratory findings and clinical features were assessed. Literature search was conducted.

Results: All five patients met the Yamaguchi criteria for AOSD and were treated with corticosteroid (CS) after the diagnosis of AOSD. Systemic inflammation deteriorated in one patient and one patient developed acute respiratory failure despite initial high-dose CS treatment. Tocilizumab was briefly given with prompt control of inflammation and respiratory failure. All five patients flared when PD was tapered to 0 - 20 mg/day. Along with a short-term increase in CS, MTX 15-25 mg/week was added. During further attempt to taper CS, patients flared again and LEF 10-20 mg/day was added. With MTX-LEF combination, all patients reached and remained in remission. CS was tapered off except in one patient who required 5 mg of prednisolone.

Conclusion: To the best of our knowledge, this is the first case series of chronic refractory AOSD that was successfully treated with the combination of MTX and LEF after initial MTX failure. Further prospective studies are warranted to definitively evaluate the efficacy and safety of MTX-LEF combination in AOSD.

Table 1. Summary of the treatment and clinical outcome of the five patients.
Figure 2. Clinical course after the diagnosis of AOSD of patient 1 (A), patient 2 (B), patient 3 (C) and patient 4 (D)

Disclosure: E. E. Lee, None; J. K. Park, None.

Abstract Number: 1330

Dyskeratotic Cells in Persistent Pruritic Skin Lesions Are Apoptotic and Associated with High Levels of Serum IL-18, and Possibly Predict the Outcomes in Adult-Onset Still's Disease

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster II: Interstitial Lung Disease, Still's Disease, FMF, Polychondritis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To assess the clinical significance of dyskeratotic cells (DCs) in skin lesions of adult-onset Still's disease (AOSD).

Methods: We assessed clinical characteristics, serum markers, outcomes and histology of skin lesions in Japanese patients with AOSD (n=15). Moreover, we comparatively studied the histological findings of AOSD, dermatomyositis (DM) (n=6), drug eruptions (DE) (n=7), and graft versus host disease (GVHD) (n=6).

Results: AOSD with persistent pruritic skin lesions (n=10) histologically showed DCs only in upper layer of epidermis and horny layer without inflammatory cells infiltrations, indicating dyskeratosis. AOSD with evanescent rash (n=5) histologically showed no DCs. In contrast, the histology of DM, DE and GVHD demonstrated that DCs existed in all layers of epidermis with inflammatory cells infiltrations. DCs in AOSD were positive by ssDNA staining, suggesting apoptotic cells. Serum IL-18 showed significantly higher in AOSD patients with DCs (n=10) than without DCs (n=5). The majority of AOSD patients with DCs required higher doses of glucocorticoids, immunosuppressants and biologic agents than without DCs. 2 of 10 AOSD patients with DCs died because of infectious complications or hemophagocytic syndrome.

Conclusion: Persistent pruritic skin lesions in AOSD are specific by prominent epidermal apoptosis involving the upper layers of epidermis, and hyper IL-18 is significantly related with dyskeratosis. The appearance of DCs in AOSD seems to be associated with poor prognosis.

Disclosure: H. Nishikawa, None; Y. Taniguchi, None; N. Maeda, None; S. Inotani, None; K. Nakajima, None; K. Arai, None; Y. Terada, None.

Abstract Number: 1331

Moving from Dermatomyositis Associated with Anti-Melanoma Differentiation-Associated Gene 5 Antibody to Anti-Melanoma Differentiation-Associated Gene 5 Syndrome

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster II: Basic and Translational Science

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Dermatomyositis (DM) is a heterogeneous group of diseases ranging from skin limited disorders to non-specific auto-immune diseases with patients suffering from additional extra-cutaneous manifestations. The myositis specific antibody (Ab) anti-melanoma differentiation-associated gene 5 antibody (MDA5+) delineates a group of patients with a DM skin rash, arthralgia and an interstitial lung disease (ILD), sometimes severe because rapidly progressive (RP-ILD), whereas clinical signs of myositis are absent.

The variety and the predominance of the extra-muscle manifestations question the term of 'myositis specific Ab' and the homogeneity of the related disease. Precising the clinical phenotype, as well as the prognosis of MDA5+ patients is necessary to improve the management of this severe disease.

Methods: MDA5+ patients were defined as patients with a DM skin rash and/or arthralgia and/or ILD without other aetiology in presence of anti-MDA5 Ab. Clinical, laboratory and imaging data were collected (multicentric study). As control, a cohort of anti-MDA5- myositis patients was used. Unsupervised analyses were performed either on both groups (anti-MDA5+ and control) or on anti-MDA5+ patients only.

Results: Anti-MDA5+ patients' (n=121) characteristics were in line with the previous reports. Patients were mainly female, 49 years old [34-58], with a DM skin rash (87.5%) and signs of vasculopathy (Raynaud phenomenon, skin ulcers, calcinosis and/or digital necrosis), with ILD (77%; RP-ILD, 32.7%) and with arthralgia (69%). Death occurred in 25.4% of cases. MDA5+ patients' phenotype was clearly distinct from controls (n=323). Unsupervised analysis (without including data of the serological status) showed clearly two clusters. One was characterized by more frequent DM skin rash, skin ulcers, calcinosis, mechanics hands, ILD, arthralgia/arthritis and patients with a higher mortality rate. In this cluster 87% of patients were MDA5+.

Within MDA5+ group, analysis showed three clusters. As previously reported, one corresponds to patients with RP-ILD (ILD 100% and RP-ILD 95%; $p<0.0001$), but mechanics' hands were frequent (65%; $p<0.0001$). Two new subgroups were identified. One is an 'athro-cutaneo-form' (arthralgia/arthritis, 85%; $p<0.0001$; RP-ILD, 9.5%; $p<0.0001$) and another is a 'vasculo-cutaneo-muscular-form' corresponding to male patients (71.4%; $p<0.0001$) with a severe skin vasculopathy (frequent Raynaud phenomenon, skin ulcers, digital necrosis and calcinosis) and with frequent sign of myositis (weakness 71.3%; $p<0.0001$).

The outcome depends on the form of the disease. A very high mortality rate is observed in the 'RP-ILD form' (65%), in contrast to the good outcome in the 'athro-cutaneo-form' (0% of mortality) and intermediate one in the 'vasculo-dermatomyo-form' (19% of mortality).

Conclusion: MDA5+ patients are a distinct group from myositis patients, characterised by a systemic syndrome composed by three different entities with different outcomes.

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Proteomic Discovery Analysis Identifies Unique Proteins and Pathways Correlating with Different Clinical Activity and Damage Measures in Juvenile Dermatomyositis (JDM)

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster II: Basic and Translational Science

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: JDM is a complex heterogeneous autoimmune disease. To define biomarkers and better understand JDM pathogenesis, aptamer-based proteomic technology was used to mine the serum proteome in a well-characterized JDM cohort.

Methods: Sera from 41 JDM patients (prevalent cases on variable treatment) were compared with 28 age- and gender-matched healthy controls (HC). Broad proteomic analysis of 1306 targets with a slow off-rate modified aptamer-based assay (SomaLogic, CO) generated simultaneous quantitative serum levels. Internal discovery/validation was done with 2 independently-analyzed groups (Group1: JDM 27, HC 19; Group 2: JDM 14, HC 9) assessed for Mann Whitney U FDR corrected p values of <0.10 (JDM vs. HC) common to both groups with expression ratio of >1.3. Significant protein levels were positively correlated by Spearman rank with Physician Global Activity (PGA) and Physician Global Damage (PGD) by visual analog scale (VAS), Manual Muscle Testing (MMT8), Childhood Muscle Assessment Scale (CMAS), Childhood Health Assessment Questionnaire (CHAQ), and disease activity by VAS specific to skin and muscle using the Myositis Disease Activity Assessment Tool (MDAAT) selecting for p values <0.05. Proteins were also analyzed by Ingenuity Pathway Analysis (Qiagen, CA) and Gene Ontology (GO) (Ashburner et al, 2000) biologic processes to identify pathway clusters.

Table 1. Proteins with significant correlation with JDM clinical measures

PGA	PGD	Skin VAS	Muscle VAS	CHQ	Protein	Protein Full Name
				x	B7-H1	Programmed cell death 1 ligand 1
x					Calpain I	Calpain I
x					CXCL16, soluble	C-X-C motif chemokine 16
x					D-dimer	D-dimer
				x	Ferritin	Ferritin
x				x	Integrin $\alpha 1 \beta 1$	Integrin $\alpha 1 \beta 1$ complex
x		x	x	x	IP-10	C-X-C motif chemokine 10
		x	x	y	LEG9	Galectin-9
				x	Mcl-1	Induced myeloid leukemia cell differentiation protein Mcl-1
				x	MCP-3	C-C motif chemokine 7
x			x	x	MIC-1	Growth/differentiation factor 15
x					MMP-3	Stromelysin-1
x					NPS-PLA2	Phospholipase A2, membrane associated
x					NUDC3	NudC domain-containing protein 3
				x	RNase H1	Ribonuclease H1
	x				STAT1	Signal transducer and activator of transcription 1- α/β
x					tPA	Tissue-type plasminogen activator
		x			UCRP	Ubiquitin-like protein ISG15
x					vWF	von Willebrand factor
x	x				XTP3A	dCTP pyrophosphatase 1

This is an alphabetical list of proteins and the clinical measure with which there was a Spearman correlation with a p value of ≤ 0.05 . r_s values ranged from 0.31 to 0.54. No proteins were significantly associated with CMAS or MMT8.

Results: Fifty-nine proteins met significance criteria in both groups of JDM versus HC sera. Of those, 20/59 had significant correlation with 1 to 4 clinical measures (Table 1). Nine proteins correlated with PGA ($r_s = 0.31-0.37$), most commonly associated with acute phase response (APR) and endothelial activation/adhesion (Endo). Three proteins uniquely correlated with PGD ($r_s = 0.33-0.54$), and associated with Endo, IFN, and proteolysis/remodeling (Remodeling) pathway clusters. Four proteins correlated with skin VAS ($r_s = 0.37-0.41$); most associated with IFN and Th1 pathway clusters, with 1 unique to skin and 2 overlapped with muscle VAS. Nine proteins correlated with CHAQ and 4 proteins with muscle VAS (3 overlapping with CHAQ and 1 unique to muscle VAS); overall most associated with Endo and IFN ($r_s = 0.35-0.53$). Nonsignificantly correlated with MMT or CMAS.

Conclusion: Broad quantitative proteomic analysis identified some novel serum markers that point to key differentiating pathway clusters in JDM versus HC which may provide insights into JDM pathogenesis. Moderate correlation was observed between top proteins and clinical measures, including some distinct markers foreskin versus muscle activity, and for PGD. These proteins emphasize pathway clusters including APR, Endo, IFN, Th1, and Remodeling, that may be important to distinct aspects of JDM features and outcomes.

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Abstract Number: 1333

Abnormal Function of High Density Lipoproteins in Idiopathic Inflammatory Myopathies

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster II: Basic and Translational Science

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Damage to the vascular endothelium is strongly implicated in the pathogenesis of dermatomyositis (DM) and to a lesser degree other idiopathic inflammatory myopathies (IIM). Normal high density lipoproteins (HDL) protect the vascular endothelium from damage due to oxidized phospholipids, which accumulate under conditions of oxidative stress. The current work evaluated the function of HDL in a longitudinal cohort of 182 IIM patients.

Methods: The anti-oxidant capacity of HDL was measured by a cell free assay as described previously (*A&R*2009; 60(10): 2870-9) and reported as the HDL inflammatory index (HII). Lipoprotein cholesterol levels were measured by standard methods and traditional cardiovascular risk factors, medication use, and myositis disease characteristics were assessed for all patients. Univariate analysis evaluated the clinical characteristics of IIM patients by three groups of HDL function defined by HII; tertile 1 contained patients with the highest HII, consistent with severe HDL dysfunction, and tertile 3 contained patients with the lowest HII, consistent with the most protective HDL. Multivariate logistic regression analyses were performed to evaluate correlates of dysfunctional HDL in the IIM cohort.

Results: Patients with the most dysfunctional HDL, (tertile 1 HII) had the highest myositis disease activity levels, as measured by both physician global visual analogue scales (VAS) as well as serum CPK levels, compared to lower HII tertiles (Table 1). DM diagnosis was most prevalent in tertile 1 of HDL function (Table 1). There were no significant differences in demographics or traditional cardiovascular risk factors between tertiles. Disease activity measures and DM diagnosis remained significantly associated with dysfunctional HDL in independent multivariate models, after controlling for variables significantly different between tertiles in univariate analysis, as well as variables previously associated with abnormal HDL function including age and statin use (Table 2).

Conclusion: Abnormal anti-oxidant function of HDL was significantly associated with myositis disease activity and DM diagnosis in a large cohort of 182 IIM patients. Abnormal HDL function may warrant further investigation as a mechanism of microvascular damage and increased cardiovascular risk in DM patients.

Table 1. Clinical data of IIM patients by tertiles of HDL anti-inflammatory function.

Table . (Cont'd)

	Tertile 1 (n=61)	Tertile 2 (n=61)	Tertile 3 (n=60)
	Tertile 1 (n=61)	Tertile 2 (n=61)	Tertile 3 (n=60)
HDL Inflammatory Index (HII)	1.21 ± 0.62*†	0.53 ± 0.09*	0.23 ± 0.05†
Age (years)	50 ± 14	51 ± 15	51 ± 15
Female, (%)	72	69	73
Race, (% Caucasian)	72	83	73
Ethnicity, (% Hispanic)	22	18	17
ESR	34 ± 29	28 ± 24	27 ± 25
HSCRP	7.7 ± 12.0	4.7 ± 8.3	6.5 ± 9.7
Lipid panel			
Total Cholesterol	209 ± 50	210 ± 52	205 ± 50
LDL Cholesterol	121 ± 44	128 ± 46	113 ± 3
HDL Cholesterol	59 ± 24	57 ± 20	58 ± 19
Triglycerides	182 ± 137	156 ± 93	169 ± 124
Traditional CVD risk factors			
Body Mass Index	27.7 ± 6.3	27.8 ± 6.5	27.6 ± 5.8
Hypertension, %	26	30	28
Diabetes, %	11	11	17
Current Smoker, %	3	2	0
Past Smoker, %	15	30	17
H/o CVD (% yes)	2	2	3
Statin use, %	11	8	14
IIM characteristics			
Disease Duration (yrs)	4.5 ± 7.8*	3.6 ± 7.4	4.3 ± 5.0†
DM Disease Diagnosis, (% DM)	75	75	50#
CPK Level, (U/L)	867 ± 1989†	405 ± 1123	562 ± 1199
Physician Global Disease Activity (VAS)	43 ± 21*	40 ± 18	34 ± 17
Physician Global Disease Activity (Likert)	1.89 ± 0.95	1.69 ± 0.73	1.56 ± 0.65
Physician Global Disease Damage (VAS)	37 ± 23	31 ± 25	34 ± 21
Physician Global Disease Damage (Likert)	1.63 ± 0.96	1.40 ± 1.11	1.51 ± 0.85
% ILD	47	28	47
Rituximab (% use)	10	5	5
Cyclophosphamide (% use)	7	7	3
Hydroxychloroquine (% use)	18	18	28
IVIG (% use)	21	23	19
Mycophenolate mofetil (%use)	28	18	25
Prednisone (% use)	70	64	76
Prednisone dose (daily)	19 ± 24	15 ± 19	15 ± 18
Methotrexate (% use)	18#	36	19
Leflunomide (% use)	2	0	5
Azathioprine (% use)	12	5	19

* p value < 0.05 compared to tertile 3.

† p value < 0.05 compared to tertile 2.

p<0.05 for Chisquare test of categorical variables.

Table 2. Multivariable logistic regression models of dysfunctional HDL (tertile 1 HII).

Explanatory Variable	Model 1	Model 2
Age, years	1.009 (0.98-1.04) 1.75 (0.29-11.15)	1.004 (0.98-1.03) 1.32 (0.21-8.34)
Disease duration, years	1.03 (0.96-1.10) 2.44 (0.26-25.7)	1.02(0.95-1.09) 1.80(0.19-20.84)
DM diagnosis (vs PM)	3.73 (1.51-9.78)*	4.9 (1.7-15.8) *
MTX use	0.84 (0.30-2.34)	0.84 (0.29-2.39)
Statin use	0.43 (0.11-1.64)	0.94 (0.24-3.78)
Physician Global Disease Activity	1.03 (1.01-1.05)* 10.7 (1.7-76.8)	-
CPK level	-	1.0002 (1.0000-1.0006)* 26.7 (1.08-1653.4)*

* p<0.05.

Model 1: Physician global disease activity in VAS.

Model 2: CPK level.

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Low Density Granulocytes As Biomarkers of Disease Activity and Damage in Patients with Idiopathic Inflammatory Myopathies

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Session Information

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Session Title: Muscle Biology, Myositis and Myopathies Poster II: Basic and Translational Science

Session Type: ACR Poster Session B

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Background/Purpose: Low density granulocytes (LDGs) are a subset of neutrophils that spontaneously produce neutrophil extracellular traps (NETs) and type I IFN. The latter correlates with disease activity and IFN regulated genes had been found in atrophic muscle fibers of patients with idiopathic inflammatory myopathies (IIM). However, the role of this subset of neutrophils has not been fully addressed in IIM. The aim of this study was to assess the relationship between LDGs, disease activity and damage in patients with IIM.

Methods: We recruited 65 adult patients with dermatomyositis, polymyositis, and anti-synthetase syndrome according to the respective classification criteria. The percentage and absolute number of LDGs were assessed by flow cytometry as those CD10⁺, CD15⁺ and CD14⁺ cells in the mononuclear fraction. Disease activity and damage were evaluated by two Rheumatologists. Complete clinical response was defined as the absence of muscular and extra muscular disease activity with immunosuppressive therapy.

Results: The most frequent diagnosis was adult onset dermatomyositis (67.6%). Patients with calcinosis and dysphagia had higher amount of LDGs (Table 1). There was a trend towards higher amount of LDGs in patients with anti MDA5 antibodies. LDGs correlated with disease activity scales (MMT8, muscle enzymes, the patient's and physician's visual analogue scale (VAS) of disease activity) as well as with the extension and severity of damage (Table 2). Only 23.9% of patients had clinical complete response and those subjects had significantly lower levels of LDGs (0.17 (0.08-0.49) vs 0.46 (0.23-1.35), P=0.030).

Conclusion: LDGs are expanded in subjects with active IIM, especially in those with signs of vasculopathy (calcinosis) and dysphagia. LDGs correlate with disease activity and damage scales. Also, patients with anti MDA5 antibodies whom are characterized by an intense IFN signature have higher amount of LDGs. Our findings support the role of LDGs in the induction of disease activity and damage in patients with IIM and suggest that they may serve as a biomarker to identify patients with active disease in contrast with those with complete clinical response.

Table 1.

Feature	Present	Absent	P
Calcinosis	1.17 (0.35-2.52)	0.32 (0.15-0.91)	0.035
Dysphagia	1.66 (0.28-2.7)	0.32 (0.15-0.83)	0.028
Anti-MDA5	2.37 (2.17-)	0.27 (0.1-0.84)	0.076

Table 2.

Feature	Rho	P	Feature	Rho	P
MMT8	-0.4	0.001	Neutrophil/ lymphocyte ratio	0.31	0.013
Physician VAS	0.310	0.012	Patient VAS	0.308	0.013
ALT	0.319	0.011	AST	0.298	0.018
Muscle damage VAS	0.339	0.001	Cutaneous damage VAS	0.31	0.011
Damage extension	0.324	0.009	Damage severity	0.297	0.017

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Extracellular Vesicles Induce Pro-Inflammatory Cytokines in Dermatomyositis

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Session Information

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Extracellular vesicles (EVs) are micron-scale bilayer membrane vesicles released from almost all cell types under activation or apoptosis. They have been detected in various bodily fluids, organs, and tissues in different pathologic states. EVs harbor molecules from their parental cells, which may mediate intercellular communications, and are thought to play an important role in autoimmune inflammation as they have been shown to induce the synthesis of various proinflammatory cytokines in several immune cell types. Previous studies have demonstrated that circulating EVs are increased in a variety of autoimmune diseases, including dermatomyositis (DM). In the current study, we aim to characterize the induction of pro-inflammatory cytokines by EVs isolated from patients with dermatomyositis.

Methods: Fourteen DM patients and nine healthy controls were recruited in the dermatology clinic at the Hospital of the University of Pennsylvania. Peripheral blood mononuclear cells (PBMCs) were isolated from the DM patients and healthy controls and subsequently stimulated with either no treatment, EVs isolated from the homologous plasma, or homologous EV-free plasma. The levels of TNF- α , IFN- α , IFN- β , IL-8, and IL-6 secreted by the PBMCs in the conditioned medium were then quantified with an enzyme-linked immunosorbent assay (ELISA). A one-way analysis of variance (ANOVA) was used to compare cytokine levels secreted by cells stimulated with either EVs, EV-free plasma, or no treatment.

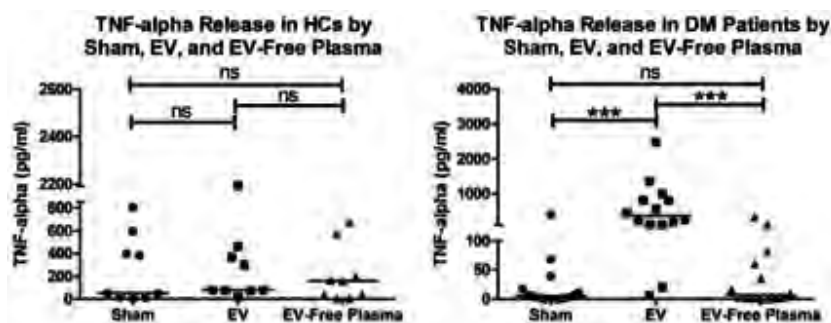


Figure 1: TNF-alpha release by PBMCs of DM patients and HCs stimulated with either no treatment (i.e. sham), EVs isolated from homologous plasma, or homologous EV-free plasma.

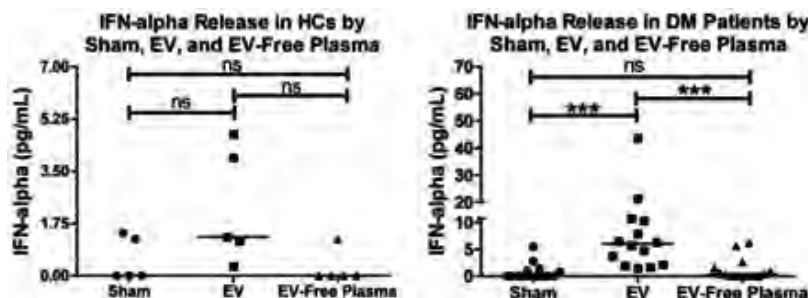


Figure 2: IFN-alpha release by PBMCs of DM patients and HCs stimulated with either no treatment (i.e. sham), EVs isolated from homologous plasma, or homologous EV-free plasma.

Results: In the DM patients, EVs significantly increased the cellular secretion of TNF- α , IFN- α , IL-8, and IL-6 from homologous PBMCs compared to no treatment ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, respectively) and EV-free plasma ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, respectively). In the healthy controls, EVs either did not significantly or less significantly increased TNF- α , IFN- α , IL-8, and IL-6 secretion from the homologous PBMCs compared to no treatment ($p>0.05$, $p>0.05$, $p<0.01$, $p<0.05$, respectively) and EV-free plasma ($p>0.05$, $p>0.05$, $p>0.05$, $p<0.05$, respectively). In both the DM patients and the healthy controls, the EVs did not significantly increase IFN- β secretion.

Conclusion: Therefore, EVs from DM patients induce secretion of key immuno stimulatory cytokines from their homologous immune cells, suggesting that EVs likely play a role in the pathogenesis of DM. Our preliminary studies indicate that circulating EVs are important proinflammatory mediators that amplify proinflammatory responses in patients with DM.

Disclosure: K. Desai, None; M. Zeidi, None; M. L. Liu, None; V. P. Werth, None.

Abstract Number: 1336

Functional, Radiographic and Serologic Correlates of Anti-SSA52 Kd – Associated Interstitial Lung Disease

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster II: Basic and Translational Science

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Autoantibodies against the SSA52 Kd protein (anti-SSA52) have been cataloged as myositis-associated antibodies, occurring in up to 30% of cases idiopathic inflammatory myopathies (IIM), commonly with anti-synthetase (AS) antibodies, mainly anti-Jo1. This study sought to describe the association of ILD with the presence of anti-SSA52, including the pattern and severity of interstitial lung disease (ILD) and the correlation of other serological markers co-expressed with anti-SSA52 and ILD.

Methods: We retrospectively identified all anti-SSA52 positive patients evaluated at our center from 2015-2018 for myositis and/or ILD and had myositis-associated autoantibodies tested using a commercial panel (MyoMarker Panel 3®, RDL Reference Laboratories), and collected information on the high-resolution computed tomography (HRCT) pattern, pulmonary function tests (PFT) and serology. The presence of various antibodies were entered into a logistic regression model with ILD as the outcome, using interaction terms based upon univariate analyses.

Results: Our sample included 62 patients positive for anti-SSA52. They most commonly had dermatomyositis/polymyositis (22%), AS syndrome (21%) and systemic sclerosis (9%); 11.3% had non-rheumatic diagnoses. ILD was found in 66% with a HRCT pattern of non-specific interstitial pneumonia (NSIP) in 39%, organizing pneumonia (OP) in 27%, usual interstitial pneumonia (UIP) in 17% and NSIP/OP in 26.8%. Among those with ILD there was concurrent positivity for anti-SSA52 and other antibodies included in the MyoMarker Panel 3, mainly anti-Jo1 (24%), anti-MDA5, anti-TIF1 γ and anti-U1RNP (12.2% each). PFT in patients with ILD and anti-SSA52 showed diminished median FVC: 2.12 L (IQR 0.97) and DLCO: 36% (IQR 29). Those positive for both anti-SSA52 and anti-Jo1 had worse function, with median FVC: 1.6 L (IQR 0.89) vs 2.13 L (IQR 0.65) and median DLCO: 26% (IQR 10) vs 44% (IQR 33). No correlation for anti-Jo-1 was found in the multivariable model (β -coefficient 5.55, $p=0.96$). Anti-Mi2 (β -coefficient 17.2, $p=0.034$) and anti-PM-Scl (β -coefficient -17.2, $p=0.034$) were strongly correlated with ILD, with the latter showing an inverse correlation.

Conclusion: Anti-SSA52 antibody was commonly associated with IIM. NSIP and OP were the most frequent HRCT findings and PFT showed a restrictive pattern with worse FVC and DLCO in those co-expressing anti-SSA52 and anti-Jo1 than those mono-specific for anti-SSA52. In the presence of anti-SSA52 there was a positive correlation of anti-Jo1 and anti-Mi2 with ILD, and anti-PM-Scl seemed to be a protective factor for pulmonary involvement. Additional study of the interaction of autoantibodies with clinical outcomes is underway.

Disclosure: E. Calle Botero, None; B. Wang, None; J. J. Maya, None; I. Mira-Avendano, None; A. Abril, None.

Myocardial Fatty Acid Metabolism and Perfusion Mismatch in Scintigraphy Predicts Worse Prognosis in Clinically Amyopathic Dermatomyositis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster II: Basic and Translational Science

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Session Time: 9:00AM-11:00AM

Background/Purpose: Clinically amyopathic dermatomyositis (CADM) patients are frequently manifested by rapidly progressive interstitial lung disease (ILD) and associated with a poor prognosis. Recently cardiac involvement is recognized as a poor prognostic factor in several diseases including inflammatory myositis, however its clinical significance has been rarely investigated in CADM. Here, we determined factors associating with poor prognosis in patients with CADM by focusing on cardiac involvement using cardiac scintigraphy.

Methods: All patients who visited our hospital from 2009 to 2015 and performed cardiac scintigraphy using ^{99m}Tl and ¹²³I-BMIPP were retrospectively evaluated. Patients who fulfilled Bohan and Peter's criteria for DM and Sontheimer's criteria for CADM were selected. We calculated the mismatch score in cardiac scintigraphy by subtracting the uptake of ¹²³I-BMIPP (metabolism) from that of ^{99m}Tl (perfusion) on each 17 myocardial segments standardized by American Heart Association. The perfusion-metabolic mismatch indicates an area of hypometabolism without ischemia and a functional abnormality due to myocardial injury. We compared the mismatch scores between patients with classic DM and CADM. Furthermore, independent prognostic factor for poor outcome defined as death or receiving home oxygen therapy was determined in CADM group.

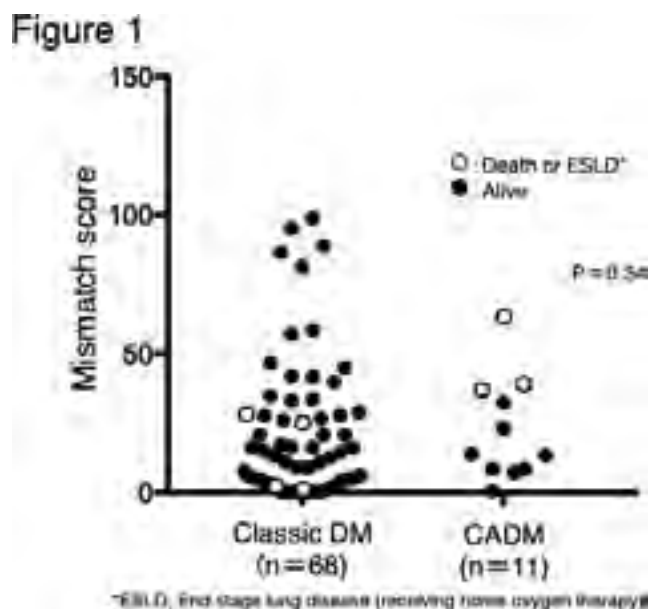


Table I. Multivariate analysis for prognostic factors

Parameters	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Mismatch score	1.10 (1.03-1.23)	<0.01	1.30 (1.00-1.71)	0.03
%VC	1.01 (0.98-1.10)	0.85		
Fe _{crit} (mmHg)	0.99 (0.98-0.99)	0.00	0.61 (0.42-1.01)	0.10
Lactate	0.95 (0.81-1.07)	0.43	—	—

Results: One-hundred and seventy-seven patients were evaluated. We investigated 68 patients with classic DM and 11 patients with CADM. Higher prevalence of poor outcome was seen in CADM patients than classic DM patients (27.2% vs 5.9%, $p=0.02$), but there was no difference in %VC and level of cardiac enzyme between the groups. We compared the result of cardiac scintigraphy and found the mismatch scores was not different between the 2 groups ($p=0.34$) (Figure 1). However, a significantly higher level of mismatch score was detected in patients with poor outcome in only CADM group ($p=0.02$). Multivariate analysis revealed mismatch score was selected as the predictive factor with poor outcome in CADM (odds ratio, 2.30; 95% confidence interval, 1.00–3.31; $p=0.04$) (Table 1).

Conclusion: High mismatch score in cardiac scintigraphy may predict poor outcome in CADM.

Disclosure: H. Iida, None; H. Hanaoka, None; K. Ishimori, None; T. Kiyokawa, None; Y. Takakuwa, None; K. Kawahata, None.

Abstract Number: 1338

Validation of the Diagnostic Accuracy of Myositis-Related Antibodies in a Large Patient-Cohort

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster II: Basic and Translational Science

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Myositis-specific antibodies (MSA) and myositis-associated antibodies (MAA) are used for the diagnosis of idiopathic inflammatory myopathies (IIM). A careful evaluation of these antibodies is needed, because of their relevance for establishing the diagnosis and stratification into specific disease subsets. The aim of this study was to assess the diagnostic accuracy of a line immunoassay for IIM in a large real-life patient cohort and to determine the clinical significance of the Myositis-autoantibodies.

Methods: In this retrospective analysis, we retrieved the clinical diagnoses of all patients submitted to our diagnostic laboratory for MSA and MAA testing between October 2014 and October 2017. A line-immunoassay (Euroline

			IIM (n=64)					
	n,	n,	Sensitivity	Specificity	PPV	NPV	posLR	negLR
	negative tested	positive tested						
Myositis AB								
Jo-1	1092	19	12.50	98.99	42.11	95.05	12.34	0.88
TIF1γ	1092	19	3.13	98.43	10.53	94.52	2.00	0.98
MDA-5	1098	13	4.69	99.08	23.08	94.64	5.09	0.96
NXP-2	1100	11	4.69	99.26	27.27	94.64	6.36	0.96
SAE	1108	3	1.56	99.82	33.33	94.51	8.48	0.99
PM-Sci100	1086	25	6.25	98.07	16.00	94.67	3.23	0.96
PM-Sci75	1046	65	4.69	94.29	4.62	94.38	0.82	1.01
PL-7	1087	24	9.38	98.34	25.00	94.85	5.66	0.92
EJ	1110	1	0.00	99.91	0.00	94.43	0.00	1.00
OJ	1108	3	0.00	99.72	0.00	94.42	0.00	1.00
PL-12	1084	27	1.56	97.61	3.70	94.39	0.65	1.01
SRP	1078	33	12.50	97.70	24.24	94.99	5.43	0.90
Mi-2α	1100	11	12.50	99.72	72.73	95.08	45.25	0.88
Mi-2β	1090	21	7.81	98.53	23.81	94.77	5.30	0.94
Ku	1087	24	6.25	98.16	16.67	94.67	3.39	0.96

Autoimmune Inflammatory Myopathies Immunoblot, Lübeck, Germany) was used to detect autoantibodies directed against Jo-1, Mi-2 α , Mi-2 β , TIF1 γ , SRP, MDA-5, NXP-2, SAE, PL-7, PL-12, EJ, OJ, PM-Scl100, PM-Scl75, Ku as indicated by the manufacturer. We calculated specificity, sensitivity, negative (NPV) -and positive predictive values (PPV) as well as the positive and negative likelihood ratios (LR) for each autoantibody.

Results: In total, 3167 samples were analyzed. After exclusion of samples with repeated measurements, records were reviewed and patients without sufficient clinical data were excluded. In total 1111 patient were included in the final analysis. A total of 64 IIM patients were identified. 242 patients had at least one positive antibody testing result, of which 39 patients had an IIM diagnosis. 25 patients with a diagnosis of IIM tested negative for all autoantibodies. The test accuracy of the line-immuno-assay is shown in table 1.

Conclusion: Using the line-immuno-assay for diagnostic work-up for IIM in a real-life setting revealed that this method is a suitable alternative to more time-consuming procedures. However, clinicians should be aware that PPVs for most autoantibodies are low, due to a low pre-test probability.

Table 1: Test-accuracy of Myositis-antibodies.

Disclosure: A. Lackner, None; V. Tiefenthaler, None; J. Mirzayeva, None; W. Graninger, None; M. Stradner, None.

Abstract Number: 1339

Myositis Specific Anti-Histidyl tRNA Synthetase (HisRS) Autoantibodies Display High Reactivity Against Hisrs Conformational Epitopes and Associate with Lung and Joint Involvement

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Background/Purpose: Autoimmune myositis (rheumatic muscle inflammation) associated with interstitial lung disease (ILD) and arthritis is strongly correlated with the presence of anti-histidyl tRNA synthetase (HisRS) autoantibodies. The aims of this study were to investigate: 1) myositis IgG reactivity against HisRS conformational epitopes; and 2) associations between clinical manifestations and anti-HisRS reactivity profiles.

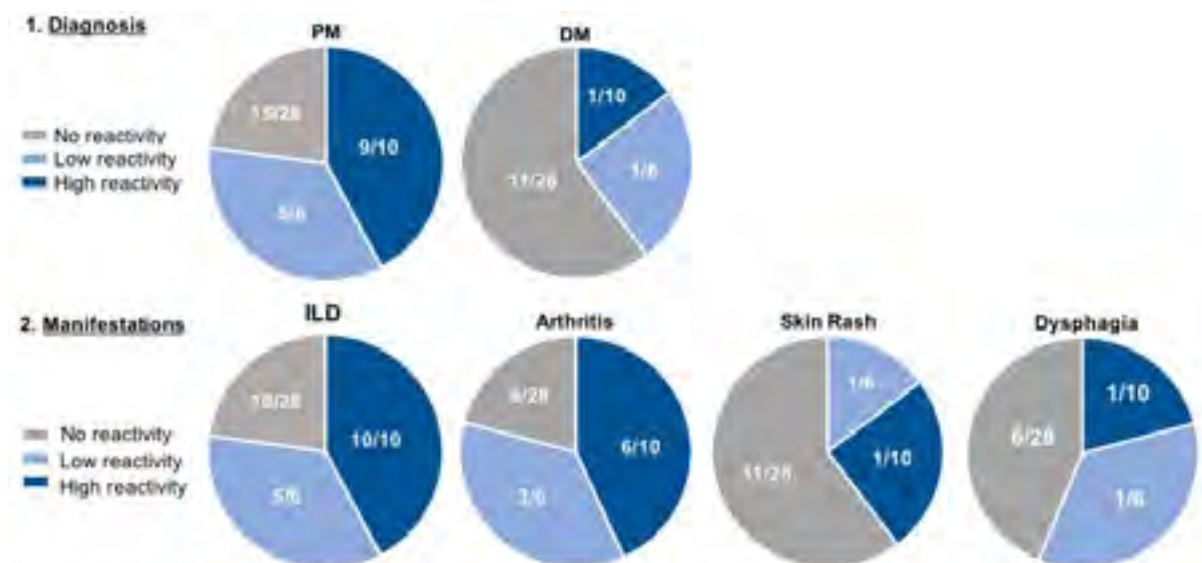


Figure. Anti-full-length HisRS IgG reactivity in myositis patients diagnosed with either polymyositis (PM) or dermatomyositis (DM), and presenting manifestations of interstitial lung disease (ILD), arthritis, skin rash and dysphagia. Numbers represent the patients included in the analysis.

Methods: Serum IgG was isolated using a protein G affinity column (from 25 anti-HisRS negative (-) and 19 anti-HisRS positive (+) myositis sera and 24 age/gender matched healthy controls, HC). Autoantibody reactivity was tested by in house ELISA developed against HisRS full-length protein and three HisRS conformational epitopes (WHEP domain - localized in the N-terminal; HisRS without WHEP (HisRS_WHEP); and ABD - anticodon-binding domain located in the C-terminal). Correlations between diagnosis, clinical manifestations and anti-HisRSIgG reactivity were evaluated.

Results: HisRS⁺ myositis IgG displayed stronger reactivity against full-length HisRS and HisRS_WHEP (median 372 ng/mL and 334ng/mL, respectively), compared to WHEP and ABD (6.38 and 6.48 ng/mL). The strongest anti-full-length HisRS reactivity (>371 ng/mL) was detected in HisRS⁺ patients presenting ILD (10 of 10 of patients, figure below), arthritis (6/10) and polymyositis diagnosis (PM 9/10), in comparison to HisRS⁺ patients with low anti-HisRS reactivity (<23 ng/mL, ILD - 5 of 6; arthritis - 3/6; PM- 5/6) or subjects with no anti-HisRS reactivity (ILD - 10/28; Arthritis - 8/28; PM - 15/28). On the contrary, patients displaying no anti-HisRS reactivity were largely diagnosed with DM (11/28), skin rash (11/28) and dysphagia (6/28) when compared to patients with the highest anti-full-length HisRS reactivity (1 out of 10 patients was diagnosed with DM, skin rash or dysphagia). Similar associations were observed between anti-HisRS_WHEP, anti-WHEP or anti-ABD reactivity and manifestations of ILD, arthritis, skin rash or dysphagia, and DM or PM diagnosis. No anti-HisRS reactivity was detected in the HC group.

Conclusion: This study provides evidences for a possible underlying role of anti-HisRS autoantibodies in the pathogenesis of myositis with interstitial lung disease and joint involvement.

Disclosure: C. Fernandes-Cerqueira, None; N. Renard, None; A. Notarnicola, None; E. Wigren, None; P. J. Jakobsson, None; S. Graslund, None; I. E. Lundberg, Bristol-Myers Squibb, 2,AstraZeneca, 2,AstraZeneca, 5,UCB, Inc., 5,Corbus Pharmaceuticals, 5,Novartis, 1,Roche, 1.

Abstract Number: 1340

Anti-Aminoacyl-tRNA-Synthetase Antibodies Which Are Positive By ELISA but Negative By RNA-Immunoprecipitation Suggest Different Antigen Recognition and Clinical Relevance Different from Typical Anti-Synthetase Syndrome

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Session Information

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Background/Purpose: Anti-aminoacyl-tRNA-synthetase (ARS) antibodies are myositis specific autoantibodies and associated with common clinical characteristics called anti-synthetase syndrome (ASS). Recently anti-ARS detecting enzyme-linked immunosorbent assay (ELISA) in which mixture of 5 ARS antigens are coated have been established and utilized in daily practice (MESACUPTM MBL, Japan). However, we sometimes encounter patients who are positive for anti-ARS by ELISA but negative by RNA-immunoprecipitation (IP). We verified the authenticity and clinical relevance of these anti-ARSs with discrepant results between different detection systems.

Methods: We examined medical records of 1628 samples that were screened for anti-ARS by ELISA between 2014 and 2017. There were 78 patients (134 samples) who were positive for anti-ARS by ELISA, and among these patient, we further analyzed 61 patients by RNA-IP. We found 16 patients who were positive for anti-ARS by ELISA but negative by RNA-IP. We examined clinical characteristics of these 16 patient sera. Statistical analysis was performed by using Fisher's exact test. Furthermore, 7 of 16 patients were examined by protein-IP and individual ELISA methods to verify the authenticity of the discrepant results. The individual ELISA was also confirmed whether the serum autoantibody was absorbed to the antigen.

Results: Compared to the previous report (Love LA. et al. Medicine (Baltimore), 1991), the frequency of all symptoms of ASS other than interstitial lung disease (ILD) were significantly lower in 16 discrepant cases (Table 1). The radiological patterns of ILD frequently showed nonspecific interstitial pneumonia and/or organizing pneumonia (11/16 cases). Most

Clinical Features	Frequency	Previous report	Statistical analysis
Fever	0% (0/16)	87% (41/47)	$p < 0.01$
Polymyositis	31% (5/16)	94% (44/47)	$p < 0.01$
Raynaud's phenomenon	25% (4/16)	82% (39/47)	$p < 0.05$
Mechanic's hands	6% (1/16)	71% (33/47)	$p < 0.01$
Myositis	19% (3/16)	100% (47/47)	$p < 0.01$
Interstitial lung disease	81% (13/16)	89% (42/47)	$p < 0.41$

No	RNA-IP	Protein-IP	Individual ELISA	Absorbed by
1	—	Jo-1	Jo-1	Jo-1
2	—	Jo-1	Jo-1	Jo-1
3	—	Jo-1	Jo-1	Jo-1
4	—	KS	KS	KS
5	—	Jo-1	Jo-1, EJ	Jo-1, EJ
6	—	—	EJ	EJ
7	—	—	KS	KS

cases showed good response to initial glucocorticoid therapy, but 46% of them had recurrence. The results of protein-IP showed that 5 of 7 patient sera reacted with either Jo-1 or KS but 2 did not immunoprecipitated any ARS proteins. The individual ELISA and absorption study showed all these samples reacted with some of the ARS antigens, of which Jo-1 was the most frequently recognized (Table 2).

Conclusion: There are some anti-ARS antibodies which are detected by ELISA but not RNA-IP. These antibodies might inhibit RNAs binding to ARS proteins or recognize denatured ARS antigens. Patients with such atypical anti-ARS showed significant association with ILD but less with the other characteristics of ASS. Furthermore, the ILD with atypical anti-ARS showed similar clinical response and course with that of ASS. Further investigation is needed to clarify whether such patients have distinct form of ASS.

Disclosure: T. Sasai, None; R. Nakashima, Medical & Biological Laboratories Co., Ltd., 9; Y. Ishikawa, None; T. Isayama, Medical & Biological Laboratories Co., LTD., Japan, 3; T. Mimori, Research grants, 2.

Abstract Number: 1341

Autoantibodies to Mi-2 Alpha and Mi-2 Beta in Patients with Myositis

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Session Information

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Background/Purpose: Myositis specific antibodies (MSA) represent not only important diagnostic tools, but also help stratify myositis patients with particular clinical features, treatment responses and disease outcomes. These antibodies also have the potential to be used in classification criteria. Consequently, standardization of MSA is of high importance. Many laboratories rely on immuno precipitation (IP) for the detection of MSA which, however, are met with logistic,

standardization, and regulatory challenges. Therefore, reliable alternatives to IP are mandatory. The objective of this study was to compare the results obtained from different assays for the detection of anti-Mi-2 antibodies.

Methods: The study included 82 patients (68 females/14 males), most of whom had dermatomyositis (DM, n=57), followed by polymyositis (PM, n=16) and juvenile DM (n=9). All samples were tested using a novel particle-based multi-analyte technology (PMAT, Inova Diagnostics, research use only; Mi-2b, OJ, TIF1y, PL-12, SAE, EJ, MDA5, HMGC, PL-7, SRP, NXP2) in parallel with a line immunoassay (LIA, Euroimmun, not FDA approved; OJ, EJ, PL-12, PL-7, SRP, Jo-1, PM-75, PM-100, KU, SAE, NXP2, MDA5, TIF1y, Mi-2b, Mi-2a). To assess clinical specificity for the PMAT assay, a total of 775 disease controls and healthy individuals were tested.

Results: A total of 24 patients were positive for anti-Mi-2a and 5 patients for anti-Mi-2b antibodies by LIA. For PMAT, 23 patients tested positive for anti-Mi-2b antibodies. The comparison shows varying agreement between the different methods as shown by *kappa* statistics (0.27-0.77). When the results obtained from the LIA were used as reference for ROC analysis,

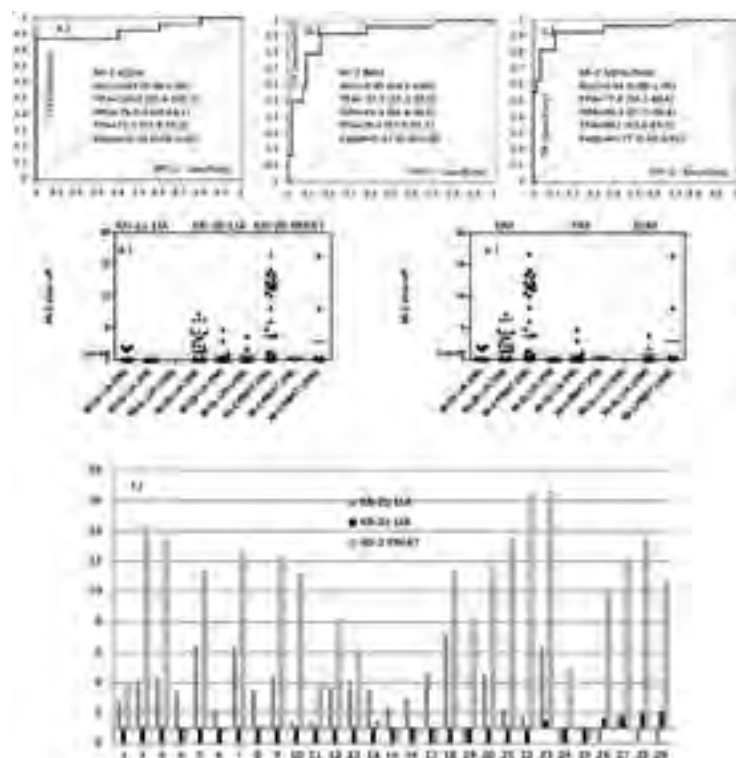


Figure 1 Antibodies to Mi-2 Alpha and Mi-2 Beta measured using two different methods. In a.) - c.) using ROC analysis, the discrimination between line immunoassay (LIA) positive and negative samples is shown for anti-Mi-2 Beta antibodies using the particle-based multi-analyte technology (PMAT). Panel d.) shows the levels of antibodies by methods and panel e.) by myositis subform. Panel f.) exhibits the reactivity profile of all 29 samples that are positive by at least one method.

good discrimination and high area under the curve values were found for both PMAT vs. LIA Mi-2 Alpha and LIA Mi-2 Beta. A total of 29 samples were positive by at least one test for anti-Mi-2 antibodies. Of those, 24 were positive by Mi-2b LIA, 5 by Mi-2a LIA and 23 by Mi-2 PMAT. When analyzing the results in the context of the myositis phenotype, LIA Mi-2 Alpha was positive in 5/57 (8.8%) DM, in 0/16 (0.0%) PM and 0/9 (0.0%) JDM patients. For LIA Mi-2 Beta, 19/57 (33.3%) DM, 2/16 (18.8%) PM and 2/9 (22.2%) JDM patients were positive. In addition, for PMAT Mi-2 Beta, 21/57 (36.8%) DM, 0/0 (0.0%) PM and 2/9 (22.2%) JDM patients were positive. Lastly, in the control group, 3 controls were positive for anti-Mi-2 antibodies resulting in a sensitivity and specificity of 28.1% and 99.6%, respectively.

Conclusion: Overall good agreement was found between LIA and PMAT for anti-Mi-2 antibodies. Anti-Mi-2 Beta antibodies measured by PMAT tended to be more highly associated with the clinical phenotype of DM. Larger multicenter studies are needed to confirm the findings and to compare the results of LIA and PMAT to IP.

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Myositis Specific Antibodies Measured Using a Novel Particle Based Multi-Analyte Assay Resemble Myositis Subsets By Principle Component Analysis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster II: Basic and Translational Science

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Session Time: 9:00AM-11:00AM

Background/Purpose: Myositis specific antibodies (MSA) represent important diagnostic tools and also help stratify idiopathic inflammatory myositis (IIM) patients with particular clinical features, treatment responses, and disease outcomes. Standardization of MSA is of high importance because these antibodies also have the potential to be used in classification criteria. Many laboratories rely on immunoprecipitation (IP) for the detection of MSA but this approach is compromised by logistic, standardization, and regulatory challenges. Therefore, reliable alternatives top are mandatory. The objective of this study was to compare the results obtained from different assays for the detection of MSA.

Methods: The study included 82 patients (68 females/14 males), most of whom haddermato myositis (DM, n=57), followed by polymyositis (PM, n=16) and juvenile DM (n=9). All samples were tested using a novel particle-based multi-analyte technology (PMAT, Inova Diagnostics, research use only; Mi-2b, OJ, TIF1y, PL-12, SAE, EJ, MDA5, HMGCR, PL-7, SRP, NXP2) in parallel with a line immunoassay (LIA: Euroimmun, not FDA approved; OJ, EJ, PL-12, PL-7, SRP, Jo-1, Ro52,

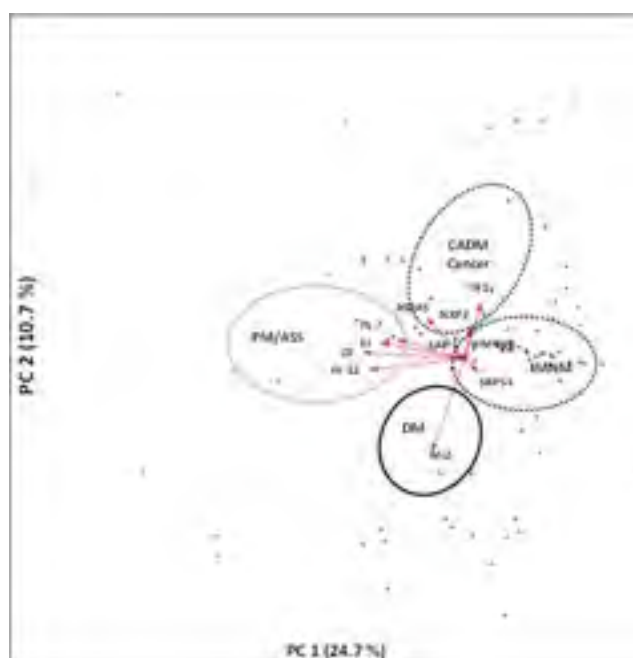


Table 1 Prevalence of autoantibodies in, Mexico, Central, and South American IIM patients

	Dermatomyositis Associated Antibodies					Anti-tRNA Synthetase Syndrome / Polymyositis Associated Antibodies				Necrotizing Myopathy Associated Antibodies	
Particle-based multi-analyte system (PMAT)											
Group	Mi-2	TIF1y	NXP2	SAE	MDA5	PL-7	PL-12	OJ	EJ	HMGCR	SRP
DM (n=57)	36.8%	21.1%	3.5%	1.8%	7.0%	1.8%	0.0%	0.0%	1.8%	5.3%	0.0%
JDM (n=9)	22.2%	0.0%	11.1%	11.1%	11.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
PM (n=16)	0.0%	0.0%	0.0%	0.0%	0.0%	6.3%	0.0%	0.0%	6.3%	0.0%	6.3%
IIM (total)	28.0%	14.6%	3.7%	2.4%	6.1%	2.4%	0.0%	0.0%	2.4%	3.7%	1.2%
EUROUNE Autoimmune Inflammatory Myopathies 16 Ag											
Group	Mi-2	TIF1y	NXP2	SAE	MDA5	PL-7	PL-12	OJ	EJ	HMGCR	SRP
DM (n=57)	38.6%	10.5%	5.3%	1.8%	7.0%	1.8%	5.3%	0.0%	0.0%	N/A	3.5%
JDM (n=9)	22.2%	0.0%	11.1%	0.0%	11.1%	0.0%	0.0%	0.0%	0.0%	N/A	11.1%
PM (n=16)	18.8%	0.0%	0.0%	0.0%	0.0%	6.3%	0.0%	0.0%	0.0%	N/A	6.3%
IIM (total)	32.9%	7.3%	4.9%	1.2%	6.1%	2.4%	3.7%	0.0%	0.0%	N/A	4.9%

PM-75, PM-100, KU, SAE1,NXP2, MDA5, TIF1y, Mi-2b, Mi-2a). Principle component analysis (PCA) was carried out to analyze the relationship between the individual markers.

Results: In our cohort of Mexico, Central, and South American myositis patients, anti-Mi-2 antibodies were the most common autoantibody detected with an overall prevalence of 28%. The prevalence of the individual MSA antibodies in the sera of IIM clinical subsets is detailed in Table1. PCA analyses (based on PMAT results) displayed clusters of auto antibodies which are consistent with previously reported IIM clinical associations (see Figure 1). Close proximity was observed for the antibodies to synthetase (PL-7, PL-12, EJ, OJ), for HMGCR and SRP, as well as for NXP2 and TIF1y.

Figure 1. Principle component analysis (PCA) of the different auto antibodies in myositis. DM=Dermatomyositis; CADM=clinically amyopathic DM; IMNM=immune mediated necrotizing myopathies; PM=polymyositis;ASS=anti-synthetase syndrome

Conclusion: The novel PMAT used to detect spectrum of MSA in IIM represents a potential alternative to IP and other diagnostic assays. Our data was consistent with previously published associations of MSA with IIM clinical phenotypes and provides further evidence that autoantibodies are useful biomarkers for accurate diagnosis, patient stratification, as well as future classification criteria.

Disclosure: M. Richards, Inova Diagnostics, 3; I. Garcia de la Torre, None; Y. Gonzalez-Bello, None; M. Vazquez-Del Mercado, None; L. Andrade-Ortega, None; G. Medrano-Rameriz, None; J. E. Navarro-Zarza, None; M. Maradiaga, None; E. Loyo, None; A. Rojo-Mejía, None; G. N. Gómez, None; A. Seaman, Inova Diagnostics, 3; M. J. Fritzler, Inova Diagnostics Inc., BioRad, Euroimmun GmbH, Mikrogen GmbH, Dr. Focke Laboratorien GmbH, ImmunoConcepts, SKF Canada, Amgen and Pfizer, 5,ImmunoConcepts, Inova Diagnostics, Euroimmun GmbH, and Alexion Canada, 7; M. Mahler, Inova Diagnostics, 3.

Abstract Number: 1343

A Novel Autoantibody Against DNA Damage Binding Protein-1 in Idiopathic Inflammatory Myopathy

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Background/Purpose: Many kinds of autoantibodies are detected in idiopathic inflammatory myopathy (IIM) patients. Some of them are useful to diagnose, predict the clinical course, and assess therapy in IIM at an early stage. Here we describe and characterize the clinical significance of a novel autoantibody in IIM directed against the DNA damage binding protein1.

Methods: Three-hundred and eighty patients with various connective tissue diseases (CTDs) and 20 healthy controls (HCs) were screened for autoantibodies by immunoprecipitation with [³⁵S] methionine-labeled HeLa cells. The target autoantigen was immunoaffinity-purified from HeLa cell extracts and was subsequently identified by peptide mass fingerprinting. Antigen specificity of the serum was further examined by immunoblotting.

Results: An antibody directed against a 120kDa protein was detected in serum from 6 patients with IIM, but not in the serum of other CTD patients or HCs. No patient with anti-120kDa antibodies was positive for other myositis-specific autoantibodies. 50% (3 of 6) were underwent a muscle biopsy compatible with inflammatory myopathy. Most anti-DDB1 positive patients (4 of 6, 67%) showed spontaneous improvements without immunosuppressant treatment. Peptide mass fingerprinting identified the DNA damage binding protein-1 (DDB1) as the autoantigen recognized by anti-120KDa autoantibodies. Immunoblotting experiments using recombinant full-length DDB1 protein confirmed that this was the autoantigen recognized by the anti-120KDa autoantibodies.

Conclusion: Anti-DDB1 antibodies are found in mild forms of IIM. Its detection may be helpful for diagnosis and have prognostic and therapeutic implications in patients with IM. This finding may shed new insights into the pathogenesis of IIM.

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Abstract Number: 1344

Anti-Splicing Factor Proline/Glutamine-Rich autoantibodies Rarely Co-Exist with Anti-Melanoma Differentiation-Associated Gene 5 Autoantibodies in a Cohort of Dermatomyositis Patients from the United States

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Background/Purpose: Anti-melanoma differentiation-associated gene 5 (MDA5) autoantibodies are common among Japanese dermatomyositis (DM) and clinically amyopathic DM (CADM) patients who develop rapidly progressive interstitial lung disease (RP-ILD). Recently, autoantibodies recognizing the 100 kDa splicing factor proline/glutamine-rich (SFPQ) were discovered to co-exist in half of Japanese anti-MDA5-positive DM patients. Anti-SFPQ autoantibodies were often absent in initial serum samples but appeared later during the course of disease and in a seasonal pattern. Anti-MDA5-positive patients with anti-SFPQ autoantibodies were older and had a higher prevalence of mechanic's hands than those without the co-existing autoantibodies. To date, anti-SFPQ autoantibodies have not been described in anti-MDA5-positive patients outside of Japan. Thus, the purpose of this study was to identify the prevalence and clinical significance of anti-SFPQ autoantibodies among anti-MDA5-positive DM patients in a cohort of DM patients from the United States.

Methods: We included all anti-MDA5-positive DM patients enrolled in a longitudinal cohort study at the Johns Hopkins Myositis Center. Anti-SFPQ autoantibodies were detected in patient serum samples collected at the first and most recent visits by immunoprecipitating radioactively-labeled proteins from [³⁵S]-methionine-labeled HeK cells. The identities of immunoprecipitated proteins were confirmed by peptide mass fingerprinting.

Results: Fifty-five anti-MDA5-positive DM/CADM patients were included in this study. From among these, autoantibodies recognizing the 100kDa autoantigen were detected in 4 (7.3%) of the DM/CADM patients. The corresponding polypeptide was confirmed to be SPFQ by mass spectrometry. Among the 4 patients with co-existing anti-MDA5 and anti-SFPQ autoantibodies, 1 was also positive for anti-U1-RNP autoantibodies and 1 was anti-Ro52-positive. All anti-SFPQ autoantibodies were detected at the time of first visit to the Johns Hopkins Myositis Center rather than appearing later during the disease course. 75% (3/4) of the anti-SFPQ antibody positive patients at initial symptom onset in March-April, and all had ILD; one of these died from severe ILD. The remaining patient had diagnosis in October and did not have ILD.

Conclusion: Although more than half of Japanese anti-MDA5-positive DM patients eventually have co-existing anti-SFPQ autoantibodies, only 7.3% of anti-MDA5-positive DM patients in this United States cohort were positive for anti-SFPQ autoantibodies. These findings highlight an important difference between anti-MDA5-positive DM/CADM patients in the United States and Japan.

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Abstract Number: 1345

Association of HLA-DRB1*0301 with Antisynthetase Syndrome in Spanish Patients

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Session Information

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Background/Purpose: Antisynthetase syndrome (ASSD) is an inflammatory connective tissue disease characterized by the classic triad: arthritis, myositis, and interstitial lung disease (ILD) [1-3]. Raynaud's phenomenon, mechanic's hands, and fever are other relevant but less prevalent clinical findings observed in this condition [1, 3, 4]. The pathophysiology of ASSD is not entirely understood, but genetic predisposition, viral infections and medication use may play a role in the development of this disease [5]. In this regard, the human leucocyte antigen (HLA) region has been described as a genetic factor involved in ASSD in different populations. Taking all these considerations into account, the main objective of our study was to evaluate the potential influence of the HLA region in the susceptibility of ASSD in a cohort of patients from Spain.

Methods: Our study population included 83 Spanish patients diagnosed with ASSD and 303 sex and ethnically matched controls. Patients were recruited from Hospital Universitario Marqués de Valdecilla (Santander), Hospital Clínico San Cecilio (Granada), Complejo Hospitalario Universitario de Santiago (Santiago de Compostela), Hospital General Vall

d'Hebron (Barcelona) and Hospital Universitario La Princesa, Hospital Universitario Fundación Jiménez Díaz, Hospital Universitario La Paz and Hospital General Universitario Gregorio Marañón (Madrid). HLA-DRB1 alleles were determined using the polymerase chain reaction–sequence-specific oligonucleotide probe method.

Results: *HLA-DRB1*03* was significantly increased in patients with ASSD compared to controls (53.0% versus 18.2%, $p < 0.01$, odds ratio=5.09 [95% confidence interval: 2.92-8.84]). Specifically, the susceptibility effect of *HLA-DRB1*03* was due to the *HLA-DRB1*0301* allele.

Conclusion: Our study suggests that the *HLA-DRB1*0301* allele is associated with the susceptibility to ASSD in Spanish patients.

[1] *Medicine (Baltimore)* 2015;94:e1144; [2] *Clin Exp Rheumatol* 2018;36:44-9; [3] *Joint Bone Spine* 2003;70:161-8; [4] *Autoimmun Rev* 2014;13:883-91; [5] *Curr Med Chem* 2015;22:1963-75.

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Abstract Number: 1346

Anti-NT5c1A Autoantibodies As Biomarkers in Inclusion Body Myositis

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Background/Purpose: Sporadic Inclusion Body Myositis (sIBM) is an insidious onset, idiopathic inflammatory myopathy (IIM) with high morbidity. There has not been a reliable biomarker to aid in the diagnosis until autoantibodies to the 44 kDa cytosolic 5'-nucleotidase 1A (NT5c1A: Mup44) were reported. The objectives of our study were to determine the sensitivity and specificity of anti-NT5c1A for sIBM in a cohort of neuromuscular patients and to determine if indirect immunofluorescence (IIF) anti-nuclear antibodies (ANA) assay is a useful serological screen for anti-NT5c1A.

Methods: Sera from sIBM patients, various rheumatic and neuromuscular disease comparator groups, and apparently healthy controls were stored at -80C until required for analysis. All sIBM and IIM patients satisfied the 2017 EULAR/ACR classification criteria for IIM. IgG antibodies to NT5c1A were detected by an addressable laser bead immunoassay (ALBIA) using a full length human recombinant protein (Origene, Rockville, MD: Cat. #TP324617). Autoantibodies to other autoimmune inflammatory myopathy antigens were detected by line immunoassay (LIA) (Euroimmun GmbH, Luebeck, Germany), chemiluminescence assay (CIA) (Inova Diagnostics, San Diego, CA, USA) or enzyme linked immunoassay (ELISA). ANA was detected by IIF (Inova Diagnostics) on HEp-2 substrates. Demographic and clinical data was obtained by chart review.

Results: 27/43 (62.7%) of the sIBM sera were positive for anti-NT5c1A (sensitivity 0.63). 3/43 (7.0%) and 1/43 (2.3%) were positive for anti-SMN (Survival of Motor Neuron) and anti-HMGCR (3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase), respectively, but all were negative for the other myositis-related antibodies (Jo-1, OJ, TIF1y, PL-12, SAE, EJ, MDA5, PL7, SRP, NXP2, MI-2). By comparison, the frequency of anti-NT5c1A in the non-sIBM control group was 9% (specificity 0.91). Of note, 12/60 (20.0%) of systemic lupus erythematosus (SLE) patients were positive for anti-NT5c1A. Furthermore, the two IIM comparator groups (which did not include sIBM) showed 4/40 (10.0%) and 5/104 (4.9%)

positivity for anti-NT5c1A. Review of ANA results for anti-NT5c1A positive (n=34) and anti-NT5c1A negative sera (n=37) indicated that there was no consistent IIF staining pattern associated with anti-NT5c1A positive sera, regardless of disease.

Conclusion: The sensitivity and specificity of anti-NT5c1A for IBM was 0.63 and 0.91, respectively. Therefore, a normal anti-NT5c1A test does not rule out sIBM (moderate sensitivity) whilst a positive test may be helpful with the canonical features of sIBM to support the diagnosis (high specificity). The clinical significance of anti-NT5c1A in SLE requires further study. Anti-NT5c1A antibodies were not associated with a specific IIF staining pattern, hence screening using HEp-2 substrate is unlikely to be a useful predictor for the presence of these autoantibodies.

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Abstract Number: 1347

A Semi-Quantitative Whole Body Magnetic Resonance Imaging Assessment Tool to Define Musculoskeletal Abnormalities in Patients with Idiopathic Inflammatory Myopathies

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Background/Purpose: There is a lack of standardized methodology for assessing whole body MRI (WBMRI) in idiopathic inflammatory myopathy (IIM) patients. This leads to difficulty in comparing results across studies and combining data in meta-analysis. The goal of this study was to develop a new standardized assessment tool to characterize WBMRI findings in IIM patients.

Methods: Thirty patients with probable or definite Bohan and Peter juvenile or adult dermatomyositis (JDM, DM) or juvenile or adult polymyositis (JPM, PM) or definite IBM by Grigg's criteria underwent WBMRI, including T1, T2, and STIRMRI sequences. A tool was developed to record scores for these patients based on consensus opinion among radiologists with expertise in musculoskeletal assessment and rheumatologists with myositis expertise. Images were scored in a blinded manner across 34 compartments (Fig. 1) by 3-4 radiologists without an expertise in musculoskeletal disease. Each compartment was assessed for abnormal findings in muscle, subcutaneous tissue, and myofascia. The intensity of muscle signal abnormality (STIR intensity score), extent of muscle inflammation (STIR involvement score) and fatty infiltration (T1 fatty infiltration score) were scored using a 0-3-point scale. The presence of fasciitis and subcutaneous tissue signal intensity (Skin/SC T2 signal) and muscle atrophy (T1 atrophy) were evaluated on a binary scale (0=negative; 1=positive signal abnormality).

Clinical assessments included physician global disease activity visual analogue scale (PGA), the Myositis Disease Activity Assessment tool (MDAAT) and manual muscle testing (MMT). Interrater reliability was assessed by intra-class coefficient. Correlations were assessed by Spearman correlation coefficient.

Results: Patients included 12 JDM, 2 JPM, 9 DM, 4 PM, and 3 IBM. Most patients were female (80%) and 25 patients (83%) were non-Hispanic Caucasians, 3 (10%) were non-Hispanic African-Americans, and 2 (7%) had Hispanic ethnicity. The median age at the time of MRI was 26 years (IQR: 12 – 55), and the median duration between IIM diagnosis and MRI was 12.7 months (IQR: 6.7 – 23.3). There was fair to excellent agreement for 29/34 compartments (ICC>0.40). Among all IIM patients, PGA correlated with adjusted global total muscle and total disease WBMRI scores ($r_s=-0.525$, $P=0.005$ and $r_s=-0.500$, $P=0.008$, respectively). Adjusted global total muscle and total disease scores also had significant

correlations with MMT ($r_s=-0.399, P=0.032$ and $r_s=-0.388, P=0.038$, respectively). There were no significant correlations between MDAAT cutaneous disease activity and WBMRI fasciitis or subcutaneous edema scores.

Conclusion: WBMRI correlated well with physician assessment of disease activity and MMT. This assessment tool offers a reliable semi-quantitative assessment of MRI findings in IIM patients.

WB-MRI compartments	WB-MRI Scores with ranges		
Head & Neck	Muscle activity score = STIR intensity score* STIR involvement score		
Right Shoulder	Potential range: (0 – 9)	(0 – 3)	(0 – 3)
Left Shoulder	Disease activity score = Muscle activity score + Fasciitis + Skin/SC T2 signal		
Right Arm anterior	Potential range: (0 – 11)	(0 – 9)	(0 – 1)
Right Arm posterior	Muscle damage score = T1 fatty infiltration score + T1 atrophy		
Left Arm anterior	Potential range: (0 – 4)	(0 – 3)	(0 – 1)
Left Arm posterior	Total muscle score = Muscle activity score + Muscle damage score		
Right Forearm anterior	Potential range: (0 – 13)	(0 – 9)	(0 – 4)
Right Forearm posterior	Total disease score = Disease activity score + Muscle damage score		
Left Forearm anterior	Potential range: (0 – 15)	(0 – 11)	(0 – 4)
Left Forearm posterior			
Right Hand			
Left Hand			
Chest			
Abdomen			
Right Pelvis gluteal			
Right Pelvis Iliopsoas			
Right Pelvis Hip Girdle			
Left Pelvis gluteal			
Left Pelvis Iliopsoas			
Left Pelvis Hip Girdle			
Right Thigh anterior			
Right Thigh medial			
Right Thigh posterior			
Left Thigh anterior			
Left Thigh medial			
Left Thigh posterior			
Right Leg anterior			
Right Leg posterior			
Left Leg anterior			
Left Leg posterior			
Right Foot			
Left Foot			
Paraspinal			

Figure 1. :

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Abstract Number: 1348

Quantitative High Throughput Screening of Small Molecules to Inhibit Interferon-Stimulated Major Histocompatibility Complex Class I in Myositis Muscle

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster II: Basic and Translational Science

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Common molecular and histological features of idiopathic inflammatory myopathies (myositis) include activation of the type 1 interferon (IFN) response and aberrant expression of major histocompatibility complex (MHC) classes I and II in myofibers. The IFN response correlates with myositis disease activity, and IFN is known to up-regulate MHC in muscle. MHC is directly involved in autoimmune attack by presenting self-antigens to T cells, and certain of its alleles (human leukocyte antigens (HLAs)) confer susceptibility to myositis. These molecules are not expressed in healthy myofibers, and over-expression of MHC class I in mouse muscle recapitulates many characteristics of myositis including inflammation, atrophy, and ER stress. Here we report the development of a series of cell-based assays for quantitative high throughput screening (qHTS) for small molecule inhibitors of IFN-stimulated MHC class I expression in muscle.

Methods: The primary screen involves immunofluorescence of HLA-ABC in immortalized human myoblasts stimulated with IFN-beta and treated with large and diverse chemical libraries containing approved, well-characterized, or novel compounds, and then analyzed by laser cytometry and high content imaging. Active molecules displaying concentration-response profiles for inhibition of HLA-ABC expression will be validated in primary myoblasts from myositis patients by both immunofluorescence and RT-qPCR of several HLA genes. In addition, we are developing a CRISPR/Cas9 genome-edited myoblast with reporter genes inserted into the endogenous HLA loci to measure its expression level.

Results:: We have developed both high throughput RT-qPCR and immunofluorescence assays for HLA-ABC in immortalized human myoblasts, have measured concentration-response profiles for IFN-beta, and are currently screening chemical libraries. We sequenced the HLA loci of this cell line, designed guide RNAs, and are optimizing Cas9 transfections to create a reporter gene edited cell line.

Conclusion: These efforts will be the first application of qHTS technology with a chemical genomics approach to interrogating the IFN-MHC response in myositis muscle.

Disclosure: T. Kinder, None; P. Dranchak, None; J. Inglese, None.

Abstract Number: 1349

Rnaseq of Peripheral Blood Mononuclear Cells from Juvenile Dermatomyositis, Necrotizing Myopathy and Controls Are an Aid in Diagnosis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster II: Basic and Translational Science

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The HMG-Cr form of Necrotizing Myopathy (NM) is a relatively newly recognized entity within the constellation of pediatric inflammatory myopathies. The purpose of this study is to assess peripheral blood mononuclear cells (PBMCs) from 2 children with NM, one with documented IgG antibody to HMG-Cr, for their pattern of gene dysregulation, compared with JDM and control PBMCs, using RNASeq.

Methods: After obtaining the appropriate informed consent, the following were enrolled in the CureJM Juvenile Myositis Registry: 4 girls with JDM (mean age 12.4±4.6 SD years), 2 girls with NM, (mean age 7.5± 8.8 years) and 4 controls (mean age 8.5± 4.4 years); all participants were White/Hispanic. Sera for all current Myositis Specific Antibody as well as SRP and SAE antibody was tested by Oklahoma Research Labs. They were also tested for SAE and HMG-Cr antibody by RND labs (Culver, Ca.). RNASeq libraries were generated from PBMC RNA using the Clontech stranded high input ribosomal depletion total RNA kits. The samples were sequenced on an Illumina HiSeq2500 or HiSeq3000 in paired-end mode. Sequence reads were aligned to the reference genome GRCh38 by STAR. Read count normalization and differential expression analysis were performed by DESeq2.

Results: The MSAs of the 4 JDM were: p155/140=3; negative=1; the entire group was negative for SAE and SRP antibodies. Of the NM group, one was positive for IgG antibody to HMG-Cr. Cluster analysis of the RNAseq data suggests three distinct JDM subgroups (2 JDM each), with the two NM patients (one HMGCr +) which had very similar expression patterns. Overall, these 6 myositis transcriptome patterns were quite different from the 4 controls. One of the two groups of JDM was more similar to the controls (termed normal-like JDM). Using DESeq, we identified 209 genes that were differentially expressed in both HMGCr-normal-like JDM comparison and HMGCr-control comparison (False Discovery Rate (FDR) < 0.15). Pathway analysis by WebGestalt revealed several enriched pathways including neutrophil degranulation (29 genes, FDR<0.00001); innate immune system (46 genes, FDR<1.6*E-8), Toll-like receptors cascades (11 genes, FDR=0.0023), complement and coagulation cascades (6 genes, FDR=0.048), which play a role in autoimmune disease. Of note, several genes with critical roles in T-cell receptor signaling (i.e., CD3D, CD8A, ICOS, ITK) were consistently down-regulated in the 2 NM children. Using weighted correlation network analysis, we identified 156 genes that were highly connected with the HMG-Cr gene. WebGestalt shows that this gene network is enriched in circadian clock/NAD metabolism and degradation of beta-catenin by the destruction complex.

Conclusion: Specific patterns of gene dysregulation determined by RNASeq appear to characterize PBMCs from these children with necrotizing myopathy. There is wide variation in gene dysregulation in PBMCs compared to JDM, revealing some shared modes of muscle destruction. When serological diagnosis is not established, characterization of the patient's RNASeq pattern, using PBMCs, may be helpful in assessing necrotizing myopathy.

Disclosure: C. C. Huang, None; E. D. O. Roberson, None; G. A. Morgan, None; H. Huang, None; V. Hans, None; L. M. Pachman, None.

Abstract Number: 1350

Elevated Serum Levels of Soluble CD146 and CD146 Autoantibody in Patients with Polymyositis/Dermatomyositis

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Session Information

Session Date: Monday, October 22, 2018

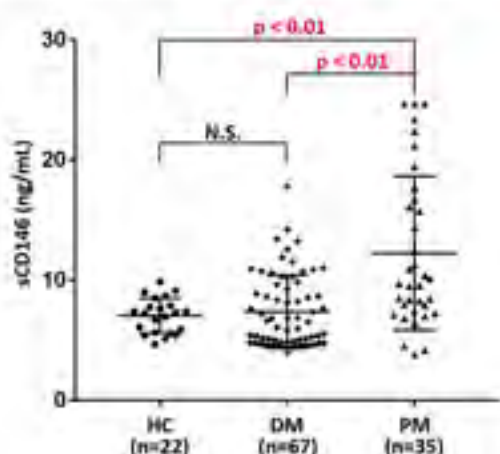
Session Title: Muscle Biology, Myositis and Myopathies Poster II: Basic and Translational Science

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: CD146 is a transmembrane glycoprotein belonging to the immunoglobulin superfamily, acts as an adhesion molecule for the maintenance of cell monolayer. Human endothelial cells constitutively express CD146 which is involved in angiogenesis and inflammation. Recently, we established a sandwich ELISA for detecting soluble CD146 (sCD146) in human serum and reported presence of elevated level of sCD146 in patients with Behcet's disease and systemic sclerosis.

Figure 1. Serum levels of soluble CD146 (sCD146) in patients with Dermatomyositis (DM) or Polymyositis (PM) and healthy controls (HC)



However, an association of sCD146 with PM/DM remains unknown. The aims of this study are to examine serum levels of sCD146 in patients with PM/DM and their association with clinical features and to clarify the mechanism of the difference in levels of sCD146.

Methods: Serum levels of sCD146 were quantified in 102 patients with PM/DM who visited our hospital from January 2001 to 2017 and compared with those of 22 healthy controls (HC). Recombinant CD146 protein was used to obtain a standard curve to measure quantity of sCD146. We also established another ELISA for detecting autoantibody against CD146 by using human recombinant CD146 protein.

Results: Serum levels of sCD146 were higher in the PM/DM subset than in HC but not statistically significant difference. Especially, the levels of sCD146 was significantly higher ($P < 0.01$) at mean 12.2 ng/mL in the PM subset, as compared to the DM subset or HC (Figure 1). Inverse correlations were observed between the levels of sCD146 and those of C-reactive protein in the PM/DM subset, and between the levels of sCD146 and those of creatine kinase in the PM subset. The levels of sCD146 were significantly higher ($P < 0.05$) in the patients with anti-ARS antibody than in patients with anti-TIF1-gamma antibody. There was no correlation between the levels of sCD146 and other clinical features such as complication of interstitial lung disease or malignancy. We hypothesized the existence of CD146 autoantibody in patients with DM and its involvement in the mechanism of the difference in the levels of sCD146. We measured serum CD146 autoantibody by established ELISA and found out the presence of serum CD146 autoantibody in PM/DM and significant high levels ($P < 0.05$) in the DM subset at 2 folds higher than mean level of the PM subset. These findings suggested the presence of CD146 autoantibodies could make disturbance to detect sCD146 in DM. Additionally, the levels of CD146 autoantibody showed a significant correlation with disease activity in patients with DM.

Conclusion: We identified higher levels of sCD146 in patients with PM than DM, and higher levels of CD146 autoantibody in DM than PM. CD146 could be one of the key factors involved in the pathophysiology of PM/DM.

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Abstract Number: 1351

In Situ Dendritic Cell Characterization in Idiopathic Inflammatory Myopathies

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster II: Basic and Translational Science

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The Idiopathic Inflammatory Myopathies (IIM) are the largest number of acquired and potentially treatable muscle disorders. Nevertheless, there are currently no FDA or EMA-approved medications apart from corticosteroids, and the mortality and morbidity of these diseases pairs the ones of rheumatoid arthritis in the pre-biologic era. In the last 10 years, interest has been raised about the roles of dendritic cells (DCs) in the pathogenesis of IIM. In this pilot study, we aim to apply previously validated approach of multi-channel confocal microscopy using fluorescent antibodies for identification and characterization of DC populations in biopsies of patients with Dermatomyositis (DM) and Inclusion Body Myositis (IBM).

Methods: This study was performed with deidentified samples from patients with IIM. This study was approved by the University of Chicago institutional IRB. A total of 3 DM and 3 IBM samples were stained for myeloid dendritic cells (mDCs) with BDCA1 and CD11c; plasmacytoid DCs (pDCs) with BDCA 2 and CD123; and cell nuclei with DAPI (Hoechst 33342). These slides were imaged with the SP8 3D 3-color STED laser scanning confocal microscope with time gating at a magnification of 630x, using a pixel size of 1024x1024 and 12 bit depth. Single fluorochrome controls were utilized to ensure no cross-bleeding was present in between fluorescent channels. Given the large amount of tissue, pertaining to each biopsy, and to minimize potential bias, we performed a random acquisition protocol by means of tiling. Using a mechanized stage, the entire tissue section of interest was mapped, automatically segmented into Regions of Interest (ROIs), corresponding to individual High Power Fields (HPFs), and acquired by random means. An average of 50

ROIs per biopsy was acquired in this manner. In addition, manual imaging was performed for areas of significant inflammation, identified during the above process. The resulting image data was reviewed and manually analyzed for number of DCs by a blinded observer (IBV) using Fiji Software. Mann-Whitney U test was used to calculate statistical significance for all analyses.

Results: Subjects with IBM and DM had high counts of mDCs, particularly in DM, with an average of 14 mDCs in DM and 7 mDCs in IBM per biopsy. The difference between DM and IBM in regards to mDCs was decreased after normalization, maybe reflecting the rich inflammatory milieu of DM, in comparison to IBM. The counts of pDCs were also high in both diseases, and significantly higher compared to the ones of mDCs in IBM ($p=.02$), even when normalized by cell density ($p=.032$).

Conclusion: Our findings challenge the classic correlation between DM, IBM, pDCs and mDCs. This pilot study illustrates the complexity behind the cellular drives of IIM in regards to DCs. Priorly established patterns of inflammation used to describe these diseases must be revisited, as new therapeutic targets are urged in IIM.

Disclosure: I. Bauer Ventura, None; D. Reilly, None; P. Pytel, None; V. Liarski, None.

Abstract Number: 1352

Low Density Granulocytes in Idiopathic Inflammatory Myopathy

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Session Information

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Session Title: Muscle Biology, Myositis and Myopathies Poster II: Basic and Translational Science

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Idiopathic Inflammatory Myopathy (IIM) is a group of autoimmune diseases characterized by immune-mediated injury to skeletal muscle, including polymyositis (PM) and dermatomyositis (DM). Recent studies have shown that IIM patients exhibit a type I interferon (IFN) signature, which is also present in systemic lupus erythematosus (SLE) (1). Low density granulocytes (LDG) have been identified as an important source of IFN production in SLE patients (2). Given the importance of IFN in the pathogenesis of SLE, DM, and PM, we hypothesized that LDG numbers would be increased in patients with IIM.

Methods: Healthy donors (HD) and patients with undifferentiated connective tissue disease (UCTD) were enrolled in the Hospital for Special Surgery UCTD Registry. SLE patients were enrolled in the FLARE lupus registry, and all met at least 4 of 11 ACR classification criteria for SLE. Myositis subjects in the present study were enrolled in the Hospital for Special Surgery Myositis Registry. All patients with IIM either 1) met Bohan and Peter criteria for probable or definite PM or DM, or 2) met Bohan and Peter criteria for possible PM/DM and were positive for a myositis-specific or myositis-associated antibody. PBMC were isolated from whole blood using Ficoll density centrifugation, then stained and fixed with paraformaldehyde until analyzed by flow cytometry. Cells were stained with antibodies against CD16, CD15, CD14, CD64, and CD56. LDGs were identified as cells in the PBMC fraction staining CD15hi/CD14lo. Differences between groups were analyzed using 2-tailed Student's T tests. No correction for multiple comparisons was made in this exploratory analysis.

Results: 18 patients with IIM (10 DM/8 PM), 14 healthy donors, 3 SLE patients, and 4 patients with UCTD were evaluated. The mean proportion of LDGs in IIM was numerically greater than HD, but the difference did not reach statistical significance (all presented as mean +/- standard error: 4.13% +/- 1.61 vs 0.91% +/- 0.27, $p=0.104$). However, when PM and DM patients were compared to HD in a subgroup analysis, DM patients had a significant elevation of LDGs (4.22% +/- 1.75, $p=0.045$). There was no significant correlation between strength as assessed by manual muscle testing (MMT8), or with creatine kinase levels. In accordance w/ prior studies, LDGs in SLE were elevated relative to HD (14.48% +/- 11.67, $p=0.015$), while the level in UCTD was closer to HD (0.61% +/- 0.14, $p=0.558$).

Conclusion: We did not find an increase in LDGs in PBMC of patients with IIM relative to HD, though a subgroup analysis showed DM patients exhibit a significant elevation of LDGs. Our study may not have had sufficient power to distinguish a difference in IIM patients relative to HD in the aggregate, possibly due to the heterogeneity and complexity of IIM patients. LDGs may be of importance in subgroups of IIM patients.

References: 1. Higgs BW, *et al.* Patients with systemic lupus erythematosus, myositis, rheumatoid arthritis, and scleroderma share activation of a common type I interferon pathway. *Ann Rheum Dis.* **70**, 11 (2011).
2. Smith CK, Kaplan MJ. The role of neutrophils in the pathogenesis of systemic lupus erythematosus. *Curr Opin Rheumatol.* **27**, 5, (2015).

Disclosure: D. Fernandez, None; L. Jia, None; M. Olfieriev, None; A. M. Fernandez, None; J. Vega, None; K. Merritt, None; M. Lockshin, None; P. Crow, None.

Abstract Number: 1353

Autophagy Marker LC3 Accumulates in Immune-Mediated Necrotizing Myopathy Muscle Fibres

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster II: Basic and Translational Science

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To investigate the expression of autophagy marker LC3, localization of macrophages and accumulation of misfolded proteins in myofibres of immune-mediated necrotizing myopathy (IMNM) muscle biopsies.

Methods: The analysis was made on muscle sections of 12 IMNM, 12 Dermatomyositis (DM), 5 Polymyositis (PM), 8 sporadic Inclusion Body Myositis (sIBM) patients and 6 healthy, age-matched controls immuno labelled with anti: - autophagy markers LC3b, -ubiquitin, - SQSTM1/p62, -TDP-43 (TAR DNA binding protein), -SMI31, -C5b-9, -CD68, - NCAM (neural cell adhesion molecule), -MHC I (major histocompatibility complex-I), -MHC II.

Results: In IMNM, inflammation was mild compared with DM, PM, sIBM; sporadic endomysial and/or perivascular inflammatory cells were CD68+ macrophages. The number of myofibres containing LC3b was statistically higher in IMNM and IBMs rather than in DM and PM.

In IMNM, LC3b was mainly located in regenerating myofibres, CD56 + and was associated with MHC-II⁺ vesicles. In sIBM, a high number of LC3b was found in vacuolated myofibers, whereas CD56+ myofibers appeared less pronounced. SMI31 and p62 aggregates were significantly higher in sIBM rather than in the other IIMs, even if, also in IMNM they accumulated in non-necrotic myofibres, the latter colocalizing with LC3 as small puncta in IMNM myofibres and large vacuoles in sIBM myofibres. However, the highest number of ubiquitin⁺ myofibres was revealed in IMNM.

Conclusion: These findings suggest an involvement of cellular clearance systems in the pathophysiology of IMNM, like that of sIBM. LC3b⁺ puncta in regenerating myofibres can be considered a peculiar biomarker in IMNM. Further studies of larger patients' cohorts are needed to better define IMNM.

Disclosure: M. Giannini, None; F. Girolamo, None; A. Lia, None; A. Amati, None; L. Serlenga, None; D. D'Abbicco, None; M. Tampoia, None; M. Trojano, None; F. Iannone, None.

Abstract Number: 1354

Correlates of Neuropathic Pain in Knee Osteoarthritis: The Modified Pain detect Questionnaire and the Osteoarthritis Initiative

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Cumulative evidence suggests central sensitization contributes to a neuropathic-like phenotype in a subset of patients with knee osteoarthritis (OA). Using a variety of validated neuropathic pain (NP) questionnaires in musculoskeletal patient cohorts, factors including gender, body mass index, and depression, insomnia and pain catastrophizing have been associated with neuropathic symptoms. In the current study, the modified pain Detect Questionnaire (mPDQ) was administered to subjects enrolled in the Osteoarthritis Initiative (OAI), a well-established, longitudinal knee OA cohort, with the aim of further exploring the prevalence and correlates of NP specific to knee OA. A better understanding of the factors associated with NP in knee OA can help identify affected patients who may benefit from alternative treatment approaches that target NP pathways.

Methods: The mPDQ was administered to 699 subjects enrolled in the Baltimore OAI cohort during their scheduled 72-month follow up visit. Standard demographic, clinical, and radiographic data were collected as per the OAI study protocol. The presence of NP was determined using a previously defined mPDQ cut-point. Correlates of NP were evaluated through univariate analysis and logistic regression, and included factors relating to demographics, knee OA symptom severity, markers of chronic pain and pain intensity, psychological factors, functional disability, medical comorbidities and concurrent medication usage.

Results: Of the 699 subjects in the cohort, 476 were eligible for the analysis; 99 (21%) subjects were found to have NP symptoms (mPDQ score ≥ 13). Knee Injury and Osteoarthritis (KOOS) pain score, The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score, WOMAC physical function score, Von Korff pain score (VKP) and the Late Life Disability Instrument (LLDI) - limitation dimension were shown to be different between patients with and without NP ($p < 0.01$). Independent correlates ($p < 0.01$) of NP were: WOMAC total score (OR=1.93), coping strategies - pain catastrophizing subscale (OR=1.23), VKP (OR=1.06), WOMAC physical function score (OR=1.02) and LLDI – limitation dimension (OR=0.98). Multivariate modelling found WOMAC total score (OR=2.07, $p=0.018$), coping strategies – pain catastrophizing subscale (OR=1.22, $p=0.035$) and VKP (OR=1.07, $p < 0.001$) to be significant predictors of NP.

Conclusion: Similar to other studies, a subset of the Baltimore OAI knee OA cohort had a NP phenotype, which was associated with more pain catastrophizing and greater symptom burden. This study additionally found that a NP phenotype was associated with greater disability. Further studies are needed to determine if treatment targeted to the NP phenotype reduces knee OA symptom severity and functional impairment in affected individuals.

Table 1: Variables associated with neuropathic pain. * $p < 0.01$; ** $p < 0.001$

Domain	Variable	NP ⁺ Median (Range)	NP ⁻ Median (Range)	NP ⁺ Odds Ratio (95% CI)	NP ⁺ (p-value)
Demographics	Age	63 (52-83)	65 (51-85)	0.98 (0.96-1.01)	0.159
Knee OA Symptom Severity	KOOS: Pain Score	83.3 (18.8-100)	91.7 (0-100)	0.99 (0.98-1.00)	0.014
	WOMAC: Total Score	15.35 (0-75.4)	7 (0-76)	1.01 (1.00-1.03)	0.013
	WOMAC: Pain Score	3 (0-15)	1 (0-20)	1.05 (0.99-1.10)	0.085
Pain Intensity	Von Korff Pain Score	63.33 (10-100)	26.67 (0-100)	1.06 (1.05-1.08)	< 0.001**
Psychological Factors	Coping Strategies - Pain Catastrophizing Subscale	1 (0-6)	0 (0-6)	1.23 (1.08-1.40)	0.002*
	Center for Epidemiologic Studies Depression Scale Score	8 (0-36)	5.50 (0-40)	1.03 (1.00-1.05)	0.023
	KOOS: Quality of Life Score	68.8 (6.3-100)	68.8 (0-100)	0.99 (0.98-1.00)	0.017
Functional Disability	Late Life Disability Instrument: Frequency Dimension	52.23 (35.23-70.61)	53.71 (37.39-76.31)	0.96 (0.93-1.00)	0.046
	Late Life Disability Instrument: Limitation Dimension	68.19 (39.63-100)	77.57 (41.54-100)	0.98 (0.97-0.99)	0.003*
	WOMAC: Physical Function Score	10.1 (0-54.4)	4.3 (0-53.1)	1.02 (1.01-1.04)	0.005*
Domain	Variable	NP ⁺ Frequency (%)	NP ⁻ Frequency (%)	NP ⁺ Odds Ratio (95% CI)	NP ⁺ (p-value)
Demographics	Gender (female)	68 (68.7)	218 (57.8)	1.6 (1.00-2.56)	0.051
Knee OA Symptom Severity	WOMAC: Total Score, (≥ 17)	48 (48.5)	172 (36.1)	1.93 (1.23-3.03)	0.004*
Psychological Factors	Center for Epidemiologic Studies Depression Scale Score (≥ 16)	26 (26.3)	84 (17.7)	1.96 (1.15-3.32)	0.013

Disclosure: J. Bernick, None; W. M. Hopman, None; M. C. Hochberg, None; J. Hochman, None.

Asymptomatic Hyperuricemia Is Associated with Increased Prevalence of Symptomatic Knee Osteoarthritis: Data from Third National Health and Nutrition Examination Survey

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Inflammation plays a pathogenetic role in OA, and catabolic cytokines including IL-1 β potentiate joint space narrowing. Elevated serum urate (sUA) levels promote crystal-induced stimulation of inflammasome IL-1 β production, potentially contributing to OA incidence and/or progression. Additionally, intraarticular urate concentrations associate with radiographic knee OA (RKO) severity. However, there is limited research on associations of asymptomatic hyperuricemia (AH) and knee OA outcomes. Therefore, we sought to examine the association of AH with RKO and symptomatic RKO (sRKO) using the National Health and Nutrition Examination Survey III (NHANES III), a large nationally representative survey. We also examined whether body mass index (BMI) modifies the association between AH and RKO.

Methods: NHANES III was a cross-sectional health examination survey conducted between 1988 and 1994. It used a multistage, stratified probability cluster design to select a representative sample of noninstitutionalized civilian in the US, and included data on sUA, gout, clinical and radiographic knee OA. We analyzed data (n=2213) for adults over age 60, excluding individuals with self-reported gout. Hyperuricemia was defined as serum urate > 6.8, mg/dL. One non-weight bearing AP knee X-ray was performed with RKO defined as KL grade \geq 2, and sRKO as RKO plus pain in the affected joint on most days for the prior 6 weeks. Wald chi-square tests were used to examine differences in proportions between different study characteristics. Multivariate log binomial models were used to examine the association between AH and knee OA outcomes and estimate prevalence ratios (PRs) and 95% confidence intervals (CIs).

Results: Among US adults age 60 years and older, prevalence of AH was 17.9% (CI 15.3-20.5). AH prevalence was significantly greater among men vs women (24.5% vs. 13.3%, $p < 0.01$) and persons with obesity (BMI ≥ 30 kg/m²) vs persons without obesity (27.4% vs. 14.8%, $p < 0.01$). Prevalence of RKO was 37.7% (CI 35.0-40.3) and was significantly greater in women vs men (42.1% vs. 31.3%, $p = 0.01$). The prevalence of RKO was highest among subjects with greater age, obesity, non-Hispanic Black race, and less education. RKO prevalence among adults with AH was 44.0% vs 36.3% for those with normuricemia ($p = 0.056$). Importantly, sRKO was significantly higher in the AH group (17.4 vs 10.9%, $p = 0.04$). After adjusting for age, sex, race, and education, adults with AH were more likely to have RKO (PR = 1.26, 95% CI: 1.06, 1.36) and sRKO (PR = 1.69, 95% CI: 1.19, 2.42). These associations were observed for persons without obesity, but were severely attenuated among persons with obesity, suggesting that obesity status may modify the association between AH and knee OA.

Conclusion: We identified a greater prevalence of RKO among persons with AH, along with a greater prevalence of sRKO, suggesting urate may participate in OA pathogenesis. This association appeared to be modified by obesity status with non-obese adults (but not adults with obesity) reporting a greater prevalence of knee OA among participants with AH. Longitudinal studies are needed to verify these findings.

Disclosure: S. Wang, None; M. Pillinger, Horizon Pharmaceuticals, 5, Ironwood, 5, SOBI, 5; S. Krasnokutsky Samuels, None; K. E. Barbour, None.

Increasing Oral Doses of GLPG1972 Administered Daily for 29 Days Show a Strong Target Engagement in Patients with Knee and/or Hip OA

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoarthritis (OA) is characterized by structural changes of the joint, of which degradation of articular cartilage is one of the major signs¹. The main proteoglycan component of the extracellular matrix of articular cartilage is aggrecan. GLPG1972 as a potent and selective inhibitor of ADAMTS-5, a key aggrecan-cleaving enzyme involved in cartilage degradation, is being developed as a potential disease-modifying OA drug (DMOAD). Aggrecan cleavage by ADAMTS-5 results in release of N-terminal ARGS neoepitope fragments of which serum levels significantly decreased in healthy subjects treated with GLPG1972 during 14 days in a previous study².

The objective was to assess safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD, i.e. serum ARGS-aggrecan levels) during and following administration of GLPG1972 in patients with knee and/or hip OA.

Methods: This was a single center, randomized, double-blind, placebo-controlled, age and gender stratified, ascending dose Phase Ib study, with three semi-sequential cohorts of 10 patients each, randomized to GLPG1972 or placebo in a 4:1 ratio. Doses tested were once daily 100, 200 or 300 mg given orally. Treatment duration was 29 days. Patients had follow-up visits 14 and 21 days after last dosing for additional PD assessments. Methods for PD have been described previously³.

Results: Thirty patients were included. Of these, 24 patients (M/F rate 8/16, 14 aged 50-64 and 10 aged 65-75) received GLPG1972. All adverse events (AE) were mild and transient. No serious AEs were reported during the study; one female patient in the 300-mg group was discontinued after 15 days of treatment due to drug-related elevated transaminase values which returned to normal 9 days after treatment discontinuation while her bilirubin levels remained normal. There were no overall trends in lab abnormalities over time or significant changes in vital signs, ECG and Holter parameters. Steady state in plasma exposure was reached after 3-5 days of dosing. Exposure increased dose-proportionally. Mean serum ARGS levels (SEM) decreased steadily over time in all patients receiving GLPG1972: -40% (2.9), -46% (4.5) and -53% (2.8) at day 15 compared to baseline in the 100, 200 and 300 mg group respectively. These levels remained stable until last dose on day 29, then consistently returned to pre-dose levels for all groups 14 and 21 days after last dose. Placebo group levels remained unchanged.

Conclusion: When administered daily for 29 days in patients with knee and/or hip OA, GLPG1972 at oral doses of 100, 200 and 300 mg q.d. was generally well tolerated and safe. Serum ARGS levels, as a marker for target engagement and potential proxy of cartilage degradation, showed a decrease over time up to 53% below baseline in the 300 mg group. These findings are consistent with what we observed in a previous study in healthy subjects² and reinforce the rationale for developing GLPG1972 as a DMOAD.

References: 1. Hunter, D. J., et al. *Curr. Opin. Rheumatol.* 2009, 21, 110–117

2. van der Aar E, et al. *Arthritis Rheumatol.* 2017; 69 (suppl 10)

3. Larsson et al. *Osteoarthritis Cartilage* 2014, 22(2):242-9

Disclosure: H. Deckx, Galapagos N.V., 1, 3; S. Hatch, Galapagos NV, 3, 5; M. Robberechts, Galapagos NV, 3; S. Dupont, Galapagos NV, 3; J. Desrivot, Galapagos NV, 3; H. Coleman, None; S. Larsson, None; A. Struglics, None; E. van der Aar, Galapagos N.V., 1, 3; A. Fieuw, Galapagos NV, 3.

Flexion Contractures Are Associated with Worse Pain, Stiffness, and Function in Patients with Knee Osteoarthritis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

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Background/Purpose: Knee osteoarthritis (OA) causes pain, disability, and affects ~20% of the population in the United States [Wallace2017]. Knee flexion contractures (FCs) are limitations to knee extension [Campbell 2015]. Despite >1/3 of patients with knee OA having a FC [Ritter 2007], little is known regarding FC effect on their OA symptoms and function. Our objective was to determine if the presence and severity of a knee FC affected joint pain, stiffness and function in patients at risk of developing, or with knee OA.

Methods: Cross-sectional study using the Osteoarthritis Initiative (OAI) cohort divided into 3 subcohorts: those at risk of knee OA (n=3284), those with radiographic knee OA (n=1390), and controls (n=122). At enrollment, knee FCs were graded based on the loss of maximum knee extension ($\leq 5^\circ$ none, $6-14^\circ$ mild, $\geq 15^\circ$ moderate-to-severe). Pain was evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale and the numeric

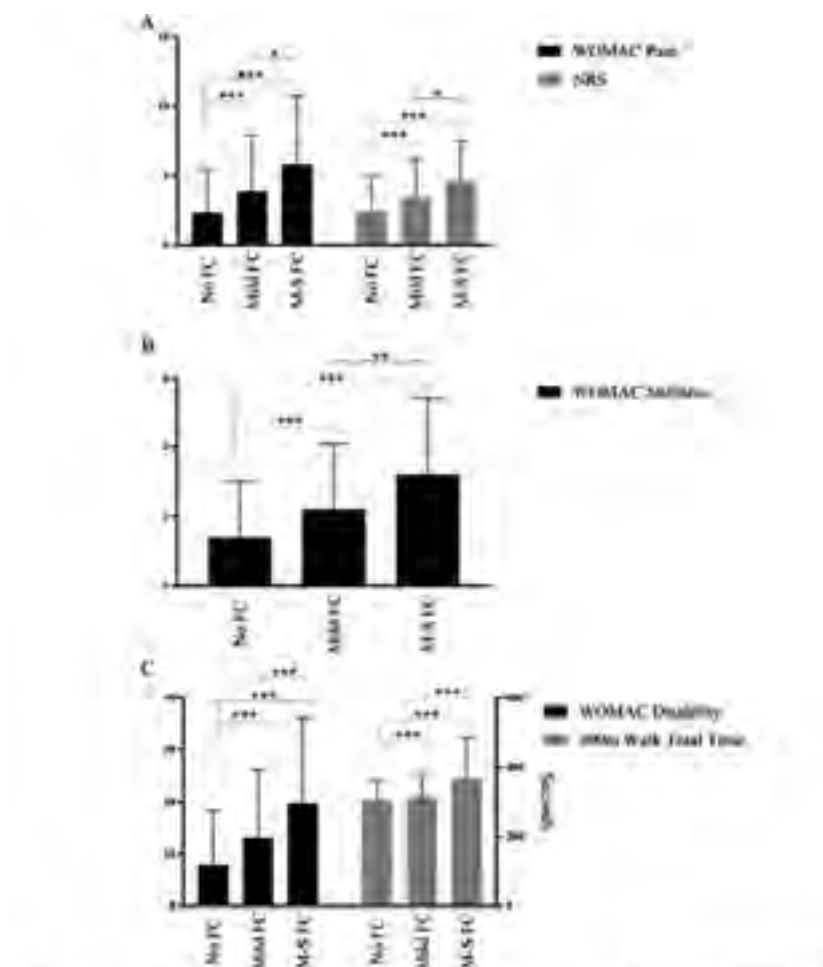


Figure 1: Outcome measures for OAI participants. (A) Pain outcomes as measured by WOMAC and NRS pain scales. (B) Stiffness as measured by WOMAC Stiffness subscale. (C) Disability outcomes measured using WOMAC Disability scale and 400m walk time. All outcomes show a dose-dependent worsening with increasing contracture severity. *p<0.05; **p<0.01; ***p<0.001.

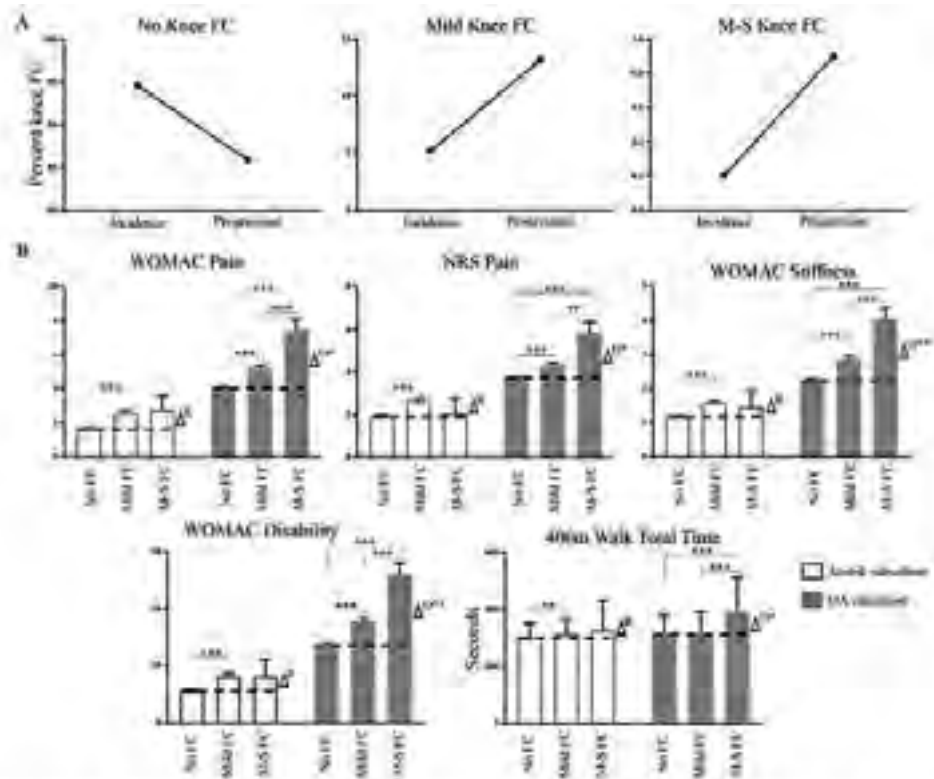


Figure 2. Prevalence of knee flexion contracture, pain, knee dysfunction and stiffness in patients at-risk of OA and with OA. All outcomes were worse with dose-dependency on knee contracture severity and all were amplified in the OA subcohort compared to the at-risk subcohort. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; Δ =difference in outcome between no FC vs moderate to severe FC for at-risk (Δ^R) and OA (Δ^O) participants.

Table 1. Demographic characteristics of participants with and without knee flexion contracture

	No contracture (n=424)	Mild knee FC (n=118)	Mod-to-severe knee FC (n=38)***
Age, mean \pm SD years	60.9 \pm 9.1	63.0 \pm 9.4***	63 \pm 9.4*
Height, mean \pm SD cm	167.9 \pm 92.0	169.8 \pm 91.3***	170.0 \pm 92.1
Weight, mean \pm SD kg	80.6 \pm 16.2	85.7 \pm 16.5***	91.8 \pm 17.4
BMI, mean \pm SD kg/m ²	28.4 \pm 4.8	29.9 \pm 5.0***	31.5 \pm 5.6
Male, %	40.3	50.6***	59.5*
Race, no. (%) †			
White	3376 (79.6)	384 (74.1)	50 (78.9)
Black	746 (17.6)	123 (23.7)	5 (13.2)
Asian	42 (1.0)	3 (0.6)	0 (0)
Other	74 (1.7)	6 (1.2)	2 (5.3)
K&L grade, mean \pm SD	1.5 \pm 1.2	2.3 \pm 1.2***	2.4 \pm 1.4*

*** $p < 0.001$ versus no contracture group (includes all moderate to severe characteristics)

† $p < 0.05$ versus no contracture group

* $p < 0.05$ versus mild knee FC group

FC = flexion contracture; ROM = range of motion; K&L = Kellgren and Lawrence grade

rating scale. Stiffness was evaluated using the WOMAC stiffness subscale. Function was evaluated using the WOMAC function subscale and 400m walk time. Between-group outcomes were compared using ANOVA with post-hoc testing corrected for multiple comparisons. Two-way ANOVA tested for knee FC interaction with subcohort grouping. Multiple linear regression tested for an independent association between knee FC and outcomes, correcting for age, sex, BMI, race, and radiographic severity.

Results: Participants with knee FC tended to be older males with larger BMI and worse radiographic severity (all $p < 0.001$; Table 1). They reported worse knee pain, stiffness and function (all scales $p < 0.001$; Figure 1). Knee FC showed a severity-dependent association with WOMAC pain ($p = 0.020$), WOMAC stiffness ($p = 0.006$) and 400m walk time ($p < 0.001$), with the magnitude increase being greater in the OA group versus those at risk of OA (Figure 2). This association was maintained following multiple linear regression ($p < 0.001$).

Conclusion: Knee FC was associated with pain, stiffness, and dysfunction in participants at risk of, and with knee OA in a FC severity-dependent manner. These associations were strongest in those with knee OA. Measuring knee extension should be a routine component of the clinical assessment. Addressing FC in clinical care may lead to better OA outcomes.

Disclosure: T. M. Campbell, None; M. Monsour, None; G. Trudel, None.

Abstract Number: 1358

The Association of Microbial Translocation and WOMAC Function in Patients with Knee Osteoarthritis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoarthritis (OA) affects 33.6% of population ≥ 65 . Knee OA (KOA) is the most prevalent OA and it is one of five leading causes of disability of non-institutionalized adults. Aging and excessive body mass are the two strongest risk factor for KOA. Biomechanical theory suggests that increase in axial load would promote degeneration in cartilage. However, it is undermined by the fact that even OA of non weight bearing joint such as carpometacarpal joint of the thumb is associated with obesity. Both obesity and aging, risk factors for OA are associated with low grade inflammation. Microbial translocation (MT) is defined as the passage of both viable and nonviable microbial products such as LPS across an anatomically intact intestinal barrier. A higher burden of microbial translocation with aging is reported both in animal and human studies. Obesity is also known to be associated with increased MT. Recently, MT is thought to be the source of low grade inflammation in obesity and aging, and it is possible that MT activates innate immunity which in turn causes the low grade inflammation seen in OA.

Methods: The Intensive Diet and Exercise for Arthritis (IDEA) study is a prospective, randomized controlled trial of 454 overweight and obese older adults with tibiofemoral osteoarthritis. Two subgroups were selected from IDEA study ($n=22$ each): a group that showed radiographic progression (≥ 0.7 mm decrease in joint space width, JSW) and age, gender, and BMI matched group who did not progress (≤ 0.35 mm decrease in JSW). Stored baseline blood samples were analyzed for markers of MT: lipoprotein binding protein-1 (LBP-1) and soluble cluster of differentiation 14 (sCD14). Multivariate analyses were performed to examine the association with baseline MT and KOA progression as well as the OA outcomes using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Results: The mean age was 66 (SD 5.3), 68% female, and mean BMI was 30.5 (SD 4.6). There was no association between baseline MT translocation and OA progression. However in multivariate analysis baseline Scd14 is positively associated functional limitation for 18 months WOMAC function measure (coefficient 0.37, $p=0.03$) after controlling for age, weight, randomization group.

Conclusion: In this secondary analysis of IDEA study, a microbial translocation marker at baseline is predictive of 18 months functional outcome. Future study to explore the mechanisms of this association is warranted.

Disclosure: S. Kim, None; R. Loeser, None; D. Ang, None; S. P. Messier, None.

Abstract Number: 1359

A Machine Learning Approach to Knee OA Phenotyping: The Johnston County Osteoarthritis Project

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Session Information

Session Date: Monday, October 22, 2018

Hypotheses	Overall z	Variables used for clustering					
		All*	Function	SES	Health	Medic	Genetic
OA: no rKOA vs. rKOA (prevalent)	13.95						
a: NP vs. Pain only progression	3.05	h	h	kh	kh		
b: NP vs. rKOA only progression	-0.43			k			kh
c: Pain only vs. Both progression	7.74	h		kh		h	
d: rKOA only vs. Both progression	2.77	h	h	k	k	kh	kh
e: NP vs. Both progression	5.32						
f: No rKOA vs. rKOA progression	0.75		k	h			kh
g: No pain vs. pain progression	4.25				kh		kh
h: NP vs. Any progression	1.55				kh	h	kh

Abbreviations: rKOA=radiographic knee OA; NP=non-progressors by pain or rKOA; Both=progressors by both pain and rKOA.
*All variables: Function includes gait/stride strength, walk time, self-reported function; SES includes education, marital status, employment; Health includes comorbidities and family history; Medic includes medications for pain, cardiovascular disease, and NSAID use; Genetics includes T-type from a recent genome (RAD 2775517); Note that clustering and k-means hierarchical methods did not result in significant clusters.

Session Title: Osteoarthritis – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Knee osteoarthritis (KOA) is a heterogeneous condition characterized by changes in a variety of joint tissues and driven by a number of different potential mechanisms. The purpose of this study was to explore machine learning approaches to phenotyping in KOA in order to better define the progression phenotype(s) that may be more responsive to interventions.

Methods: We focused on identifying baseline differences in the Johnston County OA Project (T1) between 1) knees with and without prevalent radiographic KOA (rKOA, Kellgren-Lawrence grade [KLG] 2 or more, “OA”), and 2) those that did or did not have worsening KLG and/or symptoms (progression) at follow-up. The dataset included observations on 741 participants with 78 baseline variables selected to represent clinically relevant characteristics of this sample. Both k-means and hierarchical clustering methods were applied to identify important subgroups of observations within the dataset. Two high-dimension low-sample size (HDLSS) methods were used: SigClust, to assess statistical significance of clusters and 2) DiProPerm, a projection and permutation-based approach, to compare groups (e.g., prevalent rKOA vs. no OA, progression vs non-progression) by testing equality of distributions (by z-score) over all variables. Given multiple comparisons, a z-score of at least 2 (p value<0.05) was considered statistically significant.

Results: When considering all observations and all variables simultaneously, significant differences were observed for 5 comparisons (Table 1, hypotheses “OA”, a, d, e, and g). Both-means and hierarchical clustering methods identified clusters with greater significance than using all the observations, suggesting the existence of groups of observations where the difference between progressors and non-progressors is enhanced. For example, when focusing on the genetic data, both clustering methods identified different clusters of observations using SigClust (p<0.01), and further showed that when observations were clustered according to the genetic variables, there were stronger results for hypothesised (rKOA only vs. both radiographic and symptomatic progression). Statistically significant clusters were also identified when clustering was based on physical function, socioeconomic status, health, and medication variables. Clustering on all variables resulted in significant clusters only under hierarchical methods.

Conclusion: These innovative methods provide a way to assess numerous variables of different types and scalings simultaneously in relation to KOA prevalence and progression and could be used for assessing other outcomes of interest. Such methodology could identify both known and novel KOA phenotypes, potentially improving patient selection for specific interventions and providing insight into pathophysiology this heterogeneous condition.

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Abstract Number: 1360

The Role of Personality in Patients with Knee Osteoarthritis

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Session Information

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Background/Purpose: Kneeosteoarthritis (OA) is a leading cause of disability and no effective disease-modifying treatment currently exists. Identifying factors associated with clinical outcomes may help to better understand the disease and provide insight for new treatment. Previous studies have found that personality, the multifaceted characteristics underlying a person's affect, cognition, and behavior, may influence OA impact. The aim of the study was to clarify whether personality dimensions are associated with pain, function, psychosocial health, self-efficacy, and outcome expectations among patients with knee OA.

Methods: We performed a secondary analysis using baseline data from a randomized controlled comparative effectiveness trial between TaiChi and physical therapy for knee OA. Patients enrolled were 40 years or older and met American College of Rheumatology criteria for symptomatic knee OA with radiologic evidence. Personality was assessed using the NEO-Five Factor Inventory, a validated measure of five basic personality dimensions: agreeableness, conscientiousness, extraversion, neuroticism, and openness. Outcome measures included Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function scores, patients global assessment for OA severity, six-minute and twenty-meter walk tests, health-related quality of life, depression, self-efficacy, and outcome expectations for exercise. Pearson correlation analysis was performed to assess the associations between personality dimensions and health outcomes.

Results: There were 34 participants, 71% female, mean age years, body mass index 33 kg/m², 56% white, and mean duration of knee pain 11 years. Higher conscientiousness was associated with better outcome expectations and physical component of quality of life as well as marginally correlated with better self-efficacy. Both higher openness and extraversion were also associated with higher outcome expectations, and higher openness had significant correlation with better self-efficacy. Higher neuroticism marginally correlated with worse depression. Agreeableness was nonsignificantly associated with any outcome. None of the five personality dimensions were significantly associated with WOMAC pain and function, patients global assessment, walk test performance, or mental health (**Table 1**).

Conclusion: Personality significantly correlated with a variety of health outcomes including outcome expectations, physical component of quality of life, and self-efficacy, but was not associated with the level of pain or function in patients with knee OA. The results further elucidate characteristics of OA patients, and implicate that individualized interventions taking personality into consideration may promote well-being in patients with knee OA. Future longitudinal studies with a larger sample are warranted to further inform clinical practice.

Table 1. Associations Between Personality and Osteoarthritis Health Outcomes

Dependent Variable	Mean	Personality Dimension ^à Pearson's correlation coefficients (p-value)				
		Agreeableness	Conscientiousness	Extraversion	Openness	Neuroticism
WOMAC Pain Score [Range: 0-500]	257 ± 107	-0.15 (0.41)	0.01 (0.97)	0.05 (0.79)	-0.26 (0.17)	0.17 (0.37)
WOMAC Physical Function Score [Range: 0-1700]	911 ± 423	-0.13 (0.50)	0.10 (0.57)	0.07 (0.69)	-0.26 (0.17)	0.17 (0.38)
Patient's Global Assessment Score [Range: 0-10]	4.8 ± 2.2	0.05 (0.78)	0.21 (0.25)	0.05 (0.78)	-0.18 (0.34)	0.16 (0.39)
Six-Minute Walk Test (meters)	414 ± 100	-0.08 (0.67)	0.01 (0.95)	-0.07 (0.70)	0.27 (0.16)	0.01 (0.96)
Twenty-Meter Walk Test (seconds)	17.4 ± 3.7	0.02 (0.91)	-0.07 (0.72)	-0.02 (0.93)	-0.33 (0.08)	0.07 (0.71)
SF-36 Physical Component Score [Range: 0-100]	37.3 ± 8.2	0.03 (0.87)	0.38 (0.03)	0.00 (1.00)	0.27 (0.15)	-0.19 (0.31)
SF-36 Mental Component Score [Range: 0-100]	54.1 ± 9.3	0.09 (0.64)	0.23 (0.22)*	0.22 (0.24)*	0.26 (0.17)*	-0.28 (0.15)*
Beck Depression Inventory-II Score [Range: 0-63]	7.2 ± 9.2	-0.07 (0.71)	-0.28 (0.13)*	-0.06 (0.76)*	-0.31 (0.11)*	0.36 (0.06)*
Arthritis Self-Efficacy Scale Score [Range: 1-10]	6.4 ± 2.0	0.25 (0.18)	0.35 (0.05)	0.14 (0.44)	0.44 (0.02)	-0.21 (0.26)
Outcome Expectations for Exercise Scale Score [Range: 1-5]	4.2 ± 0.9	0.28 (0.13)	0.44 (0.01)	0.42 (0.02)	0.54 (0.003)	-0.05 (0.78)

Note: WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; SF-36 = Short Form-36, a measure of quality of life

Bolded correlations and p-values indicate statistical significance (p-value < 0.05)

^à Higher scores indicate worse health

^à Higher scores indicate higher levels of that personality trait

*After removal of highly influential points

Disclosure: M. Zhou, None; R. R. Bannuru, Fidia, 8; L. L. Price, None; M. Park, None; C. Wang, None.

Predictive Modeling of Therapeutic Response in Knee Osteoarthritis

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Session Information

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Background/Purpose: Phenotype identification in knee osteoarthritis (KOA) population could be useful for predicting drug response, allowing personalized interventions. In order to optimize therapeutic outcome in KOA, we aimed to predict drug response of patients treated with COX-2 selective nonsteroidal anti-inflammatory drug Celecoxib (CLX) or pharmaceutical grade Chondroitin sulfate plus glucosamine hydrochloride (CS+GH) combining the analysis of multiple clinical variables and *omics* data.

Methods: A shotgun proteomic analysis by iTRAQ was performed on sera from 80 patients enrolled in the Multicentre Osteoarthritis inter Ventiontrial with Sysadoa (MOVES). Then, a panel of 10 serum proteins was qualified using ELISA Kits in the whole MOVES cohort (n=1043). Patients were classified as responders (R) and non-responders (NR), either to CLX or CS+GH according to the OMERACT-OARSI criteria and the WOMAC pain score recorded after 6 months of treatment. Logistic regression analyses, adjusted by significant confounder variables, were used to analyze the contribution of the measured proteins to our prediction models of drug response in KOA. Appropriate receiver-operating-characteristics (ROC) curves were also calculated.

Results: In the *discovery phase* of the study, the proteomic screening led to the identification of 83 proteins significantly altered at baseline in R compared to NR. Among the proteins presenting the highest iTRAQ ratios and exclusively altered in one of the therapeutic groups, we selected 4 proteins specific for CLX treatment and 6 proteins specific for CS+GH treatment for the development of the *validation* assays in a larger cohort of KOA patients (Fig. 1). In the *qualification phase*, the sensitivity and specificity of the validated proteins were tested in blind in the whole MOVES cohort at baseline. In the CLX group, an increased level of TSP1 was detected at baseline in R compared to NR (363,03ng/mL vs 331,95ng/mL; $p=0,041$). The inclusion in the regression model of 4 predictive variables (2 clinical and 2 analytical) and TSP1 as covariate revealed a specific interaction between response to CLX and baseline protein levels ($p=0,045$) thus increasing the predictive power of this model up to AUC=0,749 (Model 1, Fig. 1). In CS+GH group, ORM 2 levels were significantly higher in NR compared to R (261,6ug/mL vs 192,8 ug/mL; $p=0,042$). 5 clinical and 2 analytical parameters recorded at baseline significantly influence patients' response. The inclusion of ORM 2 as covariate revealed a specific interaction between response to CS+GH and baseline protein levels ($p=0,007$) thus increasing the power of our prediction model up to AUC=0,843 (Model 2, Fig.1).

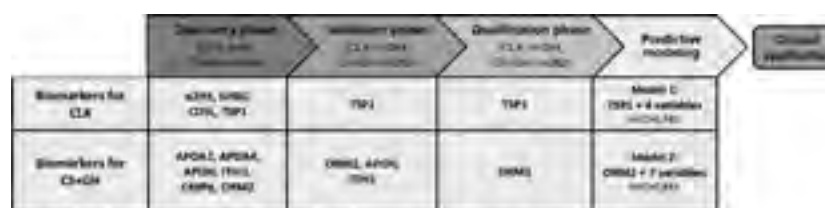


Fig. 1: Predictive biomarkers development: from the discovery phase to clinical qualification.

Conclusion: Combining clinical and analytical parameters, we qualified 2 panels of biomarkers that could efficiently predict OA patients' response told with an accuracy of 74,9% or to CS+GH with an accuracy of 84,3%.

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Magnetic Resonance Imaging Features Can Classify Adults Who Will Develop Accelerated Knee Osteoarthritis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Accelerated knee osteoarthritis (AKOA) is a painful disorder and is associated with several risk factors and pre-radiographic structural features. While no single factor can accurately predict who is at risk for AKOA, it would be beneficial to recognize the combinations of factors that identify adults at risk for AKOA. We examined the benefit of adding magnetic resonance (MR)-based features to clinical and demographic characteristics for classifying adults who develop AKOA.

Methods: We conducted a case-control study using Osteoarthritis Initiative data from baseline and the first 4 annual visits. Eligible participants had no radiographic KOA in either knee at baseline (Kellgren-Lawrence [KL]<2). We classified 2 sex-matched groups: 1) AKOA: ≥ 1 knee developed advance-stage KOA (KL=3 or 4) within 48 months and 2) did not develop AKOA within 48 months. MR images were assessed at OAI baseline for 3 quantitative measures (effusion-synovitis volume, cartilage damage, and bone marrow lesion volume) and 9 semi-quantitative features (cruciate/collateral ligaments, extensor mechanism, gastrocnemius tendon, synovitis, medial/lateral meniscal pathology, medial/lateral meniscal effusion) that were read by two musculoskeletal radiologists. We performed 2 classification and regression tree (CART) analyses to determine classification rules and important variables for 1) a base model with baseline clinical (serum and radiographic measures) and demographic (age, sex, body mass index [BMI]) characteristics and 2) a combined model with baseline MR-based features in addition to the variables in the base model. Pruning and 10-fold cross-validation were performed to avoid overfitting.

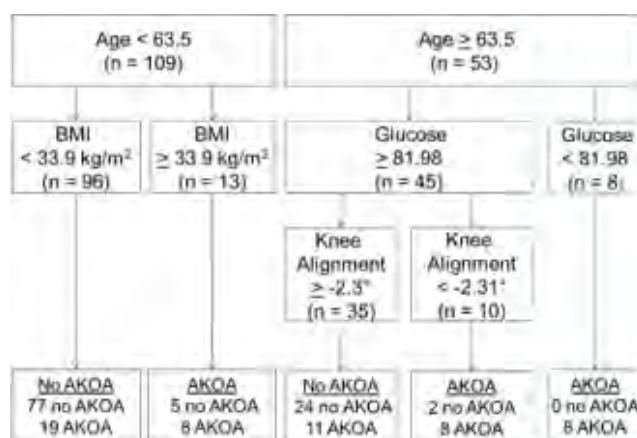
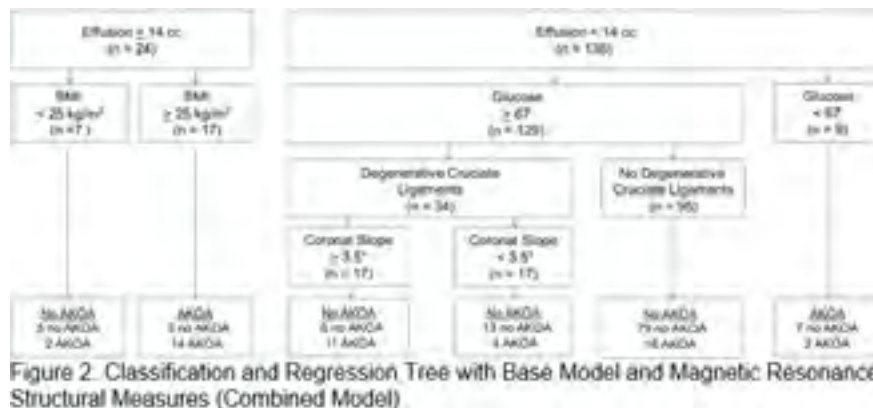


Figure 1. Classification and Regression Tree without Magnetic Resonance structural measures (Base Model)



Results: The most important variables for classifying individuals with incident AKOA in the base model (in order of importance) were age, serum glucose, and body mass index [BMI] (Figure 1). The most important variables in the combined model were effusion, serum glucose, presence of degenerative cruciate ligaments, and coronal tibial slope (Figure 2). The base model explained 31% of the variance, while the combined model explained 39% of the variance. Both the base and combined models offered good specificity (0.94 and 0.90) and moderate sensitivity (0.44 and 0.59, respectively).

Conclusion: MR-based features help classify adults who will develop AKOA; however, the cost of collecting standard MR-based features may outweigh the incremental improvement in classification in some settings.

Disclosure: L. L. Price, None; M. Harkey, None; R. J. Ward, None; J. MacKay, None; M. Zhang, None; J. Davis, None; T. E. McAlindon, None; G. H. Lo, None; M. Amin, None; C. B. Eaton, None; B. Lu, None; J. Duryea, None; M. Barbe, None; J. B. Driban, None.

Abstract Number: 1363

Progression of Pain, Stiffness, Function Changes, and Ultrasound Detected Synovitis and Osteophyte Formation in Patients with Hand Osteoarthritis over Three Years

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

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Session Time: 9:00AM-11:00AM

Background/Purpose: Hand osteoarthritis (HOA) is a common and frequent cause of pain. HOA is a heterogeneous group of disorders with two main subsets including non-erosive and erosive disease. Few studies demonstrated inflammatory ultrasound changes and more severe clinical symptoms in patients with erosive compared with non-erosive disease, however the results are inconsistent. The aim of this study was to evaluate progression of pain, stiffness, physical impairment and ultrasound features in patients with erosive and non-erosive HOA in a three years longitudinal study.

Methods: Patients with symptomatic HOA fulfilling the American College of Rheumatology (ACR) criteria were included in this study. Joint pain and swelling were assessed. Pain, joint stiffness and disability were assessed by the Australian/Canadian OA hand index (AUSCAN). Radiographs of both hands were examined, and erosive disease was defined by at least one erosive interphalangeal joint. Synovial hypertrophy and power Doppler signal (PDS) were scored with ultrasound. Synovitis was graded on a scale of 0–3 and osteophytes were defined as cortical protrusions seen in two planes. Patients were examined at baseline and at the first, second and third year of follow up.

Results: Altogether, 97 patients (7 male) with symptomatic nodal HOA were included in this study and followed between April 2012 and January 2018. Out of these patients, 57 had erosive disease. The number of painful and clinically swollen

joints ($p<0.05$) was significantly higher in patients with erosive compared with non-erosive disease at baseline. The number of painful and clinically swollen joints fluctuate over the second and third year of follow up, but it still remains statistically higher ($p<0.01$) at the third year of follow up in patients with erosive disease.

According to the AUSCAN, patients with erosive disease had more pain ($p<0.05$) and stiffness ($p<0.01$) at baseline. Pain and stiffness, but not function, worsened in patients with erosive compared with non-erosive disease after second year ($p<0.01$). Pain ($p<0.01$), stiffness ($p<0.05$) and also function ($p<0.01$) worsened in patients with erosive disease at the third year of follow up.

US-detected pathologies such as gray-scale synovitis ($p<0.001$), intensity of PDS ($p<0.01$) and number of osteophytes ($p<0.01$) were significantly higher in patients with erosive disease at baseline. There were improvements in gray-scale synovitis total score and intensity of PDS in patients with non-erosive disease while patients with erosive disease worsened after the second and third year of follow up ($p<0.01$). The progression of US-determined osteophyte formation was observed in both groups after the second year of follow up but were significantly higher in patients with erosive than with non-erosive disease after the third year of follow up ($p<0.05$).

Conclusion: The findings of this study show that pain and number of clinically swollen joints associated with US-detected synovial changes and osteophyte formation is more severe in patients with erosive HOA than in patients with non-erosive disease. In addition, osteophyte formation is more likely to progress independent of synovial inflammation. Supported by the project MH 023728 and AZV 18-00542.

Disclosure: O. Sleglova, None; O. Ruzickova, None; K. Pavelka, None; L. Šenolt, None.

Abstract Number: 1364

Treatment of Knee Osteoarthritis with SM04690 Improved WOMAC A1 “Pain on Walking” – Results from a 52-Week, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of a Novel, Intra-Articular, Wnt Pathway Inhibitor

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Knee osteoarthritis (OA) is characterized by pain, functional limitation, and physical disability due to articular cartilage degradation and bone remodeling. Wnt signaling is involved in these cellular processes. SM04690, a small molecule, intra-articular (IA), Wnt pathway inhibitor, is in development for treatment of knee OA as a potential disease-modifying OA drug (DMOAD). A phase 2, multicenter, 52-week, randomized, double-blind, placebo (PBO)-controlled trial of SM04690 was conducted. Safety and efficacy outcomes including the Western Ontario and McMaster Universities Arthritis Index (WOMAC) were evaluated.

Methods: Subjects with ACR-defined knee OA, Kellgren-Lawrence (KL) grades 2-3, received a single 2 mL IA injection of SM04690 (0.03, 0.07 or 0.23 mg) or PBO in the target (most painful) knee. WOMAC was assessed at baseline and 4, 13, 26, 39 and 52 weeks post-injection. WOMAC question A1, (“how much pain have you had when walking on a flat surface?”), was analyzed as a post-hoc exploratory outcome. Analysis of covariance adjusted for baseline WOMAC A1 score in the intent-to-treat (ITT) population was conducted. Two subgroups identified in the primary analysis (Yazici Y et al., *Arthritis Rheumatol* 2017) were also explored: 1) subjects with unilateral symptomatic knee OA (pre-specified) and 2) subjects with unilateral symptomatic knee OA without widespread pain or comorbid symptoms (Widespread Pain Index ≤ 4 and Symptom Severity ≤ 2 [WP-], post-hoc).

Results: 455 subjects (mean age 60.3[\pm 8.7] years, BMI 29.9 [\pm 4.6] kg/m², female 58.9%, KL 3 [64.1%], unilateral symptomatic OA [36.0%]) were enrolled; 402 [88.4%] completed the study. No safety signals were observed. For WOMAC A1, in the ITT population, no statistically significant differences between treatment groups and PBO were seen, although the 0.07 mg dose demonstrated improvements compared with PBO at all time points (**Figure**). In unilateral symptomatic subjects, 0.07 mg showed significant improvements in WOMAC A1 compared with PBO at Weeks 39 (-1.2, 95% CI [-2.3, -0.0], $P=0.043$) and 52 (-1.1, 95% CI [-2.0, -0.1], $P=0.027$).

Improvement of SM04690 over Placebo

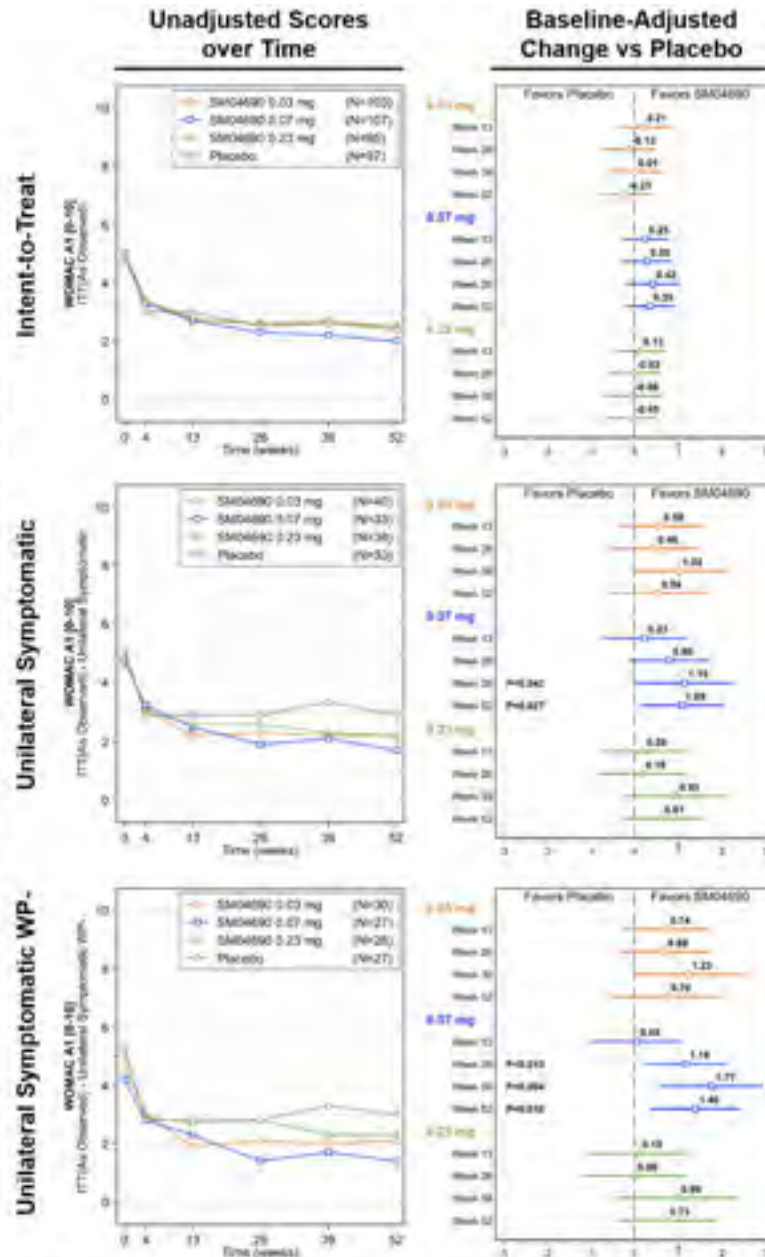


Figure. Change and Ladder plots depicting average WOMAC A1 improvement in SM04690 over placebo adjusted for baseline WOMAC A1.

*Minimal clinically important difference (MCID) defined as 10% of WOMAC A1, or 1 point.

In unilateral symptomatic WP- subjects, the 0.07 mg dose showed significant improvements in WOMAC A1 compared with PBO at Weeks 26 (-1.2, 95% CI [-2.1, -0.2], P=0.015), 39 (-1.8, 95% CI [-3.0, -0.6], P=0.004) and 52 (-1.4, 95% CI [-2.5, -0.4], P=0.010).

Conclusion: In this phase 2 study, improvements compared with PBO in WOMAC A1 were seen in clinically relevant unilateral symptomatic and unilateral symptomatic WP- subgroups. The improvements seen in this combined, multi-dimensional outcome of pain and function suggested SM04690 has a potential role in the treatment of signs and symptoms of knee OA.

Disclosure: J. Tambiah, Samumed, LLC, 1, 3; S. Kennedy, Samumed, LLC, 1, 3; H. Ghandehari, Samumed, LLC, 1, 3; C. Swearingen, Samumed, LLC, 1, 3; M. C. Hochberg, Bioberica, 5, EMD Serono, 5, Novartis Pharma AG, 5, Plexxikon, 5, Pfizer, Inc., 5, Proximagen, 5, Regeneron, 5, Samumed, LLC, 5, Theralogix LLC, 5.

A Phase IIa Study of Anti-GM-CSF Antibody GSK3196165 in Subjects with Inflammatory Hand Osteoarthritis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Previous data showed that neutralization of granulocyte/monocyte colony stimulating factor (GM-CSF) rapidly abolished pain in an experimental OA model suggesting GM-CSF may be a promising therapeutic target in human OA (1).

Objective: Evaluate anti-GM-CSF GSK3196165 treatment on the signs and symptoms of hand OA.

Methods: Subjects with hand OA per ACR criteria, ≥ 2 swollen and tender IP joints in the same hand, hand pain ≥ 5 (numeric rating scale [NRS] 0-10, averaged over 7 days), signs of inflammatory changes by MRI and intolerance or unresponsiveness to NSAIDs, were randomized to 5 weekly SC doses of 180mg GSK3196165 or placebo (PBO), followed by 3 further doses every other week. Self-assessed 24h average and worst hand pain was recorded daily by electronic patient-reported outcome (ePRO) for the study duration. The primary outcome was ePRO change from baseline in average hand pain at Week 6. Secondary outcomes included safety, proportion of subjects showing 30% and 50% reductions in hand pain, change in Australian/Canadian Hand Osteoarthritis Index (AUSCAN) 3.1 NRS and changes in number of swollen and tender joints. Exploratory MRI endpoints included change in inflammatory and structural features.

Results: Of 44 treated subjects (91% women; mean age 58.8 years), 21/22 randomised to PBO and 20/22 to GSK3196165 completed the 12 week treatment period. Patient characteristics were well balanced between the groups. Measured GSK3196165 exposures were lower than anticipated from previous studies. Maximum pre-dose concentrations were achieved after 5 loading doses, but dropped significantly during every other week dosing.

Patients receiving GSK3196165 showed numerically larger reductions in hand pain than PBO at all time points, difference over PBO at W6: -0.36 (-1.31, 0.58; $p=0.442$), at W12: -0.89 (-2.06, 0.28; $p=0.132$); >2 points reduction from baseline seen from W8 to W12.

The proportion of subjects achieving 30% and 50% reductions of average hand pain was higher in the GSK3196165 group vs PBO at each assessment visit. At W12 the difference between GSK3196165 and PBO groups showing 30% reduction was 23% (odds ratio 3.2, 95% CI 0.86, 11.99; $p=0.083$) and for 50% reduction, was 27% (odds ratio 4.9, 95% CI 1.06, 22.59; $p=0.042$). AUSCAN pain (0-50) and function (0-90) showed difference vs PBO of -4.7 (-10.1, 0.6; $p=0.082$) and -8.2 (-19.1, 2.7; $p=0.136$) at W12 respectively. There was little difference from PBO on tender and swollen joints or MRI endpoints.

GSK3196165 was well tolerated. No serious infections or pulmonary events were observed. :

Conclusion: This exploratory 12 week study showed that treatment of patients with inflammatory hand OA with GSK3196165 was well tolerated and while not statistically significant, resulted in reductions in pain accompanied by improvement in functional impairment. These results support findings from preclinical OA models and suggest that GM-CSF may play a role in the pain associated with inflammatory hand OA in man.

(1) Cook, Arthritis Res Ther 2012;14:R199

Disclosure: G. Schett, None; C. Bainbridge, None; M. Berkowitz, None; K. Davy, GlaxoSmithKline, 1, 3; S. Fernandes, GlaxoSmithKline, 1, 3; E. Griep, None; S. Harrison, GlaxoSmithKline, 1, 3; M. Layton, GlaxoSmithKline, 1, 3; N. A. Nowak, None; J. Patel, GlaxoSmithKline, 1, 3; J. Rech, BMS and Celgene, 2, Abbvie, BMS, Celgene, Fresenius, GSK, Medicap, MSD, Novartis, Pfizer, and Roche, 8; S. Watts, GlaxoSmithKline, 1, 3; P. P. Tak, GlaxoSmithKline, 1, 3.

Assessment of Health-Related Quality of Life in a 52-Week, Phase 2, Randomized, Controlled Trial of a Novel, Intra-Articular, Wnt Pathway Inhibitor (SM04690) for Treatment of Knee Osteoarthritis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: SM04690, a small molecule, intra-articular (IA) Wnt pathway inhibitor, is in development for knee OA treatment. A phase 2, 52-week, trial evaluated changes in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain & Function and medial joint space width (mJSW) by x-ray. Health-related quality of life (HRQoL) was measured by Short Form Survey SF-36. The objective of this study was to assess the effect of SM04690 treatment on HRQoL.

Methods: Subjects with ACR-defined knee OA, Kellgren-Lawrence grades 2-3, received 2 mL IA SM04690 (0.03, 0.07, 0.23 mg) or placebo (PBO) in the target (most painful) knee. SF-36 was assessed (Weeks 0, 4, 13, 26, 39, 52). Baseline-adjusted analysis of covariance (with multiple imputation for missing data) was conducted in the intent-to-treat (ITT) population, with improvements \geq minimum clinically important differences (MCID) noted. Two subgroups were explored: 1) unilateral symptomatic knee OA (pre-specified: UNI) and 2) unilateral symptomatic knee OA without widespread pain or comorbid symptoms (Widespread Pain Index ≤ 4 and Symptom Severity ≤ 2 , post-hoc: UNI-WP).

Results: 455 subjects (mean age 60.3 [± 8.7] years, BMI 29.9 [± 4.6] kg/m², female 58.9%, KL 3 [64.4%], with UNIOA [36.0%]) were enrolled (n=402 [88.4%] completers).

In ITT, improvements from baseline were reported in 0.03 mg (n=112), 0.07 mg (n=117), 0.23 mg (n=110) and PBO (n=116) groups, with scores \geq MCID in Physical Component Summary (PCS), Physical Functioning (PF), Role-Physical

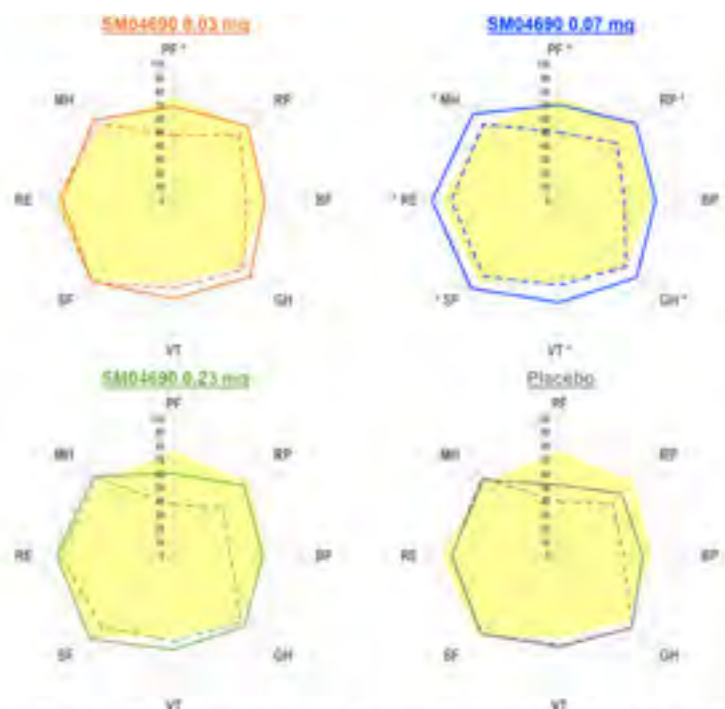


Figure. Spidergrams of baseline (dash line) and Week 52 (solid line) in each SF-36 domain score over age- and gender-matched normative scores (yellow) within the Unilateral Symptomatic without Widespread Pain subgroup analysis.

* Baseline-adjusted ANCOVA reported analysis compared to PBO with $P < 0.05$

PF: Physical Functioning; RP: Role-Physical; BP: Bodily Pain; GH: General Health; VT: Vitality; SF: Social Functioning; RE: Role-Emotional; MH: Mental Health

(RP), and Bodily Pain (BP) domains at Weeks 13 to 52. Improvements vs PBO reported in 0.07 mg at Week 13 were significant in Mental Component Summary (MCS [P=0.024]) and Role-Emotional (RE [P=0.036]) domains.

In UNI subgroup, at Week 52, all groups reported improvements \geq MCID as in the ITT across all domains with 0.07 mg (n=35) significant vs PBO (n=39) in MCS (P=0.015), General Health (GH [P=0.028]), RE (P=0.009), and Mental Health (MH [P=0.011]) domains.

In UNI-WP subgroup at Week 52, all groups reported changes \geq MCID in PCS, PF, RP, and BP domains, and across all domains with 0.07 mg. Improvements vs PBO (n=32) with 0.03 mg (n=34) were significant in PF (P=0.025), and with 0.07mg (n=29) in MCS (P=0.002) and all domains excluding BP (PF [P=0.025], RP[P=0.027], GH [P=0.035], Vitality (VT [P=0.014]), Social Functioning (SF[P=0.028]), RE [P=0.003], MH [P=0.003]), which met or exceeded normative scores across all domains, except PF (**Figure**).

Conclusion: In this phase 2 trial, subjects receiving 0.07 mg SM04690 reported statistically significant and clinically meaningful HRQoL improvements in the ITT and subgroup analyses compared with BO. In the UNI and UNI-WP subgroups at Week 52, HRQoL improvements mirrored changes observed from analyses in WOMAC Pain and Function and mJSW (Yazici et al., *Arthritis Rheumatol* 2017) and support further investigation of SM04690 for treatment of knee OA.

Disclosure: V. Strand, Samumed, LLC, 5, AbbVie Inc., 5, Amgen, 5, EMD Serono, 5, Eupraxia, 5, Flexion, 5, Iroko, 5, Novartis, 5, Pfizer, Inc., 5, Regeneron, 5, Sanofi, 5, SKK, 5; H. Ghandehari, Samumed, LLC, 1, 3; C. Swearingen, Samumed, LLC, 1, 3; J. Tambiah, Samumed, LLC, 1, 3.

Abstract Number: 1367

Efficacy of Intra-Articular Cntx-4975 for Knee OA Pain Varies with Radiographic Presence of OA in the Opposite Knee

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Nearly 60% of patients with knee OA have unilateral OA; most of those patients develop bilateral OA. CNTX-4975 is highly purified, synthetic *trans*-capsaicin that targets transient receptor potential vanilloid 1, producing analgesia via reversible desensitization of primary afferent pain fiber terminals. CNTX-4975 1.0 mg was well tolerated and effective in the phase 2b TRIUMPH study; this post hoc analysis evaluated efficacy and safety in subjects with unilateral knee pain with and without radiographic evidence of OA in the opposite knee.

Methods: Subjects aged 45–80 y with chronic knee OA and stable moderate to severe knee OA pain in 1 knee (index knee; nonindex knee, no to mild pain) who failed oral/IA therapies were randomized 2:1:2 to a single IA injection of placebo, CNTX-4975 0.5 mg, or CNTX-4975 1.0 mg. ACR criteria were met by 89% for knee OA as assessed by knee pain, radiographic findings (Kellgren-Lawrence [K-L] grade 2–4), and age >50 y; 11% had K-L grade 2–4 and were age \leq 50 years. Randomization was stratified by K-L grade (2–3 vs 4) and BMI (<30 vs \geq 30 kg/m²). Unilateral OA: K-L grade 0, 1, or missing (see **Table**) in the nonindex (untreated) knee; bilateral OA: grades 2–4 in both knees. Least squares mean differences (P values) for CNTX-4975 groups vs placebo were calculated using a mixed model for repeated measures. WOMAC question A1 (QA1; pain with walking on a flat surface), B (stiffness), and C (physical function) scores were assessed weekly through weeks 12 and 24. Statistical tests were 2-sided (alpha, 0.10). Safety assessments included treatment-emergent adverse events (TEAEs).

Results: The safety analysis comprised 175 subjects: unilateral OA, n=52 (placebo, n=17; CNTX-4975 0.5 mg, n=18; CNTX-4975 1.0 mg, n=17); bilateral OA, n=123 (placebo, n=53; 0.5 mg, n=16; 1.0 mg, n=54). Efficacy analysis included 172 subjects (3 in bilateral subgroup excluded before unblinding). Mean baseline WOMAC QA1 pain score (index knee) was 7.3 (numeric rating scale, 0–10) in each subgroup. WOMAC QA1 scores with CNTX-4975 1.0 mg were significantly improved vs placebo in the unilateral (week 12, P=0.0178; week 24, P=0.0022) and bilateral subgroups (week 12, P=0.0101). WOMAC QA1, B, and C results are in the **Table**. The incidence of TEAEs for CNTX-4975 1.0 mg was similar to placebo through week 24. All TEAEs were mild to moderate, with most unrelated to treatment.

Conclusion: A single IA injection of CNTX-4975 1.0 mg, the dose used in phase 3 trials, improved pain with walking, knee stiffness, and physical function vs placebo in the index knee and was well tolerated in subjects with moderate to severe

unilateral or bilateral knee OA. Greater absolute improvements in WOMAC QA1, B, and C were seen in unilateral versus bilateral knee OA, though the nonindex knee had no to mild baseline pain.

Table. Mean Changes From Baseline in Average WOMAC QA1, WOMAC B, and WOMAC C at Weeks 12 and 24 vs Placebo								
Endpoint	CNTX-4975 0.5 mg				CNTX-4975 1.0 mg			
	Unilateral (n=18)		Bilateral (n=16)		Unilateral (n=17)		Bilateral (n=53)	
	Week 12	Week 24	Week 12	Week 24	Week 12	Week 24	Week 12	Week 24
WOMAC QA1								
LSMD vs placebo	-1.0	-1.6	-1.0	-0.0	-2.1	-2.7	-1.3	-0.3
95% CI	(-2.4, 0.5)	(-3.0, -0.1)	(-2.1, 0.2)	(-1.4, 1.4)	(-3.5, -0.7)	(-4.2, -1.3)	(-2.1, -0.5)	(-1.2, 0.6)
P value	0.2754	0.0787	0.1769	0.9921	0.0178	0.0022	0.0101	0.5615
WOMAC B								
LSMD vs placebo	-0.0	0.3	-1.8	0.1	-3.7	-2.4	-2.1	-0.7
95% CI	(-2.7, 2.7)	(-2.5, 3.0)	(-4.0, 0.4)	(-2.2, 2.5)	(-6.2, -1.1)	(-5.0, 0.3)	(-3.5, -0.6)	(-2.2, 0.9)
P value	0.9842	0.8669	0.1877	0.9204	0.0221	0.1460	0.0230	0.4691
WOMAC C								
LSMD vs placebo	3.6	12.2	-11.1	-1.0	-25.0	-17.5	-16.0	-3.6
95% CI	(-19.0, 26.1)	(-10.3, 34.8)	(-26.7, 6.6)	(-18.7, 20.6)	(-47.2, -2.8)	(-39.7, -4.7)	(-27.8, -4.2)	(-17.0, 9.3)
P value	0.7922	0.3667	0.3004	0.9361	0.0653	0.1929	0.0268	0.6288
LSMD, least squares mean difference; Prespecified alpha, 0.10. Mixed model for repeated measures in modified intent-to-treat population. Missing patients: placebo, n=3; CNTX-4975 0.5 mg, n=2; CNTX-4975 1.0 mg, n=2. WOMAC: 11-point numerical rating scale: 0 (none) to 10 (extreme); WOMAC B dimension score is the sum of the 2 stiffness subscale responses (range, 0 to 20); WOMAC C dimension score is the sum of the 17 function subscale responses (range, 0 to 170).								

Disclosure: R. Stevens, 1Centrexion Therapeutics, 3; J. Campbell, Centrexion Therapeutics, 3; K. Guedes, Centrexion Therapeutics, 3; R. Burges, Centrexion Therapeutics, 3; V. Smith, Premier Research, 3; P. Hanson, Centrexion Therapeutics, 3.

Abstract Number: 1368

Diabetes Mellitus Is Not a Risk Factor for Knee Osteoarthritis, a Systematic Review and Meta-Analysis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

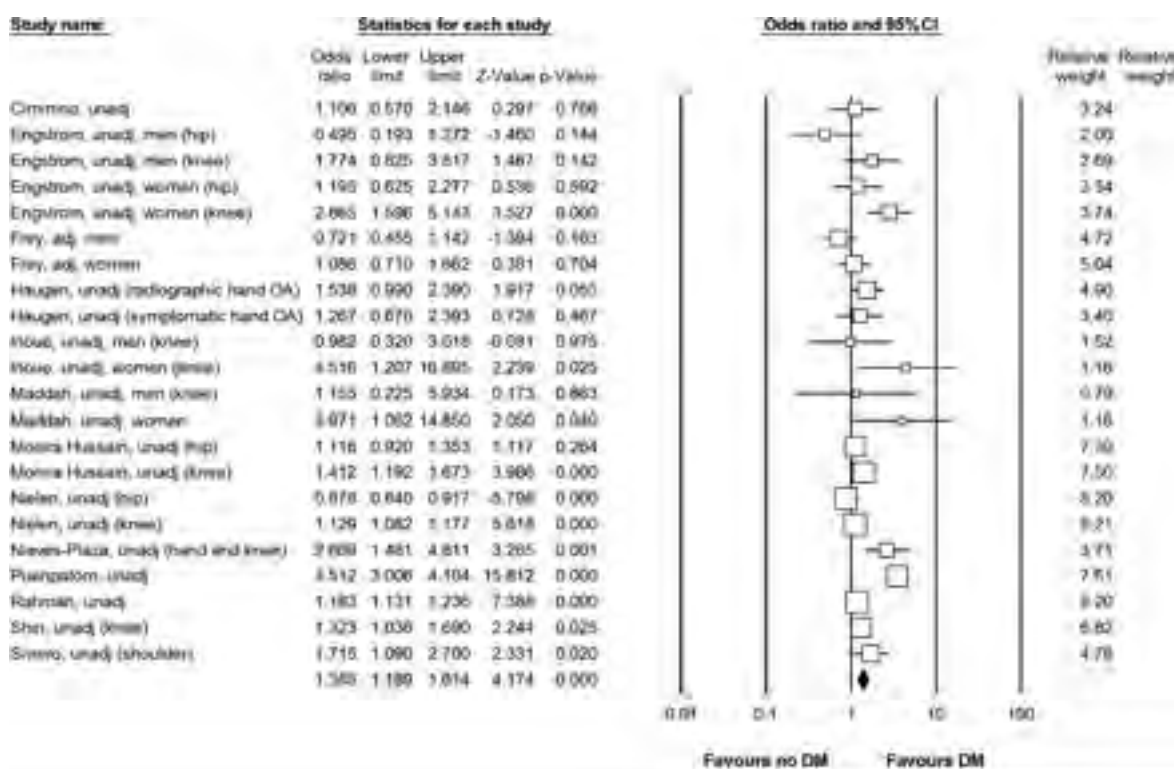
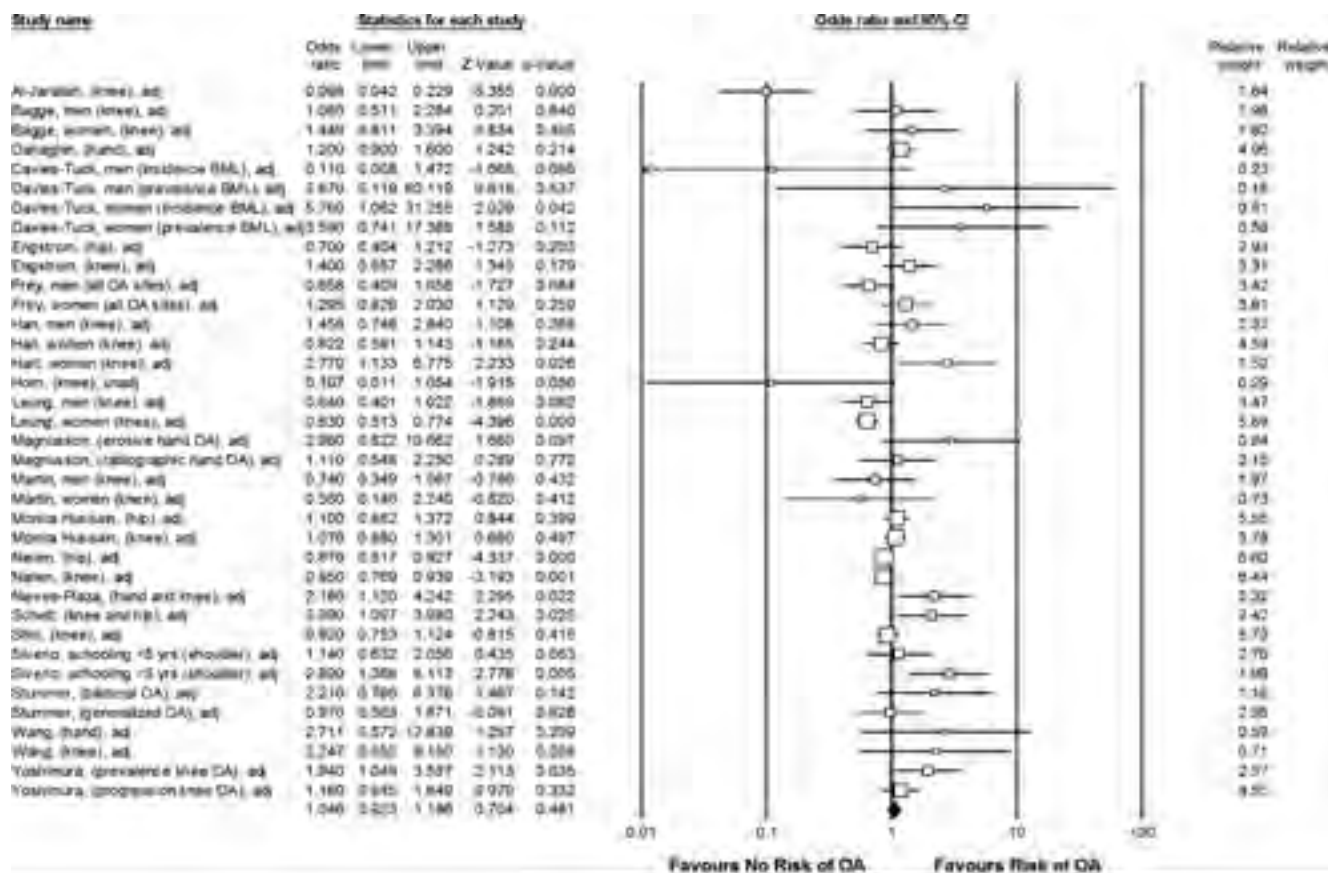
DiabetesMellitus is Not a Risk Factor for Knee Osteoarthritis, a Systematic Review and Meta-analysis

Background/Purpose: Obesity is a strong risk factor for both osteoarthritis(OA) and diabetes mellitus (DM). Reported associations between DM and risk of OA may be confounded by high body mass index (BMI). We conduct a systematic literature review on the risk of OA in relation to DM or hyperglycemia.

Methods: We performed PubMed and Web of Science database searches for relevant studies in the English literature published between 1966 to 22 Jan 2018. Searches focused on original research articles that gave information on the association between DM or hyperglycemia and the risk of onset or progression of osteoarthritis. Two meta-analysis model were performed for 1) risk estimate of DM comparing subjects with or without OA; and 2) risk estimate of OA, comparing people with or without DM. The risk estimates from studies that have been adjusted for BMI were utilized as far as available.

Results: From 270 publications, a total of 32 articles were reviewed, including 10 cross-sectional, 13 case-control and 9 cohort studies. The pooled population size in our systematic review was 386,516. 16 studies reported positive associations

between DM and OA, while 16 studies reported null or inverse associations. Among studies that reported positive associations between DM and OA, only 62.5% had adjusted for BMI. For studies that reported null or inverse association between DM and OA, 100% had adjusted for BMI, of which 6 studies had comparable BMI at baseline between comparison groups. In meta-analysis model 1 pooling data from 13 studies and 307, 473 subjects, there was an increased prevalence of DM comparing subjects with OA to those without OA (OR 1.385, 95% confidence intervals (CI): 1.189 –



1.614) (Figure 1). 92.3% of these studies did not adjusted for BMI. In model 2, pooling data from 21 studies and 391, 203 subjects, there was no increased risk of onset or progression of OA, comparing subjects with DM to those without (OR 1.046, 95% CI: 0.923 – 1.186, $p = 0.481$) (Figure2). 95.2% of these studies had adjusted for BMI. In sensitivity analyses, the risk of OA was not higher comparing subjects with or without DM as stratified by study design, gender, and site of OA.

Conclusion: This meta-analysis showed higher prevalence of DM among subjects with OA compared with those without. However, it does not support DM as an independent risk factor for OA. BMI was probably the most important confounding factor.

Disclosure: C. Hong, None; A. Y. K. Khor, None; C. A. P. W. Ma, None; L. L. Y. Hui, None; Y. Y. Leung, None.

Abstract Number: 1369

The Influence of Hand Osteoarthritis on Bone Microstructure and Biomechanical Properties of Radial Bone

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Session Information

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Background/Purpose: Primary hand osteoarthritis (HOA) is a heterogeneous disease, with erosive and osteoproliferative changes of the finger joints. [1] Due to the lack of treatment options, HOA patients suffer from progressive functional impairment of the affected joints, which is associated with pain. Despite these severe functional changes, the impact of HOA on bone microstructure and biomechanics of the affected limb remains poorly investigated. Therefore we aimed to assess bone microstructure and biomechanical properties in HOA patients.

Methods: HOA patients fulfilled the 1990 American College of Rheumatology criteria for the classification of hand osteoarthritis [2]. For comparison, sex- and age-matched healthy controls (HC), free of present or past signs of rheumatic diseases, osteoporosis, diabetes mellitus, renal or hepatic disease were analyzed. All participants received a high-resolution peripheral quantitative computed tomography (HR-pQCT, XtremeCT 1, Scanco, Switzerland) scan of the distal radius. Volumetric bone mineral density (vBMD) parameters such as total vBMD, trabecular vBMD, cortical vBMD (in mg HA/cm³) as well as micro-finite element analysis (μFEA) parameters such as stiffness (kN/mm) and failure load (N) were determined.

Results: 105 subjects were included (76 HC/29 HOA). Mean age was 55.6±13.3 (HC) and 60.5±66.9 years respectively (HOA), while 31 HC and 6 HOA were male. HOA patients revealed significantly decreased trabecular vBMD compared to HC (139±35 vs. 159±38, $p=0.026$), while cortical vBMD was comparable between HOA and HC. Microstructural parameters such as trabecular number (1.9±0.3 vs. 2.0±0.3 1/mm, $p=0.027$) or cortical thickness (0.06±0.01 vs. 0.07±0.01 mm, $p=0.035$) were significantly reduced in HOA. Regarding biomechanical bone properties HOA patients showed a significantly lower stiffness and failure load compared with HC (stiffness: 36.2±10.2 vs. 45.3±14.7, $p=0.010$; failure load: 1770±452 vs. 2164±679, $p=0.009$).

Conclusion: This study shows that HOA affects bone microstructure and biomechanical properties of the affected limb. Impaired mobility might be an explanation for this strong reduction of biomechanical properties and trabecular bone density. These results underline the clinical importance of HOA-related functional impairment and suggest that HOA patients need to receive awareness for increased risk of fractures and anti-osteoporotic Treatment

1. Kloppenburg, M. and W.Y. Kwok, *Hand osteoarthritis--a heterogeneous disorder*. Nat Rev Rheumatol, 2011. **8**(1): p. 22-31.
2. Altman, R., et al., *The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand*. Arthritis Rheum, 1990. **33**(11): p. 1601-10.

Disclosure: D. Simon, None; S. Unbehend, None; S. Bayat, None; J. Rech, Bristol-Myers Squibb, 2, 8, Celgene Corporation, 2, 8, AbbVie Inc., 8, Fresenius, 8, Medac, 8, MSD, 8, Pfizer, Inc., 8, Roche, 8; A. J. Hueber, None; G. Schett, BMS, Celgene, GSK, Lilly, Novartis, 2, AbbVie, BMS, Celgene, Janssen, Lilly, Novartis, UCB, 5, AbbVie, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, 8; A. Kleyer, None.

Detection of an Autoantibody Profile to Characterize Patients with Early (Pre-symptomatic) Knee Osteoarthritis: Data from the Osteoarthritis Initiative

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Session Information

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Session Title: Osteoarthritis – Clinical Poster II

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Background/Purpose: Although osteoarthritis (OA) has not been considered as an autoimmune disorder, there are increased evidences of the role of the immune system in OA pathogenesis. Since autoantibodies (AAbs) are produced also at asymptomatic stages, they have been proposed as potential biomarkers to identify patients without clinical symptoms. A previous work from our group demonstrated the presence of AAbs in sera from OA patients. In this study, we aimed to identify an AAbs profile associated with an increased risk for the disorder, which might be useful in the very early diagnosis of knee OA.

Methods: Nucleic-Acid Programmable Protein Array (NAPPA) platform was used to screen AAbs against 2200 human proteins in 200 sera at baseline belonging to participants enrolled in the Incidence and Non-exposed subcohorts from the Osteoarthritis Initiative (OAI). Patients from the Incidence subcohort included in the screening had developed OA at 72 months of follow-up. After a panel of 6 AAbs was established as associated to OA risk, levels of AAbs against MAT2B were validated by ELISA-based immunoassay in 136 and 113 sera from the same Incidence and Non-exposed subcohorts, respectively. In addition, 119 sera from patients belonging to the Incidence subcohort at baseline who have not developed OA at 72 months, named as Control-Incidence subcohort, were included in this validation step. The Kruskal-Wallis test was used to define significance, and a logistic regression analysis, adjusted by age, gender and BMI, was used to analyze the contribution of these AAbs levels to our prediction model of OA risk. Appropriate receiver-operating-characteristics (ROC) curves was also calculated.

Results: In the *discovery phase* of the study, the NAPPA array resulted in the identification of a panel of 6 AAbs against different human proteins significantly modulated at baseline in those patients showing specific OA risk factors. The list of proteins against which altered levels of AAbs have been found is shown in Table 1, together with the statistical metrics obtained for each AAb. MAT2B was selected to enter the *validation phase* owing to its implication in the methylation processes. MAT2B is the regulatory subunit of the enzyme in charge of the production of the main methyl group donor, S-adenosylmethionine. An increased levels of AAbs against MAT2B were detected in the Incidence subcohort compared to the Non-exposed subcohort (mean OD= 0.628 ± 0.22 vs 0.553 ± 0.21 ; $p=0.032$). The regression model of the 3 clinical variables and MAT2B AAbs levels showed a predictive power up to AUC=0.809.

Conclusion: This is the first work to screen a large number of human proteins (2200) for the detection of OA-associated AAbs. A potential panel of 6 AAbs for very early diagnosis has been defined, and MAT2B levels have been validated in individual sera from the OAI cohort. These results suggest the putative utility of a serum AAbs profile to facilitate the diagnosis of OA in a stage prior to the disease.

Table 1. Panel of 6 AAbs defined by comparing the Incidence and the Non-exposed subcohort at baseline

Protein name	Symbol	Wilcoxon test p value	Specificity at 95%	AUC	AUC p value
Vacuolar protein sorting-associated protein 4B	VPS4B	0.005	80.80	0.885	0.0473
UDP-glucuronosyltransferase 1-7	UGT1A7	0.015	79.59	0.82	0.0481
Res-Related C3 botulinum toxin substrate 3	MVD	0.003	76.30	0.88	0.0496
Diphosphomevalonate decarboxylase	RAC3	0.002	75.60	0.9	0.0426
Methionine adenosyltransferase 2 subunit beta	MAT2B	0.005	80.80	0.86	0.0497
Ankirin repeat and SOCS box protein 7	ASB7	0.002	76.90	0.885	0.0499

Disclosure: M. Camacho, None; F. Picchi, None; I. Rego-Pérez, None; R. Manzano-Román, None; V. Calamia, None; J. VanDuine, None; J. Qiu, None; C. Ruiz-Romero, None; M. Fuentes, None; J. LaBaer, None; F. J. Blanco, None.

Abstract Number: 1371

Systemic Exposure of Triamcinolone Acetonide Following Bilateral Injection of Extended-Release Triamcinolone Acetonide and Standard Triamcinolone in Patients with Bilateral Knee Osteoarthritis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Current ACR guidelines recommend the use of IACS for short-term acute pain relief in patients (pts) with knee OA.¹ Bilateral knee OA can occur concurrently or subsequently develop in 80-90% of pts with unilateral disease.^{2,3} These pts may benefit from simultaneous IACS treatment of both knees. Triamcinolone acetonide extended-release (TA-ER; formerly FX006) is an extended-release, microsphere-based formulation of triamcinolone acetonide (TA) recently approved by the FDA for knee OA pain.⁴ In a phase 2 study, a single TA-ER injection demonstrated reduced systemic TA exposure relative to standard TA crystalline suspension (TAcS).⁵ Here, we assessed safety and systemic TA exposure following IA injection of TA-ER or TAcS into both knees in pts with bilateral knee OA.

Methods: In this phase 2, randomized, open-label study (NCT03378076), pts (≥ 40 years, BMI ≤ 40 kg/m²) meeting ACR clinical/radiographic criteria for bilateral knee OA received 2 IA injections (one in each knee) of TA-ER 32 mg (total 64 mg) or TAcS 40 mg (total 80 mg) and followed for 6 weeks. Safety was evaluated based on adverse events (AEs), physical exams, knee assessments, vital signs, and laboratory evaluations. Blood samples for plasma pharmacokinetics (PK) were collected at baseline (within 1 hour prior to injection), at Hours 1-6, 8, 10, and 12 postinjection, and on Days 2, 8, 15, 29, and 43. Plasma TA concentrations were assayed with a validated LC-MS/MS method.

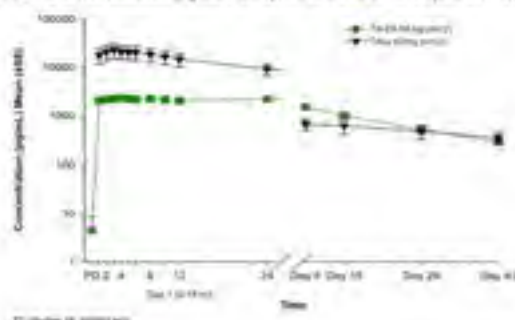
Results: Twenty-four pts (TA-ER, n=12; TAcS, n=12) were randomized and included in safety and PK analyses. Baseline characteristics were well balanced. Eight of 12 and 5 of 12 pts had ≥ 1 treatment-emergent AE in the TA-ER and TAcS treatment group, respectively. AE profiles were similar, and both treatments were well tolerated. TA-ER plasma concentrations peaked at median 4.5 hours with a mean C_{max} (\pm SD) of 2577.8 (1225.22) pg/mL, whereas TAcS peaked at median 6.5 hours with a mean C_{max} (\pm SD) of 24289.4 (27123.34) pg/mL (**Figure 1** and **Table 1**).

Conclusion: In pts with bilateral knee OA, IA injection of TA-ER into both knees was generally safe and well tolerated. Peak plasma TA concentrations were substantially lower in patients treated with TA-ER, demonstrating reduced systemic exposure relative to TAcS consistent with the PK profile of a single TA-ER injection.

References:

1. Hochberg M et al. *Arthritis Care Res* (Hoboken). 2012;64(4):465-74
2. Metcalfe A et al. *BMC Musculoskelet Disord*. 2012;13:153
3. Jones R et al. *J Rheumatol*. 2013;40(3):309-15

Figure 1: Plasma TA concentrations (log-linear scale) over time after bilateral injection of TA-ER or TAcS



Parameter	TA-ER 54 mg	Tace 80 mg
C_{max} mean (s.d.), pg/mL	3,537.8 (2,207.2)	24,209.4 (27,628.34)
$AUC_{0-\infty}$ mean (s.d.) h pg/mL	50,443.1 (24,504.98)	362,904.8 (388,596.38)
AUC_{0-24} mean (s.d.) h pg/mL	156,913.8 (285,628.87)	1,584,348.1 (908,892.06)
AUC_{0-48} mean (s.d.) h pg/mL	1,117,367.3 (241,103.68)	2,052,441.7 (722,754.52)
$T_{1/2}$ median (range), h	8.9 (3–26.0)	8.5 (2–38.0)
$T_{1/2}$ median, h	77.6	563.8
W_{0-24} mean (s.d.) mL/kg	1.0 (0.01)	0.0567 (0.0817)
CL_{0-24} mean (s.d.) h mL/kg	0.000054 (0.000124)	0.000044 (0.000018)
MT_{0-24} mean (s.d.) h	126.5 (69.88)	240.8 (291.61)

AUC, area under the curve; CL, clearance; C_{max} , maximum concentration; MT, mean retention time; SD, standard deviation; $T_{1/2}$, half-life; $T_{1/2}$ and W_{0-24} are derived; W_{0-24} , amount of drug excreted in 24 h.

5. Kraus V et al. *Osteoarthritis Cartilage*. 2018;26(1):34-42

Disclosure: A. J. Kivitz, Flexion Therapeutics, 8; L. Kwong, Flexion Therapeutics, 2, 8, Bone Support, 2, Janssen, 2, Pfizer, Inc., 2, Regeneron, 2, Stryker, 2, ConvaTec, 8, Journal of Surgical Orthopaedic Advances, 6, Zimmer, 1, 2, 5, 8; T. Shlotzhauer, None; J. Lufkin, Flexion Therapeutics, 1, 3; T. Curto, None; S. Kelley, Flexion Therapeutics, 1, 3.

An Analysis of the Quality and Readability of Online Osteoarthritis Information with Historical Comparison

Session Time: 9:00AM-11:00AM

OA is the most common cause of disability in people >65 years old. : Most patients in the USA use the internet for healthcare information. The quality and readability of this is variable. Guidelines state health information for the general public should be at a 7–8th grade reading level. Health on the Net Foundation Code of Conduct (HONcode) is a well-known quality label for medical and health websites. The DISCERN instrument and JAMA Benchmark criteria are standardized validated tools to assess healthcare information quality. In 2003, online OA information was graded as “poor” by DISCERN. This study reviews the quality and readability of current online OA information.

There was a significant difference in quality between author types (ANOVA $r^2=0.24, p=0.028$). Non-doctor health professional authors scoring the highest and non-medical authors scoring the lowest. HONCode endorsed websites (n=16) were of a statistically significantly higher quality.

Readability varied by assessment tool from 8th to 12th grade level.

Conclusion: Quality of online health information for OA is “fair”, an improvement from 2003. Readability was equal to or more difficult than recommendations. HONcode certification was indicative of higher quality, but not readability.

Summary of Results:

Producer	Age (years)	HONcode certified	DISCERN Score				JAMA Benchmark Criteria				Readability		
			Readability	Treatment Choices	Quality	Total	Authorship	Attribution	Currency	Disclosure	FRES	FKGL	GFI
All	1.4	43.2%	23.1	16.6	2.6	42.3	29.7%	24.3%	59.4%	24.3%	51.4	7.8	9.0
Not-for-profit, (governmental and NGOs) (n=14)	0.9	21.4%	24.1	17.2	2.6	43.9	0%	21.4%	50%	21.4%	50.8	7.9	9.4
Professional Society (n=4)	1.3	0%	22.6	16.3	2.5	41	50%	25%	75%	25%	49.4	8.2	8.8
For-Profit Company (n=15)	1.5	80%	23	16.9	2.6	42.5	53.3%	26.7%	73.3%	33.3%	53.2	7.6	8.6
Healthcare Providers (n=4)	0.4	25%	20.5	14	2.3	36.8	0%	25%	25%	0%	48.5	8.2	9.2

All results are mean values.

JAMA=Journal of the American Medical Association HONcode=Health On the Net certification NGO=Non-governmental organisation FRES=Flesch Reading Ease Score FKGL=Flesch-Kincaid Grade Level GFI=Gunning-Fog Index.

Disclosure: K. Murray, None; T. Murray, None; A. O'Rourke, None; C. Low, None; D. J. Veale, None.

Abstract Number: 1373

Predictive Probabilities Are Superior in Communicating the Clinical Relevance of Cartilage Thickness As an Imaging Biomarker of Knee Osteoarthritis Progression

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Establishing a threshold of clinically important cartilage loss is of great interest for the design and interpretation of knee OA trials of structure-modifying treatments. Our objective was to obtain predictive probabilities of knee replacement (KR) based on the combination of femorotibial joint (FTJ) cartilage thickness (CtTh) loss over 2 years, and CtTh at baseline.

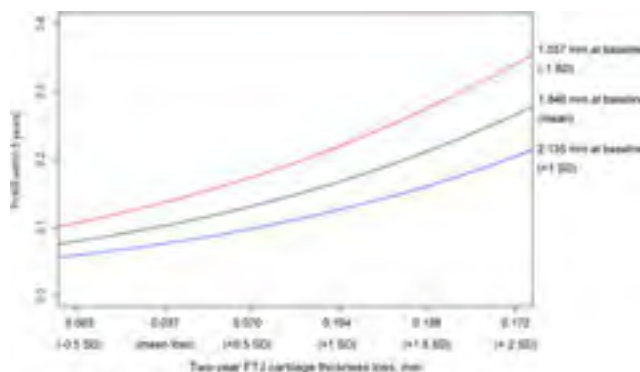


Figure 1. Predictive Probability of Knee Replacement within Five Years.

Methods: Knees with symptomatic OA, defined by definite osteophyte (OARSI atlas grade 1-3) and participant-reported frequent knee symptoms at baseline, were selected prospectively from the Osteoarthritis Initiative (Project 09B). FTJ cartilage thickness at baseline and year 2 were measured quantitatively with MRI (3T; sagittal DESS sequence) and calculated as total femorotibial cartilage volume divided by the cartilage surface area. KRs reported up to 7 years following the 2-year imaging window were self-reported and confirmed. We used a Bayesian discrete time logistic survival model with intercepts (α_k) for each year of follow-up: $\text{logit}[p_k(x)] = \alpha_k + \beta'x$. Diffuse reference prior distributions for the model parameters, $\alpha_k, \beta_j \sim N(0, 10^4)$ were specified. Posterior densities of the regression coefficients were estimated with 10,000 Markov Chain Monte Carlo samples generated with the Rpackage R2OpenBUGS. Models were compared using deviance information criteria. Sensitivity of the results to the prior specification was considered.

Results: Among 582 knees (one knee per participant), 95 underwent KR up to 7 years following the initial 2-year imaging window (median follow-up 6 years). Mean baseline CtTh was 1.85 mm (SD0.29), while mean CtTh loss over 2 years was 0.04 mm (SD 0.07). Greater CtTh at baseline (standardized) was associated with lower odds of KR (OR=0.73 [95% credible interval (CI): 0.59, 0.90]; $\Pr(\text{OR}<1 \mid \text{data}) = 0.9995$). Greater 2-year loss of CtTh (standardized) was associated with higher odds of KR (OR=1.71[95%CI: 1.41, 2.05]; $\Pr(\text{OR}>1 \mid \text{data}) = 1.0$). The figure presents three representative curves of predictive probabilities of KR as a function of 2-year CtTh loss corresponding to three baseline CtTh values. For example, a knee with baseline CtTh of 1.85 mm and 2 year loss of 0.17 mm has a probability of KR within 5 years of 0.27. A knee with less baseline CtTh, 1.56 mm (-1SD), has a probability of KR of 0.34 with the same measured loss, while a knee with greater CtTh at baseline, 2.14 mm (+1SD), has probability of KR of 0.20.

Conclusion: The same rate of 2-year FTJ cartilage thickness loss has varying predictive probability of future KR, depending on the baseline cartilage thickness, highlighting the difficulty of defining minimum clinically important differences in a tissue that eventually disappears entirely at the end-stage disease process. Predictive probabilities of clinically relevant outcomes provide a more interpretable way to communicate the clinical relevance of imaging biomarkers beyond traditionally reported odds ratios.

Disclosure: C. K. Kwoh, EMD Serono, 2, 5; E. L. Ashbeck, EMD Serono, 5; E. J. Bedrick, None; F. Eckstein, None.

Abstract Number: 1374

The Relationship between Loneliness and Osteoarthritis in US Adults from a Nationally Representative Survey

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Loneliness in adults is a growing phenomenon across the Western world. It is associated with increased mortality, depression, coronary heart disease and stroke. Moreover, over the last 2 decades, physicians have increasingly prescribed opioids to address chronic pain from osteoarthritis (OA) resulting in increased hospital stays associated with narcotic-analgesic overuse in people aged above 85 years. Our study evaluated whether presence of OA is associated with higher loneliness and if there is a difference in loneliness score among narcotic analgesic, non-narcotic and non-analgesic groups.

Methods: Data from wave 2 (2010-2011) of National Social Life, Health and Aging Project (NSHAP) were analyzed. Data were collected via in-home face-to-face interviews as well as leave-behind respondent administered questionnaires. The study was comprised of community residing adults born between 1920 and 1947, and their co-resident partners, with an oversampling of African-Americans and Hispanics and other key subgroups. Respondents were categorized as narcotic-analgesic, non-narcotic-analgesic or non-analgesic users based on medication logs obtained by interviewers, and as having or not having osteoarthritis if they specified it as a medical problem. Physical function was assessed by self-reported ability to walk one block and gait speed measured by 3-meter timed walk. Loneliness was measured with the 3-item UCLA loneliness scale in which ratings were summed to produce a loneliness score ranging from 0 to 9, with a higher score indicating greater loneliness. Ordinal logistic regression analyses were performed; survey weights were applied.

Results: Among adults with OA (n=624 out of 2572), 70 % were female, 86 % were non-Hispanic white and the mean age was 72.7 years (± 9.06 y). 12 % of those with OA reported taking narcotic-analgesics, which was higher than the rate among those without OA (6%, $p < 0.001$). Those with OA tended to be lonelier than those without OA (mean 3.3 vs. 3.1; $p = 0.008$). Among older adults with OA, those taking non-narcotic-analgesics were lonelier than those taking no analgesics, and this association persisted when adjusting for pain and walking difficulty ($p = 0.043$). In the OA group, the pain levels were higher in the narcotic-analgesic users as 92 % of them had at least moderate pain levels compared to 65 % and 61% in non-narcotic-analgesic and non-analgesic users ($p < 0.001$). There was no difference between pain levels in non-narcotic-analgesic users and those in non-analgesic users. Pain levels did not correlate with loneliness in those with OA. Both narcotic and non-narcotic-analgesic groups reported greater difficulty walking a block compared to non-analgesic users even after the analysis was adjusted for pain, age and gender ($p = 0.004$).

Conclusion: People with OA were found to be lonelier than those without OA. In the OA group, those taking non-narcotic-analgesics were found to be lonelier. Due to higher degree of loneliness in people with OA, devising strategies to reduce loneliness is important for quality of life and wellbeing. Future research should explore associations between analgesic medication classes, physical function and loneliness in people with OA.

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Abstract Number: 1375

Comparative Safety of Flavocoxid (Limbrel) Versus Nsaids Among Osteoarthritis Patients

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Flavocoxid is a medical food formulated to assist in the management of patients with osteoarthritis (OA). Safety concerns based on case reports have been raised related to an association with acute liver injury and hypersensitivity pneumonitis (HP). However, the absolute and comparative risk of these events relative to NSAIDs is unclear. Our objectives were to determine the incidence rate (IR) of severe acute liver injury, HP and other outcomes in a cohort of OA patients who were new users of flavocoxid versus prescription NSAIDs

Methods: MarketScan claims data (2006-2016) was used to identify patients age ≥ 50 initiating flavocoxid or prescription NSAIDs with a history of OA or back pain and ≥ 6 months coverage before initiation. Patients were excluded if they had prior events or malignancy. New users defined by 6-month baseline period of non-use prior to initiation. Exposure was defined by days of supply + a 30 day extension, with a sensitivity analysis conducted with a 90 day extension. Primary outcomes included hospitalization for HP and drug-induced liver injury, based on ICD-9 codes. Secondary outcomes included hospitalized GI bleed and acute myocardial infarction (MI). Poisson regression was used to calculate crude incidence rates per 1000 person-years (PY) and 95% confidence intervals (CI). Propensity scores (PS) were used to match (1:2) flavocoxid to NSAID users based on demographics and >200 comorbidities (based on AHRQ's CCS groupings). Cox regression was used for calculating adjusted hazard ratios (aHR).

Results: A total of 4800 flavocoxid and 2,129,727 NSAID new users met eligibility criteria. Prior to PS matching, many imbalances between flavocoxid and NSAID users were observed, all of which were greatly attenuated after PS matching. Post-match mean age for flavocoxid was 57, NSAIDs was 57. Flavocoxid users had higher prevalence of comorbidities and more healthcare utilization. The IR for HP associated with flavocoxid was 1.0 (95%CI 0.3-3.2) and for hospitalized liver injury was 4.1/1000, which after adjustment, was significantly elevated (aHR for HP: 5.6, 95%CI 0.5–68.6; a HR for hospitalized liver injury: 3.9, 95%CI 1.4-10.8 referent to NSAID use). Rates and aHR for GI bleed were lower (aHR=0.5, 95%CI 0.3-0.9) and there were no significant differences for MI.

Conclusion: The absolute risk for HP and severe liver injury associated with flavocoxid is low (1-4/1000py) but higher than in NSAID users, with a rate difference $\sim 2/1000$ py). The risk-benefit profile of flavocoxid needs to be considered in light of its efficacy and overall safety profile including lower rates of hospitalized GI bleeding

Table: Incidence Rates, Adjusted Hazard Ratios

Outcome	Exposure	Event	Person Years	Incidence Rate per 1000 PY	PS-matched Adjusted HR
Hypersensitivity pneumonitis	FLAVOCOXID	3	2913.3	1.0 (0.3-3.2)	5.6 (0.5-68.6)
	NSAID	1	5506.3	0.2 (0.0-1.3)	Reference
Hospitalized drug induced liver injury	FLAVOCOXID	9	2911.9	3.1 (1.6-5.9)	3.6 (1.2-11.2)
	NSAID	5	5505.8	0.9 (0.4-2.2)	Reference
Hospitalized liver injury	FLAVOCOXID	12	2910.4	4.1 (2.3-7.3)	3.9 (1.4-10.8)
	NSAID	6	5505.8	1.1 (0.5-2.4)	Reference
Hospitalized GI bleeding (sensitive)	FLAVOCOXID	14	2910.0	4.8 (2.8-8.1)	0.5 (0.3-0.9)
	NSAID	55	5493.3	10.0 (7.7-13.0)	Reference
Hospitalized GI bleeding (specific)	FLAVOCOXID	5	2911.6	1.7 (0.7-4.1)	0.6 (0.2-1.6)
	NSAID	18	5501.7	3.3 (2.1-5.2)	Reference
Myocardial infarction	FLAVOCOXID	20	2905.7	6.9 (4.4-10.7)	1.7 (0.9-3.1)
	NSAID	22	5500.7	4.0 (2.6-6.1)	Reference

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Abstract Number: 1376

The Omeract-Oarsi Core Set of Outcome Domains to Measure in Clinical Trials for People with Hip and/or Knee Osteoarthritis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

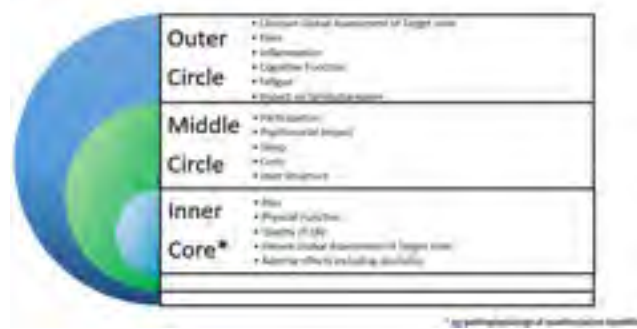
Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: It has been over 20 years since the OMERACT core outcome set (COS) to measure in clinical trials with people who have hip and/or knee osteoarthritis (OA) was presented. An OMERACT-OARSI Working Group was established to update this COS using contemporary OMERACT methodologies.

Methods: A review of the COMET database of COS was undertaken to identify all domains reported in previous COS that including individuals with hip and/or knee OA. These were presented in a series of patient and public (PP) meetings involving 70 individuals across the UK, Australia and Canada to review the domain list and identify additional important domains. Based on these, a three-round international Delphi survey was undertaken recruiting patients, healthcare professionals, researchers and industry representatives to gain consensus on key domains which should be included in this core domain set. Using the Delphi results, an OMERACT 'onion' was formulated with the following rules: Inner core

Figure 1. OMERACT2018 core outcome domain set for trials of people with hip and knee OA.



inclusion (mandatory for all trials) was defined as domains reported as ‘critical’ to assess by over 70% of Delphi responses in the patient AND others stakeholder groups; Middle circle inclusion (recommended by optional in trials) was defined as domains reported as ‘critical’ to assess by over 70% of Delphi responses in the patient OR others stakeholder groups; Outer circle inclusion was defined as areas which need further research with insufficient evidence supporting middle circle placement. The findings were discussed at OMERACT2018 and a consensus vote was obtained on the core domain set.

Results: From the COMET review, four previous COS were identified including the 1997 OMERACT core outcome set. These were reviewed across the PP meetings to identify 50 potential domains which formed the Delphi survey. In total 424 (217 patients; 207 non-patients) contributed data to the Delphi exercise from 25 different countries. The OMERACT2018 delegates (129 participants) voted on those domains which met the criteria for inclusion. From this, four domains gained agreement on inner core inclusion to be mandatory in all clinical trials with people with hip and/or knee OA: ‘pain’ (100% of vote), ‘physical function’ (100%), ‘quality of life’ (90%) and ‘patient global assessment of the target joint’ (91%) in addition to the mandated core domain of ‘adverse events including mortality’. Adherence was specified as a critical contextual factor which should be assessed. The core domain set (inner core, middle and outer circle) is presented in Figure 1.

Conclusion: The updated core domain set for hip and/or knee OA has been agreed. We will now build on this work to determine which instruments should be recommended to measure each of the inner core domains based on the OMERACT Filter 2.1 guidance.

Figure 1

*no pathophysiological manifestation identified.

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Abstract Number: 1377

Knee Osteoarthritis Symptom Duration Is Associated with Conditioned Pain Modulation and Vibration Perception Threshold Impairment

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Session Information

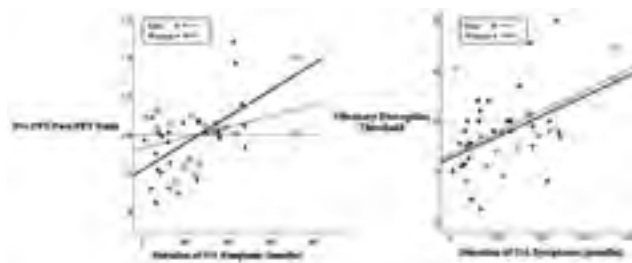
Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Impaired descending pain inhibition has been observed in people with knee OA and may be associated with development of chronic pain as well as poorer treatment outcomes. In addition, higher (worse) vibration



perception threshold (VPT) has also been observed in people with OA and linked to radiographic OA severity. It is not known how duration of symptoms may influence these neurophysiological measures. Our purpose was to evaluate the relationship between reported duration of symptoms and conditioned pain modulation (CPM), a measure of descending pain inhibition, as well as VPT. A secondary purpose was to determine whether these relationships differed in men and women.

Methods: We evaluated 18 men and 27 women with moderate to severe knee OA. All subjects satisfied ACR OA classification criteria. Subjects were asked how long they had had OA symptoms. We assessed CPM using a sub maximal-effort tourniquet test: Pressure pain threshold (PPT) at the symptomatic knee was evaluated before and after a noxious stimulus. CPM impairment was indicated by a ratio of pre-to-post stimulus PPT ≥ 1 . VPT was assessed using a biothesiometer at the medial femoral condyle. Pearson correlations were used to determine whether there were associations between symptom duration and CPM and VPT. Chi-square and t-tests were used to identify potential sex differences.

Results: 72% of men and 44% of women exhibited CPM impairment ($p = 0.062$). VPT was also similar in men (29.5 ± 7.8) and women (28.2 ± 1.6 , $p = 0.667$). Duration of symptoms (Figure 1) was associated with CPM impairment in women ($R=0.566$, $p=0.003$) but not men ($R=0.366$, $p=0.135$). Duration of symptoms was also associated with VPT in both men ($R = 0.580$, $p = 0.012$) and women ($R = 0.406$, $p = 0.039$).

Conclusion: These results suggest that longer duration of knee OA may predict more severe pain sensitization and development of hypoesthesia. In addition, important sex differences may exist in descending pain inhibition in people with chronic knee OA that may affect disease and course of treatment in male and female patients.

Figure 1. Association between duration of symptoms and CPM (L) and VPT (R). In left panel, values above dotted horizontal line indicate impaired CPM.

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Validation of a Spanish Version of the Functional Index for Hand Osteoarthritis (FIHOA)

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Hand Osteoarthritis (HOA) is a highly prevalent disease with important impact on the patient's daily activity performance and quality of life. Dreiser et al. developed the Functional Index for Hand Osteoarthritis (FIHOA), a questionnaire (either physician or self-patient administered) designed to assess the functional impact of HOA on daily living activities, and it is expected to change with the progression of the disease or under the effect of treatment. To translate FIHOA into Spanish and to validate the Spanish version in patients with HOA.

Methods: Prospective, analytical, cross-sectional observational study. The English version of FIHOA was translated into Spanish according to the Beaton et al. guidelines. Patients 18 years of age and older with diagnosis of HOA (ACR1990) were included. Those with secondary OA or any condition affecting upper limbs were excluded. All patients completed the questionnaire, along with other subjective measures: Pain and patient global assessment of the disease using a visual analogue scale (Pain and PtGA VAS), and Health Assessment Questionnaire (HAQ-A). For a patient subgroup, an occupational therapist performed an evaluation of hand function, using the Sequential Occupational Dexterity Assessment (SODA-A) and the Jebsen Hand Function Test (JHFT). To assess reproducibility, a subgroup of patients with similar clinical and therapeutic conditions to their first evaluation completed the questionnaire again one week later. Statistical analysis: Demographic and clinical characteristics were described. Construct validity was analyzed through the correlation of FIHOA with HAQ-A, SODA-A test and JHFT using the Spearman coefficient. Internal consistency was assessed using Cronbach's α coefficient and inter-item correlation. Reproducibility was estimated using test-retest reliability. A multiple regression model was constructed with FIHOA as the outcome variable and those variables that proved significant on bivariate analysis.

Results: Eighty-seven patients were included (93% women), mean age 67.8 years (SD 9.3). Educational mean level was 8 years (SD 3.7). Mean Pain VAS score was 4.57 (SD 2.54) and mean PtGA 4 (SD 2.63). Median TJC was 5 (IQR 3-8) and median SJC was 0 (IQR 0-1). We observed a good correlation between FIHOA and HAQ-A ($r=0.69$). FIHOA also showed a positive correlation with Pain VAS score ($r=0.57$), TJC ($r=0.70$), SODA-A ($r=0.47$) and the activities with small objects performed with the non-dominant hand in JHFT ($r=0.50$). FIHOA demonstrated good internal consistency (Cronbach's $\alpha=0.85$) and reproducibility (0.76). A multiple linear regression adjusted by age, gender and Pain VAS showed TJC as the main determinant of FIHOA. Median time to complete the test was 70 seconds (IQR 50-100). FIHOA showed good acceptance.

Conclusion: The Spanish version of the FIHOA questionnaire proved to be a valid, reliable, and reproducible assessment of functional capacity in patients with HOA, providing a valuable tool for the evaluation of our patients.

Disclosure: B. Barrios, None; J. Sosa, None; S. B. Papasidero, None; M. A. Medina, None; D. S. Klajn, None; J. Á. Caracciolo, None; J. Giantinoto, None; F. Pelagagge, None; M. G. Battaglia, None.

Abstract Number: 1379

Appraisal of the Educational Needs in Patients with Osteoarthritis Using the Educational Needs Assessment Tool Questionnaire

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Osteoarthritis – Clinical Poster – ARHP

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The SpENAT, a Spanish version of the Educational Needs Assessment Tool (ENAT), is a self-completed questionnaire that assesses educational needs (ENs) in osteoarthritis (OA) patients, with the purpose of providing tailored and patient-centered information.

Objectives: To establish the sources of information that patients use as well as to describe the educational needs of OA patients by using the SpENAT.

Methods: International multicenter, prospective cross-sectional study in patients with OA (Altman R. *et al.* 1986). Those patients with inability to read, write or understand the questionnaire were excluded. Demographic data, educational level, clinics and sources of information consulted were recorded. SpENAT Questionnaire: 39 questions grouped into 7 domains (pain, movement, feelings, OA, medical treatments, self-help and help from others); Likert scale of 0-4; score of ENs 0 to 156. Analysis of variables according to type and distribution: Fisher exact test, Student, Mann-Whitney U and X². Spearman correlation test.

Results: 1158 patients (79% women) from 8 Latin American countries were included. Mean age 65.5 years (SD +/- 11 IC95% 65-66). Mestizos 50%, whites 33%, LA / Africans 7%, and Amerindian 3%. With 79% urban residence and rural 21%. Average years of study 9 (RIC 6-12). Occupation: housewives 47%, trade 10%, administrative 2.2%, teachers 3%, professionals 4%, unemployed 6.4%, retired 14%, students 0.2%; Work disability 1.5%. BMI: low 1%, normal 22%, overweight 46%, obese 29%, and morbid obesity 2%. Average of years of evolution 3 (RIC 2-6). Comorbidities at 69%. (HTA 45%, DM 16%, Osteoporosis 6%, hypothyroidism 4%, dyslipidemias 4%, gastrointestinal 1.2%, others 6%). EVA of pain 50 mm (RIC 9-80) and activity 50 mm (RIC 10-80), EVA medical activity 40 (RIC 10-70). RAPID3 Average 16 (RIC 12-20). Treatment with NSAIDs 63%, paracetamol 58.4%, opioids 4.4%, PPI 33% and SYSADOAs 63.9% (Degree of Satisfaction: Medium 7 (RIC: 5-8) Tolerance Level: Medium 8 RIC: 7-9). Intra-articular treatment: 29% (3.6% with Hyaluronic Ac). SpENAT median 117 (RIC 102-134); median for pain domain 18 (RIC 14-20), mobility 15 (RIC 12-18), feelings 12 (RIC 10-16), OA 21 (RIC 18-25), medical treatments 21 (RIC 16-24), self-help 18 (RIC 15-21). Search for information: Rheumatologist 85%, Traumatologist 18%, Clinician 10.4%, other health professionals 9%, TV 1%, internet 16% and family and friends 12.3%.

Conclusion: The majority of patients show considerable educational needs and a greater interest in knowing about OA and its treatment. There is a low correlation between SpENAT and RAPID3. The greatest value of SpENAT was associated with resorting to the rheumatologist for better information. We consider it important to recognize both the NEs and the sources of communication with our patients and then have a starting point to develop better therapeutic strategies.

Disclosure: A. Garcia Coello, None; O. Rillo, None; A. Brigante Jr., None; M. Quintero, None; Y. Ponce, None; R. Espinoza, None; S. B. Papasidero, None; G. Rodriguez, None; J. Sosa, None; M. P. Kohan, None; D. Pereira, None; D. Capelusnik, None; L. Heredia, None; C. Pineda, None; M. González de Urizar, None; A. M. Sapag Durán, None; C. Rossi, None; P. Santos-Moreno, None; V. Juarez, None; J. Esquivel-Valerio, None; V. Khoury, None; B. Herrera Velasco, None; R. Souto, None.

Abstract Number: 1380

Complications Following Total Hip Arthroplasty in Inflammatory Versus Osteoarthritis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: THAs are commonly performed in patients with a history of inflammatory arthritis. These patients are likely at higher risk of complications, from both the underlying disease and immunosuppressive medications. The purpose of this study was to perform a population-based comparison of the risk of postoperative complications between patients with inflammatory arthritis and osteoarthritis.

Methods: A national private insurance database was used to select patients undergoing unilateral primary THA. Patients were categorized to the inflammatory cohort if they had an ICD diagnosis of inflammatory arthritis as well as treatment

Table 1: Characteristics of the Total Hip Replacement Cohort

	Not Inflammatory	N	Inflammatory w/ Meds (1 year)	N
Number by ICD Only	n/a		1254	472
Number	67880		1464	212
DMARDs	n/a		1838	91.38
Biologics	n/a		216	54.77
SLE Specific Medications	n/a		154	10.53
Steroids within 3 months	8803	7.53	613	87.83
Age 49 and under	1253	4.37	123	6.38
Age 50-59	7144	10.63	331	15.80
Age 60-69	20739	31.01	489	33.65
Age 70-79	46020	68.90	502	34.64
Age 80-89	6776	10.12	107	7.88
Age 90 and over	1054	2.77	22	0.62
Gender (F)	48668	59.81	1164	78.56
Gender (M)	38212	42.19	308	20.40
LOS 0	1840	5.84	91	6.32
LOS 1	1880	8.79	89	6.77
LOS 2	14289	22.71	263	16.96
LOS 3	15322	37.86	578	26.33
LOS 4	8157	12.30	191	13.09
LOS >4	8097	13.60	338	16.90
Congestive Heart Failure	2730	4.10	83	4.12
Cardiac Arrhythmias	7669	11.47	134	8.08
Heart Valvular Disease	2761	6.14	58	3.89
Pulmonary Circulation Disorders	636	0.85	22	1.50
Peripheral Vascular Disorders	2031	3.04	30	2.05
Hypertension	17051	25.46	783	53.50
Paralysis	152	0.23	3	0.045
Other Neurologic Disorders	1261	1.89	24	1.64
Chronic Pulmonary Disease	10548	15.77	290	19.89
Diabetes	17829	26.88	383	26.76
Hypothyroidism	8852	14.77	284	19.22
Renal Failure	1446	3.00	40	2.78
Liver Disease	850	0.97	18	0.86
Peptic Ulcer Disease	649	0.97	14	0.96
HIV/AIDS	85	0.14	0	0.075
Lymphoma	298	0.43	3	0.075
Metastatic Cancer	214	0.32	7	0.075
Solid Tumors without Metastasis	8118	7.68	88	4.86
Rheumatoid Arthritis/Collagen	0	0.002	146	10.00
Vascular Diseases				
Coagulopathy	1886	2.82	58	2.42
Obesity	8316	14.29	193	13.47
Weight Loss	384	0.57	11	0.88
Fluid and Electrolyte Disorders	2094	10.55	161	11.01
Blood Loss Anemia	1267	1.89	31	2.12
Deficiency Anemias	8866	14.75	277	18.95
Alcohol Abuse	728	1.09	11	0.75
Drug Abuse	423	0.63	16	1.13
Psychoses	1303	1.80	30	2.00
Depression	7647	10.84	210	14.88
Smoking	6212	8.68	118	8.02

Table 2: Complications (CMS Reportable, Age/Gender/Unresolvable/Steroid Controlled)

	Not Inflammatory		Inflammatory		OR	95% CI	p-value
	n	%	n	%			
DVT (30d)	1002	1.25	39	2.87	3.18	(0.82, 1.60)	0.34
Transfusion RBCs (30d)	11508	17.48	301	24.80	1.29	(1.13, 1.48)	0.00 *
Myocardial Infarction (7d)	183	0.57	6	0.70	1.33	(0.58, 3.04)	0.44
Pneumonia (7d)	1088	1.61	27	3.82	1.10	(0.72, 1.62)	0.64
Sepsis (7d)	505	0.76	6	0.75	0.78	(0.34, 1.51)	0.51
Surgical Site Bleeding (30d)	81	0.19	1	0.75	0.88	(0.27, 3.48)	0.88
Pulmonary Embolism (30d)	870	0.89	18	1.21	1.19	(0.68, 1.92)	0.49
Mechanical Complications (30d)	8158	4.77	103	8.98	1.35	(1.07, 1.67)	0.01 *
Infection (30d)	750	1.05	98	7.33	1.96	(1.32, 2.81)	0.00 *
Readmission (30d)	4888	7.22	304	23.90	1.35	(1.13, 1.58)	0.00 *

with a DMARD, biologic, or SLE-specific medication within the year prior to surgery. Patients with no diagnosis of inflammatory arthritis were assigned to osteoarthritis. Postoperative complications were identified using Reportable CMS Complication Measures. Risk of each complication was compared between cohorts using multivariate logistic regression controlling for age, gender, length of stay, comorbidities, and steroid use within 3 months prior to THA.

Results: 68,348 patients were included; 2.12% met criteria for inflammatory arthritis as described above. Independent of age, gender, LOS, comorbidities, and recent steroid use, inflammatory patients were found to have higher risk of transfusion (OR 1.29, $p < 0.01$), mechanical complications (OR 1.35, $p = 0.01$), infection (OR 1.96, $p < 0.01$), and readmission (OR 1.35, $p < 0.01$). There were no differences in risk of VTE or medical complications.

Conclusion: Independent of other comorbidities, patients with inflammatory arthritis are at high risk of transfusion, mechanical complications, infection, and readmission following THA. Treatment of these patients is likely more costly and efforts should be made to optimize their health and treatment medications prior to THA to minimize their complication risk. Additionally, these results have important implications for evolving bundled payment models. Hospitals should receive commensurate resources to maintain access to THA for patients with inflammatory arthritis that are prone to higher resource utilization.

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Abstract Number: 1381

Association of Omeract Core Domains of Pain and Function with Patient Satisfaction after Total Joint Replacement

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Table 1 Satisfaction Questions and Distribution

Satisfaction with	n (%) 4,796 TKR	n (%) 5,294 THR
Pain relief		
Very satisfied	3754 (78.3)	4801 (90.7)
Somewhat satisfied	623 (13.0)	303 (5.7)
Neither satisfied nor dissatisfied	108 (2.3)	61 (1.2)
Somewhat dissatisfied	168 (3.5)	62 (1.2)
Very dissatisfied	143 (3.0)	67 (1.3)
Improving ability to do housework or yard work		
Very satisfied	3214 (67.0)	4361 (82.4)
Somewhat satisfied	918 (19.1)	585 (11.1)
Neither satisfied nor dissatisfied	301 (6.3)	169 (3.2)
Somewhat dissatisfied	217 (4.5)	102 (1.9)
Very dissatisfied	146 (3.0)	77 (1.5)
Improving ability to do recreational activities		
Very satisfied	2774 (57.8)	3981 (75.2)
Somewhat satisfied	1177 (24.5)	810 (15.3)
Neither satisfied nor dissatisfied	356 (7.4)	234 (4.4)
Somewhat dissatisfied	273 (5.7)	155 (2.9)
Very dissatisfied	216 (4.5)	114 (2.2)
Overall satisfaction with surgery results		
Very satisfied	3581 (74.7)	4593 (86.8)
Somewhat satisfied	721 (15.0)	462 (8.7)
Neither satisfied nor dissatisfied	100 (2.1)	56 (1.1)
Somewhat dissatisfied	206 (4.3)	94 (1.8)
Very dissatisfied	188 (3.9)	89 (1.7)
Improved quality of life		
More than ever dreamed possible	956 (19.9)	1581 (29.9)
Great improvement	2722 (56.8)	3128 (59.1)
Moderate improvement	704 (14.7)	400 (7.6)
A little improvement	204 (4.3)	91 (1.7)
No improvement at all	104 (2.2)	55 (1.0)
Quality of life is worse	106 (2.2)	39 (0.7)

Table 2: Association between Outcomes and Satisfaction

Association between outcomes and Satisfaction	TKR Satisfaction score median [IQR]	p-value	THR Satisfaction score median [IQR]	p-value
2-year pain*		<0.001		<0.001
Q1	72 [43, 86]		84.5 [67, 96]	
Q2	91 [81, 96]		96 [91, 96]	
Q3	96 [91, 96]		96 [96, 100]	
Q4	96 [96, 100]		N/A	
A pain		<0.001		<0.001
Q1	77 [47, 96]		96 [81, 96]	
Q2	91 [77, 96]		96 [91, 96]	
Q3	96 [86, 96]		96 [93, 100]	
Q4	96 [91, 100]		96 [96, 100]	
2-year function**		<0.001		<0.001
Q1	72 [43, 86]		86 [72, 96]	
Q2	91 [81, 96]		96 [91, 100]	
Q3	96 [91, 96]		96 [96, 100]	
Q4	96 [96, 100]		96 [96, 100]	
A function		<0.001		<0.001
Q1	81 [49, 96]		96 [77, 96]	
Q2	92 [81, 96]		96 [91, 96]	
Q3	96 [86, 96]		96 [96, 100]	
Q4	96 [95, 100]		96 [96, 100]	
Baseline expectations		<0.001		<0.001
Q1	91 [76, 96]		96 [86, 96]	
Q2	96 [81, 96]		96 [91, 96]	
Q3	96 [82, 96]		96 [91, 100]	
Q4	96 [86, 96]		96 [96, 100]	

Scores are summarized as median [interquartile range] and compared using the Kruskal-Wallis test.

*The median 2-year pain score for THR was 100, so the third and fourth quartiles are the same. The median 2-year pain score for TKR was 95, quartiles were as follows: 71.3, 95, 100 and 100.

**The median 2-year function score for THR was 95.6, quartiles were as follows: 86.8, 95.6, 100 and 100. The median 2-year function score for TKR was 91.2, quartiles were as follows: 77.9, 91.2, 98.4 and 98.4.

Quartiles differ for THR and TKR.

Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Up to 20% of Total Joint Replacement (TJR) patients are dissatisfied, but this is difficult to study as it is challenging to pool data due to the lack of unified core outcome measures. The OMERACT TJR Working Group has recently endorsed a core domain set for Knee and Hip TJR trials that include pain, function and patient satisfaction among others, and now seeks validation prior to development of a TJR trial core measurement set. We aim to assess the association of pain relief and improved function with patient satisfaction 2 years after TJR.

Methods: We identified all patients undergoing total hip (THR) and knee (TKR) replacement enrolled in a hospital-based registry from 2007-2011, and evaluated those with 2-year satisfaction scores. Pain and function were measured using the Knee and Hip injury and Osteoarthritis Outcome Score (KOOS, HOOS) and satisfaction was measured using 5 primary questions, each rated on a Likert scale. Each question was weighted equally and a satisfaction summary score was calculated (range 0-100, higher scores corresponding to greater satisfaction). Expectations were measured using the validated HSS Expectations survey. Correlation was analyzed with Spearman coefficients, and scores were compared by quartiles using the Kruskal-Wallis test. Rasch modeling was attempted but a unidimensional construct could not be achieved.

Results: We included 4,796 primary unilateral TKR and 4801 THR. 78% of TKR and 90.7% of THR were very satisfied with pain relief, and 6.5% of TKR and 2.5 % of THR were somewhat or very dissatisfied (**Table 1**). Satisfaction correlated moderately with pain (TKR $\rho=0.61$, THR $\rho=0.47$) and function (TKR $\rho=0.65$, THR $\rho=0.51$) at 2 years; there was no correlation with baseline expectations. When comparing satisfaction by pain, function and expectation quartiles, there were statistically significant differences (**Table 2**); those with the best scores and greatest change in pain and function were the most satisfied.

Conclusion: These findings confirm that with increasing relief of pain and functional improvement, the strength of the association of 2 core domains with satisfaction increases, further validating these core domains for use in TJR clinical trials. The range of correlation of satisfaction measure of 0.47-0.61 with pain and function, indicates that satisfaction

domain is somewhat independent of pain and function, further validating its inclusion in the core domain set. A core outcome measurement set needs to be defined for use in TJR clinical trials that includes validated measures of these domains.

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Abstract Number: 1382

Evaluating Results of an Interferon- γ Release Assay in Patients with Autoimmune Skin Disease on Hydroxychloroquine

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: QuantiFERON-TB Gold is commercial interferon- γ release assay used to screen patients for tuberculosis before starting or while on immunosuppressive therapies. Clinical studies on efficacy of QuantiFERON-TB Gold testing show higher rates of indeterminate results among immunosuppressed populations compared to the general population. An indeterminate QuantiFERON-TB Gold result may preclude patients from starting certain therapies or enrolling in clinical trials. Hydroxychloroquine (HCQ) is proposed to reduce levels of interferon- γ and therefore may affect the results of a QuantiFERON-TB Gold test, however, its relationship to QuantiFERON-TB Gold results has not been studied

Methods: The medical records of 119 patients enrolled in prospective longitudinal databases for cutaneous lupus, dermatomyositis, and autoimmune blistering disease with QFT-G testing were reviewed. Patients were sorted into groups based on the presence or absence of HCQ use within one year of QuantiFERON-TB Gold testing. We also evaluated the concomitant use of prednisone and disease modifying anti-rheumatic drugs (DMARDs).

Results: In the study population of 119 patients, 46 were in the HCQ group, while 73 did not use HCQ in the year prior to testing. There were 24 (20%) indeterminate, 92 (77%) negative, and 3 (2.5%) positive QuantiFERON-TB Gold results total. The HCQ group had significantly more indeterminate QuantiFERON-TB Gold results (37%) compared to the non-HCQ group (9.6%) ($p < 0.001$). There was no significant difference in concomitant use of prednisone or DMARDs ($p = 0.437$, and $p = 0.085$, respectively) between groups.

Conclusion: These results reveal that patients taking HCQ at the time of QuantiFERON-TB Gold testing are significantly more likely to have an indeterminate result compared to those not taking the medication, and this finding is not explained by concomitant use of prednisone or DMARDs. An indeterminate QuantiFERON-TB Gold result represents a major barrier to receiving treatment and therefore future studies are needed to evaluate the most appropriate tuberculosis screening in patients taking hydroxychloroquine.

Disclosure: R. Gaffney, None; V. P. Werth, None.

Abstract Number: 1383

Examining Cutaneous Disease Activity As an Outcome Measure for Clinical Trials in Dermatomyositis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The FDA encourages clearance of skin findings as a primary outcome of clinical trials for inflammatory skin conditions. However, some DM patients retain signs of inflammation and damage despite having an acceptable quality of life. The current standardized quality of life instruments, Skindex-29 and Dermatology Life Quality Index, are shown to correlate with Cutaneous Dermatomyositis Activity and Severity Index activity scores and have been validated for use in clinical trials. However, Skindex-29 and Dermatology Life Quality Index scores have not been examined in patients with mild disease (Cutaneous Dermatomyositis Activity and Severity Index activity score ≤ 14), who may have an acceptable quality of life despite their cutaneous manifestations

Methods: This is a retrospective review of 171 patients enrolled in a prospective longitudinal database for DM. We evaluated the correlation of individual Skindex-29 and Dermatology Life Quality Index scores vs. the Cutaneous Dermatomyositis Activity and Severity Index activity scores in patients with DM skin disease. A linear model was fitted to determine the “Cutaneous Dermatomyositis Activity and Severity Index cut-off value”, which is the lowest Cutaneous Dermatomyositis Activity and Severity Index activity score at which the instrument correlates well with quality of life.

Results: The Dermatology Life Quality Index had the lowest Cutaneous Dermatomyositis Activity and Severity Index cut-off value at 3, compared to the other Skindex-29 subscales (Emotions, 9; Functioning, 7; Symptoms, 6). Below these Cutaneous Dermatomyositis Activity and Severity Index values, the Skindex-29 and Dermatology Life Quality Index are not shown to directly correlate with cutaneous disease activity, and further improvement in Cutaneous Dermatomyositis Activity and Severity Index activity score does not lead to further improvement in quality of life.

Conclusion: Our findings suggest that quality of life is not directly affected by the minimal cutaneous disease activity below these Cutaneous Dermatomyositis Activity and Severity Index cut-off values and therefore total clearance of skin findings may be irrelevant as a meaningful outcome for patients. Additionally, the linear correlation of Cutaneous Dermatomyositis Activity and Severity Index with quality of life until the cut-off values suggests that changes in Cutaneous Dermatomyositis Activity and Severity Index scores are relevant over the spectrum of disease activity above these cut-offs. The results of this study should encourage design of trials that reach a meaningful endpoint in terms of quality of life for patients.

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Abstract Number: 1384

Health-Related Quality of Life in Patients with Ankylosing Spondylitis in the United States

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

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Session Time: 9:00AM-11:00AM

Background/Purpose: Ankylosing spondylitis (AS) is a chronic, systemic, inflammatory disease that affects primarily the sacroiliac joints and spine and can cause irreversible damage. Measuring disease activity and quality of life of AS patients can be complex due to the slow progression and invisible nature of the disease. The objective of this web-based survey was to describe the impact of AS on health-related quality of life (HRQoL) from the US patient perspective.

Methods: US adults aged ≥ 18 years with a self-reported diagnosis of AS were recruited through Creaky Joints (www.CreakyJoints.org), an online patientsupport community comprising patients with arthritis and arthritis-related diseases and their caregivers, as well as through outreach on social media. Respondents completed a web-based survey that

Table. Impact of AS on Health-Related Quality of Life

	Total (N = 235)	Men (n = 61)	Women (n = 174)	P Value
RAPID3 cumulative score (5-30), mean (SD)	15.4 (5.4)	13.6 (6.0)	16.0 (5.1)	0.01
PROMIS10, mean (SD)				
Global Physical Health T-Score	35.8 (7.4)	39.2 (7.8)	34.8 (6.8)	<0.01
Global Mental Health T-Score	59.9 (8.8)	62.3 (9.2)	59.1 (8.5)	0.02
Impact on work, n (%)	N = 117	n = 33	n = 84	
Difficulty sitting or standing for long hours	94 (71.8)	25 (75.8)	59 (70.2)	0.65
Missed work	55 (47.3)	13 (39.4)	42 (50.0)	0.31
Difficulty doing physical tasks	49 (41.9)	12 (36.4)	37 (44.0)	0.53
Loss of productivity at work	48 (41.0)	10 (30.3)	38 (45.2)	0.15
Need accommodations at work	44 (37.6)	9 (27.3)	35 (41.7)	0.20
Had to switch careers/jobs	25 (21.4)	5 (15.2)	20 (23.8)	0.45
Only able to work part-time	23 (19.7)	3 (9.1)	20 (23.8)	0.12
AS has no effect on my work	5 (5.1)	3 (9.1)	2 (3.6)	0.35
Unemployment related to AS, n (%)	N = 118	n = 28	n = 90	
Yes, completely because of AS	56 (47.5)	15 (53.6)	41 (45.6)	0.51
Yes, partially related to AS	51 (43.2)	12 (42.9)	39 (43.3)	
No	11 (9.3)	1 (3.6)	10 (11.1)	
Impact on relationships, n (%)				
Difficulty spending time with my friends	147 (62.6)	37 (50.8)	110 (58.7)	0.03
Lack of understanding from family and friends about my AS	127 (54.0)	29 (37.7)	104 (59.8)	<0.01
Difficulty spending time with my family	110 (46.8)	23 (31.7)	87 (50.0)	0.10
Difficulty maintaining friendships	93 (39.5)	15 (24.5)	78 (44.3)	<0.01
Difficulty maintaining my relationship with my spouse/partner	75 (31.9)	17 (27.9)	58 (33.3)	0.52
Lack of support from my family and/or friends	68 (28.9)	9 (14.8)	59 (33.9)	0.05
I don't have any difficulties with my relationships because of AS	40 (17.0)	20 (32.8)	20 (11.5)	<0.01

AS, ankylosing spondylitis; PROMIS10, Patient-Reported Outcomes Measurement Information System Global Health Short Form.

RAPID3, Revised Assessment of Patient Index Data-3.

* Percentages could have exceeded 100% due to rounding.

was designed to collect information on sociodemographic characteristics, clinical symptoms, disease burden, and the impact of AS on work productivity and relationships. Survey questions were developed following analysis of qualitative interviews of patients with AS and clinical experts, as well as targeted literature review. Survey results were compared between men and women using 2-sample *t* tests for continuous variables and chi squared tests for categorical variables.

Results: Among 235 respondents, 174 (74.0%) were women, and the mean (SD) age was 49.8 (10.7) years. The mean (SD) and median (IQR) time since AS diagnosis was 8.5 (9.3) and 5.0 (2-12) years. Depression (62.1%), anxiety (54.5%), and fibromyalgia (35.7%) were the most commonly reported comorbidities among respondents. Women had significantly higher mean RAPID3 scores and lower PROMIS10 Global Physical and Mental Health T-Scores than men (**Table**).

Approximately 90% of respondents reported either complete or partial unemployment due to AS. Most respondents (71.8%) had difficulty sitting or standing for long hours; other common issues related to work included missed work (47.0%), difficulty doing physical tasks (41.9%), and loss of productivity (41.0%) (**Table**). Although the impact of AS on work was not significantly different between men and women, the percentage of women with negative impact of AS on work was numerically higher in most categories. The most common impacts of AS on relationships were difficulty spending time with friends (62.6%), lack of understanding from friends and family about AS (54.0%), and difficulty spending time with family (46.8%) (**Table**).

Conclusion: Whereas the study findings demonstrate a considerable impact of AS on patients' HRQoL including work productivity and relationships, these topics are often not discussed with their treating physicians, friends, and families. Encouraging patients to share their disease burden with their physicians and caregivers may help to optimize medical care and outcomes in patients with AS.

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Abstract Number: 1385

Subjective Well-Being Among Rheumatoid Arthritis Patients

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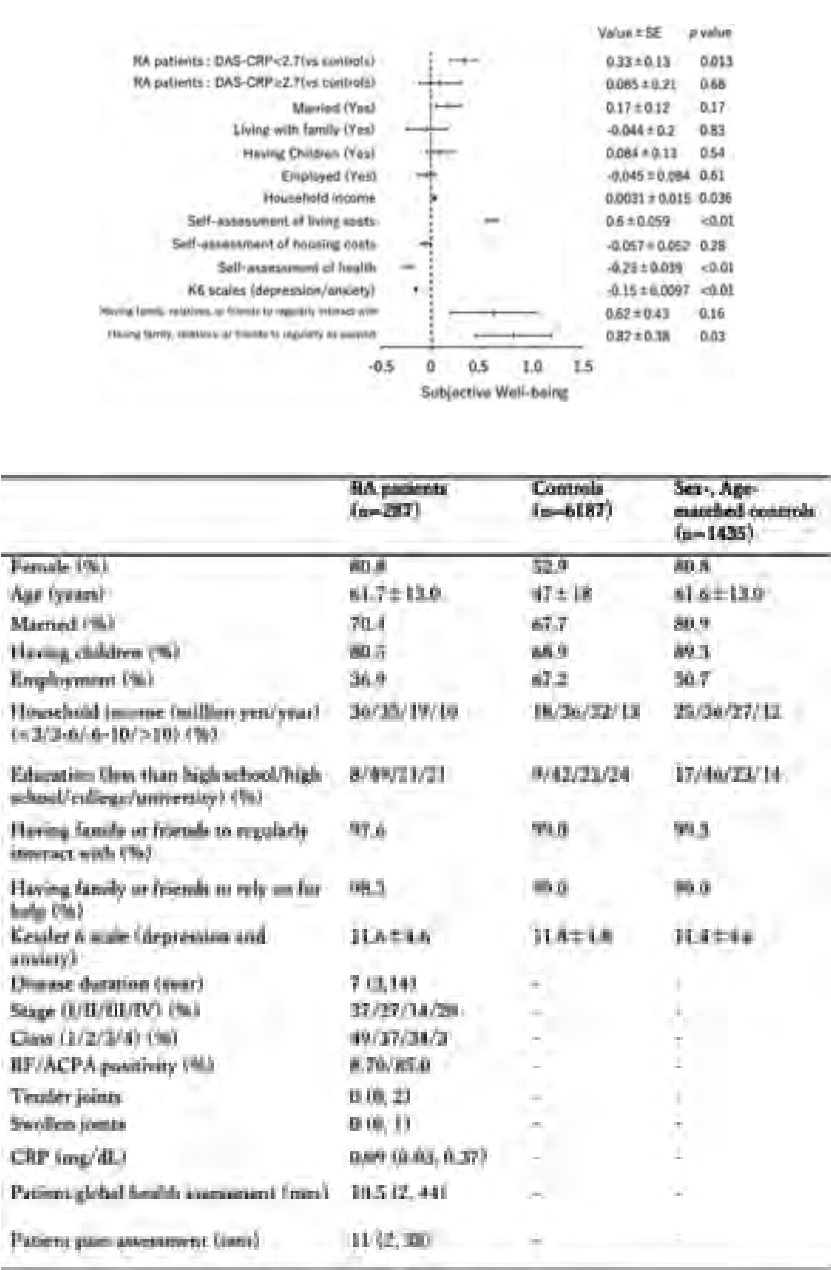
Session Information

Session Date: Monday, October 22, 2018
Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes
Session Type: ACR Poster Session B
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Background/Purpose: Subjective well-being (SWB) is a psychological construct that is synonymous with happiness. Many variables including age, sex, income, employment, and marital status are related to SWB. Health is also an important determinant of SWB that can be adversely affected in patients with chronic conditions such as rheumatoid arthritis (RA). In this study, we evaluated the SWB of RA patients and compared it with that of healthy controls.

Methods: We obtained the original dataset from the Quality of Life Survey, 2013, which was conducted by the Economic and Social Research Institute, Cabinet Office, Government of Japan. In this survey, SWB was determined by asking participants to rate their happiness on a scale from 0(very unhappy) to 10 (very happy). The survey also included a 56-point questionnaire regarding variables related to well-being. This questionnaire was administered to RA patients recruited from Kobe University Hospital. Clinical data regarding disease duration, stage, class, disease activity, health activity, complications, and treatment data were collected simultaneously.

Results: Multivariate analysis revealed that RA patients had significantly better SWB than age- and sex-matched controls (p =0.025). In addition, RA patients with high or moderate disease activity had SWBscores that were similar to those of



controls. However, the SWB scores of RA patients in remission or with low disease activity were higher than those of controls ($p=0.013$). SWB was associated with household income, financial status, psychological distress, self-assessment of health, and social connection.

Conclusion: For RA patients, achieving the therapeutic target can result in better SWB. Socioeconomic factors, financial status, psychological stress, self-assessment of health, and social network are also important for better SWB of RA patients. **Table** Summary of demographic characteristics of the study cohort

Figure.

When RA patients were stratified according to the degree of disease activity (DAS28-CRP ≥ 2.7 vs DAS28-CRP < 2.7), multivariate analysis shows that RA patients with DAS ≥ 2.7 had SWB scores similar to those of controls. However, the SWB of RA patients with DAS < 2.7 was higher than that of controls. SWB was also associated with socioeconomic factors, psychological stress, self-assessment of health and social network.

Disclosure: G. Kageyama, None; A. Onishi, None; Y. Ueda, None; K. Akashi, None; S. Sendo, None; J. Saegusa, None; A. Morinobu, None.

Abstract Number: 1386

Golimumab Improves Work Productivity and Activity As Well As Quality of Life in Patients with Rheumatoid Arthritis (RA), Psoriasis Arthritis (PsA) and Axial Spondyloarthritis (axSpA): Interim Results from a Non-Interventional Study in Austria (Go Active)

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Session Information

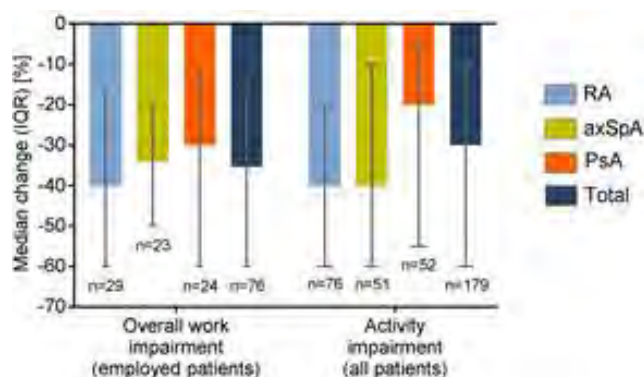
Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Golimumab has shown clinical efficacy and tolerability within its clinical trial program. No systematic outcome data regarding patient-reported outcomes and health economic parameters reflecting real-world use of golimumab in Austria are currently available.



Methods: Go Active is a prospective, non-interventional, multi-center study in Austria. The impact of golimumab therapy on work productivity and activity (WPAI) and quality of life (RAQoL for RA patients, AsQoL for axSpA patients, PsAQoL for PsA patients) is assessed by using patient-reported outcomes. Patients (target recruitment: n = 220) are followed up to 2 years. In this interim analysis (data cut-off: 03 May 2018) changes in WPAI and QoL from baseline to month 3 are analyzed after recruitment was completed

Results: At total of 234 patients were enrolled in the study and 189 patients were included in this analysis (81 patients with RA, 56 patients with axSpA, and 52 patients with PsA). Median age at registration was 52 years (patients with RA: 56 years, patients with axSpA: 40 years, and patients with PsA: 53.5 years). Almost two thirds of patients were female (81% of patients with RA, 39% patients with axSpA, and 58% of patients with PsA). Most patients were biological-naïve at study entry (78% of all patients, 75% of patients with RA, 79% of patients with axSpA, and 83% of patients with PsA). 38% of patients were not employed (54% of patients with RA, 25% of patients with axSpA and SpA); 14% due to incapacity for work (11% of patients with RA, 21% of patients with axSpA, and 15% of patients with SpA) and 55% due to age-related pension (61% of patients with RA, 21% of patients with axSpA, and 69% of patients with SpA). Most of the patients, who worked for a fee, worked full time. 179 of all patients and 92 of employed patients completed the WPAI questionnaire at baseline and after 3 months. Overall work productivity improved by 35% (40% for patients with RA, and 34% for patients with axSpA and 30% for patients with PsA) and activity impairment by 30% (40% for patients with RA and axSpA, and 20% for patients with PsA; Fig. 1). Quality of life scores improved by 7.5 for patients with RA, by 5 for patients with axSpA, and by 3 for patients with PsA. Fig. 1: WPAI questionnaire – changes from baseline after 3 months of golimumab treatment

Conclusion: This interim analysis shows that golimumab is an effective treatment for patients with RA, axSpA and PsA and leads to an improvement of work productivity and daily activities as well as of quality of life already within the first 3 months of treatment. At study entry, most patients were biological-naïve and employed.

Disclosure: C. Dejaco, Speaker Bureau < 5000€ received from Sponser MSD, 8; T. Mueller, None; O. Zamani, MD, None; U. Kurtz, MD, None; S. Egger, MD, None; J. Resch Passini, MD, None; A. Totzauer, MD, None; W. Eisterer, None; B. Yazdani-Biuki, MD, Univ.Doc., None; T. Schwingenschloegl, MD, None; P. Peichl, MD, Univ.Doc. Msc, None; A. Kraus, None; G. Naerr, PhD, Employee of Merck Sharp and Dohme, 3; V. Rickert, MD, MBA, Employee of Merck Sharp and Dohme, 3.

Abstract Number: 1387

Fatigue in Patients with Rheumatoid Arthritis As Compared to Different Groups of Cancer Patients

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Fatigue is a common symptom in patients with rheumatoid arthritis (RA) as well as patients with cancer. Fatigue considerably reduces the quality of life of patients. The present project investigated the prevalence of fatigue in RA patients as compared to cancer patients.

Methods: The RA study was based on a survey involving a representative, nationwide sample of German physicians specialized in RA and their patients [1]. The patient questionnaire included the EORTC measure of fatigue. Data of cancer patients were taken from the international psychometric validation study of the EORTC quality of life module measuring cancer related fatigue (EORTC QLQ-FA12). Thus, both studies used the same fatigue assessment, allowing for comparative analyses. The EORTC questionnaire assesses five components of fatigue: physical, emotional, cognitive, interference with daily life, and social sequelae. All scores are presented on a linear scale ranging from 0 to 100, with higher scores representing higher symptom burden.

Results: Data of 708 RA patients (Mean DAS28 2.77, SD 1.20, mean HAQ 0.75 SD 0.70) and 944 cancer patients were available for analysis. Based on clinical considerations with regard to the degree of fatigue, the cohort of cancer patients was divided into four groups: curative therapy (active treatment), palliative treatment, 3 year survivor, 5 years survivor.

N = 1652	Rheumatoid arthritis		Group A curative therapy		Group B palliative therapy		Group C 3 years survivors		Group D 5 years survivors	
	n = 708		n = 311		n = 222		n = 212		n = 199	
Age	M 59.5		M 59.5		M 61.5		M 57.6		M 58.3	
Gender	n	%	n	%	n	%	n	%	n	%
male	193	27.3	154	49.5	104	46.8	87	41.0	89	44.7
female	514	72.3	157	50.5	118	53.2	125	59.0	110	55.3
FA 1	M	95% CI	M	95% CI	M	95% CI	M	95% CI	M	95% CI
FA 2	44.4	42.3 - 46.5	34.5	31.4 - 37.6	45.9	42.5 - 49.3	33.9	30.4 - 37.4	30.7	26.9 - 34.4
FA 3	26.6	24.5 - 28.7	26.0	23.0 - 29.0	36.7	32.7 - 40.8	21.6	18.0 - 25.1	19.6	16.0 - 23.1
FA 4	11.0	9.5 - 12.4	11.5	9.3 - 13.8	17.0	14.0 - 20.1	13.9	10.8 - 17.0	12.9	9.9 - 15.9
FA 5	35.3	32.9 - 37.7	34.6	30.9 - 38.4	51.4	47.0 - 55.8	32.4	28.4 - 36.4	30.5	26.1 - 34.8
FA 5	20.2	17.9 - 22.6	9.8	7.5 - 12.1	10.8	7.6 - 13.9	15.2	11.6 - 18.7	13.5	9.8 - 17.1

FA 1 = physical Fatigue, FA 2 = emotional Fatigue, FA 3 = cognitive Fatigue, FA 4 = interference with daily life, FA 5 = social sequelae. High values in fatigue scores represent high symptom burden.

As shown in Table 1, RA patients suffered from a high level of physical fatigue (M = 44.4; CI 95% 42.3 - 46.5) that was almost identical to the value obtained in palliative care cancer patients. Furthermore, RA patients reported high burden with regard to social consequences (M = 20.2; CI 95% 17.9 - 22.6), more so than all groups of cancer patients (Ms ranging from 9.8 to 15.2). Multiple regression analyses indicated that sex and patient group were significant predictors of all five components of fatigue.

Conclusion: This study showed that RA patients suffer from a considerable level of fatigue that is comparable to cancer patients.

[1] Kuipers et al.: Adherence and health literacy as related to outcome of patients treated for rheumatoid arthritis. *Z Rheumatol.* 2018 Apr 24. <https://doi.org/10.1007/s00393-018-0449-y>)

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Abstract Number: 1388

Characteristics and Symptom Severity in 21,101 Patients Reporting Systemic Lupus Erythematosus in the Patientslikeme Online Health Community

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Online health communities and research networks such as PatientsLikeMe (PLM) provide important insight into understanding chronic diseases, including systemic lupus erythematosus (SLE). We aimed to characterize PLM SLE population by their initial reported patient characteristics.

Methods: Retrospective observational study in PLM online health network. Patients were included in the study if they had registered with PLM between 2011-2017, were aged over 18 years at the time of registration, and reported both SLE and treatment with one or more SLE medications (anti-malarials, immunosuppressive, corticosteroids, calcineurin inhibitors and biologics). Information reported within 30 days of registration was used to assess eligibility and in descriptive analysis to characterize the demographic and clinical characteristics, co-morbidities, treatment of patients and the severity of symptoms they reported, both general (included in symptom panel for all PLM patients) and additional SLE symptoms.

Results: 21,101 patients met the inclusion criteria and were identified as patients with SLE. The median age at registration was 46 years (IQR 38-53), the majority were female (96.8%, N=21 050), and 94.8% (18,491) of the 19,502 patients who reported country were US residents. The 17,994 patients who recorded race were predominately Caucasian (67.8%) and African-American (22.4%). In the 6 489 patients who reported when they headfirst experienced SLE symptoms the median age of onset was 30 years (IQR 21-39) and age at first diagnosis was 36 years (IQR 27-44) (N=6 936). The most commonly

reported comorbidities were fibromyalgia 7.9%, discoid lupus 6.8%, lupus nephritis 6.3%, rheumatoid arthritis 4.8%, subacute cutaneous lupus 4.7%, Sjogren's Syndrome 3.9%, CNS lupus 3.9%, and lupus pneumonitis 3.1%. At registration patients reported having tried an average of 2.2 SLE medications, most commonly; anti-malarials 83.8%, corticosteroids 78.8%, immunosuppressive 32.3%, and biologic treatment 9.4%. Around 31% of patients (N=6,448) entered any symptom report at registration, and >80% of the patients who reported them rated the severity of fatigue, pain, and joint pain as moderate or severe (Table 1).

Table 1. Severity of symptoms in patients with SLE in PLM community

Symptoms	Severity n (%)				Total (N)
	None	Mild	Moderate	Severe	
General					
Fatigue	135 (2.1%)	832 (13.0%)	2665 (40.8%)	2815 (44.1%)	6387
Pain	286 (4.5%)	975 (15.5%)	2834 (44.5%)	2213 (35.1%)	6308
Symptoms (all diseases)	1274 (20.4%)	2256 (36.2%)	1935 (31.0%)	770 (12.3%)	6235
Depressed mood	1378 (18.3%)	2072 (28.6%)	2214 (30.9%)	748 (10.3%)	6412
Anxious mood	938 (15.3%)	1442 (23.6%)	3025 (48.1%)	1717 (28.0%)	6122
Insomnia					
Joint pain	251 (4.1%)	882 (14.4%)	2548 (41.5%)	2457 (40.0%)	6138
Butterfly rash	2493 (44.8%)	1781 (31.9%)	1019 (18.3%)	288 (5.2%)	5581
Brain fog	206 (10.6%)	687 (35.2%)	796 (40.7%)	263 (13.5%)	2952
Muscle pain	144 (7.4%)	406 (20.8%)	806 (41.3%)	506 (26.5%)	2962
Additional symptoms (SLE)	260 (13.7%)	565 (29.8%)	702 (37.0%)	371 (19.5%)	1900
Joint swelling					
Chest pain	807 (42.5%)	589 (36.4%)	312 (16.5%)	86 (4.5%)	1694
Sun sensitivity	356 (18.2%)	532 (28.1%)	582 (30.7%)	423 (22.3%)	1893
Hair loss	361 (23.4%)	620 (40.2%)	403 (26.2%)	157 (10.2%)	1541
Muscle weakness	175 (11.7%)	423 (28.2%)	606 (40.5%)	294 (19.6%)	1498
Headaches	192 (19.3%)	327 (32.6%)	303 (30.2%)	181 (18.0%)	903
Raynauds	194 (47.7%)	111 (27.3%)	75 (18.4%)	27 (6.6%)	407

Conclusion: The age, gender and race of SLE patients in the PatientsLikeMe community are broadly consistent with what is known about the US SLE population. The PLM SLE population provides a unique source of real world information on the patient experience of symptoms of SLE outside the clinical environment that can be utilized to improve understanding of SLE.

Disclosure: E. Nyman, AstraZeneca, 3; E. R. Hammond, AstraZeneca, 1, 3; T. Vaughan, PatientsLikeMe, 3; B. Desta, AstraZeneca, 1, 3; X. Wang, AstraZeneca, 1, 3; V. Barut, AstraZeneca, 1, 3; C. Emmas, AstraZeneca, 1, 3.

Abstract Number: 1389

Depression and the Patient Reported Outcomes Measurement Information System in Systemic Lupus Erythematosus

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Health-related quality of life (HRQoL) is reduced in SLE. Depression is a possible contributor to reduced HRQoL. The relationship between major depression and HRQoL measured using NIH's Patient Reported Outcomes Measurement Information System (PROMIS) has not been well characterized.

Methods: Data were obtained from the California Lupus Epidemiology Study (CLUES), a cohort of adult patients in San Francisco County with physician-confirmed SLE. Subjects attended a research clinic encounter with a physician and completed a structured interview with a research assistant. The primary outcomes were T-scores on 13 PROMIS short forms (Table 1), scaled to a population mean of 50 and SD of 10. The primary predictor variable was major depression, defined as a score of 10 or greater on the Patient Health Questionnaire (PHQ-8) depression scale. Mean T-scores in depressed and non-depressed patients were compared using linear regression models with and without adjustment for age, sex, race/ethnicity, disease activity measured by the SLEDAI, BMI, and education less than high school graduate.

Table 1		Unadjusted Mean PROMIS T-Score			Adjusted* Mean PROMIS T-Score		
PROMIS Domain	N	No Depression [PHQ<10]	Depression [PHQ≥10]	p	No Depression [PHQ<10]	Depression [PHQ≥10]	p
Physical Health							
Physical Function	326	50.3	41.3	<0.001	49.8	42.6	<0.001
Pain Interference	323	58.4	60.0	<0.001	59.7	59.2	<0.001
Fatigue	323	48.4	63.6	<0.001	48.6	63.1	<0.001
Sleep Disturbance	323	50.1	59.2	<0.001	50.8	58.6	<0.001
Sleep Impairment	301	48.5	63.7	<0.001	49.7	63.1	<0.001
Mental Health							
Applied Cognitive Abilities	195	50.8	43.8	<0.001	50.1	43.4	<0.001
Applied Cognitive Concerns	119	54.7	46.2	<0.001	54.8	46.0	<0.001
Psychosocial Illness: Impact - Negative	169	49.8	60.1	<0.001	49.9	59.9	<0.001
Psychosocial Illness: Impact - Positive	267	50.4	41.3	<0.001	50.3	41.9	<0.001
Social Health							
Ability to Participate in Social Roles - Activities	186	53.3	43.8	<0.001	53.0	43.8	<0.001
Satisfaction, Discretionary Social Activities	301	55.9	43.6	<0.001	55.6	44.5	<0.001
Satisfaction, Social Roles	289	54.2	41.6	<0.001	53.8	42.6	<0.001
Social Isolation	296	43.7	54.3	<0.001	43.9	53.7	<0.001
SF-36[†] scores							
SF-36 Physical Component Score	324	45.4	34.6	<0.001	44.9	36.2	<0.001
SF-36 Mental Component Score	324	52.1	35.1	<0.001	52.2	37.9	<0.001

*PHQ = Patient Health Questionnaire

†SF-36 = Medical Outcomes Study Short Form

*Adjusted for age, sex, race/ethnicity, SLEDAI, SLICC, BMD, high school graduate

Results: 296 of 326 study participants met at least 4 of 11 ACR criteria for SLE, 20 met 3 ACR criteria and had SLE confirmed by a rheumatologist, and 10 had a diagnosis of lupus nephritis. Approximately 89% were female, 29% white, 23% Hispanic, 10% black, and 36% Asian. A quarter had a PHQ-8 score consistent with major depression. Depression was independently associated with worse mean T-scores on all 13 PROMIS short form domains tested ($p < 0.001$, Table 1). In multivariable analyses, depressed subjects scored more than 10 points (1 SD) worse on Fatigue, Sleep Impairment, Negative Psychosocial Impact of Illness, Applied Cognitive Concerns, Satisfaction in Discretionary Social Activities, and Satisfaction in Social Roles. Depressed patients also had worse scores on the Medical Outcomes Study Short Form (SF-36) Physical Component Summary and Mental Component Summary ($p < 0.001$).

Conclusion: Major depression was independently associated with substantially worse patient-reported outcomes on every tested PROMIS domain of physical, mental, and social health, as well as on SF-36 mental and physical subcomponents, even after adjusting for disease activity and sociodemographic characteristics. Assessment of comorbid major depression may be an important part of interpreting and targeting HRQoL in SLE patients when using PROMIS.

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Impact of Psoriatic Arthritis from the Patient's Perspective in the Context of the Psoriatic Arthritis Impact of Disease (PsAID) Questionnaire: An Online Global Survey

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Session Information

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Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

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Background/Purpose: Psoriatic arthritis (PsA) is a complex disease with high impact on quality of life (QoL). The PsA core domain set¹ includes pain, patient (pt) global assessment, physical function, QoL and fatigue. To evaluate the impact of PsA on health domains, a global survey was developed; we report results in the context of the PsA Impact of Disease (PsAID) questionnaire due to its high content validity for pts.²

Methods: A pt-based survey was conducted online from Nov 2 2017 to Mar 12 2018. Eligible pts (≥18 yrs) had PsA for >1 yr, had visited a rheumatologist/dermatologist in the past 12 months and reported using ≥1 synthetic/biologic DMARD for PsA. Pts reported current symptoms and impact of PsA on daily life. Post-survey, responses were aligned with PsAID health domains. Analyses included descriptive statistics and binomial tests.

Results: 1286 pts were surveyed across 8 countries; mean age 41 yrs, 52% female, 84% reported moderate/severe PsA. Pt-perceived PsA social and work impacts were reported by 1075 (84%) and 1035 (81%) pts; 56% stopped participating in certain sports/recreational activities and 42% reported decreased work productivity. The most commonly reported major/moderate impacts of PsA were on physical activity (78%), ability to perform activities (76%), and emotional/mental well-

	Global total ^a (n=1286)	Australia (n=152)	Brazil (n=152)	Canada (n=155)	France (n=124)	Spain (n=135)	Taiwan (n=109)	UK (n=159)	USA (n=101)
Social impacts of PsA, n (%) ^b	1075 (84)	32 (82)	277 (87)	47 (35)	41 (82)	78 (92) ^{c,d,e,f,g}	34 (83)	90 (82)	427 (83)
Work impacts of PsA, n (%) ^b	1035 (81)	32 (83)	285 (89) ^{c,d}	43 (36)	49 (80)	74 (87) ^h	31 (74)	83 (83) ^h	388 (73)
Negative impact of PsA on n (%) ^b									
Physical activity	1005 (78)	27 (78) ⁱ	242 (82) ^{c,d}	44 (72) ⁱ	59 (81) ⁱ	64 (74) ⁱ	22 (54)	46 (77) ⁱ	488 (79) ⁱ
Ability to perform routine activities	979 (76)	23 (66)	250 (78) ^{c,d}	59 (64)	66 (78) ^{c,d}	57 (87)	23 (57)	41 (74) ^h	412 (79) ^{c,d}
Emotional/mental well-being	889 (69)	22 (57)	254 (89) ^{c,d}	31 (58)	35 (74) ^{c,d}	62 (73) ^{c,d}	23 (55)	76 (77) ^{c,d}	354 (64) ⁱ
Work productivity	782 (62)	22 (57)	233 (79) ^{c,d,e,f}	29 (47)	71 (88) ^{c,d}	42 (50)	20 (48)	62 (57)	313 (60) ^{c,d}
Career path	736 (57)	22 (56) ⁱ	214 (67) ^{c,d,e,f}	25 (43)	71 (88) ^{c,d}	39 (46)	20 (48)	60 (55) ⁱ	286 (55) ⁱ
Romantic relationship/intimacy	714 (56)	26 (52)	197 (62) ^{c,d}	25 (41)	59 (54) ^c	40 (47)	17 (40)	63 (57) ^h	292 (56) ⁱ
Relationships with family/friends	564 (44)	15 (40) ⁱ	145 (45) ^c	20 (32)	56 (50) ⁱ	33 (39) ⁱ	10 (24)	68 (48) ⁱ	237 (46) ⁱ
Decision to start a family	456 (35)	9 (23)	147 (48) ^{c,d,e,f}	14 (23)	45 (41) ^{c,d}	36 (42) ^{c,d}	15 (37) ^h	36 (38) ^h	184 (36)
Education	386 (30)	11 (30) ⁱ	146 (47) ^{c,d,e,f}	10 (18)	32 (29) ⁱ	17 (20)	6 (15)	29 (28) ^h	132 (25) ⁱ

^aRaw data were not weighted at the individual country level. For the global total, a post-weight was applied to adjust for the relative size of each country's adult population within the total adult population across all countries surveyed. The unweighted sample sizes reflect the total number of pts who completed the survey, while all reported percentages are calculated based on the weighted global total.

^bHave you done any of the following as a result of PsA? Please select all that apply. Data shown here reflect a positive response to either the Social or Work impacts of PsA. Social impacts included emotional distress, stopping doing or participating in certain sports/recreational/social activities, experienced social shame or disapproval. Work impacts included sick days, decreased productivity at work, medical leave, quit or been let go from work, went on permanent disability, lost job.

^cHow much of a negative impact, if any, has PsA had on each of the following aspects of your life (slight/moderate/major)? Data represent sum of moderate/major impact.

^dSignificant difference (p<0.05) between countries indicated using log₁₀ odds ratio (Australia, b-Brazil, c-Canada, d-France, e-Spain, f-Taiwan, g-UK, h-USA).

being (69%). A greater proportion of pts in Brazil, France, Spain and UK reported negative impact on emotional well-being compared with Australia, Canada and Taiwan ($p < 0.05$; Table). Social impacts included emotional distress (58%), social shame or disapproval (32%), and ceased participation in social activities (45%). Most respondents (62%) reported a major/moderate impact on work productivity. A greater proportion of pts in Brazil, France and USA reported negative impact on work productivity compared with Canada, Spain and Taiwan ($p < 0.05$). Overall, 97% of pts reported musculoskeletal symptoms in the past year, most commonly joint pain, tenderness, swelling, stiffness or inflammatory back pain (IBP) (79%, 60%, 60%, 57%, 53%, respectively). Of these, joint pain and IBP were considered most bothersome (32%, 12% respectively), and 53% pts currently taking prescription medication reported joint pain. Skin/nail symptoms occurred in 80% of pts (skin patches/plaques, 58%; skin discomfort, 55%; nail changes, 34%) and unusual fatigue in 52% of pts.

Conclusion: All health domains that pts reported on were impacted by PsA in this survey aligning with life impact domains of the pt-derived PsAID questionnaire. Most pts reported an impact of PsA on social, work, and physical life aspects. These results highlight the impact of PsA on multiple health domains from a pt perspective that should be considered during shared decision-making processes between physicians and pts.

1. Orbai AM et al. Ann Rheum Dis 2017; 76:673-80
2. Gossec L et al. Ann Rheum Dis 2014; 73:1012-9

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Abstract Number: 1391

Patient-Acceptable Symptom State in Psoriatic Arthritis: Prevalence and Associated Factors in Real Clinical Practice

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Treatment goals in psoriatic arthritis (PsA) are remission or low disease activity. We know little about whether these objectives correlate well with a patient-acceptable symptom state (PASS). To analyze the frequency of PASS in routine clinical practice, we used the Psoriatic Arthritis Impact of Diseases (PsAID) questionnaire proposed by EULAR.

Methods: Cross-sectional multicenter study including patients with PsA according to CASPAR criteria. Patients with at least one year of disease evolution and under treatment with synthetic (s) and / or biological DMARDs were included. The MDA, VLDA, DAPSA remission and clinical (c) DAPSA remission (without CRP) were measured as treatment targets. A PsAID value < 4 was defined as PASS. Factors associated with PASS were analyzed by uni and multivariate models.

Results: This study included 227 patients, 123 men and 104 women, with a mean age of 53.2 ± 12.4 years. The average duration of PsA was 9.6 ± 7.7 years. One hundred and thirty three (58.6%), 26 (11.5%), 52 (30.6%), 65 (36.9%) and 125 (55%) patients were in MDA, VLDA, DAPSA remission, cDAPSA remission, and PASS, respectively. Mean PsAID was significantly lower in patients reaching any of the treatment targets ($p < 0.0001$). Unadjusted associations with PASS ($p < 0.25$) were: age, BMI, level of education, work situation, smoking, debut pattern, DIP disease, family history of PsA, ischemic heart disease, obesity, CRP, NSAID use, corticoids use, structural damage in hands, and sindesmophytes. Involvement of DIP joints (OR 0.40, 95%CI: 0.20-0.79, $p = 0.009$), PsA family history (OR 0.25, 95%CI: 0.09-0.72, $p = 0.010$) and higher CRP values (0.92, 95% CI: 0.85-0.99), $p = 0.036$, decreased the odds of PASS in the multivariate model.

Conclusion: More than half of patients treated with systemic therapies under routine clinical practice reach a PASS status according to the PsAID. The involvement of DIP joints, higher CRP levels and PsA family history are associated with lower odds of achieving that status.

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Abstract Number: 1392

Decreased Injection Site Pain Associated with New Etanercept Formulation in Patients with Rheumatoid Arthritis or Psoriatic Arthritis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

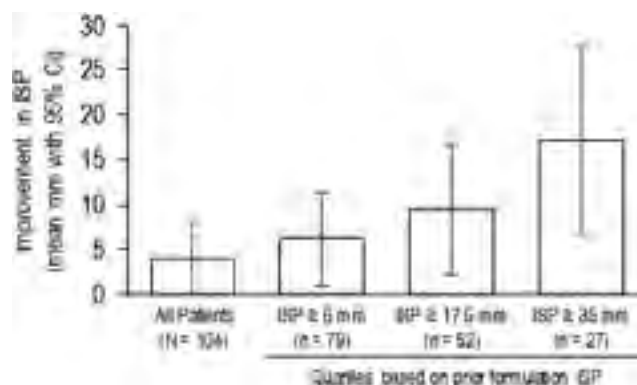
Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Injectionsite pain (ISP) is a component of the patient experience with injectable drugs. A new formulation of etanercept was developed to reduce ISP. In this work, we assessed ISP associated with a new formulation of etanercept compared to the prior formulation in patients with rheumatoid arthritis (RA) or psoriaticarthritis (PsA).

Methods: This phase 3b, randomized, double-blind, 2-period, 2-sequence crossover study (NCT02986139) enrolled etanercept-naïve patients with RA or PsA (inclusion based on the Classification criteria for Psoriatic Arthritis [CASPAR criteria]). The 2-week treatment period was followed by a 30-day safety follow-up. Patients were randomized 1:1 to prior formulation first followed by new formulation or new formulation first followed by prior formulation; administered 1 week apart, consistent with labeled dosing (50mg weekly). ISP was assessed within 30 seconds after administration and was measured using a validated ISP scale based on a visual analog scale ranging from 0 mm (no pain at all) to 100 mm (worst pain imaginable).

Results: Of 111 patients enrolled (56 prior 77.5%/new sequence; 55 new/prior sequence), 77.5% had RA, 22.5% had PsA. Of these, 104 patients received both doses. Overall, the mean change (least squares mean; 95% confidence interval [CI]) in ISP between prior and new formulations was 4.0 mm (0.03, 7.98) (Table). Patients with higher ISP scores from the prior formulation (by quartile cut points) had greater ISP improvements with the new formulation (Table, Figure). The reduction in ISP(95% CI) for those with prior formulation ISP scores above the arithmetic mean(23.6 mm) was 12.2 mm (3.1, 21.3) and for those below the mean was -0.9 mm(-3.9, 2.1). Injection site reactions were few in number and similar between formulations.



Conclusion: The new formulation of etanercept was associated with lower mean ISP compared to the prior formulation. Patients with higher levels of pain with the prior formulation showed greater pain reduction with the new formulation.

	n	Prior Formulation Mean ISP (mm)	New Formulation Mean ISP (mm)	Reduction in ISP Mean (95% CI) [%]	P-value
All patients	104	23.1	19.1	4.0 (0.03, 7.98) [17.3%]	0.048
Cut point analyses based on: Prior formulation ISP quartiles					
≥ 6 mm	79	30.8	24.5	6.2 (1.1, 11.3) [20.2%]	0.017
≥ 17.5 mm	52	43.4	33.9	9.5 (2.3, 16.8) [22.0%]	0.011
≥ 35 mm	27	58.0	40.8	17.2 (6.6, 27.8) [29.6%]	0.003
Prior formulation ISP mean					
≥ 23.6 mm	39	52.3	40.1	12.2 (3.1, 21.3) [23.3%]	0.01
< 23.6 mm	65	9.1	10.1	-0.9 (-3.9, 2.1) [-10.2%]	0.539

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Abstract Number: 1393

Fatigue in Men and Women with Psoriatic Arthritis: An International Qualitative Study

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Fatigue is prevalent and important to people with psoriatic arthritis (PsA)¹. Women with PsA have worse symptom and life impact scores than men, including fatigue², and men are more likely to reach PsA remission³. We aimed to identify how patients experience fatigue in an international qualitative study conducted to identify PsA domains for clinical trials⁴. Prior research suggested possible differences in how men and women experience fatigue.

Methods: We conducted and audio-recorded focus groups (FG) in six countries (Australia, Brazil, France, Netherlands, Singapore, US) and in-depth interviews in the US with participants with PsA. Two bilingual moderators (native and English languages) facilitated each FG in the native language using broad areas of inquiry: experience of, and life changes since, diagnosis; disease activity; key PsA features; and medical care. Recordings were transcribed verbatim, translated into English, checked for accuracy, and imported into Atlas.ti qualitative software. Two qualitative researchers coded each transcript independently using an iterative comparative process. Codes were reconciled and organized into themes. In analyzing fatigue, we considered variability by participant category (men/women).

Results: There were 16 FG with 2-9 participants each and 90 participants in total; and 25 in-depth interviews (Table1). We identified the following themes that describe the experience of fatigue for patients with PsA: 1) intersection of PsA disease activity and fatigue, 2) fatigue meaning and explanatory theories, 3) attitudes and communication about fatigue, 4) strategies people use when living with fatigue, and 5) feelings associated with fatigue. We found differences between men and women especially for attitudes and communication, and feelings/emotional impact associated with fatigue. Women

were more likely to discuss sharing their fatigue experience and relying on close relationships for support. Men were more likely to describe seeking control and not communicating their fatigue. Both men and women reported associating fatigue with negative attitudes (Table2).

Conclusion: The experience of fatigue in PsA is diverse and there are variations between men and women. Fatigue impacts what people do, how they communicate and how they feel. This has implications for fatigue assessment and treatment in PsA. Patients may benefit from provider validation of their fatigue and from individualized treatment strategies.

References: 1. Gossec L. Ann Rheum Dis 2014; 2. Holland R. Ann Rheum Dis 2018 ; 3. Theander E. Ann Rheum Dis 2014; 4. Orbai AM. Ann Rheum Dis 2017;

Table 1. Patient characteristics by country.

Participant characteristics (N=115)	Australia 2 FG, n=8	Brazil 3FG, n=12	France 2FG, n=12	Netherlands 2FG, n=18	Singapore 2FG, n=13	USA	
						5FG, 3 sites, n=27	Interviews, 1 site, n=25
Women n (%)	6 (75)	8 (67)	5 (42)	10 (56)	6 (46)	17 (63)	16 (64)
Age mean (SD) yrs	58 (10)	60 (9)	55 (14)	57 (12)	45 (15)	53 (11)	53 (11)
PsA duration mean (SD) yrs	11 (9)	12 (9)	6 (6)	13 (8)	5 (5)	13 (12)	12 (11)
MHAQ (0-3)	0.7 (0.6)	0.9 (0.6)	0.5 (0.6)	0.6 (0.5)	0.2 (0.4)	0.3 (0.3)	0.3 (0.4)
Pain VAS (0-100)	47 (33)	56 (25)	29 (28)	45 (24)	15 (19)	38 (33)	38 (28)
Patient global VAS (0-100)	51 (35)	76 (19)	32 (30)	46 (24)	23 (25)	42 (31)	34 (30)
Patient global joints (0-100)	56 (36)	73 (18)	34 (29)	51 (24)	20 (22)	38 (33)	40 (29)
Patient global skin (0-100)	38 (35)	61 (40)	32 (32)	20 (20)	31 (26)	29 (27)	31 (34)
Fatigue VAS (0-100)	55 (25)	54 (38)	34 (33)	53 (28)	19 (20)	47 (32)	38 (32)
Stiffness VAS (0-100)	50 (34)	62 (29)	30 (31)	47 (30)	21 (25)	42 (34)	41 (29)
DMARD (%)	100	58	92	50	77	56	36
Biologic (%)	12	1	33	55	54	67	64

Abbreviations: FG focus group, SD standard deviation, MHAQ Modified Health Assessment Questionnaire, VAS visual analog scale, DMARD disease modifying anti-rheumatic drug (most commonly methotrexate, less common leflunomide, sulfasalazine or apremilast).

Table 2. Illustrative quotes for each theme from participants with psoriatic arthritis

Themes	Representative quotes
1. Intersection of PsA disease activity and fatigue	<i>I am still wondering whether fatigue, which already played a role for a long time in my life, has anything to do with it. Maybe that is linked to [PsA] while I also have linked it to the way I cope with stress. (M2.3, Netherlands)</i> <i>Fatigue, in the morning, when I was suffering the most, it would take me a long time even to think about getting out of bed, and it is not just the stiffness, it is just absolute tiredness. It is not about strength, it is about just feeling really, really, tired, physically unable to roll out of bed. (W1.1, Singapore)</i> <i>I think it was just a real fatigue syndrome, because I got stiff, I got sore, I stopped pretty much all physical activity, I was just going through the motion of getting through all that I had to do in a day. But there was nothing, there was no recreational joy or release. I was just miserable. (W22, US)</i>
2. Fatigue meaning and explanatory theories	<i>For me, it is the illness that is wearing me out. (W1.3, France)</i> <i>When I first fell ill, my medication indeed made me extremely tired. Nowadays this is not so much the case anymore. (M1.3, France)</i> <i>Not really pain but I do not have much energy, I feel a bit weak. If I did not take my medicine. Pain for me is not so much. (M2.1, Singapore)</i>
3. Attitudes and communication about fatigue	<i>You cannot show your fatigue to others, you need to support your family. (W2.2, France)</i> <i>None of my co-workers are aware of my illness. [...] Chances are that the people around you will think that they cannot rely on you. [...] I do not want them to judge me as an unable-bodied person. When the fatigue kicks in, I take a short leave of absence. (M1.1, France)</i> <i>I do not allow myself to be tired. I have pain, not always, especially in the hands. That restricts me somehow. (M2.1 Netherlands)</i> <i>I am functional, and I do not want to admit that I have fatigue with anybody, but sometimes I get tired, I just want to take a nap. (M1.1 US)</i>
4. Strategies people use when living with fatigue	<i>If you have a dinner party, you are going to have 3 days to recover. Therefore, you just cannot be bothered. (W1.2, Australia)</i> <i>When I am very tired then I just go and lie in bed for an hour. Then I can do something again. I just need to go flat for a moment and then I take another pain reliever and then, everything just must go on. That seems to be going well. (M2.2, Netherlands)</i> <i>I don't feel like going out at all, my wife, let's go out for lunch or meal, I said I'm sorry, I'm not joining you all, but somehow, I am able to go to church in the morning. After that, when I come back home, I will not go out again. (M1.1, Singapore)</i>
5. Feelings associated with fatigue	<i>At times I cry because I want to do things, I am used to doing my housework. I do it, but it is not like it was before, it wears me out a lot, I get tired. (W2.1, Brazil)</i> <i>I had to stop completely all my sports activities to ensure saving my energy level for my job. [...] You develop a feeling as if... you feel incapacitated. You try to hang on to your essential daily routines. You really have to fight for it. (W2.2, France)</i> <i>I also think that you become frustrated, stressed out because of your fatigue. (W1.2, Netherlands)</i> <i>For me it is the fatigue and the pain that make me depressed. (W1.1, Singapore)</i>

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Abstract Number: 1394

Development and Pilot of a Patient Satisfaction Scale in Rheumatology

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Patient satisfaction has been studied as a performance improvement measure in clinical practice among patients with a variety of diseases, but to date there are no validated scales that evaluates it in rheumatic diseases. As part of the Patient Centered Care project in the Rheumatology Division, we developed and piloted a simple questionnaire to study patient satisfaction with the care they receive for their arthritis.

Methods: We developed a 12-item scale, and tested it on 70 patients in the Rheumatology clinic at Stanford University Hospital and Clinics. Based on these responses, we subsequently tested a revised 10-item scale (5 items targeting helpfulness of rheumatology team, and 5 items targeting satisfaction) on a national self-selected sample of 130 arthritis patients. Demographic data were collected including age, gender, race and ethnicity, country of origin, years of education, and perception on rheumatology team members. Following psychometric analysis of this larger sample, we developed a shorter and reliable six-item patient satisfaction scale.

Results: Our sample (N=130) characteristics included 94% female, 88.4% self-identified as Caucasian, 3.9% Asian, 6.2% Black/African-American and 8.7% Hispanic/Latino ethnicity. Majority of patients (44.6%) were 60-69 years old, and 41.5% had a College degree. 37.7% identified a rheumatologist as part of their rheumatology team, whereas 39.2% mentioned other (e.g. PCP), 13.1% were not sure of the composition of their team, and only 10% mentioned their medical assistant. In addition, 82.9% identified themselves as part of their rheumatology team. 38.5% were seeing a rheumatologist. For the final scale development, we included only items with correlations below 0.9 to reduce redundancy in items. The final scale included 6 items (Table 1). Reliability of the final scale was very high; coefficient Alpha was 0.94 (raw) and 0.95 (standardized). Based on the results of this survey, mean patients satisfaction factor was 6.1 ± 2.7 . Item scale correlations ranged from 0.60 to 0.87. The only demographic variable found to be correlated with satisfaction was identifying a rheumatologist as part of the rheumatology team (correlation 0.37 ± 0.5 , p -value $< .0001$).

Conclusion: A simple and practical questionnaire to measure patient satisfaction with their rheumatology care was developed and piloted on 130 patients. This is a condition-specific scale, which may be useful in determining satisfaction with specific practices and possibly physicians.

Table 1. Items included in final rheumatology patient satisfaction scale

On a scale from 1 to 10, how satisfied are you with how your arthritis team works with you to:

1. Know more about your arthritis
2. Get to see your team when you feel you need to see them
3. Solve problems related to my arthritis
4. Set goals for the treatment of my arthritis
5. Manage your emotions related to arthritis
6. Decide when I need to make an office visit for my arthritis

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Could the Shortening of the Electronic Osteoarthritis Knee and Hip Quality of Life (OAKHQOL) Questionnaire Improve Its Metric Properties?

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

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Background/Purpose: The aim of this study was to assess the validity of a short version of the electronic OAKHQOL questionnaire in a combined analysis with classical test theory (CTT) and a Rasch measurement model for item response theory.

Methods: Patients with knee osteoarthritis (ACR criteria) were consecutively recruited by their general practitioners. They responded to the electronic version of the OAKHQOL questionnaire, called e-OAKHQOL¹. It contains 43 items and describes health-related quality of life (HRQoL) in 5 dimensions: physical activity, mental health, pain, social functioning and social support. Each total score is normalized to a score from 0 (worst HRQoL) to 100 (best HRQoL). A shortened version of the OAKHQOL has been developed, the mini-OAKHQOL. It retains 20 items of the original instrument and maintains the same structure with five dimensions. The scoring method was kept as the original, for items and dimensions. For the present study, only items of the e-OAKHQOL retained in the mini-OAKHQOL were included in the statistical analysis. Metric properties were assessed by the CTT approach and a Rasch measurement model (partial credit model).

Results: The confirmatory factor analysis showed that the five-factor model best fitted the data (RMSEA= 0.067 (90% confidence interval: 0.059-0.075), CFI=0.94, TLI=0.93). Cronbach's alpha coefficients were good to excellent for four of the five subscales. As expected, discrimination was good for the physical activity and the pain dimensions. In Rasch analysis, one item ("Staying for a long time in the same position") showed underfit (item not discriminative enough). A lack of fit to the model was observed for the social support and the social functioning dimensions (significant item-trait interaction). Internal consistency was excellent for the physical activity (Person Separation Index (PSI) = 0.92) and pain (PSI = 0.84) dimensions but were less than 0.80 for the other dimensions. Examination of person-item threshold distribution map demonstrated good targeting between persons and items in the physical activity and the pain dimensions while it was fairly good in the three other dimensions. No statistical differential item functioning was detected for all 5 dimensions by gender, age, educational level, low-back pain or body mass index.

Conclusion: Analysis with CTT and Rasch measurement of the mini e-OAKHQOL questionnaire revealed the good measurement properties of the 5 dimensions of the questionnaire. The shortening of the e-OAKHQOL has considerably improved its structural properties. However, some shortcomings remain such as item-trait interaction. Further research is needed to confirm or refute these findings in an independent sample.

Reference: ¹ Wiecezorek M, Rotonda C, Guillemin F, Rat AC. The Electronic Osteoarthritis Knee and Hip Quality of Life (OAKHQOL) Questionnaire: A Useful and Valid Alternative to Measure Health Related Quality of Life in Knee Osteoarthritis [abstract]. Arthritis Rheumatol. 2016; 68 (suppl 10)

Disclosure: M. Wiecezorek, None; C. Rotonda, None; J. Epstein, None; F. Guillemin, None; A. C. Rat, None.

Factors Associated with Specific Quality of Life Evolution in SLE Patients: A French Prospective Longitudinal Multicenter Study

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Session Information

Session Date: Monday, October 22, 2018

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To analyze variables associated with evolution of disease-specific health related quality of life (HRQoL) in systemic lupus erythematosus (SLE) patients.

Methods: We conducted a prospective longitudinal multicenter French cohort of SLE patients followed over 2 years. All patients fulfilled ACR 1997 SLE criteria. Disease-specific HRQoL was evaluated using Lupus Quality of Life (LupusQoL) and Systemic Lupus Erythematosus Quality of Life (SLEQOL) every 3 months. Domain scores were rescaled from 0 to 100 (best HRQOL). Disease Activity (DA) and flare were recorded every six months utilizing SELENA-SLEDAI, SELENA-SLEDAI Flare Index (SFI) and revised SELENA-SLEDAI Flare Index (SFI-R). Each SLEQOL and LupusQoL domains' scores evolution were explained by fitting a multivariate linear mixed model. For each independent variable, interaction with time was tested to see if was linked with a greater decline in HRQOL. Social deprivation is defined it as an unstable state concerning one or more basic securities (a job, health, family status) that prevented people from enjoying fundamental rights and that could lead to poverty. It was identified as having an EPICES score greater than 30.

Results: Between December 2011 and July 2015, 336 patients were included (89.9% female). Mean (SD) SELENA-SLEDAI was 3.9(4.3). Twenty-two percent were taking immunosuppressive drugs. Each HRQoL domain was significantly impaired in patients with a poor social deprivation status (mean difference in HRQoL score ranging from -9 to -15, $p<0.01$ in all domains). Social deprivation was also associated with a greater decline in HRQOL scores across visits in two domains: LupusQoL Physical Health (p for interaction with time $p=0.03$) and fatigue (p for interaction with time: $p=0.02$). SFI flares were significantly associated with a decrease in the following domains of LupusQoL Pain, Planning, Emotional Health and Burden to Others) and SLEQOL (Physical Functioning, Symptoms and Mood; $p<0.05$) SFI-R musculo-skeletal flares resulted in a significant decrease in all domains of the SLEQOL and LupusQoL (mean difference ranging from -5 to -15 points difference with $p<0.01$), interaction with time being significant in the LupusQoL Pain (-0.5 every 3 months, $p=0.03$) and SLEQOL Social Activities domain scores (-0.6 every 3 months, $p<0.01$). Corticosteroids daily dosage >10 mg was associated with significant decrease of the Body Image LupusQoL score: -6 ($p<0.05$) without time interaction.

Conclusion: Variation in disease activity, according to SFI and SFI-R, is associated with specific HRQoL evolution, independently of patient's other characteristics. musculoskeletal flares negatively impacted both disease specific HRQoL tools in SLE. Socio-economic status is a major risk factor of HRQoL decline for SLE patients and thereby should be recorded to allow a correct interpretation of HRQoL, and to identify those at risk, so that appropriate interventions can be targeted to those at risk.

Disclosure: H. Devilliers, GSK, 2; M. Corneloup, None; F. Maurier, None; D. Wahl, None; G. Muller, None; O. Aumaître, None; P. Sève, AbbVie Inc., 5, Novartis, 5; G. Blaison, None; J. L. Pennaforte, None; T. Martin, None; N. Magy, None; S. Berthier, None; L. Arnaud, GSK, 2, 5, AstraZeneca, 5, Roche, 5, Janssen, 5, Eli Lilly and Co., 5, Novartis, 5, UCB, Inc., 5; A. Bourredjem, None; Z. Amoura, None.

Abstract Number: 1397

Item Responses to Disease-Specific Quality of Life Questionnaires in the 18 Months Following a Flare in SLE: An Item Response Theory Analysis of a French Prospective Longitudinal Multicenter Study

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To explore, at an item-level, the effect of disease activity (DA) on disease specific health related quality of life (HRQoL) factors in systemic lupus erythematosus (SLE) patients using an item response theory (IRT) longitudinal model.

Methods: This prospective longitudinal multicenter French cohort followed SLE patients over 2 years. All patients fulfilled ACR 1997 SLE criteria. Disease specific HRQoL according to LupusQoL and SLEQOL was collected every 3 months. DA according to SELENA-SLEDAI, and flare assessment according to SELENA-SLEDAI Flare Index (SFI) and organ-based revised ELENA-SLEDAI Flare Index (SFI-R) was evaluated every 6 months. Response to SLEQOL and LupusQoL items were compared between remitting and non-flaring patients, in the 18 months following a flare, using an IRT approach fitting a linear logistic model with relaxed assumptions for each dimension of the questionnaires. Parameters estimations for an item are interpreted as a difference in improvement measured by a given item according to QoL in given domain resulting in being remitting from a flare compared to patients with no flare. A parameter is considered statistically significant when different from 0 according to its 95% confidence interval.

Results: Between December 2011 and July 2015, 336 patients were included (89.9% female). Mean (SD) SELENA-SLEDAI score was 3.9(4.3). twenty-two percent were taking immunosuppressive drugs. Among patients remitting from an SFI-R musculoskeletal flare (image 1), remission led to significant improvement in HRQoL among items of LupusQoL in the physical health and pain domains (going to the market, pain interference with the quality of sleep), and SLEQOL physical functioning, symptoms and treatment domains (walking 3 km, joint pain, fear of needles, inconvenience of clinic visits). SFI-R Cutaneous flares impacted items related to self-image issues and intimate relationships (anxiousness, attractiveness linked to skin rashes, being less interested in sex or sexual relationship). Patients HRQoL remained adversely impacted up to 18 months after a flare. LupusQoL Item "weight gain due to treatment" was negatively impacted after an osteoarticular flare.

Conclusion: IRT analyses pinpoint HRQoL items most important to patients in specific situations. LupusQoL and SLEQOL items related to physical HRQoL (physical health, physical functioning and pain domains) were most influenced by musculoskeletal or cutaneous flares.

Image 1 : summary of significant HRQoL changes in remitting patients compared with non-flaring patients for one item with both modeling features (a model estimating variations between time points - baseline to 6, then to 12 and to 18 months - and a model considering a constant amount of change between time points).

LupusQoL Domain	Impacted item	Flare involved	HRQoL changes of remitting patients regarding non-flaring ones
Physical health	2 - need help to do moderate physical jobs	Renal	↑
	3 - need help to do light physical jobs	Constitutional symptoms	↑
	7 - going to the market	Orthopaedic	↑
Pain	9 - prevented from performing activities like I would due to pain	Cutaneous	↑
	10 - the pain I experience interferes with the quality of my sleep	Orthopaedic Cutaneous	↑
	11 - the pain due to my lupus is so severe that it limits my mobility	Cutaneous	↑
Planning	14 - commitment issues	Constitutional symptoms	↑
Intimate relationship	15 - less interested in sexual relationship due to pain	Cutaneous	↑
	16 - not interested in sex because of my lupus	Cutaneous	↑
Burden to others	17 - concern that my lupus is stressful for those closer to me	Constitutional symptoms	↑
Emotional health	23 - my lupus make me anxious	Cutaneous	↑
Body image	27 - my appearance makes me avoid social situations	Neurological or psychiatric	↓
	28 - lupus related skin rashes make me feel less attractive	Cutaneous	↑
	29 - The hair loss I have experienced makes me feel less attractive	Renal	↑
	30 - weight gain due to my treatment makes me feel less attractive	SFI Orthopaedic	↓
Fatigue	33 - I need to have early nights	Neurological or psychiatric	↑
STARQoL domain			
Physical functioning	1 - walking outdoors on level ground	Cutaneous	↑
	2 - Shopping	SFI	↑
	4 - Going to the market	SFI	↑
	6 - walking 3 km	Orthopaedic Cutaneous	↑
Activities	9 - missed work or school	Renal	↑
	11 - sports	SFI	↓
	12 - sex	Constitutional symptoms	↑
	13 - difficult social activities	Renal	↑
Symptoms	17 - loss of appetite	Renal	↑
	22 - sore skin	Cutaneous	↑
	23 - joint pain	Orthopaedic Cutaneous	↑
Treatment	24 - fear of needles	Orthopaedic	↑
	27 - inconvenience of clinic visits	Orthopaedic	↑
Mood	29 - feeling low	Neurological or psychiatric	↑
	30 - depression	Neurological or psychiatric	↑
	31 - anxiety	Neurological or psychiatric	↑
Self-image	37 - trouble because of concern medicines don't	SFI	↑
	40 - consuming more alcohol or tobacco	Cutaneous	↑

Legend for image 1

- ↑ Significant HRQoL improvement of remission patients compared to non-flaring patients present with both IJRA modelling features (following estimator' variations between time points (baseline to 6, then to 12 and to 18 months) and model considering a constant amount of change between time points)
- ↓ Significant HRQoL deterioration of remission patients compared to non-flaring patients present with both IJRA modelling features

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Inflammatory Arthritis DMARD Adverse Effects Are Pervasive and Can Greatly Impact Quality of Life and Work and Social Roles: Initial Results from the Omeract Safety Working Group

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: There is suboptimal reporting of adverse events (AE) in trials. The OMERACT Safety Working Group is developing a patient-centered AE collection and reporting approach to complement existing methods. Our initial goal was to hear from inflammatory arthritis (IA) patients about their perspectives on the benefit-harm balance of DMARDs.

Methods: Using an interview schedule, experienced interviewers conducted focus groups with IA patients in the US (n=14), Canada (n=10), and Australia (n=15) that were recorded, transcribed, and analyzed using a pragmatic thematic analysis approach based in grounded theory.

Results: Almost all patients reported AE ranging from mild to severe. The majority learn to live with AE, but some lives were completely changed.

"It was like I was domiciled on the toilet. . . I couldn't go anywhere because you never knew when you needed a toilet." (M 60s, CA)

"I'm on MTX and I'm finally friends with it. It took 2 years. . . I feel normal. . . except med day. . . But I'm happy to give up half a day. . . to have my life." (F 20s, USA)

Many patients reported making adjustments to diet, sleep, and lifestyle to address AEs. Patients used different complementary and alternative approaches to self-manage their AEs but continued to live with ongoing disruption of function, self-confidence, work, and social roles due to AE.

"I feel like I can't think anymore, and that really affects my work. And that's my biggest problem. I can push through the pain and. . . fatigue, but I can't think clearly. I just can't do my job." (F 30s USA)

The cumulative burden of AEs often led to patient-initiated discontinuation.

"I would open the fridge and look at the little brown envelope that the syringes were in. The nausea would start just looking at the envelope. . . I took it for a few more years, but I just couldn't stand it anymore. It's just like, get me off of this stuff." (M 70s CA)

Underreporting was common due to embarrassment and uncertainty whether and how to discuss AEs. Providers were often perceived to react with disinterest, minimization, or irritation. Long-term safety was less concerning to patients with longer IA duration who had more symptoms and decreased function but greater treatment benefits despite repeated drug failures and serious AE.

Conclusion: The prevalence and importance of AEs, especially "nuisance AEs" is viewed differently by patients and clinicians. AEs negatively impacted function, participation, and QOL. Acceptability, tolerability and self-management of SEs varied among patients, by drug type and life stage, and in response to disrupted social and work roles. Patients learned to underreport SE when they perceived disinterest/minimization by clinicians.

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Abstract Number: 1399

Assessing a Conceptual Framework of Quality of Life in a Cutaneous Lupus Erythematosus Population

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: In order to better discern medication efficacy for CLE, a better understanding of CLE's impact on quality of life (QoL) in individuals with CLE is required. Further, the use of a theoretical framework allows for the development, validation, and eventual use of patient-reported outcome measures that identify empirical factors significantly impacting QoL of patients with CLE. Thus, the purpose of this study was to examine multiple factors associated with CLE that affect QoL, using the Revised Wilson and Cleary's Model (WCM) for QoL. The WCM is a disease-based, physiological framework that links biological and physiological factors, symptoms status, functioning, general health perceptions, individual and environmental characteristics, and overall QoL.

Methods: A cross-sectional, correlational study was conducted in 101 CLE patients recruited from an outpatient university-based dermatology clinic in Dallas, Texas. Demographic, clinical characteristics, and QoL data were collected from patients. Descriptive statistics were calculated, and multiple regression was employed to determine significant ($p < 0.05$) predictors of overall QoL. Data were analyzed using SPSS v24.

Results: The overall QoL - CLEQoL regression model was significantly different from zero, $F=24.96$; $df=14, 76$; $p < 0.001$. Approximately 85 percent of the variation in overall QoL ($R^2=0.85$) was accounted for by predictor variables within the WCM model, where the adjusted R^2 was 82 percent ($R^2=0.82$). Disease activity ($\beta=0.13$, $p=0.027$), fatigue ($\beta=0.24$, $p=0.002$), and body image ($\beta=0.62$, $p < 0.001$) were significant, positive predictors of overall QoL while controlling for other predictor variables ($\beta=0.19$, $p=0.03$). Pain ($\beta=-0.23$, $p=0.019$) and side-effects ($\beta=-0.13$, $p=0.041$) were negative predictors of overall QoL. Patients who experienced higher levels of disease activity, higher fatigue severity, and greater degree of body dissatisfaction had significantly poorer QoL. Lower pain intensity and fewer side effects experienced from CLE medications were significantly associated with higher QoL.

Conclusion: Hence, in addition to performing thorough skin exams, asking patients about symptoms, body perception, and medication toxicities can aid providers in better understanding CLE's impact on patients' QoL. Using a theoretical framework, patient-centered and clinical outcomes were integrated to facilitate a fuller understanding of the several factors impacting QoL in CLE patients. As such, future studies aimed at understanding QoL in CLE patients can consider using a theoretical framework as healthcare becomes more patient-centered.

Disclosure: M. E. Ogunsanya, None; A. Hudson, None; R. Vasquez, None; B. F. Chong, Biogen Incorporated, 2, Daavlin Incorporated, 2, Celgene Corporation, 5, Pfizer Incorporated, 9.

Abstract Number: 1400

Effects of Childhood-Onset SLE on Academic Achievements and Employment in Adult Life

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To investigate the effects of cSLE on education, vocation and employment in a large cohort of adults with cSLE.

Methods: Patients were seen by the CHILL-NL (CHILdhood Lupus in the NetherLands) study team for a single study visit containing a structured history and physical examination. Medical records were retrieved to supplement the information obtained during the study visit. Education and employment status were assessed by structured and/or validated questionnaires. Health-related quality of life (HRQOL) was measured with the SF36.

Results: 106 cSLE patients (93% female, 73% white) were included with median disease duration of 20 years. Almost all patents stated that the disease had influenced their education but level of completed education was higher than the general Dutch population. Half of patients had adjusted their vocational choice due to the disease but still 44% of patients who had finished education did not have a paid job. Of the employed patients, the majority (61%) worked part-time. Disease damage was more prevalent in the patients without paid employment. A high percentage of patients (51%) were declared work disabled and this was related to damage, specifically neuropsychiatric damage. Not having paid employment and work disability were closely related and both had a clear negative influence on HRQOL.

Conclusion: The effect of cSLE on academic achievements and employment is substantial, despite adjusting educational and vocational choices to the disease. Ongoing support, not only to help patients find suitable education and vocation, but also to offer guidance regarding potential adjustments during their career, is necessary to optimise participation in the community.

Disclosure: N. Groot, None; M. Bijl, None; R. J. E. M. Dolhain, None; E. J. Zirkzee, None; R. D. E. Fritsch-Stork, None; Y. K. O. Teng, None; K. de Leeuw, None; I. E. M. Bultink, None; S. S. M. Kamphuis, None.

Abstract Number: 1401

Is There a Specific Effect of Jak-Inhibitors on Pain and Fatigue in Rheumatoid Arthritis?

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Session Information

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Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Pain and fatigue are common symptoms for patients with rheumatoid arthritis (RA). JAK inhibitors (JAKi) already proved similar efficacy on disease activity as bDMARD (anti-TNF, anti-IL6, abatacept and rituximab). Moreover, some trials suggest that JAKi may have a supplementary interest on the patient's reported outcomes (PRO). Based on a systematic review of the literature, our goal was to determine the impact of each treatment on the pain and fatigue.

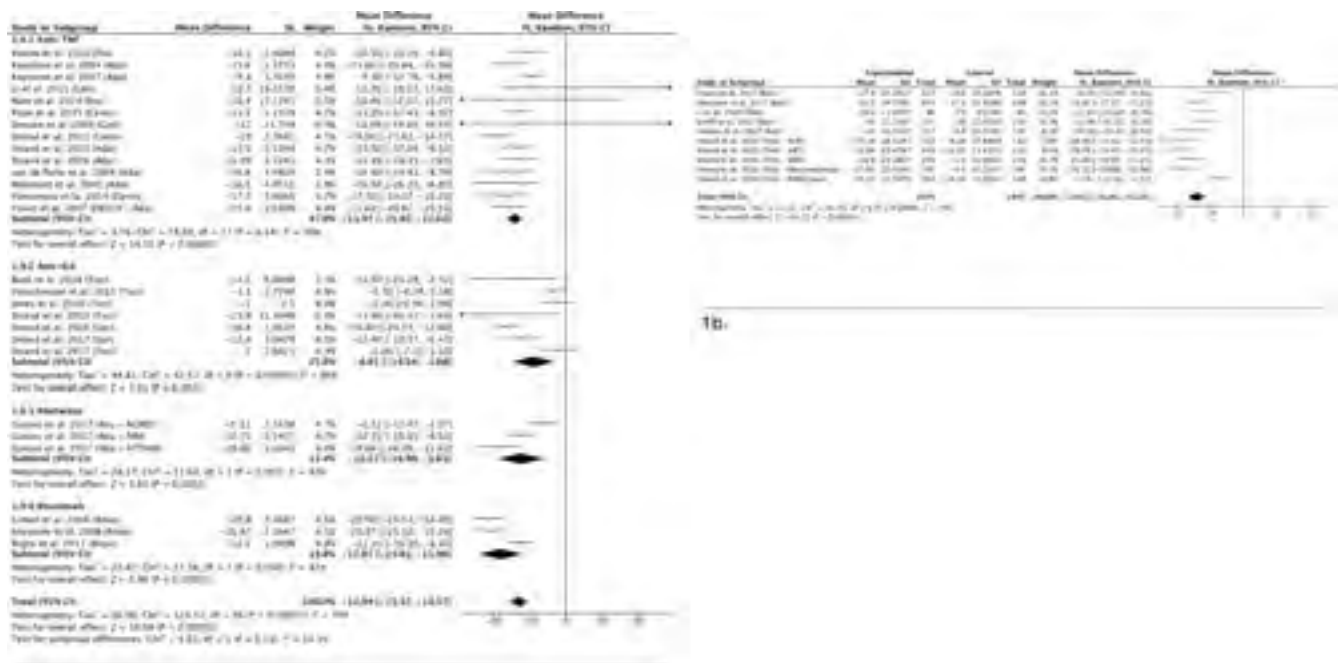


Figure 1. Improvement of pain with bDMARDs (1a) and with JAKi (1b)

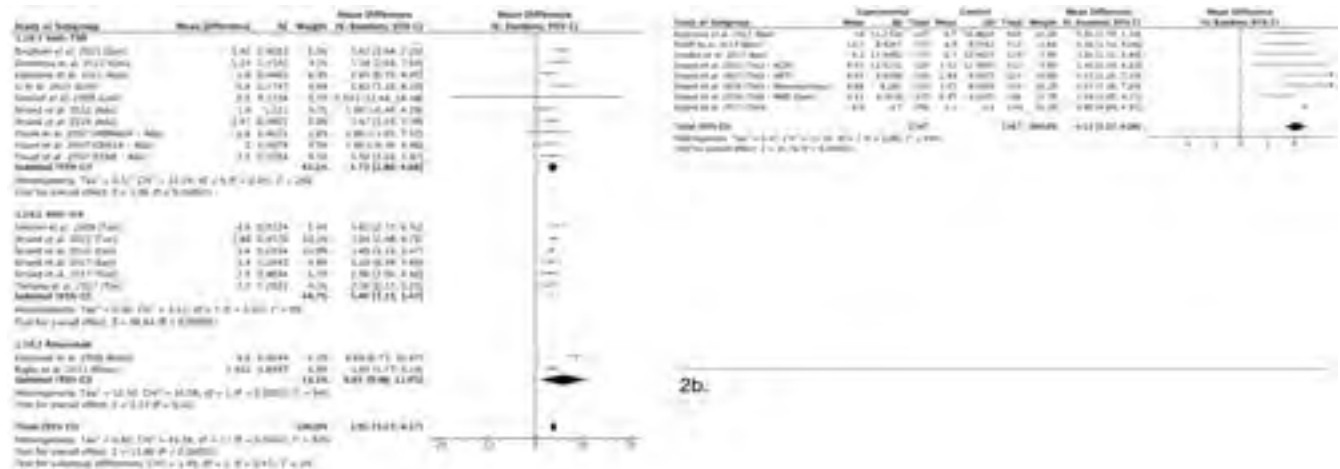


Figure 2. Improvement of fatigue (FACIT) with bDMARDs (2a) and JAKi (2b).

Methods: We screened the literature for clinical trial comparing biological DMARDs or one of the JAKi to placebo for pain and/or fatigue, using PubMed , Cochrane Library, Embase. For JAKi, we restricted our investigation to baricitinib and tofacitinib that are registered by the FDA and the EMA in RA treatment. Among 1488 articles initially identified, 33 randomized controlled trials evaluated pain VAS and 17 investigated fatigue using the FACIT-F score were selected. Data was extracted independently by two authors. For each study, we calculated the change of VAS pain and FACIT between baseline and study endpoint for the DMARDs and the placebo. Meta-analyses were performed to estimate pooled mean difference (MD) with their 95% confidence interval using the inverse variance approach. Heterogeneity was assessed (Cochran's Q-test and I^2).

Results: The result of pain improvement with all bDMARDs versus Placebo is MD:-12,94 (IC95% (-15,32; -10,57); $I^2=79\%$). In subgroup analysis, for antiTNFs MD: -13.97 (IC95% (-15,92; -12,02); $I^2=30\%$), for anti-IL6 MD:-8,81(IC95% (-14,54;-3,08); $I^2=86\%$), for AbataceptMD: -12,27 (IC95% (-18,90; -5,63); $I^2=83\%$) and for Rituximab MD:-17,87 (IC95% (-23,85; -11,9); $I^2=82\%$). For the JAKi, improvement of pain is MD: -13,81 (IC95% (-16,46 ; -11,16); $I^2=70\%$)(figure 1).

Fatigue improvement with bDMARDs versus Placebo is MD: 3,92 (IC95% (3,27; 4,57); $I^2=63\%$). In subgroup analysis, for antiTNFs MD: 3,73 (IC95% (2,80;4,66); $I^2=26\%$), for anti-IL6MD: 3,4 (IC95% (3,33; 3,47); $I^2=0\%$), and for Rituximab MD: 6,01(IC95% (0,96; 11,05) $I^2=94\%$). For the JAKi, MD: 4,13 (IC95% (3,37; 4,88); $I^2=48\%$) (figure 2).

Conclusion: Our results indicate that the impact of JAKi on pain and fatigue is not significantly different than biologic DMARDs, at least during the short and middle term corresponding to the duration of clinical trials.

Disclosure: I. Odriozola, None; C. S. Coste, None; T. Barnetche, None; C. Richez, None; B. Bannwarth, None; T. Schaeffer, None.

Abstract Number: 1402

The Relationship of Pain, Fatigue and Emotional Distress with Quality of Life in Juvenile Myositis

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Session Information

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Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

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Background/Purpose: Juvenile Myositis (JM) is an autoimmune disease that negatively impacts quality of life (QoL) outcomes via muscle weakness and vasculopathic rashes. The relative contribution of pain, fatigue, and emotional distress to QoL in JM is incompletely understood. In this cross-sectional study, we assessed the relationships of pain, fatigue and emotional distress to QoL in JM.

Methods: JM patient-parent dyads (5-17 yo) were enrolled at routine visits. Descriptive statistics were calculated for demographic and clinical variables. Generic QoL was measured by PedsQL Generic Core Scales (PedsQL-GC) self-report (8-17yo) and parent-proxy report(5-17yo), while Patient-Reported Outcomes Measurement Information System (PROMIS) patient (8-17yo) and parent-proxy (5-17yo) fixed short forms were used to assess depressive symptoms, anxiety, fatigue, and pain interference. Since PedsQL-GC were not normally distributed, multivariable quantile regression was performed with PROMIS domains on the median PedsQL-GC measures.

Results: Seventy-five JM patient-parent dyads were enrolled, with typical demographic features (n =71 [94.7%] with dermatomyositis, n = 59 [78.7%]female, n = 59 [78.7%] white, median age = 11.7 yo [IQR:8.1-14.3]). Descriptive statistics for clinical/patient-reported outcome variables are shown in Table 1. Patient PROMIS Fatigue was significantly associated with PedsQL-GC Physical and Psychological scores across most quartiles. Parent-proxy PROMIS Fatigue was significantly associated with PedsQL-GC Physical scores across all quartiles, but this relationship was not as consistent for PedsQL-GC Psychological scores. While patient/parent-proxy PROMIS Depressive Symptoms, Anxiety, and Pain Interference were significantly associated with most PedsQL-GC Physical and Psychological score quartiles in univariable models (not shown), these relationships did not persist in multivariable models. Table 2 displays statistically significant multivariable quantile regression results.

Conclusion: Our findings demonstrate a uniquely strong relationship between fatigue and physical QoL as measured by both patients and parents. Patient and parent perceptions differed with regards to the relationship of fatigue to psychological QoL, reinforcing the need for both respondents to be engaged. The relationship between disease activity, treatments, fatigue, and QoL warrants further study, as fatigue may be an important target for interventions to improve QoL.

Table 1: Clinical and Patient-Reported Outcome Variable Descriptives

Clinical and Lab Assessments:	Median (IQR)
Physician's Global Assessment of Disease Activity (PGA)	1 (0-3)
Disease Activity Score (DAS) Total	3 (0-6)
DAS-Muscle	0 (0-2)
DAS-Skin	1.5 (0-5)
Childhood Myositis Assessment Scale (CMAS)	52 (47-52)
CPK	103 (77.5-141.5)
AST	27 (21.5-31)
ALT	14 (10.5-18.5)
LDH	237 (210-267.5)
Aldolase	5.2 (4.5-6.2)
Nail fold Capillary End Row Loops (NFC-ERL)	6.6 (5.7-7.2)
Patient-Reported Outcomes*	
<i>PROMIS (pediatric self-report)</i>	
Anxiety	38.8 (33.5-47.4)
Depressive Symptoms	35.2 (35.2-50.9)
Fatigue	34.2 (30.3-48.1)
Pain Interference	39.4 (34-50.2)
<i>PROMIS (parent-proxy report)</i>	
Anxiety	47.2 (34.6-56.8)
Depressive Symptoms	42.2 (36.2-54.6)
Fatigue	44.3 (34.1-54.3)
Pain Interference	38.1 (37.8-59.4)
<i>PedsQL-Generic Core Scales (PedsQL-GC) (pediatric self-report)</i>	
Physical	93.3 (80.5-100)
Emotional	95 (78.8-100)
Social	100 (85-100)
School	85 (72.5-100)
Psychological	90 (79.6-98.3)
Total	90.2 (78-97.8)
<i>PedsQL-GC (parent-proxy report)</i>	
Physical	87.5 (75-100)
Emotional	90 (70-100)
Social	95 (75-100)
School	85 (65-100)
Psychological	83.3 (73.3-96.7)
Total	83.7 (73.9-95.7)

* PROMIS domains reported as t-scores; n = 56 PROMIS patient self-report (except Pain Interference, n = 55); n = 75 PROMIS parent-proxy report; n = 56 PedsQL-GC patient self-report (except PedsQL-GC School, n = 55); n = 73 PedsQL-GC parent-proxy report

Table 2: Multivariable Quantile Regression*

	<u>PedsQL-GC Physical</u>		<u>PedsQL-GC Psychological</u>	
	Regression Coefficient (95% CI)	p-value	Regression Coefficient (95% CI)	p-value
<u>PROMIS pediatric self-report</u>				
á Depressive Symptoms	0.235 (-0.853, 0.413)	0.522	-0.268 (-0.857, 0.217)	0.342
á Anxiety	0.000 (-0.229, 0.854)	1.000	-0.307 (-0.773, 0.055)	0.135
á Fatigue	-0.795 (-1.146, -0.134)	0.021	-0.643 (-1.073, -0.258)	0.003
á Pain Interference	-0.644 (-1.191, -0.099)	0.088	-0.123 (-0.358, 0.100)	0.575
<u>PROMIS parent-proxy report</u>				
á Depressive Symptoms	-0.065 (-0.809, 0.156)	0.845	-0.457 (-1.291, 0.217)	0.225
á Anxiety	0.132 (-0.030, 0.784)	0.621	-0.26 (-1.044, 0.062)	0.341
á Fatigue	-1.082 (-1.512, -0.763)	<0.001	-0.565 (-0.773, 0.068)	0.29
á Pain Interference	-0.365 (-0.732, 0.073)	0.066	0.000 (-0.610, 0.394)	1.000

* Results modeled on the median (0.5 quantile).

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Estimates of Minimally Important Differences and Patient Acceptable Symptom State in Five Patient-Reported Outcomes Measurement Information System Short-Forms Among Individuals with SLE

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Session Information

Session Date: Monday, October 22, 2018

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Session Type: ACR Poster Session B

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Background/Purpose: As the NIH PROMIS (Patient-Reported Outcomes Measurement Information System) measures are used more widely, information is needed to enhance interpretation. Minimally important differences (MIDs; estimate of clinical significance of change; “feeling better/worse”) and patient acceptable symptom state (PASS; state at which patients consider symptoms to be acceptable; “feeling good”) are important components in interpretation. We estimated MIDs and PASS for five PROMIS domains in SLE.

Methods: Data were from the Forward/National Data Bank for Rheumatic Diseases. Participants complete questionnaires every 6 months. In July 2015 to July 2017 (five administrations), 4-item short-forms for 5 PROMIS domains were added: Physical Function, Fatigue, Sleep Disturbance, Pain Interference and Satisfaction with Social Roles. PROMIS scales were scored to derive T-scores scaled to population means of 50 and SD of 10. Changes were calculated for consecutive administrations, yielding 4 change periods. MID estimates were calculated using both anchor- and distribution-based methods.¹ Anchors were comparisons of each domain and overall health to 6 months before (rated as much better, somewhat better, neither better nor worse, somewhat worse, much worse).² Domain-specific comparisons (e.g., “compared to 6 months ago, is your fatigue now...?”) were asked only once; overall health comparisons were asked in all questionnaires. PASS was estimated as the 75th percentile positive score of those who stated their current health was acceptable.³

Results: The number of respondents ranged from 389 – 462 in the 5 administrations. Table 1 shows characteristics of respondents from one administration. Tables 2 and 3 show MID and PASS estimates, respectively.

Conclusion: MIDs for PROMIS scales in SLE appear to be similar to those reported elsewhere (± 2 points).⁴ PASS estimates have not been examined previously for PROMIS. PASS estimates for PROMIS T-scores are 0.5 to 1 standard deviation better than the population mean of 50. Such information will improve interpretation of PROMIS scores and changes in those scores.

References: 1. Revicki D et al. *J Clin Epidemiol* 2008;**61**:102

2. Bellamy N et al. *Arthritis Care Res* 2015;**67**:972

3. Tubach F et al. *Arthritis Care Res* 2012;**64**:1699

4. Hays RD et al. *Ann Rheum Dis* 2015;**74**:104

Table 1. Characteristics of Respondents to July 2017 Questionnaire (N=397)

<u>Sociodemographic</u>	
Age, years	60.6 \pm 12.4
Female, %	94.5
Race, White, %	81.8
<u>Health characteristics</u>	
SLE duration, years	24.2 \pm 12.5
Physician-confirmed SLE diagnosis, %	73.0
Rheumatic Disease Comorbidity Index	2.7 \pm 2.0
HAQ score	0.93 \pm 0.70
Fatigue, NRS†	4.4 \pm 3.0
Sleep problems, NRS†	4.3 \pm 3.1
Pain, NRS‡	3.7 \pm 2.9
Lupus activity, NRS§	2.5 \pm 2.5
<u>PROMIS® scores</u>	
Physical function	42.7 \pm 9.6
Fatigue	55.2 \pm 11.5
Pain interference	56.8 \pm 9.9
Sleep disturbance	53.0 \pm 9.6
Satisfaction with social roles	47.4 \pm 10.3

† Scale: 0=no problem, 10=severe problem

‡ Scale: 0=no pain, 10=severe pain

§ Scale: 0=no activity, 10=severe activity

Values are mean ±SD unless otherwise noted

NRS=numeric rating scale; PROMIS®=Patient-Reported Outcomes Measurement Information System

Table 2. MID Analyses

	Anchor-based analysis				Distribution-based analysis				MID best estimate	
			ΔPROMIS®	SE of measurement		0.35 SD				
				Better*	Worse*	Mean	Range	Mean	Range	Better
PROMIS® scale	Compared with 6 months before									
Fatigue	Fatigue	−2.2	1.8	1.44	1.38–1.52	2.51	2.41–2.67	−2	+2	
	Overall health†	−2.4	1.8							
Pain Interference	Pain interference	−2.1	1.7	2.20	2.19–2.22	3.45	3.43–3.47	−2	+2	
	Pain†	−1.9	1.4							
	Overall health†	−1.4	1.8							
Sleep disturbance	Sleep	−3.0	2.7	4.14	4.00–4.31	3.26	3.13–3.37	−3	+3	
	Overall health†	−2.6	1.0							
Satisfaction with social roles	Social functioning	0.8	−2.1	2.01	1.95–2.06	3.51	3.41–3.61	+2	−2	
	Overall health†	1.2	−2.0							
Physical function	Function†	1.1	−1.2	2.34	2.32–2.35	3.34	3.31–3.64	+2	−2	
	Overall health†	1.1	−1.4							

*Change shown for “somewhat worse” and “somewhat better” groups. “Much worse” and “much better” groups were excluded, as per Bellamy²

†ΔPROMIS® and standardized response mean were averaged over four change periods

Δ=change; MID=minimally important difference; PROMIS®=Patient-Reported Outcomes Measurement Information System

Table 3. PASS Estimates

	Based on “last 48 hours” question	Based on satisfaction with health question*	Best estimate of PASS
Fatigue†	46	47.6	47
Pain interference†	41.6	50.6	42
Sleep disturbance†	46.2	47.1	47
Satisfaction with social roles	64.2	53.3	60
Physical function	56.9	49.8	55

Population mean ±SD T-scores are 50±10

* Scores averaged over four change periods

† Lower scores reflect better health status. Otherwise, higher scores reflect better health status

PASS=patient acceptable symptom state

Disclosure: P. Katz, Bristol-Myers Squibb, 2; E. Alemao, Bristol-Myers Squibb, 1, 3; J. Mukherjee, Bristol-Myers Squibb, 1, 3; K. Michaud, University of Nebraska Medical Center and FORWARD, The National Databank for Rheumatic Diseases, 3, Rheumatology Research Foundation and Pfizer, 2.

Abstract Number: 1404

Responsiveness of Promis (Patient Reported Outcomes Measurement Information System) Measures in a Multi-Racial, Multi-Ethnic Systemic Lupus Erythematosus (SLE) Cohort

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

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Session Time: 9:00AM-11:00AM

Background/Purpose: Recent studies have demonstrated the reliability and validity of the NIH PROMIS (Patient-Reported Outcomes Measurement Information System) measures in SLE. Analyses of their responsiveness to changes in SLE disease and health status have not yet been reported.

Methods: Data were from the California Lupus Epidemiology Study (CLUES), a population-based, multi-ethnic cohort with physician-confirmed SLE. Subjects participated in structured interviews in English, Spanish, Mandarin, or Cantonese. Follow-up (FU) interviews were conducted an average of 12.8 months after baseline. Eight PROMIS short-forms (Tables) were administered and scored to derive T-scores scaled to population means of 50 and SD of 10. Race and ethnicity were self-reported. To determine the PROMIS measures' responsiveness to change, we examined whether PROMIS score changes occurred in the appropriate direction and magnitude for individuals classified as improved or worse for two anchor items: self-rated health (SRH; 5 categories: excellent, very good, good, fair, poor) and self-reported lupus disease activity (Systemic Lupus Activity Questionnaire, SLAQ, score range 0–44). Improvement/worsening in SRH was defined as a 2-category change from baseline to FU (e.g., “good” to “poor”). Improvement/worsening in SLAQ scores was defined as a 4-point change in score (0.5 SD of baseline score). Changes in PROMIS scales from baseline to FU were calculated. Mean PROMIS change scores and standardized response means (SRM; mean change / SD of change) were calculated for the better and worse groups for each anchor item. SRMs were defined as small (0.20), medium (0.50), or large (0.80). Analyses were repeated within each of 4 racial/ethnic groups (white, Hispanic, black, Asian).

Results: 432 individuals completed baseline interviews; 337 have completed FUs to date (83% of eligible). 92% met 4/11 ACR criteria for SLE; the rest either had a diagnosis of lupus nephritis, or met 3 ACR criteria and were diagnosed by a rheumatologist. Mean age was 46 years, mean disease duration was 18 years. 89% were female, 97 (29%) white, 83 (25%) Hispanic, 37 (11%) black, and 120 (36%) Asian. Mean PROMIS changes and SRMs for better/worse groups (all race/ethnicities combined) are shown in the table. SRMs were medium to large for improvement and worsening for all scales except for Sleep Disturbance and Cognitive Ability (improvement). No substantive differences in responsiveness were noted by racial/ethnic group.

Conclusion: PROMIS scales appeared to be responsive to positive and negative changes in general health status and lupus disease activity, including within racial/ethnic groups, with the exception of the Sleep Disturbance and Cognitive Ability scales. Qualitative studies may be needed to determine reasons for lower responsiveness of these two scales. Overall, however, results add to the evidence supporting the use of PROMIS scales in lupus.

Table. Changes in PROMIS scores and Standardized responses means by change in self-rated health and disease activity (SLAQ)

	Change in self-rated health			
	Better (n=42; 12.6%)		Worse (n=64; 19.2%)	
PROMIS scale	Mean change	SRM	Mean change	SRM
Physical Function*	9.4	0.82	-10.8	-0.88
Pain Interference	-8.7	-0.64	10.0	0.82
Fatigue	-11.1	-0.79	11.2	0.80
Sleep Disturbance	-0.8	-0.08	8.3	1.08
Sleep Impairment	-8.0	-0.61	9.7	0.81
Applied Cognition, Abilities*	3.9	0.27	-7.3	-0.74
Satisfaction with Participation in Discretionary Activities*	11.6	0.81	-9.9	-0.80
Ability to Participate in Social Roles and Activities*	11.7	0.82	-11.8	-0.95
Change in disease activity (SLAQ)				
	Better (n=111; 32.9%)		Worse (n=123; 36.5%)	
	Mean change	SRM	Mean change	SRM
PROMIS scale	7.7	0.69	-9.5	-0.95
Physical Function*	-8.0	-0.68	9.0	0.77
Pain Interference	-9.6	-0.79	10.7	0.79
Fatigue	1.1	0.11	6.2	0.68
Sleep Disturbance	-8.0	-0.70	8.4	0.70
Sleep Impairment	4.6	0.42	-6.2	-0.65
Applied Cognition, Abilities*	6.9	0.52	-8.4	-0.74
Satisfaction with Participation in Discretionary Activities*	10.8	0.98	-8.9	-0.79
Ability to Participate in Social Roles and Activities*				

* Higher scores = better status; otherwise, higher scores = worse

Disclosure: P. Katz, None; S. Rush, None; J. Yazdany, None; L. Trupin, None; L. Murphy, None; C. Lanata, None; L. A. Criswell, None; M. Dall'Era, None.

Abstract Number: 1405

Assessment of the Psychometric Properties of Patient-Reported Outcomes of Depression in SLE

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Session Information

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Session Time: 9:00AM-11:00AM

Background/Purpose: Mood disorders, including depression, are amongst the most common manifestations of neuro-psychiatric SLE. Currently, the screening and diagnosis for depression in ambulatory settings are delayed and often missed due to the lack of standardized valid questionnaires for assessing depression in patients with SLE. This study aims to: 1) Determine the prevalence of depression in SLE patients using the Center for Epidemiological Studies-Depression Scale [CES-D] and Hospital Anxiety and Depression Scale [HADS] questionnaires. 2) Study the criterion validity and interpretability of CES-D and HADS, and 3) evaluate their diagnostic accuracy when compared to the assessment of an independent psychiatric assessment using the Mini-International Neuropsychiatric Interview (MINI), based on the DSMV, as the gold standard.

Methods: A cross-sectional study of consecutive consenting SLE patients (n=227), aged 18-65 and attending the Toronto Lupus Clinic between June 2017–September 2017, was performed. Participants were screened for depression using the CES-D and HADS, and underwent the MINI on the same date of their clinic visit. Conventional cut-off scores were used to indicate the prevalence of depression: CES-D ≥ 16 and HADS-D ≥ 8 . Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were evaluated against the MINI. Receiver operator characteristic (ROC) curves and the Youden Index were utilized to determine the optimal cut-off scores for CES-D and HADS-D.

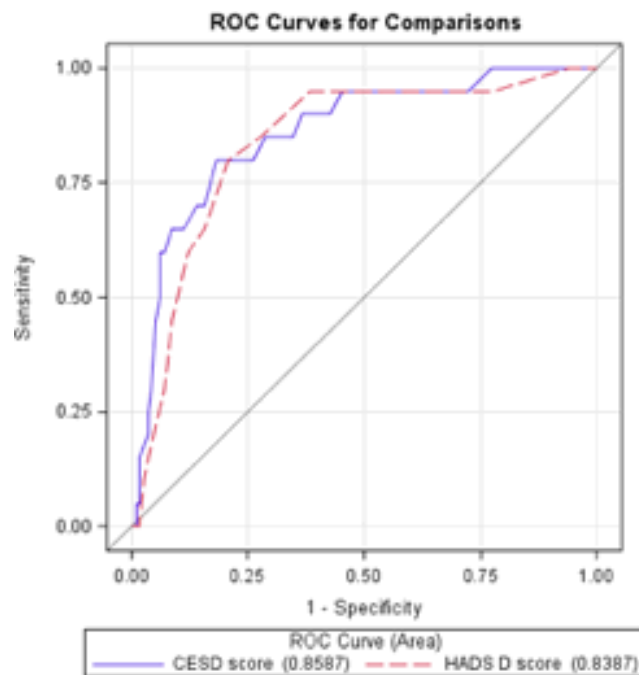


Table 1: Cut-offs to predict depression by Youden Index

Cutoffs	Sensitivity	Specificity	PPV	NPV
CES-D				
26*	0.80	0.82	0.43	0.96
24	0.80	0.77	0.37	0.96
21 [†]	0.85	0.71	0.34	0.97
16 [†]	0.95	0.55	0.27	0.98
HADS-D				
8* [†]	0.80	0.79	0.40	0.96
7	0.85	0.72	0.35	0.97
6	0.95	0.62	0.30	0.99

*Optimal cutoff as determined by the Youden Index

[†]Conventional cutoffs found in literature

Results: Among 227 patients, the prevalence of depression ranged from 27.8% (HADS-D) to 46.3% (CES-D). ROC curves showed that the CES-D (AUC 0.86, 95% CI: 0.78-0.95) slightly outperformed HADS-D (AUC 0.84, 95% CI: 0.75-

0.93) when compared to the MINI. The sensitivity, specificity, PPV, and NPV for CES-D at the optimal cut-off of 26 was 80%, 82%, 43%, and 96%, respectively. The Youden index exhibited optimal cut-offs for CES-D at 26 and HADS-D at 8 that optimized their sensitivity and specificity as screening metrics for depression in SLE patients. The performance of the CES-D and HADS-D at various cut-offs are displayed in Table 1 below.

Conclusion: This study assessed the criterion validity and interpretability of patient-reported outcome tools HADS, and CES-D for depression screening in SLE patients. Compared to the gold standard, CES-D outperformed HADS-D. These results suggest that SLE-specific cut-offs may improve the diagnostic accuracy of current screening metrics in lupus.

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Abstract Number: 1406

Longitudinal Construct Validity of the Psaid Individual Items: Can We Eliminate Other Questionnaires If Using the Psaid?

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Table. Construct Validity among PsAID items and other similar measures

Question	N	Mean (SD)	Correlation	N	Mean Change (SD)	Median (IRQ)	Correlation over time (longitudinal)
	At Baseline			Change between two visits			
PsAID Pain	301	4.03 (2.81)	BASDAI Pain: 0.66 SF12 Pain: 0.76 RAPID3 Pain: 0.89	652	0.2 (2.34)	0 (-1, 1)	RAPID3 Pain: 0.71
PsAID Tired	301	4.13 (2.89)	FACIT-F Total: -0.81 BASDAI Tired: 0.74 PsAQoL Tired: 0.61	650	0.15 (2.35)	0 (-1, 1)	FACIT F Total: -0.45
PsAID Skin	302	2.62 (2.84)	PGAxBSA: 0.65 Skin Physician Global: 0.63 DLQI Total: 0.73 PalmPASII: 0.82 PalmPASIZ: 0.70	652	0.12 (2.41)	0 (-1, 1)	PalmPASII: 0.40 PalmPASIZ: 0.46
PsAID Activity	302	3.18 (2.91)	PsAID Function: 0.88 RAPID3 HAQ: 0.71 RAPID3 Total: 0.76 DLQI Work1: 0.14 DLQI Work2: 0.27 PsAQoL Active: 0.50 PsAQoL Travel: 0.49 PsAQoL Limitations: 0.50	654	0.14 (2.38)	0 (-1, 1)	RAPID3 HAQ: 0.45
PsAID Function	302	3.27 (2.89)	PsAID Activity: 0.88 RAPID3 HAQ: 0.74 RAPID3 Total: 0.81	652	0.15 (2.3)	0 (-1, 1)	RAPID3 HAQ: 0.36
PsAID Anxiety	299	2.75 (2.93)	HADS Total: 0.77 HAQ Anxiety: 0.53 FACIT-F Total: -0.66	649	0.19 (2.31)	0 (-1, 1)	HADS Total: 0.33 HAQ Anxiety: 0.24
PsAID Depression	301	2.12 (2.74)	HADS Total: 0.61 HAQ Depression: 0.62 FACIT-F Total: -0.65	651	0.14 (2.28)	0 (0, 1)	HADS Total: 0.31 HAQ Depression: 0.44

Background/Purpose: The Psoriatic Arthritis Impact of Disease (PsAID) questionnaire is a patient reported measure of disease impact. The 12-item questionnaire has many advantages including demonstrated validity, reliability, responsiveness and discrimination. However, few studies have examined the use of individual items as surrogates for important patient reported outcomes. For example, we were interested in whether the single PsAID fatigue item could be used in place of the 13 item FACIT-F instrument. Likewise, the pain, function, depression, and anxiety items could be used in place of additional questionnaires if the items correlated well with validated instruments both in cross-sectional and longitudinal settings. The objective of this study was to examine the longitudinal construct validity of the individual PSAID items for pain, fatigue, function, depression and anxiety.

Methods: Patients with PsA were enrolled in the Psoriatic Arthritis Research Consortium (PARC) between 2015-2017. PARC is a longitudinal observational cohort at four institutions: University of Pennsylvania, Cleveland Clinic, New York University, and University of Utah. Two of these institutions (Utah and Penn) administered the PSAID. Patient characteristics at the first/baseline visit were descriptively reported. The correlations were calculated among individual PSAID items with similar constructs (e.g., “tired” item with FACIT-F, BASDAI tired item, etc.) at baseline using Spearman’s correlation coefficients. The change scores (e.g., score at visit 1 – score at visit 0) and the correlation among change scores between the individual items and related constructs were also calculated.

Results: PSAID data were available from 862 visits; 302 patients completed at least one PSAID and 208 patients completed PSAIDs at ≥ 2 visits. Most patients were in low disease activity (mean 66/68 swollen and tender joint counts were 2.6 and 5.3, respectively). At baseline, the mean PsAID9 and PsAID12 scores were 3.39 (SD2.45) and 3.22 (2.40) respectively. The individual PsAID items were moderately correlated ($\rho = 0.5-0.8$) with similar constructs at baseline. However, aside from the moderate to strong correlation between the PsAID pain question with the RAPID3 pain question ($\rho = 0.71$), change scores were only slightly correlated with like instruments ($\rho = 0.2-0.45$, Table).

Conclusion: The individual PsAID items did not correlate well with change in similar constructs over time. This may be due to the attribution of each symptom to PsA in the PSAID questionnaire. The assessed PsAID items cannot be used as close substitutes for the validated questionnaires with which they were compared.

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Differences in the Measurement Properties of the Patient-Reported Outcomes Measurement Information System Physical Function Short-Form 10a Among Racial/Ethnic Minorities with Rheumatoid Arthritis

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Most studies evaluating patient-reported outcomes such as the PROMIS Physical Function Short Form 10a (PF10a) in rheumatoid arthritis (RA) have been performed in white and English-speaking populations. We assessed the measurement properties of the PF10a in a racially/ethnically diverse population with RA. We determined the effect of on-English language proficiency, insurance status and race/ethnicity, on the validity and responsiveness of the PF10a.

Methods: Data were derived from electronic health records for all RA patients seen in a university rheumatology clinic between February 2013 and October 2017. We evaluated the PF10a’s floor and ceiling effects across categories of language preference, insurance and race/ethnicity. To assess convergent and discriminant validity, we examined Spearman’s correlation coefficients (r) between the PF10a and other patient-reported outcomes (patient global assessment and pain), clinical outcomes (tender and swollen joint counts) and inflammatory markers (ESR and CRP) across population

Table: Construct validity analysis, showing Spearman's correlation coefficients between PROMIS PF10a scores and patient reported outcomes, physician assessed outcomes, and inflammatory markers among different subgroups

	Spearman's correlation coefficients with PF10a (r)					
	Patient reported outcomes		Physician assessed outcomes		Inflammatory markers	
	PGA (VAS)	Pain (VAS)	TJC	SJC	CRP	ESR
Language						
English, N=512	0.71*	0.68*	0.45*	0.34*	0.31*	0.29*
Spanish, N=43	0.60*	0.61*	0.35*	0.24	0.02	0.12
Chinese, N=40	0.52*	0.52*	0.28	0.19	0.13	0.08
Insurance						
Private, N=236	0.72*	0.66*	0.61*	0.49*	0.33*	0.24*
Medicare, 281	0.62*	0.60*	0.29*	0.17*	0.23*	0.24*
Medicaid, 78	0.53*	0.61*	0.42*	0.31*	0.14	0.14
Race/Ethnicity						
White, N=297	0.69*	0.67*	0.44*	0.33*	0.34*	0.28*
African American, N=38	0.62*	0.53*	0.45*	0.12	0.04	0.32
Hispanic, N=38	0.62*	0.64*	0.25	0.05	-0.05	-0.08
Asian, N=115	0.64*	0.65*	0.40*	0.33*	0.26*	0.13
Other, N=118	0.69*	0.65*	0.48*	0.41*	0.14	0.31*

PGA: Patient global assessment; VAS: Visual analog scale; TJC: Tender joint count; SJC: Swollen joint count; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; PF10a: Physical function short-form 10a

*P<0.05

≥0.6: Strong correlation; ≥0.3: Moderate correlation; <0.3: Weak correlation

subgroups. We used linear mixed effects models to evaluate the responsiveness of the PF10a to longitudinal changes in the Clinical Disease Activity Index(CDAI) across population subgroups.

Results: We included 595 patients with complete data in across-sectional analysis of validity and 341 patients in longitudinal analyses of responsiveness. The group was racially/ethnically diverse (50% non-white)and 14% preferred a language other than English. Most patients had Medicare(47%) or private (40%) insurance. Mean (SD) PF10a score was 40 (11), nearly a standard deviation lower than the overall US population mean. PF10a had acceptable floor (≤7.5%) and ceiling (≤11%) effects across population subgroups. As expected, we observed strong correlations($r \geq 0.6$) with patient-reported outcomes, and moderate correlations($r \geq 0.3$) with clinical outcomes among whites, English speakers and privately insured patients (Table). However, constructs evaluated by the PF10a were less correlated with clinical outcomes among Chinese speakers and Hispanics ($r < 0.3$ and statistically non-significant), and less sensitive to clinical improvements among Medicaid patients ($p=0.005$) and Spanish speakers($p=0.029$) (Figure).

Conclusion: Consistent with published research, the PF10a had good measurement properties among whites, English speakers and privately insured patients. However, we also found important differences across racial/ethnic groups and those with limited English proficiency that warrant further investigation.

Disclosure: Z. Izadi, None; P. Katz, Bristol-Myers Squibb, 2; G. Schmajuk, None; J. Gandrup, None; J. Li, None; M. Gianfrancesco, None; J. Yazdany, AstraZeneca, 5.

Using Patient Reported Outcomes at Point of Care in Immune Mediated Diseases: Minimal Clinically Important Differences

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Patient reported measures of global health and disease activity are increasingly used in routine care; however, detecting meaningful change in clinical status (responsiveness) is difficult to define. Minimal clinically important

Table1. A summary of PROMIS and RAPID3 data, total and by diagnosis group, is shown below.

Factor	Overall		Psoriatic arthritis		GPA		Lupus		Rheumatoid arthritis	
	Statistics		Statistics		Statistics		Statistics		Statistics	
	N		n		n		n		n	
PROMIS GH T-score										
Visit 1	4,845	43.0±8.3	595	43.4±8.5	302	44.9±8.7	785	41.7±8.8	3,163	43.0±8.1
Visit 2	4,845	43.3±8.4	595	43.6±8.1	302	45.6±9.0	785	41.8±8.9	3,163	43.4±8.2
Change	4,845	0.33±5.5	595	0.21±5.6	302	0.72±5.7	785	0.09±5.8	3,163	0.37±5.4
Change P-value		<0.001*		0.36*		0.030*		0.67*		<0.001*
MCID	4,845		595		302		785		3,163	
. MCID worsened (5+ point decrease)		761(15.7)		98(16.5)		53(17.5)		136(17.3)		474(15.0)
. No change (< 5 point change)		3,194(65.9)		404(67.9)		184(60.9)		500(63.7)		2,106(66.6)
. MCID improved (5+ point increase)		890(18.4)		93(15.6)		65(21.5)		149(19.0)		583(18.4)
RAPID3 weighted score (0-10)										
Visit 1	6,837	3.5±2.0	823	3.5±2.1	425	2.4±1.9	1,093	3.6±2.1	4,496	3.5±2.0
Visit 2	6,837	3.4±2.0	823	3.4±2.1	425	2.3±1.9	1,093	3.5±2.1	4,496	3.4±2.0
Change	6,837	-0.11±1.5	823	-0.08±1.6	425	-0.12±1.5	1,093	-0.08±1.4	4,496	-0.12±1.6
Change P-value		<0.001*		0.17*		0.11*		0.048*		<0.001*
MCID	6,837		823		425		1,093		4,496	
. MCID worsened (1.2+ point increase)		1,129(16.5)		139(16.9)		74(17.4)		165(15.1)		751(16.7)
. No change (< 1.2 point change)		4,332(63.4)		522(63.4)		267(62.8)		726(66.4)		2,817(62.7)
. MCID improved (1.2+ point decrease)		1,376(20.1)		162(19.7)		84(19.8)		202(18.5)		928(20.6)

differences (MCID) are patient derived scores that reflect changes in clinical care that are meaningful for the patient. Little is known about MCID in many immune mediated diseases. Since small differences in PROs may be statistically significant yet clinically unimportant, it is important to study across disease states. We evaluated the MCID of PROMIS Global Health (GH) and RAPID3 in multiple immune mediated diseases at point of care.

Methods: Data from patients with diagnosis codes of rheumatoid arthritis(RA), psoriatic arthritis (PsA), lupus and granulomatosis with polyangiitis(GPA) who had completed PROMIS GH and RAPID3 via My Rheum using computerized adaptive testing (CAT) at two separate visits, six months apart, were included. Paired t-tests were performed to assess the change in PROMIS and RAPID3. PROMIS MCID change of 5 and RAPID3-weighted score of 1.2 (improvement or worsening) was used to identify important differences.

Results: The analyses included more than 7,463 patients (age 58.3 ± 14 , female 76.8%, white 86.2%). The complete dataset included 4,845 patients for PROMIS and 6,837 patients for RAPID3. The differences in PROMIS and RAPID3 scores by diagnosis are displayed in Table 1. The change in PROMIS score was statistically significant overall ($p < 0.001$) as well as for those with a diagnosis of either GPA ($p = 0.030$) or RA ($p < 0.001$), even though the mean change in PROMIS was less than 1 point for all groups. Approximately 15-20% of patients showed an improvement or worsening of MCID by 6 months. 60-70% had no change between visits. The change in RAPID3 score (table b) from the first to second visit was significant ($p < 0.001$), as was the change for lupus ($p = 0.048$) and RA ($p < 0.001$). Thresholds for clinically meaningful change in PROMIS GH were most significant in GPA and RA compared to PsA and lupus and in RAPID3 were most significant in lupus and RA compared to PsA and GPA.

Conclusion: This study supports the feasibility of collecting PROMIS GH and RAPID3 scores at point of care in patients with immune mediated diseases and using CAT with significantly reduced patient question burden. There was improvement on average for PROMIS and RAPID3 scores among all immune mediated diseases after 2 visits. This study highlights that it is unlikely to have a single MCID value applicable across all chronic diseases. The variability in MCID observed in the My Rheum cohort implies that some patients improve, while others worsen, and this study provides an opportunity to better understand patient characteristics and therapies that may explain these changes in the future.

Disclosure: M. E. Husni, None; C. Deal, None; L. H. Calabrese, None; G. Strnad, None; J. Bena, None; A. Abelson, None.

Abstract Number: 1409

Empowerment in Hispanic Rheumatoid Arthritis Patients: A Validation Study

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I: Patient-Reported Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The World Health Organization describes empowerment in health promotion work as a process in which the person receives more control over decisions and actions that affect their own life and health (1998). Empowerment (E) is an important concept in rheumatoid arthritis(RA), where it has been associated to favorable outcomes. Currently, there is no validated E instrument for use with Spanish speaking RA patients. Objective of the study were to adapt the Spanish version of the Health Empowerment Scale(S-HES) (1) for RA (S-ERA) and to perform its psychometric validation.

Methods: The S-ERA instrument was adapted from the already existing S-HES (1). Adaption was performed by 3 researchers who at first, substitute the word “health” with “rheumatoid arthritis” in each item from the S-HES. A first proposal of the S-ERA included 2 alternative sentences per item. Then, an external Committee integrated by 6

rheumatologists and 2 psychiatrists rated each sentence according to 3 categories: Unnecessary, important but not necessary or essential. One sentence per item was retained when $\geq 80\%$ of the validators agree that the sentence/item was essential. A first version was obtained and it was pilot tested in a convenience sample of 50 RA outpatients (Cronbach's $\alpha=0.84$). After that, minor modifications were adopted and a final version of the S-ERA integrated by 8 items scored on a 5 point Likert scale, was applied to 109 additional consecutive RA patients from the outpatient Clinic of a tertiary care level Center (Table 1). Test-retest exercise was performed in a sample of 50 patients. All the patients gave written informed consent.

Results: The 109 RA outpatients were primarily females (89%) and 99 (91%) had low-medium socioeconomic status; their (mean \pm SD) age was 50.6 \pm 13.3 years and their formal education was 9.7 \pm 3 years. Ninety-four (86.2%) patients had rheumatoid factor and 56 (51.4%) were in remission according to their attending rheumatologist, meanwhile 27 patients (25%) had a major comorbidity.

The (mean \pm SD) score of the S-ERA was 34.4 \pm 3.8(8-40, where 40 indicates the strongest level of RA related E). S-ERA instrument had a good internal consistency (Cronbach's $\alpha=0.82$); construct validity was examined by factor analysis that showed a single factor explaining 46.2% of the variance. The intra-class coefficient correlation in the test-retest was 0.79, $p\leq 0.0001$. Table 2 summarizes additional psychometric properties.

Conclusion: The S-ERA instrument is easy to apply and had adequate validity and reliability to evaluate E in Hispanic RA patients.

Reference: 1. Serrani ADJL. Colombia Médica 2014; 45

Table 1. Empowerment properties and items included in the final version of the S-ERA

Instrument			
No. of item	Dimensions	Properties	Items
1	Psychosocial-coping/ Self-support Support Motivation	Stress management	I can deal positively with the stress that RA causes me.
2		Request support	I can find support to take care of my RA.
3		Self-motivation	I recognize what helps me to be motivated to take care of my RA.
4	Decision-making	Making cost/benefit decisions about making behavior changes	I know myself enough to choose what is best for me to take care of my RA.
5	Self-control	Satisfaction and dissatisfaction related to health	I know well what aspects of my RA-care I am dissatisfied with.
6	Self-efficacy	Identification and achievement of personally meaningful goals	I am capable to reach the goals that I have set for my RA through concrete actions.
7	Problem solving	Application of a systematic problem solving process	I can do different things to overcome obstacles and achieve the goals I have set for my RA.
8	Psychosocial-coping	Coping with the emotional aspects of living with health	I can find ways to feel good by having RA.

Table 2. Statistics of the S-ERA instrument

# Item / Dimension	Mean	Standard deviation	Cronbach's α if item deleted	Confirmative Factor Loading*
1 / Psychosocial-coping/Self-support	3.99	0.811	.816	0.605
2 / Support	4.33	0.708	0.807	0.652
3 / Motivation	4.36	0.646	0.801	0.690
3 / Decision-making	4.54	0.617	0.798	0.716
5 / Self-control	4.03	0.810	0.827	0.531
6 / Self-efficacy	4.32	0.706	0.795	0.729
7 / Problem solving	4.30	0.727	0.796	0.736
8 / Psychosocial-coping	4.39	0.679	0.792	0.722

* Kaiser-Meyer-Olkin measure of sampling adequacy (KMO): 0.791
Bartlett's sphericity test: $p<0.001$.

Disclosure: E. Ruiz-Medrano, None; I. Contreras-Yañez, None; L. D. C. Hernández, None; V. Pascual-Ramos, None.

Assessment of Work Outcomes with Truncation from Job Loss in an Arthritis Randomized Clinical Trial

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster I – ARHP

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Methods for causal analysis in randomized clinical trials (RCT) where functional outcomes may be *truncated* by death of participants have been developed but are not widely used in arthritis. To demonstrate one of these methods, based on a composite score, we applied it to WORK-IT, a parallel-arm RCT of a work disability prevention intervention for persons with musculoskeletal conditions (ClinicalTrials.gov NCT01387100.). In WORK-IT the primary outcome was the 2-year (104-week) value of the Output Job Demand subscale (OJD) of the Work Limitations Questionnaire. The OJD measures the percentage of time an employee has job output limited by health, (0% best -100% worst). Unemployment at 104-weeks *truncated* the OJD for some participants and made these values missing. The rate of unemployment was significantly lower in the intervention arm (11/11744 vs. 25/12535 in controls [Events/Person-Week], $p=0.03$ Logrank test), however the OJD was not different by arm (Intervention: 25.9 ± 1.8 , Control: 28.0 ± 1.9 [Mean \pm SE], $p=0.44$ t-test).

Methods: We derived a composite score (CS) defined as $CS = \#(\text{Follow-up weeks employed}) + (100 - \text{OJD})$. A participant employed at 104 weeks with no OJD limitation would have the highest $CS=204$; and participants unemployed at 104 weeks would have $CS < 104$, depending on when they became unemployed. An intent-to-treat (ITT) analysis with multiple imputation was used to obtain OJD values for participants who withdrew or provided incomplete responses. A complete case analysis excluding these subjects was also performed. The CS combines different outcomes, so a Wilcoxon test-based estimate of the probability that an intervention subject had a better outcome than a control subject $P(I > C)$ quantified the difference between treatments, with values above 0.5 indicating intervention subjects had better outcomes. The difference between arms was significant if a 95% bootstrap confidence interval (CI) for $P(I > C)$ excluded 0.5.

Results: We studied 143 intervention and 144 control participants, 36 were unemployed at 24 months and unable to provide OJD, but used in CS. The median CS value of 179 for the intervention group (see table) indicates that at least half the intervention subjects were employed at follow-up with no more than 25% time of limited output. In both analyses $P(I > C)$ is above 0.5 indicating that intervention subjects have higher probability of a better outcome than control subjects, and since the lower bounds on the 95% CI exclude 0.5, both the complete case and ITT analysis find a statistically significant difference between the arms.

Conclusion: Use of composite scores allow consistent estimation of treatment effects in clinical trials where outcomes are truncated by a related event. This approach could be extended to other longitudinal studies where a measured outcome is truncated, such as knee pain evaluation in osteoarthritis being truncated by knee replacement.

Composite Score (CS) Results for the WORK-IT Study

	Complete Case		Intent-to-Treat (Multiple Imputation)	
	Intervention	Control	Intervention	Control
Subjects	119	132	143	144
Median CS [0-204]	179	172	179	173
Interquartile Range CS [0-204]	160 – 192	151 – 192	160 – 192	154 – 192
$P(I > C)^*$ (95% CI)	0.571 (0.519, 0.625)		0.558 (0.505, 0.610)	

* Probability that an intervention subject has a better outcome than a control subject on the composite score, based on Wilcoxon test statistic.

Disclosure: M. P. LaValley, None; C. Brown, None; D. T. Felson, None; J. Keyser, None.

Long-Term Safety of Different Doses of Canakinumab (<2, 2–<4, and 4–<8 mg/kg) in Patients Aged <4–≥65 Years: Results from the β-Confident Registry

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Canakinumab (CAN), a human anti-interleukin-1 monoclonal antibody, has shown to be efficacious and safe in the treatment of all phenotypes of cryopyrin-associated periodic syndrome (CAPS).¹ However, no real-life data are available on the effect of different doses of CAN in CAPS patients (pts) of different age groups. Here, we analyze the safety of different doses of CAN (<2, 2–<4 and 4–<8 mg/kg) in pts of different age groups (<4–≥65 years; yrs) with CAPS and other auto inflammatory syndromes from a real-life study (β-CONFIDENT Registry; NCT01213641).

Methods: The β-CONFIDENT Registry was a multicenter, long-term, prospective, observational study conducted at 38 sites across 13 countries. Pts with CAPS and those with other auto inflammatory diseases receiving CAN at physician's discretion were enrolled in the registry. Cumulative safety data were reported as exposure-adjusted incidence rate per 100 pt-yrs (IR/pyr) from enrollment of the first pt (November 2009) until the end of study (December 2015). Pts were followed up for at least 1 yr. The protocol did not mandate any visits or procedures. All observed and reported adverse events (AEs) and serious AEs (SAEs) were recorded for the following age groups: <4, 4–<12, 12–<18, 18–<65, and ≥65 yrs.

Results: Of the 285 pts enrolled, 21% (n=60) discontinued the study mainly due to loss to follow-up (35%, n=21), followed by AEs (10%, n=6), poor efficacy (8%, n=5), and pt preference (3%, n=2). In total, 1114 AEs and 155 SAEs were reported in 223 pts (110.7 IR/100 pyr) and 83 pts (15.4 IR/100 pyr), respectively. Incidence rates of AEs (IR/100 pyr) among pts in the <4 and 4–<12 yrs age group were lowest in pts who received <2 mg/kg (130.3 and 59.7, respectively) compared with pts who received 2–<4 mg/kg (450.8 and 169.6, respectively) and 4–<8 mg/kg (121.5 and 90.0, respectively) CAN. In pts aged 12–<18 yrs, IR/100 pyr were lowest in pts who received 2–<4 mg/kg doses (118.2) compared with pts who received <2 mg/kg (169.6) and 4–<8 mg/kg (139.4) CAN. Similarly, in the 18–<65 yrs age group, IR/100 pyr were lowest in pts who received <2 mg/kg (93.1) compared with pts who received 2–<4 mg/kg (100.7) and 4–<8 mg/kg (154.4) CAN. In the ≥65 yrs age group, IR/100 pyr decreased with increasing dose (<2 mg/kg: 26, 2–<4 mg/kg: 17). Overall, 5, 13, 19, 84, and 7 SAEs were reported in the <4, 4–<12, 12–<18, 18–<65, and ≥65 yrs age groups, respectively. One death (metastatic rectal adenocarcinoma in a 76-yr-old Muckle-Wells syndrome pt) was reported.

Conclusion: These results from the β-Confident Registry demonstrated that in general the incidence of adverse events in each dose group of canakinumab increased with age (<4–<65 years). However, an increase in canakinumab dose from 2–<4 mg/kg to 4–<8 mg/kg in each age group was not associated with an increased rate of AEs, which corroborate the need of treat-to-target strategies for different age groups. Canakinumab demonstrated a safety profile consistent with previous reports^{2,3}, and is well tolerated in CAPS patients aged <4–≥65 years.

References: 1. Kuemmerle-Deschner JB, et al. *Ann Rheum Dis.* 2015;74 (S2): 850. 2. Hoffman HM, et al. *Arthritis Rheumatol.* 2016;68(suppl10). 3. Kuemmerle-Deschner JB, et al. *Ann Rheum Dis.* 2016;75:617.

Disclosure: J. B. Kuemmerle-Deschner, Novartis, 2, Novartis, SOBI, 5; U. A. Walker, None; H. H. Tilson, Novartis, 5; P. N. Hawkins, None; T. van der Poll, None; K. Franke, Novartis, 5; A. Speziale, Novartis, 3; E. Vritzali, Novartis, 3; H. M. Hoffman, Burroughs-Wellcome, 2, Novartis, SOBI, 5, Novartis, 8.

A Systematic Literature Review of Efficacy and Safety of Current Therapies for the Treatment of Hyperimmunoglobulinemia D Syndrome and TNF Receptor-Associated Periodic Syndrome

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Hyperimmunoglobulinemia D syndrome (HIDS), also known as mevalonate kinase deficiency (MKD), and TNF receptor-associated periodic syndrome (TRAPS) are rare auto-inflammatory diseases grouped as periodic fever syndromes. There is limited evidence on treatment outcomes for these syndromes. We assessed the efficacy/effectiveness and safety of current treatments used for HIDS and TRAPS.

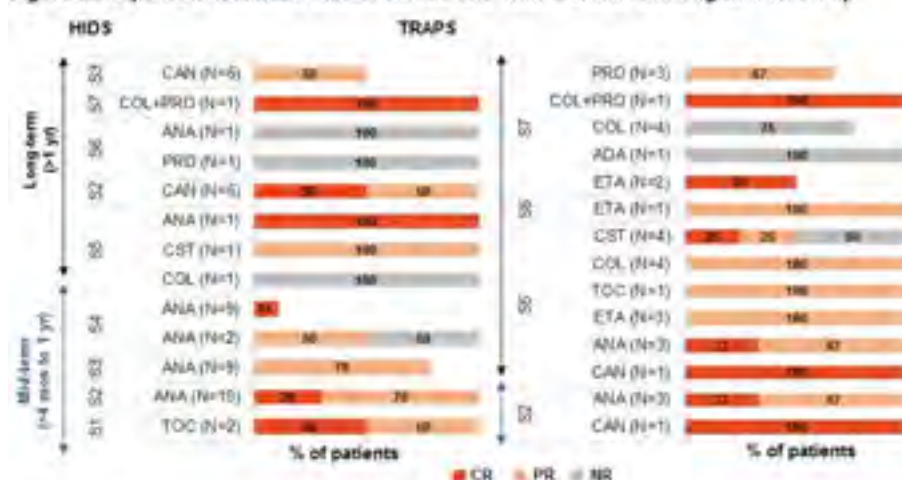
Methods: A systematic literature review was conducted using Embase®, MEDLINE®, MEDLINE®-In Process and Cochrane library to identify randomized controlled trials (RCTs) and real-world (prospective and retrospective) studies of HIDS/TRAPS patients (pts) published in English language as full-text articles (2000 to September 2017) or conference abstracts (2014 to September 2017). Studies with <5 pts were excluded.

Results: Of the 3342 retrieved publications, 27 studies were included (11 HIDS, 9 TRAPS, and 7 had both cohorts). The majority of studies were full-text (20), published after 2010 (21), and retrospective (13). Studies included two RCTs [one for canakinumab (CAN) vs placebo (PBO); one for simvastatin (SIM) vs PBO]. HIDS pts were most often treated with anakinra (ANA; 9), CAN (7), and corticosteroids (CST; 5); and TRAPS pts with etanercept (ETA; 10), CAN (6), ANA (6), and CST (5).

In the CAN RCT, at 16 weeks (wks), a significantly higher proportion of CAN treated pts vs PBO achieved clinical response (i.e., resolution of the index flare at Day 15 and no new disease flare over 16 wks) in both cohorts (HIDS: 35% vs 6%; TRAPS: 45% vs 8%). The clinical response was higher with CAN vs PBO up to 40 wks. A crossover RCT of SIM in HIDS pts showed a decrease in urine mevalonic acid levels in 100% of pts at 24 wks and reduced the number of febrile days in 83% of pts.

In real-world studies, complete (CR) or partial response (PR) was often assessed, and their definitions and follow-ups (FUP) varied (Table 1; Figure 1). At mid-term FUP, in HIDS pts, CR was 50% [for tocilizumab (TOC)] and 11%-30% (ANA); in TRAPS pts, CR was 100% (CAN) and 33% (ANA). At long-term FUP, in HIDS pts, CR was 100% (ANA),

Figure 1. Response in real-world studies of HIDS and TRAPS at mid- and long-term follow-up



ST 52... denotes studies the details of which are provided in Table 1. N is the number of patients.

In studies where the response does not add up to 100%, the missing information was not reported in that study.

ADA, atakinumab; ANA, anakinra; CAN, canakinumab; COL, colchicine; CR, complete response; CST, corticosteroid; ETA, etanercept; mos, months; NR, no response; PR, partial response; PRD, prednisone; TOC, tocilizumab; wks, weeks; yr, year.

Table 1. Definitions of complete, partial and no response used in HIDS and TRAPS real-world studies with follow-up details reported				
Study (S)/Design	Patients	Definition of response		
		Complete	Partial	No
Storck, 2015 (S1)/Prospective	HIDS	Doing very well and not had an inflammatory attack in last 3 months	Milder but recurrent inflammatory symptoms despite normalization of acute phase response	Had very active disease despite continuous treatment
Roasi-Semerano, 2015 (S2)/Retrospective	HIDS, TRAPS	CR or remission was defined when signs of active disease were absent and inflammatory markers had normalized	PR was defined when CR was not achieved but clinical improvement was evident as per treating physician	Not reported
Gileotti, 2012 (S3)/Retrospective	HIDS	Not reported	Partial clinical remission was defined by a decline of both the symptoms and the frequency of attacks	Not reported
Bodar, 2011 (S4)/Prospective	HIDS	Complete cessation of fever attacks	Febrie episode recur occasionally and CRP was intermittently elevated	No response
Hernández-Rodríguez, 2015 (S5)/Retrospective	HIDS, TRAPS	Good response	Partial response	No response
Cervinski, 2014 (S6)/Retrospective	HIDS, TRAPS	Not reported	Partial response	No response
Chandrasekar, 2014 (S7)/Retrospective	HIDS, TRAPS	Good response	Partial response	Poor response
S1, S2, ... were used to simplify the name of study to use in Figure 1 CR, complete response; CRP, C-reactive protein; PGA, Physician Global Assessment of the disease; PR, partial response; SAA, serum amyloid A.				

100% [colchicine (COL) + prednisone (PRD)] and 50% (CAN); in TRAPS pts, CR was 100% (CAN), 100% (COL + PRD), 50% (ETA) and 33% (ANA). CAN, TOC, SIM, ETA and ANA were generally well-tolerated by HIDS and TRAPS pts; but for ETA and ANA, local injections site reactions were commonly reported.

Conclusion: CAN was efficacious in controlling and preventing flares in HIDS and TRAPS pts in the studies assessed. Although response criteria and treatments were not directly comparable, the available evidence suggested higher effectiveness of CAN in the real-world setting.

Disclosure: J. B. Kuemmerle-Deschner, Novartis, 2, 5; R. Gautam, Novartis Healthcare Pvt. Ltd., 3; A. T. George, Novartis Healthcare Pvt. Ltd., Hyderabad, India, 3; S. Raza, Novartis Healthcare Pvt. Ltd., Hyderabad, 3; K. G. Lomax, Novartis Pharmaceuticals Corporation, 1, 3; P. Hur, Novartis Pharmaceuticals Corporation, 3.

Abstract Number: 1413

Safety of Tocilizumab in Patients Aged <2 Years with Active Systemic Juvenile Idiopathic Arthritis Treated for One Year

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The US Food and Drug Administration approved intravenous (IV) tocilizumab (TCZ) for patients (pts) ≥ 2 years of age with systemic JIA (sJIA) in 2011 based on the phase 3 TENDER study.¹ Approval was associated with a post marketing requirement to investigate TCZ in pts with sJIA < 2 years of age (study NP25737; ClinicalTrials.gov, NCT01455701). Results from the 12-week main evaluation period (MEP) have been reported.² Safety results following completion of the optional extension period (OEP) of NP25737 (until 52 weeks from baseline or 2 years of age was reached) are now reported.

Methods: NP25737 was a multicenter, open-label, single-arm study to evaluate pharmacokinetics and safety of IV TCZ 12 mg/kg every 2 weeks for 12 weeks in pts aged < 2 years with active sJIA for ≥ 1 month whose treatment with glucocorticoids and nonsteroidal anti-inflammatory drugs failed and who were receiving stable background therapy. After the MEP, pts could continue TCZ treatment (no requirement for stable background therapy) in the OEP to evaluate long-term safety. Cumulative adverse events (AEs) over the entire study period are reported.

Results: Of 11 pts enrolled in the MEP, 7 entered the OEP and received ≥ 1 dose of TCZ. For the entire study period (n = 11), the median number of TCZ doses was 11.0 (range, 2-26), and median duration of TCZ exposure was 22.1 weeks (range, 4.1-58.1). Most pts (10/11; 90.9%) had ≥ 1 AE; most were mild or moderate and unrelated to TCZ. The most common AEs were upper respiratory tract infection (6/11 pts; 54.5%) and hypersensitivity, neutropenia, rash, viral upper respiratory tract infection, and vomiting (each 3/11 pts; 27.3%). Seven serious AEs occurred in 5/11 pts (45.5%): 2 during the OEP (transaminases increased, histiocytosis hematophagic), 3 during the MEP (3 hypersensitivity events), and 2 during safety follow-up of the MEP (sJIA flare, hand-foot-and-mouth disease). AEs leading to dose modification occurred in 5/11 pts (1 in the MEP, 4 in the OEP) mostly because of infections, neutropenia, and elevated liver enzymes, all mild or moderate in intensity. AEs leading to withdrawal occurred in 5/11 pts (45.5%): during the OEP, 1 pt withdrew because of a serious AE of increased transaminases; during the MEP, 3 pts withdrew because of serious hypersensitivity reactions to TCZ and 1 because of thrombocytopenia. No deaths were reported. AE rates are shown in Table 1.

Table 1. Rates of AEs

	TCZ 12 mg/kg IV Every 2 Weeks		
	MEP n = 11	OEP n = 7	Entire Study n = 11
Total PY at risk	2.3	5.1	7.4
No. of events (AE rate per 100 PY at risk)			
Any AE	32 (1396.4)	47 (926.5)	79 (1072.7)
Serious AE	5 (218.2)	2 (39.4)	7 (95.1)
AE with fatal outcome	0	0	0
AE leading to withdrawal	4 (174.6)	1 (19.7)	5 (67.9)
AE leading to dose interruption	1 (43.6)	12 (236.5)	13 (176.5)

AE, adverse event; IV, intravenously; MEP, main evaluation period; OEP, optional extension period; PY, patient-years.

Conclusion: During the OEP, long-term treatment with TCZ was well tolerated in sJIA pts aged < 2 years. No additional safety signals were reported in the OEP beyond those reported in the MEP or observed previously for pts with sJIA aged > 2 years. **References:** 1. De Benedetti F et al. *N Engl J Med.* 2012;367:2385-2395. 2. Mallalieu NL et al. *Arthritis Rheumatol.* 2017;69(suppl 10):abstract 2856. Medical writing: Sara Duggan, PhD, funded by F. Hoffmann-La Roche Ltd.

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Abstract Number: 1414

Pharmacovigilance of Biologics for Systemic Juvenile Idiopathic Arthritis Patients By the German Biologics Registry

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

Background/Purpose: Long-term surveillance of biologic drugs is particularly important in pediatric patients(pts). Since 2001, the German Biologics JIA Registry (BIKER) is allowing to follow up of an unlimited number of patients in routine clinical care. Safety with regard to adverse events of special interest was assessed.

Methods: The BIKER database was used to identify systemic JIA pts exposed to biologics. Safety assessments were based on adverse events (AE) reports for 25 predefined AEs of special interest (AESI). Events per 100 patient-years (PY) of exposure were calculated using AEs reported after first dose through 70 days after last dose. Rates were compared by Wald test. Only 5 pts receiving abatacept and 2 with infliximab were excluded from the Analysis.

Results: 278 pts received 388 biologics courses with a total exposure time of 765 PY. 152 pts received Etanercept (ETA,366 PY), 95 Tocilizumab (TOC,171 PY), 73 Anakinra (ANA,121 PY), 49 Canakinumab (CAN,69 PY) and 19 Adalimumab (ADA,38 PY). Differences in pts characteristics and concomitant treatment between these cohorts were noted. A total of 456 AE (rate 59.5/100 years), 94 SAE (12.3) and 95 AESI (12.4) were reported. The most common AESI were serious or medically important infections (30), cytopenias (21), macrophage activation syndrome (MAS,13), anaphylaxis (11), hepatic events (10), malignancies (4) and others occurring only once (other autoimmuneopathies, chronic inflammatory bowel disease, depression, demyelination, thrombotic disorder, uveitis). There were marked differences in the rate of AESI between the cohorts with different biologics (table). Risk Ratios for serious and medically important infections were significantly higher with TOC and lower with ETA. Risk ratios for cytopenias were significantly higher with CAN and TOC. MAS occurred significantly more frequently with TOC and CAN and less frequently with ETA. Risk ratios for hepatic events were significantly higher in the TOC cohort and lower with ETA. Risk ratio for cytopenias was significantly higher with TOC. Risk ratios for anaphylaxis were significantly higher with TOC probably due to the intravenous route of application. There was no death, no cardiovascular event, no bleeding, no intestinal perforation, pregnancy or opportunistic infection in this cohort

Biologic	ADA	ANA	CAN	ETA	TOC
Pat/exposure years	19/37.6	73/120.9	49/69.0	152/366.2	95/171.7
AE n(rate/100PY)	5(13.3)	47(38.9)	109(157)	86(23.4)	209(121)
SAES n(rate/100PY)	0	12(9.9)	17(24.6)	17(4.6)	48 (27.9)
AESI n(rate/100PY)	0	12(9.9)	18(26.1)	14(3.8)	52(30.2)
Serious and medically important Infection	0	8(6.62) 1.9(0.9-4.4)	4(5.8) 1.6(0.5-4.4)	4(1.09) 0.16(0.1-0.5) P<0.0001	14(8.15) 3.0(1.5-6.2) P=0.025
Cytopenia	0	2(1.65) 1.8(0.4-7.7)	6(8.7) 4.0(1.5-10) P=0.0039	1(0.27) 0.1(0-0.4) P=0.04	12(6.99) 4.7(1.9-11) P=0.0005
MAS	0	1(0.83) 0.5(0.1-4.2)	3(4.35) 3.8(1.0-14) 0.0495	3(0.82) 0.3(0.1-1.1)	6(3.49) 4.2(1.3-14) P=0.019
Anaphylaxis	0	0	1(1.45) 0.9(0.1-7.1)	0	10(5.82) 17(3.7-79) P=0.0002
Hepatic Event	0	0	1(1.45) 1.1(0.1-8.8)	1(0.27) 0.1(0-1.0) P=0.045	8(4.66) 13.8(2.9-65) P=0.0009
Malignancy	0	1(0.83) 1.8(0.2-17)	0	2(0.55) 1.1(0.1-7.7)	1(0.58) 1.2(0.1-11)
Autoimmune disease	0		1(1.45) 10(0.6-161)		
IBD	0			1(0.27) 1.1(0.1-17)	
Depression	0		1 (1.45) 10(0.6-161)		
Demyelination	0	0		1(0.27) 1.1(0.1-17)	
Thrombotic event	0	0	0	0	1(0.58) 3.5(0.2-55)
Uveitis	0			1(0.27) 1.1(0.1-17)	

* Data outlined as n(rate/100 years), RR=Risk ratio[95% CI], p-value.

Conclusion: These data provide support for the long-term and comparative safety of biologics in JIA pts. Overall, tolerance is acceptable. Surveillance of pharmacotherapy as provided by BIKER is an import approach especially in the case of long-term treatment of children. Differences between several biologics were noted and should be considered in daily patient care. Interpretation of these data requires caution.

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Emapalumab, an Anti-Interferon Gamma Monoclonal Antibody in Two Patients with NLRC4-Related Disease and Severe Hemophagocytic Lymphohistiocytosis (HLH)

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Session Information

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Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Interferon gamma (IFN γ) plays a pathogenic role in primary and secondary HLH. An ongoing phase 2/3 trial with emapalumab in primary HLH provides encouraging preliminary data and a pilot trial in MAS in the context of sJIA has just been initiated. Gain-of-function mutations in NLRC4 are associated with a distinct auto inflammatory syndrome, with recurrent HLH.

Methods: We report safety and efficacy of emapalumab treatment in 2 patients carrying de novo missense mutations in NLRC4, with severe early onset HLH. Cytokine levels were measured by multiplex assay and by specific ELISAs and expression of IFN γ in freshly isolated PBMCs by cytometry.

Results: Pt 1. Caucasian male, presented, at age 20 days, fever and rash and progressively developed clinical and laboratory features of HLH leading to multi-organ failure. A de novo missense mutation in NLRC4 (T337N) was found. High-dose glucocorticoids and cyclosporine-A (CyA) led only to partial improvement. A sepsis triggered HLH reactivation. Emapalumab was started on background of dexamethasone (13.6mg/m2) and CyA. After 3 months, the child was discharged in excellent conditions. Infections resolved during treatment with emapalumab. After 7 months of emapalumab treatment, all therapies, including emapalumab, were discontinued, without signs of HLH reactivation. Pt 2. This is 16 months old Caucasian boy with recurrent HLH and vasculitic skin lesions, since 1 month of life, secondary to a de novo missense mutation in NLRC4 (I343N). His disease was not controlled despite treatment with repeated methylprednisolone pulses and chronic daily glucocorticoid therapy, CyA and anakinra (ranging from 5 to 25 mg/kg/day). When anakinra was withdrawn prior to start emapalumab he immediately developed high-grade fever, skin rash with vasculitic lesions and diarrhea with laboratory features of HLH. Emapalumab was started on background of methylprednisolone and CyA with rapid resolution of fever and improvement in biochemical parameters. During emapalumab treatment the patient resolved his initial HLH flare and presented two HLH episodes of mild intensity controlled with moderate intensification of glucocorticoid therapy. These episodes were triggered by systemic infections caused by pathogens translocated from the gut. His diarrhea persisted with low grade inflammation; emapalumab was eventually withdrawn after 3 months. His subsequent course was characterized by additional mild episodes of HLH. In both patients increased production of IFN γ was demonstrated by high levels of CXCL9 (pt.1: 5670 pg/ml, pt.2: 3310 pg/ml), a chemokine induced specifically by IFN γ , by increased IFN γ expression in NK cells and CD8T cells, and by presence of high levels of total IFN γ bound to circulating emapalumab.

Conclusion: In both patients, treatment with emapalumab was well tolerated, no safety concerns emerged, normalization of all HLH clinical and laboratory abnormalities was achieved. Pt. 1 showed no disease reactivation even in the absence of treatments. In pt. 2 IFN γ neutralization has provided control of HLH, while his underlying disease and, in particular, gut inflammation and gut colonization by MDR pathogens remained unchanged.

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Risk Score of Macrophage Activation Syndrome in Patients with Systemic Juvenile Idiopathic Arthritis

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Session Information

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Background/Purpose: Macrophage Activation Syndrome (MAS) is a severe, life-threatening, complication of rheumatic diseases in childhood, particularly of systemic Juvenile Idiopathic Arthritis (sJIA), occurring in approximately 25% of the patients with sJIA. The mortality rate of MAS is still significantly high. A score that identify sJIA patients who are at high risk to develop MAS would be useful in clinical practice. There are no parameters available to identify from onset sJIA patients with high risk to develop MAS in their disease course. We evaluated whether routine laboratory parameters at disease onset may predict the development of MAS in patients with active sJIA. To define a risk score of MAS for sJIA patients using these parameters.

Methods: Laboratory parameters of disease activity and severity (WBC, N, PLT, Hb, ferritin, AST, ALT, gGT, LDH, TGL, fibrinogen, D-dimer and CRP), were retrospectively evaluated in 56 sJIA patients referred to our Division of Rheumatology from 1998 to 2016 with at least one year of follow-up. Laboratory parameters were evaluated during active sJIA, without MAS, at time of hospitalization (T1) and before treatment for sJIA was started (T2). Patients were divided in two groups: group 1 (patients without history of MAS), group 2 (patients with at least one MAS episode during disease course). In order to calculate a MAS risk score, laboratory parameters, collected at T2, with a statistical significant difference between the two groups of patients were selected.

Results: Fourteen patients, that fulfilled the 2016 classification criteria for MAS [1] at time of sampling, were excluded from the analysis. Therefore, we analyzed laboratory parameters of 42 patients with sJIA, 27 of whom without history of MAS (group 1) and 15 who developed at least one episode of MAS during disease course (group 2). Levels of ferritin, AST, LDH, gGT and TGL, collected at T2, were statistically significant higher in patients with a history of MAS compared to those without a history of MAS. For each of these parameters an arbitrary cut-off was defined. In order to define the final score an arbitrary rate was attributed to each parameter. Sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) were calculated to define the best scoring system. The scoring system with the best sensitivity was chosen (Table 1). A MAS risk score >3 identified 14 out of 15 sJIA patients with a history of MAS and 3 out of 27 sJIA patients without history of MAS.

Table 1. Laboratory parameters and cut-off used to create the MAS risk score in sJIA patients.

Laboratory parameters	Cut-off	Rate
Ferritin (ng/ml)	>900	1
AST (UI/L)	>35	1
LDH (UI/l)	>550	1
gammaGT (UI/L)	>30	2
Triglycerides (mg/dl)	>150	2
Sensitivity (Se)	0.933	CI95% 0.680-0.998
Specificity (Sp)	0.889	CI95% 0.708-0.977
Positive predictive value (PPV)	0.824	CI95% 0.566-0.962
Negative predictive value (NPV)	0.96	CI95% 0.797-0.999

* Patients with score >3 were identified to have high risk for MAS

Conclusion: We developed an MAS risk score based on routine laboratory parameters that are available worldwide, that can help clinicians to identify these patients early in the disease course. Our results are preliminary and a validation in a larger population is ongoing.

Reference: 1. Ravelli A et al. Ann Rheum Dis. 2016 Mar;75(3):481-9.

Disclosure: S. Carbogno, None; D. Pires Marafon, None; G. Marucci, None; M. Pardeo, None; A. Insalaco, None; V. Messina, None; R. Nicolai, None; F. De Benedetti, Abbvie, Sobi, Novimmune, Roche, Novartis, Sanofi, UCB, Pfizer, 2; C. Bracaglia, None.

Hemophagocytic Lymphohistiocytosis (HLH) Mimickers: CXCL9 As a Potential Biomarker Distinguishing HLH from Other Hyperferritinemic Syndromes

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Background/Purpose: Increased ferritin is considered biomarker highly suggestive of primary and secondary HLH and it is one of the HLH-2004 diagnostic and MAS guidelines (1,2), nevertheless it could also be elevated in other inflammatory conditions. Interferon-gamma (IFN γ) and IFN γ -induced chemokines, particularly CXCL9, have been demonstrated to be markedly elevated in patients with primary and secondary HLH.

Methods: We describe eight patients with hyperferritinemia who fully or partially met the HLH-2004 diagnostic guideline, but in which the subsequent clinical course and further investigations led to different diagnosis that required different therapies and to investigate the CXCL9 levels in identify diseases that may mimic HLH. To be noted that soluble CD25 was not measured in these patients. Serum CXCL9 levels were analyzed by DuoSet ELISA KIT DY392 (R&D Systems, Minneapolis, Minn). Normal values of CXCL9 are lower than 700 pg/ml.

Results: We identified 8 patients with laboratory features suggestive of HLH, included high ferritin levels (>500 ng/ml). Three of these patients met five of the HLH-2004 criteria, two of them met four criteria and the others two met three criteria. One patient presented only high serum ferritin level and cytopenia. CXCL9 levels were <300 pg/ml in seven of them and approximately 600 pg/ml in one patient. The clinical disease course and the other investigations ruled out the diagnosis of HLH and every patient received a different diagnosis. None of them received treatment for HLH (Table 1).

Table 1. Patients' features.

Pt	Gender	Months at onset	HLH-2004 Criteria	Ferritin ng/ml	CXCL9 pg/ml	Final diagnosis
1	M	1	5	9.849	<300	Osteopetrosis
2	M	6	5	800	<300	Vitamin B12 deficiency
3	M	1	5	543	<300	Chronic granulomatous disease
4	M	1	4	15.629	<600	Short bowel syndrome
5	M	3	4	4.378	<300	Cobalamin deficiency
6	F	2	3	37.232	656	Shaken baby syndrome
7	M	165	3	1.400	<300	Ghosal hematodiaphyseal dysplasia
8	M	172	2	1.184	<300	Primitive myelofibrosis

Conclusion: Since HLH is a life-threatening condition, early recognition and promptly therapy are essential to modify the disease course. One of the most typical feature of primary and secondary HLH is high ferritin level. Due to the severity of the disease, sometimes patients need to be treated before all criteria are fulfilled. The eight patients reported had features highly suggestive of HLH and met the HLH-2004 criteria, or part of them. However they all received a different final diagnosis. Despite all presented with high ferritin levels, CXCL9 was low in all. CXCL9 is a chemokine specifically induced by IFN γ , and has been demonstrated to be markedly elevated in patients with primary and secondary HLH due to the activation of the IFN γ pathway. In these cases CXCL9 was able to differentiate diseases with high ferritin that mimics HLH. High CXCL9 levels appear to be a potential specific biomarker for HLH diagnosis. Early dosage of CXCL9 levels in patients with hyperferritinemia and with clinical suspicion of HLH may be helpful for a timely differential diagnosis.

Reference: 1. Henter JI et al. *Pediatr Blood Cancer* 2007 Feb; 48(2):124-31.

2. Ravelli A et al. *Ann Rheum Dis*. 2016 Mar;75(3):481-9.

Disclosure: G. Marucci, None; I. Caiello, None; M. Pardeo, None; V. Messina, None; G. Prencipe, None; A. Pascarella, None; F. De Benedetti, Abbvie, Sobi, Novimmune, Roche, Novartis, Sanofi, UCB, Pfizer, 2; C. Bracaglia, None.

External Validation of the Autoinflammatory Disease Activity Index (AIDAI) in Patients with Colchicine-Resistant FMF, Hids/Mkd, and TRAPS: Results from a Pivotal, Phase 3 Trial of Canakinumab

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Session Time: 9:00AM-11:00AM

Background/Purpose: AIDAI is an ovel and unique, validated patient (pt)-reported assessment tool to evaluate disease activity in familial Mediterranean fever (FMF), hyper-IgD syndrome/mevalonate kinase deficiency (HIDS/MKD) and TNF receptor-associated periodic syndrome (TRAPS).¹ Here we performed an external validation of AIDAI by calculating scores over 40 weeks (wks) of canakinumab (CAN) treatment in pts enrolled into the CLUSTER trial (NCT02059291) and assessed correlation between AIDAI and disease/response characteristics.

Methods: CLUSTER consisted of one cohort per disease (crFMF, HIDS/MKD and TRAPS).² AIDAI was calculated as the sum of 12 items (Yes=1; No=0)¹ for 30 consecutive days. AIDAI score was calculated if the first score was recorded before ≥ 29 days. Missing items beyond last evaluable measurement were imputed by last observation carried forward (LOCF). Inactive disease (ID) was defined as AIDAI score < 9 . Correlation analysis of AIDAI with Sheehan disability score (SDS), child health questionnaire–psychological/physical (CHQ–PSC/PCS), physician global assessment (PGA), short form 12–physical/mental component summaries (SF12–PCS/MCS), C-reactive protein (CRP), and serum amyloid A (SAA) were performed. Significance was set at $p < 0.05$.

Figure 1. Median AIDAI scores over 40 weeks

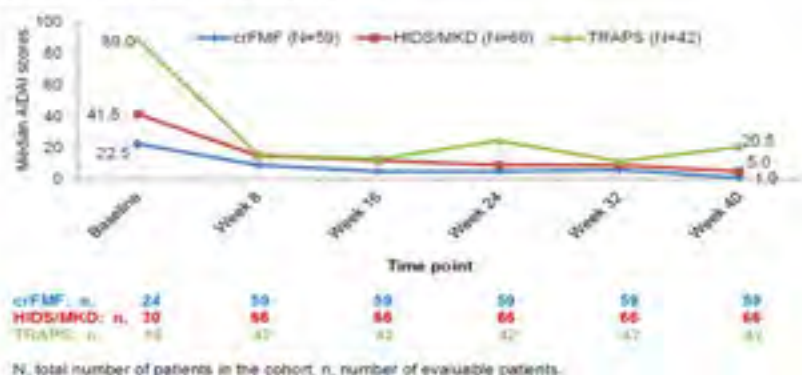


Table 1. Correlation between AIDAI and disease activity variables at Week 40								
	Correlation coefficient (95% CI)							
	SDS	CHQ-PSC	CHQ-PCS	PGA	SF12-PSC	SF12-MCS	SAA	CRP
crFMF (n=59)	20	12	12	42	11	18	39	42
	0.54* (0.22; 0.78)	-0.43* (-0.66; -0.19)	-0.38* (-0.60; -0.16)	0.34 (-0.08; 0.61)	-0.47* (-0.72; -0.21)	-0.43* (-0.70; -0.05)	-0.39 (-0.58; -0.20)	-0.37 (-0.58; -0.24)
HIDS/MKD (n=60)	23	20	20	54	9	0	32	33
	0.39* (0.05; 0.65)	-0.47* (-0.70; -0.23)	-0.32 (-0.57; 0.14)	0.24 (-0.03; 0.47)	-0.06 (-0.71; 0.61)	-0.19 (-0.76; 0.54)	0.06 (-0.22; 0.32)	0.28 (-0.19; 0.54)
TRAPS (n=42)	20	12	12	32	14	14	20	31
	0.41* (0.02; 0.69)	-0.57 (-0.82; 0.53)	-0.32 (-0.59; 0.56)	0.37* (0.02; 0.63)	-0.40* (-0.66; -0.11)	-0.13 (-0.62; 0.43)	-0.17 (-0.50; 0.20)	-0.18 (-0.51; 0.16)

* $p < 0.05$; N, total number of patients in the cohort; n, number of evaluable patients.

Results: Overall, 167 (crFMF: N=59; HIDS/MKD: N=66; TRAPS: N=42) pts were randomized to CAN 150 mg or placebo every 4 wks. Median AIDAI scores in all 3 cohorts decreased from baseline (BL) to Wk 16 (crFMF: 22.5 to 5.0; HIDS/MKD: 41.5 to 12.0; TRAPS: 89.0 to 13.0) and through Wk 40 (crFMF: 1.0; HIDS/MKD: 5.0; TRAPS: 20.5; Fig 1). In all cohorts, the proportion of pts with ID (AIDAI score <9) was higher at Wk 40 versus BL (crFMF: 69.5% vs 5.1%; HIDS/MKD: 56.1% vs 6.1%; TRAPS: 42.9% vs 2.4%). AIDAI at Wk 40 correlated significantly with: SDS in all 3 cohorts; CHQ-PsCS in crFMF and HIDS/MKD; CHQ-PCS in crFMF; PGA in TRAPS; SF12-PCS in crFMF and TRAPS. SF12-MCS, CRP, and SAA did not correlate with AIDAI (Table1).

Conclusion: AIDAI scores decreased markedly over 40 weeks of treatment with canakinumab in crFMF, HIDS/MKD and TRAPS, with a relevant percentage of patients having inactive disease score. AIDAI improvements at Week 40 correlated with patient- and physician-driven evaluations. AIDAI is a validated patient-reported tool to assess disease activity and appears to have good sensitivity to change to be used in comparative trials. Patient's experience on disease activity does not strictly correlate with CRP and SAA, as these reflect more closely biological inflammation than clinical symptoms.

References: 1. Piram M, et al. *Ann Rheum Dis.* 2014;73:2168-73. 2. DeBenedetti F, et al. *NEJM.* 2018;378:1908-19.

Disclosure: I. Koné-Paut, None; M. Piram, Novartis, Pfizer, Abbvie, 5; Novartis, 8; S. Benseler, Novartis, SOBI, AbbVie, 5; J. B. Kuemmerle-Deschner, Novartis, 2; Novartis, SOBI, 5; A. F. Jansson, Novartis, 2; I. Rosner, None; A. Tommasini, None; S. Murias, None; O. Karadag, None; J. Levy, Novartis, 5; S. Smeets, Novartis, 3; F. De Benedetti, Novartis, Roche, Pfizer, SOBI, AbbVie, Novimmune, BMS, Sanofi, 2.

Abstract Number: 1419

Long-Term Outcome of 50 Patients with Linear Scleroderma Treated with Methotrexate

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Linear Scleroderma (LS) is the most common subtype of localized Scleroderma in children and the one most frequently associated with tissue damage and functional disability. During the last decade, methotrexate (MTX) has been used as first choice agent for LS but, to date, available data on long-term outcome are partial and incomplete. Aim of this study was to assess the disease recurrence and the long-term outcome of children with LS treated with MTX since diagnosis.

Methods: We conducted a retrospective and cross-sectional study including children with LS followed at our Paediatric Rheumatology Centre between 2000 and 2016. Patients treated with MTX for at least one year, then followed for at least 2 years were included. Disease course was evaluated by retrospective analysis of clinical features, treatment and number of flares. Outcome at the last visit was assessed by evaluation of disease activity and severity of tissue damage and/or functional impairment by Localized Scleroderma Cutaneous Assessment Tool (LoSCAT) and thermography. Clinical remission (CR) was defined in presence of inactive disease off treatment for more than two years; clinical remission on medication (CRM) in presence of inactive disease while on treatment.

Results: 50 patients, 24 with LS of the trunk/limbs and 26 with LS of the face, entered the study. MTX treatment duration was 3.1 years (median 2.9, range 1.8-8.5 years). Only 16% patients did not respond to the first therapy with MTX, 16% had at least one flare of the disease, on average 30 months after starting MTX and 10% presented recurrent relapses. The mean follow-up was 7.8 years (median 6.8, range 2.1-16.3). Within 5 year follow-up, 81.8% of patients achieved CRM and by 10 year follow-up, 80.0% obtained CR. In the group of 16 patients with >10 years, CR was reported in 87.5%. At the last evaluation, tissue damage was very mild in 42% of patients, moderate in 32% and severe in 26%. Various degree of functional limitation was reported in 41.7% of patients with LS of the limbs. Severity of tissue damage was not related to the part of the body involved or to the disease duration, while functional disability was more frequent in LS of the limbs (p=0.039). LS body site and severity of tissue damage were not associated with disease recurrence or remission, while the length of therapy was related to number of disease relapses (p=0.040) and severity of tissue damage (p=0.003).

Conclusion: Most patients with LS treated with MTX achieve complete remission without flares and only a minority present repeated relapses or active disease after more than 10 years. The long-term monitoring of the patients, even after stopping MTX treatment is crucial to promptly identify possible flares and treat them properly. Overall aesthetic and functional sequelae are moderate and develop early in the disease course as their severity is not related to the disease duration.

Disclosure: G. Martini, None; G. Fadanelli, None; A. Agazzi, None; F. Vittadello, None; A. Meneghel, None; F. Zulian, None.

Abstract Number: 1420

Prospective Validation of Cone Beam Computed Tomography for the Assessment of Disease Progression in Linear Scleroderma of the Face

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Currently, the techniques used for the monitoring of Localized Scleroderma of the face (LSF) have significant limitations. We prospectively evaluated the reliability of the Cone Beam Computed Tomography (CBCT), a non-invasive, reproducible technique with a radiation dose lower than a conventional CT, to quantify changes of facial asymmetry over time as compared with the clinical and instrumental methods currently in use.

Methods: Consecutive patients with LSF, followed from January 2009 to December 2017 at our Pediatric Rheumatology Center, entered the study. CBCT was carried out following the same method previously described¹. Measurements of total thickness, soft tissue and bone thickness were taken in both affected and unaffected sides of the case. These data allowed us to calculate the Absolute Rate of Change (ARC) of the lesion over time and the comparison with the ARC obtained from the healthy side, allowed us to calculate the Relative Rate of Change (RRC). The judgment of stability or worsening of the lesion was compared with the one derived from the physician global assessment (PGA), infrared teletermography (IT) and sequential clinical photographs (SCP). The Sensitivity-to-change of CBCT was assessed by Standardized Response Mean (SRM) and Effect Size (ES).

Results: 26 subjects with LSF, 15 females and 11 males, mean age 7.6 years (range 1.2-17.8) entered the study. 18 patients presented Parry Romberg syndrome (PRS), 5 En coup de sabre (ECDS) and 3 facial hemiatrophy (FH). The disease duration at the first CBCT was 3.7 years (range 0-28). During the study period, 69 CBCTs have been performed. On average, each patient underwent 2.7 CBCTs, 15 patients underwent two CBCTs, 8 patients three, and one patient 4, 5 or 6 CBCTs each, respectively. In all, the total thickness of the affected and unaffected side were evaluated. A worsening of CBCT with RRC > 5%, was found in 10 out of 40 evaluations (25%). The agreement between the CBCT and SCP was found in 20 out of 37 evaluations (54%). The comparison of the four clinical-instrumental methods performed in 40 evaluations, revealed an overall agreement of 66.7%. CBCT results were consistent with the PGA in 67.6% evaluations, with IT in 62.2%. The sensitivity to change of CBCT over time was very good at the mandibular condyle level (SRM values ranging from 0.53 to 0.77, ES 0.40-0.50) on the healthy side. The affected side reported SMR and ES values <0.5.

Conclusion: CBCT is an innovative technique that allows to assess the changes of the affected side, usually the *non-growth*, of LSF in comparison with the healthy side, during the developmental phase of pediatric patients. CBCT represents a reliable and objective tool for monitoring LSF over time in association with the other clinical-instrumental methods currently in use. Its practical benefit lies in its potential of correctly addressing therapeutic changes including the timing of start the reconstructive surgical process.

1. Di Giovanni C. et al. Cone beam computed tomography for the assessment of linear scleroderma of the face. *Pediatric Rheumatology* 2018; 16: 1.

Disclosure: A. Meneghel, None; S. Puggina, None; E. Kamburi, None; G. Martini, None; F. Vittadello, None; F. Zulian, None.

Evaluating the Validity of SIX-Minute Walk Test in Juvenile Systemic Sclerosis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Pulmonary vascular disease and interstitial lung fibrosis are the leading causes of morbidity and mortality in Juvenile Systemic Sclerosis (JSSc). Six-minute walk test (6MWT) is a self-paced sub maximal exercise test used for evaluating functional exercise capacity, prognosis and response to therapy in patients with cardiopulmonary diseases. While the results of studies on the availability of the test in adults are contradictory, there are limited data concerning the usefulness of 6MWT in children with JSSc. We aimed to evaluate the walking distance and oxygen desaturation during the 6MWT in JSSc, and to establish correlations between the 6MWT results and other clinical findings in children with JSSc.

Methods: 25 JSSc, 27 Juvenile Systemic Lupus Erythematosus (JSLE) and 30 healthy controls were included. The test is conducted according to the guidelines recommended by the American Thoracic Society (ATS), standardized in 2002. The Borg Scale which is a well-validated scoring system on a 0-10 point scale was used to determine the patient self reported fatigue and dyspnea levels.

Results: Demographic data are shown in Table 1. Mean walking distance was 480,18 ± 47,22 m in JSSc; 513,66 ± 51,70 m in JSLE and 553,21 ± 41,65 m in healthy controls. JSSc patients walked significantly less distance comparing to controls (p <0.001). The mean oxygen saturation in JSSc was 98.0 ± 0.9% before the test and 97.5 ± 1.6% after the test (p = 0,01). JSSc patients with lung involvement walked less than those without lung involvement (476.08 ± 47.13 m vs .483.96 ± 48.89 m), but without statistically significant difference (p = 0.68). JSSc patients with carbon monoxide diffusion capacity (DLco) ≤ 60% walked less than those with DLco ≥ 60% (466.92 ± 45.74 m vs. 485,33 ± 48,05 m). However, no statistically significant correlation was detected. (p = 0.39). No significant difference was found when patients walking distances were compared to activity scores (Juvenile Systemic Sclerosis Severity Score (J4S)) (p = 0.26). Lower extremity pain during and after the test was more statistically significant in JSSc patients (p = 0.001). Patients with myalgia were found to walk less than those without myalgia (498.61 ± 46.94 m vs. 460.20 ± 40.29 m) (p = 0.038).

Total	Juvenile Systemic Sclerosis N=25	Juvenile Systemic Lupus Erythematosus N=27	Healthy children N=30	p-value
Gender , Female, n(%)	22 (88%)	21 (77.8%)	16 (53.3%)	p=0,04
Age mean±SD (years)	16,44±3,19 years	16,74±3,59 years	15,57±1,50 years	p=0,27
Body mass index, mean±SD	18,75±2,99 kg/m ²	20,43±3,05 kg/m ²	19,94±1,69 kg/m ²	p=0,06

Conclusion: The findings of our study showed that patients with JSSc have limited walking distances. The pulmonary involvement and associatively high disease activity score are unable to determine the results of the 6MWT in JSSc patients. However, the musculoskeletal involvement may influence the walk distance and complicate interpretation of the 6MWT in JSSc patients. Since there are a limited number of studies regarding the role of 6MWT in the evaluation of JSSc, we believe that the results of our study will enlighten the future studies.

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Impact of Juvenile Localized Scleroderma on Longitudinal Quality of Life

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Juvenile localized scleroderma (jLS) is a chronic autoimmune disease, with cutaneous and extra-cutaneous manifestations (ECM) requiring long-term immunosuppressive therapy. Few studies have evaluated the effect of jLS on health-related quality of life (HRQoL). We describe parental HRQoL findings in a multi-center prospective jLS study.

Methods: A prospective, pilot study of 50 jLS subjects beginning immunosuppressive therapy and followed for 1 year was conducted in 10 Childhood Arthritis and Rheumatology Research Alliance centers. Clinical assessments, treatment effects, and HRQoL measures (including Peds QLTM Family Impact (PedsQLTM FI) reports and ACR functional class) were collected at study visits. Domains of Peds QLTM FI include effect of child's disease on parental Physical, Emotional, Social and Cognitive Functioning, the family's Daily Activities, and Family Relationships. The Worry module relates to parental worry about treatment and disease related issues affecting the child and family. Peds QLTM FI scores were analyzed for association with patient characteristics, with change in domain scores over time analyzed by mixed effects models. Dunnett post-hoc tests were used to compare follow-up scores against baseline.

Results: Twenty-five subjects completed parental Family Impact QOL data at 0, 6, and 12 month visits. Most were female (68%), Caucasian (88%), had linear subtype (60%), and ECM (84%), and experienced at least one treatment-related adverse effect (72%). Seventeen percent of subjects had ACR global functional > class 1. At all visits, the lowest scores were found in the Peds QLTM FI domains of Worry and Emotional Functioning (Table). Overall, scores for Emotional Functioning, Daily Activities, and Family Relationships improved from 0 to 12 months (p = 0.015- 0.035, Table). Parents of female subjects were more likely to report higher Physical Functioning and lower (worse) Worry scores over time (p <0.0001, 0.0264, respectively). Parents of subjects with ACR class 2 or higher reported lower Daily Activities scores, with improvement in scores over time (p<0.0001).

Conclusion: Our study supports the hypothesis that jLS impacts HRQoL. Parents of female subjects were found to worry more about disease issues and treatment, while poorer subject global function impacted family daily activities. Over time, scores improved for parental Emotional Functioning, family Daily Activities, and Family Relationships, possibly related to treatment. Head involvement and ECM were not specifically associated with poorer parental HRQoL scores. Future studies should evaluate the potential impact of jLS on parental and family HRQoL, and how these relate to patient HRQoL to improve long-term management of this disease.

Table. Summary of PedsQLTM Family Impact Scores at Three Study Timepoints

	0 months (study entry)		6 months		12 months		
DOMAINS*	Mean	SD	Mean	SD	Mean	SD	p-value
Physical Functioning	72.0	24.3	81.2	17.7	86.7	14.9	0.08
Emotional Functioning	64.4	26.8	76.0	18.4	80.9	20.3	0.04
Worry	54.6	22.0	61.1	20.1	65.4	17.6	0.10
Daily Activities	83.7	26.0	88.4	15.8	95.7	9.4	0.02
Family Relationships	84.6	17.6	87.6	14.1	95.2	8.9	0.02

* Scores range from 100 (no issues) to 0 (almost always has issues). P-values refer to change over time.

Disclosure: V. Sivaraman, None; K. S. Torok, None; M. Moore-Clingenpeel, None; F. Dedeoglu, Novartis, 9; P. Ferguson, None; E. Pope, None; T. G. Mason II, None; M. L. Becker, None; G. Higgins, None; C. E. Rabinovich, None; S. Hong, None; M. Ibarra, None; R. M. Laxer, None; R. Fuhlbrigge, None; K. Stewart, None; M. Punaro, None; S. Li, None.

Abstract Number: 1423

Autoantibody Testing in Pediatric Localized Scleroderma (LS)

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

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Session Time: 9:00AM-11:00AM

Background/Purpose: Pediatric localized scleroderma (LS) is typically categorized by the depth and extent of skin lesions into main subtypes: linear scleroderma, including linear trunk/limb and linear head, circumscribed morphea(superficial or

	MagPix SSc Profile (ALBIA)		SSc Profile (LIA-EUROIMMUN)		RDIS ENA Profile (RDIS Connective 13)		Chi-square Clinical association (p<0.05)
	(n=69)						
Autoantibody	#	%	#	%	#	%	
CENP A	-	-	10	14%	-	-	Joint contracture, pain at lesion, subcutaneous atrophy, MSK involvement
CENP B	-	-	4	6%	-	-	Lesion pain, tingling
Centromere	6	9%	-	-	-	-	None
KU	-	-	5	7%	-	-	None
Nor90	-	-	8	12%	-	-	New lesions, Renal involvement
PM-75	-	-	4	6%	-	-	Shiny lesion, hypopigmented, Pulmonary involvement
PM-SCL	7	10%	10	14%	-	-	Subcutaneous atrophy, pain at onset, Endocrine involvement
Ribosome	-	-	-	-	7	10%	Shiny lesion, hypo & hyperpigmented
RO-52	-	-	7	10%	21	30%	Thick skin, joint contracture, Neurologic involvement
RP11 (RNA Pol III)	1	1%	8	12%			New lesion, texture lesion, joint contracture (onset and current)
SCL-70	6	9%	7	10%	-	-	Skin texture, pain at lesion, subcutaneous atrophy, joint contracture
SM	-	-	-	-	8	12%	Shiny lesion, hypo & hyperpigmented
SM-RNP	-	-	-	-	11	16%	Shiny lesion, hyperpigmented, Renal involvement
SSA-60	-	-	-	-	10	14%	Skin thickness
SSB	-	-	-	-	5	7%	Tight skin, hypopigmented

deep), generalized plaque morphea, and mixed subtype. It has become increasingly recognized that LS effects more than the skin; greater than 50% of patients are affected by extra-cutaneous manifestations (ECMs), such as musculoskeletal and neurologic involvement. In systemic sclerosis (SSc), a related but typically more serious type of scleroderma, distinctive clinical subsets and specific patterns of organ involvement can be anticipated by autoantibody serological findings, which aid in the treatment and preventive care for these patients. The role of autoantibodies (autoAbs) in LS as a disease risk stratifier or ECM associations has only been partially evaluated with select antibodies. We suggest a wide array of SSc-associated autoAbs to investigate patterns with clinical associations in LS.

Methods: Plasma from 69 pediatric LS patients and 46 pediatric healthy controls were tested for anti-nuclear antibody (ANA) and various SSc-specific and SSc-associated auto Abs including those to extractable nuclear antigens (ENE) in the FIDIS™ Connective Profile, and to those contained in a SSc line immunoassay (LIA) (Euroimmun, Germany) and a MagPix® (Luminex™) addressable laser bead immunoassay (ALBIA), for a total of 29 distinct autoAbs. Normal cutoffs were determined from the healthy pediatric samples (2 SD above the mean) and then applied to the LS samples to determine positivity. Chi-square analysis was used to determine relationships with clinical variables.

Results: ANA positivity ($\geq 1:80$ titer) was present in 70% of the LS patients, half of them with a speckled pattern, followed by cytoplasmic (17%), homogenous (12%), nucleolar (10%) and centrosome (9%) pattern. Fifteen of the 28 specific antibodies tested were seen in $> 5\%$ of the LS patients and are summarized in Table, along with their significant clinical associations.

Conclusion: Certain 'classic' SSc-associated auto-antibodies, such as Scl-70, centromere (CENP A) and RNA Pol III (RP11) were found in a frequency ranging from 6 – 14%, and these 3 auto-antibodies were associated with deep tissue involvement, signified by joint contractures, nerve entrapment and muscle involvement. Interestingly, none of the 15 auto Ab associated with LS subtype designation. Although internal organ involvement is uncommon in LS, when it was present, it did associate with an autoantibody. Therefore, supporting the use of these SSc-associated antibodies as potential classifiers or predictors of disease involvement in LS, though may be different manifestations from SSc. Further analyses of the details of ECMs, and associations of autoAbs with traditional labs (WBC, ESR, CPK), other autoAbs, and cytokines are underway.

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Abstract Number: 1424

After 24 Months Observation Period the Patients Related Outcomes Improve Significantly in the Juvenile Scleroderma Inceptions Cohorte

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

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Session Time: 9:00AM-11:00AM

Background/Purpose: Juvenile systemic sclerosis (jSSc) is an orphan disease with a prevalence 3 in a 1 000 000 children(1). Published data is limited regarding the course of jSSc with standardized assessment of patients. We report our data from the juvenile sclerosis inception cohort over the first 24 months after enrollment.

Methods: The juvenile sclerosis inception cohort is a prospective multicenter registry of patients with jSSc, who fulfill the adult classification criteria, are less than 16 years old at onset, and are less than 18 years at the time of inclusion in the cohort. We evaluated the clinical characteristics of those followed at least 24 months in the registry.

Results: Forty jSSc patients met this criteria. The majority were female (80%) with diffuse cutaneous subtype (77.5%) and 20% had overlap features. Mean disease duration at time of inclusion was 3.2 years. Mean age of onset of Raynauds was 8.2 years and the first non-Raynauds 8.7 years. Those on DMARDs increased from 73% at the time of inclusion and to 95% after 24 months. 85% of the patients were ANA positive, approximately 25% anti-Scl70 positive and 3% antitopoisomerase positive. The mean modified skin score decreased from 14.4 to 12.9. The frequency of Raynaud's stayed around 87.5%. The frequency of the nail fold capillary changes increased from 55% to 62%, but the frequency of active ulcerations decreased from 23% to 20%. The number of patients with FVC <80 % decreased from 42% to 39% (p=0.8). The number of patients with DLCO < 80% decreased from 54 to 44% (p=0.58). The number of patients with pulmonary hypertension assessed by ultrasound increased from 5% to 10% (p=0.396). No patient developed hypertension or renal crisis. Gastrointestinal involvement decreased from 32.5% to 22.5% (p=0.317). Number of swollen joints decreased from 23% to 17.5% (p=0.53). Total muscle weakness decreased from 5 % to 0% (p=0.224) and elevated CK decreased from 17% to 11% (p=0.54). Several patient related outcomes improved significantly. Patient global disease activity (VAS 0-100) from 49.2 to 29.4(p=0.001), patient global disease damage (VAS 0-100) from 43.9 to 29.8 (p=0.013) and patient Raynaud activity VAS 0-100) from 26.7 to 14.2 (p=0.045) as physician global disease activity (VAS 0-100) from 48.3 to 33.2 (p=0.021).

Conclusion: Over the 24 months observation period patient related outcomes improved significantly and fortunately most other clinical parameters did not reveal any significant deterioration. It seems, that the current treatment can reach improvement judged by the patients and stabilization of the disease outcomes.

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Abstract Number: 1425

Update from the Juvenile Sclerosis Inception Cohort

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Session Information

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Background/Purpose: Juvenile systemic scleroderma (jSSc) is an orphan disease with a prevalence of 3 in 1 000 000 children(1). There is limited data published regarding the clinical presentation of jSSc. The juvenile systemic scleroderma inception cohort is a multinational cohort with a prospective standardized assessment of the patients. We present the clinical characteristics of the patients at time of the inclusion in the cohort.

Methods: The juvenile scleroderma inception cohort is a prospective multicenter registry of patients with jSSc, who fulfill the adult classification criteria, are less than 16 years old at disease onset, and are less than 18 years of age at the time of inclusion in the cohort. We evaluated the patient’s characteristics at time of inclusion in the cohort.

Results: One hundred and nine jSSc patients were enrolled and analyzed as of April 15th, 2018. The majority are female (79%) and Caucasian (90%). Diffuse cutaneous subtype was the most common (80%), with 15% having overlap features. The mean age of onset of Raynauds was 9.7 years in the diffuse subtype (djSSc) and 10.5 years in the limited subtype (ljSSc) (p=0.62). The mean age of non-Raynauds was 10.2 in the djSSc and 11.2 in the ljSSc (p=0.52). Mean disease duration at time of inclusion was 3.4 in the djSSc and 2.5 in the ljSSc group. Approximately 80% of all jSSc patients received DMARDs. ANA positivity was around 86% in both groups. Anti-Scl70 was 32% in djSSc and 39% in the ljSSc group. Anticentromere positivity was 4% in the djSSc and 11% in the ljSSc group(p=0.28). Mean Modified Rodnan skin score was 18.2 in the djSSc and 7.7 in the ljSSc (p=0.001). Gottron papulae were significantly more common the djSSc with 27% compared to 7% in the ljSSc group. History of ulceration was significantly more common in the djSSc with 57% compared to 29% in the ljSSc group (p=0.010). FVC<80% occurred in 34% in the djSSc and 21% in the ljSSc group (p=0.295). DLCO <80% occurred 44% in the djSSc and 43% in the ljSSc group. Pulmonary hypertension assessed by ultrasound occurred 7% in both groups. No hypertension or renal crisis was reported or observed. Gastrointestinal involvement occurred 35% in the djSSc and 24% in the ljSSc (p=0.28). Number of swollen joints were observed around 20% in both groups. Muscle weakness with joint contractures were present in 12% in the djSSc and 28% in the ljSSc group. Tendon friction rub was present in 4 % in djSSc and 7% in the ljSSc group. djSSc patients had significantly worse scores for physician global disease activity (VAS 0-100), 41.6 compared to 30.7 (p=0.041) and for physician global disease damage (VAS 0-100) 38.2 compared to 18.9 (p=0.023).

Conclusion: In this large cohort of jSSc patients there are surprisingly not many significant differences between djSSc and ljSSc. According to the physician global, the djSSc patients have significantly more severe disease.

1. Beukelman T, Xie F, Foeldvari I. Assessing the Prevalence of Juvenile Systemic Sclerosis in Childhood Using Administrative Claims Data from the United States. Journal of Scleroderma and Related Disorders. 2018;3.

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The Utilization of S100 Proteins Testing in Pediatric Rheumatology Patients in a Tertiary Care Institution and Implications for Care

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Background/Purpose: S100 proteins are calcium-binding proteins of increasing value as biomarkers in various inflammatory conditions (e.g. auto inflammatory diseases, vasculitides, inflammatory bowel disease). The two highly studied members in this family; S100A12 and S100A8/9 complex have been proven useful as diagnostic markers. Our study evaluated the utilization of S100 proteins in the clinical setting. We studied the correlation between those markers and other widely used inflammatory markers, disease activity, medication use in our JIA population.

Methods: Subjects were patients seen at the hospital's specialty clinics (mainly rheumatology) who had S100 proteins tested at some point during their care. The lab reports S100 proteins results as a numeric value above zero. Obtaining S100 proteins is considered part of clinical practice in our institution in the investigation of certain inflammatory conditions. This is a relatively recent addition to practice, and therefore, there are no standard guidelines on specific indications and

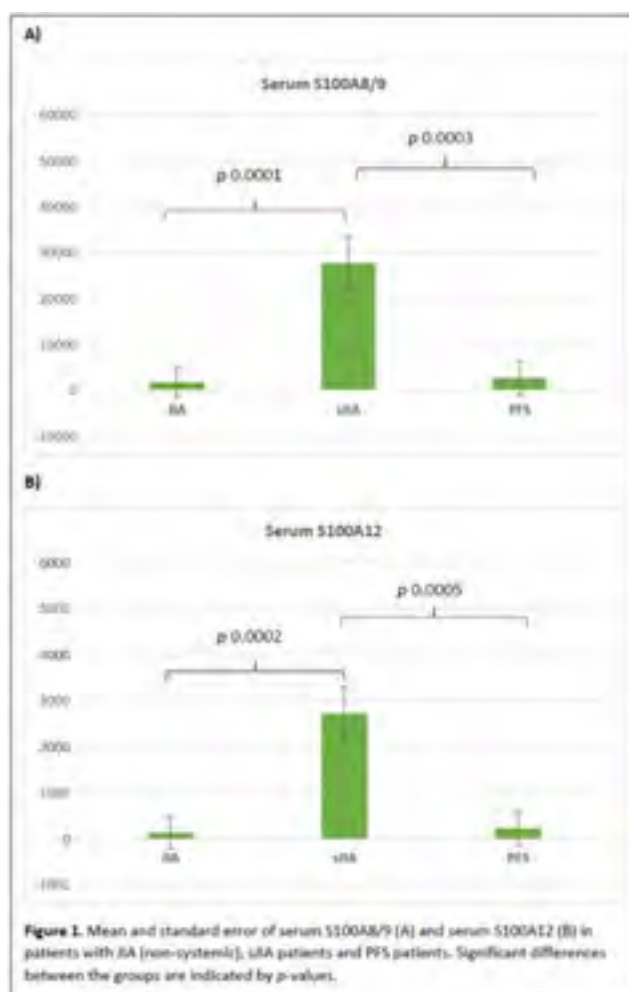


Table 2. Correlation between serum S100 protein levels and clinical and laboratory variable in JIA patients.

S100 level	Diagnosis							
	JIA				sJIA			
	CRP	ESR	AJC	LROM	CRP	ESR	AJC	LROM
A8/9	0.53***	0.35	-0.21	0.00	0.97***	0.82*	0.30	0.46
A12	0.25	0.26	-0.17	-0.09	0.98***	0.81*	0.53*	0.79*

* p<0.05 ** p<0.01 ***p<0.001
CRP (C-reactive protein), ESR (erythrocyte sedimentation rate), AJC (active joint count), LROM (limited range of motion).

follow-up tests. A retrospective chart review was performed to collect data on serum S100 protein levels, other inflammatory markers and disease activity. Descriptive statistics were calculated for all variables. SAS software was used to perform all analyses. For continuous variables, mean and standard errors are reported, and comparisons were calculated using two-sample t-tests. For categorical variables, frequency and percentage are reported. Correlation was studied using Pearson Correlation Coefficient.

Results: A total of 118 patient charts with S100 protein levels were reviewed. most patients have a diagnosis of JIA. Patients with systemic JIA (sJIA) had higher levels of S100A8/9 and S100A12 compared to patients with non-sJIA and periodic fever syndrome (PFS) (Figure 1).Correlation analysis revealed strong correlation between CRP and S100A8/9 as well as S100A12 in sJIA patients. S100A12 was found to have moderate to strong correlation with disease activity in sJIA patients. However, other variables including disease activity showed weak to moderate correlation (Table 2).

Conclusion: S100A8/9 and S100A12 were found to be particularly elevated in sJIA patients with a strong correlation with concomitant CRP values. Elevated S100A12 was linked to disease activity in sJIA patients. More data points are needed to delineate correlation between disease activity over time and S100 proteins. S100 proteins can serve as markers to aiding the diagnostic work-up of fever and sJIA and potentially disease activity monitoring in JIA.

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Abstract Number: 1427

A New Model of Care for Pediatric Rheumatology in Ontario: Preliminary Results from Pilot Telemedicine Clinics Utilizing Advanced Clinician Practitioners in Arthritis Care

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Background/Purpose: Twenty-five pediatric rheumatologists (PR) service a population of 14 million Ontarians. To facilitate care to patients living in distance communities we proposed a new model of care using a local Advanced Clinician Practitioners in Arthritis Care (ACPAC) to engage with PRs via tele medicine. The first phase of this project reported our needs assessment of patients seen in London and Toronto. Of a total of 265 patient/caregiver respondents, 80% of patients travelled > 50 km with 13% travelling > 200 km with an associated cost >\$50 in 37% and ≥1 missed day of work in 56% to attend PR visits. We present preliminary results from the second phase of this project: a survey of patient/parent satisfaction in attending an ACPAC-PR tele health clinic visit.

Methods: Twenty-five ACPACs interested in additional pediatric rheumatology training attended a two-day training program occurred in September 2016. Of the four ACPAC therapists participating in the pilot clinic phase, 3 had extensive

pediatric experience and fourth received on-site training. Patient/caregiver perception of visit burden and satisfaction of the ACPAC-PR telehealth visit were surveyed. Quantitative data were summarized using descriptive statistics and qualitative data were analyzed using grounded theory.

Results: Four telehealth clinics in both Windsor ACPAC-London PR (28 visits, 20 unique patients) and Thunder Bay ACPAC-Toronto PR (18 unique patient visits) have occurred to date. 19/23 surveys were returned from the Windsor-London clinic and 12/18 distributed at the Thunder Bay-Toronto site. 26/31 (84%) travelled < 25 km to the clinic. 21/31 (68%) spent <\$ 25 on travel with 32% spending nothing. 12/45 (27%) of parents/guardians missed 1/2 to 1 full day of work with no one missing more than 1 day. >90% of respondents strongly agreed/agreed that they were satisfied with the telemedicine process and interaction with the ACPAC and PRs. 30/31 (96%) indicated that “the care I received today was equal to the care I receive in person” and that the wait time to see the PR was adequate (versus too short or too long) compared with an in person visit (87%).

Conclusion: A model of care integrating ACPACs, telemedicine and PRs improves local access to pediatric rheumatology care while reducing the burden of travel and cost to families. Barriers to the full implementation of this model include the lack of funding for ACPACs to provide these outreach clinics as well as lack of (pediatric) ACPACs in distant communities to sustainably provide this valuable service.

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Abstract Number: 1428

Parental Involvement and Adolescents/Young Adults Self-Management during the Transition Period: A Cross-Sectional Survey in Childhood Onset Rheumatic Diseases

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Background/Purpose: A NIH focus group study found that adolescents and young adults (AYA) with active disease relied heavily on their parents for disease management. It was reported that increased parental involvement demonstrated less AYA control and responsibility. It was further recommended to reduce the role of the parent in order to enable the AYA to manage the disease into adulthood (Huang, JS et al. Transition to Adult Care: Systematic Assessment of Adolescents with Chronic Illnesses and their Medical Teams, J Ped, 159;6, Dec 2011). This study examines parental involvement and AYA self-management of healthcare responsibilities and decision-making in pediatric rheumatology.

Methods: A cross sectional study of 42 adolescent/young adult patients ages 14-25 yrs with a childhood onset rheumatic disease and 32 of their parents were prospectively recruited from consecutive ambulatory visits at single center urban academic institution. Both groups were asked to complete separate surveys that assessed transition readiness perception, parental involvement, and AYA management skills. Healthcare providers were asked to complete a questionnaire assessing age appropriate parental involvement at each encounter. Patient and parent demographics were obtained.

Results: There were 23 AYAs between ages 13-17 (16 yrs, SD 0.93) and 17 AYAs between 18-25 (20 yrs, SD 1.98). AYA self-reported ethnicity showed 38% (16) were white, 21% (9) were Hispanic, and 7% (3) were Hispanic. Diagnosis composed of 55%(23) JIA, followed by 19% (8) SLE. Of the parents, 64% (27) were mothers and 48% (20) were white. Table 1 demonstrates that parents agreed that AYA self-management was somewhat/very important. Both groups of parents reported to be somewhat/very involved in the patient's health and consistently performed most tasks for the AYA. (Figure 1a). Yet 53% of all parents answered that AYA should self-manage between ages 16-18. Both adolescents (87%) and young adults (84%) also agreed that self-management was somewhat/very important. There was a discrepancy between young adult involvement (89%) and the tasks performed by the AYA (Figure 1b).



Table 1. Descriptive Statistics-Primary Variable. Figure 1. Survey Results

Physicians perceived a progression in decision-making from the adolescent to young adults, but reported that only a minority of young adults(41%) demonstrated independent healthcare responsibility again. AYAs and parents perceived increased parental and less AYA decision-making from adolescent to young adult (Figure 1c).

Conclusion: In this cohort of childhood onset rheumatic diseases there was a failure to demonstrate progress towards independence from the adolescent to the YA cohorts. The majority of patients over age 18 were nonindependent in making health care decisions and one third of young adults took over health related specific tasks from their parents. Further prospective longitudinal study is needed to determine the optimal goals and methods to successfully achieve health care independence.

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A Quality Update: Improved Transfer Time Among Rheumatology Patients Transferring from Pediatric to Adult Care at an Academic Medical Center

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Background/Purpose: Transfer from pediatric- to adult-oriented health care is challenging for patients with childhood-onset rheumatologic disease, and may be associated with treatment on-adherence, disease flares and urgent healthcare utilization. This study aimed to measure transition outcomes among young adults transferring from pediatric to adult care at a single US academic medical center, before and after implementation of transition process improvements.

Methods: Transition process improvements implemented by the pediatric rheumatology practice between 2012 and 2017 included the creation of a transition policy, systematic identification of transition-age patients, and quarterly transition planning rounds. Electronic health record (EHR) query was used to identify patients who transferred from pediatric to adult rheumatology care within the institution during 2012-2017. Primary endpoints were transfer time (time from last pediatric to first adult appointment) and successful transfer. Successful transfer was defined as 1) transfer time from pediatric to adult care <6 months and 2) completion of >2 visits with an adult provider within a 12-month period. Secondary endpoints were pre- and post- transfer disease activity as measured by physician global assessment or SLEDAI score (active v. inactive), and insurance type (public, private, both). We compared outcomes to those of patients who transferred during 1995-2005, prior to the implementation of transition support processes. Bivariate statistics were used to compare differences between groups.

Results: 87 patients transferred from pediatric to adult rheumatology care during 2012-2017, and 31 patients transferred during 1995-2005 (Table 1). Diagnoses were similar in both groups. During 2012-2017, median transfer time was significantly shorter (3.5 vs. 7.1 months, $p=0.03$), and 52% of patients transitioned successfully. Transitioning patients were more likely to have active disease in 1995-2005, both pre-transfer (61% vs 29%, $p=0.001$) and post-transfer (61% vs 26%, $p=0.001$). More patients were publicly insured pre-transfer during 1995-2005 (74% public and 26% private vs. 42% public, 55% private and 2% both, $p=0.009$), but there were no differences in insurance type post-transfer.

Conclusion: During the implementation of transition initiatives, median transfer time from pediatric to adult rheumatology significantly decreased, and over half of patients transferred successfully. Disease activity at the time of transfer also improved, which may reflect improvements in disease management or differences in disease severity. Although direct causal associations between transition support interventions and transfer success cannot be made, this study suggests that implementation of structured transition processes may positively impact the transfer to adult care.

Table 1. Characteristics and Transition Outcomes of Young Adults Transferring from Pediatric to Adult Rheumatology Care at an Academic Medical Center, 1995-2005 and 2012-2017

Variable	Transferred 1995-2005 (N = 31)	Transferred 2012-2017 (N = 87)	P
<i>N (%) unless noted</i>			
Demographics			
Female	23 (74)	73 (84)	NS
Age pre-transfer, mean (SD)*	19.6 (1.2)	20.4 (1.2)	0.001
Race			NS
White	10 (32)	29 (33)	
African American	2 (6)	8 (9)	
Asian	7 (23)	25 (29)	
Other	12 (38)	25 (29)	
Disease characteristics			
Rheumatologic diagnosis			0.07
JIA	5 (16)	30 (34)	
SLE	16 (52)	27 (31)	
Other	10 (32)	30 (34)	
Active disease pre-transfer*	19 (61)	25 (29)	0.001
Active disease post-transfer*	19 (61)	23 (26)	0.001
Health Insurance			
Pre-transfer			0.009
Public	23 (74)	37 (42)	
Private	8 (26)	48 (55)	
Both	0 (0)	2 (2)	
Post-transfer			NS
Public	14 (45)	32 (36)	
Private	17 (55)	53 (60)	
Both	0 (0)	2 (2)	
Transition Outcomes			
Transfer time (months), median (range)+	7.1 (0.7-33.6)	3.5 (0.3-45.7)	0.03
Successful transfer^	53.8%	N/A	

JIA = Juvenile Idiopathic Arthritis, SLE = Systemic Lupus Erythematosus

* Active disease = presence of active disease according to physician global assessment or SLEDAI, Pre-transfer = final pediatric rheumatology visit, post-transfer = first adult rheumatology visit

+ Transfer time = Time from last pediatric appointment to first adult appointment.

^ Successful transfer = 1) transfer time <6 months, and 2) completion of >2 visits with an adult provider within a 12-month period.

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Research Priorities for Addressing Mental Health Needs of Pediatric Patients with Rheumatologic Disease

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

Session Type: ACR Poster Session B

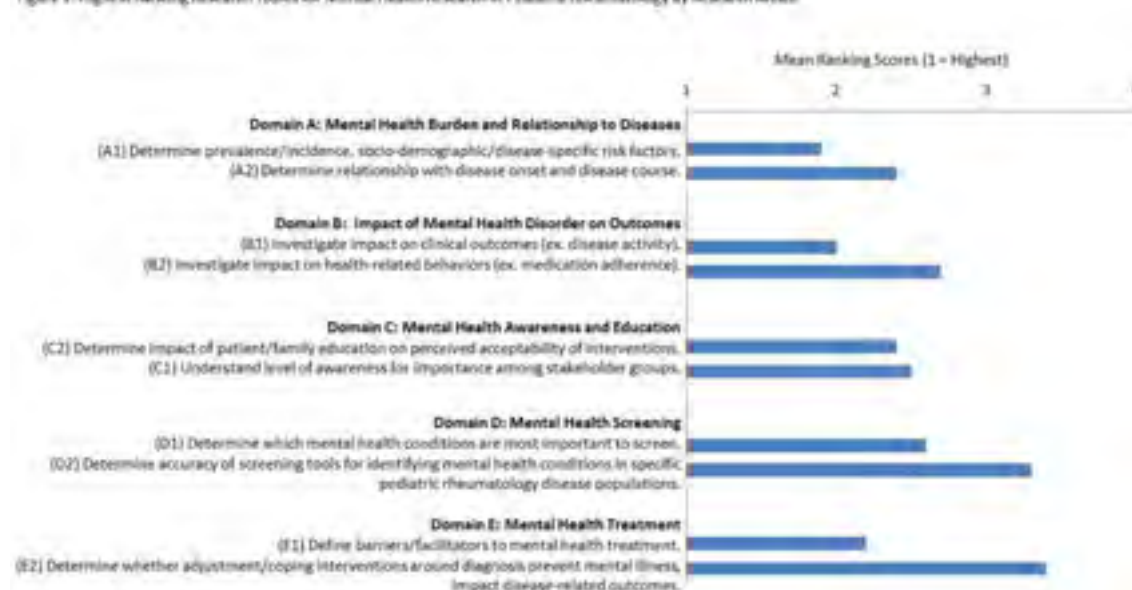
Session Time: 9:00AM-11:00AM

Background/Purpose: Mental health problems are prevalent in pediatric rheumatology patients. Gaps in knowledge exist regarding the detection, effective treatment, and the impact of mental illness on patients with rheumatologic disease. To address these gaps and direct research efforts to improve mental health for children and adolescents with rheumatologic diseases, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Mental Health Workgroup developed and prioritized an agenda of research topics.

Methods: A systematic review of the literature on mental health in pediatric rheumatology was completed and published. From the review, 5 major research domains in further need of study were identified: (A) mental health burden and relationship to pediatric rheumatologic disease, (B) impact of mental health disorders on outcomes, (C) mental health awareness and education, (D) mental health screening, and (E) mental health treatment. Research topics within these areas were developed and presented at the CARRA Mental Health Workgroup Annual Meeting in April 2018, where they were discussed and refined. An online survey was created to prioritize the 33 refined topics. The survey was emailed to 132 people who expressed interest in the workgroup, including pediatric rheumatologists, patients/parents, research coordinators, psychologists, social workers, and members of industry. Participants were asked to: i) grade each research topic on a 5-point Likert scale on how important, feasible, and actionable they were, and ii) provide an overall ranking of the research topics within each research area.

Results: Fifty-six (42%) responded to the survey, and 45 of the respondents completed the survey (80%). Topics related to the impact of mental health on clinical outcomes were rated most important, and those related to mental health screening

Figure 1. Highest Ranking Research Topics for Mental Health Research in Pediatric Rheumatology by Research Area:



Ranking of 33 mental health research topics by domain from the results of a survey of CARRA Mental Health Workgroup. Number of topics per domain was as follows: domain A had 5 topics, domain B 6 topics, domain C, 5 topics, domain D 9 topics, and domain E 8 topics.

were rated most feasible and actionable (Table 1). Overall rankings revealed additional topics of high priority within each research domain (Figure 1).

Conclusion: Addressing gaps in knowledge about how mental health affects youth with rheumatologic disease and how best to address mental health for these patients is an important step in improving care. We have identified high priority research topics regarding mental health of pediatric rheumatology patients in need of further investigation, that are feasible to study and believed to lead to actionable results in patient care.

Table 1. Highest Scored Research Topics for Mental Health Research in Pediatric Rheumatology by Importance, Feasibility, and Actionability.

Research Topic:	Mean Score (\pm SD) (1=Low, 5=High):
Most Important:	
(B1) Investigate the impact of mental health on clinical outcomes, such as disease activity.	4.7 (\pm 0.5)
(A1) Determine the prevalence and incidence of mental health disorders in pediatric patients with rheumatologic disease, as well as socio-demographic and disease-specific risk factors.	4.7 (\pm 0.5)
(B2) Investigate the impact of mental health on long-term clinical outcomes, such as disease damage and mortality.	4.6 (\pm 0.6)
Most Feasible:	
(D4) Determine barriers and facilitators to mental health screening for pediatric patients with rheumatologic disease.	4.2 (\pm 0.9)
(D2) Determine the accuracy of mental health screening tools for identifying mental health conditions in specific pediatric rheumatology disease populations (i.e. validation of tools for disease-specific diagnostic cut-points).	4.1 (\pm 0.7)
(A1) Determine the prevalence and incidence of mental health disorders in pediatric patients with rheumatologic disease, as well as socio-demographic and disease-specific risk factors.	4.1 (\pm 0.8)
Most Actionable:	
(D1) Determine which mental health conditions are most important to screen for in pediatric patients with rheumatologic disease.	4 (\pm 0.8)
(D2) Determine the accuracy of mental health screening tools for identifying mental health conditions in specific pediatric rheumatology disease populations (i.e. validation of tools for disease-specific diagnostic cut-points).	3.9 (\pm 0.7)
(D5) Determine acceptability of mental health screening in pediatric rheumatology clinics for patients, caregivers, and clinicians, and identify strategies to improve acceptability.	3.9 (\pm 0.8)

Means and standard deviations presented of the highest ranking research topics from 33 developed research topics addressing mental health in pediatric rheumatology around importance (relevance of the topic to advancing clinical care and research, considering existing knowledge), feasibility (ease with which research related to the topic can be conducted and completed), and actionability (ability to apply the results of research on the topic towards advancing clinical care and pediatric rheumatology research). Likert scale responses were 1 = Low, 2 = Somewhat Low, 3 = Neutral, 4 = Somewhat High, 5 = High.

Disclosure: T. Rubinstein, None; L. Waqar, None; J. Woo, None; E. Ogbu, None; W. B. Lapin, None; L. Ng, None; E. Treemarcki, None; A. M. Knight, None.

Abstract Number: 1431

Kikuchi-Fujimoto Disease: A Retrospective Analysis of 23 Pediatric Cases from a US Center

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Session Information

Session Date: Monday, October 22, 2018

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Kikuchi-Fujimoto Disease (KFD) is often described as a benign self-limited disease. However, there is a risk of recurrence. It is most common in adult Asian females but has been reported in other races and in children. Prior studies have noted differences between pediatric and adult cases and suggest that male children are more affected than female children. However, these were mostly Asian studies raising the question of racial and sex differences of this disease in other populations. In particular, studies from North America is lacking. As we have one of the largest, diverse centers in the US, our objective was to describe our cohort of pediatric patients with KFD and to examine racial and gender differences in clinical and laboratory parameters.

Methods: We conducted a retrospective study of patients diagnosed at our center from January 1, 2007 to January 1, 2017. Using natural language selection, patients with biopsy-proven KFD were identified from our institutional pathology database and included in our study. We extracted corresponding clinical and laboratory data from our electronic medical records. We excluded patients older than 18 years at the time of diagnoses and patients with a concurrent or pre-existing

diagnosis of systemic lupus erythematosus. IRB approval of the study protocol with waiver of informed consent was obtained from our institution.

Results: We identified 23 patients with KFD who met our inclusion and exclusion criteria as shown in table 1 with racial and sex comparisons in table 2. The majority of our patients were Black (74%). Female to male ratio was 1.3:1. Mean age for males was significantly lower than for females. Bilateral cervical lymphadenopathy, fever, fatigue and elevated lactose dehydrogenase were common. There were more males with severe KFD, consisting of fever and weight loss, than females. The odds of having severe KFD in males was 12.831 times the odds in females (95% CI 1.694, 97.172 p-value 0.0135). Median follow-up period was 4 months. Four patients (17%) had a recurrence of disease during their follow-up. We found no significant difference in clinical or laboratory data in Black patients compared to other races.

Conclusion: To the best of our knowledge, this is the largest pediatric study of KFD in the US. Our findings show a slight female predominance and higher recurrence rate relative to prior pediatric reports. This strengthens the need for longitudinal studies on patients with KFD to determine risk factors for recurrence.

Table 1: Descriptive Characteristics of Patients with Kikuchi- Fujimoto Disease

Characteristic	N (%) (n=23)	Missing = N
Demographics		
Sex		
Female	13 (56.52)	
Male	10(43.48)	
Race		
Black or African American	17 (73.91)	
Other	6 (26.09)	
Ethnicity		
Non-Hispanic or Latino	22 (95.65)	
Hispanic or Latino	1 (4.35)	
Age in years	13 (3.59) ^a	
Clinical characteristics		
Fever	19 (82.61)	
Arthritis	1(4.35)	
Headache	10 (45.45)	1
Arthralgia	5 (21.74)	
Fatigue	18 (78.26)	
Sore throat	5 (21.74)	
Weight loss	10 (43.48)	
Cervical lymphadenopathy	22 (95.65)	
Bilateral	10 (43.48)	
Left only	8 (34.78)	
Right only	4 (17.39)	
Deep lymphadenopathy	4 (19.05)	
Hepatomegaly	1 (4.35)	
Splenomegaly	3 (13.04)	
Severe KFD (Fever and weight loss)	9 (39.13)	
Laboratory characteristics		
Positive ANA ($\geq 1:80$)	4 (66.67)	17
Anemia (hemoglobin ≤ 10 g/dl)	6 (27.27)	1
Thrombocytopenia (<150000 /uL)	4 (18.18)	1
Leukopenia (<3500 /uL)	13 (59.09)	1
Lymphopenia (<1000 /uL)	7 (30.43)	1
Neutropenia (<1500 /uL)	10 (45.45)	1
Low albumin (<3.5 g/dl)	9 (52.94)	6
Elevated Alanine Transaminase (>24 U/L)	15 (75.00)	3
Elevated Aspartate Transaminase (>33 U/L)	17 (85.00)	3
Elevated C-Reactive Protein (>1.0 mg/dl)	13 (72.22)	5
Elevated Erythrocyte Sedimentation Rate (>20 mm/hr)	15 (65.22)	
Elevated Ferritin (>67.4 ng/ml)	10 (100.00)	13
Elevated Lactate Dehydrogenase (>400 U/L)	15 (88.24)	6
Elevated Uric Acid (>5.4 mg/dl)	1(5.26)	4
Outcome		
Symptom onset to diagnosis in weeks	4 (3.00) ^b	
Follow-up in months	4 (23.90) ^b	3
Received treatment	11 (50.00)	1
Recurrence	4 (17.39)	

Abbreviations: ANA = Anti-nuclear antibody; KFD = Kikuchi-Fujimoto Disease.

a Mean (SD) ^b Median (IQR)

Table 2: Comparison of Patients with Kikuchi- Fujimoto Disease by Sex and Race

	Female N (%) (n=13)	Male N (%) (n=10)	P-value ^c	Black N (%) (n=17)	Other race N (%) (n=6)	P-value ^c
Age in years a	15(2.24)	10(4.30)	0.05 ^S	14(3.76)	15(4.00)	0.76
Female				9(52.94)	4(66.67)	0.66
Black	9(69.23)	8(80.00)	0.66			
Clinical characteristics						
Fever	10(76.92)	9(90.00)	0.60	14(82.35)	5(83.33)	1.00
Arthritis	1(7.69)	0(0.00)	1.00	1(5.88)	0(0.00)	1.00
Headache	6(50.00)	4(40.00)	0.69	6(37.50)	4(66.67)	0.35
Arthralgia	3(23.08)	2(20.00)	1.00	4(23.53)	1(16.67)	1.00
Fatigue	10(76.92)	8(80.00)	1.00	14(82.35)	4(66.67)	0.58
Sore throat	2(15.38)	3(30.00)	0.62	4(23.53)	1(16.67)	1.00
Weight loss	3(23.08)	7(70.00)	0.04 ^S	6(35.29)	4(66.67)	0.34
Cervical lymphadenopathy	12(92.31)	10(100.00)	1.00	16(94.12)	6(100.00)	1.00
Bilateral	5(38.46)	5(50.00)		7(41.18)	3(50.00)	
Left only	5(50.00)	3(30.00)		5(29.41)	3(50.00)	
Right only	2(15.38)	2(20.00)		4(23.53)	0(0.00)	
Deep lymphadenopathy	3(25.00)	1(11.11)	0.60	3(20.00)	1(16.67)	1.00
Hepatomegaly	0(0.00)	1(10.00)	0.43	1(5.88)	0(0.00)	1.00
Splenomegaly	0(0.00)	3(30.00)	0.07	2(11.76)	1(16.67)	1.00
Severe KFD (Fever and weight loss)	2(15.38)	7(70.00)	0.01 ^S	5(29.41)	4(66.67)	0.16
Laboratory characteristics						
Anemia (hemoglobin \leq 10g/dl)	4(33.33)	2(20.00)	0.65	4(25.00)	2(33.33)	1.00
Thrombocytopenia ($<150000/uL$)	2(16.67)	2(20.00)	1.00	3(18.75)	1(16.67)	1.00
Leukopenia ($<3500/uL$)	6(50.00)	3(30.00)	0.42	9(56.25)	4(66.67)	1.00
Lymphopenia ($<1000/uL$)	5(38.46)	2(20.00)	0.41	6(35.29)	1(16.67)	0.62
Neutropenia ($<1500/uL$)	5(41.67)	5(50.00)	1.00	7(43.75)	3(50.00)	1.00
Low albumin ($<3.5g/dl$)	5(55.56)	4(50.00)	1.00	7(53.83)	2(40.00)	0.62
Elevated Alanine Transaminase ($>24U/L$)	8(72.73)	7(77.78)	1.00	11(73.33)	4(80.00)	1.00
Elevated Aspartate Transaminase ($>33U/L$)	9(81.82)	8(88.89)	1.00	13(86.67)	4(80.00)	1.00
Elevated C-Reactive Protein (>1.0 mg/dl)						
Elevated Erythrocyte Sedimentation Rate ($>20mm/hr$)	10(76.92)	5(50.00)	0.22	10(58.82)	5(83.33)	0.37
Elevated Lactate Dehydrogenase ($> 400U/L$)	7 (87.50)	8(88.89)	1.00	12(92.31)	3(75.00)	0.43
Outcome						
Symptom onset to diagnosis in weeks ^b	4(4.00)	4(2.00)	0.05 ^S	4(1.00)	6(4.00)	0.16
Follow-up in months ^b	3(22.00)	6(25.88)	0.92	13(33.00)	4(4.00)	0.03 ^S
Received treatment	7(58.33)	4(40.00)	0.67	7(43.75)	4(66.67)	0.64
Recurrence	2(15.38)	2(20.00)	1.00	4(23.53)	0(0.00)	0.54

Abbreviations: ANA = Anti-nuclear antibody; KFD = Kikuchi-Fujimoto Disease.

a Mean (SD) ^b Median (IQR) ^c Fishers exact test ^SStatistically significant with p-value <0.05 .**Disclosure:** E. Ogbu, None; S. Chandrakasan, None; S. Park, None; S. Prahalad, None.**Abstract Number:** 1432

Engaging Patients and Parents to Improve Mental Health for Youth with Rheumatologic Disease

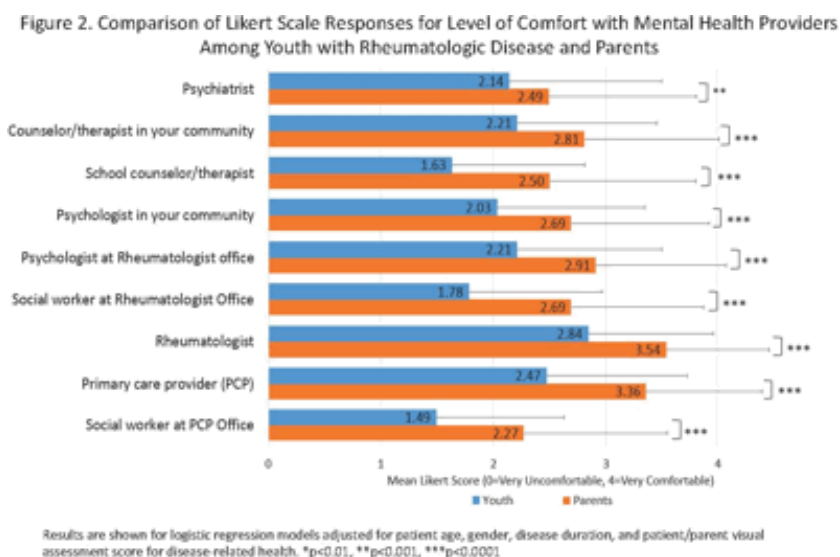
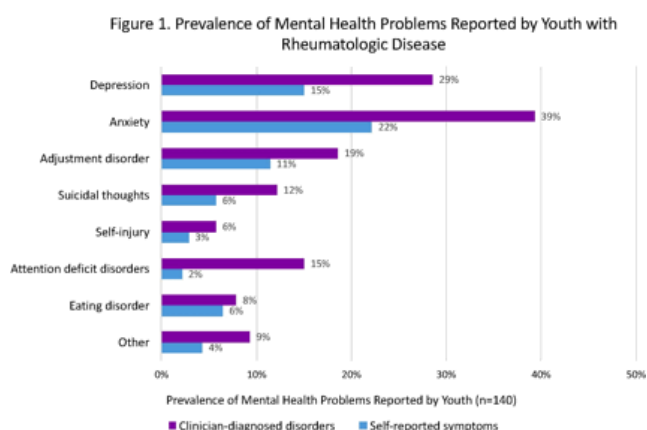
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Session Information

Session Date: Monday, October 22, 2018

Background/Purpose: Mental health conditions are common in youth with rheumatologic disease, yet intervention strategies are under studied. We used a patient-engaged approach to investigate the mental health needs of youth with rheumatologic disease.

Methods: An anonymous online survey examined beliefs and experiences with mental health for youth with rheumatologic disease. Eligible youth ages 14-24 years had a diagnosis of juvenile arthritis, juvenile dermatomyositis, or systemic lupus erythematosus, and reported specific treatment for the condition. Parents of youth 8-24 years meeting the above criteria were also eligible to participate. The survey was developed in collaboration with patient and parent advisors, the Childhood Arthritis & Rheumatology Research Alliance (CARRA), and the Patients, Advocates, and Rheumatology Teams Network for Research and Service (PARTNERS). Participants were recruited through the Arthritis Foundation, Lupus Foundation of America, and Cure JM Foundation. We compared youth and parent responses using regression models (adjusted for demographic and disease covariates) to examine: 1) reported prevalence of mental health problems, categorized into mutually exclusive clinician-diagnosed disorders and self-reported symptoms, 2) mean Likert ratings (0=low, 4=high) forth impact of disease aspects on mental health, and 3) comfort level with potential mental health providers.



Results: 485 respondents included 140 patients(29%) and 345 (71%) parents. Clinician-diagnosed anxiety was reported by 39% of youth, depression by 29%, and adjustment disorders by 19% (Figure 1); another 22%, 15% and 11% had self-reported symptoms of these disorders, respectively. Mean Likert ratings by youth indicated that disease aspects most impacting mental health were physical limitation at 2.7 (SD 1.1), taking medications at 2.6(1.2), and dealing with disease flares at 2.5 (1.2). Adjusted models showed no difference between youth and parents for reported mental health problems or impacting factors. Youth were significantly less comfortable interacting with potential mental health providers than

parents, particularly social workers and school counselors (Figure 2); both groups felt most comfortable with rheumatologists and primary care providers.

Conclusion: Youth with rheumatologic disease have high rates of diagnosed and undiagnosed mental health problems, which are impacted by their disease. Mental health intervention in primary care and subspecialty care settings may improve mental health education, screening and treatment for these youth.

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Abstract Number: 1433

The Role of Patient and Parental Resilience in Amplified Musculoskeletal Pain Syndrome

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Resilience is a dynamic process of positive adaptation in the context of significant adversity. While higher levels of resilience have been associated with improved physical function and reduced depression and pain in adults

Table. Clinical Characteristics and Resilience Levels Among Children with AMPS and Their Caregivers

	Patients (n=20)	Parents (n=20)
Demographics		
Female, n (%)	19.0 (95.0)	15.0 (75.0)
Age (years), median (IQR)	15.0 (13.0, 15.5)	48.0 (45.0, 51.0)
Caucasian, n (%)	14.0 (70.0)	19.0 (95.0)
Non-Hispanic, n (%)	16.0 (80.0)	17.0 (85.0)
Clinical Variables, median (IQR)		
Pain visual analog scale (0-100)	63.0 (30.5, 79.5)	27.0 (7.5, 62.0)
Energy level (0-100)	55.0 (41.8, 72.5)	80.0 (62.5, 90.0)
Functional Disability Inventory (FDI) (0-60)	23.5 (17.5, 39.0)	28.0 (18.5, 33.5)
Widespread Pain Index (WPI)* (0-19)	5.0 (2.5, 11.0)	—
Symptom Severity Score (SSS)* (0-12)	6.0 (5.0, 7.5)	—
Resilience Measures, mean (SD)		
RS-14	74.1 (12.9)	79.4 (11.7)
CD-RISC-10	26.5 (7.0)	28.8 (6.5)
The 7 Cs Tool	3.1 (1.7)	—

AMPS = amplified musculoskeletal pain syndrome; IQR = interquartile range; SD = standard deviation; FDI scores range from 0-60 with greater scores indicating more functional disability; RS-14 (14-item Resilience Scale) scores range from 14-98, with greater scores indicating greater resilience. Scores are categorized into very low (14-56), low (57-64), on the low end (65-73), moderate (74-81), moderately high (82-90) and high (91-98). The Connor-Davidson Resilience Scale 10-item scores range from 0-40 with higher scores indicating greater resilience. The mean CD-RISC-10 level of patient resilience in this study is lower than that previously reported in adolescents with cancer, type 1 diabetes and inflammatory bowel disease, which all range from 27.3-30.4 (Rosenberg et al 2015; Carlson et al 2017). The 7 Cs Tool is validated for an adolescent population only (≥ 13 years). Scores range from 0-14 with higher scores indicating lower resilience and a cut off of ≥ 3 considered low resilience (Garg et al 2017). *WPI and SSS defined according to the 2010 American College of Rheumatology Criteria for Fibromyalgia Syndrome

with chronic musculoskeletal pain, our knowledge regarding the role of resilience in children with amplified musculoskeletal pain syndrome (AMPS) is limited. We aimed to 1) measure the level of resilience among patients with amplified musculoskeletal pain syndrome and one of their caregivers and 2) determine factors associated with patient resilience.

Methods: This was a prospective inception cohort study of children ages 13-17 years diagnosed with AMPS and one of their caregivers. Eligible subjects were seen for an initial consultation in the pediatric rheumatology pain clinic from March 2018 – May 2018. Subject-caregiver pairs completed online questionnaires including demographic surveys and two measures of resilience: The 14-Item Resilience Scale (RS-14) and the Connor-Davidson Resilience Scale 10-item (CD-RISC-10). Children completed another resilience measure, the 7 Cs Tool. Clinical and demographic variables were abstracted from electronic medical records. We performed multivariate linear regression analyses, using stepwise forward selection with $p < 0.2$, to explore the relationship between patient resilience (using CD-RISC-10) and variables of interest including parental resilience.

Results: 20 patient-proxy pairs were included. The majority of patients were female (75%) and Caucasian (70%). Parents were predominantly mothers (95%) and Caucasian (95%). Table 1 shows other demographic variables. 95% of children had ≥ 1 adverse childhood experience (ACEs) with parental separation being the most common (20%). According to the RS-14, both children and parents had moderate resilience (Table). On the CD-RISC-10, children had a mean score of 26.5 (SD 7.0) and parents had a mean score 28.9 (SD 6.5). This compares to a mean level of resilience of 30.1 (SD 5.3) among a normative student sample (Hartley MT, 2012). According to the 7 Cs Tool, the mean level of patient resilience was low (total score ≥ 3), with a mean of 3.05 (SD 1.7). All measures of resilience were statistically significantly correlated with one another ($p < 0.05$). From the final regression model, higher patient resilience was found to be associated with lower pain scores ($\beta = -0.17$), less depression ($\beta = -4.9$), more ACEs ($\beta = 1.93$), older age ($\beta = 1.92$), and a lower symptom severity score ($\beta = -0.63$) (all $p < 0.02$). Parental resilience did not contribute significantly to the model ($p > 0.2$).

Conclusion: Children with AMPS and their parents had low to moderate levels of resilience. Higher patient resilience was associated with lower disease burden among children with AMPS. Resilience-training interventions serve as potential treatment modalities for this patient population.

Disclosure: S. Gmuca, None; A. Urquhart, None; P. F. Weiss, Lilly, 5, 9; J. S. Gerber, None; D. D. Sherry, None.

Abstract Number: 1434

Patient-Proxy Agreement on Health-Related Quality of Life in Juvenile Fibromyalgia Syndrome

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Session Information

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Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The administration of proxy-reported health-related quality of life (HRQoL) measures in the assessment of juvenile fibromyalgia syndrome (JFMS) is common but its added clinical value to patient-reported measures is unclear. The aim of this study was to examine the level of agreement between patient- and proxy-reports of the Pediatric Quality of Life Inventory Short Form 15 (PedsQL SF-15) among children with JFMS and to examine potential factors influencing patient-proxy agreement. Given the strong parent-child pain relationship, we hypothesized good agreement.

Methods: This was a cross-sectional cohort study of children 8-17 years old presenting for initial evaluation to a pediatric rheumatology pain clinic from April 2017 – April 2018. Included subjects met the 2010 American College of Rheumatology criteria for fibromyalgia syndrome. All patients and proxies completed electronic questionnaires, including the PedsQLSF-15, as part of routine clinical care. Additional information collected included age, sex, race, ethnicity, verbal pain score (0-10), and pain duration (months). Descriptive statistics were performed to assess patient characteristics. Intra-class correlation (ICC) estimates and their 95% confidence intervals were calculated based on a mean-rating, absolute-agreement, 2-way mixed-effects model to examine patient-proxy agreement on the PedsQL SF-15. We performed multiple regression analyses to explore the relationship between different independent variables and patient-proxy agreement.

Results: Over the study interval, 54 patient-proxy pairs met criteria and completed the HRQoL measures. The majority of patients were non-Hispanic (94%), Caucasian (79%), and female (83%). The median age at time of presentation was 15

Table 1.

PedsQL SF-15 Scores and Level of Patient-Proxy Agreement (ICC's)

PedsQL Domain	Patient-report (N=54) median (IQR)	Proxy-report (N=54) median (IQR)	Patient-proxy ICC (95% CI)
Physical Functioning	35.0 (25.0, 60.0)	35.0 (20.0, 55.0)	0.83 (0.71, 0.90)
Emotional Functioning	56.3 (43.8, 75.0)	50 (38.0, 56.3)	0.73 (0.52, 0.84)
Social Functioning	91.7 (66.7, 100)	83.3 (66.7, 100)	0.85 (0.73, 0.91)
School Functioning	50.0 (33.3, 66.7)	58.3 (41.7, 75.0)	0.72 (0.52, 0.84)
Physical Health Summary Score	35.0 (25.0, 60.0)	35.0 (20.0, 50.0)	0.83 (0.71, 0.90)
Psychosocial Health Summary Score	65.0 (52.5, 77.5)	60.0 (52.5, 70.0)	0.84 (0.72, 0.91)
Total Summary Score	59.2 (48.3, 68.3)	53.3 (43.3, 61.7)	0.85 (0.74, 0.91)

Legend: PedsQL SF-15 = pediatric quality of life inventory short form 15 item. HRQoL = health-related quality of life. PedsQL SF-15 scores range from 0-100 with higher scores indicating better HRQoL. Intra-class correlations (ICC's) were rated as 0-0.40: poor agreement; 0.41-0.60: moderate agreement; 0.61-0.80: good agreement; and 0.81-1.00: excellent agreement. The Psychosocial Health Summary Score is the sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales. The Physical Health Summary score is equal to the Physical Functioning Scale Score. The Total Summary Score is the sum of all items over the number of items answered on all of the scales.

years (IQR: 14, 16). The median verbal pain score was 5 (IQR: 4, 7). Median duration of pain was 24 months (IQR: 12-36). Cronbach's alpha coefficient for the PedsQL SF-15 exceeded 0.70. All domains demonstrated good to excellent agreement between patients and proxies (Table 1). Multiple regression analyses, adjusting for patient sex, Caucasian race, age, current pain level and pain duration showed that the greater the child's pain, the greater the patient-proxy agreement on the Total Scale ($\beta = -1.20$, $p < 0.05$) and the Emotional Functioning Scale ($\beta = -2.03$; $p < 0.05$).

Conclusion: The high levels of patient-proxy agreement in this study suggest that children with JFMS and their parents communicate their feelings and opinions well to one another and this agreement is associated with greater pain severity in the child. These findings reflect the enmeshed relational and communication styles between children with JFMS and their parents. In order to facilitate adolescents becoming partners in their own healthcare and to decrease the burden of multiple questionnaires, we propose focusing on children's own perceptions of HRQoL.

Disclosure: S. Gmuca, None; A. Urquhart, None; D. D. Sherry, None.

Abstract Number: 1435

Hormonal Contraception Use and Capacity to Self-Screen for Contraindications Among Adolescents in a Pediatric Rheumatology Clinic

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Many states allow pharmacists to prescribe combined hormonal contraception (HC), eliminating the barrier of a provider visit. For adolescent rheumatology patients, however, a clinician visit can be an opportunity to discuss specific hormonal contraindications. We examine adolescent rheumatology patients' HC experience, ability to self-screen for HC contraindications, and acceptability of pharmacist prescribing HC.

Methods: After IRB approval, females ages 14-21 were recruited from pediatric rheumatology (RC), primary care (PC), and other subspecialty (OS) clinics. Participants completed a demographic and behavioral survey, including Child with Special Health Care Needs (CSHCN) screener, perceived severity of pregnancy (1 item, range 1-5) and acceptability of pharmacist prescribing HC (2 items). Adolescents and physicians separately completed checklists for potential contraindications to HC per the CDC Medical Eligibility Criteria (MEC). The checklist was a screener, capturing broad categories rather than specific high-risk diagnoses (e.g. lupus in general, vs. + antiphospholipid antibodies). Discordance was any difference between adolescent and physician for a potential level 3/4 MEC contraindications. Unsafe discordance was Adol No/Physician Yes for a level 3/4 MEC contraindication (under-report) while safe discordance was Adol Yes/Physician No (over-report). We used Chi Square, ANOVA and logistic regression.

Results: We recruited 47 (16%) RC adolescent/physician pairs, 175 (58%) PC pairs, and 77 (26%) OS pairs. In RC, 71% identified as white, 11% African American, 2% Latino, and 16% multiracial or other. PC were more likely to be African American or Latino, and OS White. The mean age for RC was 16.3 +/- 1.3 years, similar to PC and OS (p=NS). 94% of RC were CSHCN, compared to PC 45% and OS 88% (p<.001). 19% of RC were sexually active, compared to 45% PC and 13% OS (p<.001).

In RC, 13 (28%) had ever used HC (combined pills, injection, ring, patch), and 2 (4%) LARC (implant, IUD), lower than PC (45% HC, 9% LARC) or OS (35% HC, 6.5% LARC) (p=.05 for HC). Thirty-two (68%) of RC patients had at least 1 potential MEC level 3/4 contraindication, higher than PC (14%) or OS (26%) (p<.001). The most common for RC were lupus, migraines, and hypertension. RC reported a higher perceived severity of pregnancy (RC 4.1 +/- 1.1 vs PC 3.2 +/- 1.6 and OS 3.6 +/- 1.4, p<.05). Although the rate of overall discordance between adolescent and providers for RC was high (RC 36% vs. PC 17% and OS 25%, p<.05), the rate of unsafe discordance was low (RC 11%, PC 6%, OS 9%, P=NS). Adolescents in RC were equally interested in pharmacist prescribing HC (RC 45%, PC 43% and OS 51%). Logistic regression among RC patients, controlling for age, only sexual experience was associated with (lower) unsafe discord.

Conclusion: Despite adolescent rheumatology patients' high rates of potential contraindications and low rates of HC use, they are interested in pharmacist access. When discordant, they are more likely to over-report (safe) rather than under-report (unsafe) potential contraindications. Clinicians caring for these adolescents should proactively address HC and associated risks.

Disclosure: S. Tarvin, None; T. Wilkinson, None; T. Vielott, None; A. Meredith, None; C. Meagher, None; M. Ott, Eli Lilly and Co., 3, 9.

Abstract Number: 1436

Pregnancy Outcomes in Partners of DMARD Exposed Men with Juvenile Idiopathic Arthritis – an Observational Study

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Males account for about one third of all cases of juvenile idiopathic arthritis (JIA). During the course of the disease and often into adulthood, they are exposed to various disease-modifying antirheumatic drugs (DMARDs). If men with JIA wish to have a child, they have to weigh the risk of disease flare on drug withdrawal against a not yet clearly defined impact of drugs on offspring.

The study objective was to investigate the outcomes of pregnancies in partners of male JIA patients who were exposed to DMARDs.

Methods: In the JIA biologic registry JuMBO (Juvenile arthritis MTX/Biologics long-term Observation), male patients with pregnancies in partners were identified. Standardized patient interviews were conducted and the outcome of pregnancies inquired. In addition, prospectively collected physician-reported data on treatment and disease activity of JIA patients were considered in the analysis.

Results: Out of the 1,397 patients enrolled in JuMBO, a total of 243 pregnancies in 125 women and in partners of 26 men with JIA were reported. Until February 2018, detailed information was available for 39 pregnancies of partners of 21 men

with JIA. Most male patients (43%) had polyarticular JIA, 24% enthesitis-related arthritis, 10% psoriatic arthritis. At first pregnancy, the mean paternal age was 23.2 ± 4.2 years, the mean disease duration was 13.3 ± 6.0 years and the mean disease activity according to cJADAS-10 4.8 ± 4.5 .

All men had been exposed to 2.5 ± 1.0 DMARDs for a mean of 7.1 ± 3.1 years until 1st pregnancy, 90.5% had received biological DMARDs. Of the 39 pregnancies, there were 26 (66.7%) with paternal DMARD exposure during time of conception. Exposures included etanercept in 12, adalimumab in 3, infliximab in 3, certolizumab in 2, anakinra in 1, methotrexate in 9 and leflunomide in 2 pregnancies. Pregnancy outcomes with paternal exposure (n=26) and without (n=13) were as follows: 22 and 10 live births, 1 and 1 elective pregnancy termination, 2 and 2 spontaneous abortions, 1 and 0 stillbirth, respectively. Of the 9 pregnancies with paternal MTX exposure, 6 (66.7%) resulted in a live birth, one (11.1%) was terminated electively and 2 (22.2%) resulted in an early miscarriage.

In the 32 pregnancies with live births, pregnancy complications were reported in 22% of the cases (in exposed pregnancies in 18%, in unexposed pregnancies in 30%). Adverse neonatal outcomes like preterm delivery and neonatal hospitalizations were reported in 3 (13.6%) and 3 (30.0%) and 5 (22.7%) and 3 (30.0%) cases, respectively. No children were born small for gestational age or with low APGAR score at 5 minutes, no child died in the neonatal period. Two children were born with major congenital anomalies (club foot, agenesis of the corpus callosum) according to the EUROCAT classification, both fathers were exposed (leflunomide, corticosteroids, NSAIDs, and MTX, certolizumab, corticosteroids, NSAIDs, respectively).

Conclusion: Men with JIA who are still undergoing treatment in young adulthood often procreate children under medication, why more information on the effect of medication on male reproduction is needed. For this, more patient data must be carefully evaluated.

Disclosure: P. Drenches, None; J. Klotsche, None; M. Niewerth, None; G. Horneff, None; K. Minden, Pfizer, Abbvie, Roche, 2, Abbvie, Roche, Chugai, Sanofi, MedCon, 5.

Abstract Number: 1437

Use, Safety and Efficacy of Thalidomide from a Tertiary Level Pediatric Rheumatology Centre in India

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Thalidomide is an effective agent for several pediatric rheumatic diseases: SOJIA, Behcet's disease and recalcitrant skin disease in cSLE to name a few.

Systemic onset Juvenile idiopathic arthritis is a common subtype of JIA seen in India. Patients with SOJIA are often steroid dependent and relapse on dose reduction. Tocilizumab though available is prohibitively expensive. Thalidomide also has a role to play for the therapy of recalcitrant oral aphthae in Behcet's disease and is also used for the calcinosis of Juvenile dermatomyositis. This study was undertaken to study the usage, safety & efficacy of thalidomide in children with pediatric rheumatic diseases.

Methods: This study was a retrospective chart review of all children with pediatric rheumatic diseases who had been prescribed Thalidomide from 01/06/2009 to 15/05/2018.

The safety & side effects were studied for all patients (71/71). Efficacy was studied for patients with SOJIA (65/71) due to small sample size of other diseases.

Results: Use: Thalidomide was taken by 71 children. SOJIA:65, SLE:1, Behcet's disease:3, Juvenile dermatomyositis with calcinosis universalis:1, Muckle wells syndrome:1

Safety and Side effects: Thalidomide was safe in all patients at a maximum daily dose of 5.7mg/kg/day. No NCV screening was done in children prior to starting thalidomide.

11/71 children (15.5%) reported minor side effects, 2 had constipation that necessitated dose reduction, 9 had increased somnolence. No neurological adverse events were noted. Thalidomide was used as a single bedtime dose to decrease somnolence. Maximum dose used was 200mg/day.

Efficacy in SOJIA patients: Thalidomide taken by 65/208(31%)patients with SOJIA followed at our unit. 23 girls and 42 boys.

Demographic Details		range
Median age at disease onset	4.5 years	0.7-16 years
Median age at disease diagnosis	5.4 years	1-16.16 years
Median delay to diagnosis	4 months	1-48 months
Median age at thalidomide commencement	7 years	1.7-18.08 years
Median duration of therapy with thalidomide	16 months	1-110 months
Median dose of thalidomide	3.1 mg/kg	1-5.7 mg/kg
Median dose of oral steroids prior to thalidomide	0.4 mg/kg	0-3.5 mg/kg
Median dose of oral steroids 6 months after thalidomide	0.01 mg/kg	0-1.18 mg/kg (P<0.001)
Steroids stopped after 6 months of Thalidomide	28/65	43%
Response in systemic features	60/65	92%
Response in articular features	37/65	57%
No response to Thalidomide(systemic features/articular features)	5/65	7.6%
Median time taken for response in systemic features	1 month	0.5-18 months
Median time taken to response for articular ds.	4 months	1-16 months
Longitudinal follow up		
No flare ever		30/65=46%
Only articular flare		13
Both articular and systemic flare		17
Thalidomide stopped		37/65=57%
No response/step up to Tocilizumab		5/37=13.5%
Disease remission		17/37=46%
Persistent articular disease not responding to Thalidomide after 6 months		15/37=40.5%

Conclusion: 1.Thalidomide is a safe drug with no neurological side effects noted in 71 children with a maximum daily dose of 5.7mg/kg/day over the maximum follow up period of 110 months.

2. It was used in 1/3 of total SOJIA patients

3. It was effective in 92% for systemic and in 57% for articular disease.

Disclosure: M. Agarwal, None; S. Sawhney, None.

Abstract Number: 1438

Treatment and Response of Down Syndrome Arthropathy

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

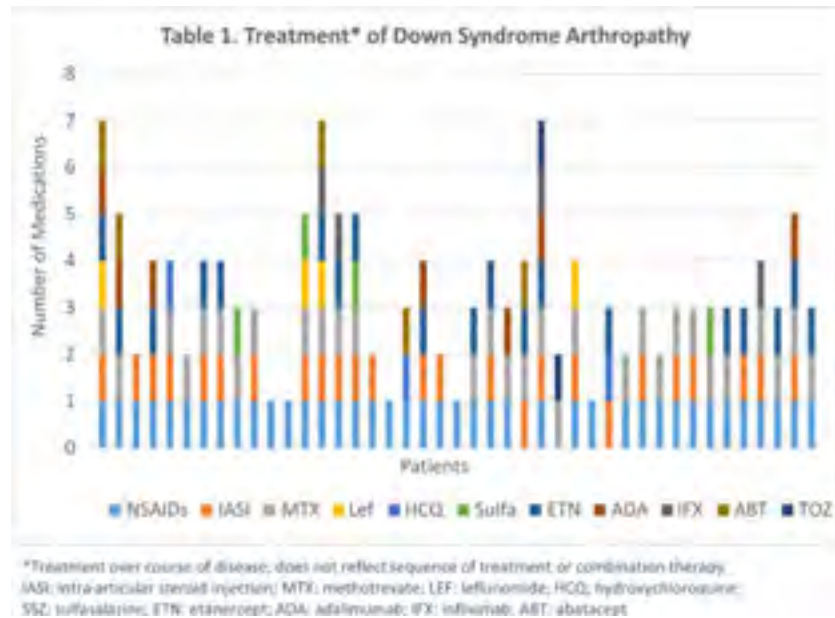
Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Of the very few studiesdescribing Down syndrome arthropathy (DA), crude prevalence estimates indicate DA maybe as common as juvenile idiopathic arthritis (JIA), however, DA is still largely under recognized at onset. Previous studies indicate the majority of DA present with greater than 5 affected joints and bony changes at diagnosis. Additionally, treatment is complex and most require a second-line therapy after Methotrexate (MTX) due an increased methotrexate toxicity. Further, gaps in literature exist around optimal treatment approach, escalation and response. The objective of this study was to investigate treatment and response of DA.

Methods: In a retrospective chart review that took place at two tertiary care hospitals, potential DA patients were identified through electronic medical record system (EMR) from January 1, 1995 to December 31, 2015. ICD-9-CM codes were used to identify patients (less than 18 years of age) with both Down Syndrome (DS; 758.0) and JIA (714.3, 714.31, 714.32,714.33). Individual charts were then manually reviewed to confirm diagnosis of DS and JIA. Chart review included analysis of all documents included in EMR, including demographic data, clinical visits, imaging studies and laboratory results.

Results: Forty-three patients met inclusion criteria with a mean follow-up period of 6 years (SD 4.4). Patients had a mean 7.4 year (SD 3.9) age at onset of musculoskeletal symptoms with a mean 19 months(SD 17) to JIA diagnosis. Patients were mostly female (58%). At JIA diagnosis 63% had a polyarticular, RF negative presentation, 70% reported morning stiffness with an average of 15 active joints (SD 13), 14 limited joints (SD 13), and mean physician global of disease activity 4.5



(SD 2.2). Most patients (93%) were started on nonsteroidal anti-inflammatory drugs (NSAIDs) at diagnosis with 28% simultaneously starting a disease modifying antirheumatic drug (DMARD), and 5% a Biologic. Over the course of disease 74% used a DMARD (94% MTX) and 47% used a biologic (83% Enbrel). Eight patients (25%) had at least one change in DMARD and nine patients (39%) had at least one change in biologic therapy (Table 1). At the last visit there were significantly ($p < 0.001$) less active (3 [SD 5]) and limited joints (5 [SD 9]), and the mean physician global of disease activity was 1.3 (SD 1.5). Of those on DMARD therapy 60% were discontinued due to side effects and 39% had inadequate response to first-line biologic therapy.

Conclusion: Down syndrome arthropathy remains under recognized, but does have a significant reduction in active and limited joints when treated with NSAIDs, DMARDs, and biologics, however, treatment approach, optimal therapy and escalation is unclear. Other barriers that inhibit optimal treatment and response are DMARD toxicity and anti-TNF effectiveness. More research is currently needed to determine optimal therapy approach.

Disclosure: J. T. Jones, None; N. Talib, None; D. J. Lovell, AstraZeneca, Amgen, Abbott, Pfizer, 5, Wyeth, 8; M. L. Becker, None.

Abstract Number: 1439

Yellow Fever Vaccination in Brazil: Short-Term Safety in Pediatric Autoimmune Rheumatic Diseases

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II: Autoinflammatory Disorders, Scleroderma, and Miscellaneous

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Yellow fever (YF) immunization is not routinely performed in juvenile autoimmune rheumatic disease (ARD) patients. However, during the recent epidemic campaign in state of Sao Paulo this live attenuated vaccine was indicated for patients under low immunosuppression (PAHO and WHO). There are no data regarding YFV safety in

Table – Longitudinal analysis of variance in white blood cells of patients and controls

Patients	D0	D5	D10	D30	P*
Leukocytes, cells/mm ³	6100 (4050-9300)	5370 (3300-8240)	5250 (3400-10020)	6340 (3800-9670)	0.002**
Leukopenia, n (%)	0 (0)	3 (10)	4 (15)	1 (4)	>0.05
Neutrophils, cells/mm ³	2900 (1890-4870)	2680 (1250-4590)	2420 (1260-4980)	3260 (1580-5790)	0.007**
Neutropenia, n (%)	1 (3)	3 (10)	3 (10)	0 (0)	>0.05
Lymphocytes, cells/mm ³	2040 (1220-5250)	1680 (850-3940)	1480 (1080-3140)	2110 (1130-4000)	<0.001**
Lymphopenia, n (%)	3 (10)	8 (27)	3 (10)	3 (10)	>0.05
Controls					
Leukocytes, cells/mm ³	6500 (2790-11050)	6405 (3580-10940)	5130 (2580-11160)	6025 (3180-10540)	<0.001**
Leukopenia, n (%)	2 (7)	2 (7)	7 (23)	2 (7)	>0.05
Neutrophils, cells/mm ³	3115 (1110-6740)	3005 (960-6090)	2260 (470-4440)	3240 (940-6680)	<0.001**
Neutropenia, n (%)	3 (10)	2 (7)	5 (17)	2 (7)	>0.05
Lymphocytes, cells/mm ³	2985 (1620-4210)	2640 (1080-7110)	2000 (1140-6370)	2795 (1330-3940)	<0.001**
Lymphopenia, n (%)	0 (0)	3 (17)	2 (7)	1 (3)	>0.05

* Comparison of medians between D0 and D5 with p<0.05

** Comparison of medians between D5 and D10 with p<0.05

*** Comparison of medians between D5 and D10 with p<0.05

**** Comparison of medians between D5 and D10 with p<0.05

***** Comparison of medians between D10 and D30 with p<0.05

juvenile ARD patients. Therefore, the aim of this study was to evaluate the short-term safety of immunization with fractional YFV in juvenile ARD.

Methods: Thirty pediatric patients with inactive rheumatic diseases treated with low dose immunosuppression (sulfasalazine, prednisone<0.5mg/Kg/day or 20mg/day, MTX<0.4mg/Kg/week or 20mg/week, leflunomide) and living in high risk area [16 juvenile idiopathic arthritis, 6 Henoch-Schönlein purpura, 4 juvenile systemic lupus erythematosus, 3 juvenile dermatomyositis and 1 juvenile systemic sclerosis] and 30 healthy controls with comparable ages were vaccinated with a fractional dose of the 17 DD YF vaccine [one fifth (0.1 ml) of the standard dose]. All participants were evaluated pre-vaccination (D0) and after 5 days (D5), 10 days (D10) and 30 days (D30) for clinical and laboratory parameters (AST, ALT, complete blood count, CRP). Disease activity was evaluated according to specific tools for each juvenile ARD at D0 and D30. A rigorous follow-up of adverse events was performed during the first 30 days after vaccination. Serious adverse events were defined as those resulting in hospitalization or death.

Results: Patients and controls had comparable median age [12.4(6.3-18.2) vs. 12(6.9-18.7) years, P= 0.25]. Disease activity parameters of ARD patients (JADAS-71, SLEDAI-2K, CMAS, DAS, MMT, ESR and CRP) remained stable 30 days after YFV (P>0.05). Patients and controls reported only mild symptoms during follow-up, with comparable frequencies of fever, muscle pain, abdominal pain, nausea and diarrhea (P>0.05). Both groups presented similar median white blood cells counts kinetics with transient decreases in leukocytes and neutrophils levels in D10, followed by full recovery to baseline levels in D30 (P<0.05) (Table1). For lymphocytes the decrease occurred at D5, with complete recovery in D30 (P<0.05). Of note, new onset leukopenia (<4,000mm³), neutropenia (<1,500mm³) and lymphopenia (<1,500mm³) were rarely observed in these patients after vaccine (Table1). Liver enzymes alterations and acute kidney injury were not observed in patients and healthy controls, and none of the patients and controls had serious adverse events.

Conclusion: Fractional dose of 17DD YFV was safe and well tolerated in juvenile ARD. We further demonstrated that this vaccine did not trigger disease flare. Therefore, this study may contribute to future recommendation for YF vaccine in pediatric patients, under low immuno suppression, living or travelling in endemic areas. (ClinicalTrials.gov, NCT03430388)

Disclosure: N. E. Aikawa, None, 2; V. A. Balbi, None; A. C. Tonacio, None; A. M. E. Sallum, None; L. M. A. Campos, None; K. T. Kozu, None; M. B. Vendramini, None; N. Fontoura, None; A. M. Sartori, None; L. Antonangelo, None; C. A. Silva, Fundação de Amparo à Pesquisa do Estado de São Paulo, 2; E. Bonfa, Fundação de Amparo à Pesquisa do Estado de São Paulo, 2, Conselho Nacional de Desenvolvimento Científico e Tecnológico, 2.

Abstract Number: 1440

Systemic Sclerosis in Pediatric Patients: An Epidemiological Study in a Large Insured Population in the US

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical Poster I – ARHP

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic sclerosis (SSc) is a very rare autoimmune disorder and only very few population-based epidemiological studies described its incidence and prevalence in children. In a nationwide, prospective hospital-based case-series from Finland, the incidence of SSc was 0.05 per 100,000 person-years in children aged 0–15 years based on 2 cases (Pelkonen et al. 1994). A field study in the UK by Herrick et al. (2010) that collected SSc cases from all secondary care physicians to whom childhood systemic sclerosis could be referred, reported an estimate of 0.027 cases per 100,000 person-years, based on 7 pediatric SSc cases. For North America, we could not identify any previous study on pediatric SSc epidemiology.

Methods: We conducted a retrospective cohort study in the Market Scan Commercial Claims and Encounters Database of IBM Watson Health, a large US-based claims database containing data from over 50 million patients from over 150 large employers geographically distributed throughout the US that covers employees and their dependent family members. The database is frequently used for studies in the area of descriptive disease epidemiology. Study period was 01. Jan 2010 until 31. Dec 2015. Following manual review of electronic patient profiles from a sample of patients with SSc claims in Market Scan, cases of SSc were defined using the following minimal-criteria:

- Raynauds Syndrome diagnosis and two SSc outpatient diagnosis (at least 30 days apart) **or**
- Raynauds Syndrome diagnosis and one SSc inpatient diagnosis **or**
- Three SSc outpatient diagnoses (two of these diagnosis should be at least 30 days apart) **or**
- One SSc inpatient diagnosis plus one SSc outpatient diagnosis (on different dates)

Yearly incidence and prevalence estimates and 95% confidence intervals were calculated for each calendar year from 2010 until 2015. Incident cases were required to have no recorded claim of SSc any time before the entry date.

Results: In the overall pediatric population (<18 years of age), yearly incidence estimates ranged from 0.29 (95% CI: 0.11–0.47) to 0.69 (95% CI: 0.43–0.95) cases per 100 000 person-years, based on 10-27 incident pediatric cases per year. Overall female to male ratio was 2.34 (75/32). Rates were highest in the 12-17 year age group (table 1).

Yearly prevalence ranged from 0.95 (95% CI: 0.78–1.16) to 1.20 (95% CI: 0.95–1.51) per 100 000 children, based on 77-165 prevalent cases per year.

Age (years)	Incidence rates per 100,000 person-years (95% CI)					
	2010	2011	2012	2013	2014	2015
<2	0.00 (–)	0.00 (–)	0.00 (–)	0.00 (–)	0.00 (–)	0.00 (–)
2–11	0.45 (0.17 – 0.72)	0.23 (0.05 – 0.41)	0.03 (0.00 – 0.10)	0.17 (0.00 – 0.34)	0.08 (0.00 – 0.20)	0.05 (0.00 – 0.15)
12–17	1.03 (0.54 – 1.52)	0.73 (0.35 – 1.11)	0.83 (0.45 – 1.22)	0.86 (0.43 – 1.30)	0.56 (0.21 – 0.91)	0.61 (0.21 – 1.00)

Conclusion: Pediatric SSc is a very rare disorder. Our study based on a large pediatric population in the Market Scan claims-database in the US yielded higher incidence estimates than those observed previously in smaller studies conducted in Europe. The female/male disproportionality of SSc may be less pronounced in children than known from the adult population.

Disclosure: A. Michel, Bayer, 3; M. Rivera, Full time employee in Bayer AG, 3; T. Vaitsiakhovich, Bayer AG, 1, 3; S. Teal, Bayer AG, 1, 3; J. Pena, Bayer AG, 3.

Abstract Number: 1441

Diagnostic Performances of Antibodies Against Carbamylated Proteins in US Based Populations with Rheumatoid Arthritis and Other Autoimmune Rheumatic Diseases

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Recently, antibodies directed against carbamylated antigens (anti-CarP antibodies) were identified in rheumatoid arthritis (RA). Studies have established the predictive and prognostic value of this antibody system. As most of the previous reports described the performance characteristics of anti-CarP assay in European populations using a two-step research assay, we analyzed the performances characteristics of a single step anti-CarP assay in US based population of RA subjects and control groups.

Methods: Anti-CarP antibodies were measured using fetal calf serum based single step assay (research use only, Inova Diagnostics, San Diego, USA). The analytical and diagnostic performances of the anti-CarP assay were established using a biobank of specimens collected from consented subjects (640 RA subjects fulfilling the 1987 or 2010 criteria, 197 normal healthy volunteers and 636 other disease subjects). The median age of RA subjects at diagnosis was 60 years and it ranged from 41 to 55 years in control groups. Mean disease duration in RA was 12 years, versus 3 to 12 years in control groups. Anti-citrullinated protein antibodies (ACPA) and rheumatoid factor IgM (RF-IgM) status were tested using EliA CCP and RF IgM assays, respectively (ThermoFisher, Upsala, Sweden). Diagnostic performances in distinguishing RA from other control groups were analyzed using sensitivity, specificity, likelihood ratio (LR) and diagnostic odds ratio (DOR).

Results: The intra-assay and inter-assay variations of the anti-CarP ELISA were 7.0% and 11%, respectively. Anti-CarP antibodies, anti-CCP antibodies and RF-IgM were present in 34%, 66% and 67% of RA subjects, respectively. The overall specificity of anti-CarP antibodies was 78%. When stratified by anti-CCP status, the prevalence of anti-CarP antibodies was 42% and 16% among anti-CCP positive and negative RA subjects, respectively, a finding consistent with previous studies. The prevalence of anti-CarP antibodies in various control groups ranged from 5.9% to 30% (Table 1), thereby yielding specificities ranging from 70% (systemic lupus erythematosus, SLE) to 94% (primary fibromyalgia). Diagnostic odds ratios (DOR) for RA versus the different control groups ranged from 1.2 to 8.2.

Conclusion: These data replicate previous studies and support the notion that anti-CarP antibodies are helpful in the setting of ACPA negative RA subjects. However, clinicians should be aware of the low specificity of this marker in certain autoimmune rheumatic diseases, particularly SLE.

Table 1: Diagnostic performances of anti-CarP antibodies in RA versus other control groups

Control groups	Anti-CCP+	RF-IgM+	Anti-CarP+	Specificity	LR+	LR-	DOR
	%	%	%	%	[95% CI]	[95% CI]	[95% CI]
Systemic lupus erythematosus	4.1%	13%	30%	70%	1.1 [0.94,1.4]	0.94 [0.87,1.0]	1.2 [0.91,1.6]
Sjogren's syndrome	4.7%	41%	27%	73%	1.3 [0.83,1.9]	0.90 [0.77,1.1]	1.4 [0.79,2.3]
Autoimmune thyroid/hepatitis	2.4%	7.1%	26%	74%	1.3 [0.77,2.2]	0.90 [0.74,1.1]	1.4 [0.71,2.9]
Idiopathic inflammatory myopathies	3.5%	6.9%	21%	79%	1.6 [0.79,3.4]	0.84 [0.69,1.0]	2.0 [0.78,4.9]
Systemic sclerosis	6.1%	27%	15%	85%	2.2 [0.99,5.0]	0.78 [0.67,0.91]	2.9 [1.1,7.5]
Other autoimmune diseases	0%	14%	14%	86%	2.4 [0.65,8.6]	0.77 [0.62,0.96]	3.1 [0.68,14]
Primary fibromyalgia	1.2%	1.2%	5.9%	94%	5.7 [2.4,14]	0.70 [0.65,0.76]	8.2 [3.3,20]
Normal Healthy Individuals	0.50%	6.2%	14%	86%	2.4 [1.7,3.4]	0.77 [0.71,0.84]	3.1 [2.0,4.7]

The sensitivities of anti-CarP antibodies, anti-CCP antibodies and RF-IgM in RA subjects were 34%, 66% and 67%, respectively.

Disclosure: J. Shi, Exagen Diagnostics, 3; J. Milo, Inova Diagnostics, 3; K. Bradey, Exagen Diagnostics, 3; C. Bentow, Inova Diagnostics, 3; J. Conklin, Exagen Diagnostics Inc., 3; T. O'Malley, Exagen Diagnostics, 3; A. Sace, None; R. Lafon, None; D. Poling, Exagen Diagnostics, Inc., 3; C. Ibarra, Exagen Diagnostics, 1, 3; M. Mahler, Inova Diagnostics, 3; T. Dervieux, exagen, 3.

Abstract Number: 1442

Differential Chemical Isotope Labeling Liquid Chromatography Mass Spectrometry and a Universal Metabolome Standard Reveals a Metabolome Profile with Consistent Accuracy for Rheumatoid Arthritis

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Session Information

Session Date: Monday, October 22, 2018

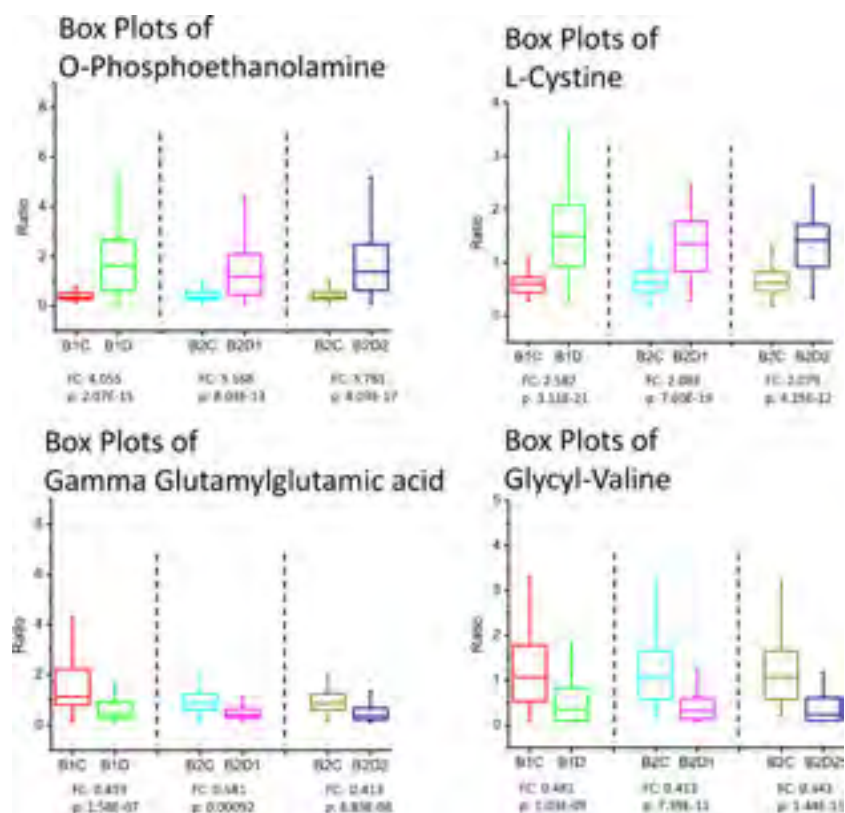
Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Early diagnosis of rheumatoid arthritis(RA) is hampered by suboptimal accuracy of currently available serological biomarkers. Recent advancements in metabolomic profiling include dansylation liquid chromatography mass spectrometry (LC-MS),resulting in 1000-fold increase in detection sensitivity of amine/phenol-containing metabolites, and universal metabolome-standard (UMS)methodology in conjunction with differential chemical isotope labeling (CILLC-MS), to provide long-term analytical reproducibility and facilitate metabolome comparisons among different data sets. CIL LC-MS uses different labeling reagents to target chemical group-based sub metabolomes to provide in-depth metabolomic analysis. We aimed to identify a metabolite signature with consistently high accuracy for RA.

Methods: 12C-dansylation and acid labeling of individual serological samples and 13C-dansylation and acid labeling of pooled samples from 2 RA cohorts was undertaken. Cohort A samples were from 50 RA patients, 39 female (mean age 49.9), 11 male (mean age 47.8), symptom duration <3 years, DAS >3.7, naïve to b-DMARD, and 50 age and sex-matched healthy controls. Cohort B samples were from 50 RA patients, 40 female (mean age 53.4), 10 male(mean age 57.2),



symptom duration <5 years, samples from both pre- and post-(3 months) treatment with TNFi and a second set of 50 age and sex-matched healthy controls.

Results: A total of 3415 amine/phenol metabolites were commonly detected in 80% of the samples, of which 116 metabolites were positively identified using dansyl standard library search. Orthogonal partial least squares discriminant analysis showed a clear separation of the groups for each cohort ($R^2=0.98/Q^2=0.92$ for cohort A and $R^2=0.93/Q^2=0.79$ for separation of controls, pre- and post-treatment cohort B). 18 positively identified metabolites from cohort A and 23 from cohort B were identified as potential RA biomarkers with ROC AUC(95%CI) of 0.99(0.96-0.99) and 0.98(0.93-0.99) for the top 10 metabolites, respectively. L-Cystine, O-Phosphoethanolamine, Gamma Glutamylglutamic acid, Glycyl-Valine, and 3 unidentified metabolites were significant in both cohorts, with the combination ROC AUC(95%CI) of 1.0(1.0-1.0) and 1.0(0.99-1.0) for cohorts A and B, respectively. For the 4 positively identified metabolites, sensitivity/specificity plus AUC (95%CI) were 89%/88% plus 0.95(0.87-0.99) and 91%/91% plus 0.97(0.92-1.0) for cohorts A and B, respectively. None of these biomarkers correlated with age, gender, or symptom duration.

Conclusion: 7 metabolites, 4 of which are positively identified, have consistently high discriminatory capacity for RA.

Disclosure: W. P. Maksymowych, CaRE Arthritis, 9; X. Wang, None; J. Paschke, None; R. Dadashova, None; E. Hutchings, None; L. Li, None.

Abstract Number: 1443

Ultrasonographic Criteria for the Diagnosis of Erosive Rheumatoid Arthritis Disease Using Osteoarthritic Patients As Controls Compared to Validated Radiographic Criteria

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is the most prevalent chronic inflammatory joint disease (1,2) responsible for structural damage. Radiography (RX) is considered as the gold standard for visualizing and quantifying bone lesions in RA (3). Musculoskeletal ultrasound (US) is booming in clinical practice for the diagnosis of RA. US can detect more erosions than RX at the joint level, especially at an early stage of the disease.(4) The objectives are to determine thresholds for the diagnosis of erosive RA by US in RA and OA patients and to compare these US thresholds with RX ACR/EULAR 2013 criteria for erosive RA.

Methods: Patients fulfilling ACR 1987 and/or ACR/EULAR 2010 criteria for RA or hand OA criteria were prospectively included. A modified Sharp erosion score was assessed by two blinded readers and one adjudicator for discordant cases (number of eroded joints \leq three). Erosions in US were scored on six bilateral joints (MCP2-3, 5; MTP2-3, 5) with a four-grade scale to calculate total US score for erosions (USSe).

Results: A total of 168 patients were included: 122 RA (32 early RA <2 years; 90 late RA \geq 2 years); 46 OA patients. On RX: 42 RA patients (6 early; 36 late) and 5 OA patients were eroded according to ACR/EULAR 2013 criteria with sensitivity at 34.4% and specificity at 89.1%. On US, 95 RA patients (21 early; 78 late) and 12 OA patients were eroded. Considering at least two joint facets eroded or at least one joint facet eroded at grade 2 on US, sensitivities were good (68-72.1%) and specificities excellent (89.1-100%). Agreement between RX and US was excellent (90-92%). US diagnosed two times more patients than RX as erosive disease in both early and late RA patients.

Conclusion: USSe can differentiate RA from OA in erosive disease and detect two times more patients with erosive RA than RX with excellent specificity and agreement, according to two different criteria (number of facets eroded and severity of erosion at the joint facet level).

References: 1. Guillemin F, Saraux A, Guggenbuhl P, Roux CH, Fardellone P, Le Bihan E, et al. Prevalence of rheumatoid arthritis in France: 2001. *Ann Rheum Dis*. 2005 Oct;64(10):1427–30.
2. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin Arthritis Rheum*. 2006 Dec;36(3):182–8.
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4. Wakefield RJ, Gibbon WW, Conaghan PG, O'Connor P, McGonagle D, Pease C, et al. The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. *Arthritis Rheum*. 2000 Dec;43(12):2762–70.

Disclosure: C. Roux, None; F. Gandjbakhch, None; A. Pierreisnard, None; M. Couderc, None; C. Lukas, None; R. Masri, None; J. P. Sommier, None; I. Clerc-Urmès, None; C. Baumann, None; I. Chary-Valckenaere, None; D. Loeuille, None.

Abstract Number: 1444

Optimization of Ultrasonographic Examination for the Diagnosis of Erosive Rheumatoid Arthritis Versus Erosive Osteoarthritis with Radiography Considered As Gold Standard

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

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Background/Purpose: Rheumatoid arthritis (RA) is the most prevalent chronic inflammatory joint disease (1,2) responsible for structural damage. Radiography (RX) is considered as the gold standard for visualizing and quantifying bone lesions in RA (3). Musculoskeletal ultrasound (US) is booming in clinical practice for the diagnosis of RA. US can detect more erosions than RX at the joint level, especially at an early stage of the disease. (4) The Objectives are to determine thresholds and better scenarios for the diagnosis of erosive RA by US in RA and osteoarthritic (OA) patients.

Methods: Patients fulfilling ACR 1987 and/or ACR/EULAR 2010 criteria for RA or hand OA criteria were prospectively included. A modified Sharp erosion score was assessed by two blinded readers and one adjudicator for discordant cases (number of eroded joints \leq three). Erosions in US were scored on six bilateral joints (MCP2-3, 5; MTP2-3, 5) with a four-grade scale.

Results: A total of 168 patients were included: 122 RA (32 early RA <2 years; 90 late RA ≥ 2 years); 46 OA patients. On RX: 42 RA patients (6 early; 36 late) and 5 OA patients were eroded according to ACR/EULAR 2013 criteria (sensitivity: 34.4%, specificity: 89.1%). On US, 95 RA patients (21 early; 78 late) and 12 OA patients were eroded. Considering at least two joint facets eroded (threshold 1) or at least one joint facet eroded at grade 2 (threshold 2), sensitivities were good (68-72.1%) and specificities excellent (89.1-100%). With only six targeted joint facets examined, 73 and 74 patients were classified as erosive RA with threshold 1 and 2 with good sensitivities (59.8-60.0%) and excellent specificities (95.6-100%) respectively. For all scenarios, agreement between RX and US for the diagnosis of erosive RA was excellent (88.1% to 92.8%).

Conclusion: US erosion assessment of six targeted joint facets permitted to detect 1.7 times more erosive RA patients than RX in late and early RA.

References: 1- Guillemin F, Saraux A, Guggenbuhl P, Roux CH, Fardellone P, Le Bihan E, et al. Prevalence of rheumatoid arthritis in France: 2001. *Ann Rheum Dis*. 2005 Oct;64(10):1427–30.
2- Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin Arthritis Rheum*. 2006 Dec;36(3):182–8

- 3- Baillet A, Gaujoux-Viala C, Mouterde G, Pham T, Tebib J, Saraux A, et al. Comparison of the efficacy of sonography, magnetic resonance imaging and conventional radiography for the detection of bone erosions in rheumatoid arthritis patients: a systematic review and meta-analysis. *Rheumatol Oxf Engl*. 2011 Jun;50(6):1137–47.
- 4- Wakefield RJ, Gibbon WW, Conaghan PG, O'Connor P, McGonagle D, Pease C, et al. The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. *Arthritis Rheum*. 2000 Dec;43(12):2762–70.

Disclosure: C. Roux, None; F. Gandjbakhch, None; A. Pierreisnard, None; M. Couderc, None; C. Lukas, None; R. Masri, None; J. P. Sommier, None; I. Clerc-Urmès, None; C. Baumann, None; I. Chary-Valckenaere, None; D. Loeuille, None.

Abstract Number: 1445

MRI Bone Erosions in RA Patients Relatives with Clinically Suspicious Arthralgia

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) has a preclinical phase without symptoms that progress to symptomatic phases. Clinically suspect arthralgia (CSA) refers to patients with symptoms without clinically apparent synovitis. The presence of erosions of grade 2 or greater by MRI was reported to be specific to the diagnosis of RA. We do not know the frequency of RA specific erosions, defined by RAMRIS in CSA patients.

Methods: Cross-sectional and observational study with 60 patients older than 18 years, divided into two groups: CSA group: n = 23 (38%) RA first-degree relatives with hand arthralgia without clinical inflammation, and RA group: n = 37 (%) patients who met 2010 ACR/EULAR criteria. MRI images were evaluated looking for synovitis, bone erosion, and bone marrow edema (BME). The bone erosions were scored on a scale of 0 to 10 based on the proportion of eroded.

Results: Baseline and clinical characteristics are depicted in table 1. No difference was found in the frequency of patients without any bone erosion in MCP between CSA versus RA, 7/22(31.8%) and 12/38(31.6%), respectively. However, 18/60 (30%) patients had ≥ 2 bone erosions, 6/22(27.3%) in CSA patients and 12/38(31.6%) in established RA patients (p=0.72).

Conclusion: There were a similar number of patients with bone erosions Grade ≥ 2 in both groups. The presence of the combination of the MCP joints of bone erosions with bone edema and synovitis is more frequent in patients with RA compared to patients with CSA.

Table 1: Baseline characteristics of CSA patients and RA patients

	Total n = 60 (100%)	CSA n = 22 (36.6%)	RA n = 38 (63.3%)
TOTAL (N=60)			
Age in years. median (IQR)	41.5(26)	35(12)	49.5(23)
> 40 years. n(%)	31(51.7)	5(22.7)	26(68.4)
≤ 40 years. n(%)	29(48.3)	17(77.3)	12(31.6)
Female. n(%)	50(83.3)	17(77.3)	33(86.8)
Dominant Hand: Right	55(91.7)	21(95.4)	34(89.5)
Symptoms duration in months. Median (IQR):		6(8)	65(33.5)
PVAS (0-100), median(IQR)	20(50)	0(0)	3.5(3)

Table . (Cont'd)

TOTAL (N=60)	Total n = 60 (100%)	CSA n = 22 (36.6%)	RA n = 38 (63.3%)
66 SJC, median (IQR)	3(9)	0(2)	5(8)
68 TJC: median (IQR)	5(12)	0(5)	8(11)
ACPA positivity, n(%)	19/45(42.2)	8/21(38.0)	11/24(45.8)
RF positivity, n(%)	42/50(84)	20/21(95.2)	22/29(75.8)
CRP (mg/dl), median(IQR)	0(1)	0(1)	0.5(1)

CSA, clinically suspect arthralgia (CSA); RA, rheumatoid arthritis; ACPA, anti-citrullinated protein antibodies; CRP, C-reactive protein; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; PVAS, Patient Global Assessment of the Disease Activity; SJC, swollen joints count; TJC, tender joint count.

Table 2: Frequencies of patients with RA and CSA with erosions and with erosions and with the simultaneous presence of local inflammation in MCP joints.

Total of Patients N=60	Erosion+ BME- Synovitis-n=1	Erosion+ BME+ Synovitis- n=3	Erosion+ BME- Synovitis+ n=18	Erosion+ BME+ Synovitis+ n=19	Number of MCP bones without erosions, n=19
RA < 40 years n= 12 pt	0	0	3(2.5%)	6(50%)	3(25%)
RA ≥ 40 years n=26 pt	0	0	8(30.7%)	9(34.6%)	9(34.6%)
CSA < 40 years n=17 pts	1(5.8%)	1(5.8%)	6(35.3%)	3(17.6%)	6(35.2%)
CSA ≥ 40 years n=5 pts	0	2(40%)	1(20 %)	1(20%)	1(20%)

Inflammation was defined as the presence of synovitis and/or bone marrow oedema; The presence of BME and/or synovitis was defined as a score of ≥1; MCP, metacarpo-phalangeal joint; RA, rheumatoid arthritis; CSA, clinically suspect arthralgia (CSA).

Disclosure: D. Vega-Morales, None; J. Esquivel-Valerio, None; M. A. Garza-Elizondo, None; D. A. Galarza-Delgado, None; M. A. Villarreal-Alarcón, None; C. Skinner-Taylor, None; D. Flores-Alvarado, None; J. Riega-Torres, None; L. Pérez-Barbosa, None; B. Vazquez-Fuentes, None; M. D. C. Larios-Forte, None.

Abstract Number: 1446

The Optimal Joint Set for Ultrasound Assessment of Synovitis in RA: Results from the Rasch Measurement Model

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Background/Purpose: The recently introduced composite OMERACT-EULAR power Doppler (PD)/grey scale (GS) ultrasound (PDUS) scoring system for RA with a proposed 18 joint set was developed without reference to modern psychometric analysis. We aimed to assess the scoring system and joint selection using the Rasch measurement model, which sets out criteria for measurement of an underlying 'latent' quantity, and to propose a refined tool.

Methods: We included biologic-naïve patients with ACR 1987 RA diagnosis, disease duration <6 months who received abatacept and methotrexate for 24 weeks in a clinical trial[1]. US was performed at weeks 0, 1, 2, 4, 6, 8, 12, 16, 20 & 24. Bilateral MCPs 1–5, PIPs 1–5, wrist, elbow, shoulder (glenohumeral), knee, ankle (tibiotalar), hind foot (talonavicular and calcaneocuboidal) and metatarsophalangeal joints (MTPs) 1–5 (44 total) were scored 0-3 for GS, PD & PDUS. The scoring system and joint set were assessed for fit to the Rasch model and acceptable reliability (person separation index (PSI) >=0.7). Standardised response mean at 24 weeks was calculated.

Results: We included 96 patients (mean age 56.5, disease duration <=2 years 43%, 2-10+ years 57%; 83% female). Analysis of the composite score showed that the probability of a joint being assigned a higher score did not consistently

increase with the underlying latent quantity i.e. level of inflammation, indicating that assessors were not completely able to distinguish the categories. Shifting the point of transition between a score of 1 and 2, and reserving 3 for GS=3 PD=3 resulted in ordered thresholds. We also found residual correlation between some joints within the proposed 18 joint set, indicating that their scores were not independent. Joints that were only likely to score >0 at high levels of inflammation, beyond the observed range, were prioritised for exclusion. Using revised scoring in a set of 15 joints (bilateral MCPs 1-5, right side wrist, PIPs 2&5, MTPs 2&5) yielded fit to the Rasch model (item-trait interaction Chi-square $p=0.647$) and acceptable reliability (PSI=0.77; Cronbach's $\alpha=0.81$). Using linear-scaled (transformed) estimates from the Rasch model for the revised scoring in the 15 joint set showed significantly greater sensitivity to change than using original scoring in either the 44 joint set (mean difference (bootstrapped 95% CI)= -0.33 (-0.59, -0.06), $p=0.016$) or 18 joint set (-0.42 (-0.71, -0.13), $p=0.004$) in 74 patients with 24 week data available (Table 1).

Conclusion: Refining both the scoring system and the joint set using the Rasch model resulted in enhanced sensitivity to change. Future work will validate these findings in external data in order to confirm that the proposed changes further improve the sensitivity and reliability of US in clinical trials.

1. D'Agostino et al. Ann Rheum Dis 75:1763-9

Table 1: Standardised response means calculated using original or revised PDUS scoring

Joints included	Standardised response mean at 26 weeks (n=74)	
	Original PDUS scoring	Revised PDUS scoring
44 (22 paired)	-1.05	-1.11
18 (9 paired)	-0.96	-0.98
15 (5 paired, 5 single) – raw score	-1.20	-1.40
15 (5 paired, 5 single) – Rasch-transformed	N/A	-1.38

Disclosure: E. M. A. Hensor, None; A. Tennant, None; P. G. Conaghan, None; H. B. Hammer, None; R. J. Wakefield, None; M. A. D'Agostino, None.

Abstract Number: 1447

Decreased Lymphatic Drainage in the Hands of Flaring RA Patients As Measured By Indocyanine Green Clearance Via Real Time Near Infrared Imaging

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Session Information

Session Date: Monday, October 22, 2018

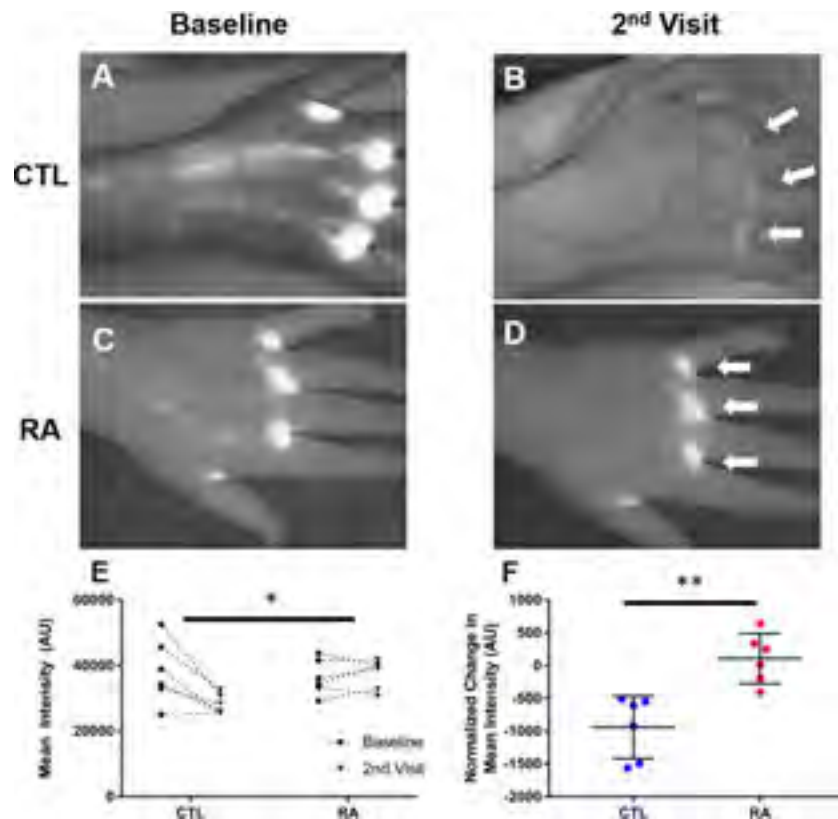
Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Near infrared (NIR) imaging studies of subdermalindocyanine green (ICG) in murine models of inflammatory arthritis established abnormally lymphatic vessel (LV) function during arthritic progression. Quantitatively, this LV dysfunction is primarily assessed by ICG clearance from the injection site via longitudinal (days) NIR imaging. As the role of LV function in rheumatoid arthritis (RA) pathogenesis is unknown, we tested the hypothesis that ICG clearance from the hands of RA patients experiencing flare is significantly decreased from that of normal healthy volunteers.

Methods: The web spaces of both hands of 8 healthy controls (Ctl) and 4 subjects in RA flare were injected with 0.1ml of 100µM ICG on 2-4 separate occasions and the NIR fluorescence of the dorsal aspect of the hands were imaged. To measure clearance of ICG from the web spaces, a subset of 3 Ctl and 3 RA subjects returned to the clinic 8-15 days after the first injections and any remaining NIR fluorescence in each hand was measured via region of interest analysis (n=6 per group, Wilcoxon Signed-RankTest). Controlling for the number of days between subjects, the change in intensity between the initial and second visit was divided by the number of days between visits. To assess the branching structure of the vessels, two independent graders quantified the total number of bifurcations of the LVs. Median values for each hand across all visits and graders were used to test for differences (n=13 Ctl, n=8 RA, Wilcoxon on Rank-Sum Test).



Results: Representative NIR images of Ctl and RA hands at baseline and at the second visit are presented in **Fig 1A-D**, demonstrating the dramatic retention of ICG at the injection sites (WhiteArrows) in RA subjects. Statistical analysis revealed a decrease in ICG clearance in the RA subjects compared to Ctls (**Fig 1E**, $*p<0.05$). When controlling for days between the initial visit and second visit the relationship holds (**Fig 1F**, $**p<0.01$). Interestingly, no differences were observed in bifurcation counts between RA and Ctl ($p=0.11$).

Conclusion: Imaging outcome measures of LV function in mice demonstrated diminished clearance of lymph from the inflamed joint during arthritic progression and we recently described functional and anatomic differences in the hands of RA subjects in joint flare compared to controls. Herein, we expand upon these findings by demonstrating a significant reduction in ICG clearance in RA patients during flare. Surprisingly, there was no difference in the bifurcations of LVs, however, this is likely due to relatively small sample size or differences in clinical characteristic in our cohort. The accumulation and retention of inflammatory cells and molecules in rheumatoid joints as are result of diminished lymphatic clearance likely triggers synovitis. This clinical pilot demonstrates the feasibility of quantifying LV function, and warrants formal investigation in clinical trials

Disclosure: R. Bell, None; H. Rahimi, None; A. Lieberman, None; R. Wood, None; E. Schwarz, None; C. T. Ritchlin, AbbVie, Amgen, UCB, 2,AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer Inc, 5.

Abstract Number: 1448

Clinical Impact of Articular Ultrasound in Diagnosis and Follow-up of Patients with Polyarthritis

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Session Information**Session Date:** Monday, October 22, 2018**Session Title:** Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis**Session Type:** ACR Poster Session B**Session Time:** 9:00AM-11:00AM

Background/Purpose: It is well established in the literature that musculoskeletal ultrasound (MSUS) is more sensitive than clinical examination in the detection of synovitis. MSUS can help rheumatologists with the diagnosis and follow-up of uncertain cases. The main objective of this study is to validate the added value of MSUS in the diagnosis and follow-up of patients presenting with arthritis in the rheumatology department of the CHUS.

Methods: We reviewed retrospectively the medical records of patients with an uncertain initial diagnosis of arthritis (Group 1: n=58) and patients with clinically uncertain disease activity on follow-up (Group 2: n=103). We examined the contribution of MSUS in the diagnosis of arthritis and its impact on treatment decision making.

Results: In group 1, 56.9% of patients were confirmed with polyarthritis after MSUS (n=33). 54.5% of them were diagnosed with rheumatoid arthritis (n=18). There were no statistically significant predictors for a positive MSUS. In the follow-up group, 27.2% had a positive MSUS (n=28). 67.9% had their treatment optimised (n=19). 44.4% of patients with positive ultrasound but without treatment modification had articular infiltrations following the MSUS (n=4). Within patients with negative ultrasound (n=75), 10% had a decrease in their medication (n=8) while 71% had no change in their treatment (n=53). The result of the ultrasound had a statistically significant impact on the treatment decision making ($p < 0.0001$).

Conclusion: Our results support the added value of MSUS in the diagnosis and management of polyarthritis, mainly in patients with a doubtful clinical picture. Similar results can be found in the current literature. We did not succeed to identify predictive factors of a positive ultrasound.

Disclosure: J. Lafleur-Careau, None; F. Taschereau, None; A. J. de Brum-Fernandes, None; A. Bruns, None; G. Boire, None; A. Masetto, None.

Abstract Number: 1449

Microwave Radiometry As a Novel Additional Method for Rheumatoid Arthritis Disease Activity Assessment: A Prospective Single-Center Study

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Session Information**Session Date:** Monday, October 22, 2018**Session Title:** Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis**Session Type:** ACR Poster Session B**Session Time:** 9:00AM-11:00AM

Background/Purpose: Microwave Radiometry (MR) is an easy-to perform, rapid, non-invasive method detecting in-depth tissue temperature that may be useful for joint inflammation assessment in RA (1,2). We tested the hypothesis that MR can diagnose and grade (teno)synovitis in small and large joints in RA; thus, may be used for the development of an MR-derived combined joint-temperature score to measure RA disease activity.

Methods: Eighty-two RA patients and 23 age- and sex-matched healthy individuals, underwent MR, clinical and laboratory assessments and joint ultrasound, as described (2); 21 patients were re-examined 2 months after treatment initiation. The temperature of each joint was expressed by Δt (difference between MR-derived temperature of pre-defined joint points resulting in lower Δt values in warmer joints). A thermo-score was created by summing the Δt of 7 small joints according to the US7 ultrasound score (wrist, 2nd-3rd MCP, 2nd-3rd PIP, 2nd and 5th MTP), as well as of elbow, knee and lower leg of the clinically dominant upper/lower extremity. This thermo-score was reproducible among healthy individuals (Intraclass Correlation Coefficient 0.714).

Results: At the joint level, MR performed better than clinical examination in the knees to predict ultrasound confirmed joint effusion [area under the curve (AUC) 0.815 vs. 0.688, respectively], or power Doppler (AUC 0.901 vs. 0.791, respectively), whereas a $\Delta t \leq 0.2$ had 80% sensitivity and 82% specificity for power Doppler. Also, 85% of knee joints with

subclinical inflammation could be diagnosed by MR. In all other joints MR performed similarly to clinical examination and its diagnostic performance was moderate. At individual patient level, the thermo-score strongly correlated to DAS28 score, tender and swollen joint counts, patient's and physician's visual analogue scale, CRP and ESR levels (all $p < 0.001$), as well as to the US7 ultrasound scores ($p < 0.026$). Moreover, the thermo-score could discriminate patients in high/moderate disease activity ($\text{mean} \pm \text{SD} = 4.6 \pm 3.0$), low disease activity/remission (8.0 ± 2.9) ($p < 0.001$), or healthy subjects (8.8 ± 1.9) ($p < 0.001$). A thermo-score ≤ 7.4 could distinguish highly/moderately active patients from healthy controls with a sensitivity and specificity of 81% and 83%, respectively (AUC 0.866), whereas a cut-off of 8.1 could distinguish highly/moderately active from patients in low activity/remission with both a sensitivity and specificity of 71% (AUC 0.802). Finally, individual changes from baseline to follow-up mirrored the corresponding DAS28 changes in 17/21 patients ($p = 0.001$).

Conclusion: Increased in-depth joint temperature detected by MR performed well for the detection of knee joint inflammation in RA. The MR-derived score of 10 selected joints correlated to clinical, laboratory and ultrasound measures of RA disease activity, could discriminate disease activity stages, as well as mirrored treatment-induced disease activity changes. Multicenter studies are needed to confirm these novel findings.

References: 1. Zampeli E, et al. PLoS ONE 2013;8(5):e64606
2. Pentazos G, et al. J Clin Rheumatol 2018. E-pub ahead of print.

Disclosure

K. Laskari, None; G. Pentazos, None; G. Konstantonis, None; M. Tektonidou, None; E. Siores, None; P. Sfikakis, None.

Abstract Number: 1450

Clinical Radiology Reports Are Unreliable for Assessment of Radiographic Structural Progression in US Veterans with Rheumatoid Arthritis Initiating Tumor Necrosis Factor Inhibitor Therapy

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatologists rely on hand radiograph findings including bone erosions (BE) and joint space narrowing (JSN) to make treatment decisions for patients with rheumatoid arthritis (RA). Radiographic progression (RP) on serial hand radiographs may prompt changes in therapy. We assessed whether radiology reports reliably identify BE, JSN, and RP in a cohort of Veterans Affairs (VA) patients initiating tumor necrosis factor inhibitor (TNFi) therapy.

Methods: Subjects were US veterans with RA initiating TNFi therapy who had two sets of bilateral hand radiographs: baseline obtained between 6 months prior to and 1 month after TNFi initiation and follow-up obtained 10-18 months after TNFi initiation. An expert reader, blinded to radiograph sequence, quantified BE, JSN, and RP at baseline and follow-up by modified Sharp Score (mSS). An independent chart abstractor reviewed the corresponding radiology reports in the electronic medical record. BE and JSN were coded "present" or "absent" if the report specifically stated they were present or absent and were coded "not specified" if the report did not comment on their presence. RP was coded "present" or "absent" if the follow-up report specifically stated it was present or absent and was coded "not compared" if it did not include comparison to baseline. BE, JSN, and RP from radiology reports were then compared to BE, JSN, and RP as quantified by the expert reader. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy ($\text{true positive} + \text{true negative} \div \text{total cases}$) were calculated for baseline reports that reported BE and JSN, and for follow-up reports that reported RP.

Results: 249 patients from 84 VA sites were included. Baseline demographics: age 58 ± 11 years, 81% male, 68% positive rheumatoid factor, 65% positive anti-cyclic citrullinated peptide antibody. Baseline mSS: 19.5 ± 33.2 (median 8, range 0-214). Mean change in mSS: 0.5 ± 4.6 (median 0, range -19-45). BE or JSN not reported in 65 (26%) and 83 (33%) baseline cases respectively. In 70 (35%) of cases with comparison radiographs at the same site, the follow-up radiology report did not include comparison of baseline and follow-up radiographs.

Conclusion: Many clinical radiology reports may be of limited value and reliability for assessing RP in patients with RA during TNFi therapy because reports often fail to include important data, do not include comparisons, and disagree with findings reported by an expert reader. Reports of radiologist assessments of BE and JSN are also of limited utility—while

Bone Erosions on Baseline Radiographs

		Expert Reader				
		Present	Absent	Total		
Clinical Radiologist	Present	71	10	81	Sensitivity	55.5%
	Absent	57	46	103	Specificity	82.1%
	Total	128	56	184*	PPV	87.7%
					NPV	44.7%
					Accuracy	63.6%

*249 reports reviewed. 65 did not specify presence/absence of BE and were excluded.

Joint Space Narrowing on Baseline Radiographs

		Expert Reader				
		Present	Absent	Total		
Clinical Radiologist	Present	106	12	118	Sensitivity	79.1%
	Absent	28	20	48	Specificity	62.5%
	Total	134	32	166*	PPV	89.8%
					NPV	41.7%
					Accuracy	75.9%

*249 reports reviewed. 83 did not specify presence/absence of JSN and were excluded.

Radiographic Progression on Follow-Up Radiographs

		Expert Reader				
		Present	Absent	Total		
Clinical Radiologist	Present	14	14	28	Sensitivity	30.4%
	Absent	32	70	102	Specificity	83.3%
	Total	46	84	130*	PPV	50.0%
					NPV	68.6%
					Accuracy	64.6%

*249 reports reviewed. 49 with baseline and follow-up at different sites were excluded. Of the remaining 200, 70 did not specify presence/absence of progression and were excluded.

a report positive for BE or JSN appears to be accurate, a negative report does not reliably exclude these findings. Rheumatologists should be aware of the limitations of radiology reports when using these assessments to make changes in RA management. Standardization of radiologist reporting and terminology may be of clinical utility.

Disclosure: K. R. Lammert, None; A. R. Erickson, Amgen Inc., 2; B. C. Sauer, Amgen Inc., 2; G. W. Cannon, Amgen Inc., 2.

Abstract Number: 1451

The Value of Adding MRI to a Clinical Treat-to-Target Strategy in Rheumatoid Arthritis Patients in Clinical Remission: Clinical and Radiographic Outcomes from the Imagine-RA Randomized Controlled Trial

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Session Information

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

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Background/Purpose: Targeting MRI remission in rheumatoid arthritis (RA) patients in clinical remission may improve clinical outcome and halt joint damage progression.

The purpose of the trial was to determine whether a treat-to-target (T2T) strategy based on structured MRI assessments targeting absence of osteitis/bone marrow edema (BME) would lead to improved clinical and radiographic outcomes, compared with a conventional T2T strategy in RA patients in clinical remission.

Methods: The IMAGINE-RA study was a 2-year investigator-initiated, randomized, open-label multicentre study. Two hundred RA patients in clinical remission (defined as: DAS28-CRP<3.2 and no swollen joints) receiving conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) were randomly assigned 1:1 to a conventional DAS28-CRP guided T2T strategy, targeting DAS28-CRP<3.2 and no swollen joints or an MRI guided T2T strategy based on the same clinical T2T strategy and MRI targeting absence of BME. Patients were followed every 4 months over a 2-year follow-up period. In the MRI T2T arm contrast-enhanced MRI of the dominant hand 2nd-5th metacarpophalangeal joints and wrist was performed ahead of the clinical visit and evaluated for presence/absence of BME. Treatment was escalated according to a predefined treatment algorithm if target was not reached, starting with increments in csDMARD mono/combination therapy and then adding biologic DMARDs. The co-primary endpoints were 1) proportion of patients achieving DAS28-CRP remission (DAS28-CRP<2.6) and 2) proportion of patients with no radiographic progression (change in total Sharp/vdHeijde score≤0) 24 months from baseline. Secondary outcomes included various clinical, functional, radiographic and MRI variables. Pearson's chi-square statistics and repeated-measures logistic regression models were used to assess primary and secondary outcomes.

Results: Primary and secondary clinical and radiographic outcomes at 24 months are presented in the table. 76 patients in the MRI T2T arm and 95 patients in conventional T2T arm completed the study. Of them 64 patients (85%) in the MRI T2T arm and 83 patients (88%) in the conventional T2T arm reached the primary clinical endpoint (chi-square=0.324, p=0.569) and 49 patients (66%) in the MRI T2T arm and 58 (62%) in the conventional T2T arm reached the primary radiographic endpoint (chi-square=0.265, p=0.606). ACR/EULAR remission rates, swollen joint count, patient VAS global and HAQ favoured the MRI T2T arm (p<0.038).

	MRI T2T	Conventional T2T	Difference between groups (95% CI)	P value*
Primary endpoints				
Radiographic:				
No radiographic progression, n (%)	49 (66.2%)	58 (62.4%)	OR, 1.19 (0.04 to 39.47)	0.922
Clinical:				
DAS28-CRP remission (DAS28<2.6), n (%)	64 (85.3%)	83 (88.3%)	OR, 1.03 (0.31 to 3.43)	0.958
Secondary endpoints				
Clinical				
ACR-EULAR Boolean remission, n (%)	37 (49.3%)	30 (31.9%)	OR, 4.19 (1.30 to 13.57)	0.017
SDAI remission (SDAI≤3.3), n (%)	48 (64.0%)	56 (62.2%)	OR, 1.67 (0.59 to 4.71)	0.336
CDAI remission (CDAI≤2.8), n (%)	53 (69.7%)	59 (64.8%)	OR, 2.75 (0.90 to 8.36)	0.075
DAS28-CRP	1.9 (0.1)	2.1 (0.1)	-0.2 (-0.3 to 0.0)	0.093
Morning stiffness, min	13.1 (3.2)	10.1 (2.9)	3.0 (-5.4 to 11.4)	0.486
Tender joint count (0-28)	0.2 (0.1)	0.5 (0.1)	-0.2 (-0.6 to 0.1)	0.171
Swollen joint count (0-28)	0.0 (0.1)	0.3 (0.1)	-0.3 (-0.5 to -0.0)	0.038
Patient VAS global (0-100)	15.5 (1.8)	21.2 (1.6)	-5.7 (-10.4 to -0.9)	0.019

Table . (Cont'd)

	MRI T2T	Conventional T2T	Difference between groups (95% CI)	P value*
Patient VAS pain (0-100)	14.2 (1.7)	18.7 (1.6)	-4.5 (-9.0 to 0.0)	0.052
Patient VAS fatigue (0-100)	21.8 (1.9)	24.4 (1.7)	-2.6 (-7.7 to 2.4)	0.311
Physician VAS global (0-100)	4.7 (0.8)	6.9 (0.8)	-2.3 (-4.4 to -0.1)	0.041
Radiographic				
Change in TSS	1.0 (0.3)	1.3 (0.3)	-0.3 (-1.1 to 0.6)	0.559
Function and quality of life				
Change in HAQ	-0.052 (0.024)	0.091 (0.023)	-0.143 (-0.209 to -0.078)	<0.001
Patient with normal function (HAQ≤0.5), n(%)	61 (80.3%)	75 (79.8%)	OR, 0.73 (0.08 to 7.14)	0.790
Change in SF-36 PCS	1.1 (1.0)	-0.2 (0.9)	1.3 (-1.3 to 4.0)	0.330
Change in SF-36 MCS	-0.5 (1.0)	-0.9 (0.9)	0.5 (-2.1 to 3.0)	0.727
Change in EQ-5D	0.040 (0.015)	0.019 (0.013)	0.021 (-0.017 to 0.060)	0.279

95% CI, 95% confidence interval; ACR=American College of Rheumatology; CDAI=Clinical Disease Activity Index; CRP=C-reactive protein; DAS28-CRP=Disease activity score in 28 joints based on four variables, including CRP; EQ-5D=EuroQol-5 dimensions; EULAR=European League Against Rheumatism; HAQ=Health Assessment Questionnaire; MCS= Mental Component Summary score; MRI=Magnetic Resonance Imaging; PCS=Physical Component Summary score; RAMRIS=RA magnetic resonance imaging scoring system; SDAI=Simplified Disease Activity Index; SF-36=Short Form 36 item questionnaire; T2T=treat-to-target; TSS=Total Sharp/van der Heijde score; VAS=Visual Analogue Scale. Data are presented as least square means (SE) unless otherwise stated. Analyses are based on full analysis set (patients having a baseline visit and at least one follow-up visit) with no data imputation to replace missing data.*P values are based on repeated-measures logistic regression models. For some of the variables, fewer patients were included in the analyses due to missing data, with the minimum being 86 patients in the MRI T2T arm (range 86-98) and 91 (range 91-99) in the conventional T2T arm.

Conclusion: Targeting absence of MRI BME in addition to a conventional T2T strategy in RA patients in clinical remission had no effect on the probability of achieving DAS28-CRP remission or halt radiographic progression. However, more patients achieved ACR/EULAR remission and positive effect on physical function was seen when MRI was used for treatment guidance.

Clinicaltrials.gov Identifier: NCT01656278

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Combination of Ultrasound Power Doppler-Verified Synovitis and Seropositivity Accurately Identifies Patients with Early Rheumatoid Arthritis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

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Background/Purpose: We conducted this retrospective study to determine objective and comprehensive diagnostic criteria for early rheumatoid arthritis (RA) that are based on ultrasound (US) and serologic findings.

Methods: From August 2014 to May 2016, we recruited 216 consecutive patients at Hospital 1 and 223 consecutive patients at Hospital 2 who were suspected to have RA and underwent US of bilateral hands. The duration from the appearance of the patient's symptoms to his or her entry into the study was ≤6 months. In the US of bilateral hands from

22 sites, the findings obtained by grayscale (GS) and power Doppler (PD) assessments were graded on a semi-quantitative scale from 0 to 3. We also examined the assessment of the novel Outcome Measures in Rheumatology (OMERACT)-European League Against Rheumatism (EULAR) combined power Doppler ultrasound (PDUS) score (i.e., thecPD score) and the Global OMERACT-EULAR Synovitis Score (GLOESS). The diagnostic performance of the patients was evaluated using US findings and the combination of US and serologic findings.

Results: Seventy patients (32.4%) at Hospital 1 and 59 patients (26.5%) at Hospital 2 were diagnosed as having RA. The best-balanced diagnostic performance at each hospital was achieved using a combination, such as (1) the presence of PD grade ≥ 2 articular synovitis or (2) the presence of PD grade ≥ 1 articular synovitis and serologic positivity, as well as (1) the presence of cPD grade = 3 or (2) a cPD grade ≥ 2 and serologic positivity (Table 1 and 2).

Conclusion: The combination of a PD assessment or the cPD score with the measurement of autoantibodies of rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies can accurately identify the patients with early RA.

Table 1. Diagnostic performance of RA classification criteria, and serologic and ultrasound findings

	Hospital 1					Hospital 2				
	Sensitivity	Specificity	PPV	NPV	Accuracy	Sensitivity	Specificity	PPV	NPV	Accuracy
2010 ACR/EULAR criteria	71.4	84.9	69.4	86.1	80.6	57.6	93.3	75.6	86.0	83.9
Seropositivity										
RF-positive	75.7	78.1	62.4	87.0	77.3	74.6	73.1	50.0	88.9	73.5
ACPA-positive	64.3	90.4	76.3	84.1	81.9	67.8	92.1	75.5	88.8	85.7
RF- and/or ACPA-positive	77.1	73.3	58.1	87.0	74.5	78.0	70.7	48.9	89.9	72.3
US findings										
Articular synovitis										
Synovial hypertrophy:										
GS grade $\geq 1^*$	98.6	31.5	40.8	97.8	53.2	89.8	62.8	46.5	94.5	70.0
GS grade $\geq 2^*$	85.7	85.6	74.1	92.6	85.6	79.7	79.9	58.8	91.6	79.8
GS grade 3^*	44.3	97.9	91.2	78.6	80.6	5.1	98.8	60.0	74.3	74
Vascularity:										
PD grade $\geq 1^*$	91.4	86.3	76.2	95.5	88.0	86.4	78.0	58.6	94.1	80.2
PD grade $\geq 2^*$	84.3	95.2	89.4	92.7	91.7	67.8	94.5	81.6	89.1	87.4
PD grade 3^*	17.1	99.3	92.3	71.4	72.7	3.4	99.4	66.7	74.1	74.0
Total PD score ≥ 2	88.6	90.4	81.6	94.3	89.8	79.7	90.9	75.8	92.5	87.9
OMERACT-EULAR combined scoring system:										
cPD grade $\geq 1^*$	98.6	31.5	40.8	97.8	53.2	89.8	62.8	46.5	94.5	70.0
cPD grade $\geq 2^*$	90.0	86.3	75.9	94.7	87.5	81.4	79.9	59.3	92.3	80.3
cPD grade 3^*	51.4	97.9	92.3	80.8	82.9	8.5	98.1	62.5	74.9	74.4
Total cPD score ≥ 3	94.3	62.3	54.5	95.8	72.7	NT	NT	NT	NT	NT
GLOESS ≥ 2	78.6	68.5	54.5	87.0	71.8	NT	NT	NT	NT	NT

* Presence of at least one joint or tendon. ACPA, anti-cyclic citrullinated peptide antibody; ACR, American College of Rheumatology; cPD, combined power Doppler; EULAR, European League Against Rheumatism; GLOESS, Global OMERACT-EULAR Synovitis Score; GS, grayscale; NPV, negative predictive value; PD, power Doppler; PPV, positive predictive value; RA, rheumatoid arthritis; RF, rheumatoid factor; NT, not tested.

Table 2. Diagnostic performance of combination of ultrasound and serologic findings

	Hospital 1					Hospital 2				
	Sensitivity	Specificity	PPV	NPV	Accuracy	Sensitivity	Specificity	PPV	NPV	Accuracy
GS grade ≥ 2 and PD grade $\geq 1^*$	84.3	91.1	81.9	92.4	88.9	78	86.6	67.6	91.6	84.3
GS grade ≥ 2 or PD grade $\geq 1^*$	92.9	82.9	72.2	96.0	86.1	88.1	71.3	52.5	94.4	75.8
(1) PD grade $\geq 2^*$ or	88.6	91.1	82.7	94.3	90.3	80	86.6	68.1	92.2	84.8
(2) GS grade ≥ 2 + PD grade $\geq 1^*$										
(1) PD grade $\geq 2^*$ or	88.6	93.2	86.1	94.4	91.7	81.4	78.7	57.8	92.1	79.4
(2) PD-positive tenosynovitis*										
(1) PD grade $\geq 1^*$ and (2) RF/ACPA-positive	70	97.3	92.5	87.1	88.4	64.4	97	88.4	88.3	88.3
(1) PD grade $\geq 2^*$ and (2) RF/ACPA-positive	62.9	100	100	84.9	88.0	50.8	99.4	96.8	84.9	86.5
(1) PD grade $\geq 2^*$ or	91.4	92.5	85.3	95.7	92.1	81.4	92.1	78.8	93.2	89.2
(2) PD grade $\geq 1^*$ and RF/ACPA-positive										
(1) cPD grade $\geq 1^*$ and (2) RF/ACPA-positive	75.7	77.4	61.6	86.9	76.9	67.8	89.6	70.2	88.6	83.9
(1) cPD grade $\geq 2^*$ and (2) RF/ACPA-positive	68.6	97.9	94.1	86.7	88.4	59.3	95.7	83.3	86.7	86.1
(1) cPD grade $\geq 2^*$ or	97.1	67.8	59.1	98.0	77.3	91.5	73.8	55.7	96.0	78.5
(2) cPD grade $\geq 1^*$ and RF/ACPA-positive										
(1) cPD grade = 3^* or	85.7	95.6	90.9	93.3	92.6	66.1	93.9	79.6	88.5	86.5
(2) cPD grade $\geq 2^*$ and RF/ACPA-positive										

* Presence at least one joint or tendon. ACPA, anti-cyclic citrullinated peptide antibody; cPD, combined power Doppler; GS, grayscale; NPV, negative predictive value; PD, power Doppler; PPV, positive predictive value; RA, rheumatoid arthritis; RF, rheumatoid factor.

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Correlation between Clinical and Ultrasonographic Remission? the Effect of Non-Inflammatory Patient-Based Factors on Different Remission Definitions

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Session Information

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Background/Purpose: In this study, we aimed to investigate the concordance of ultrasonographic remission with other remission criteria and to show the influence of non-inflammatory patient-induced factors such as depression, anxiety, fibromyalgia and fatigue on both clinical and ultrasonographic remission.

Methods: Fifty consecutive patients with clinical remission (DAS-28-ESR <2.6) who were diagnosed according to the 2010 ACR / EULAR criteria were recruited to this study.

Patients were also assessed whether they met the Boolean and SDAI remission criteria. 28 joint gray scale (GS) and power Doppler (PD) ultrasonography were performed. Patients' depression and anxiety were assessed by The Hospital Anxiety and Depression Scale (HADS), and their fatigue was assessed by multidimensional Assessment of Fatigue (MAF) scores and patients' fibromyalgia was assessed by widespread pain index (WPI) and symptom severity score (SS).

Results: Patients were divided into 4 groups according to different remission definitions by ultrasonography. (Group1: PD=0 and GS=0, Group2: PD=0 and GS≥0, Group3: PD=1 or 0 and GS=1 or 0, Group4: PD=1 or 0 and GS≥0). Although it is not statistically significant, the highest agreement with all the clinical remission criteria was found in the USG remission group 4 (table).

Patients with ultrasonographic remissions at their first visit in 2011 were reevaluated with clinical remission criteria at the end of 5 years. The highest remission rates were found in patients with USG remission group 3 (DAS28 58%, Boolean 29%, SDAI 47%). There was no significant difference between fatigue, fibromyalgia, depression and anxiety measures between remission and non-remission in all USG remission groups. In contrast, depression (p <0.05) and anxiety (p <0.03) were significantly higher in patients without SDAI remission. Depression (p <0.008) and anxiety (p <0.014) were also significantly higher in patients without Boolean remission.

Conclusion: Clinical and ultrasonographic remission was found to be compatible in half of the patients.

The compliance of the USG remission in Group 4 with the clinical remission definitions was good, and clinical remission continuity was higher in the group meeting the definition of group 3. In contrast the ultrasound remission, the high levels of depression and anxiety in patients without SDAI and Boolean remission suggest that non-inflammatory patient-derived measures have less influence on the ultrasound remission.

Table. The concordance between Ultrasound remission and other remission criteria

		Das28 (n=50)	SDAI (n=23)	Boolean (n=22)
Group 1: PD=0 GS=0	n (%)	13 (% 26)	8(%34,7)	5 (%22,7)
Group 2: PD=0 GS≥0	n (%)	22 (% 44)	10 (%43,4)	8(%36,3)
Group 3: PD=1 or 0 and GS=1 or 0	n (%)	17 (%34)	8 (%34,7)	7 (%31,8)
Group 4: PD=1 or 0 and GS≥0	n (%)	28 (%56)	13(%56,5)	11 (%50)

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Levels of 14-3-3eta Are an Independent Predictor of Long-Term Radiographic Erosive Progression and of Short-Term Rapid Radiographic Erosive Progression in Patients with Inflammatory Polyarthritis

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Background/Purpose: Our objective is to examine the additional contribution of 14-3-3 η levels to known predictors of radiographic progression in inflammatory polyarthritis, both over several years and over the following year.

Methods: All variables were measured at initial and annual visits up to 4 years in patients with recent onset polyarthritis treated to remission. HIGH 14-3-3 η was ≥ 0.50 ng/ml; elevated CRP ≥ 8 mg/L; rapid radiographic progression (RRP) was ≥ 5 Units per year in Sharp van der Heijde (Sharp) Erosion score. General linear models (Glimmix) combining baseline predictors and treatments over time were performed with random effect for repetitions over time to assess the independent effect of 14-3-3 η on radiographic progression; Model 1: Positive anti-CCP2; Model 2: Positive Rheumatoid Factor (RF); Model 3: Positive anti-CCP2 and RF plus elevated CRP; Model 4: Age, Gender, Symptom Duration, Smoking, DAS28-CRP, Sharp, HAQ and Treatments, Model 5: All variables in Models 3 and 4. Generalized Estimated Equations (GEE) assessed the association with RRP of anti-CCP2, elevated CRP, and HIGH 14-3-3 η , alone and in combination.

Results: Mean age was 58.5 years, 60.2% women; median duration at inclusion 3.4 months. Out of 1529 complete evaluations (including baseline) in 533 patients, 511 (33.4%) were HIGH 14-3-3 η , 590 (38.6%) positive anti-CCP2, 554 (36.2%) positive RF, 476 (31.1%) elevated CRP; 157 (10.3%) RRP episodes. In univariate analyses, baseline 14-3-3 η levels (as did positive anti-CCP2, positive RF and elevated CRP) predicted erosion scores at 42 months (median (IQR): 5.0 (1.0-10.0) vs 2.0 (0.0-7.0), $p < 0.001$) and radiographic progression (mean \pm SD: 5.7 ± 10.2 vs 3.3 ± 8.5 , $p < 0.001$). HIGH 14-3-3 η , positive anti-CCP2 and elevated CRP were each associated with increased Relative Risks (RR) of RRP: 1.82 (1.36-2.43) $p < 0.001$; 2.33 (1.65-3.30) $p < 0.001$; 2.21 (1.65-2.95), $p < 0.001$, respectively. In multivariate Glimmix models, continuous 14-3-3 η remained a highly significant independent predictor of Erosion progression in all Models, including the 5 described above (all $p < 0.001$). In GEE, relative to being negative for all three, being positive for all of HIGH 14-3-3 η , anti-CCP2, and CRP was associated with a RR of 6.19 (3.82-10.05), $p < 0.001$; RRP occurred following 34.1% of visits when all three were positive. Being positive for only 2 variables identified subsets of patients at intermediate RR (1.84 to 4.42) of RRP. The contribution of HIGH 14-3-3 η to predict RRP was highest in patients with positive anti-CCP2 and/or elevated CRP; sensitivity was then 46.2%, specificity 84.0% and negative predictive value 93.3%.

Conclusion: In patients treated to remission, baseline 14-3-3 η levels were predictive of erosion scores and erosion progression, but not of narrowing, over the following 4 years, even when combined with multiple baseline predictors of erosive progression and taking into account treatments received from baseline. The presence of HIGH 14-3-3 η amplified the risk (up to 34%) for RRP conferred by anti-CCP2 and/or CRP. Adding 14-3-3 η measurement to anti-CCP2 and clinical measures over the course of RA may inform therapeutic strategies tailored to halt rapid joint damage progression in the most susceptible patients.

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Development of a Predictive Model of Radiological Damage in Patients with Rheumatoid Arthritis Based on Artificial Intelligence

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with increased mortality and disability. Although different factors have been associated with prognosis, it is still difficult to predict the evolution of a specific patient. Therefore, our objective was to train and validate a predictive model of disease severity using radiological damage as a surrogate marker, based on Artificial Intelligence techniques, and using clinical and genetic data as predictors.

Methods: Four independent cohorts were included (959 patients with 1902 hand X-rays). Radiological damage was measured using the hands and wrists Sharp / van-der-Heijde score (SvdH). The variables to be predicted [total value of SvdH, erosion component (ES) and joint narrowing (NS)] were logarithmically transformed before analysis. As clinical predictors, age at onset of symptoms, sex, duration of the disease at the time of each radiograph, year of onset of symptoms and presence of rheumatoid factor were used. As genetic variables, the single nucleotide polymorphism data obtained from the Immunochip genotyping platform (Illumina) were used. In addition to an additive effect of the genetic variants, an interaction between each polymorphism and the duration of the disease was introduced in the analysis. Three cohorts were used for the selection of variables, generation of predictive models and internal validation. The fourth cohort was used to perform the external validation of the models. Regression trees with random effects (RTRE) were generated using the R package “REEMtree”. The goodness of fit of the models was measured using the root mean squared error (RMSE) and the intraclass correlation coefficient (ICC).

Results: After the variable selection step, for the prediction of total SvdH, ES and NSLS, the RTRE selected 253, 235, and 192 unique sets of variables composed of a median (interquartile) 31 (26-38), 21 (17-26), and 34 (28-38) elements, respectively. Regarding interval validation, the lowest RMSEs were 3.16, 1.25 and 2.43 units of the Sharp / van-der-Heijde score, for total SvdH, ES and NSLS, respectively. The highest ICCs were 0.91, 0.88 and 0.92, respectively. Regarding external validation, the lowest RMSEs were 5.79, 3.34 and 4.09 units of the Sharp / van-der-Heijde score, respectively. The highest ICCs were 0.90, 0.77 and 0.89, respectively. We selected those sets of variables located in the lowest deciles of the RMSE for both the internal and the external validation cohorts: 4 data sets were selected for Total SvdH, 16 for ES, and 14 for NSLS, with 88 polymorphisms in combination.

Conclusion: It is possible to generate predictive models of radiological damage of great precision using Artificial Intelligence techniques. This could allow early stratification of patients according to prognosis. It is necessary to validate these models in other populations.

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Neutrophil Activation Is Associated with Disease Activity and Predicts Development of Erosive Disease and Extra Articular Manifestations in Rheumatoid Arthritis

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Background/Purpose: Neutrophil activation is associated with inflammation and autoimmunity, including rheumatoid arthritis (RA), where neutrophil infiltration into joints participates in tissue destruction and development of arthritis. In RA, neutrophils may undergo a programmed form of necrosis, NETosis, upon which neutrophil extracellular traps (NETs) are extruded. Due to their inflammatory capacity *in vitro*, as well as containing key autoantigens such as citrullinated histones and vimentin, NETs have been suggested to be an important contributor in the pathogenesis of RA. However, the clinical utility, and in particular the prognostic capacity, of neutrophil biomarkers has not been carefully addressed.

Methods: Markers of neutrophil activation (S100A8/A9) and NETosis were analyzed by ELISA in healthy controls (HC, n=24, and n=100) and RA patients from two independent cross-sectional cohorts (n=101 and n=93), as well as one longitudinal inception RA cohort (n=250) followed for a median of 8.3 years (4.4-19.8 years). The first cohort focused on disease activity measures, whereas the other cohorts were designed to study outcome measures.

Results: Levels of S100A8/A9 and NETs were markedly elevated in all three RA cohorts as compared to healthy individuals (p<0.0001). Both markers, particularly S100A8/A9, were associated with clinical markers of disease activity, including CDAI (r=0.52, p<0.0001) and the presence of swollen joints (r=0.50, p<0.0001). Patients who met the 1958 criteria for probable or definite RA but did not fulfill the 1987 ACR criteria (n=32), had significantly lower levels of circulating NETs as compared to individuals fulfilling the 1987 ACR criteria for RA (n=250, p<0.0001), and were indistinguishable from healthy individuals (p=0.16). Levels of NETs showed high specificity for patients fulfilling the 1987 ACR criteria for RA, as compared to healthy individuals (90%), as well as compared to symptomatic individuals not fulfilling the 1987 ACR criteria (94%), indicating a potential diagnostic utility of the test. Using the inception cohort, levels of NETs and S100A8/A9 were able to predict future development of extra articular nodules (OR=2.8, p<0.05, and OR=3.4, p<0.01, respectively). Furthermore, S100A8/A9 levels could predict future joint space narrowing (OR=4.4, p<0.0001) and erosive disease (OR=5.5, p<0.0001). A small number (12.5%) of newly diagnosed RA patients had noticeable erosive changes when recruited. Excluding these individuals from the analysis further strengthened the results with S100A8/A9 predicting joint space narrowing (OR=8.8, p=0.003) and the development of erosive disease (OR=5.7, p<0.0001).

Conclusion: Our results demonstrate a clear contribution of neutrophils in RA pathogenesis. Neutrophil-derived biomarkers may be able to monitor and predict disease activity and severity in RA patients. Thus, therapies targeting exaggerated neutrophil activation are anticipated to be beneficial in RA. Finally, monitoring of neutrophil biomarkers may allow for early preventive treatment avoiding long-term disabling disease in RA, including extra articular manifestations and erosive changes.

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Association between Disease Activity and Radiographic Progression in the Current Treat-to-Target Paradigm of Rheumatoid Arthritis: Real World Data from the Dutch Rheumatoid Arthritis Monitoring (DREAM) Registry

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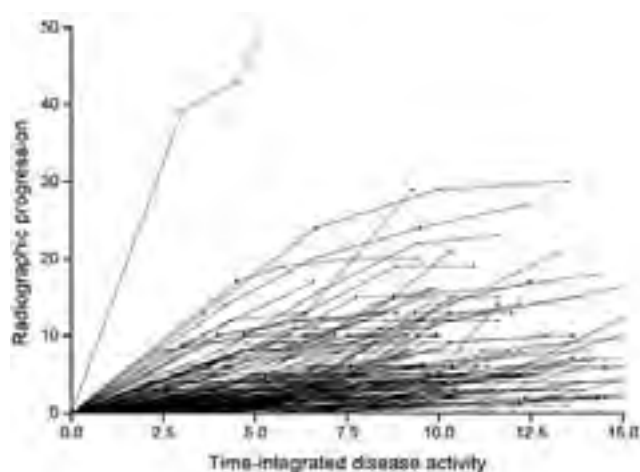
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Background/Purpose: Recent studies suggested a disconnect between disease activity and radiographic damage in rheumatoid arthritis (RA) patients treated with more aggressive treatment (1). Therefore, the aim of this retrospective study was to examine the longitudinal association between disease activity and radiographic damage in a real world cohort of consecutive patients with early RA treated according to treat-to-target (T2T) of remission step-up therapy.

Methods: Baseline to 3-year follow-up data were used from patients with early RA (79% fulfilling ACR 1987 criteria) included in the DREAM remission induction cohort (2). Patients were treated according to protocolized T2T, aimed at 28-joint disease activity score-erythrocyte sedimentation rate (DAS28-ESR) <2.6. Disease activity assessments were performed every 3 months; X-rays of the hand and feet were assessed at baseline and after 0.5, 1, 2 and 3 years of treatment and scored using modified Sharp/van derHeijde scoring (SHS). Between and within-person relations between time-integrated disease activity scores (DAS28-ESR and CRP) and radiographic change scores overtime were examined using Pearson correlations.

Results: 229 patients (63.3% female, mean age 57.5 years, baseline median symptom duration 13 weeks) with at least two radiographic assessments in the first 3 years were available for analysis. At the between-patient level, time-integrated DAS28-ESR scores were not significantly correlated with progression at the 6 month ($r=0.06$) and 2-year follow-up ($r=0.11$) and only weakly at the 1-year ($r=0.17$, $P<0.05$) and 3-year follow-up ($r=0.21$, $P<0.05$). Within individual patients, however, a different but fairly linear relationship between disease activity and progression existed over time (Figure). Individual slopes of the relationship between disease activity and progression were significantly correlated at each time point (Table) and the slope of the first 6 months was moderately significantly associated with this slope at later time points. Analyses using CRP showed similar results.



	6 months	1 year	2 year	3 year
6 months	–			
1 year	0.394***	–		
2 year	0.527***	0.172*	–	
3 year	0.592***	0.252**	0.478***	–

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Conclusion: In early RA patients treated according to T2T, radiographic progression appears to be an individually determined disease process, driven by factors other than consistent high disease activity. Within individual patients, the association between disease activity and radiographic damage during the first 6 months in individuals seems to be a good indicator for the progression and its association with disease activity in later years.

References:

1. Ann Rheum Dis. 2013;72(2):307–8.
2. Arthritis Rheum. 2011;63(10):2865–72.

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Impact of the Joint Presence of Erosions and ACPA on Rheumatoid Arthritis Disease Activity over Time: Results from the Meteor Registry

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Background/Purpose: Despite efforts to predict treatment response, treatment of rheumatoid arthritis (RA) patients remains mostly a case of trial and error. Previous research, mostly in clinical trials, focused mainly on radiological outcomes after treatment with methotrexate and identified baseline presence of erosions and ACPA as risk factors. We investigated in newly diagnosed RA patients if erosions and/or ACPA at baseline are associated with functional outcomes in the first year of treatment in daily practice.

Methods: Newly diagnosed patients with a clinical diagnosis of RA, ≥ 3 months follow-up and available data on ACPA, erosions and medication use were identified in the international, observational METEOR registry (n patients=4623). Timing and frequency of follow-up visits were non-protocolled and according to daily practice. We focussed at results after a maximum follow-up duration of 6 months or of 1 year from baseline. Associations between the presence of erosions and/or ACPA (4 groups) with the change of DAS and HAQ over time were assessed using linear mixed models. Missing data were imputed using multiple chained equations (40 cycles) and models were adjusted for the potential confounders age, gender, smoking, symptom duration, BMI, initial medication and country. In case of statistically significant effect modification ($p < 0.20$) by country, medication group (csDMARD monotherapy, csDMARD combination therapy, csDMARD + glucocorticoid and other) or symptom duration group (< 1 year, 1-2 years, 2-5 years and > 5 years), results were stratified.

Results: Baseline characteristics and follow-up duration of each ACPA/erosions group are shown in table 1. Baseline DAS and HAQ were slightly higher in erosions+ patients. Follow-up was similar between the 4 groups. We found statistically significant differences in DAS and HAQ change over time between the 4 groups, both after maximum follow-up durations of 6 months and 1 year (table 1). The adjusted change in DAS over time was slightly larger in the erosions+ groups and the adjusted change in HAQ over time was slightly smaller in the erosions-/ACPA+ group, but differences were small and not clinically relevant. No effect modification was found by country, medication or symptom duration.

Conclusion: In this analysis of worldwide real life data, we found statistically significant, but no clinically relevant differences in treatment response to initial DMARD therapies as measured by DAS and HAQ in ACPA-/erosions-, ACPA-/erosions+, ACPA+/erosions- and ACPA+/erosions+ RA patients. Instead, all groups had a similar response to initial treatment.

Table 1. Baseline characteristics and follow-up duration of each ACPA/erosions group.

		ACPA negative		ACPA positive	
		Erosions negative n=701	Erosions positive n=344	Erosions negative n=1585	Erosions positive n=1993
Female (%)		83.0	83.4	81.4	84.9
RF (% positive)		31.0	33.5	33.0	35.1
Smoking (%)	Never	81.2	88.8	85.1	91.6
	Current	7.3	4.7	9.3	5.2
	Stopped	11.6	6.7	5.4	3.2
Age (years) mean (SD)		51 (16)	50 (14)	48 (13)	49 (12)
BMI mean (SD)		27.7 (6.0)	27.0 (6.0)	25.9 (5.9)	25.7 (5.7)
Symptom duration (months) median (IQR)		12 (4-36)	36 (12-72)	18 (4-48)	48 (19-108)
HAQ mean (SD)		0.98 (0.61)	1.1 (0.6)	0.88 (0.59)	1.1 (0.6)
DAS mean (SD)		3.5 (0.93)	4.0 (1.0)	3.6 (0.97)	4.0 (0.95)
ESR mean (SD)		47.5 (32.8)	60.1 (37.8)	65.5 (36.0)	72.8 (36.0)
Initial treatment (%)	csDMARD mono	51.8	42.2	55.5	29.1
	csDMARD combi	14.3	17.4	17.9	22.6
	csDMARD + GC	27.5	37.2	23.9	45.1
	Other	6.43	3.2	2.7	3.2
	Follow-up duration median (IQR)	9.2 (6.0; 10.6)	8.8 (6.0; 10.7)	9.0 (6.2; 10.6)	9.3 (6.7; 10.6)

Based on non-imputed data. ACPA = anti-citrullinated protein antibodies; RF = rheumatoid factor; BMI = body mass index; HAQ = health assessment questionnaire; DAS = disease activity score; ESR = erythrocyte sedimentation rate; mono = monotherapy; combi = combination therapy; GC = glucocorticoid.

Table 2. Associations between the presence of erosions and/or ACPA on the change of DAS and HAQ over time (n=4623).^a

	6 months p-value ^a	12 months p-value ^a	6 months B(95% CI)	12 months B(95% CI)
	Interactions with time		Stratified analyses: evolution over time (months)	
DAS				
Ero- ACPA-	0.481	0.551	-0.24 (-0.27; -0.22)	-0.11 (-0.12; -0.10)
Ero+ ACPA-	0.001	<0.001	-0.30 (-0.34; -0.26)	-0.14 (-0.16; -0.12)
Ero- ACPA+	<i>Ref</i>	<i>Ref</i>	-0.24 (-0.25; -0.22)	-0.11 (-0.11; -0.099)
Ero+ ACPA+	<0.001	<0.001	-0.30 (-0.32; -0.29)	-0.12 (-0.13; -0.12)
HAQ				
Ero- ACPA-	0.035	0.121	-0.081 (-0.096; -0.065)	-0.034 (-0.040; -0.027)
Ero+ ACPA-	0.072	0.034	-0.084 (-0.10; -0.064)	-0.038 (-0.047; -0.029)
Ero- ACPA+	<i>Ref</i>	<i>Ref</i>	-0.062 (-0.072; -0.053)	-0.027 (-0.031; -0.023)
Ero+ ACPA+	<0.001	0.047	-0.086 (-0.095; -0.078)	-0.033 (-0.037; -0.029)

^aResults stem from multivariable linear mixed models analyses with random intercept and slope and exchangeable covariance matrix, adjusted for age, gender, smoking, symptom duration, BMI, initial medication and country. Regression coefficients represent the units of change in the outcome per unit of time, in this case, per month. Missing data were imputed using multiple chained equations (40 cycles).

^aP-values are only shown for the interaction between erosions/ACPA and time in months. In the presence of a statistically significant interaction, results are stratified by gender and the evolution of DAS and HAQ over time is shown for the erosions/ACPA groups separately.

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Bone Erosion Volume Changes Measured By HR-pQCT at 3-Months after Initiation of Anti-TNF Treatment Predicted Erosion Volume Changes at 1-Year in RA

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Background/Purpose: Bone erosions and joint space narrowing (JSN) are significant aspects of structural damage in rheumatoid arthritis. High resolution peripheral quantitative computed tomography (HR-pQCT) allows detailed analysis of bone erosion, joint space and bone microstructure. We previously reported bone erosion and microarchitecture evaluation using HR-pQCT within the first three months after the initiation of anti-tumor necrosis factor (TNF α) treatment. However, no study has yet reported if early bone changes such as three months would predict the future changes of bone destruction. Hence, the goal of this study was to quantify erosion volume, bone microarchitecture, joint space volume and width from prior to anti-TNF α therapy to one year after initiation using HR-pQCT, and to investigate if development of erosions at 3-months can predict progression of erosions after 1 year.

Methods: Twenty-one RA patients receiving MTX treatment were recruited and divided into two groups according to disease activity scores (low (DAS28 \leq 3.2) (N=9) and high (DAS28>3.2) (N=12) DAS group). Patients in the high DAS group were treated with anti-TNF α and MTX immediately after the baseline MRI (BL). All patients underwent HR-pQCT scans of the MCP at BL, 3-months (3M) and 1-year (1Y). HR-pQCT-derived erosion volume, joint space volume and width and bone microarchitecture at the MCP2 and MCP3 were measured using in-house developed software with previously reported excellent in-vivo reproducibility.

Results: 37 bone erosions were detected at BL. In the high DAS group, one erosion was full repaired, while two new erosions were observed at 1-year. Although there were no significant changes of mean bone erosion volume in the high DAS group from BL to 1Y, the low DAS group showed increases in mean bone erosion volume from BL to 1Y regardless of lower disease activity (P=0.006). Changes of bone erosion volume from BL to 3M were significantly correlated with changes of bone erosion volume from 3M to 1Y (P=0.001). On the other hand, both groups showed significant joint space narrowing at 1Y compared to BL (P=0.008).

Conclusion: Our findings suggest that early changes in bone erosion volume can predict future disease progression. Therefore, additional treatment may be necessary for patients whose bone erosion volume increases during the early period despite good response for DAS28. HR-pQCT provides sensitive technique to measure erosion progression even within 3-months after treatment.

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Plasma Mir-146a-5p Associates with Beneficial Body Composition and Plasma Metabolic Profiles in Rheumatoid Arthritis

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Background/Purpose: In rheumatoid arthritis (RA), sarcopenic obesity is associated with significant cardio metabolic disease and mortality. Biomarkers of disease activity in RA and obesity are complicated by inflammation associated with both conditions. The microRNA miR-146a is implicated as a biomarker in both RA pathogenesis and adiposity. However, it is unclear whether systemic miR-146a is impacted primarily by autoimmunity or obesity in RA. Here, we investigated relationships of miR-146a with RA disease activity, body composition and metabolic intermediates associated with obesity.

Methods: All RA patients in this study satisfied 1987 ACR criteria. Plasma miR-146a-5p expression was measured via PCR as delta cycle threshold (Δ Ct) using a reference microRNA sequence in 48 persons with RA and 23 age-, sex- and BMI-matched healthy controls. Plasma acylcarnitine and amino acid measurements were made via flow injection tandem mass spectrometry. Body composition was assessed using CT scan analyses to determine central and muscle adipose and thigh muscle tissue size and tissue density. Disease activity in RA was assessed by DAS-28-ESR. Plasma miR-146a-5p was compared in RA versus control subjects using the Wilcoxon signed rank test. Correlations were evaluated using Spearman ρ . Strengths of associations for the two groups were compared with Fisherr-to-z transformations.

Results: There was no significant difference in plasma miR-146a-5p expression between RA (-0.158 ± 0.98 (SD) Δ Ct) versus controls (-0.086 ± 1.53 Δ Ct; $p=0.69$). miR-146a-5p was not correlated with RA disease activity ($r=-0.03$, $p=0.84$). In RA, greater expression of miR-146a-5p was associated with younger age, lower BMI, smaller waist circumference, less adiposity, and greater thigh muscle density (Table 1). Body composition correlations were not significantly different between groups (Fisher r-to-z $p>0.05$ for all). In RA, greater miR-146a-5p was also associated with lower concentrations of adiposity-related (Newgard et al. Cell Metabolism (2009); 9: 311–326) metabolic intermediates, acylcarnitines and branched chain amino acids (Table 2).

Conclusion: Greater plasma miR-146a-5p was associated with multiple indicators of reduced adiposity: smaller central and thigh fat areas, less intra-muscular adiposity, and less circulating adiposity-related metabolic intermediates. Plasma miR-

Table 1: miR-146a-5p expression relationships in Rheumatoid Arthritis and Controls

Variable	Rheumatoid arthritis (n=48)	miR-146a-5p [Δ Ct]	Controls (n=23)
Age (years)	-0.33*		-0.27
BMI (kg/m ²)	-0.40*		-0.10
Waist circumference (cm)	-0.42*		-0.25
Abdominal total adipose area (cm ²)	-0.40*		-0.29
Abdominal subcutaneous adiposity (cm ²)	-0.26		0.09
Abdominal visceral adiposity (cm ²)	-0.89*		-0.18
Abdominal liver density (Hz)	0.16		-0.07
Thigh total area (cm ²)	-0.33*		-0.18
Thigh total adipose area (cm ²)	-0.29*		0.16
Thigh subcutaneous adiposity (cm ²)	-0.28		0.20
Thigh intermuscular adiposity (cm ²)	-0.38*		-0.28
Thigh muscle area (cm ²)	0.04		-0.18
Thigh muscle density (Hz)	0.35*		0.89*

Data are shown as Spearman correlation coefficients. miR (microRNA), Δ Ct (delta cycle threshold).

* $p < 0.05$ for Spearman correlation. *Fisher r-to-z $p < 0.05$ for all.

Table 2: Plasma metabolite relationships in Rheumatoid Arthritis

Variable	miR-146a-5p (ΔCt)	BMI (kg/m ²)	Abdominal total adipose area (cm ²)	Thigh total adipose area (cm ²)
<i>Acylcarnitines</i>				
Free carnitine:C0	-0.18	0.35*	0.37*	0.17
C2	-0.31*	0.13	0.13	0.09
C3	-0.21	0.24	0.23	0.07
C4/C54	-0.09	0.18	0.22	0.14
C5:1	-0.18	0.01	0.11	0.17
C5	-0.14	0.56*	0.49*	0.15
C4OH	-0.41*	0.20	0.19	0.11
C6	-0.32*	0.20	0.25	0.31*
C5OH/C1DC	-0.18	0.06	0.03	-0.17
C4DC/C54DC	-0.38*	0.24	0.20	0.21
C8:1	-0.45*	-0.45*	0.41*	0.39*
C8	-0.15	0.18	0.13	0.08
C5DC	-0.31*	0.78*	0.22	0.21
C8:1OH/C6:1 DC	-0.28	0.14	0.12	0.21
C6DC/C8OH	-0.16	-0.02	0.05	0.05
C10:3	-0.45*	0.33*	0.29*	0.38*
C10:2	-0.42*	0.35*	0.29*	0.35*
C10:1	-0.29*	0.27*	0.25	0.27
C10	-0.17	0.12	0.16	0.11
C7DC	0.06	-0.05	-0.07	-0.09
C8:1 DC	-0.45	0.34*	0.27	0.35*
C10OH/C8DC	-0.29*	-0.18	-0.22	-0.10
C12:1	-0.38*	-0.31*	0.29*	0.30*
C12	-0.38*	0.14	0.10	0.09
C12OH/C10DC	0.01	0.08	0.00	-0.01
C14:2	-0.37*	0.12	0.19	0.16
C14:1	-0.39*	0.21	0.25	0.28
C14	-0.40*	0.26	0.21	0.17
C14OH/C12DC	-0.38*	0.30*	0.43*	0.36*
C16:2	-0.23	0.11	0.12	0.21
C16:1	-0.40*	0.16	0.17	0.23
C16	-0.38*	0.23	0.15	0.06
C16:1OH/C14:1 DC	-0.35*	0.17	0.19	0.20
C16OH/C14DC	-0.34*	0.11	0.22	0.09
C18:2	-0.31*	0.11	0.07	0.09
C18:1	-0.33*	0.09	0.04	0.03
C18	-0.18	0.00	-0.04	-0.13
C18:1OH/C16:1 DC	-0.16	0.17	0.14	0.27
C18OH/C16DC	-0.18	0.14	0.18	0.05
C20:4	-0.05	0.05	0.02	-0.11
C20	-0.27*	0.00	0.06	-0.13
C20OH/C18DC	-0.23	0.17	0.06	-0.09
C22	-0.18	0.22	0.21	0.30*
<i>Amino acids</i>				
Glycine	0.21	-0.03	-0.08	0.14
Alanine	-0.24	0.42*	0.47*	0.39*
Serine	0.40*	0.00	-0.09	-0.04
Proline	-0.16	0.33*	0.30*	0.13
Valine	-0.10	0.33*	0.28	0.00
Leucine/isoleucine	-0.04	0.31*	0.26	-0.03
Methionine	0.03	0.26	0.26	0.15
Histidine	0.09	0.03	0.02	-0.04
Phenylalanine	-0.42*	0.53*	0.52*	0.43*
Tyrosine	-0.29*	0.42*	0.49*	0.27
Aspartate/asparagine	-0.24	0.04	0.21	0.17
Glutamate/glutamine	-0.11	0.31*	0.31*	0.10
Ornithine	-0.22	0.38*	0.33*	0.20
Citrulline	-0.23	0.21	0.22	0.28
Arginine	-0.07	0.15	0.16	0.16

Data are shown as Spearman correlation coefficients. miR (microRNA), ΔCt (delta cycle threshold).
*p < 0.05 for Spearman correlation

146a-5p expression in RA was similar to controls and not associated with DAS-28 scores. These findings suggest that rather than disease activity, in established RA, plasma miR-146a-5p inversely reflects adiposity.

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Peptidylarginine Deiminase-4 Antibodies Are Not Associated with Worse RA Activity, Symptoms or Impacts

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Background/Purpose: Antibodies to peptidylarginine deiminase (PAD) enzymes have been implicated in the pathogenesis of RA. Previous studies have shown that patients with PAD4 antibodies have more erosive joint disease compared to patients who do not. We hypothesized that patients with PAD4 antibodies would have more severe disease and report higher levels of RA symptoms and functional impacts than those without antibodies.

Methods: Adults with MD-diagnosed RA enrolled in a longitudinal cohort study with serum available from the visit were included; almost all (96%) met 2010ACR/EULAR RA criteria. Anti-PAD4 antibodies were detected by immunoprecipitation. Independent t-tests and chi-square were used to compare patient and RA characteristics and selected patient reported outcomes (PROs: PROMIS™ pain intensity, physical function, fatigue, ability to participate in social roles and activities, anxiety, depression, and sleep disturbance) by antibody status.

Results: Patients (n=151) had a mean age of 55 +/-13, were mostly female (80%), and white (85%). Most had longstanding RA (11 +/-10 years) with 35% in CDAI remission and 34% with low disease activity. Nearly half (47%) were on a

Table 1. Patient characteristics.

Mean (SD) or N(%)	None N=109 (72%)	Anti-PAD4+ N=42 (28%)	p-value
Age, median (IQR)	57 (49, 64)	54 (47, 66)	0.77
Duration, median (IQR)	7 (3, 12)	14 (8, 26)	<0.001
Non-Caucasian	16 (15%)	7 (17%)	0.76
Female	87 (80%)	33 (79%)	0.87
Methotrexate Use	75 (69%)	28 (67%)	0.80
Biologic Use	46 (47%)	17 (45%)	0.78
Prednisone Use	26 (24%)	12 (29%)	0.54
Erosions	51 (47%)	26 (63%)	0.08
CDAI	8.2 (8.7)	6.2 (6.2)	0.17
Remission	38 (35%)	16 (38%)	0.49
Low	34 (31%)	17 (40%)	
Moderate	24 (22%)	6 (14%)	
High	13 (12%)	3 (7%)	
SJC (SD)	2.2 (3.4)	1.6 (2.5)	0.37
TJC (SD)	1.9 (3.4)	0.6 (1.4)	0.02
EGA (SD)	15.0 (16.2)	11.6 (11.8)	0.23
PGA (SD)	26.1 (26.5)	27.2 (26.8)	0.82
Stiffness Severity (SD)	1.5 (1.0)	1.4 (0.8)	0.74
ESR mm/hr (SD)	20.7 (20.1)	19.8 (19.3)	0.82
CRP mg/dl (SD)	0.72 (1.2)	1.1 (2.9)	0.34

Table 2. Patient reported outcomes by anti-PAD4 antibody status.

	None Mean (95% CI)	Anti-PAD4+ Mean (95% CI)	p- value
Pain Intensity	44.8 (43.0-46.6)	44.0 (41.1-46.8)	0.64
Physical Function	43.8 (42.0-45.7)	43.8 (41.0-46.6)	0.99
Fatigue	53.9 (52.0-55.8)	52.9 (49.1-56.6)	0.60
Social Roles	50.1 (48.4-51.8)	51.5 (48.7-54.4)	0.39
Anxiety	50.2 (48.4-52.0)	49.6 (47.1-52.0)	0.70
Depression	48.8 (47.0-50.6)	48.1 (45.5-50.8)	0.68
Sleep Disturbance	52.7 (49.6-53.8)	51.6 (49.0-54.2)	0.96

biologic, and 68% were on MTX. Anti-PAD antibodies and PROs were available on 135 patients (89%); baseline characteristics did not differ between those with and without completed PROs. A total of 38 (28%) patients were anti-PAD4+. No significant differences were evident between groups in mean CDAI, SJC, PGA, EGA, stiffness severity, ESR, or CRP (Table 1). Although a higher proportion of anti-PAD4+ patients had erosions, there was no statistically significant difference between groups (Table 1). Mean PROMIS scores (pain intensity, physical function, fatigue, ability to participate in social roles and activities, anxiety, and depression) were in the normal range (i.e., 55-65) except pain intensity and physical function which were lower in both groups (Table 2); however, PRO scores were similar between groups.

Conclusion: In this well characterized cohort of RA patients, anti-PAD4+ patients had longer disease duration and a slightly lower TJC compared to patients without PAD antibodies. Anti-PAD4+ patients had a trend toward more erosive disease; but PROs were similar between groups. Contrary to expectations, anti-PAD4+ patients did not have clinical evidence of worse symptoms or functional impacts. The lack of congruency between bony damage and disease activity may suggest a difference in pathogenesis between these processes

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Abstract Number: 1462

Fibrin Deposition and Neutrophil Infiltration of Rheumatoid Arthritis Synovium Are Associated with Duration of Morning Stiffness

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Background/Purpose: Stiffness is a hallmark of RA, but little is known about the etiology. We investigated stiffness association with RA disease activity and determined whether synovial histologic features are associated with stiffness severity or stiffness duration.

Methods: 194 patients with RA meeting ACR criteria undergoing arthroplasty were included (Table 1). Morning stiffness duration was determined using the RADAI question, “Were your joints stiff when you woke up today? If yes, how long did the stiffness last?”; “no stiffness, <30 min, 30-60 mins, 1-2 hrs, 2-4 hrs, >4 hrs, all day”. Stiffness severity was measured by the OMERACT Flare question, “How severe was your stiffness over the past week” on a 10 point Likert scale. Histopathology of synovium was scored for 10 features: synovial lining hyperplasia, lymphocytes, plasma cells, Russell

Table 1. Patient Characteristics	N = 194
Age at baseline (Years)	62.7 ± 11.5
Sex (Female)	156 (80%)
Duration of Disease (Years)	11.4 [4.2, 21.0] n=180
BMI (kg/m ²)	28.0 [24.1, 33.7] n=186
Anti-CCP Interpretation	
Low Positive	53 (27%)
High Positive	80 (41%)
RF Interpretation, Positive	73 (38%)
DAS28-ESR	3.7 [2.8, 4.6] n=159
DAS28-CRP	3.6 [2.8, 4.5] n=156
ESR (mm/hr)	13.5 [6.0, 31.0] n=180
CRP (mg/dL)	1.2 [0.0, 2.2] n=176
Number of Tender Joints	1.0 [0.0, 5.0] n=173
Number of Swollen Joints	3.0 [1.0, 8.0] n=174
NSAIDs	101 (52%)
Opioids	67 (35%)
Steroids	69 (36%)
Methotrexate	96 (49%)
Non-methotrexate DMARD	51 (26%)
Biologic	95 (49%)
Morning Stiffness ("Yes")	147 (76%)
Morning Stiffness Duration (hr)	
<0.5	49 (16%)
0.5-1	36 (25%)
1-2	17 (18%)
2-3	9 (5%)
3-4	11 (6%)
>4	10 (5%)
All day	15 (8%)
Morning Stiffness Severity	
0, no stiffness	8 (4%)
1	5 (3%)
3	17 (9%)
4	11 (6%)
5	29 (15%)
6	16 (8%)
7	15 (8%)
8	26 (13%)
9	9 (5%)
10, extreme stiffness	29 (15%)

bodies, binucleate plasma cells, fibrin, synovial giant cells detritus, neutrophils and mucin. Severity was modeled as a continuous outcome and duration was modeled as a binary outcome using < 30 mins vs ≥ 30 mins. Simple regression models were performed to examine the association between DAS28-ESR and RAPID3, with severity and duration. Multivariable regression models were performed with (either DAS28-ESR or RAPID3) and the following clinical variables: age, gender, BMI, duration of diagnosis, anti-CCP, and RF. Chi-squared or Fisher's exact test was used to test the association between 10 histology features and morning stiffness outcomes. FDR-adjusted p-values were reported to correct for multiple comparisons.

Results: Morning stiffness duration of greater than 30 minutes was significantly associated with both DAS28-ESR (OR: 1.79 [1.26, 2.55], p value = 0.001) and RAPID3 (OR: 1.17 [1.06, 1.29], p value = 0.002) and remained significantly associated after incorporating age, gender, BMI, duration of diagnosis, anti-CCP and RF. Stiffness severity was also significantly associated with both DAS28 (β = 0.51, p value = 0.006) and RAPID3 (β = 0.29, p value < 0.0001) and remained significantly

associated after incorporating age, gender, BMI, duration of diagnosis, anti-CCP, and RF into the model. After adjusting for multiple comparisons, neutrophils (P_{adj}=0.005) and fibrin (P_{adj}=0.005) were significantly associated with greater than 30 minutes of morning stiffness. None of the 10 synovial features examined were significantly associated with stiffness severity.

Conclusion: Both stiffness severity over the past week and duration of morning stiffness were significantly associated with the disease activity measurement instruments, DAS28 and RAPID3. Fibrin deposition and neutrophil infiltration are associated with the duration of morning stiffness in RA, suggesting acute synovial inflammation and relatively recent or ongoing neutrophil recruitment may play a role in the pathogenesis of this symptom.

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Do Anti-Citrullinated Protein Antibodies and Anti-Sjögren's-Syndrome-Related Antigen a Double Positive Patients with Secondary Sjögren's Syndrome and RA Have Higher Joint Disease Activity?

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Background/Purpose: Secondary Sjögren's syndrome (sSS) is considered an extra-articular manifestation of RA and is an autoantibody-mediated condition similar to RA. Thus, patients (pts) with sSS could be anti-citrullinated protein antibodies (ACPA) and anti-Ro/Sjögren's-syndrome-related antigen A (SSA) autoantibody double positive (double+). There are limited data on the impact of double positivity on RA disease burden. The objective of this analysis was to compare pts with sSS with and without double positivity.

Methods: Data from adult pts with RA enrolled in a longitudinal sequential RA registry were analyzed. Pts in the registry were evaluated annually by a rheumatologist for disease activity and treatment, and semi-annually on multiple clinical patient-reported outcomes (PROs) and resource utilization parameters. Pts with sSS were identified with a clinician's diagnosis or based on meeting the 2016 ACR/EULAR classification of primary Sjögren's syndrome. Pts with sSS were divided into two mutually exclusive groups: pts with and without double positivity (the latter including single positive or double negative pts). The two cohorts were compared using descriptive statistics to summarize baseline differences in demographics, disease activity measures, sero status and treatments. A Kruskal–Wallis test for continuous variables and a chi-square test for categorical variables were performed with a significance level of 0.05. Mean changes from baseline to 12 months in disease activity measures and PROs were assessed for pts with available data at baseline and follow-up.

Results: A total of 415 pts were identified as having sSS associated with RA, with 80 (19.3%) and 86 (20.7%) pts in the cohorts with and without double positivity, respectively. The double+ pts with sSS were diagnosed with RA at a younger age, had longer duration since onset of RA symptoms and a higher number of swollen joints compared with pts with sSS without double positivity (Table 1). In addition, the mean changes in disease activity were lower in pts with versus without double positivity, though these were not statistically significant, potentially due to the limited sample size (Table 2).

Conclusion: Pts with sSS with versus without double positivity for ACPA and SSA had greater RA disease burden at baseline and 12-month follow-up. Further analysis with a larger sample size is warranted.

Table 1. Baseline Characteristics of Pts With sSS With and Without ACPA and SSA Positivity

	Double+ pts with sSS		Pts with sSS without double positivity*		p value
	N	Mean (SD)	N	Mean (SD)	
Age, years	80	54.6 (13.9)	86	55.1 (13.5)	0.683
Age at RA diagnosis, years	80	41.3 (14.3)	85	48.7 (13.5)	0.001
RA symptoms duration, years	80	15.3 (12.8)	85	10.0 (10.5)	0.001
Female, n (%)	80	74 (92.5)	86	79 (91.9)	0.878
BMI	71	27.5 (7.6)	69	27.6 (5.9)	0.388
RADAI	72	4.0 (2.4)	80	4.0 (2.1)	0.896
DAS28 (CRP)	66	4.0 (1.8)	69	3.5 (1.4)	0.072
CDAI	64	25.1 (19.2)	67	17.9 (13.6)	0.065
Number of swollen joints	74	7.4 (7.5)	76	4.0 (5.3)	0.002
Number of painful joints	74	9.3 (9.3)	76	6.2 (6.5)	0.105
Total swollen painful joints	74	16.8 (15.6)	76	10.2 (10.8)	0.021
MDHAQ fatigue scale	72	47.4 (30.4)	80	53.5 (29.9)	0.252
Comorbidities, n (%)					
Vasculitis, cutaneous	80	7 (8.8)	86	0 (0.0)	0.005
Vasculitis, other	80	2 (2.5)	86	1 (1.2)	0.609
Lymphoma	80	1 (1.3)	86	0 (0.0)	0.482
Neuropathy	80	2 (2.5)	86	4 (4.7)	0.683
Lung cancer	80	0 (0.0)	86	1 (1.2)	1.000
Pulmonary fibrosis	80	1 (1.3)	86	0 (0.0)	0.483
Pulmonary nodules	80	3 (3.8)	86	1 (1.2)	0.353

Values are mean (SD) unless otherwise stated

* Includes single positive and double negative pts

ACPA=anti-citrullinated protein antibodies; double+=double positive; MDHAQ=Multidimensional Health Assessment Questionnaire; pts=patients; RADAI=Rheumatoid Arthritis Disease Activity Index; SSA=Sjögren's-syndrome-related antigen A; sSS=secondary Sjögren's Syndrome

Table 2 Change in Disease Activity Measures and Fatigue at 12 Months

	12 months		Change from baseline		p value for change from baseline
	sSS pts with ACPA and Ro positivity	sSS pts without ACPA and/or Ro positivity	sSS pts with ACPA and Ro positivity	sSS pts without ACPA and/or Ro positivity	
RADAI	3.7 (2.3)	3.6 (2.0)	-0.3 (2.0)	-0.2 (1.4)	0.427
N	64	70	64	70	
DAS28 (CRP)	3.9 (1.8)	2.8 (1.2)	-0.1 (1.6)	-0.6 (1.3)	0.149
N	47	50	47	50	
CDAI	23.0 (20.6)	12.5 (11.1)	-0.8 (19.8)	-4.2 (12.3)	0.702
N	47	45	47	45	
Swollen joint count	6.7 (8.2)	1.9 (4.1)	-1.0 (7.6)	-1.7 (4.0)	0.911
N	60	59	60	59	
Painful joint count	7.7 (8.4)	3.6 (5.7)	-1.3 (8.7)	-2.1 (6.4)	0.808
N	60	59	60	59	
Total joint count	14.4 (16.5)	5.6 (8.3)	-2.2 (15.2)	-3.7 (8.9)	0.934
N	60	59	60	59	
Fatigue scale	49.2 (27.4)	46.9 (24.9)	2.1 (24.5)	-5.6 (21.0)	0.082
N	64	69	64	69	

Value are mean (SD) N

ACPA=anti-citrullinated protein antibodies; pts=patients; RADAI=Rheumatoid Arthritis Disease Activity Index; sSS=secondary Sjögren's Syndrome

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Newer Generation Cyclic Citrullinated Peptide (CCP) 3.1 Assay in the Diagnosis of Rheumatoid Arthritis

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Background/Purpose: Rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (CCP) are important serum markers used in clinical diagnosis of rheumatoid arthritis (RA). Multiple studies have investigated previous generations of CCP assays, and several have shown CCP to be a highly specific and predictive marker for the diagnosis of RA. There are differences in sensitivity, specificity, and predictive value between the various generations of the CCP test. Previous studies of the CCP3.1 assay indicate that it may have a similar degree of specificity with a greater sensitivity than prior generations. However, these studies examined CCP levels in patients with already established RA. Our aim was to investigate the predictive value of the new CCP3.1 assay in identifying RA versus other conditions.

Methods: We performed a retrospective systematic chart review of patients with a positive CCP level (≥ 20) from July 2016 to June 2017 at Cedars-Sinai Medical Center (CSMC) ordered by physicians from all specialties for any indication. Among those with a positive CCP, we investigated the different associated underlying diagnoses present at least 6 months after testing was performed, including RA and other autoimmune and non-autoimmune diagnoses. RA diagnoses were confirmed by a rheumatologist according to the 1987/2010 ACR criteria. The data was further stratified into low (≥ 20 and < 40) and high (≥ 40) CCP levels and analyzed. Anti-CCP3.1 antibody levels were assessed using QUANTA Lite CCP 3.1 IgA/IgG ELISA (Inova Diagnostics, Inc., San Diego, CA). The tests were performed by ETI-Max 3000 analyzer with manual dilution of the specimens.

Results: Of the 2027 CCP tests performed at CSMC, 307 positive CCP tests were reported among 281 unique patients. Among 281 patients, 48% (135/281) had a final diagnosis of RA, 46.3% (130/281) had a non-RA diagnosis, and 5.7% (16/281) did not have any diagnosis. 105 patients (37.4%) had a low CCP level, and 176 (62.6%) had a high CCP level. The positive predictive value of RA in patients with a high CCP (109/176, 61.9%) was 2.5-fold higher than those with a low CCP (26/105, 24.7%). Among the 130 non-RA diagnoses, the other most common autoimmune diseases included systemic lupus erythematosus (15.4%), primary Sjogren's syndrome (8.5%) and polymyalgia rheumatica (3.8%). The most common non-autoimmune diagnoses were osteoarthritis (13.8%), interstitial lung disease (7.7%), malignancy (7.7%) and fibromyalgia (3.8%).

Conclusion: Of the 281 patients with a positive CCP, nearly half were found to have a diagnosis other than RA. There seems to be a higher likelihood of RA with higher CCP levels. Overall, there were similar rates of autoimmune and non-immune mediated diseases between low and high CCP levels. Interestingly, certain autoimmune conditions, such as lupus, Sjogren's and psoriatic arthritis were more likely to have a low CCP titer than a high one. Further research needs to be conducted to investigate the utility of this CCP3.1 assay.

Disclosure:

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Abstract Number: 1465

Absolute Number of Regulatory T Cells Decreased While Osteopontin Increased in Peripheral Blood of New Onset Patients with Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is a progressive immune-mediated disease involving the synovitis that can culminate in joint destruction and early mortality. IL-17-producing T (Th17) cells and regulatory T (Treg) cells have been showed to play critical roles in the pathogenesis of RA. Osteopontin (OPN) is a matricellular protein that mediates diverse biological functions. OPN mediates cell migration, adhesion, and survival in many cell types. OPN also functions as a Th1 cytokine, promotes cell-mediated immune responses, and plays a role in chronic inflammatory and autoimmune diseases. Recently, studies revealed that OPN produced in RA SF was responsible for markedly increased Th17 and Both Treg-intrinsic and Treg-extrinsic factors maintaining Bcl6 are important for controlling Treg cell stability. Recently, our studies have found that absolute number of CD4⁺CD25⁺Foxp3⁺ regulatory T cells (CD4⁺Tregs) was significantly decreased in peripheral blood from patients with RA as compared to that from normal controls. The purpose is to investigate the absolute number of Th17, CD4⁺CD25⁺Foxp3⁺Treg cells as well as OPN content in peripheral blood of patients with RA and the correlation between OPN content with Th17 and Treg cells, to find a possible pathogenesis related to RA and new therapy for the RA treatment.

Methods: A total 67 of new-onset diagnosed patients with RA fulfilled the 2010 ACR/EULAR Classification Criteria of Rheumatoid Arthritis were enrolled and 93 healthy donors were used as control. The absolute number of peripheral CD4⁺Tregs cell was detected by multicolor flow cytometry. ELISA was used to detect OPN. Meanwhile, Test parameters were anti-cyclic citrullinated peptide antibody (Anti-CCP), erythrocyte sedimentation rate (ESR), C reactive protein (CRP), rheumatoid factor (RF). At the same time, the DAS28 score of RA group was calculated.

Results: The levels of OPN in RA patients were increased significantly [(14.84±8.64) vs (10.59±3.40), P<0.001] and significantly positively correlated to ESR, DAS28 score, and RF (r=0.284, P=0.02; r=0.290, P=0.039; r=0.376, P=0.007). The absolute number of Treg cells was significantly decreased in RA patients as compared with the controls [(23.63±2.80) vs (33.67±26.83) ng/μl, P<0.001]. However, the absolute number of Treg cells was negatively to OPN levels, and the difference was statistically significant (r=-0.459, P=0.000). The absolute number of Th17 cells tends to reduce and there was no statistical significance [(7.64±6.44) vs (6.64±4.26) ng/μl, P=0.0129]. There is no significant correlation between OPN and Th17 (r=0.006, P=0.963).

Conclusion: The levels of OPN in peripheral blood plasma in RA were significantly higher than in healthy group, OPN was positively correlated with the laboratory parameters of disease activity. There was a negative correlation between Treg cells and OPN in RA group, which suggested that the reduction of Treg cell levels may be associated with OPN concentration. The correlation of decreased CD4⁺Tregs and OPN may be involved in the pathogenesis of RA. Whether OPN lays a role in the reduction of Treg cells need to study further

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Abstract Number: 1466

Altered Count of NK Cells and Non-Classical Monocyte Subpopulation in the Pre-Clinical Phase of Rheumatoid Arthritis

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Background/Purpose: Anti-citrullinated protein antibodies (ACPA) are detectable long before the manifestation of rheumatoid arthritis (RA). EULAR provided a clinical definition of individuals with arthralgia suspicious for progression

to RA (clinically suspect arthralgia, CSA). The alteration of monocyte subpopulations in patients with established RA has been described. We aimed to evaluate possible predictive value of the monocyte and lymphocyte subpopulations in individuals in the preclinical phase of RA.

Methods: Thirty-four individuals with arthralgia (mean age 45.11 ± 12.6 years; 91% females) and 80 age and gender matched healthy controls (HC) were included. Leukocytes from peripheral blood were analysed by flow cytometry. Lymphocyte subpopulations were defined as CD19+CD3-, CD3+CD4+, CD3+CD8+ and CD16/56+CD3- (NK) cells, monocytes were segregated into classical (CD14+CD16-), intermediate (CD14+CD16+/++) and non-classical (CD14-/dimCD16++) subsets. Data were analysed using t-test and Spearman's correlation and are expressed as median and interquartile range (IQR).

Results: Out of 34 patients with arthralgia, 27 were ACPA+ and 17 met CSA definition (10 of them were ACPA+), with symptoms duration 36 months (IQR: 77.5), CRP 2.27 mg/L (IQR 3.35), DAS28 2.13 (IQR 1.32). As per definition, there was no clinical synovitis at baseline. Five individuals developed RA within 3-9 months of follow up. Patients with arthralgia had higher %CD3+ ($p=0.002$) and %CD3+CD8+ ($p=0.034$) T cells and lower %NK ($p=0.003$) and absolute count of NK cells ($p=0.002$) compared to HC. This was confirmed in a subgroup of ACPA+ patients. The count of tender joints correlated positively with %CD3 ($p=0.009$; $r=0.491$) and %CD3CD8 ($p=0.034$; $r=0.410$) T cells and negatively with %NK cells ($p=0.019$; $r=0.045$). Moreover, individuals who developed RA during follow up, had higher baseline %CD3+ cells ($p=0.046$) with the trend for lower %NK cells ($p=0.065$). No differences were seen between patients meeting CSA definition and non-CSA individuals. Expansion of intermediate ($p=0.012$) and non-classical ($p=0.007$) monocytes with reduction of classical monocytes ($p=0.001$) were demonstrated in all patients with arthralgia compared to HC. Importantly, ACPA+ patients had higher non-classical ($p=0.041$) and lower classical monocytes ($p=0.022$) than ACPA- patients. Similarly, ACPA+ patients had higher intermediate ($p=0.006$) or non-classical ($p=0.012$) and lower classical ($p=0.004$) monocytes compared to HC, while no differences were seen between ACPA- patients and HC.

Conclusion: We demonstrate lower NK cells, expansion of intermediate and non-classical monocyte subpopulation in patients in the preclinical phase of RA, especially in ACPA+ individuals. Since this pattern has been described so far in patients with established RA, our data suggest their role even in early phases of RA development. These leukocyte subpopulations could be considered as prognostic biomarkers for further development of RA.

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Rheumatoid Arthritis Activity Monitoring and Multiplex Biomarker Verification By Tageted Proteomics

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Background/Purpose: Rheumatoid arthritis (RA) is a long-lasting inflammatory autoimmune disorder that ultimately leads to the destruction of joint architecture. The activity of this disease is measured by the assessment of clinical symptoms. The aim of this study was to apply a proteomic strategy to find plasma biomarkers able to discriminate patients with different RA activities.

Methods: 80 plasma samples from the IMID (Immune-Mediated Inflammatory Diseases) Consortium, classified according to the DAS28 score into low (40 samples with DAS28: 2,6-3,2) and high (40 samples with DAS28>5,1) activity were randomly selected to be analyzed by mass spectrometry (MS). This study was conducted in two stages: a panel of proteins were firstly selected based on the regulation of the RA activity in an initial discovery phase, followed by the verification and absolute quantitation of this set of proteins on the 80 independent RA samples, using targeted MS.

A shotgun MS strategy was performed in the discovery phase. For this aim, four independent pools of each condition were firstly albumin-depleted, digested and differentially labelled with iTraQ 8-plex reagents. Subsequently, the 8 labelled pools were combined, cleaned using StageTips-C18, fractionated by HPLC and analyzed by nanoLC-MS/MS using three different MS equipments. Afterwards, the verification phase was performed by a targeted Multiple Reaction Monitoring (MRM) strategy on a QTRAP 5500 on the 80 independent samples, using 26 synthetic heavy-labelled peptides as internal standards for absolute protein quantitation. The results were analyzed using the proteomic software Skyline and statistical tools from SPSS and PRISM.

Results: In the discovery stage, 186 proteins were identified by shotgun MS. The abundance of 11 of these proteins was found to be significantly different ($p<0.05$) between patients with high and low RA activities. To verify these results, a method for the absolute quantitation of this 11-protein panel, based on targeted MS and the use of labelled internal standards, was developed and applied on the 80 RA plasma samples. The data obtained in this verification step showed a significant increase in four of these proteins, in accordance with that observed in the discovery phase: Haptoglobin, Serum Amyloid A1, Alpha-1-antichymotrypsin and Alpha-1-acid Glycoprotein 1. The increased abundance of these four proteins in plasma was significantly associated ($p<0.05$) with a high disease activity in RA patients. These proteins are related with the RA process and its effects (inflammation and immune disorder in joints), giving significance to the results obtained. This protein panel is being validated in a larger cohort of samples of similar characteristics (including healthy and disease controls) to qualify them for clinical applications.

Conclusion: A two-step proteomic approach (including both discovery and verification phases) has been followed for the identification of protein biomarkers associated with disease activity in RA patients. A panel of four proteins has been verified as increased in the plasma of patients with high activity, and could be useful for the molecular monitoring of the disease.

Disclosure: L. González-Rodríguez, None; V. Calamia, None; P. Fernández, None; C. Ruiz-Romero, None; A. Julià, None; A. Fernández-Nebro, None; J. Tornero, None; S. Marsal, None; F. J. Blanco, None.

Abstract Number: 1468

Minor Salivary Gland Biopsy: Its Importance in Rheumatoid Arthritis and Secondary Sjögren's Syndrome

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

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Session Time: 9:00 AM-11:00 AM

Background/Purpose: Secondary Sjögren's Syndrome (sSS) is a common extraarticular manifestation in patients with Rheumatoid Arthritis (RA). According to the 2002 European American criteria (EA 2002) classification for Sjögren's Syndrome (SS), the secondary term is used for all cases present concomitantly with another connective tissue disease. There is little evidence regarding the difference between patients with SS associated with RA with minor salivary gland biopsy with and without focal lymphocytic sialadenitis (FLS).

Objective: Determine whether FLS is associated with clinical and serological differences in a group of patients diagnosed with RA and sSS.

Methods: Patients with RA diagnosis were included according to ACR 1987 and / or ACR-EULAR 2010 criteria, and who also met criteria EA 2002 for sSS. Ocular tests, sialometry and minor salivary gland biopsy were performed. Clinical, serological and treatment characteristics were compared between patients with positive FLS and negative FLS. For continuous variables, t-test or Mann Whitney test was used, and for the categorical variables Chi square or Fisher's exact

test was used. A multivariate logistic regression analysis was performed taking the presence of FLS as a dependent variable.

Results: We included 88 patients with SS associated with RA. 92% were women, with a mean age of 53 years (SD \pm 11.3) and 12.5 years of RA evolution (IQR 6-17). 63.6% had FLS vs. 36.4% that did not. In the univariate analysis, patients who presented FLS had higher current HAQ (1.12 IQR 0.5-1.62 vs 0.55 IQR 0.06-1.37, p 0.04); parotid swelling frequency (23% vs 0%, p 0.003); interstitial lung disease (25% vs 6.25%, p 0.04); autoimmune liver disease (14.3% vs 0%, p 0.047); hypergammaglobulinemia (51.8% vs 3%, p <0.001); anemia (35.7% vs 15.6%, p 0.04); hypocomplementemia (51.9% vs 16%, p 0.001); double seropositivity for RF and ACPA (87.5% vs. 68.7%, p 0.03); Positive ANA (94.6% vs 71.8%, p 0.007) and extra-joint and extraglandular manifestations (66% vs 21.9%, p <0.001). No differences were found regarding the positivity of RO and / or LA, in the positivity of ACPA (92.8% vs 81.3%), nor in treatments and total number of immunosuppressants received. The variables that were found to be independently associated with the presence of FLS were the presence of extra-joint and extraglandular manifestations (OR 5.67 CI95% 1.6-20), positive ANA (OR 11.7 CI95% 1.6-83) and hypergammaglobulinemia (OR 21 CI95% 2.46-179).

Conclusion: Patients with RA and sSS who have FLS in the minor salivary gland present greater frequency of extra-articular and extraglandular manifestations, as well as serological differences with respect to patients without FLS.

Disclosure: M. F. Rodriguez, None; C. Troitino, None; E. Guerra, None; F. Melo, None; A. Secco, None; N. Tamborenea, None; M. V. Martire, None; M. Mamani, None.

Abstract Number: 1469

Measurement of Anti-Amyloid β Autoantibodies in Patients with Rheumatoid Arthritis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

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Background/Purpose: Amyloid β (A β) accumulation in the brain is a risk factor for Alzheimer's disease (AD). The incidence of AD increases with age. Rheumatoid arthritis (RA) patients have been reported to be at a lower risk of AD, and the non-steroidal anti-inflammatory drugs (NSAIDs) used to treat RA have also been shown to have an effect against AD. In this study, we measured the concentration of anti-A β autoantibodies (anti-A β AAB) in the serum of treatment-naive RA patients who had not previously undergone drug therapy.

Methods: The study subjects were 174 patients with no treatment history, who presented for initial outpatient examination, complaining of joint pain between the years 2010 and 2014. They comprised of 106 patients (mean age 55.5 ± 17.2 years) diagnosed with RA based on the 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis, and 68 (mean age: 59.1 ± 12.8 years) with unclassified arthritis (UA) who were not classifiable as having RA. Serum was collected at initial examination and stored frozen at -80°C , with all samples measured at the same time. Anti-A β AAB was measured by an ELISA assay developed in our department. We investigated the association among anti-A β AAB titers, age, and laboratory test results (C-reactive protein, rheumatic factor, anti-CCP antibodies [CCP], IgG, IgA, and IgM). Similar measurements were also made in 50 healthy individuals (mean age: 54.6 ± 14.3 years) as control.

Results: Anti-A β AAB titer values were 17.0 ± 2.3 units in the RA group, 11.2 ± 0.95 units in the UA group, and 8.3 ± 0.87 units in the control group, being significantly higher in the RA group than in the UA ($p < 0.02$) or control ($p < 0.002$) group. An investigation of the association between anti-A β AAB titer and laboratory test results identified a weak positive correlation with age in the control and UA groups ($r = 0.240$, $r = 0.234$), and a negative correlation with age in the RA group ($r = -0.418$). An investigation of the association between anti-A β AAB titer and CCP classified RA patients into the following three groups: in half ($n = 57$) both anti-A β AAB titer and CCP were low (anti-A β AAB < 20 units, CCP < 200 IU/ml), in one quarter ($n = 25$) anti-A β AAB titer was high and CCP was low, and in the other quarter ($n = 24$) anti-A β AAB titer was low and CCP was high.

Conclusion: The anti-A β AAB titer was significantly higher in treatment-naïve RA patients. In the RA group, the anti-A β AAB titer negatively correlated with age. RA patients with high anti-A β AAB titer tended to have low levels of CCP, and those with high CCP tended to have low levels of anti-A β AAB. Studies involving larger numbers of patients to investigate changes in anti-A β AAB titer during treatment are required, but our results suggest that CCP levels may be implicated in the relationship between RA and AD.

Disclosure: M. Sato, None; M. Takemura, None; T. Tani, None; T. Ohashi, None.

Abstract Number: 1470

Russell Bodies and Serological Status in Rheumatoid Arthritis

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Session Information

Session Date: Monday, October 22, 2018

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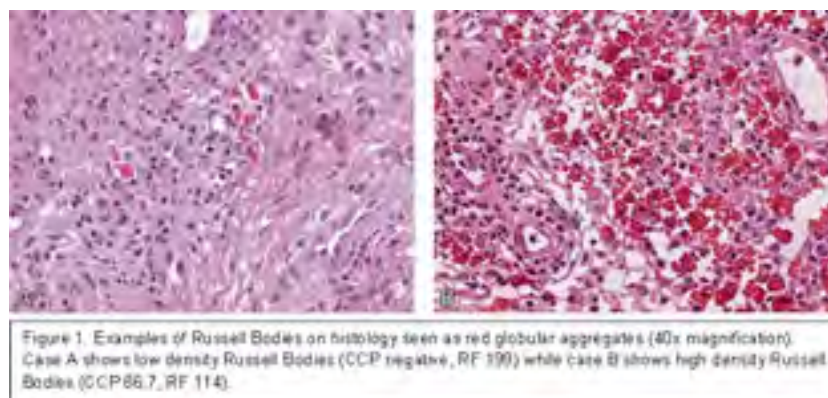
Session Time: 9:00 AM-11:00 AM

RussellBodies and Serological Status in Rheumatoid Arthritis

Background/Purpose: Russell bodies (RBs) are globular aggregates of immunoglobulin produced by plasma cells and identified both within the plasma cells (PCs) and free in inflamed tissues. ¹It has been suggested that RBs form when antibody production surpasses protein transportation mechanisms in the cell, possibly indicating heightened production of the antibodies. Rheumatoid factor (RF) and anti-cyclicitrullinated peptide (aCCP) are antibodies commonly identified in serum of patients with rheumatoid arthritis (RA). In some patients with RA undergoing arthroplasty, synovial tissue is highly inflamed and the histologic features include the presence of plasma cells with and without RBs. The molecular features and clinical significance of RBs are unknown. Here we test the hypothesis that RBs associate with the degree of positive serology in RA.

Methods: Tissue samples from 191 RA patients undergoing total hip, knee, shoulder, or elbow arthroplasty were scored for the proportion of PCs, the presence of binucleate plasma cells (bnPC), and RBs. Serological test results for RF and aCCP were collected. Logistic regression was used to calculate an odds ratio for positive serological results with the presence of RBs seen histologically. The concordance of bnPCs and RBs was evaluated.

Results: Of the 191 RA patients, 170 (89%) cases had suitable synovium for histologic characterization. Of the 170 synovial samples assessed, 37 (22%) contained RBs. Demographics (age, sex, joint replaced) of RB positive cases were similar to RB negative cases. Clinical measures (tender and swollen joint counts, patient global, and MD global) were similar between groups. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were significantly elevated in the RB-positive cohort ($p < 0.001$). Significantly more RB-negative patients were in DAS28-ESR remission ($p = 0.024$). RF and a CCP status were both significantly different between groups ($p < 0.001$ and $p = 0.024$, respectively) as well as the proportion of patients with both RF and aCCP positive results ($p < 0.001$). The unadjusted odds ratio of having a positive serological test (RF or CCP) when RBs are found on histology is 3.94 (1.13-13.72, $p = 0.031$). There was good concordance between bnPCs and RBs (kappa coefficient [95% CI], 0.62 [0.48 - 0.75]).



Conclusion: The presence of RBs in synovial histology is not specifically incorporated into most synovial pathology scoring schemes. This study suggests that the presence of RBs is a significant histological finding that parallels serological status in RA, perhaps in patients with undiagnosed or untreated disease. Additionally, the association of RBs and bnPC may suggest a mechanistic connection that stands to be further explored.

References: 1. Blom J, Mansa B, Wiik A. Acta Pathologica Microbiologica Scandinavica. 1976 84A: 335-349.

Disclosure: M. A. McNamara, None; S. M. Goodman, Roche, Novartis, 4; L. T. Donlin, None; D. Orange, None; S. Z. Mirza, None; J. Szymonifka, None; M. P. Figgie, None; V. P. Bykerk, None; E. F. DiCarlo, None.

Abstract Number: 1471

ECV304 Cells Self-Citrullinate Proteins Targeted By Anti-Citrullinated Protein/Peptide Autoantibodies from Rheumatoid Arthritis Patients

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Background/Purpose: Anti-citrullinated protein/peptide autoantibodies (ACPAs) define a major subset of rheumatoid arthritis (RA) patients. Cyclic citrullinated peptides (CCP) are commonly used as the antigen for assessing ACPAs. However, these synthetic peptides may not represent the citrullinated proteins found *in vivo*. We have utilized ECV304, a human cell line containing high protein arginine deiminase (PAD) levels, to generate a naturally derived citrullinome. Next, we assessed by proteomics the ECV304 antigens recognized by antibodies present in RA sera. Finally, we compared the performance of an *in house* ECV304-based ELISA with that of a commercial anti-CCP2-ELISA for RA diagnosis.

Methods: Citrullination was assessed in ECV 304 and other human cell lines (n=7) by Western blot and the amount of citrulline generated was quantified by a colorimetric assay. PAD isotypes present in ECV304 were determined by PCR. ECV304 citrullinated proteins/peptides were immunoprecipitated by autoantibodies present in RA sera, and characterized by mass spectrometry. The ECV304-based ELISA contained a citrullinated ECV304 cell extract and myelin basic protein (MBP, an arginine-rich potential citrullinated -epitope carrier). The performance of this assay was tested in sera from 1) 74 patients with a clinical diagnosis of RA (55 CCP positive, 50 rheumatoid factor [RF] positive; 8 CCP and RF negative), 2) 51 patients with non-RA rheumatic diseases (non-RA controls), and 3) 25 healthy controls.

Results: Among 7 human cell lines tested, ECV304 was the only one that abundantly citrullinated self-proteins and exogenous MBP. ECV304 expressed PAD2 and PAD3 iso-enzymes, and the ECV304 citrullinated proteins/peptides were detected by autoantibodies present in RA sera. Proteomic analysis confirmed the presence of known citrullinated RA antigens (i.e., calreticulin, profilin 1 and vinculin), as well as novel targets such as: 14-3-3 protein beta/alpha, 14-3-3 protein zeta/delta, mitochondrial peroxiredoxin-5, and transketolase in the ECV304 extracts. The net binding to ECV304 citrullinated proteins (compared to non-citrullinated proteins) was the ELISA readout, and the cut-off of the test was defined to optimize specificity. The sensitivity, specificity, positive and negative predictive values of the ECV304-based ELISA were 39%, 98%, 97% and 63%, respectively.

Conclusion: The human cell line ECV304 possesses all the molecular machinery to citrullinate self-proteins that are recognized by ACPA-positive RA sera. Due to its high specificity, and low cost, the ECV304-based ELISA could represent an alternative to ACPA tests for the diagnosis of RA in resource-limited settings.

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Preliminary Analysis of Genetic Variants in the Immune System Related to the Body Mass Index in Early Arthritis Patients

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Background/Purpose: We have observed in previous analyzes in our early arthritis (EA) cohort that patients with a higher body mass index (BMI) are, more frequently, ACPA negative and these patients carry, with a lower frequency, HLA-DRB1 alleles that encode for the shared epitope. The **objective** of this study is identifying SNPs (Single Nucleotide Polymorphisms) of immune system genes related to BMI in EA patients.

Methods: The 257 patients of the PEARL (Princess Early Arthritis Register Longitudinal) cohort in whom high density genotyping was available (using the ImmunoChip array of Illumina Inc) were included. As a previous step, those SNPs that did not meet the requirements of a genotyping call rate lower than 98%, being out of Hardy-Weinberg equilibrium ($p < 10^{-4}$) and minor allele frequency lower than 1% were excluded. IMPUTE v.2 was used for the genotype imputation of the SNPs that failed in the immunoChip, using as reference the data of phase III of the 1000G project. The association analysis of the remaining SNPs was made by linear regression adjusted by sex, age and study level with PLINK v1.9. Of the 1384 SNPs associated with BMI with a value of $p < 0.01$, 250 SNPs were selected according to the lowest values of the division of p divided by the absolute value of its β coefficient. After analyzing and excluding the SNPs that were in linkage disequilibrium, the importance of the 186 resulting SNPs was quantified with the “Random Forest” and “Boosted Regression Tree” techniques using %IncMSE (Mean Decrease Accuracy).

Results: Table 1 shows the selection of the 15 SNPs that were more important in both “machine learning” techniques according to BMI. Although most of these SNPs are located in non-coding regions (intergenic or intronic), some of the genes where the SNPs belong or the neighboring genes have shown association in some GWAS (Genome-Wide Association) with a minor (BMP7) or a greater (RSPO3) BMI; and some of them have shown to have a regulatory role in the immune system in patients with RA (WDFY4, BMP7).

Table 1. SNPs related to BMI in our early arthritis registry.

SNP	Gene	β Coef. [CI 95%]	p
rs2746187	LOC728666 / RSPO3	2.018 [0.949,3.087]	2.646x10 ⁻⁴
rs8103026	SIGLEC6 / ZNF175	-2.135 [-3.09,-1.18]	1.724x10 ⁻⁵
rs2419678	LOC100132349	-2.001 [-2.826,-1.175]	6.623x10 ⁻⁶
rs17842463	SULT2B1	-3.515 [-5.446,-1.585]	3.402x10 ⁻³
rs1131878	UGT2B4	1.337 [0.542,2.131]	1.114x10 ⁻³
rs12757445	CDC73 / KCNT2	1.804 [0.737,2.871]	1.057x10 ⁻³
rs1638020	PTPRN2	-1.329 [-2.1,-0.558]	8.409x10 ⁻⁴
rs11019575	MULTIPLE GENES: 399942, 100131364	3.356 [1.309,4.307]	2.939x10 ⁻⁴
rs72917213	MEX3C / LOC729051	2.319 [1.172,3.466]	9.677x10 ⁻⁵
rs6014959	BMP7	-1.942 [-3.122,-0.762]	1.434x10 ⁻³
rs2870662	DOK5 / CBLN4	1.455 [0.615,2.295]	7.993x10 ⁻⁴
rs10776644	WDFY4	-2.159 [-3.49,-0.828]	1.661x10 ⁻³
rs7800039	STEAP4 / ZNF804B	1.564 [0.76,2.368]	1.725x10 ⁻⁴
rs12517451	ANKRD34B / DHFR	1.629 [0.695,2.562]	7.351x10 ⁻⁴
rs12722531	IL2RA	-3.544 [-5.713,-1.376]	1.535x10 ⁻³

Conclusion: Our preliminary approach allowed us to select 15 SNPs that may have more relevance related to BMI in patients with early arthritis. However, this is a preliminary study and it is necessary to validate these results in other populations to ensure their involvement in the relationship between the BMI and EA.

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Abstract Number: 1473

Performance of the Meso Scale Multiplex Platform in the Assessment of Serum Cytokines / Chemokines in Rheumatoid Arthritis

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Background/Purpose: Cytokines and chemokines (CK) are central to RA pathogenesis, a fact underscored by the emergence of multiplex immunoassays for quantifying CK values in both research and clinical endeavors. Intrinsic factors to RA, namely rheumatoid factor (RF), may interfere with assay outcomes by non specifically binding detection analytes. Thus, we evaluated the performance of a commercially available multiplex platform using banked serum samples and assessed the impact of RF depletion on these measurements.

Methods: Forty-five CK analytes were tested in a central laboratory using the Meso Scale Discovery V-PLEXTM immunoassays and serum from 40 RA and 40 OA patients. True serum duplicates were tested for 20 RA and OA samples, while 20 additional samples from seropositive RA patients were depleted of RF using a commercial binder and compared to duplicates spiked with equal volumes of saline. Intra-assay coefficients of variation (CV) and intraclass correlation coefficients (ICC) were calculated for each analyte measured using true duplicates. The percent change in analyte concentrations were determined. Finally, rank sum tests were used to compare CK concentrations between RA and OA. Analytes were determined to be “high performers” if the CV was <10% and there was <15% change following RF depletion. Conversely, “low performers” were defined as those with a CV >20% or if RF depletion altered values >30%.

Results: CVs and ICCs generated using true serum duplicates for the 45 analytes tested are shown in Table 1. Of the 45 analytes, 22 yielded CVs <10%; all but two were “high performers”. ICCs universally exceeded 0.85 with the exception of 7 analytes (6 were “low performers”). RF depletion altered CK values by <15% for 35 analytes with larger changes (>30%) seen only for IL-2 and TNF- α (Figure1). IL6,IL8, IL10, TNF α , and TNF β concentrations were increased in RA vs. OA (p<0.05); IL16 was decreased(p<0.05).

Conclusion: In this study, a commercially available multiplex assay performed well in the context of RA. For most analytes, results were highly reproducible with minimal interference from RF. Additional testing will be needed to identify the source of variability observed for the analytes with higher CVs.

Table 1. Intra-assay coefficient of variation (CV) using true serum duplicates

CV <10%		CV 10-20%	CV >20%
Eotaxin (0.98)	IL-27 (0.95)	GM-CSF (0.96)	Eotaxin-3 (0.98)
IL-12-23p40 (0.99)	IL-6 (1.00)	IFN- γ (0.99)	IL-17A-cyto (0.85)
IL-12-p70 (0.99)	IL-7 (0.97)	IL-10 (0.99)	IL-17A-F (0.47)
IL-13 (1.00)	IL-8-chem (0.99)	IL-17D (0.68)	IL-17B (0.60)
IL-15 (0.93)	IL-8-pro (1.00)	IL-2 (0.91)	IL-17C (0.71)
IL-16 (0.96)	MCP-1 (0.97)	IL-22 (0.96)	IL-1 α (0.90)
IL-17A-TH17 (0.98)	MCP-4 (0.95)	IL-5 (0.96)	IL-3 (0.17)
IL-1RA (0.98)	MDC (0.89)	IP-10 (0.92)	IL-31 (0.96)
IL-1 β (1.00)	MIP-1 α (1.00)	MIP-3 α (0.98)	IL-4 (0.99)
IL-21 (0.88)	MIP-1 β (1.00)	TARC (0.96)	IL-9 (0.43)
IL-23 (0.97)	VEGF (0.98)	TNF- α (1.00)	TNF- β (0.95)
			TSLP (0.49)

* Intraclass correlation coefficient (ICC) shown in parentheses

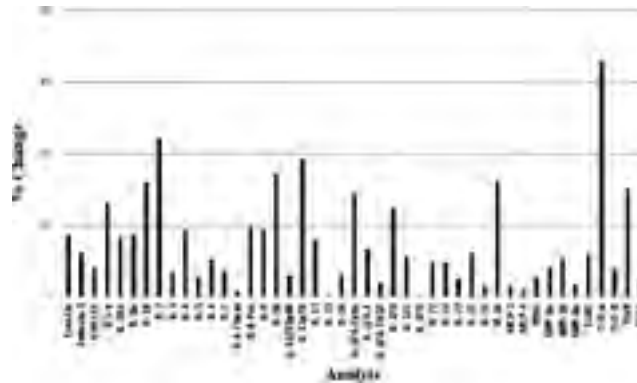


Figure1. Mean percent change in cytokine/chemokine analyte concentration following RF depletion.

*35 of 45 analytes exhibited <15% change; 8 analytes showed intermediate changes (15-30%) and two (IL-2 and TNF- α) demonstrated >30% change.

Disclosure: P. M. Maloley, None; B. R. England, None; H. Sayles, None; G. M. Thiele, None; M. J. Duryee, None; J. Payne, None; T. R. Mikuls, BMS, Ironwood, Horizon, 2, Pfizer, Inc., 5.

Abstract Number: 1474

Circulating Transfer RNA-Derived Small RNAs Are Altered in Patients with Rheumatoid Arthritis

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Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Small RNAs (sRNAs) are important gene regulators and markers of disease. Transfer RNA (tRNA)-derived sRNAs (tDRs), including tRNA fragments (tRFs) and halves (tRHs), are novel regulatory sRNAs, which are often upregulated in the setting of cellular stress to downregulate metabolic processes. Rheumatoid arthritis (RA), a common autoimmune disease, is associated with excessive cellular stress due to immune activation. We hypothesized that circulating tDRs are altered in patients with RA and serve as novel markers for RA and RA disease activity.

Methods: Plasma sRNA sequencing was performed on archived samples from 167 RA patients, and 91 matched controls using Illumina NextSeq500. tDRs were quantified by TIGER pipeline, permitting one mismatch. Total tDRs, individual tDRs and tDRs based on amino acid of the parent tRNA normalized to total reads were compared between RA and control subjects by DESeq2 with adjustment for age, race, sex, and batch with 5% false discovery rate and multiple test correction.

Results: RA patients had 1.16-fold higher proportion of plasma tDRs compared to controls ($P=0.04$). Among RA patients a higher proportion of total plasma tDR reads was associated with higher disease activity by DAS28 score ($\rho=0.17$, $p=0.03$), erythrocyte sedimentation rate ($\rho=0.21$, $p=0.007$) and swollen joint count ($\rho=0.18$, $p=0.02$). Several individual tDR sequences were increased (3.7-fold to 1.5-fold), while one individual tDR sequence was decreased 2.2-fold among RA patients. tDRs aligning to a suppressor tRNA were increased 1.7-fold, while tDRs aligning to tRNAs encoding for asparagine, isoleucine, and aspartic acid were decreased (1.8-fold to 1.5-fold) among RA patients.

Conclusion: RA patients have a greater proportion of plasma tDRs compared to controls, and total tDRs were correlated with disease activity. Several individual tDRs and tDRs aligning to a suppressor tRNA and several other amino acid encoding tRNAs were altered in RA patients. Circulating tDRs may be novel markers of RA diagnosis and disease activity.

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Eicosanoid Mediators of Systemic Inflammation and Arthritis in the Elderly

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Elderly-onset RA, EORA, which is defined as rheumatoid arthritis (RA) starting at >60 years of age, has received less attention than young-onset RA. Polymyalgia rheumatica (PMR) is also a common rheumatic disease in the elderly. Eicosanoids are biological lipids that serve as specific role as either activators or suppressors of systemic inflammation and have been involved in the development and progression of arthritis. We hypothesized that eicosanoid-related perturbations are related to arthritic symptoms in the elderly, and by defining the eicosanoid profile we might be able to define elements of inflammation pathobiology in this population.

Methods: ARTIEL (Arthritis in the Elderly) is a recent collection cohort with newly diagnosed arthritis in patients older than 60 years, with blood samples collected at baseline (pre-treatment), 1, 3 and 12 months after treatment, along with physician and patient outcome measures through 12 months. They are compared with randomly control individuals of the same age and gender. A thorough clinical examination was conducted. Patients completed a health assessment questionnaire (HAQ). Disease activity score (DAS)28CRP was calculated. Serum eicosanoids were determined by mass spectrometry at baseline and after 3 months of treatment and were classified in groups according to their eicosanoid precursor: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) or arachidonic acid (AA). Data processing and statistical analysis were performed in R.

Results: 64 patients (average: 75.15, standard deviation (SD) 6.80) and 18 controls (average: 75.39, SD, 6.04) were analyzed. Of these, 44 were diagnosed with RA and 20 with PMR. At the start of the study, patients had a mean DAS28CRP of 5.72 (SD, 1.05), mean HAQ was 1.64 (SD, 0.73). In addition, 84% of the patients reported scapular pain,

Precursor	Eicosanoid	Control	0 Months	3 months
Eicosapentaenoic Acid	5-HEPE	1338.75(842.38)	960.30(646.58)*	1287.1(888.6)#
	8-HEPE	67.73(40.30)	42.72(29.37)*	69.9(44.8)#
	9-HEPE	99.21(55.52)	64.00(43.33)*	97.3(64.8)#
	11-HEPE	153.42(86.10)	100.81(70.87)*	124.6(79.4)
	12-HEPE	102.95(59.24)	68.14(46.83)*	97.2(66.0)#
	15-HEPE	149.39(97.00)	79.22(55.92)*	105.3(69.1)#
	18-HEPE	110.94(68.45)	66.81(43.57)*	133.2(85.5)#
	4-HDoHE	3105.71(1116.79)	2562.86(1163.34)	3522.9(1172.2)#
Docosahexaenoic Acid	10-HDoHE	105.75 (36.73)	87.54(44.82)	110.9(36.4)#
	11-HDoHE	115.79(37.59)	98.19(50.91)	155.2(52.6)*#
	13-HdoHE	237.11(76.44)	209.50(120.22)	192.4(70.6)*
	16-HdoHE	326.52(92.95)	272.28(132.71)	264.7(89.4)*
	17-HdoHE	373.60(113.81)	287.66(135.44)*	358.0(115.6)#
	20-HdoHE	223.33(81.24)	175.25(77.91)*	205.7(70.1)
	19,20-diHDPA	1.91(0.85)	1.82(0.89)	2.4(0.9)#
	Arachidonic Acid	326.20(81.90)	299.31(126.19)	600.7(188.2)*#
Arachidonic Acid	15-HETE	658.18(149.85)	553.94(213.11)	656.5(209.6)#
	tetranor 12-HETE	2.21(1.42)	2.91(1.96)	2.2(1.5)#
	12-HETE	486.57(125.10)	505.32(208.71)	645.7(255.1)*#
	HXB3	45.10(19.98)	37.29(21.17)	83.4(27.2)*#
	12-oxoETE	16.34(8.22)	18.84(9.92)	33.7(16.5)*#
	5-HETE	9496.31(2185.48)	8380.60(2231.88)	12814.0(2604.3)*#
* = significant when compared to control				
# = significant when compared to 0 months				

and 56% of the patients reported pelvic pain at baseline. After three months of treatment, patients had a DAS28CRP of 2.38 (SD, 1.23), and a HAQ of 0.36 (SD, 0.41). As shown in table 1, several eicosanoids, especially anti-inflammatory species derived from EPA and DHA were significantly downregulated in patients at the start of the study as compared to normal controls. Moreover, similar anti-inflammatory species were even further downregulated in patients with DAS >5.1 compared to patients with DAS <5.1. Three months after treatment, the levels of anti-inflammatory species derived from EPA and DHA went back to normal in responders (DAS28CRP <3.2). However, new proinflammatory species from AA were significantly elevated in non-responder patients (table 1).

Conclusion: These results suggest that certain eicosanoids may be key effectors in arthritis in the elderly and that the disbalance between pro and anti-inflammatory eicosanoids before and after treatment might be related to clinical and therapeutic outcomes in this population.

Disclosure: R. Coras, None; R. Narasimhan, None; A. Kavanaugh, None; L. Mateo, None; O. Quehenberger, None; M. Martinez-Morillo, None; M. Guma, None.

Abstract Number: 1476

Implication of CXCL5 (Epithelial neutrophil-activating peptide 78) in the Development of Insulin Resistance in Patients with Rheumatoid Arthritis

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Background/Purpose: The chemokine molecule CXCL5 (C-X-C motif chemokine ligand 5, also known as epithelial neutrophil activating peptide 78 -ENA78-) constitutes a link between obesity, inflammation and insulin resistance (IR) in the general population. CXCL5 has also been found to play a role in rheumatoid arthritis (RA) pathogenesis. Since chronic inflammation promotes IR and impairs pancreatic beta cell function in RA patients, we assessed the role of CXCL5 in the development of IR in RA.

Methods: Cross-sectional study that encompassed 141 non-diabetic patients with RA. IR assessed by homeostatic model assessment (HOMA2), insulin and C-peptide serum levels and lipid profile, and CXCL5 serum levels were studied. Regression analysis was performed to evaluate how CXCL5 was related to IR, disease activity, and disease characteristics in RA patients.

Results: HOMA2-IR indexes showed high values for both IR and beta cell production (%B), and low insulin sensitivity (%S) in patients with RA. C reactive protein (beta coef. 0.2 [95%CI -1.5-1.9], p=0.80) and disease activity through DAS28 (beta coef. 13 [95% CI -14-41], p=0.34) revealed no relation with CXCL5. Other disease characteristics, such as disease duration, serological status, or use of methotrexate or anti-TNF alpha therapies, were not associated with CXCL5 serum levels. While glucocorticoids were related to insulin, C-peptide serum levels, and HOMA2-IR and HOMA2-%B-C peptides, the use of prednisone was not associated with CXCL5 serum levels. Insulin and C peptide serum levels and IR indexes showed strong correlations among each other, but not with CXCL5 (insulin r²=0.034, p=0.69; C peptide r²=0.050, p=0.56).

Conclusion: CXCL5 is not related to IR in RA patients. Therefore, the mechanisms leading to IR in patients with RA may be different from those in the general population.

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Serum Autoantibody Multi-Analyte Testing in Rheumatoid Arthritis Can Reduce Avoidable Costs Associated from False Positive Results. A Simulation Study in the United States of America

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Session Information

Session Date: Monday, October 22, 2018

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Serum Autoantibody Multi-Analyte Testing in Rheumatoid Arthritis Can Reduce Avoidable Costs Associated from False Positive Results. A Simulation Study in the United States of America

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Background/Purpose: Rheumatoid arthritis (RA) diagnosis requires a combination of clinical, laboratory, and imaging investigations. In clinical practice, testing for both Rheumatoid Factor (RF) and cyclic citrullinated peptides (CCP) is considered beneficial; however, when interpreting laboratory test results together, the clinician advertently decides whether test sensitivity or specificity is preferable. The individual patient characteristics with the presence of appropriate signs and symptoms help the health care practitioner assign diagnostic value to:

A) a singular “positive result or positivity to at least one test” increases overall sensitivity by minimizing the number of False Negative (FN) results at the expense of specificity, or

B) “positivity of all the tests” increases overall specificity by minimizing the number of False Positives (FPs), but overall sensitivity is lower than that of any single test.

FP results can lead to incorrectly managed individuals, who undergo further investigations, and bring about extra costs until a correct diagnosis is made.

The first aim of the present study was to evaluate the diagnostic performance of RF IgA, RF IgM and CCP, used alone or in multi-analyte combinations, in distinguishing a true positive diagnosis from a FP RA diagnosis. The secondary goal focused on the economic consequences brought about by FP serology results in the USA.

Methods: Single-/multi-analyte testing diagnostic performance was assessed in 190 established RA patients and 197 controls. A 12-month Markov model simulated 10,000 RA-suspected individuals tested with mono-/multi-analyte testing. Costs came from the published literature [1].

Results: Multi-analyte testing increased diagnostic accuracy, reduced the number of FP results, and allowed for important cost savings due to a reduction of clinical procedures and resource utilization (Table 1).

Conclusion: Simultaneous multi-analyte testing can improve the diagnostic accuracy over testing for the individual RF IgA, RF IgM and CCP tests by helping to maximize sensitivity (when disease is defined as “positivity to at least one test”) as well as maximizing specificity (if “positivity to all tests” occurs). Double- and triple-positive serology combinations minimize the number of FPs, thus reducing avoidable costs. Simultaneous multi-analyte testing demonstrates superior value from the patient and payer perspective.

N=10,000 RA-suspected individuals	Sensitivity [95% CI]	Sensitivity [95% CI]	Number of FP (80% from PC, 20% from SC)	Total Costs of FPs (\$) [1]
SINGLE ANALYTE TESTING OPTION:				
RF IgM	59.0 [51.6-66.0]	89.3 [84.2-93.3]	880	5,438,487
RF IgA	40.5 [33.5-47.9]	92.4 [87.8-95.7]	625	3,862,851
CCP	59.5 [52.1-66.5]	96.5 [92.8-98.6]	288	1,778,944
MULTI-ANALYTE TESTING OPTION:				
RF IgA+ and RF IgM+	39.5 [32.5-46.8]	95.9 [92.2-98.2]	337	2,083,906

Table . (Cont'd)

N=10,000 RA-suspected individuals	Sensitivity [95% CI]	Sensitivity [95% CI]	Number of FP (80% from PC, 20% from SC)	Total Costs of FPs (\$) [1]
RF IgM+ and CCP+	50.0 [42.7-57.3]	99.5 [97.2-100.0]	41	254,135
RF IgA+ and CCP+	36.3 [29.5-43.6]	99.5 [97.2-100.0]	41	254,135
RF IgA+ and RF IgM+ and CCP+	35.8 [29.0-43.1]	100.0 [98.1-100.0]	0	0

Disclosure: B. Mascialino, Thermo Fisher Scientific, 3; S. Swiniarski, Thermo Fisher Scientific, Phadia GmbH, 3; I. Gehring, Thermo Fisher Scientific, 3; M. Poorafshar, Thermo Fisher Scientific, 3; T. Tarrant, Thermo Fisher Scientific, 5.

Abstract Number: 1478

Factors Associated with Disability and Health-Related Quality of Life in Biologic-Treated Patients with Rheumatoid Arthritis in Persistent Moderate Disease Activity

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Session Information

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: A treat-to target (T2T) strategy is recommended for the management of rheumatoid arthritis (RA), with the target being remission or at least low disease activity. Many do not reach these targets (45% at our centre), some remaining in moderate disease activity with DAS28 between 3.2 and 5.1 (MDAS). We recently reported that baseline disability predicted persistent poor function and health-related quality of life (HRQOL) at 12-months in biologic-naïve patients in persistent MDAS(1). In patients receiving biologic DMARDs (bDMARDs) the outcomes of those in persistent MDAS are less certain. We therefore studied factors that predicted function and HRQOL in patients taking/previously receiving bDMARDs.

Methods: We analysed data from the RA Centre, which has aimed for DAS28 remission in all patients since 2006, in a Health Research Authority-approved study, studying outcomes over 12-months. Persistent MDAS was defined as patients with two consecutive MDAS scores, with the second score taken as “baseline”. Linear regression models tested relationships between baseline variables and a) 12-month Health Assessment Questionnaire-Disability Index (HAQ-DI) scores, b) rank-transformed EQ-5D-3L index scores, and c) 12-month changes in HAQ-DI and EQ-5D-3L index scores. Factors with associations achieving $p < 0.1$ in univariate analysis, were included in multivariate models.

Results: 188 patients currently/previously taking biologics with persistent MDAS were identified (Table). Most were female, seropositive, and had established disease. In multivariate analysis, only HAQ-DI associated with 12-month HAQ-DI scores ($P < 0.001$); the β -value of 0.76 suggested that per unit increase in baseline HAQ-DI, end-point HAQ-DI scores were 0.76 units higher. In multivariate analysis, HAQ-DI ($\beta = -0.21$; $P < 0.001$) and tender joint counts ($\beta = -0.03$, $P = 0.006$) associated with 12-month changes in HAQ-DI, indicating that higher baseline HAQ-DI scores associated with larger 12-month reductions in HAQ-DI. In multivariate analysis, baseline HAQ-DI ($\beta = -0.35$; $P = 0.003$) and EQ-5D ($\beta = 1.23$, $P = 0.014$) associated with 12-month EQ-5D scores, and baseline EQ-5D scores associated with 12-month changes in EQ-5D scores ($\beta = -0.40$, $P = 0.003$).

Conclusion: These data show that many patients with persistent MDAS have ongoing disability despite intensive treatment. Also of note, 96% patients score moderate to severe pain on EQ-5D pain scale. Baseline HAQ-DI was a key predictor of end-point disability and HRQOL, with higher baseline HAQ-DI scores associating with higher and lower 12-month HAQ-DI and EQ-5D scores, respectively. Despite this, in routine practice, the HAQ-DI is rarely measured. These findings highlight the importance of measuring and focussing on patient-reported outcome measures like the HAQ-DI, in managing patients with RA. (1) Scott I.C. *et al*, *Rheumatology*, Volume 57, Issue suppl_3, 1 April 2018

Table. Patient Characteristics

Characteristic	Summary Statistic (n,% or mean, sd)
Age in Years	55.4 (14.1)
Female Gender	153 (82%)
RA Duration in Years	21.1 (12.0)
Ethnicity	White 112 (74%)
	Black 25 (17%)
	Asian 6 (4%)
	Mixed 3 (2%)
	Other 5 (3%)
RF-Positive	131 (80%)
Anti-CCP Positive	65 (59%)
DMARDs	DMARD Monotherapy 51 (30%)
	Biologic Monotherapy 25 (15%)
	DMARD-Biologic 94 (55%)
Steroids	38 (20%)
EQ-5D Anxiety/Depression	None 91 (49%)
	Moderate 87 (47%)
	Severe 8 (4%)
EQ-5D Pain	None 8 (4%)
	Moderate 153 (82%)
	Severe 26 (14%)
End-Point Time from Baseline in Months	12.5 (2.9)
DAS28	Baseline 4.12 (0.53)
	End Point 3.78 (1.22)
HAQ-DI	Baseline 1.46 (0.74)
	End Point 1.47 (0.76)
MCID HAQ-DI (Change in HAQ-DI ≥ 0.22)	56 (30%)
EQ-5D-3L	Baseline 0.50 (0.26)
	End Point 0.49 (0.31)

Disclosure: I. C. Scott, Eli Lilly and Company, 2; J. Mount, Eli Lilly and Company, 1, 3; J. Barry, Eli Lilly and Company, 1, 3; B. Kirkham, Arthritis Research UK, Abbvie, Eli Lilly and Company, Roche, UCB, 2, Abbvie, Celgene, Eli Lilly and Company Janssen, Novartis, Pfizer, 5.

Abstract Number: 1479

The Predictive Utility of Anti-Cyclic Citrullinated Peptide Antibodies to Diagnose Rheumatoid Arthritis in Patients with Hepatitis C and Polyarthralgias

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

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Background/Purpose: Joint pain is a common extra-hepatic manifestation of chronic hepatitis C (HCV) infection. HCV infection is often associated with the presence of autoantibodies such as rheumatoid factor (RF), seen in approximately 50% of patients, and anti-nuclear antibodies (ANA). Consequently, it can be difficult to distinguish HCV arthralgias from rheumatoid arthritis (RA), especially in early RA when erosions or joint space narrowing are often lacking. Recent studies suggest that antibodies to cyclic citrullinated peptides (anti-CCP antibodies) are highly specific for RA and are absent in patients with HCV arthralgias. In this study, we determined the sensitivity, specificity, and positive and negative predictive values of RF and anti-CCP antibodies for RA in patients with HCV arthralgias.

Methods: We enrolled 97 patients with HCV and arthralgias (defined as pain in >3 joints) in this St. Louis VA Medical Center-based cross-sectional study. Patients were classified as HCV with RA (RA+) or HCV without RA (RA-) based on the presence of HCV antibodies, HCV RNA, or consistent liver biopsy, and meeting 1987 ACR criteria for the diagnosis of RA. Demographic, clinical and serologic information was collected on all patients during a standardized in-person medical evaluation. Patients were excluded if they had other major autoimmune extrahepatic manifestations of HCV (vasculitis, glomerulonephritis, monoclonal gammopathy, lymphoma or multiple myeloma) or were on current anti-viral treatment for HCV infection. Categorical and continuous variables were analyzed using Fisher's exact test and t-tests respectively. A two-sided p-value <0.05 demonstrated statistical significance.

Results: Of the 97 patients with HCV and polyarthralgias, 17 met ACR criteria for RA (HCV RA+) and 80 had arthralgias from non-RA causes (HCV RA-): HCV arthralgia (31), osteoarthritis (28), crystalline arthropathy (9), spondyloarthropathy (7), fibromyalgia (3), polymyalgia rheumatica (2). Both groups were predominantly male (94.1% and 88.8%) and mainly consisted of African Americans in the HCV RA+ group (64.7%) and Caucasians in the HCV RA- group (50%). In the HCV RA+ group, 94.1% had synovitis, while only 6.9% of HCV RA- patients did. RF was the most sensitive (100%) serology, while anti-CCP was highly specific (98.8%). Anti-CCP antibodies exhibited high positive and negative predictive values, 94.1% and 98.8% respectively. Synovitis had a high negative predictive value of 98.6%.

Conclusion: The presence of anti-CCP antibodies and synovitis is highly specific for the diagnosis of RA in patients with HCV arthralgias.

Table 1: Demographic and clinical characteristics of 97 patients with HCV arthralgias with and without RA

Characteristics	HCV arthralgia with RA (n=17)	HCV arthralgia without RA (n=80)	P value
Age	57.2	55.2	0.26
Female	1 (5.9%)	9 (11.3%)	1.00
Caucasian	6 (32.3%)	40 (50.0%)	0.60
AM stiffness (>30mins)	13 (92.9%)	32 (42.7%)	0.0008
Symmetrical joints	17 (100%)	59 (76.6%)	0.036
Hand involvement	16 (94.1%)	49 (63.6%)	0.018
Synovitis	16 (94.1%)	5 (6.9%)	0.00001
Radiographic erosions	7 (41.2%)	4 (5.3%)	0.0004
Positive RF	17 (100%)	53 (69.7%)	0.009
Positive Anti-CCP	16 (94.1%)	1 (1.3%)	0.00001
Positive ANA	9 (52.9%)	14 (18.0%)	0.0046

Anti-CCP-Anti cyclic citrullinated peptide antibody, RF-Rheumatoid factor, ANA-Antinuclear antibody

Table 2. Sensitivity, specificity, positive and negative predictive values of serologies and synovitis for RA, in 97 patients with HCV arthralgias

	Sensitivity	Specificity	PPV	NPV
RF	100%	33.80%	24.30%	100%
Anti CCP antibody	94.10%	98.80%	94.10%	98.75%
ANA	52.90%	80%	39.10%	88.89%
Synovitis	94.10%	93.10%	76.20%	98.55%

ANA-Antinuclear antibody, RF-Rheumatoid factor, PPV-Positive predictive value, NPV-Negative Predictive value

Disclosure: D. Jayakumar, None; X. Huang, None; S. Eisen, None; P. Ranganathan, None; A. Joseph, None.

Abstract Number: 1480

Prognosis of Pneumonia in Rheumatoid Arthritis Patient: An Analysis of Using a Nationwide Administrative Database

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Session Information

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Background/Purpose: Pneumonia is the leading cause of mortality in RA patients. No research has been conducted on the prognosis of pneumonia in RA patients. This study aimed to investigate the prognostic factors for RA patients hospitalized due to pneumonia.

Methods: This study used data from the Diagnosis Procedure Combination database, a nationwide inpatient database in Japan. We reviewed the abstract data and medical actions between 2014 and 2016, and identified RA patients with pneumonia who received RA treatment (conventional synthesis DMARD [cs-DMARD] or biological and targeted synthetic DMARD [b/ts-DMARD]) before admission within 8 weeks. We examined the predictor of in-hospital mortality and worsening of activities of daily living (ADL) from before admission and readmission to after discharge. The covariate included the patients' background data (age, sex, body mass index (BMI), etc.), RA treatment (cs-DMARD alone, b/ts-DMARD, or corticosteroids), assessment of ADL (Barthel index), comorbidities (diabetes mellitus, chronic obstructive pulmonary disease, chronic heart failure, coronary heart disease, cancer, hypertension, and chronic renal disease), a history

of hospitalization for pneumonia within a year, and pneumonia severity at admission. Predictors were identified using a multiple logistic regression analysis.

Results: For this study, 2951 patients from 194 hospitals were eligible. Of these patients, 560 (19%) received b/ts-DMARD. The multivariate analysis revealed that severe ADL impairment at admission (odds ratio [OR], 95% confidence interval [CI]: 9.12, 2.26–33.2), severe pneumonia severity (3.13, 1.92–5.11), and male sex (1.98, 1.12–3.51) were independent risk factors of in-hospital mortality. Use of b/ts-DMARD (OR, 95% CI: 0.93, 0.56–2.27) and corticosteroids (1.45, 0.66–3.02) just before admission was not associated with increased risk of in-hospital mortality as compared with cs-DMARD alone after adjustment for covariates. The risk of ADL worsening at discharge was slight to moderate ADL impairment at admission (OR, 95% CI: 2.81, 0.49–4.54). Use of b/tsDMARD was the factor that reduced the risk of ADL impairment at discharge (OR, 95% CI: 0.44, 0.22–0.80). The risk of readmission was male sex (OR, 95% CI: 2.55, 1.21–5.35), severe ADL impairment at admission (2.32, 1.01–5.11), and corticosteroid use (2.02, 1.04–3.84).

Conclusion: The prognosis of pneumonia in RA patients was mainly associated with patient status on admission, patient sex, ADL, pneumonia severity, and BMI. The use of b/ts-DMARD immediately before admission was not attributed to increase in-hospital mortality and length of hospital stay and decreased risk of ADL impairment at discharge as compared with cs-DMARD alone.

Disclosure: E. Uechi, None; K. Fushimi, None.

Abstract Number: 1481

Are ACPA Associated with More Bone Loss over Time in Patients with RA?

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Anti-citrullinated protein antibodies (ACPA) are one of the most important serological markers for rheumatoid arthritis (RA) and have been suggested to play a pathophysiologic role in osteopenia, a common RA comorbidity, by directly binding to osteoclasts. However, the effect of ACPA on systemic bone mineral density and in particular their effect on changes in bone mineral density over time is currently unknown. Therefore, we determined whether ACPA associate with changes in bone mineral density over time in patients with rheumatoid arthritis.

Methods: Yearly dual X-ray absorptiometry scores were performed during 5 years of follow-up in 412 patients with recent-onset RA participating in the IMPROVED study¹, a clinical trial in which patients were treated according to a remission- (disease activity score<1.6) steered strategy. The effect of the presence of ACPA on 1) Z-scores of lumbar spine and hip over time, and 2) prevalence of osteopenia/osteoporosis (defined as a T-score ≤ -1) over time was analysed using generalized estimating equations. Analyses were adjusted for age, gender, BMI, and symptom duration (determined at baseline), as well as smoking status, disease activity, prednisone intake, bisphosphonate use, calcium intake, and serum 25-OH vitamin D levels (determined longitudinally).

Results: ACPA-positive patients had a significantly lower lumbar spine ($p=0.04$) and hip ($p=0.01$) Z-score at baseline. There was no difference in prevalence of osteoporosis/osteopenia at baseline between ACPA-positive and ACPA-negative patients (OR (95% CI) 1.02 (0.55 to 1.19)). We hypothesised that ACPA-positive patients would have more bone loss over time compared to ACPA-negative patients. However, ACPA positivity did not associate with a stronger decline in Z-score over time at lumbar ($p=0.43$) or femoral sites ($p=0.66$). Additionally, no effect of anti-citrullinated protein antibody positivity was found on the development of osteoporosis/osteopenia over time ($p=0.23$).

Conclusion: ACPA-positive patients have a significantly lower bone mineral density at baseline compared to ACPA-negative patients. Surprisingly, in this cohort of patients treated according to a tight control strategy, ACPA do not associate with a decrease in bone mineral density over time. These results indicate that in the absence of inflammation/disease activity, ACPA do not contribute to increased bone loss after disease onset.

References: ¹Wevers-de Boer et al. Ann Rheum Dis. 2012 Sep;71(9):1472-7.

Disclosure: E. de Moel, None; J. Amkreutz, None; L. Heimans, None; C. F. Allaart, Abb Vie, 2; T. W. J. Huizinga, BMS, 2,EU, 2,Arthritis Foundation, 2,IMI, 2,LUMC, 3,Abblynx, 5,Merck & Co., 5,UCB, Inc., 5,BMS, 5,Biotest AG, 5,Janssen, 5, Pfizer, Inc., 5,Novartis, 5,Roche, 5,Sanofi-Aventis, 5,Abbott, 5,Consulting Bioscience, 5,Galapagos, 5,Nycomed, 5, Boeringher, 5,Takeda, 5,Zydus, 5,Epirus, 5,Eli Lilly and Co., 5; D. van der Woude, None.

Abstract Number: 1482

Is 14.3.3 η a Predictor of Development of Rheumatoid Arthritis in Patients with Early Undifferentiated Arthritis?

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Optimal management of rheumatoid arthritis (RA) requires early diagnosis and therefore sensitive methods for early identification of RA to prevent joint damage and disability. 14.3.3 η is a novel protein biomarker involved in the upregulation of inflammatory and joint damage factors. The serum/plasma concentration of 14.3.3 η has been shown to differentiate patients with established RA from healthy controls¹ and may therefore have predictive value in early arthritis.

The purpose of the study was to investigate if the serum 14.3.3 η concentrations can predict development of RA in patients with early undifferentiated arthritis.

Methods: In this study, 117 patients with early undifferentiated arthritis, i.e. without a specific rheumatological diagnosis, but with ≥ 2 tender and/or 2 swollen joints among the metacarpophalangeal, proximal interphalangeal, wrist, or metatarsophalangeal joints for >6 weeks but <24 months, were included². Clinical examination, imaging and blood samples were obtained at baseline with follow-up after 1-2 years.

Baseline serum samples were analysed with 14.3.3 η ELISA kits (JOINTstatTM, Augurex, Canada). Previously established cut-offs for 14.3.3 η were applied, as follows: negative (-): <0.19 ng/ml, mildly-moderately positive (+): $0.19-0.79$ ng/ml, strongly positive (++) : ≥ 0.80 ng/ml.

Twenty-one healthy controls were also examined. Descriptive statistics were used to describe baseline characteristics, and Fisher's exact test and univariate logistic regression analysis were used to assess the ability of 14.3.3 η to predict development of RA according to the American College of Rheumatology (ACR) 1987 criteria within the follow-up period of 1-2 years (Table 2).

Results: Baseline data are shown in Table 1. Significantly more patients with baseline positive (+ and ++) 14.3.3 η values developed RA compared to patients with negative (-) 14.3.3 η (Fisher's exact test $p=0.003$, Table 2). The sensitivity and specificity of a 14.3.3 η cutoff at <0.19 ng/ml vs ≥ 0.19 ng/ml were 0.36 and 0.90, respectively. The negative predictive value of a 14.3.3 η <0.19 ng/ml was 0.82. If the 14.3.3 η cut-off was set at 14.3.3 η ≥ 0.80 ng/ml (++) , the sensitivity decreased to 0.21 while the specificity increased to 0.94.

Univariate logistic regression analysis confirmed a relation between baseline 14.3.3 η and development of RA($p=0.003-0.02$ depending on the selected cut-off, Table 2).

Conclusion: Serum 14.3.3 η predicted development of RA in patients with early undifferentiated arthritis.

¹ Maksymowych et al, J Rheumatol 2014; 41: 2104-13
² Duer-Jensen et al., Arthritis Rheum 2011; 63: 2192-202

Table 1: Baseline clinical, biochemical, and radiographic characteristics of the patients with early undifferentiated arthritis and healthy controls.

	All patients (n=117)	Patients with early UA		P, RA(+) vs. RA(-)	Healthy controls (n=21)	P, healthy controls vs. RA(+)
		RA(+) (n=28)	RA(-) (n=89)			
Clinical data						
Sex, no. W/M (% W)	89/28 (76.1)	23/5 (82.1)	66/23 (74.2)	ns	14/7 (66.6)	ns
Symptom duration, months*	6 (4-12)	4.5 (4-10.3)	7 (4-12)	ns	-	-
Age*	48 (40-57)	49.5 (37-57.3)	48 (41-57)	ns	46 (36-61)	ns
Morning stiffness >1 hour ^γ	36/66 (35.3)	15/10 (60.0)	21/56 (27.3)	<0.001	-	-
Arthritis in ≥ 3 joint areas ^γ	9/107 (7.8)	2/25 (7.4)	7/82 (7.9)	ns	-	-
Arthritis of the hand (wrist/MCP/PIP joints) ^γ	62/54 (53.4)	21/6 (77.8)	41/48 (46.1)	<0.01	-	-
Symmetric arthritis ^γ	22/94 (81.0)	9/18 (33.3)	13/76 (14.6)	<0.05	-	<0.01
Rheumatoid factor positive ^γ	33/83 (28.4)	16/12 (57.1)	17/71 (19.3)	<0.001	3/18 (14.3)	<0.01
40-joint tender joint count ^γ	8 (4-15)	10 (6-19)	7 (4-15)	ns	-	-
40-joint swollen joint count ^γ	0 (0-2)	1 (0.5-2.5)	0 (0-1.5)	0.01	-	-
Elevated CRP (≥ 5 mg/ liter) ^γ	49/66 (42.6)	16/11 (59.3)	33/55 (37.5)	ns	2/18 (10.0)	<0.001
Elevated anti-CCP (≥10 units/ml) ^γ	16/99 (13.9)	8/18 (30.8)	8/81 (9.0)	0.01	2/19 (9.5)	ns
HAQ score*	0.4 (0-0.9)	0.6 (0-1.1)	0.4 (0-0.8)	ns	-	-
Pain VAS (0-100 mm)*	34 (17-54)	47.5 (22.3-68.3)	29 (15.5-51.5)	<0.05	-	-
Patient global health VAS (0-100 mm)*	39 (17.3-59)	46 (28-70)	34.5 (14.8-57.3)	ns	-	-
DAS28 score*	3.6 (2.8-4.3)	4.0 (3.1-4.3)	3.5 (2.7-4.2)	ns	-	-
Radiographic data						
X-ray positive† ^γ	18/96 (15.8)	4/23 (14.8)	14/73 (16.1)	ns	0/21 (0)	ns
Circulating biomarker						
Serum 14.3.3η (ng/ml)*	0.0 (0-0.1)	0.0 (0-0.5)	0 (0-0)	<0.05	0 (0-0.1)	ns
14.3.3η status -/+ /++ (%) ^γ	98/8/11 (83.3/6.8/9.4)	18/4/6 (64.3/14.3/21.4)	80/4/5 (89.9/4.5/5.6)	-	18/2/1 (85.7/9.5/4.8)	-

anti-CCP: Anti-cyclic citrullinated peptide, **CRP:** C-reactive protein, **DAS28:** disease activity score 28, **14.3.3 η(-):** <0.19 ng/ml, **14.3.3 η(+):** 0.19-0.79 ng/ml, **14.3.3 η(++):** ≥ 0.80 ng/ml, **HAQ:** health assessment questionnaire, **M** men, **MCP:** metatarsophalangeal joint, **ns:** not significant, **PIP:** proximal interphalangeal joint, **RA(+):** patients who had developed rheumatoid arthritis at follow up, **UA:** undifferentiated arthritis, **VAS:** visual analogue scale, **W:** women.

For certain variables (but not serum 14.3.3 η and 14.3.3 η status) there were missing data (range 1-15) in some patients.

* Numerical data. Values are median (IQR)

^γ Categorical parameters. Values are numbers of patients with yes/no (%yes)

† Typical radiographic rheumatoid arthritis erosion in the hand and/or periarticular osteopenia

Table 2: Sensitivity, specificity, positive predictive value, negative predictive value and logistic regression analysis of s-14.3.3 η as a predictor of development of RA in patients with early undifferentiated arthritis

Development of RA based on baseline 14.3.3 η (-) vs 14.3.3 η (+/++)					
	RA(-)	RA(+)	Total	Sensitivity	0.36
14.3.3η(-)	80	18	89	Specificity	0.9
14.3.3η(+ /++)	9	10	19	NPV	0.82
Total	89	28	117	PPV	0.53
				P-value*	0.003
Development of RA based on baseline 14.3.3 η (-/+) vs 14.3.3 η (++)					
	RA(-)	RA(+)		Sensitivity	0.21
14.3.3η(-/+)	84	22	106	Specificity	0.94
14.3.3η (++)	5	6	11	NPV	0.79
Total	89	28	117	PPV	0.55
				P-value*	0.02
Univariate logistic regression, prediction of RA based on baseline 14.3.3 η					
	Estimate (logit)	P	OR		
14.3.3 η (ng/ml)	0.2624	0.02	1.30†		
14.3.3 η (-) vs 14.3.3 η (+/++)	1.597	0.003	4.94		
14.3.3 η (-/+) vs 14.3.3 η (++)	1.5221	0.02	4.58		

CI: confidence interval, **14.3.3 η(-):** <0.19 ng/ml, **14.3.3 η(+):** 0.19-0.79 ng/ml, **14.3.3 η(++):** ≥ 0.80 ng/ml, **NPV:** negative predictive value, **OR:** odds ratio, **PPV:** positive predictive value, **RA:** rheumatoid arthritis, **RA(+):** patients who had developed rheumatoid arthritis at follow up, **RA(-):** patients who had not developed rheumatoid arthritis at follow up

† Odds ratio based on a 1 unit increment of the independent variable

* Fisher's exact test

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Abstract Number: 1483

Comparison of Clinical Features of Seronegative and Seropositive Early Rheumatoid Arthritis: Blinded Data from the Ongoing Phase IIb Trial with the EP4 Receptor Antagonist CR6086 in DMARD-Naïve Patients

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Rheumatoid arthritis patients positive for rheumatoid factor (RF) or anti-cyclic citrullinated peptide antibody (ACPA) are considered to manifest an aggressive disease course compared with seronegative RA patients. On the other hand, the relationship between seropositivity and measures of disease severity other than radiologic outcome is disputed. Recently, the comparison of disease characteristics of seropositive versus seronegative DMARD-naïve patients showed that seronegative patients had higher levels of inflammation as assessed clinically and by ultrasound [1], and manifested more active disease at baseline [2]. We aimed to compare the clinical features of seronegative and seropositive patients screened to participate in the ongoing Phase IIb trial of CR6086 in DMARD-naïve patients with early RA.

Methods: We used blinded data from the ongoing trial with the EP4 receptor antagonist CR6086 in early rheumatoid arthritis, DMARD-naïve patients (the CREATIVE study). This is a randomized, placebo-controlled, double-blind, dose response, Phase IIb, multicentre trial of CR6086 administered for 12 weeks in combination with methotrexate (NCT03163966). All DMARDs-naïve patients with early RA (disease duration < 1 year) who fulfilled the 2010 ACR/EULAR classification criteria were included in the analysis, regardless of whether they were actually randomized in the trial. Demographic and disease characteristics at enrolment were compared between seropositive (RF+ and/or ACPA+) and seronegative patients (RF- and ACPA-) using independent samples t test or Chi-square test, as applicable.

Results: A total of 257 patients could be included in the analysis, and 44 patients (17%) were seronegative. Age, gender distribution and disease duration were similar between groups (overall mean age 52.4 years, 77% females and mean disease duration 7 months). Joint counts at enrolment were significantly higher in the seronegative patients compared to seropositive patients (68-tender joint count: 29±16 vs. 20±11 P=0.002; 66-swollen joint count: 18±12 vs. 13±7 P=0.009), whereas DAS28, CRP, ESR, patient's arthritis pain, patient's and physician's global assessment of arthritis did not differ significantly between the two subsets of patients.

Conclusion: Among the newly diagnosed RA patients screened to participate in the ongoing Phase IIb trial with CR6086, seronegative patients have higher disease activity compared to seropositive patients, as assessed by tender and swollen joint counts. These results are in line with recent literature and may be influenced by the role of serology within the 2010 ACR/EULAR classification criteria, in that more involved joints are required for seronegative patients to fulfil the criteria.

[1] Nordberg LB et al. Ann Rheum Dis. 2017; 76:341–345.

[2] Choi S-T, Lee K-H. 2018; PLoS ONE 13(4): e0195550.

Disclosure: G. Giacobelli, Rottapharm Biotech, 3; B. Barbetta, Rottapharm Biotech, 3; C. Vitalini, Rottapharm Biotech, 3; N. Brambilla, Rottapharm Biotech, 3; M. D'Amato, Rottapharm Biotech, 3; F. Girolami, Rottapharm Biotech, 3; L. C. Rovati, Rottapharm Biotech, 3.

Value of Anti-RA33 Isotypes in an European Rheumatoid Arthritis Patient Cohort

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Session Information

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

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Background/Purpose: Early diagnosis of rheumatoid arthritis (RA) leading to effective treatment is essential to improve prognosis and to prevent disease progression. Anti-cyclic citrullinated peptide (CCP) antibodies (ACPA) offers similar sensitivity, but higher specificity for RA than rheumatoid factor (RF) in early RA. In single analyte-testing scenarios, ACPA can detect approx. 70% of RA patients but fewer during early RA (~ 60%). As a biomarker for RA, anti-RA33 IgG antibodies are known to be specific, especially in the early stage of the disease. Recent studies show an emerging role of all three anti-RA33 isotypes in diagnosis and prognosis of RA¹.

The aim of this study was to evaluate anti-RA33 isotypes IgM, IgA, and IgG for the diagnosis of early RA and to examine the added value compared to anti-CCP antibodies and RF within two independent European RA cohorts.

Methods: The first cohort provided by Medical University of Vienna, Austria, includes in total 654 patient samples, 257 RA patient samples and 357 control samples; various autoimmune (n=128), non-autoimmune diseases (n=130) and healthy individuals (n=99). To validate the data, a second patient cohort (MATURA, United Kingdom) consisting of 295 patient samples, 100 RA patient samples, 75 autoimmune, 70 non-autoimmune diseases and 50 healthy subjects was measured. Serum samples of both cohorts were analyzed for the presence of anti-RA33, anti-CCP and RF (each IgM, IgA, IgG) using the EliATM instrument platform (Phadia AB, Uppsala, Sweden).

Results: Analyzing both cohorts, one third of RA patients were positive for at least one of the anti-RA33 isotypes, whereas anti-RA33 IgM showed the highest sensitivity (23%) followed by IgA (12%) and IgG (9%). Both cohorts revealed a specific pattern of all three anti-RA33 isotypes with a diverse distribution among RA patients and little overlap between the immunoglobulin classes. The combination of all three anti-RA33 isotypes detects 26% of the seronegative RA patients and the specificity of each isotype is $\geq 90\%$.

Conclusion: Anti-RA33 isotype distribution shows remarkably little overlap of IgM, IgA and IgG in European RA patient cohort. Therefore, the combination of all three anti-RA33 isotypes provides a considerable added value for the diagnosis of RA in the anti-CCP- and RF-negative group. To fully evaluate the importance of the different anti-RA33 immunoglobulin classes within the pathogenesis of RA, further investigations are required.

¹Sieghart, D; Platzer, A; Studenic, P; Alasti, F; Grundhuber, M; Swiniarski, S; Horn, T; Haslacher, H; Blüml, S Smolen, J; Steiner, G. Determination of Autoantibody Isotypes Increases the Sensitivity of Serodiagnostics in Rheumatoid Arthritis. *Frontiers in Immunology*; v:9 p:876; 2018

Disclosure: M. Grundhuber, Thermo Fisher Scientific, Phadia GmbH, 3; D. Sieghart, None; G. Steiner, Thermo Fisher Scientific, 2, 5; M. Poorafshar, Thermo Fisher Scientific, 3; S. Swiniarski, Thermo Fisher Scientific, Phadia GmbH, 3.

Surviving Measurements Improve Prediction of Rheumatoid Arthritis Among Patients with Unexplained Arthralgia

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Session Information

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

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Background/Purpose: Early recognition of rheumatoid arthritis (RA) is believed to be the key to successful treatment of this disease. Symptoms of arthralgia often predate development of RA. A set of clinical features assisting recognition of patients during their transition from arthralgia to RA, has been recently proposed. We therefore designed a study, in which we followed patients with unexplained arthralgia prospectively aiming to find new cases of RA and to explore a combination of clinical features and serological markers predicting transition from arthralgia to RA. The aim of the present study was to improve recognition of imminent RA among patients with arthralgia (ALG) using a combination of clinical symptoms with RA-specific antibodies RF and anti-CCP and survivin, serological markers predating transition from ALG to RA.

Methods: All new cases of RA, undifferentiated arthritis (UA) and unexplained ALG were identified among the total of 1743 first-visit patients attending the rheumatology ward in Gothenburg during 12 consecutive months. The ALG patients were prospectively followed for 48 months and development of additional RA cases was recorded. The set of 13 joint symptoms was applied to the first-visit records aiming to distinguish patients with arthritis from ALG and from the new RA cases. The symptoms with odds ratio >2.0 between ALG and pre-RA and information about RF/aCCP and survivin dichotomised were included in predictive models. Receiver operating characteristic (ROC) curves and Kaplan-Meiers curves were constructed.

Results: Among the first-visit patients, 63 were classified as RA, 73 had undifferentiated arthritis and 180 had ALG. Additional 32 new RA cases developed during 48 months of follow-up and comprised pre-RA group. The analysis of joint symptoms at the first visit distinguished ALG from RA/UA (both, $p < 0.001$). A combination of symptoms in several small joint areas, increasing number of joints with symptoms, and patient's experience of swelling in small hand joints at the first visit discriminated pre-RA from ALG with 93% sensitivity ($p = 0.005$, $AUC = 0.660$). Presence of survivin in serum strongly associated with 7 of 13, and RF/aCCP with 1 of 13 joint symptoms. Grouping those symptoms with age >50y, gender, survivin and RF/aCCP in the final algorithm allowed reaching 50% sensitivity for transition from ALG to RA ($AUC = 0.767$, $p < 0.001$).

Conclusion: Clinical and serological parameters in combination aid recognition of imminent RA among ALG patients with appropriate sensitivity.

Disclosure: M. C. Erlandsson, None; M. Turkila, None; R. Pullerits, None; M. I. Bokarewa, None.

Abstract Number: 1486

Incidence of Subclinical Signs of Inflammation in Patients with New Onset of Non-Specific Musculoskeletal Symptoms and Anti-Citrullinated Peptide Positivity: First Interims Analysis of the Panora Trial

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Session Information

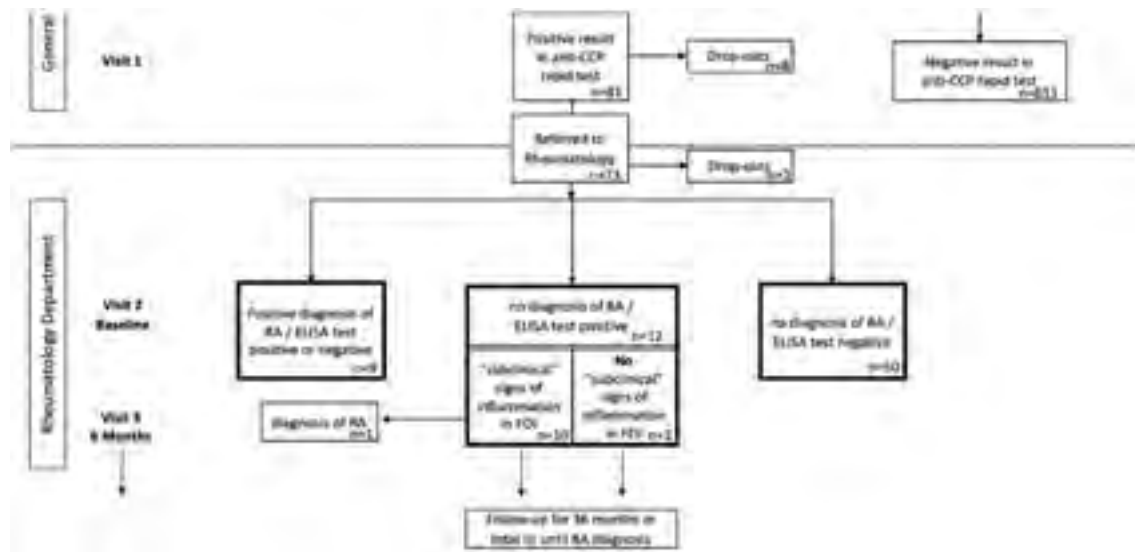
Session Date: Monday, October 22, 2018

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Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Rheumatoid Arthritis (RA) is a chronic inflammatory joint disease affecting approx. 1% of the adult population of Northern Europe and North America. Strategies for its early diagnosis are of high importance as prompt treatment improves clinical and structural outcome significantly. Formation of autoantibodies against cyclic citrullinated proteins (anti-CCP) are identified to be associated to RA-development. Non-specific musculoskeletal (nsMSK) pain often precedes RA-development. Fluorescence-optical imaging (FOI) technique is a new ICG-tailored technique to display changes in microvascularisation which might be useful for early detection of joint inflammation in high-risk populations.



Methods: In this prospective study (PANORA), patients presenting with new onset of nsMSK pain at General Practitioners (GP) and with evidence for anti-CCP positivity (rapid-test, CCPoint®) were included to be referred to Rheumatology Department for rheumatologic assessment and RA-evaluation. At Rheumatology Department, validation of anti-CCP testing (using ELISA) and a rheumatological examination including ultrasound was performed. Subclinical signs of inflammation defined as increase of microvascularisation were monitored by FOI. In case of ELISA positivity but missing evidence of clinical RA, patients were monitored for RA-development every 6 months for a total follow-up of 36 months or until RA-diagnosis.

Results: For this interim analysis, data from the first 692 patients was analyzed. 12% of the patients showed a positive anti-CCP rapid-test at GP, of which 40% were confirmed positive by ELISA. 10 patients were diagnosed with RA (1 in the ELISA negative group), thereof one case of a newly detected RA at month 6 of the follow-up period. In the three groups at baseline (figure 1), age was well balanced, the proportion of female patients was highest in the RA-diagnosis cohort (77.8%) and the proportion of patient with current or past smoking-status was prominent in the ELISA negative group (52.9%). Signs of unspecific subclinical inflammation defined as increased microvascularisation were detected by FOI in 83% of the ELISA positive patients compared to 39% in the ELISA negative cohort. Moreover, descriptive characteristics in FOI signals clear differ in both groups. After the first follow-up at month 6 (data from 40% available), 2 patients exhibited changes in the FOI from baseline towards "RA-suspicious" imaging patterns but without evidence of clinical RA.

Conclusion: The combination of serological biomarkers and imaging using FOI might represent a strategy for sensitive detection of early stages in RA-development in an at-risk population for improvement of a timely initiation of appropriate treatment options to prevent aggressive diseases courses. The continuation of PANORA will give more insights in specific characteristics of the RA-risk population at early stages of the disease.

Disclosure: M. Koehm, BMS, Pfizer, Janssen, Roche, 2; Celgene, Pfizer, Janssen, 8; U. Henkemeier, BMS, Pfizer, Janssen, Roche, 2; T. Rossmannith, BMS, Pfizer, Janssen, Roche, 2; S. Dauth, BMS, Pfizer, Janssen, 2; T. Oberwahrenbrock, BMS, Pfizer, Janssen, 2; A. C. Foldenauer, BMS, Pfizer, Janssen, 2; K. Mergenthal, None; H. Burkhardt, BMS, Pfizer, Janssen, Roche, 2; BMS, Pfizer, Janssen, Roche, 8; F. Behrens, Abbvie, Pfizer, Roche, Chugai, Prophylix, Novartis, Iron4U, 2, Abbvie, Pfizer, Roche, Chugai, UCB, BMS, Celgene, MSD, Novartis, Biotest, Janssen, Genzyme, Sanofi, Lilly, Sandoz, 5, 8; Abbvie, Pfizer, Roche, UCB, Celgene, Novartis, Biotest, Janssen, Genzyme, Sanofi, Lilly, Boehringer, BMS, Sandoz, 6.

Abstract Number: 1487

Correlation between Cytokine Levels and Power-Doppler Ultrasound Activity Is BMI Dependent, and Different in ACPA Positive and ACPA Negative RA with Wrist Arthritis

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Fig.1: Correlation Matrix for ACPA+ patients; ACPA+nw below the diagonal, ACPA+ow above the diagonal

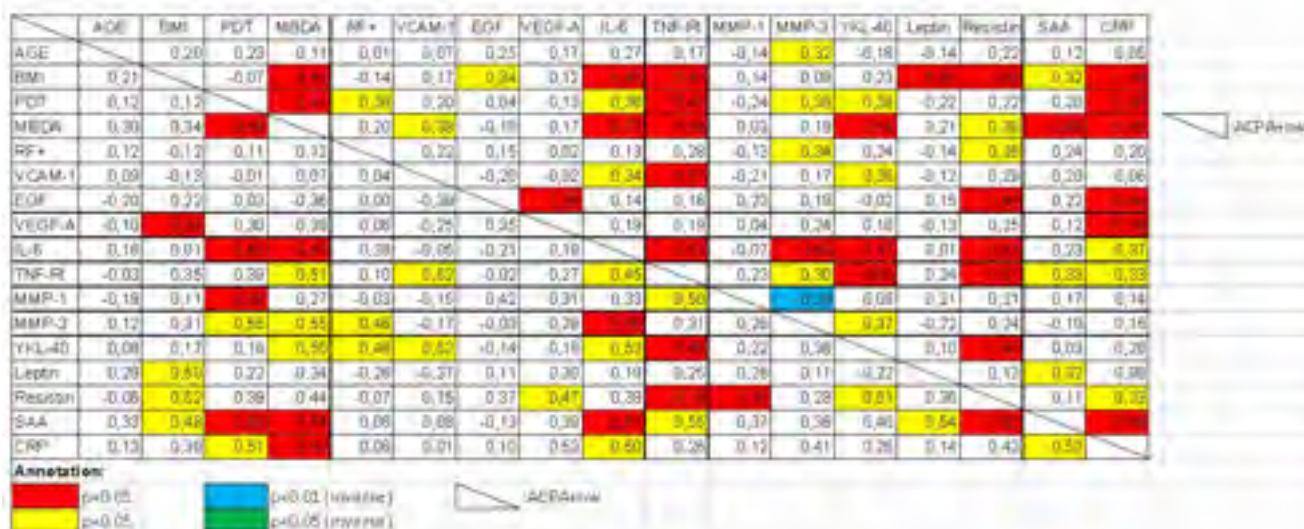
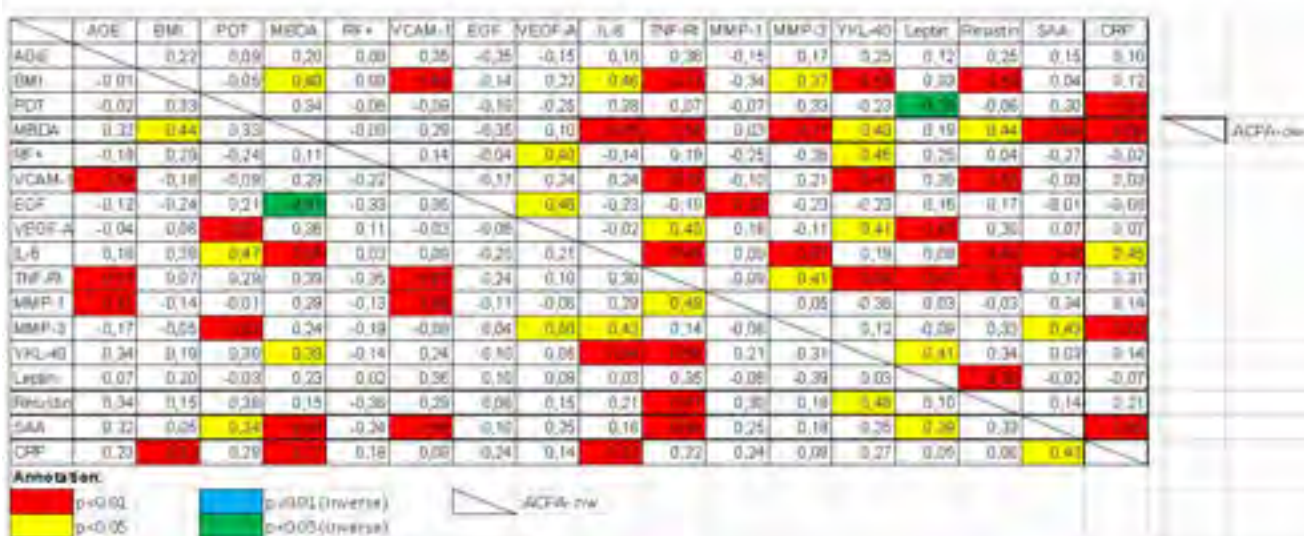


Fig.2: Correlation Matrix for ACPA- patients; ACPA-nw below the diagonal, ACPA-ow above the diagonal



Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Multiple cytokines are assumed to be involved in RA pathogenesis. It has been hypothesized that ACPA-negative RA with wrist affection constitutes a separate entity. Differences in cytokine profile between ACPA positive and negative RA are not known. A Multi-Biomarker Disease Activity (MBDA) assessment is commercially available. Intraarticular inflammatory activity can be measured using power-Doppler (PD) sonography. This study examines whether PD activity is correlated with different cytokines in ACPA positive (ACPA+) and ACPA negative (ACPA-) RA, and whether such differences are BMI dependent.

Methods: 120 visits by 89 patients from a single centre were evaluated retrospectively. All patients fulfilled the 2010 ACR criteria, and were treated with FDA-approved DMARDs. All ACPA- patients had PDS positive wrist arthritis. Patients were divided according to BMI: normal weight (NW, BMI 18.5-25) or overweight (OW, BMI >25), as well as ACPA status (+/-), yielding four groups. Bilateral sonography of MCP 2 and 3, ECU, wrist, and MTP 2 and 5 was performed by a single

technician, activity was graded semiquantitatively (0-3), and a total PD score (PDT) was calculated. An MBDA was performed in all patients. Correlations between cytokines and BMI/PDT were calculated using Spearman's r. The means between groups were compared using the Wilcoxon-Mann-Whitney test. A multiple linear regression was performed for each group using a conditional inference trees approach.

Results: Overall treatment did not differ between the groups. PDT and MBDA total scores did not differ significantly between groups. Leptin correlated significantly with BMI in ACPA+ both normal and overweight, but neither in ACPA-normal nor overweight. In the linear regression, the following variables best predicted PDT: ACPA+nw: log(IL-6) (p=0.1, n.s); ACPA-nw: Log(IL-6)(p=0.04); ACPA+ow: Log(CRP)(p=0.03); ACPA-ow:Log(MMP-3)(p=0.01). Further cytokine associations were also different indifferent groups (Fig. 1 and 2).

Conclusion: Different cytokines are associated with PD activity in ACPA+ and ACPA- RA. This finding supports the theory that the etiology of the two forms is different. The differences appear to be BMI dependent. Further research into cytokines in RA should take BMI into account.

Disclosure: O. Gadeholt, None; E. Arnold, Crescendo Bioscience, Inc., 5; C. Gorman, None; T. Mueller, None; W. Arnold, Crescendo Biosciences, Inc, 5.

Abstract Number: 1488

Identification of Joint Locations That Are Poor Prognostics in an Early Seropositive Erosive RA Cohort

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Patients (pts) with early RA often present with multiple and different areas of joint involvement. While the ACR and EULAR guidelines specify high disease activity, erosions, seropositivity and other factors for a poor prognostic RA, limited data exist to identify which specific joints or joint locations may be indicative of disease severity and poorer prognosis.¹ This analysis investigated the distribution of affected joints at baseline (BL) as well as the correlation between BL swollen joint status and disease characteristics and prognostic factors in early RA pts.

Methods: Data from AGREE (NCT00122382), a double-blind Phase III study of abatacept (ABA) plus methotrexate (MTX) (n=256) vs MTX (n=253) in MTX-naïve pts who were seropositive for RF and/or ACPA with early (≤2 years [yrs]) erosive RA, were analyzed post hoc by baseline swollen joint status (present, absent) for 8 different joint locations: hands,

Table 1. BL Disease Characteristics for BL swollen versus non-swollen knee, jaw, elbow or wrist joints

	Knee		Jaw		Elbow		Wrist	
	SJC n=348	No SJC n=151	SJC n=45	No SJC n=464	SJC n=245	No SJC n=264	SJC n=468	No SJC n=41
Baseline (mean [SD])								
Tender joints	33.1 (14.9) ^{***}	26.5 (12.2)	40.0 (15.1) ^{***}	30.1 (14.1)	34.1 (15.0) ^{***}	28.1 (13.3)	31.4 (14.6) ^{**}	26.3 (12.0)
Swollen joints	24.6 (11.2) ^{***}	17.2 (7.3)	35.9 (13.0) ^{***}	21.1 (9.8)	25.3 (11.2) ^{***}	19.8 (9.6)	23.0 (10.7) ^{***}	15.5 (9.4)
DA 528 (CRP)	6.5 (0.9) ^{***}	5.8 (1.0) n=160	6.7 (1.0) ^{**}	6.2 (1.0) n=463	6.5 (1.0) ^{***}	6.0 (0.9) n=263	6.3 (1.0) ^{***}	5.6 (1.0)
SDAI	51.7 (14.4) ^{***}	41.2 (12.6) n=159	57.4 (16.1) ^{***}	47.6 (14.3) n=462	52.6 (14.8) ^{***}	44.5 (13.5) n=262	49.4 (14.5) ^{***}	37.8 (12.1)
CDAI	47.8 (12.9) ^{***}	39.2 (12.4) n=159	53.3 (14.3) ^{***}	44.3 (13.0) n=462	48.5 (13.0) ^{***}	41.6 (12.7) n=262	45.9 (13.1) ^{***}	35.3 (11.3)
HAQ DI	1.5 (0.6) ^{***}	1.5 (0.7) n=159	1.9 (0.5) ^{**}	1.7 (0.7) n=460	1.8 (0.6) ^{***}	1.6 (0.7) n=262	1.7 (0.7) n=464	1.7 (0.7)

P-values are from Wilcoxon rank-sum tests comparing swollen versus non-swollen joint status for each parameter.
***p < 0.001, **p < 0.01, *p < 0.05, vs No SJC.

Table 2. Pairwise association of BL swollen joint status (Chi-Square test)

	Elbow	Foot	Jaw	Knee	Shoulder	Wrist
Ankle	0.0022 *	0.0016 *	0.0046 *	<0.0001 **	0.0712	0.0028 *
Elbow		0.0825	0.0004 **	<0.0001 **	<0.0001 **	0.1227
Foot			0.0083 *	0.0815	<0.0001 **	0.4777
Jaw				0.0019 *	<0.0001 **	0.8295
Knee					<0.0001 **	0.0016 *
Shoulder						0.8933

**p < 0.001, *p < 0.05, †p < 0.01

wrists, elbows, shoulders, jaw, knees, ankles and feet. Pairwise associations of BL swollen joint status were evaluated for all evaluable joint locations. Overall characteristics and study results were previously reported.

Results: In this early RA cohort with poor prognostic factors, (n=509), BL swelling was most frequently observed in the hands (99%), followed by the wrist (92%), ankle (79%), knee (69%), foot (66%), elbow (48%), shoulder (34%) and jaw (9%). Pts with a BL swollen knee, jaw, elbow or wrist have a poorer prognosis and more aggressive RA. When these joints were involved in this MTX-naïve, seropositive, early erosive cohort, these pts had more tender and swollen joints, higher DAS28 (CRP), SDAI and CDAI than those without swelling (Table 1). Higher HAQ-DI was seen in pts with a swollen knee versus those without knee swelling (1.8 [0.6] vs 1.5 [0.7], respectively (p < 0.001)). Swollen shoulder status was significantly associated with swelling status of almost all other joint locations (elbow, foot, jaw and knee: p < 0.001), whereas swelling status of the foot and wrist were the least associated with swelling status of other joints (Table 2). Presence of BL synovitis was not associated with greater BL ACPA or RF positivity, probably due to the inclusion of mainly seropositive pts.

Conclusion: In this cohort of early, seropositive erosive RA, swelling in the knee, jaw, wrist or elbow suggests that large joint locations are associated with the poorest prognosis. Pts with such a presentation might be considered for more intensive treatment.

References: 1. Bergstra SA, et al. *RMD Open* 2017;3:e0005682. Westhovens R, et al. *Ann Rheum Dis* 2009;68:1870–7

Disclosure: P. Durez, BMS, Lilly, Sanofi, Pfizer, 8; S. Robert, Bristol-Myers Squibb, 3; A. Thiry, Bristol-Myers Squibb, 3, Bristol-Myers Squibb RSUs, 1; H. A. Ahmad, Bristol-Myers Squibb, 1, 3.

Abstract Number: 1489

“Continuous Reduction” in Serum RF Titers Predicts Low Disease Activity and Good Therapeutic Response in RA Patients Treated with TNF Inhibitors, but Does Not Relate to Clinical Outcomes during ABT Treatment

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Relative change of serum RF titer has been reported to correlate with those of RA disease activity. However, it is debatable whether serum RF decrease was associated with clinical improvements in RA. Therefore, to clarify whether “Continuous Reduction” in serum RF during biologics therapy was associated with better clinical outcomes, we examined serum RF titers and disease activity in RA patients treated with TNF inhibitors (TNFIs) or abatacept (ABT) as 1st-biologics.

Methods: Subjects were RA patients who filled RA criteria 2010, were biologics-naïve, were treated with TNFIs (adalimumab and golimumab) or ABT, and had active diseases (DAS28-CRP ≥ 2.7) and high titer in serum RF (≥ 45 IU/ml). Their medical records were reviewed retrospectively. RF titers were measured at 0, 4 and 12 month (mo.) after

starting biologics. More than 10% decline in RF titer was considered as significant decrease, and “Continuous Reduction” was defined as significant decreases during both 0-4 and 4-12 months. DAS28-CRP was calculated for each patients, and RA disease activity and therapeutic efficacy was assessed by achievement of clinical remission or low disease activity (CR+LDA, DAS28-CRP<2.7) and “Good Response” of EULAR response criteria.

Results: Subjects were 66 RA patients with 25 male and 41 female, 67.9 years (median) of age, 2.1 years (median) of disease duration and 8 mg/week (median) of MTX dosage. TNFIs and ABT were administered in 36 and 30 patients, and improved DAS28-CRP (median) from 4.16 at 0 mo. to 2.00 at 12 mo. and from 3.87 to 2.07, respectively. Serum RF titers (median) were decreased during 0-4 months in TNFI-treated patients (RF titer; 104 at 0 mo., 58 at 4 mo. and 43.5 IU/ml at 12 mo.), whereas RF among ABT-treated cases was increased during 4-12 months after decline during 0-4 months (RF; 188 at 0 mo., 75 at 4 mo. and 94 IU/ml at 12 mo.). “Continuous RF reduction” was found in 19 (52.8%) of 36 TNFI-treated patients and in 8 (26.7%) of 30 ABT-treated ones, and was significantly fewer in cases receiving ABT. Among TNFI-treated patients, CR+LDA at 12 mo. was found in 17 (89.5%) of 19 “Continuous RF Reduction” and in 9 (52.9%) of 17 patients without “Continuous RF Reduction”, and proportion of CR+LDA was significantly higher in “Continuous RF Reduction” ($p=0.0248$). Additionally, percentage of “Good Response” at 12 mo. was significantly higher in “Continuous RF reduction” (84.2% ($n=16$) vs 35.3% ($n=6$), $p=0.0054$). Among ABT-treated patients, CR+LDA at 12 mo. was found in 7 (89.5%) of 8 “Continuous RF Reduction” and in 13 (59.1%) of 22 patients without “Continuous RF Reduction”, and proportion of CR+LDA was not different in these patients. Similarly, ratio of “Good Response” at 12 mo. was not higher in “Continuous RF reduction” (75.0% ($n=6$) vs 50.0% ($n=11$), $p=0.4069$).

Conclusion: “Continuous RF reduction” was associated with lower disease activity and better therapeutic response only in RA patients treated with TNFIs, not ABT. Therefore, “Continuous reduction” in serum RF titers reflects low RA disease activity and predicts good therapeutic response during TNFI therapy, but does not relate to clinical outcomes during ABT treatment.

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Abstract Number: 1490

Effects of Biologic Drugs on Prognosis of Rheumatoid Arthritis Among Patients with Poor Glycated Hemoglobic A1c (HbA1c) Control

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Poor control of glycated hemoglobic A1c (HbA1c) worsens prognosis for diabetes mellitus and various complicated diseases. Corticosteroids exacerbate poor HbA1c control. This study, investigated the effects of biological disease-modifying antirheumatic drugs (bDMARDs) on HbA1c control among patients with RA, as it has not been examined before.

Methods: In total, 632 patients with RA from the All Showa University of RA database (ASHURA) were used for our study. The following background factors were investigated: age; gender; type of bDMARD; dosage of methotrexate and prednisolone (PSL); usage of conventional synthetic DMARD and nonsteroidal anti-inflammatory drugs; body mass index; smoking history; HbA1c; presence or absence of hypertension and dyslipidemia; and levels of serum creatinine, C reactive protein, and matrix metalloproteinase-3. We also used the simplified disease activity index (SDAI) and health assessment questionnaire (HAQ) to evaluate RA disease activity and activities of daily living, respectively. Poor HbA1c control was defined as HbA1c ≥ 6.0 ; accordingly, we divided the patients into good and poor HbA1c control groups. Primary and secondary failures, adverse drug events, missing data, and patients who moved or had care withdrawn were excluded. SDAI and PSL dosage were the primary and secondary endpoints, respectively. Repeated measures analysis of variance (ANOVA) evaluated the HAQ scores before treatment and 1 year later.

Results: Of 632 patients, 296 patients enrolled in this study. The SDAI was from 27.7 ± 15.6 to 7.1 ± 8.0 in the poor HbA1c control group ($n = 83$) and from 22.9 ± 14.0 to 6.3 ± 7.6 in the good HbA1c control group ($n = 213$). There was no interaction between the groups. Repeated measures ANOVA showed a significant difference between the groups ($p =$

0.011) and during the treatment period ($p = 0.001$). PSL dosage was from 3.5 ± 3.6 (mg/day) to 2.2 ± 3.0 in the poor HbA1c control group and from 2.3 ± 3.0 to 1.6 ± 3.6 in the good HbA1c control group. A significant difference was observed between the groups ($p = 0.007$) and during the treatment period ($p = 0.001$). Notably, there was no significant difference in HAQ. No patient reported HbA1c increasing by 1.0 or more during 1 year.

Conclusion: Results showed that bDMARD therapy reduced RA disease activity and PSL dosage in both groups. Therefore, we recommend bDMARD treatment for RA regardless of good or poor HbA1c control

Disclosure: Y. Miwa, Astellas Pharma Inc., 2, Mitsubishi Tanabe Pharma Corporation, 2, AbbVie CK, 2, Pfizer Japan Inc., 2, Chugai Pharmaceutical Co., Ltd., 2, Ono Pharmaceutical Co., Ltd., 2; T. Kasama, None.

Abstract Number: 1491

Oestrogen Levels and the Outcome of Leflunomide Treatment in Rheumatoid Arthritis

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Session Information

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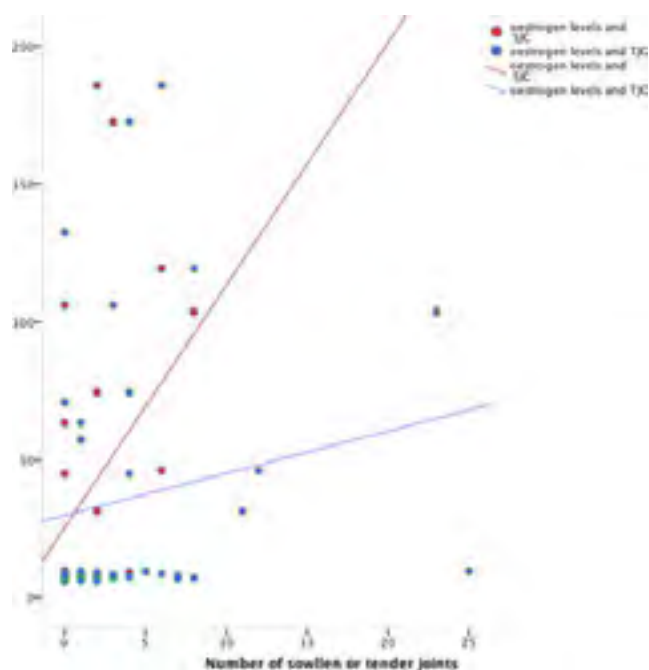
Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune and inflammatory polyarthritis involving mainly the synovial joints, and causing destruction of the articular cartilage and disabilities. Leflunomide is one of the anti-proliferative drugs proved to be effective in controlling the disease by suppressing the inflammatory cytokines and inducing apoptotic genes in synovial macrophages. However, regulation of the disease seems to be complex where the sex hormone, oestrogen, is incriminated in counteracting the effect of leflunomide in vitro. Moreover, detected oestrogen receptors polymorphisms were supposed to play a role in disease resistance. We aimed in this study to unravel the relationship between oestrogen levels and leflunomide outcome in RA.

Methods: RA patients fulfilling the ACR/EULAR 2010 RA criteria and receiving only leflunomide (20 mg daily) and hydroxychloroquine were gathered from the outpatient clinics after being consented. Disease activity of the patients was evaluated by the disease activity score (DAS)-28 and the clinical disease activity index (CDAI). Serum oestrogen levels were detected by enzyme-linked immunosorbent assay (ELISA). Descriptive and correlation studies were used as appropriated.



Results: RA patients (n=50) were recruited. 98% were females and mean age was 47.2 ± 10.3 years. Median (IQR) levels of oestrogen were 8.6 (7.4- 50.5) IU/mL. Minimal and maximal levels of oestrogen were 6 IU/mL and 185.5 IU/mL respectively. Values of DAS-28 and CDAI did not correlate with oestrogen levels. Neither the patient's global assessment using 100 mm visual analogue scale nor the erythrocyte sedimentation rate correlated with oestrogen levels. Contrarily, swollen joint count (SJC) and tender joint count (TJC) correlated positively with oestrogen levels ($\rho = .433$, $p = .006$ and $\rho = .33$, $p = .04$ respectively) as shown in Fig 1.

Conclusion: The changes in oestrogen levels among RA patients could be responsible for the different outcome of leflunomide therapy in these patients. Further studies on bigger cohorts and longitudinal observations are required.

Fig.1 Correlations between oestrogen levels and the number of swollen or tender joints

Disclosure: A. A. A. Mohamed, None; M. Hassanien, None; E. A. Ahmed, None.

Abstract Number: 1492

Methotrexate Response in Early Rheumatoid Arthritis Predicted Using a Somamer Proteomic Assay

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Background/Purpose: Available clinical tools do not adequately identify treatment non-responders in early rheumatoid arthritis (RA) leading to delayed disease control. Tools informed by molecular phenotype may aid treatment decisions. Using an aptamer based assay that measures the relative quantity of 1310 proteins, (SOMAscan), we sought to identify predictors of Methotrexate (MTX) response in Disease Modifying Anti-rheumatic Drug (DMARD) naïve patients with less than 1 year of RA (ERA).

Methods: Sera from 36 DMARD naïve seropositive ERA (female 67%, rheumatoid factor (RF) positive 47%, baseline symptom duration 4 (1.9) months, baseline DAS28CRP 5.1 (SD 1.2) were assayed for SOMAmer protein expression. All patients met ACR/EULAR 2010 criteria for RA and all received MTX monotherapy. At one year, clinical response was defined by change in DAS28CRP (dDAS) and radiographic outcome by the presence of erosions on hand and feet radiographs and Sharp score. Pre-treatment protein expression levels were log2 transformed and correlated with their corresponding log2 transformed dDAS using a Pearson's R-squared (RSQ) applied across the cohort. A constant offset was included to account for negative dDAS values. The proteins with RSQ over a threshold had their expression values weighted into a linear combination SCORE. The value of the threshold was manually, iteratively tuned to yield an optimal correlation of SCORE against dDAS using the smallest number of proteins. Biological processes of included proteins were identified using an in-house enrichment tool. The SCORE was included in logistical regression models to predict radiographic outcome.

Results: The mean dDAS at one year was -1.9(SD1.6), 47% achieved remission ($\text{DAS} < 2.6$) and 19(53%) had erosions at one year (median Sharp score 3 (range 0-18)). A panel of 9 proteins each with $\text{RSQ} > 0.18$ correlated with dDAS (overall $\text{RSQ} 0.58$). Three proteins enriched to processes regulating cell proliferation (BIRC7, MMP7, CXCL9). SCORE did not correlate with one year radiographic Sharp scores and were similar between patients with or without erosions. In multivariable models including RF, age and sex, SCORE predicted remission (OR 0.01; 95% confidence interval 0.001-0.2) but did not predict the presence of erosions at one year. The dynamic range of protein expression values suggests this assay could be transferable to more clinically accessible protein quantification technologies.

Conclusion: High content proteomic approaches based on aptamers can assist the development of biologically based prediction tools. While further validation in cohorts with expanded disease activity and broader treatment is needed, this pilot study suggests a panel of proteins reflecting cellular proliferation predicts treatment response to MTX monotherapy in ERA however, different biomarkers are needed to predict erosions.

Disclosure: C. Hitchon, Pfizer, Inc., 2; V. Spicer, None; N. Carrier, None; A. Gao, None; H. El-Gabalawy, None; J. Wilkins, Somalogics, 2; G. Boire, None.

Abstract Number: 1493

Clinical Predictor Factors Associated with Sustained Disease Activity Among Patients with Early Rheumatoid Arthritis

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Background/Purpose: In rheumatoid arthritis (RA) patients the disease outcome has an unpredictable course and may differ even with an early diagnosis and treatment. Low disease activity is associated with favourable outcome and a normal level of functionality. It is desirable to identify patients with a high probability of sustained disease activity in an early stage. The purpose is to identify clinical baseline predictor factors associated with sustained disease activity after 12 months of follow up in patients with early RA.

Methods: Demographic, clinical, laboratory and treatment data of patients with an established diagnosis of RA (according to physician diagnosis) were recruited from an early arthritis clinic at baseline and after 12 months of follow-up. Sustained disease activity at 12 months was defined as DAS28 >3.2 and SDAI >11. Univariate and multivariate logistic regression of DAS28 and SDAI disease activity were performed at baseline and after 12 months

Results: 566 patients diagnosed of RA were included. 75.8% (429) were women with a predominance of Caucasian (74.7%; 423) an age average of 54 +/- 17 years old at the baseline visit and a mean of 16+/- 15 weeks since symptoms onset. 440 (77.7%) had positive rheumatoid factor and 373 (65.9%) had positive ACPA. 508 (89.8%) patients received Methotrexate as first line treatment and 459 (81.1%) received glucocorticoids. At baseline 88.8% (487) had moderate-high disease activity with DAS28 and 77.6% (439) with SDAI. After one year of follow-up, 34% (170) had moderate-high activity with DAS28 and 30.9% (175) with SDAI. Univariate logistic regression analysis results are shown in Table 1. On multivariate analysis we found that a higher DAS 28 score at baseline visit (OR 1.34; p=0.02) was associated with sustained disease activity after 12 months. Higher tittle of rheumatoid factor (OR 2.6; p=0,019), higher HAQ (OR 1.06; p=0.005) and high doses of glucocorticoids at baseline visit (OR 2.1; p=0.025) were associated with sustained disease activity after 12 months with SDAI score.

Table 1. Univariate logistic regression analysis results (baseline visit)

	DAS28		SDAI	
	OR	P value	OR	P Value
Age	1.00	0.6	0.03	1.02
Sex (women)	1.64	0.06	0.599	1.14
Tabaco	0.66	0.1	1.12	0.690
Nonsmokers (ref)	0.58	0.05	1.08	0.804
Past smokers				
Smokers				
RF (+)	1.61	0.09	0.444	0.007
ACPA (+)	0.685	0.1	0.691	0.14
DAS28	1.5	<0.001		
SDAI			1.00	0.008
HAQ	1.05	0.001	1.07	<0.001
ESR	1.01	0.001	1.01	<0.001
PCR	1	0.804	1.0	0.91
Pain	1.02	<0.001	1.01	<0.001
Patients Global Assessment	1.01	<0.01	1.01	0.002
Evaluator Global Assessment	1.02	<0.001	1.02	<0.001
Swollen Joint count 28	1.07	<0.001	1.07	<0.001
Tender Joint Count 28	1.07	<0.01	1.06	<0.001
Methotrexate use	8,2	<0.05	2,4	0,2
Glucocortoids use	1.8	<0,05	2,7	<0.001

Conclusion: 34% of RA patients had moderate-high activity with DAS28 and 30.9% with SDAI after 12 months of follow up even with an early diagnosis and intensive treatment. With the DAS28 score, high clinical activity at baseline can predict a sustained disease activity after one year; however with the SDAI score a high rheumatoid factor tittle, an

impaired functionality and the need of higher doses of glucocorticoids at baseline can predict a sustained disease activity after one year, showing a poor correlation between both indexes

Disclosure: G. Gonzalez, None; J. Molina, None.

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Predictors of Persistence to Methotrexate Treatment in RA – Assessment of Different Modelling Approaches

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Session Information

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

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Background/Purpose: As a step towards personalized medicine, we seek to identify patients with new-onset RA who are likely to remain well on MTX monotherapy. Patients unlikely to persistently respond could potentially avoid adverse effects such as pain, functional impairment, structural damage, reduced work ability, or co-morbidities if offered alternative treatments already at diagnosis.

This project aims at assessing the performance, and marginal gains, of different statistical approaches to modelling predictions of persistence to methotrexate DMARD monotherapy at 1 year after RA diagnosis in patients with new-onset RA. Here, we report first results.

Methods: A cohort of incident RA diagnosed 2006-2014, starting treatment with MTX and DMARD monotherapy, and with clinical and treatment data available from diagnosis, was identified through the Swedish Rheumatology Quality (SRQ) register. Through linkages to nationwide population health and demographics registers, information on age, gender, educational level, income, hospital admissions and outpatient visits (coded using ICD10-codes), and prescribed drugs (coded using ATC codes) was collected. With regards to previous medical conditions and drug use, we compiled three sets of covariates, with increasing complexity: A) including 20 a priori defined co-morbid conditions only, B) including all ICD and ATC codes irrespective of time before RA, and C) including all ICD and ATC codes but with each ICD codes assessed in three different time periods before RA (<1 year, 1-4.9, and 5-10 years before RA). For B) and C), the ICD and ATC codes were further included at four levels of resolution (1 to 5-digit covariates). The outcome was defined as remaining on MTX as DMARD monotherapy, without any other type of DMARDS added or switched to, after 12 months.

We first assessed the association between all variables in covariate set C and the outcome in a univariate logistic regression. We then computed a logistic regression model for only gender and age as a baseline predictor, followed by L1-regularized logistic regression (“Lasso”) models based on the full covariate sets A, B, and C, respectively. Predictive capacity is estimated as average ROC AUC under 10-fold nested cross-validation

Results: A total of 6225 patients with new-onset RA starting MTX as DMARD monotherapy were included. After 1 year, 4497 (72%) remained on MTX DMARD monotherapy. In the association analysis, 254 of the 1449 covariates had a p-value < 0.05. The logistic regression model with age and sex as the only covariates had an average ROC AUC of 0.596. The Lasso models showed mean ROC AUC values of 0.634 for set A, 0.650 for set B and 0.646 for set C.

Conclusion: Prediction of persistence to MTX treatment is difficult and advanced analytical methods based on diagnostic codes and co-medication can potentially increase ROC AUC as compared to a baseline model. We are currently decomposing the main outcome into different subcomponents, e.g. early stopping due to side effects, to understand predictive potential more granularly and are exploring several machine learning methods such as random forest and deep learning to improve predictive performance.

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Baseline Characteristics of Methotrexate Inadequate Responder Patients with RA Who Achieved Low Disease Activity with Tofacitinib Monotherapy

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Session Information

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. ORAL Strategy (NCT02187055) was a Phase 3b/4, 1-year, double-blind, triple-dummy, active comparator-controlled trial in patients (pts) with moderate to severe RA who were inadequate responders (IR) to MTX.¹ In ORAL Strategy, tofacitinib + MTX showed non-inferiority to adalimumab + MTX, clinically important improvement was seen with tofacitinib monotherapy, although non-inferiority vs tofacitinib + MTX oradalimumab + MTX was not demonstrated. The current investigation was a post hoc analysis of baseline (BL) characteristics in patients from the tofacitinib 5 mg BID monotherapy group in ORAL Strategy.

Methods: The (binary) efficacy outcome measure was achievement of low disease activity (LDA) at Month (M)6. LDA was defined using three different response variables separately: Simplified Disease Activity Index (SDAI) ≤ 11, Clinical DAI (CDAI) ≤ 10, or Disease Activity Score in 28 joints, erythrocyte sedimentation rate (DAS28-4[ESR]) < 3.2.² BL characteristics by response/no response at M6 were summarized; BL covariates were evaluated for association with each efficacy outcome

Table 1. Descriptive statistics of select baseline characteristics in patients receiving tofacitinib 5 mg BID monotherapy in ORAL Strategy, by SDAI LDA status at Month 6

Parameter	Responders, SDAI ≤11 (N=167)	Non-responders, SDAI >11 (N=199)
Female, n (%)	131 (78.4)	168 (83.4)
Age, mean age (SD)	49.2 (12.4)	51.6 (12.0)
<65, n (%)	146 (87.4)	166 (83.4)
≥65, n (%)	21 (12.6)	34 (16.6)
Weight, mean kg (SD)	74.6 (18.7)	74.0 (19.3)
Race, n (%)		
White	127 (76.1)	147 (73.4)
Black	7 (4.2)	8 (4.0)
Asian	15 (9.0)	22 (11.1)
Other	22 (13.2)	17 (8.5)
CRP, mean mg/L (SD)	17.3 (21.1)	15.8 (17.1)
SJC, mean (SD)	10.1 (5.0)	12.1 (5.8)
TJC, mean (SD)	13.7 (6.1)	16.9 (6.4)
DAS28-4[ESR], mean score (SD)	6.3 (0.9)	6.7 (0.9)
SDAI, mean score (SD)	17.2 (12.4)	42.8 (12.8)
CDAI, mean score (SD)	35.3 (11.8)	41.2 (12.3)
HAQ-DI, mean score (SD)	1.4 (0.6)	1.7 (0.6)
SF-36 PCS, mean score (SD)	34.0 (7.5)	31.3 (7.2)
RF/ACPA, n (%)		
RF+/ACPA+	102 (61.1)	123 (61.8)
RF+/ACPA-	9 (5.4)	8 (4.0)
RF-/ACPA+	22 (13.2)	27 (13.6)
RF-/ACPA-	34 (20.4)	33 (16.6)

ACPA, anti-citrullinated protein antibody; BID, twice daily; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28-4[ESR], Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; LDA, low disease activity; PCS, physical component summary; RF, rheumatoid factor; SD, standard deviation; SDAI, Simplified Disease Activity Index; SF-36, Short Form-36 Health Survey; SJC, swollen joint count; TJC, tender joint count

using univariate logistic regression analysis without adjustment for other covariates. Category cut-offs of BL variables were defined by existing publications, clinical practice, or expert opinion provided to the study sponsor.

Results: Overall, 357 pts were included in the analysis for SDAI; Table 1 shows selected BL characteristics by SDAI LDA status at M6. From univariate analysis, more BL covariates showed significant association with M6 SDAI LDA (Table 2) than CDAI or DAS28-4(ESR) LDA. M6 CDAI LDA univariate results showed similar trends to SDAI LDA, but with fewer factors showing associations. The BL covariates significantly associated with any of the three LDA measures at M6 included age, gender, disease severity (eg, tender joint count [TJC], DAS28-4[ESR], SDAI, and rheumatoid factor/anti-citrullinated protein antibody status) and Short Form-36 Health Survey physical component summary (SF-36 PCS; Table 2).

Conclusion: This post hoc analysis suggests that for MTX-IR pts who use to facitinib monotherapy, age, gender, and BL disease severity (e.g. by TJC) and SF-36 PCS score may be associated with achieving LDA at M6. Multivariable analysis will be performed to further explore the associations; additional prospective research is warranted to confirm the findings.

1. Fleischmann R et al. *Lancet* 2017; 390: 457-68. : 2. Singh JA et al. *Arthritis Care Res* 2016; 68: 1-25.

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Sex Differences in the Achievement of Clinical Remission and Low MRI Synovitis Scores in Rheumatoid Arthritis

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Background/Purpose: Several prior studies have demonstrated poor clinical responses and reduced likelihood of achievement of remission among women with rheumatoid arthritis (RA). We aimed to determine if this observation represents a biologic effect versus a bias in the performance of clinical disease activity measures and their components. Specifically, we compared rates of treatment response in men and women based on different clinical composite and component scores as well as by MRI definitions of low activity in two large clinical trials.

Methods: This is an ancillary study of patients who completed the 52-week MRI sub-studies of two large clinical trials of golimumab. MRI of the dominant hand was performed and RAMRIS synovitis scores were determined at baseline, and at week 52. Standard clinical assessments and patient-reported measures were recorded at all time-points and composite scores were determined including the DAS28 (ESR), DAS28 (CRP), and CDAI. Remission was defined according to standard thresholds and using Boolean criteria for individual components. A low synovitis score on MRI was defined according to prior published thresholds (≤ 3). Multivariable logistic regression models assessed relationships between sex and achievement of remission or MRI low inflammatory activity by 52 weeks adjusting for age, race, study and treatment group.

Results: Men (N=58) and women (N=295) had similar DAS28 (CRP) and CDAI at baseline, but women had higher DAS28 (ESR) and higher patient global and tender joint counts (Table 1). Women were less likely to achieve remission by 52 weeks when remission was defined by the DAS28 (ESR) or CDAI (Table 2). However, there was not a significant difference in the achievement of remission between men and women for DAS28 (CRP). Among component scores, women were less likely to reach a low patient global score and a low ESR (<30 mm/hr) and tended to be less likely to reach a low tender joint count ($p=0.056$). Men and women were equally likely to achieve low CRP, a low swollen joint count, and a low evaluator global score. Men and women also achieved low MRI synovitis scores with similar frequency.

Table 2. Partial data from univariate logistic regression analyses of baseline characteristics by SDAI-LDA at 56 (≤11.0)

Baseline characteristic	Overall p value	Association with SDAI-LDA (reference level/unit)*	OR (95% CI)	P value
Gender	0.0119	Male (vs female)	2.10 (1.18, 3.74)	0.0119
Age category	0.9871	<65 (years) (vs ≥65 years)	1.01 (0.54, 1.88)	0.9871
Age	0.0282	Lower age (unit=1 year [†])	0.98 (0.96, 1.00)	0.0282
TJC count	<0.0001	4–8 (vs >12)	2.94 (1.00, 8.41)	0.0005
		9–12 (vs >12)	2.82 (1.70, 4.69)	<0.0001
TJC	<0.0001	Lower count (unit=1 [†])	0.92 (0.89, 0.96)	<0.0001
SF-36 PCS	0.0006	Higher score (unit=1 [†])	1.05 (1.02, 1.08)	0.0006

*Associated with higher proportion of responders.

[†]In Unit(s), 'x' is the increment/unit in the continuous variable corresponding to which the change in odds is observed.

Results for other parameters not shown: the following parameters were also assessed and will be provided in the final presentation: BMI, CRP, DAS28-4(ESR), geographic region, glucocorticoid dose, HAQ-DI, pain VAS, SF-36 MCS, smoking status, RA duration, race, weight, CDAI, SDAI, SJC, and RF/ACPA status.

ACPA, anti-citrullinated protein antibody; BMI, body-mass index; CDAI, Clinical Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; LDA, low disease activity; MCS, mental component summary; OR, odds ratio; PCS, physical component summary; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; SE, standard error; SF-36, Short Form-36 Health Survey; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

Conclusion: Although women were less likely to achieve DAS28 (ESR) and CDAI remission, they were equally likely to achieve a low CRP, swollen joint count, and low MRI synovitis. These findings suggest that there is not a biologic difference in treatment response in men and women, but that differences in the performance of subjective clinical measures of disease activity and expected sex differences in ESR may explain differences in observed response rates. Table 1: Baseline characteristics of the combined study populations from the combined population from GO-BEFORE, and GO-FORWARD studies.

	Men	Women	p
N	58	295	
Age (years)	51.3 (14.2)	48.9 (10.9)	0.14
Caucasian, N (%)	36 (62%)	181 (61%)	0.92
BMI (kg/m ²)	26.3 (5.5)	26.2 (5.6)	0.93
GO-BEFORE, %	55%	56%	0.86
Disease Activity			
DAS28 (ESR)	5.70 (1.36)	6.13 (1.10)	0.009
CDAI	32 (15.2)	35 (13.0)	0.16
DAS28(CRP)	5.26 (1.24)	5.50 (1.02)	0.11
Clinical Components			
ESR mm/hr	40.2 (27.9)	43.8 (27.8)	0.37
CRP mg/dL	2.21 (2.52)	1.82 (2.38)	0.26
Tender Joint Count	10 (5, 17)	12 (7, 19)	0.07
Swollen Joint Count	8 (5, 11)	8 (5, 12)	0.90
Patient Global	5.3 (2.9, 7.5)	6.5 (4.8, 7.9)	0.01
Evaluator Global	5.7 (4.3, 7)	6.2 (4.9, 7.4)	0.25

*continuous variables presented as mean (SD) or as median (IQR) for skewed data.

Table 2: Logistic regression evaluating the odds of achievement of remission or low disease activity at 52 weeks by different composite and component clinical and MRI measures of disease activity.

	Remission 52 Weeks OR for Women (95% CI)	P value
Clinical Composite Scores		
DAS28 <2.6	0.39 (0.21, 0.72)	0.003
CDAI <2.8	0.50 (0.26, 0.94)	0.03
DAS28(CRP) <2.6	0.71 (0.39, 1.28)	0.26
Clinical Components		
ESR <30 mm/sec	0.40 (0.21, 0.77)	0.006
CRP <1.0 mg/dL	1.31 (0.66, 2.60)	0.44
Tender Joint Count ≤1	0.57 (0.32, 1.01)	0.056

Table . (Cont'd)

	Remission 52 Weeks OR for Women (95% CI)	P value
Swollen Joint Count ≤ 1	0.96 (0.54, 1.72)	0.90
Patient Global ≤ 10	0.37 (0.20, 0.68)	0.001
Evaluator Global ≤ 10	0.81 (0.45, 1.45)	0.48
MRI Measures (N=353)		
Synovitis ≤ 3	0.93 (0.52, 1.67)	0.82

* adjusted for age, white v. non-white race, study, and treatment group.

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Abstract Number: 1497

PRISM-RA: A Personalized Medicine Test That Accurately Predicts Rheumatoid Arthritis Patients Who Will Not Respond Adequately to Tumor Necrosis Factor Inhibitors

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Session Information

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

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Background/Purpose: Rheumatoid arthritis (RA) is a complex disease affecting about 1.3 M adults in the US. The patient population is very heterogeneous; no single drug mechanism achieves treatment targets in the majority of patients. Tumor necrosis factor inhibitors (anti-TNFs) are the first line therapy in >90% of biologic naïve patients, although less than half of patients achieve treatment targets on them. This is despite the fact that in the past decade therapies with alternative mechanisms have been approved. The case for a test to predict which therapy a patient will respond to is overwhelming because of the disease heterogeneity, and because the approved therapies for RA are molecularly targeted. Scipher is developing PRISM-RA to accurately predict from a baseline blood sample, using a gene expression profile, which patients will not reach their treatment target on anti-TNFs. Identified non-responders will be offered alternative approved therapies much earlier in their treatment course than currently in clinical practice. This will lead to better patient outcomes and significant savings of healthcare costs.

Methods: The test user requirements were developed based on in depth discussions with payers and rheumatologists. The overwhelming consensus is that PRISM-RA must identify non-responders (NRs) with >90% accuracy and with sufficient specificity to identify the majority of NRs. Response is defined as achieving ACR-defined treatment targets, equating to a minimum of ACR50 improvement in disease activity after 3 months of therapy. Independent patient cohorts treated with anti-TNFs with associated baseline gene expression data were analyzed to train a classifier to predict response.

Results: In a 50 subject training cohort PRISM-RA achieved >90% accuracy (NPV) with the required specificity. PRISM-RA passed proof of concept (POC) by exceeding the pre-specified user requirements in a blinded fashion across an independent cohort of 39 subjects. Scipher is validating PRISM-RA in an ongoing observational study of >150 patients; the results of this confirmatory study will be presented in the near future. Thereafter, Scipher will conduct an appropriately powered, double-blinded prospective interventional trial to confirm both clinical performance and utility of PRISM-RA. PRISM-RA will be offered commercially as CLIA certified laboratory developed test (LDT). During the prospective trial, data will be collected to train classifiers to predict responders across all classes of approved targeted therapies for RA

Conclusion: PRISM-RA has achieved POC and will provide rheumatologists with a scientific rationale for selecting therapies based on a biologic naïve patient's molecular data before initiating treatment, meaning that more patients will achieve their treatment targets than is the case today. By de-selecting non-responders the overall rate of achieving treatment targets on anti-TNFs will increase significantly. Ultimately, PRISM-RA will provide response predictions for all approved targeted therapies for RA, providing rheumatologists with a validated scientific rationale for the selection of the right therapeutic agent for an individual patient.

Disclosure: K. Johnson, Scipher Medicine, 1, 3; N. Schoenbrunner, Scipher medicine, 1, 3; D. Ghiassian, Scipher Medicine, 1, 3.

Serum MMP-3 More Than 155ng/ML at Baseline Predicts One-Year Radiographic Progression in Patients with Rheumatoid Arthritis

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Background/Purpose: Core disease activity indicators of rheumatoid arthritis (RA) have been found to be limited in predicting joint destruction progression. We previously reported that continuously elevated serum matrix metalloproteinase (MMP)-3 predicted one-year radiographic progression (RP) in RA patients. Here we aimed to develop a cutoff value of serum MMP-3 for clinical practice.

Methods: Consecutive patients with active RA (DAS28-CRP more than 2.6) were retrospectively recruited and divided into study cohort (naïve patients without previous DMARDs and corticosteroids treatment, $n=102$) and confirmatory cohort (others, $n=140$). Clinical data were collected at baseline and visits at month 1, 3, 6, and 12, and a change in modified total Sharp score more than 0.5 from the 12th month to baseline was defined as RP.

Results: RA patients in study cohort had shorter disease duration but higher disease activity and HAQ-DI at baseline than that of patients in confirmatory cohort. However, there were significantly higher rate of remission and lower rate of RP in study cohort than that in confirmatory cohort (Table 1). In study cohort, patients in progressive group had higher serum MMP-3 at baseline than that in non-progressive group ($P=0.014$), whereas there was no different of CRP, ESR, RF, ACPA and DAS28-CRP between these two group (all P more than 0.05). ROC curve analysis showed that the area under the curve (AUC) of serum MMP-3 in predicting one-year RP was 0.671 with the cutoff value of 155 ng/ml according to Youden index, whereas there was no significance of CRP, ESR, RF and ACPA (AUC: 0.491~0.570, all P more than 0.05). Univariate and multivariate logistic regression showed that baseline serum MMP-3 (more than 155 ng/ml) was a significant predictor of one-year RP after adjusted for sex, age, disease duration, baseline DAS28-CRP and HAQ-DI (Table 2). This cutoff value of serumMMP-3 was validated by the confirmatory cohort (Table 2).

Table 1 Baseline characteristics and outcome of RA patients in study and confirmatory cohorts

Characteristics	Study cohort ($n=102$)	Confirmatory cohort ($n=140$)	P
Baseline			
Age, years	50 (40-60)	49 (36-58)	0.125
Female, n (%)	84 (82.4)	113 (80.7)	0.746
Disease duration, months	24 (9-84)	47 (12-108)	0.014
ESR, mm/h	54.5 (37.5-75.0)	42.0 (23.0-68.0)	0.005
CRP, mg/L	17.7 (7.0-40.0)	12.0 (5.0-32.0)	0.107
DAS28-CRP	5.1 (4.2-5.9)	4.6 (3.5-5.5)	0.004
Positive RF, n (%)	82 (80.4)	102 (72.9)	0.175
Positive ACPA, n (%)	81 (79.4)	105 (75.0)	0.422
Serum MMP-3, ng/ml	213 (106-455)	185 (92-368)	0.147
HAQ-DI	1.00 (0-2.00)	0.13 (0-1.00)	<0.001
Bony erosions, n (%)	82 (80.4)	113 (80.7)	0.950
Total Sharp score	9 (3-20)	11 (2-32)	0.330
Joint narrow scores	4 (1-10)	5 (1-16)	0.534
Erosion score	4 (1-10)	6 (1-16)	0.267
At the 12th month			
Remission, n (%)	63 (61.8)	60 (42.9)	0.004
HAQ-DI	0 (0-0.13)	0 (0-0.50)	0.173
Radiographic progression, n (%)	22 (21.6)	52 (37.1)	0.009

Table 2 Performance of baseline laboratory indicators as predictors for one-year radiographic progression

Indicators	Cutoff value [△]	Study cohort (n=102)				Confirmatory cohort (n=140)			
		PPV	NPV	OR (95%CI)	P	PPV	NPV	OR (95%CI)	P
CRP	>5mg/L	32%	80%	1.125 (0.334–3.788) #	0.849*	36%	61%	0.832 (0.396–1.967) #	0.760*
ESR	Female: >20mm/h Male: >15mm/h	22%	84%	1.400 (0.155–12.640) *	0.764*	36%	57%	0.741 (0.319–1.720) *	0.485*
RF	>20IU/ml	26%	95%	0.541 (0.024–51.894) *	0.076*	40%	71%	1.650 (0.738–3.690) *	0.223*
ACPA	>18IU/ml	22%	81%	1.214 (0.363–4.066) *	0.753*	38%	66%	1.179 (0.529–2.629) #	0.686*
MMP-3 (1)	Female: >60ng/ml Male: >120ng/ml	24%	100%	NA	NA	42%	86%	4.498 (1.261–16.039) *	0.020
MMP-3 (2)	>155ng/ml	32%	97%	17.182 (1.203–183.985)* 14.726 (1.863–116.437) [‡]	0.007* 0.011 [‡]	49%	81%	4.200 (1.875–9.407) [‡]	<0.001 [‡]

△ The cutoff values of CRP, ESR, RF, ACPA and MMP-3 (1) were determined according to the upper limit of normal range. The cutoff value of MMP-3 (2) was determined according to the Youden index in ROC curve analysis. *OR of predictors was determined by univariate logistic regression according to the cutoff value, # OR of MMP-3 was determined by multivariate logistic regression adjusted for sex, age, disease duration, baseline DAS28-CRP and HAQ-DI.

Conclusion:

Elevated serum MMP-3 with a cutoff value of 155 ng/ml is an applicable predictor for one-year RP in RA. : Fundings: This work was supported by National Natural Science Foundation of China (81471597,81671612), Guangdong Natural Science Foundation (2017A030313576,2017A030310236), Guangdong Medical Scientific Research Foundation (A2017109).

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Abstract Number: 1499

Elevated Serum MMP-3 in Remission Predicts Relapse in Patients with Rheumatoid Arthritis

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Session Information

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

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Background/Purpose: Our previous study showed continuously elevated serum matrix metalloproteinase (MMP)-3 predicted one-year radiographic progression (RP) in RA and the cutoff value at 6th month was 161 ng/ml (*ArthritisRes Ther.* 2015). Here we aimed to explore whether elevated serum MMP-3 predicted relapsed in RA.

Methods: RA patients with moderate to high disease activity (DAS28-CRP>3.2) were recruited. Clinical data were collected and serum MMP-3 was detected by ELISA at baseline and each visit (1st, 3rd, 6th and 12th months). The cutoff value of MMP-3 at 6th month was 161 ng/ml. RP was defined as modified total Sharp score (mTSS) changed more than 0.5 from baseline to the 12th month.

Results: There were 214 RA patients finished one-year follow-up and 64 (29.9%) showed RP (Table 1). There were 59 (27.6%), 102 (47.7%), 112 (52.3%) and 106 (49.5%) patients reached remission at each visit, respectively. Among 112 patients reached remission at 6th month, there were 30% relapsed at 12th month. Among 102 active patients at 6th month, there were 27% achieved remission at 12th month. Patients who relapsed from 6th to 12th month had significant higher one-year RP than those sustained remission (15.4 %vs. 35.3%, $P=0.018$), accompanied with higher HAQ-DI, PtGA, PrGA and pain VAS at 12th month (all $P<0.05$). Patients who relapsed from 6th to 12th month had significantly higher CRP [3.1 (3.0–7.0)mg/L vs.3.0 (3.0–3.1)mg/L], DAS28 [2.0 (1.6–2.3) vs. 1.6 (1.5–2.0)] and the ratio of elevated MMP-3 [19 (55.9%) vs. 26 (33.3%); all $P<0.05$] at 6th month than those sustained remission. Univariate and multivariate logistic regression

showed that elevated serum MMP-3 was a significant predictor of one-year RP after adjustment of sex, age and disease duration (adjusted OR 2.599, 95% CI 1.087~6.216, $P=0.032$).

Conclusion:

Elevated serum MMP-3 at 6th month in remission RA patients may be a useful predictor for relapsed at one-year. :

Fundings: This work was supported by National Natural Science Foundation of China (81471597, 81671612), Guangdong Natural Science Foundation (2017A030313576,2017A030310236),Guangdong Medical Scientific Research Foundation (A2017093, A2017109).

Figure1 Cumulative probability of change in mTSS among patients who sustained remission or relapse from 6th to 12th month.

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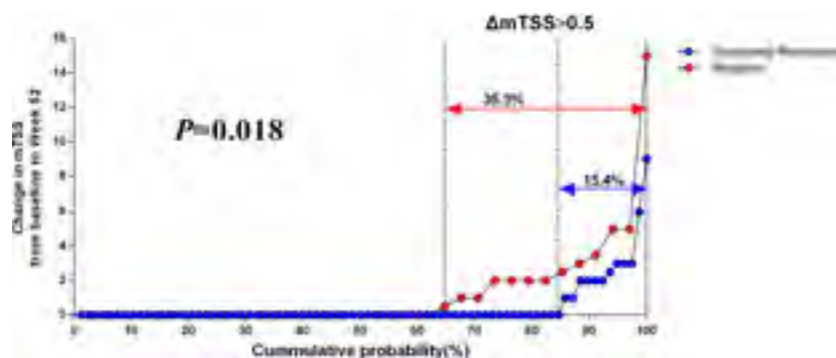


Table 1 Baseline characteristics of 214 RA patients

characteristics	All patients (n=214)
Age, years	49 (38-58)
Female, n (%)	174 (81.3)
Disease duration, months	33 (12-84)
28TJC	7 (4-13)
28SJC	5 (2-8)
PtGA	5 (4-7)
PrGA	5 (4-7)
Pain VAS	5 (4-6)
ESR, mm/h	52.5 (32.0-75.3)
CRP, mg/L	16.9 (7.4-39.7)
DAS28-CRP	4.9 (4.1-5.8)
Positive RF, n (%)	164 (76.6)
Positive ACPA, n (%)	162 (75.7)
HAQ-DI	0.8 (0.3-1.4)
Bony erosions, n (%)	132 (61.7)
Total Sharp score	10 (2-27)
Joint narrow score	4 (1-13)
Erosion score	5 (1-14)
Serum MMP-3, ng/ml	212.5 (108.9-433.8)

The Multi-Biomarker Disease Activity Score Tracks Response to Rituximab Treatment in Rheumatoid Arthritis Patients

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Session Information

Session Date: Monday, October 22, 2018

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Background/Purpose: A multi-biomarker disease activity (MBDA) score was developed to objectively measure disease activity for patients with rheumatoid arthritis (RA).¹ The MBDA score is calculated by an algorithm using concentrations of 12 serum biomarkers and has been shown to track response to treatment with several DMARDs.²⁻⁴ We aimed to assess the ability of the MBDA score to track response to rituximab treatment in RA patients.

Methods: Data were used from 3 cohorts (1 in the United Kingdom, 2 in the Netherlands) of RA patients treated with rituximab 1000 mg and methylprednisolone 100 mg at days 1 and 15. The MBDA score was assessed in serum samples at baseline (BL, n=57) and at 6 months (n=46). Wilcoxon signed-rank test was used to statistically compare the medians at BL and 6 months. Spearman's rank correlation (r) was used to analyse relationships between BL and 6 month values and change (Δ) from BL to 6 months for MBDA score vs. the following endpoints: DAS28-ESR, DAS28-hsCRP, ESR, hsCRP and Health Assessment Questionnaire (HAQ). Logistic regression analysis with adjustment for age, sex, smoking, ACPA and RF was used to assess the association between Δ MBDA score and non-response, using EULAR response categories at 6 months. $p < 0.05$ was considered statistically significant.

Results: At baseline the median MBDA score and DAS28-ESR were 56.0 (range 16.0-84.0) and 6.2 (range 2.5-8.4), respectively. The improvement in both scores after 6 months was statistically significant (both $p < 0.01$). MBDA score correlated with DAS28-ESR, DAS28-hsCRP, ESR and hsCRP at BL and 6 months, respectively (Table 1). Δ MBDA score from BL to 6 months correlated with changes in these measures. Spearman's correlation for Δ MBDA score vs. Δ DAS28-ESR was $r=0.60$, $p < 0.01$ (Table 1). Δ MBDA score also correlated with EULAR non-response (n=38), with adjusted

Table 1: Correlations between the MBDA score and disease activity measures

Measure	Timepoint or period for comparison with MBDA score	Number of available patients	Spearman's ρ	p-value
DAS28-ESR	BL	46	0.52	<0.01*
	6M	42	0.49	<0.01*
	Δ	38	0.60	<0.01*
ESR	BL	44	0.75	<0.01*
	6M	42	0.66	<0.01*
	Δ	41	0.48	<0.01*
DAS28-hsCRP ^(b)	BL	25	0.40	0.05*
	6M	24	0.46	0.03*
	Δ	23	0.46	0.02*
hsCRP ^(b)	BL	25	0.60	<0.01*
	6M	24	0.60	<0.01*
	Δ	23	0.71	<0.01*
HAQ	BL	39	0.02	0.91
	6M	41	-0.03	0.86
	Δ	34	0.19	0.28

MBDA: multi-biomarker disease activity; DAS28: disease activity score using 28 joints; ESR: erythrocyte sedimentation rate; hsCRP: high-sensitivity C-reactive protein; HAQ: Health Assessment Questionnaire; BL: MBDA score and measure at baseline; 6M: MBDA score and measure at 6 months; Δ : changes in MBDA score and measure; BL: from baseline at 6 months; (b) United Kingdom cohort only
* Statistically significant, $p < 0.05$

OR=0.91 (95% CI=0.84-0.99, p=0.02), which corresponds to an OR of 0.39 for every 10-unit decrease in MBDA score. Correlations were not observed between MBDA scores or Δ MBDA score and the corresponding HAQ measurements (Table 1).

Conclusion: We have shown, for the first time, that the MBDA score tracked disease activity in RA patients treated with rituximab and that change in MBDA score reflected the degree of treatment response.

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Assessment of Treatment Response Using the Multi-Biomarker Disease Activity Score in Rheumatoid Arthritis Patients Initiating Methotrexate

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SESSION INFORMATION

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Background/Purpose: The Multi-Biomarker Disease Activity (MBDA) score was developed to provide an objective measure of rheumatoid arthritis (RA) disease activity. Demonstrating moderate correlations with conventional measures of RA disease activity, the capacity of the MBDA to predict treatment response may vary among available disease-modifying agents. The performance of the MBDA in patients initiating methotrexate (MTX), a cornerstone therapy in RA, has not been evaluated to date.

Methods: We conducted a secondary analysis of a 16-week, open-label study of RA patients initiating MTX (15mg/wk) with dose escalation to 20mg/wk for those failing to achieve disease remission (DAS28 <2.6) at 8 weeks. The primary study outcome was the proportion achieving ACR50 response at week 16. MBDA scores were measured using banked serum collected at baseline (N=130) and week 16 (N=95). The association of baseline MBDA with treatment response was assessed using multivariable regression models adjusting for age, sex, race, smoking status, and rheumatoid factor (RF) concentration. Convergent validity and responsiveness were determined by calculating correlations of the MBDA with DAS28-ESR, ESR, patient global assessment (PtGA), Health Assessment Questionnaire (HAQ), as well as correlations of MBDA change with changes in alternative disease activity measures and through the calculation of standardized response means (SRM).

Results: Patients had a mean age of 54 yrs and were predominantly female (75%), seropositive (73% for RF, 75% for anti-CCP), and had high baseline disease activity (DAS28-ESR of 5.3, SD 1.2). Mean baseline MBDA score was 48.3 (SD 17.2) with 12%, 28%, and 61% categorized as low, moderate, and high disease activity by MBDA. After 16 weeks, the MBDA improved by a mean of 9.4 (SD 14.5) and DAS28-ESR improved by a mean of 1.9 (SD 1.5). Patients achieving an ACR50 response demonstrated greater reductions in MBDA than those failing to achieve an ACR50 response ($p=0.01$). However, baseline MBDA scores (OR 1.01, 95% CI 0.99, 1.04) and categories (moderate: OR 1.55, 95% CI 0.45-14.20; high: OR 2.55, 95% CI 0.50-12.98) were not predictive of response. Higher baseline MBDA scores were associated with greater improvement in DAS28-ESR ($p=0.01$), as were baseline DAS28-ESR values ($p<0.001$). The MBDA demonstrated moderate correlations with DAS28-ESR and ESR, but weaker correlations with the HAQ and PtGA (Table 1). Treatment responsiveness was greater for DAS28-ESR (SRM -1.32) than MBDA (SRM -0.65).

Conclusion: In this 16-week open-label study of MTX in RA patients, baseline MBDA was associated with greater reductions in DAS28-ESR but was not a robust predictor of ACR50 response. Although demonstrating moderate convergent validity with standard disease activity assessments, the MBDA yielded lower responsiveness than the DAS28-ESR in the context of MTX treatment.

Table 1 Correlation (r) of the MBDA Score with disease activity measures and functional status in RA patients initiating MTX

	DAS28-ESR		ESR		PtGA		HAQ	
	r	p-value	r	p-value	r	p-value	r	p-value
MBDA	0.44	<0.001	0.59	<0.001	0.23	0.008	0.34	<0.001
Baseline	0.30	0.004	0.51	<0.001	0.19	0.07	0.23	0.03
Week 16								
Δ MBDA	Δ DAS28-ESR	<0.001	Δ ESR	<0.001	Δ PtGA	0.02	Δ HAQ	0.02
	0.42		0.46		0.23		0.25	

Abbreviations: MBDA, Multi-Biomarker Disease Activity Score; ESR, erythrocyte sedimentation rate; PtGA, patient global assessment; HAQ, Health Assessment Questionnaire

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Predicting Response to Methotrexate Therapy in New-Onset RA: No Value of Adding Protein Biomarkers to Clinical Predictors

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SESSION INFORMATION

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Background/Purpose: We previously identified higher disease activity score assessing 28 joints (DAS28) at baseline, current smoking and no alcohol consumption as clinical predictors for inadequate response (IR) to a methotrexate (MTX) strategy.¹ In addition, we showed the potential of protein biomarkers to improve the prediction of clinical response in patients likely to show IR to MTX.² In this analysis, we aimed to validate predictive protein biomarkers with additive value to the clinical predictors mentioned above in predicting IR to MTX.

Methods: Data was used from patients initiating MTX therapy in the U-Act-Early trial for developing the prediction model.³ If remission (DAS28) <2.6 with ≤4 swollen joints for ≥24 weeks) was not achieved, hydroxychloroquine was added and thereafter replaced by tocilizumab if remission still was not achieved. Serum was collected at baseline and analyzed using multi-analyte (n=85) profiling; relevant proteins were identified using partial least square discriminant analyses. Data of patients treated with MTX plus glucocorticoid (GC) in the Rotterdam Early Arthritis Cohort trial were used for validation.⁴ These patients switched to MTX plus etanercept, if remission (DAS44 <2.4) was not achieved. IR to MTX was defined for both studies as the need of adding abiological DMARD within the first year to MTX, including additional conventional synthetic disease modifying anti-rheumatic drug (csDMARD) or GC therapy (here designated as 'MTX+').

Results: None of the potentially relevant proteins (n=7) in the development sample were found to be significant (IR vs. no IR) in the validation sample. Although not statistically significant, the best performing biomarker was vascular cell adhesion protein 1 (VCAM-1, odds ratio (OR) 1.36, 95%-confidence interval (CI), 0.84-2.32; p=0.19), and was further investigated. In the development sample, the area under the receiver operator characteristics curve (AUROC) of the combined model (*i.e.* clinical predictors plus VCAM-1) was 0.80 (95%-CI 0.71-0.88); no significantly improved discriminative ability compared to clinical model (AUROC 0.75, 95%-CI 0.65-0.84; p=0.051). When applying the linear predictor to the validation sample, an AUROC of 0.67 (95%-CI 0.55-0.80) was found for the combined model: neither significantly different from clinical model (AUROC 0.68, 95%-CI 0.55-0.80).

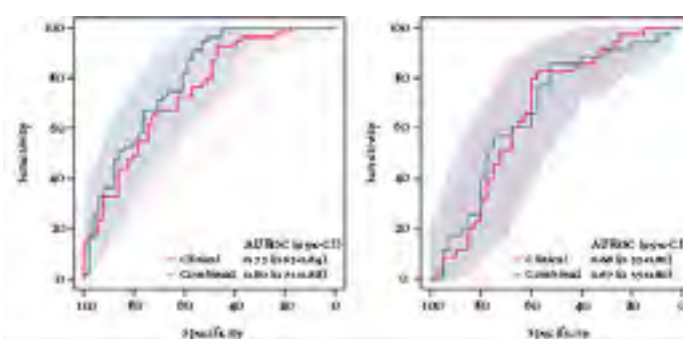


Fig. 1: ROC curves of predicting IR to MTX therapy in the development (left) and validation (right). The clinical model contains baseline DAS28, current smoking and alcohol consumption as predictors; the combined model contains the predictors of the clinical model plus VCAM-1. AUROC = area under the receiver operator characteristics curve, CI = confidence interval, DAS28 = disease activity score assessing 28 joints, IR = inadequate response, MTX = methotrexate, ROC = receiver operator characteristics, VCAM-1 = vascular cell adhesion protein 1.

Conclusion: No protein biomarkers with additive value to clinical predictors for predicting IR to 'MTX+' in new-onset RA could be externally validated. The relatively easily obtainable clinical predictors still remain the most accurate factors to predict the need for adding a biologic DMARD to the initial MTX-based treatment strategy.

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Abstract Number: 1503

Rheumatoid Factor Positivity Is Related with Higher Discontinuation Rate of Tumor Necrosis Factor Inhibitor Therapy Due to Adverse Event and Insufficient Response in Rheumatoid Arthritis: A Multiple Imputation Method for COX Proportional Hazard Model

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Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

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Background/Purpose: Discontinuation of tumor necrosis factor inhibitor (TNFi) therapy in rheumatoid arthritis (RA) is attributable to various reasons. Above all, adverse event (AE) and insufficient response (IR) are principal and crucial. In this study, we investigate association between covariates including rheumatoid factor (RF) positivity and discontinuation of TNFi therapy due to AE and IR using COX proportional hazard analysis. Additionally, multiple imputation analysis for COX proportional hazard regression was performed. This approach is becoming increasingly popular for handling missing data. Excluding participants who have one or more missing values, a so-called complete case analysis can introduce selection bias as participants who have complete data may be different to those with missing data.

Methods: This study included patients enrolled in the Tsurumi Biologic Communication Registry which comprises Nagoya University and 18 affiliated institutions in Japan. We assessed relationships between individual characteristic components and patient outcomes using multiple imputation method for COX proportional hazard model. All analyses were conducted in R version 3.5.0.

Results: There was a higher crude discontinuation rate in RF positive patients than in RF negative patients using Kaplan-Meier survival curve and log-rank test ($P < 0.05$; Figure). The difference was significant in COX proportional hazard analysis adjusting for baseline characteristics including age, sex, stage, das28 using erythrocyte sedimentation rate at baseline, methotrexate use, and prednisolone use ($n = 643$, HR = 1.47, $P < 0.05$; Table 1), and multiple imputation method for COX proportional hazard model ($n = 2352$, HR = 1.31, $P < 0.05$; Table 2).

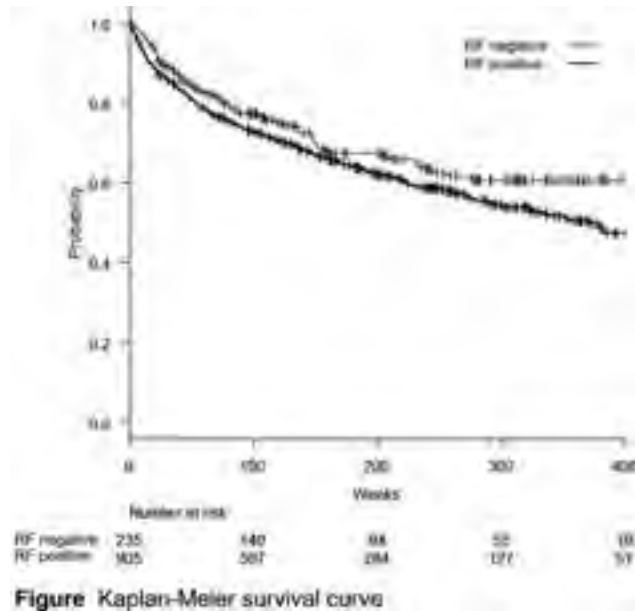
Conclusion: Using multiple imputation method for COX proportional hazard regression, we demonstrated that RF positivity is related with higher discontinuation rate of TNFi therapy due to AE and IR on bio-naïve RA patients.

Table 1 Complete-case analysis ($n = 643$)

	Hazard ratio	Lower 95%CI	Upper 95%CI	p-value
RF positivity	1.47	1.05	2.04	$p < 0.05$
Age	1	0.99	1.01	0.92
Sex	0.95	0.7	1.31	0.78
Stage	1	0.99	1.01	0.54
DAS28ESR	1.15	1.04	1.28	$p < 0.05$
MTX use	1.22	0.65	1.7	0.26
PSL use	1.4	1.07	1.83	$p < 0.05$

Table 2 Multiple imputation analysis (n = 2352)

	Hazard ratio	Lower 95%CI	Upper 95%CI	p value
RF positivity	1.31	1.02	1.66	p < 0.05
Age	1	0.99	1.01	0.06
Sex	0.89	0.74	1.08	0.27
Stage	1	0.99	1.01	0.94
DAS28ESR	1.1	1.02	1.19	p < 0.05
MTX use	1.16	0.95	1.47	0.12
PSL use	1.41	1.18	1.68	p < 0.05



Disclosure: Y. Ogawa, None; N. Takahashi, None; T. Kojima, None; N. Ishiguro, None.

Abstract Number: 1504

Utility of Serial ACPA Measurements in Rheumatoid Arthritis: Results of a Prospective Cohort Study

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Background/Purpose: Anti-citrullinated peptide antibody (ACPA) and rheumatoid factor (RF) define “seropositive” rheumatoid arthritis (RA). Both predict disease course, development of extra-articular features and treatment outcomes. ACPA is more specific than RF for the diagnosis of RA. There is little evidence to determine if repeat testing of ACPA and RF is required. We investigated the incidence of seroconversion to ACPA after commencement of treat-to-target therapy in patients with early RA.

Methods: DMARD-naïve patients presenting between September 1998 - July 2017 with RA according to the 1987 ACR criteria, with a disease duration of <12 months were enrolled. All patients received combination triple DMARD therapy (methotrexate, sulfasalazine and hydroxychloroquine) according to a treat-to-target strategy. Adjustments to treatment by predefined protocol were contingent on failing to reach a target DAS28-ESR score of <2.6. ACPA and RF were recorded at baseline and at least 6 monthly. Before 2011, ACPA was analysed using ELISA and then by immunoassay. Before 2011, RF was measured by latex nephelometry and then by turbidimetry with excellent correlation between methods. Normal ranges were defined for ACPA as <6 units/mL and for RF <14 IU/mL. Differences between seroconverters and non-seroconverters were assessed via Mann Whitney test (for continuous variables) and Fisher Exact Test (for categorical variables).

Results: 368 patients had a total of 2889 ACPA and 4170 RF measurements. Median follow up was 272 (IQR 53-467) weeks. Median disease duration at diagnosis was 20.4 weeks (IQR 11-26). At 1 year, 44% of patients were in DAS28 remission and 10% progressed to require a biologic DMARD during study follow up. At baseline, 154 (41.8%) patients were seronegative for ACPA, 10 (6.5%) of whom seroconverted at some time during follow up. Four (2.6%) patients had persistent seroconversion. Of the 10 ACPA seroconverters, 9 patients were RF positive at baseline. Baseline RF titre predicted seroconversion to ACPA (mean 10IU/ml vs 55IU/ml in non-converters, $p < 0.001$). Of the 107 patients who were RF negative and ACPA negative at baseline, ACPA became positive at 10 IU/ml in a single patient who subsequently reverted to negative. Median time to seroconversion for ACPA was 29 months (range 3-192). No patient seroconverted from negative to positive for both RF and ACPA.

Conclusion: Persistent seroconversion of ACPA from negative to positive after diagnosis in patients with RA is uncommon. ACPA and RF double negative patients are highly unlikely to ever develop ACPA positivity with a risk of < 1%. It is therefore unlikely to be helpful or cost effective to perform serial ACPA measurements in patients with seronegative RA.

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Abstract Number: 1505

The Point-of-Care Ichroma Anti-CCP Test Showed a Competitive Measurement Accuracy, in Comparison to the Conventional Automated Tests

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Anti-cyclic citrullinated peptide (CCP) antibody test is a very important test for the diagnosis of rheumatoid arthritis (RA), but one of the disadvantages of the existing enzyme-linked immunosorbent assay (ELISA) is that its method is labor-intensive and time-consuming. The aim of this study was to assess the measurement characteristics of a rapid point-of-care (POC) anti-CCP test compared to the conventional anti-CCP test.

Methods: We used the POC ichroma anti-CCP test of Boditech Med and two anti-CCP assays (Elecys[®] Anti-CCP by Roche Diagnostics and the FCCP600 of Axis-Shield Diagnostics) and rheumatoid factor (RF) by latex agglutination test (LAT) respectively.

Results: A total of 430 subjects (199 RA patients, 112 non-RA patients and 119 healthy controls) were enrolled in this study. For the RA patients, the anti-CCP test were positive for 136 (68.3%), 155 (77.8%), and 158 patients (79.3%) with the ichroma anti-CCP, the Elecys anti-CCP, and FCCP600, respectively. For the non-RA patients, the anti-CCP test were positive for 5 (4.5%), 7 (6.3%), and 5 patients (4.5%) with the ichroma anti-CCP, the Elecys anti-CCP, and FCCP600, respectively. The overall agreement between the ichroma system and other tests was 91.6% (Elecys) and 88.8% (FCCP) and 76.7% for RF. The difference between three areas under the ROC curves, including the POCT test, was not statistically significant (ichroma, 0.903(0.874-0.933); Elecys, 0.909 (0.877-0.941); and FCCP600, 0.892 (0.858-0.926)). There was, however, a significant difference from RF (0.770 (CI 0.721-0.819)).

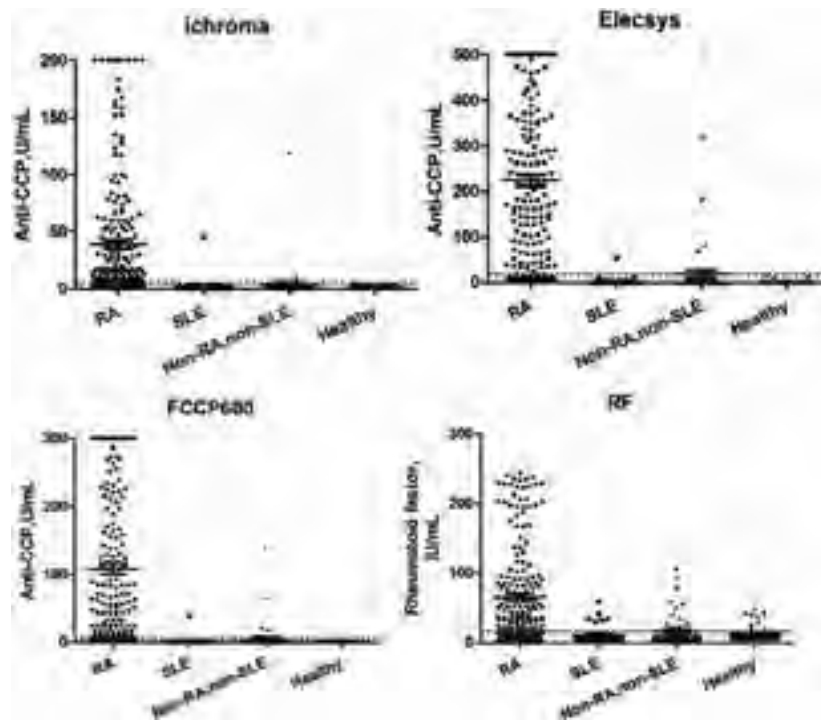


Fig. Scatter plots of anti-CCP level according to the concentrations of anti-CCP antibodies and rheumatoid factor for different groups of patients

Conclusion: The POC ichroma anti-CCP test is not only a quick and convenient test, but also provides a comparable and reliable diagnostic performance of conventional methods.

Table. Diagnostic performance of the three anti-CCP assays and one rheumatoid factor test for diagnosis of RA

	Ichröma	Elecys	FCCP600	RF
Manufacturer's cut-off	50 U/mL	17 U/mL	5 U/mL	13 U/mL
Sensitivity (%) (95% CI)	88.1 (81.4-94.7)	77.9 (71.5-83.5)	78.9 (72.6-84.3)	66.8 (59.8-73.3)
Specificity (%) (95% CI)	97.8 (95.0-99.3)	97.4 (94.4-99.0)	97.8 (95.0-99.3)	86.1 (81.0-90.3)
Adjusted PPV (%)	89.2	73.9	42.3	8.9
Adjusted NPV (%)	99.3	99.5	99.6	99.2
Cut-off based on ROC curves	1.2 U/mL	5.3 U/mL	4.8 U/mL	12 U/mL
Sensitivity (%) (95% CI)	76.9 (70.4-82.8)	82.4 (78.1-86.7)	79.4 (73.1-84.3)	71.4 (64.5-77.5)
Specificity (%) (95% CI)	94.4 (90.6-97.6)	96.5 (93.2-98.5)	97.8 (95.0-99.3)	84.0 (78.6-88.3)
Adjusted PPV (%)	21.9	32.7	42.4	8.4
Adjusted NPV (%)	99.5	98.1	99.8	99.1

Abbreviation: PPV, positive predictive value; NPV, negative predictive value

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Synovial Tissue Histopathology Findings in EARLY RA. Is It Usefull? Analysis of the Belgian CAP48 Cohort

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: The development of ultrasound (US) guided synovial biopsy will enable synovial tissue collection from small joints and will facilitate histopathological studies, thus improving the understanding of early rheumatoid arthritis (ERA). The CAP48 cohort is an original multicentre prospective observational study of ERA patients (pts) up to 50 years old supported by a charity program of the Belgian French speaking radio-television (RTBF). The objectives of this cohort are to observe if a tight control favours remission at 6 months and to define synovial markers for disease severity and response to therapy.

Methods: ERA pts fulfilling the ACR/EULAR 2010 criteria and naive to DMARDs therapy were recruited. Synovial biopsies before treatment were obtained using an US guided needle biopsy (US-NB) of the small joints or mini arthroscopy of the knee and used for blinded tissue pathology description. ERA disease activity measures including DAS28CRP were evaluated every 3 months and treatment was adapted by the treating physician. Tissues were assessed for quality. Pts were classified according 3 types of synovial histopathology findings: pts whose synovial tissue showing mostly lymphoid (CD3+ and CD20+) infiltrates, myeloid (CD68+) infiltrates and a group with low inflammation, combined or not with a fibroid aspect of the stroma, clustered, respectively in Lymphoid, Myeloid and Pauci-Immune groups.

Results: A synovial biopsy was performed in 37 pts. Baseline characteristics of the cohort and different histologic pattern groups are summarized in Table.

	All patients n=37	'Lymphoid' group n=18	'Myeloid' group n=6	'Pauci-Immune' group n=13
Age mean (SD)	34.6 (± 11.6)	31.2 (± 10.9)	38.4 (± 11.7)	37.7 (± 11.9)
Gender	30F/7M	14F/4M	5F/1M	11F/2M
ACPA %	37.8% (n= 14)	22.2% (n=4)	0% (n=6)	76.9% (n=10)
RF %	48.6% (n=18)	38.9% (n=7)	16.7% (n=1)	76.9% (n=10)
Erosion %	32.4% (n=12)	27.8% (n=5)	33.3% (n=2)	38.4% (n=5)
Baseline DAS28CRP	4.60 (± 1.37)	4.46 (± 1.42)	5.24 (± 1.52)	4.50 (± 1.26)
6 Month DAS28CRP	2.68 (± 1.13)	2.19 (± 0.89)*	2.83 (± 1.44)	3.15 (± 1.13) * p=0.023

ACPA negative pts were classified in the Myeloid (100%) or in Lymphoid (77.8%) groups compared to a majority of the ACPA positive pts (76.9%) in the Pauci-Immune group. Since the myeloid pattern can be associated with a lymphoid infiltration, it raised a question on the relevance to maintain a distinct subgroup. The Pauci-Immune RA group showed lower DAS28-CRP response than the other groups.

Conclusion: Synovial tissue analysis could provide a step change towards personalized medicine in daily clinical practice for disease stratification and treatment selection of ERA. In the CAP48 cohort, a high number of these young and ERA pts achieved remission at 6 months but a lower response was observed in the Pauci-Immune group. Further analyses are ongoing to define individual synovial markers of severity and response.

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Predictors of Fatigue and Persistent Fatigue in Early Rheumatoid Arthritis: A Longitudinal Observational Study

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster II: Diagnosis and Prognosis

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Background/Purpose: Fatigue is a multifactorial and persistent symptom reported by patients with rheumatoid arthritis (RA). It is considered as frequent as pain. It would be of value to identify potential predictive factors of fatigue that could influence on its evolution.

Methods: *The Etude et Suivi des polyarthrites Indifférenciées Récentes (ESPOIR)* is a multicenter French cohort of patients with early arthritis. We selected patients fulfilling the 2010 ACR/EULAR criteria for RA during the first year of follow-up. We recorded fatigue (SF vitality score ≤ 40), persistent fatigue (SF vitality score ≤ 40 at the end of the study and at least in 50% of visits in the 5 years follow up) and disease variables at baseline and every 6 months up to 5 years. The association between fatigue/persistent fatigue and disease characteristics were evaluated by bivariate logistic regression models / tests. A multivariate logistic regression model was used to determine independent predictors of fatigue at baseline and persistent fatigue at 5 years of follow-up. Moreover, to analyse the association between the course of fatigue and disease characteristics over the time, baseline variables associated with fatigue at the multivariate analysis were analysed by a repeated measures logistic regression model at various time points (M12, M24, M36, M48 and M60).

Results: We included 677 patients (73.4% women, mean \pm SD age 48.6 ± 12 years); 46.5%, 28% and 22% of patients presented fatigue at baseline, 6 months and 5 years of follow up respectively. At baseline, fatigue was independently and significantly associated with single patients (OR = 2.5 95% CI [1.42-3.33] $p < 0.001$), abnormal BMI (OR = 1.1 95% CI [1.01 – 1.10] $p = 0.007$), higher DAS28 (OR = 1.3 95% CI [1.08-1.60] $p = 0.006$), higher severity of morning stiffness (scored 0-10) (OR = 1.0 95% CI [1.00-1.01] $p = 0.012$), higher HAQ (OR = 2.4 95% CI [1.70-3.44] $p < 0.001$), negativity of FR (OR = 1.5 95% CI [1.09-2.29] $p = 0.016$) and history of depression or anxiety (OR = 6.1 95% CI [3.90-9.83] $p < 0.001$).

The most important predictors of fatigue over 5 years were disability ($p < 0.001$) and depression/anxiety ($p < 0.001$).

A 14.9% of patients presented persistent fatigue. Its independent predictors at 5 years of follow-up were HAQ (OR = 0.5 95% CI [1.66-3.73] $p < 0.001$), history of depression/anxiety (OR = 3.6 95% CI [1.48-8.82] $p = 0.005$), >3 comorbidity (OR = 2.1 95% CI [1.18- 3.66] $p = 0.010$), dry syndrome (OR = 2.3 95% CI [1.39- 4.17] $p = 0.002$), and anti CCP negativity (OR = 1.96 95% CI [1.1-3.44] $p = 0.021$).

Conclusion: Fatigue was a frequent symptom in this cohort of early RA patient; its presence decreased at 6 months and remained stable over time. Baseline fatigue and persistent fatigue were both predicted by functional impairment and history of depression or anxiety. Disease activity measured by DAS28 was strongly associated to fatigue at baseline but it was not a predictor of persistent fatigue.

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Relationship between BMI and Lower Limb Dysfunction in Japanese Female Patients with Rheumatoid Arthritis (the data from NinJa registry)

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestions, and Outcomes Poster – ARHP

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: To clarify the relationship between Body Mass Index (BMI) and lower limb dysfunction in patients with rheumatoid arthritis (RA).

Methods: The data of 8,332 Japanese female patients with RA registered in the nation-wide observational cohort of RA in Japan (National database of rheumatic diseases in Japan: NinJa) in 2015 were used in this study. According to the BMI category, they were divided into 4 groups; Underweight (n=1,275), Normal weight (n=5,538), Overweight (n=1287), and Obese (n=232). “Lower limbs dysfunction” was defined here as the values (≥ 2) of questionnaire related to the lower limbs function in health assessment questionnaire (HAQ). Operation related to the lower limbs included replacement of hip, knee, or ankle joint. We examined the relationship between BMI and lower limbs dysfunction and/or operation. This study was reviewed and approved by Research Ethics Committees in each facilities. Informed consent was obtained from all study participants. This study was conducted in accordance with the principles expressed in the Declaration of Helsinki.

Results: Rates of lower limbs dysfunction were significantly higher not only in Overweight (16.9%) and Obese (23.7%) but also in Underweight (17.3%) than in Normal weight (12.6%) ($p < 0.0001$). Operation rate of lower limbs was also significantly higher in Overweight (17.6%), Obese (20.3%) and Underweight (15.6%) than those in Normal weight (12.9%). Patients with operation showed significantly elder and longer disease duration than those without operation in all groups. Lower limbs dysfunction by disease duration was smallest in Normal weight except early onset patients. Compared with Normal weight, other groups showed higher values of DAS28-CRP and HAQ-DI.

Conclusion: This study indicated that both higher and lower BMI correlated with lower limbs dysfunction in female patients with RA. It is difficult to interpret whether this relationship is the cause or the result, but total care considering nutritional guidance and weight management is important as well as medication in RA patients.

Disclosure: T. Matsui, None; A. Hashimoto, None; K. Masuda, None; S. Tohma, None.

Abstract Number: 1509

Associations between Perceived Stress and Joint Signs in an Anti-Cyclic Citrullinated Peptide Antibody Positive at-Risk Population

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Background/Purpose: Psychosocial factors have been associated with rheumatoid arthritis (RA) outcomes, but have not been well characterized in the early development of RA. We examined the associations of perceived stress, measured by the Perceived Stress Scale-14 (PSS), with joint signs in an anti-cyclic citrullinated peptide (CCP) antibody positive population.

Methods: At community health fairs from 2014-2018, 56 subjects without previously diagnosed RA were found CCP positive through the CCP3 test (Inova). Subjects were recruited into a prospective cohort, and at their immediate post-health fair research visit (baseline) 14 had at least 1 tender joint, 7 had at least 1 swollen joint based on a rheumatologist exam, and 2 were classified as RA by 2010 ACR/EULAR Criteria only. The PSS responses were summed to obtain a total score, in which a higher score indicates greater perceived stress. Additionally, responses on the PSS underwent an explanatory factor analysis which suggested two meaningful factors: 1) perception of control, named ‘helplessness’ and 2) ability to cope with stress, named ‘self-efficacy.’ These factors align with other studies suggesting a two-factor structure for the PSS. T-tests and multivariable logistic regression assessed the associations of PSS-related scores with joint signs.

Results: Individuals with at least 1 tender joint compared to those without a tender joint have a higher total PSS score, higher helplessness or poor self-efficacy sub-scores (Table). A one point increase in the total PSS score was associated with a 12% increase in the odds of having a tender joint. Similarly, increases in the helplessness and self-efficacy sub-scores

were associated with a 16% and 21% increase in the odds of tender joints, respectively. A sensitivity analysis removing the two individuals with newly classified RA at their baseline visit found that the absolute differences in the mean total PSS and self-efficacy scores remained, while ORs were slightly attenuated and not significant.

Conclusion: In a cohort of untreated CCP positive individuals, we found a significant association between higher perceived stress and joint tenderness. The ability to cope or control stressors may be an important component of the evolution from CCP positivity to joint signs that could indicate early inflammatory arthritis even if a swollen joint consistent with clear inflammatory arthritis is not seen. Further longitudinal study is needed to better understand the direction of the relationships between these factors, underlying immune dysregulation and transitions to classified RA. This is important because a relationship between perceived stress and clinical signs of disease in individuals at-risk for developing RA may support the incorporation of stress-targeted therapy management and other global health improvement activities, with the potential for increased quality of life.

Table 1 Associations between PSS-related scores and Joint Signs

	At least 1 Tender Joint Sign (N=14)	No Tender Joint Signs (N=42)	Odds Ratio (95% CI)
Total PSS score, mean (SD)*	25.8 (6.8)	19.1 (9.2)	1.12 (1.02, 1.23)
PSS Helplessness score, mean (SD)*	14.1 (5.6)	10.1 (5.7)	1.16 (1.02, 1.32)
PSS Self-efficacy score, mean (SD)*	10.0 (3.7)	6.7 (4.6)	1.21 (1.01, 1.45)
	At least 1 Swollen Joint Sign (N=7)	At least 1 Swollen Joint Sign (N=49)	Odds Ratio (95% CI)
Total PSS score, mean (SD)	27.1 (7.8)	19.8 (9.0)	1.11 (0.95, 1.32)
PSS Helplessness score, mean (SD)	14.1 (5.6)	10.1 (5.7)	1.11 (0.98, 1.25)
PSS Self-efficacy score, mean (SD)*	11.3 (3.7)	7.0 (4.5)	1.28 (0.99, 1.67)

* indicates T-test p-value of <0.05 for comparison of mean PSS-related scores

Abbreviations: standard deviation (SD); odds ratio (OR); confidence interval (CI).

Odds ratios obtained from logistic regression models adjusted for age, race, and ever smoking status. The joints assessed on the examination include the elbow, wrist, metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal.

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Abstract Number: 1510

Depression Is a Major Driver of Functional Capacity in Patients with Rheumatoid Arthritis Regardless of Disease Activity

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestions, and Outcomes Poster – ARHP

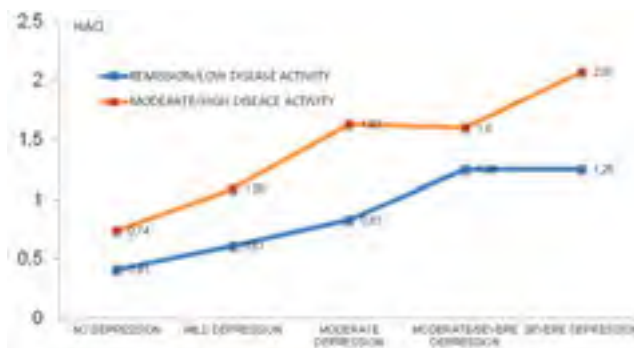
Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Depression is one of the most frequent comorbidity in RA patients. It's presence is associated with higher healthcare costs, mortality rate and reduced odds of achieving a good treatment response. The aim of our study was to determine the prevalence of depression in Argentinean patients with RA and to establish its relationship with different sociodemographic and clinical factors.

Methods: Consecutive patients ≥18 years old, with a diagnosis of RA according to ACR-EULAR2010 criteria were included. Sociodemographic data (sex, age, work and marital status, physical activity), comorbidities, RA characteristics (disease duration,

RF and anti-CCP, presence of erosions), disease activity (joint count (28), composite indexes, pain, patient's and physician's global assessment-NVS-, morning stiffness), CRP, ESR and current treatment were registered. Questionnaires were administered to assess quality of life by EQ-5D-3L and QOL-RA, functional capacity by HAQ-A and depression by PHQ-9. Major depression was defined as a PHQ-9 score ≥ 10 . PHQ-9 scores of 5-9, 10-14, 15-19, ≥ 20 represented mild, moderate, moderate/severe and severe depression, respectively. Patients with difficulties in answering the questionnaires (illiterate, blind) and with decompensated comorbidities were excluded. *Statistical analysis:* Student's T, ANOVA and χ^2 tests. Multiple logistic regression.



Results: 258 patients were included. 85.7% were females, with a median (*m*) age of 54 years (IQR 45-62) and *m* disease duration of 9 years (IQR 3.6-16.7). Disease activity by DAS28-ESR was *m* 3.5 (IQR 2.5-4.5). The *m* PHQ-9 score was 6 (IQR 2-12.3). The prevalence of mayor depression was 33.7%. 66 (25.6%), 42 (16.3%), 27 (10.5%) and 18 (7%) patients presented mild, moderate, moderate/severe and severe depression, respectively. Patients with mayor depression had worst functional capacity (HAQ mean 1.56 ± 0.78 vs 0.69 ± 0.65 , p 0.0001), poorer quality of life (QOL-RA mean 5.38 ± 1.78 vs 7.31 ± 1.61 , p 0.0001), more pain (NVS mean 56.15 ± 27.48 mm vs 33.42 ± 25.72 mm, p 0.0001) and higher disease activity (DAS28-ERS mean 4.33 ± 1.39 vs 3.3 ± 1.28 , p 0.0001). Unemployment, presence of comorbidities, and less physical activity were more frequent in this group. No differences between early arthritis patients (≤ 2 years) and established rheumatoid arthritis (> 2 years) were seen. In the multivariate analysis, worst functional capacity and quality of life were independently associated to the presence of mayor depression. Patients with moderate and severe depression had worse functional capacity, independently of disease activity. (Fig.1)

Conclusion: The prevalence of mayor depression measured by PHQ-9 score in this Argentinean cohort of rheumatoid arthritis patients was 33.7%. Patients with depression had a significant impact on functional capacity and quality of life regardless of disease activity.

Disclosure: C. A. Isnardi, None; D. Capelusnik, None; E. E. Schneeberger, None; M. Bazzarelli, None; L. Barloco, None; E. S. Blanco, None; A. Benitez, None; F. L. Benavidez, None; S. Scarafia, None; M. A. Lázaro, None; R. Perez-Alamino, None; F. Colombres, None; M. P. Kohan, None; J. Sosa, None; L. Gonzalez Lucero, None; A. L. Barbaglia, None; H. Maldonado Ficco, None; G. Citera, Bristol-Myers Squibb, Pfizer, AbbVie, Roche, Eli Lilly, Genzyme, 5.

Abstract Number: 1511

The Relationship between Lipid Profile Changes and Inflammation across the Phase 3 Sarilumab Rheumatoid Arthritis (RA) Developmental Program

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

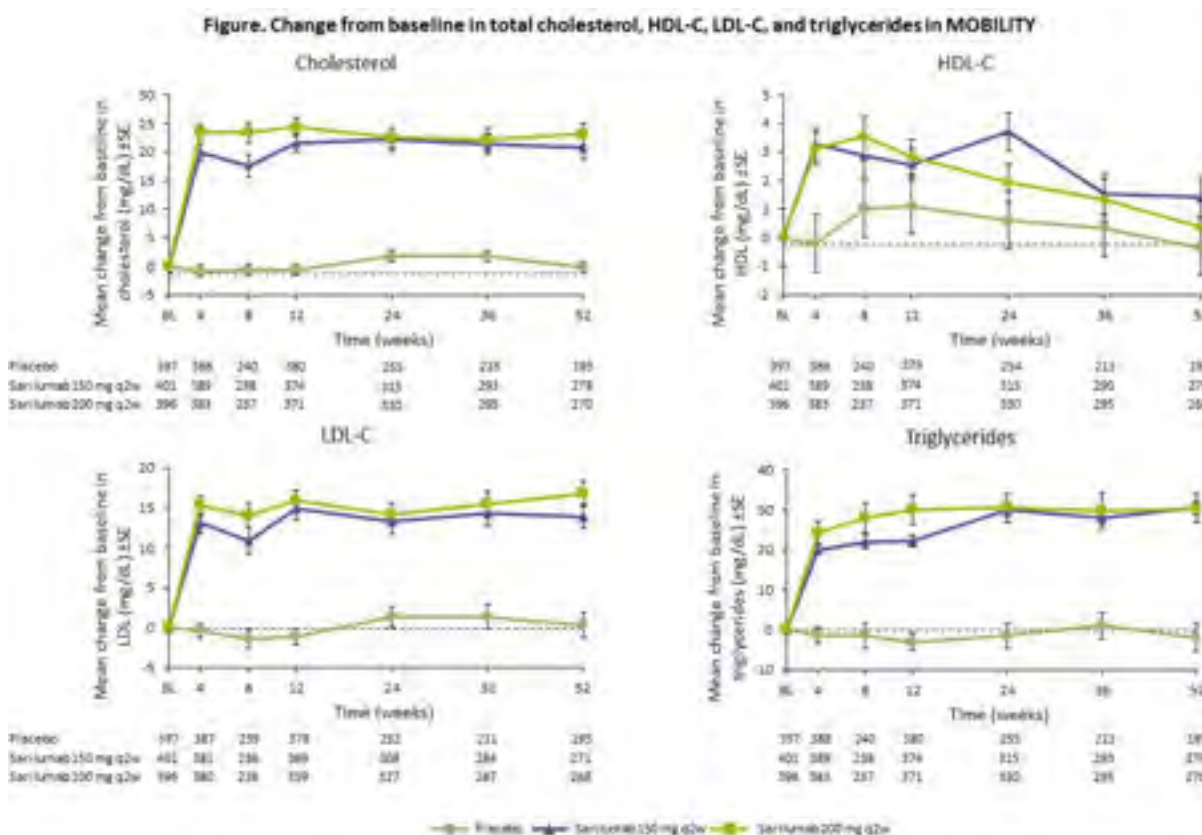
Session Time: 9:00 AM-11:00 AM

Background/Purpose: Sarilumab showed superiority to placebo and adalimumab in Phase 3 trials. Serum lipids may be reduced in the setting of chronic inflammation associated with active RA and may increase following effective response to RA therapy. In this post hoc analysis we investigated the relationship between lipid levels and markers of inflammation.

Methods: Fasting total, HDL and LDL cholesterol, triglycerides, lipoprotein(a) (Lp(a)), and apolipoproteins (Apo) A and B were evaluated in two placebo-controlled studies of sarilumab (150 mg and 200 mg q2w) +csDMARDs inpatients with

inadequate response to MTX (MOBILITY; NCT01061736) or intolerance or inadequate response to TNF inhibitors (TARGET; NCT01709578) and a monotherapy study of sarilumab vs adalimumab (MONARCH; NCT02332590). Spearman and Pearson correlations compared relationships between lipid levels and inflammatory markers (CRP and SAA [MOBILITY only]).

Results: Safety has been previously reported with no evidence of increased risk of major adverse cardiac events with sarilumab.¹⁻³ In 52-wk MOBILITY (Figure) and 24-wk TARGET, both sarilumab doses led to increases in total cholesterol, HDL-C, LDL-C, and triglyceride levels vs placebo (as early as Wk 2), which were maintained throughout the studies. In MONARCH, sarilumab treatment led to a greater mg/dL increase from baseline in total cholesterol (16.3 vs 1.4), HDL-C (1.4 vs -0.2), LDL-C (10.5 vs 0.5), and triglycerides (26.6 vs 5.7) and a greater decrease in Lp(a) (-41% vs -2.8%).⁴ Changes from baseline in total cholesterol/HDL-C ratio for sarilumab 200 mg q2w vs placebo were 0.41 vs 0.01 (MOBILITY Wk 52), 0.32 vs -0.06 (TARGET Wk 24) and vs adalimumab were 0.22 vs 0.02 (Wk 24). Sarilumab reduced CRP and SAA (MOBILITY) vs placebo and adalimumab.⁴ Negative Spearman correlations ($P < 0.001$ or $P < 0.0001$) between decreases from baseline in CRP and increases in lipid levels were seen with sarilumab 200 mg q2w for total cholesterol (-0.26 [MOBILITY Wk 52] and -0.33 [TARGET Wk 24]), HDL-C (-0.26 TARGET Wk 24), LDL-C (-0.21 [MOBILITY Wk 24] and -0.25 [TARGET Wk 24]), and triglycerides (-0.21 [MOBILITY Wk 52]) and with adalimumab (data not shown).



Conclusion: Sarilumab, an IL-6R blocker recently approved for the treatment of RA, showed an increase in various lipid parameters vs placebo or adalimumab and reduction in Lp(a). This was seen relatively quickly and stabilized after 4 weeks. Lipid elevation was associated with a reduction in inflammatory markers and was consistent with IL-6 blockade.

- References:** 1. Genovese MC, et al. *Arthritis Rheumatol* 2015;67:1424-37
 2. Fleischmann R, et al. *Arthritis Rheumatol* 2017;69:277-90
 3. Burmester GR, et al. *Ann Rheum Dis* 2017;76:840-7
 4. Gabay C, et al. *Ann Rheum Dis* 2017;76:570 (Abstract FRI0227)

Acknowledgements: Study funding and medical writing support (Zach Dixon, Adelphi Communications) provided by Sanofi and Regeneron Pharmaceuticals, Inc.

Disclosure: C. Charles-Schoeman, Bristol Myers Squibb, AbbVie, Octapharma, and Pfizer, 2, Regeneron-Sanofi, Pfizer, Octapharma, Amgen, and Gilead, 5; G. St. John, Regeneron Pharmaceuticals Inc., 1, 3; H. Leher, Regeneron Pharmaceuticals Inc., 1, 3; T. Kimura, Regeneron Pharmaceuticals Inc., 1, 3; H. van Hoogstraten, Sanofi, Novartis, 1, Sanofi, 3; M. T. Nurmohamed, AbbVie, Pfizer, Merck, Roche, BMS, UCB, Sanofi, Eli Lilly, Celgene and Janssen, 2, 8; M. A. González-Gay, AbbVie, Roche, Sanofi, Eli Lilly, and Novartis, 2, 5; E. C. Keystone, AbbVie, Amgen, Bristol-Myers

Squibb, F. Hoffmann-La Roche Inc, Gilead, Janssen Inc, Lilly Pharmaceuticals, Pfizer Pharmaceuticals, Sanofi-Aventis, 2, AbbVie, Amgen, AstraZeneca Pharma, Biotest, Bristol-Myers Squibb Company, Celltrion, Crescendo Bioscience, F. Hoffmann-La Roche Inc, Genentech Inc, Gilead, Janssen Inc, Lilly Pharmaceuticals, Merck, Pfizer Pharmaceuticals, Sandoz, UCB, 5, Amgen, AbbVie, Bristol-Myers Squibb Canada, F. Hoffmann-La Roche Inc., Janssen Inc., Merck, Pfizer Pharmaceuticals, Sanofi Genzyme, UCB, 8.

Abstract Number: 1512

Reduction in Power Doppler Ultrasound Score with Tocilizumab Treatment Associates with Improvement in the Protective Profile of HDL in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Musculoskeletal ultrasound (MSUS) can detect synovitis by Power doppler (PDUS) and can predict erosive progression on xrays in rheumatoid arthritis (RA) patients. We previously reported an association of active RA with impairment in HDL function, changes in HDL-associated protein levels, and suppression of paraoxonase-1 (PON1) activity, a novel risk factor for cardiovascular disease (CVD), which has been associated with carotid plaque in RA patients. In the current work, we evaluated an association of tocilizumab treatment with PDUS changes and the “protective profile” of HDL including HDL’s ability to inhibit low density lipoprotein (LDL) oxidation, PON1 activity, HDL-associated apoA-I (HDL-apoA-I) and haptoglobin (HDL-Hp) in patients with RA.

Methods: Assessment of PDUS was performed on 46 RA patients in a 6 month (mos) open-label study of IV tocilizumab initiated at 4mg/kg and dose escalated to 8mg/kg if DAS28 >3.2 at 12wks. 34 joints were scanned by MSUS (bilateral wrists, MCP1-5, PIP1-5, knees, and MTP2-5). PDUS was scored semiquantitatively according to published consensus definitions (*J Rheum.* 2005; 32:2485-7). HDL’s anti-oxidant function was measured by a cell free assay as described previously (*A&R* 2009; 60(10): 2870-9). PON1 activity was measured by previously published assays and HDL-associated apoA-I and Hp were measured by sandwich ELISA.

Results: Treatment with tocilizumab for 6 mos was associated with increases in traditional cholesterol levels including significant increases in HDL-C (baseline: 59± 23mg/dL; 6 mos: 71 ± 26 mg/dL, p<0.05), and improvements in HDL’s overall antioxidant function (baseline: 2347± 1710 FU; 6 mos: 1570 ± 1050 FU, p<0.05), increases in PON1 activity (baseline: 10.2± 3.8; 6 mos: 11.9 ± 4.4 , p<0.05), and trends for increases in HDL-apoA-I levels and decreases in HDL-Hp (p values >0.05). Greater decreases in PDUS scores over 6 mos were significantly associated with greater improvements in the HDL particle profile including increases in HDL-C (r= -0.32, p<0.05), PON1 activity (r= -0.30, p<0.05), HDL-apoA-I (r= -0.31, p<0.05), HDL’s anti-oxidant capacity (r= 0.38, p= 0.009) and trends for decreases in HDL-Hp (r= 0.24, p= 0.11). Associations between other disease assessments (DAS28 and CDAI) and HDL function/structure were noted, but were generally of lesser magnitude and consistency across the HDL profile. Increases in total and HDL-C levels with tocilizumab treatment were strongly correlated with improvement in HDL function (r= -0.41, p= 0.005, r= -0.60, p < 0.0001) and PON1 activity (r= 0.73, p< 0.0001, r= 0.43, p = 0.003).

Conclusion: Improvements in PDUS scores with tocilizumab treatment were significantly associated with improvements in the protective profile of HDL including increased HDL’s anti-oxidant capacity, PON1 activity, and HDL-apoA-I levels. This data supports previous work suggesting a direct association of joint inflammation with abnormal HDL function, and suggests that further evaluation of PDUS as a non-invasive CV risk assessment tool in RA may be warranted.

Disclosure: C. Charles-Schoeman, Bristol Myers Squibb, AbbVie, Octapharma, and Pfizer, 2, Regeneron-Sanofi, Pfizer, Octapharma, Amgen, and Gilead, 5; G. Kaeley, None; J. Wang, None; A. Shahbazian, None; J. Brook, None; D. Elashoff, Genentech, Inc., 2, Pfizer, Inc., 2, mallinkrodt, 2, Amgen Inc., 5; V. K. Ranganath, Genentech, Inc., 2, Pfizer, Inc., 2, mallinkrodt, 2, Amgen Inc., 5.

Efficacy of Etanercept By Body Mass Index in Women and Men with Rheumatoid Arthritis: A Post Hoc Analysis of Three Randomized Trials

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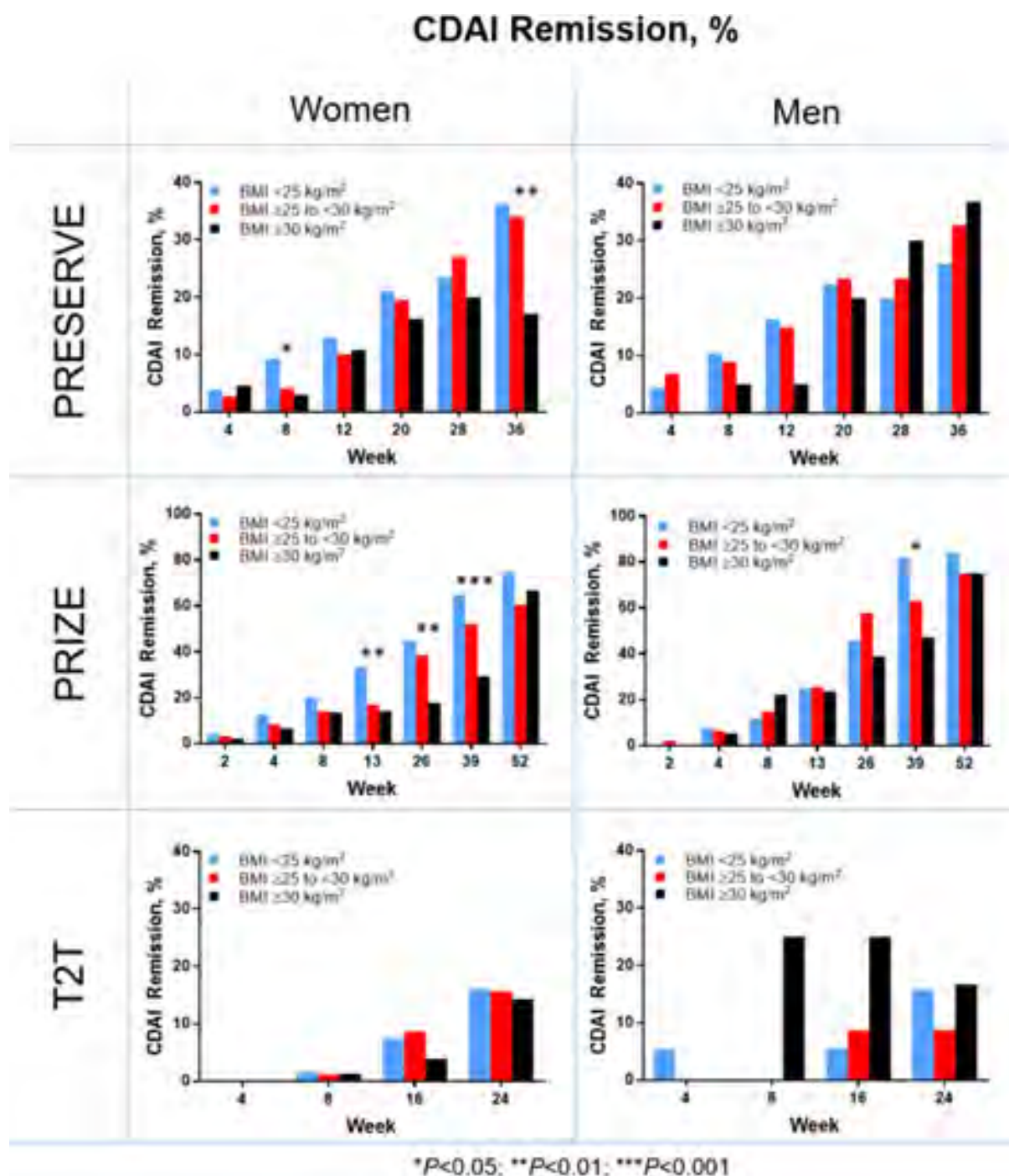
SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM



Background/Purpose: In patients with RA treated with TNF- α inhibitors, a higher BMI has been associated with lower odds of achieving disease remission. We evaluated the effect of BMI on response to etanercept (ETN) treatment in women and men with RA, (a) during open-label treatment and (b) following dose reduction or dosing off in patients who achieved low disease activity (LDA) or remission.

Methods: In this post hoc analysis, data were collected from three randomized trials (PRESERVE, N=834; PRIZE, N=306; T2T, N=489) in which patients with RA were assigned to an open-label treatment with ETN (50 mg) and MTX for 24-52 weeks, followed by randomized double-blind treatment with ETN (25 mg or 50 mg) + MTX, placebo + MTX, or placebo for 28-52 weeks in those who achieved LDA or remission. Observed cases data were analyzed by BMI (<25 kg/m², \geq 25 and <30 kg/m², or \geq 30 kg/m²) for women and men separately, using a one-way analysis of covariance model for continuous variables and a logistic regression model for categorical variables. The outcomes included changes from baseline in Clinical Disease Activity Index (CDAI), 28-joint DAS with CRP level (DAS28 CRP) or ESR (DAS28 ESR), and HAQ –Disability Index (HAQ-DI), as well as the percentages of patients who achieved CDAI remission (CDAI \leq 2.8) or LDA (CDAI >2.8 and \leq 10). The analysis was sponsored by Pfizer Inc. Medical writing assistance was provided by Vojislav Pejović of Engage Scientific Services.

Results: In the open label periods of all three studies, there was no significant BMI effect on treatment response to ETN in male patients, except for CDAI remission at a single visit in PRIZE (Figure). In open-label periods of the PRIZE and T2T trials, a significantly smaller decrease in DAS28 CRP and DAS28 ESR in women with BMI \geq 30 kg/m², compared with the other two BMI categories, was observed at most visits. In addition, in PRIZE trial (but not in PRESERVE or T2T), women, but not men, with BMI \geq 30 kg/m² had a significantly smaller decrease in CDAI and HAQ-DI scores and lower rates of CDAI LDA at most visits, compared with their counterparts with BMI <30 kg/m². For CDA remission, there was evidence of the effect of BMI \geq 30 kg/m² in women in both PRIZE and PRESERVE (Figure). Overall, these nominally significant differences between women with BMI \geq 30 kg/m² and <30 kg/m² were transient: most of them diminished or were no longer significant toward the end of the open-label periods. In randomized, double-blind periods, there were no discernible trends attributable to BMI category in either women or men.

Conclusion: Results of this post hoc analysis suggest that, in men with RA, there was no impact of BMI on ETN efficacy. In women, there was evidence of a transient negative impact of BMI \geq 30 kg/m² on ETN efficacy in open-label periods, but it diminished by the end of the induction period and was not consistent across trials. There was no evidence of BMI effect in men or women during the double-blind periods.

Disclosure: R. Alten, Gilead Science Inc, Galapagos, 2; E. Mysler, Pfizer, Abbvie, Lilly, BMS, Roche, 5; A. Wajdula, None; H. Jones, Pfizer, Inc., 1, Pfizer, Inc., 3; R. Pedersen, Pfizer, Inc., 1, Pfizer, Inc., 3; L. Marshall, Pfizer, Inc., 1, Pfizer, Inc., 3.

Abstract Number: 1514

Impact of Comorbidity Burden and Obesity on the Effectiveness of Tocilizumab in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Few real-world studies have evaluated the impact of comorbidity burden or obesity on the effectiveness of tocilizumab (TCZ) for the improvement of rheumatoid arthritis (RA) disease activity. This study compared the effectiveness of TCZ in treating RA in patients with high vs low comorbidity burden and in obese vs non obese patients in US clinical practice.

Methods: Patients in the Corrona RA registry who initiated TCZ and had follow-up visits at 6 and 12 months after initiation were included. To assess the impact of comorbidity burden on TCZ effectiveness, outcomes were stratified by patients with low Charlson Comorbidity Index (CCI = 1) vs high (CCI \geq 2). To assess the impact of obesity, outcomes were stratified by patients with BMI < 30 (non obese) vs \geq 30 (obese). The primary outcome was mean change in CDAI at 6 and 12 months. Secondary outcomes were mean change in HAQ, the proportions of patients with change \geq the minimum clinically important difference (MCID) in CDAI and HAQ and the proportion who achieved low disease activity (LDA);

CDAI ≤10). Baseline demographics, clinical characteristics, disease activity and treatment history in the comorbidity and BMI cohorts were compared separately using standardized differences; characteristics with |standardized difference| >0.1 were identified as covariates for inclusion in adjusted comparisons. Outcomes were compared between cohorts using two-sample *t*-tests or χ^2 tests in unadjusted analyses and linear or logistic regression models to adjust for covariates.

Table. Study Outcomes at 6 and 12 Months in Patients With RA Who Initiated TCZ, Stratified by Comorbidity Burden and Obesity Status

	Comorbidity Burden				Obesity			
	Low* (CCI† = 1) [n = 575]	High (CCI† ≥ 2) [n = 195]	Unadjusted Difference	Adjusted Difference‡	Nonobese* (BMI < 30) [n = 449]	Obese (BMI ≥ 30) [n = 356]	Unadjusted Difference	Adjusted Difference§
Outcomes at 6 Months¶								
			β (95% CI)	β (95% CI)			β (95% CI)	β (95% CI)
Change in CDAI, mean (SD)	-7.57 (13.65)	-7.72 (13.62)	-0.15 (-2.37, 2.07)	0.72 (-1.92, 3.36)	-7.77 (13.12)	-7.38 (14.05)	0.39 (-1.49, 2.28)	1.29 (-0.41, 2.99)
Change in HAQ, mean (SD)	-0.05 (0.41)	-0.09 (0.43)	-0.04 (-0.11, 0.30)	0.01 (-0.09, 0.10)	-0.06 (0.41)	-0.05 (0.42)	0.003 (-0.06, 0.06)	0.04 (-0.02, 0.09)
			OR (95% CI)	OR (95% CI)			OR (95% CI)	OR (95% CI)
Change in CDAI > MCID, % patients¶	51.1	44.6	0.77 (0.56, 1.07)	0.79 (0.45, 1.40)	51.2	46.6	0.83 (0.63, 1.10)	0.83 (0.60, 1.16)
Change in HAQ > MCID, % patients¶	30.4	31.8	1.07 (0.75, 1.51)	0.47 (0.23, 0.98)	30.7	30.3	0.98 (0.73, 1.33)	0.86 (0.59, 1.27)
Achievement of LDA, % patients**	24.7	21.5	0.84 (0.57, 1.24)	0.85 (0.45, 1.62)	27.0	19.7	0.66 (0.47, 0.93)	0.70 (0.48, 1.01)
Outcomes at 12 Months¶								
			β (95% CI)	β (95% CI)			β (95% CI)	β (95% CI)
Change in CDAI, mean (SD)	-8.42 (14.24)	-7.82 (14.52)	0.59 (-1.74, 2.92)	-1.22 (-4.22, 1.77)	-8.24 (13.39)	-8.09 (15.27)	0.15 (-1.84, 2.14)	1.53 (-0.33, 3.39)
Change in HAQ, mean (SD)	-0.05 (0.40)	-0.11 (0.42)	-0.06 (-0.13, 0.01)	-0.06 (-0.15, 0.03)	-0.07 (0.40)	-0.04 (0.42)	0.03 (-0.02, 0.09)	0.07 (0.01, 0.13)
			OR (95% CI)	OR (95% CI)			OR (95% CI)	OR (95% CI)
Change in CDAI > MCID, % patients¶	52.7	49.7	0.89 (0.64, 1.23)	1.21 (0.69, 2.13)	53.5	49.4	0.85 (0.64, 1.12)	0.72 (0.52, 1.01)
Change in HAQ > MCID, % patients¶	27.7	29.7	1.11 (0.77, 1.58)	0.86 (0.42, 1.76)	27.8	28.1	1.01 (0.74, 1.38)	0.83 (0.55, 1.24)
Achievement of LDA¶, % patients**	30.4	31.3	1.04 (0.73, 1.48)	1.52 (0.85, 2.71)	32.1	27.5	0.80 (0.59, 1.09)	0.75 (0.53, 1.06)

BMI, body mass index; CCI, Charlson Comorbidity Index; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; LDA, low disease activity; MCID, minimum clinically important difference; OR, odds ratio.

* Reference group.

† The CCI used for this analysis is a modified CCI and is the sum of prior reported comorbid conditions that are captured in Corrona at the time of drug initiation, including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, peptic ulcer disease, diabetes mellitus, leukemia, lymphoma, solid tumor cancer (excluding nonmelanoma of the skin) and liver disease. The CCI also includes connective tissue disease, which was coded as 1 to account for rheumatoid arthritis.

‡ Adjusted for age, duration of RA, race, college educated, smoking status, alcohol consumption, BMI, work status, insurance type, number of prior csDMARDs, current csDMARD use, number of prior biologics used, current prednisone use, CDAI at initiation, HAQ at initiation, patient-reported fatigue at initiation and length of morning stiffness at initiation.

§ Adjusted for age, duration of RA, race, college educated, smoking status, work status, insurance type, comorbidity burden category at initiation, number of prior csDMARDs, current csDMARD use, number of prior biologics used, CDAI at initiation, HAQ at initiation, patient-reported fatigue at initiation and patient-reported pain at initiation.

¶ The 6-month visit occurred in a window of 4 to 8 months; the 12-month visit occurred in a window of 10 to 14 months.

¶ CDAI ≤ 10 at baseline, MCID = 2; CDAI > 10 to ≤ 22 at baseline, MCID = 6; CDAI > 22 at baseline, MCID = 11.

** MCID = 0.22.

** LDA, CDAI ≤ 10.

Results: Of 770 patients who initiated TCZ and had CCI data available at baseline (93.8% treated with intravenous [IV] TCZ and 6.2% with subcutaneous [SC] TCZ), 575 (74.7%) had a low CCI and 195 (25.3%) a high CCI. Patients with a high CCI were older (mean [SD] age, 61.5 [12.3] vs 56.9 [13.1] years), were more likely to be obese (52.8% vs 41.7%), had a longer disease duration (mean [SD], 12.8 [9.9] vs 11.6 [8.9] years) and had higher mean (SD) baseline CDAI (25.7 [13.4] vs 23.9 [13.9]) and HAQ (0.71 [0.57] vs 0.57 [0.51]) scores than those with a low CCI.

Of the 805 TCZ initiators with BMI data available at baseline (93.9% treated with IV TCZ and 6.1% with SC TCZ), 449 (55.8%) were not obese and 356 (44.2%) were obese. Obese patients were younger (56.7 [12.0] vs 59.0 [13.7] years), had shorter disease duration (11.4 [8.6] vs 12.6 [9.7] years) and had higher baseline CDAI (25.4 [14.3] vs 23.6 [13.4]) and HAQ (0.65 [0.53] vs 0.57 [0.53]) scores than non obese patients.

Patients in all cohorts had improvement from baseline in CDAI at 6 and 12 months, with no significant differences between those with a low vs high CCI or between obese vs non obese patients (Table). Secondary outcomes yielded similar results (Table).

Conclusion: In this real-world analysis, the effectiveness of TCZ for the improvement of RA disease activity was comparable among patients regardless of comorbidity burden or obesity.

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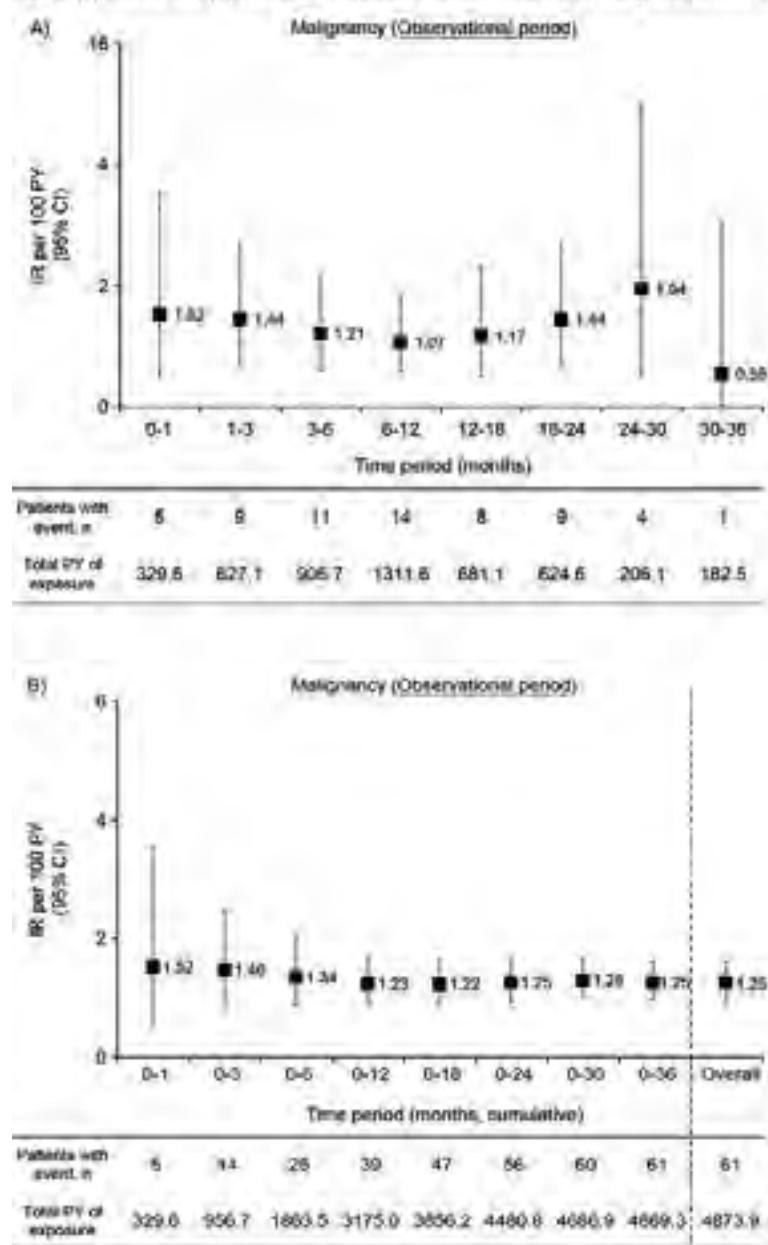
Malignancy in Japanese Patients with Rheumatoid Arthritis Treated with Tofacitinib: Interim Analysis of All-Case Post-Marketing Surveillance

Naoto Tamura¹, Masataka Kuwana², Tatsuya Atsumi³, Syuji Takei⁴, Masayoshi Harigai⁵, Takao Fujii⁶, Hiroaki Matsuno⁷, Tsuneyo Mimori⁸, Shigeki Momohara⁹, Kazuhiko Yamamoto¹⁰, Yoshinari Takasaki¹¹, Kazuto Nomura¹², Yutaka Endo¹², Tomohiro Hirose¹², Yosuke Morishima¹², Naonobu Sugiyama¹², Noritoshi Yoshii¹² and Michiaki Takagi¹³, ¹Juntendo University, Tokyo, Japan, ²Nippon Medical School, Tokyo, Japan, ³Hokkaido University, Sapporo, Japan, ⁴Medical Center for Children, Kagoshima, Japan, ⁵Tokyo Women's Medical University, Tokyo, Japan, ⁶Wakayama Medical University, Wakayama, Japan, ⁷Matsuno Clinic for Rheumatic Diseases, Toyama, Japan, ⁸Kyoto University, Kyoto, Japan, ⁹Hakkeikai Inc Medical Institution, Shizuoka, Japan, ¹⁰The University of Tokyo, Tokyo, Japan, ¹¹Juntendo Koshigaya Hospital, Juntendo University Faculty of Medicine, Saitama, Japan, ¹²Pfizer Japan Inc, Tokyo, Japan, ¹³Yamagata University Faculty of Medicine, Yamagata, Japan

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Figure. (A) Interval and (B) Cumulative exposure estimates and IRs for Malignancies over 36 months



CI, confidence interval; IR, incidence rate; PY, patient-years

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. The efficacy and safety of tofacitinib have been demonstrated in patients (pts) with RA in global Phase (P)2, P3, and long-term extension (LTE) studies, and also in two P2 and one LTE study in Japanese pts. In this interim analysis (IA) of post-marketing surveillance (PMS) data, we report rates of serious adverse events (SAEs), malignancies, and deaths in Japanese pts with RA receiving tofacitinib.

Methods: All Japanese pts with RA receiving tofacitinib were prospectively registered in an ongoing three-year PMS study, and a 6-month IA of safety data was conducted (November 5, 2017 data-cut). All AEs were collected during tofacitinib treatment, and were coded using MedDRA ver.20.1. Follow-up surveillance after discontinuation of tofacitinib was conducted for serious infections, malignancy and death (up to 36 months). Incidences of malignancy or death were determined for the 6-month period. All-period (36-month) data were used to calculate cumulative incidence rates (IRs; pts with events/100 pt-years [PY]) over time for malignancies.

Results: Overall, 3929 pts received tofacitinib (1704.1 PY of exposure at six months). Mean age (standard deviation [SD]) was 62.7 (12.6) years, 80.5% of pts were female, and mean duration of RA was 11.8 years. A total of 3037 pts (77.3%) completed six months of treatment; 892 pts (22.7%) discontinued treatment, mainly due to AEs (351 pts; 8.9%), or lack of efficacy (335 pts; 8.5%). At least one AE (all causality) was observed in 1313 pts (33.4%). The most frequent AE by system organ class was Infections and Infestations (12.5%), and SAEs (all causality) occurred in 287 pts (7.3%). Over the six-month period, malignancy (all causality) was reported in 25 pts (0.6%); 12 cases were reported to be related to treatment. There were 21 deaths (0.5%) during the six-month period. The most common cause of death (including pts with multiple causes listed) was infection (six cases); malignancy was the second most common cause of death (five cases). From all-period (36-month) data, malignancies occurred in 61 pts (1.6%); gastric cancer occurred in eight pts (0.2%), lung neoplasm malignant in six pts (0.2%), breast cancer in five pts (0.1%), and diffuse large B-cell lymphoma, ovarian cancer, uterine cancer, colon cancer, and pancreatic carcinoma in four pts each (0.1%). Over 36 months, the IR of malignancy was 1.25 (61 pts; 4874 PY). The IR of malignancy did not increase in the time intervals representative of longer tofacitinib treatment, suggesting no cumulative toxicity related to malignancy, though exposure time for intervals were limited (Figure).

Conclusion: In this IA of tofacitinib PMS in Japanese pts with RA, rates of malignancies and death were comparable with those in the tofacitinib RA clinical program; no new or unexpected safety risks were identified.

Disclosure: N. Tamura, Astellas, Asahi-Kasei, Ayumi, Chugai, Esai, Mitsubishi-Tanabe, Takeda, 2, AbbVie, Bristol-Myers Squibb, Chugai, Esai, Janssen, Mitsubishi-Tanabe, 8; M. Kuwana, Astellas, Chugai, Esai, Mitsubishi-Tanabe, Ono, Pfizer Inc, 2, Ayumi, Chugai, Janssen, Mitsubishi-Tanabe, Ono, Pfizer Inc, 8; T. Atsumi, Alexion, Astellas, Bristol-Myers Squibb, Chugai, Esai, Janssen, Mitsubishi-Tanabe, Sanofi, 2, AbbVie, Astellas, Chugai, Esai, Mitsubishi-Tanabe, Pfizer Inc, Takeda, UCB, 8, Astellas, Bayer, Chugai, Daiichi-Sankyo, Esai, Mitsubishi-Tanabe, Takeda, 9; S. Takei, AbbVie, Ayumi, Bristol-Myers Squibb, Chugai, Esai, Mitsubishi-Tanabe, Novartis, Ono, Sanofi, Taisho Toyama, 8; M. Harigai, Eisai, Takeda, Teijin, 2, Bristol-Myers Squibb, Chugai, Janssen, Pfizer Inc, 5; T. Fujii, Pfizer Inc, 2, Pfizer Inc, 8; H. Matsuno, Ayumi, Meiji Seika, Mochida, Nichi-Iko, 5; T. Mimori, Astellas, Ayumi, Chugai, Daiichi-Sankyo, Eisai, MSD, Mitsubishi-Tanabe, Sanofi, Taisho Toyama, 2, Astellas, Bristol-Myers Squibb, Chugai, Eisai, Mitsubishi-Tanabe, 8; S. Momohara, None; K. Yamamoto, AbbVie, Astellas, Ayumi, Chugai, Eisai, Mitsubishi-Tanabe, Nippon Kayaku, Pfizer Inc, Takeda, Taisho Toyama, Teijin, UCB, 2, Asahi-Kasei, AstraZeneca, Ayumi, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer Inc, Sanofi, Sumitomo Dainippon, Taisho Toyama, Takeda, Teijin, Toyama Chemical, UCB, 8; Y. Takasaki, None; K. Nomura, Pfizer Inc, 1, Pfizer Inc, 3; Y. Endo, Pfizer Inc, 1, Pfizer Inc, 3; T. Hirose, Pfizer Inc, 1, Pfizer Inc, 3; Y. Morishima, Pfizer Inc, 1, Pfizer Inc, 3; N. Sugiyama, Pfizer Inc, 1, Pfizer Inc, 3; N. Yoshii, Pfizer Inc, 1, Pfizer Inc, 3; M. Takagi, Astellas, Chugai, Eisai, Pfizer Inc, Takeda, Tanabe-Mitsubishi, Teijin-Pharma, 2, Ayumi, Johnson and Johnson, MDM, Ono, Pfizer Inc, Tanabe-Mitsubishi, 8.

Abstract Number: 1516

Infection Events in Japanese Patients with Rheumatoid Arthritis Treated with Tofacitinib: Interim All-Case Post-Marketing Surveillance

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Previously, the efficacy and safety of tofacitinib were demonstrated in patients (pts) with RA in global Phase (P)2, P3, and long-term extension (LTE) studies, and in Japanese pts with RA in two P2 studies and one LTE study. Safety is being evaluated in Japanese pts with RA in an ongoing three-year post-marketing surveillance (PMS) study. Here, we report incidence of serious infection events (SIEs), *Pneumocystis jirovecii* pneumonia (PCP), tuberculosis (TB), and herpes zoster (HZ) among Japanese pts with RA treated with tofacitinib, using interim PMS data.

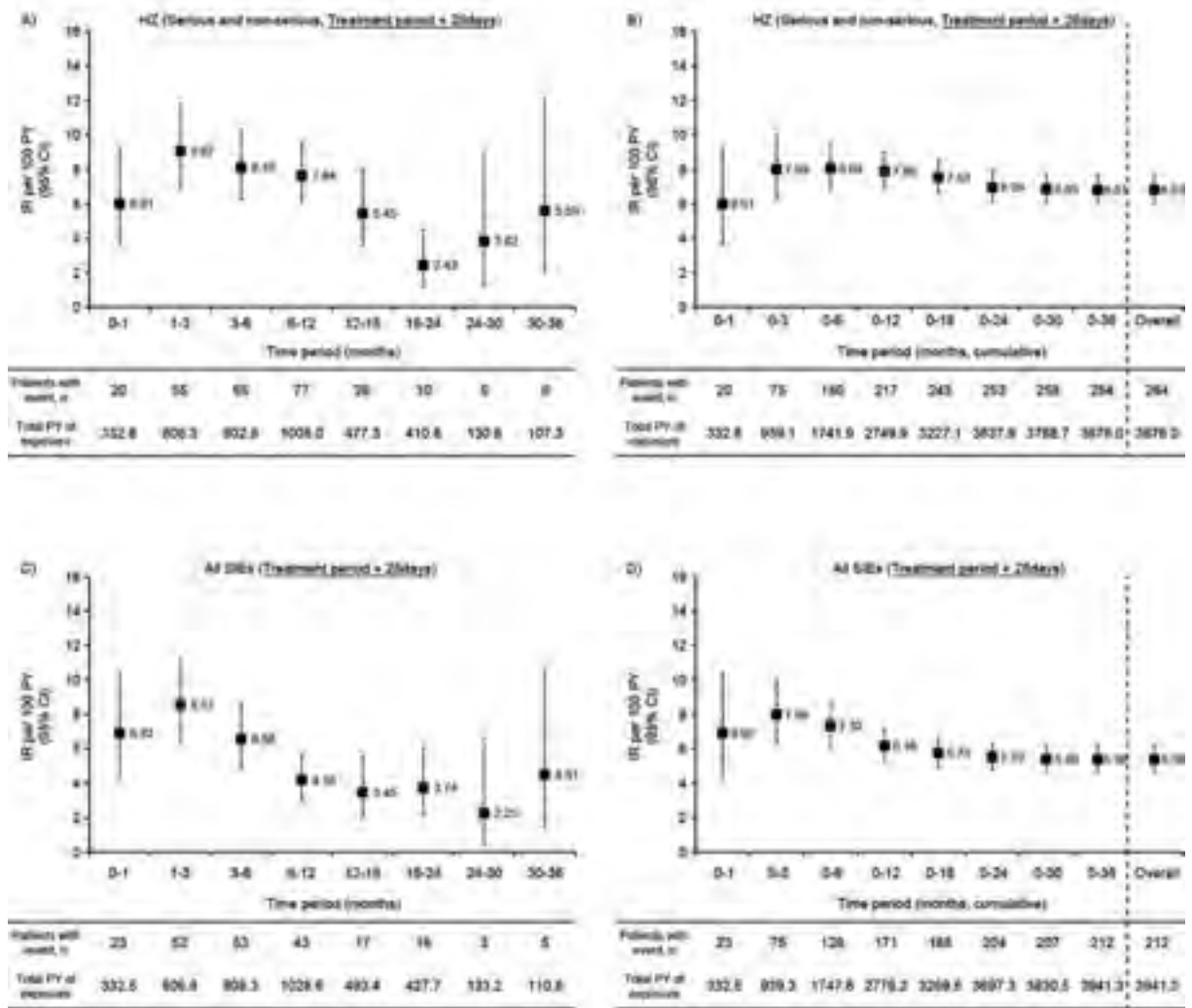
Methods: All pts treated with tofacitinib in Japan were consecutively registered in this PMS study. Adverse events (AEs) in pts with RA receiving tofacitinib were collected throughout the PMS study (36 months; data-cut: November 5, 2017), and were coded using MedDRA ver.20.1. For SIEs, follow-up surveillance after discontinuation of tofacitinib was conducted up to Month 12, and the frequency and types of SIEs, PCP, TB, and HZ are reported for the PMS first six-month observation period. All-period data (up to 36 months) were used to calculate cumulative incidence rates (IRs: pts with events/100 pt-years [PY]) over time for HZ and SIEs during treatment +28 days.

Results: In total, 3929 pts received tofacitinib (3956.4 PY of exposure at 36 months). At baseline, 80.5% of pts were female; mean age (standard deviation [SD]) was 62.7 (12.6) years; 32.6% of pts were ≥ 70 years. In the six-month observation period, 2041 AEs (all causality) were reported in 1313 (33.4%) pts. The most frequently reported AE by system organ class was Infections and Infestations (n=493; 12.5%) and the most frequently reported AE by preferred term was HZ (n=145; 3.7%), including one HZ meningoencephalitis (serious) and two disseminated HZ (one serious; one non-serious). PCP was reported in 16 (0.4%) pts (15 serious; one non-serious). There were three TB cases (including one serious bone tuberculosis); no pts with TB had received chemoprophylaxis with isoniazid before starting tofacitinib. At Month six, 130 (3.3%) pts had SIEs; most common by preferred term were HZ (n=24; 0.6%), pneumonia (n=23; 0.6%), PCP (n=15; 0.4%), and pneumonia bacterial (n=10; 0.3%). The IRs of HZ and SIE were highest at Months 1-3 and stabilized after Month 12 (all-period data; overall IR was 6.81 [n=264; 3876.0PY] and 5.38 [n=212; 3941.3 PY] for HZ and SIEs, respectively [Figure]).

Conclusion: This interim analysis of PMS data from Japan did not reveal any new or unexpected safety risks vs tofacitinib RA clinical trials, although exposure time was short. HZ IR was similar to that reported in P2, P3, and LTE trials in Japanese pts with RA; SIE IR was within the range of IRs in prior PMS studies of RA biologic treatment.

Disclosure: N. Tamura, Astellas, Asahi-Kasei, Ayumi, Chugai, Esai, Mitsubishi-Tanabe, Takeda, 2, AbbVie, Bristol-Myers Squibb, Chugai, Esai, Janssen, Mitsubishi-Tanabe, 8; M. Kuwana, Astellas, Chugai, Esai, Mitsubishi-Tanabe, Ono, Pfizer Inc, 2, Ayumi, Chugai, Janssen, Mitsubishi-Tanabe, Ono, Pfizer Inc, 8; T. Atsumi, Alexion, Astellas, Bristol-Myers Squibb, Chugai, Esai, Janssen, Mitsubishi-Tanabe, Sanofi, 2, AbbVie, Astellas, Chugai, Esai, Mitsubishi-Tanabe, Pfizer Inc, Takeda, UCB, 8, Scholarship donations - Astellas, Bayer, Chugai, Daiichi-Sankyo, Esai, Mitsubishi-Tanabe, Takeda, 9; S. Takei, AbbVie, Ayumi, Bristol-Myers Squibb, Chugai, Esai, Mitsubishi-Tanabe, Novartis, Ono, Sanofi, Taisho Toyama, 8; M. Harigai, Eisai, Takeda, Teijin, 2, Bristol-Myers Squibb, Chugai, Janssen, Pfizer Inc, 5; T. Fujii, Pfizer Inc, 2, Pfizer Inc, 8; H. Matsuno, Ayumi, Meiji Seika, Mochida, Nichi-Iko, 5; T. Mimori, Astellas, Ayumi, Chugai, Daiichi-Sankyo, Eisai, MSD, Mitsubishi-Tanabe, Sanofi, Taisho Toyama, 2, Astellas, Bristol-Myers Squibb, Chugai, Eisai, Mitsubishi-Tanabe, 8; S. Momohara, None; K. Yamamoto, AbbVie, Astellas, Ayumi, Chugai, Eisai, Mitsubishi-Tanabe, Nippon Kayaku, Pfizer Inc, Takeda, Taisho Toyama, Teijin, UCB, 2, Asahi-Kasei, AstraZeneca, Ayumi, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer Inc, Sanofi, Sumitomo Dainippon, Taisho Toyama, Takeda, Teijin, Toyama Chemical, UCB, 8; Y. Takasaki, None; K. Nomura, Pfizer Inc, 1, Pfizer Inc, 3; Y. Endo, Pfizer Inc, 1, Pfizer Inc, 3; T. Hirose, Pfizer Inc, 1, Pfizer Inc, 3; Y. Morishima, Pfizer Inc, 1, Pfizer Inc, 3; N. Sugiyama, Pfizer Inc, 1, Pfizer Inc, 3; N. Yoshii, Pfizer Inc, 1, Pfizer Inc, 3; M. Takagi, Astellas, Chugai, Eisai, Pfizer Inc, Takeda, Tanabe-Mitsubishi, Teijin-Pharma, 2, Ayumi, Johnson and Johnson, MDM, Ono, Pfizer Inc, Tanabe-Mitsubishi, 8.

Figure. (A) Interval and (B) Cumulative exposure estimates and IRs for HZ; and (C) interval and (D) Cumulative exposure estimates and IRs for SIEs, over 30 months



(A) and (B) Two patients were excluded because there was no data of the time of onset
CI, confidence interval; HZ, herpes zoster; IR, incidence rate; PY, patient-years; SIE, serious infection event.

Abstract Number: 1517

Integrated Safety Analysis across Phase 3 Clinical Studies Including the Controlled and Uncontrolled Periods for Intravenous Golimumab in Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00 AM-11:00 AM

Background/Purpose: The GO-FURTHER, GO-VIBRANT, and GO-ALIVE randomized controlled trials evaluated the efficacy and safety of intravenous (IV) golimumab (GLM) in patients (pts) with active rheumatoid arthritis (RA), psoriatic

arthritis (PsA), and ankylosing spondylitis (AS), respectively. This integrated analysis assessed safety events across indications in pts who received IV GLM.

Methods: Integrated safety data from 3 Phase 3, double-blind, placebo (PBO)-controlled trials were analyzed up to week (WK) 112 in RA pts and up to WK 60 in PsA and AS pts. Pts received either IV PBO or IV GLM (2 mg/kg) at 0, 4, 12, and 20 WKS. PBO pts crossed over to IV GLM at WK 24, except RA pts randomized to PBO who met early escape criteria crossed over at WK 16 and AS pts randomized to PBO who crossed over at WK 16. Cumulative adverse events (AEs) were reported by indication and pooled by treatment. Anti-drug antibodies (ADAs) were evaluated.

Results: Overall, 1248 pts were treated with IV GLM across indications. A numerically greater proportion (%) of IV GLM pts with RA reported safety events than pts with PsA or AS (Table 1): SAEs (18.2 vs 5.2 vs 3.4), infections (49.1 vs 22.8 vs 32.8), serious infections (6.2 vs 2.2 vs 1.5), and infusion reactions (4.6 vs 0.9 vs 1.5). Incidence (per 100 pt-years) of opportunistic infections, malignancy, active tuberculosis, and death with IV GLM was low (≤ 0.5) across indications (Table 2). Infections were the most commonly reported type of SAE among pooled IV GLM pts; the most frequent was pneumonia (10 [0.8%]). Incidence (per 100 pt-years) of serious infections was similar among IV GLM pts with and without corticosteroid use (3.35 vs 3.37, respectively). Overall, 1 IV GLM pt (PsA) experienced a demyelination event. A numerically greater proportion of IV GLM pts discontinued due to an AE than PBO pts (5.0% vs 0.9%, respectively). In IV GLM pts with baseline alanineaminotransferase (ALT) \leq upper limit of normal (ULN), 1.2% had post-baseline ALT elevations $\geq 5X$ ULN. The proportion of IV GLM and PBO pts with post-baseline ALT elevations $\geq 5X$ ULN was 2.1% vs 0% with methotrexate and 0.7% vs 1.4% without methotrexate use at baseline, respectively. Using a drug-tolerant enzyme immunoassay, the incidence of ADAs was 22% through WK 52 across indications, which primarily consisted of low titer ADAs.

Conclusion: IV GLM demonstrated a consistent safety profile across indications in the PBO-controlled (up to WK 24) and uncontrolled study periods. Similar to WK 24, more safety events occurred in RA pts, who represented the largest study population with older pts, longer disease duration, and more concomitant medication use.

Table 1 Summary of Adverse Events During the Placebo-controlled and Uncontrolled Study Periods

Variables	RAa IV GLM	PsAb IV GLM	ASb IV GLM	All IV GLM
Treated patients, n	584	460	204	1248
Average duration of follow up, wks	95.9	47.2	51.8	70.7
Patients who discontinued due to an AE	41 (7.0)	17 (3.7)	4 (2.0)	62 (5.0)
Patients with ≥ 1 AE	462 (79.1)	234 (50.9)	113 (55.4)	809 (64.8)
Patients with ≥ 1 SAE	106 (18.2)	24 (5.2)	7 (3.4)	137 (11.0)
Patients with ≥ 1 infection	287 (49.1)	105 (22.8)	67 (32.8)	459 (36.8)
Patients with ≥ 1 serious infection	36 (6.2)	10 (2.2)	3 (1.5)	49 (3.9)
Patients with ≥ 1 infusion reaction	27 (4.6)	4 (0.9)	3 (1.5)	34 (2.7)
ADA-positive patientsc, %	23.4	22.0	20.2	22.3

Patients n (%) reporting safety events during the placebo-controlled and uncontrolled study periods are reported, unless otherwise specified.

a Based on safety events that occurred up to week 112

b Based on safety events that occurred up to week 60

c Assessed using a drug-tolerant enzyme immunoassay based on IV GLM patients with appropriate samples through week 52 (RA, n=552; PsA, n=450; AS, n=203; and All, n=1205)

ADA, anti-drug antibody; AE, adverse event; AS, ankylosing spondylitis; IV GLM, intravenous golimumab; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SAE, serious adverse event

Table 2 Incidence of Safety Events Per 100 Patient-Years

Variables	RAa		PsAb		ASb		All	
	IV GLM	Placebo	IV GLM	Placebo	IV GLM	Placebo	IV GLM	Placebo
Treated patients, n	584	197	460	239	204	103	1248	539
Average duration of follow up, wks	95.9	21.0	47.2	23.2	51.8	16.1	70.7	21.0
Opportunistic infections (95% confidence interval)	0.4 (0.1, 1.0)	0 (0, 3.8)	0 (0, 0.7)	0 (0, 2.8)	0 (0, 1.5)	0 (0, 9.4)	0.2 (0.1, 0.6)	0 (0, 1.4)
All malignancies (95% confidence interval)	0.5 (0.2, 1.1)	0 (0, 3.8)	0.5 (0.1, 1.7)	1.9 (0.2, 6.8)	0 (0, 1.5)	0 (0, 9.4)	0.4 (0.2, 0.9)	0.9 (0.1, 3.3)
Active TB (95% confidence interval)	0.2 (0, 0.7)	0 (0, 3.8)	0.5 (0.1, 1.7)	0 (0, 2.8)	0.5 (0, 2.7)	0 (0, 9.4)	0.3 (0.1, 0.7)	0 (0, 1.4)
Death (95% confidence interval)	0.5 (0.2, 1.1)	1.3 (0, 7.0)	0.2 (0, 1.3)	1.9 (0.2, 6.8)	0 (0, 1.5)	0 (0, 9.4)	0.4 (0.1, 0.8)	1.4 (0.3, 4.0)

Incidence per 100 patient-years are reported, unless otherwise specified.

a Based on safety events that occurred up to week 112

b Based on safety events that occurred up to week 60

AS, ankylosing spondylitis; IV GLM, intravenous golimumab; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TB, tuberculosis

Disclosure: A. Kavanaugh, Janssen Research Development, LLC, 2; A. A. Deodhar, Janssen Research & Development, LLC, 2; S. Schwartzman, Janssen Research & Development, LLC, 2; S. Kafka, Janssen Scientific Affairs, LLC, 3; S. D. Chakravarty, Janssen Scientific Affairs, LLC, 3; E. C. Hsia, Janssen Research & Development, LLC, 3; D. D. Harrison,

Abstract Number: 1518

Baricitinib and Tofacitinib in Real Life – Does Obesity Impact Response to Janus Kinase Inhibitor Therapy in Rheumatoid Arthritis?

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The influence of obesity on treatment response of tumor necrosis factor inhibitors in patients with rheumatoid arthritis (RA) is described in literature, but data on Janus kinase inhibitors (JAKi) are scarce. We investigated the impact of obesity on the achievement of low disease activity (LDA = DAS28-ESR<3.2) in RA patients treated with JAKi.

Methods: In the German prospective longitudinal observational cohort RABBIT (Rheumatoid Arthritis: Observation of biologic therapy) RA patients are enrolled when they start a therapy with biologics, biosimilars, JAKi or new csDMARDs. We used RABBIT data reported between March 2017 and April 2018 of patients who started either baricitinib or tofacitinib. The time of JAKi treatment start was considered as baseline. Patients were stratified according to their BMI into normal weight (<25 mg/m²), overweight (25 - <30 mg/m²) and obese (≥30 mg/m²). Treatment response of patients with a baseline DAS28 ≥3.2 and available follow-up information within the first 6 months was investigated. Adjusted logistic regression models were applied to analyze the impact of BMI categories on LDA achievement (vs. non-response or stopping JAKi treatment).

Results: A total of N=539 patients started a treatment with JAKi; n=355 (66%) received baricitinib and n=184 (34%) tofacitinib. Baseline characteristics stratified by BMI category are given in table 1. Obese patients were not considerably older, but less often female compared to normal weight patients. Despite lower frequency of seropositivity, obese patients presented with higher values for DAS28 and fatigue, and had a worse physical function at baseline. Most of the patients received JAKi in recommended standard dosages.

Out of n=217 patients with available information, LDA was reached within the first 6 months of treatment by 42% of patients with normal weight and 41% with overweight, but only by 19% obese patients. Remission rates (DAS28<2.6) were 20%, 24% and 11% in the respective groups.

The regression model revealed a high negative impact of obesity on the achievement of LDA compared to normal weight (table 2). A better physical function at baseline and no prior biologic treatment increased the chance for LDA. We did not find an impact of JAKi dosage or mono-/ combination therapy on the response to treatment (data not shown).

Conclusion: Obesity but not overweight had a negative impact on the achievement of LDA in RA patients treated with JAKi. Further studies are needed to investigate factors that affect treatment response in obese patients.

Table 1 Baseline characteristics of patients starting JAKi stratified by BMI categories

	Normal weight N=204 (37.8%)	Overweight N=157 (29.1%)	Obesity N=158 (29.3%)
Age in years	57.9 ± 13.6	60.5 ± 11.3	59.6 ± 10.3
Female gender	169 (83.8%)	127 (72.8%)	109 (69.0%)
RA disease duration in years	14.5 ± 10.3	13.3 ± 8.6	11.4 ± 9.3
Rheumatoid factor or anti-CCP positivity	157 (77.3%)	130 (74.7%)	106 (67.5%)
DAS28-ESR	4.3 ± 1.3	4.6 ± 1.3	4.9 ± 1.5
% of full physical function (FFbH)	64.1 ± 23.3	63.3 ± 23.8	52.3 ± 25.8
Fatigue (NRS 0-10)	4.8 ± 2.6	5.0 ± 2.7	5.8 ± 2.8
BMI in kg/m ²	22.3 ± 1.8	27.3 ± 1.5	34.3 ± 3.8
Patients without comorbidities	44 (21.6%)	28 (15.8%)	9 (5.7%)
Patients with ≥ 3 comorbidities	94 (46.1%)	75 (42.4%)	88 (55.7%)
No. of prior biologic treatment failures	1.4 ± 1.8	1.1 ± 1.4	1.1 ± 1.4
No. of prior csDMARD treatment failures	2.4 ± 1.2	2.1 ± 1.1	2.1 ± 1.1
Start of baricitinib	138 (67.6%)	121 (68.4%)	96 (60.8%)
Start of tofacitinib	66 (32.4%)	56 (31.6%)	62 (39.2%)
JAKi monotherapy	75 (36.8%)	63 (35.6%)	58 (36.7%)
JAKi standard dosage (baricitinib 4 mg/d or tofacitinib 10mg/d)	178 (87.7%)	149 (84.2%)	132 (84.1%)

Values are given as N (%) or mean ± standard deviation

Table 2 Results of the logistic regression model for the probability of achieving LDA during the first 6 months of treatment

	Odds ratios	95% Confidence interval
Female gender	0.98	0.48; 2.05
RA disease duration	1.00	0.96; 1.04
DAS28-ESR at baseline	0.76	0.56; 1.02
Physical function	1.02	1.003; 1.03
No prior biologic (vs. ≥ 1 prior biologic)	1.97	1.03; 3.78
Therapy with Tofacitinib (vs. Baricitinib)	1.23	0.61; 2.43
Overweight (vs. Normal weight)	1.01	0.51; 2.01
Obesity (vs. Normal weight)	0.44	0.19; 0.99

Disclosure: Y. Meißner, Pfizer, Inc., 8; L. Baganz, None; M. Schneider, None; I. Schwarze, None; M. Feuchtenberger, MSD, 5, AbbVie Inc., 5, Roche, 5, Chugai, 5, Pfizer, Inc., 5, Lilly, 5, UCB, Inc., 5; A. Zink, BMS, Lilly, Pfizer, Roche, UCB, 8; A. Strangfeld, AbbVie, BMS, Lilly, MSD, Pfizer, Roche and UCB, 8.

Abstract Number: 1519

Patient Characteristics Associated with Discontinuation of Tofacitinib for the Treatment of Rheumatoid Arthritis in Open-Label, Long-Term Extension Studies up to 9.5 Years

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SESSION INFORMATION

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. We explored characteristics of patients (pts) who discontinued (d/c) open-label, long-term extension (LTE) studies.

Methods: Data were pooled from 2 LTE studies (NCT00413699 [ORAL Sequel LTE main study database locked at time of analysis: March 2017] and NCT00661661) in pts with RA who participated in qualifying Phase 1/2/3 index studies. Pts (N=4967) received tofacitinib 5 or 10 mg BID as monotherapy or with conventional synthetic DMARDs. We analyzed pts who d/c within: ≤1 yr, >1–≤3yrs, and >3 yrs, and study completers (Table 1). BL was that of the index study if pts began LTE treatment within 14 days of completing index study. Otherwise, LTE BL values were used. Demographics, reasons for

discontinuation, disease activity (DAS28-4[ESR]), physical function (HAQ-DI), serology (CRP, RF, anti-cyclic citrullinated peptide [CCP]), concomitant medications, and treatment-emergent adverse events (TEAEs) were analyzed descriptively for all tofacitinib-treated pts.

Table 1. Baseline demographics and disease characteristics at baseline and adverse event summary for all tofacitinib-treated patients

	Discontinued ^a			Completed ^b
	≤1 yr	>1 to ≤3 yrs	>3 yrs	
N	702	984	832	2416
Age (yrs, mean [SD])	54.4 (12.9)	53.7 (12.3)	54.2 (11.9)	52.3 (10.7)
Female (%)	80.2	82.6	82.1	82.5
BMI (kg/m ² , mean [SD])	28.3 (7.3)	27.0 (6.4)	27.4 (6.4)	26.4 (6.0)
Race (%)				
White	64.8	50.8	73.3	61.5
Black	4.4	3.5	2.5	2.2
Asian	21.7	26.2	15.4	26.8
Other	9.1	10.6	8.8	9.5
Geographic region (%)				
USA/Canada	38.2	26.2	31.6	19.7
Europe (EU and other)	24.5	26.4	35.5	36.7
Latin America	13.8	18.7	15.0	15.2
Asia	23.5	28.7	17.3	28.4
Smoking status (%)				
Never smoked	58.8	62.5	62.7	65.3
Previous or current smoker	39.6	35.9	34.6	33.6
Concomitant medications (%)				
Methotrexate	57.0	60.9	56.4	58.2
Glucocorticoids ^c	56.1	49.8	52.5	47.7
HAQ-DI (mean [SD])	1.5 (0.7)	1.5 (0.7)	1.4 (0.7)	1.4 (0.7)
DAS28-4[ESR] (mean [SD])	6.3 (1.0)	6.3 (1.0)	6.4 (1.0)	6.3 (1.0)
Disease duration (yrs, mean [SD]) ^d	8.1 (8.4)	8.2 (8.4)	8.8 (8.2)	7.3 (7.4)
CRP (mg/L, mean [SD])	18.7 (22.5)	18.9 (23.2)	18.2 (23.5)	19.0 (24.0)
RF+ (%)	62.8	71.0	66.3	71.2
Anti-CCP+ (%)	49.7	55.1	44.8	58.9
Total years of exposure	334	1880	3639	11,504
Reasons for discontinuation				
Adverse event ^e	353 (50.3)	500 (50.8)	378 (45.4)	
No longer willing to participate	137 (19.5)	207 (21.0)	160 (19.2)	N/A
Insufficient clinical response	72 (10.3)	57 (5.8)	50 (6.0)	

^aDiscontinued subgroups are defined based on the time of discontinuation during the active treatment period relative to baseline for the long-term extension study. ^bCompleted is defined as patients (completers) who remained in the study until the study was closed in their respective country, or who completed the study due to their respective country's regulatory authority's requirements. ^cIncludes prednisone or equivalent. ^dDisease duration is defined from first diagnosis to Day 1 of this qualifying study. ^eRelated and not related to study drug according to investigator. BMI, body mass index; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS28-4[ESR], Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; RF, rheumatoid factor; SD, standard deviation; yrs, years.

Table 2. Disease activity for all tofacitinib-treated patients by time period

	Discontinued ^a			Completed ^b		
	≤1 yrs	>1 to ≤3 yrs	>3 yrs	≤1 yrs	>1 to ≤3 yrs	>3 yrs
All tofacitinib-treated patients, mean (SE)						
N ^c	561	975	831	18	180	228
CRP	8.97 (0.61)	8.29 (0.53)	8.29 (0.65)	6.99 (2.45)	8.82 (0.77)	8.99 (0.21)
ΔCRP	-9.55 (0.96)	-10.56 (0.84)	-8.89 (1.00)	-2.46 (2.82)	-13.44 (1.88)	-4.19 (0.53)
N ^c	623	951	776	18	137	220
DAS28-4[ESR]	4.22 (0.06)	3.78 (0.05)	3.88 (0.05)	4.58 (0.38)	3.23 (0.11)	3.22 (0.02)
ΔDAS28-4[ESR]	-2.11 (0.06)	-2.55 (0.01)	-2.55 (0.01)	-1.88 (0.39)	-2.80 (0.13)	-0.88 (0.01)
N ^c	652	974	822	18	140	225
HAQ-DI	1.87 (0.03)	0.88 (0.02)	0.90 (0.02)	1.03 (0.16)	0.82 (0.05)	0.84 (0.01)
ΔHAQ-DI	-0.43 (0.02)	-0.58 (0.02)	-0.52 (0.02)	-0.21 (0.19)	-0.68 (0.05)	-0.60 (0.01)

^aDiscontinued subgroups are defined based on the time of discontinuation during the active treatment period relative to baseline for the long-term extension study; values are from the last available visit before discontinuation.

^bCompleted subgroups are defined based on the time between enrollment and study completion for patients (completers) who remained in the study until the study was closed in their respective country, or who completed the study due to their respective country's regulatory authority's requirements.

^cN, the number of patients with non-missing data for a given analysis.

ΔCRP, change from baseline in C-reactive protein level; ΔDAS, change from baseline in disease activity score; ESR, erythrocyte sedimentation rate; ΔHAQ-DI, change from baseline in Health Assessment Questionnaire-Disability Index; SE, standard error; yrs, years.

Results: Of 4934 pts in this analysis, 2518 (51.0%) d/c (702 within<1 yr; 984 >1–≤3 yrs; 832 >3 yrs), predominantly due to AEs (n=1231; 48.9%), and 2416 (49.0%) pts were completers (Table 1); 33 pts ongoing in the LTE at database lock were not included. At BL, pts who d/c had numerically longer disease duration and more pts were from USA/Canada, current or ex-smokers, or used glucocorticoids than completers. Pts who d/c >1 yr had numerically lower values and a greater change from BL in CRP, DAS28-4(ESR), and HAQ-DI than pts who d/c ≤1yr, and had higher values and a lower change from BL than completers for all parameters (Table 2). TEAEs were reported by 91.4% of evaluable completers and 80.6%, 92.0%, and 97.0% of evaluable pts who d/c within ≤1, >1–≤3, and >3yrs, respectively. Of pts with TEAEs, 62.4%, 55.2%, and 46.8% d/c due to TEAEs within ≤1, >1–≤3, and >3 yrs, respectively. Among the most common TEAEs experienced by all groups were nasopharyngitis, upper respiratory tract infection, urinary tract infection, herpes zoster, and bronchitis. Pneumonia was more frequently observed in pts who d/c (5.7% [≤1 yr], 7.1% [>1–≤3 yrs], and 6.9% [>3 yrs]) than in completers (2.9%).

Conclusion: Pts who d/c had a longer disease duration at BL, and were more likely to use glucocorticoids, be smokers/ex-smokers, and be from USA/Canada than completers. Pts who d/c ≤1 year had higher disease activity than those who d/c >1 year; pts who d/c >1 year had higher disease activity than completers, supporting close monitoring of pts. Of pts with TEAEs, discontinuation due to TEAEs was more frequently observed in pts who d/c ≤1 yr.

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DMARD Hepatotoxicity in Rheumatoid Arthritis and Its Association with the Surrogates of Metabolic Syndrome

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Background/Purpose: Hepatotoxicity is a common reason why DMARDs are abandoned or changed in RA. We hypothesize that features of metabolic syndrome (such as obesity, dyslipidemia, and diabetes) are risk factors for DMARD hepatotoxicity in RA.

Methods: We conducted a retrospective chart review of 361 patients with RA listed as the primary diagnosis code for ≥ 3 consecutive visits. Demographic information, BMI, lipid panel, prior alcohol use, smoking status, viral hepatitis serologies,

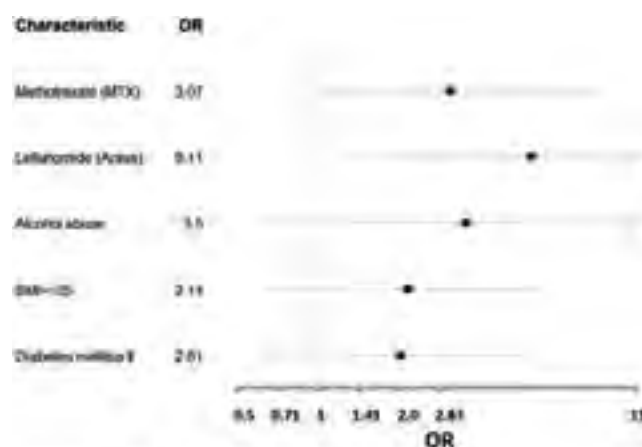


Figure 1: Adjusted Odds Ratios [OR] for DMARD Hepatotoxicity

Characteristic	Percentage
Gender	
Female	82.3
Male	17.7
Race	
African American	47.1
Asian	1.9
Caucasian	47.6
Other	3.3
BMI ^a	7.6
<25	31.2
25 - 35	53.6
≥35	15.1
Smoking status ^b	
Yes, current	24.4
Former	22.8
Never	52.8
Alcohol use ^c	
Active alcohol abuse	1.3
Previous alcohol abuse	3.5
Current use	42.2
No alcohol use	53.0
CCP +	50.7
RF +	51.9
Current statin	21.1
Reported diabetes mellitus II	17.8
DMARD started: methotrexate	57.3
DMARD started: leflunomide	6.4
DMARD started: hydroxychloroquine	40.7
DMARD changed / decreased due to hepatotoxicity	5.5

Table 1: Baseline Characteristics

statin use, seropositive status, and type of DMARD used were recorded at the initial visit. Patients with active hepatitis B and C were excluded from analysis. DMARD hepatotoxicity was defined as change of DMARD or dose decrease of DMARD with corresponding provider documentation of concern for hepatotoxicity. Using exact logistic regression, odds ratios for the risk factors of DMARD hepatotoxicity were calculated.

Results: Out of the 361 patients reviewed: 15.1% had BMI > 35 and 17.8% had a diagnosis of diabetes mellitus II. Table 1 has additional baseline information. 20 of 361 patients (5.5 %) had DMARD hepatotoxicity. Methotrexate (OR 3.07) and leflunomide (OR 6.11) were significantly associated with risk of DMARD hepatotoxicity. Figure 1 demonstrates the adjusted odds ratios for BMI, diabetes, and alcohol abuse as risk factors for DMARD hepatotoxicity. HDL ≤ 40 had an unadjusted OR of 2.98 (0.74 – 12; p 0.119) toward being a risk factor for DMARD hepatotoxicity. RF or anti-CCP seropositivity, statin-use, age, and sex did not demonstrate a correlation value to suggest they are risk factors.

Conclusion: Our study does suggest that several surrogates of metabolic syndrome such as BMI and diabetes mellitus are likely risk factors for development DMARD hepatotoxicity, especially with methotrexate and leflunomide. Though the study was underpowered for the statistical significance on some of these variables, clinicians should consider features of metabolic syndrome as potential risk factors for hepatotoxicity with DMARD use. Further studies need to be performed examining this relationship.

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Anti-IL-6 Therapy Modulates Leptin in Patients with Rheumatoid Arthritis

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Background/Purpose: Leptin is an adipokine that plays an important role in the regulation of body weight and also participates in immune homeostasis and inflammatory processes^{1,2}. Chronic systemic inflammation is of major importance in the development of atherosclerosis in rheumatoid arthritis (RA)³. IL-6 blocker yields a rapid improvement of endothelial function⁴. Therefore, the aim of this study was to determine whether the infusion of IL-6 blockade improves the endothelial function by altering circulating leptin concentrations in patients with RA.

Methods: 50 Spanish patients on treatment with anti-IL-6 monoclonal antibody-Tocilizumab who fulfilled the 2010 classification criteria for RA⁵ were recruited. Patients with diabetes mellitus or plasma glucose >110 mg/dl were excluded. Leptin serum levels were determined immediately prior to (time 0) and after (time 60 minutes) Tocilizumab infusion by ELISA.

Results: A significant reduction in leptin concentration was observed following Tocilizumab infusion (mean \pm standard deviation (SD): 9.24 ± 7.98 ng/ml versus 7.91 ± 7.36 ng/ml, $p < 0.0011$). In addition, a significant positive correlation between leptin concentration and insulin resistance (HOMA at the time of the study) was found ($r=0.40$; $p=0.0046$). Furthermore, a significant negative correlation between leptin levels and insulin sensitivity (QUICKI) was disclosed ($r = -0.46$; $p=0.0009$).

Conclusion: Our study confirms that circulating leptin concentrations are modulated by anti-IL-6 treatment. In addition, leptin concentration correlates with insulin resistance and sensitivity. The beneficial effect of anti-IL-6 blockage on cardiovascular mortality in RA may be mediated by reduction in serum levels of leptin.

References: [1] Nat Rev Immunol 2006; 6: 772-83. [2] Nat Rev Immunol 2006; 6: 772-83. [3] Autoimmun Rev 2016; 15: 1013-30. [4] Atherosclerosis 2011; 219: 734-6. [5] Arthritis Rheum 2010; 62: 2569-81.

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Time Dependent Effect of Biologic Therapy on Overall Survival in Patients with Rheumatoid Arthritis and Cancer

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Background/Purpose: Biologic disease-modifying anti-rheumatic drugs (bDMARDs) are commonly used in the treatment of rheumatoid arthritis (RA). But the use of bDMARDs in patients with RA and cancer is controversial.

Methods: We performed a retrospective cohort study of patients with prevalent RA and cancer seen at MD Anderson Cancer Center between 2002 and 2014. Cancer patients were identified from the institutional tumor registry and RA patients were identified through ICD-9 codes and verified by chart review. Patients were followed until 2016 to assess overall survival (OS). We built Cox Proportional Hazard regression models using bDMARD therapy as a time-varying covariate.

Results: We identified 431 patients with RA of which 111 received bDMARDs at various times after a cancer diagnosis. Of these 111 patients, 60 received bDMARDs prior to the cancer diagnosis and remained on bDMARDs following the cancer diagnosis. In a multivariable model stratified by tumor type and stage and after adjusting for age at diagnosis, OS in patients that received tumor necrosis factor (TNF) inhibitors was compared to patients who never received bDMARDs with a hazard ratio (HR) of 0.67 (95% confidence interval (CI), 0.31, 1.44). Patients who received non-TNF bDMARDs had a HR of 1.10 (95% CI, 0.26, 4.60) compared to those without treatment. These differences were not statistically significant (overall effect $p=0.58$). We evaluated the effects of bDMARDs in a subgroup of 175 breast cancer patients (the largest subgroup, to remove the confounding effect of tumor type on OS) with RA. Of these patients 25% ($n=44$) received bDMARDs, 35 received TNF inhibitors and 9 received non-TNF bDMARDs. Fifty-two percent of these patients were on bDMARDs prior to cancer and continued after a cancer diagnosis. Another 16% were started on bDMARDs within the first 5 years after cancer diagnosis and the remaining 32% received the first dose > 5 years after cancer diagnosis. Only two patients with distant stage received bDMARDs. In a multivariable model, after adjusting for age at diagnosis and tumor stage, compared to the patients who never received bDMARDs, the patients who received TNF inhibitors (HR, 1.21; 95% CI, 0.38, 3.87) or non-TNF bDMARDs (HR, 1.86; 95% CI, 0.34, 10.3) had inferior OS. However, these differences were not statistically significant (overall effect $p=0.75$).

Conclusion: We did not observe any statistically significant differences in OS between those that received bDMARDs and those that did not in patients with RA and cancer. More research is necessary to evaluate the effects of bDMARDs in a larger sample of cancer patients, especially with respect to individual tumors, and also in those with early or advanced cancer.

Disclosure: X. Pundole, None; N. Zamora, None; H. Siddhanamatha, None; J. Tayar, None; C. H. Leung, None; H. Lin, None; M. Suarez-Almazor, None.

Pain Is Improved in Around 50% of Patients and Fatigue in 40% of Patients with Rheumatoid Arthritis Treated with Sarilumab in the Target, Mobility and Monarch Trials

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SESSION INFORMATION

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Background/Purpose: Pain and fatigue are common symptoms of rheumatoid arthritis (RA) and can severely impact patients' quality of life. With multiple biologic disease-modifying antirheumatic drugs (bDMARDs) available for RA, symptoms such as pain and fatigue may play an increasing role in shared decision-making. Sarilumab is a human monoclonal antibody that blocks interleukin-6 (IL-6) from binding to both membrane-bound and soluble IL-6 receptor- α ; it is indicated for the treatment of moderate-to-severely active RA in adult patients who have had an inadequate response to ≥ 1 DMARDs. The objective of this study was to explore the effect of sarilumab on pain and fatigue in patients with moderate-to-severely active RA.

Methods: *Post hoc* statistical analyses were performed using data from sarilumab randomized controlled trials: TARGET (NCT01709578) and MOBILITY (NCT01061736) (sarilumab 150 or 200 mg every 2 weeks [q2w] vs placebo, combined with conventional synthetic DMARDs), and MONARCH (NCT02332590), (sarilumab 200 mg q2w vs adalimumab 40 mg q2w). At each study visit, pain was assessed using a 0–100 mm visual analog scale (VAS); fatigue was assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale. The proportion of patients achieving $\geq 30\%$ / $\geq 50\%$ / $\geq 70\%$ pain VAS and FACIT-F improvement, and median time to first pain VAS and FACIT-F $\geq 50\%$ improvement was assessed at Week 24 in TARGET and MONARCH, and Weeks 24 and 52 in MOBILITY (not pooled). Median time to first pain VAS and FACIT-F $\geq 50\%$ improvement was analyzed by Kaplan–Meier. *P*-values were considered nominal.

Table. Pain and fatigue 30%/50%/70% improvement in TARGET, MOBILITY, and MONARCH

	30% improvement			50% improvement			70% improvement		
	Patients (%)	OR (95% CI)	P-value ¹	Patients (%)	OR (95% CI)	P-value ¹	Patients (%)	OR (95% CI)	P-value ¹
Pain VAS									
TARGET²									
Placebo + cDMARDs	53.7			24.2			11.3		
Sarilumab 150 mg + cDMARDs	50.3	2.16 (1.39, 3.27)	0.0016	38.7	3.00 (1.29, 7.03)	0.0037	24.3	2.21 (1.29, 3.91)	0.0048
Sarilumab 200 mg + cDMARDs	54.3	2.63 (1.67, 3.97)	<0.0001	43.5	3.43 (1.34, 8.63)	0.0001	28.8	3.26 (1.79, 5.93)	0.0003
MOBILITY²									
Placebo + MTX	53.7			50.1			12.6		
Sarilumab 150 mg + MTX	52.3	2.37 (1.77, 3.18)	<0.0001	58.3	2.19 (1.36, 3.85)	<0.0001	25.8	2.41 (1.88, 3.06)	<0.0001
Sarilumab 200 mg + MTX	50.1	3.04 (2.27, 4.07)	<0.0001	45.9	2.84 (1.69, 4.89)	<0.0001	38.8	3.08 (2.13, 4.41)	<0.0001
MONARCH²									
Placebo (Week 52)	49.8			27.1			12.8		
Sarilumab 150 mg + MTX (Week 52)	49.2	2.28 (1.71, 3.08)	<0.0001	41.3	2.46 (1.62, 3.88)	<0.0001	30.3	3.06 (2.13, 4.42)	<0.0001
Sarilumab 200 mg + MTX (Week 52)	53.1	2.71 (2.03, 3.63)	<0.0001	42.9	2.86 (1.84, 4.67)	<0.0001	33.3	3.06 (2.12, 4.42)	<0.0001
MOBILITY²									
Adalimumab 40 mg	52.6			33.4			38.4		
Sarilumab 200 mg	65.2	1.76 (1.12, 2.78)	0.0131	48.4	3.05 (1.34, 6.93)	0.0009	37.7	1.76 (1.04, 2.98)	0.0338
FACIT-F									
TARGET²									
Placebo + cDMARDs	22.8			22.1			48.0		
Sarilumab 150 mg + cDMARDs	39.8	1.56 (1.03, 2.48)	0.0424	32.8	1.71 (1.09, 2.67)	0.0204	27.8	2.02 (1.18, 3.43)	0.0093
Sarilumab 200 mg + cDMARDs	48.2	1.86 (1.22, 2.84)	0.0041	38.4	2.05 (1.38, 3.06)	0.0024	27.2	1.94 (1.17, 3.23)	0.0088
MOBILITY²									
Placebo + MTX	38.3			38.8			15.6		
Sarilumab 150 mg + MTX	38.3	1.63 (1.29, 2.21)	0.0016	27.5	1.94 (1.07, 3.54)	0.0300	15.3	1.91 (1.27, 2.88)	0.0016
Sarilumab 200 mg + MTX	43.9	2.33 (1.64, 3.31)	<0.0001	37.3	2.58 (1.69, 3.88)	<0.0001	21.1	2.60 (1.49, 4.58)	<0.0001
MONARCH²									
Placebo (Week 52)	23.8			13.3			40.2		
Sarilumab 150 mg + MTX (Week 52)	35.9	1.84 (1.31, 2.61)	0.0001	27.3	2.19 (1.43, 3.38)	<0.0001	17.3	1.87 (1.24, 2.81)	0.0027
Sarilumab 200 mg + MTX (Week 52)	35.8	1.87 (1.37, 2.55)	<0.0001	27.3	2.11 (1.46, 3.03)	<0.0001	21.3	2.59 (1.58, 4.38)	<0.0001
MOBILITY²									
Adalimumab 40 mg	44.3			32.4			50.2		
Sarilumab 200 mg	51.7	1.50 (1.07, 2.08)	0.0190	48.2	1.85 (1.03, 3.31)	0.0330	28.8	1.52 (0.88, 2.63)	0.2032

cDMARDs: conventional synthetic disease-modifying antirheumatic drugs; MTX: methotrexate; OR, odds ratio.
Data reported at Week 24 (Week 52/Week 52).
¹Values placebo; ²Values sarilumab 150 mg/sarilumab 200 mg.

Results: 546 patients from TARGET, 1197 from MOBILITY, and 369 from MONARCH were included. In TARGET and MOBILITY, more patients receiving sarilumab 150 or 200 mg achieved $\geq 30\%$ / $\geq 50\%$ / $\geq 70\%$ improvements in pain and fatigue than placebo. In MONARCH, more patients receiving sarilumab 200 mg achieved $\geq 30\%$ / $\geq 50\%$ / $\geq 70\%$ improvements in pain and fatigue than adalimumab. (**Table**). Overall, pain was improved by at least 30% in around 50% of patients and fatigue in 40% of patients (**Table**). Median time to first pain $\geq 50\%$ improvement was shorter for patients receiving sarilumab 200 mg than both placebo (12 vs 24 weeks) in TARGET and MOBILITY or adalimumab (12 vs 16 weeks) in MONARCH. Median time to first fatigue $\geq 50\%$ improvement was shorter for patients receiving sarilumab 200 mg vs placebo (TARGET: 12 vs 24 weeks, MOBILITY 52 weeks vs not reached) with no significant advantage vs adalimumab. In these clinical studies, sarilumab had a safety profile consistent with IL-6 inhibition.

Conclusion: In this study of patients with moderate-to-severely active RA, sarilumab demonstrated faster and greater pain improvement vs placebo or adalimumab. In addition, sarilumab demonstrated faster and greater fatigue improvement vs placebo but not adalimumab. These results are important to consider in RA treatment decision-making.

Disclosure: L. Gossec, Pfizer, Inc., 2, 9; S. Boklage, Regeneron Pharmaceuticals, Inc., 1, 3; G. St. John, Regeneron Pharmaceuticals Inc., 1, 3; H. van Hoogstraten, Sanofi, Novartis, 1, Sanofi, 3; T. Kimura, Regeneron Pharmaceuticals Inc., 1, 3.

Abstract Number: 1524

Malignancies and Serious Infections in Randomized Controlled Trials of Janus Kinase Inhibitors in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Two JAK inhibitors are currently approved by different agencies worldwide for their use in patients with rheumatoid arthritis. The safety profile of these agents has been of interest since the approval of the first JAK inhibitor, particularly the risk of developing malignancies or serious infections. Therefore, we conducted a systematic review and meta-analysis of phase 2 and phase 3 trials to evaluate these two outcomes in patients receiving JAK inhibitors for rheumatoid arthritis.

Methods: We performed a search in 5 electronic databases and also searched <http://clinicaltrials.gov/>, Food and Drug Administration, and European Medicines Agency. In addition, the bibliography list of included studies was also screened to search for further citations not retrieved from other sources. We included controlled trials evaluating the efficacy of a JAK inhibitor (i.e., tofacitinib, baricitinib, filgotinib, peficitinib, ABT-494, or decenotinib). Two reviewers independently screened studies, evaluated their risk of bias, and extracted data. Primary outcome data included number and type of malignancies and infections and time point of occurrence when available. The reported publications were considered the primary source of data for all trials. Serious infections were defined as those meeting the criteria for a serious adverse event such as a fatal, life threatening, or leading to hospitalization.

Results: Thirty-six trials were analyzed, reporting data on 15,602 patients. Follow-up of the included trials ranged between 4 and 52 weeks with a median of 24 weeks. The risk of attrition bias was judged low for most studies. The reported rates of malignancies and serious infections across studies ranged from 0% to 1.7% and 0% to 5.5%, respectively. Most commonly reported malignancies were lung cancer, melanoma, non melanoma skin cancer, basal cell and squamous cell carcinoma. Patients receiving the combination of JAK inhibitor plus methotrexate or JAK inhibitor monotherapy had higher rates of malignancies, compared with methotrexate between 12 and 24 weeks before the rescue treatment was

implemented, but the difference did not reach statistical significance (odds ratio (OR) 1.92, 95% confidence interval (CI) 0.78 to 4.76 and 1.40, 95% CI 0.26 to 7.59, respectively). Regarding serious infections, the JAK inhibitor groups had similar rates to those observed in the control groups (OR 1.07, 95%CI, 0.68 to 1.67, and 0.95, 95% CI, 0.46 to 1.98, respectively). However, there was a dose-response effect with higher rates of serious infections observed in those patients receiving higher doses of JAK inhibitors.

Conclusion: Although not reaching statistical significance, in the currently available RCTs, the rates of malignancy were higher in the JAK inhibitors groups compared to their controls. The rates of serious infections were similar between JAK inhibitor groups and their controls, but were dose-dependent. Future studies should aim to indirectly compare each JAK inhibitor to evaluate if these safety signals are also drug dependent and to assess risk per type of malignancy or infection.

Disclosure: M. A. Lopez-Olivo, None; J. Tayar, None; N. Zamora, None; G. Pratt, None; M. Suarez-Almazor, Pfizer, Inc., 5,Endo Pharmaceuticals, 5,Bristol-Myers Squibb, 5.

Abstract Number: 1525

Effect of JAK-Inhibitor Versus Bdmards on Quality of Life in Rheumatoid Arthritis : A Meta Analysis of Randomized Controlled Trials

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Recent studies comparing JAK-inhibitors (Jak-i) and adalimumab seem to show a better efficacy of JAK-i on patient-reported outcomes in rheumatoid arthritis (RA). As there is no study comparing directly the JAK-i with other biologic DMARDs (bDMARDs), we performed a meta-analysis and compared the effect size of JAK-i and bDMARD versus synthetic DMARDs (sDMARDs) on quality of life

Methods: We performed a systematic review of the literature until May 2018 using database including : MEDLINE (via PUBMED), EMBASE and abstracts from the ACR and EULAR congresses 2015-2017. We selected all randomized controlled trials (RCT) comparing quality of life (evaluated by SF36) in patient with rheumatoid arthritis treated with bDMARD or JAK-i versus sDMARDs. We performed meta-analysis comparing the effect size of JAK-i (versus sDMARDs) and bDMARD (versus sDMARDs) on PCS SF36 and MCS SF36 at 12 weeks. Statistical analysis determined in each study effect size. Pooled ES were computed by meta-analysis. Data were analyzed using the inverse variance approach.

Results: The literature search identified 240 articles plus one found by manuel search and no congress abstract. Finally, 44 articles met the inclusion criteria.

JAK-i and bDMARD showed higher level of quality of life than sDMARDs. The results concerning the meta-analysis comparing the effect size are:

- For the SF36 PCS at 12 weeks: JAK-i: +4,82 IC95% [3,88, 5,77] and bDMARDs : +3,99 IC95% [2,81, 5,18]
- For the SF36 MCS a 12 weeks: JAK-i: +3,42 IC95% [2,24, 4,60] and bDMARD: 2,99 IC95% [2,02, 3,96]

The range of the confidence intervals seems similar between JAK-I and bDMARDs.

SF36 PCS at 12 weeks:

-Results for JAK-i:

Conclusion: In this meta-analysis, JAK-inhibitor and bDMARD showed better SF36 PCS and MCS at 12 weeks in comparison with sDMARDs.

The range of the confidence intervals seems similar between JAK-I and bDMARDs, suggesting a similar efficiency on the components of the SF36.

More head-to-head studies are needed to draw definitive conclusions on potential efficacy differences between JAK-inhibitor and bDMARDs in RA.

Disclosure: M. Boudhabhay, None; T. Barnetche, Roche SAS, 5,Chugai Pharma France, 5; P. Vergne-Salle, None.

Baseline Characteristics and Outcomes in Patients with Anemia in Clinical Studies of Tofacitinib

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SESSION INFORMATION

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. The purpose of this study is to describe the profile of patients (pts) with RA and clinically significant anemia, and the impact of tofacitinib on those with anemia.

Methods: In this post hoc analysis, data were pooled from Phase (P)2, P3, and P3b/4 studies across the tofacitinib clinical program. Pts received tofacitinib 5 or 10 mg BID with/without background csDMARDs, or placebo (PBO). Pts with grade ≥ 2 anemia (G2A; Hgb < 10 g/dL) at baseline (BL) were compared to pts without G2A (Hgb ≥ 10 g/dL) at BL. Demographic and BL characteristics, Hgb levels and efficacy (DAS28-4[ESR]) at Month (M)6, and treatment-emergent adverse events (TEAEs) were summarized descriptively.

Results: The proportion of pts with G2A at BL was similar for tofacitinib (3.2%, 152 of 4736 pts) and PBO (2.4%, 27 of 1125 pts) groups. Presence of G2A at BL was higher in those with female gender, Asian ethnicity, never smoker status, lower age and BMI, and higher CRP and ESR, compared to pts without G2A; RA duration was generally similar across groups (Table). Tofacitinib seemed to improve anemia more rapidly than PBO: among pts with G2A at BL, a lower proportion of those receiving tofacitinib had G2A at M1 and M3 compared with those receiving PBO (48.8 vs 75.0% and 36.1 vs 57.1%), while the proportions were similar at M6 (28.9 vs 30.6%). Among pts receiving tofacitinib, mean Hgb levels gradually increased from BL to M6 in those with G2A at BL (1.25 g/dL change), but not in those without G2A at BL (0.15 g/dL change). In pts receiving tofacitinib with and without G2A at BL, DAS28-4(ESR) scores decreased from BL to M6 by -2.40 and -2.42, respectively. DAS28-4(ESR) low disease activity rate at M6 was lower in tofacitinib-treated pts with G2A at BL than in those without G2A at BL (18.3 vs 28.4%). Among pts receiving tofacitinib, those with BL G2A had a higher incidence of TEAEs than those without BL G2A in the following MedDRA system organ classes (with incidence $> 20\%$ in pts with and without BL G2A): gastrointestinal disorders (30.9% vs 22.5%) and infections and infestations (44.1% vs 39.0%).

Conclusion: In these studies, female gender, Asian ethnicity, never smoker status, low BMI and elevated ESR/CRP seemed to be associated with G2A at BL. G2A resolved within 6 months in most pts with RA receiving tofacitinib, while inflammation and disease activity (assessed by DAS28-4[ESR] scores) decreased. G2A appeared to resolve more rapidly in pts receiving tofacitinib than in those receiving PBO. These data suggest that tofacitinib can be a treatment option for pts with active RA and anemia. In pts with Hgb < 8 g/dL or a decrease in Hgb > 2 g/dL, however, it is recommended that tofacitinib dosing is interrupted until Hgb levels have normalized.¹

1 US Food and Drug Administration. XELJANZ[®] (tofacitinib) highlights of prescribing information. Available at: <http://labeling.pfizer.com/ShowLabeling.aspx?id=959>. Accessed June 4, 2018.

Disclosure: B. Moeller, None; A. Finckh, AbbVie, A2Bio, Bristol-Myers Squibb, MSD, Roche, Pfizer Inc, UCB, 5; J. M. Alvaro-Gracia, AbbVie, Bristol-Myers Squibb, Eli Lilly, MSD, Novartis, Pfizer Inc, Roche, Sanofi, UCB, 5; AbbVie, Bristol-Myers Squibb, Eli Lilly, MSD, Novartis, Pfizer Inc, Roche, Sanofi, UCB, 8; G. Scholz, None; D. Aletaha, AbbVie, Bristol-Myers Squibb, MSD, 2; AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Medac, Merck, MSD, Pfizer Inc, Roche, UCB, 5; AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Medac, Merck, MSD, Pfizer Inc, Roche, UCB, 8; F. Biondo, Pfizer Inc, 1, Pfizer Inc, 3; S. Strengtholt, Pfizer Inc, 1, Pfizer Inc, 3; J. L. Rivas, Pfizer Inc, 1, Pfizer Inc, 3; C. A. Connell, Pfizer Inc, 1, Pfizer Inc, 3; H. Shi, Pfizer Inc, 1, Pfizer Inc, 3.

Table. Demographics and disease characteristics at baseline

Hgb levels at baseline	<10 g/dL (with G2A)		≥10 g/dL (without G2A)	
	Tofacitinib 5 + 10 mg BID	Placebo	Tofacitinib 5 + 10 mg BID	Placebo
N	152	27	4584	1098
Age group, yrs (%)				
18–45	40.8	63.0	27.3	34.3
45–65	46.1	25.9	58.6	50.7
≥65	13.2	11.1	14.1	16.0
Age, yrs (mean [SD])	48.9 (13.1)	45.1 (13.7)	52.0 (12.0)	53.1 (12.0)
Female (%)	96.1	96.3	82.7	81.2
BMI, kg/m ² (mean [SD])	23.9 (5.3)	24.7 (7.1)	27.3 (6.5)	27.5 (6.7)
Race (%)				
White	39.5	37.0	64.4	66.9
Black	3.3	14.8	3.4	3.2
Asian	47.4	33.3	21.7	22.1
Other	8.9	14.8	10.5	7.7
Smoking status (%)				
Never smoked	85.5	85.2	65.2	56.0
Previous or current smoker	13.8	14.8	33.5	37.9
Unknown	<1.0	0.0	1.3	6.1
HAQ-DI (mean [SD])	1.7 (0.7)	1.6 (0.7)	1.5 (0.7)	1.4 (0.7)
DAS28-4(ESR; mean [SD])	6.9 (0.9)	7.0 (0.9)	6.4 (1.0)	6.3 (1.0)
Disease duration, yrs (mean [SD])	7.1 (7.8)	7.3 (7.0)	7.7 (7.9)	9.4 (8.6)
ESR, mm/hr (mean [SD])	77.8 (31.5)	69.7 (31.5)	49.5 (26.6)	45.4 (24.7)
CRP, mg/L (mean [SD])	39.1 (37.7)	34.7 (27.6)	17.7 (22.4)	16.0 (18.2)
RF+ (%)	73.4	65.2	72.3	68.6
Anti-CCP+ (%)	61.8	51.9	52.4	47.5
Hgb, g/dL (mean [SD])	9.4 (0.4)	9.3 (0.6)	12.8 (1.4)	12.9 (1.3)

Data were pooled from the following Phase 2, Phase 3 and Phase 3b/4 studies across the tofacitinib clinical program: NCT00147498; NCT00413660; NCT00960440; NCT00550446; NCT00603512; NCT00687193; NCT00847613; NCT00814307; NCT00856544; NCT00853385; NCT01164579; NCT01039688; NCT00976599; NCT01059864; NCT01359150; NCT02147587; NCT02187055

Treatment groups are based on initial randomized study drug.

BID, twice daily; BMI, body mass index; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; G2A, grade ≥2 anemia; HAQ-DI, Health Assessment Questionnaire-Disability Index; Hgb, hemoglobin; RF, rheumatoid factor; SD, standard deviation; yrs, years

Tofacitinib Improves Left Ventricular Mass and Cardiac Output in Rheumatoid Arthritis Patients with Chronic Heart Failure

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SESSION INFORMATION

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Background/Purpose: Rheumatologists need to develop primary and secondary prevention strategies for cardiovascular disease (CVD) in rheumatoid arthritis (RA) patients. We reported tofacitinib (Tofa) (with or without methotrexate) improved left ventricular mass index (LVMI) in patients with rheumatoid arthritis^{1,2}. We have experienced RA patient with chronic heart failure (CHF). We couldn't use some TNF blockers in RA patients with CHF³. There is no evidence that Tofa effects on left ventricular (LV) morphology and function in RA patients with CHF. To study the effect of Tofa on LV morphology and function in conventional synthetic (cs) DMARDs resistant active RA patients with CHF, in a cohort study design.

Methods: RA patients with CHF were eligible if they had active disease despite treatment with cs DMARDs. Consecutive 42 patients with moderate to severe active RA patients (DAS28>3.2) despite cs DMARDs were received Tofa plus cs DMARDs. LV morphology and function was assessed with cardio-MRI at baseline and 24 weeks follow-up. Cardiovascular risk factors and clinical data were collected at regular visits.

Results: 37 patients completed 24 weeks. New York heart association functional classification (NYHA) class 1 is 24 cases, class 2 is 9 cases, and class 3 is 4 cases respectively. Left ventricular mass index (LVMI) was attenuated significantly by Tofa (week 0-week24, -9.45 ± 7.8 g/m²; $p=0.02$). Cardiac output (CO) was attenuated significantly by Tofa (week 0-week24, 0.4234 ± 1.1 l/min). DAS28 and CRP improved significantly by Tofa (week 0-week 24; DAS28: -1.96 ± 0.88 ; CRP: -2.11 ± 5.7 mg/l) ($p<0.05$). Surprisingly, the change of disease activity (DAS 28 and CRP) is no correlation with the change of LVMI or CO in this study. Observationally, 3 cases significantly improved right ventricular mass as well as left ventricular mass (10 % improved right ventricular mass index from baseline).

Conclusion: Tofa improved LVMI and CO in active RA despite cs DMARDs with CHF. Tofa might be improving LVMI and CO independently of its effects on disease activity. Tofa might be improved right ventricular mass. JAK-STAT pathway might be an important role of LV hypertrophy. Tofa, JAK-STAT pathway blocking, may prevent cardiovascular morbidity and mortality in RA with CHF.

References: 1) Tofacitinib improves left ventricular mass and cardiac output in patients with rheumatoid arthritis. Kume K, et al. presentation at annual meeting of EULAR 2017
2) Tofacitinib monotherapy improves left ventricular mass and cardiac output in patients with rheumatoid arthritis. Kume K, et al. presentation at annual meeting of ACR 2017
3) The benefit/risk profile of TNF-blocking agents: findings of a consensus panel. Hochenberg MC et al. Semin Arthritis Rheum. 2005 Jun; 34(6):819-36.

Disclosure: K. Kume, None; K. Amano, None; S. Yamada, None; T. Kanazawa, None; K. Hatta, None.

Abstract Number: 1528

Unique Changes in Hemoglobin with Sarilumab Versus Adalimumab Are Independent of Better Disease Control in Patients with Rheumatoid Arthritis (RA)

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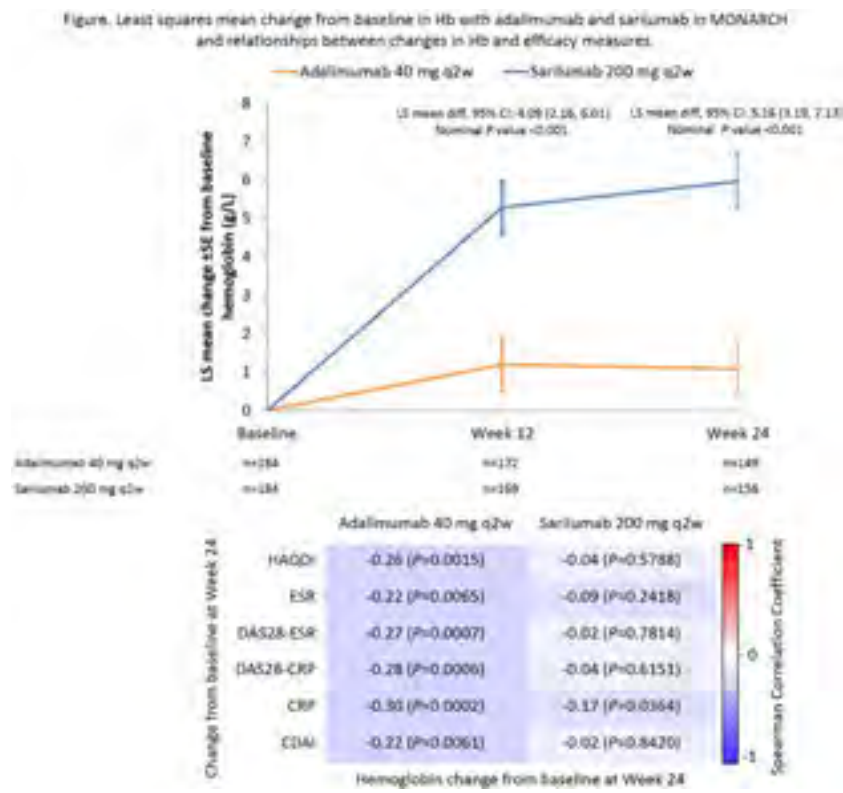
SESSION INFORMATION

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Session Type: ACR Poster Session B
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Background/Purpose: Anemia (WHO criteria: Hemoglobin [Hb] levels <12.0 g/dL [females] or <13.0 g/dL [males]) is a common finding associated with increased joint inflammation in patients with RA and changes in Hb levels are associated with changes in disease activity; therefore, the influence of sarilumab on Hb is of clinical interest. This post hoc analysis assessed potential relationships between Hb, disease activity, and physical function in the adalimumab-controlled MONARCH study (NCT02332590).

Methods: In the MONARCH study, adult patients intolerant of, inappropriate for, or inadequate responders to methotrexate were randomized to SC sarilumab 200 mg q2w or adalimumab 40 mg q2w monotherapy for 24 wks. The primary endpoint was change from baseline in DAS28-ESR at Wk 24. Post hoc analyses were conducted on changes in Hb using a mixed-effects model for repeated measures assuming an unstructured covariance structure: Model = baseline, treatment, region, visit, and treatment-by-visit interaction. Missing data were not imputed. Proportion of anemic patients was summarized by visit. Relationships between Hb and efficacy measures were explored.

Results: At baseline, mean Hb levels were 13.0 g/dL in sarilumab(n=184) and adalimumab (n=185) groups and 25% of patients had anemia (WHO criteria). For the primary endpoint of change from baseline in DAS28-ESR, sarilumab was superior to adalimumab (−3.28 vs −2.20; $P<0.0001$). Compared with adalimumab, at Wks 12 and 24, sarilumab resulted in larger increases in Hb (Wk 24 least squares mean change from baseline 0.591 vs 0.075 g/dL; least squares mean difference 0.516 [95% CI: 0.319, 0.713]; nominal $P<0.001$ [Figure]). By Wk 24, 16.2% of adalimumab-treated and 10.9% of sarilumab-treated patients were classified with anemia. In the adalimumab group, at Wk 24, correlations between increases in Hb and decreases in markers of disease activity and physical disability were noted (Figure). In the sarilumab group, increases in Hb and decreases in disease activity and physical disability were not correlated. Most common adverse events were neutropenia and injection-site reactions (sarilumab) and headache and worsening RA (adalimumab). There were three adverse event reports of anemia (none were serious or led to treatment discontinuation): 1 report of microcytic anemia (adalimumab) and 2 of worsening of anemia (sarilumab). Decreases from baseline in hepcidin and ferritin were similar for sarilumab and adalimumab at Wk 2, but not measured thereafter.



Conclusion: Sarilumab treatment was associated with larger increases in Hb and reductions in patients with anemia than adalimumab, unrelated to its better control of RA disease activity. Sarilumab appears to be a good treatment choice in patients with RA and anemia.

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Abstract Number: 1529

Long-Term, Real-World Safety of Adalimumab in Rheumatoid Arthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: The incidence of adverse events (AE) among rheumatology medication users has not been well documented in real-world disease registry datasets in the US. We quantified the incidence of AEs of interest among rheumatoid arthritis (RA) patients treated with adalimumab in the Corrona RA registry.

Methods: Adult RA patients from the US Corrona RAregistry who initiated treatment with adalimumab between 1/1/2008 and 6/1/2017 and had at least one follow-up visit were included. AE of interest included serious infections, malignancy (excluding non-melanoma skin cancer), hospitalized congestive heart failure (CHF) and all-cause mortality. The incidence of patients experiencing at least one new event of that type was calculated. Person-time at risk was estimated from time of drug initiation to either the occurrence of first event or 90 days after discontinuation of adalimumab (serious infections and hospitalized CHF) or last Corrona visit (censored). All time post adalimumab initiation regardless of discontinuation was considered for both malignancy and mortality. Incidence rates (IR) per 100 person-years were calculated with 95% confidence intervals assuming a Poisson distribution.

Results: There were 2798 adalimumab initiators available for analysis with mean age of 54.5 years, 77% were female, and mean duration of disease was 8.3 years. Nearly half (48%) were biologic naïve at the time of adalimumab initiation. Prednisone use of ≥ 10 mg occurred in 9% of patients at the time of adalimumab initiation and the majority of the patients (74%) used adalimumab for 3 years or less.

The IR per 100 person years for serious infections, CHF requiring hospitalization, malignancy excluding non-melanoma skin cancers, and all-cause mortality were 1.86 (1.50, 2.31), 0.15 (0.07, 0.31), 0.64 (0.50, 0.84), 0.33(0.24, 0.48), respectively. The incidence of events by duration of adalimumab exposure categories (≤ 1 year, >1 -3 years, >3 -5 years, > 5 years) are provided in the Table. Serious infection was higher in the first year of therapy (3.44 [95% CI 2.45-4.84) and other AEs did not vary by duration of exposure.

Conclusion: The IR of serious infection, CHF, malignancy and mortality in this prospective real-world registry are reassuring as they appear consistent with adalimumab RA clinical trial data and other observational registry data.¹⁻⁴

Table. Incidence of events by subgroups of overall exposure to adalimumab

	Adalimumab initiators	
	# Events	Unadjusted Rate (95% CI) Events/100 PYs
Serious Infections*		
≤1 year	33	3.44 (2.45-4.84)
>1-3 years	30	2.03 (1.42-2.90)
>3-5 years	15	1.40 (0.84-2.32)
>5 years	5	0.53 (0.22-1.28)
Congestive heart failure requiring hospitalization		
≤1 year	2	0.20 (0.05-0.80)
>1-3 years	3	0.19 (0.06-0.59)
>3-5 years	1	0.09 (0.01-0.62)
>5 years	1	0.10 (0.01-0.71)
Malignancy**		
≤1 year	29	0.73 (0.51-1.05)
>1-3 years	17	0.69 (0.43-1.12)
>3-5 years	8	0.63 (0.32-1.26)
>5 years	2	0.20 (0.05-0.80)
Mortality		
≤1 year	15	0.35(0.21-0.58)
>1-3 years	11	0.42 (0.23-0.76)
>3-5 years	4	0.29 (0.11-0.79)
>5 years	1	0.10 (0.01-0.68)

* Serious Infections included infections that led to hospitalization or IV antibiotics. **Malignancy excluded NMSC.

References: 1. Burmester GR, et al. Long-term safety of adalimumab (Humira) in adult patients from global clinical trials across multiple indications. Presented at the Am Coll of Rheum Annual Meeting, 2017, San Diego, CA.

2. Rutherford, AI, et al. *Ann Rheum Dis*. 2018;77:905-10.

3. Mercer LK, et al. *Ann Rheum Dis*. 2015;74:1087-93.

4. Simard JF, et al. *Arth Rheumatism*. 2012;64:3502-10.

Disclosure: L. R. Harrold, Corrona, LLC, 1, Corrona, LLC, 3, Pfizer, Inc., 2, Roche and Bristol Myers Squibb, 5; J. Griffith, AbbVie Inc., 1, AbbVie Inc., 3; H. J. Litman, Corrona, LLC, 3; B. Gershenson, None; S. Islam, AbbVie Inc., 1, 3; C. J. Barr, Corrona, LLC, 3; D. Guo, AbbVie Inc., 1, 3; P. Zueger, AbbVie Inc., 1, 3; J. Fay, AbbVie Inc., 1, 3; J. Greenberg, Corrona, LLC, 1, 3, Genentech, Janssen, Novartis and Pfizer, Eli Lilly, 5.

Abstract Number: 1530

CRP Changes during Bacterial Infections in Baricitinib-Treated Patients with RA

Oliver Hendricks¹, Stavros Chrysidis², Jens Gerwien³, Chadi Saifan³, Francesco de Leonardis³, Pedro Lopez-Romero³, Jinglin Zhong⁴, Kevin Winthrop⁵ and Josef S. Smolen⁶, ¹King Chr.Xs Rheumatology Hospital, Graasten, Denmark, ²Rheumatology Department Sydvestjysk Sygehus, Esbjerg, Denmark, ³Eli Lilly and Company, Indianapolis, IN, ⁴Quintiles, Rockville, MD, ⁵Oregon Health Sciences University, Portland, OR, ⁶Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

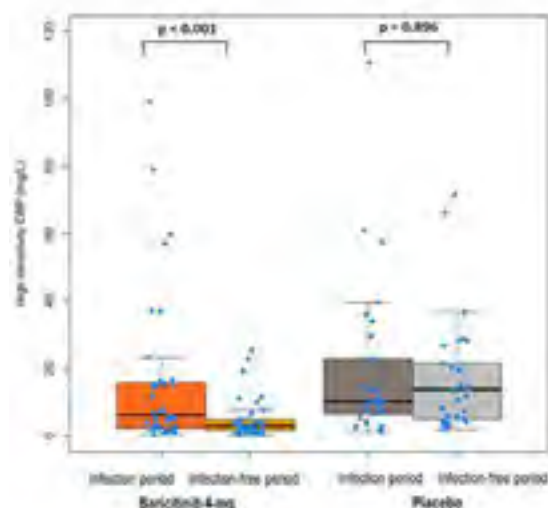
Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Baricitinib (BARI) is a selective inhibitor of Janus kinase 1/2, modulating responses to inflammatory cytokines, e.g. IL-6 or IFNs¹. During acute inflammation, including those caused by bacterial infections (BI), IL-6 induces hepatic CRP synthesis; elevated CRP levels often represent a non specific, yet clinically useful marker of infections². IL-6 blockers can lead to blunting of CRP signals^{3,4}. This analysis evaluated CRP levels during BI in RA patients treated with BARI or placebo (PBO).

Methods: Using a high sensitivity (hs) assay, CRP values were obtained from patients with moderate to severe active RA pooled from the BEAM, BUILD and BEACON studies who were treated with BARI 4-mg or PBO for 24 weeks and had BI TEAEs (Tab.1). Patient inclusion was based on the experience of ≥1 BI before rescue and availability of a CRP measure within ± 3 days of the start of the BI. Multiple CRP measures per patient were aggregated into the median resulting in 2 observations per patient corresponding to the infection and infection-free period (Fig.1). Paired comparisons

Fig.1. Distribution of the CRP (mg/L) Values per Patient within Treatment and Infection Status



Footnote to Fig.1: CRP values during bacterial infection period (measured \pm 3 days around the start of infectious TEAE) and during infection-free period (measured \pm 2 weeks of bacterial infectious TEAE) are shown. During the infection period, only 3 patients (2 BARI, 1 PBO-treated) had 2 CRP measures; all others had 1 CRP. During the infection-free period, all patients had multiple CRP measures. Multiple CRP measures per patient were aggregated into the median, resulting in 2 observations per patient corresponding to the infection and infection-free period, shown as blue dots in Fig.1. For each treatment, the p-values correspond to the comparisons of CRP within patients between infection and infection-free period from Wilcoxon Signed-Rank test.

Tab.1: Preferred terms* for bacterial infectious events

<p>Acute tonsillitis, Arthritis infective, Atypical pneumonia, Bacterial infection, Bronchitis bacterial, Brochococciuria, Campylobacter gastroenteritis, Cellulitis, Cystitis, Ear infection, Escherichia urinary tract infection, Eye infection, Folliculitis, Gingivitis, Infected skin ulcer, Lobar pneumonia, Lung infection, Mycobacterial infection, Periodontitis, Pharyngitis bacterial, Pneumonia, Pulmonary tuberculosis, Sinusitis bacterial, Staphylococcal infection, Tonsillitis bacterial, Tuberculosis, Upper respiratory tract infection bacterial, Urinary tract infection, Urinary tract infection bacterial, Vaginitis bacterial, Wound infection, Wound infection staphylococcal, *as defined in the MedDRA version 18.0</p>
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between CRP at infection and infection-free states were done within the same patients for each treatment group and p-values for the two differences were obtained from a Wilcoxon Signed-Rank test.

Results: Overall, 36 and 30 patients treated with BARI and PBO (Tab.2) had CRP values during BI TEAEs, of which 60% were urinary tract infections. For BARI, the median CRP were 6.2 and 3.0 mg/L in the infection and infection-free period, ($p < 0.001$; Fig.1) and the maximum values were 99.2 and 25.4 mg/L, respectively. For PBO, the median CRP were 10.1 and 13.7 mg/L for the infection and infection-free period ($p = 0.896$); and the maximum values were 110.8 and 71.4 mg/L.

Conclusion: CRP remains a useful monitoring tool for BI in BARI-treated patients. CRP elevations were observed in BARI-treated patients during BI, with no apparent blunting of response. In the PBO patients, elevations of CRP also were observed in infection-free periods, in line with the presence of active RA, and these values may be comparable to the CRP values observed on those patients during BI.

References: ¹O'SheaJJ, Plenge R. Immunity 2012;36(4):542-50

²SchaperF, Rose-John S. Cytokine & Growth Factor Review;https://doi.org/10.1016/j.cytogfr.2015.07.004

³Bari SF et al. BMJ Case Rep;https://doi.org/10.1136/bcr-2013-010423

⁴Fujiwara H et al. ModRheumatol 2009;19:64-8

Tab. 2: Baseline Demographics and Disease Characteristics

Patients with bacterial infection and CRP data available (pooled from phase 3 studies BEAM, BEACON and BUILD)	Placebo (n=30/N=892)	Baricitinib 4-mg (n=38/N=891)
Age, years	47.8 (12.6)	51.8 (13.8)
Female, n (%)	30 (100)	35 (97.2)
Duration of RA*, years	8.2 (6.6)	8.8 (7.9)
Baseline MTX use, yes, n (%)	27 (90)	33 (91.7)
Glucocorticoid use, yes, n (%)	19 (63.3)	18 (50)
ACPA positive, n (%)	22 (73.3)	27 (75)
RF positive, n (%)	26 (86.7)	30 (83.3)
SJC, swollen joint counts of 66	14	16.3
CRP, mg/L	22.8	16
ESR, mm/hour	44.3	39.1
CDAI	39.2	39.9
DAS28-ESR	6.5	6.4
DAS28-CRP	5.9	5.8

Data are mean (SD) unless otherwise indicated.

*Time from RA diagnosis.

Abbreviations: ACPA=anti-citrullinated peptide antibody; BMI=body mass index; CDAI=Clinical Disease Activity Index; DAS28=Disease Activity Score 28 joints; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein.

MTX=methotrexate; N=overall population; n=patient population; RA=rheumatoid arthritis; RF=rheumatoid factor; SD=standard deviation.

RA studies: BEAM (MTX-IR study population), BEACON (DMARD-IR study population), BUILD (DMARD-all study population).

DMARD=biological disease-modifying antirheumatic drugs; cDMARD=conventional disease-modifying antirheumatic drugs; IR=insufficient response; MTX=methotrexate.

Disclosure: O. Hendricks, None; S. Chrysidis, None; J. Gerwien, Eli Lilly and Company, 3; C. Saifan, Eli Lilly and Company, 1, 3; F. de Leonardis, Eli Lilly and Company, 1, 3; P. Lopez-Romero, Eli Lilly and Company, 1, 3; J. Zhong, None; K. Winthrop, Pfizer, BMS, 2, Pfizer, UCB, Abbvie, Eli Lilly and Company, Amgen, BMS, 5; J. S. Smolen, AbbVie, Janssen, Eli Lilly and Company, MSD, Pfizer, Roche, 2, AbbVie, Amgen, Astra-Zeneca, Astro, BMS, Celgene, Celltrion, Chugai, Gilead, Glaxo, ILTOO, Janssen, Eli Lilly and Company, Medimmune, MSD, Novartis-Sandoz, Pfizer, Roche, Samsung, Sanofi-Aventis, UCB, 5.

Abstract Number: 1531

Tofacitinib Show Similar Retention When Used with and without Methotrexate. Analysis from the Rhumadata® Clinical Database and Registry

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Tofacitinib (TOFA), a targeted synthetic DMARD has recently appeared on the Canadian market. It is an oral agent, targeting the JAK 1 and JAK 3 subunits of the Janus Kinase pathway, indicated in the treatment of rheumatoid arthritis (RA). We describe here the experience that we have accumulated in the last four years on 131 patients.

Methods: The data of all patients with RA exposed to TOFA at the *Institut de Recherche en Rhumatologie de Montréal* and the *Centre de l'Ostéoporose et de Rhumatologie de Québec* either in monotherapy or in combination with other conventional

synthetic DMARDs (csDMARDs) was extracted from the database. All patients' data were obtained from the Rhumadata® clinical database and registry. Descriptive statistics include age, gender, diagnosis, previous and actual exposure to other csDMARDs and biologic agents, CDAI at the initiation of TOFA, duration of treatment, response to treatment, and the reason for ceasing therapy.

Results: The 131 patients exposed to TOFA since its launch were mostly female (82%), with a mean age and disease duration at treatment initiation of respectively 58.1 (11.8) and 11.5 (10.3) years. Most patients were rheumatoid factor positive (73%) and 47% ACPA positive. At the time of the analysis, 63% remained on treatment. Reasons for stopping are inefficacy (66%), adverse events (21%), infections (4%) and other/unknown (11%). Of all patients, 31% had previously been treated with csDMARDs only. Prior biologic agent exposure ranges from 1 to 9, and 62% had been exposed to less than five biologic agents. The 6, 12, 24 and 36 months' retention rates of patients treated with tofacitinib were respectively 75.0 (SE=4.0), 65.4 (4.5), 54.7(5.2), and 52.3 (47.7) percent. Subjects treated with and without methotrexate (MTX) had similar retention curves (see figure). Baseline CDAI for this sub population is 22.1 (SD=13.1) with improvements (decreases in CDAI) of 3.3 (SD=10.8) and 10.7 (SD=15.2) units from baseline for patients stopping and remaining on therapy respectively. At their last evaluation, 14.8%, of patients were in remission, and 3.3%, 55.7% and 26.3% had low, moderate and high disease activity.

Conclusion: Patients treated with TOFA often had severe long-standing disease and had been exposed to numerous prior treatments, the majority being biologic agents. These patients show improvement in their disease activity score compared to baseline and the addition of MTX did not provide better sustainability over time.

Disclosure: D. Choquette, None; L. Bessette, None; J. Brown, None; B. Haraoui, AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Merck, Pfizer, Roche, and UCB, 2, 5, 8; F. Massicotte, None; J. P. Pelletier, None; J. P. Raynauld, None; M. A. Rémillard, None; D. Sauvageau, None; A. Turcotte, None; É. Villeneuve, None; L. Coupal, None.

Abstract Number: 1532

Impact of Immunogenicity on Clinical Efficacy and Administration Related Reaction in TNF Inhibitors: A Pooled-Analysis from Three Biosimilar Studies in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: SB4, SB2, and SB5 are biosimilars of reference etanercept, infliximab, and adalimumab, respectively. The phase III randomized, double-blind clinical studies comparing the efficacy and safety of each biosimilar with its reference product had similar study designs, patient demographics, and the same primary end point of the ACR20 response rate. In this study, the immunogenicity of three TNFi and the potential impact of anti-drug antibodies (ADABs) on efficacy and injection site reactions (ISR) or infusion related reactions (IRR) were assessed by a pooled analysis of three biosimilar studies.^{1,2,3}

Methods: In each study immunogenicity was measured using a validated ECL assay tagged with the biosimilar and patients who had immunogenicity results from each phase III study were pooled. Data to the time of the primary endpoint for each study (week 24 for etanercept and adalimumab studies and week 30 for infliximab study) are included. Efficacy (ACR responses, clinical response [defined as good or moderate EULAR response], change in disease activity [DAS28, SDAI, CDAI]) and ISR/IRR were evaluated in relation to the presence of ADAB (at least one ADAB positive result up to when the primary endpoint was measured).

Results: The analysis included 1710 patients and the incidence of ADAb by treatment group is presented in the Table. Across treatment groups, efficacy was greater in patients without ADAb compared to those with ADAb. In all treatments combined, the ACR20 response rate was lower in the presence of ADAb (OR 2.01, 95% CI: 1.60-2.53, $p<0.0001$) (Figure) and the mean improvement in DAS28 was significantly greater in patients without ADAb (estimated difference: 0.33, 95% CI: 0.19-0.48, $p<0.0001$). The ADAb effect on reducing efficacy parameters was similarly observed in other treatment combinations.

In all treatments combined, the presence of ADAb was associated with increased ISR/IRR (OR 1.78, 95% CI: 1.05-3.02, $p=0.033$), predominantly with the infliximab combined (OR 2.67, 95% CI: 1.04-6.89, $p=0.041$) rather than the etanercept combined (OR 1.72, 95% CI: 0.38-7.77, $p=0.478$) and adalimumab combined (OR 1.14, 95% CI: 0.41-3.13, $p=0.804$).

Conclusion: In a pooled analysis, the development of ADABs to TNFi is associated with reduced clinical efficacy and increased incidence of ISR/IRR in patients with RA.

References: 1. Emery et al. *Ann Rheum Dis.* 2017 Jan;76(1):51-57; 2. Choe et al. *Ann Rheum Dis.* 2017 Jan;76(1):58-64; 3. Weinblatt et al. *Arthritis Rheumatol.* 2018 Jan;70(1):40-48

Disclosure: P. Emery, Pfizer, MSD, AbbVie, Bristol-Myers Squibb, UCB, Roche, Novartis, Samsung, Sandoz and Lilly, 5; M. E. Weinblatt, Amgen, BMS, Crescendo Bioscience, Sanofi/Regeneron, 2, Abbvie, Amgen, BMS, Crescendo Bioscience, Corrono, GSK, Gilead, Eli Lilly and Company, Lycera, Merck, Novartis, Pfizer, Roche, Samsung, Set Point, UCB, 5, Lycero, Can-fite, Scipher, Vorso, Inmedix, 1; J. S. Smolen, AbbVie, Janssen, MSD, Pfizer, Roche and UCB, 2, AbbVie, Amgen, AstraZeneca, Astra-Pharma, Celgene, GSK, Janssen, Lilly, Medimmune, MSD, Novartis-Sandoz, Novo Nordisk, Pfizer, Roche, Samsung Bioepis, Sanofi and UCB, 5; E. C. Keystone, Abbott, AstraZeneca, Bristol-Myers Squibb, Crescendo Bioscience, F. Hoffmann-La Roche, Genentech, Janssen, Lilly, Merck, Pfizer, UCB, Samsung Bioepis, 5; M. C. Genovese, Samsung, Merck, Abbvie, Amgen, BI, 5; J. Vencovsky, Samsung Bioepis, Biogen, 5; J. Kay, Alexion; Amgen; AbbVie; AstraZeneca; Boehringer Ingelheim; BMS; Crescendo Bioscience; Eli Lilly; Epirus; Genentech; GlaxoSmithKline; Hospira; Janssen; MSD; Novartis; Pfizer; Samsung Bioepis; Sandoz; Roche; UCB, 5; E. Hong, Samsung Bioepis, 3; J. Ghil, Samsung Bioepis, 3.

Abstract Number: 1533

Simulating Population Disability Outcomes for Alternative Treatment Pathways in Patients with Active Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

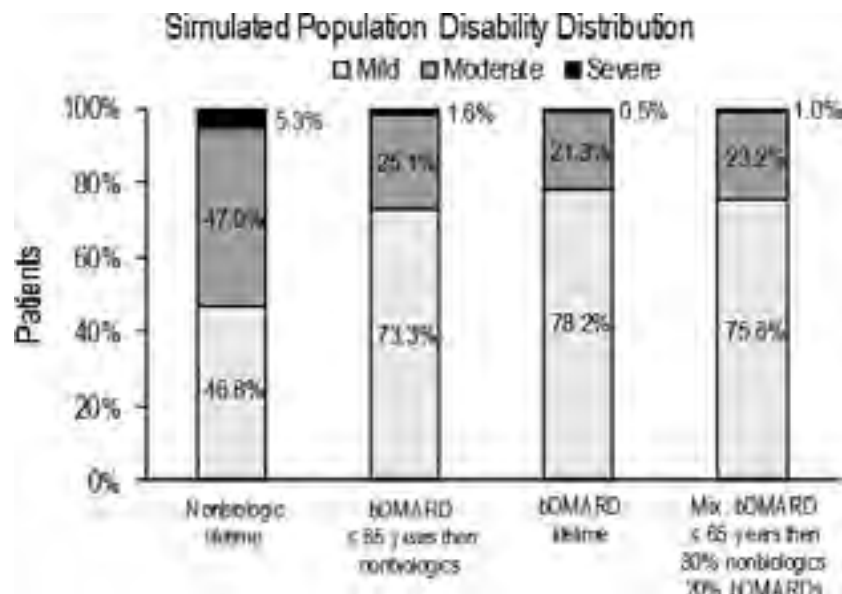
Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that causes joint pain and swelling, bone erosions, and deformity. This debilitating disease can severely impact patients' quality of life, employment opportunities, daily activities, and life expectancy. Over time, RA can cause the joints to become permanently deformed, which may lead to disability. Because of advances in treatment options such as biologic disease-modifying antirheumatic drugs (bDMARDs), many patients with RA are now able to continue to work and lead full lives, whereas decades ago this was not possible. The goal of this study was to assess the impact of introducing bDMARDs as a treatment option for patients with RA.

Methods: A population simulation model was developed to assess the impact of different treatment pathways on disability based on clinical trial data and real-world evidence. The model included patients diagnosed with RA with symptoms <2 years (median 6 months) who were DMARD-naïve. The following treatment pathways were evaluated: 1) non biologics (including nonsteroidal anti-inflammatory drugs, glucocorticoids, and synthetic DMARDs) for remaining lifetime, 2) bDMARDs for remaining lifetime, 3) bDMARDs until age 65 years then either 100% or 80% of patients switch to non biologics while the remaining patients continue on bDMARDs. A cohort of 1,000 patients newly diagnosed with RA, aged 56 years, with mean HAQ score of 1.2 were added every year. We assumed a decrease in mean HAQ of ~0.2 for non biologics and ~0.6 for biologics for the first year. For subsequent years, we assumed an annual change in HAQ of +0.002 at ages <65 years and +0.027 at ages ≥65 years for non biologics and of -0.009 at ages <65 years and +0.016 at ages ≥65 years for bDMARDs. The primary model outcomes were: expected population distribution of disability defined by HAQ score (score <0.5 to <1.1 = mild; score 1.1 to < 2.1 = moderate; score 2.1 to 3.0 = severe disability), and patient life expectancy. The impact of introducing bDMARDs on societal cost will be evaluated in the final analysis.



Results: For each simulated treatment pathway, the figure presents an expected distribution of disability in an RA population at steady state. Individual cohort life expectancy ranged from 22.11 years (non biologics) to 24.11 years (bDMARDs). Results were sensitive to starting age and disease severity. Greater benefits (ie, greater reduction in severe disability) associated with bDMARDs compared to non biologics can be seen in patients with higher mean HAQ scores entering the simulation model.

Conclusion: The simulation model estimates show that biologics will reduce the RA population disability burden and increase the life span of RA patients. The model can be used to estimate additional population outcomes including costs and healthcare resource use.

Disclosure: J. Mauskopf, RTI Health Solutions, 3; M. Gharaibeh, Amgen Inc., 3, Amgen Inc., 1; D. Wamble, RTI Health Solutions, 3; D. H. Collier, Amgen Inc., 3, Amgen Inc., 1; B. S. Stolshek, Amgen Inc., 3, Amgen Inc., 1; E. L. Matteson, Amgen Inc., 5, Amgen Inc., 9, Pfizer Inc., 9, Roche, 9, Janssen, 9.

Abstract Number: 1534

Comparative Risk of Diabetes Mellitus in Rheumatoid Arthritis Patients Treated with Different Biologics- a Cohort Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with rheumatoid arthritis (RA) often develop diabetes mellitus (DM), potentially due to aggravated systemic inflammation. Reducing inflammation with disease-modifying antirheumatic drugs (DMARD) may alter the risk of DM in RA. To date, few head-to-head comparisons of individual biologic or targeted synthetic DMARDs on the risk of DM in patients with RA are available.

Methods: We conducted a cohort study to compare DM risk in RA patients treated with different biologics or tofacitinib, using claims data from Truven Market scan (2005-2015). RA patients free from DM at baseline were selected into one of eight exposure groups based on treatment initiation: abatacept, infliximab, adalimumab, golimumab, certolizumab, etanercept, tocilizumab, or tofacitinib. From the treatment initiation date (i.e. index date), patients were followed for the outcome of

incident DM, defined as a combination of a diagnosis code and initiation of antidiabetic treatment, in an as-treated approach. To account for 60 baseline covariates including demographics, co-morbid conditions, and co-medications, we used a stabilized inverse probability (IP) weighted Cox-proportional hazard model to estimate hazard ratios (HR) of different treatments versus abatacept. All analyses were conducted separately in the following two groups: 1) new biologic initiators, who did not use any biologic DMARD in 365 days pre-index and 2) biologic switchers, who used one TNF inhibitor in 365 days pre-index and switched to a different biologic DMARD. HR estimates were then combined using inverse variance pooling.

Results: A total of 56,014 new biologic initiators and 27,152 biologic switchers with an average age of 50 years in both groups were included, of which 75% and 78% were females, respectively. Infliximab, adalimumab, and etanercept represented a large majority in both groups (86% initiators and 62% switchers), while abatacept was the most frequently used non-TNF biologic (6% initiators and 16% switchers). We observed 335 DM events in the new initiator group and 155 events in the switcher group, corresponding to incidence rates/1,000 person-years (95% CI) of 6.7 (6.0-7.5) and 7.3 (6.2-8.5), respectively. After IP weighting, a higher risk was observed among infliximab and etanercept initiators compared to abatacept initiators (**Table 1**). The risk was similar with all other drugs compared to abatacept.

Conclusion: In this large cohort study, we found a greater risk of incident DM in patients initiating infliximab or etanercept compared to abatacept initiators. The risk of DM was similar between other biologic or tofacitinib and abatacept initiators. Our findings corroborate observations from earlier smaller studies, which showed potentially improved insulin sensitivity and glycemic profile with abatacept.

Table 1 Inverse probability weighted hazard ratios (95% confidence intervals) for the risk of diabetes mellitus in patients with rheumatoid arthritis treated with different biologics

	New biologic initiators	Biologic-switchers	Pooled
Abatacept	Reference	Reference	Reference
Adalimumab	2.08 (1.07-4.08)	0.54 (0.31-0.94)	0.94 (0.61-1.44)
Certolizumab	1.03 (0.27-3.86)	0.45 (0.17-1.18)	0.60 (0.27-1.31)
Etanercept	2.28 (1.17-4.45)	1.30 (0.76-2.21)	1.62 (1.07-2.45)
Golimumab	1.05 (0.34-3.21)	0.60 (0.26-1.35)	0.73 (0.37-1.41)
Infliximab	3.00 (1.5-6.00)	1.23 (0.72-2.11)	1.72 (1.12-2.63)
Tocilizumab*	-	0.96 (0.40-2.32)	0.96 (0.40-2.32)
Tofacitinib	1.13 (0.30-4.3)	1.24 (0.44-3.48)	1.20 (0.53-2.71)

* No events were observed in the tocilizumab group among biologic naïve patients

Disclosure: R. J. Desai, None; S. Dejene, None; Y. Jin, None; J. Liu, None; S. C. Kim, Bristol-Myers Squibb, 2,pfizer, 2, Roche, 2.

Abstract Number: 1535

Enhancing Patient Ability to Process and Use Information about Medication Risks and Benefits

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Guidelines for the treatment of rheumatoid arthritis (RA) underscore the importance of an early and targeted approach to control inflammation. However, patients are often reluctant to agree to aggressive therapy when they believe their symptoms are tolerable, despite high disease activity scores. This study is based on the premise that educating patients about treatment risks and benefits requires a two-pronged approach: (1) Simplifying written materials to reduce user burden and (2) Teaching patients the skills needed to process complex information. Drug Facts Boxes® are designed to address the former; Gist Reasoning (GIST) Training is designed to address the latter.

Methods: The study is a randomized controlled trial in which participants with doctor-diagnosed RA are randomized to one of four groups: (1) Medication Guide without GIST Training, (2) Medication Guide with GIST Training, (3) Drug Facts Box® without GIST Training, and (4) Drug Facts Box® with GIST Training. Data are collected at baseline (prior to

intervention implementation) and at 6 weeks, 3 months, and 6 month follow-up. The primary outcome is informed decision making regarding the use of disease-modifying anti-rheumatic drugs (DMARDs). Patients using a DMARD are classified as having made an informed decision if they have adequate knowledge (≥ 85 on a 100 point scale) and values that favor aggressive treatment of RA. Patients not using a DMARD are classified as having made an informed decision if they have adequate knowledge and have values that do not favor aggressive treatment. Knowledge is a secondary outcome variable. Data were analyzed using logistic and linear regression.

Results: Data collection is ongoing. To date, 297 participants have completed baseline data collection and 135 have completed the 6-month follow-up. Controlling for baseline knowledge, participants assigned to GIST Training exhibited greater knowledge at the 6-month follow-up, compared to those not assigned to training (Means: 86.1 vs 83.4, $p = .06$). In a logistic regression predicting informed decision making at the 6-month follow-up, there was a significant interaction between (1) whether the participant met the criteria for informed decision making at baseline and (2) assignment to GIST Training ($p = .003$). Among those classified as not meeting the criteria for informed decision making at baseline, 56.7% ($n = 17$) of those assigned to GIST Training met the criteria at the 6-month follow-up, compared to 25% ($n = 11$) of those not assigned to training ($p = .007$). However, among those classified as meeting the criteria at baseline, 35.0% ($n = 7$) of those assigned to GIST Training did not meet the criteria at the 6-month follow-up, compared to 14.7% ($n = 5$) of those not assigned to training ($p = .09$). No differences were observed between those randomized to Medication Guides versus Drug Facts Box®.

Conclusion: These findings provide preliminary support for the effectiveness of GIST Training in helping patients develop the skills needed to process complex information about medication risks/benefits. RA Treatment benefits appear to be limited to those who do not meet the criteria for informed decision making prior to the initiation of training.

Disclosure: G. Hickey, None; C. Hunt, None; M. Keebler, None; D. M. Carpenter, None; E. Solow, None; V. Reyna, None; W. B. Nowell, None; C. Edmonds, None; K. O'Neill, None; S. J. Blalock, None.

Abstract Number: 1536

Mean Platelet Volume Changes with Baricitinib Indicate Reduced New Platelet Production in Baricitinib-Treated Rheumatoid Arthritis Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

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Session Time: 9:00AM-11:00AM

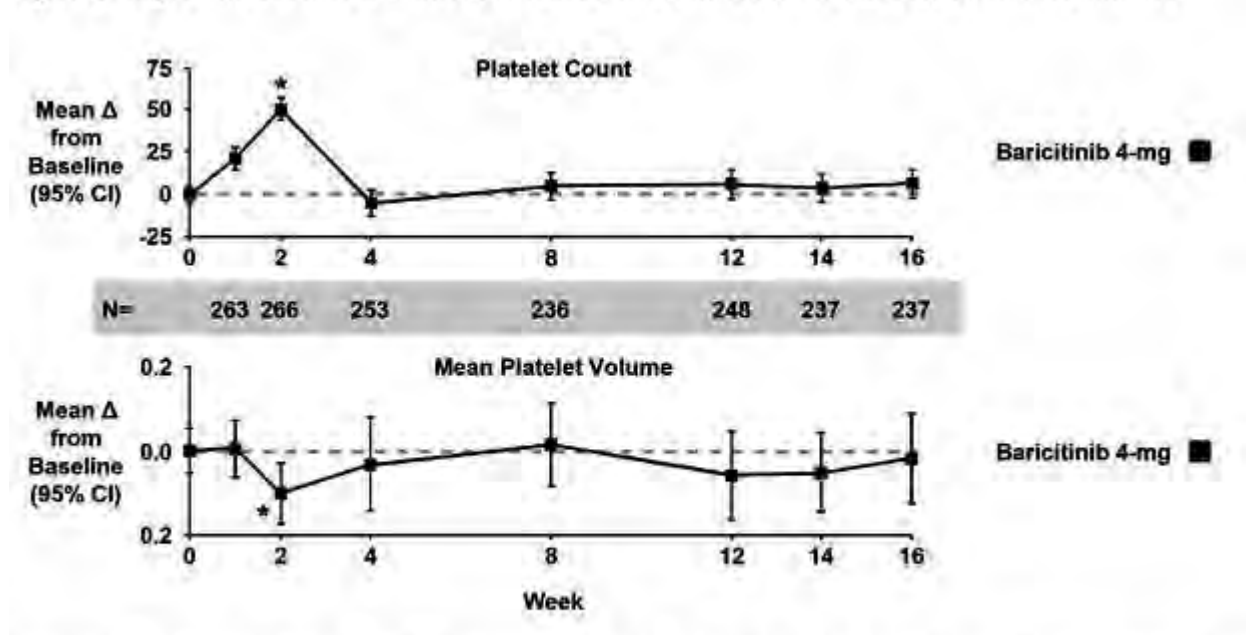
Background/Purpose: Transient increases in circulating platelets were observed in patients with RA treated with baricitinib, an oral selective Janus kinase 1/2 inhibitor, approved for the treatment of RA in over 40 countries. We assessed mean platelet volume (MPV) in relation to platelet count to determine whether treatment-associated patterns of platelet change are indicative of altered platelet synthesis, release, and/or clearance.

Methods: MPV and platelet count were measured in a subset of patients with RA treated for up to 16 weeks ($N = 629$), enrolled in the phase 3 RA-BEAM trial (NCT01710358), a 52-week, randomized, double-blind, placebo- and active-controlled study of moderately-to-severely active methotrexate-inadequate responders. Adalimumab (40-mg every other week), a monoclonal antibody against TNF-alpha, was included as an active comparator to baricitinib (4-mg once daily).

Results: There was a significant increase in platelet count at Week 2 with baricitinib treatment, which then returned toward baseline and remained stable (though slightly above baseline) thereafter for the 16-week time-period (Figure). In contrast, adalimumab treatment resulted in a decrease in platelet count starting at 2 weeks that persisted over 16 weeks. The corresponding MPV changes with baricitinib treatment demonstrated a decrease in MPV at 2 weeks, which then returned to baseline, mirroring the platelet count change over time (Figure). By contrast, adalimumab treatment resulted in an increase in MPV at Week 2 and remained elevated through Week 16. Platelet count and MPV changes in the placebo arm were not significant throughout the 16-week time-period.

Conclusion: These analyses indicate that the increase in platelet count observed with baricitinib treatment at 2 weeks maybe caused by a transient increase in circulating older, smaller platelets, accounting for the MPV decline; this finding is most consistent with a period of decreased platelet clearance rather than an increase in platelet production. By contrast,

Figure. Changes from Baseline in Platelet Count and Mean Platelet Volume with 95% Confidence Intervals



Baricitinib 4-mg-treated patients with individual N shown for each time point. The mean baseline platelet count was 8.8×10^9 /L and the mean baseline mean platelet volume was 302.7×10^9 cells/L for baricitinib 4-mg-treated patients. Bari=baricitinib, CI=confidence interval. * $p \leq 0.05$ compared with baseline.

the prolonged platelet changes with adalimumab are consistent with increased platelet clearance and resultant increased platelet production. The association of changes in MPV with platelet function should be explored in future studies.

Disclosure: J. T. Giles, Pfizer, 2, Eli Lilly and Company, Genentech, Horizon, 5; M. T. Nurmohamed, Eli Lilly and Company, 5; H. M. Rinder, Eli Lilly and Company, 5; V. Krishnan, Eli Lilly and Company, 1, 3; B. J. Crowe, Eli Lilly and Company, 1, 3; C. Saifan, Eli Lilly and Company, 1, 3; T. Dörner, Chugai, Janssen, Sanofi, 2, AbbVie, Celgene, Eli Lilly, Roche, UCB, MSD, Pfizer/Hospira, Novartis, 5.

Abstract Number: 1537

Frequency and Duration of Early Non-Serious Adverse Events in Rheumatoid Arthritis Patients Treated with Tofacitinib 5 Mg Twice Daily As Monotherapy and Combination Therapy

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Tolerability remains ill-defined in clinical trials and most commonly refers to non-serious adverse events (AEs) that may impact patient (pt) satisfaction and adherence to treatment. Tofacitinib is an oral Januskinase inhibitor for the treatment of RA. This update to a previously reported post hoc analysis¹ describes the frequency and duration of the most commonly reported non-serious AEs related to tolerability in pts with RA treated with tofacitinib 5 mg twice daily (BID) as monotherapy or in combination with conventional synthetic (cs)DMARDs in Phase (P)3 and P3b/4 studies.

Methods: Data were pooled from the following studies of tofacitinib in pts with moderate to severe RA: ORAL Step (NCT00960440); ORAL Solo (NCT00814307); ORAL Scan (NCT00847613); ORAL Sync (NCT00856544); ORAL Standard (NCT00853385); and ORAL Strategy (NCT02187055). This analysis included data from pts receiving tofacitinib 5 mg BID monotherapy (ORAL Solo, ORAL Strategy), placebo (PBO; ORALSolo), or tofacitinib 5 mg BID or PBO in combination with csDMARDs (all studies except ORAL Solo). Non-serious AEs with an incidence rate (IR, pts with events per 100 pt-years [PY]) ≥ 5 were evaluated up to Month 3. Non-serious AEs were defined as AEs affecting pts' day-to-day experience and ability to tolerate treatment. Infections, laboratory test abnormalities, general disorders, or events not reported directly by pts, and musculoskeletal events likely to be due to underlying RA, were excluded, to focus on AEs which could impact treatment adherence.

Results: In total, 2657 pts were included in the analysis; 1976 received tofacitinib 5 mg BID (monotherapy: N=627; combination therapy: N=1349); 681 received PBO (monotherapy: N=122; combination therapy: N=559). Up to Month 3, the most frequently reported non-serious AEs which met the search criteria for either tofacitinib or PBO groups were headache, diarrhea, nausea, vomiting, dyspepsia, and abdominal pain upper; an IR of ≥ 10 was observed for headache and diarrhea in pts receiving tofacitinib 5 mg BID, and for nausea in pts receiving PBO (Table). Duration of AEs was ≤ 4 weeks for the majority of pts experiencing headache, diarrhea, or gastric discomfort (defined as any gastrointestinal pain,

Table. Non-serious, non-infectious treatment-emergent AEs* in Phase 3 studies up to Month 3

Non-serious AE, # (%) IRs per 100 PY (95% CI)	Monotherapy		Combination therapy		Overall	
	Tofacitinib 5 mg BID (N=627)	PBO† (N=122)	Tofacitinib 5 mg BID (N=1349)	PBO† (N=559)	Tofacitinib 5 mg BID (N=1976)	PBO† (N=681)
Headache	21 (3.3) 13.72 (8.49, 20.88)	3 (2.5) 10.60 (2.87, 29.39)	58 (3.7) 15.27 (11.33, 20.17)	13 (2.3) 9.52 (3.97, 16.28)	71 (3.6) 14.8 (11.3, 18.9)	16 (2.3) 8.6 (3.5, 13.6)
Diarrhea	18 (2.9) 11.23 (6.97, 16.34)	3 (2.5) 10.60 (2.68, 29.22)	41 (3.0) 13.48 (9.84, 18.91)	13 (3.3) 9.54 (3.88, 16.32)	50 (3.6) 12.2 (9.3, 15.8)	16 (2.3) 9.5 (3.3, 13.6)
Nausea	15 (2.4) 9.74 (3.46, 16.08)	3 (2.5) 4.99 (2.06, 29.20)	29 (2.1) 8.77 (3.87, 12.59)	15 (2.7) 11.00 (6.16, 18.13)	44 (2.2) 9.1 (6.8, 12.2)	18 (2.6) 10.6 (6.4, 17.1)
Vomiting	7 (1.1) 4.38 (1.1, 8.33)	2 (1.6) 8.11 (1.1, 3.3)	20 (1.5) 5.01 (3.21, 8.33)	7 (1.3) 5.87 (2.31, 11.44)	27 (1.3) 8.1 (3.3, 9.6)	10 (1.5) 8.0 (2.9, 11.6)
Dyspepsia	4 (0.6) 2.51 (0.6, 5.33)	4 (3.3) 16.39 (3.68, 36.29)	6 (0.2) 1.48 (0.68, 3.29)	3 (0.5) 2.30 (0.88, 6.00)	7 (0.3) 1.4 (0.3, 3.2)	7 (1.0) 4.0 (1.1, 8.6)
Abdominal pain upper	7 (1.1) 4.38 (1.1, 8.33)	9 (7.4) 36.89 (12.97, 81.18)	17 (1.3) 4.10 (2.97, 8.18)	8 (1.4) 5.88 (1.40, 9.49)	25 (1.2) 4.9 (3.3, 7.4)	10 (1.5) 8.0 (2.9, 11.6)

*Defined as AEs with an IR ≥ 5 per 100 PY in at least one treatment group under monotherapy, combination therapy or overall therapy. IRs listed (95% CI) are IRs per 100 PY (95% CI). IR < 5 per 100 PY is not listed. †Includes pts receiving PBO without background csDMARDs in ORAL Solo study; otherwise, background medications were allowed. ‡Includes pts receiving PBO with background csDMARDs in Phase 3b studies.

AE, adverse event; BID, twice daily; CI, confidence interval; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; IR, incidence rate; PBO, placebo; PY, pt-year.

dyspepsia, epigastric discomfort, or abdominal discomfort or pain). Overall, in pts receiving tofacitinib 5 mg BID and PBO, respectively, 43.2% and 64.7% experienced headache; 66.1% and 81.3% experienced diarrhea; and 36.2% and 58.6% experienced gastric discomfort, for ≤ 2 weeks. The majority of AEs were mild or moderate.

Conclusion: Overall, non-serious, non-infectious AEs were mild or moderate and self-limiting. The frequency of non-serious AEs was comparable for pts receiving tofacitinib as monotherapy, or in combination with csDMARDs, and was generally similar for pts receiving tofacitinib compared with pts receiving PBO.

1. Dikranian A et al. Arthritis Rheumatol 2013; 65: S192.

Disclosure: A. Dikranian, AbbVie, Pfizer Inc, 5, AbbVie, Pfizer Inc, 8; J. Wollenhaupt, Pfizer Inc, 1, Pfizer Inc, 5, Pfizer Inc, 8; V. F. Azevedo, AbbVie, Pfizer Inc, 2, AbbVie, Celltrion, Janssen, Novartis, Pfizer Inc, Sandoz, 5, AbbVie, Celltrion, Janssen, Novartis, Pfizer Inc, Sandoz, 8; L. Bessette, AbbVie, Amgen, Eli Lilly, Janseen, Merk, Novartis, Pfizer Inc, 2, AbbVie, Amgen, Eli Lilly, Janseen, Merk, Novartis, Pfizer Inc, 5; D. Gold, Pfizer Inc, 1, Pfizer Inc, 3; J. L. Rivas, Pfizer Inc, 1, Pfizer Inc, 3; H. Shi, Pfizer Inc, 1, Pfizer Inc, 3; L. Wang, Pfizer Inc, 1, Pfizer Inc, 3; J. Woolcott, Pfizer Inc, 1, Pfizer Inc, 3; A. Shapiro, Pfizer Inc, 1, Pfizer Inc, 3; P. Nash, AbbVie, Bristol-Myers Squibb, Eli-Lilly, Janssen, Novartis, Pfizer Inc, Roche, Sanofi, UCB, 2, AbbVie, Bristol-Myers Squibb, Eli-Lilly, Janssen, Novartis, Pfizer Inc, Roche, Sanofi, UCB, 5, AbbVie, Bristol-Myers Squibb, Eli-Lilly, Janssen, Novartis, Pfizer Inc, Roche, Sanofi, UCB, 8.

Moderate Adverse Drug Reactions Due to Disease Modifying Drugs in a Cohort of Patients with Incident Rheumatoid Arthritis

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

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Background/Purpose: In rheumatology, we are aware of the possibility to develop adverse drug reactions (ADR) to the widely used Disease Modifying Drugs (DMARD). We are certain of the efficacy of the DMARD in the treatment of rheumatoid arthritis (RA) and we know their safety profile in clinical trials. However, it is necessary to increase our knowledge of their ADR, especially those that lead to discontinuation, in real life conditions. **Purpose:** to describe the incidence and characteristics of moderate ADR (MADR) to DMARD in patients with incident RA as well as the factors related to their development.

Methods: Observational longitudinal study. **Patients:** all recent on set RA diagnosed between April 15th 2007 and December 31st 2014 followed in outpatient clinic at Hospital Clínico San Carlos until December 31st 2016, which used any DMARD (synthetic and biologic). **Primary outcome:** development of a MADR (discontinuation of the DMARD due to the ADR). Incidence rates of discontinuation (IR) per 100 patient-years were estimated using survival techniques with their respective 95% confidence interval [CI]. Comparisons between associated factors were run by Cox bivariate and multivariate regression models. Results were expressed by hazard ratio (HR) and [CI].

Results: We included 2388 courses of DMARD treatment in 814 patients (3706.14 patient-years). 77.52% were women with a mean age at diagnosis of 57.53±15.50 years. From the courses of DMARD, 13.74% were biologicals (72.04% anti-TNF) and 60% were used in monotherapy. There were 591 ADR in 335 patients, 90.52% of them moderate. Gastrointestinal was the most frequent cause of MADR (31.96%), followed by hepatic (10.15%). IR are shown in table 1. We performed a multivariate analysis (table 2) adjusted by ESR at the beginning of each drug. We repeated the model changing the reference category of DMARD: Golimumab (HR: 2.21, p=0.010), Leflunomide (HR: 1.84, p=0.000), Sulfasalazine (HR: 1.47, p=0.012), Chloroquine (HR: 1.37, p=0.004) and Hidroxicloroquine (HR: 0.77, p=0.030); the rest of DMARD did not achieve statistical significance in the models performed.

Conclusion: The IR of MADR estimated was 14.4%, being gastrointestinal the main cause. We found differences in discontinuation rates among DMARD due to MADR, with Golimumab, Leflunomide, Sulfasalazine and Chloroquine being the drugs with the highest risk. Methotrexate and Hidroxicloroquine are a protective factor for the development of MADR. Caution should be taken in patients of female gender, with positive rheumatoid factor, receiving combined therapy, higher dose of corticoids and with certain comorbidities.

Table 1

	Patient-years	n	IR	95% CI
Global	3706.14	535	14.44	13.26-15.71
Women Men	2976.78729.35	45877	15.3910.56	14.04-16.868.44-13.20
By age category	908.37	135	14.86	12.55-17.59
< 46 years	1963.68	283	14.41	12.83-16.19
46.01-69.99 years> 70 years	834.09	117	14.03	11.70-16.81
By treatment course	1666.32	162	9.72	8.33-11.34
First Other courses	2039.82	373	18.29	16.52-20.24
By therapy regimen	2556.40	263	10.29	9.12-11.61
Monotherapy Combined treatment	1149.74	272	23.66	21.01-26.65
By type of DMARD	3319.50	469	14.13	12.91-15.47
Synthetic	295.10	50	16.94	12.84-22.36
Anti-TNFOther biologicals	91.54	16	17.48	10.71-28.53
By drug	14.77	7	47.38	22.56-99.40
Golimumab	12.68	5	39.44	16.41-94.75
Abatacept	224.45	65	28.96	22.71-36.93
Sulfasalazine	482.82	138	28.58	24.19-33.77
Leflunomide	136.77	39	28.52	20.83-39.03
Gold	242.69	54	22.25	17.04-29.05
Methotrexate sc	684.53	143	20.89	13.73-24.61

Table . (Cont'd)

	Patient-years	n	IR	95% CI
Chloroquine	16.56	3	18.11	5.84-56.16
Tocilizumab	101.30	18	17.77	11.19-28.20
Etanercept	626.88	100	15.95	13.11-19.41
Hidroxicloroquine	31.36	5	15.94	6.64-38.30
Certolizumab	123.95	17	13.72	8.53-22.06
Adalimumab	37.61	5	13.29	5.53-31.94
Azathioprine	62.30	8	12.84	6.42-25.68
Rituximab	23.72	3	12.65	4.08-39.21
InfliximabMethotrexate	2234.58	271	12.13	10.77-13.66

Table 2

	Hazard ratio	CI 95%	p
Age at diagnosis	0.99	0.98-1.01	0.507
Male gender	0.60	0.43-0.83	0.002
Retired patients	1.34	0.99-1.81	0.052
Rheumatoid factor	0.76	0.36-0.92	0.005
Diabetes Mellitus	1.51	1.15-1.99	0.003
Renal insufficiency	3.04	1.74-5.32	0.000
Other treatment courses	1.71	1.33-2.21	0.000
Combined therapy	2.36	1.86-2.98	0.000
Corticoids dose	1.29	1.14-1.47	0.000
Methotrexate vs other DMARD	0.67	0.56-0.80	0.000

Disclosure: L. A. Alcazar, None; D. Freitas Núñez, None; I. Hernández-Rodríguez, None; J. Font Urgelles, None; P. M. Lois, None; B. Fernández-Gutiérrez, None; J. A. Jover Jover, None; Z. Rosales Rosado, None.

Abstract Number: 1539

Safety of Methotrexate and Leflunomide Combination Therapy in the Treatment of Rheumatoid Arthritis

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Background/Purpose: Best treatment of Rheumatoid Arthritis (RA) requires to begin early, with a tight control, including nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, disease-modifying antirheumatic drugs (DMARDs) and biologic therapies (BT).

High cost limits use of BT, especially in the low-middle income countries. In this setting, a common therapeutic strategy is the use of combination therapy (CT) with methotrexate (MTX) plus leflunomide (LEF). There is not too much information about the efficacy of this CT, and there are some concerns about its safety. Our purpose was to assess the safety of CT in our RA patients.

Methods: An observational, retrospective study in adult RA patients controlled in our center was conducted. Patients with prescription of MTX plus LEF by June 2016 in pharmacy records were included. We found 253 cases, and randomly 127 were selected for review of clinical records. Five patients with incomplete information were excluded. Demographic, underlying diseases, time and dose in RA medications, adverse events (AE) and clinical activity data were collected.

Results: In 121 patients included, 95.9% were females. The mean age was 60.6 (31-86) years. Only 5 of them (4.1%) had pre-existing liver disease, all with fatty liver disease. None of the patients reports alcohol use. Active smoking was reported in 28 cases (23.1%). Continuous use of NSAIDs was documented in 11 patients (9.1%). Average dose of MTX was 18.6 (7.5-25) mg/wk, with oral route being the most frequent (77.7%). Average dose of LEF was 19.75 (10-20) mg/d, initial loading dose was not used.

In 101 (83.5%) patients CT was retained, with a mean duration therapy of 70.0 (17-162) months. In 20 patients (16.5%) CT was discontinued, with mean time to discontinuation of 49.9 (2-180) months. Kaplan-Meier analysis of survival in CT showed more than 85% of patients still on CT after 5 years.

AE were reported in 31 patients (25.6%), with estimated rate of 4.37 x 100 person-year. Most of them (62.1%) were mild and resolved by reducing doses of one CT drug. AE presented in nine patients lead to a suspension of CT, one of these was considered as serious adverse event (SAE): pulmonary tuberculosis. We didn't find association between dose of MTX and the risk of adverse effects ($p = 0.6$).

In the beginning of CT, 90.9% of patients used prednisone, with an average dose of 7.1 mg/d. With CT use, the average dose was significantly reduced to 4.9 mg/d ($p < 0.0001$).

In 7 cases (5.8%) a BT was initiated because of the persistent high clinical activity RA. All of them suspended CT, continuing with only MTX or LEF.

In 60 of 101 patients remaining on CT, clinical activity of RA was registered by DAS 28 during follow-up. In 50% of them remission or low activity was achieved.

Conclusion: In this group of Chilean RA patients, the MTX plus LEF CT show to be safe, with a good survival rate.

AE were observed in the 25% of the patients on CT, and most of them resolved with the reduction of the dose of MTX or LEF. Frequency of SAE was very low.

A half of the patients who remained on CT, and evaluated with DAS 28 during follow up achieved remission or low RA activity, with a significant steroid-sparing effect.

CT is a reasonable therapeutic alternative when there is a limited access to the BT.

Disclosure: M. Badilla, None; N. Moldenhauer, None; D. Neira, None; L. Muñoz, None; O. Neira, None.

Abstract Number: 1540

Validation of Hepatic Fibrosis Markers in People with Rheumatoid Arthritis on Methotrexate

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: MTX is the cornerstone of treatment of RA. A relatively rare side effect is liver fibrosis and cirrhosis, the incidence in patients on long-term therapy is thought to be less than 3%. Neither dose nor duration of MTX are associated with liver fibrosis, and abnormal liver enzymes in RA patients do not accurately detect liver fibrosis, making screening problematic. The gold standard for diagnosing liver fibrosis is by biopsy. Routine biopsy is invasive and associated with risks. Other screening tests include hepascor, aminoaspartate transaminase (AST) to platelet ratio index (APRI) and transient elastography (fibroscan) – which have been validated in patients with liver disease but have not been validated in patients with RA.

Methods: Patients were recruited from Fiona Stanley Hospital (FSH) outpatient general rheumatology and inflammatory arthritis clinics from July 2017, and is ongoing. A DAS-28 (ESR) was completed, BMI, alcohol intake and dose and duration of MTX noted. FBC, UEC, LFT, ESR, CRP, AST, coagulation profile and hepascor were performed at FSH Path West. Fibroscan was performed on the same day.

An APRI score of >0.7 , hepascor of >0.45 and fibroscan of >7 kPa (=F2 metavir score) were used as cut-offs for significant fibrosis.

Statistical analysis was performed using SPSS with non-parametric statistics for non-normally distributed data and parametric for normally distributed data. Comparison between outcome tools was made using Spearman rank correlation (Rs).

Results: To the end of February 2018, 17 patients have been recruited, with unexpectedly low recruitment due to exclusions mainly from high BMI and treatment with leflunomide. The age range of patients is 53-74 years old, with 41% female, 59% male and duration of methotrexate ranging from 3-240 months. 1 patient was found to have significant fibrosis based on fibroscan and hepascor, however liver biopsy reported no significant fibrosis. 1 patient was found to have cirrhosis based on fibroscan,

hepascare and APRI, awaiting liver biopsy. 6 patients had raised hepascare indicative of significant fibrosis in the absence of correlated fibroscan or APRI scores. Duration of methotrexate ranged from 12-240 months, and was not statistically significant. 4 of 8 patients with raised hepascare had raised inflammatory markers. CRP was shown to be associated with fibrotic hepascare values (Rs 0.557, $p=0.028$), but not ESR (Rs 0.149, $p=0.574$) or DAS-28 (Rs -0.136, $p=0.645$). Fibrosis detected by APRI was highly correlated with fibrosis detected by fibroscan (Rs 0.683, $p=0.04$), but not hepascare (Rs 0.258, $p=0.334$). Hepascare detection of fibrosis did not correlate.

Conclusion: Results suggest that screening for liver fibrosis in RA patients may be indicated. Fibroscan and APRI correlate and are useful in detecting significant fibrosis in RA patients on methotrexate, however fibroscan may have limited utility in obese patients. Hepascare may be useful in detecting significant fibrosis though may also be falsely elevated in those with raised CRP, therefore limiting its utility in RA patients.

Disclosure: D. Olsson-White, None; J. Olynyk, None; W. Raymond, None; S. Paramalingam, None; H. Keen, None.

Abstract Number: 1541

The Safety Profile of Igaratimod in Real Clinical Practice: Analysis of 491 Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

The retention rate and safety profile of igaratimod in real clinical practice: Analysis of 456 patients with Rheumatoid arthritis.

Background/Purpose: Igaratimod is one of the disease modifying anti-rheumatic drugs (DMARDs) with anti-inflammatory and immunomodulatory actions. Previous RCTs shows the efficacy, but tolerance in daily practice is unknown. The aim of our study is to show the tolerability of igaratimod in real clinical practice.

Methods: We retrospectively collected data of all the 456 RA patients treated with igaratimod from the electrical chart of St Luke's International Hospital, Tokyo, Japan. We extracted following parameters during the period between April 2012 and March 2018; patients baseline characteristics, duration of using igaratimod, and reasons of discontinuation. To assess the safety of in igaratimod in patients with various complications, we further evaluated whether concomitant conditions such as, malignancy, tuberculosis, and interstitial lung disease, affect retention rate or not. Drug retention rates were calculated using the Kaplan-Meier method, which were analyzed using SPSS software version 21.

Results: During the study period, 74(16.2%) patients discontinued igaratimod. The reasons are 19(4.1%) renal injury, 15 (3.2%) liver function abnormality, 13(2.9%) GI symptoms, 9(2.0%) skin, 3(0.6%) interstitial lung disease, 1 edema, 1 IgG depletion. All the adverse events recovered after discontinuation. The number of the patients who have malignancy, tuberculosis, and interstitial lung disease is 35(7.7%), 39(8.6%), and 38(8.3%), respectively. The retention rates show no significant difference between the groups with concomitant conditions and without them.

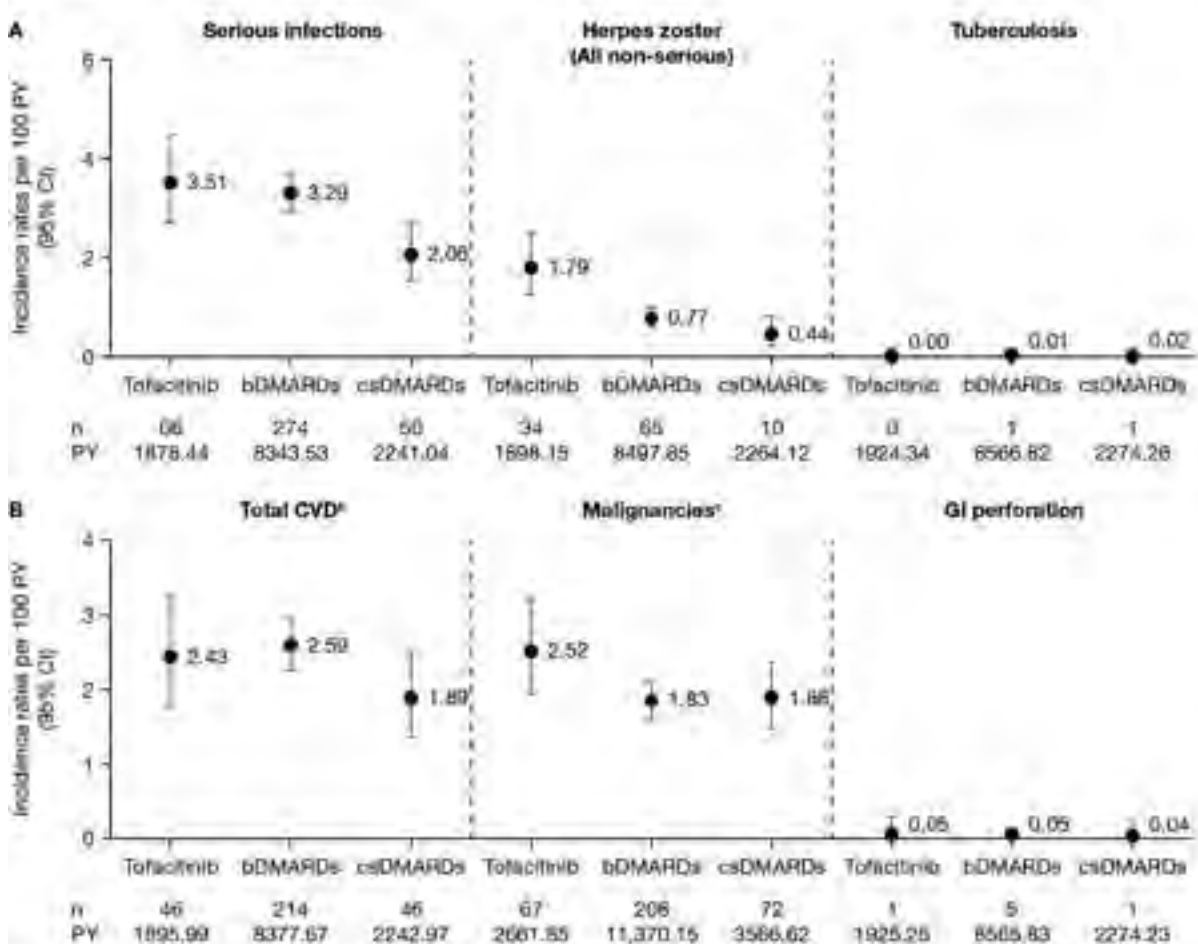
Conclusion: Igaratimod shows considerable retention rate in real clinical practice. Although adverse events of renal injury and liver function abnormality are common, all of them recovered after discontinuation. In addition, igaratimod is well tolerated even in patients with complications such as malignancy, tuberculosis, and interstitial lung disease.

Disclosure: Y. Ikeda, None; R. Rokutanda, None; S. Fukui, None; H. Sawada, None; M. Watanabe, None; A. Koido, None; Y. Kataoka, None; R. Kawato, None; H. Yanaoka, None; M. Suda, None; Y. Ohara, None; H. Tamaki, None; H. Shimizu, None; T. Tsuda, None; K. I. Yamaguchi, None; M. Kishimoto, None; M. Okada, None.

Real-World Data from a Post-Approval Safety Surveillance Study of Tofacitinib Vs Biologic Dmards and Conventional Synthetic Dmards: Five-Year Results from a US-Based Rheumatoid Arthritis Registry

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Figure. Standardized incidence rates* of safety events per 100 PY, by treatment: Available data for Corrona study period 11/2012-12/2017 (A) Serious infections, herpes zoster, tuberculosis (B) Total CVD, malignancies, GI perforation



Malignancies, all cancer including non-melanoma skin cancer

Bars indicate 95% CI

*Age- and gender-standardized rates were estimated using direct standardization using the Tofacitinib population as the standard population, and defined as new events per 100 PY; *Major adverse cardiac events (MACE) (myocardial infarction, stroke, TIA, CV death), hypertension requiring hospitalization, cardiac revascularization, ventricular arrhythmia, cardiac arrest, myocardial infarction, acute coronary syndrome, unstable angina, CHF requiring hospitalization, stroke, TIA, deep vein thrombosis, peripheral arterial thromboembolic event, urgent peripheral arterial revascularization, peripheral ischemia or gangrene, pulmonary embolism and other CVD; *All cancer including non-melanoma skin cancer
bDMARD, biologic disease-modifying antirheumatic drug (includes TNF inhibitors, abatacept, anakinra, rituximab, tocilizumab); CHF, congestive heart failure; CI, confidence interval; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, cardiovascular; CVD, cardiovascular disease; GI, gastrointestinal; MACE, major adverse cardiovascular event; n, number of events; PY, patient years; TIA, transient ischemic attack; TNF, tumor necrosis factor

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. A prospective observational 5-year study, embedded within the US Corrona RA registry, was initiated to evaluate the safety of tofacitinib after US Food and Drug Administration approval on November 6, 2012. The study has now completed 5 years of data collection. The objective of the study was to assess the rates of adverse events (AEs) in patients initiating tofacitinib vs biologic DMARDs (bDMARDs) and conventional synthetic DMARDs (csDMARDs). This analysis describes the age- and sex-standardized rates of AEs for the completed 5-year study period.

Methods: AEs were evaluated in three patient populations: 1) initiators of tofacitinib; 2) initiators of a bDMARD (with no prior/current tofacitinib exposure); and 3) initiators of a csDMARD (with no prior/current tofacitinib or bDMARD exposure). AE data were captured from prescribing physicians during follow-up. Patients who had at least one visit or AE at any time after initiation were included in the analysis. Standardized incidence rates and 95% confidence intervals were estimated across the 5-year period (November 6, 2012–December 31, 2017) using the age and gender distribution of tofacitinib initiators as the reference population.

Table. Baseline characteristics of patients with RA newly exposed to tofacitinib or comparator bDMARD/csDMARD in the Corrona study

	Tofacitinib initiators, N=1482		bDMARD initiators, N=6881		csDMARD initiators, N=2115	
	N	%	N	%	N	%
Gender (female), %	1482	80.6	6881	80.9	2115	74.6
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Age, years	1482	59.3 (12.1)	6881	58.2 (11.0)	2115	60.3 (13.4)
Time since diagnosis, years	1471	13.7 (10.2)	6828	10.5 (10.0)	2097	4.6 (7.5)
Tender joint count	1461	6.6 (7.2)	6874	6.7 (7.2)	2113	6.8 (8.9)
Swollen joint count	1460	8.8 (5.0)	6873	8.8 (4.1)	2113	8.9 (5.1)
PGA score	1479	47.4 (26.8)	6853	45.3 (27.0)	2110	37.1 (26.8)
Number of prior bDMARDs	1482	2.7 (1.8)	6881	1.5 (1.4)	2115	0.0 (0)
Number of prior TNF inhibitors	1482	1.8 (1.1)	6881	1.1 (1.0)	2115	0.0 (0)

bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; N, number of patients evaluated; PGA, patient global assessment; RA, rheumatoid arthritis; SD, standard deviation; TNF, tumor necrosis factor.

Results: Age- and gender-standardized incidence rates of safety events per 100 patient-years [PY] were calculated for 1482 tofacitinib, 6881 bDMARD, and 2115 csDMARD initiators with 1925.34 PY, 8566.82 PY, and 2274.51 PY of follow-up, respectively. Patient characteristics are shown in the Table. Disease duration was longer, and both the number of prior bDMARDs and number of prior TNF inhibitors were higher, in tofacitinib initiators compared with bDMARD and csDMARD initiators. Standardized incidence rates for serious infections, cardiovascular events, malignancies, and gastrointestinal perforation were generally similar for the three groups (Figure). Non-serious herpes zoster incidence rates were higher for tofacitinib compared to bDMARDs and csDMARDs, consistent with the known safety profile.

Conclusion In this analysis, despite patients in the tofacitinib group having longer disease duration and more prior biologic treatments, patients initiating tofacitinib, bDMARDs, and csDMARDs for the treatment of RA experienced comparable age- and gender-adjusted rates of serious infections, cardiovascular events, and malignancies. Tofacitinib initiators had a higher rate of non-serious herpes zoster than bDMARD and csDMARD initiators. A formal, propensity-matched analytic comparison of these data is planned.

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The Efficacy, Safety and Adherence of Biologic biological Disease-Modifying Anti Rheumatic Drugs, Infliximab, Tocilizumab and Abatacept, in Elderly Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Elderly patients with rheumatoid arthritis (RA) have declined physical performances and increased various complications. We are concerned about decrease of efficacy and increase of adverse events in elderly RA patients treated with biologic disease-modifying anti rheumatic drugs (bDMARDs) under conditions of insufficient dose of MTX or increased risk of infections. The purpose of this study is to examine the efficacy, safety and adherence of bDMARDs including infliximab (IFX), tocilizumab (TCZ) and abatacept (ABT) in elderly patients with RA.

Methods: RA patients (n=253) who received IFX (n=73), TCZ (n=104) or ABT (n=76) in Saitama Medical University Hospital between 2008 and 2016 were divided into 2 groups. The younger group consists of patients with younger than 64 years old (n=158) and the elderly one over 65 years old (n=95). In these 2 groups, we analyzed retrospectively the patients' background, disease activity, physical performance, safety and continuation rate of those bDMARDs.

Results: The patients' background (younger/elderly, p value) was as follows; mean age of onset (44/61 year-old, p<0.001), rate of female (75.3/81.1%), naïve rate of bDMARDs (54.4/46.3%), mean disease duration (6.9/10.5 years, p=0.001), rate of MTX use (82.9/46.3% p<0.001), rate of PSL use (55.7/75.8% p=0.001), mean dose of MTX (7.3/3.7 mg/week p<0.001), mean dose of PSL (3.3/3.9 mg/day), CDAI (22.3/20.9), DAS28-ESR4 (5.37/5.49), HAQ-DI (1.03/1.56 p<0.001), positive rate of RF (79.3/87.9%) and positive rate of anti-CCP antibody (83.9/93%). In efficacy, CDAI and HAQ significantly decreased in both groups during one year after bDMARDs exposure (P<0.001). There was no significant difference in the prevalence of patients who achieved remission by CDAI between the groups (younger vs. elderly: 30.5% vs. 22.2%). The continuation rate of bDMARDs in elderly patients did not inferior to that in younger patients (82% vs 79%). Moreover, we could not find significant difference in continuation rate of each 3 bDMARDs between the 2 groups (younger vs. elderly: IFX 75% vs. 77%, TCZ 83% vs. 84%, ABT 89% vs. 75%). The reasons for bDMARDs discontinuation within one year (younger/elderly) were adverse events (8.2/14.7%), ineffective (10.1/5.3%) and remission (0.0/1.1%).

Conclusion: The efficacy, safety and adherence of bDMARDs in elderly patients were not inferior to those in younger patients. These results suggest that the utility of bDMARDs would not be affected by age.

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Tofacitinib Safety and Efficacy in the Treatment of Rheumatoid Arthritis in a Central/Eastern European Subpopulation

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Piešťany, Slovakia, ⁴Vinnitsia Regional Clinical Hospital, Vinnitsia, Ukraine, ⁵Medical Centre Synexus, Sofia, Bulgaria, ⁶Pfizer Inc, Collegeville, PA, ⁷Pfizer Regional Medical Europe, Brussels, Belgium, ⁸Pfizer Inc, New York, NY, ⁹Pfizer Innovative Health, Prague, Czech Republic

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. This post hoc analysis assessed tofacitinib safety and efficacy in the Central and Eastern European (CEE) subpopulation of the tofacitinib clinical program vs the rest of the world (ROW; not including CEE countries).

Methods: Data for safety analyses were pooled from two Phase (P)1, ten P2, six P3, one P3b/4, and two long-term extension (LTE; ORAL Sequel LTE main study database locked at time of analysis: March 2, 2017) studies in patients with RA. Safety comparisons evaluated were adverse events (AEs), serious AEs (SAEs), and AEs of special interest for combined tofacitinib doses. Pooled data from five pivotal P3 studies (DMARD-IR pts) were assessed for efficacy of tofacitinib 5 and 10 mg twice daily and placebo at Month 3; endpoints are listed in the table. CEE countries in the efficacy analyses from five P3 studies included: Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Poland, Russian Federation, Slovakia, and Ukraine; safety analyses based on the 21 above studies included these countries plus Hungary, Romania, and Turkey.

Safety (all tofacitinib doses; pooled Phase 1, 2, 3, 3b/4, and LTE data)						
	CEE N=1765	ROW N=5296				
Total years of exposure, pt-years	8557	16,083				
Tofacitinib mean treatment duration, years	3.7	3.1				
Treatment-emergent AEs, n (%)	1428 (80.5)	4787 (88.9)				
Discontinuations due to AEs, n (%)	316 (17.9)	1011 (28.5)				
SAEs, n (%)	423 (24.0)	1434 (27.1)				
Most common AE class: infections and infestations, n (%)	976 (55.3)	3527 (66.6)				
Adverse events of special interest						
TB (unpublished), n, IR (95% CI)*	2, 0.03 (0.00, 0.11)	76, 0.22 (0.15, 0.30)				
Opportunistic infections (incl TB), n, IR (95% CI)*	6, 0.09 (0.03, 0.19)	84, 0.50 (0.40, 0.63)				
Serious infections, n, IR (95% CI)*	93, 1.36 (1.10, 1.67)	485, 2.94 (2.68, 3.21)				
Malignancies (incl. NMSC), n, IR (95% CI)*	36, 0.43 (0.33, 0.54)	141, 0.84 (0.71, 1.00)				
MACI (unpublished), n, IR (95% CI)*	16, 0.23 (0.14, 0.40)	88, 0.43 (0.34, 0.55)				
Mortality within 30 days (all causes), n, IR (95% CI)*	14, 0.24 (0.11, 0.35)	45, 0.27 (0.20, 0.36)				
Efficacy at Month 3 (data pooled from five Phase 3 trials)*						
Endpoint, % (95% CI)	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		Placebo	
	CEE N=260	ROW N=943	CEE N=260	ROW N=920	CEE N=134	ROW N=541
ACR28	54.4 (48.0, 60.8)	60.8 (57.4, 64.0)	63.4 (57.5, 69.2)	67.6 (64.4, 70.7)	29.4 (21.6, 38.1)	28.5 (24.5, 32.7)
ACR50	34.2 (19.0, 50.0)	33.0 (29.9, 36.2)	37.9 (27.6, 55.7)	37.7 (34.3, 41.1)	7.1 (3.3, 13.1)	10.6 (8.0, 13.6)
ACR70	7.7 (4.7, 11.7)	13.0 (11.4, 16.0)	15.1 (11.8, 20.0)	17.1 (14.7, 19.8)	1.6 (0.2, 5.6)	3.3 (1.9, 5.2)
DAS28-4(ESR) ≤2.6†	4.0 (1.9, 7.5)	7.8 (6.0, 9.0)	7.2 (4.3, 11.3)	11.1 (9.0, 13.6)	0.9 (0.0, 4.8)	2.4 (1.2, 4.3)
ASAC	-4.3 (-9.1, -7.3)	-6.7 (-9.4, -4.1)	-6.7 (-9.6, -7.8)	-9.7 (-9.9, -8.7)	-5.2 (-6.7, -3.7)	-4.6 (-5.4, -3.8)
ASAS (swollen)	-17.2 (-19.9, -14.3)	-15.5 (-17.2, -13.7)	-18.4 (-21.5, -16.1)	-16.8 (-18.5, -15.0)	-6.7 (-10.2, -3.3)	-2.5 (-4.7, -0.3)
CRP (mg/L)	-0.8 (-12.1, -7.5)	-11.6 (-13.3, -9.8)	-12.8 (-14.7, -10.0)	-12.1 (-14.6, -10.3)	0.4 (-2.3, 3.1)	0.8 (-0.9, 2.4)
HAQ-DI	-0.31 (-0.38, -0.25)	-0.49 (-0.53, -0.45)	-0.45 (-0.52, -0.38)	-0.30 (-0.60, -0.52)	-0.16 (-0.24, -0.08)	-0.16 (-0.21, -0.11)

*IR as patients with events/100 patient-years; †N values are pt numbers for the full analysis set; numbers of pts assessed for each endpoint may be lower; ‡Incidence rate
A, change from baseline; ACR, American College of Rheumatology; AE, adverse event; BID, twice daily; CEE, Central and Eastern Europe; CI, confidence interval; CRP, C-reactive protein; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; IR, incidence rate; LTE, long-term extension; MACI, major adverse cardiovascular safety events; NMSC, non-melanoma skin cancer; pt, patient; ROW, rest of world; SAE, serious adverse event; SOC, swollen joint count; TB, tuberculosis

Results: 1765 patients (pts) from CEE and 5296 from ROW were included in the safety analyses. Demographics and baseline characteristics were generally similar between CEE and ROW aside from race (99.9% vs 53.1% white), prior TNF inhibitor use (2.2% vs 20.8%) and non-TNF inhibitor biologic DMARD use (1.0% vs 6.4%); mean duration of RA was 7.6 years (range 0–65) in CEE and 8.2 years (range 0–55) in ROW. Safety results based on 21 studies and efficacy results based on five P3 studies are summarized in the table. Efficacy outcomes improved with tofacitinib vs placebo in CEE and ROW pts at Month 3. Improvements in composite measures (ie, ACR response rates and Disease Activity Score in 28 joints using erythrocyte sedimentation rate [DAS28-4(ESR)] ≤2.6) and Health Assessment Questionnaire-Disability Index (HAQ-DI) were numerically greater for ROW vs CEE pts; changes in objective measures (ie, swollen joint count and inflammatory markers) were more similar.

Conclusion: Tofacitinib showed substantial improvements in efficacy vs placebo in CEE and ROW. Results were generally consistent between CEE and ROW subpopulations. Following tofacitinib treatment, incidence rates of serious and

opportunistic infections were lower for CEE vs ROW, which may reflect the marginally lower RA duration beforehand; the lower prior biologic DMARD use in CEE may also have impacted efficacy and safety. Major limitations include the post hoc nature of this analysis and the small CEE population vs ROW, therefore results should be interpreted with caution. Previous analyses have revealed consistent safety and efficacy with tofacitinib in US and Western European subpopulations vs ROW.^{1,2}

References: 1. Wollenhaupt J et al. Deutschen Gesellschaft für Rheumatologie – 44 kongress 2016; Abstract 16080.
2. Cohen SB et al. Clin Exp Rheumatol 2016; 34: 32-6.

Disclosure: J. Vencovsky, None; J. Badurski, None; Š. Forejtová, None; O. Lukáčová, None; M. Stanislavchuk, None; D. Yaneva-Bichovska, None; H. Shi, Pfizer Inc, 1, Pfizer Inc, 3; R. Vasilescu, Pfizer Inc, 1, Pfizer Inc, 3; T. Lukic, Pfizer Inc, 1, Pfizer Inc, 3; M. Kabina, Pfizer Inc, 1, Pfizer Inc, 3.

Abstract Number: 1545

Exploring the Effects of Depressive Symptoms on the Efficacy of Sarilumab and Improvements in Health-Related Quality of Life

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

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Background/Purpose: The pro-inflammatory cytokine IL-6 has been found to play a critical role in mood disorders, with symptoms such as anxiety and depression having implications for RA disease activity. Studies have shown poorer disease outcomes in RA patients with depression.¹ This study evaluated the effect of baseline depressive symptoms on the efficacy of sarilumab and improvements in health-related quality of life (HRQOL).

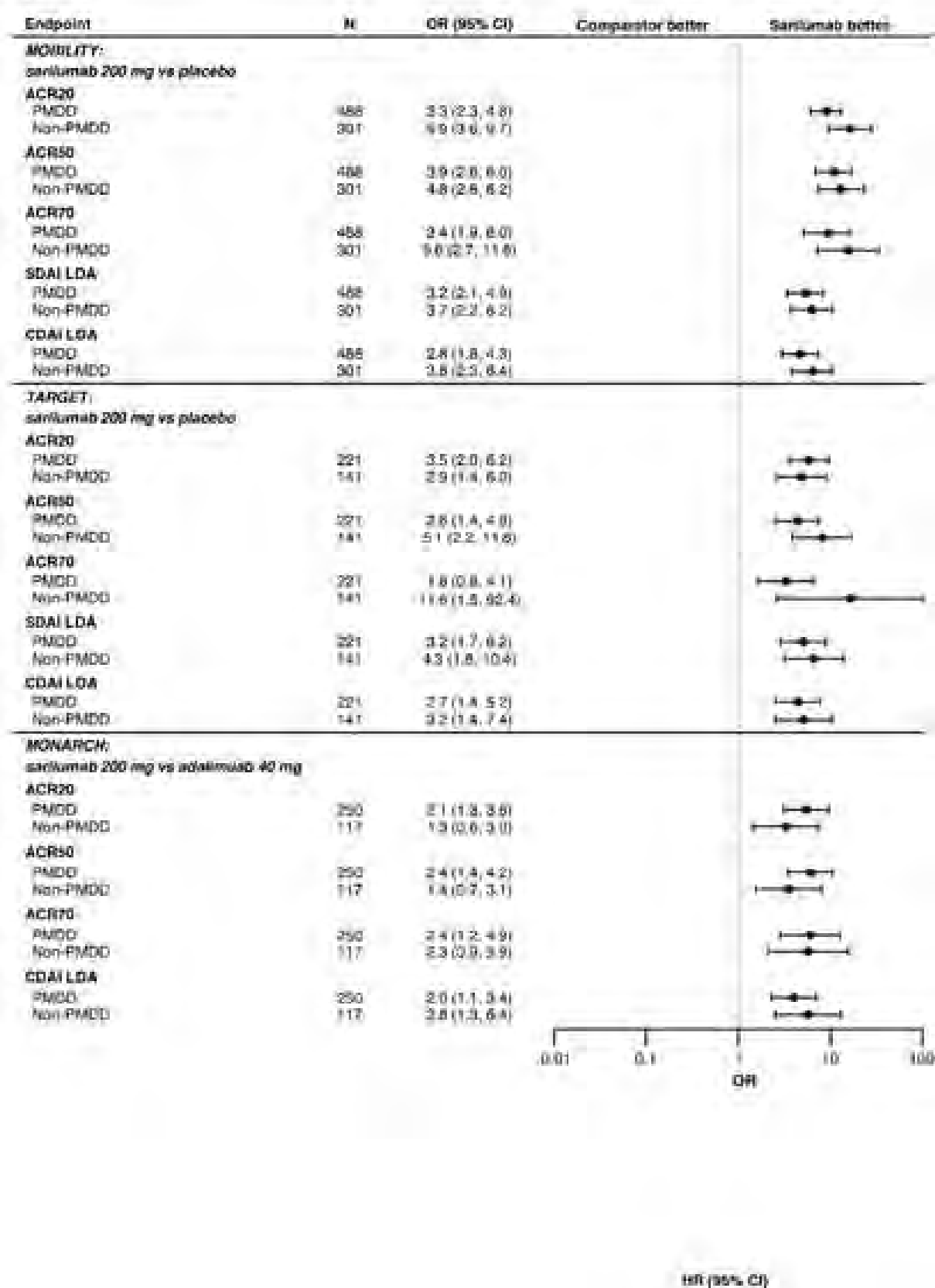
Methods: Post hoc statistical analyses of clinical and patient-reported outcomes (baseline; Week 24) were conducted in patients with moderately-to-severely active RA from 3 Phase 3 randomized controlled trials (RCTs) comparing the efficacy and safety of subcutaneous (SC) sarilumab 200 mg every 2 weeks (q2w) plus methotrexate (MTX) in MOBILITY [NCT01061736], plus csDMARDs in TARGET [NCT01709578] and as monotherapy versus adalimumab SC 40 mg q2w in MONARCH [NCT02332590]. Patients were categorized with probable Major Depressive Disorder (PMDD)² at baseline defined by a Mental Health (MH) domain score ≤ 56 on the Medical Outcomes Study 36-item short form (SF-36) questionnaire.

Results: Of 1197, 546 and 369 patients in MOBILITY, TARGET and MONARCH, respectively, 60.2%, 59.5% and 67.8%, were classified as PMDD. Disease duration, baseline DAS-28 CRP, tender and swollen joint counts and SF-36 MH scores were similar between sarilumab 200 mg plus MTX in MOBILITY and sarilumab 200 mg plus csDMARDs in TARGET versus placebo, and versus adalimumab in MONARCH in the PMDD subgroups. Interaction between PMDD and non-PMDD subgroups was non-significant for all endpoints except change from baseline in Patient Global Assessment of disease activity in MOBILITY (nominal $P < 0.05$). Odds ratios for responses by ACR20/50/70, SDAI ≤ 11 and CDAI ≤ 10 at Week 24 were nominally higher with sarilumab 200 mg versus placebo in both PMDD and non-PMDD subgroups in MOBILITY (nominal $P < 0.0001$), TARGET (nominal $P < 0.01$), and in PMDD by ACR20/50/70 in MONARCH (nominal $P < 0.05$) (Figure 1). MH scores for PMDD subgroups were nominally higher ($P < 0.05$) in ACR20 responders with sarilumab 200 mg versus placebo at Week 24 in MOBILITY (Figure 2). Sarilumab safety was consistent with IL-6R blockade.

Conclusion: These post-hoc analyses suggest that sarilumab treatment is equally efficacious irrespective of baseline PMDD status.

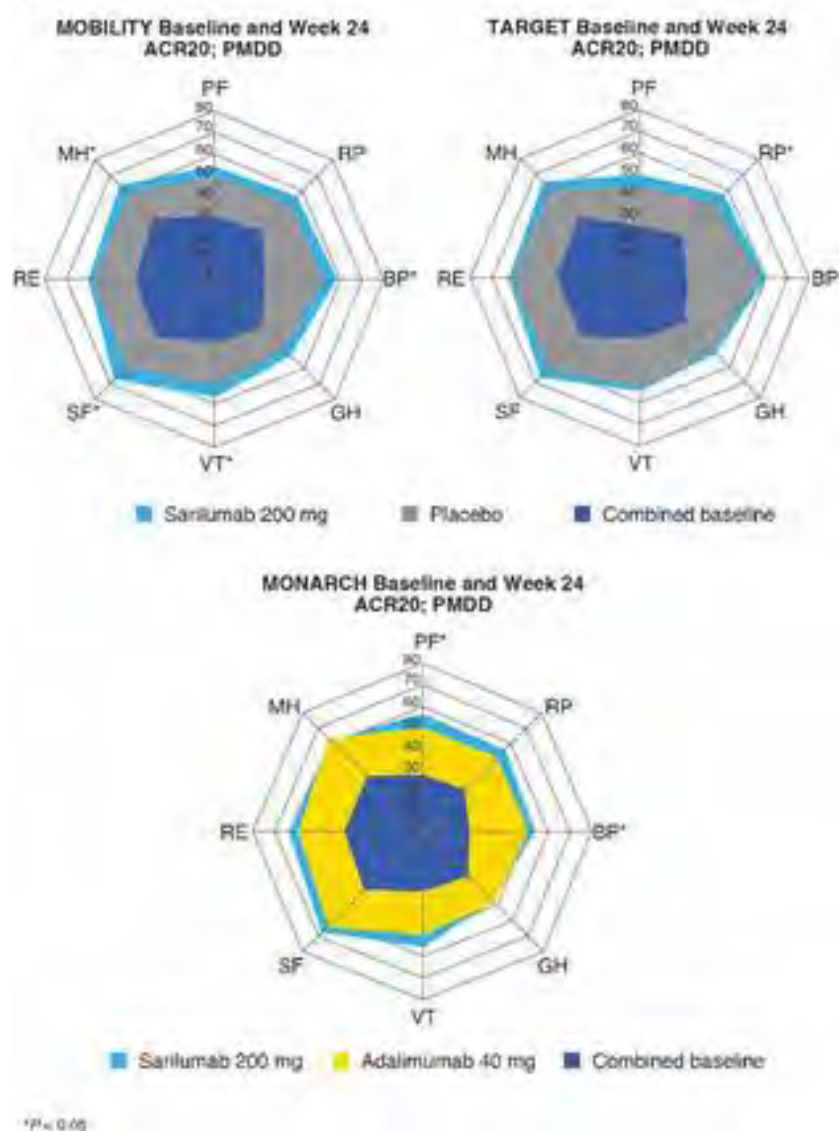
1. Matcham F et al. *BMC MusculoskeletalDisorders*. 2016;17:155.
2. Matcham F et al. *BMC MusculoskeletalDisorders*. 2016;17:224.

Figure 1



Disclosure: V. Strand, Abbvie, Amgen, BMS, Boehringer Ingelheim, Celltrion, Janssen, Lilly, Merck, Novartis, Pfizer, Samsung, Sandoz, UCB, 5; E. Mangan, Regeneron Pharmaceuticals Inc., 1, 3; O. Hagino, Sanofi Genzyme, 1, 3; J. Sadeh, Sanofi, 1, 3; S. Boklage, Regeneron Pharmaceuticals, Inc., 1, 3; T. Kimura, Regeneron Pharmaceuticals Inc., 1, 3.

Figure 2



Abstract Number: 1546

Efficacy and Safety of Corticosteroids in Rheumatoid Arthritis: Systematic Literature Review and Practical Recommendations

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Corticosteroids are effective in rheumatoid arthritis (RA) patients but their adverse events limit their use. The aim of this study was to: 1) To systematically and critically review the evidence on the characteristics, efficacy and safety of corticosteroids in RA; 2) To generate practical recommendations on its use.

Methods: We performed sensitive systematic literature searches in Medline and Cochrane (up to September 2017), screened EULAR and American College of Rheumatology meeting-abstracts. An expert librarian designed the strategies that included Mesh and text word terms. The search was limited to human RA, adults and the English and Spanish language. The inclusion criteria were as follow: 1) RA patients on corticosteroids; 2) Placebo and an active comparator were accepted as comparators; 3) Articles including typical efficacy and safety variables such as pain, DAS-28, radiographic progression or the infections rate; 4) Only meta-analyses, systematic reviews and clinical trials were selected. Two reviewers screened the titles and abstracts of the retrieved articles independently. They also collected the data from the studies included by using ad hoc standard forms. All collection was double by article and independent. Subsequently, a secondary manual search of the bibliography of the articles that were finally included was performed. Evidence tables were produced. The quality was evaluated with Jadad scale. In a nominal group meeting, based on their results, a panel of experts discusses this evidence and generated practical recommendations. The level of evidence and grade of recommendation was assessed according to the Center for Evidence Based Medicine de Oxford.

Results: A total of 47 articles were included. Corticosteroids in combination with DMARDs help control disease activity and radiographic progression, especially in the short-medium term and in early RA. Corticosteroids can also improve function and pain. Different types and routes of administration are effective, but there is not a standardized scheme (initial dose, de-escalation and duration of treatment with corticosteroids) superior to others. Adverse events when using corticosteroids are very frequent, dose-dependent although most are mild. Seven recommendations were generated on the use and risk management of corticosteroids (see table).

Conclusion: These recommendations aim to resolve some common clinical questions and facilitate decision-making with the use of corticosteroids in RA.

#	Recommendations
1	In patients with early RA, treatment with corticosteroids in combination with synthetic DMARDs is recommended (NE 1b; GR A)
2	In established RAs it is recommended to individualize the use of corticosteroids as a symptomatic treatment (NE 5; GR D)
3	Corticosteroids are recommended as bridging therapy in early RA, using low doses (≤ 7.5 mg/day of prednisone or equivalent), or medium doses (30 mg/day) following a rapid tapering scheme (NE 1b; GR A)
4	In patients with RA it is recommended to use the lowest effective dose of corticosteroids and to stop them as soon is possible (NE 1b; GR B)
5	When using corticosteroids in patients with RA, it is recommended to rule out comorbidities and risk of infection before their prescription (NE 5; GR D)
6	If corticosteroids are prescribed in the medium to long term, in patients with RA, close monitoring of cardiovascular risk factors and bone mineral density is recommended (NE 5; GR D)
7	If corticoids are prescribed in the medium to long term, in patients with RA, the prophylaxis of osteoporosis induced by corticosteroids is recommended (according to the recommendations of the international guidelines) (NE 5; GR D)

Disclosure: R. Sanmartí, None; J. Tornero Molina, None; F. J. Narváez, None; A. Muñoz, None; E. Garmendia, None; A. M. Ortiz Garcia, None; M. A. Abad, None; P. Moya, None; M. L. Mateo, None; D. Reina, None; J. Salvatierra Osorio, None; S. Rodriguez, None; A. Rubial Escribano, None; N. Palmou-Fontana, None; J. Calvo-Alén, None.

Abstract Number: 1547

Impact of Obesity on Drug Survival of Tofacitinib in Patients with Rheumatoid Arthritis: Analysis from the Turkbio Registry

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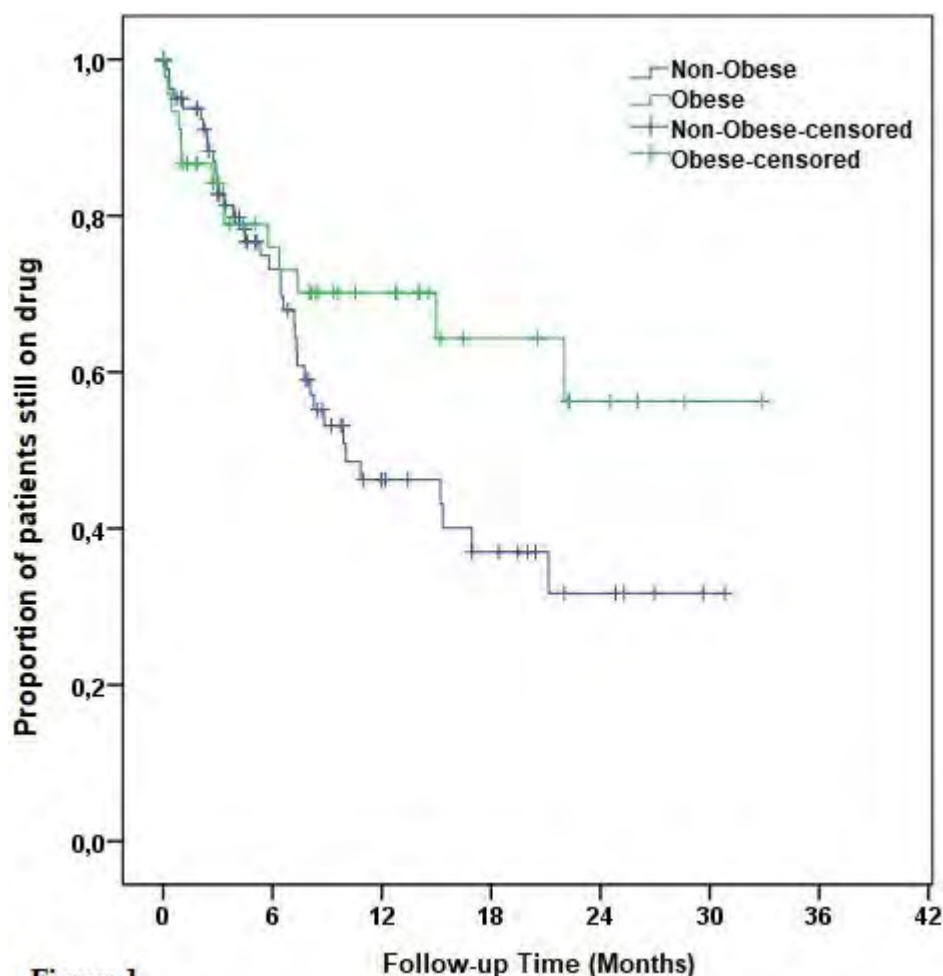


Figure 1

Table 1 Clinical and laboratory data in obese and non-obese patients

N=143	Non-Obese (<30 kg/m ²), N=92	Obese (≥30 kg/m ²), N=48	p
Age, years	50,4 (37,5-58,8)	56,4 (49,7-62,3)	0,002
Females, %	80,4	91,7	0,083
Disease duration, years	11 (6-17,5)	11 (8,5-15,5)	0,789
RF positivity, %	66,3	70,7	0,618
Anti-CCP positivity, %	72,7	65,9	0,436
Smoking, %	22,8	27,1	0,577
Diabetes Mellitus, %	8,1	27,8	0,014
Hypertension, %	20,5	52,4	<0,001
Methotrexate, %	79,3	85,4	0,381
Previous anti-TNF use, %	75,6	91,7	0,155
Previous non-TNF biologic drug use, %	58,8	39,1	0,136
Concomitant prednisolone dose >7,5 mg, %	9,4	17,4	0,441
Tofacitinib ongoing, %	59,8	70,8	0,197

Data are expressed as median (min-max). * reflects the mean of variables of patients through the observation. RF: rheumatoid factor, CCP: cyclic citrullinated peptide, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, DAS: disease activity score, HAQ: Health Assessment Questionnaire, VAS: visual analog scale

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Several previous reports suggest that obesity impairs the effectiveness and drug survival of anti-TNF- α agents in rheumatoid arthritis (RA). The aim of the study was to analyze the impact of obesity on drug survival of tofacitinib inpatient with RA, based on their baseline body mass index (BMI).

Methods: Data on patient characteristics, demographics, diagnosis, disease duration, treatment and outcomes have been collected since 2011 in Turkish Biologic (TURKBIO) Registry. By the end of May 2018, 140 RA patients received tofacitinib and were included. Demographic and clinical data including age, sex, disease type, disease duration and previous or current treatment with DMARDs and biological drug durations are stored in the database. Kaplan-Meier survival analysis was performed to estimate the drug survival.

Results: All patients received tofacitinib 5 mg BID. Patients were grouped according to BMI. Forty-eight were obese (BMI >30), 92 were non-obese patients. Obese patients were found to be older, had more DM and HT compared to non-obese patients as expected (Table 1). Gender distribution, disease duration, serologic positivity, previous or current treatment with DMARDs, previous TNF inhibitor or non-TNF biological drug use, concomitant prednisolone use and mean clinical and laboratory parameters through the observation period did not differ between groups. Tofacitinib treatment was ongoing in 59.8% in non-obese and 70.8% in obese patients. Median drug survival duration was 10 months in non-obese patients and 24 months in obese ones ($p=0.1$). Estimated drug survival rates for tofacitinib were not statistically significantly different between groups (Figure 1).

Conclusion: Real life experience from this nationwide TURKBIO registry suggests obesity does not adversely affect drug survival of tofacitinib in patients with RA. Further studies are needed to study impact of obesity on its clinical efficacy.

Disclosure: H. Babaoglu, None; B. Goker, None; N. İnanc, None; M. Birlik, None; S. S. Koca, None; A. Cefle, None; E. Dalkilic, None; A. Tufan, None; S. Yilmaz, None; S. Senel, None; S. Akar, None; N. Akkoc, None; F. Onen, None; U. Gazel, None.

Abstract Number: 1548

Favorable Effect of Hydroxychloroquine in Patients with Rheumatoid Arthritis and Diabetes or Impaired Glucose Control

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Hydroxychloroquine (HCQ) is widely prescribed for patients with Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE). It is fairly well tolerated with multiple well studied side effects, including those on insulin homeostasis and glucose metabolism. In this study, we review the long term effects of HCQ on blood glucose control in patients with RA and Impaired Glucose tolerance (Pre-DM) or Diabetes (DM).

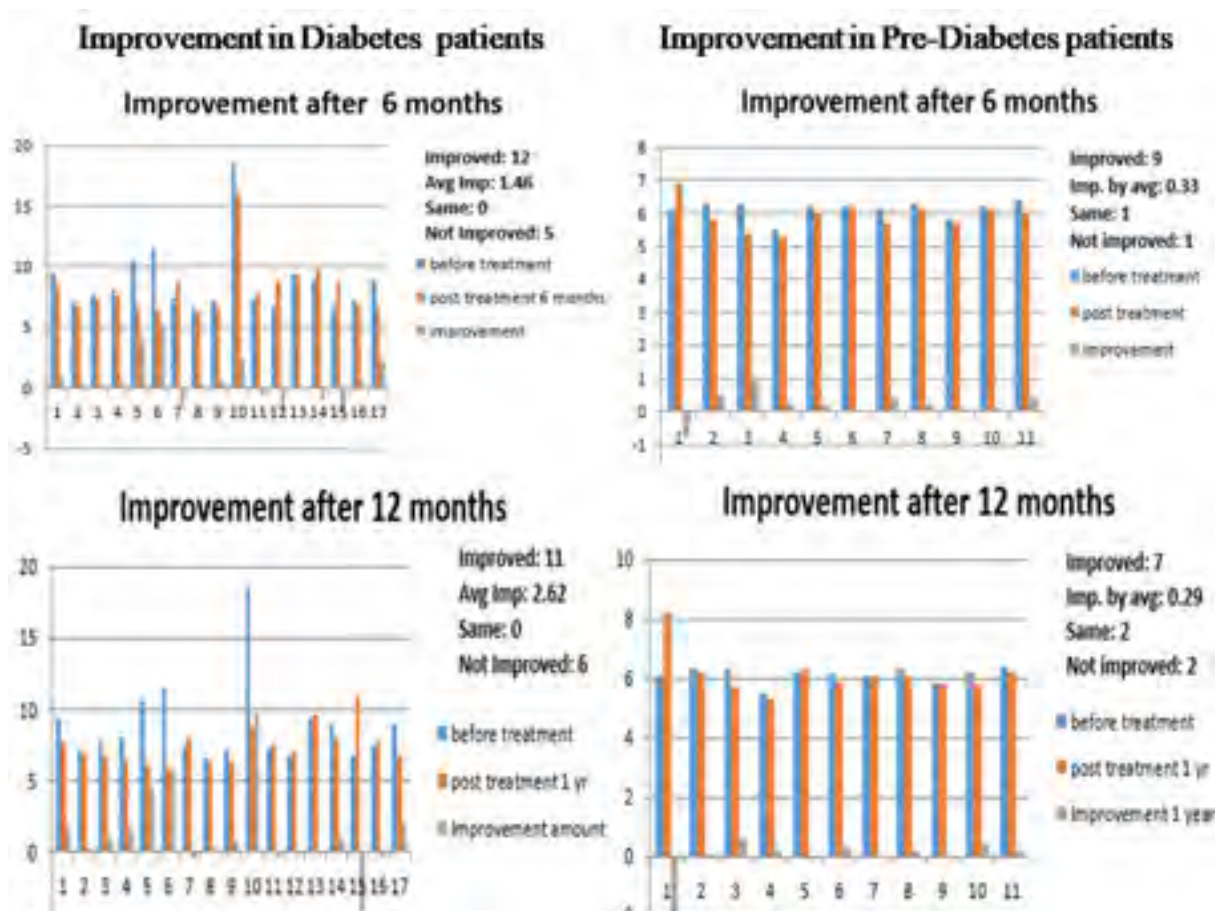
Methods: 155 patients with RA who were prescribed HCQ from Jan, 2014 to Jan, 2017 were identified. These patients were grouped into patients HgbA1c ranging from 5.7 to 6.4 as Pre-DM and those with HgbA1c >6.4 as DM. HgbA1c levels 6 months prior to initiation of therapy was identified and compared to HgbA1c levels 6 months and 1 year after the initiation of HCQ. We also compared LDL levels of these patients 1 year prior to and 1 year after the initiation of HCQ.

Results:

- 19 patients were identified as DM. 17 (89%) patients had a repeat HgbA1c at 6 months of which 12 (70%) had improvement and 5 (30%) had worsening. The average improvement in HbA1c in all these patients was 1.46% at 6 months. 17 patients had HgbA1c at 1 year. Of them, 11 (64%) had improvement, 5 (22%) had worsened and 1 (6%) had no change. The average improvement in HbA1c in all these patients was 2.62% at 1 year. These patients were on different combination of diabetes medications.

- 25 patients were identified as Pre DM prior to start of therapy. Of these, 11 patients (44%) had a HgbA1c at 6 months, 9 (81%) of them showed improvement and 3 (19%) showed worsening. The average improvement in HbA1c in all these patients at 6 months was 0.33%. 9 patients had followed up HgbA1c at 1 year after their HCQ therapy. Of them, 7 (77%) showed improvement while 2 (12%) had similar and 2 (11%) patient had worsening of their HgbA1c. The average improvement in HbA1c at 1 year was 0.29%. None of these patients were on any form of glucose control medication.
- We also reviewed 58 patients with LDL levels approximately 6 months prior to and 1 year after treatment with HCQ. 30 (51%) patients showed a decrease and 28 (49%) showed an increase in their LDL level.

Conclusion: HCQ has been shown to reduce the risk of development of DM in patients with RA. Studies have also shown reduction of HgbA1c in patients with RA and DM on treatment. HCQ also improves glucose control in patients with DM without any rheumatologic disease. This has been postulated to be from its effect on increased insulin secretion and decreased degradation leading to insulin accumulation at cellular level increasing their insulin sensitivity and this is independent of its anti-inflammatory activity. Our study suggests the positive effect of HCQ on average blood glucose levels represented by the drop in HgbA1c by 2.62% in DM patient and a drop of 0.29% in the PreDM group of patients. This favorable effect of HCQ on glucose control could makes it a preferred anti-inflammatory in those patients that have RA along with PreDM or DM.



Disclosure: F. Polara, None; M. I. Gora, None; S. Hinson, None.

Abstract Number: 1549

Comparison of Adverse Events and Survival of Treatment in Patients with Rheumatoid Arthritis Receiving Combined Treatment of Methotrexate and Leflunomide Versus Those Receiving Biological Therapy

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: According to clinical practice guidelines for patients with rheumatoid arthritis (RA), after failure to a c-DMARD (conventional disease modifying antirheumatic drug) can be chosen either by the combination with another c-DMARD, or by the addition of b-DMARD (biological) or ts-DMARD (target synthetic). The most frequent c-DMARD combination therapy in our country is methotrexate (MTX) plus lefunomide (LEF).

The objective is to compare the survival and safety of treatment between two cohorts of patients with RA who have failed to c-DMARD monotherapy: one with combination of MTX + LEF (cohort A) and the other with the first b-DMARD (cohort B).

Methods: Patients ≥ 18 years old with RA (ACR 1987 or ACR/EULAR 2010 criteria), who received treatment with MTX plus LEF or with the first b-DMARD therapy after failing c-DMARD monotherapy were included. Sociodemographic, clinical and therapeutic variables were recorded. Disease activity was assessed by DAS28. The adverse events (AE) that occurred during the treatment, the severity of them, as well as, the interruptions of the treatment were consigned. The causes of discontinuation and survival of both types of treatment were evaluated. *Statistical analysis:* Descriptive statistics. Chi ² test, Student's T test and/or Mann Whitney test. Multiple logistic regression analysis. Kaplan Meier curves and Log Rank test for survival analysis.

Results: 202 patients were included, median age was 58 years old (IQR 50.7-65), 86.6% were female and the median disease duration was 15 years (IQR 9-22). 69.8% had associated comorbidities. 100 patients (49.5%) were in cohort A and 102 (50.5%) were in cohort B. No baseline differences were found related to the clinical characteristics, except for the prevalence of previous tuberculosis (Cohort A 5.2% vs cohort B 0%, $p = 0.02$) and heart failure (Cohort A 7.4% vs cohort B 1%, $p = 0.03$). We did not observe differences in treatment survival between both cohorts [Cohort A: mean 121.2 months (95%CI: 100.3-142) and cohort B: mean 77.1 months (95%CI 63.3-91), $p = 0.2$]. 47.6% of cohort A permanently or temporarily suspended therapy vs 52.4% of cohort B ($p = 0.67$), being the most frequent causes of discontinuation: for cohort A inefficacy (31.1%) and AE for cohort B (55.8%). 56.9% suffered at least one AE and 60% of them were receiving concomitant corticosteroids. The infections were more frequent in cohort B 39.7% vs cohort A 19.6% ($p = 0.02$). In multivariate analysis, adjusting for age and disease duration, corticosteroid treatment was associated with the presence of AE (OR: 19.8, 95% CI: 6.23-57.6, $p < 0.001$) regardless of the type of treatment, and the use of biological therapy was associated with higher risk of infections (OR 2.7, 95%CI: 1.15-6.34, $p = 0.02$) regardless of the use of concomitant corticosteroids.

Conclusion: Treatment survival in both cohorts was comparable. The frequency of infections was higher in cohort with b-DMARD. Concomitant treatment with steroids increased the risk of AE, regardless of the type of treatment.

Disclosure: M. Cavalieri, None; R. Rolon Campuzano, None; E. E. Schneeberger, None; F. Dal Pra, None; D. Capelusnik, None; C. A. Isnardi, None; M. N. Fornaro, None; G. Citera, Novartis, Pfizer Inc, 2, AbbVie, Bristol-Myers Squibb, Eli Lilly, Genzyme, Novartis, Pfizer Inc, Roche, 5.

Abstract Number: 1550

Improvement of HbA1c in Patients with Rheumatoid Arthritis and Diabetes Type 2 during Treatment with Tocilizumab

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Interleukin 6 (IL-6) and C-reactive protein (CRP) are independent risk factors for type 2 diabetes mellitus [1], and IL-6 plays a role in insulin resistance [2]. Ogata et al. demonstrated a tocilizumab (TCZ) induced a reduction of HbA1c in patients with diabetes and rheumatoid arthritis (RA) [3]. The present analysis of the non-interventional study ICHIBAN (final dataset) investigated whether there is a difference in the effectiveness and safety of TCZ in RA patients with and without diabetes.

Table 1: Comparison of effectiveness and safety of TCZ between diabetic and nondiabetic patients.

	Total	Diabetics	Nondiabetics
Baseline characteristics, % (n)	100.0 (3164)	9.9 (314) ^a	89.9 (2844) ^a
Sex (male), % (n)	25.2 (797)	27.7 (87)	24.9 (709)
Age [years], mean ± SD	55.5 ± 13.1	63.0 ± 10.4	54.7 ± 13.1
Duration of RA [years], median	7.0	8.0	7.0
BMI [kg/m ²], mean ± SD	26.9 ± 5.3	29.6 ± 6.3	26.6 ± 5.1
Comedication; % (n)			
• csDMARDs	50.7 (1605)	45.5 (143)	51.4 (1462)
• Glucocorticoids	80.6 (2550)	80.6 (253)	80.7 (2296)
Comorbidity, % (n)			
• Depression	7.5 (236)	11.5 (36)	7.0 (200)
• CHD	4.4 (140)	11.5 (36)	3.7 (104)
• Osteoporosis	17.1 (542)	25.2 (79)	16.3 (463)
Effectiveness, % (n)	100.0 (2902)	10.0 (290) ^a	89.8 (2606) ^a
DAS28-ESR			
• Week 0 (BL), mean ± SD (median)	5.2 ± 1.4 (5.3)	5.5 ± 1.3 (5.7)	5.2 ± 1.4 (5.2)
• LV under TCZ, mean ± SD (median)	3.1 ± 1.7 (2.9)	3.3 ± 1.6 (3.2)	3.0 ± 1.7 (2.8)
• Change vs BL, mean ± SD (median)	-2.1 ± 1.7 (-2.2)	-2.2 ± 1.7 (-2.2)	-2.1 ± 1.7 (-2.2)
VAS [mm]; median (Q1, Q3)			
• Exhaustion/tiredness BL	60.0 (40, 80)	69.0 (45, 81)	60.0 (40, 79)
• LV	45.0 (18, 70)	50.0 (17, 71)	45.0 (18, 69)
• Pain severity BL	66.0 (47, 80)	67.0 (49, 82)	66.0 (47, 80)
• LV	40.0 (17, 67)	44.0 (25, 65)	40.0 (16, 67)
• Sleep disturbances BL	52.0 (21, 76)	60.0 (25, 80)	51.0 (21, 76)
• LV	35.0 (10, 66)	42.0 (10, 70)	35.0 (10, 65)
HbA1c [%] ^b			
• Week 0 (BL), mean ± SD	5.96 ± 1.35	7.46 ± 1.19	5.25 ± 0.64
• Week 104, mean ± SD	5.83 ± 0.95	6.73 ± 0.59	5.40 ± 0.78
• Change vs BL, mean ± SD	-0.13 ± 0.96	-0.73 ± 1.26	0.15 ± 0.62
Safety (event rate per 100 patient-years), % (n)	100.0 (3164)	9.9 (314) ^a	89.9 (2844) ^a
Adverse events (TEAEs)	108.4	108.8	108.4
Serious AEs (TESAEs)	23.9	34.6	22.8
Infections (TEAEs) ^c	29.4	27.6	29.6
Infections (TESAEs) ^c	3.9	7.2	3.5

Table 1: Comparison of effectiveness and safety of TCZ between diabetic and nondiabetic patients.

BL: Baseline; LV: last visit under TCZ; Q1, Q3 = lower, upper quartile; SD: standard deviation; TCZ: tocilizumab; TEAE: treatment-emergent adverse events; TESAE: treatment-emergent serious adverse events; VAS: visual analog scale; CHD: coronary heart disease.

^a For 6 patients (0.2% of Total) the diabetes status was not documented.

^b Analysis based on 31 patients with HbA1c values available at BL and Week 104 (10 diabetic and 21 nondiabetic patients).

^c Two patients with a HbA1c >7.5% were classified as diabetic.

^d Infections: all AEs/SAEs with MedDRA preferred term indicating any kind of infection.

Methods: The ICHIBAN study (NCT 01194401) observed patients with RA during treatment with TCZ iv (max. 2 years) between 2010 and 2017. All 3164 patients who had received at least 1 dose TCZ were included in the analysis (Total). Classification of diabetes mellitus was based on the data provided by the investigators at baseline (BL).

Results: At BL, 9.9% (N=314) of the patients were diabetic and 89.9% (N=2844) were nondiabetic.

Diabetic patients were markedly older compared to nondiabetic patients (mean age: 63.0 vs 54.7 years), had a higher BMI (mean: 29.6 vs 26.6 kg/m²), a higher disease activity (mean DAS28: 5.5 vs 5.2), a more severe functional impairment at BL (mean HAQ: 1.6 vs 1.3%), and a higher comorbidity rate, particularly regarding coronary heart disease (11.5% vs 3.7%), osteoporosis (25.2% vs 16.3%) and depression (11.5% vs 7.0%).

Both subgroups had a comparable response regarding all investigated variables, despite the differences in BL characteristics. DAS28-ESR improved by 2.2 vs 2.1 points in patients with and without diabetes; HAQ improved by 0.2% in both subgroups. HbA1c was markedly decreased (-0.73%) after 104 weeks of TCZ treatment in diabetic patients, whereas there was no change in nondiabetic patients (Tab. 1).

The rates of serious adverse events (20.7% vs 14.3%) and of serious infections (5.4% vs 3.4%) were higher in patients with diabetes than in those without; there was no difference regarding non-serious adverse events.

Conclusion: The proportion of diabetic patients was slightly higher in the ICHIBAN study (9.9%) compared to the general population (~8%) [4]. An effective clinical response was observed during TCZ iv therapy. Despite a higher disease activity and comorbidity rate at BL, patients with diabetes benefitted to the same extend as nondiabetic patients with regard to all investigated efficacy variables. The safety data underscore the higher risk for infection in diabetic patients. HbA1c decreased from 7.46% to 6.73% in diabetic patients. Further research is necessary to clarify the underlying mechanisms.

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Disclosure: C. Specker, AbbVie DE GmbH & Co. KG, Bund Deutscher Internisten, CHUGAI PHARMA MARKETING, LTD, Celgene GmbH, Deutsche Gesellschaft f. Innere Medizin, KLINIKVERBUND WUPPERTAL, KOOP. RHEUMAZ.R.-R.EV, KV Westfalen-Lippe, KV Nordrhein, Ludwig Max. Universität München, Luk, 8, AbbVie DE GmbH & Co. KG, Janssen-Cilag, CHUGAI PHARMA MARKETING, LTD, MSD SHARP UND DOHME GMBH, NOVARTIS, UCB PHARMA GMBH, Lilly, BOEHRINGER INGELHEIM, 5, Boehringer, Chugai, DRFZ, GSK, Pfizer, Roche, 2; A. Alberding, None; M. Aringer, Roche, Chugai, 5, Roche, Chugai, 8; G. R. Burmester, Sanofi, Roche, Janssen, 5, Sanofi, Roche, Janssen, 8; J. P. Flacke, Roche Pharma AG, 3; M. Hofmann, Chugai Pharma Europe Ltd., 3; P. Kaestner, Chugai, 5, Novartis, 5; H. Kellner, Roche, 5; F. Moosig, None; M. Sieburg, None; H. P. Tony, Roche Pharma, Abbvie, BMS, Chugai, Janssen, Novartis, Sanofi, Lilly, 5, Roche Pharma, Abbvie, BMS, Chugai, Janssen, Novartis, Sanofi, Lilly, 8; G. Fliedner, None.

Abstract Number: 1551

Anti-Drug Antibodies to Certolizumab Pegol Are Associated with Low Drug Levels and Reduced Clinical Response at 3 Months in Patients with Inflammatory Joint Diseases

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Anti-drug antibodies (ADAb) to biological drugs predispose patients (pts) to low drug levels and lack of treatment response. For certolizumab pegol (CP) knowledge about the frequency and clinical relevance of ADAb is limited in pts with inflammatory joint diseases (IJD).

Objectives: To assess the frequency and clinical relevance of early ADAb development in pts with inflammatory joint diseases treated with CP.

Methods: Pts from the NOR-DMARD study (n=310) with a clinical diagnosis of RA (91), PsA (61), axSpA (116) and other IJD (42) starting treatment with CP, who had available biobank sample at 3 months follow-up, were included. Serum samples are non-trough samples collected at 3 months. Drug concentrations were analysed using an in-house immunofluorometric assay automated on the AutoDELFLIA immunoassay platform. ADAb was detected by a principal assay measuring neutralising ADAb and two confirmational tests (antigen-bridging test and a 3-step immuno fluorometric assay). Pts with RA, PsA and axSpA were included in response analyses. Treatment response was defined by EULAR good/moderate response in RA, DAS28 improvement ≥ 0.6 in PsA, and ASDAS clinically important improvement (CII) in axSpA.

Results: After 3 months of treatment, 19 of 310 (6.1%) patients were ADAb positive (5 RA, 4 PsA, 6 axSpA and 4 other IJD). ADAb positive pts had significantly lower CP levels than ADAb negative pts, median 1.0 (IQR 0.2-6.8) vs 34.4 (IQR 21.2-44.7) mg/L ($P < 0.001$).

Response data were available for 245 pts. Of these, only 1/11 (9%) ADAb-positive pts was classified as a responder, while 10/11 (91%) were non-responders. Among ADAb-negative pts with response data, 129/234 (55%) were responders, while 105/234 (45%) were non-responders.

Conclusion: ADAb against CP were detected in 6.1% of patients after 3 months of treatment and were associated with low drug levels and reduced treatment response. These results suggest that drug levels and ADAb may be important for the monitoring efficacy of treatment with TNF inhibitors, but the clinical significance needs to be examined in randomised clinical strategy trials.

Disclosure: J. Gehin, Roche, 5; G. L. Goll, AbbVie, Boeringer Ingelheim, Eli Lilly, Novartis, Pfizer, Orion Pharma, Roche, Sandoz, 5; S. W. Syversen, None; D. J. Warren, None; J. Sexton, None; E. Kvein Strand, Pfizer, Inc., 5; T. Kvien, AbbVie, Biogen, BMS, Boehringer Ingelheim, Celgene, Celltrion, Eli Lilly, Epirus, Hospira, Merck-Serono, MSD, Mundipharma, Novartis, Oktal, Orion Pharma, Hospira/Pfizer, Roche, Sandoz and UCB, 5, 8, AbbVie, BMS, MSD, Pfizer, Roche, UCB, 2; E. Lie, None; N. Bolstad, Roche, 5, Orion Pharma, 5, Napp Pharma, 5, Pfizer, Inc., 5, Takeda, 5, Janssen, 5.

Abstract Number: 1552

No Effect of Concomitant Glucocorticoid Therapy on Efficacy and Safety of Tocilizumab Monotherapy Found in Rheumatoid Arthritis Clinical Trials

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

No effect of concomitant glucocorticoid therapy on efficacy and safety of tocilizumab monotherapy in rheumatoid arthritis clinical trials

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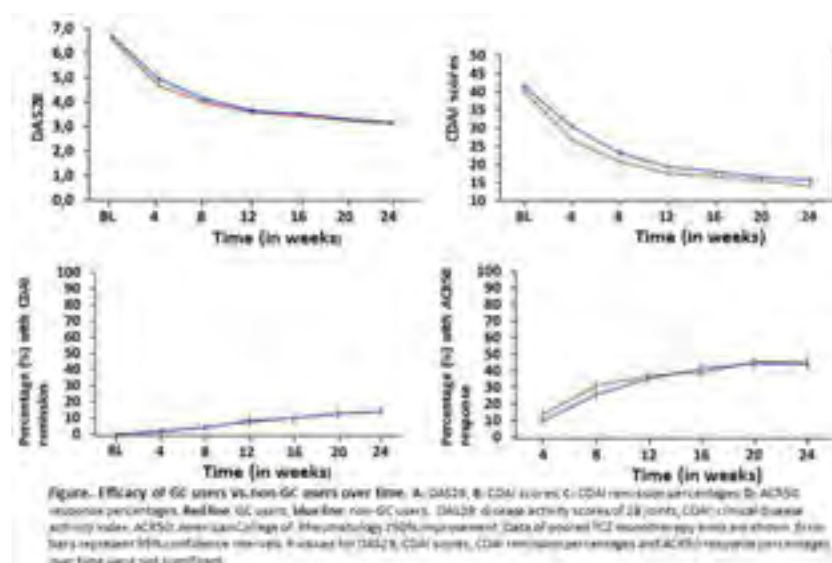
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Background/Purpose: Among RA patients in clinical trials, background treatment with glucocorticoids (GCs) is common. The potential impact of GCs on safety of the DMARD tested in these trials has rarely been evaluated. Our aims were to establish whether a stable concomitant GC treatment influenced: 1) efficacy and safety of tocilizumab (TCZ) monotherapy initiated in RA patients in TCZRCTs and 2) efficacy and safety in the comparator arms of these trials, in which adalimumab (ADA) or methotrexate (MTX) was initiated.

Methods: Data were used from 4 RCTs including AMBITION, ACT-RAY, ADACTA and FUNCTION with TCZ monotherapy arms. Patients had discontinued bDMARDs or were bDMARD naïve and MTX-naïve, MTX-intolerant or MTX inadequate responders. Stable GC dose at baseline was allowed. Differences in change from baseline up to week 24 in CDAI and DAS28 between GC-users and non-GC-users were analysed using ANCOVA. Difference in radiographic progression up to week 104 between GC-users and non-GC-users was analysed. Incidence rates of SAEs were assessed by GC use.

Results: Baseline characteristics were comparable between GC users and non-GC users within RCTs. No significant differences were found in DAS28 change or CDAI change from baseline to 24 weeks, nor in CDAI remission percentages and ACR50 response at 24 weeks, between GC users and non-GC users in TCZ, ADA, or MTX arms (Figure). In the MTX arm a significant difference in radiographic progression was found, in favour of GC use. SAE rates were numerically higher for GC users vs non-GC users in MTX and ADA arms (Table), however this difference was not tested statistically.

Conclusion: In 4 RA TCZ clinical trials, no effect of stable concomitant GC treatment at baseline and continued during the trial was found on efficacy of MTX or TCZ or ADA monotherapy. The SAE rate was numerically higher in GC users compared to non-GC users in the MTX and ADA monotherapy arms.



Disclosure: M. Safy, AstraZeneca, 2; J. W. G. Jacobs, None; M. Edwardes, Everest Clinical Research, 3; M. J. de Hair, None; X. M. Teitsma, None; P. M. Welsing, None; M. E. Borm, Roche, 3; Y. Luder, F. Hoffmann-La Roche, 1, F. Hoffmann-La Roche, 3; J. van Laar, Roche, 5, Genentech, Inc., 2; A. Pethö-Schramm, Roche, 3; J. W. J. Bijlsma, Roche, SUN, 5.

Abstract Number: 1553

An Analysis of Real-World Data on the Safety of Etanercept in Elderly Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

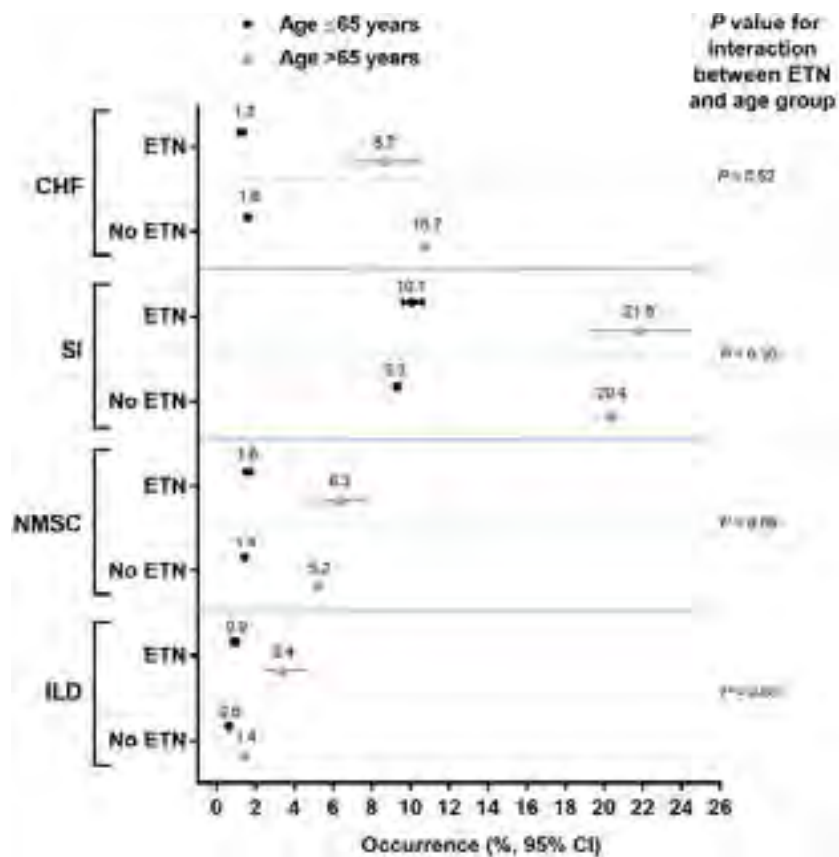
Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Both rheumatoid arthritis (RA) and older age are associated with a higher risk of comorbidities, and the appropriate treatment approach for older patients is unclear. We evaluated real-world data (RWD) to determine whether there is an association between etanercept (ETN) and select adverse events (AEs) in patients with RA, stratified by age. We hypothesized that there is no difference in risk of AEs between younger (aged ≤65 yr) and older (aged >65 yr) patients.

Methods: Data from 2013 to 2018 were analyzed from the IBM Watson Health Markets can Database which contains information on 104.5 million distinct patients, including 531,996 with RA. Patients were required to be rolled ≥1 yr prior to RA diagnosis; the first exposure to ETN was after RA diagnosis and before the AE of interest: congestive heart failure (CHF), serious infection (SI), non-melanoma skin cancer (NMSC), or interstitial lung disease (ILD). Proportion of patients experiencing each AE was determined for patients ≤65 yr and >65 yr receiving and not receiving ETN. Differences were evaluated using Fisher's Exact test. Logistic regression models assessed the interaction between ETN and age group.



Propensity matching was performed, and logistic regression was applied using the propensity-score-matched cohort. Patients receiving and not receiving ETN were matched by age, age >65 yr, gender, and geographical region.

Results: Average age of patients with RA was 56.1 ± 14.9 yr; 73.5% were female. Risk of experiencing CHF did not differ significantly for patients receiving vs not receiving ETN: odds ratio (OR) = 0.883, 95% CI: 0.770-1.009; $p=0.072$. However, the risks of SI, NMSC, and ILD were significantly higher in the patients receiving ETN (SI: OR=1.14, 95% CI: 1.07-1.21, $p<0.001$; NMSC: OR=1.20, 95% CI: 1.05-1.37, $p=0.008$; and ILD: OR=1.89, 95% CI: 1.56-2.29, $p<0.001$). In patients >65 yr, the occurrence of CHF was lower for patients receiving vs not receiving ETN (8.7% vs 10.7%, $p=0.025$) (Figure); the occurrence of SI and NMSC did not differ significantly; SI: 21.8% vs 20.4% for ETN vs no ETN, respectively, $p=0.186$; NMSC: 6.3% vs 5.2%, $p=0.952$. The occurrence of ILD was higher for patients receiving ETN: 3.4% vs 1.4%, $p<0.001$. The difference in AE occurrence between patients ≤65 yr and >65 yr did not differ significantly for patients receiving vs not receiving ETN for any of the AEs (Figure).

Conclusion: In this analysis of RWD of patients with RA, the risk of CHF, SI, NMSC, and ILD between younger and older patients was not modified by ETN usage. This analysis suggests an overall acceptable safety profile of ETN; however, clinicians should use caution when treating older patients.

Figure. Occurrence of AEs according to age group and ETN treatment status

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Abstract Number: 1554

Cigarette Smoking Does Not Affect Treatment Response to Tofacitinib in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II: PROs, Safety and Comorbidity

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Smoking is one of the described risk factors for rheumatoid arthritis (RA) since smoking may induce citrullination of peptide antigens and thus the trigger anti-citrulline immunity. Moreover, smoking increases the disease activity and radiological progression in RA. Current smoking is associated with poor responses to therapy with anti-rheumatic drugs including methotrexate and anti-TNF agents in RA. The aim of our study was to investigate whether cigarette smoking influences the response to tofacitinib treatment in patients with RA.

Methods: Data on patient characteristics patients receiving targeted treatments have been collected since 2011 in Turkish Biologic (TURKBIO) Registry. By the end of May 2018, 115 RA patients received tofacitinib from the TURKBIO registry, were included in the analysis. Patients were divided into subgroups as current smokers and non-smokers (never+ex-smokers). Demographic and clinical data including age, sex, disease type, disease duration, and previous or current treatment with disease-modifying anti-rheumatic drugs and tofacitinib usage durations are compared. Kaplan-Meier survival analysis was performed to estimate the drug survival of tofacitinib.

Results: There were no significant differences in gender, seropositivity, tender and swollen joint counts at baseline in the study groups, although current smokers were significantly younger ($p<0.001$). Almost all baseline parameters were similar in the current smokers and non-smokers. 71.6% and 65.1% of current smokers and 68.2% and 48.6% of non-smokers were going on the treatment at 6th and 12th months, respectively ($p=0.378$). There was no significant difference between groups in terms of drug survival rates for tofacitinib.

Table 1 Clinical and laboratory characteristics

	Current Smokers (n=27)	Non-Smokers (n=88)	p
Age, year	44.5 (35.8-53)	56.5 (47.6-63)	<0.001
Gender (Females), n (%)	20 (74.1)	77 (87.5)	0.128
Disease duration, years	10 (4-16)	10.5 (5-16.5)	0.835
Tofacitinib is 1 st choice biologic or targeted DMARD, %	48.1	56.8	0.509
Concomitant glucocorticoid usage, %	41.1	51.1	0.346
Glucocorticoid dosage, mg/day	4 (4-5)	5 (4-6)	0.173
RF positivity, n (%)	77.8	65.6	0.328
CCP positivity, n (%)	25.1	28.8	0.763
Baseline swollen joint count, n	2 (0-4)	3 (0-5)	0.521
Baseline tender joint count, n	3.5 (2-7)	5 (2-9)	0.371
Baseline ESR, mm/h	24 (19-38)	36 (17-55)	0.099
12 th month ESR, mm/h	16 (12-31)	28 (21-52)	0.063
Baseline CRP, mg/dl	4 (3-8)	5.4 (3.33-15.45)	0.232
12 th month CRP, mg/dl	3 (1-6)	8 (3.02-11)	0.139
Baseline DAS28-CRP	4 (3-4.8)	4.4 (3.5-4.9)	0.279
12 th month DAS28-CRP	1.7 (1.3-3)	2.1 (1.9-3.1)	0.233
Baseline HAQ	1 (0.625-1.5)	1 (0.75-1.5)	0.849
12 th month HAQ	0 (0-0.25)	0.75 (0.25-1.375)	0.020

DMARD; disease modifying anti-rheumatic drug, RF; rheumatoid arthritis, CCP; cyclic citrullinated peptide, ESR; erythrocyte sedimentation rate, CRP; C-reactive protein, DAS; disease activity score, HAQ; Health Assessment Questionnaire.

Conclusion: Current smoking does not affect the response and drug survival for tofacitinib in RA. However, it is obvious that smoking is related with high morbidity and mortality in RA, since it increases pulmonary disabilities and the risks of atherosclerosis and malignancies. Moreover, it is known to increase the risk for RA, and the clinical and radiological progression of RA. Therefore, the cessation of tobacco use should be still advised to all smoker RA patients.

Disclosure: A. Karatas, None; B. Oz, None; E. Dalkilic, None; G. Can, None; Y. Pehlivan, None; S. Senel, None; A. Yazici, None; N. Inanc, None; Z. Erturk, None; A. Cefle, None; S. Akar, None; S. S. Koca, None; M. Birlik, None; F. Onen, None.

Quality of Life of Rheumatoid Arthritis Patients Treated with Biologics

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster II – ARHP

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Major advances in the management of rheumatoid arthritis (RA) have been recorded over the last decade thanks to the introduction of biologics. However, medical needs concerning functioning and quality of life of patients are not completely fulfilled⁽¹⁾. In France, the quality of life of RA patients treated with long-term biotherapy in real life has never been the subject of a specific study.

Methods: In partnership with two patients' associations, a cross-sectional observational survey of RA patients treated with biologics since at least one year, with the aim of assessing their functioning (using the HAQ-DI⁽²⁾ questionnaire) and quality of life (EQ-5D⁽³⁾ questionnaire) on a daily basis was carried out. Treatment satisfaction and expectations have been also evaluated.

Results: A total of 504 RA patients have been included in the study (mean age = 62.4 years; 18% male and 82% female). The average RA duration was 19.2 years and the mean treatment period with biologics was 8 years. About 40% of patients received first-line biologic treatment and 30% received 2nd- or 3rd-line biologic treatment. When RA was poorly controlled with first-line treatment, patients changed their treatment every 3 years on average. Reasons for switching biologics included poor efficacy (60% of patients) and tolerance problems (31%). Hospitalization due to RA progression during the last 12 months were reported by 22% of patients in 1st line-treatment and by 32% of patients in 2nd line and more. Functional disability, particularly affecting manual activities of daily living, also increased with the number of treatment lines. In addition, more than 50% of the patients in professional activity had to adapt or change their activity because of their state of health. Regarding health perception, only 14% of patients were satisfied with their symptom improvement (scored 80 to 100 on a scale from 0 to 100). The average score was 63.5 (quite satisfying). In addition, whether on symptoms or well-being, only a third of patients were satisfied with their condition. If patients recognize the major contribution of biologics (average satisfaction score was 7.5/10), they are more than 80% to expect the arrival of new biologics to improve their quality of life.

Conclusion: Despite the major therapeutic progress achieved with biologics for the management of rheumatoid arthritis, the results of this survey conducted with patient associations demonstrate a persistent functional disability in patients with RA as well as a reduced quality of life. The level of expectation of these patients remains high concerning future therapeutic alternatives.

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Disclosure: S. Tropé, Nordic Pharma, 6; G. Thibaud, Pfizer, Inc., 6, MSD, 6, Sanofi, 6, UCB, Inc., 6; F. Alliot, XXX, 6; D. Formont, X, 3, 5; S. Krouri, SANOFI, 3.

How Phenotype of the Small Fibre Neuropathy in Primary Sjögren Syndrome Differs from Others Causes of Small Fibre Neuropathy ?

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science Poster

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Small fibre neuropathy (SFN) is a peripheral neuropathy characterized by neuropathic pain associated with normal routine nerve conduction study but rarefaction of intraepidermal nerve fibres (IEFN). Primary Sjögren Syndrome (pSS) is one of the many aetiology of SFN. To compare phenotype of SFN in pSS, transthyretin (TTR) familial amyloidosis and idiopathic SFN. To describe evolution of SFN in pSS.

Methods: All patients referred since 2012 with a skin biopsy-proven SFN associated with either pSS (ACR/EULAR 2016 criteria), TTR amyloidosis or idiopathic were included in this monocentric retrospective study. Diagnosis of SFN was confirmed by normal nerve conduction study and abnormal lower limb skin biopsies. All patients undergo standardized diagnosis procedures during an outpatient day-clinic, pSS patients were further followed and undergo a second evaluation. Characteristics of SFN were compared between 3 groups: pSS, TTR-amyloidosis and idiopathic. Outcome of pSS associated SFN was analysed.

Results: We included 15 patients with pSS (13 (86.7 %) women, median age: 55 years [IQR:47.5-66.5], 7 (46.7%) anti-SSA positive, 12 (80%) focus score ≥ 1), 17 with TTR-amyloidosis (7 (41.2%) women, median age: 47 years [35-56]) and 11 with idiopathic SFN (7 (63.6%) women, median age: 47 years [36-56.5]). Patients with pSS had a median ESSDAI of 5 [5-8]. One had monoclonal gammopathy (6.7%), 5/13 (38.5%) rheumatoid factor, 2/13 (15.4%) hypergammaglobulinemia and none had cryoglobulin. Time to diagnosis SFN was significantly higher for pSS (21 months [9-54]) and idiopathic group (35 months [11.5-65]) than for TTR group (6 months [0-15]). Clinical presentation was length dependent in 2 (13.3%) pSS patients compared to 10 (58.8%) in TTR amyloidosis ($p=0.01$) and 2 (18.2%) in idiopathic group ($p=1$). A "patchy" presentation (defined as asymmetrical and/or proximal symptoms involving limb, trunk and/or face), was significantly more frequent in pSS than in TTR amyloidosis (7 (46.7%) vs. 1 (5.9%); $p=0.01$). This more frequent non-length dependent course was confirmed by skin biopsies (IEFN at proximal site $<$ IEFN at distal site) in 7/14 (50%) pSS patients compared to 1 (9.1%) in idiopathic ($p=0.04$) and 2/15 (13.3%) in TTR groups ($p=0.05$). Lauria score was significantly higher in pSS than in TTR, (5 [4-7.5] vs. 2 [2-5], $p=0.007$), mainly due to items of sicca symptoms ($n=14/15$) and peripheral limb pain ($n=13/15$). Ten patients with pSS have been reassessed with a median follow up of 37 months [20.5-56.3]. At reassessment, the Lauria score did not significantly differ (6.5 [5.3-7.8], $p=0.48$) from baseline, patchy presentation was still predominant (50%). Patients did not evolve through large fibre neuropathy, except one patient who had received a neurotoxic chemotherapy by platin for ovarian cancer, between the 2 evaluations.

Conclusion: Compared to other causes of SFN, in pSS SNF was characterized by a more frequent non-length dependent and patchy presentation and a higher Lauria score. After a median follow-up of >3 years, SFN in pSS did not evolve through large fibre neuropathy, which supports the hypothesis that it is related to a specific mechanism and does not represent the beginning of an axonal neuropathy like it is for TTR amyloidosis.

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Abstract Number: 1557

Visualization of Dorsal Root Ganglionitis with Three-Tesla Magnetic Resonance Neurography in Sensory Ataxic Neuropathy Associated with Sjögren's Syndrome

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science Poster

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Sjögren's syndrome (SS)-associated neuropathy manifests as various forms of neuropathy, including sensory ataxic neuropathy (SAN). Dorsal root ganglionitis, pathologically defined as the lymphocytic infiltration of the

dorsal root ganglion (DRG),causes SAN. This study aimed to determine whether 3-Tesla magnetic resonanceneurography (3T-MRN) is useful for detecting abnormalities of DRGs, and making diagnoses in patients with SS-SAN.

Methods: We conducted a retrospective chart review from 2015 to 2017 and enrolled 3 patients with SS-SAN fulfilling American–European Consensus Group classification criteria. We evaluated with a3T MRI scanner and used the coronal short-tau inversion recovery (STIR) technique because of its advantages in depicting a symmetric normal hyperintensityof DRGs and nerves. On measuring a pair of DRGs, regions of interest (ROI) were manually drawn by using ImageJ (<http://rsb.info.nih.gov/ij/>). The area, medianSI, and transverse diameter of each DRGs were measured and compared with those of the corresponding proximal nerve roots. The SI ratio (SI within a DRG/SIwithin a proximal nerve root) and diameter ratio (transverse diameter of aDRG/width at the middle point of a proximal nerve root) were subsequently calculated. For each nerve root level, data from SS patients were compared with those of age- and sex-matched non-neuropathy controls (20 DRGs from 10 cases). All statistical analyses were performed with EZR, a graphical user interface for R(The R Foundation for Statistical Computing, Vienna, Austria). The Mann–WhitneyU test was applied for the statistical analysis.

Table 1. Clinical and Laboratory Findings, and Treatment Responses.

Patient Age/sex	Onset duration	Clinical presentation	Laboratory findings	Genetic findings	PTB findings	Immunological findings	Immunohistochemical findings	Treatment and responses
1/73/Female	3 years	Sensory ataxia, Romberg's test (+)	DRG: 4-6 MUSC: 4-6 Normal Cytology	Positive	PTB: 2-4 MUSC: 4-6	Normal (CBC, complement, and IgG)	Normal (CD3, CD4, CD8, CD20, CD45, and IgG)	Normal (CD3, CD4, CD8, CD20, CD45, and IgG)
2/67/Female	4 months	Sensory ataxia, Romberg's test (+)	DRG: 4-6 MUSC: 4-6 Normal Cytology	Positive	PTB: 2-4 MUSC: 4-6	Normal (CBC, complement, and IgG)	Normal (CD3, CD4, CD8, CD20, CD45, and IgG)	Normal (CD3, CD4, CD8, CD20, CD45, and IgG)
3/58/Female	2 years	Sensory ataxia, Romberg's test (+), parosmia, and parosmia	DRG: 4-6 MUSC: 4-6 Normal Cytology	Positive	PTB: 2-4 MUSC: 4-6	Normal (CBC, complement, and IgG)	Normal (CD3, CD4, CD8, CD20, CD45, and IgG)	Normal (CD3, CD4, CD8, CD20, CD45, and IgG)

Abbreviations: ATR: Achilles tendon reflex; CBC: complete blood count; DTRs: deep tendon reflexes; IVIG: intravenous immunoglobulin; MUSC: minor salivary gland biopsy; PTB: posterior tibial nerve; SEP: somatosensory evoked potential; SNAP: sensory nerve action potential; SS: Sjögren's syndrome; SS-A: anti-SS-A antibody; SS-B: anti-SS-B antibody; SS-C: anti-SS-C antibody; SS-D: anti-SS-D antibody; SS-E: anti-SS-E antibody; SS-F: anti-SS-F antibody; SS-G: anti-SS-G antibody; SS-H: anti-SS-H antibody; SS-I: anti-SS-I antibody; SS-J: anti-SS-J antibody; SS-K: anti-SS-K antibody; SS-L: anti-SS-L antibody; SS-M: anti-SS-M antibody; SS-N: anti-SS-N antibody; SS-O: anti-SS-O antibody; SS-P: anti-SS-P antibody; SS-Q: anti-SS-Q antibody; SS-R: anti-SS-R antibody; SS-S: anti-SS-S antibody; SS-T: anti-SS-T antibody; SS-U: anti-SS-U antibody; SS-V: anti-SS-V antibody; SS-W: anti-SS-W antibody; SS-X: anti-SS-X antibody; SS-Y: anti-SS-Y antibody; SS-Z: anti-SS-Z antibody; SS-AA: anti-SS-AA antibody; SS-AB: anti-SS-AB antibody; SS-AC: anti-SS-AC antibody; SS-AD: anti-SS-AD antibody; SS-AE: anti-SS-AE antibody; SS-AF: anti-SS-AF antibody; SS-AG: anti-SS-AG antibody; SS-AH: anti-SS-AH antibody; SS-AI: anti-SS-AI antibody; SS-AJ: anti-SS-AJ antibody; SS-AL: anti-SS-AL antibody; SS-AM: anti-SS-AM antibody; SS-AN: anti-SS-AN antibody; SS-AO: anti-SS-AO antibody; SS-AP: anti-SS-AP antibody; SS-AQ: anti-SS-AQ antibody; SS-AR: anti-SS-AR antibody; SS-AS: anti-SS-AS antibody; SS-AT: anti-SS-AT antibody; SS-AU: anti-SS-AU antibody; SS-AV: anti-SS-AV antibody; SS-AW: anti-SS-AW antibody; SS-AX: anti-SS-AX antibody; SS-AY: anti-SS-AY antibody; SS-AZ: anti-SS-AZ antibody; SS-BA: anti-SS-BA antibody; SS-BB: anti-SS-BB antibody; SS-BC: anti-SS-BC antibody; SS-BD: anti-SS-BD antibody; SS-BE: anti-SS-BE antibody; SS-BF: anti-SS-BF antibody; SS-BG: anti-SS-BG antibody; SS-BH: anti-SS-BH antibody; SS-BI: anti-SS-BI antibody; SS-BJ: anti-SS-BJ antibody; SS-BL: anti-SS-BL antibody; SS-BM: anti-SS-BM antibody; 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SS-CX: anti-SS-CX antibody; SS-CY: anti-SS-CY antibody; SS-CZ: anti-SS-CZ antibody; SS-DA: anti-SS-DA antibody; SS-DB: anti-SS-DB antibody; SS-DC: anti-SS-DC antibody; SS-DD: anti-SS-DD antibody; SS-DE: anti-SS-DE antibody; SS-DF: anti-SS-DF antibody; SS-DG: anti-SS-DG antibody; SS-DH: anti-SS-DH antibody; SS-DI: anti-SS-DI antibody; SS-DJ: anti-SS-DJ antibody; SS-DK: anti-SS-DK antibody; SS-DM: anti-SS-DM antibody; SS-DN: anti-SS-DN antibody; SS-DO: anti-SS-DO antibody; SS-DP: anti-SS-DP antibody; SS-DQ: anti-SS-DQ antibody; SS-DR: anti-SS-DR antibody; SS-DS: anti-SS-DS antibody; SS-DT: anti-SS-DT antibody; SS-DU: anti-SS-DU antibody; SS-DV: anti-SS-DV antibody; SS-DW: anti-SS-DW antibody; SS-DX: anti-SS-DX antibody; SS-DY: anti-SS-DY antibody; SS-DZ: anti-SS-DZ antibody; SS-EA: anti-SS-EA antibody; SS-EB: anti-SS-EB antibody; SS-EC: anti-SS-EC antibody; SS-ED: anti-SS-ED antibody; SS-EE: anti-SS-EE antibody; SS-EF: anti-SS-EF antibody; SS-EG: anti-SS-EG antibody; SS-EH: anti-SS-EH antibody; 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SS-PO: anti-SS-PO antibody; SS-PP: anti-SS-PP antibody; SS-PQ: anti-SS-PQ antibody; SS-PR: anti-SS-PR antibody; SS-PS: anti-SS-PS antibody; SS-PT: anti-SS-PT antibody; SS-PU: anti-SS-PU antibody; SS-PV: anti-SS-PV antibody; SS-PW: anti-SS-PW antibody; SS-PX: anti-SS-PX antibody; SS-PY: anti-SS-PY antibody; SS-PZ: anti-SS-PZ antibody; SS-QA: anti-SS-QA antibody; SS-QB: anti-SS-QB antibody; SS-QC: anti-SS-QC antibody; SS-QD: anti-SS-QD antibody; SS-QE: anti-SS-QE antibody; SS-QF: anti-SS-QF antibody; SS-QG: anti-SS-QG antibody; SS-QH: anti-SS-QH antibody; SS-QI: anti-SS-QI antibody; SS-QJ: anti-SS-QJ antibody; SS-QK: anti-SS-QK antibody; SS-QL: anti-SS-QL antibody; SS-QM: anti-SS-QM antibody; SS-QN: anti-SS-QN antibody; SS-QO: anti-SS-QO antibody; SS-QP: anti-SS-QP antibody; SS-QQ: anti-SS-QQ antibody; SS-QR: anti-SS-QR antibody; SS-QS: anti-SS-QS antibody; SS-QT: anti-SS-QT antibody; SS-QU: anti-SS-QU antibody; SS-QV: anti-SS-QV antibody; SS-QW: anti-SS-QW antibody; SS-QX: anti-SS-QX antibody; SS-QY: anti-SS-QY antibody; SS-QZ: anti-SS-QZ antibody; SS-RA: anti-SS-RA antibody; SS-RB: anti-SS-RB antibody; SS-RC: anti-SS-RC antibody; SS-RD: anti-SS-RD antibody; SS-RE: anti-SS-RE antibody; SS-RF: anti-SS-RF antibody; SS-RG: anti-SS-RG antibody; SS-RH: anti-SS-RH antibody; SS-RI: anti-SS-RI antibody; SS-RJ: anti-SS-RJ antibody; SS-RK: anti-SS-RK antibody; SS-RL: anti-SS-RL antibody; SS-RM: anti-SS-RM antibody; SS-RN: anti-SS-RN antibody; SS-RO: anti-SS-RO antibody; SS-RP: anti-SS-RP antibody; SS-RQ: anti-SS-RQ antibody; SS-RR: anti-SS-RR antibody; SS-RS: anti-SS-RS antibody; SS-RT: anti-SS-RT antibody; SS-RU: anti-SS-RU antibody; SS-RV: anti-SS-RV antibody; SS-RW: anti-SS-RW antibody; SS-RX: anti-SS-RX antibody; SS-RY: anti-SS-RY antibody; SS-RZ: anti-SS-RZ antibody; SS-SA: anti-SS-SA antibody; SS-SB: anti-SS-SB antibody; SS-SC: anti-SS-SC antibody; SS-SD: anti-SS-SD antibody; SS-SE: anti-SS-SE antibody; SS-SF: anti-SS-SF antibody; SS-SG: anti-SS-SG antibody; SS-SH: anti-SS-SH antibody; SS-SI: anti-SS-SI antibody; SS-SJ: anti-SS-SJ antibody; SS-SK: anti-SS-SK antibody; SS-SL: anti-SS-SL antibody; SS-SM: anti-SS-SM antibody; SS-SN: anti-SS-SN antibody; SS-SO: anti-SS-SO antibody; SS-SP: anti-SS-SP antibody; SS-SQ: anti-SS-SQ antibody; SS-SR: anti-SS-SR antibody; SS-SS: anti-SS-SS antibody; SS-ST: anti-SS-ST antibody; SS-SU: anti-SS-SU antibody; SS-SV: anti-SS-SV antibody; SS-SW: anti-SS-SW antibody; SS-SX: anti-SS-SX antibody; SS-SY: anti-SS-SY antibody; SS-SZ: anti-SS-SZ antibody; SS-TA: anti-SS-TA antibody; SS-TB: anti-SS-TB antibody; SS-TC: anti-SS-TC antibody; SS-TD: anti-SS-TD antibody; SS-TE: anti-SS-TE antibody; SS-TF: anti-SS-TF antibody; SS-TG: anti-SS-TG antibody; SS-TH: anti-SS-TH antibody; SS-TI: anti-SS-TI antibody; SS-TJ: anti-SS-TJ antibody; SS-TK: anti-SS-TK antibody; SS-TL: anti-SS-TL antibody; SS-TM: anti-SS-TM antibody; SS-TN: anti-SS-TN antibody; SS-TO: anti-SS-TO antibody; SS-TP: anti-SS-TP antibody; SS-TQ: anti-SS-TQ antibody; SS-TR: anti-SS-TR antibody; SS-TS: anti-SS-TS antibody; SS-TT: anti-SS-TT antibody; SS-TU: anti-SS-TU antibody; SS-TV: anti-SS-TV antibody; SS-TW: anti-SS-TW antibody; SS-TX: anti-SS-TX antibody; SS-TY: anti-SS-TY antibody; SS-TZ: anti-SS-TZ antibody; SS-UA: anti-SS-UA antibody; SS-UB: anti-SS-UB antibody; SS-UC: anti-SS-UC antibody; SS-UD: anti-SS-UD antibody; SS-UE: anti-SS-UE antibody; SS-UF: anti-SS-UF antibody; SS-UG: anti-SS-UG antibody; SS-UH: anti-SS-UH antibody; SS-UI: anti-SS-UI antibody; SS-UJ: anti-SS-UJ antibody; SS-UK: anti-SS-UK antibody; SS-UL: anti-SS-UL antibody; SS-UM: anti-SS-UM antibody; SS-UN: anti-SS-UN antibody; SS-UO: anti-SS-UO antibody; SS-UP: anti-SS-UP antibody; SS-UQ: anti-SS-UQ antibody; SS-UR: anti-SS-UR antibody; SS-US: anti-SS-US antibody; SS-UT: anti-SS-UT antibody; SS-UU: anti-SS-UU antibody; SS-UV: anti-SS-UV antibody; SS-UW: anti-SS-UW antibody; SS-UX: anti-SS-UX antibody; SS-UY: anti-SS-UY antibody; SS-UZ: anti-SS-UZ antibody; SS-VA: anti-SS-VA antibody; SS-VB: anti-SS-VB antibody; SS-VC: anti-SS-VC antibody; SS-VD: anti-SS-VD antibody; SS-VE: anti-SS-VE antibody; SS-VF: anti-SS-VF antibody; SS-VG: anti-SS-VG antibody; SS-VH: anti-SS-VH antibody; SS-VI: anti-SS-VI antibody; SS-VJ: anti-SS-VJ antibody; SS-VK: anti-SS-VK antibody; SS-VL: anti-SS-VL antibody; SS-VM: anti-SS-VM antibody; SS-VN: anti-SS-VN antibody; SS-VO: anti-SS-VO antibody; SS-VP: anti-SS-VP antibody; SS-VQ: anti-SS-VQ antibody; SS-VR: anti-SS-VR antibody; SS-VS: anti-SS-VS antibody; SS-VT: anti-SS-VT antibody; SS-VU: anti-SS-VU antibody; SS-VV: anti-SS-VV antibody; SS-VW: anti-SS-VW antibody; SS-VX: anti-SS-VX antibody; SS-VY: anti-SS-VY antibody; SS-VZ: anti-SS-VZ antibody; SS-WA: anti-SS-WA antibody; SS-WB: anti-SS-WB antibody; SS-WC: anti-SS-WC antibody; SS-WD: anti-SS-WD antibody; SS-WE: anti-SS-WE antibody; SS-WF: anti-SS-WF antibody; SS-WG: anti-SS-WG antibody; SS-WH: anti-SS-WH antibody; SS-WI: anti-SS-WI antibody; SS-WJ: anti-SS-WJ antibody; SS-WK: anti-SS-WK antibody; SS-WL: anti-SS-WL antibody; SS-WM: anti-SS-WM antibody; SS-WN: anti-SS-WN antibody; SS-WO: anti-SS-WO antibody; SS-WP: anti-SS-WP antibody; SS-WQ: anti-SS-WQ antibody; SS-WR: anti-SS-WR antibody; SS-WS: anti-SS-WS antibody; SS-WT: anti-SS-WT antibody; SS-WU: anti-SS-WU antibody; SS-WV: anti-SS-WV antibody; SS-WX: anti-SS-WX antibody; SS-WY: anti-SS-WY antibody; SS-WZ: anti-SS-WZ antibody; SS-XA: anti-SS-XA antibody; SS-XB: anti-SS-XB antibody; SS-XC: anti-SS-XC antibody; SS-XD: anti-SS-XD antibody; SS-XE: anti-SS-XE antibody; SS-XF: anti-SS-XF antibody; SS-XG: anti-SS-XG antibody; SS-XH: anti-SS-XH antibody; SS-XI: anti-SS-XI antibody; SS-XJ: anti-SS-XJ antibody; SS-XK: anti-SS-XK antibody; SS-XL: anti-SS-XL antibody; SS-XM: anti-SS-XM antibody; SS-XN: anti-SS-XN antibody; SS-XO: anti-SS-XO antibody; SS-XP: anti-SS-XP antibody; SS-XQ: anti-SS-XQ antibody; SS-XR: anti-SS-XR antibody; SS-XS: anti-SS-XS antibody; SS-XT: anti-SS-XT antibody; SS-XU: anti-SS-XU antibody; SS-XV: anti-SS-XV antibody; SS-XW: anti-SS-XW antibody; SS-XX: anti-SS-XX antibody; SS-XY: anti-SS-XY antibody; SS-XZ: anti-SS-XZ antibody; SS-YA: anti-SS-YA antibody; SS-YB: anti-SS-YB antibody; SS-YC: anti-SS-YC antibody; SS-YD: anti-SS-YD antibody; SS-YE: anti-SS-YE antibody; SS-YF: anti-SS-YF antibody; SS-YG: anti-SS-YG antibody; SS-YH: anti-SS-YH antibody; SS-YI: anti-SS-YI antibody; SS-YJ: anti-SS-YJ antibody; SS-YK: anti-SS-YK antibody; SS-YL: anti-SS-YL antibody; SS-YM: anti-SS-YM antibody; SS-YN: anti-SS-YN antibody; SS-YO: anti-SS-YO antibody; SS-YP: anti-SS-YP antibody; SS-YQ: anti-SS-YQ antibody; SS-YR: anti-SS-YR antibody; SS-YS: anti-SS-YS antibody; SS-YT: anti-SS-YT antibody; SS-YU: anti-SS-YU antibody; SS-YV: anti-SS-YV antibody; SS-YW: anti-SS-YW antibody; SS-YX: anti-SS-YX antibody; SS-YZ: anti-SS-YZ antibody; SS-ZA: anti-SS-ZA antibody; SS-ZB: anti-SS-ZB antibody; SS-ZC: anti-SS-ZC antibody; SS-ZD: anti-SS-ZD antibody; SS-ZE: anti-SS-ZE antibody; SS-ZF: anti-SS-ZF antibody; SS-ZG: anti-SS-ZG antibody; SS-ZH: anti-SS-ZH antibody; SS-ZI: anti-SS-ZI antibody; SS-ZJ: anti-SS-ZJ antibody; SS-ZK: anti-SS-ZK antibody; SS-ZL: anti-SS-ZL antibody; SS-ZM: anti-SS-ZM antibody; SS-ZN: anti-SS-ZN antibody; SS-ZO: anti-SS-ZO antibody; SS-ZP: anti-SS-ZP antibody; SS-ZQ: anti-SS-ZQ antibody; SS-ZR: anti-SS-ZR antibody; SS-ZS: anti-SS-ZS antibody; SS-ZT: anti-SS-ZT antibody; SS-ZU: anti-SS-ZU antibody; SS-ZV: anti-SS-ZV antibody; SS-ZW: anti-SS-ZW antibody; SS-ZX: anti-SS-ZX antibody; SS-ZY: anti-SS-ZY antibody; SS-ZZ: anti-SS-ZZ antibody.

Table 2. Summary of ST-MRN Findings.

Measurement	Patient 1	Patient 2	Patient 3	SS	Control	P-value
Area (mm ²)	12.91	16.34	16.63	15.35	16.89	0.69
Diameter ratio	1.53	1.72	2.28	1.45	2.18	0.17
SI ratio	0.83	1.047	1.40	0.97	1.35	0.21
Area (mm ²)	17.61	16.78	16.00	16.55	27.36	0.014
Width ratio	1.22	1.41	1.45	1.40	2.21	0.00054
SI ratio	0.823	1.24	1.17	1.00	1.092	0.49
Area (mm ²)	25.44	16.78	16.24	20.84	30.11	0.016
Diameter ratio	1.66	2.34	1.67	1.67	2.176	0.0094
SI ratio	0.82	1.12	1.07	0.96	1.38	0.011
Area (mm ²)	21.33	26.68	33.05	27.38	31.89	0.095
Diameter ratio	0.95	1.19	2.67	1.85	2.12	0.48
SI ratio	0.72	1.24	1.53	1.11	1.24	0.53
Area (mm ²)	42.46	37.04	58.90	47.66	52.71	0.9
Diameter ratio	0.94	1.60	1.63	1.39	1.81	0.16
SI ratio	0.76	1.21	1.08	1.04	1.32	0.28

Results: Table 1 summarizes the clinical data of the 3 patients. These SS-SAN patients presented with sensory ataxia with positive Romberg's test and also had various painful symptoms. All 3 patients showed normal motor strength. Compared with the control data, all DRGs in SS patients were numerically smaller and had a lower SI through the L2-S1 level. Moreover, the area, diameter ratio, and SI ratio were significantly reduced in L3-L4 DRGs (Table 2).

Conclusion: We revealed that the DRGs in patients with SS-SAN were atrophic and showed a decreased SI than those in the controls. We suggest the visualization of DRGs by 3T-MRN as a potentially useful imaging biomarker for the clinical diagnosis, as well as the assessment of pathophysiological mechanisms. DRG atrophy and decreased signal intensity may reflect the sensory neuronal loss caused by chronic lymphocytic inflammation in DRGs.

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Abstract Number: 1558

Intravenous Immunoglobulin Efficacy for Primary Sjögren's Syndrome Associated Small Fiber Neuropathy

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science Poster

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To analyze the efficacy and tolerance of intravenous immunoglobulin (IVIG) therapy in 11 patients with primary Sjögren's syndrome (pSS)-associated small-fiber neuropathy (SFN).

Methods: Retrospective, single-center study of the efficacy and safety of IVIG therapy for 6 months (0.4 g/kg/day monthly for 5 days) in 11 consecutive pSS-SFN patients. The primary endpoint was a decrease in pain intensity (scored on a 0-10 Numeric Rating Scale, NRS) $\geq 30\%$ between the onset (M0) and the end of treatment (M6). The impact of treatment on quality of life (SF-36 scale) and small fiber neurophysiological tests was also evaluated.

Results: The median (95%CI) age at treatment onset was 52 (48-63) years with a median duration of SFN symptoms until treatment of 6.5 (3-11) years. Between M0 and M6, the median NRS score decreased from 7 (5.5-8) to 3 (1.8-5) ($P < 0.00001$). The primary endpoint was achieved in 8 patients (72%). The median SF-36 physical component subscore also significantly improved from 23/100 to 48/100 ($P = 0.003$). Regarding neurophysiological tests, only the warm detection threshold improved from 5.5°C to 4.6°C ($P = 0.01$), others remaining stable. The most common side effect was transient headache during infusion (73%), while no major side effect was reported.

Conclusion: IVIG treatment appears to be effective and well tolerated in pSS-associated SFN, leading to a significant pain relief and improvement of quality of life and thermal sensory testing. These encouraging results need to be interpreted with caution and have to be confirmed in a randomized double-blinded placebo-controlled trial.

Disclosure: A. Gaillet, None; K. Champion, None; J. P. Lefaucheur, None; H. Trout, None; J. F. Bergmann, None; D. Sène, None.

Abstract Number: 1559

Development of Lymphoma in Patients with Sjogren's Syndrome

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SESSION INFORMATION

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Background/Purpose: Non-Hodgkin lymphoma (NHL) is one of the most feared complications of primary Sjögren's syndrome (pSS). The most frequent is MALT type lymphoma, with localization in the parotid glands being usual. There

are no multicentric data in the Argentine population regarding the frequency of appearance of this type of cancer in patients with pSS and the possible predictors for this outcome.

The aim of this study was to describe the prevalence and incidence rate of lymphoma in patients with pSS in nine centers in Argentina. To determine the frequency of commitment of the domains of the baseline clinical ESSDAI in the patients who developed lymphoma in the course of their follow-up and compare it with the rest of the sample.

Methods: To respond to the primary objective, the design will be observational, descriptive and retrospective. To evaluate the predictors of lymphoma development, the design will be observational, analytical, retrospective cohort. We included patients older than 18 years with a diagnosis of pSS according to ACR / EULAR 2002 criteria, included in a multi-center Argentine database. Patients diagnosed with another associated autoimmune rheumatic disease were excluded.

Results: We included 708 patients, 95% female, with a mean age of 54.44 years (SD +/- 13.67), mean age at diagnosis of 49.72 years (SD +/- 13.32) and mean age of onset of symptoms 47.19 (SD +/- 13.03). Fifteen patients presented lymphoma (prevalence: 2.12%). Six hundred thirty-six patients provided information for the survival analysis. The average follow-up time was 5 years (SD +/- 6.5). The incidence rate of lymphoma was 0.47 per 100 patient-years. The median time from the diagnosis of pSS to the development of lymphoma was 4 years (ric: 1-6). The most frequently lymphoma type was MALT. The main predictor of lymphoma development was recurrent parotidomegaly (H.R: 4.17, 95% CI: 1.42-12.22). Table 1 reports the results regarding the clinical ESSDAI.

Conclusion: The prevalence of lymphoma was 2.12% and the incidence rate of 0.47 lymphomas per 100 patients per year. Patients who developed lymphoma had a higher frequency of involvement of most of the domains of the baseline clinical ESSDAI compared to patients who did not present this complication. We found recurrent parotidomegaly as the main predictor of the development of this cancer.

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Abstract Number: 1560

Usefulness of 18F-FDG Positron Emission Tomography for Lymphoma Diagnosis in Patients with Primary Sjögren'S Syndrome

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Background/Purpose: primary Sjögren's syndrome (SS) is the autoimmune disease having the highest risk of lymphoma. The differential diagnosis between benign and malignant lymphoproliferation is sometimes difficult. Among imaging procedures, 18F-FDG PET could be useful for that purpose.

The purpose was to compare 18F-FDG PET results between patients with and without lymphoma to identify PET pattern associated with lymphomas in primary SS.

Methods: Retrospective study conducted in 2 centers including primary SS patients (according to ACR/EULAR 2016 criteria) who undergo 18F-FDG PET. We compared PET abnormalities in patients with and without lymphoma, the PET having been done before any chemotherapy. Two independent readers analyzed PET blind to lymphoma diagnosis. PET score previously described by Cohen *et al.* was calculated.

Results: 45 patients were included; 15 had lymphoma: MALT (n=12), nodal marginal zone with plasmacytic differentiation (n=2), diffuse large B-cell (n=1). Patients with lymphoma had more frequently parotid gland swelling (67% vs 20 %,

p=0.003) and higher ESSDAI score (24 [13.5-29] vs 9 [5-20], p=0.03), even after exclusion of lymphoma item (19 [11-27] VS 9 [5-20], p=0.03).

Compared to non-lymphoma patients, mean size (45.5 [38-56] mm vs. 40 [37-41] mm; p = 0.048) and maximum standardized uptake value (SUVmax) of the parotid glands (5.6 [5-6.9] vs 3.8 [3.2-4.4]; p = 0.001) were higher in lymphoma patients. 53.3% of patients with lymphoma and 43.3% without lymphoma had lymph node FDG uptake, but neither their number nor their repartition or mean SUV differ between them.

Pulmonary uptake was observed in 6 (40%) patients with lymphoma and 6 (20%) without lymphoma (p=0.17). But in lymphoma patients, this uptake was focal in 5 (33.3%) patients (nodules or condensation) and in only one (3.3%) patient without lymphoma (p=0.01). Remaining patients had interstitial FDG uptake. Mean PET score (4 [2-4] vs. 2 [1-3] p=0.04) and SUVmax at any site (6.3 [5.6-7.3] vs. 4.2 [3.7-5.9] p =0.02) were significantly higher in lymphoma group.

The best combination retained for identifying patients with a currently evolving lymphoma was the highest SUVmax at parotid gland ≥ 4.7 and the pulmonary focal condensation or nodular lesions as being sensitive (sensitivity=80.0%) and specific (specificity=83.3%) .

20 patients had PET guided biopsy of a hypermetabolic lesion that conducted to lymphoma diagnosis in 7 cases (46.6%). After chemotherapy for lymphoma, PET was available for 10 patients: complete regression of hypermetabolic lesions was observed in 6 patients (60%), and decreased uptake intensity in the 4 remaining patients. After a median follow-up of 19 months [13.5-30.3] months , one patient with diffuse large B-cell lymphoma relapsed.

Conclusion: some of the systemic manifestation of primary SS (lung, lymph nodes and salivary glands) can be assessed by 18F-FDG PET. Lymph nodes hypermetabolism is frequent and not associated with lymphoma. The best 18F-FDG PET abnormalities associated with lymphoma diagnosis are the highest SUVmax at parotid gland ≥ 4.7 , and/or the pulmonary focal condensation or nodular lesions. Finally, PET can be helpful to guide biopsy toward the most hypermetabolic structure for diagnosing lymphoma

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Abstract Number: 1561

B Lymphocyte Depletion Therapy with Rituximab in Primary Sjögren's Syndrome: Indications , Effectiveness and Ultrasonographic Response

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SESSION INFORMATION

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Session Title: Sjögren's Syndrome – Basic and Clinical Science Poster

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Aim of this study was to assess indications, effectiveness, clinical and ultrasonographic response to rituximab (RTX) therapy in primary Sjögren's syndrome (pSS), focusing in particular on the safety of multiple courses of B-cell depletion therapy .

Methods: Out of a single centre cohort of 378 pSS patients (AECG 2002) we retrieved the clinical charts of patients treated with RTX, focusing particularly on those that received multiple courses. In addition to patients' demographics, clinical and serological features, we analyzed the following data: indications for RTX therapy, changes in the ESSDAI, lab parameters and in salivary gland ultrasonography (SGUS), number of RTX courses, regimens, time to re-treatment and adverse events.

Results: We included in the study 34 patients (M/F = 3/31) who received RTX during their disease course for the following indications: lymphoproliferative disease (16/34), cryoglobulinemic vasculitis (7/34), systemically active disease $5 \leq$ ESSDAI<13 with at least 1 extraglandular domain moderate (7/34), and highly active disease in the haematological (2/34), articular (1/34) or pulmonary (1/34) ESSDAI domains. B-depletion therapy resulted in a significant reduction of disease activity (p <0.05) producing a partial response only for lung involvement. SGUS was performed in 7 patients, showing a significant improvement of the score in one case and stable findings in the others. Six female received at least a second infusion of RTX: in 3/6 only a second cycle was administered "on demand" (after 1, 3 and 4 years, respectively), in the other 3 cases multiple maintenance courses were administered (6, 6 and 11, respectively). Each course of re-treatment consisted in 1 or 2 g bi-weekly infusion; median interval between courses was 9 months (IQR 6-31.5). Multiple courses of RTX resulted in significant improvement of ESSDAI (median ESSDAI before RTX re-treatment =13.5 (IQR 11.25-25.25) vs median ESSDAI post-retreatment =3.5 (IQR 2-5), p=0.008). Re-treatment with RTX was well-tolerated in five cases;

one patient developed allergic drug reaction. Infectious events included: recurrent urinary tract infection (2/6), skin infection and Herpes Zoster reactivation (1/6). One patient who received multiple courses of RTX (in association with plasma-exchange therapy) developed a severe hypogammaglobulinemia complicated with recurrent infections that required Ig replacement therapy.

Conclusion: Single or multiple courses of B-depletive therapy with RTX seem to be effective, relatively safe and tolerated in pSS. Allergic reactions and infections remain still an issue. Further studies are needed to optimize repeated depletion therapy with RTX for pSS remission maintenance.

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Abstract Number: 1562

Large Granular Lymphocyte Proliferations in Primary Sjögren's Syndrome: An Iatrogenic Manifestation

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Background/Purpose: Large granular lymphocyte (LGL) proliferations can be observed in some auto-immune disorders, especially rheumatoid arthritis. However, reports of LGL proliferations in primary Sjogren's syndrome (pSS) are extremely rare. We here described the main characteristics and outcome of 9 patients presenting LGL proliferation in the context of pSS.

Methods: All patients from the reference centre for systemic autoimmune diseases (in particular for pSS) diagnosed with pSS (ACR/EULAR 2016 criteria) and having a LGL proliferation were included. LGL proliferations were characterized by blood lymphocyte immunophenotyping and their TCR clonality by PCR. Clinical data and outcome were analyzed for all patients.

Results: Nine pSS patients (8 women; median age of 67 [range 52 to 87] years) were diagnosed with LGL proliferation. All but one had active disease at the time of LGL diagnosis (median ESSDAI 11 [range 6 to 35]). Two patients had a history of lymphoma, one developed LGL proliferation under chemotherapy and the other in the context of an indolent and untreated lymphoma. In 8/9 patients, LGL proliferations were T-CD8 (T-LGL), and only one was of NK-type (NK-LGL). LGL proliferation was monoclonal in 4/9 and oligoclonal in 4/9 (data missing for patient with NK-LGL proliferation). A STAT3 mutation was searched in 2 patients and was negative in both. Neutropenia was the main reason for searching for a LGL proliferation ; neutrophil count was < 1500/mm³ in 7/9 and < 500/mm³ in 3/9 patients. At diagnosis, median lymphocyte cell count was 1120/mm³ (range 480 to 7250) and median LGL cell count was 440/mm³ (range 150 to 6000) representing 23% (range 13 to 64%) of the total lymphocyte count. Interestingly, 6 patients had received Rituximab (for lymphoma in 2, for pSS systemic manifestations or cryoglobulinemia in 4). The median time between LGL proliferation diagnosis and first Rituximab injection was 7 months (range 15 days to 13 months). Neutropenia occurred in 5/6 patients having received RTX. One patient with neutropenia, was retreated with Rituximab for a cryoglobulinemia relapse. Neutropenia occurred after the first injection (1200/mm³) and even worsened after the second (700/mm³). In 2 patients, severe neutropenia required treatment by G-CSF which only led to transient efficacy between the injections. Methotrexate was added in these 2 patients and allowed normalization in one case whereas neutrophil count partly improved in the other case. Spontaneous remission occurred in 1/7 patients and non-severe neutropenia persisted in 4/7 others at last evaluation.

Conclusion: This is one of the largest study analyzing LGL proliferation in pSS. As in other auto-immune diseases, LGL were mainly T-LGL, their main feature is neutropenia and they were observed in patients with high activity. Interestingly, the majority occurred in patients treated by Rituximab and could have a link with this treatment. This study suggest that neutropenia occurring after Rituximab treatment in patients with lymphoma or systemic auto-immune disease (but rarely

in patients with rheumatoid arthritis) could be the consequence of a minimal LGL proliferation that should be searched in this context.

Disclosure: A. Baber, None; G. Nocturne, None; X. Mariette, None; R. Seror, Roche, 5.

Abstract Number: 1563

Risk of Overall Malignancies in Korean Patients with Primary Sjögren Syndrome

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose: A significant association has been found between primary Sjögren syndrome (pSS) and non-hodgkin's lymphoma (NHL), but few studies have been conducted to explore the association of pSS with the risk of overall malignancies. We conducted the study to investigate the association between pSS and the risks of malignancy including overall and site-specific malignancies.

Methods: Using the Korean nationwide claims database, a retrospective cohort of prevalent pSS patients between January 2012 and December 2014 was constructed. After exclusion of patients who had a previous history of malignancy, each patient was observed up to the development of any malignancy, or December 2015. The crude incidence rate (IR) of overall and site-specific malignancies in patients with pSS over 19 years old was estimated. To assess excess occurrence of overall malignancies in patients over 50 years of age, we calculated standardized incidence ratios (SIR) by dividing the observed number of malignancies of pSS patients by the expected number of malignancies calculated from the accumulated person-years and the age-, sex-, calendar period-specific malignancy incidence rates of knee OA patients.

Results: A total of 9,826 patients with pSS over 19 years of age were enrolled in this study. During 30,082 person-years (PYs) of observation, 424 cases of solid malignancies (IR 140.6/10,000 PYs) and 62 cases of hematologic malignancies (IR 20.2/10,000 PYs) occurred in adult pSS patients. For patients with pSS aged over 50 (n=6,359), 314 cases of solid malignancy (IR 160.8/10,000 PYs) and 42 cases of hematologic malignancies (IR 21.0/10,000 PYs) were diagnosed during 19,474 PYs of follow-up. For the patients over 50 years of age, the SIRs of overall (1.29, 95% CI 1.16-1.43), solid (1.21, 95% CI 1.07-1.34), and hematologic malignancies (4.54, 95% CI 3.17-5.92), in patients with pSS increased compared to those of OA patients (n=5,476,302). Patients with pSS were at a significantly increased risk of non-hodgkin's lymphoma (SIR 5.75, 95% CI 3.58-7.92), multiple myeloma (SIR 4.88, 95% CI 2.00-7.76), lung cancer (SIR 1.59, 95% CI 1.08-2.09), and lip and oropharyngeal cancer (SIR 4.16, 95% CI 1.90-6.42).

Conclusion: Our study indicates that pSS is significantly associated with increased risks of overall malignancy, NHL, multiple myeloma, lung cancer, and lip and oropharyngeal cancer.

Disclosure: H. Kim, None; J. Kang, None; S. Choi, None; J. Kim, None; S. Y. Jung, None; E. J. Jang, None; S. K. Cho, None; Y. K. Sung, None.

Abstract Number: 1564

Severe, Life-Threatening Phenotype of Primary Sjögren Syndrome: Clinical Characterization and Outcomes in 1580 Patients (GEAS-SS Registry)

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SESSION INFORMATION

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Background/Purpose: To analyse the clinical features and outcomes of patients presenting with life-threatening systemic disease in a large cohort of Spanish patients with primary Sjogren syndrome (SjS).

Methods: The GEAS-SS multicenter registry was formed in 2005 with the aim of collecting a large series of Spanish patients with primary SS, and included more than 20 Spanish reference centers with substantial experience in the management of SS patients. By January 2018, the database included 1580 consecutive patients fulfilling the 2002 classification criteria for primary SS. Severe, life-threatening systemic disease was defined as an activity level scored as “High” in at least one ESSDAI domain.

Results: Among 1580 patients, 208 (13%) were classified as presenting a severe, potentially life-threatening systemic disease: 193 presented one ESSDAI domain classified as high, 14 presented two high scored domains and only one presented three high activity domains. The ESSDAI domains involved consisted of lymphadenopathy in 78 (37%) cases, CNS in 28 (13%), PNS in 25 (12%), pulmonary in 25 (12%), renal in 21 (10%), cutaneous in 19 (9%), articular in 18 (9%), hematological in 7 (3%) and muscular in 4 (2%). Patients with severe systemic disease were more frequently men ($p=0.001$) and had a higher frequency of anemia ($p<0.001$), lymphopenia ($p<0.001$), rheumatoid factor ($p=0.021$), low C3 levels ($p=0.015$), low C4 levels ($p<0.001$) and cryoglobulins ($p<0.001$). From a therapeutic point of view, systemic patients received more frequently glucocorticoids ($p<0.001$), immunosuppressants ($p<0.001$), intravenous immunoglobulins ($p=0.008$) and rituximab ($p<0.001$). We found an overall mortality rate of 20% in severe systemic patients, a rate that reach to 33% in patients presenting two or more high systemic involvements; these patients had a higher frequency of low C4 levels ($p=0.012$) and cryoglobulins ($p=0.001$) in comparison with those with a single severe organ involved.

Conclusion: A 13% of patients with primary SjS develop a potentially life-threatening systemic disease (mainly lymphoma, but also severe internal organ involvements including nervous system, the lungs and the kidneys). This subset of patients requires intensive therapeutic management with a mortality rate of nearly 20% of cases.

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Comorbidity Burden in Primary Sjögren's Syndrome: A Long-Term Observation in Clinical Practice

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SESSION INFORMATION

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Background/Purpose: Primary Sjögren's syndrome (pSS) is a complex disorder that may affect any organ and system. In this new era of personalized medicine, a growing interest has arisen for a more tailored patient care designed on individual's specific features and comorbidities. However, to date a limited number of studies have analysed the prevalence of chronic comorbidities in pSS, especially during the long-term evolution of the disease. Aims of the study were therefore: 1) to describe the prevalence of comorbidities in a cohort of patients with pSS and a minimum follow-up of 10 years from the time of the diagnosis; 2) to explore any association between comorbidities and pSS clinical phenotypes, disease activity and treatments.

Methods: Out of a single-centre cohort of 542 pSS patients we identified 112 subjects who had a minimum follow-up of 10 years from the time of the diagnosis. Information on patients' demographics, clinico-serological features and treatments were retrieved. Conventional statistics and autocontractive map analysis were used to define pSS clinical phenotypes. An adapted version of the Charlson Comorbidity Index (CCI) was used to score the comorbidity burden.

Results: We included 112 (109 F: 3 M) pSS patients, median age 65 years (IQR 53-73), and median follow-up of 14 years (min 10-max 34 yrs). The comorbidities most frequently observed included: osteoporosis (53/112, 47.3%), autoimmune thyroiditis (35/112, 31.3%), arterial hypertension (27/112, 24.1%) depression and anxiety (23/112, 20.5%), dislipidemia (19/112, 17%), diabetes (9/112, 8%), cerebrovascular disease (8/112, 7.1%) and myocardial infarction (4/112, 3.6%). To explore the association between comorbidities and pSS features, patients were stratified by conventional and autocontractive map analysis in three subsets: "glandular" (30/112, 26.8%), "systemic vasculitic" (16/112, 14.3%) and "systemic not-vasculitic" (66/112, 58.9%). The "vasculitic" subset presented the highest ESSDAI scores ($p < 0.001$), the highest glucocorticoid ($p = 0.001$) and DMARDs ($p = 0.001$) use and the highest comorbidity burden ($p < 0.001$). The mean (SD) CCI of the "vasculitic" subset was significantly higher with respect to the CCI of the other pSS subgroups (2.9(2.3) vs 1.0(1.2) vs 1.2(1.1), $p < 0.001$), particularly regarding cerebrovascular diseases. CCI correlated significantly with the use of glucocorticoids ($r = 0.298$, $p = 0.001$), DMARDs ($r = 0.290$, $p = 0.002$) and with the age of the patients ($R = 0.426$, $p < 0.001$).

Conclusion: Long term comorbidities are common in pSS and are related to both the disease and its treatment. The data suggest that it would be advisable to reduce glucocorticoid use, especially in older pSS patients.

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Prevalence and Prognosis of Interstitial Lung Disease in a Large Cohort of Chinese Primary Sjögren's Syndrome Patients

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Background/Purpose: To determine the prevalence and identify the prognosis associated with pulmonary involvement in pSS patients.

Methods: A total of 1341 hospitalized patients (853 with pSS and 488 with secondary Sjögren's syndrome [sSS]) were recruited.

Results: Pulmonary involvement rates were 19.34% (165/853) and 25.82% (126/488) for pSS and sSS patients, respectively. Of the 165 pSS-ILD patients, 69 patients underwent HRCT in this hospital. Non-specific interstitial pneumonia (NSIP) was the predominant HRCT pattern (n = 27, 39.1%). Chest HRCT findings revealed a lymphocytic interstitial pneumonia (LIP) pattern in 12 patients (17.4%), a NSIP+LIP pattern in 4 (5.8%), and a usual interstitial pneumonia (UIP) pattern in 11 (15.9%). The rest of the findings were as follows: 1 (1.4%) cryptogenic organizing pneumonia (COP), 1 (1.4%) respiratory bronchiolitis-interstitial lung disease (RBILD), and 13 indeterminates. The total HRCT score was 9.71 ± 4.77 . Impairment in diffusion capacity was the most common manifestation of pulmonary involvement (74.3%) and the most severe complication. The 5-year survival rate for pSS-ILD patients was 88.5%. Thirty-five (21.2%) of 165 patients died during the follow-up period. Causes of death were as follows: respiratory failure (n = 27), progression of malignant disease (n = 5), gastrointestinal bleeding (n = 1), viral meningoencephalitis (n = 1), and cerebral hemorrhage (n = 1). Multivariate analysis showed that age, disease duration, smoke, HRCT scores, and TLC, TLco/VA, FEV1 were independent risk factors for mortality for pSS-ILD patients.

Conclusion: Lung involvement is a common complication of pSS and the outcome is not favorable.

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Abstract Number: 1567

The Risk Factors and Prognosis of Interstitial Lung Disease Associated with Primary Sjogren's Syndrome: A Multi-Center Cohort Study

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SESSION INFORMATION

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Background/Purpose: The present study aimed to investigate the risk factors and prognosis of primary Sjogren's syndrome-associated interstitial lung disease (pSS-ILD).

Methods: Data were retrospectively collected from 28 hospitals in China during August 2008 and May 2018. ILD was confirmed by chest high resolution CT (HRCT). Baseline demographic data, clinical manifestations, laboratory tests, pulmonary function, radiology patterns, and treatment regimens were analyzed. Patients were followed up every 6 to 12 months. The primary end point was all-cause death.

Results: Of the 184 patients enrolled, 90.2% were female, with a mean age of 59.8 ± 10.7 years at baseline. The median disease duration of pSS was 39 (0-324) months, while the median disease duration of ILD was 13 (0-236) months. In 50.5% patients, ILD was the initial clinical manifestation of pSS. Presenting ILD manifestations were: dry cough (19%), productive cough (23.4%), dyspnea on exertion (41.8%), and asymptomatic patients exhibiting abnormalities consistent with ILD on HRCT and/or pulmonary function test (47.8%). NSIP was the most common HRCT pattern, including f-NSIP (23.9%) and c-NSIP (15.9%). Pulmonary function presented restrictive ventilation impairment as well as reduced diffuse function, with FVC 68.8 ± 33.5 % of predicted and DLCO 48.8 ± 28.3 % of predicted. Steroid was administered in 123 (66.8%) patients. Intensive immunosuppressive treatment included cyclophosphamide (32.6%), mycophenolate mofetil (9.2%), and azathioprine (3.3%). Nine patients died in this cohort. Predictive risk factors of ILD in pSS was older age (OR 1.222, 95%CI 1.076-1.169, p <0.001), late onset of pSS (OR 1.041, 95%CI 1.006-1.080, p = 0.024), elevated ESR (OR

2.011, 95%CI 1.107-3.653, $p = 0.022$), and positive anti-Ro52 antibody (OR 3.658, 95%CI 1.780-7.514, $p < 0.001$). Predictive factors of death in pSS-ILD were older age ($p < 0.001$), history of smoking ($p = 0.002$), and honeycomb lung pattern on HRCT ($p = 0.026$).

Conclusion: ILD can be the initial manifestation of pSS. The results provide strong evidence that patients with older age, late onset of pSS, and positive anti-Ro52 antibody were more likely to complicate ILD. We also suggest that patients with older age, history of smoking, and honeycomb pattern in HRCT may need a closer follow-up.

Table 1. Comparing the demographic and clinical data in pSS patients with and without ILD

	pSS-ILD	pSS-non-ILD	p-value
N	184	1000	
Female, n(%)	166 (90.2)	953 (95.3)	0.005*
Age, year	59.8 \pm 10.7	51.0 \pm 13.1	<0.001*
Age of pSS onset, year	52.8 \pm 13.0	46.3 \pm 13.1	<0.001*
Age of pSS diagnosis, year	56.6 \pm 11.1	48.9 \pm 13.0	<0.001*
Enlargement of parotid gland	16 (8.7)	193 (19.3)	0.001*
Schimer test +, n(%)	102 (55.4)	685 (68.5)	0.001*
Ocular staining + ^c , n (%)	40 (21.7)	302 (30.2)	0.020*
Labial salivary biopsy +, n(%)	69 (37.5)	459 (45.9)	0.035*
Purpura, n (%)	4 (2.2)	40 (4.0)	0.229
Leukopenia, n (%)	7 (3.8)	105 (10.5)	0.004*
Elevated ESR, n (%)	81/123 (65.9)	181/352 (51.4)	0.006*
Elevated IgG, n (%)	76/173 (43.9)	485/889 (54.6)	0.010*
Hypocomplementemia, n (%)	30/132 (22.7)	61/303 (20.1)	0.541
ANA+, n (%)	160/179 (89.4)	835/891 (93.7)	0.038*
Anti-SSA+, n(%)	144/182 (79.1)	780/899 (86.8)	0.008*
Anti-SSB+, n(%)	64/179 (35.8)	455/887 (51.3)	<0.001*
Anti-Ro52+,n(%)	132/166 (79.5)	553/849 (65.1)	<0.001*

Table 2. Prognostic factors of pSS-ILD

	Survivors	Non Survivors	P-value
N	175	9	
Age, year	59.1 \pm 10.3	74.3 \pm 5.5	<0.001*
Duration of pSS, month	72.6 \pm 94.3	65 \pm 45.7	0.812
Time between onsets of pSS and ILD, month	49.0 \pm 81.2	21.8 \pm 48.2	0.446
ILD as the initial manifestation, n (%)	86 (49.1)	7 (77.8)	0.094
History of smoking, n (%)	12 (6.9)	3 (33.3%)	0.002
Dry cough, n (%)	32 (18.3)	3 (33.3)	0.262
Productive cough, n (%)	39 (22.3)	4 (44.4)	0.126
Dyspnea on exertion, n (%)	73 (41.7)	4 (44.4)	0.871
Ground glass occupation, n (%)	88 (50.3)	0	0.022
Honeycomb pattern, n (%)	17 (9.7)	3 (33.3)	0.026*
FVC, %pred	72.7 \pm 30.1	69.2 \pm 32.9	0.734
TLC, %pred	61.7 \pm 34.2	50.2 \pm 31.0	0.355
DLCO, %pred	54.4 \pm 25.1	27.0 \pm 17.0	0.003*
FEV1, %pred	72.3 \pm 27.3	58.6 \pm 46.0	0.168

Disclosure: Z. Liu, None; M. Li, None; Q. Wang, None; Y. Zhao, None; D. Xu, None; X. Zeng, None.

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Azathioprine and Mycophenolate for Management of Sjögren's Syndrome-Related Interstitial Lung Disease: A Retrospective Cohort Study

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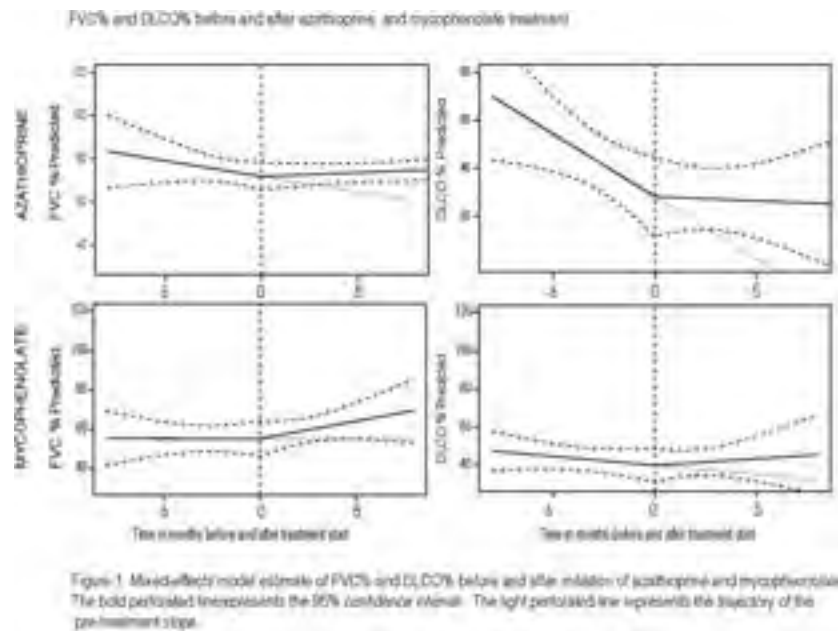
SESSION INFORMATION

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Background/Purpose: Interstitial lung disease (ILD) is a common extraglandular manifestation of Sjögren's syndrome (SS). There is a paucity of literature on the management of SS-ILD. The aim of this retrospective cohort study is to assess the efficacy of immunosuppressive therapy in the treatment of adult patients with SS-ILD.

Methods: A retrospective electronic health record search using codes for ILD and SS was performed for patients seen between 2000-2017 at an academic medical center. Records were reviewed to include adults meeting the 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for SS and to exclude those with other connective tissue diseases. ILD was confirmed by characteristic CT pattern or histopathology findings. Sociodemographic, clinical, and pulmonary function test (PFT) data were abstracted for patients with and without azathioprine, mycophenolate, and rituximab treatment and followed longitudinally from the date of ILD diagnosis. PFT values were anchored (T_0) on time of treatment start. Linear mixed-effects modeling and paired t-tests were used to analyze changes in diffusion capacity for carbon monoxide (DLCO) and forced vital capacity (FVC) before and after treatment initiation.

Results: We identified 19 subjects who had SS-ILD, of whom 89% were female, with ages ranging from 37-84 years at the time of ILD diagnosis. Seven patients were treated with azathioprine, seven patients were treated with mycophenolate, and six patients were treated with rituximab. Five patients were not treated with immunosuppressive therapy and five patients were treated with more than one agent. Within the azathioprine group, paired t-test showed a significant improvement in FVC% after treatment was initiated ($p=0.01$) with mixed model effect similarly showing improvement although with a non-significant change in slope ($p=0.22$) (Figure 1). A trend toward improvement in slope was also seen in DLCO% after treatment with azathioprine ($p=0.16$). Similarly, among those treated with mycophenolate, there was a trend toward improvement in slopes of both FVC% and DLCO% (FVC% $p=0.4$, DLCO% $p=0.45$), although these did not reach statistical significance (Figure 2). Among those patients treated with rituximab, there was a post-treatment decline in FVC% and DLCO%, although only three patients had PFTs measured before and after treatment.

Conclusion: Azathioprine appears to improve PFTs of SS-ILD patients and a similar non-significant trend is seen after mycophenolate treatment. Further prospective studies are needed to further evaluate these findings.

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Diagnostic Performance of Labial Salivary Gland Biosy, Serological and Clinical Data in Sjogrens Syndrome. in Argentinian Multicenter

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Background/Purpose: Labial salivary gland biopsy (LSGB) is a safe and minimally invasive procedure used in the diagnostic evaluation of Sjögren's Syndrome (SS). The objectives of this study are: to describe the demographic, clinical and histological characteristics of patients submitted for LSGB; to examine the usefulness of this procedure as a diagnostic tool for SS; to assess the association between histological findings and antibodies.

Methods: An observational, analytical, cross-sectional study was performed between June 1996 and July 2017. Patients with SS were classified according the AECG-2002 and ACR-2012 criteria. Grades III and IV biopsy of the Chisholm and Mason's classification/focus score ≥ 1 were considered positive. Data was analyzed using the statistical package SPSS 21.

Results: 1101 patients were included, 91 % females. The mean age was $52 \pm$ years(range18–86). SS was diagnosed in 413 (37.5%) patients. 34% of the biopsies were positive. Table 1 shows the clinical characteristics and complementary studies in patients with nonspecific dryness syndrome (No-SS) and SS. In bivariate analysis there was an association between antiRo, ANA and RF antibodies and LSGB. In multivariate analysis the significance for anti-Ro (OR: 6.33; 95% CI 3.22 to 12.15), ANA (OR: 3.26; 95% CI 2.15 to 4.94) and RF (OR: 3.05; 95% CI 2.04 to 4.56) was maintained.

Table 1

Parameters	SS n (%)	No-SS n (%)	p	OR
Female	380/413 (92)	619/688 (90%)	0.284	1.284 (0.832-1.981)
Xerostomia	351/410 (85.6)	518/679 (76.3)	<0.001	1.85 (1.33-2.57)
Xerophthalmia	368/409 (90)	559/679 (82.3)	0.001	1.93 (1.32-2.81)
Parotidomegaly	90/404 (22.3)	58/673 (8.6)	<0.001	3.04 (2.13-4.34)
Abnormal ophtalmic test	260/277 (93.9)	237/355 (66.9)	<0.001	7.62 (4.45-13.04)
Abnormal salivary test	66/76 (86.8)	84/115 (73)	0.03	2.44 (1.11-5.33)
antiRo/SS-A	120/366 (32.8)	18/558 (3.2)	<0.001	14.63 (8.72-24.56)
antiLa/SS-B	49/366 (13.4)	3/557 (0.5)	<0.001	28.55 (8.83-92.33)
ANA	194/387 (50.1)	82/606 (13.5)	<0.001	6.42 (4.73-8.73)
RF	176/394 (44.7)	115/618 (18.6)	<0.001	3.53 (2.66-4.69)
LSGB G III	143/413 (34.6)	0/687 (0)	<0.001	3.54 (3.2-3.9)
LSGB G IV	227/413 (55)	0/687 (0)	<0.001	4.69 (4.13-5.33)

Parameters	Sensitivity	Specificity	PPV	NPV	LR
Ro/SS-A*	32.8	96.8	86.9	68.7	8
La/SS-B*	13.4	99.5	94.2	63.6	13
ANA*	50.1	86.5	70.2	73.1	3.57
RF*	44.7	81.4	60.4	69.7	2.3

Conclusion: LSGB is a simple, safe, and useful tool for the diagnosis of Sjögren's syndrome. It exhibits an adequate balance between sensitivity, specificity, positive and negative predictive value. Antibodies showed a significant association with a positive LSGB with low sensitivity for SS screening but high specificity. LSGB has a great value in “seronegatives patients”.

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Clinical Utility of a Second Minor Salivary Gland Biopsy in Patients with Suspected Sjögren's Syndrome: A Retrospective Cohort Study

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Background/Purpose: To determine whether the repetition of minor salivary gland biopsy (MSGB) has a clinical diagnostic utility in patients with suspicion of primary Sjögren's syndrome (pSS).

Methods: We studied retrospectively patients with suspected pSS who had routinely benefited from two MSGB at our institution between January 1, 1990 and January 14, 2015. We collected for each of these patients the clinical and biological features and the results of the two MSGB, as well as the diagnoses performed by the evaluating physician after each biopsy. We compared the characteristics of patients with and without a clinical diagnosis of pSS after the first MSGB, and analysed the changes between the two MSGB.

Results: We included 93 patients, 18 pSS and 75 npSS (clinical diagnosis after the first MSGB). pSS patients were significantly older and more often had renal or pulmonary involvement, and, as expected, had more often rheumatoid factor, anti-SSA and anti-SSB antibodies and positive biopsy with focus score ≥ 1 or Chisholm score > 2 . The mean time between the 2 MSGB was 5.7 \pm 4.3 years. The concordance between the results of the 2 biopsies was low ($k=0.345$). Diagnosis changed after the second MSGB in 23 cases, but in only 13 patients the second biopsy was considered clinically useful to revise the initial diagnosis.

Conclusion: There was a low concordance between two MSGB in patients with suspected pSS in our study. Despite this variability, performing a second MSGB changed the initial diagnosis in a minority of the patients.

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RNA Sequencing Detection of Gene Dysregulation in Epithelial Cells Sorted from Salivary Gland Tissue Reveals Interesting Pathways Involved in Primary Sjögren's Syndrome Pathophysiology

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Background/Purpose: Primary Sjögren's syndrome (pSS) is a chronic autoimmune disorder characterized by lymphocytic infiltrates and destruction of the salivary glands. Several lines of evidence support the hypothesis that salivary gland

epithelial cells (SGECs) are not only the target of autoimmunity in pSS patients but may also play a role for its initiation and maintenance.

The objective of this study was to establish a transcriptomic map of differentially expressed genes in SGEC from pSS patients compared to controls using RNASeq analysis.

Methods: Patients had pSS according to 2016 EULAR/ACR criteria and controls had sicca symptoms without any antibodies and with normal lip biopsy. SGEC, B, T CD4 and CD8 lymphocytes were sorted from salivary gland biopsies from 9 pSS patients and 4 controls, using a FACS ARIA. Total RNASeq profiling was performed using MiSeq (Illumina). For SGEC subset, 4 samples were excluded due to a contamination by B lymphocytes, thus analysis was performed on 5 pSS and 4 controls. We identified transcriptional differences between pSS and controls SGEC using R software. Functional enrichment analysis was performed with Ingenuity Pathway Analysis software.

Results: In SGEC, 495 genes were differentially expressed between pSS and controls. 280 genes were up-regulated, and 215 genes were down-regulated. Enrichment analysis (**Table 1**) highlighted IL-7 signaling pathways (including IL-7, STAT5A, STAT1 genes) and interferon signaling (including OAS1, IFIT3, IFI6, TAP1 genes). Other genes potentially involved in immune responses and interactions between SGEC and lymphocytes were significantly up-regulated, including bone marrow stromal cell antigen 2, HLA-DRA, BAFF-R and IL-23 A (**Table2**). These results need to be confirmed by RT qPCR. However, consistent results have already been obtained in our laboratory, showing that IL-7 serum level is increased in pSS patients compared to controls and that SGECs secrete IL-7 after interferon stimulation. The analysis of the other sorted cells subtypes is ongoing.

Conclusion: Immune interactions between SGEC and B or T lymphocytes could represent a key in the understanding of the initiation and/or maintenance of autoimmunity in pSS. Our study highlights the key role of epithelial cells in activation of immune cells. In vitro experiments are needed to confirm these results and elucidate the molecular mechanisms.

Table 1 Pathways identified as statistically over-represented with Ingenuity Pathways Analysis in epithelial cells from pSS compared to controls.

Pathway	-log p-value
Primary Immunodeficiency Signaling	4,08
Interferon Signaling	3,52
B Cell Development	2,89
Role of JAK2 in Hormone-like Cytokine Signaling	2,73
IL-7 Signaling Pathway	2,51

Table 2 Selection of genes differentially expressed between pSS and controls in SGEC

Gene Symbol	log2 fold-change	p-value
IL-7	2.56	0.002
BST2	4.08	0.0002
HLA-DRA	1.84	0.0372
IL-23 A	3.59	0.0155
BAFF-R	4.94	0.0097

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Salivary Flow Rates and Oral Health Related Quality of Life Are Associated with Ultrasonographic Scoring of the Major Salivary Glands in Sjogren Syndrome

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Background/Purpose: Ultrasonography (USG) of major salivary glands (SG-USG) as a non-invasive method is widely used to evaluate salivary gland involvement in Sjögren's syndrome (SjS). Since decreases in salivary flow rates (SFRs) due to chronic inflammation and destruction of the salivary glands limit the functional and protective capacities of saliva in the oral environment, poor oral health related quality of life (OHRQoL) is commonly seen in patients with SjS. The aim of the study was to assess the relationships between SFRs, OHRQoL and USG changes of major salivary glands in patients with primary SjS.

Methods: Sixty-seven SjS patients (F/M:66/1) with the mean age of 51.1 ± 11.8 years. The duration of follow-up period of 60 ± 49 months fulfilling ACR-EULAR classification criteria (2002) were included. Major salivary glands (bilateral parotis and submandibular glands) were scored according to two different scoring systems which are Hocevar A. (0-48) and Milic VD. (0-12). Unstimulated saliva were collected in patients between 9 a.m. and 10 a.m. in the morning. Then, salivary flow rate (SFR) were calculated as millilitres per minute (ml/min) in laboratory conditions (FTO). Oral health related quality of life (OHRQoL) as a patient reported outcome measure (PROM) was evaluated by using Oral health impact profile (OHIP-14). High scores indicated poor OHRQoL status. Oral health (GM) and USG images (NI) were evaluated by two authors as double-blind in the same visit.

Results: Unstimulated SFR was 0.9 ± 0.8 ml/min and xerostomia (SFR ≤ 0.1 ml/minute) was seen 31,3% (n=21) of the group. Scores of Hocevar, Milic and OHIP-14 were found to be poor in patients with dry mouth compared to those of others (p<0.05). Scores of homogeneity and hypoechogenic areas in Parotid glands were also higher in patients with xerostomia than the others (p<0.05) (Table 1).

Conclusion: Unstimulated SFRs were associated with the structural changes of Parotid glands. Poor OHRQoL as a PROM was shown in patients due to reduced salivary outputs. In clinical practice, USG images of salivary glands could give insight to physicians about SFR and OHRQoL in patients with SjS.

Tablo-1: Salivary Flow Rates, OHIP-14 and Parotid Glands-USG Scores of SjS Patients

	Salivary Flow Rates (SFR)		p
	$\leq 0,1$ ml/minute (n=21)	$>0,1$ ml/minute (n=46)	
Parotid R-homogeneity	$1,7 \pm 0,7$	$1,02 \pm 0,7$	0.001
Parotid R-hypoechogenic areas	$1,3 \pm 1,1$	$0,4 \pm 0,7$	0.001
Parotid L-homogeneity	$1,6 \pm 0,9$	$1,1 \pm 0,7$	0.007
Parotid L-hypoechogenic areas	$1,2 \pm 0,9$	$0,5 \pm 0,8$	0.001
Hocevar-total score	$24,6 \pm 9,1$	$15,4 \pm 8,7$	0.001
Milic-total score	$7,4 \pm 2,2$	$4,8 \pm 2,4$	0.000
OHIP-14 score	$27,4 \pm 20,4$	$8,04 \pm 13,9$	0.000

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Salivary Dysbiosis Correlates with Clinical Status of Anti-Ro Positive Mothers of Children with Neonatal Lupus

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Background/Purpose: Neonatal lupus is linked to the presence of circulating anti-Ro antibodies in the mother. These antibodies are present in asymptomatic individuals, who in a subset years later progress to develop overt autoimmune disease. This study was initiated to investigate whether an environmental trigger such as oral colonization by autoreactivity-inducing commensals may contribute to pathogenesis. This goal was approached by leveraging agnostic profiling of the salivary microbiome to identify pathobionts associated with disease outcome in high titer anti-Ro positive women of children with neonatal lupus.

Methods: The study included 24 anti-Ro⁺ women from the Research Registry for Neonatal Lupus (RRNL) with nine being asymptomatic or having insufficient criteria for Sjögren's Syndrome (SS) and/or ACR/SLICC SLE (incomplete diagnoses) and 9 SS, 2 SLE, and 4 SS/SLE (established diagnoses). The rheumatologic diagnoses of the RRNL women were independently determined by two rheumatologists via questionnaire, telephone interview, and/or in-person history/physical exam, and review of medical records. An additional 7 healthy women served as controls. After extraction of host and non-host genomic DNA from saliva (without use of artificial saliva or stimulants), the microbiome was assessed by 16S rRNA gene library analysis using standard protocols (mean of 20k reads per sample). Operational taxonomic units (OTUs) were identified by closed-reference OTU-picking using Green Genes as reference. Shannon's index, a mathematical measure of species diversity (H') and relative abundance, was tested for differences using the Kruskal-Wallis tests.

Results: H' was different for virtually all taxa. At the phylum level, H' was significantly lower in RRNL vs controls (1.33 vs 1.53 respectively, $p=0.018$). Significance was retained down to the family level (2.46 vs 2.82 respectively, $p=0.007$). Contrasting RRNL with controls identified six phyla and 19 families having significant differences in relative abundance ($p<0.05$). For example, at the family level, *Porphyromonadaceae*, *Fusobacteriaceae*, *Pasteurellaceae*, and *Flavobacteriaceae* were less abundant in RRNL compared to controls ($p=0.003$, $p=0.004$, $p=0.030$, $p=0.038$, respectively). In contrast, *Peptostreptococcaceae*, *Weeksellaceae*, *Coriobacteriaceae* and *Prevotellaceae* were significantly more abundant ($p=0.001$, $p=0.003$, $p=0.0081$, $p=0.0421$, respectively) in the RRNL. Using a model with comparisons to healthy controls and with RRNL divided into the two subgroups (i.e., incomplete and complete, as described in the methods), the three-group test retained this pattern of significance and differential relative abundance down to the family phylogenetic level, except for *Flavobacteriaceae* which still showed a similar trend ($p=0.08$).

Conclusion: These data support a decrease in the diversity of the oral microbiota in anti-Ro positive women, especially in those with established autoimmune diseases such as SS. Our evidence of concurrent increases in relative abundance of organisms, such as inflammatory-provoking *Prevotellaceae*, may provide insight into disease evolution in a predisposed host.

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Autoantibodies Present in Saliva from Sjogren's Syndrome and Non-Sjogren's Sicca Patients Are Not Detectable in Serum

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Background/Purpose: There is evidence for B cell involvement in the pathogenesis of Sjögren's syndrome by the presence of autoantigen-specific B cells. Autoantibodies toward Ro/SSA and La/SSB are classification criteria. Autoantibodies are produced by plasmablasts within the salivary glands, but whether the serum autoantibodies originate from these cells is

unknown. We hypothesized that if serum autoantibodies originate from the antibody secreting cells in the glands, they may be present in the saliva prior to their detectable levels in the plasma. As a first step to explore this, we tested the saliva autoantibody profiles in a group of SS patients and sicca controls and compared them to their respective IgG serum autoantibody profiles.

Methods: 27 subjects, symptomatic for dry eyes and mouth, were evaluated for American/European Consensus Group (AECG) primary SS inclusion/exclusion criteria. 14 subjects met the AECG primary SS criteria, and 1 also met the ACR criteria for SLE. 13 subjects did not meet the SS classification criteria and served as non-Sjogren's sicca controls. Serum and stimulated parotid saliva samples were obtained from all subjects. Enzyme-linked immunosorbent assays (ELISAs) were performed by applying saliva (1:20, in duplicate) to antigen-coated (Ro/SSA, La/SSB, Sm, and Sm-RNP) plates and detected using anti-human IgA-, or IgG-alkaline phosphatase and substrate. 4 control subjects negative for all SS inclusion criteria and all other measures were used to establish positive thresholds for each ELISA (mean+5SD). To confirm stringency of this measure, we determined that the $Q3+1.5*IQR$ threshold was similar. mAbs produced from salivary gland plasmablasts from 4 SS and 5 sicca control patients were tested for antigen reactivity. Each subject's saliva specificities were compared to their mAb and serum specificities measured by DID, ELISA, INNO-LIA, and Bioplex 2200.

Results: In the glands from 14 patients, 12 had focal lymphocytic sialadenitis (FLS) and 2 had non-specific chronic inflammation (NSCI). Of the 13 sicca controls, 12 had NSCI, one had FLS, and one was histologically normal. Two sicca controls were seropositive for Ro and seronegative for all other antigens. The SS patients had a wide range of serum specificities for Ro/SSA, La/SSB, Sm, and nRNP. In both the SS patients and sicca controls there were saliva reactivities not detectable in the serum; in SS patients, 5/14 were Ro+, 4/14 La+, 4/14 Sm+ and 3/14 smRNP+, and in sicca controls, 8/13 were Ro+, 6/13 La+, 3/13 Sm+ and 3/13 smRNP+. The mAb specificities from SS patients correlated well with the serum specificities, however the monoclonal antibodies from the sicca controls had specificities for all four antigens not detected in the serum.

Conclusion: These findings suggest that the salivary gland may be a source of SS serum autoantibodies. Future studies will evaluate saliva positive, seronegative subjects longitudinally for development of serum autoantibodies. If this does occur, it would be likely that certain sicca controls would then fulfill the criteria for primary SS classification, suggesting that testing of saliva for autoantibodies may be indicated for prediction of progression to systemic disease.

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Abstract Number: 1575

The Association between Salivary Gland Ultrasonography and Clinical Manifestation in Patients with Early Primary Sjögren's Syndrome

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Background/Purpose: To investigate the clinical manifestations in patients with early primary Sjögren's syndrome based on different severity score under salivary gland ultrasonography.

Methods: We enrolled 44 newly diagnosed patients with early primary Sjögren's syndrome at Chang Gung Memorial Hospital in Taiwan (Figure 1). We divided patients into two groups according to baseline salivary gland ultrasonography grade scores. Severe group was defined score 2-3 and mild group was score 0-1. Student's t-test was used to compare the two groups.

Results: The mean age of patients were 50.02 years old. The mean duration of sicca symptoms were 0.86 years. The mean score of ESSPRI and ESSDAI were 16.98 and 3.35, respectively. Higher rheumatoid factor titer was statistically significant in severe group ($p=0.04$). Higher titer of autoantibodies such as anti-SSA/SSB, anti-dsDNA and IgG were found in severe group but not reached significant. However, ESSDAI and ESSPRI was not associated with sonography severity score.

Conclusion: Only higherrheumatoid factor titer is associated with higher salivary glandultrasonography grade score. However, severe ultrasonography grade score was not related to clinical disease activity such as ESSDAI. Previous study showedsalivary gland ultrasonography as a good diagnostic tool of Sjögren's syndromeand as a predictor of clinical activity in Sjogren's syndrome, but the diseasemean duration is around 7.5 years. Our study enrolled patients with earlyprimary Sjögren's syndrome with mean disease duration less than one year. Theclinical manifestations are not associated with salivary ultrasonographyseverity score in early primary Sjögren's syndrome.

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Soluble Semaphorin 4D/CD100 Is Increased in the Saliva of Sjögren's Syndrome

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Background/Purpose: Sjögren's syndrome (SS) is an autoimmune disease characterized by lymphocytic infiltration in exocrine organs with dry mouth and dry eyes. Semaphorin 4D (SEMA4D) / CD100 was reported to be highly expressed in salivary gland. Its abnormal expression in immune cells has been reported to be associated with autoimmunity. Membrane-bound SEMA4D could be proteolytically cleaved to soluble SEMA4D (sSEMA4D). This study was aimed to evaluate the sSEMA4D from saliva in patients with SS.

Methods: Total 47 SS patients, 34 sicca patients with non-SS and 28 healthy controls were examined. Saliva samples were collected on ice, centrifuged, and stored at -80°C with treatment of protease inhibitors. Salivary sSEMA4D was measured by ELISA kit. Area under the ROC curve (AUC) was analyzed to assess the sSEMA4D as a diagnostic marker of SS. Levels of sSEMA4D were presented as median (interquartile ranges [IQR]).

Results: The levels of salivary sSEMA4D were increased in patients with SS compared to healthy controls (median [IQR], 290.8 [188.3-478.0] vs. 170.0 [95.6-265.6] ng/mL, $p = 0.002$). The sSEMA4D from sicca patients with non-SS (220.0 [135.8-330.5] ng/mL, $p = 0.123$) was similar to that of HC. Salivary sSEMA4D was not correlated with ESR (Spearman's rho = 0.196, $p = 0.274$) or CRP (Spearman's rho = -0.225, $p = 0.280$) in SS. In analysis of ROC curve, the levels of salivary sSEMA4D showed acceptable accuracy to distinguish the SS patients from healthy controls (AUC = 0.710, 95% confidence interval : 0.594-0.827, $p = 0.002$), and optimal cut off value for diagnosis of SS is 235.5 ng/mL, with a sensitivity of 63.8% and a specificity of 71.4% (chi-square test $p = 0.003$).

Conclusion: Salivary sSEMA4D was increased in patients with SS and may be useful as a potential marker to diagnose SS by non-invasive method.

Disclosure: S. E. Kang, None; J. S. Lee, None; J. S. Park, None; J. H. Lee, None; J. Y. Kim, None; H. J. Yoo, None; Y. J. Lee, None; E. Y. Lee, None; E. B. Lee, None; Y. W. Song, None.

Abstract Number: 1577

Soluble Siglec-5 Is a Novel Salivary Biomarker for Primary Sjogren's Syndrome

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science Poster

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Background/Purpose: Despite advances in the understanding of the pathogenesis, disease-specific biomarkers have not been included in the classification criteria for Primary Sjogren's syndrome (pSS). Based on the microarray of peripheral blood mononuclear cell (PBMC) of pSS patients, we aimed to investigate whether sialic acid-binding immunoglobulin-like lectin (siglec)-5 might serve as a biomarker for pSS.

Methods: Microarray of PBMCs obtained from 26 pSS patients and 10 healthy control (HC)s was performed to screen potential biomarkers for pSS. The concentration of siglec-5/14 in saliva and sera was determined by ELISA. Clinical parameters related with pSS were obtained from pSS registry and correlation with salivary siglec-5/14 level was evaluated. Receiver operating curve (ROC) analysis was performed to determine cut off value. A separate validation cohort consisted of subjects with suspicious pSS was evaluated to determine the performance.

Results: The level of salivary siglec-5/14 was significantly higher in pSS patients compared with HCs or sicca patients (1346.8 [202.8-4280.0] pg/mL, 6.08 [0-134.0] pg/mL, and 0 [0-385.3] pg/mL, median [interquartile range], $P < 0.001$), meanwhile the serum level was not different between the groups. Clinical parameters were available in 170 patients in pSS registry. Salivary siglec-5/14 level negatively correlated with salivary flow rate (spearman's rho: -0.420, $P < 0.001$), and positively correlated with ocular surface score (rho: 0.331, $P < 0.001$) and serum immunoglobulin G level (rho = 0.202, $P = 0.008$). However, the level of salivary siglec-5/14 was not correlated with ESSDAI or focus score. On ROC analysis, area under the curve was 0.835(0.782-0.888). With cut off value 200pg/mL, sensitivity and specificity was 0.75 and 0.75 respectively. In validation cohort where patients without sicca symptom but have 1 or more positive items in ESSDAI were included, sensitivity and specificity of siglec-5/14 was 68.2% and 71.7%, respectively.

Conclusion: The level of soluble siglec-5/14 is significantly increased in the saliva of pSS patients and reflects the severity of hyposalivation and ocular surface damage. Although the mechanism of the contribution to gland dysfunction is unclear yet, this easily obtainable salivary biomarker may add benefits on the diagnosis of pSS.

Disclosure: J. Lee, None; H. K. Min, None; J. W. Kim, None; S. K. Kwok, None; S. H. Park, None.

Abstract Number: 1578

Exercise Increases Aerobic Capacity in Primary Sjögren's Syndrome: A Randomized Controlled Trial

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science Poster

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Recent studies have shown increased cardiovascular risk in patients with primary Sjögren's syndrome (pSS). As physical exercise is one of the pillars in primary and secondary prophylaxis of cardiovascular events, we evaluated whether the combination of resistance and aerobic exercises is able to increase aerobic capacity and quality of life and to improve echocardiographic parameters and the metabolic profile of patients with this rheumatic disease.

Methods: 60 women with pSS (age 18-90 years) were evaluated from the SF-36 Short-Form Health Survey (SF-36) and EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) questionnaires. The participants performed ergospirometry in an electromagnetic braking cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands), coupled to a computerized gas analyzer (Quark CPET, Cosmed, Italy) and echocardiography on the Philips IE33 device; blood samples were collected to evaluate the metabolic profile (glycemia, glycated hemoglobin, total cholesterol and fractions) by the central laboratory of the Hospital São Paulo - UNIFESP. Patients were divided into 2 groups: a training group (30 patients) that participated in the supervised training program and a control group (30 patients) that did not participate in the program. All variables were analyzed at baseline and after 28 weeks for both groups. The training program was divided into two phases according to the nature of the exercise. The first stage consisted of 16 weeks of resistance exercises, in the form of a 45 minute circuit, and each muscle group was exercised in 3 sets of 12 repetitions each. From the seventeenth week, the exercise became aerobic, performed on an electromagnetic braking cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands), the same instrument used to perform the ergospirometric test. The intensity and duration of the training increased progressively, until the last 3 weeks with sessions of 50 minutes and intensity of 60 to 84% of the VO_2max . Statistical analysis included Wilcoxon's rank sum test, chi-square test, and ANOVA test. P values <0.05 were considered to be statistically significant.

Results: The 2 groups were homogeneous and comparable at baseline. The training group showed a significant improvement in aerobic capacity measured by oxygen maximum volume (VO_2max) (19.64 ± 3.47 vs 22.95 ± 4.01 , $p < 0.001$) and by anaerobic threshold VO_2 (16.86 ± 2.86 vs 19.56 ± 3.18 , $p < 0.001$). Comparison of the training group and control group after 28 weeks showed a significant difference relating to VO_2max [$F(1; 58) = 31.43$; $p < 0.001$] and in the anaerobic threshold VO_2 [$F(1; 58) = 5.41$; $p < 0.001$]. After cardiovascular training, we found a small but significant decrease in glycated hemoglobin (5.88 ± 0.73 vs 5.75 ± 0.66 , $p = 0.006$). We did not find statistically significant difference in echocardiographic parameters, lipemic profile, quality of life (SF-36) and disease activity (ESSDAI).

Conclusion: This study showed significant improvement in aerobic capacity and glycated hemoglobin after a supervised training program in patients with pSS with safety.

Disclosure: A. B. Andreo Garcia, MD, None; V. Fernandes Moca Trevisani, None; L. Dardin, None; P. A. Minali, None.

Abstract Number: 1579

Sjögren's Syndrome Is Associated with Reduced Sex Hormone Exposure: A Case-Control Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science Poster

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Sjögren's Syndrome (SS) is an autoimmune disease with female predominance and frequent perimenopausal onset, indicating a potential pathogenic role for sex hormones. The goal of this study was to evaluate if cumulative sex hormone exposure impacts the risk of development of SS.

Methods: We performed a case-control study of 2860 women from the Sjögren's International Collaborative Clinical Alliance registry, including 1320 SS participants, 1106 participants with sicca symptoms but no key objective phenotypic features of SS ("sicca controls"), 371 participants with no sicca symptoms or phenotypic features of SS ("non-sicca controls"), and 63 participants with positive SSA antibody but not meeting criteria for SS (participants were not included in analysis due to low number). Individual reproductive and menstrual factors were used to create composite scores. Composite estrogen score (CES) was calculated by point assignment for early menarche (≤ 10 years), high parity,

hysterectomy, use of hormone therapy, and late menopause (≥ 53 years). Cumulative menstrual cycling (CMC) years for premenopausal registrants was calculated as the age of the registrant minus years since first sicca onset, menarche age, and time pregnant. Covariates included age, referral source, race, education level, employment status, smoking status, and recruitment site. Multivariable logistic regression was used for outcomes against the predictors of interest and all results are interpreted in terms of odds ratios (ORs).

Association between CES and CMC and SS

	SS	Non-Sicca Control					SS	Sicca Control				
		n(%)	n(%)	P	OR	95% CI		n(%)	n(%)	P	OR	95% CI
CES	0	167(51)	152(41)	0.01	ref		167(51)	425(38)	<0.001	ref		
	1	462(35)	165(44)		0.74	0.56-0.98	462(35)	430(39)		0.84	0.69-1.03	
	2	164(12)	48(13)		0.91	0.60-1.39	164(12)	294(18)		0.70	0.53-0.93	
	3	25(2)	8(2)		1.19	0.43-3.34	25(2)	46(4)		0.43	0.25-0.75	
	4	2(0.2)	0				2(0.2)	3(0.2)		1.48	0.09-25.0	
CMC	Premenopausal	Q1	114(21)	26(16)	0.003	ref	121(23)	55(5)	0.01	ref		
		Q2	118(22)	21(13)		1.06	0.49-2.25	111(21)	64(6)		0.78	0.45-1.33
		Q3	103(19)	38(22)		0.42	0.19-0.90	112(21)	64(6)		0.73	0.42-1.29
		Q4	93(17)	47(29)		0.26	0.11-0.68	91(17)	59(8)		0.47	0.26-0.87
		Q5	105(20)	23(7)		0.36	0.12-1.07	98(18)	74(7)		1.03	0.49-2.17
	Postmenopausal	Q1	164(21)	33(16)	0.05	ref	160(21)	153(14)	0.56	ref		
		Q2	160(21)	43(21)		0.82	0.47-1.46	164(21)	143(13)		0.98	0.69-1.40
		Q3	109(21)	51(15)		1.08	0.59-1.97	109(21)	145(13)		0.93	0.65-1.34
		Q4	143(18)	40(23)		0.68	0.39-1.22	144(18)	142(13)		0.91	0.63-1.31
		Q5	145(19)	51(25)		0.55	0.31-0.96	144(19)	100(14)		0.75	0.52-1.07

SS: Sjögren's Syndrome; CES: Composite Estrogen Score; CMC: Cumulative menstrual cycling; Q: Quintile

Results: Using a regression model adjusting for age, recruitment site, ethnicity, education, employment status, and smoking, we observed a progressive inverse trend between SS and both CES and CMC. For each stratum of greater cumulative estrogen exposure (CES1-3), there was a progressive and significant decrease in SS risk relative to sicca controls. The ORs and 95% confidence interval(95% CI) were as follows for the sicca control group:CES1, OR 0.84 [95% CI, 0.7-1.0]; CES 2, OR 0.7 [95% CI, 0.5-0.9]; CES 3, OR0. 43 [95% CI, 0.25-0.75]. Similar trends were seen in the non-sicca control group(Table). The higher stratum of CES were not significant, but numbers of registrants were small, leading to wide confidence intervals. This finding was corroborated by analysis of the CMC. At the highest level of CMC within the non-sicca control and sicca control postmenopausal groups there was a 45% and 25% reduction in cumulative sex hormone exposure among SS registrants relative to controls, after adjusting for covariates.

Conclusion: Women with SS have lower estrogen exposure and cumulative menstrual cycling compared to non-autoimmune sicca and non-sicca control groups. As estrogen exposure and cumulative menstrual cycling increased, there was a trend toward decreased risk of SS. Further longitudinal studies of sex hormone exposure in SS are needed to confirm these findings.

Disclosure: S. S. McCoy, None; E. Sampene, None; A. N. Baer, None.

Abstract Number: 1580

Persistent Serological Activity in Primary Sjögren's Syndrome

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science Poster

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To assess presence of persistent serological activity and its association with clinical outcomes in a cohort of patients with primary Sjögren's syndrome (pSS).

Methods: We retrospectively reviewed the clinical charts of 275 patients with pSS according to the AECG criteria, attending a tertiary referral center. We defined persistent serological activity as increase IgG \geq 1.6 g or globulins $>$ 3.7 gr or diminished C3 $<$ 52 mg/dL or C4 $<$ 12 mg/dL at least during two consecutive visits during a year period (index period). We selected whenever possible, the closest period to the diagnosis of SS. We defined clinical activity, as the presence of at least 1 point in the clinESSDAI at the index period. We also scored the cumulative clinESSDAI as well as the SSDDI at the last medical appointment. We excluded patients with incomplete serological data or with $<$ 1 year of follow-up after the

index period. We registered demographics, glandular and extraglandular features, anti-Ro/SSA, anti-La/SSB and RF determinations. We used descriptive statistics and used regression logistic analysis.

Results: We excluded 115 patients due to incomplete data. Thus we included 160 patients with available serological data and follow-up: most females (95%), 94% with ocular symptoms, 91.2% oral symptoms, 46.9% parotid enlargement, 90% anti-Ro/SSA and 58% anti-La/SSB antibodies and median disease duration of 10.2 years. We identified persistent activity in 85 patients (53.1%): 57 due to hyperglobulinemia, 5 due to low C3 or C4, and 23 patients due to both. In only 13 patients, the serological status changed during the follow-up from active to inactive.

At the moment of the assessment (index period) we identified 58 patients with both clinical and serological activity, 49 with only clinical activity, 27 with only serological activity and 27 without clinical or serological activity. When we compared patients with (n=85) vs. without serological activity (n=74), the first group had a higher prevalence of impaired whole non-stimulated salivary flow (94% vs. 79.2%, p=0.01), anti-La/SSB antibody (70.6% vs. 44.6%, p=0.001) and RF (84.5% vs. 51%, p=0.0001). In addition, the persistent active serological group had a higher cumulative clinESSDAI at the last medical appointment (11 vs. 6 points 0.0001), being the main affected domains the constitutional (30.6% vs. 13.5%, p=0.02), glandular (52.9% vs. 32%, p=0.01), cutaneous (21.2% vs. 5.4%, p=0.005), renal (17.6% vs. 2.75, p=0.002) and hematological (42.4% vs. 17.6%, p=0.001). The SSDDI score was similar among groups (3 vs. 2 points, p=0.18), however the active serological group had more damage at the oral (92.5% vs 80%, p=0.03) and renal domain (12.6% vs. 2.7%, p=0.02). At the logistic regression analysis, the variables that remained associated were renal involvement (OR 12.8, 95% CI 1.7-92, p=0.01), hematological involvement (OR 4.7, 95% CI 1.6-13.4, p=0.004) and RF (OR 6.4, 95% CI 1.8-22, p=0.003).

Conclusion: Half of the patients with pSS had persistent serological activity, being this status constant during the follow-up. Persistent serological activity was associated with renal and hematological features, as well as with the presence of RF.

Disclosure: J. Lopez-Morales, None; D. Cortes-Muñoz, None; G. Hernandez-Molina, None.

Abstract Number: 1581

Lack of Specificity in Testing for Murine Tissue Specific Autoantibodies for the Diagnosis of Sjogren's Syndrome

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SESSION INFORMATION

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Background/Purpose: A group of murine parotid tissue specific autoantibodies (TSAs) which includes anti-SP1 (salivary protein 1), anti-PSP (parotid secretory protein) and anti-CA6 (carbonic anhydrase) are markers for early disease in the IL-14 α transgenic mouse model of Sjogren's (SS). These TSAs are also found in NOD mice, patients (pts) classified with SSA+ or - Sjogren's according to the American European Consensus Group criteria and in pts with idiopathic dry eyes.

Methods: We tested serum for TSAs from 6 patient groups followed in a rheumatology clinic for > 1 year at a university medical center including: 1) SS who met published classification criteria (n=152), 2) non-autoimmune controls (n=36), 3) SLE (n=22), 4) RA (n=17), 5) scleroderma (n=7) and 6) chronic nonspecific sialadenitis (n=16). Saliva samples were also obtained from groups 1,2 & 6. Electronic medical records were reviewed to verify diagnoses & all pts were questioned re: the presence & duration of dry eyes/mouth & medical history. Volunteers with history of dry eyes/mouth, any autoimmune diseases or family history of autoimmune disease were excluded as controls. Serum samples were anonymously coded & assayed by a modified ELISA (Trinity Biotech, Inc., Buffalo, NY). All laboratory personnel were blinded to pts diagnoses. Analyses was performed to determine the sensitivity, specificity & discriminative ability of the presence of ≥ 1 TSAs to differentiate SS from other groups.

Results: Of the 152 SS pts, 9% had disease duration ≤ 3 years. TSAs were detected in both the serum and saliva of pts with SS. The most frequently detected TSA in SS was anti-PSP IgG (13%) (**Table 1**). The presence of ≥ 1 TSA was similar in SS (40%), controls (44%), chronic sialadenitis (50%), and patients with other CTD (35%). No particular TSA or

isotype was specific for SS. Results suggested a sensitivity and specificity of 40% and 56% respectively for the presence of ≥ 1 TSAs in SS. Prevalence of + ANAs/ RF IgM in each group were as follows: SS (57%/ 44%), controls (14%/ 39%), chronic sialadenitis (31%/ 31%) and other connective tissue diseases (65%/ 47%) (**Table 2**). Prevalence of ≥ 1 TSAs did not significantly vary between ANA+ vs. ANA- or between SSA+ vs. SSA- individuals.

Conclusion: The presence of ≥ 1 TSAs in the serum does not distinguish between established SS and other patient groups. The value of the serum assay, as presently performed, for confirmation of early or undiagnosed SS (≤ 3 years) in humans is doubtful given the lack of assay specificity. Assay of TSAs in saliva or calculation of a saliva/serum TSA ratio may prove to be a more valuable diagnostic test.

Table 1 Frequency of Positive Murine Parotid Tissue Specific Autoantibodies in Different Patient Groups

	Primary Sjogren's (N = 152)	Controls (N = 36)	Chronic Sialadenitis (N = 16)	CTD (N = 46)
CA6 IgG ≥ 20	7 (4.6%)	0 (0.0%)	1 (6.3%)	0 (0.0%)
CA6 IgM ≥ 20	5 (3.3%)	4 (11.1%)	0 (0.0%)	3 (6.5%)
CA6 IgA ≥ 20	8 (5.3%)	0 (0.0%)	2 (12.5%)	1 (2.2%)
CA6 any ≥ 20	19 (12.5%)	4 (11.1%)	2 (12.5%)	4 (8.7%)
PSP IgG ≥ 20	20 (13.2%)	5 (13.9%)	3 (18.8%)	8 (17.4%)
PSP IgM ≥ 20	13 (8.6%)	5 (13.9%)	3 (18.8%)	5 (10.9%)
PSP IgA ≥ 20	7 (4.6%)	1 (2.8%)	3 (18.8%)	3 (6.5%)
PSP any ≥ 20	38 (25.0%)	9 (25.0%)	7 (43.8%)	11 (23.9%)
SP1 IgG ≥ 20	6 (3.9%)	3 (8.3%)	1 (6.3%)	4 (8.7%)
SP1 IgM ≥ 20	16 (10.5%)	6 (16.7%)	0 (0.0%)	7 (15.2%)
SP1 IgA ≥ 20	12 (7.9%)	3 (8.3%)	0 (0.0%)	2 (4.3%)
SP1 any ≥ 20	31 (20.4%)	11 (30.6%)	1 (6.3%)	10 (21.7%)
Any novel Ab ≥ 20	61 (40.1%)	16 (44.4%)	8 (50.0%)	16 (34.8%)

All p > 0.05 in pairwise comparison with primary Sjogren's with Fisher's exact test

	Primary Sjogren's	Controls	Chronic Sialoadenitis	CTD*
N	152	36	16	46
Female	145 (95.4%)	22 (61.1%)	14 (87.5%)	38 (82.6%)
Age, years	± 13.8	± 22.3	± 18.7	± 12.4
ANA $\geq 1:160$	86 (56.6%)	5 (13.9%)	5 (31.2%)	30 (65.2%)
RF IgM ≥ 10	67 (44.1%)	14 (38.9%)	5 (31.2%)	21 (46.7%)
SSA ≥ 20	92 (60.5%)	2 (5.6%)	0 (0%)	14 (31.1%)
SSB ≥ 20	50 (32.9%)	1 (2.8%)	2 (12.5%)	13 (28.9%)

\pm standard deviation. *22 lupus, 17 rheumatoid arthritis, 7 scleroderma

Disclosure: F. B. Vivino, Biogen Idec, 2, Novartis, 5, Trinity Biotech, 2; M. D. George, Bristol Myers Squibb, 2; C. Johr, None; N. Sandorfi, None; V. Bunya, None; G. Massaro-Giordano, None; A. Diederich, None; B. Eilberg, None; L. Suresh, Trinity Biotech, Inc., 3; L. Shen, Trinity Biotech, Inc., 3.

Abstract Number: 1582

Clinical Correlations and Expression Pattern of the Autoimmunity Susceptibility Factor Dora-1 in Primary Sjögren's Syndrome

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Background/Purpose: Genome-wide association studies of multiple autoimmune diseases, including primary Sjögren's syndrome (pSS), systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) have revealed an association with the chromosome 8 locus *FAM167A-BLK*. The disease-associated genotypes of SNPs in the locus have been linked to a significantly increased expression of FAM167A in B cells. While BLK (B lymphocyte kinase) has a well-established role in

B cells, little is known about FAM167A (family with sequence similarity 167 member A). We recently cloned and investigated the gene product of FAM167A, identifying an encoded protein with high content of intrinsic disorder which we denoted Disordered Autoimmunity 1 (DIORA-1). In the present study we investigated the expression of DIORA-1 in human immune cells and in salivary glands of patients with pSS, as well as assessed DIORA-1 expression in relation to pSS clinical manifestations to begin understanding the role of DIORA-1 in rheumatic disease pathogenesis.

Methods: Primary cells were purified from peripheral blood or buffy coats by MACS beads, and cell lines representing discrete differentiation stages of B cells were cultured under standard conditions. DIORA-1 mRNA expression was assessed by qPCR. Immunohistochemistry was performed to identify DIORA-1 expressing cells in salivary gland biopsies, and characterization of the cells and DIORA-1 localization performed by immunofluorescence using double staining. Characterization of DIORA-1 expressing cells was performed by immunofluorescence. In all, 55 patients with pSS, 20 sicca patient controls and 29 healthy donors were included in the study.

Results: We observed expression of DIORA-1 in CD19+ B cells from peripheral blood, while CD3+ T cells and CD14+ monocytes expressed little or no DIORA-1. To further define the expression pattern of DIORA-1 in B cells, we analyzed cell lines representing discrete differentiation stages of B cells. Interestingly, we observed a graded expression of DIORA-1 in these various cell lines, with the highest expression found in the two plasma cell myeloma lines and intermediate expression in other B cell lines, whereas little or no expression was observed in T cells and other investigated cell lines. CD138+ plasma cells expressing DIORA-1 intracellularly were observed within the salivary glands of pSS patients. Spatially, DIORA-1+ cells were detected within the focal infiltrates and interstitially in salivary gland biopsies. Notably, expression of DIORA-1 correlated to salivary gland focus score, as well as serum IgG levels and the presence of Ro/SSA autoantibodies.

Conclusion: These findings indicate a role for DIORA-1 in select B cell subsets, and moreover suggest that DIORA-1 potentially contribute to the inflammatory process and disease pathogenesis in pSS through B cell involvement.

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Abstract Number: 1583

Low-Dose IL-2 Promotes the Proliferation of Peripheral Regulatory T Cells in Primary Sjögren's Syndrome to Restore Its Balances with Pro-Inflammatory Lymphocytes

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science Poster

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To investigate the effect of low-dose IL-2 on the balance of Treg with Teff and other pro-inflammatory lymphocytes in peripheral blood of pSS patients.

Methods: A total of 190 pSS patients and 30 healthy controls were included in the study. The absolute numbers of total CD4+ T, CD8+ T, B, and NK cells in peripheral blood were determined using flow cytometry and BD Trucount™ tubes, while the percentage of each cell subpopulation and CD4+ cell subsets was measured, and then calculated their absolute numbers. Of the 190 patients, 88 were given subcutaneous injections of small doses of recombinant human IL-2 (rhIL-2, 50*10⁶ IU/day for 5 days) in combination with standard therapy, including glucocorticoids, immunosuppressants, Treatment of biologics or their combinations, while other patients received only standard therapies.

Results: (1) The absolute number of peripheral Treg cells of pSS patients was significantly lower than that of normal controls. (2) The absolute number of Th17 and CD8+ T cells before treatment was not different from that of normal controls, whereas the ratios of Th17/Treg and CD8+T/Treg were higher than normal, indicating that the imbalance of them was caused by insufficient number of Treg cells. Although Th17 and CD8+ T cells increased, Treg cells increased

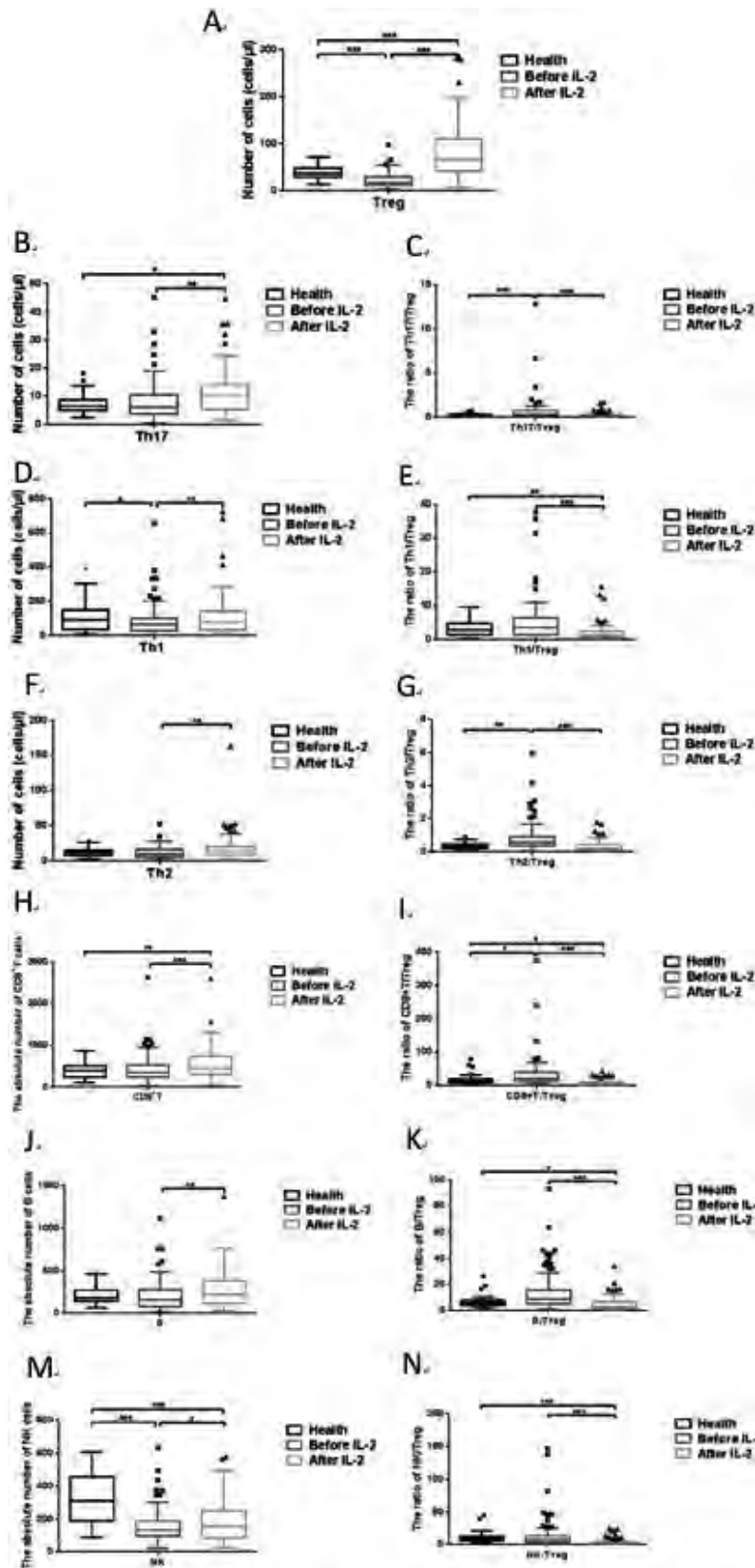


Figure legends. Changes in the absolute number of cells (A, B, D, F, H, J, M) and ratios of individual cells to Treg cells after short-dose, low-dose IL-2 treatment (C, E, G, I, K, N). The data is represented by the median (Q1, Q3). Statistical analysis uses the two-way analysis of variance of the relevant sample Friedman. Compared with healthy controls, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. Shows asymptotic significance (two-tailed test). The significance level was $p < 0.05$.

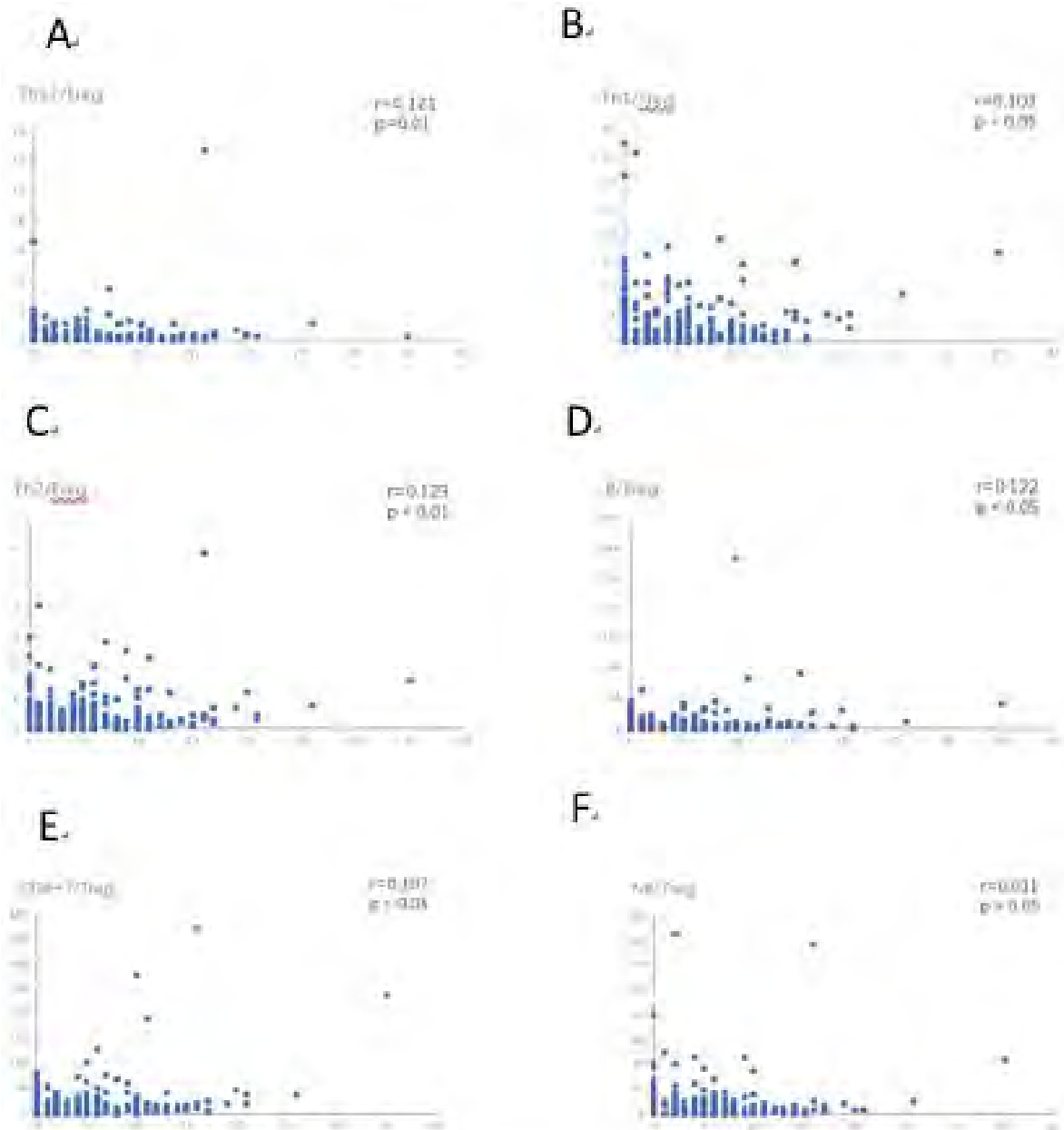


Figure 2 legends: There were positive correlations between ESSDAI value and the ratios of Th17/Treg ($r=0.121$, $P=0.01$), Th1/Treg ($r=0.103$, $P<0.05$), Th2/Treg ($r=0.123$, $P<0.01$), B/Treg ($r=0.122$, $P<0.05$), CD8+T/Treg ($r=0.107$, $P<0.05$).

There was no correlation between ESSDAI value and the ratio of NK/Treg ($r=0.011$, $P>0.05$). Statistical analysis used Spearman's rank correlation. The significance level was $p < 0.05$.

more dramatically, so the ratio returned to normal. Similarly, Th1, Th2, NK, and B cells had similar changes, as shown in Figure 2. (3) Compared with the standard treatment group, low-dose IL-2 increased the proportion of the patients with balanced Th17/Treg, who had a more pronounced improvement in symptoms, and less usage of glucocorticoid and HCQ. (4) There were positive correlations between ESSDAI value and the ratios of Th17/Treg ($r=0.121$, $P=0.01$), Th1/Treg ($\rho=0.103$, $P<0.05$), Th2/Treg ($\rho=0.123$, $P<0.01$), B/Treg ($\rho=0.122$, $P<0.05$), CD8+T/Treg ($\rho=0.107$, $P<0.05$), but no correlation between ESSDAI value and the ratio of NK/Treg ($\rho=0.011$, $P>0.05$).

Conclusion: Low-dose rhIL-2 treatment can promote the proliferation of various cell subsets, but mainly Treg cells, indicating that this treatment can restore the overall balances of Treg/Teff, B/Treg, and NK/Treg. Thus, due to improvement of ESSDAI, the overall balances between Treg and pro-inflammation cells are more important than the change in the single cell subset.

Disclosure: M. Miao, None; Z. Hao, None; Y. Guo, None; X. Zhang, None; S. X. Zhang, None; J. Luo, None; J. Zhao, None; C. Gao, None; X. F. Li, None.

Abstract Number: 1584

Evaluation of the Performance of the 2016 American College of Rheumatology-European League Against Rheumatism (Acr-Eular) Classification Criteria for Primary Sjögren`S Syndrome in Different Centers of Argentina

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science Poster

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Session Time: 9:00AM-11:00AM

Background/Purpose: Primary Sjögren`s Syndrome (pSS) is a multisystemic, autoimmunity disease, characterized mainly by the hypofunction of the salivary and lacrimal glands, however the clinical spectrum of this disease extends from SICCA symptoms to the presence of extra-glandular manifestations being able to compromise multiple systems. The recent 2016 ACR-EULAR classification criteria were designed to be applied not only in patients with dryness symptoms, but also in those with clinical manifestations included in the ESSDAI domains (EULAR primary Sjögren's syndrome disease activity) which would allow to classify those patients who debuted with extra-glandular manifestations.

Objetives: To evaluate the performance of the 2016 ACR-EULAR classification criteria for pSS in adult population of different centers in Argentina.

Methods: A multi-center study of 5 national centers was carried out. We included patients older than 18 years of age, who presented clinical and/or analytical manifestations suggestive of pSS. To discriminate between cases and controls, the opinion of experts from different centers, blind to the previous diagnosis of the patients, (with a degree of agreement $\geq 70\%$) was used as gold standard. The exclusion criteria were similar to those present in the 2002 American-European and the 2012 ACR classification criteria. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and positive likelihood ratio (LR +) were evaluated.

Results: A total of 226 patients were included, 97.3% were women, with an average age of 55 years (SD ± 12), and a mean duration of symptoms of 7.9 years (SD ± 6.8). 178 patients (78.7%) had a diagnosis of pSS according to expert opinion, of which 171/178 (96.1%) had xerophthalmia, 172/178 (96.6%) xerostomia, 162/178 (91%) positivity at least one domain of the ESSDAI and 3/178 (1.7%) did not present xerostomia or xerophthalmia at the time of diagnosis. A

sensitivity of 94.9% (95% IC: 92.1 - 97.8%), a specificity of 95.8% (95% IC: 93.2 - 98.4%), a PPV of 98.8% (95% IC: 97.4 - 100%), a NPV of 83.6% (95% IC: 78.8 - 88.4%) and an LR + of 22.7 (95% IC: 13.6 - 62.7) was obtained.

Conclusion: The recent classificatory criteria showed a performance comparable to the precedents 2002 American-European and 2012 ACR classification criteria, with the advantage that the new ones allow to classify those patients who debuted with extra-glandular manifestations.

Disclosure: H. Najera, None; M. Mamani, None; A. Secco, None; F. Melo, None; C. Troitiño, None; F. Romanini Sr., None; E. Guerra, None; A. Catalan Pellet, None; S. B. Papasidero, None; R. Aguila Maldonado, None; M. Garcia, None; M. Rivero, None; J. C. Barreira, None; I. remolina, None; A. perdomo, None; Q. mayorga, None; M. J. santacruz, None; J. demarchi, None.

Abstract Number: 1585

Primary Sjögren's Syndrome Stratification Based on the Severity of Patient-Reported Fatigue

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science Poster

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Fatigue is one of the most common symptoms reported by patients affected by primary Sjögren's syndrome (pSS), and a major contributor to impaired quality of life. The purpose of this study was to analyze the clinical, serological and histological features of pSS patients stratified according to the severity of their self-reported fatigue.

Methods: Among pSS patients undergoing clinical evaluation in our Sjögren's Clinic in a six-months period (January-June 2017), 86 consecutive unselected patients, fulfilling the latest ACR/EULAR pSS classification criteria, accepted to report their degree of fatigue on a 10-cm VAS (range 0-100) and to complete the ESSPRI questionnaire. Four subgroups of fatigue severity were defined, as previously published (1): no fatigue (VAS=0); low fatigue (VAS=1-24); moderate fatigue (VAS=25-74); high fatigue (VAS=75-100). For each subgroup demographic, serological, histological features and the ESSDAI score were collected, as well as the prevalence of pSS-related lymphoma, fibromyalgia (FM), autoimmune thyroiditis, and anemia.

Results: Fatigue was reported by the 87.2% (n=75) of pSS patients, distributed in subgroups as following: 25.3% (n=19) with low fatigue, 58.7% (n=44) with moderate fatigue and 16% (n=12) with high fatigue. Lymphoma was significantly (p=0.0133) more frequent in the pSS subgroup with high fatigue (33.4%, by considering active lymphoma cases; 50%, by considering also the cases with lymphoma in remission). FM patients were a minority (4.7%; n=4), and never complained of high fatigue, all of them reporting moderate fatigue. A significant correlation was finally found between fatigue severity and ESSPRI (p<0.0001), but not with ESSDAI (p=0.31). No significant age or sex difference was observed between subgroups. Also, autoimmune thyroiditis, anemia, anti-SSA and/or anti-SSB positivity, rheumatoid factor positivity, and cryoglobulinemia showed no significant different frequency between subgroups.

Conclusion: When fatigue is better stratified in pSS, it appears that it is usually moderate or severe, rather than mild. Furthermore, it is unrelated to FM. Overall, fatigue appears as a consequence of pSS itself. Of note, severe fatigue was related in this study with the most important complication influencing patient survival in pSS, i.e., lymphoma. Further studies are needed to disclose the pathogenetic events leading to fatigue in pSS, and investigation of lymphoma in pSS might be also helpful to this end.

Reference: (1) Ng WF et al. PLoS One. 2015 Dec 22;10:e0143970.

Disclosure: S. Gandolfo, None; E. Doriguzzi Breatta, None; C. Fabro, None; S. De Vita, None.

Expression of JAK Proteins and Autophagy Markers in Sjögren's Syndrome Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science Poster

Session Type: ACR Poster Session B

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Background/Purpose: Sjögren's syndrome (SS) is an autoimmune epitheliitis that mainly affects the salivary and lacrimal glands. The glandular hypofunction has been associated to loss of epithelium by apoptosis. However, several lines of evidence indicate the existence of survival mechanisms that counteract the apoptosis, one of them being the autophagy. This mechanism is involved in decreasing inflammation by selectively removing proteins related to Toll-like receptors and inflammasomes, among other pathways. A previous study on SS showed increased autophagy in T lymphocytes of salivary glands, but the glandular epithelium was not evaluated. Interestingly, IL-6 implicated in SS pathogenesis mediates its response activating the JAK-STAT signaling pathway. In macrophages and other cellular types, activation of the JAK-STAT pathway inhibits autophagy. Studies in SS have shown increased expression of STATs, however, expression of JAK proteins has not been evaluated. The aim of this study was to evaluate the expression of JAKs proteins and autophagy markers in labial salivary glands from SS-patients.

Methods: In labial salivary glands of 11 SS patients and 10 control subjects, mRNA levels of JAK1, JAK2, mTOR and ATG5 were measured by qPCR.

Results: A significant decrease of JAK1 mRNA levels ($p=0.0068$), as well as decreased mRNA levels of genes that participate in autophagy such as mTOR and ATG5 ($p=0.0074$ and $p=0.02$, respectively) were observed in labial salivary glands of SS-patients.

Conclusion: Low JAK1 mRNA levels in SS-patients suggest a downregulation mechanism in response to previously reported hyperactivation of JAK-STAT signaling pathway in SS patients. On the other hand, decreased mRNA levels of autophagy markers, such as ATG5 and mTOR, could indicate an attenuation of this pro-inflammatory mechanism in SS.

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Pathogenic Role of Interleukin 27 in the Nonobese Diabetic Mouse Model of Sjögren Syndrome

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science Poster

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Sjögren syndrome is an immunologically complex autoimmune disease characteristically targeting the lacrimal and salivary glands leading to progressively worsening oral and ocular health and poor quality of life. No effective treatments for reversing the exocrine gland inflammation have been identified owing in part to a lack of understanding the

early immunological events responsible for initiation of lacrimal and salivary gland inflammation. Interleukin 27 (IL27) is a heterodimeric cytokine that was elevated in serum of Sjögren syndrome patients. IL27 may have immunostimulatory or immunomodulatory properties depending on the context, so this elevation in Sjögren syndrome may represent a pathologic process or a compensatory anti-inflammatory process. Similar to Sjögren syndrome in humans, nonobese diabetic (NOD) mice develop spontaneous autoimmune dacryoadenitis and sialadenitis and represent a well-characterized model of Sjögren syndrome. Our objective here was to evaluate the role of IL27 in the development of dacryoadenitis and sialadenitis in the NOD mouse model of Sjögren syndrome.

Methods: NOD mice with deletion mutations disrupting expression of genes encoding the p28 component of IL27 (*Il27*) or the alpha chain of the IL27 receptor (*Il27ra*) were developed through Zn-finger nuclease or CRISPR/Cas9 mediated gene editing, respectively. Development of dacryoadenitis and sialadenitis were determined by histological analyses, and T cell phenotypes were characterized by flow cytometry. *In vivo* regulatory T cell (Treg) depletion with anti-CD25 monoclonal antibody (PC61) and adoptive transfers were performed to determine the effects of disrupted IL27 signaling on development of dacryoadenitis. Studies were approved by the Institutional Animal Care and Use Committee of the University of Iowa.

Results: NOD mice lacking IL27 or IL27Ra failed to develop spontaneous autoimmune dacryoadenitis or sialadenitis. Phenotypically, T cells from IL27-deficient or IL27Ra-deficient NOD mice showed no evidence of defective T cell activation based on expression of T cell activation markers analyzed by flow cytometry *ex vivo*. Depletion of Treg cells in IL27-deficient NOD mice failed to drive dacryoadenitis in these mice. In our adoptive transfer model, wild-type T cells transferred dacryoadenitis to NOD-SCID recipient mice, but IL27Ra-deficient T cells failed to transfer dacryoadenitis. When co-transferred with wild-type cells, IL27Ra-deficient CD8 and CD4 effector T cells each demonstrated a significant competitive disadvantage in their ability to infiltrate lacrimal glands.

Conclusion: IL27 is required for development of dacryoadenitis and sialadenitis in NOD mice. T cell-intrinsic IL27 signaling is required to transfer disease. Defective infiltration of lacrimal glands by IL27Ra-deficient effector T cells suggests IL27 signaling may drive upregulation of homing receptors required for lacrimal gland inflammation. More extensive gene expression and flow cytometric analyses to determine the effects of IL27 signaling on pathogenic immune cell populations in NOD mice are currently underway.

Disclosure: S. Lieberman, None; J. Barr, None; X. Wang, None; Y. G. Chen, None.

Abstract Number: 1588

Risk of Cancer in Patients with Psoriasis/Psoriatic Arthritis: A Population-Based Study in the Province of British Columbia

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriasis (PsO) is a relapsing chronic autoimmune disease of the skin. Up to one-third of patients (pts) also develop inflammatory arthritis, known as psoriatic arthritis (PsA). PsO/PsA, like other forms of chronic inflammatory arthritis, are often associated with complications such as cardiovascular disease and infections. However, data on the risk of cancer in pts with PsO/PsA at population level are limited.

Methods: We created a population-based matched retrospective cohort of PsO/PsA pts diagnosed between 1 January 1997 and 31 December 2012 using administrative health data from British Columbia, Canada. We identified all incident cases of PsO/PsA and an equal number of controls matched on sex, age and calendar year. PsO/PsA cases met ≥ 1 of the following: 1 diagnostic code for PsO/PsA by a rheumatologist/dermatologist; ≥ 2 diagnostic codes for PsO/PsA, ≥ 2 months apart in a 2-year period by a non-rheumatologist/dermatologist; or ≥ 1 hospitalization with diagnostic code for PsO/PsA. We evaluated incident cancers during follow-up from the Cancer Registry in both cohorts. Adjusted risk of cancers was estimated using a generalized estimating equation extension of multivariate Poisson regression models.

Results: We identified 81,568 incident cases of PsO/PsA (mean age 48.5 years [SD=17.8], 51.5% female). Individuals with PsO/PsA were at significantly higher risk of being diagnosed with 8/41 types of cancer examined, including eye and orbit (4

fold), female genital (3 fold), non-melanoma skin (2 fold), prostate (males; 1.1 fold) (Table). Incidence of rectum and colon cancer was lower among PsO/PsA pts relative to the non-PsO/PsA cohort (Table)

Conclusion: This general population-based study demonstrates that pts with PsO/PsA have an increased risk of several types of cancer, and a decreased risk of rectum and colon cancer. This association highlights the need to further explore potential risk factors and pathways that contribute to these complications.

Outcome	PsO/PsA events	Non-PsO/PsA events	PsO/PsA follow-up (PY)	Non-PsO/PsA follow-up (PY)	PsO/PsA IR (per 100,000 PY)	Non-PsO/PsA IR (per 100,000 PY)	IRR (95% CI)
Eye and orbit	13	<5	623,843.5	<5	2.08	-	4.25 (1.21, 14.91)
Female genital other than cervix uteri, corpus uteri and ovary	55	21	623,625.8	611,542.1	8.81	3.43	2.57 (1.55, 4.25)
Other urinary	31	16	623,818.6	611,585.4	4.97	2.62	1.90 (1.04, 3.47)
Non-melanoma skin	401	217	621,233.8	610,223.9	64.54	35.56	1.82 (1.54, 2.14)
Lung	705	589	622,877.2	610,834.8	113.18	96.42	1.17 (1.05, 1.31)
Prostate	760	664	620,065.8	608,124.9	122.57	109.19	1.12 (1.01, 1.25)
Melanoma	218	200	622,791	610,672.1	35.0037	32.7508	1.07
Colon	286	332	622,845.1	610,410.5	45.91	54.39	0.84 (0.72, 0.99)
Rectum	157	194	623,196.9	610,811.7	25.19	31.76	0.79 (0.64, 0.98)

IRR=incidence rate ratio; PY=patient years

Disclosure: J. Tan, None; J. A. Avina-Zubieta, Bristol-Myers Squibb, 2; A. Dominique, Bristol-Myers Squibb, 3; H. Tavakoli, None; T. A. Simon, Bristol-Myers Squibb, 3.

Abstract Number: 1589

Cardiac Biomarkers and Carotid Atherosclerosis and Its Progression in Psoriatic Disease

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Laboratory biomarkers indicative of cardiac ischemia or dysfunction improve cardiovascular(CV) risk stratification in the general population. Their utility in patients with psoriatic disease (PsD) is unknown. Our objective was to evaluate the levels of cardiac biomarkers in patients with PsD vs. non-psoriatic controls and to assess their association with the burden of carotid atherosclerosis and plaque progression.

Methods: Patients with psoriasis only (PsC) or psoriatic arthritis (PsA) from a longitudinal PsD cohort were enrolled. Non-psoriatic controls were recruited through advertisements and from hospital personnel. Baseline evaluation included clinical assessment of CV risk factors, joint and skin disease activity and medication use. Ultrasound assessment of the carotid arteries was performed only in patients with PsD. Total Plaque Area (TPA) was measured at baseline and after 2-3 years. The average annual progression rate of atherosclerosis was calculated by subtracting the baseline from the follow-up TPA divided by the number of years between the visits. Concentrations of high sensitivity Troponin I (TNT-I) and N-terminal pro-brain natriuretic peptide (NT-proBNP) were measured using automated clinical assays. The association between cardiac biomarkers and carotid atherosclerosis was assessed by multivariable regression analysis after adjusting for age, sex, diabetes, hypertension, smoking, BMI, lipid lowering therapy, LDL-c, HDL-c and creatinine.

Results: A total of 391 patients with PsD (71% PsA, 29% PsC) and 88 controls were included. Their mean age was 54.1±11.7 years (53.4% men). Unadjusted levels of TNT-I were higher in patients with PsD compared to controls (Odd Ratio (OR) 1.41, 95% Confidence Interval (CI) 1.11, 1.81),however, after controlling for age, sex and creatinine levels, no

significant differences were found. The unadjusted and adjusted levels of NT-pro BNP were similar in patients with PsD and controls. Higher levels of NT-Pro-BNP were associated with PsA vs. PsC (adjusted OR 1.35, 95% CI 1.09, 1.68). Higher levels of TNT-I were associated with the burden of carotid atherosclerosis at baseline in unadjusted models (β 0.66, 95% CI 0.46, 0.87; Table 1) and after controlling for CV risk factors (adjusted β 0.27, 95% CI 0.08, 0.46; Table 1). However, baseline TNT-I levels did not predict carotid atherosclerosis progression ($p=0.47$). No significant association was found between baseline levels of NT-pro BNP and carotid atherosclerosis at baseline (adjusted $P=0.15$) or the rate of atherosclerosis progression (adjusted $p=0.64$). No interaction was found between each of the biomarkers and sex.

Conclusion: Higher TNT-I is associated with more pronounced atherosclerosis in patients with PsD independently of usual CVD risk factors. The utility of hsTnI in improving CV risk stratification in these PsD patients warrants assessment.

Table 1 The Association between Troponin I levels and Total Plaque Area* at Baseline by Linear Regression Model in Patients with Psoriatic Disease (N=391)

Variable	Adjusted β	95% Confidence Interval	P value
High-Sensitivity Troponin I* (ng/L)	0.27	0.08, 0.46	0.006
Age (10 year increase)	0.06	0.05, 0.07	<0.001
Sex: Female	-0.18	-0.49, 0.12	0.25
BMI (kg/m ²)	0.01	-0.01, 0.04	0.32
Hypertension (y/n)	0.22	-0.11, 0.56	0.18
Diabetes (y/n)	0.24	-0.30, 0.78	0.38
Smoking (Current vs. No)	0.46	0.04, 0.88	0.03
LDL-c (mmol/L)	0.27	0.12, 0.42	<0.001
HDL-c (mmol/L)	0.002	-0.37, 0.38	0.99
Use of lipid lowering drugs (y/n)	0.68	0.36, 1.01	<0.001
Creatinine (μ mol/L)	0.21	-0.62, 1.05	0.61

* log transformed

Disclosure: L. Eder, None; V. Chandran, None; I. B. McInnes, None; R. J. Cook, None; D. D. Gladman, None; P. Welsh, None; N. Sattar, None; P. Harvey, None.

Abstract Number: 1590

Metabolomics Profile Predicts Carotid Atherosclerosis Progression in Psoriatic Disease

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

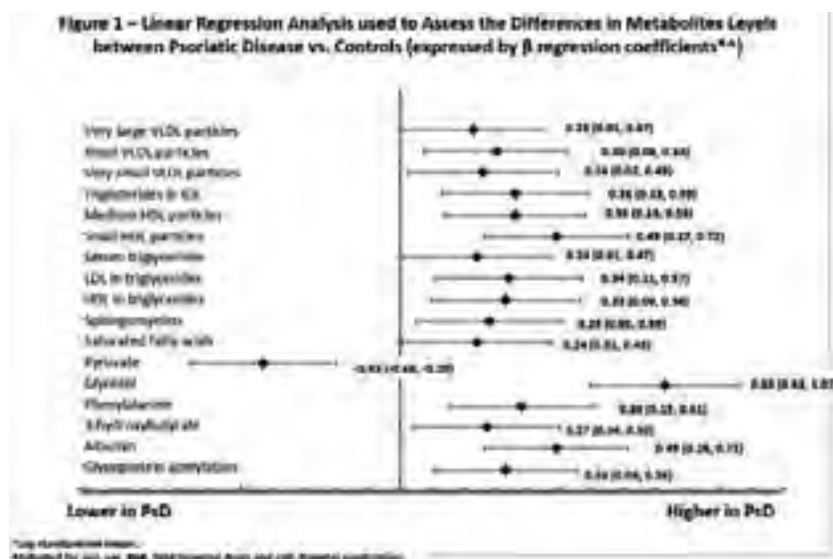
Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Metabolomic profiling of patients with psoriatic disease (PsD) offers unparalleled opportunity to unravel the molecular and clinical interactions linking PsD with cardiovascular (CV) risk. Our objective was to evaluate the metabolomics profile in patients with PsD vs. non-psoriatic controls and to assess its association with carotid atherosclerosis progression.

Methods: Patients with psoriasis only or psoriatic arthritis from a longitudinal PsD cohort were enrolled. Non-psoriatic controls were recruited through advertisements and from hospital personnel. Baseline evaluation included clinical assessment of CV risk factors, joint and skin disease activity and medication use. Ultrasound assessment of the carotid arteries was performed only in patients with PsD. Total plaque area was measured at baseline and after 2-3 years. The average annual progression rate (APR) of atherosclerosis was calculated by subtracting the baseline from the follow-up TPA divided by the number of years between the visits. Atherosclerosis progression was defined as being in the top quartile of APR. A high-throughput serum nuclear magnetic resonance metabolomics platform was used to quantify the baseline levels of 58 lipoprotein subclasses, fatty acid composition, amino acids glycolysis precursors and ketone bodies. Multivariable logistic regression analysis was performed to assess the association between metabolite levels and the following outcomes: 1) disease status (PsD vs. controls); 2) carotid atherosclerosis progression.

Results: A total of 392 patients with PsD and 88 controls were included in the analysis. Their mean age was 54.1 ± 11.7 years (53.4% men). 19 metabolite measures were found to be significantly associated with PsD compared to controls after adjusting for age, sex, BMI and medication use (Figure 1). The metabolites included lipoprotein subclasses, fatty acids, amino acids and intermediates of glycolysis. We then evaluated the incremental value of adding circulating metabolites to established CV risk factors for prediction of atherosclerosis progression using regression analysis. 13 metabolites, primarily atherogenic lipid particles, predicted atherosclerosis progression after adjusting for CV risk factors (Table 1).



Conclusion: Substantial differences were found in the metabolomic profile between patients with PsD and non-psoriatic controls. Atherogenic lipoprotein particles across the non-HDL-c spectrum predicted atherosclerosis progression in PsD independently of conventional CV risk factors.

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Abstract Number: 1591

Is Enthesitis a Marker of Disease Severity in Early Psoriatic Arthritis?

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

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Session Time: 9:00AM-11:00AM

Background/Purpose: Enthesitis is a key feature in psoriatic arthritis (PsA) affecting approximately a third of the patients. Ultrasound improves the detection of enthesitis compared to clinical examination. However, there is little information about the construct validity of sonographic enthesitis scores in PsA. We aimed to evaluate the correlation between the severity of sonographic enthesitis and measures of disease activity in patients with early PsA.

Methods: Sixty-four patients with early PsA (duration <5 years) who were naïve to biologic medications, were enrolled. PsA disease activity was assessed in each of the key domains using validated measures of disease activity, laboratory markers of inflammation and patient reported outcomes. The severity of sonographic enthesitis was assessed in 14 enthesal sites using a modification of the Madrid Enthesitis Scoring Index (MASEI) with power Doppler scored on a scale of 0 to 3. We considered the total score of modified MASEI(mod-MASEI) and the total Doppler scores (mod-MASEI-Dop) as the outcomes of interest. Pearson correlation coefficients were calculated between sonographic enthesitis scores and measure of disease activity. Since sonographic enthesitis confounded by aging and mechanical stress we used

Table 1 - The Association between Metabolemic Biomarkers* and Atherosclerosis Progression by Logistic Regression Model		
Each model is adjusted for: Age, sex, systolic blood pressure, anti hypertensive therapy, lipid lowering therapy, BMI, smoking, diabetes and disease status (PsA vs psoriasis)		
Biomarker	Odds Ratio (95% Confidence Interval)	P value
Very small VLDL particles	1.43 (1.09, 1.88)	0.009
IDL particles	1.51 (1.14, 1.99)	0.004
Phospholipids in IDL	1.52 (1.16, 2.01)	0.003
Total cholesterol in IDL	1.42 (1.09, 1.85)	0.009
Triglycerides in IDL	1.30 (1.00, 1.72)	0.05
Large LDL particles	1.51 (1.14, 1.99)	0.004
Medium LDL particles	1.47 (1.12, 1.93)	0.006
Small LDL particles	1.40 (1.07, 1.84)	0.01
Large HDL particles	0.73 (0.54, 0.98)	0.03
Remnant cholesterol	1.35 (1.03, 1.75)	0.03
Total cholesterol in LDL	1.42 (1.09, 1.84)	0.009
Apo-B	1.29 (1.00, 1.68)	0.05
Creatinine	0.75 (0.57, 0.99)	0.04
*log standardized values		

regression analysis to evaluate the association between diseases related measures and sonographic enthesitis after adjusting for age, sex and BMI.

Results: The mean age was 46.6 ± 13.7 (53.1% males) and mean disease duration was 1 ± 1.3 years. Clinical enthesitis was found in 51.6% (≥ 1 tender enthesial site) and active sonographic enthesitis was found in 57.8% of the patients. A mild to moderate correlation was found between sonographic enthesitis and tender and swollen joint counts, damaged joint count, clinical enthesitis count, physician global assessment and health assessment questionnaire (HAQ)(Table 1). In multivariable analysis the following variable were associated with higher sonographic enthesitis score (Table 2): nail pitting (β 9.3, 95% confidence interval (CI) 1.7, 16.8), physician global assessment (β 1.9, 95% CI 0.3, 3.5), HAQ (β 9.7, 95% CI 3.9, 15.5), swollen joint count (β 1.3, 95% CI 0.6, 1.8) and tender joint count (β 1.2, 95% CI 0.6, 1.8).

Conclusion: The severity of sonographic enthesitis correlates with measures of disease activity, joint damage and patient function in early PsA. These findings suggest that sonographic enthesitis has construct validity and may be considered as a marker of severity in early PsA.

Table 1- The correlation sonographic enthesitis and measures of PsA disease activity

	Modified MASEI - Total			Modified MASEI – Doppler score		
	r	P value	N	r	P value	N
Swollen joint count	0.44	<0.001	64	0.36	0.004	64
Tender joint count	0.44	<0.001	64	0.34	0.005	64
Damaged joint count	0.31	0.01	64	0.25	0.05	64
Tender enthesitis count	0.25	0.048	64	0.16	0.20	64
Dactylitis count	0.03	0.83	64	-0.02	0.86	64
Nail pitting	0.36	0.004	64	0.24	0.05	64
Nail onycholysis	0.02	0.89	64	0	0.94	64
PASI	0.09	0.47	64	0.06	0.62	64
MD global assessment	0.36	0.003	64	0.28	0.02	64
CRP	0.12	0.35	60	0.05	0.70	60
ESR	0.25	0.06	60	0.08	0.56	60
HAQ	0.31	0.01	61	0.21	0.10	61
Pain score	0.04	0.75	62	0	0.99	62
PGA arthritis	0	0.99	61	-0.04	0.77	61
PGA psoriasis	0.03	0.82	62	0.06	0.66	62
FACIT	-0.10	0.46	55	0	0.99	55
DLQI	0.08	0.53	59	0	0.98	59

ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; DLQI: Dermatology Life Quality Index; FACIT: Fatigue Functional Assessment of Chronic Illness; HAQ: Health Assessment Questionnaire; MD: physician; PASI: psoriasis area and severity index; PGA: Patient Global Assessment

Table 2- The Association Between total Modified-MASEI and PsA Disease Related Variables by Linear Regression Model (N=64)

	Univariate		Age-, Sex- and BMI adjusted model	
	β (95% CI)	P value	β (95% CI)	P value
Duration of Morning stiffness (>30 minutes)	4.7 (-2.7, 12.1)	0.21	6.3 (-0.6, 13.2)	0.08
Inflammatory back pain (yes)	2.7 (-5.4, 10.8)	0.51	5.1 (-2.2, 12.4)	0.17
Nail lesions (yes)	1.6 (-5.9, 9.1)	0.67	0.3 (-6.7, 7.2)	0.94
Nail pitting (yes)	12.2 (4.4, 20)	0.002	9.3 (1.7, 16.8)	0.02
Nail Onycholysis (yes)	0.5 (-7.7, 8.8)	0.89	-0.04 (-7.6, 7.6)	0.99
PASI	0.3 (-0.4, 1.0)	0.46	0.2 (-0.5, 0.9)	0.55
Dactylitis (yes)	-4.7 (-14.6, 5.2)	0.35	-2.4 (-11.6, 6.8)	0.61
Physician global assessment (0-10)	2.6 (1.0, 4.3)	0.002	1.9 (0.3, 3.5)	0.02
CRP (mg/dL)	0.1 (-0.1, 0.4)	0.33	0.1 (-0.1, 0.4)	0.40
ESR (mm/hr)	0.3 (0, 0.6)	0.05	0.2 (-0.04, 0.5)	0.09
BASDAI	0.7 (-1.1, 2.4)	0.47	0.9 (-0.7, 2.4)	0.28
FACIT	-0.1 (-0.4, 0.2)	0.46	-0.1 (-0.4, 0.2)	0.55
DLQI	0.2 (-0.3, 0.6)	0.52	0 (-0.4, 0.4)	0.95
HAQ	8.2 (1.9, 14.4)	0.009	9.7 (3.9, 15.5)	0.001
Pain (0-10)	0.7 (-0.6, 2.1)	0.26	0.8 (-0.4, 2.0)	0.20
PGA arthritis (0-10)	0.4 (-0.8, 1.7)	0.48	0.6 (-0.6, 1.7)	0.34
PGA skin (0-10)	0.6 (-0.6, 1.7)	0.35	0.7 (-0.4, 1.8)	0.19
Dactylitis count (0-20)	-0.4 (-3.9, 3.1)	0.83	0.6 (-2.6, 3.9)	0.70
Damaged joint count (0-68)	2.3 (0.6, 4.1)	0.008	1.5 (-0.3, 3.2)	0.10
Enthesitis count (0-14)	2.7 (0.1, 5.2)	0.04	2.3 (-0.2, 4.7)	0.07
Swollen joint count (0-66)	1.7 (0.8, 2.5)	<0.0001	1.3 (0.4, 2.1)	0.003
Tender joint count (0-68)	1.4 (0.7, 2.0)	0.0001	1.2 (0.6, 1.8)	0.0002
Radiographic sacroiliitis (Yes)	0.3 (-9.4, 9.9)	0.96	4.3 (-4.6, 13.1)	0.34

BASDAI – Bath Ankylosing Spondylitis Disease Activity Index, CRP- C Reactive Protein, DLQI – Dermatology Life Quality Index, ESR – Erythrocyte Sedimentation Rate, FACIT – Functional Assessment of Chronic Illness Therapy, HAQ – Health Assessment questionnaire, PASI – psoriasis area and severity index, PGA – Patient Global Assessment

Disclosure: L. Eder, None; C. Farrer, None; D. Jerome, None.

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Frequency and Pattern of the Uveitis in Spondyloarthritis with Biological Therapy

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SESSION INFORMATION

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Background/Purpose: Uveitis is the most frequent extra-articular manifestation (EAM) of spondyloarthritis (SpA). Its prevalence is approximately 30% and increases with the duration of the SpA. The characteristic pattern is anterior, acute, recurrent and unilateral uveitis. However, the frequency and characteristics of uveitis in SpA treated with biological therapy (BT) are unknown. The main target is to describe the frequency and characteristics of uveitis in SpA with BT in a single center.

Methods: Descriptive and retrospective study (January 2003-December 2017) of SpA that develops uveitis in a reference hospital. The epidemiological variables, type of SpA, presence of uveitis and its characteristics, presence of BT at the time of onset and treatment received are collected. For the analysis, frequencies and percentages were used in qualitative variables, and mean and standard deviation (SD) for quantitative variables. Statistical analysis was performed with IBM SPSS v.23.

Results: We studied 246 patients with SpA. The subtypes of SpA were: ankylosing spondylitis (AS) (n=125, 50.8%), psoriatic arthritis (PsA) (n=101, 41.1%), undifferentiated SpA(n=13, 5.3%), non-radiographic axial SpA (n=3, 1.2%), enteropathic arthropathy (n=3, 1.2%) and reactive arthritis (n=1,0.4%). Uveitis was observed in 41 patients (16.7%) after an average time of development of 109.47 (73.9) months of the SpA. The incidence rate was 5.5 cases of uveitis/100 patients-year of follow-up. Men were 70.7% of the patients and the mean age(SD) was 47.4(12.06) years. The HLA B27 was positive in 87.8% of the cases and 41.5% had family history of SpA. Uveitis was observed in 33 patients (80.5%) with AS, in 6 (14.6%) with PsA, in 1(2.4%) with non-Rx axial SpA and in 1 (2.4%) with undifferentiated SpA. (TABLE) The uveitis pattern was anterior (100%), acute (92.7%), unilateral (87.8%) and in 12.2% bilateral (80% in PsA). At the time of onset of uveitis, the mean ESR was 30.11 mm1sth, CRP 3.56 mg/dL, DAS 28 3.66 and BASDAI 3.21. Regarding the diagnosis of SpA, uveitis was after (85.4%), before (12.2%) and simultaneous (2.4%). At the time of the onset of uveitis, 14 patients (34.1%) were with BT (35.7% etanercept, 28.6% infliximab, 21.4% adalimumab, 7.1% golimumab and 7.1% certolizumab). BT was modified in 3 of the cases. The treatment of uveitis was topical (78%), corticoids in oral regimen (57.5%), conventional DMARDs (12.5%), with methotrexate predominating in 60% of cases and BT (15%). The most used biologics were adalimumab (60%) and infliximab (40%).

Conclusion: In our series, uveitis was observed in 16.7% of patients with SpA of which 80.5% were AS and 14.6% PsA. The most frequent uveitis was anterior, unilateral, acute and recurrent. In PsA, the association with HLA B27 was less frequent and was more bilateral. In most cases, the diagnosis was later than the SpA.

TABLE. CHARACTERISTICS OF THE UVEITIS IN SpA SUBTYPES

	AS (n=125)	PsA (n=101)	undifferentiated SpA (n=13)	non-radiographic axial SpA (n=3)	enteropathic arthropathy (n=3)	reactive arthritis (n=1)
Age (mean)	47.4	47.4	47.4	47.4	47.4	47.4
Sex (M/F)	88/37	70/31	8/5	2/1	2/1	1/0
HLA B27	110/15	14/87	1/12	1/2	1/2	1/0
Family history of SpA	52/73	41/60	6/7	1/2	1/2	1/0
Time of onset of uveitis (months)	109.47	109.47	109.47	109.47	109.47	109.47
Pattern of uveitis	Anterior	Anterior	Anterior	Anterior	Anterior	Anterior
Acuity	Acute	Acute	Acute	Acute	Acute	Acute
Laterality	Unilateral	Unilateral	Unilateral	Unilateral	Unilateral	Unilateral
Simultaneous	12.2%	12.2%	12.2%	12.2%	12.2%	12.2%
Time of diagnosis of SpA	After	After	After	After	After	After
Treatment	Topical	Topical	Topical	Topical	Topical	Topical
Biologics	Adalimumab	Infliximab	Adalimumab	Infliximab	Adalimumab	Infliximab

AS, ankylosing spondylitis; PsA, psoriatic arthritis; undifferentiated spondylarthritis; or axial SpA non-radiographic axial spondylarthritis; DMARD, disease-modifying antirheumatic drug; BT, biologic therapy; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS, Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Index.

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Extra-Articular Manifestations, Neoplasms and Cardiovascular Events in a Series of Spondyloarthritis from a Single Center

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SESSION INFORMATION

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Background/Purpose: Spondyloarthritis(SpA) is characterized by axial, peripheral and extra-articular manifestation(EAMs). Its frequency depends on the series, being the psoriasis(Ps), uveitis and inflammatory bowel disease(IBD) the most frequent. Neoplasms and cardiovascular events(CVE) are the comorbidities which have the highest mortality. The main target is to describe the prevalence of EAMs, neoplasms and CVE in a series of patients with SpA of a reference hospital.

Methods: Descriptive and retrospective study (January 2003-December 2017) of patients with SpA with biological therapy (BT). For the analysis, frequencies and percentages were used for qualitative variables, and mean and standard deviation (SD) for quantitative. Statistical analysis was performed with IBM SPSS.

Results: We studied 246 patients (74.4% males) with a mean age(SD) of 52.9(13.3) years. The types of SpA were: ankylosing spondylitis (AS) (50.8%), psoriatic arthritis (PsA) (41.1%), undifferentiated SpA (5.3%), non-radiographic axial SpA (1.2%), enteropathic arthritis (1.2%) and reactive arthritis (0.4%) (TABLE). In the diagnosis of SpA, age was 39.7(12) years, ESR 37.4mm1sth, CRP 3.15mg/dL, DAS28 3.01 and BASDAI 4.9. Entesitis was present in 28.9% and 23.2% presented dactylitis. At the final study visit, the average duration of the SpA was 158(106.7) months. In 130 patients (59.8%) one EAM was observed, and two in 17 patients (6.9%).

Ps was observed in 102 patients (41.5%) after a mean development of the SpA of 241.4(163) months. In 20 cases, Ps was paradoxical (55% with adalimumab and 15% infliximab). The most frequent form was plaques (75.5%) and palmoplantar localization (29.7%). Uveitis was observed in 41 patients (16.7%) after a mean development of the SpA of 109.5(73) months. The most frequent associations of uveitis were with AS (80.5%), men (70.7%) and HLAB27+ (87.8%). The pattern was anterior (100%), unilateral (87.8%) and acute (92.7%). 14 patients (34.1%) were with BT (35.7% etanercept, 28.6% infliximab, 21.4% adalimumab). The incidence rate was 5.5 cases of uveitis/100 person-years of follow-up. We found IBD in 21 patients (8.5%) after a mean development of the SpA of 165(118.1) months. Three of the 21 presented it with BT (2 etanercept and 1 infliximab). Other MEAs were observed in 25.6%: osteoporosis (20.6%), cardiac arrhythmias (15.7%) and nephropathy (16%). A CVE was observed after a mean period of SpA of 133(115) months in 6.9% of the patients with an average CRP of 1.64 mg/dL. Neoplasms were observed in 7.3% of the patients (66.7% were solid tumors (58.3% urothelial and 25% breast) and 27.8% lymphoproliferative).

Conclusion: The AS and the PsA were the most frequent SpA in our series. The appearance of at least one EAM was observed in 60% of the patients, being a significant proportion (46.3%) before the diagnosis of SpA. The frequency of CVE and neoplasm seems similar to the population.

TABLE. SUBTYPES OF SpA AND ASSOCIATION WITH MEAs

	MEN/ WOMEN	AGE (average in years)	HLA- B27+	FAMILY HISTORY	UVEITIS		PSORIASIS		IBD (CD/AA/UC)	
					N	PREV/SIMUL/AFTER	N	PREV/SIMUL/AFTER	n	PREV/SIMUL/AFTER
AS (n=125)	102/23	46.9	113	40	33 (26.4%)	1/1/22	10 (8.0%)	1/0/9	34 (27.2%)	1/0/9
PsA (n=104)	76/28	45.7	21	8	6 (5.8%)	0/0/6	91 (86.2%)	83/6/22	2 (1.9%)	0/0/2
USpA (n=17)	3/14	39.4	6	0	3 (17.6%)	0/0/3	1 (5.9%)	0/0/1	2 (11.8%)	0/0/2
nr-axSpA (n=8)	2/6	33.7	3	1	1 (12.5%)	0/0/1	0		0	
ESpA (n=3)	3/0	36.7	0	0	0		0		3 (100%)	2/1/0
ReA (n=1)	1/0	28	0	0	0		0		0	
TOTAL 246	188/58 (76.4%/23.6%)	46.8	143 (57.7%)	48 (19.5%)	43	1/1/22 (23.2%/2.3%/74.5%)	101	84/6/10 (82.7%/5.9%/11.4%)	41	1/0/12 (2.4%/0%/77.6%)

AS: ankylosing spondylitis, PsA: psoriatic arthritis, USpA: undifferentiated spondylarthritis, nr-axSpA: non-radiographic axial spondylarthritis, ESpA: enteropathic spondylarthritis, ReA: reactive arthritis, CD: Crohn's disease, UC: ulcerative colitis, PREV/SIMUL/AFTER: before the diagnosis of SpA simultaneously/after

Disclosure: I. Calvo Zorrilla, None; E. Guerrero Basterretxea, None; O. Ibarguengoitia, None; D. Montero, None; M. L. Garcia Vivar, None; E. Ruiz Lucea, None; I. Torre Salaberri, None; O. B. Fernandez Berrizbeitia, None; J. M. Blanco Madrigal, None; A. R. Inchaurre Pellejero, None; C. E. Perez Velasquez, None; N. Rivera-García, None; M. J. Allande Lopez Linares, None; I. Gorostiza-Hormaetxe, None; E. Galíndez Agirregoikoa, None.

Liver Enzyme Elevation in Patients with Ankylosing Spondylitis Treated with TNF Inhibitor: A Single-Center Historical Cohort Study

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Background/Purpose: TNF inhibitors have been known to cause liver enzyme elevation in rheumatologic disease. However, liver enzyme elevation could be affected easily by other causes including concomitant medications and underlying liver disease. In ankylosing spondylitis (AS), there has been little analysis related to the study of liver enzyme elevation. The use of disease-modifying anti-rheumatic drugs (DMARDs) for treating AS has become less common after the introduction of TNF inhibitor treatment. Therefore, we identified the incidence and risk factors of liver enzyme elevation after TNF inhibitor exposure in patients with AS.

Methods: Retrospectively, we collected 363 AS patients who had normal liver enzyme levels before treatment with TNF inhibitor in a tertiary hospital from Jan. 2003 to Dec. 2017. Patients did not have evidence of viral or alcoholic liver disease before treatment with TNF inhibitor. TNF inhibitor medications included adalimumab, etanercept, infliximab, and golimumab. Clinical, laboratory and medication data were collected from the electronic medical records. Liver enzyme elevation was defined as aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels $>1\times$ upper limit of normal (ULN) and consecutively elevated for two or more visits without evidence of new exposure to hepatotoxic drugs. The Cox proportional hazards model was used to evaluate hazard ratio (HR) with 95% confidence interval (CI) for liver enzyme elevation.

Results: The incidence of liver enzyme elevation was 23.7% (86/363). AST and/or ALT elevation $>2\times$ ULN occurred in 37.2% (32/86) of patients with liver enzyme elevation. The median duration of TNF inhibitor exposure before liver enzyme elevation was 3.72 months (IQR 1.77-12.51). There was no difference in the occurrence of liver enzyme elevation in the DMARDs and TNF inhibitor users compared with TNF inhibitor alone users (24.5% vs 22.9%, $p=0.718$). In multivariable analysis, the HRs for liver enzyme elevation were 3.41 (95% CI 1.44-8.06) for males, 3.02 (95% CI 1.68-5.43) for fatty liver disease, and 2.54 (95% CI 1.54-4.19) for hyperlipidemia. Among TNF inhibitors, infliximab was weakly associated with liver enzyme elevation compared with adalimumab, etanercept, and golimumab (HR=0.75, 95% CI 0.59-0.96). Among patients with liver enzyme elevation, 13 patients switched to another TNF inhibitor during the follow-up period. The normalization of the liver enzyme levels after switching was observed in four patients.

Conclusion: Liver enzyme elevation was observed in approximately a quarter of AS patients after treatment with TNF inhibitors. Male gender, fatty liver disease, and hyperlipidemia were independent risk factors for liver enzyme elevation. Switching to another TNF inhibitor had limited effect on normalization of the liver enzyme levels.

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Malignancy in Psoriatic Disease

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SESSION INFORMATION

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Background/Purpose: There are conflicting data between studies of psoriasis and psoriatic arthritis (PsA), and there have been recent concerns about the potential of anti-TNF agents to facilitate malignancy. We aimed to estimate the prevalence and incidence of malignancy and its types in PsA and psoriasis without arthritis (PsC) patients, in comparison to the general population, and to identify the predictive factors for developing cancer in psoriatic disease (PsD).

Methods: Patients with PsA have attended the PsA Clinic and have been followed prospectively since 1978. Patients with PsC have been assessed by a rheumatologist to confirm the absence of PsA and have been followed since 2006. Patients have been evaluated at 6-12 month intervals according to a standard protocol which includes demographics, lifestyle habits, medical history, co-morbidities, and disease-related outcomes. Malignancies are recorded prospectively. In addition, a linkage with Cancer Care Ontario and the Death Registry was carried out to confirm the identification of malignancy and the type of malignancy to the end of December 2016. Non- melanoma skin cancers were not included. Descriptive statistics are provided. Standardized incidence ratios (SIR) were calculated for overall cancers and by sex. Multistate analysis was performed.

Results: 2124 patients (PsA and PsC) were included in the study of whom, 235 developed cancer (11%). 168 patients developed cancer after first clinic visit and are included in this report. Overall malignancy SIR is 0.89 (0.74, 1.07), SIR for females is 1.13 (0.87, 1.45), and for males 0.72 (0.55, 0.94). The most common malignancies were skin, breast, and male reproductive system. No predictor for malignancy was identified for PsD overall nor for PsA or PsC individually.

Conclusion: In this long-term prospective follow up of patients with PsA and PsC the malignancy risk is not increased. No predictors for malignancy could be identified. In particular there was no increased risk associated with biologics use.

Table 1 **Demographic and disease features by groups**

demographics	PsA				PsC			
	malignancy group		no malignancy group		malignancy group		no malignancy group	
	(N=148)		(N=1267)		(N=20)		(N=622)	
Age**	50.8	(11.7)	43.2	(12.9)	56	(9.9)	45.5	(13.5)
AGE_PS**	33.3	(15.5)	27.6	(14.2)	41.9	(17.5)	29.8	(15.7)
AGE_PSA**	42.9	(13)	37.1	(13.4)				
Smoker*	61	(42%)	491	(39%)	16	(80%)	308	(50%)
Alcohol use*	45	(56%)	560	(60%)	14	(70%)	424	(69%)
Married*	63	(43%)	605	(48%)	8	(40%)	338	(54%)
Employed*	55	(37%)	670	(53%)	14	(70%)	474	(76%)
Education ³ college*	60	(41%)	671	(53%)	17	(85%)	480	(77%)
Deceased*	58	(39%)	132	(10%)	4	(20%)	9	(1%)
Gender*								
. FEMALE	72	(49%)	546	(43%)	11	(55%)	262	(42%)
. MALE	76	(51%)	721	(57%)	9	(45%)	356	(58%)
Disease features								
BSA**	1	(6.9)	2.1	(8.1)	4.6	(6.5)	5.2	(10.1)
PASI**	3.1	(6.3)	3.9	(7.0)	4.9	(4.5)	5.7	(6.1)
DAMGTOT**	3.5	(8.1)	2.4	(6.4)	0.3	(0.9)	0	(0.4)
AJTOT**	9.8	(9.0)	9.4	(10.1)	0.2	(0.7)	0.1	(0.7)
Depression*	5	(3%)	94	(7%)	4	(20%)	47	(8%)
Obesity*	8	(36%)	177	(35%)	6	(32%)	160	(28%)
Cardio Vascular Disease*	5	(3%)	21	(2%)	2	(10%)	15	(2%)
Diabetes*	11	(9%)	67	(6%)	3	(15%)	41	(7%)
Dactylitis*	49	(33%)	343	(27%)	0	(0%)	1	(0%)
Enthesitis*	17	(11%)	225	(18%)	1	(5%)	7	(1%)
Inflammatory Back pain*	11	(7%)	219	(17%)	2	(10%)	15	(2%)
Axial*	31	(23%)	241	(22%)	1	(33%)	0	(0%)

* number of cases (%)

** mean (st.d)

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Atherosclerotic Cardiovascular Disease in Psoriatic Arthritis: Evaluation of Risk Factor Management and Use of Aspirin and Statin for Prevention in a Primary Care Setting

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Background/Purpose: There is accumulating evidence that shows an increased prevalence of atherosclerotic cardiovascular disease (ASCVD) risk factors among the psoriatic arthritis (PsA) population. The aim of this study is to assess the ASCVD morbidity in PsA and the management of this group's ASCVD risk according to national guidelines in the primary care setting.

Methods: A retrospective study at a Veterans Affairs Hospital involving PsA patients (n=99) and controls (n=99) without autoimmune diseases was performed. The groups were matched on age, sex, race, BMI and ASCVD risk factors (hypertension, diabetes, and hyperlipidemia). Their ASCVD risk was evaluated using the American College of Cardiology/American Heart Association's (ACC/AHA) ASCVD risk score. The odds ratio (OR) for myocardial infarctions (MI), congestive heart failure (CHF), and cerebral vascular accidents (CVA) were calculated. The yearly ASCVD management outcomes in a primary care setting, averaged over five years, were evaluated according to the frequency of primary care provider (PCP) visits, laboratory checks for Hgb A1c and lipid profile, non-pharmacological ancillary referrals, and use of cardio-protective supplements like niacin and fish oil. The appropriate statin intensity prescribed, and the use of aspirin (ASA) and statin for primary and secondary ASCVD prevention according to the US Preventative Services Task Force (USPSTF) and ACC/AHA guidelines were also evaluated.

Results: PsA and controls have an ASCVD risk score of 23.8% and 17.1% (p=0.003). PsA patients have twice the risk for developing ASCVD events (OR 2.18; 95% CI 1.19 to 3.98). CHF (OR 4.17; 95% CI 1.48 to 11.75) was the most likely event to develop when compared to CVA (OR 2.03; 95% CI 0.82 to 5.03) or MI (OR 1.72; 95% CI 0.89 to 3.29). PsA patients had similar, if not worse, average yearly PCP visits (1.0 vs 1.4), A1c checks (2.3 vs 1.2), and lipid panel checks (1.2 vs 1.2). Fewer PsA patients received non-pharmacological ancillary referrals (6% vs 69%) and cardio-protective supplements (7% vs 11%). In PsA patients, ASA was underutilized for primary (0% vs. 26%; p=0.018) and secondary prevention (52% vs. 60%; p=0.25). Similarly, statin therapy was underutilized (37% vs. 60%; p=0.006) (40% vs. 86%; p=0.009) and the statin intensity prescribed was often inappropriate (28% vs 63%; p=0.0001).

Conclusion: PsA patients have an increased risk for developing ASCVD and yet, receive worse risk factor management by PCPs. The use of ASA and statin is underutilized in PsA, and the statin intensity prescribed to this group is inadequate according to current national guidelines. Additional studies are warranted to elucidate whether shifting the responsibility of managing ASCVD risk from PCPs to rheumatologists, or providing greater education to PCP on this topic could improve ASCVD outcomes in the PsA population.

Disclosure: L. Truong, None; N. Ridolfi, None; M. Wong, None.

Bone Mineral Density and Serum Biomarkers of Bone Turnover in Ankylosing Spondylitis Patients Treated with Secukinumab: 2-Year Data from the Pivotal Phase 3 Study

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Background/Purpose: Low bone mass is common in ankylosing spondylitis (AS) and patients (pts) with AS have an increased risk of bone fracture.¹⁻³ Treatment of AS pts with TNF inhibitors has resulted in bone mineral density (BMD) increases;^{4,5} however, this has not been studied for IL-17A inhibitors yet. This is a *post hoc* analysis of the pivotal MEASURE 1 study⁶ with secukinumab 150 mg (approved dose for AS), in which changes in BMD and bone turnover biomarkers from baseline were assessed over 2 years.

Methods: A total of 104 pts originally randomized to the secukinumab 150 mg group with baseline BMD and at least one post-baseline lumbar spine BMD value at Week 52 or 104 were included in the analysis. BMD was assessed by dual-energy X-ray absorptiometry of the lumbar spine, total hip, and femoral neck at baseline, with the change from baseline in group mean calculated for the 150 mg group at Weeks 52 and 104. Additionally, to account for the variability in baseline BMD, the mean of individual percent changes in BMD at the lumbar spine, total hip, and femoral neck at Weeks 52 and 104 was also calculated. Bone turnover biomarkers (osteocalcin, procollagen type 1 N-terminal propeptide, procollagen-1 carboxy-terminal peptide, bone specific alkaline phosphatase, osteoprotegerin, sclerostin, and type I collagen C-telopeptides) were assessed at baseline, Weeks 52 and 104. Descriptive statistics were used to examine changes over time.

Results: At baseline, 66% were male pts and 34% female, with a mean age of 40.3 ± 12.3 years. Change from baseline in mean values for the 150 mg group at Weeks 52 and 104 for BMD (lumbar spine, total hip, and femoral neck) and bone turnover biomarkers are shown in the **Table**. The mean of individual BMD percent changes at Week 52 were 2.6% for lumbar spine, 0.9% for total hip, and 0.8% for femoral neck. Corresponding changes at Week 104 were 4.7% for lumbar spine, 0.5% for total hip, and 0.2% for femoral neck.

Conclusion: BMD increased over 2 years in AS patients treated with secukinumab 150 mg, with more pronounced increases observed in the lumbar spine. No consistent pattern was observed in the changes in bone turnover biomarkers through 2 years of treatment, although levels of the bone resorption biomarker Type I collagen C-telopeptides remained stable. References: 1. Davey-Ranasinghe N, Deodhar A. *Curr Opin Rheumatol*. 2013;25:509-16; 2. Malochet-Guinamand S, et al. *BMC Musculoskelet Disord*. 2017;18:357; 3. Ulu MA, et al. *Chin Med J (Engl)*. 2014;127:2740-7; 4. van der Weijden MA, et al. *J Rheumatol*. 2016;43:758-64; 5. Li H, et al. *J Rheumatol*. 2015;42:1413-7; 6. Baeten D, et al. *N Engl J Med*. 2015;373:2534-48.

Table: Summary of results

	Baseline, Mean (SD)	Mean change from baseline in the 150 mg group	
		Week 52, Mean (SD)	Week 104, Mean (SD)
BMD (g/cm ²)			
Lumbar spine	n = 104 1.026 (0.20)	n = 104 0.023 (0.05)	n = 61 0.042 (0.061)
Total Hip	n = 96 0.902 (0.16)	n = 96 0.007 (0.025)	n = 59 0.005 (0.035)
Femur Neck	n = 96 0.819 (0.17)	n = 96 0.005 (0.042)	n = 59 0.001 (0.036)
Bone turnover biomarkers			
Anabolic biomarkers			
Osteocalcin (ug/L)	n = 99 21.84 (7.56)	n = 95 1.53 (6.58)	n = 71 -0.39 (7.13)
Bone specific alkaline phosphatase (U/L)	n = 100 25.01 (8.24)	n = 96 9.07 (12.89)	n = 73 -2.66 (6.54)
Procollagen type 1 N-terminal propeptide (ug/L)	n = 99 50.76 (20.80)	n = 95 -1.81 (15.98)	n = 71 1.79 (21.97)
Procollagen-1 carboxy-terminal peptide (ug/L)	n = 100 107.25 (46.83)	n = 96 -5.73 (47.13)	n = 73 10.04 (51.53)
Bone resorption biomarkers			
Type I collagen C-telopeptides (ug/L)	n = 99 0.42 (0.20)	n = 94 -0.01 (0.15)	n = 71 -0.03 (0.14)
Other biomarkers			
Sclerostin (pmol/L)	n = 73 21.66 (8.17)	n = 63 0.05 (6.90)	n = 52 2.38 (6.52)
Osteoprotegerin (pmol/L)	n = 98 4.13 (1.50)	n = 93 -0.91 (1.20)	n = 71 0.49 (1.53)

Data presented as observed. The total number of pts who had baseline BMD plus at least one post-baseline lumbar spine BMD value (at Week 52 or 104) was 104. n, reflects the number of evaluable pts for each parameter at a particular visit. SD, standard deviation

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Depression and Anxiety Reduce Probability of Achieving a State of Minimal Disease Activity in Patients with Psoriatic Arthritis

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SESSION INFORMATION

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Background/Purpose: Depression and/or anxiety are comorbidities associated with psoriatic arthritis (PsA) that may affect treatment response. We aimed to determine whether the presence of depression/anxiety is associated with lower probability of achieving minimal disease activity (MDA) in patients with PsA.

Methods: Patients with PsA from a large cohort evaluated at 6-12-month intervals according to a standard protocol were studied. Those with a minimum number of 2 visits between 2008 and 2017 were eligible for this study. Given the lack of a formal psychiatric assessment, patients were classified as having depression/anxiety based on 3 definitions: 1) if they scored ≤ 38 on the Mental Component Summary of the SF-36 questionnaire (Definition 1); 2) if they scored ≤ 56 on the Mental Health subscale (Definition 2); and 3) if the physician reported a diagnosis of depression/anxiety in the PsA clinic protocol (Definition 3). The primary outcome was the achievement of sustained MDA, defined as meeting 5 of the 7 following: tender joint count ≤ 1 , swollen joint count ≤ 1 , tender enthesal points ≤ 1 , Psoriasis Activity and Severity Index ≤ 1 or Body Surface Area $\leq 3\%$, patient pain visual analogue scale (VAS) ≤ 20 , patient global disease activity VAS ≤ 20 ; Health Assessment Questionnaire ≤ 0.5 , for at least two consecutive visits. Univariable and multivariable proportional odds discrete time to event analyses were conducted to identify predictors for sustained MDA.

Results: 743 patients were included in the study (Table 1). The total number of patients identified as having depression/anxiety according to the 3 definitions was: Definition 1- 331 (44.54%), Definition 2- 364 (48.99%), and Definition 3- 211 (28.39%). A total of 337 patients (45.35%) failed to achieve sustained MDA during follow-up. The presence of depression/anxiety was associated with reduced probability of achieving sustained MDA in the multivariable regression analysis (reduced model), (OR 0.29 $p < 0.0001$ [Definition 1], OR 0.33 $p < 0.0001$ [Definition 2] and OR 0.44 [Definition 3] $p < 0.0001$). Male sex and daily alcohol intake was associated with a higher probability of achieving sustained MDA, whereas Charlson Comorbidity index reduced the probability. Similar results were observed when using the definitions 2 and 3 for anxiety/depression.

Conclusion: The presence of anxiety/depression reduces the probability of achieving sustained MDA in PsA. Comprehensive management of PsA thus should include measures for addressing these comorbidities.

Table 1 Descriptive statistics of baseline demographic and disease features (N=743)

Demographics	Statistics	
Age of PsA**	38.3	(13.8)
Age at baseline visit**	50.2	(13.2)
Sex (male)*	419	(56%)
Employed*	457	(62%)
Education ³ college*	546	(73%)
Married*	484	(65%)
Daily alcohol use*	407	(55%)
Disease features		Statistics
Active (swollen or tender) joints**	5.8	(8.7)
Damaged joints**	5.8	(11.3)
Body Surface Area affected by psoriasis**	4.8	(11.5)
PASI**	4.0	(6.3)
Pain score VAS**	32.9	(27.4)
HAQ**	0.5	(0.6)
Patient global assessment score VAS**	4.3	(2.7)
Sacroiliitis (NY criteria)*	184	(30%)
Arthritis Mutilans*	75	(12%)
Enthesitis*	131	(18%)

Charlson Comorbidity index**	0.8	(0.9)
Body Mass Index**	21.3	(14.3)
Obesity*	211	(28%)
Treatment with DMARDs*	394	(53%)
Treatment with biologics*	200	(27%)

*number of cases (%) **mean (st.d)

Table 2 Univariable and Multivariable analyses for sustained MDA, adjusted by age, sex obesity, and smoking

Univariable analysis			Multivariable analysis			
Variable	Odds Ratio	p-value	Full Model		Reduced Model	
			Odds Ratio	p-value	Odds Ratio	p-value
Depression/anxiety (Def 1)	0.284	<0.0001	0.299	<.0001	0.297	<0.0001
Charlson Comorbidity index	0.694	<0.0001	0.734	<.0001	0.733	<0.0001
Daily alcohol intake	1.958	0.0002	1.686	0.0050	1.754	0.0023
DMARDs	0.771	0.0176	0.849	0.1468		
Biologic treatment	0.835	0.0946	1.017	0.8770		
Married	1.211	0.0961	1.132	0.2947		
Sacroiliitis (NY criteria)	1.243	0.103				
Damaged joint count	1.005	0.3344				
Arthritis mutilans	0.955	0.7973				
Adjusted for						
Smoking	0.940	0.5598	1.011	0.9207	1.006	0.9607
Age	0.994	0.1496	1.000	0.9977	1.001	0.9146
Obesity	0.760	0.0152	0.907	0.4096	0.91	0.4243
Sex (male vs female)	1.551	<0.0001	1.385	0.0037	1.409	0.0021

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Abstract Number: 1599

Performance of Referral Strategies for Spondyloarthritis: A Population-Based Nationwide Study

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Background/Purpose: Several strategies have been proposed to promote early referral of patients with SpA, but consensus on the 'best' strategy is yet to be achieved. Moreover, few studies compared referral strategies (RS) head-to-head and none has neither evaluated these in a 'nationwide' setting (external validity) nor assessed the entire spectrum of SpA (i.e. ax SpA and peripheral SpA). We aimed to evaluate the performance of the screening strategy for SpA of a nationwide epidemiological study(EpiReumaPt), as compared to previously proposed RS.

Methods: EpiReumaPt was a three-stage national health survey (2011-2013) where, in the first phase, 10,661 adult participants were randomly selected and interviewed using a structured face-to-face questionnaire that included screening for rheumatic diseases (RD),such as SpA. In the second phase, positive screenings for ≥1 rheumatic complaint plus 20% negative screenings were invited for an assessment by the rheumatologist. Finally, 3 rheumatologists revised all the information and defined the final diagnosis by consensus. All participants of the second phase were included (N=3,877). Each RS (table) was tested against the SpA revised diagnosis using the following metrics: sensitivity, specificity, positive predictive value (PPV), and post-test probability of disease given a negative test (1-negative predictive value). RS with an imaging(e.g. MRI) or laboratory component (e.g. CRP, HLA-B27) were modified (by excluding these components) given limited data obtained in the survey (table). A weighting factor was used to take the survey design into account.

Table. Performance of the referral strategies against the rheumatologist clinical diagnosis (N=3,877; pre-test probability: 1.6% = weighted national SpA prevalence)

	Sensitivity (%)	Specificity (%)	PPV (%)	1-NPV (%)
ASAS	85.4	38.8	2.2	0.6
EpiReumaPt	72.1	67.6	3.5	0.7
CafaSpA one	56.3	69.7	2.9	1.0
Brandt I	49.2	79.3	3.7	1.0
Braun I/II	47.5	78.7	3.5	1.1
MASTER	36.7	87.7	4.6	1.2
Brandt II	27.7	92.4	5.6	1.3
Herrmann	22.4	93.2	5.1	1.3
CafaSpA two	15.2	95.2	4.9	1.4
Braun 2 step	15.1	95.7	5.3	1.4
Brandt III	7.9	98.4	7.6	1.5

ASAS (21/54): IIP (ASAS definition), good response to NSAIDs, family history of SpA, peripheral manifestations (arthritis, enthesitis and/or dactylitis), extra-articular manifestations (uveitis, psoriasis and/or IBD); EpiReumaPt (21/54): previous SpA/PSA diagnosis, IIP ($\geq 3/8$ features), CRP (≥ 3 months) starting <45 years and $\geq 1/6$ SpA features, dactylitis, enthesitis; CafaSpA one (21/34): IIP (ASAS definition), good response to NSAIDs, family history of SpA; CafaSpA two (22/34): see CafaSpA one; Brandt I ($\geq 1/3$): IIP (morning stiffness ≥ 30 min, pain at night/early morning, improvement by exercise; 21/31); Brandt II ($\geq 1/1$): 22/3 IIP features (see Brandt I); Brandt III ($\geq 1/1$): 21/3 IIP features (see Brandt I); Braun I/II ($\geq 2/5$): start IIP ≥ 35 years, waking second half of the night, alternating buttock pain, improvement by movement, not rest; MASTER ($\geq 2/3$): IIP (morning stiffness ≥ 30 min, improvement exercise, not rest, swimming in the night because of IIP), good response to NSAIDs, family history of AS; Herrmann (21/31): IIP (Gellin's criteria); Braun 2 step ($\geq 2/3$): psoriasis, alternating buttock pain, improvement BP by exercise; HEA-827 excluded from ASAS, Brandt I-III and Braun 2 step; elevated CRP/ESR excluded from ASAS.

Results: From the total 3,877 participants, 92 received a SpA diagnosis [weighted prevalence:1.6% (95%CI: 1.2; 2.1)], 3,107 other RD diagnosis [e.g. knee osteoarthritis(31%)] and 678 no RD diagnosis. The ASAS RS was the most sensitive (85%) followed by the EpiReumaPt strategy (72%) (Table). The ASAS and EpiReumaPt RS had the lowest post-test probabilities of SpA in the presence of negative screening(0.6% and 0.7% respectively), thus, yielding a marked decrease in the probability of disease if negative [(1.6-0.6)/1.6*100=63%; (1.6-0.7)/1.6*100=56% respectively). On the other hand, the likelihood of SpA increased by 38% (2.2-1.6)/1.6*100) and 119% (3.5-1.6)/1.6*100) in case of a positive ASAS and EpiReumaPt RS, respectively. Brandt III was the least sensitive strategy in this study and not contributive to excluding SpA (1-NPV: 1.5%; pre-test probability: 1.6%), but expectedly increased the likelihood of SpA by 3.8 times if positive. The performance of the remaining RS is described in the table.

Conclusion: For the first time, a wide range of SpA RS were tested in a population-based setting where the ASAS and EpiReumaPt RS were shown to be the most sensitive. Our data suggest that these strategies can be effectively used as screening tools for SpA especially when laboratory and imaging data are not available.

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Abstract Number: 1600

Psychometric Properties of the Assessment of SpA International Society Health Index in Patients with Active As/Radiographic Axial SpA in a Phase 3 Clinical Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

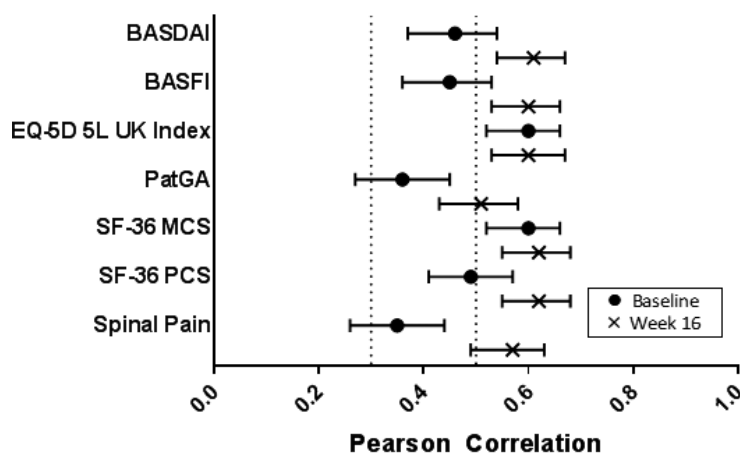
Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The Assessment of SpA international Society Health Index (ASAS HI) was developed to assess function, disability, and health in patients (pts) with SpA. This is the first time that the ASAS HI has been included in a Phase 3 clinical study. Psychometric properties of the ASASHI in pts with active radiographic axial SpA (r-ax SpA) in a Phase 3 study of ixekizumab, an IL-17A monoclonal antibody (COAST-V [NCT02696785]) are presented.

Methods: The ASAS HI questionnaire consists of 17 items, total score ranging from 0 (good health) to 17 (poor health). The psychometric properties of the questionnaire, including test-retest reliability, convergent and discriminant validity, as well as responsiveness, were evaluated using pooled data from 4 treatment groups (placebo, adalimumab 40 mg every 2 weeks, and ixekizumab 80 mg every 2 or 4 weeks). COAST-V enrolled biologic DMARD-naïve adults with active r-ax SpA per ASAS criteria (sacroiliitis defined centrally by modified New York Criteria and ≥ 1 SpA feature), BASDAI ≥ 4 , back pain ≥ 4 , and inadequate response or intolerance to NSAID therapy.

Figure. Construct validity.



Magnitude of correlation is presented regardless of direction. Thresholds for moderate (>0.3) and high (>0.5) correlations are based on Cohen (1988).^{*} Abbreviations: MCS = mental component score; PatGA = patient's global assessment of disease activity; PCS = physical component score; SF-36 = 36-item short-form health survey ^{*} Cohen, J. (1988). Statistical power analysis for the behavioral sciences (2nd ed.). New Jersey: Lawrence Erlbaum.

Results: A total of 341 pts were randomized at Week 0. Mean (SD) ASAS HI score at baseline in the pooled group was 8.05 (3.6). Test-retest reliability of ASAS HI between screening and baseline was evidenced by intraclass correlation (0.76). Construct validity analyses demonstrated that the ASAS HI score is moderately correlated with Spinal Pain, Short-Form 36 physical and mental component scores, EQ-5D 5-Level UK Population-based Index, Patient's Global Assessment, BASDAI, and BASFI at baseline ($|r| > 0.30$, Figure [circles]) and strongly correlated at Week 16 ($|r| > 0.50$; Figure [crosses]). Known-group validity of ASAS HI was demonstrated by significant difference among ASDAS categories at baseline and Week 16 ($p < .001$ for all comparisons). Greater improvements in disease activity were associated with greater improvements in ASAS HI scores at Week 16 (Table). Changes in ASAS HI from baseline at Week 16 were highly correlated with ASDAS, BASDAI, and BASFI changes (all correlations $> .50$).

Conclusion: The ASAS HI demonstrated reliability, construct validity, and responsiveness in adults with r-ax SpA, supporting measurement properties of this instrument in an external study. Based on its content validity, the data suggest that the ASAS HI provides additional information beyond core disease activity and response criteria traditionally used in randomized clinical studies. This includes a balanced characterization of treatment effects from the patient perspective.

Table. Association between ASAS HI Change from Baseline and Disease Activity at Week 16 (Pooled Treatment Groups)

	ASAS20 Nonresponder	Patient Achieving ASAS20, But Not ASAS40	ASAS40 Responder
N	143	67	130
ASAS HI (LSM [SE])	-0.7 (0.2)	-1.6 (0.3)*	-4.2 (0.2)***,§
N	171	101	68
ASAS HI (LSM [SE])	-0.9 (0.2)	-2.5 (0.2)***	-4.9 (0.3)***,§
N	226	114	
ASAS HI (LSM [SE])	-1.2 (0.2)	-4.3 (0.2)***	

ASAS HI = Assessment of SpA International Society Health Index; ASDAS = AS Disease Activity Score; CII = clinically important improvement; LSM = least-squares mean; MI = major improvement.

* $p < .05$; ** $p < .001$ versus lowest response group.

§ $p < .001$ versus middle response group.

Note: An analysis of covariance model with change in ASAS HI score as dependent variable and clinical outcome (ASAS, ASDAS, or BASDAI50) response and baseline ASAS HI as independent variables was applied. Post hoc comparison was conducted with Scheffe's correction.

Disclosure: U. Kiltz, AbbVie Inc., 2, 5, Chugai, 2, 5, Eli Lilly and Co., 2, 5, Grunenthal, 2, 5, Janssen, 2, 5, MSD, 2, 5, Novartis, 2, 5, Pfizer, Inc., 2, 5, Roche, 2, 5, UCB, Inc., 2, 5; D. van der Heijde, Imaging Rheumatology BV, 3, AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Daiichi, Eli-Lilly, Galapagos, Gilead, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi and UCB Pharma, 5; A. Boonen, Eli Lilly and Co., 5; L. S. Gensler,

AbbVie Inc., 2, Amgen Inc., 2, Novartis, 2, 5, UCB, Inc., 2, Galapagos, 5, Janssen, 5, Eli Lilly and Co., 5, Pfizer, Inc., 5; **T. Hunter**, Eli Lilly and Company, 1, 3; **Y. Dong**, Eli Lilly and Company, 1, 3; **K. Wyrwich**, Eli Lilly and Company, 1, 3; **H. Carlier**, Eli Lilly and Company, 1, 3; **J. Braun**, None.

Abstract Number: 1601

Impact of Clinical Specialty Setting and Geographic Regions on Disease Management in Patients with Psoriatic Arthritis: Results from a Cross-Sectional Observational Study in the United States

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Table 1. Current Disease Activity and Disease Burden by Clinical Specialty in US Patients with PsA from LOOP Study

Measure ^a	Rheum (n=366)	Derm (n=147)	P-value*
TJC68	8.2 (10.8)	9.9 (10.3)	.095
SJC66	3.4 (6.4)	4.3 (6.0)	.154
DAS28 (CRP)	3.2 (1.5) ^b	4.2 (2.0) ^c	.095
DAS28 (ESR)	3.1 (1.6) ^d	3.8 (2.1) ^e	.192
Enthesitis based on LEI	1.0 (1.6)	1.5 (1.8)	.005
Dactylitis count	0.6 (1.5)	0.8 (1.7)	.241
BASDAI	4.6 (3.2) ^f	4.3 (3.3) ^g	.248
BSA (%)	5.0 (10.9)	8.1 (14.5)	.024
Psoriatic nail count	1.9 (3.1) ^h	2.0 (3.1)	.734
PASI	3.0 (5.1) ⁱ	5.5 (7.9) ^j	<.001
PtGA at the time of diagnosis	6.7 (2.7) ^k	5.9 (3.1) ^l	.003
PtGA during last visit	4.7 (2.9) ^m	4.7 (3.0) ⁿ	.976
HAQ-DI	0.9 (0.7)	0.7 (0.7)	.057
SF1v2 PCS	40.6 (10.5) ^m	41.8 (10.3)	.244
SF12v2 MCS	46.9 (11.1) ^m	47.9 (11.9)	.361
DLQI	5.4 (5.9) ^o	7.8 (7.4)	<.001

*P-value from two sample t-test: Rheumatologist vs Dermatologist.

^aAll data are presented as mean (SD) unless otherwise specified.

^bn=40; ^cn=8; ^dn=67; ^en=13; ^fn=361; ^gn=144; ^hn=321; ⁱn=314; ^jn=145; ^kn=365; ^ln=138; ^mn=341; ⁿn=65; ^on=361.

BSA = body surface area with psoriasis; DAS28 (CRP) = 28-joint disease activity score based on C-reactive protein; DAS28 (ESR) = DAS28 based on erythrocyte sedimentation rate; Derm = dermatologist; DLQI = Dermatology life quality index; HAQ-DI = health assessment questionnaire – disability index; LEI = Leeds enthesitis index; MCS = mental component score; PASI = psoriasis area and severity index; PCS = physical component score; PGA = physician global assessment; PsA = psoriatic arthritis; PtGA = patient's global assessment of disease; Rheum = rheumatologist; SF12v2 = Short form 12-item health survey version 2.0; SD = standard deviation; SJC66 = swollen joint count, 66 joints; TJC68 = tender joint count, 68 joints.

Background/Purpose: Inpatients (pts) with psoriatic arthritis (PsA), early diagnosis and effective treatment has been shown to decrease functional disability and structural progression (Gladman DD, et al., *Ann Rheum Dis*, 2011; 70:2152-4). However, factors influencing treatment management decisions are poorly understood. The objective of this LOOP study was to evaluate the impact of clinical specialty setting and geographic regions on the management of pts with PsA in the United States (US).

Table 2. Current Disease Activity and Disease Burden by Geographical Regions in US Patients with PsA from LOOP Study

Measure ^a	East (n=348)	Central (n=94)	West (n=71)	P-value [*]
TJC68	8.8 (10.7)	10.6 (12.3)	5.7 (7.4)	.012
SJC66	4.0 (5.7)	4.6 (9.2)	1.2 (2.1)	.001
DAS28 (CRP)	3.5 (1.2) ^b	5.0 (2.1) ^c	2.7 (1.2) ^d	<.001
DAS28 (ESR)	3.4 (1.8) ^e	2.9 (2.0) ^f	2.6 (1.3) ^g	.188
Enthesitis based on LEI	1.3 (1.7)	0.9 (1.6)	0.4 (1.1)	<.001
Dactylitis count	0.7 (1.6)	0.9 (1.7)	0.3 (0.7)	.039
BASDAI	4.9 (3.2)	4.8 (3.2) ^h	2.7 (2.8)	<.001
BSA (%)	6.3 (12.6)	6.1 (13.8)	3.6 (5.3)	.230
Psoriatic nail count	1.9 (3.2) ⁱ	1.5 (2.6) ^j	2.6 (3.1) ^k	.103
PASI	3.8 (6.6) ^l	4.0 (6.3) ^m	3.5 (3.6) ⁿ	.884
PtGA at the time of diagnosis	6.8 (2.8) ^o	6.0 (2.9) ^p	5.6 (2.9)	<.001
PtGA during last visit	4.8 (2.9) ^q	5.4 (3.1) ^r	3.5 (2.8) ^s	.001
HAQ-DI	0.9 (0.7)	0.8 (0.7)	0.4 (0.5)	<.001
SF1v2 PCS	39.9 (9.8) ^t	40.4 (11.3)	46.5 (10.9)	<.001
SF12v2 MCS	47.1 (11.5) ^u	47.1 (10.6)	48.0 (11.7)	.829
DLQI	6.0 (6.5) ^v	6.6 (6.3) ^w	6.1 (6.0)	.753

^{*}P-value from one-way ANOVA.

^aAll data are presented as mean (SD) unless otherwise specified.

^bn=15; ^cn=8; ^dn=25; ^en=59; ^fn=4; ^gn=17; ^hn=86; ⁱn=312; ^jn=87; ^kn=69; ^ln=306; ^mn=85; ⁿn=68; ^on=345; ^pn=87

^qn=298; ^rn=57; ^sn=51; ^tn=347; ^un=90.

ANOVA = analysis of variance; BSA = body surface area with psoriasis; DAS28 (CRP) = 28-joint disease activity score based on C-reactive protein; DAS28 (ESR) = DAS28 based on erythrocyte sedimentation rate; Derm = dermatologist; DLQI = Dermatology life quality index; HAQ-DI = health assessment questionnaire – disability index; LEI = Leeds enthesitis index; MCS = mental component score; PASI = psoriasis area and severity index; PCS = physical component score; PGA = physician global assessment; PsA = psoriatic arthritis; PtGA = patient's global assessment of disease; Rheum = rheumatologist; SF12v2 = Short form 12-item health survey version 2.0; SD = standard deviation; SJC66 = swollen joint count, 66 joints; TJC68 = tender joint count, 68 joints.

Methods: LOOP was a multi-center, cross-sectional, observational study conducted across 44 sites in the US. Adult pts with a suspected or an established diagnosis of PsA who were routinely visiting a rheumatologist (rheum) or a dermatologist (derm) were eligible to participate in this study. Each enrolled pt was assessed by both rheum and derm. The association between enrolling or diagnosing clinical specialty setting or geographic regions (East, Central, and West) and time from symptom onset to PsA diagnosis and to different disease management steps were examined.

Results: Of 681 pts enrolled, 513 pts with a confirmed diagnosis of PsA were included in this analysis. Pt demographics and disease characteristics were comparable between PsA pts enrolled by rheum and derm settings. Current disease activity and disease burden were also mostly similar between rheum and derm settings (Table 1), although pts enrolled in derm setting had higher scores on skin measures and enthesitis. Interestingly, skin-related disease activity measures were similar among pts in East, Central, and West regions of the US, but there were significant differences in most other disease activity measures (Table 2). The median (95% CI) time from symptom onset to PsA diagnosis was 1.0 (0.5, 1.1) and 2.6

(1.7, 4.1) years (y) in pts enrolled in rheum and dermatology settings, respectively ($P < .001$). After PsA diagnosis, the median times to first csDMARD and to first bDMARD were 1.0 and 2.4 y, respectively. The median time from symptom onset to PsA diagnosis and from PsA diagnosis to first csDMARD and bDMARD did not differ significantly based on geographic regions.

Conclusion: The duration from symptom onset to PsA diagnosis was shorter in pts enrolled by rheumatologists compared with dermatologists. The median time was longer for treatment with first bDMARD compared with first csDMARD. There were differences in current disease activity and burden among pts based on enrolling specialty and geographic regions. Current disease activity and disease burden highlight the delay in PsA diagnosis and the need for appropriate management of PsA pts, irrespective of clinical specialty setting or geographic region.

Disclosure: P. J. Mease, AbbVie, Amgen, Bristol Myers Squibb, Celgene, Genentech, Janssen, Lilly, Novartis, Pfizer, Sun Pharma, and UCB, 2, 5, 8; C. Liu, AbbVie, Celgene, Janssen, Lilly, Novartis, Ortho, Regeneron, and Sanofi, 2, 5, 8; E. Siegel, AbbVie, Amgen, Celgene, Janssen, Lilly, Sanofi, and UCB, 2, 5, 8; H. Richmond, AbbVie Inc., 2; M. Wu, AbbVie Inc., 1, 3; L. Chen, AbbVie Inc., 1, 3; K. Douglas, AbbVie Inc., 1, 3; B. Lockshin, AbbVie, Janssen, Lilly and Novartis and research from Celgene and Strata, 2, 5, 8, Board of Directors for National Psoriasis Foundation (NPF), 6.

Abstract Number: 1602

Disease Characteristics, Quality of Life, and Work Productivity By Enthesitis Sites: Real-World Data from the US Corrona Psoriatic Arthritis/Spondyloarthritis (PsA/SpA) Registry

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Prior studies showed psoriatic arthritis (PsA) patients with enthesitis had greater disease burden than patients without enthesitis, yet it is unknown whether the impact of enthesitis differs by its location. This study compared patients with PsA who had enthesitis in different locations vs patients without enthesitis.

Methods: This study included adult patients with PsA enrolled in the Corrona PsA/SpA Registry between March 2013 and March 2018. Enthesitis at enrollment was assessed via the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index. Those with enthesitis were further classified by affected site locations as upper extremities only, lower extremities only, or both upper and lower. Enrollment demographics, clinical characteristics, treatment profile, disease activity, quality of life, and work productivity in each of the 3 enthesitis groups were compared to PsA patients without enthesitis using t tests or χ^2 tests.

Results: Of 2003 patients with PsA, 391 (19.5%) had enthesitis, among whom 80 (20.5%) had upper sites only, 137 (35.0%) had lower sites only, and 174 (44.5%) had both upper and lower sites. In patients with enthesitis, 61.5% were treated with biologics and 21.7% with csDMARD monotherapy, and there was a higher prevalence of fibromyalgia vs those without enthesitis (10.7% vs 3.4%; $P < 0.05$). Patients with lower sites only had increased prevalence of depression, and patients with upper sites only and both upper and lower sites had increased nail psoriasis compared to patients without enthesitis (**Table 1**). Regardless of enthesitis site location, patients with enthesitis had worse disease activity (modified MDA, tender and swollen joint counts, CDAI scores, DAPSA and cDAPSA scores, modified DAS28 scores, and physician global assessment) and quality of life (pain, fatigue, patient global assessment, HAQ scores, EQ VAS scores, and percentage impairment while working and overall activity impairment) than patients without enthesitis (**Table 2**). Patients with both upper and lower site involvement tended to have worse disease activity and quality of life than those with either location alone, and patients with lower sites only tended to have worse patient-reported outcomes vs patients with upper sites only (**Table 2**).

Conclusion: These results confirm the previously observed relation between presence of enthesitis and higher disease activity and worse quality of life; however, this study suggests that some aspects of disease burden may differ according to site location. Further analyses are needed to determine whether lower, upper, or specific sites have greater impact on disease burden.

Table 1. Demographic, Clinical, and Treatment Characteristics at Enrollment, Stratified by Location of SPARCC Enthesitis Sites

Characteristic*	Without Enthesitis (n = 1612)	All Patients With Enthesitis (n = 391)	Upper Sites Only (n = 80)	Lower Sites Only (n = 137)	Both Upper and Lower Sites (n = 174)
Age, years	53.9 (13.2)	52.7 (12.6)	51.8 (12.6)	50.9 (12.1) [†]	54.5 (12.7)
Female, n (%)	796 (49.9)	245 (63.0) [†]	42 (52.5)	80 (58.8) [†]	123 (71.1) [†]
White, n (%)	1467 (94.5)	355 (92.4)	73 (94.8)	123 (90.4) [†]	159 (93.0)
Patient-reported work status, n (%)					
Full time	869 (54.7)	208 (53.9)	48 (61.5)	78 (57.4) [†]	82 (47.7)
Part time	134 (8.4)	32 (8.3)	7 (9.0)	10 (7.4) [†]	15 (8.7)
Disabled	137 (8.6)	48 (12.4)	3 (3.6)	21 (15.4) [†]	24 (14.0)
Retired	346 (21.8)	70 (18.1)	14 (17.9)	18 (13.2) [†]	38 (22.1)
Other	104 (6.5)	28 (7.3)	6 (7.7)	9 (6.6) [†]	13 (7.6)
BMI, kg/m ²	31.6 (7.4)	31.6 (7.0)	30.3 (6.2)	31.2 (6.2)	32.5 (7.7)
Symptom duration, years	11.4 (10.3)	10.8 (10.1)	10.6 (10.5)	9.7 (9.3)	11.6 (10.5)
Disease duration, years	8.7 (8.9)	7.0 (8.0) [†]	6.9 (7.9) [†]	6.5 (7.7) [†]	7.4 (8.2) [†]
Physician-reported history of comorbid conditions, n (%)					
Psoriasis	1404 (87.1)	354 (90.5)	74 (92.5)	121 (88.3)	159 (91.4)
Cardiovascular disease	802 (49.8)	199 (50.9)	41 (51.3)	66 (48.2)	92 (52.9)
Hypertension	590 (36.6)	149 (38.1)	26 (32.5)	53 (38.7)	70 (40.2)
Nail psoriasis	444 (27.5)	166 (42.5) [†]	42 (52.5) [†]	43 (31.4)	81 (46.6) [†]
Hyperlipidemia	388 (24.1)	95 (24.3)	20 (25.0)	32 (23.4)	43 (24.7)
Depression	199 (12.3)	76 (19.4) [†]	11 (13.8)	36 (26.3) [†]	29 (16.7)
Fibromyalgia	55 (3.4)	42 (10.7) [†]	9 (11.3) [†]	17 (12.4) [†]	16 (9.2) [†]
History of prior biologic use, n (%)	404 (25.1)	143 (36.6) [†]	25 (31.3)	51 (37.2) [†]	67 (38.5) [†]
No. of prior biologics, n (%)					
0	1208 (74.9)	248 (63.4) [†]	55 (68.8)	86 (62.8) [†]	107 (61.5) [†]
1	267 (16.6)	91 (23.3) [†]	21 (26.3)	31 (22.6) [†]	39 (22.4) [†]
≥ 2	137 (8.5)	52 (13.3) [†]	4 (5.0)	20 (14.6) [†]	28 (16.1) [†]
History of prior csDMARD use, n (%)	369 (22.9)	132 (33.8) [†]	26 (32.5) [†]	49 (35.8) [†]	57 (32.8) [†]
Current biologic use, n (%) [‡]	939 (58.3)	240 (61.5)	46 (57.5)	91 (66.4)	103 (59.5)
Current csDMARD use only (no biologics or tsDMARDs), n (%)	442 (27.4)	85 (21.7)	19 (23.8)	21 (15.3) [†]	45 (25.9)

BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; SPARCC, Spondyloarthritis Research Consortium of Canada; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

* All values are presented as mean (SD) unless otherwise stated.

[†] P < 0.05 for comparisons vs PsA patients without enthesitis.

[‡] Not including tsDMARDs.

Disclosure: P. J. Mease, Celgene, Novartis, AbbVie, Amgen, Bristol-Myers Squibb, Lilly, Pfizer, and UCB, 2; Celgene, Corrona, Novartis, AbbVie, Amgen, Bristol-Myers Squibb, Crescendo, Genentech, Janssen, Lilly, Merck, Pfizer, and UCB, 5; AbbVie, Amgen, Bristol-Myers Squibb, Crescendo, Celgene, Genentech, Janssen, Pfizer, and UCB, 8; M. Liu, Corrona, LLC, 3; S. Rebello, Corrona, LLC, 3; W. Hua, Corrona, LLC, 3; R. R. McLean, Corrona, LLC, 3; P. Hur, Novartis Pharmaceuticals Corporation, 3; A. Ogdie, Amgen, AbbVie, BMS, Celgene, Lilly, Novartis, Pfizer, and Takeda, 5; National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases, Rheumatology Research Foundation, Pfizer, and Novartis, 2.

Table 2. Disease Activity, Quality of Life, and Work Productivity at Enrollment, Stratified by Location of SPARCC Enthesitis Sites

Characteristic*	Without Enthesitis (n = 1612)	All Patients With Enthesitis (n = 391)	Upper Sites Only (n = 80)	Lower Sites Only (n = 137)	Both Upper and Lower Sites (n = 174)
Modified MDA, n (%)	408 (30.9)	27 (8.0) [†]	6 (8.6) [†]	13 (11.0) [†]	8 (5.4) [†]
Tender joint count (0-68)	2.8 (6.0)	12.0 (12.3) [†]	8.2 (9.0) [†]	7.7 (10.2) [†]	16.9 (13.4) [†]
Swollen joint count (0-66)	1.8 (3.5)	3.7 (6.0) [†]	3.7 (6.0) [†]	4.0 (6.9) [†]	3.6 (5.2) [†]
SPARCC Enthesitis Index (1-16)	0	3.9 (3.0)	2.2 (1.2)	2.1 (1.4)	6.1 (3.0)
Dactylitis, n (%)	131 (8.1)	55 (14.1) [†]	10 (12.5)	25 (18.2) [†]	20 (11.5)
Dactylitis count (1-20)	2.2 (1.7)	2.4 (1.8)	2.2 (1.4)	3.0 (2.3)	1.8 (1.0)
CDAI	9.5 (8.3)	16.8 (11.9) [†]	14.9 (10.8) [†]	16.0 (12.1) [†]	18.4 (12.0) [†]
BSA, % affected	5.7 (11.6)	6.1 (12.1)	5.5 (8.7)	6.0 (13.0)	6.4 (12.7)
DAPSA	15.3 (13.8)	29.2 (19.6) [†]	26.9 (18.0) [†]	24.2 (19.4) [†]	34.9 (19.2) [†]
cDAPSA	12.3 (10.6)	26.1 (18.3) [†]	22.1 (16.2) [†]	22.1 (17.9) [†]	31.2 (18.5) [†]
Modified DAS28	3.1 (1.1)	4.2 (1.3) [†]	4.0 (1.3) [†]	4.0 (1.3) [†]	4.4 (1.2) [†]
Physician global assessment (VAS 0-100)	16.1 (18.4)	28.9 (21.1) [†]	24.1 (19.4) [†]	29.1 (22.2) [†]	30.9 (20.7) [†]
Patient pain (VAS 0-100)	35.8 (29.3)	52.1 (27.5) [†]	46.3 (28.5) [†]	52.6 (28.6) [†]	54.4 (25.8) [†]
Patient-reported fatigue (VAS 0-100)	38.3 (29.3)	52.5 (26.1) [†]	47.5 (30.2) [†]	52.2 (29.8) [†]	55.1 (25.5) [†]
Patient global assessment (VAS 0-100)	41.6 (31.0)	49.5 (27.6) [†]	51.9 (29.4) [†]	47.5 (26.8) [†]	49.9 (27.5) [†]
HAQ (0-3)	0.6 (0.6)	0.9 (0.7) [†]	0.7 (0.7) [†]	0.9 (0.7) [†]	1.0 (0.6) [†]
EQ VAS (0-100)	73.1 (20.9)	63.4 (22.1) [†]	66.7 (23.7) [†]	63.5 (22.8) [†]	61.9 (20.8) [†]
WPAI domains					
% Work time missed	3.8 (14.3)	6.2 (15.6) [†]	3.5 (9.9)	6.0 (17.9) [†]	8.0 (16.0) [†]
% Impairment while working	16.3 (21.6)	27.1 (25.3) [†]	25.2 (27.8) [†]	26.9 (25.5) [†]	26.6 (23.6) [†]
% Overall work impairment	17.9 (23.2)	30.5 (27.5) [†]	26.9 (29.2)	30.2 (26.6) [†]	33.2 (27.5) [†]
% Activity impairment	25.0 (27.8)	43.2 (30.4) [†]	35.8 (31.8) [†]	43.9 (29.9) [†]	46.2 (29.9) [†]
Current employment, n (%)	960 (62.2)	220 (60.1)	50 (68.5)	65 (62.5)	85 (54.1) [†]

BSA, body surface area; CDAI, Clinical Disease Activity Index; cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; DAPSA, Disease Activity Index for Psoriatic Arthritis; DAS28, Disease Activity Score using 28 joints; HAQ, Health Assessment Questionnaire; MDA, minimal disease activity; SPARCC, Spondyloarthritis Research Consortium of Canada; VAS, visual analog scale; WPAI, Work Productivity and Activity Impairment questionnaire.

* All values are presented as mean (SD) unless otherwise stated.

[†] P < 0.05 for comparisons vs PsA patients without enthesitis.

Abstract Number: 1603

Gender-Specific Differences in Chinese Patients with Ankylosing Spondylitis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Growing evidence suggests gender-specific differences in the phenotypes of ankylosing spondylitis (AS). However, a literature search failed to reveal evidence of such differences in Chinese AS patients. We aimed to assess the gender-specific associations with disease patterns of Chinese AS patients.

Methods: This study included 223/60 male/female AS patients, and 98.6% were of Han descent. All AS patients fulfilled the modified New York criteria. Structural damage of sacroiliac (SI) joints, hip joints and spine were evaluated by computed tomography (CT) scans, lumbar and cervical X-ray, respectively. Structural damage of AS was assessed by

mSASS, BASRI-SI, BASRI-spine and BASRI-hip (modified) by a trained rheumatologist and musculoskeletal radiologist with high test inter-rater reliability (average κ :87.3%). The association of gender with BASRI-spine category, expressed as odds ratio (OR) and 95% confidence interval (95% CI), was calculated using ordinal logistic regression.

Table 1. Baseline characteristics of study participants

Characteristic	Female AS Patients (n=68)	Male AS Patients (n=221)	p Value
Age (years)	57.99 (10.54)	52.79 (10.66)	0.000
BMJ (kg/m ²)	23.06 (3.43)	23.77 (8.24)	0.397
HLA-B27 (+)	48 (80%)	207 (94%)	0.000
Duration of symptoms (years)	9.22 (6.76)	10.28 (7.81)	0.272
Onset (age) (years)	5.39 (7.21)	6.32 (5.24)	0.005
Diagnostic delay (years)	3.83 (7.80)	3.76 (5.94)	0.942
Age of AS onset (years)	38.77 (10.68)	22.50 (9.40)	<0.000
Family history of AS	22 (36.67%)	41 (38.39%)	0.025
Occupation (1-2)	4 (3/14)	6 (3/34)	0.000
Ever smoking	2 (3.33%)	68 (30.99%)	<0.000
Current smoking	2 (3.33%)	65 (29.85%)	<0.000
Smoking duration	0.27 (1.32)	3.75 (7.07)	<0.000
Cigarettes per day	0.17 (2.00)	4.15 (7.74)	<0.000
ESR (mm/h)	23.37 (24.34)	21.64 (18.32)	0.366
CRP (mg/dL)	1.09 (1.83)	1.48 (2.20)	<0.000
ASDAS-CRP	1.88 (0.85)	1.79 (0.73)	0.0284
BASRI score	1.47 (2.40)	1.46 (3.64)	0.370
BASDAI score	3.11 (1.66)	3.29 (1.21)	0.3292
BASRI spine	1.32 (2.14)	2.06 (2.01)	0.0178
Right pain (VAS)	3.87 (1.80)	4.15 (1.90)	0.2502
PGA	3.80 (3.80)	4.07 (1.97)	0.4170
Modified Schober (cm)	4.49 (1.70)	3.64 (1.95)	0.3346
Chest expansion (cm)	4.79 (1.80)	4.33 (1.60)	0.2413
BASRI-SI joint (left)	3 (2.3)	3 (2.4)	0.8919
BASRI-SI joint (right)	2 (2.3)	3 (2.4)	0.8098
BASRI-SI joint (average)	2.5 (3.3)	3 (3.4)	0.0807
Asymmetric sacroiliitis	9 (13.0%)	19 (8.5%)	0.130
BASRI-hip (left)	0 (0.3)	0 (0.3)	0.0586
BASRI-hip (right)	0 (0.3)	0 (0.3)	0.0546
BASRI-hip (average)	0 (0.3)	0 (0.3)	0.1338
Hip flexion/extension	3.3 (28.89%)	76 (44.53%)	0.119

mSASS (modified spine)	9 (8.14)	9 (8.81)	0.8962	
mSASS (bathir spine)	3 (2.7)	6 (3.113)	0.6785	
mSASS (combined)	1 (0.14)	2 (0.22)	0.3277	
BASRI-overall	0 (0.3)	0 (0.3)	0.1406	
BASRI-shoulder	3 (0.2)	9 (8.7)	0.714	
BASRI-spine	4 (2.823)	4 (3.8)	0.8978	
IBD history	3 (7%)	9 (8.4%)	0.6032	
CA history	8 (13.33%)	12 (5.38%)	0.0329	
Pasture history	0 (0.0%)	1 (1.35%)	0.3664	
Medication use				
NSAID	Full	28 (48.33%)	122 (56.02%)	0.3786
	Current	34 (56.67%)	124 (56.61%)	0.8221
DMARD	Full	33 (56.33%)	125 (56.65%)	0.7519
	Current	14 (23.27%)	89 (40.97%)	0.8221
TNF- α inhibitor	Full	8 (13.0%)	41 (18.39%)	0.5435
	Current	8 (13.07%)	41 (18.39%)	0.0432
Proteasome	Full	1 (1.67%)	7 (3.15%)	0.3173
	Current	2 (3.33%)	7 (3.15%)	0.0528

Abbreviations: AS, ankylosing spondylitis; HLA-B27, human leukocyte antigen B27; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ASDAS-CRP, ankylosing spondylitis disease activity score; BASFI, bath ankylosing spondylitis functional index; BASDAI, bath ankylosing spondylitis disease activity index; VAS, visual analog scale; BASRI, Bath Ankylosing Spondylitis Radiology Index; BASRI-hip (modified) (0: normal, 1: suspicious/mild/moderate, 2: severe, 3: complete joint fusion, 4: joint replacement); BASMI, Bath Ankylosing Spondylitis Mennings Index; mSASS, modified sickle ankylosing spondylitis spine score; IBD, inflammatory bowel disease; CA, celiac disease; Occupation was categorized as without occupation (described as 0), manual occupation (described as 1) and physical occupation (described as 2). Data are expressed as either mean (standard deviation) or median (interquartile range) or count (per cent). The p value was calculated by t test or Wilcoxon rank-sum (Mann-Whitney) test or Chi-squared test, where appropriate.

Table 2. Associations of male gender with Bath Ankylosing Spondylitis Radiographic Index Spine score category, with adjustments for age or duration of ankylosing spondylitis and multivariate modeling*

Independent variable	Age-adjusted OR (95% CI)	p Value	Duration adjusted OR (95% CI)	p Value
Male	2.04 (1.15 to 3.62)	0.016	1.21 (0.70 to 2.10)	0.500
Multivariable analysis*				
Male	1.91 (0.99 to 3.69)	0.054	1.46 (0.77 to 2.75)	0.247

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval. *Additional adjustment for HLA-B27, age of AS onset, family history, occupation, smoking (ever and current), smoking duration, cigarettes per day, ESR, CRP and BASDAI. OR represents the likelihood that men were more likely than women to be in a higher BASRI-spine category than in the same or in a lower category.

Results: Female AS patients were older than males ($p=0.0003$), and they also had older age of AS onset ($p<0.0001$), a lower frequency of HLA-B27 ($p=0.018$), a higher family history of reported AS in first-degree relatives ($p=0.0025$) than male patients. Both genders had similar disease duration. Mean levels of CRP ($p<0.0001$) and ASDAS-CRP ($p=0.0284$) were significantly higher in male patients than in female patients (Table 1). As previously reported, male AS patients from

non-Chinese cohorts had more radiographic damage, more hip impact, worse function and higher diagnostic delays than female patients [PMID:20357993, 17127685, 26385369]. However, in Chinese AS patients, no gender-associated diagnostic delays or functional impairment were observed. Structural damage severity was worse among male AS patients only at the SI joint, but not at lumbar or cervical spine and hip. After adjusting for age or disease duration and other risk factors (Table 2), no gender-specific association with categorized BASRI-spine was noted (OR=1.91 or 1.46, 95% CI: 0.99 to 3.69 or 0.77 to 2.75, $p=0.054$ or 0.247).

Conclusion: In a Chinese cohort, female AS patients were observed to have later age of disease onset, but similar severe spine and hip joint structure damage and limited function as male patients. Compared with other racial groups, Chinese female AS patients may have more severe disease and worse outcome.

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Abstract Number: 1604

Impact of Time to Minimal Disease Activity and Quality of Life One Year after Diagnosis of Psoriatic Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

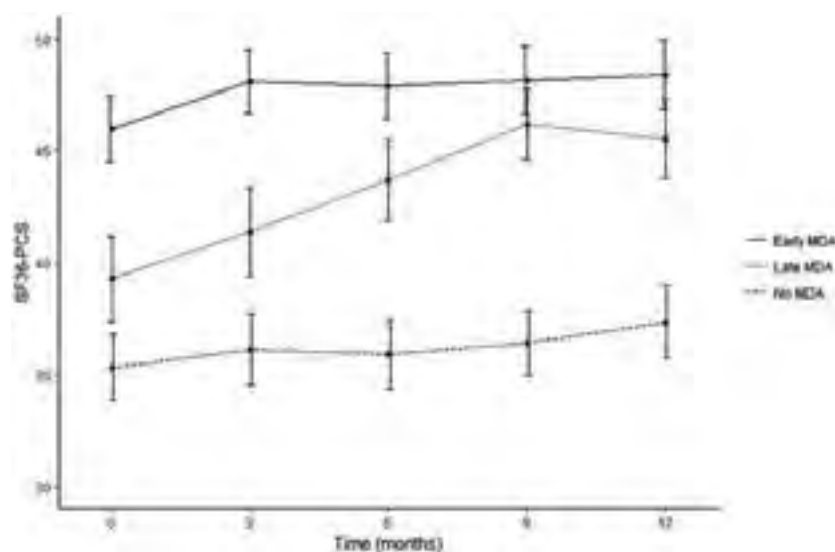
Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: From previous cross-sectional research we know that minimal disease activity (MDA) is associated with better health-related quality of life (HRQoL) in psoriatic arthritis (PsA). Whether being in MDA early is related to better outcomes is unknown. We aimed to evaluate the impact of time to MDA on HRQoL at one year follow up in patients newly diagnosed with PsA.

Methods: Data collected in the Dutch southwest early PsA cohort (DEPAR) study was used. PsA patients with a new diagnosis of PsA and not yet treated for PsA with disease-modifying antirheumatic drugs are eligible to participate. MDA status was determined every three months in the first year by trained research nurses. Short Form 36 (SF36) Physical Component Scores (SF36-PCS) and Mental Component Scores (SF36-MCS) were used to assess HRQoL.



Results: In July 2017, 296 patients had had their 1-year visit (mean age 51 years, 53% male). Of those, 96 (32%) were in MDA within three months (early MDA), 78 (26%) between 3 and 12 months (late MDA), 98 (33%) were not in MDA at any time during the first year (no MDA) and 24 (8%) patients could not be assigned to either group due to missing data. 43 early MDA patients (46%) had sustained MDA and 46 (60%) of the late MDA patients. Late MDA patients and no MDA patients had significantly higher baseline tender joint counts, enthesitis scores, and VA S scores than early MDA patients. Methotrexate was also prescribed more frequently in no MDA (81%) and late MDA (79%) groups than early MDA (62%). At baseline SF36-PCS scores were significantly lower in the late and no MDA groups, but after one year only the scores of the no MDA group were significantly lower (Figure 1).

Conclusion: HRQoL of early MDA patients and late MDA patients did not differ significantly at twelve months, but patients not in MDA in their first year after diagnosis had significantly worse HRQoL than patients that are in MDA. A quarter of patients was in MDA within three months and in total 58% within the first year.

Research support for this analysis was funded by Pfizer. The company had no role in the study design, collection of data, analysis or interpretation of data, nor in the preparation or approval of the abstract and the decision to submit the abstract

Figure 1. SF36-PCS scores in MDA groups over first year follow up

SF36-PCS: Short-Form 36 Physical Component Summary; MDA: Minimal Disease activity; Early MDA: MDA within three months; Late MDA: MDA within three to twelve months; No MDA: no MDA in first year. Data shown as mean with 95% Confidence Intervals.

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Abstract Number: 1605

Prevalence of Anterior Uveitis in Patients with Spondyloarthropathy in a Single US Academic Center: A Retrospective Study from Routine Care

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Acute anterior uveitis (AAU) is the most common extra-articular feature of spondyloarthropathies (SpA) over the course of the disease. Around 33% of patients with SpA present with AAU¹. To better characterize patients with SpA and AAU we aimed to determine the prevalence of AAU in patients with SpA seen in our clinic, and to compare demographic, clinical characteristics and treatment in patients with and without uveitis.

Methods: We conducted a retrospective study of all patients with SpA with and without uveitis seen at our rheumatology clinic between January 2016 and June 2017. Patients were identified from our rheumatology repository using ICD-10 codes (M45, M46.1, M46.8, M46.9, H20.00-02, H20.04, H20.1, H20.9, H22) and administrative claim codes for the same period of time. Charts were reviewed to confirm the diagnoses. Extracted data included patient demographics, laboratory investigations, HLA-B27 typing, current and previous treatments with nonsteroidal anti-inflammatory drugs (NSAIDs), non-biologic and biologic disease-modifying antirheumatic drugs (DMARDs). To assess disease activity, we calculated RAPID3 scores based on a Multidimensional Health Assessment Questionnaire (MDHAQ) routinely completed by our patients. RAPID3 has been previously shown to be useful in this population². Comparison between patients with and without uveitis was performed using Student's t-test for differences between means and chi² for proportions.

Results: A total of 190 patients with SpA were identified: 48% with ankylosing spondylitis (AS), 26% with psoriatic arthritis (PsA), 22% with undifferentiated SpA and 4% with SpA associated with inflammatory bowel disease (IBD). Prevalence of uveitis differed by etiology: 17% in SpA in this series, 25% in AS, 4% in PsA-associated SpA, 9.5% in undifferentiated SpA, and 57% in IBD-associated SpA (p=0.001, Table). Overall, 39.5% of patients were HLA-B27 positive, the antigen was more frequently detected in patients with uveitis than without uveitis, 69.7% and 33.1%, respectively (p<0.001), and interestingly, those with AAU had less pain (p=0.03). Delay to SpA diagnosis tended to be longer in patients with uveitis, 12.3 (11.2) versus 7.9 (9.5) years but did not reach statistical significance. There were no significant differences in age, gender, clinical, laboratory characteristics and treatment between the two groups (Table).

Conclusion: In our SpA population the prevalence of uveitis was lower than expected, and there were significant differences by underlying disease. There was a delay to diagnosis of SpA of about 8 years, which tended to be longer in patients with uveitis. New screening strategies in collaboration with ophthalmology may lead to earlier diagnosis, treatment and better patient outcomes.

References:: 1. Ann Rheum Dis 2008; 67:955-9.
2. RMD Open. 2016; 2(2): e000235).

Table: Patient Demographics and Clinical Characteristics according to presence of uveitis

	ALL N=190	Non-uveitis n = 157 (83%)	Uveitis n = 33 (17%)	p
Age, yrs. mean (SD)	45.9 (15.1)	45.5 (15.5)	47.8 (13.1)	0.43
Male, n (%)	113 (59.5%)	93 (59.2%)	20 (60.6%)	0.88
Diagnostic delay for SpA, years (SD)	7.9 (9.5)	7.2 (9.1)	12.3 (11.2)	0.09
SpA subgroup				
AS	92 (48%)	69 (75%)	23 (25%)	<0.001
PsA-Associated	49 (26%)	47 (96%)	2 (4%)	
Undifferentiated	42 (22%)	38 (90%)	4 (10%)	
IBD-Associated	7 (4%)	3 (43%)	4 (57%)	
HLA-B27 positivity, n (%)	75 (39.5%)	52 (33.1%)	23 (69.7%)	<0.001
Family History of SpA, n (%)	24 (12.6%)	17 (10.8%)	7 (21.2%)	
Enthesitis, n (%)	21 (11.1%)	19 (12.1%)	2 (6.1%)	
Peripheral Arthritis, n (%)	123 (64.7%)	103 (65.6%)	20 (60.6%)	
Abnormal CRP (>8mg/L), n (%)	61 (32.1%)	49 (31.2%)	12 (36.4%)	0.65
Imaging evidence of Sacroiliitis, n (%)	123 (64.7%)	97 (61.8%)	26 (78.8%)	0.08
RAPID3 (0-30), mean (SD)	17.4 (1.42)	18.2 (11.7)	13.7 (13.2)	0.12
Pain on a VAS (0-10), mean(SD)	4.7 (0.38)	5.1 (3.1)	3.1 (3.1)	0.03
Current treatment				
NSAIDs, n (%)	188 (98.9%)	156 (99.4%)	32 (96.9%)	0.67
Non-biologic DMARDs				
- Methotrexate	27 (14.2%)	24 (15.3%)	3 (9.1%)	0.26
- Sulfasalazine	7 (3.7%)	6 (3.8%)	1 (3%)	
- Combination	6 (3.1%)	5 (3.2%)	1 (3%)	
- Others (HCQ, leflunomide, AZA)	10 (5.3%)	8 (5.1%)	2 (6.1%)	
Biologic DMARDs				
- Adalimumab	50 (26.3%)	37 (23.6%)	13 (39.4%)	0.13
- Etanercept	33 (17.4%)	29 (18.5%)	4 (12.1%)	
- Infliximab	24 (12.6%)	20 (12.7%)	4 (12.1%)	
- Others (golimumab, secukinumab, ...)	21 (11%)	16 (10.2%)	5 (15.2%)	

Abbreviations: SpA, spondyloarthropathy; AS, ankylosing spondylitis; PsA, psoriatic arthritis; IBD, inflammatory bowel disease; CRP, C-reactive protein; NSAID, nonsteroidal anti-inflammatory drug; DMARD, disease-modifying antirheumatic drug, HCQ-hydroxychloroquine, AZA-azathioprine

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Abstract Number: 1606

The 66/68 Joint Count for the Measurement of MSK Disease Activity/ Peripheral Joint Activity in PsA: A Grappa-Omeract Working Group Initiative

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic arthritis (PsA) core domain set to be measured in randomized controlled trials (RCT) and longitudinal observational studies (LOS) was developed by Group for Research and Assessment of Psoriasis and PsA (GRAPPA) and endorsed by Outcome Measures in Rheumatology (OMERACT) in 2016. Joint counts are central to the measurement of musculoskeletal (MSK) disease activity, one of the key domains. Having reviewed the 28 as well as 76/78 joint counts, the 66/68-swollen and tender joint count (SJC66/TJC68) was identified as the target instrument for peripheral joint assessment. We assessed the domain match, feasibility, construct validity, reliability, responsiveness, discrimination and thresholds of meaning of SJC66/TJC68 in PsA to secure endorsement of this instrument for inclusion in the PsA Core Outcome Measurement Set at OMERACT.

Table. Summary of measurement properties of the SJC66/TJC68

Author/Year	Truth Domain Match*	Feasibility*	Truth	Discrimination				
			Construct Validity	Test-Retest Reliability	Interrater Reliability	Long'l Construct Validity	Clinical Trial Discrimination	Thresholds of Meaning
Aalbers, 2015						+	+/-	
Chandran, 2009					+(TJC)/-(SJC)			
Fransen, 2006						+	+	
Gladman, 2004					+(TJC)/-(SJC)			
Gladman, 2007					+(TJC)/-(SJC)			
Husic, 2014			+					
Leung, 2012			+					
Lubrano, 2015			+					
Tillet 2012					-			
Salvarani, 2016		+			+(TJC)/-(SJC)			
Duarte-Garcia 2018 draft			+/-			+	+	
Tillet 2018 draft				+				+
GRAPPA and Working Group Surveys	+	+						
Patient input	+	+						
Thompson, 1991				+				
Deandrade 1965				+				
Total available studies for each property	2	3	4	3	5	3	3	1
Total studies available for synthesis	2	3	4	3	5	3	3	1
Rating (RAGW)	Green	Green	Green	Amber	Green for TJC Amber for SJC	Green	Green	Amber
Overall Rating for Instrument across properties	Green: Working Group is Recommending Endorsement							

*The color indicates the good methods checklist/recommendation; the +/- sign indicates the adequacy of the data in support of the instrument.

*For test-retest reliability, we have provided primary [unpublished] data for test-retest reliability in PsA (1 study) but also additional evidence to support the intra-rater reliability of the joint count in RA (2 studies).

Methods: A multi-prong protocol was designed to assess the properties of the joint counts. A provider and methodologist focus group at GRAPPA, an international web-based working group survey, and patient research partner survey and web-based focus groups were conducted to assess domain match and feasibility. To address reliability, construct validity, responsiveness and discrimination, we conducted a systematic literature review and analyzed data from one LOS and 8PsA RCTs using a standardized protocol. These results were summarized in a “Summary of Measurement Properties Table,” (developed by OMERACT), and presented and discussed at OMERACT2018. OMERACT participants voted on endorsement of the SJC66/TJC68 as an instrument for the PsA Core Outcome Measurement Set.

Results: Participants in the preconference work and within our working group agreed that the SJC66/TJC68 joint count matched the domain “MSK disease activity: peripheral arthritis” and is feasible for use in RCT and LOS. Construct validity was demonstrated in four published studies and within our primary data analyses. Test-retest reliability was only examined in one cohort of 14 patients with PsA but was found to be excellent (0.8-0.9). Inter-rater reliability has been previously shown to be low for the SJC66 (intraclass correlation [ICC], 0.24) but good for the TJC68 (ICC, 0.78). The SJC66/TJC68 was responsive and able to discriminate between patients receiving placebo and active treatment. Finally, the minimally important difference was found to be 2.5 joints for both SJC66 and TJC68 in a new analysis of an LOS. Overall, 17 (100%) of patient research partners and 96/113 (85%) of other stakeholders (eg, clinicians, methodologists) voted for full endorsement of the SJC66/TJC68.

Conclusion: SJC66/TJC68 is a feasible, valid and reliable instrument for the measurement of peripheral joint activity in RCT/LOS and is recommended over the 76/78 and 28 joint counts. The SJC66/TJC68 is the first fully endorsed instrument within the PsA Core Outcome Measurement Set.

Disclosure: A. Duarte-Garcia, None; L. Eder, None; N. Goel, None; R. Christensen, None; M. de Wit, None; O. FitzGerald, None; D. D. Gladman, None; R. Holland, None; Y. Y. Leung, None; C. Lindsay, None; N. McHugh, None; P. J. Mease, None; A. M. Orbai, Abbvie, Celgene, Eli Lilly and Company, Horizon, Janssen, Novartis, Pfizer, 2, Eli Lilly and Company, Janssen, Novartis, Pfizer, UCB, 5; B. Shea, None; V. Strand, None; W. Tillett, None; L. C. Coates, None; A. Ogdie, Pfizer, Inc.; Novartis, 2, Abbvie, Amgen, BMS, Corrona, Lilly, Novartis, Pfizer, Takeda, 5.

Abstract Number: 1607

Achievement of Cdapsa Low Disease Activity or Remission Is Associated with Control of Articular and Extra-Articular Manifestations of Active PsA in Subjects Treated with Apremilast

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

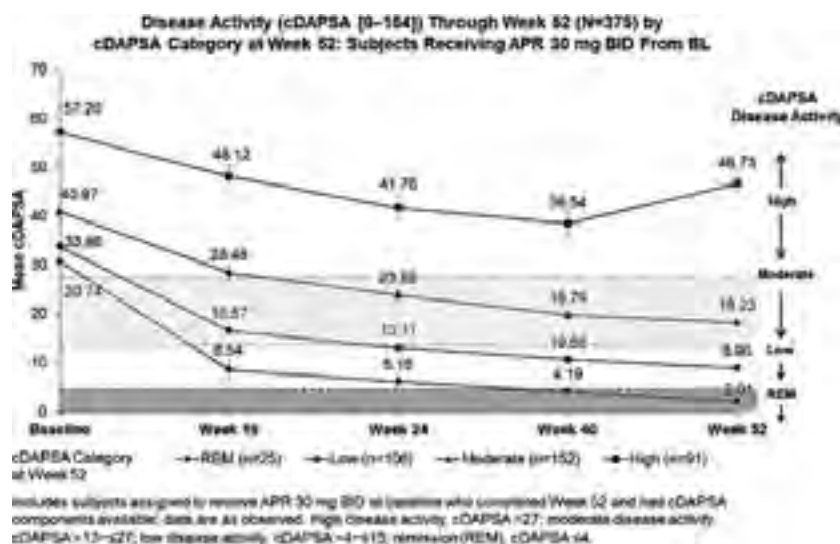
Session Time: 9:00AM-11:00AM

Background/Purpose: Therapeutic targets for psoriatic arthritis (PsA) include the achievement of remission (REM) or low disease activity (LDA), measured by the Clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA), a composite of swollen and tender joints counts (SJC and TJC), Patient's Assessment of Pain (PAP), and Patient's Global Assessment of Disease Activity (PtGA). We examined the trajectories for improvement in cDAPSA and PsA manifestations not measured by cDAPSA among subjects achieving cDAPSA LDA or REM at Week 52.

Methods: Pooled analyses of 3 phase III studies (PALACE 1-3) were performed for subjects assigned to receive apremilast 30 mg BID (APR) at baseline (BL). Subjects with cDAPSA components available to calculate responses at Week 52 were included and grouped according to the cDAPSA categories reached at Week 52 (REM: ≤ 4 ; low: >4 to ≤ 13 ; moderate: >13 to ≤ 27 ; high: >27 disease activity). We then traced their mean cDAPSA trajectory from BL to Week 52. Mean disease activity in core PsA domains were also reported longitudinally by cDAPSA category reported at Week 52, including SJC (0-76), TJC (0-78), PAP (visual analog scale [VAS] 0-100 mm), PtGA (VAS 0-100mm), Physician's Global Assessment of Disease Activity (PhGA; VAS 0-100 mm), Psoriasis Area and Severity Index (PASI; 0-72), enthesitis (Maastricht Ankylosing Spondylitis Enthesitis Score [MASES]; 0-13), dactylitis count (0-20), and HAQ-DI (0-3).

Results: A total of 375 APR subjects were included in the analyses. Achievement of LDA or REM at Week 52 was associated with lower mean cDAPSA at BL, and these subjects had continuous improvements in disease activity from BL to Week 52 (Figure). Among subjects who achieved LDA at Week 52, most were classified as having moderate (mean cDAPSA: 16.6) or low (mean cDAPSA: 8.5) disease activity at Week 16. At Week 24, these subjects had mean cDAPSA scores of 13.1 (moderate disease activity) and 6.2 (LDA). Furthermore, subjects who achieved REM at Week 52 had already shown early improvement to either no or mild articular and extra-articular disease activity by Week 16. Patients in REM and LDA showed parallel improvements in extra-articular disease activity at Week 52 with APR (Table).

Conclusion: In the subgroup who achieved cDAPSA REM or LDA, early improvement was seen in disease activity by Week 16 and sustained to Week 52 with continued treatment. Patients achieving control of peripheral arthritis (classified as REM or LDA by Week 52) with APR also exhibited REM or LDA in other manifestations of PsA, including enthesitis, dactylitis, function, and skin psoriasis.



Articular and Extra-Articular Disease Activity in Subjects With LDA or REM at Week 52								
Mean	Subjects With REM at Week 52 n=25				Subjects With LDA at Week 52 n=106			
	Time Point				Time Point			
	BL	Week 16	Week 24	Week 52	BL	Week 16	Week 24	Week 52
SJC (0-78)	0.2	2.3	1.2	0.2	0.3	3.7	2.2	1.2
TJC (0-78)	12.6	3.5	2.6	0.5	15.7	6.4	4.6	2.6
PAP (VAS 0-100 mm)	50.6	14.4	13.1	7.2	51.2	32.5	32.5	25.1
PGA (VAS 0-100 mm)	44.5	17.0	18.6	7.7	51.5	36.7	34.2	26.0
PGA (VAS 0-100 mm)	43.6	16.0	12.4	6.4	50.7	24.0	18.9	13.7
PRAP (0-72)	9.5	4.2	3.5	2.7	8.2	3.7	3.4	4.0
MASSP (0-13)	1.6	0.4	0.1	0.4	3.3	1.7	1.2	1.2
Dactylitis count* (0-20)	2.3	0.7	0.2	0.0	2.6	1.0	0.6	0.5
HAQ-DI (0-3)	0.6	0.3	0.2	0.1	1.0	0.7	0.7	0.6

Includes: subjects assigned to receive APR 30 mg BID at baseline who completed Week 52 and had cDAPSA (as classified with SJC [0-48] and TJC [0-48]) components available. Data are as observed and n values vary by time point based on number of subjects with available data for a given end point.

***Assessed in subjects with ≥7% psoriasis-affected body surface area at baseline.**

†Assessed in subjects with enthesitis at baseline.

‡Assessed in subjects with dactylitis at baseline.

Low disease activity (LDA): cDAPSA =4-13; remission (REM): cDAPSA ≤4.

Disclosure: L. C. Coates, AbbVie, Celgene, Janssen, Novartis, Pfizer Inc, 2, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Galapagos, Janssen, MSD, Novartis, Pfizer Inc, Prothena, Sun Pharma, UCB, 5; P. J. Mease, Abbott, Amgen, Biogen Idec, BMS, Celgene Corporation, Eli Lilly, Genentech, Janssen, Novartis, Pfizer, Roche, UCB, 2, 5, Abbott, Amgen, Biogen Idec, BMS, Eli Lilly, Genentech, Janssen, Pfizer, UCB, 8; F. Behrens, Abbvie, Pfizer, Roche, Chugai, Prophylix, Novartis, Iron4U, 2, Abbvie, Pfizer, Roche, Chugai, UCB, BMS, Celgene, MSD, Novartis, Biotest, Janssen, Genzyme, Sanofi, Lilly, Sandoz, 5, 8, Abbvie, Pfizer, Roche, UCB, Celgene, Novartis, Biotest, Janssen, Genzyme, Sanofi, Lilly, Boehringer, BMS, Sandoz, 6; A. M. Orbai, Abbvie, Celgene, Eli Lilly and Company, Horizon, Janssen, Novartis, Pfizer, 2, Eli Lilly and Company, Janssen, Novartis, Pfizer, UCB, 5; A. Ogdie, Pfizer, Novartis, 2, Abbvie, BMS, Lilly, Pfizer, Novartis, Takeda, 5; M. Brunori, Celgene Corporation, 3; L. Teng, Celgene Corporation, 3; B. Guerette, Celgene Corporation, 3; J. S. Smolen, Abbvie, Janssen, Lilly, MSD, Pfizer and Roche, 2, Abbvie, Amgen, Astra-Zeneca, Astro, Celgene, Celtrion, Glaxo, ILTOO, Janssen, Lilly, Medimmune, MSD, Novartis-Sandoz, Pfizer, Roche, Samsung, Sanofi and UCB, 8.

The Value of Carotid Ultrasound in Cardiovascular Risk Stratification in Patients with Psoriatic Disease

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SESSION INFORMATION

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with psoriatic disease (PsD) are at a high risk of developing cardiovascular events (CVE). The performance of clinical algorithms for cardiovascular risk stratification, such as the Framingham Risk Score (FRS), is sub-optimal in this patient population. The study aims were: 1) to assess whether subclinical atherosclerosis, as evaluated by carotid ultrasound, could predict future CVE in patients with PsD and 2) to determine whether incorporation of imaging data could improve the prediction of CVE beyond clinical cardiovascular algorithms.

Methods: Patients with PsD from a large longitudinal cohort underwent ultrasound assessment of the carotid artery at baseline. The extent of atherosclerosis was assessed using mean carotid intima media thickness (cIMT in μm) and total plaque area (TPA in cm^2). Patients were followed according to a standardized protocol at 6-12 month intervals. Incident CVE that occurred following the ultrasound assessment were identified from the cohort database and through linkage with national hospitalization and death registries. A cardiologist reviewed the medical records related to each CVE and classified them to major CVE (myocardial infarction, stroke, revascularization or cardiovascular death) and minor CVE (angina, TIA, CHF exacerbation). The association between measures of carotid atherosclerosis and the risk of developing future CVE was evaluated using Cox proportional hazard models after adjusting for FRS categories.

Results: Overall, 607 patients with PsD (66.7% with PsA) were assessed and 37 patients developed incident CVE confirmed by the cardiologist (28 major CVE). Their mean age was 57.1 (SD 11.7) and 57.7% were males. 26% and 34.8% had unilateral and bilateral carotid plaques, respectively. The incidence rate of CVE was higher in patients with bilateral carotid plaques compared with unilateral/no plaques (3.96 vs. 0.54 events per 100 person years; $p < 0.001$, Figure 1). In multivariable regression models, TPA (Hazard Ratio (HR) 2.20, 95% Confidence Interval (CI) 1.51, 3.22; $p < 0.001$), mean cIMT (HR 1.21, 95% CI 1.08, 1.34; $p < 0.001$) and bilateral carotid plaques (HR 2.89, 95% CI 1.07, 7.77, $p = 0.03$) predicted incident CVE after controlling for FRS. The results were similar after restricting the analysis to patients with major CVE and after excluding patients with a history of CVE at baseline.

Conclusion: Patients with PsD with subclinical carotid atherosclerosis are more likely to develop future CVE. Carotid ultrasound could potentially improve the identification of patients with PsD who are at high cardiovascular risk.

Disclosure: C. Sobchak, None; S. Akhtari, None; P. Harvey, None; D. D. Gladman, None; V. Chandran, None; R. J. Cook, None; L. Eder, None.

Table 1- The association between subclinical atherosclerosis and incident cardiovascular events (N=607, 37 events) – Cox proportional hazard model

	Univariate analysis		Adjusted for Framingham risk score	
	HR (95% CI)	P value	HR (95% CI)	P value
TPA	3.48 (2.54, 4.79)	<0.0001	2.20 (1.51, 3.22)	<0.0001
Mean IMT	1.37 (1.25, 1.51)	<0.0001	1.21 (1.08, 1.34)	0.0009
Max IMT	1.19 (1.12, 1.26)	<0.0001	1.11 (1.03, 1.19)	0.003
Plaques	0.84 (0.20, 3.50)	0.81	0.57 (0.14, 2.38)	0.44
Unilateral vs. none	6.82 (2.64, 17.62)	<0.0001	2.89 (1.07, 7.77)	0.03
Bilateral vs. none				

CI- confidence interval, HR- hazard ratio, IMT- intima media thickness, TPA – total plaque area

The Incidence Rate of Spondyloarthritis in Slovenia

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose: Spondyloarthritis (SpA) are heterogeneous group of inflammatory diseases, affecting both, axial and peripheral skeleton. Incidence studies in SpA are sparse. There is no data for peripheral SpA as an entity. In axial SpA, recent incidence study reported a decrease of the incidence over decades (1). As data for our country are lacking, we aimed to determine the incidence of SpA in a well defined country region.

Methods: The study was conducted at rheumatology department of an integrated secondary/tertiary teaching hospital, which provides services to region of around 704,000 adult residents. A retrospective chart review of adult patients diagnosed with SpA for the first time between January 2014 and December 2016 was performed. Potential cases were ascertained by searching the electronic medical records for ICD-10 codes M02*, M07*, M13*, M45*, K50*, K51* and L40*. SpA cases were further stratified into axial and peripheral subgroup. The annual incidence rate of SpA was calculated.

Results: During the three year period we identified 294 new SpA cases (55.1% males, median (IQR) age 46.7 (35.0-57.7) years). We diagnosed ankylosing spondylitis, psoriatic arthritis, reactive arthritis, enteropathic arthritis and undifferentiated SpA in 22.4%, 39.8%, 7.1%, 3.7%, and 26.9% cases, respectively. We classified 98 patients (33.3%) with axial SpA and the rests with peripheral SpA. Characteristics of SpA cohort and both subgroups are presented in Table 1. The estimated annual incidence rate of SpA in our region was 13.9 cases per 100,000 adults per year (95% CI 12.4-15.6), in axial SpA 4.6 per 100,000 adults (95% CI 3.8-5.6), and in peripheral SpA 9.3 per 100,000 adults (95% CI 8.0-10.6). Gender specific incidence rates are presented in Table 1.

Table 1: Characteristics of Spodyloarthritis

Characteristics	All SpA	Peripheral SpA	Axial SpA
No. (%) of cases	294 (100%)	196 (66.7%)	98 (33.3%)
Male gender (%)	162 (55.1%)	95 (48.5%)	67 (67.4%)
Age (years) [#]	46.7 (35.0-57.7)	49.9 (36.4-58.6)	39.9 (33.7-55.8)
Symptom duration (months) [#]	7.1 (1.9-24.7)	3.5 (1.0-12.1)	31.7 (10.8-73.2)
HLA B27 positivity (%)	158/261 (60.5%)	81/166 (48.8%)	77/95 (81.1%)
Incidence rate ^{&}	13.9 (12.4-15.6)	9.3 (8.0-10.6)	4.6 (3.8-5.6)
Incidence in females ^{&}	12.2 (10.2-14.4)	9.3 (7.6-11.3)	2.9 (2.0-4.0)
Incidence in males ^{&}	15.8 (13.5-18.3)	9.2 (7.5-11.3)	6.5 (5.1-8.2)

Legend: SpA spondyloarthritis; # median (IQR); & incidence per 100,000 adults per year and 95% confidence interval.

Conclusion: The incidence rate of SpA is similar to the incidence of rheumatoid arthritis in our country (2). Peripheral SpA is two times more frequent than axial SpA.

References: 1) Wright KA, Crowson CS, Michet CJ, Matteson EL: Time trends in incidence, clinical features and cardiovascular disease in ankylosing spondylitis over three decades: a population-based study. *Arthritis Care Res* (Hoboken) 2015; 67:836-841.

2) Ješe R, Perdan Pirkmajer K, Hočevar A, Rotar Ž, Markez S, Pavić Nikolić M, et al. The Incidence Rate of Rheumatoid Arthritis in Slovenia. (2018 ACR submitted abstract)

Disclosure: N. Potocnik Pucelj, None; A. Hočevar, None; R. Jese, None; Z. Rotar, None; M. Tomšič, None.

Incremental Benefits to Quality of Life Associated with Achieving Higher Levels of American College of Rheumatology Response and Skin Clearance in Patients with Psoriatic Arthritis

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SESSION INFORMATION

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Session Type: ACR Poster Session B

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Background/Purpose: PsA is a chronic inflammatory disease associated with psoriasis. For optimal quality of life (QoL) improvements, all PsA symptoms should be managed. We examine the association between improvements in joint or skin-related symptoms and QoL in patients (pts) with active PsA.

Response by PASI Category From Baseline at Week 24*				
	<PASI 75	PASI 75 but not PASI 90	PASI 90 but not PASI 100	PASI 100
EQ-5D VAS, mean (SD)	2.9 (22.6) N=198	12.8 (26.6)* N=38	17.0 (23.6)* N=45	19.2 (25.0)* N=107
SF-36 MCS, mean (SD)	2.1 (10.9) N=198	4.5 (9.8) N=38	4.9 (8.6) N=45	5.3 (12.3)* N=107
DLQI (0,1), n (%)	25 (12.1) N=207	25 (65.8)* N=38	27 (57.4)* N=47	91 (82.7)* ^{†‡} N=110
DLQI (0), n (%)	11 (5.3) N=207	11 (28.9)* N=38	14 (29.8)* N=47	60 (54.5)* ^{†‡} N=110
Response by ACR Category From Baseline at Week 24*				
	<ACR20	ACR20 but not ACR50	ACR50 but not ACR70	ACR70
EQ-5D VAS, mean (SD)	-0.7 (23.6) N=351	9.7 (18.4) [†] N=107	16.7 (20.5) ^{†‡} N=89	26.0 (20.7) ^{†‡} N=107
SF-36 PCS, mean (SD)	0.8 (6.9) N=351	3.5 (6.0) [†] N=107	10.0 (8.1) ^{†‡} N=89	14.7 (8.5) ^{†‡} N=107
SF-36 physical functioning domain, mean (SD)	2.7 (17.9) N=351	8.4 (16.4) [†] N=107	21.7 (19.3) ^{†‡} N=89	33.8 (24.6) ^{†‡} N=107

*p<.05 vs. <PASI 75

[†]p<.05 vs. PASI 75 but not PASI 90

[‡]p<.05 vs. PASI 90 but not PASI 100

*p<.01 vs. <ACR20

[†]p<.01 vs. ACR20 but not ACR50

[‡]p<.01 vs. ACR50 but not ACR70

*Missing PASI, ACR, and DLQI data were imputed using NRI and missing health outcomes were imputed using LOCF. PASI data are based on patients with baseline psoriasis ≥3% BSA and ACR data are based on all ITT patients. ACR20/50/70=20%, 50%, 70% improvement in American College of Rheumatology response criteria; BSA=body surface area; DLQI=Dermatology Quality of Life Index; ITT=intent-to-treat; LOCF=last observation carried forward; MCS=Mental Component Score; N=number of patients in each category after imputation; NRI=non-responder imputation; PASI 75/90/100=75%, 90%, 100% improvement in Psoriasis Area and Severity Index; PCS=Physical Component Score; SD=standard deviation; SF-36=36-Item Short Form Health Survey; VAS=visual analog scale

Methods: Data from the 24-week(wk), randomized, double-blind, placebo-controlled periods of 2 Phase 3 clinical trials (SPIRIT-P1, NCT01695239; SPIRIT-P2, NCT02349295) were combined to assess pts with active PsA who were biologic-naïve (N=316) or were intolerant to TNF inhibitors (N=363) and received sc placebo or 80 mg ixekizumab every 2 or 4 wks, after a 160 mg starting dose.^{1,2} All pts met the Classification Criteria for PsA. QoL outcomes were assessed in categories of pts based on Psoriasis Area and Severity Index (PASI) or ACR responses at Wk 24. ACR response categories included pts not achieving ACR20, pts achieving ACR20 and <ACR50, ACR50 and <ACR70, and ACR70. PASI response categories included pts with baseline (BL) psoriasis ≥3% body surface area not achieving PASI 75, pts achieving PASI 75

and <PASI 90, PASI 90 and <PASI 100, and PASI 100. The percentage of pts achieving Dermatology Quality of Life Index (DLQI) score 0-1 or 0, indicating no impact on QoL, and mean change in EQ-5D visual analog scale (VAS) and 36-Item Short Form Health Survey (SF-36) Mental Component Score (MCS) was evaluated across PASI categories at Wk 24. Mean change in EQ-5D VAS, SF-36 Physical Component Score (PCS), and SF-36 physical functioning was evaluated across ACR categories at Wk 24. Missing data were imputed using non-responder imputation for categorical data and last observation carried forward for continuous data. Response categories were compared using logistic model for categorical outcomes; analysis of covariance was used for continuous outcomes, with BL health outcome score as a covariate.

Results: At Wk 24, the greatest improvements in QoL as assessed by EQ-5D were associated with achieving PASI 100 or ACR 70. Also, the proportion of pts achieving DLQI score 0-1 or 0 and the mean change in SF-36 MCS increased with PASI improvement, with the greatest QoL improvements in pts achieving PASI 100. Similarly, from BL-Wk 24, SF-36 PCS and SF-36 physical functioning improved with ACR response, with the greatest improvements alongside ACR50 and ACR70 responses.

Conclusion: Incremental QoL benefits were observed across PASI and ACR response categories. Clear skin (PASI100) was associated with the greatest improvements in skin-specific QoL, mental aspects, and general QoL. Pts achieving ACR50 and ACR70 achieved the greatest improvements in physical aspects and general QoL. These data provide more evidence that optimal QoL improvements are associated with greater improvements in joint and skin-related PsA symptoms.

References: 1. Mease PJ et al. *Ann Rheum Dis* 2017;76:79-87
2. NashP et al. *Lancet* 2017;389:2317-27

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Abstract Number: 1611

Hospitalizations for Serious Infections in Psoriatic Arthritis Patients: Data from the National Inpatient Sample 2000-2014

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SESSION INFORMATION

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Background/Purpose: Increased risk of infections has been recognized in patients with psoriatic arthritis (PsA) compared to those without PsA. Immunomodulatory effects of PsA, immunosuppressive therapies and associated comorbidities might all play a role. However, the rate of hospitalizations with serious infections in patients with PsA is largely unknown. We used the National Inpatient Sample (NIS) to compare hospitalizations for serious infections in patients with and without PsA in the US from 2000-2014.

Methods: Using NIS data from 2000-2014, we identified patients ≥ 18 years with PsA at any secondary diagnosis positions based on ICD-9 code 696.0. For each patient with PsA, a matched control of the same age (± 1 year), sex, race/ethnicity and NIS stratum (based on hospital's census region or division, ownership/control, location/teaching, and bed size) was randomly selected. We evaluated 8 different infections as primary diagnoses: sepsis/bacteremia, pneumonia, urinary tract infection, skin and soft tissue infections, septic arthritis, osteomyelitis, brain/spinal cord infections and opportunistic infections. We compared the hospitalization rates for each infection among all hospitalizations with and without a secondary diagnosis of PsA. Hospitalized infection rates were estimated as the number of hospitalizations with primary discharge diagnosis of infection divided by the total number of hospitalization in the groups. Analyses were weighted to account for the sampling design of the NIS.

Results: NIS database from 2000-2014 contained 53,788 (weighted count, N=265,842) hospitalizations in the PsA and (weighted count, N=266,082) in the matched non-PsA cohort. Mean age at hospitalization for patients with PsA was 60 years (SD: 14.3) and 56% were female. Overall, there were an estimated 25,681 PsA and 15,014 non-PsA hospitalizations with a primary discharge diagnosis of infection, which corresponded to rates of 9.6 and 5.6 per 100 hospitalizations observed in the PsA and non-PsA cohorts, respectively (Rate ratio: 1.79, 95% CI: 1.71 - 1.88). While highest number of hospitalizations was observed for skin/soft tissue infections, sepsis/bacteremia and pneumonia in both groups, the highest differences in the rate ratio among the two groups were observed for septic arthritis, brain/spinal cord infections and opportunistic infections (Table).

Conclusion: Our study shows that patients with PsA have a higher proportion of hospitalizations for serious infections compared with non-PsA patients. Whether this difference is secondary to the immunosuppressive agents used in PsA or due to the immunologic disturbance associated with PsA itself would require careful evaluation in dedicated PsA studies. Future work will estimate rates of serious infections among all patients with PsA in the US and will also examine yearly trends in the rates of serious infections for patients with PsA.

Infection type	Estimated number of hospitalized infections (rate per 100 hospitalizations)		Rate ratio (95% CI)
	PsA	Non-PsA	
Total	25681 (9.65)	15014 (5.65)	1.79 (1.71, 1.88)
Pneumonia	9878 (3.71)	8242 (3.10)	1.21 (1.13, 1.30)
Sepsis/bacteremia	10017 (3.76)	7702 (2.90)	1.31 (1.22, 1.40)
Urinary tract	1216 (0.46)	811 (0.30)	1.49 (1.22, 1.81)
Skin and soft tissue	11253 (4.23)	5285 (1.99)	2.20 (2.04, 2.37)
Septic Arthritis	1011 (0.38)	276 (0.10)	3.76 (2.77, 5.09)
Osteomyelitis	1000 (0.38)	458 (0.17)	2.24 (1.75, 2.86)
Brain/spinal cord	254 (0.10)	84 (0.03)	3.06 (1.76, 5.31)
Opportunistic	928 (0.35)	399 (0.15)	2.31 (1.78, 2.99)

Disclosure: P. Karmacharya, None; C. S. Crowson, None; D. Poudel, None; P. Shrestha, None; K. Wright, None.

Abstract Number: 1612

Myocardial Infarctions Among Ankylosing Spondylitis Patients in a Large US Insurance Database

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Risk of myocardial infarction (MI) is estimated to be increased up to 60% in ankylosing spondylitis (AS). Studies in patients with rheumatoid arthritis, psoriatic arthritis and psoriasis have demonstrated reduced risk of MI in users of TNF inhibitors relative to users of other treatments. We sought to evaluate risk of MI in AS patients with use of TNFi, either alone, or in combination with other therapies, in a large US health insurance claims database.

Methods: We conducted a nested case-control study using 1994-2017 data from the OptumLabs® Data Warehouse which includes de-identified claims data and demographic information on enrollees. We included adults aged 18-89 with an AS diagnosis after at least 6 months of claims data prior to their AS diagnosis. Incident MI cases were defined by diagnostic codes. Four controls without MI were matched to each case based on sex, age (+/- 2 years) and year of AS diagnosis (+/- 2 years). AS treatment was assessed within the year prior to MI or the matched date in controls. Treatment was categorized as: NSAID only, symptom-modifying anti-rheumatic drugs (SMARD) only, TNFi only, combinations these categories, hormone. Odds of MI was assessed in each exposure category, relative to NSAID use alone, with adjustment for potential confounders (smoking, obesity, diabetes, chronic kidney disease stage 2 or greater, hypertension and ischemic heart disease at any time prior to AS diagnosis date) using conditional logistic regression. Additionally, a sensitivity analysis was performed assessing for exposure within the 6 months prior to index date.

Results: Among 23249 adults with AS meeting inclusion criteria, we identified 629 MI cases and 2385 matched controls. The mean age of included subjects was 59.1 (SD 11.9) years, and 48.9% were female. Relative to NSAID use, the RR for

MI among TNFi only users was 1.03 (95% CI 0.59-1.78), and for SMARD only users 0.95 (95% CI 0.68-1.32). No combinations of NSAID, SMARD and TNFi use resulted in a significantly increased or decreased OR after adjustment for potential confounders. Results were not materially changed with an assessment period of 6 months prior to index date.

Conclusion: In this large health insurance claims database, use of TNFi among AS patients, either alone or in combination with NSAIDs or SMARDs was not associated with a reduced risk of MI. While this study is limited a small study sample, and there is the potential for bias related to confounding by disease severity, these findings suggest that TNFi are not cardio protective in AS.

Table 1. Odds of Myocardial Infarction among ankylosing spondylitis patients within each drug treatment category

	Cases, N	Controls, N	Crude Odds Ratio (95% CI)	Adjusted+ Odds Ratio (95% CI)
NSAID only	284	998	1.0 (ref)	1.0 (ref)
SMARD only	60	211	0.97 (0.71-1.34)	0.95 (0.68-1.32)
TNFi only	<20*	69	0.95 (0.56-1.64)	1.03 (0.59-1.78)
NSAID and SMARD	79	227	1.23 (0.92-1.65)	1.27 (0.94-1.70)
NSAID and TNFi	<20*	78	0.72 (0.41-1.27)	0.76 (0.42-1.35)
TNFi and SMARD	<20*	56	0.43 (0.19-0.97)	0.42 (0.18-0.96)
NSAID, SMARD and TNFi	23	60	1.37 (0.83-2.26)	1.42 (0.85-2.38)
None of the above	141	686	0.65 (0.52-0.83)	0.64 (0.50-0.81)

* Small cells are suppressed to prevent the possibility of patient identification

NSAID: Non-steroidal anti-inflammatory drug. SMARD: Symptom-modifying anti-rheumatic drugs, including sulfasalazine, azathioprine, methotrexate, leflunomide, tofacitinib and apremilast. TNFi: tumor-necrosis alpha inhibitors; etanercept, adalimumab, golimumab, certolizumab and infliximab.

+ Adjusted for sex, and baseline age, smoking, obesity, diabetes, hypertension, chronic kidney disease stage 2 or greater, and ischemic heart disease

Disclosure: M. Dubreuil, None; C. Pelloquin, None; D. T. Felson, None; T. Neogi, None.

Abstract Number: 1613

Dactylitis in Early Spondyloarthritis. Baseline Data from a Prospective French National Cohort

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SESSION INFORMATION

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Background/Purpose: Dactylitis is a particular feature shared across the several phenotypical forms of spondyloarthritis (SpA), part of the classification criteria. There are only few data available about impact of dactylitis in early stage of SpA, and factors associated with the presence/history of dactylitis.

Aim: To study, at baseline of the DESIR cohort the presence/history of dactylitis in an attempt to evaluate frequency of dactylitis in SpA and to look at the factors associated with presence of dactylitis.

Methods: DESIR is a prospective observational cohort of patients with recent onset (less than 3 years) inflammatory back pain, beginning before 50 years, suggestive of axial SpA. All available factors in the database (clinical, biological, imaging and medico economic) were compared between patients with and without past or present dactylitis at baseline (for categorical variables : odds-ratio +/- 95% CI and chi-square/Fisher tests, for continuous variables : unpaired t-tests / Mann-Whitney) , by uni and then multivariate analysis(logistic regression). Significance: p less than 0.05.

Results: At baseline, 708 patients were analyzed. 97 had a past history or a concomitant dactylitis [prevalence 13.7% (CI 95% : 11.6 – 16.2)]. Dactylitis occurred before axial symptoms in 41.3 % and before any other symptom in 14.1 % of the cases. By univariate analysis, dactylitis was significantly associated with history of arthritis, enthesitis, psoriasis, with elevated CRP and ESR, enthesitic and arthritis scores, BASDAI, ASDAS,BASFI, SF-36, HAQ, ASQoL, shorter disease duration, systemic and local steroids use, and with lower structural damage (sacro iliac, spine)

Table shows the result of the multivariate analysis.

item	OR	CI 95%
Arthritis history or presence	2.9	[11.2 – 30.9]
csDMARD use during the past 6 months	5.2	[2.9 – 9.1]
Calcaneal enthesitis history or presence	6.7	[3.0 – 14.7]
BASDAI > median	1.08	[1.05 – 1.11]
BASFI > median	1.04	[1.02 – 1.06]
SF36 phys <median	0.92	[0.87 – 0.97]
Systemic steroids during the past 6 months	5.49	[2.93 – 10.28]
Sacro iliac erosion (MRI central reading)	0.02	[0.004 – 0.13]
mSASSS (central reading)	0.37	[0.21 – 0.66]

Conclusion: In the DESIR cohort of patients suspected for early SpA, history of dactylitis is present in 13.7 % of the cases at baseline. It is an early feature associated with peripheral involvement, and associated with more burden of the disease, more frequent use of DMARDs and steroids, but with less structural damage.

Disclosure: D. Wendling, None; C. Prati, None; A. Saraux, None; A. Molto, None; T. Pham, None; M. Dougados, None; X. Guillot, None.

Abstract Number: 1614

Prevalence of Sonographic Enthesitis in Patients with Psoriasis without Arthritis and Its Association Risk Factors of Psoriatic Arthritis

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SESSION INFORMATION

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Background/Purpose: Enthesitis is one of the hallmarks of psoriatic arthritis (PsA) and may be the initial site of musculoskeletal inflammation. Enthesitis affects up to 50 % of patients with PsA and is a marker of more severe disease. However, clinical evaluation of enthesitis may be difficult. Ultrasound (US) is more sensitive than physical examination in detecting enthesitis. In patients with psoriasis alone (PsC) US can detect subclinical enthesitis which may predict future development of PsA. The aim of this study was to assess the association between the severity of sonographic enthesitis and risk factors for developing PsA. These risk factors include included obesity, severity of psoriasis, nail psoriasis in addition to physically demanding occupation and the presence musculoskeletal symptoms.

Methods: A cross-sectional study was conducted in patients with a dermatologist confirmed diagnosis of psoriasis. Each patient was assessed by a rheumatologist to exclude the presence of PsA. Information was collected about lifestyle habits, medical history, musculoskeletal symptoms and the skin activity using validated measures. The Madrid Sonography Enthesitis Index (MASEI) was used to quantify the severity of enthesitis in 12 enthesal sites. The sonographer was blinded to the clinical data. MASEI score³20 was considered as high score based on a previously validated cut-off in spondyloarthritis. Logistic regression analysis was used to assess the association between PsA-related risk factors and high MASEI score after adjusting for age, sex and BMI. The results were expressed as odds ratio (OR) and their 95 confident interval (CI).

Results: A total of 180 patients were studied. Of those, 52% were male with a mean age of 51.1±13.6 yrs. Majority of the patients (97%) did not have tender enthesal site on the examination. The mean total MASEI score was 9.3±8.3 and high MASEI (≥20) was found in 17 (9.4%) of the patients. The results of the regression analysis are shown in Table 1. Univariate regression analyses found an association between high MASEI score and Health Assessment Questionnaire (HAQ) (OR 14.8; *P* 0.006), the presence of morning stiffness (OR = 4.7; *P* 0.009) physically demanding occupation (OR = 5.5; *P* 0.01). The multivariable analysis showed that the presence of inflammatory back pain (OR 22.9, 95% CI 1.3, 401.8), morning stiffness (OR 5, 95% CI 1.03, 24.3), physically demanding occupation (OR 5.1, 1.01, 25.8) and HAQ (OR 13.9, 95% CI 1.02, 190.5) were associated with high MASEI.

Conclusion: In PsC patients, the severity of subclinical enthesitis was associated with occupational related physical stress and with inflammatory musculoskeletal complaints. Enthesitis might be playing a role in explaining the patients MSK complains in the absence of clinical features of PsA.

Table 1 D The association between high MASEI score (≥ 20) and PsA-related risk factors in patients with PsC by logistic regression multivariable analysis

Variable	Odds Ratio	95% Confidence Interval	P value
Age (years)	1.12	1.04, 1.21	0.002
Inflammatory back pain (yes)	22.98	1.31, 401.86	0.03
Morning stiffness (yes)	5.00	1.03, 24.29	0.045
Work class (physical occupation)	5.11	1.01, 25.78	0.048
HAQ	13.93	1.02, 190.46	0.048
Sex (Male)	2.08	0.36, 12.19	0.42
BMI	1.03	0.90, 1.17	0.67

Disclosure: A. Albasri, None; J. Y. Ye, None; C. F. Rosen, None; V. Chandran, None; D. D. Gladman, None; L. Eder, None.

Abstract Number: 1615

Comparative Risk of Atrial Fibrillation and Cardiovascular Events between TNF-Inhibitors and Ustekinumab in Patients with Psoriasis and Psoriatic Arthritis: A Population-Based Multi-Database Study

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Background/Purpose: Cardiovascular disease is a major comorbidity in patients with psoriasis (PsO) and psoriatic arthritis (PsA). Increasing evidence suggests a potential reduction in the risk of cardiovascular (CV) events with biological disease-modifying antirheumatic drugs (bDMARDs) treatment, mainly including tumor necrosis factor inhibitors (TNFi) with the more recent focus on atrial fibrillation (AF). However, the comparative CV risk with different bDMARDs has not been adequately studied in this patient population.

Methods: Using two large US commercial insurance databases, Optum Clinformatics and MarketScan, we identified patients with PsO or PsA diagnosis initiating ustekinumab or TNFi (i.e., adalimumab, etanercept, infliximab, certolizumab, and golimumab) from September 25, 2009 to September 30, 2015. The primary outcome was incident AF and the secondary outcome was a composite CV event including myocardial infarction, stroke, and coronary revascularization. Patients were followed until the first occurrence of the following events: 1) outcomes, 2) death, 3) plan disenrollment, 4) switching or 5) discontinuing treatment. To account for potential confounding, we estimated propensity score (PS) as the predicted probability of receiving ustekinumab conditioning on 62 covariates including demographic and clinical factors in each database. We used weighting based on PS fine stratification with 50 strata to control for confounding. The adjusted hazard ratio (HR) of each outcome was estimated using a weighted Cox proportional hazards regression model. We performed all the analyses separately in each of the databases and then combined the HR by a random-effects meta-analysis.

Results: We identified 60,028 (15,470 in Optum and 44,558 in MarketScan) adult patients with PsO or PsA and no prior AF. The mean age of the cohort was 47.2 ± 12.7 , and 51% were female. 81% had diagnosis for PsO while 46% had PsA, and 27% had both PsO and PsA. After PS stratification, covariates were well balanced between the two groups. As presented in **Table 1**, 60 incident AF occurred in 9,071 ustekinumab initiators while 323 incident AF did in 50,957 TNF inhibitor initiators (IR=4.7 and 5.0 cases per 1,000 person-year, respectively). MACE occurred in 74 patients among ustekinumab initiators, and 421 of patients initiated TNF inhibitors (IR=6.2 and 6.1 cases per 1,000 person-year,

respectively). The combined HR for AF among the ustekinumab initiators compared to those initiated TNFi was 1.15 (95% CI 0.70-1.89), and for MACE, the HR was 1.14 (95% CI 0.89-1.46).

Table 1. Comparison of phenotypic characteristics of Akpa patients													
Phenotype	n=46 (pts)						n=weight						
	Age (yr)	Sex (M/F)	Height (cm)	Weight (kg)	BMI (kg/m ²)	Waist circumference (cm)	Age (yr)	Sex (M/F)	Height (cm)	Weight (kg)	BMI (kg/m ²)	Waist circumference (cm)	
Age (yr)	37.3 (5.4)	34.3 (5.0)	33.3 (5.3)	35.4 (5.1)	33.3 (5.1)	33.3 (5.1)	37.3 (5.4)	34.3 (5.0)	33.3 (5.3)	35.4 (5.1)	33.3 (5.1)	33.3 (5.1)	
Sex (M/F)	14 (30.4%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	14 (30.4%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	
Height (cm)	161.5 (10.5)	161.2 (10.2)	161.0 (10.2)	161.2 (10.2)	161.2 (10.2)	161.2 (10.2)	161.5 (10.5)	161.2 (10.2)	161.0 (10.2)	161.2 (10.2)	161.2 (10.2)	161.2 (10.2)	
Weight (kg)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	
BMI (kg/m ²)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	
Waist circumference (cm)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	
Age (yr)	37.3 (5.4)	34.3 (5.0)	33.3 (5.3)	35.4 (5.1)	33.3 (5.1)	33.3 (5.1)	37.3 (5.4)	34.3 (5.0)	33.3 (5.3)	35.4 (5.1)	33.3 (5.1)	33.3 (5.1)	
Sex (M/F)	14 (30.4%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	14 (30.4%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	
Height (cm)	161.5 (10.5)	161.2 (10.2)	161.0 (10.2)	161.2 (10.2)	161.2 (10.2)	161.2 (10.2)	161.5 (10.5)	161.2 (10.2)	161.0 (10.2)	161.2 (10.2)	161.2 (10.2)	161.2 (10.2)	
Weight (kg)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	
BMI (kg/m ²)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	
Waist circumference (cm)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	
Age (yr)	37.3 (5.4)	34.3 (5.0)	33.3 (5.3)	35.4 (5.1)	33.3 (5.1)	33.3 (5.1)	37.3 (5.4)	34.3 (5.0)	33.3 (5.3)	35.4 (5.1)	33.3 (5.1)	33.3 (5.1)	
Sex (M/F)	14 (30.4%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	14 (30.4%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	
Height (cm)	161.5 (10.5)	161.2 (10.2)	161.0 (10.2)	161.2 (10.2)	161.2 (10.2)	161.2 (10.2)	161.5 (10.5)	161.2 (10.2)	161.0 (10.2)	161.2 (10.2)	161.2 (10.2)	161.2 (10.2)	
Weight (kg)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	
BMI (kg/m ²)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	
Waist circumference (cm)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	
Age (yr)	37.3 (5.4)	34.3 (5.0)	33.3 (5.3)	35.4 (5.1)	33.3 (5.1)	33.3 (5.1)	37.3 (5.4)	34.3 (5.0)	33.3 (5.3)	35.4 (5.1)	33.3 (5.1)	33.3 (5.1)	
Sex (M/F)	14 (30.4%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	14 (30.4%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	
Height (cm)	161.5 (10.5)	161.2 (10.2)	161.0 (10.2)	161.2 (10.2)	161.2 (10.2)	161.2 (10.2)	161.5 (10.5)	161.2 (10.2)	161.0 (10.2)	161.2 (10.2)	161.2 (10.2)	161.2 (10.2)	
Weight (kg)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	
BMI (kg/m ²)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	
Waist circumference (cm)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	
Age (yr)	37.3 (5.4)	34.3 (5.0)	33.3 (5.3)	35.4 (5.1)	33.3 (5.1)	33.3 (5.1)	37.3 (5.4)	34.3 (5.0)	33.3 (5.3)	35.4 (5.1)	33.3 (5.1)	33.3 (5.1)	
Sex (M/F)	14 (30.4%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	14 (30.4%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	40 (86.3%)	
Height (cm)	161.5 (10.5)	161.2 (10.2)	161.0 (10.2)	161.2 (10.2)	161.2 (10.2)	161.2 (10.2)	161.5 (10.5)	161.2 (10.2)	161.0 (10.2)	161.2 (10.2)	161.2 (10.2)	161.2 (10.2)	
Weight (kg)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	74.5 (15.5)	
BMI (kg/m ²)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	29.1 (3.1)	
Waist circumference (cm)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	101.5 (10.5)	

Conclusion: In this large cohort study of 60,028 patients with PsO or PsA, we found no substantially different risk of AF or CVD after initiation of ustekinumab or TNFi. However, a possible small effect cannot be ruled out warranting further studies with a longer follow-up.

Table 1. Risk of atrial fibrillation and composite CVD (ustekinumab vs. TNFi) adjusted through PS weighting

		Atrial fibrillation		Composite CVD	
		Ustekinumab	TNFi	Ustekinumab	TNFi
Optum	PS weighted total	2,731	12,671	2,731	12,671
	Cases	17	49	13	66
	Rate per 1,000 PY	5.0	3.2	3.8	4.3
	HR (95% CI)	1.56 (0.90-2.71)		0.88 (0.49-1.60)	
MarketScan	PS weighted total	6,331	38,138	6,331	38,138
	Cases	43	265	60	288
	Rate per 1,000 PY	5.0	5.4	7.0	5.8
	HR (95% CI)	0.93 (0.68-1.29)		1.20 (0.91-1.58)	
Combined *	HR (95% CI)	1.15 (0.70-1.89)		1.14 (0.89-1.46)	

* HR is combined by a random-effects meta-analysis

Disclosure: M. Lee, None; R. J. Desai, None; Y. Jin, None; G. Brill, None; A. Ogdie, Pfizer, Inc.; Novartis, 2, Abbvie, Amgen, BMS, Corrona, Lilly, Novartis, Pfizer, Takeda, 5; S. C. Kim, Bristol-Myers Squibb, 2, Pfizer, 2, Roche, 2.

Abstract Number: 1616

Region-Specific Differences in Clinical Presentation of Patients with Axial Spondyloarthritis – Results from a Large Multinational Cohort Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: There is limited evidence on the phenotypic characteristics of axial spondyloarthritis (axSpA) patients (pts) in various geographic regions around the world. This analysis aimed to compare demographic and disease-related characteristics in axSpA pts included in PROOF study in different regions.

Methods: PROOF is an ongoing 5-year prospective observational study inputs with recently (≤ 1 year prior to study enrollment) diagnosed axSpA and fulfilling the ASAS classification criteria. Baseline data of pts with centrally confirmed sub-classification as non-radiographic (nr)-axSpA or radiographic (r)-axSpA, based on the absence or presence of definite radiographic sacroiliitis (\geq grade 2 bilaterally or \geq grade 3 unilaterally), were considered in the current analyses. Twenty-nine participating countries were divided into 4 geographic regions: 1. Europe and Canada (EC), 2. Middle East and South Africa (MEA), 3. Asia (China only), and 4. Latin America (LA).

Results: A total of 1583 axSpA pts were centrally sub-classified as nr-axSpA (n=544) or r-axSpA (n=1039). The proportion of patients with r-axSpA was highest in China (81%), followed by MEA (64%), EC (61%) and LA (54%) (Table). Gender distributions were similar across the regions in nr-axSpA (M:49% vs. F:51%), while in r-axSpA the proportions of men differed, with the highest in China (79%) and lowest in MEA (58%). In both nr-axSpA and r-axSpA, Chinese patients were the youngest, reported the shortest time since chronic back pain onset and had the highest HLA-B27 prevalence. The frequency of peripheral manifestations did not differ between nr-axSpA and r-axSpA within the regions, however, significant differences were observed in the frequency between the regions: peripheral arthritis was most common in LA ($>50\%$ pts); enthesitis in LA and MEA regions ($\approx 50\%$), while dactylitis was not frequent with the highest prevalence again in LA ($\approx 12\%$). Similarly, the prevalence of Extra-articular manifestations (EAMs) also did not differ between nr-axSpA and r-axSpA patients within the regions. Uveitis was significantly more frequent in r-axSpA pts in LA (19%) and EC ($\approx 12\%$) vs China (6%). Psoriasis was almost absent in China, and had the highest frequency in EC and LA ($\approx 10\%$). There were no IBD cases reported in China, while the highest IBD prevalence was reported in EC (3 and 6% for r-axSpA and nr-axSpA, respectively). Use of NSAIDs did not differ between regions, but there were differences in the frequency of therapy with conventional DMARDs, glucocorticoids and TNF inhibitors.

Conclusion: The results showed differences between axSpA phenotypes between the geographic regions: peripheral manifestations were more prevalent in LA and MEA. EAMs were least frequent in Asian (Chinese) pts who were also the youngest, had the lowest disease activity and impairment in physical function.

Disclosure: **D. Poddubnyy**, AbbVie, Janssen, MSD, Novartis, Pfizer, BMS, Boehringer, UCB and Roche, 2, 5, 8; **R. D. Inman**, AbbVie, Amgen, Janssen, Lilly, Novartis, and Pfizer., 2, 5, 8; **J. Sieper**, AbbVie, Merck, Janssen, Lilly, Novartis, Pfizer, UCB, and Roche, 2, 5, 8; **F. Ganz**, AbbVie Inc., 1, 3; **M. Hojnik**, AbbVie Inc., 1, 3.

Abstract Number: 1617

Influence of Disease Activity in the Physical Activity of Psoriatic Arthritis Patients

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: It is generally assumed that patients with chronic arthritis conditions tend to exercise less than what is currently recommended. Although several evidences support this contention in rheumatoid arthritis patients, there is little data on the level of daily physical activity (PA) in psoriatic arthritis (PsA) patients vs. healthy controls, using objective procedures, such as accelerometry. Moreover, there is currently no evidence that decisively answers an important question concerning PA vis-à-vis PsA: Does disease activity influence PA in PsA patients?

The purposes of this study were to compare PA in a group of PsA patients versus healthy controls through both objective (triaxial accelerometry) and subjective (International Physical Activity Questionnaire- IPAQ) methods, and to explore the impact of disease levels on PA in these patients. We also sought to determine the potential role of PA assessment as a measure of PsA disease activity.

Methods: A group of 53 PsA patients and 36 age- and sex-matched healthy controls were included in this cross-sectional study. PA was assessed by accelerometry and with IPAQ in both groups. We performed multiple regression analysis not only to compare PA between groups, but also to explore the relationship between PsA features, including disease activity (assessed by DAS28-ESR, DAS28-PCR and DAPSA) and PA. In a randomized group of 36 PsA patients a test/re-test study was carried out 6 month after the first evaluation in order to determine the correlation between variation in disease activity and PA.

Results: The number of minutes of moderate and vigorous activity (MVPA)/day, as evaluated by accelerometry and adjusted for sex, age work activity was similar in PsA patients and in healthy controls (40 ± 29 vs 33 ± 15 min/day, $p=0.2$). In PsA patients, accelerometry and IPAQ demonstrated concordance to a moderate degree. When PA between the two visits of PsA patients was compared, a significant differences in minutes of MVPA was found (40 ± 29 vs 30 ± 22 min/day, $p=0.035$). Interestingly, variations in PA, as measured by accelerometry, inversely correlated with RA disease activity by DAS28-PCR ($r=-0.37$, $p=0.04$) and DAPSA ($r=-0.43$, $P=0.01$). When this analysis was done assessing disease activity by DAS28-ESR, a similar, but not significant tendency was observed ($r=-0.34$, $p=0.07$).

Conclusion: In PsA patients, accelerometry is a reliable technique to evaluate PA. This study not only showed that PsA patients spend similar time doing MVPA than healthy controls, but also PA, as assessed by accelerometry, was sensitive to any changes in disease activity.

Disclosure: M. V. Hernandez-Hernandez, None; H. Sanchez-Perez, None; E. Delgado-Frías, None; I. Ferraz-Amaro, None; F. Díaz-González, None.

Abstract Number: 1618

Adipose Tissue Inflammation in Psoriatic Arthritis: Overexpression of a Wide Array of Inflammatory Mediators and Associations with Disease and Treatment Characteristics

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SESSION INFORMATION

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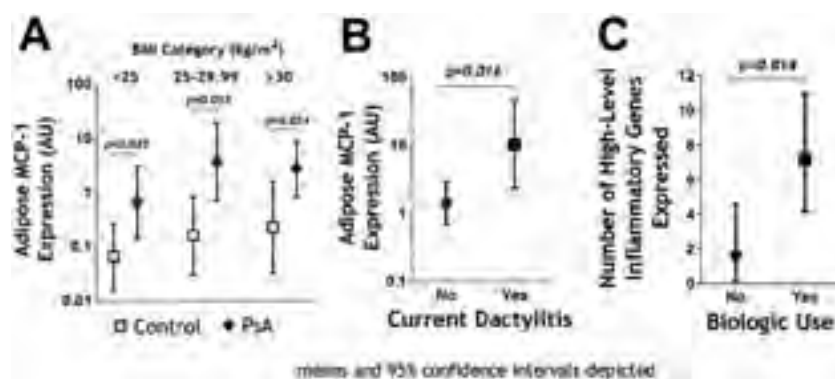
Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Obesity is associated with PsA risk, severity, and lack of response to DMARDs. However, no studies have explored adipose tissue inflammation at the molecular level and its associations with PsA features.

Methods: Periumbilical subcutaneous adipose tissue was obtained from 26 PsA patients without diabetes and compared with individuals with RA (n=42) and controls without rheumatic disease (n=21). Using real time polymerase chain reaction (RT-PCR), gene expression profiles for selected inflammatory cytokines, chemokines, macrophage and T cell markers, adipokines, and mediators of glucose and lipid metabolism were assessed and their correlations with PsA disease characteristics were compared between groups. Multivariable linear and logistic regression were used to adjust for relevant confounders.



Results: The PsA group [54% female, mean age 56 years, mean BMI 31.1 kg/m², median Composite Psoriatic Disease Activity Index (CPDAI)=4 units] did not differ significantly on age distribution compared with the RA or control groups. However, the PsA group was more frequently male and mean BMI was higher by 3.0-3.3 kg/m². In general, adipose expression of inflammatory and metabolism genes was many fold higher in the PsA group compared with the RA and control groups, with 17 genes meeting the Bonferroni corrected threshold of $p < 0.002$ [adiponectin, C3, MCP-1, CD4, HIF1a, IL-17R, IL-1, IL-4, IL-8, insulin receptor, leptin, NFkB, PPAR-gamma, PAI-1, osteopontin, STAT1, and TLR4], ranging from 4 to >450-fold higher in PsA vs. non-rheumatic controls, with little change after adjustment for sex and BMI. For each, higher expression was observed across all strata of BMI (Fig A depicted for MCP-1 as a representative example). Adipose MCP-1 expression was significantly associated with CPDAI (Spearman's $\rho = 0.402$; $p = 0.042$). CPDAI was also inversely associated with adipose GLUT4 expression, a key glucose transporter and indicator of insulin sensitivity (Spearman's $\rho = -0.434$; $p = 0.030$). The PsA feature with the strongest association with adipose MCP-1 expression was dactylitis (Fig B). Somewhat unexpectedly, those treated with biologics [$n = 18$; TNF inhibitors ($n = 16$), IL-17 inhibitors ($n = 2$)] had more extensive adipose expression of inflammatory genes, even with adjusting for CPDAI, BMI, and demographics. Those using biologics had an average of 7.2 adipose inflammatory genes expressed at high level (i.e. >75th percentile) vs. an average of 1.6 genes among those not treated with biologics ($p = 0.014$; Fig C).

Conclusion: PsA adipose tissue is a potent producer of inflammatory mediators that may contribute to disease phenotype. The potential for an off-target detrimental effect of biologics on adipose inflammation warrants additional study, particularly in light of reports of weight gain with TNF inhibitor use and a blunted effect of biologics among obese PsA patients.

Disclosure: J. H. Yun, None; R. Winchester, None; H. Z. Zhang, None; C. Depender, None; J. T. Giles, None.

Abstract Number: 1619

Patterns and Outcomes on AS Patients Disease Activity Using Smart System of Disease Management (SSDM): Analysis of T2T Pattern Shift and the Correlation between Disease Activity and Mental Health

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

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Session Time: 9:00AM-11:00AM

Background/Purpose: Ankylosing Spondylitis Disease Activity Score (ASDAS) was adopted to evaluate the degree of disease activity and the inflammatory response in AS patients. ASDAS score ≤ 1.3 represents inactive disease (ID) status and achievement of T2T. Hospital anxiety and depression scale (HADS) is commonly used to evaluate the mental health of chronic disease patients.

The purpose of this study is to evaluate pattern shifts and outcome trends of treat-to-target (T2T) under standard of care in ankylosing spondylitis (AS) patients and potential correlation between disease activity and mental health with interactive Smart System of Disease Management (SSDM).

Methods: SSDM is a set of disease management tool based on mobile internet. The patients were trained to master SSDM by health care professionals and conducted their ASDAS and HADS self-evaluations, then were required for repeated self-evaluation after leaving the hospital. After data entry, patients can synchronize data to the mobile terminal of their authorized rheumatologist.

Results: From Jan 2015 to May 2018, 8,175 AS patients from 373 hospitals registered on SSDM, with mean age of 34.17 ± 11.22 years and mean disease duration of 45.01 ± 56.42 months. Among them, 5,480 patients performed ASDAS evaluation at least once, totally 9,601 times; 1,368 (male 906, female 462) patients carried out repeated evaluation for 4,121 times and 551 patients performed HADS for 970 times during >6 months follow-up. Among patients repeated evaluate ASDAS, the final T2T rate was significantly increased to 38% from the baseline rate of 23% ($\chi^2 = 468.253$, $p < 0.001$) after median evaluation of 3 (2-29) times per patient. The mean score of ASDAS decreased from 2.22 ± 1.08 to 1.83 ± 1.07 (mean improvement -0.39 ± 0.58 , $p < 0.001$). Among T2T patients in baseline (318/1,368, 23%), 214/318 (67%) remained T2T and 104/318 (33%) relapsed at the end of follow-up. Among patients failed to T2T at baseline (1,050/1,368, 77%), 300/1,050 (29%) patients achieved T2T and 750/1,050 (71%) patients remain failure of T2T. The mean evaluation interval of the T2T achievers was significantly shorter than that of the failures (25 days vs. 42 days and 27 days vs. 40 days, $p < 0.05$). Analysis of the correlation between ASDAS and HADS showed that patients who achieved T2T had lower depress morbidity compared with the group which didn't achieve T2T (13% vs 27%, $p < 0.05$), but there was no difference of anxiety morbidity between the two subgroups (17% vs 21%, $p > 0.05$).

Conclusion: Significant improvement is observed under applying SSDM through empowering patients. The depress morbidity is higher in AS patients doesn't achieve T2T but anxiety stay same. Regularly performing self-management with SSDM associates with the achievements of maintaining T2T pattern and converting the patterns from failure of T2T to T2T. SSDM warrant a further evaluation and clinical application.

Disclosure: J. Xue, None; H. Song, None; J. Yang, None; Z. Zhang, None; C. Li, None; H. Li, None; Z. Wu, None; H. Wei, None; J. Huang, None; H. Wang, None; Y. Li, None; X. Wang, None; H. Wu, None; M. Zhang, None; Y. Jia, None; H. Xiao, None; F. Xiao, None; H. Wu, None.

Abstract Number: 1620

Lateral DXA More Effective in Detecting Osteoporosis Than Conventional DXA in Axial Spondyloarthritis

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Background/Purpose: The severe consequences of osteoporosis in the general population are well outlined. In axial spondyloarthritis (axSpA), osteoproliferation of the spine means posterioranterior (PA) dual-energy x-ray absorptiometry (DXA) can't discriminate between new bone formation and vertebral body, potentially overestimating BMD. To understand the impact of low BMD in axSpA, we need an accurate and reproducible method of assessment. Lateral DXA of the spine avoids spinal osteoproliferation and is an attractive option. The aim of this study was to compare lateral DXA of the lumbar spine with PA DXA, and determine patient variables that render conventional DXA unreliable.

Methods: Patients fulfilling modified New York (mNY) or Assessment of Spondyloarthritis International Society (ASAS) criteria were consecutively recruited from rheumatology clinics in this twin-centre cross-sectional study. A detailed assessment of patients included demographics, clinical exam, laboratory assessment and validated measures of disease severity (BASDAI, ASDAS-CRP, BASMI, mSASSS). BMD of the spine was assessed using DXA in the lateral and PA projections. BMD of the hip was assessed in the conventional manner. R software was used for statistical analysis.

Results: One hundred and ten patients were assessed, 100 of whom had paired AP and lateral DXAs: 76% (n=84) male, 92% Caucasian, 81% mNY criteria. Median(IQR) age was 52 (17) years, disease duration 23.5 (20) years, delay to diagnosis 7 (12) years, body mass index (BMI) $27.6 (6.3)$ kg/m², BASDAI 3.9 (2.1-5.6), BASMI 4.1 (2.8-5.8), ASDAS-CRP 2.2 (1.5-3), mSASSS 8.5(2-36).

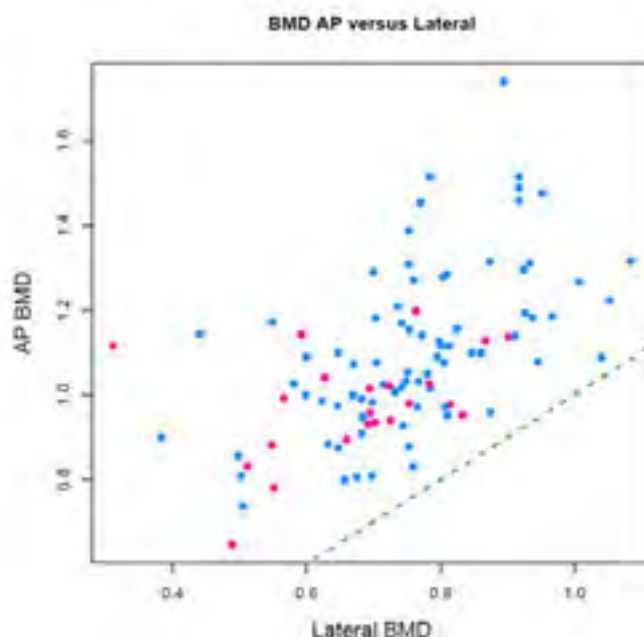
Lateral spine BMD is significantly lower than PA BMD (see figure 1), with a mean difference between AP and lateral lumbar spine DXA of 0.337 g/cm² (95% CI 0.3-0.37), and detects more cases of both osteopenia (27% versus 17%) and osteoporosis (16% versus 2%) at the spine ($p < 0.01$). The prevalence of osteopenia at the hip is 25% and osteoporosis is

1%. When combined with hip DXA to assess for low BMD at any site, using lateral DXA characterises 52% of the cohort as having low BMD, in comparison to 36% when AP DXA is used ($p<0.01$).

The following variables correlate with a larger difference between the measurement of AP and lateral DXA: BASMI ($r=0.54$), disease duration($r=0.37$), BMI ($r=0.32$), mSASSS ($r=0.52$).

In multiple regression analysis, a model with disease duration, BMI, BASMI and shorter time to diagnosis predicts a greater difference between AP and lateral BMD ($p<0.05$).

Figure1: Plot of difference between AP and lateral BMD. The dashed line indicates equal BMD for both scanning methods.



Conclusion: Lateral DXA detects more cases of low BMD than PA DXA, particularly in patients with higher BASMI and BMI and longer disease duration. Continuing to rely on AP DXA will miss a significant number of axSpA patients with low BMD. Lateral DXA is a practical and feasible tool suitable for use in clinical practice and should be considered as an alternative to PA when measuring BMD in the lumbar spine.

Disclosure: G. Fitzgerald, None; J. Wyse, None; T. Anachebe, None; R. Mullan, None; D. Kane, None; K. McCarroll, None; F. O' Shea, None.

Abstract Number: 1621

Higher Serum Uric Acid Levels Protect Against Osteoporosis in Patients with Axial Spondyloarthritis

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Background/Purpose: High serum urate (SUA) is a risk factor for metabolic disease, including hypertension and coronary artery disease. However, SUA has an antioxidant effect and can play a role in protecting against diseases characterised by high oxidative stress, such as neurodegenerative disease. Osteoporosis, a condition defined by bone loss and fragility fractures, is also characterised by high oxidative stress levels, mediated through increased osteoclastic activity. Therefore,

antioxidants are of considerable interest due to theoretical protective properties against bone loss. Existing literature examining SUA and its impact on bone mineral density (BMD), particularly in axial spondyloarthritis (axSpA), is limited. The aim of this study is to examine the relationship between SUA and BMD in a well-characterised axSpA cohort.

Methods: Patients fulfilling modified New York (mNY) or Assessment of SpondyloArthritis International Society (ASAS) criteria were consecutively recruited from 2 centres in this cross-sectional study. Patients underwent a detailed assessment: demographics, disease-related variables (validated measures of disease activity included BASDAI, ASDAS-CRP, BASMI), clinical examination, laboratory parameters (routine bloods, SUA, CRP, vitamin D). BMD was assessed using dual-energy x-ray absorptiometry of the lumbar spine and hip (total hip and femoral neck). SUA >360 µmol/L (>6 mg/dL) was considered high. Analysis was performed using SPSS.

Results: A total of 107 patients were included: 76% male, 81% fulfilling mNY criteria, median (IQR) age 51.5 (17.8) years, disease duration 23.5 (20.4) years. Median BMI was 27.6 (6.5) kg/m², with 31% of the cohort obese. The median (interquartile range [IQR]) BASDAI was 3.9 (3.6), ASDAS-CRP 2.1 (1.5) and BASMI 4.1 (3.2). Low BMD was present in 38.5% of the cohort and 44% had a previous fracture.

Median (IQR) SUA in the cohort was 312 (119) µmol/L, with a SUA >360 µmol/L present in 34% (n=36). More men than women had high SUA (94% v 5.6%, p<0.01). BMI was significantly higher in those patients with SUA above 360 µmol/L than patients with normal levels (mean difference 4.2 kg/m², 95% CI 2.1-6.3). Age, disease duration, axSpA disease severity, psoriasis prevalence, vitamin D and CRP were equal in patients with high and normal levels of SUA.

SUA correlated positively (p<0.01) with BMD at the spine (r=0.3) and total hip (r=0.3). The cohort was subsequently examined in 3 groups of SUA: <300 µmol/L (43% of cohort), 300-360 µmol/L (23%) and >360 µmol/L (34%); mean BMD increased at the spine and total hip across the 3 groups (p<0.05), but not at the femoral neck.

Patients with a high SUA had significantly less osteopenia or osteoporosis (19%) than patients with a normal SUA (46%) (OR 3.5, 95% CI 1.4-9.3).

In univariate logistic regression analysis, low SUA and low BMI were associated with low BMD. After correcting for obesity, patients with high SUA remained independently associated with normal BMD compared to those patients with a normal SUA (OR 3.4, 95% CI 1.2-9.6).

Conclusion: This study demonstrates that high SUA levels are independently associated with normal BMD, suggesting a protective effect of SUA against osteoporosis in axSpA patients.

Disclosure: G. Fitzgerald, None; T. Anachebe, None; R. Mullan, None; D. Kane, None; K. McCarroll, None; F. O' Shea, None.

Abstract Number: 1622

ASAS Consensus on Spanish Nomenclature for Spondyloarthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: In the last three decades, major advances in the spondyloarthritis (SpA) field have been achieved leading to new terminology. Whilst this terminology is well established in English, there is concern about the disparity of translated words and acronyms in Spanish, which is used by more than 437 million people in 21 countries. Our aim was to develop a consensus to standardize the use of Spanish terms, abbreviations and acronyms in the field of Spondyloarthritis (SpA).

Methods: An international task force comprising all ASAS Spanish-speaking members, the executive committee of GRESSER, two methodologists, two linguists from Real Academia Nacional de la Medicina Española (RANM) and two patients from CEADE was established. A literature review was performed to identify the conflicting terms/abbreviations/acronyms in SpA. This review examined written sources in Spanish including manuscripts, ICF and ICD, guidelines, recommendations and consensus. A nominal group meeting and three-round Delphi was followed. There were commendations from the RANM based on the Pan-hispanic dictionary were followed throughout the process.

Results: Consensus was reached for 46 terms, abbreviations or acronyms related to the field of SpA. A Spanish translation was accepted for 6 terms and 6 abbreviations to name or classify the disease, and for 6 terms and 4 abbreviations related to SpA (Table 1). In addition, it was agreed not to translate into Spanish 15 acronyms because these are very well established. However, when mentioning these, it was decided to recommend following this structure: type of acronym in Spanish and acronym and expanded form in English (Table 2). With regards to 7 terms or abbreviations attached to acronyms, it was agreed to translate only the expanded form and a translation was also selected for all of them.

Conclusion: Through this standardisation, it is expected to establish a common use of the Spanish nomenclature for SpA. The implementation of this consensus across the community will be of substantial benefit, avoiding misunderstandings and time-consuming procedures.

Table 1. Terms and abbreviations recommended by the group of experts.

#	English term (abbreviation)	Spanish term	Spanish abbreviation
1	Spondyloarthritis (SpA)	Espondiloartritis	EspA
2	Axial spondyloarthritis (axSpA)	Espondiloartritis axial	EspAax
3	Ankylosing spondylitis (AS), radiographic spondyloarthritis (r-SpA)	Espondilitis Anquilosante	EA
4	Non radiographic axial spondyloarthritis (nr-axSpA)	Espondiloartritis axial no radiografica	EspAax-nr
5	Peripheral spondyloarthritis (pSpA)	Espondiloartritis periferica	EspAp
6	Psoriatic arthritis (PsA)	Artritis psoriasica	APs
7	Inflammatory back pain (IBP)	Dolor lumbar inflamatorio	DLI
8	Magnetic resonance imaging of the sacroiliac joints (MRI-SI)	Resonancia Magnética de articulaciones sacroilíacas	RM-SI
9	Bone marrow edema (BME)	Edema de médula ósea	EMO
10	Modified New York criteria (mNY)	Criterios de Nueva York modificados	NYm

Table 2. Recommended structure to name acronyms and terms related to these acronyms.

2A	Acronyms	LoA
1	Grupo ASAS (Assessment in SpondyloArthritis International Society)	100%
2	Índice de actividad ASDAS (Ankylosing Spondylitis Disease Activity Score)	100%
3	Índice de actividad BASDAI (Bath Ankylosing Spondylitis Disease Activity Index)	100%
4	Índice de calidad de vida ASQoL (Ankylosing Spondylitis. Quality of Life)	100%
5	Índice de calidad de vida PsAQoL (Psoriatic Arthritis Quality of Life)	100%
6	Índice ecográfico MASEI (Madrid Sonographic Enthesitis Index)	100%
7	Índice de entesitis MASES (Maastricht Ankylosing Spondylitis Enthesitis)	100%
8	Índice funcional BASFI (Bath Ankylosing Spondylitis Functional Index)	100%
9	Índice global BAS-G (Bath Ankylosing Spondylitis patient Global score)	94%
10	Índice metroológico BASMI (Bath Ankylosing Spondylitis Metrology Index)	94%
11	Índice de psoriasis PASI (Psoriasis Area and Severity Index)	100%
12	Índice radiográfico BASRI (Bath Ankylosing Spondylitis Radiology Index)	100%
13	Índice radiográfico mSASSS (modified Stoke Ankylosing Spondylitis Spine Score)	100%
14	Índice radiográfico PARS (Psoriatic Arthritis Ratingen Score)	100%
15	Índice radiográfico RASSS (Radiographic AS Spinal Score)	94%
2B	Terms related to these acronyms	
1	Índice de salud ASAS-HI (Assessment in SpondyloArthritis international Society- Health Index)	94%
2	Criterio de mejora ASAS 20 (ASAS 20 improvement criteria)	91%
3	Criterio de mejora ASAS 40 (ASAS 40 improvement criteria)	100%
4	Criterio de mejora ASAS 5/6 (ASAS 5/6 improvement criteria)	100%
5	Gran mejora-ASDAS [ASDAS-MI (major improvement)]	83%
6	Mejora clínica-ASDAS [ASDAS-CI (clinical improvement)]	72%
7	Remisión parcial-ASAS (ASAS partial remission)	70%

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Insight into the Quality of Life of Patients with Ankylosing Spondylitis: Real-World Data from a US-Based Life Impact Survey

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

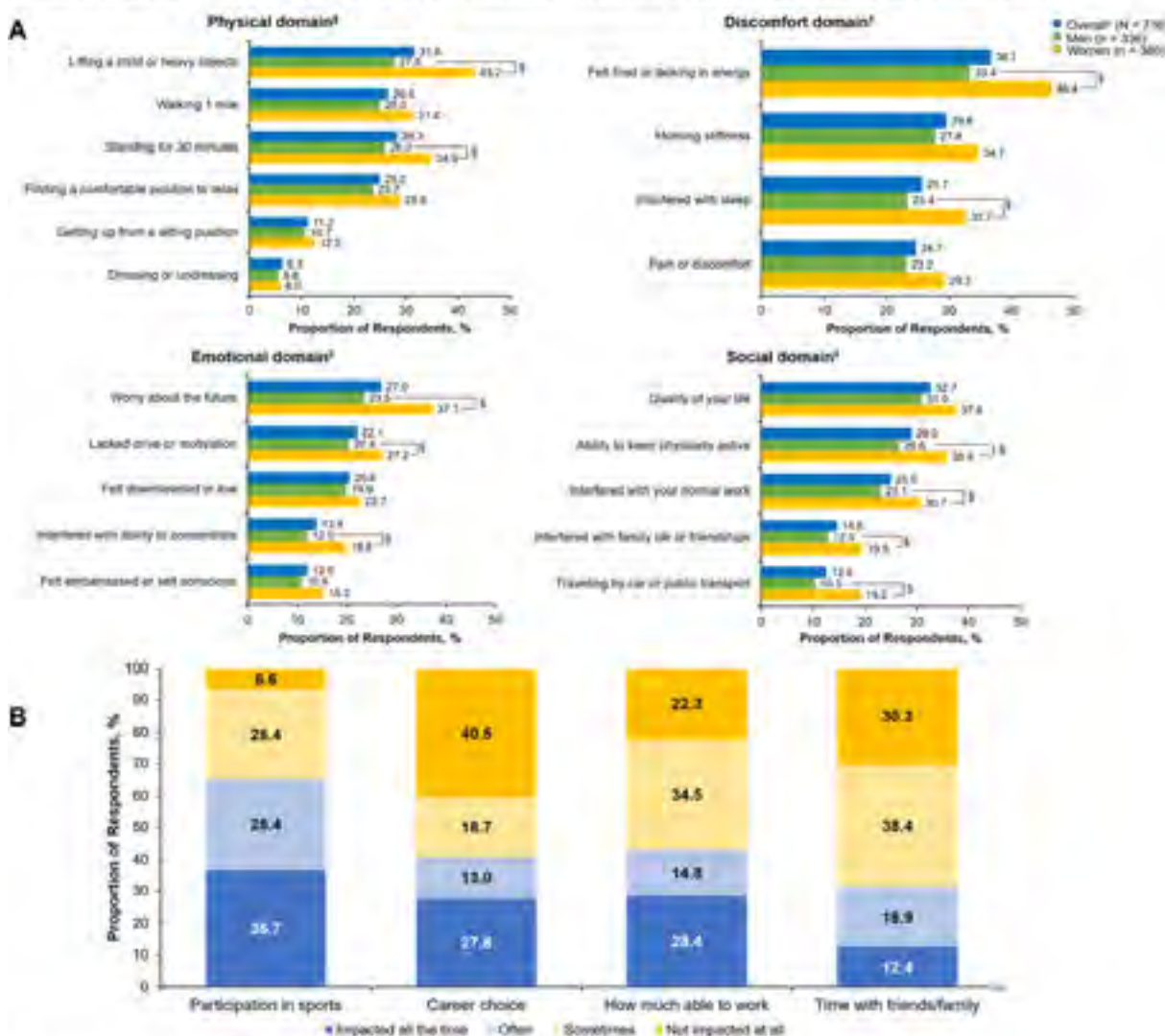
Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: While severe pain and stiffness are common hallmarks of ankylosing spondylitis(AS), disease progression is slow and not always visible; however, the quality of life (QoL) of patients with AS is still significantly impacted. We aimed to assess patient-reported impact of AS on QoL in the physical, discomfort, social, and emotional domains among US patients with AS in a real-world setting.

Figure 1. (A) Proportion of respondents with AS reporting the top two levels of impairment by their disease across 4 domains of disease stratified by sex,* and **(B)** respondent-reported impact of AS on lifestyle characteristics†



AS, ankylosing spondylitis; QoL, quality of life.

* Respondents were "very limited" or "totally limited/unable to do" each activity as a result of their AS.

† Weighted 3:1 (male to female).

‡ For activities related to the physical domain, respondents were queried on the impact of AS on their QoL on the day of survey participation.

§ P < 0.05, male vs female.

¶ For activities related to the discomfort, emotional, and social domains, respondents were queried on the impact of AS on their QoL during the previous week.

Methods: Descriptive data on demographics and QoL were collected from a random sample of patients associated with the Spondylitis Association of America (SAA). QoL measures were based on the Evaluation of Ankylosing Spondylitis Quality of Life (EASi-QoL) questionnaire (scale, 0-80, with higher score indicating more severe impact). Between July 7 and December 31, 2017, 820 interviews were conducted with SAA contacts via web survey or follow-up over the phone. Of 820 participants who completed the survey, 716 self-reported receiving a diagnosis of AS from their doctor and were included in this study. Participants were queried on the impact of AS on their QoL within the day of survey participation with regard to the physical domain, and within the past week prior to participation with regard to the discomfort, social, and emotional domains. A 3:1 (male to female) weighting was performed to reflect the reported prevalence of spondyloarthritis in US adults.

Results: The mean age of the 716 respondents was 55.5 years; 46.9% were male. The most common locations of pain reported were the lumbar spine (86.8%), neck (84.1%), and hip joint (80.2%). The mean total EASi-QoL score was 28.9; overall, 33.7%, 31.7%, and 34.7% of respondents, respectively, reported low (EASi-QoL score 0-17), medium (18-35), and high (≥ 36) impact of AS on QoL (weighted). Physical aspects of the disease contributed the most impact, with 41.9% of respondents (weighted) reporting high impact of AS on the physical domain (EASi-QoL score ≥ 10). The proportion of respondents reporting high impact of AS (ie, the top 2 levels of impairment for each question) in the 4 QoL domains is shown in **Figure 1A**. Women were significantly more likely than men to report high impact of AS in several aspects in all QoL domains, such as lifting a child or heavy objects (43.2% vs 27.8%), worrying about the future (37.3% vs 23.5%), feeling tired or lacking in energy (46.4% vs 33.4%), sleep interference (32.7% vs 23.4%), trouble keeping physically active (35.9% vs 26.6%), standing for 30 minutes (34.9% vs 26.0%), and traveling by car or public transport (19.2% vs 10.5%). AS also impacted their lifestyle, as shown in **Figure 1B**.

Conclusion: Negative impacts in all QoL domains were reported, with a mean overall EASi-QoL score of 28.9. Sex differences were also pronounced in several aspects, including lifting a child or heavy objects, and worrying about the future. Incorporating subjective measures of disease via patient-reported outcomes should be considered with evaluation of disease progression.

Disclosure: J. T. Rosenbaum, Alcon Research Institute, the Spondylitis Association of America (SAA), and Pfizer, 2, AbbVie, Gilead, Novartis, Regeneron, and UCB, 5; Novartis, 1; UpToDate, 7; L. Pisenti, UCB, Inc., 3; Y. Park, Novartis Pharmaceuticals Corporation, 3; R. Howard, Spondylitis Association of America, 3.

Abstract Number: 1624

Real-World Insight into the Disease Burden and Treatment of Spondyloarthritis from a US-Based Life Impact Survey

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

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Session Time: 9:00AM-11:00AM

Background/Purpose: Spondyloarthritis (SpA) is a group of chronic, inflammatory diseases associated with severe pain in the joints and entheses. There is limited evidence on real-world disease burden and treatment patterns in the overall SpA population, as well as individual SpA conditions. This study surveyed self-reported burden of disease and medication use in US patients with SpA in a real-world setting.

Methods: Descriptive data on demographics, disease definition and history, and medication were collected from a random sample of patients with SpA associated with the Spondylitis Association of America (SAA). Between July 7 and August 31, 2017, 820 interviews were conducted with SAA contacts, including 720 completed via Websurvey (from 7750 emails) and 100 via follow-up over the phone (from 10,784 phone calls made to 5000 unique numbers). All 820 participants self-reported receiving a diagnosis of SpA from their doctor and were included in this study.

Results: The mean age of the 820 respondents was 55.1 years, and 44.3% were male. The most common self-reported SpA disease was ankylosing spondylitis (AS; 87.3%), followed by uveitis/iritis (28.3%). The most frequently reported comorbidities were high blood pressure (34.8%), high cholesterol (26.5%), and depression (23.4%). Compared with women, men were more impacted by high blood pressure (42.7% vs 28.5%) and heart disease (14.0% vs 4.0%), and less impacted by fibromyalgia (4.2% vs 22.1%). Acid reflux (50.7%) and eye inflammation (45.2%) were also common issues experienced among respondents. On average, respondents with AS first noticed disease symptoms 26.6 years ago, and

Table 1. Summary of Treatment History and Overall Satisfaction With Current Treatment Among Respondents With SpA

Treatment, n (%)	Respondents With SpA (N = 820)		
	Currently Taking	Taken in the Past	Never Taken
Analgesics			
Acetaminophen	191 (23.3)	485 (59.1)	144 (17.6)
Biologics			
Adalimumab	145 (17.7)	253 (30.1)	428 (52.2)
Certolizumab pegol	28 (3.4)	42 (5.1)	750 (91.5)
Etanercept	82 (10.0)	245 (29.9)	493 (60.1)
Golimumab	16 (2.2)	62 (7.6)	740 (90.2)
Infliximab	85 (10.4)	133 (16.2)	602 (73.4)
Secukinumab	48 (5.9)	21 (2.6)	751 (91.6)
Ustekinumab	0	15 (1.8)	801 (97.7)
Cannabis			
Medical marijuana	54 (6.6)	64 (7.8)	702 (85.6)
NSAIDs			
Ibuprofen	153 (18.7)	544 (66.3)	123 (15.0)
Indomethacin	33 (4.0)	267 (32.6)	520 (63.4)
Naproxen	105 (12.8)	510 (62.2)	105 (25.0)
Opioids			
Hydrocodone	67 (8.2)	289 (35.2)	464 (56.6)
Oxycodone	55 (6.7)	198 (24.2)	566 (69.0)
PDE4 inhibitor			
Apremilast	0	19 (2.3)	799 (97.4)
SAARDs			
Methotrexate	78 (10.9)	221 (27.0)	510 (62.2)
Sulfasalazine	80 (9.8)	235 (28.7)	505 (61.6)
Steroids			
Cortisone	22 (2.7)	320 (44.7)	440 (53.6)
Hydrocortisone	22 (2.8)	272 (33.2)	525 (64.0)
Prednisone	82 (10.0)	459 (56.0)	279 (34.0)
Overall Satisfaction With Current Treatment, n (%)	Respondents with SpA (N = 820)		
Completely satisfied		127 (15.5)	
Mostly satisfied		319 (38.9)	
Somewhat satisfied		178 (21.7)	
Slightly satisfied		73 (8.9)	
Not satisfied		59 (7.2)	
Unsure/not available		64 (7.8)	

NSAIDs, nonsteroidal anti-inflammatory drugs; PDE, phosphodiesterase; SAARDs, slow-acting anti-rheumatic drugs; SpA, spondyloarthritis.

received an AS diagnosis \approx 8.2 years later. Respondents saw an average of 2.2 doctors about their back pain, joint pain, or inflammatory problems within the last 2 years, including 20.7% of respondents who saw \geq 4 doctors. Regarding treatment, 76.7% of respondents with AS received care from rheumatologists, 8.7% from primary care physicians, and 3.8% from orthopedic surgeons; 57.5% of respondents with AS discussed medication options with their doctor and jointly participated in treatment decisions. Prior and current medications are shown in **Table 1**. More than one-half of respondents (54.4%) were at least mostly satisfied with their current treatment. Many respondents also applied non-medicinal treatment to their lifestyle, including stretching and strengthening exercises (66.2%); biking, running, or walking (57.4%); practicing proper posture techniques (56.5%); and special diets (39.4%).

Conclusion: In this real-world survey, most respondents reported substantial delays in diagnosis of AS, received care from rheumatologists, and participated in making treatment decisions. Many respondents indicated making lifestyle modifications in addition to using pharmacologic treatment. These data provide valuable insight into patient-reported disease burden and treatment profile of US patients with SpA.

Disclosure: J. T. Rosenbaum, Alcon Research Institute, the Spondylitis Association of America (SAA), and Pfizer, 2, AbbVie, Gilead, Novartis, Regeneron, and UCB, 5; Novartis, 1; UpToDate, 7; L. Pisenti, UCB, Inc., 3; Y. Park, Novartis Pharmaceuticals Corporation, 3; R. Howard, Spondylitis Association of America, 3.

Association of HLA-B Type and Sacroiliitis in Patients with Psoriatic Arthritis

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SESSION INFORMATION

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Background/Purpose: Psoriatic arthritis (PsA) is a heterogeneous disease with strong genetic heritability. Class I major histocompatibility complex (MHC) genes have been associated with PsA phenotype (1), though data is limited. The goal of this study was to establish the frequency of human leukocyte antigen (HLA)-B alleles in patients with PsA at our center and evaluate associations of allele frequency with radiographic sacroiliitis and other clinical features of PsA.

Methods: This was a retrospective observational study of patients with PsA at a tertiary academic medical center where patients were identified by ICD code and confirmed to have PsA by an experienced treating rheumatologist. Patients with HLA-B locus testing by reverse sequence specific oligonucleotide (SSO) hybridization were included in the study. Background demographics including age, sex, and ethnicity as well as available radiographs of the sacroiliac joints and MRI exams of the pelvis were collected. Clinical features of psoriatic skin disease, dactylitis, enthesitis, uveitis, and nail disease were also noted. Frequencies of HLA-B alleles were calculated for PsA patients with and without sacroiliitis, then compared to estimates from the general population based on ethnic mix (2). Associations between HLA-B alleles and sacroiliitis on imaging were evaluated with Fisher's exact test

Results: We identified 234 patients using ICD coding for psoriatic arthritis from outpatient visits with the treating rheumatologist. Of those, 89 patients did not have HLA-B locus testing and were excluded. 146 PsA patients were included in the study with mean age 48.6 ± 13.5 years, 56.8% female, 76.7% Caucasian, 8.2% Asian, 7.5% Hispanic, and 1.4% African American. The most common HLA-B alleles amongst PsA patients were HLA-B*35, B*44, B*8, B*7, B*27, and B*38 (Figure 1). X-rays of the sacroiliac joints were available in 86 patients, with 11 cases of radiographic sacroiliitis (12.8%). MRI of the pelvis was available in 25 patients, with 8 cases of sacroiliitis found (six previously noted on x-ray, and two pre-radiographic). Among patients with imaging-proven sacroiliitis, HLA-B*35, B*8, and B*38 were the most common alleles and significantly associated with sacroiliitis ($p = 0.03$).

Conclusion: In patients with psoriatic arthritis, HLA-B alleles B*35, B*8, and B*38 may be associated with sacroiliitis. Further larger studies would be helpful in determining the role of HLA-B gene subtypes as predictors of disease features in psoriatic arthritis.

Reference: 1. Haroon M, et al. Ann Rheum Dis 2016;75:155-162

2. Maier M, et al. Hum Immunol 2007;68(9):779-88

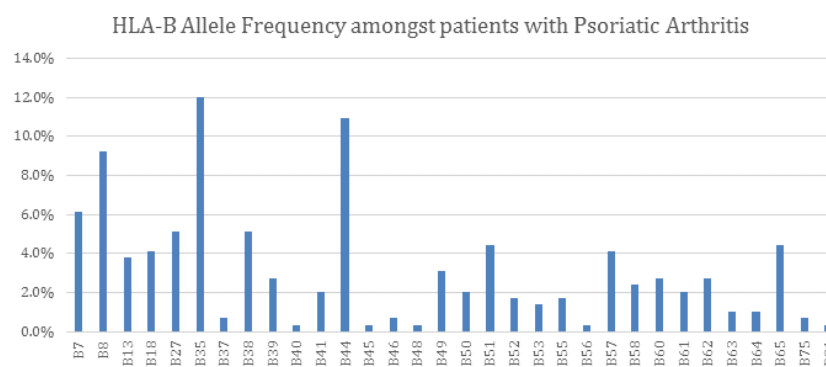


Figure 1

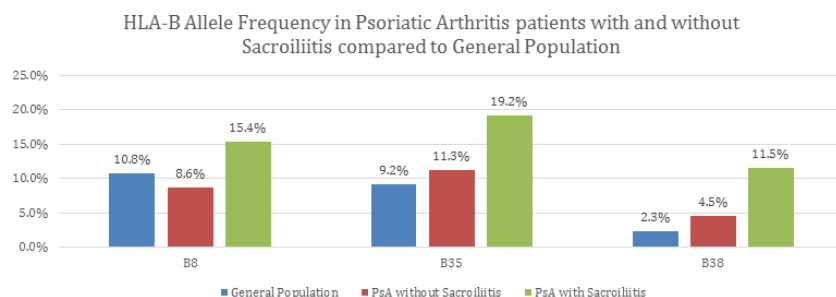


Figure 2

Disclosure: D. Kuo, None; I. Valera, None; M. Taylor, Celgene Corporation, 8, AbbVie Inc., 8; R. Altman, Ferring, 5, Flexion, 5, GlaxoSmithKline, 5, Novartis, 5, Olatec, 5, Pfizer, Inc., 5; V. K. Ranganath, Genentech, Inc., 2, Pfizer, Inc., 2, Mallinckrodt, 2, Amgen Inc., 5; T. Aung, None; J. Louie, Novartis, 5, Eli Lilly and Co., 5, AbbVie Inc., 5, AbbVie Inc., 8, Amgen Inc., 8, Pfizer, Inc., 8; S. Kafaja, None.

Abstract Number: 1626

The Disease Expression in Familial and Sporadic Axial Spondyloarthritis Patients

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SESSION INFORMATION

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Background/Purpose: Familial aggregation of the SpA in particular AS has long been known and up to 40% of AS patients have a positive family history of SpA. However differences in disease expression in familial and sporadic cases were evaluated in a few studies and there are some discrepancies among those reports. Therefore our aim was to explore the frequency of familial cases in our axial SpA (axSpA) patients and to evaluate the effects of family history of SpA according to the ASAS recommendations on disease phenotype.

Methods: In total 526 patients with axSpA (325 [62%] male; mean age 42.3 ± 11.9 years) followed up in one center were included in the analysis. The study group was consisting 358 (68%) AS and 168 (32%) non radiographic-axSpA patients. Family history of SpA is determined as in ASAS classification criteria and defined as the presence of any of the followings in the first or second-degree relatives; AS, acute anterior uveitis (AAU), ReA, psoriasis, or IBD. Demographic data and disease related characteristics including disease activity, function, quality of life and spinal mobility were collected with a structured method. Structural damage was evaluated by using modified Stoke Ankylosing Spondylitis Spine Score (mSASSS).

Results: 134 (25.5%) of our patients had family history of SpA. AS (102/134; 76.1%) and psoriasis (46; 34.3%) were most frequently found diseases in family history. 89 patients (66%) had affected FDR and 40 (29.8%) had more than one affected family member. Female sex, psoriasis and HLA-B27 positivity were more frequent in familial cases in comparison with sporadic ones. They also had longer symptom duration (Table). However other disease related characteristics including disease activity, spinal mobility and structural damage at the time of assessment were similar between familial and sporadic axSpA patients. Among patients with positive family history, men had higher mSASSS scores (19.0 ± 26.1 vs 3.4 ± 12.4 $p < 0.001$) than women. However in sporadic cases this was not statistically significant (19.0 ± 26.1 vs 14.6 ± 22.8 $p: 0.481$).

Conclusion: In our study group familial axSpA had longer disease duration and more frequent HLA-B27 positivity. However disease expression including functional limitation and structural damage did not differ between familial and sporadic cases.

Table 1 Demographics and clinical features Axial Spondyloarthritis patient with or without family history

Variables	Familial axSpA patients (n=134)	Sporadic axSpA patients (n=392)	P
Age; mean \pm SD	43.7 \pm 12.0	41.8 \pm 11.8	0.086
Female; %	47.0	35.2	0.015
Symptom duration; mean \pm SD	16.6 \pm 11.7	13.6 \pm 9.4	0.018
Delay in diagnosis;	7.4 \pm 8.7	6.7 \pm 7.4	0.379
Smoking (ever); %	71.6	70.5	0.797
BMI ; mean \pm SD	26.6 \pm 4.8	26.4 \pm 8.8	0.135
Peripheral arthritis (ever), %	49/132; 37.1	121/346; 35.0	0.661
Enthesitis (ever), %	53.4	48.4	0.380
Dactylitis (ever), %	1.5	2.3	0.734
Uveitis (ever), %	11.9	10.9	0.750
Psoriasis, %	12.0	2.3	<0.001
IBD, %	2.3	3.4	0.762
IBP (any criteria), %	88.8	91.3	0.400
NSAID response rate, %	89.2	89.1	0.983
HLA B27 positivity, %	71.2 (74/104)	57.4 (155/270)	0.018
CRP mg/dl; mean \pm SD	13.6 \pm 21.0	15.5 \pm 23.6	0.261
BASFI; mean \pm SD	3.7 \pm 2.8	3.5 \pm 2.7	0.374
BASDAI; mean \pm SD	4.4 \pm 2.3	4.2 \pm 2.3	0.615
ASDAS-CRP; mean \pm SD	2.9 \pm 1.1	2.9 \pm 1.1	0.755
BASMI; mean \pm SD	2.8 \pm 2.2	2.6 \pm 2.2	0.493
mSSASS; mean \pm SD	12.2 \pm 22.5	11.8 \pm 20.8	0.649
Presence of syndesmophyte , %	55.3 (52/94)	60.9 (176/289)	0.338
Hip involvement , %	14.2 (18/127)	20.5 (76/369)	0.117

Disclosure: D. Solmaz, None; O. Gercik, None; G. Kabadayı, None; S. Akar, None.

Abstract Number: 1627

Assessment of Myocardial Dysfunction Using Speckle Tracking Echocardiography in Patients with Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that mainly affects axial skeleton. Although some differences like sex and objective signs of inflammation were described between ankylosing spondylitis and non-radiographic (nr-) axSpA patients, overall disease burden was found to be similar in these subgroups of axSpA. The association of chronic inflammation with cardiac dysfunction was well documented in many inflammatory rheumatic diseases. However it was not assessed in the subgroups of axSpA. Advanced two-dimensional (2D) speckle tracking echocardiographic analysis is more sensitive and accurate method of early detection of myocardial dysfunction than the conventional 2D transthoracic echocardiography (TTE). Therefore the aim of this study was to evaluate the left ventricular function by using speckle tracking echocardiography in patients with both r- and nr-axSpA.

Methods: In total 72 patients with ankylosing spondylitis (72% male) and age- and sex-matched 38 patients with nr-axSpA (58% male) and 56 healthy control subjects (54% male) were included in the analysis. Patients with hypertension, diabetes and known cardiac disease were excluded. All patients underwent detailed echocardiographic examination including M-mode, pulsed-wave Doppler imaging, pulsed-wave tissue Doppler imaging and 2D speckle tracking.

Results: Age and sex distribution were not different between groups. Some demographic and disease related characteristics were shown in the table. BASDAI, BASFI, global assessment of disease activity and ASAS-HI scores were found to be similar between r- and nr-axSpA patient groups. Although ejection fraction (EF) (P=0.449) and the other echocardiographic variables were similar between groups, global longitudinal strain (GLS) (P=0.004) was found to be different among groups (table) in ANOVA analysis. Post-hoc tests showed that GLS was similar between nr-axSpA and

control groups however GLS was significantly low in r-axSpA patients. In univariate analysis GLS was correlated with age (P=0.032) and peripheral arthritis (P=0.035). However in regression analysis peripheral arthritis (P=0.009) was found as the only independent predictor of GLS.

Conclusion: The results of the present study showed that left ventricular function had impaired in ankylosing spondylitis patients and impaired ventricular function might also be the other differentiating factor between radiographic and nr-axSpA patients.

Table. The demographic and disease related characteristics of study groups.

	Ankylosing Spondylitis (n=72)	Non-radiographic axSpA patients (n=38)	Control subjects (n=56)	p
Age, years (mean \pm SD)	39.2 \pm 9.9	37.0 \pm 10.6	40.9 \pm 7.2	0.137
Duration of disease, years (mean \pm SD)	12.9 \pm 8.1	8.0 \pm 7.8	N/A	N/A
BASDAI, (mean \pm SD)	2.8 \pm 2.3	3.0 \pm 1.7	N/A	N/A
BASFI, (mean \pm SD)	2.7 \pm 2.5	2.2 \pm 1.9	N/A	N/A
Ejection fraction, (mean \pm SD)	59.2 \pm 5.3	59.9 \pm 4.6	60.3 \pm 4.6	0.449
Global Longitudinal Strain, (mean \pm SD)	20.5 \pm 3.3	21.1 \pm 3.5	22.3 \pm 2.4	0.004

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Is Axial Psoriatic Arthritis Distinct from Ankylosing Spondylitis with and without Concomitant Psoriasis?

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Background/Purpose: Spondyloarthritis include two major phenotypes: ankylosing spondylitis (AS) and psoriatic arthritis (PsA). 10% of AS patients have concomitant psoriasis, while 25% - 70% of PsA patients have axial disease. The question arises whether AS with concomitant psoriasis and axial PsA are essentially the same disease?

The aim of this study was to compare the demographic, genetic, clinical and radiographic characteristics of patients with AS, with and without psoriasis, to axial PsA patients.

Methods: A retrospective analysis of prospective observational cohorts was performed. Four cohorts of patients were recruited from AS and PsA clinics at one center: 1. AS without psoriasis, 2. AS patients with psoriasis (ASPs), 3. Axial PsA patients (radiographic sacroiliitis: \geq bilateral grade 2 or unilateral grade 3), 4. Peripheral PsA patients. All patients were 18 years old and were followed prospectively according to the same protocol. The four groups were compared using ANOVA and Pearson chi-square tests. Axial PsA was subsequently compared specifically to the ASP group using the appropriate tests. Adjusted means (AM) were used for variables that change over time. They were calculated by plotting the values of the variables over time and calculating the area under the curve. AM more accurately account for the varying time intervals between visits that are common in the usual clinic setting. A logistic regression was performed to assess the differences in clinical and radiographic features between ASP vs. axial PsA adjusting for demographic and genetic variables and follow-up duration. When $p < 0.05$ the results were considered statistically significant.

Results: Table number 1: Four group comparison

Variable	Ankylosing spondylitis		Psoriatic arthritis		P Value
	Without psoriasis (N=675)	With psoriasis (N=91)	Axial (N=477)	Peripheral (N=826)	
Age at diagnosis	30.4 (12.0)	28.7 (11.0)	35.6 (13.3)	39.3 (13.7)	z0.001
Male gender n (%)	489 (72%)		303 (64%)	414 (50%)	<0.001
HLA-B*27 n (%)	509 (75%)	75 (82%)	91 (19%)	77 (9%)	<0.001
Adjusted mean active arthritis (tender + swollen joints) (SD)	0.9 (2.2)	1.5 (3.5)	5.4 (6.2)	5.6 (6.6)	<0.001
Back pain at presentation n (%)	82 (90%)	618 (92%)	89 (19%)	253 (31%)	<0.001
Adjusted mean ASDAS ESR - (SD)	2.2 (0.9)	2.3 (0.9)	2.2 (1.0)	2.1 (0.8)	0.58
Adjusted mean BASDAI - (SD)	3.9 (2.1)	4.1 (2.0)	3.5 (2.2)	3.6 (2.0)	0.017
Adjusted mean BASMI - (SD)	2.2 (2.1)	2.9 (2.2)	1.8 (1.4)	1.4 (1.2)	<0.001
Adjusted mean patient global assessment - (SD) (range 0-10)	4.1 (2.2)	4.3 (2.2)	4.0 (2.3)	3.9 (2.0)	0.34
Adjusted mean physician global assessment - (SD) (range 0-10)	2.2 (0.8)	2.4 (0.9)	2.1 (0.6)	2.0 (0.7)	<0.001
Biologic treatment n (%) at baseline	145 (21%)	26 (29%)	34 (7%)	56 (7%)	<0.001
Sacroiliitis grade 3,4 (unilateral or bilateral) at baseline	576 (79%)	82 (87%)	282 (51%)	—	<0.001

ASDAS=ankylosing spondylitis disease activity score; BASDAI=Bath ankylosing spondylitis disease activity index; BASMI=Bath ankylosing spondylitis metrology index.

Table number 2: The Comparison of ASPs and axial PsA

Variable	ASPs (N=91)	Axial PsA (N=477)	P Value
Age of diagnosis	28.7 (11.0)	35.6 (13.3)	<.001
Male, n (%)	69 (76%)	303 (64%)	0.024
HLA B27, n (%)	75 (82%)	91 (19%)	<.001
Adjusted mean active arthritis (tender and swollen joints)	1.5 (3.5)	5.2 (6.5)	<.001
Presence of back pain at presentation, n (%)	82 (90%)	100 (21%)	<.001
Adjusted mean ASDAS ESR	2.3 (0.9)	2.2 (1.0)	0.47
Adjusted mean BASDAI	4.1 (2.0)	3.5 (2.2)	0.028
Adjusted mean BASMI	2.9 (2.2)	1.8 (1.4)	<.001
Adjusted mean physician global assessment	2.4 (0.9)	2.1 (0.6)	<.001
Adjusted mean patient global assessment	4.3 (2.2)	4.0 (2.3)	0.27
Biologic treatment at baseline, n (%)	26 (29%)	70 (15%)	0.001

ASDAS=ankylosing spondylitis disease activity score; BASDAI=Bath ankylosing spondylitis disease activity index; BASMI=Bath ankylosing spondylitis metrology index

Table number 3: Logistic regression, outcome: ankylosing spondylitis with psoriasis compared to axial PsA (axial PsA reference group)

Variable	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Adjusted mean active arthritis (tender and swollen joints)	0.68	0.61 - 0.76	<.0001	0.75	0.64- 0.86	<.0001
Adjusted mean ASDAS – ESR	1.1	0.83- 1.45	0.51			
Adjusted mean BASMI	1.41	1.21- 1.63	<.0001	1.44	1.02- 2.03	0.04
Sacroiliitis (grade 3,4) at diagnosis	7.58	3.68- 15.59	<.0001	3.24	1.10- 9.49	0.03

Adjusted variables: follow-up duration, age of diagnosis, sex, HLA-B*27, biologic/NSAIDS treatment.

ASDAS-ESR=ankylosing spondylitis disease activity score; BASMI=Bath ankylosing spondylitis metrology index; NSAIDS=non-steroidal anti-inflammatory drugs

Conclusion: AS patients, with or without psoriasis, are different demographically, genetically, clinically and radiographically to axial PsA patients. AS patients are younger, male predominant with higher HLA-B*27 rates. They have worse axial disease, while axial PsA have worse peripheral arthritis.

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Hyperlipoproteinemia (a) in Patients with Spondyloarthritis. Results of the CARMA Study

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Background/Purpose: Cardiovascular disease (CVD) is one of the main cause of mortality and morbidity in patients with spondyloarthritis (SpA), partially explained by traditional CV risk factors (CVRF). Other non-conventional CVRF, probably related to chronic systemic inflammation, may be involved. In this sense, lipoprotein (a) [Lp (a)], an non-conventional risk factor with proatherogenic and thrombogenic properties, could be involved, since it seems to act as an acute-phase reactant, however, there are few data on this aspect in these patients. The purpose of this study is to evaluate the prevalence of hyperlipoproteinemia (a) in patients with SpA and analyze the possible related factors.

Methods: Analysis of the baseline visit of patients with ankylosing spondylitis (AS) and psoriatic arthritis (PsA) of the CARMA project (CARDiovascular in Reumatology), a prospective cohort study of 10 years of follow-up, to evaluate the cardiovascular risk in chronic rheumatic inflammatory diseases, including rheumatoid arthritis, AS and PsA, followed in 67 Spanish rheumatology centers. A multivariate logistic regression model was performed, in which the dependent variable was hyperlipoproteinemia (a), defined as the plasma concentration of lipoprotein (a) [Lp (a)] > 50 mg/dl. Sociodemographic factors and those related to the disease itself, classic CVRF, lipid profile and apolipoproteins, and treatments have been included as independent variables.

Results: 1459 patients were analyzed, 738 with AS and 721 with PsA, and 677 controls. Plasma concentrations of Lp(a) were available in 57.7% of the patients with AS and in 57.1% of the patients with PsA, and in 58% of the controls. A 19.2% (95% CI: 16.80-22.05) of the patients with SpA, 20.7% (95% CI: 16.91-24.82) of AS and 17.7% (95% CI: 14.15-21.75) of PsA, respectively, and a 16.7% (95% CI: 13.23-20.86; p=0.326) of the control group, had hyperlipoproteinemia (a), without statistically significant differences between groups. After adjusting for age and sex, SpA patients were more likely to have hyperlipoproteinemia (a) than control group (OR : 1.43, CI :1.00-2.04; p=0.05), especially in patients with AS (OR: 1.81, 95% CI: 1.18-2.77; p=0.007). In the model adjusted for possible confounding factors, high values of apolipoprotein B in all patients, non-steroidal antiinflammatories in AS, and sex (women) in PsA, were associated with a higher probability of presenting hyperlipoproteinemia (a).

Conclusion: Patients with SpA show a moderately increased risk of hyperlipoproteinemia (a) compared to the control group, especially in those with AS. No specific factors of the disease have been identified that are associated with hyperlipoproteinemia (a) in each of the analyzed groups. The determination of Lp (a) may be of potential interest to improve the assessment of CV risk in patients with SpA, especially in those with a moderate / high CV risk according to the algorithms of the risk tables.

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Abstract Number: 1630

Do Symptoms of Depression and Anxiety Influence Treatment Response and Long-Term Physical Health Outcomes in Ankylosing Spondylitis?

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SESSION INFORMATION

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Background/Purpose: Psychological disturbances, frequently observed in inflammatory rheumatic diseases, seem to negatively influence patient's clinical status and treatment response. The aim of this study was to examine the longitudinal impact of depression (D)/anxiety (A) in treatment response, disease activity, physical disability and quality of life in patients with Ankylosing Spondylitis (AS).

Table 1. Difference-in-differences estimation results. (p-value<0.05).

Difference-in-differences		Baseline Mean difference (p-value)	3 Months Mean difference (p-value)	Global Mean difference (p-value)
Anxiety symptoms (HADS ₂₁)	ASDAS-CRP	0.27 (0.308)	0.30 (0.317)	0.03 (0.317)
	BASDAI	1.63 (0.009†)	1.08 (0.106)	-0.55 (0.541)
	BASFI	2.04 (0.006†)	1.62 (0.044†)	-0.42 (0.693)
	ASQoL	7.32 (<0.001†)	4.53 (0.005†)	-2.79 (0.199)
	ESR	-7.24 (0.208)	-2.99 (0.644)	4.26 (0.622)
	CRP	-10.05 (0.017†)	-0.503 (0.914)	9.54 (0.128)
	Patient's VAS	21.43 (0.003†)	21.52 (0.006†)	0.09 (0.993)
	Physician's VAS	-0.70 (0.909)	-0.54 (0.931)	0.16 (0.986)
	Fatigue	1.90 (0.014†)	1.05 (0.204)	-0.84 (0.452)
Depression symptoms (HADS ₂₁)	ASDAS-CRP	0.35 (0.339)	0.19 (0.665)	-0.17 (0.789)
	BASDAI	0.93 (0.293)	0.56 (0.587)	-0.37 (0.784)
	BASFI	2.94 (0.003†)	1.88 (0.100)	-1.06 (0.476)
	ASQoL	5.84 (0.004†)	5.26 (0.022†)	-0.58 (0.846)
	ESR	9.85 (0.168)	-1.48 (0.859)	-11.33 (0.301)
	CRP	-4.44 (0.450)	1.36 (0.843)	5.80 (0.522)
	Patient's VAS	15.25 (0.121)	1.70 (0.881)	-13.55 (0.366)
	Physician's VAS	25.76 (0.005†)	-3.16 (0.721)	-28.92 (0.023†)
	Fatigue	0.69 (0.509)	0.271 (0.825)	-0.424 (0.793)

Methods: Data from patients who fulfilled the modified New York criteria for AS were collected at baseline, weeks 2 and 14 post-treatment with Adalimumab. The Hospital Anxiety and Depression Scale (HADS) was used to evaluate D/A symptoms severity. The primary outcomes were AS disease activity score - C reactive protein (ASDAS-CRP), Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI) and AS Quality of Life (ASQoL) Scale. Secondary outcomes were patient and physician global assessment by Visual Analogue Scale (VAS), erythrocyte sedimentation rate (ESR), CRP and BASDAI question 1 (fatigue). Difference-in-differences estimation took into account the covariates gender, age at baseline and disease duration.

Results: Data from 54 patients were included (Table 1). At baseline, D/A symptoms significantly influenced the mean value of BASFI ($p=0.006$; $p=0.003$) and ASQoL ($p<0.001$; $p=0.004$). On the other hand, BASDAI ($p=0.009$), CRP ($p=0.017$), patients' VAS ($p=0.003$) and fatigue ($p=0.015$) were only influenced in the individuals with A symptoms, while the physician's VAS ($p=0.005$) was only influenced in patients with D symptoms. After 14 weeks of treatment, significant differences in ASQoL mean values were found in patients with both D/A symptoms at baseline ($p=0.005$; $p=0.022$) and in BASFI ($p=0.044$) and patient VAS ($p=0.006$) for the population showing only A symptoms at the baseline. Apart from the physician's VAS ($p=0.023$), D/A baseline symptoms did not affect the treatment response.

Conclusion: Psychological status does not seem to affect response to treatment with Adalimumab, even if the overall characteristics of the population are different at baseline between patients with/without D/A symptoms.

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Incidence of Uveitis in Patients with Spondyloarthritis: The Impact of Biologics Era. a Multicenter Study Using Data from International ASAS-Comospa Study

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Background/Purpose: Uveitis is a common extra-articular manifestation in Spondyloarthritis (SpA). The purpose of this study was to analyze incidence of uveitis in SpA patients during the last decade and to evaluate the impact of the biologic therapies on this incidence.

Methods: This study is an ancillary analysis of the ASAS-COMOSPA study and included patients fulfilling ASAS SpA criteria from 22 countries. We calculated overall cumulative incidence of uveitis and evaluated difference across continents and clinical phenotypes. Patients were stratified according to date of disease onset [before 2000 and after 2000 (Biologics Era)]. We performed univariate and logistic multivariate models looking for risk factors associated with uveitis. A p-value of 0.05 was considered statistically significant.

Results: We included 3984 patients. 65% were male with a mean disease duration was 15 ± 12 years and mean age at disease onset of 28 ± 13 years. HLA-B27 were positive in 72%. 805 patients developed uveitis, with a cumulative incidence of 0.20 in 32137 patient-years from disease onset. Median time to develop uveitis was 9 ($p_{25-p75}=3-16$) years and it was present at disease onset in 5% of patients. Inflammatory bowel disease (IBD) showed the higher frequency of uveitis (33%), enthesitis (24%), axial involvement (22%), peripheral arthritis (20%), dactylitis (19%) and psoriasis (13%). 94% of patients with IBD and 89% of patients with enthesitis, also presented axial involvement. 88% of patient with uveitis were HLA-B27 positive and 17% had first/second degree relatives with uveitis. Patients who meet ASAS Peripheral Criteria

showed less frequency of uveitis than those who meet ASAS Axial Criteria (11% vs 23%, $p<0.01$). Europe show a significantly higher cumulative incidence of uveitis (0.23) than Asia (0.20), Latin-America (0.17), North-America 0.15 and Africa 0.18. Patients with disease diagnosis after 2000 showed a lower cumulative incidence of uveitis than those with disease diagnosis before 2000 year (14% vs 27%, $p<0.01$). Risk factors associated with uveitis were HLA-B27 positive, family history of uveitis, enthesopathy and/or IBD. (table 1).

Conclusion: One fifth of patient with SpA developed uveitis. HLA-B27 positive and family history of uveitis were associated with higher risk of uveitis. Patients from Europe showed the highest frequency. Patients with disease onset after biologics development had a lower cumulative incidence of uveitis, but after adjust for multiple confounders, did not reach statistical significance.

Table 1. logistic multivariate analysis using uveitis as dependent variable.

Dependent variable=Uveitis	Adjusted Odd Ratios	
	OR (CI ⁹⁵)	p
Female	1.06 (0.85-1.31)	>0.20
Disease duration (years)	1.03 (1.02-1.05)	<0.01
HLA-B27 positive	3.25 (2.41-4.39)	<0.01
Family history of uveitis	4.33 (3.07-6.12)	<0.01
Peripheral arthritis	1.00 (0.80-1.24)	>0.20
Peripheral enthesitis	1.27 (1.03-1.57)	0.03
Dactylitis	1.08 (0.78-1.48)	>0.20
Axial involvement	0.83 (0.50-1.40)	>0.20
Psoriasis	0.68 (0.50-0.93)	0.02
IBD	2.20 (1.51-3.21)	<0.01
Continent (Africa=0)		
Asia	0.85 (0.51-1.40)	>0.20
Europe	0.76 (0.46-1.24)	>0.20
Latin-America	0.83 (0.47-1.47)	>0.20
North-America	1.13 (0.57-2.27)	>0.20
ASAS peripheral criteria	0.89 (0.60-1.33)	>0.20
Disease onset >=2000 year (Biologics Era)	0.79 (0.58-1.08)	0.14

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Abstract Number: 1632

Ultrasonographic Evaluation of the Enthesis in Patients Affected By Enteropathic Spondyloarthritis. Focus on Distal Enthesis of the Patellar Tendon

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SESSION INFORMATION

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Background/Purpose: Enteropathic arthritis (EA) belongs to the spondyloarthritis (SpA) spectrum of diseases and occurs in patients affected by inflammatory bowel diseases (IBD). Several works demonstrated that ultrasonography (US) is feasible, reliable and easily accessible means of detecting chronic and active enthesal abnormalities even in a subclinical context (1,2) in SpA patients. Aim of our study was to evaluate the prevalence of US enthesal involvement in patients with EA at the level of the distal insertion of patellar ligament.

Methods: Twenty-two consecutive AE patients (12 with Crohn's disease and 10 with ulcerative colitis; 8 females and 14 males; mean age 44.7 years, range 18-72 years; mean AE duration 10.1 years range 4-21 years) and 18 healthy age- and gender-matched controls (8 females and 10 males; mean age 48 years, range 24-68 years) underwent an US examination (ESAOTE MyLAB 70 6-18 MHz linear array transducer) according with the validated Madrid Sonographic Enthesis Index (MASEI). Clinical and clinimetric variables were assessed in both groups according with daily clinical practice.

Results: Focusing on the 44 distal patellar entheses we identified a higher prevalence of all the elementary lesion analysed. In 34 entheses we identify a dishomogeneous echostructure (77.3% vs 33.3%; $p=0.0001$), in 38 structural thickness (86.4% vs 66.7%; $p=0.03$), in 16 power Doppler positivity (36.3% vs 16.7%; $p=0.04$), in 17 presence of calcifications (38.6% vs 16.7%; $p=0.03$) and in 8 entheses the presence of erosions (18.8% vs 0%; $p=0.007$). A simultaneous presence in the same entheses of dishomogeneous echostructure, structural thickness and power Doppler positivity suggestive for US active enthesitis was found in the 45% of the examined patients.

Conclusion: US detectable signs of enthesopathy and enthesitis are very frequent in EA patients even when we analyse only the distal entheses of the patellar ligament. Further studies involving a larger number of patients are needed to confirm these preliminary data.

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Abstract Number: 1633

Fragility Fractures in Psoriatic Arthritis Patients: A Matched-Control Study

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Background/Purpose: Patients with Psoriatic Arthritis (PsA) in spite of having bone production as one of their characteristic features, very often have osteoporosis, but scarce data is available on fracture risk. Our objective was to compare incidence of osteoporotic fractures in PsA patients diagnosed after year 2000 with matched controls from a university hospital-based health management organization (HMO).

Methods: Consecutive PsA patients diagnosed after year 2000, from the HMO, were matched (age and sex) with controls (1:2). The follow-up period began at the first medical claim at the HMO. Subjects were then followed until they voluntarily left the HMO, a fracture occurred, the end of study (May 1st 2018), or death. Electronic medical records were reviewed and demographic, clinical and treatment data were collected. Incidence rates per 1000 persons-years (PY) of distinct types of fractures after index dates were calculated and compared between groups. A multivariate cox regression analysis was performed to investigate determinants of fractures.

Results: 92 PsA patients were included. Patients characteristics are shown in table 1. 92 PsA patients contributed with 788.2 PY of follow up, and 184 controls contributed 1718.4 PY. Media age at psoriasis and PsA diagnosis was 34.5 years (SD 19.3) and 49.1 years (SD 17.7) respectively. 8.7 % (95% CI 4.4-16.5) of PsA patients had axial involvement. 84.6 % (95% CI 75.5-90.8) of PsA patients were treated with conventional DMARDs and 29.7% (95% CI 21.1-40.0) received biologic treatment. Topical corticosteroids were used by 60.9% (95% CI 50.5-70.4) of PsA patients and 22.8% (95% CI 15.3-32.6) received oral corticosteroids. No difference was found in the overall fracture incidence rate per 1000 PY between PsA and controls (10.2, 95% CI 5.1-19.3, vs 8.7, 95% CI 5.2-13.9, $p=0.36$). Vertebral fractures were more frequent in PsA patients with an incidence rate of 10.2 per 1000 persons-years (95% CI 5.1-19.3) versus 4.6 per 1000 persons-years in the control group (95% CI 2.4-9.2), but it did not reach statistical significance ($p=0.06$). In the Cox regression analysis, after adjusting for bisphosphonate use, only age (HR 1.10, 1.05-1.16, $p<0.001$) and a female sex (HR 3.94, 1.11-13.91, $p=0.03$) were associated with fractures while PsA diagnosis and use of corticosteroids were not.

Conclusion: In this cohort of PsA patients diagnosed after year 2000, no overall increased risk of fractures was found in comparison with matched controls. This may be due to a rational use of corticosteroids.

	PsA patients (n=92)	Controls (n=184)	p
Mean Age at first HMO claim, years , (SD)	50.2 (16.2)	48.5 (16.0)	0.41
Female, n (%)	44 (47.8)	88 (47.8)	1
Median Follow up , years, (IQR)	8.8 (5.6-11.9)	10.1 (4.8-13.8)	0.19
BMI <20, n (% , 95% CI)	1 (1.1, 0.2-7.7)	4 (2.3, 0.9-6.1)	0.49
Ever Smoker, n (% , 95% CI)	42 (50.0, 39.3-60.6)	75 (43.1, 35.9-50.6)	0.29
BMD ever, n (% , CI)	22 (23.9, 16.2-33.8)	46 (25.0, 19.2-31.8)	0.84
Topical steroids > 3 months, n (% , 95% CI)	56 (60.9, 50.5-70.4)	7 (3.8, 1.8-7.8)	<0.001
Oral Corticosteroid use, ever, n (% , 95% CI)	21 (22.8, 15.3-32.6)	6 (3.3, 1.5-7.1)	<0.001
Biphosphonate use, n (% , 95% CI)	6 (6.5, 2.9-13.9)	13 (7.1, 4.1-11.8)	0.87
Prior fracture, n (% , 95% CI)	0	7 (3.8, 1.8-7.8)	0.06
Any fracture, n (% , 95% CI)	8 (8.7, 4.4-16.5)	15 (8.2, 4.9-13.1)	0.88
Any fracture, incidence rate per 1000 persons-years (95% CI)	10.2 (5.1-19.3)	8.7 (5.2-13.9)	0.36
Vertebral fracture, n (% , 95% CI)	8 (8.7, 4.4-16.5)	8 (4.3, 2.2-8.5)	0.14
Vertebral fracture, incidence rate per 1000 persons-years (95% CI)	10.2 (5.1-19.3)	4.6 (2.4-9.2)	0.06
Radius fracture, n (% , 95% CI)	1 (1.1, 0.1-7.4)	7 (3.8, 1.8-7.8)	0.21
Radius fracture, incidence rate per 1000 persons-years (95% CI)	1.27 (0.1-8.5)	4.1 (1.9-8.4)	0.14
Rib fracture, n (% , 95% CI)	0	3 (1.6, 0.5-4.9)	0.22
Rib fracture, incidence rate per 1000 persons-years (95% CI)	0	1.7 (0.5-5.3)	0.16
Hip fracture, n (% , 95% CI)	1 (1.1, 0.1-7.4)	1 (0.5, 0.1-3.8)	0.62
Hip fracture, incidence rate per 1000 persons-years (95% CI)	1.27 (0.1-8.5)	0.6 (0.1-4.4)	0.31
Pelvis fracture, n (% , 95% CI)	0	2 (1.1)	0.32
Pelvis fracture, incidence rate per 1000 persons-years, (95% CI)	0	1.2 (0.3-4.5)	0.24

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Abstract Number: 1634

The Impact of Comorbidities on Physical Function in Patients with Ankylosing Spondylitis and Psoriatic Arthritis Attending Rheumatology Clinics. Results of a National Study

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SESSION INFORMATION

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Background/Purpose: Functional status gets worse with comorbidities regardless of disease activity in patients with rheumatoid arthritis (RA). However, the impact of comorbidities on physical function in ankylosing spondylitis (AS) and psoriatic arthritis (PsA) is less known.

The aim of this study is to assess the impact of comorbidities on physical function in patients with AS and PsA.

Methods: Analysis of the baseline visit from the ongoing multicentric, observational, prospective, CARdiovascular in rheuMATology (CARMA) study. For this study, data from patients with AS and PsA were analyzed. Two different multivariate models were performed, where physical function was the dependent variable (using BASFI in AS and HAQ in PsA) and the following independent variables: comorbidities, a proxy for the Charlson index (CCIp) (minimum 0; maximum 27), sociodemographic (age, sex and educational level), disease activity (ESR, CRP and BASDAI in AS; while SJC, TJC, CRP, ESR, DAS, dactylitis count and PASI in PsA), disease duration, radiographic damage (defined as “spinal radiographic changes” in AS and “presence of erosions” for PsA), and treatments (for the rheumatic disease and comorbidities); adjusted for disease activity, radiographic damage and sociodemographic variables. Results are presented as β coefficients and p-values.

Results: 38 patients with AS and 721 with PsA included (mean age at inclusion 48.1 ± 11.7 and 51.8 ± 12 years, respectively, $p < 0.001$). Patients with AS: median BASFI 3.1 [interquartile range (IQR): 1.3-5.2], BASDAI 3.5 [IQR: 1.7-5.3], mean CCIp 1.32 ± 0.73 . PsA patients: HAQ 0.4 [IQR: 0.0-0.9], DAS 28 2.9 [IQR 2.0-3.8], mean CCIp 1.30 ± 0.66 . A CCIp > 1 was found in 21% of the patients. Patients with PsA have higher BMI and more hypercholesterolemia; on the other hand, we found more smokers among patients with AS (all $p < 0.001$). No differences between the two groups were found regarding the different comorbidities, except for a higher prevalence of chronic pulmonary disease in patients with AS. Patients with PsA with higher CCIp showed worse adjusted physical function (β : 0.09; $p = 0.005$). In patients with AS, the CCIp was not independently associated with physical function, but thyroid disease (β : 1.18, $p = 0.002$), disease activity (BASDAI; β : 0.81, $p < 0.001$) and spinal radiographic damage (β : 0.61, $p < 0.001$) were independently associated. In patients with PsA, obesity (β : 0.09; $p = 0.04$), disease duration (β : 0.01; $p = 0.009$), disease activity (DAS-28, β : 0.19; $p < 0.001$) and NSAIDs (β : 0.1; $p = 0.014$), corticosteroids (β : 0.12; $p = 0.02$) and biologic DMARD use (β : 0.15; $p < 0.001$) were associated with worse physical function. In contrast, a higher educational level was associated with less disability (β : -0.27; $p = 0.004$).

Conclusion: The presence of comorbidities in patients with PsA is independently associated with worse physical function, similar to what happens in RA. Early detection and control may yield an integral management of the disease and better final outcomes.

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Abstract Number: 1635

Validity of Patient-Reported Outcomes Measurement Information System Measures in Ankylosing Spondylitis Patients

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SESSION INFORMATION

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Background/Purpose: The Patient-Reported Outcomes Measurement Information System (PROMIS) developed by the US National Institutes of Health is a patient-reported outcomes system designed to measure disease burden across a wide array of chronic diseases and the general population¹. We sought to evaluate the validity of selected PROMIS measures in Ankylosing Spondylitis (AS) patients across self-reported Assessment in Spondyloarthritis International Society core set and patient-identified domains.

Methods: Patients at the Houston, Texas site of the Prospective Study of Outcomes in Ankylosing Spondylitis, a longitudinal, prospective, AS cohort from Sept 2017-May 2018 were enrolled in a sub-study in which they completed PROMIS short forms (SFs) assessing global health, depression, fatigue, pain and physical function in addition to the other legacy measures collected in the cohort study. PROMIS SFs ranged from 3-12 questions. We assessed internal

consistency using Cronbach's alpha. Content validity was assessed by asking patients if the PROMIS SF questions related to their disease. We assessed construct validity through examination of score distributions, floor effects and through examination of the Spearman's correlation coefficients between PROMIS measures and existing legacy AS measures (e.g. BASDAI, BASFI, Global Numeric Rating Scale (NRS), Pain NRS and CES-D) of similar domains. We hypothesized that there would be moderate to strong correlation (e.g., 0.6-1) between the PROMIS measures and the target legacy measures.

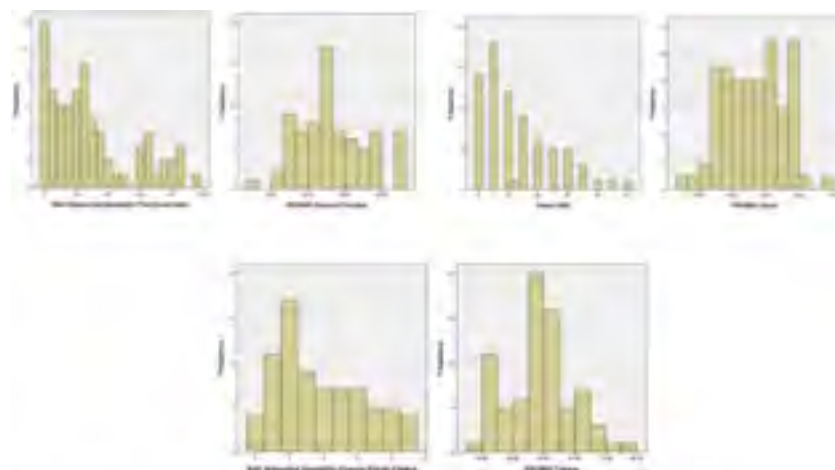


Figure 1. Distribution of select PROMIS and legacy scores in Ankylosing Spondylitis patient sample (N=82). Representative histograms (Physical Function, Global, and Fatigue) show legacy measures floor effects not observed in PROMIS measures. Similar results seen on all domains analyzed

Table 1. PROMIS and legacy measure scores in AS patients

	N	Mean	Median	Std. Deviation	Range	Minimum	Maximum	Cronbach's alpha (95% CI)	Correlation Coefficients ^a
Patient Global									
PROMIS Global	82	46.3256	46.3000	8.55506	44.20	23.50	67.70	.843 (.787, .889)	.838**
Global NRS	82	25.67	20.00	23.462	100	0	100	—	—
Depression									
PROMIS Emotional Distress-Depression	82	43.9451	38.2000	8.05124	31.10	38.20	69.30	.938 (.916, .957)	.884*
Center for Epidemiologic Studies-Depression	80	10.5375	9.0000	8.29205	33.00	0.00	33.00	—	—
Fatigue									
PROMIS Fatigue	82	48.8768	48.6500	10.64216	51.80	26.00	77.80	.970 (.958, .979)	.574*
Bath Ankylosing Spondylitis Disease Activity Index-Fatigue	82	3.7805	3.0000	2.553	9.00	0.00	9	—	—
Pain									
PROMIS Pain Intensity	82	44.8171	43.5000	9.14456	33.40	30.70	64.10	.925 (.902, .949)	.861**
PROMIS Pain Interference	82	51.0341	51.2000	9.73802	36.30	40.70	77.00	.973 (.963, .981)	.757*
Pain NRS	82	31.34	25.00	26.516	100	0	100	—	—
Physical Function									
PROMIS Physical Function	78	46.8551	45.2000	9.56299	39.90	26.20	66.10	.911 (.878, .937)	.865*
Bath Ankylosing Spondylitis Functional Index	82	2.8549	2.2000	2.62279	9.40	0.00	40	—	—

a. Spearman's correlation coefficient between legacy and PROMIS measure in each domain.

** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed)

Results: Participants (n=82) were mostly male (75%), white (84%), college educated (82%) with a mean age of 53 years. All patients felt the PROMIS SFs addressed AS disease aspects. Legacy measures demonstrated a floor effect that was not present in the PROMIS SFs (Figure 1). Strong internal consistency was noted in the PROMIS SFs ranging from .843-.973. PROMIS Global, Depression, Fatigue, Pain, Physical Function correlated moderately-strongly (rho .684-.865) with the appropriate legacy measures (Table 1). Patients reported time to complete the entire PROMIS SFs packet was <10 minutes overall.

Conclusion: This study demonstrates the content and construct validity of PROMIS SFs to assess AS symptoms from a single-center sample of AS patients. Further research is needed to assess discrimination (the ability of PROMIS SF to distinguish disease activity groups), responsiveness, feasibility/resource burden, and translations for AS patients.

1. Health Measures. Intro to PROMIS [Internet. Accessed June 4,2018.] Available from: <http://www.healthmeasures.net/>

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Abstract Number: 1636

Frequency and Specificity of MRI Lesions in the Sacroiliac Joints of Patients with Axial Spondyloarthritis and Non-Specific Back Pain: First Analysis of MRI Scans from the Assessments in Spondyloarthritis International Society Classification Cohort

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Background/Purpose: A broad spectrum of MRI lesions has been described in the sacroiliac joint (SIJ) of patients with axial spondyloarthritis and a recent consensus from the ASAS MRI group has culminated in updated lesion definitions (ASAS_MRI_defⁿ). There has been no detailed evaluation of MRI scans from the ASAS Classification Cohort (ASAS-CC)¹ to determine the spectrum of MRI lesions in the SIJ in this cohort according to these definitions. We conducted a multi-reader exercise of ASAS-CC MRI scans comprising 7 experts from the ASAS-MRI group to compare the frequencies and specificity of different lesion types according to diagnostic category.

Methods: ASAS_MRI_defⁿ were recorded in an eCRF that comprises global assessment (lesion present/absent), links to reference images, and detailed scoring (SPARCC SIJ inflammation, SPARCC SIJ structural). MRI images were available from 278 of the 495 cases that had MRI performed in the ASAS-CC and were available in a variety of formats (DICOM (n =175), JPEG (n =71), DICOM film (n =32)) and sequences, axial and semicoronal orientations. Image quality was considered sufficient for global assessment in all cases by all readers. Detailed SPARCC scoring data was based only on assessment of images in DICOM format (n =175). Comparison of active and structural lesion frequencies was assessed according to individual and majority agreement ($\geq 4/7$ readers) data. MRI lesions were compared between axial SpA and non-axial SpA back pain patients according to diagnostic ascertainment by local rheumatologists.

Results: Active and structural lesions discriminated equally well between axSpA and non-axSpA patients, and the frequency of active and structural lesions in each subgroup of patients was comparable. SPARCC BME, erosion, and fatty lesion scores were significantly higher in those with axSpA (Table). 8.6% and 11.4% of axSpA and non-axSpA, respectively, had subchondral BME which was not deemed typical of axSpA. Inflammation in the erosion cavity and enthesitis were only reported in axSpA. Erosion was the most frequently observed structural lesion (36.6%) followed by fatty lesion (25.2%) in patients with axSpA with <5% of non-axSpA having these lesions.

Conclusion: In this first central reader analysis of MRI images from the ASAS-CC we demonstrate similar frequencies of active and structural lesions typical of axSpA. Erosions and fatty lesions are common structural lesions in axSpA. Some degree of subchondral inflammation, which was not considered typical of axSpA, was also detected, both in axSpA and non-axSpA.

1. Rudwaleit et al. Ann Rheum Dis 2009;68:777-831.

Table. Frequencies of MRI lesions in the SIJ in the ASAS-CC (majority reader ($\geq 4/7$) data).

Variable	Local Rheumatologist Diagnosis		P VALUE
	AxSpA (n=199)	NOT AxSpA (n=77)	
Active lesions typical of axSpA and meets ASAS definition for positive MRI	85 (42.7%)	2 (2.6%)	<0.0001
Subchondral inflammation	102 (51.3%)	10 (13.0%)	<0.0001
Inflammation in erosion cavity	20 (7.2%)	0 (0%)	0.0014
Capsulitis	8 (2.9%)	0 (0%)	0.11
Joint Fluid	16 (8.0%)	2 (2.6%)	0.17
Enthesitis	14 (5.0%)	0 (0%)	0.013
SPARCC BME score, mean (SD)	5.9 (11.8)	0.4 (0.6)	0.0006
Structural lesions typical of axSpA	69 (39.4%)	6 (9.7%)	<0.0001
Structural lesions typical of axSpA and level of confidence ≥ 3 (scale of 1-4) (-4(not SpA) to +4 (SpA) NRS scale)	48 (27.4%)	2 (3.2%)	<0.0001
Subchondral sclerosis	32 (18.3%)	8 (12.9%)	0.26
Erosion	64 (36.6%)	3 (4.8%)	<0.0001
Fatty lesion (any)	44 (25.1%)	3 (4.8%)	0.0001
Fatty lesion (>1cm)	20 (11.4%)	3 (4.8%)	0.14
Bone bud (yes)	1 (0.6%)	0 (0%)	1.00
Fat metaplasia in joint space	16 (9.1%)	2 (3.2%)	0.17
Ankylosis	6 (3.4%)	0 (0%)	0.19
SPARCC erosion score, mean (SD)	2.7 (4.8)	0.7 (2.2)	0.0032
SPARCC fatty lesion (any), mean (SD)	3.0 (6.1)	0.6 (3.5)	0.0065
SPARCC fatty lesion (>1cm), mean (SD)	1.4 (3.7)	0.3 (2.3)	0.041
SPARCC sclerosis, mean (SD)	1.8 (4.1)	1.5 (5.5)	0.69
SPARCC backfill, mean (SD)	0.6 (3.9)	0.01 (0.06)	0.26
SPARCC ankylosis, mean (SD)	0.06 (0.2)	0.04 (0.2)	0.54

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Abstract Number: 1637

Serious Infections Among Psoriatic Arthritis Patients Taking TNF Inhibitors Versus Non-TNF Biologics: A Systematic Review and Network Meta-Analysis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic arthritis (PsA) is an inflammatory condition of peripheral joints. If left untreated, it can lead to significant pain and joint deformity. Its treatment has undergone a revolution with the advent of TNF inhibitors and non-TNF biologics. Generally, these agents are well tolerated but due to their immunosuppressive properties there has been concerns for the increased risk of infections. The aim of this study was to estimate the risk of serious infections among patients with active PsA who are receiving either TNF inhibitors or non-TNF biologics.

Methods: We conducted a systematic review and random-effects network meta-analysis of randomized clinical trials in STATA 15.1 assessing the occurrence of serious infections with the use of TNF inhibitors (etanercept, adalimumab, infliximab, certolizumab pegol, golimumab) and non-TNF biologics (apremilast, secukinumab, ixekizumab, brodalumab, ustekinumab, abatacept, tofacitinib, guselkumab, rituximab, tildrakizumab) in adult patients with PsA. We used random effects model to estimate the pooled odds ratios (ORs) and 95% confidence interval (CI). Serious infections in included trials were defined as those requiring hospitalization or discontinuation of therapy. Studies from five databases: PubMed, EMBASE, Cochrane, Web of Science and Clinicaltrials.gov databases were included from date of inception to June 4, 2018. The risk of bias of each study was evaluated using Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool for clinical trials.

Results: 2,052 citations were identified and on reviewing full-text papers 16 randomized clinical trials (n=4705) met our inclusion criteria. Based on 12 to 24-week placebo-controlled follow-up data, we identified seven trials using TNF inhibitors (infliximab, adalimumab, certolizumab and golimumab) and 9 trials using non-TNF biologics (apremilast, secukinumab, ixekizumab, bimekizumab, ustekinumab, abatacept, tofacitinib). There was no statistically significant difference in odds ratio of serious infection between TNF inhibitors and non-TNF biologics. Overall, ustekinumab had lowest odds of serious infections (0.17, 95% CI: 0.01-4.1) followed by golimumab (0.23 95% CI: 0.06-0.92) and apremilast (0.50, 95% CI: 0.07-3.50). Highest rate of serious infection was observed with infliximab (OR 2.95, 95% CI: 0.30-28.16).

Conclusion: TNF inhibitors were not found to confer a higher risk of serious infection than non-TNF biologics. These results provide a better understanding of the risk of serious infection from psoriatic arthritis pharmacotherapy in patients.

Disclosure: S. U. Malik, None; K. Muzaffar, None; J. Bilal, None; W. Faridi, None; S. Muddassir, None.

Abstract Number: 1638

Impact of Extra-Articular Manifestations on Patient-Reported Outcomes in Ankylosing Spondylitis and Psoriatic Arthritis: Interim Results from the Complete Studies

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Extra-articular manifestations (EAMs) in rheumatic diseases have been previously found to negatively impact health outcomes including quality of life and work capacity. Even though EAMs may be directly associated with worse response to treatment, differences in patient-reported outcomes (PROs) based on the presence of EAMs could be an important contributory variable. The objective of this study was to assess the impact of EAMs on PROs among patients with active AS or PsA followed in Canadian routine clinical care.

Methods: Patients eligible for the COMPLETE studies are anti-TNF α naïve adults, with active AS or PsA per the judgment of the treating physician, who require change in their treatment regimen. In the current analysis, patients enrolled between July 2011 and June 2017 were included. The EAMs were defined as the presence of the following at baseline: enthesitis, uveitis, IBD or psoriasis (EAM_{AS1} for AS); enthesitis, uveitis, or IBD (EAM_{AS2} for AS); enthesitis or dactylitis (EAM_{PsA} for PsA). The PROs included the Short Form Health Survey (SF-12), Work Limitations Questionnaire (WLQ), and Beck's Depression Inventory (BDI). The PROs were compared between patients with and without EAMs using the independent samples t-test. The independent association between presence of EAMs and PROs at baseline was assessed with multivariate generalized linear models adjusting for disease state (high/very high vs. inactive/low/moderate disease based on the BASDAI for AS and the DAS28 for PsA), disease type, and ever smoking.

Results: A total of 609 AS and 406 PsA patients were included with a mean (SD) age of 43.1 (13.4) and 51.3 (12.3) years, respectively. The EAM_{AS1} and EAM_{AS2} prevalence among AS patients was 33.9% and 25%, respectively, while among PsA patients EAM_{PsA} prevalence was 45.4%.

In univariate analysis, presence of EAMs in AS was associated with significantly higher disease activity, BDI total score, WLQ mental interpersonal demands (only for EAM_{AS1}), WLQ physical demands, WLQ time demands, SF-12 physical function, SF-12 role physical, SF-12 bodily pain, SF-12 vitality, SF-12 mental health (only for EAM_{AS1}), and the SF-12 physical component summary score (PCS). Among PsA patients, patients with EAM_{PsA} had higher disease activity but no significant association was observed between EAM_{PsA} and PROs.

Upon adjusting for disease state, disease type, and ever smoking, presence of EAM_{AS1}/EAM_{PsA} for AS/PsA patients was associated with significantly higher BDI total score (14.0 vs. 12.6, $p=0.046$) and lower SF-12 physical function (38.4 vs. 44.8, $p=0.047$). When evaluating the impact of EAM_{AS2}/EAM_{PsA} for AS/PsA patients no significant differences were observed in PROs; however, BDI was notably higher among patients with EAMs (14.1 vs. 12.7, $p=0.056$).

Conclusion: In a Canadian routine clinical care setting, a substantial proportion of AS and PsA patients requiring a change in treatment report EAMs. Presence of EAMs, particularly psoriasis for AS patients, was found to be a significant independent predictor of depressive symptoms and reduced quality of life due to worse physical functioning.

Disclosure: L. Bessette, Amgen, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Lilly, Novartis, 2, 5, 8; M. Khraishi, AbbVie Inc., 2, 5, 8; B. Florica, Janssen, Merck, Abbvie, Roche, BMS, Novartis, Pfizer, Celgene, UCB, 2, 5, 8; Y. Setty, AbbVie Inc., 5; M. Teo, AbbVie, Amgen, Celgene, Janssen, Merck, Novartis, Pfizer, Roche, Sanofi-Genzyme UCB, 5, 8; V. P. Remple, AbbVie Inc., 1.

Abstract Number: 1639

Uveitis As First Symptom in Patients with Spondyloarthritis. Data from the Spanish Registry Regisponser

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

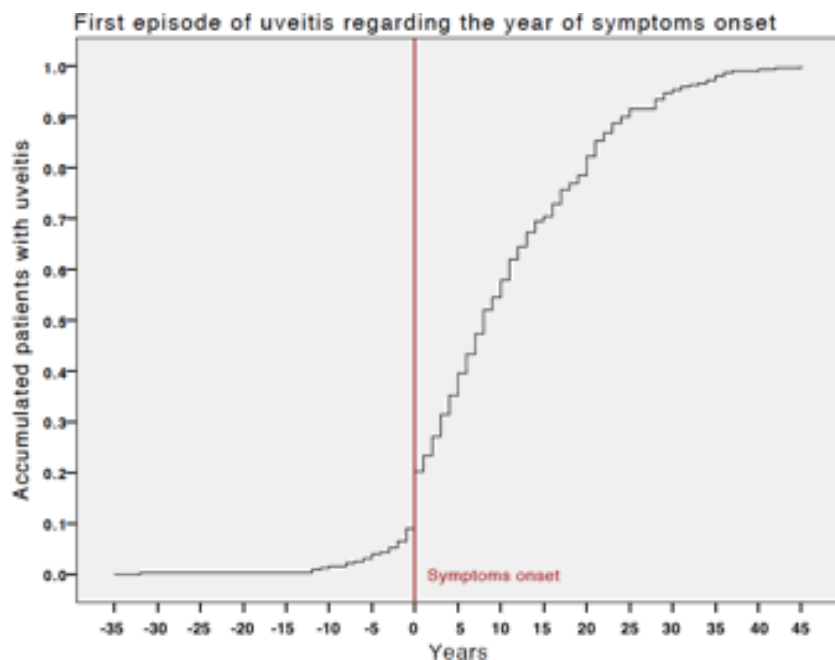
Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The objectives of this study were: a) to assess the prevalence of uveitis in patients with Spondyloarthritis(SpA) in the Spanish registry REGISPONSER; b) to describe the moment of appearance of the uveitis regarding other SpA symptoms and the date of SpA diagnosis; c) to evaluate the impact of the moment of appearance of uveitis on the use of bDMARDS.

Methods: Data from the Spanish registry REGISPONSER were analysed. The prevalence of uveitis was assessed regarding the time of occurrence of other SpA symptoms (before/ at the same time/ after) and the date of SpA diagnosis. Among patients who had suffered uveitis before SpA diagnosis, we evaluated whether this group presented other SpA features, in order to determine potential diagnostic delay of SpA. Finally, we compared the use of bDMARDS regarding the time of appearance of uveitis through Chi-square test.



Results: From the 2367 patients included in REGISPONSER, 410 (17.5%) patients reported uveitis at anytime of the course of disease. Among these, the date of first uveitis episode was available in 321 patients. Among patients with uveitis, a total of 9.0%, 11.2% and 79.8% had suffered the first episode of uveitis before, at the same time and after other SpA symptoms, respectively (Figure 1). Among patients who had suffered the first episode of uveitis before other SpA symptoms (i.e., uveitis as first SpA manifestation), the median time passed between this episode and the appearance of a second SpA manifestation was 3.0 years. However, considering the date of SpA diagnosis, a total of 36.8%, 13.3% and 49.8% of patients had suffered the first episode of uveitis before, at the same time and after SpA diagnosis, respectively (Figure 2). Among patients who had suffered the first episode of uveitis before SpA diagnosis, the median time passed between this episode and the date of SpA diagnosis was 5.0 years and, among these, 80.2% were HLA-B27 positive. We did not find statistically significant differences ($p=0.827$) in the use of bDMARDs regarding the moment of appearance of uveitis (17.4% vs. 16.7% vs. 19.1% for patients with uveitis before, at the same time and after SpA diagnosis).

Conclusion: Among patients with history of uveitis from REGISPONSER, 36.6% suffered a gap time between the first episode of uveitis and the date of SpA diagnosis (around 5 years) and, among these, 80% were HLA-B27 positive, suggesting a diagnostic delay in these patients. However, this diagnostic delay did not have an impact on the use of bDMARDs.

Disclosure: C. López-Medina, None; M. L. Ladehesa-Pineda, None; P. Font-Ugalde, None; M. C. Castro-Villegas, None; L. Pérez Sánchez, None; I. Gómez-García, None; A. Escudero-Contreras, None; E. Collantes-Estévez, None.

Abstract Number: 1640

Work Disability in Psoriatic Arthritis Patients

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic Arthritis (PsA) is an inflammatory disease with an important impact on the quality of life and work productivity. Although the activity of the disease is better controlled by the new treatments, work disability remains a frequent problem. Our objectives were to identify associated factors with work disability and fatigue in Psoriatic Arthritis and to compare Work disability and productivity loss in patients with psoriatic arthritis and rheumatoid arthritis.

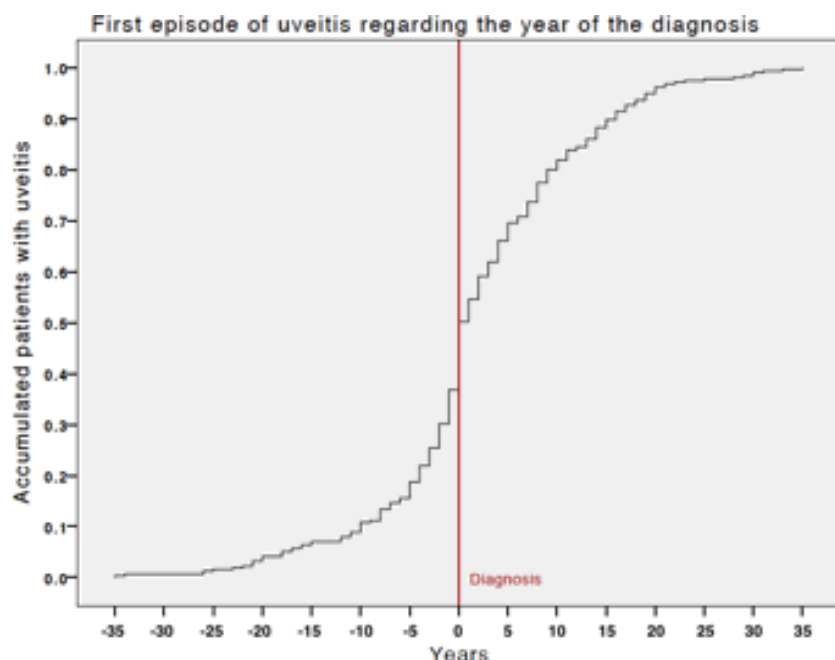
Methods: A cross-sectional and observational study was conducted. Consecutive patients older than 18 years old, with diagnosis of PsA (CASPAR criteria) and RA (ACR / EULAR 2010 criteria) from 3 centers of Argentina between June 2015 and May 2016 were included.

Variables: Demographic, socio-economics, clinimetric and treatment variables were measured.

Productivity loss was evaluated with Work productivity and Activity Impairment (WPAI) questionnaire and fatigue with the first question of BASDAI. All patients with disability certificate and / or disability benefit were considered "disabled".

Results: 7 patients (37 PsA and 60 RA) were included. PsA PATIENTS: Mean age 46 ± 7.6 years, 67% females. Mean disease duration at diagnosis 62.7 ± 26.2 months and mean age at diagnosis of 40.3 ± 3.3 years. The mean fatigue value was 6.7 ± 2.4 . Seventy percent were unemployed (26/37) and 11 patients were working; 62% (23) of the patients had disability certificates and 38% disability benefits (14). The mean HAQ was significantly higher in the non-working group (1.4 vs 0.6 , $p = 0.002$). In working patients group, the mean productivity loss was 46% and mean daily life activities (DLA) commitment was 58%. BASDAI correlated significantly with greater productivity loss and greater fatigue ($R = 0.64$ and $R = 0.86$ respectively). There was no correlation between productivity loss and DAS28.

RA PATIENTS: Mean age 48.4 ± 3.7 years, 85% females. Mean disease duration at diagnosis 15.4 ± 9.6 months and mean age at diagnosis of 37.7 ± 5.3 years; 80% (48/60) of the patients were unemployed, 71.6% (43) had a disability certificate and 53.3% (32) were receiving disability benefits. There were no differences in HAQ and DAS 28 among working and unemployed patients. The percentage of productivity loss was 29% and the commitment of DLA was 60%. Higher value of EQ5D correlated with lower productivity loss ($r = -0.7$). Age, HAQ, DAS 28, educational level and



socioeconomic status were similar in RA and PsA groups. Mean disease duration at diagnosis was higher for APs (89.7 vs 33.8 months, $p = 0.02$). The frequency of patients with certificate of disability, unemployed and commitment of DLA were similar in both groups.

Conclusion: In PsA patients, disease activity correlated with higher productivity loss and greater fatigue. Work disability and productivity loss were similar between Rheumatoid Arthritis and Psoriasis Arthritis patients.

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Abstract Number: 1641

Spa-Net: A Disease-Specific Integrated Ehealth System and Quality Registry for Spondyloarthritis in Daily Practice in the Netherlands

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Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

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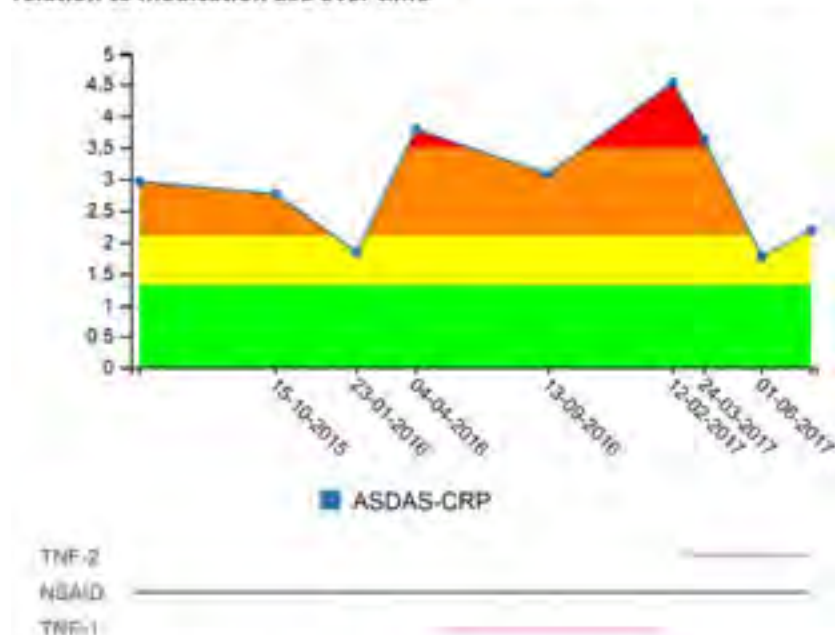
Session Time: 9:00AM-11:00AM

Background/Purpose: Regular and personalised monitoring of disease activity, functioning, medication use and side effects is essential to improve and maintain patients' health-related quality of life in spondyloarthritis (SpA). Transparency on outcomes and efficiency of care are increasingly demanded, and patient-centeredness is considered essential for quality of care. An integrated eHealth system including an electronic patient medical record (EMR) and real-time quality management system could support these aspects of care. The aim of the current study was to develop and test the usability and acceptability of a disease-specific integrated eHealth system and quality registry for SpA in the Netherlands ('SpA-Net').

Methods: The eHealth system was developed in four phases. First, content and design were discussed with experts in the field of SpA and patients. Second, the database, EMR and quality management system were developed. Third, multiple

rounds of internal and external testing were performed in collaboration with IT specialists, care providers and patients. Fourth, the eHealth system was implemented in practice, usability and acceptability were tested among patients (semi-structured focus interviews) and care providers (feedback meetings).

Figure. Example of graph in SpA-Net reporting the evolution of ASDAS in relation to medication use over time



Results: SpA-Net was designed and developed in 2015 and implemented in May 2016. All patients entered into SpA-Net have a clinical diagnosis of SpA. Information prospectively collected at routine outpatient consultations on diagnosis, demographics, specific SpA manifestations, patient reported outcome measures, clinical outcomes, comorbidities, medication use and safety, supplemented with data from the hospital information system, is directly stored in a database and readily available to care providers. Patients can access an excerpt of these data and complete online questionnaires prior to their visit. The information is presented in graphs wherever possible (Figure). As of May 2018, 1215 patients participated in SpA-Net (mean [SD] age 54.3[14.5] years, 48.4% females). Focus interviews and feedback meetings were held with 16 patients, 9 rheumatologists, and 5 nurses. Patients considered SpA-Net as an accessible and intuitive system that was beneficial to patient-physician communication and had additional value to current care. Points of improvement were the login process and providing more details about the care provider's notes. Care providers appreciated the additional information for (preparing) consultations. Barriers against use were the initial time required to adopt the EMR and the quantity of data entry.

Conclusion: SpA-Net enables (tele-)monitoring of patients with SpA and optimizes knowledge and communication among patients and care providers. Both patients and care providers considered SpA-Net acceptable and a valuable addition to current care for SpA.

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Abstract Number: 1642

Systematic Screening of Comorbidities Improves Vaccination Rates, Skin Cancer Screening and Vitamin D Supplementation in Patients with Axial Spondyloarthritis: Results of a Prospective, Controlled ,One Year Randomised Trial

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SESSION INFORMATION

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Background/Purpose: Specific recommendations for the detection/prevention of comorbidities have been proposed for patients with SpA. However, we know that often a gap exists between recommendation and their implementation in daily practice. The objective was to evaluate the impact of a program of systematic screening of comorbidities and its management (detection/prevention).

Methods: Prospective, randomized controlled open, 12-month trial (COMEDSPA, NCT02374749). Patients: Axial SpA (according to rheumatologist). Study treatment: Collection of data by the nurse during a specific out-patient visit for the 5 studied SpA comorbidities (i.e. cardiovascular disease (CVD), osteoporosis, cancer, infection and peptic ulcer) according to the recommendations of the French Society of Rheumatology. In the event of non-agreement with the recommendation the patient was informed. A report summarizing the results of this program prepared by the nurse was sent to the patient's attending physician and rheumatologist. Treatment allocation: After written informed consent, the study treatment was allocated randomly. Outcome variables: the main outcome was the change after one year of a comorbidity score. This weighted composite comorbidity score ranged from 0 to 100, where 0= optimal management of the 5 studied comorbidities and its weights were derived from the percentage of attributed mortality in SpA to each comorbidity in the literature, i.e. 40 points for CV disease, 20 points for cancer and infection, 10 points for osteoporosis and 10 points for peptic ulcer. The number of patients with actions undertaken against comorbidities according to the recommendations during the 12 months following this program were defined as secondary variables

Results: There were no differences in the baseline characteristics of the 502 recruited patients (252 and 250 in the active and control groups, respectively): Age: 46.7±12.2 years, male gender: 62.7%, disease duration: 13.7±11.0y, Xray sacroiliitis 62.8%, MRI sacroiliitis 65.7%, current biologic treatment: 78.3%, ASDAS-CRP: 1.9 ± 0.8, BASFI: 25.6±22.3. During the 1 year follow-up period, the comorbidity score decreased more in the active group, but this difference was not significant (-3,20 vs. -1.85). The number of actions per patient was statistically higher in the group comorbidities : 4.54 ± 2.08 vs 2.65 ± 1.57 (p< 0.001); the number of patients with actions performed to be in agreement with recommendations during the 12-months follow-up was higher in the active group for infections (flu vaccination : 28.6% vs. 9.9%, p<0.01; pneumococcal vaccination: 40.0% vs. 21.1%, p=0.04), skin cancer screening (36.3% vs. 17.2%; p=0.04), and osteoporosis (BMD performed: 22.6% vs. 8.7%, p<0.01; Vitamin D supplementation initiation: 51.9% vs. 9.4%, p<0.01).

Conclusion: This study highly suggests the short-term benefit of program on the systematic screening of comorbidities for its management in agreement with recommendations, even if this young age population of axSpA patients.

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Abstract Number: 1643

Psa Impact of Disease Questionnaire Scores Are Correlated with Disease Activity, As Measured By Cdapsa in Patients with Psa

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

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Session Time: 9:00AM-11:00AM

Background/Purpose: We examined clinical correlations between disease activity, as measured with the Clinical Disease Activity for PsA (cDAPSA) components and PsA life impact/health-related quality of life (HRQoL) assessed with the PsA Impact of Disease Questionnaire (PsAID12). We hypothesized that PsAID12 scores will be statistically different among the disease activity categories and there will be moderate correlation between PsAID12 and cDAPSA.

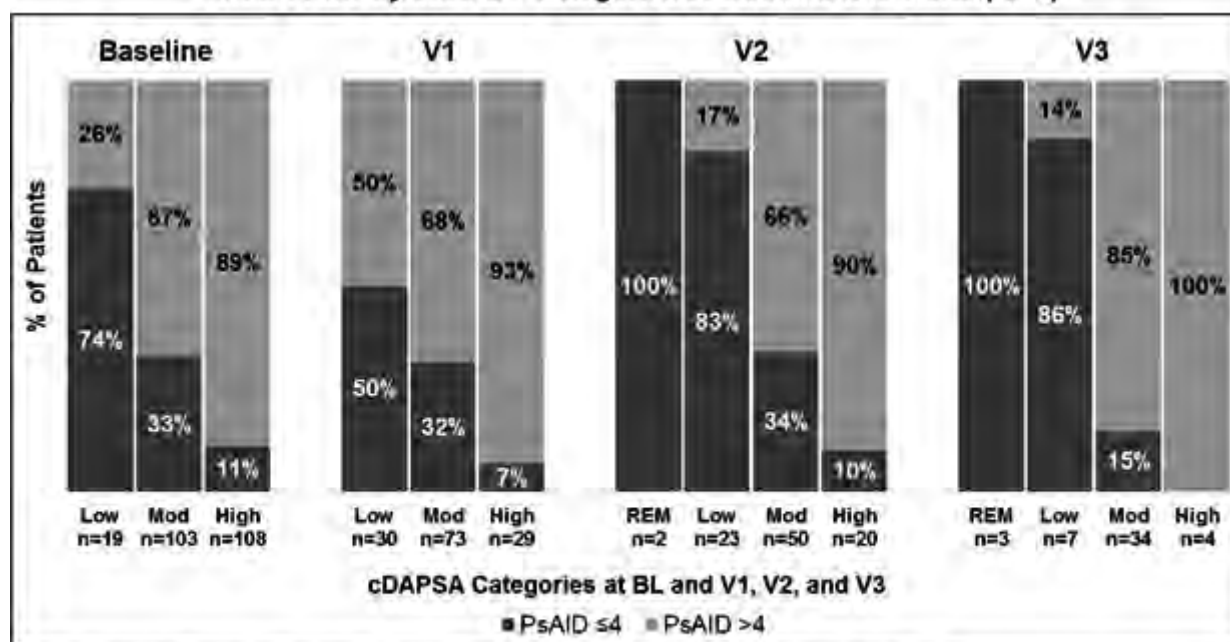
Methods: LAPIS-PsA is a multicenter, prospective, non-interventional study assessing long-term apremilast (APR) treatment in adult patients with active PsA in routine clinical practice in Germany. Analyses were performed in patients treated with APR 30 mg BID who had cDAPSA and PsAID12 scores at baseline (BL). We also report data from Visits 1 to 3 (V1: ≥ 1 month; V2: ≥ 4 months; V3: ≥ 7 months). Mean PsAID12 scores and proportions of patients meeting the PsAID12 Patient-Acceptable Symptom State (PASS), defined as PsAID12 of 4, were assessed among each cDAPSA category at BL. PsAID12 scores were compared among the cDAPSA categories at BL and each visit using the ANOVA method. Pearson correlations were calculated between cDAPSA and PsAID12 at BL, V1, V2, and V3.

Clinical Characteristics and Disease Assessments at Visits

	BL (Baseline) N=328*		V1 (21 Month) N=259*		V2 (24 Months) N=251*		V3 (27 Months) N=168*	
	n†	Mean (SD)	n†	Mean (SD)	n†	Mean (SD)	n†	Mean (SD)
SJC (0-66)	251	5.6 (4.5)	148	4.2 (3.9)	150	3.9 (4.3)	48	2.4 (1.9)
TJC (0-66)	296	11.4 (11.1)	205	6.3 (10.6)	198	8.9 (9.6)	97	5.7 (10.4)
Pain (VAS 0-100 mm)	326	52.9 (22.4)	256	46.1 (23.2)	251	39.8 (25.5)	164	36.1 (26.3)
PGA (VAS 0-100 mm)	324	56.1 (22.5)	248	44.8 (23.9)	248	37.7 (26.6)	165	35.7 (26.5)
cDAPSA (0-154)	235	28.6 (14.2)	130	22.5 (13.3)	90	18.7 (11.7)	40	17.7 (9.5)
PsAID (0-12)	318	5.4 (2.0)	263	4.7 (2.1)	234	3.9 (2.2)	160	3.6 (2.3)

Data as observed. *Number of patients included at each visit. †Number of patients with data for the given assessment at both baseline and post-baseline (V1, V2, and V3).
SJC=swollen joint count; TJC=tender joint count; VAS=visual analog score; PGA=patient's Global Assessment of Disease Activity; cDAPSA=Clinical Disease Activity Index for Psoriasis; PsAID=Psoriasis Affecting Impact of Disease.

PsAID PASS by cDAPSA Categories at Baseline and Visits (APR)



Data as observed. Includes patients with both PsAID12 and cDAPSA scores at the specific visit. PsAID12=PsA Impact of Disease Questionnaire; PASS=Patient-Acceptable Symptom State; cDAPSA=Clinical Disease Activity for PsA; REM=remission (cDAPSA ≤ 4); Low=low disease activity (cDAPSA > 4 to ≤ 13); Mod=moderate disease activity (cDAPSA > 13 to ≤ 27); High=high disease activity (cDAPSA > 27).

Results: A total of 330 patients were included in the analysis population. At BL, patients had a mean PsAID12 of 5.4 and a mean cDAPSA of 28.6. Mean PsAID12 and cDAPSA scores are reported at all visits (Table). Patients reported incrementally reduced mean cDAPSA and consistent improvements in PsAID12 scores from BL to V3. Patients with low disease activity (cDAPSA > 4 – ≤ 13) at BL had a mean(SD) PsAID12 score of 3.2 (1.5) with 74% in PsAID12 PASS

(Figure). Those with moderate (cDAPSA >13–≤27) and high (cDAPSA >27) disease activity had mean (SD) PsAID12 scores of 5.0 (2.0) and 6.1 (1.7), with 33% and 11% showing PsAID12 PASS, respectively. Consequently, proportions of patients achieving PsAID12 PASS decreased with higher disease activity (Figure). At BL and V1-3, PsAID12 scores were significantly different among the cDAPSA categories ($P<0.001$). Additionally, significant moderate to high correlations were observed between cDAPSA and PsAID12 at V1 (Pearson's coefficient $r=0.41$; $P<0.0001$), V2 ($r=0.64$; $P<0.0001$), and V3 ($r=0.70$; $P<0.0001$).

Conclusion: Results from this observational PsA study of APR demonstrate a significant correlation between disease activity, as assessed by cDAPSA, and PsA-specific life impact/HRQoL, as measured by PsAID12. More patients met the PsAID12 PASS cutoff at lower disease activity levels, suggesting that improvements in PsA disease activity lead to decreased impact of disease.

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Abstract Number: 1644

Improvement in Morning Stiffness in Subjects with PsA Is Associated with Improvements in Pain, Physical Function, and Patient Global Response to Treatment

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SESSION INFORMATION

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Background/Purpose: Stiffness is an important component of inflammatory arthritis and plays a role in PsA flare. Patients with inflammatory arthritis report difficulty with activities, “slowing down” due to stiffness, and reduced quality of life. Stiffness is hard to quantify because it cannot be measured directly. We examined morning stiffness in PsA patients treated with apremilast (APR) for 16 weeks in the ACTIVE study and explored the relationship between improvements in morning stiffness and pain, physical function, and Patient's Global Assessment of Disease Activity (PtGA).

Methods: Subjects who met CASPAR criteria for PsA, were biologic-naïve, and had prior exposure to ≤1 conventional disease-modifying anti-rheumatic drug (DMARD) were randomized (1:1) to APR 30 mg BID or placebo (PBO) for 24 weeks; thereafter, all subjects received active treatment with APR. In the post-hoc analysis, changes in morning stiffness severity and effect on pain, physical function, and PtGA from baseline (BL) to Week 16 were compared between treatment arms. Duration of morning stiffness and severity, assessed by subjects' reported categories of stiffness (none, mild, moderate, moderately severe, severe), were reported. An ANCOVA model adjusting the BL value was used in the analysis, where missing values were imputed using the last-observation-carried-forward approach.

Results: A total of 219 subjects were randomized (APR: n=110; PBO: n=109), and 192 remained in the study through Week 16. Most subjects (84%) reported moderate to severe morning stiffness at BL (Table 1). As early as Week 2, a significantly greater proportion of APR vs. PBO subjects experienced morning stiffness severity improvements (≥1 category improvement) (43% vs. 21%; $P=0.0007$). Significant improvements in morning stiffness severity were sustained through Week 16 in APR vs. PBO subjects (46% vs. 26%; $P=0.0015$). Subjects with improvements in morning stiffness severity in the APR and PBO groups showed consistent improvements at the group level in pain, physical function, and PtGA at Week 16 (Table 2). In patients with unchanged stiffness severity, greater improvements were observed across outcome measures in the APR vs. PBO group, although to a lesser extent compared with the improved stiffness group. Worsened morning stiffness was associated with lack of improvement in other patient-reported outcome measures.

Conclusion: In biologic-naïve subjects with PsA treated with APR for 16 weeks, improvement in morning stiffness severity was evident as early as Week 2 and associated with improvements in pain, physical function, and PtGA response.

Table 1. Baseline Subject Demographic and Clinical Characteristics

Characteristic	APR n=110	PBO n=109
Tender joint count, mean (SD)	17 (13)	18 (14)
Swollen joint count, mean (SD)	9 (5)	10 (6)
Duration of morning stiffness, minutes Mean (SD) Median	48 (49) 30	72 (127) 30
Severity of morning stiffness, n (%)		
None	7 (6.4)	8 (7.3)
Mild	6 (5.5)	14 (12.8)
Moderate	43 (39.1)	39 (35.8)
Moderately severe	44 (40.0)	40 (36.7)
Severe	9 (8.2)	8 (7.3)
Missing	1 (0.9)	0 (0)
PGA, mean (SD) [†]	5.9 (2.1)	6.1 (2.0)
Subject's Assessment of Pain, mean (SD) [‡]	6.1 (1.9)	5.8 (2.2)
HAQ-DI score, mean (SD) [§]	1.3 (0.6)	1.2 (0.6)
SF-36v2 PCS, mean (SD)	32.4 (9.2)	33.9 (8.3)
SF-36v2 PF, mean (SD)	33.2 (11.2)	34.2 (10.1)
Previous use of DMARD, n (%)		
Yes	74 (67)	76 (72)
No	36 (33)	31 (28)
Previous use of methotrexate, n (%)		
Yes	81 (55)	86 (81)
No	49 (45)	43 (39)
Oral corticosteroid use, n (%)		
Yes	13 (12)	14 (13)
No	97 (88)	95 (87)

The n reflects the number of subjects randomized to the group; actual number of subjects having data available for each parameter may vary.
[†]0 indicates no pain, 10 indicates most severe pain. [‡]Range of 0 to 3. [§]0 indicates not active, 10 indicates very active.
 HAQ-DI=Health Assessment Questionnaire-Disability Index, PGA=Patient's Global Assessment of Disease Activity, SF-36v2=36-item Short-Form Health Survey version 2, PF=Physical Functioning domain.

Table 2. Stiffness Dynamics With APR Treatment and PBO and Improvement in Pain, Physical Function, and PGA Response From BL to Week 16

Change in Stiffness Scores*	Improved			No Change			Worsened		
	APR n=58	PBO n=36	P Value	APR n=37	PBO n=37	P Value	APR n=14	PBO n=22	P Value
Outcomes, Mean (SD) Change									
HAQ-DI	-0.36 (0.47)	-0.34 (0.58)	0.876	-0.14 (0.29)	-0.01 (0.32)	0.016	0.40 (0.45)	0.16 (0.46)	0.129
PGA	-1.95 (2.52)	-1.79 (1.90)	0.414	-0.05 (1.05)	-0.14 (2.01)	0.132	1.64 (1.74)	0.77 (3.34)	0.911
Pain VAS	-2.16 (2.13)	-1.77 (1.78)	0.425	-0.97 (2.12)	-0.04 (1.69)	0.016	1.14 (1.83)	1.5 (2.29)	0.875
SF-36v2 PCS	6.37 (7.63)	4.29 (5.38)	0.358	3.18 (6.44)	-0.82 (5.29)	0.005	-3.76 (6.86)	-5.44 (7.32)	0.518
SF-36v2 PF	4.79 (8.61)	5.58 (10.02)	0.095	5.07 (7.23)	-0.06 (5.15)	0.013	-6.01 (8.38)	-3.64 (6.43)	0.641
SF36v2 Bodily Pain	8.63 (8.63)	6.65 (7.59)	0.428	3.34 (6.38)	-0.21 (6.13)	0.023	-2.23 (6.81)	-8.19 (7.48)	0.103

*Improved/worsened is defined as a shift by at least 1 stiffness severity category (none, mild, moderate, moderately severe, very severe); subjects with BL value and at least 1 post-BL value are included.
 VAS=visual analog scale; PCS=Physical Component Summary.

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Clinical Features of Axial Spondyloarthritis Patients Diagnosed in Secondary Versus a Tertiary Hospital

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SESSION INFORMATION

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Background/Purpose: Diagnosis of axial spondyloarthritis (axSpA) often relies on a positive MRI of the SI joints. However, pitfalls in interpretation of MRI images were recently acknowledged (1). Thus reader's expertise might be a source of heterogeneity in patient populations diagnosed with non-radiographic axSpA. Therefore we compared clinical characteristics between axSpA patients diagnosed in general (secondary) hospitals (MRI evaluation by local experts) versus a university-affiliated (tertiary) hospital (MRI central reading by trained radiologists and rheumatologists). In all centers, patients were free to visit a rheumatologist of their choice without necessity for referral by a general practitioner.

Methods: Patients originate from the Be-Giant cohort, a nationwide observational registry of axSpA patients diagnosed by expert opinion. Included patients fulfill the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA (2) and are anti-TNF- α naïve prior to inclusion. Patient enrollment started in 2010 and 2012 at the outpatient clinic of 1 tertiary and 7 secondary centers respectively. An extensive patient description was performed at baseline, followed by a 6-monthly follow-up.

Results: By June 2018, 223 axSpA patients were included. Demographic and clinical features are presented according to the diagnostic echelon (Table 1). The HLA B27 positivity rate was 52,9% and 74,6% in secondary versus tertiary centers ($p = 0,013$). The patient fraction fulfilling the imaging arm of the ASAS classification criteria was similar in both (89,9% vs. 85,3%, $p = 0,418$), but significantly more patients both fulfilled the imaging and the clinical arm in the tertiary versus secondary centers (64,5% vs. 38,2%, $p = 0,004$).

Conclusion: Patients diagnosed with axSpA in secondary versus a tertiary hospital generally show similar demographic and clinical characteristics. For axSpA patients diagnosed in a tertiary center, fulfillment of both ASAS classification arms and HLA B27 positivity rate was significantly higher, indicating that rheumatologists in secondary hospitals seem to assign more value to MRI findings compared to HLA B27 status in the diagnostic process.

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2. Rudwaleit M, Van Der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): Validation and final selection. *Ann Rheum Dis*. 2009;68(6):777-83.

Table 1 xx

	Secondary centers (n = 34)	Tertiary center (n = 189)	p-value ($\alpha = 0.05$)
Age at diagnosis (years) *	32,7 (7,19)	30,5 (9,32)	0,070
Male gender **	14 (41,2)	100 (52,9)	0,208
Caucasian ethnicity **	33 (97,1)	179 (94,7)	0,560
HLA B27 positivity **	18 (52,9)	141 (74,6)	0,013
Symptom duration at time of diagnosis (months) *	58,2 (68,54)	52,3 (67,55)	0,747
ASAS classification criteria:			
fulfilling the imaging arm **	29 (85,3)	170 (89,9)	0,418
fulfilling the clinical arm **	18 (52,9)	141 (74,6)	0,010
fulfilling both the imaging and the clinical arm **	13 (38,2)	122 (64,5)	0,004
Family history of SpA (1 st or 2 nd degree relative) **	12 (35,3)	77 (40,7)	0,549
Peripheral manifestations:			

Table . (Cont'd)

	Secondary centers (n = 34)	Tertiary center (n = 189)	p-value ($\alpha = 0.05$)
<i>Arthritis (history or current) **</i>	5 (14,7)	34 (18,0)	0,643
<i>Dactylitis (history or current) **</i>	0 (0)	9 (4,8)	0,194
<i>Enthesitis (history or current) **</i>	4 (11,8)	18 (9,5)	0,687
Extra-articular manifestations:			
<i>Psoriasis (history or current) **</i>	6 (17,6)	19 (10,1)	0,196
<i>Inflammatory bowel disease (history or current) **</i>	1 (2,9)	8 (4,2)	0,725
<i>Acute anterior uveitis (history or current) **</i>	4 (11,8)	28 (14,8)	0,640
Clinical measurements:			
<i>BMI (kg/m²) *</i>	23,6 (3,63)	24,6 (4,16)	0,169
<i>BASMI *</i>	1,5 (1,52)	1,5 (1,40)	0,865
<i>Maastricht Ankylosing Spondylitis Enthesitis Score + fascia plantaris (/15) *</i>	1,7 (3,05)	0,9 (1,56)	0,397
Patient reported outcomes:			
<i>BASDAI (/100) *</i>	42 (19,3)	42 (19,9)	0,956
<i>BASFI (/100) *</i>	26 (21,7)	27 (21,8)	0,785
<i>HAQ (/60) *</i>	4,7 (5,07)	4,8 (5,69)	0,826
<i>Ankylosing Spondylitis Disease Activity Score - CRP *</i>	2,43 (1,022)	2,57 (0,961)	0,405

*Numbers indicate mean (SD). **Numbers indicate absolute counts (%).

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Abstract Number: 1646

Prevalence of Spondyloarthritis in Patients with Anterior Uveitis

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Background/Purpose: Anterior uveitis (AU) is a common extraarticular manifestation in spondyloarthritis (SpA). The disease can precede the typical axial and peripheral features. Additionally, some studies had described the imaging signs of sacroiliac involvement in patients with AU lacking chronic back pain. The aim of this study was to examine patients with AU, to determine whether the patients already fulfil criteria for axial and/or peripheral SpA and to stratify risk factors for SpA development.

Methods: We recruited 41 patients without prior rheumatologic diagnosis who developed at least one episode of AU. The clinical data were collected and rheumatology examinations were performed by trained rheumatologists. Magnetic resonance imaging (MRI) of sacroiliac joints (SIJ) was read by trained rheumatologist who was blinded to the patient data. Patients were further divided into SpA subsets (axial: imaging and clinical arm and peripheral SpA) fulfilling The Assessment of SpondyloArthritis international Society (ASAS) classification criteria¹ and non-SpA subset. The ASAS modified Berlin algorithm for diagnosis of axial SpA² (axSpA) was also applied.

Results: Altogether, 22.0% (n=9) patients referred inflammatory back pain, 48.8% (n=20) referred non-inflammatory back pain and 29.3% (n=12) did not refer back pain. Bone marrow edema (BME) was found in 48.8% (n=20) of all patients with AU, however 31.7% (n=13) had highly suggestive BME³ corresponding to typical findings in sacroiliitis. The diagnosis of SpA was confirmed in 41.5% (n=17) of all patients with AU, 26.8% (n=11) patients fulfil the imaging arm and 12.2% (n=5) fulfil the clinical arm of ASAS classification criteria for axSpA, 4.9% (n=2) patients fulfil ASAS classification criteria for peripheral SpA (one patient fulfil both axial and peripheral criteria). Two patients lacking back pain developed highly suggestive BME on SIJ. The diagnosis of axSpA according to the Ankylosing Spondylitis Disease Activity Score (ASDAS) modified berlin algorithm was confirmed in 41.5% (n=17) patients. Analysis of clinical characteristics showed significant difference between ASDAS in SpA vs. non-SpA (1.6 ± 0.7 vs 0.8 ± 0.6 , $p < 0.001$, respectively), and remained significant in axSpA and also in those fulfilling only imaging arm of axial SpA (i-axSpA) ($p = 0.002$, $p = 0.016$, respectively). The levels of CRP were significantly higher in SpA and axSpA compared to non-SpA subsets (9.5 ± 10.3 , 8.7 ± 10.1 vs. 2.2 ± 2.2 mg/L,

p=0.005, p=0.009, respectively). Presence of back pain and inflammatory back pain were more often in SpA compared to non-SpA subsets (94.1% and 47.1% vs. 54.2% and 4.2%, p=0.006 and p=0.002 respectively).

Conclusion: More than one third of patients with anterior uveitis fulfilled the criteria for axial or peripheral SpA. Furthermore, these patients had significantly higher presence of back pain, increased ASDAS and serum CRP levels. Inflammatory back pain was significantly more often in patients classified as axSpA.

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Uveitis, the Most Faithful Partner of Axial Spondyloarthritis

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Background/Purpose: Acute Anterior Uveitis (AAU) is the most frequent extra-articular manifestation in axial Spondyloarthritis (axSpA), with an overall prevalence of 32.7%. It is a manifestation of great socioeconomic impact, since it generates considerable disability. The objective of this study was to determine the prevalence of AAU in a cohort of patients with axSpA and to describe their clinical characteristics, frequency of episodes, response to treatment and long-term prognosis, as well as, their association with general disease characteristics.

Methods: A cross-sectional study was carried out. We included patients diagnosed with axSpA (ASAS 2009 criteria) from ESPAXIA cohort. Sociodemographic data, type of axSpA, extra-articular manifestations, comorbidities, disease duration and treatments received, numbers of episodes of uveitis, incidence date, and its characteristics, treatment and complications were consigned. Morning stiffness, night pain, global pain and patient's and physician's global assessment (NVS), number of swollen joints (44), axial mobility (BASMI), enthesitis (MASES), ESR, CRP and *HLA-B27* were registered. BASDAI, BASFI and ASQoL self-questionnaires were administered. *Statistical analysis:* Descriptive statistics. Student's T-test, Chi² test and multiple logistic regression analysis. Kaplan Meier curves. A p value <0.05 was considered significant.

Results: Two hundred and thirty one patients with axSpA were included, 174 male (75.3%) with a median age of 46 years (IQR 36-57) and median disease duration of 20.5 years (IQR 10.5-30.5). Sixty patients (26%) had at least one episode of uveitis, being the first manifestation of the disease in 22 of them (37.9%). Acute anterior uveitis was the most frequent form, and it was observed in 59 patients (98.3%). The mean number of episodes was 4.78 (SD 5.64). Recurrences were unilateral in 48.8% of cases. The treatment received was local in 42 (79.2%) of the patients. Twenty patients (33.33%) where in treatment with Tumor Necrosis Factor α inhibitors (TNF α -i) by the time of the data collection: 17 patients with monoclonal antibodies and 3 with Etanercept (ETN). Patients with axSpA and UAA received monoclonal agents more frequently (85% vs 15%, p=0.018). The presence of UAA was associated with a lower survival of biological medication, with a median of 91.42 months (SD 19.74) vs 109.44 months (SD 12.34). Twelve patients (22.2%) presented a complication after the first episode, being the decrease in visual acuity and cataracts, the most frequent ones (16.7% and 5.6%, respectively). The presence of uveitis was significantly associated with longer disease duration (24.9 years vs 20.7 years, p=0.038) and with the presence of *HLA-B27*, (69% vs 47.4%, p=0.006) and these associations were maintained in the multivariate analysis, after adjusting for other variables.

Conclusion: The prevalence of uveitis in our cohort was 26%, and it was significantly more frequent in patients *HLA-B27* (+) and with longer disease duration.

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Smoking Status in Patients with Psoriasis and Psoriatic Arthritis: An Irish Perspective

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SESSION INFORMATION

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The BIOmarkers of COMorbidities (BIOCOM) in psoriasis study is a longitudinal study which aims to identify clinical, genetic or protein biomarker features associated with the development of co-morbidities, notably Psoriatic Arthritis (PsA), in patients with psoriasis.

There is a well-established association between smoking and psoriasis, and between smoking and PsA, in the general population. Paradoxically, smoking has been shown to be negatively associated with the development of PsA in patients with established psoriasis. Herein we describe the prevalence of smoking in this BIOCOM cohort.

Methods: Patients with psoriasis were recruited from the dermatology clinics at St. Vincent's University Hospital, Dublin. Inclusion criteria included disease duration of less than 10 years and an age of 18 years or older. Patients with another serious active medical illness, a previous diagnosis of inflammatory arthritis or those who were receiving systemic immunosuppressant therapy for psoriasis were excluded.

Patients with PsA were recruited from the rheumatology clinics at St. Vincent's University Hospital. Patients had to meet CASPAR (CLASSification criteria for Psoriatic Arthritis) criteria for inclusion in the study.

Results: To date 190 patients with psoriasis have been recruited. Of those, 9 were excluded due to a diagnosis of psoriasis > 10 years previously. One was excluded due to a previous diagnosis of JIA. This left 180 patients with psoriasis who were brought in for an initial assessment. After the initial assessment 7 patients were diagnosed with PsA, meeting CASPAR criteria. This left 173 patients for inclusion in the analysis.

100 patients with established PsA were recruited and were included in the study.: Table 1 describes demographic and clinical characteristics of the study population at baseline assessment.

	Psoriasis	PsA
Age, mean +/- SD years	41.3 +/- 14.9	52.4 +/- 10.5
Male Sex, number (percentage)	105 (60.7)	55 (55.0)
Duration of Psoriasis, mean +/- SD years	6.2 +/- 2.9	26.1 +/- 13.1
Duration of PsA, Mean +/- SD years		17.9 +/- 10.0
PASI score, mean +/- SD	7.3 +/- 3.9	3.6 +/- 3.2
Type 1 Psoriasis, number (percentage)	107 (61.9)	86 (86.0)

The proportion of smokers (current and past) was lower in the PsA group compared to the psoriasis group: 52.0 versus 63.6. Table 2 shows smoking characteristics of patients with PsA and psoriasis.

Smoking Status	Psoriasis	PsA	p Value
Never Smoked, number (percentage)	63 (36.4)	48 (48.0)	0.06
Current, number (percentage)	49 (28.3)	10 (10.0)	<0.001
Past, number (percentage)	61 (35.3)	42 (42.0)	0.268

Conclusion: Analysis of patients recruited to date for the BIOCOM-Pso study shows a higher percentage of smokers (current and past) in the psoriasis group compared to the PsA group. The proportion of smokers (current and past) in the PsA group was comparable to the general Irish population.

These findings are consistent with previous studies that showed a negative association between smoking and the development of PsA in patients with psoriasis. However, prospective follow-up of patients with psoriasis, which is ongoing in this BIOCOT cohort, is required to further elucidate the role of smoking in the development of PsA.

Disclosure: C. Magee, None; O. FitzGerald, AbbVie, Bristol-Myers Squibb, Novartis, Pfizer Inc, 2,AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Novartis, Pfizer Inc, UCB, 9; F. Farkas, None; N. Ikumi, None; P. Gallagher, None; A. Szentpetery, None; B. Kirby, None.

Abstract Number: 1649

Cohort Identification of Axial Spondyloarthritis in a Large Healthcare Dataset: Current and Future Methods

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Background/Purpose: Big data research is important for studying uncommon diseases in real-world settings. Most big data studies in axial spondyloarthritis (axSpA) have been limited to populations identified with billing codes for ankylosing spondylitis (AS). axSpA is a more inclusive concept, and reliance on AS codes does not produce a comprehensive axSpA study population. The first objective was to describe our process for establishing an appropriate sample of patients with and without axSpA for developing novel axSpA identification methods. The second objective was to determine the classification performance of AS billing codes against the chart-reviewed reference standard.

Methods: Veteran Health Affairs data, between January 2005 and June 2015, were used to randomly select patients with phenotypes determined by expert opinion to represent high, moderate, and low likelihoods of an axSpA diagnosis. A risk stratified sampling approach was applied to balance chart review feasibility(enrichment with high risk patients) with generalizability (inclusion of low risk patients). With chart review, the sampled patients were classified as Yes, No, or Uncertain axSpA status. These classification assignments were used as the reference standard for determining the positive predictive value (PPV) and sensitivity of AS ICD-9 codes for axSpA

Results: A higher percentage of patients were included from the high risk stratum than the moderate and low risk strata (0.83%, 0.25%, 0.01%, respectively) (Table 1). Six hundred patients were classified as Yes axSpA (26.8%), No axSpA (68.3%), and Uncertain axSpA (4.8%) (Table 2). The PPV of an AS ICD-9 code for axSpA was 83.3% and the sensitivity was 57.3% (Figure 1).

Conclusion: Standard methods of identifying axSpA patients with AS diagnosis codes lacked sensitivity. An appropriate sample of patients with and without axSpA was established for developing novel axSpA identification methods that are anticipated to enable previously impractical big data research

Table 1. Selection of patients sampled for the chart review population

Subgroups	Subgroup Criteria (ICD-9 or laboratory data)	No. of Veterans	No. of Veterans selected to chart review population	% from each risk stratum selected to the chart review population
High risk for AxSpA				
Ankylosing spondylitis	720.0	15,862	100	0.83
HLA-B27 positivity	positive B27 test result	8,168	100	
Moderate risk for AxSpA				
Sacroiliitis	720.2	50,603	100	0.25
SpA subtype other than AS			100*	
Spondyloarthritis NOS	720.8x and/or 720.9x	6,319		
Reactive arthritis	711.x and/or 99.3	1,072		
Psoriatic arthritis	696.0	22,625		
Enteropathic arthritis	713.1 AND either 555.x OR 556.x	521		
Low risk of AxSpA				

Table . (Cont'd)

Subgroups	Subgroup Criteria (ICD-9 or laboratory data)	No. of Veterans	No. of Veterans selected to chart review population	% from each risk stratum selected to the chart review population
Chronic back pain	(≥2 ICD-9 codes for back pain ≥ 3 months apart [724.1, 724.2, 724.5])	2,069,644	100	0.01
Non-SpA rheumatologic disease			100*	
DISH	721.6	2,963		
Crystal arthritis	274.x and/or 712.x	675,799		
Rheumatoid arthritis	714.x	143,620		
Other inflammatory arthritis	CTD (710.x), vasculitis (273.2, 446.0, 446.4, 446.5, 446.7), PMR (725), Paget's (731.0), sarcoidosis (135)	135,608		

* 25 patients from each subcategory of spondyloarthritis NOS, reactive arthritis, psoriatic arthritis, enteropathic arthritis, DISH, crystal arthritis, rheumatoid arthritis, and other inflammatory arthritis.

Table 2. AxSpA classification by chart review

All	High risk for AxSpA		Moderate risk for AxSpA		Low risk for AxSpA	
No. [%] (95% CI) n=600	AS No. (95% CI) n=100	B27+ No. (95% CI) n=100	Non-AS SpA subtype No. (95% CI) n=100	Sacroiliitis No. (95% CI) n=100	SpA mimics No. (95% CI) n=100	Chronic back pain No. (95% CI) n=100
Yes AxSpA	162 [27.0] (23.5-30.6)	87 (80.4-93.6)	38 (28.5-47.5)	27 (18.3-35.7)	7 (2.0-12.0)	2 (0.0-4.7)
No AxSpA	409 [68.2] (64.4-71.9)	4 (0.2-7.8)	57 (47.3-66.7)	63 (53.5-72.5)	89 (82.9-95.1)	97 (93.7-100.0)
Uncertain AxSpA	29 [4.8] (3.1-6.5)	9 (3.4-14.6)	5 (0.7-9.3)	10 (4.1-15.9)	4 (0.2-7.8)	1 (0.0-3.0)
						0 (0.0-0.0)

No. = number. CI = Confidence interval

Disclosure: G. Penmetsa, None; J. Walsh, None.

Abstract Number: 1650

Subclinical Atheromatosis and Estimation of Cardiovascular Risk in Patients with Axial Spondyloarthritis

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Background/Purpose: There is evidence that shows an increased cardiovascular risk in patients with Axial Spondyloarthritis (axSpA). Ultrasonography (US) is a simple imaging tool used to assess cardiovascular risk by the detection of atherosclerotic lesions. **Objectives:** To evaluate the association between the cardiovascular (CV) risk estimated by a traditional score and the prevalence of subclinical atheromatosis detected by carotid US in patients with axSpA

Methods: A cross-sectional study was designed including consecutive patients with a diagnosis of axSpA (ASAS 2009 Criteria) without previous history of CV events. Patient's demographic and disease characteristics were recorded. The presence and history of traditional CV risk factors were evaluated. The cardiovascular risk was stratified according to the Framingham score [percentage of risk of presenting a 10-year cardiovascular event]. All patients underwent bilateral US carotid artery examination (common and internal carotid) to assess subclinical atherosclerosis. The presence of intima-media thickness (IMT) >0.9 mm and/or carotid plaques was used to define carotid atherosclerosis (US Carotid Atherosclerosis=USCA) as a marker of high cardiovascular risk. The association between clinical characteristics and US findings was assessed by univariate and multivariate analysis. ROC curves were developed to estimate cut-off values.

Results: Fifty-one patients with axSpA were included. The mean age was 43 ± 13 years, and 75% were men. The median disease duration was 12 years (IQR: 6-23), and the mean BASFI and BASDAI were 3.8 ± 2.9 and 3.9 ± 2.6 , respectively. Sixty-five percent were receiving NSAIDs and 51% biological treatment. Eleven patients (22%) had hypertension, 13 (25%) dyslipidemia, and 9 (18%) were smokers. The mean score of the Framingham index was 8.6 ± 1.3 . The patients

were stratified in: low risk: 34 (67%), moderate risk: 12 (23%) and high risk: 5 (10%). The US evaluation detected the presence of USCA (plaque and / or IMT > 0.90 mm) in 21 (41%) patients, presence of plaques in 19 (37%), and IMT > 0.9 mm in 13 (25%). The frequency of USCA found in patients stratified by the different Framingham categories were: low risk: 6/34 (18%); moderate risk: 10/12 (83%); high risk: 5/5 (100%). In the univariate analysis the presence of USCA was more frequent in older patients ($p < 0.0001$), longer disease duration ($p = 0.008$), hypertension ($p = 0.001$), dyslipidemia ($p = 0.008$) and higher BMI ($p = 0.02$). After adjusting for multiple confounding factors, age was the only variable associated with the presence of USCA. In the ROC analysis, the optimal cut-off value for age to predict the presence of USCA was 42.5 years, with a sensitivity and specificity of 85% and 82%, respectively (AUC: 0.90). The USCA prevalence was 82% ($n = 18$) in patients with age ≥ 42.5 years, compared to only 10% ($n = 3$) in those with age < 42.5 years.

Conclusion: Subclinical atherosclerosis detected by US was found in a significant proportion (35%) of patients classified in low to moderate risk by the Framingham score. The majority of patients over 42.5 years of age presented high risk US lesions, and may require intensive CV risk management.

Disclosure: T. Cazenave, None; M. C. Orozco, None; G. Citera, None; E. E. Schneeberger, None; M. G. Rosemffet, None.

Abstract Number: 1651

Epidemiology of Depression and Anxiety in Patients with Psoriatic Arthritis: A Systematic Review and Meta-Analysis

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Background/Purpose: Shared inflammatory processes underscore a substantial burden and risk of psychiatric complications—namely depression and anxiety—in patients with psoriatic arthritis (PsA), yet to our knowledge there is no synthesis of the evidence to date. We conducted a systematic review and meta-analysis with the following aims: 1) determine the prevalence and incidence of depression and/or anxiety; 2) assess the impact of depression and/or anxiety on patient outcomes; and 3) describe treatment of depression and/or anxiety among patients with PsA.

Methods: We conducted a systematic literature review of Medline, Embase, Cochrane Database of Systematic Reviews, CINAHL and PsycINFO. We included full-length studies that: 1) utilized an observational design; 2) involved a sample of patients with PsA, with/without a comparator group; 3) reported depression and/or anxiety as an outcome, comorbidity, or predictor of a health outcome; and 4) reported relevant estimates (e.g. prevalence proportion, odds ratio, hazard ratio) or sufficient data to allow calculation. We extracted information on study setting and design, sample size, methods of assessing depression and anxiety and reported prevalence and incidence of depression and/or anxiety. When relevant data was provided, we pooled estimates using random effects models.

Results: Of 683 titles identified in our search 10 studies met inclusion criteria. Several methods were used to assess depression and anxiety including the Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire (PHQ-9) and International Classification of Diseases 9th Revision Codes (ICD-9). The majority of included studies assessed the prevalence of psychiatric complications; the pooled prevalence proportion of depression based on 6 studies and a total of 22,163 PsA patients was 20% (95% confidence interval (CI), 15% to 25%) and the pooled prevalence proportion of anxiety based on 4 studies and 15,878 PsA patients was 27% (95% CI, 12% to 43%) (Figure 1). The incidence of depression in PsA patients as compared to the general population was reported in 3 studies and meta-analysis yielded a pooled incidence rate ratio (IRR) of 1.34 (95% CI, 1.20 to 1.49). Depression and anxiety were reported to be associated with increased inflamed joint count, pain, disability and fatigue. Treatment for depression in PsA patients included antidepressant/anxiolytic medications and/or psychotherapy. In studies reporting antidepressants use, only a small minority of patients take antidepressants.

Conclusion: We found a high prevalence of depression and anxiety in patients with PsA, and 30% higher risk of incident depression as compared to the general population. A clinical approach that includes screening and early treatment of psychiatric complications by health care professionals may impact mental health in patients with PsA.

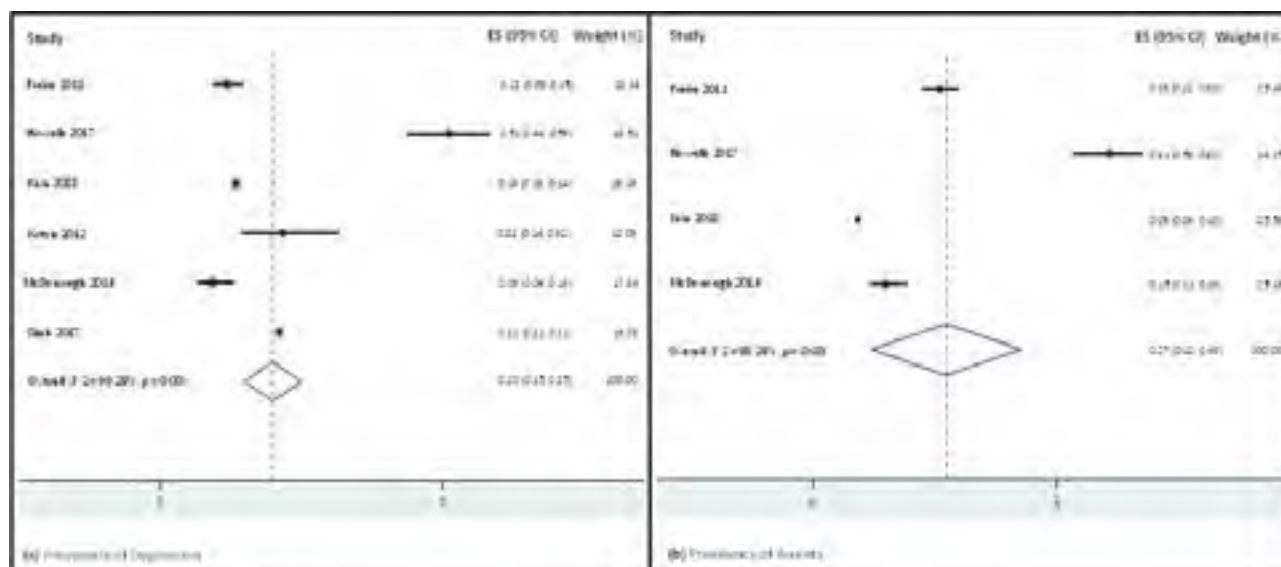


Figure 1. Pooled prevalence estimates (ES) of depression (a) and anxiety (b) in psoriatic arthritis.

Disclosure: E. Z. Zusman, None; A. Howren, None; J. Dutz, None; M. A. De Vera, None.

Abstract Number: 1652

Musculoskeletal Involvement in Inflammatory Bowel Disease'S Patients: A Mono Centric Experience

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Background/Purpose: Musculoskeletal symptoms are frequently reported by patients with inflammatory bowel diseases (IBD). Those symptoms may vary from arthralgia to arthritis, involving peripheral or axial joints, with a prevalence ranging from 17% to 62% when considering any SpA manifestation (with a similar range for axial or peripheral involvement from 5 to 30%) and a definite SpA diagnosis up to 46%. To date, a more comprehensive approach is needed, also because the use of DMARDs or biologics could improve both gastrointestinal and musculoskeletal symptoms. The purpose of the study is to evaluate the rate of MSK involvement in a mono centric cohort of IBD patients.

Methods: A questionnaire based on the features of SpA was used in the IBD out-patient clinic from January 1st to December 31st 2017. When there was a positivity for any feature, the patients were evaluated by a rheumatologist (with more than 18 years of experience in SpA). All the visits were performed in 2-3 weeks from the moment the questionnaire was performed (varying according to the seasonal time for holidays). When there were some doubts about the diagnosis, further examinations were requested.

Results: A total of 403 patients were visited in the out-patient clinic (220 affected by CD, 172 affected by UC and 11 with a not defined IBD). Fifty-nine patients were sent to the rheumatologist (33 CD, 24 UC and 2 not defined IBD). Eleven patients had 2 or more rheumatologic visits (to follow-up the disease and check the results of the exams requested). To allow a diagnosis, 4 sacroiliac joints MRI and 1 ultrasound assessment of the feet were requested. A diagnosis of peripheral SpA was given in 9 patients while axial SpA was diagnosed in 7 subjects. The diagnosis was fibromyalgia, osteoarthritis and arthralgia in 1, 2 and 40 patients, respectively. Therapy was modified in 16/59 patients after the rheumatologic assessment (DMARDs were prescribed in 12 subjects while anti-TNFα in 4 of them). In 1 patient (with absolute contraindication for biologic therapy), two courses of SI joint injection were performed, improving local pain.

Conclusion: The results of our study confirm the already published prevalence of musculoskeletal involvement in IBD patients (15% of our IBD population complained musculoskeletal pain and 27% of the patients sent to the rheumatologist

were given an enteropathic arthritis diagnosis). As for the already existing literature, we did not notice any evident difference in the prevalence of axial and peripheral involvement. An established collaboration between gastroenterologists and rheumatologists is necessary to provide an integrated and more comprehensive management of IBD, improving the quality of life of the patients.

Disclosure: A. Delle Sedie, None; L. Ceccarelli, None; L. Carli, None; F. Costa, None; S. Marchi, None; M. Mosca, None.

Abstract Number: 1653

Psychological Distress in Patients with Axial Spondyloarthritis in Europe. Results from the European Map of Axial Spondyloarthritis Survey

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Background/Purpose: To assess the association between sociodemographic characteristics, disease activity, and psychological distress in patients with axSpA.

Methods: Between July 2017 and February 2018, 2,846 axSpA patients participated in the patient survey of the European Map of Axial Spondyloarthritis (EMAS) across 13 countries. The General Health Questionnaire (GHQ-12), ranging from 0 to 12, using a score of ≥ 3 as a threshold for risk of psychological distress, was employed. Sociodemographic characteristics (age, gender, relationship status, educational level, job status), disease assessments (BASDAI, spinal stiffness ranging from 3-12, functional restriction in 18 daily activities), and diagnosis of depression and/or anxiety were collected. The chi-square independence test and Mann-Whitney tests were applied, and a level of significance of 5% was adopted, to compare those at risk of distress (GHQ-12 ≥ 3) and those not at risk of distress (GHQ-12 < 3). Rank-based test was applied to stiffness index, BASDAI and age to determine if their distributions were different based on level of distress. In addition, correlation between age, spinal stiffness and BASDAI scores with GHQ-12 scores were assessed using Pearson correlation coefficient. To assess the degree to which these factors explain the variance in distress scores, a stepwise forward regression was conducted.

Results: All variables, except educational level, showed significant univariate correlation with distress (Table 1). Total GHQ score showed a significant inverse correlation with age indicating that younger participants had greater distress scores ($r = -0.154$). Higher GHQ scores also showed significant positive correlation with spinal stiffness and BASDAI scores, implying that higher BASDAI scores and stiffness are associated with more distress ($r = 0.405$ and 0.201 respectively). From the regression analysis, explanatory variables were indicated as significant in the following order from higher to lower explanatory power: BASDAI scores, anxiety, gender, job status, age and relationship status (Table 2).

Conclusion: In axSpA, clinical characteristics such as degree of disease activity and spinal stiffness are good predictors of psychological distress. Therefore, in patients with greater disease activity and more physical restriction, psychological evaluation and intervention should be considered as part of a holistic medical treatment.

Table 1. Sample characteristics according to the risk of distress GHQ-12 (N=2,846, unless other specified).

	No Risk of Distress (GHQ-12 < 3) (mean \pm SD or %)	Risk of Distress (GHQ-12 ≥ 3) (mean \pm SD or %)	P
Age, mean \pm SD	46.39 \pm 12.84	42.1 \pm 11.48	<0.001
Sex, No. of men	43.9%	34.7%	<0.001
Having a couple, No. of participants (N= 1,380)	63.9%	55.0%	0.002
Educational level, No. with university studies	47.2%	48.8%	0.596
Job Status			<0.001
Employed	58.8%	46.1%	
Temporary sick leave	5.2%	14.8%	
Permanent sick leave	9.0%	11.3%	
Early retirement	1.4%	1.6%	
BASDAI, (≥ 4), No.	49.7%	86.9%	<0.001

Table . (Cont'd)

	No Risk of Distress (GHQ-12 < 3) (mean ± SD or %)	Risk of Distress (GHQ-12 ≥ 3) (mean ± SD or %)	P
BASDAI, (0-10) mean ± SD (N=2,584)	4.57 ± 2.01	6.04 ± 1.77	<0.001
Stiffness index, (3-12) mean ± SD (N=605)	7.26 ± 2.53	8.06 ± 2.44	<0.001
Depression, No. (%)	8.8%	37.1%	<0.001
Anxiety, No. (%)	10.6%	41.9%	<0.001

Table 2. Stepwise regression model.

Regression Model	R ²	R ² adjusted	Change in R ²	Significance of change in R ²
BASDAI	,688	,687	,688	,000
BASDAI, Anxiety	,691	,690	,003	,002
BASDAI, Anxiety, Gender	,696	,695	,005	,000
BASDAI, Anxiety, Gender, job status	,697	,696	,001	,032
BASDAI, Anxiety, Gender, job status, age	,698	,697	,001	,028
BASDAI, Anxiety, Gender, job status, age, relationship status	,700	,699	,002	,006

Disclosure: M. Garrido-Cumbrera, None; D. Galvez-Ruiz, None; L. Gossec, None; V. Navarro-Compán, None; D. Poddubnyy, None; S. Makri, None; R. Mahapatra, None; P. Plazuelo-Ramos, None; C. J. Delgado Dominguez, None; C. Bundy, None.

Abstract Number: 1654

Improvement of Cytological Grade and Tear Production in Ankylosing Spondylitis Patients Under Anti-TNF Therapy: A Long-Term Follow-up

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Background/Purpose: Clinical expression and pathophysiology of dry eye disease (DED) have recently changed and pro-inflammatory cytokines, such as TNF- α , may play a role in the multifactorial mechanism of DED. Few studies evaluated the effect of TNF blockage in DED and there are no data regarding this complication in ankylosing spondylitis (AS). The aim of the study is to analyze the ocular surface (OS) in AS patients according to the DED severity grade and conjunctival impression cytology (IC) and the effect of anti-TNF therapy in a subgroup of patients with a one-year follow-up.

Methods: Thirty-six AS patients and 39 controls with strict exclusion criteria for DED were enrolled at study entry, and 14 were followed prospectively post-anti-TNF therapy at 3months (3M), and 12 months (12M). AS disease parameters were performed for all patients. Ocular evaluation included OS Index Disease questionnaire, Schirmer I test, break-up time, vital staining, and conjunctival IC. DED severity grade was also applied.

Results: AS patients presented higher frequency of DED (80.5% vs. 43.6%, p=0.01), a worse score of severity [1(0-3) vs. 0 (0-1), p=0.001], and a higher frequency of altered IC (55.5% vs. 12.8%, p=0.007) when compared to controls. The 14 patients under anti-TNF therapy presented an improvement in all clinical AS disease activity parameters throughout the one-year treatment (p<0.05). A concomitant increase in the Schirmer test was also observed [BL:10(2-35) mm, 3M:17.5(4-35) mm and 12M:20(4-30) mm, respectively, p=0.04] as well as a significant amelioration in the altered IC to a normal IC was noticed (p=0.006).

Conclusion: DED is a frequent and under-diagnosed ocular disease in AS patients. The long-term parallel improvement of disease activity and OS parameters in AS patients receiving anti-TNF therapy suggests that the OS is an additional target of systemic inflammation in AS.

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Achieving Remission in Psoriatic Arthritis By Early Initiation of TNF Inhibition: A Double-Blind, Randomized, Placebo-Controlled Trial of Golimumab + Methotrexate Versus Placebo + Methotrexate

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

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Background/Purpose: In inflammatory arthritis such as RA, early initiation of highly effective targeted treatments is a successful strategy to aim for sustained remission.¹ Here we aimed to assess if a similar strategy is effective in psoriatic arthritis (PsA) by assessing the efficacy and safety of golimumab + methotrexate (MTX) vs. MTX alone in PsA patients with early, active disease.

Methods: This investigator-initiated, multicenter, double blind, randomized, placebo-controlled trial included MTX and bDMARD-naïve patients with PsA fulfilling the CASPAR criteria and with active disease at baseline (≥ 3 SJC/TJC). Patients were randomized to either golimumab (50mg SC monthly) + MTX (n=26) (TNFi arm) or matched placebo + MTX (n=24) (MTX arm). MTX was started 15mg/week orally and increased to 25mg/week over 8 weeks. Primary efficacy endpoint was % of patients achieving DAS remission (<1.6) at week 22. Key secondary endpoints included changes in DAS CRP, VAS global, VAS pain, VAS physician, SJC (66) and TJC (68) and achievement of MDA. Safety was assessed throughout the study.

Results: The baseline demographics and disease characteristics were similar between both groups. The median disease duration at inclusion was 0.5 (0.5-2) (yrs), disease activity at baseline was: DAS CRP 2.25 (1.86-2.78) swollen joint count (66) 5 (4-8.25); tender joint count (68) 10 (5-15.3), PASI 1.75 (0.35-4.48). The median MTX dosage used was 19.2 (4.5) mg/week in the TNFi arm and 21.2 (2.4) in the MTX arm. There were 6 early drop-outs due to withdrawal of informed consent: 1 in the TNFi arm (wk14), 1 in the MTX arm (wk14); due to AE: 1 in the TNFi treatment arm (wk14) and 3 in the MTX arm (wk14). The study met the primary efficacy endpoint with DAS remission at week 22 achieved by 81% of the subjects in the TNFi arm versus 42% in the MTX arm ($p=0.004$). This difference in DAS remission was already observed at week 8 (73% vs. 42%, $p=0.025$). MDA was achieved by 81% vs. 29% at week 22 ($p<0.001$) and in 58% vs. 21% at week 8 ($p=0.008$). A

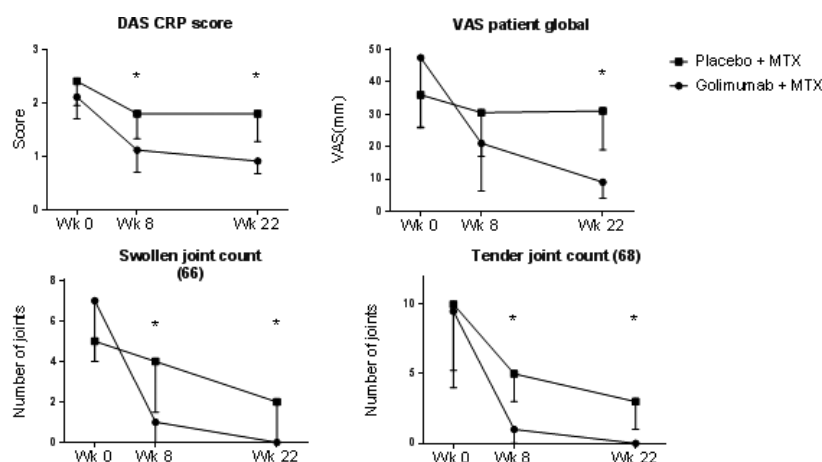


Figure 1 - Changes in clinical disease activity parameters during treatment with golimumab + MTX and placebo + MTX from baseline to week 22. The panels represent the DAS CRP score, VASpt global on a 100mm visual analogue scale, swollen joint count and tender joint count. Data are presented as median and interquartile range. * statistically significant

significant difference in favor of the TNFi arm at week 22 was also observed for several key secondary endpoints, most secondary parameters were already significantly different in favor of the TNFi arm at week 8 (Figure 1). As to safety, one SAE occurred in a patient in the MTX arm (cervical spine stenosis), which was considered not to be study related and did not result in early withdrawal. 43/50 patients experienced ≥ 1 AE (range 1-7), all of which were graded mild to moderate. The occurrence rates of AE and TEAE were similar in both arms.

Conclusion: DAS remission at week 22 was achieved by almost double the number of patients with early PsA treated with golimumab + MTX versus placebo +MTX. This double-blind, randomized, placebo-controlled study supports the concept that early initiation of TNFi in patients with active PsA favors rapid and sustained remission.

1 Bijlsma et al, U-ACT-EARLY study, Lancet, 2016

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Abstract Number: 1656

Is a Positive Family History of Spondyloarthritis Relevant for Diagnosing Axial Spondyloarthritis Once HLA-B27 Status Is Known? Data from the ASAS, DESIR, and SPACE Cohorts

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Table 1 Logistic regression analysis between ASAS-PFH, HLA-B27, and clinical axSpA diagnosis in the ASAS, DESIR, and SPACE cohort

	axSpA+	axSpA-	OR (95%CI)	p-value
ASAS cohort				
<i>Univariable analysis: HLA-B27</i>				
HLA-B27+	254	56	6.7 (4.7-9.8)	<0.001
HLA-B27-	114	170	1.0 (ref)	(ref)
<i>Univariable analysis: ASAS-PFH</i>				
ASAS-PFH+	91	44	1.4 (0.9-2.0)	0.138
ASAS-PFH-	277	182	1.0 (ref)	(ref)
<i>Multivariable analysis: HLA-B27 and ASAS-PFH</i>				
HLA-B27+	254	56	6.9 (4.7-10.2)	<0.001
ASAS-PFH+	91	44	0.9 (0.6-1.4)	0.561
DESIR cohort				
<i>Univariable analysis: HLA-B27</i>				
HLA-B27+	204	172	2.1 (1.5-2.9)	<0.001
HLA-B27-	98	172	1.0 (ref)	(ref)
<i>Univariable analysis: ASAS-PFH</i>				
ASAS-PFH+	117	132	1.0 (0.7-1.4)	0.900
ASAS-PFH-	185	213	1.0 (ref)	(ref)
<i>Multivariable analysis: HLA-B27 and ASAS-PFH</i>				
HLA-B27+	204	172	2.1 (1.5-2.9)	<0.001
ASAS-PFH+	117	132	1.0 (0.7-1.3)	0.772
SPACE cohort				
<i>Univariable analysis: HLA-B27</i>				
HLA-B27+	205	41	10.3 (6.9-15.5)	<0.001
HLA-B27-	108	223	1.0 (ref)	(ref)
<i>Univariable analysis: ASAS-PFH</i>				
ASAS-PFH+	132	86	1.5 (1.1-2.1)	0.018
ASAS-PFH-	181	178	1.0 (ref)	(ref)
<i>Multivariable analysis: HLA-B27 and ASAS-PFH</i>				
HLA-B27+	205	41	10.4 (6.9-15.7)	<0.001
ASAS-PFH+	132	86	1.0 (0.7-1.5)	0.921

Statistically significant associations are printed in bold. ASAS, Assessment of SpondyloArthritis International Society; (ax)SpA, (axial) spondyloarthritis; CI, confidence interval; HLA-B27, human leukocyte antigen B27; OR, odds ratio; PFH, positive family history.

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

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Background/Purpose: A positive family history (PFH) of spondyloarthritis (SpA), in particular aPFH of ankylosing spondylitis (AS) or acute anterior uveitis (AAU), can be used to identify HLA-B27 carrier ship in chronic back pain patients¹. It is unknown if a PFH contributes to diagnosing axial spondyloarthritis (axSpA) once HLA-B27 status is known.

Methods: Baseline data of patients suspected of axSpA in the ASAS, DESIR, and SPACE cohorts were analysed. Logistic regression analyses were performed with HLA-B27 status and PFH according to the ASAS definition (ASAS-PFH) as determinants and clinical axSpA diagnosis as the outcome. Analyses were repeated with a PFH of AS or AAU.

Table 2 Logistic regression analysis between a PFH of AS, HLA-B27, and clinical axSpA diagnosis in the ASAS, DESIR, and SPACE cohort

	axSpA+	axSpA-	OR (95%CI)	p-value
ASAS cohort				
<i>Univariable analysis: HLA-B27</i>				
HLA-B27+	254	56	6.7 (4.7-9.8)	<0.001
HLA-B27-	114	170	1.0 (ref)	(ref)
<i>Univariable analysis: PFH of AS</i>				
PFH of AS+	65	22	2.0 (1.2-3.3)	0.009
PFH of AS-	303	204	1.0 (ref)	(ref)
<i>Multivariable analysis: HLA-B27 and PFH of AS</i>				
HLA-B27+	254	56	6.9 (4.6-10.2)	<0.001
PFH of AS+	65	22	0.9 (0.5-1.7)	0.800
DESIR cohort				
<i>Univariable analysis: HLA-B27</i>				
HLA-B27+	204	172	2.1 (1.5-2.9)	<0.001
HLA-B27-	98	172	1.0 (ref)	(ref)
<i>Univariable analysis: PFH of AS</i>				
PFH of AS+	63	64	1.2 (0.8-1.7)	0.461
PFH of AS-	239	283	1.0 (ref)	(ref)
<i>Multivariable analysis: HLA-B27 and PFH of AS</i>				
HLA-B27+	204	172	2.1 (1.5-2.9)	<0.001
PFH of AS+	63	64	1.0 (0.6-1.4)	0.829
SPACE cohort				
<i>Univariable analysis: HLA-B27</i>				
HLA-B27+	205	41	10.3 (6.9-15.5)	<0.001
HLA-B27-	108	223	1.0 (ref)	(ref)
<i>Univariable analysis: PFH of AS</i>				
PFH of AS+	63	41	1.4 (0.9-2.1)	0.153
PFH of AS-	250	223	1.0 (ref)	(ref)
<i>Multivariable analysis: HLA-B27 and PFH of AS</i>				
HLA-B27+	205	41	13.4 (8.4-21.4)	<0.001
PFH of AS+	63	41	0.4 (0.2-0.8)	0.004

Statistically significant associations are printed in bold. AS, Ankylosing Spondylitis; ASAS, Assessment of SpondyloArthritis International Society; (ax)SpA, (axial) spondyloarthritis; CI, confidence interval; HLA-B27, human leucocyte antigen B27; OR, odds ratio; PFH, positive family history.

Results: In total, 1,964 patients suspected of axSpA were analysed (ASAS n=594, DESIR n=647, and SPACE n=577). Patients from the ASAS, DESIR, and SPACE cohorts, respectively had a mean (SD) symptom duration of 85.7 (108.4), 18.2 (10.5), and 13.3 (7.1) months; 46%, 47%, and 38% were male; 23%, 39%, and 38% had an ASAS PFH, 52%, 58%, and 43% were HLA-B27 positive, and 62%, 47%, and 54% were diagnosed with axSpA. In the univariable analysis, HLA-B27 status was significantly associated with an axSpA diagnosis in all three cohorts (Table 1). An ASAS-PFH and a PFH of AAU were univariately associated with an axSpA diagnosis in the SPACE cohort, but not in the ASAS and DESIR

cohorts. A PFH of AS was associated with an axSpA diagnosis in the ASAS cohort, but not in the DESIR and SPACE cohorts. In the multivariable models, HLA-B27 was independently and positively associated with an axSpA diagnosis in each cohort but such an independent positive association was not found for an ASAS-PFH in any cohort (Table 1). Similarly, a PFH of AS did not have an independent positive association with an axSpA diagnosis in any cohort (Table 2). Similar results were found for PFH of AAU (ASAS cohort: HLA-B27 OR:6.9 (95%CI:4.7-10.1), ASAS PFH OR:0.4 (95%CI:0.08-1.8);DESIR cohort: HLA-B27 OR:2.1 (95%CI:1.5-2.9), ASAS PFH OR:1.1 (95%CI:0.5-2.3);SPACE cohort: HLA-B27 OR:10.7 (95%CI:7.0-16.3), ASAS PFH OR:0.8 (95%CI:0.3-1.8)).

Conclusion: A PFH did not contribute independently of HLA-B27 to a diagnosis of axSpA in axSpA suspected patients.

References: 1. Ez-Zaitouni et al (2017), AR&T2017;19(1):118.

Disclosure

M. van Lunteren, None; D. van der Heijde, None; A. Sepriano, None; I. Berg, None; M. Dougados, None; L. Gossec, None; L. Jacobsson, None; R. Ramonda, None; M. Rudwaleit, None; J. Sieper, None; R. B. M. Landewé, None; F. van Gaalen, None.

Abstract Number: 1657

The Effect of Guselkumab on Enthesitis: Results from a Phase 2 Study in Patients with Active Psoriatic Arthritis

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SESSION INFORMATION

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: In a Phase 2 study, Guselkumab (GUS) was shown to be safe & effective in pts w/active PsA w/ meaningful improvements in enthesitis. To evaluate the effect of GUS on enthesitis in a subset of pts w/enthesitis at baseline (BL) from the Phase 2 PsA study of GUS.

Methods: Pts w/active PsA & $\geq 3\%$ BSA of plaque PsO, despite current or previous treatment, were randomized 2:1 to 100mg SC GUS or PBO at wks 0,4, \rightarrow q8w during a 24-wk double-blind treatment period. At wk16, pts w/ $<5\%$ improvement in swollen & tender joint counts(SJC&TJC) early escaped(EE) to open-label ustekinumab. At wk24, the PBO group crossed over to GUS at wks24,28 \rightarrow q8w(PBO \rightarrow GUS) & the GUS group continued receiving GUS(GUS \rightarrow GUS) through wk44. Enthesitis was assessed using the Leeds enthesitis index(LEI). Enthesitis scores during the 24wk double-blind treatment was analyzed using LOCF imputation for missing data & EE. Enthesitis after wk24 was analyzed using observed data.

Results: Of 149 total pts w active PsA,107(72%) presented w/enthesitis at BL(PBO N=31,mean[SD] LEI=2.6[1.48], median [range]=2.0[1, 6]; GUS N=76,mean(SD) LEI=2.7[1.54], median[range]=2.0[1, 6])& 85 continued at Wk24(PBO \rightarrow GUS N=18;GUS \rightarrow GUS N=67). Except for higher TJC/SJC & CRP, BL characteristics of enthesitis subset was similar to overall population. GUS significantly reduced the LEI by wk8(mean[SD]] change from BL, PBO:-0.4[1.59]; GUS:-1.2[1.65]; p=0.037),& through wk24(mean[SD] change from BL, PBO:-0.7[1.53]; GUS:-1.5[1.81];p=0.045). GUS also significantly increased the % of pts w/enthesitis resolution(Figure). After wk24, PBO \rightarrow GUS group achieved rapid, sustained resolution (wk56: mean[SD] change from BL=-2.1[1.65];62.5% of pts w/resolution), similar to GUS \rightarrow GUS group(wk56:mean[SD] change from BL=-1.9[1.59],70.8% of pts w/resolution). Improvement in enthesitis was observed at each enthesitis site assessed, & was greater in ACR20(Table) responders vs non-responders in GUS-treated pts & was correlated w/ improvement in TJC (R=0.37, p=0.001) & SJC (R=0.27,p=0.020), physician's(R=0.47,p<0.0001) & pts global assessment of disease activity(R=0.32,p=0.005), & SF36 PCS(R=0.27,p=0.02) & MCS(R=0.35,p=0.002).

Conclusion: GUS treatment produces rapid & sustained improvement of enthesitis in pts w/active PsA, which correlates w/ improvement in joint symptoms & pt-reported outcomes.

Figure. Proportion of Patients with Enthesitis Resolution over Time

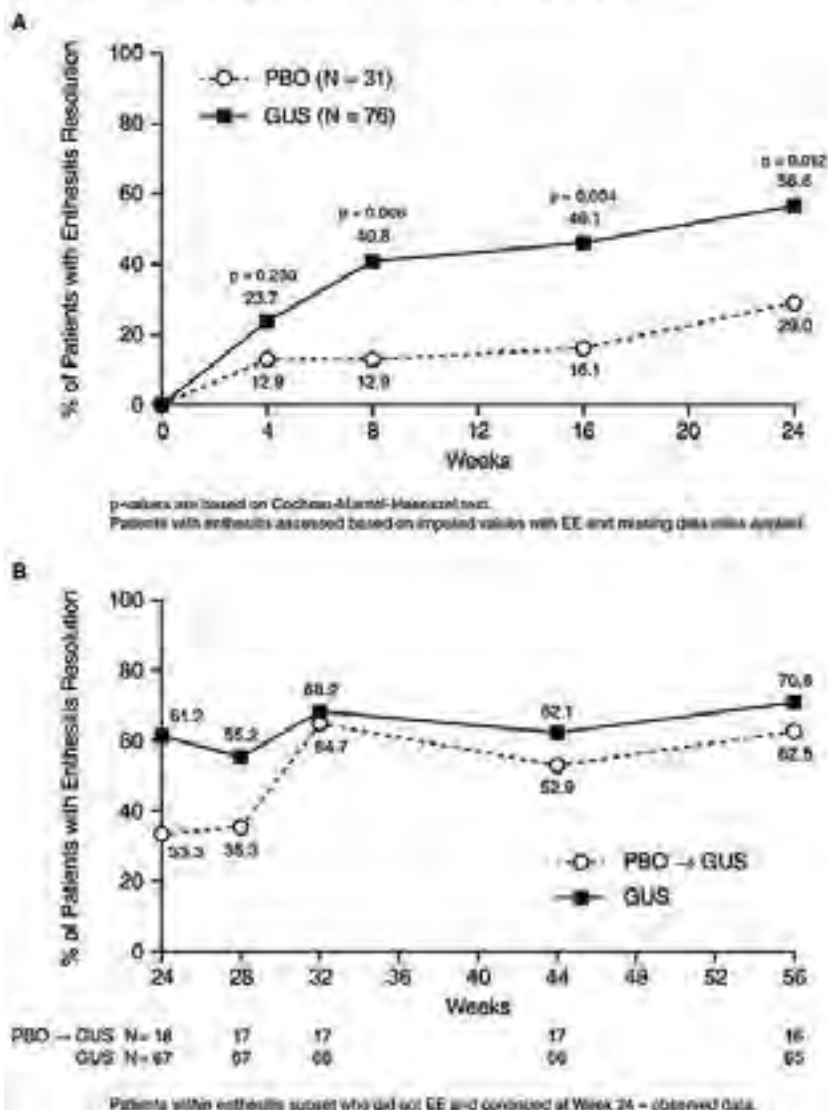


Table. Change in LEI in ACR20/50 and PASI75 Responders and Non-responders

	Mean (SD) change from BL in LEI at Wk24		p-value
	Non-responders	Responders	
ACR 20	-0.93(2.054), n=28	-2.06(1.660), n=47	0.002
ACR 50	-1.55(2.190), n=49	-1.81(1.132), n=26	0.057
PASI 75	-1.25(1.138), n=12	-1.71(1.995), n=63	0.524

Disclosure: P. Helliwell, Janssen Research & Development, LLC., 2; A. B. Gottlieb, Janssen Research & Development, LLC., 2; A. A. Deodhar, Janssen Research & Development, LLC, 2; W. H. Boehncke, Janssen Research & Development, LLC, 2; D. McGonagle, Janssen Research & Development, LLC, 2; X. L. Xu, Janssen Research & Development, LLC, 3; S. Xu, Janssen Research & Development, LLC, 3; Y. Wang, Janssen Research & Development, LLC, 3; E. C. Hsia, Janssen Research & Development, LLC, 3; C. S. Karyekar, Janssen Research & Development, LLC, 3; P. J. Mease, Janssen Research & Development, LLC, 2.

Abstract Number: 1658

Which Factors Influence the Diagnostic Delay in Patients with Axial Spondyloarthritis?

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SESSION INFORMATION

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Background/Purpose: The interval from symptom onset till diagnosis in axial spondyloarthritis (axSpA) was reported a decade ago to be between five and ten years. The objective of this study was to explore if the diagnostic delay has improved over the past years and to analyse factors associated with the delay.

Methods: A sample of persons with axSpA (ICD-10 M45) stratified by age and sex was drawn from claims data of a large nationwide statutory health insurance fund in Germany. Each person in the sample received in 2015 a questionnaire gathering information on demographic, disease-related and socioeconomic characteristics. Disease-related parameters comprised the date of first symptoms, the date of diagnosis, the HLA-B27 status as well as the presence of extra-articular manifestations (uveitis, psoriasis, chronic-inflammatory bowel disease). Multivariable linear regression analysis was used to analyse factors associated with the diagnostic delay.

Results: A total of 1,677 persons with axSpA were included in the analysis. The mean age was 56 years and 46% were female. The mean (95% confidence interval [CI]) diagnostic delay in the whole group was 5.7 (5.4 – 6.0) years and the median was 2.3 years (Fig. 1). Overall, 407 persons were diagnosed between 1996 and 2005 and 484 persons between 2006 and 2015. The diagnostic delay was not substantially different in both periods: For patients diagnosed between 1996 and 2005 the mean (95% CI) diagnostic delay was 6.3 (5.6 – 7.0) years and the median was 2.6 years. For patients diagnosed between 2006 and 2015 the mean (95% CI) diagnostic delay was 7.4 (6.6 – 8.1) years and the median was 2.7 years. Persons with a long diagnostic delay were more often female and had less often a positive HLA-B27 status compared to persons with a short diagnostic delay (Tab. 1). Multivariable linear regression revealed that female sex, negative HLA-B27 status, prevalence of psoriasis and younger age at symptom onset are factors associated with a longer diagnostic delay (Tab. 2).

Conclusion: The mean diagnostic delay of about 7 years represents currently one of the major challenges in field of SpA. Female sex, negative HLA-B27 status, presence of psoriasis and younger age at symptom onset had a negative impact on the diagnostic delay.

Table 1 Main demographic, disease-related, lifestyle and socioeconomic characteristics of patients with axSpA stratified by the delay to diagnosis.

	Total N=1677	Delay to diagnosis <2.3 years N=814	Delay to diagnosis ≥2.3 years N=863	P value
Sex, female	45.9	40.6	50.8	<0.0001
Age, years	55.9 ± 0.1	54.3 ± 0.3	57.3 ± 0.3	<0.0001
Age at symptom onset, years	30.6 ± 0.3	33.1 ± 0.4	28.3 ± 0.3	<0.0001
Age at diagnosis, years	36.3 ± 0.3	33.8 ± 0.4	38.6 ± 0.4	<0.0001
HLA-B27 (+)	86.3	89.2	83.8	0.0103
BASDAI*, 0-10	4.5 ± 0	4.3 ± 0.1	4.7 ± 0.1	0.0002
BASFI*, 0-10	4.1 ± 0.1	3.8 ± 0.1	4.4 ± 0.1	<0.0001
Swollen/tender joints, 0-44	7 ± 0.2	6.6 ± 0.3	7.4 ± 0.3	0.1065
WHO-5 *, 0-100	45 ± 0.5	46.8 ± 0.7	43.3 ± 0.7	0.0012
Inflammatory bowel disease, ever	9	9.6	8.5	0.4481
Uveitis, ever	27.8	26.4	29.1	0.2347
Psoriasis, ever	15.1	13.9	16.2	0.2000
Educational level				0.0057
low	29.1	31.9	26.6	
middle	42.8	38.8	46.4	
high	28.1	29.3	27	
Smoking, current*	19	20	18.1	0.3454
Pharmacological treatment*				
NSAIDs	58.9	56.7	60.9	0.0883
non-opioid analgesics	22.2	20.3	24	0.0692
opioids	15.4	14	16.8	0.1265
bDMARDs	17.5	15.7	19.1	0.0609
csDMARDs	11.5	12.7	10.4	0.1403
steroids	19.5	18.7	20.2	0.4357
No pharmacological treatment*	22.5	25.1	20	0.0148

* referring to the time of questionnaire, not the time of diagnosis.

Values are presented as mean ± standard error of the mean for continuous characteristics and as percentages otherwise. P-values were assessed using analyses of variance for continuous characteristics and Rao-Scott chi-square tests otherwise.

WHO-5, 5-item World Health Organization Well-Being Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index, NSAIDs, Nonsteroidal Anti-Inflammatory Drugs; csDMARDs, conventional synthetic Disease-Modifying Anti-Rheumatic Drugs; bDMARDs, biological Disease-Modifying Anti-Rheumatic Drugs.

Table 2 Factors associated with diagnostic delay: results from multivariable linear regression analysis.

	Reference	Estimate (95% CI)
Sex, female	male	1.85 (1.06, 2.65)
Age at symptom onset	per 10 years	-1.91 (-2.29 , -1.53)
HLA-B27 status, positive	negative	-3.61 (-5.14 , -2.07)
Psoriasis, yes	no	1.4 (0.08 , 2.73)
CI, Confidence Interval		

Disclosure: I. Redeker, None; J. Callhoff, None; F. Hoffmann, None; H. Haibel, None; J. Sieper, None; A. Zink, None; D. Poddubnyy, None.

Abstract Number: 1659

Sustained Improvements in Physical Function, Quality of Life, and Work Productivity after Ixekizumab Therapy in Patients with Active Psoriatic Arthritis: 3-Year Results

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose: Ixekizumab (IXE), a high-affinity mAb that selectively targets IL-17A, has shown improvements compared to placebo not only in disease activity but also in various patient-reported outcomes (PROs) assessing physical function, fatigue, quality of life, and work productivity in PsA patients treated for 24weeks.¹ Herein, we report the effects of treatment with IXE on these PROs after up to 3 years of treatment.

Methods: InSPIRIT-P1¹ (NCT01695239), a Phase 3 trial, 417 biologic-DMARD-naïve patients with active PsA were randomized to IXE 80 mg every 4 weeks (IXE Q4W; N=107) or every 2 weeks (IXE Q2W; N=103), adalimumab 40 mg every 2 weeks (ADA; N=101), or placebo (PBO; N=106) in the double-blind treatment period (Weeks 0-24). Both IXE regimens had a starting dose of 160 mg. Results are reported from a subset of the intent-to-treat population defined as patients randomized to IXE at baseline (Week 0). The following PROs were assessed in the study (during Weeks 0-156):HAQ-DI (minimally clinically

Table: Overview of Patient-Reported Outcomes at Week 156 of the Intent-to-Treat Population: Patients Randomized to IXE at Baseline				
	Baseline		At Week 156	
	IXE Q4W (N=107)	IXE Q2W (N=103)	IXE Q4W (N=107)	IXE Q2W (N=103)
Completed 156 Weeks of Treatment n (%)	—	—	61 (58.9)	62 (60.2)
	Baseline		Change from Baseline*	
	Mean (SD)	Mean (SD)	mBOCF Mean (SD)	mBOCF Mean (SD)
HAQ-DI	1.3 (0.5)	1.3 (0.6)	-0.77 (0.6)	-0.79 (0.6)
SI-36 PCS Score	32.8 (10.1)	34.2 (8.7)	7.9 (10.1)	8.3 (9.6)
SI-36 MCS Score	46.5 (13.4)	48.0 (9.8)	3.3 (11.6)	3.8 (10.3)
EQ-5D VAS	0.6 (0.2)	0.6 (0.2)	0.8 (24.8)	1.7 (21.7)
Fatigue	3.8 (2.3)	3.5 (2.4)	-2.0 (2.7)	-2.3 (2.6)
WPAI Abolitionism	0.2 (23.0)	1.7 (23.0)	-4.8 (18.8)	6.2 (27.7)
WPAI Activity Impairment	47.9 (26.3)	47.6 (25.1)	-21.3 (26.1)	-26.1 (26.0)
WPAI Productivism	40.0 (26.7)	35.9 (21.6)	-18.0 (27.2)	-21.2 (21.8)
WPAI Work Productivity	42.3 (28.3)	37.4 (21.6)	-17.3 (26.0)	-18.2 (25.6)
Responder Rate [n/N] (%)				
HAQ-DI MCTD*	—		mNRI n (%)	mNRI n (%)
	—		51 (100) (50.5)	46 (96) (50.8)
Abbreviations: EQ-5D= European Quality of Life 5 Dimension Questionnaire; HAQ-DI=Health Assessment Questionnaire-Disability Index; IXE=ixekizumab; mBOCF=modified baseline observation carried forward; MCTD= minimal clinically important difference; MCS= Mental Component Summary; mNRI=modified nonresponder imputation; n=number of patients with nonmissing data; N=number of patients in the analysis population; PCS=Physical Component Summary; Q4W/Q2W=80 mg ixekizumab once every 4 or 2 weeks; SD=standard deviation; SI-36=Short Form (36 items) Health Survey; VAS=visual analog scale; WPAI=Work Productivity and Activity Impairment Questionnaire.				
*Data presented as mean (SD) for mBOCF analysis.				
*Patients with baseline HAQ-DI score ≥0.35.				
MCTD defined as patients achieving improvement (decrease in score) ≥0.33.				

important difference [MCID]: improvement ≥ 0.35 from baseline), medical outcomes survey Short Form-36 (SF-36) Physical and Mental Component Summary (PCS and MCS), European Quality of Life 5 Dimensions Visual Analog Scale (EQ-5D VAS; 0-100 scale), fatigue Numeric Rating Scale (NRS; 0 [no fatigue] to 10 [as bad as you can imagine] scale), and Work Productivity and Activity Impairment Questionnaire-Specific Health Problem (WPAI-SHP; absenteeism, presenteeism, work productivity, and activity impairment). Missing values were imputed by modified nonresponder imputation (mNRI) for categorical data and by modified baseline observation carried forward (mBOCF) for continuous data.

Results: Mean baseline (Week 0) scores for HAQ-DI, SF-36 (PCS and MCS), fatigue NRS, WPAI-SHP, and EQ-5D VAS (Table) indicated impaired physical function and quality of life. Patients receiving IXE up to 3 years reported improvements in SF-36 (PCS and MCS), EQ-5D VAS, fatigue NRS, and WPAI-SHP (presenteeism, work productivity, and activity impairment) (Table). The percentage of IXE patients achieving MCID for HAQ-DI (improvement >0.35) was sustained at 3 years.

Conclusion: In bDMARD-naïve patients with active PsA, improvements with IXE in all the measured PROs, including physical and mental function, quality of life, fatigue, and work productivity are maintained up to 3 years.

Reference: ¹Mease PJ, et al. *Ann Rheum Dis*. 2017;76(1):79-87.

Disclosure

R. Fleischmann, AbbVie, Amgen, AstraZeneca, BMS, Celgene, EMD-Serono, Eli Lilly, Merck, Novartis, Pfizer, Roche, Sanofi-Genzyme, UCB, 2, AbbVie, ACEA, Amgen, BMS, GSK, Eli Lilly, Novartis, Pfizer, Sanofi-Genzyme, UCB, 5; V. Chandran, AbbVie Inc., 2, AbbVie Inc., amgen, celgene, eli lilly, Janssen, Novartis, Pfizer and UCB, 5, Eli Lilly and Co., 9; E. Lespessailles, Novartis, Lilly, Servier, Amgen, 2, Novartis and Eli Lilly and Co., 8; J. Birt, Eli Lilly and Company, 1, 3; O. Benichou, Eli Lilly and Company, 1, Eli Lilly and Co., 3; J. Erickson, Eli Lilly and Company, 1, Eli Lilly and Co., 3; C. Shuler, Eli Lilly and Co., 1, previous employee Eli Lilly and Co., 3.

Abstract Number: 1660

Depression Has a Greater Impact on Psoriatic Arthritis Than Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Depression has been shown to be more common in patients with psoriatic arthritis (PsA) and rheumatoid arthritis (RA), than in the general population. The extent of this disease has not been studied in comparison between patients with PsA and those with RA. We studied the prevalence of depression in patients with PsA in comparison to those with RA.

Methods: A retrospective observational study was done using data collected from a community-based rheumatology clinic. All patients with data on depression were included for analysis. Baseline demographics, tender joint count (TJC), swollen joint count (SJC), Physician Global Assessment (PhGA), Pain Scale, Patient Global Assessment (PtGA), Function, Routine Assessment of Patient Index Data 3 (RAPID3) (a composite score of patient pain, PtGA, and Function), and Clinical Disease Activity Index (CDAI) (a composite score of TJC, SJC, PtGA, and PhGA) were collected. A validated depression scale was used to assess depressed mood. Data from random visits were chosen and analyzed using an ordered logistical regression. Both a univariate analysis and an analysis controlling for potential confounding variables were performed, using either CDAI or RAPID3 as the marker for disease activity.

Results: The study population consisted of 146 patients who had PsA and 366 who had RA. On a 0-3 scale for depressed mood, patients with PsA reported a mean of 0.55 ± 0.73 , whereas patients with RA reported a mean of 0.40 ± 0.64 (Table 1). When assessing the data using an ordered logistical regression, patients with PsA were 57% ($p=0.02$) more likely to report a higher level of depression than those with RA. When adjusted for disease activity using the CDAI and the RAPID3, the likelihood of PsA having a higher level of depression was 78% ($p=0.01$) and 58% ($p=0.04$) compared to RA, respectively. Lastly, a T-test was performed revealing a statistically significant difference between the PsA and RA groups ($p<0.02$).

Table 1 Data comparison of patients with PsA vs patients with RA

	PsA	RA
Number of Patients	146	366
Age (years)	55.21 ± 12.77	63.27 ± 14.89
Sex (% male)	36.99	28.49
Disease Duration (years)	7.49 ± 7.72	9.40 ± 11.06
Depression Problems (0-3)	0.55 ± 0.73	0.40 ± 0.64
Pain (0-10)	4.80 ± 2.88	4.23 ± 3.01
Global Severity (0-10)	4.33 ± 2.63	4.31 ± 2.91
Function (0-10)	2.15 ± 1.89	2.15 ± 2.05
Tender Joint Count (0-28)	1.65 ± 3.64	2.31 ± 4.94
Swollen Joint Count (0-28)	2.87 ± 4.00	4.60 ± 5.09
Physician Global (0-10)	2.42 ± 2.21	2.26 ± 2.22
RAPID3 (0-30)	11.35 ± 6.74	10.68 ± 7.29
CDAI (0-76)	11.21 ± 9.16	13.47 ± 11.25
Patients on Any Biologic Agents (%)	32.88	24.32

Conclusion: In this cohort, patients with PsA were more likely to report higher levels of depression than those with RA. Furthermore, this occurred independently from levels of disease activity as measured by either the CDAI or the RAPID3. Although causality is yet to be determined, this study enforces the importance of depression screening in rheumatology practice, and early treatment.

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Abstract Number: 1661

Factors That May be Associated with Uveitis in Patients with Spondyloarthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Background/Purpose: It is known that uveitis is present in the extra-articular findings of spondyloarthritis (SPA) patients. Sufficient information is available in the literature on the frequency and characteristics of uveitis in SpA patients. The factors associated with uveitis in SPA patients are not clear. In this study, uveitis-related factors were analyzed in SPA patients in a large cohort.

Methods: In patients with and without uveitis, age, gender, duration of illness, delayed onset, body mass index, educational status, smoking habit, SPA subgroup, SPA clinical findings as well as co-morbid diseases, HLA B27 and acute phase responses, VAS pain, VAS patient global, VAS fatigue, BASDAI and BASFI values, swollen and painful joint counts, and direct X-ray findings were evaluated retrospectively. The history of uveitis was accepted only if diagnosed by ophthalmologists.

Results: As of May 2018, there are 2359 registered SPA patients. Among the total number of patients, 2096 patients had axial spondyloarthropathy (axSPA) (1249 ankylosing spondylitis, 100 non-radiographic axSPA), 179 psoriatic arthritis, 50 peripheral SPA and 51 enteropathic arthritis. Overall, 269 (11.4%) patients had experienced one or more episodes of uveitis. Median (Q1-Q3) uveitis beginning age was 36 (27-43) years. Duration between SpA symptom beginning age and first uveitis attack were 6.8 (2.6-12.8) years. Median (Q1-Q3) uveitis attacks number was 2 (1-4). Uveitis was usually unilateral (78.9%). 19/184 (10.3%) patients had permanent damage in the eye. Patients with permanent eye damage had more frequent uveitis attack (4 (2-10) vs 2 (1-3), $p=0.018$), and had tendency of bilateral uveitis attack (37.5% vs 16.6%, $p=0.082$). Demographic and clinical feature of patients were given in table 1. In multivariate analysis, only disease duration was related with uveitis OR 1.069 (1.05-1.09).

Conclusion: In our cohort, genetic background, radiographic severity, enthesitis, and particularly disease duration may be related with uveitis. Although uveitis is usually self-limited, however almost 10% of SpA patients may have permanent eye damage.

Table 1: Comparison of demographic, clinical and laboratory findings of patients with and without uveitis

	Uveitis (-) n=2359	Uveitis (+) n=269	p
Gender (Male/Female, %)	56.4/43.6	60.2/39.8	0,233*
Age	41 (34-49)	44 (37-52)	0,001*
Delay time of diagnosis	2 (0-6)	3 (1-8)	0,005*
Duration of illness	6 (3-11)	10 (6-16)	<0,001*
Arthritis n (%)	34 (64.2)	3 (100)	0,202**
Enthesitis n (%)	293 (25.1)	53 (42.1)	<0,001**
Dactylitis n (%)	88 (6.8)	11 (7.5)	0,743**
Psoriasis n (%)	361 (15.5)	12 (4.5)	<0,001**
HLA B27 (+)n (%)	688 (49.5)	117 (69.2)	<0,001**
Family history for SPA n (%)	635 (29.5)	102 (41.5)	<0,001**
Syndesmophitis n (%)	219 (24.7)	52 (43.0)	<0,001**
Bamboo spine n (%)	117 (12.1)	32 (23.7)	<0,001**
BASDAI	5.9 (4.2-7.1)	5.8 (4.0-7.0)	0,183*
BASFI	4.4 (2.4-6.1)	3.7 (1.9-5.2)	0,007*
Sedimentation (mm/h)	23 (11-40)	28 (11-48)	0,063*
CRP (mg/L)	12.1 (4.6-27.6)	13.5 (6.1-34)	0,042*

*Mann Whitney U, **Ki-Kare, data was given as median (Q1-Q3)

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Abstract Number: 1662

Interplay Among Inflammation, Adipokines and Endothelial Dysfunction in Patients with Psoriatic Arthritis. Relationship with Cardiovascular and Metabolic Comorbidities. Modulation By Apremilast

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: 1) To evaluate the association of inflammation, adipokines and endothelial dysfunction with the cardiovascular risk profile and the metabolic comorbidities associated with psoriatic arthritis (PsA). 2) To explore the effects of the inflammation on the glucose and lipid metabolism in the PsA context. 3) To analyze the effect of apremilast in the adipo/cytokine pattern, metabolic components and endothelial dysfunction in patients with PsA and metabolic syndrome (MetSyn).

Methods: Human study: 60 PsA patients and 30 age and gender-matched healthy donors (HD) were analyzed. An extensive clinical analysis was performed. Endothelial function was measured through post occlusive hyperemia using Laser-Doppler. Twelve PsA patients having metabolic syndrome were given apremilast 30 mg twice daily for 6 months. The levels of cytokines, endothelial dysfunction markers and adipokines were analyzed on serum and leukocytes by ELISA and RT-PCR, respectively. **Treatment of adipocytes with serum from PsA patients:** 3T3L1 adipocytes were treated with serum 10% of PsA patients and HD for 24h. The expression of genes and proteins involved in inflammation, lipid metabolism and insulin signalling was analysed.

Results: MetSyn, obesity and insulin resistance (IR) were increased in PsA. PsA patients had impaired endothelial function. Levels of cytokines, adipokines and endothelial function markers were altered in PsA serum and leukocytes. Increased levels of HOMA-IR correlated with DAS28, clinical and serological inflammatory markers, and diverse adipokines. In addition, PsA serum induced inflammation and modified lipid and glucose metabolism in adipocytes, suggesting a link between the degree of systemic inflammation and the development of IR in these patients. After 6 months of treatment, Apremilast reduced BMI, insulin resistance, inflammation, and levels of ApoB. Adipokines profile was reversed and levels of Apo A increased. Endothelial dysfunction was significantly restored shown by an increase of the peak flow and hyperaemia area and decreased adhesion molecules in serum.

Conclusion: 1) PsA is associated with an increase of inflammatory cytokines and adipokines, alongside with an endothelial dysfunction. These alterations are related to the disease activity and the presence of metabolic comorbidities such as insulin resistance or obesity, contributing to the burden of cardiovascular disease risk. 2) The inflammatory components are directly involved in the development of IR in PsA. 3) Apremilast might reduce IR, inflammation and endothelial dysfunction, parameters strongly involved in cardiovascular disease.

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Abstract Number: 1663

Correlation between Biologics and Bath Ankylosing Spondylitis Metrology Index within the First 12 Months of Treatment in Patients with Axial Spondyloarthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster – ARHP

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Several studies demonstrate efficacy of biologics on disease activity measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in patients with axial spondyloarthritis (AxSpA). The Bath Ankylosing Spondylitis Metrology Index (BASMI) is a measure of spinal and hip mobility using 5 domains. To our knowledge no studies have specifically looked at the impact of biologics on BASMI. The aim of our study was to assess if biologics appear to have an effect on BASMI.

Methods: We retrospectively collected the data from a cohort of patients with AxSpA reviewed within a designated clinic in the North West of England who were treated for at least 12 months with a biologic . BASMI scores were recorded at pre biologic, 3 month and 12 month follow up.

Results: Data from 68 patients were analysed (57 AS, 7 PsA, 4 enteropathic arthritis). 58 (85.3%) were male; median age was 52 years (IQR 43,61) Overall 63/68 patients (92.6%) were treated with TNF-inhibitors - including etanercept n=25 (originator or biosimilar), adalimumab n=31, golimumab n=5, infliximab n=2 , 5/68 patients (7.4%) were treated with secukinumab. Median BASMI at baseline was 4.55 (IQR 2.7,6.05). Improvements of BASMI scores were demonstrated with a reduction to a median BASMI of 3.6 (IQR 2,5) at 3 months and 3 (IQR 1.7, 5.2) at 12 months. Improvement appeared to be independent of age. There was no difference identified in improvement between TNF and IL-17 drugs.

Conclusion: Biologics drugs appeared to improve BASMI scores in our cohort through a 12 month period. Due to the small cohort we were unable to highlight any differences between patients treated with aTNF and IL-17 inhibitor medication. Multiple factors can be associated with BASMI changes including motivation, disease duration and progression, use or non use of NSAIDs, exercise behaviours, gender (women may be more flexible in the lumbar spine than men due to less radiographic changes in the hips, lumbar spine and sacroiliac joints (3 BASMI domains) but may have more progression in the neck and upper thoracic spine (2 BASMI domains). We know there is variance in exercise behaviours in that when some feel better they don't perceive the need to physiotherapy exercise so much and therefore don't, but may be more likely to participate in a more active lifestyle and others who are more motivated to do their exercise therapies. We also know that other factors such as anxiety and depression also have a bearing on exercise behaviours and are likely to be related to how they would rate on BASMI and Bath Ankylosing Spondylitis Functional Index (BASFI) scoring. Unfortunately some of the above aspects are difficult to measure but we are planning to further analyse our data inclusive of disease duration prior to commencement of biologics and correlation between BASDAI and BASMI and radiological progressions.

Disclosure: C. Longton, None; M. Massarotti, None; M. Bukhari, None.

Abstract Number: 1664

Fatigue Measurements in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Fatigue is one of the most frequent and disabling issues in systemic lupus erythematosus (SLE). It is, however, difficult to quantify. The Ad Hoc Committee on SLE Response Criteria for Fatigue in 2007 recommended use of the Krupp Fatigue Severity Scale (FSS). Since then, the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score has also been validated in SLE. We performed a review of instruments used to measure fatigue in adult SLE patients from 2007 onward.

Methods: We used Medline and EMBase from 2008 to Oct. 2017 search terms to identify clinical trials and observational studies in adult SLE, where fatigue was an outcome. All English and French studies were reviewed to determine the fatigue measures used, and study results.

Results: 22 studies met our inclusion criteria. Eight fatigue scales were used. The most frequently used instruments were the Visual Analogue Scale (VAS) for fatigue (used in 32%), the FSS (32%) and the FACIT-Fatigue scale (14%). The FSS was used in the majority of clinical trials (5 of 12; 42%) with the remaining evenly divided between the two other scales. The VAS was used by the majority of observational studies (5 of 10; 50%), followed by the FSS (2 of 10; 20%). Fourteen of the 22 studies demonstrated a difference in fatigue levels in terms of statistical and clinically meaningfulness. Of the 8 studies which did not, 3 used the FFS, 3 used the VAS and 2 used other scales (MFI and BFI). All 3 studies using FACIT detected clinically and statistically significant differences.

Conclusion: The VAS, FSS and FACIT Fatigue scale were the most frequently used instruments to measure fatigue in adult SLE studies from 2008-2017. Several studies detected clinical important changes in fatigue with these instruments. If

fatigue is considered a core data element of observational studies in SLE, this review may help inform choice of instruments.

Table 1: Fatigue scales used in studies of adults with systemic lupus (SLE)

Measure	Description	Psychometrically Validated in SLE(38)	Minimal Clinically Important Difference (MCID) in SLE (39)
Visual Analogue Scale (VAS) (40)	Single 100mm line to measure fatigue	No*	Δ 10%
Krupp Fatigue Severity Scale (FSS) (33)	9-item questionnaire on impact of fatigue on specific types of functioning	Yes	Δ 9.7%
Functional Assessment of Chronic Illness Therapy (FACIT)- Fatigue Scale (5)	13-item questionnaire on aspects of physical and mental fatigue and its impact on daily living over the past 7 days.	Yes	Δ 11.5%
Multidimensional Assessment of Fatigue (MAF) (33)	16 item scale that measures fatigue over the past week according to four dimensions: severity, distress, timing and its impact on daily living.	No	Δ 11.5%
Multidimensional Fatigue Inventory (MFI) (41)	20-item self-reported instrument that covers general, physical and mental fatigue as well as reduced motivation and activity.	No	Δ 14.3%
Fatigue Assessment Scale (FAS) (42)	Self-administered 10 item fatigue measure	No	N/A**
Brief Fatigue Index/Inventory (BFI) (43)	Multidimensional self-assessment tool which assesses severity of pain and fatigue in patients with chronic conditions	Yes	N/A**
Vanderbilt Fatigue Severity VFS) (4)	Consists of a fatigue subscale originally developed in Rheumatoid arthritis patients	No	N/A**

* Validated in other populations, including chronic fatigue syndrome, and stroke.

** N/A= not available

Table 2: Summary of Clinical Trials with Fatigue as an Outcome in SLE

Authors	Data collection/ publication	Scale	Intervention	N	Findings	Country
Greco et al.(15)	2004-2006	FSS	Acupuncture versus minimal needling	24	No difference detected	USA
Strand et al. (9)	2007-2010	FACIT	Belimumab or placebo	1684	Clinically significant improvement *	Multicenter
Hartkamp et al. (14)	Published 2009	MFI	Dehydroepiandrosterone versus placebo	60	No difference detected	Netherlands
Uppal et al. (8)	Published 2009	VAS	Standard therapy +/- infliximab	27	No difference detected	Kuwait
Lai et al. (12)	2009-2011	FAS	Placebo versus escalating doses of N-acetylcysteine	36	Statistically significant improvement	USA
Merrill et al. (7)	Published 2010	VAS	Abatacept versus placebo	175	Clinically significant improvement *	Multicenter
Petri et al. (10)	2010-2012	FACIT	Blisibimod or placebo	547	Clinically significant improvement *	USA & Brazil
Davies et al. (18)	Published 2012	FSS	Low glycemic index (GI) diet and low-calorie (LC) diet versus placebo	23	Clinically significant improvement with GI diet*, but only statistically significant improvement with LC diet (did not meet MCID)	UK
Avaux et al. (17)	2012-2013	FSS	Exercise versus controls	45	Clinically significant improvement *	Belgium
Merrill et al. (11)	2011-2014	BFI	Tabalumab vs. placebo	1124	No difference detected	Multicenter
Bogdanovic et al. (16)	Published 2015	FSS	Aerobic and isotonic exercise	60	Clinically significant improvement *	Serbia
Arriens et al. (13)	Published 2015	FSS	Fish oil versus placebo	50	No difference	USA

* Met minimal clinically important difference (MCID)

Table 3: Summary of Observational Studies Reporting Fatigue as an Outcome in SLE

Authors	Data collection/ publication	Scale	Predictor (independent) variable	N	Results	Country
Petri et al. (26)	2003-2004	FSS	Depression	160	Clinically significant association *	USA
Ruiz-Irastorza et al. (20)	2008	VAS	Vitamin D levels	80	No difference detected	Spain
Fischin et al. (28)	2009	VFS	Pain, coping and catastrophizing	447	Statistically significant association (MCID not available)	Germany
Fragoso et al. (24)	2009-2010	VAS	Vitamin D levels	142	No difference detected	Brazil
Kasitanon et al. (25)	2009-2011	FACIT	Sleep disturbances	56	Clinically significant association *	Thailand
Stockton et al. (23)	Published 2012	FSS	Vitamin D levels	45	No difference detected	Australia
Waldheim et al. (27)	Published 2013	MAF	Pain severity	175	Statistically significant association (MCID not available)	Sweden
Salman-Monte et al. (21)	2012-2014	VAS	Vitamin D deficiency & insufficiency	102	Clinically significant association* between increased fatigue & low vitamin D	Spain
Parodis et al. (19)	2011-2015	VAS	Belimumab	58	Clinically significant improvement*	Sweden & France
Abaza et al. (22)	Published 2016	VAS	Vitamin D levels	90	Clinically significant association* between increased fatigue & low vitamin D	Egypt

* Met minimal clinically important difference (MCID)

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Abstract Number: 1665

Longitudinal Stratification of Gene Expression Reveals Three SLE Groups of Disease Activity Progression

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The highly heterogeneous clinical presentation of lupus is characterized by the unpredictable appearance of flares of disease activity and important organ damage. Attempts to stratify lupus patients have been limited to clinical information, leading to unsuccessful clinical trials and controversial research results. Our aim was to develop and validate a robust method to stratify patients with lupus according to longitudinal disease activity and whole-genome gene expression data in order to establish subgroups of patients who share disease progression mechanisms.

Methods: We applied a clustering-based approach to stratify SLE patients based on the correlation between disease activity scores and longitudinal gene expression information. Clustering robustness was evaluated by bootstrapping and the clusters were characterized in terms of clinical and functional features.

Results: Using two independent sets of patients, one pediatric and another adult, our results show a clear partition into three different disease clusters not influenced by treatment, race or other source of bias. Two of the clusters differentiate into a neutrophil correlated disease group and a lymphocyte correlated disease group, while the third that correlated to a lesser extent with neutrophils, was functionally more heterogeneous. The neutrophil-driven clusters were associated with increased development towards proliferative nephritis.

Conclusion: We found three subgroups of patients that show different mechanisms of disease progression and are clinically differentiated. Our results have important implications for treatment options, the design of clinical trials, the etiology of the disease, and the prediction of severe glomerulonephritis.

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Abstract Number: 1666

The Use of Patient-Reported Outcome Measures to Assess Clinical Features of Fibromyalgia in SLE

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Patient-reported outcome measures (PROs) in SLE can capture patient specific information and the patient perspective, but clinical use can be challenging due to confounding conditions like fibromyalgia (FM). We employed three PROs to evaluate clinical features and patient assessment of disease activity in SLE patients with and without FM.

Methods: This was across sectional study of SLE patients (ACR 1997 or SLICC 2012 criteria) in a university lupus clinic from January to May 2018. All patients completed these PROs: Systemic Lupus Activity Questionnaire (SLAQ), Patient Health Questionnaire-9 (PHQ9), and 2011 ACR FM criteria. Active SLE was defined as SLEDAI ≥ 6 , clinical SLEDAI ≥ 4 , or active lupus nephritis. We identified 4 groups based on SLE activity and FM criteria: active SLE without FM, active SLE with FM, inactive SLE with FM, and inactive SLE without FM. Clinical variables assessed included self-reported lupus symptoms, flare, disease activity level, hospital/ER admission, medication adherence, SLEDAI, and PGA. Relationships between variables in different groups were analyzed by Fisher's exact test and ANOVA. A step-wise linear regression analysis analyzed predictors of treatment for FM.

Results: 212 patients completed PROs (92% female, mean age 45 years). In our cohort, 31% had active SLE without FM, 13% active SLE with FM, 8% inactive SLE with FM, and 48% inactive SLE without FM. Regardless of SLE disease activity, patients with FM (21% of respondents), reported more muscle weakness, muscle pain, fatigue, sicca, oral/nasal ulcers, dyspnea, chest pain, forgetfulness, headache, numbness, abdominal pain, cognitive dysfunction and waking unrefreshed. There was no difference in reported ER/hospitalization rates (24%) or self-reported medication compliance (86.4%) between the 4 groups in the preceding 3 months. Active and inactive SLE patients with FM self-reported higher disease activity, rates of lupus flare, and had higher SLAQ scores, compared to inactive or active SLE without FM. FM symptoms were addressed (education or intervention) at 38% of visits. In regression models, FM counseling increased with increasing PHQ9 score (OR: 1.21; 95% CI: 1.11, 1.33) and for patients who self-reported a lupus flare (OR: 3.05; 95% CI: 1.16, 8.03). In contrast, FM counseling decreased with increasing PGA score (OR: 0.17; 95% CI: 0.07, 0.44). Without FM, there was moderate correlation between patient and physician disease activity measures in active SLE, but there was discordance between patient and physician assessments as measured by the SLEDAI, PGA, SLAQ and patient reported lupus activity in SLE patients with FM.

Conclusion: FM is common in SLE patients and is associated with a unique set of self-reported symptoms. FM in SLE results in discordance between patient reported lupus activity and physician assessment as patients with FM report higher levels of disease activity.

Table 1

	No Fibromyalgia		Fibromyalgia		p-value*
	Inactive SLE n=102 Mean (SD)	Active SLE n=65 Mean (SD)	Inactive SLE n=17 Mean (SD)	Active SLE n=28 Mean (SD)	
Full SLEDAI	1.6 (1.6)	8.4 (4.0)	1.1 (1.4)	6.8 (3.3)	<0.0001†‡ #
Patient Disease Activity (0-10)	3.0 (2.5)	4.3 (2.8)	6.2 (2.1)	6.9 (2.2)	<0.0001† #
SLAQ	8.6 (5.5)	11.0 (6.5)	17.3 (5.1)	19.4 (7.0)	<0.0001† #
Physician Global Assessment (0-3)	0.2 (0.3)	0.8 (0.6)	0.3 (0.5)	1.0 (0.5)	<0.0001†‡
PHQ9 Depression Score	4.5 (4.4)	5.6 (5.0)	10.6 (4.6)	11.6 (4.7)	<0.0001† #
Patient-reported flare (any severity)	35 (38.9%)	39 (63.9%)	13 (81.3%)	26 (100%)	<0.0001†‡ #
Muscle Weakness	26 (26.0%)	19 (30.2%)	10 (58.8%)	20 (71.4%)	<0.0001† #
Muscle Pain	37 (37.0%)	23 (36.5%)	14 (82.4%)	22 (78.6%)	<0.0001† #
Fatigue	42 (41.6%)	40 (64.5%)	15 (88.2%)	25 (89.3%)	<0.0001† #
Dry Eyes	25 (24.8%)	10 (16.1%)	11 (64.7%)	12 (42.9%)	0.0003† #
Oral/Nasal Ulcers	8 (8.0%)	5 (8.1%)	5 (29.4%)	6 (21.4%)	0.02† #
Dyspnea	10 (9.9%)	7 (11.1%)	4 (23.5%)	12 (42.9%)	0.0005† #
Forgetfulness	24 (24.0%)	15 (24.2%)	8 (47.1%)	14 (50.0%)	0.02† #
Headaches	12 (12.0%)	7 (11.1%)	6 (35.3%)	16 (57.1%)	<0.0001† #
Numbness	8 (8.0%)	5 (8.1%)	8 (47.1%)	11 (39.3%)	<0.0001† #
Abdominal Pain	9 (9.0%)	9 (14.3%)	4 (23.5%)	12 (42.9%)	0.0005† #
Symptom Severity (from ACR Fibromyalgia Criteria)					
Fatigue	47 (46.1%)	36 (55.4%)	15 (88.2%)	28 (100%)	<0.0001† #
Cognitive Function	20 (19.6%)	14 (21.5%)	10 (58.8%)	11 (39.3%)	0.003† #
Waking Unrefreshed	44 (43.1%)	34 (52.3%)	16 (94.1%)	27 (96.4%)	<0.0001†, #

*across all 4 groups; †p<0.05 excluding inactive SLE without FM; ‡p<0.05 inactive SLE with FM vs. active SLE with FM; # p<0.05 Active SLE without FM vs. Inactive and active SLE with FM

Disclosure: J. Rogers, AstraZeneca, 5; A. M. Eudy, None; L. Criscione-Schreiber, GlaxoSmithKline, 2; D. Pisetsky, None; K. Sun, None; J. Doss, None; M. E. B. Clowse, AstraZeneca, 5.

Abstract Number: 1667

Confirmatory Factor Analysis of the Patient-Reported Perceived Deficits Questionnaire in Systemic Lupus Erythematosus: Cautions for Use of Subscales

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Approximately 38% of adults living with Systemic Lupus Erythematosus (SLE) experience cognitive impairment (CI) that can detrimentally affect employment, disease self-management, and quality of life. Identifying those with SLE related CI is critical, but is difficult to do in busy and resource-limited clinics. The patient-reported 20-item Perceived Deficits Questionnaire (PDQ-20), used to screen for SLE related CI, could be less time and cost-burdensome than other objective instruments. However, there is a dearth of published measurement property evidence for using the PDQ-20 with SLE patients. In adults with Multiple Sclerosis the PDQ-20 is purported to have four factors (subscales): attention/concentration, retrospective memory, prospective memory, and planning/organization. This structure has not been examined in adults with SLE. The purpose of this study is to examine the factor structure and the internal consistency of the PDQ-20 in an SLE cohort.

Methods: Consecutive SLE patients aged 18-65 years were recruited from a single rheumatology center between July 2016 and March 2018. Patients completed the PDQ-20. Analyses included socio-demographic descriptive analyses and confirmatory factor analyses (CFA) of the purported PDQ-20 four-factor structure. Sample size calculations indicated that a cohort of $n=177$ was sufficient to perform the CFA (power=0.99). Analysis was completed on returned baseline PDQ-20 data using SAS[®] software.

Results: Patient demographics are presented in Table 1. There was no missing PDQ-20 data. CFA model fitting was adequate (standardized root mean square residual=0.05; root mean square error of approximation=0.10; Bentler comparative fit index=0.90). All factor loadings were statistically significant (factor loading range 0.55-0.88; all t -value >9.82). All factors highly correlated with each other (correlation range: 0.87-0.97; all $p<0.01$). Lagrange Multiplier (LM) tests indicated that multiple alternate item-factor pathways could improve the four-factor model (ten largest significant LM statistics range from 7.92-20.78; new possible pathways for 7 items to other factors). Item 19 (forget to take medication) had low reliability to its purported factor (prospective memory; $R^2=0.30$). The internal consistency (Cronbach's alpha) for the four factors ranged from 0.82 to 0.91.

Conclusion: The CFA analyses indicate that while the fit of the four-factor model for the PDQ fits, the model could be improved. Particularly concerning is the different factor-pathways for seven items, the current low item-factor reliability for item 19, and the increased correlations between factors. In adult SLE patients, researchers and clinicians should be cautious in interpreting PDQ-20 results using the current four factors (subscales). Further validity analyses, including exploratory factor analyses, are needed.

Table 1 Socio-demographic information of recruited patients ($n=208$) who returned and did not return PDQ-20

	PDQ-20 returned ($n=177$)	PDQ-20 not returned ($n=31$)
Sex (% female)	89.8%	83.9%
Age at study visit (mean \pm SD years)	42.75 \pm 12.12	41.97 \pm 12.75
Age at SLE diagnosis (mean \pm SD years)	28.16 \pm 10.48	28.57 \pm 10.19
Highest education level obtained at study visit (% of sample*)	High-school or less 25.1% College/University 74.9%	High-school or less 16.1% College/University 83.9%

Table . (Cont'd)

	PDQ-20 returned (n=177)	PDQ-20 not returned (n=31)
Employment status at study visit (% of sample#)	Employed 51.7% Retired 2.9% Homemaker 6.9% Student 5.2% Disability/sick leave 27.6% Looking for work 4.0% Other 1.7%	Employed 73.3% Retired 0.0% Homemaker 3.3% Student 6.7% Disability/sick leave 16.7% Looking for work 0.0% Other 0.0%

Note: All demographic variables not statistically significantly different between groups ($p > 0.05$); all data from baseline visits of longitudinal study.

* n=170 (7 patients missing data) for returned group; n=31 for not returned

n=174 (3 patient missing data) for returned; n=30 (1 missing) for not returned

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Abstract Number: 1668

Construction and Validation of a Frailty Index As a Novel Health Measure in Systemic Lupus Erythematosus

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SESSION INFORMATION

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Background/Purpose: Clinical outcomes in SLE are challenging to predict. In non-SLE populations, susceptibility to adverse outcomes has been measured using a frailty index (FI), which quantifies vulnerability via the accumulation of health deficits. Using data from the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort, we constructed and validated a frailty index for patients with SLE.

Methods: Patients fulfilling ≥ 4 ACR classification criteria for SLE were recruited within 15 months of diagnosis and were assessed annually for medication use, comorbidities, disease activity (SLEDAI-2K), organ damage [SLICC/ACR Damage Index (SDI)], health-related quality of life [Short-Form 36 (SF-36)] and other measures.

For our analysis, the baseline visit was defined as the first at which both SDI and SF-36 data were available. From this baseline dataset, health deficits were identified for inclusion in the SLICC frailty index (SLICC-FI). Using standard criteria, a health deficit was defined as any symptom, disease process, functional impairment, or laboratory abnormality that is: (i) acquired, (ii) associated with increasing age, (iii) associated with adverse outcomes, (iv) present in $\geq 1\%$ and $\leq 80\%$ of patients, and (v) missing values for $< 5\%$ of patients. Once selected, the health deficits were used to calculate a baseline SLICC-FI score for each patient.

To assess validity, we estimated correlations of the SLICC-FI with existing SLE instruments, including the SDI and the SLEDAI-2K. Multivariable Cox regression was used to estimate associations between baseline SLICC-FI values and mortality risk, adjusting for relevant demographic and clinical variables.

Results: 1682 SLE patients (92.1% of the cohort) were eligible for inclusion and were predominantly female (89%) with mean (SD) age 35.7 (13.4) years and mean (SD) disease duration 18.8 (15.7) months at baseline. Of 222 candidate variables, 48 met the required criteria for inclusion as health deficits in the SLICC-FI. These included items related to organ damage, disease activity, comorbidities, and functional status. The mean (SD) baseline SLICC-FI score was 0.17 (0.08) with a range from 0 to 0.51. At baseline, SLICC-FI values were weakly correlated with both SDI ($r=0.262$; $p<0.0001$) and SLEDAI-2K ($r=0.227$; $p<0.0001$) scores. These correlations persisted after removing overlapping SDI and SLEDAI-2K items from the SLICC-FI.

Sixty-six deaths occurred during a mean (SD) follow-up of 6.7 (4.0) years. Higher baseline SLICC-FI values (per 0.05 increase) were associated with increased mortality risk (Hazard Ratio [HR] 1.59; 95% CI 1.35-1.87), after adjusting for age, sex, baseline steroid use, race/ethnicity, geographic region, and baseline SDI scores. The association between baseline SLICC-FI scores and mortality risk persisted when damage items were omitted from the SLICC-FI (HR 1.37; 95% CI 1.22-1.53) and when a subgroup of patients without baseline organ damage (SDI=0) was analyzed (HR 1.47; 95% CI 1.18-1.83).

Conclusion: The SLICC-FI is a relevant health measure in SLE. It predicts future mortality risk independent of the SDI and is a potentially valuable tool for identifying SLE patients who are most vulnerable to adverse outcomes.

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iC3b/C3 Ratios More Strongly Correlate with SLE Disease Activity in African-Americans Compared to Whites

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM iC3b/C3 Ratios More Strongly Correlate with SLE Disease Activity in African-Americans Compared with Whites

Background/Purpose: Complement activation is a hallmark of systemic lupus erythematosus (SLE) pathophysiology. iC3b is a complement split product of C3b formed during complement activation. We have previously found that iC3b/C3 ratios associated with both active disease and clinically meaningful changes in SLE disease activity. Since SLE is more severe in nonwhite populations, we hypothesized that iC3b/C3 ratios would be a more sensitive marker of disease activity and examined this relationship in African-American (AA) and white subjects with SLE.

Methods: 159 adult SLE (92 AA and 67 white) patients were enrolled. C3 and C4 were measured by nephelometry; iC3b by a lateral flow assay. SLE disease activity was measured using the SLEDAI 2K Responder Index-50 (S2K RI-50). Statistical analyses were performed using SAS v9.4. Multilevel regression models examined associations with SLE disease activity. Ordinal logistic regression models with generalized estimating equation (GEE) modeling examined associations with clinically meaningful changes since the outcome variable is ordinal. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using Proc GLIMMIX and Proc GENMOD.

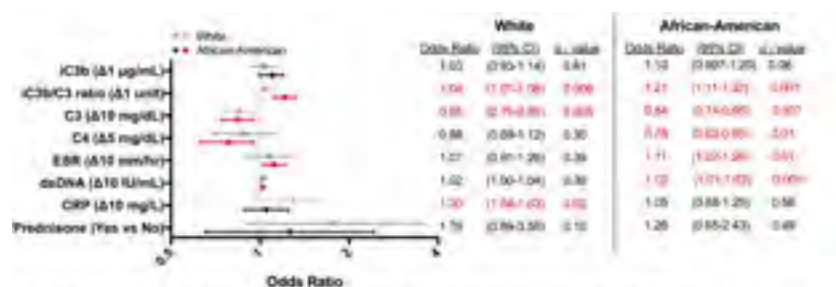


Figure 1. Univariate regression analysis of the association of biochemical variables with active SLE. Red (AA) and pink (whites) whiskers represent statistically significant variables, while grey (white) and black (AA) represent non-significant variables.

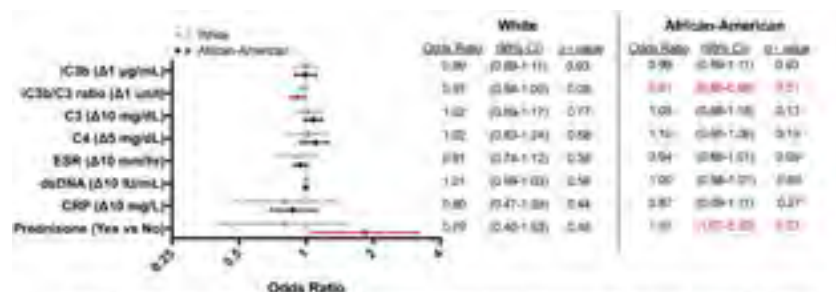


Figure 2. Univariate regression analysis of the association of biochemical variables with clinically meaningful changes in disease activity. Red (AA) and pink (whites) whiskers represent statistically significant variables, while grey (white) and black (AA) represent non-significant variables.

Results: Both iC3b/C3 ratios and C3 associated with active disease in AA and whites in univariate regression analysis, although association of the iC3b/C3 ratio was stronger in AA (Figure 1). In AA, active disease also associated with C4, ESR, and dsDNA levels, whereas it was CRP in whites. Association of iC3b/C3 ratios was independent of other variables in multiple regression analysis (AA: OR=1.48, 95% CI=1.21-1.82; whites: OR=1.17, 95% CI=1.02-1.34).

We next examined whether there were differences in clinical meaningful changes in disease activity and iC3b/C3 ratios with race. In univariate regression analysis, iC3b/C3 ratios were associated with clinically meaningful changes in disease activity in AAs; less so in whites. (Figure 2). In multiple regression analysis, an association was demonstrated in both races; stronger in AA (AA: OR=0.89, 95% CI=0.83-0.96; whites: OR=0.92, 95% CI=0.88-0.97).

Conclusion: iC3b/C3 ratios were more strongly associated with active SLE and clinically meaningful changes in disease activity in AA compared with whites. This likely reflects either racial differences in complement activation or disease phenotypes. Our data suggest that the iC3b/C3 ratio is a valuable biomarker in AA SLE patients.

Disclosure: D. Sen, None; V. Strand, None; N. Mathis, Kypha, Inc., 5; Q. Fu, Kypha, Inc., 5; A. Kim, Kypha, Inc., 2, Exagen Diagnostics, Inc., 5, 8.

Disease Course Patterns in Systemic Lupus Erythematosus: Impact on Long-Term Outcomes

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Background/Purpose: Previous studies have described three patterns of disease activity over time in systemic lupus erythematosus (SLE), namely long quiescence, relapsing remitting, and persistently active. However, they all enrolled prevalent patients, many of whom in the late stages of the disease. As such, the patterns of disease course since diagnosis are not known. The aim of the present study was to assess the impact of these patterns on damage accrual, flare and mortality in an inception cohort.

Methods: Inception patients of our long-term longitudinal cohort (enrolled within 18 months of diagnosis), with at least 10 years of follow-up and no time interval >18 months between consecutive visits, were investigated. Prolonged remission (PR) was defined as a clinical SLEDAI-2K=0 [serology (anti-dsDNA antibodies and C3/C4 levels) excluded], achieved within five years since enrolment and maintained for ≥10 years after that. Relapsing-remitting (RR) pattern was defined based on ≥2 remission periods (one remission period equals two consecutive visits with a clinical SLEDAI-2K=0), while patients with no remission were categorized as persistently active (PA). Patients with only one remission period (“hybrids”) were re-allocated to the RR and PA groups according to the lower quartile of the time spent in remission for the RR patients (3.5 years). Multivariable analysis was performed using baseline demographic, clinical, immunological and therapeutic variables as well as disease-related variables at two years to identify predictors for disease course. Descriptive and regression analyses were used to compare groups regarding cumulative damage at 10 years, mortality and flare rate beyond 10 years (median follow-up 17.5 years).

Results: Of 267 patients who fulfilled the inclusion criteria, 27 (10.1%) achieved prolonged remission, 180 (67.4%) RR and 25 (9.4%) PA disease. Thirty-five patients (13.1%) had only one remission period (“hybrids”). At enrollment, there were no significant differences in demographic, clinical, immunological and therapeutic characteristics among the PR, RR and PA groups. Multinomial regression analysis for the identification of predictors for group membership showed Black race [OR=2.78, 95%CI=1.05-7.31, $p=0.039$] and higher adjusted mean SLEDAI-2K over the first two years [OR=1.21, 95%CI=1.11-1.32, $p<0.0001$] to be associated with a more severe disease course. Outcomes at 10 years and beyond are given in Table 1.

Table 1 Outcomes at 10 years after enrolment and beyond for all groups

	PR (n=27)	RR (n=180)	PA (n=25)	<i>p</i>
Outcomes at 10 years				
SLICC/Damage Index (mean±SD)	0.93±1.07	1.22±1.33	2.36±1.60	<0.001
Outcomes at the last visit				
Flare incidence (/100 patient-years)	1.0±1.8	4.9±7.0	5.0±4.0	<0.001
All-cause mortality (%; n)	11.1% (3)	13.3% (24)	24.0% (6)	0.22
Time to death (since diagnosis, years±SD)	24.0±4.1	20.1±7.2	18.4±4.4	0.11

P value from Cochran-Armitage trend test for all groups

Re-allocation of the hybrids into the RR and PA groups (17 and 18 patients respectively) provided similar results.

Conclusion: Black race and more severe disease over the first two years were associated with a worse disease course over time. Disease course was, in turn, associated with a gradual increase in damage accrual (from PR to RR to PA) as well as flare rate. Differences in mortality did not reach statistical significance.

Disclosure: K. Tselios, None; D. D. Gladman, None; Z. Touma, None; J. Su, None; N. Anderson, None; M. Urowitz, None.

Laboratory Investigation Results Influence Physician's Global Assessment of Disease Activity in Systemic Lupus Erythematosus

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Background/Purpose: The Physician Global Assessment (PGA) is a frequently-used outcome measure in Systemic Lupus Erythematosus (SLE). The PGA is intended to encapsulate the physician's judgement of overall disease *activity*. Consensus on whether the PGA should be performed prior to, or after the receipt of laboratory values is lacking. A single-clinician pilot study in a US-outpatient clinic suggested that there are significant differences between the PGA score determined pre and post knowledge of labs¹. The primary objective of the current study was to determine, in a diverse international group of lupus experts, whether there is a difference in PGA scores with and without awareness of laboratory test results.

Methods: Fifty clinical vignettes based on real-life cases, spanning the spectrum of SLE manifestations and severity (SLEDAI-2K ranging from 0 to 28), were presented via an online survey to 194 international SLE experts. Respondents were asked to rate the PGA pre and post inclusion of laboratory test results for each case, with only forward progression through the survey allowed. Scoring of the PGA was done on an anchored scale of 0-3 with 0=none, 1=mild, 2=moderate and 3=the most active disease imaginable. Measures of central tendency and spread were used to describe responses, and Pearson's correlation coefficient (CC) was used to evaluate the relationship between pre- and post-lab PGA for each case. Inter-rater reliability of PGA responses was assessed using the Intraclass Correlation Coefficient (ICC), and the correlation between PGA and SLEDAI-2K was also determined.

Results: There were 60 complete surveys (North America n=24, South America n=5, Europe n=15, Asia n=10, Australia n=6), comprising a data set of 3000 unique paired responses. The inter-rater reliability for PGAs was excellent (pre-lab ICC 0.98; post-lab ICC 0.99). Post-lab PGA were higher than pre-lab PGA: median (IQR) pre-lab PGA 0.5(1.05), post-lab PGA 1(1.3) ($p<0.001$), and the median (IQR) difference in post- and pre-lab PGA (delta-PGA) for all case pairs was 0.2(0.45). The correlation between pre and post-lab PGA was moderately strong (Pearson CC 0.79, 95% CI: 0.67-0.88, $p<0.001$). In 20 cases the CC was ≥ 0.8 and in 14 cases the CC was 0.6-0.79. In the 16 cases where the CC was ≤ 0.59 , delta-PGA was median (IQR) 0.58 (0.68); these were mostly cases where lab data revealed lupus nephritis and/or hematologic manifestations. In general, all abnormal labs, including elevated anti-dsDNA and low complement level, impacted the PGA assessments. The correlation between SLEDAI-2K and PGA was higher for post-lab than pre-lab PGA (CC 0.79 and 0.67, respectively).

Conclusion: Although the PGA is known to be a subjective measure, we found excellent inter-rater reliability in a group of international lupus experts from six continents. Post-lab PGA scores had stronger correlation with SLEDAI-2K, and were generally higher than pre-lab PGA scores, with abnormalities on urinalysis and cytopenias having the greatest impact. Overall, our findings indicate that the PGA should be performed with knowledge of the pertinent laboratory values.

1. Aranow C. *Immunol Res.* 2015; 63(1-3):167-9.

Disclosure: C. Aranow, None; A. Askanase, None; M. Huq, None; S. Oon, None; A. Calderone, None; E. Morand, AstraZeneca, 2, AstraZeneca, 5, Bristol-Myers Squibb, 2, Janssen, 2, Janssen, 5, Eli Lilly and Co., 5, Merck Serono, 5, UCB, Inc., 2, GlaxoSmithKline, 5; M. Nikpour, Actelion, GSK, Pfizer, BMS, Eli Lilly, UCB, Astra Zeneca, Janssen, 2, 5.

Poor Sleep Quality Predicts Worsening SLE Disease Activity

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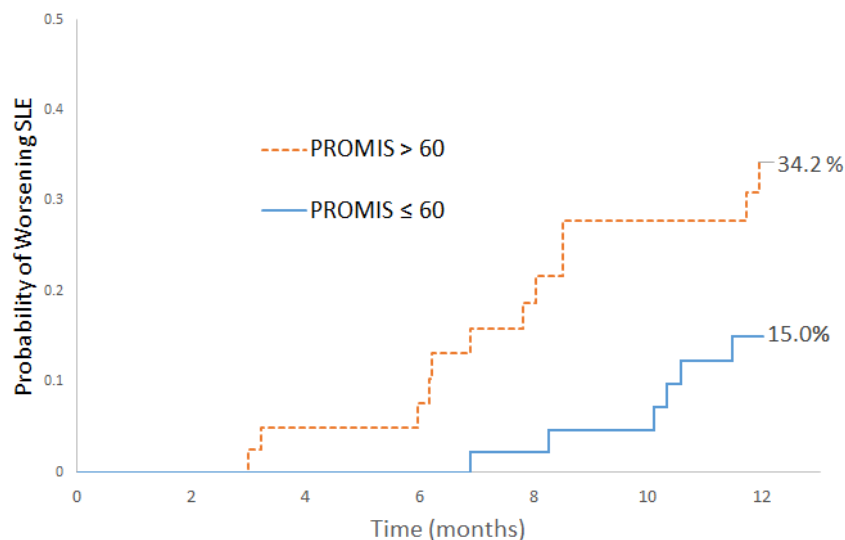
Background/Purpose: Poor sleep quality is commonly observed in patients with SLE. We hypothesize that poor sleep contributes to worsening SLE. The aims of this study are to evaluate the relationship between subjective sleep measures and SLE activity over time.

Methods: A prospective, longitudinal, observational study evaluated the relationship between sleep and SLE disease activity. 151 patients were enrolled. Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Patient Reported Outcomes Measurement Instrument System (PROMIS)-Sleep Related Impairment (SRI), and PROMIS-Sleep Disturbance (SD) survey instruments measured patient reported sleep quality. The population mean for the PROMIS instruments is 50. The SLEDAI-2000 Responder Index-50 (S2KRI-50) was used to define active SLE as S2KRI-50 >4 and worsening SLE at subsequent visits as an increase in S2KRI-50 ≥ 4 . Baseline comparisons were calculated using non-parametric tests. Kaplan-Meier and Cox proportional hazards methods examined the relationship between poor sleep and worsening SLE activity over time.

Results: At baseline, the median age was 42, 90.7% were female, 54.3% were African American, 24.5% were on prednisone doses >7.5mg/day, and 36.4% had active SLE. Patients with active SLE had significantly higher SRI scores (median 64.3) vs inactive SLE (median 56.6) as well as significantly higher SD scores (median 58.3 vs 52.2), whereas PSQI and ESS were not significantly different.

Data from 109 patients with ≥ 2 visits were used for longitudinal studies. Kaplan-Meier analysis, stratified by SRI T-score of >60 vs ≤ 60 demonstrated that worse sleep (SRI >60) at the previous visit predicted worsening SLE activity at the next visit (Figure 1). Over a 12 month period, the probability of SLE activity worsening was 21.4% overall, 34.2% for SRI >60, and 15.0% for SRI ≤ 60 ($p=0.024$). Cox proportional hazards regression analysis showed that SRI >60 (hazard ratio (HR) 3.06), male sex (HR 4.66), and prednisone use (>7.5mg/day) (HR 3.59), but not age (HR 0.97), were significantly associated with worsening SLE.

Figure 1. Poor sleep at prior visit predicts worsening SLE



Conclusion: Our study reinforces that patients with SLE report worse subjective sleep compared to the general population, and patients with active SLE have worse sleep than patients with inactive SLE. Our longitudinal data demonstrate that poor sleep predicts worsening SLE disease activity. Thus, variation in subjective sleep may have an important role in SLE flares.

Disclosure: P. Chu, None; A. M. Hinze, None; N. Al-Hammadi, None; L. Feigl, None; N. Mathis, Kypha, Inc., 5; D. Sen, None; S. Eisen, None; Y. E. Ju, Philips-Respironics, 2; A. Kim, Kypha, Inc., 2, Exagen Diagnostics, Inc., 5, 8.

Validation and Evaluation of the Spanish Version of the Systemic LUPUS Activity Questionnaire in an Argentine Population

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Background/Purpose: Disease activity in Systemic Lupus Erythematosus (SLE) leads to damage, comorbidities and increased overall mortality. Frequent assessment is needed to adapt patients' management. The Systemic Lupus Activity Questionnaire (SLAQ) is a patient self-reported instrument to screen for disease activity outside the clinical setting. Our aim was to validate the SLAQ in Spanish and evaluate its association with other validated disease activity scores.

Methods: The SLAQ questionnaire was translated and adapted in Spanish. For its validation, we included consecutive SLE patients (fulfilling the 1997 ACR classification criteria) from 3 Rheumatology centers in Argentina who responded the questionnaire. A rheumatologist blinded to S-SLAQ results examined each patient and completed a SLEDAI and Physician's Global Assessment (PGA). Internal consistency (Cronbach's alpha), test-retest reliability (intraclass correlation coefficient), and construct validity (Spearman's correlation coefficient) were examined. We further evaluated the questionnaire in a larger cohort of consecutive patients from 8 Rheumatology centers. Correlations with SLAM, SLAM-no lab, SLEDAI and Patient's Global Assessment (PGA2) were assessed (Pearson's correlation coefficient). Sensitivity, specificity, and positive and negative predictive values for clinically significant disease activity (SLEDAI ≥ 6) of different S-SLAQ cut-off points (ranging 0-35) were evaluated.

Results: In the first part of the validation, we included 40 patients [97% female, mean age 40 SD13], with a median disease duration of 116 months (IQR 49-112). The median time of answering was 2.65 minutes (IQR 1.46-4.83). The internal consistency was good to excellent (Cronbach's alpha=0.84, $p<0.001$) and the intraclass correlation coefficient was 0.95 ($p<0.001$). Correlation with other scores was weak (SLEDAI $r=0.1$, PGA $r=0.2$). In the larger cohort where we continued to evaluate construct validity, we included 97 consecutive patients ([93% female, mean age: 40 years (SD14.7)]. 42% were “Mestizos”, 33% Amerindians and 25% Caucasians. Mean score of S-SLAQ was 8.24 (SD 7.31); mean SLAM-no lab was 2.06 (SD 2.38); mean SLAM was 3.68 (SD 3.17), mean SLEDAI-2K was 2.75 (SD 3.96) and mean PGA2 was 0.52 (SD 0.79). No differences in SLAQ score were detected when comparing different gender, ethnic, educational and socioeconomic groups. Correlation of S-SLAQ with PGA2 was moderate ($r=0.63$ $p<0.001$); and weak with SLAM-no lab ($r=0.42$, $p<0.001$) and SLAM-R ($r=0.38$, $p<0.0001$). It was very weak with SLEDAI-2K ($r=0.15$, $p=0.1394$). Using the S-SLAQ cut-off of five points the sensitivity was 72.2 % and specificity 37.9 %, for clinically significant disease activity (SLEDAI 2K ≥ 6).

Conclusion: The S-SLAQ showed good validity and reliability. A good correlation was observed with patient's global disease activity. No correlation was found between S-SLAQ and standard disease activity measures like SLEDAI 2K and SLAM. The S-SLAQ cut-off point of 5 showed a good sensitivity to identify the active SLE population and therefore could be an appropriate screening instrument for disease activity in clinical and epidemiological studies.

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Abstract Number: 1674

Lupus Impact Tracker Validation in a Large European Spanish Lupus Registry Cohort

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Background/Purpose: Lupus Impact Tracker (LIT) is a ten item unidimensional patient reported outcome tool developed from and for patients with systemic lupus erythematosus (SLE). It has been widely validated and shown to have good psychometric properties and responsiveness, to patient reported changes in health, physician based disease activity and composite response Index. Herein we report functioning of LIT in the largest European SLE registry cohort.

Methods: Multi-center data collected prospectively, two years apart, from 1,364 adult patients SLE meeting 1997 ACR criteria were obtained. This included demographics, patient reported tools (LIT, EuroQoL- EQ5D) and SLE (activity-SLEDAI & SLAQ; damage-SDI). We evaluated LIT for reliability (Internal consistency), validity (construct (convergent and factor analysis), and criterion). Cronbach alpha was obtained for internal consistency reliability. Spearman correlation coefficient (r) of LIT against EQ5D and factor analysis were obtained for Construct validity. Correlation of LIT with

SLEDAI, SLAQ and SDI were made for Criterion Validity. Responsiveness of LIT to changes in SLEDAI (cutoff 5) and SLAQ (cutoff 5) from baseline and year 1 data were obtained using mixed model analysis.

Results: 1232/1364 (90%) were women, and 95% were Caucasian. Mean (SD) SLEDAI, NRS-SLAQ and SDI were 2.6 (3.5), 3.1 (2.5) and 0.7 (1.1) respectively. Mean (SD) LIT and EQ5D VAS were 29.2 (23.2) and 67.3 (21.4). Internal consistency reliability of LIT was good (Cronbach α 0.92). Construct-convergent validity with EQ5D domains and VAS were as follows: Mobility (r 0.46, $p < 0.001$), Self-Care (r 0.38, $p < 0.001$), Usual Activities (r 0.62, $p < 0.001$), Pain/Discomfort (r 0.63, $p < 0.001$), Anxiety/Depression (r 0.60, $p < 0.001$), and EQ5D-VAS (r -0.62, $p < 0.001$). Single factor explained 58% of variance in LIT (Eigenvalue 5.8), confirming its uni-dimensionality and construct validity. LIT scores were correlated with SLEDAI (r 0.12, $p < 0.001$), NRS-SLAQ (0.71, $p < 0.001$ & 0.67, $p < 0.001$) and SDI (0.16, $p < 0.001$) supporting criterion validity. EQ5D VAS also correlated with SLEDAI, SLAQ and SDI. Mean decline in LIT in response to improvement in SLEDAI and SLAQ were -2.9 (SRM -0.17, ES 0.08, P 0.04) and -13.1 (SRM -0.74, ES -0.30, $p < 0.001$); while mean increase in LIT in response to worsening in SLEDAI and SLAQ were 0.91 (SRM 0.04, ES 0.03, p 0.06) and 12.6 (SRM 0.65, ES 0.43, $p < 0.001$) respectively.

Conclusion: Lupus Impact Tracker documented good measurement properties among Spanish SLE patients enrolled in this observational largest European SLE registry.

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Lupus Impact Tracker Responds to Changes in Low Disease Activity and Remission Outcomes in a Large Spanish Lupus Registry Cohort

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

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Background/Purpose: Remission & Low Disease activity state (LDAS) are the two new health outcome measures developed with “treat to target” strategy in mind for Systemic Lupus Erythematosus (SLE). Lupus Impact Tracker (LIT), a ten item unidimensional patient reported tool has good psychometric properties and responsiveness to patient reported changes in health, physician based disease activity (DA) & composite response Index (SRI). Herein we report responsiveness of LIT to changes in LDAS & remission status among SLE patients from the largest European SLE registry- cohort.

Methods: One year longitudinal, observational, multi-center data from 1,364 adult patients with SLE meeting 1997 ACR criteria were obtained from baseline (B) and year 1 visit (Y1). This included demographics, patient reported tools (LIT), SLE (activity-SLEDAI) and medications. Remission off therapy was defined as SLEDAI=0 without prednisone or Immunosuppressive/s. Remission on-therapy was SLEDAI=0 & a prednisone dose ≤5mg/day and/or Immunosuppressive/s (maintenance dose). LDAS (modified) was defined as SLEDAI ≤4, prednisone dose ≤9mg/day and/or maintenance immunosuppressive/s. Non-optimal (NO) disease status was SLEDAI >4 and/or prednisone dose >9mg/day and/or immunosuppressive/s in induction dose. Use of hydroxychloroquine was permitted in all groups. LIT values were compared between groups with various disease activity using mixed models & both visits data. Due to relatively less number of observations in remission on and off therapy groups, both were combined into one remission group for responsiveness analysis. Latter was calculated by standard response means (SRM) in groups with a change of DA (NO was referent category). Due to relatively less number of observations in remission on and off therapy groups, both were combined into one remission group for responsiveness to change analysis.

Results: 1232/1364 (90%) were women, and 95% were Caucasian. Mean (SD) SLEDAI and SDI were 2.6 (3.5) and 0.7 (1.1) respectively. Distribution for each group is shown in Table 1 a. LIT scores were significantly lower among those in combined Remission (lower by average 9.4, SE 1.4, p<0.001) and LDAS (lower by average 6.2, SE 1.2, p <0.001) when compared with “non-optimal” activity group (Mean 34.0, SE 1.0).

LIT showed significant small to moderate responsiveness in the appropriate direction with improvement and worsening in disease activity status over time (Table 1 b). Mean changes to and from “LDAS” to “non-optimal” activity state ranged from 2-3.5, while they ranged from 5-8 for to and from “Remission” to “non-optimal” activity state.

Conclusion: Lupus Impact Tracker is able to differentiate between remission off and on treatment, LDAS and non-optimal disease activity state. LIT shows responsiveness to change in disease activity state over time, in the appropriate direction among Spanish SLE patients enrolled in the largest observational, European SLE registry.

Table 1a LIT scores by Disease Activity State

	n	Mean	SE P value	
Remission Off treatment	1359	24.63	1.38	<0.001
Low Disease Activity State	1359	27.8	1.05	<0.001
Remission On Treatment	1359	31.9	1.04	0.13
Non Optimal Activity State	1359	34.0	1.03	Reference
Table 1b: Responsiveness of Lit				
Disease Status Change	n	Mean Δ LIT	Std Dev	SRM
Non optimal activity to remission	33	-7.83333	17.940675	-0.44
Non optimal activity to LDAS	94	-2.16667	18.00588	-0.012
Non optimal to non-optimal Activity	75	-0.07142857	16.397148	-0.04
LDAS to non-optimal activity	86	3.3783784	21.331662	-0.16
Remission to non-optimal Activity	28	5.208333	17.413086	0.30

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de Salazar, None; J. García-Villanueva, None; P. Vela-Casasempere, None; M. E Ruiz-Lucea, None; F. J Toyos-Sáenz-de-Miera, None; J. Hernández Beiraín, None; E. Díez Álvarez, None; G. Bonilla-Hernán, None; J. Narváez-García, None; J. Andréu-Sánchez, None; M. Moreno-Martínez-Losa, None; A. Sánchez Atrio, None; M. L. Horcada, None; T. Cobo-Ibáñez, None; C. Marras Fernandez-Cid, None; T. R. Vazquez Rodriguez, None; E. Salgado-Pérez, None; V. Torrente, None; J. Alegre-Sancho, None; C. Mouriño-Rodríguez, None; J. A. Block, None; J. Pego-Reigosa, None.

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Health Related Quality of Life over Time in a Multi-Ethnic Cohort of Patients with Systemic Lupus Erythematosus and Correlation with Disease Activity and Organ Damage

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Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic disease affecting the physical, social, and psychological well-being of patients. Health related quality of life (HRQoL) measures add a new dimension to treatment response. However, their longitudinal correlation with clinical indicators such as disease activity and organ damage are not known. We aimed to determine HRQoL over time in a multi-ethnic Asian SLE cohort and to study its relationship with disease activity and damage.

Methods: Adult patients with SLE (ACR or SLICC criteria fulfilled) attending rheumatology clinics at our institution are recruited in a longitudinal observational study since 2013. Demographic and clinical data including SLEDAI-2K are collected at enrollment and every three months while organ damage (SLICC-ACR damage index [SDI]) is assessed annually. HRQoL is measured using SF-36 survey at enrollment and annually. Patients with 4 or more HRQoL measures from enrollment to December 2016 were included in the current analyses. Linear mixed effect model was used to compare the subsequent SF-36 scores with baseline, and among different races. Moreover, linear mixed effect model was used to evaluate the effect of disease activity (SLEDAI-2K) and damage (SDI) on the SF-36 scores, after adjustment for baseline scores, ethnicity, and time.

Results: A total of 196 patients were studied; mean \pm SD age at enrollment was 47.05 ± 12.54 years, 180 (90.9%) were women. 140 (70.7%), were Chinese; 28 (14.1%) Malays, 17 (8.6%) Indians, and 13 (6.6%) were other races. Majority were non-smokers (91.9%) and 10.1% had a family history of SLE.

Baseline mean \pm SD score of physical component summary (PCS) was 47.8 ± 8.2 , while mental component summary (MCS) score was 48.5 ± 9.8 (Table 1). The mean PCS improved significantly in second ($p < 0.008$) and third year ($p < 0.001$) as compared to baseline scores while no significant change was noted in MCS scores in second ($p < 0.76$) or third year ($p < 0.25$).

Significant association was noted between PCS and SLEDAI 2K scores ($p < 0.006$). For every unit increase in the SLEDAI-2K, the mean PCS would reduce by 0.808 (95% CI 0.236 – 1.381). SDI was negatively associated with MCS ($p < 0.035$); for every unit increase in SDI, the mean MCS would reduce by 0.363 (95% CI 0.026 – 0.701). Indian ethnicity was associated with worse MCS scores ($p < 0.008$).

Conclusion: This study demonstrated that HRQoL improves over time in SLE patients with proper management. Disease activity affects physical health while organ damage dictates psychosocial aspect of life in these patients. Therefore, HRQoL should be considered as an essential outcome measure in management of SLE patients.

Table 1. Yearly scores for PCS, MCS, and subscales (Mean and Standard Deviation)

Domains	Baseline	Y1	Y2	Y3
PCS	47.887 \pm 8.26	49.001 \pm 8.037	49.531 \pm 8.377	50.232 \pm 7.618
MCS	48.566 \pm 9.89	49.909 \pm 9.753	48.598 \pm 10.673	49.177 \pm 10.059
Physical function (PF)	48.513 \pm 9.0114	49.842 \pm 8.8	50.259 \pm 8.589	50.846 \pm 8.46

Table . (Cont'd)

Domains	Baseline	Y1	Y2	Y3
Role Physical (RP)	48.165±10.15	49.32±9.41	49.905±9.67	51.146±9.15
Bodily pain (BP)	50.016±10.73	52.144±9.747	51.620±10.672	52.47±9.457
General Health (GH)	44.261±8.8	44.854±9.5	43.898±10.28	44.215±9.275
Vitality (VT)	49.252±9.225	50.319±9.914	49.621±8.775	50.372±9.0315
Social Function (SF)	47.834±10.058	48.57±10.5	47.739±11.65	49.328±11.41
Role Emotional (RE)	48.314±11.0619	50.094±9.530	49.397±10.60	50.199±10.027
Mental Health (MH)	48.916±10.073	50.322±9.766	49.336±10.362	49.313±9.587

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Evaluation of Erythrocyte Sedimentation Rate As a Marker of Disease Activity in Patients with Systemic Lupus Erythematosus

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SESSION INFORMATION

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Background/Purpose: SLEDAI is a global disease activity index for SLE and includes anti-DNA and complement levels. However, elevated anti-DNA or low C3 & C4 levels may not be normalized in certain patients when SLE disease activity improve with treatment. In previous studies, ESR was associated with disease activity in SLE. In this study, we evaluated if ESR was a better marker for SLE disease activity compared with anti-DNA and complement.

Methods: We examined the data of patients with SLE who were enrolled in University of Washington Lupus Repository from 2014 through 2018. We included SLE patients who presented with arthritis, mucocutaneous symptoms, serositis or nephritis and excluded those with active CNS lupus, interstitial lung disease, myositis or hemolytic anemia. Additionally, we excluded patients with concomitant diagnosis of other rheumatic diseases including RA, SSs, chronic infection including HBV, HCV, HIV, any significant comorbidities including chronic kidney disease or malignancy, and recent infection, thrombosis or surgery within 4 weeks of the visit. We selected the most recent visit from each patient and examined the relationship between disease activity measured by clinical SLEDAI scores vs. ESR, anti-DNA, C3 and C4. Clinical SLEDAI was defined as SLEDAI without anti-DNA and complement levels in this study. Next, we selected patients who had a minimum of two visits with different clinical SLEDAI scores over the study period and examined whether there were differences in ESR, anti-DNA, C3 and C4 between the two visits in individual patients.

Results: Eighty-three patients met the eligibility criteria. There was a significant correlation between ESR and clinical SLEDAI ($r = 0.3$, $p = 0.007$), which remained significant after adjusting for hemoglobin or hematocrit. Anti-DNA, C3 and C4 did not correlate with clinical SLEDAI. ESR was significantly higher in patients with moderate to severe activity (clinical SLEDAI ≥ 3) than in patients with no activity (clinical SLEDAI = 0) ($p = 0.009$). No differences in anti-DNA, C3 or C4 were found between the two groups. Twenty patients had a minimum of two visits with different clinical SLEDAI and mean difference in clinical SLEDAI between two visits in these patients were 4.5 ± 3.4 . ESR and anti-DNA were significantly different between the two visits and C3 and C4 were not different (Fig 1).

Conclusion: ESR correlated with clinical SLEDAI in SLE patients and was higher in patients with moderate to severe activity compared to those with no activity. Anti-DNA, C3 or C4 did not correlate with clinical SLEDAI and were not different between active and inactive patients. ESR and anti-DNA were different between two visits with different clinical SLEDAI scores in individual patients while there were no differences in C3 and C4. These results suggest that ESR may be a better test than anti-DNA, C3 or C4 in assessing SLE disease activity.

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How Consistently Do Publications Define SLE? a Systematic Review

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Session Type: ACR Poster Session B

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Background/Purpose: Systemic lupus erythematosus (SLE) is clinically heterogeneous. ACR and/or SLICC classification criteria provide homogeneous populations for research purposes, but studies differ in selection and exclusion criteria and in definitions of SLE. We examine recent publications to determine how consistently they characterize SLE patients.

Methods: We reviewed English-language studies, using “systemic lupus erythematosus” as the search term, and filtering for full text availability, publication dates 4/2//2013-4/2/2018, and human. We excluded reviews, letters, and papers from <2 impact factor journals and/or irrelevant to the question and classified papers as translational if they examined pathophysiology or biological factors that lead to treatment interventions or clinical/epidemiological if patients or populations were studied. We evaluated these papers for inclusion and exclusion criteria, disease activity, overlap syndrome (SLE coexisting with another rheumatic illness), disease stability (defined as no change in treatment regimen for a specified duration), diagnostic antibody status (including antinuclear (ANA), anti-double stranded DNA (anti-dsDNA) and/or anti-Smith (anti-Sm) antibodies), and disease duration.

Results: 402 of 732 papers were suitable for analysis, of which 80 were translational and 322 clinical/epidemiological. 71% of translational studies and 66% of clinical/epidemiological studies used only ACR and/or SLICC classification criteria to define SLE, of which only 9% of translational and 7% of clinical/epidemiological studies specified requirement for both ACR and/or SLICC criteria and diagnostic antibodies. 30% of clinical/epidemiological and only 16% of translational studies specified exclusion criteria. Of the 402 studies overall, only 6% specified exclusion of patients with overlap syndrome, 14% specified disease activity using either SLEDAI score or BILAG index, and 8% specified disease stability. 2% of clinical/epidemiological studies, but no translational studies, specified disease duration.

Conclusion: Although translational and clinical/epidemiological studies all use the term SLE, only 67% specify use of ACR and/or SLICC criteria, 27% specify exclusion criteria; ≤15% of both types of studies exclude patients with overlap syndromes, specify SLE-specific autoantibodies, disease activity, or duration. Improved consistency in the use of these study characteristics might better standardize current literature on SLE.

Table. Characteristics of SLE studies published between 2013-2018 by study type

Study Characteristics	Study Type (n)		
	Translational (80) %	Clinical/Epidemiological (322) %	All (402) %
ACR and/or SLICC SLE Classification Criteria	71	66	67
ACR Criteria + ANA or anti-dsDNA/anti-Smith	9	7	7
Anti-dsDNA or anti-Smith	8	7	7
Exclusion criteria	16	30	27
Exclusion of overlap syndrome	5	7	6
Activity by SLEDAI or BILAG	15	14	14
Disease duration	-	2	1
Disease stability*	6	8	8

ACR and/or SLICC, American College of Rheumatology and/or Systemic Lupus International Collaborating Clinics; ANA, antinuclear antibody; anti-double stranded DNA antibodies (anti-dsDNA), anti-Smith (anti-Sm) antibodies; SLEDAI, systemic lupus erythematosus disease activity index; BILAG, British Isles Lupus Assessment Group.

* defined as no change in treatment regimen for a specified duration

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Usefulness of Cardiac Screening in Patients with Systemic Lupus Erythematosus and Anti-Ro Positive Antibodies

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Background/Purpose: Cardiac block in neonatal lupus is associated with placental transfer of anti-Ro antibodies. The effect of these antibodies on cardiac conduction disorders in adult patients is controversial. Association between anti-Ro antibodies and heart rhythm disorders have been described in isolated cases. However, there are just a few studies that analyse the relationship between autoimmune diseases and electrocardiographic disturbances. Our aim is to determine if there are differences in cardiac conduction of SLE patients in presence of anti-Ro antibodies.

Methods: All patients included fulfilled the SLE criteria (SLICC 2012) and were followed up in a single centre. Patients taking drugs that alter cardiac conduction (except antimalarial drugs) and those who had heart or thyroid disease were discarded. All patients were assessed blindly by a cardiologist who performed an interrogation and physical examination, an electrocardiogram, an echocardiogram and a 24-hour Holter study. Besides, a rheumatologist performed a clinical and analytical assessment including a qualitative analysis by immunoblotting of anti-Ro Ab and a quantification by chemiluminescence of the anti-Ro52 and Ro60 Ab. The presence of other SLE specific Ab (ANA, DNA, antiphospholipid) was also analysed by immunoblot, indirect immunofluorescence and ELISA. Clinical, analytical activity and damage indexes were collected (SLEDAI and SLICC).

Results: 145 patients were included: 92% women, mean age 45 ± 2 , average disease duration 11 years. Patients were undergoing the following treatments: antimalarial 91%, mycophenolate 20%, azathioprine 12%, biological treatment 5% and glucocorticoids 70%. The clinical characteristics are summarized in table 1.

There were no significant differences between positive and negative anti-Ro Ab in terms of gender, age, clinical characteristics or cardiovascular risk factors. None of the patients was affected by an atrio-ventricular block and the rest of the electrocardiographic alterations had no clinical significance and did not predominate in the positive Ro Ab group. Additionally, no differences in heart rate, ventricular extrasystoles or PR, QT or QRS intervals were detected between both groups. The echocardiogram's findings were not relevant and there were no differences between groups. Since the majority of patients with SLE are double positive differences between two subspecificities of Ro (52 and 60) could not be analysed. On the other hand, no differences were found in cardiac conduction regarding the treatments received, the activity or damage indexes, or the analytical or clinical characteristics of the patients.

Conclusion: The study results show that there are no differences in cardiac conduction according to the presence of anti-Ro antibodies in SLE patients. Thus, the cardiac screening in SLE patients with anti-Ro positive antibodies seems not helpful in clinical practice.

Cumulative clinical manifestations (%)	
Articular	80
Cutaneous	63
Leuco-lymphopenia	42
Renal	24
Serositis	30
Neurologic	9
Secondary antiphospholipid syndrome	10
Secondary Sjögren syndrome	10
Activity and damage indexes	
SLICC	0,32 \pm 0,7
SLEDAI at diagnosis	7,97 \pm 4,2
SLEDAI at inclusion	1,82 \pm 2,48
Laboratory	
Increased DNA	51 %
Mean DNA	207,86 \pm 357 (UI/L)
Hypocomplementemia	39 %
Anti-Ro positive antibodies	31 %

Disclosure: J. Camins Fàbregas, None; M. Martinez-Morillo, None; A. Teniente-Serra, None; A. Riveros, None; S. Heredia, None; A. Prior, None; S. Holgado, None; L. Mateo, None; M. Aparicio, None; L. Gifre, None; I. Casafont-Solé, None; Y. García, None; G. Juncà, None; R. Villuendas, None; A. Bayés-Genis, None; E. Martínez-Cáceres, None; A. Olivé-Marqués, None.

Abstract Number: 1680

Serum Calprotectin in Systemic Lupus Erythematosus: Is It a Good Activity Biomarker?

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Clinical manifestations of systemic lupus erythematosus (SLE) and infections sometimes are difficult to distinguish. In clinical practice low complement and anti(ds)DNA levels are used to assess lupus activity but its determination usually requires some days. Leukocyte count, CRP and ESR cannot discriminate SLE from infectious processes. Calprotectin could be a good biomarker to assess lupus activity since it is more specific than CRP and ESR and faster to analyse than anti(ds)DNA. Our aim is to determine serum calprotectin levels in patients with SLE, and its correlation with analytical and clinical manifestations, especially with disease activity.

Methods: A total of 148 patients were included. All patients included fulfilled the SLE criteria (SLICC 2012). A quantitative ELISA analysis was performed to assess levels of serum calprotectin (CALPRO AS, Norway). Other biomarkers of lupus disease activity were also assessed (levels of anti(ds)DNA, hypocomplementemia, ESR and CRP). Clinical variables and activity/damage index (SLEDAI/SLICC) were also evaluated. The study was approved by the Clinical Research Ethics Committee of the hospital and all patients signed an informed consent. The results were compared with a healthy control group of similar age and sex (n=20).

Results: 134 patients (92%) were women with a mean age of 46±12 years and an average SLE evolution of 12±7 years. Mean SLEDAI was 2±2 (105 inactive [<3], 43 mild [4-12], 0 severe [>13]). Mean SLICC was 0.31±0.70. No significant differences were observed in serum calprotectin levels between patients with SLE and healthy controls (2.93±2.35 vs 2.17±1.49 µg/mL, p=0.160). Calprotectin was positively correlated with CRP (r=0.447, p=<0.001) and leukocyte count (r=0.462, p=<0.001). Additionally, patients with higher anti(ds)DNA levels (>100UI/mL) had higher calprotectin compared to patients with lower anti(ds)DNA (3.20±2.63 vs 2.42±1.57 µg/mL; p=0.027), however this pattern was not observed with hypocomplementemia. Contrary to what we expected, we did not observe significant differences on calprotectin levels depending on SLEDAI index classification (cutoff at 4 and 12). Moreover, no differences were observed on calprotectin levels between those patients with/without clinical manifestations such as serositis, arthritis or glomerulonephritis. Patients with antiphospholipid antibodies had higher calprotectin levels (3.75±2.04 vs 2.77±2.38 µg/mL; p=0.045).

Conclusion: Serum calprotectin levels were positively correlated with CRP levels and leukocyte count. Patients with higher anti(ds)DNA levels had higher calprotectin levels, however we did not observe significant differences depending on SLEDAI index or the presence of arthritis, serositis neither glomerulonephritis. Even that calprotectin determination is faster than anti(ds)DNA levels and could be helpful in assessing inflammatory activity. There is an interesting relation between antiphospholipid antibodies and calprotectin. This study should be continued in a larger sample of active SLE patients to assess its utility in clinical practice as a discriminating biomarker for flares and even infections.

Disclosure: J. Camins Fàbregas, None; M. Martinez-Morillo, None; L. Gifre, None; S. Holgado, None; L. Mateo, None; M. Aparicio, None; A. Riveros, None; I. Casafont-Solé, None; Y. García, None; A. Prior, None; A. Teniente-Serra, None; E. Martínez-Cáceres, None; A. Olivé-Marqués, None.

Performance of the Proposed American College of Rheumatology / European League Against Rheumatism 2017 Classification Criteria for SLE in Adult and Juvenile Systemic Lupus Erythematosus and Other Anti-Nuclear Antibody Related Rheumatic Diseases

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: A new classification criteria for SLE was proposed at the ACR/ARHP 2017 annual meet. The aim of this study was to compare the performance of the proposed ACR/EULAR'17 criteria against the 2012 SLICC (SLICC'12) and ACR 1997 (ACR'97) classification criteria for SLE in the adult (A-SLE) and juvenile SLE (J-SLE) cohort from India.

Methods: Patient records were chosen from the disease registry collected over the past 8 years for A-SLE, J-SLE, MCTD, Primary SS and primary APS from a tertiary care center in South India. The records were screened to include only ANA associated rheumatic diseases (AARD). Patients who were diagnosed as SLE at their first visit by trained rheumatologists were designated as cases and the other rheumatic diseases as controls. The performance of ACR 97, SLICC'12 and ACR/EULAR'17 criteria at the first visit was analysed. Sensitivity of the three criteria were analysed by sub classifying the patients based on the duration of illness as <18, 19-36, 37-54 and >54 months.

Results: We analysed 273 j-SLE and 884 a-SLE patients as cases and 435 other AARDs (MCTD-119, UCTD-69, SS-217, APS-30) as controls. The demography, clinical and immunological profile of the cases and controls are shown in table 1. The sensitivity, specificity, positive and negative predictive values of each of these criteria are depicted in table 2. The subgroup of adult patients with <54 months disease had the largest difference in sensitivity between the ACR'97 and the other two criteria; whereas the difference was seen in the j-SLE patients presenting within 18 months of disease onset (table 3). False positivity was seen in 41, 71 and 66 patients in ACR'97, SLICC'12 and ACR/EULAR'17 criteria respectively. A score of +4 for low serum c3 and c4 led to the false diagnosis of 15 controls by the ACR/EULAR'17 who were not diagnosed by ACR'97 criteria.

Conclusion: The proposed ACR/EULAR '17 criteria has higher sensitivity and lower specificity than the ACR'97 criteria but is similar to the SLICC'12 criteria among J-SLE and A-SLE. A score of +4 for low c3 and c4 was the probable cause for lower specificity and needs consideration. Assigning an appropriate negative or positive score in case of negative or positive antibodies to either of anti-nucleosome, anti-ribosomal p or anti-histone in all the anti-dsDNA and anti-Smith negative patients may overcome this shortcoming.

Table 1 Demography, Clinical and immunological profile of patients with juvenile SLE, Adult SLE and other ANA associated rheumatic diseases.

	Juvenile SLE (N=273)	Adult SLE (N=884)	Controls (N= 435)
Age (Mean \pm SD, In Years)	18.45 \pm 7.48	31.46 \pm 9.29	38.23 \pm 12.55
Duration of Illness (Median, IQR, In Months)	12 (4,25)	12 (5,16)	36 (12,72)
Gender (M:F)	32:241	53:831	14: 421
Photosensitivity	67 (24.5)	242 (27.4)	27 (6.2)
Malar Rash	134 (49.1)	435 (49.2)	5 (1.1)
ACLE	149 (54.6)	488 (55.2)	19 (4.4)
SCLE	7 (2.6)	25 (2.8)	3 (0.7)
DLE	46 (16.8)	148 (16.7)	7 (1.6)
Non-Scarring Alopecia	106 (38.8)	318 (36.0)	14 (3.2)
Oral Ulcer	128 (46.9)	387 (43.8)	19 (4.4)
Arthritis	149 (54.6)	547 (61.9)	229 (52.6)
Serositis	34 (12.5)	143 (16.2)	11 (2.5)
Acute pericarditis	9 (3.3)	29 (3.3)	0 (0)
Class III/IV LN	45 (16.5)	157 (17.8)	0 (0)
Class II/ V LN	10 (3.7)	51 (5.8)	1 (0.2)
Neurological disorder	61 (22.3)	177 (20)	6 (1.4)

Table . (Cont'd)

	Juvenile SLE (N=273)	Adult SLE (N=884)	Controls (N= 435)
Autoimmune hemolytic anemia	55 (20.1)	147 (16.6)	3 (0.7)
Leucopenia	78 (28.6)	236 (26.7)	27 (6.2)
Lymphopenia	79 (28.9)	241 (27.3)	13 (3.0)
Thrombocytopenia	74 (27.1)	165 (18.7)	20 (4.6)
Fever	103 (37.7)	264 (29.9)	6 (1.4)
Anti dsDNA positivity	120 (43.9)	450 (50.9)	26 (6.0)
Lupus Anticoagulant / ACLA/Beta 2 GP1 positivity	98 (35.9)	47 (5.3)	59 (13.6)
C3 or C4 low	125 (45.8)	393 (44.5)	30 (6.9)
Both C3 and C4 low	72 (26.4)	219 (24.8)	16 (3.7)
Positive coombs test	55 (20.1)	167 (18.9)	33 (7.6)

Table 2: Performance of each classification criteria in patients with SLE

Criteria	Juvenile SLE			Adult SLE		
	ACR 1997	SLICC 2012	ACR 2017	ACR 1997	SLICC 2012	ACR 2017
Sensitivity (CI)	80.95 (75.78-85.43)	97.07 (94.31- 98.73)	92.67 (88.91-95.47)	82.13 (79.44- 84.60)	95.59 (94.02- 96.84)	92.31 (90.35- 93.98)
Specificity (CI)	90.80 (87.69- 93.35)	83.68 (79.86- 87.03)	85.29 (81.60- 88.48)	90.80 (87.69-93.35)	83.68 (79.86- 87.03)	85.29 (81.60- 88.48)
Positive predictive value (CI) (As calculated in study cohort)	84.67 (80.35- 88.19)	78.87 (75.09- 82.21)	79.81 (75.87-83.25)	94.78 (93.10- 96.07)	92.25 (90.58- 93.64)	92.73 (91.04- 94.12)
True PPV (Assuming Prevalence = 3.2/1,00,000)	0.01 (0.01-0.02)	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.03 (0.02- 0.03)	0.02 (0.02-0.02)	0.02 (0.02-0.02)
Negative predictive value (CI) (As calculated in study cohort)	88.37 (85.59-90.67)	97.85 (95.83-98.90)	94.88 (92.39-96.59)	71.43 (68.39- 74.28)	90.32 (87.26- 92.71)	84.51 (81.23- 87.31)
True NPV (Assuming Prevalence = 3.2/1,00,000)	100 (100- 100)	100 (100- 100)	100 (100- 100)	100 (99.99-100)	100 (100- 100)	100 (100- 100)
Positive Likelihood Ratio	8.80 (6.52-11.89)	5.95 (4.8-7.36)	6.30 (5.01-7.92)	8.93 (6.64- 12.02)	5.86 (4.73-7.25)	6.27 (5.00- 7.87)
Negative Likelihood Ratio	0.21 (0.16- 0.27)	0.04 (0.02-0.07)	0.09 (0.06- 0.13)	0.20 (0.17- 0.23)	0.05 (0.04- 0.07)	0.09 (0.07-0.11)
Diagnostic Odds ratio (CI)	41.96 (26.92-65.41)	169.82 (80.38-358.76)	73.33 (43.29- 124.20)	45.37 (31.40- 65.55)	111.08 (73.75- 67.29)	70.60 (49.06- 101.58)

Table 3: Sensitivity for each classification criteria for groups with different disease durations

	Sensitivity of ACR 97	Sensitivity of SLICC 2012	Sensitivity of ACR/EULAR 2017
Adult SLE			
<18 months (n=539)	81.08 (77.51- 84.30)	95.36 (93.23- 96.98)	92.57 (90.01- 94.64)
19-36 months (n=164)	87.20 (81.09- 91.90)	96.95 (93.03- 99.0)	95.73 (91.40-98.27)
37-54 months (n=65)	72.31 (59.81- 82.69)	90.77 (80.98- 96.54)	89.23 (79.06- 95.56)
>54 months (n=114)	85.96 (78.21- 91.76)	97.37 (92.50- 99.45)	89.47 (82.33- 94.44)
Juvenile SLE			
<18 months (n=183)	78.69 (72.04- 84.38)	96.72 (93.0-98.79)	91.80 (86.84-95.34)
19-36 months (n=35)	88.57 (73.26- 96.80)	100 (90-100)	94.92 (80.84- 99.30)
37-54 months (n=11)	100 (71.51-100)	100 (71.51-100)	100 (71.51-100)
>54 months (n=44)	79.55 (64.70-90.20)	95.45 (84.53- 99.44)	93.18 (81.34-98.57)

Disclosure: C. KG, None; G. Kumar, None; S. R P, None; V. S. Negi, None.

Abstract Number: 1682

Correlation between SLE Specific and Generic Health Related Quality of Life Surveys, and Their Association with Patient Global Rating of Change and Lupus Low Disease Activity State: A Longitudinal Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To determine the correlation between SLE-specific and generic patient reported outcomes measures (PROs), and to examine their associations with patients' global rating of change (GRC) in their health-related quality of life (HRQoL), and Lupus Low Disease Activity State (LLDAS).

Methods: SLE patients who full-filled either the 1997 ACR or the 2012 SLICC classification criteria, and attended a rheumatology clinic in Thailand between 2013 and 2017, were recruited for this study. They completed the SLEQoL-TH and SF36-TH surveys (Thai versions), and rated their GRC compared to their previous visit using a 7-point Likert scale (GRC -7 to +7) on the same day of clinic visits. Based on GRC scores, patients were categorised as 'no change' (-1 to +1), 'deterioration' (-2 to -7) or 'improvement' (+2, to +7) in HRQoL. SLE disease activity was determined by the SLEDAI-2K. Physician global assessment (PGA) of disease activity was rated 0-3. LLDAS was defined as described (*Franklyn K. Ann Rheum Dis* 2016). Correlation between SLEQoL-TH and SF36-TH was examined using Person's correlation coefficients. Associations of GRC and LLDAS with SLEQoL-TH/SF36-TH surveys were examined using generalised estimating equations.

Results: 337 patients (2,062 visits) were included. Median [inter-quartile range (IQR)] values of patients' age at enrolment, disease duration, and study duration was 37 [28, 48] years, 7 [3, 13] years, and 3.18 [1.55, 3.46] years, respectively. 56% of patients experienced at least one flare. Median [IQR] time adjusted mean (TAM) -SLEDAI and TAM-PGA scores were 3.5 [2.0, 5.6] and 0.4 [0.3, 0.7], respectively. During the study, 81% of patients achieved LLDAS at least once, and were in LLDAS in approximately 50%. TAM SLEQoL-TH score, and SF36-TH physical component summary (PCS) and mental component summary (MCS), were 89.8 [81.7, 94.9], 46.8 [42.0, 52.1] and 49.4 [42.9, 55.0], respectively. SLEQoL-TH total scores correlated significantly with both SF36-TH PCS and MCS scores ($r = 0.55$ and 0.60 , respectively, $p < 0.01$). Patients who were in LLDAS had statistically significantly higher scores in both SLEQoL-TH and SF36-TH surveys when compared to patients who were not in LLDAS. Patients reported improvement in 58%, deterioration in 15% and no change in HRQoL in 27% of all visits. Compared to the 'no change' control group, patients who reported deterioration in HRQoL were significantly less likely to be in LLDAS (OR 0.53, 95% CI: 0.39-0.72, $p < 0.001$), but HRQoL improvement was not associated with significant increased likelihood of LLDAS. The PGA showed a weak association with the GRC ($r = -0.14$).

Conclusion: The SLE specific PRO, SLEQoL-TH, correlated significantly with the generic PRO, SF36-TH. LLDAS was associated with better HRQoL, and improving HRQoL was predictive for LLDAS attainment.

Disclosure: W. Louthrenoo, None; N. Kasitanon, None; E. Morand, None; R. Kandane-Rathnayake, None.

Abstract Number: 1683

Variation in HEp-2 Antinuclear Antibody (ANA) Titer Is Strongly Associated with the ANA Kit Manufacturer

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SESSION INFORMATION

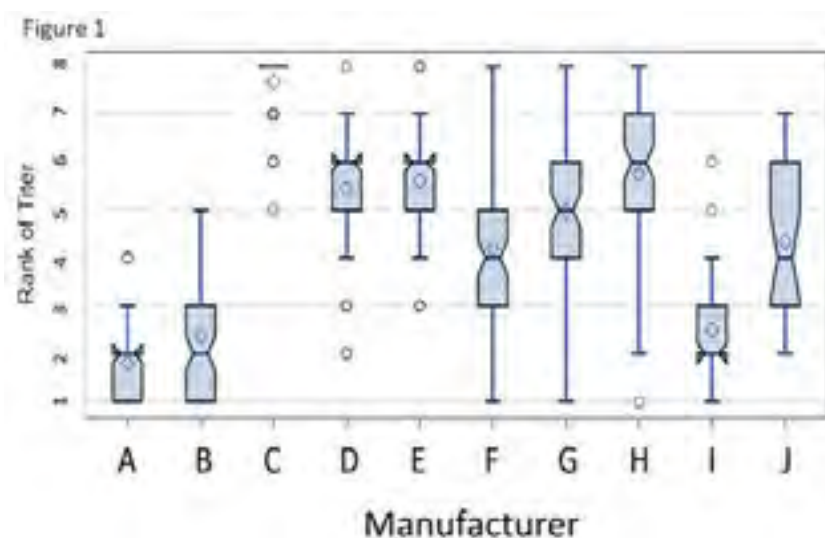
Session Date: Monday, October 22, 2018

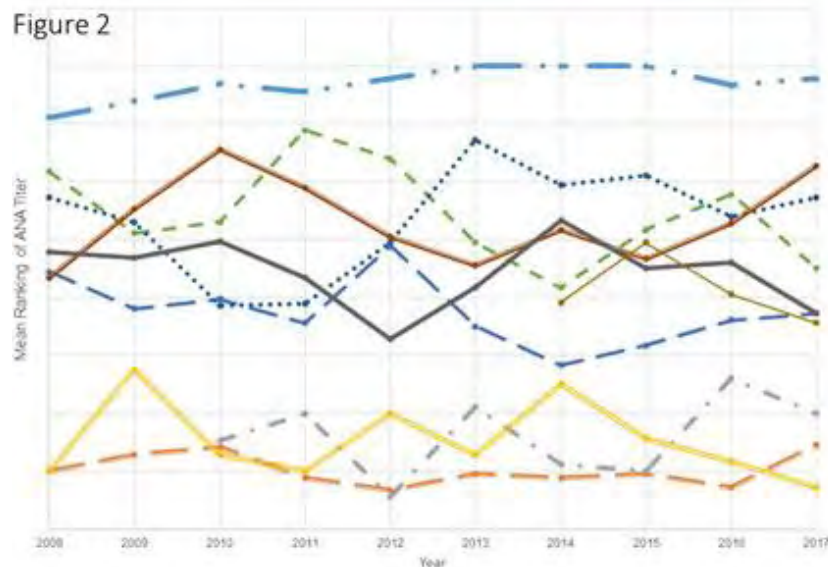
Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Titers of HEp-2 ANAs vary between laboratories, with many contributing factors. We sought to systematically determine the contribution of different ANA kit manufacturers to ANA variation.





Methods: Proficiency surveys involve sending aliquots of the same specimen to performing laboratories, allowing labs to compare results. Positive HEp-2 ANA titers reported by over 500 participant labs in ANA proficiency surveys by the College of American Pathologists between 2008 and 2017 were analyzed according to the kit manufacturer used by labs. The mean positive ANA titers reported for each specimen were ranked by kit manufacturer, relative to other manufacturers reporting on the same specimen. A total of 79 positive ANA specimens and up to 10 manufacturers were available for analysis, totaling 733 specimen-manufacturer combinations, with a median 46 laboratories reporting results for each combination.

Results: ANA titers of individual specimens differed by up to 5 2-fold dilutions (e.g. ANA 1:40 and 1:1280 reported by one or more laboratories testing the same specimen). The geometric mean titers for different methods differed from the overall mean titer by as much as 2-fold, and the difference between the geometric means of the highest method and the lowest method testing a given specimen over 3 2-fold dilution titers. ANA titer results were strongly influenced by the HEp-2 manufacture used by the labs ($p < 0.0001$ by analysis of variance). Each manufacturer tended to have a fairly consistent rank, relative to the other manufacturers, (figure 1, median rank is indentation, diamond is mean for each manufacturer). Over the 10 years studied, the rank order of the ANA titer for each method was remarkably consistent (figure 2; each line tracks a manufacturer's mean rank by year). The ANA patterns did not significantly affect these results.

Conclusion: The variability in ANA titers is strongly influenced by the manufacturer of the HEp2 kit used in the assays and the differences between kits are generally consistent. Since much of the variability is systematic and associated with the kit manufacturer, harmonizing manufacturers' kits could improve consistency of ANA reporting.

Disclosure: M. Wener, Medical Training Software, 7, UpToDate, 7; M. H. Wener, University of Washington, 9.

Abstract Number: 1684

Prolonged Remission/Low Disease Activity State Is Associated with a Better Health-Related Quality

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Session Type: ACR Poster Session B

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Background/Purpose: Achieving remission and low lupus disease activity state (LDAS) in systemic lupus erythematosus (SLE) patients improves their prognosis in terms of damage accrual. But, the impact of these states on health-related quality of life (HRQoL) has only been sparsely assessed (1,2). The aim of these analyses is to evaluate the association between the duration of remission and LDAS and HRQoL, after adjustment for possible confounders.

Methods: Patients from a single center cohort started in 2012 and who had at least two visits were included in this study. Visits were performed every six months. Socioeconomic and clinical data were recorded at every visit. Disease activity was ascertained with the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), disease damage with the SLICC/ACR Damage Index (SDI) and HRQoL with the Spanish version of the Lupus QoL. Remission was defined as a SLEDAI-2K=0, prednisone≤5mg/d, immunosuppressants on maintenance dose, LDAS was defined as not on remission and a SLEDAI-2K≤4, prednisone≤7.5mg/d, immunosuppressants on maintenance dose. Disease activity states were recorded in each visit. The outcomes were each of the Lupus QoL's domains at the last visit. Univariable and multivariable linear regression models, adjusted by age at diagnosis, disease duration, socioeconomic status, antimalarial use, damage, comorbidities and baseline value of the same domain were performed. Duration of remission/LDAS was categorized as ≤25%; >25 but ≤50%; >50 but ≤75%; and >75. Due to the relatively small number of patients on remission, remission and LDAS were examined together.

Results: Two hundred and thirty-five patients were included, 217 (92.3%) were female, mean (SD) age at diagnosis was 35.42 (13.30) years. Disease duration at baseline was 7.32 (6.69) years. The mean follow-up was 3.29 (1.27) years, and they had 4.93 (1.99) visits. Mean percentages of visits on each state during the follow up were 24.23 (31.38) for remission 32.16 (32.63) for LDAS and 43.60 (38.71) for active. The association between the percentage of follow-up on remission/LDAS is depicted in Table 1.

Conclusion: A longer duration on remission/LDAS is associated with a better HRQoL (Physical Health, Pain, Fatigue and Burden to Others) independently of possible confounders.

Table 1: Duration of follow-up on remission/LDAS and HRQoL

Domain	Percent of follow up time on remission/LDAS	Univariable B (CI95%)	p value	Multivariable B (CI95%)	p value
Physical Health	>75%	13.30 (6.14; 20.46)	<0.001	15.19 (6.33; 20.05)	<0.001
	>50% and ≤75%	9.91 (0.75; 19.08)	0.034	9.65 (0.95; 18.35)	0.030
	>25% and ≤50%	-3.09 (-4.99; 13.18)	0.377	-4.56 (-4.06; 13.22)	0.259
	≤25%	Ref.		Ref.	
Emotional Health	>75%	8.39 (0.50; 16.28)	0.037	5.11 (-1.32; 11.55)	0.119
	>50% and ≤75%	5.20 (-3.90; 16.30)	0.239	6.14 (-1.97; 14.25)	0.138
	>25% and ≤50%	-1.20 (-11.21; 8.82)	0.815	-0.09 (-8.14; 7.96)	0.982
	≤25%	Ref.		Ref.	
Body Image	>75%	5.02 (-3.68; 13.72)	0.224	4.11 (-5.59; 13.81)	0.406
	>50% and ≤75%	-2.65 (-14.98; 9.68)	0.673	-4.19 (-16.25; 7.89)	0.498
	>25% and ≤50%	1.93 (-10.40; 14.26)	0.758	0.75 (-11.31; 12.81)	0.903
	≤25%	Ref.		Ref.	
Pain	>75%	11.33 (3.28; 19.38)	0.006	9.42 (2.43; 16.40)	0.008
	>50% and ≤75%	5.88 (-4.42; 16.18)	0.263	3.52 (-5.34; 12.37)	0.436
	>25% and ≤50%	-4.01 (-6.21; 14.22)	0.442	4.91 (-3.87; 13.69)	0.273
	≤25%	Ref.		Ref.	
Planning	>75%	9.39 (0.84; 17.94)	0.031	4.41 (-2.91; 11.73)	0.238
	>50% and ≤75%	1.69 (-9.25; 12.63)	0.762	-1.08 (-11.22; 7.25)	0.674
	>25% and ≤50%	5.70 (-5.14; 16.55)	0.303	1.32 (-7.95; 10.39)	0.794
	≤25%	Ref.		Ref.	
Fatigue	>75%	8.31 (0.16; 16.46)	0.046	7.00 (0.09; 13.92)	0.047
	>50% and ≤75%	1.25 (-3.27; 11.76)	0.617	0.93 (-7.94; 9.78)	0.839
	>25% and ≤50%	-3.64 (-6.70; 13.97)	0.490	5.36 (-3.15; 14.27)	0.211
	≤25%	Ref.		Ref.	
Intimate relationship	>75%	9.32 (-2.64; 21.28)	0.127	9.49 (-0.81; 19.78)	0.072
	>50% and ≤75%	9.68 (-6.15; 24.31)	0.243	5.10 (-8.21; 18.42)	0.452
	>25% and ≤50%	-2.68 (-18.43; 13.14)	0.743	1.14 (-12.21; 14.49)	0.887
	≤25%	Ref.		Ref.	
Burden to others	>75%	12.53 (3.05; 21.98)	0.009	9.62 (1.00; 18.24)	0.029
	>50% and ≤75%	3.13 (-8.96; 15.21)	0.612	3.39 (-7.54; 14.32)	0.543
	>25% and ≤50%	5.01 (-8.97; 15.00)	0.422	1.32 (-8.99; 12.76)	0.729
	≤25%	Ref.		Ref.	

Multivariable models were adjusted by age at diagnosis, disease duration, socioeconomic status, antimalarial use, damage, comorbidities and baseline value of the same domain

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2. Golder V, Kandane-Rathnayake R, Hoi AY, Huq M, Louthrenoo W, An Y, et al. Association of the lupus low disease activity state (LLDAS) with health-related quality of life in a multinational prospective study. *Arthritis Res Ther.* 2017;19(1):62.

Disclosure: M. Ugarte-Gil, None; R. Gamboa-Cárdenas, None; M. Medina-Chinchon, None; C. Reategui-Sokolova, None; F. Zevallos, None; C. Elera-Fitzcarrald, None; V. R. Pimentel-Quiroz, None; E. Noriega, None; Z. Rodriguez-Bellido, None; C. A. Pastor-Asurza, None; G. S. Alarcón, None; R. Perich-Campos, None.

Abstract Number: 1685

IL2 Decrease Is Associated to ANTI-DNA Positivity in Systemic LUPUS Erythematosus Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by deregulation of cytokine production. IL2 is an anti-inflammatory cytokine in SLE, but its loss leads to the Th2 system activation and in consequence, Th2 proinflammatory cytokines as IL10 are produced. The aim is to analyze the association between IL2 serum levels and clinical activity in SLE. The secondary objective is to characterize the correlation between IL2 and IL10 serum levels.

Methods: A cross-sectional, observational study of 142 patients diagnosed of SLE (according to SLICC 2012 criteria), and 35 healthy controls, was performed. A complete blood-test and an interview were carried out to collect their clinical data. We analyzed IL2 and IL10 serum levels by colorimetric methods. SLE patients were dichotomized as high and low levels for IL2 based on the 5% and 95% percentile values in healthy controls. Biostatistical analysis with R was performed.

Results: 142 SLE patients were evaluated; 94.4% of them were female. Mean values were as follow: age at diagnosis 33.29±13.53 years, disease duration 15.82±10.56 years, SLEDAI 5.91±5.06, IL2 levels 4.34 ±12.2 ng/mL and IL10 levels 12.29 ± 32.82 ng/mL.

We observed lower values of IL2 in SLE patients than in healthy controls (P=0.002), and higher values of IL10 in SLE patients than in healthy controls (P<0.001). Statistical analysis indicates that decreased levels of IL2 is associated with anti-DNA positivity (P=0.045). We did not observe a statistically significant association between IL2 serum levels and SLEDAI scores or complement consumption.

Due to this finding, we categorized SLE patients by low IL2 levels (n=37), normal IL2 levels (n=98) and high IL2 levels (n=7).

	IL2 high levels (n = 7) Mean (SD)	IL2 normal levels (n = 98) Mean (SD)	IL2 low levels (n = 37) Mean (SD)
IL2 levels (ng/mL)	40.05 (41.08)	3.37 (3.52)	0.16 (0.08)
Anti-dsDNA (ng/mL)	12.63 (15.49)	27.49 (57.84)	35.31 (63.12)
C3 (ng/mL)	103.71 (40.13)	107.46 (28.77)	107.89 (24.27)
C4 (ng/mL)	15.86 (6.72)	18 (9.05)	18.35 (8.1)
SLEDAI	7.29 (5.68)	5.63 (5.12)	6.38 (4.82)

The statistical analysis did not yield differences in the clinical activity, anti-DNA or C3-C4 serum levels among patients with lower, normal and higher IL2 levels. Despite the fact that no specific IL2 profile associated with clinical activity was observed, those patients with low IL2 profile had increased anti-DNA levels.

Conclusion: In our series, we observed a decrease in IL2 levels and an increase of IL10 levels, according to the production of the Th2 proinflammatory cytokines in IL2 low levels context. We noted a statically significant association between low IL2 levels and anti-DNA high levels. We have found no statistical evidences on the relationship of IL2 levels and clinical activity in our series of patients.

Disclosure: E. Grau Garcia, None; F. M. Ortiz-Sanjuán, None; C. Alcañiz Escandell, None; K. Arevalo Ruales, None; I. Chalmeta Verdejo, None; M. De la Rubia Navarro, None; J. J. Fragio Gil, None; R. Gonzalez Mazario, None; L. Gonzalez Puig, None; J. Ivorra Cortes, None; I. Martinez Cordellat, None; R. Negueroles Albuixech, None; J. E. Oller Rodriguez, None; E. Vicens Bernabeu, None; C. Najera Herranz, None; I. Canovas Olmos, None; D. Hervás Marín, None; M. Fernandez Matilla, None; N. Fernandez-Llanio Cornella, None; J. A. Castellano Cuesta, None; C. A. Pavez Perales, None; J. A. Roman Ivorra, None.

Abstract Number: 1686

Rule-Based Algorithm Using Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria to Identify Patients with Systemic Lupus Erythematosus (SLE) from Electronic Health Record (EHR) Data

Anika S. Ghosh¹, Theresa L. Walunas², Kathryn L. Jackson¹, Ahn H. Chun³, Daniel L. Erickson³, Karen Mancera-Cuevas⁴, Abel N. Kho³ and Rosalind Ramsey-Goldman⁵, ¹Center for Health Information Partnerships, Northwestern University, Chicago, IL, ²Department of Medicine, Division of General Internal Medicine and Geriatrics, Northwestern University, Chicago, IL, ³Northwestern University, Chicago, IL, ⁴Rheumatology, Northwestern University, Chicago, IL, ⁵FSM, Northwestern University, Chicago, IL

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic Lupus Erythematosus(SLE) is an autoimmune disease that can affect many parts of the body including skin, lungs, brain, heart, kidneys, joints, and blood vessels. How lupus looks in one patient is different than in another patient. Because of this, it is hard to diagnose a patient as having SLE. EHRs are widely used in healthcare settings and are a rich source of information about patients that can be mined for earlier diagnosis identification.

Methods: We identified 513 patients we knew had SLE from the Chicago Lupus Database (CLD) in the Northwestern Medicine Electronic Data Warehouse (NMEDW). We built an algorithm of SLICC classification criteria using ICD9/10 and labs to see if we are finding the same SLICC classification criteria that are in the CLD. According to SLICC classification rules, to have definite lupus you need at least 1 clinical criteria, at least 1 immunologic criteria, and a total of 4 or more criteria.

Results: As shown in Table 1, of 513 patients with SLE in the CLD, we detected the following SLICC classification criteria correctly in the NMEDW: clinical- chronic cutaneous 97%; acute cutaneous 98%;renal 65%; serositis 52%; arthritis 34%; neuro 29%; ulcers 16%; alopecia 3%;and labs - thrombocytopenia 99%; dsDNA 89%; hemolytic anemia 80%; complement 74%; leukopenia/ lymphopenia 73%; Anti-Sm Antibody 72%; Antiphospholipid Antibodies 64%; Antinuclear Antibody 60%; Coombs 17%; Of the 513 patients with SLE in the CLD, all had at least 1 clinical criteria, 469 had at least 1 immunologic criteria, and 498 had 4 or more criteria. Using EHR data from the NMEDW and rules for the SLICC classification criteria, we categorized 467/513(91%) patients as having definite lupus correctly.

Conclusion: Based the results, we are able to capture over 90% of patients in the NMEDW correctly. Future work includes implementing NLP on criteria like alopecia, oral ulcer, arthritis, and renal biopsy to improve identification of individual criteria in EHR data that ICD9/10 and labs missed. Once we develop an algorithm that is able to capture the same criteria in the NMEDW that are in the CLD, we can use that algorithm to identify patients that might have a missed diagnosis of lupus. If we are able to find patients who have lupus earlier in their disease progression, we can improve their quality of care and treat earlier with the goal of minimizing disease damage.

Table 1. SLICC Classification Criteria Identified in CLD and NMEDW

SLICC Criteria	Identified in CLD (N)	Identified in NMEDW (N)	Identified in CLD and NMEDW (%)
Clinical			
acute cutaneous	435	425	98%
Chronic cutaneous	146	141	97%
Renal	182	118	65%
Serositis	221	115	52%
Arthritis	472	161	34%
Neurological	205	59	29%
Oral ulcers	281	46	16%
Alopecia	96	3	3%

Table . (Cont'd)

SLICC Criteria	Identified in CLD (N)	Identified in NMEDW (N)	Identified in CLD and NMEDW (%)
LABORATORY			
Thrombocytopenia	454	453	100%
Anti-dsDNA Ab	348	310	89%
Hemolytic Anemia	5	4	80%
Complement	500	368	74%
Leukopenia/Lymphopenia	508	369	73%
Anti-Smith antibody	109	79	72%
Anti-phospholipid antibody	131	84	64%
Anti-nuclear antibody	433	259	60%
Coombs	12	2	17%

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Abstract Number: 1687

Systemic Lupus Flares Based on BILAG and Sledai Rules Are Inconsistent, but May be Better Understood Using Visual Analogue Scales

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Evaluation of lupus flares is inconsistent using glossary-based definitions for grading (1). BILAG 2004 rates flares by new/worse organ scores. The SELENA-SLEDAI flare index (SFI) combines treatment change, new/worse features, and a weighted physician's global assessment (SFI-PGA) visual analogue scale (VAS). A modified SFI (mSFI) improves accuracy by excluding medication criteria while clinicians differentiate mild from moderate flare (2). The Rapid Evaluation of Activity in Lupus (LFA-REALTM) expands the SFI-PGA and other earlier systems (3) for comprehensive VAS-based evaluation of individual symptoms, organs, or global disease. We compared mSFI and BILAG flares during a clinical trial, using SFI-PGA and LFA-REALTM to clarify their differences.

Methods: Disease activity (SLEDAI, BILAG 2004, mSFI, SFI-PGA, and LFA-REALTM) was rated monthly in a clinical trial. Severity of mSFI and BILAG flares was compared to SFI-PGA and LFA-REALTM changes by receiver operating characteristic (ROC) curve analysis.

Results: 50 SLE patients were examined at 430 monthly visit pairs. The mSFI defined 108 flares (73 mild, 34 moderate, 1 severe); BILAG only 77 (63 mild, 8 moderate, 6 severe) (Table 1). The mSFI rated 36 mild BILAG flares as mild and 26 as moderate. These were effectively discriminated by SFI-PGA or LFA-REALTM ($p < 0.001$). There were 34 moderate mSFI flares vs only 8 by BILAG (new/worse B in ≥ 2 organ domains). Also, mSFI flare was scored in 32 of 353 visit pairs with no BILAG flare (27 with mild flare in < 3 BILAG domains). Both SFI-PGA and LFA-REALTM captured flares by mSFI or BILAG (ROC analysis, $p < 0.0001$ for all). Mild vs moderate/severe mSFI flares were distinguished by SFI-PGA or LFA-REALTM. Only LFA-REALTM reflected mild vs moderate/severe flares by BILAG (Table 2).

Table 1. Flares by mSFI and BILAG 2004.

		mSFI flares				
		none	mild	moderate	severe	total
BILAG flares	none	321	32	0	0	353
	mild	1	36	26	0	63
	moderate	0	5	3	0	8
	severe	0	0	5	1	6
	total	322	73	34	1	430

Table 2 ROC analysis of changes in SFI-PGA and LFA-REAL™ in differentiating mild from moderate/severe flares by mSFI and BILAG 2004.

		mSFI	BILAG
Δ LFA-REAL™	AUC	0.7714	0.7466
	p value	<0.0001	0.0041
Δ SFI-PGA	AUC	0.8348	0.6587
	p value	<0.0001	0.0645

Conclusion: BILAG and mSFI flares are captured by changes in SFI-PGA or LFA-REAL™. BILAG flare thresholds are higher (mild flares require increase in 3 organs; moderate flares in a single organ default to mild). SFI compresses these into “mild-moderate”, which hinders clinically significant distinctions. The mSFI clinician’s discrimination of mild vs moderate/severe flare is supported by SFI-PGA or LFA-REAL™ changes. LFA-REAL™ can also distinguish mild vs moderate/severe BILAG flares, likely due to its expanded multisystem scale.

References: 1. Isenberg D, *et al.* Arthritis Care Res. 2018;70:98-103, 2. Thanou A, *et al.* Rheumatology 2014;53:2175-2181, 3. Petri M, *et al.* J Rheumatol.1992;19:53-9.

Disclosure: A. Thanou, None; A. Askanase, None; C. Arriens, AstraZeneca, 5; T. Aberle, None; S. Kamp, None; E. Chakravarty, None; J. A. James, None; J. T. Merrill, BMS, GSK, 2,BMS, GSK, UCB, Questcor, EMD Serono, Amgen, Celgene, Pfizer, RemeGen, Exagen, MedImmune, Lilly, Janssen, Xencor, Sanofi, Neovacs, Immunopharma, Astellas, Glenmark, ILToo, 5,Have given talks for BMS but not for Speaker’s bureau, 9.

Abstract Number: 1688

Changes in Heart Rate Variability Reflect Clinical Improvement and Flare in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Decreased heart rate variability (HRV) reflects autonomic dysfunction and inflammatory dysregulation and has been observed in SLE. We examined associations of HRV with clinical improvement and flare in patients with SLE participating in a clinical trial.

Methods: HRV was evaluated by a 5 minute electrocardiogram in SLE patients completing ≥2 visits in an ongoing investigator-initiated clinical trial of a targeted biologic. HRV parameters were calculated in the time (RMSSD, SDNN, pNN50) and frequency domains [high frequency (HF), low frequency (LF) and the LF/HF ratio]. Mixed effects linear models (adjusted for baseline HRV) with generalized estimating equations were used to compare changes in HRV between paired visits.

Results: Fifty-eight patients (age 46±11, 55 female) were followed in 505 consecutive visit pairs with complete data on HRV and disease activity available. Categorical improvement (≥1 letter grade improvement in BILAG A/B scores and no new BILAG A/B) occurred in 96 (19%) visit pairs and no improvement or worsening in 409 (81%). RMSSD, pNN50 and HF increased in improving vs. non-improving visit pairs [group differences: 26.1±13.3 (p=0.05), 3.9±1.8 (p=0.038) and 16.9±4.2 (p<0.0001), respectively] and the LF/HF ratio decreased (group difference: -2.1±1.0, p=0.032), suggesting a favorable change in sympathovagal balance (Table 1). There were 82 mild and 43 moderate/severe flares, assessed by a modification of the SELENA-SLEDAI flare index (mSFI) that excludes medication criteria and differentiates mild from moderate flares by physician’s global opinion (1). RMSSD, SDNN, pNN50 and HF decreased [group differences: -37.8±2.5 (p<0.0001), -63.4±31.8 (p=0.04), -10.8±2.1 (p<0.0001) and -69.1±1.8 (p<0.0001), respectively] and LH and LF/HF increased [group differences: 17.6±6.5 (p=0.007) and 5.3±1.9 (p=0.008)] in flaring compared to non-flaring visit pairs (Table 2). Moreover, SDNN, HF and LF/HF deteriorated [group differences: -23.8±5.1 (p<0.0001), -58.9±6.1 (p<0.0001) and 2.8±0.9, (p=0.002), respectively] in moderate/severe compared to mild mSFI flares.

Table 1. Average per visit changes in HRV in improving vs non-improving visit pairs.

Variable	Improving (n=96)	Non-improving (n=409)	P value
RMSSD	26.7±14.5	0.6±4.7	0.05
SDNN	21.6±14.7	0.4±3.4	0.09
pNN50	4.0±1.5	0.1±1.2	0.038
HF	18.8±3.8	1.9±1.7	<0.0001
LH	-0.4±2.6	1.3±1.9	0.72
LF/HF	-2.2±1.0	-0.1±0.2	0.032

Table 2. Average per visit changes in HRV in flaring vs non-flaring visit pairs.

Variable	Flare (n=125)	No Flare (n=380)	P value
RMSSD	1.9±3.5	39.7±4.7	<0.0001
SDNN	1.1±2.6	64.5±31.7	0.04
pNN50	0.1±1.2	10.9±1.7	<0.0001
HF	2.5±1.8	71.6±1.9	<0.0001
LF	0.6±1.9	-17.0±6.2	0.007
LF/HF	0.1±0.1	-5.2±1.9	0.008

Conclusion: Changes in HRV reflecting improved autonomic function correlate with clinical improvement and absence of flare in SLE. These data suggest that HRV may be a simple non-invasive tool to gauge transitions of SLE disease activity. The role of HRV parameters as targets for SLE therapy warrants further investigation.

References: 1. Thanou A, *et al.* Rheumatology 2014;53:2175-81.

Disclosure: A. Thanou, AliveCor, Inc., 5; S. Stavrakis, AliveCor, Inc., 5; S. Kamp, None; P. Kamp, None; T. Aberle, None; C. Arriens, None; E. Chakravarty, None; J. A. James, None; J. T. Merrill, None.

Abstract Number: 1689

Explaining the Discrepancy between Physician and Patient-Reported Measures of Disease Activity in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

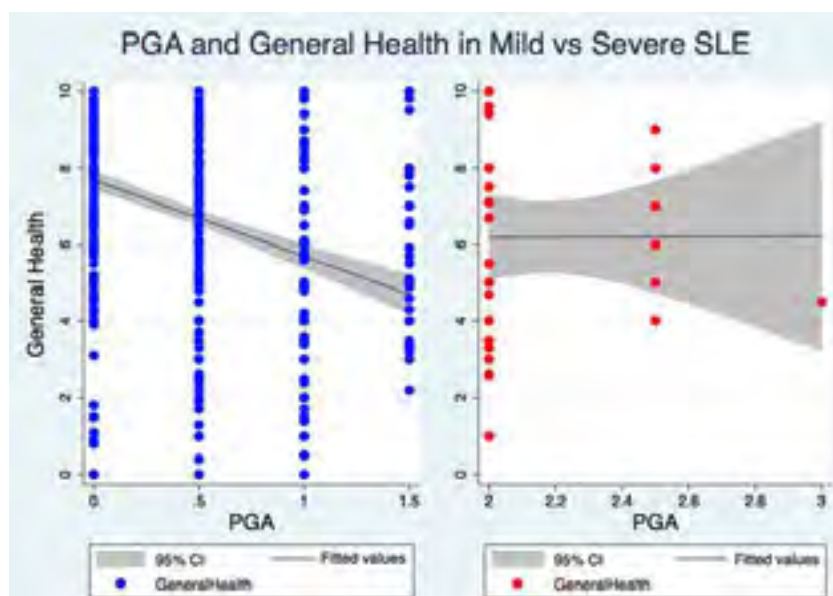
Session Time: 9:00AM-11:00AM Explaining the Discrepancy between Physician and Patient-Reported Measures of Disease Activity in Systemic Lupus Erythematosus

Background/Purpose: Patient-reported measures of disease activity provide useful adjuncts to physician-reported measures in identifying patients and pregnancies at greater risk for adverse outcomes. Comparatively little is known about the utility of these measures in SLE patients, and it is unclear how well these measures correspond to physician measures of disease, why they may differ, and if they work for the myriad presentations of SLE.

Methods: Data on patient-reported disease activity during pregnancy were collected on 178 patients with SLE enrolled in a prospective registry at a single academic center from 2008-2018. Physician assessment of disease activity was measured by physician global assessment (PGA) and compared to patient-reported measures in patients with SLE. The patient-reported measures used include domains of the SF-36, as well as visual analog scales assessing pain and general health. We used univariate and multivariable regression models to assess the strength of the relationship between patient and physician-reported measures of disease activity.

Results: Among 178 women with SLE, the mean age was 30 and 49% were black. There was a weak but significant correlation between measures of general health and PGA (R^2 SF-36=0.11; visual analog scale=0.09). However, this relationship was not consistent across all severity levels of SLE. In particular, in women with internal organ disease (PGA 2-3) there was no relationship between patient assessment of general health and PGA (R^2 =0.0). In contrast, those with less severe disease showed a stronger correlation between patient-reported measures and PGA (R^2 SF36=0.18, VAS=0.13). Pain was the most important variable correlating with patient-reported disease (R^2 = 0.5).

Conclusion: Patient-reported measures of disease activity such as general health appear to correlate with physician measures; however, this relationship only holds for those with lower levels of disease activity. For women with internal organ disease, patient self-assessment of health had no relationship with the physician assessment. In addition, our findings suggest that pain is one of the primary symptoms driving patients' health assessments. Our findings continue to show the need for the development of patient-reported measures that more accurately reflect lupus disease activity, particularly among those with the most dangerous manifestations of the disease.



Disclosure: N. J. Harris, None; A. M. Eudy, GSK, 9; M. E. B. Clowse, UCB Pharma, 5, Janssen, Pfizer, 2, 5, AbbVie, Bristol-Myers Squibb, 2.

Abstract Number: 1690

Increased Sensitivity Of The New (2017) And The 2012 SLICC As Compared To The Acr 1997 Classification Criteria In Early Systemic Lupus Erythematosus (SLE): The 2017 And 2012 Criteria May Classify Non-Overlapping Subgroups Of Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: SLE diagnosis can be challenging especially at the early stages, and existing classification criteria are biased towards classifying patients with long-standing disease. A joined ACR/EULAR initiative has introduced a new set of criteria (herein referred to as 2017 criteria), using positive ANA test as an entry criterion coupled with variably-weighted clinical and immunological criteria (Tedeschi et al., 2018). We compared the sensitivity of the 2017 criteria against the SLICC 2012 and ACR 1997 criteria in an early SLE cohort.

Methods: Consecutively registered patients aged ≥ 15 years diagnosed with SLE during 01/2012-12/2016 by an expert physician and followed-up for ≥ 6 months in the University Hospitals of Heraklion and "Attikon" (Athens). All sets of

criteria (ACR 1997, SLICC 2012, 2017) were applied at the time (\pm 3 months) of physician-based diagnosis and also at last follow-up. Cases were assessed for disease severity (according to the BILAG definitions and the use of lupus treatments) and the SLICC/ACR organ damage index.

Results: 341 patients were included [91.5% women, 98.8% Caucasian, mean (SD) age at diagnosis 42.1 (15.3) years] with mean disease duration 32.3 (SD 18.2) months. At the time of diagnosis, more patients were classified with the 2017 criteria (79.5%), followed by the SLICC (75.4%) and the ACR (67.2%) criteria. A total 39 patients (11.4%) met only the 2017 criteria and 25 patients (7.3%) met only the SLICC criteria. The former had increased frequency of fever, synovitis, anti-dsDNA or anti-Smith autoantibodies. In contrast, SLICC-only classified patients had increased rates of chronic cutaneous lupus, alopecia, mouth ulcers, haematological disease, anti-phospholipid antibodies and hypocomplementemia (**Table 1**). At last follow-up, the sensitivity of the 2017, SLICC and ACR criteria were 84.5%, 89.4% and 78.6%, respectively. Among 25 patients (7.3%) who were ANA negative, thus failing to meet the entry criterion, 23 scored above the threshold of ≥ 10 points in the 2017 criteria. Patients classified according to the 2017 criteria did not differ from SLICC-classified patients regarding disease severity (mild/moderate/severe: 46.5%/33.7%/19.8% vs. 46.2%/33.8%/20.0%, respectively) and organ damage.

Conclusion: Both the 2017 and the 2012 SLICC criteria are more sensitive than the ACR criteria in classifying early SLE. The new criteria enable the classification of more patients with synovitis and positive autoantibodies whereas the SLICC criteria have increased sensitivity for hematologic disease, suggesting that they may need to be combined to assure maximum capture of patients for clinical trials. The majority of ANA-negative patients scored above the 2017 classification threshold, suggesting that inclusion of ANA as an additional item (instead of entry criterion) could further enhance the sensitivity of the new SLE criteria at early stages.

Table 1 Prevalence of each manifestation included in the SLICC 2012 criteria and the 2017 criteria, in patients who fulfil only the SLICC or the 2017 criteria at the time of SLE diagnosis.

	Time of SLE diagnosis according to physician	
	Fulfilling only SLICC 2012 (%)	Fulfilling only 2017 criteria (%)
No of patients (%)	25 (7.3%)	39 (11.4%)
SLICC 2012 items		
acLE/scLE	72%	74.4%
cdcLE	24%	10.2%
Non-scarring alopecia	52%	20.5%
Mucosal ulcers	44%	7.7%
Synovitis	52%	94.9%
Serositis	8%	10.2%
Renal disorder	4%	2.6%
Neurologic disorder	4%	7.7%
Haemolytic anemia	12%	2.5%
Leukopenia	36%	25.6%
Thrombocytopenia	28%	12.8%
Anti-dsDNA	4%	15.4%
Anti-Smith	0	5.1%
aPL	20%	7.7%
Low complement	40%	17.9%
Coombs test	8%	2.5%
ANA	84%	100%
Biopsy-proven nephritis	4%	2.5%
2017 criteria items		
ANA (entry criterion)	84%	100%
Constitutional	4%	12.8%
Alopecia or ulcers	56%	23.1%
acLE	48%	74.3%
scLE or DLE	16%	7.7%
Synovitis	52%	94.9%
Delirium	0	0
Psychosis	0	0
Seizures	0	2.5%
Acute pericarditis	12%	2.5%
Serositis	0	5.1%
Leukopenia	20%	25.6%
Thrombocytopenia or hemolysis	32%	15.4%
Proteinuria	0	0
Class III or IV LN	0	2.5%
Class II or V LN	4%	0
aPL	20%	5.1%
Low C3 or low C4	24%	7.7%
Low C3 and low C4	16%	10.2%
Anti-dsDNA or anti-Smith	4%	20.5%

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Abstract Number: 1691

Application of the Doris Algorithm for the Definition of Disease Remission and Its Relation with Damage Accrual over a 2-Year Period in a Cohort of Italian Patients with Systemic Lupus Erythematosus Classified According to Clinical Disease Patterns

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic Lupus Erythematosus (SLE) is characterized by a fluctuating course. To achieve sustained remission is the ultimate goal of maintenance treatment. However the definition of remission is difficult in SLE. In 2014, an international Task Force named DORIS proposed four definitions of remission. The aim of this study was to evaluate the performance of the DORIS algorithm, to identify the frequency of remission as determined by DORIS for each clinical disease pattern, and to evaluate the impact of remission on damage accrual.

Methods: Monocentric retrospective study. Among all SLE patients followed at the Lupus Clinic between 2014 and 2017, we enrolled patients fulfilling the SLICC 2012 criteria who were visited at least once in 2017 and who had at least 5 biannual medical examinations in the previous 2 years. Definitions of remission according to DORIS and disease patterns are reported in Table 1. Damage accrual was measured by the SDI score¹.

Results: 101 SLE patients were enrolled for this study (94% female, mean age 45 years). 505 time-points were evaluated: 211 (42%) were defined as “remission” according to DORIS and in particular 181 (85.5%) were “remission on treatment”. 17.8% of patients were in remission in all the 5 time-points, vice versa 29.7% of patients never got into remission. 17.8% of patients have been in remission for 24 months, while 21.8% of patients less than 6 months. Mean duration of DORIS remission was 7.96 months. The most frequent disease patterns were RR (41,6%) and CQ (41,6%), while CA pattern was present in 16,8% of patients. DORIS remission was most frequently achieved in CQ pattern (65.2% of visits), less frequently in CA (5.9%). At the end of follow-up 50% of patients had a SDI \geq 1, and cumulative dosage of steroids was significantly associated to damage accrual (p:0.04 OR: 1.04 CI: 1.001-1.088). Moreover patients with at least one time-point in remission according to DORIS had a significantly lower damage accrual (p: 0.01) when compared to patients who never got into remission.

Conclusion: The DORIS algorithm is easy to be employed in clinical practice. In this cohort 30% of patients never achieved remission. Since damage accrual was associated with both cumulative dosage of steroids and unremitted disease, the goal in SLE management should be sustained remission with the lowest dose of steroids.

1) Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for systemic lupus erythematosus. *Arthritis Rheum.* 1996;39:363–369.

Table 1: Definition of Remission according to DORIS; Definition of disease pattern. PGA: Physician Global Assessment; cSLEDAI: clinical SLEDAI (without anti-dsDNA and C3/C4 levels)

Definition of Remission	Clinical Items			Treatment	
	cSLEDAI	PGA	Daily dose of prednisone	Antimalarials	Immunosuppressants/Biologics
Remission “off treatment”	= 0	< 0.5	0	yes	no
Remission “on treatment”	= 0	< 0.5	≤ 5 mg	yes	yes
No Remission	≠0	≥0.5	>5 mg	yes	yes
Definition of disease patterns					
Chronic active (CA)	Persistent disease activity over time with a cSLEDAI ≥1 in each visit for at least one year				
Relapsing-remitting (RR)	Characterised by periods of disease activity with cSLEDAI ≥1 interspersed with periods of disease inactivity with cSLEDAI = 0 in different visits for at least one year				
Clinically quiescent (CQ)	Defined as absence of disease activity with a cSLEDAI = 0 for at least one year				

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Abstract Number: 1692

Using ICD-10-CM Codes to Identify Patients with Systemic Lupus Erythematosus in the Electronic Health Record

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The electronic health record (EHR) serves as a powerful tool to enable researchers to collect a large cohort of patients across the healthcare system. To assemble these patients, algorithms are needed to identify these patients accurately. We have previously validated and published algorithms to identify systemic lupus erythematosus (SLE) subjects in the EHR using ICD-9 billing codes, labs, and keywords. Currently, there are no published algorithms using ICD-10-CM codes. We aimed to develop algorithms using ICD-10-CM codes and clinical data to identify SLE patients accurately in the EHR. **Methods:** We analyzed data from a de-identified version of Vanderbilt’s EHR that contains over 2.8 million subjects with longitudinal data. We identified 7399 potential SLE subjects with at least one count of the SLE ICD-9 (710.0) or ICD-10-CM (M32.1*,M32.8, or M32.9) codes. Of these subjects, we randomly selected 200 as a training set for chart review to identify true case status. A subject was defined as a case if diagnosed with SLE by a Vanderbilt or external rheumatologist, nephrologist, or dermatologist (specialist). We selected the following algorithm components based on clinical knowledge and available data: SLE ICD-10-CM codes, positive anti-nuclear antibody (ANA)(titer ≥ 1:160), and ever use of antimalarials. Positive predictive values (PPVs) and sensitivities were calculated for ICD-10-CM codes and combinations of the above algorithm components. Of the 200 subjects, 88 had ICD-10-CM codes with 13 missing clinic notes and excluded from the analysis. Ten subjects had unsure or “probable” SLE diagnoses by a specialist and were not counted as cases. **Results:** Table 1 provides the PPVs and sensitivities of the algorithms. PPVs were higher for algorithms using ICD-10-CM codes compared to those using the ICD-9 code. Algorithms that used only ICD-10-CM codes without clinical data had PPVs from 71 to 92%. When adding a positive ANA, PPVs slightly increased and ranged from 69 to 100%. PPVs also slightly increased with adding ever antimalarial use with PPVs from 76 to 95%. The algorithms with the highest PPVs of 100% were 1) ≥ 4 counts of the ICD-10-CM codes and ANA positive and 2) ≥ 4 counts of the ICD-10-CM codes and ANA positive or ever antimalarial use. **Conclusion:** Overall, the PPVs for algorithms using ICD-10-CM codes were higher compared to PPVs for ICD-9 codes. Adding clinical data to ICD-10-CM codes slightly improved the algorithms’ PPVs but may not be required. Since “probable” cases were treated as not cases, PPVs could be underestimated. ICD-10-CM codes can identify SLE cases accurately in the EHR. Studies are underway to investigate the performance of algorithms that combine both ICD-9 and ICD-10-CM codes with clinical data.

Table 1.

Algorithm	Positive Predictive Value	Sensitivity
ICD-9 codes only		
≥ 1 count of the ICD-9 code (710.0)	58%	100%
≥ 2 counts	69%	78%
≥ 3 counts	77%	67%
≥ 4 counts	79%	60%
ICD-10-CM codes only^a		
≥ 1 count of the ICD-10-CM codes	71%	76%
≥ 2 counts	85%	63%
≥ 3 counts	83%	54%
≥ 4 counts	92%	50%
ICD-10-CM codes AND ANA positive^b		
≥ 1 count of the ICD-10-CM codes AND ANA positive	69%	62%
≥ 2 counts	87%	55%
≥ 3 counts	89%	45%
≥ 4 counts	100%	45%
ICD-10-CM codes AND ever antimalarial use		
≥ 1 count of the ICD-10-CM codes AND ever antimalarial use	76%	70%
≥ 2 counts	90%	57%
≥ 3 counts	88%	50%
≥ 4 counts	95%	46%
ICD-10-CM codes AND ANA positive OR ever antimalarial use		
≥ 1 count of the ICD-10-CM codes AND ANA OR every antimalarial use	68%	72%
≥ 2 counts	86%	62%
≥ 3 counts	82%	48%
≥ 4 counts	100%	48%

a ICD-10-CM codes included M32.1*, M32.8, or M32.9

b Anti-nuclear antibody (ANA) positive (≥ 1:160)

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Abstract Number: 1693

Innate, Adaptive, and TNF-Superfamily Immune Pathways Inform a Lupus Disease Activity Immune Index That Characterizes Disease Activity in SLE

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune disease marked by immune dysregulation. A comprehensive but cost-effective tool to track relevant mediators of altered disease activity would help improve disease management and prevent organ damage. The goal of this study was to identify critical components of a practical biometric to distinguish active from low lupus disease activity

Methods: SLE-linked immune mediators and autoantibodies were evaluated in 311 plasma samples from 198 patients with classified SLE procured on dates of low clinical disease (SLEDAI < 4, range 0-3, n=132) or more active disease (SLEDAI ≥ 4, range 4-30, n=179) as well as healthy controls (HC) matched for race, sex, and age (n=48). Thirty two soluble mediators and SLE-associated autoantibody specificities, including dsDNA, chromatin, Ro/SSA, La/SSB, Sm, SmRNP, and RNP, were assessed by multiplex bead-based assay or sandwich ELISA (BLyS, APRIL, and TGF-β). Soluble mediator levels were compared across clinical disease activity levels in conjunction with the presence of autoantibodies.

Results: Patients with low or active disease were similar in age, ethnicity, and sex. After adjusting for multiple comparisons (Bonferroni corrected $p < 0.0018$), IL-6, IL-1α, IP-10, and IL-8 were significantly correlated with SLEDAI scores (Spearman $r = 0.179-0.253$), yet 22/32 soluble mediators significantly correlated with the number of SLE-associated

autoantibodies accrued, including those listed above, as well as SCF, IFN- α , IFN- γ , IL-17A, IL-10, MIG, MIP-1 β , TNFR1I, and BLyS ($r=0.318$ [IL-17A]-0.468 [IP-10]). The regulatory mediator IL-10 was highest in samples ($p<0.05$) from patients with low disease activity, while inflammatory mediators were highest in active disease samples with accrued autoantibody specificities ($p<0.001$). We integrated these findings to build a Lupus Disease Activity Immune Index (LDAII), calculated utilizing normalized (case vs. control) soluble mediator levels ($n=32$) weighted by the number of SLE-associated autoantibodies in each individual. The LDAII distinguished patients with clinically active (CA) vs. quiescent (CQ) disease who were either serologically (dsDNA binding and low complement) active (SA) or quiescent (SQ) ($p<0.0001$), whereby the number of accumulated autoantibodies ($p<0.0001$) as well as IL-6, IL-8, and IP-10 levels ($p\leq0.0006$) were most significantly altered. In addition, the LDAII was able to differentiate clinically and serologically quiescent (CQSQ) SLE patients vs. HC ($p=0.019$). Finally, the LDAII significantly correlated with SLEDAI scores in patients ($p<0.0001$) and identified patients with renal organ involvement ($p=0.002$), in whom SCF, TNFR1I, and MCP-1 were also most significantly altered ($p\leq0.005$).

Conclusion: Clinically meaningful components of immunological profiles may help illuminate disease pathogenesis, guide therapy, improve clinical trial design, and detect serious autoimmune disease with subtle presentation.

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Abstract Number: 1694

The Lupus Severity Index Accurately Identifies Patients with Severe SLE in a Multi-Ethnic Cohort

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

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Background/Purpose: The Lupus Severity Index (LSI)* was recently proposed to stratify patients by disease severity for clinical research. The LSI ranges from 0-10, is calculated using ACR classification criteria (ACRc) and demonstrated high predictive accuracy for severity anchored to major immunosuppressive drug use. We investigated the performance and characteristics of the LSI in a large multiethnic lupus cohort.

Methods: Patients from a single academic center were followed from 1990-2016 using a custom database. Records of all SLE patients were abstracted. Variables included birthdate, diagnosis date, self-reported ethnicity, ACRc, SLICC Damage Index (SDI), treatment and date of death. Ethnicity was categorized into White (WHI), Asian (ASN), Indigenous (IND), and Other. The LSI was calculated from ACRc, and compared between ethnic groups and demographic variables known to be associated with severe SLE using t-tests, ANOVA, Pearson correlation coefficient and logistic regression.

Results: Eight hundred thirty-two SLE patients were identified: 497 (60%) WHI; 220 (26%) IND; 91 (11%) ASN; 24(3%) Other. Mean age was 49 ± 16 years, mean disease duration 15 ± 11 years, 90% female, mean age at diagnosis 35 ± 15 ; 163 (20%) of patients had died. The mean LSI was 6.9 ± 1.7 , range 3.2-9.7. The distribution of the LSI was similar to that in the original dataset (Fig 1A) and the area under the ROC curve, measured against prescription of major immunosuppressive drugs, was 0.69 (95% CI 0.65-0.73). LSI was higher in males compared to females (7.3 ± 1.6 vs.

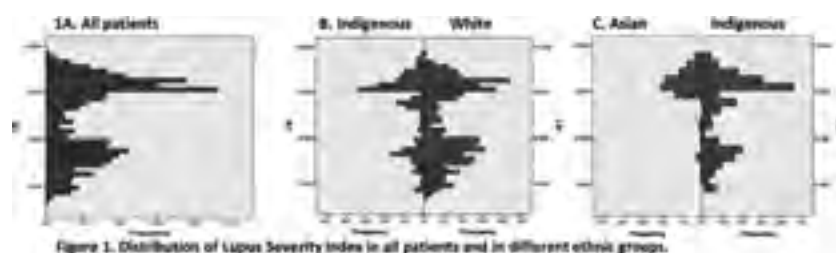


Figure 1. Distribution of Lupus Severity Index in all patients and in different ethnic groups.

6.9±1.7; p<0.019), and was negatively associated with onset age (Onset< 18 yrs LSI=7.8±1.3; 18-50 yrs LSI= 6.8±1.7; >50 yrs LSI=6.6±1.6; p<0.001). LSI correlated with SDI (Pearson 0.28, p<0.001), and was a predictor of accruing any damage (SDI>1) (OR 1.2 95% CI 1.1-1.3). LSI was higher in non-whites compared to whites: WHI LSI=6.6±1.7; IND LSI=7.2±1.6; Other LSI=7.3±1.3; ASN LSI 8.1±1.1; p<0.001). LSI was a predictor of early mortality (Death at age<50, or disease duration<10 years): OR 1.2; 95% CI 1.0-1.3). The distribution of the LSI varied by ethnic group with more uniformly severe disease in ASN patients (Figure 1 B,C) compared to WHI and IND.

Conclusion: Similar to the original publication, a higher LSI correlated with male sex, younger onset age, and non-white ethnicity; all groups shown to have more severe SLE. LSI was also a predictor of damage and early mortality. In addition we also found the distribution of LSI to differ between ethnicities. These findings confirm the utility of the LSI in stratifying patients by severity, and supports further exploration of the LSI to investigate contributors to severe SLE.

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Abstract Number: 1695

Differences between Early and Adult-Onset Systemic Lupus Erythematosus in Cohort of Argentinian Patients

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SESSION INFORMATION

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Background/Purpose: Approximately 20% of patients with Systemic Lupus Erythematosus (SLE) begin their illness in childhood or adolescence. These patients are described with a phenotype of greater severity. The aim of this study was to evaluate the prevalence of early onset SLE and the clinical and laboratory manifestations of these patients.

Methods: A total of 659 consecutive patients were included in one year. All met at least four diagnostic criteria from the American College of Rheumatology (ACR 82/97). Early-onset SLE was defined as disease diagnosed before 18 years of age and late onset or adult when age at diagnosis was ≥ 18 years. Criteria for diagnosis and damage were measured by

cumulative Systemic Lupus Collaborating Clinical Damage Index (SLICC-SDI). Disease activity was measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) at the time of entry into the study. SLEDAI ≥ 12 was considered as severe activity. Manifestations were compared between early and late-onset SLE patients. Statistical analysis for categorical variables was performed with chi-square test or Fisher exact test as appropriate and for continuous variables with Student t-test. Strength of association were obtained by odds ratio and 95% confidence interval (CI). Multivariate analysis was performed using early-onset Lupus as outcome variable.

Results: 82/659 (12.44 %) met criteria for early-onset SLE, 90% of these patients were women vs. 87% late onset ($p = 0.408$, OR: 1.38, 95% CI: 0.63-3.45). Mean age at diagnosis was 15 ± 2 (7-17) vs. 32 ± 11 years (18-76), with a median time of 134 ± 86 vs. 96 ± 92 months ($p = 0.00034$) at diagnosis. Mean number of classification criteria was 7 vs. 6 ($p = 0.016$), and for SLEDAI score was 2 (0-36) vs. 2 (0-73), $p = 0.955$. At the time of their inclusion in the study, they had severe activity: 18% vs. 8.5% ($p = 0.005$, OR: 2.41, 95% CI: 1.19-4.6). Mean SLICC score was 1.14 (0-8) vs. 1.02 (0-9), $p = 0.57$. Univariate analysis also showed that Malar erythema ($p: 0.014$), nephritis ($p: 0.010$), glomerulonephritis Class IV ($p: 0.0001$), CNS ($p: 0.019$), cataracts ($p: 0.019$) were statistically significant. In the multivariate analysis, there was a significant association with early onset-SLE mestizo ethnicity: OR: 1.65, 95% CI: 1.01-2.69, $p = 0.041$; Malar erythema: OR: 1.81, 95% CI: 1.009- 3.25, $p = 0.046$ and renal disease: OR: 1.86, 95% CI: 1.15-3.006, $p = 0.01$.

Conclusion: In this cohort of SLE patients, 12.4% were classified as early onset, with a mean age at diagnosis of 15 years (7-17). Multivariate analysis persisted as independent variables associated with early-onset Lupus, mestizo ethnicity, cutaneous involvement with malar erythema and nephropathy. Association with damage index was not significant.

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Abstract Number: 1696

Impact of Hurricane Maria on a Cohort of Systemic Lupus Erythematosus Patients from Puerto Rico

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: On September 20, 2017, Puerto Rico was devastated by Hurricane Maria causing severe damage to the Island infrastructure and essential services such as electricity, water supply, communications, and access to health care. Catastrophic natural disasters can have negative effects on the health and outcome of patients with chronic diseases. Thus, we sought to determine the impact on disease activity and patient-reported outcomes of health in a group of Puerto Ricans with SLE.

Methods: Hispanics from Puerto Rico participating in PROFILE, a longitudinal multiethnic cohort, were studied. Disease activity (per Systemic Lupus Erythematosus Activity Index [SLEDAI]) and patient-reported outcomes of health (per Short Form-36 [SF-36]) were examined before and after Hurricane Maria. SF-36 scores were transformed into a 0-100 scale in which higher scores represent better health. Patients seen between October 2017 and April 2018 were included in the analysis. SLEDAI and SF-36 scores were compared before and after Hurricane Maria using paired t test and Wilcoxon signed rank test, as appropriate.

Results: A total of 127 patients had their scheduled annual visits during the study period; 90 patients were seen, 15 missed their scheduled visit, 15 migrated to continental United States, 6 were unable to reach, and 1 died. Among patients seen at their study visits, 81 (90%) were women and the mean age was 45.3 ± 11.7 years. Forty-four percent had private healthcare

insurance, 39% had public insurance, 14% had Medicare, and 2% had no insurance coverage. No significant changes were seen for disease activity or overall SF-36 scores before and after Hurricane Maria. However, differences were observed for some mental and physical health components of the SF-36. Significantly lower scores were seen after Hurricane Maria in the mental health (60.2 ± 24.9 vs. 65.2 ± 22.6 , $p=0.011$) and bodily pain (43.6 ± 31.1 vs. 50.8 ± 30.8 , $p=0.011$) components when compared to the visit prior to the hurricane. Similarly, a tendency was observed for lower scores in the social functioning (59.4 ± 31.9 vs. 65.0 ± 29.0 , $p=0.051$) and role emotional (67.7 ± 29.3 vs. 73.1 ± 26.7 , $p=0.096$) components.

Conclusion: In this cohort of SLE patients from Puerto Rico, 71% were seen at their scheduled study visits after Hurricane Maria. Among these patients, worse patient-reported outcomes of health were seen for some mental and physical components of the SF-36. No differences were observed for disease activity. Nonetheless, longer follow up is needed to determine the long-term impact of Hurricane Maria on this cohort of SLE patients.

Disclosure: L. M. Vilá, None; Y. Berríos-López, None; C. Santiago-Burgos, None; L. González-Sepúlveda, None; I. Vázquez-Otero, None; E. Brown, None.

Abstract Number: 1697

Refractory Lupus Patients: How Frequent Do We See Them in the 21st Century?

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

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Session Time: 9:00AM-11:00AM

Background/Purpose: management of systemic lupus erythematosus (SLE) patients is challenging because of the heterogeneity of the disease. While treatment of renal nephritis is more standardized, treatment of non-renal refractory lupus remains controversial. Our objective was to identify non-renal non-neurologic refractory SLE patients in our cohort and described therapeutic behaviors in these patients.

Methods: All SLE patients (ACR and/or SLICC criteria) seen at a university based hospital between 2000 and 2017 were included and electronic medical records manually reviewed. Patients' characteristics, clinical manifestations and treatment patterns were recorded. Refractory lupus was defined as a patient with a SLEDAI score ≥ 6 (excluding renal and CNS manifestations) despite being on a stable treatment regimen for ≥ 30 days. Stable treatment could include prednisone alone (7.5 to 40 mg/d) or combined (0 to 40 mg/d) with antimalarial drugs and immunosuppressant therapies.

Results: A total of 257 lupus patients were included, 230 females (89.5%, 95% CI 85.1-92.7), mean age at diagnosis 29.9 years (SD 16.4). 211 patients (82.1%) fulfilled ACR criteria and 255 (99.2%) SLICC criteria. Type of clinical manifestations and treatments received during first year of disease, and cumulative are shown in table 1. After a median follow-up of 5.7 years (IQR 2.4-10.2), 16 patients (6.2%, 95% CI 3.8-9.9) met the refractory lupus criteria, with a median disease duration of 9.6 years (IQR 3.9-19.1). At that time, 87.5% of patients (95% CI 56.9-97.4) had low complement and 81.3 % (95% CI 51.4-94.7) had positive antiDNA antibodies. Main reasons for being refractory were mucocutaneous disease (50%, 95% CI 24.9-75.0) and arthritis (37.5%, 95% CI 16.1-65.2). Treatments received after being refractory were: corticosteroids > 20 mg/d of prednisone in 8 patients, mycophenolate in 1, rituximab in 5 and belimumab in 7, with optimal response in all of them (table 2). In a multivariate logistic regression analysis, only a younger age was associated with refractory disease (OR 0.93, 95% CI 0.87-0.99, $p=0.03$).

Conclusion: Despite receiving intensive treatments during follow-up (prednisone >20 mg/d in 73.5% of patients, antimalarial in 94.9% and immunosuppressant in 67.5%), 6.2% of patients met refractory criteria.

Table 1. SLE patients' clinical manifestations and treatments at first year and cumulative

	At first year of SLE(n=257)	Cumulative(n=257)
Acute cutaneous lupus (SLICC definition), n (% , 95% CI)	140 (54.7, 48.5-60.7)	160 (62.3, 56.1-68.1)
Chronic cutaneous lupus, n (% , 95% CI)	11 (4.3, 2.4-7.6)	15 (5.8, 3.5-9.5)
Oral/nasal ulcers, n (% , 95% CI)	57 (22.3, 17.5-27.8)	68 (26.5, 21.4-32.2)
Alopecia, n (% , 95% CI)	93 (36.3, 30.6-42.4)	122 (47.5, 41.4-53.6)
Arthralgia, n (% , 95% CI)	188 (73.4, 67.6-78.5)	205 (79.8, 74.4-84.3)
Arthritis, n (% , 95% CI)	133 (51.9, 45.8-58.1)	140 (54.5, 48.3-60.5)

Myositis, n (% ,95% CI)	2 (0.8, 0.2-3.1)	3 (1.2, 0.4-3.6)
Pleural effusion, n (% ,95% CI)	27 (10.6, 7.3-14.9)	33 (12.8, 9.2 -17.5)
Pericardial effusion, n (% ,95% CI)	34 (13.3, 9.6-18.1)	45 (17.5, 13.3-22.7)
Hemolytic anemia, n (% ,95% CI)	11 (4.3, 2.4-7.6)	13 (5.1, 2.9-8.5)
Leukopenia < 3000, n (95% , CI)	55 (21.5, 16.8-26.9)	73 (28.4, 23.2-34.3)
Thrombocytopenia < 100000, n (% ,95%CI)	30 (11.7, 8.3-16.3)	43 (16.7, 12.6-21.8)
Renal involvement, n (% ,95%CI)	110 (42.8, 36.8-48.9)	148 (57.6, 51.4-63.5)
Neurologic involvement, n (% , 95% CI)	15 (5.9, 3.5-9.5)	24 (9.3, 6.3-13.6)
SLEDAI >= 6, n (% , 95% CI)	171 (66.5, 60.5-72.1)	196 (76.3, 70.6-81.1)
Corticosteroids low dose, < prednisone 7.5 mg/d, n (% ,95% CI)	234 (91.1, 86.9-93.9)	241 (93.8, 90.1-96.2)
Corticosteroids dose > 20 mg/d prednisone, n (% , 95%CI)	152 (59.1, 52.9-65.1)	189 (73.5, 67.8-78.6)
Antimalarial, n (% , 95% CI)	210 (82.1, 76.8-86.3)	244 (94.9, 91.4 - 97.1)
Methotrexate, n (% , 95% CI)	18 (7.1, 4.5-10.9)	37 (14.4, 10.6 - 19.3)
Azathioprine, n (% , 95%CI)	36 (14.1, 10.3-18.9)	88 (34.2, 28.7-40.3)
Mycophenolate, n (% , 95%CI)	45 (17.6, 13.4-22.8)	111 (43.2, 37.2-49.3)
Cyclophosphamide, n (% , 95% CI)	57 (22.2, 17.5-27.7)	98 (38.1, 32.3-44.3)
Cyclosporine, n (% , 95% CI)	2 (0.8, 0.2-3.1)	7 (2.7, 1.3-5.6)
Rituximab, n (% , 95% CI)	3 (1.2, 0.4-3.6)	30 (11.7, 8.3- 16.2)
Belimumab, n (% , 95% CI)	0	7 (2.7, 1.3-5.6)
Other biologics, n (% , 95% CI)	0	1 (0.4, 0.1-2.7)
Any immunosuppressant, n (% , 95% CI)	127 (45.8, 40.0-51.8)	187 (67.5, 61.7-72.8)

Table 2. Refractory SLE Patients' characteristics

	Refractory patients (n=16)
Female, n (% ,95% CI)	15 (93.7, 64.7-99.2)
Median age at SLE diagnosis, years (IQR)	20.9 (19.5-25.7)
Median age at refractory disease, years (IQR)	35.7 (27.6-39.0)
Median disease duration at refractory time, years (IQR)	9.6 (3.9-19.1)
Median SLEDAI score at refractory time (RIC)	9.5 (8-11)
Clinical involvement at refractory time:	
Vasculitis , n (% , 95% CI)	2 (12.5, 2.6-43.0)
Mucocutaneous disease, n (% , 95% CI)	8 (50, 24.9-75.0)
Fever, (% , 95% CI)	2 (12.5, 2.6-43.0)
Low Complement levels, (% , 95% CI)	14 (87.5, 56.9-97.4)
DNA antibodies, (% , 95% CI)	13 (81.3, 51.4-94.7)
Arthritis, n (% , 95% CI)	6 (37.5, 16.1-65.2)
Miositis, n (% , 95% CI)	0
Pleural effusion, n (% , 95% CI)	1 (6.3, 0.7-39.3)
Pericardial effusion, n (% , 95% CI)	0
Hemolytic anemia, n (% , 95% CI)	0
Leukopenia < 3000, n (% , 95% CI)	3 (18.7, 5.3-48.6)
Thrombocytopenia < 100000, n (% , 95% CI)	2 (12.5, 2.6-43.0)
Renal involvement, n (% , 95% CI)	3 (18.7, 5.3-48.6)
Neurologic involvement, n (% , 95% CI)	0
Treatments received after being refractory:	
Corticosteroids, any dose, n (% , 95%CI)	11 (68.7, 40.1-87.8)
Prednisone dose (or equivalent) > 20 mg/d, n (% , 95% CI)	8 (50, 24.9-75.0)
Mycophenolate, n (% , 95% CI)	1 (6.3, 0.7-39.3)
Rituximab, n (% , 95% CI)	5 (31.2, 12.2-59.8)
Belimumab, n (% , 95% CI)	7 (43.7, 20.4- 70.2)

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Abstract Number: 1698

The Association between Periodontitis and the Disease Activity of Systemic Lupus Erythematosus: A Cross-Sectional Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Periodontitis is common disease. Recently, it is pointed out that periodontitis was associated with systemic disease. There were a few studies of assessing the relationship between periodontitis and the disease activity of systemic lupus erythematosus(SLE). However, it was unclear that there was evidence to support the relationship. Our hypothesis is that periodontitis is associated with the disease activity of SLE. This study aimed to assess the association between periodontitis and the disease activity of SLE.

Methods:

Design: A cross-sectional study.

Participants: SLE patients (according to the criteria revised in 1997 by the American College of Rheumatology) who diagnosed at Showa University Hospital, who were under 65-years-old and were collected from June 2016 to December 2016.

Exposure: Our main exposure was periodontitis assessed with pocket of depth, attachment loss by dentists. We divided a grade of periodontitis into four categories (Non-periodontitis, Mild periodontitis, Moderate periodontitis, Severe periodontitis) by Centers for Disease Control and Prevention – The American Academy of Periodontology (CDC-APP) definition.

Outcome measures: Main outcome was Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2000). Secondary outcome were anti-dsDNA antibody level, and complement level.

Statistical Analysis: In the main analysis, a multiple regression analysis using the score of SLEDAI-2000 as outcome was conducted to assess the association between periodontitis and the disease activity of SLE with adjustment for age, sex, current smoking status, current prednisolone(PSL) dose, the maximum dose of past PSL treatment and current immunosuppressant therapy. In the secondary analysis, a multiple regression analysis was conducted to analyze the association between periodontitis and the anti-dsDNA antibody level, complement level under the same conditions as above. In multivariable analysis, missing variables were replaced by multiple imputation.

Results: Among 119 SLE patients, mean age was 40.0 years, and 88.2% was female. The prevalence of periodontitis was 69% (1.7% in mild periodontitis, 58.8% in moderate periodontitis, 8.4% in severe periodontitis). Compared with non-periodontitis, the regression coefficients [95% Confident Interval] for SLEDAI of mild periodontitis, moderate periodontitis and severe periodontitis were -4.74 [-11.23 to 1.76], -1.07 [-2.99 to 0.83] and 0.54 [-4.08 to 3.01], respectively. In the secondary analysis, compared with non-periodontitis, the regression coefficients [95%CI] for SLEDAI of severe periodontitis for anti-dsDNA antibody titer was statistically significant (44.6 [7.3-81.9]).

Conclusion: This study demonstrated for the first time in Japan that the prevalence of periodontitis in SLE patients was remarkably high. Our data raise the important possibility that physicians pay attention to periodontitis in SLE practice. Our result did not provide a clear association between periodontitis and the disease activity of SLE. Further studies are needed to test our hypothesis in a longitudinal study in the future.

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Abstract Number: 1699

Autoantibodies to M-Phase Phosphoprotein I (MPP-1: KIF20B) in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: M-phase phosphoprotein (MPP-1), also termed kinesin interacting protein (KIF20B), is a 210 kDa protein that is highly expressed during cell division. Autoantibodies to MPP-1 were first described in approximately 25% of patients with idiopathic ataxia, but recent studies have indicated that they are also found in systemic lupus erythematosus (SLE). The goals of this study were to determine the frequency of anti-MPP-1 in a local SLE cohort and then identify demographic, clinical, and serologic correlations.

Methods: Patients fulfilling the American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for SLE were enrolled in a local cohort. Demographic, clinical information (disease activity – SLEDAI-2K; damage – SLICC/ACR DI), and sera were collected at time of enrollment. Antibodies to MPP-1 were determined by an addressable laser bead immunoassay (ALBIA) utilizing an *in vitro* expressed MPP-1 cDNA construct inserted into a GFP vector (Clontech Laboratories Inc., Saint-Germain-en-Laye, France). ALBIA results were expressed as median fluorescence units (MFU) and a dilution of greater than or equal to 1:500 MFU was considered highly positive. Univariable and multivariable analysis were performed to determine associations between the prevalence of high positive anti-MPP-1 and demographic (age, sex, race/ethnicity), clinical features (SLEDAI-2K and SLICC/ACR DI total scores and subscales and neurological subscale of the ACR and SLICC Classification Criteria), medications, and other autoantibodies (anti-dsDNA, extractable nuclear antigens, and anti-phospholipid antibodies).

Results: One hundred and fifty-six SLE patients were included; 89.8% were female with a mean age of 47.5 years (SD 15.8) and disease duration of 13.6 years (SD 11.8). The prevalence of high titre anti-MPP-1 was 14.1% (22/156). Univariable analysis demonstrated that high anti-MPP-1 positivity was associated with a higher total SLEDAI-2K score (Odds Ratio (OR), 1.1 [95% CI 1.0, 1.3]), particularly with the serositis (OR 2.7, [95% CI 1.3, 5.6]) and immunological SLEDAI-2K subscales (OR 1.9, [95% CI 1.3, 2.7]). High anti-MPP-1 positivity was also associated with anti-dsDNA (OR 4.7 [95% CI 1.7, 13.4]) and anti-phosphatidylserine/prothrombin complex (aPS/PT)-IgG (OR 3.2 [95% CI 1.1, 9.9]). In the multivariable analysis, only the serositis (OR 2.5, [95% CI 1.1, 5.7]) and immunological SLEDAI-2K subscales (OR 1.9, [95% CI 1.3, 2.7]) were independently associated with anti-MPP-1 positivity.

Conclusion: High titer anti-MPP-1 antibodies were relatively common in this SLE cohort (14.1%) and may be associated with greater clinical and serologic SLE disease activity. A larger study is currently underway to more clearly delineate its role as a biomarker in SLE.

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Abstract Number: 1700

Remission and Low Disease Activity State Prevent Hospitalizations and Emergency Room Visits in Systemic Lupus Erythematosus Patients

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SESSION INFORMATION

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Session Type: ACR Poster Session B

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Background/Purpose: Although the survival rate of patients with Systemic Lupus Erythematosus (SLE) has improved over the years, patients are frequently hospitalized or evaluated in the Emergency Room; these events account for most of the direct cost of these patients' care. The objective of this study was to determine whether remission and low disease activity state (LDAS) are protective of hospitalizations and Emergency Room visits in our SLE patients.

Methods: All hospitalizations and Emergency Room visits of Peruvian SLE patients members of a single center cohort were identified during the two-years following their baseline visit. We used the baseline data (at cohort entry) to determine which factors were associated with hospitalizations and Emergency Room visits in these patients. Remission was defined as a SLEDAI-2K=0, prednisone ≤ 5 mg/d and immunosuppressants on maintenance dose, LDAS was defined as not on remission and a SLEDAI-2K ≤ 4 , prednisone ≤ 7.5 mg/d and immunosuppressants on maintenance dose; antimalarials were allowed in both groups(1). Univariable and multivariable Poisson regression models were used to determine the impact of being on remission or LDAS on the risk of hospitalization and Emergency Room visits, adjusting for gender, age at diagnosis, socioeconomic status, disease duration, damage, comorbidities, time of exposure to prednisone and antimalarial use.

Results: Of the 314 cohort patients, 92.7% (n = 291) were female, the median age of the patients was 40.7 (32.9-51.1) years, with a disease duration of 5.5 (2.6-10.3) years. Fifty-nine of the patients included were hospitalized, a total of 165 times (range 2.8 per patient). In the multivariable analysis we found that remission [RR 0.036 (0.005-0.259), p=0.001] and LDAS [RR 0.289 (0.182-0.457), <p=0.001] at baseline decrease the risk of hospitalization in SLE patients. Similarly, remission [RR: 0.019 (CI95%: 0.107-0.815), p=0.019] and LDAS [RR=0.383 (CI95%: 0.222-0.661), p=0.001] decrease the risk of Emergency Room visits. One hundred- thirty-five of the 165 hospitalizations presented a defined cause, being disease activity the most common cause of hospitalization with 73 admissions (54.1%); within them, renal disease was the leading cause, with 37 admissions (50.7%).

Conclusion: Remission and LDAS decrease the risk of hospitalizations and Emergency Room visits in SLE patients. Disease activity was the most frequent cause of hospitalization and within them, renal disease. These findings have economic implications for the health care system.

Reference:: 1. Ugarte-Gil MF, Wojdyla D, Pons-Estel GJ, Catoggio LJ, Drenkard C, Sarano J, et al. Remission and Low Disease Activity Status (LDAS) protect lupus patients from damage occurrence: data from a multiethnic, multinational Latin American Lupus Cohort (GLADEL). *Ann Rheum Dis.* 2017 Dec;76(12):2071-2074

Disclosure: C. Reategui-Sokolova, None; R. Gamboa-Cárdenas, None; M. Medina-Chinchon, None; F. Zevallos, None; C. Elera-Fitzcarrald, None; V. R. Pimentel-Quiroz, None; M. Cucho-Venegas, None; Z. Rodriguez-Bellido, None; C. A. Pastor-Asurza, None; R. Perich-Campos, None; G. S. Alarcón, None; M. Ugarte-Gil, None.

Abstract Number: 1701

Lupus Low Disease Activity State: Predicting Organ Damage Accrual and Cardiovascular Risk in Patients with Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a heterogeneous disease that can cause multisystem inflammation and damage. There are currently no widely agreed upon targets for determining adequate disease control. Lupus Low Disease Activity State (LLDAS) is a new clinical evaluation tool that assesses low disease activity state in lupus patients (Franklyn, et al. *Ann Rheum Dis.* 2016; 75: 1615-1621). Our study examines the relationship between the percentage of time patients spend in LLDAS and organ damage accrual, cardiovascular events, and death.

Methods: We studied a prospective longitudinal cohort of 246 patients with SLE during a 5-year follow-up period. Disease activity was measured using the SLE Disease Activity Index 2000 (SLEDAI-2K) and SELENA-SLEDAI physician global

assessment (PGA). Cumulative organ damage was assessed at 1-year, 3-year, and 5-year intervals using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). The determination of LLDAS $\geq 50\%$ of the time (LLDAS-50) was done retrospectively through clinical chart review. The following criteria for LLDAS included: (SLEDAI)-2K ≤ 4 without major organ activity, no new disease activity, PGA ≤ 1 (scale 0–3), ≤ 7.5 mg/day and stable dose of maintenance treatments. The longitudinal presence of carotid plaque and intima-media thickness (IMT) was measured at baseline and follow-up three years later. We determined the relationships between LLDAS, SDI, IMT, carotid plaque, and PREDICTS profile using multivariate regression analysis. T-tests were used for analysis of continuous variables and chi-squared for parametric variables.

Results: The average age was 42.8 years for patients in LLDAS-50 and 39.5 years for those not in LLDAS-50 ($p = 0.048$). Patients in LLDAS-50 or higher during the year after cohort entry had a mean SDI score of 1.5 (± 1.8) at 1 year, a mean SDI of 1.6 (± 1.9) at 3 years, and 1.9 (± 2.1) at 5 years after cohort entry. On average, patients who were in LLDAS-50 during the first year after cohort entry had lower SDI scores at 3 years and 5 years than patients who were not, reaching near significance ($p = 0.06$) for both.

There was no significant difference in measured IMT or plaque at baseline or at 3- or 5-year follow-up between patients in LLDAS-50 and those not in LLDAS-50 for the first year after baseline. However, patients in LLDAS-50 were significantly less likely to have major cardiac events (major stroke, myocardial infarction, positive stress test, angioplasty or percutaneous coronary intervention) or death compared with patients who were not in LLDAS-50, 20.7% and 38.2%, respectively ($p = 0.02$).

Conclusion: We assessed SLE patients in LLDAS from our cohort of 246 patients. With regard to damage progression, there was near significantly less damage among those in LLDAS 50% of the time during the first year after cohort entry. Interestingly, although there were no differences between IMT, presence of carotid plaque, or plaque progression at any of the three time points, there was a statistically significant difference in number of cardiovascular events or death in the LLDAS-50 group. This supports LLDAS as a valid predictor of lower overall and cardiovascular damage in SLE patients.

Disclosure: R. Tesfamichael, None; H. Lam, None; O. Lu, None; R. Kapadia, None; C. Siegel, None; L. Sahakian, None; J. M. Grossman, None; M. A. McMahon, None.

Abstract Number: 1702

Utility of the Avise Connective Tissue Disease Test in Predicting Lupus Diagnosis and Progression of Disease

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The AVISE Connective Tissue Disease test is a newly approved, commercially available test that combines autoantibody and biomarker levels to help diagnose systemic lupus erythematosus (SLE) and other connective tissue diseases. However, few studies have examined whether AVISE can predict future clinical diagnosis and outcomes in a real-world cohort. We evaluated the utility of AVISE in predicting SLE diagnosis and damage progression.

Methods: This longitudinal observational study enrolled patients of a single adult rheumatologist who underwent AVISE testing between April 1, 2014 and April 30, 2016. A \odot positive \odot AVISE test for SLE was defined as positive or moderate-positive scores. \odot Non-positive \odot tests were defined as negative, moderate negative, equivocal, or indeterminate scores. SLE diagnosis was confirmed using SLICC/ACR classification criteria. Damage was evaluated using SLICC/ACR damage index (SDI) at baseline ($t=0$) and two years ($t=2$) after AVISE testing. Statistical analyses were performed using SPSS.

Results: The cohort consisted of 77 women and 6 men; 7 patients had long-established SLE at $t=0$. Among the remaining 76 patients, the most common confirmed diagnoses in those with a positive test was SLE, followed by UCTD and RA, at both $t=0$ and $t=2$ (Table 1). Among those without established SLE at $t=0$, 53% of patients with a positive test vs. 25% in those with a negative test ($p=0.04$) had an SLE diagnosis at $t=2$.

There was a significant difference in the number of SLICC clinical and immunologic diagnostic criteria fulfilled at t=0 and t=2 by patients with a positive vs. a non-positive AVISE test (Table 2). There was also a significant difference in SDI between positive and non-positive patients, with positive patients having higher SDI at t=2 (Table 2). Among the individual AVISE result biomarkers, BC4d levels significantly correlated with the number of clinical SLE classification criteria at t=0 ($r=0.24$, $p=0.02$) and the SDI at t=0 ($r=.28$, $p=0.01$) and t=2 ($r=0.34$, $p=0.002$), yet EC4d and dsDNA levels did not.

Conclusion: AVISE CTD test results are predictive of eventual rheumatologic diagnosis, and BC4d levels are predictive of both SLICC/ACR classification criteria fulfillment and SDI in SLE patients. These data suggest that AVISE may be useful in standard rheumatologic care for establishing a SLE diagnosis and identifying patients at higher risk for adverse clinical outcomes.

Table 1 Suspected diagnoses at t=0 and t=2 in those without an established SLE diagnosis at baseline.

	AVISE Neg (n=63)		AVISE Pos (n=13)	
	t=0	t=2 years	t=0	t=2 years
SLE	0%	9.5%	0%	53.8%
RA	15.9%	23.8%	7.7%	15.3%
UCTD	31.7%	30.1%	38.4%	15.3%
Other autoimmune	27%	23.8%	15.3%	7.7%
Non-inflammatory (OA)	7.9%	4.8%	15.3%	7.7%
Fibromyalgia without connective tissue disease	9.5%	6.3%	7.7%	0%
Discoid lupus without SLE	1.6%	1.6%	0	0%
Unclear Dx	6.3%	0	15.3%	0%

Table 2 Differences in mean SDI and number of SLICC lupus classification criteria met at t=0 and t=2 years between AVISE result groups

AVISE test results	Negative, equivocal, or indeterminate (n=66)	Positive or moderately positive (n=17)	p= (Student's t-test)
SLICC/ACR criteria met t=0	2.0 ± 1.4	3.6 ± 1.9	0.004
SLICC/ACR criteria met t=2	2.3 ± 1.4	3.7 ± 1.9	0.01
SDI t=0	0.8 ± 1.3	1.5 ± 1.6	0.06
SDI t=2 years	1.0 ± 1.4	2.0 ± 1.4	0.02

Disclosure: E. Liang, None; M. Taylor, Celgene Corporation, 8, AbbVie Inc., 8; M. A. McMahon, None.

Abstract Number: 1703

Fragmented Qrs in Patients with Systemic Lupus Erythematosus: Relation to the Disease Activity: A Cross-Sectional Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Cardiovascular disease is an important contributor to mortality in Systemic Lupus Erythematosus (SLE). It has been reported that disease activity at diagnosis was associated with the occurrence of myocarditis and coronary artery disease (CAD) in SLE. Fragmented QRS (fQRS) is a convenient marker of myocardial scar by electrocardiogram (ECG) defined as additional spikes within the QRS complex. FQRS is useful for identification of myocardial scars such as CAD and cardiac sarcoidosis, and for identifying high-risk patients of various cardiac diseases. It has reported that the prevalence of fQRS in a patient with SLE appears to be higher than that in controls. However, no clinical studies have investigated the prevalence at the time of diagnosis. In addition, there is no report that examined the association of disease activity of SLE and fQRS. In this study, we aimed to assess the relationship between disease activity of SLE and fQRS in SLE patients at the time of diagnosis. We hypothesized that the frequency of fQRS on ECGs would be higher in SLE patients with high disease activity.

Methods: The study design was a cross-sectional study. The participants were SLE patients who diagnosed at Showa University Hospital and Showa University Koto Toyosu Hospital from January 2010 to December 2017. The participants who satisfied American College of Rheumatology criteria were included. The patients with cardiac disease, other

rheumatic diseases, and already treatment at the time of an ECG measurement were excluded. The exposure was the appearance of fQRS. All ECGs were evaluated by two experienced cardiologist blinded for patient characteristics. The primary outcome was Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K). The secondary outcomes were the complement level and the anti-dsDNA antibody level. In the main analysis, a multiple regression analysis was conducted to assess the association between fQRS and SLE activity adjusted for age, sex and period from the estimated date of onset to the date of diagnosis. In the secondary analysis, a multiple regression analysis was conducted to analysis the association between fQRS and the serological activity of SLE (the complement level, the anti-dsDNA antibody level) under the same conditions as above. Interobserver variabilities were assessed using Cohen's kappa coefficient.

Results: In total, 45 participants were enrolled. The mean age was 42.3 years, and 37 (82%) were female. The median SLEDAI-2K was 14 [IQR, 10 to 20]. The median period from the estimated date of onset to the date of diagnosis was 3 months [IQR, 2 to 14.5]. 25 patients (56%) had fQRS. In the main analysis, the regression coefficients [95%CI] of fQRS for SLEDAI were 2.99 [1.15 to 4.84, $p=0.002$] with reference to non-fQRS. In the secondary analysis, there were no significant associations between fQRS and the blood test. There was a good agreement between two blinded experienced cardiologists reading of fQRS. There was a 91.1% consensus ($\kappa=0.81$, 95% CI 0.63 to 0.98, $p<0.001$).

Conclusion: Our results demonstrated that fQRS positive SLE patients tended to have high disease activity. It was suggested that fQRS could be expressed by myocardial scar in SLE cases with high disease activity.

Disclosure: M. Hosonuma, None; N. Yajima, None; R. Yanai, None; R. Takahashi, None.

Abstract Number: 1704

Clinical SLE Disease Activity Index Score of Zero May be a More Pragmatic Outcome Measure in SLE Studies

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SESSION INFORMATION

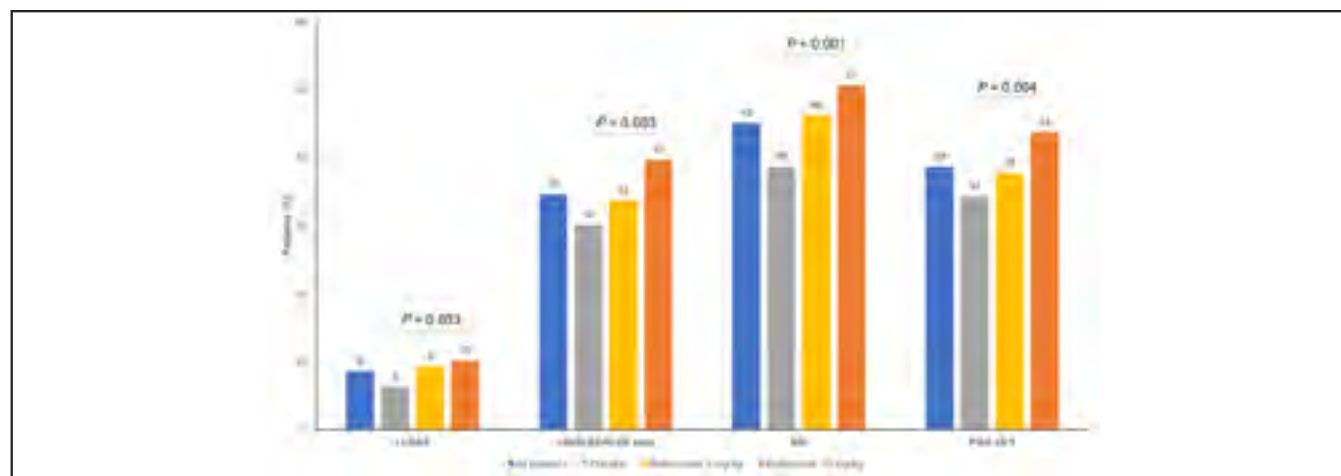
Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Drug development in systemic lupus erythematosus (SLE) has been challenging. One of the reasons can be traced in the choice of outcome measures. In the clinical trials of belimumab, the primary endpoint was the SLE responder index (SRI) at week 52. In the present analysis, we investigated the frequency of the Lupus Low Disease Activity State (LLDAS) and a clinical SLE disease activity index 2000 (clinSLEDAI-2K) score of zero in relation to SRI.



Methods: A total of 1684 patients with SLE from the BLISS-52 (n=865) and BLISS-76 (n=819) trials were analysed. Data were accessed through a data sharing agreement with GSK. The clinician-based evaluation was defined as a Physician Global Assessment (PGA) score <0.5 in a 3-point scale, one of the conditions in the recently developed Definitions of Remission in SLE (DORIS), and was used for comparative purposes. For correlations, we used the Pearson correlation coefficient. For comparisons, we used the chi-square test.

Results: At week 52, the LLDAS definition was met in 8.6% of the patients (n=1332), and 34.5% had aclinSLEDAI-2K score of zero (n=1332). According to data from the initial studies, 45.1% were SRI responders at week 52 (n=1684). Among the three measures, clinSLEDAI-2K zero showed the strongest correlation with PGA <0.5 (r=0.36, P<0.001), whereas the correlations with SRI (r=0.25, P<0.001) and LLDAS (r=0.21, P<0.001) were more moderate. Comparing the placebo and 10mg/kg belimumab treatment arms, SRI performed best at revealing the superiority of belimumab to placebo (P<0.001), followed by clinSLEDAI-2K zero (P=0.003), PGA <0.5 (P=0.004), and LLDAS (P=0.033) (Figure).

Conclusion: LLDAS appears to be a stringent outcome measure, being met by only 8.6% of the patients. AclinSLEDAI-2K score of zero showed the best correlation with the clinician-based evaluation. Since it is only based on one index (SLEDAI-2K), clinSLEDAI zero may be considered a more pragmatic outcome measure compared to SRI and LLDAS for use in SLE studies and clinical trials.

Disclosure: I. Parodis, None; S. Emamikia, None; I. Gunnarsson, None; R. F. van Vollenhoven, Amgen, Abbvie, BMS, Biotest, Crescendo, GSK, Janssen, Lilly, Merck, Pfizer, Roche, UCB, Vertex, 5; K. Chatzidionysiou, None.

Abstract Number: 1705

Trajectory Analysis of Combined Disease Activity and Physical Component Summary Scale in an Inception Cohort of Adults with Systemic Lupus Erythematosus: Latent Classes Inform Different Patterns

William Fung¹, Lily Lim², George A. Tomlinson³, Lisa Engel⁴, Jiandong Su⁴ and Zahi Touma⁴, ¹Medicine, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, ²Hospital for Sick Children, Toronto, ON, Canada, ³Medicine, Mount Sinai Hospital, Toronto, ON, Canada, ⁴University of Toronto, Toronto Western Hospital, Toronto, ON, Canada

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

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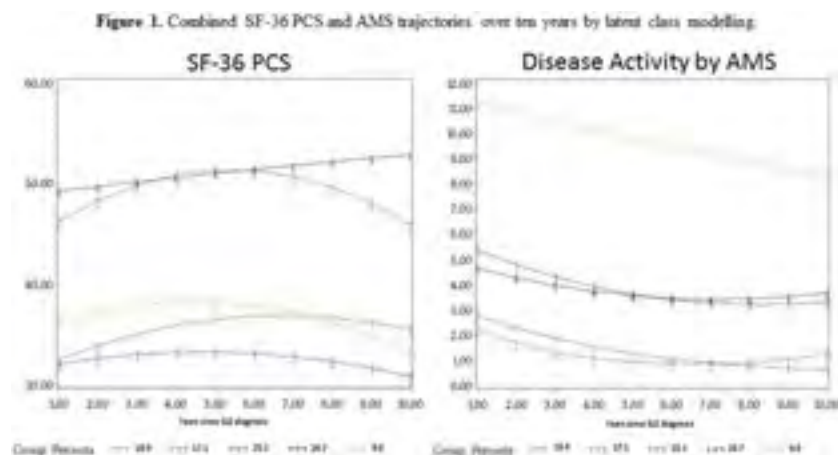
Background/Purpose: For patients with SLE, disease status, physical functioning, and participation in daily activities affect health-related quality of life. This study aims to: 1) describe physical functioning and disease activity trajectories over time; 2) determine latent classes of different physical functioning and disease activity trajectory combinations; 3) identify membership predictors of these latent classes.

Methods: This retrospective longitudinal study used single centre inception adult patient data. Physical functioning was measured using patient-reported annual Medical Outcomes Study Short Form 36 (SF-36). Only the physical component summary (PCS) scale was used. Patients with ≥ 2 SF-36 questionnaires, within the first 2 years of diagnosis, were studied. Disease activity was measured by adjusted mean SLEDAI-2K (AMS) for the year, measured annually. Latent class trajectory modelling was used to combine PCS and AMS trajectories. Models with 2-6 classes were examined. The best model was determined by a combination of clinical and statistical interpretability. The nature of the different classes was explored by examining for annual distribution of clinical features, damage (SDI), cumulative glucocorticoid (GC) dose, and fibromyalgia presence.

Results: Out of 826 inception patients, 222 were analyzed. Data up to 10 years after diagnosis was examined. Mean age at SLE diagnosis was 35.5 ± 13.2 years. 5 latent classes was the best fit (Figure 1). The 5 classes are: 1) low PCS, very low disease activity (18.9%); 2) high PCS, very low disease activity (17.1%); 3) very low PCS, moderate disease activity (25.3%); 4) high PCS, moderate disease activity (29.7%); and 5) low PCS, high disease activity (9%). More patients in classes 1 and 3 (low to very low PCS) had fibromyalgia than other classes, suggesting this affected their PCS rather than disease activity. Although less class 5 patients had fibromyalgia, more still had this compared to those in classes 2 and 4 patients. Class 1 had more activity in CNS and skin systems, more damage, and higher cumulative GC dose (30.2 ± 8.2 vs 20.7 ± 8.7 grams) compared to class 2. Class 3 had more activity in skin and musculoskeletal systems, more damage, and more GCs

(38.0 ± 17.9 vs 29.2 ± 11.5 grams) compared to class 4. Class 5 had significant vasculitis and renal involvement, damage, and the highest cumulative dose of GCs.

Conclusion: There are 5 distinct classes of combined physical component summary scale and disease activity. PCS trajectories seemed more related to the presence of fibromyalgia, except in those with the most severe disease (vasculitis and renal). Identification of comorbid fibromyalgia and targeted supportive measures may help improve the physical component summary scale of 44% (class 1+ 3) of SLE adults.



Disclosure: W. Fung, None; L. Lim, None; G. A. Tomlinson, None; L. Engel, None; J. Su, None; Z. Touma, None.

Abstract Number: 1706

Development of an Online Lupus Self-Management Program Based on the Transtheoretical Model of Change

Sarah Gilman¹, Deborah Levesque², Carol Cummins², Daniel J. Wallace³, Victoria P. Werth^{4,5}, Rosalind Ramsey-Goldman⁶, Margaret Kaniewski⁷ and Patricia Davidson⁸, ¹Wayfinder Health Strategies, Falls Church, VA, ²ProChange Behavior Systems Inc., West Kingston, RI, ³Division of Rheumatology, Cedars Sinai Medical Center, Los Angeles, CA, ⁴Philadelphia Veterans Affairs Medical Center, Philadelphia, PA, ⁵University of Pennsylvania, Philadelphia, PA, ⁶FSM, Northwestern University, Chicago, IL, ⁷Centers for Disease Control & Prevention, Atlanta, GA, ⁸Lupus Foundation of America, Washington, DC

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The Lupus Foundation of America is in Year 3 of a 5-year cooperative agreement with the Centers for Disease Control and Prevention to develop an online self-management program for individuals newly diagnosed with lupus. This presentation will summarize 1) formative research to identify the key self-management behaviors that will be the focus of the program, and 2) initial steps in the application of the Transtheoretical Model of Change (TTM) to those key behaviors. Meeting the needs of individuals with lupus requires an intervention designed to promote behavior change for those who are not ready, getting ready, and ready to manage their condition. The TTM provides an evidence-based framework for matching interventions to stage of change--Precontemplation, Contemplation, Preparation, Action and Maintenance.

Methods: Two literature reviews and a landscape analysis were completed with the goal of identifying and classifying: 1) the top needs of individuals with lupus (particularly those of minorities); and 2) key self-management strategies that best meet those needs. Next, based on findings from the literature review and landscape analysis, draft operational definitions of those key behaviors were developed. In a series of interviews, the definitions were reviewed and refined by four cultural experts—three of whom had expertise on lupus--and three lupus subject matter experts. Upcoming activities will include nine interviews with individuals with lupus. The first step in applying the TTM to those behaviors is to develop and validate measures of stage of change for each behavior. Stage measures begin with an operational definition of the target

behavior, and then ask questions about current behavior and intentions, using simple decision rules to assign individuals to stages. This summer, an online survey will be administered to 150 individuals with lupus to validate the stage of change measures. Analyses will examine the degree to which stage of change for each behavior is related, as predicted, to measures of lupus self-management and well-being.

Results: Four key self-management behaviors have been identified: 1) communicating with one's health care team; 2) managing medications; 3) managing symptoms of lupus; and 4) managing stress and distress related to lupus. Operational definitions for each are being finalized. The online survey described above will examine the degree to which stage of change measures for each behavior relate to well-being and other indicators of effective lupus self-management.

Conclusion: Meeting the needs of individuals with lupus requires an intervention matched to readiness to engage in key behaviors for lupus self-management. This is particularly important given the waxing and waning of lupus symptoms, and the heterogeneity of the disease in terms of severity and manifestations. The relationships between stage of change and the program's behavior change constructs provide an evidence-based framework for developing and delivering tailored feedback that may be more likely to be considered relevant, credible and memorable and to lead behavior change among people with lupus.

Disclosure: S. Gilman, Program Consultant to the Lupus Foundation of America, 5; D. Levesque, Contractor to Lupus Foundation of America, 5; C. Cummins, Contractor to Lupus Foundation of America, 5; D. J. Wallace, Program Advisor to Lupus Foundation of America, 5; V. P. Werth, Program Advisor to Lupus Foundation of America, 6; R. Ramsey-Goldman, Consultant to Centers for Disease Control and Prevention, 5; M. Kaniewski, Project Officer for a collaborative agreement between the LFA and CDC, 3; P. Davidson, Lupus Foundation of America, 3.

Abstract Number: 1707

Prolactin and Dehydroepiandrosterone Sulfate in Women with Active Systemic Lupus Erythematosus of Recent Onset Versus Chronic Inactive Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Prolactin has a role in pathogenesis of Systemic Lupus Erythematosus (SLE); high levels have been associated with activity. In contrast, a decrease in dehydroepiandrosterone sulfate (DHEAS) has been observed with low disease activity.

Objective: To evaluate serum PRL levels and DHEAS levels in patients with active SLE of recent onset vs patients with inactive chronic and healthy controls and their correlation with activity and chronicity scores.

Methods: Serum PRL levels and DHEAS levels were studied, as well as their correlation with SLEDAI and SLICC scores. Group 1: 15 patients with SLE of recent onset (active SLEDAI >3) Group 2: 20 patients with inactive chronic SLE (SLEDAI<3) and Group 3: 20 healthy controls. SLEDAI and SLICC were calculated in group 1 and group 2 respectively. PRL and DHEAS was measurement by radioimmunoassay in all groups. Statistical analysis: U-Mann Whitney and Spearman correlation.

Results: Group 1: serum PRL levels were 27.82±9.96 ng/dl vs group 2: 20±5.02 ng/dl (p= 0.004) and group 3:19.58±4.57 ng/dl (p=0.004). Group 1: serum DHEAS levels were 14.58±9.26 µg/dl, group 2: 19.36±7.21 µg/dl (p=0.04) and group 3: 154.43±50.88 µg/dl (p =0.001). The average DHEAS was lower in patients with chronic SLE vs controls (p = 0.001). A positive linear correlation was found between serum PRL levels and SLEDAI score (Rho 0.92, p=0.001). No correlation was found between PRL and SLICC score. A negative linear correlation was shown between DHEAS concentration and SLICC score (Rho-0.46, p =0.03).

Conclusion: PRL levels were higher in active SLE patients VS. chronic inactive SLE and healthy controls. In contrast, serum DHAS levels were lower in patients with active SLE vs. inactive chronic SLE. We found a positive correlation between SLEDAI score and PRL serum concentrations and an inverse correlation between SLICC score and DHAS serum levels.

Disclosure: O. Vera-Lastra, None; C. Vázquez, None; M. P. Cruz-Dominguez, None; L. J. Jara-Quezada, None.

Abstract Number: 1708

Serum Complement Regulatory Proteins and Disease Activity of Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Although aberrant complement activation is involved in the pathogenesis of systemic lupus erythematosus (SLE), the role of complement regulatory proteins in disease activity of SLE remains limited.

Methods: We enrolled the pediatric-onset SLE patients from our cohort study over 10 years. The clinical and laboratory data including SLEDAI disease activity score, and serum complement factor H (CFH), CFI, CD46, C5a, and C5b-9 in the active and remission phases were determined. Glomerular C5b-9 deposition as a complement activity marker was also examined.

Results: Forty patients (35 female and 5 male, aged 13.9 ± 3.8 years) met the criteria of investigation and were assessed. Fever and kidney were the most common symptom and organ involved, respectively. Mean SLEDAI in the active and remission phases were 12.6 vs 1.7, respectively. All patients exhibited lower serum C3, C4, CFH and CFI and higher serum anti-dsDNA and CD46 in the active phase. There was a significant difference in serum CFH, CFI and CD46 between active and remission phases. Serum CFI but not CFH and CD46 level was negatively correlated with SLEDAI score in active phase. Compared to classical activity markers, serum CFI was superior to C4 and anti-dsDNA in reflecting disease activity and also significantly correlated with white blood count and hemoglobin. Glomerular C5b-9 depositions were detected in patients with nephritis during active phase but not in disease controls.

Conclusion: Serum CFI level may not only be a promising biomarker for disease activity of SLE, but also reflects the hematological features of SLE.

Disclosure: M. H. Tseng, None; J. L. Huang, None.

Abstract Number: 1709

Utilization of Complementary and Integrative Medicine Among Lupus Patients: a Patient Centered Analysis of Perceived Effectiveness and Preference

Lindsey Warner and Shazia Beg, University of Central Florida College of Medicine, Orlando, FL

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Lupus is an autoimmune disease with multitude of symptoms that are often not fully controlled by standard biomedical treatments. This study was designed to gauge current patient use and perspective on Complementary

and Integrative Medicine (CIM) therapies. To our knowledge the last poll of CIM use in this patient population was that of the tri-nation study in 1997.

Methods: 85 participants were recruited from an academic rheumatology practice, lupus support groups, lupus foundation listservs and lupus walks. Of the 85 participants, 77 completed the Qualtrics survey and were used in the data analysis. The survey was organized into five sections correlating with 5 major branches of CIM therapies: manipulative and body based, mind body, biologically based, alternative medical systems and energy healing. The participant was then asked to answer five questions regarding each of the 20 modalities included. These questions ask the following: (1) whether they have used the therapy, (2) how often, (3) what motivates them to utilize the therapy, (4) what symptoms are they trying to address, and (5) how effective do they perceive the therapy to be.

Results: The three most commonly used modalities among patients with lupus were non-herbal natural products 44 (57%), aromatherapy/ essential oils 32 (41.5%) and meditation 31 (40.2%). Non-herbal natural products include chondroitin, coenzyme Q 10, fish oil, omega 3 and DHA, glucosamine, lutein, melatonin, Methylsulfonylmethane (MSM), and sesame oil. The most commonly utilized were natural fats 40 (90.9%) (fish oil, omega 3, and DHA). This was followed by melatonin 13 (29.5), and glucosamine 11 (25 %). Despite their high rate of utilization, over a third of participants [17 (38.6%)] felt that they were not effective or only somewhat effective. 21 (67.7%) of the meditation users found their therapy to be effective, very effective, or extremely effective. The majority of respondents in all three groups indicated that their motivation for utilizing these therapies was because “they believed it worked” and when asked about their desired benefit indicated “general wellness.” This was a common theme for and was reported as the motivation and benefit for 10 of the 19 therapies. The most striking deviation from this theme however was herbal medicine, with (22; 84.6%) reporting motivation was relief of a lupus related symptom. 91.7% of the 26 respondents that utilized herbs did so specifically to alleviate lupus-related symptoms rather than general wellness, with 20 (76.9%) reporting benefit. Of the 20 herbs listed, turmeric (7; 26.9%), marijuana (6; 23.1%), and green tea (2; 7.6%) were reported to be most beneficial for lupus-related symptoms.

Conclusion: The rate of CIM utilization reported by our lupus patient sample was 87.6%, which is approximately three times higher than the 2012 National Health Statistic Reports estimated 33.2% for the general U.S. population. Like the general public, our respondents gravitated towards the supplement industry. Modalities that had highest perceived effectiveness included massage, herbal medicines, and meditation and may provide therapeutic benefit. Future research should be done to explore efficacy of these therapies in larger lupus population.

Disclosure: L. Warner, None; S. Beg, None.

Abstract Number: 1710

Polypharmacy in Older Adults with Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Polypharmacy is a strong risk factor for drug toxicity and adverse clinical outcomes, including delirium, falls, hospitalizations, and death. Polypharmacy is correlated with the prescribing of potentially inappropriate medications (PIMs) and of combining medications with adverse drug-drug interactions. Systemic lupus erythematosus (SLE) is an inflammatory disease associated with significant comorbidity and medication toxicities. While long-term treatment reduces flares and mortality, SLE patients have high rates of medication non-adherence due at least in part to polypharmacy. However, the extent of polypharmacy in this vulnerable population is not known. We aim to gauge the following in older adults with SLE: 1. Prevalence of use of >5 and >10 prescription medications, 2. Prevalence of use of benzodiazepines and non-benzodiazepine sedative-hypnotics (Z-drugs), opioids, and antipsychotics, 3. Prevalence of concurrent use of opioids and benzodiazepines/Z-drugs, and 4. Compare patients ≥ 75 to <75 years of age with respect to polypharmacy and PIM use.

Methods: Adults ≥ 67 years old, meeting the ACR/SLICC classification for SLE seen at least once at the Health Sciences Centre (HSC) Rheumatology Clinic in the 2 years preceding chart review were included. Patients lacking data on prescriptions in the Manitoba Drug Program Information Network (DPIN), such as those from Ontario, were excluded.

For each patient meeting study criteria, the DPIN was reviewed in April 2018 to document all unique medications dispensed in the preceding 4 months. Medication were categorized using the Anatomical Therapeutic Chemical (ATC) codes. Number of medications per patient, as well as the number of patients with prescriptions for one or more opioids, benzodiazepines, Z-drugs, and antipsychotics were calculated. The χ^2 tests, or Fisher's Exact Tests, where appropriate, were used to assess differences between groups, with statistical "significance" (α) predefined at the 5% level.

Results: The charts of 66 patients were reviewed, of whom 54 (48 female, 6 male; 24 ≥ 75 years old) met our study criteria. Of the 12 excluded, 6 were deceased, 4 were from outside Manitoba, and 2 did not meet ACR/SLICC classification for SLE. Almost 2/3 of the patients were dispensed ≥ 5 medications; of those ≥ 75 years old, close to 75% met this definition of polypharmacy. About 1/5 of all patients were dispensed benzodiazepines or Z-drugs. More than 5% were dispensed a combination of opioids and sedative-hypnotic medications. The prevalence of polypharmacy, using either definition, and opioid use, was higher in the older age group and in females, but the differences were not statistically significant ($p > 0.1$). Those on ≥ 5 medications (or ≥ 10 medications) were more likely to be on one or more PIM compared to those on < 5 medications.

Conclusion: This is the first study to assess and document the prevalence of polypharmacy and use of PIMs in older SLE patients. The rates of polypharmacy in our SLE cohort are just slightly higher than the 2012 rates reported for Canadian seniors on public drug programs.

Disclosure: D. Seguin, None; C. A. Peschken, None; R. Grymonpre, None; P. St. John, None; A. Tisseverasinghe, None.

Abstract Number: 1711

Utility of the Lupus Low Disease Activity State (LLDAS) in Discriminating Responders in the BLISS-52 and BLISS-76 Phase 3 Trials of Intravenous Belimumab in Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Measurement of treatment response in SLE clinical trials has been based on measurement of change from baseline; however a treat-to-target analysis has seldom been applied. The Lupus Low Disease Activity State (LLDAS), a potential response indicator for lupus clinical trials, has been found to correlate with reduced damage accrual in SLE¹, indicating it may be a useful treatment target in the clinic. In a trial setting, LLDAS correlated with key outcome measures and discriminated responders from non-responders in a *post-hoc* analysis of the phase IIb MUSE trial of anifrolumab².

We evaluated the utility of LLDAS in this *post-hoc* analysis of the BLISS-52³ and BLISS-76⁴ trials of intravenous belimumab in patients with moderate-severe SLE.

Methods: LLDAS attainment was assessed at baseline and week 52. LLDAS is defined as having all of the following: a) SLEDAI-2K ≤ 4 without major organ activity; b) no new disease activity; c) physician global assessment of activity score (PGA, 0-3) ≤ 1 ; d) prednisolone dose ≤ 7.5 mg/day; and e) standard immunosuppressants allowed. Attainment of LLDAS, association with the primary trial endpoint (SRI-4), discrimination between belimumab and placebo-treated patients, and predictors of LLDAS attainment, were evaluated using descriptive statistics and the Chi-square test, using R (v3.4.3).

Results: Few patients were in LLDAS at study entry (0-2.2%). At week 52, in both studies, fewer patients attained LLDAS compared to the SRI-4 (Table 1). At week 52, for belimumab 10mg/kg, 17.0% of patients in BLISS-52 and 19.3% of patients in BLISS-76 who achieved an SRI-4 also attained LLDAS. In BLISS-52, significantly more patients attained LLDAS at week 52 on belimumab 10mg/kg compared to placebo (12.5% vs 5.8%, $p=0.02$), with a near significant difference at the same time-point in BLISS-76 (14.4% belimumab 10mg/kg vs placebo 7.8%, $p=0.06$). Numerically more patients were in LLDAS at week 52 for both studies for the belimumab 1mg/kg group compared to placebo. In subgroup analysis, LLDAS attainment at week 52 was more likely on belimumab 10mg/kg than placebo in patients with high anti-

dsDNA antibody levels ≥ 30 IU/ml (both studies), low C3 (<90 mg/dl)/C4 (<16 mg/dl) (both studies), high anti-dsDNA antibody levels or low complement levels (both studies), SLEDAI-2K ≥ 10 (BLISS-52), or prednisone dose ≥ 7.5 mg/d (BLISS-52) at study entry.

Conclusion: In BLISS-52, LLDAS was able to discriminate responders from non-responders in the belimumab 10mg/kg group. Fewer patients met LLDAS criteria at week 52 compared to the SRI-4, suggesting that LLDAS is a more stringent measure of treatment response than the SRI-4. Our findings support the discriminant validity of LLDAS as a useful outcome measure in SLE RCTs.

- Franklyn K, et al. *Ann Rheum Dis*. 2016;75:1615-21
- Morand E, et al. *Ann Rheum Dis*. 2018;77:706-13
- Navarra S, et al. 2011;377:721-31
- Furie R, et al. *Arthritis Rheum*. 2011;63:3918-30

Table 1: Assessment of LLDAS and SRI-4 at week 52 in BLISS-52 and BLISS-74 studies

	BLISS-52			BLISS-74		
	Placebo	Belimumab 1mg/kg	Belimumab 10mg/kg	Placebo	Belimumab 1mg/kg	Belimumab 10mg/kg
LLDAS	3.8%	15.6% p=0.07	12.8% p=0.07	7.8%	11.8% p=0.05	16.4% p=0.06
High dsDNA*	5.0%	12.1% p=0.12	12.1% p=0.03	5.2%	8.8% p=0.78	16.2% p=0.01
Low C3/C4†	5.8%	9.4% p=0.50	14.0% p=0.03	4.6%	5.3% p=1.02	13.0% p=0.05
High dsDNA or low C3/C4†	5.3%	9.8% p=0.71	13.0% p=0.03	8.8%	8.0% p=0.87	14.4% p=0.01
SLEDAI-2K ≥ 10	4.2%	9.4% p=0.19	13.8% p=0.03	5.8%	8.8% p=0.86	19.2% p=0.01
Prednisone dose ≥ 7.5 mg/d†	3.8%	5.7% p=0.61	15.7% p=0.07	7.7%	4.2% p=0.58	6.7% p=1.00
SRI-4	81.5%	81.4% p=0.97	87.8% p=0.001	12.3%	42.7% p<0.001	81.2% p<0.001

*subgroup analysis for LLDAS endpoint

Disclosure: S. Oon, None; M. Huq, None; V. Golder, None; E. Ong, None; E. Morand, None; M. Nikpour, Actelion, GSK, Pfizer, BMS, Eli Lilly, UCB, Astra Zeneca, Janssen, 2, 5.

Validation of Proposed EULAR/Acr SLE Classification Criteria Versus SLICC SLE Classification Criteria

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The SLICC 2012 SLE classification criteria and the revised ACR-11 criteria count each SLE manifestation equally. We validated the recently proposed EULAR/ACR classification rule that uses a weighted approach against these criteria and also against a weighted version of the SLICC classification criteria.

Methods: The physician-rated patient scenarios used to develop the 2012 SLICC classification criteria were re-employed to devise a weighted SLICC classification rule. A multiple linear regression model was constructed with the 2012 SLICC criteria variables as predictors and the binary outcome (physician classification of SLE) as the outcome. To generate the weights for each criteria, we then multiplied each criteria's coefficient by 100 and rounded to the nearest integer. The 'Direct Coombs' criteria (coefficient <1) was deleted for simplicity. The weights for the remaining manifestations were: acute cutaneous (26), chronic cutaneous (12), oral ulcers (16), arthritis (9), serositis (16), renal without biopsy (9), neurologic (9), hemolytic anemia (1), leukopenia or lymphopenia (14), thrombocytopenia (15), alopecia (9), ANA (17), anti-dsDNA (19), anti-Sm (16), antiphospholipid antibodies (8), low complement (11). A cutoff for classification was chosen as the score that maximized overall agreement (i.e., the sum of sensitivity and specificity) of the new weighted criteria with physician diagnosis. Patients with lupus nephritis or the new weighted classification rule of 56 or more with at least one clinical component and one immunologic component were classified as SLE. We evaluated the performance of this revised SLICC criteria, on an independent set of patient scenarios, and compared this to the performance of the older revised ACR criteria, the previous SLICC 2012 criteria, and the newly proposed EULAR/ACR criteria.

Results: Table 1 shows the performance of the four classification rules. There was no statistically significant difference (at the .05-level) between any pair of rules with respect to overall agreement with the physician diagnosis.

Table 1: Sensitivity and specificity of four different SLE classification rules based on physician diagnoses of patient scenarios

Classification Rule	Sensitivity (n=349)	Specificity (n=341)	Overall Agreement (n=690)
Proposed EULAR/ACR	317 (89%)	302 (90%)	619 (90%)
Revised ACR-11	290 (83%)	326 (96%)	616 (89%)
SLICC 2012	340 (97%)	288 (84%)	628 (91%)
Weighted SLICC 2012 criteria	310 (88%)	304 (89%)	614 (89%)

Conclusion: We validated the new EULAR/ACR criteria against both ACR-11 and SLICC classification criteria. Weighted SLICC criteria were a trade-off with less sensitivity but better specificity. The two newly derived weighted classification rules did not perform better than the existing list-based rules in terms of over-all agreement. Given that the list-based rules are easy to calculate, they may be preferred in most clinical settings.

Disclosure: M. Petri, EMD Serono, 5, Exagen, 2, Janssen, 5, GSK, 5, AstraZeneca, 2, Inova Diagnostic, 5, Novartis, 5, Amgen Inc., 5, Decision Resources, 5, Medscape, 5, Eli Lilly and Co., 5, Quintiles, 5; D. Goldman, Merck & Co., Pfizer, 1; L. S. Magder, None.

Attainment of Low Disease Activity and Remission in SLE Patients Who Started with High Disease Activity in the Atacicept Phase IIb Address II Study and Its Long-Term Extension

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster II: Biomarkers and Outcomes

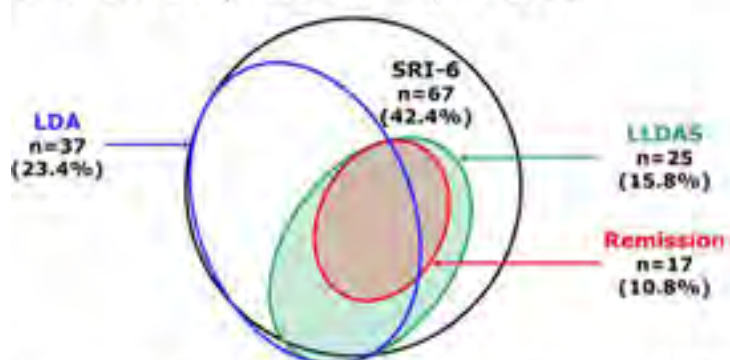
Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

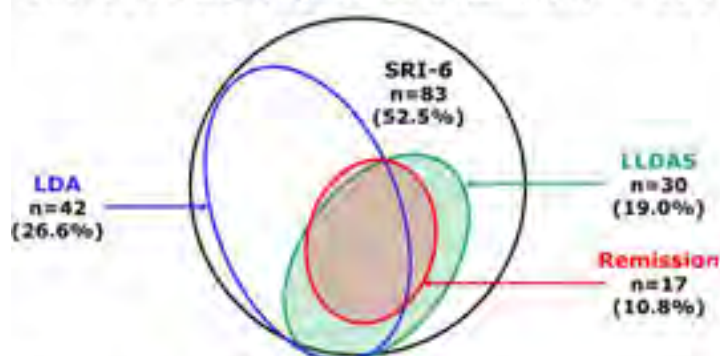
Background/Purpose: Low disease activity (LDA) and remission are important goals in the treatment of patients (pts) with SLE.^{1,2} Lupus Low Disease Activity State (LLDAS) is associated with reduced damage accrual,² and has been shown to be a feasible clinical trial endpoint.³ In pts with high disease activity (HDA; SLEDAI-2K \geq 10) enrolled in the ADDRESS II study, atacicept improved SRI-6 response rates and flare prevention at Week 24 vs placebo (PBO).⁴ Atacicept was also shown to have an acceptable safety profile. We present a post-hoc analysis of data from ADDRESS II and its long-term extension describing 48-week LDA and remission rates in pts with HDA at Screening.

Figure 1. Endpoint stringency of LDA, LLDAS and remission attainment versus SRI-6 response in all patients with high disease activity at Week 24 (A) and Week 48 (B)

A. Week 24 (ADDRESS II; n=158)



B. Week 48 (Long-term extension; n=158*)

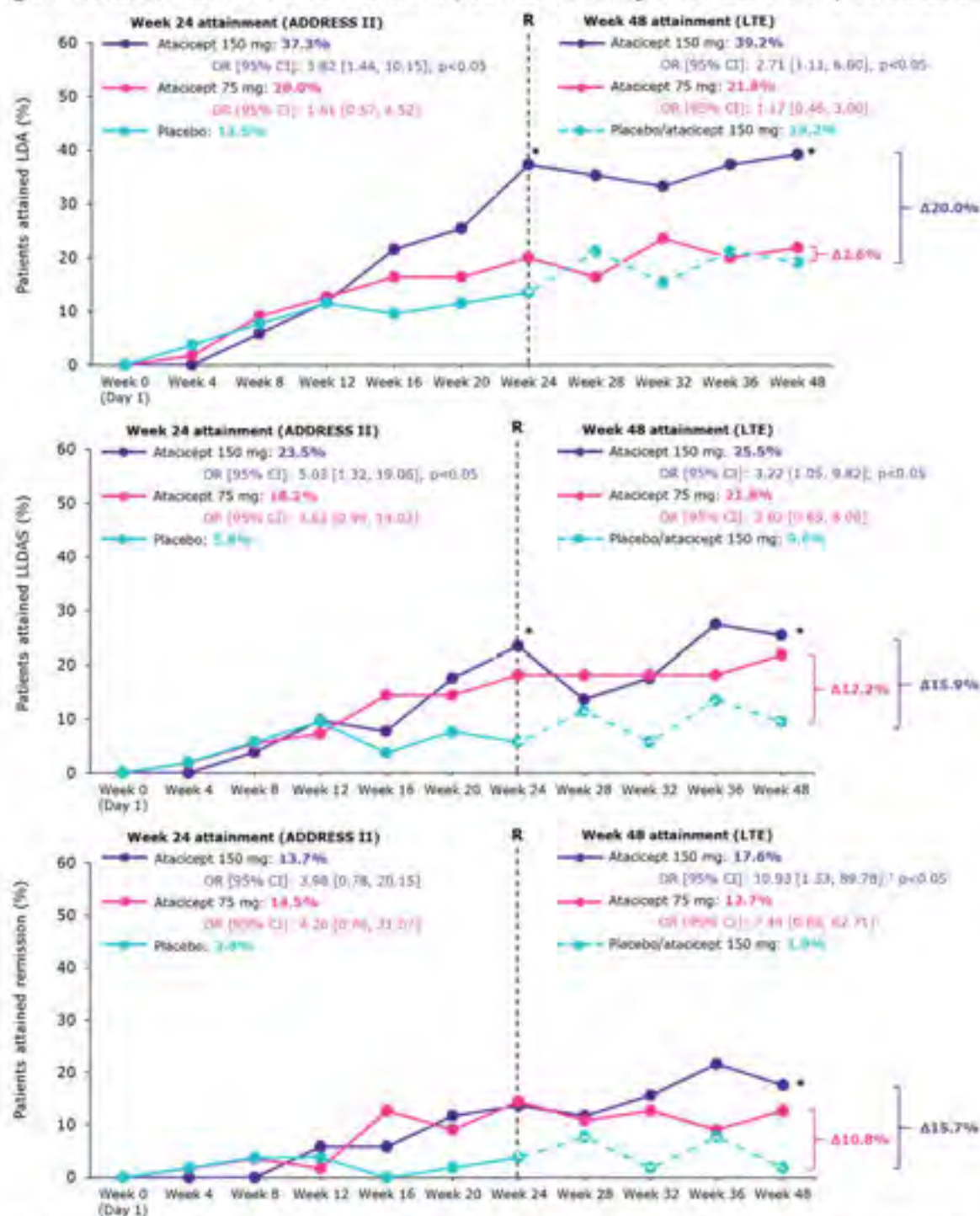


*26 patients who had HDA at Screening and who did not enter the LTE following ADDRESS II were considered non-responders for this analysis.
LDA, Low disease activity; LLDAS, Lupus Low Disease Activity State; SRI, SLE responder index

Methods: In ADDRESS II, pts were randomized (1:1:1) to weekly subcutaneous PBO or atacicept 75 or 150 mg for 24 weeks. Atacicept completers continued at the same dose in the extension study; PBO pts were switched to atacicept 150 mg (PBO/atacicept 150 mg). This post-hoc analysis assesses: LDA (SLEDAI-2K \leq 2), LLDAS (SLEDAI-2K \leq 4 without major organ activity, no new disease activity vs previous visit, Physician's Global Assessment [PGA] \leq 1, prednisone-equivalent \leq 7.5mg/day, and stable immunosuppressants),² and remission (clinical SLEDAI-2K=0, PGA \leq 0.5, prednisone \leq 5 mg/day), as proposed by the task force on definitions of remission in SLE (DORIS).¹

Results: A total of 158/306(52%) ADDRESS II pts had HDA at study entry. At Week 24, 42.4% achieved SRI-6, 23.4% attained LDA, 15.8% LLDAS and 10.8% remission (Figure 1A). At Week 48, 52.5% achieved SRI-6, 26.6% attained LDA, 19.0% LLDAS and 10.8% remission (Figure 1B). Among 83 SRI-6 responders with HDA at Screening, 49.4% (n=41)

Figure 2. LDA, LLDAS and remission in patients with high disease activity at Screening



*p<0.05 versus placebo (24 weeks) or placebo/atacicept 150 mg (48 weeks); †Results should be interpreted with caution due to the wide CI; CI, Confidence interval; LDA, Low disease activity; LLDAS, Lupus Low Disease Activity State; LTE, Long-term extension; OR, Odds ratio

attained LDA, 34.9% (n=29) LLDAS and 20.5% (n=17) remission at Week 48. At 48 weeks, LDA, LLDAS and remission rates were higher in pts treated with atacicept 150 mg vs PBO/atacicept 150 mg and vs atacicept 75 mg (Figure 2).

Conclusion: ADDRESS II pts with HDA at Screening receiving atacicept 150 mg were more likely to attain LDA, LLDAS and remission at Week 48 than those treated with atacicept 75 mg or PBO/atacicept 150 mg. These endpoints were more stringent and discriminatory than SRI-6, confirming LLDAS, LDA, and remission to be robust and meaningful endpoints for SLE trials. In addition, these data further support future studies of atacicept in SLE.

References: (1) VanVollenhoven et al, Ann Rheum Dis 2017. (2) Franklyn et al, Ann Rheum Dis 2016. (3) Morand et al, Ann Rheum Dis 2018. (4) Merrill et al, Arthritis Rheum 2018.

Disclosure: E. Morand, AstraZeneca/Medimmune, Janssen, UCB, BMS, 2, 5; J. T. Merrill, BMS, GSK, 2, BMS, GSK, UCB, Questcor, EMD Serono, Amgen, Celgene, Pfizer, RemeGen, Exagen, MedImmune, Lilly, Janssen, Xencor, Sanofi, Neovacs, Immupharma, Astellas, Glenmark, ILTo, 5, Have given talks for BMS but not for Speaker's bureau, 9; D. A. Isenberg, EMD Serono, 5; A. H. Kao, EMD Serono Research & Development Institute, Inc. (a business of Merck KGaA, Darmstadt, Germany), 3; C. Vazquez-Mateo, EMD Serono, 3; S. Wax, EMD Serono, 3; P. Chang, EMD Serono Research & Development Institute, Inc. (a business of Merck KGaA, Darmstadt, Germany), 3; K. Pudota, EMD Serono, 3; C. Aranow, EMD Serono; GSK; AstraZeneca/Medimmune, 2, 5; D. J. Wallace, Merck KGaA, 5.

Abstract Number: 1714

Global Consensus Building and Prioritization of Major Challenges in Lupus Diagnosis, Care, Treatment and Research

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster – ARHP

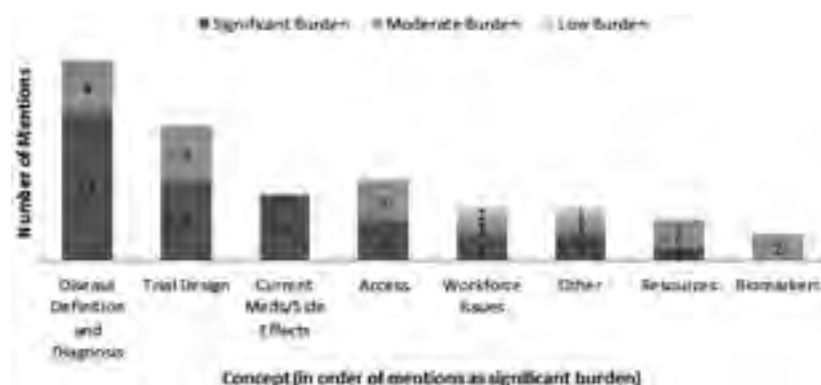
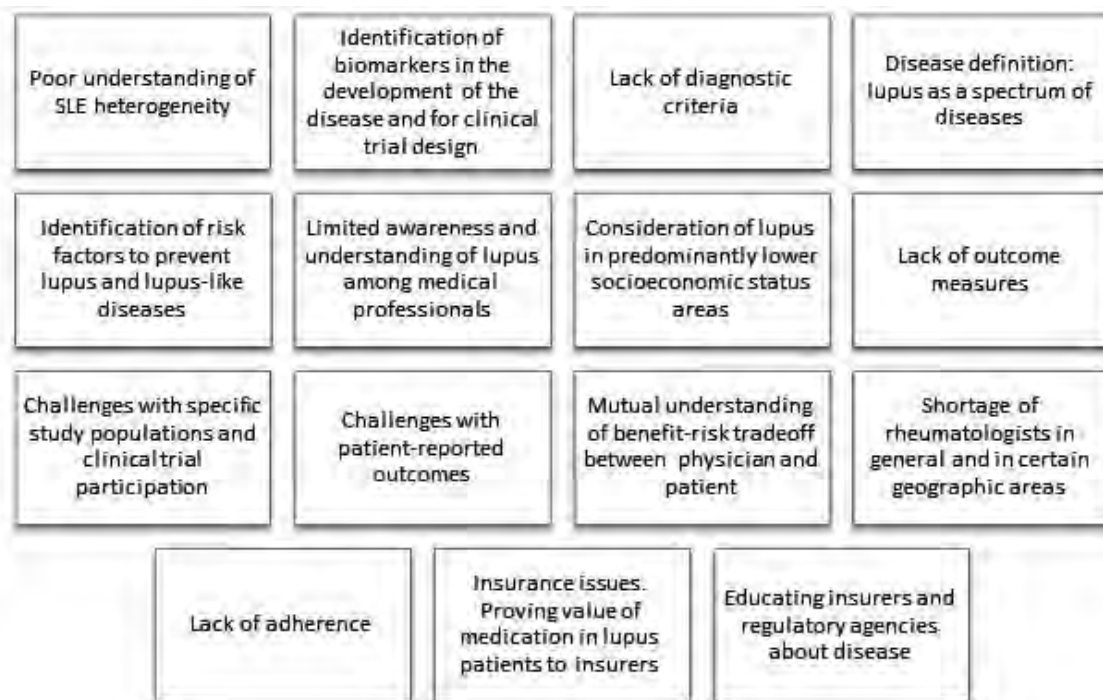
Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The Addressing Lupus Pillars for Health Advancement (ALPHA) Project is a global consensus initiative seeking to identify and prioritize top barriers in lupus impacting diagnosis, care, treatment and research, with the goal of improving rates of accurate and timely diagnosis, increasing access to care, and improving short and long-term patient outcomes. This abstract presents Phase I consensus building and prioritization process methodology, and findings of initial project activities.

Methods: The Lupus Foundation of America and its research partner, Tufts Center for the Study of Drug Development, assembled a Global Advisory Committee (GAC) of 13 lupus experts across 5 countries to provide input and support throughout the effort. A mixed methods approach is being used to elicit concepts seen as major barriers in lupus diagnosis, care, treatment and research, then consolidate and confirm those selected as most urgent. First, a brief web survey was distributed to each GAC member to begin concept elicitation. Identified items were then ranked during a GAC meeting, and will be presented through an in-depth semi-structured interview among 22 stakeholders representing industry, academia, regulatory bodies, patient/advocacy groups, clinicians, and researchers. Finally, an online survey among 200-500 individuals will further validate and demonstrate consensus around top barriers in a broader audience for this Phase I initiative.

Results: GAC member response rate was 85% for the concept elicitation exercise. Findings are shown in Figure 1. 15 main concepts were identified, with substantial discussion on lupus heterogeneity, lupus as a spectrum of diseases, and the



importance of biomarkers in trial design and understanding of the disease. Categorization and prioritization of these concepts is seen in Figure 2. Notably, all GAC members cited issues surrounding disease definition and diagnosis as the most significant burden in lupus. Half also cited clinical trial design and availability and side effects of current medications as significant burdens.

Conclusion: The ALPHA Project is a collective, iterative research effort among lupus key opinion leaders and diverse stakeholder groups to build consensus and create actionable steps to advance the field. Findings from the GAC meeting showed initial consensus on key priority issues, such as lupus heterogeneity, disease definition, and clinical trial design. Figure 1. Concept Elicitation of Top Barriers in Lupus Diagnosis, Care, Treatment and Research

Figure 2. Concept Prioritization from GAC Survey of Top Barriers to Lupus Diagnosis, Care, Treatment and Research

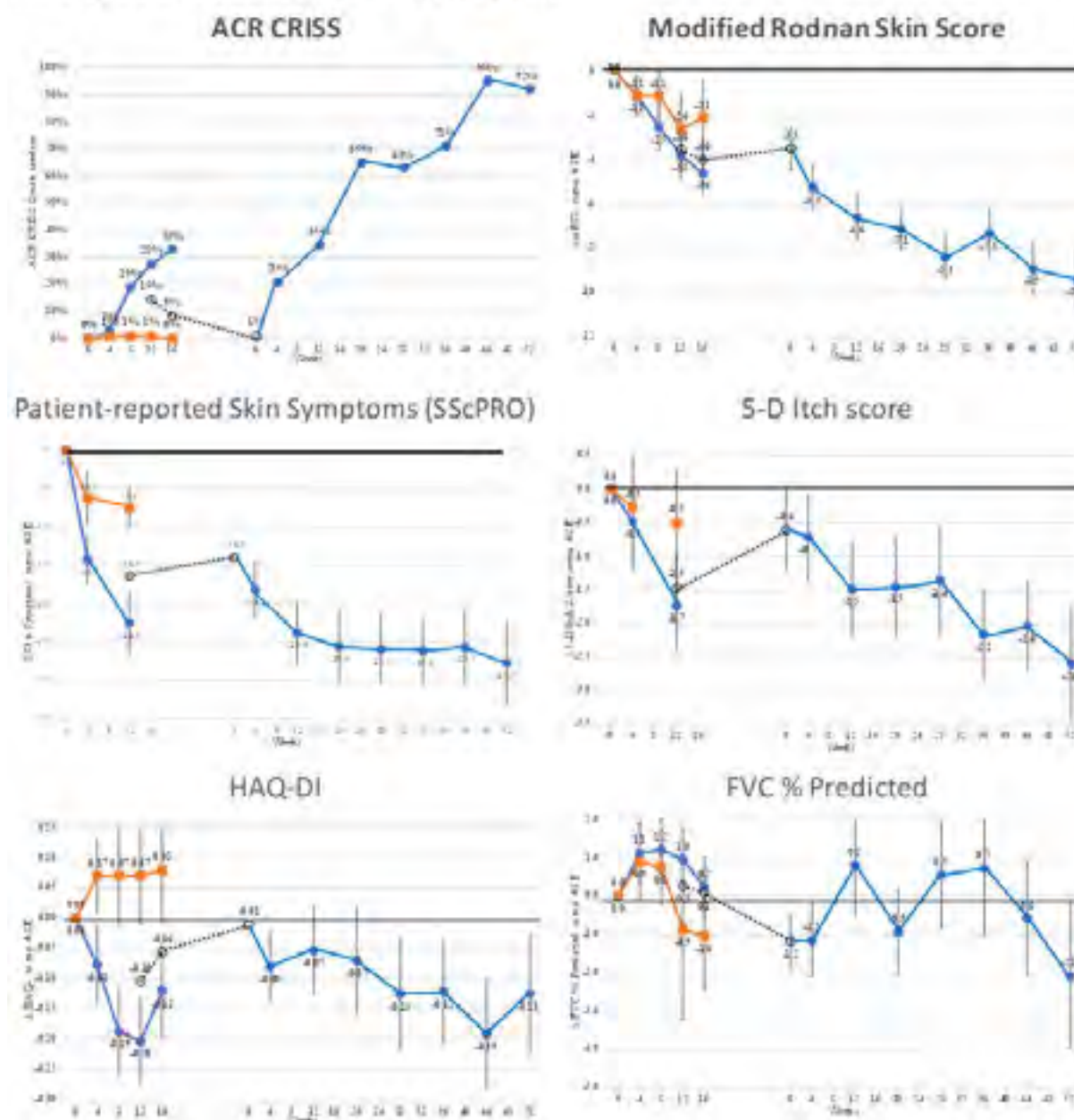
Disclosure: K. Tse, None; R. P. Daly, Lupus Foundation of America, 3; L. Hanrahan, None; A. Anderson, None; K. Arntsen, None; S. C. Bae, None; I. N. Bruce, None; K. Costenbader, None; T. Dörner, None; A. H. Kao, EMD Serono Research & Development Institute, Inc. (a business of Merck KGaA, Darmstadt, Germany), 3; S. Manzi, None; E. Morand, None; S. Raymond, None; B. H. Rovin, None; L. E. Schanberg, None; V. P. Werth, None; J. Von Feldt, None; K. Getz, None.

Safety and Efficacy of Lenabasum in an Open-Label Extension of a Phase 2 Study in Diffuse Cutaneous Systemic Sclerosis Subjects

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Figure 1. Selected Efficacy Outcomes in OLE of Phase 2 Study of Lenabasum in Diffuse Cutaneous Systemic Sclerosis

Blue circle = lenabasum. Orange square = placebo. Black open circle = maintenance background treatment alone (no investigational product) before start of OLE, mean 19.1 weeks duration.



SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Lenabasumis a synthetic, non-immunosuppressive, selective cannabinoid receptor type 2 agonist that activates resolution of innate immune responses. Lenabasum had acceptable safety and tolerability, and improved multiple efficacy outcomes in the double-blinded, randomized, placebo-controlled Part A of Phase 2 trial JBT101-SSc-001 (NCT02465437) in diffuse cutaneous SSc (dcSSc) subjects.

Objective: To provide long-term open-label safety and efficacy data in dcSSc subjects in study JBT101-SSc-001.

Methods: Subjects who completed Part A were eligible to receive oral lenabasum 20 mg BID in an open-label extension (OLE) that assessed safety and efficacy at 4 weeks, then every 8 weeks.

Results: 36/38(95%) eligible subjects enrolled in the OLE, with mean interval of 134 (range 33-392) days or 19.1 weeks from end of dosing in Part A to start of OLE when subjects received only standard-of care drugs. 34/36 (94%) subjects were on stable doses of immunosuppressive drugs. At the time of data cut-off, 5/36 (13.9%) subjects had discontinued the OLE for reasons all unrelated to lenabasum: difficulty coming for study visits (n = 2), fatigue, inflamed tendons, and high dose steroid-induced scleroderma renal crisis. Of the remaining 31 subjects, 27(87.1%) had already completed ≥ 1 year of dosing in OLE. Adverse events(AEs, n = 180) occurred in 33/36 (91.7%) subjects, with 7/36 (19.4%) subjects having ≥ 1 AE related to lenabasum. No subject had a serious or severe AE related to lenabasum. Three serious AEs occurred: renal crisis, thumb fracture, and digital ulcer. AEs that occurred in $\geq 10\%$ of subjects (n, % of subjects) were: upper respiratory tract infection (8, 22.2%), skin ulcer, arthralgias, urinary tract infection (5, 13.9% each), and diarrhea (4, 11.1%). Mild dizziness occurred in 3 (8.3%) subjects.

Improvement was seen in multiple physician- and patient-reported efficacy outcomes compared to study start and start of OLE (examples in Figure 1), including Combined Response Index in diffuse cutaneous Systemic Sclerosis (CRISS), mRSS, HAQ-DI, Physician Global Assessment, skin symptoms, itch, and multiple PROMIS-29 domains. FVC % predicted was relatively stable. Compared to baseline at study start, the CRISS median score was 92% (23%, 100% IQR) at Week 52 and mRSS declined by mean (SD) = 9.4 (8.43) and 41.3% (32.7%) from baseline, with 35% of subjects newly achieving a low mRSS ≤ 10 .

Conclusion: In OLE of Phase 2 trial JBT101-SSc-001, lenabasum continues to have acceptable safety and tolerability in dcSSc with no severe or serious AEs or study discontinuations related to lenabasum. Only about 1 in 5 subjects had an AE related to lenabasum over 1-year OLE dosing. ACR CRISS score, mRSS, Physician Global Assessment, and multiple patient-reported outcomes show continued improvement, although background therapy, potential for spontaneous improvement, and open-label dosing limit what can be definitely attributed to lenabasum.

Disclosure: R. F. Spiera, Roche-Genentech, 2, 5, GSK, 2, 5, BMS, 2, Boehringer Ingelheim, 2, Cytos, 2, Chemocentryx, 2, Corbus Pharmaceuticals, 2, Sanofi, 5, CSL Behring, 5; L. K. Hummers, None; L. Chung, None; T. M. Frech, None; R. T. Domsic, None; V. Hsu, None; D. E. Furst, BMS, 2, 5, Amgen Inc., 2, 5, GSK, 2, 5, Genentech/Roche, 2, 5, Corbus Pharmaceuticals, 2, 5, Novartis, 5, Pfizer, Inc., 5, NIH, 5; J. K. Gordon, None; M. D. Mayes, Bayer, 2, Boehringer-Ingelheim, 2, 6, Corbus Pharmaceuticals, 2, Reata, 2, Sanofi, 2, Astellas, 6, Galapagos, 6, Mitsubishi-Tanabe, 6, Medtelligence, 5; R. W. Simms, None; E. Lee, Corbus Pharmaceuticals, Inc, 3; S. Constantine, Corbus Pharmaceuticals, Inc., 3; B. White, Corbus Pharmaceuticals, Inc., 3.

Abstract Number: 1716

Evaluation of American College of Rheumatology Provisional Composite Response Index in Systemic Sclerosis in a Phase II Trial of Abatacept Vs. Placebo

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster II

Background/Purpose: Treatment with CTLA4Ig, abatacept (ABA), in early diffuse cutaneous systemic sclerosis (dcSSc; the Phase 2 ASSETtrial) showed evidence of improvements in modified Rodnan skin score (mRSS) and secondary outcome measures at month 12 (2018 ACR abstract submitted); however, statistical significance was not always shown vs. placebo. The CRISS index, a composite outcome measure for trials in SSc¹, is a 2-step process that assigns a probability of improvement for each subject ranging from 0 [no improvement] to 1 [marked improvement]. Step 1 assesses clinically meaningful decline in cardio-pulmonary-renal involvement with a probability of 0. For remaining subjects, probability of improvement is based on 5 variables: changes from baseline to month 12 in FVC%, mRSS, patient (PTGA) and physician global assessments (MDGA), and HAQ-DI. We assessed the performance of CRISS, a secondary outcome measure, in ASSET at month12.

Methods: ASSET was an investigator-initiated, multicenter double-blind, randomized placebo-controlled trial. Eligible subjects were randomized in a 1:1 ratio to either 12 months 125 mg SC ABA or matching placebo, stratified by duration of dcSSc (≤ 18 vs >18 to ≤ 36 months). Investigators reported SSc end organ involvement (Step 1 for CRISS) prospectively using a case report form. These and all AEs and SAEs were reviewed for cardio-pulmonary and renal involvement by the study PI. Step 2 calculated the CRISS index as previously defined. Treatment differences, adjusted for duration of dcSSc, in the CRISS score were assessed by the non-parametric Van Elteren test and by ANCOVA for individual CRISS components. We calculated Spearman's correlation coefficients to assess the relationship between the CRISS score and its individual components. Multiple imputation was used for analysis, creating 25 complete datasets with estimates, standard errors and p-values pooled over each imputed dataset.

Results: 88 subjects (44 ABA, 44 PBO) were randomized; 63 (72%) had complete data for all relevant outcomes at month 12. 5 PBO and 5 ABA subjects met the pre-defined definition of worsening cardio-pulmonary-renal involvement(Step 1) and were given a score of 0. There is evidence of improved CRISS scores on ABA compared to the PBO at month 12 and the difference was statistically significant ($p=0.03$; Table). For individual variables, MDGA and HAQ-DI were statistically significant ($p=0.004$ and $p=0.05$) favoring ABA. Most variables, except HAQ-DI and PTGA, had statistically significant correlations with the CRISS (Table).

Conclusion: Although the degree of correlation is high between the mRSS and CRISS, there is evidence that CRISS may be more sensitive to clinically meaningful treatment changes than the standard skin score endpoint. This suggests further validation of CRISS as an independent primary endpoint for scleroderma clinical trials.

References:: 1. Khanna D. Arthritis Rheumatol. 2016

Table: Spearman Correlations between CRISS and individual components at 12 months and Comparison of ABA and PBO using CRISS index and individual components at 12 months;

Outcome		ABA N=44	PBO N=44	Treatment Difference (ABA-PBO)	P-value ^
CRISS (0.0-1.0) median (IQR)		0.68 (1.00)	0.01 (0.86)		0.03
	Spearman Correlation	LS mean (SE)	LS mean (SE)	LS mean (SE)	P-value ^ ^
Δ mRSS (0-51)	-0.75*	-6.7 (1.30)	-3.8 (1.23)	-2.9 (1.75)	0.10
Δ FVC% predicted	0.36*	-1.4 (1.30)	-3.1 (1.20)	1.7 (1.72)	0.32
Δ PTGA (0-10)	-0.17	-0.50 (0.392)	-0.30 (0.385)	-0.20 (0.557)	0.73
Δ MDGA (0-10)	-0.47*	-1.34 (0.282)	-0.18 (0.284)	-1.16 (0.403)	0.004
Δ HAQ-DI (0-3)	-0.21	-0.11 (0.079)	0.11 (0.076)	-0.22 (0.108)	0.05

^ p-value for treatment comparisons based on Van Elteren test

^ ^ p-value for treatment comparisons based on ANCOVA model with treatment, duration of SSc and baseline value as covariates

* $p < 0.01$ using Spearman correlation coefficient

Acknowledgment: This project was supported by NIH/NIAID Clinical ACE grant (5UM1AI110557-05) and an investigator-initiated grant by Bristol-Myers Squibb.

Negative score denotes improvement, except for FVC% where negative score denotes worsening; LS mean = least squares mean; SE = standard error

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Expert Consensus on the Screening, Treatment, and Management of Patients with Systemic Sclerosis-Interstitial Lung Disease, and the Potential Role of Anti-Fibrotics in a Treatment Paradigm for Systemic Sclerosis-Interstitial Lung Disease: A Delphi Consensus Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic sclerosis (SSc), or scleroderma, is a rare, autoimmune, multisystem connective tissue disorder characterized by vascular damage, autoimmunity, and fibrosis of the skin and other internal organs ¹⁻³. Pulmonary manifestations account for 60% of SSc-related deaths, and interstitial lung disease (ILD) is identified more often in SSc than in any other connective tissue disease (CTD), with the prevalence of ILD in SSc patients ranging from 75% to 90% ^{1,4}. There are many gaps in our understanding of the methodology for screening and the management of SSc-ILD. Hence, the objective of the current Delphi study was to solicit the opinions of rheumatologists and pulmonologists with expertise in the management of patients with SSc-ILD in order to develop consensus on screening and treatment criteria, and to evaluate the potential role of anti-fibrotics in a treatment paradigm for SSc-ILD.

Methods: A three-stage Delphi method was designed to query rheumatologists and pulmonologists with expertise in SSc-ILD on identifying the criteria for screening, treatment, and management of patients with SSc-ILD. The potential role of anti-fibrotics in the treatment paradigm for patients with SSc-ILD was also explored. Here preliminary data at the completion of the second survey by 9 panelists are presented. Survey two had panelists rate their agreement on a Likert scale from -5 (complete disagreement) to +5 (complete agreement). Consensus was defined as a score of 2.5 or more with standard deviation not crossing zero.

Results: Preliminary data, based on two rounds of Delphi, show high agreement regarding how to screen, how to identify the patient population to treat, treatment paradigms, and how to monitor progression and eventually successfully manage patients with SSc-ILD (Table 1: Mean \pm SD).

Conclusion: Preliminary data suggest consensus on screening and treatment with initial immunosuppressive therapy in SSc-ILD. The group was amenable to concomitant use of anti-fibrotics with CYC/MMF in SSc-ILD patients. Further guidance should be available in the near future with ongoing and recently completed trials.

Table 1:

How do you screen?

Screening for the general scleroderma population for ILD should include Spirometry with DLCO (4.78 \pm 0.44) Full PFT (4.89 \pm 0.33) HRCT (3.67 \pm 1.94) Autoantibody testing (4.22 \pm 0.97) Echocardiogram and (3.89 \pm 1.69) Chest auscultation (4.44 \pm 1.33)

Who do you screen?

In determining which patients to screen for ILD, I would consider Patients with symptoms (4.56 \pm 1.01) High risk patients (ex: diffuse cutaneous SSc (dcSSc), positive Scl-70 antibodies, African American ethnicity, and/or a high modified Rodnan Skin Score (4.78 \pm 0.67)

Who do you treat?

When deciding whether to treat patients for ILD I consider Extent of ILD or fibrosis on HRCT (4.44 \pm 0.88) Clinically meaningful change in PFT value (4.89 \pm 0.33)

Based on high resolution computed tomography (HRCT), I treat patients that have Worsening HRCT with symptoms or declining PFTs (5.00 \pm 0.00) >20% involvement on HRCT with abnormal PFTs (4.78 \pm 0.44)

Based on forced vital capacity (FVC) and symptom status (assume all patients have ILD on HRCT), I treat patients that have FVC >80% with ILD on HRCT in a high-risk patient (early diffuse disease, Topo+) (3.89 \pm 0.60) Decline in FVC by >10% in one year (4.78 \pm 0.44)

To determine the phenotype of patients that are likely to respond to treatment, I would likely employ Findings or changes on HRCT (3.56 \pm 1.33) Findings or changes on PFTs (3.89 \pm 1.45)

Additional tests that can help make the decision PFTs (Spirometry with DLCO) (1.00 \pm 0.0) HRCT (2.0 \pm 0.0) Autoantibodies (3.6 \pm 0.89)

How do you treat?

Once I have decided to treat SSc-ILD, the initial therapy I use is Mycophenolate Mofetil (CellCept) (4.78 ± 0.44) The typical/target dose for mycophenolate (MMF) I recommend is 3,000 mg daily (4.78 ± 0.44)

With regard to anti-fibrotics...

I see anti-fibrotics (nintedanib [OFEV] and pirfenidone [Esbriet]) fitting into the management of SSc-ILD as first line therapy (0.44 ± 2.83) I see anti-fibrotics (nintedanib [OFEV] and pirfenidone [Esbriet]) fitting into the management of SSc-ILD **after CYC/MMF** (2.22 ± 3.11) I see anti-fibrotics (nintedanib [OFEV] and pirfenidone [Esbriet]) fitting into the management of SSc-ILD **concomitant with CYC/MMF**: (3.44 ± 1.88) I **do not** see anti-fibrotics fitting into the management of SSc-ILD (-2.56 ± 3.28)

How long do you treat?

I typically treat patients with SSc-ILD for 5 years (3.89 ± 1.17)

What is progression to you, and how do you monitor it?

I monitor progression as follows: Changes in PFTs over time (FVC or DLCO) (4.67 ± 0.71) Features on HRCT (ILD pattern or extent of fibrosis) (3.56 ± 1.33) Changes in HRCT over time (4.11 ± 1.05) Changes in symptoms over time (2.78 ± 3.15)

What is success to you?

I consider the following elements in defining success in SSc-ILD: FVC improvement (4.33 ± 0.71) DLCO improvement (4.11 ± 0.93) HRCT improvement (4.22 ± 0.97) Symptom stabilization / improvement (3.89 ± 0.93)

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4. SolomonJJ, Olson AL, Fischer A, Bull T, Brown KK, Raghu G. Scleroderma lung disease. *EurRespir Rev*. 2013; 22 (127):6-19.

Disclosure: D. Khanna, Eicos Sciences, 1,Pfizer, Inc., 2,Horizon, 2,BMS, 2,Actelion, 5,Bayer, 5,Bayer, 2,Corbus, 5,Cytori, 5,EMD Serono, 5,Genentech, Inc., 5,Sanofi-Aventis, 5,GSK, 5,Boehringer Ingelheim, 5; M. Streck, Boehringer Ingelheim, 5; B. Southern, Boehringer Ingelheim, 5; R. Saggar, Boehringer Ingelheim, 5; V. Hsu, Boehringer Ingelheim, 5; M. D. Mayes, Boehringer-Ingelheim, 2, 5,Corbus, 2,Reata, 2,Sanofi, 2,Mitsubishi-Tanabe, 5,Roche-Genentech, 2; R. Silver, Boehringer-Ingelheim, 5; V. D. Steen, CSL Behring, 2, 5,Bayer, 2, 5,Berhlinger Ingelheim, 2, 5,Roche, 2, 5,Reata, 2, 5,Sanorif, 2,EMD serrano, 2,Corbus, 2, 5,Immune Tolerance Network, 2,cytori, 2, 5; D. Zoz, Boehringer-Ingelheim, 3; F. Rahaghi, Boehringer-Ingelheim, 5.

Abstract Number: 1718

Skin Gene Expression Profiling Predicts Longitudinal Modified Rodnan Skin Score Change

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

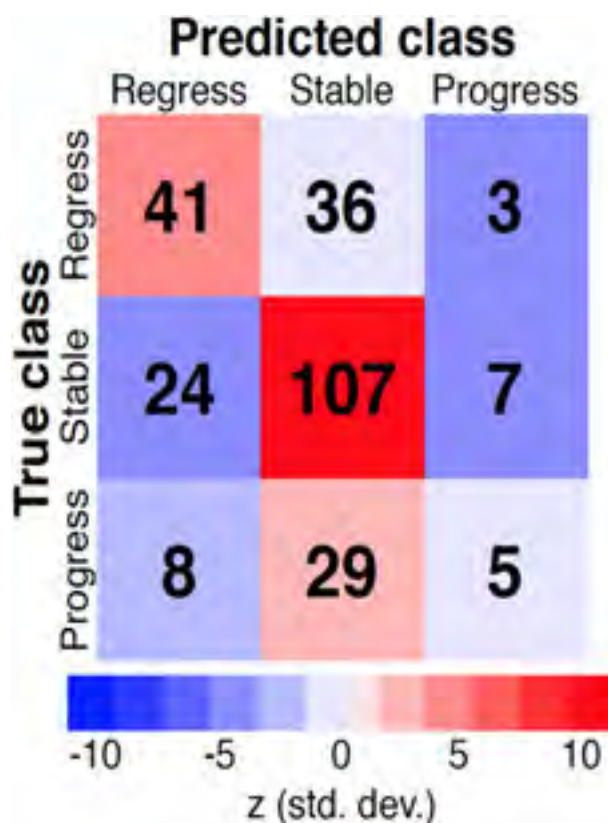
Background/Purpose: Systemic sclerosis (SSc) causes varying degrees of skin fibrosis with varying trajectory. Extent of skin involvement is measured by the modified Rodnan skin score(mRSS), a semi-quantitative clinical method of pinching the skin to determine fibrosis. Previously, a 415-gene signature in skin was identified whose change between baseline and 12 months predicted mRSS at 24 months. We identified a skin gene expression signature at a single time point that predicts mRSS 6 or 12 months later.

Methods: Gene expression profiles were obtained from 260 skin biopsies from 45 SSc patients treated with mycophenolate mofetil (MMF) and 22 healthy controls. Participants were classified into progressing, stable, or regressing groups based on the mRSS change between the baseline skin biopsy and the subsequent time point 6 or 12 months later. A multinomial generalized linear model determined the probability of skin trajectory from gene expression profiles and clinical information.

Results: The mRSS regressing group compared to the mRSS progressing and stable groups combined demonstrated 762 differentially expressed genes (823 probes). A multinomial generalized linear model that included genomic and clinical data was developed to predict skin trajectory with 58.8% total accuracy compared to 40% using a random permutation null model. Up-regulated genes in improvers were enriched for extracellular matrix (ECM) metabolism, transforming growth factor-pathway expression, and angiogenesis.

Conclusion: We demonstrate proof-of-principle that significant prognostic information may be obtained from analysis of skin gene expression at a single time point. Further investigation is warranted to determine the generalizability of the model. Future directions include incorporating additional information such as serum protein data and histologic data to increase the predictive accuracy of the model.

Figure 1. Error matrix comparing the performance of the experimental model to a null model. The null model permutes 1000 times yielding a mean prediction accurate to 0.1. The experimental model more accurately predicts patients whose mRSS improves or remains stable compared to the null model.



Disclosure: C. Correia, None; M. A. Carns, None; K. Aren, None; M. Hinchcliff, None; J. M. Mahoney, None.

Abstract Number: 1719

High-Throughput Quantitative Histology in Systemic Sclerosis Skin Disease Using Computer Vision

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

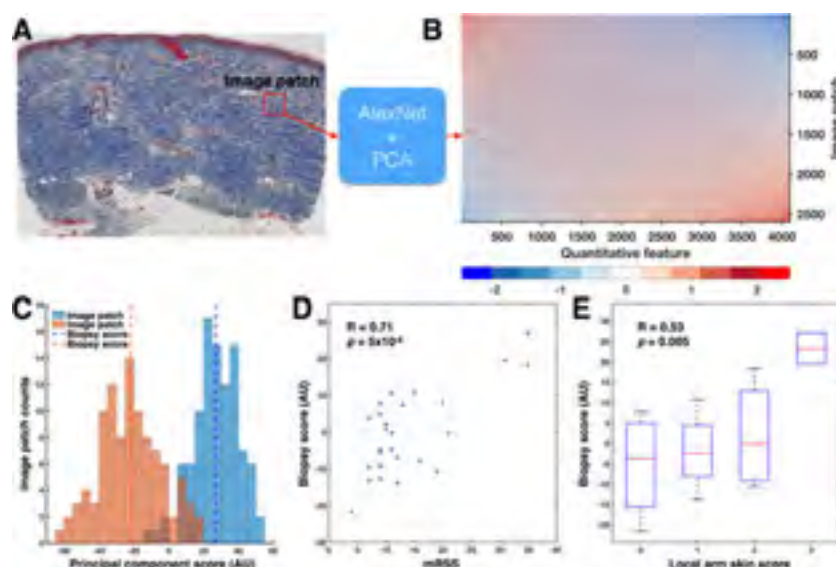
Background/Purpose: The lack of a reproducible and quantitative method to accurately assess histological skin fibrosis in patients with systemic sclerosis (SSc) has long plagued clinical studies. Deep neural network(DNN) analysis, a computer vision technique, has the potential to radically augment histopathological analyses for myriad diseases including SSc. DNN analysis is a computational tool that extracts and quantifies complex image patterns. To test the hypothesis that DNN analysis applied to SSc skin biopsies is a useful method for dermal fibrosis quantification, the association between DNN outputs and skin score was determined.

Methods: One rheumatologist performed modified Rodnan skin score (mRSS) assessments followed by four mm dermal, punch biopsies of the non-dominant volar forearm, in patients with SSc. Biopsies were repeated at 6-, 12- 24-, and 36-months. Trichrome-stained sections were photomicrographed and transformed into quantitative features using AlexNet in the Matlab Neural Network Toolbox. Principal component analysis was used to identify the combination of quantitative features that captured the most quantitative feature variance. The correlation between the first principal component, mRSS, and local arm skin score was assessed.

Results: Twenty-six photomicrographs were analyzed. DNN analysis identified 4096 unique quantitative features. The first principal component of these 4096 quantitative features strongly correlated with local skin score ($R = 0.52$) and mRSS ($R = 0.71$).

Conclusion: This investigation demonstrates that DNN-derived quantitative features of SSc biopsies are sensitive to both local skin score and mRSS. Future directions include testing for generalizability in a larger sample and evaluating whether DNN are sensitive to biochemical measures of fibrosis. If validated, this suggests that DNN analysis can dramatically expand the quantifiable SSc phenome to permit inclusion of histological information into SSc trajectory models.

Figure 1: A) 100 *image patches* (red square) were randomly sampled from the dermis and input to AlexNet. B) For each image patch, AlexNet identified 4096 *quantitative features*, resulting in a 2600 x 4096-dimensional matrix. The rows and columns of the quantitative feature matrix have been sorted by the first principal component (PC). C) Histograms of the principal component scores for image patches from the patients with the highest(35) and lowest (4) mRSS show little overlap. Across all 2600 image patches grouped by biopsy, the biopsy accounted for 30% of the total variance in the principal component scores ($p < 10^{-100}$, one-way ANOVA). Therefore, biopsies were summarized into *biopsy scores* by taking the mean of the 100 patches. D) Biopsy score significantly correlated with mRSS (Pearson's $R = 0.71$, $p = 5 \times 10^{-5}$). E) Biopsy score significantly correlated to local skin score (Pearson's $R = 0.53$, $p = 0.0049$).



Disclosure: C. Correia, None; S. Mawe, None; M. A. Carns, None; K. Aren, None; A. Hoffman, None; M. Hinchcliff, None; J. M. Mahoney, None.

Abstract Number: 1720

Higher Neutrophil Count Predicts More Severe Skin/Lung Disease and Increased Mortality in Early Systemic Sclerosis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster II

Background/Purpose: Our recent global blood transcript studies show that systemic sclerosis (SSc) patients have a prominent neutrophil signature. Mechanistic studies with neutrophils are hampered by their short half-life in-vitro, and the fact that neutrophils are not the predominant leukocyte in mice, underscoring the importance of direct human data for their relevance. Herein, we investigated whether higher neutrophil counts were associated/predictive of more severe disease and worse mortality in SSc.

Methods: Neutrophil counts were prospectively obtained as part of complete blood count examination in the GENISOS cohort. All patients had a disease duration < 5 years. Mixed effect linear regression analysis was used to examine the relationship between neutrophil count and longitudinal FVC% / modified Rodnan Skin Score (mRSS) measurements.

Results: At the time of analysis, 444 patients with SSc were enrolled from whom 392 had a baseline neutrophil count available (88.2%). The mean disease duration (SD) was 2.4 (1.5) years, 59.6% of patients had diffuse SSc. For the longitudinal analysis of serially obtained neutrophil counts, the number of concomitantly obtained mRSS and FVCs were 1676 and 1030, respectively.

At the baseline visit, higher neutrophil count was associated with male gender ($p<0.001$), diffuse disease type ($p<0.001$), higher mRSS ($p<0.001$), lower FVC% ($p=0.013$), and anti-topoisomerase positivity ($p=0.015$). There were no significant associations with age, disease duration, race, and RNA polymerase positivity.

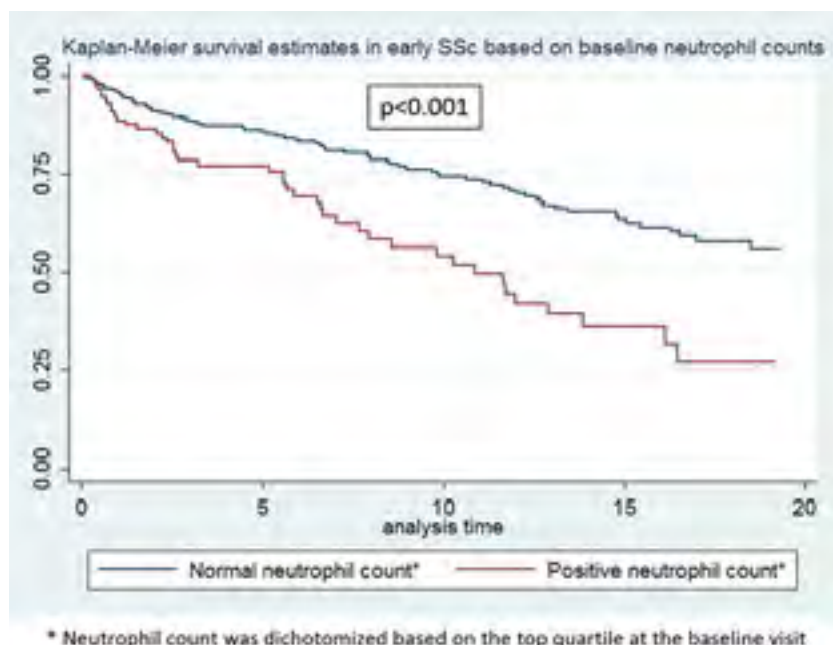
Higher longitudinal neutrophil counts were associated with higher serially obtained mRSS and lower FVC% (s ($p<0.001$ for both).

Next, the neutrophil count was dichotomized based on the top quartile value at the baseline study visit (6100 cells/ul). Patients with a positive neutrophil count at the baseline visit had on average 6.4 points higher serially obtained mRSS ($p<0.001$) and had on average 6.9% lower longitudinal FVC% (s ($p=0.007$). Moreover, positive neutrophil count was predictive of higher mortality in the univariable model ($p<0.001$ - Figure), as well as after adjustment for age, gender, topoisomerase status, diffuse disease type and prednisone use (Table). Specifically, patients with a positive neutrophil count had 1.9 times higher mortality during the follow-up time.

Conclusion: We show for the first time higher neutrophil count is predictive of more extensive skin/lung involvement and higher mortality in SSc. Neutrophils might play a role in SSc pathogenesis and their baseline counts can serve as an easily obtainable prognostic biomarker for disease severity.

	Hazard Ratio	95% CI	p-value*
Positive neutrophil count	1.93	1.25, 2.99	0.003
Age at enrollment	1.03	1.02, 1.05	<0.001
Female gender	0.74	0.45, 1.22	0.24
Prednisone use (>5mg per day)	1.51	0.93, 2.45	0.096
Positive topoisomerase I	1.54	0.97, 2.44	0.066
Diffuse disease type	1.05	0.7, 1.56	0.815

* p-value based on multivariable Cox regression analysis for all-cause mortality



Disclosure: R. Taherian, None; V. Mohan, None; J. Ying, None; S. Theodore, None; J. Charles, None; H. Pham, None; M. Wu, None; M. D. Mayes, Boehringer-Ingelheim, 2, 5, Corbus, 2, Reata, 2, Sanofi, 2, Mitsubishi-Tanabe, 5, Roche-Genentech, 2; S. Assassi, Bayer, 2, Biogen Idec, 2, Boehringer Ingelheim, 2, Momenta, 2, Boehringer Ingelheim, 5.

Abstract Number: 1721

Racial Differences in SSc Disease Presentation: A Cross-Sectional European Scleroderma Trials and Research Group Study

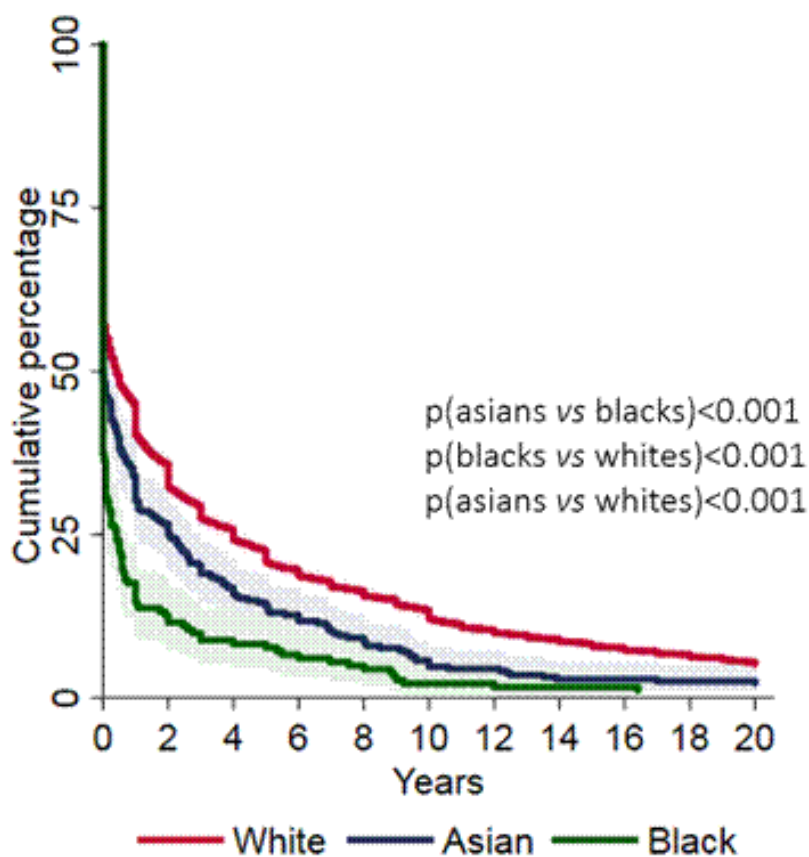
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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Figure. Kaplan-Meier curves with 95% CI of the first non-RP feature after RP onset according to racial group.



Patients who experienced their first non-RP feature of the disease before the onset of RP were included with a simultaneous onset.

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Genetic and environmental factors play a significant role in SSc. African Americans are known for a higher SSc incidence, an earlier age of onset, and a greater prevalence of interstitial lung disease and pulmonary hypertension (PH) compared to white patients. Data on blacks mostly stem from African Americans and studies on Asians are mostly from outside Asia and lack direct comparison with other racial groups.

We aimed to further evaluate differences of SSc presentations between white, Asian and black patients.

Methods: Characteristics of self-reported white, Asians or black SSc patients from the EUSTAR cohort were compared across racial groups; cox/logistic regression analyses were adjusted for age, sex, disease duration and antibody status.

Results: 9161 white, 341 Asian (208 patients from within, 133 from 34 centres outside Asia) and 198 black patients (82 patients from within, 116 from 35 centres outside sub-Saharan Africa [SSA]) were included.

Asian and black patients were on average 10 years younger than white patients ($p<0.001$). Black patients developed the first non-Raynaud's phenomenon (RP) SSc feature faster than Asian and white patients (all $p<0.01$; Figure) also after adjustment (HR [blacks] 1.4, $p<0.001$; HR [Asians] 1.1, $p=0.009$ vs whites). Asian patients treated within Asia (China) developed the first non-RP comparably to Asian patients treated outside Asia (HR [within Asia] 1.09, $p=0.48$). Black patients treated within SSA (South Africa) had a slightly faster disease onset than those treated outside SSA (HR [within SSA] 1.16, $p=0.37$).

Among ANA specificities, ACA predominated in white patients (whites: 42%, Asians: 16%, blacks: 10%; $p<0.001$) and anti-Scl-70 in Asian patients (whites: 35%, Asians: 47%, blacks: 34%; $p<0.001$). The prevalence of diffuse skin involvement was similar in Asian (28%) and white patients (26%), but more common in black patients univariately (56%; $p<0.001$) and multivariably (OR [Asians] 0.7, $p=0.06$; OR [blacks] 2.7, $p<0.001$ vs whites).

The prevalence of PH (defined as PAPsys >40 mmHg as estimated by echocardiography) was lower in white patients (whites 12%, Asians 18%, blacks 17%; $p=0.004$; OR [Asians] 2.6, $p=0.001$, OR [blacks] 2.8, $p=0.020$ vs whites). Asians had a higher prevalence of an impaired diffusing capacity for carbon monoxide ($<80\%$ of predicted; 84%) than black (74%) or white patients (70%, $p<0.001$) also in multivariable analysis (OR [Asians] 2.4, $p<0.001$; OR [blacks] 1.2, $p=0.55$ vs whites). Both, Asians (44%) and black patients (50%), had a higher prevalence of a reduced forced vital capacity ($<80\%$ of predicted) compared to white patients (23%, $p<0.001$) univariably and multivariably (OR [Asians] 2.5, $p<0.001$; OR [blacks] 2.4, $p=0.002$ vs whites).

Conclusion: Our analysis replicates the known clinical and serological differences between black and white patients and suggests that Asian have high prevalences of anti-Scl-70, PH and lung involvement.

Disclosure: V. K. Jaeger, None; E. Siegert, None; E. Hachulla, None; P. Airò, None; G. Valentini, None; M. Matucci-Cerinic, None; O. Distler, None; F. Cozzi, None; Y. Allanore, None; M. Li, None; M. Tikly, None; U. A. Walker, None.

Abstract Number: 1722

Patient-Level Factors Associated with Hospital Readmission Among Patients with Systemic Sclerosis Associated Pulmonary Hypertension

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SESSION INFORMATION

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Background/Purpose: Repeat hospitalizations in patients with pulmonary hypertension from all causes are associated with worse survival. However, predictors of systemic sclerosis associated pulmonary hypertension (SSc-PH) readmissions are unknown. The objective of this study is to identify patient-level factors associated with readmission among SSc-PH patients.

Methods: This retrospective study used clinical data from the prospective observational Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) registry. All patients met the 2013 ACR/EULAR classification criteria for SSc. PH was defined as a mean pulmonary artery pressure ≥ 25 mmHg on right heart

catheterization. The PHAROS investigators collected data for each hospitalization's primary reason and admission date. Readmission was defined as a subsequent hospitalization for any reason within 12 months. We compared patient-level characteristics of individuals with vs. without readmission using Fisher's exact test and the Wilcoxon rank-sum test. Logistic regression models were used to estimate associations between clinical variables and likelihood of readmission. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for all estimates. Survival comparisons were made using the log-rank test.

Results: Of 335 SSc-PH patients, 169 (50%) had at least 1 hospitalization. Of these, 48 (28%) had are admission. Patients with vs. without readmission more commonly had diffuse disease ($p=0.02$), positive Scl-70 autoantibody status ($p=0.03$), World Health Organization (WHO) Group 2 PH ($p=0.01$), higher modified Rodnan Skin Score($p=0.01$), and did not require home oxygen ($p=0.01$) (Table 1). Patients with diffuse vs. limited disease were significantly more likely to have a readmission (OR 2.49; 95% CI 1.23-5.06). Readmission was less likely in individuals who required vs. did not require home supplemental oxygen (OR 0.28; 95% CI 0.09-0.88) and in those with vs. without desaturation during a 6 minute walk test (0.11; 95% CI 0.01-0.90). Fifty-four patients died. Mortality rates were higher in patients with ≥ 2 vs. 0-1 readmission (66%

Table 1. Characteristics of Analytic Cohort.

Variable	Total (N=169)	No readmissions within 12m (n=121)	≥ 1 readmission within 12m (n=48)	p-value
Age, years	58.9 \pm 11.3	59.4 \pm 10.8	57.6 \pm 12.4	0.339
Sex, female, n (%)	136 (80.9%)	97 (80.6%)	39 (81.3%)	0.820
Race, n (%)				0.295
White	122 (74.9%)	90 (78.3%)	32 (68.7%)	
Black	27 (16.6%)	16 (13.9%)	11 (22.9%)	
Other	14 (8.6%)	9 (7.8%)	5 (10.4%)	
Antibody subtype, n (%)				0.031*
Anti-centromere	43 (27.0%)	37 (32.5%)	6 (13.3%)	
Anti-topoisomerase (Scl-70)	27 (17.0%)	20 (17.5%)	7 (15.6%)	
Isolated nucleolar ANA	32 (20.3%)	22 (19.3%)	10 (22.2%)	
Scleroderma subtype, n (%)				0.020*
Limited	103 (62.1%)	81 (68.6%)	22 (45.8%)	
Diffuse	57 (34.3%)	34 (28.8%)	23 (47.9%)	
Unclassified	6 (3.6%)	3 (2.5%)	3 (6.3%)	
PH Type				0.008*
At risk**	26 (24.1%)	16 (21.9%)	10 (28.6%)	
WHO Group I	53 (49.1%)	39 (53.4%)	14 (40.0%)	
WHO Group II	16 (14.8%)	6 (8.2%)	10 (28.6%)	
WHO Group III	13 (12.0%)	12 (16.4%)	1 (2.9%)	
Disease duration	8.7 [4.7, 15.1]	8.6 [4.6, 15.5]	9.5 [4.8, 14.5]	0.643
WHO functional class, n (%)				0.713
I	41 (24.7%)	29 (24.4%)	12 (25.5%)	
II	75 (45.2%)	51 (42.9%)	24 (51.1%)	
III	46 (27.7%)	36 (30.3%)	10 (21.3%)	
IV	4 (2.4%)	3 (2.5%)	1 (2.1%)	
Digital ulcers, n (%)	61 (39.9%)	43 (38.4%)	18 (43.9%)	0.579
Cough present, n (%)	70 (45.8%)	51 (45.5%)	19 (46.3%)	1.000
MRSS	5 [3, 10]	4 [2.5, 9]	6 [4, 12]	0.011*
Home oxygen, n (%)	45 (27.6%)	39 (33.1%)	6 (13.3%)	0.011*
History of calcinosis, n (%)	78 (47.9%)	54 (46.6%)	24 (51.1%)	0.609

WHO=World Health Organization; MRSS=modified Rodnan Skin Score, ANA=antinuclear antibody.
Note: * denotes p-values <0.05 . **At Risk = high-risk for PH SSc patients with (1) carbon monoxide diffusing capacity (DLCO) $<55\%$ predicted, (2) forced vital capacity to DLCO ratio ≥ 1.6 , or (3) estimated right ventricular systolic pressure >35 mmHg on echocardiography, but without right heart catheterization mean pulmonary artery pressure ≥ 25 mmHg.

vs. 30.6%, $p=0.009$) and similar in patients with 0 vs. 1 readmission (30.6% vs. 31%, $p=0.561$). Race, age, sex, SSc disease duration, and patient reported outcomes were not significantly associated with readmission.

Conclusion: Readmission was more common among SSc-PH patients with diffuse disease, WHO Group 2 PH, and positive Scl-70 autoantibody status. These patients may benefit from closer post-hospitalization follow-up. Home oxygen use was associated with lower likelihood of readmission and can be routinely assessed at the time of discharge in SSc-PH patients. Future studies should determine if universal testing for the need for home supplemental oxygen at the time of discharge reduces readmission among SSc-PH patients.

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Abstract Number: 1723

Intensified B-Cell Depletion Therapy in Progressive Systemic Sclerosis Patients: 24 Months Follow-up

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SESSION INFORMATION

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Background/Purpose: Systemic sclerosis (SSc) is a connective tissue autoimmune disease with systemic involvement and a serious medical condition with a high rate of mortality, especially due to interstitial lung disease (ILD). The exact pathophysiology is still unclear, but B cells seem to play a crucial role in the initiation and the progression of the disorder. Therefore, the use of Rituximab (RTX) might have a rational in the treatment of SSc.

Methods: We retrospectively collected data from SSc patients resistant or intolerant to previous therapies, treated with intensified B-depletion therapy, between 2013 and 2016. Therapeutic protocol comprehends: RTX 375 mg/sm on days 1, 8, 15, 22, and two more doses after one and two months, associated with two intravenous administrations of 10mg/kg of cyclophosphamide and three methylprednisolone pulses (15 mg/kg) followed by oral prednisone (0.8mg/kg/day, rapidly tapered to 5mg/day by the end of the 3rd month after RTX).

Results: The study included 20 SSc patients (18 females and 2 males; mean age 66.7 ± 11.0 years). Patients presented with severe multi organ involvement: ILD (19/20, 95%), pulmonary hypertension (12/20, 60%), and skin thickening (17/20, 85%). After a follow-up of 24 months, we observed a decrease in the levels of NT-proBNP (mean baseline: 385.4 ± 517 , mean at 24 months: 283 ± 648 , $p < 0.05$), and in the Modified Rodnan Skin Score (mRSS) (mean mRSS baseline: 14.4 ± 10.5 , mean after 24 months of follow-up: 12.9 ± 10 , $p < 0.05$). Four out of 19 (21%) patients experienced a significant improvement of ILD, as assessed by high-resolution computed tomography, while in 12/19 (63%) patients the intensified B-cell depletion therapy was associated with a stabilization of the imaging features with no sign of progression. Three out of 19 (16%) patients showed a deterioration of the ILD.

Patients showed no significant decrease in forced vital capacity (FVC) (mean baseline FVC: 93.6 ± 19.3 , mean after 24 months of follow-up: 92.2 ± 23.3), no significant decrease in forced expiratory volume in one second (FEV1) (mean baseline FEV1: 89.5 ± 15.6 , mean FEV1 at 24 months: 87 ± 21.2), no significant decrease in diffusing capacity (DLCO) (mean baseline DLCO values: 58.8 ± 8.6 , mean at 24 months: 60.3 ± 14), no significant change in the ejection fraction (EF)

(mean baseline EF values: 62.8 ± 6.4 , mean EF values at 24 months: 58.6 ± 7.1) and in pulmonary artery pressure (PAP) (mean baseline PAP: 30.2 ± 10.5 , mean at 24 months: 31.1 ± 11.05).

Conclusion: Our data suggest that the intensified B-depletion therapy protocol might represent a promising tool for the management of SSc in terms of controlling the progression of the disease, especially when considering pulmonary and skin manifestations.

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Effectiveness and Safety of Rituximab for the Treatment of Refractory Systemic Sclerosis Associated Calcinosis: A Case Series

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Background/Purpose: To analyze the effectiveness and safety of rituximab (RTX) for the treatment of refractory systemic sclerosis (SSc)–associated calcinosis.

Methods: We undertook an observational study of patients with this complication treated with 1 or more cycles of RTX (1 g x 2 weeks) and evaluated for at least 12 months after RTX treatment in a single center. The end point of patient follow-up was the date of the last clinic visit. All patients had baseline pre-rituximab (RTX) and follow-up X-rays every 12 months. The primary outcome measures of the study were the improvement of calcinosis symptoms (pain, signs of local inflammation, and new episodes of skin ulceration) and the radiologic evolution of the calcification(s). Clinical response was defined as a sustained improvement in the VAS of $\geq 50\%$ and no new episodes of local inflammation or skin ulceration. Radiologic response was defined as the complete resolution of the calcification(s) on the X-ray or as a significant reduction in calcification size ($\geq 20\%$ using the measurement functionality of the DICOM viewer), without appearance of new lesions.

Results: Thus far, we have treated 8 SSc patients with calcinosis with RTX (off-label use).

The mean number of previous treatments tested for calcinosis was 3. Of the 8 patients, 4 (50%) presented limited cutaneous scleroderma, and 4 (50%) had diffuse cutaneous involvement. The main indications for RTX were complicated calcinosis unresponsive to previous therapies with concomitant arthritis in 2 patients and refractory arthritis or interstitial lung fibrosing disease in the remaining 6 patients.

The mean number of RTX cycles administered was 3.12 ± 2.1 (range, 1-7), the median duration of RTX treatment was 9 months (interquartile range [IQR], 7.5-36 months), and the median follow-up after the first infusion of RTX dose was 19 months (IQR, 15-45 months).

Four patients (50%) had a significant improvement in clinical symptoms (sustained improvement in the visual analog scale for pain of at least 50% and no new episodes of local inflammation or skin ulceration). Two of these patients (25%) also had a complete resolution or significant reduction in the size of the calcification(s) on X-ray. None of them had drainage or surgical removal of these deposits that could explain the improvement of symptoms.

In the remaining 4 patients (50%), RTX did not provide any significant clinical or radiological benefit for calcinosis. In one of these patients, RTX was discontinued due to inefficacy; in the other three, treatment was maintained due to its beneficial effect in arthritis and interstitial lung disease.

No clinical predictor of response could be identified.: The frequency of adverse effects was low, occurring in only 1 patient (12.5%), who developed upper-respiratory tract infections not requiring hospitalization.

Conclusion: There is no definitely effective treatment for SSc-associated calcinosis to date. Our results and those previously reported suggest that RTX may be helpful in some patients with SSc-related calcinosis. These positive data remain preliminary and need to be viewed with caution, restricting for the moment its off-label use as a rescue therapy in selected cases of severe and refractory SSc-related calcinosis.

Disclosure: F. J. Narváez, None; J. P. Pirola, None; J. Lluch, None; P. Juárez, None; I. Morales, None; J. M. Nolla, None.

Fecal Microbiota Transplantation in Patients with Systemic Sclerosis- a Pilot Study

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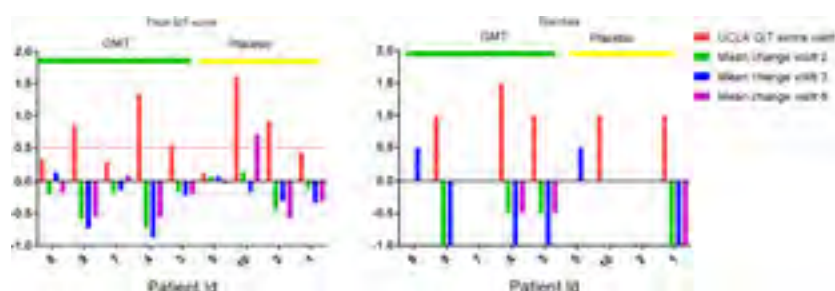
Session Time: 9:00AM-11:00AM

Background/Purpose: Upto 90% of patients with systemic sclerosis (SSc) have symptoms from the gastrointestinal (GI) tract. Earlier studies have shown a distinct alteration of the intestinal microbiome in SSc patients, compared to healthy adults. We therefore postulated that a normalization of the GI microbiota could improve some of the GI symptoms in this patient group. We aimed to determine the safety and efficacy of gut microbiota transplantation (GMT) in SSc patients and assess the effect on GI-symptoms and the general disease activity.

Methods: In this double-blind, placebo controlled pilot trial patients were randomized to the patented single-donor Anaerobically Cultivated Human Intestinal Microbiome (ACHIM) developed by ACHIM AB or placebo (culture media) (clinicaltrials.gov: NCT03444220). All participants had objective GI-involvement, were female >18 years old with limited cutaneous SSc and fulfilled the 2013 SSc classification criteria. Treatment was installed during upper gastroscopy twice with two weeks apart (week 0 and 2). Patients were followed for 16 weeks with six visits (week 0, 2, 4, 8, 12 and 16). GI-symptoms were reported using the ULCA-GIT score questionnaire. Primary end-point was defined as the minimally clinically important difference - the smallest change in score that patients perceive as beneficial. Disease activity was assessed by the validated SSc Disease Activity Index (DAI). Adverse events/safety were registered at each visit.

Baseline characteristics

Characteristics	
Number patients	10
Age, yrs (SD)	61.5 (5.5)
Time from disease onset, yrs (SD)	12.6 (10.1)
Sex, n (%)	10 (100)
lcSSc, n (%)	10 (100)
AC/A ₂ , n (%)	8 (80)
mRSS	4.1 (2.1-6.1)
DLI ₁ , n (%)	0 (0)
FVC, % (SD)	97.7 (88.9-106.5)
DLCO, % (SD)	74.4 (63.5-85.4)
UCLA GIT score	0.72 (0.13-1.62)
Bristol stool index (IQR)	4 (0.5)
Hb	13.1 (12.5-13.7)
CRP	5.1 (0.1-10.3)
ESR	13.4 (8.1-18.7)



Results: Ten patients were enrolled and randomly assigned to GMT or placebo. One patient was excluded due to laryngospasms during the first gastroscopy. GMT was safe, mostly mild and short-term side effects were reported like abdominal bloating (n=4), intermittent diarrhea (n=4), nausea (n=1) and constipation (n=1). One patient suffered a severe side effect during biopsy with duodenal perforation, requiring intravenous antibiotics. Baseline and prospective changes in UCLA-GIT score are demonstrated in figure 1, showing clinical improvement in total UCLA GIT-score and diarrhea. Five patients reported fecal incontinence at visit 1; three received GMT and reported restoration of continence. DAI-score in the GMT group was 2.4 (SD 1.4) at week 0 and 2.1 (SD 1.9) at week 16. In the placebo group mean DAI at week 1 was 2.5 (SD 1.5) and 1.8 (SD 1.5) at week 16.

Conclusion: The first double-blind, randomized clinical trial on GMT in SSc patients shows promising effects on GI symptoms. There was a clinically meaningful improvement in diarrhea and fecal incontinence after treatment with GMT. Larger trials are needed to confirm the results of this pilot study.

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Abstract Number: 1726

Sexual Dysfunction in Systemic Sclerosis Female Patients

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Background/Purpose: Systemic sclerosis (SSc) is a chronic autoimmune disease leading to various physical and psychological impairments including sexual dysfunction. The aim of this study was to assess sexual functions/quality of life and pelvic floor function in female SSc patients compared to age-/sex-matched healthy controls (HC), and to analyze the potential impact of disease activity, fatigue, physical activity and depression.

Methods: In total, 41 women with SSc (mean age: 50.9, disease duration: 5.8 years, lcSSc/dcSSc: 18/23, mRSS: 13.6, ESSG activity index: 2.5), who fulfilled the ACR/EULAR 2013 criteria, and 41 healthy controls (mean age: 50.9) without rheumatic diseases filled in 12 well-established and validated questionnaires assessing sexual function/quality of life, pelvic floor function, fatigue, physical activity and depression. Full names of questionnaires are listed in the table. Data are presented as mean±SEM.

Results: Compared to HC, patients with SSc had significantly higher prevalence and greater severity of sexual dysfunction (FSFI, BISF-W: in all subscales as well as total scores), dysfunction of pelvic floor (PISQ-12, PFIQ7), and worse sexual quality of life (SQol-F) (table). Worse scores in SSc patients were associated with higher disease activity [ESSG activity index: SQol-F ($r=-0.364$, $p=0.0443$), PFIQ7-gynaecological subscale ($r=0.492$, $p=0.0036$)], greater fatigue [all three questionnaires FSS/FIS/MAF correlated negatively with FSFI, BISF-W], more severe depression [BDI-II: FSFI ($r=-0.553$, $p=0.0002$), BISF-W ($r=-0.514$, $p=0.0007$), PFIQ7 ($r=0.495$, $p=0.0010$)], deteriorated quality of life [SHAQ: FSFI ($r=-0.536$, $p=0.0003$), BISF-W ($r=-0.563$, $p=0.0001$), SQol-F ($r=-0.338$, $p=0.0382$), PISQ-12 ($r=0.563$, $p=0.0051$), PFIQ7 ($r=0.380$, $p=0.0142$)], and worse ability to perform physical activities [HAP: FSFI ($r=0.407$, $p=0.0082$), BISF-W ($r=0.409$, $p=0.0078$)].

Conclusion: Women with SSc reported significantly impaired sexual function, sexual quality of life and pelvic floor function than age-matched healthy controls. Worse scores in SSc were associated with disease activity, physical activity, fatigue, depression and quality of life.

Questionnaire: score range	Systemic sclerosis (n=41)	Healthy controls (n=41)	p-value
FSFI: Female Sexual Function Index: 2(worst)-36(best)	15.2±1.7	25.0±1.7	p<0.0001
BISF-W: Brief Index of Sexual Function for Women: -16(worst)-75(best)	17.5±2.8	29.7±2.8	p=0.0027
PISQ-12: Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire short form: 0(best)-48(worst)	13.9±0.9	8.5±0.7	p<0.0001
PFIQ7: Pelvic Floor Distress Inventory Questionnaire – short form 7: 0(best)-300(worst)	26.4±5.9	7.1±2.2	p=0.0092
SQoL-F: Sexual Quality of Life Questionnaire – Female: 0(worst)-100(best)	56.7±3.9	78.8±3.3	p<0.0001
FSS: Fatigue Severity Scale: 9(best)-63(worst)	40.7±2.2	6.9±1.0	p<0.0001
FIS: Fatigue Impact Scale: 0(best)-160(worst)	59.2±4.9	28.8±4.3	p<0.0001
MAF: Multidimensional Assessment of Fatigue Scale: 1(best)-50(worst)	26.0±1.6	13.6±1.3	p<0.0001
BDI-II: Beck's Depression Inventory II: 0(best)-63(worst)	14.2 ±1.3	4.8± 0.8	p<0.0001
HAP: Human Activity Profile-adjusted activity score: 0(worst)-94(best)	49.4±3.7	81.1±1.5	p<0.0001
HAQ: Health Assessment Questionnaire: 0(best)-3(worst)	0.9±0.1	0.1±0.0	p<0.0001

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Abstract Number: 1727

Prospective Confirmation of Potential Link between Proton Pump Inhibitor Exposure and Calcinosis in Systemic Sclerosis

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SESSION INFORMATION

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Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Long-term use of proton pump inhibitors (PPI) have been linked to safety concerns. In a previous retrospective analysis, a potential association between PPI use and calcinosis in systemic sclerosis (SSc) was identified. We explored this in a prospective study.

Methods: Data from prospectively recruited patients were collected by patient survey, clinical review and medical records. Calcinosis was graded; size (+= <1cm, ++= ≥1≤3cm, +++= >3cm) and number of sites involved (NSI) (I = 1 body site, II = 2-3, III = >3). A total daily PPI equivalent dose (TDED) was calculated for each patient. We computed PPI exposure score (PPE) by multiplying the total duration of use in years (y) by TDED. For analysis, PPE was categorised into four groups; 0 = no exposure, 1 = up to 5y, 2 = 6-10y, 3 = >10y. Fishers exact test assessed categorical variables. Logistic regression assessed association between calcinosis and independent variables.

Results: 216 patients were recruited. Table 1 outlines patient and disease characteristics, including calcinosis and PPI use. Gastroesophageal reflux symptoms occurred in 83.3% of patients. Eleven (73.3%) of patients with large volume calcinosis (>3cm) had a PPE for > 10 years and all with calcinosis > 3cm had exposure to PPI. Of patients with only one body site involved 7/16 (43.75%) had PPE category 3 (>10 y). While of those patients with > 1 body site involved 36/49 (73.5%) had a PPE cat >10 years. The most frequent sites for calcinosis were finger (70.8%), elbow (35.4%) and knee (18.5%). Univariable analysis found associations between calcinosis at any time (CAT) and; disease duration (CAT OR 1.07, CI 1.04-1.11, p <0.001), PPE (CAT OR 1.03, CI 1.01-1.05, p =0.003) and increasing age (CAT OR 1.02, CI 1.00-1.04, p = 0.043). ATA and ANA positivity was associated with a risk reduction of CAT (ATA OR 0.27, CI 0.12-0.58, p = 0.001, ANA+ OR 0.25, CI 0.09-0.70, p =0.009). Greater than 10 years of exposure to PPI increased the odds of calcinosis by 4 times (CAT OR 4.07, CI 1.68-9.85, p = 0.002) compared to no exposure. Multivariable logistic regression results are shown in Table 2. Although the effect of PPI on calcinosis was attenuated after adjusting for disease duration and antibodies, higher exposure to PPI remained a significant predictor of calcinosis, with PPE category 3 (>10) increasing risk of CAT (OR 3.34, CI 1.16-9.17, p = 0.025).

Conclusion: We confirm a significant association between PPI exposure with calcinosis in SSc. Given the clinical impact of calcinosis, a potentially modifiable risk factor of PPI exposure warrants further study.

Table 1. Patient and disease characteristics.

Characteristic	Patients (n =216) Number (%)
Sex	
Female	176 (81.5)
Age (mean yrs)	57.46 (SD 13.5)
SSc Subtype	
Limited	122 (56.5)
Diffuse	68 (31.5)
Overlap	21 (9.7)
Juvenile Onset	4 (1.9)
Sine	1 (0.5)
Antibody category	
ACA	68 (31.5)
ATA	55 (25.5)
ARA	26 (12.0)
ANA+ ENA -	25 (11.6)
U3RNP	11 (5.1)
ANA- ENA -	9 (4.2)
PmSCL	8 (3.7)
Other ^a	14 (6.5)
Disease Duration (mean yrs)	10 (SD 9)
Calcinosis	
Current (CC)	65 (30.1)
Past	21 (9.7)
CAT	86 (39.8)
Never	130 (60.2)
Current Calcinosis no. body site/s	
I (1)	16 (24.6)
II (2-3)	28 (43.1)
III (>3)	21 (32.3)
Current Calcinosis Size	
+ (<1cm)	32 (49.2)
++ (≥1 ≤3cm)	18 (27.7)
+++ (>3cm)	15 (23.1)
PPI use	
Current	175 (81)
Past	32 (14.8)
PPIAT	182 (84.26)
Never	34 (15.74)
Mean Years on PPI	7.1 (SD 5)

ACA anti-centromere antibodies, ATA anti-topoisomerase I antibodies, anti-JD antibody, ANA anti-nuclear antibodies, ENA extractable nuclear antigens, U3RNP U3 ribonucleoprotein antibody, PmSCL protein synthesis defecting, Other^a anti-p157 (n=1), anti-PP1 (n=1), Anti-PLA2 (n=1), Anti-B (12, 0.05), 4090 (1, 0.1%), Anti-11 (0.05%), Ku (1, 0.1%), anti-RNP (1, 0.1%).

CC current calcinosis, CAT calcinosis at any time, PPIAT PPI at any time.

Table 2. Results of multiple logistic regression analysis for calcinosis at any time (CAT) vs experimental variables

Experimental Variables	Calcinosis and any time OR (95%CI)	p value
Disease duration (yrs)	1.07 (1.03-1.11)	0.001
Antibody (n, %)		
ACA (68, 31.5)	Reference cat	
ATA (55, 25.5)	0.32 (0.14-0.75)	0.008
ARA (26, 12.0)	0.61 (0.22-1.67)	0.332
ANA+, ENA ^Δ (25, 11.6)	0.17 (0.06-0.54)	0.002
U3RNP (11, 5.1)	0.90 (0.22-3.63)	0.8842
ANA-ENA- (9, 4.2)	0.13 (0.02-0.79)	0.026
PmSCL (8, 3.7)	2.75 (0.43-17.53)	0.285
Other ^Δ (14, 6.5)	0.18 (0.04-0.77)	0.021
PPE category		
0	Reference cat.	
1 (25)	0.955 (0.279-3.269)	0.942
2 (>5 ² 10)	1.953 (0.645-5.917)	0.263
3 (>10)	3.336 (1.159-9.173)	0.025

ACA anti-centromere antibody, ATA anti-topoisomerase I antibody/ anti-Scl-70 antibody, ARA anti-RNA polymerase III antibodies, ANA antinuclear antibody, ENA extractable nuclear antigen, U3RNP U3 ribonucleoprotein antibody, PmScl PmScl antibody, Other^Δ: nRNP, antiPR3, Th, Anti Scl, NOR90, Mi2, Ku, hnRNP, CC: current calcinosis, CAT: Calcinosis at any time, PPE: Proton Pump Inhibitor Exposure

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Abstract Number: 1728

Pharmacokinetics of Cyclophosphamide in Scleroderma Treated By Cyclophosphamide Versus Transplantation

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The pharmacokinetics (PK) of cyclophosphamide (CP) and its primary active metabolite, 4-hydroxycyclophosphamide (4-OH-CP) have not been adequately studied in scleroderma. The hypothesis of this sub-study of the Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial (Sullivan, KM et al., N Engl J Med 2018;378:35-47) was that response to CP, defined as event-free survival (EFS) at 54 months, will correlate with exposure (C_xT) to the active metabolite 4-OH-CP. Secondary objectives were to determine whether the initial CP exposure enhances activation of a second dose (auto-activation) and to evaluate the effect of CP on myelosuppression.

Methods: CP was infused over 1 to 2 hours in both study arms. Subjects in the transplant arm received a conditioning regimen of 120 mg/kg (mean 2099 mg/m²). Subjects in the CP arm received an initial infusion of 500 mg/m², then twelve doses of 750 mg/m²; PK analyses were only done after the first two doses. For transplant, 3 ml blood samples were drawn pre-dose and at 2, 4, 6, 8, 10, and 23 hours after infusion. For the CP arm, samples were collected at pre-dose, 0.5, 1, 2, and 24 hours. All samples were immediately derivatized with O-(2,3,4,5,6-pentafluorobenzyl) hydroxylamine and the 4-OH-CP oxime product analyzed by gas or liquid chromatography-mass spectroscopy. Separate blood draws (5 ml) were collected at ~24 and 48 hours following CP infusion in the transplant arm to determine white blood cell count (wbc). The single-dose PK parameters for CP and 4-OH-CP were computed from the drug C-T data using non-compartmental methods within WinNonLin Phoenix Version 6.2. Metabolic ratio was computed as the ratio of the AUC over 24h for 4-OH-CP to that for CP.

Results: Of the 12 subjects in the transplant arm and 9 in the CP arm, 75-89% were Caucasian women of median age 44 and 49, respectively. While the metabolic ratio varied 14-fold (0.6 – 8.3), the CxT profiles for both treatment arms were similar with a single elimination phase for both CP and 4-OH-CP. In the CP arm, CxT profiles for both parent drug and active metabolite were very similar in both cycles 1 and 2. When normalized for dose, the median AUC for 4-OH-CP in cycles 1 and 2 were 173 and 171 µg-h/ml, hence there was no auto-activation. There was a significant Pearson product-moment correlation between decrease in wbc and metabolic ratio at 48 h (p = 0.026) in the transplant arm. Odds ratios via logistic regression among PK parameters and EFS were not statistically significant. Odds Ratios - Likelihood of not meeting Event-Free Survival Endpoint¹

Arm	Parameter	Odds Ratio	Lower 95% CI	Upper 95% CI	P value
Cyclophosphamide	CP AUC242	1.0	1.0	1.0	0.94
Cyclophosphamide	CP Cmax	1.1	0.8	1.7	0.51
Cyclophosphamide	Metabolic Ratio3	0.9	0.3	2.1	0.74
Cyclophosphamide	4-OH-PC AUC24	1.1	0.7	1.8	0.70
Cyclophosphamide	4-OH-CP Cmax	3.3	0.1	126.3	0.53
Transplant	CP AUC24	1.0	1.0	1.0	0.20
Transplant	CP Cmax	0.8	0.5	1.1	0.15
Transplant	Metabolic Ratio	1.8	0.5	6.7	0.36
Transplant	4-OH-CP AUC24	1.0	0.7	1.6	0.89
Transplant	4-OH-CP Cmax	1.2	0.1	12.5	0.91

1 Event-free survival is survival without respiratory, renal or cardiac failure as defined in Sullivan, KM et al., N Engl J Med 2018;378:35-47.

2 AUC24, area under the concentration-time curve at 24 hrs.

3 Ratio of AUC24 for 4-OH-CP to that for CP.

Conclusion: This pilot study, the first of its kind, revealed variable metabolism of CP in scleroderma subjects and drug-induced myelosuppression in the transplant setting. However, in this small cohort of patients, CP exposure did not correlate with EFS in either treatment arm.

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Abstract Number: 1729

Increased Risk of Valvular Heart Disease in Patients with Systemic Sclerosis: Results from a Population-Based Cohort (1980-2016)

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic Sclerosis (SSc) is a complex, heterogenous autoimmune disease characterized by microvascular injury and widespread fibrosis of the skin and internal organs, particularly lungs and heart. The heart is one of the major organs affected in SSc, although the recognition of cardiac abnormalities is probably underestimated due to the occult nature and variable reports of prevalence. Clinically evident cardiac involvement is associated with a poor

prognosis, with up to 70% mortality at 5 years. In this population-based cohort study, we aimed to examine the occurrence of moderate/severe valvular heart disease (VHD) in patients with SSc relative to comparators.

Methods: Medical records of patients with a diagnosis or suspicion of SSc in a geographically well-defined area from Jan 1, 1980 to Dec 31, 2016 were reviewed to identify incident cases of SSc (defined by physician diagnosis). Fulfillment of the 1980 and 2013 SSc classification criteria was ascertained. A 2:1 cohort of age- and sex-matched non-SSc subjects from the same population base was randomly selected for comparison. Data on SSc characteristics, cardiovascular risk factors including smoking status, obesity, hypertension, dyslipidemia, diabetes mellitus, use of aspirin, known coronary heart disease, peripheral artery disease, abdominal aneurysm, atrial fibrillation, and heart failure were collected by manual record review. Echocardiogram reports were reviewed for occurrence of moderate/severe VHD including aortic, pulmonary, mitral or tricuspid valve stenosis or regurgitation. Cumulative incidence of VHD adjusting for the competing risk of death was estimated. Cox models were used to examine potential associations between baseline factors of interest and the development of VHD.

Results: The study included a total of 79 incident SSc cases and 158 non-SSc comparators [mean age 55.8 years (SD 15.7), 90% female for both cohorts]. There was a nearly 4 fold increase in the prevalence of moderate/severe VHD prior to SSc diagnosis compared to non-SSc subjects (11% vs 3%; $p=0.011$). During a median of 9.0 years of follow-up in patients with SSc and 10.5 years of follow-up in non-SSc comparators, 15 SSc and 15 non-SSc patients developed VHD. The cumulative incidence of VHD at 10 years after SSc incidence/index was 23.6% (95% confidence interval [CI]: 14.5-38.4%) in patients with SSc compared with 7.4% (95% CI: 4.0-13.5) in non-SSc subjects (Hazard Ratio: 2.86; 95% CI: 1.38- 5.91, $p=0.004$). No significant risk factors for VHD were found.

Conclusion: SSc patients have a 3 fold increased risk of developing moderate/severe valvular dysfunction after diagnosis of SSc compared to Non-SSc subjects. They also have a 4 fold increased prevalence of moderate-severe VHD at diagnosis compared to non-SSc patients. Underlying mechanisms for this association require further elucidation.

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Abstract Number: 1730

A Role for Duplex Ultrasound of Hand Arteries in the Assessment of the Vasculopathy Associated to Systemic Sclerosis-like Diseases

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SESSION INFORMATION

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Background/Purpose: Small vessel arteriopathy precedes the development of organ damage and tissue fibrosis in systemic sclerosis (SSc) and related disorders. It is currently considered that providing early vascular protection might result in a slower and milder progression of the disease. However, there is still no standard of care for this poorly understood process, besides symptomatic measures and treatment of complications. A major reason could be the lack of available tools for the routine assessment of the microcirculation at the clinic. In order to overcome this hurdle, we have launched a study addressing the utility of ultrasonography (US) in identifying robust outcome measures in patients with relevant SSc-like vasculopathy. Our first objective was to look for associations between US-based hemodynamic measures and features of vascular injury in a cohort of patients with Raynaud's Phenomenon (RP).

Methods: 26 real-life patients have been enrolled, 10 of which had primary RP (PRP) and 16 secondary RP (SRP), with 11p diagnosed with SSc. 5 of the patients with SRP had a past history of complications, and 10 had macroscopic alterations at the time of the study. All patients had a recent nailfold videocapillaroscopy (NVC) recording which had been pathologic in 15p. Of these, 10p had an SSc typical NVC pattern of lesions. Patients underwent a Duplex US evaluation of 6 arterial regions (cubital, radial, 1st, 2nd, and 3rd digital branches and the superficial palmar arch) at the non-dominant hand. Systolic peak (PS), end diastolic velocity (ED), maximum speed, resistance index and the PS to ED ratio (PS/ED)

were registered. Global and specific health questionnaires were recorded as independent variables, and their association with the US data was established with non-parametric tests. An alpha value of 5% was considered significant.

Results: Globally, no single US parameter discriminated between PRP and SRP. However, patients with anti CENP-B antibodies, history of RP-associated complications, concurrent macroscopic alterations and/or an SSc-type of NVC pattern of lesions showed significantly lower PS and/or ED, at least at one region, in particular at the cubital artery and the 2nd digital branch, while a decreased PS/ED at the palmar arch was associated to CENP-B antibodies and to a past history of complications. Interestingly, the SF36 domain of global health was lower in the SRP subgroup (p 0.035) and associated to a lower PS/ED at the cubital artery (p 0.019). Also associated to this hemodynamic parameter were SF36 social performance (p 0.037) and mental health (p 0.04) domains, while both the RP severity scale and number of episodes were negatively associated with the cubital artery PS values (p 0.002, p 0.019, respectively).

Conclusion: In this initial approach we have observed that Duplex US is able to distinguish patients with SSc-associated vasculopathy from those with milder RP. Our results point to reduced PS and PS/ED in the ulnar territory as potential outcome measures for further research.

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Abstract Number: 1731

Vertebral Fracture Prevalence and Measurement of the Scanographic Bone Attenuation Coefficient on CT-Scan in 70 Patients with Systemic Scleroderma

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Background/Purpose: Osteoporosis screening is not systematic in sclerodermic patients but some studies demonstrated a similar risk between rheumatoid arthritis and systemic scleroderma [1,2,3]. Thoracic and/or TAP (thoraco-abdomino-pelvic) CT (Computed Tomography) scans are classically performed in the follow-up of scleroderma, mainly to evaluate lung involvement.

Objectives: To study vertebral fracture (VF) prevalence and the scanographic bone attenuation coefficient of the first lumbar vertebra (SBAC-L1) on CT scans in systemic scleroderma patients. Secondary objectives are to study specific risk factors of SBAC-L1 \leq 145 Hounsfield Units (HU) and to evaluate SBAC-L1 measurements reliability.

Methods: This monocentric retrospective study included patients followed from 2000 to 2014 and fulfilling ACR/EULAR 2013 criteria for systemic scleroderma and who underwent a thoracic or TAP CT scan. Osteoporotic risk factors, Dual Energy X-ray Absorptiometry (DXA) measurements and clinical characteristics were collected. For CT scan, the VFs were determined according to Genant's classification on sagittal sections. The SBAC-L1 was measured in Hounsfield Units (HU) on axial section of L1 in a Region of Interest drawn in trabecular bone. Intra- and inter-reader reliabilities for SBAC-L1 were calculated. An SBAC L1 \leq 145 HU (fracture threshold) was used to define patients at risk of VF [4]. Predictive factors for VF or SBAC-L1 \leq 145 HU were studied.

Results: A total of 70 patients were included (mean age: 62.3 (\pm 15.6) years, women 88.5%, diffuse scleroderma 22.9% (n=16)) in the study. Sixty patients (85.7%) presented with at least one clinical risk factor for osteoporosis. Eighteen patients (25.7%) received vitaminocalcic supplementation and 10 (14.3%) received antiresorptive therapy. DXA was only performed on 30 patients (42.8%), and 5 (16.7%) of them presented a T-score \leq -2.5 DS. 3 VFs were detected in 3 patients (4.3%). The mean SBAC-L1 was 157.26 HU (\pm 52.1), and 35 patients (50%) presented a SBAC-L1 \leq 145 HU. SBAC-L1 measurements were highly reliable (Kappa $>$ 0.9 for both intra- and inter-reader reliability). For the univariate analysis, a SBAC-L1 \leq 145 HU was significantly associated with age (OR=1.09, CI 95%: 1.04-1.13), calcinosis (OR=6.3, CI

95%: 1.61-24.75) and periarticular calcifications (OR=3.22, CI 95%: 1.06-9.77). For the multivariate analysis, age (especially patients older than 63 years), calcinosis and acro-osteolysis were independently associated with a SBAC-L1 \leq 145 HU.

Conclusion: On a large sample of sclerodermic patients with clinical risks of osteoporosis, only 42.8% were screened for DXA and 16.7% of them were osteoporotic. The VF prevalence on CT scan was 4.3% and the SBAC-L1 measurement identified 50% of the population at the fracture threshold. The presence of calcinosis, periarticular calcifications or acro-osteolysis should lead to an osteoporosis screening, especially for patients under 63 years old.

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Abstract Number: 1732

Alterations of Body Composition in Patients with Systemic Scleroderma Are Associated with Disease Activity, Physical Activity and Serum Levels of Inflammatory Cytokines

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Background/Purpose: Fibrosis of the skin and visceral organs, especially digestive tract, and musculoskeletal involvement in systemic sclerosis (SSc) can have a negative impact on body composition and physical activity. The aim was to assess body composition and physical activity of SSc patients and healthy controls (HC) and the association with selected inflammatory cytokines in SSc.

Methods: 59 SSc patients (50 females; mean age 52.5; disease duration 6.7 years; lcSSc:34/dcSSc:25) and 59 age-/sex-matched HC (50 females, mean age 52.5) without rheumatic or tumour diseases were included. SSc patients fulfilled ACR/EULAR 2013 criteria. We assessed body composition (densitometry: iDXA Lunar, bioelectric impedance: BIA-2000-M), physical activity (Human Activity Profile, HAP questionnaire), disease activity (ESSG activity index) and serum levels of 27 cytokines (commercial multiplex ELISA kit, Bio-Rad Laboratories). Data are presented as mean \pm SD.

Results: Compared to HC, SSc patients had significantly lower body mass index (BMI), body fat % (BF%) and visceral fat weight (VF), and also significantly decreased lean body mass (LBM), and bone mineral density (BMD). Compared to HC, SSc patients had increased extracellular mass/body cell mass (ECM/BCM) ratio, reflecting deteriorated nutritional status and worse muscle predispositions for physical activity (Table 1). Increased ECM/BCM in SSc positively correlated with disease activity (ESSG), skin score (mRSS) and inflammation (CRP, ESR), and was associated with worse quality of life (HAQ, SHAQ), fatigue (FSS), and decreased physical activity (HAP). ESSG negatively correlated with BF%. HAP positively correlated with BMD (Table 2). Increased serum levels of several inflammatory cytokines were associated with alterations of body composition (Table 3).

Table 1			
Correlated parameters	SSc (n=59)	JRC (n=59)	p-value
BMI (Body Mass Index) (kg/m ²)	22.4±4.3	27.4±8.3	<0.001
BF% (Body Fat %) (iDXA)	32.6±8.2	38.0±7.6	<0.001
BF% (Body Fat %) (BIA)	24.3±7.9	31.3±7.6	<0.001
VF (Visceral Fat) (kg)	0.5±0.5	1.0±0.3	0.001
LBM (Lean Body Mass) (kg, iDXA)	47.8±7.0	51.9±8.4	0.005
LBM (Lean Body Mass) (kg, BIA)	40.9±6.8	45.4±7.3	0.005
ECM/BCM (Extracellular Mass/Body Cell Mass ratio)	1.28±0.4	1.03±0.1	<0.001
BMD (g/cm ²)	1.0±0.1	1.2±0.1	<0.001
HAP (Human Activity Profile)	64.1±17.2	84.7±6.6	<0.001

Table 2			
Correlated parameters	r	p-value	
ECM/BCM:ESSG (European Scleroderma Study Group activity Score)	0.273	0.044	
BF% (iDXA):ESSG (European Scleroderma Study Group activity Score)	-0.324	0.014	
ECM/BCM:mRSS (Modified Rodnan Skin Score)	0.171	0.005	
ECM/BCM:CRP (C-reactive Protein)	0.292	0.028	
ECM/BCM:ESR (Erythrocyte Sedimentation Rate)	0.302	0.023	
ECM/BCM:HAQ (Health Assessment Questionnaire)	0.438	0.001	
ECM/BCM:SHAQ (Scleroderma Health Assessment Questionnaire)	0.268	0.044	
ECM/BCM:FSS (Fatigue Severity Scale)	0.366	0.004	
ECM/BCM:HAP (Human Activity Profile)	-0.644	<0.001	
BMD:HAP (Human Activity Profile)	0.28	0.032	

Table 3			
Correlated parameters	r	p-value	
LBM (Lean Body Mass) (kg, iDXA, BIA):IL-1b	0.347; 0.289	0.009; 0.034	
LBM (Lean Body Mass) (kg, iDXA, BIA):IL-6	0.275; 0.280	0.035; 0.035	
LBM (Lean Body Mass) (kg, iDXA, BIA):IL-17	0.387; 0.388	0.002; 0.003	
LBM (Lean Body Mass) (kg, iDXA, BIA):EOTAXIN	0.267; 0.299	0.041; 0.024	
LBM (Lean Body Mass) (kg, iDXA, BIA):TNF	0.284; 0.267	0.031; 0.047	
BMR (Basal Metabolic Rate) (kcal):IL-1b; IL-6; IL-17; EOTAXIN; TNF	0.339; 0.282; 0.383; 0.258; 0.288	0.011; 0.03; 0.003; 0.048; 0.028	
TBW (Total Body Water) (%):IL-1b; IL-6; IL-5; IL-8; EOTAXIN	0.441; 0.314; 0.361; 0.367; 0.338	<0.001; 0.017; 0.009; 0.005; 0.01	
TNF:VF (Visceral Fat) (kg); FFM (Fat Free Mass) (kg); A/G (Android/Gynoid ratio); BMD (Bone Mineral Density) (g/cm ²)	0.299; 0.287; 0.369; 0.262	0.023; 0.029; 0.004; 0.047	

Conclusion: Compared to healthy age-/sex-matched individuals we found significant negative changes in body composition of our SSc patients, which are associated with the disease activity and physical activity, and could reflect their nutritional status, and gastrointestinal and musculoskeletal involvement. Serum levels of certain inflammatory cytokines were associated with alterations of body composition in SSc patients. Acknowledgement: AZV-16-33574A, MHCR 023728 and GAUK 312218.

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Abstract Number: 1733

Should We Perform Exercise Echocardiogram As a Screening Test for Pulmonary Arterial Hypertension (PAH) for All Systemic Sclerosis (SSc) Patients?

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Prevalence of pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc) is 8-12%, and 3-year survival rate is 47-56%. Rest echocardiogram is used to screen for this pathology; recent studies suggest that systolic pulmonary artery pressure (sPAP) increase >18 mmHg with exercise may be a marker for early PAH diagnosis in SSc patients. However, left diastolic dysfunction, comorbidities, and sarcopenia may impair exercise echocardiogram interpretation. We explored its use as a screening tool for early PAH detection in SSc patients.

Methods: Cross-sectional, observational study that included SSc patients (ACR/EULAR 2013 criteria) NYHA classes I-II, and peak tricuspid regurgitant jet velocity at rest echocardiogram <3m/s. We excluded patients with established PAH, interstitial lung disease (ILD) >20% of extent, cardiac disease, renal failure, diabetes mellitus, lipid disorders, systemic arterial hypertension, untreated thyroid disease, pulmonary embolism, tobacco use (>2 pkg/year), use of vasodilators, pregnancy or contraindication to perform the tests (echocardiogram with cycloergometer, starting at 10W and increasing 5W every min, maximum 60W; cardiopulmonary exercise test (CPET) with modified Bruce protocol on a computer-controlled cycle ergometer, and body mass composition). All the patients read and signed an informed consent form. The study was approved by the local IRB and was performed according to the Declaration of Helsinki contents.

Results: We included 19 patients. Fourteen (73.7%) with limited cutaneous (lc) SSc and 5 (26.3%) with diffuse cutaneous (dc) SSc; 17 were female. Mean age was 50.8 (\pm 8.6 SD) years and mean duration of the disease was 78.2 (\pm 53.7 SD) months. Mean modified Rodnan Skin Score (mRSS) was 3.6 (\pm 3.1 SD) in lcSSc and 13.4 (\pm 6.1 SD) in dcSSc patients. Twelve patients had NYHA I (63.2%). Mean BNP was 47.8 (\pm 48.1 SD). Mean forced vital capacity (FVC) was 87.4%. Cardiovascular evaluation: Mean rest sPAP was 28 mmHg (\pm 6.4 SD), sPAP at maximum effort was 52 mmHg (\pm 8.4 SD), with mean delta sPAP of 24 mmHg (\pm 6.4 SD). A sPAP increase of >18mmHg was observed in 15 (78.9%) of our patients. Pulmonary Vascular Reserve (PVR) was elevated (mean 3.4 ± 0.8 mmHg/ml/m² SD), suggesting pulmonary vasculopathy, while E/E' ratio was normal (8.3 ± 1.9 SD), suggesting normal left diastolic function. At CPET, mean peak oxygen uptake was normal (80.6%), suggesting early, non-severe, pulmonary vasculopathy. The normal relative skeletal muscle mass index (RSMI) (6.5 ± 0.95 kg/m² SD) ruled out sarcopenia as a cause of low exercise performance.

Conclusion: Seventy nine percent of SSc patients without cardiovascular risk factors and with normal mPAP at rest echocardiogram, showed changes suggestive of pulmonary vasculopathy in exercise echocardiogram. This finding was not related to diastolic dysfunction or muscular impairment, and may reflect vascular changes that may lead to overt PAH. Standardized exercise echocardiogram may be useful to screen SSc patients for PAH.

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Abstract Number: 1734

Association of Short-Term Longitudinal Changes in Clinical and Physiologic Variables with Overall Survival in Patients with Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster II

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Session Time: 9:00AM-11:00AM

Background/Purpose: Interstitial lung disease (ILD) is one of the leading causes of morbidity and mortality in patients with SSc. However, the impact of changes in pulmonary function on clinical outcomes in SSc-ILD patients is not well understood. We assessed the association of changes in clinical and physiologic variables with survival in SSc-ILD patients.

Methods: Adult patients from the EUSTAR (European Scleroderma Trial and Research) database enrolled since January 2009, fulfilling 1980 ACR or 2013 ACR/EULAR criteria for SSc, with signs of lung fibrosis on X-ray and/or HRCT and/or an available date of ILD diagnosis, with ≥ 1 follow-up visit within 12 months after the first visit with ILD diagnosis (index visit) were eligible for the study. 12-month absolute changes in lung function including predicted forced vital capacity (FVC% pred) and predicted diffusing capacity of carbon monoxide (DLco%pred), changes in the modified Rodnan skin score (mRSS) and occurrence of digital ulcer (DU) were assessed for associations with overall survival. 2 disease progression definitions were analysed for association with survival: (A) lung and skin progression defined as 'absolute decline in $>10\%$ FVC pred or mRSS $>25\%$ & >5 points' (FVC/mRSS) and (B) 'absolute decline in $\geq 10\%$ FVCpred or $\geq 5\%$ FVCpred. & DLco $\geq 15\%$ pred' (FVC/DLco). Survival time was defined as the duration between the visit where change was determined and the last visit with survival status, censored after 5 years of observation. Kaplan–Meier (KM) survival was analysed by Breslow test, and Cox's proportional hazards models (Cox-PH) adjusted for age, gender, pulmonary hypertension, smoking and treatment status.

Results: Of 7752 patients enrolled in the EUSTAR database between 2009 and April, 2018, 857 fulfilled the inclusion criteria. In the KM analysis, a deterioration of $\geq 10\%$ FVC pred within 12 months since index date as well as both FVC/mRSS and FVC/DLco progression definitions were associated with significantly lower survival (Fig.1). No associations with survival were found for changes in DLco%pred, mRSS, or occurrence of DU. Cox-PH multivariate models confirmed lower survival in patients with FVC decline $\geq 10\%$ pred (OR=3.1 [1.6;6.0]), with FVC/DLco decline (OR=2.7 [1.5;4.9]), or with FVC/mRSS deterioration (OR=1.9 [1.1;3.4]).

Conclusion: Our study showed that a decline in FVC of $\geq 10\%$ pred within 12 months follow up is associated with lower survival in SSc-ILD patients. Also both disease progression definitions showed an association with reduced survival. Short term changes in clinical and physiological variables over 12 months should be considered for prognostic stratification of SSc-ILD patients in addition to baseline values.

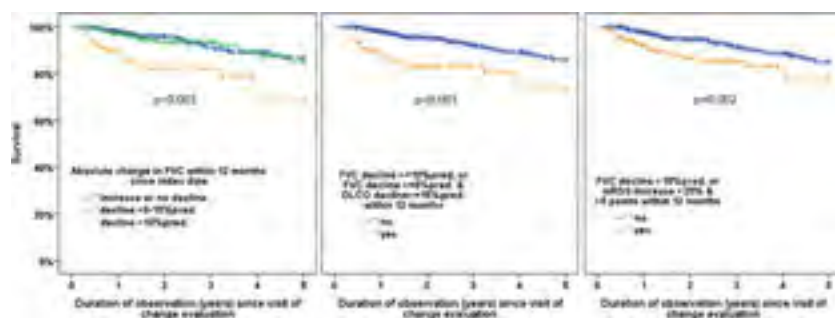


Figure 1: KM survival analysis:(L-R) Change in FVC% pred; FVC/DLco; FVC/mRSS

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Diagnostic Accuracy of MR Angiography in a Cohort with Systemic Sclerosis Compared to Other Rheumatic Diseases with Acral Hypoperfusion

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SESSION INFORMATION

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Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster II

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Background/Purpose: Vasculopathy is a major feature of systemic sclerosis (SSc). It leads to intimal proliferation and adventitial fibrosis of small and large arterial blood vessels. Videocapillaroscopy (VC) for nailfold-capillaries and MR-angiography (MRA) for arteries are established methods to assess pathologies. However, little is known about the correlation between VC and MRA and about the evolution of changes in response to therapy over time.

Methods: We included consecutive patients of our tertiary center who had a MRA between 1.1.2008 - 30.04.2018. We present an intermediate analysis performed in 03/2015: twenty-one patients with SSc (mean age 55.2 ± 15.6 ; 13 females, 8 males; 4 diffuse SSc, 17 limited SSc) and 22 patients with other inflammatory rheumatic diseases (OD; mean age 50.1 ± 18.8 ; 15 females, 7 males) had a total of 71 MRA acquired by a 3T MR scanner. We analyzed digital arteries and calculated a semiquantitative vascular score. We compared the MRA with the VC in correlation with clinical and laboratory data. We further analyzed a subgroup of 8 patients who had both a MRA and VC twice or more. We used SPSS version 23 program, Pearson's Chi-Test, Fisher's test for statistics.

Results: ANA were significantly more frequent in SSc- (85%) than in OD-patients (50%) ($p < 0.001$), ACA in 38% and 10% ($p = 0.02$), Scl70 in 38% and 4% ($p < 0.001$) respectively. Raynaud was present in 95% of SSc patients and 61% in OD, DU in 71.4% and 73.5% respectively. Duration of Raynaud was significantly longer ($p = 0.005$) in limited vs diffuse form (72.2 vs 30 months). However, prevalence of DU was similar in both limited and diffuse SSc.

The subgroup analysis of patients with 2 or more pairs of VC/MRA are showed in table 1.

In 7 out of 11 cases, the clinical changes correlated with MRA changes, in 2 cases they didn't; 2 cases cannot be analyzed because of missing data. VC only correlated with the clinical course in 2 cases, while 5 cases had missing or unclear data. VC status did not improve, even if the clinical status did. Two patients with OD and 2 of 6 with SSc showed clinical improvement.

In case of DU, there was a good correlation with vessel damage, but damaged vessels did not necessarily result in DU of the corresponding finger.

Table 1: Course of VC, MRA and clinical status in a subgroup of 8 patients. \leftrightarrow stable status; \uparrow better status; \downarrow worse status; * the patient 8 had 5 pairs of VC/MRA; each letter depicts the course between two such pairs; x the patient had the medication mentioned above. NA not available; ? status could not be interpreted

Conclusion: MRA assesses reliably and accurately the vasculopathy of the hand in SSc. It may unveil important subclinical vessel damage and bears the potential to guide preventive drug treatment. Unlike VC, MRA appears to correlate with the clinical course.

Patient	VC	MRA	Clinic	Iloprost	Bosentan	Sildenafil
1	\leftrightarrow	\leftrightarrow	\leftrightarrow	2x	x	x
2	\leftrightarrow	\uparrow	\uparrow		x	
3	?	\leftrightarrow	\leftrightarrow	x	x	x
4	\downarrow	\downarrow	\downarrow	7x	x	
5	\leftrightarrow	\leftrightarrow	\uparrow	x	x	
6	\leftrightarrow	\uparrow	\uparrow	x		
7	\leftrightarrow	\uparrow	\uparrow		x	
8a	?	\uparrow	\leftrightarrow	x	x	
8b*	?	\leftrightarrow	\leftrightarrow		x	
8c*	?	\downarrow	NA	x	x	
8d*	\leftrightarrow	\downarrow	NA		x	

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Abstract Number: 1736

Incidence and Risk Factors for Gangrene in Patients with Systemic Sclerosis from the Eustar Cohort

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SESSION INFORMATION

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Background/Purpose: In patients with systemic sclerosis (SSc), peripheral vasculopathy can promote critical ischemia and gangrene that are very severe complications with potential life-threatening consequences. Recently the DUO registry suggested a 18% prevalence of gangrene in SSc patients with digital ulcers (DUs), with smoking and a high number of DUs being predictive factors. However, little is known about gangrene in unselected SSc patients. The aim of this study was to investigate the prevalence, incidence and risk factors for gangrene in the EUSTAR cohort.

Methods: We included patients from the EUSTAR database fulfilling the ACR 1980 or the ACR/EULAR 2013 classification criteria for SSc, with at least one visit recording data on gangrene. We extracted from this database data regarding the reporting of DUs, DU history and gangrene. Centers were asked for supplementary data on traditional cardiovascular (CV) risk factors. We analyzed by uni- and multivariable logistic regression the cross-sectional relationship between gangrene and its potential risk factors such as history of DUs, cutaneous subset, disease duration, autoantibodies, classical cardio-vascular risk factors. Longitudinal data were analyzed by Cox proportional hazards regression.

Results: 1757 patients matched the inclusion criteria (age at inclusion 55.9 ± 14.5 years, disease duration since first non-Raynaud's symptom 7.9 ± 10.3 years, male sex 16.7%, 24.6% diffuse cutaneous subset (DcSSc)). At inclusion, 8.9% of patients had either current or previous digital gangrene, 15.7% had current DUs and 42.7% have had DUs ever. Among the potential risk factors, older age, a history of DUs and the DcSSc subset were statistically significant risk factors in the cross-sectional multivariable model (Table).

For the longitudinal part, during the entire follow-up (median [Q1,Q3] 13.1 [9.6, 19.3] months), 16/771 patients had incident gangrene (0.9%), accounting for an incidence of 1.94/100 patient-years. All 16 patients who developed incident gangrene had previously had DUs and gangrene. Further risk factors for incident gangrene were the DcSSc subset and longer disease duration.

Table. Factors associated with gangrene in patients with SSc from the EUSTAR cohort: univariable and multivariable logistic regression on cross-sectional data from the first visit mentioning data on gangrene.

	Univariable logistic regression		Multivariable logistic regression	
	OR (CI 95%)	p	OR (CI 95%)	p
Age	1.009 (0.997-1.021)	0.131	1.024 (1.001-1.049)	0.044
Male sex	1.206 (0.793-1.834)	0.382	1.208 (0.555-2.628)	0.634
Disease duration	1.039 (1.023-1.055)	0.000	1.010 (0.981-1.040)	0.505
Digital ulcers ever	26.171 (13.24-51.73)	0.000	38.37 (9.16-160.73)	0.000
DcSSc	2.262 (1.609-3.179)	0.000	2.498 (1.226-5.093)	0.012

Table . (Cont'd)

	Univariable logistic regression		Multivariable logistic regression	
	OR (CI 95%)	p	OR (CI 95%)	p
Anti-centromere+	0.709 (0.499-1.008)	0.055	0.998 (0.446-2.186)	0.976
Anti-topoisomerase+	1.727 (1.229-2.427)	0.002	0.720 (0.331-1.568)	0.408
Cigarette smoking ever	1.246 (0.745-2.083)	0.402	1.243 (0.641-2.411)	0.519
Dyslipidemia	1.155 (0.788-1.693)	0.459	0.998 (0.464-2.147)	0.997
Diabetes mellitus	2.097 (1.103-3.989)	0.024	0.519 (0.099-2.711)	0.437
Arterial hypertension	1.008 (0.687-1.479)	0.967	0.829 (0.389-1.765)	0.627
History of CV events	2.829 (1.747-4.580)	0.000	2.468 (0.956-6.371)	0.062

Conclusion: In unselected SSc patients, gangrene still occurs in 9% of SSc patients. A history of DUs and, to a lesser extent, the DcSSc subset are strongly and independently associated with gangrene, while traditional CV risk factors were not identified as risk factors. Our results confirm that gangrene is still a concern in SSc. They emphasize on the importance of microvascular SSc-associated disease in the pathogenesis of gangrene and suggest that the DcSSc subset should be prioritized for risk-stratification of the patients.

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Abstract Number: 1737

Multiplexed Autoantibody Profiles in a Systemic Sclerosis Clinical Trial Comparing Autologous Hematopoietic Stem Cell Transplantation and Cyclophosphamide

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SESSION INFORMATION

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Background/Purpose: In a randomized, open-label, phase II clinical trial (SCOT, Scleroderma: Cyclophosphamide or Transplantation)¹, subjects were randomly assigned to treatment with myeloablative CD34⁺ selected autologous hematopoietic stem-cell transplantation (HSCT) or high-dose monthly cyclophosphamide (CYC). Global rank composite scores at 54 months post-randomization revealed significant benefits of HSCT vs CYC. We used multiplexed antigen arrays to profile serum IgG autoantibodies in all subjects at all available time points.

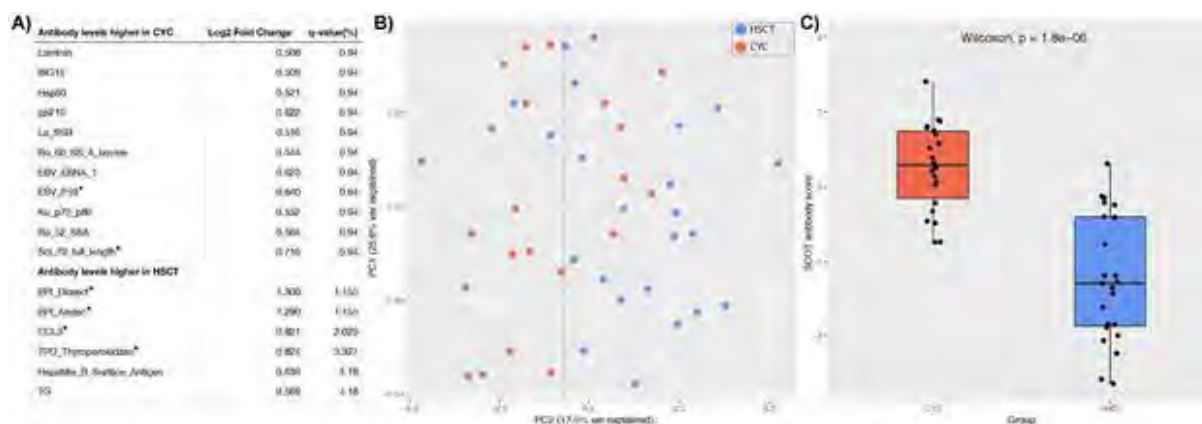
Methods: We fabricated a 288-plex, bead-based array containing 223 protein antigens, including 113 autoantigens, 87 soluble proteins such as cytokines, chemokines, and growth factors, and 23 control or viral proteins. A total of 193 serum samples from 63 SCOT subjects, and 20 samples from healthy controls, were profiled for the presence of serum IgG autoantibodies. We compared autoantibody profiles from subjects at month 26 (n=23 HSCT, n=22 CYC) using Significance Analysis of Microarrays (SAM) to identify differences in mean fluorescence intensity values between groups (q value ≤5%; abs(log2 fold change) ≥0.5).

Results: No significant baseline differences were found in autoantibody profiles between the CYC and HSCT groups. Control subjects had significantly less or no reactivity to any of the 223 arrayed proteins. At 26 months, SAM identified antibodies against 17 antigens that were significantly different between treatment groups (11 increased in CYC, 6 increased in HSCT, Fig 1, panel A). Using Principal Component Analysis (PCA), PC1 and PC2 explained 43% of the variance (Fig 1, panel B). Wilcoxon rank sum scores generated using the 17 antigens were significantly different between groups (p=1.8e-06, Fig 1, panel C). Antibodies to Epstein Barr Virus (EBV) antigens were higher in the CYC group. Anti-Hepatitis B surface antigen levels were higher in the HSCT group, consistent with vaccination in the HSCT but not CYC group. Levels of antibodies against the chemokine CCL3 and two different commercial sources of the neutrophil protein bactericidal

permeability increasing protein (BPI) were higher in the HSCT group. The top loadings in PC2 included CCL3 and BPI, as well as Scf70, EBV p18, and thyroperoxidase (TPO).

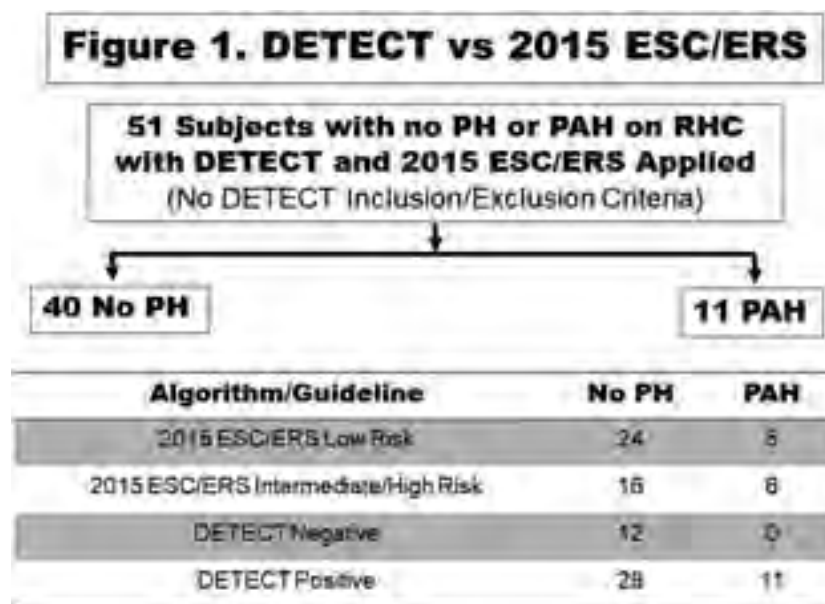
Conclusion: Antibodies to traditional autoantigens, infectious agents and secreted factors differed between HSCT and CYC groups post-treatment. Ongoing analyses include comparison of responder status, and assessment of time-dependent trends in antibody levels in individual subjects that could serve as actionable biomarkers.

1. Sullivan K.M. *et al.* *NEJM* 2018;378:35-47.



had PAH. DETECT had 100% sensitivity and NPV whereas 2015 ESC/ERS had 54.5% sensitivity and 82.8% NPV as 5 subjects with PAH were missed(Figure 1). DETECT was able to detect PAH even in those with DLCO \geq 60% (N=3).

Conclusion: Evidence based screening algorithms using composite measures and not just echocardiography alone improve screening for SSc-PAH. Although use of DLCO < 60% enriches the probability for SSc-PAH, subjects with SSc-PAH can have higher DLCO values. Although our sample size is small, it appears that DETECT performs well in those with DLCO \geq 60%.



Disclosure: A. Young, None; V. M. Moles, None; V. Nagaraja, None; D. Vummidi, Boehringer Ingelheim, 5; S. H. Visovatti, None; V. McLaughlin, Consultancies Bayer, Arena, Medtronic, Merck, SteadyMed, United Therapeutics, St. Jude Medical, Actelion., 5, Grant / Research Support: Actelion, Eiger, Sonovie, Arena, Bayer., 2; D. Khanna, Eicos Sciences, 1, Pfizer, Inc., 2, Horizon, 2, BMS, 2, Actelion, 5, Bayer, 5, Bayer, 2, Corbus, 5, Cytos, 5, EMD Serono, 5, Genentech, Inc., 5, Sanofi-Aventis, 5, GSK, 5, Boehringer Ingelheim, 5, Civi BioPharma, 3.

Abstract Number: 1739

What Do Patient Reported Outcomes for Routine Monitoring of Gastrointestinal Tract Symptoms in a Systemic Sclerosis Center Tell Us about Clinical Features of Potential Small Intestinal Bacterial Overgrowth?

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The implementation of patient reported outcome measures (PROMs) is increasingly recognized as a critical aspect of clinical practice. The use of gastrointestinal (GI) PROMs is particularly important in systemic sclerosis (SSc), especially for the identification of small intestinal bacterial overgrowth (SIBO), where hydrogen breath testing for definitive diagnosis is difficult to perform. In this report, we examine the clinical correlates of two validated GI PROM scores in SSc to inform the design of a pragmatic trial in SSc SIBO.

Methods: Patients seen at a single center SSc Clinic, who met the 2013 ACR/EULAR Criteria and were enrolled in the INSYNC registry received an electronic link to a personal health assessment questionnaire that included the Scleroderma

Clinical Trials Consortium University of California Los Angeles Gastrointestinal Tract (GIT2.0) and gastrointestinal global symptom score (GSS), which have previously been validated in the SSc population. The GIT 2.0 (34 questions) provides a total score of GIT severity, and is calculated by an average of all scales (questions 1-8 reflux, 9-12 distention/boating, 13 soilage, 14-15 diarrhea, 16-21 social function, 22-30 emotional well-being, 31-34 constipation), except constipation. The scores range from mild (0-0.49) to severe-to very-severe (1.01-3). The GSS assesses nausea, vomiting, abdominal pain/discomfort, bloating, diarrhea, constipation, abdominal tenderness, dysuria, tenesmus, fever and general illness/malaise, with each symptom scored from 0 (absent) to 3 (severe). It has previously been reported in the SSc population that a GSS ≥ 5 is predictive of SIBO. We compared the GIT 2.0 scores in those with GSS <5 and ≥ 5 , using the t-test, with significance set at 5%.

Results: From January to May 2018, 43 SSc patients completed both the SCTC GIT 2.0 and GSS (59 % completion rate). These patients were 95% female, 67% limited cutaneous subtype, 73% scleroderma-specific autoantibodies (40.5% centomere, 13.5% SCL70, 18.9% RNA pol3), with an average disease duration of 13.5 years. The subscales of GIT 2.0 according to GSS are shown in Table 1. As expected the potential SIBO patients with a GSS ≥ 5 had significantly more distention/bloating ($p=0.001$), but unexpectedly more constipation ($p=0.04$) on the GIT 2.0.

Conclusion: Gastrointestinal complaints are common in SSc and PROM questionnaires are an essential aspect of care, but the optimal number of questions and mode of questionnaire delivery are important as evidenced by our completion rate. If a GSS ≥ 5 represents SIBO, then this study suggests that subscales of the GIT 2.0 may be able to effectively capture this disease entity. The social functioning and emotional well-being domains of GIT 2.0 warrant further study in SIBO patients.

Table 1: Subscales of the GIT 2.0 according to GSS(with ≥ 5 possibly identifying SIBO)

GIT 2.0 Subscales	GSS ≥ 5 (n=24)	GSS < 5 (n=19)	p-value
Reflux	0.83	0.46	0.051
Distention/Bloating	1.28	0.57	0.001
Diarrhea	0.65	0.34	0.093
Social	0.56	0.13	0.002
Emotional	0.65	0.15	0.001
Constipation	0.67	0.29	0.043
Soilage	0.33	0.11	0.171

Disclosure: J. Zhu, None; C. Gale, None; J. Biber, None; M. Nikpour, Actelion, GSK, Pfizer, BMS, Eli Lilly, UCB, Astra Zeneca, Janssen, 2, 5; M. Baron, None; T. M. Frech, None.

Abstract Number: 1740

Effectiveness and Safety of Tocilizumab for the Treatment of Refractory Systemic Sclerosis Associated Interstitial Lung Disease: A Case Series

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To evaluate the efficacy and safety of TCZ as a rescue therapy in patients with refractory scleroderma-associated interstitial lung disease (SSc-ILD).

Methods: We undertook an open observational study of patients with progressive SSc-ILD despite treatment with immunosuppressants and rituximab (RTX), treated with TCZ for at least 6 months. The main efficacy variables evaluated at the end of the follow-up period were the evolution of the respiratory functional tests, distance traveled during the 6-minute walk test (6MWT), and changes in high-resolution chest computed tomography scan (HRCT).

Results: Thus far, we have treated 9 patients with TCZ (off-label use). All of them were women, with a mean (\pm SD) age at TCZ onset of 57 ± 7 years (range, 40-64 yrs). Of the 9 patients, 5 (55%) presented limited cutaneous scleroderma, and 4 (45%) had diffuse cutaneous involvement. The median durations of SSc and ILD were 8 years (range, 2-15 yrs) and 7 yrs (range, 2-12 yrs), respectively. All cases corresponded to fibrosant nonspecific interstitial pneumonia (NSIP). Regarding their autoantibody profile, 67% (6/9) of the patients tested positive for anti-Scl-70 antibodies, whereas ACA antibodies were positive in 33% (3/9); anti-Ro 52 antibodies were tested in 5 patients, being positive only in 1 case.

Previous or ongoing therapies for SSc-ILD included mycophenolate (100%), cyclophosphamide (67%), azathioprine (11%), and rituximab (100%). The mean number of RTX cycles previously administered was 2.6 ± 1.9 (range, 1-6); in three patients (33%) RTX was discontinued due to adverse effects (mainly respiratory or urinary infections and transient neutropenia).

The median follow-up after the first dose of TCZ dose was 12 months (interquartile range [IQR], 25th-75th: 6-33 months). The outcome of the main efficacy variables evaluated during the follow-up period is detailed in these tables.

	Pre-TCZ (mean \pm SD)	Post-TCZ (mean \pm SD)	Delta (mean)	p
FVC % predicted	74.2 \pm 24.7	76.1 \pm 29.1	1.2	0.627
TLC% predicted	88 \pm 7	75.6 \pm 10.1	-11.5	0.034
DLCO% predicted	50.4 \pm 18.9	47.3 \pm 17.4	-1.8	0.492
Mean distance covered in 6MWT	398.3 \pm 13.7	357.2 \pm 47.3	-41.3	0.949

	FVC	DLCO	HRCT (performed only in 5 patients)
No change / Stabilization	5	4	2
Improvement	1	0	0
Worsening	3	5	3

Considering the total sample, at the end of the follow-up period, only 4 patients (45%) were still in treatment. In the other 5 (55%) TCZ was discontinued due to inefficacy. One (9%) of these 5 patients died due to progression of ILD. The frequency of adverse effects was low, occurring in only 1 patient (11%), who developed several infections (upper respiratory tract infection not requiring hospitalization, herpes zoster, and osteomyelitis complicating one scleroderma digital ulcer).

Conclusion: According to this preliminary real-life experience, the effectiveness of TCZ as a rescue treatment in patients with refractory SSc-ILD seems modest but not negligible, achieving a stabilization of pulmonary function in 45% of patients.

Disclosure: J. Lluch, None; I. Castellvi, None; J. Alegre, None; P. Juárez, None; J. M. Nolla, None; F. J. Narváez, None.

Abstract Number: 1741

Disease Duration and Autoantibodies Predict Distinct Skin Score Trajectories in Diffuse Cutaneous Systemic Sclerosis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

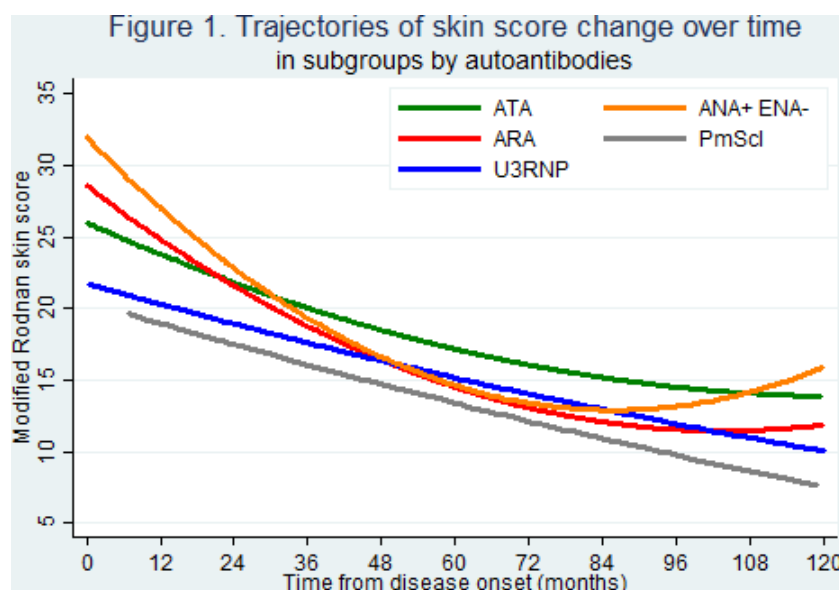
Background/Purpose: Although severity of skin involvement and change in skin thickness over time vary substantially between patients with diffuse cutaneous systemic sclerosis (dcSSc), for the majority of patients, skin tends to improve over time. We were interested in determining the effect of autoantibodies on the patterns of change in skin thickness over time in patients with dcSSc.

Methods: Subjects with confirmed diagnosis of dcSSc and at least one modified Rodnan skin score assessment were included. Linear mixed models were used to assess association between changes in mRss over time and autoantibody specificities.

Results: In total, 572 dcSSc patients were included. Of those, 127(22.2%) were male and mean \pm SD age at disease onset was 44.5 \pm 13.7 years. The most common scleroderma-specific antibodies were anti-topoisomerase I (ATA), present in 174 (30.4%) and anti-RNA polymerase (ARA) in 153 (26.8%) of the subjects. Anti-U3RNP was found in 39 (6.8%), anti-PmScl in 28 (4.9%) and ACA in 17 (3%). A substantial proportion of the cohort was ANA+, but ENA- (n=99,17.3%). Other antibody specificities included anti-nRNP, SL, Ku, Jo1, Ro, PL7, hnRNP and Sm. In 24 subjects (4.2%) ANA was negative. Three or more mRss assessments were available for 72.2% (n=413). For 66.4% of the patients (n=380), first mRss assessment was made within 3 years from disease onset.

For the cohort as a whole, the average mRss at 12 months from disease onset was estimated to be 23.5 (SD 9.4; 95% CI 22.6, 24.5) and this gradually declined following a non-linear trajectory ($mRss = 23.5 - 2.3 * \text{years} + 0.1 * \text{years}^2 - 0.002 * \text{years}^3$, $p < 0.001$ for all parameters). Thus skin improvement was greater in earlier disease (average drop in mRss was 2.2 between years 1 and 2, compared to 1.58 between years 4 and 5, and 0.8 between years 9 and 10, for example). There was a moderately strong, negative association between mRss at 1 year and drop in mRss over time (correlation coefficient = -0.62), suggesting that higher initial skin scores are associated with greater subsequent improvement. Focusing on the first 10 years of disease, autoantibodies showed significant association with both baseline mRss and changes in mRss overtime (Figure 1). At 1 year from disease onset, highest average mRss (27.0) was observed in ANA+ ENA- patients. Compared to those, mRss in ARA+ patients was 24.9, $p = 0.166$; in ATA+ 23.8, $p = 0.043$; in anti-U3RNP+ 20.3, $p = 0.008$ and in anti-PmScl+19, $p = 0.009$. Over subsequent years, the greatest improvement was observed in ANA+ ENA- and ARA+ patients with respective drop in mRss of 4.2 and 3.3 between year 1 and 2, compared to 2 in ATA+ patients ($p < 0.005$) and 1.4 in anti-U3RNP+ ($p < 0.020$).

Conclusion: Skin score change is significantly associated with autoantibody specificity and disease duration. While mRss can be much higher in ARA+ and ANA+ENA- patients compared to other antibodies, those patients experience the greatest improvement over time.



Disclosure: S. I. Nihtyanova, None; A. Sari, None; V. H. Ong, None; C. P. Denton, Roche, Actelion, GlaxoSmithKline, Sanofi-Aventis, Inventiva, SCL Behring, Boehringer-Ingelheim, Bayer., 5.

Abstract Number: 1742

Disease-Specific Autoantibodies Associate with Remarkably Different Risk of Development of Significant Lung Fibrosis in Systemic Sclerosis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Pulmonary fibrosis (PF) is a leading cause of disease-related death in SSc patients. Some studies suggest that the timing of PF development differs between patients with different autoantibodies. We set out to assess a large single-center SSc cohort, focusing on the timing of clinically significant PF (csPF), and to compare this within

subgroups with different disease-specific autoantibodies, in particular ACA, anti-Scl-70 and anti-RNA polymerase antibody (ARA).

Methods: Patients with confirmed SSc and information on autoantibodies were included. PF was confirmed on high-resolution CT and defined as clinically significant based on at least one of the following: FVC<70%; a drop in FVC>15%; DLCO<70% with no pulmonary hypertension (PH) present; or a drop in DLCO>15% with no PH. Only subjects who had first available lung function test result within the first 3 years from onset were included. 1-Kaplan-Meier (1-KM) estimation was used to calculate cumulative incidence of csPF. To assess the timing of highest rates of csPF development, hazard rates were calculated within intervals of 12 months over the follow-up.

Results: A total of 450 subjects, 75 (16.7%) male, mean age of onset 47.4 years, were included in the study. Of those 225 (50%) had dcSSc, 105 (23.3%) carried ACA, 113 (25.1%) Scl-70 and 72 (16%) ARA. Mean follow-up was 12 years, interquartile range 8-16 years. Over the entire follow-up period, 196 (43.6%) of the subjects developed csPF. Using 1-KM estimation, for the whole cohort, over the first 20 years of disease, approximately half of the patients developed csPF. Three quarters of those had reached this endpoint by 5 years (38.2%) with much lower incidence thereafter (at year 10, 15 and 20 - 43%, 47% and 49.6%, respectively). Subgroup analysis showed that ACA was associated with a very low risk of csPF development (cumulative incidence of 5.9%, 8.1%, 9.8% at 5, 10 and 15 years from SSc onset). On the other hand, Scl-70+ patients had a remarkably high risk of csPF development, which ultimately occurred in the majority of cases, with cumulative incidence of 77.6% at 5 years, 82.7% at 10 years and 87.1% at 15 years. Rates of csPF development among ARA+ patients were higher than those in ACA+, but still much lower than ATA+, and even after 20 years of follow-up, the cumulative incidence of csPF among them was less than a half of that among ATA+ patients (23.7%, 33% and 41% at years 5, 10 and 15). The hazard of csPF among ACA+ patients was highest in the second year from SSc onset (3%) and in the subsequent years varied between 0 and 1.8%. On the other hand, among Scl-70+ patients hazard of csPF was 28.3% in year 1, 44.9% in year 2, peaked at 52.5% in year 3 and went down sharply thereafter. Although hazard was much lower among ARA+ patients, this still peaked at year 3 (2.8%, 6.1% and 12.1% at year 1, 2 and 3 respectively) and declined after.

Conclusion: Our analysis demonstrates that overall risk of csPF differs by antibodies but csPF tends to develop early in the disease course, regardless of antibody specificity. The overall risk is highest at around 3 years from disease onset and goes down thereafter. These findings can inform clinical monitoring and trials recruitment.

Disclosure: S. I. Nihtyanova, None; A. Sari, None; A. Leslie, None; V. H. Ong, None; C. P. Denton, Roche, Actelion, GlaxoSmithKline, Sanofi-Aventis, Inventiva, SCL Behring, Boehringer-Ingelheim, Bayer., 5.

Abstract Number: 1743

Serum Markers Potentially Associated with PAH in Systemic Sclerosis; A Targeted Screening Approach

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SESSION INFORMATION

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Background/Purpose: Pulmonary arterial hypertension (PAH) is a feared complication in systemic sclerosis (SSc). Detection of PAH at a preclinical stage is important as early diagnosis seems to improve outcome. Serum markers of PAH are in demand as detection of PAH to date relies on echocardiography and right heart catheterization (RHC), which are both time- and cost consuming. Also, identifying mechanistic pathways may aid the development of novel treatment strategies for PAH. Several serum markers are to date proposed to be altered in PAH patients, but studies are often conflicting, stressing the necessity for validation studies.

Methods: All SSc patients referred to the Oslo University Hospital are included in the prospective SSc cohort. Serum samples are collected at first visit. RHC is performed on patients suspected of pulmonary hypertension (PH) based on echocardiography, DETECT calculator or clinical suspicion. We defined PAH as precapillary PH (mean pulmonary arterial pressure, mPAP ≥25 mmHg) in the absence of significant interstitial lung disease (ILD), based on high resolution

computed tomography and lung function tests. Patients with group II or III PH were excluded from analyses on PAH, as well as patients with combined high tricuspid regurgitant velocity (TRV) on echocardiography and normal or absent RHC. Serum markers previously shown to be associated with immunologic diseases and/or cardiopulmonary organ involvement were quantified by ELISA (Table 1). Observation period was defined as time from serum sampling to death or study end (May 2018).

Results: The cohort included 297 SSc patients of whom 37 were excluded due to PH group II/III, while 11 were excluded due to conflicting TRV and RHC. Patients were compared to 99 healthy controls. RHC was performed in 132 patients and PAH was diagnosed in 43 patients (15% of total) during the observation period. PAH-patients presented with higher age (64 vs 53 years, $p<0.001$), more frequent limited disease (93% vs 73%, $p<0.001$) and anti-centromere antibodies (84% vs 48%, $p<0.001$) than patients without PH. Besides previously shown associations of CCL21 and endostatin, patients with PAH presented higher values of osteoprotegerin, osteopontin, and activin-A compared to other SSc patients (Table 1). Activin-A (OR 1.15, 95%CI 1.03-1.29, $p=0.013$) and osteopontin (OR 1.01, 95% CI 1.01-1.01, $p=0.018$) also showed association with PAH-status in multivariable logistic regression adjusted for age and sex.

Conclusion: In this study we show associations between higher levels of osteoprotegerin, osteopontin and activin-A with SSc-PAH.

Table 1: Serum levels of the individual marker panel proteins in patients and controls

	SSc-PAH (n=43)	SSc, no PH (n=206)	Controls (n=99)
CCL21, ng/μl (SD)	0.50 (0.22)*, †	0.33 (0.24) ‡	0.18 (0.06)
CCL19, ng/μl (SD)	1.12 (1.66)	0.81 (1.35)	0.62 (1.21)
Osteopontin, ng/μl (SD)	60 (48)*, †	38 (32) *, †	21 (10)
Endostatin, ng/μl (SD)	109 (35)*, †	89 (36) ‡	65 (11)
Activin-A, ng/μl (SD)	6.62 (3.14)*, †	5.30 (3.03) ‡	3.90 (2.50)
Osteoprotegerin, ng/μl (SD)	3.82 (1.12)*	3.32 (1.03)	-
PTX3, ng/μl (SD)	7.74 (14.30) †	4.44 (10.64)	3.14 (6.28)
CXCL10, ng/μl (SD)	1323 (2666)	793 (2113)	458 (1306)
NGAL, ng/μl (SD)	176 (120)	150 (97)	159 (53)
VEGF-A, ng/μl (SD)	0.30 (0.21) †	0.25 (0.22) ‡	0.18 (0.13)
CD166, ng/μl (SD)	110 (28) †	103 (31) ‡	85 (13)
CCL2, ng/μl (SD)	0.54 (0.20)	0.64 (0.82) ‡	0.42 (0.54)
DKK1, ng/μl (SD)	3.71 (2.95) †	3.50 (2.67) ‡	2.13 (1.55)
CXCL3, ng/μl (SD)	2.79 (4.04)	2.63 (5.31) ‡	1.14 (1.35)
TARC, ng/μl (SD)	0.66 (0.53) †	0.62 (0.51) ‡	0.39 (0.32)

* $p<0.05$ between SSc-PAH and non-PAH; † $p<0.05$ between SSc-PAH and controls; ‡ $p<0.05$ between SSc non-PAH and controls, tested by ANOVA with Tukeys posthoc test.

Disclosure: A. Heiervang Tennøe, None; H. Fretheim, None; O. Midtvedt, None; T. Garen, None; T. Ueland, None; P. Aukrust, None; A. K. Andreassen, None; E. Gude, None; Ø. Molberg, None; A. M. Hoffmann-Vold, None.

Abstract Number: 1744

Prognostic Value of Right Heart Involvement in Systemic Sclerosis: Not Only Pulmonary Arterial Hypertension

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster II

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Background/Purpose: In SSc, cardiac dysfunction is associated with poor prognosis. Right ventricular involvement is frequently secondary to PAH. Echocardiography is the routine imaging tool to detect cardiac involvement and pulmonary hemodynamic. Our aim was to evaluate right ventricular function and non-invasive hemodynamic by standard trans-thoracic Doppler echocardiography in SSc patients without known cardiac involvement and PAH, compared to healthy controls.

Methods: 343 SSc patients (mean age, 54.2±14.8 years) and 340 healthy age-matched controls (mean age 52.0±16.9 years, p=ns) prospectively underwent a comprehensive trans-thoracic 2D and Doppler echocardiography, including tissue Doppler imaging analysis (TDI) of both the right and left heart. Patients with known cardiac involvement and/or a diagnosis of PAH were excluded. Patients were followed-up and cardiac events were recorded as new onset of heart failure (HF), development of PAH, significant ventricular or supra-ventricular arrhythmias requiring therapy or implantable cardioverter-defibrillator (ICD).

Results: Compared to controls, SSc patients did not show differences in systolic left ventricular function, while a worse diastolic left ventricular function, as well as worse right ventricular function and pulmonary circulation parameters were found (table). Mean follow-up was 32 ± 28 months. During the follow-up a total of 52 events occurred. Echocardiographic predictors of cardiac events at univariate analysis were E/e' (e' as mean of TDI lateral and septal values), right ventricular (RV) end-diastolic diameter, pulmonary artery systolic pressure (PASP), and presence of even trivial pericardial effusion. At multivariate analysis, only PASP was an independent predictor (hazard ratio 1.05, C.I. 1.01-1.10, p<0.0001).

Conclusion: SSc patients without overt cardiac dysfunction and no PAH show worse parameters of right ventricular function and pulmonary hemodynamic compared to controls, although still within normal values. These indexes of subclinical right heart involvement provide prognostic information and are independent predictors of further cardiac events, even in patients without PAH.

Disclosure: L. Gargani, Geeneral Electronics, 5, GlaxoSmithKline, 5; C. Bruni, None; A. Moreo, None; L. Belloli, None; S. Bellando-Randone, None; O. M. Epis, None; F. Ferrara, None; O. Vríz, None; E. Bossone, None; P. M. Seferovic, None; D. E. Furst, None; M. Matucci-Cerinic, None.

Abstract Number: 1745

Efficacy of Eosinophilic Granulomatosis with Polyangiitis (Churg–Strauss) Treatments According to the Type of Manifestations Based on Analysis of 376 Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss) is a small-vessel necrotizing vasculitis characterized by blood and tissue eosinophilia and asthma. Glucocorticoids (GCs) represent the cornerstone of treatment. So far, EGPA management has been based on conventional immunosuppressants, but relapses and/or GC-dependence are frequent. More recently, biotherapies targeting B cells and interleukin-5 have been used, but data on large cohorts are lacking. This study aimed to describe therapeutic management and efficacy of conventional immunosuppressants and targeted biotherapies in EGPA patients.

Methods: We started a multicenter European collaborative initiative that included 376 EGPA patients from tertiary referral centers. Remission was defined as the absence of vasculitis manifestations (BVAS=0), asthma and ENT manifestations with a GC dose <7.5 mg/d. Treatment failure was defined as no improvement or worsening and the inability to taper GCs.

Results: After median follow-up of 58.5 (IQR 26.7–101) months, 175 (46.5%) patients were in prolonged remission, 141 (37.5%) had GC-dependent asthma and/or ENT manifestations and 108 (28.7%) had had [≥]1 vasculitis relapse(s). For remission induction, cyclophosphamide was the most frequently used immunosuppressant (54%), mainly because of cardiac, renal and/or nervous system involvement. Induction conventional immunosuppressants (cyclophosphamide, azathioprine or methotrexate), prescribed based on disease severity, achieved remission rates similar to GCs alone, in terms of overall survival, relapse-free survival and evolution towards 4 different identified profiles. At the first vasculitis relapse, having GC-dependent asthma and/or ENT manifestations and a high GC-dependency threshold were associated with a higher risk of treatment failure (57% vs. 32%, P=0.008). As for induction, conventional immunosuppressants seemed to be similar to GCs alone to achieve remission and lower the relapse risk. Rituximab was prescribed as first-line therapy for 5 patients and for 6 relapsing patients, and achieved remissions in 82%. During follow-up, GC-dependent asthma and/or ENT manifestations were treated with azathioprine (48%), methotrexate (35%), mycophenolate mofetil (16%), cyclophosphamide (10%), cyclosporine (6%) or rituximab (6%), achieving GC-tapering to <7.5 mg/d for 27%, 41%, 42%, 15%, 71% and 29%, respectively. Mepolizumab

Conclusion: Despite their beneficial impact on overall survival of EGPA patients, the efficacies of conventional immunosuppressants proved disappointing, as achieving remissions, preventing vasculitis relapses and controlling GC-dependent asthma and/or ENT manifestations were not improved. Notwithstanding a small number of treated patients, eosinophil-targeted therapies seemed to be promising but their efficacies against vasculitis, asthma and/or ENT manifestations require further investigation.

Disclosure: M. Papo, None; G. Emmi, None; F. Schiavon, None; M. Groh, None; M. L. Urban, None; C. Marvisi, None; J. E. Kahn, None; A. Sinico, None; M. Samson, None; P. Cohen, None; X. Puéchal, None; L. Mouthon, None; L. Guillevin, None; A. Vaglio, None; B. Terrier, None.

Abstract Number: 1746

Impact of Interstitial Lung Disease on the Long-Term Survival in 76 Japanese Patients with Microscopic Polyangiitis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

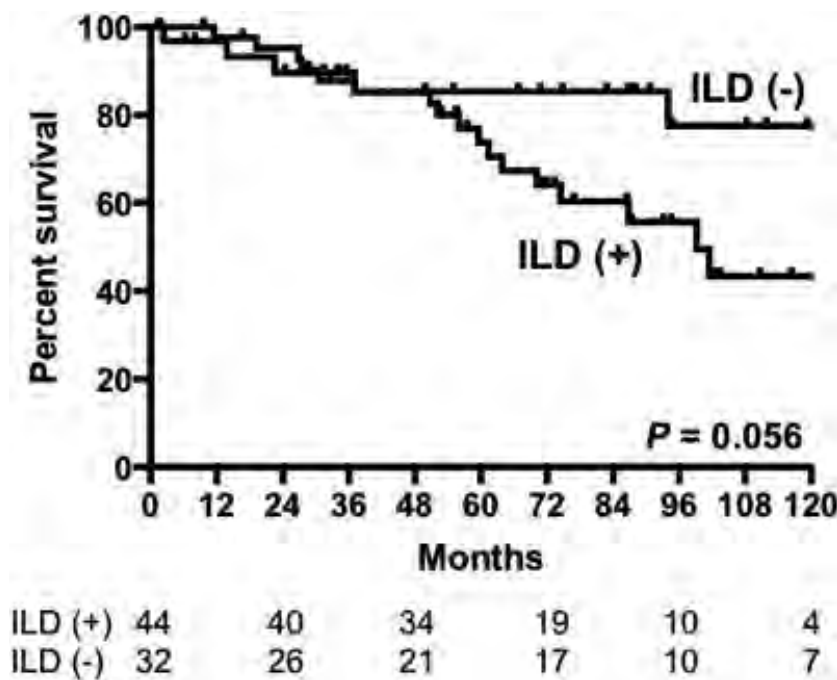
Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: ANCA-associated vasculitis including microscopic polyangiitis (MPA) involves multiple organs including lungs. Clinical characteristics and impact on long-term survival in MPA patients with interstitial lung disease (ILD) have not been well characterized. The aim of this study is to clarify clinical characteristics and long-term survival in MPA patients with and without ILD.

Methods: All our patients suspected to have MPA are admitted to our hospital for evaluations. We retrospectively investigated consecutive 76 Japanese patients, classified as MPA with algorithm by Watts, with (n = 44) or without ILD (n = 32) from 2006 through 2014. We compared between-group differences. All patients underwent chest CT.

Results: The 76 patients (female, 88%) had mean follow-up period (SD) of 66 (42) months. Mean age (SD) was 71 (8) and 67 (15) in patients with and without ILD, respectively (NS). The frequency of nephritis was lower in patients with ILD (57%) than in those without ILD (84%) (P = 0.01). Eight (18%) and 4 (13%) patients with and without ILD had mononeuritis multiplex, respectively. Treatment in patients with / without ILD included prednisolone alone (with / without ILD, 30% / 41%) or combination with immunosuppressants such as cyclophosphamide (43% / 41%), rituximab (5% / 0%), or azathioprine (23% / 16%). Patients with ILD tended to have low survival compared with those without ILD (P = 0.056). The survival of both groups was similar at the first 4 years. Notably, death in patients with ILD was continuously observed even after 4 years, which was in contrast to those without ILD (figure). Seventeen (39%) and 5



(16%) of patients with and without ILD died during the follow-up, respectively ($p = 0.04$). Death in 14 patients with ILD (82%) was associated with MPA ($n = 8$) including deterioration of ILD ($n = 5$), heart failure ($n = 2$), and alveolar hemorrhage ($n = 1$) or with infection ($n = 6$) including sepsis ($n = 3$), bacterial pneumonia ($n = 2$), and pneumocystis pneumonia ($n = 1$). Among 12 patients with ILD who died after 4 years, death in 9 (75%) patients was associated with lung disease such as deterioration of ILD ($n = 6$) or infectious pneumonia ($n = 3$), whereas only one without ILD died from late-stage renal failure. Hazard ratios (HR) for ILD and renal disease were 2.56 (95% CI 0.94-6.97) and 0.89 (95% CI 0.36-2.20), respectively. Patients over age 70 and ILD had independent risk for death (HR 2.61, 95% CI 1.12-6.10).

Conclusion: Death associated with MPA and infections were seen at any period in patients with ILD, which affected the survival. Establishment of more efficient maintenance as well as induction therapy with less side effects is needed in MPA patients with ILD.

Disclosure: H. Matsushita, None; Y. Yamasaki, None; Y. Takakuwa, None; H. Yamada, None; K. Kawahata, None.

Abstract Number: 1747

Long-Term Outcomes of Patients with Nonsevere Eosinophilic Granulomatosis with Polyangiitis Given Azathioprine and Glucocorticoids for Remission Induction

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Background/Purpose: At month 24 (M24), CHUSPAN2-trial patients with nonsevere eosinophilic granulomatosis with polyangiitis (EGPA), who received 1 yr of azathioprine (AZA) and glucocorticoids (GC) as remission-induction therapy, did not have lower remission failure, vasculitis relapse-risk or asthma/rhinosinus-exacerbation (ARE) rates, or steroid-sparing (1). These EGPA patients' long-term outcomes were analyzed to determine whether vasculitis-relapse or isolated ARE rates differed thereafter.

Methods: After M24, treating physicians chose treatments. Long-term outcomes were analyzed according to randomization group (AZA vs placebo). Flares and reasons for GC escalation or immunosuppressant use were reviewed to distinguish vasculitis relapses from isolated AREs according to EGPA Task Force recommendations. Trial entry parameters were evaluated as potential prognostic factors for vasculitis relapse or isolated ARE during follow-up.

Results: The 50 EGPA patients (25 men, mean age 53.4 yr, mean eosinophilia 5,900/ μ L) were followed for a median [IQR] of 6.3 [5.4–7.6] yr. Two (4%) patients (1 after remission-induction failed) died 11 months postinclusion. At M24, 21/48 (43.8%) patients had vasculitis relapse and 14/50 (28%) had isolated AREs. Among the 48 follow-up patients analyzed, 1 died 4.8 yr postinclusion (probable infection); 19.6% (9/46) had subsequent vasculitis relapses of whom 3 had their 1st relapse after M24; 25/45 (55.6%) patients had later isolated AREs, the 1st for 17 only after M24. From M24 to last update, conventional immunosuppressants were prescribed for 22/48 (45.8%) patients to control flares (17 AZA, 5 MTX, 4 cyclophosphamide, 1 leflunomide) and, after immunosuppressants failed, rituximab for 7; 4 received mepolizumab and 3 omalizumab, mostly for AREs. At 5 yr, respective vasculitis relapse and isolated ARE rates were 48.3% (95% CI: 34.0–62.6) and 56.2% (95% CI: 41.7–70.8), with no long-term between-arm differences ($P=0.16$ and $P=0.06$). For the AZA and placebo arms, respective 5-yr overall survival (OS) rates were 100% and 91.3% (95% CI: 79.7–100; $P=0.15$). At last update, 78.7% of patients still required GC (median dose: 5 [3.0–8.0] mg/d) to control AREs and/or as vasculitis maintenance therapy. Damage resulted from asthma ($n=42$), followed by peripheral nerve involvement ($n=28$) and chronic sinusitis/nasal obstruction ($n=27$); Vasculitis Damage Indexes (mean \pm SD) were comparable for AZA (2.8 ± 1.5) and placebo (2.2 ± 0.9) groups ($P=0.42$). Among the 18 (36%) patients MPO-ANCA+ at entry, 13 had ANCA ELISA results at M24: 6 became ANCA– (none relapsed later) and 7 were ANCA+, after having been transiently ANCA– for 3, (2/7 subsequently relapsed). Analyses retained no entry clinical or biological parameter, including blood eosinophil count and ANCA status, as significantly associated with vasculitis relapse or ARE during follow-up.

Conclusion: These results confirmed that 1 yr of AZA and GC obtained good OS but had no long-term benefit for EGPA patients. Extrapulmonary vasculitis relapses, occurring mostly during the first 2 yr, and isolated AREs, predominating thereafter, remain worrisome and require further studies to prevent them.

1 Puéchal X. et al. Arthritis Rheumatol 2017;69:2175–86.

Disclosure: X. Puéchal, None; C. Pagnoux, None; G. Baron, None; F. Lifermann, None; L. Geffray, None; T. Quémeneur, None; J. L. Saraux, None; M. Wislez, None; V. Cottin, None; M. Ruivard, None; N. Limal, None; A. Aouba, None; B. Bonnotte, None; A. Neel, None; C. Agard, None; P. Cohen, None; B. Terrier, None; C. Le Jeunne, None; L. Mouthon, None; P. Ravaud, None; L. Guillevin for the French Vasculitis Study Group, None.

Abstract Number: 1748

Interstitial Lung Disease in ANCA-Positive Vasculitis Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Rarely, ANCA-positive vasculitis patients are found to have interstitial lung disease (ILD). Clinical characteristics and prognosis are not well known in these patients. The largest report to date is from Japan, describing microscopic polyangiitis (MPA) as the most common type of ANCA vasculitis associated to ILD.

Methods: We retrospectively reviewed 26 patients at Mayo Clinic Florida for the past 10 years diagnosed with both ANCA-positive vasculitis and ILD(AAV-ILD). We compared the clinical characteristics of AAV-ILD to idiopathic pulmonary fibrosis (IPF) and idiopathic pneumonia with autoimmune features(IPAF) patients

Results: There were 24 AAV patients. 11 were male and 13 were female. 14 patients had microscopic polyangitis (MPA), 8 patients had granulomatosis polyangitis (GPA), and 2 patients had eosinophilic granulomatosis polyangitis (EGPA). Usual interstitial pneumonia (UIP) pattern was found in 11 patients and other patterns were inconsistent with UIP. P-ANCA and anti-MPO were positive in most MPA patients and c-ANCA and anti-proteinase-3 were positive in most GPA patients. Cyclophosphamide and corticosteroids were the mainstay of therapy, and rituximab was used in 13 patients. A total of 5 patients died. Death was directly related to the progression of ILD in 4 patients.

Conclusion: We were able to identify the characteristics of ILD in ANCA-positive vasculitis patients. We observed that a fair number of PR3-positive/GPA patients do have ILD, comparable to MPA. This is to our knowledge the largest case series of clinically confirmed ANCA vasculitis with ILD reported in North America.

Table 1 Comparison between AAV-ILD, Idiopathic pulmonary fibrosis (IPF), and idiopathic pneumonia with autoimmune features (IPAF)

Characteristic	AAV-ILD (N=24)	IPF (N=29)	IPAF (N=22)	P value
Male gender	11 (45.8%)	17 (58.6%)	9 (40.9%)	0.42
Age, years	73 (19, 94) ^a	71 (55, 86) ^a	67 (35-84) ^b	0.016
Smoking history, pack-years	13 (0, 75)	10 (0, 70)	0 (0, 60)	0.22
Pulmonary hypertension	12/22 (54.5%) ^{ab}	16/20 (80.0%) ^a	2/8 (25.0%) ^b	0.025
Autoantibodies				
ANA	10/22 (45.5%)	7/19 (36.8%)	10 (45.5%)	0.82
RF	12/19 (63.2%) ^a	5/15 (33.3%) ^{ab}	3 (13.6%) ^b	0.004
Anti CCP	0/15 (0.0%)	0/7 (0.0%)	0 (0.0%)	1.00
SS-A	3/17 (17.6%)	0/11 (0.0%)	7 (31.8%)	0.089
SS-B	1/17 (5.9%)	0/11 (0.0%)	1 (4.5%)	1.00
RNP	0/17 (0.0%) ^a	0/11 (0.0%) ^a	5 (22.7%) ^a	0.045
Anti Smith	0/17 (0.0%)	0/11 (0.0%)	0 (0.0%)	1.00
Jo-1	0/17 (0.0%)	0/11 (0.0%)	2 (9.1%)	0.50
SCL-70	1/17 (5.9%)	0/12 (0.0%)	1 (4.5%)	1.00
Centromere	0/12 (0.0%)	0/1 (0.0%)	0/19 (0.0%)	1.00
Myositis specific antibodies	0/1 (0.0%)	N=0	19/21 (90.5%)	0.14
ds-DNA	1/15 (6.7%)	0/1 (0.0%)	1/7 (14.3%)	1.00
serum IgG4	1/3 (33.3%)	0/1 (0.0%)	0/1 (0.0%)	1.00
anti-GBM antibody	1/1 (100%)	0/1 (0.0%)	0/1 (0.0%)	1.00
Pulmonary function tests at initial visit				
Forced vital capacity, L/sec	2.7 (1.5, 4.8), n=23	2.5 (0.9, 3.5), n=28	2.2 (1.1, 3.7), n=22	0.25
Forced vital capacity, % of predicted	76 (41, 106), n=23 ^a	71 (41, 102), n=28 ^b	63 (45, 124), n=22 ^b	0.049
DLCO, ml CO(STPD)/min/mmHg	13.7 (5.0, 19.5), n=21	9.3 (6.0, 19.8), n=25	12.4 (2.2, 22.7), n=20	0.062
DLCO, % of predicted	55 (20, 87), n=21 ^a	41 (26, 77), n=25 ^b	49 (12, 79), n=20 ^{ab}	0.019
Follow-up after initial evaluation, years	3.5 (0.0, 12.0)	2.2 (0.0, 10.0)	0.9 (0.1, 3.6)	-

AAV-ILD, ANCA-associated vasculitis with interstitial lung disease; DLCO, diffusing capacity; Data are given as median (minimum, maximum) for numeric variables and number (percent) for categorical variables. P values result from the nonparametric Kruskal-Wallis test for numeric variables and the Fisher exact test for categorical variables. Pairwise comparisons were performed when the P value was less than 0.05; superscripts a and b are given to indicate pairwise differences (P<0.05) where groups without a common superscript were considered to have a statistically significant difference.

Disclosure: A. Abril, None; M. Kwon,, None; I. Mira-Avendano, None; C. Rojas, None; A. Koor, None.

Abstract Number: 1749

Long-Term Renal Outcome in Pulmonary-Limited Microscopic Polyangiitis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with pulmonary-renal or renal-limited microscopic polyangiitis (MPA) frequently manifested with rapidly progressive glomerular nephritis resulting in chronic renal failure if clinical response to the remission

induction treatment was not successfully obtained. In contrast, pulmonary-limited MPA lacks renal involvement at diagnosis and its long-term renal outcome after remission induction treatment has been poorly investigated. Here, we compared long-term renal outcome of pulmonary-limited MPA with that of pulmonary-renal and renal-limited MPA.

Methods: We retrospectively examined the patients who met the MPA diagnostic criteria and received induction therapy. We divided them into 3 groups, pulmonary-renal, renal-limited and pulmonary-limited MPA and evaluated estimated glomerular filtration rate (eGFR) for 5 years. We further investigated the pathological features of kidney on available sample.

Results: Twenty-five patients with pulmonary-renal, 28 with renal-limited, and 19 with pulmonary-limited type were enrolled. At baseline, significantly higher eGFR, lower incidence of active sediment, lower BVAS, and lower titer of MPO-ANCA were observed in pulmonary-limited type comparing with other types ($p<0.01$, $p<0.01$, $p<0.01$, $p=0.02$, respectively). Initial treatment regimens including glucocorticoid dose, %cyclophosphamide use, and %rituximab use were not significantly different among the groups. The eGFR of patients with pulmonary-renal and renal-limited types was significantly improved ($p=0.01$, $p=0.03$) whereas that of pulmonary-limited was deteriorated ($p=0.05$), resulting in no difference of eGFR at year 5 in all types comparison (Figure 1). By multivariate analysis, eGFR at baseline was

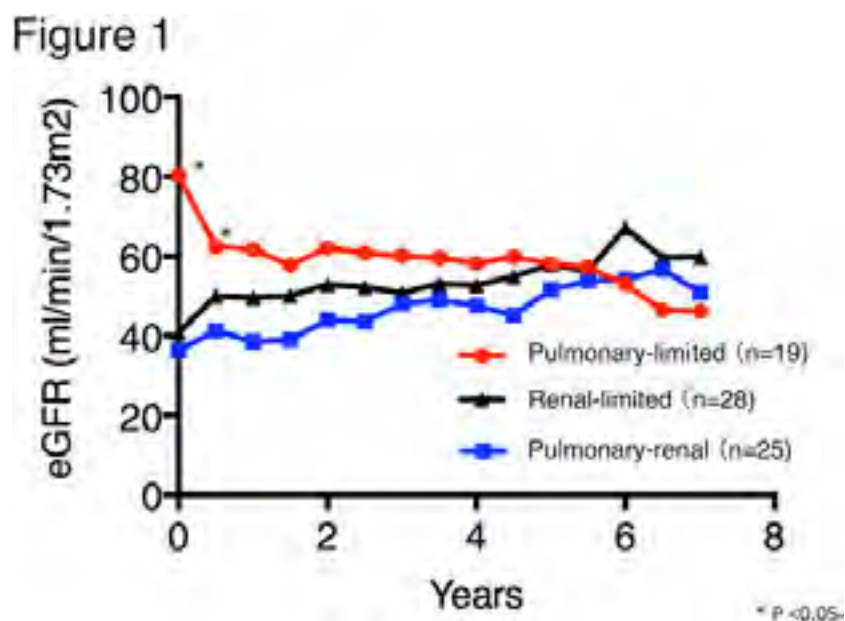


Table 1. Independent factor associating with deterioration of renal function*

Parameters	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Pulmonary-limited	23.03 (6.47-101.9)	<0.01	1.97 (0.16-21.1)	0.57
Renal-limited	0.13 (0.03-0.47)	<0.01	0.19 (0.01-1.61)	0.13
Pulmonary-renal	0.36 (0.09-1.14)	0.08	-	-
eGFR at Week 0	4.40 (2.70-6.65)	<0.01	1.19 (1.00-1.32)	0.01
Proteinuria >1+	0.05 (0.01-0.19)	<0.01	0.18 (0.01-1.46)	0.10
Hematuria >1+	0.08 (0.02-0.25)	<0.01	0.77 (0.04-10.0)	0.86
c-RBC >1+	0.20 (0.05-0.64)	<0.01	0.89 (0.09-8.39)	0.91
PSL (mg/day)	1.08 (0.96-1.04)	0.94	-	-
IVCY	0.77 (0.26-2.16)	0.62	-	-

PSL, prednisolone; IVCY, intravenous cyclophosphamide

*deterioration of renal function was defined as more than 25%eGFR decline from baseline [1].

independently associated with the deterioration of renal function (OR 1.2, 95%CI 1.00-1.32, $p=0.01$) (Table 1). Renal specimen showed a higher percentage of interstitial cell infiltrate was observed in patients with high eGFR (≥ 60 ml/min) at baseline than those with low (< 60 ml/min).

Conclusion: Renal outcome of pulmonary-limited MPA was not significantly different from that of pulmonary-renal and renal-limited MPA for 5 years observation. Subclinical renal involvement or interstitial inflammation may proceed in some patients with pulmonary-limited MPA and careful observation is required.

Reference: 1. Mukhtyar C, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis*. 2009;68:1827-32.

Disclosure: H. Hanaoka, None; H. Iida, None; T. Kiyokawa, None; Y. Takakuwa, None; K. Kawahata, None.

Abstract Number: 1750

Rheumatoid Factor Titer Is Inversely Correlated with ANCA Titer and Relates to Characteristic Manifestations in Patients with Eosinophilic Granulomatosis with Polyangiitis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which is characterized by vasculitis with allergic features such as asthma and eosinophilia. Although rheumatoid factor (RF) positivity is known to be as high as 37-50% in AAV patients [1] the clinical significance of RF-positivity remains unknown. The aim of this study is to investigate clinical features in patients with RF in EGPA.

Methods: Consecutive patients who were diagnosed with EGPA between January 2008 and January 2018 in Keio University Hospital were enrolled. Clinical information were collected from medical records retrospectively. We divided patients into 2 groups according to RF positivity, and compared clinical features.

Results: Seventeen patients were enrolled in the study. The mean age was 57.4 years old, and 82% were female. Among them, 11 patients were RF positive (RF positive group) and 6 patients were negative (RF negative group). The female rate tended to be higher in the RF positive group than the negative group (82% vs 50%, $p=0.087$). While the Birmingham Vasculitis Activity Score was comparable between the two groups (21.5 vs 17.3, $p=0.329$), general symptoms (fever and weight loss) and gastrointestinal lesions were more frequent in the RF positive group (55% vs 17%, $p=0.072$; 45% vs 17%, $p=0.137$) and central nervous involvement was less frequent (18% vs 67%, $p=0.024$). No patient with negative RF presented with arthralgia/arthritis. The count of eosinophil and IgA levels at diagnosis were significantly higher in the RF positive group than the RF negative group (15704/ μ L vs 4751/ μ L, $p=0.009$; 238mg/dL vs 162mg/dL, $p=0.048$). Interestingly, ANCA positivity was negatively correlated with RF positivity. MPO-ANCA was positive in 27% of the RF positive group and in 66% of the RF negative group, and PR3-ANCA was positive in none of the RF positive group and 17% of the RF negative group. Double negative was more frequent in RF positive group (73% vs 33%, $p=0.060$).

Conclusion: RF positivity was associated with clinical and serological characteristics in patients with EGPA, suggesting different pathogenesis or immunological disturbances is related.

Reference: [1] Pagnoux C, Seror R, Bérezné A, Rouabhia S, Goulvestre C, Guillevin L. Remittent non-destructive polysynovitis in P-ANCA-positive vasculitis patients with anti-CCP antibodies. *Joint Bone Spine*. 2010;77(6):604-7.

Disclosure: J. Inamo, None; Y. Kaneko, None; Y. Ota, None; T. Takeuchi, None.

Interstitial Lung Disease during ANCA-Associated Vasculitis: A Poor-Prognosis Factor

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

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Background/Purpose: Interstitial lung disease (ILD), rarely described in ANCA-associated vasculitis (AAV) patients, was mainly associated with anti-MPO ANCA. ILD's prognostic value remains unclear. This study focused on the outcomes of patients with ILD associated with AAV (ILD–AAV).

Methods: This case–control study compared ILD–AAV cases and to AAV patients without ILD (controls). Case AAVs were microscopic polyangiitis (MPA) or granulomatosis with polyangiitis (GPA) (meeting Chapel Hill definitions) and ILD was either usual interstitial pneumonia (UIP) or nonspecific interstitial pneumonia (NSIP) (satisfying the 2001 American Thoracic Society/European Respiratory Society criteria). Eosinophilic granulomatosis with polyangiitis, non-fibrosing pulmonary involvement, ILD without AAV criteria and late ILD (>2 yr after AAV diagnosis) were excluded. Two controls with MPA or GPA without ILD were matched to each case for age (> or ≤65 years), ANCA status (PR3- or MPO-positive, or negative) and creatininemia (≥ or <150 µmol/L).

Results: Sixty-five cases were included: 88% MPO-ANCA–positive and 83% with MPA. Median (IQR) age at AAV diagnosis was 65.7 (56.6–74.0) yr. ILD was mainly diagnosed before (53%) or simultaneously (39%) to AAV. CT-scan pattern was mostly UIP (65%). Median case follow-up was 40 (21–62) months vs. 60 (27–128) months for controls ($P=0.001$). Cases, compared to 130 controls, had less frequent fever ($P=0.002$), peripheral neuropathy ($P=0.03$), or ear nose & throat ($P=0.03$) or gastrointestinal involvement ($P=0.002$). Five Factor Scores (1996 version) at AAV diagnosis were similar for the 2 groups ($P=0.08$). Cases more frequently received immunosuppressants for induction (91% vs. 76%; $P=0.01$) and maintenance (84% vs. 58%; $P<0.001$). Notably, 17/65 (26%) cases suffered relapses vs. 56/130 (43.1%) controls ($P=0.03$). Relapses were mainly minor for cases (12/17; 70.6%) vs. controls (19/56; 33.9%) ($P=0.01$). Only 2 cases experienced ILD exacerbation at relapse. Major-relapse–free survival was comparable for cases and controls ($P=0.90$). During follow-up, 19 cases died: 6 of acute respiratory failure related to pulmonary fibrosis exacerbation, 2 end-stage respiratory failure, 2 infections (1 pneumonia, 1 endocarditis), 1 lung cancer, 1 digestive hemorrhage and 7 unknown causes. For cases and controls, respective 1-, 3- and 5-year overall survival rates were: 97%, 83% and 77% vs. 93%, 91% and 87% ($P=0.008$). Compared to controls, case survival was shorter for those with UIP ($P<0.001$) and unchanged for NSIP ($P=0.50$). Multivariate analyses retained age >65 yr (hazard ratio (HR) 4.366; $P<0.001$), alveolar hemorrhage (HR 2.38; $P=0.01$) and UIP (HR 2.63; $P=0.003$) as independently associated with shorter survival.

Conclusion: For ILD–AAV patients, UIP, but not NSIP, was associated with poorer prognosis. Although the greater majority of ILD–AAV patients included in this study received immunosuppressants for induction and maintenance, their survival was shorter than that of controls, mainly due to pulmonary fibrosis exacerbation, suggesting that anti-fibrosing agents should be evaluated in these patients.

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Abstract Number: 1752

Asthma in Eosinophilic Granulomatosis with Polyangiitis Treated with Rituximab

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Eosinophilic Granulomatosis with Polyangiitis (EGPA) is a rare systemic small-vessel necrotizing vasculitis presenting with asthma and eosinophilia. Anti-neutrophil cytoplasmic antibodies (ANCA) association may influence disease presentation, treatment and outcomes. Rituximab (RTX) is effective in ANCA-associated vasculitis (AAV), but specific potential benefits in EGPA are less clear. Difficult-to-treat or glucocorticoid (GC) dependent asthma is one of the main challenges in EGPA management. Our aim was to characterize asthma control and GC dependency in EGPA patients treated with RTX.

Methods: Retrospective cohort study of patients diagnosed with EGPA between 2000 and 2017 presenting with GC dependent asthma and treated with RTX for remission induction in a single center. Standardised data collection was performed, including disease activity assessment, RTX treatment, asthma characterization and control.

Results: A total of 17 patients (52.9% men) were included. According to BVAS/WG, lower respiratory tract was most commonly affected at presentation (16, 94.1%), followed by nervous system (15, 88.2%) and ENT (14, 82.4%). There were no differences in disease extent index (DEI). Five Factor Score was ≥ 1 in 11 patients (64.7%). At diagnosis, the majority were myeloperoxidase (MPO)-ANCA positive (13, 76.5%). Non-controlled asthma symptoms were present in 13 (76.5%) patients. Atopy was present in 13 (76.5%) and radiographic changes in 8 (47.1%).

RTX was used in three different clinical scenarios: for initial remission induction (5, 29.4%) in patients with new onset of severe disease (BVAS/WG >3), after failed remission induction attempts with other immunosuppressants (12, 70.6%) or for remission maintenance (9, 52.9%). GC were used in all maintenance regimens at a median dose of 25 (16.25 – 37.5) mg/day.

Median time of *follow-up* since EGPA diagnosis was 38 (17-107) months. Three patients (17.6%) relapsed after RTX and 6 (35.3%) were refractory to RTX. As maintenance treatment in 9 (52.9%) patients, RTX choice was guided mainly by B-cell reconstitution during the follow-up (7, 41.2%). At the end of follow-up, remission was achieved in 15 (88.2%) patients. After induction with RTX, more than one asthma exacerbation occurred in 8 (47.1%) patients but the use of bronchodilators was not significantly different after the relapse. Mepolizumab was used for refractory symptomatic asthma in 2 patients (11.8%), after RTX effect worn off.

At the end of follow-up, median serum eosinophils and C-reactive protein were lower than before RTX treatment (0.10 vs. 1.06 $\times 10^9/L$, $p=0.012$; 5 vs. 27 mg/dL, $p=0.001$; respectively). Pulmonary function tests (PFTs) remained unchanged.

Induction treatment with RTX allowed a more predictable GC tapering: to a median dose of 5 mg/day at 12 months and a rise from 12 to 24 months was seen (no GC pattern pre RTX treatment). However, in the patients on maintenance treatment with RTX, asthma symptom control was not dependent on GC at 12 months.

Conclusion: RTX seems a safe drug with some GC sparing efficacy in EGPA. Improvement in inflammatory markers and eosinophilia was observed, but not in PFTs. RTX deserves more detailed studies in prospective randomized controlled clinical trials in EGPA.

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Interstitial Lung Disease in ANCA-Associated Vasculitis Defines a Unique Subgroup of Patients at High Risk for Respiratory Death: A Cluster Analysis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: ANCA-associated vasculitis (AAV) has a propensity for heterogeneous organ involvement. ANCA specificity has increasingly been favored over clinical diagnosis (e.g., microscopic polyangiitis) for subgrouping AAV patients but also has its limitations. Latent class analysis (LCA) is an unbiased method to identify patient subgroups who share similar manifestations and might therefore share risk factors and/or outcomes.

Methods: The Partners AAV (PAAV) Cohort is a retrospective cohort established at Partners HealthCare, a large US hospital system. All PAAV patients are PR3- or MPO-ANCA+. We performed LCA to identify clusters according to baseline manifestations. We fitted models with 2-5 clusters and analyzed the one with superior fit statistics. Cases were assigned to a cluster based on posterior probability. We compared the distribution of baseline features between clusters using Chi square tests or analysis of variance, as appropriate. We used multivariable Cox regression to compare the rates of cardiovascular disease (CVD), deep vein thrombosis/pulmonary embolism (DVT/PE), end-stage renal disease (ESRD), and all-cause and cause-specific death between clusters. We adjusted for the competing risk of death and cause-specific death.

Results: A 3 cluster model fit best. Cluster 1 (N=143) was characterized by GN whereas cluster 2 (N=236) was characterized by upper respiratory tract disease and lung nodules more often than renal disease (**Table 1**). Cluster 3 (N=35) was distinguished by interstitial lung disease (ILD) which was present in <1% of clusters 1 and 2. In contrast to clusters 1 and 2, cluster 3 patients tended to be male (51%) and older (63.9 ± 13.4 yrs vs 58.9 ± 18.4 yrs and 54.1 ± 17.6 yrs, respectively). PR3- and MPO-ANCA status were distributed evenly in cluster 2 (PR3-ANCA=53%) whereas MPO-ANCA+ was more common in clusters 1 (71%) and 3 (91%). Compared to cluster 2, patients in cluster 1 had a higher risk of ESRD (HR 6.48, 3.39-12.36), DVT (HR 2.98, 1.65-5.39), and death (HR 1.62, 1.12-2.34). Patients in cluster 3 had a higher risk of death from respiratory causes compared to cluster 2 (HR 4.43, 1.19-16.58); a similar trend was noted when comparing clusters 3 and 1 (HR 3.89, 0.95-16.04). The risk of CVD was not different across the 3 clusters.

Conclusion: In contrast to traditional AAV phenotyping by ANCA type or clinical diagnosis (e.g., granulomatosis with polyangiitis), LCA identified three unique AAV clusters. Besides organ involvement, clusters were distinguishable by baseline features and risk of key outcomes. AAV patients with ILD represent a unique subgroup, characterized by MPO-ANCA positivity, older age, and death from respiratory causes. In contrast, patients with primarily GN (i.e., Cluster 1) are at higher risk of DVT, ESRD, and all-cause death. Future studies might evaluate the cluster-specific response to treatment.

Table 1. AAV Clusters: Baseline Features and Long-Term Outcomes

	Glomerulonephritis Cluster (N=143)	Upper Respiratory Tract and Nodule Cluster (N=236)	ILD Cluster (N=35)
Proportion of Cohort (%)*	34.6%	56.4%	9.0%
Cluster Input Variables (%)*			
Arthralgia/Arthritis	13.9%	26.7%	18.3%
Purpura	2.2%	5.5%	<1%
Conjunctivitis/Episcleritis	0.7%	4.7%	<1%
Scleritis	2.2%	8.5%	0.2%
Nasal	11.4%	27.2%	6.0%
Sinus	12.7%	30.6%	19.7%
Subglottic	<1%	3.9%	<1%
Conductive Hearing Loss	1.4%	5.6%	2.7%
Nodules/Cavitary Lesions	13.3%	19.9%	9.2%
Other Infiltrate	9.0%	11.6%	99.2%
ILD	<1%	<1%	85.6%
DAH	24.7%	7.4%	12.1%
Hematuria	<1%	12.4%	10.6%
RBC Cast	97.3%	10.3%	42.0%

Table. (Cont'd)

	Glomerulonephritis Cluster (N=143)	Upper Respiratory Tract and Nodule Cluster (N=236)	ILD Cluster (N=35)
Acute Kidney Injury	95.1%	12.0%	36.5%
Sensory Neuropathy	1.4%	4.3%	2.7%
Mononeuritis Multiplex	1.6%	8.4%	5.5%
<i>Probability of Cluster Membership (mean, \pmSD)**</i>	87.2% (\pm 12.6%)	96.2% (\pm 9.4%)	88.5% (\pm 13.9%)
<i>Case Demographics</i>			
Male (N, %)	58 (41%)	90 (38%)	18 (51%)
Age(mean, \pm SD)†	58.9 (\pm 18.4)	54.1 (\pm 17.6)	63.9 (\pm 13.4)
BVAS/WG†	5.4 (\pm 1.5)	3.6 (\pm 2.0)	4.1 (\pm 1.8)
PR3-ANCA+†	41 (29%)	126 (53%)	3 (9%)
Former or Current Smoker	65 (46%)	117 (50%)	21 (60%)
<i>Outcomes (Adjusted for Age, Sex, and ANCA-type)</i>			
Risk of Death (HR, 95% CI)	1.62 (1.12-2.34)	1 (ref)	0.94 (0.50-1.77)
Risk of Respiratory Death‡	1.14 (0.35-3.74)	1 (ref)	4.43 (1.19-16.58)
Risk of ESRD††	6.48 (3.39-12.36)	1 (ref)	2.50 (0.80-7.83)
Risk of CVD††	1.13 (0.69-1.88)	1 (ref)	0.98 (0.51-1.90)
Risk of DVT††	2.98 (1.65-5.39)	1 (ref)	1.34 (0.45-4.02)

* All reported proportions are probabilities conditional on latent class membership

** Generally, a probability of cluster membership > 70% is considered strong

† P<0.01 by Chi Square or ANOVA

‡ Adjusted for competing risk of other causes of death

†† Adjusted for competing risk of death

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Abstract Number: 1754

Clinical and Economic Characteristics of Patients Diagnosed with Eosinophilic Granulomatosis with Polyangiitis (EGPA, formerly Churg-Strauss Syndrome) in the United States

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Eosinophilic granulomatosis with polyangiitis (EGPA), formerly Churg-Strauss Syndrome, is a rare, complex multisystem disorder belonging to a group of autoimmune inflammatory diseases characterized by vascular inflammation, multisystem organ damage that manifests as chronic rhinosinusitis, asthma, and peripheral blood eosinophilia. In part due to the rare nature of EGPA and lack of specific ICD-9 codes, there is an absence of burden of illness data. Introduction of an EGPA-specific ICD-10 diagnosis code (M30.1) should facilitate such analyses. In this regard, this study aims to describe EGP Aburden of illness in the United States (US).

Methods: This is a retrospective analysis of two US administrative claims databases. The index date was defined as the first medical claim with an ICD-10 diagnosis for EGPA. The study period spanned from ICD-10 introduction (01 October 2015) through the most recent data availability (Database #1 [DB#1]: 31 December 2016; Database#2 [DB#2]: 31 March 2017). Patients were \geq 18 years of age, had \geq 1 medical claim with an ICD-10 diagnosis code for EGPA, and had 6 months of continuous health plan enrollment post-index. Six-month post-index clinical and economic characteristics are reported as counts (percentages) and means (standard deviations [SD]).

Results: Approximately 0.0017% of the population had an EGPA diagnosis (DB#1: 567/33,293,530; DB#2:413/23,796,590) (Table 1). Mean (SD) age was 54.9 (14.1) in DB#1 and 59.7(16.0) in DB#2; and overall, approximately 60% of patients were female. Mean (SD) Quan-Charlson Comorbidity Index score was 1.3 (1.3) in DB#1 and 1.6 (1.7)in DB#2 (AHRQ top 5 comorbidities were similar across databases). Post-index concomitant medications included (DB#1/DB#2): asthma-related medications (non-biologic: 65.5%/55.9%; biologic: 5.2%/3.4%), immunosuppressive medications (84.8%/75.5%), and oral corticosteroids (OCS; 73.5%/59.0%). Among patients receiving OCS, mean (SD) prednisone-equivalent daily dose was 53.9 mg/day (248.1) in DB#1 and 18.8 mg/day (13.8) in DB#2 (median dose was 15 mg/day in both databases). Post-index, all-

cause healthcare resource utilization was similar across databases with 16.9% of patients in DB#1 incurring an inpatient admission (mean [SD] admissions: 1.5 [1.1] and 20.3% of patients in DB#2 (mean [SD] admissions: 1.3 [0.7]). Mean (SD) all-cause total costs incurred in the post-index period were \$32,388 (113,895) in DB#1 and \$20,865 (33,665) in DB#2.

Conclusion: This study descriptively characterizes the substantial clinical and economic burden associated with EGPA. While EGPA is a rare disease, the introduction of an EGPA-specific ICD-10 diagnosis code should allow researchers to better quantify the burden of illness.

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Abstract previously presented at ATS 2018, A4951 (P162)

Table 1. Study Results

Variables	Database #1 (Truven MarketScan Commercial Claims and Encounters)	Database #2 (Optum Clinformatics Data Mart)
Study period	01 Oct 2015 – 31 Dec 2016	01 Oct 2015 – 31 March 2017
Total N (≥1 day of enrollment during study period)	33,293,530	23,796,590
≥1 medical claim EGPA ICD-10 diagnosis code, N (%)	567 (0.0017%)	413 (0.0017%)
≥18 years, N (%)	558 (0.0017%)	412 (0.0017%)
6 months of continuous enrollment post-index	362 (0.0011%)	261 (0.0011%)
Age, mean (SD)	54.9 (14.1)	59.7 (16.0)
Female, N (%)	219 (60.5%)	154 (59.0%)
Charlson-Quan Comorbidity Index, mean (SD)	1.3 (1.3)	1.6 (1.7)
AHRQ Top 5 Comorbid Conditions, N (%)		
Factors influencing health care	290 (80.1%)	213 (81.6%)
Asthma	211 (58.3%)	154 (59.0%)
Other lower respiratory disease	186 (51.4%)	143 (54.8%)
Respiratory infections	186 (51.4%)	133 (51.0%)
Symptoms; signs; and ill-defined conditions	148 (40.9%)	129 (49.4%)
Concomitant Medication Utilization, N (%)		
Non-biologic asthma-related medications	237 (65.5%)	146 (55.9%)
Biologic asthma-related medications	19 (5.2%)	9 (3.4%)
Immunosuppressive medications	307 (84.8%)	197 (75.5%)
Rituximab	34 (9.4%)	22 (8.4%)
Azathioprine	66 (18.2%)	40 (15.3%)
Methotrexate	48 (13.3%)	30 (11.5%)
Cyclophosphamide	16 (4.4%)	7 (2.7%)
Mycophenolic acid/mycophenolate mofetil	30 (8.3%)	17 (6.5%)
Corticosteroids	287 (79.3%)	171 (65.5%)
Oral corticosteroids (OCS)	266 (73.5%)	154 (59.0%)
Injectable or intravenous corticosteroids	94 (26.0%)	54 (20.7%)
Daily prednisone-equivalent OCS dose, mg/day		
Mean (SD)	53.9 (248.1)	18.8 (13.8)
Median	15.0	15.2
Daily prednisone-equivalent OCS dose, N (%)		
≤4 mg/day	27 (10.3%)	5 (3.3%)
>4 mg/day to ≤7.5 mg/day	46 (17.5%)	25 (16.3%)
>7.5 mg/day to ≤15 mg/day	65 (24.7%)	44 (28.8%)
>15 mg/day	125 (47.5%)	79 (51.6%)
All-cause healthcare resource utilization, N (%)		
Inpatient admission	61 (16.9%)	53 (20.3%)
ER visit (ER inpatient & outpatient visit)	91 (25.1%)	86 (33.0%)
Physician office visit	344 (95.0%)	245 (93.9%)
Hospital-based outpatient visit	245 (67.7%)	188 (72.0%)
Service in other settings	189 (52.2%)	166 (63.6%)
Outpatient pharmacy prescriptions	358 (98.9%)	228 (87.4%)
All-cause healthcare resource utilization, mean (SD)		
Inpatient admission	1.5 (1.1)	1.3 (0.7)
ER visit (ER inpatient & outpatient visit)	1.8 (1.2)	1.9 (2.2)
Physician office visit	10.8 (8.3)	9.4 (7.7)
Hospital-based outpatient visit	5.1 (5.1)	7.1 (9.5)
Service in other settings	4.9 (9.1)	12.5 (65.9)
Outpatient pharmacy prescriptions	25.6 (18.9)	27.1 (19.9)
All-cause healthcare costs (US\$), mean (SD)		
Medical Cost	\$25,279 (112,525)	\$15,755 (28,605)
Pharmacy Cost	\$7,109 (12,012)	\$5,111 (10,759)
Total Costs	\$32,388 (113,895)	\$20,865 (33,666)

Disclosure: C. F. Bell, GlaxoSmithKline, 1, 3; M. Lau, GlaxoSmithKline, 1, 3; Q. Shen, GlaxoSmithKline, 1, 3.

Burden of Illness Associated with Eosinophilic Granulomatosis with Polyangiitis (EGPA, formerly Churg-Strauss Syndrome): Evidence from a Managed Care Database in the United States

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

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Background/Purpose: Eosinophilic granulomatosis with polyangiitis (EGPA), is a rare, complex multisystem disorder, characterized by vascular inflammation and multisystem organ damage. EGPA manifests as asthma, rhinosinusitis, blood/tissue eosinophilia, and vasculitis. In part due to its rare nature, there is an absence of burden of illness data. This study aims to quantify healthcare resource utilization and costs associated with EGPA from the managed care perspective in the United States (US).

Methods: A retrospective analysis was conducted using a large, US administrative claims database (study period: 01 July 2007 to 31 March 2017). Patients were 18 years of age or older with continuous health plan enrollment (6-months pre-index and 12-months post-index). The index date was the date of EGPA diagnosis. Prior to the implementation of ICD-10 (October 2015), EGPA diagnosis was based on published algorithms.^{1,2} Post October 2015, EGPA diagnosis was based on ICD-10 code M30.1 (polyarteritis with lung involvement [Churg-Strauss]). An unmatched asthma control group was identified to evaluate the incremental impact of EGPA. Clinical and economic characteristics are reported as counts, percentages and means, with statistical comparisons evaluated at $\alpha=0.05$ level.

Results: The study included 2,226 EGPA and 48,252 asthma patients (Table 1). The EGPA cohort was older, predominantly female and had greater comorbidity (top three: hypertension, other lower respiratory conditions and other connective tissue conditions) as compared with the asthma cohort. In the pre-index period, the proportion of patients utilizing services and the mean number of services utilized were significantly greater in the EGPA cohort compared with the asthma cohort (all $p<0.001$, except ambulatory). Pre-index costs were significantly greater in the EGPA cohort compared with the asthma cohort (mean: \$14,325 vs.\$5,050; $p<0.001$). In the 12-month post-index period, significant differences between the EGPA and asthma cohorts were observed for the proportion of patients utilizing services (ambulatory: 73.0% vs. 77.0%, $p<0.001$; emergency department [ED]: 42.1% vs. 31.7%, $p<0.001$; inpatient [IP]: 29.0% vs. 16.2%, $p<0.001$; prescriptions (Rx): 70.3% vs. 75.9%; $p<0.001$), the mean number of services utilized (ambulatory: 31.7 vs. 18.5, $p<0.001$; ED: 1.4 vs. 1.0, $p<0.001$; IP: 0.6 vs. 0.2, $p<0.001$, IP length of stay [days]: 5.4 vs. 1.9, $p<0.001$; Rx: 45.1 vs. 32.9, $p<0.001$) and mean costs (total: \$31,914 vs.\$13, 822; $p<0.001$; medical: \$26,441 vs. \$10,694; $p<0.001$; pharmacy: \$5,473 vs. \$3,128, $p<0.001$).

Conclusion: This study provides valuable real-world data about the substantial burden of EGPA, which was significantly greater in terms of resource utilization and costs when compared with an asthma cohort.

Funded by GlaxoSmithKline (Study #: HO-17-17742)

¹Sreih et al. *Pharmacoepidemiol Drug Saf.* 2016;25:1368-74

²Harrold et al. *Pharmacoepidemiol Drug Saf.* 2004;13:661-7

Table 1. Study Results

Variables	EGPA Cohort	Asthma Cohort	p-value
N	2,226	48,252	
Index date prior to 01 October 2015, N (%)	2,173 (97.6%)	46,368 (96.1%)	<0.001
Age, mean (SD)	59.7 (14.2)	56.5 (15.8)	<0.001
Female, N (%)	1,558 (70.0%)	31,757 (65.8)	<0.001
Quan-Charlson Comorbidity Index, mean (SD)	1.8 (1.7)	0.7 (1.2)	<0.001
Pre-index comorbidities, N (%)			
Hypertension	1,322 (59.7%)	19,862 (44.7%)	<0.001
Other lower respiratory diseases	1,260 (56.9%)	15,409 (34.7%)	<0.001
Other connective tissue diseases	1,213 (54.8%)	13,180 (29.7%)	<0.001
6-month pre-index healthcare utilization, N (%)			
Ambulatory visit	1,611 (72.4%)	34,063 (70.6%)	0.072
Emergency department visit	735 (33.0%)	8,309 (17.2%)	<0.001
Inpatient stay	416 (18.7%)	2,849 (5.9%)	<0.001
Prescriptions	1,530 (68.7%)	34,139 (70.8%)	0.041
6-month pre-index healthcare utilization, mean (SD)			
Ambulatory visit	14.4 (14.9)	7.7 (10.1)	<0.001

Table. (Cont'd)

Variables	EGPA Cohort	Asthma Cohort	p-value
Emergency department visit	0.8 (2.2)	0.4 (1.8)	<0.001
Inpatient stay	0.3 (0.7)	0.1 (0.3)	<0.001
Length of stay (days)	3.0 (14.0)	0.6 (5.1)	<0.001
Prescriptions	20.2 (22.7)	14.0 (17.7)	<0.001
6-month pre-index cost (US\$), mean (SD)			
Medical	\$11,973 (30,262)	\$3,726 (13,750)	<0.001
Pharmacy	\$2,352 (5,176)	\$1,323 (3,140)	<0.001
Total	\$14,325 (31,605)	\$5,050 (14,585)	<0.001
12-month post-index healthcare utilization, N (%)			
Ambulatory visit	1,624 (73.0%)	37,145 (77.0%)	<0.001
Emergency department visit	937 (42.1%)	15,295 (31.7%)	<0.001
Inpatient stay	645 (29.0%)	7,814 (16.2%)	<0.001
Prescriptions	1,564 (70.3%)	36,639 (75.9%)	<0.001
12-month post-index healthcare utilization, mean (SD)			
Ambulatory visit	31.7 (31.9)	18.5 (20.9)	<0.001
Emergency department visit	1.4 (3.1)	1.0 (3.2)	<0.001
Inpatient stay	0.6 (1.2)	0.2 (0.7)	<0.001
Length of stay (days)	5.4 (18.0)	1.9 (11.1)	<0.001
Prescriptions	45.1 (48.3)	32.9 (37.2)	<0.001
12-month post-index cost (US\$), mean (SD)			
Medical	\$26,441 (59,035)	\$10,694 (28,543)	<0.001
Pharmacy	\$5,473 (12,166)	\$3,128 (6,255)	<0.001
Total	\$31,914 (63,450)	\$13,822 (30,492)	<0.001

Disclosure: C. F. Bell, GlaxoSmithKline, 1, 3; C. Blauer-Peterson, GlaxoSmithKline, 5; J. Mao, GlaxoSmithKline, 5.

Abstract Number: 1756

Systematic Review of the Clinical Effectiveness of Treatments in Eosinophilic Granulomatosis with Polyangiitis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To better understand the available clinical effectiveness data in eosinophilic granulomatosis with polyangiitis (EGPA), a systematic literature review was undertaken. The primary objective of this review was to collect randomised controlled trial (RCT) data on the efficacy, impact on quality of life, safety, and tolerability of all available treatments for EGPA. Secondary objectives were to collect similar endpoint data in observational-study or single-arm trials.

Methods: The review was undertaken to meet the requirements of the National Institute for Health and Care Excellence (NICE), the Centre for Reviews and Dissemination's Guidance for Undertaking Reviews in Health Care, the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting methods. Searches were conducted in electronic databases (PubMed, Embase, Cochrane and BIOSIS); conference abstracts (EULAR; ACR), and trial registry sites. Searches were not limited by date, language, or geographical location. The quality assessment of each RCT was performed to standards recommended by NICE and Cochrane guidance. The quality assessment of each observational study was performed using the Critical Appraisal Skills Programme (CASP) Cohort Study or Case-Control Study checklists.

Results: A total of 1,063 records were selected for manual screening. After the initial screening of titles/abstracts, 217 publications were progressed for further screening. 57 articles were included after the second screening, and an additional data-on-file article was added. The review identified five RCTs that assessed various treatments in EGPA (e.g. mepolizumab, prednisone, immunosuppressants). Most RCTs included a small sample of patients (n=30-136); therefore, the conclusions derived regarding the efficacy and safety of the treatments are limited. Twenty-one prospective studies were included with seven different comparators treatments. Generally, the treatments identified in the prospective studies were effective in inducing remission, reducing relapse rates, and reducing corticosteroid use in patients with EGPA, but maintenance treatments were limited in their efficacy. In many of the studies, there was no comparative arm and low numbers of patients with EGPA (n=3-118), and the outcomes reported were not consistent, making it hard to draw definitive conclusions on the effectiveness of many of the therapies for EGPA. Of the 30 retrospective studies that assessed

treatments in EGPA, 26 were single-arm. Most patients received other medications in combination with the treatments of interest, and as there was no control arm in all but three studies, the interpretation of outcomes is limited.

Conclusion: The clinical evidence for treatments of EGPA is sparse with many trial featuring small sample sizes, inconsistent reporting of outcomes, open trial designs, or lack of comparators. Additional RCTs would be beneficial to further evaluate treatment efficacy in patients with EGPA, particularly in relation to outcomes such as symptom scores, steroid sparing, and HRQOL due to the minimal amount of data available from the included RCTs.

Disclosure: S. Doyle, GlaxoSmithKline, 1, 3; A. Njue, None; M. Lyall, None; R. Rushton, None; A. Heyes, None; M. Kelly, GlaxoSmithKline, 3.

Abstract Number: 1757

An Economic Systematic Literature Review of Eosinophilic Granulomatosis with Polyangiitis

Scott Doyle¹, Emily Moss², Louise Hartley², Chris Knight², Judith Bell², Outi Ahdesmäki² and Maebh Kelly³, ¹Value Evidence and Outcomes, GlaxoSmithKline, London, United Kingdom, ²RTI Health Solutions, Manchester, United Kingdom, ³Pope Woodhead, London, United Kingdom

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To better understand the available economic evaluations in eosinophilic granulomatosis with polyangiitis (EGPA), a systematic literature review was undertaken. The primary objective of this review was to collect economic evidence including economic evaluations and models, cost-utility analyses, utility studies, and prospective and retrospective studies reporting costs or resource utilisation for patients treated for EGPA. Secondary objectives were to explore the natural history of EGPA.

Methods: The review was undertaken to meet the requirements of the National Institute for Health and Care Excellence (NICE), the Centre for Reviews and Dissemination's Guidance for Undertaking Reviews in Health Care, the Cochrane Collaboration, and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting methods. Searches were conducted in electronic databases (PubMed, Embase, Cochrane, BIOSIS, Econlit); conference abstracts (ISPOR; EULAR; ACR), and key international health technology assessment websites. Searches were not limited by date, language, or geographical location. Quality assessments were conducted on economic evaluations using the Drummond checklist in line with NICE requirements. Quality assessments were not conducted for other types of economic evidence.

Results: The databases yielded a total of 2,055 titles (439 duplicates), internet searches yielded 335, and hand-searching 12. After initial screening of abstracts, a total of 294 publications were progressed for further screening leaving 85 articles deemed acceptable for data extraction. Of the 85 studies identified:

- Only a single economic evaluation was identified which had limited applicability to the research question as it focused on the cost-effectiveness of pneumonia prophylaxis in Wegener's granulomatosis (WG);
- 31 studies reported health related quality of life or symptom burden outcomes (17 reported SF-36 Health Survey (SF-36), 4 reported Health Assessment Questionnaire (HAQ) outcomes, and 1 reported EQ-5D outcomes);
- 22 reported cost and resource-use outcomes (14 studies reported medication usage, 9 studies reported productivity lost, 4 studies reported on impact of disease on income, 3 studies reported resource use, 2 reported overall cost, and 1 study reported medication costs);
- 45 natural history studies were identified (18 reported the outcome 'achieved remission', and 26 reported relapse rates. 34 of the studies reported all-cause mortality; 14 studies reported EGPA-related mortality).

Conclusion: This systematic literature review has identified many gaps in the literature regarding EGPA and its treatments, particularly in economic evaluations. This is perhaps not surprising, given that EGPA is a rare disease with limited treatment options. Of the studies identified there was a considerable amount of heterogeneity. The lack of standardised data collection methods makes the synthesis of economic evidence in EGPA challenging.

Disclosure: S. Doyle, GlaxoSmithKline, 1, 3; E. Moss, None; L. Hartley, None; C. Knight, None; J. Bell, None; O. Ahdesmäki, None; M. Kelly, GlaxoSmithKline, 3.

A 24 Month Analysis of Rituximab Safety and Efficacy in Eosinophilic Granulomatosis with Polyangiitis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

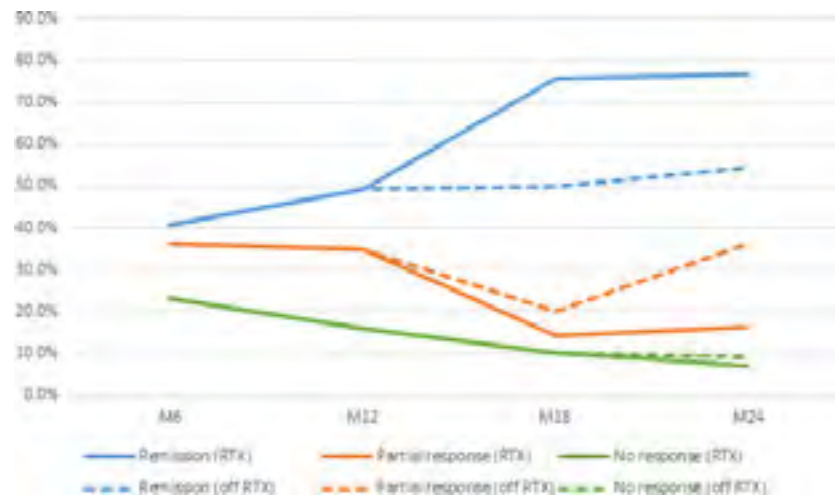
Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Eosinophilic granulomatosis with polyangiitis (EGPA) frequently pursues a refractory course leading to high glucocorticoid exposure and toxicity. A previous retrospective study found rituximab (RTX) to result in remission in a proportion of patients with refractory and relapsing EGPA, but the observation time was limited to 12 months (M) and the report focused on response to a single course. We aim to report a two years evaluation of RTX efficacy and safety in a cohort of EGPA patients with relapsing or refractory disease.

Sex F/M	44/25
Age at first RTX, median (IQR)	51 (39.5-58.0)
ANCA, number of patients (%)	
Positive (including IF)	24 (34.8)
Negative (including IF)	45 (65.2)
Positive C- or P-ANCA (only IF)	20 (29.0)
PR3-ANCA	9 (13.0)
MPO-ANCA	16 (23.2)
Number of prior immunosuppressive therapies: Mean ± SD; Median (IQR)	2.37 ± 1.46; 2 (1-3)
Immunosuppressive drugs prior to RTX, number of patients (%)	
Cyclophosphamide	34 (49.3)
Azathioprine	46 (66.7)
Mycophenolate mofetil	39 (56.5)
Methotrexate	17 (24.6)
Intravenous immunoglobulin	11 (15.9%)
Sulfasalazine	1 (1.4)
Alemtuzumab	3 (4.3)
Etanercept	1 (1.4)
Infliximab	2 (2.9)
Mepolizumab	1 (1.4)
Omalizumab	1 (1.4)
DEI score at first RTX treatment, mean ± SD	8.8 ± 2.4
BVAS at first rituximab, mean ± SD; median (IQR)	7.05 (±5.22); 6 (3-8.5)
Organ involvement according to DEI, number of patients (%)	
Lung (including asthma)	68 (98.6)
Ear, nose and throat	61 (88.4)
Arthralgia/Arthritis	32 (46.4)
Skin	41 (59.4)
Peripheral nervous system	40 (58)
Renal	11 (15.9)
Gastrointestinal tract (including biliary system)	12 (17.4)
Heart	15 (21.7)
Eyes	8 (11.6)
Central nervous system	3 (4.3)
Urogenital tract	2 (2.9)
Refractory asthma	46 (66.6%)
Refractory ENT disease	23 (33.3%)
Eosinophilia at diagnosis	60 (87)



Mean relapses/person	0.9 ± 1.27	
Percentage of patients who suffered relapse(s)	53.6%	
Median time to relapse after RTX start	ANCA negative: 21 months (95% CI 13.37 to 28.63) ANCA positive: 33 months (95% CI 9.57 to 56.43) $\chi^2(2) = 2.166, p = .141$.	
Median time to relapse after RTX suspension	ANCA negative: 6.4 months (95% CI 0 to 24.5) ANCA positive: 13.6 months (95% CI 0 to 49.6) $\chi^2(2) = 1.497, p = .22$	
Manifestations driving relapse during RTX treatment, mean relapses/person (% persons who suffered at least one relapse)		
Asthma/Lung	0.68 ± 1.13	(43.5%)
ENT	0.17 ± 0.38	(17.4%)
Skin	0.26 ± 0.8	(13.0%)
Kidney	0	(0)
Heart	0.03 ± 0.169	(2.9%)
Joint	0.16 ± 0.41	(14.5%)
Digestive	0.03 ± 0.17	(2.9%)
Number of patients who suffered a severe infection, N (percentage)	11 (15.9%)	
Severe infections/patient, mean ± SD	0.25 ± 0.60	
Type of infections, N (%)		
Respiratory tract	12 (71%)	
Urogenital tract	3 (17.6%)	
Mastoiditis	1 (5.9%)	
Cellulitis	1 (5.9%)	

Methods: Retrospective analysis of single-center cohort of EGPA patients who received RTX and standardised data collection of baseline clinical characteristics, disease activity (Birmingham Vasculitis Activity Score(BVAS)), eosinophilia, prednisolone (PDN) dose and serious infections over the two years from first RTX treatment. Remission was defined as a BVAS of zero and partial response as a $\geq 50\%$ reduction in BVAS compared with baseline. Relapse was an increase in BVAS and in PDN dose $\geq 5\text{mg/day}$ or institution of i.v. corticosteroids or new DMARD.

Results: 69 patients were identified and 54 received > 12 months treatment (Table 1). Remission at 6 and 12 months after RTX was achieved in 40.6% and 49.3% of patients, respectively, and increased at 18 and 24 months in those patients who received repeat dose RTX (Figure 1). Median time to remission was less in the ANCA positive group. RTX led to a median decrease in the BVAS of 4 at 12 M and of 6 at 24 M ($p < .0005$). At 12 months there was a median decrease of 5 mg/day in the PDN dose and of 7.25 mg/day at 24 months. No differences were found in eosinophilia. During treatment, 53.6% of patients relapsed at least once (mean 0.9 ± 1.27 (SD) relapses/patient). Relapses were mainly driven by asthma (Table 2). Median survival time to relapse after RTX was less for ANCA negative patients. Severe infections occurred in 15.9% of patients during treatment, mainly derived from the respiratory tract (Table 2).

Conclusion: RTX led to overall decreases in disease activity and prednisolone requirements in our cohort with additional benefit from repeat dosing over 24 months. However, fewer than 50% achieved stable remission and there lapse rate was high, driven mainly by asthma. The risk of severe infections was consistent with previous studies of refractory vasculitis.

Disclosure: V. Teixeira, None; A. Mohammad, None; D. Jayne, None.

Eosinophilic Granulomatosis with Polyangiitis: A Monocentric Cohort Analysis of Manifestations and Relapses of ANCA-Positive and ANCA-Negative Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To compare clinical features at diagnosis, relapse rates, therapy as well as long-term outcome of a cohort of patients with Eosinophilic Granulomatosis with Polyangiitis (EGPA) based on their ANCA status.

Methods: This study was conducted as a retrospective analysis of EGPA patients who were treated between 2008 and 2017 in a tertiary referral center. Diagnosis for EGPA was based both on American College of Rheumatology criteria and Chapel Hill definitions. Patient characteristics, clinical manifestations, organ involvement, therapy regime, relapse rates and follow-up outcomes were evaluated and compared in sub groups based on ANCA status.

Table 1. Clinical features, relapses and therapy regimen

	PR3-ANCA positive	MPO-ANCA positive	ANCA negative	Total	p-value
No. of patients (n=55)	1	5	49	55	
Female sex	1	2	27	30	
Age (mean)	40	55.8	46.75	47.45	
Asthma	1	5	47	52 (94.5%)	n/a
Eosinophilia	1	3	46	49 (89.9%)	0.10
Neuropathy	1	4	21	26 (47.3%)	0.03
Pulmonary infiltrate	1	2	35	38 (69.1%)	0.06
Paranasal sinus opacities	1	4	36	41 (74.5%)	0.06
Extracranial eos. infiltrate	0	1	23	24 (43.6%)	0.04
Cardiomyopathy	0	2	22	24 (43.6%)	0.05
Insomnia	0	1	20	21 (38.1%)	0.06
Abnormal haemoglobin	0	0	2	2 (3.6%)	n/a
Monoclonal gammopathy	1	1	0	2 (3.6%)	n/a
Arthritis	0	2	15	17 (30.9%)	0.04
Other (see table 2)	0	1	13	13 (23.6%)	0.07
B-symptoms	1	0	25	26 (47.3%)	0.07
Severe disease	1	5	41	47	n/a
Non-Severe Disease	0	0	8	8	n/a
Total no. of relapses	2	3	19	24	0.05
Major relapse	0	2	5	7	0.05
Minor relapse	2	1	14	17	0.05
CY/RTX treatment	1	5	16	22	n/a
Follow-up time [mean]	32	38.8	32.69	33.23	
	32	0-111	0-115	0-115	
Relapse free up to year	22.5	8	41.53	34.88	
	25	0-15	0-99	0-99	

Table 2. Specific organ involvement in lung, heart and other manifestations

	PR3-ANCA positive	MPO-ANCA positive	ANCA negative	Total
Lung				
Asthma	1	5	47	53
Pulmonary infiltrates	1	2	35	38
Alveolar haemorrhage	0	0	2	2
Heart				
Perimyocarditis	0	0	8	8
Hypertension	0	0	2	2
Arrhythmia	0	0	1	1
Coronariitis	0	0	1	1
Myocarditis	0	1	4	5
Pericardial effusion	0	1	2	3
Congestive heart failure	0	0	1	1
Necrotizing myocarditis	0	0	1	1
Not specified	0	0	2	2
Other				
Polyserositis	0	0	1	1
Myositis	0	0	2	2
GI symptoms	0	1	4	5
Raynaud's	0	0	2	2
Muscle fascitis	0	0	1	1
Eosinophilic colitis	0	0	1	1
Mediastinal lymphadenopathy	0	0	1	1

Results: Six ANCA-positive (5 with MPO-ANCA, one with PR3-ANCA) and 49 ANCA-negative patients were included overall. Patients were followed up for a median \pm SD of 33.2 (\pm 32.7 SD) months. The most common clinical features (table 1 and 2) were asthma (94.5%), ear, nose and throat (ENT) manifestations (74.5%), pulmonary infiltrates (69.1%), peripheral neuropathy (47.3%) and skin lesions (38.1%).

ANCA-positive patients had a higher incidence of peripheral neuropathy (83.3% vs. 42.8%) and glomerulonephritis (33.3% vs. 0%). ANCA-negative patients had more frequent cardiac involvement (44.8% vs. 33.3%). Relapse rates were significantly higher in ANCA-positive patients (83.3% vs., 36.7%). Severe relapses also occurred more often in ANCA-positive patients (33.3% vs. 8.1%). Initial eosinophil count did not predict severity both at diagnosis or relapse.

Interestingly, three patients suffered from a major relapse with peripheral neuropathy while presenting normal eosinophil counts. All ANCA-positive patient had severe disease and required induction therapy with cyclophosphamide or rituximab either at diagnosis or at the time of a severe relapse. Among the ANCA-negative patients, 67.3 % had no severe manifestations and were successfully treated with a combination of glucocorticoids and conventional immunosuppressants like methotrexate and azathioprine.

Conclusion: Our observations support recent reports showing that the ANCA status of EPGA patient is both relevant for clinical manifestations as well as relapse rates and relapse severity. ANCA-positive patients often require a more aggressive immunosuppressive therapy than ANCA-negative patients.

Disclosure: J. Mahrhold, None; B. Hellmich, None; E. Csernok, None.

Abstract Number: 1760

Fungal Composition of the Nasal Mucosa in Patients with Granulomatosis with Polyangiitis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: While prior studies have demonstrated that granulomatosis with polyangiitis (GPA; Wegener's) is associated with an altered composition of nasal bacteria and that use of an antibiotic may reduce the risk of relapse, no studies have evaluated the role of nasal fungi in GPA. It has been suggested that fungi may stabilize bacterial communities and interact with the immune system. Using deep sequencing methods, this study evaluated the composition of nasal fungi in GPA compared to healthy controls and examined interactions between nasal fungi and bacteria.

Methods: Fungal internal transcribed spacer (ITS) and bacterial 16S rRNA gene sequencing were performed on DNA isolated from nasal swabs of 60 participants with GPA and 41 healthy controls. Main results of bacterial DNA sequencing were previously reported. Total fungal content was determined by PicoGreen-quantification. Using Wilcoxon rank sum test and generalized linear models, the abundance of total fungi and the most abundant fungal taxa (*Malasseziales*) were compared in GPA vs controls as well as within GPA subgroups: disease activity according to the BVAS/WG, ANCA type, sinonasal damage, and use of medications (immunosuppressants and antibiotics). Correlation in the abundance of fungi and bacteria were assessed using Spearman's correlation coefficient.

Results: *Malasseziales* was the most abundant fungal taxa present followed by the genera *Penicillium* and *Aspergillus*. There was a non-significant trend towards lower abundance of total fungi in GPA vs controls ($p = 0.06$). When evaluating the most abundant taxa *Malasseziales*, we found a significantly lower abundance of *Malasseziales* in GPA vs controls ($p = 0.04$) and this difference was most pronounced in the group with active GPA which had a significantly lower abundance compared to GPA in remission ($p = 0.04$) and healthy controls ($p = 0.01$) (Figure 1). No associations were found among the other co-variables. There was significant positive correlation in the 5 most common bacterial species present in the samples and abundance of total fungi (Figure 2) as well as abundance of *Malasseziales* (data not shown).

Conclusion: The abundance of *Malasseziales* is significantly lower in the nasal mucosa of GPA vs controls and is associated with disease activity in GPA. Co-variation in the abundance of fungi and several bacterial species suggests fungi and bacteria may interact in the nose. These results support the possibility that commensal fungal communities and their interactions with bacteria may be involved in disease pathogenesis of GPA.

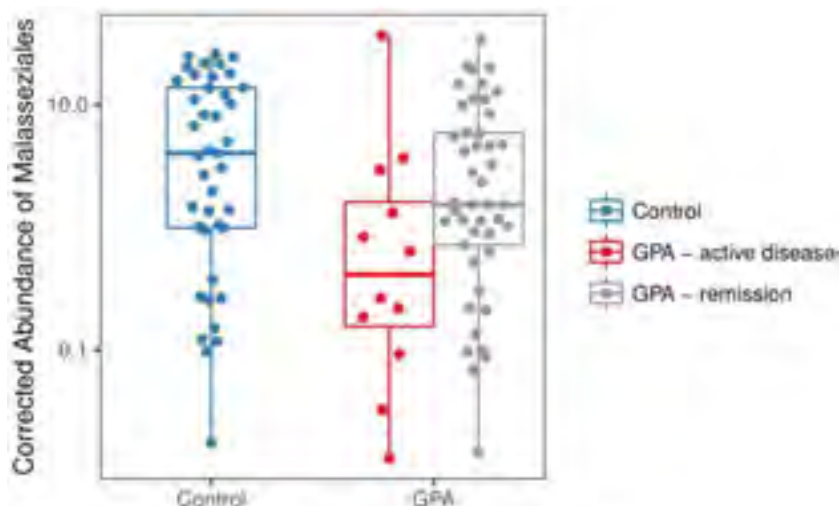


Figure 1. Differential abundance of *Malasseziales* between controls and patients with granulomatosis with polyangiitis (GPA) stratified by disease activity. Abundance of *Malasseziales* was significantly lower in GPA with active disease (red) compared to controls (blue) ($p = 0.01$) and GPA in remission (gray) ($p = 0.04$). No difference was seen between participants with GPA in remission and controls ($p = 0.19$).

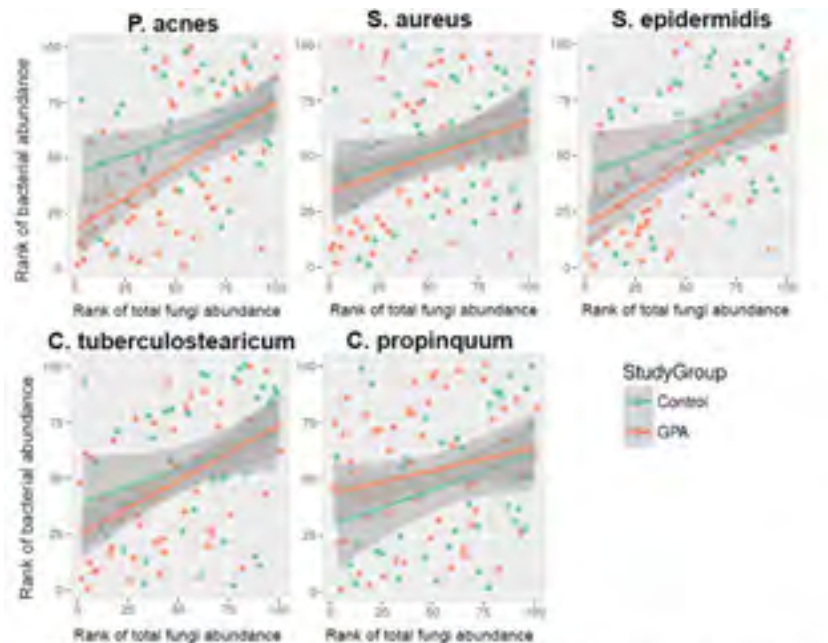


Figure 2. Abundance of total fungi is correlated with abundance of several types of bacteria, suggesting a possible interaction between fungi and bacteria. Among all participants, there was a significant correlation between abundance of total fungi and *Propionibacterium acnes* ($r = 0.51$, $p < 0.01$), *Staphylococcus aureus* ($r = 0.31$, $p < 0.01$), *S. epidermidis* ($r = 0.50$, $p < 0.01$), *Corynebacterium tuberculostrictum* ($r = 0.43$, $p < 0.01$), and *C. propinquum* ($r = 0.23$, $p = 0.02$). In linear regression models, fungi abundance remained independently associated with abundance of *P. acnes* and *S. epidermidis*, the same species which our group previously demonstrated have differential abundance in GPA vs controls. Similar findings were seen when examining abundance of *Malassezia* species. This suggests fungi may interact with nasal bacteria and these interactions may be involved in the disease process of GPA.

Disclosure: R. L. Rhee, None; A. G. Sreih, None; C. E. Najem, None; P. C. Grayson, None; C. Zhao, None; K. Bittinger, None; R. Collman, None; P. A. Merkel, None.

Abstract Number: 1761

Evaluation of the Functional Activity of Endothelial Progenitor Cells in Patients with ANCA-Associated Vasculitis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: ANCA-associated vasculitis (AAV) are relapsing diseases with high morbidity and mortality. The vascular damage present in these patients requires continuous repair with the participation of the endothelial progenitor cells (EPC). The circulating EPC have a fundamental role in angiogenesis, repair and vascular homeostasis. These cells isolated from peripheral blood generate in vitro endothelial colony-forming cells (ECFC) that have high proliferative capacity and stable phenotype throughout the culture. It is believed that there is a deficiency of the EPC's repair capacity in AAV. There are no studies on the functional capacity of EPC and ECFC in AAV. Understanding the functional disturbances of EPC in AAV patients will result in a better knowledge of its pathogenesis and possible future therapeutic targets. The aim of the study was to evaluate the functional capacity of ECFC in patients with AAV in vitro through angiogenesis and migration assays.

Methods: Patients with a previous diagnosis of AAV without immunosuppression for at least 18 months and healthy controls were selected. First, we isolated ECFC from peripheral blood and characterized them by flow cytometry (FACS). After expansion, we evaluated angiogenesis on Matrigel™ plates and ECFCs migration capacity. For angiogenesis, ECFC were evaluated and photographed 15 and 24 hours after the preparation. The ECFC migration was performed by the scratch (wound-healing assay) methodology and photographed hourly in an phase-contrast microscope using the Aviocam 506zen 2Pro, for 24 hours after the scratch. The images obtained in both experiments were analyzed using the Image J® software. All the tests consisted of the evaluation of ECFC from patients, healthy controls and human umbilical vein endothelial cells (HUVEC), performed in triplicate.

Results: Peripheral blood was collected from 12 patients diagnosed with AAV. The collection of 7 of these patients was performed at the diagnosis, 5 with granulomatosis with polyangiitis (GPA) and 2 with eosinophilic granulomatosis with polyangiitis (EGPA). The other 5 patients were on follow-up and without immunosuppression for at least 18 months and had a maximum prednisone dose of 10mg daily, three of which were diagnosed with GPA, one with EGPA and one with microscopic polyangiitis (MPA). Success in the isolation and growth in ECFC culture was obtained in 8/12 (66%) of the cases. ECFC from GPA patients had lower rates of migration compared to healthy controls and HUVEC ($p=0.002$ and $p=0.0079$, respectively). ECFC from patients with AAV had a higher angiogenesis capacity as shown by a significantly higher number of structures (meshes, nodes and junctions) when compared with ECFCs from healthy controls ($p=0.0023$, $p<0.00001$ and $p=0.0371$, for each structure) and HUVEC ($p=0.00001$, $p=0.0001$ and $p=0.056$).

Conclusion: These findings suggest distinct functional profiles in ECFC from patients with AAV, which could influence disease pathogenesis.

Disclosure: A. P. T. Del Rio, None; S. O. Prieto, None; B. K. L. Duarte, None; M. B. Bertolo, None; M. D. C. Ozelo, None; Z. Sachetto, None.

Abstract Number: 1762

Plasma iC3b Level As a Biomarker of Disease Relapse in ANCA-Associated Vasculitis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

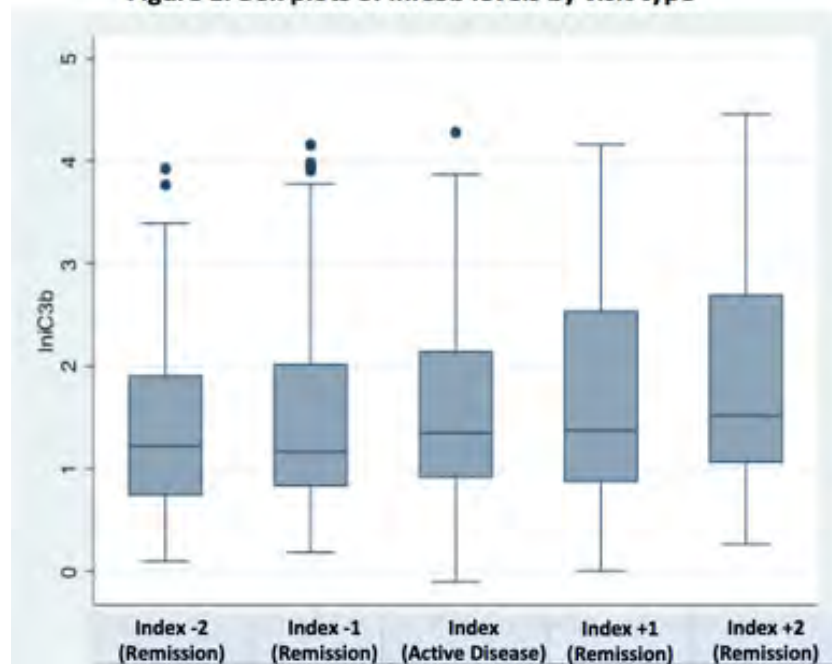
Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: C3, the central protein of the complement cascade, participates in an amplification loop that can lead to complement deposition and host tissue damage. If elevated, downstream C3 activation products, including C3a and iC3b, can reflect an underlying tissue inflammation and potential disease activity, such as previously demonstrated in lupus nephritis. Complement 5a, which is preceded by iC3b in the complement cascade, and its receptor C5aR (CD88), are involved in the pathogenesis of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). This study examined plasma iC3b levels as a biomarker of active disease in AAV.

Methods: Data and plasma samples from patients with AAV enrolled in a prospective multicenter longitudinal cohort were utilized for this analysis. The index visit was defined as a time of severe active disease with any new/worse major item, or

Figure 1. Box plots of ln iC3b levels by visit type



³³ minor items, on the BVAS/WG. Plasma iC3b levels were measured at 1-2 visits prior to, and at 1-2 visits after the index visit; all pre and post index visits were at time of remission (BVAS/WG=0). To evaluate the association of the plasma iC3b levels with disease activity, a mixed effect model was used with the biomarker measurement as the outcome, adjusting for ANCA type (c-ANCA/MPO or p-ANCA/PR3), sex, age, race, time to index, and visit type (pre- or post-index). Plasma iC3b levels were log transformed for all analyses.

Results: Data from 110 patients with active AAV were included. 89% of the patients were Caucasian, and 66% were female. 80% of the patients had GPA with c-ANCA/PR3 positivity, with a median disease duration of 4.1 years at baseline (range 0.2 - 23.8 years). The median Ln (iC3b) at the time of active disease was 1.3 µg/ml (range 0.0 - 4.5 µg/ml). Plasma for measurement of iC3b levels were available for 147 pre-index visits and 161 post-index visits.

In an adjusted mixed effects model where plasma iC3b level served as the dependent variable, the mean plasma iC3b level at index visit (active disease) was not higher than the mean plasma iC3b level at pre-index visit ($p=0.17$) or at post-index visit ($p=0.37$) (Table 1 and Figure 1). In the same adjusted mixed effects model, patients positive for p-ANCA/MPO, had higher levels of plasma iC3b compared to patients positive for c-ANCA/PR3 ($p<0.01$). Plasma iC3b levels increased for each one year increase in age ($p=0.05$) (Table 2).

Conclusion: In AAV, plasma iC3b levels are not associated with disease activity. Older patients and patients with positive p-ANCA/MPO have higher levels of plasma iC3b, possibly indicating increased systemic inflammation in these patients. Total number of characters: 2241

Table 1. Mixed effects models examining the association of ln iC3b levels with disease activity (outcome: ln iC3b level)

	Estimate	95% CI	p-value
Visit Type (Ref: Index)			
Pre-index	-0.14	(-0.34; 0.06)	0.17
Post-index	0.09	(-0.11; 0.29)	0.37
Time to index	<0.01	(-<0.01; <0.01)	0.13
Sex (Ref: Female)	-0.12	(-0.46; 0.22)	0.49
Male			
Race (Ref: Caucasian)	0.53	(-0.20; 1.26)	0.16
Non-Caucasian			
ANCA type	-0.56	(-0.98; -0.14)	<0.01
(Ref: p-ANCA/MPO) c-ANCA/PR3			
Age	0.07	(<0.01; 0.13)	0.05

CI: confidence interval; Ref: reference group; ANCA: anti-neutrophil cytoplasmic antibody; p: perinuclear; c: cytoplasmic; MPO: myeloperoxidase; PR3: proteinase 3

Disclosure: C. E. Najem, None; M. Schmidt, None; C. Stiening, None; D. Cuthbertson, None; S. Carette, None; N. A. Khalidi, None; C. L. Koenig, None; C. Langford, None; C. A. McAlear, None; P. A. Monach, None; L. W. Moreland, None; C. Pagnoux, None; P. Seo, None; U. Specks, None; A. G. Sreih, None; S. R. Ytterberg, None; P. A. Merkel, None.

Characterizing the Gut and Plasma Metabolomes in Patients with ANCA-Associated Vasculitis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To explore the mechanisms by which an altered gut microbiota might predispose to ANCA-associated vasculitis (AAV), a comprehensive metabolic profiling of fecal and plasma bile acids, amino acids, and short chain fatty acids was performed in patients with AAV (granulomatosis with polyangiitis; microscopic polyangiitis; and eosinophilic granulomatosis with polyangiitis) and in healthy controls.

Methods: Using cross-section a land longitudinal designs, the fecal and plasma metabolomes of patients with newly diagnosed AAV (active and in remission) were compared to chronic AAV(active and in remission), and to healthy controls. All samples were collected using standardized methods, and analyzed by Liquid Chromatography/Mass Spectrometry for bile acids, amino acids, and short chain fatty acids. The gut microbiome was analyzed on the same fecal samples by sequencing the bacterial 16S rRNA gene (V1-V2 region). The association between bacterial tax a and fecal metabolites was studied using logistic regression models, correcting for multiple comparisons. Bacterial taxa were tested if their mean abundance was >1%.

Results: 78 fecal samples were studied: 37 active AAV (20 new diagnosis and 17 chronic), 25 remission, and 16 controls. 32 plasma samples were studied: 20 active AAV, 6 remission, and 6 controls.

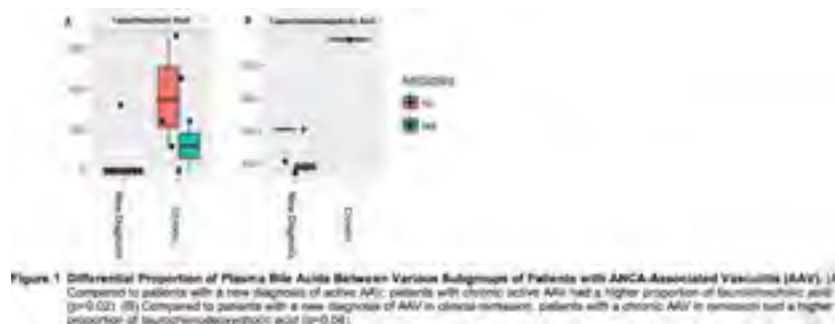
Compared to remission states, the fecal amino acid sphenylalanine and tyrosine were significantly diminished in active disease. Patients with chronic AAV in remission had higher levels of plasma phenylalanine and tyrosine compared to patients with a new diagnosis of AAV in remission ($p=0.02$ for both).

There was no statistical difference in fecal bile acids between the disease states of AAV. Patients with a chronic active AAV had higher levels of plasma tauroolithocholic bile acid compared to patients with an active new diagnosis of AAV (**Figure 1A**). *Faecalibacterium* was found to be associated with this plasma bile acid ($p=0.02$). Plasma glycholic and glycodeoxycholic acids were strongly associated with active disease ($p<0.01$ and $p=0.01$ for both).

Patients with chronic AAV in remission had higher levels of plasma taurochenodeoxycholic bile acid compared to patients with a new diagnosis of AAV in remission (**Figure 1B**). *Phascolarctobacterium*, *Sutterella*, and *Ruminococcus* were found to be associated with this plasma bile acid ($p<0.05$).

There was no statistical difference in plasma or fecal short chain fatty acids.

Conclusion: Active AAV is associated with an altered fecal and plasma metabolome. Plasma taurochenodeoxycholic bile acid, and plasma and fecal amino acids are higher in chronic remission states compared to new diagnosis remission states, suggesting potential anti-inflammatory effects of these metabolites. Diminished metabolic diversity may be a feature of active AAV and potential biomarker to predict disease activity in AAV.



Disclosure: C. E. Najem, None; J. J. Lee, None; C. Tanes, None; C. Strange, None; E. Friedman, None; A. G. Sreih, None; R. L. Rhee, None; A. Geara, None; H. Li, None; K. Bittinger, None; J. D. Lewis, None; G. Wu, None; P. A. Merkel, None.

Abstract Number: 1764

The Utility of Serum Angiopoietin-1 and Angiopoietin-2 in Patients with Anti-Neutrophil Cytoplasmic Autoantibody-Associated Vasculitis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Angiopoietin-1 (Ang-1) and Angiopoietin-2 (Ang-2) are antagonistic ligands which bind with similar affinity to the extracellular domain of the tyrosine kinase with Ig-like and epidermal growth factor-like domains 2 (Tie-2) receptor, which is almost exclusively expressed by endothelial cells. Ang-1/Tie-2 signalling maintains vessel integrity, inhibits vascular leakage, suppresses inflammatory gene expression and prevents recruitment and transmigration of leukocytes. In contrast, binding of Ang-2 disrupts protective Ang-1/Tie-2 signalling and facilitates endothelial inflammation. The purpose of this study is to examine the serum Angpt1 and Angpt2 levels in patients with AAV, and explore the utility as biomarkers.

Methods: Seventy-one patients who had been diagnosed as AAV and referred to Niigata University Medical and Dental Hospital between 2009 and 2017, were participated in this study. Serum Ang-1 and Ang-2 levels were measured by enzyme-linked immunosorbent assay, before the initiation of remission-induction therapy. Laboratory findings, disease activity using Birmingham vasculitis activity score (BVAS) at the time of diagnosis, and patients' kidney and overall prognosis at August 2017, were corrected from patients' clinical records. The correlations between these findings and serum Ang-1, Ang-2 levels, and Ang-1/Ang-2 ratio were analyzed by Spearman correlation coefficient and stepwise multiple regression analysis. A value of $p < 0.05$ was taken to indicate statistical significance.

Results: In Spearman correlation coefficient analysis, serum Ang-1 was positively correlated with estimated glomerular filtration ratio (eGFR) ($r=0.3979$, $p=0.0006$) and C-reactive protein (0.2574 , $p=0.0302$), and negatively correlated with serum creatinine (Cr) ($r=-0.3438$, $p=0.0033$), initiation of dialysis therapy ($r=-0.2559$, $p=0.0312$), and death ($r=-0.3057$, $p=0.0095$). Serum Ang-2 was positively correlated with age ($r=0.2466$, $p=0.0382$), BVAS ($r=0.3090$, $p=0.0087$), serum Cr ($r=0.3945$, $p=0.0007$), and negatively correlated with eGFR ($r=-0.4278$, $p=0.0002$). The Ang-1/Ang-2 ratio was positively correlated with eGFR ($r=0.5715$, $p<0.0001$), and negatively correlated with age ($r=-0.2359$, $p=0.0476$), BVAS ($r=-0.3456$, $p=0.0032$), Cr ($r=-0.5234$), 24-hour urinary protein excretion ($r=-0.2863$, $p=0.0155$), initiation of dialysis therapy ($r=-0.3251$, $p=0.0057$), and death ($r=-0.2556$, $p=0.0314$). In stepwise multiple regression analysis, eGFR was selected as a positive independent variable for serum Ang-1 levels ($\beta=0.4138$, $p=0.0003$) and Ang-1/Ang-2 ratio ($\beta=0.4305$, $p=0.00017$), whereas initiation of dialysis therapy was selected as a positive independent variable ($\beta=0.2803$, $p=0.033$), and UP/Cr ($\beta=-0.3908$, $p=0.0043$) and eGFR ($\beta=-0.4897$, $p=0.0001$) were selected as negative independent variables for serum Ang-2 levels.

Conclusion: These findings showed the protective effect of kidney functions for Ang-1 and the utility of Ang-2 as a predictive factor for kidney prognosis.

Disclosure: Y. Wada, None; T. Kuroda, None; M. Nakano, None; I. Narita, None.

Abstract Number: 1765

Cerebrospinal Fluid Biomarker of Disease Activity: Significance in ANCA-Related Hypertrophic Pachymeningitis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Hypertrophic pachymeningitis (HP), which becomes the cause of chronic headache, seizure, and cranial neuropathy, is an inflammatory disorder demonstrating focal and diffuse thickening of dura mater. It has been recognized that ANCA-associated vasculitis is the underlying disease as the common cause of HP whose histopathology indicates inflammatory cells infiltration and granulomatous lesion as well as fibrosis; meanwhile, definite immune-mediated mechanism is still elusive. In this study, we demonstrated the useful cerebrospinal fluid (CSF) biomarkers in ANCA-related HP (ANCA-HP).

Methods: We reviewed the clinical records of 22 Japanese patients with immune-mediated HP (mean age, 65 years; 9 women and 13 men). They were divided into patients with ANCA-HP (n = 11), or those with other autoimmune disorders related HP (other HP) including IgG4-related disease/multifocal fibrosclerosis (n = 4), relapsing polychondritis (n = 1), sarcoidosis (n = 2), and idiopathic HP (n = 4). HP associated with infection and/or neoplasm was excluded in this study. As the controls, 11 patients with multiple sclerosis (MS) and 8 with non-inflammatory neurological disorders (NIND) were enrolled. The routine laboratory examinations of serum C-reactive protein (CRP) levels and CSF, including cell counts, protein levels, and IgG-index were detected. In addition, B-cell activation factor of the TNF family (BAFF) and a proliferation-inducing ligand (APRIL) in the CSF and serum samples were measured using commercially available ELISA kits. To determine the characteristics of ANCA-HP, the laboratory data from them were statistically compared between patients with ANCA-HP, other HP, and controls.

Results: CSF levels of BAFF and APRIL were significantly higher in patients with both ANCA-HP and other HP than in patients with MS and NIND ($p < 0.05$). Serum levels of BAFF and APRIL were significantly higher in patients with both ANCA-HP and other HP than in patients with NIND ($p < 0.05$). In patients with both ANCA-HP and other HP, neither BAFF nor APRIL expression indicated no correlation between in the CSF and serum, suggesting that BAFF and APRIL were locally produced within the central nervous system (CNS). Meanwhile, both BAFF and APRIL expression in the CSF significantly demonstrated the correlation with IgG-index in patients with ANCA-HP ($p < 0.05$). In patients with other HP, BAFF and APRIL expression in the CSF had significant correlation with cell counts and protein levels ($p < 0.05$).

Conclusion: BAFF and APRIL expression in the CSF is associated with disease activity as the immunological biomarker in immune-mediated HP. Furthermore, it was suggested that increased levels of BAFF and APRIL produced in the CNS may impact on developing ANCA-HP by promoting the B cell lineage.

Disclosure: Y. Shimojima, None; D. Kishida, None; Y. Sekijima, None.

Abstract Number: 1766

Abdominal Adipose Tissue Predicts Incident Major Cardiovascular Events in Systemic Necrotizing Vasculitis Patients: Data from a Prospective Cohort Study on 120 Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

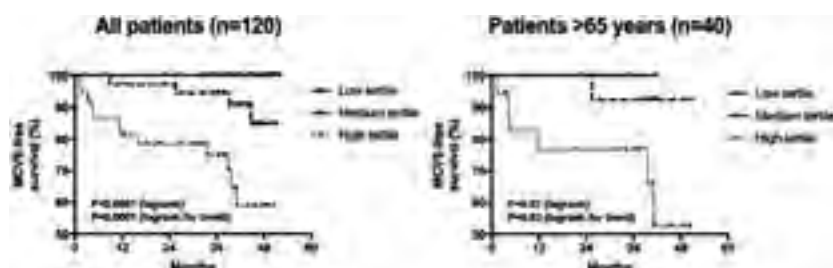
Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Cardiovascular (CV) events are highly prevalent in patients with systemic necrotizing vasculitides (SNV). The visceral/subcutaneous adipose tissue (VAT/SAT) ratio has been shown to be associated with CV events in various diseases. Using prediction scores, we found elevated VAT/SAT ratios to be associated with higher CV risk in SNV patients. However, no prospective data are available to confirm those findings for incident major CV events (MCVE).

Methods: Patients with ANCA-associated vasculitides or polyarteritis nodosa (PAN) were successively included in a longitudinal study assessing CV complications and other sequelae. At inclusion, DXA evaluation of body composition and abdominal adipose tissue (SAT and VAT) was obtained. Patients were prospectively followed for MCVEs, defined as myocardial infarction, unstable angina, stroke, arterial revascularization and/or hospitalization for or death from CV causes.



Results: Among the 120 patients enrolled (54 men; mean age 53 ± 18 years; median disease duration: 54 months), at inclusion, 28 (23%) had high CV risk, including 16 (13%) with preexisting CV disease, 11 (9%) with diabetes and 9 (8%) with a Framingham CV risk score $\geq 20\%$. Age and VAT/SAT ratio were independently associated with high CV risk. Framingham CV risk score was correlated with the VAT/SAT ratio ($r^2 = 0.36$, $P < 0.0001$). Also, the high VAT/SAT-ratio tertile (according to gender-specific tertiles) was associated with age and metabolic risk factors.

After median follow-up of 42 months, 19 (16%) patients experienced MCVE: arterial revascularization for 6 (including 4 with myocardial infarction or unstable angina), stroke for 5, hospitalization for CV causes for 5 and 3 CV-caused deaths. The highest VAT/SAT ratio was significantly associated with higher cumulative incident MCVE ($P < 0.0001$; log rank test and log rank test for trend). Hazard ratios (95% CI) for incident MCVE compared with 1st tertile were 7.22 (1.02-51.3; $P = 0.048$) and 9.90 (3.15-31.2; $P = 0.0002$) in the 2nd and 3rd tertile, respectively (Fig). In contrast, age > 65 years (HR 1.98 [0.72-5.43]; $P = 0.19$) and body mass index > 30 kg/m² (HR 1.37 [0.41-4.61]; $P = 0.61$) were not associated with higher cumulative incident MCVE. The VAT/SAT ratio remained associated with incident MCVEs even for only patients > 65 years ($P = 0.07$, log rank test; and $P = 0.03$ log rank test for trend) (Fig).

Conclusion: This study shows a significant association between a high DXA-assessed VAT/SAT ratio and incident MCVE in SNV patients. The VAT/SAT-ratio prognostic value remained significant even for patients > 65 years. Abdominal adipose tissue should be probably be evaluated routinely in these patients to assess CV risk.

Disclosure: S. Henriquez, None; B. Dunogu , None; A. R gent, None; P. Cohen, None; A. B rezn , None; S. Kolta, None; C. Le Jeunne, None; L. Mouthon, None; C. Roux, None; L. Guillevin, None; K. Briot, None; B. Terrier, None.

Abstract Number: 1767

Occurrence and Etiology of Gastrointestinal Perforation in Patients with Vasculitis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

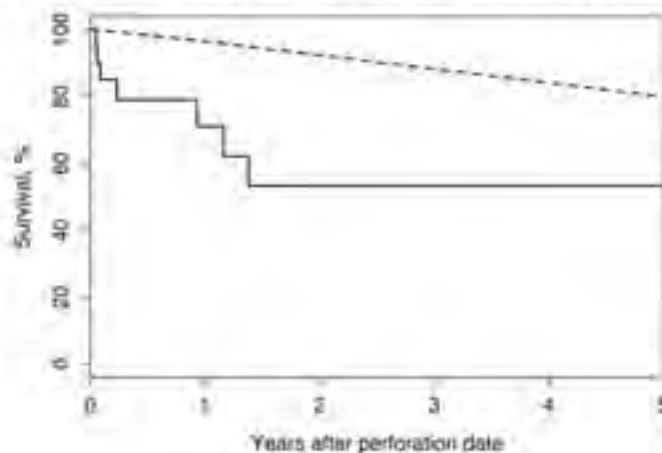
Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: This study aimed to characterize the presenting features and outcomes of patients with small- or medium-vessel vasculitis and gastrointestinal perforation.

Methods: Using a retrospective cohort design, we identified cases with verified granulomatosis with polyangiitis (GPA), eosinophilic GPA (EGPA), microscopic polyangiitis (MPA), or polyarteritis nodosa (PAN) by ACR criteria along with confirmed gastrointestinal perforation at our institution between 1998 and 2017. The standardized mortality ratio (SMR) was estimated using persons of the same age, sex, and calendar year derived from United States white population life tables.

Figure 1. Overall survival of entire cohort (solid) compared to expected (dashed)



Results: Over the twenty year time period, 20 total patients with small or medium-vessel vasculitis experienced bowel perforation. Three had EGPA, 11 GPA, three MPA, and three PAN. Four of the twenty cases experienced vasculitis-induced perforation. Cases with perforations due to vasculitic involvement had more small bowel involvement, longer duration of abdominal pain prior to perforation (41 days vs 0 days, $p = 0.005$), and a higher proportion of active tobacco use (75% vs 7%, $p = 0.01$) compared to the cases with non-vasculitis perforation. A majority (88%) of the non-vasculitis-induced perforations were associated with glucocorticoid use. The median cumulative glucocorticoid dose at perforation in patients with additional, non-vasculitic risk factors for perforation was 4,320 mg prednisone and was 22,170 mg for those without such risk factors. Mortality rates for the whole cohort were higher than the general population (SMR 2.19, 95% confidence interval 1.05 to 4.02, Figure 1). The cases with vasculitis-induced perforation tended to have increased number of surgeries and length of stay; however, those differences failed to reach statistical significance.

Conclusion: In patients with known history of vasculitis, small bowel location and longer abdominal pain duration may help distinguish vasculitis-induced bowel perforation from other etiologies. Overall mortality in patients with vasculitis and bowel perforation is increased, highlighting the importance of a high index of suspicion and prompt management.

Disclosure: V. L. Kronzer, None; D. Larson, None; C. S. Crowson, None; K. J. Warrington, GlaxoSmithKline, 2, Eli Lilly and Co., 2, Sanofi, 5; S. R. Ytterberg, None; A. Makol, None; M. J. Koster, None.

Abstract Number: 1768

Kidney Involvement, Poor Performance Status, and Higher Cumulative Dose of Glucocorticoid Are the Risk Factors of the Discontinuation of Immunosuppressant in Patients with Antineutrophil Cytoplasmic Antibody Associated Vasculitis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The use of immunosuppressant (IS) with glucocorticoid is recommended as remission induction treatment for severe cases with antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV). However, we sometimes experience the discontinuation of IS due to its adverse event. We examined the clinical characteristics of patients with AAV who received IS treatment to identify the risk factors of the discontinuation of IS.

Methods: We retrospectively analyzed the clinical data of patients with AAV from 2005 to 2016. The clinical data included patients-demographics, the use of IS, the adverse event of IS, the cumulative dose of glucocorticoid until the start of IS, and the continuity of IS. The definition of discontinuation of IS was switch to glucocorticoid-single therapy, switch to another IS, or delay of IS re-administration due to the adverse event of IS. First IS used for remission induction treatment was analyzed in each patient. Activity of daily living was assessed by performance status (PS) proposed by Eastern Cooperative Oncology Group. The survival of IS use was estimated by Kaplan-Meier method, and the difference between the survival curves was statistically analyzed by log rank analysis.

Figure 1. The survival curve of immunosuppressant use in patient with or without kidney involvement.

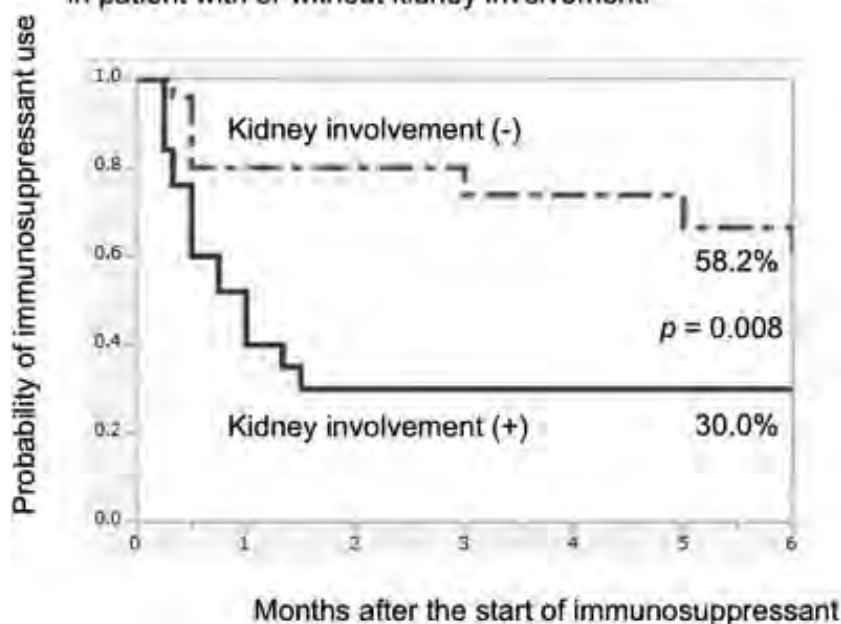


Figure 2. The survival curve of immunosuppressant use according to performance status.

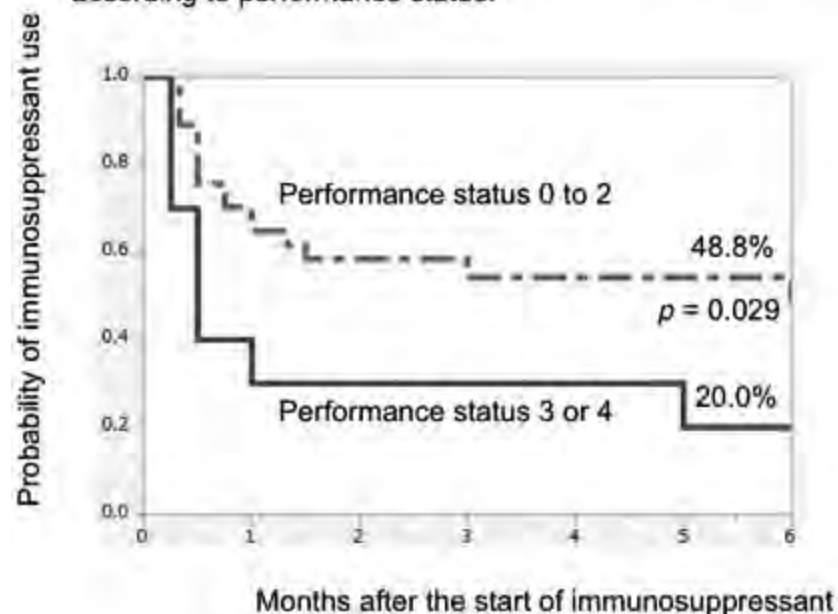
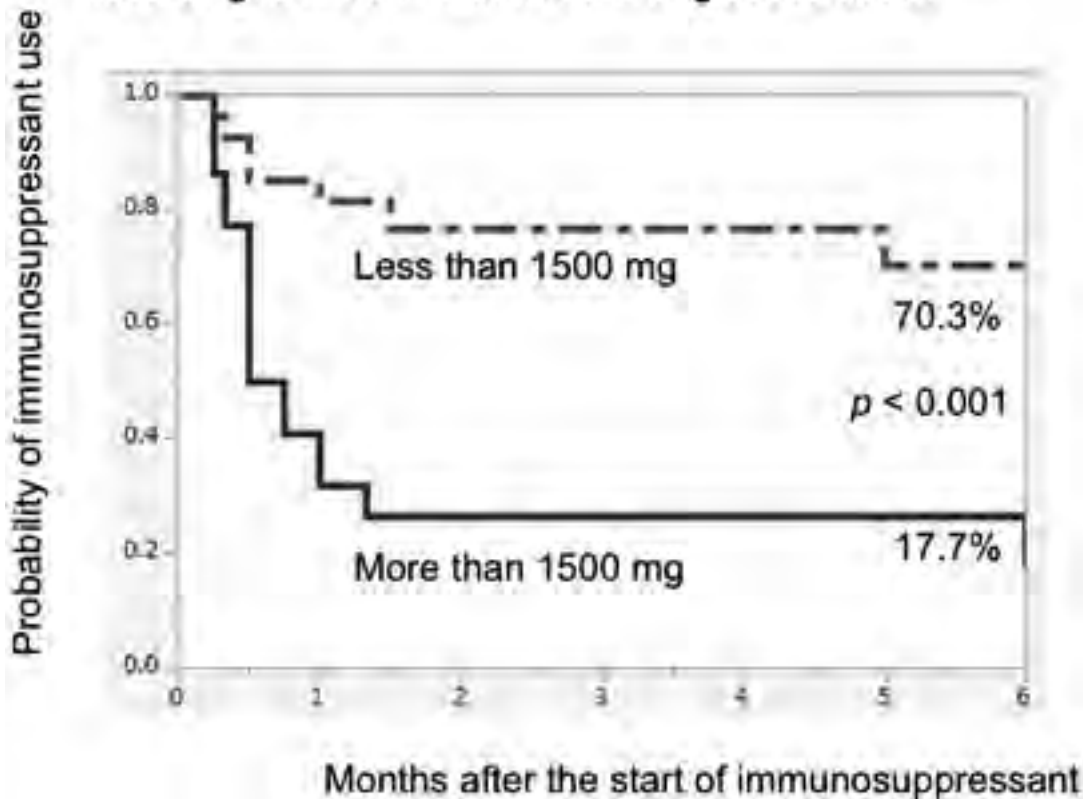


Figure 3. The survival curve of immunosuppressant use according to the cumulative dose of glucocorticoid.



Results: We found 162 patients with AAV, and 50 patients were treated with IS for remission induction treatment. Among 50 patients, 26 patients experienced the discontinuation of IS due to its adverse event. The use of IS were as follows: intravenous cyclophosphamide 34, oral cyclophosphamide 11, methotrexate 4, and cyclosporine 1. Kaplan Meier analysis showed significant differences in the survival rate of IS use between patients with or without kidney involvement (30.0% vs. 58.2%, $p = 0.008$, Figure 1), between PS scores with 0 to 2 and 3 to 4 (48.8% vs. 20.0%, $p = 0.029$, Figure 2), and between the cumulative doses of glucocorticoid of less and more than 1500 mg (70.3% vs. 17.7%, $p < 0.001$, Figure 3) at 6 months.

Conclusion: This study showed that kidney involvement, poor PS, higher cumulative dose of glucocorticoid until the start of IS were the risk factors of the discontinuation of IS. We suggest that physicians should pay attention to these factors to reduce the risk of discontinuation of IS when treating patients with AAV using IS.

Disclosure: T. Murosaki, None; T. Sato, None; K. Nagatani, None; S. Minota, Mitsubishi Tanabe Pharma, 2, Ono Pharmaceutical Co., Ltd., 2, Takeda Pharmaceutical Company Limited, 2, Astellas Pharma Inc., 2, Chugai Pharmaceutical Co., Ltd., 2, Eisai Co., Ltd., 2, AbbVie Inc., 2, Pfizer, Inc., 2, Chugai Pharmaceutical Co., Ltd., 7, Shionogi & Co., Ltd., 2.

Abstract Number: 1769

Efficacy and Safety of Biomimic Rituximab in Granulomatosis with Polyangiitis – Experience from a Single Tertiary Care Centre in India

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Though rituximab(RTX) has become a standard of care for remission induction and maintenance in Granulomatosis with Polyangiitis(GPA), there is very limited data on the efficacy and safety of biomimic RTX in GPA. The purpose of this study was to analyse the efficacy and safety of biomimic RTX in GPA since these drugs are widely used in various developing countries due to their lower costs.

Methods: The details of GPA patients diagnosed according to the ACR/EMA criteria who received biomimic RTX from July 2009 to May 2018 for remission induction or maintenance were analysed retrospectively. Patients achieving complete remission (BVAS-v3 =0) at 6, 12 and 24 months was noted. The details of relapses, infections and deaths were also noted.

Results: Out of 184 GPA patients seen during the study period, 56 (30.43%) received biomimic RTX. The baseline characteristics of the study population are given in table 1. Forty five patients (80.36%) received biomimic RTX for remission induction (primary induction in 20 and re-induction in 25) and 43(76.79%) received biomimic RTX maintenance. Mean BVAS-v3 at the start of induction with biomimic RTX was 14.63 (SD 10.37). Complete remission at 6,12 and 24 months was achieved in 71.43%, 71.43% and 85.71% respectively. Mean BVAS-v3 at 6 , 12 and 24 months was 1.22 (SD 2.46), 1.02 (SD 2.28) and 0.45 (SD 0.98) respectively. Fifteen relapses were noted in 13 patients. Average time to first relapse was 10.15 months. 18 episodes of infections were noted in 17 patients (30.36%). The infections noted were UTI in four; sepsis in three; hepatitis C and superficial mycosis in two patients each; pulmonary tuberculosis, bacterial pneumonia, lung abscess, aspergilloma, H1N1 influenza, pyomyositis and bacterial nasal septal abscess in one patient each. Mean duration of follow up on biomimic RTX therapy was 23.66 months (SD 18.25). Seven patients (12.5%) died during follow up. The cause of death was disease activity in four and sepsis in three patients. Of the four patients who died due to disease activity, three died at the time of presentation and the fourth died within two months of biomimic RTX initiation.

Conclusion: Biomimic RTX is effective in controlling disease activity in patients with GPA. Infections though common were treatable in most of the patients.

Table 1. Characteristics of 56 GPA patients receiving biomimic rituximab

Characteristics	Numbers	Percentage (%)
Number of GPA patients	184	
No. of patients receiving biomimic rituximab	56	30.43
Age	40.48(SD15.99)	-
Male	22	39.28
Female	34	60.71
Clinical Features		
Constitutional	36	64.29
Upper Respiratory Tract	39	69.64
Eye	20	35.71
Ear	16	28.57
Lung	39	69.64
Renal	19	33.93
Skin	16	28.57
Joint	25	44.64
Peripheral nervous system	5	8.93
Central nervous system	16	28.57
Gastro-intestinal	9	16.07
Cardiac	4	7.14
PR3 positive	37	66.07
MPO positive	2	3.57
cANCA positive	40	71.43
pANCA positive	3	5.36
Patients receiving rituximab induction	45	80.36
Primary induction	20	35.71
Re-induction	25	44.64
Patients on rituximab maintenance	43	76.79
Mean duration of follow up (months)	23.66(SD18.25)	-
Mean BVAS at the time of induction with Rituximab	14.63(SD10.37)	-
Mean BVAS at 6 months	1.22(SD2.46)	-
Mean BVAS at 1 year	1.02(SD2.28)	-
Mean BVAS at 2 years	0.45(SD0.98)	-
Number of relapses	15	26.78
Mean time to first relapse (months)	10.15 (SD6.94)	-
Number of infectious complications	18	32.14
Deaths	7	12.50

Disclosure: A. Sharma, None; S. Mittal, None; G. Naidu, None; S. Jha, None; M. Rathi, None; V. Sharma, None; A. Chattopadhyay, None; V. Dhir, None; K. Sharma, None; R. Minz, None; R. Nada, None; S. Jain, None.

Abstract Number: 1770

Subglottic Stenosis and Endobronchial Disease in Granulomatosis with Polyangiitis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Damage to the large airways is a devastating complication of granulomatosis with polyangiitis (GPA). Identification of patient sub sets at particular risk for airway disease and development of non-invasive screening methods to detect tracheobronchial disease is an unmet need in GPA. This study aimed to characterize patients with subglottic stenosis (SGS) and bronchial disease and test whether dynamic expiratory-phase CT is useful to detect airway damage in patients with GPA.

Methods: i) A retrospective analysis of a multi-center cohort of patients with GPA identified demographic and clinical features associated with the presence of SGS or endobronchial involvement; ii) A sub set of patients with GPA underwent a dynamic chest CT at a single center, assessed by a central reader blinded to clinical status. Differences were assessed by the chi square test and ANOVA with post-hoc Tukey test to account for multiple comparisons.

Results: Data from 962 patients with GPA from 9 centers were used for the initial phase analyses. As outlined in Table 1, SGS was identified in 95 (10%) patients with no differences in ANCA subtype in patients with SGS compared to the overall cohort. Patients with SGS were more likely to be female (72% vs 53%, $P < 0.01$), younger at time of diagnosis (36 vs 49 years, $p < 0.01$), and less likely to have constitutional, cardiovascular, renal, or nervous system involvement. Among 95 patients in the cohort within nasal septal perforation and saddle nose deformities, 28 (29%) and 27 (30%), respectively, also had SGS.

Endobronchial disease was seen in 59 (6%) patients. Compared to the full cohort, patients with endobronchial involvement were younger at time of diagnosis, more likely to have ENT involvement and be PR3-ANCA positive (78% vs 63%, $p = 0.02$), but less likely to be ANCA-negative (0% vs 9%, $p = 0.02$) or have renal disease. There was no association between endobronchial involvement and sex. Patients with SGS were more likely to have endobronchial involvement. Concomitant SGS and endobronchial involvement (25 patients) was not associated with sex (60% vs 55% female, $p = 0.60$).

Six of ten patients screened by dynamic chest CT had large-airway pathology. Isolated SGS was confirmed by imaging in two female patients. Previously unknown tracheobronchomalacia was discovered in 4 patients, including one male patient thought to have isolated SGS.

Conclusion: Both SGS and endobronchial disease are moderately common in GPA and each manifestation is associated with various other aspects of GPA. SGS is more commonly seen in female patients with GPA, whereas bronchial

involvement is not associated with sex. There should be a low threshold to evaluate airway disease in GPA, especially in younger patients, and those with destructive sinonasal disease. Dynamic expiratory phase chest CT is a potential non-invasive screening test for tracheobronchial disease in GPA.

Table 1 Clinical Features in Patients with Granulomatosis with Polyangiitis with Subglottic Stenosis and/or Endobronchial disease

	SGS-Yes N=95	SGS-No N=867	P-value	Endobronchial-Yes N=59	Endobronchial-No N=886	P-value
Sex (Female, %)	68 (72%)	457 (53%)	<0.01	33 (56%)	485 (55%)	0.86
Age at diagnosis (Years \pm SD)	35.7 \pm 15	48.7 \pm 17	<0.01	39.8 \pm 2.3	47.7 \pm 0.6	<0.01
Age at symptom onset (Years \pm SD)	33.8 \pm 14	47.6 \pm 17	<0.01	39.2 \pm 2.3	46.5 \pm 0.6	<0.01
Race (Caucasian,%)	90 (95%)	788 (92%)	0.31	55 (93%)	813 (92%)	0.69
Anti-PR3-ANCA	60 (63%)	549 (64%)	0.9	46 (78%)	557 (63%)	0.02
Anti-MPO-ANCA	20 (21%)	199 (23%)	0.6	8 (14%)	205 (23%)	0.09
ANCA-negative	81 (90%)	748 (92%)	0.5	0 (0%)	76 (9%)	0.02
CLINICAL FEATURES						
Constitutional	66 (70%)	690 (81%)	0.02	47 (87%)	610 (80%)	0.21
Musculoskeletal	53 (56%)	544 (63%)	0.17	36 (61%)	556 (63%)	0.74
Cutaneous	23 (24%)	251 (29%)	0.32	16 (27%)	257 (29%)	0.73
Eye	29 (31%)	232 (27%)	0.49	14 (24%)	247 (28%)	0.47
ENT	95 (100%)	640 (75%)	<0.01	53 (98%)	582 (77%)	<0.01
SGS	N/A	N/A	N/A	25 (42%)	66 (8%)	<0.01
Nasal perforation	28 (29%)	67 (11%)	<0.01	10 (18%)	84 (13%)	0.24
Saddle nose deformity	27 (30%)	62 (10%)	<0.01	12 (21%)	78 (12%)	0.04
Cardiovascular	0 (0%)	35 (4%)	0.04	1 (2%)	23 (3%)	0.39
Gastrointestinal	2 (2%)	27 (3%)	0.57	1 (2%)	28 (3%)	0.52
Pulmonary	69 (72%)	574 (67%)	0.29	59 (100%)	577 (66%)	<0.01
Endobronchial	25 (38%)	34 (6%)	<0.01	N/A	N/A	N/A
Renal	37 (39%)	540 (63%)	<0.01	22 (42%)	495 (65%)	<0.01
Nervous system	12 (13%)	202 (24%)	0.02	12 (23%)	197 (23%)	0.76

SGS=subglottic stenosis, Endobronchial=endobronchial disease, SD=standard deviation, ANCA=anti-neutrophil cytoplasmic antibody, PR3=proteinase 3, MPO=myeloperoxidase

Disclosure: K. Quinn, None; C. Sibley, None; A. Gelbard, None; A. Sirajuddin, None; M. A. Ferrada, None; M. Chen, None; D. Cuthbertson, None; S. Carette, None; N. A. Khalidi, None; C. L. Koenig, None; C. Langford, Bristol-Myers Squibb, 2, GlaxoSmithKline, 2, ChemoCentryx, 2, Genentech, Inc., 2, Bristol-Myers Squibb, 9, AbbVie Inc., 9; C. A. McAlear, None; P. A. Monach, None; L. W. Moreland, None; C. Pagnoux, None; P. Seo, None; U. Specks, None; A. G. Sreih, None; S. R. Ytterberg, None; P. A. Merkel, None; P. C. Grayson, None.

Abstract Number: 1771

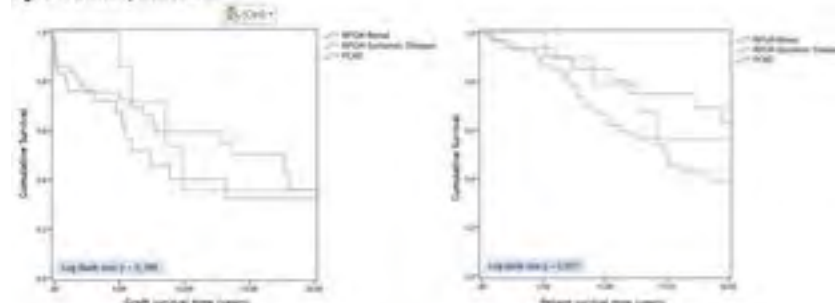
Long-Term Survival of Renal Transplantation in Rapidly Progressive Glomerulonephritis (RPGN). Study of 43 Cases from a Single Center

Belén Atienza-Mateo¹, Lara Sánchez-Bilbao¹, José Luis Martín-Varillas¹, Marina de Cos-Gómez², Íñigo González-Mazón¹, Diana Prieto Peña³, Monica Calderón Goercke³, Emilio Rodrigo Calabia², Juan Carlos Ruiz San Millán², Miguel Angel González-Gay¹ and Ricardo Blanco⁴, ¹Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Universidad de Cantabria. Spain, Santander, Spain, ²Nephrology, Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Universidad de Cantabria. Spain, Santander, Spain, ³Rheumatology, Rheumatology. Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Universidad de Cantabria. Spain, Santander, Spain, ⁴Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, IDIVAL, Santander, Spain

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Figure 1. Graft and patient survival



Session Title: Vasculitis – ANCA-Associated Poster I

Session Type: ACR Poster Session B

Session Time: 9:00am-11:00am

Background/Purpose: Rapidly Progressive Glomerulonephritis (RPGN) is characterized histology by presence of crescents and clinically by rapid and severe decline in kidney function. Thus, it may lead to an end stage renal disease (ESRD), with renal transplantation (RT). RPGN can be primary, with no extra-renal involvement (RPGN-renal-limited), or secondary to systemic autoimmune disorders (RPGN-SAD), infections or drugs. RT in RPGN-SAD may be associated to a worse outcome. In a series of patients with first RT due to RPGN our aim was to assess: **a)** long-term post-transplant survival (PTS) in RPGN-SAD, **b)** comparison of PTS between RPGN-SAD and RPGN-renal-limited and **c)** comparison of both RPGN(SAD and renal-limited) with a control group of non-immunological disorder, the polycystic kidney disease (PCKD).

Methods: We studied 3 groups: **a)** RPGN-SAD (granulomatosis with polyangiitis (3), microscopic polyangiitis (6), Good pasture syndrome (2)), **b)** RPGN-renal-limited and **c)** PCKD (control). All were transplanted in a single reference University Hospital. Main outcome variables were: **a)** graft and patient PTS up to 20 years and **b)** evolution of renal function (serum creatinine and proteinuria) in the first 5 years. Cumulative survival rates after RT were estimated by the Kaplan-Meier method and compared between groups with the log-rank test. Kruskal-Wallis or chi²/Fisher's exact tests were used to compare quantitative or qualitative variables, respectively.

Results: We included 100 patients with RT: **a)** RPGN-SAD group (11), **b)** RPGN-renal-limited group (32), and **c)** PCKD group (57). There were no significant differences at baseline between the two RPGN groups in sex, age and cardiovascular risk factors. RPGN group showed higher cholesterol levels than PCKD at the time of RT ($p=0.041$) with no other significant differences. Renal biopsy had been performed in the 43 patients with RPGN: types I (27.9%), II (4.7%) and III RPGN (41.9%); 25.6% had not classified RPGN (no immunofluorescence was performed at the time of the biopsy). From 89 patients (of 100) in which a renal biopsy was performed during the first-year post-transplant, rejection was found in 33 patients (37.1%) with no significant differences between the 3 groups (5 cases in RPGN-SAD group, 11 in RPGN-renal-limited group and 17 in PCKD group; $p=0.592$). Evolution of serum creatinine and the proteinuria after the transplant is shown in TABLE 1. There were no significant differences between the 3 groups in serum creatinine, graft and patient PTS.

Conclusion: RT could be the best option in ESRD due to RPGN regardless of systemic manifestations.

Table 1. Evolution of creatinine and proteinuria levels after RT

Serum Creatinine mg/dL	1 Month					6 Months					1 Year					3 Years					5 Years				
	1 Month					6 Months					1 Year					3 Years					5 Years				
	RPGN-renal-limited	RPGN-SAD	PCKD	Total		RPGN-renal-limited	RPGN-SAD	PCKD	Total		RPGN-renal-limited	RPGN-SAD	PCKD	Total		RPGN-renal-limited	RPGN-SAD	PCKD	Total		RPGN-renal-limited	RPGN-SAD	PCKD	Total	
N	27	11	51	89		24	9	48	81		24	8	46	78		20	9	41	70		10	10	36	60	
Mean±SD	1.81±0.9	2.09±1.65	2.23±1.75	2.08±1.52		1.97±1.34	1.54±0.37	1.74±0.77	1.79±0.95		1.80±1.11	1.48±0.40	1.74±0.88	1.73±0.92		1.69±0.76	1.70±0.69	1.69±0.91	1.69±0.83		1.64±0.80	1.81±0.99	1.82±1.29	1.77±1.13	
Proteinuria mg/24 h	RPGN	RPGN	PCKD	Total		RPGN	RPGN	PCKD	Total		RPGN	RPGN	PCKD	Total		RPGN	RPGN	PCKD	Total		RPGN	RPGN	PCKD	Total	
N	22	9	45	76		23	6	45	74		7	7	41	68		19	7	40	66		13	8	31	52	
Mean±SD	474.86±	1127.67±	408.22±	512.71±		611.87±	797.00±	362.98±	475.53±		656.10±	340.57±	282.54±	398.38±		510.79±	272.57±	340.65±	382.41±		238.23±	443.88±	579.26±	473.17±	
	432.03	2590.44	449.00	968.84		832.20*	556.29*	323.38*	561.34*		1206.68	175.22	272.35	698.81		832.90	291.20	344.17	527.44		311.19	300.87	1114.5	887.08	

* p<0.05

Disclosure: B. Atienza-Mateo, None; L. Sánchez-Bilbao, None; J. L. Martín-Varillas, None; M. de Cos-Gómez, None; Í. González-Mazón, None; D. Prieto Peña, None; M. Calderón Goercke, None; E. Rodrigo Calabia, None; J. C. Ruiz San Millán, None; M. A. González-Gay, None; R. Blanco, None.

Abstract Number: 1772

Apremilast in Refractory Oral and/or Genital Ulcers in Behçet's Disease. Multicenter Study of 37 Cases

Belén Atienza-Mateo¹, José Luis Martín-Varillas¹, Javier Loricera², Genaro Graña Gil³, Gerard Espinosa⁴, Clara Moriano Morales⁵, Trinidad Pérez-Sandoval⁶, Manuel Martín-Martínez⁶, Elvira Díez⁶, Maria Dolores García Armario⁷, Ivan Castellví⁸, Francisca Sivera⁹, Jaime Calvo-Alén¹⁰, Isabel de la Morena¹¹, Francisco Ortiz-Sanjuán¹², José Andrés Román-Ivorra¹³, Ana Pérez Gómez¹⁴, Sergi Heredia¹⁵, Carolina Díez¹⁶, J Alegre¹⁷, Amparo Ybáñez¹⁷, Javier Narváez¹⁸, Ana Turrión Nieves¹⁹, Susana Romero-Yuste²⁰, Alejandro Olivé-Marqués²¹, Águeda Prior²², Esperanza Martínez⁷, Ignasi Figueras²³, Pilar Trénor²⁴, Carmen Gonzalez Vela²⁵, Diana Prieto Peña²⁶, Monica Calderón Goercke²⁶, José Luis Hernández², Miguel Angel González-Gay¹ and Ricardo Blanco¹, ¹Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Universidad de Cantabria. Spain, Santander, Spain, ²Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Universidad de Cantabria. Spain, Santander, Spain, ³Rheumatology Division, Complejo Hospitalario Universitario A Coruña. Spain, La Coruña, Spain, ⁴Department of Autoimmune Diseases, Hospital Clinic. Barcelona. Spain, Barcelona, Spain, ⁵Rheumatology, Complejo Asistencial Universitario de León. León. Spain, León, Spain, ⁶Rheumatology, Hospital Universitario de León. Spain, León, Spain, ⁷Rheumatology and Dermatology, Hospital Lluís Alcanyís. Valencia. Spain, Valencia, Spain, ⁸Rheumatology, Hospital Universitari de la Santa Creu i Sant Pau. Barcelona. Spain, Barcelona, Spain, ⁹Rheumatology, Hospital General Universitario de Elda. Comunidad Valenciana. Spain, Elda, Spain, ¹⁰Rheumatology Department, Hospital Universitario Araba. Vitoria-Gasteiz, Alava, Spain, ¹¹Hospital General Universitario de Valencia. Spain, Valencia, Spain, ¹²Rheumatology, Hospital La Fe. Valencia. Spain, Valencia, Spain, ¹³Hospital La Fe. Valencia. Spain, Valencia, Spain, ¹⁴Rheumatology, Hospital Universitario Príncipe de Asturias. Alcalá de Henares. Madrid. Spain, Alcalá de Henares, Madrid, Spain, ¹⁵Rheumatology, Hospital Moisès Broggi-Hospital General de L'Hospitalet. Consorci Sanitari Integral,, Barcelona, Spain, ¹⁶Rheumatology, Hospital de El Bierzo. León. Spain, León, Spain, ¹⁷Rheumatology, Hospital Universitario Doctor Peset. Valencia. Spain, Valencia, Spain, ¹⁸Rheumatology, Hospital Bellvitge. Barcelona. Spain, Barcelona, Spain, ¹⁹Rheumatology, Hospital Universitario de Salamanca. Spain, Salamanca, Spain, ²⁰Hospital de Pontevedra. Spain, Pontevedra, Spain, ²¹Rheumatology, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, ²²Rheumatology, Hospital Universitari Germans Trias i Pujol. Barcelona. Spain, Barcelona, Spain, ²³Rheumatology and Dermatology, Hospital Bellvitge. Barcelona. Spain, Barcelona, Spain, ²⁴Rheumatology, Hospital Clínico Universitario de Valencia. Spain, Valencia, Spain, ²⁵Pathology, Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Universidad de Cantabria. Spain, Santander, Spain, ²⁶Rheumatology, Rheumatology. Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Universidad de Cantabria. Spain, Santander, Spain

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IGG4-Related Disease

Session Type: ACR Poster Session B

Session Time: :00AM-11:00AM

Background/Purpose: Behçet's disease (BD) is characterized by recurrent oral and/or genital ulcers accompanied by ocular, cutaneous, articular, gastrointestinal, and/or neurologic manifestations. Oral and/or genital aphthous ulcers are often refractory to conventional treatment. Apremilast is an orally-active small molecule which inhibits phosphodiesterase-4 (PDE-4) that modulates some inflammatory pathways. Our aim was to assess the efficacy and safety of apremilast in BD patients with oral and/or genital ulcers refractory to conventional treatment.

Methods: National multicenter open-label study on 37 BD patients treated with apremilast at maintained standard dose of 30 mg twice daily, with the initial 5-day titration schedule in 31 cases. The main outcome was achievement of oral and/or genital ulcers remission. The diagnosis of BD was performed according to the proposed International Criteria for BD (1990) in 30 patients and according to the recently proposed criteria (2014) for BD in the rest of cases.

Results: We included 37 patients (26 women/11 men), mean age of 43.4±12.9 years. Before apremilast, all patients had received several systemic conventional drugs: oral corticosteroids (34), colchicine (36), methotrexate (21), azathioprine (20), mycophenolate mofetil (1), cyclosporine (7), dapsone (5), adalimumab (10), infliximab (5), tocilizumab (3), etanercept (1), and/or golimumab (1). The main clinical symptoms for starting apremilast were oral aphthous ulcers (36) and genital ulcers (22). Other manifestations present at apremilast onset were folliculitis/pseudofolliculitis (9), arthralgia/arthritis (8), asthenia (7), furunculosis (2), paradoxical psoriasis by TNFi (2), deep venous thrombosis (2), erythema nodosum (1), erythematous and scaly skin lesions (1), ileitis (1) and fever (1). None of the patients presented visual

manifestations at apremilast onset. TABLE shows the evolution of the patients. After a median follow-up of 6 [interquartile range, 4.5-11.5] months, most of the patients experienced clinical improvement. In this period of time, 26 patients developed any side-effect, most of them mild and during the first 3 months of treatment: nausea (10), diarrhea (10), dyspepsia (5), abdominal pain (5), headache (5), loss of appetite (4), weight loss (1), halitosis (1) and dry mouth (1). Four patients had to reduce the dose to 30 mg/day. Apremilast was discontinued in 10 patients due to: not obtaining the expected improvement (5), intense gastrointestinal adverse effects (3), desire of pregnancy (1) and development of neurological involvement (1).

Conclusion: Apremilast leads to a rapid and maintained improvement in many patients with refractory mucocutaneous ulcers of BD. Even in patients refractory to several systemic drugs including biologic therapy.

Table Evolution of symptoms and reduction of prednisone dose with apremilast therapy. Data are expressed as mean \pm SD or median[IQR]

	Basal n= 37	Week 1-2 n= 37	Week 4 n= 35	Month 3 n= 31	Month 6 n= 22	Month 12 n= 7
Resolution of main symptom, oral and/or genital ulcers n, (%)						
Complete		17/37 (45.9)	19/35 (54.2)	20/31 (64.5)	13/22 (59.1)	4/7 (57.1)
Partial		14/37 (37.8)	6/35 (17.1)	1/31 (3.1)	2/22 (9.1)	2/7 (28.6)
Resolution of other symptoms n, (%)						
Complete		10/23 (43.5)	8/21 (38.1)	11/17 (64.7)	4/8 (50.0)	4/6 (66.7)
Partial		3/23 (13.1)	3/21 (14.3)	4/17 (23.5)	3/8 (37.5)	2/6 (33.4)
Dose of prednisone (mg/day), median [IQR]	2.5 [0-10]	2.5 [0-10]	0 [0-8.1]*	0 [0-5]*	0 [0-3.7]*	0 [0-3.7]*

* p<0.05

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Abstract Number: 1773

Comparative Study of Infliximab Versus Adalimumab in Refractory Uveitis Due to Behçet's Disease. National Multicenter Study of 177 Cases

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Uveitis is one of the major causes of disability of Behçet's disease (BD). According to the "Expert panel recommendations" (Ophthalmology. 2014; 121:785-96), anti-TNF therapy with infliximab (IFX) or adalimumab (ADA) may be considered as first- or second-line therapy for patients with ophthalmic manifestations of BD. Our aim was to compare IFX versus ADA as first biologic drug in refractory uveitis due to BD for 1-year period.

Methods: Multicenter study of BD-associated uveitis refractory to conventional non-biologic treatment. Dosing schedule was: IFX: 3-5 mg/kg iv at 0, 2 and 6 weeks and then every 4-8 week, and ADA: 40 mg/sc/every other week without loading dose. The main comparative outcome measures were safety and efficacy, assessing the intraocular inflammation, macular thickness, visual acuity, degree of immunosuppression load, drug retention, and glucocorticoid-sparing effect.

Results: 177 patients (316 affected eyes) were included. IFX was used in 103 cases and ADA in 74. No significant differences at baseline were observed between IFX vs ADA groups regarding main demographic features, previous therapy and ocular severity. After one year of therapy, we observed an improvement in all ocular parameters in both groups; IFX vs ADA groups: AC inflammation (78.18% vs 92.31%; p=0.06), vitritis (78.95% vs 93.33%; p=0.04), retinal vasculitis (97% vs 95%; p=0.28), macular thickness (264.89±59.74 vs 250.62±36.85; p=0.15), and BCVA (0.67±0.34 vs 0.81±0.26; p=0.001). Drug withdrawal was observed in 57 (55.33%) of IFX group and in 21 (28.37%) of ADA group; p<0.01. TABLE 1 shows main baseline features and follow-up of both groups.

Conclusion: After one year of therapy in refractory BD-associated uveitis, ADA showed a statistically better outcome than IFX in improvement of BCVA, vitritis and drug retention.

Table 1. Main baseline features and follow-up of a series of 177 patients with refractory uveitis due to Behçet's disease undergoing infliximab (IFX) or adalimumab (ADA) therapy

	IFX group (N=103)	ADA group (N=74)	p
Number of patients/affected eyes, (n/n)	103/185	74/131	
Age, mean (SD) years	40.4 (10.1)	38.7 (11.3)	0.29
Sex, men/women, n/n	55/48	39/35	0.92
HLA-B51 positive, (%)	69.4	68.9	0.74
Duration of uveitis before anti-TNFα, median [IQR] months	36 [12-72]	24 [12-60]	0.69

Table 1. (Cont'd)

	IFX group (N=103)	ADA group (N=74)	p
Ocular features at the time of anti TNF- α onset			
AC cells, median [IQR]	1 [0-2]	1 [0-2]	0.25
Vitritis, median [IQR]	1 [0-2]	1 [0-2]	0.12
BCVA, mean (SD)	0.50 (0.35)	0.56 (0.34)	0.08
Macular thickness, mean (SD)	331.11 (131.97)	346.37 (136.14)	0.49
Presence of retinal vasculitis, n (%)	114 (58)	78 (55)	0.51
Presence of choroiditis, n (%)	41 (21)	10 (7)	<0.01
Pattern of uveitis, n (%)			
Bilateral	82 (79.61)	57 (77.03)	0.68
Unilateral	21 (20.39)	17 (22.97)	0.68
Anterior	11 (10.68)	14 (18.92)	0.19
Posterior	28 (27.18)	14 (18.92)	0.19
Panuveitis	64 (62.14)	45 (60.81)	0.19
Intermediate	0 (0)	1 (1.35)	0.19
Treatment before anti TNF- α onset, %			
Oral corticosteroids	95	88	0.08
Intravenous pulses of MP	31	31	0.98
CsA	75	78	0.65
AZA	57	42	0.049
MTX	44	42	0.77
Other treatments	3.84	1.92	0.41
Prednisone dose at anti TNF- α onset, mean (SD), mg/d	54.35 (15.84)	53.37 (17.52)	0.37
Combined treatment, %	76.5	70.3	0.35
AZA	21.8	19.2	
CsA	41.1	55.7	
MTX	33.3	21.1	
CFM	1.3	0.0	
MMF	1.3	3.8	
FK-506	1.3	0.0	
Follow-up on anti TNF α therapy, mean (SD), months	31.52 (23.51)	26.48 (18.57)	0.13
Remission, n (%)	78 (76.47)	61 (82.43)	0.34
Relapses, mean (SD)	1.13 (2.62)	1.66 (8.62)	0.61
Drug withdrawal, n (%)	57 (55.33)	21 (28.37)	<0.01
remission, n (%)	20 (19.41)	6 (8.45)	0.58
inefficacy, n (%)	18 (17.47)	11 (14.86)	0.09
severe side-effects/toxicity, n (%)	8 (7.76)	4 (3.88)	0.58
others, n (%)	11 (10.68)	0 (0)	0.03
Serious side-effects, n (per 100 patients/year)	4 (1.48)	4 (2.46)	0.40

Abbreviations: ADA, adalimumab; AZA, azathioprine; CFM, cyclophosphamide; CsA, cyclosporine A; FK-506, tacrolimus; IFX, infliximab; IQR: interquartile range; MMF, mycophenolate mofetil; MTX, methotrexate; MP, methylprednisolone; SD: standard deviation; TNF- α : tumor necrosis factor alpha.

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Abstract Number: 1774

The Relationship between Serum Cholinesterase, Dickkopf-1 and Number of Organ Involvement in Japanese Patients with IgG4-Related Disease

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To evaluate the relationship between serum cholinesterase (ChE) level, number of organ involvement, serum fibrotic markers and imaginal outcomes in Japanese patients with IgG4-related disease (IgG4-RD).

Methods: The clinical symptoms, laboratory, pathological and FDG-PET/CT findings of Japanese patients with IgG4-RD (n=20) were assessed. Several laboratory data of IgG4-RD with multiple organs' involvements (IM) (n=10), IgG4-RD with limited organ's involvement (IL) (n=10), ANCA-associated vasculitis (AAV) (n=10) and Sjogren syndrome (SjS) (n=10) were comparatively examined. Furthermore, we studied the relationship between the numbers of organ involvement (NOI), several fibrotic markers (ELF score and serum Dickkopf-1 (Dkk-1)) and imaginal outcome in IgG4-RD group.

Results: Serum ChE levels were significantly lower in IM group than IL, AAV and SjS groups. In total IgG4-RD cases, ChE levels inversely correlated with NOI and fibrotic score, and fibrotic score positively correlated with NOI. Finally, Dkk-1, one of Wnt inhibitors, levels in IM were significantly lower than IL and healthy subjects ($p<0.05$). Moreover, low level of Dkk-1 before and after treatment could predict the progression of organ atrophy.

Conclusion: The ELF score and serum Dkk-1 level might be clinically useful indicators of active fibrosis and the extent of IgG4-RD. Notably, continuous lower levels of Dkk-1 were related to organ atrophy and serum ChE levels could predict these phenomena.

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Abstract Number: 1775

IgG4-Related Disease, Clinical Series on Chilean Patients

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SESSION INFORMATION

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Background/Purpose: IgG4-related disease (IgG4-RD) is a chronic fibro inflammatory condition that can affect almost any organ. Gold standard for diagnosis, biopsy, can shows lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis and IgG4+ plasma cell infiltrate. High serum IgG4 levels is observed only in 50% of patients. Disease is more frequent in males, around 60 years old, affecting one or multiple organs with sub acute development of tumors or organomegaly. Lymphadenopathies are common, and 40% of patients have a history of allergies. Umehara's diagnostic criteria (2012), based on clinical features, serum IgG4 levels and histopathology are the most accepted. Disease was described in 2003, and Chilean reports are scarce.

We describe clinical, laboratory, histopathology findings, and treatment on Chilean IgG4-RD patients.

Methods: We analyzed retrospectively clinical records of 48 patients with IgG4-RD from nine medical centers. Patients with possible, probable and definitive diagnosis, according to Umehara criteria, were included.

Results: Our cohort was 56% male, with a mean age of 52 (18-76) years. Histological confirmation of IgG4-RD was obtained in 44 of 45 patients who underwent a biopsy. Twenty-three percent of patients had allergic background, 27% had eosinophilia and 43% had elevated plasma levels of IgG4 (≥ 135 mg/dl). The clinical involvement was: pleural and lung disease 38%, kidney 27%, orbital pseudotumor 25%, lymphadenopathy 21%, retroperitoneal fibrosis 19%, aortitis 19%, sialoadenitis 17%, pancreas 17%, pericardium 15% and meninges in 8%. There were three patients with hypophysitis and two with mediastinal fibrosis.

Multiple organ involvement (≥ 2 organs), observed in 69%, was significantly more frequently in males ($p < 0.05$). There was a statistically significant association between renal disease and low complement levels ($p < 0.01$). All patients who had renal or pulmonary disease had multiple organ involvement. Multiple organ involvement was not related with immunosuppressive treatment requirement.

Pathology confirmation, in 44 patients, showed: lymphoplasmacytic infiltrate in 43 (98%), storiform fibrosis in 29 (66%) and none had obliterative phlebitis. All tissues had diagnostic IgG4 (+) immunohistochemical staining. Storiform fibrosis was present in all lung and kidney biopsy, but only half of salivary gland, orbital and retroperitoneal tissue.

Regarding treatment, all patients received glucocorticoids. In 30 patients (63%) was required immunosuppressive treatment: azathioprine, followed by methotrexate and mycophenolate mofetil were drugs most used. Rituximab was used in 8 patients. Clinical response was good, but one patient dies because extensive mediastinal disease.

Conclusion: IgG4-RD in Chilean patients is similar that described elsewhere. In most of patients serum levels of IgG4 were normal, then biopsy was essential to diagnosis. Multiple organ involvement was frequent, being pleuropulmonary, kidney, orbital and lymph node most usual localizations. Renal and pulmonary localization occurred always in context of multi organic disease.

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Abstract Number: 1776

Clinical Significance of Allergy in IgG4-Related Disease

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease And IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00am-11:00am

Background/Purpose: IgG4-related disease (IgG4-RD) is a relatively newly defined disease entity, which can affect multiple organs and exhibit clinical heterogeneity. Recently, it has been reported that allergy was associated with the pathogenesis and clinical performance of IgG4-RD in some part. Still, little is known about the role of allergy in IgG4-RD, large cohort study is needed. We aim to investigate the role of allergy in IgG4-RD patients in the largest prospective IgG4-RD cohort in China.

Methods: Three hundred and ninety IgG4-RD patients who referred to Peking Union Medical College Hospital between January 2011 and April 2018 were enrolled. Using the definitions of the European Academy of Allergy and Clinical Immunology, we classified the subjects as either allergic or non-allergic. Clinical features of all the participants were collected and analyzed statistically.

Results: We found that 47.95%(187/390) of our patients had a history of allergy. Allergic patients showed elevated incidence of salivary glands, paranasal sinus, and skin affection, while non-allergic patients had more renal, large artery involvement and retroperitoneal fibrosis. Allergic patients also exhibited significantly up-regulated eosinophil, serum IgG4, IgE levels and IgG4/IgG ratio, while non-allergic patients presented with increased ESR, CRP, IgG1 levels, IgG1/IgG ratio, and higher incidence of anemia. No significant differences were found in baseline treatment options and the recurrence rate during follow-up.

Conclusion: Clinical study put forward that allergic reaction did relate to different characteristics in IgG4-RD patients, therefore, basic research is needed to clarify the potentially related mechanism.

Disclosure: X. Zhang, None; P. Zhang, None; W. Zhang, None.

Abstract Number: 1777

Factors Related to Deterioration of IgG4-Related Disease in Untreated Patients with IgG4-Related Disease

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SESSION INFORMATION

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Background/Purpose: In IgG4-related disease (IgG4-RD), spontaneous, or at least temporary, remissions without treatment have been reported, and watchful waiting may be appropriate in certain patients with asymptomatic and inactive disease. However, the outcomes of patients with IgG4-RD who do not undergo treatment are still unclear. This study aimed to clarify the outcomes of untreated patients with IgG4-RD and the factors related to the outcomes.

Methods: We retrospectively evaluated clinical features including laboratory data and involved organs at diagnosis in 107 patients (pts) with IgG4-RD, who were followed up for more than 6 months, at a single center in Japan. Among them, 27 patients were followed up without treatment after the initial diagnosis. We compared the clinical features of these 27 patients with those of the 80 patients who underwent treatment. The outcomes of untreated patients were investigated, and logistic regression analysis was performed to assess factors related to the outcomes. Deterioration of IgG4-RD was defined as symptomatic, radiological, or functional exacerbation of the organ involved or new organ involvement.

Results: The patients comprised 73 men and 34 women (mean age 65.7 years). The mean follow-up periods were 64.1 (range 7–252) months, and the serum IgG4 levels at diagnosis were 706 (range 10.7–3,610) mg/dL. The 27 untreated patients had significantly lower IgG4-RD responder index (10.8 ± 5.1 vs 13.8 ± 6.8 , $P=0.048$), fewer affected organs (1.9 ± 1.2 vs 3.0 ± 1.6 , $P=0.001$), and lower frequency of ophthalmic and renal parenchymal lesions (25.9% vs 53.8%, $P=0.015$, and 3.7% vs 26.3%, $P=0.012$, respectively) than did the 80 patients who underwent treatment. Of these 27 patients, 8 experienced deterioration of IgG4-RD 62.8 (range 3–232) months after the diagnosis. New organ involvement was observed in all 8 patients, 2 of whom concurrently suffered exacerbation of the organs involved. In age- and sex-adjusted logistic regression analysis, serum IgG4 elevation (per 100 mg/dL, odds ratio 1.194, 95% confidence interval 1.017–1.402, $P=0.030$) was the only significant factor related to deterioration of disease in untreated patients with IgG4-RD, whereas serum IgG4 levels did not relate to deterioration in patients who underwent treatment (per 100 mg/dL, odds ratio 0.995, 95% confidence interval 0.921–1.075, $P=0.901$).

Conclusion: The present study suggests that serum IgG4 levels may be a useful predictor of the outcomes of untreated patients with IgG4-RD, who tend to have fewer affected organs and lower IgG4-RD responder index.

Disclosure: I. Mizushima, None; K. Yamada, None; S. Hara, None; K. Ito, None; H. Fujii, None; M. Kawano, None.

Abstract Number: 1778

Comparison of Clinical and Angiographic Features of Arterial Involvement in Takayasu's Arteritis and Behçet's Disease

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Background/Purpose: Systemic vasculitis is one of the major manifestations of Behçet's disease (BD). Takayasu's arteritis (TA) is a chronic vasculitis that primarily affects the aorta and its branch. While BD and TA differ in their clinical characteristics, it is difficult to differentiate them in particular when BD presented with major arterial involvement. Our study was to compare clinical characteristics and angiographic findings between TA and BD patients with arterial involvement.

Methods: We retrospectively reviewed medical records of 206 TA patients and 50 BD patients between 1995 and 2015. Angiographic lesions were evaluated based on CT, MRI and/or angiography findings. The diagnosis was confirmed according to the American College of Rheumatology 1990 criteria for TA and the International Criteria for BD.

Results: Patients with TA were more likely female than those with BD (83.5% vs 40.0%, $p = 0.000$). In clinical manifestation, fever (9.2% vs 30.0%, $p = 0.000$) and arthralgia (7.3% vs 36.0%, $p = 0.000$) were more frequently seen in patients with BD. Serum levels of C-reactive protein was significantly higher (2.08mg/dL vs 5.84mg/dL, $p=0.000$) in BD than in TA. Stenosis (89.8% vs 60%, $P=0.000$) and occlusion (65.5% vs 32%, $P=0.000$) were more frequently observed in patients with TA than in those with BD. In contrast, BD patients were more likely to have aneurysmal lesions (62% vs 20.9%, $P=0.000$). In terms of the site of vascular lesions, subclavian artery (71.4% vs 16%, $p=0.000$), carotid artery (73.3% vs 30%, $p=0.000$), descending aorta (35% vs 12%, $p=0.002$), brachiocephalic trunk (13.6% vs 2%, $p=0.020$), superior mesenteric artery (18.4% vs 4%, $p=0.012$) and renal artery (23.8% vs 10%, $p=0.032$) were more commonly involved in TA, whereas femoral artery (10% vs 2.4%, $p=0.027$) was more frequently involved in patients with BD.

Conclusion: TA patients differ from BD patients with arterial involvement in terms of clinical features and vascular involvement pattern.

Table 1. Angiographic findings in TA and BD with arterial involvement

	Stenosis		Occlusion		Dilatation		Aneurysm	
	TA (n=206)	BD (n=50)	TA (n=206)	BD (n=50)	TA (n=206)	BD (n=50)	TA (n=206)	BD (n=50)
All	89.8%	60%***	65.5%	32%***	26.7%	30% ^{NS}	20.9%	62%***
Aorta	41.7%	6%***	3.9%	0% ^{NS}	11.7%	20% ^{NS}	11.7%	46%***
Arteries of head and neck	69.4%	30%***	34.5%	8%***	10.2%	12% ^{NS}	8.7%	8% ^{NS}
Arteries of upper extremity	42.2%	8%***	38.3%	2%***	2.9%	2% ^{NS}	5.3%	6% ^{NS}
Arteries of abdomen	31.6%	14%*	11.2%	6% ^{NS}	3.9%	2% ^{NS}	2.4%	6% ^{NS}
Arteries of pelvis and lower extremity	6.3%	6% ^{NS}	3.9%	10% ^{NS}	1%	0%	1%	12%*

NS, $P \geq 0.05$; *, $P < 0.05$; **, $P < 0.01$; and ***, $P < 0.001$

Disclosure: S. J. Choi, None; D. H. Lim, None; J. S. Oh, None; S. Hong, None; Y. G. Kim, None; C. K. Lee, None; B. Yoo, None.

Abstract Number: 1779

Is the Number of IgG4+ Plasma Cells Observed By Immunostaining Important Beyond Its Diagnostic Utility in IgG4-Related Disease?

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Background/Purpose: The histopathological findings in IgG4-related disease (IgG4-RD) includes the presence of dense lymphoplasmacytic infiltrate, obliterative phlebitis, storiform fibrosis and the presence of marked IgG4+ plasma cell infiltration observed by immunostaining. The latter has been used in clinical practice only as a diagnostic tool. Whether

the number of IgG4+ plasma cells in tissue is associated with any clinical or serological feature has not been previously evaluated. The purpose of this study was to evaluate if the grade of IgG4+ plasma cell infiltration is associated with any clinical or serological outcome.

Methods: We included patients with biopsy proven IgG4-RD according to the Comprehensive Diagnostic Criteria (definitive and probable IgG4-RD) who regularly attended a tertiary referral center in Mexico City (2000-2017). We collected demographics, clinical (organ involvement, relapses and the disease activity assessed by the IgG4-RD Responder Index [IgG4-RD RI] at baseline) as well as baseline laboratory data (C3, C4, total eosinophil count, IgG4 levels). Patients were divided in three groups according to the number of IgG4+ plasma cells in biopsies as follows: <50 IgG4+ plasma cells/HPF, 50-100 IgG4+ plasma cells/HPF, and >100 IgG4+ plasma cells/HPF.

Results: We included 30 patients, 17 (56.6%) women, mean age 53 ± 13.9 years and median disease duration 13 months. The biopsies were from the following tissues: lacrimal gland (n=6), pancreas (n=5), orbit (n=4), kidney (n=4), lymph node (n=3), mediastinum (n=2), salivary gland (n=2) and other tissues (n=4). Eleven patients (36.6%) had <50 IgG4+ plasma cells/HPF, 9 patients (30%) 50-100 IgG4+ plasma cells/HPF and 10 (33.3%) patients >100 IgG4+ plasma cells/HPF. We did not find any difference regarding age, gender, time of follow up, number of involved organs and relapses. The median baseline IgG4-RD RI was 9, 6 and 15, for the <50 IgG4+ plasma cells/HPF, 50-100 IgG4+ plasma cells/HPF, and >100 IgG4+ plasma cells/HPF groups respectively, however, there was not a statistical difference. The group with >100 IgG4+ plasma cells/HPF had more frequently lymphadenopathy when compared with the other groups (36.4%, 66.7% and 80%, $p=0.02$; respectively) while the proportion of involvement of the remaining anatomic sites were similar. We found a statistical difference in serum C3 levels (99.5 mg/dl, 159 mg/dl, 78.5 mg/dl, $p=0.04$) and a tendency for serum C4 levels (20 mg/dl, 27 mg/dl, and 6 mg/dl, $p=0.08$) among the groups with >100 and ≤ 100 IgG4+ plasma cells/HPF, respectively; whereas the levels of serum IgG4 and the eosinophil count were similar. The C3 and C4 serum levels negatively correlated with the basal IgG4-RD RI ($t=-0.48$, $p=0.005$ and $t=-0.58$, $p=0.001$).

Conclusion: Our results show that the number of IgG4+ plasma cells observed by immunostaining in IgG4-RD may be of value in identifying a subset of patients with hypocomplementemia, lymphadenopathy and higher baseline disease activity. The finding of an association between hypocomplementemia and higher tissue infiltration by IgG4+ plasma cells expands the evidence that complement activation may contribute to the pathogenesis of IgG4-RD.

Disclosure: E. Martín Nares, None; J. Guerrero Castillo, None; A. Angeles Angeles, None; G. Hernandez-Molina, None.

Abstract Number: 1780

Shear Wave Elastography in the Evaluation of Submandibular Gland Characteristics in IgG4-Related Disease

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

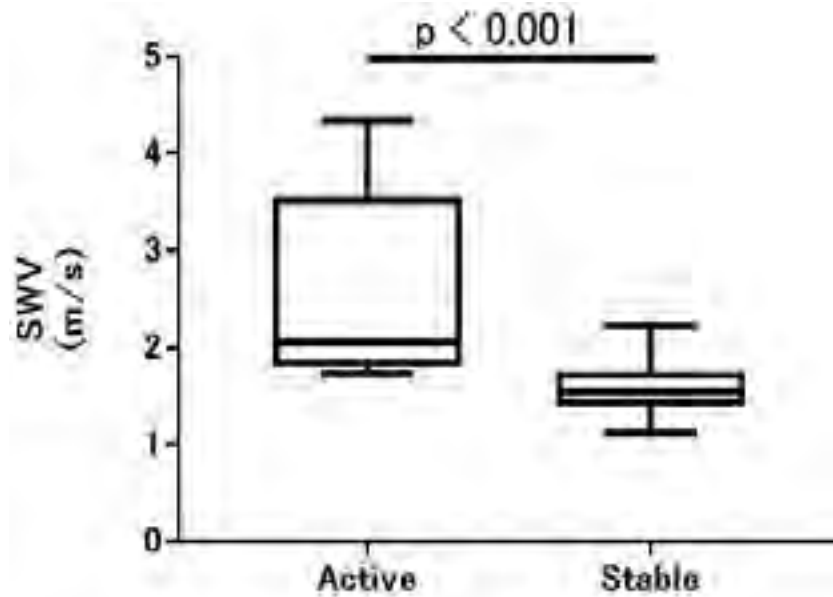
Session Type: ACR Poster Session B

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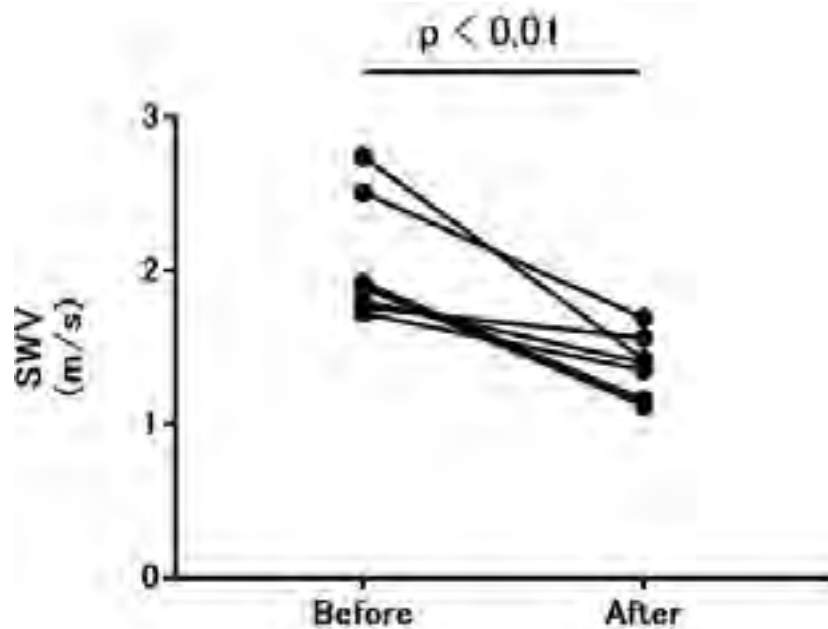
Background/Purpose: IgG4-related disease (IgG4RD) is a chronic and systemic disease that can involve multiple organs. One of the most commonly involved organs are the salivary glands. Shear wave elastography is an ultrasonography technique that provides an estimate of tissue elasticity. We present the salivary gland sonographic findings in IgG4RD patients.

Methods: We retrospectively investigated the salivary gland sonographic features of IgG4RD patients who fulfilled the diagnostic criteria for IgG4RD. Salivary gland ultrasonography was performed in our hospital from April 2016 to April 2018. We assessed sex, age, symptoms, and ultrasonographic findings. Shear wave elastography was performed in 9 patients with IgG4RD, 33 patients with Sjogren syndrome and 13 healthy controls. Mean shear wave velocity (SWV) in m/s was compared between IgG4RD patients, Sjogren syndrome patients and healthy controls.

Results: The mean age of IgG4RD patients was 69.7 ± 8.58 years old. From 11 IgG4RD patients (7 males and 4 females), 7 patients had multiple hypoechoic lesions in the submandibular glands. Only one IgG4RD patient had multiple hypoechoic lesions in the parotid glands. For the submandibular glands, mean SWV was significantly higher in the active IgG4-related sialadenitis group than in the stable IgG4RD group (2.54 ± 0.92 vs 1.58 ± 0.29 , $p < 0.001$). A significant decrease in both SWV and the volume of the glands was also observed in active IgG4-related sialadenitis patients who achieved remission ($p < 0.01$, $p < 0.05$, respectively). For the submandibular glands, mean SWV values were significantly



Submandibular shear wave velocity in IgG4-related disease patients.



Changes in submandibular shear wave velocity in IgG4-related disease patients.

higher in the active IgG4-related sialadenitis group than in the Sjogren syndrome group (2.54 ± 0.92 vs 1.54 ± 0.24 , $p < 0.001$), and in the active IgG4-related sialadenitis group than in the healthy controls (2.54 ± 0.92 vs 1.66 ± 0.27 , $p < 0.001$), respectively.

Conclusion: Changes in the submandibular glands affected by IgG4-RD could be easily detected using ultrasonography. Shear wave elastography of submandibular gland may contribute to the evaluation of disease activity in IgG4-related sialadenitis.

Disclosure: K. Nishimura, None; K. Kadoba, None; H. Mukoyama, None; R. Saito, None; D. Waki, None; T. Yokota, None.

Retrospective Analysis of IgG4-RD Patient Population at the Cleveland Clinic between 2007-2017

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SESSION INFORMATION

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Background/Purpose: IgG4-related disease (IgG4-RD) is a rare multisystem fibro-inflammatory condition, characterized by organ mass lesions, IgG4+ lymphoplasmacytic infiltrate, and storiform fibrosis. To gain better understanding of its prevalence, clinical presentation, and outcomes of treatment, we conducted a retrospective study of patients with IgG4-RD at Cleveland Clinic.

Methods: The Cleveland Clinic pathology database search for IgG4 staining between 2007-2017 found 1,481 results. Of 119 cases positive for tissue IgG4+plasma cells ≥ 10 and/or IgG4/IgG plasma cells ratio $>40\%$, 57 cases were classified as highly likely (N=28; 49%) if they met at least two of three pathology criteria of lymphoplasmacytic infiltration, fibrosis, and obliterative phlebitis, or probable IgG4-RD (N=29; 51%) if they met only one criteria. Serum IgG4 levels were available in only 15 patients, thus this criterion was not used for classification. Patients' age, gender, type of treatment, and outcome were retrieved from medical records. Patients were designated as being in "remission" if indicated in the chart and/or symptom and objective findings-free for >6 months, "relapsed", if symptoms/findings recurred following remission, "active" if no remission was achieved during follow up, and as "unable to determine" if duration of follow-up was <60 days or lost to follow up.

Results: Of 57 patients, 63% were males, age 57.9 ± 14.8 years, 57.9% were white, 26.3% African-American, 1.8% Asian, 1.8% multi-racial and 12.3% unknown. The average follow-up was 2.7 ± 2.2 years. Organs involved were pancreas (26.4%), salivary glands (8.8%), lacrimal glands (7%), biliary ducts (7%), aorta (7%), thyroid (5.3%), orbit (3.5%), lung (3.5%), lymph nodes (1.8%), and others (24.6%). On histopathologic examination, 94.7% had lymphoplasmacytic infiltration, 68.4% fibrosis, 31.6% obliterative phlebitis, and 14 patients (24.6%) met all three criteria. Eosinophilic infiltration was present in 8 patients (14%). Average IgG4+ plasma cell count was 49.7 ± 36.2 /hpf. Almost half of the patients (45.6%; N=26) were managed surgically, 21.1% (N=12) medically only, and 24.6% (N=14) received both. Medical treatment included prednisone (45.6%), methotrexate (5.3%), azathioprine (7%); 58.3% of patients took more than one medication, and 5 patients received rituximab (8.8%). Remission was achieved by 52.6% of surgical, 21.1% of medical, and 26.3% of recipients of both treatments. Two of five patients treated with Rituximab achieved remission, during the follow up period of 2.39 (0.33-6.46) years.

Conclusion: In this retrospective study, one of the largest to date, we confirm that IgG4-RD is more common in middle age/elderly men. Only about half of the cases who met the IgG4 staining criteria satisfied the IgG4-RD histopathology criteria. Pathology findings were variable, with only half of the patients having at least two of the characteristics of lymphoplasmacytic infiltration, fibrosis and obliterative phlebitis, and a quarter displaying all three. These results underline the difficulty of making a definitive diagnosis of IgG4-RD. In our cohort, surgical treatment compared to medical treatment appeared to be more successful in achieving remission.

Disclosure: C. M. Lee, None; M. Alalwani, None; R. Prayson, None; C. E. Gota, None.

Cigarette Smoking Is a Risk Factor for IgG4-Related Disease

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SESSION INFORMATION

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Background/Purpose: IgG4-related disease (IgG4-RD) is a fibroinflammatory condition characterized by tumefactive lesions that can occur at nearly any site, often associated with an elevated serum IgG4 concentration. Despite advances in the recognition and treatment of IgG4-RD, its etiology and pathogenesis remain unknown. Prior studies suggest that cigarette smoking may be a risk factor for IgG4-RD. We performed a case-control study to evaluate the association between cigarette smoking and the risk of IgG4-RD.

Methods: All patients seen in the Center for IgG4-RD at Massachusetts General Hospital who were diagnosed with IgG4-RD between 2010 and 2018 and completed a smoking questionnaire were included in this study. Participants in the Partners HealthCare Biobank who completed a smoking questionnaire (N=30,536) were used as a source of controls. For each case and control, a smoking status (never, former, current) was determined. Each case was matched to up to 5 controls based on age (5-year category) and sex. We used conditional logistic regression to compare the proportion of cases and controls with a history of cigarette smoking using odds ratios (OR) and 95% confidence intervals (CIs).

Results: We identified 194 IgG4-RD cases which were matched to 970 controls (**Table 1**). The mean age for cases and controls was 57 years (± 13) and 57 years (± 13), respectively, and the majority of patients were male (62% and 62% in both groups). There was a greater proportion of current and former smokers among IgG4-RD cases (Current=23 [12%], Former=58 [30%]) compared with controls (Current=72 [7%], Former=211 [22%]). Compared with controls, IgG4-RD cases had nearly a two-fold higher odds of being current smokers (OR 1.85 [95% CI 1.11-3.07]) or former smokers (OR 1.66 [95% CI 1.16-2.39]). The association between cigarette exposure and the risk of IgG4-RD seemed to be driven by a strong association among the subgroup of patients with retroperitoneal fibrosis (RPF, 16% of cases) (OR 4.91 [95% CI 1.81-13.34]).

Conclusion: In this case-control study of patients with IgG4-RD, current and former smoking statuses were strongly associated with the risk of IgG4-RD, especially among IgG4-RD patients with RPF. Biologically, cigarette smoking is known to stimulate fibrogenesis, a key feature of IgG4-RD. While these findings require additional confirmation, cigarette smoking may be the first recognized modifiable risk factor for IgG4-RD. Further research is necessary to understand the mechanism by which smoking increases the risk of IgG4-RD. Patients with IgG4-RD may need to be counseled against smoking.

Table 1. Association Between Cigarette Smoking and Risk of IgG4-RD

	IgG4-RD (N [%])	Controls (N [%])	OR (95% CI)
All			
Current Smoker	23 (12%)	72 (7%)	1.85 (1.11-3.10)
Former Smoker	58 (30%)	211 (22%)	1.66 (1.16-2.39)
Male			
Current Smoker	14 (12%)	53 (9%)	1.61 (0.84-3.09)
Former Smoker	38 (31%)	118 (20%)	2.17 (1.35-3.48)
Female			
Current Smoker	9 (12%)	19 (5%)	2.50 (1.10-5.67)
Former Smoker	2 (27%)	93 (26%)	1.16 (0.66-2.03)
RPF			
Current Smoker	6 (19%)	N/A	4.91 (1.81-13.34)
Former Smoker	14 (45%)	N/A	3.25 (1.01-10.45)
Non-RPF			
Current Smoker	17 (10%)	N/A	1.38 (0.92-2.05)
Former Smoker	44 (27%)	N/A	1.63 (0.92-2.90)

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Abstract Number: 1783

Salivary Gland Disease in IgG4-Related Disease Is Associated with Allergic Histories

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Background/Purpose: The etiology of IgG4-related disease (IgG4-RD) remains unknown. The role of T-helper type 2 (Th2) cells in the pathogenesis of IgG4-RD is controversial. Given Th2 cells' involvement in allergic responses and prior IgG4-RD studies suggesting their importance in the pathogenesis, it has been hypothesized that allergic mechanisms contribute to the development of IgG4-RD. We investigated the association between allergies and IgG4-RD.

Methods: The Center for IgG4-RD at Massachusetts General Hospital maintains a database of all IgG4-RD patients, including details of demographics and disease history. Allergy histories were obtained from patients via a 34-question allergist-developed survey administered at their baseline visit. Patients were considered to have a history of allergies if they reported prior symptoms or diagnosis. We included all patients who completed the allergy survey; for certain analyses, some patients were excluded because of missing data. Statistical significance was determined by Fisher's exact test or unpaired t-test, as appropriate. P values < 0.05 were considered significant.

Results: Our study included 185 IgG4-RD patients from a database of 289 patients. Of the 185 patients, 140 (76%) reported any allergic symptom or diagnosis (**Table 1**). There was no significant difference with regard to age (P=0.1) or sex distribution (P=0.7) between patients with and without allergy symptoms. Skin allergies (41%), food allergies (20%), and anaphylaxis (8%) were less common than respiratory allergies (61%) in IgG4-RD. Patients with allergies tended to have any ear, nose, and throat (ENT) manifestations of IgG4-RD more often than those who did not have allergies (55% vs 36%, P=0.058). This trend was largely driven by a significant difference in the proportion of patients with salivary gland IgG4-RD (e.g., sialoadenitis) among those with allergies compared with those without a history of allergies (41% vs 22%, P=0.03). We found a similar difference when comparing salivary gland involvement between those with and without respiratory allergies (72% vs 28%, P=0.039).

Conclusion: In a large IgG4-RD cohort, we found a significant association between IgG4-related salivary gland disease and allergic histories. More generally, we found a trend towards an association between ENT involvement and allergic histories. Of the reported allergies, respiratory allergies were most common. Respiratory allergies appear more prevalent in this cohort than the general US population: 61% of cohort patients reported a history of respiratory allergies, compared to 30% of Americans who completed a similar survey (*Allergy Asthma Proc* 2008; 29:600). While it is possible that shared pathogenesis is responsible for these observations, a shared upper respiratory exposure may also explain our observations given the associations between head and neck disease with allergic histories.

Table 1. Characteristics of IgG4-RD relative to history of allergies

	All	History of any allergies*	No history of allergies	P-value
N	185 (100%)	140 (76%)	45 (24%)	
Age (yrs)				
Age at first visit, mean ± SD	57.2 (±14.7)	56.8 (±15.0)	58.7 (±13.5)	0.096
Age distribution				
<20	5 (3%)	5 (4%)	0 (0%)	
20-29	4 (2%)	3 (2%)	1 (2%)	
30-39	11 (6%)	7 (5%)	4 (8%)	
40-49	28 (15%)	22 (16%)	6 (13%)	
50-59	43 (23%)	33 (24%)	10 (22%)	
60-69	59 (32%)	44 (31%)	15 (33%)	
70-79	30 (16%)	23 (16%)	7 (16%)	
80-89	5 (2%)	3 (2%)	2 (4%)	
Sex				
Male sex	114 (62%)	85 (61%)	29 (64%)	0.726
Allergy Specificity				
History of air allergies	112 (61%)	112 (61%)	--	
History of food allergies	37 (20%)	37 (20%)	--	
History of skin reactions ^	76 (41%)	76 (41%)	--	
History of anaphylaxis	15 (8%)	15 (8%)	--	
Select Organ/system involvement				
Total ENT organ involvement†	94 (51%)	77 (55%)	17 (38%)	0.058
Orbits, lacrimal glands	41 (22%)	34 (24%)	7 (16%)	0.381
Salivary glands	67 (36%)	57 (41%)	10 (22%)	0.03
Other ENT	22 (12%)	18 (13%)	4 (9%)	0.784
Lymph nodes	54 (29%)	38 (27%)	16 (36%)	0.219
Lungs	26 (14%)	20 (14%)	6 (13%)	1.000
Aorta	12 (6%)	8 (6%)	4 (9%)	0.474
Retroperitoneum	23 (12%)	17 (12%)	6 (13%)	0.788
Pancreas	46 (25%)	37 (26%)	9 (20%)	0.530
Bile duct	20 (11%)	13 (9%)	7 (16%)	0.251
Kidney	23 (12%)	20 (14%)	3 (7%)	0.284

* Includes air allergies, food allergies, skin reactions, and anaphylaxis

† Includes orbits, lacrimal glands, salivary glands, and/or other ENT manifestations

^ Includes atopic dermatitis, urticaria

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Abstract Number: 1784

Serum IgG4 Test Characteristics: Immunonephelometry Versus Liquid Chromatography Tandem Mass Spectrometry

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: IgG4-related disease (IgG4-RD) is a fibroinflammatory condition that may involve essentially any organ. The disease spectrum is also often associated with elevated serum IgG4, and thus serum IgG4 level remains an important biomarker in the diagnosis and monitoring of IgG4-RD. Immunonephelometry is the most common method used internationally to measure IgG4 (and other IgG subclass) levels, with IgG4 test results varying by reagent vendor. Mass spectrometry is a less costly approach pioneered at our institution with fewer errors in the measurement of other subclasses as compared to nephelometry. In this study, we aim to determine the difference in the Binding Site immunonephelometry (BSIN) method and liquid chromatography tandem mass spectrometry (LC-MS/MS), with regard to the respective clinical test characteristics for the diagnosis of IgG4-RD.

Methods: This retrospective chart review study was approved by the Research Ethics Board at the University of British Columbia. IgG subclass data was retrieved from the laboratory for the period from December 2011 to December 2017. BSIN was the method in use between December 2011 and September 2016, and LC-MS/MS was the method in use from September 2016 to December 2017. For both assays, elevated IgG4 levels were defined as any value above the upper limit of the reference range 1.25 g/L, with both methods calibrated to the same standard. Cases of IgG4-RD were defined as those with histopathologic findings meeting consensus guidelines for IgG4-RD and non-biopsy proven, but possible IgG4-RD cases, were excluded. Only the first IgG4 level at baseline and off of treatment were reported for a given patient using each method. Test performance characteristics were compared using the Fisher exact test.

Results: In total there were 908 IgG4 subclasses measured. For BSIN, there were 33 IgG4-RD positive cases and 161 disease negative cases. For LC-MS/MS, there were 27 IgG4-RD positive cases and 105 disease negative cases. The IgG4-RD patients in the BSIN group were a mean age of 62 ± 13 years and for LC-MS/MS it was 64 ± 11 years and the sexes were well-matched (2.3:1 versus 2:1 M:F ratio, respectively). False positive diagnoses were comparable between BSIN and LC-MS/MS IgG4 measurements with hypereosinophilic syndrome (n=4; n=1), hypergammaglobulinemia (n=4; n=3) and connective tissue disease (n=3; n=2) being the most common, respectively. The specificity of both BSIN and LC-MS/MS was 85%. Sensitivity was 81% for BSIN and 70% for LC-MS/MS. Positive and negative predictive values, respectively, were 53% and 96% for BSIN and 54% and 92% for LC-MS/MS. The sensitivity and specificity of BSIN versus LC-MS/MS were equivalent ($p=0.36$, $p=1.0$).

Conclusion: Not surprisingly, since the two methods are calibrated to the same standard for IgG4, they have similar sensitivity and specificity for the diagnosis of IgG4-RD. Given the potential advantages, a lower incidence of measurement errors, and a lower cost, the LC-MS/MS could be considered instead of BSIN where possible.

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Results: We analyzed 214 mimickers. IgG4-RD, Erdheim-Chesterdisease (ECD), Rosai-Dorfman disease (RDD) and multicentric Castleman's disease (MCD) were male predominant, whereas SS, vasculitis, lymphoma and sarcoidosis tended to be female predominant (**Table 1**). IgG4-RD, lymphoma and GCA tended to have an older age of onset compared with SS, ANCA-associated vasculitis (AAV) and other mimickers. Organ involvement differed by mimicker, as expected. Submandibular gland involvement was equally common in IgG4-RD and SS, but isolated parotid involvement was more typical of SS and lacrimal gland more characteristic of IgG4-RD. Lymphadenopathy, serum IgG4 elevations,

Diagnosis	Number (%)	Male (%)	Concomitant diagnosis	Excluded diagnosis	Excluded diagnosis	Excluded diagnosis	Age-related diagnosis
All cases	443 (100.0)	415 (93.7)	1.9%	1.7%	1.7%	1.7%	1.7%
Diagnosis (London 85)	31 (7.0)	33 (3.1)	20.0%	40.0%	10.0%	4.0%	40.0%
Diagnosis with Polymyalgia (PM)	29 (6.6)	27 (2.4)	20.0%	32.0%	1.0%	60.0%	90.0%
Polymyalgia Rheumatica with Monoclonal IgG (PMR)	12 (2.7)	21 (4.8)	100.0%	52.0%	0.0%	57.0%	100.0%
Monoclonal Polymyalgia (MPM)	7 (1.6)	20 (4.5)	0.0%	100.0%	0.0%	100.0%	100.0%
Small Cell Carcinoma (SCC)	17 (4.0)	30 (6.8)	0.0%	0.0%	0.0%	0.0%	0.0%
Alcohol (1) Arthritis (1A)	1 (0.2)	2 (0.4)	0.0%	0.0%	0.0%	0.0%	0.0%
Chronic Gout	1 (0.2)	2 (0.4)	0.0%	0.0%	0.0%	0.0%	0.0%
Systemic Lupus Erythematosus (SLE)	27 (6.1)	49 (11.1)	40.0%	0.0%	0.0%	0.0%	0.0%
Systemic Sclerosis (SSc)	1 (0.2)	2 (0.4)	0.0%	0.0%	0.0%	0.0%	0.0%
Myositis (1) Arthritis (1A)	1 (0.2)	2 (0.4)	0.0%	0.0%	0.0%	0.0%	0.0%
All Monoclonal	17 (4.0)	30 (6.8)	0.0%	0.0%	0.0%	0.0%	0.0%

[illegible]

lymphoplasmacytic infiltrates and significant IgG4+ cell infiltrates were observed in many mimickers. Exclusion criteria were crucial to differentiating mimickers from IgG4-RD despite these similarities. 91.1% of mimickers fulfilled exclusion criteria as compared to only 7.1% of IgG4-RD cases (Table 2). Ro or La excluded 78.7% of SS cases. In AAV, ANCA, fever and necrotizing vasculitis on pathology excluded IgG4-RD in 81.2%, 71.0% and 52.2% of cases, respectively. In lymphoma, rapid radiographic progression, splenomegaly and a malignant infiltrate on pathology excluded IgG4-RD in 45.5%, 27.3% and 100% of cases, respectively. Exclusion by pathology (71.4-100%) was vital in separating ECD, MCD, RDD and sarcoidosis from IgG4-RD.

Conclusion: IgG4-RD and mimickers share many features, including demographics, organ involvement and elevated serum IgG4 levels. Exclusion criteria were critical to the 2018 ACR/EULAR classification criteria development, identifying key features that distinguish IgG4-RD from its mimickers. These clinical, serologic, radiologic and pathology features serve as a useful guide for clinicians considering the IgG4-RD differential.

Disclosure: M. A. Matza, None; Z. Wallace, None; J. H. Stone, None.

Abstract Number: 1786

Favourable Response to Rituximab for the Treatment of IgG4-Related Disease: Long-Term Follow-up of 10 Patients Resistant to Glucocorticoids and Immunosuppressives

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Immunoglobulin G4-related disease (IgG4-RD) is a systemic, immuno-mediated fibro-inflammatory disease that affects various organ systems, with typical pathological findings and increased IgG4 levels. Glucocorticoids are the first-line of treatment however relapse rates are high and our knowledge is limited regarding the effects of immunosuppressives. Case reports on rituximab efficacy in the treatment of IgG4-RD are published in addition to an open-label pilot study. The objective of this study was to evaluate the efficacy and safety of treatment with rituximab in 10 subjects diagnosed with IgG4-RD and followed-up in our clinic.

Methods: This study retrospectively investigated the demographic data, clinical features, laboratory findings, immunosuppressive therapies and the outcomes in 10 subjects who had been followed in our clinic for at least 6 months and met the diagnostic criteria for IgG4-RD by clinical, serological and/or tissue biopsy findings and received at least one course of treatment with rituximab (1000 mg twice two weeks apart). IgG4-RD Response Index (IgG4-RD RI), PET-CT and acute phase reactants were used for disease activity evaluation. 8 subjects receiving rituximab treatment had an exacerbation of the disease under low-dose prednisolone therapy and conventional immunosuppressive treatments. In 2 subjects, rituximab was the first choice of immunosuppressive treatment in addition to prednisolone therapy.

Results: IgG4-RD patients had a mean age of 55 years (43-63; 8 male/2 female) and the mean follow-up period was 47 months. Aortitis-chronic periaortitis was found in 8 subjects followed for IgG4-RD, renal involvement in 4, hepatobiliary-pancreatic involvement in 3, and pericardial and pulmonary involvement in 2. The mean IgG4 level was 519.5 mg/dL (145-1160) and IgG4-RD RI was 10.9 (6-21) at the time of diagnosis. The median follow-up period after the first course of rituximab was 18 months (12-24). Remission was achieved in 9 of 10 patients treated with rituximab and the mean daily prednisolone dosage was reduced to below 5 mg/day. Prednisolone therapy was permanently discontinued in 2 subjects. The unresponsive case had membranous glomerulonephritis. After treatment, the mean IgG4 level was 51.3 mg/dL (6-145) and IgG4-RD RI was 1.2 (0-7). No exacerbation was observed during the follow-up period in 9 subjects in whom remission was achieved, and rituximab was repeated as a maintenance therapy at 6 months of treatment. The subject who had severe nephrotic syndrome during follow-up and was given high-dose prednisolone plus cyclosporine in addition to rituximab treatment died due to pneumonia at 6 months of treatment.

Conclusion: The case series for which the retrospective data are presented, consist mainly of patients managed by rheumatology with predominant involvement being aortitis/periaortitis. Rituximab treatment was found to be effective in

terms of achieving and preserving remission, and reducing glucocorticoid doses although retreatment is often necessary. No safety issues that require discontinuation of treatment were identified in this group of patients except a case of severe infection with nephrotic syndrome

Disclosure: E. Oguz, None; G. Dagci, None; M. Erdugan, None; B. Artim-Esen, None; A. Gül, None; L. Ocal, None; M. Inanc, None.

Abstract Number: 1787

How to Better Diagnose IgG4 Related Disease: a Single-Center Based Experience

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Pathology associated with IgG4-related disease (IgG4-RD) has been described in virtually every tissue and organ of the body. The heterogeneous clinical manifestations of IgG4-RD are a consequence of the variation in clinical presentation for any given IgG4-RD patient. The clinical presentation in early IgG4-RD is rarely definitive especially in the absence of more obvious manifestations such as pancreatitis. For example, more apparent clinical presentations such as swollen salivary glands and lymph nodes, swollen eyelids, and intraocular discomfort may not be readily diagnosed as IgG4-RD. When combined with prevalent tumefactive modules in the lung and/ spleen, all of these clinical manifestations are diagnostic for IgG4-RD. Swelling or nodules of multi-sites combined with histopathological features of tumefactive lesions and laboratory examinations to exclude neoplasm and infection may improve better and more rapid diagnosis of IgG4-RD. Given the propensity of IgG4-RD to progressively affect more tissues and organs, the latter concern is critical.

Methods: We retrospectively examined the clinical and laboratory records for 59 patients with definite IgG4-RD collected from all departments of West China Hospital between January 2012 and December 2017.

Results: A total number of 59 patients were enrolled, including male 41 (70%), female 18 (31%). The maximum and minimum onset age were 85 and 15 respectively. The majority of patients had multiple sites and/or organs involved: 90% of patients were suffering from 3 and more sites or organs affected; 8.5% of patients, 2 sites or organs involved; and only 1.7% with single site or organ involvement. The mostly commonly recorded pathologies involved sites were lung, manifested as small nodules (71%) and lymph nodes (54%). Other involved sites included: salivary glands (42%) which included submandibular (29%), parotid (12%), and labial (1.7%) glands; kidney (36%); pancreas (32%); periorbital tissues (31%) including intraorbital lesions (14%) and swollen eyelids (17%); liver (27%); biliary tree (19%); spleen (15%); nasal sinus (15%); lacrimal glands (15%); and thyroid glands (14%). Other involved tissues included gastrointestinal tract, skin, glottis/pharynx, peritoneum, pericardium, pleura, and large arteries (3.4-8.5%). Rarely involved sites were gingiva, spine, pituitary glands, and mediastinum (1.69%). Elevated serum IgG4 was found in 44 (75%) patients, and antinuclear antibody in 17 (29%) of patients.

Conclusion: Almost any tissue or organ can be affected in IgG4-RD. The most commonly involved organs identified in this retrospective study were lung, lymph node, salivary glands, kidney, and pancreas, respectively. Clinical manifestations may be more obvious with pancreatitis and enlarged lymph nodes; however, small nodules in lung, liver and spleen may be overlooked due to the absence of accompanying symptoms. Our goal is to increase awareness among physicians in general that tumefactive lesions in any site or organ, especially if they occur in multiple tissues or organs, in asymptomatic early stage disease may be indicators for diagnosis of IgG4-RD.

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Abstract Number: 1788

Predictive Factors for Work-Day Loss in a Multi-Center Study in Behçet's Disease: Indirect Costs for Healthcare

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: In chronic diseases, work-day loss due to health problems is associated with indirect costs for healthcare management. The aim of this multi-center study is to assess predictive factors for work-day loss as a productivity measure in Behçet's disease (BD).

Methods: In this cross-sectional, multi-center study, 834 BD patients (F/M: 441/393, mean age: $38,4 \pm 10,9$ years) were included. Data were collected by a questionnaire regarding organ involvement, treatment protocols, disease duration (less than 5 years vs ≥ 5 years), smoking pattern, frequency of medical visits/ during the previous year (>4 visits vs ≤ 4 visits) and self-reported work-day loss during the previous year. Cut-off points of these variables were calculated according to median levels for the binary logistic regression analysis.

Results: Work-day loss was observed in 16,2% of the group ($n=135$). The majority of these patients were males ($n=103$, 76,3%). The mean work-day loss was $30,8 \pm 57,7$ days (1-365 days) and was higher in males ($31,7 \pm 54,2$ vs $27,9 \pm 68,8$ days, $p=0.007$). The mean age and disease duration were lower ($34,3 \pm 8,4$ and $7,04 \pm 6,04$ years, respectively) in patients with work-day loss compared to others during the previous year ($39,2 \pm 11,2$ and $9,4 \pm 7,8$ years, respectively, $p<0.0001$). Increase in the work-day loss was prominent in patients with vascular involvement ($19M/1F$, $56,1 \pm 85,9$ vs $26,4 \pm 50,6$ days) ($p=0.046$), whereas no similar relationship was observed with any other organ involvement. Being a smoker (OR:1,7), disease duration less than 5 years (OR:2,05), male gender (OR:3,9) and more than 4 visits/previous year (OR:2,5) were found to be predictive factors for work-day loss according to binary logistic regression analysis ($p<0.05$).

Conclusion: Work-day loss was associated with vascular involvement in our study. Male gender, increase in the frequency of visits, being a current smoker and early period of the disease were predictive factors for work-day loss in patients with BD.

Disclosure: H. Direskeneli, None

Abstract Number: 1789

Mucocutaneous Activity Index As a Patient-Reported Outcome Measure in Behçet's Disease: A Multi-Center Study from Turkey

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Organ-specific patient-reported outcome (PRO) measures may help management decisions of Behçet's disease (BD). The aim of this prospective study was to evaluate the factors associated with the score of mucocutaneous activity index (MI), a validated patient-reported outcome tool, for Behçet's Disease (BD).

Methods: In this study, 834 BD patients (F/M: 441/393, mean age: $38,4 \pm 10,9$ years) followed in twelve tertiary centres from Turkey were included. Validated mucocutaneous activity index (MI) and its subgroup activity indices regarding oral ulcer (OI), genital ulcer (GI) and erythema nodosum (EI) were assessed. Scores of each subgroup were between 0=inactive and 10=very active. Total MI score composed of these subgroups (0-30 points). Transformed Behçet's disease current activity form (BDCAF) was used to evaluate global activity.

Results: Active BD patients (n=567, 67,9%) were mainly in the mild group with mucocutaneous involvement (n=420). Disease duration was lower ($9,7\pm6,9$ vs $11,1\pm8,1$ years, $p=0.001$) and patients were younger ($36,4\pm10,2$ vs $41,9\pm11,2$ years, $p=0.001$) in the active group. The ratio of non-smokers was also higher in active patients (76,1% vs 67,6%, $p=0.011$). A higher MI score was observed in females ($8,2\pm4,6$) compared to males ($7,3\pm3,9$) among active patients ($p=0.023$). It was higher in females ($8,1\pm4,3$) than males ($6,7\pm3,6$) in non-smokers (n=419) ($p=0.002$), whereas a significant relationship was not present in current smokers (n=132, $p=0.85$) with gender. MI score was also higher in patients whose disease durations were less than 5 years ($6,5\pm2,6$) than the others ($4,7\pm4,7$) ($p=0.001$).

Being a non-smoker (OR:1,7), disease duration less than 5 years (OR:2,4) and female sex (OR:1,5) were found as predictive factors for mucocutaneous activity according to binary logistic regression analysis ($p<0.05$). Increases in both MI score and BDCAF score were observed in immunosuppressive (IS) medication group (n=86; $9,6\pm5,3$; $6,6\pm2,9$) compared to non-IS group (n=316; $7,7\pm4,1$; $5,5\pm2,5$) in active patients with mucocutaneous involvement ($p=0.001$ and $p=0.008$).

Conclusion: Female gender, smoking and disease duration were associated with higher MI scores in our study. An organ-specific and reliable PRO measure such as mucocutaneous index might be a candidate scale for future clinical studies and clinical follow-up of mucocutaneous manifestations in BD patients.

Disclosure: H. Direskeneli, None;

Abstract Number: 1790

An Unmet Need for Oral Ulcer Activity in Patients with Behcet's Disease: A Multi-National Study

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SESSION INFORMATION

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Background/Purpose: Efficacy of current management approaches for oral ulcer treatment in routine clinical practice is insufficiently explored in Behcet's disease (BD) patients. The aim of this multi-national study was to assess whether an unmet need for oral ulcer activity is present in patients with Behcet's disease.

Methods: Behcet's disease (n=197) patients from Jordan (n=50), Brazil (n=46), United Kingdom (n=41) and Turkey (60) (F/M: 100/97, mean age: $40,7\pm11,6$ years) were included in this cross-sectional study. Data were collected by a questionnaire regarding oral ulcer activity during the previous month, treatment protocols and smoking patterns. Transformed BDCAF score was used to evaluate the general disease activity during the last month.

Results: In the whole BD group, 41,1% (n=81) of patients were treated with non-immunosuppressive medications (non-IS) and 53,3% (n=105) by ISs, irregular medication use/no medication was observed in 5,6% (n=11). The number and healing time of oral ulcers were $3,3\pm3,2$ and $6,5\pm4,6$ days, respectively in patients with active oral ulcers (n=114, 57,9%). The number of oral ulcers were significantly higher in patients treated with non-IS medications ($4,04\pm3,9$) and non-smoker patients ($3,6\pm3,4$) than those treated with ISs ($2,5\pm2,1$) and current smokers ($2,3\pm2,1$) ($p<0.0001$ and $p=0.021$, respectively). In binary logistic regression, non-IS medication use was found to be a predictive factor for oral ulcer activity (OR:2,3; $p=0.011$). Transformed BDCAF score was also lower in patients treated with ISs ($4,02\pm3,5$) than those using a non-IS treatment protocol ($6,6\pm3,1$) ($p=0.009$).

Conclusion: Since oral ulcer activity and global activity assessed by BDCAF were higher in patients treated with non-IS medications, an 'unmet need' was observed with milder, non-IS-based treatment protocols in a multi-national setting of clinical practice in BD patients.

Disclosure: G. Mumcu, None; A. Adesanya, None; A. Aksoy, None; J. M. F. M. Belem, None; N. Borges Cardin, None; F. Alibaz-Oner, None; T. Ergun, None; N. Inanc, None; A. W. S. Souza, None; W. Madanat, None; F. Fortune, None; H. Direskeneli, None.

Abstract Number: 1791

Efficacy of Apremilast for Oral Ulcers Associated with Active Behçet’s Syndrome in a Phase III Study: A Prespecified Analysis By Baseline Patient Demographics and Disease Characteristics

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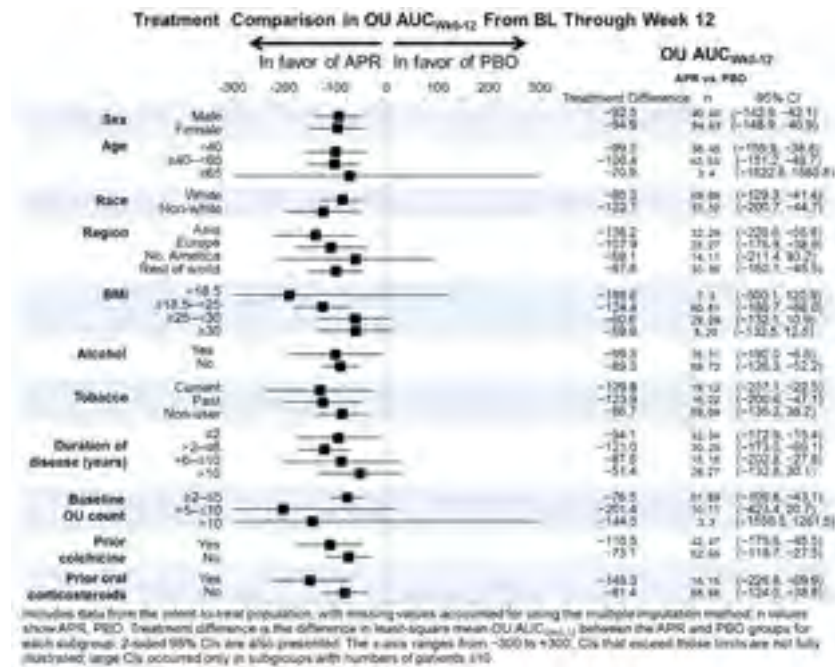
SESSION INFORMATION

Session Date: Monday, October 22, 2018
Session Title: Vasculitis Poster II: Behçet’s Disease and IgG4-Related Disease
Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: Behçet’s syndrome is a chronic, multi-systeminflammatory disorder characterized by recurrent oral ulcers (OU) that can bedisabling and negatively affect quality of life. Apremilast (APR), an oralphosphodiesterase 4 inhibitor that modulates inflammatory pathways, has demonstratedefficacy in the treatment of OU of Behçet’s syndrome in a phase III, multicenter,randomized, double-blind, placebo (PBO)-controlled study (RELIEF).

Methods: In this phase III, multicenter study,adult patients with active Behçet’s syndrome (with ≥3 OU at randomizationor ≥2 OU at screening + randomization, without active major organinvolvement) were randomized (1:1) to receive APR 30 mg BID or PBO BID for 12weeks followed by a 52-week active-treatment phase. The primary endpoint was area under the curvefor total number of OU over 12 weeks (OU AUC_{Wk0-12}). AUC reflectsthe change in the number of OU over time, accounting for the clinicalcharacteristic that OU repeatedly remit and recur. In a planned analysis, OUAUC_{Wk0-12} was examined among subgroups of patients defined by BLdemographics and disease characteristics.

Results: A total of 207 patients were randomized and received ≥1 dose of study medication (APR:n=104; PBO: n=103). At BL, mean numbers of OU were 4.2 for APR and 3.9 for PBO. At Week 12, least-squares mean OU AUC_{Wk0-12} (LSmean ±SE) was significantly lower in patients receiving APR vs. PBO (129.5 ± 15.9 vs. 222.1 ±15.9; P<0.0001). A treatment effect in favor of the APR treatment group vs. PBO was observed for AUC_{Wk0-12} for OU counts in each of the



prespecified subgroups examined. A favorable treatment effect was observed for each demographic subgroup, BL disease characteristic (including duration of disease and BL OU count), geographic region, and prior use of colchicine and corticosteroids (Figure). The incidence of adverse events (AEs) was comparable between APR and PBO (78.8% and 71.8%, respectively). The most common AEs were diarrhea, nausea, headache, and upper respiratory tract infection; most AEs were mild or moderate in severity.

Conclusion: Subgroup analyses of the AUC for the number of OU from BL through Week 12 demonstrated the consistent efficacy of apremilast in all of the subgroups analyzed. The safety profile was consistent with the known safety profile of APR.

Disclosure: G. Hatemi, Celgene Corporation, 2; A. Mahr, None; M. Takeno, Celgene Corporation, 2; D. Y. Kim, None; M. Melikoglu, None; S. Cheng, Celgene Corporation, 3; S. McCue, Celgene Corporation, 3; M. Paris, Celgene Corporation, 3; M. Chen, Celgene Corporation, 3; Y. Yazici, Celgene Corporation, 2.

Abstract Number: 1792

Work Productivity Is Impaired in Patients with Behcet's Syndrome

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease And IgG4-related disease

Session Type: ACR Poster session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Behcet's syndrome (BS) is most active during young adulthood and working years, thus affecting productivity. Work disability was previously reported especially among BS patients with eye, vascular and joint involvement.

	Behçet's syndrome (n=125)	Ankylosing spondylitis (n=90)	Healthy controls (n=30)
Male, n (%)	103 (82)	25 (82)	18 (60)
Mean (SD) current age	36.3 ± 7.8	36.7 ± 8.9	37.9 ± 6.3
Mean (SD) disease duration	8.1 ± 5.7	8.1 ± 5.7	N/A
WIS (mean±SD)	12.2 ± 3.8	11.8 ± 5.0	8.1 ± 4.3
WPAI-Absenteeism (mean±SD)	10.0 ± 18.6	7.7 ± 18.1	1.7 ± 7.0
WPAI-Presenteeism (mean±SD)	17.0 ± 13.9	17.3 ± 14.8	9.3 ± 23.0
WPS-Absenteeism (mean±SD)	1.8 ± 4.2	1.3 ± 3.4	0.1 ± 0.3
WPS-Presenteeism (mean±SD)	4.2 ± 7.0	4.1 ± 6.2	1.7 ± 3.3
BDCAF (mean±SD)	4.1 ± 2.7	N/A	N/A
BSAS (mean±SD)	20.5 ± 17.0	N/A	N/A
BDQoL (mean±SD)	19.7 ± 8.2	N/A	N/A
BASDAI (mean±SD)	N/A	3.4 ± 1.7	N/A
BASFI (mean±SD)	N/A	3.0 ± 2.8	N/A

N/A: Not applicable; Behçet Disease Quality of Life: BDQoL; Behçet's Disease Current Activity Index (BDCAI); Behçet's Syndrome Activity Score (BSAS)

In this study, we aimed to evaluate the work productivity and instability of patients with BS compared to ankylosing spondylitis (AS) patients and healthy controls (HC).

Methods: 125 (103 M/22 F) consecutive BS patients who were routinely followed in our dedicated BS center were studied. Patients with AS (30; 25 M/5 F) who were followed in the rheumatology outpatient clinic of our unit and HC (30; 18 M/12 F) were included as controls. Work Productivity and Activity Impairment Questionnaire (WPAI), Work Productivity Survey (WPS), Work Instability Scale (WIS) were used. Quality of life was assessed with the Behcet Disease Quality of Life (BDQoL) scale and disease activity with the Behcet's Disease Current Activity Index.

Results: The mean age of BS patients was 36 ± 7.8 and the mean disease duration was 8.2 ± 5.6 years (Table). 35 of BS patients with only mucocutaneous, 40 with eye, 28 with vascular and 22 with neurologic involvement were included. Among BS patients 42% reported missing work days (mean 1.8 days/mo), and 48% reported that their productivity was reduced at least by half (mean 4.3 days/mo). The mean WIS score was 12.2 (9.8) in BS patients. 59 BS patients had moderate and 18 BS patients had high work instability. Patients with BS had significantly higher absenteeism (10.0% vs. 1.7%), presenteeism (37.0 % vs. 9.3%), and daily activity impairment (26.4% vs. 8.6%) than HCs ($p < 0.001$) assessed by WPAI. Scores were similar between BS and AS patients. WIS and WPS scores were also similar between BS and AS patients and worse than healthy controls. Work impairment was more pronounced in patients with eye involvement compared to mucocutaneous involvement ($p = 0.04$) and there were no differences between other BS groups. The WPAI presenteeism score was moderately correlated with Behcet Disease Quality of Life scale score ($r = -0.57$). Multivariate analysis showed that QoL ($OR = 0.77$, 95% $CI = 0.66-0.88$) and disease activity ($OR = 1.66$, 95% $CI = 1.01-2.50$) were related with WPAI-presenteeism.

Conclusion: Work productivity is impaired in BS patients, especially among those with eye involvement. Work instability is frequent and correlated with disease activity and quality of life.

Disclosure: N. Serin, None; Y. Ozguler, None; S. N. Esatoglu, None; V. Hamuryudan, None; G. Hatemi, None.

Abstract Number: 1793

The Omeract Core Domain Set for Clinical Trials in Behçet's Syndrome

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: There is an unmet need for reliable, validated, and widely-accepted outcome measures for clinical trials in Behçet's syndrome (BS). The Outcome Measures in Rheumatology Clinical Trials (OMERACT) Behçet's Syndrome Working Group has worked to advance the creation of a data-driven Core Domain Set for use in all clinical trials.

Methods: The Core Domain Set was developed through a comprehensive, iterative, multi-stage, multi-year project that followed the methodologically rigorous processes and standards set forth by OMERACT: i) a systematic review; ii) a survey among experts in BS; iii) an outcome measures interest group meeting during the International Conference on Behçet's Disease; iv) qualitative patient interviews; v) a three-round modified Delphi exercise involving both patients with BS and a multidisciplinary set of physicians expert in BS, focused on obtaining consensus on the domains of illness necessary in the study of BS; and vi) utilization of the data, insight, and feedback generated by the outlined processes to develop a final Core Domain Set. The final Core Set was presented and put up for a vote of endorsement at the 2018 OMERACT meeting.

Results: All steps in the processes outlined were completed. The systematic review clearly demonstrated the substantial variability in the domains studied in clinical trials of BS and a lack availability of validated outcome measures in BS. The

survey of physicians, the in-person meeting of experts, and the qualitative research with patients all helped generate an extensive list of candidate domains and sub-domains to consider for use in clinical trials. It also became clear that there was a need and strong interest in delineating domains across the several major organ systems involved in this disease and in recognizing that clinical trials in BS often focus on specific manifestations and not the disease in its entirety. The Delphi involved 74 physicians expert in BS from 21 countries and from a wide range of specialties, and 64 patients from 10 countries. The Delphi utilized both ratings and rankings to prioritize the 56 domains and sub-domains originally under consideration.

The final proposed Core Set included 5 sub-domains mandatory for study in all trials in BS, with additional sub-domains mandatory for study of specific organ-systems when that system is the focus of a trial: mucocutaneous (2 additional sub-domains), ocular (4), central nervous system (3), musculoskeletal (2), vascular (4), and gastrointestinal (2). The final Core Set was strongly endorsed at the 2018 OMERACT meeting.

Conclusion: Multiple disease-related domains in BS have been identified by physicians and patients as important to address in clinical trials, leading to the development and endorsement of a final Core Set of Domains for use in clinical trials in BS. The Core Set provides the foundation through which the international research community, including clinical investigators, patients, the biopharmaceutical industry, and government regulatory bodies can harmonize the study of this complex disease, compare findings across studies, and advance development of effective agents.

Disclosure: G. Hatemi, Celgene Corporation, 2; A. Meara, None; Y. Ozguler, None; H. Direskeneli, None; A. Mahr, None; B. Shea, None; E. Cam, None; A. Gül, None; Y. Yazici, Celgene Corporation, 2; P. Tugwell, None; H. Yazici, None; P. A. Merkel, None.

Abstract Number: 1794

Venous Vessel Wall Thickness in Lower Extremity Is Increased in Male Behcet's Disease Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behcet's Disease And IGG4-Related Disease

Session Type: ACR poster session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Vascular involvement is seen in up to 40% of the patients with Behcet's Disease (BD), especially in young males and is one of the major causes of mortality and morbidity. Lower extremity vein thrombosis due to vascular inflammation is the most frequent form of vascular involvement in BD. Recently, assessment of vessel wall thickness (VWT) and venous dilatation by US is suggested to be valuable in patients with vascular inflammation. In this study, we investigated whether vessel wall thickness or dilatation is present in young male BD patients prone to venous vascular disease.

Methods: Thirty male patients with BD without major organ involvement and 29 male patients with Vascular BD (VBD) followed in Marmara University Behcet's Clinics, 24 healthy male controls and 27 male patients with ankylosing spondylitis (AS) were included the study. Bilateral lower extremity venous doppler ultrasonography (US) was performed by an experienced radiologist blinded to cases. No patients except VBD were under immunosuppressive treatment. Bilateral common femoral vein (CFV) wall thickness and great/small saphenous vein dilatations were examined. Behcet Syndrome Activity Score (BSAS) was used for the general assessment of disease activity. In 10 patients, CFV wall thickness was measured by 2 different radiologist (RE, RA) in the same day to calculate "inter-observer reliability". Correlation between radiologists was good ($r = 0.765$, $p < 0.001$).

Results: Mean disease duration was 9.1 ± 6 years in patients with BD. BSAS score was 24 ± 17 . All venous measurements were significantly higher in BD compared to AS and healthy controls ($p < 0.001$ for all, Table 1). When we compared mucocutaneous BD (m-BD) vs VBD, all measurements of patients with VBD were higher than m-BD, however only left CFV thickness and width of right great saphenous vein reached statistical significance ($p < 0.001$, and $p = 0.028$, respectively). There were no correlations between BSAS, acute phase reactants and venous wall measurements.

Disclosure: H. Nishikawa, None; Y. Taniguchi, None; S. Inotani, None; M. Kawano, None; Y. Terada, None.

Table 1 Venous wall measurements of lower extremity in study groups.

	Behçet's Disease (n=59)	Ankylosing Spondylitis (n=27)	Healthy Controls (n=28)	P Value
Age, years	32.5 (23-42)	32 (20-37)	31.5 (25-42)	0.23
Body Mass Index (kg/m ²)	25.1 (18-33)	25 (18-32)	23.8 (20-29)	0.213
Right Common femoral VWT (mm)	0.8 (0.04-1.8)	0.3 (0.1-0.6)	0.25 (0.06-0.4)	<0.001
Left Common femoral VWT (mm)	0.8 (0.3-1.6)	0.3 (0.1-0.5)	0.2 (0.04-0.6)	<0.001
Right Great saphenous width (mm)	3.1 (0-6.4)	2.5 (1.1-3.5)	2.1 (1.3-3.5)	<0.001
Left Great saphenous width (mm)	3.1 (0-7.4)	2.6 (0.3-4.8)	2.4 (1.6-3.6)	<0.001
Right Small saphenous width (mm)	2.8 (0-5.3)	1.7 (1-3.1)	1.4 (0.9-3.7)	<0.001
Left Small saphenous width (mm)	2.7 (0-5.2)	1.8 (1.1-3.4)	1.6 (0.8-3.6)	<0.001

VWT: Venous wall thickness

Conclusion: In our study, an increased venous vessel wall thickness in lower extremity was shown in male BD patients with or without vascular involvement. As a similar change was not observed in control groups, increased VWT might be an early sign of venous inflammation in patients with BD rather than a result of non-specific systemic inflammation.

Disclosure: F. Alibaz-Oner, None; R. Ergelen, None; A. Mutis, None; Z. Erturk, None; R. Asadov, None; T. Ergun, None; H. Direskeneli, None.

Abstract Number: 1795

New Major Organ Involvement Is Lower in Young Male Behçet's Patients Compared to Retrospective Series: Five-Year Results of a Prospective Cohort

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Major organ involvement such as vascular or ocular disease, especially in young males, is one of the main causes of mortality and morbidity in Behçet's Disease (BD). However, the prognosis and predictors of major organ involvement is insufficiently studied. We aimed to follow young, male BD patients with only mucocutaneous symptoms which have the highest risk for new major organ involvement prospectively.

Methods: Thirty-six male patients with BD consecutively consulted in the outpatient clinics of Marmara University, Istanbul, 35 males with ankylosing spondylitis and 36 healthy males were included in the study. Bilateral upper and lower extremity venous doppler ultrasonography (US) and brachial and carotid arterial US (for assessing endothelial dysfunction) were performed in baseline visit for all study groups and in the first year follow-up visit for BD patients. Patients with BD were assessed prospectively with 3-6 months intervals and in any urgent visits.

Results: At baseline, the mean disease duration was 3.3 years in patients with BD. The rate of venous insufficiency was higher in male BD patients without vascular events compared to healthy controls (BD vs HC: 30.5% vs 0%) and similar to patients with AS (BD vs AS: 30.5% vs 32%). Markers of endothelial dysfunction (FMD and NID) were similar between BD patients and healthy controls, however CIMT (Carotid intima media thickness) was significantly higher in BD (0.54 mm vs 0.47 mm, p=0.033). The mean follow-up duration was 56.6 months. Major organ involvement developed in 5 (13.8%, 3 vascular and 2 ocular involvement) patients during follow-up. Immunosuppressive (IS) therapy was required in 27% (n=10) of patients, due to major organ involvement in 5 (13.8%), refractory mucocutaneous symptoms in four (11%) and chronic arthritis in one (2.7%) patient. In the first year follow-up visit, endothelial functions and CIMT were observed to be significantly improved compared to baseline (Baseline vs Follow-up: 6.8±4 vs 10.9±4.5, p=0.003 for FMD, 0.55±0.13 vs 0.47±0.1 for CIMT, p=0.004). Patients requiring IS treatment in the follow-up had significantly lower FMD at baseline compared to the rest of the group (4.4 vs 8.5, p=0.005).

Table 1. Clinical characteristics of patients with immunosuppressive need during follow-up

	Reason for IS use	Age at Diagnosis	Disease duration when IS started	IS agent
Patient 1	Pulmonary aneurysm	35	1 year	Azathioprine
Patient 2	Refractory OU	25	5 years	Cyclosporine
Patient 3	Deep venous thrombosis	38	10 years	Azathioprine
Patient 4	Uveitis	20	5 years	Azathioprine
Patient 5	Refractory OU	28	7 years	Azathioprine
Patient 6	Refractory OU	23	6 years	Cyclosporine
Patient 7	Refractory EN	35	1 years	Azathioprine
Patient 8	Deep venous thrombosis	23	1 years	Azathioprine
Patient 9	Atrhritis	28	7 years	Methotrexate
Patient 10	Uveitis	18	4.	Azathioprine

F/U:Follow-up, IS: Immunosuppressive, OU: Oral ulcer, EN: erythema nodosum

Conclusion: Our study demonstrated a lower incidence of major vascular events in male BD patients during prospective follow-up compared to historic controls in the literature. The decreased rate of baseline FMD in patients with later IS requirement suggest that FMD might be a predictor for major organ involvement in BD.

Disclosure: F. Alibaz-Oner, None; B. Aldag, None; E. Karatay, None; G. Mumcu, None; T. Ergun, None; H. Direskeneli, None.

Abstract Number: 1796

Retrospective Analysis of Initial Presentation Findings of Behcet's Syndrome throughout 4 Decades

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: There is some evidence that incident Behcet's syndrome (BS) might be becoming less severe (1, 2). We compared clinical findings at presentation of BS patients registered in a large, long standing dedicated multidisciplinary outpatient clinic at 4 time points during a 40-years period.

Methods: There were 4 groups. Group 1 included patients registered in 1979- 1981, Group 2 those registered in 1990, Group 3 in 2000 and Group 4 in 2010. Only demographic and clinical findings at initial presentation were recorded on prepared forms.

Results: As shown in Table 1, over 4 decades, male/female ratio decreases gradually. While mean age at presentation does not change, the median disease duration got shorter. Almost all clinical manifestations except genital ulcers and neurological involvement tended to decrease in frequency. This was also true when genders were separately analyzed. Importantly the severity of vascular and eye disease decreased (Table 2). The slope of vascular disease was more obvious.

Conclusion: Our observations support the notion that incident BS might be getting milder. There might be a list of explanations for this observation. 1. It might be a true biological phenomenon due to changing environmental causes. In this line the significant decrease in papulopustular lesions could be due to a more sanitary environment while the rather unchanging frequency of neurologic involvement might be its possible independence from the environment. 2. It might be that the awareness of BS is increasing and we are recognizing less severe cases earlier. 3. Another explanation might be the more effective treatment these patients received before they were referred which was not specifically sought in this survey.

References:

1. Yoshida A, et al. Comparison of patients with Behçet's disease in the 1980s and 1990s. *Ophthalmology*. 2004.
2. Cingu AK, et al. Comparison of presenting features and three-year disease course in Turkish patients with Behçet uveitis who presented in the early 1990s and the early 2000s. *Ocul Immunol Inflamm*. 2012.

Table 1 Initial demographic and clinical characteristics of cohorts

	Group 1 1979-81 cohort n=211	Group 2 1990 cohort n=170	Group 3 2000 cohort n=225	Group 4 2010 cohort n= 270	P
Male /Female	140/71	110/ 60	142/ 83	150/ 120	0.069
Male/Female ratio	1.97	1.83	1.71	1.25	
Mean age at disease onset	31.5 ± 8.3	30.9 ± 9.0	30.7± 9.3	32.3 ± 9.6	NS
Median disease duration	2.5 [1.0-6.0]	2.0 [1.0-5.0]	1 [0.5-3]	1 [0.6-4]	0.06
Mucocutaneous inv. , n (%)					
Genital ulceration	187 (88.6)	137 (80.6)	184 (81.7)	220 (81.4)	NS
Papulopustular lesion	174 (82.5)	130 (76.5)	187 (83)	185 (68.5)	<0.001
Erythema nodosum	132 (62.6)	88 (51.8)	101 (44.8)	112 (41.4)	<0.001
Ocular involvement, n (%)	107 (50.7)	107 (62.4)	97 (43.1)	129 (47.7)	0.001
Vascular involvement, n (%)	49 (23.2)	29 (17.0)	41 (18.2)	31 (11)	0.008
Large vessel involvement, n (%)	21 (42.9)	11 (38.0)	13 (31.7)	7 (22.5)	<0.001
Neurologic involvement, n (%)	7 (3.3)	6 (3.5)	5 (2.2)	10 (3.7)	NS
Arthritis, n (%)	79 (37.4)	37 (21.8)	53 (23.6)	56 (20.7)	<0.001

Table 2. Severity of ocular involvement at presentation

Ocular involvement	1979-81 cohort n =107	1990 cohort n=106	2000 cohort n=97	2010 cohort n= 129	p
Visual acuity < 0.1 in bilateral eyes, n (%)	17 (15.7)	8 (7.5)	6 (6.5)	9 (6.9)	0.03*
Visual acuity < 0.1 in unilateral eye, n (%)	23 (21.3)	19 (17.9)	18 (19.7)	22 (17)	0.39**
Visual acuity > 0.5 in bilateral eyes	39 (36.1)	54(55.6)	55 (60.4)	73 (56.6)	0.002**

* Cohort 1 vs 4 and Cohort 1 vs 3;

** Cohort1 vs 4

Disclosure: E. Dincses, None; Y. Ozguler, None; D. Ucar, None; Y. Ozyazgan, None; S. Ugurlu, None; G. Hatemi, None; M. Melikoglu, None; S. Yurdakul, None; H. Yazici, None; E. Seyahi, None.

Abstract Number: 1797

An Update on Pulmonary Artery Involvement in Behçet's Syndrome: More Pulmonary Artery Thrombotic Disease and a Better Outcome

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease And IGG4-Related Disease

Session Type: ACR Poster Session B

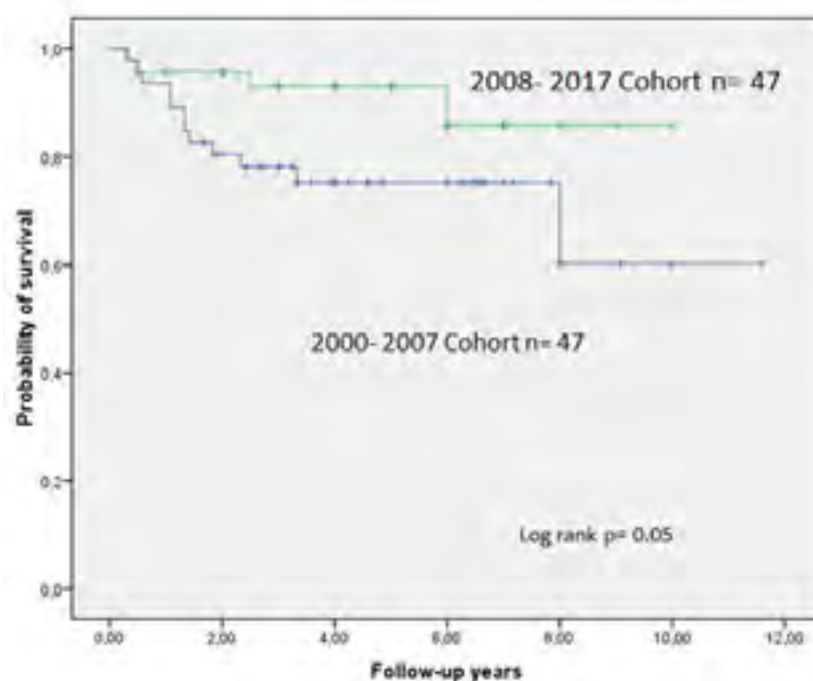
Session Time: 9:00am-11:00am

Background/Purpose: Pulmonary artery involvement (PAI) is the most common form of arterial involvement in Behçet's syndrome (BS). A previous survey (1) by our group had analyzed the clinical characteristics and outcome in 47 pts with PAI registered between 2000-2007 and, as compared to our previous experience showed that: 1.the overwhelming male predominance was decreasing; 2.1/4th of the pts had isolated pulmonary artery thrombosis (IPAT); and 3. the mortality rate was 26% after a mean follow-up of 7 yrs. Recently we had the impression the percentage of female pts was perhaps further increasing; the number of pts with IPAT were increasing and we started to use more biologics. We aim to look at these assumptions formally in a recent group of BS pts with PAI.

Methods: We reviewed the records of 3390 pts with BS in our multidisciplinary clinic between Jan 2008 and Jan 2018. We identified 47 (42M/5F) pts with PAI and recorded all information regarding clinical characteristics, outcome, radiological studies and treatment.

Results: The prevalence of pts with PAI decreased from 1.9% to 1.4% in the recent cohort. The M/F ratio, the mean age at the onset of PAI and the frequencies of other vascular involvement were similar across the 2 cohorts. However, there were more pts with neurological disease in the recent cohort. As usual, PAI were mostly bilateral and involved descending lobar arteries. On the other hand, types of PAI involvement at presentation had changed substantially: those with IPAT

Figure. Kaplan-Meier survival curve comparing two cohorts



reached a share of 45%. Forty-five (96%) pts received cyclophosphamide (Cy) for a mean of 6 ± 4 courses, which was significantly shorter compared to the previous cohort. Twenty-three (49%) pts received anti-TNF because of relapsing course, side effects or unresponsiveness for a mean follow-up of 8 ± 4 mo while only 2pts received anti-TNF's in the older cohort. 4 pts had lung surgery, lobectomies in 3 due to giant rapidly progressing aneurysms and a cavectomy in 1. Bronchial artery embolization was done in 3 pts due to refractory hemoptysis. The outcome of information was available on 45/47 pts: 4 pts (8%) had died, 2 were lost to follow-up after 12 and 16 mo of follow-up and the remaining were alive after a median follow-up of 5 [IQR:3-9] yrs. The causes of deaths were massive hemoptysis in 3, severe pulmonary hypertension in 1. The survival has improved significantly in the recent yrs (figure).

Conclusion: The surveys of 2 cohorts showed the prevalence of PAI perhaps mildly decreased, IPAT type of involvement was with considerably higher frequency and the outcome was getting better. Cy was still the first agent however its duration of use became much shorter and anti-TNF's were used in about half of the cohort. The survival seems to have improved significantly. This could have been due to a decreased severity of the type of PAI, with IPAT becoming the most frequent type and or a better management.

1)Seyahi E, Medicine (Baltimore). 2012

Disclosure: Y. Ozguler, None; E. Dincses, None; S. Bakan, None; G. Hatemi, None; M. Melikoglu, None; S. Yurdakul, None; H. Yazici, None; E. Seyahi, None.

Abstract Number: 1798

Leg Ulcers in Behçet's Syndrome: An Observational Survey in 24 Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Table. Demographic and clinical characteristics of the pts with leg ulcers in 24 pts with BS	
n (Male/ Female)	24 (23/1)
Mean age at disease onset	27.5 ± 7.1
Median time interval between disease onset and ulcer development	4.0 [2.5-11.5]
Median follow-up duration	7.8 [2.9-14.2]
Unemployment due to the leg ulcers (%)	11 (46)
Eye disease, n (%)	7 (29)
Large vessel involvement (%)	9 (38)
Dural sinus thrombosis (%)	3 (12.5)
Vena cava sup./thr (%)	1 (4)
Pulmonary artery inv. (%)	5 (21)
Other arterial inv. (%)	1 (4)
Vena cava inferior-iliac vein thrombosis (%)	8 (33)
Lower extremity vein thrombosis (%)	20 (83)
Bilateral (%)	15 (62.5)
Femoral vein (%)	20 (83)
Popliteal vein (%)	14 (58)
Superficial vein (%)	7 (29)
No venous thrombosis or insufficiency (%)	4 (17)
Pts with a solitary ulcer (%)	12 (50)
Pts with more than 1 ulcer (>1) (%)	12 (50)
Pts with healed ulcers (%)	11 (46)
Pts with active ulcers (%)	13 (54)
Anatomical localization (total n = 14)	
Medial malleolus (%)	15 (44 %)
Anterior surface of the tibia (%)	14 (41 %)
Other (%)	5 (5 %)

Background/Purpose: Formal experience with leg ulcers in Behcet's syndrome (BS) is limited. It is a relatively rare complication that can be seen during the course of mainly post-thrombotic syndrome. They can be difficult to manage and cause disability leading to unemployment and severe impairment in quality of life. In this observational survey, we aimed to describe clinical characteristics of pts with leg ulcers.

Methods: A total of 24 pts (23 M/ 1F) that were seen in our out-patient BS clinic between May 2016 and Jan 2018 were evaluated with the help of a standardized questionnaire. Venous Doppler US and if necessary abdominal CT were used to evaluate localization of venous involvement. Biopsies were done if needed. Medical and other interventional treatments were recorded.

Results: The mean age at disease onset was 27.5 ± 7.1 yrs (Table). The median time interval between the disease onset and ulcer development was 4.0 [2.5-11.5] yrs. The median follow-up was 7.8 [IQR:2.9-14.2] yrs. Eleven (46 %) were unemployed due to leg ulcers. Venous involvement was present in 20 pts (83 %). Lower extremity vein thrombosis was present in all 20. It was mostly bilateral (15/20). The same 9/20 pts had other large vessel involvement. Four pts did not have any venous thrombosis or insufficiency. Histopathologic studies could be done in 3 and showed features of necrotizing vasculitis in 2 and venous stasis in the 3rd. Twelve pts (50 %) had solitary ulcers while the remaining had 2 or more. We observed a total of 34 ulcers in 24 pts. They were mostly found around the medial malleolus (15/34) and the anterior surface of the tibia (14/34). Five pts had leg ulcers at unusual places such as lateral malleolus (n=2), popliteal fossa (n=1) and posterior surface of the tibia (n=2). Immunosuppressives including azathioprine, cyclophosphamide, interferon-alpha, infliximab and corticosteroids were used. Iloprost infusions were given in 13 (54 %) for a median duration of 6 mo. Additionally, larvae of *Lucilia sericata* were tried in 9 pts. Skin graft insertion was used in 2 pts, however, was successful only in 1. 17 ulcers in 11 (46 %) pts healed in a median 24 mo [IQR: 9- 78]. In the remaining 13 (54 %) pts 17 ulcers remained unhealed for a median 7 yrs [IQR: 5- 11], despite all treatment. The mean age at BS onset was significantly younger (24.4 ± 5.4 vs 30.4 ± 7.3 yrs; p< 0.05) and the median time between disease onset and ulcer development was significantly shorter (3 [IQR: 1-4.5] vs 10 [IQR: 4-14 yrs, p< 0.05] in pts with the healed ulcers. There were no apparent associations with the type of management and the severity of venous involvement.

Conclusion: Leg ulcer develops mainly due to venous disease in the lower extremities. Peripheral arterial occlusive disease seems to be rarely associated. Leg ulcers may cause unemployment and be resistant to treatment. Ulcers that appear early during the disease course heal faster and are more responsive to treatment.

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Increased Vein Wall Thickness in Behçet's Syndrome

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease And IGG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00 am-11:00 am

Background/Purpose: Lower extremity vein thrombosis (LEVT) is the key feature of vascular involvement in Behçet's syndrome (BS). Vein wall thickness (VWT) is proposed to be a surrogate marker of venous disease. A pilot MR study done in 7 BS patients and controls, had demonstrated increased VWT and signal enhancement in the lower extremity veins of BS patients without vascular disease. Another study, using USG, found that VWT was increased among BS patients without vascular disease compared to patients with ankylosing spondylitis and healthy controls. We reassessed VWT in proximal lower extremity veins in BS patients with LEVT and suitable controls in a formal, masked protocol.

Methods: We studied 47 (40 M/ 7 F) BS patients with LEVT, 50 (43 M/ 7 F) BS patients without any vascular involvement and 38 (31 M/ 7 F) age and gender matched apparently healthy controls. Two independent radiologists, blinded to the diagnosis of BS, used USG to measure VWT of common femoral vein (CFV), superficial femoral vein (SFV) and vena saphena magna (VSM) in both legs.

Results: As shown in Table 1, mean age at disease onset and the disease duration were similar between BS study groups. The mean age at thrombosis onset of the patients with LEVT was 26.4 ± 5.8 years. There was good concordance between the 2 observers (kappa: 0.9) The mean VWT was significantly increased among both BS patients with LEVT and those without any vascular involvement when compared to the healthy controls while those with LEVT had the thickest veins.

Table 1. Disease duration and VWT

	BS with vascular involvement (n=47; 40 M/ 7 F)	BS without vascular involvement (n=50; 43 M/ 7 F)	Healthy controls (n=38; 31 M/ 7 F)	P value
Age, years	37.06 ± 5.26	36.98 ± 4.47	34.87 ± 7.22	0.296
Disease duration	10.96 ± 6.45	9.68 ± 5.89	-	0.31
Vein wall thickness, mean \pm SD, mm				
Right CFV 1st observer	0.91 ± 0.67	0.69 ± 0.15	0.57 ± 0.11	0.001
Right CFV 2nd observer	0.93 ± 0.76	0.70 ± 0.18	0.58 ± 0.09	<0.001
Left CFV 1st observer	1.04 ± 0.85	0.66 ± 0.11	0.56 ± 0.07	<0.001
Left CFV 2nd observer	1.09 ± 0.83	0.69 ± 0.16	0.57 ± 0.07	<0.001
Right SFV 1st observer	0.79 ± 0.38	0.60 ± 0.11	0.51 ± 0.9	<0.001
Right SFV 2nd observer	0.80 ± 0.42	0.62 ± 0.13	0.52 ± 0.07	<0.001
Left SFV 1st observer	0.88 ± 0.38	0.62 ± 0.12	0.49 ± 0.09	<0.001
Left SFV 2nd observer	0.90 ± 0.40	0.63 ± 0.13	0.51 ± 0.07	<0.001
Right VSM 1st observer	0.60 ± 0.22	0.52 ± 0.11	0.43 ± 0.07	<0.001
Right VSM 2nd observer	0.64 ± 0.25	0.53 ± 0.13	0.46 ± 0.08	<0.001
Left VSM 1st observer	0.67 ± 0.23	0.53 ± 0.11	0.42 ± 0.09	<0.001
Left VSM 2nd observer	0.65 ± 0.27	0.53 ± 0.11	0.43 ± 0.07	<0.001

CFV: common femoral vein, SFV: superficial femoral vein, VSM: vena saphena magna

Conclusion: VWT of proximal deep and superficial lower extremity veins was found to be increased among BS patients without any clinical and radiological vascular involvement.

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A Declining Trend in Frequency of Secondary Amyloidosis in Behçet's Syndrome

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

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Session Time: 9:00AM-11:00AM

Background/Purpose: A decline in the frequency of AA amyloidosis secondary to RA and infectious diseases has been reported. This is probably due to more effective treatment strategies. We had previously reported that although amyloidosis occurs in less than 0.5% of BS pts. It is one of the leading causes of death (1-3). We aimed to determine the change in the frequency of AA amyloidosis over years in BS pts in addition to elaborating on clinical characteristics and outcome.

Methods: We performed a chart review to identify all pts with amyloidosis in our BS center since 1976. We noted demographic characteristics, BS manifestations, age at BS and AA amyloidosis diagnosis, treatment modalities of these pts. Our endpoints were death and end stage renal disease (ESRD) requiring renal replacement therapy. The prevalence of AA amyloidosis was calculated separately for 2 periods (pts registered between 1976-2000 and 2000-2017)

Results: Among our 9410 BS pts, 27 (0.29%) had amyloidosis. We identified 24 pts with amyloidosis among the 3820 pts in the earlier cohort and 3 additional amyloidosis among the 5590 pts in the recent cohort. The frequency of AA amyloidosis had declined from 0.62% to 0.054% in the recent cohort. M/F ratio was 22/5 and mean age at BS diagnosis was 29.5±7.4 yrs. Twenty-two (82%) of the pts with AA amyloidosis had major organ involvement (vascular inv. in 15, eye inv.in 13 and neurologic inv.in 2). AA amyloidosis was diagnosed after a mean duration of 9.8±6.7 yrs and was confirmed with renal biopsy in 14 pts and rectal biopsy in 13. Eight pts had non-nephrotic range proteinuria at amyloidosis diagnosis. After amyloidosis diagnosis, 24 pts continued their previous immunosuppressives and colchicine. Two of these 24 were on anti-TNFs at amyloidosis diagnosis. Biologics were initiated in 3 pts who were most recently diagnosed to have amyloidosis, anti-TNFs in 2 and tocilizumab in 1. Fourteen (52%) pts had died after a median follow-up of 3 (IQR:1-8.75) yrs, 3 were lost to follow-up just after amyloidosis diagnosis and 10 (37%) are still alive after a median follow up of 16 (IQR:10-23) yrs. The reasons for death were infections in 5, related to ESRD in 5, subarachnoid hemorrhage, gastric adenocarcinoma, liver cirrhosis probably associated with amyloidosis and iatrogenic bowel perforation in 1 pts each. 10 (71%) of these 14 pts had developed ESRD before their deaths. Overall, 15/27 pts developed ESRD after a median follow-up of 3.5 (IQR:1.25-6.5) yrs after amyloidosis diagnosis. 5 of them had renal transplantation, all but 1 are still alive after 3, 4, 6, and 12 yrs. The last one died 11 years after transplantation due to subarachnoid hemorrhage as explained above.

Conclusion: AA amyloidosis appears to be a rare, but fatal complication of BS. Around 50% of pts died after a median follow-up of 3 yrs after amyloidosis. This study showed a decreasing trend of amyloidosis due to BS similar to that observed in other inflammatory and infectious causes. The shorter follow-up duration may be contributing for the lower prevalence of amyloidosis in the recent cohort.

References : 1)Yurdakul S,Arthritis Rheum.1990 2)Melikoğlu M,Rheumatology (Oxford).2001 3)Kural-Seyahi E,Medicine (Baltimore).2003

Disclosure: G. Karatemiz, None; S. N. Esatoglu, None; Y. Ozguler, None; S. Yurdakul, None; V. Hamuryudan, None; M. Melikoglu, None; I. Fresko, None; E. Seyahi, None; S. Ugurlu, None; H. Ozdogan, None; H. Yazici, None; G. Hatemi, None.

Factors Associated with Damage Progression in Behçet's Syndrome Uveitis

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SESSION INFORMATION

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Background/Purpose: Uveitis in Behçet's syndrome (BS) follows a recurrent disease course with inflammatory exacerbations causing damage in the uvea, retina and optic nerve even with treatment. Frequent attacks and posterior involvement are considered as predictors of poor visual outcome. The aim of this study is to delineate the predictors of damage in more detail using a standard screening method among a group of BS patients with long-term regular follow-up.

Methods: Patients with uveitis who were registered in our multidisciplinary BS clinic between 1990 and 2008 were screened. Among these, 50 patients who were followed for at least 10 years, who were regularly seen in our clinic at least once in every 4 months, who did not have > Grade 2 damage at baseline, and who represented different levels of damage severity during the last visit (between Grade 0 and 5) were selected. The damage severity was graded according to a validated damage grading instrument (5=worst) specifically developed for BS uveitis (Ozyazgan et al. in preparation). One patient was later excluded because it was realized that he did not fulfill these criteria. A standard form was used for retrieving data on demographics, baseline and final visual acuities, number and localization (anterior/posterior / panuveitis) of attacks during follow-up, presence of retinal infiltration, retinal hemorrhage and hypopyon uveitis. Candidate factors for damage progression were compared between patients who had a progression in damage score and those who did not.

Results: 98 eyes of 49 patients (M:F 35:14, mean age at baseline 27 ± 8 years, mean follow-up duration 20.9 ± 5.5 years, mean number of visits 76.5 ± 35.2) were evaluated. The mean visual acuity was 0.02 ± 0.08 at baseline and 0.47 ± 0.52 at the final visit. The mean number of attacks was 13.2 ± 9.4 . Damage grades at baseline were Grade 0 in 79, Grade 1 in 16 and Grade 2 in 3 eyes. Damage grades at final visit were Grade 0 in 15, Grade 1 in 21, Grade 2 in 32, Grade 3 in 12, Grade 4 in 10 and Grade 5 in 8 eyes. There was damage progression in 81/98 eyes at the final visit. Isolated anterior uveitis attacks were not associated with progression of damage (2.5 ± 2.9 vs 2.8 ± 5.5 , $p=0.7$). Parameters that were significantly more frequent among patients with damage progression were: number of attacks (14.5 ± 10.8 vs 23.3 ± 12.3 ; $p=0.008$), number of posterior attacks (0.4 ± 1.2 vs 6.5 ± 4.9 , $p<0.001$), number of panuveitis attacks (0.8 ± 1.3 vs 6.6 ± 5.0 , $p<0.001$), number of attacks with severe vitreous opacity preventing examination of the retina (0 vs 3.2 ± 3.8 , $p<0.001$), retinal infiltration (0.2 ± 0.4 vs 1.4 ± 1.9 , $p<0.001$) and retinal hemorrhages in the arcuate region (0.1 ± 0.2 vs 0.7 ± 1.4 , $p<0.001$), and the number of hypopyon attacks (0.2 ± 1.0 vs 0.9 ± 1.3 , $p=0.019$).

Conclusion: This study confirmed that the anterior uveitis attacks are not associated with progressive damage in BS, whereas posterior and panuveitis attacks, attacks causing severe vitreous opacity, retinal infiltrates and hemorrhage in the arcuate region and hypopyon attacks are important predictors of damage. Patients showing these features should be treated more aggressively.

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Behçet's Disease in the Southwestern United States

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

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Background/Purpose: Behçet's disease (BD) in the US is estimated to have a prevalence of 5.2-6.6 per 100,000 populations which is similar to that of European countries but lower than that reported along the Silk Road and in Turkey (400 per 100,000). We now report the demographic and clinical characteristics of BD in understudied populations in Southwest US.

Methods: Under IRB approval, we identified BD patients actively seen during 2014 to 2017 and determined the demographic and clinical characteristics of BD. BD was defined using the International Behçet's Study Group criteria. Incomplete BD patients were excluded.

Results: 63 patients (82.5% female, 17.5% male, female: male ratio: 4.7:1) were identified who fulfilled definite BD criteria in a service population of 710,000 individuals, resulting in an estimated prevalence of 8.9 per 100,000 which is higher than reported previously in the US. 84.1% (53/63) were incorrectly diagnosed with other primary diagnoses like inflammatory arthritis (15.9%), primary fibromyalgia (7.9%), other forms of vasculitis (7.9%), or systemic lupus erythematosus (7.9%) prior to BD diagnosis. Most common BD manifestations were oral ulcers (100%) (Figure 1), genital ulcers (61.9%) (Figure 2), acneiform lesions (69.8%), papulopustular lesions (52.4%) (Figure 2), pseudofolliculitis (42.9%), inflammatory arthritis (41.3%), anterior uveitis (23.8%), posterior uveitis (15.9%), pathergy (15.9%), deep vein thrombosis (14.3%), non-ocular vasculitis (11.1%), erythema nodosum (7.9%), arterial thrombosis (6.3%), and retinal vasculitis (1.6%). 50.8% of BD had concomitant fibromyalgia. BD was distributed ethnically as follows: 49.2% Spanish-American (SA), 31.7% Non-Spanish European-American (EA), 14.3% Native American (NA), and only 1.7% Silk Road. HLA-B51 was present in 70.5% percent of the total BD population and demographically segregated as to HLA-B51 more commonly in NA (89.0%, $p=0.02$) and SA (74.2%, $p=0.02$) compared to EA (42.1%).

Conclusion: BD is more common in Southwester US than anticipated from prior US-based studies. BD occurs amongst all local ethnic groups including EA, SA, and NA. 84.1% of BD patient have been incorrectly diagnosed with some other disease prior to the BD diagnosis, and 50.8% have concomitant fibromyalgia, complicating the diagnosis. The prevalence of HLA-B51 in BD amongst SA and NA is high (74-89%) and greater than in EA (42%). This is one of the first reports of the characteristics of BD in Southwest US, and specifically in SA and NA populations, and provides the basis for further future study.



Figure 1 Oral ulceration



Figure 2 Genital ulceration and Papulopustular Lesions

Disclosure: M. Muruganandam, None; N. Rolle, None.

Abstract Number: 1803

Assessment of Severity and Risk Factors of Post-Thrombotic Syndrome in Vascular Behçet Disease: Muticentered Retrospective Study

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SESSION INFORMATION

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Background/Purpose: Vascular involvement is seen in about one third of patients with Behçet Disease (BD). DVT (deep venous thrombosis) is the most common form of vascular Behçet Disease (VBD). Post-thrombotic syndrome (PTS) developing after a thrombotic event in lower extremity is one of the major complications of DVT and affects negatively patients' quality of life. In this study, we aimed to assess the presence, severity and risk factors of PTS and venous disease specific quality of life in VBD.

Methods: This study included 96 patients with BD (Female/Male: 18/78, mean age: 38.8±8.74 years) having history of DVT from 3 tertiary Rheumatology centers in Turkey. Villalta scale was used to assess PTS. According to scale; PTS is present if score >4 and degree of PTS mild, moderate and severe if score 5-9, 10-14, >14 respectively. The Venous Disability Score (VDS) and the Venous Clinical Severity Score (VCSS) were used for the assessment of venous disease. All patients were assessed with color Doppler ultrasonography (US) by experienced radiologists within 1 week following the clinical examination. In each patient, a total of 16 superficial and deep veins in both legs were assessed for the presence or absence of obstruction, recanalization, reflux and collaterals.

Results: When vascular involvement developed, mean age was 32.7±8.65. Venous assessment was done after 6(0-26) years first vascular event. During venous assessment, median disease duration was 9(0-34) years. Eighty (84.2%) patients were under immunosuppressive (IS) treatment and 13 of these patients were under anticoagulation treatment in addition to ISs. Median IS time 37.5 (1-256); anticoagulation time 12 (1-156) months. PTS was present in 57(61.3%) out of 93 patients and severe PTS was present in 19(19.8%) patients. There was no association between presence of PTS and sex, age during DVT, compression stocking treatment usage, presence of relaps, duration of thrombosis. There was no difference between patients with or without anticoagulant usage regarding PTS presence (p=0.817) and also there is no difference at duration of IS and AC treatment between patients with or without PTS. Doppler US examination shows no abnormalities at 10 (10.6%) patients, 5(50%) of these patients had PTS. Bilateral leg vessel involvement was present in 31(31.4%) patients. Forty (47.6%) patients had both upper

and lower leg vessel involvement. But we didn't find any association with PTS presence and doppler US findings such as bilateral involvement, upper and lower leg vessel involvement, reflux or thrombosis at any vessel in the affected leg.

When VBD patients with and without PTS were compared, quality of life (VEINES-QoL/Sym) and VCSS were significantly worse. The Behçet Syndrome Activity Score was also significantly higher in patients with PTS

Conclusion: We found that PTS develops in more than half of the patients with VBD during follow-up. We didn't find any predictor factor for development of PTS. About one third of patient with PTS were severe PTS. Our results confirm that PTS is very frequent clinical problem for physicians treating VBD in daily practice. During management of patients with VBD, PTS should be taken into account as much as preventing vascular relapses.

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Abstract Number: 1804

Optimization Protocol for Adalimumab Treatment in Refractory Uveitis Due to Behçet's Disease

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

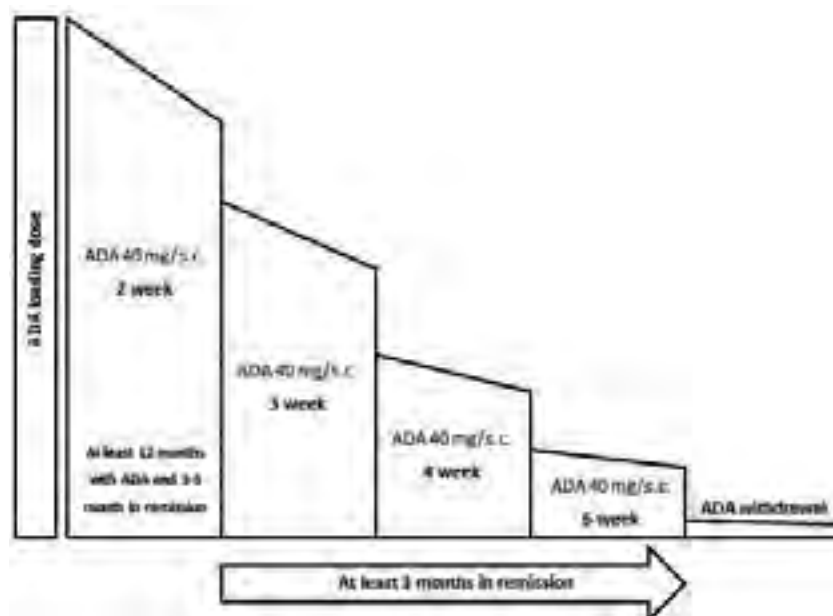
Session Time: 9:00AM-11:00AM

Background/Purpose: Uveitis is the most common ocular manifestation in Behçet Disease (BD), which can cause irreversible blindness. Once the efficacy, safety and cost-effectiveness of Adalimumab (ADA) have been demonstrated in a

large series of patients with uveitis due to BD (Martín-Varillas *et al. Ophthalmology* 2018), we propose, based on this report, a treatment optimization protocol.

Methods: Multicenter study of 65 ADA-treated patients with BD uveitis refractory to conventional immunosuppressants. Following remission, based on a shared decision between the patient and treating physician, ADA optimization was performed by increasing the ADA dosing interval progressively.

Results: Based on our experience we propose an optimization protocol of ADA treatment as follow: after 12 months of treatment with ADA and once remission was achieved and sustained for at least 3-6 months, we recommend increase very slowly but progressively the dosing interval with regular monitoring of ocular inflammation parameters. Once the dosing interval has been increased up to every 6 weeks and there is no ocular inflammation data, we recommend discontinuing treatment but keeping close monitoring (FIGURE).



If relapse occurs, the patient should be switched to the standard dose of 40 mg/s.c./2 weeks.

Following this protocol, we perform an annual-cost analysis in which we compare the optimized and non-optimized patients, finding a statistically significant (6101.25 euros/patient/year vs.12339.48; $p < 0.01$). In addition, no severe side effects were observed after optimization.

Conclusion: ADA optimization in BD uveitis refractory to conventional therapy is effective, safe and cost-effective.

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Abstract Number: 1805

Strong Association of HLA-DRB1*0901 with Japanese Patients with Chronic Progressive Neuro-Behçet's Disease

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Central nervous system involvement is one of the most serious complications in Behçet's disease (BD). This condition is referred to as neuro-BD (NB) and can be classified into acute type (ANB) and chronic progressive type (CPNB) based upon differences in the clinical course and responses to corticosteroid treatment. It has been well appreciated that Human Leukocyte Antigen (HLA)-B51 is significantly associated with BD. Of note, HLA-B51 has been found in >80% of patients with CPNB. Thus, genetic factors, such as Major Histocompatibility Complex (MHC), have been implicated in the pathogenesis of CPNB. However, there have been no reports on MHC class II antigen in CPNB. The current studies were carried out to examine whether there is any association of MHC class II antigen in CPNB.

Methods: Forty Japanese BD patients meeting the International Criteria for Behçet's Disease (ICBD) were enrolled for analysis, including 11 patients with ANB and 15 patients with CPNB. Since CPNB has high positivity for HLA-B51, 14 patients of HLA-B51-positive non-NB were included as a control group. The diagnosis of ANB and CPNB was performed according to the diagnostic criteria proposed by the Japanese research committee for BD (Mod Rheumatol (2012) 22:405-413). The genotype determination of HLA-DR was performed using peripheral blood by polymerase chain reaction (PCR)-sequence based typing.

Results: The HLA-B51-positive rate was 36.4% in ANB(4/11), 86.7% in CPNB (13/15), and 100% in non-NB (14/14). HLA-DRB1*0901 were found in 9.1%, 66.7%, and 4.3% of ANB, CPNB and non-NB HLA-B51 positive control, respectively. The relative risk and odds ratio of ANB and CPNB due to the presence of HLA-DRB1*0901 was 2.727 (Fisher's exact test: $p=0.0052$) and 20.0 (95% confidence interval (CI): 1.966 to 203.4), respectively. The relative risk and odds ratio of CPNB and HLA-B51-positive non-NB due to the presence of HLA-DRB1*0901 was 2.833 (Fisher's exact test: $p=0.0078$) and 12.0 (95% CI: 1.901 to 75.75), respectively. The results of HLA-DR genotyping are shown in Table.

Table. HLA-DRB1 allele frequencies in Japanese BD patients

ANB (n=11)			CPNB (n=15)			non-NB (n=14)		
Alleles	No.	Freq. (%)	Alleles	No.	Freq. (%)	Alleles	No.	Freq. (%)
HLA-DRB1*01:01	1	10.0	HLA-DRB1*01:01	1	6.7	HLA-DRB1*01:01	1	7.1
HLA-DRB1*04:01	1	10.0	HLA-DRB1*04:01	2	13.3	HLA-DRB1*04:01	1	7.1
HLA-DRB1*04:05:01	1	36.4	HLA-DRB1*04:05:01	1	6.7	HLA-DRB1*04:05:01	4	28.6
HLA-DRB1*04:10:01	1	10.0	HLA-DRB1*04:10:01	4	26.7	HLA-DRB1*04:10:01	1	7.1
HLA-DRB1*08:01:01	4	45.5	HLA-DRB1*08:01:01	1	6.7	HLA-DRB1*08:01:01	5	35.7
HLA-DRB1*08:03:01	1	10.0	HLA-DRB1*08:03:01	10	66.7	HLA-DRB1*08:03:01	3	21.4
HLA-DRB1*08:03:02	1	10.0	HLA-DRB1*08:03:02	3	20.0	HLA-DRB1*08:03:02	2	14.3
HLA-DRB1*08:04:01	1	10.0	HLA-DRB1*08:04:01	1	6.7	HLA-DRB1*08:04:01	3	21.4
HLA-DRB1*08:08:01	1	10.0	HLA-DRB1*08:08:01	2	13.3	HLA-DRB1*08:08:01	1	7.1
HLA-DRB1*12:01:01	1	10.0	HLA-DRB1*12:01:01	1	6.7	HLA-DRB1*12:01:01	2	14.3
HLA-DRB1*12:02:01	1	10.0	HLA-DRB1*12:02:01	1	6.7	HLA-DRB1*12:02:01	1	7.1
HLA-DRB1*13:01:01	1	10.0	HLA-DRB1*13:01:01	2	13.3	HLA-DRB1*13:01:01	4	28.6
HLA-DRB1*13:02:01	1	10.0	HLA-DRB1*13:02:01	1	6.7	HLA-DRB1*13:02:01	1	7.1
HLA-DRB1*14:01:01	1	10.0	HLA-DRB1*14:01:01	1	6.7	HLA-DRB1*14:01:01	1	7.1
HLA-DRB1*14:02:01	1	10.0	HLA-DRB1*14:02:01	1	6.7	HLA-DRB1*14:02:01	1	7.1
HLA-DRB1*15:01:01	1	10.0	HLA-DRB1*15:01:01	1	6.7	HLA-DRB1*15:01:01	1	7.1
HLA-DRB1*15:02:01	1	10.0						

ANB=acute neuro-Behçet's disease; CPNB=chronic progressive neuro-Behçet's disease; Freq.=frequency.
HLA=Human Leukocyte Antigen; BD=Behçet's disease.

Conclusion: These results disclosed that HLA-DRB1*0901 is significantly associated with CPNB. Moreover, the data suggest that HLA-B51 as well as HLA DRB1*0901 might be involved in the pathogenesis of CPNB possibly continuing production of interleukin (IL)-6.

Disclosure: H. Kikuchi, None; T. Tomizuka, None; T. Itamiya, None; K. Asako, None; T. Yanagida, None; H. Kono, Celgene Corporation, 2; S. Hirohata, None.

Abstract Number: 1806

Spinal Cord Involvement in Behçet's Disease- Experience of a Vasculitis Centre at Silk Road

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Spinal cord involvement may occur in the course Behcet's Disease (BD). It may present with distinct manifestations such as sphincter and/or sexual dysfunction. We aimed to investigate the frequency and clinical features of spinal cord involvement of BD in our Hacettepe University Vasculitis Center (HUVAC) cohort.

Methods: Patients enrolled in prospective HUVAC database were searched in terms of spinal cord involvement of BD. Of 1585 patients recorded since October 2014, 419 patients were BD patients (329 complete and 90 incomplete for ISG Criteria), and 77(18.4%) of them had NBD (61 definite, 16 possible) according to International Consensus Recommendations (ICR). Spinal cord involvement was diagnosed with neurological examination and spinal magnetic resonance imaging (MRI). Demographics, clinical features and treatment characteristics of patients were evaluated.

Results: Fifty two (12.4%) patients had parenchymal central nervous system involvement (CNS) whereas 12 (2.8%) had spinal cord involvement. The mean age at diagnosis was not different for spinal with pNBD and spinal without pNBD (24.9 ± 5.4 vs. 29.2 ± 9.24 , $p=0.22$). Median time period between diagnosis of BD and NBD is 5.29 years (IQR=9.95). Detailed clinical features of BD patients with spinal cord involvement were summarized in Table. Three patients had total atrophy of spinal cord. Cervical and/or thoracic segments of spinal cord was predominantly involved. Twenty five percent of spinal with pNBD had only one attack of NBD. Corticosteroids (IV pulse = 37/49, 75.5% and oral maintenance =45/50, 90%), interferon (40/52 79%) and cyclophosphamide (28/49,57.1%) were the most frequently preferred treatment regimens for parenchymal NBD. Over half of them had more than one attack. Almost all had sphincter dysfunction. One third of patients had deceased.

Table. Demographic and clinical features of parenchymal NBD patients with spinal cord involvement

No	Age (years)	Sex	Duration (years)	Oral ulcers	Genital ulcers	Skin lesions	Joint symptoms	Abdominal symptoms	Neurological symptoms	Spinal cord involvement	Spinal cord segment	Treatment	Outcome
1	25, M	-	-	-	-	-	-	-	-	-	-	-	-
2	20, M	-	-	-	-	-	-	-	-	-	-	-	-
3	26, M	-	-	-	-	-	-	-	-	-	-	-	-
4	41, M	-	-	-	-	-	-	-	-	-	-	-	-
5	35, M	-	-	-	-	-	-	-	-	-	-	-	-
6	27, F	-	-	-	-	-	-	-	-	-	-	-	-
7	36, M	-	-	-	-	-	-	-	-	-	-	-	-
8	28, F	-	-	-	-	-	-	-	-	-	-	-	-
9	26, M	-	-	-	-	-	-	-	-	-	-	-	-
10	41, M	-	-	-	-	-	-	-	-	-	-	-	-
11	33, M	-	-	-	-	-	-	-	-	-	-	-	-
12	22, F	-	-	-	-	-	-	-	-	-	-	-	-

Abb: Not Available
*Had both parenchymal and vascular (NBD) involvement

Conclusion: Spinal cord involvement is very rare in BD. However, it has a big impact on morbidity and mortality of BD patients. Awareness, early diagnosis and recent effective biologic agents might decrease this dramatic scenario.

Disclosure: E. C. Bolek, None; A. Sari, None; L. Kilic, None; A. Akdogan, None; M. A. Tuncer, None; O. Karadag, None.

Abstract Number: 1807

Clinical Features and Disease Course of Neurologic Involvement in Behcet's Disease

Ertugrul Cagri Bolek, Alper Sari, Berkan Armagan, Abdulsamet Erden, Levent Kilic, Umut Kalyoncu, Meryem Asli Tuncer, Sedat Kiraz and **Omer Karadag**, Hacettepe University Vasculitis Center (HUVAC), Ankara, Turkey

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

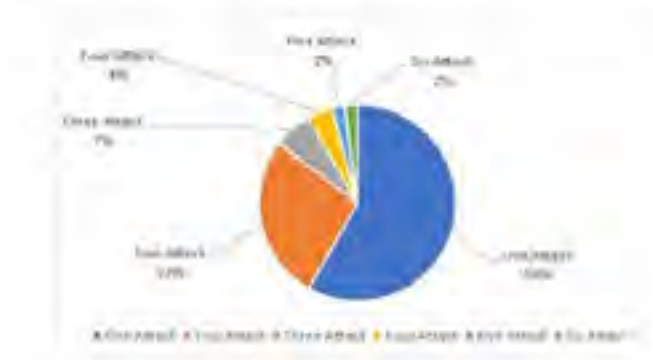
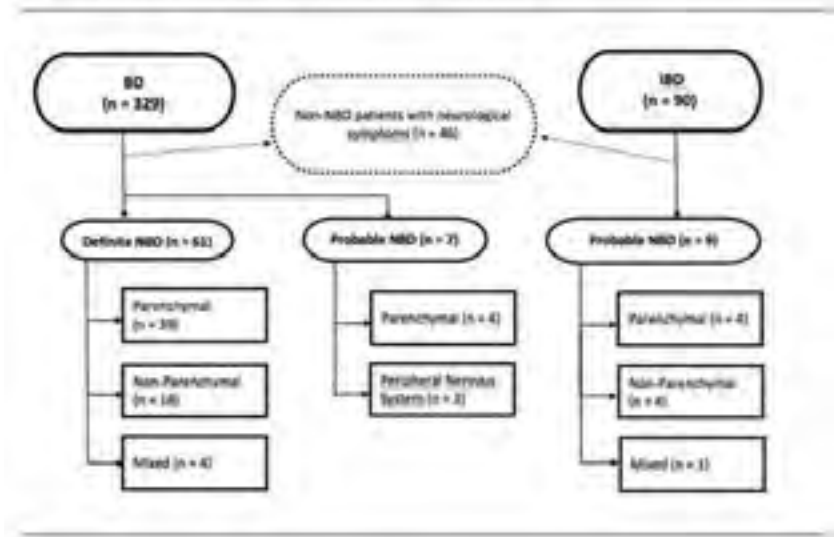
Background/Purpose: Neurological involvement (NBD) is a rare complication of BD. Although NBD is not common in the course of BD, it is related with significant mortality and morbidity. We aimed to evaluate disease course and outcome of NBD patients registered in Hacettepe University Vasculitis Center (HUVAC) prospective data base starting from October 2014.

Methods: Totally, 456 patients were recorded as BD and 329 of them had fulfilled International Study Group (ISG) criteria. Ninety patients who did not meet criteria were considered to have incomplete BD after a review of an experienced rheumatologist. Altogether, 419 patients with complete or incomplete BD were included in this study. One hundred and seventeen patients with neurological complaints/symptoms were retrospectively evaluated. Forty-six patients who did not meet definite or probable NBD ICR criteria were excluded from the study. In final analysis, 77 NBD patients (61 definite, 16 possible) were included.

Table: Clinical features and comparison of all BD and NBD patients

	All (n = 419)	Non-NBD (n = 342)	Paraneuronal NBD (n = 25)	Non-paraneuronal NBD (n = 22)	Mixed NBD (n = 30)	p
Female (%)	52.7%	52.9%	48.0%	45.5%	53.3%	0.38
Age at diagnosis, mean (SD)	47.0 (13.3)	47.3 (13.3)	46.2 (13.3)	47.4 (13.3)	47.3 (13.3)	0.74
Median Disease Duration, years	3.0 (0.0-10.0)	3.0 (0.0-10.0)	3.0 (0.0-10.0)	3.0 (0.0-10.0)	3.0 (0.0-10.0)	0.74
Age at NBD diagnosis, mean (SD)	47.3 (13.3)	47.3 (13.3)	46.2 (13.3)	47.4 (13.3)	47.3 (13.3)	0.74
Age at NBD diagnosis, range	18-70	18-70	18-70	18-70	18-70	0.74
Median time to NBD after diagnosis, years (IQR)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.74
ICR criteria						
Definite	61 (14.5%)	0 (0.0%)	25 (100%)	16 (72.7%)	10 (33.3%)	0.00
Probable	16 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (53.3%)	0.00
Possible	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.00
Not NBD	358 (85.5%)	342 (81.5%)	0 (0.0%)	6 (27.3%)	20 (66.7%)	0.00
Organ involvement						
Central nervous system	10 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (33.3%)	0.00
Peripheral nervous system	10 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (33.3%)	0.00
Eye	10 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (33.3%)	0.00
Ear, nose, throat	10 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (33.3%)	0.00
Oral	10 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (33.3%)	0.00
Respiratory	10 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (33.3%)	0.00
Gastrointestinal	10 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (33.3%)	0.00
Genitourinary	10 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (33.3%)	0.00
Skin	10 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (33.3%)	0.00
Blood	10 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (33.3%)	0.00
Other	10 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (33.3%)	0.00

Figure: Distribution and number of attacks of NBD patients



Results: Demographic and clinical features of BD patients with and without neurological involvement are summarized in Table. Neurologic involvement of BD is seen more frequently in patients with eye involvement (Table). Distribution of patients having parenchymal, non-parenchymal and mixed NBD are 47 (61%), 22 (28.5%), 5 (6.5%), respectively. Median time period between diagnosis for BD and parenchymal NBD is 5.7 years (IQR=11). Brainstem is the most frequently affected parenchymal area (72.9%), followed by white matter and diencephalon (64.6%, 37.5%). Twelve (25.5%) patients had spinal cord involvement. Fifty-eight percent of patients with acute onset parenchymal disease had only one attack. Corticosteroids (IV pulse: in 75.5% and oral in 90%), cyclophosphamide (57.1%), interferon (79%) and Anti-TNFagents (%23.5) were the most frequently preferred treatment options for parenchymal NBD. Ten, twenty and thirty year survival rates was 97.4%, 89.6% and 89.6% in NBD and 100%, 99.7% and 98.8% in non-NBD group, respectively (log rank $p<0.001$). Nine deaths were observed in all patients with NBD whereas no death was observed in patients with non-parenchymal NBD.

Conclusion: Neurologic involvement was seen median 5 years after BD diagnosis and these patients had more eye involvement compared to non-NBD group. Over half of patients had just one attack and no death was seen in non-parenchymal group. Interferon-alpha and anti-TNF agents were used in majority of patients.

Disclosure: E. C. Bolek, None; A. Sari, None; B. Armagan, None; A. Erden, None; L. Kilic, None; U. Kalyoncu, None; M. A. Tuncer, None; S. Kiraz, None; O. Karadag, None.

Abstract Number: 1808

Increased Frequency of Obstructive Sleep Apnea Syndrome in Behçet's Syndrome Patients with Vena Cava Superior Thrombosis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Superior vena cava syndrome (SVCS), is a medical emergency and can also be seen in Behçet's syndrome (BS). Contrary to the severe outcome seen in malign conditions, SVCS in BS usually has a benign course, complicated rarely by hemoptysis, pleural effusion and a chylothorax. We had noted that BS patients with SVCS frequently complained of sleep disturbances, snoring and sleep apnea, suggesting an obstructive sleep apnea (OSA) disorder. We formally surveyed the degree of risk for OSA among BS patients with SVCS and suitable controls using the Berlin questionnaire, a screening questionnaire for OSA with a high sensitivity and modest specificity (1).

Methods: Because of the lower frequency of female patients with VCSS (n= 2), only males were included. We studied 28 BS patients with SVCS (Group 1), 80 BS patients with vascular involvement without a SVCS (Group 2), and 59 BS patients with no vascular involvement (Group 3). Also 80 apparently healthy individuals (Group4) of similar age and gender to BS patients were studied. The Berlin questionnaire was used to assess risk of OSA (1). Polysomnography was performed in patients at high risk for OSA according to the Berlin questionnaire.

Results: There were no differences regarding demographic characteristics, disease duration and variables associated with OSA among the groups (Table). The Berlin questionnaire categorized 57.1 % (16/28) of the BS patients with SVCS (Group 1) as having a high risk for OSA and this was significantly higher compared to that found in the control groups. The frequency of those at high risk for OSA was 15 %, 8.5 %, 11.3 % in Group 2, 3 and 4, respectively ($p>0.05$). Until now, polysomnography was performed in 12 subjects (5 patients with SVCS, 1 patient with vascular involvement without a SVCS and 6 healthy controls). OSA was detected in 3/5 patients with SVCS and 1/1 patient with vascular involvement without a SVCS and 4/6 healthy controls.

Conclusion: This study shows that BS patients with a history of VCSS are at high risk of OSA. This is probably due to the external pressure of the significant venous collaterals on the upper airways.

Reference1: Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med.* 1999 Oct 5;131(7):485-91

Table. Demographic characteristics and variables associated with obstructive sleep apnea

	Group 1 (BS patients with SVCS) (n=28)	Group 2 (BS patients with vascular involvement without SVCS) (n=80)	Group 3 (BS patients with no vascular involvement) (n=59)	Group 4 (Healthy controls) (n=80)	p value
Age, mean \pm SD, years	44.3 \pm 9.7	42.1 \pm 7.8	41.9 \pm 5.9	42.7 \pm 9.7	0.051
Disease duration, mean \pm SD, years	18.7 \pm 9.4	14.6 \pm 7.7	12.5 \pm 6.5		0.001
Hypertension, n (%)	4 (14.3)	6 (7.5)	2 (3.4)	4 (5)	NS
BMI, mean \pm SD	26.8 \pm 4.7	26.4 \pm 3.9	26.2 \pm 3.3	27.0 \pm 3.5	NS
High risk for OSA, n (%)	16 (57.1)	12 (15)	5 (8.5)	9 (11.3)	<0.001

Disclosure

A. Gokturk, None; S. N. Esatoglu, None; Y. Ozguler, None; E. Atahan, None; B. Musellim, None; V. Hamuryudan, None; H. Yazici, None; E. Seyahi, None.

Abstract Number: 1809

Clinical Characteristics of Older Age-Onset Behçet Syndrome Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The usual onset of Behçet syndrome (BS) is in the 3 decade. Older age-onset defined as fulfilling the International Study Group (ISG) criteria after 40 years (yrs) of age is rare and our knowledge about it is limited. One

Table 1. Clinical characteristics of older age-onset and classical-onset BS pts (Males/Females)

	Older onset males (n=70)	Classical onset males (n=163)	P	Older onset females (n=64)	Classical onset females (n=105)
Age at ISG criteria fulfilling, yrs	47.0 \pm 6.0	24.2 \pm 4.3		46.6 \pm 5.7	23.1 \pm 4.4
Oral ulcer, n (%)	69 (99)	163 (100)	-	64 (100)	105 (100)
Genital ulcer, n (%)	60 (86)	137 (84)	0.845	51 (80)	90 (86)
Papulopustular lesions, n (%)	49 (70)	135 (82)	0.050	19 (31)	71 (68)
Nodular lesions, n (%)	15 (21)	76 (47)	0.0001	29 (45)	60 (57)
Arthritis, n (%)	10 (14)	43 (26)	0.028	13 (20)	25 (24)
Eye involvement, n (%)	24 (34)	88 (54)	0.006	26 (41)	41 (39)
Only vitreous cells (+), n (%)*	2 (8)	25 (28)	0.058	7 (27)	14 (34)
VA: \geq 0.1 on either or both eyes*	8 (33)	27 (33)	0.941	4 (15)	9 (23)
Vascular involvement, n (%)	13 (19)	27 (17)	0.710	2	0
Pathergy positivity, n (%)**	19 (56)	94 (58)	0.878	14 (53)	49 (47)
CNS involvement, n (%)	3	3	-	2	2
GIS involvement, n (%)	1	1	-	0	1
Activity score, mean \pm SD	3.60 \pm 3.36	6.38 \pm 3.15	0.020	3.28 \pm 2.21	4.79 \pm 2.19

*): Calculations are made only among those with eye involvement.

**): Pathergy test was made only in 70 older onset and 163 younger onset male pts, 64 older onset and 105 younger onset female pts. VA: visual acuity

early study from our center had reported the severity of eye disease was not different between early onset (≤ 24 yrs) and late onset (≥ 25 yrs) group, while the total clinical activity scores were smaller in the late onset group (1). While there is ambiguity in the definition of older onset, a few case series (2-4) coming mostly from ophthalmology or dermatology settings describe a similar or less severe clinical picture among late onset patients (pts) compared to that seen in early onset. The aim of this retrospective study was to evaluate clinical characteristics of pts with older onset BS pts, to compare them with a group of classic onset BS pts.

Methods: The charts of 3335 BS pts who were registered between Jan 2000 and Dec 2010 were reviewed retrospectively. Pts who fulfilled the ISG criteria for BS after 40 yrs of age (≥ 40) were defined as older onset, while those who fulfilled the criteria before 30 yrs of age as classic onset. For each older onset chart, 2 consecutively registered early onset charts were selected. Only clinical manifestations at initial presentation were recorded. A clinical activity index (1) was modified, calculated for each pt.

Results: There were only 134(70M/64 F) pts with older onset BS, which gave a prevalence of 4% in the whole cohort. Age of onset was 40-44 yrs of age in 54 pts, 45-49 yrs in 47 and 50+ in 32. As controls 268(163 M/105 F) classic onset pts were selected. Demographic/Clinical characteristics among older and classic onset pts are described for males and females separately, in Table. The frequency of skin manifestations, arthritis and eye disease as well as the mean clinical activity scores were significantly higher among male classic onset pts compared to older onset male pts. Interestingly, frequency of those with positive pathergy test, vascular involvement and severe eye involvement did not seem to be different among older onset and classic onset male pts. Clinical characteristics and total activity scores were similar between the older onset and classic onset groups among females (Table). The main limitation is that the information was based solely on patient's charts and outcome information was not available.

Conclusion: Compared to classic onset pts, males tend to be less frequent in the older cohort. At presentation, older onset male pts had significantly less frequent skin, joint, eye disease, and significantly lower total activity scores compared with classic onset pts. There was no difference between the classic and older onset group, among females.

References:

1-Yazici H et al. *Ann Rheum Dis*.1984.2-Tsai J et al. *J Eur Acad Dermatol Venereol*.2008.3-Hamzaoui A et al. *Acta Medica Iranica* 2014.4-Citirik M et al. *Ophthalmologica*.2011.

Disclosure: G. Guzelant, None; Y. Ozyazgan, None; C. Mat, None; V. Hamuryudan, None; H. Yazici, None; E. Seyahi, None.

Abstract Number: 1810

Initial Visit Symptoms in Probable Behçet's Predictive of ISG Criteria Behçet's: Data from New York and Amsterdam Cohorts

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

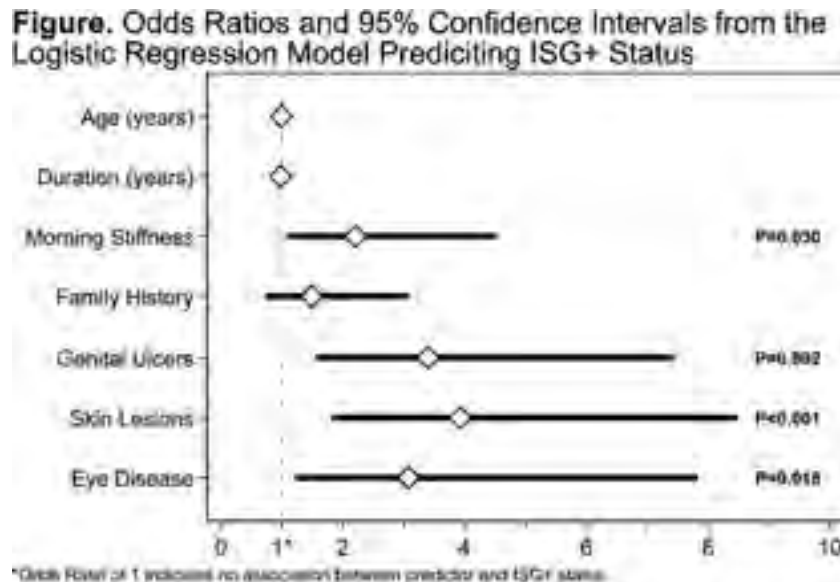
Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Behçet's syndrome (BS) is formally diagnosed using the International Study Group (ISG) criteria, where recurrent oral ulceration and any two other symptoms (recurrent genital ulceration, uveitis, skin lesions and pathergy positivity) are required. The allowance of various symptomology in the ISG criteria has led to the reporting of varied manifestations, and differences in clinical presentation can complicate BS diagnosis, especially in areas where the disease prevalence is low. The purpose of this study was to explore clinical BS symptoms present at initial patient visit that are predictive of ISG criteria diagnosis at follow-up.

Methods: Data from consecutive patients monitored in outpatient clinics in New York and Amsterdam were abstracted. Patients were included if diagnosis at initial visit was "suspected" or "probable BS"; patients given a formal diagnosis by ISG criteria at initial visit or a non-BS diagnosis at initial visit were excluded. Demographic data, including ancestry/ethnicity, clinical symptoms, duration of symptoms and RAPID3 were abstracted from initial visit, with follow-up ISG status (defined as meeting criteria ISG+ vs not meeting criteria ISG-) abstracted from last visit. Univariable logistic regression was used to screen initial visit clinical features and symptoms with follow-up ISG status. All variables that passed screening at $P \leq 0.10$ were included in the final multivariable model².

Results: 189 patients were included: 169 from NY and 20 from Amsterdam. 71 (37.6%) patients were classified as ISG+ with an average of 9.4 years (\pm 8.3 years) of symptoms. Age, gender, ethnicity, duration of symptoms at enrollment, duration of follow up as well as RAPID3 and almost all clinical manifestations at baseline were comparable between ISG+ And ISG- patients.



Presence of morning stiffness, family history of BS, genital ulceration, labial ulceration, skin lesions, eye disease and retinitis were each identified in the univariable model as being possibly associated with prevalence of ISG+. The final multivariable model did not include correlated symptoms (i.e. genital and labial ulceration as well as eye disease and retinitis). In the final model, presence of morning stiffness, genital ulcers, skin lesions, and eye disease were associated with increased odds of ISG+, adjusting for age, symptom duration and family history (**Figure**). Area under the curve was 0.718, indicating acceptable predictive capability of the final model.

Conclusion: Based on our data, over a third of patients with suspected or probable Behçet's developed new manifestations over time that led to classification as ISG+ Behçet's. Despite development of these new manifestations, the presence of morning stiffness, genital ulcers, skin lesions, and eye disease at initial visit were independently associated with significantly higher odds in developing ISG+ Behçet's during followup.

Disclosure: F. Kerstens, None; C. J. Swearingen, None; F. Turkstra, None; Y. Yazici, Celgene Corporation, 2.

Abstract Number: 1811

Efficacy and Safety of Interferon α 2a As an Add-on Treatment for Refractory Behçet's Uveitis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Uveitis is one of the leading causes of morbidity in Behçet's patients which may result in irreversible vision loss. Evidence is accumulating that interferon (IFN) α 2a might be a promising treatment for Behçet's Uveitis (BU) refractory to conventional immunosuppressive agents. The practical value of these studies, however, is limited by their heterogeneity in terms of ethnic and racial backgrounds of the patients, indication, dosage and duration of IFN treatment. In addition, while IFN was commonly given only with corticosteroids, whether and (if so) how it could be used as a

combinatorial agent to conventional immunosuppressants remains to be further elucidated. In this study, we aimed to investigate the efficacy and safety of IFN α 2a as an add-on treatment for refractory BU.

Methods: Twenty-six refractory BU patients who received IFN α 2a treatment in Peking Union Medical College Hospital between February 2015 and October 2017 were retrospectively reviewed. IFN α 2a was used mainly as an add-on treatment for BU patients who underwent relapse under corticosteroids and conventional immunosuppressive agents. The primary outcomes were treatment success rate and changes in ocular relapse rates before and after initiation of IFN α 2a. Disease activity, corticosteroid- and immunosuppressant-sparing effects, as well as side effects were secondary outcomes.

Results: A total of 26 patients (23 males and 3 females) with a mean age of 30.5 ± 8.6 years were included. Eighteen patients (69.2%) were treated with at least 2 immunosuppressive agents before the initiation of IFN α 2a. Treatment success was achieved in 24 patients (92.3%), and the median uveitis relapse rate decreased from 8 (range 2-12) to 0 (range 0-6) per patient-year ($p=0.000008$) during a mean follow-up of 13.6 ± 6.0 months, corticosteroids were lowered in 20 cases (76.9%) and completely withdrawn in 2 (7.7%). In addition, immunosuppressive agents were reduced in number and dosage in 16 (61.5%) and 23 patients (88.5%), respectively, and were completely withdrawn in 5 cases (19.2%). No severe adverse events were observed and serum autoantibodies remained negative during the treatment of IFN α 2a.

Conclusion: IFN α 2a is effective and relatively safe in refractory BU, with significant steroid- and immunosuppressant-sparing effects.

Disclosure: J. Shi, None; C. Zhao, None; J. Zhou, None; J. Liu, None; F. Gao, None; X. Zeng, None; M. Zhang, None; W. Zheng, None.

Abstract Number: 1812

Characterization and Prevalence of Morbus Behçet in Switzerland

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To evaluate the clinical presentation of patients with Morbus Behçet (MB) in a cohort from Switzerland and to calculate the prevalence of MB in Switzerland. To identify differences in diagnostic delay and clinical presentation regarding Swiss or non-Swiss ethnic background.

Methods: MB patients fulfilling the revised International Criteria for Behçet's Disease were recorded in a database. Medical history, clinical and laboratory examinations were performed at inclusion and at regular intervals. Disease severity was calculated with respect to major organ affections and their respective intensity. Prevalence was calculated based on geographic distribution of the patients and the respective population density (data of the federal statistical office).

Results: 52 MB patients were recorded with a mean age of 47.8 years (range 34-57) at inclusion into the database. Male to female distribution was almost equal (54% male, 46% female, ns). Ethnic background was Swiss in 61%, and Turkish, South-East European, Italian, Spanish, Portuguese, Indian, and other in the remaining patients. Median time from onset of first symptoms to diagnosis was 8 years in the entire cohort (range 2.8 – 17) with a tendency to delayed diagnosis in Swiss versus non-Swiss background (9 versus 7 years, respectively). Disease severity reached the highest mean values of 5 points (range 4-7) at a mean age of 36.4 years (range 27-44). Women showed a higher severity score than men (6 versus 5 points, $p=0.02$). All patients were diagnosed at the time of maximum disease intensity with 96% of patients receiving medication at time of inclusion into the database. Most frequent medication were systemic and topic glucocorticoids (80 and 60%, respectively), azathioprine (60%), colchicine (52%), non-steroidal anti-inflammatory drugs (50%), methotrexate (40%), infliximab (30%), adalimumab and cyclosporine (24% each). We calculated a prevalence of 5.8 / 100.000 inhabitants in Switzerland.

Conclusion: MB patients in Switzerland are diagnosed with substantial delay in time and at maximum intensity of disease severity regardless of their ethnic background. The higher disease severity in women might reflect a tendency to delayed diagnosis due to a lack of knowledge of MB manifestations in women. The calculated prevalence of 5.8 is within mid-European range of e.g. 4.9 in Germany and 7.1 in France.

Disclosure: S. Adler, None; R. Villiger, None; L. Buetikofer, None; P. M. Villiger, None.

Abstract Number: 1813

Non-Aphthous Beginning As an Independent Risk Factor for the Course of Behçet's Disease

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Behçet disease (BD) is a multisystem inflammatory disorder characterized by recurrent manifestations in mucocutaneous tissues, eyes, joints, blood vessels, intestines and brain. Since there is no pathognomonic clinical and laboratory finding, diagnosis of BD relies on constellation of a group of manifestations. Recurrent oral aphthous ulcers (ROU) are the commonest manifestation, and widely used classification criteria require ROU in all patients. However, some patients may not have ROU at disease onset, which may cause a challenge and delay in the diagnosis of BD. This study aimed to investigate the disease course and appearance of the manifestations in those patients with or without ROU at the disease onset.

Methods: The study group consisted of 570 patients, who fulfilled the International Study Group (ISG) diagnostic criteria and followed between 1976 and 2016. All patients interviewed personally for their disease course and their medical records were investigated retrospectively. Differences in the disease course were analyzed according to the type of manifestations at the disease onset, sequence of appearance of other manifestations, and their smoking status.

Results: Non-aphthous beginning (NAB) at the disease onset was found in 13.6% of patients, and it was more frequent among smokers compared to non-smokers (18.4% vs 6.8% in males, $p=0.019$; 22.9% vs 9.7% in females, $p=0.038$). Frequency of uveitis (54.1% vs 30.2%, $p<0.001$) and cardiovascular involvement (39.3% vs 24.2%, $p=0.019$) was higher in patients with NAB compared to the patients with ROU at onset. Both NAB group and ROU at onset group fulfilled the ISG diagnostic criteria within similar disease duration (median 48 vs 54 months). However, a 3-month delay in diagnosis was noted after the fulfillment of ISG criteria in patients with ROU at onset despite a 5.3-month delay in NAB group ($p=0.003$). Overall, the most frequent manifestations developing at the onset of BD were ROU, genital ulcers, and uveitis; and the latest manifestation during the course was pulmonary parenchymal involvement. Erythema nodosum-like lesions as initial findings were more frequent in females (11.3% vs 5.1%, $p=0.024$), and deep-vein thrombosis (DVT) was more frequent in males (4.6% vs 0.9%, $p=0.04$). NAB was identified as an independent risk factor for the development of uveitis ($OR=2.06$) and DVT ($OR=2.25$) by logistic regression analysis. None of the BD patients had arterial aneurysms or thrombosis, pulmonary parenchymal, gastrointestinal or genitourinary involvement as initial manifestations.

Conclusion: This retrospective study revealed that 13.6% of BD patients may not have ROU at the disease onset, and those patients with NAB may have different features in their disease course with a tendency for higher risk of uveitis and DVT. Smoking may also have a role in the increased frequency of NAB in BD patients.

Disclosure: M. Aydin, None; B. Artim-Esen, None; M. Inanc, None; L. Ocal, None; A. Gül, None.

Abstract Number: 1814

Interferon-Alpha for the Management of Lower Extremity Deep Vein Thrombosis in Behçet's Syndrome: A Case Series

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Lower extremity deep vein thrombosis (LEDVT) is a disabling complication of Behçet's syndrome (BS). Relapses are frequent and cause permanent disability due to post-thrombotic syndrome (1). The management of LEDVT in Behçet's syndrome (BS) constitutes mainly of azathioprine (AZA) and corticosteroids (CS) as first-line agents (2). Interferon- α (IFN) has been used with good results in the management of eye involvement of BS. However, data regarding its efficacy for vascular involvement has been scarce (3). We aimed to evaluate the efficacy and safety of IFN for LEDVT in BS.

Methods: All BS pts who had a first episode of acute LEDVT since March 2010 are being prospectively followed with a standard protocol in our dedicated BS center. Acute LEDVT is confirmed by Doppler ultrasonography (DUS) at initial diagnosis and serial DUS assessment is performed and also repeated in case of clinical suspicion of relapse. Our standard treatment strategy consists of AZA and CSs in pts with LEDVT. IFN has been used in pts who were refractory or intolerant to this regimen, or who had co-existing eye involvement. Our endpoints for assessing the efficacy of IFN have been recanalization of the index thrombus and prevention of relapses. Recanalization has been assessed in the transverse plane and defined as the ratio of the vein area at maximum compressibility to the non-compressed vein area. Good recanalization was defined as a ratio of at least 50%. Adverse events during IFN use were recorded.

Results: 33 pts with LEDVT (26 M/7 F) were prospectively followed for a mean of 40.7 ± 13.4 mo. Among these IFN was started in 17/33 for mainly vascular involvement. In 2 pts IFN was started at the first episode of LEDVT due to co-existing uveitis. Seven pts were treated with IFN due to LEDVT relapses under AZA. In the remaining 9 pts, the reasons for switching from AZA to IFN were adverse events with AZA (n=2), relapse of superficial thrombophlebitis (n=4), leg ulcers due to severe post-thrombotic syndrome (n=2) and eye involvement (n=1). Among 17 pts treated with IFN during a mean follow-up of 29 ± 20 mo, 3 pts already had good recanalization when starting IFN. In the remaining 14 pts, 13 (93%) had good recanalization under IFN. Two pts (11%) experienced relapses. One of the 2 pts who had a relapse had had poor recanalization despite IFN. In contrast, among the 29 pts treated with AZA with a mean follow-up of 20.2 ± 15.8 mo, only 13 (45%) had good recanalization. 13 (45%) pts experienced relapses under AZA treatment and 9 (69%) of those pts had poor recanalization. Overall we observed 23 LEDVT relapses in 15 pts. Relapse rates were 29%, 37% and 45% at 6, 12 and 24 mo respectively. The only adverse event with IFN causing drug withdrawal was thyroiditis in 1 patient.

Conclusion: The relapse rate for LEDVT in BS is high despite AZA treatment. IFN seems to be a promising agent for preventing LEDVT relapses and achieving good recanalization, an important predictor of relapse. The small number of pts and the lack of a parallel control group are the limitations of this prospective study.

References: 1) Melikoglu M. Arthritis Rheumatol 2014

2) Alibaz-Oner F. Medicine (Baltimore) 2015

3) Calguneri M. Ann Rheum Dis. 2003

Disclosure: Y. Ozguler, None; G. Hatemi, None; F. Cetinkaya, None; K. Tascilar, None; S. Ugurlu, None; E. Seyahi, None; H. Yazici, None; M. Melikoglu, None.

Abstract Number: 1815

Aneurysmal Lesions in Behçet's Disease: A Report of 69 Cases from a Single Center

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis Poster II: Behçet's Disease and IgG4-Related Disease

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To analyze the clinical features of patients with Behçet's disease (BD) complicated with aneurysmal lesions.

Methods: We retrospectively reviewed the clinical data of patients with BD complicated with aneurysmal lesions in Peking Union Medical College Hospital from 1997 to 2017, the treatment and outcome were also studied.

Results: A total of 69 patients (56 male and 13 female) were included. The average period between BD onset and diagnosis of aneurysmal lesion was 5.4 ± 5.5 years. A total of 120 arterial aneurysmal lesions were found, including 29 aneurysms, 68 pseudo aneurysms, 2 dissecting aneurysms, and 21 with uncertain classification. Thirty-four patients (49.3%) presented with two or more aneurysmal lesions. Abdominal aorta was the most common site of involvement (29/120), followed by pulmonary artery (20/120), femoral artery (15/120), thoracic aorta (11/20), coronary artery (10/120) and iliac artery (9/120). Swelling, pain and palpable masses in the affected artery's area are major symptoms. Patients are more intended to have other types of vascular involvement. 48 (69.6%) patients were treated with large dose of glucocorticosteroids (prednisone at 0.8-1.2 mg/kg per day, or equivalent doses) and 7 (10.1%) patients received methylprednisolone pulse therapy. Cyclophosphamide was the most commonly used immunosuppressant (60/69). Biological agents were administered in 5 refractory cases. 40 patients received surgical therapy or interventional procedures. With a mean follow up of 3.8 ± 3.5 years, 48 patients (69.6%) achieved clinical improvements with no newly-onset arterial lesions occurred, while 3 received a second interventional therapy, 5 died (mortality rate 7.2%).

Conclusion: Aneurysmal lesions are severe and life-threatening complications in BD patients. BD patients diagnosed with aneurysmal lesions should be further evaluated to detect possible associated vascular involvements or aneurysmal lesions at other sites. Achieving BD remission and performing surgical or interventional procedures are both important in the treatment of BD patients with aneurysmal lesions.

Disclosure: J. Zhou, None; J. Shi, None; X. Wu, None; J. Liu, None; W. Zheng, None.

Abstract Number: 1816

Five-Year Outcome of Operative and Nonoperative Management of Meniscal Tear in the Presence of Osteoarthritic Changes

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: ACR Abstract: Plenary Session II

Session Type: ACR Plenary Session

Session Time: 11:00AM-12:30PM

Background/Purpose: While recent trials have examined short-term (~ 2 year) outcomes of surgical and nonoperative treatment of meniscal tear in the setting of osteoarthritis there has been little study of longer term outcomes of these treatments.

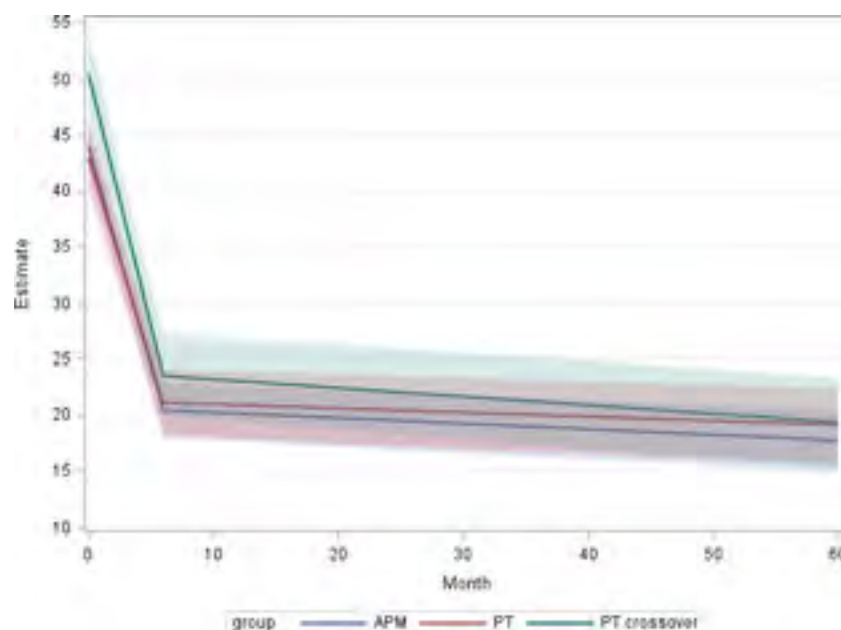


Fig: KOOS Pain (shaded 95% CI) stratified by treatment in piecewise linear model

Methods: We examined 5-year outcomes of subjects in MeTeOR (Clintrials.govNCT00597012), a multicenter randomized trial of physical therapy (PT) vs. PTplus arthroscopic partial meniscectomy (APM) for subjects with knee pain, meniscal tear and OA changes on xray or MRI. The primary outcome for this analysis was the Knee Osteoarthritis and Injury Outcome Score (KOOS) Pain Scale (0-100, 100 worst). Total knee replacement (TKR) was a secondary outcome. To address changes in KOOS Pain over 5 years, we used a piecewise linear mixed model, stratified by treatment group (randomized to and received APM; randomized to and received PT; randomized to PT but received APM during follow-up). The model censored subjects who had TKR and adjusted for age, sex, BMI, and mental health status. We used a pattern mixture model to assess whether the findings were biased by missing data due to TKR or losses to follow-up. We calculated the frequency of TKR over follow-up and used a Cox proportional hazards model to estimate the risk of TKR for treatment groups and KL grades, adjusting for baseline factors.

Results: The 351 subjects had mean age 58; 57% were female. 164 were randomized to and received APM; 109 were randomized to and received PT; 68 were randomized to PT and crossed over to receive APM. 10 subjects were randomized to but did not receive APM and were not analyzed. 66% of subjects completed ≥ 9 of 12 follow-up questionnaires, with similar completion rates across treatment groups. The piece wise linear model (Figure) showed similar pain improvement in the 3 treatment groups, with baseline KOOS Pain scores of 40-50 improving to 20-25 by 6 months and little change between 6 and 60 months. The pattern mixture models demonstrated similar patterns in pain scores as the main analysis, suggesting TKR and other losses to follow up did not bias these findings. 25 participants (7%) had TKR over follow-up. In the Cox model, the hazard of TKR was higher in those treated surgically (randomized to APM or crossed over) than those randomized to and receiving PT (HR 5.0, 95% CI: 1.2, 21.8), and in those with KL-3 radiographs vs. KL0-2 (HR 2.7, 95% CI 1.2, 6.4).

Conclusion: Pain relief was similar across treatment groups, while the few TKR's were more common in those with KL3 and those receiving APM. These data suggest that persons with degenerative meniscal tear generally experience substantial pain relief over 5 years, irrespective of initial treatment. The greater risk of TKR in those treated with APM could reflect selection effects and/or faster progression of OA following surgery than following PT, and merits further study.

Disclosure: J. N. Katz, None; S. Shrestha, None; E. Losina, Samumed, 5,JBJS, 5; L. A. Mandl, None; B. Levy, Arthrex, 2, 5, 7,Smith and Nephew, 2, 5; K. Spindler, None; J. E. Collins, None.

Abstract Number: 1817

MicroRNA-128 Impairs Cartilage Integrity and Deteriorates Osteoarthritis Pathogenesis through Deregulating Chondrocyte Autophagy

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: ACR Abstract: Plenary Session II

Session Type: ACR Plenary Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Autophagy gets rids of unwanted proteins or organelle keeping cells to stay functional upon encountering adverse stresses. While non-coding microRNAs interfere with mRNA targets engaging in tissue metabolism, their actions to chondrocyte autophagy during osteoarthritis (OA) pathogenesis remain elusive. This study is aimed to utilize human knee OA specimens, and chondrocyte-specific microRNA-128 (miR-128) knockout mice to verify the role of miR-128a signaling in chondrocyte autophagy and OA.

Methods: OA articular were harvested from 28 patients with end-stage knee OA who required total knee arthroplasty, non-OA cartilage tissues were collected from 17 participants with a femoral neck fracture. Articular integrity in chondrocyte-specific miR-128 knockout mice (Col2 α 1-cre miR-128(f/f)) and wild-type mice upon destabilized medial meniscus (DMM) surgery or intra-articular injection of collagenase were characterized using equilibrium partitioning ionic contrast- μ CT imaging, histomorphometry, and immunostaining. Autophagosome, autophagic marker expression, and apoptosis of chondrocytes were quantified using RT-PCR, immunofluorescence, and annexin V-probed flow cytometry.

Results: Human OA cartilage showed 60-72% decreases in autophagic markers Atg4, Atg12, p62, and Beclin expression, and weak autophagosome component LC3 immunostaining along with 2.3-fold increases in miR-128 expression. In vitro, forced miR-128 expression significantly inhibited autophagic program, like LC3-II conversion, Atg12 expression, and fluorescent autophagic puncta formation, speeding up apoptosis and cartilage matrix underproduction of chondrocytes. Silencing miR-128 shielded them off the IL-1 β -induced inhibition of survival, autophagy, and chondrogenesis. Of interest, chondrocyte-specific miR-128 knockout mice showed abundant cartilage development within joints, like spacious cartilage morphology, dense matrix synthesis, and intensive chondrocyte proliferation along with strong autophagic reactions. More strikingly, these effects significantly compromised the severity of DMM- or collagenase-mediated cartilage breakdown, synovitis, and osteophyte deposition in affected joints improving walking patterns, body axis, and mobility. Mechanistically, miR-128 hindered chondrocyte autophagy through targeting 3'-untranslated region of Atg12 impeding its mRNA expression as evident from luciferase reporter assays. Epigenetic pathway histone methyltransferase EZH2-mediated trimethyl lysine 27 of histone 3 signaling reciprocally controlled miR-128 transcription in inflamed chondrocytes.

Conclusion: Increased miR-128 signaling correlates with aberrant chondrocyte autophagy in human knee OA. miR-128 is detrimental to autophagy causing apoptosis and matrix loss in chondrocytes. miR-128 deletion promotes cartilage development and wards off excessive articular damage slowing down OA progression. Robust analyses shed light on the inhibitory actions of miR-128 to chondrocyte function and convey a perspective of miR-128 signaling blockade strategy beneficial for cartilage anabolism.

Disclosure: F. S. Wang, None; W. S. Lian, None; Y. C. Sun, None; J. Y. Ko, None; Y. S. Chen, None.

Abstract Number: 1818

Greater BMD Gains with Denosumab Vs Risedronate in Glucocorticoid-Treated Subjects: Results from the Final 24-Month Analysis of a Randomized, Double-Blind, Double-Dummy Study

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Session Date: Monday, October 22, 2018

Session Title: ACR Abstract: Plenary Session II

Session Type: ACR Plenary Session

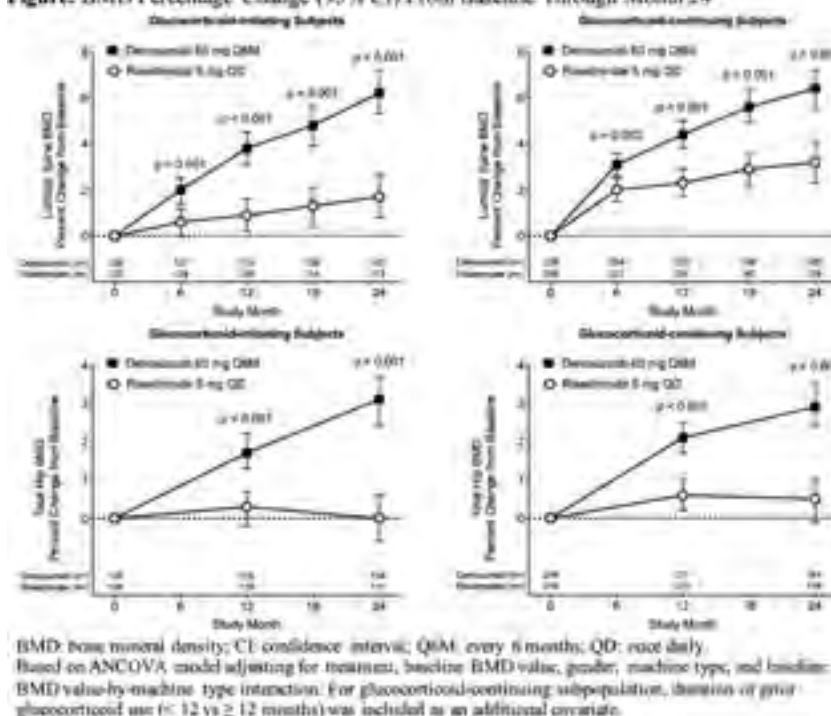
Session Time: 11:00AM-12:30PM

Background/Purpose: Denosumab 60mg subcutaneously every 6 months (Q6M) increased spine and hip BMD significantly more than risedronate 5 mg orally once daily (QD) at 12 months in glucocorticoid-treated subjects (as previously reported¹). This analysis compared the BMD effects of denosumab vs risedronate and further characterized denosumab safety in this population at 24 months.

Methods: This phase 3, randomized, double-blind, double-dummy study enrolled adults ≥ 18 years receiving ≥ 7.5 mg daily prednisone (or equivalent) for < 3 months (glucocorticoid-initiating subpopulation) or ≥ 3 months (glucocorticoid-continuing subpopulation). All subjects < 50 years had to have a history of osteoporotic fracture. Glucocorticoid-continuing subjects ≥ 50 years had to have a lumbar spine, total hip, or femoral neck BMD T-score ≤ -2.0 , or ≤ -1.0 and a history of fracture. Subjects were randomized 1:1 to denosumab 60 mg subcutaneously Q6M or risedronate 5 mg orally QD for 24 months. This analysis assessed denosumab superiority over risedronate for percentage change from baseline in lumbar spine and total hip BMD at 24 months.

Results: Of 795 randomized subjects, 590 (74.2%) completed the 24-month study (glucocorticoid-initiating: 109/145 denosumab, 117/145 risedronate; glucocorticoid-continuing: 186/253 denosumab, 178/252 risedronate). Denosumab was superior to risedronate for increases from baseline in lumbar spine and total hip BMD at all time points assessed through 24 months in each subpopulation (Figure). Adverse events, serious adverse events (including infection), and fractures were similar between groups.

Figure. BMD Percentage Change (95% CI) From Baseline Through Month 24



Conclusion: Denosumab was superior to risedronate for increases in spine and hip BMD through 24 months. The overall safety profile was similar between groups. Denosumab may offer a valuable osteoporosis treatment option for patients receiving glucocorticoids.

Reference:

1. Saag KG, et al. Denosumab versus risedronate in glucocorticoid-induced osteoporosis: a multicentre, randomised, double-blind, active-controlled, double-dummy, non-inferiority study. *Lancet Diabetes Endocrinol.* 2018: [https://doi.org/10.1016/s2213-8587\(1018\)30075-30075](https://doi.org/10.1016/s2213-8587(1018)30075-30075).

Disclosure: K. Saag, Amgen Inc., 2, 5, Merck & Co., 2, 5, Lilly, 5, Radius, 5; N. Pannacciulli, Amgen Inc., 1, 3; P. Geusens, Amgen Inc., 2, 5, Lilly, 2, 5, Abbott, 2, Bristol-Myers Squibb, 2, Celgene Corporation, 2, Janssen, 2, Merck & Co., 2, Novartis, 2, Pfizer, Inc., 2, Roche, 2, UCB, 2, Will Pharma, 2; J. D. Adachi, Amgen Inc., 2, 5, 8, McMaster University, 3; O. D. Messina, None; J. Morales-Torres, Amgen Inc., 5, 8; R. Emkey, Amgen Inc., 5, 8; P. W. Butler, Amgen Inc., 1, 3; X. Yin, Amgen Inc., 1, 3; W. F. Lems, Amgen Inc., 5, 8, Merck & Co., 5, 8, Eli Lilly, 5, 8.

Abstract Number: 1819

MUC5B promoter Variant rs35705950 Is a Risk Factor for Rheumatoid Arthritis – Interstitial Lung Disease

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: ACR Abstract: Plenary Session II

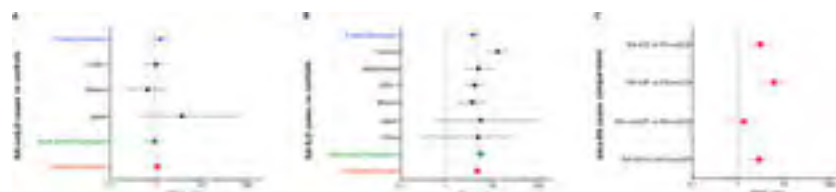
Session Type: ACR Plenary Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Given phenotypic similarities between rheumatoid arthritis-associated interstitial lung disease (RA-ILD) and idiopathic pulmonary fibrosis (IPF), we hypothesized that the strongest risk factor for the development of IPF, the gain-of-function *MUC5B* promoter variant rs35705950, would also contribute to the risk of ILD in patients with RA.

Methods: Using a discovery population and multi-ethnic validation case series, we tested the association of the *MUC5B* promoter variant in RA-ILD (N=620), RA without ILD (N=614), and unaffected controls (N=5448).

Results: The discovery population revealed an association of the *MUC5B* promoter variant minor allele with RA-ILD when compared to unaffected controls ($OR_{adj}=3.8$ 95%CI [2.8-5.2]; $P=9.7 \times 10^{-17}$). Similar to the discovery population, the *MUC5B* promoter variant was significantly over-represented among the RA-ILD cases in the multi-ethnic study case series when compared to unaffected controls ($OR_{adj}=5.595$ 95%CI [4.2-7.2]; $P=4.7 \times 10^{-35}$), and when the discovery population and the multi-ethnic case series were combined ($OR_{combined}=4.795$ 95%CI [3.9-5.8]; $P=1.3 \times 10^{-49}$). Additionally, the *MUC5B* promoter variant was found to increase the risk of ILD among patients with RA ($OR_{combined}=3.195$ 95%CI [1.8-5.4]; $P=7.4 \times 10^{-5}$), however, no statistical association with the *MUC5B* promoter variant was observed for RA alone. The association of the *MUC5B* promoter variant with RA-ILD increased significantly when restricted to usual interstitial pneumonia (UIP) pattern by high-resolution computed tomography ($OR_{combined}=6.1$ 95%CI [2.9-13.1]; $P=2.5 \times 10^{-6}$). Given our results, we decided to explore 12 other common variants previously reported to be associated with IPF (*LLRC34* rs6793295, *FAM13A* rs2609255,



TERT rs2736100, *EHMT2* rs7887, *DSP* rs2076295, rs4727443, *OBFC1* rs11191865, *TOLLIP* rs5743890 and rs111521887, *ATP11A* rs1278769, *IVDr*s2034650 and *DPP9* rs12610495). In this exploratory analyze, we found that 2 other IPF risk variants, *TOLLIP*rs5743890 and *IVD* rs2034650, were also preliminarily associated with RA-ILD (OR_{combined}=2.1 95%CI [1.1-4.1]; P=0.02 and OR_{combined}=0.5995%CI[0.4-0.9]; P=0.01, respectively). These findings should be replicated to further conclude to their role in the RA-ILD genetic background.

Conclusion: Our findings demonstrate that the *MUC5B* promoter variant rs35705950 is a risk factor for RA-ILD specifically associated with radiologic evidence of the UIP pattern. Furthermore, other IPF related common variants may also participate in RA-ILD genetic susceptibility

Disclosure: P. A. Juge, None; J. S. Lee, None; E. Ebstein, None; H. Furukawa, None; E. Dobrinskikh, None; S. Gazal, None; C. Kannengiesser, None; S. Ottaviani, None; S. Oka, None; S. Tohma, None; N. Tsuchiya, None; J. Rojas-Serrano, None; M. I. González-Pérez, None; M. Mejía, None; I. Buendía-Roldán, None; R. Falfan-Valencia, None; E. Ambrocio-Ortiz, None; E. Manali, None; S. A. Papiris, None; T. Karageorgas, None; D. Boumpas, None; K. Antoniou, None; C. H. M. van Moorsel, None; J. van der Vis, None; Y. A. de Man, None; J. C. Grutters, None; Y. Wang, None; R. Borie, None; L. Wemeau-Stervinou, None; B. Wallaert, None; R. M. Flipo, None; H. Nunes, None; D. Valeyre, None; N. Saidenberg, None; M. C. Boissier, None; S. Adam-Marchand, None; A. Frazier, None; P. Richette, None; Y. Allanore, None; J. Sibilia, None; C. Dromer, None; C. Richez, None; T. Schaefferbeke, None; H. Lioté, None; G. Thabut, None; N. Nathan, None; S. Amselem, None; M. Soubrier, None; V. Cottin, None; A. Clément, None; K. D. Deane, None; A. D. Walts, None; T. Fingerlin, None; A. Fischer, None; J. H. Ryu, None; E. L. Matteson, None; T. B. Niewold, None; D. Assayag, None; A. Gross, None; P. Wolters, None; M. I. Schwartz, None; V. M. Holers, None; J. J. Solomon, None; T. Doyle, None; I. O. Rosas, None; C. Blauwendraat, None; M. A. Nalls, None; M. P. Debray, None; C. Boileau, None; B. Crestani, None; D. A. Schwartz, None; P. Dieude, None.

Abstract Number: 1820

Myeloablative Autologous Hematopoietic Stem Cell Transplantation for Severe Scleroderma: Long-Term Outcomes 6-11 Years after Entry on a Randomized Study Comparing Transplantation and Cyclophosphamide

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: ACR Abstract: Plenary Session II

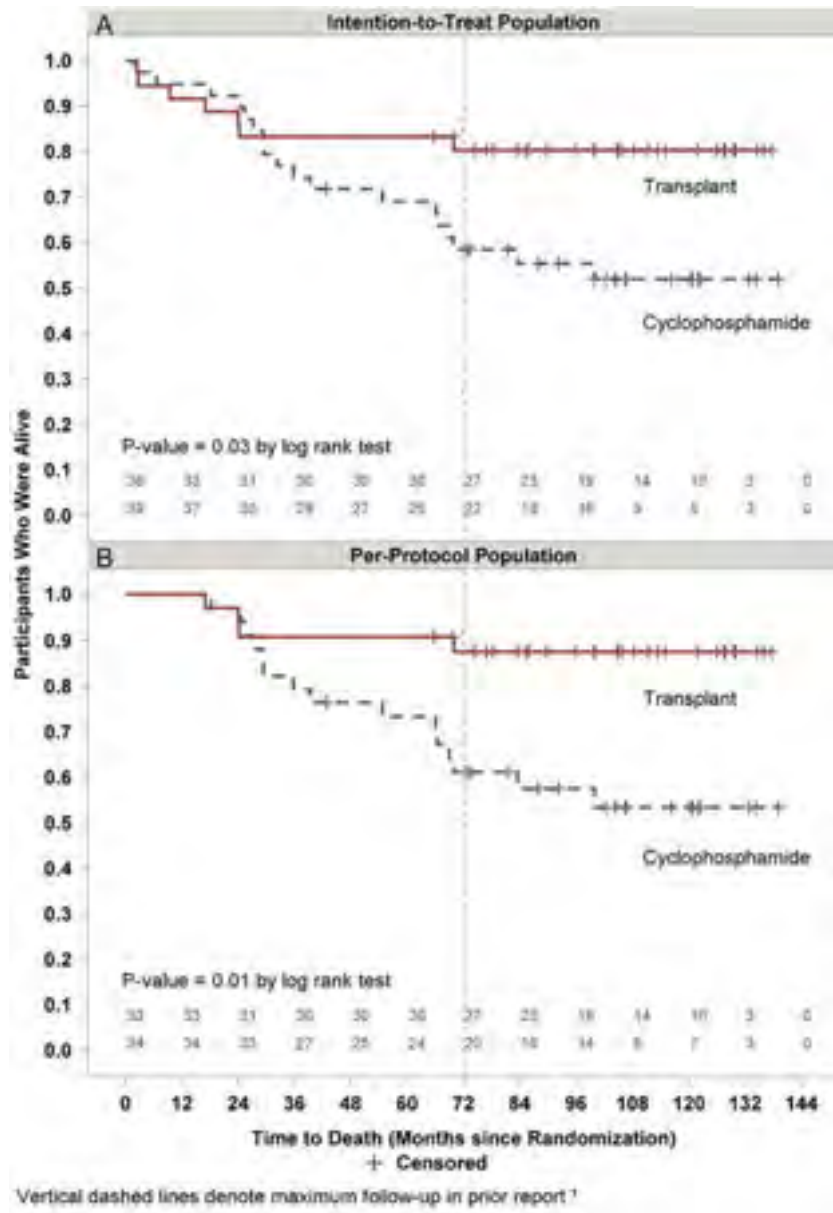
Session Type: ACR Plenary Session

Session Time: 11:00AM-12:30PM

Background/Purpose: The Scleroderma:Cyclophosphamide or Transplantation (SCOT) trial demonstrated that for adults with severe scleroderma (ACR 1995 criteria) and internal organ involvement, myeloablative CD34+ selected autologous hematopoietic stem cell transplantation(HSCT) led to significantly improved clinical outcomes compared to 12 monthly infusions of cyclophosphamide (CYC)¹. Participants were randomized between 2006 and 2011 and followed to 72 months. We report here survivor status, late effects and outcomes 6-11 years after randomization on the SCOT trial.

Methods: We conducted scripted telephone interviews with survivors and searched public death records in mid-2017. Endpoints included time to death or organ failure (see table). Current health status, physical functioning, toxicities, DMARD use and quality of life measures were solicited, and the current HAQ disability index and SF-36 health surveys compared to last assessments. Events are listed as occurring before or after prior reporting¹.

Results: Of 75 randomized SCOT participants, 7HSCT and 18 CYC recipients have died. For HSCT, no new deaths were identified in the follow-up study compared to 4 new deaths for CYC (table A). Overall survival is depicted in the intention-to-treat (figure A) and per-protocol (received HSCT or >= 9 doses CYC) (figure B) populations. At 11 years



after randomization, Kaplan Meier estimates of overall survival were 80% vs 52% and 88% vs 53% (HSCT vs CYC; Figure A and B, $p=0.03$ and 0.01 , respectively).

Among the 25 HSCT and 18 CYC follow-up participants, physical functioning and weight gain were improved following HSCT (table B). Organ failure developed in 2 HSCT (cardiac ablation and pacer) and 6 CYC recipients (3 heart failure, 2 oxygen use and lung transplant). No subsequent malignant or myelodysplastic events were observed. Performance status was significantly better after HSCT while employment rates and measures of physical and social functioning trended higher but were not statistically different. DMARDS were being taken by 2 HSCT and 7 CYC recipients, with 92% and 61% of the two respective treatment groups remaining DMARDS-free ($p=0.01$).

Conclusion: This follow-up analysis demonstrates that the clinical benefits of HSCT previously reported¹ are durable 6-11 years after randomization. Survival and functional status were significantly better with HSCT, and continuing control of scleroderma was demonstrated by 92% of transplant survivors remaining free of DMARDS and disease.

Reference:

¹Sullivan KM, et al. N Engl J Med 2018; 378:35-47.

Disclosure: K. Sullivan, None; A. Pinckney, None; E. Goldmuntz, None; B. Welch, None; D. Khanna, None; R. W. Simms, None; S. Kafaja, None; G. Georges, None; J. Storek, None; M. E. Csuka, None; R. Nash, None; D. E. Furst, None; L. Crofford, None; P. McSweeney, None; M. D. Mayes, None; L. Keyes-Elstein, None.

A. Identification of study participants			
	Transgender	Cisgender	Total
Randomized NCOT Participants	86	88	
Declining NCOT	7	34	
Death identified in follow-up study	0	6	
Lost to Follow-up	4 (11%)	3 (5%)	
Refused Follow-up Study	0	5 (5%)	
Completed Follow-up Study	23 (27%)	18 (40%)	

B. Characteristics of Participants at Time of Follow-up Study (Excludes 2017 Study)			
	Transgender	Cisgender	p-value
Total Number Follow-up Participants	25	18	
Any Organ Failure	0	0	0.98
Respiratory Failure	0	1	
Cardiac Failure	2	3	
Renal Failure	0	1	
Development of HIV at 180d	0	0	0.98
Taking OATART	2	7	0.02
17- Versus 18- Year Gender	1	4	0.67
Weight Gain - mean (SD)	77 (12)	84 (13)	0.68
BMI - mean (SD)	26.8 (3.4)	24.8 (3.4)	0.27
17- Versus 18- Year HIV	0	0	0.98
Hemoglobin A1c (HbA1c)	33 (93%)	33 (93%)	
Alcohol use (10/10)	3 (12%)	7 (39%)	0.14
17- Versus 18- Year HIV	0	0	0.98
Employed, total (n/total)	0 (0/0)	0 (0/0)	
Unemployed, total (n/total)	13 (52%)	12 (67%)	
Unemployed, total (n/total)	13 (52%)	12 (67%)	
17- Versus 18- Year HIV	0	0	0.98
Hemoglobin A1c (HbA1c)	33 (93%)	33 (93%)	
Alcohol use (10/10)	3 (12%)	7 (39%)	0.14
17- Versus 18- Year HIV	0	0	0.98
Hemoglobin A1c (HbA1c)	33 (93%)	33 (93%)	
Alcohol use (10/10)	3 (12%)	7 (39%)	0.14
17- Versus 18- Year HIV	0	0	0.98
Hemoglobin A1c (HbA1c)	33 (93%)	33 (93%)	
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Alcohol use (10/10)	3 (12%)	7 (39%)	0.14
17- Vers			

^a Events reported in the study publication.

F Organ failure: Lung, supplemental oxygen, lung transplant, renal, dialysis, renal transplant; Cardiac, cardiac ablation, pacemaker, heart rate heart resuscitation Percutaneous Coronary Intervention, heart bypass, heart transplantation

Scenes on the H&O frequency index range from 0 to 3, with higher scores indicating more displays.

Abbreviations: BMI, body mass index; JAK2RFL, disease-modifying anti-rheumatic drug; IL-6, interleukin 6.

Post Number: 1821

Filgotinib, an Oral, Selective Janus Kinase 1 Inhibitor, Is Effective in Psoriatic Arthritis Patients with an Inadequate Response to Conventional Disease-Modifying Anti-Rheumatic Drugs: Results from a Randomized, Placebo-Controlled, Phase 2 Study

Methods: This was a 16-week, randomized, placebo (PBO)-controlled, double-blind, multicenter, Phase 2 study. Eligible pts had PsA (meeting CASPAR criteria) for ≥ 12 weeks, active arthritis (≥ 5 tender and ≥ 5 swollen joints), prior/current plaque psoriasis, IR to ≥ 1 cDMARD and prior exposure to ≤ 1 TNF-inhibitor. Pts were allowed to continue cDMARDs during the trial.

Pts were randomized 1:1 to FIL 200 mg once daily (qd) or PBO. Disease activity was assessed at screening, baseline and weeks 1, 2, 4, 8, 12 and 16. The primary endpoint was the percentage of pts achieving a 20% American College of Rheumatology (ACR20) response at week 16. Secondary endpoints included the proportion of pts achieving ACR50/70, improvement from baseline in HAQ-DI, Minimal Disease Activity (MDA), 75% reduction in the Psoriasis Area and Severity Index (PASI75), Leeds Enthesitis Index (LEI) and Leeds Dactylitis Index (LDI).

Results: Of 131 pts randomized, 124 pts (94.7%) completed the study. Demographics and baseline disease characteristics were similar between the 2 groups: mean age 50 years, 50.4% female, mean duration of PsA 7 years, mean HAQ-DI 1.40, mean PASI 11.3 (in pts with $\geq 3\%$ body surface area (BSA)).

For FIL and PBO pts respectively, ACR20 response at week 16 was achieved by 80.0% and 33.3% ($p < 0.0001$), MDA was achieved by 23.1% and 9.1% ($p = 0.0212$), HAQ-DI change from baseline was -0.57 and -0.28 ($p = 0.0009$) and PASI75 was achieved by 45.2% and 15.0% ($p = 0.0034$).

Week 16, %, NRI	Filgotinib 200mg qd	Placebo	p-value
All randomized and exposed pts	N=65	N=66	
ACR20	80.0	33.3	<0.0001
ACR50	47.7	15.2	<0.0001
ACR70	23.1	6.1	0.0037
HAQ-DI improvement from baseline ≥ 0.35	65.1	41.9	0.0085
MDA	23.1	9.1	0.0212
Pts with baseline BSA $\geq 3\%$	N=42	N=40	
PASI75	45.2	15.0	0.0034
Pts with baseline LEI > 0	N=33	N=43	
LEI resolution (LEI = 0)	51.5	25.6	0.0089
Pts with baseline LDI > 0	N=19	N=27	
LDI resolution (LDI = 0)	73.7	65.5	0.6310

NRI: non-responder imputation

Adverse event (AE) rates (FIL: 56.9%; PBO: 59.1%), infection rates (FIL: 21.5%; PBO: 21.2%) and discontinuation rates (FIL: 7.7%; PBO: 3%) were similar between the groups. There were 2 serious AEs; 1 hip fracture (PBO) and 1 pneumonia (FIL), which was the only serious infection and the only fatal outcome in the study. There were no malignancies/lymphomas, venous thromboembolic events or opportunistic infections (including tuberculosis). There was 1 case of Herpes zoster, confined to a single dermatome (FIL). One patient permanently discontinued the FIL treatment for safety reason (endometrial hypertrophy). Safety laboratory results over 16 weeks in the FIL group included increased hemoglobin (+6 g/L), decreased platelets (-16 GI/L), stable NK cell counts, and increased total cholesterol (+0.45 mmol/L), mainly driven by increased HDL (+0.37 mmol/L) with a 15% decrease in LDL/HDL ratio vs. baseline.

Conclusion: FIL showed superior efficacy versus PBO in pts with PsA, by ACR20 response and by secondary outcomes. No new safety signals were identified.

Disclosure: **P. J. Mease**, AbbVie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, Sun, UCB, 2, AbbVie, Amgen, BMS, Celgene, Galapagos, Janssen, Lilly, Novartis, Pfizer, Sun, UCB, 5, AbbVie, Amgen, BMS, Celgene, Genentech, Janssen, Novartis, Pfizer, UCB, 8; **D. D. Gladman**, Abbvie, Amgen, BMS, Celgene, Galapagos, Gilead, Janssen, Eli Lilly, Novartis, Pfizer, UCB, 5, Abbvie, Amgen, Celgene, Eli Lilly, Novartis, Pfizer, UCB, 2; **F. van Den Bosch**, AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly and Co., Janssen, Merck, Novartis, Pfizer, Sanofi, UCB, 5, 8, AbbVie, Janssen, Merck, UCB, 2; **A. Rychlewska-Hanczewska**, None; **A. Dudek**, None; **C. Tasset**, Galapagos NV, 1, 3; **L. Meuleners**, Galapagos, 3; **P. Harrison**, Galapagos NV, 3; **R. Besuyen**, Galapagos, 3, 5; **R. Kunder**, Gilead Science, Inc, 1, 3; **N. Mozaffarian**, Gilead Science Inc, 1, 3; **L. C. Coates**, Abbvie, Celgene, Novartis, Pfizer, 2, Abbvie, Amgen, BMS, Celgene, Galapagos, Janssen, Lilly, MSD, Novartis, Pfizer, Prothena, Sun Pharma, UCB, 5, Abbvie, Celgene, Janssen, Lilly, Novartis, UCB, 8; **P. Helliwell**, AbbVie, Janssen, 2, AbbVie, Amgen, Janssen, Novartis, Pfizer Inc, ucb, 9.

Abstract Number: 1822

RNA-Sequencing of Mouse and Human Synovial Fibroblasts Reveals Fibroblast Subset-Specific Responses to Inflammation

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Animal Models

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: In rheumatoid arthritis (RA), synovial fibroblasts secrete inflammatory cytokines, degrade cartilage and mediate bone destruction. We have previously identified three synovial fibroblast subsets with distinct transcriptomic profiles. However, whether synovial fibroblast subsets exhibit differential effector functions during inflammatory arthritis remains unclear. Here, we sought to determine if fibroblast subsets display unique or shared effector functions using a K/BxN serum transfer arthritis model in mice.

Methods: Synovial tissue was isolated from bilateral knees of normal, non-arthritic mice (n = 25) or mice after K/BxN serum transfer (n = 35). Following enzymatic digestion, synovial fibroblasts were divided into three fibroblast subsets: CD90+, CD90-CAD11+, and CD90-CAD11-. In parallel, we isolated human synovial fibroblast subsets (CD90+C34+, CD90+CD34-, and CD90-) from RA and OA (n=10) synovial tissue. Transcriptomic profiles were generated using 1000 cells from each fibroblast subset by Smart-Seq2. Synovial leukocyte (CD45+) infiltration for each tissue sample was determined by flow cytometry to identify inflamed samples (>45% leukocytes).

Results:

1. **CD90+ fibroblast subset corresponds to sublining fibroblasts in mice.** Principal component analysis using the top 3000 most variable genes identified distinct transcriptomic profiles among mouse fibroblast subsets sorted based on expression of CD90 and CAD11. Consistent with synovial lining fibroblasts, lining markers *PRG4* and *FN1* were significantly upregulated in CD90- fibroblasts ($p < 9.1 \times 10^{-5}$ and $p < 3.84 \times 10^{-6}$, respectively). In contrast, sublining markers *CD34* and *MEAP5* were highly expressed by CD90+ fibroblasts. PCA of human synovial fibroblast subsets separates lining from sublining fibroblast subsets, suggesting conserved subsets between human and mouse.
2. **Lining and sublining fibroblasts exhibit markedly distinct responses in the setting of serum transfer arthritis.** We identified 999, 537, and 122 significantly upregulated genes ($P < 0.0088$) in CD90-CAD11+ lining fibroblasts, CD90-CAD11- lining fibroblasts, and sublining fibroblasts, respectively. While there were many genes that were significantly up-regulated by both CD90-CAD11+ and CD90-CAD11- subsets (61), there were only a few that were up-regulated by both CD90+ and CD90-CAD11+ (9) as well as CD90+ and CD90-CAD11- (2). Remarkably, no genes were significantly up-regulated by all three fibroblast subsets, suggesting lining and sublining fibroblasts exhibit unique responses to serum transfer induced arthritis.

Conclusion: Transcriptomic profiling of mouse and human synovial fibroblasts reveals distinct lining and sublining fibroblast subsets. During inflammatory arthritis, synovial fibroblasts exhibit distinct subset-specific responses to inflammation, suggesting they play different pathologic roles in arthritis.

Disclosure: A. Gao, None; K. Wei, None; I. Korsunsky, None; M. Brenner, Roche, 2.

Abstract Number: 1823

Loss of Synovial Tissue Resident Macrophages Permits Monocyte to Macrophage Differentiation and Inflammation in Hupo Mice

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¹Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, ²Medicine/Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, ³Medicine/pulmonary, Northwestern University Feinberg School of Medicine, Chicago, IL, ⁴Medicine/Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, ⁵Department of Medicine Division of Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Animal Models

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: We established a mouse model (HUPO) by deletion of Flip in CD11c+ cells that spontaneously develops erosive inflammatory arthritis resembling rheumatoid arthritis (RA). Since CD11c is expressed in F4/80(hi) macrophages (MΦs) and since MΦs and MΦ-derived cytokines are important in RA and are increased in the joints of HUPO mice, we examined the phenotype and function of MΦs in the joints of HUPO mice.

Methods: HUPO arthritis was evaluated by clinical score. Five subsets of synovial tissue MΦs were defined by flow cytometry: three F4/80(int) (FI) subsets included Ly6C+MHCII- (FI1), Ly6C+MHCII+ (FI2) and Ly6C-MHCII+ (FI3);

and 2 F4/80^{hi} (FH) subsets were further defined as MHCII⁻ (FH1) and MHCII⁺ (FH2). These synovial MΦ populations, as well as classical (CM) and non-classical (NCM) monocytes from HUPO mice with arthritis and littermates controls, were sorted by flow cytometry and processed for RNAseq. The gene expression profiles and pathways were analyzed by Genee software and GOrilla database. The origin of monocytes and macrophages from monocyte bone marrow progenitors was performed by BrdU labeling, bone marrow chimeras and treatment with clodronate liposomes (CL).

Results: The total number of synovial MΦs was increased in HUPO mice, especially the FI2, FI3 and FH2 subsets, while there was a significant reduction of FH1 MΦs. Further, the % of FH1 MΦs, which are the tissue resident MΦs (TRM) of the synovial tissue in control mice, but not other MΦ subsets, inversely correlated with clinical arthritis and granulocyte accumulation. Bone marrow chimera experiments confirmed that arthritis developed after the FH1 population decreased. Fifty-60% of CMs and FI1 and FI2 MΦs were BrdU⁺ within 24 hours, similar to the controls. In HUPO mice FI3, FH1 and FH2 MΦs became BrdU⁺ on days 3 and 5, consistent with their origin from monocytes. Examination of cells 30 minutes after BrdU injection and following treatment with CL, suggested that at least a portion of the FI1 population derived directly from the bone marrow monocytes in HUPO mice, rather than the circulation. Further, the reduction of the FI2 and FI3 populations following CL is consistent with their origin from circulating monocytes. HUPO FI3 MΦs demonstrated the most distinct gene expression pattern from controls, suggested that FI3 subset may represent a turning point in synovial MΦ homeostasis. Comparing FH subsets between HUPO and control mice, the differentially expressed genes (DEGs) down regulated were those regulating intracellular signaling, wound healing and lipid homeostasis. In contrast, the DEGs up regulated related to pro-inflammatory signaling, endogenous TLR ligands, angiogenesis and joint destruction in HUPO mice.

Conclusion: HUPO arthritis develops following the reduction of FH1 TRMs, which inversely correlate with inflammation. In HUPO mice with arthritis, in contrast to controls, bone marrow monocytes, at least in part, have direct access to the joint. These observations suggest a potential new paradigm in which a reduction of TRM may contribute to the pathogenesis of RA.

Disclosure: Q. Q. Huang, None; R. E. Doyle, None; A. Misharin, None; S. Y. Chen, None; D. R. Winter, None; R. M. Pope, None.

Abstract Number: 1824

Osteoclast Derived-Autotaxin, a Distinguishing Factor for Inflammatory Bone Loss

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Animal Models

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Rheumatoid arthritis (RA) patients in sustained clinical remission or low disease activity may continue to accrue periarticular bone erosions despite control of inflammation. Osteoclasts are responsible for bone erosions and systemic bone loss in RA. However current anti-resorptive drugs are suboptimal in RA because they could lead to issues by shutting down physiologic remodeling in long term treatment supporting the need for alternative therapies. Autotaxin (ATX) is a secreted lysophospholipase D converting lysophosphatidylcholine into lysophosphatidic acid. ATX is upregulated in the synovial liquid of patients with RA and contributes to synovial inflammation. However, ATX role in bone resorption is totally unknown.

Methods: ATX was targeted by conditional genetic ablation in osteoclasts (Δ ATX^{Ctsk} mice) and by treatment with anti-ATX drug (BMP22). Arthritic and erosive diseases were studied in arthritis models using human tumor necrosis factor transgenic (*hTNF*^{+/+}) mice and K/BxN serum-treated mice. Systemic bone loss was in addition analysed after ovariectomy (OVX) and in the Lipopolysaccharide (LPS)-induced inflammation model. Joint inflammation and osteoclasts were assessed by histology and bone mass and bone erosion by microcomputed tomography (micro-CT). ATX expression was assessed using RT-qPCR and Western blot. The role of ATX on osteoclastogenesis and osteoclast activity were analysed by murine and human assays.

Results: Here, we found that ATX was up regulated during the course of osteoclastogenesis and LPS or TNF applied to mature osteoclasts further enhanced ATX expression. *In vitro* osteoclast-derived ATX was necessary for bone resorption activity that was blocked by pharmacological ATX inhibitors (PF-8380, BMP22). LPS injections induced a 43 % decrease

of the trabecular BV/TV in control mice but had no impact on bone in $\Delta\text{ATX}^{\text{Ctsk}}$ mice. The challenge with K/BxN serum transfer which induces severe arthritis revealed that $\Delta\text{ATX}^{\text{Ctsk}}$ mice were protected from systemic bone loss, and displayed almost no bone erosion. Intriguingly, in a non-inflammatory bone loss condition as observed in mice after OVX, $\Delta\text{ATX}^{\text{Ctsk}}$ and control mice revealed similar impact on bone 4 weeks post-OVX with a 30% decrease in BV/TV. As supported by an absence of bone phenotype at steady state on $\Delta\text{ATX}^{\text{Ctsk}}$ mice, these results indicate that osteoclast-derived ATX might be dispensable for osteoclast function under non-inflammatory conditions. By using a pharmacological approach on a second inflammatory mouse model exploiting hTNF mice, we found that albeit inefficient on synovitis, BMP22 induced a 28% increase in BV/TV and a 50% decrease in the extent of bone erosion (BS/BV).

Conclusion: These results establish that ATX is a new factor produced by osteoclasts that controls inflammation-induced bone loss without interfering with osteoclast function in non-inflammatory conditions. ATX might be a promising therapeutic target for the prevention of bone erosion occurrence in RA.

Disclosure: O. Peyruchaud, None; S. Flammier, None; F. Bourguillault, None; F. Duboeuf, None; G. Tigyi, None; I. Machuca-Gayet, None; F. Coury, Pfizer, Inc.; Abbvie; Novartis; MSD; 5.

Abstract Number: 1825

Rheumatoid Arthritis Associated Haploinsufficiency in PTPN2 Enhances Severity of IL-17 Mediated Autoimmune Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Animal Models

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Genetic polymorphisms at the *PTPN2* locus, which encodes the tyrosine phosphatase TC-PTP, cause reduced gene expression and are linked to rheumatoid arthritis (RA). *PTPN2* is an important regulator of cytokine signaling, however it remains unknown by which mechanism polymorphisms in *PTPN2* promotes RA. We model the effect of *PTPN2* haplo insufficiency in the SKG mouse, a spontaneous CD4⁺ T-cell-driven model of autoimmune arthritis.

Methods: Development of spontaneous and/or mannan-induced arthritis was evaluated in SKG mice. CD4⁺ SKG T-cells were transferred to RAG2^{-/-} mice. Clinical scoring of arthritis was followed by histological assessment. Flow cytometry was used to assess T-cell populations. Mann-Whitney or un-paired T tests were used for statistical differences.

Results: In SKG mice, haplo insufficiency of *PTPN2* caused increased severity of both spontaneous ($P=0.003$) and mannan-induced ($P=0.003$) arthritis. Furthermore, increased susceptibility to arthritis could be transferred to RAG2^{-/-} mice by *PTPN2*^{+/-} CD4⁺ T-cells ($P=0.011$ vs *PTPN2*^{+/+} CD4⁺ T-cells). Next we generated a novel C57BL/6 mouse carrying the SKG mutation and the H2^d haplotype (B6.H2^d.SKG), which showed similar arthritis development as BALB/c SKG mice. B6.H2^d.SKG carrying T-cell specific haplo insufficiency of *PTPN2* (Lck-Cre⁺.*PTPN2* floxed/wild type) developed increased severity of arthritis ($P=0.002$) when compared to WT mice. Further investigation revealed an increased accumulation of Th17 cells in arthritic ankles ($P=0.007$) of *PTPN2*^{+/-} mice. Importantly, neutralization of IL-6 and IL-17 equalized development of arthritis between *PTPN2*^{+/-} and *PTPN2*^{+/+} SKG mice, indicating that enhanced arthritis in *PTPN2* haplo insufficient mice were mediated through the IL-6/IL-17 pathway. Mechanistically this was supported by an increased sensitivity to IL-6 induced activation of STAT3 in *PTPN2*^{+/-} CD4 T-cells.

Conclusion: Haplo insufficiency of human RA-associated *PTPN2* mediates autoimmune arthritis in mice by promoting expansion of pathogenic Th17 cells. We also validate our newly generated B6.H2^d. SKG model as a novel powerful tool for mechanistic studies of RA pathogenesis.

Disclosure: M. N. D. Svensson, None; K. M. Doody, None; S. Yang, None; D. J. Wu, None; C. Sacchetti, None; I. Aubry, None; P. Mydel, None; M. Kronenberg, None; M. L. Tremblay, None; N. Bottini, Roche, 2, Eli Lilly and Co., 2, Kyowa Kirin Pharmaceutical Research, Inc., 2.

Abstract Number: 1826

From Cancer to Autoimmunity : A New Model of Rheumatoid Arthritis Emerging from a Constitutional Genetic Approach Used in Low Penetrance Cancers

Geraldine Falgarone^{1,2}, Morad El Bouchtaoui³, Marcio Do Cruzeiro⁴, Christophe Leboeuf^{5,6,7}, Irmeline Loisel-Ferreira^{5,6}, Carèle Frédonie⁷, Chrystophe Ferreira⁸, Rachida Ait El Far⁵, Marc Espié⁹, Bruno Cassinat¹⁰, Jean-Jacques Kiladjian¹¹, Jean-Paul Feugas^{12,13}, Anne Janin^{5,6,14} and Guilhem Bousquet^{2,5,15}, ¹HUPSSD, Avicenne Hospital, Rheumatology, APHP, Bobigny, France, ²Paris 13 University, SMBH, Bobigny, France, ³INSERM UMR-S 1165, PARIS, France, ⁴Plateforme de Recombinaison Homologue, Institut Cochin, INSERM U1016, Paris, France, ⁵INSERM UMR-S 1165, Paris, France, ⁶Université Paris Diderot, Paris, France, ⁷INSERM U944, Paris, France, ⁸Plateforme ANIMA5, Université Paris Descartes, Paris, France, ⁹Centre des Maladies du Sein, APHP, Hôpital Saint-Louis, Paris, France, ¹⁰Laboratoire de Biologie Cellulaire, APHP, Hôpital Saint-Louis, Paris, France, ¹¹Centre d'Investigation Clinique, APHP, Hôpital Saint-Louis, Paris, France, ¹²INSERM U1137, Paris, France, ¹³Département de Biologie, Université Franche-Comté, Besançon, France, ¹⁴Service de Pathologie, APHP, Hôpital Saint-Louis, Paris, France, ¹⁵Service d'Oncologie médicale, APHP, Hôpital Avicenne, Bobigny, France

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Animal Models

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: High-speed technologies for genome sequencing have completely changed the study of disease genetics, but with limited knowledge of the functional value of most genetic changes. Using an innovative individual approach by studying tissue samples from a young woman with an unusual association of breast cancer, polycythemia vera and rheumatoid arthritis (RA), we identified hypothetic mutations involved in her cancer and autoimmune diseases then used a mice model to validate the implication of these mutations both in cancer and autoimmune diseases. We here present a new model of autoimmune disruption displaying RA features for studying pathophysiological pathways of articular dysimmunity.

Methods: Using whole genome analyses, we identified one cMET point mutation common to the breast cancer cells and to the CD34+ bone-marrow progenitors of the patient. We established a Knock-in transgenic mice using CRISPR-Cas9 technology and obtained *MET*-mutated transgenic mice.

Results: *MET*-mutated transgenic mice show a cancer skin disease and myeloproliferative disorders. Moreover they develop a 90% of penetrance arthritis, with autoantibodies (both ACPA, and auto-SSA and anti-SSB) and histological signs of Sjögren disease. Using ELISA, serum levels of anti-SSA and anti-SSB murine antibodies are significantly higher in the mutated mouse than in the wild-type mouse. Histological signs of synovial hyperplasia of a distal joint are observed in the mutated mouse concomitantly with high serum levels of ACPA. Transgenic mice also display signs of thyroiditis with lymphocyte infiltrate between abnormal thyroid follicles. Using an anti-MET drug, we were able to modulate the biological signs of auto-immunity and myeloproliferation, and the occurrence of skin cancers. We finally demonstrated for the first time a genetic link between myeloproliferative disorders, rheumatoid arthritis, and cancers.

Conclusion: Our study opens a large field of application in the domain of constitutional genetics but above all describes a new model for studying autoimmunity in mice through a non destructive RA model with ACPA. This non-destructive RA model is of major interest to decipher pathways that could lead from articular autoreactivity to autoimmunity. Furthermore, anti-immune-regulatory checkpoint molecules are now currently used in metastatic cancers and enlighten the close relation between cancers and autoimmune diseases because new autoimmune disorders can rise out in anti-PD1 treated cancer patients. This new arthritis model observed because of a cancer gene mutation could be an original approach to explore the autoimmune disruption in the context of cancer disease.

GF and MEB are first co-authors. AF et GB are co-authors

Disclosure

G. Falgarone, None; M. El Bouchtaoui, None; M. Do Cruzeiro, None; C. Leboeuf, None; I. Loisel-Ferreira, None; C. Frédonie, None; C. Ferreira, None; R. Ait El Far, None; M. Espié, None; B. Cassinat, None; J. J. Kiladjian, None; J. P. Feugeas, None; A. Janin, None; G. Bousquet, None.

Abstract Number: 1827

Genetic Ablation of Phd Finger Protein 19 Gene Promotes Autoimmune Arthritis in Mice

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Understanding the genetic and epigenetic background of rheumatoid arthritis (RA) is complex since multiple genes and environmental factors are involved. By conducting congenic mapping in mice and genome-wide association studies (GWAS) in humans a number of arthritis risk loci were explored. One of the arthritis loci was identified on human chromosome 9 that is syntenic with mouse chromosome 2. Transcriptome analyses identified the PHD finger protein 19 (*PHF19*) gene in this chromosomal region that showed differential expression in arthritic samples. PHF19 is a component of a multiprotein complex, which is responsible of heritable silencing of genes. To understand the molecular function of *PHF19* in autoimmune arthritis, Phf19^{-/-} KO animals were generated and investigated in a murine model of RA.

Methods: Phf19 gene was ablated from the mouse genome by conventional KO methodology. Human proteoglycan (PG)-induced arthritis (PGIA) model was used to investigate Phf19 function in arthritis. Since PGIA is MHC-controlled autoimmune disease, speed congenic approach was employed to put the ablated Phf19 region into full BALB/c genetic background. PGIA susceptibility was tested in Phf19^{-/-} KO and wild type BALB/c mice. Flow cytometry was used to identify the affected cell types in bone marrow and secondary lymphoid organs. Phf19 ablation provoked gene expression profile change was explored using gene expression microarray platforms. Quantitative reverse transcription PCR was employed to verify microarray data.

Results: Phf19-ablated adult mice had normal body weight, and no visible skeletal malformation was observed. Genetic deletion of *Phf19* did not affect fertility and embryogenesis and normal pups of normal litter size was born from Phf19^{-/-} KO animals. However, Phf19^{-/-} KO female mice were more susceptible for PGIA. We detected altered B cell development in bone marrow and secondary lymphoid organs. The genetic ablation triggered gene expression profile changes are under investigation.

Conclusion: Our studies provide the first experimental evidence that Phf19, an epigenetic factor, is directly involved in arthritis pathogenesis and can be considered as a risk factor in autoimmune arthritis. The exact role of Phf19 in arthritis must be explored by investigating the associated gene regulatory network, which might reveal some additional druggable genes.

Disclosure: T. T. Glant, None; T. Ocskó, None; D. M. Tóth, None; A. Markovics, None; T. A. Rauch, None.

Abstract Number: 1828

Gut-Joint T Cell Trafficking in a Model of Bacteria-Driven Murine IBD-Spa

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Significant bacterial dysbiosis occurs in individuals with IBD and SpA, and individuals with SpA have evidence of circulating intestinal-derived cells, lending credence to the gut-joint hypothesis. In order to understand the mechanistic linkage between microbiota, mucosal immune development, and subsequent pathogenic targeting of joints in SpA, we utilized the TNF^{ΔARE/+} murine model of ileitis and arthritis, which spontaneously develop around 6 weeks of age due to increased TNF-α mRNA stability. We hypothesized that bacteria are required to generate disease, and that gut-joint trafficking could be observed in this model.

Methods: The microbiome was evaluated in 4-8 week old mice by sequencing the V3V4 region of bacterial 16S rRNA in fecal samples from TNF^{ΔARE/+} mice and littermate controls. Then microbiota were depleted by administration of broad-spectrum antibiotics (ampicillin, neomycin, metronidazole, and vancomycin) in the drinking water from 4-8 weeks of age. Assessment of ileitis and arthritis was done by histology. Cells from intestinal tissue and Achilles' entheses were evaluated by flow cytometry. To demonstrate trafficking of cells from the intestine to the joints, we utilized transgenic KikGR mice, which contain a transgene for a photoconvertible green-to-red fluorescent protein, that were crossed with the TNF^{ΔARE/+} line. Endoscopy-guided violet light allowed photoconversion of the distal colon in vivo. Trafficking of photoconverted lymphocytes was determined by flow cytometry.

Results: TNF^{ΔARE/+} mice become increasingly dysbiotic as disease develops between 4 and 8 weeks of age. Ileitis and arthritis were dependent upon an intact microbiota as mice treated with antibiotics had significantly decreased histologic damage. At 4 weeks of age, TNF^{ΔARE/+} mice had significantly expanded colon TCRβ+ and TCRγδ+ intraepithelial lymphocytes (IELs, T cells residing in the epithelium) compared to littermate controls, that decreased to control numbers by 8 weeks of age. These IELs produced significant TNF-α as compared to littermate controls. At 8 weeks of age, both TCRβ+ and TCRγδ+ T cells were significantly expanded in the Achilles entheses of TNF^{ΔARE/+} mice compared to littermate controls. Finally, we observed trafficking of TCRγδ+ IELs from the colon to the joint in both TNF^{ΔARE/+} mice and littermate controls within 72 hours and sustained up to 1 week after photoconversion.

Conclusion: These data demonstrate a key role of bacterial dysbiosis in the development of both ileitis and arthritis as mice depleted of bacteria through the administration of antibiotics had significantly reduced tissue damage. Furthermore, we observe an expansion of colon IELs prior to disease onset that return to control numbers at the time when T cells are expanding in the inflamed joints. TCRγδ+ IELs specifically were identified to traffic from the colon to the joint. These data suggest a working hypothesis that bacteria educate T cells in the gut that traffic to the joint where they may initiate inflammation. Studies are now directed at understanding the specific mechanisms underlying this hypothesis.

Disclosure: E. Norman, None; A. Lefferts, None; K. A. Kuhn, None.

Abstract Number: 1829

Perturbations of the Gut Fungal and Bacterial Microbiome with Biologic Therapy in Spondyloarthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The microbiome serves a number of important functions, including modulation of the immune system and protection from pathogenic microorganisms¹. Many autoimmune diseases have been associated with intestinal microbial dysbiosis¹. Recent studies have also demonstrated that microbiota can affect the lifetime, bioavailability and efficacy of drugs². Conversely, even drugs designed to specifically target human cells have been associated with changes in microbial composition³. To date, most research has focused on bacterial microorganisms and little is known about the role that fungal microorganisms (the mycobiome) play, including their interactions with bacteria. In this study, we characterized the ecological effects of biologic therapies on the intestinal mycobiome.

Methods: Fecal samples were collected from SpA patients pre- and post-treatment with either tumor necrosis factor inhibitors (TNFi; n=15) or secukinumab (n=14), an anti-IL-17A monoclonal antibody (IL-17i). Subjects treated with TNFi were naïve to biologic therapy, whereas those treated with secukinumab previously failed or had incomplete response to TNFi. Samples underwent DNA extraction, amplification, and gene sequencing of the ITS1 region conserved in fungi. In parallel, gene sequencing of the 16S rRNA gene region conserved in bacteria was also performed. Sequences were analyzed with R and Quantitative Insights into Microbial Ecology (QIIME).

Results: ITS fungal data revealed that, on average, subjects treated with TNFi and IL-17i did not have major differences in overall microbial alpha or beta diversity pre- and post-treatment. However, there were dramatic shifts in the relative abundance of specific taxa, such as *Candida albicans*, which were more prominent in the IL-17i cohort compared to the TNFi cohort (p=0.04). The IL-17i cohort also demonstrated similar changes in certain 16S bacterial taxa, including Clostridia (p=0.02) and Clostridiales (p=0.02).

Conclusion: We characterized, for the first time, the effects of two biologic therapies on human intestinal fungal and bacterial microbiota composition. Treatment with biologics, particularly IL-17i, leads to a gut microbial dysbiosis characterized by significant changes in abundance of *C. albicans* and Clostridia in a subgroup of SpA patients. This is in line with the known increased risk of candidiasis seen with IL-17i, and may at least partially explain the potential link between IL-17 blockade, intestinal dysbiosis, and the subclinical and clinical gut inflammation observed in some patients treated with these molecules. Further studies to understand the downstream effects of these perturbations may allow for the development of precision medicine approaches in PsA and SpA.

References:

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3. Maier L, Pruteanu M, Kuhn M, Zeller G, Telzerow A, Anderson EE, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature*. 2018;555(7698):623-8.

Disclosure: J. Manasson, None; L. Yang, None; G. E. Solomon, None; S. M. Reddy, Novartis, Pfizer Inc., 9; P. V. Girija, None; A. L. Neimann, None; L. N. Segal, None; C. Ubeda, None; J. C. Clemente, None; J. U. Scher, Janssen, 5, Novartis, 5, UCB, Inc., 5, AbbVie Inc., 5.

Abstract Number: 1830

Role of BMP2 in Enthesal Bone Formation in Inflammatory Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Spondyloarthritis (SpA) is common, with a prevalence of ~1% in the United States. Patients with SpA suffer from pain and disability due to inflammation and ossification at enthesial sites, the mechanism of which remains unclear. BMP2 has been reported to be upregulated in mesenchymal stem cells derived from AS patients and has been implicated as an essential factor in bone formation and fracture repair in other settings, but the specific role of BMP2 in enthesal bone formation in SpA is not known.

Methods: Bone forms at enthesial sites in SpA through the process of endochondral bone formation, in which cartilage is laid down and subsequently remodeled into bone. We used a murine model of inflammatory arthritis, the antigen-induced arthritis (AIA) model, in which enthesial bone formation occurs at predictable sites around the knee, to determine the essential role of BMP2 in enthesal bone formation. By crossing the BMP2^{fl/fl} mouse with limb mesenchymal cell-specific (Prx1) Cre transgenic mice, we generated conditional knockout mice (KO) in which BMP2 expression is deleted in limbs, and littermate control mice (WT). We induced AIA in knee joints at 8 and 14 weeks of age.

Results: At 8 and 14 weeks, both KO and WT mice showed similar degrees of inflammation in arthritic knees. Histologic analysis of 8 week-old WT mice revealed endochondral bone formation with cartilage development by day 9, angiogenesis (CD-31 expressing cells), TRAP-positive osteoclasts and bone at entheses by day 15. In contrast, KO mice developed only

cartilage, but not bone, at entheses. Furthermore, angiogenesis and osteoclasts were absent at entheses in KO mice. To determine whether enthesal bone formation was simply delayed in KO mice, we prolonged AIA until day 36. Bone formation, angiogenesis and osteoclasts were still not observed at entheses of KO mice. AIA induced in 14 week-old WT mice showed enthesal bone formation by day 15. In contrast, KO mice did not develop cartilage or bone at the enthesis. Enthesal cells and bone marrow stromal cells (BMSCs) were then harvested from 14 week-old WT and KO mice. After 3 weeks in osteoblast differentiation media, enthesal cells and BMSCs from WT mice differentiated and mineralized, but cells from KO mice did not. To determine the molecular mechanism, we dissected entheses from 14 week-old WT and KO mice with AIA (day 9) using laser capture microscopy. Gene expression was analyzed using Affymetrix whole transcriptome arrays. The Wnt antagonist, Sfrp4 (known to inhibit Wnt signaling and osteoblast proliferation), was upregulated but chondroadherin (known to mediate chondrocyte adhesion) and Cxcl5 (known to promote bone metastasis) were downregulated in KO entheses. qPCR analysis revealed that Sfrp4 mRNA was also upregulated in BMSCs from KO mice.

Conclusion: These results demonstrate that in this model, mesenchymal cell-derived BMP2 is essential for enthesal bone formation in the setting of inflammation. A role for Wnt signaling is likely in this process. These results have implications for the inhibition of enthesal bone formation in SpA.

Disclosure: Y. Maeda, None; J. Karman, AbbVie Inc., 1, 3; E. M. Gravallese, AbbVie Inc., 2, 3, 7.

Abstract Number: 1831

Intestinal Inflammatory Regulation in Murine and Human Spondyloarthropathy Requires High-Affinity T Cell Receptor-Zeta Chain-Associated Protein (ZAP)70-Mediated Runt-Related Transcription Factor (Runx)3 Activity

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Loss of function *RUNX3* variants are associated with ankylosing spondylitis (AS) risk but the mechanism is unknown. Disturbances in immune regulation, intestinal microbial dysbiosis and subclinical intestinal inflammation characterize AS, and flares in intestinal inflammation are associated with arthritis severity. Intestinal regulatory T cells (Foxp3⁺ Treg) limit inflammation, and TCRαβ+CD4+CD8⁺ cytotoxic T cells (CD4CTL) control intracellular bacteria at epithelial interfaces. CD4CTL develop in response to antigen presented by retinoic acid (RA)-producing dendritic cells. TGF-β and RA enhance CD4⁺ T cell Runx3 and suppress ThPOK for CD4CTL trans-differentiation. ZAP70^{W163C} mutant (SKG) mice have reduced ZAP70 signaling, spondyloarthritis and ileitis. We investigated ZAP70 in Runx3 signaling and CD4CTL development.

Methods: We isolated ileal intraepithelial and lamina propria lymphocytes and analysed Treg and CD4CTL. CD4CTL were generated in vitro by culture of OVA-specific DO11.10 and SKG.DO11.10 T cells with OVA peptide, TGF-β and RA, and in vivo by transfer of OVA-specific T cells to immune-deficient mice fed OVA. Differentially-expressed genes from terminal ileum of 8 naïve SKG and 3 BALB/c mice were assessed by RNA microarray (Illumina). We compared enrichment of Runx3-regulated genes uncovered by ChIP-seq and transcriptome analysis in SKG and BALB/c mice. T cells isolated from human colon, ileum and blood of 5 AS patients and 5 healthy controls (HC) were analyzed.

Results: CD4CTL and Runx3 expression were reduced, while Foxp3⁺ pTreg were increased SKG relative to BALB/c ileum. Tissue resident memory T cell-associated genes e.g. *Cd3e*, *Ilgae*, *Ccl5*, and *Ilgb7*, and antigen processing and presentation genes e.g. *H2-ab1*, *H2-Dma*, *H2-ea*, *Tap1*, and *H2-q8*, were downregulated in SKG relative to BALB/c ileum. 36% of differentially-expressed genes are Runx3-regulated genes, previously identified by ChIP-Seq. The SKG ZAP70-mediated TCR loss of function prevented effective intestinal CD4CTL but not pTreg differentiation in context of TGF-β

and RA in vitro and in vivo, resulting in Runx3 and ThPOK dysregulation. CD4CTL and their expression of perforin, IFN- γ , NFAT and Runx3 were decreased in intestine and blood of AS patients compared with HC.

Conclusion: High-affinity TCR-ZAP70 signaling is required for RUNX3-mediated intestinal CD4CTL differentiation and the balance with Foxp3⁺ Treg. Runx3 deficiency links intestinal pathology in mice and humans through CD4CTL. Since deficiency of CD4CTL cells with cytotoxic function should limit host control of intracellular pathobiont species, reduced TCR-ZAP70-RUNX3 is a key pathogenetic pathway in spondylo arthropathy.

Disclosure: Z. A. Bhuyan, None; M. A. Rahman, None; M. Maradana, None; A. Mehdi, None; G. Guggino, None; P. Leo, None; L. Rehaume, None; M. Brown, None; F. Ciccia, None; R. Thomas, Janssen, 2, 5, Dendright Pty Ltd, 6, Merck & Co., 2, 5.

Abstract Number: 1832

Proteomic and Transcriptomic Profiling of Cells in Ankylosing Spondylitis Patients Identifies a Novel, Synovial-Resident CD8⁺ T Cell

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Current data suggests that immune events in the gut may impact on joint inflammation in ankylosing spondylitis (AS) but what directs cells in the gut-joint axis is undefined. For this reason, we examined the expression of trafficking molecules on immune cells using Cytometry by Time-of-flight (CyTOF), and the expression of differentially regulated genes using bulk RNA-sequencing (RNA-seq). Our objectives are to utilize proteomic and transcriptomic analysis to 1) assess differential expression patterns of trafficking molecules between patients and controls, 2) generate joint-specific cellular signatures, and 3) obtain genetic profiles of noteworthy cell subpopulations.

Methods: Male subjects under 40 years of age fulfilling the mNY criteria were recruited. The following cells were surface stained using a 36-marker antibody panel: (i) Peripheral blood mononuclear cells (PBMC) from AS patients, and healthy controls; (ii) Synovial fluid mononuclear cells (SFMC) from AS and rheumatoid arthritis (RA) patients. After acquiring on CyTOF2, data were analysed using SPADE, viSNE and FlowJo programs for data visualization and statistical analysis. Additionally, bulk RNA-seq was performed on CD8⁺ T cell subpopulations from the synovial fluid. Pathway analysis of differentially expressed genes was conducted using the ClueGo application from the Cytoscape program.

Results: Mature CD8⁺ T cells were increased in frequency in AS SFMC, with significant changes in their phenotype: β 7⁺, CD103⁺, CD29⁺ and CD49a⁺ integrin expression was increased in CD8⁺CD45RO⁺ cells in AS SFMC vs paired AS PBMC (mean 7.51% vs 0.87%, $p=0.0035$). A similar comparison in RA SFMC vs paired RA PBMC revealed less dramatic changes (mean 3.11% vs 0.33%, $p=0.0056$). RNA-seq data analysis of CD103⁺CD49a⁺ cells in AS SFMC revealed elevated GZMA, GZMB, PRF1 and IL-10 cytokines, in addition to a cytotoxicity regulation profile. Signaling molecules, such as TNFAIP3 and TIAF1, and transcription factors, such as RUNX1 and IRF4, were elevated as well.

Conclusion: We identified a novel integrin-expressing mature CD8⁺ T cell subset (CD49a⁺CD103⁺ β 7⁺CD29⁺) that appears to be more prevalent in AS SF than RA SF. These cells possess a dual proinflammatory and regulatory profile, suggesting these roles may be microenvironment-dependent. Further experiments are ongoing to provide evidence of gut-joint trafficking capabilities using murine models. Examinations of patient gut and synovial tissue biopsies, as well as murine gut and joint tissue are essential to determine the arthritogenic potential of these cells. A global analysis encompassing transcriptional and proteomic changes is mandated to provide crucial insights into the inflammatory relationship between the gut and joint, which in turn would be important to design innovative immunotherapy for AS.

Disclosure: Z. Qaiyum, None; E. Gracey, None; Y. Yao, None; R. D. Inman, None.

The V δ 2 Subset of $\gamma\delta$ T-Cells Are Present at Healthy Human Enthesis and Have Transcriptional and Functional Characteristics Consistent with a Capacity for IL-17A Production in Response to IL-23

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Recent mouse studies of SpA pathogenesis have suggested that $\gamma\delta$ T-cells accumulate at enthesal regions in an IL-23 overexpression model and that these cells are responsible for the majority of local IL-17A production. Moreover a specific subset of $\gamma\delta$ T-cells (V δ 6) has been implicated in murine enthesitis and bone regeneration. This study aimed to examine the local distribution of $\gamma\delta$ T-cell subsets in normal human entheses and identify which are most likely to participate in IL-23/17 axis driven inflammation.

Methods: Human enthesal soft tissue (EST) and peri-enthesal bone (PEB) was harvested from normal spinous process in patients undergoing elective spinal orthopaedic procedures. Interspinous EST was dissected from PEB and enzymatically digested. Cell sorting was used to isolate $\gamma\delta$ T-cells expressing the V δ 1 or V δ 2 isoforms of the TCR receptor $\gamma\delta$ T-cells expressing other V δ isoforms were also collected. Following isolation RNA was purified and analysed by TaqMan array. Healthy enthesal tissue and peripheral blood collected from patients with either PsA or AS was stimulated with phorbol 12-myristate 13-acetate (PMA)/ionomycin and intracellular IL-17A production was measured in T-cell subsets.

Results: Healthy EST contained a similar proportion of $\gamma\delta$ subsets, (37%V δ 1 and 57%V δ 2) as was observed in peripheral blood (28%V δ 1 and 63%V δ 2), PEB contained a higher proportion of the V δ 1 subset and a lower proportion of the V δ 2 subset (50% and 39% respectively). The V δ 2 subset expressed a high relative abundance of IL-23/17 pathway associated transcripts including IL-23R, RORC and CCR6 they also expressed high relative abundance of TGF β 1 transcript, a cytokine associated with immunomodulation and tissue residency. Following PMA stimulation IL-17A was robustly detected in CD4⁺ T-cells and in $\gamma\delta$ T-cells was detected predominantly in the V δ 2 subset although some signal was also observed in V δ 1 cells.

Conclusion: The V δ 2 subset of $\gamma\delta$ T-cells are present in enthesal tissues, their transcriptional profile and functional characteristics are consistent with IL-23 responsive IL-17 producing cells and closely resemble enthesitis associated murine V δ 6 $\gamma\delta$ T-cells. This data suggests that in humans the V δ 2 subset of $\gamma\delta$ T-cells are most likely to participate in SpA pathogenesis.

Disclosure: R. Cuthbert, None; E. M. Fragkakis, None; C. Bridgewood, None; R. Dunsmuir, None; A. Watad, None; A. Rao, None; A. Khan, None; H. Marzo-Ortega, Janssen, 2, Abbvie, Celgene, Janssen, Lilly, Novartis, UCB, 5, Abbvie, Celgene, Lilly, Novartis, UCB, 6; D. Newton, None; D. McGonagle, Novartis, Janssen, Pfizer, AbbVie, 2, Novartis, Janssen, Pfizer, AbbVie, 8.

Sleep Apnea and Fibromyalgia: Data from the Cleveland Clinic Fibromyalgia Registry

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Up to 50% of sleep apnea (SA) patients have fibromyalgia (FM). Little is known about the prevalence and associations of SA and FM, and the impact of continuous positive airway pressure (CPAP) use in patients with FM.

Methods: Consecutive patients diagnosed with FM by clinical and/or ACR 2010 criteria, were enrolled and classified according to reported history of SA and CPAP use. Sleep characteristics and FM measures of severity, depression and function were compared between groups.

Results: Characteristics of 667 FM patients were: age 45.9 ± 37.6 , 89.5% female, 79.9% white, BMI 30 ± 8.7 , Fibromyalgia impact questionnaire score 63.5 ± 20.1 , Epworth Sleepiness Scale 9.5 ± 5.9 , hours of sleep 6.1 ± 2.0 , 85.9% reported unrefreshing sleep, 65% trouble falling asleep, 73.7% trouble staying asleep. Prior diagnosis of SA was reported by 154 (21%) FM patients, of which 50 patients (32.4%) used CPAP, for 6.4 ± 1.4 days/week. Comparisons between FM with SA and without, and between CPAP users and non users are presented in Table 1 and Table 2.

Table 1 Comparison between FM patients with and without a prior history of sleep apnea.

	No prior diagnosis of sleep apnea N 513	Prior diagnosis of sleep apnea N 154	p
Age	45.4 ± 11.1	48.12 ± 11.8	0.746
BMI	29 ± 7.7	33.6 ± 10.5	0.000
Hours of sleep/night	6.0 ± 1.9	6.3 ± 2.2	0.559
ESS	9.1 ± 5.9	10.5 ± 5.7	0.014
Patient health questionnaire -9 (PHQ-9)	12.2 ± 6.1	11 ± 6.94	0.006
Fibromyalgia impact questionnaire (FIQ)	63.6 ± 18.5	64.3 ± 23.7	0.587
Health assessment questionnaire -disability index (HAQ-DI)	1.0 ± 1.46	1.2 ± 1.1	0.411
Widespread pain index (WPI)	12.1 ± 9.0	12.4 ± 4.4	0.905
Symptom severity scale (SS)	8.8 ± 2.3	9.3 ± 2.4	0.021
Fibromyalgianess scale (PSD)	21.1 ± 10.0	22.1 ± 5.4	0.559
Unrefreshing sleep	89.5% N 459	86.4% N 133	0.000
Trouble falling asleep	67.6% N 347	65.6% N 101	0.000
Trouble staying asleep	78% N 400	75.3% N 116	0.000

Table 2 Comparison between FM patient with sleep apnea who used CPAP regularly with those who did not use CPAP

	Not using CPAP N 104	Using CPAP N 50	p
Age	47.6 ± 13.0	49.5 ± 9.4	0.7
BMI	32.0 ± 10.2	36.3 ± 11.0	0.000
Hours of sleep/night	6.2 ± 2.4	6.4 ± 2.0	0.491
ESS	9.6 ± 7.0	12.0 ± 5.9	0.006
PHQ9	14.4 ± 7.0	13.1 ± 6.8	0.013
FIQ	63.5 ± 23.9	65.9 ± 24.0	0.405
HAQDI	1.2 ± 1.3	1.2 ± 1.1	0.487
WPI	12.0 ± 4.5	12.8 ± 4.3	0.812
SS	9.1 ± 2.5	9.4 ± 2.0	0.408
PSD	21.5 ± 5.5	22.5 ± 5.3	0.684
Unrefreshing sleep	88.7% N 86	84.7% N 42	0.259
Trouble falling asleep	71.5% N 69	56% N 29	0.215
Trouble staying asleep	82.5% N 80	60% N 30	0.033

Conclusion: Quality of sleep was poor in FM; SA was reported by 1/5 FM patients, who had higher BMI, SS, and were more depressed; 1/3rd of FM SA patients used CPAP; compared to those who did not, CPAP users were more obese, had higher daytime sleepiness, were less depressed and had less trouble staying asleep. Longitudinal studies are needed to determine the true prevalence of sleep apnea in FM, confirm and understand the directionality of these observations.

Abstract Number: 1835

Diagnosis of Fibromyalgia: Disagreement between Fibromyalgia Criteria and Clinician-Based Fibromyalgia Diagnosis in a University Clinic

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

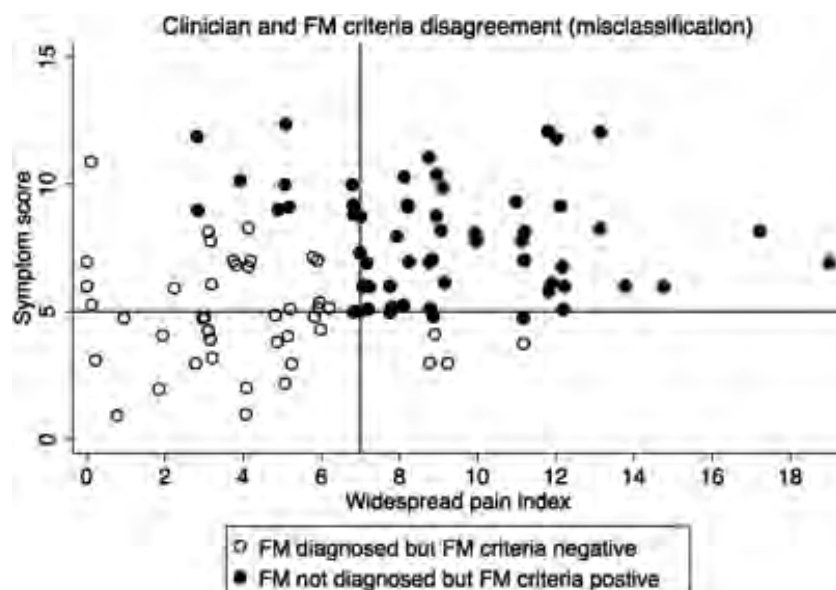
Background/Purpose: Recent studies have suggested that fibromyalgia is inaccurately diagnosed in the community, and that approximately 75% of persons reporting a physician diagnosis of fibromyalgia would not satisfy published criteria. To investigate possible misclassification, we studied fibromyalgia diagnosis by comparing expert physician diagnosis with published criteria.

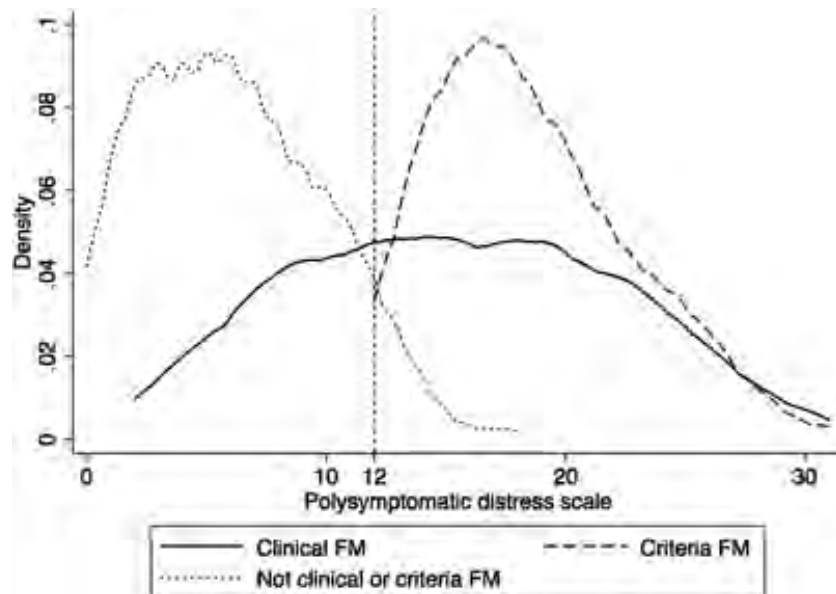
Methods: In a university rheumatology clinic, 497 consecutive unselected patients completed the Multi-dimensional Health Assessment Questionnaire (MDHAQ) as well as the 2010 American College of Rheumatology (ACR) preliminary diagnostic criteria for fibromyalgia questionnaire (FCQ) modified for self-administration during their ordinary medical visit. Patients were evaluated and diagnosed by university rheumatology staff who did not review the FCQ.

Results: Of the 497 patients, 121 (24.3%) satisfied fibromyalgia criteria while 104 (20.9%) received a clinician ICD diagnosis of fibromyalgia. The overall agreement between clinicians and criteria was 79.2%. However, agreement beyond chance was only fair: kappa 0.41 [probabilistic category 0.20 -0.40]. Physicians failed to identify 60 (49.6%) of criteria positive patients and incorrectly identified 43 (11.4%) of criteria negative patients as shown in Figure 1.

As shown in Figure 2, clinician diagnosed case varied widely in PSD scores, while criteria positive cases and criteria and clinician negative cases had appropriate PSD scores.

Because there were approximately 4 times as many clinical fibromyalgia negative patients, the total counts of positive and negative misclassifications (60 vs. 43) were closer than the percentages suggested. In a subset of 88 patients with rheumatoid arthritis, the kappa statistic was 0.32, indicating slight to fair agreement [0.00-0.20]. Universally, higher PSD scores and criteria based diagnosis were associated with more abnormal MDHAQ clinical scores. Women, patients with





more symptoms but fewer pain areas, and those with lower polysymptomatic distress (PSD) scores were more likely to receive a clinician's diagnosis than to satisfy fibromyalgia criteria.

Conclusion: There is considerable disagreement between clinical diagnosis as recorded in ICD codes and criteria determined diagnosis of fibromyalgia, confirming diagnostic problems found in the community and calling into question ICD based fibromyalgia studies. Fibromyalgia criteria were easy to use, but problems regarding clinician bias, meaning of a fibromyalgia diagnosis, and the validity of physician diagnosis were substantial.

Disclosure: S. Srinivasan, None; J. Schmukler, None; S. Jamal, None; I. Castrejón, None; K. A. Gibson, None; W. Häuser, None; T. Pincus, None; F. Wolfe, None.

Abstract Number: 1836

Fibromyalgia Diagnosis and Biased Assessment: Sex, Prevalence, Biology and Bias

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

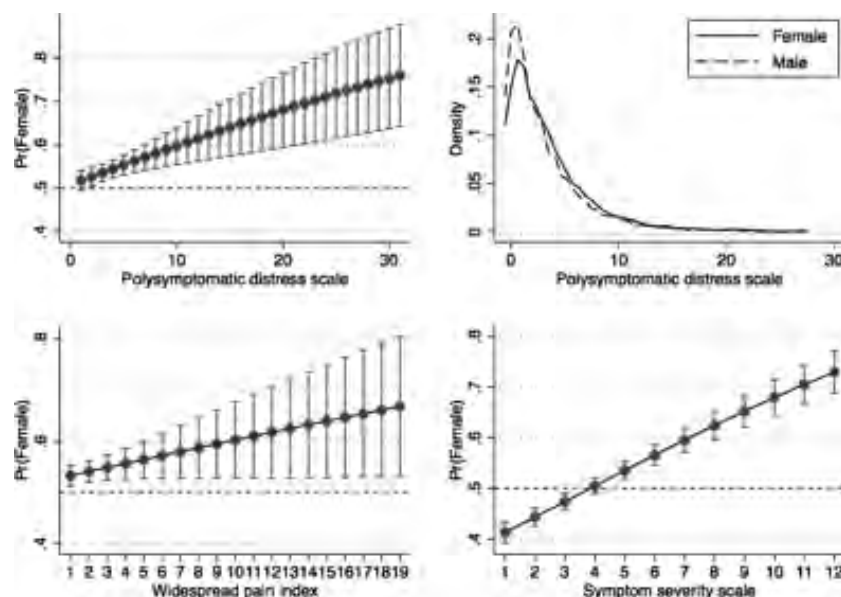
Session Title: Fibromyalgia and Other Clinical Pain Syndromes

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Multiple clinical and epidemiological studies have provided estimates of fibromyalgia prevalence and sex ratio, but different criteria sets and methodology, as well as bias, have led to widely varying (0.4%->11%) estimates of prevalence and female predominance (>90% to <61%). In general, studies have failed to distinguish Criteria based fibromyalgia (CritFM) from Clinical fibromyalgia (ClinFM) or fibromyalgia diagnosed by clinicians. In the current study we compare CritFM with ClinFM to investigate gender and other biases in the diagnosis of fibromyalgia.

Methods: We used a rheumatic disease databank and 2016 fibromyalgia criteria to study prevalence and sex ratios in a selection biased sample of 1761 referred and diagnosed fibromyalgia patients and in an unbiased sample of 4342 patients with no diagnosis with respect to fibromyalgia. We compared diagnostic and clinical variables according to gender, and were analyzed a German population study (GPS) (n=2435) using revised 2016 criteria for fibromyalgia.



Results: In the selection-biased sample of referred patients with fibromyalgia, more than 90% were women. However, when an unselected sample of rheumatoid arthritis (RA) patients was studied for the presence of fibromyalgia, women represented 58.7% of fibromyalgia cases. Women had slightly more symptoms than men, including generalized pain (36.8% vs. 32.4%), count of 37 symptoms (4.7 vs. 3.7) and mean polysymptomatic distress score (10.2 vs. 8.2), and we found a linear relation between the probability of being females and fibromyalgia and fibromyalgia severity – as shown in the figure below. Women in the GPS represented 59.2% of cases.

Conclusion: The perception of fibromyalgia as almost exclusively (90% or greater) a disorder of women is not supported by data in unbiased studies. Using validated self-report criteria and unbiased selection, the female proportion of fibromyalgia cases was less than or equal to 60% in the unbiased studies, and the observed CritFM prevalence of fibromyalgia in the GPS was approximately 2%. ClinFM is the public face of fibromyalgia, but is severely affected by selection and confirmation bias in the clinic and publications, underestimating men with fibromyalgia and overestimating women. We recommend the use of 2016 fibromyalgia criteria for clinical diagnosis and epidemiology because of its updated scoring and generalized pain requirement. Fibromyalgia and generalized pain positivity, widespread pain (WPI), symptom severity scale (SSS) and polysymptomatic distress (PSD) scale should always be reported in order to adequately characterize subjects in fibromyalgia studies.

Disclosure: B. Walitt, None; F. Wolfe, None; S. Perrot, None; J. Rasker, None; W. Häuser, None.

Abstract Number: 1837

Validity of the Cognitive Index of the Symptom Severity Scale (SSS-Cog) in Assessing Cognitive Impairment in Fibromyalgia Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Fibromyalgia Syndrome (FMS) is a multi-symptom disorder, characterized by somatic and cognitive manifestations, such as impaired working memory, executive function and attention (1,2).

The updated criteria for diagnosis of FMS (2016) recognize cognitive symptoms as a valid feature of the disease (3). These criteria use the Widespread Pain Index (WPI), a patient – reported tool reflecting the degree of pain dispersion, as well as

the Symptom Severity Scale (SSS), reflecting a sum of accompanying symptoms. The SSS itself includes a cognitive index score (SSS-Cog), focused on cognitive manifestations experienced by FMS patients (4,5,6).

Previous studies have shown inconsistency in correlating subjective and objective cognitive impairment in FMS patients (7,8). This study aims to check the validity of the SSS-Cog, by evaluating the correlation between patient-reported cognitive symptoms of FMS and a battery of computerized normalized cognitive tests.

Methods: FMS patients were recruited at a specialized FMS clinic. Participants were over 18 and diagnosed with FMS according to the 2010/2011 ACR diagnostic criteria (n=50, 86% women, 7% men). Secondary FMS patients were excluded. NeuroTrax™ computerized cognitive assessment battery was used for evaluation of cognitive function, in addition to filling up the Fibromyalgia impact questionnaire (FIQ), WPI and SSS.

Depressive symptoms, which may alter cognition, were assessed by the Beck Depression Inventory (BDI)-II. Level of effort during cognitive testing was evaluated with the Test of Memory Malingering (TOMM).

A Spearman correlation coefficient was used to assess whether the SSS-Cog index correlated with performance on the computerized cognition tests. Further correlations were performed between the SSS-Cog and other questionnaires used in the study (WPI, FIQ, BDI-II).

Results: The SSS-Cog results did not correlate with scores of the NeuroTrax™ cognitive assessment battery (rs= -.132, p= .361). Positive correlations were found between the SSS-Cog and the FIQ (rs= .438, p= .001), especially the pain measures utilized in it (VAS-pain, rs= .304, p= .032), as well as with the WPI (rs= .333, p= .018). The lack of correlation between the SSS-Cog and objective cognitive performance persisted when excluding a subgroup of 8 low-effort participants with a TOMM score ≤45. Age and BDI-II (depression) scores were also shown not to be confounding factors.

Conclusion: There is a strong correlation between FMS patients' subjective evaluations of cognitive impairment and self-measures of daily functioning, symptom intensity and experienced pain. However, a notable lack of correlation was found between patients' self-reported cognitive impairment and objective cognitive scores, indicating that the SSS-cog does not reflect its self-proclaimed purpose – assessing cognitive impairment. These findings highlight the need for development of alternative tools in assessing cognitive impairment in FMS patients.

Disclosure: O. Elkana, None; A. Falcofsky, None; R. Shorer, None; T. Bar-On Kalfon, None; R. Tzadok, None; J. N. Ablin, None.

Abstract Number: 1838

Fibromyalgia, Beyond the 2016 Establishment. an Analysis of Novel Symptom Clusters for Differentiating Fibromyalgia from Other Chronic Pain Disorders

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Clinicians must commonly differentiate fibromyalgia (FM) from other chronic pain diagnoses. Numerous symptoms, including those from the 2016 criteria, have been proposed to accomplish this differentiation -- but little is known about their relative importance. Moreover, other potential symptom candidates have been neglected. Herein we rank 26 symptoms according to how well (or not) they differentiate FM patients from other chronic pain patients. We highlight symptoms that are most important and identify others that have received little or no attention.

Methods: The data for this study was taken from a previously published paper (2018, J of Evaluation in Clinical Practice, 24(1): 173-179). A total of 352 patients (mean age 50 ± 16.3 years, 70% female) were studied. They comprised of 52 patients (14.8%) who carried a chart diagnosis of FM, 108 (30.7%) with chronic pain but not FM, and 192 who had neither pain nor FM. All patients completed a questionnaire that documented pain at 28 locations, the Revised Symptom Impact Questionnaire (SIQR) which included 10 symptoms and 16 additional novel questions related to other common symptoms often co-occur with FM. The 26 symptoms were ranked in their capacity to predict FM vs. chronic pain no FM using the Somers' D statistic.

Results: These data suggests that VAS pain itself is not a useful symptom in diagnosing FM in a population of patients with chronic pain (lowest rank). The most useful clusters for differentiating FM patients from chronic pain patients without FM were: “*I have a persistent deep ache over most of my body*” combined with 4 other symptoms (*poor balance, sensitivity to noise, environmental sensitivity and pain after exercise*; *Odds ratio =9.30*), or the deep ache question in association with *poor balance, environmental sensitivity, pain after exercise and tenderness to touch*; *Odds ratio =9.27*). Symptoms used in the Symptom Severity Scale (SSS) of the 2016 Revised Fibromyalgia Criteria, (unrefreshing sleep, dyscognition, fatigue , IBS symptoms, depression and headache) have relatively low discriminatory value (*Odds ratio = 2.96*).

Conclusion: These data attest to the potential usefulness of a cluster of symptoms that are not commonly used in current diagnostic guidelines for FM. Furthermore, they are notably different from symptoms advocated in the established 2016 revised guidelines.

Somers'D (rank)	Symptom VAS (range 0-10)	FM Mean n=50 (rank)	Pain No FM Mean n=108 (rank)	Mean difference
.641 (1)	Persistent Deep Ache*	7.40 (5)	3.14 (17)	4.26
.592 (2)	Intolerance to Noise	6.98 (6)	3.27 (15)	3.71
.574 (3)	Environmental Sensitivity*	6.82 (9)	3.04 (20)	3.78
.552 (4)	Balance*	6.26 (16)	3.06 (18)	3.20
.534 (5)	Pain after Exercise*	8.08 (1)	4.07 (7)	4.01
.524 (6)	Muscles Feel Weak	6.92 (7)	3.77 (10)	3.15
.511 (7)	Tenderness to Touch*	6.82 (9)	3.61 (11)	3.21
.505 (8)	Muscle Stiffness	7.68 (3)	4.86 (4)	2.82
.492 (9)	Intolerance to Bright Lights	6.58 (13)	3.41 (14)	3.17
.491 (10)	Tender Muscles	7.90 (2)	4.94 (2)	2.96
.473 (11)	Anxiety	6.26 (15)	3.50 (12)	2.76
.453 (12)	Restless Leg Symptoms	6.02 (18)	3.02 (22)	3.00
.452 (13)	Poor Sleep†	7.54 (4)	4.60 (5)	2.94
.421 (14)	Poor Memory†	5.66 (20)	3.03 (21)	2.63
.414 (15)	Intolerance to Cold	6.62 (12)	3.82 (8)	2.80
.412 (16)	Irritable Bowel Symptoms†	5.68 (19)	3.05 (19)	2.63
.409 (17)	Swollen Joints	6.16 (17)	3.78 (9)	2.39
.398 (18)	Depression†	5.44 (22)	3.17 (16)	2.27
.396 (19)	Stiffness	6.92 (7)	4.54 (6)	2.38
.390 (20)	Chronic Headaches†	5.62 (21)	3.45 (13)	2.17
.371 (21)	Irritable Bladder Symptoms	4.36 (25)	2.25 (26)	2.11
.349 (22)	Energy (Fatigue) †	6.82 (9)	4.92 (3)	1.90
.348 (23)	Skin Bruising	4.90 (23)	2.99 (23)	1.91
.336 (24)	Abdominal Swelling	3.98 (26)	2.44 (25)	1.54
.327 (25)	Intolerance to Perfumes	4.72 (24)	2.86 (24)	1.86
.320 (26)	Pain	6.54 (14)	5.12 (1)	1.42

Symptoms (italicized) measured on Revised Symptom Impact Questionnaire (SIQR)

† symptoms measured on the Symptom Severity Scale (SSS) of the 2016 proposed fibromyalgia criteria

* 5 items that best predict fibromyalgia

Disclosure: K. Jones, None; R. M. Bennett, None; A. W. St. John, None; R. Friend, None.

Abstract Number: 1839

Association of Diet Quality with Overall Fibromyalgia Impact, and Psychosocial and Quality of Life Outcomes in Women with Fibromyalgia

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Fibromyalgia and Other Clinical Pain Syndromes

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Lifestyle modifications, including of diet and exercise, have been widely disseminated for the prevention and treatment of chronic pain. However, the relationships between dietary habits and fibromyalgia (FM) impact, and psychosocial or quality of life (QoL) outcomes have not been well studied.

Table 1. Associations of diet quality (HEI-2010 scores) with pre-intervention fibromyalgia impact scores, various psychosocial and quality of life measures, self-efficacy, and sleep quality in 26 women with fibromyalgia

Pre-intervention measure (maximum score range)	Healthy Eating Index 2010 (HEI-2010) (0-100 points)
Physical health Quality of Life (SF-36 PCS) [0-100 points]	$r = 0.32$ ($p < .12$)
Mental health Quality of Life (SF-36 MCS) [0-100 points]	$r = 0.20$ ($p < .30$)
Chronic Pain Self-Efficacy Scale [0-10 points]	$r = 0.07$ ($p = .91$)
Revised Fibromyalgia Impact Questionnaire (FIQR) [0-10 points]	$r = 0.27$ ($p = .10$)
Beck II Depression Inventory (BDI) [0-63 points]	$r = -0.17$ ($p = .40$)
Pittsburgh Sleep Quality Index (PSQI) [0-21 points]	$r = -0.10$ ($p = .48$)
Hospital Anxiety Score (HADS) [0-21 points]	$r = -0.24$ ($p = .08$)
Hospital Depression Score (HADS) [0-21 points]	$r = -0.47$ ($p < .02$)

r : > 0.30 , 0.15 , and 0.7 indicates weak, moderate, and strong association, respectively.

^aHigher score is better.

^bHigher score is worse.

Table 2. Healthy Eating Index 2010 (HEI-2010) Total and Component Scores in the Study Participants (n=26), and in the U.S. Adults and Older Adults

HEI-2010 Dietary Component (maximum score)	Study Participants 24-75 years (n=26)	U.S. Adults 18-64 years (n=4,044) ^a	U.S. Older Adults ≥ 65 years (n=1,032) ^a
Adequacy (higher score indicates higher consumption)	Mean Score (standard error)		
Total Fruit ^b (5)	4.20 (0.25)	2.61 (0.11)	3.84 (0.22)
Whole Fruit ^b (5)	4.38 (0.23)	3.52 (0.15)	4.99 (0.08)
Total Vegetables ^b (5)	4.24 (0.22)	3.54 (0.09)	4.16 (0.19)
Greens and Beans ^b (5)	4.09 (0.31)	3.03 (0.16)	3.58 (0.47)
Whole Grains (10)	2.48 (0.31)	2.75 (0.18)	4.23 (0.34)
Dairy ^b (10)	4.99 (0.57)	6.78 (0.13)	8.99 (0.18)
Total Protein Foods ^b (5)	4.46 (0.18)	6.00 (0.00)	6.00 (0.00)
Seeds and Plant Protein ^{b,c} (3)	4.52 (0.19)	3.98 (0.22)	4.93 (0.18)
Fatty Acids (10)	7.13 (0.46)	4.02 (0.19)	6.60 (0.36)
Moderation (higher score indicates lower consumption)			
Refined Grains (10)	6.04 (0.30)	6.36 (0.17)	7.34 (0.31)
Sodium (10)	6.62 (0.51)	4.04 (0.08)	3.66 (0.26)
Empty Calories (20)	18.89 (0.84)	12.53 (0.38)	14.90 (0.44)
Total HEI-2010 score (100)	71.42 (1.63)	58.27 (0.98)	68.29 (1.76)

^a Calculated using the population ratio method. Data source: National Health and Nutrition Examination Survey, 2011-2012 (available from <https://www.cdc.gov/nchs/data/healthyeatingindex/>)

^b Includes 100% fruit juice.

^c Includes all forms except juice.

^d Includes any beans and peas not counted as Total Protein Foods.

^e Includes all milk products, such as fluid milk, yogurt, and cheese, and fortified soy beverages.

^f Beans and peas are included here (and not with vegetables) when the Total Protein Foods standard is otherwise not met.

^g Includes seafood, nuts, seeds, soy products (other than soybeans), as well as beans and peas counted as Total Protein Foods.

^h Ratio of poly- and monounsaturated fatty acids (PUFAs and MUFA) to saturated fatty acids (SFA).

ⁱ Calories from solid fats, alcohol, and added sugars, threshold for counting alcohol is > 13 grams/1,603 kcal.

Methods: Participants in a large comparative effectiveness randomized trial of Tai Chi versus aerobic exercise for FM were recruited. Participants were excluded from this study if they had participated in any dietary intervention since the end of the original trial. The National Cancer Institute Diet History Questionnaire (DHQ-II past year recall without portion sizes) was used to assess diet quality, using the Healthy Eating Index 2010 that assesses compliance with the 2010 U.S. Dietary Guidelines for Americans (DGA). Associations of diet quality with the pre-intervention FM impact scores, various psychosocial and QoL measures, self-efficacy, and sleep quality (Table 1) were examined using Pearson's correlation coefficient (r)

Results: A total of 26 female participants (mean age = 56 y; mean pre-intervention BMI =29.6) were included in the analyses. Of which, six (3 in each intervention arm) participants reported that their diet has changed since the end of the original trial. Diet quality of these participants was better than general U.S. adult population (Table 2). Higher pre-intervention self-efficacy and physical health QoL were associated with higher diet quality ($r = 0.62$ and 0.32 , respectively). Higher pre-intervention levels of anxiety and depression were associated with lower diet quality ($r = -0.43$ and -0.47 , respectively). There were no significant associations between diet quality and pre-intervention severity of depressive symptoms, mental health QoL, sleep quality, or FM impact scores (Table 1).

Conclusion: Better diet quality as recommended by the 2010 DGA may be associated with more favorable psychosocial and physical health QoL outcomes in women with FM. Our results are consistent with a large cross-sectional study in women with FM from Spain (J Acad Nutr Diet. 2017 Mar; 117(3):422-432). Future studies evaluating the effects of healthy dietary patterns on psychosocial and physical outcomes in individuals with FM are warranted.

Funding: Tufts Collaborates Seed Grant Program of Tufts University

Abstract Number: 1840

Disease Activity in Rheumatoid Arthritis Patients Is Influenced By Countries' Socioeconomics: Results from the Meteor Registry

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Healthcare Disparities in Rheumatology

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The treatment and prognosis of rheumatoid arthritis (RA) patients have improved tremendously, but patients across the world may not benefit similarly. One of the potentially critical factors may be poorer access to expensive biologic (b) DMARDs. We aimed to investigate daily practice data regarding bDMARD use in different countries worldwide and assess if a lower country's socioeconomic status (SES) is associated with worse clinical outcomes and lower usage of bDMARDs.

Methods: Data on disease activity and drug use from countries that contributed ≥ 100 RA patients after 1-1-2000 were extracted from the daily practice, observational METEOR database. Missing data were imputed using multivariate normal imputation (30 cycles). Gross domestic product (GDP) per capita in international dollar (Intl\$) was used as indicator of SES. Per country average DAS28 and the proportion of patients in DAS28-remission ($\text{DAS28} < 2.6$) were calculated by taking the average of all patients at the last available visit. Univariable logistic regression analyses were performed to assess associations between GDP, bDMARD-use and disease outcomes at a country level.

Results: In total, 20,379 patients were included from 12 countries: United States, Mexico, South-Africa, Japan, Brazil, United Kingdom, Spain, Ireland, Portugal, France, India and the Netherlands. The number of patients ever using a bDMARD varied between 0.9% (South-Africa) and 75% (Ireland). The proportion of patients in remission at the final visit varied between 2% (India) and 39% (Netherlands).

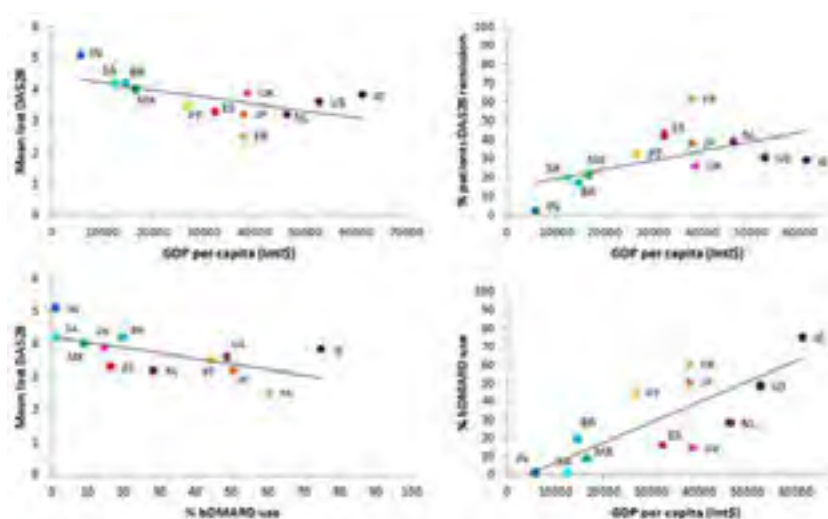


Figure 1. Associations between 'GDP per capita (Intl\$)', '% bDMARD use' and 'disease activity', IN=India, SA=South-Africa, BR=Brazil, MX=Mexico, PT=Portugal, ES=Spain, JP=Japan, UK=United Kingdom, FI=France, NL=Netherlands, US=United States, IE=Ireland

Patients in countries with a higher GDP per capita had a lower average DAS28 and consequently, a higher proportion of them were in DAS28-remission: -0.32 (95%CI -0.41; -0.021) lower DAS28 and an additional 4.2% (0.14; 8.26) of patients in DAS28-remission for every 10,000 Intl\$ additional GDP.

To underscore the assumption that the association between SES and DAS28 is mediated by bDMARD use, we assessed whether SES was associated with bDMARD use per country. Indeed, a higher GDP per capita was associated with a higher proportion of patients using a bDMARD: 11.2% (95% CI 4.82; 17.5) more patients using a bDMARD per 10,000 Intl\$ additional GDP. Furthermore, DAS28 was -0.14 (-0.28; -0.0054) lower and 2.8% (-0.13; 5.8) more patients achieved DAS28-remission per 10% increase in proportion of patients using a bDMARD, figure 1.

Conclusion: RA patients in countries with a lower SES had worse disease activity. Although patients in countries with a lower SES less often used bDMARDs, the effect of bDMARD use on disease activity was smaller than expected, indicating that other factors than access to bDMARDs may contribute to the effectiveness of RA-treatment.

Disclosure: S. A. Bergstra, None; J. Tavares Costa, None; D. Vega-Morales, None; K. Salomon-Escoto, None; N. Govind, None; C. F. Allaart, None; R. B. M. Landewé, None.

Abstract Number: 1841

Current Rheumatology Fellows Experiences with Health Disparities and Disparity Education: A Qualitative Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Healthcare Disparities in Rheumatology

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Health disparities (HD) are pervasive across all specialties including rheumatology; such that the ACGME has mandated that all programs teach house officers about HD. To inform future curriculum development, we conducted a qualitative study to explore rheumatology fellows perceptions of and experiences with HD instruction.

Methods: We conducted 5 focus groups (FG) in New York and Pennsylvania using a semi-structured interview guide. Questions focused on fellows' experiences with HD in their practices and if/how they have been taught to address these issues. FG audio recordings were transcribed by a third party contractor, de-identified and systematically analyzed using grounded theory by 2 reviewers. FG were conducted until there was a saturation of themes. This project was approved by the Einstein IRB and fellowship names/locations are not reported to protect the fellows' anonymity.

Results: 25 fellows participated in our FG --most saw what they considered to be urban/suburban populations; 1 program treated rural patients. 3 major themes emerged from our data: **1. HD Create a Sense of Being Overwhelmed 2. Scarcity of Role-Modeling 3. Learning is Haphazard.**

1. BEING OVERWHELMED

All fellows felt that they were seeing evidence of disparate care among their patients and were at a loss on how to address these issues: *"you can't do things for the patients, and I think over time it gets really burdensome and frustrating."* *"I think these are the things we bang our heads against the wall on".*

2. ROLE-MODELS

Fellows were not observing their faculty regularly address these issues and potentially encounters can be problematic. *"...there are a few faculty members who I think understand certain barriers and certain patients as opposed to others who can't."* *"I know I have seen their implicit bias play out. ... I've had patients who may get frustrated if they find out who the precepting attending is for them. Like oh, I got to see this one - -. It exists. Then the fellow role actually becomes sometimes protecting the patient a little bit. Which is awkward."*

3. HAPHAZARD LEARNING

In addition to this lack of informal instruction and occasional negative role modeling, there is a lack of formal instruction. *"I can't remember it being done. I don't know, but maybe I'm blanking but I don't remember having anything formal."* Fellows are left to discuss issues with each other: *"I was going to say talk about it amongst each other case by case, but not as a group, not as a division officially. Just a lot of complaining in the fellow's office".* This is reinforced by the programs *"A lot of social aspects of medicine we put on the back burner because I don't know, in two years of fellowship I still feel like there's so much other stuff that I also need to know."* *"It's just the culture but it has what's expected and what's expected is you pick a topic that is rheumatology ... like a good randomized controlled trial study and then you talk about that..."*

Conclusion: Currently fellows are not learning about HD in a formal way or how to address HD in their patients, despite the fact that this is mandated by the ACGME, . The development of GME specialty-specific curricula will be key if we are to train providers that will advocate for our most marginalized populations and contribute to health equity.

Disclosure: I. Blanco, None; C. Gonzalez, None.

Abstract Number: 1842

Implementation of an African American Popular Opinion Leader Model to Address Disparities in Lupus Knowledge and Care

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Healthcare Disparities in Rheumatology

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Lupus is a chronic, auto immune disease that disproportionately affects African American individuals. Community-based educational interventions that capitalize on rich social networks can be used to promote positive health-seeking norms and behaviors. Our academic-community partnership adapted the CDC's Popular Opinion Leader (POL) evidence-based practice to develop and implement an African American POL program that leverages community leaders' social networks to disseminate culturally appropriate lupus education and promote care-seeking norms. The first phase of implementation was in greater Boston neighborhoods with a higher demographic representation of African Americans.

Methods: Academic lupus clinicians and disparities researchers partnered with two local lupus support groups comprised primarily of women of African descent, and a local community-based health education, research and service organization, to recruit POLs. Recruitment targeted community and neighborhood organizations, churches and support groups in medically underserved, predominantly African American neighborhoods. Participants attended four, 2-3 hour POL training sessions at an urban community center. An interactive, live-streaming webinar option was also available. The training included lupus and disparities education, application of the POL model, and strategies to disseminate lupus education, change norms, and document impact. Detailed observational and qualitative data were collected at the trainings and analyzed the matically. POLs disseminated information formally and informally through their social networks and communities and documented conversations, venues and number of people reached.

Results: We trained 18 Boston area POLs, 11 with lupus, 7 without (3/7 with relatives with lupus). Seventeen were female, 3 were ≤45 years, 11 were 45-65 years, 4 were >65 years. 16 were African American, 1 African American/Native American, and 1 Caucasian. Nine held graduate degrees, 6 associates/bachelors', and 3 high school. Key themes raised by POLs at the trainings included challenges with patient-MD communication, stigma/misconceptions surrounding lupus as a disfiguring or contagious disease, racial and gender discrimination in healthcare, challenges engaging family members, and the importance of support networks for lupus patients. Within 2 months of the training, POLs engaged 269 individuals in 14 neighborhoods in conversations about lupus and the importance of early and sustained care (**Table**).

Conclusion: We implemented a community-based African American POL model in the greater Boston area which resulted in the ongoing dissemination of lupus-related information through diverse social networks. A parallel implementation initiative is underway in Chicago, as well as quantitative data analysis at both sites, to prepare to scale the intervention nationally.

Table. Community dissemination data collected by trained lupus Popular Opinion Leaders (POL) in the two months following POL training

	# of POLs	# of People Reached	POL Reported Community-based Venues
Urban Boston Neighborhoods			
Dorchester	6	87	Lupus Support Group, Elementary School, Neighborhood Development Coalition, Community Health Center, Hair Salon, Market, Convenience Store, Library, Gym, Grocery Store, Community Resource Fair, Square Park Meeting, Community Event, Golf Course, Fraternity/ Masonic Lodge, Parking Lot, National Alliance on Mental Illness
Roxbury	4	23	Community Health Center, High School, Athletic Center, Mall, Courthouse, Courthouse, Cash Checking Place, Church
Jamaica Plain/ West Roxbury	3	37	Baby Shower, AME Church, Ice Cream Shop, Coffee Shop, Health Center, Laundromat, Grocery Store, League of United Latin American Citizens
Boston proper/ South Boston	3	32	Sleep Clinic, Police Captain's Meeting, Educational Seminar, City Health Department, Academic Medical Center, Pharmacy, Bank, Post Office
Mattapan Near Boston Suburbs	3	14	Church, Barbershop
Buzzards Bay	1	17	Apartment Building, Public Library
Quincy	1	2	Dental Office
Milton	1	8	Café, Apartment Building
Springfield	1	35	Prayer Breakfast
Lakeville	1	10	Friend's Home
Mashpee	1	1	Tribal Council

Venues for Cambridge (N=1) and Brockton (N=2) were not reported; Boston-based POLs also reported dissemination in the following states: New York (N=2), Connecticut (N=1), Rhode Island (N=1), New Hampshire (N=1), Virginia (N=1), Florida (N=1)

Disclosure: C. Phillip, None; C. Leatherwood, None; E. Freeman, None; G. Granville, None; G. Sealy, None; T. Wiley, None; C. Correia, None; K. Mancera-Cuevas, None; P. Canessa, None; R. Ramsey-Goldman, None; C. H. Feldman, None.

Abstract Number: 1843

Improving Access to Rheumatology Care for High-Risk Lupus Patients Can Help Decrease Hospitalizations

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SESSION INFORMATION

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Background/Purpose: We previously demonstrated that a small group of high risk, high cost patients (HRHC) account for majority of the hospitalizations, length of stay (LOS) and overall cost among all lupus patients admitted to an academic medical center. Herein, we assessed the impact of an intervention to improve access to rheumatology care for HRHC lupus patients by comparing the number of hospital admissions and LOS in the HRHC cohort compared to hospitalized lupus patients not meeting HRHC criteria.

Methods: Lupus patients who required 3 or more admissions over a 3-year period between 2013 and 2016 were categorized as HRHC patients. Most of these patients were from the poor, urban communities and were mostly African American. A project to improve quality for low-income, underprivileged, poor, underage, SLE (IQ-LUPUS) patients was started in July 2018. One of the goals of the IQ-LUPUS project is to enhance access for the HRHC patients to rheumatology care by offering direct access to a nurse care coordinator and a social worker who provide medical advice, remind and facilitate outpatient visits, enable educational activities and organize home visits. Additionally, we opened a clinic in the urban community. We compared the no show rates for the HRHC patients with all lupus patients and all rheumatology patients seen in the outpatient clinics at URM for the fiscal year (FY) 2017 (prior to project) with FY 2018 (since starting project). We also determined the hospitalization rates and LOS for all admissions among the HRHC patients enrolled in the project, for first 10 months of FY 2017 with the first 10 months of FY 18. The gender, age and the diagnoses on admission were all documented.

Results: A total of 54 HRHC patients are enrolled in the IQ-LUPUS project to date. No show rates for these HRHC patients was 12.1% for FY 2017, 5.8% for all lupus patients and 4.3% for all patients seen at the Rheumatology clinic. The no show rates for the HRHC patients decreased 1.3% for FY 2018 (p=0.62) but increased in all lupus patients (0.8%) and all rheumatology patients (0.7%). In 2017, 16 of the HRHC patients had 52 admissions in 2017 for a total LOS of 231 days. All patients were female with a mean age of 32.9 years. In 2018, the number of admissions decreased to 36 (p=0.3). These admissions included 17 patients and a total LOS of 159 days (p=0.5)). All patients were female with a mean age of 32.5 years. The number of 30-day readmissions also decreased from 21 in 2017 to 14 in 2018. Although no statistical significance was noted early results of the IQ-LUPUS project suggests that improving access can decrease hospitalizations.

Conclusion:: Methods aimed at improving access to rheumatology care through care coordination and special clinics can decrease the number of hospitalizations and LOS among high risk SLE patients. Further studies are needed to further define and implement targeted interventions that decrease hospital admissions and improve quality of care for this vulnerable population.

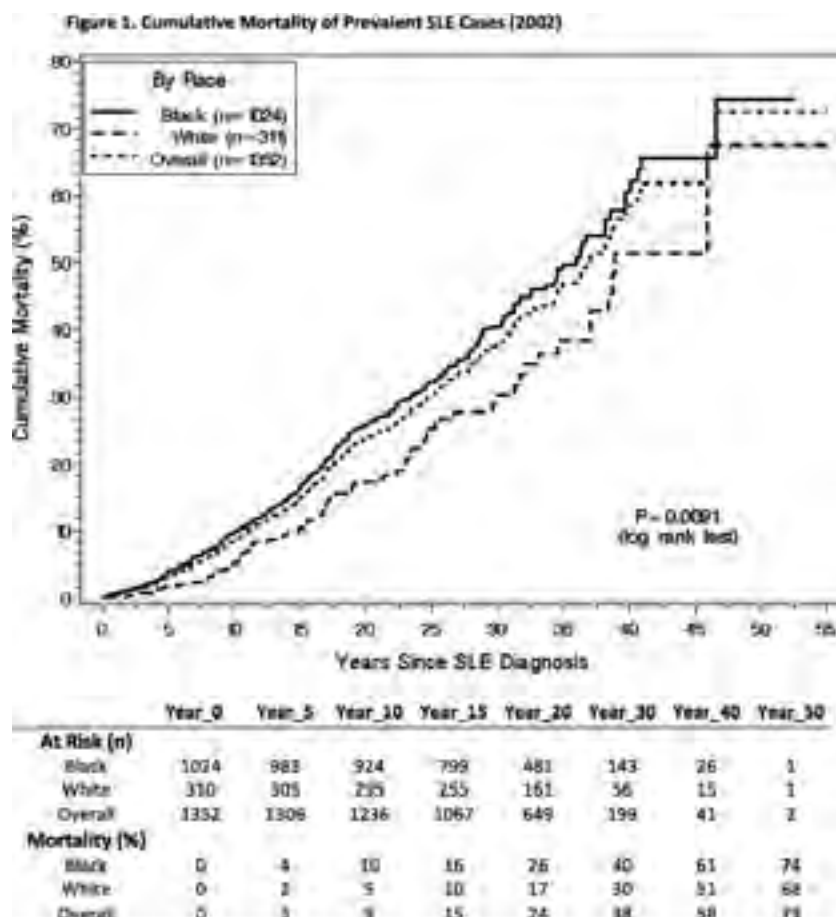
	High-Risk, High-Cost Lupus patients		All lupus patients	
	2017	2018	2017	218
No show rates	54 (12.1%)	43 (10.8%)	178 (5.8%)	147 (6.6%)
Admissions	52 (36.6%)	36 (21.3%)	142	169
Length of stay	231 (21.8%)	159 (12.9%)	1060	1225

Disclosure: A. P. Anandarajah, None; S. McMahon, None; A. Ostronic, None; C. Feng, None; J. Anolik, None; C. T. Ritchlin, AbbVie, Amgen, UCB, 2,AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer Inc, 5.

Abstract Number: 1844

Racial Disparities and Accelerated SLE Mortality from a Population-Based Registry: The Georgia Lupus Registry

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Session Date: Monday, October 22, 2018

Session Title: Healthcare Disparities in Rheumatology

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Session Time: 2:30PM-4:00PM

Background/Purpose: Population-based SLE mortality studies have depended on administrative data from vital statistics records to identify cases. However, a high proportion of SLE deaths have no SLE code. We studied mortality trends from a population-based registry that overcame many of these limitations.

Methods: The Georgia Lupus Registry is a CDC funded population-based registry of validated SLE patients in Atlanta, Georgia from 2002-04. The state privacy exemption for surveillance allowed health care providers and facilities to provide access to protected health information without written patient consent, allowing for validation of diagnoses on a population level using ≥ 4 ACR criteria or 3 ACR criteria with a final diagnosis of SLE by a board-certified rheumatologist. All incident and prevalent SLE cases were matched to the National Death Index, which contains information for all deaths

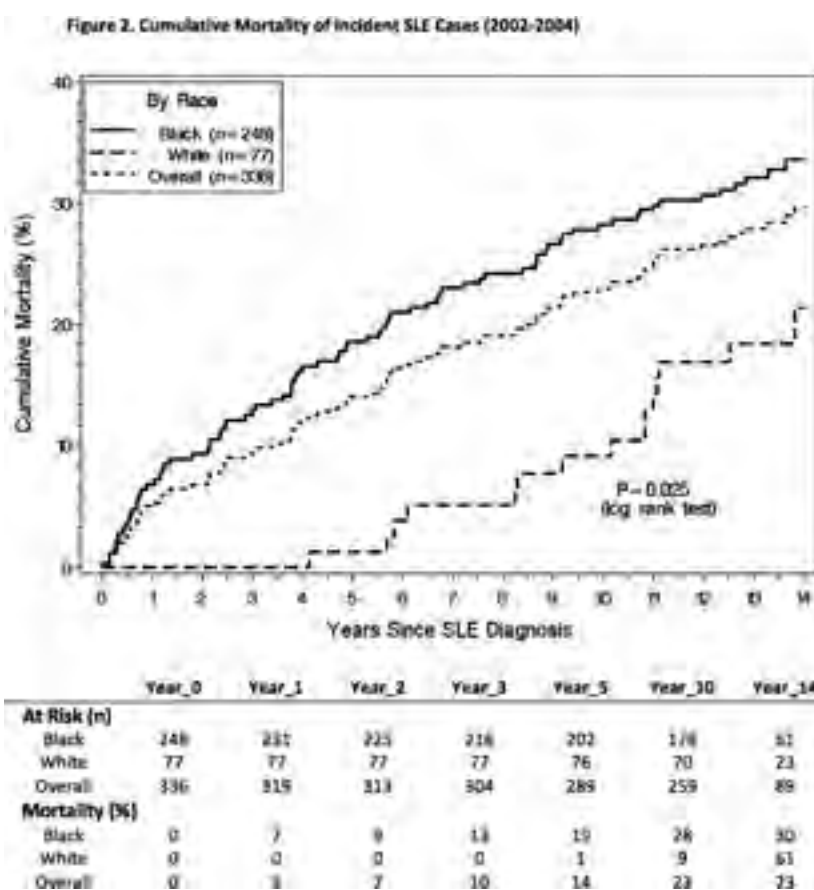


Table 1. Standardized Mortality Ratios of Prevalent SLE Patients, adjusted by age, gender, and race

Sub-Group	Total Cases	Mortality		Standardized Mortality Ratio (95% CI)
		Observed	Expected	
Overall	1335	29	8	3.63 (2.52-5.22)
Male	135	4	1	4.00 (1.50-10.7)
Female	1200	25	7	3.57 (2.41-5.29)
Black	1024	24	6	4.00 (2.68-5.97)
White	311	5	2	2.50 (1.04-6.01)
Black Female	924	21	5	4.20 (2.74-6.44)
White Female	276	4	2	2.00 (0.75-5.33)

*Adjusted for age, gender, and race

*Sample sizes too small for non-black or non-whites

*Age at 7/1/2002 was used for adjustment

in the U.S. as derived from information on death certificates and provided by local vital records offices, through 2016. Cumulative mortality survival analysis and standardized mortality rates (SMR) were analyzed.

Results: Of 336 incident SLE patients in 2002-04, 86.9% were female, 73.8% black and 22.9% white, and mean age of 40.6 years at SLE diagnosis. Of 1353 prevalent SLE patients in 2002, 89.9% were female, 75.7% black and 23% white, and mean age of 34.6 years at SLE diagnosis. There were 97 deaths through 2016. Blacks had significantly greater cumulative mortality than whites (Figs. 1 and 2) and were younger at death for both incident (51.8 ± 17.5 vs. 64.4 ± 18.9 , $P=0.013$) and prevalent (52.3 ± 15.9 vs. 65.0 ± 16.3 , $P<0.0001$) cases. Whites had a marked lower mortality after diagnosis compared with blacks; For incident cases, whites did not die until 5 years after SLE diagnosis, whereas blacks had significant and persistent higher mortality from the start. There were no significant differences by gender. SMR's were calculated for prevalent patients (Table 1).

Conclusion: Despite increasing awareness and advancements in treatment, mortality in SLE continue to remain high and disparate across combined gender and race groups with the highest standardized mortality ratio in black females. Defining and addressing reversible mortality factors must be high priorities in mitigating racial disparities and improving overall outcomes in SLE.

Disclosure: S. S. Lim, None; C. G. Helmick, None; G. Bao, None; C. Gordon, None; J. M. Hootman, None; C. Drenkard, Centers for Disease Control and Prevention (CDC) grant U01DP005119; NIH (R01AR065493-01; R01MD010455-01; R01AR070898-01), 2, Emory University, 3.

Abstract Number: 1845

Defining and Examining Retention in Care in an Urban Lupus Cohort

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Healthcare Disparities in Rheumatology

Session Type: ACR Concurrent Abstract Session

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Background/Purpose: Systemic Lupus Erythematosus (SLE) disproportionately impacts black patients and those of low socioeconomic status who experience higher rates of kidney disease and premature mortality. Similar disparities are being addressed in HIV care by defining a care continuum starting with "retention in care." Studies show that retention in care, defined as one visit or viral load every 6 months by CDC and WHO, correlate with viral suppression, an apt comparison for SLE care. Current SLE research is limited regarding factors that impact retention in care across diverse populations. The objectives of this study were to validate a cohort of patients with confirmed SLE to define retention in lupus care and examine its predictors.

Methods: Potential cases were identified from an academic urban medical center, with at least one ambulatory rheumatology encounter and an ICD code for SLE between 1/1/2013 and 6/30/2014. Inclusion required age > 17 years old, SLE diagnosis, and living through 2015. Manual record abstraction entered in Redcap system confirmed SLE diagnosis by the 1987 ACR or 2012 SLICC classification criteria. Abstraction included sociodemographics, tobacco use, first SLE diagnosis date, and 30 items examining ACR and SLICC criteria. Predictors examined included sociodemographic factors (age, sex, race, ethnicity), socioeconomic status (neighborhood poverty using a zip code area deprivation index [ADI]), number of SLE criteria, and health behavior data (tobacco use).

Retention in SLE care outcomes were defined using a variation of the WHO/CDC definitions in HIV requiring one ambulatory visit and one lab test (complement level) every 6 months. Multivariable logistic regression was used to model predictors using STATA v.15.0.

Results: A total of 397 individuals met ACR or SLICC classification criteria for SLE. Most were female (91%) and race varied (60% white, 40% black, 5% Hispanic). Overall, 60% met visit retention definitions, and 39% met complement lab testing definitions. There was no statistical difference seen with retention in care based on age, gender or race in either model. However, individuals residing in the most disadvantaged neighborhood are as (ADI quartile 4) were 60% less likely to have at least two clinic visits annually (Table 1). Data also showed 50% of black patients living in ADI quartile 4. Smoking history was also a negative predictor for visit retention.

Conclusion: Defining retention in lupus care is a critical step to meet the unmet need to identify and assist SLE patients at risk for gaps in care and outcome disparities. Race did not seem to predict retention; however, the most disadvantaged neighborhoods (ADIquartile 4) were a strong predictor of poor retention in care. Future interventions could prospectively identify such at-risk populations and explore approaches such as multi-disciplinary care models to reduce care disparities.

Table 3 Odd ratios (95% CI) of predictors of SLE retention in care

Visit defined retention Adjusted OR (CI)	
Age 18-29	ref
30-40	0.81 (0.36, 1.81)
40-60	0.66 (0.32, 1.38)
60-80	0.71 (0.30, 1.68)
80+	1.15 (0.11, 12.41)
Female	0.50 (0.22, 1.11)
White	ref
Black	1.69 (0.88, 3.22)
Other	0.99 (0.29, 3.37)
Ethnicity (% Hispanic)	0.64 (0.18, 2.30)
Urban	ref
Suburban	1.22 (0.55, 2.71)
Large town	1.19 (0.35, 4.08)
Small town	0.39 (0.13, 1.15)
Smoking (ever)	0.62 (0.39, 0.97)*
Area Deprivation Index 1st (least disadvantage)	ref
2nd	1.03 (0.55, 1.93)
3rd	1.04 (0.53, 2.04)
4th (most disadvantage)	0.44 (0.20, 0.996)*
Number of ACR Criteria	1.14 (0.99, 1.31)

Disclosure: U. Ahmad, None; I. Chang, None; M. Johnson, None; A. Rosenthal, None; A. Perez, None; C. M. Bartels, Pfizer, Inc., 2.

Abstract Number: 1846

Menarchal Status at Diagnosis and Final Height in Females with Childhood-Onset Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical I: Outcomes and Comorbidities

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The diagnosis of systemic lupus erythematosus (SLE) in childhood affects growth due to disease and therapy. To date, there are few studies of final adult height achieved in children diagnosed with SLE and no study examining the relationship of pubertal status at diagnosis and final height. Our aim was to examine the relationship between age at menarche and final adult height, accounting for ethnicity.

Methods: We completed a retrospective cohort study, reviewing 564 female patients < 18 years of age at diagnosis, and followed at a tertiary care, pediatric center from July 1982 to March 2016. All patients met American College of Rheumatology and/or Systemic Lupus International Collaborating Clinics classification criteria for SLE. Patients with documented vertebral collapse (15 patients) or growth hormone therapy (4 patients) were excluded. We reviewed prospectively collected demographic and clinical data including self-reported ethnicity, height, age at menarche, age at diagnosis, disease activity, disease damage and medication use. Final height was the height achieved after <1 cm growth per year for 2 years following menarche or height at 18 years of age. We compared age at diagnosis and menarche as well as final height between patients diagnosed with SLE pre- and post-menarche using a t-test. We divided patients diagnosed post-menarche into females who grew >1 cm post-menarche and females who had achieved final height at diagnosis (no growth). We examined SLE diagnosis post-menarche, compared with pre-menarche in association with final height, adjusting for ethnicity, in linear regression models.

Results: Our cohort included 401 female SLE patients with final height and menarche data. Of those, 115 patients (29%) were diagnosed pre-menarche (mean age of diagnosis 10.7 years [SD 2.2 years]) and 286 patients (71%) were diagnosed post-menarche (mean age of diagnosis 15.1 years [SD 1.6 years]). Age of menarche was 13.5 years (SD 1.4 years) in the

pre-menarche group, compared to 12.5 years (SD 1.4 years) in the post-menarche group ($P < 0.001$). The mean final height for females diagnosed post-menarche was greater than those diagnosed pre-menarche (Table 1). In subgroup analysis of the post-menarche group, the mean final height of girls with no growth (161.9 cm [SD 6.8 cm]) was greater than girls diagnosed pre-menarche ($p=0.001$). In regression analysis, those diagnosed post-menarche were significantly taller than those diagnosed pre-menarche, adjusted for ethnicity (Beta = 2.6cm, SD 0.7cm, $P < 0.001$).

Conclusion: In this large cohort study of females with childhood-onset SLE, patients diagnosed post-menarche achieved a taller final height than those diagnosed pre-menarche even after accounting for ethnicity. Future analyses will explore the relationship of disease activity, damage and medication use with growth velocity and final adult height.

Table 1 Comparison of final height between females diagnosed with SLE pre-menarche and post-menarche

	Number (%)	Final height (cm), mean \pm SD		P value
		SLE diagnosis pre-menarche	SLE diagnosis post-menarche	
Total cohort*	401	158.8 \pm 7.3	161.4 \pm 6.9	0.001
European	114 (28%)	161.8 \pm 7.1	164.0 \pm 5.7	0.088
East and Southeast Asian	106 (26%)	156.2 \pm 7.3	158.9 \pm 5.8	0.053
African and Caribbean	69 (17%)	159.0 \pm 7.2	162.0 \pm 7.4	0.112
South Asian	55 (14%)	156.8 \pm 7.2	159.2 \pm 7.2	0.249
Hispanic and Amerindian	17 (4%)	160.6 \pm 5.5	159.1 \pm 7.7	0.723
Mixed ethnicity	23 (6%)	158.5 \pm 7.8	165.6 \pm 8.5	0.073

* Ethnicity was missing in 17 patients

Disclosure: W. Sontichai, None; D. Dominguez, None; L. Ng, None; D. M. Levy, None; J. Wasserman, None; E. Silverman, None; L. Hiraki, None.

Abstract Number: 1847

Screening Youth with Lupus for Depression and Anxiety in Pediatric Rheumatology Clinics

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical I: Outcomes and Comorbidities

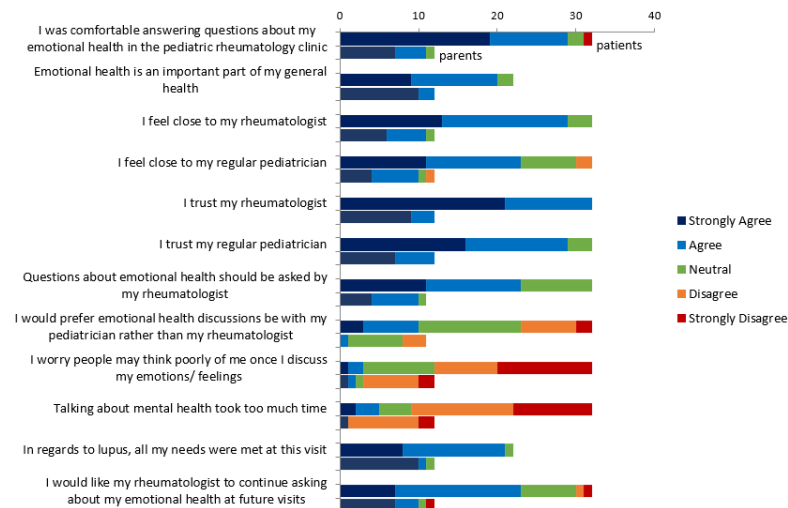
Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Despite high rates of depression and anxiety in pediatric lupus, standardized mental health screening is not routinely practiced by pediatric rheumatologists. Our objectives were to screen youth with lupus for depression and anxiety in pediatric rheumatology clinics and assess patient and parent acceptability of screening in this clinical setting.

Methods: In a multi-center study of 6 collaborating clinics from the Childhood Arthritis and Rheumatology Research Alliance, patients with lupus ages 12-21 years were consecutively screened with the Patient Health Questionnaire-9 (PHQ9) for depression and the Generalized Anxiety Disorder 7-item scale (GAD7) for anxiety. Screens were administered by tablets prior to and reviewed during clinical visits. Patient reported outcomes (PROs) for depression, anxiety, fatigue, pain, and physical and social functioning were collected using the Patient Reported Outcomes Measurement Information System. Correlation analyses examined the relationship between these PROs, the PHQ-9 and GAD-7 scores. Follow up surveys emailed to patients and/or parents assessed acceptability of screening. All patients had to meet either the ACRSLE Classification Criteria or the SLICC Classification Criteria.

Figure 1. Beliefs and preferences of youth with lupus and their parents: survey responses after mental health screenings in the pediatric rheumatology clinic



Results: Fifty-three patients were screened and follow up surveys completed for 74%. The median age was 16.2 years, 87% were female, and 75% were of minority race/ethnicity. Of those screened, 26% screened positive for depression, 19% for anxiety, and 15% had suicidal ideation. Only 17% of patients reported previously screenings by their general pediatricians; 15% were newly identified as having symptoms of depression or anxiety. PHQ9 and GAD7 scores were highly correlated to PROs of fatigue ($r=0.7$, $p<0.0001$; $r=0.6$, $p<0.0001$) and pain interference (both $r=0.5$, $p<0.0001$) as well as depression ($r=0.7$, $p<0.0001$; $r=0.7$, $p<0.0001$) and anxiety ($r=0.6$, $p<0.0001$; $r=0.7$, $p<0.0001$) (Table 1). In follow up surveys, 91% felt comfortable being screened by their rheumatologist, and 74% felt they should continue to be routinely screened by their rheumatologist (Figure 1).

Conclusion: Mental health screening in pediatric rheumatology clinics may improve symptom detection for depression, anxiety and suicidal thoughts in young patients with lupus. Screening in this setting was important and acceptable practice to patients and parents across diverse demographics. Using patient-reported outcome measures alongside validated mental health screening tools may enhance our understanding of mental health in these patients.

Table 1 Correlations between depression (PHQ9) score, anxiety (GAD7) score, and patient reported outcomes in youth with lupus

	PHQ9 score	GAD7 score
GAD7 score	0.8, $p<0.0001$	1.00
PROMIS measures:		
Worse depression	0.7, $p<0.0001$	0.7, $p<0.0001$
Worse anxiety	0.6, $p<0.0001$	0.7, $p<0.0001$
Worse fatigue	0.7, $p<0.0001$	0.6, $p<0.0001$
Stronger peer relationships	0.2, $p=0.6$	0.1, $p=0.6$
Lower physical functioning	0.4, $p=0.003$	0.3, $p=0.02$
Higher pain interference	0.5, $p=0.0004$	0.5, $p=0.0002$
Higher pain severity	0.4, $p=0.003$	0.4, $p=0.002$

PHQ9 (Patient Health Questionnaire-9) scores ranged from 0-27; GAD7 (Generalized Anxiety 7-item scale) scores ranged from 0-21. PROMIS (Patient Reported Outcome Measurement Information System) scores were measured as T-scores, except for pain severity measured on a scale of 1-10. Spearman rho correlation coefficients shown.

Disclosure: T. Rubinstein, None; M. Dionizovik-Dimanovski, None; C. Smith, None; R. Kraus, None; J. T. Jones, None; J. Harris, None; M. Rodriguez, None; L. Faust, None; B. Rutstein, None; R. Puplava, None; M. Teshar, None; A. M. Davis, None; K. Onel, None; S. Sule, None; E. von Scheven, None; A. M. Knight, None.

Abstract Number: 1848

Cardiovascular Risk Factors in Adults with Juvenile Idiopathic Arthritis in Sustained Remission

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical I: Outcomes and Comorbidities

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Juvenile Idiopathic Arthritis (JIA) is one of the more common chronic diseases of childhood that often persists into adulthood and can result in significant long-term morbidity. Cardiovascular disease (CVD) is an important cause of mortality and morbidity in patients with rheumatoid arthritis and possibly other forms of adult inflammatory arthritis. However, the long-term risk of CVD for individuals with JIA remains uncertain

Objective: To determine whether adults with JIA in remission and medium-long duration of the disease have an increased risk of CVD.

Methods: This is a cross-sectional study including 27 patients diagnosed with JIA according to the International League of Associations for Rheumatology criteria (ILAR 2001) were compared to 27 age- and sex-matched controls. Remission was determined by JADAS27<1 and according to Wallace criteria. An extensive clinical analysis including body index mass, lipid profile, HOMA-IR and intra-arterial blood pressure was performed. Intima media thickness of the common carotid artery (CIMT) was measured as a marker of subclinical atherosclerosis. Proinflammatory cytokines (TNF α , IL1b and IL6), molecules involved in endothelial dysfunction (VEGF, ICAM-1 and E-Selectin) and adipokines (leptin, adiponectin, resistin and visfatin) were analyzed on serum by ELISA

Results: Mean duration of the disease was 14.51 ± 2.20 years. Mean age was 29.31 ± 0.78 . Time in remission was 4.22 ± 0.64 years. Metabolic comorbidities such as obesity and metabolic syndrome were more prevalent in our cohort of JIA patients compared to controls. Levels of cholesterol were significantly elevated in patients. CIMT was higher in JIA patients compared to controls, although it did not reach the statistical significance. Serum levels of cytokines (TNF α , IL6 and IL1b) and endothelial activation markers (VEGF and ICAM-1) were elevated in JIA adult patients. Serum levels of adiponectin were significantly decreased. In contrast, levels of resistin and visfatin were higher in JIA patients. Disease duration significantly correlated with CIMT values, cholesterol and TNF α levels. In addition, there was an association among levels of lipids, adipokines and inflammatory mediators.

Conclusion: In adult JIA patients with clinical remission, CIMT and levels of inflammatory cytokines, adipokines and endothelial activation markers were elevated, molecules with a relevant role in the onset and progression of endothelial dysfunction and atherosclerosis. These results might suggest that long-term JIA patients could have higher cardiovascular risk, although they are in sustained remission. Thus, cardiovascular risk assessment should be considered as part of routine clinical care in those patients.

Disclosure: I. Arias de la Rosa, None; I. C. Aranda-Valera, None; R. Roldan, None; M. C. Abalos-Aguilera, None; M. D. de la Rosa-Garrido, None; Y. Jiménez-Gómez, None; C. Perez-Sanchez, None; A. Escudero-Contreras, None; C. Lopez-Pedrerá, None; E. Collantes-Estévez, None; N. Barbarroja, None.

Abstract Number: 1849

Remission Status after 18 Years of Follow-up in the Population-Based Nordic Juvenile Idiopathic Arthritis (JIA) Cohort

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical I: Outcomes and Comorbidities

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Innovative changes towards targeted treatment have improved the outcome dramatically for juvenile idiopathic arthritis (JIA) but the question remains how well these patients perform during long-term follow-up. The aim of the study was to assess the disease activity, remission rate and damage 18 years after JIA onset in a population-based setting.

Methods: 510 consecutive cases of JIA with disease onset between 1997 and 2000 from Denmark, Norway, Sweden and Finland were prospectively included in a close to population-based 18-year (mean 17.5 years; range 14.2-20.2) follow-up study. The follow-up visit included an update on the demographic and clinical data such as a joint examination and remission status (preliminary Wallace criteria).

Results: In total 434/510 (85%) eligible JIA participants with a mean age (\pm SD) of 24.0 (\pm 4.4) years were included. Of those, 76 participants (15%) were lost to follow-up. Out of the included participants 329 (76%) attended a follow-up visit, and 105 participants (24%) were evaluated by a telephone interview.

The distribution of the JIA categories was as follows: 3% systemic, 27% persistent oligoarticular, 20% extended oligoarticular, 16% polyarticular RF negative, 1% polyarticular RF positive, 7% psoriatic, 10% enthesitis-related arthritis (ERA) and 15% undifferentiated JIA.

Treatment with synthetic disease-modifying anti-rheumatic drugs were given to 66 participants (15 %) and biologics to 84 patients (19%) at the follow-up.

For the 329 participants the median active joint count was 0 (range 0-15), however during the 18 years of disease course the median cumulative joint count was 8 (range 1-59). The median composite juvenile arthritis disease activity score JADAS71 was median 1.5 (range 0-31.6) with the ERA category having the highest median score of 4.5 (range 0-16.5) ($p=0.003$). In the cohort 48% had a JADAS71 score <1 indicating inactive disease.

Articular damage (JADI-A) was found in 20% of the participants who had a follow-up visit and 12.5% had developed extra-articular damage (JADI-E), most commonly as ocular damage, found in 26/41 (63%). The highest JADI-A and JADI-E scores were found in the polyarticular RF negative and psoriatic categories.

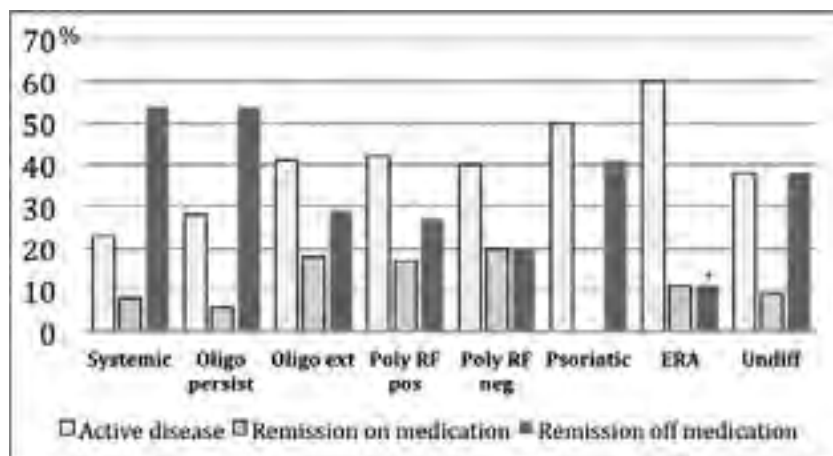
Remission off medication (CR) was documented in 44%, but still 39.8% had active disease (Fig. 1). Extensive variability was found among the categories. Achievement of CR was most often seen in persistent oligoarticular and systemic arthritis in contrast to the lowest rate observed in ERA (*: $p<0.001$, fig 1).

Conclusion: A significant proportion of the JIA cohort does not reach remission despite new treatment options. Notably more than one third receive systemic treatment even 18 years after disease onset. The worst outcome was evident in the ERA category and in general the JIA disease burden in adulthood remains extensive.

Figure 1

Disease status 18 years after disease onset (n=329)

Disclosure: M. Glerup, None; V. Rypdal, None; E. D. Arnstad, None; M. Ekelund, None; S. Peltoniemi, None; K. Aalto, None; M. Rygg, None; P. Toftedal, None; S. Nielsen, None; A. Fasth, None; L. Berntson, None; E. Nordal, None; T. Herlin, None.



A Population Based Study of High School Academic Outcomes in Individuals with Childhood-Onset Chronic Rheumatic Diseases in Manitoba, Canada

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Pediatric Rheumatology – Clinical I: Outcomes and Comorbidities

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Childhood-onset chronic rheumatic diseases (ChildCRD) are rheumatic diseases with onset <18 years old, including juvenile arthritis (JA) and systemic autoimmune rheumatic diseases (SARD). ChildCRD patients experience poor health during their school years, which could impact educational performance and future employment. Previous studies have not demonstrated poorer educational outcomes in ChildCRD, but were limited to clinic populations and therefore may not produce generalizable results. We have used a population-based approach to compare the grade 12 academic performance of ChildCRD individuals to that of matched controls without ChildCRD.

Methods: *Population* All ChildCRD patients for the province of Manitoba, Canada: JA and SARDs (systemic lupus erythematosus, Sjogren's syndrome, inflammatory myositis and systemic sclerosis), were ascertained from a clinic registry (1984-2014) maintained by a single pediatric rheumatologist. Registry data were anonymously linked to the administrative health, education and social data housed at the Manitoba Centre for Health Policy (MCHP), including: health insurance registry (to ascertain healthcare coverage and demographics), hospital records, physician billing claims, education, social services and employment records. The ChildCRD cohort included individuals from the 1979- 1998 birth cohorts (i.e., completed grade 12 in 1996- 2015). The control population was derived by matching 5:1, by age, sex and residential postal codes. **Outcomes:** MCHP has developed a language arts achievement index (LAI) and maths achievement index (MAI), using scores from the grade 12 standards tests and enrollment information. **Prognostic factors:** Socioeconomic status was defined from an area-based socioeconomic factor index 2 (SEFI2) based on census data. Psychiatric comorbidity was defined using validated diagnostic algorithms. Social factors included maternal age at first childbirth, family ever on income assistance, family ever involved with child welfare services.

Results: A total of 541 Manitoban ChildCRD patients (497 JA, 44 SARD), 70 % females, mean age at diagnosis 9.33 (\pm 4.91) years, were linked to the administrative data. A total of 2713 matches without ChildCRD (controls) were selected. ChildCRD patients have lower score categories (worse performance) than controls (LAI: -0.220, 95% CI -0.314 – -0.125, $p < 0.0001$; MAI: -0.214, 95% CI -0.310 – -0.119, $p < 0.0001$). In multivariable linear regression models adjusted for birth cohort, SEFI2, maternal age at first childbirth, family on income assistance, child in care and disease course psychiatric comorbidity, ChildCRD patients still had lower LAI and MAI test score categories (LAI: -0.232, 95% CI -0.315 – -0.149; MAI: -0.228, 95% CI -0.313 – -0.142) than controls.

Conclusion: This population-based study of patients with ChildCRD shows that ChildCRD has a detrimental effect on educational results, compared to matched, disease-free individuals. ChildCRD exerts an independent effect on standardized education outcomes independent of socioeconomic, demographic and psychiatric comorbidities.

Disclosure: S. H. L. Lim, None; R. A. Marrie, None; O. Ekuma, None; M. Brownell, None; C. A. Peschken, None; C. A. Hitchon, None; K. Gerhold, None; L. Lix, None.

Abstract Number: 1851

Physical Function Trajectories in Children with Juvenile Myositis

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SESSION INFORMATION

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Session Title: Pediatric Rheumatology – Clinical I: Outcomes and Comorbidities

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Background/Purpose: Juvenile myositis (JM) is an inflammatory disease that causes muscle weakness, skin rashes, and significant deconditioning. Little is known about long-term resolution of physical disability. We examined trajectories of physical function in JM.

Methods: JM registry data were collected at routine visits (January 2000 to June 2014) to Ann & Robert H. Lurie Children's Hospital of Chicago and analyzed in this study. Only patients whose baseline visit was < 3 months after initiation of treatment were included. The following variables were extracted: parent-proxy reported Childhood Health Assessment Questionnaire (CHAQ), gender, race, duration of untreated disease, Disease Activity Score (DAS) - muscle/skin domains, Childhood Myositis Assessment Scale (CMAS), muscle enzymes, nail fold capillary end row loops (NFC-ERL), von Willebrand factor antigen (vWFAg), calcinosis (ever experienced), lipodystrophy (ever experienced), TNFalpha-308A allele, and treatments. Descriptive statistics were calculated. Latent trajectory analysis was performed assessing probability of CHAQ > 0 (binary outcome 0 vs > 0). Baseline values for demographic/clinical variables above were compared across identified trajectories (Fisher's exact; Kruskal-Wallis).

Results: Baseline descriptive statistics for n = 104 included patients with median 13.5 study visits and median follow-up 54 months are shown in Table 1. Three trajectories corresponding to mild (n = 46 [44%]), moderate (n = 32 [31%]), and severe disability (n = 26 [25%]) were identified (Figure 1). Statistically significant differences in baseline variables for mild vs moderate vs severe groups were noted for: CHAQ (0.13 vs 0.88 vs 1.35, p < 0.001), DAS-Muscle (4 vs 6 vs 6, p = 0.001), and CMAS (40 vs 31 vs 34, p = 0.01). Median baseline NFC-ERL differed, with higher counts in the mild group (= 5) vs moderate and severe groups (= 3.83 and 4.14), p = 0.047. Race trended toward significance (p = 0.08), with fewer white patients in the severe group (n = 13 white patients vs n = 26 total patients in severe group).

Conclusion: To our knowledge, this is the first study describing longitudinal trajectories of physical function (distinct from disease activity) in JM. Baseline physical function (i.e. CHAQ) and muscle weakness (i.e. DAS-Muscle, CMAS) predict long-term physical function trajectory. Baseline vasculopathy (i.e. NFC-ERL) may be less prominent in JM patients following the mild physical function trajectory. There may also be racial disparities in physical function trajectories among youth with JM, though this requires further study.

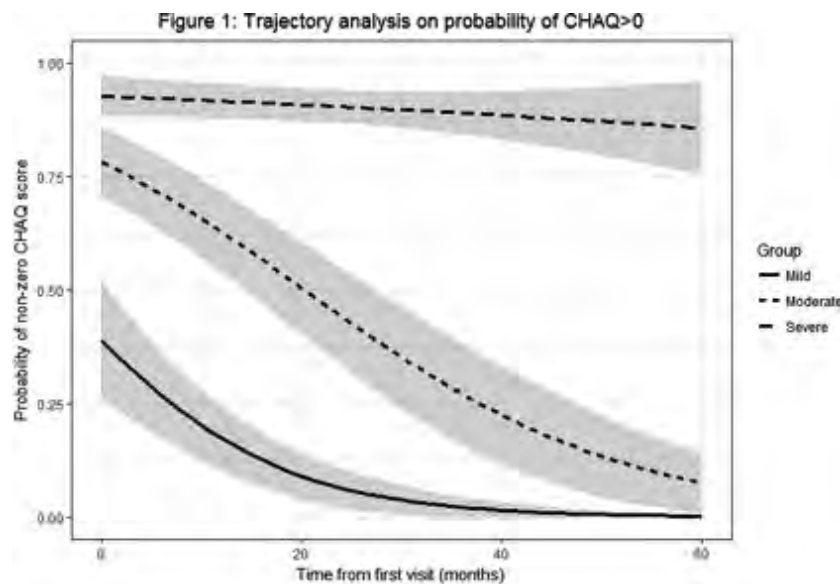


Table 1 Baseline Demographic and Clinical Descriptives (n = 104 patients)

	n = # with baseline data	n (%) / median (IQR)
Race	104	
White		71 (68.3%)
Hispanic		20 (19.2%)
Black		7 (6.7%)
Other*		6 (5.8%)
Female Gender	104	78 (75%)
Age of Onset (years)	104	5.3 (2.7-7.7)
Age at Initial Visit (years)	104	5.85 (3.6-8.2)
Duration of Untreated Disease (months)	104	5.5 (2.4-11.9)
CHAQ summary score value	101	0.62 (0.12-1.37)
CHAQ summary score > 0	101	76 (75.2%)
DAS-Skin	102	6 (5.6)
DAS-Muscle	102	5 (3.7)
CMAS	67	37 (30.5-44)
AST	86	41 (30-63.3)
CPK	90	106 (54.3-379.3)
LDH	88	306 (243.8-463.5)
Aldolase	86	10.2 (7.2-14.7)
NFC-ERL	91	4.3 (3.7-5.6)
vWF Ag (abnormal value)	87	67 (77%)
Calcinosis (ever experienced)	104	9 (8.7%)
Lipodystrophy (ever experienced)	104	31 (29.8%)
TNFalpha-308A Allele	100	
AA		1 (1%)
GA		29 (29%)
GG		70 (70%)
Medications		
On any medication at initial visit	90	52 (57.8%)
Oral or IV Steroids	101	42 (41.6%)
Methotrexate	101	29 (28.7%)
Other treatment (IVIG, etc)	55	15 (27.3%)

*Other race group comprised of: 3 Asian, 1 Indian, 1 American Indian/Alaskan, and 1 Other patient

Disclosure: K. Ardalan, None; E. L. Gray, None; J. Lee, None; M. L. Wolfe, None; G. A. Morgan, None; L. M. Pachman, None.

Abstract Number: 1852

Pregnancy in Lupus: 17-Year U.S. Nationwide Trend in Obstetric and Maternal Outcomes

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Reproductive Issues in Rheumatic Disorders

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Pregnancies in systemic lupus erythematosus (SLE) are considered high risk and associated with medical and obstetric complications [1]. Our objective was to study the national trends of obstetric and medical complications in pregnant SLE patients over the past 2 decades.

Methods: Our study analyzed yearly retrospective trends of cross-sectional data using National Inpatient Sample (NIS) database from 1998 to 2014. Diagnoses and procedures were identified using ICD-9 codes. We included pregnancy-related admissions (diagnosis codes 632-649, 650-669, 670-679, V27, procedure code 72-75) with and without SLE (ICD 9 code 710.0). We studied multiple medical and obstetric complications including maternal mortality, cesarean section, intrauterine fetal death, preeclampsia/eclampsia, length of stay and inflation adjusted hospital charges. Univariable logistic regression was performed to assess temporal trend in SLE and non-SLE pregnancies. Logistic regression with interaction term between SLE and year was performed to detect whether SLE was an effect modifier for our outcomes. Weights were applied to represent the nationwide estimates.

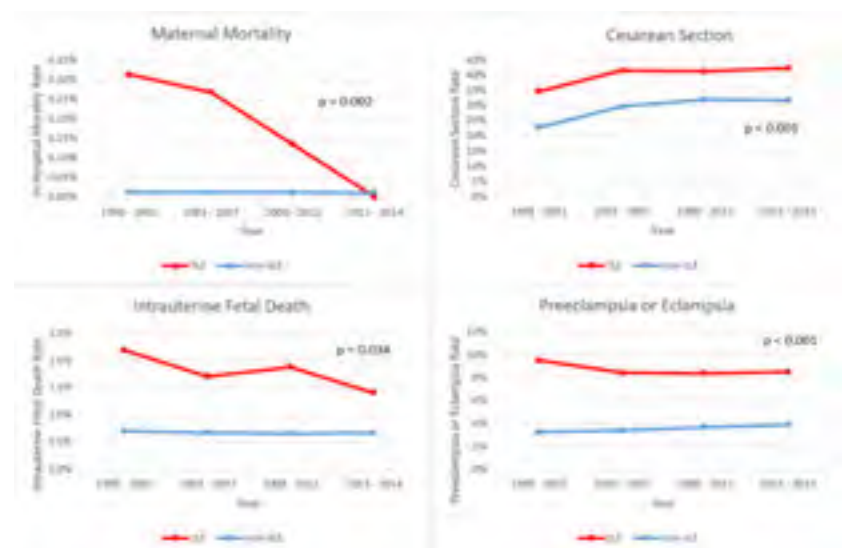
	SLE pregnancies n = 87,065	Non SLE pregnancy n = 73,860,579
Number of Deliveries	70,134	68,461,097
Mean Age	29.2 ± 5.8	27.5 ± 6.2
Race		
Caucasian	39%	42%
African American	21%	12%
Hispanic	15%	17%
Other*	25%	29%
Obstetric Outcomes		
Cesarean Section	40%	29%
Intrauterine Fetal Death	1.80%	0.65%
Preeclampsia or Eclampsia	8.7%	3.5%
Antepartum Bleeding	3.9%	2.0%
Postpartum Bleeding	4.1%	2.8%
Medical Comorbidities/Complications		
Maternal Mortality (per 10,000 patients)	188	12
Venous Thromboembolism	0.56%	0.06%
Seizure Disorder	2.93%	0.49%
Chronic Kidney Disease or Glomerular Disease	11.07%	0.08%
Hypertension (including Gestational)	15.23%	5.01%
Diabetes Mellitus (including Gestational)	7.74%	6.48%
Packed Red Blood Cell Transfusion	4.09%	0.99%
Length of Inpatient Stay (days)	4.1	2.6
Total Hospital Charges (USD)†	22,654	12,799

*Other includes Asian or Pacific Islander, Native American, other races and missing data

†Inflation Adjusted by Yearly Personal Health Care Price Indices - Hospital Care

Temporal Trend Data Table	1999 - 2002 (5 years)	2003 - 2007 (5 years)	2008 - 2012 (5 years)	2013 - 2018 (6 years)	Adjusted Difference
Number Pregnancies	13,811	25,283	28,884	22,249	
Number of Deliveries	13,811	25,283	28,884	22,249	
Obstetric Outcomes					
Cesarean Section	39%	40%	41%	42%	p < 0.001
Intrauterine Fetal Death	1.8%	1.7%	1.6%	1.5%	p < 0.001
Preeclampsia or Eclampsia	8.7%	8.8%	8.9%	9.0%	p < 0.001
Antepartum Bleeding	3.9%	3.9%	4.0%	4.1%	p < 0.001
Postpartum Bleeding	4.1%	4.1%	4.2%	4.3%	p < 0.001
Medical Comorbidities/Complications					
Maternal Mortality (per 10,000 patients)	188	188	188	188	p < 0.001
Venous Thromboembolism	0.56%	0.56%	0.56%	0.56%	p < 0.001
Seizure Disorder	2.93%	2.93%	2.93%	2.93%	p < 0.001
Chronic Kidney Disease or Glomerular Disease	11.07%	11.07%	11.07%	11.07%	p < 0.001
Hypertension (including Gestational)	15.23%	15.23%	15.23%	15.23%	p < 0.001
Diabetes Mellitus (including Gestational)	7.74%	7.74%	7.74%	7.74%	p < 0.001
Packed Red Blood Cell Transfusion	4.09%	4.09%	4.09%	4.09%	p < 0.001
Length of Inpatient Stay (days)	4.1	4.1	4.1	4.1	p < 0.001
Total Hospital Charges (USD)†	22,654	22,654	22,654	22,654	p < 0.001

†Inflation Adjusted by Yearly Personal Health Care Price Indices - Hospital Care



Results: 87,065 pregnant women with SLE and 70,162,163 without SLE had hospitalizations in US from 1998 to 2014. Pregnant SLE patients were older (29.2 \pm 5.8 vs 27.5 \pm 6.2), had a higher proportion of African Americans (21% vs 12%) and had a higher maternal mortality, and intrauterine fetal death, compared to those without SLE. (Table 1) Increased obstetric as well as maternal complications and comorbidities are observed in SLE patients compared to non-SLE patients. There was a decline in maternal mortality and intrauterine fetal death overtime and this decline was greater in SLE patients compared to those without SLE ($p = 0.002$ and 0.034 , respectively).(Figure 1) There was an increase in cesarean section in both SLE and non-SLE pregnancies and the increase in SLE pregnancies was less than non-SLE pregnancies ($p < 0.001$). Length of stay decreased in SLE pregnancies however increased in non-SLE pregnancies ($p < 0.001$). (Table 2)

Conclusion: Maternal and fetal mortality and important clinical outcomes in SLE pregnancies have improved over the past two decades. This is the largest study of SLE pregnancies in the U.S..

[1] Peart E et al, Curr Opin Rheumatol. 2014

Disclosure: Y. Luo, None; J. Xu, None; B. Y. Mehta, None.

Abstract Number: 1853

Paternal Use of Methotrexate (MTX) and Congenital Malformations – a Systematic Review and Meta-Analysis

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SESSION INFORMATION

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Session Title: Reproductive Issues in Rheumatic Disorders

Session Type: ACR Concurrent Abstract Session

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Background/Purpose: In rheumatology, fertile men and women are commonly treated with methotrexate (MTX). Maternal preconceptional MTX exposure is teratogenic, but less is known about paternal MTX exposure. Due to possible teratogenic risk, current treatment recommendations advocate that men should discontinue MTX three months before conception. This may lead to impaired adherence to treatment, fear among the future parents and even unnecessary induced abortions.

Here we systematically review and meta-analyse the collective data on paternal MTX exposure and the risk of congenital malformations.

Methods: Systematic searches in the databases PubMed, Embase, Cochrane central, and cinahl were performed 1st March 2018. We included studies with an English abstract that assessed pregnancy outcome following paternal exposure to MTX. No time restriction was applied. Review Manager Version 5.3 was used for the meta-analysis.

Results: We identified twelve studies assessing congenital malformations following paternal exposure to MTX of which 3 were case reports. Three studies were included in the meta-analysis including in total 265 fathers exposed to MTX and 1,004,834 controls. Among the MTX-exposed 13 had malformations of which 7 was major, and among the non-exposed 50,576 had malformations, of which 33,816 was major. Odds ratio for major malformations was 1.02 (95% confidence interval [CI] 0.48-2.20). Odds ratio for all malformations was 0.86 (CI 0.48-1.54). Thus no association was found.

Conclusion: In a systematic review and meta-analysis we found no association between preconceptional paternal MTX use and major or all congenital malformations. Thus, there is no evidence supporting the current recommendations to avoid paternal MTX use before conception.

Disclosure: T. B. Jensen, None; M. Bring Christensen, None; J. Trærup Andersen, None.

SLE Flares during and after Pregnancy Are Mild and Occur at Similar Rates

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SESSION INFORMATION

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Session Title: Reproductive Issues in Rheumatic Disorders

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Background/Purpose: Systemic lupus erythematosus (SLE) disproportionately affects women of childbearing age. Low disease activity for 6 months prior to conception leads to the best outcomes; however, there is little prospective data describing the relative frequency and predictors of flares during and after pregnancy under such conditions.

Methods: Analyses used data from the PROMISSE study, a multicenter, prospective observational study (2003-2014) of 384 pregnant women meeting ≥ 4 ACR SLE criteria. Subjects were enrolled <12 wks gestation and samples collected

A. Association Between Baseline Characteristics and Occurrence of Mild/Moderate or Severe Flare During Pregnancy				
Characteristic	Total (n = 384)	No Flares (n = 284)	Flares (n = 100)	P Value
Ethnicity/Race				0.019
Non-Hispanic White	188 (49)	149 (52.5)	39 (39)	
Other	196 (51)	135 (47.5)	61 (61)	
Mean Age (SD) (n = 384), y	30.92 (4.89)	31.4 (4.73)	29.56 (5.08)	0.0018
Renal Disease				0.75
No	264 (68.8)	197 (69.4)	67 (67)	
Yes	120 (31.2)	87 (30.6)	33 (33)	
Anti-dsDNA antibodies				0.85
Negative	217 (58)	162 (58.5)	55 (56.7)	
Positive	157 (42)	115 (41.5)	42 (43.3)	
aPLs				0.25
Negative	322 (83.9)	234 (82.4)	88 (88)	
Positive	62 (16.1)	50 (17.6)	12 (12)	
LAC				0.17
Negative	350 (91.1)	255 (89.8)	95 (95)	
Positive	34 (8.9)	29 (10.2)	5 (5)	
Urinary protein excretion >500 mg/d				1
No	338 (91.1)	251 (91.3)	87 (90.6)	
Yes	33 (8.9)	24 (8.7)	9 (9.4)	
Platelet Count				
Mean (SD), $\times 10^3$ cells/L	253.07 (84.32)	252.96 (84.25)	253.39 (84.94)	0.97
$<100 \times 10^3$ cells/L				0.095
No	369 (97.6)	276 (98.6)	93 (94.9)	
Yes	9 (2.4)	4 (1.4)	5 (5.1)	
Low Complement Level				0.021
No	251 (65.9)	195 (69.4)	56 (56)	
Yes	130 (34.1)	86 (30.6)	44 (44)	
SLEPDAI				
Mean score (SD) (n = 380)	2.79 (2.99)	2.55 (2.89)	3.47 (3.18)	0.012
Median score (n = 380)	2	2	4	0.0022
Score >4				
No	324 (85.3)	247 (88.2)	77 (77)	0.011
Yes	56 (14.7)	33 (11.8)	23 (23)	
PGA				
Mean score (SD) (n = 366)	0.4 (0.54)	0.33 (0.5)	0.59 (0.6)	0.00014
Median score (n = 366)	.1	0	.5	1e-06
Score >1				
No	327 (89.3)	249 (92.2)	78 (81.2)	0.0051
Yes	39 (10.7)	21 (7.8)	18 (18.8)	
B. Occurrence of Mild/Moderate or Severe Flare During Pregnancy from Logistic Regression Models				
Baseline Predictor Variables	OR (95% CI)		P Value	
Age at Screening (per increase of 10 years)	9.3 (8.9 – 9.8)		0.0096	
Non-Hispanic white (yes vs no)	0.65 (0.40 – 1.08)		0.096	
Screening SLEPDAI Low Complement (yes vs no)	1.55 (0.93 – 2.55)		0.087	
Screening SLEPDAI PGA Score (per increase of 1)	2.11 (1.38 – 3.24)		0.0006	

throughout pregnancy and post-partum. Exclusion criteria were multi-fetal pregnancy, active disease (prednisone >20 mg/d), or renal disease (proteinuria >1 gm/24h, and creatinine > 1.2 mg/dL). Mild/moderate and severe flares were defined using the SELANA-SLEDAI Flare Index. Flares during pregnancy were assessed in all 384 patients, and post-partum flares in those with study visits 2-6 months post-partum. Logistic regression models were fit to the data to identify independent predictors of experiencing any type of flare during pregnancy and post-partum.

Results: Rates of Flare: 105 flares were recorded during pregnancy (3.8% 1st Trimester, 53.3% 2nd, 42.9% 3rd). Counting one flare per person, 100 of 384 patients (26%) flared at any point during pregnancy; 20.8% of patients had mild/moderate flares and 6.25% had severe. 57 of 234 patients (24.4%) with a study visit 2-6 months post-partum flared; 22.7% had mild/moderate flares and 1.7% severe. Post-partum flares were mild, and 19 of 57 (33.3%) were treated; 13 with an increase in prednisone, 6 with NSAID or hydroxychloroquine, and 1 with mycophenolate mofetil. The rate of any type of flare was 0.39/person-year at any point during pregnancy and 0.84/person-year post-partum. The proportion of subjects who had any flares during and after pregnancy was similar, but the post-partum flares occurred over a shorter duration of follow-up.

Correlates of Flare: Among baseline variables considered (Table) only age, ethnicity/race, low complement, and PGA were independently predictive of having any flare during pregnancy. Clinical features associated with adverse pregnancy outcome (platelet count, antihypertensive use, and LAC) were not predictive of flare. The mean time from the last visit during pregnancy to the post-partum visit was 20 weeks and ranged from 9 to 34 weeks. Neither baseline clinical variables nor clinical variables of the last visit during pregnancy were associated with occurrence of any post-partum flare.

Conclusion: Flares during pregnancy are correlated with clinical and serological activity during the first trimester. Flares during and after pregnancy are typically mild, infrequently require treatment, and occur at similar rates.

Disclosure: J. Davis-Porada, None; S. Stern, None; M. M. Guerra, None; C. Laskin, None; M. Petri, None; M. Lockshin, None; L. R. Sammaritano, None; D. Branch, None; A. D. Sawitzke, None; J. T. Merrill, None; J. P. Buyon, None; M. Kim, None; J. E. Salmon, None.

Abstract Number: 1855

Erythrocyte Bound C4d in the Presence of Adverse Pregnancy Outcome Events in Pregnant Women with Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Reproductive Issues in Rheumatic Disorders

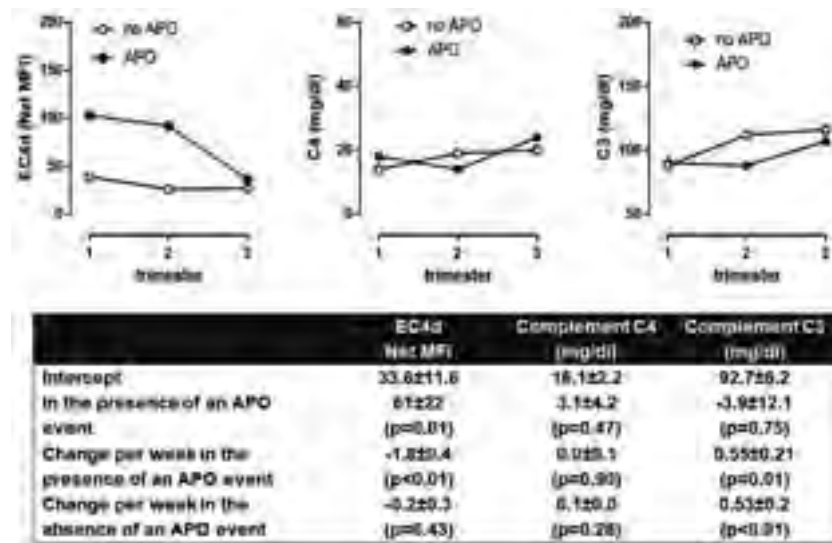
Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Activation of the alternative and terminal attack complex of the complement system has been associated with adverse pregnancy outcomes (APOs) in stable/quiescent systemic lupus erythematosus (SLE). This prospective study examined erythrocyte bound C4d (EC4d), a marker demonstrating classical pathway activation, and complement C3/C4 levels in relationship to APO in pregnant SLE patients regardless of disease activity at entry.

Methods: Consecutive pregnant women (fulfilling ACR or SLICC criteria) were enrolled with no restrictions on disease activity or prednisone dosage. Serum C3 and C4 levels were measured using immunoturbidimetry and EC4d was measured from EDTA blood using flow cytometry and expressed as net mean fluorescence intensity (MFI). Whole blood Hydroxychloroquine (HCQ) levels were measured using liquid chromatography. Measures of disease activity consisted of Physician Global Assessment (PGA) visual analogue scale (0-3 cm) and clinical SLE Pregnancy Disease Activity Index (SLEPDAI) without immunology components. Estimates relating EC4d, complement C3 and C4 levels during gestation in the presence or the absence of APO events were analyzed using t-test and linear mixed effect models.

Results: A total of 29 consecutive women (mean age 32±1 years [SEM], 58% Caucasians and 21% African Americans) were enrolled and followed for an average of 3.1±0.2 visits during gestation. At baseline, mean PGA was 0.4±0.1 points and mean clinical SLEPDAI was 1.7±0.6 points, with 92% subjects ANA positive [titers≥1:80]. Six pregnancies (21%) resulted in APO events (two fetal deaths [at 27 and 28 weeks], three pre-term deliveries [range 27-35 weeks] and one



delivery with small gestational age). The Figure highlights the change in EC4d, complement C4 and C3 levels in the patients with or without an APO. As presented in the Table and Figure, EC4d levels were higher during the first trimester in patients who went on to have APOs than in patients without APO (102 ± 34 and 36 ± 11 net MFI; $p < 0.05$). In contrast, C3 and C4 levels were similar irrespective of APO status ($p > 0.47$). During gestation, EC4d levels decreased by 1.8 units per week in those with APOs ($p < 0.01$) but did not vary in those without APOs (estimate = -0.2; $p = 0.43$). C3 increased during pregnancy irrespective of APOs (0.5 mg/dl per week). PGA and clinical SLEPDAI were not associated with APO ($p > 0.08$). 25 patients were prescribed HCQ and there were no differences in the levels between the APO and non-APO groups (mean 1253 ± 253 vs 850 ± 196 ng/ml; $p = 0.28$). In fact, all subjects with APO received HCQ and levels were > 500 ng/ml (range 571-2139 ng/ml).

Conclusion: This prospective study suggests that EC4d is elevated early pregnancy in those destined for APOs, despite compliant HCQ levels in women with SLE. Classical pathway activation as measured by cell based complement products may be an important early biomarker and reveal pathogenesis of APO in SLE.

Disclosure: J. P. Buyon, Exagen, 2; P. M. Izmirly, Exagen, 2; H. M. Belmont, Exagen, 2; J. Conklin, Exagen Diagnostics Inc., 3; N. Kaiden, Exagen, 2; J. E. Salmon, None; R. Alexander, Exagen Diagnostics, Inc., 3; T. Dervieux, exagen, 3.

Abstract Number: 1856

Low Aspirin Use and High Prevalence of Preeclampsia Risk Factors Among Pregnant Women in a Multi-National SLE Inception Cohort

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Reproductive Issues in Rheumatic Disorders

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Because aspirin reduces the risk of preeclampsia in high-risk pregnancies by more than half, best practice guidelines recommend that aspirin be initiated in pregnant women with ≥ 1 high-risk factors for preeclampsia, including SLE. Our objective was to assess the prevalence of aspirin use in SLE pregnancies within a multi-national inception cohort, and compare aspirin use among those with and without additional preeclampsia risk factors.

Methods: Premenopausal women aged 18-45 were enrolled in the Systemic Lupus International Collaborating Clinics (SLICC) Registry (2000-2017) within 15 months of SLE diagnosis. Study visits with a current pregnancy were assessed for aspirin use and preeclampsia risk factors (hypertension, renal disease, diabetes, nulliparity, BMI ≥ 35 , age > 40). Aspirin use was compared among those with and without such risk factors, as well as disease-specific risk factors (e.g. antiphospholipid antibodies [+aPL]), and over time.

Results: We identified 300 women with 475 pregnancies. Half (51%) had ≥ 1 traditional preeclampsia risk factors (in addition to SLE), and a third (33%) had +aPL. We observed aspirin use in 25% of pregnancies (95%CI 22,29), which did not differ among pregnancies with and without ≥ 1 traditional risk factor [25% (95%CI 20,31) versus 26% (95%CI 21,32)]. Aspirin use was higher among those with +aPL [38% (95%CI 24,55)] versus those without [23% (95%CI 15,34)], and was higher in whites [32% (95%CI 26,39)] compared with black women [10% (95%CI 5,18)]. Regional variability was observed in aspirin use (12-37%). We could not establish a trend of increasing aspirin use over time.

Conclusion: In this multi-centre analysis of SLE pregnancies, we observed that most women were not on aspirin and that half had additional preeclampsia risk factors. It is possible that aspirin was introduced at/or following the study visit when the pregnancy was documented, highlighting the importance of the rheumatologist in reviewing aspirin use and initiating it, if not already done, in pregnant SLE women. Our findings suggest black SLE women as a potentially vulnerable group during pregnancy, having the lowest prevalence of aspirin use.

Table 1 Demographic and disease characteristics according to aspirin use

Characteristic	All pregnant visits (n=475)	Pregnant visits with aspirin (n=121)	Pregnant visits without aspirin (n=354)
Patient characteristic			
Age, mean (SD)	31.0 (4.9)	30.5 (4.6)	31.2 (5.0)
Ethnicity, n (%)	66 (14)	7 (11)	59 (89)
Asian	7 (2)	6 (86)	1 (14)
Black	88 (19)	9 (10)	79 (90)
Caucasian	205 (43)	67 (33)	138 (67)
Hispanic	62 (13)	20 (32)	42 (68)
Indian subcontinent	25 (5)	8 (30)	17 (68)
Other	22 (5)	4 (18)	18 (81)
Country, n (%)	121 (25)	27 (22)	94 (77)
Canada	105 (22)	20 (19)	85 (81)
United States	52 (11)	19 (37)	33 (63)
Mexico	146 (31)	49 (34)	97 (66)
Europe	51 (11)	6 (12)	45 (88)
South Korea			
Years of education prior to college or university, mean (SD)	11.6 (2.0)	11.1 (2.1)	11.8 (2.0)
Years of post-secondary education, mean (SD)	2.6 (2.7)	2.4 (2.7)	2.7 (2.7)
Any post-secondary education, n (%)	310/452 (69)	69/310 (22)	241/310 (77)
BMI, mean (SD)	25.8 (5.9)	26.3 (5.2)	25.6 (6.1)
Obstetrical history			
Parity, mean (SD)	1.1 (1.0)	1.1 (1.0)	1.2 (1.0)
Nulliparous, n (%)	134/461 (30)	37/134 (28)	97/134 (72)
Previous fetal loss <24 weeks, n (%)	84/456 (18)	22/84 (26)	62/84 (74)
SLE characteristics			
Disease duration, mean (SD)	5.6 (3.3)	5.6 (3.3)	5.6 (3.3)
SLEDAI, mean (SD)	3.3 (3.8)	3.0 (3.6)	3.4 (3.9)
SLICC damage score, mean (SD)	0.5 (1.0)	0.6 (1.0)	0.5 (1.0)
Any positive aPL n (%)	34/104 (33)	13/34 (38)	21/34 (62)
LAC n (%)	19/104 (18)	6/19 (32)	13/19 (68)
ACL n (%)	12/104 (12)	3/12 (25)	9/12 (75)
GPI IgG* n (%)	18/104 (17)	9/18 (50)	9/18 (50)
History of nephritis, n (%)	53 (11)	11/53 (21)	42/53 (79)
Co-morbidities			
Any renal disease†, n (%)	83 (17)	17/83 (20)	66/83 (80)
CKD (eGFR ≤ 90) n (%)	43/459 (9)	6/43 (14)	37/43 (86)
CKD stage 3 or less (eGFR ≤ 60) n (%)	11/459 (2)	5/11 (45)	6/11 (55)
Hypertension, n(%)	79 (17)	24/79 (30)	55/79 (70)
Anticoagulant use, n(%)	28 (6)	12 (43)	15 (54)

SD, standard deviation; BMI, Body Mass Index; CKD, Chronic kidney disease; eGFR, estimated glomerular filtration rate; PE, preeclampsia; aPL, antiphospholipid antibody; LAC, lupus anticoagulant; ACL, anti-cardiolipin antibody; GPI, anti-B2-glycoprotein-1; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SDI, Systemic Lupus International Collaborating Clinics

* no positive GPI IgM identified in any group

† including CKD, nephritis, nephrotic syndrome within the last year

Table 2 Prevalence of aspirin use according to preeclampsia risk factors

Risk factor	Prevalence of aspirin use	
	With risk factor	Without risk factor
Age >40	2/14 (14, 4-40)	119/461 (26, 22-30)
BMI ≥ 35	8/33 (24, 13-41)	113/442 (26, 22-30)
Nulliparous	37/134 (28, 21-36)	79/327 (24, 20-29)
Any renal disease	17/83 (20, 13-30)	104/392 (27, 22-31)
CKD stage 3 or worse	5/11 (45, 21-72)	112/448 (25, 21-29)
Nephritis	11/53 (21, 12-23)	109/417 (26, 22,30)
Hypertension	24/79 (30, 21-41)	97/396 (24, 21-29)
Diabetes	0/2 (0, 0-1)	121/473 (26, 22-30)

Table. (Cont'd)

Risk factor	Prevalence of aspirin use	
	With risk factor	Without risk factor
≥1 traditional PE risk factor*	58/234 (25, 20-31)	63/241 (26, 21-32)
aPL +	13/34 (38, 24-55)	16/70 (23, 15-34)
Anticoagulant use	12/28 (43, 27-61)	109/447 (24, 21-29)

BMI, Body Mass Index; CKD, Chronic kidney disease; PE, preeclampsia; aPL, antiphospholipid antibody; LAC, lupus anticoagulant

* Any of Age >40, BMI≥35, Nulliparity, Any renal disease, Hypertension, or Diabetes

Disclosure: A. Mendel, None; S. Bernatsky, None; E. Vinet, None.

Abstract Number: 1857

Low Molecular Weight Heparin and Aspirin Combination Therapy Modulates Th1/Th2 Cell Imbalance in Pregnant Patients with antiphospholipid Antibody-Associated Recurrent Pregnancy Loss

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Reproductive Issues in Rheumatic Disorders

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Type 1/type 2 T helper (Th1/Th2) cells and their cytokines are implicated in the pathogenesis of autoimmune diseases^[1]; however, their roles in antiphospholipid antibody-associated recurrent pregnancy loss (APA-RPL) remain unclear^[2,3]. Low molecular weight heparin (LMWH) and aspirin combination therapy is a first-line treatment for APA-RPL, but its mechanism remains unclear^[4]. This study aimed to investigate the effect of combination therapy with LMWH and aspirin on Th1/Th2 cells and their cytokines in pregnant patients with APA-RPL.

Methods: Pregnant patients with a history of APA-RPL (n=89) were enrolled in this study. After confirming a positive pregnancy test result, the patients were treated with LMWH and aspirin combination until 35–37 weeks of pregnancy or up to the time of miscarriage. Blood was drawn before starting and after stopping treatment. The therapeutic outcome was evaluated by using live-birth as an efficacy measurement. 31 age matched healthy pregnant women who delivered in our hospital were used as a control group. ELISA was conducted to detect serum levels of the Th1 cytokines interleukin (IL)-2 and tumor necrosis factor alpha (TNF-α) and the Th2 cytokines IL-4 and IL-10. The percentages of CD4⁺-interferon gamma (INF-γ)+ and CD4⁺-IL-4+ cells among the CD4⁺ T cells in peripheral blood were assessed by flow cytometry, and the expression of *T-bet* and *GATA 3* was determined by quantitative real-time PCR.

Results: Of the 89 patients receiving LMWH-aspirin combination therapy, 72(80.9%) had a live birth and the remaining 17 had miscarriages. At 5-7 weeks of gestation in patients with APA-RPL, serum IL-2 ($P=0.006$) and TNF-α ($P<0.001$) levels were significantly higher, while serum IL-4 ($P=0.037$) and IL-10 ($P<0.001$) levels were significantly lower compared to healthy pregnant control women (Figure 1). Similarly, the CD4⁺-INF-γ+-labeled Th1 cell subset was also significantly increased ($P<0.001$), while the CD4⁺-IL-4+-labeled Th2 cell subset was significantly reduced ($P<0.001$) in patients with APA-RPL (Figure 2). Furthermore, gene expression of *T-bet* was significantly elevated ($P=0.003$), while *GATA3* mRNA expression was significantly reduced in patients with APA-RPL ($P=0.002$) (Figure 3). This Th1-biased pattern was reversed in patients who had live birth while receiving the combination therapy. Patients with miscarriages continued to exhibit Th1-bias.

Conclusion: Th1/Th2 cell frequencies and the protein and gene expression levels of their cytokines are perturbed in patients with APA-RPL, suggesting a possible role of Th1/Th2 imbalance in the pathogenesis of APA-RPL. Importantly, LMWH and aspirin combination therapy effectively reverse Th1 cell polarization for APA-RPL patients attaining live births, providing a new understanding of potential immunomodulatory mechanism of LMWH and aspirin combination therapy on APA-RPL.

Disclosure: M. Wang, None; P. Zhang, None; G. zhou, None; J. lv, None; C. guo, None; Q. Wang, None.

An Assay Panel Combining Anti-Protein Arginine Deiminase 4 with Rheumatoid Factor Isotypes Distinguishes Anti-Citrullinated Peptide Antibody Negative Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes II: Diagnosis and Prognosis I

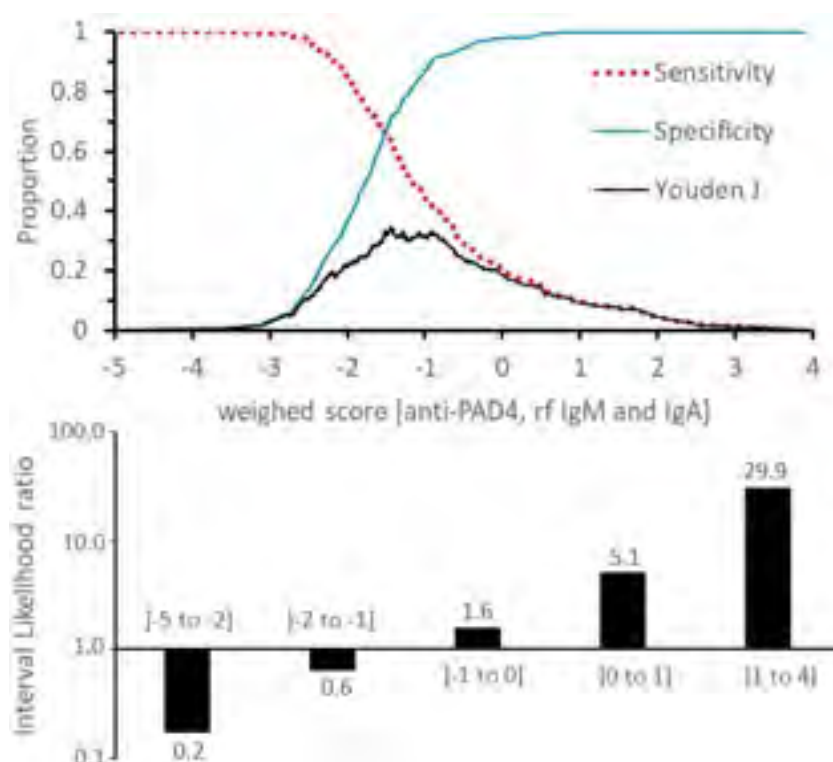
Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Anti-citrullinated peptide antibodies (ACPAs) are highly specific for rheumatoid arthritis (RA) but lack sensitivity. We evaluated autoantibodies to protein-arginine deiminase 4 (anti-PAD4) in distinguishing ACPA negative RA from other ACPA negative rheumatic diseases, either alone or in combination with rheumatoid factor (RF) isotypes.

Methods: ACPA negative subjects (n = 1011, 205 RA and 806 non-RA [193 normal healthy individuals, NHV]) were selected from a cohort of 622 RA (34% ACPA negative, all fulfilling the 1987 or 2010 ACR criteria), and 830 non-RA (97% ACPA negative) consented subjects. ACPA status and IgM/IgA RF titers were measured using fluoroenzyme immunoassays (ThermoFisher, Upsala Sweden). Anti-PAD4 titers were measured using a novel particle-based multi-analyte technology (research use only, Inova Diagnostics, San Diego, CA). ACPA negative subjects were grouped into a training set of 554 subjects (157 RA, and 397 non-RA [172 NHV]), and a subsequent independent validation set of 457 consecutive subjects (48 RA and 409 non-RA [21 NHV]). From the training set, a weighted scoring system cumulating log normalized anti-PAD4/RF isotypes titer estimates from multivariate logistic regression was calculated to distinguish ACPA negative RA from ACPA negative non-RA, and was applied to subsequent validation set. Diagnostic performances were estimated using area under the receiver operating curve (AUC), sensitivity, and specificity.

Results: Overall, anti-PAD4 (>1000 Units) was 19% sensitive and 95% specific in distinguishing ACPA negative RA from ACPA negative non-RA subjects (AUC = 0.65±0.02). AUCs for IgM and IgA RF isotypes were 0.67±0.02 and 0.51±0.02, respectively. From training set, multivariate logistic regression estimates for anti-PAD4 (0.36±0.11), and IgM/IgA RF isotypes



(0.66 ± 0.11 and -0.65 ± 0.14 , respectively) antibody systems were significantly and independently associated with RA ($p < 0.001$; intercept = -2.59 ± 0.66), and weighted cumulative score was 37% sensitive and 90% specific (cutoff > -0.4) (AUC = 0.72 ± 0.02 , Figure). In subsequent validation set, the training set based weighted cumulative score distinguished ACPA negative RA and ACPA negative non-RA groups with 35% sensitivity and 95% specificity (AUC = 0.68 ± 0.02). Specificities in distinguishing ACPA negative RA from other ACPA negative rheumatic diseases was 92% for systemic lupus erythematosus (327/354), 97% for Sjogren's syndrome (59/61), 95% for fibromyalgia (80/84), and 91% for NHV. Positivity rate of the weighted cumulative score was 30% among RA diagnosed for less than 2 years and rose to 50% among RA diagnosed for more than 10 years.

Conclusion: These preliminary data establish the feasibility of combining anti-PAD4 with RF isotypes to distinguish ACPA negative RA from other ACPA negative rheumatic diseases.

Disclosure: T. Dervieux, exagen, 3; L. Martinez Prat, None; J. Conklin, Exagen Diagnostics Inc., 3; C. Ibarra, Exagen Diagnostics, 1, 3; M. Mahler, Inova Diagnostics, 3; M. E. Weinblatt, None; J. Kremer, None.

Abstract Number: 1859

The Prognostic Value of Autoantibody Isotypes for Predicting Therapeutic Responses to Methotrexate in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes II: Diagnosis and Prognosis I

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) are the most specific diagnostic markers of rheumatoid arthritis (RA). Lately we showed that the determination of multiple isotypes of RF and ACPA as well as RA33 antibodies may provide an added diagnostic value since the presence of multiple reactivities in sera of RA patients as compared to disease controls was found to be highly specific for RA¹. Moreover, determination of autoantibody isotypes might even provide a predictive value regarding the response to therapy. It was the aim of this study to investigate the potential predictive value of IgA, IgG and IgM isotypes of RF, ACPA and RA33 antibodies regarding therapeutic response to methotrexate (MTX) in patients with RA.

Methods: An inception cohort of 165 patients starting MTX therapy was analysed for the presence of IgA, IgG and IgM isotypes of RF and ACPA using EliATM assays (Phadia AB, Sweden). RA33 antibody isotypes were detected by newly developed prototype assays using the EliATM platform (Phadia AB, Sweden)¹. Therapeutic responses were analysed after 3-6 months using the American College of Rheumatology (ACR)20 and simplified disease activity index (SDAI)50 response criteria. For generating classification models the machine learning tool Weka was employed.

Results: Patients testing positive for four or more antibodies were found having an increased likelihood to reach an ACR20 response (41%) compared to seronegative patients (24%, $p=0.0038$) or patients with 1 to 3 antibody reactivities (26%, $p=0.0152$). Interestingly, further analyses revealed high levels of IgM-RF (>133 IU/ml) to be associated with the therapeutic response to MTX as 71% of the patients (i.e. 15 of 21) achieved an ACR20 response compared to 28% of patients with IgM-RF <133 IU/ml ($p<0.0001$) and 27% of RF-negative patients ($p<0.0001$). Moreover, also the presence of RA33 antibodies was associated with a favorable MTX response since 47% of patients positive for IgG, IgA or IgM RA33 antibodies achieved an ACR20 response compared to 28% in the RA33 negative population ($p=0.0005$). Remarkably, by combining the RF and RA33 data a population of MTX non-responders could be characterized showing IgM-RF <133 IU/ml and IgG-RA33 <3.2 μ g/l since 91% of these patients ($n=47$) did not reach an ACR20 response compared to 58% non-responders in the total cohort ($p<0.0001$). Virtually identical results were obtained when SDAI50 was used as outcome measure. Interestingly, ACPA isotypes did not appear to be associated with the therapeutic response to MTX.

Conclusion: The detection of antibody isotypes especially IgM-RF and IgG-RA33 may provide valuable additional information regarding the prediction of response to MTX.

Reference: 1. Sieghart D *et al.* Determination of Autoantibody Isotypes Increases the Sensitivity of Serodiagnostics in Rheumatoid Arthritis. *Front Immunol.* 2018 Apr 24;9:876.

Disclosure: D. Sieghart, None; A. Platzter, None; F. Alasti, None; P. Studenic, None; M. Grundhuber, Thermo Fisher Scientific, Phadia GmbH, 3; S. Swiniarski, Thermo Fisher Scientific, Phadia GmbH, 3; S. Blüml, None; H. Haslacher, None; J. S. Smolen, Abbvie, Astra-Zeneca - to Institution, 2, Abbvie, Chugai, Gilead, ILTOO, Janssen, Lilly, MSD, Novartis-Sandoz, Pfizer, Samsung, Sanofi, 5, Abbvie, Celgene, Chugai, Janssen, Lilly, MSD, Pfizer, Samsung, Sandoz, UCB, 9; G. Steiner, Thermo Fisher Scientific, 2, 5.

Abstract Number: 1860

Development and Validation of a Microrna Panel to Differentiate between Patients with Rheumatoid Arthritis, Systemic Lupus Erythematosus, and Control Subjects

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes II: Diagnosis and Prognosis I

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: MicroRNAs (miRNAs) are short non-coding RNAs that regulate genes and have utility as disease biomarkers. Use of small RNA (sRNA) sequencing along with unbiased bioinformatics methods has the capacity to reveal new miRNA markers of disease. The objective of this study was to use sRNA sequencing and machine learning methodology to determine a miRNA signature panel capable of reliably differentiating patients with rheumatoid arthritis (RA) from control subjects, and from patients with another autoimmune disease.

Methods: Plasma samples from 167 patients with RA and 91 control subjects frequency-matched for age, race and sex were used for RNA extraction and sequencing library preparation. Sequencing was performed using Illumina NextSeq500. Our in-house pipeline, TIGER, was used to quantify miRNAs. DESeq2 and random forest analyses were used to develop a prioritized list of differentially expressed miRNAs in RA compared to control subjects. Each of the miRNAs was validated by PCR in the same plasma samples. Using the PCR-based plasma concentrations of the miRNAs, we used lasso regression to select a final miRNA panel to distinguish between RA and control subjects. This panel was validated in a separate cohort of 32 patients with RA and 32 control subjects and in 12 patients with SLE. Panel efficacy was assessed by area under the receiver operative characteristic curve (AUC) analyses.

Results: Among the top 15 miRNAs selected separately by DESeq2 and random forest analyses, 12 miRNAs overlapped using both methodologies, thus a total of 18 miRNAs were selected for PCR validation. Using the PCR-based concentrations of the 18 miRNAs, a final panel that included miR-22-3p, miR-24-3p, miR-96-5p, miR-134-5p, miR-140-3p, and miR-627-5p was selected. The panel had an AUC=0.81 for differentiating RA and control subjects, and it was robust among those with seronegative RA (AUC=0.84), among patients whose RA was in remission (AUC=0.85), in a separate RA validation cohort (AUC=0.76), and among patients with SLE compared to control subjects (AUC=0.97). Three of the miRNAs had weak association with disease activity in RA by DAS28 score (miR-24-3p: $\rho = -0.16$, $P = 0.04$; miR-96-5p: $\rho = 0.16$, $P = 0.04$; miR-140-3p: $\rho = -0.16$, $P = 0.05$), and none were associated with disease activity in SLE (SLEDAI).

Conclusion: A miRNA panel identified by unbiased bioinformatics approaches was able to differentiate between patients with RA, SLE and control subjects. The panel may represent an autoimmunity signature which is common to both RA and SLE patients and which is not dependent on active disease or seropositivity. Further studies will be necessary to confirm these findings.

Disclosure: M. J. Ormseth, None; J. F. Solus, None; Q. Sheng, None; F. Ye, None; Q. Wu, None; Y. Guo, None; A. M. Oeser, None; R. Allen, None; K. Vickers, None; C. M. Stein, None.

Lipid Screening in Medicare Beneficiaries with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes II: Diagnosis and Prognosis I

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Patients with RA have an increased risk of cardiovascular disease (CVD) accounting for over 50% of premature deaths in the RA population. EULAR recommends repeat assessment of CVD risk every 5 years or when major changes in DMARD therapies are instituted. Lipid screening should be performed to evaluate and mitigate CVD risk. Our objective was to estimate the 5-year lipid screening rate among Medicare beneficiaries with RA based on the specialties of their treating providers, including rheumatology, primary care providers (PCP) and cardiology.

Methods: We conducted a retrospective cohort study using 2011-2015 Medicare claims data (5% representative sample) that included fee-for-service beneficiaries with RA who were continuously enrolled in Parts A and B for 5 years and had at least 1 outpatient visit during continuous enrollment. Lipid screening including non-fasting total cholesterol and high-density lipoprotein (HDL) was ascertained using CPT codes. We estimated the proportion of beneficiaries receiving at least one lipid screening during the 5 years, using logistic regression, based on the specialties of their treating providers. We stratified the analysis by those with and without preexisting CVD or CVD-risk conditions (e.g., hyperlipidemia, hypertension, and diabetes mellitus).

Results: Among 40,120 beneficiaries with RA, 35,330 (88%) had preexisting CVD or CVD-risk conditions. RA patients without preexisting conditions had a 5-year lipid screening rate of 52.8% (95% CI: 51.4, 54.2), while those with preexisting conditions had a screening rate of 71.2% (95% CI: 70.8, 71.7). RA patients without preexisting conditions who only saw a rheumatologist had a lower 5-year lipid screening rate (21.6%, 95% CI: 14.6, 30.9), compared to patients who saw a PCP only (54.4%, 95% CI: 50.5, 58.3) or a cardiologist only (40.0%, 95% CI: 15.8, 70.3). RA patients with preexisting conditions who only saw a rheumatologist had a screening rate of 35.2% (95% CI: 26.7, 44.8), whereas patients who only saw a PCP or cardiologist had screening rates of 71.3% (95% CI: 69.7, 72.8) and 77.3% (95% CI: 65.7, 85.8), respectively. Screening rate estimates for combinations of physician specialties suggest that beneficiaries seen by a PCP and/or a cardiologist have higher rates of lipid screening, with little influence from rheumatology care (Table 1).

Conclusion: Five-year lipid screening rates among Medicare beneficiaries with RA did not meet EULAR recommendations, particularly among those without preexisting CVD or CVD-risk conditions. Patients that were seen by only a rheumatologist had the lowest rate of screening, when compared to patients seen by a PCP or a cardiologist. Rheumatologists need to devise screening implementation strategies to improve comprehensive coordinated CVD preventative care.

Disclosure: N. Kumar, None; W. H. Lo-Ciganic, None; L. Zhou, None; E. L. Ashbeck, None; C. K. Kwoh, None.

Table 1. Five-year lipid screening rate, by specialties of treatment providers

Beneficiary class	Beneficiaries with preexisting conditions	Lipid screening %	(95%CI)	Beneficiaries without preexisting conditions	Lipid screening %	(95%CI)
PCP only	3,320	71.3	(69.7, 72.8)	410	54.4	(50.5, 58.3)
Rheumatologist only	140	35.2	(26.7, 44.8)	97	21.6	(14.6, 30.9)
Cardiologist only	88	77.3	(65.7, 85.8)	10	40.0	(15.8, 70.3)
PCP + Rheumatologist	4,958	65.2	(63.8, 66.5)	1,521	47.5	(45.8, 50.0)
PCP + Cardiologist	3,804	74.5	(73.7, 75.4)	470	60.7	(57.8, 64.4)
Rheumatologist + Cardiologist	115	67.8	(58.8, 75.7)	34	45.9	(27.5, 65.4)
PCP + Cardiologist + Rheumatologist	16,601	71.7	(71.0, 72.4)	1,807	56.6	(54.3, 58.9)
Without PCP, cardiologist or Rheumatologist	156	21.1	(15.5, 26.8)	51	33.7	(18.8, 48.4)

Pre-existing conditions: Hyperlipidemia, Hypertension, Diabetes, and cardiovascular disease.

PCP: Primary Care Providers, including family practice, internal medicine, general practice, nurse practitioner, and physician assistant.

Exploring the Lipid Paradox Theory in Rheumatoid Arthritis: Very Low Circulating Low-Density Lipoprotein Concentration Levels Are Associated with Pro-Atherogenic Biomarkers

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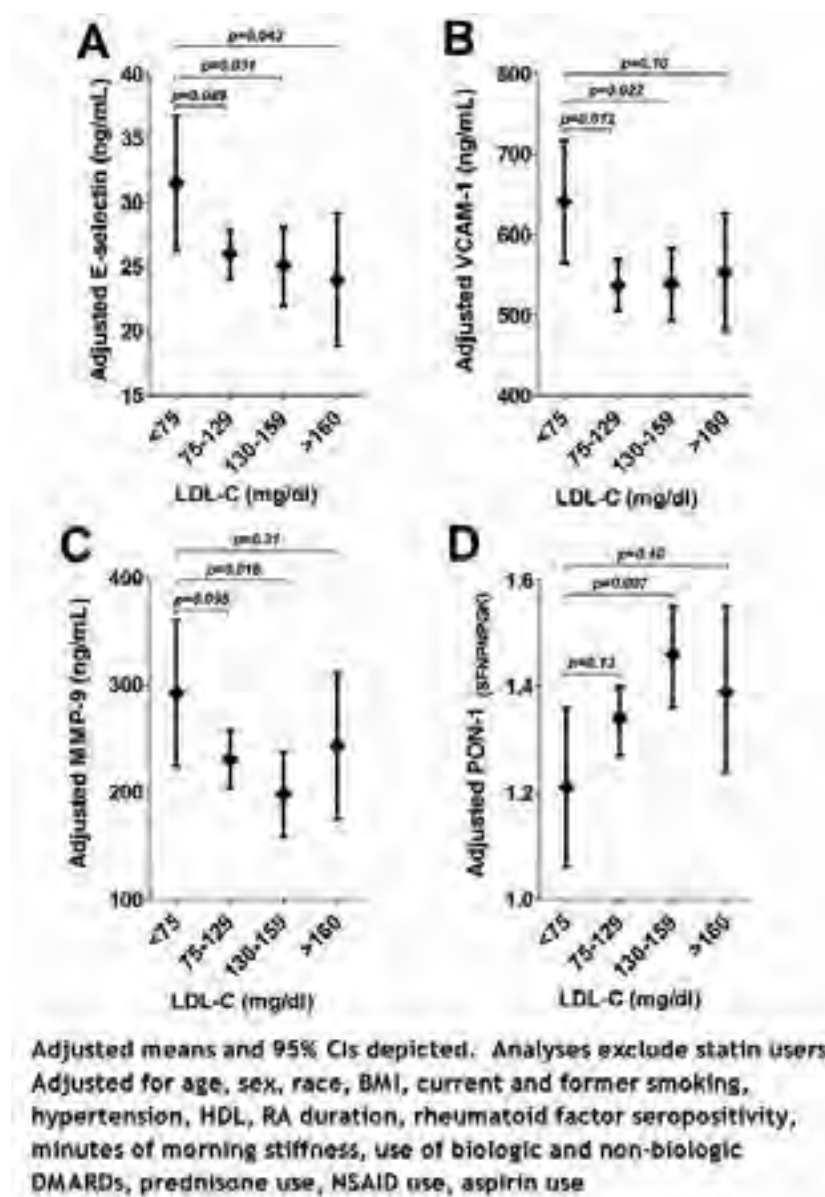
SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes II: Diagnosis and Prognosis I

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM



Background/Purpose: Rheumatoid arthritis (RA) patients with very low levels of circulating low density lipoprotein cholesterol (LDL-C) have been reported to be at particularly high risk for cardiovascular disease (CVD) events. Previously, we reported that this subgroup also had markedly elevated coronary calcium scores, a surrogate for atherosclerosis; however, the mechanisms underlying these seemingly paradoxical findings has not been explored.

Methods: RA patients from 3 cardiovascular cohort studies underwent measurement of fasting serum lipids and a panel of 32 cytokines, chemokines, metalloproteinases, and other immune mediators associated with CVD was measured from serum using various optimized methods (ELISA, Luminex, liquid chromatography/tandem mass spectrometry). Levels of each panel biomarker were compared according to LDL strata, with the lowest stratum (LDL-C<75 mg/dL) being the stratum of interest, using multivariable robust regression to adjust for pertinent confounders.

Results: A total of 454 RA patients [mean age=57 years; 74% female; median RA duration=10 years] were studied. LDL-C<75 mg/dL was observed in 10%, and 32% had an LDL-C>130 mg/dL. Excluding statin users (n=64), those in the lowest LDL-C stratum did not differ from those in higher strata on demographics, CVD risk factors, or RA disease and treatment characteristics with the exception of BMI and waist circumference, which were lower in the lowest LDL-C stratum compared with the highest, and ever and current smoking, which were more prevalent in the lowest LDL-C stratum. After adjustment, mean levels of pro-atherogenic E-selectin, vascular cell adhesion molecule-1 (VCAM-1), and matrix metalloproteinase-9(MMP-9) were higher among those in the lowest LDL-C stratum compared with those with higher LDL-C levels (Fig A-C). In contrast, levels of anti-atherogenic paraoxonase-1 (PON-1) were lowest among those in the lowest LDL-C stratum (Fig D). Seropositivity for rheumatoid factor (RF) was more strongly associated with higher E-selectin, MMP-9, and VCAM-1 levels among those in the lowest LDL-C stratum compared with those with higher LDL-C. Likewise, RF was more strongly associated with lower PON-1 levels among those in the lowest LDL-C stratum.

Conclusion: Higher levels of vascular adhesion molecules and metalloproteinases and lower levels of PON-1 suggest a pro-atherogenic state that would typically not be observed among those with low LDL-C, a group generally at low risk for CVD. Such pro-atherogenic state may account for higher CVD events and atherosclerosis among RA patients with low LDL-C levels and identify a subgroup that may benefit from heightened CVD screening and prevention.

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Abstract Number: 1863

Anti-Cyclic Citrullinated Protein Antibody at Multiple Cutoff Levels and in Combination with Rheumatoid Factor IgM and Serum Calprotectin Is Highly Specific for the Development of Rheumatoid Arthritis within 3 Years

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes II: Diagnosis and Prognosis I

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Serum elevations of antibodies to citrullinated protein antigens (ACPA) and rheumatoid factor (RF) can identify individuals at risk for developing rheumatoid arthritis (RA). Prior studies have identified serum calprotectin (seCal) as a promising biomarker for active inflammation among RA patients (Hurnakova 2018). Importantly, identifying biomarkers to accurately predict RA onset within a defined time frame may be especially useful to help design clinical trials for prevention of RA. The goal of this project was to evaluate the role of ACPA, RF and the novel marker seCal in improving the prediction of onset and timing of RA.

Methods: From the Department of Defense Serum Repository we studied pre-RA diagnosis samples from 214 RA Cases (212 meeting 1987 Criteria, and 2 diagnosed with RA by a board-certified rheumatologist), and 1,287 Controls matched to Cases on age, gender, race and duration of sample storage. All Case samples were tested for anti-cyclic citrullinated peptide-3(CCP3, Inova), RFIgM (Inova) and serum calprotectin (seCal, Inova, research only). All Controls were tested

for CCP3, and a subset were tested for RFIgM and seCal to set cutoff levels and evaluate diagnostic accuracy. CCP3 positivity was based on the established range (≥ 20 Units), and 2x and 3x the standard cutoff; RFIgM positivity was based on a level present in $< 5\%$ of a subset of Controls; seCal positivity was based on a level greater than the mean+2 standard deviations (SD) from a set of Controls. The diagnostic accuracy of CCP3 for Cases was compared to Controls. In Cases, the diagnostic accuracy for a sample being within ≤ 3 years before diagnosis was evaluated using positivity of CCP3, RFIgM and seCal in 2x2 table analyses. Across models the positive predictive values (PPV) were compared with chi-squared testing.

Results: CCP3 positivity was 98.5%, 99.2% and 99.8% specific for the Cases versus Controls at standard, 2x, and 3x cutoff values, respectively. Within Cases, CCP3 positivity in a sample was strongly associated with developing RA in ≤ 3 years at all cutoff values although the differences in PPVs across cutoffs were not significant ($p=0.43$) (Table). The addition of RFIgM to CCP3 significantly improved the PPV of an RA diagnosis in ≤ 3 years from 78.9% to 88.0% ($p=0.01$). The addition of seCal to RFIgM and CCP3 (standard cutoff) improved the PPV to 100% although this was not significant ($p=0.37$). In Cases, the mean seCal was 8.6 ng/mL (SD 7.5) and 13.3 ng/mL (SD 19.0) for > 3 and ≤ 3 years to diagnosis, respectively ($p<0.01$).

Conclusion: These findings demonstrate that CCP3 at multiple cutoffs is highly predictive of a diagnosis of RA in ≤ 3 years, with improved prediction if RFIgM positivity is included. These results can be used in the development of clinical prevention trials for RA. SeCal also shows promise in improving prediction of RA although further evaluation is needed, including comparison to other measures of inflammation (e.g. C-reactive protein). Diagnostic accuracy of CCP3 at multiple cutoff values and in combination with RFIgM or RFIgM and calprotectin for a diagnosis of RA in ≤ 3 years within preclinical RA samples from 214 individuals who developed RA identified through the Department of Defense Serum Repository

Biomarkers ¹	Sensitivity ²	Specificity	PPV	NPV	OR (95% CI, p-value) ⁵
CCP3 ≥ 20	262/377 (69.5%)	195/265 (73.6%)	262/332 (78.9%) ³	195/310 (62.9%)	6.3 (4.5-9.0), $p<0.01$
CCP3 ≥ 40	253/377 (67.1%)	208/265 (78.5%)	253/310 (81.6%)	208/332 (62.7%)	7.4 (5.2-10.7), $p<0.01$
CCP3 ≥ 60	242/377 (64.2%)	211/265 (79.6%)	242/296 (81.8%)	211/346 (61.0%)	7.0 (4.9-10.1), $p<0.01$
CCP3 ≥ 20 + RFIgM	168/377 (44.6%)	242/265 (91.3%)	168/191 (88.0%) ^{3,4}	242/451 (53.7%)	8.5 (5.3-13.6), $p<0.01$
CCP3 ≥ 40 + RFIgM	167/377 (44.3%)	242/265 (91.3%)	167/190 (87.9%)	242/452 (53.5%)	8.4 (5.2-13.4), $p<0.01$
CCP3 ≥ 60 + RFIgM	162/377 (43.0%)	242/265 (91.3%)	162/185 (87.6%)	242/457 (53.0%)	7.9 (4.9-12.7), $p<0.01$
CCP3 ≥ 20 + RFIgM + serum calprotectin	14/377 (3.7%)	265/265 (100%)	14/14 (100.0%) ⁴	265/628 (42.2%)	Unable to calculate given a cell with 0

1 CCP3 - Anti-cyclic citrullinated peptide-3, RFIgM - rheumatoid factor IgM. Listed values are: CCP3 Units, RFIgM International Units (IU), and serum calprotectin ng/mL. The cutoff for RFIgM positivity is > 21.4 IU, and for serum calprotectin positivity is > 37.0 ng/mL

2 Sensitivity, specificity, positive and negative predictive values (PPV, NPV), and odds ratios (OR) of the identified biomarkers being positive ≤ 3 years prior to RA onset compared to > 3 years.

3 The difference in PPV between CCP3 ≥ 20 and CCP3 ≥ 20 + RFIgM is significant ($p=0.01$) assuming a cutoff p-value of 0.05 for significance.

4 The difference in PPV between CCP3 ≥ 20 + RFIgM and CCP3 ≥ 20 + RFIgM + calprotectin is not significant ($p=0.37$).

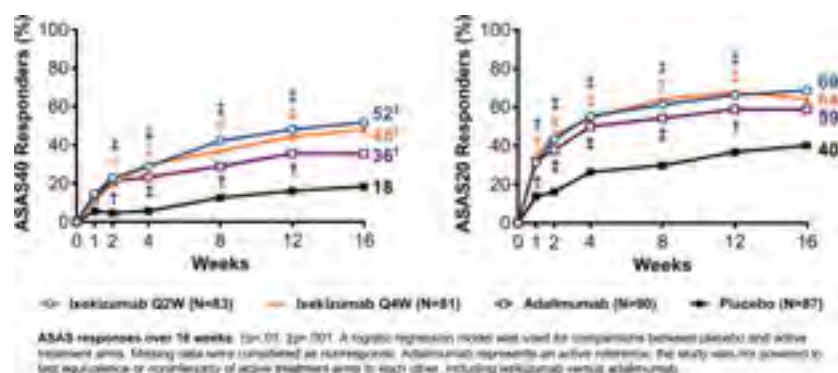
5 This p-value corresponds to the odds ratio (OR) for the association between positivity for the biomarker(s) and its presence in the sample ≤ 3 years prior to diagnosis compared to > 3 years.

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Abstract Number: 1864

Ixekizumab Significantly Improves Signs, Symptoms, and Spinal Inflammation of Active Ankylosing Spondylitis/Radiographic Axial Spondyloarthritis: 16-Week Results of a Phase 3 Randomized, Active and Placebo-Controlled Trial

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical III: Treatment of Axial SpA

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: COAST-V (NCT02696785) is the first phase 3 study of ixekizumab (IXE), a high-affinity anti-IL-17A monoclonal antibody, inpatients (pts) with active radiographic axial SpA (r-axSpA) who are biologic DMARD(bDMARD) naïve. We report the Week (Wk) 16 primary outcome and key efficacy and safety data from this ongoing 52-wk study.

Methods: Adults with active r-axSpA per Assessment of SpA international Society (ASAS) criteria(sacroiliitis centrally defined by modified New York Criteria and ≥ 1 SpA feature), BASDAI ≥ 4 , back pain ≥ 4 , and inadequate response or intolerance to NSAID therapy, were randomized 1:1:1:1 to subcutaneous placebo(PBO), 80 mg IXE every 4 (Q4W) or 2 wks (Q2W), or 40 mg Q2W adalimumab (ADA; active reference arm) up to Wk 16. The primary endpoint was ASAS40 response at Wk 16. Major secondary endpoints included ASAS20, BASDAI50, AS Disease Activity Score (ASDAS) Inactive Disease, and change from baseline (CFB) in ASDAS, BASFI, MRI spine SpA Research Consortium of Canada (SPARCC) score, Short Form 36-item Physical Component Summary (SF-36 PCS) and ASAS-Health Index (HI). All images were centrally read.

Results: Of 341 subjects randomized, 97% completed Wk 16. Baseline demographics and disease characteristics were comparable among study arms: mean age was 41.7 years; meantime since r-axSpA symptoms onset was 16.0 years, and mean BASDAI was 6.7. Significantly more patients achieved ASAS40 at Wk 16 (primary endpoint) with IXE Q2W (52%) and IXE Q4W (48%) than with PBO (18%, $p < .001$). Compared to PBO, both IXE regimens had significantly higher improvements at Wk 16 for disease activity, functional disability, and spinal and SIJ inflammation. Significant improvements were first observed at Wk 1 for ASAS20, BASFI CFB, and ASDAS CFB, at Wk 2 for ASAS40, and at Wk 4 (first time of assessment) for SF36-PCS CFB and ASAS-HI CFB. At Wk 16, ADA (active reference arm) showed significant improvements versus PBO (ASAS40 effect size vs. PBO 17.2% [95% CI 4.4, 30.0]). The frequency of treatment-emergent adverse events and serious adverse events are provided in the table below. No opportunistic infections were reported in any arm; one *Candida* infection was reported in the ADA active reference arm. One case of inflammatory bowel disease was reported in the IXE Q2W study arm. No malignancies or deaths occurred in any study arm.

Conclusion: The primary and all major secondary endpoints for IXE were met at Wk 16 with no unexpected safety findings. IXE was superior to PBO for improving r-axSpA signs and symptoms, health-related quality of life, and inflammation on MRI in pts with r-axSpA naïve to bDMARDS.

Efficacy and Safety Results at Week 16

	Placebo (N=87)	Adalimumab (N=90)	Ixekizumab Q4W (N=81)	Ixekizumab Q2W (N=83)
Responder Rate, n (%), Intent-to-treat population				
ASAS40a b	16 (18%)	32 (36%)†	39 (48%)‡	43 (52%)‡
ASAS20a b	35 (40%)	53 (59%)†	52 (64%)†	57 (69%)‡
BASDAI50a b	15 (17%)	29 (32%)*	34 (42%)‡	36 (43%)‡
ASDAS Inactive Diseasea b	2 (2%)	14 (16%)†	13 (16%)†	9 (11%)*
Change From Baseline, Least Squares Mean (Standard Error), Intent-to-treat population				
ASDASb c	-0.5 (0.1)	-1.3 (0.1)‡	-1.4 (0.1)‡	-1.4 (0.1)‡
BASFIb c	-1.2 (0.2)	-2.1 (0.2)†	-2.4 (0.2)‡	-2.4 (0.2)‡
Spine SPARCC Scoreb d	-1.5 (1.1)	-11.6 (1.1)‡	-11.0 (1.2)‡	-9.6 (1.2)‡
Sacroiliac joint SPARCC Scored e	0.9 (0.6)	-4.2 (0.6)‡	-4.0 (0.6)‡	-4.3 (0.6)‡
SF-36 PCSb c	3.6 (0.8)	6.9 (0.7)†	7.7 (0.8)‡	8.0 (0.8)‡
ASAS-Health Indexb c	-1.3 (0.3)	-2.3 (0.3)*	-2.4 (0.3)*	-2.7 (0.3)‡
High sensitivity C-reactive protein (mg/L)c f	1.4 (1.9)	-7.2 (1.9)†	-5.2 (2.0)*	-6.6 (2.0)†
Safety Overview, n (%), Safety population	Placebo (N=86)	Adalimumab (N=90)	Ixekizumab Q4W (N=81)	Ixekizumab Q2W (N=83)

Table. (Cont'd)

	Placebo (N=87)	Adalimumab (N=90)	Ixekizumab Q4W (N=81)	Ixekizumab Q2W (N=83)
Treatment-emergent adverse events	34 (40%)	44 (49%)	34 (42%)	36 (43%)
Serious adverse events	0	3 (3%)	1 (1%)	1 (1%)
Discontinued due to adverse event	0	1 (1%)	0	3 (4%)

^aLogistic regression analysis with nonresponder imputation for missing data. ^bA primary or major secondary endpoint. Comparisons between each of the ixekizumab treatment arms and placebo for primary and major secondary endpoints were all statistically significant as calculated using a graphical multiplicity testing method. ^cMixed effects model of repeated measures analysis. ^dAnalysis of covariance model based on observed case. ^eSacroiliac joint SPARCC score at baseline was 5.2. ^fAt baseline, 64% of patients had CRP>5 mg/L. *p<.05; [†]p<.01; [‡]p<.001

All statistical comparisons were made between placebo and active treatment arms. Adalimumab represents an active reference; the study was not powered to test equivalence or non inferiority of active treatment arms to each other, including ixekizumab versus adalimumab.

Intention-to-treat population: All randomized patients, analyzed according to the treatment to which they were assigned.

Safety population: All randomized patients who received ≥1 dose of study treatment, analyzed according to the treatment to which they were assigned.

Disclosure: D. van der Heijde, Imaging Rheumatology BV, 3, AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Daiichi, Eli-Lilly, Galapagos, Gilead, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi and UCB Pharma, 5; J. C. C. Wei, Pfizer, Inc., 2, 5, 8, Celgene Corporation, UCB, TSH Taiwan, 5, Chugai, 5, 8, BMS, Janssen, 2, 8, Sanofi-Aventis, Novartis, 2, Abbott, Eisai, 8; M. Dougados, Eli Lilly and Co., Pfizer, AbbVie, UCB, 2, 5; P. J. Mease, AbbVie, Amgen, Bristol Myers Squibb, Celgene, Janssen, Novartis, Pfizer, UCB, 2, 5, Genentech, Inc., 8, Eli Lilly and Co., Sun Pharma, 2, 5; A. A. Deodhar, AbbVie Inc., Eli Lilly and Co., Janssen, Novartis, Pfizer, UCB, 2, 5; W. P. Maksymowych, AbbVie Inc., Pfizer, 2, 5, 9, Eli Lilly and Co., UCB, 5, Novartis, Janssen, 5, 9; F. van Den Bosch, AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly and Co., Janssen, Merck, Novartis, Pfizer, Sanofi, UCB, 2, 5, 8; J. Sieper, AbbVie Inc., Novartis, Merck, Janssen, Pfizer, 5, 8, Eli Lilly and Co., 5, UCB, Inc., 8; T. Tomita, AbbVie, Astellas, Bristol Myers Squibb, Eisai, Eli Lilly and Co., Janssen, Mitsubishi Tanabe, Novartis, Takeda, Pfizer, 5, 8; R. B. M. Landewé, AbbVie Inc., Amgen, Pfizer, Roche, Schering, UCB, 2, 5, 8, Ablynx, Astra-Zeneca, Celgene, Eli Lilly and Co., Gilead, Galapagos, Glaxo-Smith-Kline, Novo-Nordisk, TiGenix, 5, Bristol Myers Squibb, Janssen, Merck, 5, 8, Novartis, 2, 5, Centocor, 2, 8, Rheumatology Consultancy BV, 3; L. Mallbris, Eli Lilly and Company, 1, 3; F. Zhao, Eli Lilly and Company, 1, 3; D. Adams, Eli Lilly and Company, 1, 3; B. Pangallo, Eli Lilly and Co., 1; H. Carlier, Eli Lilly and Company, 1, 3.

Abstract Number: 1865

Ixekizumab Significantly Improves Self-Reported Overall Functioning and Health in Patients with Active As/Radiographic Axial SpA Naive to Biologic DMARD Therapy: 16-Week Results of a Phase 3 Randomized, Active and Placebo-Controlled Trial

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical III: Treatment of Axial SpA

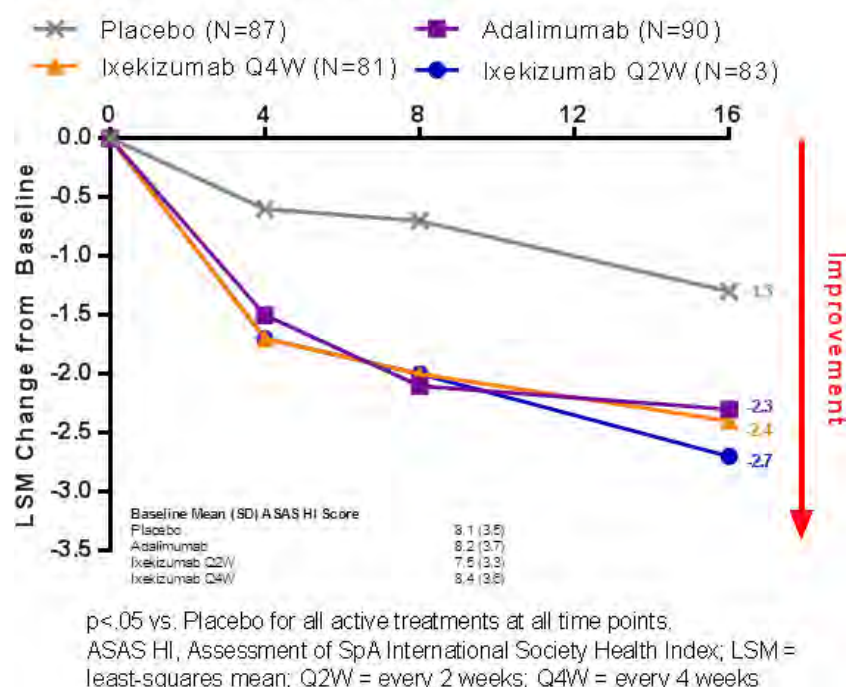
Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The Assessment of SpA international Society Health Index (ASAS HI) is a relatively new measure to assess function, disability, and health in patients with SpA. These are the first data of the ASAS HI in a Phase 3 study testing sensitivity to change and discrimination between active treatment and placebo (PBO).

Methods: The ASAS HI was assessed in biologic DMARD(bDMARD)-naive patients with active radiographic axial SpA (r-axSpA) in a Phase3 study of ixekizumab (IXE), an IL-17A monoclonal antibody (COAST-V [NCT02696785]). The ASAS HI consists of 17 dichotomous items, total score ranging from 0 (good health) to 17 (poor health). Scores ≤5 are considered “Good health state,” while the smallest detectable change (SDC) is 3. In COAST-V, the scale was administered at screening, baseline, and Weeks 4, 8, and 16 to adults with active r-axSpA per ASAS criteria (sacroiliitis defined centrally by modified New York Criteria and ≥1 SpA feature), BASDAI ≥4, back pain ≥4, and inadequate response or intolerance to NSAID therapy. Patients were randomized 1:1:1:1 to PBO, adalimumab (ADA) 40 mg every 2 weeks (Q2W), or IXE80 mg every 4 weeks (Q4W) or Q2W up to Week 16. Change from baseline in ASAS HI was analyzed using a mixed-effects

Figure. ASAS HI outcomes over time.



model of repeated measures (MMRM). Categorical analyses were performed using a logistic regression model. Association between ASAS HI changes with clinical response was assessed using ANCOVA.

Results: Changes from baseline in ASAS HI total score at Weeks 4, 8, and 16 are presented in Figure. The ASAS HI separated between PBO and all active treatment groups at all time points. At Week 16, ASAS HI scores in the IXE Q4W, IXE Q2W, and ADA groups had improved by ≥ 3 (SDC) in 41.8%, 50.6%, and 42.7%, respectively, versus 34.5% in the PBO group. At Week 16, the percentage of patients in ASAS HI Good health state in the IXEQ4W, IXE Q2W, and ADA groups were 46.3%, 45.6%, and 40.3%, respectively, versus 25.0% in the PBO group. In patients treated with IXE, better ASAS20/ASAS40 responses were associated with greater improvements in ASAS HI scores at Week16 (Table).

Conclusion: The ASAS HI separated at all time points between actively-treated and PBO-treated patients. This proves good discrimination of this new outcome measure. In a Phase 3 study of bDMARD-naïve patients with r-axSpA, those treated with ixekizumab experienced significantly better ASAS HI outcomes than PBO, with the best outcomes occurring in ASAS40 responders.

Study Sponsor Statement: This study was supported by Eli Lilly and Company. Lilly participated in the study design, data collection, and the analysis and reporting of study results.

Table. Association between ASAS HI Change from Baseline and Clinical Outcomes at Week 16

	ASAS20 Nonresponder	Patient Achieving ASAS20 But Not ASAS40	ASAS40 Responder
All IXE (Mean [SD] Baseline ASAS HI Score = 7.9 [3.5])			
N	55	27	82
ASAS HI (LSM [SE])	-0.7 (0.3)	-1.6 (0.5)	-4.1 (0.3)***,§
IXE Q4W (Mean [SD] Baseline ASAS HI Score = 7.5 [3.3])			
N	29	13	39
ASAS HI (LSM [SE])	-0.4 (0.5)	-1.4 (0.7)	-3.9 (0.4)***, ‡
IXE Q2W (Mean [SD] Baseline ASAS HI Score = 8.4 [3.6])			
N	26	14	43
ASAS HI (LSM [SE])	-1.0 (0.5)	-1.8 (0.7)	-4.3 (0.4)***, ‡
Adalimumab (Mean [SD] Baseline ASAS HI Score = 8.2 [3.7])			
N	37	21	32
ASAS HI (LSM [SE])	-0.7 (0.4)	-1.8 (0.5)	-4.6 (0.4)***, ‡
Placebo (Mean [SD] Baseline ASAS HI Score = 8.1 [3.5])			
N	51	19	16
ASAS HI (LSM [SE])	-0.7 (0.3)	-1.5 (0.5)	-3.3 (0.6)***, †

ASAS HI = Assessment of SpA International Society Health Index; IXE = ixekizumab; Q2W = every 2 weeks; Q4W = every 4 weeks.

***p<.001 versus ASAS20 nonresponders.

†p<.05; ‡p<.01; §p<.001 versus ASAS20 responder/ASAS40 nonresponder group.

Note: An analysis of covariance model with change in ASAS HI score as dependent variable and ASAS status and baseline ASAS HI as independent variables was applied. Post hoc comparison was conducted with Scheffe's correction.

Disclosure: U. Kiltz, AbbVie Inc., 2, 5,Chugai, 2, 5,Eli Lilly and Co., 2, 5,Grunenthal, 2, 5,Janssen, 2, 5,MSD, 2, 5, Novartis, 2, 5,Pfizer, Inc., 2, 5,Roche, 2, 5,UCB, Inc., 2, 5; **D. van der Heijde**, Imaging Rheumatology BV, 3,AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Daiichi, Eli-Lilly, Galapagos, Gilead, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi and UCB Pharma, 5; **A. Boonen**, Eli Lilly and Co., 5; **L. S. Gensler**, AbbVie Inc., 2,Amgen Inc., 2,Novartis, 2, 5,UCB, Inc., 2,Galapagos, 5,Janssen, 5,Eli Lilly and Co., 5,Pfizer, Inc., 5; **T. Hunter**, Eli Lilly and Company, 1, 3; **F. Zhao**, Eli Lilly and Company, 1, 3; **H. Carlier**, Eli Lilly and Company, 1, 3; **J. Braun**, None.

Abstract Number: 1866

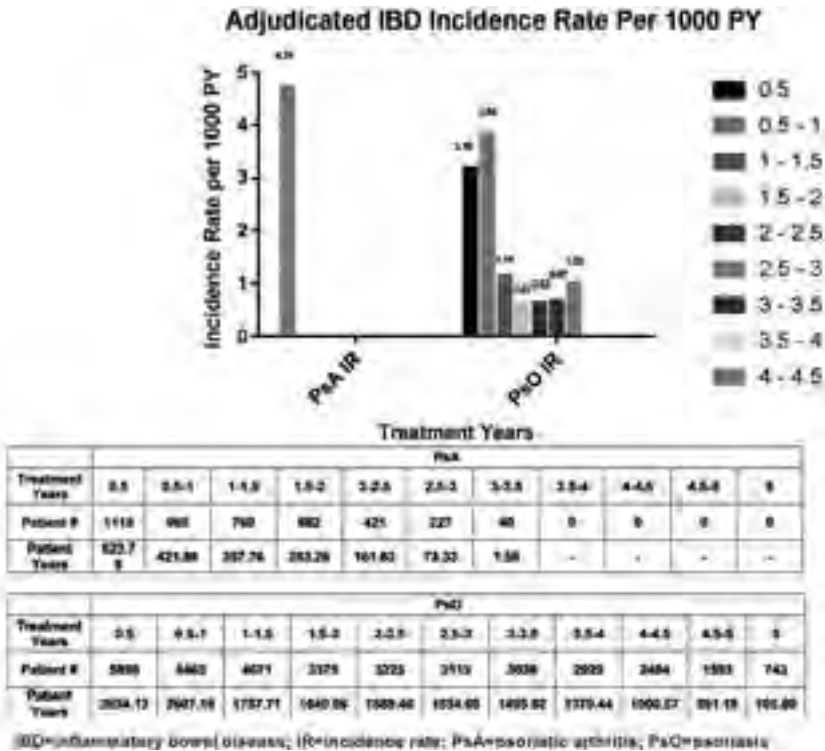
Incidence of Inflammatory Bowel Disease Among Patients Treated with Ixekizumab: An Update on Adjudicated Data from an Integrated Database of Patients with Psoriasis and Psoriatic Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018
Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical III: Treatment of Axial SpA
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: Increased incidence of IBD, such as Crohn's disease (CD) and ulcerative colitis (UC), has been observed in patients (pts) with PsA or plaque psoriasis (PsO) compared to those without. A greater incidence of IBD has been reported in pts with coexistent PsA and PsO.¹ Animal and human studies suggest a role for IL-17 in PsA, PsO, and IBD.² We report the incidence of IBD in pts treated with ixekizumab (IXE), a high-affinity mAb selectively targeting IL-17A,³ in pts with PsA, PsO, or comorbid PsA and PsO.



Methods: Adverse events of suspected IBD were collected for IXE-treated pts in an integrated database of 3(2 randomized, controlled) PsA phase 3 studies (SPIRIT-P1, -P2, -P3) and 12 studies in moderate-to-severe plaque PsO (1-phase 1, 1-phase 2, and 10-phase 3 [includes UNCOVER-1, -2, -3, -A, and -J]). Suspected IBD cases were adjudicated by internationally recognized classification criteria (EPIMAD). Adjudication data were summarized by indication. Percentage and exposure-adjusted incidence rates (IR) per 1000 patient year (PY) were calculated.

Results: During the double-blind (DB) placebo controlled period of PsO studies (Weeks 0-12), 3 (0.1%; IR=5.6/1000PY) IXE-treated pts had IBD events compared to none in placebo or etanercept arms; none were detected in any arm of the PsA DB study periods (Weeks 0-24). Of 1118 pts in PsA trials (1822 PY) who received at least one dose of IXE, 2 pts (IR=1.1/1000PY; 1 CD, 1 UC) had adjudicated IBD; both events occurred at 6 months to 1 year of treatment with IXE 80 mg every 2 weeks. Of 5898 pts in PsO trials (16313 PY) who received at least one dose of IXE, 26 pts (IR=1.6/1000PY; 7 CD, 19 UC) had adjudicated IBD. In 19 of 26 pts, events occurred within 1 year of IXE exposure (9 at <6 months; 10 at 6 months to 1 year). Among 28 adjudicated pts, 19 (PsO) were previously adjudicated;⁴ and 9 (7 PsO; 2 PsA) were newly adjudicated for IBD.

Conclusion: Events of CD and UC occurred infrequently among IXE-treated pts from 3 PsA trials and 12 PsO trials. Additional analysis and adjudication of longer-term data is currently ongoing and are required to further understand the relationship between IBD and IXE treatment.

References: 1. Egeberg A, et al. *Br J Dermatol* 2016;**175**(3):487-92.

2. Martin DA, et al. *J Invest Dermatol* 2013;**133**(1):17-26.

3. Gordon KB, et al. *N Engl J Med* 2016;**375**(4):345-56.

4. Reich K, et al. *J Am Acad Dermatol* 2017;**76**(3):441-48 e2.

Figure.

Disclosure: M. C. Genovese, AbbVie, Eli Lilly and Company, Galapagos, Gilead, Pfizer, 2, 5; J. F. Colombel, AbbVie, Amgen, Boehringer-Ingelheim, Arena Pharmaceuticals, Celgene Corporation, Celltrion, Enterome, Eli Lilly and Co., Ferring Pharmaceuticals, Genentech, Janssen and Janssen, Medimmune, Merck & Co., Nextbiotix, Novartis Pharmaceuticals Corporation, Otsu, 5, AbbVie, Ferring, Takeda, Celgene Corporation, 8, Intestinal Biotech Development, Genefit, 1, AbbVie, Takeda, Janssen and Janssen, 2; A. M. Gellert, Eli Lilly and Company, 1, 3; W. Xu, Eli Lilly and Company, 1, 3; D. Hardin, Eli Lilly and Company, 1, 3.

Abstract Number: 1867

Drug Retention and Response Rates of TNFi Treatment in 21,470 Patients with Axial Spondyloarthritis Treated in Clinical Practice– Pooled Data from the EuroSpA Research Network Collaboration

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical III: Treatment of Axial SpA

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

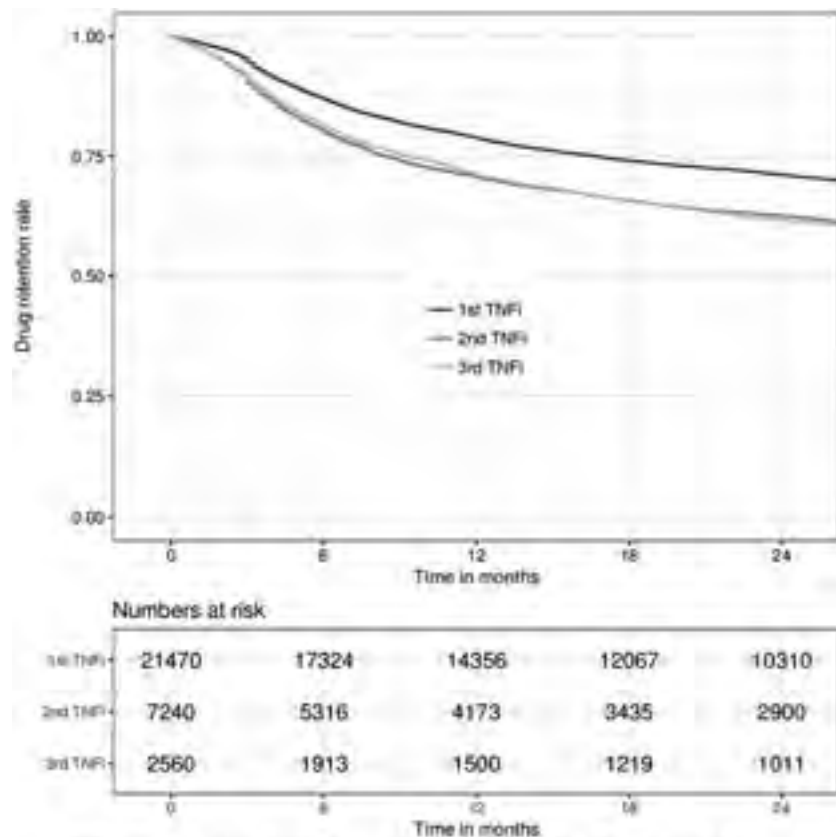


Figure. Twenty-four month drug retention rates for the 1st, 2nd and 3rd TNFi in patients with axSpA in the EuroSpA collaboration

Drug retention and response rates of TNFi treatment in 21,470 patients with axial spondyloarthritis treated in clinical practice– pooled data from the EuroSpA Research Network Collaboration

Background/Purpose: A research network collaboration of 15 European registries sharing data on patients with spondyloarthritis (SpA), “EuroSpA”, has recently been created to strengthen research capabilities in the real world setting¹. We aimed to investigate Tumour Necrosis Factor inhibitor (TNFi) retention and response rates at 6, 12 and 24 months in patients with axial SpA (axSpA) treated with their 1st, 2nd or 3rd TNFi in clinical practice across Europe.

Methods: A common data model was agreed upon by the EuroSpA Scientific Committee. Registry data managers clarified data availability and uploaded anonymized data through the secure Virtual Private Network pipelines to the EuroSpA server. Baseline characteristics, drug retention and response rates after 6, 12 and 24 months were investigated with non-parametric descriptive statistics. Kaplan-Meier estimation was used to investigate TNFi retention rates. Both crude and Lundex adjusted² response rates were calculated for BASDAI remission (BASDAI<4) and ASDAS inactive disease (ASDAS<1.3 unit).

Results: In May 2018, 10 of the 15 registries participating in EuroSpA had completed data upload to the EuroSpA server, including 21,470 patients with axSpA. Baseline characteristics of the pooled population are shown in Table. For the 1st TNFi, 6 and 24 months’ retention rates were 87% and 71%, respectively. Corresponding retention rates for the 2nd TNFi were 80% and 63%, and for the 3rd TNFi 81% and 62%, respectively (Table and Figure). For the 1st TNFi, 6 and 24 months Lundex adjusted BASDAI remission rates were 57% and 36%. Corresponding remission rates for the 2nd TNFi were 42% and 25%, and for the 3rd TNFi, 36% and 20%. For the 1st TNFi, 6 and 24 months Lundex adjusted ASDAS inactive disease rates were 26% and 17%, respectively. Corresponding ASDAS inactive disease rates for the 2nd TNFi were 16% and 11%, and for 3rd TNFi, 12% and 6%.

Conclusion: These initial analyses demonstrate that the creation of a large European database of axSpA patients treated in routine care based on a common data model is feasible, offering important opportunities for future research. In this pooled dataset from 10 European registries, we found decreasing retention rates for the 2nd and 3rd TNFi compared to the 1st TNFi, and lower response rates with increasing number of previous TNFi.

References: 1) Ann Rheum Dis, 2017, suppl. 2, p. 65

References: 2) Arthritis Rheum, 2006, 54(2), p. 600-6.

Efficacy and Safety Outcomes in Patients with Non-Radiographic Axial Spondyloarthritis Treated with Certolizumab Pegol: Results from the First 52-Week Randomized Placebo-Controlled Study (NCT02552212)

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical III: Treatment of Axial SpA

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: In the USA, certolizumab pegol (CZP) is approved for treatment of adults with active ankylosing spondylitis (AS) and not for non-radiographic axial spondyloarthritis (nr-axSpA). The Food and Drug Administration (FDA) expressed concerns that the natural history of nr-axSpA is poorly understood, with potential for spontaneous remission. C-axSpA was initiated, following FDA recommendations, to assess CZP efficacy vs conventional standard of care treatment in patients (pts) with active nr-axSpA and objective signs of inflammation (OSI) during a 52-week (wk) placebo (PBO)-controlled study.

Methods: C-axSpA (NCT02552212) was a 52-wk, phase 3, multicenter, double-blind, PBO-controlled study. Pts were randomized 1:1 to PBO or CZP (400 mg at Weeks 0, 2, and 4, then 200 mg every 2wks) and stratified by sacroiliitis on MRI and C-reactive protein (CRP) at baseline (BL) and region. Pts were ≥18 years with OSI (elevated CRP and/or

Figure: ASDAS-MI Response to Week 52

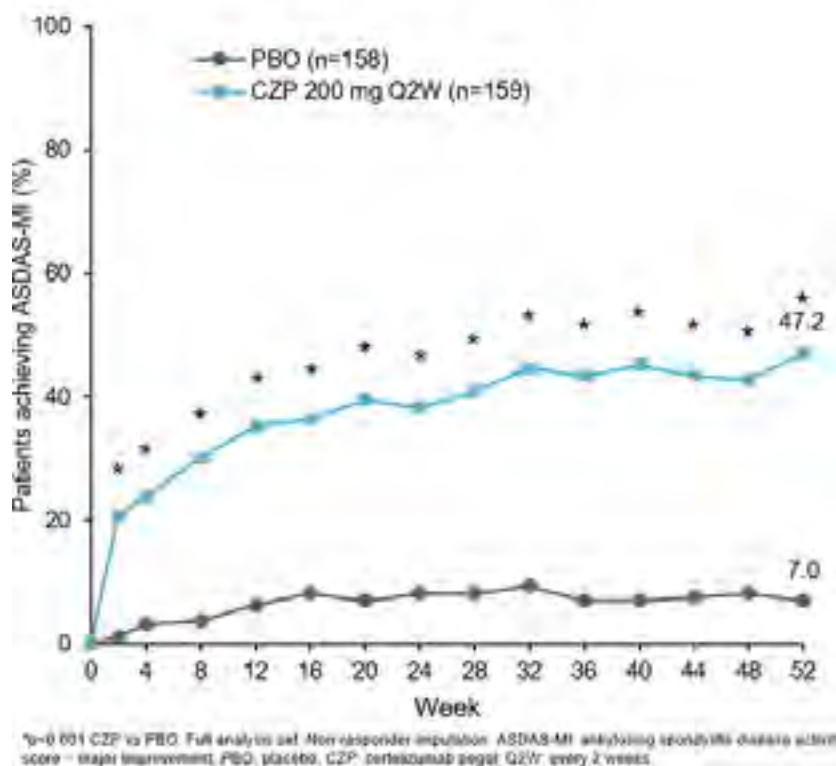


Table A: Baseline Demographics	PBO (n=158)		CZP 500 mg Q2W (n=159)	
Age, years, mean (SD)	37.4 (10.8)		37.3 (10.8)	
Female, n (%)	82 (51.9)		81 (50.9)	
Time since first diagnosis, mean years (SD) ^a	8.0 (5.4)		8.8 (4.8)	
HLA-B27 positive, n (%) ^b	133 (84.2)		128 (80.5)	
ASDAS, mean (SD)	3.79 (0.66)		3.44 (0.63)	
CRP, mg/L, mean (SD)	15.8 (17.7)		16.8 (17.8)	
SPARCC, mean (SD)	6.46 (12.3)		7.79 (16.8)	
CRP/MRI status at BL ^{c,d}				
MR+CRP+, n (%)	42 (26.6)		43 (26.3)	
MR+CRP-, n (%)	78 (49.4)		78 (48.5)	
MR-CRP+, n (%)	38 (24.1)		38 (23.9)	

Table B: Study Outcomes	PBO (n=158)		CZP 500 mg Q2W (n=159)	
	Wk12	Wk52	Wk12	Wk52
ASDAS-MI response, n (%) ^e	10 (6.3)	11 (7.0)	50 (30.2)	75 (47.2)
ASAS40 response, n (%) ^f	18 (11.4)	25 (15.8)	70 (47.8)	80 (50.9)
BASFI, mean CIB score (SE) ^g	-0.30 (0.15)	-1.29 (0.20)	-2.16 (0.17)	-2.86 (0.16)
ASQoL, mean CIB score (SE) ^g		0.79 (0.03)		-0.36 (0.02)
SPARCC, LS mean CIB score (SE)	-0.29 (0.77)		-4.67 (0.77)	

^a Full analysis set unless otherwise specified. ^b (a) randomized set; (b) 3 subjects were considered as MR-CRP-1 in the PBO arm and 1 in the CZP 500 mg Q2W arm; these were determined as (mis)classified. ^c (a) ASDAS-MI response defined as lowest from BL of at least 2 points or reaching the lowest possible value at Wk52; (b) non-responder definition, ASAS40 response defined as relative improvements of at least 40%, and absolute improvement of at least 2 units on a 0 to 10 numerical rating scale in at least 3 of the 4 domains and no worsening at all in the remaining domain. ^d (a) including inferential statistics using reference-based multiple imputation; PBO: placebo; CZP: (oral) 500 mg Q2W every 2 weeks; SD: standard deviation; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; SPARCC: Spondylarthritis Research Consortium of Canada; MRI: magnetic resonance imaging; BL: baseline; Wk: week; MR: major improvement; ASAS40: Assessment in Spondylarthritis International Society 40%; QoL: open-label; CIB: change from BL; SE: standard error; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life; LS: least square.

positive MRI of the sacroiliac [SI] joint), symptom duration ≥ 12 months, documented diagnosis of axSpA and met ASAS (but not modified New York) classification criteria. Randomized pts could switch to open-label (OL) CZP treatment or alternative OL treatment at any time, and concomitant medication could be adjusted at any point during the trial. The primary efficacy variable was Ankylosing Spondylitis Disease Activity Score Major Improvement (ASDAS-MI; defined as ASDAS decrease from BL ≥ 2.0 points or reaching lowest possible value) at Wk52. ASAS40 Wk12 response was assessed as the first secondary variable.

Results: 317 pts were randomized (PBO: 158, CZP: 159; Table). At Wk52, ASDAS-MI response was shown in 47.2% CZP vs 7.0% PBO pts (p-value: <0.001 ; Figure). All sensitivity analyses supported the primary outcome. Rapid improvement (ASDAS-MI Wk2 response) was observed in 20.8% CZP vs 1.3% PBO pts. ASAS40 response was reached in 47.8% CZP vs 11.4% PBO pts at Wk12. 60.8% PBO pts escaped to OL CZP vs 12.6% CZP pts by Wk52. No new safety signal was identified.

Conclusion: C-axSpAnd is the first study to assess efficacy of an anti-TNF in nr-axSpA using a 52-wk, PBO-controlled period. Clinically relevant and statistically significant improvements were seen in CZP vs PBO pts. This study shows clear evidence for the limitations of current standard of care to provide adequate disease control in nr-axSpA pts.

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Table/Figure

Disclosure: A. A. Deodhar, Abbvie, Eli Lilly, Janssen, Novartis, Pfizer, UCB Pharma, 2, 5; L. S. Gensler, UCB Pharma, 2; J. Kay, Eli Lilly, Gilead, UCB Pharma, 2, Amgen, Boehringer Ingelheim, Celltrion Healthcare, Janssen, Merck, Roche, Samsung Bioepis, Sandoz, 5, Pfizer, 2, 5; W. P. Maksymowych, AbbVie, Eli Lilly, Janssen, Novartis, Pfizer, UCB Pharma, 2, 5; N. Haroon, AbbVie, Amgen, Janssen, Merck, Novartis, UCB Pharma, 5; R. B. M. Landewé, AbbVie, Ablynx, Amgen, AstraZeneca, Bristol-Myers Squibb, Centocor, Galapagos, GlaxoSmithKline, Janssen, Eli Lilly, Merck, Novartis, Pfizer, Roche, Schering, UCB Pharma, 2, 5; M. Rudwaleit, AbbVie, BMS, Celgene, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, UCB, 5; S. Hall, AbbVie, Eli Lilly, Novartis, UCB Pharma, 2, 5; L. Bauer, UCB Pharma, 3; B. Hoepken, UCB Pharma, 3; N. de Peyrecave, UCB Pharma, 3; B. Kilgallen, UCB Pharma, 3; D. van der Heijde, Imaging Rheumatology BV, 3, AbbVie, Amgen, Astellas, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi, Eli Lilly, Galapagos, Gilead, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, UCB Pharma, 5.

Sustained Improvements in Signs and Symptoms of Active Ankylosing Spondylitis and Reassuring Safety with Secukinumab 300mg: 3-Year Results from a Phase 3 Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical III: Treatment of Axial SpA

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Secukinumab provided significant and sustained improvement in the signs and symptoms of ankylosing spondylitis (AS) over 2 years in the MEASURE 3 study, which evaluated the highest dose of secukinumab tested to date in spondyloarthritis (NCT02008916).^{1,2} Here we report longer term final efficacy and safety results for secukinumab from this 3-year study.

Methods: 226 patients (pts) were randomized to intravenous (IV) secukinumab 10mg/kg (baseline, Weeks (Wks) 2 and 4) followed by subcutaneous (SC) secukinumab300 or 150 mg every 4 wks (IV→300/150 mg), or matched placebo (PBO). At Wk 16,PBO pts were re-randomized to SC secukinumab 300 or 150 mg. Analysis at Wk 156 included pts initially randomized to secukinumab and those who switched from PBO to secukinumab at Wk 16 (Any secukinumab 300 mg, N = 113 and Any secukinumab 150mg, N = 110). Outcome measures at Wk 156 included ASAS20 and 40, hsCRP, ASAS5/6, BASDAI, ASAS partial remission (PR) and ASDAS-CRP inactive disease. Analyses stratified by anti-TNF α status (anti-TNF α -naïve and anti-TNF α inadequate response [IR]) were pre-specified. Data are reported as observed. Safety analyses included all pts who received ≥ 1 dose of secukinumab.

Results: 80.5% (91/113; Any secukinumab 300 mg) and 80.9% (89/110; Any secukinumab 150 mg) pts completed 156 wks of treatment. Clinical responses with secukinumab were sustained through Wk 156 (Table). At Week 156, response rates on more stringent clinical endpoints (e.g. ASAS40, ASAS PR) were higher with the 300 mg dose, particularly in anti-TNF-IR pts. The safety profile of both secukinumab doses was similar through Wk 156 (mean exposure: 980.3 days [300 mg] and 990.8 days [150 mg]). Exposure-adjusted incidence rates for *Candida* infections and serious infections/infestations were 0.7 and 0.7 per 100 patient-years, respectively, in the combined group of secukinumab doses over the entire treatment

Table: Summary of Efficacy Results at Weeks 156

Overall population				
Variable, % responders (n/N) unless otherwise specified	Any Secukinumab 300 mg	Any Secukinumab 150 mg		
ASAS20	75.0 (89/92)	68.2 (60/88)		
ASAS40	36.5 (52/92)	47.7 (42/88)		
hsCRP, mean change from baseline \pm SD (N)	-5.0 \pm 12.8 (93)	-8.6 \pm 18.3 (89)		
ASAS5/6	60.0 (40/92)	47.7 (42/88)		
BASDAI, mean change from baseline \pm SD (N)	-3.6 \pm 2.0 (92)	-2.8 \pm 2.0 (88)		
ASAS-PR	28.3 (26/92)	15.9 (14/88)		
ASDAS-CRP inactive disease	25.0 (23/92)	18.4 (16/87)		
By anti-TNF α status				
Variable, % responders (n/N)	Anti-TNF α -naïve		Anti-TNF α -IR	
	Any Secukinumab 300 mg	Any Secukinumab 150 mg	Any Secukinumab 300 mg	Any Secukinumab 150 mg
ASAS20	74.7 (56/75)	68.0 (19/28)	65.5 (12/18)	54.7 (11/20)
ASAS40	60.0 (45/75)	62.9 (17/27)	45.2 (7/15)	29.4 (5/17)
ASAS-PR	28.0 (21/75)	19.7 (14/71)	29.8 (5/17)	0 (0/17)

ASAS, Assessment of Spondyloarthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; hsCRP, high sensitivity C-reactive protein; IR, incidence of (or off of) the (naïve) group with (inadequate) PR; partial remission; SD, standard deviation

period. No cases of inflammatory bowel disease, including Crohn's disease or ulcerative colitis, were reported, and no deaths occurred in the study.

Conclusion: Secukinumab (300 and 150 mg) provided sustained improvements through 3 years in the signs and symptoms of active AS. Secukinumab was well-tolerated with a safety profile consistent with previous reports.^{1,2}

References: 1. Pavelka K, et al. *Arthritis Res Ther*. 2017;19: 285 <https://doi.org/10.1186/s13075-017-1490-y>.
2. Pavelka K, et al. *Arthritis Rheumatol*. 2017;69.

Disclosure: A. J. Kivitz, AbbVie, Pfizer, Genentech, UCB, Sanofi/Regeneron and Celgene, 5.; Celgene, Pfizer, Sanofi/Regeneron, Horizon and Merck, 8; K. Pavelka, MSD, AbbVie, Roche, UCB, Amgen, Hospira, Egis, Pfizer, Medac, BMS, 8; E. Dokoupilova, None; R. Blanco, AbbVie, MSD, and Roche, 2, AbbVie, Pfizer, Roche, Bristol-Myers, Janssen, and MSD, 2, 8; M. Maradiaga, None; H. Tahir, Novartis, Eli Lilly, and AbbVie, 8; Y. Wang, Novartis, 3; B. Porter, Novartis, 1, 3; A. Stefanska, Novartis, 1, 3; S. Rohrer, Novartis, 1, 3; H. Richards, Novartis, 1, 3.

Abstract Number: 1870

Phase 2 Trial of Induction Therapy with Anti-CD20 (Rituximab) Followed By Maintenance Therapy with Anti-BAFF (Belimumab) in Patients with Active Lupus Nephritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Edmond L. Dubois, MD Memorial Lecture: Systemic Lupus Erythematosus – Clinical

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Two randomized, controlled trials of rituximab in patients with lupus and lupus nephritis (LN) did not meet their primary endpoints. A potential explanation is the observation that after treatment with rituximab, serum BAFF levels are elevated and may lead to disease flare by facilitating expansion of and re-population with autoreactive B cells. The CALIBRATE study (NCT 02260934) was designed to test this hypothesis, to determine whether addition of anti-BAFF (belimumab) could enhance the clinical effects of anti-CD20 (rituximab), and assess safety of the combination.

Methods: 43 subjects with active, proliferative LN despite conventional therapy were enrolled in a prospective, randomized, open-label trial that compared two therapeutic regimens. All subjects received iv rituximab (1000 mg), cyclophosphamide (750 mg), and methylprednisolone (100 mg) at wks 0 and 2, and an initial prednisone dose of 40 mg/d with taper to 10 mg/d by wk 12. At wk 4, subjects were randomized to belimumab (10 mg/kg iv at wks 4, 6, 8, and every 4 wks) plus prednisone (RCB group, n=21) versus prednisone alone (RC group, n=22). Complete response (CR) was defined as: (i) urine protein:creatinine ratio (UPCR) <0.5; (ii) eGFR ≥120 or, if <120, eGFR >80% of screening; and (iii) prednisone dose of 10 mg/d. Partial response (PR) differed only in the UPCR criterion (>50% reduction).

Results: The rate of renal response at wk 48 was similar between the two groups (Table I). CR rate was 32% in the RC group and 38% in the RCB group. B cell depletion occurred in both groups by wk 12, but repopulation occurred at different rates (Table II). Median IgG levels remained well within the normal range in both groups (Table II). 5 subjects in the RC group and 2 in the RCB group experienced grade 3 or higher infectious adverse events, and all resolved.

Conclusion: There was no difference in the rate of renal response at wk 48 in subjects who received anti-CD20 therapy followed by anti-BAFF therapy compared with anti-CD20 therapy alone. Anti-BAFF resulted in delayed peripheral B cell repopulation, but was not associated with hypogammaglobulinemia or an increase in serious infectious adverse events. Further analyses at wk 96 will provide information on the effects of anti-BAFF on B cell repertoire and longer term clinical outcomes.

Table I

	CR	PR	Failed *	Withdrawn**
RC Group (n=22)	7 (32%)	2 (9%)	12 (55%)	1 (5%)
RCB Group (n=21)	8 (38%)	3 (14%)	8 (38%)	2 (10%)

* Includes subjects who failed at any point due to lack of renal response, inability to taper steroids, renal flare, or non-renal flare.

** Includes subjects withdrawn for reasons unrelated to lupus. Table II

	Median B Cell Count (cells/uL)				Median IgG Level (mg/dl)		
	Wk 0	Wk12	Wk 24	Wk 48	Wk 0	Wk 24	Wk 48
RC Group	105	1	21	31	1050	1110	1410
RCB Group	143	1	3	9	984	837	904

Disclosure: M. Dall'Era, Genentech, Inc., 5, AstraZeneca, 5; C. Aranow, GlaxoSmithKline, 5, GlaxoSmithKline, 2, EMD Serrono, 2, Xencor, 2, UCB, Inc., 2, Takeda, 2, Janssen, 2; M. Byron, None; L. Ding, None; D. Smilek, None; B. Diamond, None; D. Wofsy, Celgene Corporation, 5, GlaxoSmithKline, 5, Novartis, 5, Takeda, 5.

Abstract Number: 1871

A High Cardiovascular Biomarker Panel Risk Score Is Associated with Increased 10-Year Risk of Cardiovascular Events and Death in SLE

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Edmond L. Dubois, MD Memorial Lecture: Systemic Lupus Erythematosus – Clinical

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: There is a well-documented increase in atherosclerosis (ATH) in SLE that is not fully explained by traditional risk factors. Several non-Framingham biomarkers, including pro-inflammatory HDL (piHDL), leptin, plasma soluble TNF-like weak inducer of apoptosis (sTWEAK), and homocysteine are individually associated with subclinical ATH in SLE. We previously demonstrated that these biomarkers, combined with clinical variables such as age and diabetes, create a risk profile we have called *PREDICTS*. The *PREDICTS* profile more accurately identified SLE patients at risk for future subclinical ATH progression than any one variable alone. We set out to determine whether a high-risk *PREDICTS* score could also identify patients at risk for future cardiovascular events.

Methods: 392 SLE patients participated in this longitudinal prospective cohort study. 205 patients were included in this analysis, based on availability of 10-year cardiac event and/or mortality data. piHDL was measured using a published cell-free assay. Leptin and sTWEAK were determined at baseline using ELISA (R&D Biosystems). Homocysteine was determined by radioimmunoassay in the clinical laboratory of an academic medical center. Cardiac events were defined as myocardial infarction, a positive stress test, angioplasty, or percutaneous coronary intervention. Cerebrovascular events were defined as stroke or documented TIA. We defined high-risk *PREDICTS* as ≥ 3 of identified predictors or diabetes + ≥ 1 predictor.

Results: 16.1% (33) of SLE patients experienced a cerebrovascular accident during the 10-year follow-up period. 8.3% (17) of subjects had a cardiac event. 8.3% (17) of subjects died. Patients with a high-risk *PREDICTS* score at cohort entry were significantly more likely to have a cerebrovascular event (19.1% vs. 7.0%, $p=0.04$), or a cardiac event (10.9% vs. 0%, $p=0.012$). In addition, a high-risk baseline *PREDICTS* score also was also more likely to be found in patients that suffered any cardiovascular event or death (34.4% vs. 7%, $p<0.0001$). In multivariate analysis, baseline high-risk *PREDICTS* associated with a 3.7-fold increased odds for death or cardiovascular event over 10 years ($p=0.004$). Hypertension at baseline also was associated with increased odds for death or cardiovascular event (OR=4.9, $p=0.001$). No association with death or cardiovascular events were observed with hyperlipidemia, baseline carotid plaque, gender, or tobacco use.

Conclusion: A high-risk *PREDICTS* score and a history of hypertension at cohort entry confer significantly increased odds for a cardiovascular event or death in SLE patients over a 10-year follow-up. Further studies are necessary to identify proactive treatment strategies to prevent cardiovascular morbidity and mortality in SLE.

Disclosure: M. A. McMahon, None; J. M. Grossman, None; L. Sahakian, None; C. Charles-Schoeman, Bristol Myers Squibb, AbbVie, Octapharma, and Pfizer, 2; Regeneron-Sanofi, Pfizer, Octapharma, Amgen, and Gilead, 5; J. Fitzgerald, None; M. Taylor, Celgene Corporation, 8; AbbVie Inc., 8; A. Gorn, None; E. Olmos, None; D. J. Wallace, Program Advisor to Lupus Foundation of America, 5; B. H. Hahn, Janssen Research & Development, LLC, 2; B. Skaggs, None.

Abstract Number: 1872

Safety and Efficacy of Allogeneic Umbilical Cord-Derived Mesenchymal Stem Cells in Patients with Systemic Lupus Erythematosus: Results of an Open-Label Phase I Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Edmond I. Dubois, MD Memorial Lecture: Systemic Lupus Erythematosus – Clinical Session type: ACR concurrent Abstract Session

Session Time: 2:30pm-4:00pm

Background/Purpose: Mesenchymal stem cells (MSCs) are known to possess significant immunosuppressive and tissue protective properties, and their use in refractory systemic lupus erythematosus (SLE) is supported by promising safety and efficacy in autoimmune animal models and human trials. We conducted this phase I open-label study to test the hypothesis that a single infusion of human allogeneic umbilical cord-derived MSCs (IND 16377) is safe when added to standard-of-care therapy for active SLE.

Methods: Patients (N=6) with active SLE (SLEDAI ≥ 6) who signed informed consent and met all inclusion and exclusion criteria sequentially received 1×10^6 cells/kg umbilical cord-derived MSCs given as an IV infusion in Plasma-Lyte A solution. Post-infusion, Week 1 and 2 safety data from each participant was reviewed by the Data Safety Monitoring Board prior to enrolling the next patient. The primary safety outcome is frequency of Grade 3 or higher adverse events (AEs) by Week 24. The primary efficacy outcome is change in SLE disease activity between Baseline and Week 24 measured by SLEDAI score and prednisone dose. Each patient is followed for a total of 52 weeks.

Results: Table 1 summarizes the demographics, visit SLEDAI scores, number of AEs and serious adverse events (SAEs). The 6th participant completed her Week 24 visit on April 11, 2018. To date, there has been one SAE and no AEs higher than Grade 2 by NCI-CTCAE scoring. The SAE was prolonged hospitalization following a partial dose infusion of rituximab IV leading to anaphylaxis. Rituximab was started for persistent SLE disease activity (patient dropped out of the study after Week 8) and was given in the hospital ICU setting due to her prior history of anaphylaxis to Tween (polyethoxylated surfactant found in IV and SQ medications). Anaphylaxis resulted in a prolonged hospital stay of 2 days, resolving with treatment without sequelae. The SAE was attributed to her known allergy to ingredients in the rituximab infusion and deemed unrelated to the MSCs that she received several months earlier. The AEs “possibly” attributable to the investigational product were Grade 2 nausea, Grade 2 tachycardia, and Grade 1 flushing with Grade 1 toe paresthesias – all of which resolved without sequelae.

Among the 5 patients who completed their Week 24 evaluations, all showed improved SLE activity (mean SLEDAI score 8.6 ± 1.9 at Baseline improved to 2.6 ± 2.8 at Week 24) with stable or lower doses of prednisone and stable background immunosuppressants. Mean physician global assessment (PGA) scores also improved from 1.71 ± 0.48 at Baseline to 0.32 ± 0.17 at Week 24.

Conclusion: A single-dose of umbilical cord-derived MSCs was safe and well-tolerated in this open-label phase I trial for six patients with active SLE. Initial efficacy data for MSCs in SLE appears promising and will be further tested in a larger controlled trial.

Table 1

Subject	Baseline Age, Race/Ethnicity, Sex	SLEDAI Score					Non-Serious AEs (#)	SAE (#)
		Baseline	Week 4	Week 8	Week 12	Week 24		
1	32 yo Black Female	6	4	2	0	0	3 Grade 1 5 Grade 2 0 Grade ≥ 3	0
2	38 yo Caucasian Female	8	8	8	2	2	0 Grade 1 2 Grade 2 0 Grade ≥ 3	0
3	33 yo Caucasian Female	6	12	8	Dropped out	Dropped out	2 Grade 1 2 Grade 2 0 Grade ≥ 3	1
4	26 yo Hispanic Female	10	8	15	10	6	0 Grade 1 3 Grade 2 0 Grade ≥ 3	0
5	48 yo Caucasian Female	8	2	0	2	0	1 Grade 1 1 Grade 2 0 Grade ≥ 3	0
6	38 yo Black Female	11	5	8	8	5	1 Grade 1 1 Grade 2 0 Grade ≥ 3	0

Disclosure: D. L. Kamen, None; P. J. Nietert, None; H. Wang, None; T. Duke, None; C. Cloud, None; A. Robinson, None; G. S. Gilkeson, None.

Abstract Number: 1873

Age- and Cause-Specific Standardized Mortality Ratio of Systemic Lupus Erythematosus Patients in Ontario, Canada over 43 Years (1971-2013)

Konstantinos Tselios, Dafna D Gladman, Barry Sheane, Jiandong Su and Murray Urowitz, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada

SESSION INFORMATION

Session Date: Monday, October 22, 2018

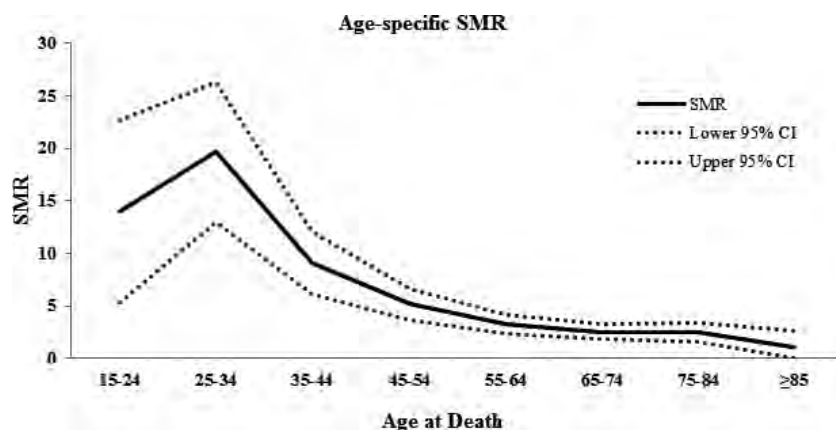
Session Title: Edmond L. Dubois, MD Memorial Lecture: Systemic Lupus Erythematosus – Clinical

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The major causes of early death in systemic lupus erythematosus (SLE) include active disease and infections, while cardiovascular complications and malignancies dominate the late stages. In recent years, there has been a significant decrease in all-cause mortality. The aim of the present study was to assess the all cause, age and cause-specific standardized mortality ratios (SMR) of lupus patients from 1971 to 2013.

Methods: Our long-term longitudinal cohort followed 1732 patients between 1971-2013. Causes of death were retrieved from death certificates, autopsy reports, hospital records or the records of the family physicians for each patient. They



were categorized as atherosclerotic (acute coronary syndrome, ischemic cardiomyopathy, cerebrovascular accident), infection (sepsis), malignancy, active lupus and others. Patients were also categorized according to the age at death in 10-year intervals (15-24, 25-34 etc.). For the calculation of the SMR, data from the general population of Ontario, Canada were used (retrieved from Statistics Canada for the same time period). Statistical analysis was performed with SAS 9.4.

Results: Two hundred and forty-nine patients (205 females) died (infections 24.5%, atherosclerosis 15.7%, active lupus 13.3%, malignancy 9.6%); mean age was 53.2±16.6 years and mean disease duration 15.2±11.7 years. The mean age at death and SMRs for all-cause and cause-specific mortality over the decades are shown in Table 1.

Table 1 Mean age at death and Standardized Mortality Ratio* (all-cause and cause-specific) for SLE from 1971 to 2013

	1971-79	1980-89	1990-99	2000-09	2010-2013
Mean age (y±SD)	42.2±12.9	50.4±16.8	57.2±16.9	54.1±15.9	58.8±14.6
All-cause	13.5 (8.6-18.5)	6.5 (4.9-8.2)	4.7 (3.6-5.8)	3.2 (2.4-4)	2.2 (1.4-3.1)
Atherosclerosis		8.3 (3.8-12.8)	6.7 (3.8-9.5)	2.3 (0.8-3.8)	3.2 (0.1-6.3)
Infection		14.2 (8-20.4)	6.5 (3.8-9.1)	2.5 (1.2-3.9)	0.9 (0-1.9)
Malignancy		14.1 (4.3-23.9)	3 (1.1-4.8)	4.4 (1.5-7.3)	1.4 (0.2-2.7)

* As compared to the general population of Ontario, Canada (1971-2013). Values are given as SMR (95% Confidence Interval)

The age-specific SMR was particularly high in younger (15-44 years old) patients [SMR=12.4, 95% CI=9.7-15.1] as compared to the patients who were older than 45 years [SMR=3.1, 95% CI=2.6-3.6]. Details are given in Figure 1.

An analysis of the cause-specific SMR in the age groups 20-39 and ≥40 showed that younger patients had a higher SMR for all these causes, details in Table 2.

Table 2 Cause-specific Standardized Mortality Ratio for patients 20-39 years old and ≥40 years (1978-2013)

Causes of death	Deaths (20-39 years), n	SMR (20-39 years)	Deaths (≥ 40 years), n	SMR (≥ 40 years)
All cause	58	12.4 (95% CI=9.7-15.1)	191	3.1 (95% CI=2.6-3.6)
Atherosclerosis	3	14.6 (95% CI=0-43.3)	36	4.7 (95% CI=3.3-6)
Infection	30	30.2 (95% CI=14.4-46)	31	3.5 (95% CI=2.5-4.5)
Malignancy	4	31.9 (95% CI 0.6-63.1)	20	3 (95% CI=1.9-4.1)

Conclusion: The SMR for all-cause and cause-specific mortality has significantly decreased over time, likely reflecting the advances in the management of SLE and atherosclerosis, infections and malignancies. The SMR is particularly high for younger patients (<40 years old) and it remains higher than that of the general population even for the older patients.

Disclosure: K. Tselios, None; D. D. Gladman, None; B. Sheane, None; J. Su, None; M. Urowitz, None.

View Abstract and Citation Information Online -

Abstract Number: 1874

Remission and Low Disease Activity State Are Protective of Intermediate and Long-Term Outcomes in SLE Patients. Data from a Multi-Ethnic, Multi-Center US Cohort

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Edmond L. Dubois, MD Memorial Lecture: Systemic Lupus Erythematosus – Clinical

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Over the last few years the importance of treating patients with SLE towards achieving either Remission or LDAS (Treat-to-Target approach) has become evident. We have now aimed at determining the beneficial effects of achieving these states in lupus patients from a multi-ethnic, multicenter lupus cohort (LUMINA for Lupus in Minorities: Nature vs. Nurture).

Methods: The LUMINA cohort was started in 1993 and up to 2009 recruited nearly 600 patients of either Caucasian (28%), African (37%) or Hispanic (35%) ancestry, at three institutions: Alabama, Texas and Puerto Rico. Visits were performed every 6 months for the first year and yearly thereafter. Socioeconomic, demographic and clinical data were obtained at all visits. Disease activity was ascertained with the Systemic Lupus Activity Measure (SLAM) and disease damage with the SLICC Damage Index (SDI). We have now examined all patients' visits and classified them as corresponding to Remission (SLAM score=0 and Prednisone \leq 5 mg/day and no immunosuppressants), LDAS [(not in Remission), SLAM score \leq 3, prednisone $<$ 7.5 mg/day, no immunosuppressants) or neither: active. Because of the relatively small number of visits corresponding to Remission, Remission and LDAS visits were examined as a single variable. The association between the last SDI and the percent of time on Remission/LDAS was modeled using Poisson regression with adjustment for variables known to affect this outcome (age, gender, ethnic/racial group, baseline disease activity and disease damage). In a separate multivariable regression model, mortality, adjusting for variables known to affect this outcome, was the end-point.

Results: Visits for 558 patients (total number of visits: 3979; median number of visits per patient: 6.8, interquartile range 4-6) were examined. The longer patients were on Remission/LDAS, the less likely they were to accrue damage [Estimate 0.3503, 95% CI 0.2497 to 0.4905 ($p < 0.001$)]. In terms of mortality the direction of the association was as expected (protective) but statistical significance was not reached [Parameter estimate OR 0.303 (Wald 95% CI 0.063 to 1.456 ($p = 0.1360$))].

Conclusion: The longer lupus patients are in remission/LDAS, the less likely they are to accrue damage. Other significant variables in this analysis, were, as expected, associated with damage (older age, male gender, not being from Puerto Rico, higher disease activity at baseline and higher damage at the baseline visit). Although the direction of the association in terms of mortality was as expected, statistical significance was not reached. These data have implications for the management of patients with lupus regardless of their ethnic/racial background.

Table 1 Poisson Multivariable Regression Model of Damage in LUMINA patients

Variable	Estimate	Wald 95% CI	p value
Age	0.0120	1.0070-1.0170	<0.0001
Gender (male)	1.1177	0.9216-1.3557	0.2581
Race/ethnic group			
Hispanic (Puerto Rico)	Ref.		
Caucasian	2.6104	2.0069-3.3950	<0.0001
African American	2.1843	1.7064-2.7960	<0.0001
Hispanic (Texas)	1.7690	1.3638-2.2945	<0.0001
SDI (baseline)	1.3214	1.2693-1.3758	<0.0001
SLAM score (baseline)	1.0258	1.0057-1.0373	<0.0001
Remission/LDAS	0.3503	0.2497-0.4945	<0.0001

Disclosure: G. J. Pons-Estel, None; G. S. Alarcón, None; M. Ugarte-Gil, None; L. M. Vilá, None; J. D. Reveille, Janssen, 5, Eli Lilly and Co., 2, 5, UCB, Inc., 5, Novartis, 5; G. McGwin, None.

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Abstract Number: 1875

Influence of Setting an Upper Limit of the Modified Rodnan Skin Score As an Inclusion Criterion in Systemic Sclerosis Clinical Trials on the Ratio of Skin Fibrosis Progression Vs. Improvement – an Analysis of the Genisys Cohort

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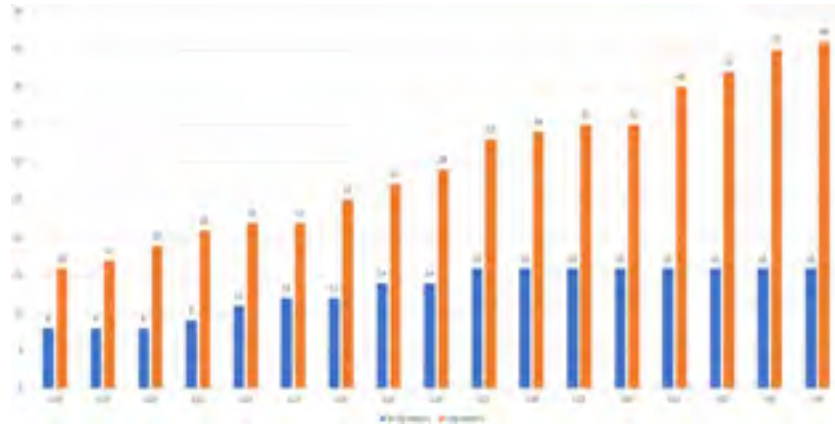
SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders– Clinical II: Clinical Trial Results, Predictors, Design

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM



Background/Purpose: Recent studies on large cohorts of patients with systemic sclerosis (SSc) have shown that lowering the upper threshold of the modified Rodnanskin score (mRSS) as a study inclusion criterion leads to cohort enrichment with patients with progressive skin disease. Limitations of these studies were lack of racial diversity and low proportion of patients with anti-RNA-Polymerase III (Pol3) antibodies. As the Texas-based GENISOS cohort is an ethnically diverse cohort, including a large proportion of Pol3-positive patients, this study aimed to assess the effect of different mRSS cut-off values at baseline on progression of skin fibrosis after one year of follow-up.

Methods: We extracted data from GENISOS for patients fulfilling the 1980 ACR criteria for SSc and the Le Roy criteria for diffuse cutaneous SSc, who had a minimum mRSS of 7 at inclusion and a follow-up visit with documented mRSS at 12±2 months. Progressors were defined as having an increase in mRSS >5 points and ≥25% from the baseline to 2nd visit, while regressors were defined as having a decrease in mRSS of >5 points and ≥25%. To identify the optimal cut-off of baseline mRSS that yields the highest sensitivity for progressive skin fibrosis, we developed ROC curves and logistic regression models with “progression” as outcome variable and a binary variable of baseline mRSS cut-off point as predictor.

Results: 152 patients (age and disease duration [median, Q1-Q3, years] 49.5, 40.2-57.3 and 2.2, 1.1-3.3 respectively, 22.4% males) matched the inclusion criteria. The proportion of patients of African American ethnicity was 32/152 and 50/152 patients were Pol3-positive.

After one year of follow-up, 17 patients (11.2%) classified as progressors and 51 (33.6%) as regressors. Progressors were more frequently positive for anti-topoisomerase antibodies (37.5% vs. 15.3%, $p=0.028$), negative for anti-Pol3 antibodies (93.8% vs. 62.3 %, $p=0.012$), had a shorter disease duration (median, Q1-Q3: 1.3, 0.5-2.2 vs. 2.4, 1.1-3.5 years, $p=0.005$) and lower mRSS (median, Q1-Q3: 21, 11-25 vs. 24, 16-31, $p=0.012$) than the remainder of the patients.

Sixteen of 17 progressors, but only 33 of 51 regressors had a baseline mRSS ≤27. The mRSS cut-off of ≤27 had the highest probability of progression (odds ratio 9.1, 95% confidence interval 1.2-70.9, $p=0.035$, area under the curve 0.652). Using this cut-off as an inclusion criterion in a clinical trial (vs. no cut-off) would have included 94% of all progressors, but only 65% of all regressors and 67% of all patients. The figure displays absolute numbers of progressors and regressors at 1 year for each mRSS cut-off.

Conclusion: This analysis reconfirmed, in a population rich in patients of African American origin and with high prevalence of Pol3 antibodies, that setting a lower upper threshold of mRSS at study inclusion increases the proportion of progressors and reduces the absolute number of regressors.

Disclosure: C. Mihai, None; R. Dobrota, None; S. Assassi, None; M. D. Mayes, None; O. Distler, Actelion, Bayer, Boehringer Ingelheim, Mitsubishi Tanabe Pharma, Roche, 2, Actelion, AnaMar, Bayer, Boehringer Ingelheim, ChemolmAb, espeRare foundation, Genentech/Roche, GSK, Inventiva, Italfarmaco, Lilly, medac, MedImmune, Mitsubishi Tanabe Pharma, Novartis, Pfizer, Sanofi, Sinoxa, UCB, 5, Patent mir-29 for the treatment of systemic sclerosis licensed, 9.

Abstract Number: 1876

Machine Learning Classification of Peripheral Blood Gene Expression Identifies a Subset of Patients with Systemic Sclerosis Most Likely to Show Clinical Improvement in Response to Hematopoietic Stem Cell Transplant

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders– Clinical II: Clinical Trial Results, Predictors, Design

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The SCOT (Scleroderma:Cyclophosphamide or Transplantation) trial (Sullivan K. *et al*, 2018) demonstrated the clinical benefit of hematopoietic stem cell transplant (HSCT) compared to cyclophosphamide(CYC) in dcSSc. We analyzed gene expression data from peripheral blood mononuclear cells (PBMCs) of SCOT participants to identify molecular changes and intrinsic gene expression subsets associated with treatment response.

Methods: PBMC gene expression data were generated from 67 SCOT participants at baseline (36 CYC, 31 HSCT) and at 48/54 months (12CYC, 14 HSCT). Significant differentially expressed genes (DEGs; False Discovery Rate <5%) were identified between baseline and 48/54 month samples using Significance Analysis of Microarrays and were annotated with

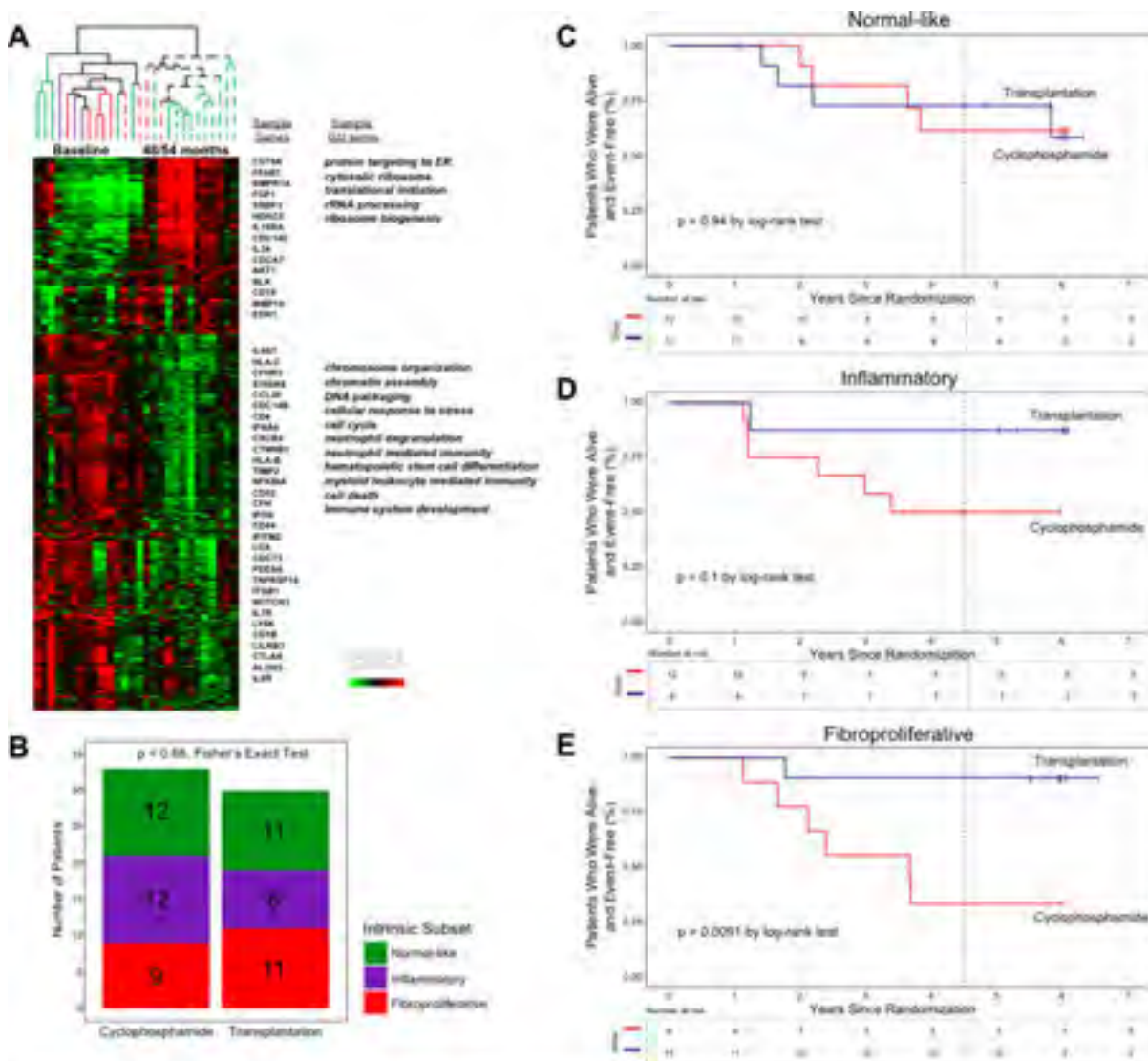


Figure 1: (A) Sample DEGs (and associated GO terms) modulated between baseline and 48/54 months of treatment for patients randomized to the HSCT arm. **(B)** Comparison between treatment arms in terms of the number of patients assigned to each intrinsic subset at baseline. **(C-E)** EFS analysis by treatment arm (HSCT in blue, CYC in red) for patients assigned to the normal-like (C), inflammatory (D), and fibroproliferative (E) intrinsic subsets.

Gene Ontology functional terms via g:Profiler. Participants who completed treatment protocol (Per-Protocol Population) were assigned to intrinsic gene expression subsets at baseline using a machine learning classifier based on elastic net multinomial regression previously trained and tested on five independent SSc cohorts. The relationship between intrinsic subsets and event-free survival (EFS) was analyzed at 54 months.

Results: The participants included in the gene expression analyses were representative of the full cohort in the SCOT trial; there were no significant differences in sex, age, race, or baseline phenotypic measures. In the subset of participants with 48/54 month samples, we observed considerably more DEGs in HSCT arm (4788 genes) than in CYC arm (21 genes). Participants in HSCT showed a decrease in the expression of genes associated with cell proliferation and immune response and an increase in expression of genes associated with translation compared to baseline (Fig. 1A). Participants were assigned to intrinsic gene expression subsets at baseline (Fig. 1B) in both treatment arms. EFS did not differ between treatment arms for the participants assigned to the normal-like subset ($p=0.94$, Fig. 1C), consistent with the lack of active immune response in these participants. Participants assigned to the inflammatory subset trended towards improved chance of EFS in HSCT arm ($p=0.1$, Fig. 2D). Participants assigned to the fibroproliferative subset who received HSCT experienced significant improvement in EFS compared to fibroproliferative participants who received CYC ($p=0.0091$, Fig. 1E).

Conclusion: The HSCT arm of the SCOT trial showed substantially larger changes in gene expression compared to CYC arm. Participants assigned to the normal-like subset did not show benefit from HSCT treatment over CYC. Importantly, participants assigned to the fibroproliferative subset, who tend not to improve on immunosuppressive therapy (e.g. MMF or abatacept), were the most likely to benefit from HSCT.

Disclosure: J. Franks, None; V. Martynov, None; T. A. Wood, None; L. Crofford, None; L. Keyes-Elstein, None; D. E. Furst, None; E. Goldmuntz, None; M. D. Mayes, None; P. McSweeney, None; R. Nash, None; K. Sullivan, None; M. L. Whitfield, None.

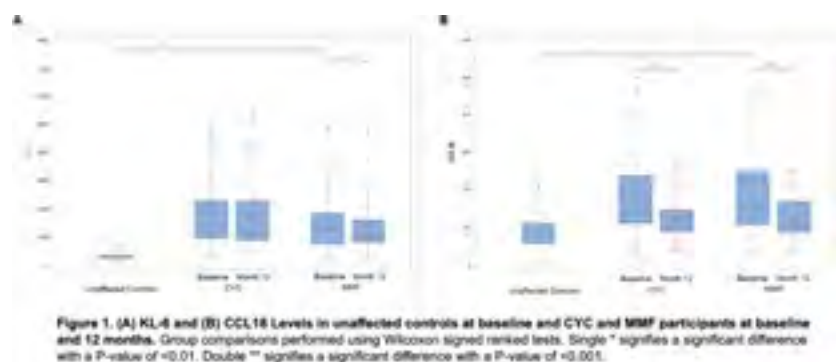
Abstract Number: 1877

Specific Pneumoproteins Predict Progression of Interstitial Lung Disease in Systemic Sclerosis Patients Undergoing Treatment with Immunosuppression

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SESSION INFORMATION

Session Date: Monday, October 22, 2018



Session Title: Systemic Sclerosis and Related Disorders– Clinical II: Clinical Trial Results, Predictors, Design

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Interstitial lung disease (ILD) is the leading cause of death in systemic sclerosis (SSc). While some SSc-ILD patients are stable or improve with immunosuppressive therapy, others have progressive decline and currently available clinical parameters do not reliably predict outcomes. We investigated whether two specific pneumoproteins, Krebs von den Lungen-6 [KL-6] and CC chemokine ligand 2 [CCL18] predict response to immunosuppression with cyclophosphamide (CYC) and mycophenolate (MMF) in SSc-ILD.

Methods: 142 patients in Scleroderma Lung Study (SLS) II were randomized to receive either mycophenolate (MMF) for 2 years or oral CYC for 1 year followed by 1 year of placebo. All available serum baseline and 12-month samples were investigated. CCL18 was assayed by commercially available ELISA while KL-6 was measured using antibody coated latex microbeads and an automated analyzer. The forced vital capacity (FVC) and the diffusing capacity for carbon monoxide (DLCO) were measured every 3 months. Quantitative Lung fibrosis (QLF) and Quantitative ILD (QILD) scores for whole lung (WL) and zone of maximum involvement (ZM) were measured at baseline. To investigate the relationship between baseline CCL18 and KL-6 and progression of ILD, joint models were created with the outcomes of the course of the FVC and DLCO over 1 year.

Results: Baseline serum KL-6 and CCL18 correlated with extent of ILD. KL-6 levels correlated with (r, *P*-value): DLCO (-0.3; 0.0002) QLF-WL (0.5; <0.0001) QLF-ZM (0.4; <0.0001), and QILD-WL (0.5; <0.0001), QILD-ZM (0.5; <0.0001); Baseline CCL18 levels were correlated with QILD-WL (*r*=0.2; *p*=0.04) and QILD-ZM (*r*=0.3; *p*=0.009), but not with the FVC or DLCO. CCL18 and KL6 levels declined significantly in the first year in both arms (Figure 1). After adjusting for baseline disease severity, higher baseline KL6 levels predicted progression of ILD as measured by the course of the FVC (CYC/MMF: Estimate -0.31/-0.74; *P*=0.024/<0.001) and DLCO (CYC/MMF: Estimate -1.30/-1.29; *P*<0.001/<0.001) over 1 year for both treatment arms. Similarly, higher baseline CCL18 levels predicted progression of ILD as measured by the course of the FVC (CYC/MMF: Estimate -1.24/-0.35; *P*<0.001; 0.007) and DLCO (CYC/MMF: Estimate -1.87/-1.24; *P*=0.001/0.002) over 1 year for both treatment arms.

Conclusion: In the context of a rigorously conducted clinical trial for SSc-ILD, baseline KL-6 and CCL18 levels correlated with several surrogate measures of ILD severity. Patients with higher baseline KL-6 and CCL18 levels were more likely to experience disease progression despite treatment with CYC and MMF. KL-6 and CCL18 could be used to identify patients with progressive ILD that require closer monitoring in clinical practice. KL-6 and CCL18 may also be used to enrich SSc-ILD clinical trials with those at risk of accelerated ILD progression with conventional immunosuppressive therapy.

Disclosure: E. R. Volkmann, None; D. P. Tashkin, None; M. Kuwana, Astellas, 2, MBL, 7, Astellas, Japan Blood Products Organization, 8; N. Li, None; J. Charles, None; F. N. Hant, None; G. S. Bogatkevich, None; T. Akter, None; M. Roth, None; H. J. G. Kim, None; J. Goldin, None; D. Khanna, Eicos Sciences, 1, Pfizer, Inc., 2, Horizon, 2, BMS, 2, Actelion, 5, Bayer, 5, Bayer, 2, Corbus, 5, Cytos, 5, EMD Serono, 5, Genentech, Inc., 5, Sanofi-Aventis, 5, GSK, 5, Boehringer Ingelheim, 5; P. J. Clements, None; D. E. Furst, None; R. Elashoff, None; R. Silver, None; S. Assassi, None.

Abstract Number: 1878

Immunosuppression in Diffuse Systemic Sclerosis Improves Outcomes Using a Novel Composite Response Index

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders– Clinical II: Clinical Trial Results, Predictors, Design

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Diffuse systemic sclerosis (dcSSc) is a devastating multi-organ disease where the mainstay of treatment is immunosuppression. Data on these therapies are mostly based on skin or organ specific outcomes such as lung involvement. However, a new composite response index in dcSSc (CRISS) was proposed to improve assessment of treatment interventions¹. Our aim is to examine the effect of current immunosuppressive therapy on the CRISS in an observational dcSSc cohort.

Methods: Adult dcSSc patients without prior immunosuppression followed in the Canadian Scleroderma Research Group (CSRG) registry between 2005 and 2017 were included. Patients newly treated with methotrexate, azathioprine, mycophenolate and/or cyclophosphamide for ≥ 2 years were the exposed group and untreated patients with at least the same follow up duration were controls. To account for disparity between treated and untreated patients, inverse probability of treatment weighting (IPTW) was performed to balance potential confounders: age, sex, disease duration and CRISS variables (modified Rodnan skin score, forced vital capacity, patient and physician global assessments, and HAQ-DI). Overall disease evolution after 1 year was qualified using CRISS which defines improvement as a score ≥ 0.6 . Missing data were multiply imputed and logistic regression was used to obtain pooled odds ratios and confidence intervals.

Results: 301 dcSSc patients were analyzed. Of these, 47 (15.7%) were treated and 254 (84.4%) were untreated. At baseline, treated compared to untreated patients were younger (50.1 ± 10.4 vs. 55.1 ± 12.3 years respectively, $p=0.008$), had significantly shorter disease duration (5.5 ± 7.4 vs. 11.7 ± 9.3 years respectively, $p<0.001$) and higher mean physician global assessment scores (4.2 ± 2.3 vs. 2.5 ± 1.9 points respectively, $p<0.001$). IPTW used to correct for the different treatment probabilities and confounders showed excellent balance between the two groups. Prior to IPTW, treated patients trended towards more improvement after 1 year. However, after IPTW correction, treated patients were significantly more likely than untreated patients to have improved disease, regardless of age, sex, or disease duration (Table 1).

Conclusion: Assessing the effects of treatment in an observational cohort is intrinsically biased as treated patients will likely have more severe disease. After balancing using IPTW to reduce these confounders, we demonstrated that patients on immunosuppression are more likely to experience substantial improvement than untreated patients after 1 year using the CRISS score, a newly proposed global measure of disease severity.

Khanna D, Berrocal VJ, Giannini EH, et al. The American College of Rheumatology Provisional Composite Response Index for Clinical Trials in Early Diffuse Cutaneous Systemic Sclerosis. *Arthritis Rheumatol* 2016;68(2):299-311.

Table 1 Odds of having improved disease after 1 year before and after IPTW adjusted for patient variables

	Before IPTW		After IPTW	
	OR (95% CI)	p	OR (95% CI)	p
Treatment exposure	2.00 (0.82, 4.92)	0.129	1.85 (1.11, 3.09)	0.018
Female	1.07 (0.41, 2.79)	0.896	1.50 (0.73, 3.05)	0.268
Age	1.00 (0.97, 1.04)	0.861	1.03 (1.00, 1.05)	0.038
Disease duration	1.01 (0.96, 1.05)	0.802	1.00 (0.97, 1.02)	0.809

Disclosure: B. Zheng, None; M. Wang, None; M. Baron, None.

Abstract Number: 1879

The Effects of Riociguat on Raynaud's Phenomenon and Digital Ulcers in Patients with Diffuse Systemic Sclerosis: Results from the Phase IIb RISE-SSc Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders– Clinical II: Clinical Trial Results, Predictors, Design

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The soluble guanylate cyclase stimulator riociguat is approved for the treatment of pulmonary arterial hypertension associated with connective tissue disease. It was anticipated that riociguat might, through its vasodilatory and anti-remodeling properties, decrease the number and severity of Raynaud's attacks and reduce net digital ulcer burden in patients with diffuse cutaneous systemic sclerosis (dcSSc). We present exploratory endpoints from the RISE-SSc study (NCT02283762) on the effect of riociguat in early dcSSc patients with Raynaud's phenomenon and digital ulcers.

Methods: RISE-SSc was a Phase IIb, multicenter, randomized, double-blind, placebo-controlled study. Inclusion criteria were: diagnosis of SSc fulfilling ACR/EULAR criteria, diffuse cutaneous involvement, disease duration ≤ 18 months, and modified Rodnan skin score ≥ 10 and ≤ 22 units. Patients were assigned to placebo or riociguat individually adjusted from 0.5 mg up to 2.5 mg 3 times daily. Exploratory efficacy endpoints included 1) change in Raynaud's attacks from baseline to Week 14, assessed by the following individual outcome measures: Raynaud's condition score (analyzed using ANOVA), patient/physician assessment of Raynaud's phenomenon (analyzed using ANOVA), attack symptoms, attack duration, and average No. of attacks per day; and 2) change in net digital ulcer burden from baseline to Week 52, assessed by ulcer count, ulcer burden, and visual analog score (as part of the Scleroderma Health Assessment Questionnaire) for patient-reported severity. Endpoints were analyzed using mixed-model repeated measures from baseline up to Week 52, unless otherwise stated.

Results: In total, 121 patients were enrolled. At Week 14, a numerically greater relative reduction in attack duration and attack frequency was observed from baseline in the riociguat group vs placebo (Table). Improvements in Raynaud's attack symptoms and disability measured by pain, numbness, tingling, and patient/physician global assessment were also observed with riociguat vs placebo (Table). At Week 52, reductions in net digital ulcer burden were -0.09 ± 0.50 for riociguat and -0.08 ± 1.47 for placebo (estimated treatment difference: -0.11 [95% CI: $-0.38, 0.17$; $p=0.44$]). At baseline, 9 patients (15.0%) had digital ulcers in the riociguat arm vs 6 patients (9.8%) in the placebo arm. At Week 52, 1 patient (2.1%) had digital ulcers in the riociguat arm vs 4 patients (8.2%) in the placebo arm.

Conclusion: There was a numerical tendency toward a reduction of Raynaud's phenomenon symptoms with riociguat treatment compared with placebo. While there was no significant difference in reduction of net digital ulcer burden between riociguat and placebo, data suggest that riociguat may prevent digital ulcer recurrence in patients with early dcSSc.

Adelphi Communications Ltd, Bollington, UK provided medical writing support. Table. Change in Raynaud's attacks from baseline to Week 14 (full analysis set)

Endpoint	Riociguat			Placebo		
	Baseline, mean \pm SD (range)	Absolute change	Relative change (%) ^a	Baseline, mean \pm SD (range)	Absolute change	Relative change (%) ^a
Duration of attacks per day (min)	38.7 \pm 54.8 (0.0–228.6)	–12.9	–33.4	73.0 \pm 139.8 (0.0–728.6)	–14.4	–19.8
Number of attacks per day	2.5 \pm 2.7 (0.0–11.6)	–1.2	–49.0	2.0 \pm 2.2 (0.0–12.3)	–0.6	–28.5
Raynaud's condition score (range 0–10)	3.1 \pm 2.5 (0.0–8.4)	–0.9	–30.3	2.7 \pm 2.6 (0.0–9.6)	–0.4	–13.4
Patient assessment (range 0–100)	29.1 \pm 26.3 (0.0–94.0)	–10.1	–34.7	26.5 \pm 26.7 (0.0–100.0)	–0.8	–3.0
Physician assessment (range 0–100)	31.5 \pm 24.2 (0.0–83.0)	–12.8	–40.5	36.9 \pm 28.3 (0.0–94.0)	–9.6	–26.1
Pain (attack symptom; range 0–100)	24.6 \pm 25.6 (0.0–82.6)	–6.9	–27.9	21.5 \pm 26.4 (0.0–90.0)	–1.8	–8.5
Numbness (attack symptom; range 0–100)	26.0 \pm 25.6 (0.0–89.3)	–5.7	–22.1	22.0 \pm 24.2 (0.0–91.4)	–0.2	–1.1
Tingling (attack symptom; range 0–100)	20.9 \pm 23.1 (0.0–81.6)	–3.0	–14.3	16.9 \pm 22.5 (0.0–80.0)	+1.4	+8.2

a Percentage calculated manually (mean change from baseline to Week 14/mean baseline value*100).

Disclosure: D. Khanna, Eicos Sciences, 1, Pfizer, Inc., 2, Horizon, 2, BMS, 2, Actelion, 5, Bayer, 5, Bayer, 2, Corbus, 5, Cytos, 5, EMD Serono, 5, Genentech, Inc., 5, Sanofi-Aventis, 5, GSK, 5, Boehringer Ingelheim, 5; Y. Allamore, Actelion, Boehringer, Roche, Sanofi, Inventiva, Medac, Bayer, BMS, Pfizer, 2, Actelion, Boehringer, Roche, Sanofi, Inventiva, Medac, Bayer, BMS, Pfizer, 5; C. P. Denton, Roche, Actelion, GlaxoSmithKline, Sanofi-Aventis, Inventiva, SCL Behring, Boehringer-Ingelheim, Bayer., 5; M. Kuwana, Ono Pharmaceuticals, AbbVie, Astellas, Chugai, Eisai, Mitsubishi-Tanabe, Pfizer, Ayumi, 2, 8; M. Matucci-Cerinic, None; J. E. Pope, Amgen Inc., 5, 9, Pfizer, Inc., 5, 9, UCB, Inc., 5, 9, AbbVie Inc., 5, Bristol-Myers Squibb, 5, 9, Actelion, 5, Eli Lilly and Co., 5, Merck & Co., 5, 9, Bayer, 5, 9, Roche, 5, 9, Novartis, 5, Sanofi, 5, Celtrion, 5, Seagen, 9, Genzyme, 5; J. Pena, Bayer AG, 3; K. Laapas, None; Z. Yao, Bayer Healthcare Co. Ltd., 3; O. Distler, Actelion, Bayer, Boehringer Ingelheim, Mitsubishi Tanabe Pharma, Roche, 2, Actelion, AnaMar, Bayer, Boehringer Ingelheim, ChemolmAb, espeRare foundation, Genentech/Roche, GSK, Inventiva, Italfarmaco, Lilly, medac, MedImmune, Mitsubishi Tanabe Pharma, Novartis, Pfizer, Sanofi, Sinova, UCB, 5, Patent mir-29 for the treatment of systemic sclerosis licensed, 9.

Cardiovascular (CV) Risk Factors and Atherosclerotic CV Events Among Incident Cases of Systemic Sclerosis: Results from a Population Based Cohort (1980-2016)

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SESSION INFORMATION

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Session Time: 2:30PM-4:00PM

Background/Purpose: Cardiac involvement, due to impairment of coronary microcirculation and myocardial fibrosis, affects prognosis in individuals with SSc, and represents one of the leading causes of death in this population. There is limited data on the risk of atherosclerotic cardiovascular disease (CVD) in SSc. We aimed to compare the prevalence of traditional CVD risk factors and incidence of atherosclerotic CVD events among incident cases of SSc vs age- and sex-matched comparators.

Methods: Medical records of patients with a diagnosis or suspicion of SSc in a geographically well-defined area from Jan 1, 1980 to Dec 31, 2016 were reviewed to identify incident cases of physician diagnosed SSc. Fulfillment of the 1980 and 2013 SSc classification criteria was ascertained. A 2:1 cohort of age- and sex-matched non-SSc subjects from the same population base was randomly selected for comparison. Data on SSc characteristics, traditional CVD risk factors (i.e., smoking status, obesity, hypertension, dyslipidemia, diabetes mellitus [DM]), and CVD events (i.e., coronary artery disease [CAD], peripheral artery disease [PAD], abdominal aortic aneurysm [AAA], cerebrovascular disease [stroke/TIA], and heart failure) were collected. Cumulative incidence was adjusted for the competing risk of death.

Results: The cohort included 79 incident SSc cases and 158 non-SSc comparators (mean age of 56 ± 16 years at diagnosis/index, 90% female for both cohorts; 87% [SSc] and 93% [non-SSc] Caucasian). Mean body mass index was significantly lower in SSc (26.5 ± 5.9 kg/m²) than non-SSc (29.3 ± 8.1 kg/m²; $p=0.01$). Diabetes mellitus was also less common in SSc than non-SSc at diagnosis/index (3% vs 9%, $p=0.05$). There were no differences in smoking, hypertension or hyperlipidemia. Prior to SSc diagnosis/index, there was no difference in the prevalence of any CVD events (15 SSc vs 19 non-SSc; $p=0.17$). During the median follow up of 9.8 y (SSc) and 8.9 y (non-SSc), 19 SSc and 15 non-SSc patients developed CVD events, for a 10-year cumulative incidence of 22.4% among SSc and 10.6% among non-SSc. This corresponded to a 3 fold increased risk (hazard ratio [HR]: 3.25; 95% confidence interval [CI]: 1.64-6.46, $p=0.001$) in SSc patients vs. comparators. This increased risk was predominately due to CAD (HR: 3.20; 95% CI: 1.56-6.72, $p=0.002$), but PAD/AAA risk also approached significance (HR: 4.20; 95% CI: 0.99-17.91, $P=0.052$). There was no evidence of increased risk of cerebrovascular events (HR: 1.06; 95% CI: 0.23-4.94, $p=0.94$).

Conclusion: Patients with incident SSc have a lower BMI and prevalence of DM than non-SSc comparators. Despite having no significant difference in the prevalence of traditional CVD risk factors and CVD events at baseline, patients with SSc have a >3 fold increase of CVD events after SSc diagnosis when compared to non-SSc comparators, predominately due to CAD. This increased rate warrants a high vigilance for CAD in patients with SSc. It may potentially be related to the increased risk of endothelial dysfunction, microvascular injury and chronic inflammation characteristic of the disease, but warrants further detailed study.

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Discovery and Validation of Novel Disease Subsets in 806 Patients with Takayasu's Arteritis across Four International Cohorts

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis I: Population-Based Studies

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Takayasu's arteritis (TAK) is characterized by variable patterns of damage throughout the large arteries. This study aimed to develop and validate a novel disease classification system in TAK based on distribution of arterial lesions using data-driven methods.

Methods: Data was used from patients with TAK from four independent cohorts: one in India and three in North America (NA). All patients underwent whole-body angiography of the aorta and branch vessels, with categorization of involvement (stenosis, occlusion, or aneurysm) in 13 arterial territories. K-means cluster analysis was performed to identify subgroups of patients based on pattern of angiographic involvement. Cluster groups were identified in the Indian cohort and independently validated in the NA cohorts. Recursive partitioning was used to develop a decision tree to predict cluster assignment.

Results: 581 and 225 patients with TAK were included from the Indian and NA cohorts, respectively. Three distinct clusters were identified in the Indian cohort and validated in the NA cohorts. Patients in Cluster 1 had significantly more disease in the abdominal aorta, renal, and mesenteric arteries ($p < 0.01$). Patients in Cluster 2 had significantly more bilateral disease in the carotid and subclavian arteries ($p < 0.01$). Compared to Clusters 1 and 2, patients in Cluster 3 had asymmetric disease with fewer involved territories ($p < 0.01$). When serial angiography was available for review, only 1 of 109 patients changed cluster assignment over time. There were more patients from India in Cluster 1 (41% vs 24%; $p < 0.01$) and more patients from NA in Cluster 3 (41% vs 32%; $p = 0.03$). Recursive partitioning predicted cluster assignment in the Indian cohort with 92% accuracy and cross-predicted cluster assignment of the NA cohorts with 87% accuracy based on involvement of the abdominal aorta, carotid, subclavian, mesenteric, and renal arteries. In the Indian and the NA cohorts, patients in Clusters 1 and 2 compared to Cluster 3 were more likely to have arterial occlusions (58% vs 82% vs 37%; $p < 0.01$) and a history of tuberculosis (8% vs 10% vs 3%; $p = 0.03$). Disease onset in childhood (28% vs 16% vs 19%; $p < 0.01$) and hypertension (71% vs 42% vs 39%; $p < 0.01$) were more common in Cluster 1. Stroke (0% vs 22% vs 5%; $p = 0.03$), vision loss (0% vs 33% vs 6%; $p = 0.01$), carotidynia (3% vs 26% vs 9%; $p = 0.01$) and persistent disease activity (46% vs 59% vs 44%; $p = 0.02$) were significantly more prevalent in Cluster 2.

Conclusion: This large study in TAK identified and validated three novel subsets of patients based on patterns of arterial disease. The same subsets were seen in patients from India and NA; however, prevalence of patients within each subset differed by country. Angiographic-based disease classification may help identify causal disease factors and enable stratified clinical decision making in this complex, clinically heterogeneous disease.

Disclosure: R. Goel, None; K. B. Gribbons, None; K. Maksimowicz-McKinnon, None; G. S. Hoffman, None; S. Kumar, None; G. Joseph, None; R. Ravindran, None; A. Nair, None; D. Cuthbertson, None; S. Carette, None; N. A. Khalidi, None; C. L. Koenig, None; C. Langford, Bristol-Myers Squibb, 2, GlaxoSmithKline, 2, ChemoCentryx, 2, Genentech, Inc., 2, Bristol-Myers Squibb, 9, AbbVie Inc., 9; C. A. McAlear, None; P. A. Monach, None; L. W. Moreland, None; C. Pagnoux, None; P. Seo, None; A. G. Sreih, None; K. J. Warrington, GlaxoSmithKline, 2, Eli Lilly and Co., 2, Sanofi, 5; S. R. Ytterberg, None; P. A. Merkel, None; D. Danda, None; P. C. Grayson, None.

Abstract Number: 1882

Characteristics and Treatment Outcomes of Takayasu Arteritis in a Nationwide, Retrospective Cohort Study in Japan

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis I: Population-Based Studies

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Takayasu arteritis (TAK) typically affects young women under 40 years old, whereas patients with onset age over 40 years are occasionally observed. It still remains unclear whether the treatment outcomes in patients with elderly onset TAK are different from those in patients with young onset TAK. The aim of this study is to compare clinical features of TAK in patients under 40 years old (yoTAK) with those over 40 years old (eoTAK).

Methods: From a retrospective, multi-center, nationwide registry of TAK and giant cell arteritis (GCA), we enrolled 130 newly diagnosed TAK patients who were treated with glucocorticoids (GCs) between 2007 and 2014. Diagnosis of TAK was made according to the criteria for TAK established by the Ministry of Health, Labour and Welfare for intractable disease in Japan. Overall, 75 of the 130 patients (58%) satisfied the ACR classification criteria for TAK; 54 of 83 (65%) patients with yoTAK (26±7 y.o.) and 21 of 47 (45%) patients with eoTAK (59±12 y.o.). None except one patient in eoTAK met the ACR classification criteria for GCA. The primary outcomes were achievement of remission (disappearance of clinical symptoms with normal C-reactive protein) and relapse-free survival rate.

Results: Among the complication of TAK, hypertension, diabetes mellitus and dyslipidemia were more frequent in eoTAK than yoTAK. No significant differences were observed in chief clinical symptoms (high fever, systemic symptoms, large-vessel lesion, cranial lesion, musculoskeletal disorders, ulcerative colitis) at onset. One-fourth of yoTAK complicated aortic regurgitation, compared with 44% in eoTAK ($p=0.0543$). Regarding laboratory data, no significant differences were observed between yoTAK and eoTAK except anemia. Serum C-reactive protein concentration in eoTAK tended to be higher than that in yoTAK (yoTAK; 5.1 ± 4.6 mg/dL eoTAK; 7.0 ± 6.7 mg/dL, $p=0.0674$) but was not statistically significant. HLA-B*52 did not differ between yoTAK (66%) and eoTAK (65%). Remission was achieved 95.2% in yoTAK and 89.4% in eoTAK throughout observational period of two years. The cumulative rate of remission of the yoTAK was significantly higher than that of eoTAK (log-rank test, $p=0.0444$). The relapse-free survival rate was 50.0% in yoTAK and 41.0% in eoTAK ($P=0.4657$). The cumulative rate of relapse was not significantly different between yoTAK and eoTAK (log-rank test, $p=0.2351$). One patient with yoTAK and two patients with eoTAK deceased; no significant difference were found in the cumulative rate of survival between yoTAK and eoTAK.

Conclusion: Clinical features such as symptoms, complications and HLA-B*52 positivity were similar between yoTAK and eoTAK, in Japan. Although both yoTAK and eoTAK achieved remission within 2 years without any significant differences, cumulative rate of remission was poorer in eoTAK.

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Infections Are Associated With Increased Risk of Giant Cell Arteritis – a Population-Based Case-Control Study From Southern Sweden

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SESSION INFORMATION

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Session Title: Vasculitis I: Population-Based Studies

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Previous studies have implicated infections as a risk factor for giant cell arteritis (GCA). The purpose of this study was to investigate the association between occurrence of infections and the development of GCA.

Methods: Patients diagnosed with biopsy-proven giant GCA between 2000 and 2016 were identified through the database of the Department of Pathology in Skane, the southernmost region in Sweden. For each GCA case, 10 controls were randomly selected from the background population matched for age, sex, and area of residence. The index date for the controls was the same as the diagnosis date of their respective cases. We identified all infection events diagnosed before the date of GCA diagnosis (and before index date for controls) between 1998 and 2016, using the Skane Healthcare Register based on International Classification of Diseases -10th version (ICD-10) codes. First, we calculated the odds ratio (OR) of being exposed to an infection in GCA cases vs controls. Second, we evaluated the type of infection closest to the biopsy-proven GCA diagnosis (or index date). Conditional logistic regression models were used to calculate OR and 95% confidence intervals (CI).

Results: 1005 patients with biopsy-proven GCA (714 women, 71%) and 10 050 controls were included in this study. In total, 476 unique infection diagnoses were assigned for GCA cases prior to the biopsy-proven diagnosis as compared to 3722 unique infections for controls. Infections were more common among patients going to develop GCA vs. controls (47% vs. 37%) yielding the OR of 1.76 (95% CI 1.51–2.05). The median time from the latest diagnosed infection to GCA diagnosis was 0.9 years (interquartile range (IQR) 0.1 - 3.5), whereas the corresponding median time for the controls was 2.2 years (IQR 0.8-4.7). Acute upper respiratory tract infections, pneumonia, influenza and non-specific bacterial infections, but not skin or gastrointestinal infections, were associated with increased probability for later biopsy-proven GCA (Figure 1).

Conclusion: Infections, especially upper respiratory tracts infections, pneumonias and influenza were associated with later development of biopsy-proven GCA. Our findings corroborate previous reports of an association between GCA and infectious pathogens of the respiratory tract. The observed associations with unspecified infections may partly reflect diagnostic uncertainty in the early phase of GCA.

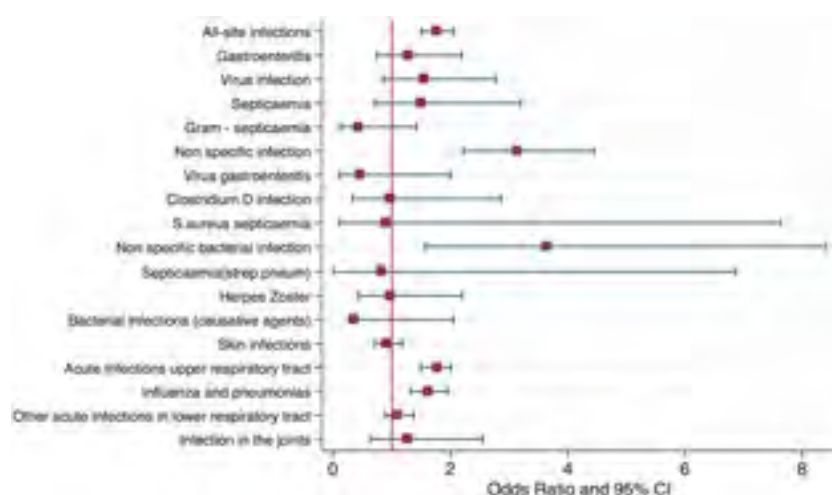


Figure 1. Odds ratios for developing GCA associated with prior exposure to infection

Disclosure: P. Stamatis, None; A. Turkiewicz, None; M. Englund, None; G. Jönsson, None; J. A. Nilsson, None; C. Turesson, None; A. Mohammad, None.

Abstract Number: 1884

Clinical Features and Outcome of Patients with Polyarteritis Nodosa – a Global Collaborative Study

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis I: Population-Based Studies

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Polyarteritis nodosa (PAN) is a rare subgroup of the primary systemic vasculitides. Furthermore, various subgroups of PAN have been described, such as hepatitis B virus (HBV)-related, cutaneous PAN and monogenic forms. There is a paucity of information on the current phenotypes, ethnic and geographic differences of PAN. This worldwide global study group collated the demographic, clinical features and outcomes of PAN cohorts from the United Kingdom (UK), Slovenia, Japan and Turkey (TR).

Methods: A retrospective survey of databases from five vasculitis centres between 1990-2016 for PAN patients fulfilling the EMEA Vasculitis Classification algorithm. Patients with typical angiographic and/or histopathologic findings consistent with PAN were included. We evaluated baseline characteristics, including demographics, organ involvement, treatment, activity and damage indices [BVAS, Five Factor Score (FFS), Disease Extent Index (DEI), Vasculitis Damage Index (VDI)] patient survival and time to relapse.

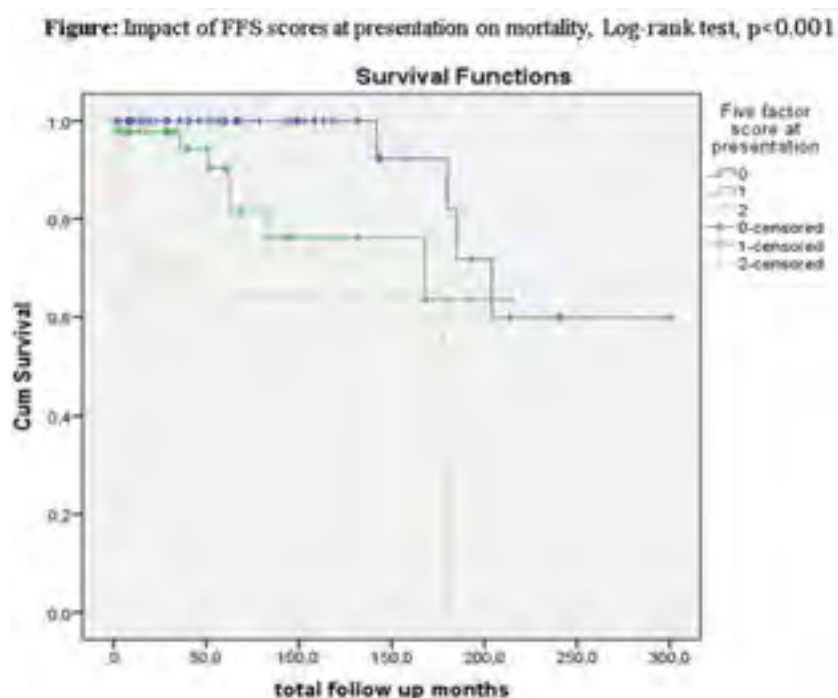


Table) Comparison of clinical characteristics and outcomes of patients with only-cutaneous and systemic PAN

	Total (n=150)	Only-cutaneous PAN (n:36)	Systemic PAN (n:114)	p
Age at onset, years	37 (23-57)	21 (24-55)	36 (25-50)	0.723
Paediatric onset, %	23.4	19.4	13.7	0.603
Any monogenic relationship, %	12.8	2.9	15.7	0.043
Sex, male, %	39.3	41.6	39.1	0.613
Time to diagnosis, months	33 (9-251)	6 (1.3-112)	34 (7-51)	0.049
Any constitutional symptoms, %	76.8	58	85.3	<0.001
• Fever	• 57.1	• 36.3	• 64.0	0.003
• Fatigue	• 60.1	• 36.3	• 77.6	<0.001
• Weight loss	• 46.7	• 21.2	• 54.9	0.002
Any cutaneous manifestations, %	76.3	100	67.2	<0.001
Follow-up, months	60 (20-109)	60 (23-100)	58 (19-131)	0.511
Response to treatment, %				0.231
• Complete	67.5	68.7	61.7	
• Partial	30.1	14.3	29.8	
• No response	6.3	0	8.5	
Any relapse, %	44.3	58.0	42.6	0.48
Time to relapse, months	12 (10-19.25)	16.5 (10.8-30.9)	12 (8.5-18)	0.119
Death, %	14.8	0	16.8	0.886

Results: 150 (M/F: 89/61) patients (UK: 47, TR: 67, Slovenia:14, Japan: 22) were included in the study. Median age at disease onset was 37.0 (IQR 25.0-57.0) years. Four were HBV-related, 23.4% had paediatric onset. Sixteen of TR patients had a monogenic form of disease (FMF association in nine, deficiency of adenosine deaminase 2, DADA2, in seven). Female predominance was found in cutaneous PAN (Table, p=0.013). No difference was found in the phenotype between paediatric and adult onset patients except for frequency of cutaneous lesions (100% vs. 63.8%, p=0.001, respectively). Neurologic, renal and abdominal involvements were seen 42%, 49.3%, and 41.4% of patients, respectively. 55% of patients had radiologic, 70.3% had biopsy-proven PAN. Distribution of patients according to FFS score 0, 1 and 2 was; 52.4%, 31.3% and 16.3%, respectively. Mean BVAS score was 13.9 (8.2), VDI 1.1 (1.4) and DEI was 5.26 (2.8). Biologic agents have been used in 32 (21.3%) of them. During median 60 (20-109) months follow-up, nearly half of the patients relapsed around a year. Twenty-one patients died (nine of them during 5-year follow-up, six deaths were related to PAN). BVAS score was significantly higher in deceased group (24.5 (7.7) vs. 11.9 (7.9), p=0.003). FFS was significantly related to mortality (Figure, p<0.001).

Conclusion: This global study showed an extremely rare presentation of HBV-related PAN and a female predominance in cutaneous PAN in contrast to systemic PAN. FFS and BVAS scores are useful indices for morbidity and mortality in PAN. Biologic agents were required in 20% of patients.

Disclosure: O. Karadag, None; S. Furuta, None; A. Hočevár, None; U. Gazel, None; S. Gopaluni, None; B. Armagan, None; M. Tomsic, None; F. Alibaz-Oner, None; I. Ertenli, None; S. Ozen, None; D. Jayne, None.

Abstract Number: 1885

Long-Term Outcome and Prognostic Factors of Complications in Thromboangiitis Obliterans (Buerger's disease): A Multicenter Study of 224 Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis I: Population-Based Studies

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Data regarding long term outcome of patients with thromboangiitis obliterans (TAO) are lacking and most series come from India and Japan. We assess long-term outcome and prognostic factors in a large cohort of TAO.

Methods: Retrospective multicenter study of characteristics and outcomes of 224 TAO patients fulfilling Papa's and/or 5 Shinoya's criteria were analyzed. Factors associated with vascular events and amputations were identified.

Results: The median age at diagnosis was 38.5 [32-46] years, 51 (23.8 %) patients were female and 81.7% were Caucasians. After a mean follow up of 5.7 years, vascular events were observed in 58.9%, amputations in 21.4% and death in 1.4%. The 5-, 10- and 15-year vascular event free survival and amputation free survival were 41% and 85%, 23% and 74% and 19% and 66%, respectively. Ethnic group (non-Caucasian) (HR 2.35 [1.30-4.27] p=0.005) and limb infection at diagnosis (3.29 [1.02-10.6] p=0.045) were independent factors of vascular events. Factor associated with amputation was limb infection (HR=12.1[3.5-42.1], p<0.001). Patient who stopped their tobacco consumption had lower risk of amputation (p=0.001) than those who continued.

Conclusion: This nationwide study shows that 34% of TAO patients will experience an amputation within 15 years from diagnosis. We identified specific characteristics that identified those at highest risk for subsequent vascular complications and amputations.

Disclosure: A. LE JONCOUR, None; S. Soudet, None; A. Dupont, None; O. Espitia, None; F. Koskas, None; P. Cluzel, None; P. Y. Hatron, None; J. Emmerich, None; P. Cacoub, None; M. Resche-Rigon, None; M. Lambert, None; D. Saadoun, None.

Abstract Number: 1886

Phenotypic Subgroups in IgG4-Related Disease – a Cluster Analysis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Vasculitis I: Population-Based Studies

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: IgG4-related disease (IgG4-RD) is a multi-organ condition of uncertain etiology characterized by substantial morbidity if not diagnosed and treated promptly. Identifying IgG4-RD subgroups based on the distribution of organ involvement may facilitate diagnosis, illuminate our understanding of the pathogenesis, and guide management. We sought to identify phenotypic clusters of IgG4-RD using an unbiased method.

Methods: Our study patients consisted of 493 IgG4-RD cases diagnosed by 76 IgG4-RD specialists from North America, South America, Europe, and Asia. For each case, investigators reported age at disease onset and diagnosis, race/ethnicity, organ involvement, and lab results. We performed latent class analysis to identify subgroups with distinct patterns of organ involvement. Cases were assigned to the cluster in which they had the highest probability of membership. We used logistic regression adjusted for baseline covariates and probability of an individual's cluster membership to estimate the odds ratio (95% CI) comparing the distribution of covariates between clusters, using one cluster as the reference group. To validate our results, we repeated the analysis in a separate cohort.

Results: Of the 493 IgG4-RD cases, the mean age was 59.5 (\pm 14.0) years and 65% were male. Of the cases, 40% were Caucasian, 45% were Asian, and 12% were Hispanic. We identified four clusters (Table 1). Cluster 1 ("Pancreato-Hepatobiliary") included 31% of patients. Cluster 2 ("Retroperitoneum/Aorta") included 24% of patients. Cluster 3 ("Head/Neck") included 24% of patients. Cluster 4 ("Mikulicz/Systemic") included 22% of patients. Compared to the "Head/Neck" cluster (Table 2), individuals in other clusters were significantly more likely to be older (OR Range 1.17-1.28) and male (OR Range 9.21-11.93). Individuals in other clusters were significantly much less likely to be Asian (OR Range 0.14-0.16) compared to the "Head/Neck" cluster. The "Mikulicz/Systemic" cluster included patients who tended to have quite elevated serum IgG4 levels compared to the "Head/Neck Cluster" [OR 1.12 (1.02-1.22)]. We replicated our results in the second cohort.

Conclusion: Using an unbiased method, we identified four phenotypic clusters of IgG4-RD patients. Besides differences in organ involvement, clusters were distinguished by age at diagnosis as well as race/ethnicity, gender distribution, and serum IgG4 concentrations. These clusters may identify patients with IgG4-RD resulting from different risk factors or exposures and those likely to respond differently to treatment.

Table 1. Clusters of IgG4-RD Using the 2018 Classification Criteria Validation Cohort (N=478)

*	Pancreato-Hepato-Biliary	Retroperitoneum and Aorta	Head and Neck	Mikulicz with Systemic Disease
Proportion of Cohort (%)	30.8%	23.7 %	23.9%	21.6%
Average Probability of Cluster Membership (Mean \pm SD)**	92.9% (\pm 11.5%)	91.6% (\pm 13.6%)	89.8% (\pm 14.1%)	90.2% (\pm 15.0%)
Input Variables / Proportion of Organ Involvement in Each Cluster†				
Pancreas	87.0%	12.3%	14.5%	46.2%
Liver	12.9%	0.9%	1.6%	5.0%
Biliary	54.5%	0.1%	0.1%	26.9%
Orbital	0.01%	3.3%	22.1%	0.02%
Extra-Ocular Muscle	0.01%	1.0%	13.1%	3.8%
Sinusitis	2.5%	0.2%	16.9%	16.3%
Parotid	1.9%	0.9%	21.6%	48.9%
Submandibular	15.3%	5.2%	50.4%	77.3%
Lacrimal	3.0%	3.0%	6.0%	47.5%
Renal	11.3%	13.0%	5.1%	35.6%
Lung	2.1%	14.8%	6.5%	38.5%
Lymph Node	15.1%	24.8%	28.8%	66.5%
Prostate	0.9%	0.01%	0.01%	14.2%
Thoracic Aorta	0.8%	10.1%	0.9%	3.3%
Abdominal Aorta	2.7%	22.4%	0.1%	13.1%
Retroperitoneum	3.5%	52.8%	1.6%	7.9%

* Only cases with complete covariate data are included in fully-adjusted latent class analysis

** Generally, a probability of cluster membership > 70% is considered very strong

† All reported proportions are probabilities conditional on latent class membership

Table 2 Logistic Regression Evaluating the Ability of Selected Covariates to Predict Cluster Membership

	“Pancreato-Hepato-Biliary”	“Retroperitoneum and Aorta”	“Head and Neck”	“Mikulicz with Systemic Disease”
Male				
Proportion of Cluster (%)	79%	74%	24%	78%
Adjusted Odds Ratio (95% CI)	11.93 (5.31-26.78)	10.33 (4.15-25.71)	1 [Ref]	9.21 (2.85-29.77)
Asian				
Proportion of Cluster (%)	37%	25%	67%	52%
Adjusted Odds Ratio (95% CI)	0.15 (0.04-0.60)	0.14 (0.04-0.48)	1 [Ref]	0.16 (0.03-0.82)
Age at Diagnosis				
Mean (\pm SD) Years	63 (\pm 13)	58 (\pm 16)	55 (\pm 13)	63 (\pm 13)
Adjusted Odds Ratio (per 5 years; 95% CI)	1.28 (1.13-1.46)	1.17 (1.01-1.36)	1 [Ref]	1.25 (1.01-1.53)
Diagnostic Delay				
Mean (\pm SD) Years	0.9 (\pm 1.8)	1.8 (\pm 4.0)	2.3 (\pm 3.4)	2.0 (\pm 3.6)
Adjusted Odds Ratio (per year; 95% CI)	0.65 (0.51-0.84)	0.88 (0.81-0.95)	1 [Ref]	0.90 (0.75-1.09)
Serum IgG4 Concentration				
Median (IQR) mg/dL	316 (147, 622)	177.5 (62.5, 322)	445.0 (183, 888)	1,170.0 (520, 2,178)
Adjusted Odds Ratio (per 100mg/dL; 95% CI)	0.98 (0.89-1.07)	0.84 (0.67-1.05)	1 [Ref]	1.12 (1.02-1.22)

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Abstract Number: 1887

Practice Variation in Prescriptions of Non-TNFi Biologics and Tofacitinib: Data from the Rheumatology Informatics System for Effectiveness (RISE) Registry

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Health Services Research – ACR/ARHP I: Focus on Big Data

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Biologic DMARDs and tofacitinib account for a large proportion of drug spending in the U.S. Although TNFi drugs have dominated sales, use of other novel agents in RA is increasing. Given the lack of comparative effectiveness studies, understanding patterns around the prescription of second-line drugs is warranted. We used data from the RISE registry to perform cross-sectional analysis of prevalent prescriptions for biologics and tofacitinib among U.S. rheumatologists.

Methods: RISE is a national, EHR-enabled registry that passively collects data on all patients seen by participating practices, thus reducing the selection bias present in single-insurer claims databases. As of June 2017, RISE held validated data from 663 providers in 110 practices, representing an estimated 19% of the U.S. clinical rheumatology workforce. We identified patients with ≥ 2 codes for RA ≥ 30 days apart between July 2016 and June 2017. We tallied the proportion of patients prescribed a TNFi, abatacept, rituximab, tocilizumab, or tofacitinib at least once during this period, overall, by region, and by practice. In this cross-sectional analysis of prevalent prescriptions, each patient was included only once; i.e., patients with >1 of these drugs were assigned to the first drug prescribed during the study period. To reduce variability in practice-level estimates, practices with < 30 RA patients (23 of the 110 practices) were excluded.

Figure. Proportion of RA patients prescribed biologics or tofacitinib, aggregated by practice, for practices with at least 30 patients with RA, between July 2016 and June 2017.

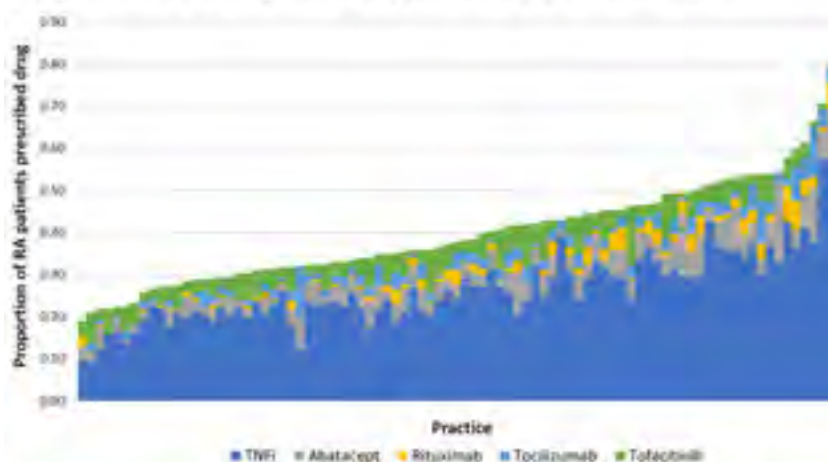


Table. Proportion of RA patients in the RISE registry who were prescribed biologics or tofacitinib, by geographic region, between July 2016 and June 2017.

	Total patients with RA (N)	TNFi (%)	Abatacept (%)	Rituximab (%)	Tocilizumab (%)	Tofacitinib (%)
Geographic Region						
New England (CT, ME, MA, NH, RI, VT)	1,170	28%	5%	3%	1%	3%
Mid Atlantic (DE, NJ, NY, PA)	6,675	19%	3%	1%	3%	4%
East North Central (IL, IN, MI, OH, WI)	11,945	27%	4%	1%	2%	3%
West North Central (IA, KS, MN, MO, NE, ND, SD)	10,656	25%	4%	1%	2%	3%
South Atlantic (FL, GA, MD, NC, SC, VA, DC, WV)	27,061	27%	5%	2%	3%	4%
East South Central (AL, KY, MS, TN)	9,637	27%	4%	2%	2%	6%
West South Central (AR, LA, OK, TX)	8,696	34%	6%	3%	3%	6%
Mountain (AZ, CO, ID, MT, NV, NM, UT, WY)	638	33%	3%	3%	4%	5%
Pacific (AK, CA, HI, OR, WA)	2,540	27%	5%	2%	4%	4%
Total	79,027	27%	5%	2%	3%	4%

Results: We included 79,027 patients from 87 practices. Overall, 40% of patients were prescribed any biologic or tofacitinib during the study period. Besides TNFi, abatacept was most commonly prescribed (4.7% of patients), followed by tofacitinib (4.2%), tocilizumab (2.7%), and rituximab (1.9%). Patterns were similar across regions (Table), but there was wide practice-level variation (Figure): For example, among practices that prescribed any abatacept (N=85), abatacept represented 2-36% of all biologics prescribed for RA within that practice. Similar patterns were seen for tocilizumab (N=83, range 1-38%), and tofacitinib (N=82, range 2-35%).

Conclusion: We found significant practice-level variation in prescriptions for newer DMARDs for RA, especially for non-TNFi biologics and tofacitinib. Future studies should assess differences in outcomes and the role of payers among populations receiving different treatments.

Disclaimer: This data was supported by the ACR's RISE Registry. However, the views expressed represent those of the authors, not necessarily those of the ACR.

Disclosure: G. Schmajuk, Pfizer, Inc., 2; M. Evans, None; J. Kay, None; M. E. B. Clowse, UCB Pharma, 5, Janssen, Pfizer, 2, 5, AbbVie, Bristol-Myers Squibb, 2; E. Morgan, None; A. Reimold, AbbVie Inc., 2; T. Johansson, None; L. Lewis, None; J. Yazdany, Pfizer, Inc., 2.

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SLE Among the Leading Causes of Years of Potential Life Lost in Young Women: Population-Based Study, 2000-2015

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Session Time: 2:30PM-4:00PM

Background/Purpose: Ten-year survival of SLE has improved from <50% in the 1950s to ~95% in the 2000s. However, the relative and true disease burden for SLE is not understood. Disease burden can be measured using a variety of indicators such as mortality, morbidity or financial cost. A recent analysis of 62,843 SLE deaths from the Centers for Disease Control (CDC)'s mortality database showed that the age-standardized mortality rate for SLE remains high relative to general population mortality rate. However, mortality rates may not adequately measure SLE burden, because among those who died, a fifth of SLE patients died before reaching 40 years of age. Premature mortality is an important way to quantify disease burden. In constructing a measure of premature death, an arbitrary limit to life is chosen, and the calculation of the difference between an age at death and this arbitrary limit is defined as the life lost as a result of that death. Here, we measured the years of potential life lost (YPLL) for SLE relative to CDC's top 15 leading causes of death and to 12 other autoimmune diseases.

Methods: This is a population-based study. Death counts were obtained from the CDC-WONDER database. Number of deaths between January 1, 2000 and December 31, 2015 were tabulated for 28 diseases, including SLE, top 15 CDC's leading causes-of-death, and 12 other autoimmune diseases. To calculate YPLL, each decedent's age at death from a specific disease was subtracted from a predetermined age of 75 years. The years of potential life lost were then added together to yield the total YPLL.

Results: SLE was recorded as the underlying or a contributing cause of death in 28,411 women from 2000 to 2015. The ranking of SLE deaths relative to the CDC's official leading-causes-of-death list in females showed that SLE is within the top 15 leading causes-of-death in reproductive age women (15-44 years) and tenth among women ages 15-24 years. Hence, we calculated YPLL for SLE relative to the top 15 leading causes-of-death in women ages 15-44 and 15-24 years. YPLL for SLE was 304.2 thousand years in women ages 15-44 and 66.2 thousand years in women ages 15-24. SLE-YPLL ranked 14th in women ages 15-44 and 8th in women ages 15-24 above diabetes mellitus, HIV disease, septicemia, chronic lower respiratory disease, anemias, nephritis, and cerebrovascular disease. Among autoimmune diseases, SLE ranked #2 above insulin-dependent diabetes mellitus, myocarditis, multiple sclerosis, systemic sclerosis, rheumatoid arthritis, Addison's disease, dermatomyositis, chronic active hepatitis, myasthenia gravis, primary biliary cirrhosis, and autoimmune hemolytic anemia in women ages 15-44 years. SLE ranked #1 autoimmune disease cause of YPLL in women ages 15-24 years.

Conclusion: SLE is among the leading causes of YPLL in young women, underscoring SLE as an important public health issue. SLE ranked #1 leading autoimmune disease cause of YPLL in women ages 15-24. These data warrant further studies on SLE disease burden, which can be used to develop and prioritize public health programs, assess performance of changes in SLE management, identify high-risk populations, and set research priorities and funding, which may eventually reduce SLE burden.

Abstract Number: 1889

Patterns of Glucocorticoid Use and Provider-Level Variation in a Commercially Insured Incident Rheumatoid Arthritis Population

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SESSION INFORMATION

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Session Time: 2:30PM-4:00PM

Background/Purpose: Glucocorticoids (GC) reduce RA-related disability and joint damage; RA guidelines endorse short term use during DMARD initiation and flares. Long-term high-dose GC exposure (>3months, ≥ 10 mg/day prednisone equivalent) can be toxic, but risk/benefit balance varies across patients. GC exposure patterns and user characteristics have not been described in a national commercially insured cohort. Provider-level factors may affect patterns of GC use in RA, and may interact with patient factors to alter risk/benefit balance. We hypothesize that GC are commonly used for incident RA and are continued inappropriately once DMARD treatment is established, and that wide provider-level variation in GC use exists.

Methods: Using OptumInsightTM commercial claims data, we identified 9,221 adults with incident RA diagnosed 2010-2014 and ≥ 12 months of preceding medical and pharmacy benefits. We assessed GC exposure for 3 months before and 12 months following diagnosis (“study period”), cumulatively and stratified by 3 month quarter and GC prescriber specialty (rheumatologist, primary care provider, other). We examined variation among 117 rheumatologists by dividing per-patient distribution of GC dose and duration for each quarter into quartiles.

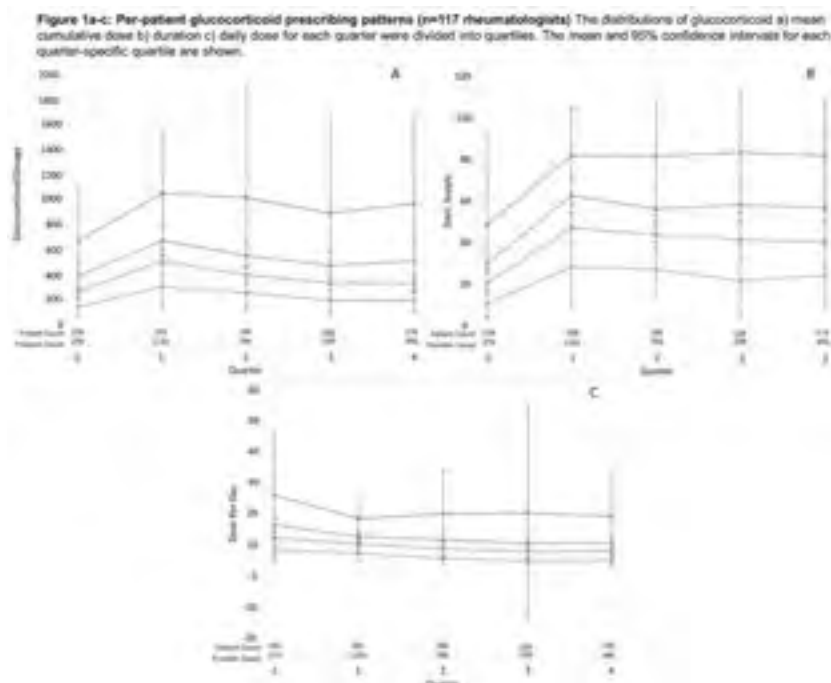


Table 1: Per-patient glucocorticoid prescribing patterns over the study period, stratified by quarter and prescriber specialty

	Quarter -1 (Days -91 to -1)	Quarter 1 (Days 0-81)	Quarter 2 (Days 92-182)	Quarter 3 (Days 183-273)	Quarter 4 (Days 274-365)
Number Enrolled	9221	9221	9108	8666	8191
Number Using GC	2866	4869	3253	2692	2394
Prescribed by rheumatologist	568	3379	2197	1701	1439
Prescribed by PCP	1316	1049	598	575	523
Prescribed by other	511	431	458	416	432
Number Using DMARD					
Any	—	6979	6502	6941	5530
Synthetic	—	6735	6124	5502	5033
TNF- α inhibitor or other biologic	—	564	1032	1252	1366
Number with RA-related office visit	—	9221	6663	6667	5389
GC Dose ¹ (Cumulative), all enrollees	132.8 (319.3) ^{***}	370.9 (573.0)	200.2 (422.6) ^{***}	164.1 (396.4) ^{***}	144.2 (345.0) ^{***}
GC Dose ¹ (Cumulative), users only					
Any provider type	423.1 (449.3) ^{***}	703.9 (623.5)	560.5 (546.0) ^{***}	528.2 (560.0) ^{***}	493.3 (484.9) ^{***}
Rheumatologist	391.3 (300.5) ^{***}	676.0 (646.0)	340.0 (485.1) ^{***}	509.1 (461.3) ^{**}	483.8 (434.8) ^{***}
PCP	338.9 (369.8) ^{***}	504.6 (525.7)	439.9 (459.7) [*]	416.4 (512.8) ^{***}	430.6 (470.1) [*]
Other	400.8 (528.3) ^{**}	590.9 (638.3)	520.0 (558.0) [*]	489.1 (591.4) ^{**}	423.1 (492.6) ^{***}
GC Duration ² , all enrollees	7.5 (16.9) ^{***}	29.9 (39.9)	16.2 (32.4) ^{***}	15.4 (30.6) ^{***}	14.0 (29.4) ^{***}
GC Duration ² , users only					
Any provider type	23.9 (22.9) ^{***}	56.7 (36.8)	51.0 (35.6) ^{***}	49.6 (36.5) ^{***}	47.8 (36.5) ^{***}
Rheumatologist	27.2 (16.2) ^{***}	58.9 (36.1)	33.8 (32.6) ^{***}	53.2 (33.3) ^{**}	52.7 (33.2) ^{***}
PCP	18.5 (22.2) ^{***}	32.4 (21.7)	31.7 (32.0)	31.4 (33.6)	31.4 (34.2)
Other	19.7 (22.4) ^{***}	42.6 (36.6)	40.4 (34.5)	38.8 (35.4)	37.0 (36.2) [*]
Mean GC Daily Dose, all enrollees	6.7 (12.8) ^{***}	7.8 (11.2)	6.1 (11.3) ^{***}	4.2 (8.8) ^{***}	4.1 (10.3) ^{***}
GC Daily Dose, users only					
Any provider type	21.4 (14.3) ^{***}	14.9 (11.6)	14.2 (15.2)	13.6 (10.9) ^{**}	14.3 (14.8)
Rheumatologist	18.7 (9.7) ^{***}	12.8 (8.3)	11.4 (8.9) ^{**}	10.9 (8.0) ^{***}	11.0 (14.3) ^{**}
PCP	24.3 (15.4) ^{***}	21.5 (17.2)	21.6 (26.5)	19.1 (13.7)	20.4 (14.8)
Other	24.7 (16.6) ^{***}	16.2 (15.1)	17.9 (16.3)	16.5 (19.5)	17.8 (16.2)

GC = glucocorticoid; PCP = primary care provider

¹Dose in prednisone equivalents²Duration in days, with maximum 90 days per quarter

*** p < 0.001, using quarter 1 value as reference

** p < 0.01, using quarter 1 value as reference

* p < 0.05, using quarter 1 value as reference

Results: 6,717 RA patients (73%) received GC during the study period. There were no clinically important differences in demographics or baseline health status between GC users and non-users, or by cumulative GC exposure level. GC use rose with frequency of rheumatologist visits and number of DMARD prescriptions. 76% of patients filled a DMARD prescription in quarter 1, and 17% received a biologic DMARD by quarter 4 (Table 1).

During quarter 1, 53% of patients received GC with per-patient mean daily dose 15mg prednisone equivalent/day and duration 57 days. During quarter 4, 29% of patients received GC with per-patient mean daily dose 14mg/day and duration 48 days. Rheumatologists prescribed >60% of all dispensed GC, with mean daily dose 11-18mg and duration 30-60 days per quarter (Table 1). Per-patient dose and duration of GC prescribed vary widely at the provider level over the study period (Fig. 1).

Conclusion: In this commercially insured incident RA cohort, rheumatologists commonly prescribe long term high dose GC up to 1 year after RA diagnosis, despite appropriate DMARD and biologic use. Rheumatologist practices regarding GC use for RA vary widely. Further work is needed to evaluate the relationship between 1) specific patient and provider-level factors and GC exposure, and 2) GC exposure and DMARD initiation and persistence in this population.

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Abstract Number: 1890

Longitudinal Deep Learning on Electronic Health Record Data to Predict Future Rheumatoid Arthritis Disease Activity

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SESSION INFORMATION

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Session Type: ACR/ARHP Combined Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Rheumatoid Arthritis (RA) is a complex systemic inflammatory disease with variable course that is difficult to precisely predict. Deep Learning (DL), a branch of artificial intelligence, has become state of the art in longitudinal predictions. It is unknown whether DL can be used to prognosticate RA outcomes. We aimed to use structured data from electronic health records (EHR) to build a deep learning model that would predict future RA disease activity.

Methods: Data were derived from rheumatology clinics at two distinct health systems (an university health center and public safety net hospital) with different EHR platforms. We extracted structured data including demographics, diagnoses, medications, and prior disease activity measured by the Clinical Disease Activity Index (CDAI). We developed a multivariate longitudinal DL method to predict disease activity, grouped as controlled disease activity (low or remission) vs. uncontrolled (moderate or high), for RA patients at their next rheumatology clinic visit. We compared the predicted disease activity from our model to actual CDAI scores and calculated Area Under the Receiver Operating Characteristic curve (AUROC). Performance was compared to predictions based on the population-level likelihood of each outcome

Figure 1 : Performance of Deep Learning Models in Predicting Rheumatoid Arthritis Disease Activity at the Next Visit

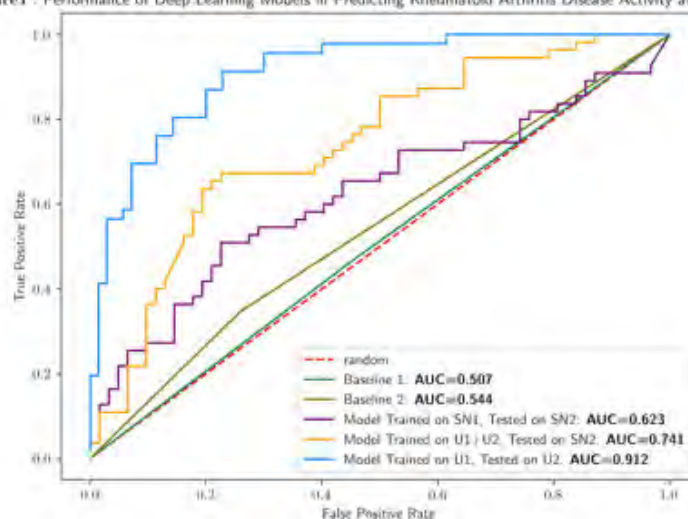


Table: Characteristics of Individuals with Rheumatoid Arthritis in the Two Health Systems Studied

	University Clinic N = 578	Safety Net Clinic N = 242
Age in years, Mean \pm SD	57 (15)	60 (15)
Female, n (%)	477 (83)	195 (81)
Race/Ethnicity, n (%)		
White	296 (51)	30 (12)
African American	33 (6)	19 (8)
Hispanic	97 (17)	89 (37)
Asian	101 (17)	70 (30)
Other	51 (9)	34 (13)
EHR System	Epic	eClinicalWorks
Average Number CDAI/person	6.9	4.3
Median Time Between CDAI	100 days	180 days
Medication, n (%)		
Conventional Synthetic	534 (94)	191 (79)
Biologic	364 (63)	70 (29)
JAK Inhibitor	29 (5)	0 (0)

N: Number; SD: Standard deviation; EHR: Electronic Health Record; DMARD: disease modifying antirheumatic drug; CDAI: clinical disease activity index

category (Baseline 1) as well as the probability of switching outcome from the prior visit (Baseline2). We evaluated whether the model developed in one health system was generalizable to a second and assessed model interoperability strategies.

Results: The university and safety net clinics were substantially different (Table). At the university hospital, the model was trained on a subset of patients (U1, n=462) and then tested on a separate group (U2, n=116) and reached an AUC of 0.91 (Figure). When trained on all patients at the university, the model generalized well (AUC 0.74) to a cohort of patients from the safety net hospital (SN2, n=117) and outperformed a model trained on a separate cohort of patients (SN1, n=125) from the safety net (AUC=0.63). In both settings the deep learning models outperformed baselines.

Conclusion: We built accurate, generalizable longitudinal DL models to forecast patient outcomes on populations that only number in the hundreds. Our findings suggest that the RA model can be shared across hospitals with different EHR systems and diverse patient populations. Testing of artificial intelligence models in clinical practice is warranted to evaluate their usefulness in helping clinicians and patients prognosticate RA outcomes or simulate outcome trajectories under different treatment scenarios.

Disclosure: B. Norgeot, None; B. Glicksberg, None; D. Lituiev, None; L. Trupin, None; M. Gianfrancesco, None; A. Butte, None; G. Schmajuk, Pfizer, Inc., 2; J. Yazdany, Pfizer, Inc., 2.

Abstract Number: 1891

Patterns of Biosimilar Use in the Rheumatology Informatics System for Effectiveness (RISE) Registry

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

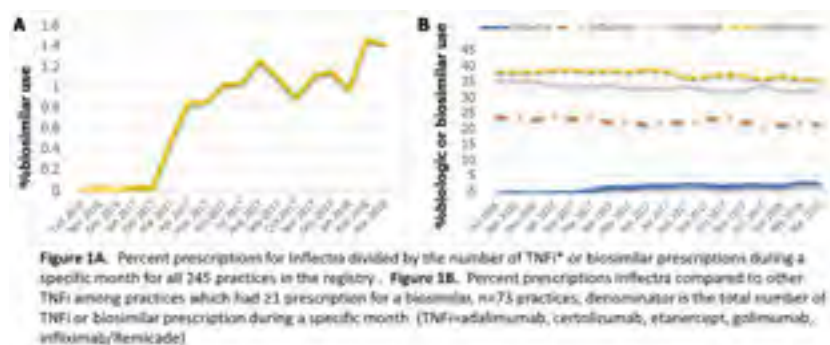
Session Title: Health Services Research – ACR/ARHP I: Focus On Big Data

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: In the U.S., the first biosimilar tumor necrosis inhibitor (TNFi) was approved in 2016. To date, only biosimilars for infliximab are available in the U.S., with limited data on biosimilar utilization. The objective of this study was to examine the early experience in prescribing patterns of biosimilar use in a U.S. based rheumatology registry.

Methods: This study was performed using the ACR's RISE Registry consisting of electronic medical record (EMR) data from 245 rheumatologist practices across the U.S. We studied data from September 9/1/2016, one month prior to the first biosimilar prescription through 3/31/18. In this time period, we studied all subjects with at least one encounter ≥ 6 months to the first biosimilar or TNFi prescription. Biosimilar data were identified through a combination of billing for procedures ('J codes') and text string searches for the two available biosimilars: infliximab-dyyb (Inflectra), infliximab-abda (Renflexis). For clarity, we refer to the trade names. Data were extracted on demographics, diagnosis codes, location of practice, and insurance. We used descriptive statistics to compare characteristics of patients who were ever treated with a biosimilar compared to Remicade.



Results: At baseline, 857 patients received a biosimilar at 73 rheumatology practices (30% of all practices in RISE), all for Inflectra. Mean age of patients receiving Inflectra was 57.5 years, 70% female; characteristics were similar to those receiving Remicade (Table). A higher %of patients prescribed Inflectra had a diagnosis code for RA compared to Remicade. In absolute numbers, the highest numbers of prescriptions for Inflectra were from California (n=137), West Virginia (n=101), and Texas (n=96). Among patients who received Inflectra, 63.4% were previously on Remicade and the rest were naïve to Remicade. Over 15 months of follow-up, there were no significant differences in the types of biologics prescribed after Inflectra vs Remicade. Inflectra use increased modestly (Figure 1A), without significant change in overall TNFi usage for patients at practices who treated ≥ 1 patient with biosimilar-infliximab(Figure 1B).

Conclusion: This preliminary study examining the first 1.5 years after biosimilar approval in the U.S., observed a modest uptake in biosimilar usage, all for Inflectra. Nationwide rheumatology registries can provide important aggregate data on early biosimilar utilization using realworld data.

Disclaimer: This data was supported by the ACR's RISERegistry, however the views expressed represent those of the authors, not necessarily those of the ACR.

Table 1 Comparison of subjects initiating biosimilar-infliximab compared to infliximab October 2016 to March 2018.

	Inflectra	Remicade
Clinical characteristics	n=857	n=4863
Age, mean years	57.5	57.5
Female (%)	70.3	72.7
Race (%)*	N=781	N=3635
White (w)	86.3	75.1
Black (b)	4.0	8.8
Other (o)	9.7	16.1
Diagnoses codes (%)		
RA	68.5	48.1
Psoriasis and PsA	20.8	16.7
AS	4.6	8.0
Type of insurance (%)*	n=484	n=2,332
Medicare	70.7	41.1
Medicaid	2.3	5.2
Commercial	27.1	52.7

* Race and insurance was available on the subset number of individuals (n) listed.

Disclosure: N. Bansback, None; J. R. Curtis, AbbVie, Amgen, Bristol-Myers Squibb, Corrona, Janssen, Lilly, Myriad, Pfizer, Radius, Roche/Genentech, UCB, 2,AbbVie, Amgen, Bristol-Myers Squibb, Corrona, Janssen, Lilly, Myriad, Pfizer, Radius, Roche/Genentech, UCB, 5; J. Huang, None; L. Lewis, None; T. Johansson, None; K. Michaud, None; K. P. Liao, None.

Abstract Number: 1892

Patient and Health System Characteristics Associated with Receipt of Disease Modifying Anti-Rheumatic Drugs in a National VA Sample

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Health Services Research – ACR/ARHP I: Focus on Big Data

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The Department of Veterans Affairs (VA) operates the largest integrated health care system in the U.S. The proportion of Veterans with RA who receive high quality care within VA is unknown. Our objective was to quantify the proportions of Veterans with RA nation wide who were prescribed a DMARD in 2016, and identify Veteran- and system-level correlates of DMARD receipt.

Methods: Cross-sectional study of national VA data examining DMARD receipt in 2016 among Veterans with RA who received care within VA. RA and DMARD use were identified using HEDIS technical specifications (including ICD-9 and ICD-10 diagnosis codes) for 2016. Veteran-level (age, gender, race, poverty level, comorbidity score, substance use disorder, post-traumatic stress disorder (PTSD)) and system-level (healthcare region, facility complexity, rheumatologist shortage area) correlates were examined using bivariate and multivariate logistic regression.

	Adjusted* Proportions for DMARD Receipt	Difference, Percentage Points (95% CI)	
Overall DMARD Use	80.5		
Gender			
Female	82.1	1.6	(1.5, 2.0)
Male	80.3	reference	
Age			
<50	82.9	reference	
Age 51 to 64	82.2	-0.7	(-0.9, -0.6)
Age 65 to 80	81.2	-0.7	(-0.8, -0.6)
Age > 80	67.5	-15.4	(-15.7, -15.2)
Race			
White	81.0	reference	
Black	79.3	-1.7	(-1.9, -1.5)
Other/Unknown	78.2	-2.8	(-3.2, -2.5)
PTSD^a Diagnosis			
Yes	80.1	-0.5	(-0.7, -0.3)
No	80.6	reference	
Substance Use Disorder Diagnosis			
Yes	74.7	-6.2	(-6.6, -5.9)
No	80.9	reference	
Charlson Comorbidity Score			
1	83.6	reference	
2	80.8	-2.8	(-3.0, -2.6)
3 or More	77.9	-5.7	(-5.9, -5.6)
Degree of Poverty in ZIP Code of Residence			
0% to 4.9%	81.1	reference	
5% to 9.9%	81.7	0.6	(0.5, 0.8)
10% to 19.9%	80.7	-0.4	(-0.5, -0.3)
≥ 20%	78.9	-2.2	(-2.4, -2.0)
VA Region of Health Care System			
Continental	81.7	reference	
MidWest	81.6	-0.1	(-0.3, 0)
North Atlantic	78.9	-2.8	(-3.0, -2.6)
Pacific	83.5	1.8	(1.7, 2.0)
Southeast	77.4	-4.3	(-4.5, -4.1)
Facility Complexity[‡]			
1a --- Most Complex	82.8	reference	
1b	82.8	0	(-0.1, 0.2)
1c	77.4	-5.4	(-5.6, -5.2)
2	77.3	-5.5	(-5.8, -5.3)
3 --- Least Complex	70.8	-12.0	(-12.4, -11.6)
Receive Care within a Rheumatology Shortage Area[§]			
Yes	72.0	-9.9	(-10.2, -9.7)
No	81.9	reference	

*Adjusted for all variables listed in table

^aPTSD = Post traumatic stress disorder - Has been associated with increased risk of RA and poorer outcomes

[‡]Facility complexity model classifies VA facilities at levels 1a, 1b, 1c, 2, or 3 with level 1a being most complex (high volume, high risk patients; large research and teaching programs) and level 3 least complex (low volume, low risk patients; small or no research and teaching programs)

[§]Rheumatology Shortage Area defined as >2,000 patients per rheumatologist

Results: 28,443 unique Veterans with RA were identified in the VA health care system: 13% were female, 77% white, and 55% age 65-80. Nearly half had a Charlson comorbidity ≥ 3 , 12% had PTSD and 6% substance use disorder. Overall, 80.5% received a DMARD in 2016. DMARD receipt was similar by race and sex, but we found significant variation based on older age, presence of substance use disorder, and higher Charlson comorbidity score (see Table). We also found significant geographic and system-level effects, including lower DMARD use in less complex facilities and those in rheumatology shortage areas (Table).

Conclusion: In 2016, quality of care among Veterans with RA (as measured by the proportion receiving a DMARD) who receive care within VA was equal to or higher than rates for those receiving care in Medicare health maintenance (HMO) or preferred-provider organization (PPO) settings (76.8% and 77.8%, respectively). It far exceeded rates reported among

Medicare beneficiaries a decade ago. However, Veterans with multimorbidity and older age were less likely to receive a DMARD as were those living in the North Atlantic and Southeast. Specialty rheumatology care plays a vital role in quality of care. Future work should examine approaches to increase the reach of this specialty care to all VA patients and aim to reduce Veteran and system level variation.

Disclosure: J. Barton, None; A. Herrndorf, None; G. Schmajuk, None; R. A. Matsumoto, None; L. Ganzini, None; K. Carlson, None.

Abstract Number: 1893

Indoleamine-2,3-Dioxygenase in Murine and Human Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis I

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Indoleamine-2,3-dioxygenase (IDO) is a tryptophan catabolizing enzyme which plays a role in immune regulation and in the pathogenesis of autoimmune disorders. Increased IDO activity was reported in systemic lupus erythematosus (SLE). The tolerogenic peptide, hCDR1, ameliorates lupus manifestations via the immunomodulation of cytokines and the induction of FOXP3 expressing regulatory T cells [1]. The aim of this study has been to determine the effect of hCDR1 on IDO gene expression in SLE.

Methods: (NZBxNZW)F1 female mice with established SLE manifestations were treated (10 weekly subcutaneously injections) with hCDR1, control peptide or vehicle alone. The effects on anti-dsDNA antibody titers, proteinuria levels and kidney immunohistology were assessed. Splenocytes were obtained for gene expression studies. Nine Lupus patients were treated for 26 weeks with hCDR1 (5) or vehicle (4) in a Phase II clinical trial by weekly subcutaneous injections [1]. Blood samples were collected, before and after treatment, in PAXgene tubes and frozen until mRNA isolation. Peripheral blood lymphocytes (PBL) of 16 lupus patients and 6 healthy controls were incubated for 48 hours with hCDR1, control peptide or medium alone prior to gene expression assays. Gene expression of IDO and FOXP3 was determined by real-time RT-PCR.

Results: Treatment of (NZBxNZW)F1 SLE afflicted mice with hCDR1 down-regulated significantly IDO gene expression (72.4% and 71% inhibition compared to vehicle, $p=0.0001$ and to control peptide $p=0.05$, respectively). This was associated with a significant reduction of anti-dsDNA antibody titers, proteinuria levels and glomerular immune complex deposits. Similarly, a significant reduction in IDO gene expression was determined in samples of hCDR1 treated lupus patients (57.4% inhibition compared to pretreatment levels, $p=0.0046$). No inhibition of IDO expression was observed in the vehicle treated patients. In agreement, as previously reported, treatment with hCDR1, but not with the vehicle, resulted in a significant decrease of disease activity [1]. Further, hCDR1 significantly reduced, in vitro, IDO gene expression in PBL of lupus patients ($p=0.00017$ and $p=0.021$ compared to medium and to control peptide, respectively). In contrast, hCDR1 up-regulated by more than two folds the expression of FOXP3 gene in PBL of the same lupus patients. hCDR1 did not affect the expression of the latter genes in PBL of healthy controls.

Conclusion: hCDR1 significantly down-regulated IDO gene expression in SLE affected mice and in lupus patients (treated in vivo as well as in vitro). This effect is specific because it was not observed in healthy donors or following treatment with the control peptide. The reduction of IDO gene expression was associated with the beneficial effects of hCDR1. We reported previously that hCDR1 affects various immune pathways and cell types, most importantly, FOXP3 expressing functional T regulatory cells [1]. Our results suggest that the up-regulation of FOXP3 in lupus is not driven by IDO but it is rather controlled by other pathways and cytokines (e.g. TGF- β) that were shown to be induced by hCDR1.

[1] Journal of Autoimmunity 54, (2014) 60-71.

Disclosure: Z. Sthoeger, None; A. Sharabi, None; H. zinger, None; I. asher, None; E. mozes, None.

Baricitinib-Associated Changes in Type I Interferon Gene Signature during a 24-Week Phase-2 Clinical SLE Trial

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis I

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: In the phase 2 study JAHH (NCT02708095), treatment with baricitinib (bari), an oral selective Janus kinase 1/2 inhibitor approved for the treatment of RA, resulted in significant improvements in patients with active SLE receiving standard background therapy compared with placebo (PBO).¹ Expression of type I-associated IFN responsive genes (IRGs) is elevated in patients (pts) with SLE.² We developed a robust quantitative assay to measure changes in the IFN signature. We then examined the relationship between the IFN signature and measures of clinical outcome.

Methods: A total of 314 pts were randomized in a 1:1:1 ratio to receive PBO, bari 2- or 4-mg once daily for 24 weeks (Wks) in study JAHH. Total RNA isolated from whole blood collected in PAX gene tubes was analyzed using a multiplex quantitative (qPCR) assay panel of 6 IRGs on the Modaplex at baseline (BL), and Wks 2, 12, and 24. The assay was developed and optimized using RNA samples from 1760 patients with SLE enrolled in phase 3 trials of tabalumab (an anti-B cell activating factor monoclonal antibody),² along with controls from healthy blood donors. The IFN signature assay produced a bimodal distribution.

Results: 70% of pts had an elevated IFN signature at BL. Bari significantly reduced the IFN signature by Wk 24 compared with PBO (2-mg: -20%, 4-mg: -24%, $p \leq 0.05$), with decreases observed as early as Wk 2. In the pts who had a high IFN signature at BL, bari 4-mg significantly reduced the IFN signature at Wk 12 (-24%) and Wk 24 (-23%) compared with PBO ($p \leq 0.01$); decreases were also observed at Wks 12 and 24 with the 2-mg dose, but the difference from PBO was not statistically significant, consistent with a dose-response effect. Bari 4-mg treatment resulted in significant clinical improvement in the resolution of arthritis or rash determined by the SLEDAI-2K.¹ However, the effect of bari on IFN signature reduction (change from BL as well as absolute BL value) did not correlate with SLEDAI-2K-defined clinical improvement at Wk 12 or 24.

Conclusion: A dose-dependent decrease in the IFN signature was observed in bari-treated pts with SLE. Treatment with bari resulted in clinical improvement across various measures of SLE disease activity.¹ Moreover, response was observed with bari regardless of the change in the IFN gene signature. These data suggest that the clinical improvement observed in bari-treated pts with SLE may be the result of bari-mediated effects on multiple cytokine pathways that may include, but are not limited to, IFN signaling.

¹Wallace D et al. <https://doi.org/10.1136/annrheumdis-2018-eular.1918>

²Hoffman R et al. *Arthritis Rheumatol.* 2017;69:643-654.

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Marked Immune Cell Subset Changes in Refractory Lupus Patients in a Phase I Trial of Allogenic Mesenchymal Stem Cells

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis I

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Reports of positive effects of allogenic mesenchymal stem cells (MSCs) in treating refractory lupus, from a single center in China, led us to investigate the clinical and immune effect of a single infusion of 1×10^6 MSCs per kg umbilical cord MSCs in a Phase I trial of 6 patients with refractory lupus. We report the immune effects of MSC infusions on 6 patients; 5 met the primary outcome of a Systemic Lupus Response Index-4 (i.e. SRI-4). Clinical responses are submitted separately.

Methods: We assessed B and T cell subsets at Wks 0, 4, 8 and 24 by Flow. We measured levels of TGF β and glycoprotein A repetitions predominant (GARP) in the serum by ELISA as the hypothesized immune effector mechanism of MSCs. B cell assays were performed at Emory; 3 Wk. 8 samples were undeliverable due to winter storms.

Results: B cell subsets were notably affected by MSC infusion with a significant decrease in CD27 IgD double negative B cells (DN) with a concomitant increase in resting naïve B cells (rN) in 4/6 (Fig. 1). Of particular note are the diminishing subsets with an activated phenotype (CD11c+CD21-), including DN2 and activated naïve (aN) B cells. Patient 004 was the single treatment failure and her B cell subsets, with a high percentage of rN B cells and few DN/aN B cells at baseline, did not change. We assessed for changes in Tregs, Th1, Th2, T_{FH} and Th17 subsets. 2/6 patients had increases in Tregs (i.e. patients 001, Fig. 2) and helios+ Tregs (Fig. 2), but there were no major shifts in subsets as seen in B cells. GARP is highly expressed on MSCs and a major regulator of TGF β bioactivity. GARP impacts Treg development, B cell activation and development of autoimmunity. We assessed if MSC infusions impacted serum GARP or TGF β levels. There were significant increases in serum GARP (Fig. 3, $p < 0.01$) and TGF β levels (not shown) following MSCs.

Conclusion: MSC infusions in a Phase I open label trial in refractory lupus led to clinical improvement in 5/6 patients and significant changes in immune cell subsets with a shift from activated B cell subsets to resting naïve B cells. Serum GARP and TGF β levels increased post MSC infusion serving perhaps as the proximate immune effector mediators. A Phase II double blind placebo controlled multi-center trial of UC-MSCs in 81 refractory lupus patients will be starting this summer.

Disclosure: C. Wallace Fugle, None; C. Wei, None; I. Sanz, None; Z. Li, None; C. Paulos, None; M. Wyatt, None; D. L. Kamen, None; G. S. Gilkeson, None.

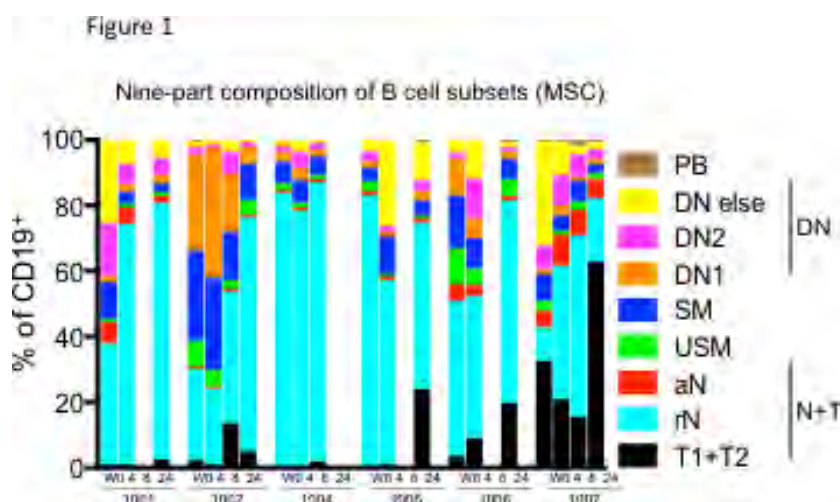


Figure 2

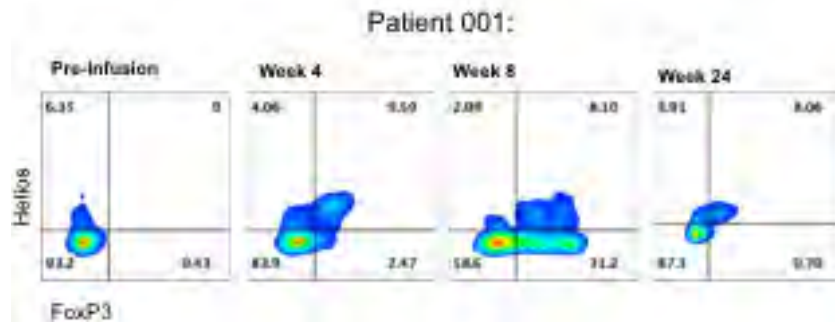
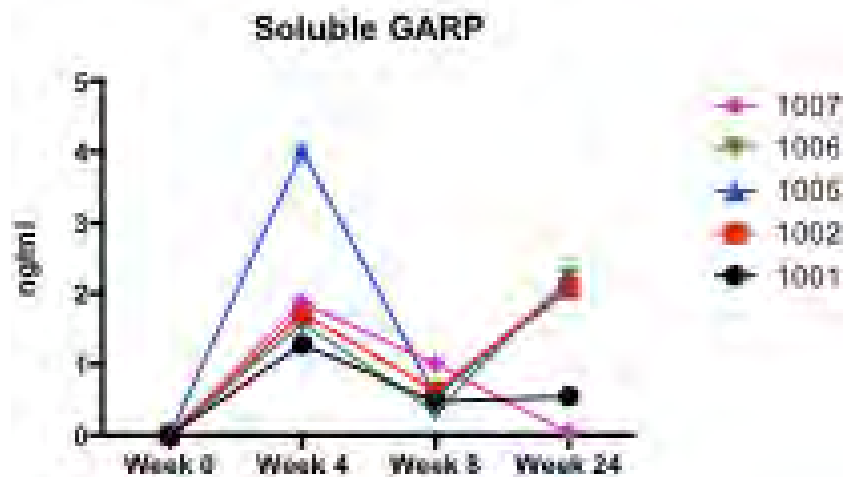


Figure 3



Abstract Number: 1896

Lupus Keratinocytes Exhibit Skewed Interferon Responses and Dysregulation of a Novel Regulator of Interferon Signaling

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis I

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune disease in which 70% of patients experience disfiguring skin inflammation (grouped under the rubric of cutaneous lupus erythematosus (CLE)). Studies have revealed that interferons (IFNs) are important mediators for SLE and CLE, but the mechanisms by which IFNs lead to disease are still poorly understood. We and others have previously identified increased type I IFN expression in non-lesional SLE keratinocytes, but whether alterations in response to IFNs also contribute to disease is unknown. We thus aimed to investigate IFN responses in SLE vs. control keratinocytes and to identify mechanisms by which differential regulation may occur.

Methods: Age and gender-matched control (n=7) and SLE (n=7) keratinocytes were isolated from non-lesional, non-sun exposed 6mm punch skin biopsies from the upper thigh and used at passage 3. All patients gave written, informed consent and were treated according to the Declaration of Helsinki. These keratinocytes were treated with or without 5 ng/mL of IFN α , IFN β , IFN κ , and IFN γ for 6 hours followed by RNA isolation and RNA-sequencing. In-depth analysis of the interferon response was conducted. PITX1 expression in normal and CLE lesional skin was evaluated by immunohistochemistry. Knockdown of PITX1 was used to examine IFN gene expression in the absence of PITX1.

Results: A significant hypersensitive response to IFNs was identified in lupus keratinocytes including genes (*IFIH1*, *STAT1*, and *IRF7*) encompassed in SLE susceptibility loci. In particular, 273 genes in SLE keratinocytes demonstrated a higher effect size ($p=5.8 \times 10^{-32}$); these genes were termed lupus sensitive interferon (LSI) responses. Importantly, 50 LSI response genes were significantly enriched among the dysregulated genes in CLE lesions ($p=1.8 \times 10^{-41}$), confirming their *in vivo* relevance. Binding sites for the transcription factor PITX1 were significantly enriched ($p=2 \times 10^{-4}$) in the LSI genes, suggesting a role for PITX1 in regulation of IFN responses. Indeed, PITX1 expression was increased in CLE lesions, and knockdown of PITX1 expression in N/TERT keratinocytes significantly abrogated interferon response gene expression after type I IFN, but not TNF α stimulation.

Conclusion: SLE patients exhibit increased interferon signatures in their skin secondary to increased production and a robust, skewed IFN response that is regulated by PITX1. Targeting of these exaggerated pathways may prove to be beneficial to prevent and treat hyper inflammatory responses in SLE skin.

Disclosure: A. Tsoi, None; G. Hile, None; C. C. Berthier, None; M. Sarkar, None; T. J. Reed, None; R. Uppala, None; M. Patrick, None; K. Raja, None; X. Xing, None; K. He, None; J. Gudjonsson, None; M. Kahlenberg, None.

Abstract Number: 1897

Single Cell RNA Expression in Lupus Nephritis Comparing African-American and Caucasian Patients Identifies Differential Expression of Interferon Pathway

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis I

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: African-American (AA) ethnicity is associated with a 3-fold higher risk of developing systemic lupus erythematosus (SLE). In addition, there is an increased risk of lupus nephritis (2-fold), high-risk histological features, and resistance to treatment. This may account for the increased mortality rate compared to Caucasian patients, especially in women. In Phase One of the Accelerating Medicines Partnership (AMP) study, we used single-cell RNA sequencing (ssRNA-Seq) on kidney biopsies from patients with active lupus nephritis to identify pathways that were differentially expressed in AA patients.

Methods: Single cells from renal biopsies obtained for clinical purpose for active nephritis were processed using CEL-Seq2. The bioinformatic pipeline to generate the expression levels of unique molecular identifiers (UMIs) from RNA reads has been previously described. We used canonical correlation analysis to identify common sources of variation between AAs and Caucasians. Cell clusters were identified using t-distributed stochastic neighbor embedding (t-SNE). Cluster identity was defined based on the presence of known cell lineage markers, enrichment of known gene set or using publicly available gene expression atlases. Next, we identified differentially expressed genes within each cluster with > 1.5 -

fold change in expression (p <0.05, Bonferroni). Finally, we applied Ingenuity Pathway Analysis (IPA) (QIAGEN Bioinformatics) to identify pathways of interest.

Results: Samples from 16 AA and 13 Caucasian patients were obtained. Of the 3829 sequenced cell libraries, we used 2358 which passed our quality filter for a total of 30155 UMIs. We identified 12 cell clusters: CD4, CD8, B cells, NK, monocytes, myeloid, NKT, distal tubule, proximal tubule, plasma cells, fibroblasts, and cell cycle. We identified 42 unique genes differentially expressed between AAs and Caucasians (Table 1). IPA identified a stronger type 1 interferon signature in AA patients, especially in CD4+ lymphocytes. In Caucasians, we identified selective expression of genes related to macrophage activation and that FKBP5, potential mediator of the immunosuppressant effect of mycophenolate and rapamycin analogues, is preferentially expressed in fibroblasts.

Conclusion: AA lupus nephritis patients have a stronger Type I interferon gene signature in immune and renal cells. In Caucasian patients, infiltrating macrophages have an activated profile and fibroblasts express FKBP5, suggesting a potential mechanism for their better response to immunosuppression. These results indicate that ethnicity may predict a response to both current and upcoming treatments, paving the way for a more personalized approach to treatment in lupus nephritis. Further work in Phase 2 of AMP will confirm and extend these findings.

Table 1.

	Gene	Log2 Fold Change	Pathway
CD4	TRAF1	0.717	IL-1/IL-18 signaling pathway
	TRAF2	0.611	IL-1/IL-18 signaling pathway
	TRAF3	0.611	IL-1/IL-18 signaling pathway
	TRAF4	0.611	IL-1/IL-18 signaling pathway
	TRAF5	0.611	IL-1/IL-18 signaling pathway
	TRAF6	0.611	IL-1/IL-18 signaling pathway
	TRAF7	0.611	IL-1/IL-18 signaling pathway
	TRAF8	0.611	IL-1/IL-18 signaling pathway
	TRAF9	0.611	IL-1/IL-18 signaling pathway
	TRAF10	0.611	IL-1/IL-18 signaling pathway
	TRAF11	0.611	IL-1/IL-18 signaling pathway
	TRAF12	0.611	IL-1/IL-18 signaling pathway
	TRAF13	0.611	IL-1/IL-18 signaling pathway
	TRAF14	0.611	IL-1/IL-18 signaling pathway
	TRAF15	0.611	IL-1/IL-18 signaling pathway
	TRAF16	0.611	IL-1/IL-18 signaling pathway
	TRAF17	0.611	IL-1/IL-18 signaling pathway
	TRAF18	0.611	IL-1/IL-18 signaling pathway
	TRAF19	0.611	IL-1/IL-18 signaling pathway
	TRAF20	0.611	IL-1/IL-18 signaling pathway
CD8	CD8A	1.01	CD8A
	CD8B	1.01	CD8B
	CD8C	1.01	CD8C
	CD8D	1.01	CD8D
	CD8E	1.01	CD8E
	CD8F	1.01	CD8F
	CD8G	1.01	CD8G
	CD8H	1.01	CD8H
	CD8I	1.01	CD8I
	CD8J	1.01	CD8J
B cells	CD19	0.611	CD19
	CD20	0.611	CD20
	CD22	0.611	CD22
	CD23	0.611	CD23
	CD24	0.611	CD24
Myeloid	CD33	0.611	CD33
	CD34	0.611	CD34
	CD35	0.611	CD35
	CD36	0.611	CD36
	CD37	0.611	CD37
NK / cytotoxic T	CD56	0.611	CD56
	CD57	0.611	CD57
	CD58	0.611	CD58
	CD59	0.611	CD59
	CD60	0.611	CD60
Distal tubule	CD68	0.611	CD68
	CD69	0.611	CD69
	CD70	0.611	CD70
	CD71	0.611	CD71
	CD72	0.611	CD72
Proximal tubule	CD73	0.611	CD73
	CD74	0.611	CD74
	CD75	0.611	CD75
	CD76	0.611	CD76
	CD77	0.611	CD77
Plasma cells	CD78	0.611	CD78
	CD79	0.611	CD79
	CD80	0.611	CD80
	CD81	0.611	CD81
	CD82	0.611	CD82
Fibroblasts	CD83	0.611	CD83
	CD84	0.611	CD84
	CD85	0.611	CD85
	CD86	0.611	CD86
	CD87	0.611	CD87

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Type I Interferon-Induced Proteins May Facilitate the Occurrence of Long QT Syndrome (LQTS) in Parallel with Anti-Ro/SSA and Anti-Ro52/TRIM21 Antibody Levels in Patients with Systemic Lupus Erythematosus (SLE): A Bench to Bedside Approach

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis I

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Long QT syndrome (LQTS) is an abnormal QT corrected (QTc) interval prolongation, strongly associated with increased risk of sudden death. Studies have associated LQTS with autoimmune conditions, and evidence points towards a link between inflammation and LQTS. We already demonstrated that LQTS occurs in SLE patients positive to anti-Ro/SSA antibodies, and interference with ventricular repolarization is linearly associated with levels of anti-Ro52/TRIM21 antibodies. However, critical cytokine pathways facilitating the development of LQTS in SLE are still unknown. This study was conducted to evaluate the cytokine milieu in SLE patients with LQTS.

Methods: Consecutive patients fulfilling the 1997 ACR criteria for SLE were included. Patients with a history of ischemic heart disease or implantable pacemakers, and those taking drugs potentially affecting QT interval (except for antimalarials) were excluded. Patients underwent a resting 12-lead ECG recording to measure QTc interval (Bazett's formula). A QTc interval duration >460 msec in women and >440 msec in men was set to define LQTS. Serum cytokine and chemokine levels were measured by multiplex bead array technology.

Results: Sixty-six patients with a mean age of 39±13 years (57 female gender) were included. A LQTS was found in 10 patients (15%), with mean QTc interval of 470±18 msec as compared to 414±23 msec in those with no LQTS. Main clinical and demographic characteristics were similar in both groups, except for a lesser use of antimalarials in patients with LQTS. Disease activity was similar between groups. Anti-Ro/SSA (75±66 U/mL versus 29±44 U/mL; P=0.005) and anti-Ro52/TRIM21 (50±55 U/mL versus 14±30 U/mL; P=0.01) antibody levels were higher in patients with LQTS. Regarding serum cytokines, levels of type I IFN-induced chemokines IP-10 (425±258 pg/mL versus 275±267 pg/mL; P=0.021) and IL-8 (58±52 pg/mL versus 29±24 pg/mL; P=0.039) were significantly higher in patients with LQTS. Notably, anti-Ro/SSA antibody levels were linearly associated with IP-10 (r=0.41, 95%CI 0.18–0.60; P=0.0002) and IL-8 (r=0.31, 0.06–0.52; P=0.005) levels. In addition, anti-Ro52/TRIM21 antibody levels also were linearly correlated with IP-10 (r=0.39, 0.16–0.58; P=0.0005) and IL-8 (r=0.23, -0.02–0.45; P=0.03) levels. Other type I IFN-induced chemokines (MCP-1 and RANTES) were similar between groups.

No differences in the cytokine circuits characterizing Th1 (IFN- γ , IL-2, IL-12, IL-27), Th2 (IL-4, IL-5, IL-13, IL-6), Th17 (IL-17, IL-21, IL-22, IL-6, GM-CSF, IL-23), Th9 (IL-9, IL-4, IL-21, IL-6), Th22 (IL-22, TNF, IL-6, IL-10), Tr1 (IL-10, IFN- γ , IL-27) were found. Additionally, no differences were found in other chemokines (MIP-1 α , SDF-1, IL-18, GRO- α , Eotaxin, MIP-1 β) characteristic of innate immunity.

Conclusion: Our results reinforce the existence of a specific LQTS mediated by anti-Ro/SSA autoantibodies, especially those specifically directed against the antigen Ro52/TRIM21. The interference in ventricular repolarization seems to be driven by proteins from the IFN gene signature, which is in line with the notion that Ro52/TRIM21 antigens are an element of response to type I IFN.

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Down-Regulation of RNA Processing Protein CFIm25 Amplifies Skin Fibrosis By up-Regulating Pro-Fibrotic Transcripts/Proteins in Systemic Sclerosis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

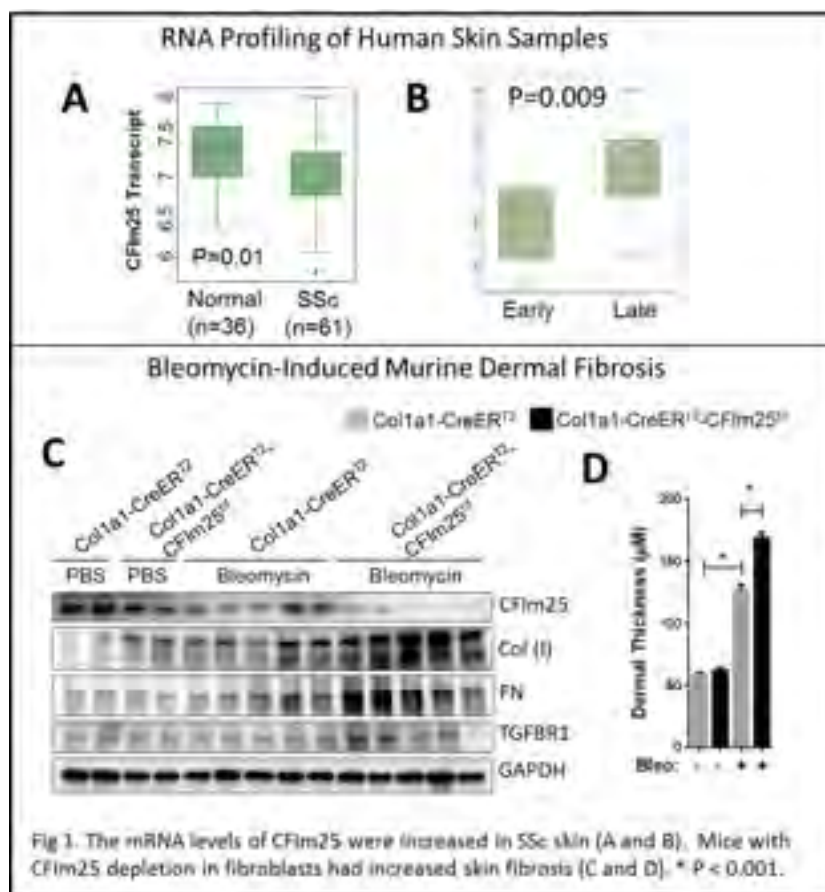
Session Title: Systemic Sclerosis and Related Disorders – Basic Science

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Persistent myfibroblast activation and associated excessive extracellular matrix protein deposition are hallmarks of systemic sclerosis (SSc). However, the mechanisms that account for this excessive fibrotic response remain elusive, hampering development of targeted treatment modalities. Alternative polyadenylation (APA) allows adding poly (A) tail to different polyadenylation sites which gives rise to transcripts with variable 3' UTR length. Cleavage factor Im 25 (CFIm25 – gene name: Nudt21) has been recently identified as a key regulator of APA¹. CFIm25 deletion leads to 3' UTR shortening of key genes involved cell fate determination. A shortened 3' UTR will often lack microRNA binding sites in comparison to its long form, resulting in increased mRNA translation due to evasion of microRNA-mediated gene repression. The goal of this study is to understand the role of CFIM25 and APA in SSc pathogenesis.

Methods: CFIm25 expression and cellular localization was investigated in skin from SSc patients and murine models. RNA sequencing was carried out using control or CFIm25 knock down fibroblasts to determine CFIm25 targets, which were



subsequently verified by Real-time PCR and Western Blot. Finally, bleomycin was administrated subcutaneously in mice with conditional CFIm25 deletion in fibroblasts to determine the effect of CFIm25 repression *in vivo*.

Results: CFIm25 mRNA was down regulated in SSc skin compared to matched controls (Fig 1A). Patients with disease duration < 2 years had significantly lower CFIm25 mRNA levels than the remainder of patients (Fig 1B). Moreover, downregulation of CFIm25 in SSc skin was primarily observed in myofibroblasts in IHC experiments. Global RNA sequencing experiments upon knock down of CFIm25 in normal skin fibroblasts (n=5 per group) resulted in 3' UTR shortening of 971 genes. TGF- β was predicted to be the top upstream regulator of this gene list. Moreover, CFIm25 depletion led to enhanced protein expression of key fibrotic genes, including COL1A1 and TGFBR1. Similarly, these genes showed 3'UTR shortening in SSc skin compared to matched controls (n=10 per group). CFIm25 protein levels were decreased in the skin of bleomycin dermal fibrosis and Tight Skin Mouse I murine models. Finally, conditional CFIm25 deletion in fibroblasts led to exaggerated skin fibrosis upon bleomycin treatment (n=10 per group), as measured by Masson's trichrome staining, collagen I and TGFBR1 Western Blot (Fig 1C), and dermal thickness (Fig 1D).

Conclusion: We link for the first time a recently discovered key RNA processing protein, CFIm25 to 3' UTR shortening and increased transcription/translation of TGF- β regulated profibrotic genes, in dermal fibrosis models and SSc. CFIm25 rescue can be a potential therapeutic target in SSc.

1.Brumbaugh J. et al. Cell. 2017

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Abstract Number: 1900

FGFR3/ FGF9 Regulates the Activity of Profibrotic Cytokine and Growth Factor Pathways to Drive Fibroblast Activation and Tissue Fibrosis in Systemic Sclerosis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Fibroblast growth factor receptor3 (FGFR3) is a member of the family of 4 different receptors (FGFR1-4) with more than 23 identified ligands FGF1-23. Each FGFR has different isoforms resulting from natural alternative splice variants and hence can bind more than one FGF ligands. Upon binding FGF ligands, fibroblast growth factor receptors (FGFRs) trigger various intracellular signaling pathways to regulate important biological processes.

Methods: Differential expression profiling of dermal cells from SSc patients and healthy volunteers were performed employing GEArray cDNA microarray, qPCR, Western Blot, immunohistochemistry and immunofluorescence analyses. Selective inhibitors in conjunction with knockdown and knockout strategies were used to target FGF9/FGFR3 signaling *in vitro* and *in vivo*. FGFR3/FGF9 target genes were identified by Affymetrix gene arrays. The anti-fibrotic potential of FGF9/FGFR3 inactivation was evaluated in two mouse models of SSc: skin fibrosis induced by bleomycin and tight skin-1 (TSK) mice.

Results: FGFR3, specifically the isoform FGFR3 IIIb, expression was significantly upregulated in the dermis and dermal fibroblasts of SSc patients as compared to healthy volunteers. In contrast, the expression of other members of the FGFR family (FGFR1,2 and 4) was not induced in SSc. FGFR3 IIIb binds only FGF1 and FGF9 and we found significant increase in the levels of FGF9, in contrast to FGF1, in SSc patients as compared to healthy people.

To screen for FGFR3 regulated genes in fibroblasts, which might contribute to the pathogenesis of SSc, FGFR3(Act) mice with constitutive FGFR3 signaling and FGFR3(KO) mice, lacking FGFR3, were differentially screened by Affymetrix gene chips. We found that FGFR3(Act) mice express significantly elevated levels of the profibrotic mediators monocyte chemoattractant protein-1(MCP-1), connective tissue growth factor(CTGF), interleukin-4 receptor α (IL4R α), endothelin-1 (ET-1) and its receptor endothelin-receptor B (EDNRB). Further analyses revealed that FGF9/FGFR3 stimulates the expression of these profibrotic mediators via ERK- and p38-dependent pathways.

Genetic knockout of FGFR3 ameliorates skin fibrosis in TSK mice and in bleomycin-induced fibrosis. TSK or bleomycin-challenged mice displayed reduced dermal thickening, decreased myofibroblast counts and lower hydroxyproline content upon inactivation of FGFR3. Confirming the translational potential of these findings, we demonstrate pharmacological inactivation of FGFR3 by PD173074 could induce the regression of experimental fibrosis in bleomycin-challenged or in TSK mice.

Conclusion: We have identified and characterized FGFR3 signaling as a novel mediator of fibroblast activation and tissue fibrosis in SSc. FGFR3, regulates a network of major profibrotic mediators including CTGF, MCP-1, ET-1 and its receptor EDNRB and IL4R α . Thus targeting of this major upstream regulator would deactivate several profibrotic pathways simultaneously. We could demonstrate successfully that the targeted inhibition of FGFR3 ameliorated fibrosis in different preclinical models of SSc. Our findings may have direct translational implications as FGFR3 inhibitors are currently in development.

Disclosure: D. Chakraborty, None; L. Summa, None; T. Trinh-Minh, None; C. W. Chen, None; A. Soare, None; A. Ramming, None; O. Distler, None; G. Schett, None; J. Distler, 4DScience, 1, 4, Anamar, Active Biotech, Array Biopharma, aTyr, BMS, Bayer Pharma, Boehringer Ingelheim, Celgene, Galapagos, GSK, Inventiva, Novartis, Sanofi-Aventis, RedX, UCB, 2, Actelion, Active Biotech, Anamar, Bayer Pharma, Boehringer Ingelheim, Celgene, Galapagos, GSK, Inventiva, JB Therapeutics, Medac, Pfizer, RuiYi and UCB, 8.

Abstract Number: 1901

Reduced SPAG17 Expression Links Dysfunctional Cilia, Morphogen Signaling Activation and Multiple Organ Fibrosis: Novel Target for Systemic Sclerosis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Persistent myofibroblast activation driving progressive fibrosis is the defining hallmark of systemic sclerosis (SSc). Uniquely, fibrosis in SSc affects the skin, heart, lungs and muscles synchronously, suggesting that pathways shared across multiple target organs could be responsible. However, the nature of the fundamental alteration common to distinct organs affected in SSc patients remains unknown. In order to identify novel therapeutic targets, we sought potential novel mechanisms accounting for multi-organ fibrosis.

Methods: We performed next generation sequencing on skin biopsies from patients with SSc (n=19) and matched healthy controls (n=14). Expression of differentially regulated genes in the skin was investigated by immunohistochemistry. Novel knockout mice were generated and at various ages analyzed for fibrosis. Regulation of morphogen signaling and fibrotic responses was examined in cell culture assays using null fibroblasts.

Results: Unbiased RNAseq transcriptome analysis identified SPAG17 as the most differentially-expressed gene in SSc skin biopsies (-4.18 fold; p< 0.0001). SPAG17 is a primary cilia gene with unknown function, previously linked to human height in GWAS. Levels of SPAG17 mRNA in SSc skin biopsies showed negative correlation with the Modified Rodnan Skin Score; low SPAG17 expression was associated with increased morphogen (Hedgehog, Wnt) activity (elevated Smoothed and Dishevelled1) in the skin. Immunofluorescence analysis of SSc skin biopsies demonstrates marked reduction in SPAG17 expression, and absence of SPAG17 in lesional myofibroblasts. SPAG17-deficient my of ibroblasts had stunted and dysfunctional primary cilia, and showed constitutive activation of Smad pathways. Moreover, loss of SPAG17 rendered

fibroblasts exquisitely sensitive to TGF- β . Since SPAG17 knockout mice generated in our lab die in the perinatal period due to severe lung involvement, we crossed SPAG17^{fl} mice with Sox-Cre mice. The offspring survive into adulthood, and are indistinguishable for their wild type littermates. Remarkably, by 4-6 months of age, SPAG17-deficient mice show notable fibrosis in skin, heart, lungs, kidney and skeletal muscle.

Conclusion: The ciliary gene SPAG17 appears to play a critical role in preventing fibrosis in multiple organs. Loss of SPAG17 renders fibroblasts markedly susceptible to fibrotic stimulation, and is associated with spontaneous scleroderma-like skin changes accompanied by fibrosis in multiple organs. Reduced expression of SPAG17 and consequent ciliary dysfunction and augmented morphogen signaling therefore appear to play a previously unrecognized role in fibrosis and could contribute to the pathogenesis of SSc. SPAG 17 KO mice represent a unique novel disease model phenocopying synchronous fibrosis in multiple organs.

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Abstract Number: 1902

Pathogenic and Therapeutic Modulation of Activating Epigenetic Memory at a Novel Enhancer for TGF β 2 in Systemic Sclerosis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Systemic Sclerosis (SSc) is an etiologically mysterious disease, in which adults acquire an inflammatory prodrome with progressive fibrosis of the skin and viscera. In the absence of a strong genetic signature in twin studies (monozygous=dizygous=4% concordance) or genome-wide association studies (only indicative of inflammatory predisposition), it remains unclear as to how dermal fibroblasts from SSc patients maintain a fibrotic synthetic repertoire (FSR) when cultured *ex vivo*. We posited epigenetic regulation of gene expression as a mechanism that “locks in” the aberrant performance of SSc fibroblasts.

Methods: Transcriptomes and epigenomes were profiled by RNA-seq and Assay for Transposase-Accessible Chromatin (ATAC)-seq, respectively, using primary dermal fibroblasts (PDF) established from skin biopsies of healthy controls or SSc patients with diffuse cutaneous involvement. PDFs were further evaluated by targeted epigenomic editing, chromatin immunoprecipitation, protein analysis, and pharmacological strategies. Organ cultures of SSc patient skins were performed to assess therapeutic agents *in vivo*.

Results: RNA-seq revealed that SSc PDFs maintain a strong FSR after many passages in culture (e.g. *COL1A1*, *SERPINH1*). This correlated with specific upregulation of TGF β 2 (but not β 1 or β 3) mRNA and protein expression that was prone to further amplification by TGF β treatment. siRNA knockdown of TGF β 2 silenced the FSR in SSc PDFs. Together, these data suggest an epigenetic mechanism to “lock in” the FSR in SSc, with particular relevance for TGF β 2. ATAC-seq revealed an open chromatin conformation for a sequence-constrained region distal to the *TGFB2* gene in SSc PDFs, with direct correlation between accessibility and TGF β 2 mRNA levels. This element showed a signature for activated enhancers: acetylated H3K27 and occupancy by the histone acetyltransferase (HAT) EP300. CRISPR-based targeted histone acetylation to this enhancer induced TGF β 2 expression, and consequentially TGF β target gene expression (*COL1A1*, *SERPINH1*), in control and SSc PDFs, validating functional enhancer status. In keeping with this result, targeted histone methylation to the *TGFB2* enhancer normalized TGF β 2 expression and the FSR in SSc PDFs. Treatment of SSc PDFs with a HAT inhibitor (HATi) was sufficient to deactivate *TGFB2* enhancer activity, but full epigenetic activation of the enhancer rebounded after drug removal. We posited that this epigenetic memory—analogue to regulation of inflammatory enhancers—might be initiated by inflammatory effectors (e.g. NF- κ B) and enforced by BRD4 recruitment. In support of this hypothesis, we found high NF- κ B and BRD4 occupancy at the TGF β 2 enhancer in SSc PDFs. Treatment with the NF- κ B or BRD4 inhibitor normalized TGF β 2 expression and the FSR, which was now refractory to drug removal. Finally, SSc skin maintained a FSR and dense fibrosis in organ culture. Both parameters were strikingly reversed upon incubation with BRD4 inhibitor for ten days.

Conclusion: These data suggest an epigenetic mechanism for fibrosis in SSc pathogenesis, identify therapeutic targets and biomarkers for use in clinical trials, and inform a new regulatory mechanism of *TGFB2*.

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Abstract Number: 1903

Molecular Analysis of a Skin Equivalent Tissue Culture Model System of Systemic Sclerosis Using RNA Sequencing, Epigenetic Assays, Histology, and Immunoassays

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Sclerosis and Related Disorders – Basic Science

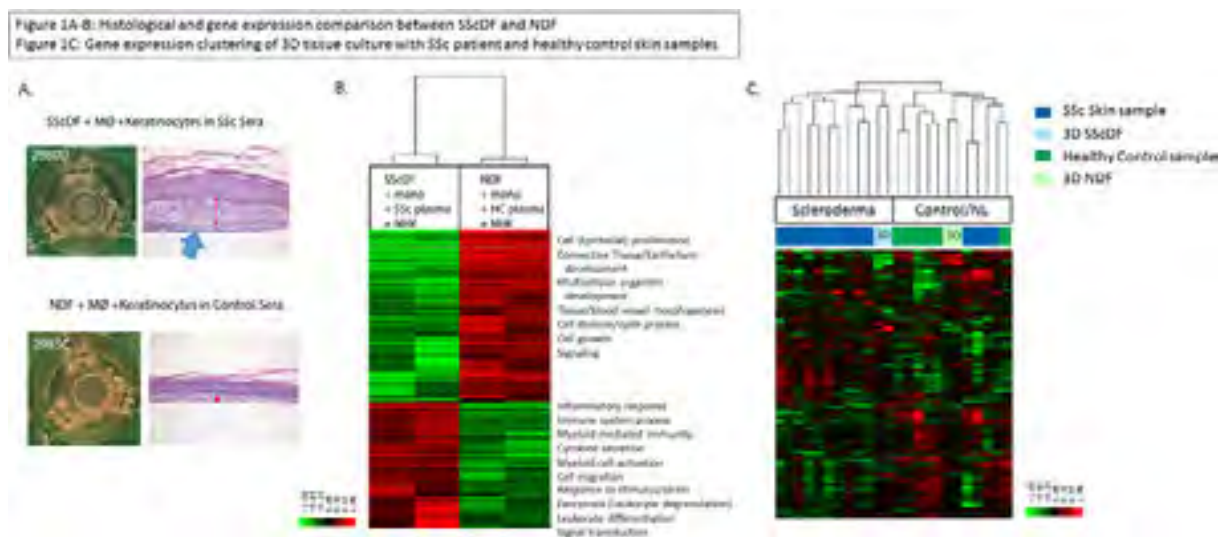
Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: The molecular mechanisms of systemic sclerosis (SSc) have been difficult to study outside of patient samples. Mouse models often lack key features of the disease, and fibroblast cultures show inconsistent results. We have developed an innovative skin-like tissue of SSc, self-assembled Skin Equivalents (sSE), where we study fibroblast behavior in a 3D micro environment with epithelial-dermal crosstalk and immune interaction. Here we investigate the molecular changes in SSc sSE and show that it is molecularly similar to SSc skin biopsies.

Methods: Fibro blasts were isolated from SSc patient skin (SScDF) and normal skin (NDF), expanded and seeded into transwell chambers +/- monocytes. SSc patient-derived plasma and healthy control (HC) plasma were incorporated into the culture media during the polarization period. Normal Human Keratinocytes were seeded at 3 weeks for epithelialization, and tissues were harvested after 5 weeks followed by IHC, atomic force microscopy (AFM), RNA-seq, DNA methylation, and ATAC-seq. Cell supernatants were used for multiplex ELISA analysis.

Results: We created 136 samples of sSE from one SScDF line and one NDF line. H&E staining of SScDF sSE showed increased dermal thickness and stiffness compared to NDF sSE (Fig 1A). Differential expression of the SScDF sSE and



NDF sSE with autologous plasma and monocytes showed increased expression of genes representing pathways involved in inflammatory/immune system response, myeloid-mediated immunity, myeloid cell activation, and leukocyte differentiation (Fig 1B). The upregulated genes in NDF sSE showed typical pathways involved in epithelial proliferation, tissue morphogenesis, and cell growth. Differential expression of the SScDF sSE +/- monocytes found that sSE tissues with monocytes had increased immune response, immune cell proliferation and activation, macrophage migration, and cell chemotaxis. In samples without monocytes, epithelial cell differentiation and collagen processes were upregulated, but the strong immune signal was missing. Additionally, IL6 and IL13 production increased in SScDF supernatant during tissue development and after the polarization period. Also, analysis of gene expression in SScDF sSE by RNA-seq data demonstrated molecular similarity to human SSc patient skin samples and NDF clustered more closely with HC skin samples (Fig1C). Lastly, 3D sSE tissues and 2D monolayer fibroblast cultures have distinct DNA methylation patterns.

Conclusion: There is a hierarchy of drivers in the creation of 3D tissues, with the origin of dermal fibroblasts being the biggest modifier of disease morphology and the addition of monocytes being the next biggest factor in developing the immune response. These 3D sSE tissues consistently replicate the molecular pathways found in SSc skin and allow for a controlled model system of SSc to manipulate and test drug therapy responses.

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Abstract Number: 1904

Orphan Nuclear Receptor Ror α Is a Key Regulator of Tgf β - and WNT-Signaling in Fibrotic Diseases

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SESSION INFORMATION

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Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: The Retinoic-acid related Orphan Receptor-alpha (ROR α) is a member of the nuclear receptor superfamily and a ligand-dependent transcription factor implicated in a wide range of physiological and pathological processes. Although individual key mediators of fibroblast activation such as TGF β and WNT pathways have been identified, the factors that coordinate the activation and interaction of those pathways remain largely enigmatic. Here, we aim to evaluate the role of ROR α in the pathogenesis of fibrotic diseases.

Methods: Mice carrying *Ror α ^{fl/fl}xCol1a2-CreER* were generated to specifically knockout *Ror α* in fibroblasts in an inducible manner. ROR α was inactivated using the selective inhibitor SR3335. The role of ROR α was investigated in different mouse models: Bleomycin- and TBRI^{CA}-induced dermal fibrosis, bleomycin-induced pulmonary fibrosis, carbon tetrachloride (CCL4)-induced liver fibrosis and in Wnt-10b transgenic mice. The activity of TGF β /SMAD signaling pathway was analyzed by reporter assays. RNA sequencing was performed to determine target genes of ROR α in fibroblasts.

Results: The expression of ROR α was upregulated in fibroblasts in both human and murine fibrotic lung and liver. Activation of canonical Wnt/ β -catenin signaling mimicked the increase of ROR α in fibrosis and potently induced ROR α expression. Reporter assays showed that canonical Wnt ligands induced the transcriptional activity of ROR α , which could be prevented by Wnt signaling antagonists Dickkopf. Inhibition of ROR α signaling by incubation with SR3335 inhibited WNT- and TGF β -dependent myofibroblast differentiation and effectively reduced the release of collagen. Reporter assay demonstrated that SR3335 dramatically inhibited TGF β /SMAD signaling pathway activity. Knockout of ROR α reduced the stimulatory effects of TGF β and WNT on fibroblast activation and collagen release. In contrast, fibroblasts overexpressing ROR α are more susceptible to the profibrotic effects of TGF β and WNT. In addition, fibroblast-specific inactivation of ROR α *in vivo* protected from experimental fibrosis induced by bleomycin injection. Furthermore, treatment with SR3335 effectively reduced Wnt-induced fibrosis *in vivo*. Dermal thickening, myofibroblast differentiation and hydroxyproline

content were all significantly reduced in Wnt10b-tg mice treated with SR3335 as compared to vehicle-treated littermates. Inhibition of ROR α also ameliorated TGF β -dependent fibrosis with potent antifibrotic effects in mice overexpressing TBRI^{CA}. Treatment with SR3335 also reduced bleomycin-induced skin and lung fibrosis and CCL4-induced liver fibrosis.

Conclusion: The present study characterizes ROR α as a key checkpoint of TGF β - and WNT- induced fibroblast activation. ROR α is induced in fibrotic diseases in a WNT-dependent manner to promote TGF β - and WNT-induced fibroblast activation and tissue fibrosis. Targeting of ROR α simultaneously interferes with TGF β - and WNT-signaling as two core pathways in the pathogenesis of fibrotic diseases. The inhibition of those core pathways translates into potent antifibrotic effects across different models and organ systems.

Disclosure: R. Kagwiria, None; R. Liang, None; A. Matei, None; N. Sihler, None; C. W. Chen, None; T. Burris, None; O. Distler, None; G. Schett, None; J. Distler, 4DScience, 1, 4, Anamar, Active Biotech, Array Biopharma, aTyr, BMS, Bayer Pharma, Boehringer Ingelheim, Celgene, Galapagos, GSK, Inventiva, Novartis, Sanofi-Aventis, RedX, UCB, 2, Actelion, Active Biotech, Anamar, Bayer Pharma, Boehringer Ingelheim, Celgene, Galapagos, GSK, Inventiva, JB Therapeutics, Medac, Pfizer, RuiYi and UCB, 8.

Abstract Number: 1905

Lower Education Level Is Associated with Higher Risk of Developing Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health II: RA Risk: Education, Obesity, Smoking, or Biomarkers?

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Lower socio-economic status (SES) has been associated with worse clinical outcomes, reduced functional ability and lower quality of life; however, little is known about the association between SES and the development of RA. A few studies have observed an inverse association between education level, a surrogate marker of SES, and risk of developing RA in Northern European populations. The purpose was to investigate the association between SES on an individual level and risk of developing RA in a Southern European Mediterranean population.

Methods: EPIC is a multicentre, pan-European prospective cohort study of apparently healthy populations. We undertook a nested case-control study to investigate risk factors for RA, by identifying incident RA cases (pre-RA) and matched controls amongst subjects enrolled in four EPIC cohorts in Italy and Spain. The lifestyle, environmental exposure, anthropometric information and blood samples were collected at baseline. Confirmed pre-RA cases were matched with controls by age, sex, centre, and date, time and fasting status at blood collection. The exposure was SES as measured by level of educational attainment categorised as university (referent), secondary school/technical/professional school, primary school completed, and none. The primary outcome was incident RA. Conditional logistic regression (CLR) analysis was adjusted for ACPA seropositivity, smoking status, and presence of shared epitope (SE). A further model also adjusted for other potential confounders, including body mass index (BMI), waist circumference, physical activity, and alcohol intake.

Results: The study sample included 398 individuals of which 99 individuals went on to subsequently develop RA. In this analysis, time to diagnosis (defined as time between date of blood sample and date of diagnosis), was 6.71 years (SD 3.43). A significant positive association was observed with level of educational attainment and RA incidence (secondary/technical vs university: OR 5.60, 95% CI 1.59-19.7, primary school vs university: OR 5.06, 95% CI 1.45-17.6, no education vs university: 7.11, 95% CI 1.37-36.8; p for trend 0.02) independent of ACPA seropositivity, SE and smoking). This association between level of educational attainment and RA incidence was confirmed in the fully adjusted model (secondary/technical vs university: OR 5.52, 95% CI 1.53-19.9, primary school vs university: OR 4.87, 95% CI 1.38-17.1, no education vs university: OR 6.48, 95% CI 1.21-34.6; p for trend 0.02).

Conclusion: Lower educational levels were associated with higher risk of developing RA in a Southern European Mediterranean population. This association was not explained by other established genetic and environmental risk factors for RA.

Disclosure: P. de Pablo, None; D. Romaguera, None; S. Panico, None; A. Mattiello, None; D. Gavrilu, None; C. Navarro, None; C. Sacerdote, None; P. Vineis, None; R. Tumino, None; W. Ollier, None; E. Riboli, None; P. Venables, None; B. Fisher, None.

Abstract Number: 1906

Abdominal Obesity and Risk of Developing Rheumatoid Arthritis in Women

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health II: RA Risk: Education, Obesity, Smoking, or Biomarkers?

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Being overweight or obese increases the risk of rheumatoid arthritis (RA) among women, particularly among those diagnosed with RA at earlier ages. Abdominal obesity is more associated with visceral fat and inflammation than overall obesity measured by body mass index (BMI). We investigated whether abdominal obesity predicts RA risk in two large prospective cohorts, the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII).

Methods: We followed 48,919 women in NHS (aged 40-67 years in 1986) and 47,220 women in NHS II (aged 29-48 years in 1993) without RA at baseline. Lifestyle and environmental exposures were collected through biennial questionnaires. Abdominal obesity was measured using waist circumference (WC) reported in 1986, 1996 and 2000 in NHS and 1993 and 2005 in NHS II. The cut off point for abdominal obesity (WC \geq 88 cm) was based on WHO recommendations for women. Incident RA cases were identified using the previously validated connective tissue disease screening questionnaire followed by a medical record review. RA serologic status was determined by positive rheumatoid factor (RF) or anti-citrullinated peptide antibodies (ACPA) in the medical record. Using pooled data from the two cohorts, we estimated hazard ratios (HR) for RA risk using time-varying *Cox proportional hazards* models. We repeated analyses restricted to young and middle aged women (age \leq 55 years) based on our pre-specified hypothesis.

Results: During 28 years of follow-up, we identified 803 incident RA cases (505 in NHS, 298 in NHSII). Women with WC $>$ 88 cm had increased RA risk compared with women with WC $<$ 88 cm (Table). The multivariable adjusted HR was 1.27 (95% CI: 1.10-1.47). Further adjustment for BMI attenuated the association. Consistently, BMI was also associated with risk of RA (HR were 1.48 with 95% CI: 1.24-1.77) for BMI \geq 30 kg/m² compared to BMI $<$ 25 kg/m². Stratified analyses by serostatus demonstrated that the association of WC with RA risk was stronger for seropositive RA than for seronegative RA. Among young and middle aged women (age \leq 55 years), abdominal obesity increased risk of all RA by 65%, and by 94% for seropositive RA. After further adjusting for BMI, abdominal obesity remained associated with risk of seropositive RA (HR 1.51, 95% CI :1.01-2.25).

Conclusion: In this prospective cohort study of women followed up to 28 years, abdominal obesity was significantly associated with increased risk of developing RA. Abdominal obesity conferred the greatest risk for seropositive RA among women \leq 55 years old independent of BMI.

Table. Hazard ratios (95% CI) for RA by waist circumference (WC) in Nurses' Health Study (NHS, 1986-2014) and Nurses' Health Study II (NHS II, 1993-2013)

	All age groups			Age \leq 55 years		
	WC \leq 88 cm	WC $>$ 88 cm	p value	WC \leq 88 cm	WC $>$ 88 cm	p value
All RA						
Case/person-years	488/1,756,204	315/842,074		177/822,620	100/258,601	
Multivariable model 1*	1.00(Ref)	1.27(1.10,1.47)	0.001	1.00(Ref)	1.65(1.28,2.12)	<0.001
Multivariable model 2†	1.00(Ref)	1.05(0.88,1.26)	0.581	1.00(Ref)	1.26(0.91,1.75)	0.161
Seropositive RA						
Case/person-years	289/1,752,701	206/840,263		106/820,518	71/257,829	

Table. (Cont'd)

	All age groups			Age ≤55 years		
	WC ≤ 88 cm	WC > 88 cm	p value	WC ≤ 88 cm	WC > 88 cm	p value
Multivariable model 1*	1.00(Ref)	1.40(1.17,1.69)	<0.001	1.00(Ref)	1.94(1.42,2.64)	<0.001
Multivariable model 2†	1.00(Ref)	1.21(0.96,1.52)	0.099	1.00(Ref)	1.51(1.01,2.25)	0.045
Seronegative RA						
Case/person-years	199/1,751,963	109/840,153		71/820,262	29/257,664	
Multivariable model 1*	1.00(Ref)	1.08(0.85,1.37)	0.552	1.00(Ref)	1.21(0.78,1.89)	0.396
Multivariable model 2†	1.00(Ref)	0.84(0.62,1.12)	0.232	1.00(Ref)	0.91(0.51,1.60)	0.733

The cutpoint for WC was based on WHO recommendations.

* Adjusted for age, cohort, census-tract household income, smoking pack-years, menopausal status and hormone use (premenopausal, PMH with never use, PMH with current use, and PMH past use).

† Additionally adjusted for BMI.

Disclosure: B. Lu, None; J. A. Sparks, None; S. K. Tedeschi, None; S. Malspeis, None; K. Costenbader, None; E. Karlson, None.

Abstract Number: 1907

High Serum Adiponectin Associates with the Incidence of Rheumatoid Arthritis in Obese Subjects

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health II: RA Risk: Education, Obesity, Smoking, or Biomarkers?

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Adiponectin, acytokine mainly produced by the adipose tissue, plays an important role in several metabolic and inflammatory processes. In obese subjects, serum adiponectin levels are surprisingly low and they associate with a higher risk for metabolic diseases, including type 2 diabetes. On the contrary, adiponectin levels are increased in serum and synovia of subjects with established RA. By exploiting a longitudinal study enrolling more than 4000 obese subjects, we aim to determine if serum adiponectin levels are a risk factor for the development of RA in obese subjects.

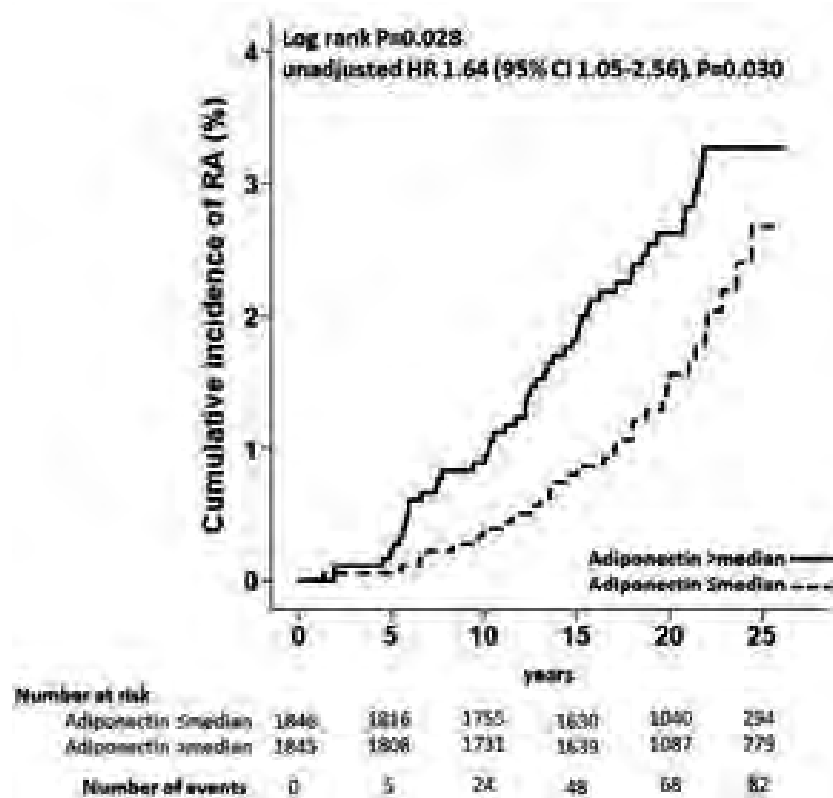
Methods: The Swedish Obese Subjects (SOS) study is a longitudinal controlled trial on the effect of bariatric surgery on the incidence of obesity-related diseases. It includes 4047 obese subjects whereof 2010 underwent bariatric surgery and 2037 constituted the matched control group. SOS study participants who developed RA were identified by searching the Swedish National Patient Register. Eleven subjects with prevalent RA at baseline are excluded by the analyses. Patients were followed up until diagnosis of RA, death, migration or end of follow-up (December 2016). Total adiponectin was measured using the Quantikine ELISA kit from Quantikine ELISA kit from Bio-Techne (Minneapolis, MN, USA).

Results: Adiponectin measurement at baseline was available for 3691 subjects. Among those subjects, 82 subjects developed RA during a follow up for up to 29 years. High serum adiponectin levels at baseline were associated with the incidence of RA, independently of bariatric surgery, sex, age, body-mass index, smoking, and C-reactive protein and erythrocyte sedimentation rate levels (adjusted Hazard Ratio HR per 10 µg/mL adiponectin 1.70, 95% confidence interval CI 1.12-2.60, P value=0.01). When stratifying the population according to the median of baseline adiponectin, subjects with adiponectin greater than 6.8 µg/mL had a higher risk to develop RA during follow up (log-rank P 0.028, unadjusted HR 1.64, 95% CI 1.05-2.56, P=0.03, Figure 1).

Conclusion: In a large cohort of obese subjects followed up for up to 29 years, serum adiponectin levels were associated with the incidence of RA years before the onset of clinical signs. The association between adiponectin and the incidence of RA is independent of other risk factors, including C-reactive protein, smoking and bariatric surgery.

Figure 1. Cumulative incidence of RA in the SOS study stratified by baseline adiponectin

Abbreviations: HR, hazard ratio; C.I., confidence interval; CRP, C-reactive protein.



Disclosure: C. Maglio, None; Y. Zhang, None; C. Herder, None; A. Rudin, None; L. Carlsson, None.

Abstract Number: 1908

Bariatric Surgery Does Not Affect the Incidence of Rheumatoid Arthritis in Obese Subjects

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

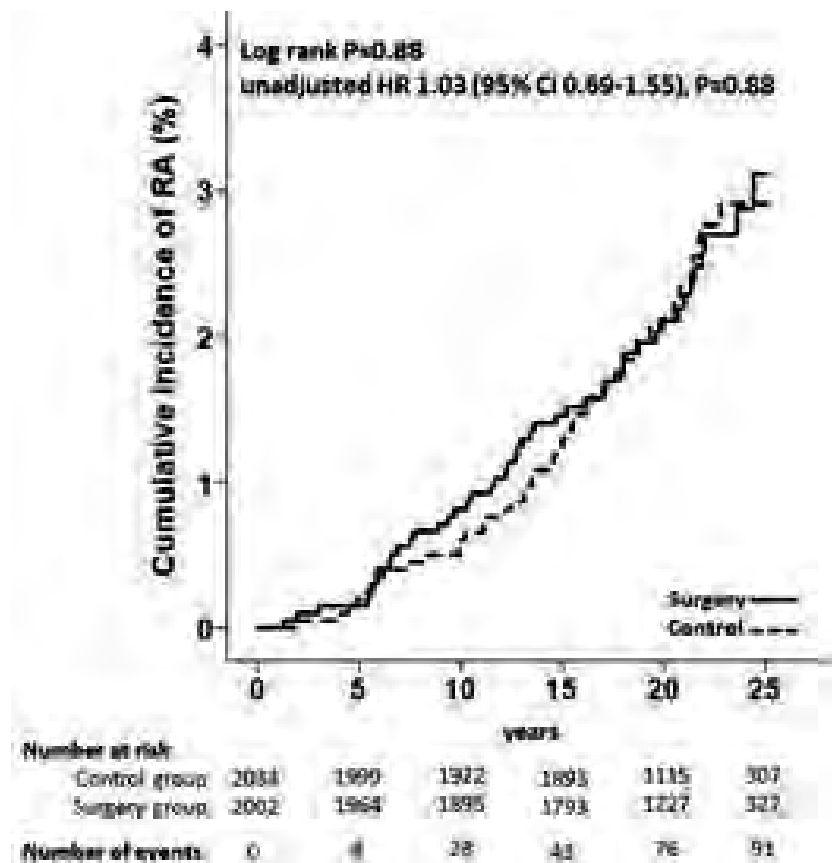
Session Title: Epidemiology and Public Health II: RA Risk: Education, Obesity, Smoking, or Biomarkers?

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Obesity is among the risk factors for rheumatoid arthritis (RA). Bariatric surgery is an effective treatment to achieve weight loss and to prevent obesity-related diseases, such as type 2 diabetes¹. Bariatric surgery-induced weight loss in subjects with RA has been associated with a lower disease activity, a decrease in inflammatory markers and a lower use of disease-modifying antirheumatic drugs². However, the effect of bariatric surgery on the prevention of RA is not known. We have previously shown that bariatric surgery reduces the risk of gouty arthritis and psoriasis in obese subjects^{3,4}. By exploiting a longitudinal study enrolling more than 4000 obese subjects, we aim to determine if bariatric surgery prevents the incidence of RA.

Methods: The Swedish Obese Subjects (SOS) study is a longitudinal controlled trial on the effect of bariatric surgery on the incidence of obesity-related diseases. It includes 4047 obese subjects: 2010 underwent bariatric surgery and 2037 constituted the matched control group. Seven Swedish local ethics review boards approved the study protocol. SOS study participants who developed RA were identified by searching the Swedish National Patient Register. Eleven subjects with



prevalent RA at baseline are excluded by the analyses. Patients were followed up until diagnosis of RA, death, migration or end of follow-up (December 2016).

Results: During a follow up for up to 29 years, 92 subjects developed RA. Fifty-one individuals (55%) had a seropositive RA. Forty-seven subjects (2.3%) developed RA in the surgery group compared to 45 subjects (2.2%) in the control group. Bariatric surgery was not associated with the incidence of RA during follow up(log-rank $P=0.88$; unadjusted Hazard Ratio-HR 1.03, 95% Confidence Interval-CI 0.69-1.55, $P=0.88$, Figure 1). Similar results were obtained if only subjects with seropositive RA were included in the analysis. Adjustment for confounding factors did not affect the results (HR for bariatric surgery after adjustment for confounding factors 0.95, 95% CI 0.60-1.50, $P=0.82$). Smoking habit, as well as baseline serum levels of C-reactive protein and erythrocyte sedimentation rate, but not female sex or body-mass index, were associated with the risk of developing RA in this obese population.

Conclusion: In a large cohort of obese subjects followed up for up to 29 years, bariatric surgery does not affect the incidence of RA years.

References: 1.Sjostrom L. J Intern Med 2013;273:219-34.
 2.Sparks JA, et al. 2015;67:1619-26.
 3.Maglio C, et al. Ann Rheum Dis 2016.
 4. Maglio C, et al. Obesity (Silver Spring)2017;25:2068-73.

Figure 1. Cumulative incidence of RA in the SOS study.
 Abbreviations: HR, hazard ratio;C.I., confidence interval.

Disclosure

Y. Zhang, None; C. Maglio, None; A. Rudin, None; L. Carlsson, None.

Impact and Timing of Smoking Cessation on Reducing Risk for Seropositive Rheumatoid Arthritis Among Women

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Epidemiology and Public Health II: RA Risk: Education, Obesity, Smoking, or Biomarkers?

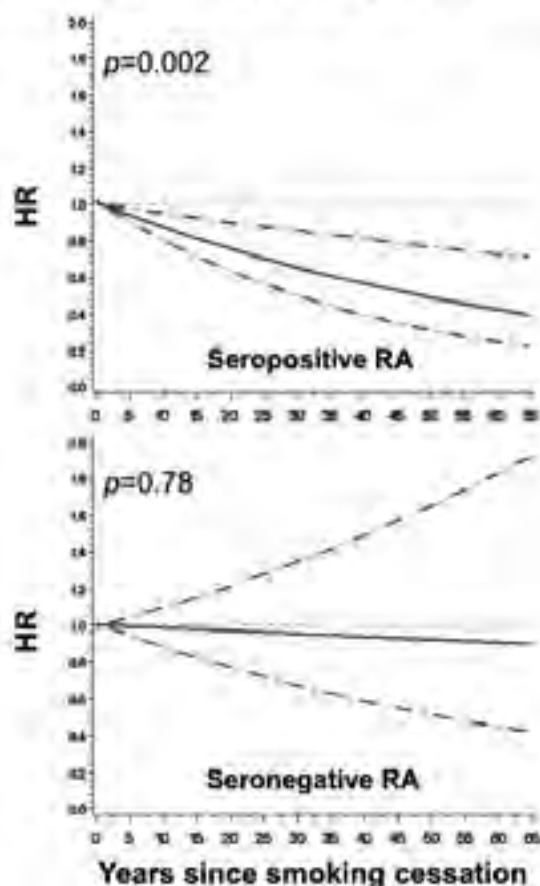
Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Compared to never smoking, past and current smoking are both associated with increased risk of seropositive rheumatoid arthritis (RA). Thus, smoking cessation may delay or even prevent RA, but previous investigations were limited for definitive conclusions by short follow-up. Therefore, we investigated the impact and timing of smoking cessation on RA risk using two large prospective cohorts with lengthy follow-up.

Methods: We investigated smoking cessation and RA risk in the Nurses' Health Study (NHS, 1976-2014) and the NHS II (1989-2015). Smoking exposure data and covariates were obtained prospectively by biennial surveys. Women self-reported RA and medical record review confirmed RA by ACR criteria. Serologic status of RA was validated by rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) by chart review. Using pooled data, Cox regression estimated HRs and 95% CIs for RA phenotypes (seropositive, seronegative) by smoking status and years since cessation adjusting for

Figure. Among the subset of past smokers (reference: 0-2 years since quitting), restricted cubic spline curves showing hazard ratios and 95% confidence bounds for seropositive and seronegative rheumatoid arthritis by years since quitting smoking. P values are for linear relation. Curves are adjusted for the covariates listed in the Table.



	Current	Post, quit 5 to <10 years ago	Post, quit 5 to <10 years ago	Post, quit 10 to <20 years ago	Post, quit 20 to <30 years ago	Post, quit ≥30 years ago	Never
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Smoking-related							
Cape Verdean people	0.0002 (0.0000, 0.0002)	0.0001 (0.0000, 0.0001)	0.0001 (0.0000, 0.0001)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Age-adjusted model ^a	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Multivariable model ^b	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Demographic							
Cape Verdean people	0.0002 (0.0000, 0.0002)	0.0001 (0.0000, 0.0001)	0.0001 (0.0000, 0.0001)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)	0.0000 (0.0000, 0.0000)
Age-adjusted model ^a	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Multivariable model ^b	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)

^a Multivariable models were adjusted for age, sex, smoking status, alcohol use, and education level. ^b Multivariable models were adjusted for age, sex, smoking status, alcohol use, education level, and duration of residence in the United States.

Methods: We performed a retrospective cohort study of CCP+ individuals seen at a US tertiary care system between 2003-2016 who were without classifiable rheumatic disease including RA per 2010 ACR/EULAR criteria by medical record review within one month of initial positive CCP. Incident RA by ACR/EULAR criteria and date of diagnosis were identified and confirmed independently by two rheumatologists through medical record review. We investigated the risk of

Table. Multivariable hazard ratios for progression to rheumatoid arthritis among patients with CCP positivity (n=340)

	Cases/person-years	Multivariable HR (95% CI)
CCP level		
>1 to 2x ULN	14/509	1.00 (Ref)
>2 to 3x ULN	10/147	2.81 (1.24, 6.37)
>3x ULN	49/314	6.18 (3.40, 11.3)
Age (continuous, per year)	73/1047	1.00 (0.98, 1.01)
Male	17/359	1.00 (Ref)
Female	56/687	1.84 (1.06, 3.19)
BMI <30 kg/m ²	51/734	1.00 (Ref)
BMI ≥30 kg/m ²	22/312	0.60 (0.54, 1.51)
Not current smoker	59/918	1.00 (Ref)
Current smoker	14/129	1.68 (0.92, 3.09)

BMI, body mass index; CCP, cyclic citrullinated peptide; CI, confidence interval; HR, hazard ratio; ULN, upper limit of normal.

progression to RA overall and stratified by CCP level (low: >1 to 2 times upper limit of normal [x ULN]; medium: >2 to 3x ULN; high: >3x ULN). We used multivariable Cox regression to evaluate the effect of CCP level on RA risk.

Results: We identified 340 CCP+ patients who at baseline were without RA or other rheumatic disease; 66% of the patients were female, and mean age was 55.0 years (SD 15.3). The most common indication for checking initial CCP was arthralgia (74%) followed by lung disease (10%). There were 73 (22%) patients who developed incident RA during 1047 person-years of follow-up. Absolute risk of progression to RA increased with higher CCP level (**Figure**), with 50% of patients progressing to RA by 5 years of follow-up. Compared to low CCP, medium (HR 2.73, 95% CI 1.21, 6.16) and high (HR 6.21, 95% CI 3.42, 11.3) CCP levels were strongly associated with progression to RA (**Table**). Women had increased risk of progression to RA (HR 1.75, 95% CI 1.01, 3.01) independent of CCP level, age, smoking, and BMI. Checking initial CCP for arthralgia was strongly predictive of progression to RA (HR 6.08, 95% CI 1.91, 19.3) compared to other indications.

Conclusion: In this study of CCP+ patients without RA identified through a US tertiary care system, RA risk increased substantially with increasing CCP level. This study provides support for close monitoring for development of RA among patients with CCP+ as well as the need for identifying strategies to mitigate this risk.

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Abstract Number: 1911

The Expanding Clinical Spectrum of Patients with Deficiency of Adenosine Deaminase 2 (DADA2)

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases I: DADA2, Cardiac Sarcoid, Cancer Immunotherapy

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: The deficiency of adenosine deaminase 2 (DADA2) was initially described in 2014 in 2 reports: one emphasizing early-onset lacunar strokes, livedoid rash and intermittent fevers; the second focusing on patients with early-onset polyarteritis nodosa. Since then, there have been reports of antibody deficiency, pure red cell aplasia and cytopenias. We now present clinical follow-up on 38 patients evaluated at the National Institutes of Health (NIH).

Patients and Methods: All 38 patients were enrolled in an IRB approved study at the NIH. Sequencing of *ADA2* (formerly known as *CECR1*), the gene encoding ADA2 (adenosine deaminase 2), was obtained on all patients. Clinical, laboratory, and radiographic testing were obtained at each visit.

Results: 35 patients had germline biallelic mutations in *ADA2*. In 3 symptomatic siblings with low ADA2 serum levels, only one mutation has been found thus far. Serum ADA2 levels were obtained in 32 patients. The mean level was 45.4% of age-matched controls (range 36.7-61.6%). 25/36 patients reported recurrent fevers. 24 (66%) patients had a history of at least one stroke, with 18 having ischemic strokes in small vessel distribution, 1 having only hemorrhagic strokes and 5 having both. The average age at the time of the first stroke was 6.2 years (range 5 months-24 years). The average number of strokes was 3 (range 1-11). Skin manifestations were found in 32 (84%) of patients and included livedo in 28, cutaneous polyarteritis nodosa in 22, and Raynaud's in 8. Abdominal ultrasound revealed hepatomegaly in 18 patients (74%) and splenomegaly in 22 patients (58%). Portal hypertension was observed in 7 patients (18%). Abdominal MRA was abnormal in 7 patients, revealing arteritis and aneurysms. Significant peripheral vasculopathy was seen in 3 patients, one requiring amputation of gangrenous digits. Systemic hypertension was observed in 10 patients (26%), with one patient developing posterior reversible encephalopathy syndrome (PRES) in relation to hypertension. Prolonged QT was noted in 5 patients (13%).

Laboratory evaluation revealed hypogammaglobulinemia, especially IgM, in 27 patients (71%). Specific antibody response to vaccines were inadequate in 5 of 16 patients tested. Lymphocyte phenotyping revealed arrested B cell class switching in 22 of 26 patients (85%) tested. 25/38 (66%) demonstrated hematologic abnormalities including anemia, leukopenia, lymphopenia and/or thrombocytopenia with 7 patients developing pancytopenia and 1 patient with pure red cell aplasia. Three patients had bone marrow failure and underwent bone marrow transplantation, with two patients requiring a second transplant.

Conclusion: The spectrum of DADA2 continues to expand to include ischemic and hemorrhagic strokes, skin findings, portal and systemic hypertension, hematologic abnormalities, vascular pathology, immune deficiency and bone marrow failure. As the phenotypic presentation is likely to continue to expand, it is important to investigate any new complaints. In addition, it is important to monitor patients closely as their phenotypic presentation can change with time.

Disclosure: K. Barron, None; A. Ombrello, None; D. Stone, None; P. M. Hoffmann, None; T. Romeo, None; A. Jones, None; N. Sampaio Moura, None; O. Schnappauf, None; I. Aksentijevich, None; J. Bergerson, None; A. Soldatos, None; C. Toro, None; T. Heller, None; J. Kanakry, None; K. R. Calvo, None; D. Kastner, None.

Abstract Number: 1912

Treatment of Cardiac Sarcoidosis: A Comparative Study of Steroids Alone Versus Steroids Associated with Immunosuppressive Drugs

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases I: DADA2, Cardiac Sarcoid, Cancer Immunotherapy

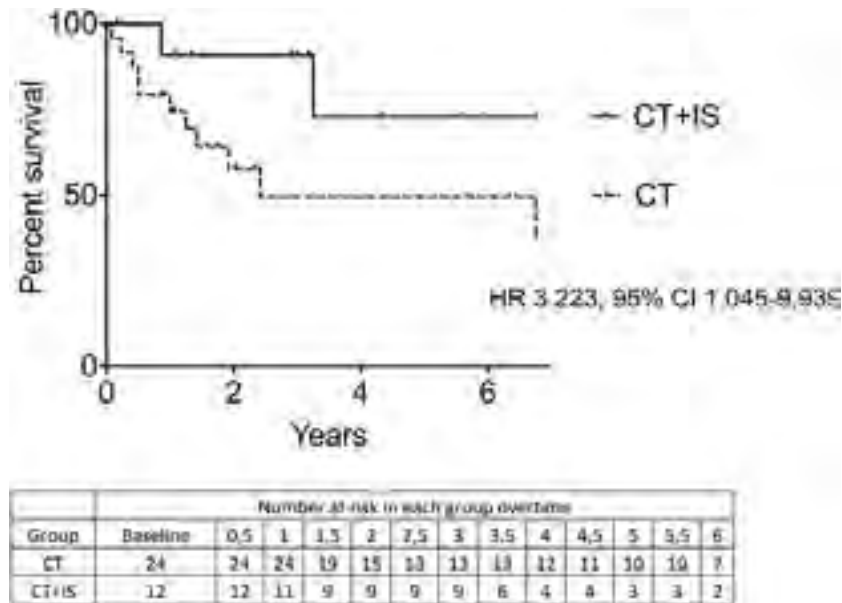
Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: To analyze the efficacy of steroids and immunosuppressive drugs in the prevention of relapse in cardiac sarcoidosis.

Methods: In this monocentric retrospective study, all consecutive patients with histologically proven sarcoidosis hospitalized from January 2012 to December 2016 were considered. All patients admitted for treatment of symptomatic cardiac sarcoidosis (CS) were included. Patients received either steroids or steroids plus immunosuppressive (IS) drugs for CS treatment. The efficacy of each treatment strategy (steroids vs steroids + IS) was assessed by the cardiac relapses rate during follow up.

Results: 326 consecutive patients with histologically proven sarcoidosis were screened. Among them, 36(11%) were admitted for symptomatic cardiac sarcoidosis (20 (55.5%) men, median age at diagnosis 48.5 [22.8-76]). 24 patients received steroids and 12 received steroids + IS (azathioprine n=5, methotrexate n=5, cyclophosphamide n=2). Over a median follow up of 3.6 [1-15.2] years, 13 (36.1%) patients suffered a cardiac relapse including third degree heart block (n=3), reduced left ventricular ejection fraction <50% (n=3), left ventricular dyskinesia (n=2) and ventricular tachycardia (n=2). The rate of cardiac relapse was 45.8% in the steroids group and 16.7% in the steroid + IS group (p=0.048). The median time to relapse did not significantly differ between groups (1.5 [0.5-6.8] vs 1.5 [1-3.2] years). Severe infection occurred in 4 patients under steroids alone and in 2 patients under steroids+ IS therapy (p=ns)



Conclusion: In cardiac sarcoidosis relapses occur frequently. The association of steroids with immunosuppressive drugs appears to reduce the risk of cardiac relapse, as compared to steroids alone.

Characteristic of patients

	All (n=36)	Steroids (n=24)	Steroids and IS (n=12)	p
Age at diagnosis of sarcoidosis, years	48.5 [22.8-76]	46 [22.8-66.3]	50.6 [27.2-76]	ns
Male, n (%)	20 (55.5)	14 (58.3)	6 (50)	ns
African American, n (%)	26 (72.2)	14 (58.3)	12 (100)	ns
Organ involvement, n (%)				
Lungs	36 (100)	24 (100)	12 (100)	ns
Skin	12 (33.3)	8 (33.3)	4 (33.3)	ns
Ear, nose, and throat	11 (30.6)	6 (25)	5 (41.7)	ns
Eyes	7 (19.4)	5 (20.8)	2 (16.7)	ns
Liver	6 (16.7)	4 (16.7)	2 (16.7)	ns
Brain	4 (11.1)	2 (8.3)	2 (16.7)	ns
Kidney	2 (5.6)	2 (8.3)	0	ns
Cardiac Involvement, n (%)				
Congestive heart failure	2 (5.5)	2 (8.3)	0	ns
Sustained AT/VT	9 (25)	5 (20.8)	4 (33.3)	ns
Second/third degree heart block	12 (33.3)	9 (37.5)	3 (25)	ns
Reduced LVEF (<50%)	12 (33.3)	6 (25)	6 (50)	ns
Hypertrophic cardiomyopathy	7 (19.4)	5 (20.8)	2 (16.7)	ns
Late gadolinium enhancement on CMR	24/34 (70.6)	15/22 (68.2)	9 (75)	ns
Myocardial FDG uptake on cardiac PET	16/25 (64)	10/17 (58.9)	6/8 (75)	ns
Follow up				
Delay to first relapse, years	1.5 [0.5-6.8]	1.5 [0.5-6.8]	1.5 [1-3.2]	ns
Cardiac relapse, n (%)	13 (36.1)	11 (45.8)	2 (16.7)	0.048
Steroids at last follow up, n (%)	30 (88.2)	21 (87.5)	9 (75)	ns
IS at last follow up, n (%)	21 (58.3)	11 (45.8)	10 (83.3)	ns
Severe infection, n (%)	6 (16.7)	4 (1.7)	2 (1.7)	ns
Death, n (%)	3 (8.3)	2 (8.3)	1 (8.3)	ns
Follow up, years	3.6 [1-15.2]	4 [1-12.9]	3.4 [1-15.2]	ns

Patients receiving steroids+ immunosuppressive drugs (CT+IS) had a lower rate of cardiac relapse than patients receiving only steroids (CT)

Disclosure: T. Ballul, None; R. Borie, None; B. Crestani, None; E. Daugas, None; V. Descamps, None; P. Dieude, None; A. Dossier, None; F. Extramiana, None; T. Papo, None; K. Sacre, None.

Management of Ventricular Tachycardia and Cardiomyopathy in the Rheumatologist World: A Retrospective Review of Diagnostic Tools and Treatment Decisions for Cardiac Sarcoidosis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases I: DADA2, Cardiac Sarcoid, Cancer Immunotherapy

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Cardiac sarcoidosis has been noted in 2-7% of patients with sarcoidosis. However, the incidence is >20% based on necropsy data. Given the poor yield of biopsy due to patchy involvement of the disease, the diagnosis of cardiac sarcoidosis has increasingly favored the use of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18-FDG PET/CT) and gadolinium enhanced cardiac magnetic resonance imaging (CMR) scans. To date, there is little data to suggest the optimal dose and duration of corticosteroids and steroid-sparing agents, and the efficacy of these agents on cardiac sarcoidosis. We aimed to study whether patients on steroids for presumed or proven cardiac sarcoidosis had fewer ventricular arrhythmias as recorded on Implantable Cardiac Defibrillator (ICD) monitoring.

Methods: We completed a retrospective review of patients diagnosed with cardiac sarcoidosis between June 1, 2006 and June 1, 2016 at our institution. Patients with evidence of cardiac involvement on either 18 FDG-PET/CT, CMR, or endomyocardial biopsy (EMB) were selected. We evaluated the effect of corticosteroids on FDG-PET/CT and performed paired T test analysis on the number of ventricular tachycardia (VT) and non-sustained ventricular tachycardia (NSVT) events for 3 months in patients on and off high dose corticosteroids (prednisone >30 mg).

Results: We identified 1,298 patients diagnosed with sarcoidosis of whom 59 met inclusion criteria for a diagnosis of presumed or proven cardiac sarcoidosis. Among 59 patients, 19 had EMB of whom 8 were positive for sarcoidosis. 25 patients had serial 18-FDG PET/CT before and after treatment with corticosteroids. Of those, 12 (48%) had complete resolution after corticosteroids, 7 (28.0%) had partial resolution, 4 (16.0%) had increased uptake after corticosteroids, and 2 (1%) had negative serial 18-FDG PET/CT scans. There was a higher mean number of VT events during the corticosteroid free period compared to the high dose corticosteroid treatment period, though not statistically significant (21 vs 1 event, p=0.2, n=16). A similar trend was seen in the number of NSVT events (372 vs 7 events, p=0.3, n=16).

Conclusion: Our data suggests that treatment of presumed cardiac sarcoidosis with corticosteroids shows improvement in hypermetabolic activity on 18 FDG-PET/CT. Although our observations are limited due to a small sample size, we found a trend towards improvement in ventricular arrhythmias while on corticosteroids. Given the difficulty in diagnosing cardiac sarcoidosis by biopsy, treatment of cardiac sarcoid purely based on imaging findings should be considered. Future prospective trials are needed to validate our findings.

Table 1: Total number of patients who had ventricular tachycardia or non-sustained ventricular tachycardia events while receiving any of the following treatments

	No. patients	n (%) with any event
Off steroids		
Ventricular tachycardia	34	17 (50.0)
Non-sustained ventricular tachycardia	35	16 (45.7)
Steroids > 30mg		
Ventricular tachycardia	24	8 (33.3)
Non-sustained ventricular tachycardia	23	5 (21.7)
Steroids < 30mg		
Ventricular tachycardia	21	7 (33.3)
Non-sustained ventricular tachycardia	21	11 (52.4)
Steroid sparing agent		
Ventricular tachycardia	21	6 (31.6)
Non-sustained ventricular tachycardia	19	8 (42.1)

References: LynchJP, Hwang J, Bradfield J, Fishbein M, Shivkumar K, Tung R. Cardiac involvement in sarcoidosis: evolving concepts in diagnosis and treatment. *Semin Respir CritCare Med.* 2014;35(3):372-90.

Disclosure: S. Ziaee, None; S. Kunchakarra, None; C. Joyce, None; M. Rabbat, None; R. A. Ostrowski, None.

Abstract Number: 1914

Rheumatic Syndromes Associated with Immune-Checkpoint Inhibitors: A Single-Center Cohort of 61 Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases I: DADA2, Cardiac Sarcoid, Cancer Immunotherapy

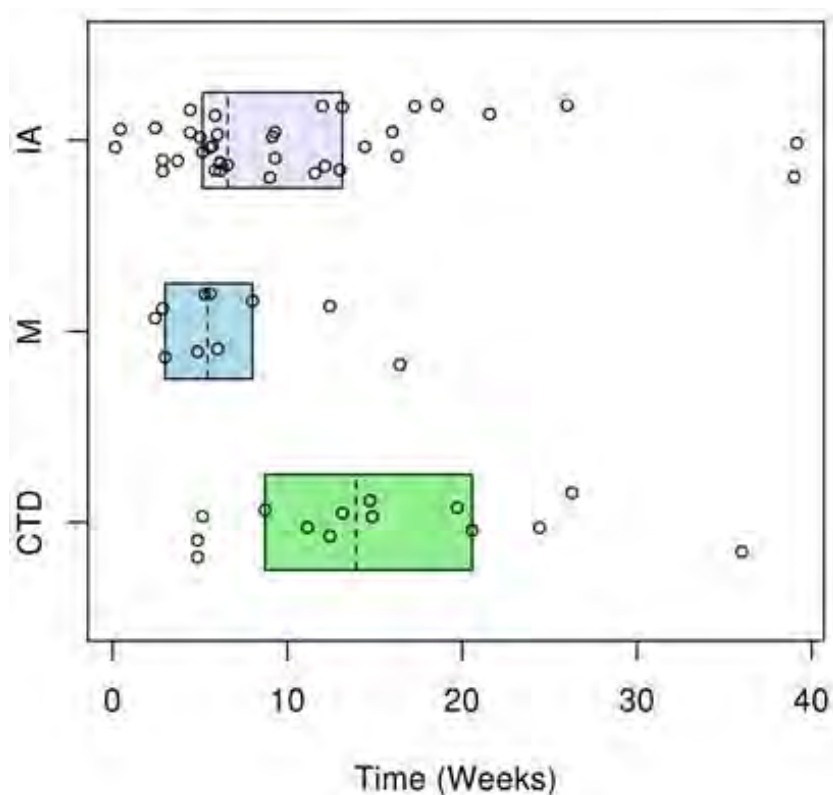
Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Rheumatologists are increasingly called upon to manage the autoimmune side effects of immune-checkpoint inhibitors (ICIs). However, these new entities are poorly understood and treatment often relies upon retrospective studies and expert opinion. The objective of this study is to describe the prevalence, clinical presentation, and management of a large cohort of patients with rheumatic immune-related adverse effects (Rh-irAEs) from immune checkpoint inhibitor therapy.

Methods: From a database of all patients who received any immune-checkpoint inhibitor at the Mayo Clinic Rochester, Minnesota campus between January 1st, 2011 and March 1st, 2018, we identified those with Rh-irAEs using diagnostic codes, search terms, and manual chart review.

Results: Of the 1,293 patients who received any checkpoint inhibitor, 43 were clinically diagnosed with Rh-irAEs. Eighteen patients with Rh-irAEs who received ICI therapy elsewhere were also analyzed. Clinical syndromes included inflammatory



arthritis (IA) (n=37, prevalence 2%), myopathy (n=10, 0.8%), and connective tissue disease (CTD) (n=14, 0.7%). IA was most commonly polyarticular and 28 patients (76%) required glucocorticoids. Mean treatment duration was 20 weeks (SD 23 weeks). Seven of these patients (19%) also received disease-modifying drugs and 3 patients (8%) required discontinuation of ICI therapy. Myopathy was treated with glucocorticoids in all cases for a mean duration of 15 weeks (SD 17 weeks) and led to two deaths and permanent ICI discontinuation in 9 patients (90%). CTD included cases of sicca syndrome, systemic sclerosis, and vasculitis. Nine of these patients (64%) were treated with glucocorticoids for a mean duration of 31 weeks (SD 30 weeks) and 3 patients (21%) had complete resolution of their Rh-irAE symptoms.

Conclusion: This study represents the largest cohort of Rh-irAEs to date. Most patients required long courses of treatment with only a minority achieving complete symptom resolution. Prospective, multicenter studies are necessary to determine the optimal management of these emerging disorders and further define immunologic phenotypes.

Figure 1. Time of Rh-irAE symptom onset after starting ICI therapy.

Abbreviations:IA; inflammatory arthritis, M; myopathy, CTD; connective tissue disease

Table 1 Inflammatory arthritis clinical features.

Characteristic	Value*
Patients	37
Age, mean (St. Dev.)	58.9 (16.8)
Prevalence	2%
Polyarticular	25 (68%)
Oligoarticular	12 (32%)
Sedimentation rate, mean (SD)	43.8 (23.1)
C-reactive protein, mean (SD)	51.4 (52.7)
Positive RF or ACPA	3 (8%)
Pre-existing inflammatory arthritis	3 (8%)
Pre-existing degenerative joint disease	27 (73%)
Treatment	
Prednisone only	21 (57%)
Prednisone plus disease modifying agent	7 (19%)
NSAIDs and/or intraarticular glucocorticoids only	8 (22%)
Starting prednisone dose, mg/day, mean (SD)	33.6 (20.5)
Weeks on prednisone, mean (SD)	20 (23.4)
Complete resolution after treatment	17 (46%)
Partial resolution after treatment	20 (54%)
ICI discontinued due to irAE	3 (8%)

* Values in table are mean (Standard deviation) or n(%).

Abbreviations: SD; standard deviation, ICI; immune-checkpoint inhibitor, Rh-irAEs; rheumatic immune-related adverse effects (Rh-irAEs)

Disclosure: M. Richter, None; C. S. Crowson, Pfizer, Inc., 2; L. Kottschade, None; H. Finnes, None; S. N. Markovic, None; U. Thanarajasingam, None.

Abstract Number: 1915

Big Data Analysis of Autoimmune Diseases Induced By Cancer Immunotherapies: Identifying Pharmacological Patterns of Organ-Specific Involvement

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

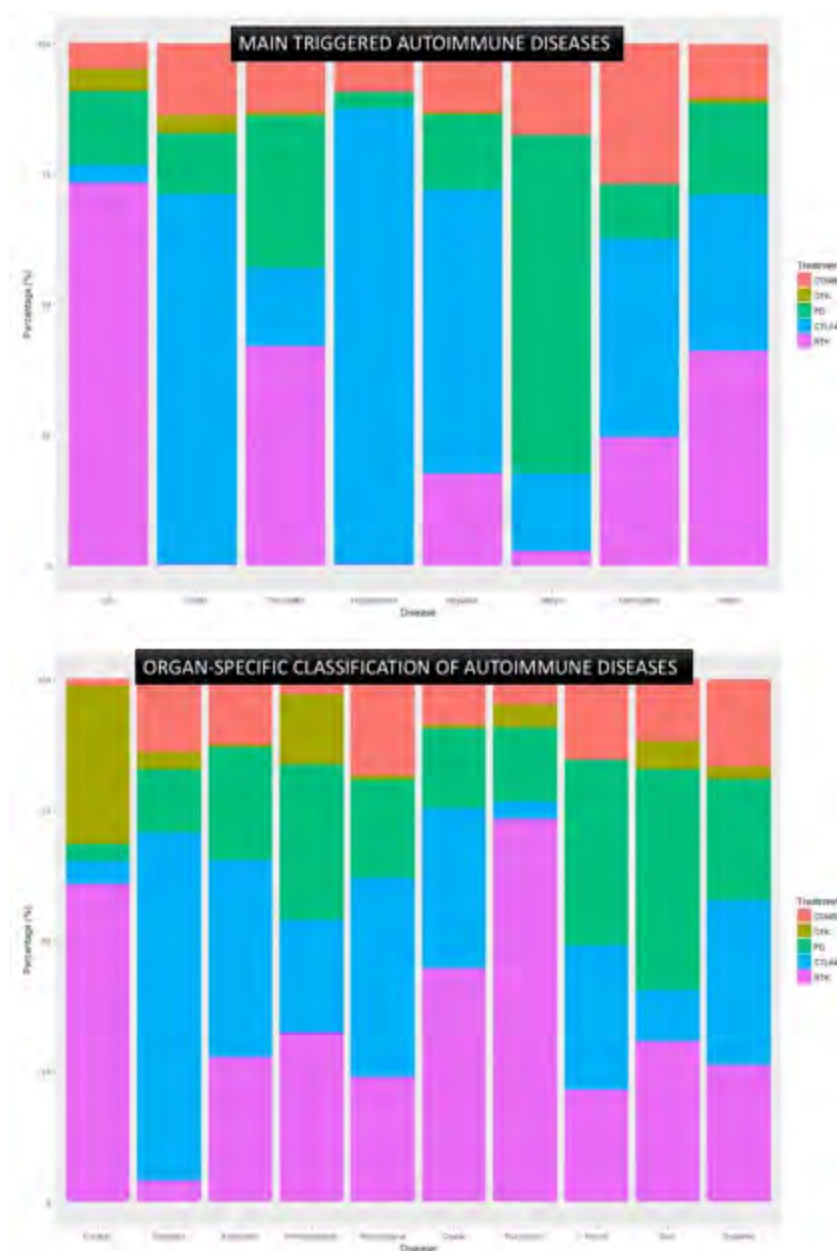
Session Title: Miscellaneous Rheumatic and Inflammatory Diseases I: DADA2, Cardiac Sarcoid, Cancer Immunotherapy

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: The scenario of biological-triggered autoimmune diseases has dramatically changed in recent years due to the increasing use of biologics in patients with solid cancers.

Methods: In 2006, the SEMI Spanish Study Group on Autoimmune Diseases (GEAS) created the BIOGEAS project, including the BIOGEAS systematic review of the literature (articles published until January 1st 2018) using the terms of the main groups of cancer immunotherapies that were crossed with autoimmune diseases using MedDRA terms (MedDRAVR 15.0). The autoimmune basis of the reported adverse event was defined according to the fulfilment of the corresponding international criteria, biopsy-proven histopathology, positive autoantibodies and/or resolution after corticosteroid treatment.



Results: We identified 6158 patients who developed 6288 autoimmune adverse events in patients with solid (n=5849) and haematological (n=309) neoplasia. The two main groups of cancer immunotherapies involved included checkpoint inhibitors in 3844 (mainly the CTL4 inhibitor ipilimumab in 1973 cases and the PD1 inhibitors pembrolizumab and nivolumab in 712 and 700 cases, respectively) and tyrosinekinase (TK) inhibitors in 2443 cases (mainly erlotinib and imatinib in 499 and 437 cases, respectively). Organ-specific classification of triggered autoimmune diseases included endocrine (n=1723), digestive (n=1591), pulmonary (n=1337), cutaneous (n=531), systemic/rheumatic (n=331), cardiac (n=304), neurological (n=218), ocular (n=150), haematological (n=38) and renal (n=69) autoimmune diseases. **Figure** shows distribution of the main pharmacological groups according to the most frequently-reported individual autoimmune diseases and to their classification by organ/system. The main organ-specific patterns of association (> 50% of cases related to a specific pharmacological pathway) are interstitial lung disease in patients treated with drugs targeting TK receptor; colitis, hepatitis and hypophysitis in those treated with CTL4 inhibitors; and vitiligo in those treated with drugs targeting the PD/PD-1 pathway.

Conclusion: More than 6000 cases of autoimmune diseases triggered by cancer immunotherapies have been reported. A multidisciplinary approach is essential, with a central role for the specialist in autoimmune diseases who should get used to managing not only spontaneous autoimmune diseases, but also the increasing number of biological-induced autoimmune diseases that may be forecast.

Disclosure: S. Retamozo, None; A. Flores-Chavez, None; B. Kostov, None; A. Sisó-Almirall, None; M. Pérez-de-Lis, None; R. Pérez-Alvarez, None; P. Brito-Zerón, None; M. A. Khamashta, None; M. Ramos-Casals, None.

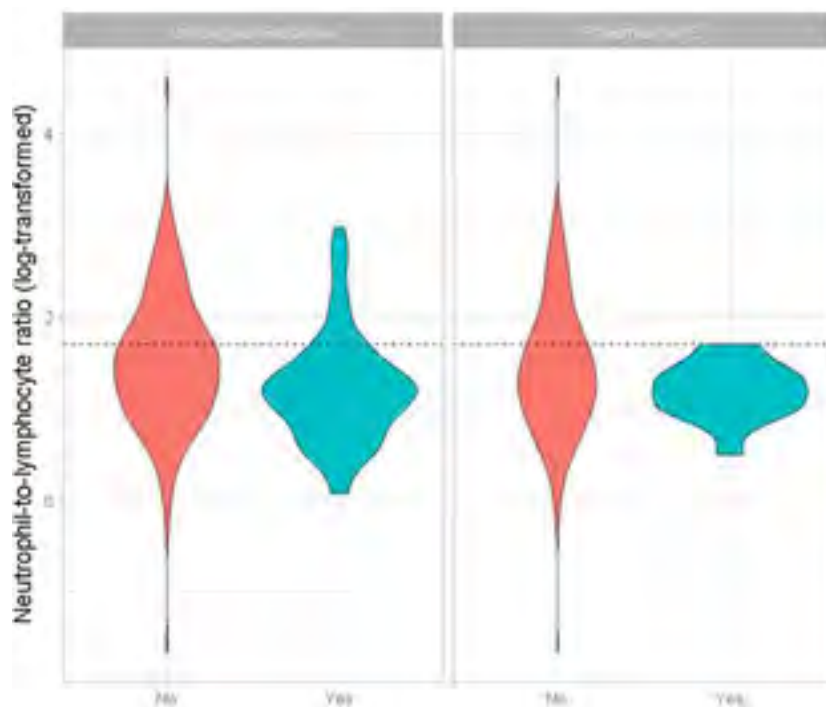
Abstract Number: 1916

Neutrophil-to-Lymphocyte Ratio Prospectively Predicts the Development of Rheumatic Immune-Related Adverse Events from PD-1 Inhibitor Therapy

Christopher McMaster^{1,2}, David Liew^{3,4}, Pallavi Shamdasani⁵, Jessica Leung^{3,4}, Albert Frauman^{6,7}, Jonathan Cebon^{7,8} and Russell Buchanan^{4,9}, ¹Department of Clinical Pharmacology and Therapeutics, Austin Health, Heidelberg, Australia, ²Health and Biomedical Informatics Centre, University of Melbourne, Parkville, Australia, ³Medicine, University of Melbourne, Parkville VIC, Australia, ⁴Rheumatology, Austin Health, Heidelberg VIC, Australia, ⁵Department of Rheumatology, Austin Health, Heidelberg, Australia, ⁶Department of Clinical Pharmacology and Therapeutics, Austin Health, Melbourne, Australia, ⁷Medicine, University of Melbourne, Melbourne, Australia, ⁸Olivia Newton-John Cancer Wellness & Research Centre, Melbourne, Australia, ⁹Medicine, University of Melbourne, Parkville, Australia

SESSION INFORMATION

Session Date: Monday, October 22, 2018



Session Title: Miscellaneous Rheumatic and Inflammatory Diseases I: DADA2, Cardiac Sarcoid, Cancer Immunotherapy

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Rheumatic immune-related adverse events (irAEs) from PD-1 inhibitor immune checkpoint immunotherapy can not only lead to cessation of immunotherapy, but also can be disabling and can also persist beyond cessation. Currently no biomarker can predict rheumatic irAEs. However, it is known that oncological response to PD-1 inhibitor therapy is predicted by pre-treatment neutrophil to lymphocyte ratio (NLR) and given that rheumatic irAEs are strongly associated with an oncological response to PD-1 inhibitor therapy, it therefore stands to reason that rheumatic irAEs and NLR prior to therapy might be associated, though this is currently unknown.

Methods: We examined the relationship between NLR and the development of rheumatic irAEs in all patients first treated with a PD-1 inhibitor in our center prior to January 1, 2017, as identified by hospital pharmacy dispensing records. Patients were included if a NLR could be calculated from a complete blood count performed at the institutional laboratory within two weeks prior to commencing treatment; this was subsequently log-transformed. The relationship between NLR and the development of rheumatic irAEs was assessed using the two-tailed Fisher's Exact Test, with NLR cut-point determined using recursive partitioning algorithm. Treatment efficacy was examined using oncological response, with responders defined as those who achieved at least partial response. The relationship between oncological response and NLR was also examined using identical methodology. Analysis was performed using R 3.5.0 and the rpart package.

Results: Out of the 211 patients included in the study, 15 developed a rheumatic irAE. The median age was 66 years and median treatment duration was 19 months. The primary cancer was melanoma in 91 patients (41%) and non-small cell lung cancer in 82 patients (39%). Nivolumab was used in 127 patients (57%). The log-NLR cut-point of 1.7 (untransformed = 5.5), as determined by recursive partitioning, is comparable to similar cut-points used in previous studies. Using this cut-point, there was a statistically significant association between lower log-NLR and the development of rheumatic irAEs ($p = 0.007$). At the same cut-point, there was also a statistically significant relationship between lower log-NLR and oncological response to therapy ($p < 0.001$).

Conclusion: Lower pre-treatment NLR prospectively predicts the development of rheumatic irAEs in our cohort, using methodology comparable to previous studies demonstrating the relationship between NLR and oncological response. Its promise as a biomarker for rheumatic irAEs should be explored in larger cohorts.

Figure 1. Violin plots of log-NLR. Left: oncological responders (blue) vs. non-responders (red). Right: experiences rheumatic irAE (blue) vs. did not experience a rheumatic irAE (blue).

Disclosure: C. McMaster, None; D. Liew, None; P. Shamdasani, None; J. Leung, None; A. Frauman, None; J. Cebon, Bristol-Myers Squibb, 2; R. Buchanan, None.

Abstract Number: 1917

Physician Opioid Prescribing Patterns and Risk for Chronic Opioid Use Among Rheumatoid Arthritis Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Pain Mechanisms – Basic and Clinical Science

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Experts have implicated physician prescribing rates as a contributing factor to the opioid crisis. However, little is known about heterogeneity in these patterns and its effects on chronic opioid use. Our objectives were to: 1) identify the extent to which US physicians varied in baseline opioid prescribing rates, and 2) determine the implications of physicians' baseline opioid prescribing rates on future probability of chronic opioid use among rheumatoid arthritis (RA) patients.

Methods: Data were obtained from the Corrona Rheumatoid Arthritis Registry. To ensure robust baseline opioid prescribing information, physicians were included in the analyses only if they contributed ≥ 10 RA patients within the first

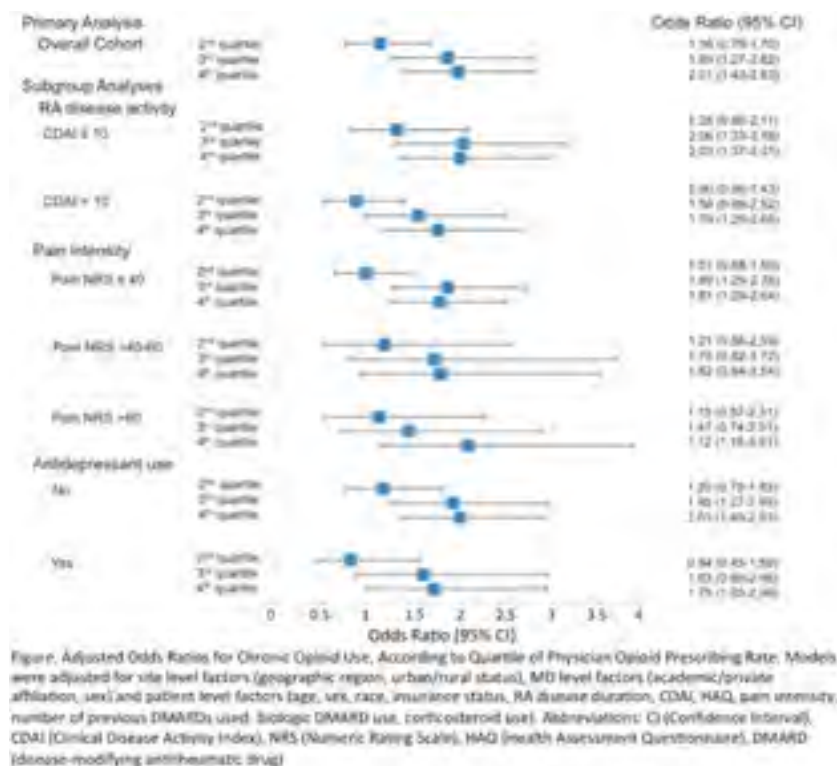


Figure 6. Adjusted Odds Ratios for Chronic Opioid Use, According to Quartile of Physician Opioid Prescribing Rate. Models were adjusted for site level factors (geographic region, urban/rural status), MD level factors (academic/private affiliation, sex) and patient level factors (age, sex, race, insurance status, RA disease duration, CDAI, HAQ, pain intensity, number of previous DMARDs used, biologic DMARD use, corticosteroid use). Abbreviations: CI (Confidence Interval), CDAI (Clinical Disease Activity Index), NRS (Numeric Rating Scale), HAQ (Health Assessment Questionnaire), DMARD (disease-modifying antirheumatic drug).

12 months of participation in the registry. RA patients were included if they: 1) were patients of the included physicians, 2) had ≥ 12 months follow-up, and 3) were not prevalent opioid users at study entry. Baseline opioid prescribing rates were calculated using data from RA patients seen within the first 12 months after a physician began participating in the registry, dividing the number of patients reporting opioid use by the number of patients seen during that year. The baseline opioid prescribing rate was then assessed as the exposure of interest in models that predicted chronic opioid use in patients seen subsequent to the baseline 12 month period. Generalized linear mixed models, controlling for relevant patient, physician and site characteristics, were used to assess the relationship between baseline prescribing rates and future chronic opioid use. Subgroup analyses were done to examine heterogeneity across the following clinical characteristics: 1) disease activity, defined by Clinical Disease Activity Index (CDAI) score ≤ 10 vs. > 10 ; 2) pain intensity (≤ 40 , $> 40-60$, > 60 out of 100); and 3) antidepressant use (yes/no). Interaction terms were used to assess the statistical significance of differences between subgroups.

Results: Among the 148 physicians in the initial cohort, baseline opioid prescribing rates varied from 0-70%, with a median of 27% and interquartile range of 18-37%. Among the 9337 RA patients included in the period after the baseline 12 months, physician opioid prescribing rates during the baseline period were significantly associated with risk for chronic opioid use (ref: lowest quartile; 2nd quartile: OR 1.16, 95% CI 0.79-1.70, 3rd quartile: 1.89, 95% CI 1.27-2.82, 4th quartile: OR 2.01; 95% CI 1.43-2.83) (Figure). No statistically significant differences were noted between subgroups.

Conclusion: Rates of baseline opioid prescribing varied widely. A physician's baseline opioid prescribing rate was a strong predictor of whether a patient would become a chronic opioid user in the future, even after controlling for patient characteristics.

Disclosure: Y. C. Lee, Pfizer, Inc., 2; Eli Lilly and Co., 6; B. Lu, None; H. Guan, None; J. Greenberg, Corrona, LLC, 3; J. Kremer, Corrona, LLC, 3; D. Solomon, None.

Abstract Number: 1918

Defining Pain That Does Not Interfere with Activities Among Rheumatoid Arthritis (RA) Patients

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Pain Mechanisms – Basic and Clinical Science

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: RA patients differ in the degree to which pain interferes with function. To improve function, an understanding of this diversity is needed. Our objectives were to: (1) understand the degree to which pain interfered with specific activities, (2) characterize the distribution of pain intensity that does not interfere with activities (ie, non-interfering pain), and (3) identify characteristics associated with non-interfering pain.

Methods: Data were derived from subjects with rheumatologist-confirmed RA in FORWARD—The National Databank for Rheumatic Diseases. Subjects completed 8 items from the PROMIS Pain Interference Item Bank that asked the degree to which pain interfered with activities (from “not at all” to “very much”). If subjects reported any pain interference, they were asked, “At what level would pain no longer interfere with this activity?” Responses were collected using a 0-10 numeric rating scale (NRS; 10 = severe pain). Internal consistency of non-interfering pain items was assessed using Cronbach’s alpha and item-total correlations to determine if an overall mean of non-interfering pain could be calculated. Multiple linear regression analyses examined associations between non-interfering pain and the following characteristics: age, sex, disease duration, BMI, Rheumatic Disease Comorbidity Index, disability (Health Assessment Questionnaire), pain intensity NRS, fatigue NRS, self-reported current depression, sleep problems NRS, and fibromyalgias (Polysymptomatic Distress Scale).

Results: As of April 2018, 1048 RA patients had completed questionnaires. Pain interference was most common for daily activities (70.1%) and least common for ability to concentrate (46.7%) (Table). The mean level at which pain no longer interfered with activities ranged from 2.7 ± 2.2 for ability to fall/stay asleep to 3.1 ± 2.1 for daily activities. Internal consistency across items was high (Cronbach’s alpha = 0.97). Overall, the mean threshold for non-interfering pain was 2.9 ± 2.0 . Independent predictors of non-interfering pain were greater pain severity ($\beta = 0.21$, $p < 0.0001$) and lower fatigue ($\beta = -0.11$, $p = 0.04$). Other characteristics tested were not statistically significant at alpha = 0.05.

Conclusion: The mean pain level that did not interfere with activities was 3 (on a 0-10 scale) and did not vary depending on activity type. This may suggest that RA patients consider non-interfering pain to be a concept similar across different situations. Factors that may contribute to high non-interfering pain levels include pain and fatigue. Future studies are needed to determine if these associations, particularly that between pain intensity and non-interfering pain, reflect an artifact in rating (eg, patients who rate pain highly may also rate non-interfering pain highly) or underlying pathways that can be targeted to decrease the functional impact of pain.

Table The proportion of RA patients who experience pain interference and the pain level at which pain does not interfere with activities (N = 1048)

Activity ¹	PROMIS Pain Interference Questions % Experienced Pain Interference	Pain Level That Would Not Interfere With Activity	
		Mean \pm SD	Median (IQR)
Daily activities	70.1%	3.1 ± 2.1	3 (2,4)
Work around the house	69.2%	3.1 ± 2.1	3 (2,4)
Household chores	66.9%	3.0 ± 2.1	2 (2,4)
Ability to fall asleep/stay asleep	61.6%	2.7 ± 2.2	2 (1,4)
Ability to work	62.9%	2.9 ± 2.2	2 (1,4)
Enjoyment of life	57.8%	2.8 ± 2.3	2 (1,4)
Social activities	55.2%	3.1 ± 2.1	3 (2,4)
Ability to concentrate	46.7%	2.8 ± 2.1	2 (1,4)

Abbreviation: IQR, interquartile range.

¹ Total number who responded to each question was 1047 for daily activities, 1046 for work around the house and household chores, 1044 for social activities, 1041 for ability to concentrate, 1040 for enjoyment of life, 1039 for fall asleep/stay asleep, and 458 for ability to work; 575 subjects did not answer the latter question because they were retired or otherwise not working.

Disclosure: Y. C. Lee, Pfizer, Inc., 2; Eli Lilly and Co., 6; P. Katz, None; A. Quebe, Eli Lilly and Company, 1, 3; L. Sun, Eli Lilly and Company, 1, 3; H. Patel, Lilly, 3; C. L. Gaich, Eli Lilly and Company, 1, 3; N. Boytsov, Lilly, 3; K. Michaud, None.

Abstract Number: 1919

Individual Short-Acting Opioids and the Risk of Opioid-Related Adverse Events in Adolescents

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Pain Mechanisms – Basic and Clinical Science

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Hydrocodone, codeine, oxycodone, and tramadol are frequently prescribed for moderate pain in adolescents. However, pharmacokinetic and pharmacodynamic differences between these short-acting opioids could affect their relative safety. Although tramadol, which is both a serotonin/norepinephrine reuptake inhibitor and a μ -opioid agonist, has been considered a safer opioid, limited data support this perception. We aimed to compare the occurrence of opioid-related adverse events for adolescents without cancer or other severe conditions taking commonly prescribed short-acting opioids.

Methods: Retrospective cohort study in Tennessee Medicaid, 1999-2011. We studied Medicaid enrollees 12 to 17 years of age without cancer, other severe conditions or evidence of substance abuse with filled prescriptions for study opioids. Exposure was defined as current or recent use of hydrocodone, codeine, oxycodone, and tramadol. The primary outcome was an emergency department visit, hospital admission, or death adjudicated after review of medical records as plausibly related to opioid use, classified as serious if there was hospitalization or opioid-related escalation of care. Propensity-score adjusted hazard ratios (HRs) were calculated with hydrocodone as the reference category.

Results: The incidence of opioid-related adverse events per 10,000 person-years of opioid exposure was 317.0 for tramadol (47/1,483 person-years), 229.7 for oxycodone (43/1,872), 91.2 for codeine (58/6,359), and 97.5 for hydrocodone (127 events/13,026). The adjusted HR for tramadol was 2.72 (1.84-4.03), with a comparable increase for serious events (HR = 2.92 [1.45-5.88]). Risk for codeine was not significantly increased (HR = 1.35 [0.95-1.90]). The risk for all events was increased for oxycodone (HR = 1.77 [1.17-2.68]), but that for serious events was not (HR = 0.94 [0.32-2.73]). The increased risk for tramadol was consistently present in multiple sensitivity analyses to reduce residual confounding or misclassification and in an analysis with codeine as the reference category (all events: HR = 1.86 [1.16-2.98]; serious events: HR = 2.74 [1.33-5.64]).

Conclusion: In this cohort of adolescents without cancer or other severe conditions prescribed short-acting opioids, the incidence of opioid-related adverse events for tramadol was consistently greater than that for either hydrocodone or codeine, including for the more serious events leading to hospitalization or escalation of care.

Disclosure: C. P. Chung, None; S. T. Callahan, None; W. Cooper, None; W. Dupont, None; K. Murray, None; A. Franklin, None; K. Hall, None; J. A. Dudley, None; C. M. Stein, None; W. Ray, None.

Abstract Number: 1920

Is There Objective Evidence of Neuropathy in Knee Osteoarthritis Based on Clinical Evaluation?

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

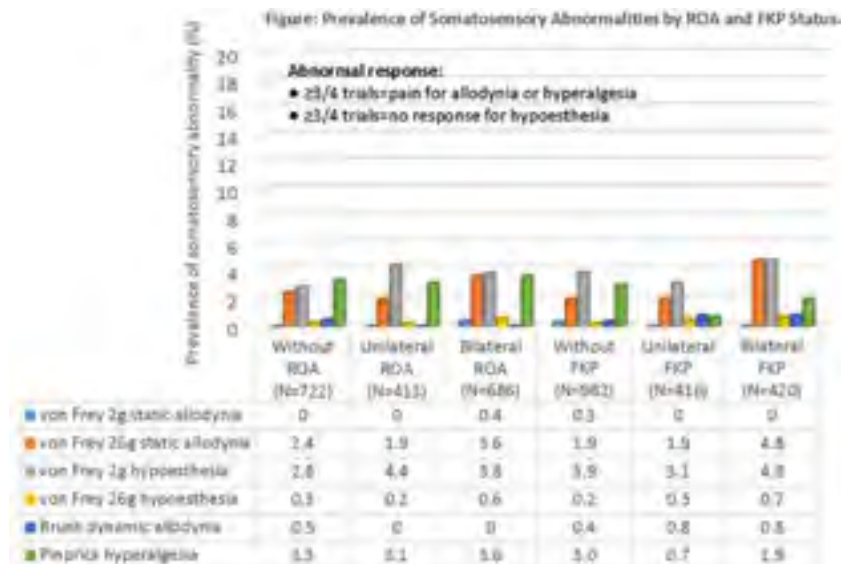
Session Title: Pain Mechanisms – Basic and Clinical Science

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Self-reported descriptors of pain in knee osteoarthritis (OA) such as burning and stabbing pain are suggestive of a neuropathic component of pain beyond that of nociceptive pain from structural pathology. However, such descriptors do not necessarily equate to specific pain mechanisms. While there is evidence of proprioceptive and vibration perception abnormalities in knee OA, to date, there have been no studies documenting objective neuropathy involving nociceptive pathways in knee OA. We used the StEP [Scholz, 2009] protocol, which distinguishes neuropathic vs. non-neuropathic pain with feasible bedside evaluations to assess the prevalence of clinical evidence of neuropathy in knee OA.

Methods: The Multicenter Osteoarthritis (MOST) Study is a NIH-funded longitudinal cohort study of persons with or at risk of knee OA. Subjects were evaluated with a peripheral neuropathy screen, and a standardized somatosensory assessment at



the knee with von Frey 2 g and 26 g monofilaments (static allodynia, hypoesthesia), brush (dynamic allodynia), and pinprick (hyperalgesia), each assessed with 4 trials. Abnormal responses were defined as pain (allodynia or hyperalgesia) or no response (hypoesthesia) in $\geq 3/4$ trials. We excluded those with TKR. We evaluated the prevalence of each somatosensory abnormality stratified by # of knees with radiographic knee OA (ROA) and with frequent knee pain (FKP).

Results: There were 1821 participants (mean age 67, mean BMI 30, 62% female, 46% with FKP in either knee, 3.9% with +peripheral neuropathy screen); 722 without ROA (39.6%), 413 with unilateral ROA (22.6%), and 686 with bilateral ROA (37.6%). The prevalence of allodynia, hyperalgesia, and hypoesthesia was $<5\%$ in all groups, regardless of # of knees with ROA or FKP (**Figure**). For those with unilateral ROA or unilateral FKP, the prevalence of abnormalities were similar in the ipsilateral and contralateral knee.

Conclusion: Using standardized bedside assessment tools for the clinical distinction between neuropathic and nociceptive pain, we observed an overall low prevalence of somatosensory changes that would be consistent with neuropathy. However, these changes did not meet the diagnostic threshold criteria of neuropathic pain, and the presence of abnormalities did not differ by # of knees with ROA or FKP, or by laterality. We cannot rule out subclinical neuropathy that could be detected by nerve conduction study or skin biopsy. Nonetheless, we did not find overt evidence of nerve lesion in those with ROA at a greater frequency than those without ROA, and similar findings for FKP vs. no FKP. Further, the prevalence of abnormalities detected did not approach that reported for “neuropathic-like” pain by self-report on Pain Detect. Patient-reported symptoms may not directly reflect underlying mechanisms, highlighting the need for identifying objective means of pain phenotyping to move towards mechanism-based treatments for OA pain.

Disclosure: P. Ballal, None; J. Scholz, Acetylon, 2, Thompson Family Foundation, 2, Biogen, 3; L. Frey-Law, None; N. Wang, None; M. C. Nevitt, None; C. E. Lewis, None; T. Neogi, None.

Abstract Number: 1921

Relation of Sensitization and Conditioned Pain Modulation to Post-Knee Replacement Pain

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Pain Mechanisms – Basic and Clinical Science

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Alterations in pain processing, such as pain sensitization and inadequate conditioned pain modulation (CPM), may contribute to the observed pain persistence post-knee replacement (KR) in 20-30% of patients, but studies to date have been conflicting. Further, many studies have been small and comprised only subjects who experienced post-KR pain improvement. It is therefore not known if altered pain processing is present in those with persistent post-KR pain. We undertook a comprehensive evaluation of pain sensitization and CPM in relation to post-KR pain.

Methods: The Multicenter Osteoarthritis MOST Study is a NIH-funded longitudinal cohort of persons with or at high risk of knee OA. We evaluated subjects prior to KR and 12-18 months post-KR with a standardized somatosensory evaluation of mechanical pressure pain thresholds PPT at the wrist and patellae, temporal summation TS at the wrist, and WOMAC pain questionnaires. CPM was assessed post-KR. PPT was assessed with an algometer 1cm² tip, 0.5 Kg/sec as the point at which pressure first changed to slight pain; 3 trials at each anatomic site were averaged. Lower PPT indicates more pain sensitivity, reflecting peripheral sensitization at a site of disease and central sensitization at a site without disease. Temporal summation, indicating central sensitization, was defined by increased pain during repeated mechanical stimulation 1 Hz x 30-sec with a 60 g monofilament. CPM was assessed using the forearm ischemia test. Inadequate CPM was defined as a ratio of <1, indicating lack of increase in post-conditioning stimulus PPT. We evaluated the relation of pre- and post-KR PPT and TS, and of post-KR CPM to post-KR WOMAC pain and to a minimal clinically important difference MCID in WOMAC pain, adjusting for potential confounders.

Results: There were 171 subjects in our study who were seen before and after their KR (mean age 69, 62% female, mean BMI 31). Pre-KR PPT and pre-KR TS were not associated with post-KR WOMAC pain (**Table**). Post-KR TS and inadequate CPM were significantly associated with a worse WOMAC pain score post-KR, and non significantly with lower likelihood of achieving the MCID.

Conclusion: Pre-KR PPT and TS were not associated with post-KR pain levels or pain improvement. Thus, while PPT and TS are associated with pain severity overall in knee OA subjects, they do not adequately predict pain response to KR. Post-KR presence of TS and inadequate CPM were associated with worse pain post-KR, suggesting a role for central altered pain processing in pain persistence post-KR, and provide support for pain phenotyping to guide mechanism-based treatment approaches.

	Post-KR WOMAC Pain		Minimal Clinically Important Difference (MCID) in Post-KR WOMAC Pain **	
	Mean difference in WOMAC Pain* (95% CI)	P-value	OR (95% CI)	P-value
Pre-KR Measures:				
Pre-KR TS	0.11 (-0.31, 0.54)	0.6	0.93 (0.70, 1.24)	0.6
Pre-KR PPT at wrist	-0.19 (-0.59, 0.20)	0.3	1.11 (0.84, 1.47)	0.5
Pre-KR PPT at patella	-0.07 (-0.32, 0.19)	0.6	1.02 (0.84, 1.23)	0.9
Post-KR Measures:				
Post-KR TS	0.82 (0.19, 1.45)	0.01	0.73 (0.44, 1.21)	0.2
Post-KR PPT wrist	-0.21 (-0.63, 0.21)	0.3	0.99 (0.75, 1.31)	0.9
Post-KR PPT patella	-0.15 (-0.45, 0.15)	0.3	1.02 (0.82, 1.26)	0.9
Inadequate CPM (<1)	1.47 (0.26, 2.68)	0.02	0.78 (0.56, 3.00)	0.6

* Mean differences refers to an increase (positive value, indicating worsened pain) or decrease (negative value indicating pain improvement) in WOMAC pain post-KR relative to pre-KR value per unit increase in continuous variables (TS, PPT) or for those with vs. without that feature for dichotomous variables (inadequate CPM)

** Defined as an improvement of at least 5.6/20 (Escobar, et al. 2007)

Analyses were adjusted for age, sex, BMI, depressive symptoms, pain catastrophizing, clinic site, time of clinic assessments relative to KR date

Disclosure: T. Neogi, None; N. Wang, None; C. E. Lewis, None; M. C. Nevitt, None; L. Frey-Law, None.

Abstract Number: 1922

Characterization of the Pharmacology and Pharmacokinetics of Cntx-4975, a High-Purity, Synthetic Trans-Capsaicin in Clinical Development for the Treatment of Moderate to Severe OA Knee Pain

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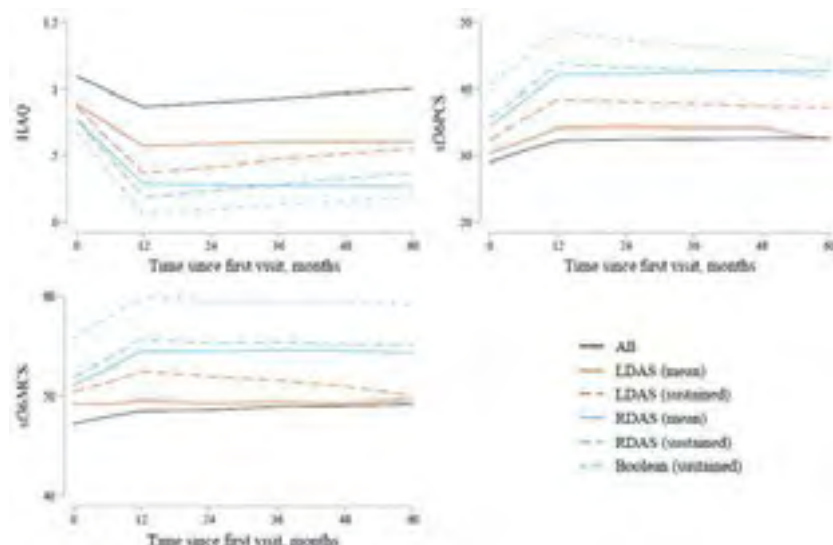
SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Pain Mechanisms – Basic and Clinical Science

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM



Background/Purpose: CNTX-4975, a highly purified, synthetic *trans*-capsaicin and long-acting, non-opioid analgesic in phase 3 trials for moderate to severe OA knee pain, has demonstrated safety and efficacy in a randomized, phase 2 study. CNTX-4975 targets the transient receptor potential vanilloid 1, producing analgesia via reversible desensitization of end terminals of primary afferent pain fibers. We report pharmacologic and pharmacokinetic (PK) data from preclinical and human studies of CNTX-4975.

Methods: An in vitro pharmacologic study, using human and rat cells, assessed the activity of 10 μ M CNTX-4975 at 113 receptors and 42 enzymes to identify potential off-target effects. In an in vivo rat model, the analgesic efficacy of a single intra-operative instillation of CNTX-4975 (0.075–7.5 mg/mL) in incised rat paws was evaluated by assessing response to thermal stimuli after surgery compared with subcutaneous buprenorphine (50 μ g/kg, 1 hour before test). Tolerability of IA or intra-tendon injections of CNTX-4975 was evaluated in 11 local tolerance studies conducted in rabbits, rats, and dogs using doses (0.12–0.60 mg/mL) that resulted in considerably higher systemic exposures than those investigated in human trials. Phase 1 and 2 human studies assessed efficacy, safety, and PK of CNTX-4975 (0.01–15 mg) across multiple indications, including moderate to severe OA knee pain. PK parameters included peak plasma concentration (C_{max}), systemic exposure (mean area under the curve to last measured time point [AUC_{0-last}]), half-life ($t_{1/2}$), and time to C_{max} (T_{max}).

Results: In the in vitro pharmacology study, CNTX-4975 10 μ M demonstrated activity at 1 benzodiazepine and 1 melatonin receptor. The 10 μ M concentration was up to 2000 times higher than that detected in plasma following the highest dose administered in human studies (15 mg intra-operatively; 2 mg IA). No pharmacologic effects from activity at these receptors are expected with clinical doses of CNTX-4975. In the postsurgical rat pain model, a single intraoperative dose of CNTX-4975 0.25 mg/mL substantially relieved thermal hyperalgesia, and 7.5 mg/mL demonstrated efficacy comparable to buprenorphine; efficacy was sustained for several days to 1 week, depending on the dose. In local tolerance studies, CNTX-4975 was well tolerated, and no local toxicity was observed following a single IA injection of CNTX-4975 into rat knees. In human trials, PK analyses demonstrated rapid absorption of CNTX-4975 following IA knee injection. C_{max} and AUC_{0-last} for CNTX-4975 were linearly related to dose over the range studied and across indications (0.1–15 mg); approximate T_{max} <1 hour was not dose-dependent. Mean $t_{1/2}$ was 0.3–3.6 hours. C_{max} and AUC_{0-last} did not exceed mean values of 2.6 ng/mL and 4 ng•h/mL, respectively.

Conclusion: A single IA injection of CNTX-4975 demonstrated rapid absorption in humans, and was associated with substantial, prolonged efficacy and no local toxicities in preclinical studies. These findings are consistent with the mechanism of action of CNTX-4975 and safety and tolerability results from open-label and randomized, phase 2 clinical trials.

Disclosure: J. Campbell, Centrexion Therapeutics, 3; R. Stevens, Centrexion Therapeutics, 3; P. Hanson, Centrexion Therapeutics, 3.

Treating Rheumatoid Arthritis to Target: Is Low Disease Activity Good Enough?

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes I: Beliefs and Behaviors

Session Type: ACR Concurrent Abstract Session

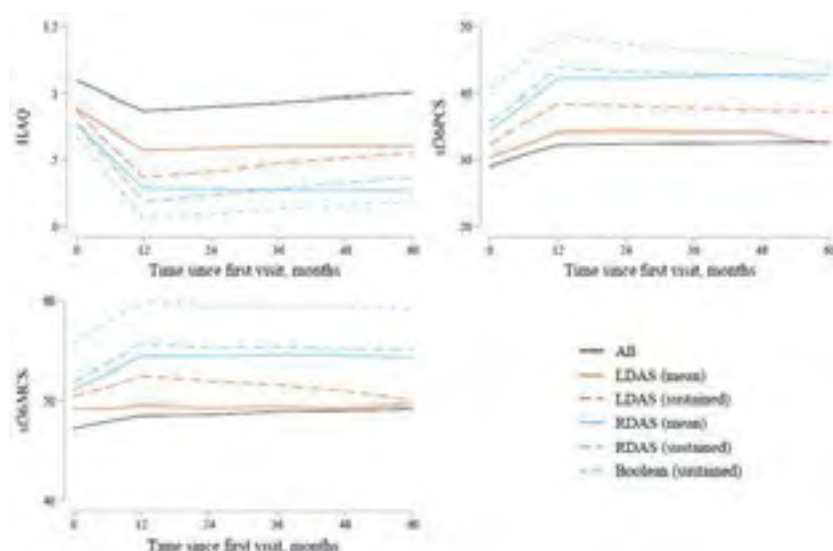
Session Time: 4:30 PM-6:00 PM

Treating Rheumatoid Arthritis To Target: Is Low Disease Activity Good Enough?

Background/Purpose: It is now widely recognised that treat-to-target (T2T) principles in rheumatoid arthritis (RA) are effective in achieving optimal disease outcomes. The aim of this study was to examine for differences in outcomes between low (LDAS) and remission (RDAS) disease activity score (DAS) categories, to establish whether LDAS is an acceptable treatment target in RA.

Methods: Data from two consecutive, similarly designed UK multi-centre RA inception cohorts, were used: the Early RA Study (ERAS) and Early RA Network (ERAN). Recruitment figures/median follow up for ERAS and ERAN were 1465/10 years (maximum 25 years), and 1236/6 years (maximum 10 years) respectively. Standard demographic and clinical variables were recorded at baseline and then annually until the end of study follow up. Disease activity was categorised by mean DAS28 score between years 1-5 as remission [mRDAS<2.6] or low [mLDAS 2.6-3.2]; as sustained low/remission DAS (sLDAS/sRDAS) based on DAS persisting in each of the two categories at years 1-2 and as Boolean remission (years 1-2). Change in HAQ and SF36 (physical [PCS] and mental [MCS] components) for each disease activity category were modelled using linear mixed models with time incorporated as a linear spline with change-point at 12 months. Year of onset, age, gender and use of steroids or conventional DMARDs at first visit were included as covariates.

Results: Out of 2701 patients, 468 (17%) were in mRDAS, 284 (11%) in mLDAS in the first five years of disease. Lower proportions had achieved sRDAS (8%), sLDAS (6%) and Boolean (2%) remission (table). Mean age was similar across categories; more women were in low vs remission DAS. Compared to mLDAS or sLDAS, inflammatory markers, DAS, functional (HAQ, PCS) and mental (MCS) scores tended to be better in the mRDAs, sRDAS or Boolean remission categories. Significant differences ($p<0.05$) were noted between the mRDAS and mLDAS between years 1-5 for all outcomes; for sRDAS compared to sLDAS, the difference was significant at one year but not by five years (figure).



Conclusion: This study demonstrates striking differences between remission and low DAS categories, suggesting worse functional and SF36 outcomes over time in the low DAS categories. The findings support that remission should be the primary T2T goal in RA.

Figure. Disease outcomes by DAS category.

Disclosure: E. Nikiphorou, None; S. Norton, None; A. Young, None; L. Carpenter, None; J. Dixey, None; D. Walsh, Pfizer, Inc., 5; P. Kiely, None.

Abstract Number: 1924

Mitigating Medication Risk Aversion in the Confident Treatment Decisions for Living with Rheumatoid Arthritis Trial

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes I: Beliefs and Behaviors

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Controlling disease activity in RA using a treat-to-target (T2T) strategy can optimize clinical and patient-important outcomes. Yet, many patients are not familiar with T2T and report medication risk aversion as a major barrier to changing therapy. To improve willingness of patients to escalate treatment, we developed and evaluated an educational, direct-to-patient video intervention that included information relevant to managing RA using a T2T strategy.

Methods: We conducted a controlled, randomized trial of our intervention among US patients with self-reported RA enrolled in the Arthritis Power patient registry. We recruited participants by email, and surveyed their satisfaction with disease control, values about RA medications, decisional conflict about treatment change and willingness to change treatment if/when recommended by their rheumatologist (Table). Intervention group participants were invited to view up to 6 videos (mean duration 2 min each) relevant to T2T; those in the control group viewed vaccination-related videos (mean duration 1:23 min each) unrelated to T2T as an “attention control”. Participants were required to view 3 (intervention) and 2 (control) videos, respectively. The primary outcome, collected using surveys, was patient-reported willingness to change RA treatment, measured by the choice predisposition scale (0-10, anchors: “Not willing at all”; “Extremely willing”) that reflected preference for RA treatment change. We stopped recruitment when 208 (N=104 per group) participants enrolled based on a priori sample size estimation. We compared the difference in pre-post differences in willingness to change RA treatment between the two groups using t-test.

Results: We invited 1264 RA patients by email. We reached our enrollment goal in 8 weeks. Study participants (N=208) were 90% Caucasian, 90% women, with mean (SD) age 50 (11) years, in good health (51%); 52% reported familiarity with T2T. A majority (89%) reported having values that favored RA medications. We observed no differences in baseline socio demographics, patient global assessment of disease activity, health literacy, willingness to change treatment, or decisional conflict (Table). We found a significant improvement in pre-post willingness to change treatment in intervention vs. control participants (0.5 vs 0.01, p=0.01). We calculated an effect size (Glass’s delta) for the intervention of 0.48 (i.e. moderate). Moreover, decisional conflict about treatment change decreased; there was no significant difference in pre-post differences in decision conflict between groups.

Conclusion: This randomized trial testing a novel patient-directed intervention advocating for T2T strategy implementation in RA care increased self-reported willingness to change RA treatment. Further studies are needed to evaluate if this effect is sustained over time and if it translates into actionable behavior change. Table: Patient Demographic, Clinical Characteristics, Values Regarding Rheumatoid Arthritis (RA) Treatment, Decisional Conflict about RA Treatment and Willingness to Change RA Treatment by Group.

Variable	Intervention (N=104)	Control (N=104)	p value
Baseline			
Age, years, mean (SD)	49.31 (10.75)	49.81 (11.15)	0.82
Race, Caucasian, N (%)	92 (88.5)	96 (92.3)	0.60
Sex, female, N (%)	92 (88.5)	94 (91.3)	0.51
Biologic DMARD use, ever, N (%)	29 (27.9)	36 (35.0)	0.27

Table. (Cont'd)

Variable	Intervention (N=104)	Control (N=104)	p value
Conventional DMARD use, ever, N (%)	33 (31.7)	43 (41.7)	0.14
General health, good or better, N (%)	53 (51.0)	54 (51.9)	0.89
Health literacy, excellent, N (%)	102 (98.1)	104 (100.0)	0.16
Familiar with T2T strategy, N (%)	54 (51.9)	54 (51.9)	1
Patient global assessment of disease activity*	5.44 (2.31)	5.68 (2.29)	0.37
Patient acceptable symptoms state, yes, N (%)	42 (40.4)	39 (37.5)	0.67
Reported values that favored RA medication use†, yes, N (%)	91 (87.5)	95 (91.3)	0.38
Prior year discussion with rheumatologist about active RA, yes, N (%)	89 (85.6)	91 (87.5)	0.69
Prior year discussion with rheumatologist about goals of RA treatment, yes, N (%)	77 (74.0)	81 (77.9)	0.52
Decisional conflict about RA treatment change‡, mean (SD)	32.59 (16.81)	32.74 (18.75)	0.98
Willingness to change RA treatment§, mean (SD)	6.72 (2.44)	7.25 (2.24)	0.15
Follow up			
Decisional conflict about RA treatment change‡, mean (SD)	29.73 (16.62)	29.82 (19.12)	0.84
Willingness to change RA treatment§, mean (SD)	7.22 (2.20)	7.26 (2.15)	0.93

DMARD, disease modifying antirheumatic drug, T2T, treat-to-target

*Patient global assessment of disease activity, 0-10 scale, 0=very well, 10=very poorly, lower scores are better; † Values that favored RA medication use assessed using a previously published tool that determines participants' agreement with 5 positive and 5 negative statements about use of medications in RA. ‡Decisional conflict about RA treatment change measured by decisional conflict scale, 16 items, 5-point Likert items ranging from "Strongly agree" to "Strongly disagree", lower scores are better; §Willingness to change RA treatment measured by choice predisposition scale, 0-10 scale anchored by "Not willing at all" and "Extremely willing" with "Unsure" at the midpoint, higher scores are better.

Disclosure: M. I. Danila, Pfizer, Inc., 2; L. Chen, None; J. K. Owensby, None; R. O'Beirne, Pfizer, Inc., 2; J. A. Melnick, None; E. M. Ruderman, Pfizer, Inc., 2, 5; L. R. Harrold, Corrona, LLC, 1, Corrona, LLC, 3, Pfizer, Inc., 2, Roche and Bristol Myers Squibb, 5; J. R. Curtis, AbbVie, Amgen, Bristol-Myers Squibb, Corrona, Janssen, Lilly, Myriad, Pfizer, Radius, Roche/Genentech, UCB, 2, AbbVie, Amgen, Bristol-Myers Squibb, Corrona, Janssen, Lilly, Myriad, Pfizer, Radius, Roche/Genentech, UCB, 5.

Abstract Number: 1925

Goal Concordance in Rheumatoid Arthritis: Beyond Pain Reduction, Is There Agreement?

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes I: Beliefs and Behaviors

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Goal concordance between patients with chronic diseases and their clinicians has been linked to improved outcomes, but not explored in rheumatoid arthritis (RA). Our objective was to assess the extent to which RA patient goals for treatment are concordant with their rheumatologists and to identify correlates of goal concordance.

Methods: Patients meeting 2010 ACR criteria for RA and seen at least once in the prior 12 months at one of two rheumatology clinics (Veterans Affairs Hospital-based or university-based) were enrolled in a cross-sectional survey study. Both enrolled RA patients and their corresponding rheumatology fellow or attending who agreed to participate completed the RA goals measure (ranked top three goals for RA treatment out of eight possible choices) prior to the clinic visit. Patients then completed a longer survey on overall health, medications, demographics, health literacy, adherence and function. Primary outcome was goal concordance defined as the patient's #1 goal being listed among any of the top three listed by the clinician. Differences in baseline patient characteristics by goal concordance were assessed using chi-square or Fisher's exact tests for categorical variables and Mann-Whitney U tests for continuous variables.

Results: A total of 171 patient-clinician dyads were analyzed. Patients were 50% female, 15% Spanish-speaking, and 25% had limited health literacy. "Have less pain" was selected by both in 82% of dyads and "have fewer problems doing daily activities" by 61% (table). The proportion of dyads in which the clinician ranked the patient's #1 goal among the top three was 80%. Given the overwhelming agreement around pain, the proportion of dyads with goal concordance after removing pain, fell to 36%. Goal concordance did not vary by age, gender, race/ethnicity, or health literacy. However, Spanish language was associated with a greater proportion being concordant with clinicians. Of note, 27% of patients ranked "feel less tired" as one of their top three compared to only 6% of clinicians, 12% of patients ranked "improve

mood” compared to 0% of clinicians, and 40% of clinicians ranked “Avoid side effects from medicine” compared with 14% of patients.

Conclusion: Among 171 RA patient and clinician dyads, the majority of patients shared their top goal with their clinicians’ top three, with “have less pain” as the most common goal. Beyond that shared goal, clinicians prioritized avoidance of side effects while patients ranked improved sleep, less fatigue, and improved mood. Tools to facilitate goal elicitation may help improve communication of what matters most to RA patients.

Table. Patient and clinician agreement on treatment goals for rheumatoid arthritis

Goal, N=171 pairs	Selected only by Patient, N (%)	Selected only by Clinician, N (%)	Not selected, N (%)	Selected by both, N (%) ¹
Have less pain	11 (6.4)	17 (9.9)	3 (1.8)	140 (81.9)
Have fewer problems doing daily activities	6 (3.5)	54 (31.6)	6 (3.5)	105 (61.4)
Be able to work outside the home	31 (18.1)	35 (20.5)	93 (54.4)	12 (7.0)
Avoid side effects from medicine	23 (13.5)	69 (40.4)	36 (21.1)	43 (25.1)
Improve sleep	32 (18.7)	6 (3.5)	130 (76.0)	3 (1.8)
Feel less tired	46 (26.9)	10 (5.8)	102 (59.6)	13 (7.6)
Improve mood	21 (12.3)	-	150 (87.7)	-
Not affect ability to have children	7 (4.1)	-	163 (95.3)	1 (0.6)
Other	15 (8.8)	5 (2.9)	151 (88.3)	-

¹One of three goals selected for both patient and clinician

Disclosure: J. Barton, None; S. Markwardt, None; A. Schue, None; S. Saha, None; E. H. Yelin, None.

Abstract Number: 1926

Effects of Social Networking on Chronic Disease Management in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes I: Beliefs and Behaviors

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: We evaluated a social networking intervention to help patients with rheumatoid arthritis become active partners in their own care. We developed a closed independent community in Facebook® for patients with rheumatoid arthritis. Three patient advocates with expertise in health communication moderated the Facebook® community.

Methods: In a randomized controlled trial we compared the use of Facebook® as an educational platform providing evidence-based health information and social networking to a static non-participatory website offering the same educational materials as Facebook but without the interactive components of social networking (intervention = Facebook® + website and control = website alone). Inclusion criteria were: (i) adults diagnosed with rheumatoid arthritis by a rheumatologist, and ongoing or prior treatment with traditional disease-modifying antirheumatic drugs or biologic agents, (ii) able to communicate in English; (iii) internet access and a personal email account; (iv) current use of internet-based social media platforms (Facebook® or similar); and (v) disease duration ≤ 10 years. Our primary outcome measures were patients’ disease knowledge, self-efficacy and empowerment. Follow-up assessment were conducted at 3 and 6 months.

Repeated measures ANOVA was used to compare the primary outcome measures between two study groups at 3-month and 6-month follow-up. All analyses were done on an intention-to-treat basis.

Results: 210 patients agreed to participate and completed the baseline questionnaire. After completion of the baseline questionnaire, participants were randomly assigned at 1:1 ratio; 105 were randomized to the intervention arm and 105 were randomized to the control arm. No statistically significant differences between the two study groups were detected at baseline. At the 3-month assessment, 90 patients from the intervention arm and 93 patients from the control arm completed the survey (87% response rate). At the 6-month assessment, 89 patients from the intervention arm and 89 patients from the control arm completed the survey (85% response rate). No statistically significant differences were observed between groups for patient knowledge, self-efficacy, or empowerment at 3 or 6 months. However, the intervention group reported more satisfaction with their perceived peer support compared with the control group at 3 and 6 months. This was reflected in the various subscales including perceived availability of peer support (i.e., peer supporter being present and ready to help), perceived assistance in daily management (i.e., peer supporter assistance in the actions needed to take every day to control the disease and protect the patients' health), social & emotional support (i.e., peer supporter addressing the emotional aspects of living with rheumatoid arthritis), and linkage to clinical care (i.e., peer supporter helping to make effective use of health services).

Conclusion: The perceived receipt of direct and nondirective support was higher in patients using Facebook®, but this was not translated into greater knowledge, self-efficacy or empowerment.

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Abstract Number: 1927

Do Remission and Low Disease Activity State Go Hand in Hand with Patient's Perception of Disease Burden and Quality of Life in Systemic Lupus Erythematosus?

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes I: Beliefs and Behaviors

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Disease remission is the ideal treatment target in SLE; when remission cannot be reached, the lowest possible disease activity state should be targeted. Available definitions of remission and low disease activity state (LLDAS) are based on physician's driven clinical data. Little data exist on the effect of remission and LLDAS on the patients' perception of the disease. Our purpose was to evaluate the relationship between the available definitions of remission and LLDAS and the patient's perspective on quality of life (QOL) and disease burden.

Methods: This is a cross-sectional analysis from our database that enrolls adult patients who fulfilled the 1997 ACR criteria for SLE. Disease activity was evaluated with the SELENA-SLEDAI while organ damage with the SLICC/DI. The remission status at last clinic visits was defined according to the European consensus criteria (DORIS), the LLDAS was defined according to the Asian Pacific Lupus Consortium definition. The QOL was assessed by the validated Italian version of the Short-Form-36 (SF36), the disease burden was evaluated by Italian version of the Lupus Impact tracker (LIT) and fatigue by the FACIT score. Patients included in this analysis are categorized according to the categories: clinical remission off treatment (ROFT), LLDAS, active disease.

Results: A total of 194 patients were included in this analysis (96.3% Caucasian, 92.2% female, mean age 45.5±13.4 years, mean disease duration 14.4 ±10.1 years); disease activity was globally low (median SLEDAI: 2, IQR 0-4); 122 patients (62.9%) were on LLDAS, 33 (17.01%) were on ROFT, 41 (21.13%) had some degree of disease activity. SF-36 and LIT scores according to the three groups are reported in table. Patients in remission off treatment have lower disease burden as compared to those with active disease status but the difference didn't reach statistical significance (p=0.3). Though LIT showed lower value also among LLDAS than active disease patients, this was not statistically significant (p=0.8). Fatigue was significantly lower in the remission group with respect to the active (p=0.01) while no differences were observed in SF-36 scores.

	ROFT	LLDAS	active	ROFT vs active	LLDAS vs active
Age (mean \pm SD)	47 \pm 13	46 \pm 12	42 \pm 15.7	p= n.s.	p= n.s.
SLEDAI median (IQR)	2 (0-2)	2 (0-2)	6 (4-8)	p =0.01	p =0.02
SLICC/DI median (IQR)	0.93	1.25 \pm 1.8	1.51 \pm 2.2	p=n.s.	p=n.s.
LIT median (IQR)	21.2 (6.25-35)	20 (7.5-45)	32.5 (7.5-40)	p= n.s.	p=n.s.
PCS median (IQR)	60 (56-68)	63 (56-78)	63 (57-72)	p=n.s.	p=n.s.
MCS median (IQR)	62 (55-67)	64(56-77.5)	61.5 (57-70)	p=n.s.	p=n.s.
FACIT median (IQR))	43 (39-46)	40 (32-46)	39 (30-45)	p=0.01	p=n.s.

Conclusion: in this cohort, PROs seem to be moderately influenced by the disease status as defined according to the clinical definition of remission and LLDAS. The small sample size, the slightly higher damage in the active group, and none to mild variation in disease activity in the three groups could have appeared the association. On the other hand, these results underly the fact that disease burden and quality of life are related to several multifaceted aspects of the disease that are not accurately captured by physician driven instruments. Further prospective studies on larger cohorts are necessary to confirm these data.

Disclosure: C. Tani, None; E. Elefante, None; C. Stagnaro, None; V. Signorini, None; L. Carli, None; M. Jolly, LIT, 4; M. Mosca, None.

Abstract Number: 1928

Patient-Physician Communication about Medication Costs in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes I: Beliefs and Behaviors

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Patients often have to pay for prescription medications out-of-pocket and cost-related non adherence is a recognized problem. The treatment of rheumatoid arthritis is associated with high out-of-pocket cost. Research has shown that while patients may have a desire to discuss medication costs with health care professionals (HCPs) these discussions often do not take place. The objective of this study was to examine the frequency with which out-of-pocket medication costs are discussed and to examine predictors of these discussions between rheumatologists and patients with rheumatoid arthritis (RA) in Canada.

Methods: A cross-sectional online survey was distributed to patients with RA and rheumatologists in Canada. Participant characteristics and medication status were assessed and participants were asked to rate the importance of discussing out-of-pocket medication costs, as well as how often medication costs are discussed between physician and patients. Stepwise, multivariable logistic regression was used to explore the predictors of (1) patients discussing costs with their rheumatologist and, (2) perceived importance of discussing medication cost for patients. Potential predictors included age, sex, income, education, use of biologics, and attitude to shared decision making.

Results: The sample contained 78 patients and 64 rheumatologists. There were no differences in the perceived importance of discussing medication costs between patients and physicians with over 65% of physicians and patients rating it as quite or very important. When asked whether they discuss medication cost during health care encounters, 22% of patients reported never talking about medication cost, whereas no physicians reported never discussing costs with their patients. Among patients who reported never talking about medication cost with their physician, 65% (n= 17) were currently taking and 6% (n=1) had taken a biologic agent in the past. There were no significant differences across responses to having talked about medication cost by income, education, age, or province. In multivariable logistic regression models, the odds of discussing cost among patients who perceived discussing cost with their HCP as 'very important' were 4.5 (p = 0.043) higher than patients who perceived discussing cost as 'neither important nor unimportant' or 'not important'. No other

characteristics were found to be significant predictors of discussing medication cost. No patient characteristics were statistically significant predictors of perceived importance of discussing cost.

Conclusion: Out-of-pocket costs have been shown to affect medication adherence; consequently patients and HCPs should discuss costs in the treatment decision making process. Our findings suggest this does not always happen. Furthermore, medication cost was more likely to be discussed by patients who perceived it as 'very important.' This finding suggests that the onus to initiate discussions about cost is currently on patients, not HCPs). In the absence of any clear predictors of the perceived importance of discussing costs to patients, treatment costs and ability to pay should be discussed routinely, as an important component of shared decision making.

Disclosure: K. J. Kaal, None; N. Bansback, None; A. Anis, None; M. Harrison, None.

Abstract Number: 1929

The Neutrophil-Lymphocyte Ratio in Newly Diagnosed Rheumatoid Arthritis and Its Ability to Predict Treatment Failure

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes III: Diagnosis and Prognosis II

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: To assess whether the neutrophil-lymphocyte ratio (NLR) can predict those who require disease modifying therapy escalation and hence progression in rheumatoid arthritis (RA).

Methods: Patients with newly diagnosed RA were recruited from the Early Arthritis Clinic at the Royal Adelaide Hospital. Those who were on glucocorticoids at the time of review were excluded. All patients were commenced on methotrexate, sulphasalazine and hydroxychloroquine and were reviewed at regular intervals, and Disease Modifying Anti-Rheumatic Drug (DMARD) therapy was adjusted according to a set algorithm. The NLR, platelet-lymphocyte ratio (PLR) and other markers of disease activity such as the ESR, CRP and DAS 28 were collected as well as current therapy. The primary outcome measure was failure of triple DMARD therapy.

Results: Two-hundred and twenty-two patients met inclusion criteria. The mean age was 54.2 ± 15.4 years with a mean duration of polyarthritis of 22.3 ± 25.0 weeks prior to their first review. Forty-five (20%) of patients had failed triple therapy by one year. The mean NLR was significantly higher in those who failed triple therapy when compared to those that did not (3.7 ± 2.8 vs 2.9 ± 1.5 ; $p=0.02$), however, the PLR was not significantly different (184.1 ± 78.6 vs 171.4 ± 84.5 ; $p=0.41$). The NLR was an independent predictor of treatment failure (OR 2.65, CI 1.23-5.72, $p=0.01$) whilst the PLR, ESR, CRP and DAS-28 ESR were not (p -values 0.41, 0.13, 0.17 and 0.28 respectively).

Conclusion: The NLR is significantly increased in those with treatment failure in RA and outperforms more conventional markers of disease activity. The NLR may be a cheap, objective and reproducible prognostic marker, however, further prospective studies are required to identify the role of the NLR in RA disease management algorithms.

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Abstract Number: 1930

Histologic and Transcriptional Evidence of Subclinical Synovial Inflammation in Rheumatoid Arthritis Patients in Clinical Remission

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SESSION INFORMATION

Session Date: Monday, October 22, 2018
Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes III: Diagnosis and Prognosis II
Session Type: ACR Concurrent Abstract Session
Session Time: 4:30 PM-6:00 PM

Background/Purpose: Rheumatoid Arthritis (RA) patients in clinical remission may still develop structural damage that has been attributed to ongoing synovial inflammation, sometimes only detectable by ultrasound or MRI. Here, we assess the clinical features, histologic characteristics, and transcriptional profiles of synovium from RA patients in clinical remission undergoing arthroplasty.

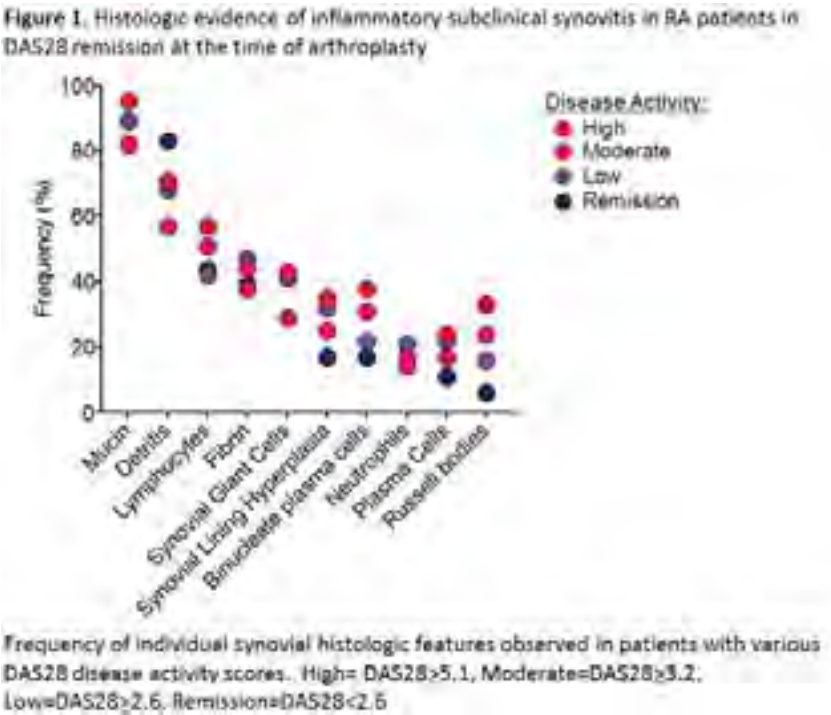


Table 1. Baseline Characteristics	Remission (DAS28<2.6) n=22, 15%	Low (DAS28<3.2) n=21, 15%	Moderate (DAS28<5.1) n=77, 53%	High (DAS28>5.1) n=24, 17%
Age at baseline (Years)	62.33±12.1	65.54±10.52	62.87±11.57	62.2±10.28
Sex: Female	73%	76%	91%	88%
Diagnosis Duration (Years)	14.6 [6.2, 23.0]	20.8 [7.5, 35.8]	10.95 [2.9, 19.0]	9.0 [0.0, 19.4]
BMI (kg/m ²)	26.0 [22.3, 49.0]	25 [21.8, 46.0]	28.8 [23.8, 52.6]	30.1 [24.3, 56.4]
Anti-CCP (Positive)	68%	62%	61%	75%
RF (Positive)	50%	52%	55%	55%
DAS28-ESR	1.94±0.34	2.80±0.17	4.09±0.55	5.78±0.67
Number of Tender Joints	0.5±1.01	0.76±1.51	1.32±3.56	10.67±6.99
Number of Swollen Joints	2.9±3.62	3.48±4.09	6.55±7.84	12.17±9.83
ESR (mm/hr)	5.4±2.91	15.14±12.59	23.03±17.24	30.46±21.56
CRP (mg/dL)	0.72±0.82	1.33±1.39	2.25±3.47	2.09±2.02
Baseline CDAI	12.14±3.46	11.41±6.31	18.82±6.89	37.18±11.88
RADAI Sum	7.78±5.17	8.66±5.61	10.7±8.36	15.54±9.45
RADAI Sum, adjusted	5.76±5.39	4.25±5.48	8.9±8.32	17.96±9.98
DMARD	68%	88%	49%	57%
Non-methotrexate DMARD	18%	18%	27%	10%
Biologics	50%	52%	52%	70%
Steroid	45%	38%	43%	26%

Methods: We studied 144 patients with long-standing RA (median disease duration of 12.5 years) undergoing total hip or knee arthroplasty between 2013 and 2017, and met classification criteria for RA using ACR/EULAR 2010 or 1987 criteria. Baseline data collected included age, sex, comorbidities, duration of disease, and medications. Disease activity was divided into remission (DAS 28 ESR<2.6), low disease activity (≥ 2.6 -3.2), moderate disease activity (≥ 3.2 -5.1), and high disease activity (≥ 5.1) [12]. Synovium was assessed by histologic analysis and RNA-Seq. Statistical analysis was descriptive. Continuous characteristics are summarized by mean \pm standard deviation or median [interquartile range], as appropriate. Categorical variables were compared using Fisher's exact tests.

Results: Of 144 participants, 15% (n=22) met DAS criteria for remission, only 1 was drug free. 17%, 53%, and 15% had high, moderate, and low disease activity at baseline as measured by DAS 28 (TABLE 1). Of the patients in DAS remission: (i) histologic analysis of synovium demonstrated that 45% had moderate to marked lymphocytic infiltrates, 17% had greater than 10% plasma cells, 39% had fibrin deposition, 6% had Russell bodies, 17% had binucleate plasma cells, 17% had neutrophils, and 29% had synovial multinucleated giant cells, all features characteristic of the high inflammatory RA subtype (Figure 1), (ii) RNA-Seq analysis demonstrated that 67% had moderate levels of synovial inflammatory gene expression, and (iii) clinical assessment demonstrated that 36% of all patients in remission prior to surgery, met DAS 28 criteria for flare, 6 weeks after joint replacement.

Conclusion: Remission is uncommon in RA patients with long-standing disease undergoing arthroplasty. Of those in remission, synovium may be characterized by ongoing inflammation, and they remain at risk for flares. The notion that RA burns out and that patients undergoing arthroplasty have inactive disease should be re-evaluated.

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Abstract Number: 1931

Abundance of Plasma Microbial Small RNAs Are Predictive of Improvement in Disease Activity after DMARD Initiation for Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes III: Diagnosis and Prognosis II

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Session Time: 4:30 PM-6:00 PM

Background/Purpose: Small RNAs (sRNAs) are important regulators of biological processes and are potential biomarkers of disease and drug response. We previously found that microbial sRNAs are abundant in human plasma, altered in patients with rheumatoid arthritis (RA) compared to control subjects, and inversely associated with disease activity in RA. The aim of this study was to determine if pre-treatment plasma levels of microbial sRNAs: 1. Predict clinical response to initiation of disease-modifying antirheumatic drugs (DMARD); or 2. Change 6 months after DMARD initiation.

Methods: Plasma samples and clinical data were provided from a longitudinal multi-center study (Treatment Efficacy and Toxicity in Rheumatoid Arthritis Database and Repository). RNA was extracted from plasma of 70 patients with RA before and 6 months after first-time starts of: methotrexate (n=24), adalimumab (n=23), or tocilizumab (n=23). Sequencing was performed using Illumina Next Seq500. Using TIGER, an in-house sRNA analysis pipeline, high quality reads were first aligned to the human genome allowing for 1 mismatch. Remaining reads were aligned to 57 genomes of bacteria previously found to be altered in RA, representative genomes of 207 human microbiome bacteria, 8 fungi, and 167 environmental bacteria. Differential expression of sRNAs and microbial genome counts were performed using DESeq2 with 5% false discovery rate. Benjamini and Hochberg method was used for multiple test correction. Clinical improvement was defined as a decrease in DAS28 score from pre-treatment to 6 months after starting DMARD treatment. Spearman correlation was used to correlate continuous variables.

Results: Baseline total microbial sRNAs were ~3-fold higher (P=0.009) (Figure) among patients whose DAS28 improved after starting a DMARD. Moreover, baseline total microbial sRNA read counts had an AUC=0.75 (P=0.009) for predicting improvement with therapy. Microbial sRNAs (total abundance, genome counts and individual sRNAs) did not significantly

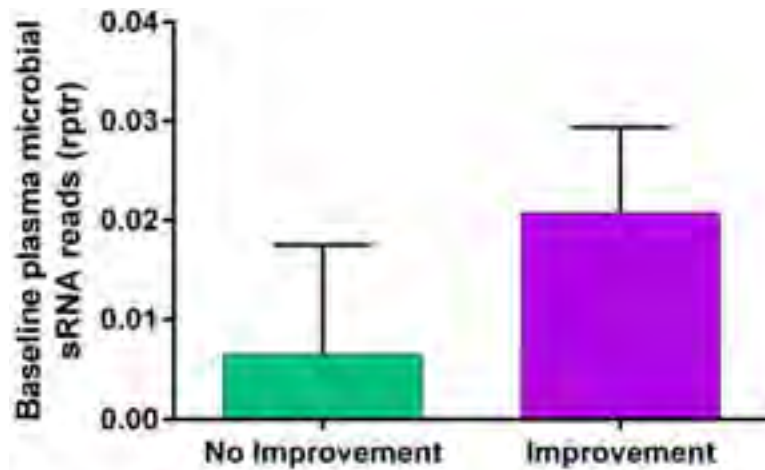


Figure. The abundance of pre-treatment plasma microbial sRNAs was approximately 3-fold higher among those whose DAS28 score improved with initiation of a new DMARD ($P=0.009$). Data are presented as geometric mean and 95% confidence interval.

change after DMARD initiation. On a cross-sectional basis a greater abundance of total microbial RNA reads were associated with lower tender joint count ($P<0.05$), which validated prior observations.

Conclusion: The abundance of plasma microbial sRNAs was predictive of improvement in DAS28 after first-time initiation of a DMARD. Initiation of these drugs did not significantly change the abundance of plasma microbial RNA. Future studies will determine if microbial sRNAs modify host immune responses in RA.

Disclosure: M. J. Ormseth, None; Q. Sheng, None; S. Zhao, None; J. F. Solus, None; Q. Wu, None; R. Allen, None; Y. Guo, None; F. Ye, None; M. Ramirez, None; K. Vickers, None; S. L. Bridges Jr., None; J. R. Curtis, None; C. M. Stein, None.

Abstract Number: 1932

Complications Following Total Knee Arthroplasty in Inflammatory Versus Osteoarthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes III: Diagnosis and Prognosis II

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: TKA is commonly performed in patients with a history of inflammatory arthritis. These patients are likely at higher risk of complications, from both the underlying disease and immunosuppressive medications. The purpose of this study was to perform a population-based comparison of the risk of postoperative complications between patients with inflammatory arthritis and osteoarthritis.

Methods: A national private insurance database was used to select patients undergoing unilateral primary TKA. Patients were categorized to the inflammatory cohort if they had an ICD diagnosis of inflammatory arthritis as well as treatment with a DMARD, biologic, or SLE-specific medication within the year prior to surgery. Patients with no diagnosis of inflammatory arthritis were assigned to osteoarthritis. Postoperative complications were identified using Reportable CMS Complication Measures. Risk of each complication was compared between cohorts using multivariate logistic regression controlling for age, gender, length of stay, comorbidities, and use of corticosteroids within 3 months prior to TKA.

Table 1: Characteristics of the Total Knee Replacement Cohort

	Not Inflammatory	%	Inflammatory w/Meds (1 year)	%
Number by ICD Only	n/a		9478	6.71
Number	164488		8667	2.28
DMARDs	n/a		1830	93.47
Biologics	n/a		436	18.25
SLE Specific Medications	n/a		799	6.42
Steroids within 3 months	8278	5.15	4128	36.78
Age 49 and under	2787	1.71	130	4.24
Age 50-59	13540	8.27	553	19.07
Age 60-69	69726	34.78	1223	39.88
Age 70-79	66191	43.78	856	31.73
Age 80-89	18899	10.81	136	6.08
Age 90 and over	7140	1.89	16	0.67
Gender (F)	83705	62.51	2487	61.88
Gender (M)	50288	37.49	580	18.91
LOS 0	7116	5.51	139	4.53
LOS 1	9772	9.04	120	3.81
LOS 2	38346	31.08	592	19.30
LOS 3	59925	44.56	1406	45.91
LOS 4	17125	12.73	446	14.18
LOS ≥4	16166	11.28	373	12.16
Congestive Heart Failure	4898	3.64	98	4.20
Cardiac Arrhythmias	14383	10.68	272	8.87
Heart Valvular Disease	4694	3.49	108	3.55
Pulmonary Circulation Disorders	1127	0.84	41	1.08
Peripheral Vascular Disorders	4879	3.81	79	2.58
Hypertension	87978	62.66	1794	58.19
Paralysis	241	0.18	4	<0.48
Other Neurologic Disorders	2379	1.77	59	1.91
Chronic Pulmonary Disease	20286	15.08	577	18.81
Diabetes	14867	25.83	437	30.13
Hypothyroidism	13861	16.37	603	31.16
Renal Failure	4061	3.01	79	2.58
Liver Disease	1706	0.82	93	1.06
Peptic Ulcer Disease	1387	1.03	45	1.87
HIV/AIDS	56	0.03	2	<0.36
Lymphoma	380	0.28	8	<0.36
Metastatic Cancer	78	0.06	3	<0.36
Solid Tumors without Metastasis	937	1.97	163	5.28
Rheumatoid Arthritis/Collagen Vascular Diseases	0	0.001	863	100.00
Coagulopathy	3079	1.79	76	2.66
Obesity	26125	19.50	486	18.17
Weight loss	353	0.25	9	<0.36
Fluid and Electrolyte Disorders	12664	9.27	320	10.43
Blood loss Anemia	7213	1.85	46	1.57
Deficiency Anemias	17966	13.86	520	18.95
Alcohol Abuse	838	0.62	6	<0.48
Drug Abuse	567	0.42	20	0.95
Psychoses	2773	1.89	75	2.95
Depressive	11641	11.56	448	14.61
Smoking	8637	5.98	273	7.08

Table 2: Complications (ICM Records, Age/Gender/Comorbidity/Steroid Controlled)

	Not Inflammatory		Inflammatory		OR	95% CI	p-value
	n	%	n	%			
DVT (30d)	4658	2.57	87	2.89	1.03	(0.89, 1.49)	0.78
Transfusion RBCs (30d)	15037	11.45	309	16.30	1.39	(1.25, 1.55)	0.00 *
Myocardial Infarction (7d)	563	0.42	10	<0.36	1.04	(0.89, 1.92)	0.92
Pneumonia (7d)	1882	1.34	18	1.28	0.81	(0.56, 1.13)	0.28
Sepsis (7d)	680	0.45	17	0.55	1.14	(0.68, 1.84)	0.60
Surgical Site Bleeding (30d)	64	0.05	7	<0.36	1.55	(0.23, 5.29)	0.55
Pulmonary Embolism (30d)	1750	1.31	41	1.34	0.85	(0.59, 1.18)	0.38
Mechanical Complications (90d)	2547	1.67	63	2.03	1.07	(0.81, 1.38)	0.63
Infection (30d)	1193	0.82	44	1.43	1.64	(1.17, 2.39)	0.00 *
Readmission (30d)	11584	8.62	385	12.55	1.46	(1.30, 1.63)	0.00 *

Results: 137,550 patients were included; 2.23% met criteria for inflammatory arthritis as described above. Independent of age, gender, LOS, comorbidities, and recent steroid use, inflammatory patients were found to have higher risk of transfusion (OR 1.39, $p < 0.01$), infection (OR 1.64, $p < 0.01$), and readmission (OR 1.46, $p < 0.01$). There were no differences in risk of VTE, medical, or mechanical complications.

Conclusion: Independent of other comorbidities, patients with inflammatory arthritis are at high risk of transfusion, infection, and readmission. Treatment of these patients is likely more costly and efforts should be made to optimize their health and treatment medications prior to TKA to minimize their complication risk. Additionally, these results have important implications for evolving bundled payment models. Hospitals should receive commensurate resources to maintain access to TKA for patients with inflammatory arthritis that are prone to higher resource utilization.

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Abstract Number: 1933

Histological Features and Tissue-Macrophage Phenotype of Synovial Biopsies Identify RA Patients in Sustained Remission at Risk of Disease Flare after Treatment Tapering or Discontinuation

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes III: Diagnosis and Prognosis II

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Flares of immune-mediated inflammatory diseases, as Rheumatoid Arthritis (RA) occur unpredictably representing a major burden for patients and clinicians. We aimed to dissect the synovial tissue (ST) features of RA in sustained remission that could predict disease flare once biological treatment is tapered or discontinued.

Methods: 48 RA patients in sustained clinical (DAS<1.6 for at least 9 months) and ultrasound (US) remission (Power Doppler negative) under biological-Disease Modifying Anti-Rheumatic Drug (bDMARD) plus Methotrexate underwent ultrasound guided ST biopsy. ST CD68⁺, CD21⁺, CD3⁺, CD20⁺, CD31⁺ cells and collagen were assessed using immunohistochemistry and Goldner's Trichrome staining, respectively. Some ST samples were digested with liberase and ST macrophages were sorted by FACS-ARIAIII and phenotyped. This included evaluation of the number of CD206 positive and negative anti-inflammatory and pro-inflammatory macrophages, respectively. After study entry, RA were randomly assigned to tapering/discontinuation group (TAP/DISC: tapering for 6 months first and discontinuing bDMARD afterwards) or to the group maintaining the same therapeutic scheme (CONT). Each RA was followed every 3 months to assess the occurrence of disease flare after treatment change for at least 6 months.

Results: At study entry, 29 RA were assigned to TAP/DISC group and 19 to CONT group, respectively. Among the TAP/DISC group, 6(20.7%) and 8/14(57.1%) experienced disease flare after bDMARD tapering only and tapering/discontinuation respectively, whereas 2 (10.5%) of RA of the CONT group experienced disease flare during the follow-up (p=0.31 for RA tapering only and p=0.001 for RA discontinuing b-DMARD). In particular, RA of the TAP/DISC group who experienced disease flare after bDMARD modifications showed, at study entry, higher IHC scores for ST sublining CD68⁺ cells (p=0.02), higher CD31⁺ vessels count (p=0.01) and lower collagen deposition (p=0.04 and p=0.01 in lining and sublining, respectively) compared to RA not experiencing flare. Logistic regression analysis revealed that CD31⁺ vessels count ≥ 12.8 at the time of sustained remission achievement [OR (95%ICs):5.7(1.0-32.1)] and TAP/DISC strategy [OR (95% ICs):5.4(1.3-22.7)] are independent factors associated to disease flare in RA patients in remission. In addition, regardless of the treatment modifications, synovial tissue of RA who experienced disease flare during the follow-up contained higher number of CD206^{neg} pro-inflammatory macrophage subpopulation at the time of sustained remission achievement, as compared to RA who maintained disease remission that showed mostly CD206^{pos} subpopulation (p=0.03).

Conclusion: Disease relapse is a common event in RA patients in sustained remission after b-DMARD discontinuation. The analysis of composition and phenotypes of synovial tissue cells identifies, at the time of remission achievement, RA patients at higher risk of disease flare after treatment discontinuation.

Disclosure: S. Alivernini, None; B. Tolusso, None; A. Elmesmari, None; L. Bui, None; G. Peluso, None; M. R. Gigante, None; S. Finlay, None; L. Petricca, None; C. Di Mario, None; S. Perniola, None; A. L. Fedele, None; F. Federico, None; I. B. McInnes, None; G. Ferraccioli, None; M. Kurowska-Stolarska, None; E. Gremese, None.

microRNA Targeting IL-33 Gene As Biomarker to Predict Subclinical Atherosclerosis in Patients with Early Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes III: Diagnosis and Prognosis II

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Session Time: 4:30 PM-6:00 PM

Background/Purpose: Patients with RA had increased risk of cardiovascular disease (CVD). Interleukin33 (IL-33) plays an important role in pathogenesis of RA and development of CVD. Plasma IL-33 level was undetectable in most subjects that limits its utility as CVD biomarker. MicroRNAs (miRNAs) function as post transcription regulators of gene expression. This study aimed to ascertain if dysregulated miRNAs targeting *IL-33* gene expression were associated with subclinical atherosclerosis in early RA patients

Methods: 76 ERA patients were recruited in this 1 year study. Potential miRNAs binding to 3'UTR of *IL-33* gene were predicted by miRanda¹. 10 miRNAs with highest possibility targeting functional sites of *IL-33* gene were quantified in cell free plasma samples by real time PCR. Carotid IMT and plaque were identified using high-resolution B mode ultrasound annually. Carotid plaque (CP+) was defined as a localized thickening >1.2 mm. Plaque progression (PP+) was defined as increased region harboring plaque

Results: miRNA were detected in >80% of subjects. CP were identified in 26/76 (34%) subjects (CP+ group) at baseline. The CP+ group were predominantly male, older, with a higher CRP level and a prevalence of multiple CV risk factors. Plasma level of miR-186-5p was significantly higher in the CP+ (Fig 1). Using multivariate logistic regression, miRNA-186-5p was independent predictor for presence of CP (Table 1). ROC showed that increased miRNA-186-5p expression level could discriminate patients with and without CP [Area under the ROC (AUC):0.658, $p=0.024$]. 73 subject were followed until year 1. 16/73 (22%) subject had plaque progression. Subjects in the PP+ group were older, had higher prevalence of multiple CV risk factors, with lower pain and patient global score at baseline. A higher proportion of them were on conventional synthetic DMARDs. miR-382-5p expression level was significantly higher in subjects in PP+ group (Fig 1). Using multivariate logistic regression, miRNA-382-5p level was an independent predictor for plaque progression (Table 1). ROC analysis showed that miR-382-5p level could discriminate patients with and without PP (AUC was 0.66, $p=0.048$)

Conclusion: Increased expression of miR-186-5p and miR-382-5p was independent predictor for presence & progression of subclinical atherosclerosis. This suggest that circulating miRNA may serve as novel biomarkers for CV risk stratification in ERA patients

Acknowledgement to Hong Kong Society of Rheumatology Project Fund for supporting this project

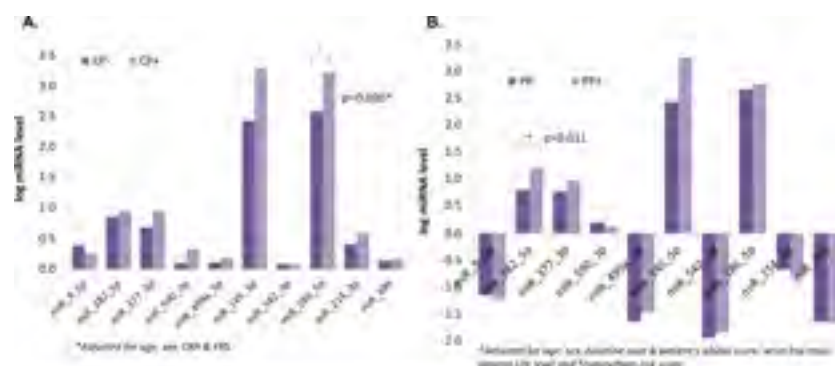


Figure1. miRNA in subject with presence of carotid plaque (A) and progression of carotid plaque (B).

Table 1 Multivariate analysis on presence and progression of carotid plaque

	OR	95%CI	<i>p</i>
<i>Model for determining presence of carotid plaque¹</i>			
Framingham Risk Score, baseline	1.113	1.033-1.200	0.005
miR_186_5p	1.919	1.096-3.361	0.023
<i>Model for determining progression of carotid plaque²</i>			
VAS Pain (0-10cm), baseline	0.513	0.318-0.827	0.006
Diastolic Blood Pressure, mmHg, baseline	1.093	1.010-1.183	0.028
Framingham Risk Score, baseline	1.188	1.057-1.336	0.004
miR_382_5p	2.534	1.079-5.952	0.033

1 Adjusted for age, gender, baseline CRP and Framingham risk score

2 Adjusted for age, gender, baseline VAS pain, diastolic blood pressure, Framingham risk score and use of csDMARDs.; CRP:C-reactive protein; csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; bDMARDs: biologic disease modifying anti-rheumatic drugs.

Reference

¹www.microRNA.org

Disclosure: I. T. Cheng, None; Q. Shang, None; J. Shen, None; M. Li, None; Q. Mak, None; K. Y. Kwok, None; I. C. Yim, None; E. K. M. Li, None; P. Wong, None; R. M. Yip, None; S. H. Pang, None; L. S. Tam, None.

Abstract Number: 1935

Multiple Dose Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ASP5094, an Anti-Alpha9 Integrin Monoclonal Antibody, in Patients with Rheumatoid Arthritis on Methotrexate

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments III: New Compounds and Biosimilars

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Joint synovium is the main tissue involved in rheumatoid arthritis (RA) lesions. Alpha9 integrin is expressed by synovial tissue lining cells and has been identified as a putative key molecule in the development and exacerbation of RA (Kanayama et al. 2009). ASP5094 is a recombinant humanized anti-human alpha9 integrin IgG1 monoclonal antibody under development for the treatment of RA. A first-in-human study in healthy subjects has demonstrated that single intravenous (IV) ASP5094 doses up to 10 mg/kg had an acceptable safety profile and were well tolerated. The purpose of this study was to establish the safety/tolerability, pharmacokinetics (PK), and pharmacodynamics of ASP5094 in patients with RA on methotrexate (MTX).

Methods: Patients (aged 18–65 years) with RA on a stable regimen (10–25 mg/week) of MTX were eligible for this phase 1, randomized, placebo-controlled, multiple ascending-dose study. Eligible patients were assigned to one of three sequential cohorts to receive increasing IV doses of ASP5094 (1, 3, 10 mg/kg) or placebo every 4 weeks for a total of three doses (Day 1, 29, and 57). A total of 10 patients were assigned to each cohort and randomized 4:1 (ASP5094, n=8; placebo, n=2). The primary objectives were to evaluate the safety, tolerability, and PK of ASP5094 in patients with RA on MTX. Exploratory objectives included the pharmacodynamics of ASP5094, assessed by the alpha9 integrin receptor occupancy rate in neutrophils as a surrogate for alpha9 integrin binding in joints at the level of synoviocytes. Formation of anti-ASP5094 antibodies was assayed using a validated method.

Results: At all dose levels, ASP5094 was well tolerated. No difference was observed between treatment groups in either the nature or frequency of treatment-emergent adverse events (TEAEs) or TEAEs considered related to ASP5094, and no dose-response relationship was observed. Two patients permanently discontinued the study due to possible treatment-related AEs: one patient treated with ASP5094 (1 mg/kg) discontinued due to a mild, intermittent tremor. The other patient, treated with placebo, discontinued due to a mild second-degree atrioventricular block, which resolved the same day. Pharmacokinetic steady state was not reached after three administrations of ASP5094 (regardless of dose level) because of slow elimination. ASP5094 exhibited nonlinear, target-mediated drug disposition pharmacokinetics. A trend of dose-dependent increase in receptor occupancy was observed. Median receptor occupancy was >90% for all ASP5094 doses on Day 1 and was maintained at >80% for approximately 2 weeks after each dose within 1 mg/kg dose cohort. For doses of 3 and 10 mg/kg, median receptor occupancy was maintained by >80% throughout the treatment period until Day 85 and Day 141, respectively. No patient had confirmed positive titers for anti-ASP5094 antibodies.

Conclusion: In this study, multiple IV doses of ASP5094 had an acceptable safety profile and were well tolerated in patients with RA on stable doses of MTX. ASP5094 exhibited a nonlinear PK disposition and demonstrated dose-dependent, high, and prolonged neutrophil alpha9 integrin receptor occupancy rates.

Disclosure: J. Huang, Astellas Pharma US, Inc., 3; T. Wojtkowski, Astellas Pharma US, Inc., 3; P. Blahunka, Astellas Pharma US, Inc., 3; R. Smulders, Astellas Pharma Europe BV, 3; C. Lademacher, Astellas Pharma US, Inc., 3.

Abstract Number: 1936

A Randomized, Double-Blind, Parallel-Group, Multicenter Study to Compare the Efficacy, Safety and Immunogenicity of a Proposed Adalimumab Biosimilar (GP2017) with Reference Adalimumab in Patients with Moderate-to-Severe Active Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments III: New Compounds and Biosimilars

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: GP2017, a proposed adalimumab biosimilar, matched reference adalimumab (refADL) in preclinical and pharmacokinetics studies.^{1,2} The confirmatory efficacy and safety study in patients with plaque-type psoriasis demonstrated equivalent efficacy and similar safety of GP2017 and refADL.³ This Phase III study compares efficacy and safety of GP2017 and refADL in patients with moderate-to-severe rheumatoid arthritis (RA) with inadequate response to disease modifying anti-rheumatic drugs, including methotrexate (NCT02744755). The study was designed to demonstrate similar efficacy of GP2017 and refADL over 24 weeks of treatment, and to evaluate long-term safety, immunogenicity and efficacy of GP2017 up to Week (Wk) 48. Data from randomization to Wk 24 are presented.

Methods: Eligible patients were randomized 1:1 to receive 40 mg subcutaneous GP2017 or refADL every other week from Wk 0 to Wk 22. The primary endpoint was change in Disease Activity Score-28 including high-sensitivity C-reactive protein (DAS28-CRP) from baseline at Wk 12. Therapeutic equivalence was confirmed if the 95% confidence intervals (CIs) for the difference in DAS28-CRP change from baseline (BL) at Wk 12 between GP2017 and refADL were completely contained within the predefined equivalence margin of [-0.6,0.6]. Secondary endpoints included time-weighted averaged change in DAS28-CRP from BL to Wk 24, safety and immunogenicity.

Results: In total, 353 patients were randomized to receive GP2017 (n=177) or refADL (n=176). Using a mixed model repeated measures method, mean change from BL at Wk 12 in DAS28-CRP was -2.16 for GP2017 (n=140) and -2.18 for refADL (n=144) ($\Delta=0.02$; 95% CI: -0.24,0.27). Time-weighted averaged change from BL in DAS28-CRP until Wk 24 was -1.85 for GP2017 (n=127) and -1.93 for refADL (n=138) ($\Delta=0.08$; 95% CI: -0.11,0.27). Treatment-emergent adverse events (TEAEs) occurred in 61.6% of patients in GP2017 group and 60.2% of patients in refADL group (Table). Most TEAEs were mild or moderate in severity. Infections and infestations were most common TEAEs, of those mild viral upper respiratory tract infections were reported by 14.7% and 9.1% of patients in GP2017 and refADL groups, respectively. Injection site reactions occurred in 7 (4.0%) and 11 (6.3%) patients in GP2017 and refADL groups. From BL to Wk 24, antidrug antibodies were detected in 21.8% and 24.4% of patients treated with GP2017 and refADL, of which >70% in both groups were neutralizing.

Conclusion: These data demonstrate equivalent efficacy of proposed adalimumab biosimilar GP2017 and refADL in patients with moderate-to-severe RA. Safety and immunogenicity of GP2017 and refADL were similar and consistent with clinical experience with refADL.

References: ¹da Silva A, et al. Am J Gastroenterol 2016;111:S284

²Jauch-Lembach J, et al. Arthritis Rheumatol 2017;69 (suppl 10)

³Blauvelt A, et al. Arthritis Rheumatol 2017;69 (suppl 10)

Table. Summary of safety and immunogenicity for the proposed biosimilar adalimumab, GP2017, and reference adalimumab from baseline to Week 24 (analysis set)

	GP2017 (n=177)	Reference adalimumab (refADL) (n=176)	Total (N=353)
Adverse events, n (%)			
≥1 TEAE	109 (61.6)	106 (60.2)	215 (60.9)
Most commonly affected SOC (≥10% in any treatment group)			
Infections and infestations	63 (35.6)	65 (36.9)	128 (36.3)
Gastrointestinal disorders	21 (11.9)	17 (9.7)	38 (10.8)
Musculoskeletal and connective tissue disorders	21 (11.9)	14 (8.0)	35 (9.9)
≥1 treatment-related TEAE	42 (23.7)	32 (18.2)	74 (21.0)
≥1 severe TEAE	3 (1.7)	3 (1.7)	6 (1.7)
≥1 SAE	5 (2.8)	4 (2.3)	9 (2.5)
Injection site reaction	7 (4.0)	11 (6.3)	18 (5.1)
Drug discontinuation due to TEAE	2 (1.1)	2 (1.1)	4 (1.1)
Death	0	0	0
Incidence of ADAs from baseline to Week 24, n/n (%)			
Positive	36/165 (21.8)	41/168 (24.4)	77/333 (23.1)
Neutralizing	27/36 (75.0)	30/41 (73.2)	57/77 (74.0)

ADAs, antidrug antibodies; AE, adverse event; SAE, serious adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event

Disclosure: P. Wiland, Eli Lilly and Co., Gedeon, Novartis, Sandoz, 5, AbbVie Inc., MSD, Novartis, Roche, Sandoz, 8; S. Jeka, None; E. Dokoupilová, None; J. M. Miranda Limón, None; J. Jauch-Lembach, Sandoz / Hexal AG, 3; A. Thakur, Sandoz / Hexal AG, 3; H. Haliduola, Sandoz / Hexal AG, 3; N. B. Gaylis, None.

Abstract Number: 1937

Low-Dose IL-2 Restored Reduced Regulatory T Cells in Patients with Rheumatoid Arthritis

Ming Yan¹, Sheng-Xiao Zhang², Ruihuan Jia², Yu-Fei Hao¹, He-Hua Sun¹, Yan-Yan Wang¹, Guang-Ying Liu¹, Cai-Hong Wang³, Chong Gao⁴ and Xiao-Feng Li³, ¹Rheumatology, The Second Hospital of Shanxi Medical University, Taiyuan, China, ²The Second Hospital of Shanxi Medical University, Taiyuan, China, ³The Second Hospital of Shanxi Medical University, Taiyuan, China, ⁴Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, Cambridge, MA

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments III: New Compounds and Biosimilars

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Patients with rheumatoid arthritis (RA) have lymphocyte dysfunction characterized by deficiency or dysfunction of regulatory T cells (Tregs), which plays crucial roles in immune tolerance. Low dose IL-2 has been reported to promote selectively the expansion of Tregs. This study aimed to investigate the alterations and their clinical significance of the absolute numbers of lymphocyte subpopulations in RA patients and to restore the immunologic balances by low-dose IL-2.

Methods: Absolute number of CD4+CD25+FOXP3+Treg, CD4+IL17+T (Th17) and other subsets in peripheral blood (PB) from 839 patients with RA and 100 healthy donors were characterized by flow cytometry combined with an internal microsphere counting standard. Total 233 of patients were treated with daily subcutaneous injections of 0.5 million IU of human IL-2 for five consecutive days, and then its effects on lymphocyte subpopulations in PB were analyzed.

Results: There was a significant disturbance in lymphocyte subpopulations mainly manifested as the decreased level of Tregs compared with the health controls ($P < 0.05$). Further, Treg values were found to be correlated negatively with DAS28, CRP and tender joint count ($P < 0.05$), suggesting an important role of Tregs in sustained high disease activity. Low dose IL-2 effectively increased the number of Tregs ($P < 0.001$) and re-balance the ratio of Teffs and Tregs ($P < 0.05$), leading to increased clinic symptom partly remission in a rapid way without observed side effects.

Conclusion: Absolute decrease of PB Tregs in patients with RA was associated with continuing disease activation and low dose IL-2, a potential therapeutic candidate, restored decreased Tregs and promoted rapidly remission of patients with RA without over-treatment and evaluated side effects.

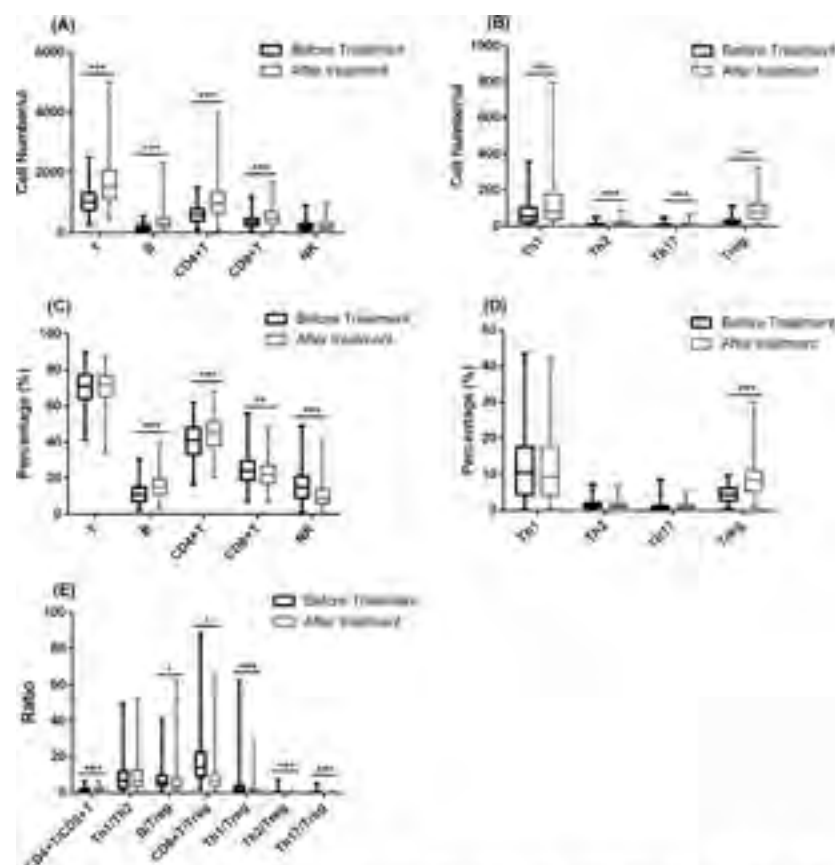


Figure 1: Low dose IL-2 modulates lymphocyte subpopulations by selectively expanding Treg cells in patients with RA ($n=235$). Data were presented as median (range) and calculated and compared with Mann-Whitney U test. (A, C) represented changes in absolute number and the percentages of lymphocyte subsets in peripheral blood. (B, D) showed changes in absolute number and the percentages of CD4+T cell subsets. (E) exhibited changes in the ratio of these cells in patients before and after the treatment. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table1: Characteristics of the study participants.

Variable	Heath Donors (N=100)	RA Patients (N=839)	P value
Female/Male	65/35	241/598	0.193
Mean age (year)	54.4 ± 8.1	55.8 ± 12.9	0.145
Peripheral blood lymphocyte subsets (number)			
T	1229 (1017, 1549)	1125 (848, 1512)	0.027
B	180 (138, 244)	159 (104, 241)	0.013
CD4+T	652 (544, 786)	665 (469, 895)	0.827
CD8+T	430 (321, 577)	388 (278, 542)	0.016
NK	267 (179, 379)	200 (125, 298)	< 0.001
T+B+NK	1713 (1405, 2172)	1575 (1209, 2030)	0.005
CD4+T subgroups (number)			
Th1	122 (77, 77)	66 (27, 125)	< 0.001
Th2	8 (5, 11)	9 (6, 15)	0.006
Th17	7 (4, 9)	6 (3, 10)	0.053
Treg	33 (25, 46)	28 (18, 42)	0.006
Peripheral blood lymphocyte subsets (percentage)			
T	72 (66, 75.9)	73.5 (66, 79)	0.077
B	10.5 (8.2, 13.5)	11 (7, 15)	0.901
CD4+T	38.7 (34, 43.2)	42 (36, 49)	< 0.001
CD8+T	25.1 (20.4, 30.9)	25 (20, 31)	0.552
NK	15 (11.2, 19.9)	13 (8, 20)	0.005
T+B+NK	98.6 (97.4, 99.2)	98.3 (97.3, 99)	0.134
CD4+T subgroups (percentage)			
Th1	17.1 (12, 25)	11 (5.2, 18.1)	< 0.001
Th2	1.2 (0.8, 1.7)	1.5 (0.9, 2.1)	> 0.001
Th17	1 (0.7, 1.4)	1 (0.6, 1.5)	0.940
Treg	4.9 (4.1, 6.2)	4.5 (3.2, 6.1)	0.011
Ratio			
CD4/CD8	1.5 (1.2, 2)	1.7 (1.3, 2.3)	0.033
Th1/Th2	14.6 (8.3, 22.6)	7.4 (3.6, 12.4)	< 0.001
B/Treg	5.8 (4.1, 7.9)	1.8 (0.3, 8.1)	< 0.001
CD8+T/Treg	13.3 (8.9, 20.2)	4.4 (1.2, 7.1)	< 0.001
Th1/Treg	2.4 (2.1, 5.3)	1.6 (0.1, 8.5)	< 0.001
Th2/Treg	0.2 (0.1, 0.4)	0.2 (0.1, 0.4)	0.473
Th17/Treg	0.2 (0.1, 0.3)	0.2 (0.1, 0.4)	0.111

Data presented as mean ± SD or median (quartile range).

Table 2: Correlation Between Disease Activity and the number of Peripheral blood lymphocyte subsets and CD4+T subgroups (N= 839).

Correlation	DAS28		ESR		CRP		28 Tender Joint Count		28 Swollen Joint Count	
	r	p	r	p	r	p	r	p	r	p
T	-0.195	<0.001	-0.186	<0.001	-0.187	<0.001	-0.166	<0.001	-0.078	0.024
B	-0.191	<0.001	-0.198	<0.001	-0.229	<0.001	-0.121	<0.001	-0.126	<0.001
CD4+T	-0.186	<0.001	-0.174	<0.001	-0.184	<0.001	-0.155	<0.001	-0.083	0.011
CD8+T	-0.161	<0.001	-0.130	<0.001	-0.128	<0.001	-0.162	<0.001	-0.041	0.242
NK	-0.080	<0.001	-0.063	0.068	-0.048	0.170	-0.076	0.028	-0.050	0.146
T+B+NK	-0.210	<0.001	-0.205	<0.001	-0.207	<0.001	-0.173	<0.001	-0.096	0.006
Th1	-0.116	0.001	-0.125	<0.001	-0.136	<0.001	-0.079	0.022	-0.051	0.141
Th2	-0.124	<0.001	-0.132	<0.001	-0.119	0.001	-0.095	0.006	-0.065	0.061
Th17	-0.125	<0.001	-0.144	<0.001	-0.143	<0.001	-0.083	0.017	-0.054	0.121
Treg	-0.099	0.004	-0.066	0.054	-0.077	0.028	-0.091	0.008	-0.045	0.193
CD4/CD8	0.004	0.910	-0.027	0.438	-0.062	0.077	0.037	0.288	-0.033	0.319
Th1/Th2	-0.040	0.244	-0.043	0.213	-0.044	0.214	-0.014	0.692	-0.018	0.607
B/Treg	-0.056	0.105	-0.073	0.034	-0.094	0.008	-0.026	0.460	-0.047	0.171
CD8+T/Treg	-0.037	0.286	-0.029	0.394	-0.032	0.362	-0.035	0.313	-0.021	0.545
Th1/Treg	-0.038	0.270	-0.048	0.163	-0.043	0.225	-0.017	0.618	-0.022	0.534
Th2/Treg	-0.025	0.474	-0.023	0.529	-0.023	0.540	-0.022	0.532	-0.026	0.453
Th17/Treg	-0.076	0.027	-0.094	0.007	-0.063	0.072	-0.042	0.228	-0.030	0.381

Spearman correlation coefficient; DAS28: 28-joint disease activity score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

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Abstract Number: 1938

A Phase IIb Dose-Ranging Study of Anti-GM-CSF with Methotrexate Treatment in Patients with Rheumatoid Arthritis (RA) and an Inadequate Response to Methotrexate

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments III: New Compounds and Biosimilars

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: GSK3196165 is a high-affinity anti-GM-CSF cytokine IgG mAb currently in development for RA, with reported efficacy using IV dosing. This study evaluated the efficacy and safety of GSK3196165 dose-ranging in RA.

Methods: 222 adult patients with active, moderate-severe RA per ACR 2010 criteria, ≥ 4 each of swollen and tender joints, DAS28(CRP) ≥ 3.2 and CRP ≥ 5.0 mg/L, were randomized equally to placebo or GSK3196165 22.5 mg, 45 mg, 90 mg, 135 mg or 180 mg SC weekly for 5 injections, then every other week until Week 50 (with blinded/automated escape to the 180 mg dose at Weeks 14 and 26 for non-responders). The primary outcome was the proportion of patients who achieved remission (DAS28 (CRP) < 2.6) at Week 24, with dose selection for further studies at Week 12.

Results: 37 patients were randomised to each treatment group; 150 patients completed the study (Week 62);86/175 (49.1%) eligible patients were escalated to the 180 mg dose after Week 12, and 57/83 (68.7%) patients after Week 24. Patient characteristics were well balanced across the groups. There were more patients in remission at Week 24 in the active groups (e.g. 16% in the 180 mg group, $p=0.134$) than those on placebo group (3%). There was a dose-related treatment effect in change from baseline in DAS28 (CRP) at Week 12, which was also reflected in other clinical endpoints with or without acute-phase reactants (see Table below).

The onset of clinical response across most endpoints was seen at Week 1, but the improvement in the GSK3196165 groups appeared to plateau from approximately Week 6 onwards, maintained to Week 52.

Observed PK exposures were lower than anticipated from previous studies. During the 5 weekly doses, maximum pre-dose concentrations were observed at Week 4 with geometric mean of 1,857 ng/mL (CV_b 176%) with the 180 mg dose, but concentrations dropped unexpectedly after reducing dosing frequency to dosing every two weeks. At Week 12, pre-dose geometric mean concentration was 680 ng/mL (CV_b 124%), which was below the anticipated threshold based on preclinical data for maximum efficacy.

GSK3196165 was well-tolerated, and adverse events were reported similarly across treatment groups. No drug-related SAEs, significant infections and/or pulmonary events were observed.

Conclusion: GSK3196165 has shown dose-related, clinically-meaningful benefit. Following dosing every two weeks, exposure to GSK3196165 was lower than predicted due to increased apparent clearance. Further studies are now required to confirm the additional clinical benefit expected with increased exposure from weekly dosing of GSK3196165 in patients with RA.

This study (NCT02504671) was funded by GSK.

Clinical endpoint at Week 12	Placebo (N=37)	180 mg (N=37)	Difference from placebo (95% CI)
	LS mean change from baseline (SE)		
DAS28(CRP)	-0.60 (0.23)	-1.87 (0.23)	-1.27 (-1.91, -0.63, $p<0.001$)
CDAI	-6.59 (2.66)	-23.23 (2.60)	-16.63 (-23.97, -9.30, $p<0.001$)
Pain	-7.07 (3.71)	-25.01 (3.65)	-17.94 (-28.18, -7.70, $p<0.001$)
HAQ-DI	-0.26 (0.09)	-0.50 (0.09)	-0.24 (-0.49, 0.01, $p=0.059$)
Patient's Global Assessment of Arthritis	-6.72 (3.66)	-23.9 (3.61)	-17.18 (-27.27, -7.10, $p<0.001$)
	Responder n (%)		
ACR20	4 (11%)	19 (51%)	40.5% (21.6, 59.5, $p<0.001$)
ACR50	3 (8%)	8 (22%)	13.5% (-2.4, 29.4, $p=0.134$)
Good/moderate EULAR	8 (22%)	28 (76%)	54.1% (34.9, 73.2, $p<0.001$)

Disclosure: C. Buckley, GlaxoSmithKline, 5; J. A. Simon Campos, None; S. Yakushin, None; V. Zhdan, None; K. Davy, GlaxoSmithKline, 1, 3; D. Inman, GlaxoSmithKline, 1, 3; E. Fischeleva, GlaxoSmithKline, 1; A. Gupta, GlaxoSmithKline, 1, 3; M. Layton, GlaxoSmithKline, 1, 3; N. Mitchell, GlaxoSmithKline, 3; J. Patel, GlaxoSmithKline, 1, 3; R. Williamson, GlaxoSmithKline, 1, 3; P. P. Tak, GlaxoSmithKline, 1, 3.

Abstract Number: 1939

Sirolimus Treatment in Patients with Refractory Rheumatoid Arthritis: A Double-Arm, Open-Label, phase1/2 Trail

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments III: New Compounds and Biosimilars

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Patients with refractory rheumatoid arthritis (RA) have T-cell dysfunction that associates the activation of mTOR that is inhibited by rapamycin, which has been developed as a medication under the generic designation of sirolimus. Recently, we have reported that absolute number of peripheral regulatory T (Treg) cells reduced in RA patients. Since rapamycin has been reported to expand Tregs, in this study, we assessed safety, tolerance, and efficacy of sirolimus for RA treatment.

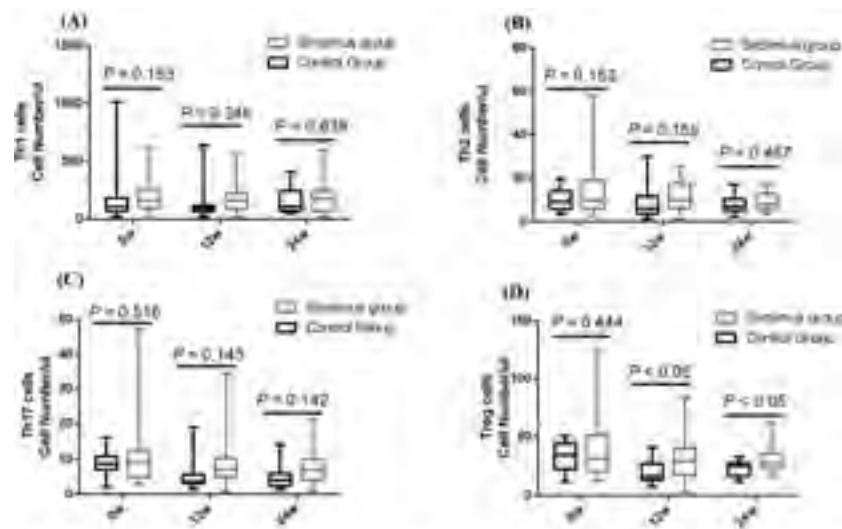


Figure 1: Sirolimus modulates CD4⁺T cell subsets by selectively expanding Treg cells in patients with RA. Absolute numbers of lymphocyte subpopulations in peripheral blood were analyzed by flow cytometry. Data were presented as median (range) and calculated and compared with Mann-Whitney *U* test. (A-C) shows no significance in the number of Th1, Th2 and Th17 cells between sirolimus groups (*n*=38) and non-sirolimus group (*n*=19). (D) shows patients had a significant increase in the number of Treg cells after 12 and 24 weeks sirolimus treatment compared with that of conventional treatments.

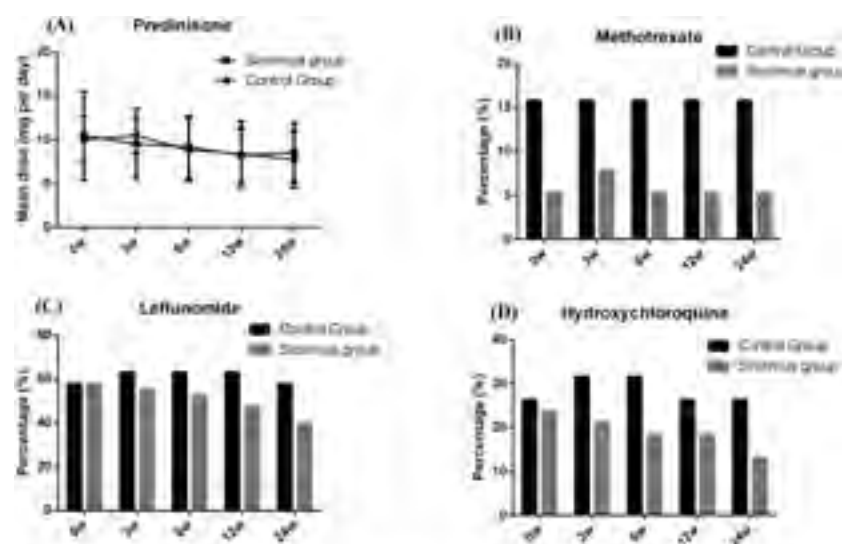


Figure 2: Baseline (conventional) therapies between sirolimus and control group. (A) no differences of prednisone dosage between these two groups. (B-D) lower proportions of the patients achieving methotrexate, leflunomide and hydroxychloroquine, respectively than that in controls (*p* < 0.05).

Methods: We did a double-arm, open-label, and phase 1/2 trial of sirolimus in patients with RA at the Second Hospital of Shanxi Medical University (Taiyuan, Shanxi, China). Eligible participants (aged 18 to 65 years) fulfill the revised the 1987 ACR/EULAR criteria for the classification of RA and did not achieve remission with the conventional treatment over at least 2 years. We excluded patients with allergy or intolerance to sirolimus, with malignant disease or a history of malignancy, or with chronic or severe infection. Patients in control group (*n*=19) were given conventional glucocorticoids and DMARDs treatment. Patients in sirolimus group (*n*=38) were given not only conventional treatment, but also oral sirolimus at a starting dose of 0.5 mg on alternate days for 24 weeks. The demographic features, clinical manifestations

and laboratory indicators were compared before and after the treatment. This trial is registered at Chinese Clinical Trial Registry, number ChiCTR-IPR-17010307.

Results: There was no difference between sirolimus and control group in gender and age ($P > 0.05$). After 24 weeks of the sirolimus treatment, except C-reaction protein, there was a significant decrease in disease activity measures including DAS28, ESR, the number of tender joints and swollen joints ($P < 0.001$). Patients with sirolimus treatment had a significant increase in the number of Tregs and a lower DMARDs usage rate ($P < 0.05$). There was no difference in blood routine, liver and renal functions both before and after the treatment between two groups ($P > 0.05$).

Conclusion: Sirolimus treatment selectively up-regulated Tregs and partly decreased the usage of DMARDs without over-treatment and evaluated side effect. The further study is required to increase the RA patients in sirolimus and conventional treatment groups.

Disclosure: J. Wang, None; S. X. Zhang, None; F. Y. Hu, None; X. J. Zheng, None; T. Cheng, None; N. N. Yu, None; W. X. Yang, None; C. Gao, None; H. Y. Wen, None; X. F. Li, None.

Abstract Number: 1940

Reductions in Absolute Neutrophil Count (ANC) with Sarilumab Resulting in Dose Delays or Dose Decreases: Effects on Efficacy and Safety

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Rheumatoid Arthritis – Treatments III: New Compounds and Biosimilars

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

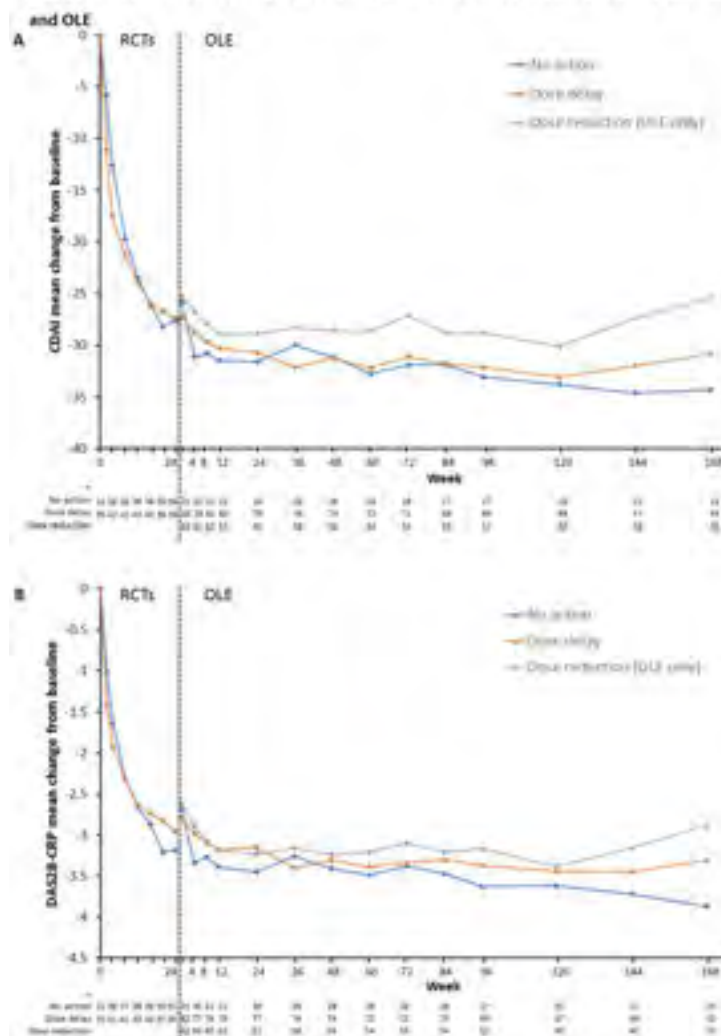
Background/Purpose: In sarilumab randomized controlled trials (RCTs), dose delay and/or reduction was recommended for management of patients who developed neutropenia Grade (G) 3 ($ANC \geq 500$ to $<1000/mm^3$). This posthoc analysis evaluated the impact of sarilumab dose delay/reduction on efficacy and safety in RCTs and open-label extension (OLE: EXTEND).

Methods: In RCTs and OLE, patients who experienced G4 or G3 neutropenia and signs of infection permanently discontinued treatment. Patients with G3 neutropenia (no signs of infection) temporarily (or permanently at investigator discretion) discontinued treatment; patients were retested $\leq 48h$ after recording decreased ANC and before next scheduled dose, and could resume if $ANC \geq 1000/mm^3$. RCTs: patients restarted sarilumab at randomized dose (150 or 200 mg q2w [MOBILITY (NCT01061736)/TARGET (NCT01709578)]; 200 mg q2w [MONARCH (NCT02332590)]). OLE (NCT01146652): patients received sarilumab 200 mg q2w, and restarted sarilumab at 150 mg q2w (per protocol) or 200 mg q2w (investigator discretion); patients requiring dose decrease to 150 mg q2w received that dose for the rest of the study. This analysis included pooled RCT data and OLE data from EXTEND patients enrolling from MOBILITY or TARGET.

Results: Of the 8–11% of patients experiencing $ANC < 1000/mm^3$ at any time (105/1346 [8%] RCT; 147/1353 [11%] OLE), 81/105 [77%] (RCT) and 132/147 [90%] (OLE) were able to continue or reinitiate sarilumab. Of the 81 RCT patients who continued or reinitiated sarilumab, 53% had a dose delay >17 days (i.e. more than one q2w dosing interval) and the remainder continued without interruption. Of 132 OLE patients who continued/reinitiated sarilumab, 82 had dose delay >17 days, 62 had dose reduction, and 31 had no action taken. No meaningful differences in DAS28-CRP or CDAI mean change from baseline over time were observed between patients with $ANC < 1000/mm^3$ who reinitiated sarilumab and those without neutropenia who continued without interruption. Among patients with $ANC < 1000/mm^3$ who continued treatment, no meaningful differences in CDAI or DAS28-CRP mean change from baseline (Figure) were observed in RCT patients with or without dose delay or in OLE patients with no action/dose delay/dose reduction, although some numerical differences were seen. Patients who were neutropenic at any time did not have an increased risk of infections or serious infections (SIEs) (RCT: infections/SIEs 35.9%/2.4% (non-neutropenia) vs 35.8%/1.2% (neutropenia); OLE: 57.8%/8.5% vs 57.6%/8.3%).

Conclusion: The majority of patients in RCTs and OLE who temporarily discontinued treatment with sarilumab due to low ANC were able to continue or reinitiate sarilumab with no apparent clinically meaningful impact on long-term efficacy or safety.

Figure. Effect of dose delay and/or reduction on (A) CDAI and (B) DAS28-CRP change from baseline in RCTs



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Abstract Number: 1941

Altered Cognitive Function in Systemic Lupus Erythematosus and Associations with Inflammation and Functional Brain Changes

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SESSION INFORMATION

Session Date: Monday, October 22, 2018
Session Title: Systemic Lupus Erythematosus – Clinical II: Renal and Neuropsychiatric Disease in SLE
Session Type: ACR Concurrent Abstract Session
Session Time: 4:30PM-6:00PM

Background/Purpose: Cognitive dysfunction is a common problem in systemic lupus erythematosus (SLE) but the cause is still unclear; measuring it can be difficult and, as such, treatment options are limited. We examined cognitive function (CF) in a stable SLE group using both behavioural and imaging techniques. Associations for cognitive dysfunction in SLE were also explored.

Methods: 36 stable SLE (SLE 1997 ACR Criteria) and 30 healthy controls (HC) were recruited. Demographics clinical features, psychological questionnaires and blood samples were collected. We compared periventricular hyperintensities (PVH), deep white matter hyperintensities (DWMH), brainstem and basal ganglia features. CF was assessed using selected tests from the CANTAB®, and fMRI was used to examine blood-oxygen-level dependent (BOLD) responses to a working memory and attention task (n-back) and a facial emotional processing task (FERT). The fMRI data was modelled using SPM12. All other data was analysed using SPSS 22.

Results: SLE patients had significantly higher scores for depression and fatigue and they also had higher levels of IL-6, high sensitivity CRP, VCAM-1 and BlyS (Table 1). The SLE group performed significantly worse on a behavioural task of sustained attention ($p=0.002$) but similarly on all other cognitive tasks. They had more and larger perivascular spaces (PVS) in the centrum semiovale (CSO-VRS), $\chi^2=15.50$, $p<0.001$, compared to the HC group. We also found altered BOLD signals compared to the HC group for the n-back task in regions associated with the default mode network during the working memory condition and in the lingual gyrus during the attention condition. For the FERT task, during the sadness condition, differences were also found (Figure 1). The attenuated BOLD signal in the right superior temporal gyrus positively correlated with VCAM-1 ($r=0.53$, $p=0.01$), and SLICC/ACR-DI score ($r_s=0.56$, $p=0.005$). The attenuated BOLD signal in the lingual gyrus positively correlated with the BILAG total score ($r_s=0.45$, $p=0.033$) and IL-6 ($r_s=0.44$, $p=0.036$).

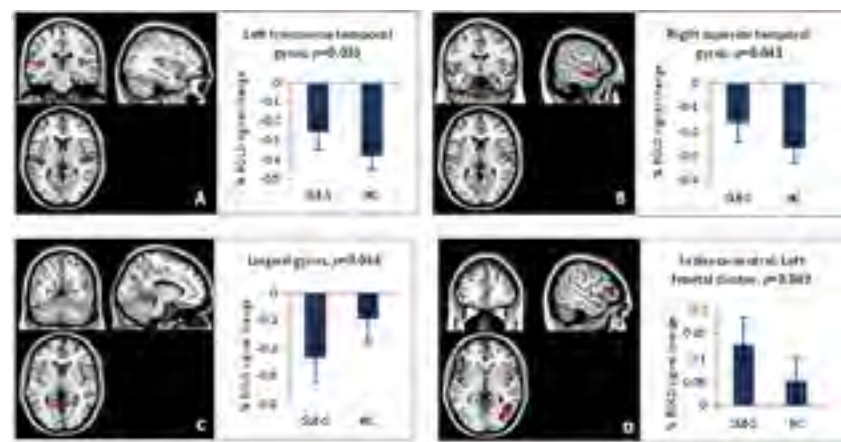


Figure 1: Significantly different BOLD responses to: A & B – the n-back task for the working memory condition in default mode network regions, C – the n-back task for the attention condition in a visual attention area and D – the FERT task for the sadness condition in a cognitive frontal cluster.

Table 1 Differences between the SLE and HC groups for demographic, psychiatric and fatigue characteristics and serological inflammatory markers

Variable	SLE (n=36)	HC (n=30)	p-value
Mean (S.D.), Median (LQ, UQ) or n (%)			
Demographic			
Age (years)	40 (32, 48.75)	32 (27, 46.5)	$p=0.14$
Gender (% female)	34 (94)	30 (100)	$p=0.19$
Handedness (% right-handed)	30 (83)	28 (93)	$p=0.34$
Years in education	16.11 (3.51)	17.97 (3.40)	$p=0.034$

Table. (Cont'd)

Variable	SLE (n=36)	HC (n=30)	p-value
WTAR (IQ)	102.5 (98.25, 108)	111 (105, 114)	<i>p</i> =0.001
Depression			
MADRS	4 (1, 8)	1 (0, 3)	<i>p</i> =0.012
HADS - D	4 (1, 9)	1 (0, 2)	<i>p</i> <0.001
BDI - II	10 (4, 20.25)	3 (0.75, 8)	<i>p</i> =0.002
Anxiety			
HADS - A	6 (3, 10.5)	5 (2, 7)	<i>p</i> =0.08
Fatigue			
FSMC - Motor score	36 (22, 40.5)	14 (11.5, 18.5)	<i>p</i> <0.001
FSMC - Cognitive score	31 (22, 40)	14 (11.5, 18.5)	<i>p</i> <0.001
FSMC - total score	67.5 (44.75, 80.5)	27 (23, 37)	<i>p</i> <0.001
Biomarkers of inflammation and endothelial activation			
hsCRP (mg/l)	1.44 (0.66, 5.06)	0.88 (0.39, 1.39)	<i>p</i> =0.013
IL-6 (pg/ml)	1.67 (0.50, 5.33)	0.50 (0.50, 1.32)	<i>p</i> =0.003
VCAM-1 (ng/ml)	474.93 (194.30)	345.66 (53.79)	<i>p</i> =0.001
VEGF (pg/ml)	66.04 (13.93, 139.60)	45.42 (6.04, 114.93)	<i>p</i> =0.275
BLyS (ng/ml)	0.51 (0.35, 0.71)	0.34 (0.27, 0.39)	<i>p</i> <0.001

WTAR: Weschler Test of Adult Reading; MADRS: Montgomery Asberg Depression Rating Scale; HADS-D: Hospital Anxiety and Depression Scale - Depression score; BDI-II: Becks Depression Inventory - II; HADS-A: Hospital Anxiety and Depression Scale - Anxiety score; FSMC: Fatigue Scale for Motor and Cognitive Functions; hsCRP: High Sensitivity C-Reactive Protein; IL-6: Interleukin 6; VCAM-1: Vascular cell adhesion molecule-1; VEGF: Vascular Endothelial Growth Factor; BLyS: B lymphocyte stimulator

Conclusion: Structural and functional changes related to cognition in SLE may, in part, be influenced by inflammation and aspects of disease including pre-existing damage. Also, the compensatory brain mechanisms used by the SLE group to maintain adequate CF may make SLE patients more susceptible to emotional interference during non-emotional cognitive tasks. Whilst multifactorial in nature, certain aspects of SLE CF may be sensitive to changes in disease status and thus to targeted therapeutic interventions.

Disclosure: M. Barraclough, Sanofi Genzyme, 2; R. Elliott, None; B. Parker, None; S. McKie, None; A. Jackson, None; P. Pemberton, None; I. N. Bruce, Sanofi Genzyme, 2.

Abstract Number: 1942

Anti-NMDA Receptor Antibodies in Systemic Lupus Erythematosus Associate with Decreased White Matter Integrity and Impaired Spatial Memory

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical II: Renal and Neuropsychiatric Disease in SLE

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Cognitive impairment is common in SLE and impacts quality of life; however, causality is limited by incomplete understanding of neurotoxic mechanisms. Diffusion tensor imaging (DTI) is an advanced MRI technique that assesses white matter integrity (WMI). In an animal model we demonstrated cross-reactive anti-dsDNA/NMDA receptor antibodies (DNRAb) that cause neuron loss, hippocampal dysfunction, and an established behavioral phenotype. In SLE patients, serum DNRAb correlates with poor spatial memory and hippocampal atrophy. We report new associations among serum DNRAb, regional microstructural integrity (DTI) and spatial memory in SLE.

Methods: 19 out of a cohort of 20 adult SLE subjects that met ACR criteria and had no history of CNS insult, well-controlled hypertension, low disease activity and corticosteroid doses (Table), and 14 age/gender matched healthy controls (HC) underwent DTI. A spatial memory task (SMT) assessed both non-spatial object recognition and memory for spatial relations in SLE subjects. Serum DNRAb assays were performed by ELISA with the DWEYS consensus sequence. Fractional anisotropy (FA) maps were compared between SLE and HC, and tract count differences were evaluated (t-test). Regression analysis (Pearson product-moment) assessed correlations between FA maps, serum DNRAb, and spatial memory performance.

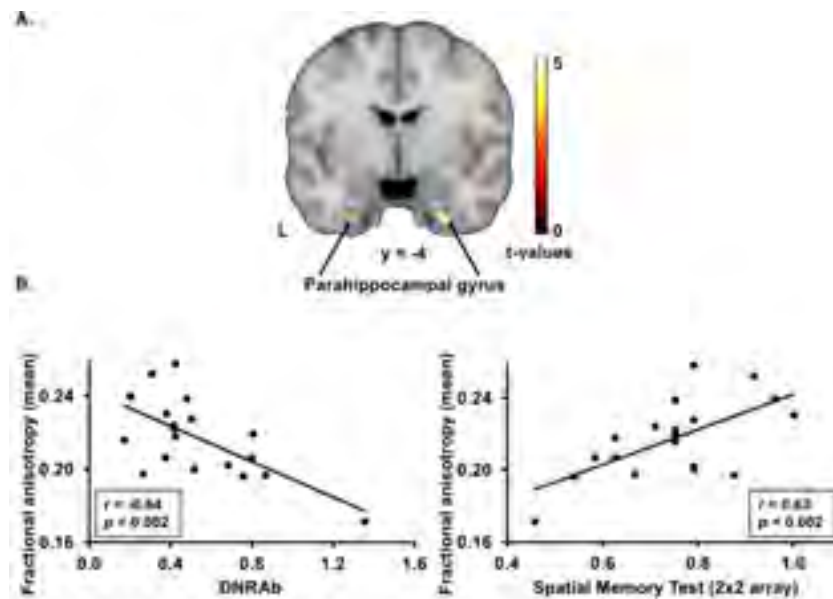


Figure 1: Microstructural integrity (FA) in the parahippocampus regions correlates with serum DNRAb titers and performance on a spatial memory test in the SLE subjects.

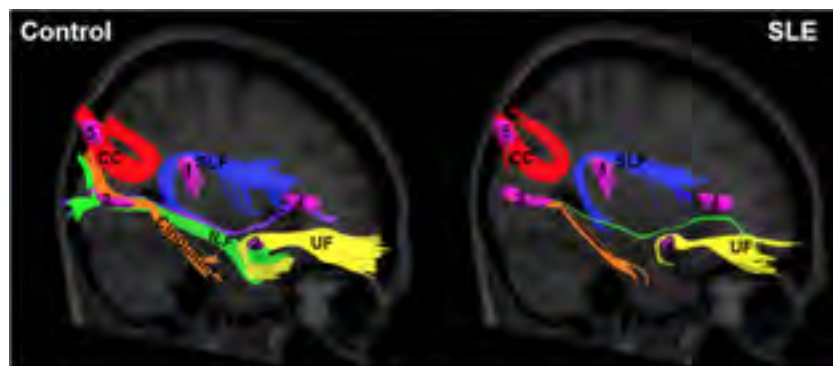


Figure 2: Connections between the abnormal SLE-related regions visualized with group tractography.

	SLE n=20
Age (years)	41 ± 10.5
Gender: female	18 (90%)
Ethnicity	
Latino/Hispanic	4 (20%)
Asian	1 (5%)
African American	14 (70%)
Caucasian	1 (5%)
Education (years)	13.3 ± 2.4
SLEDAI score	2.3 ± 2.1
SLICC Damage Index score	0.9 ± 1.1
Current medications	
prednisone dose (mg)	2.6 ± 3.7
Hydroxychloroquine	17 (85%)
DMARD*	11 (55%)
Serology	
anti-dsDNA ab +	10 (50%)
anti-Ro/L	16 (70%)
Anti-NMDAR+	9 (45%)
anti-Ribosomal P+	3 (15%)
Anticardiolipin (IgG, M or A)	1 (5%)
Co-morbid disease	
Hypertension	9 (45%)
Coronary artery disease	1 (5%)
Smoking: ever	7 (35%)

Table: Subject characteristics for SLE cohort.

* Disease Modifying Anti-Rheumatic Drug: methotrexate (n=1), azathioprine (n=3), mycophenolatemofetil (n=7)

Results: FA was significantly reduced in 5 discrete regions with abnormal WMI in SLE. FA in the parahippocampal gyrus (PHG) correlated inversely with serum DNRAb and positively with SMT performance (Fig.1). Other regional abnormalities in WM tracts (expressed as % change relative to HC) included: 1) superior longitudinal fasciculus (temporal part) (SLF, -74%), 2) uncinate fasciculus (UF, -86%), 3) cingulum (hippocampus part) (-82%), 4) inferior longitudinal fasciculus (ILF, -99.5%) and inferior frontooccipital fasciculus (IFOF, -100%), and 5) the splenium of the corpus callosum (CC, -48%) ($p < 0.001$) (Fig. 2).

Conclusion: DTI revealed PHG abnormality that correlated with serum DNRAb and SMT performance, suggesting potential roles of these assessments as biomarkers for cognitive impairment. Other discrete regions of decreased WMI, connected by diminished tracts, raise the specter of clinically unrecognized neurodegeneration in quiescent, stable SLE patients without known CNS disease.

Disclosure: E. Anderson, None; A. Vo, None; E. Ploran, None; B. Diamond, None; B. Volpe, None; C. Aranow, None; D. Eidelberg, None; M. Mackay, None.

Abstract Number: 1943

Apolipoprotein L1 Risk Variants Associate with Poor Renal Outcomes, Damage Accrual, and Death: A Prospective Ghanaian SLE Cohort

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical II: Renal and Neuropsychiatric Disease in SLE

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Two Apolipoprotein L1 (APOL1) risk variants (RV), G1 and G2, are enriched in ancestrally African populations due to a conferred superior resistance to *Trypanosoma brucei*. This improved infectious evolutionary fitness comes at the cost of propensity toward progressive renal disease by multiple causes including SLE. In Ghana's Ashanti people, Allelic frequencies for G0, G1, and G2 have been reported at 0.46, 0.49, and 0.13 respectively. Despite their high frequencies, and the established role in SLE nephritis, no study has examined outcomes in a Ghanaian SLE cohort. Accordingly, this prospective study evaluated APOL1 risk traits including renal, damage accrual, and mortality in 101 Ghanaian patients followed at Korle bu Teaching Hospital in Accra, Ghana.

Methods: From 05/2015-04/2018, 101 Ghanaian patients meeting at least 4 ACR criteria for SLE were followed prospectively with data evaluated every six months. DNA was extracted from saliva and patients were stratified by APOL1 genotype as follows: reference allele (G0/G0), RV heterozygote (RV/G0), and RV homozygotes (RV/RV). Sera were shipped to the NYU clinical lab for confirmation of anti-dsDNA. Clinical endpoints included demographics, ACR criteria, SLEDAI score, SLICC damage index, mortality, vital signs, and laboratory values as available.

Results: The frequencies of the G1, and G2 alleles were 0.24, and 0.12 respectively— lower than would be expected given the reported regional frequencies. Subjects were 100% female, with an average age of 32.1 years and disease duration of 2.9 years. There were no differences in demographics across the genotypes. The RV associated with higher BP: 108/71, 108/73, and 120/82 in the G0/G0, RV/G0, and RV/RV groups respectively ($p=0.04$ systolic; 0.009 diastolic). Among those with nephritis, RV/RV carriers presented with higher dipstick proteinuria than G0/G0 and RV/G0 carriers (2.6 vs 1.2 and 1.3 respectively; $p=0.05$; $F=3.1$). While proteinuria responded most robustly to therapy in RV/RVs, it remained higher at each time point compared to the other genotypes ($p=0.002$; $F=5.4$). SLEDAI scores were comparable across the genotypes, however RV/RV carriers had lower dsDNA titers (10.7 IU/mL) than G0/G0 (57.1 IU/mL) and RV/G0 (95.6 IU/mL) carriers ($p: 0.03$). RV homozygosity associated with elevated SLICC damage index: G0/G0 or RV/G0: 0.95 vs RV/RV: 1.7; driven by renal, CVD, and neurologic manifestations G0/G0: 0.46, RV/G0: 0.39, RV/RV: 1.25; ($p=0.03$). There were 5 deaths during the study period: 1 death in the G0/G0 group (ESRD), 1 in the RV/G0 group (post-partum sepsis plus renal), and 3 in the RV/RV group (myocarditis/heart failure; ESRD; unknown). RV carrier status associated with mortality with 25% of the RV/RV group succumbing to disease vs 2% in the G0/G0 and RV/G0 groups ($p=0.003$; $F=6.3$).

Conclusion: Taken together, APOL1 RV associates with renal progression, organ damage accrual, and mortality in this Ghanaian SLE cohort. Despite having poorer outcomes, RV homozygotes exhibited lower dsDNA titers and similar

SLEDAI scores compared to G0/G0 or RV/G0 patients suggesting a genetic effect independent of SLE activity. APOL1 genotyping could have important prognostic implications in ancestrally African SLE patients.

Disclosure: A. Blazer, None; I. D. Dey, Jansenn Pharmaceuticals, 9; M. Reynolds, None; F. Ankrah, None; N. Schmidt, None; R. M. Clancy, None; J. P. Buyon, None.

Abstract Number: 1944

Does Renin Angiotensin System Blockade in Addition to Immunosuppressive Therapy Improve Proteinuria in Acute Lupus Nephritis?

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical II: Renal and Neuropsychiatric Disease in SLE

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are currently recommended for patients with lupus nephritis (LN) as an adjunctive therapy for the optimal control of proteinuria. However, that recommendation is mainly extrapolated from studies in diabetes, hypertension and IgA nephropathy with no supportive evidence from patients with LN. The aim of this study was to assess the impact of such treatment on proteinuria in active LN.

Methods: Patients from our long-term longitudinal cohort who were treated with glucocorticosteroids (GCS) and mycophenolate mofetil (MMF, 2-3g/day) or azathioprine (AZA, 2mg/kg) for their first episode of active LN after 2001 were included. They had at least one year of follow-up with visits at 6 and 12 months. Individuals with end-stage renal disease (eGFR \leq 15ml/min/1.73m²) or LN class VI at baseline were excluded. Patients were divided into two groups according to the concurrent treatment with ACEIs/ARBs or not. Demographic, clinical, immunological and therapeutic variables were compared at baseline; cumulative GCS dose and blood pressure at baseline, 6 and 12 months were also assessed. Proteinuria (24h) and eGFR were compared at 6 and 12 months after therapy initiation. Complete renal response was defined as proteinuria $<$ 500mg/day. Statistical analysis was performed with SAS 9.4; $p<0.05$ was considered significant.

Results: One hundred forty three patients were included (77 with concomitant ACEI/ARB treatment and 66 without). There were no significant differences concerning age at LN diagnosis, gender, race, disease duration, SLEDAI-2K and SLICC/Damage Index as well as LN histopathologic class, eGFR and blood pressure at baseline. Severity of proteinuria (2.2 \pm 1.5 vs. 2.1 \pm 1.8g/day, $p=0.78$) and nephrotic syndrome (proteinuria $>$ 3g/day) were also similar (15.6% vs. 18.2%, $p=0.68$). There were no differences in the initial GCS and MMF/AZA doses as well as antimalarial usage. Cumulative GCS dose at 12 months and blood pressure at 6 and 12 months were also comparable. Overall, 55.2% of the patients achieved a complete renal response with a significant mean reduction (60%) in proteinuria at 6 and 12 months. Prevalence of complete renal response, level of proteinuria and eGFR between groups are shown in Table 1.

Table 1 Complete response and level of proteinuria and eGFR over time

	ACEIs/ARBs (+) (n=77)	ACEIs/ARBs (-) (n=66)	P
Complete renal response at 6 months (% , n)	35.1% (27)	50% (33)	
Complete renal response at 12 months (% , n)	49.4% (38)	62.1% (41)	
Proteinuria at baseline (mean \pm SD, g/day)	2.2 \pm 1.5	2.1 \pm 1.8	
Proteinuria at 6 months (mean \pm SD, g/day)	1.2 \pm 1.2	1.1 \pm 1.4	
Proteinuria reduction at 6 months (% from baseline)	45.5%	47.6%	NS
Proteinuria at 12 months (mean \pm SD, g/day)	0.9 \pm 1.0	0.8 \pm 1.3	
Proteinuria reduction at 12 months (% from baseline)	59.1%	61.9%	NS
eGFR (ml/min/1.73m ²) at baseline (mean \pm SD)	92 \pm 38	104 \pm 39	
eGFR (ml/min/1.73m ²) at 12 months (mean \pm SD)	89 \pm 35	107 \pm 34	
Change in eGFR at 12 months (% from baseline)	-3.3%	2.9%	NS

A sub-analysis of the patients who were treated only with MMF (n=81, 51 with concomitant ACEI/ARB treatment and 31 without) yielded similar results.

Conclusion: A majority of patients achieved complete renal response at 12 months without significant differences between groups. Similarly, there was a significant improvement in proteinuria at 6 and 12 months with no significant deterioration of the eGFR and no difference between groups. Renin angiotensin system blockade may not be necessary in the acute phase of LN.

Disclosure: K. Tselios, None; D. D. Gladman, AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, 2, 5; J. Su, None; M. Urowitz, None.

Abstract Number: 1945

Early Prediction of Long-Term Renal Outcomes in Lupus Nephritis Using Hazard Index Equations

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Systemic Lupus Erythematosus – Clinical II: Renal and Neuropsychiatric Disease in SLE

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Early endpoints predicting long-term outcome in lupus nephritis (LN), which could be used as outcome measures in clinical trials, are still debated. Recently, a multicentric study, using an extended international database of prospectively followed LN patients, succeeded in computing equations (hazard index; HI) predicting adverse kidney outcomes, in casu chronic kidney disease (CKD), severe kidney injury (SKI) and renal replacement therapy (RRT). These HI were validated in a replicate cohort. The HI for CKD, SKI and RRT (calculated with data measured at one year) were significantly higher in groups with long-term poor renal outcomes after a follow-up (FU) of ≥ 4 years (Mackay M et al. Arthritis Rheumatol 2016; 68 (suppl.10), abstract 967).

Objectives: To validate the HI for CKD, SKI and RRT in an independent LN cohort followed for ≥ 4 years and to check their validity to predict outcome in patients followed for ≥ 9 years.

Methods: Data from 229 consecutive LN patients followed in a single lupus center were screened. Only those for whom clinical data were available following their first episode of proliferative and/or membranous biopsy-confirmed LN were selected. Serum creatinine and proteinuria at different time points from 102 LN patients followed for ≥ 4 years were analyzed. At last FU, patients were divided according to the presence or absence of CKD, SKI and RRT. Their respective HI, measured at one year, were compared. CKD/SKI were defined as $\geq 30\%/ \geq 50\%$ decrease in eGFR (CKD-EPI equation), compared to the highest value measured within the first year.

Results: As illustrated in the Table, the mean HI for CKD and SKI, measured at one year, were significantly higher in the groups of patients who indeed developed CKD and SKI after a FU of ≥ 4 years compared to those who did not. Importantly, the HI predictive value remained valid after a FU of ≥ 9 years. The mean HI for RRT was higher in patients who developed RRT after ≥ 4 and ≥ 9 years, but the difference was not statistically significant ($p=0.08$ and $p=0.25$, respectively), most likely due to the small numbers of RRT in this series. Of note, clinical (gender, age, mean serum creatinine, mean proteinuria) and pathological (ISN/RPS class) characteristics did not differ at baseline between patients with poor long-term renal outcome compared to the others.

Conclusion: We confirm the validity of the HI equations as early predictors of poor renal outcomes (CKD and SKI after long-term FU). These HI tools could be used as outcome measures in LN clinical trials.

Renal outcome ≥ 4 years (102)	HI at one year (mean \pm SD)	Renal outcome ≥ 9 years (76)	HI at one year (mean \pm SD)
Presence of CKD (21)	0.69 \pm 0.53*	Presence of CKD (18)	0.56 \pm 0.63**
Absence of CKD (81)	0.30 \pm 0.40	Absence of CKD (58)	0.32 \pm 0.36
Presence of SKI (8)	-0.67 \pm 0.36*	Presence of SKI (9)	-0.72 \pm 0.44*
Absence of SKI (94)	-1.20 \pm 0.47	Absence of SKI (67)	-1.22 \pm 0.45
Presence of RRT (5)	-1.74 \pm 0.74	Presence of RRT (6)	-1.87 \pm 0.74
Absence of RRT (97)	-2.33 \pm 0.74	Absence of RRT (70)	-2.28 \pm 0.70

HI : hazard index; figures between brackets correspond to numbers of patients; CKD : chronic kidney disease; SKI : severe kidney injury; RRT : renal replacement therapy; *: $p<0.005$; **: $p<0.05$ (Mann-Whitney U-tests).

Disclosure: F. Tamirou, None; M. Mackay, None; M. Dall'Era, None; J. Fishbein, None; K. C. Kalunian, None; B. H. Rovin, None; F. A. Houssiau, None.

Abstract Number: 1946

Changing the Conversation about Pain: Development and Testing of an Interprofessional Pain CME Applicable for Rheumatologists and Rheumatology Health Professionals

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: ARHP I: Pain, Anxiety, and Depression

Session Type: ARHP Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Pain is a near universal symptom of rheumatic diseases. Persistent pain can cause changes in the central and peripheral nervous system transforming pain from a symptom to a chronic illness. Shifting providers' and patients' thinking about "pain as a chronic illness" requires examples of conversations that can be shared between the patient and members of the health care team. The purpose of this project is to overview the development and testing of a novel on-line CME whose goal is to promote optimal patient care and provider satisfaction by 'changing the conversation about pain'.

Methods: From January 2017 to January 2018, the Oregon Pain Management Commission deployed a team, consisting of two clinical pain leaders, a program coordinator (RN) and a producer of online training content, to revise the existing pain module mandated by the State for prescribing providers. An iterative Delphi-type process distilled multiple stakeholders' needs from 13 professional and government organizations into the final modular product.

Results: On January 30, 2018 "Changing the Conversation About Pain" was launched. <http://www.oregon.gov/oha/HPA/CSI-PMC/Pages/module.aspx> By April 1, 1,453 persons had completed the 1.0 CME (476 nurses/nurse practitioners, 108 physicians, 105 dentist, 149 physical therapists, 127 occupational therapists, 79 pharmacists, 22 chiropractors, 13 psychologists and 374 other health professionals). On evaluation, 73% of participants were 'highly committed' to change practice by using alternative communication methodologies with patients and families. Two open fields were available for feedback with comments including:

"Great Insight as to how pain is processed."

"This is by far the most positive and thorough presentation on pain I have ever experienced."

"Gave me language to use when talking with patients that are resistant to everything but pharmacological interventions."

"This module is very informative and helpful for clinicians in understanding complex pain and the available treatment options for patients to benefit from."

Conclusion: Extensive collaboration yielded an interprofessional CME that is thus far well received by a wide range of practicing professionals in addition to mandated providers. The CME is now being rolled out to law enforcement, patient navigators, certified nursing aides coaches, medical coders, health education specialists, and health administrators. These successes are furthering our goal of changing the conversation about pain to empower patients to take a self-management approach to their care.

Disclosure: K. Jones, None; C. Buist, None; D. Taray, None; R. Halperin, None; M. Stephens, None; N. Stern, None.

Abstract Number: 1947

Do Changes in Pain Sensitization and Depressive Symptoms Mediate the Effect of Extreme Weight Loss on Knee Pain Improvement?

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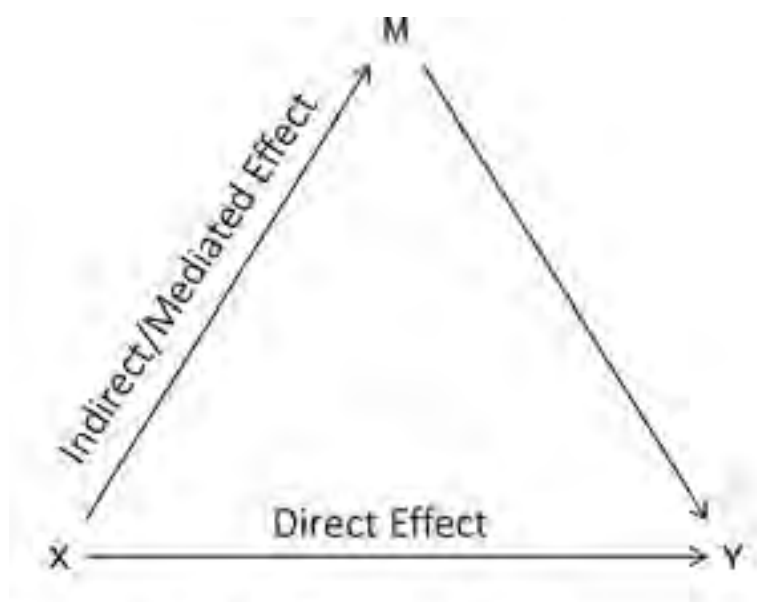
SESSION INFORMATION

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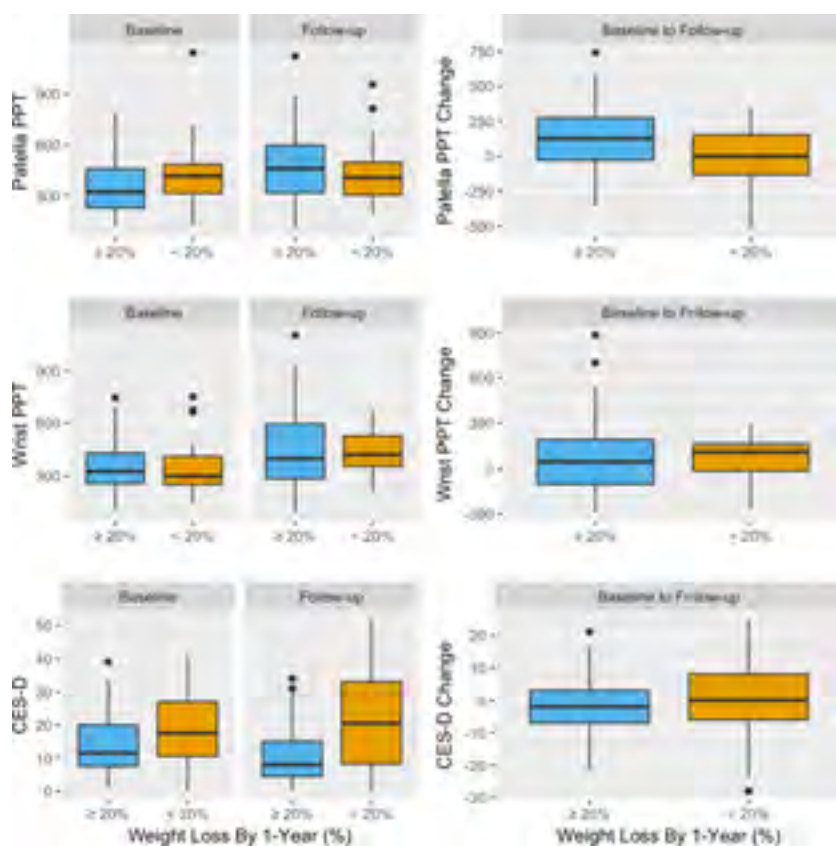
Session Time: 4:30PM-6:00PM



Exposure (X): $\geq 20\%$ Weight Loss

Mediators (M): Change in PPT, CES-D Score

Outcome (Y): $\geq 18\%$ Reduction in WOMAC Pain



Background/Purpose: We previously showed that the one-year effects of weight loss on knee pain reduction were not mediated by changes in structural features of osteoarthritis such as bone marrow lesions and synovitis. We aimed to assess whether the knee pain improvement in these persons could be explained by changes in pain sensitization or depressive symptoms.

Methods: Morbidly obese persons with body mass index ≥ 35 kg/m², from the Nutrition and Weight Management Center who had knee pain on most days of the past month were eligible. Patients were evaluated at baseline, before bariatric surgery or medical weight management, and at one-year. Measurements from both visits included WOMAC pain subscale score, pressure pain threshold (PPT) obtained at index patella and right wrist as an indication of peripheral/central and central sensitization, respectively, and depressive symptoms derived from the Center for Epidemiologic Studies Depression (CES-D) scale. Improvement in pain beyond a minimal clinically important difference (MCID) of 18% (i.e., $\geq 18\%$ reduction) in WOMAC score was defined as the outcome. We defined the exposure as weight loss of $\geq 20\%$ and focused on potential mediator's defined as the change in patella and wrist PPT and CES-D score from baseline to follow-up. For mediation analysis, we fit natural effects models to quantify the magnitude of weight loss effect on pain improvement through a mediator-specific causal pathway; this is the mediating or indirect effect, and the remaining direct effect that is independent of the mediator-specific pathway (Figure 1).

Results: Of 75 study participants, 53% (40/75) lost $\geq 20\%$ body weight by one-year follow-up. Of these 40, 39 (98%) underwent bariatric surgery compared to 23% (8/35) of participants who experienced $<20\%$ weight loss. Pain improvement at MCID level or beyond was observed in 75% (30/40) of those with $\geq 20\%$ weight loss, compared to 34% (12/35) who lost $<20\%$ body weight. Natural direct effect estimates suggested increased odds of pain improvement through changes in patella PPT (odds ratio [OR] = 1.62, 95% CI: 0.89, 2.75), wrist PPT (OR = 1.15, 95% CI: 0.77, 1.77), and CES-D score (OR = 1.22, 95% CI: 0.77, 1.87). However, the bootstrap-based confidence intervals around our reported effect sizes slightly overlapped the null value of 1.

Conclusion: Weight loss-induced knee pain improvement is partially attributable to reduced pain sensitization and to a lesser extent improvement in depressive symptoms.

Figure 1. Directed acyclic graph

Figure 2. Baseline and follow-up values for PPT and CES-D.

Disclosure: S. R. Jafarzadeh, None; T. Neogi, None; J. J. Stefanik, None; M. M. Clancy, None; J. S. Li, None; D. T. Felson, None.

Abstract Number: 1948

Beliefs and Preferences for Reducing Sedentary Time in Those with Current or Past Knee Symptoms

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: ARHP I: Pain, Anxiety, and Depression

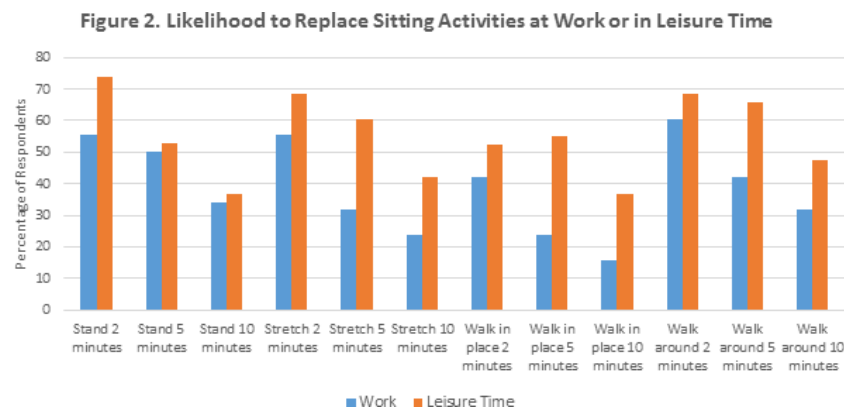
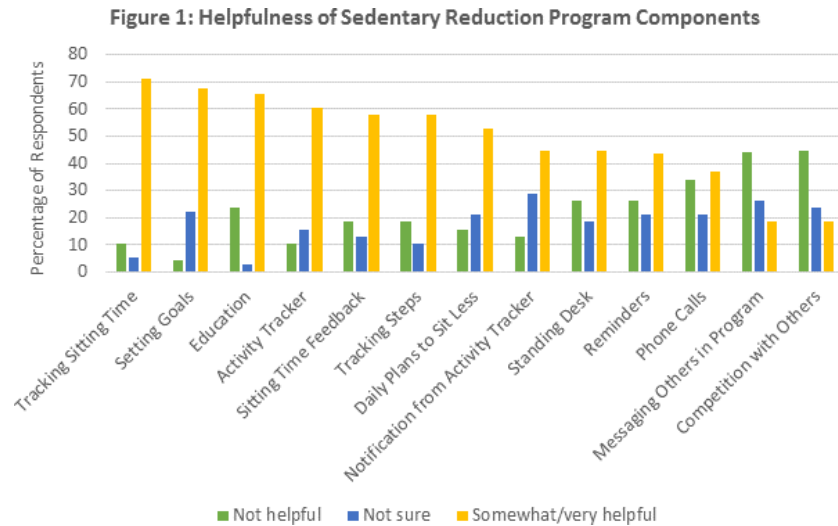
Session Type: ARHP Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Physical activity is beneficial for those with current or previous knee symptoms, yet few meet federal physical activity guidelines. Reducing sedentary time, which has harmful effects independent of physical activity, may be a more feasible approach to improve the health of this population. The purpose of this study was to identify beliefs about sedentary behavior, barriers to standing, and program preferences in adults with knee pain, knee osteoarthritis (KOA), or total knee replacement (TKR).

Methods: Adults ≥ 50 years with knee pain, KOA, or TKR were recruited via flyers, emails, social media, and healthcare professionals. Participants completed an online survey assessing demographics, pain and function (Patient-Reported Outcomes Measurement Information System [PROMIS]), time spent in moderate-to-strenuous physical activity (MVPA; Godin Leisure Time Exercise Questionnaire) and sitting (Sitting Time Questionnaire), beliefs about sedentary behavior, and preferences for a sedentary behavior reduction program.

Results: A total of 35 participants completed the survey (Table 1). TKR patients were older and experienced less pain than those with knee pain or KOA ($P < 0.05$). Participants self-reported being sedentary 10.1 ± 3.8 hours/day and engaging in



113.7±129.8 minutes/week of MVPA, with no differences between knee groups. The majority of participants own a computer (97.1%) and smartphone (82.9%). Most participants (82.9%) believe that reducing sitting time can improve health, with the majority believing brisk or light walking (91.4%) would be better than standing (65.7%) (Table 2). Over half (54.3%) of participants wish they could sit less. The most common barriers to standing were feeling pain/discomfort (48.6%) and inability to stand while using computer (48.6%) or watching TV (22.9%). Sixty-eight percent of participants were interested in participating in a sedentary reduction program and believed tracking sitting time (71%) and setting goals (67.7%) would be most helpful to reduce sitting time (Table 3).

Conclusion: Adults with knee pain, KOA, and TKR believe reducing sitting time could improve health. These results will help to inform the development of future sedentary reduction interventions tailored to the needs of those with current or past knee symptoms.

Table 1 Participant Characteristics

	Overall n=35	Knee Pain or KOA n=25	Knee Replacement n=10
Age, years, mean ± SD	61.6 ± 7.6	58.9 ± 5.6	68.5 ± 7.7
BMI, kg/m ² , mean ± SD	32.1 ± 7.5	31.2 ± 7.5	34.4 ± 7.4
Female, no. (%)	24 (69%)	14 (56%)	10 (100%)
Race, no. (%)			
White	33 (94%)	23 (92%)	10 (100%)
Education			
< College Degree	10 (29%)	7 (28%)	3 (30%)
≥ College Degree	25 (71%)	18 (72%)	7 (70%)
Employment Status			
Working Part or Full time	20 (57%)	18 (72%)	3 (30%)
Not working	15 (43%)	7 (28%)	7 (70%)
Health Conditions			
Hypertension	15 (43%)	10 (40%)	5 (50%)
Diabetes	4 (11%)	4 (16%)	-
Depression	6 (17%)	2 (8%)	4 (40%)
PROMIS Measures			

Table. (Cont'd)

	Overall n=35	Knee Pain or KOA n=25	Knee Replacement n=10
Mobility	43.3 ± 4.7	43.3 ± 5.0	43.4 ± 4.1
Pain Interference	44.2 ± 6.1	45.2 ± 6.3	41.6 ± 4.6
Pain Intensity	54.2 ± 6.1	55.8 ± 4.7	50.3 ± 7.4
Sedentary Behavior			
Average hours/day	10.1 ± 3.8	10.2 ± 3.8	9.7 ± 4.0
Physical Activity			
Average MVPA weekly	113.7 ± 129.8	120.3 ± 142.9	97.0 ± 93.9

BMI: Body mass index ; KOA: Osteoarthritis; MVPA: Moderate to vigorous intensity physical activity; PROMIS: Patient-Reported Outcomes Measurement Information System

Disclosure: C. Pellegrini, None; S. Powell, None; C. Larsen, None; S. Phillips, None.

Abstract Number: 1949

Implementation of a Health Diary for Patients with Fibromyalgia

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: ARHP I: Pain, Anxiety, and Depression

Session Type: ARHP Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Fibromyalgia (FM) is a syndrome of central sensitization that encompasses many disorders where the central nervous system amplifies sensory input across many organ systems and results in diverse and varied symptoms such as musculoskeletal pain, alteration of sleep and fatigue. FM has a severe impact on the quality of life of patients, affecting work capacity, activities of daily life, as well as social relationships. There is agreement that first-line treatment should include both pharmacological and non-pharmacological interventions. Among the latter, the completion of a health diary is included as a valuable self-help tool to assess and control symptoms and improve activity levels and quality of life. In the context of this study, we designed a health diary to support self-management in patients with FM. The health diary aimed at changing and adjusting health-related behaviors such as pain management, exercise, and rest through practical hints and self-help activities. The purpose is to explore the effect of the use of a health diary in daily self-management in patients with FM.

Methods: Patients diagnosed with primary FM, referred by the rheumatologist, were included in the study and randomly assigned into two groups. All patients received the health diary with correspondent instructions for its completion. In addition to the completion of the health diary, patients in the experimental group participated in a four-weekly guided counseling and education workshop regarding how to handle chores and health-related behaviors while dealing with FM self-management. The counseling and educational workshop was delivered by two occupational therapists. Patients in both groups completed the FIQ (Fibromyalgia Impact Questionnaire) and a visual analog scale of activity-performance (VAS) at baseline (Mi) and again the visual analog scale one month following the intervention (Mf). Means were calculated to assess the impact of the FM. Instead, the initial and final results of the analog scale were compared using the independent Student T-test. All patients received an email address to ask for support if needed.

Results: 30 women, 34 to 75 years old (M = 56), participated in the study. Participants had a moderate-high FM impact FIQ = 52.14 (18-79.08). In total, 14 patients from the experimental group and 6 patients from the control group completed the health diary. The initial and final averages of the VAS were for the experimental group: personal care Mi = 7.06 - Mf = 8.66 (P = .009); household activities Mi = 5.6 - Mf = 7.3 (P = .010); work Mi = 3.06 - Mf = 3.5 (P = .10); social activity Mi = 3.7 - Mf = 5.2 (P = .002). No statistically significant changes were observed in the group that solely completed the health diary.

Conclusion: The health diary, supported by guided counseling and education delivered through workshops, could be a useful strategy to enhance the implementation of healthy habits in patients with FM. While a tailored healthy diary may be an interesting landscape to self-management, additional support may even reinforce and enhance the promotion and maintenance of healthy habits.

Disclosure: V. De Cillis, None; A. Semerano, None; A. Pérez Dávila, None; A. Bohr, None; S. Pelaez, None; E. Scheines, None.

Abstract Number: 1950

Self-Reported Depression and Anxiety Among US Adults Aged 18-44 Years with Arthritis, National Health Interview Survey 2014-2016

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: ARHP I: Pain, Anxiety, and Depression

Session Type: ARHP Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

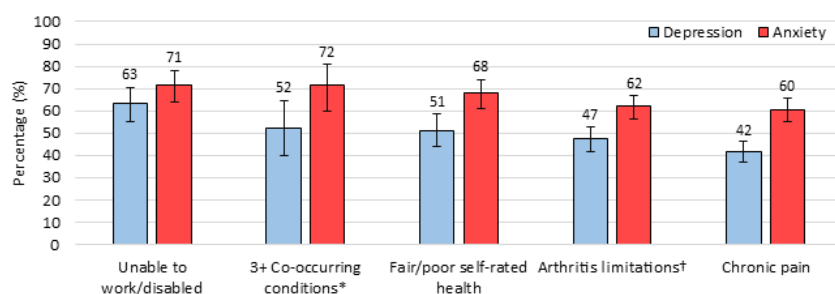
Background/Purpose: Depression and anxiety are frequent comorbid conditions among adults with arthritis, and are associated with poorer quality of life, reduced adherence and efficacy of arthritis treatment, and suicidal ideation. In the general population, younger adults have a higher prevalence of depression and anxiety than older adults. We analyzed nationally-representative population-based prevalence of self-reported depression and anxiety among 21,318 young adults (aged 18-44 years) with and without arthritis.

Methods: We combined National Health Interview Survey data from 2014, 2015, and 2016. Arthritis was “yes” to: “Have you ever been told by a doctor or other health care professional that you have arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?” We classified respondents as having self-reported depression and/or anxiety if they had high or medium frequency (daily, weekly, or monthly) of respective symptoms. Analyses accounted for the complex survey design to make estimates representative of the US civilian, non-institutionalized population. We estimated the unadjusted weighted prevalence (%) with 95% confidence intervals (CI) of depression and anxiety by arthritis and groups defined by selected characteristics.

Results: In 2014-2016, 7.7% of young adults reported arthritis and among them, 29.0% and 48.7% reported depression and anxiety, respectively. Depression prevalence was 2.4 times higher for young adults with arthritis than those without (29.0%; CI=26.0-32.2 vs. 12.3%; CI=11.7-13.0); anxiety prevalence was 1.6 times higher (48.7%; CI=45.5-52.0 vs. 29.6%; CI=28.6-30.6). Among 1,644 young adults with arthritis, depression prevalence was high among those unable to work/disabled and anxiety prevalence was high among those unable to work/disabled and those with 3+ co-occurring chronic conditions (Figure 1). Among those with arthritis and the respective conditions, 32.1% (CI=28.1-36.4) reported taking medications for anxiety and 45.0% (CI=38.7%-51.5%) reported taking medications for depression; for both, medication use was higher compared to those without arthritis (Figure 2).

Conclusion: Self-reported depression and anxiety are common in young adults and considerably more prevalent among those with arthritis than those without. Although there is substantial awareness of depression in adults with arthritis, anxiety prevalence was higher. Health care providers can help arthritis patients by screening for these conditions, especially in younger adults, and referring them to mental health specialists for diagnosis and treatment.

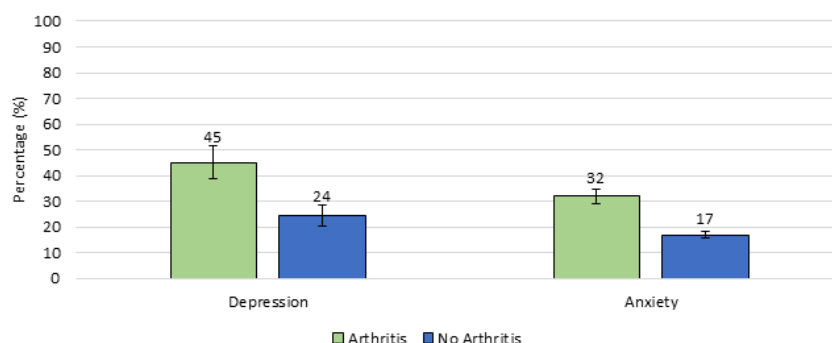
Figure 1. Prevalence of self-reported depression and anxiety among 1,644 US adults aged 18-44 with arthritis for groups defined by selected characteristics, NHIS 2014-2016



*Among nine chronic conditions (asthma, cancer, chronic obstructive pulmonary disease, diabetes, heart disease, hepatitis, hypertension, kidney disease, or stroke), not including arthritis.

†Arthritis-attributable activity limitations, which do not include work limitations.

Figure 2. Prevalence of taking medications for self-reported depression or anxiety among 21,318 US adults aged 18-44 years, by arthritis status, NHIS 2014-2016



Disclosure: D. Guglielmo, None; J. M. Hootman, None; L. Murphy, None; M. Boring, None; K. Theis, None; C. G. Helmick, None; K. E. Barbour, None; P. Katz, None.

Abstract Number: 1951

The Effect and Psychosocial Impact of a Longstanding Telephone Peer Counseling Service on Volunteers with Systemic Lupus Erythematosus

Priscilla Toral¹, Melissa T. Flores¹, Roberta Horton¹ and Jillian Rose², ¹Social Work Programs, Hospital for Special Surgery, New York, NY, ²Hospital for Special Surgery, New York, NY

SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: ARHP I: Pain, Anxiety, and Depression

Session Type: ARHP Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Studies have demonstrated the value of peer volunteers providing psychosocial support to people living with rheumatic & other chronic conditions. An evaluation was conducted with counselors of a national toll-free phone peer counseling service to assess how their role as helpers affects their psychosocial coping with SLE. Ongoing since 1988, this service provides emotional support for people with SLE & their loved ones. The program has been presented at prior ACR/ARHP, including program users' satisfaction & the impact of a revised curriculum on counselors.

Methods: A 43-item survey with Likert scale & open-ended questions was administered to 11 active peer counselors. The survey captured demographics, satisfaction with their role & examined SLE coping & actions taken since becoming a peer counselor. Surveys were completed electronically.

Results: All (100%) peer counselors completed the survey, with a reach of 44 callers matched from 2017-2018. All respondents were female, 50% identified as White, 30% Black/African-American, 20% Hispanic & 30% other race. Counselors' ages ranged from 30-79, with 30% ages 60-69. Half (50%) were either employed full time/part time, 40% retired & 10% unemployed/receiving disability. Almost half (40%) were single, 91% have SLE & have been a counselor for an average of 12 years.

When asked about satisfaction in their role, 91% indicated being very satisfied. Top reasons for becoming a counselor included an opportunity to help others affected by SLE (100%) & enhancing personal growth/ development (73%). When asked their reasons for continuing as a counselor, 82% identified to meet others impacted by SLE & 73% identified for the support of program staff.

In relation to coping, 64% indicated that they have coped better with SLE since becoming a counselor. Most (73%) reported that they had a better understanding of SLE since becoming a counselor, with 38% very much attributing this to the program. Almost half (46%) reported feeling less depressed since becoming a peer counselor with 60% very much & 40% somewhat crediting their role for this change. Counselors also reported feeling less alone (73%) with 43% very much attributing this to their peer role.

When asked what they find most useful from monthly training seminars, 89% identified group discussion & 78% indicated educational games. When asked if monthly seminars help them to better cope with SLE, 78% agreed & 89% of counselors reported that seminars provide a space for them to reflect on their SLE. Counselors shared the most rewarding part of their role is "educational information that helps me understand SLE better" & "the opportunity to be outside of my own illness & connect with others."

Conclusion: Despite limitations due to a small sample size, results reinforce the two-way flow of psychosocial support received by counselors through their support of callers, ongoing connections with peers & program staff via monthly seminars. Similar to program callers, the counselor role positively impacts volunteers' ability to better cope with SLE & reduces isolation. Findings also highlight the continued relevance of a phone support service to people with SLE and opportunities for further research on volunteer impact of peer-staffed programs.

Disclosure: P. Toral, None; M. T. Flores, None; R. Horton, None; J. Rose, None.

Abstract Number: 1952

Experimental Tendinopathy Treatment with SM04755, a Topical Small Molecule Inhibitor of the Wnt Pathway

Vishal Deshmukh, Timothy Seo and Yusuf Yazici, Samumed, LLC, San Diego, CA

SESSION INFORMATION

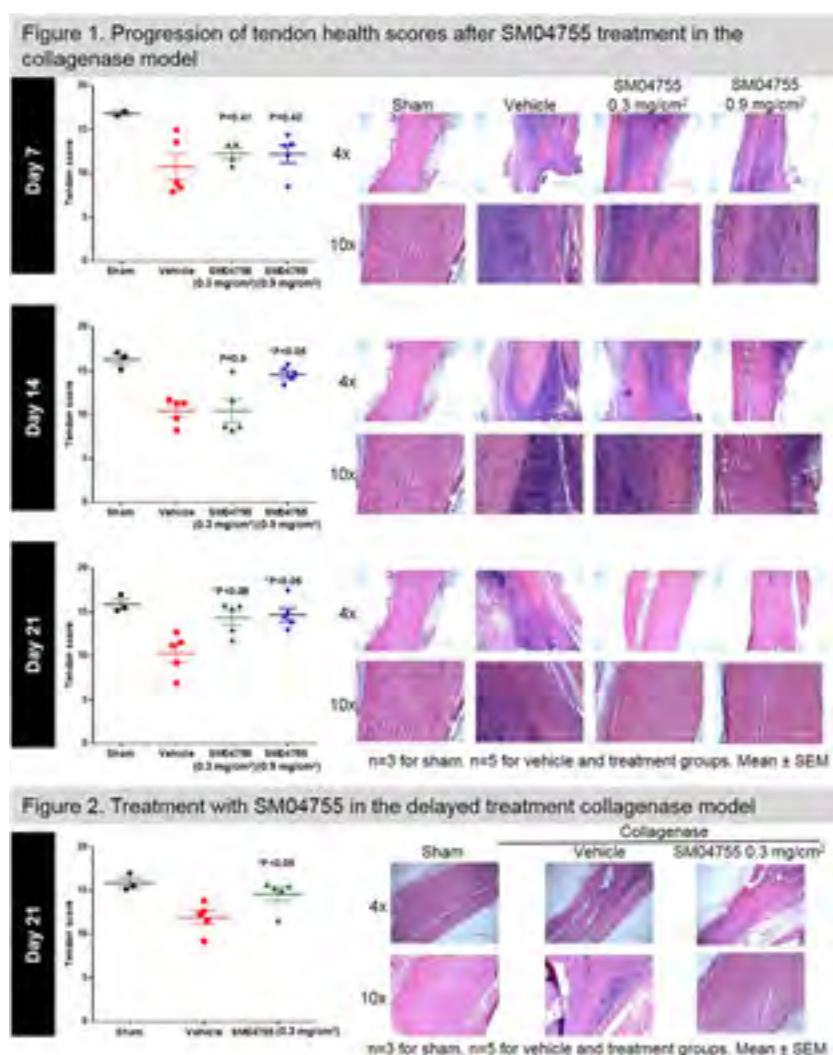
Session Date: Monday, October 22, 2018

Session Title: Orthopedics, Low Back Pain and Rehabilitation – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Tendinopathy is an inflammatory and degenerative disorder caused by injuries and overuse. The Wnt pathway is upregulated in chronic tendinopathy and involved in inflammation, tenocyte differentiation, and fibrosis. SM04755, a novel, topical, small molecule Wnt pathway inhibitor, has previously been shown to inhibit inflammation,



reduce fibrosis, and increase tenocyte differentiation (Deshmukh et al., *Arthritis Rheumatol*, 2016). Two further experiments are presented: 1. SM04755 treatment in an acute dose-response tendinopathy model and 2. SM04755 treatment in a repeat injury/delayed treatment (RIDT) tendinopathy model. These models simulate acute and acute-on-chronic clinical tendinopathy, respectively.

Methods: SM04755 was assessed in rodent Achilles tendinopathy models, induced by intra-tendon collagenase injection (500 µg). In the acute dose response model, a single injection of collagenase or sham per animal on Day -4 was followed on Day 0 by daily topical vehicle, or 0.3 mg/cm² or 0.9 mg/cm² SM04755. Achilles tendons were harvested on Days 7, 14, and 21. In the RIDT model, collagenase injections were given at Days -28 and -14, followed on Day 0 with daily topical vehicle or 0.3 mg/cm² SM04755. Achilles tendons were harvested on Days 7, 14, 21, and 28. Blinded histology analyses scored tendon health based on linearity, tendon cell shape, tendon cell density, inflammation, and hemorrhage (range 5-20). Statistical analyses: one-way ANOVA for multiple group comparisons, t-tests for two group comparisons.

Results: In the acute dose-response model, SM04755 improved tendon health from baseline compared to vehicle as assessed by tendon histology scores. Vehicle scores were 10.77 [±1.46] at Day 7, 10.44 [±0.66] at Day 14, and 10.31 [±1.02] at Day 21. SM04755 (0.3 mg/cm²) scores were 12.30 [±0.62] at Day 7 (NS), 10.45 [±1.29] at Day 14 (NS), and 14.37 [±0.82] at Day 21 (P<0.05). SM04755 (0.9 mg/cm²) scores were 12.22 [±1.02] at Day 7 (NS), 14.57 [±0.41] at Day 14 (P<0.05), and 14.67 [±0.76] at Day 21 (P<0.05) (Fig. 1). In the RIDT model, vehicle scores were 12.35 [±0.30] at Day 7, 10.09 [±0.76] at Day 14, 11.92 [±0.77] at Day 21, and 13.72 [±0.35] at Day 28. SM04755 (0.3 mg/cm²) scores were 11.86 [±2.13] at Day 7 (NS), 9.44 [±0.48] at Day 14 (NS), 14.61 [±0.77] at Day 21 (P<0.05), and 14.93 [±0.46] at Day 28 (NS) (Fig. 2).

Conclusion: In the acute dose-response model, SM04755 (0.3 mg/cm²) showed statistically significant improvements in tendon scores compared to vehicle at Day 21. The 0.9 mg/cm² dose achieved significance at Days 14 and 21, indicating faster response at higher SM04755 dose. In the RIDT model, SM04755 0.3 mg/cm² dose promoted accelerated tendon healing compared to vehicle. Therefore, SM04755 demonstrated accelerated improvement of tendon histology in acute and RIDT models compared to vehicle and has potential as a tendinopathy therapy. Clinical studies are planned.

Disclosure: V. Deshmukh, Samumed, LLC, 1, 3; T. Seo, Samumed, LLC, 1, 3; Y. Yazici, Samumed, LLC, 1, 3.

Abstract Number: 1953

Randomized Trial on Exercise at Late-Stage after Total Knee Replacement

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Orthopedics, Low Back Pain and Rehabilitation – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Total knee replacement (TKR) improves pain and quality of life; however, the functional limitations that existed for years before surgery tend to persist after surgery. Progressive and intensive exercise programs could resolve these persistent limitations but they are not tolerated by many patients until later stage (>2 months) after surgery. Evidence for the effectiveness of exercise at later stage post-TKR is limited.

The purpose of this study was to compare the effectiveness of later stage exercise programs (outpatient individualized physical therapy [PT] and group classes in community centers) with an usual medical care, at improving physical function and activity, and to explore heterogeneity of treatment effects.

Methods: The study was a 3-arm single-blind randomized clinical trial that enrolled 240 individuals at least 60 years of age, with primary TKR done at least 2 months before, who experienced moderate functional limitations, and were medically cleared to exercise. The 3 study arms were clinic-based PT exercise, community-based group exercise, or usual care (control). The control group continued their usual care whereas the exercise groups participated in supervised exercise programs during 12 weeks.

Physical function was the main outcome and was assessed primarily by the Western Ontario and McMaster Universities Osteoarthritis Index-Physical Function scale (WOMAC-PF), and secondarily by performance-based tests germane to patients with TKR, and additional patient-reported outcomes at 3 and 6 months. The trial was registered in ClinicalTrials.gov, NCT02237911.

Results: All 3 arms demonstrated clinically important improvements. At 3 months, the PT arm showed the most improvement in WOMAC-PF ($p=0.04$). Compared to community arm, the PT arm had greater improvement on performance-based tests (0.1; 95%CI: 0.002, 0.2) and percentage of responders (18% to 24% more in the PT arm). PT arm also had more improvements than control in performance-based tests (0.3, 95%CI: 0.1, 0.4) and percentage of responders (19% to 34% more in PT arm). The community arm improved performance-based tests compared to control (0.2; 95%CI: 0.02, 0.3). Most differences were sustained at 6 months. Exercise was not associated with serious adverse events. Moderator analysis showed significant interactions for obesity, anxiety/depression, and arthritis self-efficacy. Non-obese participants in both exercise arms had more improvements in physical function than the control. For obese participants, those in PT arm appear to experience more improvements than the community arm. Participants without depression/anxiety and high levels of self-efficacy in exercise arms had greater functional recovery compared to control; whereas those in the community arm with depression/anxiety symptoms and low levels of self-efficacy experienced less functional recovery.

Conclusion: This study provides novel evidence about the safety and effectiveness of late-stage intensive rehabilitation post-TKR. Individualized PT provided greater improvements in physical function than community or control arms. Patients and clinicians could benefit from studies to test models to implement late-stage rehabilitation programs post-TKR.

Disclosure: S. R. Piva, None; M. Schneider, None; C. Moore-Patterson, None; M. B. Catelani, None; A. Gil, None; B. Klatt, None; A. DiGioia, None; G. J. Almeida, None; S. S. Khoja, None; G. Sowa, None; J. Irrgang, None.

Abstract Number: 1954

Factors Associated with Overweight or Obesity in Athletes 5 Years after Anterior Cruciate Ligament Injury

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

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Session Type: ACR/ARHP Combined Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Obesity and knee injury, including anterior cruciate ligament (ACL) rupture, are strong risk factors for the development of knee osteoarthritis. Identifying participant and post-injury characteristics that are associated with obesity after knee injury may help target at risk populations for weight management interventions. The purpose of this study is to examine factors associated with overweight or obesity in athletes 5 years after ACL injury.

Methods: We analyzed data from the Delaware-Oslo ACL Cohort Study, a longitudinal cohort study of athletes after acute ACL rupture from the United States ($n=150$) and Norway ($n=150$). Inclusion criteria were sustaining a unilateral ACL rupture confirmed by MRI and regularly participating in level I/II sports prior to injury. Those with bilateral injuries or significant concomitant injuries were excluded. The outcome of interest was overweight or obesity at the 5-year follow-up. Body mass index (BMI) was calculated from self-reported height and weight, and categorized as Normal ($\text{BMI} < 25 \text{ kg/m}^2$) or Overweight/Obese ($\text{BMI} \geq 25 \text{ kg/m}^2$). Exposures of interest were age (at enrollment), sex, surgical status (ACL reconstruction vs. non-operative rehabilitation), and self-reported knee function at 2-year follow-up (IKDC, International Knee Documentation Committee Subjective Knee Form). We evaluated the association between the exposures and the

Table. Adjusted odds ratios and 95% confidence intervals evaluating the association of exposures with being overweight or obese 5 years after ACL injury			
Exposure	Odds Ratio	95% Confidence Interval	
Age (for each 1 year increase in age)	0.91	0.85	0.98
Sex (Ref = Men)	0.15	0.049	0.46
Surgical status (Ref = ACL reconstruction)	0.23	0.071	0.77
IKDC Score at 2-year follow up (per 1 point increase in IKDC score)	1.02	0.98	1.07

outcome using odds ratios with 95% confidence intervals from logistic regression, mutually adjusting for the other exposures, as well as baseline BMI, country (US vs. Norway).

Results: Of 300 participants enrolled in the study, 215 (72%) completed the 5-year follow up (mean baseline age 27.4 ± 10.1 years, baseline BMI 24.3 ± 3.5 kg/m², 48% women). At 5 years, 49% of the athletes were overweight or obese. Athletes who were older age at baseline, women, and received non-operative treatment had lower odds of being overweight or obese at 5-year follow-up, adjusting for baseline BMI and country (Table). Self-reported knee function at 2-year follow-up was not associated with being overweight or obese at 5-year follow-up.

Conclusion: Athletes who received non-operative treatment, women, and older athletes were less likely to be overweight or obese at 5-year follow-up. Those who undergo ACL reconstruction, men, and younger athletes may be appropriate targets for weight management interventions to prevent weight gain. Further research is needed to confirm these results and evaluate why those who undergo ACL reconstruction have higher odds of being overweight or obese at long-term follow-up.

Disclosure: L. Thoma, None; J. Johnson, None; D. White, None; M. A. Risberg, None; L. Snyder-Mackler, None.

Abstract Number: 1955

Race Is Associated with Discharge Disposition after Total Knee Arthroplasty (TKA), Which Is Associated with 90-Day Readmission Rate

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Orthopedics, Low Back Pain and Rehabilitation – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: To assess whether race/ethnicity is associated with differences in discharge disposition after elective primary total knee arthroplasty (TKA), and if discharge disposition is associated with 90-day hospital readmission.

Methods: This was an observational cohort study that used the Pennsylvania Health Care Cost Containment Council (PHC4) Database, which includes all patient discharges from 170 non-governmental acute care hospitals in the State of Pennsylvania. We examined the association of race/ethnicity with discharge disposition after elective primary TKA, using multivariable logistic regression models, which were adjusted for patient-level and facility-level variables.

Results: Between 2012 and 2015, there were 107,768 eligible primary TKAs had identifiable race/ethnicity. In study cohort, 7,287 (6.8%) were African-Americans; 63.4% were female, 43.1% were younger than 65 years, 40.2% had private, 3.6% Medicaid and 56.3% Medicare insurance. The 30-, 60- and 90-day readmission rates were 5.3%, 7.5% and 9.4%, respectively. Compared to younger than 65 years, 30-, 60- and 90-day readmission rates were higher in adults 65+ years. *Younger than 65 years.* Compared to whites, African-Americans were more likely to be discharged to skilled nursing facility (SNF) or inpatient rehabilitation facility (IRF), but not home health care, 2.49 (95% CI, 1.42, 4.36), 3.91 (95% CI, 2.17, 7.06) and 1.30 (95% CI, 0.91, 1.88), respectively.

65 years or older. Compared to whites, African-Americans were more likely to be discharged to SNF but not IRF or home health care, 3.30 (95% CI, 1.81, 6.02), 1.64 (95% CI, 0.91, 2.97), and 1.06 (95% CI, 0.68, 1.65), respectively.

Younger than 65 years. Compared to home self-care, discharge to IRF or SNF, but not home health care, were each associated with higher odds ratios of 90-day readmission: 3.62 (95% CI, 2.33, 5.64), 1.91 (95% CI, 1.37, 2.65) and 1.08 (95% CI, 0.96, 1.22), respectively.

65 years or older. Similarly, in multivariable-adjusted model, compared to home self-care, discharge to IRF or SNF, but not home health care, were each associated with higher odds ratios of 90-day readmission: 2.85 (95% CI, 2.25, 3.61), 1.55 (95% CI, 1.27, 1.89) and 0.96 (95% CI, 0.82, 1.12), respectively.

Sensitivity analyses by inverse probability weighting (IPW) method confirmed these findings with minimal accentuation of odds ratios, but no change in significance or interpretation of findings.

Conclusion: African-Americans were more likely than whites to be discharged to IRF and SNF. Discharge to IRF or SNF, but not home health care, were each associated with higher odds ratios of 90-day readmission. These findings indicate that race/ethnicity may predict higher utilization, and further insights into modifiable attributes associated with this higher utilization are needed.

Disclosure: J. A. Singh, Takeda, Savient, 2,Savient, Takeda, Regeneron, Merz, Iroko, Bioiberica, Crealta/Horizon and Allergan pharmaceuticals, WebMD, UBM LLC, Medscape , Fidia pharmaceuticals and the American College of Rheumatology, 5; M. Kallan, None; S. Ibrahim, None.

Abstract Number: 1956

Cohort Effects in Back Pain: The Effect of Changes in Life-Style and Co-Occurring Conditions

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Orthopedics, Low Back Pain and Rehabilitation – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: The goal of this study was to determine a) if the age-trajectory (life course) of back pain differs by birth cohort and b) whether any cohort differences are explained by changes in socio-economic status (SES), lifestyle factors, and the presence of chronic conditions.

Methods: We used biannually collected data from the 1994-2010 Canadian Longitudinal National Population Health Survey: 10,330 participants born from 1925 to 1974 grouped in five 10-year birth cohorts: Pre-World War II, born 1925-1934; World War II generation, born 1935-1944; older baby boomers, born 1945-1954; younger baby boomers, born 1955-64; and generation X, born 1965-74. The outcome was reported back pain as a long term health conditions diagnosed by a health professional. We used multilevel logistic growth models to examine cohort effects in the age-trajectory of back pain adjusting for sex, SES (education, income), lifestyle factors (BMI, physical activity, sedentary behavior, smoking status) and multimorbidity (2+ conditions up to 17).

Results: There was a trajectory of increasing back pain with age up to middle age (50-55 years) and plateauing afterwards. In addition, there were also significant cohort differences ($p < 0.0001$): when compared at the same age, each succeeding recent cohort had higher odds of reporting back pain than those in the earlier cohort. Low education, being a smoker, obesity, and sedentary behavior were associated with increased odds of reporting back pain, but did not substantially affect cohort differences. Addition of multimorbidity to the model significantly and substantially attenuated the cohort differences.

Conclusion: The results suggest that more recent cohorts of Canadian adults are more likely to have back pain and that they report back pain earlier than previous generations. These cohort differences were explained by cohort effects of increasing multimorbidity in more recent generations.¹ These findings are supported by descriptive studies showing high level of multimorbidity in people with back pain,² with important implications for our understanding of back pain and the delivery of healthcare and services.

1. Canizares M, Hogg-Johnson S, Gignac MAM, Glazier RH, Badley EM. Increasing Trajectories of Multimorbidity Over Time: Birth Cohort Differences and the Role of Changes in Obesity and Income. The journals of gerontology Series B, Psychological sciences and social sciences. 2017.

2. Badley EM, Millstone DB, Perruccio AV. Back Pain and Co-occurring Conditions: Findings from a Nationally Representative Sample. Spine (Phila Pa 1976). 2018.

Disclosure: E. M. Badley, None; A. V. Perruccio, None; M. Canizares, None.

Abstract Number: 1957

Peri-Operative Glycemic Evaluation Prior to Total Joint Replacement in Patients with and without Diabetes

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SESSION INFORMATION

Session Date: Monday, October 22, 2018

Session Title: Orthopedics, Low Back Pain and Rehabilitation – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Elevated hemoglobin A1c (HbA1c) has been associated with a 9-fold increase in wound complications after total joint replacement (TJR). Data suggest that including HbA1c in perioperative screening lowers complications. The CDC recommends perioperative glycemic control as a prevention strategy for infections in patients with and without DM. We aimed to assess how frequently HbA1c was tested prior to TJR in a large claims database.

Methods: Within Medicare Parts A/B/D (2010-2014), we identified patients who were ≥ 65 years old and underwent TJR (hip or knee). The index date was date of TJR; all patients were free of TJR and continuously enrolled in Medicare for ≥ 1 year prior to TJR. We created 4 mutually exclusive groups during the baseline period ranging from 365 to 90 days prior to TJR; 1) non-DM based on no ICD-9 code for DM or DM complications, no claim for insulin or anti-DM medication; 2) DM without medication, based on a diagnosis code for DM but no claim for insulin or non-insulin antidiabetic medication; 3) DM on non-insulin antidiabetic medication; and 4) DM on insulin with or without other antidiabetic medication. The outcome was HbA1c test ordered 90 days prior to TJR. Covariates including age, sex, race, comorbidities, medications, outpatient visits, and number of HbA1c tests, were collected during the baseline period. We calculated the proportion of patients receiving HbA1c or serum glucose test in the 90 days prior to TJR. We used logistic regression with adjustment for covariates to assess characteristics associated with HbA1c testing.

Results: Seventy-two percent were non-DM, 11% DM without medication, 13% DM on non-insulin medications, and 4% DM on insulin. Mean age was 73 -75. Patients with DM had more outpatient visits, and co-morbid diseases compared to those without DM. During the baseline period mean number of HbA1c tests was 0.1 in the non-DM group, 0.8 in DM without medication, 1.1 in DM on non-insulin medications, and 1.3 in DM on insulin. Only 5% of patients without DM had an HbA1c testing within 90 days of TJR, compared to 26% in those with DM not on medication, 39% in DM on non-insulin medications and 43% with DM on insulin. Serum glucose testing was obtained more frequently- 37% of non-DM, and 46-50% of patients with DM. In patients without DM, non-white race and obesity lead to increased HbA1c testing. In patients with DM on no medication, those with DM complications had increased HbA1c testing. For all groups having HbA1c tested in the baseline period was associated with having HbA1c tested prior to TJR (Table).

Conclusion: In this large population based cohort of patients undergoing TJR, HbA1c testing perioperatively occurred in less than half of patients with DM. The presence of diseases co-morbid to DM was not strongly associated with increased screening in the non-DM population. Further study on the utility of perioperative HbA1c monitoring and postoperative outcomes is warranted.

Table: Outcomes in 90 days prior to TJR

	No Diabetes N=335,365	Diabetes		
		Without medication N=49,965	Non-insulin medication N=59,705	Insulin N=20,531
HbA1c 90 days prior to TJR, %	5	26	39	43
Serum glucose 90 days prior to TJR, %	37	46	48	50
Odds Ratio (CI) of having HbA1c obtained in 90 days prior to TJR*				
# of HbA1c tests during baseline	4.3 (4.1, 4.4)	2.5 (2.4,2.5)	2.4 (2.3, 2.4)	2.5 (2.4, 2.6)
Female	0.9 (0.8, 0.9)	1.0 (0.9, 1.1)	1.0 (1.0, 1.0)	1.0 (0.9, 1.0)
Race				
White	ref	ref	ref	ref
Black	1.3 (1.2, 1.4)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)
Hispanic	2.1 (1.8, 2.4)	1.0 (0.8, 1.1)	1.2 (1.0, 1.3)	1.3 (1.1, 1.6)
Other	1.9 (1.7, 2.1)	1.3 (1.1, 1.5)	1.1 (1.0, 1.2)	1.0 (0.8, 1.3)
Complications of Diabetes				
Nephropathy	--	1.3 (1.2, 1.5)	1.0 (0.9, 1.1)	1.1 (1.0, 1.2)
Neuropathy	--	1.2 (1.1, 1.3)	1.0 (1.0, 1.1)	0.9 (0.9,1.0)
Retinopathy	--	1.3 (1.2, 1.5)	1.0 (0.9, 1.1)	1.1 (1.0, 1.2)
Co-Morbidities				
Hypertension	0.9 (0.9, 0.9)	1.0 (0.9,1.1)	0.8 (0.8, 0.9)	0.8 (0.7, 0.9)
Hyperlipidemia	0.9 (0.8, 0.9)	0.9 (0.9,1.0)	0.9 (0.8, 0.9)	1.0 (0.9,1.1)
Coronary Heart Disease	0.9 (0.8, 1.0)	0.9 (0.9, 1.0)	1.0 (0.9, 1.0)	1.0 (0.9, 1.2)
Peripheral Vascular Disease	1.1 (1.0, 1.1)	1.0 (0.9,1.1)	0.9 (0.9, 1.0)	1.0 (0.9, 1.1)
Obesity	1.2 (1.1, 1.3)	1.0 (0.9, 1.1)	1.0 (0.9, 1.0)	1.0 (0.9, 1.1)
Stroke	1.0 (0.9, 1.0)	1.0 (0.9, 1.0)	1.0 (0.9, 1.0)	1.1 (1.0,1.2)
Chronic Kidney Disease	1.0 (1.0, 1.1)	1.0 (0.9, 1.0)	1.0 (1.0, 1.1)	1.1 (1.0, 1.2)

* variables adjusted for other variables in tables and additionally age, atrial fibrillation, congestive heart failure, outpatient visits, and medications including ACE inhibitors, angiotensin receptor blockers, anticoagulants, antiplatelet, COX-2 inhibitor, non-steroidal anti-inflammatory, opioids, statins, insulin, and non-insulin anti-diabetic medications
TJR; total joint replacement; CI; confidence interval

Disclosure: L. A. MacFarlane, Samumed, 5; Y. Jin, None; P. D. Franklin, None; J. Lii, None; J. N. Katz, None; S. C. Kim, None.

Abstract Number: 1958

Gene Expression Pathways across Multiple Tissues in Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis Reveal Core Pathways of Disease Pathology

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Genetics, Genomics and Proteomics Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: In recent years, several studies have characterized the gene expression signatures of different tissues affected by ANCA-associated vasculitis (AAV). The purpose of this study is to test the hypothesis that there are commonly preserved disease pathways in all AAV tissues thus far characterized.

Methods: Gene expression data were collected from the three AAV tissues thus far characterized (orbit, peripheral leukocytes, and sinus brushings). The set of differentially up and down-regulated genes from each study were analyzed using the Cytoscape software application with the Reactome FI plugin—this is a pathway-based network analysis system using expert curated knowledge of protein-protein interactions. The pathways data were adjusted for multiple comparisons using a multi-dimensional local false discovery rate (md-lofdr), which estimates the probability of a false discovery of a given pathway in all three tissues analyzed.

Results: Four individual genes were upregulated in all three tissues—*IL1RN*, *TLR2*, *SCL11A1*, and *MMP9*. After multiple comparison adjustments, the network pathway analysis revealed 28 pathways associated with all three tissues. The most strongly associated pathway for all three tissues was the *neutrophil degranulation* pathway (md-lofdr=1.0x10⁻¹²), followed by the *osteoclast differentiation* (md-lofdr=3.8x10⁻⁰⁵), *cell surface interactions at the vascular wall* (md-lofdr=4.2x10⁻⁰⁴), *signaling by interleukins* (md-lofdr=6.1x10⁻⁰⁴), and *phagosome* (md-lofdr=0.003) pathways. There were no downregulated genes or pathways common to all three tissues.

Conclusion: This analysis identified individual genes and pathways of disease common to all AAV tissues thus far characterized. The use of a network pathway analysis allowed us to identify pathologic mechanisms that were not readily apparent in the commonly expressed genes alone. Many of these pathways are consistent with current theories about infectious drivers and the crossroads of innate and adaptive immune mechanisms. In addition, this analysis highlights novel pathways, such as vessel wall interactions and platelet activation, which require further investigation.

Disclosure: M. Friedman, None; D. Choi, None; S. Planck, None; J. T. Rosenbaum, None; C. Sibley, None.

Abstract Number: 1959

Stability of DNA Methylation Signature in Primary RA Synovial Fibroblasts Compared with Cultured Fibroblast-like Synoviocytes

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Genetics, Genomics and Proteomics Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is an aggressive immune-mediated joint disease with synovial inflammation and joint destruction. Fibroblast-like synoviocytes (FLS) play a key role in mediating inflammation and joint damage. FLS are usually isolated from enzymatically dispersed synovial tissue and expanded in culture for multiple passages to achieve relatively homogenous population. Epigenetic alteration in RA FLS such as DNA methylation has been demonstrated stable for many passages. One critical question is whether the pathogenic genes altered in later passage FLS reflects the epigenome in situ. Therefore, we studied DNA methylation in the primary (P0) passage synovial fibroblasts (SF) and compared the patterns to late passage cells.

Methods: Genomic DNA from cultured FLS (30 RA, 16 OA) and P0 SF (5 RA, 10 OA) was isolated from synovial tissues obtained at the time of total joint replacement. P0 SF were isolated by enzymatically disaggregating cells and negatively selecting either using anti-CD45 magnetic beads or adherence to plastic. The P0 cells were evaluated by flow cytometry for T cells (RA $1.1 \pm 0.2\%$, OA $0.4 \pm 0.1\%$), B cells (RA 0.2% , OA 0.1%). Methylation levels were measured using Illumina HumanMethylation450 chip. Differentially methylated loci (DMLs) were identified using Welch's *t*-test and mapped to gene promoter regions to define differentially methylated genes (DMGs). The overlapped DMGs were calculated using Hypergeometric test. To compare enriched biological pathways, Ingenuity pathway analysis was applied.

Results: For P0 SF, 18,537 DMLs (difference of β value > 0.1 and q value < 0.05) were identified in 2,756 DMGs. Compared to previously reported 1,714 DMGs in passage 5 (P5), 582 (34.0%) DMGs of P5 were overlapped with DMGs in P0 (p value = $1.32e-149$). 75 differentially methylated pathways were significantly enriched between RA and OA in P0, and 15 of them are overlapped with 52 pathways enriched in P5, such as "Complement System" and "NF- κ B Signaling" associated with immunity and inflammation.

Because the limited number of P0 RA samples may be underpowered, we decreased DML stringency to q value cutoff of 0.1 to allow more DMGs and enriched pathways included. As a result, 26,267 DMLs (difference of β value > 0.1 and q value < 0.1) located on 3,578 DMGs are identified between RA and OA FLS in P5, in which 798 (46.6%) DMGs of P5 were overlapped with DMGs in P0 (p value = $1.04e-241$). In addition, out of 108 significantly enriched pathways between RA and OA in P0, 19 of them are overlapped with pathways enriched in P5. Interestingly, RA-specific pathway "Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis" is overlapped.

Conclusion: In this study, we have compared the DNA methylation signatures in RA between P0 SF and classically prepared P5 FLS. Even though there were differences in cell populations and processing methods, the overlap was highly significant with nearly half of DMGs between RA and OA in P5 FLS can be found in the P0 SF. Despite potential limitations due to sample size and the fact that P0 SF includes several subsets of fibroblasts, the DNA methylation signature of classical RA FLS in established culture are consistent with the patterns observed in SF.

Disclosure: R. Ai, None; D. Hammaker, None; W. Wang, None; G. S. Firestein, Janssen Pharamceuticals, 2, 5.

Abstract Number: 1960

Exome Sequencing Reveals Rare Recessive Mutations in Multiple Genes Including FAS, RAD51B, and ISG15 in a Single Family with Lupus and Suggests a Unique Genetic Model

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Genetics, Genomics and Proteomics Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Lupus is a complex heterogeneous disease, which can affect almost any organ system. The genetic etiology of lupus is complex, with multiple genetic susceptibility loci identified. Monogenic lupus, caused by a specific single gene defect, is less common but is generally characterized by early disease onset and more severe presentation. The aim of this study was to understand the genetic basis of a consanguineous family with multiple lupus affected siblings in order to gain insights into lupus pathogenesis.

Methods: DNA samples extracted from whole blood were obtained from all members of a family of 13 (11 siblings and their parents) with 3 sisters affected by early-onset lupus with renal and central nervous system complications. Whole exome sequencing was performed for the 3 affected sisters and both parents. Because of strong consanguinity between both parents (first degree cousins both from their paternal and maternal descents), we assumed a recessive genetic model and focused on identifying rare recessive variants in the affected sisters that are present in heterozygous forms in both parents. Variants were filtered for potentially protein damaging effects using SIFT, Polyphen2, MutationTaster, Mutation Assessor, and FATHMM functional prediction algorithms. Sanger sequencing and Sequenom genotyping were used for validation and genotyping all unaffected siblings.

Results: Using whole exome sequencing, we found that each sister has multiple rare recessive mutations, including rare predicted damaging coding mutations in genes such as *FAS*, *RAD51B*, and *ISG15*, involved in apoptosis, DNA damage repair, and interferonopathy, respectively. These recessive genotypes are exceedingly rare in the general population with expected frequencies of ~1, 9, and 3 in 100,000 individuals, respectively. Interestingly, these mutations were mutually exclusive in the affected sisters. While the *ISG15* recessive mutation was not present in any unaffected sibling, homozygosity for the *FAS* and *RAD51B* mutations were not sufficient to explain lupus in the two other affected sisters as some of the unaffected siblings also have these recessive genotypes. Multiple other rare recessive variants enriched in genes related to apoptosis, inflammasome activation, and cell cycle regulation were identified in the affected sisters, suggesting that accumulation of multiple rare recessive variants underlies lupus phenotype in this family. Indeed, calculating genetic risk score using the total of 69 rare recessive variants identified in the affected sisters revealed a significantly higher genetic risk (~2 times) in the affected compared to unaffected siblings.

Conclusion: We describe a unique genetic model in a consanguineous family with lupus whereby the additive effect of a number of rare recessive variants in inflammatory pathways likely contributes to the disease phenotype within the same family.

Disclosure: J. Alperin, None; K. Mustafa, None; O. Hijjawi, None; P. Coit, None; K. Kaufman, None; A. H. Sawalha, None.

Abstract Number: 1961

Association of GTF2I Region Polymorphism with Systemic Lupus Erythematosus and Systemic Sclerosis, but Not with ANCA-Associated Vasculitis and Polymyositis/Dermatomyositis, in a Japanese Population

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Genetics, Genomics and Proteomics Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Genome-wide association studies of systemic lupus erythematosus (SLE) in Chinese and Korean populations identified striking association with a single nucleotide polymorphism (SNP) rs73366469, located upstream of *GTF2I* gene encoding a transcription factor functional in the immune system. The association of *NCF1* in linkage disequilibrium with rs73366469 has also been reported, and causative association signal of this region requires further study. The *GTF2I-NCF1* region is also associated with Sjögren syndrome (SS) and rheumatoid arthritis (RA) in the Asian populations. However, to our knowledge, association studies with systemic sclerosis (SSc), ANCA-associated vasculitis (AAV), and polymyositis/dermatomyositis (PM/DM) have not been reported. In this study, in addition to confirming association of this SNP with SLE in a Japanese population, we tested its association with clinical phenotypes of SLE. Furthermore, we examined whether the SNP is also associated with SSc, AAV and PM/DM.

Methods: Genotyping of rs73366469 was performed on 842 Japanese SLE patients, 467 SSc patients, 477 AAV patients, 153 PM/DM patients and 934 healthy controls using TaqMan SNP Genotyping Assay. Case-control and case-only association studies were performed by chi-square test. Correction for multiple testing was performed by calculating FDR q values using Benjamini-Hochberg method, and $q < 0.05$ was considered significant. Statistical power was calculated by Power and Sample Size Calculation.

Results: When compared with healthy controls, striking association of rs73366469 C was detected in SLE patients ($p = 9.5 \times 10^{-16}$, $q = 3.7 \times 10^{-14}$, odds ratio [OR] = 2.27) (Table). When the case-only analysis was performed between SLE patients with and without specific clinical phenotypes (central nervous system disorders, renal disorders, presence of anti-dsDNA, anti-Sm or anti-U1-RNP antibodies), significant difference was not observed. When the association was tested in SSc patients, the same C allele was significantly increased in SSc ($p = 0.0028$, $q = 0.012$, OR = 1.47) (Table). Similarly, the association was observed regardless of the clinical phenotypes (lcSSc or dcSSc, presence or absence of anti-centromere, anti-topoisomerase I or anti-U1-RNP antibodies, interstitial lung disease or pulmonary hypertension), significant difference was not observed. In contrast, increase in C allele frequency was not detected in AAV and PM/DM (Table).

Conclusion: Association of *GTF2I* rs73366469 C with SLE was replicated in a Japanese population. In addition, the same allele was found to be associated with SSc. This allele was associated with susceptibility to overall SLE and SSc, but not with specific clinical phenotypes. In contrast, association was not detected in AAV and PM/DM. Taken together with previous reports on RA and SS, *GTF2I* region appears to be associated with susceptibility to multiple, but not all, systemic rheumatic diseases.

Table. Association study of rs73366469 and SLE, SSc, AAV and PM/DM in a Japanese population

	n	Genotype frequency n (%)			C allele frequency (%)	Allelic association (C vs T)			Power calculation (%)
		C/C	C/T	T/T		p	q	OR (95%CI)	
SLE	842	25 (3.0)	250 (29.7)	567 (67.3)	17.8	9.5×10^{-16}	3.7×10^{-14}	2.27 (1.86-2.77)	100
SSc	467	15 (3.2)	85 (18.2)	367 (78.6)	12.3	0.0028	0.012	1.47 (1.14-1.89)	52.3
AAV	477	1 (0.2)	79 (16.6)	397 (83.2)	8.5	0.83	0.97	0.97 (0.73-1.28)	5.3
PM/DM	153	2 (1.3)	22 (14.4)	129 (84.3)	8.5	0.90	0.97	0.97 (0.63-1.50)	5.2
Healthy controls	934	7 (0.7)	149 (16.0)	778 (83.3)	8.7				

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None; **N. Chiba**, None; **E. Suematsu**, None; **S. Ohno**, None; **M. Katayama**, None; **K. Migita**, None; **H. Kono**, Celgene Corporation, 2; **M. Hasegawa**, None; **S. Kobayashi**, None; **H. Yamada**, None; **K. Nagasaka**, None; **T. Sugihara**, Chugai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co. Ltd., Mitsubishi-Tanabe Pharma Co., Astellas Pharma Inc., Bristol Myers Squibb K.K. and Abbvie Japan Co., Ltd., 5; **K. Yamagata**, None; **S. Ozaki**, None; **M. Fujimoto**, None; **N. Tamura**, None; **Y. Takasaki**, None; **H. Hashimoto**, None; **H. Makino**, None; **Y. Arimura**, None; **M. Harigai**, None; **S. Sato**, None; **T. Sumida**, None; **S. Tohma**, None; **K. Takehara**, None; **N. Tsuchiya**, Japan Rheumatism Foundation, 2.

Abstract Number: 1962

HLA Contributions to Risk and Protection for Anti-Centromere Autoantibody-Positive Scleroderma

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Genetics, Genomics and Proteomics Poster

Session Type: ACR Poster Session C

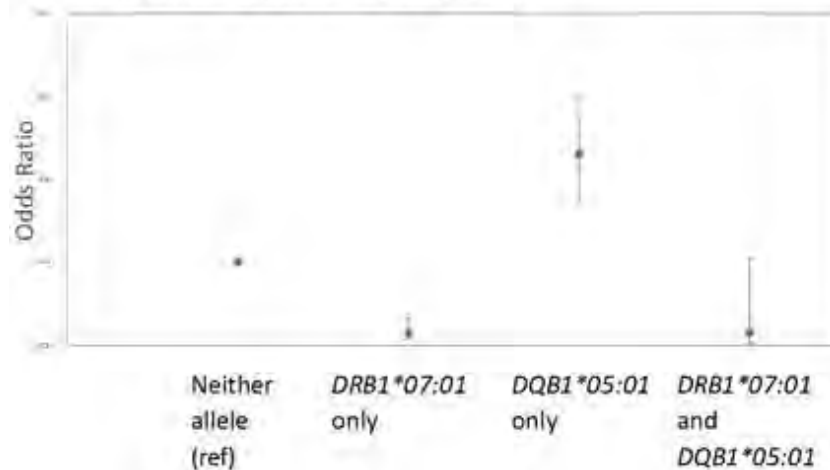
Session Time: 9:00AM-11:00AM

Background/Purpose: Anti-nuclear autoantibodies are a hallmark of scleroderma with anti-centromere antibody (ACA) recognizing centromeric antigens. ACA-positive patients have longstanding Raynaud's, limited cutaneous disease and increased risk for pulmonary arterial hypertension. We investigated the role of HLA classical genes and alleles on risk for ACA-positive scleroderma in a large collection of patients with scleroderma and genetically matched controls.

Methods: SNP genotypes of 723 scleroderma cases and 5,561 controls, all of European ancestry, were obtained from dbGaP. Classical HLA types were imputed with SNP2HLA using the Type I Diabetes Genetic Consortium reference of 5,225 individuals. Association of HLA classical alleles was tested by a dominant model regression analysis coding the HLA types as numeric values (1 for present, 0 for absent). Regression tests were corrected for genetic dissimilarity by including the top 5 principal components as covariates.

Results: Of the 723 scleroderma cases, 238 (32.9%) were positive for ACA. The most significantly ACA-positive scleroderma-associated HLA allele was *HLA-DRB1*07:01*, which was disease protective (P-value=1.8x10⁻¹⁸, odds ratio

Figure 1: *DRB1*07:01/DQB1*05:01* two-locus analysis for ACA-positive disease risk. Odds ratios are for disease risk relative to individuals with neither allele. Error bars are 95% confidence intervals for the odds ratios.



(OR)=0.11 (95%CI=0.05 to 0.22)). This allele was found in only 3.4% of the ACA-positive cases versus 23.6% of controls and 20.8% of the ACA-negative cases. Regression analysis conditioning on the disease-associated alleles identified *HLA-DQB1*05:01* as the most significantly associated disease risk allele (P-value= 3.3×10^{-08} , OR=2.18 (1.66-2.86)) with additional independent risk effects of *HLA-DQA1*04:01* and *HLA-DQA1*03:01*). A two-locus analysis of the *DQB1*05:01* disease-risk and the *DRB1*07:01* disease-protective alleles suggested the risk effect of *DQB1*05:01* is overridden by the protective effect of *DRB1*07:01*(Figure 1). The odds ratio for ACA-positive disease in individuals carrying both alleles was 0.14, similar to that in individuals carrying *DRB1*07:01* without *DQB1*05:01* (0.15). No effect of *DRB1*07:01* or *DQB1*05:01* was found in the anti-topoisomerase I autoantibody subset (P=0.98 and P=0.054, respectively). For validation, 62 African American ACA-positive cases and 946 matched controls from the Genomic Research in African American Scleroderma Patients (GRASP) Collection, were similarly analyzed. *DQB1*05:01* was associated with disease risk (P= 3.6×10^{-4} , OR=2.68 (1.57-4.58)) and *DRB1*07:01* was protective (P= 8.6×10^{-3} , OR=0.33 (0.13-0.85)) in the African American sample.

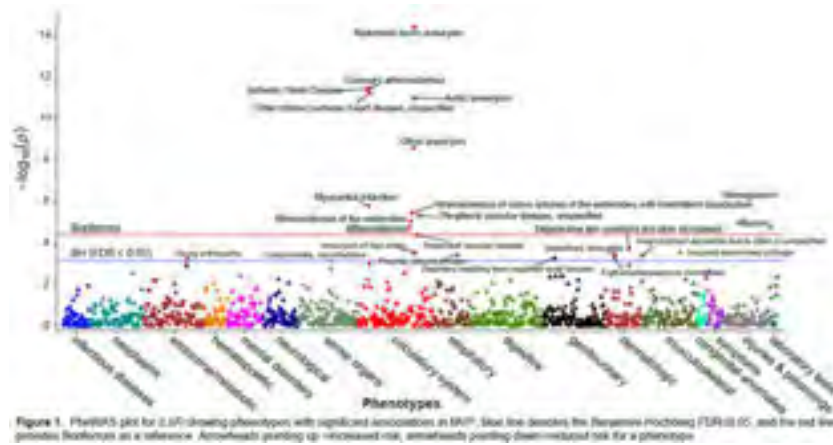
Conclusion: *HLA-DQB1*05:01* is associated with risk and *HLA-DRB1*07:01* is associated with protection for ACA-positive scleroderma. The mechanisms responsible for these effects could be exploited to prevent or treat scleroderma.

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Phenome Wide Association Study of IL6R Variant Identifies Drug Target for Cardiovascular Disease and Inflammation

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Background/Purpose: Individuals with an interleukin 6 receptor (IL6R) genetic variant not on IL6R blocking therapy have biomarker profiles similar to those treated with IL6R blockers. Individuals with the IL6 variant have impaired IL6 signaling due to reduced IL6Rs; the goal of IL6R blockade is also to impair IL6 signaling by binding to IL6R. This gene-drug pair may therefore facilitate whether the *IL6R* variant has an association with a reduced risk for a phenotype, which in turn can inform which diseases may benefit from treatment with IL6R blockade. To test this hypothesis, we performed a Phenome-Wide Association Study (PheWAS) to screen for associations between an *IL6R* genetic variant and a broad range of phenotypes in the electronic health records (EHR).

Methods: We studied veteran participants in the Veteran's Affairs Million Veteran's Project using genomic data linked to EHR. We extracted all diagnosis codes and mapped them to phenotype groups using published PheWAS methods. Routine laboratory measurements, e.g. complete blood count, were also extracted. A PheWAS was performed by constructing logistic regression models testing associations between the *IL6R* variant (Asp358Ala, rs2228145) and 1,342 phenotype groups; linear regression models were constructed to screen for associations between *IL6R* and 26 routine laboratory measurements. All models were adjusted for age, sex, population stratification, and healthcare utilization. Significance was reported using false discovery rate ≤ 0.05 ; data for Bonferroni adjustments also provided. We replicated findings using freely available online data from the Vanderbilt University Biobank (BioVU) and the UK Biobank, two biobanks with linked genetic and EHR data.

Results: We studied 330,374 participants; the minor allele frequency of the *IL6R* variant was 35.3%. *IL6R* was most strongly associated with a reduced risk of aortic aneurysm phenotypes (OR 0.87-0.90, 95% CI 0.84, 0.93) (Figure). We observed the expected association between *IL6R* and reduced C-reactive protein. We also observed known effects of IL6R blockade from clinical trials, increased hemoglobin. The protective effect of the *IL6R* variant for aortic aneurysm and coronary heart disease was replicated in BioVU and the UK Biobank, respectively.

Conclusion: In this proof of concept study, we demonstrated the application of the PheWAS using large EHR biobanks to potentially inform drug effects. The findings of a protective effect of a single *IL6R* variant with aortic aneurysms corresponded with the newest indication for IL6R blockade for giant cell arteritis, where clinical manifestation is aortic aneurysm.

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Epigenetic Changes of Energy Metabolism-Related Genes in Rheumatoid Arthritis Fibroblast-like Synoviocytes

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SESSION INFORMATION

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Background/Purpose: Epigenetic changes contribute to the pathogenesis of rheumatoid arthritis (RA) and a comprehensive epigenomic characterization of RA fibroblast-like synoviocytes (FLS) has recently been described. As previous studies indicate that energy metabolism is altered in RA FLS, we hypothesize that ChIP mark changes near energy metabolism-related genes would correlate with differences in expression of these genes.

Methods: ChIP-sequencing data, for six different ChIP marks (H3K4me1, H3K4me3, H3K9me3, H3K27ac, H3K27me3, H3K36me3) from publicly available data sets from FLS derived from 11 patients with RA and 11 patients with OA were compared to identify regions with a difference in these histone modifications. Single nearest genes to regions of interest were then utilized for pathway analyses (Gene Ontology Enrichment Analysis, KEGG pathways, PANTHER classification) to determine if particular cellular processes and pathways are associated with these chromatin changes. Pathways associated with energy metabolism were enriched near a ChIP mark change commonly associated with active transcription (H3K4me3) with the use of the whole genome as a reference. To further elucidate these findings, single nearest genes associated with any ChIP mark change and metabolism were utilized for a secondary pathway analysis. Additionally, changes in transcription of genes associated with the ChIP mark changes were assessed using RNA-sequencing data from the same cells used for the ChIP-sequencing analyses.

Results: As per the unbiased pathway analysis, 4 of the 21 pathways significantly associated with changes in H3K4me3 ($p < 0.05$) were associated with energy metabolism with the whole genome used as a background (including glucose 6-phosphate metabolic process, regulation of triglyceride biosynthetic process and arginine metabolic process). 44 different genes involved in energy metabolism were associated with a change in at least one of the ChIP marks. These 44 genes were then used in a KEGG pathway analysis. Glycolysis/Gluconeogenesis was one of the top ranked pathways with 11 out of the 44 genes involved in this pathway (adjusted $p = 2.89 \times 10^{-21}$). Of the 44 genes associated with a change in a ChIP mark, glutaminase (GLS) and the cysteine/glutamate transporter SLC7A11 were two genes with significant differences in expression as per RNA-sequencing data. Of note, both genes were shown to mediate tumor metabolic reprogramming and to promote cancer progression.

Conclusion: This study of RA FLS demonstrated changes in epigenetic marks of genes related to energy metabolism and suggests that these pathways can be critical in RA pathogenesis and be involved in the imprinted aggressive phenotype displayed by RA FLS compared to OA FLS. Additionally, this dataset has the potential to identify RA-specific targets that can be used to develop novel therapeutic agents.

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Association of HLA Class II Alleles with Relapse and Interstitial Lung Disease in Myeloperoxidase (MPO) -ANCA Positive Vasculitis in a Japanese Population

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Background/Purpose: The high prevalence of microscopic polyangiitis (MPA) and myeloperoxidase (MPO)-ANCA positive patients as well as frequent occurrence of interstitial lung disease (ILD) constitute unique epidemiological features of ANCA-associated vasculitis (AAV) in the Japanese population. Recent genome-wide association studies in European populations indicated that *HLA-class II* region was most strongly associated with AAV. In the Japanese population, we reported that *HLA-DRB1*09:01* was associated with susceptibility to, and *DRB1*13:02* with protection against, MPA and MPO-ANCA positive AAV (MPO-AAV) in Japan. In this study, we examined whether *HLA-class II* are associated with relapse of MPO-AAV, as well as occurrence of ILD in MPO-AAV, in a Japanese population.

Methods: Relapse rate and time to first relapse were analyzed in 206 MPO-AAV patients, who entered prospective cohort studies of remission maintenance therapy (RemIT-JAV and RemIT-JAV-RPGN) and achieved remission during the observation period. Association of *HLA-DRB1* alleles with relapse rate was tested by chi-square analysis or Fisher exact test, and relapse-free interval was analyzed by log-rank test. Association study with ILD was performed in 297 MPO-AAV patients (126 with ILD and 171 without ILD) and 596 healthy controls. Statistical analyses were conducted using logistic regression analysis under the additive model.

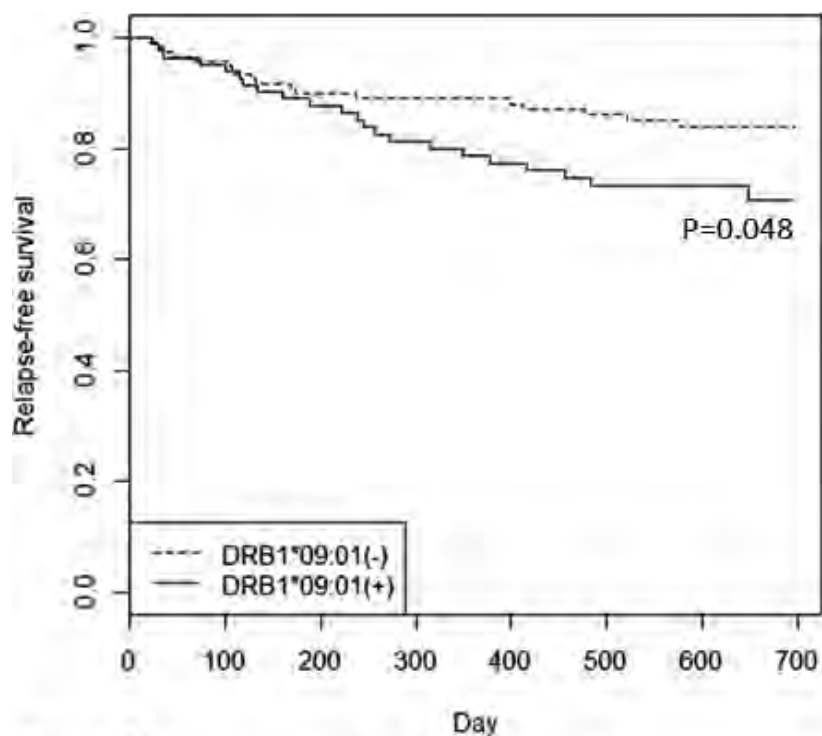


Figure 1.
Kaplan-Meier curves for relapse-free interval in MPO-ANCA positive patients with and without *DRB1*09:01*

Results: Relapse occurred more frequently in the patients with *DRB1*09:01* (*DRB1*09:01* positive: 22/85, 25.9% vs *DRB1*09:01* negative 18/121, 14.9%) (P=0.049, odds ratio [OR] 2.00), and time to relapse was significantly shorter in the patients with *DRB1*09:01* than those without (P=0.048) (Figure 1). Although patients with *DRB1*13:02* showed a tendency towards decreased relapse rate (*DRB1*13:02* positive: 1/16 6.3% vs *DRB1*13:02* negative: 39/190, 20.5%), the difference did not reach statistical significance (P=0.32, OR 0.26), nor did the time to first relapse (P=0.19). When the association of *HLA* alleles was tested between MPO-AAV with ILD and healthy individuals, *DPB1*05:01* and *DRB1*04:05* alleles were significantly decreased in MPO-AAV with ILD (Table 1). Case-case analysis between MPO-AAV patients with and without ILD also showed significant decrease of *DPB1*05:01* in MPO-AAV with ILD (Table 1).

Conclusion: Association of *DRB1*09:01* with relapse in MPO-AAV was observed in a Japanese population. In addition, *HLA-DPB1*05:01* was significantly decreased in MPO-AAV with ILD.

Table 1 Association of *HLA-class II* alleles with interstitial lung disease in MPO-ANCA positive vasculitis

	Allele frequency			vs HC		vs MPO-AAV without ILD	
	MPO-AAV with ILD	MPO-AAV without ILD	HC	P	OR	P	OR
DRB1*01:01	0.099	0.070	0.059	0.020	1.77	0.20	1.49
DRB1*04:05	0.079	0.126	0.127	0.036	0.59	0.071	0.59
DRB1*08:02	0.060	0.038	0.028	0.013	2.21	0.23	1.59
DRB1*09:01	0.210	0.249	0.153	0.027	1.47	0.26	0.79
DPB1*04:02	0.147	0.126	0.093	0.0089	1.75	0.45	1.20
DPB1*05:01	0.290	0.386	0.381	0.0072	0.67	0.020	0.67

HC: healthy controls, OR: odds ratio, MPO-AAV: MPO-ANCA positive vasculitis, ILD: interstitial lung disease.

Disclosure: A. Kawasaki, None; K. E. Sada, None; F. Hirano, Chugai Pharmaceutical Co., Ltd.; Ono Pharmaceuticals; Mitsubishi Tanabe Pharma Co.; UCB Japan; CSL Behring; Towa Pharmaceutical Co., Ltd.; Abbvie Japan Co., Ltd.; Japan Blood Products Organization; Ayumi Pharmaceutical Co.; and Nippon Kayaku Co., Ltd., 5, Sumitomo Dainippon Pharma Chugai Pharmaceutical Co., Ltd., 8; S. Kobayashi, None; H. Yamada, None; H. Furukawa, None; K. Nagasaka, None; T. Sugihara, Chugai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co. Ltd., Mitsubishi-Tanabe Pharma Co., Astellas Pharma Inc., Bristol Myers Squibb K.K. and Abbvie Japan Co., Ltd., 5; K. Yamagata, None; T. Sumida, None; S. Tohma, None; S. Ozaki, None; H. Hashimoto, None; H. Makino, None; Y. Arimura, None; M. Harigai, None; N. Tsuchiya, Japan Rheumatism Foundation, 2.

Abstract Number: 1966

Transcriptome and Methylome Integrative Molecular Analysis Uncovers a New Systemic Autoimmune Disease Classification

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SESSION INFORMATION

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Background/Purpose: Systemic autoimmune diseases (SADs) are chronic inflammatory conditions with autoimmune aetiology and many common clinical features, difficulting diagnosis and adequate treatment decisions. Finding new treatments or applying the existing ones in a more effective way is especially hard in SADs due to the heterogeneity of molecular mechanisms within the same disease class. Based on this premise, the first step towards establishing a precision medicine strategy for SADs is to reclassify these conditions at the molecular level, which might result in a more homogenous stratification in terms of pathological molecular pathways. SADs have a multi-factorial predisposition, where the interplay between genetic, epigenetic and environmental conditions is essential in the pathogenesis of the diseases. Thus, in order to capture as many aspects as possible the molecular stratification is performed using multiple layers of information (e.g. genome, transcriptome, methylome or metabolome). Among all available molecular levels of information, the most informative in terms of functionality and dimensionality are transcriptome and methylome, reflecting different aspects of regulation and environmental influence, respectively, giving a wide view of the molecular background.

Methods: We performed an unsupervised integrative clustering analysis to classify SADs patients into subtypes based on genome-wide transcriptome and methylome profiling of ~800 cases distributed across 7 different clinical entities (rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, primary Sjögren's syndrome, primary antiphospholipid antibody syndrome, mixed connective tissue disease and undifferentiated connective tissue disease) and ~200 healthy individuals.

Results: Interestingly, patients with different diagnoses were grouped statistically into new groups in terms of molecular functions. These results were replicated in two independent subsets of patients. The new groups of patients are characterized by a major subdivision, where some clusters show an increased inflammatory response and neutrophil degranulation functions, while others are enriched in lymphocyte proliferation and differentiation signatures. This major signal is subdivided into more specific subgroups defined by functional signatures such as type I interferon signaling, complement activation or neural functionalities among others.

Conclusion: This is the first attempt of integrating and characterizing SADS patients based on molecular profiles. The results show that we are able to identify new groups of patients sharing molecular features that do not reflect the clinical diagnoses. This new molecular classification might suppose a first step through precision medicine in SADS.

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Abstract Number: 1967

Detection of Association of Long Noncoding RNA ATP6V0E2-AS1 Single Nucleotide Polymorphism with Susceptibility to Myeloperoxidase-ANCA Associated Vasculitis Based on Transcriptome Analysis

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Background/Purpose: Because of the low prevalence, only three genome-wide association studies, all from the Caucasian populations, have been reported on ANCA-associated vasculitis (AAV) thus far; therefore, efficient candidate gene studies play an important role. In complex diseases, the majority of single nucleotide polymorphisms (SNPs) associated with disease susceptibility are located in the noncoding region and are suggested to affect gene expression. Recently, long noncoding RNAs (lncRNAs) are strongly implicated in the regulation of gene expression. In this study, we made an attempt to detect SNPs associated with susceptibility to AAV by focusing on candidate lncRNAs selected based on the transcriptome analysis.

Methods: Whole blood transcriptome analysis was conducted on eight patients with AAV and 14 healthy controls (HC). All subjects are Japanese. From the transcriptome data, we selected candidate lncRNAs using two approaches. The first approach took advantage of eQTL (expression quantitative trait loci) SNPs. lncRNAs significantly over- or under-expressed as compared with HC were selected. Then eQTL SNPs associated with expression levels of these lncRNAs were selected as candidate SNPs using GTEx database. In the second approach, in order to more comprehensively capture SNPs with potential relevance, we focused on the SNPs closely located to the candidate lncRNAs. Top 10 lncRNAs were selected based on the fold change (FC) in the expression levels compared with HC. Then SNPs located in the chromosomal regions encompassing the candidate lncRNAs (from 50kb upstream to 50kb downstream) were selected. The candidate SNPs were filtered based on minor allele frequency (>0.1), linkage disequilibrium ($r^2 < 0.6$) and regulome score (< 2). Finally, 96 candidate SNPs associated with 25 lncRNAs were selected for association analysis. Then these SNPs were genotyped in 525 Japanese AAV patients (315 MPA, 108 GPA, 412 MPO-ANCA positive, 70 PR3-ANCA positive) using DigiTag2 or TaqMan SNP genotyping assays, and allele frequencies were compared with 4,394 healthy Japanese controls from our laboratory and Tohoku Medical Megabank Organization (ToMMO).

Results: After quality control, association with AAV were analyzed on 74 SNPs. The SNP rs6958235, located in the upstream region of *ATP6V0E2-AS1*, showed a significant association with MPO-ANCA positive AAV ($P=5.72 \times 10^{-4}$, odd ratio 1.38, 95% confidence interval 1.15-1.65)(Table). The association remained significant after Bonferroni correction ($P_{\text{Bonferroni}}=0.042$). The expression level of *ATP6V0E2-AS1* was downregulated in AAV as compared with HC (FC -4.4).

Conclusion: A SNP rs6958235C located in the upstream region of lncRNA *ATP6V0E2-AS1* was found to be associated with MPO-AAV for the first time. *ATP6V0E2* encodes an isoform of an essential proton pump component that may play a role in the acidification of endosome and lysosome. The functional significance of this SNP requires further study.

Table. Allelic association of rs6958235T>C with AAV subsets in a Japanese population

	n	C allele frequency (%)	$P_{\text{uncorrected}}$	$P_{\text{Bonferroni}}$	OR	95% CI
MPA	315	18.3	1.88E-02	>1	1.29	1.04-1.59
GPA	108	19.4	5.79E-02	>1	1.39	0.99-1.96
MPO-ANCA positive	412	19.3	5.72E-04	0.042	1.38	1.15-1.65
PR3-ANCA positive	70	16.4	5.89E-01	>1	1.13	0.72-1.78
healthy controls	4394	14.8				

OR: odds ratio, CI: confidence interval

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Kobayashi, None; H. Yamada, None; H. Furukawa, None; K. Nagasaka, None; T. Sugihara, Chugai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co. Ltd., Mitsubishi-Tanabe Pharma Co., Astellas Pharma Inc., Bristol Myers Squibb K.K. and Abbvie Japan Co., Ltd., 5; N. Nishida, None; K. Yamagata, None; T. Sumida, None; S. Tohma, None; S. Ozaki, None; H. Hashimoto, None; H. Makino, None; Y. Arimura, None; H. Kono, Celgene Corporation, 2; M. Harigai, None; N. Tsuchiya, Japan Rheumatism Foundation, 2.

Abstract Number: 1968

eQTL Analysis of More Than 1000 Human Blood Samples Reveals Shared and Unique Signals across Seven Systemic Autoimmune Diseases : The Precisesads Project

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SESSION INFORMATION

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Background/Purpose: Systemic autoimmune diseases (SADs) are chronic inflammatory conditions with autoimmune aetiology and many common clinical features, hampering diagnosis and adequate treatment decisions. Finding new treatments or applying the existing ones in a more effective way is especially hard in SADs due to the heterogeneity of molecular mechanisms within the same disease class. Furthermore, most variants discovered by GWAS locate in non-coding regions, making it difficult for immediate interpretation. An important tool to discover the molecular mechanisms by which SADs- genetic variants exert their risk is the use of Expression Quantitative Trait Loci (eQTL) mapping.

Methods: We performed eQTL analysis using GWAS and RNA-Seq data derived from whole blood samples from ~1100 patients distributed across 7 different clinical entities (rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, primary Sjögren's syndrome, primary antiphospholipid antibody syndrome, mixed connective tissue disease and undifferentiated connective tissue disease) and ~300 healthy individuals. All samples analyzed are of European ancestry and form part of the PRECISEADS project dataset. We used matrixEQTL with 8 cofactors to correct for bias introduced by batch, RIN, age, sex, medication, fever, genetic background and blood cell composition.

Results: We show that SADs-associated variants have widespread effects on genome-wide DNA expression levels. By means of stratified and interaction analyses we further show the gender and disease-specific context of SADs-eQTL variants. Importantly > 85% of eQTLs were found in patients but not in healthy subjects and shared across diseases, suggesting how SADs context-specificity works at the molecular level.

Conclusion: Our work serves to illustrate the possible regulatory downstream effects of risk variants and will ultimately inspire the generation of new hypotheses needed to increase our limited understanding on the biology of autoimmunity.

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Abstract Number: 1969

GENE Enhancers Associated with an Increase Risk of Developing JIA Fail to DOWN Regulate RUNX1 after CELL Stimulation

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Background/Purpose: In recent years there have been tremendous strides in determining the genetic component of complex diseases, not least in Juvenile Idiopathic Arthritis (JIA). We now have 17 genetic loci robustly associated with an increased risk for developing JIA (1). In JIA, like all complex diseases, the regions of the genome harbouring genetic changes are found outside protein coding DNA, in regions of the genome shown to control gene expression, often sited some distance from the closest gene. One of these JIA associated regions, on chromosome 21q22, is labelled with the *RUNX1* gene, although the associated variants are situated over 450kb from the gene. We have previously demonstrated, through Capture HiC analysis, that the genomic region containing the JIA associated variants makes a physical contact with the *RUNX1* promoter. The next challenge in this region, therefore, is to determine how a risk genetic background effects the expression of the gene, contributing to the susceptibility to JIA.

Methods: B-lymphocyte cell lines, containing either a risk or protective JIA genetic background at the 'RUNX1' loci were interrogated for potential causative functional mechanism. Allele specific interactions were investigated using chromosome conformation capture (3C), enhancer activity (H3K4me1) with chromatin immunoprecipitation (ChIP), and the resultant expression of the *RUNX1* gene analysed by qPCR in both stimulated (IL4/anti CD40) and unstimulated cell lines.

Results: The enhancer region associated with JIA interacts with the *RUNX1* promoter in B-cell lines. A stimulation specific effect is observed in B-cell lines harbouring the protective alleles. In this protective context, prior to stimulation *RUNX1* expression is higher than in the risk genotype with enhancer enrichment detected near the proximal promoter. After stimulation the interaction between the enhancer and *RUNX1* promoter is much stronger, and whilst no enhancer enrichment was detected, this increased interaction frequency after stimulation corresponds to a sharp downregulation of *RUNX1* expression. In contrast, the risk genotype showed no stimulation dependant change, maintaining both interaction and expression levels.

Conclusion: 3C and ChIP experiments were performed to investigate genotype and stimulation specific DNA-DNA and DNA-protein interactions and identify correlation with gene expression. These results suggest that the ability for B-cells to switch from relatively high expression of the *RUNX1* transcript to low expression upon stimulation is crucial to an appropriate immune response

Disclosure: A. Yarwood, None; K. Duffus, None; C. Taylor, None; A. McGovern, None; S. Eyre, None; W. Thomson, None.

Abstract Number: 1970

Linking Genetics to T Cell Phenotype in JIA: Rationale for IL-2 Therapy

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Background/Purpose: Several genetic regions associated with susceptibility to juvenile idiopathic arthritis (JIA), harbour genes involved in the interleukin-2 (IL-2) response which is pivotal in the function of regulatory T cells (T-regs) and their ability to suppress potentially autoimmune effector T cells. Genetically JIA is similar to type 1 diabetes (T1D) which also demonstrates an enrichment of genes related to IL-2 regulation and response. Early clinical trial data has indicated recombinant IL-2 to be successful in enhancing T-regs in T1D. I hypothesise that IL-2 regulation and response is critical to the development of JIA and therefore IL-2 therapy represents an exciting and viable therapeutic option for JIA. We aim to identify a subset of JIA patients who carry a high burden of genetic risk variants in genes related to IL-2 regulation and response, who could then be targeted for IL-2 therapy. Secondly we will link genetics to cellular phenotypes using CyTOF to identify a subset of cells that are most perturbed in JIA and determine the effects of IL-2 on these cellular subsets.

Methods: A weighted genetic risk score (wGRS) was generated using 9 JIA susceptibility SNPs considered to be within or near to genes involved in interleukin (IL-2) regulation and response (1). The IL-2 wGRS was tested in an independent set of UK cases (1435) and controls (5181). The risk of developing JIA was assessed by subtype, using logistic regression. A CyTOF panel containing 33 antibodies targeting markers of T cells and T-regulatory cells was developed and tested in CD3⁺ T cells from two healthy individuals after 12 hour stimulation (anti CD3/CD28 beads plus recombinant IL-2). Cells were stained for all antibodies, Iridium and cisplatin and analysed on the CyTOF Helios. Data will be analysed with traditional biaxial gating as well commercially available packages such as cytokit.

Results: The IL-2 wGRS demonstrated an increased percentage of individuals in the high risk group in the extended oligoarthritis, RF negative and RF positive polyarthritis subtypes suggesting a higher burden of IL-2 related loci. The odds of developing JIA for those in the highest risk group (quintile 5) compared to all others was increased in these subtypes (OR 2.95% CI 1.45-2.76, OR 2.39 95%CI 1.87-3.04, OR 2.14 95% CI 1.49-3.09, respectively). Comparing this to a wGRS generated from JIA susceptibility loci excluding IL-2 related genes shows that this enrichment is specific to the IL-2 wGRS. Biaxial gating of CyTOF data showed increases in activation markers after stimulation (CD25, CD69, CD38 and HLA-DR, decrease CCR7). We demonstrated that our panel can successfully identify traditional CD4⁺ T cell subsets showing differences between stimulated and unstimulated cells and between individuals.

Conclusion: Our analysis has shown that patients with oligoarthritis and polyarthritis have an increased burden of JIA susceptibility variants in genes related to IL-2 regulation and response suggesting these individuals may benefit from IL-2 therapy. Using the CyTOF panel we can now analyse individuals with high and low GRS allowing us to identify cellular subsets which may be altered by these genetic variants.

Disclosure: A. Yarwood, None; S. Smith, None; S. Eyre, None; W. Thomson, None.

Abstract Number: 1971

PLCG2 Variants Influence CVID Susceptibility: Expanding the Spectrum of PLCG2-Associated Immune Dysregulation

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Background/Purpose: Immune dysregulation refers to alterations in immune signaling leading to development of autoimmunity, infection and atopic disease. Common variable immunodeficiency (CVID), a prototypic disorder of immune dysregulation, is characterized by hypogammaglobulinemia, recurrent infections, poor vaccine responses and diverse complications, including autoimmunity. Although small subsets of CVID have been linked with various genes, the larger genetic landscape of CVID is unknown. Two closely-related familial disorders of immune dysregulation -- phospholipase C gamma 2 (PLC γ 2) associated antibody deficiency and immune dysregulation (PLAID) and auto inflammatory PLAID (APLAID) -- are caused by dominant mutations in *PLCG2*. These disorders are marked by antibody deficiency and immune dysregulation and are strikingly similar to that observed in CVID. We therefore hypothesized that genetic variants of *PLCG2* influence CVID susceptibility.

Methods: Using a combination of Sanger sequencing and targeted deep resequencing, we examined the coding region of *PLCG2* in 185 CVID patients and 96 local controls. Variant positions were evaluated for evolutionary conservation (GERP++, SiPhy) and the functional effects of missense changes were predicted (PolyPhen2, SIFT, MutationTaster). Distributions of rare, evolutionarily conserved *PLCG2* variants were compared between CVID cases and 37,370 non-Finnish European (NFE) subjects from the Exome Aggregation Consortium using the Sequence Kernel Association Test (SKAT). Effects of *PLCG2* mutations on cell activation were examined by overexpressing mutant constructs in a *PLCG2* deficient DT40 B cell line.

Results: Among 185 CVID cases, we found 12 missense variants of *PLCG2*, including 7 rare and 2 novel variants. All rare variants occurred at evolutionarily conserved sites and were predicted to detrimentally affect protein function. Rare variants were observed in 23 CVID patients (12.4%) and SKAT revealed significant enrichment of rare, evolutionarily conserved *PLCG2* variants in CVID patients compared to the NFE population ($p=5.3E-5$). Overexpression studies revealed alterations in downstream signaling in 7 CVID variants: relative to wild type *PLCG2*, 6 variants lead to basal increases in ERK phosphorylation, while 2 produced enhanced activation following IgM stimulation.

Conclusion: Rare, evolutionarily conserved missense variants of *PLCG2* are significantly associated with CVID. Furthermore, most of the rare *PLCG2* variants found in CVID patients cause abnormal downstream signaling, *in vitro*. Based on these results, we conclude that *PLCG2* influences susceptibility to CVID. Investigations are ongoing to determine whether *PLCG2* mutations predict specific phenotypes or disease courses in CVID.

Disclosure: A. M. Szymanski, None; K. Baysac, None; H. Marcy, None; E. Baskin, None; J. Milner, None; M. Ombrello, None.

Abstract Number: 1972

Resolving the Synovial Fluid Proteome and Peptidome for Disease-Specific Mediators of Inflammatory Arthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Idiopathic inflammatory arthritis (IA) is a T-cell driven chronic condition characterized an imbalance in cell proliferation and apoptosis leading to significant synovial hyperplasia and degradation of the underlying cartilage and bone. The exact etiology of IA is still poorly understood with studies aimed at delineating the molecular pathways driving loss of immunological tolerance to the body's self-antigens. Naturally, there is a compelling need to identify markers of aberrant immune pathways which may advance current insights into the molecular mechanisms of IA and serve as clinical markers for disease monitoring and treatment responses. Using mass spectrometry (MS), we aim to provide a detailed analysis of the proteome and peptidome of IA synovial fluid (SF).

Methods: SF samples were collected from 10 patients satisfying the 1987 ACR classification criteria for rheumatoid arthritis (RA), 10 patients satisfying CASPAR classification criteria for psoriatic arthritis (PsA) and 10 controls. Samples were investigated under label-free MS-based methods. Proteomic fractions underwent reduction, alkylation, and trypsin digestion while peptidomic fractions were desalted using solid-phase extraction. All samples were subjected to liquid-chromatography tandem MS followed by data extraction using MaxQuant v.1.5.2.8.

Results: Holistic proteome mining identified a total of 419 unique proteins across all 30 SF samples, with a false discovery rate of <1.0%. Non-parametric statistical tests identified 144 IA SF-derived proteins with significant differential expression relative to the control group. Application of filtering criteria resulted in a preliminary list of 5 IA-specific candidate biomarkers, of which MMP3 and neutrophil defensin 3 have been previously investigated. Intracohort comparison of RA and PsA SF proteomes identified 4 novel RA-specific candidates and 2 PsA-specific candidates. Peptidomic profiling of IA SF identified 288 unique peptides arising from 51 unique protein precursors across all SF samples. Differential expression analyses identified peptide fragments of fibrinopeptide A (FpA), a derivative of fibrinogen alpha chain, to be significantly upregulated in IA SF. FpA peptides were predicted to have antimicrobial peptide activity according to a bioinformatic tool. Moreover, KEGG analysis identified *Staphylococcus aureus* infection as a significantly enriched pathway. Taken together,

our peptidomic findings underscore the potential for peptides to elucidate mechanistic pathways related to the etiopathogenesis of IA, including the possible interplay of the microbiome and immune system responses.

Conclusion: Chronic inflammation in IA is orchestrated by a complex network of signaling pathways which are expected to be represented in the protein and peptide expression patterns of SF. The use of high resolution MS facilitates the discovery of key modulators of disease which may ultimately, enable the development of novel therapeutic interventions and minimally-invasive biomarker panels. Verification and validation of chosen candidates in a new set of SF and serum samples, respectively, are currently ongoing.

Disclosure: S. Mahendran, None; E. Diamandis, None; V. Chandran, AbbVie Inc., 2, AbbVie Inc., amgen, celgene, eli lilly, Janssen, Novartis, Pfizer and UCB, 5, Eli Lilly and Co., 9.

Abstract Number: 1973

Leveraging Publicly Available Gene Expression Data and Applying Machine Learning to Identify Novel Biomarkers for Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Genetics, Genomics and Proteomics Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Diagnosis and monitoring the disease progression of RA is challenging requiring a combination of imaging techniques and blood tests. There is currently no biochemical test for detection of early-stage disease. In this study, we aimed to define a Rheumatoid Arthritis meta-profile and identify biomarkers by leveraging publicly available gene expression data with machine learning approaches.

Methods: We carried out a comprehensive search for publicly available microarray data at NCBI GEO database for whole blood and synovial tissue in Rheumatoid Arthritis and health controls. For the synovium, we collected 13 datasets with 312 biopsy samples. Among them, there were 276 RA samples and 36 healthy tissue biopsies. For whole blood data, we collected 11 datasets with 2,153 samples: 1,394 RA and 759 healthy controls. We computed differential expression using Significance Analysis of Microarrays (SAM) approach. We applied the cutoff of $FDR < 0.05$ and $abs(FC) > 1.2$ to the results to identify significant differentially expressed genes. For pathway analysis we leveraged the gene list enrichment analysis tool ToppGene.

Results: As a result of our analysis we were able to identify 882 genes that were significantly differentially expressed in the synovium between RA patients and healthy controls. Among them we recognized 502 up-regulated and 380 down regulated genes. We confirmed the gene regulation of the immune system process and response, and cell activation and aggregation in both innate and adaptive immune system pathways were involved in RA. As for the whole blood data, we identified 339 significantly differentially expressed genes with 166 up-regulated and 173 down-regulated genes among them. Aiming to determine RA biomarkers we performed a machine learning feature selection procedure to sets of significant genes for both tissues. First, we filtered out genes that cumulatively contribute to the biological variance less than 5%. Then we applied a Variable Selection Using Random Forests (VSURF) approach to the leftovers. Next, we performed a hypergeometric test and found 12 common genes with $p = 0.001$ with 3 common up-regulated genes: Antigen peptide transporter 1 (TAP1), Matrix Metalloproteinase 9 (MMP9), and DNA Damage Regulated Autophagy Modulator 1 (DRAM1), and 2 common down-regulated genes: DDX3Y, MYC. Finally, we built a Random Forest classification model on the synovium data with these 5 genes. We applied 5-fold cross-validation with 10 repeats technique and used Cohen's Kappa statistic as a metric. We obtained Kappa equals 0.61 with sensitivity 0.86 and specificity 0.9 on the testing set. In the final step, we validated the prediction model on the whole blood data, resulting kappa of 0.57 with sensitivity 0.54 and specificity 0.98.

Conclusion: Our computational analysis of public data allowed us to perform a comprehensive in-silico search for biomarkers in Rheumatoid Arthritis. We found three protein coding genes that have the strongest association with RA. Identification of extensive proteins secretion in blood could allow precision phenotyping on even early stages of the disease which could have a positive impact on monitoring disease progression and patient treatment.

Disclosure: D. Rychkov, None; M. Sirota, None; C. Lin, None.

Dynamics of Transcriptional Signatures from Synovial Macrophage Subsets during Acute and Chronic Murine Models of Inflammatory Arthritis

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SESSION INFORMATION

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Background/Purpose: Macrophages play an integral role in the progression and persistence of rheumatoid arthritis (RA) through production of degradative enzymes, cytokines, and chemokines and recruitment of additional immune cells which results in progressive joint destruction. We previously demonstrated that naïve mouse joints contain both MHC II⁺ (monocyte-derived) and MHC II⁻ (tissue-resident) macrophages. Interestingly, we have shown that the monocyte-derived macrophages drive inflammation, while the tissue-resident macrophages are involved in resolution of inflammation. Further, we have noticed that CX3CR1 expression dramatically changes during arthritis in both the MHCII⁺ and MHCII⁻ macrophage populations. Thus, we optimized a multi-parameter flow cytometry protocol to isolate four synovial macrophage subsets, delimited by MHCII and CX3CR1 expression, to perform subset-specific transcriptomic analysis.

Methods: We modeled arthritis in mice using an acute, inducible, K/BxN serum transfer induced arthritis (STIA), and a chronic, inducible, collagen-induced arthritis (CIA) in 10-12 week old female C57BL/6 mice. Florescence-activated cell sorting was employed to isolate macrophage subsets via expression of MHC II and CX3CR1 throughout the course of arthritis by FACS. RNA was extracted from sorted macrophage populations and processed for RNA sequencing (RNA-seq).

Results: Analysis of synovial macrophage populations by RNA-seq show that each population has a unique transcriptional profile and identifies a set of genes preferentially expressed in each population that give insight to each population's role at steady state. We then identified patterns in gene expression between two or more populations or shared between all populations to describe the relationship between macrophages. Analysis of synovial macrophage populations over the course of inflammation reveals that each macrophage subset responds differently across the phases of inflammation. At the initiation of inflammation, the CX3CR1/MHCII double positive and MHCII⁺CX3CR1⁻ macrophages show the largest transcriptional response with the peak transcriptional change occurring during the propagation stage in all macrophage populations. However, upon resolution of inflammation, CX3CR1/MHCII double positive and CX3CR1⁺MHCII⁻ macrophages contain a subset of genes that do not return to steady state expression. Macrophage response in our CIA model follows a similar transcriptional pattern to that found in our STIA model, however we do not see a distinct resolution pattern in our macrophage populations.

Conclusion: We conclude that changes in gene expression from synovial macrophage sub-populations over the course of arthritis coincide with the different phases of joint inflammation. This study provides detailed insight into the heterogeneity of synovial macrophage populations and the relationship between tissue resident and monocyte derived macrophage populations during inflammation. The novel pathways identified here provide new insight into potentially useful targets for therapy.

Disclosure: P. J. Homan, None; A. B. Montgomery, None; S. Dominguez, None; C. M. Cuda, None; H. Perlman, Galvani, 5; D. R. Winter, None.

Behcet's Disease Lies in the "B" Holder. New Associations in Disease Susceptibility and Manifestations

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SESSION INFORMATION

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Session Title: Genetics, Genomics and Proteomics Poster

Session Type: ACR Poster Session C

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Background/Purpose: Behçet's disease is a multisystem disease affecting young adults with variable vessel vasculitis as its underlying pathology. Previous studies in Behçet's disease linked it to the Human Leucocytic antigens (HLA) class I molecules however the use of High-resolution Next Generation Sequencing (NGS) wasn't adopted before for all HLA loci (both class I and II) analysis along with the haplotype analysis. This study aims to identify the Behcet disease susceptibility with class I and II HLA alleles using NGS along with their haplotype analysis to help better understand the disease process and to find a possible association with disease manifestations and severity.

Methods: Sixty patients from specified geographical distribution diagnosed according to the International Study Group (ISG) criteria for Behçet's disease along with 160 normal geographically ethnic-matched controls were typed for the class I HLA alleles and from the control group, 40 control samples were typed for class II HLA alleles.

The work was a part of participation in the 17th International Histocompatibility and Immunogenetics Workshop (IHIWS) in the disease association component during which HLA was typed for patients and 40 control subjects at the allelic level by NGS high resolution typing for 11 loci (HLA-A, B, C, DRB1, DRB3/4/5, DQA1, DQB1, DPA1, DPB1). The control group was then expanded for an additional 120 control subjects typed for HLA class I loci (A, B and C) along with data analysis and haplotype analysis for the results.

Results: Sixty patients were enrolled with mean age 35.28 (± 9.82 years) with 54 males (90%). The main clinical manifestations were oral ulcers (100%), genital ulcers (100%), eye involvement (55%) neurological involvement (28%) and vascular involvement (35%). Furthermore, (33%) had bilateral visual acuity $\leq 6/60$ fulfilling the diagnosis of legal blindness

HLA class I alleles A*68:02:01, B*51:08:01, C*16:02:01 showed highest level of association with Behcet disease patients with an OR = 3 ($p=0.01$) and OR=18.6 ($p<0.0000001$) and OR=6.7 ($p<0.000001$) respectively. As for HLA class I haplotypes HLA class I B*51:08, C*16:02 haplotype was highly associated with susceptibility (OR=17.7, $p<0.000001$). HLA class I B*51 and A*68 were significantly associated with legal blindness (OR=10.1, $p<0.005$) and (OR=8.1, $p=0.023$)

Conclusion: Among the studied Behçet's Patients, HLA-B*51:08:01 is the most frequent susceptibility allele in contrast to other reported populations. Risk of Severe ocular involvement progressing to the blindness of patients was more than 10 folds increased in HLA-B51 positive patients as compared to other patients. HLA-B51 together with HLA-A68 both hold the increased risk of blindness and permanent morbidity in patients with Behcet disease, which if known at diagnosis would modify treatment options in order to salvage the patients' eyesight. Higher resolution analysis of HLA class I alleles and haplotypes specially HLA-B is valuable in knowing susceptibility and aiding in disease control and decreasing ocular morbidity in Behcet disease patients

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Sequencing of the MHC Region Defines HLA-DQA1 As Driven Risk for Anti-Citrullinated Protein Antibodies (ACPA)-Positive Rheumatoid Arthritis in Han Population

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Genetics, Genomics and Proteomics Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The strong genetic contribution of the major histocompatibility complex (MHC) to rheumatoid arthritis (RA) susceptibility has been generally attributed to *HLA-DRB1*. However, due to the high linkage disequilibrium in the MHC region, it is difficult to define the 'real' or/and additional independent genetic risks using the conventional HLA genotyping or chip-based microarray technology.

Methods: To fine map HLA region and identify novel variants contributing to RA, we performed a deep sequencing for entire MHC region for discovery and classical HLA-typing for validation in 2773 subjects of Han ancestry (961 cases and 1812 controls). We analyzed HLA alleles, amino acids, SNPs, and indels across the MHC region to define the association for anti-citrullinated protein antibodies (ACPA)-positive RA.

Results: We identified HLA-DQA1:160D as a novel and the strongest independent genetic risk for anti-citrullinated protein antibodies (ACPA)-positive RA in Han population ($P = 6.16 \times 10^{-36}$, OR=2.29). Further stepwise conditional analysis revealed that DRB1:37N has an independent protective effect on ACPA-positive RA ($P = 5.81 \times 10^{-16}$, OR=0.49). The DQA1:160 coding allele *DQA1*0303* displayed high impact on joint radiographic severity, especially in patients with early disease and smoking ($P = 3.02 \times 10^{-5}$).

Conclusion: We provide the first evidence that *HLA-DQA1*, instead of *HLA-DRB1*, is the strongest and independent genetic risk for ACPA-positive RA in Chinese Han. DRB1:37N is an independent protective factor for ACPA-positive RA. Our study also illustrates the value of MHC deep sequencing for fine mapping disease risk variants in the MHC region.

Disclosure: J. Guo, None; T. Zhang, None; H. Cao, None; X. Li, None; M. Liu, None; Y. Zou, None; Z. G. Li, None.

Abstract Number: 1977

Transcriptional Perturbation of RA-Risk Enhancer By CRISPR-DEADCAS9 Regulates LONG Range GENE Targets

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SESSION INFORMATION

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Background/Purpose: Findings from genome wide association studies in complex diseases indicate over 90% of genetic variants associated with risk of developing disease are found outside protein coding regions, suggesting regulation of gene expression is key to disease susceptibility. For rheumatoid arthritis (RA) it has been demonstrated that risk variants are found in gene regulation regions, and are significantly enriched in T-cell specific enhancers. In addition, a significant proportion of associated variants lay some distance from the nearest gene and enhancers may not necessary regulate the closest gene, effectively 'skipping' genes. Using chromatin conformation technology (HiC) we have demonstrated that an enhancer region intronic of the COG6 gene, containing variants associated with RA, make robust physical contact with the promoter of FOXO1, almost 1Mb away on the linear chromosome. COG6 is not an obvious candidate risk gene for RA, whilst FOXO1 is involved in T-cell development and shown to be over expressed in RA synovium. The challenge now is to provide empirical evidence that the enhancer found within COG6 does regulate FOXO1 expression, and how an RA risk genetic background affects this regulation

Use CRISPR-Cas9, to perturb the COG6 intronic enhancer region and measure the downstream effect on the expression of FOXO1.

Methods: We utilised a modified form of the Cas9 enzyme, dead Cas9 (dCas9), that can precisely target DNA, but will not induce a cut. Using the dCas9 attached to either enhancers (p300) or repressors (KRAB) of expression we investigated how perturbation of the enhancer intronic of COG6 changed the expression of FOXO1.

We designed 3 guides across the COG6 enhancer, and transduced a cell line (HEK293) using a lentiviral dCas9 CRISPR system, with either dCas9-KRAB or dCas9-p300 and each of the three guides. We cultured the cells until 70-80%

confluent, GFP sorted the cells and then extracted RNA. A quantitative PCR was performed (QuantStudio) for both COG6 and FOXO1 gene transcript expression and normalised to housekeeping genes.

Results: Up to 90% of HEK cells were transduced with the dCas9 enzyme and guide, and these were sorted by FACS using GFP to sort the top 60%. The 3 guides gave consistently increased levels of FOXO1 expression with the dCas9-p300, compared to both control and dCas9-KRAB ($p=0.02$). This was particularly evident for guide 3, with a 40% increase (p300) and 10% decrease (KRAB) of FOXO1 expression observed. Expression of COG6 was also perturbed, but in a less consistent manner, with both increase and decrease expression for KRAB and p300.

Conclusion: Over 90% of HEK cells were transduced with the dCas9 enzyme and guide, and these were sorted by FACS using GFP to sort the top 60%. The 3 guides gave consistently increased levels of FOXO1 expression with the dCas9-p300, compared to both control and dCas9-KRAB ($p=0.02$). This was particularly evident for guide 3, with a 40% increase (p300) and 10% decrease (KRAB) of FOXO1 expression observed. Expression of COG6 was also perturbed, but in a less consistent manner, with both increase and decrease expression for KRAB and p300.

Disclosure: K. Duffus, None; M. Imran, None; G. Orozco, None; H. Ray-Jones, None; A. Adamson, None; S. Eyre, None.

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Genome Wide Association Studies in SLE Predict E-Genes and Gene Expression Patterns That Inform Ancestral-Specific Molecular Pathways and Targeted Therapies

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SESSION INFORMATION

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a multi-organ autoimmune disorder with an important genetic component. Genome-wide association studies (GWAS) have linked many single nucleotide polymorphisms (SNPs) to SLE. Recently, Langefeld et al (2017) conducted a large-scale transancestral association study of SLE to identify ancestry-dependent and independent contributions to SLE risk. Here, we take African ancestry (AA) and European ancestry (EA) SLE-associated SNPs, link them to E-Genes and couple those with differentially expressed (DE) genes from SLE patients to develop a better understanding of ancestral-related molecular pathways and novel treatments unique to each ancestral group.

Methods: The GTEx database was used to identify E-Genes from SLE-associated SNPs and their ancestry-specific SNP proxies. Ancestry-specific E-Genes were compared to DE genes from multiple SLE gene expression datasets. For both ancestral groups, E-Gene lists were examined for the significant enrichment of gene ontology (GO) terms, IPA and BIG-C categories, and to predict whether E-Genes were upstream regulators (UPRs). For visualization and clustering analysis, STRING-generated networks of DE E-Genes were imported into Cytoscape and partitioned with the community clustering (GLeay) algorithm via the ClusterMaker2 plugin. Drug candidates targeting E-Genes, DE genes and UPRs were identified using CLUE, REST, API, IPA and STITCH.

Results: Newly predicted E-Genes from the GTEx database were pooled by ancestry. We identified 52 AA-associated and 260 EA-associated SNPs; 1 SNP was shared across ancestries. These SNPs identified 891 distinct E-Genes, which were then compared to SLE DE datasets. We observed differential expression of 516 EA-associated E-Genes enriched in estrogen receptor signaling, neuronal signaling and cholesterol biosynthesis via IPA, and the positive regulation of synaptic transmission by GO-term enrichment. Clustering analysis showed EA E-Gene networks dominated by transcription, RNA processing, glycolysis and immune signaling. Drug candidate comparison identified 77 EA-specific drugs, including hydroxychloroquine and drugs targeting CD40LG and CXCR1/2. For AA, 48 E-Genes were DE in SLE and enriched in IPA categories for T helper cell differentiation and melatonin biosynthesis, and the GO biological process of keratinization. Clustering analysis of the AA E-Genes showed enrichment in PRRs, immune signaling and keratinocyte differentiation. AA-specific drug candidates included HDAC inhibitors, retinoids and inhibitors of IRAK4 and MAP8K4. A total of 46 DE E-Genes were shared between ancestries, with IRF7 upregulated in all SLE datasets. Drugs targeting shared E-Genes included ibrutinib, ruxolitinib and ustekinumab.

Conclusion: The ancestral SNP-associated E-Genes and gene expression profiles outlined here illustrate fundamental differences in lupus molecular pathways between AA and EA. The results indicate that unique sets of drugs may be particularly effective at treating lupus within each ancestral group.

Disclosure: K. Owen, None; C. Langefeld, None; B. Aidukaitis, None; A. Labonte, None; M. Catalina, None; P. Bachali, None; T. D. Howard, None; A. Grammer, None; P. E. Lipsky, None.

Abstract Number: 1979

Rheumatoid Arthritis-Associated Genetic Alteration Defines a New Promoter for Peptidyl Arginine Deiminase 4 Gene

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Genetics, Genomics and Proteomics Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Anti-citrullinated protein antibodies (ACPA) are frequently detected in Rheumatoid Arthritis (RA) patients and used as diagnostic biomarkers at a very early stage of the disease. ACPAs are raised against various peptide epitopes carrying citrullinated arginines generated by peptidyl arginine deiminase (PADI) enzyme family members. PADI4 gene is highly expressed in neutrophils in peripheral blood and also known to citrullinate histone proteins. RA-associated PADI4 single nucleotide polymorphisms (SNPs) do not alter amino acid composition; therefore, it is challenging to explore how they can contribute to RA pathology. We investigated the effect of SNP rs2240335 on transcriptional regulation of PADI4 gene.

Methods: We have investigated the epigenetic landscape of the human chromosome region harboring the *PADI4* gene and focused on histone modifications that predict active promoters. Using 5'RACE method we explored alternative isoform-encoding transcript of PADI4 gene. Quantitative *reverse transcription PCR* was used to explore isoform expression in human tissues. Cellular distribution of a novel short PADI4 isoform was studied by confocal fluorescence microscopy. Short PADI4 isoform's potential catalytic function was tested using *in vitro* transcription and translation system. The disease-associated SNP's effect on transcription was assessed in transient expression studies.

Results: Epigenetic profile analysis around the *PADI4* gene revealed a new promoter region, which proved to be active on bone marrow. We cloned and sequenced the corresponding transcript and designated PADI4-ΔN. PADI4-ΔN is a truncated isoform that only encodes the C-terminal catalytic domain of the enzyme, which is highly expressed in bone marrow sample and neutrophils. PADI4-ΔN was fused to red fluorescent protein (RFP) and overexpressed in cells. Confocal microscopic studies detected the RFP:PADI4-ΔN in cytoplasmic region and nuclei of the transfected cells. Studies addressed to reveal catalytic activity of PADI4-ΔN could not detect any enzymatic activity *in vitro* assays. Transient expression studies revealed that the two allele variants (i.e., G or T at rs2240335 position) can contribute differently to the novel PADI4 promoter activity, which is ultimately reflected by Luciferase activity in cell lysates.

Conclusion: The *PADI4* gene encodes at least three isoforms: (i) the well-characterized full-length isoform, (ii) a C-terminus deleted (PADI4-ΔC) isoform and (iii) the novel N-terminus truncated (PADI4-ΔN) isoform. The newly discovered isoform is not able to catalyze citrullination of vimentin (a well-characterized PADI4 target) and does not affect the enzymatic activity of the full-length isoform in *in vitro* competitive assays. These data suggest that allele variants (at the RA-associated SNP position) primarily alter the physiological ratio of the full-length and truncated PADI4 isoforms, which might lead to RA pathogenesis by an unknown mechanism.

Disclosure: D. M. Tóth, None; T. Ocskó, None; T. T. Glant, None; T. A. Rauch, None.

Comprehensive Association Analysis between Rare and Common *ABCG2* Variants and Gout Susceptibility

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Background/Purpose: We have reported that *ABCG2* has an important role in both renal and intestinal urate excretion and these common variants *asrs72552713* (Q126X) and *rs2231142* (Q141K) are risks for gout. Then, we revealed both rare and common non-synonymous *ABCG2* variants are associated with gout susceptibility. In this study, we investigated the effects of rare and common *ABCG2* variants including synonymous, non-synonymous and splice-site variants on gout.

Methods: We sequenced exons of *ABCG2* in 480 patients with gout and 480 healthy controls (Japanese males). Additionally, functional analyses of non-synonymous variants of *ABCG2* were performed. Then, the correlation between urate transport function and scaled C-score of CADDv1.3 (CADD score) was analyzed. Furthermore, we performed Receiver Operating Characteristic (ROC) curve analysis and made selections of variants with altered function of more than 50% compared to wild-type *ABCG2*. In order to assess the effects of common and rare variants on gout susceptibility, we conducted stratified association analyses and multivariate logistic regression analysis.

Results: We identified 5 common and 25 rare exonic or closely situated intronic variants of *ABCG2*. CADD scores demonstrated relationships with the urate transport function significantly ($p=0.014$, $r=-0.539$.) ROC curve analysis demonstrated an area under the curve (AUC) of 0.775. The appropriate cutoff value of CADD score was 15 when we classified variants with mutated function of more than 50% compared to wild-type *ABCG2* (sensitivity=0.88, specificity=0.67.) Therefore, we carried out the downstream analyses of variants with a CADD score greater than 15. Both intronic and synonymous variants showed low CADD scores. Then were moved them on multivariate logistic regression analysis and revealed that rare variants of *ABCG2* significantly increased gout risk and the size effect of these rare variants (odds ratio [OR]=2.7, $p=0.012$) was similar to that of common variants such as Q126X (OR=3.3, $p=4.8 \times 10^{-6}$) and Q141K (OR=2.3, $p=8.6 \times 10^{-16}$).

Conclusion: We confirmed that both common and rare variants of *ABCG2* have independent effects on risk of gout. Our findings help to better understand both eCommon Disease, Common Variantf and eCommon disease, Multiple Rare Variantf hypotheses for the association between *ABCG2* and gout susceptibility. In addition, our *in silico* analyses suggest that there are no important synonymous and splice-site variants of *ABCG2* for the pathogenesis of gout.

Disclosure: H. Matsuo, None; T. Higashino, None; T. Takada, None; H. Nakaoka, None; Y. Toyoda, None; B. Stiburkova, None; H. Nakashima, None; S. Shimizu, None; M. Kawaguchi, None; A. Nakayama, None; Y. Aoki, None; M. Ishino, None; Y. Kawamura, None; K. Wakai, None; R. Okada, None; T. Hosoya, None; K. Ichida, None; H. Ooyama, None; H. Suzuki, None; I. Inoue, None; T. J. Major, None; T. R. Merriman, None; N. Shinomiya, None.

Abstract Number: 1981

A Molecular Bayesian Network for Rheumatoid Arthritis Reveals Multiple Candidate Key Regulators for Disease Severity

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Genetics, Genomics and Proteomics Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is a common and chronic autoimmune joint disease. RA is pathologically heterogeneous with multiple contributing factors. While there has been a major emphasis in studies of the immune regulatory factors the gene networks regulating the synovial pathology remains incompletely understood. We aimed at establishing a RA synovial tissue gene network to identify new key regulators/driver of the synovial and fibroblast-like synoviocyte (FLS) pathology.

Methods: Several large RA synovial tissue gene expression data sets (GSE48780 and GSE21537, consisting of 83 and 62 synovial biopsies from RA patients, respectively) were used. We used a software suite that we developed, RIMBANet, to construct a Bayesian network model for RA. We computationally estimated cell composition in synovial biopsies (T cells, neutrophils, FLS, macrophages, others).

Results: Immune cell compositions in inflamed and non-inflamed synovial tissues were significantly different, with increased numbers of M1 macrophages in inflamed tissues than in non-inflamed tissues. We adjusted synovial tissue profiling data for cell composition, and combined the two data sets together used in network reconstruction. We identified 7,521 nodes representing expression levels of genes and 8,118 edges representing putative causal relationships between genes. We compared the constructed RA network with well-known interaction databases or canonical pathways, and showed that the RA network overlapped with existing network/pathways significantly better than random networks. Then, we collected a set of RA severity related gene sets from a variety of sources (FLS gene expression, rodent studies, etc) and projected them onto the RA network identified key regulators for disease severity. Top inferred key regulators included DLX4, SEMA3E, LCP1, TRIM22, and ZNF385B. To test whether the inferred key regulators have any impact on RA disease severity, we examined the role of DLX4 in FLS invasiveness, an in vitro phenotype that strongly correlates with joint damage in RA. DLX4 was expressed in RA FLS and its knockdown with siRNA in primary RA FLS significantly reduced FLS invasiveness by 80%.

Conclusion: We here describe a new RA synovial gene network. This study also provides encouraging validation of the new synovial gene network suggesting that it has the potential to lead to the discoveries and of new important genes involved in disease pathogenesis and potentially new targets for treatment.

Disclosure: W. Wang, None; A. Lahiri, None; T. Laragione, None; J. Zhu, None; P. S. Gulko, None.

Abstract Number: 1982

An Integrative Rheumatoid Arthritis Network for Elucidating Molecular Mechanisms Underlying RA Severity

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SESSION INFORMATION

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Session Title: Genetics, Genomics and Proteomics Poster

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Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is a pathologically heterogeneous disease with multiple contributing factors. Many models have been developed to study RA severity and progression, and several RA severity signatures have been derived. However, the molecular mechanisms underlying these RA severity signatures are not fully understood. For example, Cia25 congenic rat interval regulates arthritis severity. The congenic region is conserved among mouse, rat, and human. However, which gene or genes in the congenic region regulate RA severity and which molecular mechanisms remains incompletely understood. We recently developed a human molecular causal network for RA. We leveraged the RA network to elucidate potential molecular mechanisms that drive RA severity.

Methods: A gene expression signature comparing Cia25 congenic and parental strains was collected. A candidate gene list including HIP1 was derived by comparative genomic analysis of mouse, rat, and human genome and comparing SNPs between Cia25 congenic and parental strains.

Results: Cia25 congenic signature was projected to the human RA network that we constructed. We derived a Cia25 congenic subnetwork by using the signature as seeds and collecting nodes that were within 2 hops from the seeds. We compared the subnetwork with GO biological pathways, and found genes involved in immune response, cell adhesion, and cell migration pathways were significantly enriched in the subnetwork. We further compared transcription factor (TF) binding sites in promoter regions of genes in the subnetwork and known TF binding motifs, and found binding sites for transcription factors BACH1 and BACH2 were enriched in the subnetwork. Bach1 has been shown to regulate osteoclast in mouse models. BACH2 was identified a GWAS as a candidate gene for RA susceptibility. It is worth to note that one of the candidate genes for the Cia25 congenic strain is HIP1. In the RA network, HIP1 was regulated by STK3 and STK3 was a part of Cia25 congenic subnetwork. The HIP1 subnetwork (including genes that can be reached from HIP1 within 3 hops) significantly overlapped with the Cia25 congenic subnetwork, supporting HIP1 as a potential candidate for Cia25 congenic strain. For proof of concept we knockdown HIP1 in human fibroblast-like synoviocytes and detected significantly reduced cell invasiveness.

Conclusion: We used a new RA synovial gene network to help identify new arthritis regulatory genes by integrating complex datasets and show that this strategy led to validation and discovery of new arthritis susceptibility and severity genes.

Disclosure: W. Wang, None; T. Laragione, None; A. Lahiri, None; J. Zhu, None; P. S. Gulko, None.

Abstract Number: 1983

Mutations Associated with Clonal Hematopoiesis of Indeterminate Potential Are Found in Peripheral Blood and Synovial Fluid Macrophages from Patients with Rheumatoid and Psoriatic Arthritis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Genetics, Genomics and Proteomics Poster

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Session Time: 9:00AM-11:00AM

Background/Purpose: Myeloid mutations commonly associated to neoplasia in patients who do not meet the diagnostic criteria for myelodysplastic syndrome are coined as clonal hematopoiesis of indeterminate potential (CHIP). CHIP-related mutations are somatic DNA mutations accumulating with aging, being found in approximately 10% of over 65. Chronic inflammation, mirrored by TNF- α -exposure, has been reported to favor the expansion of CHIP-mutant clones, such as TET2- and JAK2-, but recent evidence suggests that CHIP-mutated clones contribute to chronic inflammation, as TET2-mutated myeloid clones manifest a hyper-inflammatory M1 status. We hypothesize that chronic inflammation concurs with age to CHIP-mutation appearance, i.e. they should be more precocious and frequent in rheumatic patients; moreover, CHIP-mutations are associated to more active rheumatic diseases.

Methods: We investigated the peripheral blood and synovial fluid myeloid cells from 4 rheumatoid arthritis (RA), 4 psoriatic arthritis (PsA), and 4 knee osteoarthritis (OA) patients (female 5, median age 73.5 years, range 53-91, median disease duration 10 years, range 7-20). To detect the presence of CHIP-mutations we used a high-throughput sequencing platform (Illumina NextSeq platform) for mutation screening of 78 genes known to be relevant in myelodysplastic diseases.

We evaluated only variants known as pathogenic in COSMIC database, with a population frequency (MAF) < 0.1% described in dbSNP and in 1000 Genome Project.

Results: We found somatic mutations of JAK2, TP53, and TET2 in 2/4 RA patients, GATA2-mutation in 1/4 PsA patients, and a small clone of SF3B1 in 1/4 OA cases. Mutated clones were found both in peripheral blood and synovial fluid of the patients. The patients with CHIP-mutations did not have a more active disease (DAS28-CRP 4.2 ± 0.6 vs 5.1 ± 1.2 ; $p > 0.05$), but 1 RA patient with JAK2-mutation and 1 PsA patient had < 65 years.

Conclusion: Our data suggests that CHIP-mutations are frequent in patients with chronic arthritis, also before 65 years. Understanding the mechanisms connecting somatic mutation-driven clonal hematopoiesis and chronic inflammation will be of great interest not only from a pathogenic point of view, but also in considering possible therapeutic options, such as JAK-inhibitors.

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Abstract Number: 1984

Regulation of Multiple Differentiation Potential in Mesenchymal Stem Cells Via an Intercellular Ca^{2+} Signaling Pathway

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

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Background/Purpose: Multipotent mesenchymal stem cells (MSCs) are widely used in regenerative medicine to repair damaged tissues. Regulating Ca^{2+} release-activated Ca^{2+} (CRAC) channel-mediated intercellular Ca^{2+} signaling is critical to the functional modulation of MSCs. CRACM1 in the plasma membrane is an important molecular regulator of the CRAC channel. Our study aimed to elucidate the possible effects of CRAC channel regulation on the multiple differentiation potential of MSCs.

Methods: To increase Ca^{2+} influx, we overexpressed CRACM1 by transfecting pCDNA3-CRACM1 into MSCs (m1-MSCs). Genomic CRACM1-knockout MSCs (m1-ko-MSCs) were prepared using CRISPR/Cas9 technique. YM-58483 was used as a CRAC blocker. The inhibitory effect of YM-58483 was verified by imaging. Wild-type MSCs, m1-MSCs, m1-ko-MSCs, and YM-58483-treated MSCs were differentiated to adipocytes, osteocytes, or chondrocytes. Fatty acid-binding protein 4 was used as an adipocyte biomarker and osteocalcin was used for the detection of osteocytes. Aggrecan was used as a chondrogenic differential marker.

Results: The results suggest YM-58483 inhibited Ca^{2+} influx in MSCs in a dose-dependent manner, as demonstrated by Ca^{2+} imaging of fura-4-loaded cells. Downregulation of CRACM1 function in MSCs suppressed the differentiation of osteocytes, but not of adipocytes. A decrease tendency on the potential of chondrogenic differentiation was observed in intracellular Ca^{2+} -downregulated MSCs compared to wild-type MSCs. Overexpressing CRACM1 had no effect on the differentiation of osteocytes, but suppressed adipogenic and chondrogenic differentiation, while comparing with that observed in wild-type cells.

Conclusion: The results suggest that MSC differentiation potential is related to intercellular Ca^{2+} signaling pathways. In future study, we aim to research the systemic chondrocyte differentiation *in vivo* and, eventually, to carry out experiments in animal models to further contribute to the growing field of regenerative medicine.

Disclosure: S. Liu, None; E. Takemasa, None; M. Mogi, None.

IL-1 β Inhibits the Expression of Dickkopf-1, an Antagonist of the Wnt- β -Catenin Signaling Pathway: A Possible Role of Inflammasome in Dysregulation of Endochondral Ossification

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SESSION INFORMATION

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Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

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Background/Purpose: Aberrant endochondral bone formation in the physis is a unique bone lesion in neonatal-onset multisystem inflammatory disease (NOMID), also called chronic infantile neurologic cutaneous articular (CINCA), the most severe of the cryopyrin-associated periodic syndrome (CAPS) diseases, which are interleukin 1 β (IL-1 β)-related monogenic auto inflammatory diseases. It is interesting that the pathological features of bone lesions in NOMID / CINCA are similar to those found in patients with fibrous dysplasia, a skeletal disease caused by the gain-of function mutation of the GNAS gene that leads to aberrant activation of the canonical Wnt signal. Since the importance of the Wnt signal in human skeletal development is evidenced by the existence of human diseases caused by abnormalities associated with Wnt receptors, we explored the potential role of IL-1 β on the expression of *WNT* genes and the Wnt antagonist *Dickkopf-1* (*DKK1*).

Methods: The expression of *WNT2*, *3*, *4*, *5A*, *11* and *DKK1* mRNA in fibroblast-like synoviocytes (FLS) was quantified by quantitative PCR. The concentration of DKK1 in supernatant from FLS was determined by ELISA. Additionally, we used TCF reporter transfected in U2OS cell, a cell line that does not express DKK1, to evaluate the activity of the canonical Wnt signal pathway in the presence or absence of the supernatant of cultured FLS treated with or without IL-1 β . Recombinant WNT3A or Lithium chloride (LiCl) was used to activate Wnt signal. Anti-DKK1 antibodies were used to neutralize DKK1 in supernatant from FLS culture.

Results: The mRNA expression of both canonical and non-canonical *WNT* genes as well as *DKK1* was detected in FLS. FLS secreted DKK1 comparable to bone marrow-derived mesenchymal stromal cell. The supernatant of cultured FLS suppressed the luciferase activity of the TCF reporter, and this effect was reduced by its pre-treatment with an anti-DKK1 antibody. Moreover, the supernatant from FLS cultures significantly suppressed the TCF activity induced by WNT3A or LiCl in a dose dependent manner. IL-1 β induced *WNT2* and *5A*, whereas significantly reduced *DKK1* in FLS. Furthermore, the supernatant of FLS cultured with IL-1 β showed a reduced inhibitory effect on TCF activity compared with the supernatant of untreated FLS.

Conclusion: FLS suppress Wnt signal via DKK1 production, and that IL-1 β reduce DKK1 production from the cells and, thereby, activation Wnt signal. Therefore, it is possible that the overproduction of IL-1 β in patients with NOMID/CINCA aberrantly activates the Wnt signal and leads to abnormalities in cartilage and bone differentiation. Our data, consistently with a previous report about fibrous dysplasia, suggest that two distinct genetic mutations in two different diseases lead to similar abnormal activation of the Wnt signal, and, consequently, similar bone lesions.

Disclosure: S. Yamasaki, None; Y. Yoshida, None; K. Oi, None; T. Kuranobu, None; T. Nojima, None; H. Ida, None; E. Sugiyama, None.

Adalimumab:TNF Complexes Are Cleared More Efficiently By Human Osteoclasts Than Those with Etanercept through Fc γ -Receptor Binding and Internalization

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: TNF-alpha (TNF α) has been shown to contribute to osteoclastogenesis (OCgenesis) independently and in conjunction with M-CSF or RANKL, two key cytokines involved in osteoclast (OC) development. We have previously demonstrated that TNF enhances the kinetics of RANKL-induced human OCgenesis and that its effects are mitigated more effectively by the anti-TNF biologic adalimumab (ADA) as compared to etanercept (ETN). The objective of this study was to determine whether Fc-gamma receptor (Fc γ R)-mediated internalization of the biologic:TNF complexes is a contributing mechanism responsible for the difference in effectiveness between ADA and ETN in preventing TNF-enhanced OCgenesis.

Methods: TNF biologics [ADA and ETN] alone or in preformed complexes with TNF α at 50:1 molar ratio were tested for Fc γ R binding by flow cytometry using CHO stably transfected with human FCGRs (Fc γ RI, Fc γ RIIA, -RIIB, -RIIC, Fc γ RIIIA & -RIIIB). Fc γ R expression and binding of preformed biologic:TNF complexes at 10:1 ratio +/- Fc γ R blocking antibodies to primary human OC precursors (OCP) was evaluated by flow cytometry. Fc γ R-mediated internalization was assessed by monitoring a reduction in OC survival in response to preformed biologic:TNF complexes (25:1 ratio) bound with saporin (ZAP), a ribosome-inactivating toxin, as anti-human Fc IgG Fab conjugate +/- Fc γ R blocking antibodies.

Results: The binding study to CHO (human Fc γ Rs) cell lines showed that monomeric ADA and ETN bind similarly to Fc γ R (highly on high affinity Fc γ R and loosely on low affinity Fc γ Rs) while preformed biologics: TNF complexes bind differently. ADA:TNF complexes bind to low affinity Fc γ R, whereas ETN:TNF keep a monomeric binding profile with no gain of binding to low affinity Fc γ R. OCP were found to express mostly Fc γ RII early in development with predominant binding of only ADA:TNF, not ETN:TNF, to this Fc γ R with additional binding to undefined receptor(s). Despite subsequent increases in Fc γ RI and RIII later on, ADA:TNF still preferentially bound to Fc γ RII on the matured OCP with minimal binding to RIII, whereas ETN:TNF binding was observed only to Fc γ RI. Exposure of OCP to ADA:TNF:ZAP (toxin) complexes led to a significant reduction (4-fold) in mature OC due to complex internalization as compared to human IgG:ZAP+TNF conditions that was partially rescued only with the addition of Fc γ RII blocking antibody. Interestingly, a 1.5-fold reduction in mature OC was observed with ETN:TNF:ZAP.

Conclusion: Our *in vitro* findings demonstrate that human OCP can bind and internalize ADA:TNF complexes more efficiently than ETN:TNF complexes. In addition, this process is partially mediated through Fc γ RII. Clearance of the ADA:TNF complexes may help reduce exposure of the OCP to localized TNF by removing TNF more effectively in the joint environment. Additional *in vivo* analysis need to be done to verify these *in vitro* findings.

Disclosure: B. P. Harvey, AbbVie Inc., 3, AbbVie Inc., 1; J. Cohen-Solal, AbbVie Inc., 3, AbbVie Inc., 1; Z. Kaymakcalan, AbbVie Inc., 3, AbbVie Inc., 1.

Abstract Number: 1987

Elucidation of the Function of Dendritic Cell-Specific Transmembrane Protein (DCSTAMP) in Osteoclast Differentiation

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

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Background/Purpose: Osteoclasts (OC) are bone-resorbing, multinuclear cells that originate from myeloid progenitor cells through repetitive cycles of cell-cell fusion. Dendritic cell-specific transmembrane protein (DCSTAMP) is a transmembrane protein essential for cell-cell fusion and formation of fully functional OC although the molecular mechanisms are not well understood. Utilizing RAW cell lines we previously demonstrated that during OC differentiation, heterogeneity in membrane expression levels of DCSTAMP correlated with efficient cell-cell fusion during multinuclear OC formation. Optimal fusion was observed when DCSTAMP^{low} and DCSTAMP^{high} cells interact. Herein, we examined how complete absence of DC-STAMP in the osteogenic progenitor cells (OCPs) controls their ability to participate in cell-cell fusion events required for efficient multinuclear OC formation.

Methods: We isolated bone marrow macrophages (BMMs) from wild type (WT) and *DCSTAMP* knockout (KO) mice. *DCSTAMP*^{-/-} mice show mild osteopetrosis. To analyze cell-cell fusion, we labeled *DCSTAMP*^{+/+} and *DCSTAMP*^{-/-} BMMs obtained from WT and KO mice, respectively, with red (CellVue® Red) and green (CellVue® Jade) membrane dyes, cultured them with MCSF (30 ng/ml) and RANKL (30 ng/ml), and monitored cell-cell fusion with live cell imaging. Moreover, we examined the expression dynamics and fate of DCSTAMP protein in forming OC employing retroviral-mediated expression of GFP-tagged DCSTAMP protein in *DCSTAMP*^{-/-} cells. In addition, we investigated how DC-STAMP alters expression levels of key osteoclast-related genes in WT and KO cells.

Results: We find that *DCSTAMP*^{-/-} BMMs are incorporated into forming OC, however, *DCSTAMP*^{+/+} cells are essential to initiate cell-cell fusion events. Following retroviral vector-mediated complementation of GFP-tagged DCSTAMP protein expression in *DCSTAMP*^{-/-} BMMs, we noted that during OC formation, DC-STAMP expression level remained high but progressively declined during several rounds of cell-cell fusion and levels were low or absent in mature OCs. Interestingly, we noted that the absence of DC-STAMP did not alter mRNA expression levels of *NEATc1* and other key genes involved in cell-cell fusion and other OC differentiation pathways such as *ACP5*, *CTSK* and *ATP6V0D2*. Unexpectedly we further noted that mRNA expression levels of *ACP5*, and *CTSK* genes were more than 2 fold higher in RANKL activated *DC-STAMP*^{-/-} cells compared to WT cells after 120 hours in culture.

Conclusion: Our findings indicate that DCSTAMP expression levels in OCP are high during the early cell-cell fusion events but progressively decline and are absent or low in mature OCs. While *DCSTAMP*^{-/-} OCPs cannot form multinuclear OCs, they do fuse with *DCSTAMP*^{+/+} OCPs and are incorporated into maturing OCs. These data indicate that DCSTAMP membrane expression is not required for cell-cell fusion in the presence of other cells expressing this molecule. The absence of DCSTAMP in OCPs does not alter *CTSK*, *ACP5*, *ATP6V0D2* mRNA expression levels during early fusion events but these genes were elevated in later stages in KO cells. DC-STAMP may regulate expression of key OC-specific genes in the late stages of OC differentiation.

Disclosure: A. Paine, None; M. D. L. L. Garcia-Hernandez, None; D. Li, None; M. Kim, None; C. T. Ritchlin, AbbVie, Amgen, UCB, 2,AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer Inc, 5.

Abstract Number: 1988

Effect of Different Fucoïdians on Pathological Pathways Activated in Osteoarthritic Chondrocytes and Synoviocytes

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoarthritis (OA) is a disease managed rather than cured, with a focus on alleviating its pain. Recent studies show that fucoidans, one of the main therapeutic components of brown algae, are promising candidates to address the symptoms of OA. A wide spectrum of biological activities has been registered in these polysaccharides, however these properties vary between fucoidans from different species. In this study we evaluated the protective effect of different fucoidans on catabolic pathways activated in articular cells.

[illegible]

Results: The production of NO induced by IL-1 β in chondrocytes was attenuated by the three different fucoidans at the lowest dose (5 μ g/ml). Likewise, iNOS expression was significantly reduced by FF5 ($p < 0.05$). Similar results were detected in synoviocytes. IL-1 β -induced Cox-2 expression in chondrocytes were downregulated by FF and FM, however FU failed to modulate its levels. In relation, fucoidans attenuated PGE2 production elicited by IL-1 β , achieving significant reductions with FM5. We also observed all fucoidans, especially FF5, protected chondrocytes against mitochondrial depolarization induced by AA ($p < 0.05$). Subsequently, ROS production was also downregulated by fucoidans. Finally, we activated pro-fibrotic pathways in the synoviocytes by TGF β . Although fucoidans failed to modulate cellular proliferation triggered by TGF β , these polysaccharides down regulated the gene expression of collagen1 and fibronectin as well as α -sma protein expression.

Conclusion: Our results indicate a protective effect of fucoidans against inflammatory and oxidative pathways activated in chondrocytes and synoviocytes. However, we detected that these beneficial activities vary between fucoidans from different species and further studies are warranted.

Disclosure: M. J. Lamas Vázquez, None; R. Meijide-Failde, None; F. J. Blanco, None; H. Domínguez, None; C. Vaamonde-Garcia, None.

Abstract Number: 1989

A Regulatory Role of ANTXR1 in RANKL-Induced Osteoclast Differentiation and Function

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose: Anthrax toxin receptor 1 (ANTXR1) has been known to have relationship with extracellular transmembrane protein deeply associated with the process of bone formation and exert important role in angiogenesis. However, there have been no reports to prove the effects of ANTXR1 on bone metabolism mediated by two types of bone cells, osteoclasts and osteoblasts. The aim of this study is to reveal the role of ANTXR1 in the differentiation and function of osteoclasts and osteoblasts.

Methods: To determine the effect of ANTXR1 on osteoclastogenesis or osteoblast differentiation, we examined TRAP staining, F-actin staining and Pit assay, or ALP and Alizarin Red-mineralization staining, respectively. The mechanism of ANTXR1 by transfection of retrovirus or siRNA analyzed using real-time PCR and western blot analysis. Also, the effect of ANTXR1 on osteoclast-mediated angiogenesis of endothelial cells assessed by in vitro vascular tubule formation assay of human umbilical vein endothelial cells (HUVECs).

Results: Through performing gain- and loss-of-function studies, we found that ANTXR1 positively regulated receptor activator of nuclear factor kappa B ligand (RANKL)-induced osteoclast differentiation and bone resorption with no effects on osteoblast differentiation. During ANTXR1-mediated regulation of osteoclastogenesis, phosphorylation of early signal transducers, c-jun N-terminal kinase (JNK), Akt, and inhibitor of kappa B (IκB) was affected, which in turn alteration of mRNA and protein levels of c-Fos and nuclear factor of activated T cells cytoplasmic 1 (NFATc1). In addition, genetic manipulation of ANTXR1 in bone marrow macrophages (BMMs) modulated the capillary-like tube formation by HUVECs via two kinds of angiogenic factors, matrix metalloproteinase-9 (MMP-9) and vascular endothelial growth factor-A (VEGF-A). These results explained the important role of ANTXR1 in osteoclast differentiation and functional activity, as well as, osteoclast-mediated angiogenesis of endothelial cells.

Conclusion: Taken together, it was proposed that ANTXR1 might be a promising candidate for gene therapy related with bone metabolic diseases and further, have potential to be served as an important biomarker in the research fields of bone metastasis associated with vascularization.

Disclosure: M. S. Lee, None; C. Lee, None; C. H. Chung, None; W. H. Yoo, None; J. J. Choi, None; J. M. Baek, None; J. Y. Kim, None.

Luteolin Modulates Glyco-Lipo-Oxidative Protein Modifications and Inhibits Inflammatory Cytokine Release in Human Osteoarthritic Articular Chondrocytes: Comparison with Colchicine

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The progressive destruction of osteoarthritic articular cartilage has been attributed to multifactorial cellular events, including increased oxidative modifications in proteins, abnormal inflammatory and catabolic gene expressions and early apoptosis. A plant alkaloid colchicine (Col), leads to down regulation of multiple inflammatory pathways and modulation of innate immunity. A polyphenolic antioxidant luteolin (Lut) has also been reported to have potential chondroprotective effects through inhibition of degradative enzymes and increased gene expression of collagen in animal articular chondrocytes [Kang et al., *Biomol Ther*, 22:239-45, 2014]. We aimed to study the comparative anti-glyco-lipo-oxidative and anti-inflammatory effects of Col and Lut on human osteoarthritic articular chondrocytes (OAC).

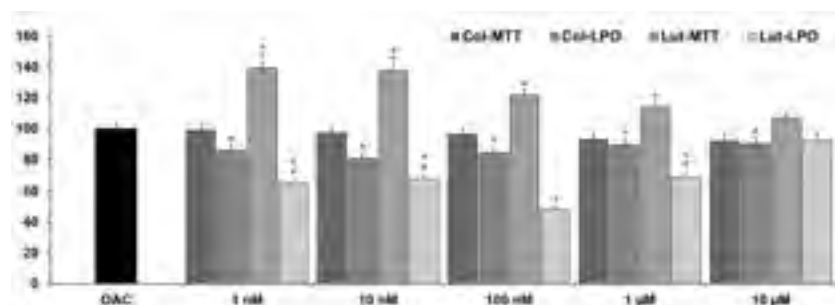
Methods: Chondrocytes were isolated from joint cartilage of KL grade 4 OA patients, during total knee arthroplasty as described previously [Naranda et al., *PeerJ*, 5:e3079, 2017]. The alterations in cell counts, viability (MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazoliumbromide)), the levels of lipid hydroperoxides (LPO), 4-hydroxy-2-nonenal (HNE)-protein adduct and advanced glycoxidation end product (AGE)-protein adduct, osteopontin and proinflammatory cytokines (IL-6, IL-1 β , TNF- α) were studied (ELISA).

Results: Cell viability (MTT) (n=6) and LPO levels (n=3) of primary chondrocytes (30th day after isolation) treated with Col or Lut for 24 h are given in Figure. Lut increased viability at relatively lower concentrations (1 nM-1 μ M). At higher concentrations (50-100 μ M), Lut and Col decreased the viability. Both inhibited LPO levels at 1 nM-1 μ M concentrations, whereas, Lut demonstrated better inhibition compared to Col. Lut diminished HNE-protein adduct levels at concentrations of 1 nM-10 μ M and Col at only 1 μ M concentration. Both compounds also inhibited AGE-protein adduct levels in similar degrees at concentrations of 10 nM-1 μ M. Col strongly blocked the production of IL-1 β in a concentration-dependent manner (1 nM-10 μ M), but not the levels of osteopontin, IL-6 and TNF- α . Lut also significantly attenuated IL-1 β and IL-6 levels in a concentration-dependent manner (1 nM-10 μ M), but had no effect on osteopontin and TNF- α .

Conclusion: Our findings suggest that both Col and Lut might have beneficial effects in OA, mediated at least partly through reduction of oxidative protein degeneration and cytokine release. Although the cytokine inhibition was achieved with both compounds, Lut exhibited more antioxidative efficacy than Col, and probably thus increased viability. (Supported by TUBITAK; The Scientific and Technological Research Council of Turkey, No: 315S012).

Figure. OAC: Osteoarthritic chondrocytes. *p < 0.05, **p < 0.01, ^fp < 0.001 versus OAC (ANOVA with Holm-Sidak *post hoc* test).

Disclosure: B. Goker, None; Z. Elmazoglu, None; B. Bitik, None; C. N. Aytekin, None; C. Karasu, None.



Measuring Balance in an Experimental Mouse Model of Osteoarthritis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Destabilization of the medial meniscus (DMM) in mice results in experimental osteoarthritis, characterized by progressive joint damage (severe damage by week 12) and associated pain-related behaviors. The purpose of this study was to determine if mice also develop changes in motor coordination and balance by using two assays designed to test these parameters: the balance beam and horizontal ladder.

Methods: A 60-cm long, 6-mm wide square wooden balance beam was elevated 35 cm. Mice were filmed from one end as they crossed the beam. Videos were analyzed for (1) Time (in seconds) the mouse took to cross the beam; (2) Whether or not the mouse used its tail.

We used a 60-cm long horizontal ladder with 4-cm long metal rungs spaced 2 cm apart in a straight line. Mice were filmed from the side as they crossed the ladder. Videos were analyzed for (1) Time (in seconds) the mouse needed to cross the ladder; (2) The number of errors made in placing the right hind paw on a rung.

DMM or sham surgery was performed in the right knee of 10-week old male C57BL/6 mice. Age-matched naïve mice were also used. Twelve or fourteen weeks after surgery, mice were tested on either the beam or ladder.

In addition, two strains of naïve DREADD (Designer Receptor Activated by a Designer Drug) male mice were used, in order to selectively silence either nociceptors (Na_v1.8-Pdi mice) or proprioceptors (PV-Pdi mice) (Ray et al, Science, 333:637, 2011). Mice were injected with either clozapine-N-oxide (CNO) (10 mg/kg, i.p.) or vehicle (PBS) (n=6-10 mice/strain/treatment). One hour post injection, mice were tested by crossing the ladder or beam. The experimenter was blinded to the groups.

Results: Balance beam - Twelve weeks after surgery, DMM mice (n=13) took longer to cross the beam than shams (n=11) (p=0.04), and DMM mice used their tail more often than sham mice while crossing the beam (p=0.03).

Ladder - By week 14 after surgery, DMM mice took longer to cross the ladder compared to naïve mice (n=5/group) (p=0.001), while sham mice were not different from either naïve (p=0.16) or DMM (p=0.1). The number of errors made was not different among the groups at this time point.

On the beam, CNO caused both naïve PV-Pdi (p=0.05) and naïve Na_v1.8-Pdi (p=0.04) mice to take longer to cross the beam compared to PBS, but only PV-Pdi mice showed a difference in tail use when given CNO (p=0.008). Together, this suggests that a mixture of nociceptors and proprioceptors are needed to accomplish the beam task.

On the ladder, naïve PV-Pdi mice given CNO took longer to cross the ladder (p=0.01) and made more errors while crossing (p=0.09) compared to PBS. There was no difference between CNO and PBS in Na_v1.8-Pdi mice, providing evidence that this assay assesses proprioceptive function.

Conclusion: Using two different balance assays, we determined that mice developed impairments following DMM surgery, particularly during the late stage of the model, when joint damage and pain-related behaviors are most apparent. Chemogenetic silencing of proprioceptors but not nociceptors resulted in deficits in the horizontal ladder assay, while the beam test appeared to require both kinds of neurons to accomplish the task depending on the parameter measured.

Disclosure: R. E. Miller, None; S. Ishihara, None; Z. Wang, None; R. J. Miller, None; A. M. Malfait, None.

Abstract Number: 1992

The Effect of 4E-BP1 on Osteoarthritis-Related Gene Expression in TGF- β 1-Stimulated Chondrocytes

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Initiation of protein synthesis is regulated by a repressor of cap-dependent translation, eukaryotic initiation factor 4E-binding protein 1 (4E-BP1), which prevents eukaryotic initiation factor 4E (eIF4E) from participating in the eukaryotic translation apparatus through its binding to eIF4E. In this study we determined whether the control of translational apparatus activity could have an effect on the expression of transforming growth factor-beta 1 (TGF- β 1)-induced catabolic or anabolic genes in primary chondrocytes and be responsible for the pathogenesis of osteoarthritis (OA).

Methods: Human articular chondrocytes were enzymatically isolated from articular cartilage and cultured in monolayer. The relative levels of mRNA and protein were analyzed by real-time quantitative reverse transcription-polymerase chain reaction and Western blot analysis, respectively. Immunoprecipitation (IP) assay was performed to investigate the binding of 4E-BP1 to eIF4E. The total protein synthesis was measured by flow cytometry using protein synthesis assay kit. 4E-BP1 and mTOR genes were knocked down by transfection with small interfering RNAs (siRNAs).

Results: The level of 4EBP-1 was significantly higher in human OA cartilage than normal cartilage. TGF- β 1 increased total protein synthesis, including aggrecan (ACAN) and collagen type II (Col II), together with activation of Akt/mTOR signaling pathway. IP data demonstrated that TGF- β 1 treatment suppressed the interaction of 4E-BP1 and eIF4E. mTOR silencing significantly suppressed ACAN and Col II expressions through decreased level of phosphorylated 4E-BP1 in TGF- β 1-treated chondrocytes. On the other hand, 4E-BP1 knockdown promoted total protein synthesis but suppressed Col II and ACAN expressions with decreased expression of Smad2/3 and Smad4 and increased expression of inhibitory Smad6 and Smad7. Furthermore, knockdown of Smad4 suppressed Col II and ACAN expression whereas increased expressions of Col II and ACAN were observed in Smad6- or Smad7-knocked down chondrocytes

Conclusion: These results demonstrated that TGF- β 1-modulated phosphorylation of 4EBP1 plays a role in the expression of Col II and ACAN through alteration of Smad signaling pathway.

Disclosure: M. H. Lee, None; J. R. Kim, None; H. S. Hwang, None; H. A. Kim, None.

Abstract Number: 1993

Evaluation of Cartilage Degeneration and Osteoarthritis Pain on Female and Male Mouse Model of Osteoarthritis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The prevalence of radiographic and symptomatic osteoarthritis (OA) is higher in women, but in animal study, male mice were more frequently used to explore pathogenesis or drug efficacy. In this study we examined whether gender dimorphism affects cartilage degeneration and pain accompanied by OA in knee joints and the activity of transient receptor potential cation channel subfamily V member 1 (TRPV1) antagonist on joint pain using destabilization of the medial meniscus (DMM)-induced OA mouse model.

Methods: DMM or sham surgery was performed on the right knee of 8-10 week old male and female C57BL/6 mice. Von Frey hair, incapacitance, rotarod, and hot plate tests were conducted to measure the degree of mechanical allodynia, sensorimotor skills, and thermal hyperalgesia in the hind paw, respectively. Degeneration of articular cartilage was assessed by safranin O staining and scored using the Osteoarthritis Research Society International (OARSI) scoring system.

Results: Male mice only showed that at the late stage post DMM surgery, paw withdrawal threshold in von Frey test and response time in hot plate test were significantly decreased relative to the sham control group. However, the pain behavior analysis using in capacitance and rotarod tests revealed no significant difference between female and male DMM group. Histology and OARSI scoring analysis showed that significant difference was not observed in male and female DMM groups. In addition, a TRPV1 antagonist, capsazepin (0.5 and 1.0 mg/kg) significantly reduced DMM-induced pain in male mice but did not in female mice.

Conclusion: These results suggest that DMM-induced pain behaviors and the effects of pain drugs, including TRPV1 antagonist, may be gender-dependent.

Disclosure: I. Y. Park, None; J. I. Hong, None; H. S. Hwang, None; H. A. Kim, None.

Abstract Number: 1994

Osteoarthritis Severity Is Reduced By Intra-Articular Administration of Hydrogen Sulfide

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018
Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II
Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: Hydrogen sulphide (H₂S) is recognized as a therapeutic target in osteoarthritis (OA). Exogenous supplementation with synthetic salts in *in vitro* models of OA has been shown to exert anti-inflammatory effects and results in reduced cartilage degradation. Here we evaluated the effects of an intra-articular treatment with an H₂S-producing compound in an *in vivo* model of OA.

Methods: Experimental OA was induced in the left knees by transecting the medial collateral ligament and removing the medial meniscus. Animals were randomized into 3 groups (6 rats/group). Group 1 (intra-articular sulphide, IS): A single intra-articular injection of GYY4137 (200uM in saline, 50 ul) at day 7. Group 2 (intra-articular control, IC): A single intra-articularly injection of vehicle (saline, 50 ul) at day 7. Group 3 (Surgical control, C): No treatment. Gross evaluation of the animals was performed at days 0 (before surgery), 7, 15 and 40 (euthanasia). Histopathological changes in articular cartilage and synovium were evaluated with the MankinScore (MS) and the Krenn Score (KS), respectively.

Results: At day 7 after surgery animals in all groups had increased left knee perimeter, deep pain levels and showed worse performance in a Rotarod test (number of falls [n#f] and time to 1st fall [t1f], Table 1). At day 40, there was no significant improvement in either of these parameters in groups C or IC (except IC n#f that returned to pre-surgical levels). In IS

Table 1. Number of falls (n#f) within a 5-min period, and time to first fall (s), measured in a Rotarod for animals in the control group (C), the intra-articular control (IC, saline) and the intra-articular sulphide (IS, 200 µM GYY4137), n=6 in each group. #p<0.05 with respect to T0; *p<0.05 with respect to C; †p<0.05 with respect to IC.

Group	Falls per 5 min				Time to 1 st fall (s)			
	T0	T7	T15	T40	T0	T7	T15	T40
C	0.8±0.25	4.20±0.89	4.40±0.88	3.51±0.78	23.3±7.73	33.3±11.88	40.0±5.56	37.80±6.36
IC	1.87±1.88	4.34±1.75	4.17±0.88	3.00±0.88	20.9±7.78	31.67±11.74	38.67±8.56	34.83±5.83
IS	1.13±0.62	4.00±1.55	4.10±0.78	3.00±0.88	18.5±15.8	26.5±10.56	37.0±18.19	38.0±12.04

Table 2. Mankin Score grading of cartilage destruction. C: control group; IC: intra-articular control (saline); IS: intra-articular sulphide (IS, 200 μ M GYY4137); M: medial; L: lateral; TP: tibial plateau; FC: femoral condyle, n=3 in each group. *p<0.05 with respect to C.

Group	Medial compartment	Lateral compartment	MTP	MFC	LTP	LFC	Whole joint
C	5.5 \pm 0.6	4.0 \pm 0.0	12.5 \pm 0.7	17.5 \pm 0.7	4.0 \pm 0.0	4.0 \pm 0.0	8.8 \pm 0.6
IC	10.0 \pm 1.7*	7.5 \pm 4.0	9.7 \pm 6.3	10.5 \pm 1.3	6.7 \pm 4.0	8.0 \pm 1.7	8.7 \pm 2.6
IS	7.0 \pm 1.3*	3.8 \pm 1.7	7.7 \pm 0.6*	6.3 \pm 1.5*	3.0 \pm 0.0	4.5 \pm 3.5	5.7 \pm 2.8

values were significantly improved with respect today 0 and both C and IC groups at days 15 and 40 (Table 1). Also left knee perimeter and deep pain levels had subsided.

Histology showed no significant differences among groups in the lateral tibial plateau (TP) or femoral condyle (FC) separately or in the compartment as a whole. Conversely, MS in the medial compartment were significantly better in the IS group vs the C group, both when considering TP or FC separately, and for the whole compartment (Table 2). No significant differences were found among groups on the Krenn Scores.

Conclusion: Intra-articular H₂S administration (200 μ M GYY4137 in 50 μ l saline) can reduce the severity of cartilage destruction in an *in vivo* model of OA as compared to no treatment or a vehicle control. H₂S also led to a reduction in inflammation and pain levels as demonstrated by gross examination and a performance test. Therefore, hydrogen sulphide is a viable pharmacological candidate for OA treatment and should be further tested, including human clinical trials.

Disclosure: E. F. Burguera, None; A. Vela-Anero, None; C. Vaamonde-Garcia, None; T. Hermida-Gómez, None; P. Filgueira-Fernandez, None; L. Gato-Calvo, None; R. Mejjide-Failde, None; F. J. Blanco, None.

Abstract Number: 1995

Heparan Sulfates from Human Osteoarthritic Cartilage Display Increased Sulfation Pattern, Decrease the Protein Binding Capacity to FGF-2 and Increase the Binding to VEGF and Induce Changes of Human Mesenchymal Stem Cell Behavior

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

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Session Time: 9:00AM-11:00AM

Background/Purpose: The major Glycosaminoglycan (GAGs) component of the cartilage ECM are Chondroitin Sulfates (CS) and Keratan sulfates (KS). Heparan Sulfates (HS) are also present in minority in cartilage and very few studies have been done. In general, However, HS act as central functional regulators of cell behavior, principally because of their capacities to interact with several growth factors.

Aim of this study: To characterize the quantity and degree of sulfation of the different GAGs from human normal and osteoarthritic cartilages and to look to the functional properties of HS to bind to growth factors and to induce change on mesenchymal stem cell behavior

Methods: Human samples were harvested from osteoarthritic knee joint (different zones) after TKR and normal counterpart from femoral neck fracture. After extraction, total GAG was quantified by dimethylene blue assay and the proportion of CS, KS and HS were determined following different enzymatic treatments and were normalized to mg of dry tissue. Structure of HS and CS was determined by HPLC analysis. The capacity of the cartilage extracted GAGs to interact

with heparin binding proteins such as FGF-2 and VEGF was evaluated by Elisa- based competition assay with heparin. Finally the effect of GAGs on human mesenchymal stem cell (MSC) was evaluated on adhesion and proliferation assays

Results: 11 OA samples and 7 controlled cartilages were used. Total GAG content was decreased by 1.5 fold in OA compared to normal controls. CS level was the same by KS level was decreased and level of HS decreased by 2 fold. The sulfation pattern of HS shows an increase in the % of di-sulfated disaccharides and a 2 fold decrease in non-sulfated HS. Compared to controls, OA total GAG showed a decrease affinity to FGF-2 binding (less 8 fold) and an increase affinity to VEGF (none in control). Those binding affinities were found to be mainly due to purified HS from OA compared to normal cartilages : FGF-2(2.5 fold decrease) and VEGF (3 fold increase). Interestingly in normal controlled cartilage, presence of CS/KS is able to inhibit HS binding to VEGF, while this inhibitory effect is lost in OA cartilage. Treatment with GAGs from controlled cartilage increased cell adhesion and a 30% increase in the cell numbers of MSC in a dose dependent manner. In the same concentration total GAG from OA did not induced any effect

Conclusion: For the first time, this study showed important effects of HS molecules from OA cartilage on growth factors binding and on cell behavior which may participate to the pathological processes of OA.

Disclosure: S. Shamdani, None; F. Eymard, None; S. Chantepie, None; C. Flageollet, None; N. Henni-Chebra, None; Y. Jouan, None; E. Hay, None; M. Cohen-Solal, None; D. Papy-Garcia, None; X. Chevalier, IBSA, 2, 5; P. Albanese, IBSA, 2.

Abstract Number: 1996

Adenosine A2A Receptor (A2AR) Stimulation Enhances Mitochondrial Metabolism and Mitigates Reactive Oxygen Species-Mediated Mitochondrial Injury

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoarthritis (OA) is the most common form of arthritis, affecting nearly 10% of the US population. With age and injury, chondrocytes have diminished mitochondrial content and mitochondrial production of ATP contributing to OA pathogenesis. We have previously reported that chondrocytes release ATP, which is converted extracellularly to adenosine and maintains chondrocyte homeostasis via endogenous stimulation of the A2AR. Injured/ inflamed chondrocytes have lower ATP levels and release less ATP resulting in diminished extracellular adenosine and A2AR stimulation. Mice and humans lacking the capacity to convert extracellular ATP to adenosine (ecto-5' nucleotidase deficient) develop spontaneous OA as do mice lacking A2AR (A2ARKO). We therefore studied the effect of A2AR stimulation on mitochondrial health and function in chondrocytes from WT and A2ARKO mice and in a human chondrocytic cell line.

Methods: A human chondrocyte cell line, T/C28-a2, or neonatal chondrocytes isolated from WT and A2ARKO mice (C57Bl6 background) were grown in culture, treated with IL-1 β (5ng/ml) or medium (4h, 37°C) and during the last hour of incubation, with either medium or the selective A2AR agonist (CGS21680, 1mM). Mitochondrial function was then analyzed by Seahorse Mito Stress Kits using the Seahorse apparatus. Mitochondrial health was assessed by analyzing mean pixel intensity (MPI) of tetramethylrhodamine (TMRM) live cell staining which correlates with reduced collapsibility of mitochondrial membrane potential. Mitochondrial content and ROS burden were assessed in live cell confocal imaging (MitoTracker; MitoSox) and by immunohistochemistry (anti-ATPase Ab; anti-8hydroxyguanosine Ab, 8OHg) in paraffin-embedded tissue from WT and A2ARKO mice.

Results: The mitochondrial membrane potential and mitochondrial content were reduced in A2ARKO chondrocytes compared to WT. In WT chondrocytes mitochondrial content increased after IL-1 β treatment and A2AR stimulation increased mitochondrial membrane potential as well. Histologic staining of knee cartilage for 8OHg, a marker of ROS-induced oxidation in mitochondria, of age-matched WT and A2ARKO mice revealed increased ROS burden in OA (A2ARKO) cartilage. In T/C28-a2 cells, neither IL-1 β nor CGS21680 affected basal O2 consumption rates (OCR), maximal respiratory rate or ATP production but IL-1 β -treated T/C28-a2 cells stimulated by CGS21680 increased all three measures

of mitochondrial function ($p < 0.03$, one-way ANOVA). Membrane potential (measured by TMRM MPI) decreased in T/C28-a2 cells after IL-1 β or CGS treatment alone, but IL-1 β + CGS21680 treatment significantly increased MPI, indicating enhanced mitochondrial health. Mitochondrial content is not significantly modulated by IL-1 β , CGS or IL-1 β +CGS *in vitro*, but IL-1 β treatment significantly increased ROS burden ($p < 0.0001$) and IL-1 β +CGS did not affect ROS-burden in T/C28-a2 cells.

Conclusion: Mitochondrial function and biomass decline with age and after injury and diminished mitochondrial function contributes to the development of OA. A2AR stimulation enhances the function of mitochondria in inflamed chondrocytes and contributes to the maintenance of healthy chondrocytes and cartilage.

Disclosure: C. Castro, None; C. Corciulo, Regenosine, 1, Intellectual property, 9; M. D. L. E. Solesio Torregrosa, None; E. Pavlov, None; B. N. Cronstein, Cantic Biopharma, Regenosine, 1, NIH Arthritis foundation, Astrazeneca, 2, Horizon Pharmaceuticals, Regenosine, 5, Patent issued and pending, 9.

Abstract Number: 1997

Adenosine A2A Receptors Maintain Chondrocyte and Cartilage Homeostasis By Maintaining Expression of Anti-Inflammatory Regulators (Nur-77) and Suppressing Expression of Pro-Inflammatory Mediators

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: We have recently reported that adenosine A2A receptor (A2AR) knockout mice develop spontaneous osteoarthritis (OA) and intra-articular injection of adenosine prevents OA progression in a rat model of post-traumatic OA. Changes in chondrocyte gene expression in A2AR KO mice are evident in neonatal mice before OA is apparent. A2AR stimulation has previously been shown to regulate expression of NURR-1, a member of the NR4a family of nuclear receptors. There are 3 members of the NR4a family of nuclear receptors Nurr77, Nurr1 and NOR1 which act as transcriptional regulators to diminish binding of NF κ B to its regulatory sites and thereby diminish inflammation. We probed overall expression differences in neonatal chondrocytes from A2AR KO and WT mice and, based on these results, examined the effect of A2AR on NR4a family expression in chondrocytes *in vitro* and *in vivo*.

Methods: Knee cartilage from human OA patients, WT and A2ARKO mice, and from OA mice treated with an intrarticular knee injection (10 μ l) of empty liposome, liposome containing adenosine or CGS21680 (selective A2AR agonist) were examined immunohistologically for expression of Nurr77, Nurr1 and NOR1. mRNA was isolated from chondrocytes from WT and A2ARKO newborn mice and subject to RNAseq analysis. Human chondrocytic cell line TC28a2 was used to study the effect of A2AR agonists on expression of NR4A receptors.

Results: RNAseq analysis revealed alteration in expression of 648 genes, of which 319 were downregulated and 329 upregulated in A2ARKO vs WT chondrocytes. Pathway analysis revealed, among other changes, upregulation of pro-inflammatory and downregulation of extracellular matrix pathways in A2ARKO mice. All 3 of the NR4a genes were downregulated ($p < 0.001$) and a number of pro-inflammatory genes were upregulated (e.g. Nfkb1, Rela and MMP-13 ($p < 0.001$)). By immunohistochemistry NOR1, but not NURR77 or NURR1, is highly expressed in knee chondrocytes in healthy human cartilage and NURR1 is upregulated in human OA cartilage. In OA cartilage of A2ARKO mice there is diminished chondrocyte expression of Nur-77 and increased NURR-1 expression. When studied in a murine obesity model of OA intra-articular injection of liposomal suspensions of CGS21680 promoted NURR-1 expression in OA chondrocytes. When studied *in vitro* in the TC28a2 cell line Nur-77 is present in nuclei and the A2AR agonist stimulated increased nuclear Nur-77, Nurr-1 and Nor-1.

Conclusion: A2AR maintain homeostasis in chondrocytes including maintenance of expression of the anti-inflammatory nuclear receptor Nur-77 in chondrocytes. Diminished Nur-77 expression in OA cartilage likely contributes to OA progression and replacement by Nurr-1 during OA progression is likely insufficient to diminish OA progression but may play a role in A2AR-mediated cartilage repair.

Disclosure: C. Corciulo, Regenosine, 1,Intellectual property, 9; C. Castro, None; S. Jacob, None; D. Fenyó, None; B. N. Cronstein, Cantic Biopharma, Regenosine, 1,NIH Arthritis foundation, Astrazeneca, 2,Horizon Pharmaceuticals, Regenosine, 5,Patent issued and pending, 9.

Abstract Number: 1998

Autophagy-Related Molecules Detected in Blood and Cartilage Are Biomarkers of Joint Damage in OA

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: In osteoarthritis (OA), defects in cellular homeostasis, and in particular in autophagy, are evident and precede joint damage. We have shown that there is a defect in autophagy in OA human chondrocytes and cartilage. Indeed, pharmacological activation of autophagy protects against joint damage. Our working hypothesis is that joint damage in OA could be due to a failure of autophagy that can be detected in the blood and tissue of patients. *Therefore, identifying biomarkers associated with autophagy defects could facilitate the development of personalized therapeutic strategies to prevent OA progression.*

Methods: A comparative analysis of 35 autophagy genes was performed in blood from a Prospective OA Cohort of A Coruña (PROCOAC) of non-OA and knee OA patients. Non-OA patients (Age: 60,13 ± 6,16 years; BMI: 24,65 ± 3,30; Sex: Females/Males; N=30) and Knee OA patients (Age: 68,4 ± 6,07 years; BMI: 29,45 ± 2,86; Sex: Females/Males; N=30, OA grade III-IV) were profiled using PrimePCR autophagy human panel array and analysed using the PrimePCR analysis software (Bio-Rad). Confirmatory studies of the candidate genes were performed in blood and cartilage by using Taqman Technology and immunohistochemistry, respectively. A quantitative proteomic analysis of defective autophagy genes regulated upon deletion of Atg5 in human OA chondrocytes was performed by iTRAQ. Protein identification and quantification were performed using Protein Pilot Software 4.0. Each MS/MS spectrum was searched in the Uniprot/Swissprot database for *Homo sapiens*. Finally, to evaluate the functional consequences of autophagy defects on human chondrocyte homeostasis, pharmacological inhibition of candidate genes was done.

Results: 15 autophagy-related genes were downregulated in blood from knee OA patients compared to non-OA patients (p<0.05). No upregulation was found. although a trend towards upregulation was found for several genes involved in the mTOR signaling pathway. Importantly, key autophagy-related genes, including ATG16L2, ATG12, ATG4B and MAP1LC3B, involved in relevant process including initiating autophagy, phagophore extension and autophagosome formation, were significant downregulated in knee OA patients (p<0.05). Interestingly, HSP90AA1 and HSPA8, chaperone-mediated autophagy genes involved in stress response and protein folding, were significant downregulated (p<0.001). In addition, several regulators of autophagy and apoptosis, such as BNIP3, BCL-2 and BCL2L1 were downregulated (p<0.01). Confirmatory studies for MAP1LC3B and HSP90AA1, showed a significant downregulation (p<0.001) in blood and cartilage from knee OA patients. Remarkably, total proteome screening of human OA chondrocytes with defective autophagy, showed a significant reduction of HSP90AA1(p<0.05). Remarkably, pharmacological inhibition of HSP90 chaperone reduces chondrocyte homeostasis, suggesting that HSP90AA1 might be a potential biomarker associated with defective autophagy in OA.

Conclusion: We identified biomarkers of defective autophagy as a mechanism of central homeostasis, which gives us a general vision of the disease mechanisms linked to OA clinical reality.

Disclosure: B. Carames, None; I. Lorenzo Gomez, None; J. A. Pinto Tasende, None; N. Oreiro Villar, None; F. J. Blanco, None.

Aberrant Expression of the GluN2B N-Methyl D-Aspartate Receptor Subunit in Osteoarthritic Chondrocytes Causes Disease-Associated Changes in Chondrocyte Phenotype through Altered Expression of Core Components of the Chondrocyte Circadian Clock

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Circadian clocks are key regulators of cell behaviour. Disruption to cell clocks is implicated in a range of diseases. Expression of two core clock components, *PER2* and *BMAL1*, is altered in chondrocytes in osteoarthritis (OA). Both *in vitro* and *in vivo* studies indicate that this altered expression contributes to OA-associated changes in chondrocyte activity and cartilage loss. Why the chondrocyte clock is altered in OA is unclear. *N*-methyl-D-aspartate receptors (NMDAR) are critical for regulating the more well studied light-sensitive clock present in the hypothalamus. Chondrocytes also express NMDAR and the type of NMDAR expressed changes in OA. The purpose of this study was to determine if NMDAR regulate the chondrocyte clock and if the change in NMDAR expression in OA chondrocytes is responsible for disease-associated changes in the circadian clock and cell phenotype.

Methods: Chondrocytes were isolated from macroscopically-normal (MN) and osteoarthritic cartilage from patients with OA. Cells were treated with NMDAR antagonists or transfected with siRNA targeting NMDAR subunits. The effect on clock gene expression, and chondrocyte phenotypic markers, was assessed by RT-qPCR and ELISA. Effects of GluN2B expression were determined by ectopic expression in the H5 chondrocyte cell line.

Results: In OA chondrocytes, NMDAR inhibition restored *PER2* and *BMAL1* expression to levels similar to MN chondrocytes and resulted in reduced RNA and protein levels of *MMP13* (the major enzyme implicated in the cartilage loss in OA) and *COLX* (type X collagen, a marker of the OA chondrocyte phenotype). Paradoxically, NMDAR inhibition in MN chondrocytes resulted in a similar reduction in *BMAL1* and increase in *PER2*, *BMAL1*, *MMP13* and *COLX* expression as seen in OA. OA chondrocytes expressed both GluN2A and GluN2B NMDAR subunits whereas MN chondrocytes only expressed GluN2A. Knockdown of GluN2A in MN chondrocytes caused OA-associated changes in *PER2*, *BMAL1* and chondrocyte phenotypic marker expression. In OA chondrocytes, GluN2A knockdown further exacerbated disease-associated increases in *PER2*, *MMP13* and *COLX*. Conversely, inhibition or knockdown of GluN2B in OA chondrocytes restored expression of *PER2*, *BMAL1* and phenotypic markers to levels similar to MN chondrocytes. Overexpression of GluN2B in the H5 chondrocyte cell line resulted in a similar reduction in *BMAL1* and increase in *PER2* expression as seen in OA and led to OA-associated changes in phenotypic markers. Knockdown of *PER2* mitigated the effects of GluN2B overexpression on chondrocyte phenotype. Notably, it completely ablated the GluN2B-induced increase in *MMP13* expression. This indicates that GluN2B causes disease-associated changes in chondrocyte phenotype in part, by altering expression of circadian clock components.

Conclusion: NMDAR regulate the chondrocyte clock. Different NMDAR subtypes have different effects on the clock. The change in NMDAR sub-type expression in chondrocytes in OA, (from GluN2A only to GluN2A and GluN2B), may contribute to disease pathogenesis by promoting OA-associated changes in chondrocyte phenotype by altering expression of core clock components.

Disclosure: M. Kalev-Zylinska, Research grant from Auckland Medical Research Foundation, 2; J. Hearn, None; J. Rong, None; M. Zhu, None; J. Munro, None; J. Cornish, None; N. Dalbeth, Horizon, 5, Kowa, 5, Amgen Inc., 2, AstraZeneca/Ironwood, 2, AbbVie Inc., 8, Pfizer, Inc., 8, Janssen, 8; R. Poulsen, Research grants from the Health Research Council of NZ and Arthritis, NZ, 2.

Interleukin-1 β , Oxidative Stress and Basic Calcium Phosphate Crystals Induce Osteoarthritis-like Changes in Chondrocyte Phenotype By Altering the Expression of PERIOD2, a Core Component of the Chondrocyte Circadian Clock

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Almost all cells contain a circadian clock. Cell clocks are key regulators of cell activity and cell differentiation. In osteoarthritis (OA), chondrocytes inappropriately undergo terminal differentiation leading to increased production of cartilage degrading enzymes. Recently, we found expression of two core circadian clock components, *PER2* and *BMAL1*, is altered in chondrocytes in OA. *In vitro* and *in vivo* evidence indicates altered *BMAL1* expression contributes to OA pathology. The purpose of this study was to determine potential causes of the altered *PER2* and *BMAL1* expression in OA, and to investigate the role of *PER2* in regulating chondrocyte behaviour.

Methods: Chondrocytes were isolated from macroscopically normal (MN) and OA cartilage from 12 patients with OA. MN chondrocytes were treated with interleukin-1 β (IL-1 β , 10ng/ml), hydrogen peroxide (100 μ M) or basic calcium phosphate (BCP) crystals (50 μ g/ml) (stimuli previously shown to induce OA-associated changes in chondrocyte phenotype) for up to 48h. Clock gene expression was measured by RT-qPCR. RNAi was used to knockdown *PER2* and chondrocyte phenotypic marker expression was assessed using RT-qPCR and ELISA.

Results: Consistent with previous findings, peak expression of *BMAL1* was lower and peak expression of *PER2* higher in OA compared to MN chondrocytes. In IL-1 β , peroxide or BCP crystal-exposed MN chondrocytes, peak expression of *BMAL1* was also lower, and *PER2* levels remained elevated for longer, compared to untreated cells. IL-1 β , peroxide and BCP-induced changes in disease-associated phenotypic markers (*SOX9*, *ADAMTS5*, *MMP13*) were partially mitigated by knockdown of *PER2*. *PER2* knockdown in OA chondrocytes was associated with restoration of phenotypic marker expression to levels more similar to the non-diseased state. Notably, both RNA and protein levels of *MMP13*, the major enzyme implicated in the cartilage loss in OA, were reduced following *PER2* knockdown in OA chondrocytes.

Conclusion: IL-1 β , peroxide and BCP crystals induce similar changes in the expression of *PER2* and *BMAL1* as occur in OA. Increased *PER2* expression contributes to the induction of OA-associated changes in chondrocyte phenotype following IL-1 β , peroxide and BCP crystal treatment and contributes to the maintenance of the diseased phenotype in OA chondrocytes. Altered expression of *PER2* and *BMAL1* may be a central mechanism by which multiple different risk factors for OA induce disease-associated changes in chondrocyte activity.

Disclosure: J. Rong, None; M. Zhu, None; J. Munro, None; G. M. McCarthy, None; J. Cornish, None; N. Dalbeth, Horizon, 5, Kowa, 5, Amgen Inc., 2, AstraZeneca/Ironwood, 2, AbbVie Inc., 8, Pfizer, Inc., 8, Janssen, 8; R. Poulsen, Research grants from the Health Research Council of NZ and Arthritis, NZ, 2.

Abstract Number: 2001

Adenosine A2A Receptor Stimulation Regulates Autophagy in Chondrocytes

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoarthritis (OA) is a debilitating condition characterized by chondrocyte dysfunction and loss of cartilage. Autophagy, a homeostatic process that occurs in times of cellular stress and starvation, is decreased in chondrocytes with aging and OA. The adenosine A2A receptor (A2AR) maintains chondrocyte homeostasis; A2AR knockout (KO) mice spontaneously develop OA. Moreover, intra-articular injection of liposomal preparations of adenosine or an A2AR-specific agonist (CGS12680 (CGS)) in rats with post-traumatic OA (PTOA) or mice with obesity-induced OA prevents development of PTOA and reverses obesity-induced OA. We sought to determine whether adenosine signaling maintains chondrocyte homeostasis, in part, by regulating autophagic flux in chondrocytes.

Methods: Autophagy proteins Beclin-1, p62/SQSTM1, and LC3 were analyzed by western blotting and IF in TC28a2 human chondrocytes $\pm 1\mu\text{M}$ CGS for various times in normal culture and starvation (FBS 10% vs 1%). Chondrocytes were pretreated with autophagy inhibitors hydroxychloroquine (prevents autophagosome destruction by lysosomes, $25\mu\text{M}$, HCQ) and/or 3-methyladenine (blocks autophagy initiation, 3MA, 5mM). Knee joint sections from obese mice treated with adenosine or CGS were analyzed by fluorescent IHC. Autophagy gene expression was determined in differential display analyses comparing wildtype (WT) vs A2AR KO mice and rats with established PTOA treated with intra-articular injections of liposomal CGS or liposomes alone.

Results: Consistent with enhanced autophagy, CGS reduced p62 levels in starved chondrocytes by western blot (4.1 ± 0.7 vs 5.7 ± 0.8 p62/actin, $p < 0.02$). More cells stained diffusely positive for p62 without punctae (less autophagy) in the control vs CGS ($67 \pm 6\%$ vs. $19 \pm 3\%$, $p < 0.0002$). With HCQ added, punctate p62 was more marked and brighter on CGS treatment ($78 \pm 5\%$ vs $13 \pm 4\%$, $p < 0.0001$). Chondrocyte pre-treatment with 3-MA (\pm HCQ) followed by starvation \pm CGS for 1h demonstrated almost complete absence of either p62 or Beclin-1. When studied *in vivo* in OA mouse knees, Beclin-1 was not visible in chondrocytes in normal and obese (OA) mouse controls whereas it was present in all of the chondrocytes in obese mice treated with either CGS or adenosine ($p < 0.0001$). Differential expression analysis of WT vs A2AR KO murine chondrocytes demonstrated significant changes in numerous autophagy genes; e.g. *p62* was elevated in WT mice. Similarly, there were significant changes in autophagy gene expression in PTOA rats given liposomal-CGS vs liposome. Of note the autophagy Atg8-family member *Gabarrap11* that integrates into autophagosomes was increased with CGS-liposome injections (FC +1.75, adj $p = 0.0049$).

Conclusion: These results demonstrate, both *in vitro* and *in vivo*, that A2AR stimulation promotes autophagy, evidenced by decreased p62, increased Beclin-1 and reversal of these effects with autophagy inhibitors. Although the precise mechanism is not known, it is possible that A2AR signaling increases Beclin-1 activity, thereby increasing downstream autophagic flux. This increase in autophagy may contribute to maintaining chondrocyte homeostasis and reversing OA.

Disclosure: B. Friedman, None; C. Corciulo, Regenosine, 1, Intellectual property, 9; C. Castro, None; B. N. Cronstein, Cantic Biopharma, Regenosine, 1, NIH Arthritis foundation, Astrazeneca, 2, Horizon Pharmaceuticals, Regenosine, 5, Patent issued and pending, 9.

Abstract Number: 2002

Dynamic Compression of Articular Cartilage Explants Increases Formation and Decreases Degradation of Type II Collagen

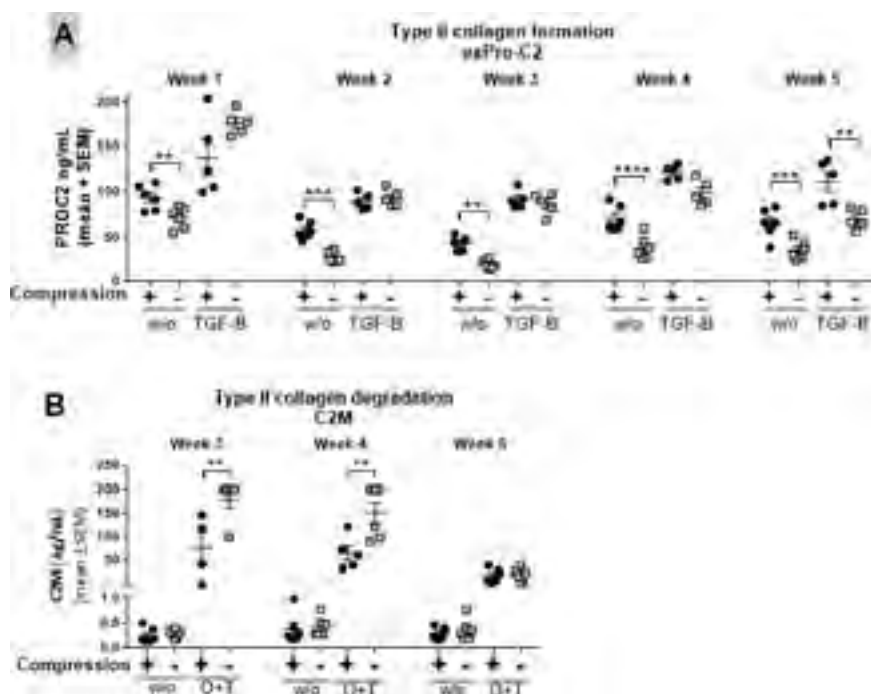
Amalie Engström^{1,2}, Anne C. Bay-Jensen², Morten A. Karsdal² and Christian S. Thudium², ¹Department of Biomedical Science, University of Copenhagen, København, Denmark, ²Nordic Bioscience, Herlev, Denmark

Session Information

Session Date: Tuesday, October 23, 2018

Background/Purpose: Mechanical loading is recognized as a major factor in initiation and progression of osteoarthritis (OA). Conversely loading is believed to play an essential role in maintaining homeostasis of healthy cartilage. Given the biomechanical function of articular cartilage and the mechanosensitivity of chondrocytes, physiological loading may be of importance in a translational cartilage model and hereby, in development of new OA drug candidates. This study investigated the effect of long-term dynamic *ex vivo* compression on articular cartilage through quantification of type II collagen formation and degradation.

Methods: Full-depth bovine cartilage explants were cultured for 5 weeks. The explants were treated 3 times a week with either OSM [10 ng/mL] and TNF- α [2ng/mL] (O+T), or TGF- β 1 [50 ng/mL]. Untreated samples were included as negative controls (w/o). For each condition, two groups were established; an unloaded group and a group compressed 3 times a week. Compression was applied using Electroforce 5500® (TA Instruments), in a sine wave with a maximum load per cycle of 1 MPa, at 1 Hz frequency for 1200 cycles. Metabolic activity was measured once a week using Alamar Blue. Biomarkers



released to the supernatant were assessed using ELISAs: Pro-C2 and C2M for measurement of type II collagen formation and degradation respectively.

Results: Compression resulted in increased Pro-C2 release throughout the 5 weeks, peaking at week 3 where application of compression without treatment increased the Pro-C2 level 125 % ($p=0.0025$) above the unloaded group. A synergistic effect was observed with compression and TGF- β treatment, increasing the Pro-C2 release by 60% at week 5 ($p=0.0048$) compared to the non-compressed TGF- β treated samples. O+T treatment stimulated a catabolic response in the cartilage explants as shown by the increase in C2M levels. This O+T-induced C2M release was partly blocked by dynamic compression. At week 4, the C2M response was reduced by 61 % ($p=0.0054$) in compressed O+T treated explants compared to the non-compressed O+T treated group.

Conclusion: Long-term dynamic compression induced an increase in type II collagen formation, which was synergistic with the effect of TGF-beta. Furthermore, compression induced a reduction in cytokine-induced type II collagen degradation. In conclusion, compression stimulates formation and attenuates degradation, which may be important when evaluating the mechanisms of different novel drug candidate targeted cartilage metabolism.

Chondrocyte Size in Articular Cartilage As a Marker of Osteoarthritis Severity

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Session Information

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Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Terminal differentiating growth plate chondrocytes are mainly characterized by an increase of their cell size and by the expression of hypertrophic markers such as type X Collagen. Likely, during osteoarthritis (OA) progression, articular chondrocytes acquire a similar protein profile, and, therefore, they have been commonly described as hypertrophic-like chondrocytes. Our aim was to study whether an increase in chondrocyte size may be a feature of the hypertrophic-like phenotype in the articular cartilage (AC) of experimental OA rabbits and in OA human cartilage. The anatomical location of these bigger cells in the deeper zones was also assessed.

Methods: New Zealand female rabbits were randomly assigned to four groups: healthy (n=8), osteoporosis (OP, n=7), OA (n=8) and OA preceded by OP (OPOA, n=8). OP was induced by ovariectomy followed by methylprednisolone administration (1mg/kg/day) during four weeks. OA was induced by anterior cruciate ligament section and partial medial meniscectomy, lasting over a period of 6 weeks. All animals were euthanized and tibias were collected for histological analysis. Cartilage damage and chondrocyte size were assessed in Safranin-O fast green stained sections. Type X Collagen presence was analyzed by immunohistochemistry. Nine human samples were obtained during total knee replacement surgery to perform identical histological studies after the informed consent was gained. Statistical comparisons were performed using Kruskal-Wallis and Mann Whitney tests, whereas correlations were done with Spearman test.

Results: Mankin score showed an increase in cartilage damage in all groups in comparison to healthy rabbits. The most severe cartilage damage was observed in the OPOA group (Healthy: 1.0 (0-1.5), OP: 2.3 (1.5-4.5), OA: 8.0 (7-13), OPOA: 13 (11-16)). Chondrocyte size in OA and OPOA cartilages were greater than that in healthy cartilage, and significantly greater in OPOA vs OA (Healthy: 133.0 (91.1-158.7), OP: 140.7 (119.7-198.3), OA: 180.9 (120.5-266.4), OPOA: 217.4 (183.6-303.5)). However, no differences in the mean chondrocyte size were found between the deepest and in the most superficial regions of the AC in any of the groups analyzed. Chondrocyte size and cartilage damage were significantly and positively correlated ($p < 0.001$, $r = 0.718$). In addition, chondrocyte size was also associated with immunoreactive type X Collagen staining ($p < 0.05$, $r = 0.444$). Regarding human OA cartilage, chondrocyte size also correlated with cartilage damage and with type X Collagen presence ($p < 0.001$, $r = 0.921$ and $p < 0.05$, $r = 0.663$ respectively).

Conclusion: We observed an increase of the chondrocyte size in OA cartilage in relation to an increased cartilage damage. These bigger chondrocytes were homogeneously distributed in the deepest and in the most superficial regions of the AC. A positive correlation was also found between the chondrocyte size and the presence of type X Collagen, both in human and experimental OA cartilage. Our results suggest that chondrocyte size could be a reliable hypertrophic marker of the OA articular cartilage.

Disclosure: P. Gratal, None; A. Mediero, CP15/00053 PI16/0991, 2, 9; I. Prieto-Potin, None; A. Lamuedra, None; G. Herrero-Beaumont, None; R. Largo, None.

Abstract Number: 2004

Effective Inhibition of Metalloproteases By a Viscosupplement Based on a Hyaluronic Acid Amide (HYADD®4)

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoarthritis (OA) is a disease which results in the degeneration of articular cartilage. The progression of OA involves inflammation in the early stage of the disease which induces the activation of cartilage-degrading enzymes, such as metalloproteases (MMPs) and aggrecanases (ADAMTSs), through different signaling pathways. Based on the literature, MMP3 can be considered a promising target in OA therapy: in detail, several clinical studies reported an increase of MMP3 level in synovial fluid (SF) in early and advanced OA patients. In our previous work a hyaluronic acid (HA) partial hexadecylamide (HYADD[®]4), contained in the viscosupplement Hymovis[®], was selected as the strongest MMP and hyaluronidase inhibitor among a series of glycosaminoglycans. The objective of these further studies was to confirm the *in vitro* efficacy and selectivity of HYADD[®]4 as MMP inhibitor and to elucidate the mechanism of inhibition through *in silico* studies

Methods: HYADD[®]4 was screened *in vitro* against 10 different human MMPs and other targets. In order to shed light on the mechanism of inhibition, the structural interactions between a HYADD[®]4 oligomer and the crystal structure of MMP3 were evaluated *in silico* by means of molecular modeling studies. Molecular docking and molecular dynamics simulations were performed to propose a hypothetical binding mode of the HYADD[®]4 oligomer on MMP3 and to evaluate the stability of the complex

Results: Among the tested glycosaminoglycans HYADD[®]4 showed the highest inhibition potency against MMP13, MMP8 and MMP3, and no activity against ADAMTS4 and elastase *in vitro*. The molecular modeling results suggest that HYADD[®]4 may behave as a competitive MMP inhibitor, because of its ability to interact with the collagen-binding groove and to participate in the coordination of the catalytic zinc ion of this class of enzymes. Moreover, the hexadecyl side chain in HYADD[®]4 is suitable to fit effectively the enzyme S1' additional pocket, increasing its affinity for MMP3

Conclusion: The HA derivative HYADD[®]4 showed an inhibitory effect on MMP activity *in vitro*; in this study, a specific mechanism for the structural inhibition of MMP3 has been proposed on the basis of molecular simulation studies. A subsequent pivotal clinical trial has been performed to confirm the efficacy of HYADD[®]4 in inhibiting MMP3 activity in the synovial fluid of OA patients in comparison with another viscosupplement based on a different HA chemistry. These findings suggest that the intra-articular administration of HYADD[®]4 (Hymovis[®]) may prevent local cartilage degradation mediated by MMPs

Disclosure: C. Secchieri, Fidia Farmaceutici, 3; D. Galesso, Fidia Farmaceutici, 3; C. Guarise, Fidia Farmaceutici, 3; M. Pavan, Fidia Farmaceutici, 3; S. Moro, Fidia Farmaceutici, 2; V. Salmaso, Fidia Farmaceutici, 2.

Abstract Number: 2005

Identification of a Human Cartilage Microbial DNA Signature and Characterization of Distinct Microbiome Profiles Associated with Osteoarthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoarthritis (OA) is both the most common form of arthritis and a leading cause of chronic disability. Bacterial products, including lipopolysaccharide (LPS), have been suggested as drivers of OA; however, an examination of the microbiota signature of human articular cartilage has not yet been performed.

Methods: Using sterile technique, OA-eroded and OA-intact cartilage was obtained from primary OA knee (intact=21, eroded=21) and hip (intact=33, eroded=34) replacements, OA-free cadaveric control tissue was obtained from the National

Disease Research Interchange (n=30). Age, race, sex, and BMI were not statistically significantly different among groups. 16s rRNA gene deep sequencing was done on an Illumina HiSeq. Operational taxonomic units (OTUs) were assigned using QIIME 1.9 and alpha and beta diversity were calculated. Group OTU differences were identified using Linear Discriminant Analysis Effect Size (LEfSe); LDA log-scores ≥ 2 or ≤ -2 ($p \leq 0.01$) significant, Benjamini-Hochberg FDR q-values were calculated ($q \leq 0.1$ significant). Differences were confirmed with clade-specific qPCR in a separate confirmation cohort (10 eroded, 10 intact, 10 control samples). The Gram status of DNA sequences for each sample was determined and compared.

Results: We found reduced alpha diversity in OA tissue vs. control (control vs. eroded $p=0.009$, control vs. intact $p=0.006$, eroded vs. intact $p=1.0$) and in hip vs. knee (knee-control vs. hip-control $p<0.0001$, knee-OA vs. hip-OA $p<0.0001$). Beta diversity was also different between groups (OA vs. control $p=0.001$, knee-OA vs. hip-OA $p=0.001$, knee-control vs. hip-control $p=0.002$). In group analysis, there were 63 clade differences between OA and control, 35 passed FDR correction; OA was dominated by *Betaproteobacteria* whereas controls characterized by *Actinobacteria* and *Clostridia*. We found 36 differences in knee-OA vs. hip-OA, 8 passing FDR correction. Hip-OA was dominated by *Proteobacteria* including *Rhodocyclaceae*, whereas knees were characterized by *Actinobacteria*. 46 differences were seen in knee-control vs. hip-control. Deep sequencing findings were confirmed by clade-specific qPCR analysis of *Alphaproteobacteria*, *Bacteroides*, *Betaproteobacteria*, *Pseudomonas*, and *Burkholderiales* in a separate confirmation cohort. We noted a shift in OA towards Gram-negative constituent DNA (OA-intact: $37\% \pm 3\%$ vs. control: $27\% \pm 2\%$, $p=0.03$; OA-eroded $38\% \pm 3\%$ vs. control $27\% \pm 2\%$, $p=0.02$, OA-intact vs. OA-eroded N/S).

Conclusion: Our results suggest that bacterial nucleic acid is present in human cartilage samples, and significant diversity and clade differences exist between OA and control tissue, and between hip and knee samples. We identified an increase in nucleic acid from Gram-negative organisms in OA samples, complementary to recent reports of elevated local LPS levels in OA. Further work should be done to confirm our findings and examine the pathogenic role of cartilage microbiota changes in OA.

Disclosure: C. Dunn, None; C. Velasco, None; A. Rivas, None; M. Andrews, None; P. Jacob, None; M. A. Jeffries, None.

Abstract Number: 2006

Murine Ear Wound Cartilage Superhealer Trait Is Associated with Gut Microbiota Changes and Is Transferable to Non-Healer Mice By Gut Microbiome Transplant

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Session Information

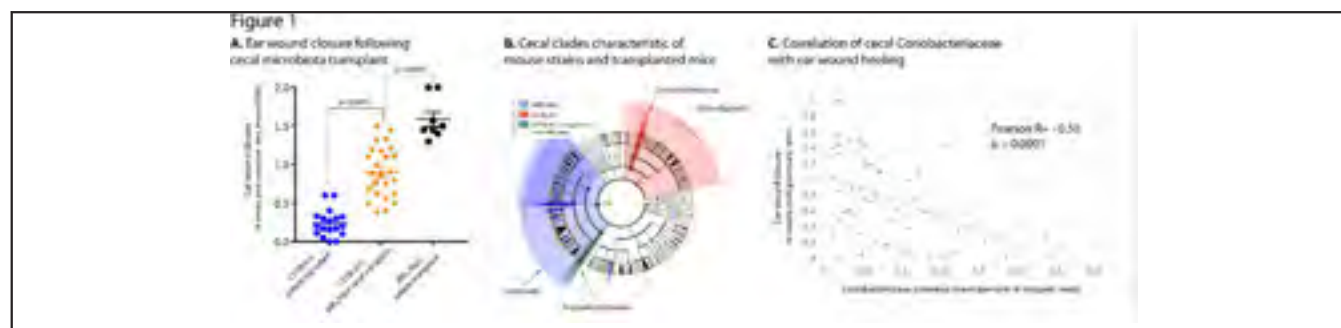
Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: MRL/MpJ mice are substantially protected from developing post-traumatic osteoarthritis (OA), a trait with strong correlation to the ability to heal ear wounds. Previous studies have shown murine ear wound healing to be genetically determined. A powerful role of the gut microbiome in OA has recently been suggested, with dietary



oligofructose supplementation resulting in protection from OA. In this study, we examined whether ear wound healing in MRL mice is associated with gut microbiota changes, and whether microbiome transplantation can transfer this superhealer trait.

Methods: Three-week-old C57BL6/J mice were inoculated by oral gavage with diluted cecal contents from adult male MRL/MpJ mice, or with vehicle control. Six-week-old transplanted B6 mice (n=26), age-matched B6 (n=18) and vehicle control MRL mice (n=8) received a 2mm ear punch. Mice were sacrificed 4 weeks later, final earhole size measured, and DNA extracted from cecal contents. The gut microbiome was characterized by 16s rRNA gene deep sequencing and analyzed using QIIME 1.9.1. Group significance-values and FDR-corrected q-values were calculated in QIIME using Kruskal-Wallis and Benjamini-Hochberg. Characteristic clades of each group were calculated and plotted in LEfSe. Microbiome clades were correlated with earhole closure via Pearson correlation.

Results: As previously reported, MRL ear wounds closed well (earhole closure, mm, MRL: 1.6 ± 0.1 mm mean \pm SEM vs. B6: 0.23 ± 0.04 , $p < 0.0001$). Transplanted B6 mice closed roughly one-half as well as MRL (MRL \rightarrow B6: 0.9 ± 0.06 vs. MRL: 1.6 ± 0.1 , $p < 0.0001$), but significantly more than B6 controls ($p < 0.0001$), (Figure 1A). Microbiome analysis demonstrated several clades that were characteristic of each group (Figure 1B); specifically in MRL and transplanted mice, increases in Lachnospiraceae (B6 mean OTU count 0.05 vs. transplant 4.4 vs. MRL 9.4, $p = 1E-5$, $q = 0.003$), Peptostreptococcaceae (B6 0.28 vs. transplant 0.46 vs. MRL 7.6, $p = 1E-4$, $q = 0.02$), and decreases in Coriobacteriaceae (B6: 10670 vs. transplant: 4982 vs. MRL: 795, $p = 0.0007$, $q = 0.02$) and Erysipelotrichaceae (B6: 0.33, transplant 3.2, MRL 2, $p = 0.002$, $q = 0.05$) were seen. The presence of several clades was highly correlated with earhole closure rates in individual mice, including Coriobacteriaceae (Pearson $R = -0.53$, $p = 3.5E-5$), Figure 1C.

Conclusion: Superhealer MRL mice have substantial differences in gut microbiota composition compared to nonhealer B6 mice. The MRL cartilage healing trait, as measured by earhole closure, is partially transferrable to B6 mice via a gut microbiome transplant, and associated with shifts in specific gut microbiotic taxa. Future work should focus on elucidating the causal mechanism underlying these findings, and further examine the therapeutic potential of gut microbiota modification in treatment of OA.

Disclosure: C. Dunn, None; C. Velasco, None; M. Andrews, None; A. Rivas, None; M. A. Jeffries, None.

Abstract Number: 2007

Generation of Human Induced Pluripotent Stem Cell Lines from Patients with Hand Osteoarthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Although hand osteoarthritis (OA) is a worldwide burden, there is no treatment able to cure it. Induced pluripotent stem cells (iPSCs) are considered ideal sources for exploring cell therapies and they have emerged as promising tools for modelling diseases. The advantages of using iPSC lines are unlimited cell source and chondrogenic differentiation potential. However, there are no studies generating iPSCs from patients with hand OA. Therefore, the aim of this study has been to generate iPSC-lines from patients with hand OA and healthy donors, which can be useful for studying the pathogenesis of the disease *in vitro* and for testing new drugs.

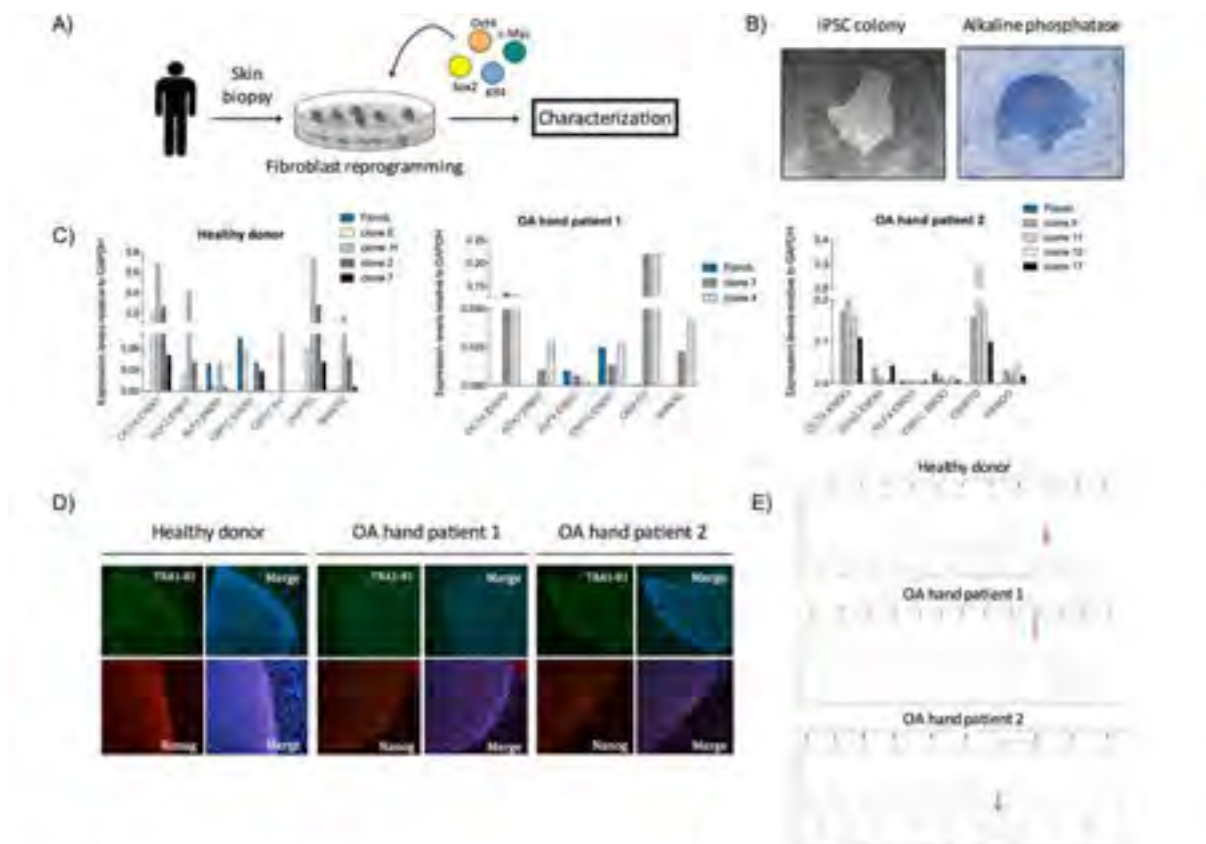


Figure 1. (A) Reprogramming process of the fibroblasts. (B) Left: Bright field image of a representative iPSC colony, Right: Alkaline phosphatase staining. (C) Relative expression levels of the endogenous reprogramming factors (OCT4 ENDO, SOX2 ENDO, KLF4 ENDO, CMYC ENDO) and pluripotency genes (CRIPTO, NANOG). (D) Immunofluorescence images of pluripotency markers of representative iPSC clones. x30 magnification. (E) Sequencing chromatograms. Red arrows point the single nucleotide polymorphism within the ALDH1A2 gene.

Methods: Patients with hand OA (rhizarthrosis) and a healthy control were selected for the study. Fibroblasts from 3mm skin biopsies of these patients were isolated. The transcriptional factors Oct4, Sox2, Klf4 and c-Myc were used for the reprogramming process; which was performed by using the non-integrating method Sendai virus (Fig 1A). Cell lines obtained were morphological, phenotypical and functionally characterized. Furthermore, to evaluate whether these iPSC lines could be used as cellular model of hand OA, presence of single nucleotide polymorphisms (SNPs) within the gene encoding the retinaldehyde dehydrogenase 2 (ALDH1A2) was studied by Sanger sequencing, before and after reprogramming. The variant rs3204689 within the ALDH1A2 gene has been associated with severe OA of the hand (OR=1.46, $p=1.1 \times 10^{-11}$) (Styrkarsdottir *et al.*, 2014).

Results: Fibroblasts were isolated from skin biopsies of two patients with radiographic hand OA and one healthy donor, which presented a normal karyotype:46,XX. Three weeks after reprogramming, embryonic stem cell-like colonies emerged in culture (Fig 1B). These cells showed positivity for alkaline phosphatase activity (Fig 1B) and the pluripotency markers Tra1-81 and Nanog (Fig 1D). Molecular analyses showed high relative expression levels of the pluripotency-related genes OCT4, SOX2, NANOG and CRIPTO in the iPSCs (Fig 1C). These cells were also able to give rise to cells from the three germ layers. Indeed, during mesodermal differentiation, spontaneously beating cardiomyocytes were seen in culture. Regarding SNPs studies, cells from one of the patients with hand OA were homozygous for the at-risk C allele, both before and after reprogramming. Cells obtained from the healthy donor and the second OA hand patient were heterozygous for this variant(Fig 1E).

Conclusion: The reprogramming process using Sendai virus enabled us to generate iPSC lines from patients with hand OA. The presence of the at-risk C allele within the ALDH1A2 gene was maintained after fibroblast reprogramming. The iPSC lines obtained will enable us to model hand OA *in vitro* and to deeper study the role of this genetic variant in the pathogenesis of hand OA.

Disclosure: R. Castro-Viñuelas, None; C. Sanjurjo-Rodríguez, None; M. Piñeiro-Ramil, None; T. Hermida-Gómez, None; F. J. De Toro Santos, None; F. J. Blanco, None; I. Fuentes-Boquete, None; S. M. Díaz-Prado, None.

Abstract Number: 2008

Vascular Adhesion Protein-1 (VAP-1) As Predictor of Radiographic Severity in Symptomatic Knee Osteoarthritis

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Session Information

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Session Time: 9:00AM-11:00AM

Background/Purpose: To investigate the expression of vascular adhesion protein -1 (VAP-1) in joint tissues and serum in knee osteoarthritis (OA) patients and examine whether VAP-1 levels predict increased risk of disease severity or progression of knee OA.

Methods: Baseline serum and synovial fluid VAP-1/semicarbazide-sensitive amine oxidase (SSAO) levels were assessed in cohorts of patients with tibiofemoral medial knee OA and healthy subjects. Standardized fixed-flexion posteroanterior knee radiographs were scored for Kellgren Lawrence (KL) grade (0–4) and medial joint space width (JSW) at the mid-portion of the joint space. Radiographic severity was defined by KL2/3 vs. KL4. Biochemical markers assessed comprised VAP-1/SSAO, IL-1Ra, IL-6, sRAGE, CCL2, CCL4, CD163, hsCRP and MMPs-1,-3,-9. Associations between biomarkers and radiographic severity (logistic regression controlling for covariates) and pain (Spearman correlation) were evaluated.

Results: VAP-1 was locally overexpressed at least 2 fold in the OA synovium based on immunohistochemical, microarray and qRT-PCR analyses compared to controls. Synovial fluid SSAO levels was also significantly higher in OA (107.94±41.42) compared to normals (38.12 ± 22.98 ng/ml; p=0.0001) and inversely associated with radiographic severity. We observed a positive correlation with the levels of SSAO in the synovial fluid and serum of OA patients (r=0.47; p=0.014). However, serum SSAO levels in OA patients were lower than in controls, and inversely correlated with pain and inflammation markers (CRP and soluble RAGE). Serum SSAO levels were also lower in radiographically severe (KL4) OA patients compared to KL2/3. Serum SSAO did not correlate with other markers of inflammation or radiographic joint space narrowing (JSN) over 24 months.

Conclusion: Synovial fluid VAP-1/SSAO levels were elevated in OA and correlate with radiographic severity. However, serum or circulating SSAO levels are lower in OA patients and inversely correlate with pain and inflammation. Serum VAP-1 levels could identify patients at increased risk for knee radiographic severity.

Disclosure: E. Bournazou, None; J. Samuels, None; H. Zhou, None; S. Krasnokutsky Samuels, None; J. Patel, None; J. Bencardino, None; L. Rybak, None; S. Abamson, None; U. Junker, None; K. Brown, None; M. Attur, None.

Abstract Number: 2009

A Novel Role of ZCCHC6 in the Regulation of MMP13 in Experimental Osteoarthritis in Mice

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Session Information

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Session Title: Osteoarthritis and Joint Biology – Basic Science Poster II

Session Type: ACR Poster Session C

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Background/Purpose: Zinc Finger CCHC Domain Containing Protein 6 (ZCCHC6) or Terminal Uridylyltransferase 7 (TUT7) is a member of terminal uridylyltransferase family that mediate terminal uridylation of mRNA or miRNA modulating their expression, stability and biogenesis. Matrix metalloprotease 13 (MMP13) is one of the key protease responsible for the degradation of cartilage extracellular matrix and plays central role in the pathogenesis of osteoarthritis (OA). In the present study we investigated the effect of ZCCHC6 deletion on the expression of MMP13 in human and mouse chondrocytes *in vitro*. We used global *zcchc6* knockout (*zcchc6*^{-/-}) mice to determine the role of *zcchc6* in OA pathogenesis and the regulation of MMP13 expression *in vivo*.

Methods: Human chondrocytes were used for ZCCHC6 knockdown and overexpression experiments. The mouse chondrocytes from *zcchc6*^{-/-} mice and corresponding wild type (*zcchc6*^{+/+}) littermate were used to determine the expression of MMP13 under pathological conditions (stimulation with IL-1 β). The expression of MMP13 mRNA was determined by qPCR using gene specific TaqMan assays and the protein expression levels were determined using Western blotting and ELISA. The *zcchc6*^{-/-} and the *zcchc6*^{+/+} control mice were subjected to destabilization of medial meniscus (DMM) surgery to determine the role of *zcchc6* in OA pathogenesis. The extent of damage to mouse joints was determined by OARSI scoring system.

Results: The expression of ZCCHC6 was upregulated in human normal and OA chondrocytes as well as mouse chondrocytes under pathological conditions. Depletion of ZCCHC6 in human normal and OA chondrocytes resulted in decreased expression of MMP13 at mRNA and protein levels in the presence or absence of IL-1 β . Overexpression of ZCCHC6 in human OA chondrocytes resulted in increased expression of MMP13. The expression of MMP13 was found to be downregulated in the mouse chondrocytes prepared from *zcchc6*^{-/-} mice in comparison to *zcchc6*^{+/+} littermate. Transfection of *zcchc6* in mouse chondrocytes derived from *zcchc6*^{-/-} mice reversed the expression of MMP13. The severity of DMM-induced OA was significantly low in *zcchc6*^{-/-} mice compared to *zcchc6*^{+/+} mice. Furthermore, the expression of MMP13 in *zcchc6*^{-/-} mice joints with DMM surgery was significantly low in comparison to *zcchc6*^{+/+} mice.

Conclusion: In the present study, we demonstrate a novel role of ZCCHC6 in the regulation of MMP13 expression in human and mouse chondrocytes and cartilage. We show here that *zcchc6* deletion has protective effect on the development of OA.

Disclosure: Y. Ansari, None; N. Ahmad, None; T. M. Haqqi, None.

Abstract Number: 2010

Anti-Endothelial Cell Antibodies in Pediatric Rheumatic Diseases

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Anti-endothelial cell antibodies (AECA) are antibodies detected in multiple autoimmune and inflammatory diseases. Increased levels of such antibodies may be involved in disease activity and/or the coexistence of vasculitis. Juvenile dermatomyositis (JDM) shows many pathological features of vasculitis. Many autoantibodies detected in JDM have specific clinical and phenotypic associations, but their relationship to disease pathology remains unclear. Juvenile idiopathic arthritis (JIA) is a heterogeneous group of inflammatory diseases. There are no useful autoantibody biomarkers for diagnosis or for characterization of the disease. We aimed to detect target antigens for AECA and to investigate the roles of AECA in both diseases.

Methods: We screened plasma from pediatric rheumatic diseases (3 children with JDM and 2 children with polyarticular JIA) and from healthy children for the presence of AECA by western blotting and two-dimensional electrophoresis (2DE) using proteins extracted from human aortic endothelial cells (HAEC) as the substrate. Selected antigens were positive only in plasma of children with pediatric rheumatic diseases but not in plasma of healthy children. We performed mass spectrometry to identify the candidate antigens from 2DE gels and used ELISA assays to confirm the presence of specific antibodies.

Results: We successfully identified more than 600 proteins that were candidate targets of AECA in JIA and JDM using proteomics. Among these antigens were proteins regulating cellular redox processes. These included peroxiredoxins (Prxs), a family of related antioxidant enzymes. Using ELISA assays, IgG autoantibodies to Prx2 were detected in 12% of the

patients with JDM (n=51) but not in healthy children (n=20). However, 24% of JDM patients with active disease (n=25) had anti-Prx2 antibodies, while these antibodies were absent ($p<0.01$) in JDM patients with inactive disease (n=26). We also noted that 17% of JIA patients with active disease (n=12) had anti-Prx2 antibodies. There was no difference in the frequency of anti-Prx2 antibodies between JIA patients with active disease and those with inactive disease. Another group of antigens that were detected were tropomyosins, a family of actin filament binding proteins, which are categorized into muscle isoforms and non-muscle isoforms. IgG autoantibodies to tropomyosin beta chain (TPM2) were detected in 24% of the patients with JIA (n=17) in contrast to 5% of healthy children (n=20). Interestingly, IgG autoantibodies to TPM2 were detected in 43% of the untreated JIA patients with active disease (n=7) in contrast to 5% ($p<0.05$) of healthy children. On the other hand, 15 % of JDM patients (n=20) had anti-TPM2 antibodies.

Conclusion: IgG antibodies to Prx2 and TPM2 in the proteome of HAEC are present in the children with JDM and with JIA. The measurement of anti-Prx2 antibodies might be useful for evaluation of disease activity in JDM.

Disclosure: R. Karasawa, None; T. Sato, None; M. Tanaka, None; M. Tamaki, None; K. Yudoh, None; J. Jarvis, None.

Abstract Number: 2011

Juvenile Arthritis-Associated Single Nucleotide Polymorphisms Identified on Whole Genome Sequencing Show Enrichment within H3K9me3-Marked Regions

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: We have found extensive alterations in chromatin accessibility when the CD4+ T cells of children with active polyarticular juvenile idiopathic arthritis (JIA) are compared with cells from healthy children (HC). These differences in chromatin accessibility are strongly linked to differences in transcription. We therefore sought to determine the extent to which chromatin re-organization in JIA CD4+ T cells is influenced by underlying genetic variation.

Methods: Using our previously published whole genome sequencing data from 48 JIA patients, we identified common SNPs that: (1) were found in all JIA patients and (2) had not been identified previously. We categorized the SNPs as loss (LoF) or gain of function (GoF), based on their likely contributions to the regulatory network of CD4+ T cells, using ATAC-seq data to identify regulatory sequences. Using data from the 1000 genomes project, we identified the SNPs that were in linkage disequilibrium with our predicted LoF and GoF SNPs to identify a set of haplotype blocks. Using data from the ENCODE and RoadMap epigenomics projects, we looked for statistical enrichment for informative histone modifications in myeloid and lymphoid cell lines within these haplotype blocks.

Results: *Results* Each of the queried cell lines showed significant enrichment for specific histone marks within the haplotypes of interest. However, findings were most significant within CD4+ T cell subsets, and specifically for histone marks regulating chromatin accessibility. For example, H3K9me3 is a histone mark that is required to maintain chromatin in a condensed state and maintain the identity of terminally differentiated cells. Regions associated with predicted loss of function SNPs were highly enriched for H3K9me3 in CD3+ ($p=7.13E-81$), CD4+ ($p=7.11E-23$) and CD8+ T ($p=9.67E-37$) cell subsets. Predicted gain of function regions were enriched for H3K4me1 marks, an epigenetic signature of poised enhancer function.

Conclusion: We identified novel, predicted genetic risk loci for JIA and identified a strong enrichment for H3K9me3 in T cell subsets. This enrichment was much stronger for regions predicted to be loss of function compared to gain of function. We hypothesize that these genetic variants may alter H3K9me3 localization in JIA, altering the chromatin landscape and leading to the misregulation of transcription.

Disclosure: S. O'Leary, None; E. Tarbell, None; K. Jiang, None; T. Liu, None; J. Jarvis, None.

The Novel G58V Mutation in the TNFRSF1A Gene Identified in a Family with Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) Decreases the Cell Surface Expression of TNFR1

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Session Information

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Background/Purpose: TNF Receptor- Associated Periodic Syndrome (TRAPS) is one of the autoinflammatory diseases characterized by recurrent inflammatory episodes. TRAPS is caused by an autosomal dominant heterozygous mutation in *TNFRSF1A* gene, which encodes tumor necrosis factor receptor 1 (TNFR1). More than 100 heterozygous *TNFRSF1A* mutations have been reported. T50M and Cysteine mutations are recognized as TRAPS mutations, the patients with the mutations develop severe TRAPS phenotypes. On the other hand, R92Q and T61I mutations are known as low-penetrant mutations which cause milder TRAPS phenotypes. The molecular pathogenesis by which the mutant TNFR1 causes TRAPS phenotypes is not yet fully understood. Recently we have identified a novel mutation, G58V (p.G87V) in *TNFRSF1A*, in two individuals in a family with recurrent inflammatory episodes. T61I mutation was also identified in the family. In this study, we examined the effect of the novel G58V mutation on the mutant cells.

Methods: The possible pathogenicity of the G58V mutation was analyzed using the four online prediction tools (SIFT, Polyphen2, PROVEAN and PANTHER). Wild-type (WT) or mutated *TNFRSF1A* (G58V/T61I, G58V, T61I, T50M, R92Q) constructs were generated by cloning. The TNFR1 constructs were transfected into HEK-293 cells. Expression levels of the TNFR1 were examined by western blotting. To analyze cell surface and intracellular expression of TNFR1, we performed the flow cytometric analysis. NF- κ B activation levels at 24 hours after the transfection were measured by the dual-luciferase reporter assay.

Results: The novel G58V mutation was predicted to be a highly damaging amino acid substitution that could affect the function of TNFR1. Expression levels of the WT and mutated TNFR1 proteins are comparable in the whole cell lysates of HEK-293 cells. The cell surface expression of TNFR1 was decreased in the T50M, G58V and G58V/T61I TNFR1-transfected cells compared to WT TNFR1-transfected cells. In contrast, the R92Q and T61I mutation did not affect the expression pattern of TNFR1. NF- κ B promoter activities in the T50M or the G58V TNFR1-expressing cells were significantly decreased compared to those in WT TNFR1-expressing cells (T50M $21.5 \pm 3.6\%$; G58V $34.8 \pm 4.4\%$; G58V/T61I $56.7 \pm 23.9\%$ vs. WT). The R92Q and T61I mutation did not suppress the NF- κ B promoter activities.

Conclusion: The T50M mutation suppressed the cell surface expression of TNFR1 and spontaneous NF- κ B promoter activity in consistent with a previous report (Blood 2006;108:1320-1327). The newly identified G58V mutation exhibited the similar phenotypes to the pathogenic T50M mutation, suggesting that the G58V is one of the responsible mutations causing TRAPS.

Disclosure: S. Tsuji, None; H. Matsuzaki, None; T. Mukai, None; A. Nagasu, None; H. Hirano, None; M. Iseki, None; T. Horiuchi, None; R. Nishikomori, Novartis, 8; Y. Morita, None.

Blood Lipids in Juvenile-Onset SLE: An Opportunity for Stratified Patient Therapy

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Session Time: 9:00AM-11:00AM

Background/Purpose: Juvenile-onset systemic lupus erythematosus (JSLE) is characterized by immune cell dysregulation, chronic inflammation and increased cardiovascular risk. JSLE patients have more aggressive disease, major organ involvement and increased standardised mortality ratios compared to adult-onset SLE patients. Our previous findings in adult-onset SLE link immune cell dysregulation with defects in plasma membrane lipids rafts; signalling platforms that facilitate immune cell signalling, activation and effector function. Here we investigate the inter-relationship between immune cell lipid rafts, lipids in the blood (transported by lipoproteins), immune cell function and disease features in JSLE patients.

Methods: Flow cytometry measured metabolic marker expression on 44 immune cell subsets from 39 healthy donors (HCs) and 35 age matched JSLE patients. Analysis of 220 metabolic biomarkers including lipoprotein composition was performed on matching serum. RNA sequencing (seq) and analysis was performed on sorted immune cell subsets from matching samples.

Results: Lipid raft expression on T- and B-cells correlated positively with disease activity ($p=0.0006$ and 0.0006), erythrocyte sedimentation rate ($p=0.026$ and $p=0.015$) and dsDNA titre ($p=0.04$ and 0.0001) and negatively with complement protein C3 ($p=0.002$ and 0.002) supporting the hypothesis that altered metabolism is associated with JSLE pathogenesis. High disease activity was associated with increased levels of pro-atherogenic circulating lipids (very low, intermediate and low density lipoproteins; VLDL, IDL and LDL respectively) and decreased anti-atherogenic circulating lipids (high density lipoproteins; HDL). Immune cell lipid rafts correlated positively with VLDL, IDL and LDL and negatively with HDL suggesting that lipoproteins alter the membrane of immune cells in JSLE. Unsupervised hierarchical clustering based on circulating lipoprotein levels stratified patients into three distinct groups, each characterised by a unique immunological, metabolic and clinical phenotype. Patients in Group 1 had markers associated with increased risk of cardiovascular disease including increased apolipoproteinB:A1 ratio ($p<0.0001$) as well as an increased expression of fats associated with pre-clinical atherosclerotic plaque in adult SLE patients. Receiver operating characteristic curve analysis identified a cut-point value for apolipoproteinB:A1 ratio allowing group identification with 83% sensitivity and 78% specificity, suggesting that this could be used as a predictor of increased cardiovascular risk. Finally, RNAseq analysis from isolated T- and B-cells showed significant differences in cholesterol and glycosphingolipid metabolism genes between the three groups highlighting potential therapeutic targets.

Conclusion: Differences in immune cell lipid metabolism in JSLE could contribute to disease pathogenesis and severity. Regulation of lipid metabolism may provide therapeutic benefit for JSLE patients by reducing both inflammation and atherosclerotic risk. Apolipoprotein measurements in JSLE can be used to pinpoint patients that would benefit from these therapies and/or diets that modify lipid metabolism.

Disclosure: G. Robinson, None; M. Adriani, None; C. Wincup, None; A. Radziszewska, None; D. A. Isenberg, None; C. Ciurtin, None; Y. Ioannou, None; I. Pineda Torra, None; E. Jury, None.

Abstract Number: 2014

Next Generation Sequencing Analysis of Familial Haemophagocytic Lymphohistiocytosis (HLH) Related Genes in Macrophage Activation Syndrome (MAS) and Secondary HLH (sHLH)

Chiara Passarelli¹, Manuela Pardeo², Ivan Caiello³, Elisa Pisaneschi¹, Antonella Insalaco², Francesca Minoia⁴, Andrea Taddio⁵, Francesco Licciardi⁶, Antonio Novelli¹, Fabrizio De Benedetti⁷ and **Claudia Bracaglia**², ¹Unit of Medical Genetics, Laboratory of Cytogenetics and Molecular Genetics, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, ²Division of Rheumatology, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, ³Division of Rheumatology, IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italy, ⁴Reumatologia Pediatrica, IRCCS Istituto Giannina Gaslini, Genoa, Italy, ⁵Institute for Maternal and Child Health - IRCCS "Burlo Garofolo", University of Trieste, Trieste, Italy, ⁶SCDU Pediatria II, Immunoreumatologia, Ospedale Pediatrico Regina Margherita, Turin, Italy, ⁷IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italy

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Macrophage activation syndrome (MAS), a severe complication of pediatric rheumatic disease, is currently classified among the secondary forms of HLH (sHLH). Primary HLH (pHLH) are caused by mutation of genes coding for proteins involved in cytotoxic functions. Mice carrying heterozygous mutations in more than 1 pHLH gene carry a higher risk to develop HLH following viral infection, suggesting that accumulation of partial genetic defects may be relevant in HLH.

Methods: Genes involved in pHLH in MAS in the context of different rheumatic diseases and in sHLH were analyzed, with next generation sequencing (NGS). A targeted resequencing was performed on all patients using a panel including the 7 principal HLH-related genes (*PRF1*, *UNC13d*, *STX11*, *STXBP2*, *Rab27a*, *XIAP*, *SH2D1A*) on MiSeq® and NextSeq550® platforms (Illumina, San Diego, CA); all variants identified were confirmed by Sanger. We took into account variants with an allelic frequency in the global population up to 5% in the dbSNP and Ensembl databases.

Results: We analysed 125 patients: 47 MAS, (40 developed this complication in the context of systemic Juvenile Idiopathic Arthritis (sJIA), and 7 in the context of different rheumatic diseases), 32 sHLH, 22 sJIA (without history of MAS) and 24 with different autoinflammatory diseases (AID). sJIA and AID patients were used as control groups. We identified at least 1 heterozygous variant in one of the pHLH-related genes in 41 patients with a detection rate of 52%, 45% of MAS and 62% of sHLH patients. More than one variant was identified in 37% patients from both groups, with 19% of both MAS and sHLH patients carrying polygenic variants. In control groups, 54% of sJIA and 33% of AID patients carry at least a variant in the analysed genes, while polygenic variants have been detected in 14% and 8% of control patients, respectively. The most involved genes in both MAS and sHLH groups were *PRF1* and *UNC13d*, while variants in *RAB27a* and *XIAP* have been found only in sHLH patients. The most frequent variants identified in both groups were A91V in *PRF1* gene and R928C in *UNC13d* gene. The A91V variant in *PRF1* gene was identified in 19% of both MAS and sHLH patients, while this variant was present, respectively, in only 5% of sJIA and 4% of AID patients. The R928C variant in *UNC13d* gene was identified in 32% of MAS and 18% of sHLH patients, and in the control group in 9% of sJIA and 17% of AID patients. Variants of *PRF1* and *UNC13d* genes were most frequently observed in patients with both MAS and sHLH, while *Rab27a* and *XIAP* variants were more frequent in sHLH. Considering the patients' clinical characteristics, relapse, CNS involvement, ICU admission and death, in sHLH we observed that three of the 6 patients (50%) carrying multiple variants had recurrent episodes of HLH and that two of them (33%) presented a severe disease with exitus.

Conclusion: Monoallelic variants in pHLH-related genes are more frequent in MAS, sHLH and sJIA and less in AID patients, suggesting different molecular mechanisms involved in the diseases. Re-occurrence and severity of disease seem to be more frequent and more severe in patients who carry mutations in two genes in sHLH group. These data may support a polygenic model of sHLH.

Disclosure: C. Passarelli, None; M. Pardeo, None; I. Caiello, None; E. Pisaneschi, None; A. Insalaco, None; F. Minoia, None; A. Taddio, None; F. Licciardi, None; A. Novelli, None; F. De Benedetti, Abbvie, Sobi, Novimmune, Roche, Novartis, Sanofi, UCB, Pfizer, 2; C. Bracaglia, None.

Abstract Number: 2015

Association of Anti-Ro52 Autoantibodies with Interstitial Lung Disease and More Severe Disease Manifestations in Juvenile Idiopathic Inflammatory Myopathies

Sara Sabbagh¹, Iago Pinal-Fernandez¹, Takayuki Kishi², Ira N. Targoff³, Frederick W. Miller², Lisa G. Rider² and Andrew Mammen^{1,4}, ¹National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, ²National Institute of Environmental Health Sciences, National Institutes of Health, Environmental Autoimmunity Group, Bethesda, MD, ³VA Medical Center, University of Oklahoma Health Sciences Center, Oklahoma Medical Research Foundation, Oklahoma City, OK, ⁴Neurology, Johns Hopkins University School of Medicine, Baltimore, MD

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Myositis specific autoantibodies (MSA) and myositis associated autoantibodies (MAA) found in adult and juvenile idiopathic inflammatory myopathies (JIIM) often confer a specific disease phenotype. In adults, the MAA anti-Ro52 is associated with anti-synthetase (ARS) autoantibodies (Abs) and more severe interstitial lung disease

(ILD). However, there are few studies examining the presence or significance of anti-Ro52 Abs in juvenile myositis. The purpose of this study was to define the prevalence and clinical features of anti-Ro52 Abs in a large cohort of patients with JIIM.

Methods: We screened sera from 307 patients with juvenile dermatomyositis (JDM), 26 patients with juvenile polymyositis (JPM), and 44 patients with juvenile connective tissue disease-myositis overlap (JCTM) for anti-Ro52 Abs by ELISA (INOVA, San Diego, CA). Clinical characteristics were compared between myositis patients with and without anti-Ro52 Abs.

Results: Anti-Ro52 Abs were found in 14% of JDM, 12% of JPM, and 18% of JCTM patients. Anti-Ro52 Abs co-existed in 64% of those with ARS ($p<0.001$) and in 31% of those with anti-MDA5 Abs ($p<0.008$). Less than 15% of those with anti-p155/140, -NXP2, -SRP, or -Mi2 Abs and less than 5% of those without an MSA were anti-Ro52+. After controlling for the presence of MSAs in multivariable analysis (including ARS and anti-MDA5), anti-Ro52 Abs were highly associated with ILD (36% vs 4%, $p<0.001$), dyspnea on exertion (59% vs 25% $p<0.001$), and a higher pulmonary score at diagnosis (0.18 vs 0.08 $p=0.004$). Even within the anti-MDA5+ subgroup, Ro52 reactivity was strongly correlated with ILD; 70% (7/10) of those with co-existing anti-Ro52 Abs had ILD compared to 9% (2/22) of those who were Ro52-. Similarly, among ARS+ patients, 100% (9/9) of anti-Ro52+ and only 40% (2/5) of anti-Ro52- patients had ILD. Disease course in anti-Ro52+ patients was more often chronic continuous (78% vs 52% $p=0.05$) and less often monocyclic (3% vs 24% $p=0.02$). Anti-Ro52+ patients were more often ACR functional class 4 (11% vs 4% $p=0.008$) and had a higher mean ACR functional class score at final evaluation (1.7 vs 1.4 $p=0.007$). Anti-Ro52 Abs were associated with an increased total number of medications received (4.8 vs 3.8 $p=0.04$) and anti-Ro52+ patients more often received intravenous pulse steroids (79% vs 52% $p=0.03$). Anti-Ro52+ patients less frequently had a documented remission (5% vs. 27% $p=0.05$). There were no significant differences in the prevalence of HLA DRB1 and DQA1 alleles between Caucasian juvenile myositis patients with and without anti-Ro52 Abs.

Conclusion: Anti-Ro52 Abs are most prevalent in juvenile myositis patients with anti-MDA5 and ARS Abs. Even after adjusting for the presence of MSAs, including anti-MDA5 and anti-ARS Abs, anti-Ro52+ patients were more likely to have ILD and other pulmonary manifestations. Furthermore, anti-Ro52+ patients have more severe disease requiring more intense treatment, less frequent remission, worse functional outcomes, and a frequent chronic disease course. The presence of anti-Ro52 Abs in JIIM may be a significant determinant of disease severity and prognosis, thereby warranting screening JIIM patients for anti-Ro52 Abs.

Disclosure: S. Sabbagh, None; I. Pinal-Fernandez, None; T. Kishi, The Myositis Association, 2; I. N. Targoff, Oklahoma Medical Research Foundation, 5; F. W. Miller, None; L. G. Rider, None; A. Mammen, None.

Abstract Number: 2016

The Chromatin Landscape Around the Juvenile Arthritis-Associated CXCR4 Locus Suggests Regulatory Functions and Genetic Roles in Both Innate and Adaptive Immunity

Laura Easton¹, Evan Tarbell², Kaiyu Jiang³, Kyle Mentkowski⁴, Shannon O'Leary⁵, Tao Liu⁵ and James Jarvis¹, ¹Pediatrics, University at Buffalo Jacobs School of Medicine & Biomedical Sciences, Buffalo, NY, ²Biochemistry, University at Buffalo, Buffalo, NY, ³Pediatrics, University at Buffalo, Buffalo, NY, ⁴Graduate Program in Biological Sciences, University at Buffalo Jacobs School of Medicine & Biomedical Sciences, Buffalo, NY, ⁵Genetics, Genomics, & Bioinformatics Program, University at Buffalo Jacobs School of Medicine & Biomedical Sciences, Buffalo, NY

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: *CXCR4* is a recently identified susceptibility locus for juvenile idiopathic arthritis (JIA). The index single nucleotide polymorphism (SNP) used to identify this locus, rs95338, lies in an intergenic region upstream of the *CXCR4* gene, suggesting that this region has regulatory functions. We sought to gain biological insight into the association between JIA and the *CXCR4* locus by examining the chromatin architecture within this locus, including the presence of epigenetically-marked regulatory elements, in relevant primary cells and cell lines.

Methods: Using the SNP Annotation and Proxy Search from the Broad Institute and standard computational methods, we first defined the linkage disequilibrium (LD) block containing the rs953387 SNP. We used BedTools to query ENCODE and Roadmap Epigenomics data to identify relevant functional epigenetic marks (e.g., H3K4me1/H3K27ac, and CTCF

binding motifs) within the *CXCR4* haplotype. For statistical analysis, each value was compared to the mean and standard deviation of 100 randomly generated files with the same number of peaks as the ENCODE file being examined. In addition, we used quantitative rtPCR analysis to confirm the presence of a non-coding, intergenic RNA transcript that we identified on RNAseq in neutrophils and assess the effects of treatment on expression of this transcript.

Results: The LD block for the rs953387 SNP comprises a genomic region of between 54,236 (r-squared of 0.9) and 69,609 bp (r-squared of 0.8) upstream from the coding region of the *CXCR4* gene. This region contains 154 JIA associated SNPs that we recently identified using whole genome sequencing, in addition to >30 variants catalogued in 1000 Genome Project. Further analysis using ENCODE and Roadmap Epigenomics data demonstrate that the LD block ($r^2 = 0.8$) includes enrichment for H3K4me1 (poised enhancer) peaks compared to randomly generated peaks from hg19 genome in primary CD4+ T-cell lines and primary CD 15+ (neutrophil) cell lines, with the LD containing 12 and 15 peaks respectively. There are 6 H3K27ac (active enhancer) peaks in the LD block from primary CD4+ cell data, which is statistically higher than the random value. CHIPSeq data from neutrophils from our own lab shows multiple H3K4me1 and H3K27ac peaks in this LD block in addition to a noncoding (intergenic) RNA. The non-coding RNA was verified using rtPCR and showed changes in expression levels when neutrophils from children with active JIA were compared to those in clinical remission on medication. Further analysis identified H3K4me1, but not H3K27ac, enrichment in CD14+ monocytes and CD20+ B cells as well as other T- lymphocyte cell lines.

Conclusion: The LD blocking containing the rs953387 SNP lies upstream of the *CXCR4* gene itself and is likely a regulatory region. This region contains enhancer elements in multiple immune cell lines, especially in CD4+ primary T-cells and CD15+ neutrophils as well as an intergenic non-coding RNA. The regulatory function of this region may or may not relate to the *CXCR4* gene itself, as enhancers do not always regulate the nearest gene. These findings corroborate our earlier studies demonstrating that the genetics of JIA impinges almost exclusively on gene regulatory functions.

Disclosure: L. Easton, None; E. Tarbell, None; K. Jiang, None; K. Mentkowski, None; S. O'Leary, None; T. Liu, None; J. Jarvis, None.

Abstract Number: 2017

Oral Microbiota in New-Onset Juvenile Idiopathic Arthritis

Albert Chow^{1,2,3}, Sriharsha Grevich^{1,2,3}, Peggy Lee⁴, Jeffrey McLean⁴, Sarah Ringold^{1,3,5}, Roger Bumgarner⁶ and Anne Stevens^{1,2,3}, ¹Pediatrics, University of Washington, Seattle, WA, ²Center for Immunity and Immunotherapies, Seattle Children's Research Institute, Seattle, WA, ³Pediatric Rheumatology, Seattle Children's Hospital, Seattle, WA, ⁴Dentistry, University of Washington, Seattle, WA, ⁵Center for Clinical and Translational Research, Seattle Children's Research Institute, Seattle, WA, ⁶Microbiology, University of Washington, Seattle, WA

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Oral microbial dysbiosis of specific organisms such as *Porphyromonas*, *Aggregatibacter*, *Tannerella*, and *Treponema* in dental plaque has been implicated in the pathogenesis of adult rheumatoid arthritis (RA) and periodontitis, while *Neisseria* may play a protective role. Whether oral dysbiosis is also associated with juvenile idiopathic arthritis (JIA) is less clear, as periodontal disease-related organisms are rare in children. Comparing the microbiomes from JIA patients with those of their mothers provide another avenue to explore the role of dysbiosis in arthritis, because healthy children derive much of their microbiome from their mothers. We previously demonstrated increased gingivitis in treated JIA patients compared to healthy children. For this current study, we hypothesized that oral microbial dysbiosis was associated with systemic inflammation, and children with JIA have an altered oral microbiome compared to their mothers. By examining only new-onset JIA patients, the confounding effects of previous treatment should be eliminated.

Methods: Saliva was collected from 14 new-onset, treatment-naïve JIA patients of all JIA subtypes, aged 3-15 years, and their mothers. Subjects who received antibiotics within the previous 3 months were excluded. V3/V4 16S rRNA sequencing was performed on the Illumina MiSeq platform. Sequences were paired and merged using BBMerge. Merged reads were trimmed to remove bases with a Q value <20, and filtered to retain only sequences greater than 400 bp and no more than 1N. Processed reads were classified by comparison to the Human Oral Microbiome 16S Database V15.1. Relative frequencies as percentages of bacterial genera and species were calculated in individual patients and compared to frequencies found in each patient's mother. Paired T-tests and signed rank Wilcoxon tests were performed on all species between probands and mothers; significance level was set at $p = 0.05$.

Results: We assessed all species detected in either probands or mothers. There were no significant differences in the relative frequencies of *Prevotella*, *Neisseria*, *Leptotrichia*, *Fusobacterium*, or *Porphyromonas* species between probands and mothers. *Tannerella forsythia* and *Treponema* species were detected at low relative frequencies in all subjects. *Aggregatibacter actinomycetemcomitans* was not detected in our cohort. With paired T-tests, three species were detected at low frequencies in mothers but not in any probands: *Bacteroidetes* HMT 511, *Veillonellaceae* HMT 155, and *Selenomonas* HMT 134. These species were identified by sequencing only; their functional nature have not been explored. Microbial diversity calculated using Shannon Diversity Index was similar in probands and mothers.

Conclusion: In an inception cohort of new-onset JIA patients, organisms implicated in the pathogenesis of adult RA were not detected at higher frequencies in probands or in their mothers. This is the first study to examine the oral microbiome of untreated JIA patients. Further work to compare the oral microbiota of JIA families against aged-matched healthy family members may elucidate patterns that predispose children to JIA.

Disclosure: A. Chow, None; S. Grevich, None; P. Lee, None; J. McLean, None; S. Ringold, None; R. Bumgarner, None; A. Stevens, None.

Abstract Number: 2018

Microenvironment Driven Re-Shaping of Pathogenic T Effector and Regulatory Subset in Active Juvenile Idiopathic Arthritic Patients

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: We have previously identified two CD4 pathogenic circulatory subsets in both T effector (CPLs) and T regulatory (iaTreg) compartments that are both HLA-DR⁺, antigen experienced, pro-inflammatory, correlating with disease activity and sharing strong TCR sequence oligoclonality with synovial T cells from JIA patients. Despite being two functionally distinct T cell subsets, their phenotype and association with clinical fate suggests that these functionally discordant subsets may originate from a common precursor. To elucidate the common pathogenic gene drivers and their associated network of pathways within these two pathogenic subsets, we decided to perform next generation RNA sequencing on sorted CPLs and iaTregs and their conventional Teff/Treg counterparts in both the circulation and the synovial micro-environment.

Methods: CPLs were sorted as CD3⁺ CD4⁺ CD14⁻ HLADR⁺ CD25/CD127 Teff gate, and iaTregs were sorted as CD3⁺ CD4⁺ CD14⁻ HLADR⁺ CD25^{hi}/CD127^{low} Treg gate with FACs Aria II from n=16 active JIA PBMCs, n=8 paired JIA SFMCs, and n=8 healthy paediatric PBMCs. As a comparative control, similar HLADR⁻ counterparts were respectively sorted from the same patients. Sorted cells were lysed and extracted for RNA, and cDNA conversion/amplification were then carried out using SMART-seq v4. Libraries are prepared and multiplexed using Nextera XT DNA library preparation kit, and ran on the Illumina HiSeq High output platform.

Results: Comparative differential gene expression (DEG) reveal strong transcriptomic convergence between CPLs and iaTregs as compared with the common pool of Teff and Treg. Phylogenetic analysis indicate the convergence has uncoupled the CPLs or the iaTregs away from their respective original compartments (Teff or Treg) into a common branch point. Restriction in TCR sequence oligoclonality in CPLs/iaTregs versus that of the common Teff/Treg pool reinforce the possibility of a common selection pressure. Pathway enrichment analysis reveal similar dysregulated pathways (IFN-g, PD1, CD28 costimulation) within T cell signalling for both CPLs and iaTregs. Furthermore, Weighted gene correlation network analysis (WGCNA) identified strongly coordinated HLA-DR gene network module and suggests its potential role as the driver of pathogenic T cell subsets away from conventional subsets. Gene set enrichment analysis (GSEA) suggest that HLA-DR module genes are involved in TNFA signalling, inflammatory response, complement, and apoptosis. Global transcription factors gene regulatory network (TF-GRN) analysis identified several key regulatory molecules (FOXP3,

CEBP, SPI and E2F1) driving the convergence of pathogenic CPLs and iaTreg populations. Taken together, we have shown that reveal several layers of mechanism operate to drive the convergence of CPLs and iaTregs, suggesting the possibility of common disease drivers in active JIA patients.

Conclusion: Overall the transcriptomic data indicate strong similarity in both pathogenic populations and underscore a potential mechanistic role of the inflammatory microenvironment in shaping two functionally dichotomic populations.

Disclosure: J. Y. Leong, None; P. Kumar, None; P. Chen, None; J. G. Yeo, None; C. Chua, None; S. Nur Hazirah, None; S. Saidin, None; T. Arkachaisri, None; A. Consolaro, None; M. Gattorno, None; A. Martini, None; S. Albani, None.

Abstract Number: 2019

Investigating Urine S100A4 and Podocyte Proteins As Biomarkers of Lupus Nephritis Activity

Jessica Turnier¹, Jianghong Deng², Pinar Ozge Avar Aydin³, David Witte⁴, Prasad Devarajan⁵, Matthew Fenchel⁶, Michael Bennett⁷ and Hermine I. Brunner⁸, ¹Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, ²Division of Rheumatology, Beijing Children's Hospital and Cincinnati Children's Hospital Medical Center, Cincinnati, OH, ³Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, ⁴Pathology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, ⁵Nephrology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, ⁶Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, ⁷Nephrology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, ⁸Pediatric Rheumatology Collaborative Study Group (PRCSG), Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

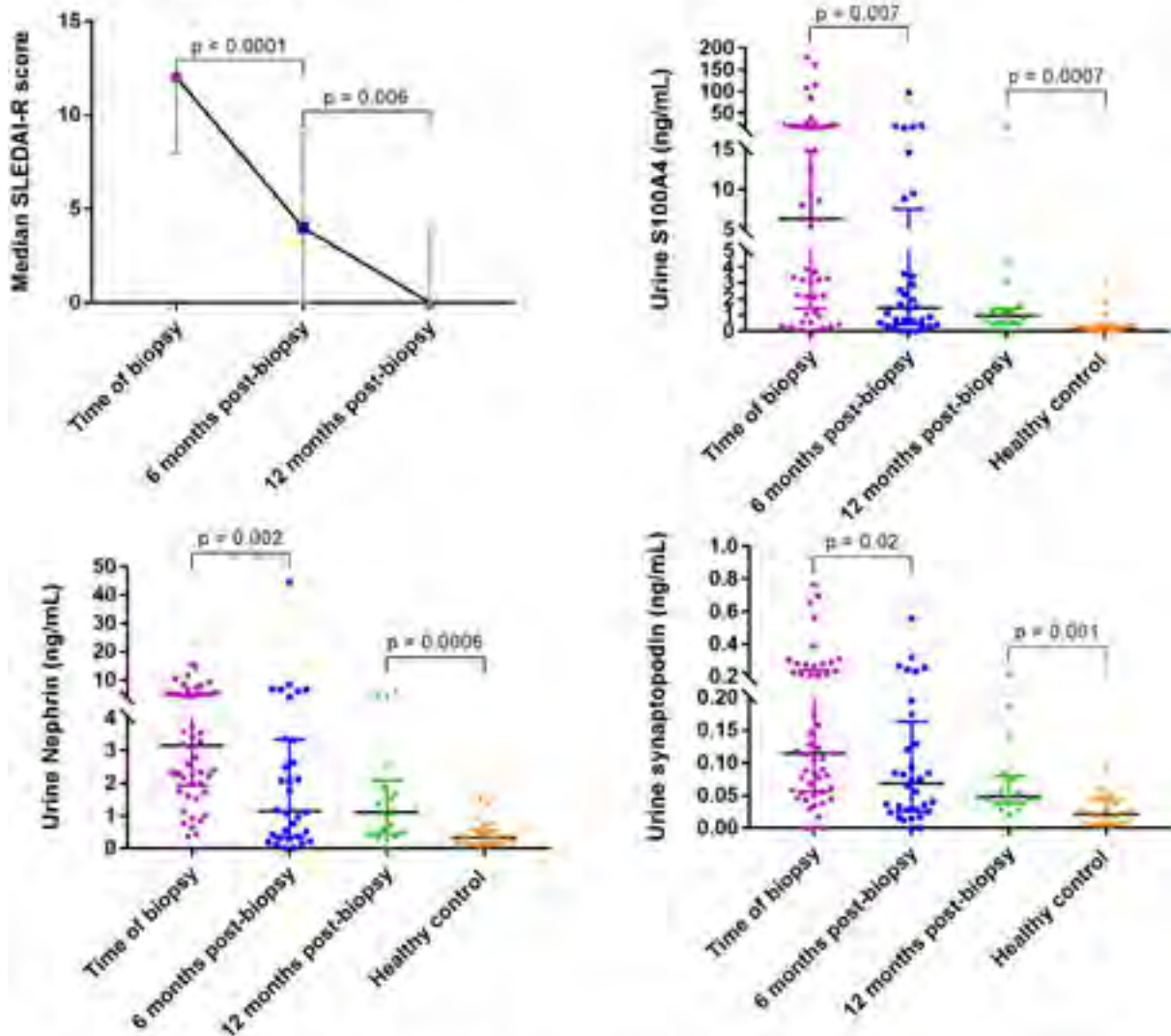
Background/Purpose: We lack accurate clinical tools to identify the degree of active renal inflammation in childhood-onset SLE (cSLE). In this study, we investigated urine S100A4 and podocyte proteins as biomarkers of lupus nephritis (LN) activity with two primary objectives, (1) assessability of candidate urine biomarkers to reflect the NIH activity index (NIH-AI) on renal biopsy and (2) determine whether changes in candidate urine biomarkers correlate with renal clinical disease activity.

Methods: We selected LN patients from an ongoing cSLE registry at Cincinnati Children's Hospital with urine available near time of biopsy and at either six and/or 12-months post-biopsy. Urine levels of S100A4, nephrin and synaptopodin were measured using commercial ELISAs. All patients met ACR classification criteria for SLE. Clinical and laboratory data were collected for patients at each time point. Spearman correlations were performed to assess the relationship between individual biomarkers and both NIH-AI and the renal domain of the SLEDAI (SLEDAI-R). We used the Mann-Whitney U test and Wilcoxon signed-rank test to determine differences in biomarker values at each timepoint.

Results: There were 52, 32 and 18 patients with urine at renal biopsy, six-months and 12-months post-biopsy, respectively. Median urine S100A4, nephrin and synaptopodin levels in the entire cohort decreased from biopsy to six-months post-biopsy (Figure 1), but only urine S100A4 showed a significant decrease within individual patients between biopsy and six-months (median difference: -1.85 ng/mL, $p = 0.01$). There was no significant correlation between NIH-AI and any biomarker when evaluating the entire cohort together at biopsy. Upon stratifying patients by those with urine collected on biopsy day, synaptopodin showed a moderate correlation with NIH-AI ($r_s = 0.47$, $p = 0.027$). Patients with class III/IV LN also had moderate correlation of nephrin with NIH-AI ($r_s = 0.37$, $p = 0.04$). At six-months post-biopsy, there was a moderate correlation between all urine biomarkers and SLEDAI-R, $r_s = 0.48$ ($p = 0.007$) for S100A4, $r_s = 0.53$ ($p = 0.003$) for nephrin and $r_s = 0.47$ ($p = 0.01$) for synaptopodin. Interestingly, the difference in S100A4 and SLEDAI-R levels between 12-months post-biopsy and biopsy showed moderate correlation ($r_s = 0.48$, $p = 0.045$). Patients who had a complete clinical response by six or 12-months, as defined by a SLEDAI-R of zero, had lower S100A4 levels at follow-up than those with an incomplete clinical response ($p = 0.0006$).

Conclusion: While urine synaptopodin and nephrin levels appear to be better indicators of the NIH-AI on renal biopsy, S100A4 or change in S100A4 seems promising as a biomarker of individual clinical response to therapy post-biopsy. It remains to be determined if elevated levels of these biomarkers at follow-up indicate persistent histologic disease activity or poor histologic response to therapy.

Figure 1. Median urine biomarker levels and SLEDAI-R scores from time since biopsy



* All biomarker levels and scores for renal domain of SLEDAI (SLEDAI-R) expressed as median and interquartile range on plots

Disclosure: J. Turnier, Lupus Foundation of America, Inc., 2; J. Deng, None; P. O. Avar Aydin, None; D. Witte, None; P. Devarajan, None; M. Fenchel, None; M. Bennett, None; H. I. Brunner, None.

Abstract Number: 2020

Novel Serum Biomarkers Monitor Disease Progression and Response to Change in Corticosteroid Therapy in Children with Juvenile Dermatomyositis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Basic Science Poster

Session Type: ACR Poster Session C

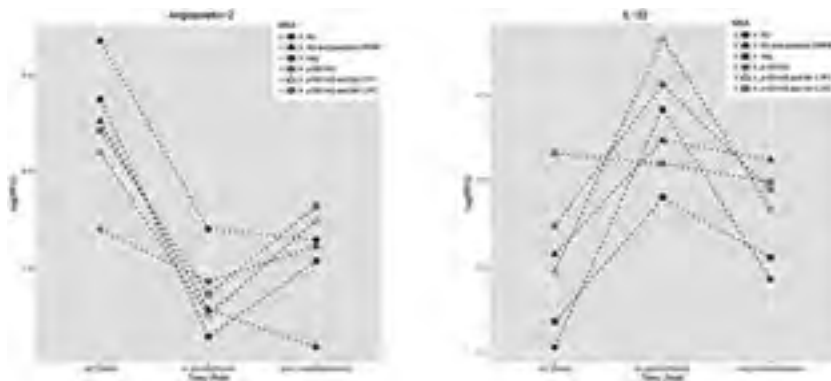
Session Time: 9:00AM-11:00AM

Novel Serum Biomarkers Monitor Disease Progression and Response to Change in Corticosteroid Therapy in Children with Juvenile Dermatomyositis

Background/Purpose: Juvenile Dermatomyositis (JDM) is a complex autoimmune disease with varying responses to therapy. Serum protein biomarkers could monitor therapy and test new drugs. The purpose of this pilot study was to identify corticosteroid-responsive serum biomarkers and determine their correlation with differing Myositis Specific Antibodies (MSA) in JDM.

Methods: The CureJM Juvenile Myositis Registry was searched for children diagnosed with definite/probable JDM who had MSA (by immunoprecipitation), and who also had sera available at three time points: 1) before start of treatment, 2) on therapy based on corticosteroids, and 3) when less clinically active and off corticosteroid therapy. Serum samples from JDM patients meeting these criteria (n=8, mean age = 6.8 ± 2.7 years) were tested for 1,300 proteins (SOMAscan proteomics). Data were benchmarked against data from 12 healthy control children, age 6-10, mean age 8.5 ± 1.7 years. To reduce heteroscedasticity the data was log transformed before statistical analysis. A two sample t test with adjustment for multiple testing was performed to compare protein levels between JDM and controls. Statistical analysis was performed with the R language for statistical computing v3.4.2.

Results: In untreated JDM, preliminary data analysis identified 44 elevated proteins and 79 proteins that were decreased compared to controls—adjusted p value of <0.001 . The elevated proteins were primarily immunologic mediators (chemokines, interleukins), confirming previous studies, and included vascular associated proteins such as angiopoietin 2 (novel biomarker), which induces apoptosis of endothelial cells and vascular regression and is an indicator of atherosclerosis. While on prednisone, levels of proteins such as angiopoietin 2, IP10 and myostatin decreased as did levels of CXCL-11, which is regulated by Interferon-beta, a major pro-inflammatory component of JDM. When prednisone was decreased, some of these biomarkers returned to their original levels, prior the treatment, while others stayed low, depending on the MSA of the child. Figure 1 below displays examples of changes in the level of 2 serum biomarkers with therapy.



Conclusion: Specific serum proteins are candidates for consideration as potential biomarkers to monitor response to therapies in children with JDM. Limitations of this pilot study include the low numbers of subjects, which will require validation in additional cohorts.

Figure 1. Two novel JDM serum biomarkers and their longitudinal trajectory with therapy in JDM by MSA. Serum levels of both proteins changed after therapy started and tended to rebound after therapy decreased. The child with MJ and possible U5RNP is the exception; angiopoietin-2 and IL-22 did not return to their original levels after therapy was stopped.

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Th22 Cells in Peripheral Blood and Synovial Fluid of Patients with Enthesitis Related Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: IL-17 and IL-22 are important cytokines in pathogenesis of spondyloarthropathy. In an IL-23 or IL-22 over-expressing mouse model it was shown that enthesitis is dependent on IL-22. IL-22 is mainly produced by T cells and innate cells. In enthesitis related arthritis (ERA) category of Juvenile arthritis enthesitis is an important clinical feature. As there is no data available on IL-22 in ERA we studied if IL-22 has any role to play in ERA and does it correlate with enthesitis by measuring the frequency of IL-22 producing T cells in blood and synovial fluid.

Methods: Forty patients with JIA-ERA as per ILAR criteria for the diagnosis of JIA were included in the study. Heparinized blood (PB) sample was collected from all cases after consent. While synovial fluid (SF) was collected from only those patients who required therapeutic joint aspiration. The disease activity was assessed by Juvenile spondyloarthropathy disease activity score (JSpADA) and enthesitis score by MASES index. Childhood Health activity score (CHAQ) was done to assess disability. Seven healthy subjects and 8 polyarticular JIA patients were included as control. The disease activity was classified as high if JSpADA score was more than 2.5.

Th1, Th17 and Th22 cell frequency in blood and synovial fluid was measured after stimulating the cells with PMA and Ionomycin for 6 hours and adding secretion inhibitor Brefeldin A 10mg/ml to prevent secretion of cytokines. Later cells were surface stained with anti-human CD3/CD4 antibody for 30 minutes. The cells were fixed and permeabilised with cytofix/cytoperm kit for 20 minutes and then stained with intracellular cytokine PE labeled anti human PerCP-IL22 for 45 minutes. The sample was acquired using FACS Canto II and analyzed using flow Jo software. All analysis was done using non-parametric tests. All frequencies are referred as median(interquartile range).

Results: There were 42 children with ERA of which 35 were male. The mean age for ERA, Polyarticular JIA and healthy controls was 15.45±2.83, 13.62±4.63 and 18 yrs respectively. Thirty-four patients (80%) had arthritis, 28 (66%) had enthesitis and 5 (12%) had uveitis. Mean JSpADA score was 3.85± 1.63.

The frequency of Th1, Th17 and Th22 cells in peripheral blood was similar between patients with ERA, Poly JIA and healthy controls.

In 10 paired samples (PB and SF) the median frequency of Th1 cells were higher in SF (9.3[4.3-19.1] as compared to peripheral blood (2.8 [2.2-3.42]; p<0.02) but the frequency of Th17 (0.4[0.2-1.1] Vs 0.2[0.2-0.325]) and Th22 (0.35[0.2-1.3] Vs 0.25 [0.2- 0.4]) though higher did not reach statistical significance.

The frequency of Th22 cells in PB was higher in children with high disease activity (0.2 [0.1-0.2]) as compared to children with minimally active/inactive disease (0.2[0.1-0.3] p<0.05). However, Th22 cell frequency had no correlation with disability as measured by CHAQ score or presence of enthesitis.

Conclusion: Th22 cells may contribute to inflammation in children with ERA however they do not have any association with enthesitis.

Disclosure: S. Kansurkar, None; A. Singh, None; R. Misra, None; A. Aggarwal, None.

Abstract Number: 2022

Evidence of Inflammation Amplification By Interleukin-6 and Interleukin-17A in Synovial Compartment of Juvenile Idiopathic Arthritis – Enthesitis Related Arthritis

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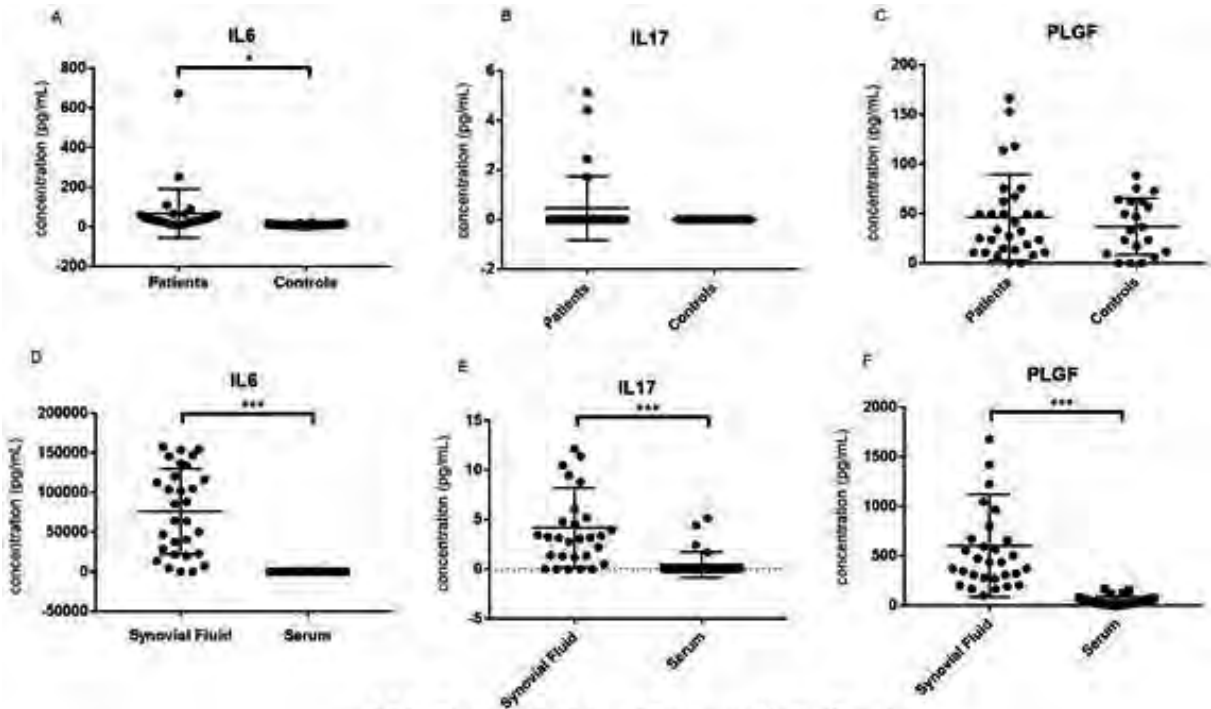
Session Time: 9:00AM-11:00AM

Background/Purpose: F759 mice with single amino-acid substitution in IL-6 receptor gp130 (Y759F) develops features of autoimmune disorders like arthritis, multiple sclerosis due to IL-17A and IL-6 mediated synergistic activation of positive-feedback loop of STAT3 and NF- κ B signaling (inflammation amplifier) in non-immune cells like fibroblasts¹. IL17A activates epiregulin/ErbB1 axis, which in turn triggers activation of multiple growth factors like Placental Growth Factor (PLGF), amphiregulin. These growth factors contribute to this amplification loop in Rheumatoid Arthritis patients² and blocking them abrogates inflammation in animal models³. In this study, we explored the possibility whether this inflammation amplifier loop is playing a role in synovitis of Juvenile Idiopathic Arthritis Enthesitis Related Arthritis (JIA-ERA) by estimating PLGF in sera and synovial fluid(SF) of patients.

Methods: Sera and Synovial Fluid(SF) of 30 adolescents of JIA-ERA, diagnosed as per ILAR classification, with effusion undergoing therapeutic aspiration were collected and stored between October 2016-April 2018. Disease activity were measured. Levels of IL6, IL17A and PLGF were measured by ELISA. IL6, IL17A and PLGF Kits were procured from BD Biosciences (IL6) and BioLegend Inc.(IL17A and PLGF), San Diego, CA. Sensitivity of the assays were 4.7 picogram(pg)/millilitres(mL), 2 pg/mL and 6.3 pg/mL respectively.

	Healthy Controls	Patients	
	Serum	Serum	Synovial Fluid
N	20	30	
Age (years)*	17.55 \pm 0.58	16.41 \pm 3.35	
Male:Female ratio	20:0	25:5	
Duration of Disease (years)*	—	4.31 \pm 1.11	
BASDAI**	—	3.11 \pm 1.96	
ASDAS-CRP**	—	2.96 \pm 0.82	
ESpADA**	—	4.11 \pm 1.36	
CHAQ**	—	1.27 \pm 0.44	
IL6* (pg/mL)*	33.23 \pm 4.56	67.31 \pm 122.72	76167 \pm 53294
IL17A* (pg/mL)*	0.00	0.46 \pm 1.29	4.18 \pm 4.02
PLGF* (pg/mL)*	17.02 \pm 28.48	46.11 \pm 43.18	602.8 \pm 517.61

*BASDAI-CRP, Ankylosing Spondylitis Disease Activity Score using C-Reactive Protein (CRP); BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CHAQ, Child's Health Activity Questionnaire; ESpADA, Swollen Joint Count/Number of Joints Swollen; IL6, Interleukin 6; IL17A, Interleukin 17A; PLGF, Placental Growth Factor; pg/mL, Picogram/Milliliter
**Rased & Unrased (Rheumatoid)



A,B,C : Comparison of Serum of Patients and Healthy Controls
D, E, F : Comparison of Serum and Synovial Fluid of Patients

Results: The mean age of patients and controls were 16.41 ± 3.35 years and 17.65 ± 0.58 years respectively ($p = 0.11$). Mean duration of disease was 4.31 years. Two third of the patients were on NSAIDS and few were on Disease Modifying Drugs. JSpADA and ASDAS CRP of the patients were 4.11 ± 1.36 , 2.96 ± 0.82 suggesting active disease with moderate disease activity. IL6, IL17A and PLGF were significantly higher in SF as compared to serum ($p < 0.0001$ for each). However, only IL6 was significantly higher in serum of patients as compared to healthy controls (IL6, $p < 0.001$; IL17A, $p = 0.092$; PLGF, $p = 0.655$). Serum IL6 correlates with SF PLGF ($r = 0.460$, $p = 0.01$) and Serum IL17A ($r = 0.443$, $p = 0.01$). However, no correlation of ILs/Growth Factors in SF with disease activity scores were found.

Conclusion: The increased SF levels of IL6, IL17A and PLGF suggest activation of IL6 and IL17A mediated amplification loop in synovial compartment of patients with JIA-ERA. Further study of other growth factors like epiregulin, amphiregulin, norepinephrine is warranted.

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Abstract Number: 2023

Different Patterns of Interferon-Response-Gene Expression May Elucidate Different Pathomechanisms That Drive IFN-Response-Gene Activation in Patients with Presumed IFN-Mediated Autoinflammatory Diseases

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Session Information

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Background/Purpose: Many infants and children with early-onset autoinflammatory diseases are mutation-negative for genetically known autoinflammatory diseases. Recent data suggest a role for Type-I interferon dysregulation in causing autoinflammatory disease phenotypes with clinical features that are distinct from those found in patients with IL-1 mediated autoinflammatory diseases. We assessed an IFN-response-gene signature (IRS), characterized the clinical phenotypes, IFN-related biomarkers and genetic causes.

Methods: We assessed IFN-response gene signatures (IRS) from 63 consecutively evaluated patients who were negative for known autoinflammatory disease-causing mutations. Whole blood gene expression of 28 selected interferon response genes (IRG) was determined by Nanostring and an IFN-score was calculated. Serum levels of 48 cytokines were measured by a multiplex immunoassay. Patients underwent clinical assessments and genetic analyses were performed by whole exome/genome sequencing (WES/WGS).

Results: Of 63 patients tested, 36 had elevated IFN-signatures. Patients with high IRS had higher frequencies of panniculitis (58 vs 0%, $p < 0.0001$), basal ganglia calcifications (45 vs 0%, $p = 0.0043$), interstitial lung disease (ILD) (48 vs 4.8%, $p = 0.0013$), myositis (65 vs 15%, $p = 0.0005$), skin vasculitis (29 vs 7.4%, $p = 0.05$), arterial hypertension (32 vs 3.7%, $p = 0.011$) and liver disease (73 vs 22%, $p = 0.0002$), than patients without an IRS. Of 8 distinct clinical patterns, one group with pulmonary alveolar proteinosis (PAP) and macrophage activation syndrome (MAS) had high IL-18 serum levels. Other groups included 2 patients with novel *LRBA* mutations, 3 patients with a novel *NEMO* splice site mutation, 5 with *de novo* truncating *SAMD9L* mutations, 2 with myositis and anti-MDA5 autoantibodies, 7 with CANDLE-like panniculitis of which 1 had a known *PSMB8* mutations and 2 had novel proteasome mutations in *PSMB8* and in *PSMG2*, respectively. Patients with PAP and MAS, *LRBA*, *NEMO*, *SAMD9L* mutations had overall lower IFN scores and significantly lower USP18 but higher SOCS1 transcript levels compared to CANDLE and SAVI, both negative regulators of IFN signaling.

SOCS1 transcription is regulated through the NF- κ B signaling pathway and SOCS1 expression dysregulation may point to a different origin of the IFN response gene signature compared to CANDLER and SAVI patients. Interestingly, many of these patients with high SOCS1 and lower USP18 levels responded to TNF inhibition. Additionally, patients with high IRS had significantly higher serum levels of IP-10, MIG, MIP1 α , MIP1 β , SCF and GRO α than those with negative IFN scores.

Conclusion: The assessment of patients with IFN signatures revealed distinct clinical pathogenically defined disease subsets. In 3 subgroups of patients, novel monogenic disease-causing mutations were detected. The contribution of SOCS1 and USP18 may assist in delineating different intracellular pathways that lead to the activation of the IFN response gene signature.

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Abstract Number: 2024

Comparison of B and T Cell Subsets, Cytokine Expression and Synovial Pathology in Down's Arthritis (DA) and Juvenile Idiopathic Arthritis (JIA)

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Session Information

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Background/Purpose: Down syndrome (DS) is a common chromosomal disorder associated with a range of medical & immune abnormalities e.g. increased susceptibility to infections & a high incidence of autoimmune diseases, including Down's Arthritis (DA). Previous work by our group suggests that the prevalence of DA is 18-21 fold greater than JIA, much higher than the previously reported DA prevalence of 8.7/1000. Children with DA most often follow a polyarticular course of disease, with erosive joint damage observed more frequently in this cohort when compared to a cohort of children with JIA. Small joint involvement is frequently observed, again in a significantly greater proportion ($p < 0.01$) of children with DA than expected in a typical JIA cohort. These characteristics suggest that DA may be distinct from JIA, however little is known about the differences in synovial pathology or immunological regulation. Indeed no studies to date have examined immunology and synovial pathology in DA. The objectives of this study were to examine B & T-cell subsets, & cytokine profiles in children with DA & JIA; & to characterise & compare the synovial membrane immunohistochemistry.

Methods: Multicolour flow cytometry was used to analyse the phenotype of B & T cells in PBMCs from 40 children (Healthy Control (HC), JIA, DS, DA). Cells were stained with the following panels; Panel 1 B cells (CD38, CD24, CD20, CD80, CD27, IgM, CD138, CD45, CD19, MHCclassII, BCMA, CD40, CD86, IgD); Panel 2 T cell cytokines analysed after 5 hours PMA/Ionomycin stimulation (CD3, CD8, CD161, IFN- γ , TNF- α , IL-17a, GM-CSF). Flow cytometry data was assessed by FlowJo software analysis.

Synovial tissue was obtained through US guided biopsy & analysed by immunohistochemistry for CD3, CD20, CD68, FVIII (DA n=3; JIA n=6). Synovial Inflammation & lining layer thickness were also scored. Analysis was performed using a semi-quantification scoring method.

Results: Flow cytometry was performed on PBMC samples from 4 distinct groups (n=10 per group); HC (50%F, age 9.2y (2.5-15.6)), JIA (91%F, age 13.2y (8.2-16.1)), DS (45%F, age 6.5y (1-11.9)) & DA (60%F, age 11.4y (3.8-17.8)). All of the children in the DA & JIA cohorts had a polyarticular RF negative pattern of disease.

Analysis revealed that children with DA have a significantly lower number of circulating CD19+CD20+ B cells when compared to children with JIA ($p < 0.05$) & HC ($p < 0.001$). However, children with DA have a greater proportion of memory B cells (CD27+) when compared to children with DS & no arthritis ($p < 0.05$).

IFN- γ & TNF- α production by CD8+/CD8- T cells was greater in DA compared to both JIA (CD8+IFN γ + p<0.001; CD8+TNF α + p<0.01; CD8-IFN γ + p<0.05; CD8-TNF α p<0.05) & HC (CD8+IFN γ + p<0.05; CD8+TNF α + p<0.05; CD8-IFN γ + p<0.05; CD8-TNF α p<0.01).

Examination of synovial tissue demonstrated higher levels of CD3+ cells (p<0.05), Macrophages (p<0.05), CD20+ cells & FVIII in the joints of children with DA.

Conclusion: There are significant differences in B cell populations, cytokine production & immunohistochemical features of synovial tissue in children with DA & JIA. More work is required to verify these results. Preliminary findings may begin to help explain the differences observed in the clinical picture of children with DA & JIA.

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Abstract Number: 2025

Fibroblast-like Synoviocytes from Juvenile Idiopathic Arthritis and Controls Influence Expression of Bone Morphogenetic Protein Antagonists in Chondrocytes

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Background/Purpose: Fibroblast-like synoviocytes (FLS) may play a role in the pathogenesis of Juvenile idiopathic arthritis (JIA) and have chondrogenic potential. Bone morphogenetic proteins (BMP) are necessary for chondrogenesis. We have previously shown increased levels of BMP4 in JIA FLS. Highly conserved antagonists of BMPs regulate signaling in both FLS and chondrocytes (Ch) by binding to BMP ligands but little is known about how these antagonists interact in JIA FLS. To examine regulation of BMP signaling in Ch and FLS, we studied gene expression levels of BMP antagonists gremlin (GREM), chordin (CHRD), noggin (NOG), and follistatin (FST), as well as the expression of these antagonists in Ch cultured in FLS conditioned media.

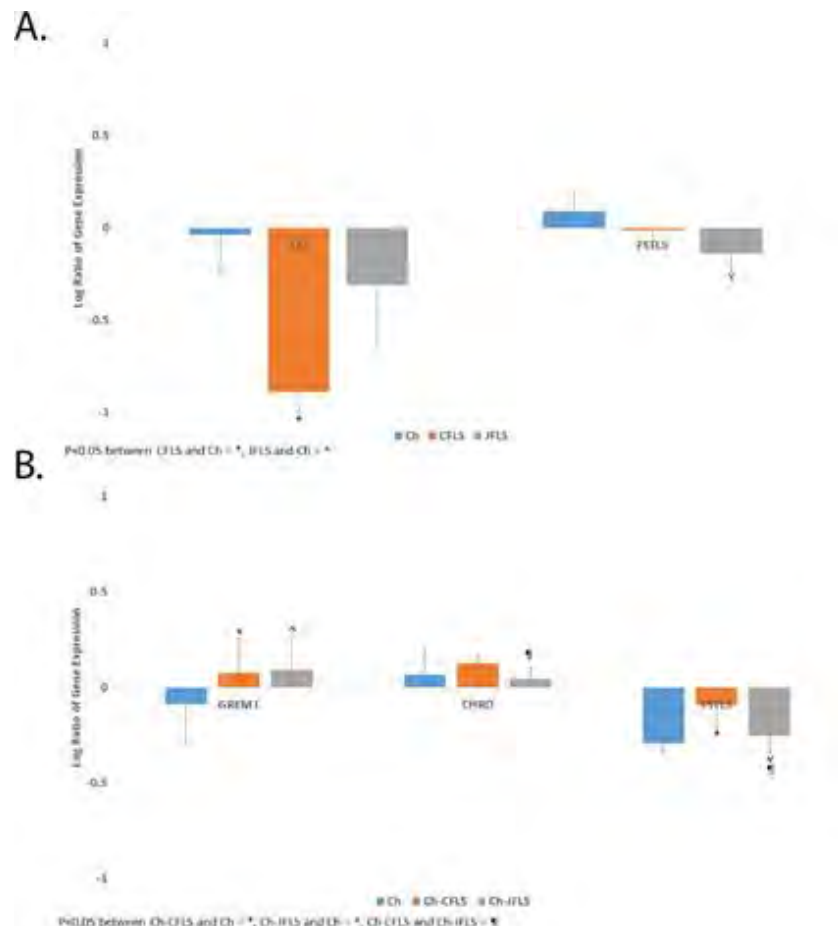
Methods: RNA was collected from three Ch, CFLS, and JFLS cell lines cultured in their respective media at 6, 12, and 24 hours. Concurrently, RNA was collected from three Ch cell lines cultured in conditioned media from CFLS or JFLS (Ch-CFLS and Ch-JFLS) at the same timepoints. Clariom S microarrays were performed on these samples and log ratios calculated using linear expression values for genes of interest.

Results: In examining the expression levels of BMP antagonists in untreated cells, FST and a follistatin-like antagonist (FSTL5), inhibitors of BMP2, BMP4, and BMP7, are downregulated in CFLS and JFLS respectively compared to Ch. When studying the influence of FLS conditioned media on Ch, FSTL3 was significantly upregulated in Ch-CFLS compared to untreated Ch and Ch-JFLS compared to Ch-CFLS. GREM, a potent inhibitor of BMP2 and BMP4 was significantly upregulated in Ch-CFLS and Ch-JFLS when compared to untreated Ch while CHRD, also an inhibitor of BMP2 and BMP4, was significantly downregulated in Ch-JFLS compared Ch-CFLS.

Conclusion: Our results suggest that untreated Ch favor FST and family members as possible BMP signaling regulators but when cultured in FLS conditioned media, GREM, but not FST or CHRD, is upregulated in both Ch-CFLS and Ch-JFLS. FLS can influence chondrocytes by causing a change in the antagonist the cells use to regulate BMP signaling. Specifically, JFLS can influence Ch to downregulate CHRD and FSTL5 expression compared to Ch-CFLS. Perhaps JFLS, who have higher levels of BMP4 than CFLS, favor a more potent inhibitor like GREM, which is expressed more during late-stage chondrogenesis as opposed to FST, which is favored during earlier chondrogenesis (1).

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Disclosure: M. Simonds, None; A. R. Schlefman, None; S. M. McCahan, None; K. E. Sullivan, None; C. D. Rosé, None; A. C. Brescia, None.



Abstract Number: 2026

Calcium Crystal-Mediated Netosis in Juvenile Dermatomyositis and Anti-RNP+ Overlap Syndrome with Skin Involvement

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Background/Purpose: Neutrophils are key immune cells participating in host defense through several mechanisms, including the formation of neutrophil extracellular traps (NETs). Although beneficial from a host-pathogen perspective, exaggerated NET formation has been linked to inflammation and autoimmunity, including lupus and adult dermatomyositis (DM). However, NETs have not been described in juvenile DM or pediatric overlap syndromes, such as RNP+ myositis. One debilitating manifestation of chronic JDM is calcinosis, the formation of calcium deposits/crystals in soft tissue. Though other crystals, including cholesterol and monosodium urate crystals are known activators of neutrophils, the role of calcium deposits/crystals in neutrophil activation and subsequent cell death is not known. In the current study, we aim to investigate if calcium crystals could mediate NETosis *in vitro*, and to determine the clinical relevance of calcium crystal-mediated NETosis in children with Juvenile Myositis.

Methods: Neutrophils were activated with synthesized calcium crystals and analyzed for NET formation in presence of reactive oxygen species (ROS) inhibitors using immunofluorescence microscopy and ELISA. Markers of neutrophil activation (S100A8/A9, peroxidase activity) and NETs (MPO-DNA complexes) were analyzed in plasma from healthy children (HC, n=20), pediatric lupus (n=10), polymyositis (n=7), JDM patients (n=66), and RNP+ myositis (9). In the Juvenile Myositis population, 74% were female, with a mean age of 11.3 years. The association of NETs with clinical parameters was tested, including disease activity scores (DAS) for skin, muscle and total, the presence of calcinosis as well as Myositis Specific Antibodies (MSA) and Myositis Associated Antibodies (MAA).

Results: Levels of S100A8/A9 and peroxidase activity were markedly elevated in JDM patients as a group ($p<0.01$), as well as in children with RNP+ antibodies ($p=0.005$), indicating systemic neutrophil activation. In children with RNP autoantibodies, S100A8/A9 levels correlated with total disease activity score ($r=0.64$, $p<0.05$) as well as disease activity score in the skin ($r=0.80$, $p<0.001$). No associations were found between NETs and MSA. Consistent with our hypothesis, calcium crystals induced neutrophil activation *in vitro*, with up-regulation of the adhesion molecules CD66b and CD11b on the neutrophil cell surface ($p<0.05$). Further, calcium crystals induced prominent NETosis ($p<0.05$) in a ROS-dependent manner, as determined by fluorimetry and immunofluorescence microscopy. Children with calcinosis had increased levels of circulating NETs as compared to calcinosis-negative children ($p=0.003$) as well as healthy controls ($p=0.02$).

Conclusion: Our results demonstrate a clear contribution of neutrophils in JM pathogenesis, and suggest calcium crystal-driven NETosis is a novel, and potentially therapeutically targetable, mechanism participating in calcinosis-associated pathology. Thus, monitoring neutrophil-derived markers may have significant clinical utility in patients with Juvenile Myositis and skin involvement.

Disclosure: C. Lood, None; G. A. Morgan, None; M. Klein-Gitelman, None; M. L. Curran, None; L. M. Pachman, None.

Abstract Number: 2027

Whole Exome Trio Sequencing Implicates DOCK2 in Juvenile Idiopathic Arthritis

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood and has a strong genetic component to disease risk. Genome-wide association studies have been the primary method for understanding genetic risk in complex diseases, including JIA, but they do not fully explain disease inheritance. This study focuses on identifying *de novo* mutations (DNMs) among sporadic oligoarticular and rheumatoid factor-negative (RF-) polyarticular JIA patients that may contribute to disease pathogenesis.

Methods: Whole exome sequencing (WES) and downstream bioinformatic analyses were used to identify rare, nonsynonymous DNMs among 10 oligoarticular or RF- polyarticular JIA patient-parent trios. All cases met either the International League of Associations for Rheumatology (ILAR) or the American College of Rheumatology (ACR) classification for JIA. Analysis of these mutations implicated a role for *DOCK2* in JIA. The impact of *DOCK2* genetic deficiency in C57BL/6 mice on arthritis development and progression was evaluated using the autoantibody-induced, K/BxN serum-transfer model.

Results: Sanger sequencing confirmed 15 nonsynonymous DNMs identified by WES among 8 JIA trios. One DNM was located in *DOCK2*, whose gene product complexes with the gene products of two JIA-associated loci identified by association testing. In mice, *DOCK2* deficiency resulted in decreased clinical measures of disease, while also reducing histopathological features in the forepaws, metacarpophalangeal joints, and knee joints induced by the K/BxN serum-transfer model. *DOCK2* expression drives neutrophil infiltration into the hindpaws that can further exacerbate disease.

Conclusion: DOCK2 is a molecular determinant of autoantibody-induced arthritis that augments disease severity and pathology through a mechanism resulting in neutrophil infiltration. Furthermore, this study demonstrates the value of rare variant detection in understanding the genetic architecture of JIA.

Disclosure: L. A. McIntosh, None; Y. Fukui, None; T. A. Griffin, None; K. Kaufman, None; J. Meller, None; S. Thornton, None; H. Moncrieffe, None; S. D. Thompson, None.

Abstract Number: 2028

Microwave and Magnetic (M²) Myocardial Proteomics in the Mouse Model of Kawasaki Disease Demonstrates Normalization of the Proteome after Interleukin-1 Inhibition, Potential Novel Biomarkers, and Suggests New Insights into Mechanism of Disease

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Kawasaki disease (KD), a predominantly coronary vasculitis of childhood, remains the most common cause of acquired heart disease of childhood in the developed world, and the developing concerns of myocardial damage in the form of cardiac fibrosis amplifies the urgency for a greater understanding both in terms of management and mechanism of this illness. At present, no biomarkers exist for the disease, response to therapy, persistence of inflammation or long term fibrosis; similarly, our understanding of the overall mechanism of the arterial remodeling and myocardial damage in KD is limited. Microwave and magnetic (M²) proteomics is a method whereby accelerated processing of proteins allows for high-throughput sample preparation and isolation of peptides for mass spectrometry. Our hypothesis was that protein biomarkers for vascular and myocardial inflammation would be identifiable in cardiac tissue from mice with a model of KD, that these markers would show response to a therapy such as interleukin-1 (IL-1) inhibition, offering insight into disease mechanisms.

Methods: KD was induced via the established model of lactobacillus casei cell wall extract (LCWE) injection in 4-6 week old male mice. Groups of mice either injected with LCWE alone, LCWE and anakinra, or saline for normal controls. After 2 weeks, mice were sacrificed and aortic root region of the heart was extracted, homogenized and processed. Tissue then underwent mass spectrometry analysis. Probability-based protein database searching of spectra was performed. Data was analyzed for pathway enrichment using STRING and REACTOME pathway analysis.

Results: Several proteins demonstrated multifold elevation in diseased animals as compared to controls, with certain proteins with primarily skeletal muscle and cardiac muscle expression notably elevated and down expressed after therapy. Proteomic analysis demonstrated clustering of diseased (KD) animals apart from controls and anakinra treated animals, which clustered together when analyzed by k-means testing. Preliminary pathway analysis suggests that in KD diseased hearts, there is enrichment for proteins involved in platelet aggregation and activation (p<0.01) and cardiac epithelial to mesenchymal transformation (p=0.04). Anakinra treated animals demonstrate enrichment for wnt signaling and downstream wnt signaling effectors beta-catenin and T cell factor (TCF) (p=0.01).

Conclusion: Potential biomarker proteins for disease activity and response to therapy were found based on the hypothesis of differential protein expression therapy and disease. These proteins require further validation. Overall, anakinra treated animals had a cardiac proteome that was more similar to normal controls than to KD mice. Preliminary pathway analysis suggested pathways for vascular injury and intimal hyperplasia in diseased animals, and induction of a regulatory immune phenotype mediated by wnt/beta-catenin in anakinra treated animals.

Disclosure: M. Gorelik, None; C. Chase, None; M. Noval Rivas, None; J. Patterson, None; M. Arditi, None; T. Forsthuber, None.

Extended Phenotypic Immunome Characterization (EPIC): A Web-Based Immune Reference Atlas

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: An atlas of the developing immune system will aid in our understanding of its normal maturation and identification of disease-associated cell subsets. The availability of high dimensional mass cytometry has provided an opportunity for the creation of this reference standard. However, the power available from these big data has not been fully harnessed due to the current focus on specific cell subsets and age groups. There is a critical unmet need for standardized datasets depicting at single cell level and with high dimensionality the entire developmental gradient of the healthy immune system from the neonatal to adult age.

Methods: To address this need, we constructed an immune atlas from the mass cytometry data obtained from the peripheral blood mononuclear cell samples of 113 healthy individuals (cord blood, newborn to adult) using 63 phenotypical and functional immune markers encompassing the major immune lineages. Quality control check and batch effect correction were done before dimensional reduction and clustering to identify the unique cell subsets. Their frequencies across the age categories were presented as 3-D frequency histograms to create the immune landscape. This database and the analytic pipeline were incorporated into a web portal that allows user to interact as well as upload their own data for comparison.

Results: Here, we described EPIC with examples of representative immune subsets over the entire age spectrum. There was a distinct segregation of the naive T cell subset enriched in the cord blood/newborn period from the memory T cell subset enriched in adulthood. The naive IL8+ and TNF α + CD4+ T cells accounted for prominent peaks in the immune landscape during the cord blood/newborn period. In contrast, the memory IFN γ + and TNF α + CD4+ T cells were enriched in adulthood.

Transition developmental milestones were observed in the TNF α + CD4+ T cells where the size of its memory subset would exceed its naive subset at 8 year old. There was a significant reduction and increase in the frequency of the naive and memory TNF α + CD4+ T cells with a Spearman's correlation coefficient, rho, of -0.4662 and 0.4164 respectively (both $p < 0.0001$). A similar intersection was present for the naive and memory regulatory T cell (CD4+, CD25+, Foxp3+, CD152+) subsets at 14 year old with a rho of -0.537 and 0.5034 respectively (both $p < 0.0001$).

Conclusion: A holistic description of the developing immunome was obtained with key developmental milestones in the T cell compartment identified. This atlas has the translational potential of aiding the identification of pathologic immune cell subsets in diseases through its comparison with this reference dataset found in the freely available EPIC web portal.

Disclosure: J. G. Yeo, None; P. Lu, None; T. Arkachaisri, None; S. L. Poh, None; F. Ally, None; J. Y. Leong, None; K. T. Yeo, None; L. D. T. Bathi, None; Y. J. A. Tan, None; S. C. E. Lee, None; S. Albani, None.

Patients with Childhood-Onset SLE (cSLE) and Hypertension Have Consistently Higher Serum Concentrations of C3 and C4 Than Those without Hypertension

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Session Information

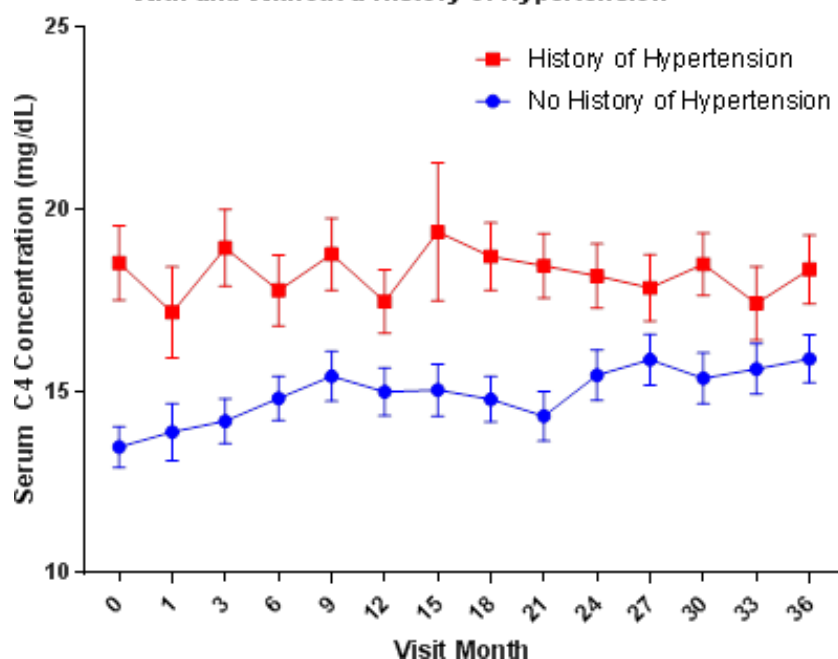
Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Basic Science Poster

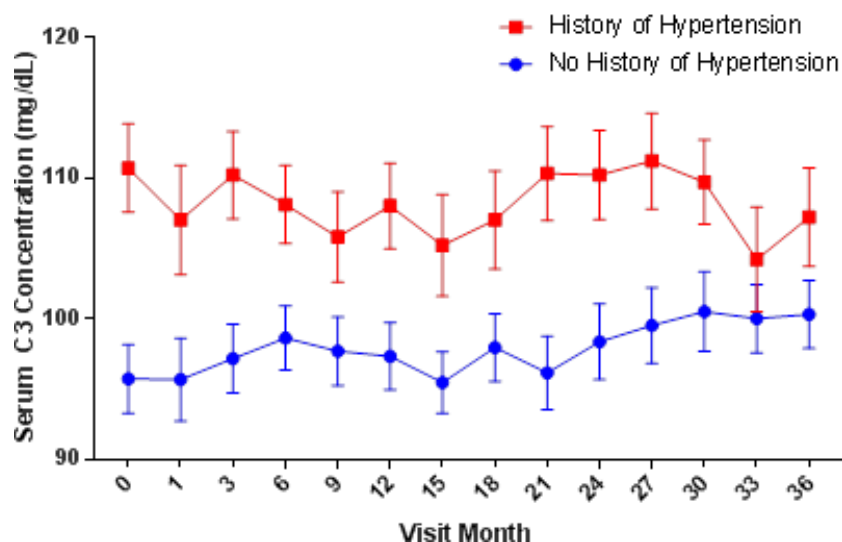
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Serial Serum C4 Concentrations in APPLE Participants With and Without a History of Hypertension



Serial Serum C3 Concentrations in APPLE Participants With and Without a History of Hypertension



Background/Purpose: Chronic systemic inflammation, mediated in part by complement, and inadequate vascular repair mechanisms affect patients with cSLE from a young age and are associated with cardiovascular morbidity. In non-SLE affected patients with cardiovascular disease (CVD) and hypertension, complement levels are increased. In contrast, complement levels are relatively low in SLE when the disease is active. We leveraged data from the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) Trial and its cSLE cohort to further investigate the relationship between complement and CVD in SLE. We hypothesized that serial levels of serum C4 and C3 would be higher in patients with hypertension than in those without. We also hypothesized that C4 levels would be influenced by total C4 gene copy number (GCN).

Methods: Clinical data for the three-year study of 221 cSLE patients, plus genomic DNA and plasma samples for 197 patients, were provided by the APPLE repository. Total C4 GCN was measured by TaqMan-based quantitative real time PCR and Southern blot analyses using genomic DNA. Baseline serum C4 levels were compared to total C4 GCN using linear regression. Least-squares regression was used to assess the effect of hypertension, defined by baseline physician-report, on serial serum C4 and C3 protein levels.

Results: A linear relationship was demonstrated between baseline serum C4 levels and total C4 GCN. A one-copy increase in GCN correlated with an increase in serum C4 of 3.28 mg/dL ($p=1.8 \times 10^{-6}$; $R^2=0.12$). Compared to normotensive individuals, individuals with a history of hypertension had significantly higher baseline levels of serum C4 (18.5 mg/dL vs 13.5 mg/dL; $p=4.7 \times 10^{-6}$) and serum C3 (110.7 mg/dL vs 95.7 mg/dL; $p=3.0 \times 10^{-4}$). A history of hypertension had a positive effect on serial serum C4 levels (Figure 1; $p=5.0 \times 10^{-25}$) and serum C3 levels (Figure 2; $p=5.8 \times 10^{-20}$).

Conclusion: In the APPLE Trial, cSLE patients who were hypertensive had significantly higher baseline and serial concentrations of serum C4 and C3 than non-hypertensive cSLE patients. Total C4 GCN directly affected total serum C4 levels. Further elucidating the relationship between complement GCN, serum complement protein levels, and CVD in SLE could allow for more precise real-time interpretation of complement data and may provide an opportunity for early identification of cSLE patients at highest risk for poor cardiovascular outcomes.

Disclosure

E. Mulvihill, None; S. P. Ardoin, None; S. D. Thompson, None; B. Zhou, None; G. Yu, None; N. G. Singer, None; D. M. Levy, None; H. I. Brunner, None; Y. L. Wu, None; H. Nagaraja, None; L. E. Schanberg, None; C. Y. Yu, None.

Abstract Number: 2031

Dysregulated NK Cell PLC

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Juvenile dermatomyositis (JDM) is a debilitating pediatric autoimmune disease manifesting with characteristic rash and proximal muscle weakness. We investigated signaling abnormalities in immune cell subsets from treatment-naïve JDM patients and healthy controls.

Methods: To delineate signaling abnormalities, mass cytometry coupled with phosphoprotein antibodies was performed with peripheral blood mononuclear cells from seventeen treatment-naïve JDM patients and controls.

Results: The percentages of peripheral NK cells were lower while frequencies of naïve B cells and naïve CD4 T cells were higher in JDM patients than controls. These cell frequency differences were attenuated in paired patient samples with cessation of active disease. A large number of signaling differences were identified in treatment-naïve JDM patients compared to controls. Classification models incorporating feature selection demonstrated that differences in PLCγ2 phosphorylation comprised 10 of the 12 features (i.e., phosphoprotein in a specific immune cell subset) distinguishing the JDM patients from healthy controls. As NK cells represented 5 of these 12 features, further studies focused on the critical PLCγ2 pathway in NK cells which is responsible for stimulating calcium flux and cytotoxic granule movement. No differences were detected in upstream kinases (Itk/Btk, Syk/ZAP70) or total PLCγ2 protein levels. The decreased phosphorylation of NK cell PLCγ2 and downstream MAPKAPK2 was partially attenuated in treatment-naïve JDM patients

with cessation of active disease. Furthermore, suppressed PLC γ 2 phosphorylation in treatment-naïve JDM patient NK cells resulted in decreased calcium flux.

Conclusion: The novel identification of dysregulation of PLC γ 2 phosphorylation and decreased calcium flux in NK cells from treatment-naïve JDM patients provides potential mechanistic insight into JDM pathogenesis.

Disclosure: A. A. Throm, None; J. B. Alinger, None; L. M. Pachman, None; A. R. French, None.

Abstract Number: 2032

Effector T Helper Cell Differentiation and Cytokine Secretion Are Increased in Young Children with Juvenile Idiopathic Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: T cells play a critical role in the body's response to pathogens. A naïve T helper (Th0) cell proliferates in response to antigen encounter and is not differentiated. Specific cytokines signal the naïve Th cell to express transcription factors causing differentiation to Th cell lineages, including Th1, Th2, and Th17 lines. Re-activation causes a differentiated effector Th cell to secrete characteristic cytokines, which are IFN γ , IL-5 and IL-13, and IL-17 for Th1, Th2, and Th17 cells respectively. In juvenile idiopathic arthritis (JIA), specific Th cell lineage differentiation and cytokine secretion have not been studied. An *ex vivo* assay was developed in adult human peripheral blood mononuclear cells (pBMCs) wherein mononuclear cells differentiate, re-activate, and then secrete cytokines. We identified a young child with JIA who has a heterozygous mutation in GATA-3, the key transcription factor that drives the Th2 pathway and suppresses the Th1 and Th17 pathways (index patient). In this study, we tested effector Th cell differentiation and cytokine secretion in pBMCs from young children, young children with JIA, and the index patient.

Methods: We enrolled healthy controls, children with seronegative polyarticular or extended oligoarticular JIA, and the index patient. All children were 2-8 years old. PBMCs underwent collection, *ex vivo* differentiation to Th0, Th1, Th2, and Th17 cells, and then re-stimulation. After this, cytokine secretion was measured by enzyme-linked immunosorbent assay. Transcription factor expression and cytokine transcription was assessed by Western blot and quantitative real time polymerase chain reaction. Whole exome sequencing identified the index patient GATA-3 mutation.

Results: Differentiated effector Th cell cultures from children with JIA secrete much higher levels of characteristic cytokines than healthy control children. The Th cell average JIA/control ratios were markedly increased for Th1 (IFN γ , 3.4), Th2 (IL-5, 6.0 and IL-13, 10.3), and Th17 (IL-17, 5.5). The index patient had increased index/control ratios for Th1 (IFN γ , 4.5) and Th17 (IL-17, 3.6) cultures and no change in Th-2 ratios. Surprisingly, the undifferentiated Th0 cells from children with JIA and the index patient secrete IFN γ , with ratios being JIA/control 5.5 and index/control 22.6. The *ex vivo* assay in healthy children produces much lower levels of cytokines than in healthy adults.

Conclusion: Young children produce differentiated effector Th cells that make much less cytokines than adult differentiated effector Th cells. Cultures from children with JIA make more cytokines than cultures from healthy children and are similar to adult cultures. The index patient does not produce differentiated Th2 cells that secrete IL-13 and IL-5, as might be predicted from a GATA-3 mutation. Both the JIA and index patient undifferentiated Th0 cell cultures secrete IFN γ , suggesting a Th1-like phenotype. Mechanisms underlying differences between effector Th cell cultures from young children, children with JIA, the index patient, and adults may reveal fundamental differences in these developmental processes, including limits on the function of the immune system in young children.

Disclosure: A. Patrick, None; T. Aune, None; J. Duis, None; T. B. Graham, None.

Multiparameter Mass Cytometry By Time-of-Flight Spectrometry (CyTOF) Phenotyping in Pediatric Localized Scleroderma

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Localized scleroderma (LS) has both inflammatory and fibrotic components affecting skin and underlying tissue. Extent and duration of inflammation during active LS is thought to be the major contributor to long-term disease damage and disability. Identifying the cellular phenotype expressed during active LS would be instrumental to improve outcomes. As a preliminary evaluation, pediatric LS and healthy pediatric control samples were analyzed by mass cytometry by time-of-flight spectrometry (CyTOF). CyTOF uses heavy metal ion tags to mark cells and perform high-dimensional phenotypic and functional analysis on single cells. Our panels focused on monocytes and T cells, respectively, to determine key phenotypic populations in LS samples.

Methods: Paired pediatric LS PBMC samples (n=9 subjects, 18 samples) from individuals with initial active and later inactive disease states and healthy pediatric controls (n=8) were collected (IRB #PRO11060222) and analyzed using CyTOF. Both monocyte and T cell panels of 34 markers each were performed at the Stanford Human Immune Monitoring Center (HIMC) using singlet and viability based analysis. Data was analyzed using SPADE and CITRUS (Cytobank) and Cytosplore software. CITRUS clusters were made from all samples, and cell types were then identified from all levels of the cluster hierarchy that were significantly associated with active LS, inactive LS, and healthy groups. SPADE trees were built using 11 marker calculated cell clusters to define key populations that differed from the subject's active PBMC sample acting as the baseline. Cytosplore software then allowed for sub-analysis of SPADE branches through t-Distributed Stochastic Neighbor Embedding (t-SNE) plots.

Results: CyTOF revealed a dramatic decrease in frequency of monocyte subsets, DC cells (both CD16+/-), and NK cells (CD56+CD16+) in the inactive state. The CD16+CD86+ monocyte subset (M1 phenotype) showed a 3-fold decrease in the inactive state, consistent with our prior LuminexTM findings of the peripheral LS blood signature. Further study of NK subsets shows NK^{CD56bright} cells having a 4-fold increase in the active state and 50% increase in IFN- γ production after lipopolysaccharide (LPS) stimulation. Further CyTOF analysis showed an overall increase in T cell (CD3+) populations in active LS, with decreased T_H1 (CD3+CD4+IFN γ) and Tc1 (CD3+CD8+IFN γ +) populations when transitioning from active to inactive disease state. Granzyme positive cytotoxic T cells (CD8+) were elevated in active LS and when comparing overall LS to healthy controls.

Conclusion: These findings support increased levels of type-1 specific M1 and NK cells during active LS. These cell types are thought to contribute to activation and stimulation of T cells and DCs through IFN γ expression, which would support the elevation of T_H1-like (IFN γ + T_H and Tc) cells and DCs observed in our cohort. Previous work showed that the IFN γ inducible chemokines (CXCL9, CXCL10 and CXCL11) are present during active LS, possibly further polarizing these phenotypes. Further study is ongoing to evaluate these phenotypes in active LS skin, and the association to the PBMC signature.

Disclosure: E. Mirizio, None; E. D. Mellins, None; C. Macaubas, None; H. T. Maecker, None; F. Gartner, None; L. Konnikova, None; K. Schollaert-Fitch, None; K. S. Torok, None.

Increased Invasive Capacity and Metabolic Activity in Synovial Fibroblasts from Children with Downs Arthropathy Compared to Juvenile Idiopathic Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Downs Arthropathy (DA) is an inflammatory joint condition affecting children with Down syndrome, which is under-recognised, has a delayed diagnoses, resulting in chronic disability. Our clinical research showed an increased risk of arthritis in children with Down syndrome, with the prevalence in Ireland for DA 18-21 times greater than Juvenile idiopathic Arthritis (JIA). Furthermore children with DA had more erosive joint damage compared to JIA. This observed increase in erosive disease suggests that DA synovial fibroblasts (SFC) which reside in the hyperplastic lining layer of the synovium may have a more invasive phenotype, however to date little is known about the underlying mechanisms that drive disease pathogenesis in DA.

The aim of the present study is to compare the function of primary synovial fibroblasts from children with DA vs JIA.

Methods: Synovial tissue biopsies were obtained from children with DA and JIA using ultrasound guided biopsies and assessed histologically for levels of vascularity, lining layer hyperplasia and sub-lining inflammation. Primary synovial fibroblasts were isolated from both DA and JIA and functional comparisons performed at passage 3. DASFC and JIASFC migration was assessed by wound repair scratch assays. Biocoat Matrigel™ Invasion Chambers were used to assess DASFC and JIASFC invasiveness. DASFC and JIASFC bioenergetic activity was assessed using the XFe96-Flux-analyser, where oxygen consumption rate (OCR) and extracellular acidification rate (ECAR), reflecting oxidative phosphorylation and glycolysis respectively were quantified. Further metabolic outputs were assessed following the mitochondrial stress test where cells were treated with oligomycin, FCCP and antimycin A. Finally, glycolytic gene expression was assessed by Real-time PCR.

Results: Synovial tissue analysis demonstrated a marked increase in synovial lining layer hyperplasia in DA vs JIA, with a median lining layer thickness score of 6(3-9) in DA vs 3(2-4) JIA, suggesting a more invasive pannus in DA compared to JIA. An increase in the migration of DASFC compared to JIASFC was observed, an effect paralleled by a significant increase in the invasive capacity of DASFC vs JIASFC. These effects were potentiated in response to TNF α stimulation. Metabolic activity was markedly different in DASFC vs JIASFC, with DASFC displaying increased basal metabolic activity compared to JIASFC. Moreover, following the mitochondrial stress test, a substantial increase in mitochondrial spare reserve capacity was observed in DASFC when compared to JIASFC, suggesting that DASFC have an enhanced ability to respond to sudden changes in the energy demands of the cell. Finally, an increase in metabolic genes HK2 and PDK2 were observed in DASFC vs JIASFC.

Conclusion: This is the first study to demonstrate differences in synovial pathology of children with DA vs JIA, demonstrating a marked increase in the invasive layer of DA synovium compared to JIA. This was paralleled by a significant increase in the migratory, invasive and bioenergetic profile of DASFC vs JIASFC, a phenotype that may contribute to the increased erosive disease observed in DA compared to JIA.

Disclosure: S. Ansboro, None; C. Foley, None; M. Biniecka, None; E. MacDermott, None; D. J. Veale, None; R. Mullan, None; O. G. Killeen, None; U. Fearon, Pfizer, Inc., 2.

Effect of Baricitinib on Joint-Related Biomarkers in Patients with Moderate-to-Severe Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Baricitinib (bari) is an oral selective inhibitor of Janus kinase (JAK) 1 and JAK2. In the phase 3 study RA-BUILD (NCT01721057), once-daily bari yielded significant clinical benefit in patients (pts) with active RA who had inadequate response or intolerance to conventional synthetic DMARDs compared to placebo (PBO).¹ Changes in serum biomarkers² associated with joint tissue remodeling, including synovial remodeling and inflammation (C1M, C3M, and C4M [matrix metalloproteinase-derived fragments of type I, III, and IV collagen, respectively] and ProC3 [N-terminal pro-peptide type III collagen]), cartilage degradation (C2M [derived from type II collagen]), and bone remodeling (CTX-I [C terminal telopeptide of type I collagen] and osteocalcin) were analyzed in a subset (N=240) of these pts.

Methods: Circulating levels of biomarkers from eighty patients per arm (PBO, bari 2- or 4-mg [added to stable background therapy]) were analyzed at baseline (BL), week (Wk) 4, and Wk 12, using a Mixed Model Repeated Measure method to identify markers that are affected by bari longitudinally. Secondly, an analysis of variance was performed to evaluate the relationship between the observed changes in biomarkers at Wks 4 and 12 (grouped as reduction or increase from BL) and the Hybrid ACR response measure (a hybrid of ordinal and continuous versions of ACR scores)³ at the primary endpoint of Wk 12.

Results: Baseline concentrations of biomarkers tested were similar between all three groups. At Wk 4, C1M was reduced by 21% from BL by bari 4-mg compared to PBO (p<0.01); suppression was sustained at Wk 12 (27%, p<0.001). Similarly, at Wk 4, C3M and C4M were reduced by 14% and 12% from BL by bari 4-mg compared to PBO (p<0.001), respectively, and remained reduced by 16% or 11% from BL at Wk 12 (p<0.001). Similar results were observed with bari 2-mg. Bari treatment did not result in appreciable changes compared to PBO for the other biomarkers tested. We further determined the relationship between changes in biomarkers in RA pts and clinical response, as measured by the Hybrid ACR score (Table). In a pooled analysis with all three treatment arms, reduction in C1M, C3M, and C4M by Wks 4 and 12 was associated with significantly greater clinical improvement in the Hybrid ACR response at Wk 12 compared to pts with RA having increased levels of these biomarkers.

Table: Greater clinical improvement, as measured by the Hybrid ACR response,³ observed in patients with a reduction in serum biomarkers

	Week 4			Week 12		
	BM Reduction	BM Increase	Difference	BM Reduction	BM Increase	Difference
C1M	-43.7	26.4	17.3***	-44.4	21.2	-23.2***
C3M	-42.5	28.9	13.6**	-44.2	24.4	-19.8**
C4M	-42.1	29.7	12.5**	-44.7	20.1	-24.6***

Hybrid ACR response measured at Week 12. Data are the mean Hybrid ACR score at Week 12 with patients grouped by a reduction or increase in biomarker change from baseline at Weeks 4 and 12. The estimated mean difference and significance are shown. **p<0.01, ***p<0.001. BM=biomarker; C1M, C3M, and C4M=matrix metalloproteinase-derived fragments of type I, III, and IV collagen, respectively.

Conclusion: A reduction in circulating biomarkers associated with tissue destruction and synovial inflammation in RA pts was observed in bari-treated RA pts, suggesting that bari inhibits key pathological processes at the site of inflammation in RA. Moreover, the decrease in these biomarkers was associated with clinical improvement.

¹Dougados M et al. *Ann Rheum Dis*. 2017;76:88-95.

²Bay-Jensen A et al. *Semin Arthritis Rheum*. 2014;43:470-478.

³Felson D. *Arthritis Rheum*. 2007;57:193-202.

Disclosure: C. S. Thudium, Nordic Bioscience, 3; A. C. Bay-Jensen, Nordic Bioscience, 1, 3, IMI APPROACH, 2; S. Cahya, Eli Lilly and Company, 1, 3; E. R. Dow, Eli Lilly and Company, 1, 3; M. A. Karsdal, Nordic Bioscience, 1, 3; A. E. Koch, Eli Lilly and Company, 1, 3; W. Zhang, Eli Lilly and Company, 1, 3; R. J. Benschop, Eli Lilly and Company, 1, 3.

Abstract Number: 2036

Adenosine Receptors Expression As Predictor of Response to Methotrexate Therapy in Patients with Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Methotrexate (MTX) is first line of therapy to treat Rheumatoid Arthritis (RA) patients and one third of patients do not respond to this drug. MTX reduces inflammation by increasing extracellular adenosine levels. Adenosine acts via four G-protein coupled adenosine receptors; ADORA1, ADORA2a, ADORA2b and ADORA3. Activation of ADORA2b and ADORA1 leads to pro-inflammatory response, whereas activation of ADORA2a and ADORA3 mediates anti-inflammatory response. MTX also modulates the expression levels of adenosine receptors. Thus, to see if baseline levels of adenosine receptors (ADORA1, ADORA2a, ADORA2b and ADORA3) can predict response to MTX we analysed their levels in whole blood RNA.

Methods: Patients with RA (ACR 2010 criteria), DMARD naïve with active disease (DAS 28 >3.2) were enrolled. Blood samples were collected at baseline before start of MTX. All patients were treated with MTX monotherapy by gradually increasing dose to a maximum of 25mg/week or the maximal tolerated dose. After 4 months of therapy EULAR response was assessed. Adenosine receptors gene expression (ADORA1, ADORA2a, ADORA2b and ADORA3) in the whole blood RNA sample was measured using real time qPCR. HPRT1 was used as a housekeeping gene. The adenosine receptor expression was correlated with response to MTX.

Results: Ninety-nine patients (86.86% females; median age 40 [17-67] years); median duration of disease 24 (2-120) months; median DAS28-CRP 4.48 (3.16-7.63) were enrolled. Among 99 patients 51 were classified as good responders, 28 moderate responders and 20 as non-responders at 4 months. In whole blood RNA, there was predominant expression of ADORA2a and ADORA3 and almost no expression of ADORA1 and ADORA2b. Baseline adenosine receptor expression did not correlate with DAS28 score.

Both adenosine receptors ADORA2a and ADORA3 expression was lower in non-responders (n=20) as compared to good and moderate responders (n=79). However, significant difference was observed only for ADORA3 between good vs non-responder (p=0.03) and moderate vs non-responder (p=0.002). ROC curve analysis showed that ADORA3 with cut-off value of less than -0.21 (Δ Ct) predicted non-response to MTX treatment with a sensitivity of 63.6% and a specificity of 65% (AUC:0.695, p=0.007).

Conclusion: Adenosine receptor A3 (ADORA3) mRNA levels in whole blood may serve as a biomarker for response to MTX.

Disclosure: A. Singh, None; R. Misra, None; A. Aggarwal, None.

Abstract Number: 2037

CTLA4 Signaling Down-Regulates Fcγ Receptor I Expression on Circulating Monocytes: A Potential Mechanism of Action of Abatacept for RA

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Abatacept is a recombinant fusion protein comprising cytotoxic T lymphocyte antigen 4 (CTLA4) and Fc region of immunoglobulin (Ig), which is efficacious against rheumatoid arthritis (RA). Its mechanism of action is believed to be competitive inhibition of T-cell co-stimulation mediated through binding of CD28 to CD80/CD86 on antigen-presenting cells. On the other hand, it has been shown that binding of CTLA4-Ig to CD80/CD86 on monocytes, macrophages, and osteoclast precursors is capable of transmitting intracellular signaling pathways. This signaling is potentially involved in the therapeutic action of abatacept, but detailed mechanisms still remain unclear. This study is aimed to investigate direct effects of CTLA4-Ig on circulating monocytes, which might contribute to its efficacy for suppressing pathogenic process of RA.

Methods: This study enrolled 34 RA patients and 13 controls, including patients with non-inflammatory rheumatic disorders or healthy individuals. Circulating monocytes were isolated from peripheral blood mononuclear cells by negative selection with magnetic-activated cell sorting system, and were cultured in the presence or absence of CTLA4-Ig, CD28-Ig, or Ig alone for 24 hours. In some experiments, anti-CD80, CD86, and/or isotype-matched control monoclonal antibody (mAb) were added in the culture. The recovered cells were subjected to flow cytometry to evaluate expression levels of CD14, CD16, CD32, CD40, CD54, CD62L, CD64, CD80, CD86, CCR2, CXCR2, CD273, CD274, and CD275, and IL-1 β , IL-6, IL-8, IL-10, IL-12p70, IFN γ , MCP-1, TNF α were measured in culture supernatants by multiplex particle-based flow cytometric assay. Expression of candidate molecules was further examined by immunoblots using total cellular extracts of monocytes cultured with CTLA4-Ig or CD28-Ig. Statistical analysis was made using non-parametric Mann-Whitney U test.

Results: In a pilot study using 5 RA patients and 5 controls, we selected CD64, CD80, CD86, CCR2, and CXCR2 as candidate molecules whose expression levels were modulated by CTLA4-Ig stimulation in a fashion different from CD28-Ig stimulation. The validation study involving 20 RA patients and 8 controls demonstrated that treatment with CTLA4-Ig significantly down-regulated expression of CD64 or Fc γ receptor I in circulating monocytes, but stimulation with CD28-Ig had no effect. The CD64 down-regulation induced by CTLA4-Ig was not found in cultures with control Ig alone, and was confirmed by immunoblots. This effect was observed in both RA patients and controls, while CD64 expression levels on circulating monocytes tended to be higher in RA patients compared with controls. Finally, CTLA4-mediated CD64 down-regulation was completely abolished by anti-CD86 mAb, but not by anti-CD80 mAb.

Conclusion: Efficacy of abatacept is associated with a high titer of anti-citrullinated protein antibodies, which form immune complexes and induce activation of monocytes/macrophages through binding to Fc γ receptors. These findings suggest that therapeutic effects of abatacept on RA are mediated, in part, through down-regulation of Fc γ receptor I on circulating monocytes via direct binding to CD86.

Disclosure: R. Fukue, None; Y. Okazaki, None; M. Kuwana, Ono Pharmaceuticals, AbbVie, Astellas, Chugai, Eisai, Mitsubishi-Tanabe, Pfizer, Ayumi, 2, 8.

Abstract Number: 2038

Subgroups By the Peripheral Immunophenotyping and Different Responses to Biological Dmards in Patients with Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

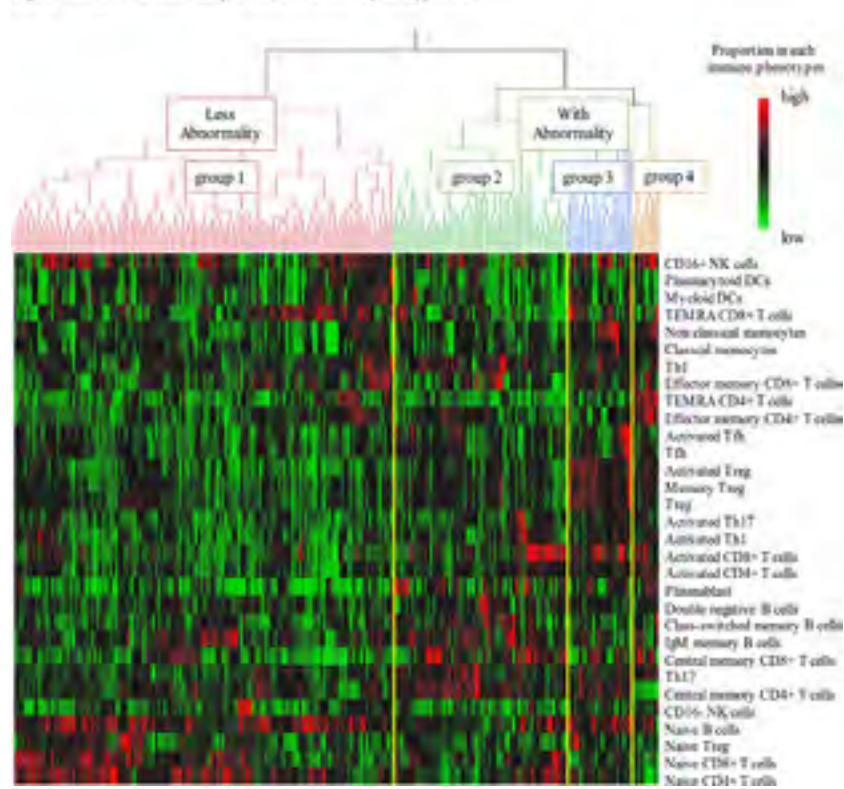
Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: In the treatment of rheumatoid arthritis (RA), molecular targeted therapies induced different changes in different immune cell phenotypes. For instance, our previous study showed that abatacept decreased the number of Tfh cells, while TNF inhibitors increased that of Tfh cells. This fact forms the basis for subgroup identification for precision medicine. In this study, we stratified RA patients based on immunophenotyping and investigated the response for targeted therapies.

Figure 1. Statistical cluster analysis based on immune phenotype in RA



Methods: Peripheral blood mononuclear cells were obtained from 224 bio-naive RA patients and 33 healthy individuals. Circulating B, T and dendritic cells were defined based on flow cytometric analysis for human immune system termed “the Human Immunology Project”. Based on these results, RA patients were classified into subgroups by cluster analysis. The human ethics review committee of our university reviewed and approved this study.

Results: The proportions of T effector and activated Tfh cells, but not Th17 and Treg cells, were higher in RA than the age matched control. Likewise, the proportions of B effector cells and plasmacytoid DCs were higher. None of them correlated with disease activity. Cluster analysis (Figure 1) stratified RA patients into 2 groups: patients with less immune abnormality and patients with immune abnormality. The group with immune abnormality was further divided statistically into 3 groups (with high proportions of B effector, Th17, and Tfh cells in all groups): patients with less T cell abnormality (T cell low dependent group), patients with high percentage of Tfh and Treg cells (Tfh/Treg dominant group), and patients with conspicuously high proportion of T effector cells (T effector dominant group). Among these 4 groups, simplified disease activity index (SDAI) and clinical disease activity index (CDAI) components were similar. However, the treatment responses by biologics were different. The number of patients with insufficient response at week 52 was more frequent in T effector dominant group. In addition, TNF inhibitors were numerically more effective in the group with less immune abnormality. In contrast, abatacept had similar efficacies in the group with less immune abnormality and the group with immune abnormality, and tocilizumab had strong efficacy in Tfh/Treg dominant group.

Conclusion: Our study indicates that active RA patients can be divided into four subgroups based on immunophenotype. The identification of immunophenotypic subgroups may enhance treatment effect of molecular targeted drugs and serve as a step towards precision medicine.

Disclosure: S. Kubo, Bristol-Myers, Pfizer, and Takeda, 8; S. Nakayamada, Bristol-Myers, UCB, Astellas, Abbvie, Eisai, Pfizer, Takeda, 8, Mitsubishi-Tanabe, Novartis and MSD, 2; Y. Miyazaki, None; M. Yoshikawa, None; H. Yoshinari, None; S. Iwata, None; K. Hanami, None; S. Fukuyo, None; I. Miyagawa, None; K. Nakano, UCB, Astellas, Mitsubishi-Tanabe, 8, Mitsubishi-Tanabe and Eisai, 2; Y. Tanaka, Daiichi-Sankyo, Astellas, Pfizer, Mitsubishi-Tanabe, Bristol-Myers, Chugai, YL Biologics, Eli Lilly, Sanofi, Janssen, UCB, 8, Mitsubishi-Tanabe, Takeda, Bristol-Myers, Chugai, Astellas, Abbvie, MSD, Daiichi-Sankyo, Pfizer, Kyowa- Kirin, Eisai, Ono, 2.

A Survey of Blood and Synovial Tissue Myeloid Cells in RA Patients By Transcriptional Profiling

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Myeloid cells – including dendritic cells (DCs), monocytes, and macrophages – are critical to the pathogenesis of rheumatoid arthritis (RA) through production of pro-inflammatory cytokines, recruitment of inflammatory cells, and activation of T cells. Various studies have shown that these cells exhibit activation markers and increased numbers in the joint synovium, but the relationship with the activity of their circulating counterparts has not been fully elucidated. Here, we perform RNA-seq on these *in vivo* cell populations from RA patients in order to compare their genome-wide transcriptional profile within and across individuals.

Methods: We obtained blood samples and ultrasound-guided minimally invasive synovial biopsy tissue (as described in Mandelin et al, *A&R* 2018¹) from RA patients with active disease. Using Fluorescence-Activated Cell Sorting (FACS), we isolated classical monocytes (MHCII+CD14++CD16-), non-classical monocytes (MHCII+CD14+CD16+), and dendritic cells (MHCII+CD1c+) from blood. After processing synovial tissue for single-cell suspension, we isolated macrophages (MHCII+CD14+CD11b+CD206+) and dendritic cells (MHCII+CD1c+) by FACS. We extracted RNA from these cell populations and prepared libraries for RNA-seq. Although the cell numbers were low, particularly for the synovial tissue populations, we have previously demonstrated our ability to reliably generate RNA-seq libraries from sorted populations down to tens of cells. These libraries were sequenced on an Illumina NextSeq 500 and assessed for quality of RNA, sequencing, and gene detection.

Results: For each cell population, we assessed the variability of gene expression across patients. As expected, the DCs were highly variable across individuals: this is likely due to the heterogeneity of subtypes within this population. In circulating monocytes, we observed varying levels of common cytokines and chemokines, such as TNF and CCL1. We also compared gene expression across cell populations to characterize transcriptional signatures that were distinctive to a given cell population. In addition to the genes previously known to be unique to dendritic cells vs. monocytes/macrophages in health, we also identified potential pathogenic factors that varied in their expression across cell types. Finally, to explore the relationship between circulating and tissue cell populations, we asked whether there were pathways that were turned on in the blood prior to extravasation into the synovium. For example, we identified genes that maintained their expression across monocytes and synovial macrophages in RA patients supporting the differentiation of the former into the latter.

Conclusion: Together, these results provide a survey of myeloid cells in the blood and synovial tissue of RA patients. We aim to understand how these cells vary across patients and what clinical variables and medication status influence their transcriptional profile across individuals. Our long-term goal is to use these studies to better understand the underlying mechanisms of pathogenesis and response to current treatments of RA as well as to identify potential targets for future therapies.

Disclosure: S. Bian, None; A. M. Mandelin II, None; S. Dominguez, None; P. J. Homan, None; G. Gadhi, None; H. Abdala-Valencia, None; A. Misharin, None; E. M. Ruderman, AbbVie Inc., 5, Amgen Inc., 5, Eli Lilly and Co., 5, GlaxoSmithKline, 5, Novartis, 5, Janssen, 5, Sandoz, 5, Pfizer, Inc., 2, 5; C. M. Cuda, None; R. M. Pope, None; H. Perlman, Galvani, 5; D. R. Winter, None.

Galectin-3 Is a Regulator of 4-1BB/CD137 Activity and Associates with Outcome in Rheumatoid Arthritis.

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Session Information

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Background/Purpose: Galectin-3 (Gal-3) and the co-stimulatory T cell receptor and glycoprotein 4-1BB are both considered important in inflammation and immune responses. This had led to the investigation of Gal-3 inhibitors in fibrotic diseases and agonistic anti-4-1BB antibodies in cancer treatment. We and others have previously shown that galectins are capable of binding to receptors of the TNF superfamily thereby modulating inflammatory signals¹. Purpose: To investigate the interplay between 4-1BB and Gal-3 in rheumatoid arthritis (RA).

Methods: Gal-3 was measured in plasma samples from newly diagnosed, active and treatment-naïve RA (eRA) patients at baseline and after 3 months of aggressive treatment (the OPERA trial, n=97)² and plasma and synovial fluid samples from chronic RA (cRA) patients (n=17) by ELISA. The 28-joint disease activity score with CRP (DAS28CRP) and radiographic damage (i.e. total Sharp score (TSS)) were used to evaluate treatment outcomes over a 2-year period. Plasma samples from age and gender matched healthy controls (HC) (n=48) were also included. Fluorescence polarization analyses were used to evaluate the binding between 4-1BB and Gal-3. Synovial fluid mononuclear cells (SFMCs) from patients with chronic RA (n=8) were cultured for 24 hours, co-incubated with either 4-1BB, 4-1BB ligand, Gal-3, or a combination hereof.

Results: Plasma levels of Gal-3 were increased in eRA (mean: 8.1 ng/ml (CI: 7.6-8.6)) compared to HC (mean: 6.4 ng/ml (5.9-6.9)) ($p < 0.0001$). Gal-3 correlated with DAS28CRP at baseline ($p = 0.27$) ($p < 0.05$). A decrease in Gal-3 levels from baseline to 3 months were significantly correlated with high disease activity after 2 years of treatment evaluated by DAS28CRP ($p = 0.23$) and radiographic damage evaluated by DTSS (0-24 months) ($p = 0.26$) both ($p < 0.05$). After 3 months of intensive treatment, the plasma levels of Gal-3 were still elevated (mean: 8.3 ng/ml (7.8-8.7)) compared with HC ($p < 0.0001$). In cRA, Gal-3 levels in synovial fluid were tripled (mean: 30.9 ng/ml (18.3-43.5)) compared with levels found in plasma (mean: 9.1 ng/ml (7.8-10.4)) ($p < 0.01$). Gal-3 was capable of binding 4-1BB ($K_d = 1.43$ mM (1-1.86 mM)). A mutant Gal-3 (Gal-3 R186S) with severely reduced affinity for endogenous glycans, did not bind to 4-1BB, thus excluding that the 4-1BB and Gal-3 binding is influenced by a protein-protein interaction. Shedding of 4-1BB was increased by addition of Gal-3 ($p < 0.05$). When SFMC cultures were stimulated with a combination of 4-1BBL and Gal-3, the level of MCP-1 decreased by 50% compared to MCP-1 production from untreated cultures and cultures stimulated with either 4-1BBL or Gal-3 separately ($p < 0.05$).

Conclusion: In early RA patients, persistent high plasma levels of Gal-3 during the first 3 months of treatment were associated with lower disease activity and less radiographic progression after 2 years of treatment. Explaining some of these associations, Gal-3 was found to be a new binding partner to 4-1BB, modulating both shedding and function of this receptor in RA. These observations support that Gal-3 is implicated in RA disease pathology at least partly by interacting with the 4-1BB receptor.

References: 1. Nielsen MA et al. Rheumatology. 2016

2. Hørslev-Petersen K et al. Ann rheum Dis. 2013

Disclosure: M. A. Nielsen, None; T. W. Kragstrup, None; K. Stengaard-Pedersen, None; K. Hørslev-Petersen, None; M. L. Hetland, None; M. Østergaard, None; P. Junker, None; M. Hvid, None; U. Nilsson, Galecto Biotech AB, Sweden, 1, 2, 5; J. Stegmayr, None; H. Leffler, Galecto Biotech, 1, 2, 5; B. Deleuran, None.

Abstract Number: 2041

Serum Level of Soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1): A New Biomarker of Disease Activity in Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

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Session Time: 9:00AM-11:00AM

Background/Purpose: Triggering Receptor Expressed on Myeloid cells-1 (TREM-1) is a cell surface receptor expressed mainly on monocytes and neutrophils, known to amplify inflammatory response. We aimed to investigate whether serum level of soluble form of TREM-1 (sTREM-1), which reflects TREM1 activation, is associated with disease activity (DA) features and/or can predict response to biologic agent in rheumatoid arthritis (RA).

Methods: In this ancillary analysis of the Rotation or Change trial in which 300 patients with an inadequate response to a first line anti-TNF agent were randomized to receive either a 2nd anti-TNF treatment or a non-anti-TNF agent, baseline serum level of sTREM-1 was assessed using ELISA kit. Levels of sTREM-1 were compared by non-parametric tests for categorical variables as gender, body mass index (BMI) and Disease Activity Score 28-C reactive protein (DAS28-CRP). Spearman correlation coefficients were calculated between sTREM-1 level and DA measures (DAS28-CRP, CRP level, tender joint count (TJC), swollen joint count (SJC) and patient global assessment (PGA)). Univariable then multivariable logistic regression analyses were used to assess whether baseline sTREM-1 level was associated with EULAR response at 24 weeks (W24) in each group of treatment.

Results: sTREM-1 was available in 272 patients: 83.1% female, mean age (standard deviation) 56.9 (12.2) years, rheumatoid factor (RF) positive in 81.0% and anti-cyclic citrullinated peptide antibody positive in 81.6%. CRP level was >5mg/L in 59.8% patients and mean DAS28-CRP was 4.8 (1.0). W24 good or moderate EULAR response was achieved in 51.9% patients in 2nd anti-TNF group vs 66.9% patients in non-anti-TNF group (p=0.01). sTREM-1 was detectable in all patients with a mean level of 471.1(242.0) pg/mL, was higher in men (585.0 (240.1) pg/mL men, 447.9 (236.3) pg/mL women, p=0.0004) but was not associated with seropositivity status nor BMI. The mean sTREM-1 level was higher in patients with DAS28-CRP>5.1 (542.5 (279.6) pg/mL) than those with DAS28-CRP<5.1 (433.3 (212.5) pg/mL; p<0.01). sTREM-1 was also positively correlated with DAS28-CRP score (R=0.25, p<0.001), due to its correlation with CRP level (R=0.38, p<0.0001), but also to specific assessments of RA (PGA R=0.14 and SJC R=0.20, p<0.05). Mean baseline sTREM-1 levels did not differ between W24 good and moderate EULAR responders vs non-responders (459.9 (217.0) vs 487.6 (275.0)pg/mL overall, 450.8 (210.2) vs 502.7 (291.6) pg/mL in 2nd anti-TNF group and 466.7 (22.7) vs 466.6 (251.7) pg/mL in non-anti-TNF group, all p>0.05), nor between W24 good EULAR responders vs non-responders.

Conclusion: Serum sTREM-1 may be a new DA marker in this large cohort of RA patients. Interestingly, sTREM-1 did not only reflect systemic inflammation (i.e. CRP level) but also clinical joint inflammation, suggesting a specific role in RA synovitis pathogenesis. In this RA population with first anti-TNF treatment failure, sTREM-1 was not associated with W24 EULAR response to treatment.

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Immunophenotypic Analysis of Tissue-Resident Memory T Cells in Rheumatoid Arthritis

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Session Information

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Session Time: 9:00AM-11:00AM

Immunophenotypic analysis of tissue-resident memory T cells in rheumatoid arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease that is characterized by an inflammation of the synovial membrane and infiltration of immune cells including T cells into the joints. Recently, discovery of tissue-resident memory T cells (Trm), which reside in peripheral tissue rather than circulation, provides a new avenue in tissue-specific immunity. However, the phenotypes and role of Trm in the patients with RA has not been investigated yet. Thus, we examined the presence and characteristics of Trm in synovial fluid cells in patients with RA.

Methods: Cells with phenotypes of Trm was identified by the expression of CD3, CD8 and CD69 but not CD45RA in the synovial fluid mononuclear cells (SFMCs) of RA patients (n=19). The expression of markers for activation, tissue-residency, pro-inflammatory cytokines and cytotoxic molecules was analyzed with or without IL-15 stimulation.

Results: A substantial portion (mean 54.98%) of the CD8⁺CD45RA⁻ T cells in the SFMCs showed the phenotypes of Trm (CD3⁺CD8⁺CD45RA⁻CD69⁺), and the frequency was significantly increased after stimulation with IL-15 (54.98% vs 79.24%, p<0.0001). The expression of activation markers CD25 and CD38 was similar between CD69⁺ and CD69⁻ CD8 T cells. CD69⁺CD8 T cells had significantly higher expression of chemokine receptor CXCR6 compared to CD69⁻ CD8 T cells (38.2% vs 17.3 %, p=0.017). In addition, CD69⁺CD8 T cells showed higher expression of markers for Trm PD-1 (P<0.001) and CD101 (P=0.07) compared to CD69⁻ CD8 T cells. Proinflammatory cytokines IFN γ (0.15% vs 0.07%, p=0.0056) and TNF α (0.25% vs. 0.10%, p=0.0013) were upregulated in CD69⁺ CD8 T cells compare to their CD69⁻ counterparts. Furthermore, CD69⁺ CD8 T cells were shown to be positive for perforin (mean 35.14%) and granzyme B (mean 46.97%) and its expression was significantly increased after IL-15 stimulation.

Conclusion: These data suggest that the presence of Trm in synovial cells from patients with RA. These cells can produce cytotoxic molecules and thus possibly contribute to tissue damage in RA.

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Monocytes and Macrophages of Patients with Rheumatoid Arthritis Respond to Pathologically Increased Ionized Calcium with Proinflammatory Cytokine Production

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Session Information**Session Date:** Tuesday, October 23, 2018**Session Title:** Rheumatoid Arthritis – Etiology and Pathogenesis Poster III**Session Type:** ACR Poster Session C**Session Time:** 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease characterized by synovitis and periarticular bone erosion. Bony erosions and cell necrosis might lead to a local increase in the concentration of extracellular calcium. We have shown in previous studies that increased extracellular calcium activates the Nlrp3 inflammasome of monocytes. Aim of the study was to evaluate the contribution of extracellular calcium to the pathogenesis of rheumatoid arthritis.

Methods: Monocytes from 42 RA patients fulfilling the EULAR/ACR 2010 diagnostic criteria and from 24 age-matched controls were isolated from the peripheral blood using magnetic separation (Miltenyi). Monocytes were differentiated into macrophages for 7 days using human serum. Synovial fluid mononuclear cells (SFMC) and peripheral blood mononuclear cells (PBMC) were isolated using density gradient centrifugation. Cells were stimulated with lipopolysaccharide (LPS) and increasing calcium concentrations (0.9-1.7 mM), and cytokine concentrations were determined in the supernatant by ELISA. Th17 cells were expanded in vitro using a co-culture of CD4⁺ T cells and LPS-activated monocytes. Arthritis was induced in 18 DBA/1 mice using collagen (CIA), 5 DBA/1 mice were used as controls.

Results: The ionized calcium concentration is increased in the synovial fluid of RA patients (n=22) compared to control patients with psoriatic arthritis/ankylosing spondylitis (n=16) (1.1 mM vs. 0.95 mM, p=0.0004) while the ionized calcium concentration in the serum is not different. Blood monocytes from RA patients responded with higher IL-1b, IL-1a, IL-18 and TNF production to an increased calcium concentration (1.7 mM) compared to healthy controls. Importantly, RA monocytes already responded to a calcium concentration of 1.1 mM with a high production of IL-1b, IL-1a and IL-18 whereas control monocytes did not produce cytokines in response to this calcium concentration. SFMCs from RA patients produced even more IL-1b in response to calcium compared to the corresponding blood PBMCs. Monocyte-derived macrophages from RA patients also secreted more IL-1b in response to an increased calcium concentration as well as mouse monocytes/macrophages in the collagen-induced arthritis mouse model. Calcium-induced monocytic IL-1b production correlated with the CIA disease score (r=0.704, p=0.001). The in vitro expansion of Th17 cells, which is in part dependent on monocytic IL-1b production, is also increased when a high calcium concentration is present.

Conclusion: The ionized calcium concentration is increased in the synovial fluid of RA patients, and monocytes/macrophages from RA patients and CIA mice respond with a higher cytokine production to ionized calcium which in turn leads to an increased Th17 expansion. This might point to a contribution of ionized calcium in the pathogenesis of RA.

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Abstract Number: 2044

Impaired microRNA Processing in Neutrophils from Rheumatoid Arthritis Patients Confers Their Pathogenic Profile. Modulation By Biological Therapies

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Session Information**Session Date:** Tuesday, October 23, 2018**Session Title:** Rheumatoid Arthritis – Etiology and Pathogenesis Poster III**Session Type:** ACR Poster Session C**Session Time:** 9:00AM-11:00AM

Background/Purpose: Neutrophils are the most abundant cells in synovial fluid, having all the features of activated cells in rheumatoid arthritis (RA), including prolonged cell survival, increased migratory capacity and the ability to produce high levels of inflammatory mediators. MicroRNAs (miRNA) have recently emerged as a new class of modulators of gene expression, regulating inflammation, degradation of extracellular matrix and invasive behavior of the resident cells in RA.

Purpose: 1) to investigate the miRNA expression pattern in rheumatoid arthritis (RA) neutrophils and its contribution to their pathogenic profile and 2) to analyze the effect of specific autoantibodies or inflammatory components and its modulation by biological therapies.

Methods: Neutrophils were isolated from peripheral blood and paired synovial fluid samples of 40 RA-patients and 40 healthy donors. A microRNA array was performed using nCounter technology. Healthy-neutrophils were treated *in vitro* with antibodies to citrullinated protein antigens (ACPAs) isolated from RA patients and TNF- α or IL-6. *In vitro* treatments of RA-neutrophils with tocilizumab (TCZ) or infliximab (IFX) was carried out. Transfections with the pre-miRNAs miR-223, miR-126 and miR-148 were performed in RA neutrophils. DICER silencing using lentiviral transfection in neutrophils was further carried out.

Results: RA-neutrophils showed a global downregulation of miRNAs and genes involved in miRNA biogenesis, alongside with an upregulation of mRNA targets related to survival, migration and inflammation. Decreased levels of miRNAs and DICER correlated with autoimmunity, inflammation and disease activity. ACPAs and TNF- α decreased the expression of numerous miRNAs and their biogenesis-related genes, and increased their mRNA targets. IFX reversed those effects. Transfections with pre-miRNAs-223, -126 and -148a specifically modulated genes regulating inflammation, survival and migration. DICER depletion influenced the neutrophils' inflammatory profile.

Conclusion: 1) RA-neutrophils exhibit a global low abundance of miRNAs induced by autoantibodies and inflammatory markers, and responsible for their pathogenic activation. 2) miRNA biogenesis is significantly impaired in RA-neutrophils and further associated with a deeper downregulation of miRNAs related to inflammation, migration and survival of synovial neutrophils. 3) Biological therapies such as anti-TNF- α restore miRNA levels, minimizing the inflammatory profile of neutrophils. Supported by the Minister of Health (ISCIII, CP15/0158, PI17/01316, PI15/01333, RIER RD16/0012/0015) cofinanced with FEDER funds.

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Abstract Number: 2045

Specific Anti-Citrullinated Protein Antibodies Profiles Are Associated with Rheumatoid Arthritis Related Interstitial Lung Disease

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Session Information

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Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

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Session Time: 9:00AM-11:00AM

Background/Purpose: The identification of peripheral blood markers of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) may facilitate an earlier diagnosis and provide insight regarding the pathogenesis of this severe disease complication. Antibodies directed against citrullinated fibrinogen (AhFibA) and the α 36-50Cit and β 60-74Cit peptides exhibiting its immunodominant epitopes are associated with radiographic damages in RA but have not been yet studied in RA-ILD. The aim of this study was to characterize the profile of anti- α 36-50Cit and anti- β 60-74Cit subfamilies of AhFibA in RA-ILD.

Methods: Anti-CCP2, AhFibA and their anti- α 36-50Cit and anti- β 60-74Cit subfamilies were assayed by ELISA in a population of RA-ILD (n=75), RA-noILD (n=75) patients and in a control group of idiopathic pulmonary fibrosis (IPF) patients (n=75). RA was diagnosed according to ACR 1987 and/or ACR/EULAR 2010 criteria. ILD status was assessed with High-resolution computed tomography (HRCT) in all the patients.

Results: Using a 98.5% specificity level, anti-CCP2, AhFibA and their anti- α 36-50Cit and anti- β 60-74C its subfamilies were detected in 66%, 65%, 36% and 62% of RA patients, respectively whereas they were not detected in the majority of IPF patients (1%) (Table 1). No significant difference was observed for the sensibility of the different antibodies for the identification of ILD among RA patients. Anti-CCP2, AhFibA and anti- β 60-74Cit titers were significantly lower in RA-ILD patients compared to RA-noILD patients (Table 1) whereas there was a trend for higher anti- α 36-50Cit autoantibodies ($P=0.145$; ns). Within AhFibA positive RA patients, anti- α 36-50Cit were more frequently observed in those having ILD (66% vs 33, $P=0.013$). In addition, anti- α 36-50Cit antibody titers correlated with those of AhFibA only in RA-ILD patients (Figure 1).

Conclusion: Specific qualitative and quantitative profiles of anti- α 36-50Cit and anti- β 60-74Cit auto antibodies subfamilies of AhFibA are associated with the occurrence of ILD in the context of RA.

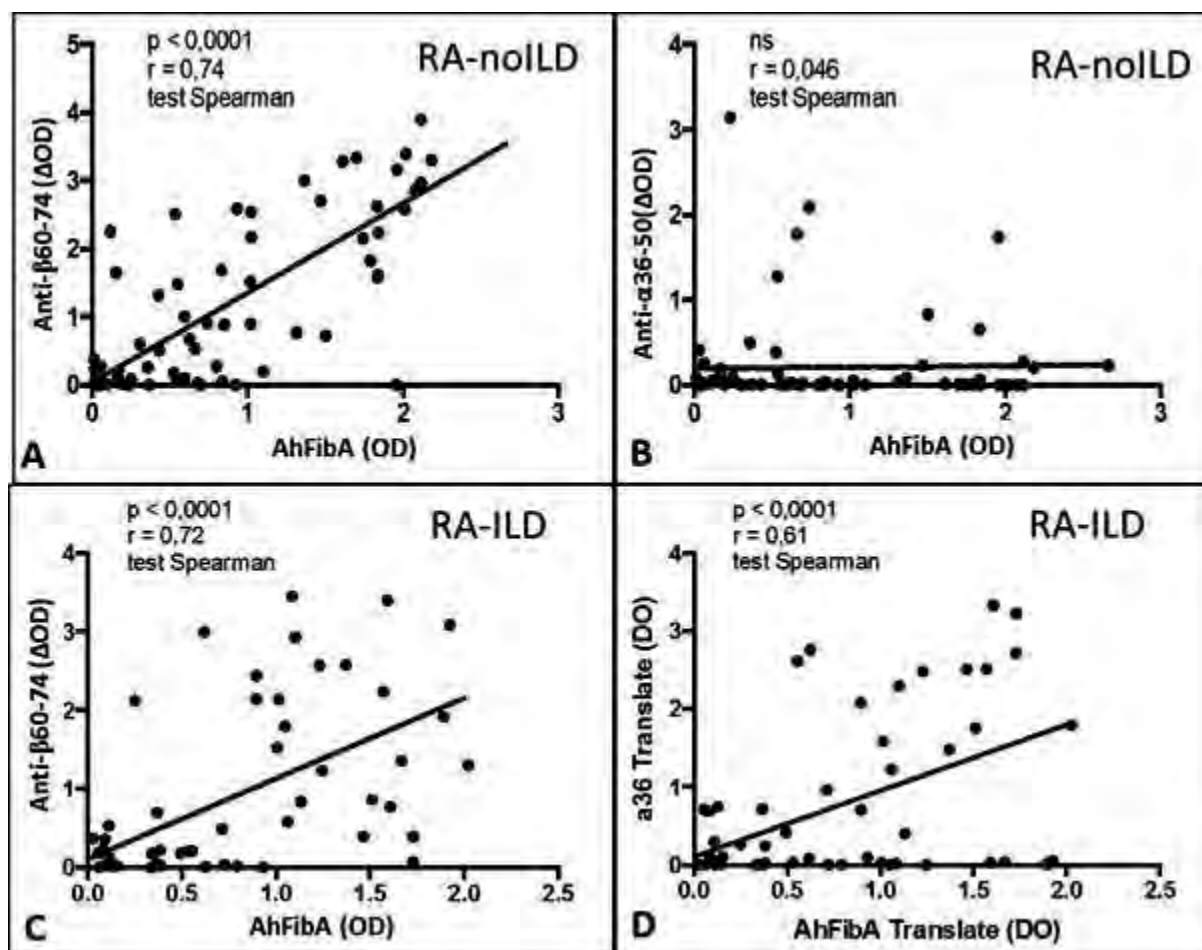


Figure 1. Correlation between AhFibA titers with anti- β 60-74Cit or anti- α 36-50Cit autoantibody titers in RA-noILD population (A and B) and in RA-ILD population (C and D).

Table 1. Distribution of different autoantibodies in the 3 groups (RA-ILD, RA-noILD, IPF). Positivity rate is expressed in number of patients (%), Titers are expressed as median (min-max).

	RA-ILD (n=75)	RA-noILD (n=75)	IPF (n=75)	P value (RA-ILD vs RA-noILD)
Positivity (n,%)				
- anti CCP2	46 (61.3)	53 (70.6)	1 (1.3)	ns
- AhFibA	43 (57.3)	54 (72.0)	1 (1.3)	ns
- anti- β 60-74Cit	42 (56.0)	51 (68.0)	2 (2.6)	ns
- anti- α 36-50Cit	31 (41.3)	23 (30.7)	1 (1.3)	ns
Titers,				
- anti CCP2 (U/mL)	327 (5-30669)	378 (5-36582)	5 (5-539)	0.028
- AhFibA (DO)	0.34 (0.00-2.02)	0.60 (0.00-2.66)	0.00 (0.00-0.53)	0.025
- anti- β 60-74Cit (Δ DO)	0.18 (0.00-3.45)	0.51 (0.00-4.64)	0.00 (0.00-0.11)	0.047
- anti- α 36-50Cit-fib (Δ DO)	0.02 (0.00-3.3)	0.01 (0.00-3.14)	0.00 (0.00-0.09)	ns
Positivity among AhFibA+ (n, %)	n=43	n=54	n=1	
- anti- β 60-74Cit	32 (74.4)	46 (85.2)	0	0.21
- anti- α 36-50Cit	26 (60.4)	18 (33.3)	0	0.013

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Abstract Number: 2046

Serum Immunoglobulin G Targets Citrulline-Containing Immunoglobulin G Peptides in Rheumatoid Arthritis Patients Who Test Positive for Rheumatoid Factor and Anti-Cyclic Citrullinated Peptide Antibodies

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Session Information

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Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

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Background/Purpose: Rheumatoid arthritis patients produce a variety of anti-citrullinated protein antibodies (ACPAs) as well as antibodies that bind homocitrullinated and malondialdehyde-acetaldehyde adducted proteins leading to the theory that rheumatoid arthritis antibodies target a range of post-translationally modified proteins. Further, protein modifications may contribute to the loss of immune tolerance in rheumatoid arthritis. However, most rheumatoid arthritis patients also generate antibodies against immunoglobulin G (IgG), called rheumatoid factor (RF), with a high incidence of co-positivity for RF and anti-cyclic citrullinated peptide (CCP) antibodies. While native proteins can be targeted in rheumatoid arthritis, their citrullinated counterparts are often preferentially targeted. IgG is citrullinated in rheumatoid arthritis, but it is not known if native, homocitrullinated, or citrullinated IgG is preferentially bound by autoantibodies. The purpose of this study is to determine if antibodies in rheumatoid arthritis bind to citrulline-containing, homocitrulline-containing, and/or native IgG peptides.

Methods: A high density peptide array was designed to include every possible 12 amino acid peptide in the constant region of the heavy chain of human IgG1, IgG2, IgG3, and IgG4. Serum from control as well as CCP+RF+, CCP-RF+, CCP+RF-, and CCP-RF- rheumatoid arthritis subjects (n=12) was obtained from our biorepository and subjected to the array. Average raw signal intensity for binding of serum IgM and IgG for each category of rheumatoid arthritis subjects was compared to controls to generate a fold increase value for each peptide. Native and citrulline-containing versions of 3 peptides with very high serum IgG binding and also high homology among IgG isotypes were used to detect serum IgG binding for control and CCP+RF+ rheumatoid arthritis subjects (n=40) by enzyme linked immunosorbent assay (ELISA). ELISA results were compared by t test with p<0.05 considered significant.

Results: RF+ subjects (RF+CCP- and RF+CCP+) demonstrate a small elevation in binding of IgM to many native, homocitrulline-containing, and citrulline-containing peptides of the constant region of IgG1, IgG2, IgG3, and IgG4. Serum from the CCP+RF+ group, and no other rheumatoid arthritis group, demonstrated high IgG binding predominantly to citrulline-containing peptides in the constant region of IgG1, IgG2, IgG3, and IgG4. When measured by ELISA, CCP+RF+ subjects had more IgG binding than controls to only 1 of the 3 native IgG peptides, whereas CCP+RF+ subjects had more IgG binding than controls to all 3 of the citrulline-containing versions of the same IgG peptides. Moreover, for the 1 native peptide with increased binding in CCP+RF+ subjects compared to controls, the binding was 3x higher to the citrulline-containing version of that peptide than the native version.

Conclusion: IgG from CCP+RF+ rheumatoid arthritis patients has high binding to citrulline-containing IgG peptides suggesting that rheumatoid factor of the IgG isotype may be an ACPA. These findings support a unified view of autoantibodies in rheumatoid arthritis and may explain how tolerance is broken against IgG.

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Synovial Fluid Cytokines /Chemokines and Proteins from the Knees of Symptomatic RA and OA Patients Which Correlate with the Magnitude of the Inflammatory Response As Measured By Synovial Fluid WBC Levels

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Synovial fluid (SF) provides nutritional support for cartilage and contains numerous catabolic and anabolic cytokines, chemokines and proteins. The precise role of these proteins in joint inflammation and cartilage injury in RA and OA, however, are not well understood. Advances in fluoresce bead based multiplex technology allows the measurement of multiple proteins from volumes < 200 mcL. Easier access to SF can allow investigators to identify patient specific wet biomarkers since most of these key regulatory cytokines in the peripheral blood correlate poorly with those measured simultaneously in the SF.

Table 1: Patient Demographics

	RA	OA
Number of SF Samples	39	13
Number of Patients	26	8
Mean Age	59	64
Gender (F vs M)	19 (73%)/ 7 (27%)	5 (62%)/3 (38%)
% on Pred/DMARD or Biologics	62%	0
CRP Normal <0.4		
Range	0.1 to 9.67	0.1 to .8
Mean	1.6	0.3
ESR Normal <20		
Range	3 to 95	2 to 21
Mean	31	15
SF WBC (cells/mm ³)		
Range	11-65,000	0-510
Mean	6,334	134
SF Samples with WBC < 300	12	13
SF Samples with WBC 300- 10,000	20	1
SF Samples with WBC > 10,000	5	0

Table 2: Comparison of Synovial Fluid Biomarker Levels Between RA and OA Patients

RA Levels > OA Levels	RA (pg/mL)		OA (pg/mL)		P-Value
	Mean	Range	Mean	Range	
MMP 9	21k	0 - >75k	6k	0 - >75k	0.03
MMP 8	18k	0 - >56k	7k	0 - >56k	0.05
PIGF	525	74 - 2k	117	54 - 198	0.004
IL-8	274	7 - 1k	15	6 - 25	0.03
IL-17	10	0 - 91	ND	N/A	0.04
IL-10	5	0 - 36	1	0 - 3	0.03
OA Levels > RA Levels	RA (pg/mL)		OA (pg/mL)		P-Value
	Mean	Range	Mean	Range	
Cystatin C	1.4M	411k - 6.8M	8.2M	1.4M - 18.9M	0.00005
Serpin E1	30k	3k - 118k	46k	20k - 114k	0.02
IGFBPp1/IGFP7	17k	9k - 54k	22k	15k - 53k	0.04
EMMPRIN/CD 147	15k	6k - 39k	21k	13k - 47k	0.02
DKK-1	2k	942 - 3k	3k	2k - 4k	0.02

Methods: We performed 54 knee aspirations from 26 symptomatic RA and 8 primary OA patients using an external pneumatic compression device and ultrasound guidance. SF was transferred into heparin containing tubes with WBC levels counted by hemacytometer, then samples were centrifuged and cryopreserved within 60 minutes. Levels of 54 separate cytokines/chemokines and proteins were quantitated in batches of 20 using Luminex or ELISA assays. A significant correlation between log-transformed cytokine levels and WBC counts was determined by a $p < 0.05$ using Pearson's product moment between log 10 concentration of specific cytokines and SF WBC levels whereas between group differences was performed using R and SAS programs.

Results: Demographic and clinical features are presented in Table 1. 92% of the OA samples had SF WBC levels < 300 cells/mm³ as did 31% of RA patients. 93% of this RA cohort were receiving prednisone, DMARD or a biologic; yet all had symptomatic knee pain. There was a significant correlation, $p < 0.05$, between all RA and OA patient's SF 10 WBC counts and log concentration of IL-1, IL-1ra, IL-6, MMP-3, MMP 8 and MMP-9 levels, but not with the other cytokines, chemokines, and proteins. Table 2 displays those specific SF proteins which were higher in either RA or OA patients whereas 43 cytokine/chemokine/protein levels did not differ statistically between both groups of patients.

Conclusion: Sufficient SF volumes were obtained using pneumatic external compression and US to measure 54 separate cytokines, chemokines and proteins from cryopreserved samples from all RA and OA patients using multiplex assays. There was a significant correlation between SF WBC levels and 6 different cytokines, chemokines and proteins, but not in 43 others; yet some biomarkers were higher in OA than RA SF samples. Despite SF WBC < 300 levels in OA and well controlled RA patients, the pro-inflammatory catabolic SF profile suggests an ongoing risk for continued cartilage injury.

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Abstract Number: 2048

In Vitro Proof-of-Concept of Pathobiology-Guided Therapy in Immune Mediated Inflammatory Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

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Background/Purpose: Immune mediated inflammatory arthritis are very heterogeneous diseases including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and spondyloarthritis (SpA). The available biological and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) target very different components of the disease processes. However, how to choose the right treatment for the individual patient is not clear. Characterization of the pathobiological subtypes of immune mediated inflammatory arthritis could provide more specific treatment approaches for each disease. E.g., RA has been proposed to consist of the three synovial phenotypes 1) "lymphocyte", 2) "macrophage", and 3) "fibroblast" and only a subgroup of patients has erosive disease. The objective of this study was to study the effects of different DMARDs on different synovial cell subsets using several human ex vivo models of immune mediated inflammatory arthritis.

Methods: Synovial fluid was obtained from a study population consisting of patients with active rheumatoid arthritis (RA) or peripheral spondyloarthritis (SpA) with at least one swollen joint. The DMARDs used in this study are shown in Table 1. Synovial fluid mononuclear cells (SFMCs) containing primarily synovial monocytes and lymphocytes were cultured for 48 hours (here termed the "*macrophage-lymphocyte model*") and assessed for secretion of monocyte chemoattractant protein-1 (MCP-1) (n=14). Fibroblast-like synovial cells (FLSs) were co-cultured with autologous peripheral blood mononuclear cells (PBMCs) (here termed the "*fibroblast model*") and assessed for secretion of MCP-1 (n=6). SFMCs were cultured for 21 days (here termed the "*osteoclast model*") and assessed for secretion of tartrate-resistant acid phosphatase (TRAP) (n=10). MCP-1 and TRAP were measured by commercially available ELISA kits.

Results: *The macrophage-lymphocyte model;* In SFMCs cultured for 48 hours, all DMARDs except anakinra decreased the production of MCP-1 (all $P < 0.05$). *The osteoclast model;* In SFMCs cultured for 21 days, only the two inhibitors of TNF α adalimumab and etanercept decreased the secretion of TRAP by roughly 25% ($P < 0.01$, $P < 0.001$). *The fibroblast model;* In FLS-PBMC 48 hour co-cultures, only tocilizumab ($P < 0.001$) and the two Janus kinase inhibitors tofacitinib and baricitinib ($P < 0.05$ and $P < 0.05$) decreased the production of MCP-1 by around 50%.

Conclusion: This study reveals differential effects of different DMARDs on different synovial cell subsets using human ex vivo models of immune mediated inflammatory arthritis. Most DMARDs were effective in the "*macrophage-lymphocyte model*", only the two TNF α inhibitors were effective in the "*osteoclast model*", whereas tocilizumab, tofacitinib and baricitinib were superior in the "*fibroblast model*". Studies like this could help guide future studies of personalizing DMARDs to treat immune mediated inflammatory arthritis.

Table 1. xxx

Generic name	Adalimumab	Etanercept	Tocilizumab	Anakinra	Abatacept	Ustekinumab	Secukinumab	Tofacitinib	Baricitinib
Brand name	Humira®	Enbrel®	RoActemra®	Kineret®	Orencia®	Stelara®	Cosentyx®	Xeljanz®	Olumiant®

Disclosure: M. A. Nielsen, None; B. Deleuran, None; T. W. Kragstrup, None.

Abstract Number: 2049

Expression and Function of a Novel Citrullinated Form of Interleukin 6 in Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by synovial hyperplasia, progressive joint destruction and the presence of anti-citrullinated peptide antibodies (ACPAs) in sera. Citrullination, a post-translational modification of arginine to citrulline by peptidylarginine deiminase (PAD), contributes to the development of RA. We and others have shown that citrullination can modulate biological roles of key inflammatory molecules in RA. Interleukin 6 (IL-6) is highly expressed in synovial fluids (SFs) and sera of RA patients and plays an important role in RA synovitis. But no information is yet available regarding whether IL-6 is citrullinated in RA.

Methods: Recombinant human (rh) IL-6 was citrullinated by rhPAD4. Liquid chromatography-mass spectrometry (LC-MS) was performed to verify citrullination of IL-6. The role of citrullinated IL-6 (citIL-6) in RA fibroblast-like synoviocytes (FLS) proliferation and migration was determined using the IncuCyte S3 live cell analysis system and scratch wound assays. We performed monocyte (MN) chemotaxis assays using a modified Boyden chamber to examine the effect of citIL-6 on MN migration. To evaluate the arthritogenic properties of citIL-6 *in vivo*, noncitrullinated IL-6 (noncitIL-6) or citIL-

6 was injected into mouse knees and joint circumference was measured at 0 hour and 24 hours after injection. We also identified the presence of citIL-6 and ACPAs against citIL-6 in RA SFs and sera by performing Western blotting and immunodot blot assay, respectively. FLS were stimulated with citIL-6 or noncitIL-6 to examine the phosphorylation of downstream signaling molecules by Western blotting without the addition of exogenous IL-6 receptor (IL-6R).

Results: LC-MS confirmed that all of the arginines in rhIL-6 can be citrullinated by rhPAD4. Both scratch wound assay and live cell imaging analysis showed that FLS proliferation and migration rates were significantly higher in the citIL-6 group compared to the noncitIL-6 group after 24 hours. We also found that citIL-6 induced more MN migration than noncitIL-6 ($p<0.001$). The change in mouse knee circumference with citIL-6 injection was approximately 7-fold higher than that with noncitIL-6 injection (0.90 ± 0.27 mm vs 0.13 ± 0.13 mm; $n=14$; $p<0.05$), indicating that citIL-6 induced much more severe inflammation in mouse knees compared to noncitIL-6. Western blot assays showed that citIL-6 was present in the SFs from RA. Immunodot blot assay showed that sera from RA patients but not healthy controls contained ACPAs react with citIL-6 but not noncitIL-6. CitIL-6, without exogenous IL-6R, upregulated phosphorylation of Erk1/2, Jnk, and Stat3 in RA FLS while noncitIL-6 did not.

Conclusion: IL-6 can be citrullinated by PAD, citIL-6 was present in RA SFs, and citIL-6 ACPAs were present in RA sera. CitIL-6 may play an important role in the pathogenesis of RA by inducing proliferation as well as migration of FLS and recruiting monocytes via a special mechanism that is different from noncitIL-6.

Disclosure: C. Lu, None; R. A. Ohara, None; P. L. Campbell, None; Y. Du, None; W. A. Stinson, None; J. Hervoso, None; E. Cealey, None; D. Fox, None; M. A. Amin, None.

Abstract Number: 2050

B and T Cell Phenotypes of First Degree Relatives of RA Patients in an Indigenous North American Cohort

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: First degree relatives (FDR) of patients with RA are known to have approximately 4 times increased risk of developing RA and prevalence of RA is increased in Indigenous North Americans (INA) compared to Caucasian populations. To gain insight into immune phenotypes in those with increased risk of developing RA, we phenotyped B and T cell subsets in an INA cohort of FDR, RA patients and healthy controls (HC).

Methods: PBMC's were isolated from FDR's ($n=10$), RA patients ($n=8$) and HC ($n=6$) of INA ethnicity. B cell phenotyping (CD19, CD20, CD27, CD80, CD86, HLA-DR, Ki-67) and CD4 T cell phenotyping (CD3, CD4, CD45RA, CCR7, CXCR5, CXCR3, CCR2, PD-1, ICOS, Ki-67, HLA-DR) was performed by flow cytometry.

Results: FDR's had increased frequency of CD20+27+ B cells (23.1% [IQR 13.8-31.1]) compared to RA patients (10.3% [8.3-12.0]) and seronegative controls (14.4% [9.5-17.9]) shown in Figure 1. The median fluorescence intensity (MFI) of CD27 in FDR was increased compared to HC (1393.5 [IQR1268.1-1530.4] vs 1067.0 [880.5-2334.8]). There were no differences in the expression of CD80, CD86, HLA-DR or Ki-67 amongst memory (CD20+27+) and naïve (CD20+27-) B cell subsets.

Distribution of CD4 T cell subsets (naïve, central memory, effector and terminal effector) between FDR, RA patients and HC was relatively similar. FDRs had double the frequency of PD-1 positive terminal effector memory (TEMRA) cells (9.7% [IQR 2.0-22.6]) compared to HC (4.4% [2.3-7.1]) shown in Figure 2. There was no difference in frequency of CXCR3, CCR2, Ki-67, ICOS or HLA-DR in these subsets amongst FDRs, HCs and RA patients.

Because CXCR5/PD-1+ and CXCR5+/PD-1+ CD4 T cells are efficient in B cell stimulation, we also explored frequency of these T peripheral helper (Tph) and T follicular (Tfh) subsets amongst FDR, HC and RA patients. The Tph subset in the RA patients demonstrated increased ICOS (31.1% vs. 8.5%), Ki-67 (14.1% vs 5.5%), CCR2 (29.2% vs 22.0%), and HLA-DR (13.1% vs 8.0%) compared to FDR's. All participants had similar frequencies of circulating Tfh and Tph subsets.

Conclusion: We found increased frequency of circulating memory B cells in the FDR population compared to unrelated controls. Whether these memory B cells are autoreactive in nature is not yet known. Increased PD-1 positive TEMRA

cells in the FDR population, similar to the RA patients, suggests ongoing antigen experience and CD4 T cell activation in this group of people. Further characterization of regulatory mechanisms which prevent this high-risk group from developing autoimmune disease will be important in understanding the balance between pre-clinical autoimmunity and autoimmune disease.

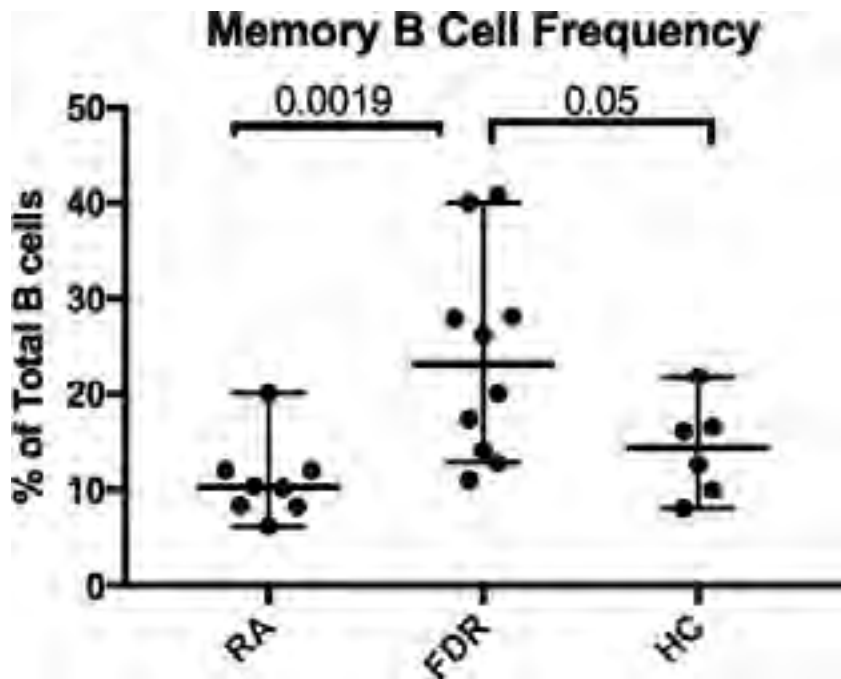


Figure 1.

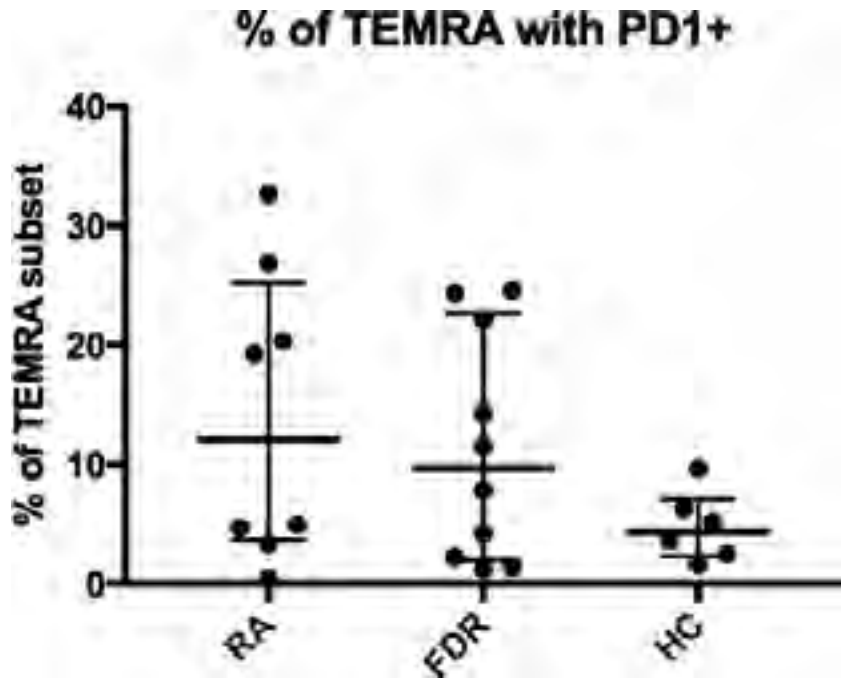


Figure 2.

Disclosure: S. Tanner, None; C. Zhang, None; I. Smolik, None; A. Marshall, None; H. El-Gabalawy, None.

Rheumatoid Factor Peptide Expression By Quantitative Proteomics Delineates Responsive and Resistant Clones after Treatment of Early Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

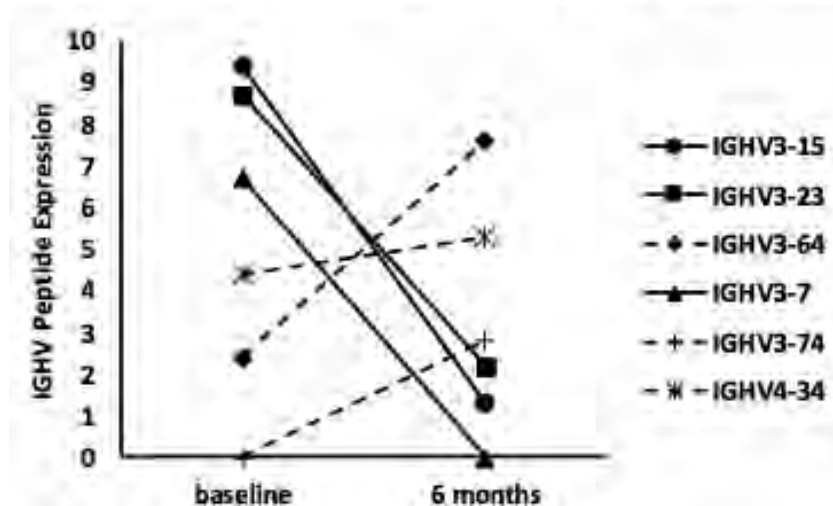
Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid factors (RFs) are associated with disease activity and joint damage in rheumatoid arthritis (RA) and thought to play a pathogenic role in disease. RFs have been measured for decades by nephelometry and/or solid-phase immunoassay, but these techniques are unable to resolve RF immunoglobulin heavy-chain variable (IGHV) composition at the level of the serum proteome. Here, we have performed the first quantitative mass spectrometry (MS) analysis of serum (secreted) IgH-RF repertoires in RA patients and reveal dynamic patterns of RF production after treatment.

Methods: Serum IgM-RFs from 16 patients with RF-positive newly diagnosed RA were purified by immunoprecipitation (1). IgH-RF V-region peptides were sequenced by LC-MS/MS followed by combined *de novo* amino acid sequencing and database matching using Peaks 8.0 software to determine IGHV composition. Full-scan multiple reaction monitoring (MRM) was used to quantitate expression of individual IGHV sub families in paired serum samples at baseline and after 6 months of tDMARD (n=9) or TNFi (n=7).

Results: High resolution MS sequencing of serum IgH-RFs demonstrated shared germline-encoded oligoclonal patterns with convergent usage of IGHV1-3, 1-69, 3-15, 3-23, 3-64,3-7, 3-74, 4-34, and 5-51 subfamilies, although each patient had an individual IgH-RF peptide expression landscape. Six-month serum RF levels were decreased in 15/16 patients by routine nephelometry and correlated with falling IgH-RF expression levels by MRM/MS ($P < 0.05$ by Spearman rank). Molecular profiling of IgH-RFs by MS proteomics revealed that RF responses in each patient comprised two clonal populations: treatment-responsive (classified as a reduction of $>30\%$ in expression levels), and treatment-resistant (classified as steady, an increase of $>30\%$, or newly emergent) (Figure). Commensurate with global reductions in RF levels after treatment, responsive IgH-RF clones comprised over 2/3rds of the RF clonal repertoire. On the other hand, patients co-expressed sizable numbers of resistant IgH-RF clones indicating molecular heterogeneity of RF responses.

Figure. Responsive (—) and resistant (---) IgH-RFs post-tDMARD



Newly emergent (de novo) clonal populations in treated patients were encoded by IGHV3 subfamilies not expressed at baseline.

Conclusion: RF production in RA is a dynamic, oligoclonal process comprising shared sets of IGHV subfamilies across unrelated patients. While most IgH-RF clonal populations are reduced by conventional therapies, the finding of resistant IgM-RF clones may reflect their production in protected niches in joints or tissues; or differences in selection and clonal expansion by immune complexes. MS-based quantitative proteomics of serum RFs offers a powerful approach for molecular characterisation of these prototypic diagnostic and pathogenic biomarkers in RA.

1. Wanget al., Arthritis Rheumatol. (2018) <https://doi.org/10.1002/art.40539>

Disclosure: J. J. Wang, None; W. Murray-Brown, None; A. Colella, None; M. D. Smith, None; T. Chataway, None; J. Walker, None; W. H. Robinson, None; M. D. Wechalekar, None; T. Gordon, None.

Abstract Number: 2052

Immune Therapy of Rheumatoid Arthritis Patients with a Microbiome-Derived, Self/Non-Self Peptide Induces Clinically Relevant Immune Tolerance Pivoting on Immune Checkpoint-Expressing, Therapy-Induced Tregs

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: We have previously reported in patients with RA abnormal inflammatory T cell responses to an E. coli peptide (dnaJP1) which shares homology with the HLA “shared epitope” as well as with human heat shock protein dnaJ. We hypothesised that these abnormal immune responses are part of pathogenesis, as they may lead to an imbalance in the microbiome and a consequent loss of systemic immune tolerance, through a multistep molecular mimicry mechanism. In an ongoing clinical development program, in which we have completed Phase I and IIa clinical trials and are approaching Phase IIb, we have shown that induction of immune tolerance to dnaJP1 results in clinical improvement in RA and thus represents a promising therapeutic intervention, conceptually similar to the induction of tolerance to an antigen in allergy. Here, we employed a combination of high dimensional cytometry and ngRNA sequencing approaches to dissect the mechanisms associated with clinically relevant induction of immune tolerance.

Methods: Peripheral Blood Mononuclear Cells (PMBCs) were obtained at the end of the Phase II trial (Day168), from clinical responders treated with dnaJP1 (n=6) and clinical non-responders treated with placebo (n=10). The T cell compartment was studied by flow cytometry using specifically designed antibody panels. Flow cytometry results were then analysed by clustering with Multi-Dimensional Automated Reduction and Visualization (MARVis). PD-1 positive and negative Tregs, and Teff were sorted viable and subject to NGRNA seq, which was analysed by gene ontology.

Results: Analysis of the T cell immunomes of dnaJP1 responders and placebo non-responders revealed a subset of CD4+FoxP3+ regulatory T (Treg) cells exclusively in dnaJP1 responders that displayed a higher expression of the inhibitory immune checkpoint receptor, PD-1. The expression of PD-1 contributes to an enhancement of the tolerogenicity of this Treg cell subset by upregulating the production of signature anti-inflammatory cytokines such as TGFβ. In addition, we observed a corresponding reshaping of the effector T (Teff) cell compartment in which the expression of pro-inflammatory cytokines such as IL-17A and IFNγ was downregulated. Importantly, epitope-specific immunotherapy also induced a subset of active antigen-experienced memory T cells (CD4+CD45RO+CD69+) which sustains the tolerogenic immune response by secreting TGFβ. Strikingly, ngRNAseq data confirmed a dichotomous effect of therapy on Treg and Teff subsets, with a prevalence of inflammatory pathways in PD1- Treg, including TNFα production, while, conversely, PD1+ Treg were bona-fide tolerogenic. Teff in RA patients who responded to therapy were characterised by a prevalence of memory and pro-apoptotic pathways.

Conclusion: Our data suggest the presence of a “molecular rheostat” between inflammation and tolerance, which pivots on an unique subset of Treg cells in which the immune checkpoint protein, PD-1 is switched on by the immune therapy.

Disclosure: S. Albani, None; J. Y. Leong, None; T. van den Broek, None.

Global Mirna Expression and Transcriptomic Profiling of Monocytes from RA Patients

Marzena Ciechomska¹, Krzysztof Bonek², Piotr Glusko², Marzena Olesinska², Bartosz Wojtas³, Vladimir Benes⁴ and Wlodzimierz Maslinski¹, ¹Department of Pathophysiology and Immunology, National Institute of Geriatrics Rheumatology and Rehabilitation, Warsaw, Poland, Warsaw, Poland, ²Department of Rheumatology, National Institute of Geriatrics Rheumatology and Rehabilitation, Warsaw, Poland, Warsaw, Poland, ³Nencki Institute of Experimental Biology, Warsaw, Poland, Warsaw, Poland, ⁴The European Molecular Biology Laboratory, Heidelberg, Germany, Heidelberg, Germany

Session Information

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Session Time: 9:00AM-11:00AM

Background/Purpose: Infiltration of the synovium by mononuclear cells, including monocytes, is one of the main features of RA. Monocytes are the first immune cells which migrate from blood to the site of inflammation leading to tissue destruction due to enhanced pro inflammatory cytokines secretion and overall RA development. It has been shown that abnormalities in miRNA expression are related to inflammatory molecules production by mononuclear cells, however miRNAs have never been fully analysed in monocytes population. The aim of this study was to explore global miRNA and transcriptomic profiling of monocytes from RA patients to predict which aberrantly expressed miRNA can negatively modulate inflammatory molecules.

Methods: Total RNAs from CD14+ monocytes of 12 RA and 10 healthy control (HC) were isolated. The samples were barcoded using Small-RNA-Library-Set for miRNA and simultaneously for RNA-Seq transcriptomic profiling using Illumina HiSeq 2000 platform. Hierarchical clustering was performed to select upregulated miRNAs and significantly downregulated transcripts which are predicted to be the putative target gene of miRNAs. Following computational analysis, selected miRNAs-mRNA candidates were validated using qPCR. Finally, the miRNA candidate was correlated (using Spearman analysis) with clinical parameters including DAS28.

Results: Using next generation sequencing (NGS), we received 10 million reads from each sample. Following computational analysis, we selected 14 specific miRNA candidates which are predicted to target inflammatory mediators out of 188 significantly changed miRNAs in RA monocytes vs HC. Based on the highest scoring in terms of negative correlation ($r = -0.97$, $p = 1.7e-07$, $FDR = 0.04$) and the number of seed regions of miRNA ($n = 5$) binding with the 3'UTR of mRNA, we selected miRNA-146b-3p and its target gene anti-inflammatory retinoic acid receptor alpha (RARA) transcript. In addition, miRNA-146b-3p was 1.12-fold upregulated ($p = 0.02$) compared to HC monocytes. Similarly to NGS studies, qPCR analysis confirmed significantly increased expression of miRNA-146b-3p in RA vs HC monocytes (3.2-fold, $p = 0.01$) and negative correlation between miRNA-146b-3p and RARA expression ($r = -0.39$, $p = 0.031$). In addition, both NGS and qPCR analyses demonstrated negative correlation between miRNA-146b-3p expression and DAS28 score ($r = -0.75$, $p = 0.009$ and $r = -0.62$, $p = 0.034$, respectively).

Conclusion: We have identified a new miRNA candidate miRNA-146b-3p which is predicated to negatively regulate anti-inflammatory RARA transcript that may elucidate an increased inflammatory phenotype of RA monocytes. Supported by 2015/16/S/NZ6/00041 from National Science Centre, Poland and EMBO ST Fellowship.

Disclosure: M. Ciechomska, None; K. Bonek, None; P. Glusko, None; M. Olesinska, None; B. Wojtas, None; V. Benes, None; W. Maslinski, None.

In Rheumatoid Arthritis, Changes in Autoantibody Levels Do Not Associate with Treatment Response, but Are a Reflection of Treatment Intensity

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis(RA) is characterized by the presence of auto antibodies like rheumatoid factor (RF), anti-cyclic citrullinated peptide-2 (anti-CCP2), & anti-carbamylated protein (anti-CarP) antibodies. It is currently unclear whether changes in auto antibody levels are associated with disease activity/treatment outcomes and whether they are modified by treatment intensity. Therefore, we investigated whether RA-autoantibody levels associate with disease activity and are affected by treatment intensity.

Methods: In 381 seropositive RA patients in the IMPROVED study¹, we measured at 4 month intervals over the first year of treatment: IgG, IgM, and IgA of anti-CCP2 and anti-CarP, IgM and IgA of RF, and auto antibodies against 4 citrullinated and 2 acetylated peptides. Following initial prednisone and methotrexate (MTX), treatment was escalated or tapered every 4 months according to whether disease activity score<1.6 had been reached. Using generalised estimating equations we investigated whether 1) baseline levels or changes in levels were associated with EULAR response at 4 and 12 months (after correction for baseline determinants), and 2) medication escalation (versus tapering) was associated with a subsequent decrease in levels.

Results: For all 14 auto antibodies, levels decreased significantly in the first 4 months and then rose until 12 months. Good EULAR response at 4 months was preceded by higher baseline levels(mean levels for anti-CCP2 IgG, a representative antibody: good-responders: 814aU/mL; moderate-responders: 490 aU/mL; non-responders: 643 aU/mL), and good responders decreased more in levels 0-4 months than did non/moderate responders(β of 0-4 month change for anti-CCP2: good-responders: -266 aU/mL; moderate-responders: -190 aU/mL; non-responders: -194 aU/mL). However, after correction for multiple testing, this pattern was only significant for 5/14 antibodies. There was no consistent association between EULAR response at 12 months and autoantibody levels or changes. Despite the lack of association with treatment outcomes, levels for most antibodies dropped following treatment escalation, and rose following tapering of treatment. This was best illustrated by the level decrease following the decision at 8 months to restart prednisone(on top of MTX), and rose if MTX was tapered to drug-free (Figure; significant for 12/14 antibodies after correction for multiple testing).

Conclusion: Changes in RA-associated antibody levels over time do not associate with better treatment response, but instead are a reflection of treatment intensity. This suggests that autoantibody levels are modifiable by currently available therapies, but that modifying levels is in itself of limited clinical relevance.

References: ¹Heimans, AR&T 2016, 18:23.

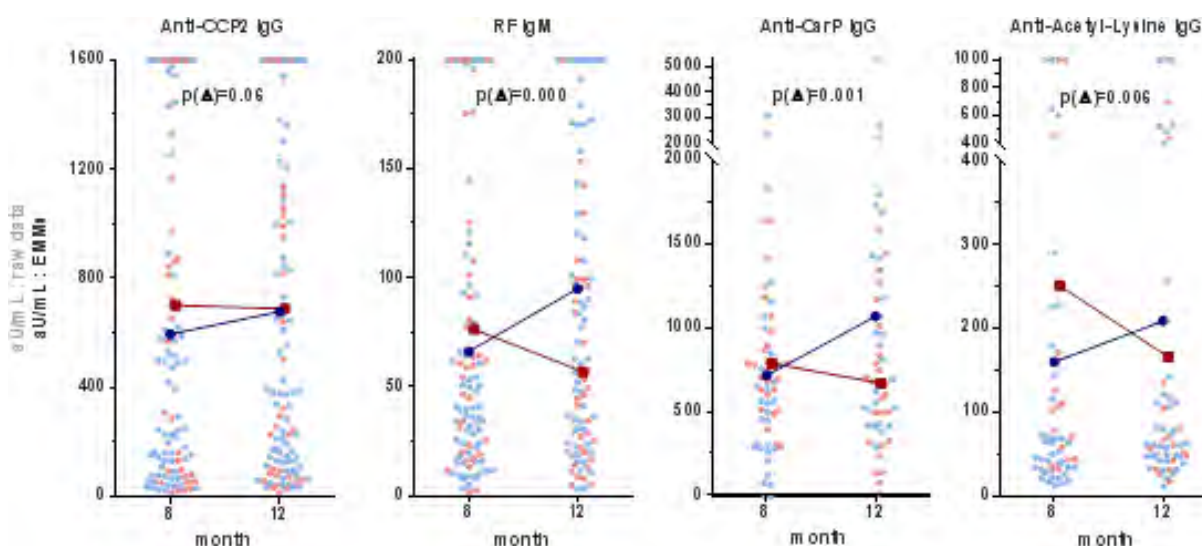


Figure: Levels in arbitrary units (aU/mL) overtime for four (of fourteen) representative antibodies, separated by whether patients restarted prednisone (red) or tapered MTX to drug -free (blue) at 8 months. Dots indicate raw data; lines indicate estimated marginal means (EMMs) calculated by GEE, adjusted for age, gender, disease duration, & smoking status. $p(\Delta)$ -values refer to the difference in the level change over time (i.e.: slope of the lines). Anti-Acetyl. Lysine = anti-acetylated lysine vimentin.

Disclosure: E. de Moel, None; V. Derksen, None; L. Trouw, None; H. Bang, None; G. Collée, None; L. R. Lard, None; T. W. J. Huizinga, BMS, 2, EU, 2, Arthritis Foundation, 2, IMI, 2, LUMC, 3, Ablynx, 5, Merck & Co., 5, UCB, Inc., 5, BMS, 5, Biotest AG, 5, Janssen, 5, Pfizer, Inc., 5, Novartis, 5, Roche, 5, Sanofi-Aventis, 5, Abbott, 5, Consulting Bioscience, 5, Galapagos, 5, Nycomed, 5, Boehringer, 5, Takeda, 5, Zydus, 5, Epirus, 5, Eli Lilly and Co., 5; C. F. Allaart, AbbVie, 2; R. E. M. Toes, None; D. van der Woude, None.

Abstract Number: 2055

Laser Capture Microdissection to Interrogate B Cells in RA Synovial Tissue

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis is an autoimmune disease characterized by immune cell infiltration in synovial tissue and progressive bone damage. B cells are abundant in the synovial tissue of a subset of RA patients, where they play critical roles in shaping local RA pathogenesis. The unique microenvironment in RA synovial tissue may drive pathogenic B cell function, but current approaches to interrogate single cells rely on disaggregation of tissue with loss of information about the spatial structure and paracrine interactions between cells. To better understand the role of B cells in RA-driven synovial pathogenesis, we are taking the novel approach of examining RNA signatures of B cells isolated from discrete anatomical areas in synovial tissue using laser capture microdissection (LCM).

Methods: Synovial tissue from RA patients was obtained from arthroplasties and immediately flash frozen in OCT freezing medium. 8 µm tissue sections were prepared under strict RNase free conditions. RA synovial sections were stained with anti-CD20 in the presence of three RNase inhibitors at 4°C. Using a PALM MicroBeam Zeiss microscope, individual B cell were marked and catapulted from the tissue section into a cap with adhesive coating. Targeted qPCR for CD19, CD3 and CD14 was performed to assess the specificity of LCM and RNA integrity numbers (RIN) of samples after LCM were quantitated. RNA sequencing was performed on captured B cells using low input SmartSeq2 methodology.

Results: In the presence of three RNase inhibitors, high quality RNA was obtained after cell capture from synovial tissue (RIN values 6.3 ± 0.4). Targeted qPCR for CD19, CD3 and CD14 showed >600-fold enrichment of CD19 transcript in captured B cells. In contrast, CD3 and CD14 were minimally detected. We performed RNA sequencing of captured synovial B cells (400 B cells, n=3). High sensitivity gene detection was achieved with over 11,000 genes at >1 CPM mapped reads. Compared to sequential sections of whole tissue, we observed higher expression of CD138 and Blimp1 in captured B cells suggesting enrichment for antibody secreting cells. Further examination of differential gene expression revealed higher expression of pro-inflammatory cytokines (IL6 400-fold, IFNγ 39-fold, TNF 10-fold) in captured B cells, suggesting that B cells contribute significantly to the pro-inflammatory synovial microenvironment. In addition, captured B cells had higher expression of CD27 and FCRL4, markers for activated memory B cells.

Conclusion: These data suggest that LCM is a valuable tool to interrogate the transcriptome of discrete cell populations in the synovial target tissue. Ongoing studies are underway to further characterize the impact of anatomical region and neighboring cell interactions on cell function.

Disclosure: J. Rangel-Moreno, None; N. Meednu, None; A. McDavid, None; L. Callahan, None; V. K. Thomas, None; J. Albrecht, None; E. F. DiCarlo, None; D. Orange, None; S. M. Goodman, Roche, Novartis, 4; L. T. Donlin, None; J. Anolik, None.

Citrullination Is Not a Determinant in the Lack of Tolerance to Peptidylarginine Deiminase 2 and 4 in Rheumatoid Arthritis

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Session Information

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Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Peptidylarginine deiminase (PAD) 2 and 4 are targets of the humoral response in RA. However, the mechanisms by which these enzymes become immunogenic in this disease are still unknown. In addition to catalyzing the conversion of arginine residues to citrulline in a broad range of substrates, these enzymes also autocitrullinate. Since citrullination is a major determinant in the lack of tolerance to autoantigens in RA, we investigated whether PAD2 and PAD4 may also be part of the anti-citrullinated protein autoantibody (ACPA) response in this disease.

Methods: We determined the prevalence of antibodies against auto-citrullinated PAD2 and PAD4 in 184 patients with established RA. ELISA assays were developed to screen sera from RA patients and healthy controls for reactivity to native and citrullinated PADs. Antibody binding to native and citrullinated PADs was compared and confirmed in blocking experiments. Recognition of native vs. citrullinated PAD at the individual level was plotted and analyzed by linear regression.

Results: Anti-native PAD4 and anti-native PAD2 antibodies were present in 42% and 18.5% of patients in the cohort, respectively. Auto antibodies against PAD4 bound similarly to both the native and citrullinated form such that anti-PAD4 levels against the citrullinated form positively correlated with that against the native form (R square = 0.863; $p < 0.0001$). Only two sera were identified that bound exclusively to citrullinated PAD4. Similar results were obtained for binding of auto antibodies to the native and citrullinated forms of PAD2 (R square = 0.908; $p < 0.0001$), with only four sera exclusively binding to citrullinated PAD2. Pre-incubation of sera with native PAD4 or PAD2 in solution significantly reduced antibody binding to the respective citrullinated protein ($p \leq 0.0001$).

Conclusion: Taken together, this study demonstrates that citrullination is not a major determinant in the breach of tolerance to PAD2 and PAD4 in RA. Although PADs are necessary for the production of ACPAs, the data suggest that anti-PAD autoantibodies and ACPAs are likely driven by distinct pathogenic mechanisms.

Disclosure: P. Naik, None; R. Davis, None; J. T. Giles, None, 7; F. Andrade, Medimmune; Pfizer; BMS, 2, 5, 7; E. Darrah, Medimmune, Pfizer, Padlock Therapeutics,, 2, 5, 7.

Alterations of the Splicing Machinery in Leukocyte Subsets of Rheumatoid Arthritis Patients Modulate Their Inflammatory, Autoimmune and Atherothrombotic Profiles

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: 1) To identify and characterize the alterations present in the splicing machinery in leukocyte subsets of Rheumatoid Arthritis (RA) patients, and 2) To evaluate their influence on the activity of the disease and its atherothrombotic profile.

Methods: The study was conducted in monocytes, neutrophils and lymphocytes purified from 74 RA patients and 29 healthy donors (HD). By using a microfluidic qPCR array, a set of 45 elements of the splicing machinery were evaluated, including the complete major and minor spliceosome components, and splicing factors with potential pathological role. In parallel, extensive clinical/serological evaluation were carried out. Leukocyte subsets from RA patients were transfected with expression plasmids of selected splicing components, and their effects on cell activity were evaluated. Lastly, leukocyte subsets from HD were incubated with serum from high-activity RA patients and changes promoted in splicing machinery and leukocytes activity were assessed.

Results: A global reduction of spliceosome components in the three leukocyte subsets from RA patients was observed, except for a key minor spliceosome component, RNU4ATAC, which was consistently over-expressed. The levels of those altered components were associated to ACPA positivity, disease activity, and radiological involvement. Correlations with inflammatory mediators, oxidative stress markers and netosis were also demonstrated. Interestingly, eight spliceosome components, including two small nuclear RNA (snRNU) of the major spliceosome (RNU1, RNU5 and U2AF2), the snRNA of the minor spliceosome, RNU4ATAC, and the splicing factors RBM3, RBM17, KHDRS1 and SRSF10 were simultaneously altered in the three leukocyte subtypes. Logistic regression and ROC analyses, including the eight spliceosome components simultaneously altered, identified several signatures as biomarkers of specific RA disease features, being able to: i) discriminate between RA patients and HD; ii) classify patients with high disease activity (DAS28>5.1); iii) recognize patients with radiological involvement; and iv) identify patients showing atheroma plaques.

Mechanistic *in vitro* studies demonstrated the involvement of several spliceosome components in the altered inflammatory profile of RA leukocytes. Likewise, splicing machinery was deregulated by effect of inflammatory/autoimmune mediators present in the serum of RA patients with high disease activity.

Conclusion: 1) We have identified specific alterations in the splicing machinery of leukocytes from RA patients, associated with the activity of the disease, as well as with its inflammatory and atherothrombotic profile. 2) Several signatures involving common altered components of the spliceosome in leukocytes subsets may be used as novel biomarkers for the typification of the disease, avoiding complementary ultrasound or radiological tests. 3) The altered expression of the splicing machinery in leukocytes of RA patients might derive from their autoimmune and proinflammatory profile, which might, in turn, contribute to the clinical shape of the disease.

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Disclosure: C. Perez-Sanchez, None; A. Ibáñez-Costa, None; E. Alors-Perez, None; S. Pedraza-Arévalo, None; A. M. Patiño-Trives, None; M. Luque Tevar, None; P. Ruiz-Limon, None; N. Barbarroja, None; Y. Jiménez-Gómez, None; M. C. Abalos-Aguilera, None; P. Seguí, None; R. Ortega-Castro, None; J. Calvo-Gutierrez, None; A. Escudero-Contreras, None; E. Collantes Estevez, None; J. P. Castaño, None; R. M. Luque, None; C. Lopez-Pedraza, None.

Abstract Number: 2058

Effects of Fatty Acid Supplementation in Modulation of Gut Microbiome and T-Regulatory Cells in Health and Psoriatic Disease

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Background/Purpose: Psoriatic Arthritis (PsA) affects up to 30% patients with psoriasis and is characterized by wide spread synovio-entheseal inflammation. Physiologically, the human gut microbiota metabolizes dietary fiber into short-chain fatty acids (FA)- which exert anti-inflammatory effects by increasing activity of regulatory T cells (Tregs). Moreover, we have previously shown decreased abundance of *Akkermansia* and *Ruminococcus* and concomitant decrease in medium-chain FA (MCFA) levels in stool of PsA patients. We therefore hypothesized that FA supplementation may have favorable effects on gut microbiome and lead to increase in tolerance, potentially serving as therapeutic target in psoriatic disease.

Methods: Wild type (WT) animals were fed SCFA-rich diet for 14 days followed by 16S rRNA sequencing and microbiota analysis of pellet specimens. We then evaluated effects of MCFA-rich diet in healthy subjects. Peripheral blood and stool samples were collected at days 0, 7 and 14 for 16S rRNA sequencing and FACS. Finally, we conducted a small, prospective, proof-of-principle study in new-onset, drug-naïve psoriatic disease patients (with or without PsA). Each participant received MCFA (1 gm 4 times a day for 6 weeks). Clinical history was obtained at baseline. Skin and joint exam were performed at baseline and follow up. Serum and stool samples were collected at baseline, weeks 3, and 6 for 16S rRNA sequencing and FACS, respectively. Wilcoxon signed-rank test was used to compare differences in Tregs before and after MCFA-rich administration.

Results: SCFA rich diet in WT mice led to statistically significant perturbations in gut bacterial composition 14 days into intervention, with a dramatic increase in commensals (Fig 1A; $p < 0.001$), most notably in *Akkermansia* (Fig 1B). MCFA administration to healthy subjects ($n=7$) also led to significant changes in community structure (Fig 2A; $p=0.03$) and associated increases in circulating Treg cells (Fig 2B; $p < 0.001$). These findings were also observed in psoriatic disease

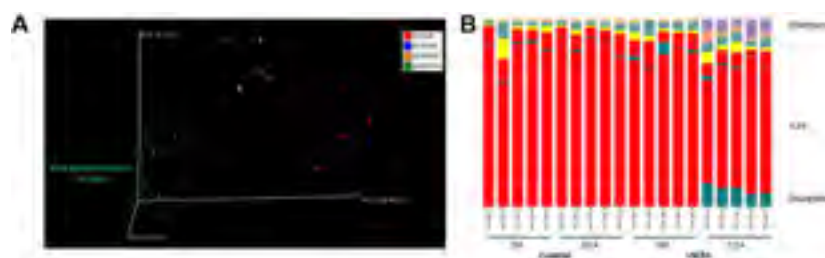


Figure 1. WT animals stool analysis showing significant alterations of microbiota from day 1 to day 14. (A) Beta diversity plot before and after SCFA administration in WT animals (color coded). (B) Expansion of Akkermansia and Bacteroides on day 14 of SCFA rich diet. DD = Day 1, D7 = Day 7, D14 = Day 14.

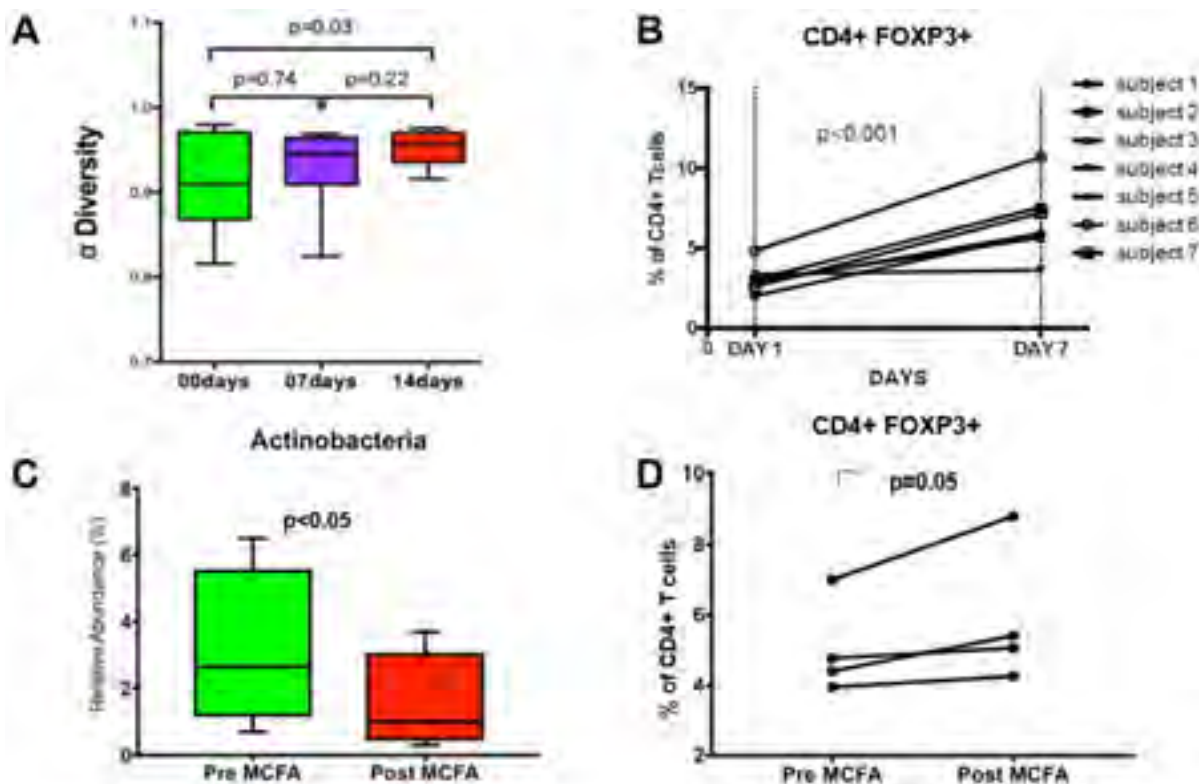


Figure 2. After administration of MCFA in healthy subjects, (A) Changes in α diversity from day 0 to day 14 (p value < 0.05) (B) increased Tregs measured by expression of FoxP3. Psoriatic disease patients after MCFA administration shows (C) decrease in Actinobacteria and (D) increase in Tregs

patients (n=4) showing a significant alteration in specific taxa, including *Actinobacteria* (Fig 2 C; $p<0.05$) and *Mollicutes* ($p=0.09$) and concomitant increase in circulatory Treg cells (Fig 2D)

Conclusion: In both health and psoriatic disease, MCFA supplementation is associated with distinct changes in human gut microbiota composition and peripheral Treg cells. These findings rationalize the need for a larger placebo controlled, prospective trial to study the effects of MCFA in patients with psoriasis and PsA as a potential therapy alone or in combination with DMARDs.

Disclosure: F. Malik, None; J. Manasson, None; A. Herrera, None; M. Attur, None; S. M. Reddy, Pfizer, Novartis, 5; L. Yang, None; S. Koralov, None; J. U. Scher, Janssen, 5, Novartis, 5, UCB, Inc., 5, AbbVie Inc., 5.

Abstract Number: 2059

Inhibition of the Transcription Factor That Drives IL-17 Expression Suppresses Inflammation, Joint Damage, and New Bone Formation in Experimental Spondyloarthritis in HLA-B27 Transgenic Rats

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The IL-17 axis has been identified as a central pathway in SpA pathogenesis. Targeting this axis in AS and PsA significantly suppresses inflammation and stops bone and cartilage destruction. Retinoic acid receptor related orphan receptor gamma t (ROR γ t) is a transcription factor required for differentiation of IL-17-producing T cells and innate immune cells. We studied the therapeutic effect of a small molecule ROR γ t antagonist on a validated animal model of SpA (*Front Immunol* 2017;8:920).

Methods: Thirty male Lewis rats transgenic for HLA-B*2705, human β 2 microglobulin, and deficiency of the gene *Dazl* (21-3x283-2x17-9, *Arthritis Rheum* 2012;64:2518), 61-90 d old, were injected i.d. with 90 μ g heat-inactivated *M. tuberculosis* in IFA. Starting on d 25, rats were divided into three matched groups and treated with (1) ROR γ t inhibitor, 100 mg/kg daily p.o., (2) vehicle only daily p.o. (disease control), or (3) mAb anti-rat IL-17, 15 mg/kg i.p. twice weekly (treatment control). Clinical measurements included weight, visual scores for arthritis and spondylitis, and hind paw volume by plethysmometry. After 5 wks of treatment, rats were sacrificed for cytokine analysis, skeletal μ CT imaging and histology.

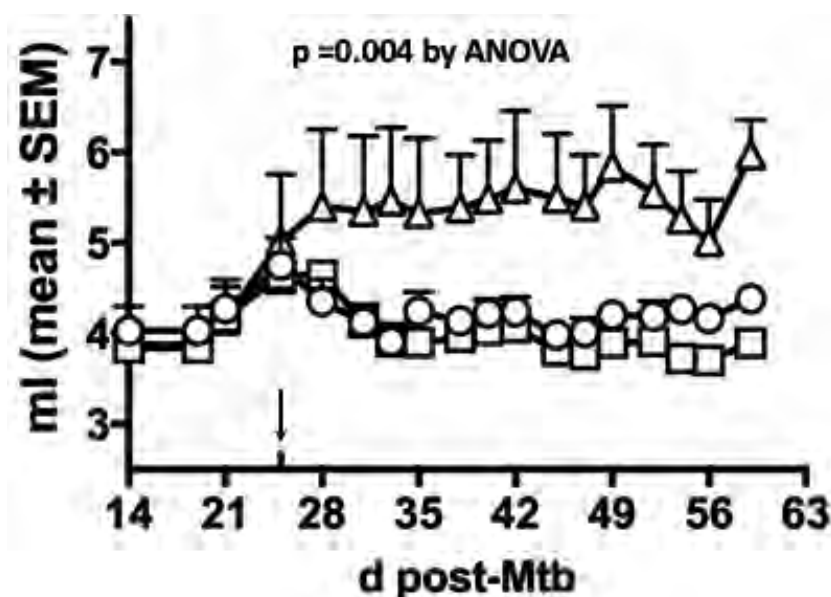


Fig. 1. Hind paw volumes(Δ vehicle only; \circ drug; \square anti-IL-17)

Results: All rats developed ankle swelling and tail spondylitis by d 25. Both ROR γ t inhibitor and anti-IL-17 significantly suppressed arthritis severity and bone damage in the arthritic ankle, compared with vehicle alone (Figs. 1, 2). Additionally, both ROR γ t and IL-17 inhibition were able to reduce damage in the axial skeleton (caudal spine) and in the paws, as measured by μ CT (Fig. 3) and histology.

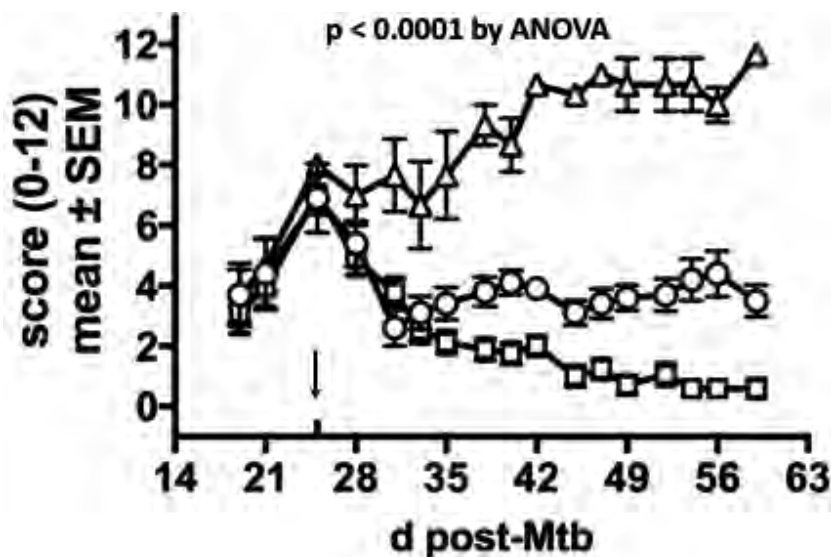


Fig. 2. Arthritis scores(4 paws)

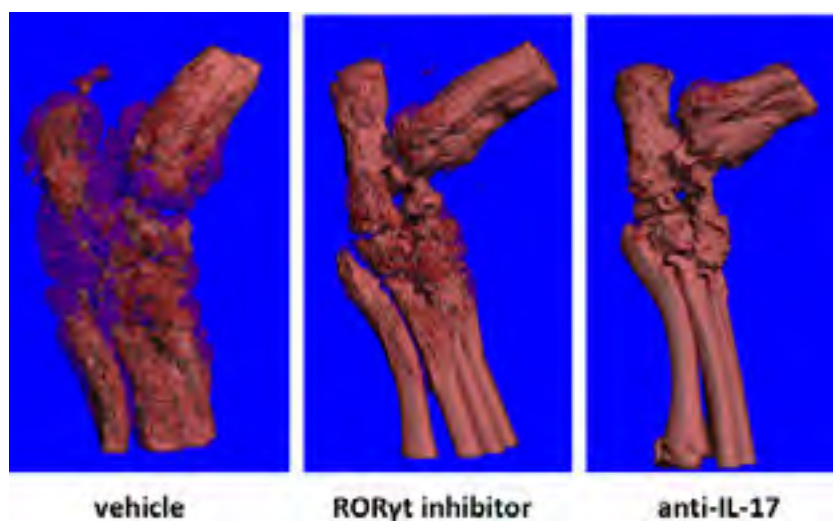


Fig. 3. μ CT of R tarsus after 5 wk of treatment

Conclusion: The ROR γ t antagonist significantly suppressed clinical signs of arthritis in both the peripheral and axial skeleton in Mtb-induced SpA in B27/h β 2m TG rats. This finding was verified by both μ CT and histologic evaluation of ankle and spine at study termination. These data provide evidence that inhibition of ROR γ t has potential clinical benefit for treatment of spondyloarthritis.

Disclosure: J. Taurog, AbbVie, Inc, 2, 9, Novartis, Inc, 9; J. Zhu, None; M. Kort, AbbVie Inc., 1, 3; S. Bryant, AbbVie Inc., 1, 3; L. Phillips, AbbVie Inc., 1; W. Waegell, AbbVie Inc., 1, 3.

Comparative Histologic and Molecular Analysis of Synovial Tissue in Early Treatment-Naïve Psoriatic and Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid Arthritis (RA) and Psoriatic Arthritis (PsA) are chronic joint conditions characterised by persistent inflammation of the synovial tissue (ST). Previous reports suggested less marked synovial lining and fewer infiltrating T cells in PsA compared to RA. Several confounders such as disease duration, treatment, sampling techniques and a predominance of large joints samples may have influenced these findings. Here we aimed at comparing the synovial features of RA/PsA early in the disease and prior to treatment intervention to highlight their histologic and molecular individual characteristics.

Methods: 183 consecutive patients with early (<12 months) treatment-naïve arthritis and active synovitis of at least one joint were recruited as part of the multicentre Pathobiology of Early Arthritis Cohort (PEAC) at the Barts Health NHS Trust and underwent a baseline US-guided synovial biopsy of an actively inflamed joint. ST inflammatory infiltrate was evaluated by H&E and semi-quantitative score (0-4) of the immunostaining for CD68 (macrophages), CD3 (T cells), CD20 (B cells) and CD138 (plasma cells). Patients were classified as: Pauci-immune, CD68 sublining (SL)<2 and/or CD3-CD20-CD138<1; diffuse-myeloid, CD68SL>2, CD20<2 or CD138<2; lympho-myeloid, CD20>2 or CD138>2. RNA sequencing was performed on 93 RA/15 PsA patients.

Results: 144/183 patients met the 2010ACR/EULAR criteria for RA and 39/183 were diagnosed with PsA (32 polyarticular 7 oligoarticular). PsA patients were significantly younger than RA. Comparison of the age-adjusted clinical variables at baseline showed no significant differences between ESR, CRP and DAS28, despite a significantly higher number of tender and swollen joints in RA. ST was retrieved from small joints in 74.4% of PsA and 82% of RA. US score of the biopsied joints showed a significantly higher synovial thickening in the PsA group and comparable power-doppler. Histopathology assessment showed a significantly lower infiltration of B/T lymphocytes, plasma cells and SL-macrophages in psoriatic synovitis. The distribution of synovial pathotypes also differed, as the pauci-immune was the most represented in PsA (43.2%) but the least frequent in RA (24.8%). Only in RA, the pauci-immune pathotype associated with significantly lower ESR, CRP and DAS28 in comparison with lympho-myeloid; these differences remained significant also in a subset of 26 RA subjects age- and gender-matched with PsA patients. Conversely, pathotypes did not define less active disease in PsA. Cellular gene modules analysis showed the expression of neutrophil, eosinophil and mast cell gene-sets in PsA but not RA pauci-immune synovitis. Overall, PsA ST differed from RA with a higher expression of the skin fibroblasts, eosinophils and neutrophils gene-sets. Finally, genes significantly up-regulated in PsA clustered in specific modules including neutrophil recruitment/enrichment and cytoskeleton remodelling.

Conclusion: The demonstration of specific histological and molecular signatures relating to early-untreated PsA and RA will help to shed new light on disease pathogenesis and identify novel therapeutic targets.

Disclosure: A. Nerviani, None; F. Humby, None; G. Llisó Ribera, None; W. S. Tan, None; M. A. Boutet, None; K. Goldmann, None; F. Bene, None; R. Hands, None; S. Kelly, None; M. Bombardieri, None; M. J. Lewis, None; C. Buckley, None; P. C. Taylor, None; I. B. McInnes, None; C. Pitzalis, None.

Genome-Wide DNA Methylation Analysis in Ankylosing Spondylitis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Ankylosing spondylitis is a chronic inflammatory disease characterized by inflammation of the sacroiliac joints and the spine leading to significant immobility. A subset of patients develops systemic organ involvement including uveitis, interstitial lung fibrosis, and cardiac manifestations. The etiology and pathogenesis of ankylosing spondylitis are incompletely understood, though most patients carry the *HLA-B*27* allele. The objective of this study was to evaluate DNA methylation changes in ankylosing spondylitis with the goal of revealing novel mechanistic insights into this disease.

Methods: Genome-wide DNA methylation analysis was performed in whole blood DNA samples using the Infinium MethylationEPIC array in patients with ankylosing spondylitis compared to age, sex, and ethnicity matched controls with osteoarthritis as a non-inflammatory disease control. We studied 24 patients with ankylosing spondylitis, including 12 patients who carry *HLA-B*27* and 12 patients who are *HLA-B*27* negative. DNA methylation analysis was performed using ‘minfi’ and ‘betareg’ in R environment, and differential DNA methylation was conducted following extensive quality control steps using beta regression with adjusting for technical co-variates as well as blood cell composition in each sample.

Results: We identified a total of 68 differentially methylated sites between ankylosing spondylitis patients and osteoarthritis controls. Of these 31 were hypomethylated and 37 were hypermethylated, representing 21 and 30 genes respectively. Hypomethylated genes found included *HCP5*, which encodes a lncRNA within the MHC region, previously associated with genetic risk for psoriasis and toxic epidermal necrolysis, the transcription factor gene *POU5F1*, *CHD5* which encodes a member of the chromodomain helicase DNA-binding protein family, *PON1* which encodes a member of the paraoxonase enzyme family, and the RAS-signaling related gene *RRAS2*. Hypermethylated genes include GTPase-related genes such as *ARHGAP6*, *RAB11FIP3*, *TBC1D3H*, *TBC1D1*, and *TBCD*. Both *HCP5* and *POU5F1* were hypomethylated in *HLA-B*27* positive compared to *HLA-B*27* negative ankylosing spondylitis patients.

Conclusion: A genome-wide DNA methylation analysis in patients with ankylosing spondylitis found DNA methylation patterns that could provide potential novel insights into this disease. While most DNA methylation changes observed between patients and controls were not dependent upon *HLA-B*27* status, two of the most hypomethylated loci in ankylosing spondylitis were directly linked to *HLA-B*27* positivity. Our findings suggest *HLA-B*27* might play a role in ankylosing spondylitis in part through ‘epigenetic linkage disequilibrium’ inducing epigenetic dysregulation.

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Omentin-1: Potential Biomarker of Cardiovascular Risk in Axial Spondyloarthritis? a Serological and Genetic Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Cardiovascular (CV) disease (mainly due to accelerated atherosclerosis) is one of the main causes of mortality in axial spondyloarthritis (axSpA). The higher incidence of CV risk factors and systemic chronic inflammation increase CV risk in axSpA.¹ This is further enhanced by dysregulated production of adipokines, molecules with key metabolic and immunomodulatory functions. In this regard, low levels of circulating omentin-1, an anti-inflammatory adipokine, have been associated with metabolic dysfunction and CV disease in general population and other conditions different from axSpA.^{2,3} Therefore, the aim of this study was to evaluate the potential role of omentin-1 as a prognostic marker of CV disease in axSpA by assessing its association with subclinical atherosclerosis and CV risk factors in a large cohort of patients, both at the serological and genetic level.

Methods: 299 patients that fulfilled the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA⁴ and 84 controls were recruited for this study. Clinical data was retrieved from medical records. Serum omentin-1 levels were assessed by ELISA. Carotid US was performed to evaluate the presence of subclinical atherosclerosis. One polymorphism of the gene coding Omentin-1 (*ITLN-1* rs12409609), previously associated with coronary artery disease, was genotyped by TaqMan probes. Statistical analysis of the data was performed using STATA® v. 11.1, adjusting the results by potential confounding factors.

Results: Serum omentin-1 levels were significantly lower in axSpA when compared to controls ($p=0.0001$). Additionally, serum omentin-1 negatively correlated with body mass index ($p=0.002$) and atherogenic index ($p=0.009$) in axSpA. Interestingly, axSpA patients with inflammatory bowel disease exhibited lower omentin-1 serum levels when compared to patients not displaying this extra-articular manifestation ($p=0.005$). Neither serum omentin-1 levels nor *ITLN-1* rs12409609 showed statistically significant association with markers of subclinical atherosclerosis. Likewise, *ITLN-1* rs12409609 did not disclose a statistically significant association with omentin-1 serum levels.

Conclusion: Serum omentin-1 is linked to obesity and adverse lipid profiles in axSpA. Additionally, serum levels of this molecule are associated with the presence of inflammatory bowel disease in axSpA. These data support a role of omentin-1 as a CV risk biomarker in axSpA.

[1] *Joint Bone Spine*. 2014; 81(1):57-63. [2] *Cardiovasc Hematol Disord Drug Targets*. 2013; 13(1):59-72. [3] *Curr Issues Pharm Med Sci*. 2015; 28(3):176-80. [4] *Ann Rheum Dis*. 2009; 68(6):777-83.

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Early Injection of TNF Inhibitor Prevents Spinal Inflammation and Deformity in Curdlan-Induced Spondyloarthritis Animal Model

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: TNF inhibitors are highly efficient in controlling disease activity and improving functional outcomes as well as quality of life in most ankylosing spondylitis patients; however, TNF inhibitors are not sufficiently effective for preventing the progression of consequent spinal damage. Recent clinical studies have shown that early control of disease by using TNF inhibitors prevents spinal damage. This study aimed to investigate the effect of early TNF inhibition on spinal inflammation in murine model of spondyloarthritis.

Methods: We injected curdlan in SKG mice at 8 weeks of age (curdlan group), and administered adalimumab (10 mg/kg) at 3 and 9 weeks after curdlan injection (ADA group). Clinical score of peripheral arthritis was evaluated, and serum cytokines were analyzed at 8 and 14 weeks after curdlan injection. T cell population in the spleen was measured by flow-cytometry. Spinal inflammation and cartilage destruction were evaluated by PET-MRI and histologic examination using H&E and toluidine blue staining. Opal multiplexed immunofluorescence staining for TNF- α , IL-17A, IL-22, and IL-23 was carried out in the spinal tissues at 16 weeks after curdlan injection.

Results: Clinical score of peripheral arthritis was decreased in the ADA group after 1 week of adalimumab injection. Serum levels of TNF- α , IL-17A, IL-22, IL-23, INF-gamma, and IL-6 at 8 weeks showed no significant difference between the two groups. According to splenocytes analysis, frequencies of CD4⁺ T cells, T_H17⁺ cells, and regulatory T cells were not significantly different between the two groups. However, H&E and toluidine blue staining of curdlan group revealed severe inflammatory cell accumulation and intervertebral cartilage destruction in the spinal tissues. ¹⁸F-FDG uptake of thoracic spine level in paravertebral tissue was significantly lower in the ADA group. Also, the densities of TNF- α and IL-17A in immunofluorescent-stained paravertebral tissue were decreased in the ADA group, whereas the serum levels of these cytokines were not significantly different between the two groups at 14 weeks.

Conclusion: Curdlan-induced murine model of spondyloarthritis developed spinal inflammation and consequent cartilage destruction. Early introduction of TNF inhibitor prevented spinal inflammation and deformity in curdlan-induced spondyloarthritis mice via blocking TNF and IL-17A.

Disclosure: D. H. Lim, None; E. J. Lee, None; S. Hong, None; Y. G. Kim, None; C. K. Lee, None; B. Yoo, None.

Aberrant Distribution and Function of Plasmacytoid Dendritic Cells in Patients with Ankylosing Spondylitis Are Associated with Unfolded Protein Response

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Although human leukocyte antigen (HLA)-B27 is strongly associated with ankylosing spondylitis (AS) and HLA-B27 misfolding induces unfolded protein response (UPR), whether UPR is associated with AS remains controversial. It has been speculated that UPR might occur in more specific immune cells. Since dendritic cells (DCs) are crucial in induction and maintenance of AS in HLA-B27-transgenic rat, and plasmacytoid DCs (pDCs) belong to one type of DCs, we here aim to study the relevance of plasmacytoid DCs (pDCs) in AS and explore if UPR in pDCs contributes to the pathogenesis of AS.

Methods: Peripheral pDCs were isolated from 43 AS patients and 39 controls. The bone marrow (BM) and synovium of inflamed hips from AS patients and controls were obtained. Functional and phenotypic analyses of pDCs and their relationship with UPR was investigated.

Results: We found a significantly higher frequency of pDCs in the peripheral blood, BM and inflamed synovium of hips in AS patients. Functional analysis further revealed that the inflammatory cytokines secreted by isolated peripheral pDCs were significantly increased in AS patients compared with those in normal controls. Remarkably, binding immunoglobulin protein (BIP) and protein kinase RNA-like endoplasmic reticulum kinase (PERK) pathway in UPR were up-regulated in unstimulated pDCs of AS patients. Of note, PERK inhibitor treatment significantly inhibited the enhanced cytokine production by pDCs isolated from peripheral blood of AS patients. Furthermore, the extent of PERK activation was significantly associated with the increased disease severity of AS patients, the increased expression of pDC development marker, FMS-like tyrosine kinase (FLT) 3, and tissue homing marker, chemokine receptor (CCR) 6, of pDCs in AS patients.

Conclusion: Our data uncover that the activation of UPR may occur in pDCs of AS patients. The up-regulated PERK pathway in pDCs not only contributes to the aberrant synovial distribution and enhanced inflammatory function of pDCs in AS patients, but also is associated with systemic disease activity of AS patients.

Disclosure: L. Chin-Hsiu, None; C. Chun-Hsiung, None; L. Kuo-I, None.

Abstract Number: 2065

Blockade of the JAK/STAT Pathway Inhibits Inflammation and Bone Formation in Two Murine Models of Spondyloarthritis

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Session Information

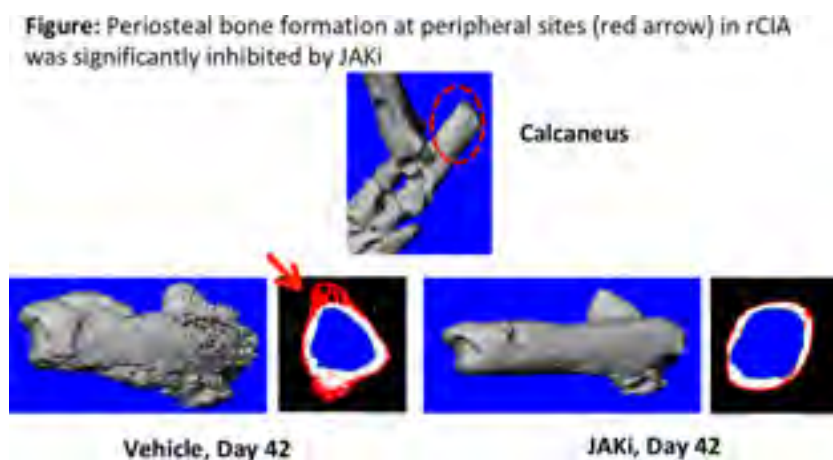
Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Spondyloarthritis (SpA) results in significant pain and loss of function due to inflammation and resulting enthesal/periosteal bone formation. Inhibition of the Janus kinase (JAK)/STAT pathway is being evaluated



clinically as a therapeutic approach in SpA. We studied JAK inhibition in two preclinical models of SpA: the SKG mouse model, in which the IL-23 pathway has been implicated as playing a key role, and rat collagen-induced arthritis (rCIA), an inflammation driven model of bone erosion and aberrant bone formation. In this model, aberrant bone formation increases significantly overtime ⁽¹⁾ and in both models, enthesal/periosteal bone formation is a prominent feature.

Methods: 9-10 week-old SKG mice were injected IP with curdlan at day 0 to synchronize onset of disease. JAKi was delivered beginning at day 0 twice daily by oral gavage for 30 days. rCIA was induced by IP injection of bovine type II collagen in incomplete Freund's adjuvant at days 0 and 6. Treatment with JAKi was initiated at peak inflammation (d17) and continued for 25 days. Clinical and histological scores were used to quantitate inflammation and periosteal/enthesal bone formation was quantitated by histology and microCT. In the SKG model, gene expression at enthesal sites was determined using laser capture microscopy from 2 sites: a reproducible site of periosteal bone formation on the tibia, and inflammatory sites around tail vertebrae at which bone formation did not occur. Whole transcriptome analysis was performed using Affymetrix gene array MTA 1.0.

Results: JAKi suppressed inflammation in both models. Clinical and histologic inflammation scores were significantly decreased by JAKi in SKG mice ($p < 0.05$). Paw volume ($p < 0.001$) and pannus scores ($p < 0.05$) were significantly decreased by JAKi in rCIA. In addition, periosteal/enthesal bone formation at peripheral sites was significantly inhibited in both models by greater than 50% (Figure). In SKG mice, global gene expression analysis of inflamed tissue from entheses identified distinct gene expression patterns at sites of bone formation and sites of inflammation without bone formation. Differentially regulated genes included cartilage and bone markers, such as biglycan and collagen type I alpha 1. IPA upstream regulator analysis identified significant enrichment of major skeletal pathway regulators at sites of periosteal bone formation, including TGF-beta, Wnt3A and AhR, the arylhydrocarbon receptor, implicated in osteoclastogenesis.

Conclusion: Treatment with JAKi suppressed both inflammation and periosteal/enthesal bone formation in two animal models of SpA, accompanied by directed changes in gene expression and activated pathways. These results demonstrate the therapeutic potential of a JAKi in the treatment of SpA, with the possibility of controlling periosteal/enthesal bone formation in these diseases.

1. Schett G, Arthritis Rheum, 2009;60(9):2644-54.

Disclosure: Y. Maeda, None; Z. Stavre, None; T. Huang, None; C. Manning, None; B. Shaughn, AbbVie Inc., 1, 3; M. Macoritto, AbbVie Inc., 1, 3; D. Hyland, AbbVie Inc., 1, 3; W. Waegell, AbbVie Inc., 1, 3; E. M. Gravallese, AbbVie Inc., 2, 3, 7.

Abstract Number: 2066

Serum IL-37 Is an Efficient Biomarker of Disease Activity and Treatment Response in Patients with Ankylosing Spondylitis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The measurement of disease activity is mainly dependent on the patient-reported outcome measures in ankylosing spondylitis (AS) patients. Current inflammatory biomarkers have insufficient sensitivity and specificity to assess the disease activity and treatment response, especially after treatment with anti-TNF- α agents. Interleukin (IL)-37 is an anti-inflammatory cytokine, induced by TNF- α , and inhibits the proliferation of Th-17 cells. In AS patients, serum IL-37 level was higher in controls, and associated with CRP level and ESR. We aimed to estimate whether serum IL-37 levels reflect disease activity, and change according to the anti-TNF agent in active AS patients.

Methods: Patients were recruited from the PLANETAS study (NCT01220518). Active AS patients with BASDAI ≥ 4 and visual analogue scale score for spinal pain were ≥ 4 were treated with infliximab originator or infliximab biosimilar, CT-P13. The serum levels of IL-37 were measured at week 0 and week 30 with specific ELISA. Other demographic, laboratory and clinical variables were evaluated simultaneously. Responders were defined as those satisfying Assessment in SpondyloArthritis International Society (ASAS 20/40) response.

Figure 1. Change of Biomarkers After Treatment

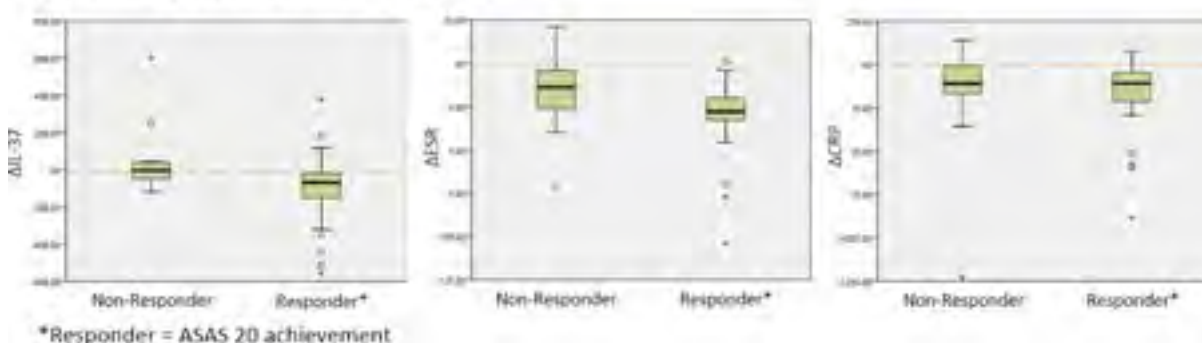


Table 1. Change of Biomarkers After Treatment in Non-responders

Variables	ASAS 20 Non-responder (N=15)			ASAS 40 Non-responder (N=21)		
	Baseline	At week 30	P	Baseline	At week 30	P
IL-37 (pg/ml)	189.1 ± 294.2	234.7 ± 170.9	0.40	206.2 ± 278.7	197.3 ± 119.9	0.85
ESR (mm/hr)	34.2 ± 17.9	37.1 ± 16.7	<0.01	39.6 ± 16.3	25.2 ± 12.6	<0.01
CRP (mg/dL)	3.27 ± 4.10	1.39 ± 2.52	0.06	3.01 ± 3.62	1.08 ± 1.99	0.10
BASDAI	6.8 ± 1.2	5.3 ± 1.5	0.31	6.6 ± 1.9	5.0 ± 1.9	<0.01
BASMI	4.3 ± 1.7	4.0 ± 1.7	0.08	4.3 ± 1.7	3.8 ± 1.7	0.02
BASFI	6.8 ± 1.3	6.3 ± 0.9	0.31	6.2 ± 2.2	6.5 ± 1.0	0.04
Patient's Assessment to Pain	69.5 ± 12.1	56.1 ± 22.2	0.08	67.3 ± 13.2	48.3 ± 24.8	<0.01
Physician's Global Assessment	61.1 ± 21.1	56.9 ± 14.9	0.53	60.1 ± 21.1	49.9 ± 19.1	0.06

IL, interleukin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Menterology Index; BASFI, Bath Ankylosing Spondylitis Functional Index

Results: Among 250 patients, 50 patients (43 males) agreed to provide their serum samples for further study. The median age of patients was 40 years old (Interquartile range [IQR], 33.8-49.5), and the median BASDAI score was 6.7 (IQR 5.3-7.9). A significant correlation between IL-37 and CRP levels (Spearman's rho $[r]=0.39$, $p<0.01$) and BASDAI ($r=0.31$, $p=0.04$) was observed at the baseline, but not at week 30. When calculating the overall differences (Δ) of parameters between baseline and week 30, Δ IL-37 was correlated with Δ CRP ($r=0.36$, $p=0.02$), Δ BASFI ($r=0.34$, $p=0.02$) and Δ BASDAI ($r=0.32$, $p=0.03$). In ASAS 20/40 responders, all the disease activity markers were significantly improved after 30 weeks of treatment. Notably, most clinical parameters except IL-37 level were decreased in both responders and non-responders. However, there was no change of serum IL-37 level in non-responders. The ROC curves for response revealed that the area under curve (AUC) value for Δ IL-37 (AUC=0.74) was similar to that for Δ ESR (AUC=0.71, $p=0.64$) and superior than that for Δ CRP (AUC=0.54, $p<0.01$).

Conclusion: Serum IL-37 levels correlated with disease activity in active AS patients. Changes in serum IL-37 levels after treatment depends on the clinical response to anti-TNF agents. Further study is required to see if earlier change of IL-37 levels after infliximab infusion can identify patients who are likely to respond to infliximab treatment.

Disclosure: G. Y. Ahn, None; S. M. Kang, None; J. Kang, None; B. Nam, None; H. H. Kwon, None; T. H. Kim, None; D. H. Yoo, None.

Abstract Number: 2067

Dysbiosis-Dependent Inflammasomes Activation Drives Innate Immune Responses in Ankylosing Spondylitis Patients

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: A growing body of evidences indicate that the aberrant activation of innate immune systems, occurring in genetically predisposed patients, drives inflammatory processes in Ankylosing Spondylitis (AS). Aim of this study was to evaluate the activation and the functional relevance of inflammasome pathways in patients with AS.

Methods: Intestinal, synovial and bone marrow expression of inflammasome pathways, pyroptosis and IL-1b and IL-18 was evaluated in AS patients. Analysis of organic acid extraction was performed on ileal samples. The expression of the metabolite-sensing receptors GPR43 and GPR109A involved in the regulation of the intestinal inflammasome was also assessed. The role of intestinal dysbiosis in modulating inflammasome activation was also studied in AS patients and HLA-B27 transgenic rats. Inflammasome activation was evaluated in isolated peripheral AS monocytes. The role of LPS, PGE2 and nicotine in inducing monocyte inflammasome activation and the role of inflammasome in modulating IL-23 production and ILC3 expansion was also evaluated.

Results: Activation of inflammasomes was observed in the inflamed gut, synovial and bone marrow samples of AS patients and associated with an increased expression of caspase-1, IL-1b and IL-18. In AS, AIM2 expression was observed in the context of tuft cells and of adherent ileal bacteria. Inflammasome activation in AS gut, was associated with the occurrence of dysbiosis and isolated bacteria from the gut of AS patients induced inflammasome activation on isolated PBMC from healthy controls. Increased pyroptosis was also observed in the gut as demonstrated by the membrane localization of Gasdermin D. Isolated intestinal bacteria from AS ileal samples, significantly modulated inflammasome activation in isolated monocytes. Reduced Short-chain fatty acids concentrations and increased expression of GPR43 and GPR109 were demonstrated in the AS ileal samples. Inflammasome activation was also observed in the inflamed gut of HLA-B27 TG rats and suppressed by antibiotics treatment. Increased expression of NLRP3, NLRC4 and AIM2 was confirmed in AS isolated peripheral monocytes, directly correlated with the ASDAS-CRP, and paralleled by increased serum levels of IL-1b. In in vitro studies, LPS and nicotine strongly activated NLRP3, NLRC4 and AIM2 pathways in AS monocytes. The CC genotype of PTGER4 SNP rs6896969 was associated with a significantly increased activation of inflammasome in AS. Inflammasome activation in AS monocytes was required for the induction of IL-23p19 expression in an IL-1b-dependent way. Finally, inflammasome inhibition blocked IL-23-induced ILC3 expansion.

Conclusion: Inflammasome activation occurs in AS patients and is modulated by a plethora of different tissue-specific and circulating stimuli. Inflammasome drives IL-23p19 production in a IL-1b-dependent mechanism and modulate ILC3 expansion in AS patients possibly representing a future area of therapeutic interventions in AS.

Disclosure: F. Ciccia, None; G. Guggino, None; A. Rizzo, None; S. Raimondo, None; S. Milling, None; R. Alessandro, None.

Abstract Number: 2068

The Role of Extracellular Matrix Metalloproteinase Inducer Emmprin in the Pathogenesis of Psoriatic Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Angiogenesis is an essential component in the pathogenesis of psoriatic arthritis (PsA). Extracellular matrix metalloproteinase inducer (EMMPRIN) is a multifunctional protein that can enhance angiogenesis by inducing vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs).

Objectives: (a) To assess the concentrations of angiogenic factors in serum of PsA patients in comparison to rheumatoid arthritis (RA) patients and healthy controls. (b) To evaluate the role of EMMPRIN as a mediator of fibroblast-macrophage interactions and angiogenesis in vitro.

Methods: Blood samples were collected from 56 PsA patients with active disease, 41 PsA patients in remission, 33 active RA patients and 33 healthy individuals. Serum levels of EMMPRIN, VEGF, MMP-9, MMP-7, MMP-3, MMP-2, and MMP-

14 were evaluated by Enzyme-Linked Immunosorbent Assay (ELISA). The secreted concentrations of EMMPRIN, VEGF and MMP-9 in a co-culture system of fibroblast (HT1080) and monocyte cell lines (U937 and MonoMac6) were compared to each single cell culture using ELISA. The role of EMMPRIN was demonstrated by the addition of a blocking anti-EMMPRIN antibody to the co-culture. Supernatants derived from single or co-cultures, with or without the addition of anti-EMMPRIN, were applied onto human EaHy926 endothelial cells that were seeded on matrigel® to assess the pro-angiogenic potential of EMMPRIN on tube formation. Statistical analysis: Multiple groups were compared using the one-way ANOVA followed by Bonferroni's multiple comparison post-hoc test, and two groups were compared using the two-tailed unpaired student t test. P values exceeding 0.05 were not considered significant.

Results: PsA patients had significantly elevated levels of serum EMMPRIN, MMP-7, MMP-14 compared to RA patients ($p<0.001$, $p<0.01$ $p<0.01$, respectively) and to controls ($p<0.0001$ $p<0.01$, $p<0.01$ respectively). The levels of VEGF ($p<0.05$), MMP-14 ($p<0.05$), MMP-3 ($p<0.0001$) were higher in PsA patients with active disease compare to patients in remission. MMP-2 levels were significantly higher in both PsA and RA groups compared to controls ($p<0.0001$). Serum concentrations of MMP-9 were significantly lower in RA and PsA patients compared to controls ($p<0.0001$), but no significant difference was noted between the two disease groups.

Secretion of EMMPRIN, VEGF and MMP-9 were synergistically enhanced in the co-culture ($p<0.01$ for the three proteins relative to each of the single cultures). The addition of the blocking anti-EMMPRIN antibody reduced the level of VEGF (1.7-folds, $p<0.001$) and MMP-9 (1.4-folds, $p<0.001$) in the co-culture. Higher number of closed lumens were generated when EaHy926 cells were incubated with supernatants from co-cultured relative to each single culture ($p<0.05$). This number significantly decreased ($p<0.05$) when EMMPRIN was blocked by anti-EMMPRIN antibody.

Conclusion: Our results collectively implicate EMMPRIN as a mediator of fibroblasts-monocytes interactions that regulates angiogenesis, and suggest it may play an important role in the pathogenesis of PsA

Disclosure: D. Zisman, None; M. Saphieh, None; J. Feld, None; A. Haddad, None; M. Elias, None; A. Kaganovitch, None; I. Lavi, None; M. A. Rahat, None.

Abstract Number: 2069

The Epigenetic Regulator Sirtuin-1 Modulates T-Helper 17 Cell Differentiation in Axial Spondyloarthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The NAD⁺-dependent protein/histone deacetylase Sirtuin 1 (SIRT1) acts as an epigenetic regulator and has recently been reported to be involved in the development of murine T_H17 cells. Here, we investigated the role of SIRT1 in polarization of human naïve T-cells in axial Spondyloarthritis (SpA).

Methods: We recruited 23 SpA patients [mean age 45 (±14); 26% female] and 11 healthy controls (HC) [mean age 39 (±11); 55% female]. *In vitro* differentiation of naïve CD4⁺ T cells under T_H17 cell- or regulatory T cell (Treg) polarizing conditions was performed. SIRT1 function was modulated using an inhibitor (Ex-527) or activator (Cay10602) of SIRT1 activity. IL-17 producing Th17 cells, CD25⁺FoxP3⁺ Tregs, and SIRT1 protein levels were measured by flow cytometry.

Results: In SpA patients disease activity measured by Ankylosing Spondylitis Disease Activity Score (ASDAS) correlated positively with T_H17 polarization [$\text{corr}_{\text{coeff}}=0.549$, $p=0.023$], and negatively with Treg polarization [$\text{corr}_{\text{coeff}}=-0.489$, $p=0.064$]. SIRT1 protein levels were higher in SpA patients as compared to HC in naïve CD4⁺ T cells [mean fluorescence intensity, SpA: 1293 (±447) vs. HC: 984 (±410), $p=0.077$] and CD4⁺ memory T cells [SpA: 1528 (±527) vs. HC: 1097 (±510), $p=0.035$].

Modulation of SIRT1 activity with SIRT1 inhibitor (Ex) during T_H17 differentiation in SpA patients decreased the level of T_H17 polarized cells significantly [T_H17: 6.28% (2.89-11.80) vs. T_H17_{Ex}: 3.42 (1.79-8.21), $p\leq0.001$]. Treatment of T_H17 differentiation culture with SIRT1 activator (Cay) showed an enhancing effect on T_H17 polarization [T_H17: 6.28% (2.89-11.80) vs. T_H17_{Cay}: 9.55% (4.17-16.20), $p\leq0.001$].

Conclusion: Our data suggest that the epigenetic regulator SIRT1 is involved in SpA pathogenesis by regulating the potential of naïve T-cells to differentiate towards the T_H17 lineage.

Disclosure: S. Unterberger, None; P. Fasching, None; E. Fliesser, None; A. Lackner, None; C. Dejaco, None; W. Graninger, None; M. Stradner, None; J. Fessler, None.

Abstract Number: 2070

Activated Tendon Stromal Cells Drive a Type 17 Immune Response Via CCL20: A Potential Role in the Pathogenesis of Enthesitis in Psoriatic Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: While the exact pathogenesis of psoriatic arthritis (PsA) remains unclear, it is recognised that several environmental factors operate in individuals with genetic susceptibility leading to sustained inflammatory responses. These involve both the innate and adaptive immune system with IL23/IL17 axis playing a central role. One suggested environmental factor is mechanical stress and accordingly, involvement of enthesal sites exposed to maximal biomechanical loading is a common feature of PsA. However, the mechanisms linking mechanical stress/damage at the enthesis/tendon which leads to immune cell activation remains unknown. We aimed to interrogate the role of tendon stromal cells (tenocytes) in the induction of a type 17 response.

Methods: Immunohistochemical staining for CCR6 was performed in paraffin embedded PsA synovial membrane and the presence of CCL20 was quantified in synovial fluid (SF) from PsA and osteoarthritis (OA) patients by ELISA. Healthy tenocytes cultured from hamstring tendons and fibroblast-like synoviocytes (FLS) from PsA patients were stimulated with human IL-1 β (1 ng/ml) and IL-17A (1, 10 and 100 ng/ml). Expression of CCL20 transcript and protein upon stimulation were assessed by qPCR and ELISA, respectively. T cell migration assays were performed with magnetically enriched CD3⁺ cells from peripheral blood of PsA patients and healthy controls using a Transwell system.

Results: We observed an abundance of CCR6 positive cells in PsA synovial membrane and higher levels of CCL20 in SF from PsA patients compared with OA (OA mean \pm -SEM 40.91 \pm -30.06 pg/ml, n=14; PsA 339.5 \pm -100.7 pg/ml, n=39; p<0.0001). Tenocytes were able to upregulate CCL20 transcript (fold change 680.5 \pm -215.2; p<0.0001, n=5) and produce CCL20 (481.8 \pm - 84.26 pg/ml; p<0.0001, n=13), following stimulation with IL-1 β . In this context, the addition of IL-17A induced a synergistic effect with IL-1 β in both tenocytes and PsA FLS. Conditioned media from tenocytes promoted T cell migration.

Conclusion: Activated tendon stromal cells and PsA synovial fibroblasts are able to produce CCL20, a chemokine that binds to CCR6 and is responsible for the recruitment of IL-17 producing cells. In conclusion, our results support a role of the tendon stromal compartment in the development of a type 17 immune response in PsA.

Disclosure: E. Garcia-Melchor, None; G. Cafaro, None; M. Akbar, None; D. Gilchrist, None; S. M. Kitson, None; S. Siebert, Pfizer, Inc., 2, 5, 8, Janssen, 2, 5, 8, Bristol-Myers Squibb, 2, Celgene Corporation, 2, 5, 8, UCB, Inc., 2, 5, 8, 9, Boehringer Ingelheim, 2, 5, 8, Novartis, 5, 8, 9, AbbVie Inc., 9; I. B. McInnes, None; N. L. Millar, Novartis, 5.

Inflammation at Distant Immunocompetent Sites Combined with a Protocol of Forced Exercise Induces Mild Joint Inflammation

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic arthritis is a chronic joint disease clinically associated with psoriasis. Some patients also have signs of inflammatory bowel disease. Enthesitis, inflammation at the attachment sites of ligaments and tendons into the bone, is put forward as key mechanism leading to the clinical manifestations of psoriatic arthritis. One of the leading hypothesis for initiation of disease is that biomechanical stress, together with other initiating factors, plays a role in altering the properties of the anatomic region, thus leading to the development of the disease and its amplification in other compartments of the synovio-entheseal complex.

In this study, we aim to understand early events leading to the onset of psoriatic arthritis, in the presence of distant inflammation in the skin and the intestine.

Methods: Eight-week-old male C57/Bl6 mice were treated with imiquimod cream (IMQ) on a shaved area of the back skin or with dextran sodium sulphate (DSS) dissolved in the drinking water to induce psoriasis-like skin or inflammatory bowel disease-like gut inflammation. Control mice were left untreated. Afterwards, half of the mice were subject to a forced treadmill running protocol to increase biomechanical stress. Control mice with or without IMQ or DSS treatment did not run. Severity of cutaneous or intestinal inflammation was assessed clinically and by histology; knees and paws were evaluated with microCT, histology and immunohistochemistry.

Results: The clinical and histopathologic assessment of skin and intestine sections confirmed that we have successfully induced the two models of inflammation in immune-competent tissues. In both models, signs of systemic inflammation were also present and a significant loss of trabecular bone was indicated by microCT analyses. Signs of synovitis have been detected both for IMQ and DSS protocol, but increased inflammation of the entheses was detected only with the IMQ model. The running protocol appear to affect the joints at the cartilage and the entheseal level.

Conclusion: The presence of cutaneous or intestinal inflammation and the associated bone loss influence the impact of biomechanical stress at the joint level.

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Beneficial Effect of Combination Therapy of Etanercept with Non-Steroidal Anti-Inflammatory Drugs Compared to Etanercept Monotherapy in a Spondyloarthritis Animal Model

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Session Information

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

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Session Time: 9:00AM-11:00AM

Background/Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line drug treatment of spondyloarthritis (SpA) which is frequently associated with inflammatory bowel disease. Biologic disease modifying anti-rheumatic drugs (bDMARDs) should be considered in patients with persistently high disease activity despite conventional treatments. Current recommendation suggests that NSAIDs should only be prescribed if patients are symptomatic due to the potential side effects when administered chronically. However, clinical trial data have suggested that the continuous use of NSAIDs in patients with an elevated CRP results in reduced progression of structural damage in comparison to on-demand use only.

The purpose of this study is to investigate the benefits and harms of NSAIDs when used with bDMARDs on the bony overgrowth and the bowel inflammation in a SpA animal model.

Table 1. Clinical, molecular, and radiologic scores in SKG mice treated with celecoxib and/or etanercept

	Saline (n=8)	Celecoxib (n=9)	ETN (n=14)	Celecoxib+ETN (n=9)
MS score	14.67±2.07	11.11±5.09 (p=0.136)	14±2.94 (p=0.544)	8.25±5.31 (p=0.006)
Peripheral Joint MPO	1.02E+06±4.5 4E+05	7.37E+05±7.22E +05 (p=0.125)	1.05E+06±7.85E+ 05 (p=0.845)	5.64E+05±3.74E+ 05 (p=0.037)
Tail MPO	5.57E+05±3.5 0E+05	3.58E+05±2.14E +05 (p=0.315)	4.97E+05±2.82E+ 05 (p=0.922)	3.30E+05±2.39E+ 05 (p=0.325)
CT erosion	3.71±2.21	2.13±1.64	6.27±3.97	4.63±4.10
CT osteophyte	5.0±2.0	2.25±1.83	5.27±4.29	1.75±1.39

The numbers shown as mean ± SD. ETN: etanercept. MS: morphology score. MPO: myeloperoxidase. CT: computed tomography. P-value < 0.05 considered significant

Table 2. Clinical and molecular scores of ileitis in SKG mice treated with celecoxib and/or etanercept

	Saline (n=8)	Celecoxib (n=9)	ETN (n=14)	Celecoxib+ETN (n=9)
Ileitis score	2.83±0.75	3.0±1.69 (p=0.254)	4.63±1.41 (p=0.021)	2.75±1.28 (p=0.946)
Bowel length	37.77±5.48	40.54±1.99	42.15±3.39	42.14±3.69
Body weight change	-3.75±1.1	-2.0±0.71	-2.46±0.97	-3.33±0.58
Intestine MPO ROI	1.92E+05±1.36 E+05	2.74E+05±2.60 E+05 (p=0.643)	4.75E+05±3.43 E+05 (p=0.051)	3.08E+05±5.06 E+05 (p=0.728)

The numbers shown as mean ± SD. ETN: etanercept. MPO: myeloperoxidase. P-value < 0.05 considered significant

Table 3. Trabecular and cortical bone mineral densities in SKG mice treated with celecoxib and/or etanercept

	Saline (n=5)	Celecoxib (n=3)	ETN (n=8)	Celecoxib+ETN (n=8)
Cortex BMD	2.01±0.04	1.97±0.02 (p=0.297)	1.87±0.12 (p=0.079)	2.02±0.03 (p=0.884)
Cortex volume	1.02±0.12	1.04±0.09 (p=0.764)	0.93±0.11 (p=0.188)	1.02±0.16 (p=0.942)
Trabeculae BMD	54.74±24.53	82.24±2.59 (p=0.180)	34.16±28.61 (p=0.079)	77.45±55.40 (p=0.770)
Trabeculae volume	0.06±0.03	0.08±0.01 (p=0.227)	0.03±0.03 (p=0.075)	0.06±0.04 (p=0.941)

The numbers shown as mean ± SD. ETN: etanercept. BMD: bone mineral densities. P-value < 0.05 considered significant

Methods: ZAP-70W163C-mutant(SKG) mice were housed under specific pathogen free conditions. All of the mice were injected intraperitoneally with 1,3-glucan (curdlan). Mice were treated with celecoxib and/or etanercept (ETN). Clinical manifestations were scored and the expression of inflammatory molecules were examined. Arthritis, spondylitis, and ileitis were assessed histologically at 8-week experimental end points. A bone mineral density tests (BMD) were conducted as well.

Results: Combination therapy of celecoxib with ETN significantly suppressed the morphology scores(MS) and the infiltration of inflammatory cells in the axial and peripheral joints(Table 1). However, ETN monotherapy did not show any efficacy and celecoxib tended to decrease the disease activity. The expression of myeloperoxidase (MPO) was decreased in peripheral and axial joints by celecoxib but not by ETN. The generation of osteophyte was inhibited by celecoxib but not by ETN in a bone CT. Interestingly, combination therapy of celecoxib with ETN showed an additive effect on the inhibition of new bone formation.

Next, we investigated the effect of celecoxib and ETN on ileitis of the SKG mice(Table 2). Celecoxib did not make any further harmful effects on ileitis, but ETN significantly aggravated the ileitis which was restored with combination therapy with celecoxib. In addition, we looked into a BMD of SKG mice depending on the treatment groups (Table 3). Celecoxib increased BMD while ETN decreased which was compensated by co-use of celecoxib.

Conclusion: These results indicate that celecoxib has beneficial effects on the arthritis, ileitis, and bone mineral density when used with ETN in SKG mice. Further clinical studies are warranted.

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Abstract Number: 2073

Role of miRNA-21-5p As a Potential Biomarker for the Inflammation Pathway in Psoriatic Disease and Response to Methotrexate Treatment

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Session Information

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Background/Purpose: Psoriaticarthritis (PsA) is an inflammatory arthritis occurring in patients with psoriasis. miRNAs are small non coding RNAs whose main function, at a posttranscriptional level, is to modulate the expression of target genes via translation inhibition or mRNA degradation. Several studies have shown links between altered miRNA expression with the pathogenesis of several autoimmune disorders. We demonstrated earlier that miR-21-5p was upregulated in PsA and psoriasis without arthritis (PsC) compared to healthy controls (HC) ($p<0.001$), thus a potential biomarker for PsA. We aimed to determine whether miR-21-5p modulates inflammation in psoriatic disease (PsD = PsA & PsC) through IL-17/IL-23 axis, and determine its role in the treatment response to methotrexate (MTX).

Methods: Serum & whole blood RNA samples were collected from 40 patients with early PsA (<2 years' disease duration and not receiving biologic therapy), 40 patients with psoriasis who have been confirmed by rheumatologist not to develop PsA (PsC >10 years disease duration, not receiving biologic therapy, and matched to PsA patients on age, sex, psoriasis duration, and age of psoriasis onset), and 42 HC(matched to patients based on age, sex). RNA was extracted using the Tempus Spin RNA Isolation Kit. miR-21-5p was validated using droplet digital PCR(ddPCR). miR-21-5p expression was also measured in 30 PsA patients before and after 24 weeks of MTX treatment. Serum levels of IL-17, IL-23, TGFβ1 and CXCL10 were measured by ELISAs from R&D Biosystems kits as per protocols. Descriptive statistics are provided, Spearman correlations were performed.

Results: miR-21-5p was significantly down regulated 24 weeks post-MTX treatment in 30 patients ($p<0.008$), the levels of expression correlated with the actively inflamed joint counts ($r=0.897$, $p<0.0001$). IL-17 levels in PsA & PsC were significantly different from HC ($p= 0.031$), but not different between PsA &PsC. IL-17 levels were down- regulated post treatment and correlated with miR-21-5p ($r=0.559$, $p= 0.0002$), CXCL10 levels ($r=0.485$, $p=0.013$), IL-23 levels ($r=0.429$, $p=0.02$) and negatively correlated with TGFβ1 ($r= -0.449$, $p=0.038$).

Conclusion: In the presence of increased levels of miR-21-5p, IL-17 and IL-23 are upregulated while TGFβ1 is down regulated. When miR-21-5p is decreased IL-17 and IL-23 downregulate, with up regulation of TGFβ1. We have thus determined the role of miR21-5p as a biomarker for inflammation pathway in psoriatic disease and response to methotrexate possibly through modulation of CXCL10 and IL-17. Table 1: Demographic, clinical and relative expression data

Variable	PsA (N=40)	PsC (N=40)	HC (N=42)	P Value
miR-21-5p	122.7 (93.1)	58.5 (36.0)	11.5 (9.6)	<0.001
IL-17	0.5(0.2)	0.5 (0.0)	0.4(0.1)	0.031
Sex				
Male	16 (40%)	15 (38%)	15 (38%)	0.96
Female	24 (60%)	25 (63%)	25 (63%)	
Age	40.7 (11.0)	41.9 (11.0)	43.8 (12.0)	0.96
PASI	7.1 (10.8)	6.2 (4.4)	N/A	0.61
AJTOT	6.4 (7.0)	11.0 (.)	N/A	0.52
CRP_p, n (%)	6 (15%)	1 (3%)	N/A	0.048

PASI-psoriasis areas severity index; AJTOT-total actively inflamed joint count; CRP-C reactive protein; PsA - psoriatic arthritis;; PsC – cutaneous psoriasis without arthritis; HT- healthy controls.

Table 2. Spearman Correlation Coefficients, N=30 Prob > |r| under H0: Rho=0

	miR-21-5p	IL-17	IL-23	TGFβ1	CXCL10
IL-17	r=-0.559, p= 0.0002	1.00000	r=0.429, p=0.02	r=-0.449, p=0.038	r=0.485, p=0.013
AJTOT	r=-0.897, p=<0.0001	r=0.415	r=0.459	r=-0.075	r=0.109
		p=0.0153	p=0.0376	p=0.7131	p=0.641
SJ	r=-0.492	r=0.329	r=0.221	r=-0.189	r=0.076
	p=0.0027	p=0.0365	p=0.4135	p=0.5042	p=0.9154
TJ	r=-0.407	r=0.386	r=0.461	r=-0.174	r=0.106
	p=0.0151	p=0.0312	p=0.0342	p=0.6025	p=0.7874
DAPSA	r=-0.354	r=0.493	r=0.513	r=-0.195	r=0.328
	p=0.034	p=0.0048	p=0.0281	p=0.5418	p=0.421

AJTOT-total actively inflamed joint count; SJ-swollen joint count; TJ- Tender Joint count; DAPSA-Disease activity in Psoriatic arthritis score.

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Abstract Number: 2074

Micrnas Deregulation in Monocytes and T CD4 Lymphocytes from Patients with Axial Spondyloarthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

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Background/Purpose: MicroRNAs have been shown to play a crucial role during innate or adaptive immune response. Deregulation of miRNAs has been described in several autoimmune or rheumatic diseases including rheumatoid arthritis, inflammatory bowel disease or psoriasis. In spondyloarthritis (SpA), only few studies on miR expression have been reported with highly diverse methodologies and involving small samples of patients. Because T CD4 lymphocytes and monocytes are important cells in SpA pathophysiology, we wanted to assess the miR expression profile in these two cell types sorted from axial SpA (AxSpA) patients.

Methods: Eighty one AxSpA patients were included in this study. Among these patients, 74 fulfilled the ASAS classification criteria (imaging arm) with sacro-iliitis on X-rays (n=56) or objective signs of inflammation on MRI (n=18). Two independent cohorts of 22 and 59 SpA patients were compared to 17 and 38 age and sex-matched controls. Both SpA

patients and controls were recruited from October 2014 to July 2017 in the department of rheumatology at Cochin Hospital in Paris, France. All SpA patients had an active disease despite NSAIDs intake (mean BASDAI score of 49 +/-19 and mean ASDAS score of 3 +/- 0.9), were free of any biologic treatment and were eligible for a TNF-blocker treatment. Seventy-seven percent were HLA-B27 positive. T lymphocytes and monocytes were isolated from PBMC by direct isolation with magnetic microbeads (CD4+ and CD14+). Three-hundred seventy two miRs were screened by q-RT-PCR on the exploratory cohort and only MiRs showing a significant differential expression in the first cohort were analyzed in the validation cohort. An unpaired T-test was used for comparison of miR expression level.

Results: In the exploratory cohort, 51 (CD14+) and 70 miRs (CD4+) were found to be differentially expressed between patients and controls. Among these, 15 miRs (in CD14+), and 12 miRs (in CD4+) were also found deregulated in the validation cohort. These validated miRNAs were found to play a key role in physiological pathways such as NFkB or TGFb, Wnt signalling and monocyte differentiation that have been involved in the pathophysiology of the disease. Neither clinical subphenotypes nor biological parameters were associated with different profiles of miR expression after adjusting for multiple tests. We found a negative correlation between miR-146a-5p level and BASDAI ($r=-0.28$, $p=0.011$) and ASDAS ($r=-0.38$, $p=5.9 \cdot 10^{-4}$) in monocytes.

Conclusion: We found a deregulation of miR expression in monocytes and T CD4 lymphocytes from patients with axial spondyloarthritis, whose consequences could contribute to the pathophysiology of the disease and be of interest for therapeutic perspective. Moreover, identifying biomarkers with the potential of diagnostic signature should help the clinician in daily practice.

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Abstract Number: 2075

Vascular Endothelial and Inflammatory Differences in Psoriasis and Psoriatic Arthritis Patients

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Background/Purpose: Psoriatic arthritis (PsA) and Psoriasis (PsO) are chronic inflammatory diseases associated with vascular inflammation and increased CVD risk. Few studies have examined vascular inflammatory differences between PsO and PsA and how these differences may impart a different CVD risk profile. We directly investigated the vascular endothelium of patients with PsA, PsO and compared to controls to better understand the inflammatory mechanism(s) that predispose psoriatic patients to CVD risk.

Methods: Twenty patients with psoriatic disease (PD) (mean age 45 years, 55% male, $11.2 \pm 19\%$ body surface area (BSA) involvement) were first compared to 10 matched controls. Next, comparisons were made between PsO ($n = 14$, average age 50 years, 57% male, $11 \pm 22\%$ BSA) and active PsA ($n = 6$, average age 36 years, 50% male, $11 \pm 10\%$ BSA, average 2 – 3 tender/swollen joints per individual). To measure vascular endothelial health, venous endothelial cells were collected from the brachial vein using guidewires inserted through an angiocatheter and isolated with CD146-conjugated magnetic beads. Following collection, endothelial mRNA was isolated, converted to cDNA and inflammatory gene profiling performed by RT-qPCR with Taqman probes and primers. Transcripts were chosen based on *in vitro* gene arrays of human aortic endothelial cells co-stimulated with IL-17 and TNF- α .

Results: PD patients compared to controls showed a trend towards higher levels of hs-CRP (2.4 ± 4 mg/dl vs. 0.8 ± 2 mg/dl, $p = 0.08$) with no overall difference noted between PsA and PsO patients (2.8 ± 2 mg/dl vs. 2.7 ± 4 mg/dl, $p = 0.24$). Transcriptomic profiling of venous endothelial cells comparing PD (PsO and PsA) to controls revealed upregulation of

inflammatory cytokine- and chemokine- associated transcripts (*lymphotoxin beta* [4 - fold], *CCL3* [11 - fold], *CXCL10* [16 - fold], *IL-8* [10 - fold] and *IL-1 β* [4 - fold], $P < 0.05$ for all) and transcripts related to intracellular adhesion (ICAM1 [2.4 - fold] and inflammation *COX-2* [3 - fold], $P < 0.05$). Increased expression of the chemokine *fractalkine* (*CX3CL1* [2.8 - fold], $p < 0.05$) and *lymphotoxin beta* [2 - fold, $p = 0.10$] were found in patients with active PsA compared to PsO. No differences in *CCL3*, *CXCL10*, *IL-8*, *IL-1 β* , *ICAM1* and *COX-2* were seen between PsA and PsO patients.

Conclusion: Endothelial cell pro-inflammatory transcripts are upregulated in patients with active PD compared with controls. Levels of *lymphotoxin beta* and *fractalkine*, a chemokine present in inflamed arthritic synovial tissue, are greater in endothelial cells of patients with PsA than PsO. These findings may underlie increased CVD risk in patients with PD and highlight the inflammatory vascular differences between PsO and PsA.

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Abstract Number: 2076

Transmembrane TNF (tmTNF) Transgenic Mice Exhibit Enlarged Lymph Nodes and Elevated Numbers of High Endothelial Cells Associated with Increased Lymphocyte Recruitment

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Session Information

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Background/Purpose: The NF- κ B family of transcription factors plays a crucial role in chronic inflammatory diseases and can be activated via two distinct pathways. Non-canonical NF- κ B signaling can be induced by different signals, including transmembrane (tm)TNF ligation to TNF receptor 2 (TNFR2), which is restricted to specific cell types including endothelial cells (EC). Activation of the non-canonical NF- κ B pathway in EC is involved in differentiation into high endothelial venules (HEV), which are specialized lymphoid vessels that play an essential role in the recruitment of B and T lymphocytes into lymph nodes (LN), resulting in LN enlargement. tmTNF transgenic (tg) mice that overexpress tmTNF develop chronic inflammatory features, including arthritis and axial inflammation.

The objective of the current study was to investigate LN size and composition, including stromal cell and lymphocyte subsets in tmTNF tg mice. We hypothesized that overexpression of tmTNF results in increased non-canonical NF- κ B signaling in HEV leading to enlarged LN due to enhanced migration of B and T lymphocytes into LNs.

Methods: Peripheral LN (PLN) and mesenteric LN (MLN) of 7 week old tmTNF tg mice and age-matched wild type (WT) mice were collected and dissected and subsequently analyzed using flow cytometry. Cellular markers were used to distinguish between different (CD31+) EC subsets, including MECA79+ high endothelial cells, and B lymphocytes (CD19+) and T lymphocytes (CD3+).

Results: Lymph nodes of tmTNF tg mice were macroscopically enlarged and had more than two-fold increased total cell numbers when compared to WT mice (tmTNF tg PLN: $23.7 \times 10^6 \pm 7.9 \times 10^6$; MLN: $24.9 \times 10^6 \pm 5.3 \times 10^6$ and WT PLN: $5.2 \times 10^6 \pm 1.0 \times 10^6$; MLN: $10.4 \times 10^6 \pm 4.6 \times 10^6$). The total number of high endothelial cells (HEC) in tmTNF tg mice LN was also increased when compared to WT (tmTNF tg PLN: $2.3 \times 10^3 \pm 0.50 \times 10^3$; MLN: $1.9 \times 10^3 \pm 0.64 \times 10^2$ and WT PLN: 714 ± 393 ; MLN: 1.199 ± 506). In addition, the total amount of capillary endothelial cells (CEC) was increased in tmTNF tg mice (tmTNF tg PLN: 2067 ± 42 ; MLN: 2425 ± 71 and WT PLN: 1097 ± 609 ; MLN: 1327 ± 230). Notably, the ratio between HEC and CEC was also increased in the LN of tmTNF tg mice when compared to WT mice (tmTNF tg PLN: 1.10 ± 0.241 and WT PLN: 0.66 ± 0.006). In addition, total B lymphocyte and T lymphocyte numbers in LN of tmTNF tg mice were strongly increased compared to WT mice (B lymphocytes: tmTNFtg PLN: $10.2 \times 10^6 \pm 3.5 \times 10^6$; MLN: $10.9 \times 10^6 \pm 1.8 \times 10^6$ and WT PLN: $2.8 \times 10^6 \pm 5.8 \times 10^5$; MLN: $5.8 \times 10^6 \pm 2.4 \times 10^6$, T lymphocytes: tmTNFtg PLN: $12.8 \times 10^6 \pm 4.5 \times 10^6$; MLN: $14.2 \times 10^6 \pm 2.8 \times 10^6$ and WT PLN: $2.5 \times 10^6 \pm 3.8 \times 10^5$; MLN: $4.7 \times 10^6 \pm 2.1 \times 10^6$).

Conclusion: Overexpression of tmTNF in mice leads to an increase in LN size which is accompanied by an increase in total HEC and CEC numbers and an increased HEC:CEC ratio. Also, B and T lymphocyte numbers in PLN and MLN were increased. The increase of HEC may be the result of enhanced non-canonical NF- κ B activation in EC, resulting in enhanced recruitment of B and T lymphocytes into LN. Consequently, interfering with non-canonical NF- κ B signaling in EC may be a promising treatment strategy to dampen inflammation in immune-mediated inflammatory diseases, which is the subject of current studies.

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Abstract Number: 2077

Pathological Osteogenesis and Inflammation in Experimental Spondyloarthritis Are Associated with Aberrant Type H Blood Vessels and Development of High Endothelial Venules Accompanied By Ectopic Lymphoid Structures in Bone Marrow

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Spondyloarthritis (SpA) is characterized by pathological osteogenesis, inflammation and extensive angiogenesis in inflamed tissues. TNF plays a central role in SpA pathology and transgenic mice that specifically overexpress transmembrane (tm)TNF exhibit features similar to SpA. tmTNF ligation to TNF receptors (TNF-R) in endothelial cells (ECs) can induce signal transduction pathways, that may promote osteogenesis and angiogenesis. Of note, osteogenesis and angiogenesis are coupled by EC differentiation towards a type H (CD31^{hi}endomucin^{hi}) blood vessel phenotype. We investigated the link between pathological osteogenesis, inflammation and angiogenesis in experimental SpA in tmTNF tg mice and the contribution of TNF-R signaling to these processes.

Methods: In this study, tmTNF tg mice, non-tg littermates, and tmTNF tg on either a TNF-RI or TNF-RII deficient background were analyzed for aforementioned SpA features. Cryosections were prepared from vertebrae isolated of these mice at various stages of diseases ranging from 6 weeks till 8 months. Markers to characterize and quantify tissue and cells involved in osteogenesis, angiogenesis and inflammation were analyzed by immune fluorescence confocal microscopy and flow cytometry.

Results: tmTNF tg mice from 6 week onwards contained an increase in type H vessels and osterix⁺ osteoprogenitor cells in the bone diaphysis (osterix mean fluorescence intensity (MFI): 82.8 \pm 7.6) compared to non-tg littermates (MFI: 46 \pm 9.1). These differences in type H vessels and osteogenesis within the vertebrae of tmTNF tg mice were maintained in mice followed up to 8 months. Non-tg littermate vertebrae only exhibited physiological osteogenesis, i.e. in the metaphysis and periosteum. tmTNF tg mice also exhibited ectopic osteogenesis at their entheses, which was not observed in non-tg littermates. Immunostainings demonstrated presence of type H vessels and osterix⁺ osteoprogenitors outside of the bone marrow (BM) at sites of ectopic osteogenesis. This was not observed in non-tg littermates. Interestingly, tmTNF tg mice also displayed altered BM architecture characterized by extensive lymphoid aggregates, which predominantly consisted of B220⁺ B cell aggregates in combination with high endothelial venules (HEV). tmTNF tg mice on a TNF-RI deficient background did not display lymphoid aggregates or HEVs, while tmTNF tg on a TNF-RII deficient background did, although to a lesser extent than tmTNF tg mice, suggesting that particularly TNF-RI-induced signaling events are necessary for the inflammatory phenotype in BM.

Conclusion: tmTNF overexpression in mice results in increased diaphyseal type H vessels and ectopic development of type H vessels associated with enhanced numbers of osteoprogenitors and pathological bone formation. In addition, extensive lymphoid aggregates associated with HEVs develop in the BM. The identification of specialized blood vessels contributing to key features of SpA pathogenesis may reveal potential novel therapeutic targets for SpA.

Disclosure: M. Kaaij, None; J. P. van Hamburg, None; G. Kollias, None; D. Baeten, None; L. van Duivenvoorde, None; S. W. Tas, None.

Abstract Number: 2078

Induction of Netosis in Ankylosing Spondylitis: Association to Disease Pathogenesis and Modulation By Anti-Tnf α Therapy

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: NETosis has been suggested to play a central role in several rheumatology diseases. Nevertheless, this process, and its modulation in therapeutic response has not been described yet in AS patients. Our aims were: 1) to evaluate and characterize the presence of NETosis in AS patients. 2) To explore the relationship among NETosis markers and clinical characteristics of this disease. 3) To analyze the *in vivo* effect of anti-TNF α therapy on NETosis.

Methods: Thirty patients with AS and 32 healthy donors (HDs) were included in a cross-sectional study. Eight AS patients were selected for a six-month longitudinal study of anti-TNF α response. Disease activity was determined by BASDAI index and, CRP and ESR levels; in parallel, plasma inflammatory markers were determined by ELISA kits. Spinal mobility of patients was measured by the BASMI index. *Ex vivo*, spontaneous NETosis generation in purified neutrophils from AS patients and HDs were measured by fluorescence (n=6) and scanning electron (n=3) microscopy after 6 h of incubation. PMA, known to promote NETosis, was used as positive control. DNA extrusion was analyzed by fluorescence microscopy and fluorimetry after SYTOX staining, whereas elastase percentage (NE) was analyzed by fluorescence microscopy after staining of neutrophils with NE antibody. *In vivo*, myeloperoxidase (MPO) and NE protein expression were measured by flow cytometry (FACSCalibur), whereas circulating cell-free DNA and NE levels was examined using fluorimetry after SYTOX staining, and commercial kits, respectively.

Results: Compared to HDs, AS neutrophils showed spontaneous extracellular release of a meshwork of DNA nuclear and granule proteins (NETs), as demonstrated by fluorescence microscopy, fluorimetry, and scanning electron microscopy. Indeed, analysis of DNA fibers staining by SYTOX revealed that NETosis rate was above baseline levels after 6 h of *ex vivo* AS neutrophil incubation as compared to those from HDs ($P<0.05$). Furthermore, higher cell free-DNA levels were observed between AS patients and HDs at 6 h ($P<0.05$). Increased spontaneous NETs production in this pathology was additionally corroborated by the observation of an enhanced percentage of NE-staining cells after 6 h of incubation ($P<0.05$). *In vivo*, higher intracellular NE levels ($P=0.036$), and circulating cell-free DNA levels ($P=0.021$) were also found in AS patients as compared to HDs.

Correlation studies showed that circulating cell-free DNA levels positively correlated with inflammatory markers (i.e. CRP, ESR and TNF α), and with BASMI index. In addition, a positive correlation was found between intracellular NE levels and plasma IL-1 β concentration.

Anti-TNF α treatment of selected AS patients decreased circulating cell-free DNA and NE levels ($p<0.05$), which paralleled the reduction of disease activity.

Conclusion: 1) NETosis is increased in AS patients. 2) Raised NETosis in AS is associated with several markers of inflammation and mobility. 3) Anti-TNF α therapy has a significant effect on NETosis inhibition. Thus, NETosis might act as a key mediator in the etiopathogenesis of AS and have potential for assessment of therapeutic effectiveness in AS patients.

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Abstract Number: 2079

Dysbiosis of Gut Microbiomes in Ankylosing Spondylitis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Ankylosing spondylitis (AS) is a common chronic, systemic, inflammatory disease. Gut microbiome has been reported to play an important role in the homeostasis of human immune system as well as the pathogenesis of AS. In this study, we conducted a research to investigate the differences of gut microbiome between AS patients and healthy controls by the metagenomics approach.

Methods: The fecal sample of 218 AS patients and healthy controls (HCs) were collected and their DNA were extracted. High-throughput sequencing methods with bioinformatics analysis were conducted to reveal the phylogenesis and functional differences of microbiome between AS patients and HCs.

Results: Different species, families and phylum were observed to be enriched in patients and controls. Bacteroidetes was the only phylum enriched in AS patients. Microbiota of intestine from HCs showed more diversity compared to patients. Both Actinobacteria, Firmicutes, Clostridia and Proteobacteria were enriched in HCs. KEGG pathway and module analysis showed that gut microbiota of patients were particularly enriched in the synthesis of LPS and non-mevalonate pathway, which may associate with the regulation of immune system and contribute to the development of disease. Gut microbiome of 27 treated patients who finished one-year follow-up were also sequenced and analyzed. The dysbiosis of the patients were partially restored. The diagnosis model based on gut microbiome information was established and tested, leading to a comparable diagnostic ability to the current criteria.

Conclusion: Dysbiosis of gut microbiota was observed in AS patients compared to HCs. Particular pathway and module enriched in patients such as LPS, may contribute to the pathogenesis of AS. Our study showed that gut microbiome could be used as biomarkers to identify AS patients. Therefore, our findings provide a novel insight of the pathogenesis and diagnosis of AS.

Disclosure: C. Zhou, None; X. Zhang, None; X. Xinyue, None.

Abstract Number: 2080

Plasmatic Glycoprotein and Lipoprotein Nuclear Magnetic Resonance Profiles Associated with Psoriatic Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Psoriatic arthritis (PsA) is an autoimmune disease characterized by the chronic inflammation of the skin and joints. Inflammatory processes translate into changes of the serum protein profiles, including changes in lipoprotein and glycoproteins. Here we investigate the association of plasmatic lipoprotein and glycoprotein profiles with PsA.

Methods: Plasma samples were obtained from 50 PsA patients -classified according to CASPAR - and 50 healthy controls. Lipoprotein and glycoprotein profiles were determined using NMR. For the lipoprotein profiles, VLDL, LDL, IDL and HDL concentration, lipid composition and particle properties were quantified. The glycoprotein profile was decomposed in four reproducible peak regions: LMW, Glyc-B, Glyc-A, Glyc-Lipid and baseline. Association analysis to disease was performed using logistic regression. Classifiers were built using rpart and accuracy was evaluated using ROCs.

Results: We found a significant reduction on cholesterol and triglyceride IDL and LDLs in PsA patients compared to healthy controls ($P < 0.05$). This was accompanied by a reduction also in the particle number for IDL and LDLs ($P < 0.005$). Substantial number of changes were also observed in the plasma glycoprotein patterns, including a decrease of Gly-A and Glyc-Lipid peaks ($P < 0.05$). Using the plasma molecular patterns to predict the presence of PsA, we found a significant classifier for the lipoprotein pattern (ROC (95%CI) = 0.87(0.81-0.94)), and an optimal classifier for the glycoprotein pattern (ROC (95%CI) = 0.91(0.85-0.97)).

Conclusion: Our results support that plasma NMR profiling could be a source of new useful biomarkers for PsA diagnosis and management.

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Abstract Number: 2081

Dysregulated MiR-125a Promotes Joint Angiogenesis in Psoriatic Arthritis through Altered Bioenergetics

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Psoriatic arthritis (PsA) is characterised by an early vascular phase essential for pannus growth, immune responses and disease progression. Recently, numerous studies have highlighted the emerging importance of endothelial cell metabolism in controlling angiogenesis. Herein, we propose microRNA, miR-125, modulates EC bioenergetics and orchestrates joint angiogenesis as characterised by *ex-vivo* associations, *in-vitro* assays and novel CRISPR/cas9 *in-vivo* zebrafish models.

Methods: MiRNA levels were quantified in synovial tissue by RT-PCR and compared to macroscopic synovial vascularity and immunohistochemical analysis of angiogenic factors (FactorVIII/VEGF/ANG2). ECs (HMVEC) were transfected with anti-miR-125a for 24hr. Angiogenic mechanisms were quantified using tube formation assays, invasion by Transwell matrigel chambers, migration by wound repair and gene expression (PFKFB3, HK2, GSK3A, G6PD by RT-PCR and western blot analysis. Real-time analysis of extracellular acidification rates (ECAR) and oxygen consumption rates (OCR) of anti-125 treated ECs was assessed using the XF-24 Extracellular Flux Analyzer (Seahorse Bioscience). To determine if altered metabolism is observed *ex vivo*, glycolysis/oxidative phosphorylation markers (GAPDH/PKM2/ GLUT1/ATP) were assessed by immunohistochemistry. *In vivo*, miR-125a CRISPR/Cas9-based knock-out zebrafish fluorescent reporter lines were generated and vascular development monitored. Finally, we examined the effect of blocking glycolysis using a small molecule, 3PO, which blocks PFKFB3, in miR-125a^{-/-} ECs and zebrafish embryos.

Results: Synovial expression of miR-125 was significantly decreases in PsA versus OA synovial tissue, levels of which were associated with macroscopic and microscopic synovial vascularity (p<0.05). Decreased expression of miR-125a in HMVEC resulted in increased tube formation, invasion and migration properties (all p<0.05). Inhibition of miR-125 significantly decreased basal, maximal and spare respiratory capacity (p<0.009) with a concurrent decrease in ATP synthesis (p<0.08). Increased glycolysis was further supported by elevation of glycolytic genes, including PFKFB3. Elevated endothelial cell glycolysis was also demonstrated *ex vivo* with vascular synovial expression of glycolytic markers, PKM2, GLUT1 and ATP5B significantly increased in PsA compared to OA controls. 3PO significantly inhibited anti-miR-125a-induced mechanism. Finally, miR-125a^{-/-} embryos displayed increased vascular sprouting, effects normalised by the presence of the glycolytic inhibitor 3PO.

Conclusion: Decreased expression of miR-125 in PsA synovium and *in-vivo* models was strongly associated pro-angiogenic mechanisms. Elevated glycolysis following miR-125 inhibition enabled ECs to meet the increased energy and biosynthetic demands for new vessel formation. Correcting these miRNA deficiencies and their resulting metabolic shift, either by conventional pharmacological or as novel drug targets, may provide therapeutic benefit, especially in early disease.

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Abstract Number: 2082

ERAP1 Deficiency Partially Relieves HLA-B27-Induced ER Stress and IL-23 Expression, but Does Not Restore Dendritic Cell Function in Experimental Spondyloarthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

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Session Time: 9:00 AM-11:00 AM

Background/Purpose: Preliminary results suggest that endoplasmic reticulum (ER) aminopeptidase 1 (ERAP1) deficiency partially protects HLA-B27/human b₂m transgenic (B27-Tg) rats from spondyloarthritis (SpA) as evidenced by a reduced frequency of arthritis and orchitis, but not gastrointestinal inflammation. Protection is associated with reduced HLA-B27 misfolding and unfolded protein response (UPR) activation in rat bone marrow macrophages (BMM). Here, we investigated whether ERAP1 deficiency impacts HLA-B27 misfolding-induced IL-23p19 expression in rat BMMs, and/or defective dendritic cell (DC) costimulatory function, both of which have been linked to pathogenesis.

Methods: BMMs from 2-3 month old B27-Tg rats, with ERAP1^{+/+} and ERAP1^{-/-} genotypes were pre-treated with IFN γ (18 hrs) then stimulated with LPS for up to 8 hrs. Relative expression of mRNAs for IL-23p19, BiP, and CHOP were measured by RT-qPCR. Allogeneic DC function was measured using splenic DCs purified from wild type (WT) and B27-Tg rats with ERAP1^{+/+} and ERAP1^{-/-} genotypes using Nycodenz followed by magnetic separation with anti-CD103 (OX62 Ab) microbeads. Resting CD4⁺ T-cells from Dark Agouti (DA) WT rats were purified by negative selection employing a combination of OX33, OX42, 3.2.3, and OX8 antibodies. DCs at 0, 1, 3, 10, 30 ($\times 10^3$) cells were co-cultured with 1×10^5 CD4⁺ T-cells for 5 days; proliferation of T-cells was analyzed by cell counting using IncuCyte.

Results: ERAP1 deficiency reduced LPS-induced IL-23p19 mRNA expression by about 50% ($p < 0.05$) in BMMs from B27-Tg rats, as well as UPR genes BiP and CHOP by 30% ($p < 0.05$). DCs from B27-Tg rats (ERAP1^{+/+}) showed a significant defect in stimulating T-cell proliferation compared to DCs from WT (ERAP1^{+/+}) rats ($p < 0.05$), confirming previous results. However, ERAP1 deficiency did not restore the function of B27-expressing DCs, as there was no improvement in T-cell proliferation.

Conclusion: These results implicate ERAP1 function in modulating aberrant HLA-B27 folding and its effects on IL-23 induction, possibly through UPR activation, in B27-Tg rats. These effects of ERAP1 on HLA-B27 are associated with partial reduction of the experimental SpA phenotype (arthritis and orchitis) but not gastrointestinal inflammation.

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Abstract Number: 2083

Epistasis between HLA-B27 and ERAP1 Affects Gut Microbial Dysbiosis and Arthritis in Experimental Spondyloarthritis

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Session Information

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

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Session Time: 9:00 AM-11:00 AM

Background/Purpose: Common variants in endoplasmic reticulum (ER)-associated aminopeptidase-1 (ERAP1) affect susceptibility to spondyloarthritis (SpA) in HLA-B27-positive human subjects, with loss-of-function/expression conferring protection. Using HLA-B27/human b2-microglobulin transgenic (HLA-B27 TG) rats, an experimental model of SpA, we have preliminary results that ERAP1 deficiency partially protects from the development of arthritis and orchitis, but not gut inflammation. The mechanism(s) underlying the protective effect of ERAP1 loss-of-function remain unknown. Here, we examined the gut microbiota of HLA-B27-TG rats with and without arthritis and with different ERAP1 genotypes, with the goal of identifying arthritis-associated gut microbes.

Methods: Cohorts of HLA-B27-TG rats with 3 ERAP1 genotypes (+/+, +/-, and -/-) were generated by crossing HLA-B27-TG Lewis (LEW) rats with Sprague Dawley (SD) rats carrying 0, 1, or 2 ERAP1 null alleles. The mixed LEW-SD background (SDM) accelerates the onset of arthritis and orchitis, while gut inflammation remains unchanged. Animals were examined 2-3 times per week for the presence of arthritis and orchitis for up to 6 months and then euthanized. Gut inflammation in the cecum and colon was assessed by histological scoring. Microbial profiles were determined using DNA isolated from the cecum luminal contents, with 16S rRNA gene sequencing performed using Illumina MiSeq. Data were quality-filtered using Quantitative Insights Into Microbial Ecology (QIIME 2). Microbe relative frequency was determined at the species level (maximum $> 0.1\%$; $p < 0.05$, $q < 0.1$).

Results: HLA-B27 TG SDM rats with arthritis have a distinct gut microbial signature compared to HLA-B27 TG non-arthritic SDM rats as measured by principal component analysis, despite similar gut histology scores. Moreover, arthritis-associated microbes differ from HLA-B27-associated dysbiotic microbes. Arthritis is associated with a significant loss of microbial alpha diversity, as well as differences in microbial community structure. HLA-B27 TG SDM rats with arthritis have increased *Bacteroides* and *Parabacteroides* at the expense of *Firmicutes*. At the species level, we see an increased relative frequency of certain microbes such as *Akkermansia muciniphila* and *Blautia*, that are often associated with inflammation, whereas other inflammation-associated microbes ([*Prevotella*], *Lachnospiraceae*, [*Ruminococcus*] *gnavus*)

were decreased in comparison with non-arthritic HLA-B27 TG rats. Further analysis based upon different ERAP1 genotypes also revealed ERAP1-associated differences on the microbial diversity and community structure.

Conclusion: In-depth analysis of HLA-B27 TG rats with and without arthritis has revealed the presence of arthritis-associated microbiota, which may explain why only some animals develop arthritis. These distinct arthritis-associated microbial communities will be further tested by microbiota transfer experiments in other genetic backgrounds. These results may provide valuable insights into the relationship between HLA-B27 and ERAP1, and their effects on arthritis and gut inflammation in experimental spondyloarthritis.

Disclosure: T. Gill, None; T. Tran, None; S. R. Brooks, None; R. Colbert, None.

Abstract Number: 2084

Targeting the Voltage-Gated K⁺ Channels: T Cell Targeted Therapies for Spondyloarthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Basic Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: TCR (T cell receptor) engagement triggers intracellular Ca⁺⁺ influx through voltage-independent Ca²⁺ channels. This crucial Ca²⁺-influx is only possible by a counterbalancing K⁺ efflux through Kv1.3 and/or KCa3.1. So, these channels are regarded as new targets for immunotherapy: KCa3.1 for acute immune reactions mediated by naïve T cells and Kv1.3 for chronic immune reactions carried by memory T cells. Here we investigated the functional significance of KCa3.1 and Kv1.3 in psoriatic arthritis (PsA) and have used rheumatoid (RA) and osteoarthritis (OA) as controls. To develop K⁺ channel targeted therapies we are working on two small molecules PAP-1 and TRAM-34 which respectively are specific blockers for Kv1.3 and KCa3.1.

Methods: 1. We studied skin tissue, synovial tissue, lymphomononuclear cells (LMNC) from blood and synovial fluid from patients with PsA and RA. In these autoimmune conditions we identified Kv1.3^{high} T cells and determined their phenotypic and functional features. 2. CIA mouse model is a well established tool to study IL-23/IL-17 driven autoimmune arthritis. To determine the functional significance of the KCa3.1 channel CIA was induced in KCa3.1^{-/-} mice and in C57BL/6 wild type mice.

Results: PsA synovial tissues (n=6) were enriched with Kv1.3⁺ T cells compared to osteoarthritis (p<.01). Further we noticed KV1.3 K⁺ channels were functionally active and Kv1.3 current in these T cell could be blocked by PAP-1, a potent small molecule inhibitor of KV1.3 K⁺ channels. 2. KCa3.1^{-/-} mice (n=10) failed to develop clinical evidence of arthritis and did not have histological evidence for joint inflammation. Wild-type C57BL/6 mice developed clinical/histopathological evidence of arthritis. Micro-PET imaging as well confirmed these findings. Compared to KCa3.1^{-/-} mice CD3⁺ T cell proliferation in response to chicken collagen II (CCII) by MTT assay was significantly higher in the C57BL/6 wild type mice (p<.001). 3. *In vitro* studies performed with synovial fluid T cells derived from PsA patients demonstrated that the small molecule Kv1.3 blocker PAP-1 dose-dependently inhibited proliferation and suppressed IL-2 and IL-17.

Conclusion: *In vitro* studies and the *in vivo* model (PET CIA mouse model) have demonstrated critical roles of the Kv1.3 and KCa3.1 potassium ion channels in the pathogenesis of T cell mediated autoimmune arthritis. Synthetic small molecules PAP-1 and TRAM-34 respectively for Kv1.3 and KCa3.1 have already been studied for safety and tolerability and these T cell ion-channels blockers provide a promising therapeutic approach for psoriatic disease and other T cell mediated human autoimmune diseases.

Disclosure: S. P. Raychaudhuri, None; S. K. Raychaudhuri, None; H. Wulff, None.

Response Gene to Complement-32 Promotes Kidney Damage in Immune Complex –Mediated Glomerulonephritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Animal Models Poster

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Response Gene to Complement (RGC)-32 is a cell cycle regulator widely expressed in normal tissues including brain, kidney, spleen, thymus, multiple tumors and in a variety of cell lines. RGC-32 is localized in the cytoplasm and translocates to the nucleus upon upregulation by complement activation, growth factors and cytokines. RGC-32 is induced by TGF- β in fibroblasts, astrocytes and human renal proximal tubular cells and mediates TGF- β dependent profibrotic pathways. In immune cells, RGC-32 is upregulated preferentially in murine and human Th17 cells and promotes their differentiation in vitro and in vivo. Increased expression of IL-17 in kidneys of SLE patients and lupus prone mice is critical for the development of LN. We have previously shown that RGC-32 expression is increased in T cells from SLE patients and in tubules and glomerular infiltrating cells in kidney biopsies of patients with LN. To directly assess whether RGC-32 plays a local role in LN downstream of antibody production, we used the anti-glomerular basement membrane Ab-induced GN (AIGN) model to compare parameters of disease severity in RGC-32 deficient and sufficient mice.

Methods: Wild type (WT) and RGC-32^{-/-} mice were immunized with sheep IgG in Complete Freund's Adjuvant followed by injection of sheep nephrotoxic serum. Mice were monitored for proteinuria and blood urea nitrogen. Kidney histopathology was scored from 0 to 3 based on cellularity, endocapillary and mesangial proliferation, crescent formation, necrosis, fibrosis, tubular casts and dilatation. RGC-32 and IL-17A mRNA expression in kidneys was determined by qRT-PCR. Circulating levels and kidney deposition of mouse anti-sheep IgG were quantitated by ELISA and IF, respectively. Splenic B and T cell responses were characterized by flow cytometry.

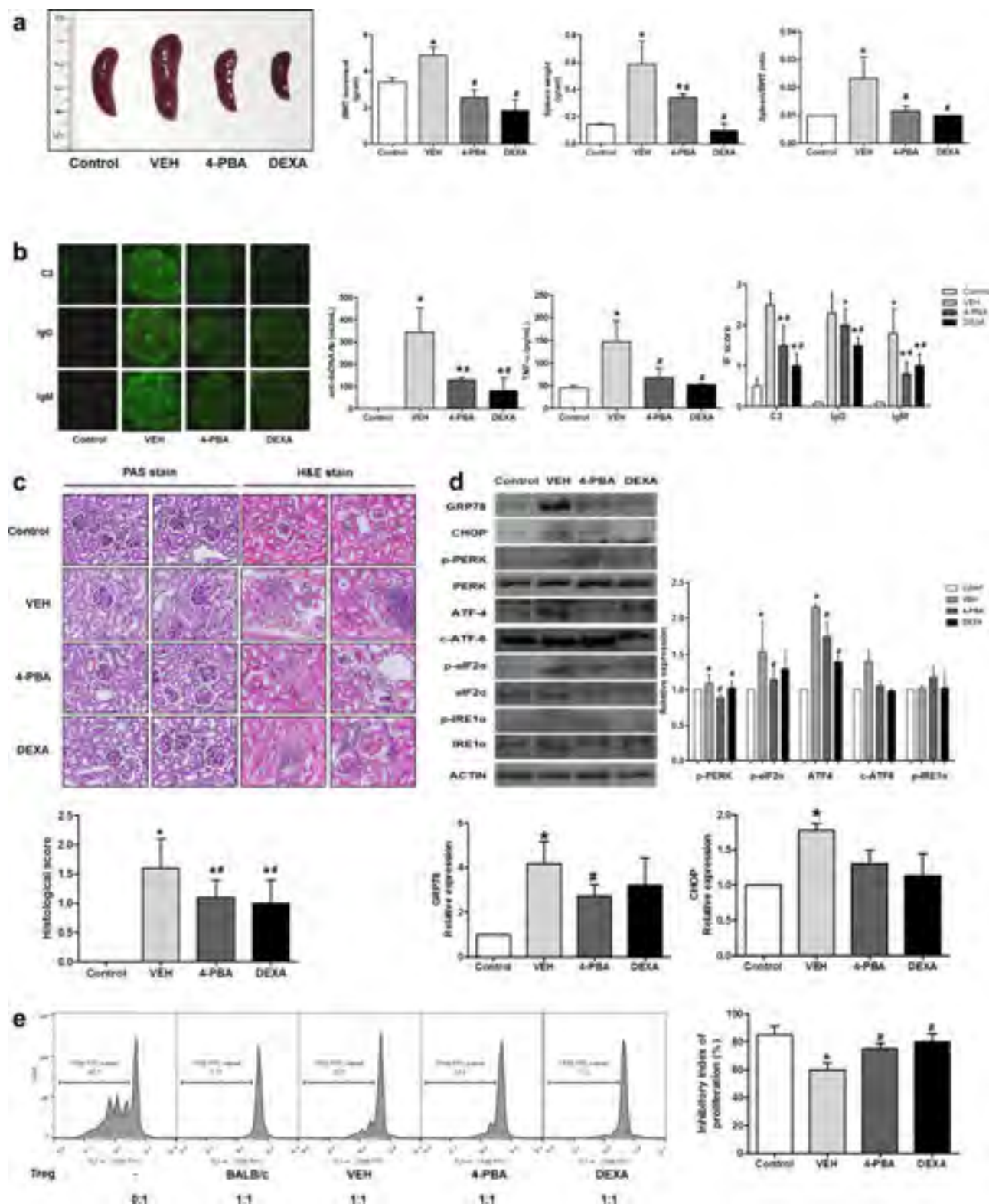
Results: RGC-32 mRNA was significantly upregulated in the kidneys of WT mice with AIGN compared to controls. RGC-32^{-/-} mice displayed an attenuated nephrotoxic injury as demonstrated by significantly decreased proteinuria, a trend for decreased blood urea nitrogen and decreased histopathological glomerular scores. Tubulointerstitial damage did not differ between RGC-32 sufficient and deficient mice. Correlating with RGC-32 expression, IL-17A mRNA expression was upregulated by 3 fold in kidneys of WT mice with AIGN while it was downregulated by 5 fold in RGC-32^{-/-} mice. RGC-32 deficiency did not interfere with the induction of AIGN as mouse anti-sheep IgG titers, percentage of splenic germinal center B cells, plasma cells, effector CD4⁺ T cells, Tregs, IL-17A and IFN- γ secreting cells did not differ between RGC-32^{-/-} and WT mice. Furthermore, kidney deposition of autologous antibodies was comparable between the two groups.

Conclusion: These results suggest that RGC-32 contributes to the pathogenesis of immune complex mediated GN by promoting local IL-17A production and subsequently the development of end-organ damage. These data support further efforts to examine the mechanisms by which RGC-32 modulates local IL-17 expression and enhances kidney damage and suggest that RGC-32 is a potential novel therapeutic target in the treatment of LN.

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4-Phenylbutyric Acid Mediates Therapeutic Effect in Systemic Lupus Erythematosus: Observations in an Experimental Murine Lupus Model

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Background/Purpose: The purpose of the present study was to investigate whether ER stress inhibition by 4-phenylbutyric acid (4-PBA) ameliorates lupus manifestations in an experimental lupus model and the effect of ER stress inhibition by 4-PBA on the frequency and function of regulatory T cells (Treg).

Methods: A murine lupus model was induced through a 4-week treatment with Resiquimod, a toll-like receptor agonist 7. From the 8th week, the mice were treated with phosphate buffered saline, 4-PBA, and dexamethasone for 4 weeks. The increment of body weight, spleen weight, anti-dsDNA antibody titer, serum cytokines level, and the pathology of glomerulonephritis were analyzed at 12 weeks of age. The population of immune cellular subset, including activated T and B lymphocytes and Treg, and suppressive functions of Treg, were measured.

Results: 4-PBA significantly decreased the level of anti-dsDNA antibodies and serum TNF- α in the murine lupus model. A significant decrease in accumulation of immunoglobulin and glomerulonephritis score was also observed in 4-PBA-treated and dexamethasone-treated mice compared to vehicle-treated group. ER stress inhibition decreased the activated T and B lymphocytes population of splenocytes, but the population of Treg was not significantly different between vehicle group and 4-PBA group. However, a markedly enhanced suppressive capacity of Treg was detected in 4-PBA-treated group.

Conclusion: Our results suggest that ER stress inhibition attenuates disease activity, especially of lupus nephritis, in an experimental model by improving the suppressive capacity of Treg. Thus, reduction of ER stress could be used as a beneficial therapeutic strategy in SLE.

Disclosure: Y. Choi, None; J. H. Jung, None; E. K. Lee, None; M. S. Lee, None; C. Lee, None; W. H. Yoo, None.

Abstract Number: 2087

Kidney Tissue Damage in Mice with Single and Combined Abnormalities in Complement, Interferon and Apoptotic Cell Clearance

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Background/Purpose: Lupus nephritis (LN) affects ~70% of systemic lupus erythematosus (SLE) patients and is one of the main contributors to morbidity and mortality. While defective clearance of apoptotic cells (AC), autoantibodies, and type 1 interferons (IFN-I), are strongly implicated in lupus pathogenesis, the precise way that each impacts kidney protection and injury is unknown.

Methods: To investigate mechanisms of kidney injury in a lupus-like disease model, we created C57BL/6 mice with defective clearance of AC (*Mfge8*^{-/-}) and anti-chromatin antibodies (*sle1*) that were also deficient in either C1q [C1q Triple

mutant (C1qTM)] or C3 (C3TM). Kidney injury was evaluated by urine albumin/creatinine ratio (UACR), PAS staining, and immunofluorescence (IF) staining. The effect of IFN-I on disease was studied in C3TM mice by a single injection of an adenovirus expressing IFN α (AdV-IFN α).

Results: *Sle1* mice deficient in MFG-E8 developed significantly higher titers of autoantibodies directed at lupus antigens compared to *sle1* mice alone. When *Mfge8*^{-/-}*Sle1* mice also had C1q or C3 deficiency, a further increase in anti-DNA and other autoantibodies was observed. Both TM strains showed AC accumulation in the kidneys and C1qTM mice had decreased survival. Remarkably, we detected glomerular deposition of C3/C3d in C1qTM and the membrane attack complex (MAC) in C3TM mice. To dissociate the effects of complement on B cells versus effects on the kidney, we studied the impact of defective AC clearance and complement deficiencies on kidney injury in double knockout (DKO) (*Mfge8*^{-/-}*C1q*^{-/-} or *Mfge8*^{-/-}*C3*^{-/-}) mice using Nephrotoxic Nephritis model (NTN). NTN in C1qDKO and C3DKO mice revealed a significantly elevated UACR compared to the single mutants, i.e. worse kidney disease. This effect was independent of antibody deposition in the kidney as similar IgG levels were detected in all NTS-treated strains. IF analyses revealed glomerular C3/C3d deposition in C1qDKO mice and MAC deposition in C3DKO mice. A single injection of AdV-IFN α accelerated kidney damage in C3TM mice, resulting in high anti-dsDNA IgG titers, UACR, renal IgG deposition, and PAS staining.

Conclusion: These findings demonstrate that, in the context of reduced clearance of AC, early complement components have two distinct functions: they prevent enhanced B cell autoreactivity and protect against kidney disease. Increased glomerular C3/C3d deposition in C1qTM and NTN C1qDKO mice suggest activation of the lectin or alternative complement pathways following AC accumulation. Increased MAC deposition in C3TM and NTN C3DKO mice indicates that, in the absence of C3 and presence of AC, a C3-independent mechanism leads to distal complement activation and MAC formation. This effect is further exacerbated by IFN α suggesting a mechanism of disease progression in human SLE in the context of C3 absence and/or consumption. These data prompt models of tissue injury in low complement states that will require assessment in human SLE and provide two distinct perspectives: i) a rationale for targeted therapeutics that are not currently used and ii) a cautionary note about the use of current complement inhibitor therapies.

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Abstract Number: 2088

Human TLR8 at the Interface between Innate and Adaptive Immunity in Systemic Lupus Erythematosus

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Session Information

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Background/Purpose: Infiltrating macrophages are one of the hallmarks of renal inflammation and kidney damage in lupus nephritis (LN). Surprisingly overexpression of TLR8, but not other endosomal TLRs, was observed in renal macrophages of nephritic NZB/W mice and in LN kidneys. Myeloid cells and neutrophils primarily express TLR8 but as its function differs from mouse to man, its role in autoimmunity remains poorly understood. Recently, TLR8 activation was shown to drive differentiation of T-follicular helper (T_{FH}) cells which are crucial regulators of the germinal-center response and humoral immunity. Herein, we aimed to evaluate the functional consequence of one or two copies of huTLR8 on autoimmunity and renal inflammation in murine SLE.

Methods: NZW/B6, NZW/B6.Yaa and Sle1.Yaa mice expressing 1 (NZW/B6 strains) or 2 (Sle1.Yaa strain) copies of huTLR8 as a BAC transgene (huTR8tg) were generated and followed clinically. HuTLR8 DNA copy number and mRNA expression was confirmed by qDigital and qRT-PCR respectively. 24-week-old huTLR8tg NZW/B6.Yaa mice were administered TL-506 (TLR8-agonist) subcutaneously for 4 weeks and spleens and kidneys were harvested for analysis at 8 weeks. Serum autoantibodies were assessed over time. Spleen weights were assessed and splenocytes, kidney cells and bone marrow cells were characterized by flow cytometric analysis.

Results: A single copy of huTLR8 did not exacerbate clinical disease, however, subcutaneous TLR8-agonist administration appeared to enhance germinal center formation and plasma cell generation in male NZW/B6.Yaa huTLR8tg mice. Strikingly, huTLR8.tg SLE1.Yaa males expressing 2 copies of huTLR8 showed accelerated renal disease and mortality by 4 months of age compared with >9 months in Sle1.Yaa controls. Anti-RNP and anti-cardiolipin antibodies developed by 7-10 weeks of age in both male and female huTLR8.tg mice but maximal titers were the same as in their SLE1.Yaa counterparts. Splenomegaly was observed in both male Sle1.Yaa- ($p<0.001$) and female Sle1-huTLR8.tg mice ($p=0.0013$). Flow cytometric analysis of splenocytes from heterozygous huTLR8.tg SLE1.Yaa males showed an acceleration of memory T cell expansion but similar numbers of germinal center (GC) B cells and T_{FH} cells as their wild type Sle1.Yaa counterparts. By contrast there was a 10 fold increase in splenic myeloid cells compared to their SLE1.Yaa counterparts including macrophages, dendritic cells and neutrophils. Interestingly, aged huTLR8tg SLE1 females often showed distended caeca, intestinal obstruction, cataract, periocular alopecia and blepharitis, indicating a disrupted epithelial and mucosal homeostasis in these mice.

Conclusion: One copy of huTLR8 does not exacerbate lupus in NZW/B6.Yaa mice. One copy of huTLR8 induces splenomegaly with myeloid cell expansion and memory T cell activation in Sle1.Yaa mice, but does not cause B cell expansion or an increase in germinal center cells; two copies of huTLR8 in this strain causes early mortality. Further elucidating how dysregulated TLR8 signaling accelerates disease and disrupts homeostasis is crucial to better understand the role of this TLR in autoimmunity and will facilitate more precise therapeutic targeting.

Disclosure: N. I. Maria, None; M. Woods, None; S. Martinez, None; C. Raparia, None; W. Huang, None; A. Davidson, None.

Abstract Number: 2089

The Differential Impact of the Abrogation of the Costimulatory Molecule CD137 Ligand on Renal and Cerebral Manifestations in C57BL/6.Fas^{lpr} mice

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Session Information

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Session Title: Systemic Lupus Erythematosus – Animal Models Poster

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Session Time: 9:00 AM-11:00 AM

Background/Purpose: Costimulatory molecules which mediate cross-talks between leukocytes, have been identified to play a pathogenetic pivotal role in systemic lupus erythematosus (SLE). Abrogation of the costimulatory CD137-CD137 ligand (CD137L) system has previously been shown to worsen systemic lupus erythematosus and yet improve experimental autoimmune encephalitis in murine models. Here, we aimed to investigate the phenotypic effects in dermatological, renal and cerebral manifestations, and the potential alterations of the immunological mechanisms when CD137L was absent in a murine lupus model.

Methods: B6.CD137L^{-/-} and lupus-prone C57BL/6.Fas^{lpr} (B6.lpr) mice were crossed to obtain mice knocked out for the CD137L and Fas genes (DKO mice). The DKO mice were studied and compared with the B6.lpr mice phenotypically regarding survival, dermatitis, glomerulonephritis, cerebral demyelination, microglial activation and hippocampal long-term potentiation (LTP) induced by theta burst stimulation (TBS). Serological studies and the frequency of splenic leukocyte subsets and helper T (Th) cell transcription factors were studied and compared between the DKO and B6.lpr mice (and B6.WT mice where required).

Results: An observation of 22 months involving 226 DKO and 137 B6.lpr mice demonstrated significantly more severe dermatitis (mean±SE unit: 1.03±0.2 vs. 0.37±0.1, $p=0.003$), more frequent proliferative glomerulonephritis (33.3% vs. 7.9%, $p=0.005$) and shorter survival (median± SE survival: 44±4.5 versus 74±3.3 weeks, $p<0.001$) of the DKO mice compared to the B6.lpr mice. Conversely, microglial activation and cerebral demyelination were milder and the synaptic efficacy in terms of hippocampal LTP was superior in the DKO than B6.lpr mice, without affecting the basal synaptic transmission. DKO mice had a significantly higher frequency of splenic Th17 (CD3⁺CD4⁺CD8⁺RoRγt⁺) cells than the B6.lpr and B6.WT mice while the frequencies of Th1 and Th2 cells were comparable between the groups. *In vitro* experiments which involved T-cell stimulation with anti-CD3 did not alter intracellular IL-10 and IL-17 expressions in splenocytes of the DKO and B6.pr mice but a lower proportion of splenic IL-10-producing CD11b⁺ cells were identified in

the DKO mice than in the B6.lpr and B6.WT mice. Serological studies revealed lower serum IL-10 levels in the DKO than in the B6.lpr mice ($p=0.017$).

Conclusion: In the absence of CD137L, higher splenic Th17 and lower IL-10-producing CD11b⁺ frequencies and lower serum IL-10 levels may explain the more severe renal and dermatological pathology of B6.lpr mice, yet this creates an environment in the central nervous system for milder cerebral damage and enhanced long-term synaptic plasticity.

Disclosure: A. Mak, None; B. Dharmadhikari, None; L. W. Wong, None; S. K. Sreedharan, None; H. Schwarz, None.

Abstract Number: 2090

Identification of a Role for Monocytes in Murine Lupus Associated Diffuse Alveolar Hemorrhage By Mass Cytometry

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Session Information

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Session Title: Systemic Lupus Erythematosus – Animal Models Poster

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Background/Purpose: Diffuse alveolar hemorrhage (DAH) is a life-threatening pulmonary complication of systemic lupus erythematosus. The inciting pathology is thought to be pulmonary capillaritis but the pathogenic cell population(s) that elicits inflammation and tissue destruction remains unclear. Mice treated intraperitoneally with the hydrocarbon pristane develop features of human SLE including autoantibodies, glomerulonephritis and DAH.

We used mass cytometry complemented with studies in informative marrow transplantation and genetic deletions to identify pathogenic cellular populations in DAH.

Methods: Wild-type and transplanted/transgenic mice (6-8 weeks of age) were treated with 0.5 mL of pristane intraperitoneally and analyzed after 2 weeks. Lung sections were analyzed by H&E staining. Lung tissue was digested using collagenase and analyzed by mass cytometry (CyTOF) and flow cytometry.

Results: Mass cytometry using heavy-metal isotopes was superior to fluorescence-based flow cytometry for unambiguous identification of cell subsets in strongly autofluorescent lung tissue digest. Using a 25-antibody mass cytometry panel, we found that alveolar macrophages and eosinophils were significantly reduced in DAH while both Ly6C^{hi} and Ly6C^{lo} monocytes increased markedly. Dendritic cells and interstitial macrophages were minimally affected by pristane treatment. Using bone marrow transplant, we found that the expanded lung monocytes in DAH are bone marrow-derived and differentiate into macrophage-like cells. The incidence of DAH was reduced in Ccr2 (CC-chemokine receptor 2)-deficient mice with impaired monocyte egress from the bone marrow (11/15 in wild-type vs. 3/15 in Ccr2^{-/-}, $p < 0.01$). Furthermore, Irf8 (interferon regulatory factor 8)-deficient mice with absent Ly6C^{hi} monocyte development were strongly protected against the development of DAH (21/25 in wild-type vs. 1/25 in Irf8^{-/-}, $p < 0.001$).

Conclusion: We demonstrate the utility of mass cytometry for unambiguous identification of immune cells in DAH. We found that monocytes infiltrate the lungs in pristane-treated mice and play an essential role in the development of DAH. These findings suggest that monocytes could represent a therapeutic target in SLE-associated human DAH.

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Mucosal-Associated Invariant T (MAIT) Cells As a Potential Therapeutic Target for Systemic Lupus Erythematosus

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Background/Purpose: Mucosal-associated invariant T (MAIT) cells are innate T cells that are restricted by the nonpolymorphic MHC-related molecule-1 (MR1) and express a semi-invariant TCR α chain: V α 7.2-J α 33 in humans and V α 19-J α 33 in mice. Previously, we reported that MAIT cells are activated in patients with systemic lupus erythematosus (SLE) and that the activation state of these cells correlated with disease activity. By using MR1 deficient mice lacking MAIT cells, we revealed that MAIT cells contribute to the disease severity of lupus in Fc γ RIIB^{-/-} *Yaa* mice. In this study, we asked how MAIT cells are involved in the pathogenesis in this lupus model and explored their potential as a therapeutic target for lupus. We also investigated whether MAIT cells infiltrate in the nephritic kidneys of lupus patients.

Methods: Fc γ RIIB^{-/-} *Yaa* mice were crossed to MR1 deficient mice lacking MAIT cells, and disease progression was compared between MR1^{-/-} and MR1^{+/+} Fc γ RIIB^{-/-} *Yaa* mice. The levels of serum anti-dsDNA antibody and urinary albumin were measured. The severity of nephritis was assessed histologically. T and B cell subsets in the spleen and kidneys at 2 months of age were analyzed by using flow cytometry. Fc γ RIIB^{-/-} *Yaa* mice were treated with a suppressive MR1 ligand (MR1L) orally three times weekly for 4 weeks starting at 4 weeks of age. Infiltration of MAIT cells was assessed in kidney biopsy specimens from lupus patients using a confocal microscope.

Results: MAIT cell deficiency improved the disease course of lupus in Fc γ RIIB^{-/-} *Yaa* mice as shown by the increased survival rate, reduced serum anti-dsDNA antibody levels, glomerulonephritis scores and IgG and C3 deposition in glomeruli in MR1^{-/-} Fc γ RIIB^{-/-} *Yaa* mice. MAIT cells enhanced germinal center reaction which was accompanied by the increase of T follicular helper cells, germinal center B and plasma cells and the reduction of T regulatory and T follicular regulatory cells. The presence of MAIT cells enhanced cytokine producing capacity of T and innate-T cells in the spleen and kidneys. Activated MAIT cells were accumulated in the kidneys and produced inflammatory cytokines. Administration of MR1L decreased serum anti-ds DNA antibody levels and reduced germinal center B and plasma cells. The deposition of IgG and C3 in the glomeruli was also reduced in Fc γ RIIB^{-/-} *Yaa* mice treated with MR1L. MAIT cells were accumulated in the nephritic kidneys of lupus patients.

Conclusion: MAIT cells exacerbated the disease severity of lupus by enhancing autoantibody production and tissue inflammation in Fc γ RIIB^{-/-} *Yaa* mice. MAIT cells were found in the nephritic kidneys of lupus patients, suggesting these cells may also contribute to lupus pathogenesis in human patients. As administration of MR1L suppressed the disease course of lupus, MAIT cells hold potential as a new therapeutic target for SLE.

Disclosure: G. Murayama, None; A. Chiba, CeUGAI PHARMACEUTICAL CO., LTD, 8; A. Nomura, None; H. Amano, None; K. Yamaji, None; N. Tamura, Chugai Pharmaceutical Co., LTD, 2, Astellas Pharma Inc., 2, ASAHI KASEI MEDICAL, 2, Sanofi K.K., 8, Bristol-Myers Squibb, 8; S. Miyake, TAIHO PHARMACEUTICAL CO., LTD., 5, Chugai Pharmaceutical Co., LTD, 8, Astellas Pharma Inc., 8, Bristol-Myers Squibb, 8, Sanofi K.K., 8, Pfizer, Inc., 8, AYUMI Pharmaceutical Co., LTD, 8.

Glucocorticoid-Induced Leucine Zipper (GILZ) Is a Novel Checkpoint Regulator of Type I Interferon (IFN) Production in SLE

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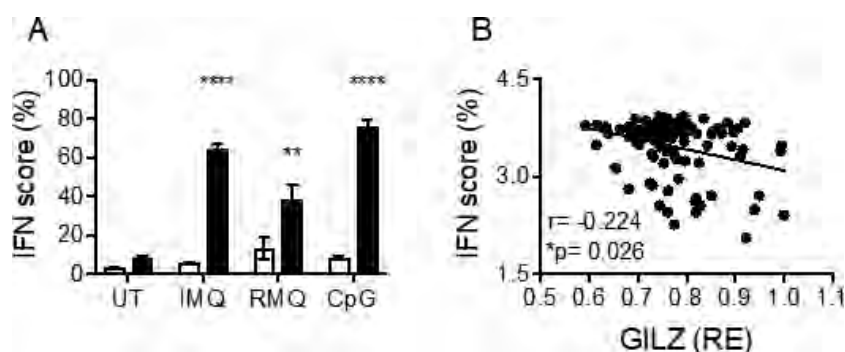
Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Glucocorticoids (GC) remain the frontline treatment in Systemic Lupus Erythematosus (SLE) despite their predictable metabolic adverse effects. Type I interferons (IFN), produced by TLR7 and TLR9 activated plasmacytoid dendritic cells (pDC), play a critical role in SLE pathogenesis, but are not suppressed by GC. Glucocorticoid-Induced Leucine Zipper (GILZ) is an endogenous anti-inflammatory protein, which regulates T and B cell activation and is suppressed in SLE; whether GILZ regulates type 1 IFN production in SLE is not known. We tested the hypothesis that GILZ inhibits Type I IFN production in SLE.

Methods: We performed *in vitro* analysis on pDC and bone marrow-derived DC (BMDC), and *in vivo* studies, of WT and GILZ^{-/-} mice using stimuli of TLR4 (LPS), TLR7 (Imiquimod), TLR7/8 (Resiquimod) and TLR9 (CpG). IFN was measured using a IFN luciferase assay, ELISA and Luminex. IFN-stimulated gene signatures (ISG) were measured by qPCR. To determine whether GILZ regulates IFN in human SLE, we mined a public gene expression dataset GSE61635. We examined IRF7 and NF- κ B involvement in GILZ effects using ChIP and reporter assays.

Results: GILZ deficiency resulted in increased pDC and BMDC secretion of IFN in response to TLR7, TLR7/8 and TLR9 stimulation. GILZ deficiency was also associated with increased ISG in naïve spleen cells, and TLR-stimulated pDC (Fig 1A) and BMDC of GILZ^{-/-} mice. Correspondingly, increased IFN was seen in GILZ^{-/-} mice in response to TLR7/8 stimulation *in vivo*. In human SLE whole blood, GILZ mRNA was negatively correlated with ISG (*IFI44*, *IFI44L*, *RSAD2*, *IFI27*) (Fig 1B). In BMDC, TLR activation suppressed GILZ, but increased IRF7 expression. CHIP-qPCR showed GILZ enrichment at the IRF7 locus in unstimulated cells, which decreased following TLR7/8/9 activation, indicating direct binding of GILZ to the IRF7 locus as the mechanism through which it regulates IFN α production. In addition, TLR7/8/9-induced NF- κ B activation was suppressed by GILZ, and increased IFN β in GILZ^{-/-} BMDC was inhibited by NF- κ B inhibition.



Conclusion: GILZ is a novel endogenous regulator of Type I IFN production *in vitro*, *in vivo*, and in human SLE, which has direct effects on both IRF7 and NF- κ B and thereby both IFN α and IFN β . This suggests that suppressed GILZ is permissive for IFN activation in SLE, and represents the mechanism through which IFN escapes glucocorticoid suppression.

Disclosure: C. Nataraja, None; E. Morand, None; J. Lee, None; T. Bennett, None; J. Flynn, None; J. Harris, None; S. Jones, None.

Glucocorticoid-Induced Leucine Zipper (GILZ) Deficiency Worsens Autoimmunity in the *Lyn*-Deficient Murine Model of Lupus By Disinhibiting the Type I Interferon (IFN) Pathway

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Session Information

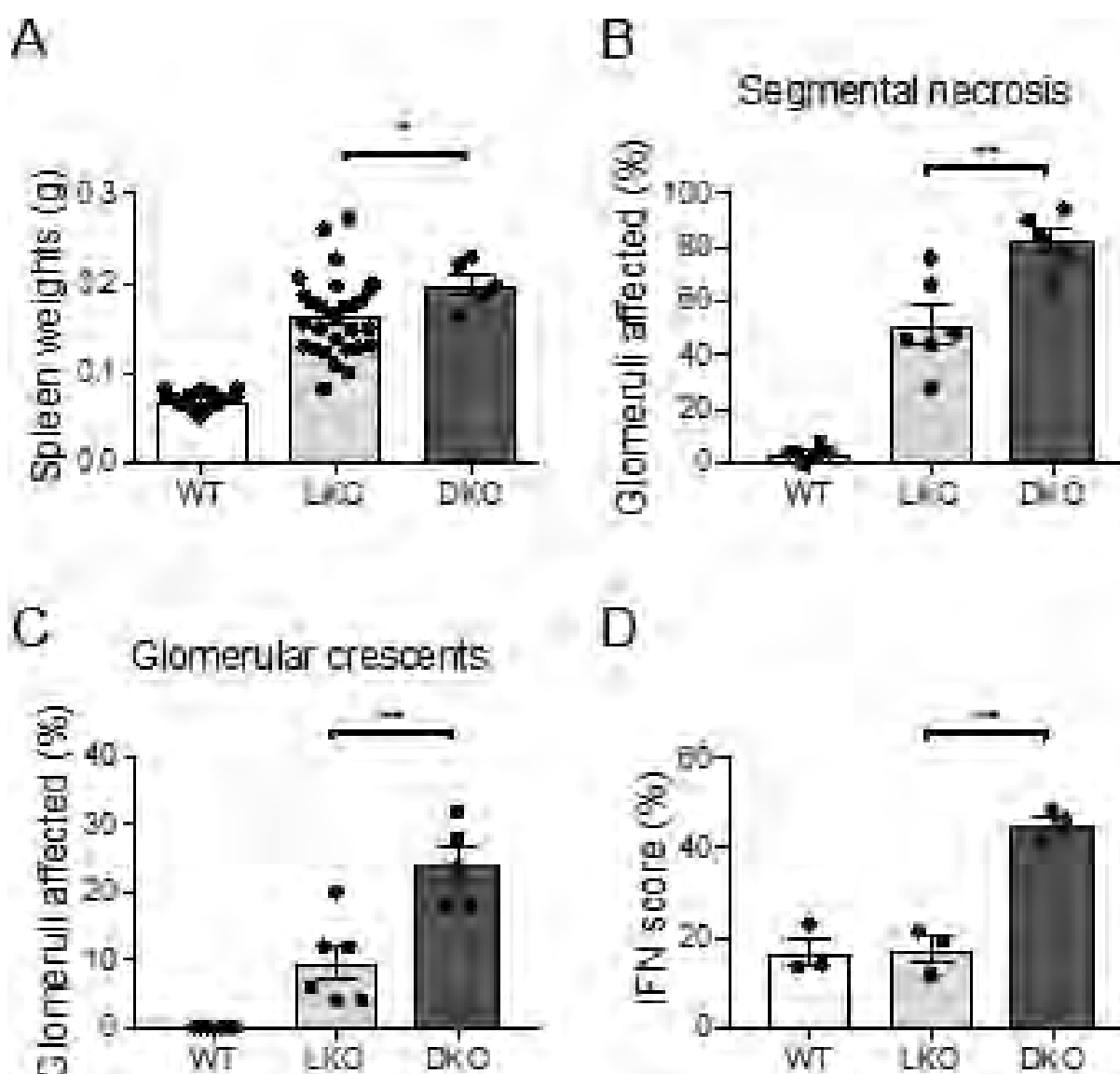
Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Animal Models Poster

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease associated with B cell hyperactivity driven by dysregulated type I IFN. *Lyn*-deficient mice develop lupus-like autoimmunity due to loss of inhibitory regulation of B cell receptor signalling, resulting in hyperactive B cells, excess IL-6 production, and tissue inflammation. Mice deficient in glucocorticoid-induced leucine zipper (GILZ), an intracellular protein involved in glucocorticoid actions, develop lupus-like autoimmunity and excess B cell activation. GILZ is suppressed in human SLE



(Jones et al., 2016), but the effects of GILZ in murine models of SLE are unknown. We tested the hypothesis that loss of GILZ exacerbates autoimmunity in the *Lyn*-deficient murine model of lupus.

Methods: We crossed GILZ-deficient mice onto a *Lyn*-deficient background (GILZ-*Lyn* double knockout (DKO)) and compared them to WT and *Lyn* KO mice. The effects of GILZ deficiency on spleen weight, nephritis, serum autoantibodies and cytokines, and spleen cell expression of Type I interferon-induced genes (ISG) were examined.

Results: We observed heightened lupus-like autoimmunity in GILZ-*Lyn* DKO mice, compared to *Lyn* KO, that include increased spleen weight ($p=0.041$) and more severe glomerulonephritis, including worse glomerular segmental necrosis ($p=0.0051$) and crescent formation ($p=0.0044$) (Fig 1A-C). Despite this, serum levels of serum autoantibodies against ENAs (dsDNA, histone, Sm, Jo-1, U1RNP, Ro52, ribosomes, and Scl-70) and a panel of serum pro-inflammatory cytokines (BAFF, IL-6, IFN γ , IL-10 and TNF α) measured by Luminex assay were unaffected. In contrast, GILZ deficiency in *Lyn* deficient mice resulted in increased expression of ISG (*ifit44*, *uspi18*, *oas3*, *isg15*, *mx1*, and *irf7*) and an overall ISG signature ($p=0.0023$) (Fig 1D).

Conclusion: In *Lyn* KO lupus-prone mice, GILZ deficiency significantly exacerbated disease expression, accompanied by activation of Type I IFN, despite serum autoantibody titres and pro-inflammatory cytokines being unaffected. This suggests an inhibitory effect of endogenous GILZ on Type I IFN pathways and consequent tissue injury in this model, downstream of autoantibodies. A GILZ-based treatment could be a potential therapeutic strategy in SLE.

Disclosure: C. Nataraja, None; E. Morand, None; J. Lee, None; T. Bennett, None; J. Flynn, None; J. Harris, None; S. Jones, None.

Abstract Number: 2094

Examining T Cell Exhaustion in Murine Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

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Session Time: 9:00 AM-11:00 AM

Background/Purpose: While T cells are important for the pathogenesis of systemic lupus erythematosus (SLE) and lupus nephritis, little is known about how T cells function after infiltrating the kidney in the setting of organ damage. The current paradigm suggests that kidney infiltrating T cells (KITs) are activated effector cells contributing to tissue damage and ultimately organ failure. We aim to examine this hypothesis by directly examining KITs.

Methods: KITs and Splenic CD4⁺ and CD8⁺ T cells were isolated from diseased mice in 3 murine models of SLE (MRL/lpr, MRL.TLR9^{-/-} (fas sufficient), and Fc γ RIIB^{-/-}.Yaa). T cells were evaluated for phenotypic, functional, metabolic, and transcriptional profiles as noted in results.

Results: The majority of CD4⁺ and CD8⁺ KITs in all three murine lupus models are not effector cells, as hypothesized, but rather, KITs mimic the “exhausted” phenotype observed in tumor infiltrating T cells. KITs exhibited a significant increase in expression of multiple inhibitory receptors including PD-1, Lag3, and Tim3, and proved highly dysfunctional with reduced cytokine production and proliferative capacity. Mechanistically this was linked directly to metabolic and specifically mitochondrial dysfunction. This phenotype is driven by the expression of an “exhausted” transcriptional signature.

Conclusion: KITs derived from lupus prone mice exhibit a phenotypic and transcriptional signature that is analogous to what has been described in the setting of chronic infection and T cell infiltrates in the tumor microenvironment. Our data reveal that the tissue parenchyma has the capability to suppress T cell responses and limit damage to self. These findings may (1) lend insights into autoimmune related adverse events associated with cancer immunotherapy, which targets T cell exhaustion (2) open novel avenues for the treatment of autoimmunity based on selectively exploiting the exhausted phenotype of tissue-infiltrating T cells and (3) inform on pathophysiologic relationships between parenchymal tissues and infiltrating cells in numerous autoimmune disease states.

Disclosure: J. Tilstra, None; L. Avery, None; A. Menk, None; R. Gordon, None; S. Smita, None; L. Kane, None; M. Chikina, None; G. Delgoffe, None; M. Shlomchik, None.

Abstract Number: 2095

Neutralizing CXCL13 Attenuates Neuropsychiatric Disease in Lupus-Prone Mice

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Session Information

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Session Title: Systemic Lupus Erythematosus – Animal Models Poster

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Session Time: 9:00 AM-11:00 AM

Background/Purpose: Despite the many lupus patients affected by neuropsychiatric signs and symptoms, the pathogenesis of neuropsychiatric disease in SLE remains unclear. MRL-lpr/lpr mice, a classic mouse model of SLE, presents with neuropsychiatric abnormalities similar to those seen in human disease including cognitive abnormalities and affective deficits. We recently found that MRL-lpr/lpr mice develop tertiary lymphoid structures (a.k.a. ectopic germinal centers) in the brain choroid plexus. Structurally and functionally, tertiary lymphoid structures resemble lymph nodes forming at the site of chronic inflammation to create more localized and specialized immune responses, which may however be detrimental in autoimmune disease. CXCL13 is a key chemokine that drives the formation of lymphoid structures. We studied whether antibody blockade of CXCL13 would prevent brain tertiary lymphoid structure formation and attenuate neuropsychiatric SLE.

Methods: Female MRL-lpr/lpr mice received intraperitoneal injections of a monoclonal anti-CXCL13 antibody, an IgG isotype control antibody, or PBS 3 times weekly for 12 weeks starting at 6-8 weeks of age. During the last week of treatment at 18-20 weeks of age, mice were assessed for cognitive dysfunction (object placement and object recognition tests), and affective deficits (Porsolt forced swim test). Brain tissues were analyzed by histology and immunofluorescent staining.

Results: Anti-CXCL13 mAb treated MRL/lpr mice displayed significant improvement in depression-like behavior as compared to the two control groups, as shown by increased mobility during the forced swim assessment ($p=0.004$). However, cognitive function assessment showed no significant improvements in visuospatial or recognition memory. Preliminary analysis of brain tissue histology showed less choroid plexus lymphocytic infiltration in anti-CXCL13 treated mice. However, there were no apparent differences in systemic disease, as spleen-to-body weight and lymph node-to-body weight ratios, as well as serum IgG anti-double stranded DNA antibody titers, were similar among the groups.

Conclusion: Preventing choroid plexus tertiary lymphoid structure formation by neutralizing CXCL13 attenuates depression-like behavior but not cognitive dysfunction in MRL-lpr/lpr mice. Our results suggest that brain tertiary lymphoid structures play an important role in the pathophysiology of affective deficits, although whether this effect of treatment was limited to the brain remains to be determined. Furthermore, CXCL13 neutralization may be a potential therapeutic strategy to target neuropsychiatric lupus.

Disclosure: M. Huang, None; A. Stock, None; C. Putterman, None.

Abstract Number: 2096

Ectonucleotidase CD73 Suppresses Autoantibody Production and Arterial Vasculopathy in Murine Lupus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Animal Models Poster

Session Type: ACR Poster Session C

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Background/Purpose: CD73 is a surface nucleotidase that extends into the extracellular space where it generates adenosine from AMP. By regulating a cell's "purinergic halo," CD73 contributes to the maintenance of immune and vascular homeostasis. Although CD73 is known to be expressed on the surface of T cells, endothelial cells, and myeloid-lineage cells, it has yet to receive intensive study in the context of lupus.

Methods: In C57BL/6 Fas^{lpr/lpr} (B6.lpr) mice, we generated littermates of 3 genotypes: CD73^{+/+}, CD73^{+/-}, and CD73^{-/-}. Autoantibody levels were measured at 16 and 32 weeks of age. At 32 weeks of age, splenocyte activation/polarization and endothelial function were also characterized. In parallel to the B6.lpr studies, we also assessed the role of CD73 in an inducible model of lupus. C57BL/6 mice with no lupus predisposition (CD73^{+/+}, CD73^{+/-}, and CD73^{-/-}) received topical dosing of the TLR7/8 agonist R848 (resiquimod) three times weekly. Autoantibody levels were measured 4 and 8 weeks after the initiation of treatment.

Results: As compared with B6.lpr CD73^{+/+} mice, B6.lpr mice with CD73 deficiency (either partial or complete) demonstrated a greater than 2-fold increase in serum anti-double-stranded-DNA antibodies at both 16 and 32 weeks; this was despite no difference in total IgG levels between groups. Beyond antibodies, CD73-deficient B6.lpr mice demonstrated additional abnormalities in peripheral blood including relative lymphopenia (5-fold decrease), neutropenia (4-fold decrease), and elevated levels of cell-free DNA. In 32-week-old B6.lpr CD73^{+/+} mice, the majority of CD73-positive cells infiltrating spleens were either T cells (CD4⁺ and double-negative) or CD11b⁺Ly6C⁺ monocytes (likely myeloid-derived suppressor cells/MDSCs). In contrast, surface CD73 was not detected on CD8⁺ T cells or granulocytic MDSCs. Endothelial function was measured in the aortas of 32-week-old B6.lpr mice by *ex vivo* exposure of aortic rings to acetylcholine in a wire myography system. As compared with CD73^{+/+} mice, CD73 deficiency resulted in impaired vessel-wall relaxation consistent with decreased nitric oxide production and resultant endothelial dysfunction. In the R848-inducible model of lupus, anti-double-stranded-DNA antibody production was again potentiated by CD73 deficiency. Studies are now underway to comprehensively phenotype the spleens of both mouse models in order to understand the dominant CD73-expressing suppressive cell type in lupus.

Conclusion: These data reveal a protective role for CD73 in lupus autoimmunity and vascular disease, and are consistent with a model whereby a key suppressive cell type (either CD4⁺ regulatory T cells or monocytic MDSCs) wields CD73 and adenosine to suppress B cell function. These data also suggest that novel therapeutic strategies might harness purinergic signaling to limit the damage inflicted by lupus upon organs and blood vessels.

Disclosure: R. A. Ali, None; N. R. Pearce, None; S. Yalavarthi, None; K. B. Atkins, None; A. A. Gandhi, None; Y. Kanthi, None; J. S. Knight, None.

Abstract Number: 2097

Monotherapy with Filgotinib, a JAK1-Selective Inhibitor, Reduces Disease Severity and Alters Immune Cell Subsets in the NZB/W F1 Murine Model of Lupus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Animal Models Poster

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Session Time: 9:00 AM-11:00 AM

Background/Purpose: SLE is a heterogeneous autoimmune disease characterized by immune system hyper-activation leading to the production of autoantibodies and immune attack on multiple organs including skin and kidney. Interferon α/β (IFN α/β) alter immune cell populations and are risk factors for SLE. Antibody blockade of the IFN α receptor has demonstrated clinical efficacy in SLE and validates targeting this pathway. JAK1 mediates signaling downstream of IFN α/β , and therefore an inhibitor of JAK1 is anticipated to reduce IFN signaling, normalize immune cell subsets, and improve SLE disease activity. The JAK1 selective inhibitor, filgotinib (FIL) is currently being evaluated in Ph2 studies in cutaneous lupus and Sjogren's syndrome. This work characterizes the disease efficacy and mechanism-of-action of FIL in the NZB/W F1 murine model of lupus.

Methods: FIL was tested in the NZB/W F1 murine model of lupus at two concentrations (0.05% and 0.1%) formulated in chow and administered ad libitum from weeks 28-40. Cyclophosphamide was used as a positive control. Efficacy was determined by proteinuria, renal histopathology, clinical pathology, and survival. Splenic lymphocyte and myeloid subsets

were analyzed by flow cytometry at study termination. Kidney gene expression was determined by qPCR, and serum cytokines by Luminex. An in vitro murine whole blood pSTAT assay and PK were used to establish a PD-PK-efficacy correlation.

Results: In the model, FIL dose-responsively decreased proteinuria and renal inflammation, improved glomerular morphology and renal function, and increased survival. Diseased mice had increased CD11⁺ dendritic cells (DCs), decreased naive T cells, and increased ratio of memory:naive T cell populations versus non-diseased mice. FIL showed a reversal of these cell populations toward non-diseased levels. Consistent with the reduction of inflammation, FIL demonstrated reduction of pro-inflammatory cytokines (e.g., TNF α , IL-6, IL-18, IL12p70, and IL9) and chemokines (e.g., CXCL1, CXCL10, MIP1 β , MCP1 and MCP3), and an increase of IL-4. FIL normalized renal expression of genes for structural damage, apoptosis, complement system, and nucleic acid sensing. Importantly, among the 16 type I interferon signature genes (ISGs) measured, 12 showed a dose-responsive decrease with FIL treatment. Calculated whole blood pSTAT inhibition is consistent with FIL pSTAT coverage achieved in clinical studies.

Conclusion: FIL demonstrated efficacy in reducing disease activity in a murine model of lupus nephritis. This effect was coupled with normalization of splenic cell subsets, ISGs, and cytokines, and provides a mechanistic basis for the evaluation of FIL in the current clinical Phase 2 studies.

Disclosure: P. Han, Gilead Sciences, 1, 3; C. Pohlmeier, Gilead Sciences, 1, 3; C. Shang, Gilead Sciences, 1, 3; Z. Cui, Gilead Sciences, 1, 3; D. Lopez, Gilead Sciences, 1, 3; A. Clarke, Gilead Sciences, 1, 3; R. Jones, Gilead Sciences, 1, 3; N. Mollova, Gilead Sciences, 1, 3; I. Mikaelian, Gilead Sciences, 1, 3; D. Newstrom, Gilead Sciences, 1, 3; S. Zaboli, Gilead Sciences, 1, 3; A. Shauf, Gilead Sciences, 1, 3; J. Di Paolo, Gilead Sciences, 1, 3.

Abstract Number: 2098

NRF2 Downregulates Inflammation and Protects Against Autoimmune Lung Disease in Experimental Lupus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Animal Models Poster

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: The transcription factor nuclear factor erythroid 2-related factor (Nrf2) is a master regulator of genes involved in cellular defense against oxidative and electrophilic stresses. It forms a cytoplasmic complex with the ubiquitin ligase KEAP1 and CUL3, which in unstressed conditions promote the ubiquitin-mediated degradation of Nrf2. Modification of the reactive cysteine residues of KEAP1 by electrophiles or ROS reduces the ubiquitin ligase activity of KEAP1/CUL3, resulting in Nrf2 stabilization and binding to antioxidant response elements (AREs) in the promoters of target genes. As there is functional cross-talk between Nrf2 and NF- κ B mediated inflammatory responses, we hypothesized that Nrf2 might downregulate chronic inflammation in mice with diffuse alveolar hemorrhage (DAH) associated with pristane-induced lupus, a disease driven by macrophages (M ϕ).

Methods: Murine M ϕ subsets were analyzed by flow cytometry and the cell subsets were flow-sorted. Binding of Nrf2 to its target sequence was determined in vitro. Gene expression in sorted M ϕ from pristane or mineral oil (MO) treated mice was determined using RNA-Seq and real-time PCR. Pristane-treated C57BL/6 mice received injections of CDDO-imidazolide every other day, a potent inducer of Nrf2/ARE signaling, or vehicle, starting 3-days after pristane treatment. DAH was assessed on day-14.

Results: M ϕ extracts from pristane-treated B6 mice exhibited lower Nrf2 binding in vitro to AREs vs. extracts from MO-treated controls. RNA-Seq showed that a series of Nrf2-regulated genes involved in the response to oxidative stress were expressed at lower levels in M ϕ from pristane vs. MO-treated mice. Low expression levels were confirmed by real-time PCR and M ϕ from pristane-treated mice had increased mitochondrial superoxide (MitoSox red staining), decreased mitochondrial membrane potential (tetramethylrhodamine staining), and increased cellular ROS (dichlorofluorescein diacetate staining) vs. controls. In vivo injection of CDDO-imidazolide decreased the number of CD11b+Ly6Chi (inflammatory) M ϕ , increased CD11b+CD138+ (pro-resolving) M ϕ , and reversed the pristane-induced changes in mitochondrial superoxide and cellular ROS while restoring mitochondrial membrane potential. Finally, CDDO-imidazolide treatment greatly attenuated the severity of DAH in pristane-treated mice (P<0.0001). A less potent Nrf2 activator, diethylmaleate, also was protective and reduced M ϕ TNF α production.

Conclusion: These observations suggest that oxidative stress is involved in the pathogenesis of chronic inflammation experimental lupus and that pharmacological Nrf2 activation can protect lupus mice from fatal lung hemorrhage.

Disclosure: S. Han, None; H. Zhuang, None; P. Lee, None; L. Yang, None; W. Reeves, None.

Abstract Number: 2099

Bruton's Tyrosine Kinase (BTK) Inhibition Modulates Multiple Cell Types Instrumental in the Pathogenesis of Lupus Nephritis

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Session Information

Session Date: Tuesday, October 23, 2018

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Background/Purpose: Lupus nephritis (LN) is a serious manifestation of systemic lupus erythematosus (SLE) that adds substantial morbidity and mortality. Passive transfer of pre-formed nephritogenic antibodies to susceptible mice, or nephrotoxic serum nephritis (NTN), results in immune-mediated nephritis that closely models LN. We have previously shown that the BTK inhibitor BI-BTK-1 reverses the functional and structural kidney disease seen following induction of NTN. In the current study, we elucidated the effects of BI-BTK-1 on various immune cell populations to determine the mechanism of protection, as well as the pathways by which BI-BTK-1 reverses established nephritis. Furthermore, we assessed the effects of early and late withdrawal of treatment on the course of nephritis.

Methods: For induction of NTN, 11-week old 129 mice were immunized with rabbit IgG in CFA, and five days later passively transferred with nephrotoxic rabbit anti-mouse antibodies. To assess the effect of early (starting day 4) and late (starting day 8) treatment with BI-BTK-1 on immune cell infiltration and kidney pathology, we sacrificed BI-BTK-1 or control treated mice on days 7, 10, and 13 (n=5 per group) (Figure 1, "Treatment Delay" experiment). Kidneys were processed for flow cytometry and histology to assess the kinetics of different immune cell populations within the kidney over the course of nephritis. In a separate experiment, we began treating mice with BI-BTK-1 on day 4, and compared the effects of withdrawing treatment early (day 6) and late (day 9) on disease remission and flare (Figure 1, "Treatment Withdrawal" experiment).

A. Effects of treatment delay



B. Effects of treatment withdrawal



Figure 1. Timeline

Results: We found that early treatment with BI-BTK-1 appears to prevent the development of nephritis, and late treatment appears to reverse established disease, in murine NTN. Interestingly, early treatment withdrawal (day 6) resulted in increasing proteinuria comparable to sick control mice. Late withdrawal (day 9), however, provided significant protection against the development of proteinuria and kidney dysfunction (increased BUN) throughout the two week duration of the study ($p < 0.001$ versus sick control, $p < 0.01$ versus early withdrawal). In the treatment delay experiment, flow cytometric analysis revealed a significant reduction of kidney infiltrating M1 (inflammatory) macrophages by day 13 in both early and late treatment, whereas control treated mice exhibited decreased M2 macrophages. Both early and late treated mice had reduced kidney B220+ cells, whereas only mice treated early showed a reduction in neutrophils and CD4+ cells. Renal histology and RT-PCR results are pending.

Conclusion: Our study demonstrates the multiple cell types affected by treatment with BTK inhibition in LN. Furthermore, these results shed light upon the effects of withdrawing treatment, which may eventually have important implication for treatment decisions in human disease.

Disclosure: S. Chalmers, None; S. Garcia, None; E. Klein, Boehringer Ingelheim, 3; J. S. Fine, Boehringer Ingelheim, 3; G. Nabozny, Boehringer Ingelheim, 3; M. Ramanujam, Boehringer Ingelheim, 3; C. Putterman, Boehringer Ingelheim, 2.

Abstract Number: 2100

Topical Endocannabinoid Administration Protects MRL-Lpr/Lpr Mice from Cutaneous Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Animal Models Poster

Session Type: ACR Poster Session C

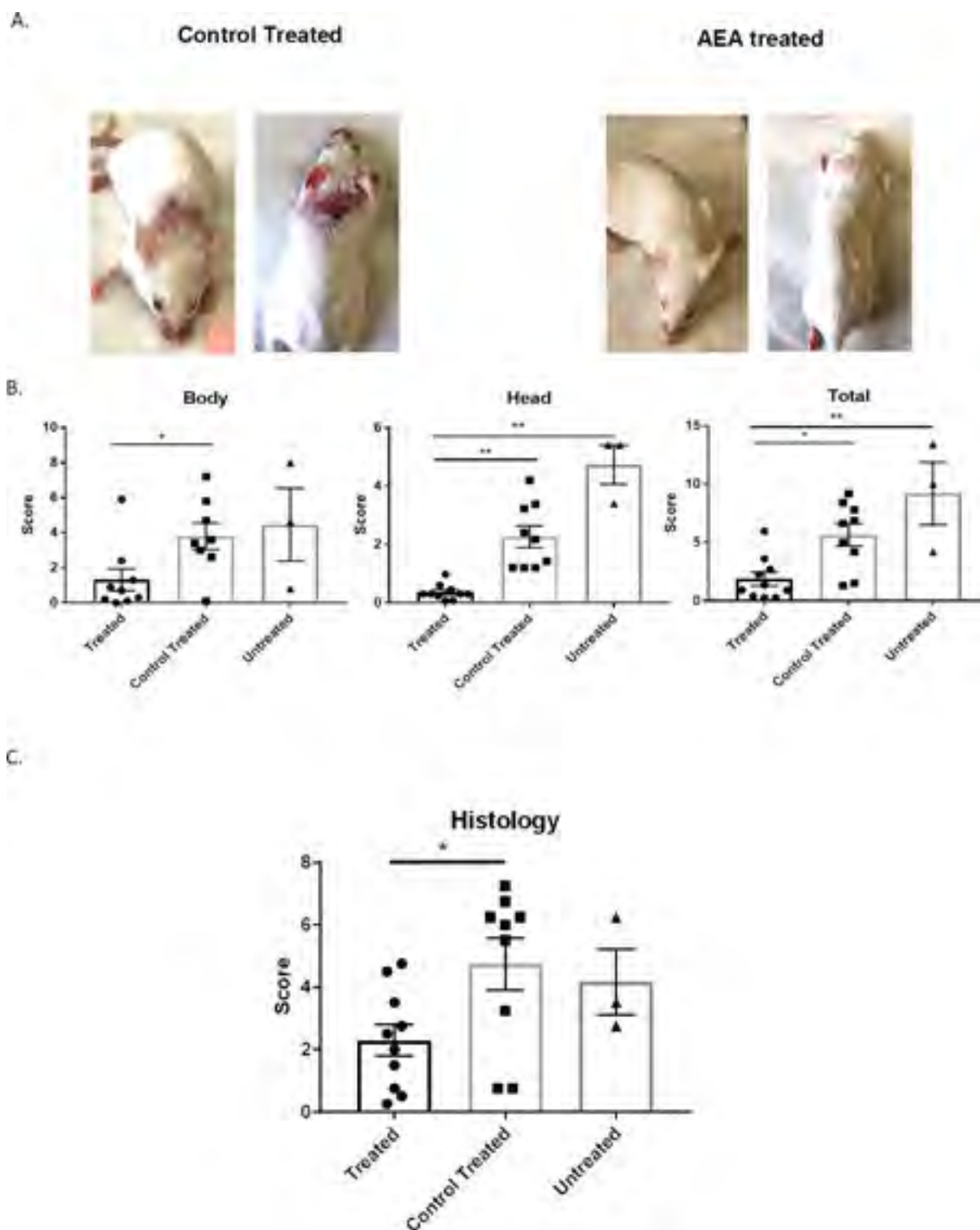
Session Time: 9:00 AM-11:00 AM

Background/Purpose: Cutaneous lupus erythematosus (CLE) affects ~75% of SLE patients and has a profound impact on quality of life. While the morbidity from CLE is significant, effective therapeutic options, including topical therapies, are limited. There is growing evidence that the manipulation of the endocannabinoid system has immunomodulatory activity which could be clinically translated to a broad range of cutaneous and systemic inflammatory diseases, although data is limited specially with respect to topical administration. In this study, local application of anandamide (AEA), a highly lipophilic endocannabinoid, was evaluated in MRL/lpr lupus prone mice, which spontaneously develop skin lesions similar to chronic CLE both clinically and histologically. To overcome known issues with respect to topical delivery of cannabinoids, nanoparticle encapsulation was employed.

Methods: Nanoparticles with 125 nm radius were loaded with 4% AEA (AEA-np) and mixed with coconut oil (25% by weight). Starting at 10 weeks of age, female MRL/lpr mice were treated twice a week with interscapular application of the AEA compound without hair removal. Control groups of mice were treated topically with empty nanoparticles ("control treated") or received only coconut oil ("untreated"). Mice were regularly scored using a validated modified CLASI tool to assess the effect of AEA on cutaneous disease. At 20 weeks of age, mice were sacrificed and the skin harvested for histological analysis.

Results: AEA-np treated mice had significantly improved skin lesions. Interestingly, this improvement was noted both where the nanoparticles were directly applied, as well as the face/snout region. At the time of sacrifice, AEA treated mice had significantly less macroscopic lesions (Figure 1A), which were scored blindly ($p < 0.0001$) (Figure 1B). Moreover, significant histologic improvement was seen as well ($p < 0.05$; Figure 1C). No differences were seen in systemic disease parameters, namely circulating anti-dsDNA antibodies and proteinuria levels. Immunofluorescent staining of skin sections to characterize cellular infiltration and mechanistic studies in vitro are in progress.

Conclusion: Together, these data demonstrate that topical administration with AEA loaded nanoparticles significantly prevents the development of CLE in an established animal model of lupus. Furthermore, this work reinforces and highlights the utility of targeting the endocannabinoid system for autoimmune rheumatic diseases.



Disclosure: S. Chalmers, None; S. Garcia, None; A. Draganski, None; J. Doerner, None; A. Friedman, Zylto Therapeutics, 5; J. Friedman, Zylto Therapeutics, 5; C. Putterman, None.

UV-Induced Skin Inflammation Is Exacerbated in Lupus-Prone Ro60 Knockout Female Mice with Interferon Priming

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Background/Purpose: Photosensitivity is a major symptom of lupus, and excessive sunlight can cause skin rashes and flares of disease activity in systemic lupus erythematosus (SLE). Although UV-induced skin inflammation has been widely studied, it remains elusive how UV triggers lupus. A previous study demonstrated that mice lacking the Ro60 autoantigen (Ro60^{-/-}) have increased photosensitivity and spontaneously develop lupus after 6 months of age. Also, it has been shown that lupus patients have elevated levels of type I interferon (IFN). To dissect molecular mechanisms by which UV-induced inflammatory responses are exacerbated in lupus, we combined IFN priming with photosensitive Ro60^{-/-} mice and investigated the effects of UV on lupus-prone skin.

Methods: A recombinant adenovirus encoding IFN- α was administered to 4–5-month-old mice by retro-orbital injection two weeks prior to UV irradiation (IFN priming). Subsequently, mice were irradiated with UVB 250 mJ/cm²/day for three consecutive days. Skin biopsies were taken at four time points and subjected to histological, flow cytometry, and gene expression analyses. Eight groups ($n = 4$ mice per group) were compared: wild type (WT) versus Ro60^{-/-} (C57BL/6 background), male versus female, and with or without IFN priming.

Results: Three consecutive UV exposures caused severe skin damage (erythema and hyperkeratosis) in IFN-primed Ro60^{-/-} females. Gene expression analysis of UV-irradiated skin revealed that many inflammatory genes were differentially upregulated among the 8 mouse groups. Specifically, a combination of IFN priming, Ro60 deficiency, and female gender augmented UV-induced upregulation of *Irf7* (regulator of type I IFN gene induction), *Isg15* (IFN-stimulated gene), and *Ccl2* (chemokine for monocyte recruitment). Consistently, flow cytometry analysis revealed that more inflammatory monocytes (CD45⁺Ly6C^{high}Ly6G^{low}) were recruited to UV-irradiated skin 1 day after the third UV in IFN-primed Ro60^{-/-} females than in IFN-primed WT females. Intriguingly, IFN-primed Ro60^{-/-} females exhibited significantly higher levels of *Ifnar2* (IFN α receptor subunit 2) following UV than their WT counterparts, likely contributing to augmented type I IFN responses.

Conclusion: Inflammatory responses to UV irradiation were augmented in IFN-primed Ro60^{-/-} female, but not in WT, male, or unprimed mice. This female predominance is comparable to that of SLE in humans. Ro60 is an RNA-binding protein and binds to small noncoding RNAs. Lack of Ro60 may disrupt RNA homeostasis and activate RNA sensors and type I IFN pathways. This study provides novel insight into lupus susceptibility factors (IFN priming, Ro60 deficiency, and female gender) that contribute to exacerbation of UV-induced skin inflammation.

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Hyaluronic Acid Synthesis Inhibition Blocks Nephritis and Extends Lifespan in Mice Prone to Lupus

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Background/Purpose: Hyaluronic acid (HA) is a component of the extracellular matrix and is known to be involved in cancer biology. Although evidence suggests that HA plays a role in the expression of kidney pathology in patients with SLE, its function is not fully understood. T cells from patients with SLE express increased amounts of CD44 to which HA binds inducing T cell polarization, adhesion, and migration (J Immunol. 2007, 178:1938-47). In this study, we asked how HA contributes to the expression of lupus pathology and whether it can be targeted therapeutically.

Methods: We analyzed HA expression in kidneys from patients with SLE and a lupus-prone MRL/lpr mice, by using immunohistochemistry. Peripheral blood mononuclear cells (PBMC) from healthy donors were stimulated with anti-CD3/CD28 in the presence or not of HA. 4-Methylumbelliferone (4-MU), an HA synthase inhibitor, was orally administrated to male MRL/lpr starting at the age of 3 months (prevention) or 5 months of age (treatment). In addition, in a third group, 4-MU was administered at the age of 3 months and discontinued at the age of 5 months. At the end of the treatment tissues (kidney and skin) were evaluated by immunohistochemistry, spleen, lymph node and kidney cells were evaluated by flow cytometry.

Results: Kidneys from MRL/lpr and patients with SLE displayed increased accumulation of HA compared to control tissues coinciding with the accumulation of immune cells. MRL/lpr mice which received 4-MU at 3 months of age did not develop any organ inflammation, but discontinuation of treatment resulted in late disease (proteinuria, kidney and skin inflammation) development. Treatment of 5 months old mice that already developed disease halted further progression of the disease with minimal reversal of tissue pathology. Treatment with 4-MU led to increased proportions of Tregs and reduced double negative (DN)T cells, Th17, and Th1 cells both in the spleen and the kidney. Exposure of PBMC from healthy donors to low molecular weight HA *in vitro* while stimulated with anti-CD3/CD28 led to the expansion of DNT cells.

Conclusion: HA expression is increased in tissues in patients with SLE and lupus-prone mice and probably enable the homing and activation of CD44 positive T cells. Inhibition of HA synthesis prevents disease development but fails to reverse established pathology. In addition, HA promotes the generation of CD4⁺CD8⁻CD3⁺ cells which are known to contribute to lupus immunopathology. The development of drugs which prevent the entrance and activation of T cells to tissues should represent novel approaches to prevent relapses in patients with SLE.

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Abstract Number: 2103

Using a *Drosophila* Model to Unravel the Genetic Complexity of Systemic Lupus Erythematosus

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Background/Purpose: The objective of our research is to understand the genetic architecture and molecular mechanisms that contribute to the development and progression of the autoimmune disease systemic lupus erythematosus (SLE). SLE occurs when the immune system loses self tolerance and triggers a self-directed immune response, often leading to inflammation and tissue damage. Recent evidence demonstrates that both the acquired and innate immune responses are implicated in SLE pathogenesis, however the role of innate immunity is largely understudied. Additionally, while a large number of genes have been linked to SLE, efforts into understanding the basis of the disease have been hindered by this genetic complexity. In order to understand the role of innate immune responses and to unravel the underlying genetics, we have developed a *Drosophila* model of SLE. *Drosophila* provides many advantages for this research, including a wealth of genetic tools, experimental tractability and a highly conserved innate immune response. To develop the SLE model, we have focused on a mutant strain of *Drosophila* which mounts a self-directed cellular inflammation response that results in the damage of self tissue.

Methods: We have characterized the *Drosophila* SLE model using a combination of cell biology approaches including immunofluorescence and cell stains, genetic mapping, and RNA interference mediated reverse genetics.

Results: We find that the *Drosophila* SLE-like phenotype arises from two distinct mutations. The first mutation is a gain of function mutation in the *Drosophila* homolog of Janus Kinase (JAK). Mutations in JAK are linked to a variety of autoimmune diseases including SLE. The second mutation is a loss of function mutation in an enzyme of the N-glycosylation pathway, and accordingly we find that the mutants have decreased N-glycosylation of extracellular matrix (ECM) proteins. Interestingly, altered N-glycosylation is seen in SLE patient samples, and mutations in ECM proteins have been linked to SLE pathogenesis. Additionally, reverse genetics suggests that the *Drosophila* homolog of the SLE-linked integrin gene ITGAM plays a central role in the self tolerance mechanism that is mediated by ECM protein N-glycosylation.

Conclusion: These results demonstrate a high degree of genetic conservation between SLE and our *Drosophila* model. Our data have uncovered a functional link between SLE risk factors, including increased JAK activity, altered N-glycosylation of ECM proteins and decreased integrin receptor signaling, that has not been previously identified in traditional SLE models. This establishes the benefit of our high-throughput and genetically tractable *Drosophila* model to better understand the genetic complexity underlying SLE pathogenesis. Our findings further suggest that additional research into the genetic basis of the *Drosophila* model will likely uncover new SLE genes and provide insight into the molecular interactions between SLE risk factors, and may therefore open new avenues for clinical research or point to new therapeutic strategies.

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Abstract Number: 2104

Glomerular and Tubular Transcriptional Profiles Reveal Gene Clusters Specific for Different Stages of Glomerulonephritis in NZM2328 Mice

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Session Information

Session Date: Tuesday, October 23, 2018

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Background/Purpose: NZM2328 mice spontaneously develop glomerulonephritis (GN) and females commonly progress to renal failure. Our previous study showed that acute GN (aGN) and chronic GN (cGN) are two pathological stages, controlled by different genetic loci, and aGN need not progress to cGN. In this study, glomerular and tubular transcriptional profiles were obtained from kidneys of NZM2328 female mice at 8-9, 26, and 36 weeks of age. Transcriptome analysis was employed to characterize the pathologic processes in the separate regions of the affected kidneys to develop better insight into the check points operative in the control of tissue pathology.

Methods: Glomerular and tubular cells were collected separately using Laser Microdissection (LMD) from the same kidneys of NZM2328 female mice at 8-9, 26, and 38 weeks of age. Total RNA from LMD-derived cells were labeled and hybridized on Affymetrix Mouse Genome 430 v2.0 microarrays. LIMMA statistical analyses in R software was used to generate lists of genes with significant differential expression (DE) compared with young mice using a FDR < 0.2 threshold. Weighted gene co-expression network analysis (WGCNA) and module preservation analyses in R were used to find the modules specific for different disease stages. Gene set variation analysis (GSVA) was used to identify the enriched gene clusters in the various GN stages. Upstream regulators(UR) were identified using Ingenuity Pathway Analysis (IPA) combined with LIMMA DE results.

Results: Hierarchical analyses using LIMMA and GSVA showed that glomerular transcriptional profiles from kidney samples can be classified into four distinct groups, normal, aGN, tGN and cGN, which correlated with tissue histology. In contrast, tubular transcriptional profiles from the same kidneys could only be separated into normal and GN, indicating common tubular gene expression profiles across GN stages. Gene clusters generated by WGCNA not only could identify

specific modules for tGN and cGN stages in the glomeruli, but also were able to identify gene modules specific for aGN, tGN and cGN stages in tubular cells. Upstream regulators, such as IL1 β , and Tgf β 1, were found in tGN glomerular modules, indicating that these genes might play an important role in the disease progression from aGN to cGN. However, UR failed to be identified in tubular gene clusters at the aGN or the tGN stage, suggesting that tubular changes at these stages might be related to changes resulting from glomerular insult.

Conclusion: Both hierarchical analysis and GSVA showed that glomeruli expression changes correlated with disease progression. However, tubules exhibited diversity in their gene expression profiles. WGCNA-generated gene clusters and their upstream regulators were identified in glomeruli at the tGN and cGN stages, as well as in tubular cells at the cGN stage. These novel co-expression gene network clusters could provide a basis to identify specific pathways and biomarkers governing the progression through different disease stages in both the glomeruli and tubules of lupus nephritis.

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Abstract Number: 2105

Genetic Analysis of a *Drosophila* Systemic Lupus Erythematosus Model Reveals Lupus Susceptibility Genes

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Animal Models Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder with various immunological abnormalities and a diverse range of clinical symptoms. In contrast to the traditional belief that SLE is solely an adaptive immune disorder, multiple studies of patient samples and mouse models have revealed the involvement of innate immune mechanisms in the initiation of SLE. However, the exact role of innate immunity in SLE pathogenesis is unknown, thus we have developed a new model to understand the genetic complexity of disease development and susceptibility. *Drosophila* is well suited to this research as the innate immune pathways are well conserved between humans and mammals including the JAK-STAT pathway which has been specifically implicated in pathology of SLE in humans. To understand the regulation of the JAK-STAT pathway and its role in SLE, we are utilizing our newly developed *Drosophila* SLE model, which has a gain of function mutation in the *Drosophila* homolog of JAK. Our goal is to identify genes that contribute to the SLE-like phenotype with a particular focus on JAK-STAT signaling.

Methods: To identify genes that modify the *Drosophila* SLE model phenotype, we performed two genetic screens. Forward genetic screening was performed in which 20% of the *Drosophila* genome was screened to look for regions containing genes involved in the autoimmune response in the *Drosophila* SLE model. To understand the role of JAK-STAT signaling in regulating autoimmunity, we conducted a reverse genetic screen in which we tested the role of candidate transcriptional factors in the SLE model autoimmune phenotype. We selected these genes based on previous links to JAK-STAT and then used RNAi to knockdown these genes in immune cells in our *Drosophila* model.

Results: We performed genetic screening and identified novel genes associated with SLE that may regulate conserved transcriptional networks which underlie self-tolerance. Our genetic modifier screen revealed 12 regions that modified the SLE phenotype. We predict that these regions contain genes that function in SLE-associated autoimmune mechanisms. Since our SLE mutant has a gain of function mutation in JAK-STAT, we conducted a reverse genetic screen that focused on understanding of the role of this pathway in autoimmunity. We discovered that RNAi mediated knockdown of candidate transcription factors in mutant immune cells suppressed the phenotype, suggesting that these genes promote JAK-STAT activity.

Conclusion: This study uncovers novel genetic interactions that may play a role in the contribution of the JAK-STAT pathway to SLE pathogenesis. The human homologs of two of our identified JAK-STAT interacting genes, AFF1 and BACH2, have been previously linked to SLE, whereas the others represent putative novel SLE risk factors. Identification of these new genes and genetic interactions will expand our knowledge of the processes which lead to autoimmune disorders, and investigating their molecular role in the *Drosophila* SLE model may well open a new window for the understanding and clinical treatment of this complex disease.

Abstract Number: 2106

Angiotensin-Converting Enzyme Inhibitors Prevent Spatial Memory Impairment in a Mouse Model of Neuropsychiatric Lupus through LAIR1-Mediated Inhibition of Microglial Activation

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Session Information

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Session Title: Systemic Lupus Erythematosus – Animal Models Poster

Session Type: ACR Poster Session C

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Background/Purpose: Cognitive dysfunction affects up to 90% of patients with systemic lupus erythematosus (SLE), however it is grossly under-recognized, the pathogenesis is poorly understood and no treatments are available. The anti-NMDAR antibody, a subset of anti-DNA antibodies termed DNRAbs, has been strongly associated with cognitive impairment, notably spatial memory impairment, in both mouse models and humans. In a mouse model, DNRAb-mediated brain pathology proceeds through two stages: excitotoxic neuron loss, followed by persistent neuroinflammation resulting in alteration in neuronal integrity and spatial memory impairment. Microglia-mediated inflammation is generally becoming well accepted as one of the main mediators of neurodegeneration. In our studies we are investigating the mechanisms of long-term neuronal dysfunction mediated by transient exposure to DNRAb. Also, with the emerging yet unknown role of the renin-angiotensin-system, notably angiotensin II, in microglia-mediated neuroinflammation in neurodegenerative diseases, angiotensin-converting enzyme (ACE) inhibition could be an attractive treatment option to test for preserving cognitive impairment through its effects on C1q and C1q's inhibitory receptor, LAIR1.

Methods: Mice immunized with DNRAb and then treated with LPS to breach the blood brain barrier and allow transient access of antibody to the hippocampus, were studied for loss of neuronal dendritic complexity using Golgi and for microglial activation with immunohistochemistry. Spatial memory was assessed with a battery of behavioral tests and CA1 hippocampal neuronal activity was assessed with electrophysiology studies. Microglia were depleted with Colony Stimulating Factor 1 Receptor (CSF1R) inhibitor PLX5622. Mice received centrally acting ACE inhibitor, captopril (or control peripherally acting ACE inhibitor, enalapril), one week after LPS for two weeks. ACE levels in brain tissue was checked before and after treatment. C1q-KO mice and LAIR1-Lyz2-Cre mice were also studied to assess the roles of C1q and LAIR-1 in glia-mediated neuroinflammation.

Results: DNRAb mice had significantly decreased dendritic complexity ($p<0.01$), and impaired spatial memory ($p<0.01$), which was preserved in CSF1R-inhibitor treated mice ($p<0.03$) and in C1q-KO mice. These findings suggest that activated microglia and C1q are critical mediators of DNRAb-associated neuronal damage and spatial memory impairment. We further showed that centrally acting ACE inhibitors can preserve neuronal dendrite complexity ($p<0.03$) and cognitive performance ($p<0.01$) in the mouse model. The effect of captopril was diminished in the LAIR1-Lyz2Cre knockout ($p<0.0001$), signifying that LAIR1 is important in the protective mechanism of captopril.

Conclusion: ACE inhibition may be considered as a safe and promising class of therapeutics in cognitive impairment in SLE and represents a strong candidate for future clinical trials aimed at mitigating cognitive dysfunction. Further studies to understand the mechanism of action of ACE inhibitors are needed.

Lupus-Prone SLE1.2.3. Mice Exhibit Loss of Thymus-Derived CD4⁺CD25⁺Helios⁺ Tregs

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Session Information

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a potentially fatal autoimmune disease that is characterized by the production of autoantibodies against nuclear antigens (ANA) and phospholipids (aPL). ANA and aPL production have been found to dependent on activation of complex 1 of the mechanistic target of rapamycin (mTORC1) in several mouse models of SLE (Arthritis Rheumatol. 68:2728-2739, 2016). Mouse models of SLE have been indispensable tools for studying disease pathogenesis, however, each model only recapitulates limited aspects of lupus. SLE1.2.3. mice are mice homozygous for three NZM2410-derive lupus susceptibility loci on the C57Bl/6J background. These mice develop systemic autoimmunity with fatal glomerulonephritis and die typically by 12 months of age. Within the last decade, metabolic pathways have been found to regulate lineage specification in the immune system, many of which have been implicated in disease. Here, we investigated immunometabolic checkpoints of disease pathogenesis in SLE1.2.3 mice.

Methods: SLE1.2.3 mice have been compared to C57Bl/6 wild-type (WT) controls. Mice were matched for age and gender. Splenic tissue were harvested at 30 weeks of age and examined for lineage specification and metabolic changes within the adaptive and innate arms of the immune system via flow cytometry. ANA and aPL were measured as earlier described (Arthritis Rheumatol. 68:2728-2739, 2016). 10,764 immunometabolic parameters were analyzed by flow cytometry and a p-value of less than 0.05 was considered significant for hypothesis testing.

Results: Male and female WT mice produced 0.520 (± 0.042) and 0.670 (± 0.057) μ g of protein per μ L of urine. In contrast, SLE mice had significantly more proteinuria with males and females producing 1.183 (± 0.041 , $p=0.000274$) and 0.906 (± 0.039 , $p=0.0279$) μ g protein per μ L urine. There was also significant elevation of autoantibody production with increases in ANA or anti-cardiolipin by as much as 55-fold. Analysis of the immune system revealed an 18% decrease of CD4⁺ cells ($p=0.02045$). Correspondingly, there was a 22% and 34% increase in CD8⁺ ($p=0.02782$) and CD4⁺CD8⁺ double negative (DN) T cells ($p=0.01505$), respectively. We further found, in male mice, a 31% decrease in CD4⁺Foxp3⁺ Tregs and that mTORC1 activity was decreased by 51% and 39% in regulatory subsets such as CD4⁺Helios⁺ and CD4⁺CD25⁺Helios⁺ Tregs ($p=0.03841$, $p=0.00631$), respectively. In the female mice, mTORC1 activity was decreased in CD4⁺CD152⁺ Tregs decreased by 56% ($p=0.004407$) and mTORC2 activity in CD4⁺CD25⁺ Tregs was decreased by 65% ($p=0.037331$). CD4⁺CD25⁺FoxP3⁺ Tregs were similar in WT and SLE1.2.3 mice.

Conclusion: SLE1.2.3. mice recapitulated lupus pathogenesis which involves ANA and aPL production and glomerulonephritis. Autoantibody production and nephritis has been responsive to mTORC1 blockade with rapamycin. The data suggest that ANA and aPL production may be controlled by mTORC1-dependent development of thymus-derived CD4⁺CD25⁺Helios⁺ Tregs which may serve as targets for therapeutic interventions in SLE.

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Dock8-Positive CD4 T Cell As Autoantibody-Inducing CD4 T (aiCD4 T) Cell That Causes Systemic Lupus Erythematosus (SLE): Proof of Concept of Self-Organized Criticality Theory As a Cause of SLE

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: We found in reproducible experiments in which the mice not prone to autoimmune disease were immunized repeatedly with antigen that overstimulation of CD4 T cells led to the development of *ai*CD4 T cell which had undergone TCR revision capable of inducing varieties of autoantibody and antigen-specific CTL *via* antigen cross-presentation, after which they caused SLE (Tsumiyama K et al., 2009). Here we identify *ai*CD4 T cell as DOCK8+CD4 T cell.

Methods: *ai*CD4 T cell was searched by transferring different fractions of CD4 T cells of x12 OVA-immunized BALB/c female mice into naïve mice and tested if autoantibodies were raised, mass spectrometry, and FACS.

Results: We focused CD45RB^{lo} CD122^{lo}PD-1+CD4 T cell as *ai*CD4 T candidate, and its membrane uniquely expressed DOCK8. DOCK8+CD4 T cell was a large lymphocyte with abundant ER and mitochondria, ICOS+ CXCR5- PD1+ Ly6C+ LFA1+, produced increased IFN γ , IL-4, IL-6, IL-17 and IL-21, and its TCR repertoire was deviated. Upon transfer to naïve mice or to the x8OVA-pre-immunized and CD4 T-depleted mice in which CTL was yet immature, DOCK8+CD4 T cells induced SLE, where anti-dsDNA/Sm Ab, glomerulonephritis of WHO IV/V types (Table, upper), skin liquefaction degeneration, splenic periarteriolar fibrosis with amyloid-like deposits classical of Onion-skin lesion, pericholangitis, pneumonitis, thyroiditis, perineuritis and panniculitis developed. Manifestations including kidney disease (Table, lower) were cured by anti-DOCK8 Ab treatment.

Conclusion: We prove the self-organized criticality theory explaining that autoimmunity arises as a natural consequence of routine but exaggerated immune response against antigen when stimulated maximally beyond immune systems self-organized criticality and show that DOCK8+CD4 T cell causes SLE.

Table.

Effect of the transfer of DOCK8+ CD4 T cell to the kidney disease of recipient mice

Immunization	Transferred cell	WHO class			
		< II	III	IV	V
PBSx12	CD4 ⁺ T cell	71.96±11.04%	28.03±11.04%	0%	0%
OVAx12	DOCK8 ⁺ CD4 ⁺ T cell	68.54±12.39%	29.31±12.75%	2.14±3.30%	0%
OVAx12	DOCK8 ⁻ CD4 ⁺ T cell	18.77±9.40%	33.99±9.78%	31.89±17.04%	15.32±9.17%

*p<0.05 **p<0.001

Effect of anti-DOCK8 Ab treatment to the kidney disease of x12 OVA-immunized mice

Immunization	Treatment	WHO class			
		< II	III	IV	V
PBSx12	Control IgG (n=3)	48.68±12.91%	28.05±9.45%	34.17±3.72%	9.08±3.01%
OVAx12	Control IgG (n=5)	7.33±5.12%	18.33±7.34%	24.04±7.55%	50.26±17.62%
OVAx12	Anti-DOCK8 Ab (n=6)	33.91±14.45%	36.37±6.98%	19.93±11.64%	8.70±8.78%

*p<0.05 **p<0.005 ***p<0.001

Disclosure: S. Shiozawa, None; K. Tsumiyama, None; Y. Miyazaki, None; K. Sakurai, None; M. Miyazawa, None.

Abstract Number: 2109

Activation of T Follicular Helper Cells through Epigenetic Regulation By STAT1 and STAT4 in Lupus Patients

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Session Information

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Session Time: 9:00AM-11:00AM

Background/Purpose: During the T cell differentiation, signal transducer and activators of transcription (STAT) family transcription factors play pivotal roles in specifying T cell lineages. T follicular helper (Tfh) cells serve important roles in the development and progression of systemic lupus erythematosus (SLE). To assess the characteristics and mechanisms of differentiation of Tfh cells, we studied the underlying epigenetic modifications by cytokine-induced STAT activation and the phenotype of circulating T helper cells in SLE patients.

Methods: Peripheral blood mononuclear cells from patients with SLE and healthy controls (HC) were analyzed by flow cytometry. The phenotype of circulating T cells was defined based on flow cytometric analysis for human immune system termed “the Human Immunology Project” proposed by NIH/FOCIS. Naive CD4⁺ T cells and memory CD4⁺ T cells were isolated and cultured with T cell receptor (TCR) and various cytokines in vitro. Expression of characteristic markers of Tfh cells and phosphorylation of STATs were analyzed by flow cytometry and qPCR. Histone modifications were evaluated by chromatin immunoprecipitation (ChIP)-PCR. Peripheral blood mononuclear cells from SLE patients and healthy controls were analyzed by flow cytometry and productions of cytokines in serum were tested by cytometric bead array.

Results: Among the immunoregulatory cytokines, IL-12 induced the differentiation of CD4⁺CXCR5⁺CXCR3⁺Bcl-6⁺Tbet⁺IL-21⁺IFN- γ ⁺ T cells, which share features of both Tfh and Th1 cells. The loci of Bcl-6 and Tbet at STAT binding sites were marked by bivalent histone modifications. After IL-12-stimulation, both STAT1 and STAT4 were phosphorylated simultaneously and directly bound on *BCL6* (encoding Bcl-6) and *TBX21* (encoding Tbet) gene loci accompanied by suppression of repressive histone mark trimethylated histone 3 lysine 27. Compared with HCs, the proportion of CD4⁺CXCR5⁺CXCR3⁺CCR6⁺CD69⁺ activated Tfh-Th1-like cells were significantly increased in patients with SLE (mean 0.7 vs 0.4, p=0.02). Levels of serum IL-12 and expression of IL-12 receptors in memory T cells were significantly increased in patients with SLE compared to HCs (p<0.01). Furthermore, the level of pSTAT1, pSTAT4 and Tbet were higher in activated Tfh-Th1-like cells than non-Tfh-Th1 cells (p<0.05).

Conclusion: The findings suggest that IL-12-mediated co-activation of STAT1 and STAT4 alters histone modification, resulting in development of Tfh-Th1-like cells that are characteristically expanded in patients with SLE. This could be one of underlying mechanisms responsible for the pathogenesis of Tfh cells in SLE. Thus, modulation of STAT-mediated gene regulation in Tfh cells potentially offer the opportunities for cell-specific treatment of SLE.

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Association of Systemic Lupus Erythematosus (SLE) Genetic Susceptibility Loci with Lupus Nephritis in Children and Adults with SLE

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex, chronic, autoimmune disease. Genome-wide association studies (GWAS) have identified multiple risk SNPs in HLA and non-HLA gene regions. There is evidence that genetics are also important in lupus nephritis (LN) risk. LN is one of the most common and severe manifestations of SLE. The purpose of this study was to determine the association of known SLE risk SNPs with LN in both childhood-onset (cSLE) and adult-onset SLE (aSLE) populations.

Methods: The study population included two tertiary care SLE cohorts; one with cSLE and the other with aSLE. Participants met American College of Rheumatology (ACR) and/or Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE, with prospectively collected clinical and laboratory data. Participants were genotyped on the Illumina MEGA or Omni1 arrays. Principal components were calculated in reference to the 1000 genomes project, and ancestry was genetically inferred. Ungenotyped SNPs were imputed. HLA alleles were imputed in Europeans only. HLA and non-HLA additive SLE weighted genetic risk scores (GRSs) were computed using published SLE GWAS weights. LN was confirmed by renal biopsy as defined by the WHO or the International Society of Nephrology/Renal Pathology Society or diagnosed with renal casts, hematuria, proteinuria, and/or pyuria on two consecutive urinalyses. HLA and non-HLA GRSs were regressed individually and jointly, against LN risk in logistic regression models stratified by cSLE/aSLE cohort and ancestry, adjusted for sex, age of SLE diagnosis, and duration of follow-up. Effect estimates from stratified analyses were meta-analyzed using inverse-variance weighted fixed effects models.

Results: The cohorts included 421 with cSLE and 878 with aSLE. The mean age of diagnosis of patients with cSLE was 12.9 years (SD=3.2), 82% were female and 41% had LN. Among the aSLE patients, the mean age of diagnosis was 30.2 years (SD=13.1), 89% were female and 39% had LN. Genotyping and imputation resulted in 11.5M SNPs with minor allele frequency ≥ 0.01 and imputation quality ≥ 0.9 . Meta-analyses demonstrated that increasing non-HLA GRS was significantly associated with increased LN risk (OR = 1.27; 95% CI: 1.11, 1.45, $p = 0.0005$). The strongest effect was observed among Europeans with cSLE (OR = 1.60; 95% CI: 1.08, 2.35, $p = 0.018$), whereas in those with aSLE the association was positive but not significant (OR=1.12; 95% CI: 0.91, 1.37, $p = 0.291$). HLA-GRS was not significantly associated with increased LN risk in meta-analysis of all Europeans, yet was significant in Europeans with cSLE (OR = 2.14; 95% CI: 1.00, 4.59; $p = 0.0499$). This association was insignificant in Europeans with aSLE (OR = 1.03; 95% CI: 0.56, 1.90; $p = 0.923$).

Conclusion We found a significant association between non-HLA SLE genetic risk SNPs and LN in our cohort of children and adults with SLE. We found that the effects were strongest among the childhood-onset SLE patients of European ancestry. The HLA risk alleles were also associated with LN risk, but did not reach statistical significance. Futures studies will include additional SLE cohorts.

Disclosure: D. Webber, None; J. Cao, None; D. Dominguez, None; D. D. Gladman, None; D. M. Levy, None; L. Ng, None; A. Paterson, None; Z. Touma, None; M. Urowitz, None; J. E. Wither, None; E. Silverman, None; L. Hiraki, None.

IFN β Affects Osteogenesis-Adipogenesis Axis in SLE Bone Marrow

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: SLE patients are especially vulnerable to corticosteroid induced avascular necrosis. While it is appreciated that multiple factors contribute to AVN, the bone-fat axis in bone marrow is critical. The goals of this project are to examine the mechanisms by which MSC differentiation was affected in SLE and to develop targeted therapies to mitigate this risk. In SLE, type I interferons are key drivers of chronic inflammation, and thus might be a predisposing factor for avascular necrosis. Our recently published data demonstrate that SLE bone marrow MSC produce increased quantities of IFN β . Moreover, SLE BMSC production of IFN β is based on a positive feedback loop involving the innate signaling molecule Mitochondrial Antiviral Signaling (MAVS) protein and that this pathway contributes to human SLE BMSCs senescence associated secretory phenotype (SASP). Here we set out to investigate the differentiation defects of SLE BM-MSCs and the potential intervention approaches.

Methods: The SLE patients recruited in this proposal satisfy the ACR classification criteria for SLE. BM MSCs were isolated with Ficoll centrifugation (1.073 g/ml) and phenotyped using flow cytometry. *In vitro* studies included real-time PCR, western blotting.

Results: Our data suggested heterogeneity in SLE patients based on IFN β level in blood serum. About 3/4 SLE patients had increased levels of IFN β (mean= 2.30pg/ml) compared to healthy controls (mean=0.11pg/ml). Moreover, serum levels of IFN β protein correlated with IFN β mRNA in BM-MSCs ($R^2 = 0.8$, $p<0.05$). We compared 6 age paired BM aspirates from healthy controls and SLE patients. BM-MSCs from SLE patients and healthy controls were isolated and cultured. The MSC surface markers are positive for CD73, CD90 and CD105, but negative for CD34 and CD45 in both healthy and SLE BM-MSCs culture. SLE BM-MSCs display significantly decreased osteogenesis markers, such as ALP (6 folds, $p<0.05$), RUNX2 (8 folds, $p<0.05$), OCN (4 folds, $p<0.05$) and BSP (4 folds, $p<0.05$). However, when adipogenesis markers were evaluated, increased C/EBP delta (7 fold, $p<0.05$), PPARG (4 fold, $p<0.05$), Fabp4 (5 fold, $p<0.05$) and Adiponectin (5 fold, $p<0.05$) were found. Because transcription factor Runx2 is a critical regulator for osteogenesis and C/EBP delta is required for early adipogenesis, we then investigated the correlation between IFN β gene expression and these two transcription factors. The results suggested that Runx2 is negatively correlated with IFN β ($R^2 = 0.78$, $p<0.05$); while C/EBP delta positively correlated with IFN β ($R^2 = 0.89$, $p<0.05$). When BM-MSCs from healthy controls were treated with IFN β , reduced ALP (12 folds, $p<0.05$), RUNX2 (11 folds, $p<0.05$), OCN (8 folds, $p<0.05$) and BSP (7 folds, $p<0.05$) were observed. In contrast to osteogenesis markers, IFN β up-regulated adipogenesis markers C/EBP delta (6 folds, $p<0.05$). Taken together, our data indicate a role of IFN β in osteogenesis-adipogenesis axis in SLE.

Conclusion: IFN-I signature is an important feature of SLE. Our present work suggests that IFN β affects osteogenesis-adipogenesis axis. By revealing the essential role of IFN β on SLE BM-MSC differentiation, our study shed light on SLE pathogenesis and provides a new potential therapeutic target for SLE treatment.

Disclosure: L. Gao, None; M. O'Connell, None; J. Anolik, None; R. J. Looney, AstraZeneca, 5.

IFN-Gene Expression Is Elevated in Subacute Cutaneous Lupus Erythematosus and DLE and Decreases with Treatment in DLE

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with SLE have increased type I IFN-regulated gene expression in peripheral blood, which has been correlated with systemic disease activity. IFN-regulated gene expression is increased in patients with cutaneous lupus erythematosus (CLE) in peripheral blood and target tissue, including skin samples from chronic cutaneous lupus erythematosus (CCLE) and DLE. The pattern of IFN-induced protein regulation, or IFN-signature, has been shown to correlate with lymphocytic infiltrates in skin and to correlate with disease manifestations of lupus, linking it to pathogenesis of disease. These findings have led to clinical trials of a variety of targeted therapies for treatment of CLE, including antibodies inhibiting B-cells and type I IFN signaling. The current study aimed to measure expression of type-I IFN-regulated genes on skin biopsies from subacute cutaneous lupus erythematosus (SCLE), DLE, and normal control patients to calculate IFN-activity scores as a measure of cutaneous IFN exposure. Patient's IFN-activity scores were compared with serologic tests and medication use at the time of biopsy to determine what factors influence cutaneous IFN-regulated gene expression.

Methods: Skin samples were collected from 47 patients with DLE, 43 patients with SCLE, and 13 healthy controls. Gene expression was evaluated via ST2.1 microarray. Expression level of five genes were translated into cumulative IFN score. Based on Feng et al. 2006, the IFN score was calculated using summation of standardized expression levels from each of the 5 genes for each sample. Each gene score was standardized to the correlating IFN-regulated gene in the control group ((mean IFN-inducible gene SLE- mean IFN-inducible gene control)/standard deviation IFN-inducible gene control). Clinical factors including autoimmune serology results and medication use at time of biopsy were based on chart review. Data was analyzed using two-tailed t-test with reported p-values.

Results: Both SCLE and DLE showed increased IFN gene expression compared to controls (p-value <0.01) and SCLE was increased compared to DLE (p-value <0.05). ANA, anti-Ro, and anti-dsDNA positivity did not correlate with cutaneous IFN gene expression. Decreased IFN-gene expression was correlated with use of hydroxychloroquine and/or prednisone in patients with DLE (p-value <0.01), but showed no difference in SCLE.

Conclusion: IFN-regulated gene expression is elevated in SCLE and DLE and decreases with medication use in DLE. Autoimmune serology did not correlate with IFN gene expression in the skin in the current study. SCLE patients may require alternative therapies to target IFN-driven pathology in the skin.

Disclosure: S. Lazar, None; R. Namas, None; C. C. Berthier, None; M. Kahlenberg, None.

Abstract Number: 2113

Identification of RNASE2 As a Novel Lupus Candidate Gene

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster III

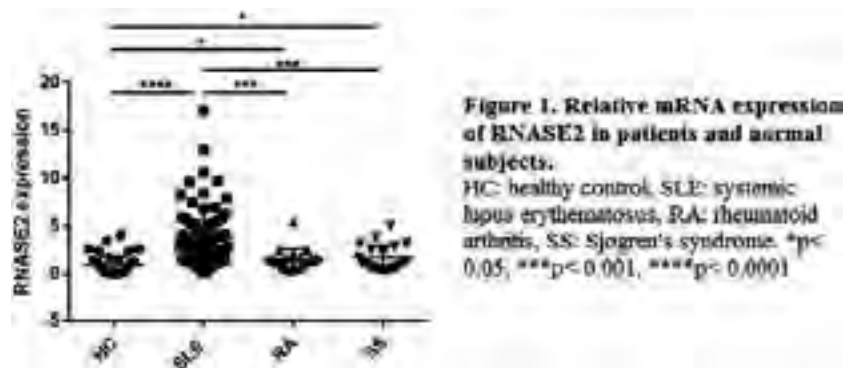
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Although many factors have been implicated to be involved in the development of systemic lupus erythematosus (SLE), the pathogenesis of this prototypical autoimmune disease has not yet been fully clarified. Here we are aimed to search for new candidate genes that contribute to SLE disease activity.

Methods: A microarray approach using the Affymetrix HUGO chip was employed for the determination of differentially expressed mRNA profiles between active SLE patients (with SLEDAI score > 8) and normal subjects. The expression of screened key genes was then verified by real-time quantitative polymerase chain reaction (RT-PCR) in peripheral blood mononuclear cells (PBMCs) from 69 SLE patients, 43 normal subjects and 40 patients with other connective tissue diseases. Clinical data of SLE patients were collected to analyze for the relationship with gene expression levels. To identify the cell type involved in specific gene production, monocytes, lymphocytes, eosinophils, neutrophils, T cells and B cells were separated from peripheral blood by flow sorting, and measured for the gene expression by RT-PCR.

Results: Gene chip analysis revealed 750 down-regulated and 597 up-regulated genes in SLE patients, among which RNASE2 (ribonuclease A2), a gene rarely reported previously and highly expressed in SLE group (fold change 6.27, $p = 3 \times 10^{-7}$), was selected for further study. RT-PCR confirmed that RNASE2 mRNA expression was elevated in PBMCs from



SLE patients compared with that from normal subjects as well as patients with primary Sjögren's syndrome or rheumatoid arthritis (Figure 1). RNASE2 mRNA level was positively correlated with SLEDAI score ($r = 0.36$, $p < 0.01$), BILAG score ($r = 0.38$, $p < 0.01$) and level of 24 hour proteinuria ($r = 0.40$, $p < 0.01$). In addition, the expression level of RNASE2 was related to serum total immunoglobulin G level ($r = 0.25$, $p < 0.05$) and elevated in anti-Sm positive group and anti-dsDNA positive group (both $p < 0.01$). The cell types mainly involved in RNASE2 production were quite different between normal subjects and SLE patients, which were neutrophils and monocytes respectively.

Conclusion: RNASE2 is highly expressed in monocytes from SLE patients, and correlated with disease activity as well as autoantibody levels. Such insight into SLE pathogenesis may suggest a novel therapeutic target for the disease in the future.

Disclosure: Y. Xu, None; X. Tang, None; X. Feng, None.

Abstract Number: 2114

Interferon Kappa Regulates Apoptotic Response to UVB in Control and Lupus Keratinocytes

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Session Information

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Session Time: 9:00AM-11:00AM

Background/Purpose: Photosensitivity, defined as increased cutaneous erythema and inflammation after ultraviolet light (UV) exposure, is a hallmark of patients with systemic lupus erythematosus (SLE), cutaneous lupus erythematosus (CLE), and many other autoimmune conditions with skin involvement. Type I interferons (IFNs) are increased in SLE and CLE skin and contribute to a propensity for inflammatory responses by keratinocytes. We have identified IFN κ as a keratinocyte-expressed type I IFN whose expression is elevated in non-lesional SLE keratinocytes, which suggests that it may contribute to the propensity for inflammation in SLE skin. Apoptosis of keratinocytes is thought to be a central pathologic response that contributes to increased photosensitivity. However, the contribution of type I IFNs, including IFN κ , to apoptosis after UVB exposure is unknown. We thus examined the role of IFN κ in regulating UVB-induced keratinocyte apoptosis in order to determine whether type I IFNs contribute to photosensitivity predisposition.

Methods: Age and gender-matched control (n=5) and SLE (n=5) keratinocytes were isolated from non-lesional, non-sun exposed 6mm punch skin biopsies from the upper thigh and used at passages 3-5 for study. All patients gave written, informed consent and were treated according to the Declaration of Helsinki. IFN κ -/- N/TERT keratinocytes were generated via CRISPR/Cas9. N/TERTs overexpressing IFN κ were generated via nucleofection of an IFN κ expressing plasmid followed by selection in G418. Primary keratinocytes and N/TERT keratinocyte lines were treated with or without 50mJ/cm² UVB followed by TUNEL staining 8 hours after UVB treatment. In some cases, baricitinib was used to block IFN signaling prior to UVB treatment.

Results: As expected, we identified increased apoptosis in CLE lesional skin vs. normal skin, especially in the basal keratinocyte layer. Importantly, SLE non-lesional keratinocytes displayed increased apoptosis vs. healthy control keratinocytes after UVB treatment. This apoptotic process was dependent on IFN κ as deletion of this protein resulted in significantly diminished TUNEL staining after UVB exposure. Further, chronic overexpression of IFN κ in N/TERT keratinocytes also induced increased apoptosis after UVB. Finally, treatment of SLE and healthy control non-lesional keratinocytes with baricitinib to block IFN signaling significantly diminished UVB-mediated apoptosis.

Conclusion: IFN κ expression serves as a regulator of apoptotic responses to UVB in keratinocytes. In SLE non-lesional skin, chronic overexpression of IFN κ predisposes to increased apoptosis after UVB exposure, which leads to increased autoantigen exposure, cytokine/chemokine production, and inflammatory cell recruitment. This increased inflammatory response likely results in the enhanced UV-triggered erythema and skin eruptions in SLE patients. Downregulation of IFN κ may serve as an excellent, specific target to prevent photosensitivity in SLE patients.

Disclosure: G. Hile, None; M. Sarkar, None; J. Liu, None; T. J. Reed, None; J. Gudjonsson, None; M. Kahlenberg, None.

Abstract Number: 2115

Identification of Systemic Lupus Erythematosus Subgroups Using Electronic Health Record and Genetic Databases

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Session Information

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Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster III

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Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a multifactorial disease with genetic and environmental risk factors, and heterogeneous manifestations that encompass a wide range of disease severity. Long-term outcomes for

Figure. Clinical lab measures associated with SLE demonstrate three distinct clusters. The x-axis represents dimension one and the y-axis represents dimension two of the k-means clustering algorithm.



Table. Percentage of individuals carrying 1-2 copies of the listed allele of each significant SNP by cluster (p<0.05)

SNP	Gene	Cluster 1	Cluster 2	Cluster 3	p-value	FDR-adjusted p-value
rs3024503 (T)	ILF3	53%	4%	23%	0.001	0.10
rs10774625 (T)	ATXN2	83%	33%	53%	0.004	0.20
rs2327832 (C)		32%	11%	28%	0.007	0.22
rs2248612 (T)	SLE	68%	82%	70%	0.006	0.22
rs48234 (C)	LOC101287204	41%	38%	57%	0.01	0.22
rs1299652 (C)	TNFRSF7/ATP16B	18%	9%	11%	0.02	0.22
rs14603023 (T)	PHLDB1	77%	62%	60%	0.02	0.22
rs3748079 (A)	ITPR3	28%	27%	48%	0.02	0.26
rs7726159 (T)	FEZF1	63%	62%	64%	0.04	0.41

individual patients are difficult to predict. Little is known about why an affected individual might develop a particular SLE phenotype. Previous studies have used phenotype-mapping approaches to identify subtypes of SLE using genome-wide association studies and gene expression data; however, studies integrating both genetic and clinical data to identify SLE phenotypes using bioinformatics analyses remain limited.

Methods: We characterized subgroups of patients using sociodemographic, clinical and genetic data from previously collected genetic cohorts and electronic health record (EHR) data for 195 individuals with SLE. Single nucleotide polymorphisms (SNPs) were typed on the ImmunoChip. We included 95 variants previously associated with SLE risk. Variables extracted from the EHR included age, sex, race, ethnicity, age at diagnosis, and disease-associated laboratories: complement C3 and C4, SSA, SSB, RNP, anti-Smith, and anti-dsDNA. We first performed K-means clustering using all lab measures on the top N eigenvectors from principal component analysis determined using a bootstrap resampling strategy. We then used Chi-squared and ANOVA tests to examine whether demographic, clinical, and genetic variables were associated with each cluster.

Results: 91% of patients were female; 47% were white, 13% African-American, 15% Asian, and 24% other/mixed race. Results demonstrated three distinct stable clusters (stability score>0.80) (Figure). Cluster 1 (n=91) was characterized as predominately white, non-Hispanic/Latino patients with higher age of onset ($p<0.05$). Cluster 2 (n=47) was significantly more likely to have + anti-dsDNA, + SSB, + RNP, and + anti-Smith antibodies ($p<0.05$). Cluster 3 (n=55) had a significantly higher percentage of abnormal C3 and C4 levels, + SSA, and lower age of onset ($p<0.05$). Nine SNPs were associated with the clusters but did not remain significant after multiple testing correction (Table).

Conclusion: Unsupervised clustering using sociodemographic and clinical variables derived from the EHR and genetic data identified three distinct subgroups of individuals with SLE. Future work will further define these genotype-phenotype clusters and perform validation studies in additional cohorts with more statistical power. Our findings may assist in identifying disease treatments for SLE using a more personalized approach.

Disclosure: M. Gianfrancesco, None; I. Paranjpe, None; J. Kay, None; J. Nitiham, None; K. Taylor, None; C. Lanata, None; M. Sirota, None; L. A. Criswell, None; G. Schmajuk, None; J. Yazdany, None.

Abstract Number: 2116

Neutrophil Extracellular Trap Formation Is Dependent on Disease Activity in Systemic Lupus Erythematosus: Determination Using a Flow Cytometry-Based Assay

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Neutrophil extracellular traps (NETs) are composed of decondensed DNA that is released during an active cell death program is known as NETosis. To date, fluorescence microscopy is the accepted method for quantification of NETs. However, this method is subjective, time consuming and yields low numbers of polymorphonuclear cells (PMNs) analyzed per sample. NETs contribute to pathogenesis of systemic lupus erythematosus (SLE) but the effects of disease activity on NETosis has not been adequately explored.

Methods: Herein, we describe a flow cytometry-based assay for detection of NETosis within mixed cell populations and applied it to quantify NETting PMNs in SLE.

Results: Using plasma membrane-impermeable DNA-binding dye, SYTOX Orange (SO), we found that cell-appendent DNA of NETting PMNs were positive for SO and DAPI (Fig.1A-B). The combination of optimally diluted antibody and

nucleic acid dyes required no washing and yielded low background fluorescence on flow cytometry (Fig. 1C-D). We then validated the assay by comparing with time-lapse live cell fluorescence microscopy and determined very good correlation ($r = 0.90$, $P < 0.001$), intra- and inter-assay variances, 3.98% and 4.66%, respectively. Significant correlations were found for NETosis from whole blood (WB) and purified PMNs ($r = 0.79$, $P < 0.001$). We examined PMA-induced NETosis in peripheral PMNs from SLE patients and controls and in bone marrow (BM) PMNs from multiple murine models (Fig 2A-C). However, most of the recruited SLE patients examined were on immunosuppressive therapy with quiescent disease activity (Table 1), which may have consequences for PMN activation (Fig. 2A). Therefore, we went on to examine NET formation in BM PMNs from young female lupus-prone mice. Stimulation with PMA resulted in an increase in the frequency of NETting BM PMNs, which was augmented in *Sle1* mice, compared to B6 controls (Fig. 2B). An analysis of BM PMNs across all lupus-prone mice (*Sle1*, *Sle1*Tg7 and *Sle1*23) showed an increase in NETosis in severe-lupus prone *Sle1*23 mice compared to the milder lupus-prone *Sle1* strain (Fig. 2C).

Conclusion: This NETosis flow cytometry-based assay is observer-independent and allows for rapid assessment of a large number of PMNs in mixed cell populations. Disease activity may prime PMNs and lead to aberrant NETosis in SLE.

Figure 1. Visualizing and Quantifying NET-DNA in mixed cell populations.

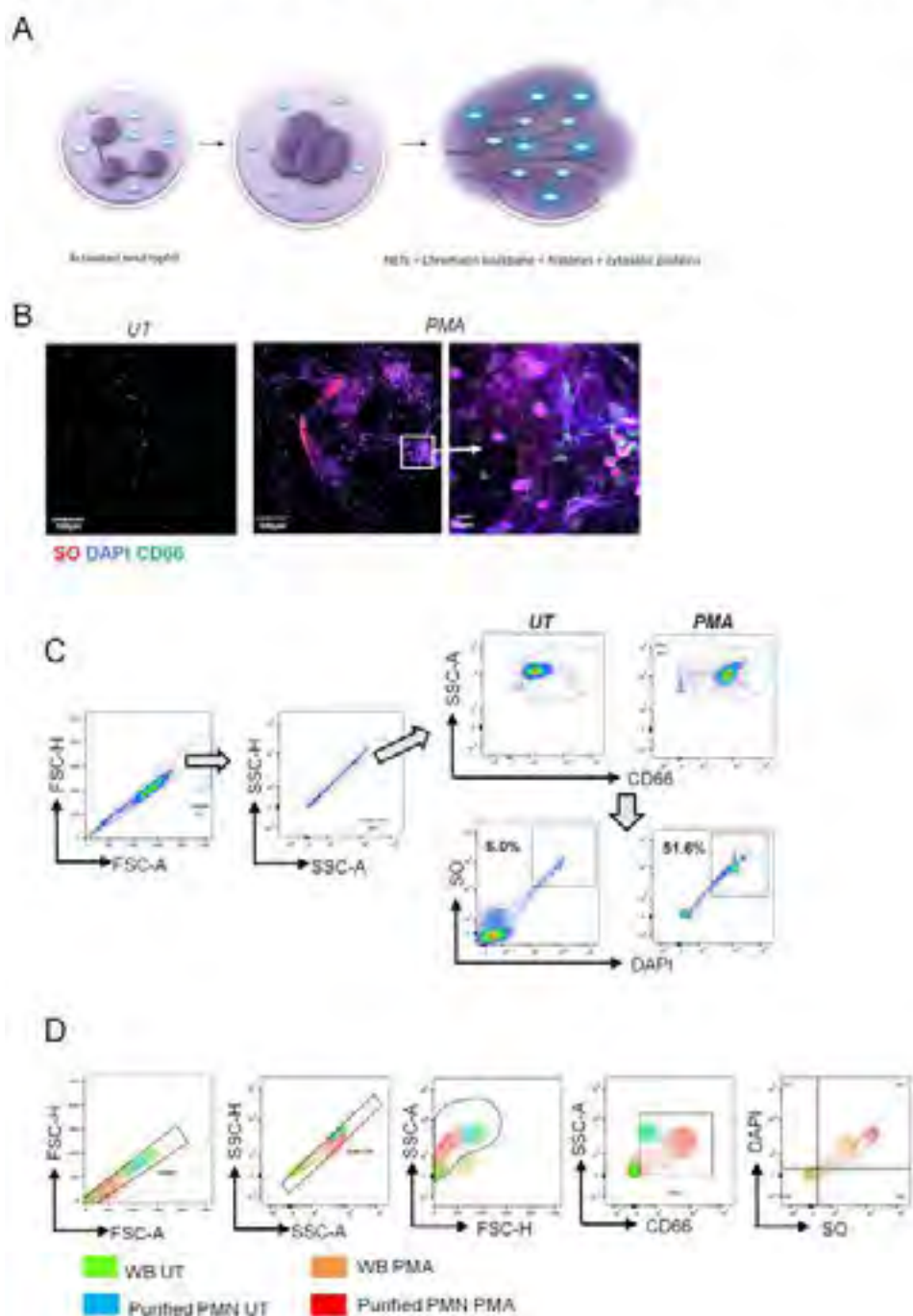


Figure 2. NETosis is increased in murine PMNs from lupus-prone mice.

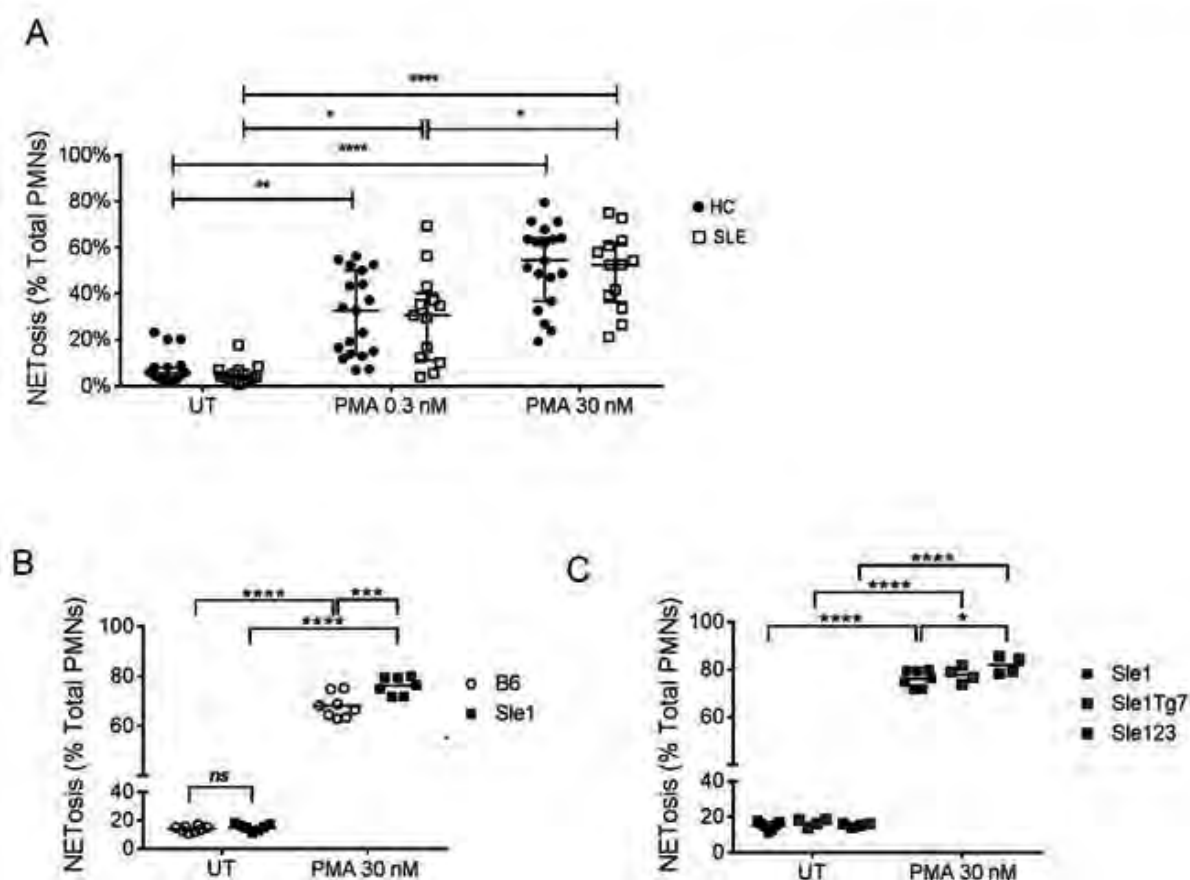


Table 1. Demographics and clinical characteristics of SLE patients versus healthy controls.

	SLE patients, n = 13	Healthy controls, n = 19	p
Age (years)	50.0 (39.0-54.5)	32.0 (30.0-39.0)	0.001
Gender (female)	10 (76.9)	16 (84.2)	0.704
Ethnicity			0.735
Chinese	8 (61.5)	10 (52.6)	
Malay	1 (7.7)	2 (10.5)	
Indian	3 (23.1)	3 (15.8)	
Others	1 (7.7)	4 (21.1)	
SELENA-SLEDAI	2 (0.0-5.0)		
0	5 (38.5)		
1-4	5 (38.5)		
> 4	3 (23.1)		
Positive anti-dsDNA	6 (31.6)		
Anti-dsDNA (IU/mL)	191.0 (9.0-352.0)		
Low C3	5 (26.3)		
C3 (mg/dL)	117.5 (66.3-125.8)		
Low C4	2 (10.5)		
C4 (mg/dL)	19.0 (11.0-40.0)		
Prednisolone	6 (31.6)		
Prednisolone dose (mg/day)	5.0 (0.0-21.0)		
Hydroxychloroquine	12 (92.3)		

Disclosure: S. H. Tay, None; O. Zharkova, None; H. Y. Lee, None; S. Tripathi, None; W. Y. Ong, None; A. Lateef, None; P. MacAry, None; L. Lim, None; J. E. Connolly, None; A. M. Fairhurst, None.

Abstract Number: 2117

Neuropsychiatric Systemic Lupus Erythematosus Is Attenuated By Sphingosine-1-Phosphate Receptor Modulation

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: About 20-40% of lupus patients suffer from diffuse neuropsychiatric manifestations of SLE, including cognitive impairment and depression. Although the pathogenesis is not well understood, brain barrier disruption and pro-inflammatory signaling within the brain parenchyma are thought to play an important role in disease development. Fingolimod, approved for the treatment of multiple sclerosis, functionally antagonizes sphingosine-1-phosphate (S1P) receptors and reduces the circulation of auto-reactive lymphocytes. In the CNS, fingolimod exerts a neuro-protective role, reducing pro-inflammatory cytokines and promoting brain barrier integrity. We have previously shown that fingolimod treatment reduces leukocyte infiltration of the choroid plexus in MRL/lpr mice and significantly attenuates cognitive dysfunction and depressive-like behavior. Here, we aimed to determine the effects of fingolimod on glial cells and pro-inflammatory cytokine signaling.

Methods: Ten-week-old female MRL/lpr mice were treated three times weekly with fingolimod (3 mg/kg) or vehicle alone (n=10/group) by intraperitoneal injection. After 10 weeks of treatment, brain cell suspensions generated from one hemisphere were analyzed by flow cytometry, and CD11b-positive CD64-positive CD45-low microglia, GFAP-positive astrocytes, and CD31-positive endothelial cells were sorted for RNA sequencing. Cortex and hippocampus samples were dissected from the other hemisphere of each brain and snap frozen for analysis of gene and protein expression.

Results: Flow cytometry revealed significant reductions in infiltrating leukocyte populations, including T cells, B cells, macrophages, neutrophils, eosinophils, and NK cells in fingolimod-treated mice. There was also a significant decrease in the number and/or activation of parenchymal cells, including microglia and astrocytes. Surprisingly, quantification of cytokine levels from cortical samples revealed a significant increase in IL-1a, IFN γ , IFN β , and IL-12p70 in fingolimod-treated mice when compared with control mice. Similarly, increased expression of IL-1a, IL-1b, and MCP-1 was present in the hippocampi of treated mice. RNA sequencing results in the sorted cell populations are pending.

Conclusion: Fingolimod treatment reduces infiltration of leukocytes from the periphery into the CNS. Despite an unexpected increase in the expression of several brain cytokines with fingolimod treatment, the neurobehavioral deficits manifested by the MRL/lpr lupus strain were significantly attenuated. Our results highlight the complex role of the S1P signaling axis in the pathogenesis of neuropsychiatric SLE.

Disclosure: E. Mike, None; C. M. Cuda, None; H. M. Makinde, None; H. Perlman, Galvani, 5; C. Putterman, None.

Abstract Number: 2118

Prevalence of Acquired Activated Protein C Resistance and Anti-Protein C Antibodies in Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster III

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Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease characterised by increased cardiovascular risk, with a 5-20 fold increased risk for venous thromboembolism (VTE) compared to the general population. Antiphospholipid antibodies (aPL) constitute a major risk factor for thrombosis in patients with SLE, who frequently also have antiphospholipid syndrome (APS). The protein C pathway has a key role in the regulation of haemostasis and inflammation and could be pivotal in the development of thrombosis in patients with SLE regardless of aPL. APS patients with VTE have been shown to have increased acquired resistance to protein C (APCr) associated with a high prevalence of anti-protein C antibodies (aPC). The role of aPC and APCr in patients with SLE, especially aPL negative (-), is less clear. The aim of this ongoing study is to determine the prevalence of aPC in association with APCr and thrombosis in aPL/APS- patients with SLE.

Methods: Sixty-one consecutively attending patients with SLE, classified according to the revised ACR criteria, have so far been enrolled and subdivided as follow: thrombotic APS (APS; n=15), aPL positive (+) no thrombosis (aPL+/T-; n=17), aPL- with a history of thrombosis (aPL-/T+; n=8), aPL- without a history of thrombosis (aPL-/T-; n=21). Patients with heritable thrombophilia were excluded. aPC levels were determined by in-house ELISA. APCr was determined using thrombin generation (TG) and was measured as %inhibition of endogenous thrombin potential by exogenous recombinant human activated protein C (rhAPC) or by Protac (specific protein C activator) for activation of endogenous protein C.

Results: In this ongoing study, aPC were detected in 44% of patients (APS: 53.3%, aPL+/T-: 47%, aPL-/T-: 48%, aPL-/T+ : 25%; p=NS). aPL+ had higher aPC levels compared to aPL- patients (median (IQR) = 36.7 (24.7-51.8) vs 26.1 (17.3-37.6) U/mL, p=0.04). Positivity to aPC was significantly associated with resistance to both rhAPC (p=0.01) and activation of endogenous protein C (p<0.001). APCr prevalence was similar in aPL+ (54%) and aPL- (45%) patients. Resistance to rhAPC was associated with resistance to activation of protein C (p=0.02), but was less frequently detected (30% vs 48% of all cases), especially in aPL- patients (13.8% vs 43.8% in aPL+; p=0.01). In comparison, resistance to rhAPC was higher in aPL+ compared to aPL- (p=0.02). There were no correlations with demographics or disease activity (assessed by BILAG-2004 or SLEDAI-2K). APCr and aPC positivity were less frequent in patients with a history of rash or serositis (p=0.01 and p=0.02 respectively).

Conclusion: aPC levels and resistance to exogenous APC were higher in aPL+ than aPL- patients. aPC were also detectable in aPL- patients with SLE, and were associated with APCr *in vitro*. In aPL- patients resistance to activation of protein C was more frequent than resistance to exogenous APC, suggesting a possible defect in the activation of protein C. Predictive clinical-pathophysiological models based on aPC-profile and APCr assays might offer an important tool for identification and management of patients with SLE at increased thrombotic risk independent of classical cardiovascular risk factors and aPL.

Disclosure: G. A. Ramirez, None; H. Cohen, None; D. A. Isenberg, None; M. Efthymiou, None.

Abstract Number: 2119

Association of the Variant Form of rs17408553 at Human Leukocyte Antigen-C Supports Evidence That Hypo-Responsive Natural Killer Cells Adversely Influence the Course of Nephritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster III

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Session Time: 9:00AM-11:00AM

Background/Purpose: In subjects with lupus nephritis (LN), tissue injury due to local immune activation involving persistently activated macrophages in the renal parenchyma is limited by non-classical natural killer (NK) cells. This protective pathway, based on a genetic effect related to the NK ligand Human Leukocyte Antigen (HLA)-C, was recently shown to limit activation of macrophages and dendritic cells by immune stimuli in vitro. A risk phenotype of HLA Class I, termed the Lys variant, or the C2 epitope or Asn80Lys, rs17408553, leads to a hypo-responsive NK cell which is secondary to high affinity of ligand by variant and an inhibitory NK receptor. The clinical impact of these pathways is understudied; the aim of this study, therefore, is to evaluate associations of clinical outcomes among subjects carrying the risk genotype in two cohorts of SLE patients.

Methods: Patients were included if there was confirmation of a diagnosis of SLE as per the ACR and access to chart review along with DNA for genotyping. There were 2 patient subsets: 96 lupus nephritis (LN) patients who were selected from SLE cohorts from the ALMS trial (27 LN) and the NYU Specimen and Matched Phenotype Linked Evaluation (SAMPLE, 69 LN), and the second subgroup was SLE absent lupus nephritis (NN) (SAMPLE, 33 NN). LN were adjudicated for response to induction therapy and DNA specimens were genotyped at rs17408553 using a Pyrosequencing assay (ADS9525-RS) and the result is reported as minor allelic frequency (MAF). While pyrosequencing is performed in the usual way, it is noteworthy that the PCR fragment of HLA-C containing the rs17408553 SNP was designed to exclude the very similar HLA-B gene by the specificity of the PCR primers, which can be monitored by one nucleic acid that differs between HLA-C and HLA-B within the PCR amplicon.

Results: Demographic characteristics of LN and NN were matched for age, gender, and ethnicity. LN biopsies encompassed all ISN/RPS classes, the majority of which were proliferative forms. For LN, 35% had hypertension, 47% had nephrotic range proteinuria, and a majority were given an induction therapy consisting of steroids plus mycophenolate mofetil. At six months, 14 LN patients were non-responders, 8 were partial responders and 74 were complete responders. For MAF at rs17408553, the C2 allele was enriched in LN patients compared to controls (0.45 vs 0.37, SLE (LN+NN) vs control; OR 1.40, P=0.01). However, for a comparison of LN and NN, the frequencies of C2 were found to be similar (0.45 vs 0.45, LN vs NN, P=1). While LN spot prot/cr ratios were similar in C1/C1 and C2/N groups at the end of induction (3.86 ± 3.02 vs 4.64 ± 3.30 , P=0.52), there was an association of an increase in variant allele and LN patients with no response at induction (0.73 vs 0.41, LN non-response vs LN response, P=0.0149). The association of variant at HLA-C and subjects with non-response was observed in both LN cohorts (ALMS trial and SAMPLE).

Conclusion: Using two distinct and well-characterized cohorts, there was an association of variant at HLA-C and subjects with non-response to induction therapy. These data support the speculation that hypo-responsive NK cells adversely influence the course of nephritis.

Disclosure: R. M. Clancy, None; H. M. Belmont, Exagen, 2; P. M. Izmirly, None; N. Bornkamp, None; S. Miller, EpigenDx, 3; M. Poulin, EpigenDx, 3; L. Yan, EpigenDx, 3; J. P. Buyon, Exagen, 2; E. M. Ginzler, None.

Abstract Number: 2120

CD47- Signal Regulatory Protein Alpha Interaction Potentiates Proinflammatory Response in Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

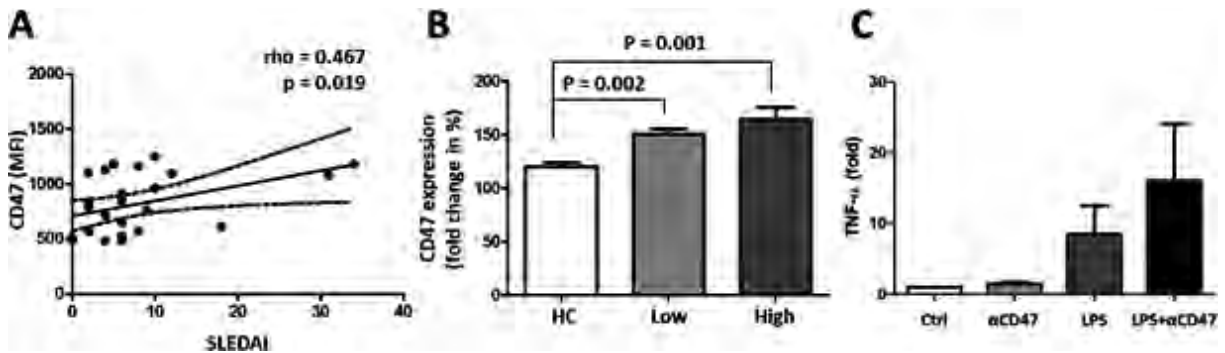
Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

CD47-Signal Regulatory Protein-Alpha Interaction Potentiates Proinflammatory Response in Systemic Lupus Erythematosus.

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease mediated by unbalanced activation of innate and adaptive immune cells with subsequent uncontrolled inflammation and organ damages. An important regulatory receptor on monocyte is signal regulatory protein alpha (SIRP-alpha) that interact with CD47. This study was aimed to investigate as to whether CD47 contributes to altered proinflammatory response in SLE.



Methods: Expression of CD47 and SIRP- α on peripheral blood mononuclear cells (PBMCs) from SLE patients and healthy controls (HCs) were examined using flow cytometry analysis. Effect of SLE serum, recombinant interferon (IFN)- α , and tumor necrosis factor (TNF)- α on CD47 expression was investigated. Monocytes and THP1 cells were stimulated with lipopolysaccharide (LPS) with or without pretreatment with anti-CD47 antibody, and TNF- α production and mitogen-activated protein kinase (MAPK) and NF κ B signaling were examined. Sera from HCs and SLE patients were screened for autoantibodies directed against CD47 using ELISA.

Results: A total of 25 patients and 16 healthy controls (HCs) were enrolled. CD47 expression on monocytes was higher in SLE patients vs. HCs ($p < 0.001$) and it correlated with SLE disease activity (Spearman rho = 0.467, $p = 0.019$). CD47 expression was upregulated by serum from SLE patients with higher disease activity and exogenous IFN- α but not by exogenous TNF- α . Pretreatment of monocytes with anti-CD47 antibody potentiated TNF- α production in response to LPS by 16.1 folds as compared to 8.5 folds after stimulation with LPS alone, whereas no to little TNF- α was produced after treatment with anti-CD47 alone. CD47 activation induced MAPK but not NF κ B signaling. Finally, autoantibodies against CD47 were detected in 30.7% of SLE patients.

Conclusion: To the best of our knowledge, this report is the first to show that CD47 expression is upregulated during active SLE and potentiates proinflammatory response in SLE. Targeting CD47-SIRP- α interaction might offer a novel therapeutic opportunity in SLE treatment.

Figure. A. CD47 expression on monocytes correlated with disease activity. B. CD47 on monocytes was upregulated after treatment with serum from patients with low ($n=6$) and higher ($n=4$) disease activity or healthy controls (HC). C. Monocytes were pretreated with anti-CD47 antibody and were stimulated with LPS (3 ng/mL) for 5 hours and TNF- α production was measured.

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Abstract Number: 2121

Serum High Type I Interferon Is Associated with Active Proliferative Lupus Nephritis in Lupus Patients Accompanied with High Interferon Signature Gene Expression and Plasmacytoid Dendritic Cell Infiltration in Lupus Nephritis Kidney

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster III

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Session Time: 9:00AM-11:00AM

Background/Purpose: Despite recent advancements in immunosuppressive therapies, lupus nephritis (LN) remains one of the most severe organ manifestations in systemic lupus erythematosus (SLE). High type I interferon (IFN) is a heritable

risk for SLE, and previous studies have suggested a link between high IFN and lupus nephritis. However, little is known about the relationships between high levels of IFN and the subtypes of LN, and whether IFN plays a critical role in the pathogenesis of LN.

Methods: We studied 221 European-American SLE patients and measured IFN in sera by performing WISH IFN bioassay as described previously. Subtypes of LN were confirmed by renal biopsy review. Complement, anti-dsDNA and other serological parameters were measured in the clinical laboratory, and standard clinical cut-offs were used to define a positive result. mRNA in situ hybridization was performed to detect IFN induced gene (IIG) expression and plasmacytoid dendritic cells in LN kidney biopsies, and Visiopharm analysis software was used for quantitative analysis. Real-time PCR was performed to measure pro-apoptotic gene expressions in human podocyte cell lines. Non-parametric analyses were used unless otherwise mentioned.

Results: Proliferative LN was significantly more common among patients with high serum type I IFN compared to patients with low levels of IFN ($p<0.001$, OR=3.0, Fisher's exact test). Notably, IFN level was significantly higher in active proliferative LN compared to inactive proliferative LN ($p<0.001$), and these findings were independent of complements and anti-dsDNA antibody levels. mRNA in situ hybridization showed increased expression of IIG accompanying plasmacytoid dendritic cell infiltration in active proliferative LN kidneys. In vitro experiments demonstrated that type I IFN induced pro-apoptotic gene expression in human podocyte cell lines.

Conclusion: Our data support an association between type I IFN and active proliferative lupus nephritis that is independent of conventional parameters such as complements and anti-dsDNA antibodies, suggesting that IFN is involved in renal pathogenesis. These data also suggest that IFN could predict renal disease activity or the future risk of developing LN, especially proliferative LN in SLE patients.

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Abstract Number: 2122

CD38 over-Expression in CD8 Positive Cells Defines a Group of Patients with SLE Prone to Infections

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Session Information

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Session Type: ACR Poster Session C

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Background/Purpose: It has been previously shown by our laboratory that CD38 gene expression is increased in the peripheral blood T cell from patients with SLE. The purpose of the current study is to further investigate the overexpression of CD38 in T cells from patients with SLE and seek correlations with clinical parameters.

Methods: T cells CD38 surface expression was analyzed from patients with SLE (n=37) by flow cytometry. Student T-test was used for statistical analyses. The relationship of CD38 surface expression and clinical parameters from patients with SLE (SLE disease activity, medications, infections rate) was analyzed using Pearson's or chi-squared test. Data is expressed as mean \pm SEM.

Results: CD38 surface expression was found to be higher in SLE CD8⁺ T cells ($30\% \pm 3$, n=37) compared to normal controls ($18.7\% \pm 1$, n=18, $p<0.001$) but not in SLE CD4⁺ T cells ($36.8\% \pm 3$, n=18) vs. ($36.9\% \pm 2.3$, n=36, p ns) respectively. Interestingly, within SLE patients, CD38 levels of expression identified two subpopulations of CD8⁺ cells those with high ($>\text{mean}+2\text{SD}$ of normal values) and those with low expression. Patients with SLE who expressed a higher percentages of CD8⁺CD38⁺ cells were more prone to infections ($p<0.0001$) most of which were of viral origin. Also, they had low WBC counts ($p<0.01$). We did not notice a correlation with disease activity or exposure to prednisone. Interestingly, none of the patients with high percentages of CD8⁺CD38⁺ cells were receiving Mycophenolate whereas 6 of

16 with low percentages were receiving Mycophenolate. In 12 patients with SLE patients, CD8⁺CD38⁺ cells were evaluated repeatedly over time but we failed to detect significant variation or association with disease activity.

Conclusion: We have identified a subpopulation of patients with SLE who have higher percentages of CD8⁺CD38⁺ cells and increased rates of infections. We propose that CD38 expression on CD8⁺ T cells can be used as a biomarker to identify patients with SLE who have an increased risk of infections.

Disclosure: L. Mulki, None; A. Suarez-Fueyo, None; E. Katsuyama, None; V. C. Kyttaris, None; G. C. Tsokos, None.

Abstract Number: 2123

Analysis of Lupus Synovitis Gene Expression Reveals Dysregulation of Pathogenic Pathways Activated within Infiltrating Immune Cells

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster III

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Background/Purpose: Arthritis is a common manifestation of SLE but the inflammatory and immune cells that infiltrate synovium and the signaling pathways activated are not well understood. Previous work delineated an IFN signature in lupus arthritis but not rheumatoid arthritis (RA) or osteoarthritis (OA)¹. A multi-pronged bioinformatic approach was utilized to analyze gene expression from RA, OA and lupus arthritis (LA) samples to gain insight into the precise pathogenic mechanisms involved.

Methods: Initial analyses examined genes that were similar and different between non-inflammatory OA, LA and RA synovial biopsy samples following LIMMA differential expression (DE) analysis or Weighted Gene Co-expression Network Analysis (WGCNA) followed by interrogation with cell type specific gene signatures using I-ScopeTM and validated by Gene Set Variation Analysis (GSVA). Genes were functionally characterized using BIG-CTM and pathways elucidated using the upstream regulator (UPR) and canonical pathway functions of IPA^O.

Results: From BIG-CTM and I-ScopeTM analysis, lupus synovitis has a clear gene signature of activated antigen presenting cells including dendritic cells, inflammatory myeloid cells, activated CD4⁺ and CD8⁺ T cells, activated B cells as well as pre- and post- switch plasma cells/plasma blasts as indicated by IgM, IgD and IgG1 heavy chain genes. The presence of both Igk and Igl as well as numerous VL genes indicates the polyclonal nature of the infiltrate. Analysis of gene expression indicated no inflammatory infiltrate in OA and that RA is dominated by activated T and B cell signatures. IPA analysis tools examining canonical pathways and UPRs revealed the role of Sphingosine-1 phosphate receptor and numerous chemokine pathways that may mediate lymphocyte organization and/or recruitment into lupus synovium. In addition, IPA elucidated ongoing signaling induced by inflammatory cytokines. Moreover, signaling pathways including NF-kB, NF-AT and mTOR were evident as well as proliferation and proteasome activity. Important differences were observed in gene expression from lupus compared to RA synovitis, including tendencies of less enrichment of Th17 and T_{cytotoxic}, less frequent enrichment of T_{FH} and increased enrichment of myeloid populations. In addition, IPA UPR analysis indicated ongoing signaling by TNF, IFNg, IFNa, CD40L, IL6, IL1b, IL15, IL21 and IL27 in lupus synovitis.

Conclusion: Bioinformatic analysis of gene expression patterns in lupus synovitis indicate trafficking and potential *in situ* activation and differentiation of immune cells during pathogenesis of LA. Interestingly, a more prominent myeloid signature is present in LA compared with RA, that might provide a unique target of therapeutic intervention.

¹Nzeusseu-Toukap, A., et al. (2007). *Arthritis & Rheumatism*, 56(5), 1579–1588.

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Bacterial Biofilm Product Curli/Edna Induces NETs and Serum Anti-Curli/Edna Levels Correlate with Bacteriuria and Lupus Activity

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Session Date: Tuesday, October 23, 2018

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Background/Purpose: Infections are a major contributor to lupus disease. We have previously demonstrated that bacterial amyloid curli, produced by E.coli, can accelerate disease in mouse models of lupus. Interestingly curli incorporates extracellular DNA, which in turn can be both adjuvant and a self-antigen in lupus. Finally, uropathogenic E. coli (UPEC) is responsible for majority of urinary tract infections in SLE.

Methods: Based on our previous results, we hypothesize that exposure to UPEC triggers anti-curli/eDNA antibodies and curli/eDNA complexes can trigger the innate immune system. We investigated 98 lupus patients who met at least 4 SLICC criteria. Results were compared to 54 age, sex and race matched healthy controls. We tested the production of anti-curli/DNA complex for both IgG and IgA subclasses. We then correlated the levels of anti-curli/DNA antibodies with clinical parameters. Finally, we treated human neutrophils with curli/eDNA complexes.

Results: We found that curli/eDNA induces neutrophil extracellular traps in a ROS manner. Anti-curli/eDNA IgG levels were detected in lupus and controls plasma and the levels correlated with persistent bacteriuria ($p < 0.05$) and disease flares in lupus patients. In addition, anti-curli/eDNA antibodies could bind to DNA demonstrating a potential molecular mimicry mechanism in lupus. IgA anti-curli/eDNA levels were higher ($p < 0.01$) in lupus donors compared to controls.

Conclusion: We conclude curli/eDNA complexes can activate the innate and adaptive immune system and could be a mechanism to sustaining disease in lupus.

Disclosure: R. Pachucki, None; C. Corradetti, None; S. Gallucci, None; C. Tukul, None; S. Tursi, None; L. Nicastro, None; L. Kohler, None; Y. Ghadiali, None; L. Kilpatrick, None; R. Caricchio, None.

Pleiotropy of a Positive Antinuclear Antibody (ANA) Test: A Phewas and GWAS Approach

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Session Information

Session Date: Tuesday, October 23, 2018

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Background/Purpose: ANAs are almost always present in systemic lupus erythematosus (SLE), but they are also present in ~12-20% of the population. A positive ANA (ANA+) can precede the onset of SLE, but for the vast majority the clinical consequences are unknown. In animal models, naturally occurring ANAs can protect against renal disease. The genetics of SLE are well established but those of ANA+ are poorly defined. We hypothesized that ANA+ is associated with increased risk of SLE-like phenotypes and that ANA+ and SLE share the same genetic structure.

associations were GWAS significant, but 118 SNPs had a $P < 1 \times 10^{-5}$. None of these SNPs were previously associated with SLE but mapped to loci (*VAV3*, *NCOA1*, *LOC285696*, *ADAMTS19*, *RPS12*, *CYP2R1*, *KKR1* and *CACNG2*) associated with immune thyroiditis, nephropathies, cancer, vitamin D levels, metabolic and psychiatric phenotypes (Fig. 2).

Conclusion: We found that ANA+ inpatients without SLE had the expected association with other autoimmune disorders; however, there was an unexpected association with reduced risk of renal and hypertension phenotypes. There was no strong overlap in the genetic structure of SLE and ANA+.

Disclosure: V. Kawai, None; J. Mosley, None; Q. Feng, None; W. Q. Wei, None; D. Carranza Leon, None; C. P. Chung, None; A. Iheword, None; C. M. Stein, None.

Abstract Number: 2126

STAT4 Activation By Type I Interferons Regulates Pathogenic IL-21 and IFN- γ in Lupus

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Session Information

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Background/Purpose: Follicular helper T cells (Tfh) cells in lupus help shape the germinal center (GC) response by delivering contact-dependent and soluble signals, including the cytokines IFN- γ and IL-21. In conventional immune responses, synthesis of Tfh-cell cytokines is regulated by the transcription factors STAT4, T-bet, and Bcl6, although their regulation in lupus is not known. To answer this question, we examined the differential expression of these transcription factors in splenic Tfh cells prior to onset of disease, after immune cell activation but before end organ disease onset, and then in later severe disease in lupus-prone B6.*Sle1.Yaa* mice. We also assess applicability to human lupus.

Methods: Spleens were harvested from 2, 4 and 6 months old B6.*Sle1.Yaa* mice. Transcription factor (T-bet and Bcl6) and cytokine production were assessed by intercellular flow cytometry. Cells were stimulated with PMA and ionomycin, and Tfh (CD4⁺CD44^{hi}Ly6c^{lo}PSGL-1^{lo}CXCR5^{hi}PD-1^{hi}) and Th1 (CD4⁺CD44^{hi}Ly6c^{hi}PSGL-1^{hi}) cells were stained for IL-21 and IFN- γ . Phosphorylation STAT4 in Tfh and Th1 cells were analyzed by flow cytometry after stimulation by IFN- α or IL-12 for 20 minutes in DMEM medium with 1% serum.

Twenty-eight SLE patients from age 18 to 75 years and twenty age-matched healthy control were enrolled in this study. All SLE patients had fulfilled the revised disease criteria of the American College of Rheumatology 1997. Disease activity was assessed with the SLE Disease Activity Index 2000 (SLEDAI2K). Mononuclear cells from the peripheral blood samples were isolated using Ficoll-Paque density gradient media and rested suspended in DMEM medium with 10% serum overnight. Phosphorylation STAT4 in circulating Follicular helper-like T cells (CD4⁺CD45RA⁻CXCR5^{hi}PD1^{hi}CCR7^{lo}) and CD4⁺ T memory cells (CD4⁺CD45RA⁻CXCR5^{hi}PD1^{lo}CCR7^{hi}) were analyzed by flow cytometry after stimulation by IFN- α or IL-12 for 20 minutes in DMEM medium with 1% serum.

Results: We determined that GC Tfh cells produced IL-21 and IFN- γ at similar rates during these three stages of disease; however, Tfh-cell STAT4 activity increased while Bcl6 and T-bet expression declined as disease progressed, suggesting a role of STAT4 in driving T-cell dependent GC B-cell maturation responses in murine lupus.

We found that circulating Tfh and circulating CD4⁺ T memory cells from patients secreted IL-21 and IFN- γ after stimulation. We next examined STAT4 activity these cells, after IFN- α and IL-12 stimulation *in vitro*, in comparison to cells from healthy controls. STAT4 phosphorylation, as an indicator of STAT4-mediated nuclear translocation, was more robust upon IFN- α than IL-12 stimulation, by contrast to canonical STAT4 phosphorylation driven by IL-12 in Th1 cells. Furthermore, the STAT4 phosphorylation correlated to greater disease activity (SLEDAI2K).

Conclusion: Our study indicates that as disease progresses in mice and humans with lupus, Tfh-cells and circulating CD4⁺ T memory cells are robustly responsive to STAT4-guided gene expression, which plays an important role in driving pathologic cytokine production in sustaining moderate and late stage disease activity.

Disclosure: X. Dong, None; F. Koumpouras, None; J. E. Craft, None; J. Weinstein, None.

A Role of Vascular Cell Adhesion Molecule 1 and Activated Leukocyte Cell Adhesion Molecule in Lupus Nephritis

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Background/Purpose: Reliable non-invasive biomarkers for lupus nephritis (LN) are lacking. We investigated two adhesion molecules as urinary biomarkers in LN, i.e. vascular cell adhesion molecule 1 (VCAM-1) and activated leukocyte cell adhesion molecule (ALCAM), the latter also known as cluster of differentiation 166 (CD166).

Methods: Patients with systemic lupus erythematosus (SLE) (n=111, all female) and non-SLE population based controls (n=99, all female) were included. At inclusion, we assessed renal activity using the renal descriptors of the SLE disease activity index 2000 (SLEDAI-2K) and the renal domain of the British Isles Lupus Assessment Group (BILAG) index. Renal BILAG was not assessed in patients with end-stage renal disease (n=2). Urine and plasma VCAM-1 and urine ALCAM levels in samples obtained from patients and controls at the time of inclusion were estimated using enzyme-linked immunosorbent assay. Urine VCAM-1 and ALCAM levels were next adjusted by urine creatinine. For comparisons, we used the Mann-Whitney *U* test.

Results: In comparative analysis between SLE patients and controls, we observed higher urine VCAM-1 levels (P=0.001) and a trend towards higher plasma VCAM-1 concentrations (P=0.051) in SLE patients, but urine levels of ALCAM did not differ between the two groups. Furthermore, urinary VCAM-1/creatinine and ALCAM/creatinine ratio levels were higher in SLE patients (P<0.001 for both). We next conducted comparative analysis between SLE patients with current renal activity (renal BILAG A–C; n=10) and SLE patients with no current renal activity or no history of renal involvement (renal BILAG D–E; n=98). In this analysis, plasma VCAM-1 and urine ALCAM levels were higher in patients with active renal SLE (P=0.007 and P=0.009, respectively), but urine VCAM-1 levels were not found to differ. Urinary VCAM-1/creatinine and ALCAM/creatinine ratio levels were higher in SLE patients with renal activity (P=0.029 and P=0.001, respectively). Finally, we compared SLE patients with a renal SLEDAI-2K>0 (n=31) with SLE patients with renal SLEDAI-2K=0 (n=80). Here, plasma VCAM-1 concentrations were higher in patients with renal SLEDAI-2K>0 (P=0.018), but urine levels of VCAM-1 and ALCAM did not differ. However, both urinary VCAM-1/creatinine and urinary ALCAM/creatinine ratio levels were higher in SLE patients with renal SLEDAI-2K>0 (P=0.023 and P=0.006, respectively).

Conclusion: A role of VCAM-1 in SLE and LN is implicated. While VCAM-1 appears to reflect SLE disease state, ALCAM might have particular importance in renal SLE. After correction for creatinine, urine levels of both VCAM-1 and ALCAM showed ability to distinguish between SLE patients with active renal involvement compared to SLE patients with quiescent nephritis or no nephritis history.

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The Effect of miRNA-21 Overexpression on the Aberrant T Follicular Helper Cells Differentiation in Systemic Lupus Erythematosus

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Session Information**Session Date:** Tuesday, October 23, 2018**Session Title:** Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster III**Session Type:** ACR Poster Session C**Session Time:** 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterized by a large number of autoantibodies and multiple organs damage. T follicular helper (Tfh) cell is a subtype of CD4⁺T cells that is characterized by high expression of CXCR5, ICOS, PD-1, Bcl-6 and IL-21, and assisting B cells to produce antibodies. Previous studies have reported increased numbers of circulating Tfh cells in patients with SLE, which play an important role in the development and progression of SLE. However, the mechanism of abnormal differentiation of Tfh cells in SLE is not yet clear. Numerous studies have reported that microRNAs (miRNAs) were involved in the differentiation and function-related genes regulation of various immune cells, contributing to autoimmune diseases. In this study, we investigated the role of miRNA-21 (miR-21) in regulating the aberrant differentiation of Tfh cells in SLE patients.

Methods: This study was approved by the ethical committee of the Second Xiangya Hospital of Central South University and written informed consent was obtained from all subjects. 24 SLE patients and 24 healthy controls were recruited. CD4⁺ T cells and naive CD4⁺ T cells were isolated by magnetic beads. All patients fulfilled at least 4 of the SLE classification criteria of the American College of Rheumatology. RT-qPCR were used to detect miR-21 and genes expression. Naive CD4⁺ T cells were transfected with miR-21 Agomir or Agomir negative control, and were induced to differentiate into Tfh cells under Tfh cells polarized-condition. SLE CD4⁺ T cells were transfected with miR-21 Antagomir or Antagomir negative control, and then were stimulated by anti-CD3/CD28. The percentage of Tfh cells was detected by flow cytometry. Western blot were used to detect the protein expression level of FOXP1 gene. Student's t-test for equality of means was used to compare values. P-values < 0.05 were considered as significant.

Results: Compared with healthy controls, the expression of miR-21, CXCR5, PD1, BCL6 and IL21 in CD4⁺ T cells of SLE patients was significantly increased (P<0.001). miR-21 expression levels positively correlated with SLEDAI scores in SLE patients. Compared with Agomir negative control, the percentage of Tfh cells was significantly increased in naive CD4⁺ T cells transfected with miR-21 Agomir under Tfh cells polarized-condition, and the expression levels of miR-21, CXCR5, PD1, BCL6 and IL21 were up-regulated significantly. Compared with Antagomir negative control, the percentage of Tfh cells was reduced in SLE CD4⁺ T cells transfected with miR-21 Antagomir, and the expression levels of miR-21, CXCR5, PD1, BCL6 and IL21 were also decreased significantly. The protein level of FOXP1, a negative regulator of Tfh cells differentiation, was significantly decreased in CD4⁺ T cells of healthy controls transfected with Agomir and was increased in CD4⁺ T cells of SLE patients transfected with miR-21 Antagomir compared with negative controls respectively.

Conclusion: miR-21 expression was increased in CD4⁺ T cells of SLE patients, which contributes to the aberrantly increased Tfh cells in SLE patients.

Disclosure: M. Zhao, None; X. Gao, None; J. Wu, None; L. Liu, None; H. Wu, None; Q. Lu, None.

Abstract Number: 2129

Precipitating Anti-dsDNA Peptide Repertoires in Lupus

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Session Information**Session Date:** Tuesday, October 23, 2018**Session Title:** Systemic Lupus Erythematosus – Etiology and Pathogenesis Poster III**Session Type:** ACR Poster Session C**Session Time:** 9:00AM-11:00AM

Background/Purpose: Anti-double-stranded (ds)DNA autoantibodies are prototypic serological markers of systemic lupus erythematosus (SLE) but little is known about their immunoglobulin variable (IgV) region composition at the level of the secreted (serum) proteome. Here, we use a novel proteomic workflow based on de novo database mass spectrometric sequencing of anti-dsDNA precipitins to analyse IgV subfamily expression and mutational signatures of high-affinity, precipitating anti-dsDNA responses.

Methods: Anti-dsDNA antibodies were purified from serum precipitins reactions prepared by agarose gel immunodiffusion between circular plasmid dsDNA and SLE serum from eight patients testing positive for anti-dsDNA by Farr

radioimmunoassays (RIA). Microgram amounts of precipitating anti-dsDNA Igs were separated by SDS-PAGE, and in-gel tryptic and chymotryptic digests were performed on the heavy (H) and light (L)-chain bands and peptides were subjected to nano-high performance liquid chromatography-mass spectrometry followed by combined de novo amino acid sequencing and database matching using Peaks 8.0 software utilising ImMunoGeneTics (IMGT) and Uniprot databases. L-chain complementarity determining region 3 (CDR3) peptides were used as biomarkers to track serum anti-dsDNA clonotypes using quantitative multiple reaction monitoring (MRM).

Results: Serum anti-dsDNA proteomes were oligoclonal with shared (public) expression of IgG heavy chain variable region (IGHV) and kappa chain variable region (IGKV) subfamilies. IgV peptide maps from eight subjects showed extensive public and random (private) amino acid replacement mutations with prominent arginine substitutions across H- and L-chains. Shared sets of LCDR3 peptides specified by arginine substitutions were sequenced from the dominantly expressed IGKV3-20 subfamily, with changes in expression levels of a clonal L-chain CDR3 peptide by quantitative MRM paralleling the rise and fall of anti-dsDNA levels by Farr RIA. The heavily mutated IgV peptide signatures of precipitating anti-dsDNA autoantibody proteomes reflect the strong selective forces that shape humoral anti-dsDNA responses in germinal centres.

Conclusion: This first comprehensive proteomic analysis of precipitating anti-dsDNA IgV peptide repertoires in lupus serum offers a fresh approach for characterising and monitoring anti-dsDNA clonal populations with MS precision and accuracy, and for comparing their molecular signatures with other high-throughput “omics” technologies. Direct sequencing of agarose gel precipitins using microlitre volumes of stored sera streamlines the antibody sequencing workflow and is generalisable to other precipitating serum antibodies.

Disclosure: J. J. Wang, None; A. Colella, None; D. Beroukas, None; T. Chataway, None; T. Gordon, None.

Abstract Number: 2130

Interferon Induced Gene Transcripts Are Differentially Upregulated in the Kidney of Lupus Nephritis Patients Irrespective of Activity or Damage

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Background/Purpose: Lupus nephritis (LN) afflicts 12-69% lupus patients. Even with the best available therapies, complete response is achieved in only 10-85% of patients. The risk of nephritis and its poor outcomes is significantly higher in blacks. To gain better understanding of the pathogenesis specific for LN, biopsy samples from LN and other glomerulopathies (controls) were evaluated for differential gene expression levels.

Methods: Patients with LN meeting ACR SLE criteria and controls consented to donate additional samples during a clinically indicated renal biopsy. Forty-one LN and 8 control samples were analyzed after rRNA was depleted from total RNA. Libraries were prepared and sequenced with Illumina HiSeq2500 and mapped onto the human genome. Differentially expressed genes (DEG) were selected by DESeq2. Signaling Pathway Impact Analysis identified pathways enriched for DEGs that were mapped to the Reactome database. Key transcripts were correlated with clinical and histologic measures. LN samples were scored using the NIH activity (AI) and chronicity indices (CI).

Results:

Demographics and glomerular involvement are listed in Table 1.

Pathways enriched for DEGs were only identified for those driven by interferon (IFN): a/b signaling, IFN signaling, and cytokine signaling. Transcripts that overlapped between all 3 of these pathways are presented in Figs. 1 and 2. Interferon pathway expression levels were increased in LN compared to controls for DEG identified transcripts. Key pathways were consistent with or without HIV-infected controls compared to LN. Expression levels for interferon induced transcripts (IIGTs) were persistently elevated in LN patients as compared to controls regardless of degree of LN activity or chronicity (represented by NIHA1 high (score>8, range 0-17) vs. low and NIHCI high (score>4, range 2-10) vs. low.

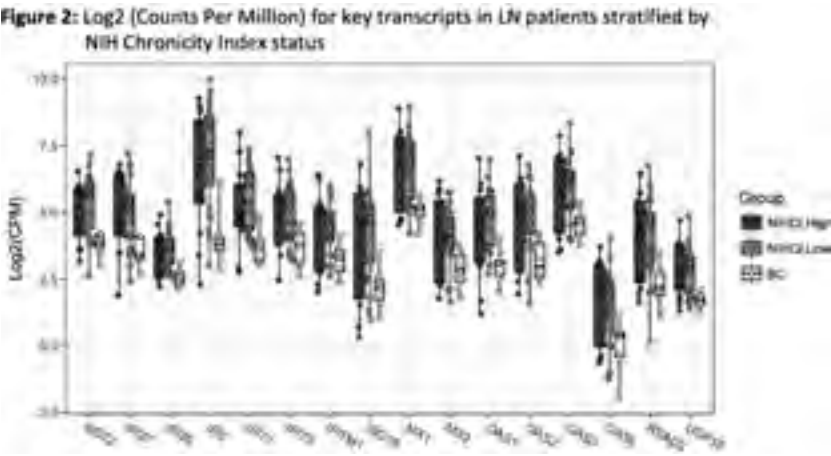
Conclusion: IIGTs are differentially upregulated in LN compared to controls. Within LN, IIGTs are not markedly different between high and low levels of histologic activity or damage. The observation that interferon persists in low activity and high damage LN biopsy samples may represent an opportunity to improve response and outcomes using agents that selectively target IFN pathways.

Table 1: Demographics and glomerular involvement

			Lupus Nephritis n=41	Controls n=8
Demographics	Gender n, (%)	female	32 (78.1)	4 (50)
		male	9 (21.9)	4 (50)
	Race n, (%)	black	37 (90.2)	5 (62.5)
		white	2 (4.9)	3 (37.5)
Glomerular involvement	Biopsy (years)	other	2 (4.9)	0 (0)
		mean age at biopsy	34.1	43.3
	Duration (years)	SLE	8.7	
	Lupus Nephritis n, (%)	class II	6 (14.6)	
		class III	10 (24.4)	
		class IV	20 (48.8)	
		class V	26 (63.4)	
		class VI	4 (9.8)	
	Other Glomerulopathies n, (%)	HIV associated nephropathy		2 (25)
		focal segmental glomerulosclerosis		2 (25)
		IgA nephropathy		2 (25)
		minimal change disease		1 (12.5)
		thrombotic microangiopathy		1 (12.5)
		diabetic nephropathy		1 (12.5)

Disclosure: S. S. Lim, MedImmune, 2; A. B. Farris, MedImmune, 2; T. Guennel, AstraZeneca, 2; S. Wang, MedImmune, 2; J. Cobb, MedImmune, 2; D. Sinibaldi, MedImmune, 1; S. Jenks, MedImmune, 2; I. Sanz, None; X. Guo, MedImmune, 1; G. Illei, MedImmune, 1; K. Shen, AstraZeneca, 2; M. Battle, MedImmune, 2; C. Wei, None; W. White, AstraZeneca, 1, MedImmune, 3.

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Prevalence of Systemic Lupus Erythematosus (SLE) and Associated Comorbidities in the 2011-2015 Medicare Population

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Session Information

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Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

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Background/Purpose: Prevalence of systemic lupus erythematosus (SLE) has been estimated in different US regions. An estimate based on the 2005 US population showed SLE affecting 161,000-322,000 adults (Helmick et al., 2008). We aimed to update estimates of SLE prevalence and associated comorbidity in the US Medicare population.

Methods: We used the 2010-2015 20% Medicare sample data. For each year (2011-2015), we required patients to have Medicare Parts A/B coverage, not have Medicare Advantage, and be alive for the entire preceding year and through the first day of the year. Using ICD-9 diagnosis code 710.0 and ICD-10 codes M32.1, M32.8, and M32.9 (for 2015), we defined SLE by presence of a diagnosis code on ≥ 1 inpatient or ≥ 2 outpatient claims separated by ≥ 30 days. The baseline period, 1 year before each SLE cohort year, was used to define comorbid conditions including: anemia, chronic kidney disease (CKD), end-stage renal disease (ESRD), glomerulonephritis (GN), rheumatoid arthritis (RA), etc. SLE prevalence was reported as the number of SLE patients per 1000 Medicare population.

Results: We included ~6 million Medicare beneficiaries each year. Demographics and baseline characteristics were similar across years. In the 2015 cohort (Table 1), SLE patient mean age was 63.7 (± 14.9) years, 89.4% were female, 21.9% were black; comorbidity percentages were 32.5% anemia, 26.0% CKD, 7.1% ESRD, and 17.9% RA. Non-SLE patient mean age was 72.3 (± 12.6) years, 56.9% were female, 9.4% were black; comorbidity percentages were 13.8% anemia, 11.3% CKD, 1.2% ESRD, and 1.9% RA. Average SLE prevalence was 3.4 (Table 2). Prevalence was higher for ages <45 years, women, and black patients, and for patients with baseline conditions. For example in 2014, SLE prevalence in patients with the following conditions was 37.6, GN; 31.6, RA; 20.5, ESRD; 13.6, psoriatic arthritis; 11.1, Crohn disease; and 10.5, liver disease.

Conclusion: Average SLE prevalence was 3.4 per 1000 Medicare beneficiaries. Prevalence in patients with kidney-related diseases or arthritis was 3-10 times the average. These results underscore the need for effective treatment and management of comorbid conditions and of SLE in the aging Medicare population.

Table 1. Baseline Characteristics and Comorbid Conditions in 2015 20% Medicare Sample

	Non-SLE		SLE		P value
	%	N	%	N	
All		6,333,180		21,652	
Age (Mean years, SD)	72.3 (12.6)		63.7 (14.9)		<.0001
Female	56.9	3,603,533	89.4	19,356	<.0001
White	84.2	5,330,297	70.2	15,205	<.0001
Black	9.4	594,500	21.9	4,734	
Other race	6.4	408,383	7.9	1,713	
Comorbid conditions					
Diabetes	23.4	1,481,478	23.8	5,161	0.1236
Arteriosclerotic Heart Disease	16.2	1,023,519	19.5	4,217	<.0001
Congestive Heart Failure	8.2	519,513	14.0	3,021	<.0001
Peripheral Vascular Disease	10.6	674,466	19.9	4,318	<.0001
Anemia	13.8	874,419	32.5	7,030	<.0001
Hypertension	54.1	3,427,585	66.0	14,298	<.0001
CKD	11.3	716,876	26.0	5,621	<.0001
ESRD	1.2	75,825	7.1	1,536	<.0001
Liver Disease	1.2	76,463	3.6	784	<.0001
Inflammatory conditions					
Glomerulonephritis	0.5	31,568	5.2	1,122	<.0001
Chronic Infection	0.6	38,046	1.3	271	<.0001
Crohn Disease	0.3	18,348	0.9	185	<.0001
Ulcerative colitis	0.3	18,397	0.7	150	<.0001

Table . (Cont'd)

	Non-SLE		SLE		P value
	%	N	%	N	
Gout	2.6	166,225	4.0	874	<.0001
Rheumatoid Arthritis	1.9	122,795	17.9	3,871	<.0001
Psoriasis	0.5	34,271	1.1	237	<.0001
Psoriatic Arthritis	0.2	10,804	0.7	144	<.0001

Table 2. Prevalence of SLE in 2011-2015 20% Medicare Sample, Overall and by Demographics and Selected Conditions

Cohort year	2011	2012	2013	2014	2015
Eligible Medicare beneficiaries in the 20% sample	5,871,667	5,884,921	5,935,011	6,000,841	6,354,832
N with SLE in the 20% sample	19,299	20,071	20,557	21,212	21,652
Number of SLE per 1000 population					
Overall	3.29	3.41	3.46	3.53	3.41
Age					
<45 years	9.98	10.40	10.51	10.72	10.48
45-64 years	8.75	8.81	8.83	8.95	8.69
65-74 years	2.50	2.61	2.63	2.72	2.65
75-84 years	1.94	2.02	2.09	2.10	2.19
85+ years	1.01	1.10	1.15	1.17	1.21
Gender					
Male	0.85	0.85	0.86	0.87	0.84
Female	5.20	5.45	5.56	5.70	5.34
Race					
White	2.76	2.86	2.89	2.95	2.84
Black	7.48	7.73	7.96	8.07	7.90
Other race	3.88	4.13	4.14	4.27	4.18
Selected Conditions					
Glomerulonephritis	39.70	37.91	37.31	37.61	34.32
Rheumatoid Arthritis	28.35	30.30	30.89	31.55	30.56
End-stage renal disease including transplant	19.41	19.23	19.77	20.46	19.85
Psoriatic Arthritis	12.48	13.71	12.91	13.59	13.15
Crohn Disease	11.17	12.10	11.12	11.07	9.98
Liver Disease	10.17	9.67	10.46	10.53	10.15
Anemia	7.37	7.68	7.94	8.17	7.98
Ulcerative colitis	7.18	7.38	6.21	8.02	8.09
Chronic kidney disease	7.76	7.83	8.04	8.00	7.78
Chronic Infection	6.82	6.98	7.19	6.75	7.07
Psoriasis	5.87	5.53	5.69	5.76	6.87
Hypertension	3.88	4.06	4.15	4.26	4.15

Disclosure: S. Li, None; T. Gong, None; Y. Peng, None; K. M. Nieman, None; D. T. Gilbertson, None.

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All-Cause Mortality, Hospitalization, and Systemic Lupus Erythematosus (SLE) Related Complications in 2011-2015 Medicare Beneficiaries with SLE

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Session Information

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Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

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Background/Purpose: Patients with systemic lupus erythematosus (SLE) are at higher risk of complications such as heart attack and renal disease. We aimed to estimate all-cause mortality, all-cause hospitalization, and SLE-related complications in US Medicare patients with SLE, 2011-2015.

Methods: We identified SLE patients during 2010-2015 in the 20% Medicare sample, requiring Medicare Parts A/B coverage, no Medicare Advantage, and being alive for the entire preceding year and through the SLE index date. Using ICD-9 diagnosis code 710.0 and ICD-10 codes M32.1, M32.8, and M32.9 (for 2015), we defined SLE by presence of a diagnosis code on ≥ 1 inpatient or ≥ 2 outpatient claims separated by ≥ 30 days. The first SLE claim date during 2011-2015 was defined as the SLE index date. Chronic kidney disease (CKD) or end-stage renal disease (ESRD) before the SLE index date was identified. Follow-up was from the SLE index date until death, end of Medicare coverage, or December 31, 2015. Outcomes included all-cause death, all-cause first hospitalization, hospitalization due to myocardial infarction (MI)

or stroke, CKD defined from all claim sources, or ESRD. Unadjusted mortality and event rates are reported as number of deaths or events per 100 patient-years.

Results: We identified 38,669 Medicare beneficiaries with SLE during 2011-2015. Mean age was 63.6 (± 14.8) years, 87.5% were female, 72.5% were white, and 20.4% were black. The mean and median follow-up was 2.9 years and the maximum was 5 years after the SLE index date. Unadjusted results are presented in Table 1 overall and by sex. Overall all-cause mortality was 8.17 (7.61%) during the first year and 6.41 (18.34%) during 5 years. In the first year of follow-up, the overall all-cause hospitalization rate was 48.81; rates were 1.79 due to MI and 3.88 due to stroke. Incidence of CKD was 11.93, and incidence of ESRD was 0.81. Within 5 years, 1.73% of SLE patients developed ESRD and 2.68% developed shingles. Compared with women with SLE in 5-year follow-up, men were more likely to die (25.72% vs. 17.28%), be admitted for MI (5.44% vs. 3.71%) or stroke (9.01% vs. 7.49%), and develop CKD (25.99% vs. 20.19%) or ESRD (2.39% vs. 1.63%).

Table 1. All-cause death and complications in 2011-2015 Medicare patients with SLE

Outcomes		Total Patients	In 1-year follow-up			In 5-year follow-up		
			N of Event	% of Event	Rate per 100 patient-year	N of Event	% of Event	Rate per 100 patient-year
All-cause death	All	38,669	2941	7.61	8.17	7,091	18.34	6.41
	Male	4,817	577	11.98	13.21	1,240	25.74	9.80
	Female	33,852	2364	6.98	7.48	5,851	17.28	5.97
All-cause hospitalization	All	38,669	13727	35.50	48.81	22,224	57.47	33.56
	Male	4,817	1898	39.40	57.22	2,879	59.77	38.38
	Female	33,852	11829	34.94	47.68	19,345	57.15	32.95
MI hospitalization	All	38,669	638	1.65	1.79	1,517	3.92	1.40
	Male	4,817	120	2.49	2.78	262	5.44	2.12
	Female	33,852	518	1.53	1.65	1,255	3.71	1.30
Stroke hospitalization	All	38,669	1369	3.54	3.88	2,970	7.68	2.80
	Male	4,817	234	4.86	5.50	434	9.01	3.63
	Female	33,852	1135	3.35	3.65	2,536	7.49	2.70
CKD ^	All	27,573	2923	10.60	11.93	5,736	20.80	8.12
	Male	2,897	418	14.43	16.85	753	25.99	11.23
	Female	24,676	2505	10.15	11.37	4,983	20.19	7.80
Incidence of ESRD ^ ^	All	36,336	272	0.75	0.81	627	1.73	0.61
	Male	4,386	50	1.14	1.26	105	2.39	0.92
	Female	31,950	222	0.69	0.75	522	1.63	0.57
Shingles	All	38,669	533	1.38	1.49	1,038	2.68	0.96
	Male	4,817	61	1.27	1.41	110	2.28	0.88
	Female	33,852	472	1.39	1.51	928	2.74	0.97

^ Excluded those CKD patients defined before SLE index date.

^ ^ Excluded ESRD patients developed before SLE index date.

Conclusion: Medicare beneficiaries with SLE experienced high mortality and SLE-related complications, including MI, stroke, renal disease, and shingles. Effective SLE treatment and prevention of SLE-related complications are needed in the aging Medicare population.

Disclosure: S. Li, None; Y. Peng, None; T. Gong, None; K. M. Nieman, None; D. T. Gilbertson, None.

Abstract Number: 2133

Comparative Disease Burden of Patients with Rheumatoid Arthritis, Psoriatic Arthritis, and Axial Spondyloarthritis: Data from the Corrona Rheumatoid Arthritis and Psoriatic Arthritis/Spondyloarthritis (PsA/SpA) Registries

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Table. Patient Demographics, Clinical Characteristics, Disease Activity, and Quality of Life at Registry Enrollment in Patients With RA vs PsA and Patients With RA vs axSpA

Characteristic*	RA (n = 11,350)	PsA (n = 2003)	AxSpA (n = 495)
Age, years	58.4 (13.5)	53.6 (13.1) [†]	47.6 (13.8) [‡]
Female, n (%)	8758 (77)	1041 (52) [‡]	178 (36) [‡]
Race, n (%)			
White	9764 (86)	1822 (94) [‡]	445 (93) [‡]
Black	874 (8)	9 (0) [‡]	7 (1) [‡]
Other	712 (6)	106 (5) [‡]	29 (6) [‡]
Education, n (%)			
Primary school	334 (3)	29 (1) [‡]	5 (1) [‡]
High school or equivalent	4430 (41)	629 (32) [‡]	147 (30) [‡]
College/university	6169 (56)	1324 (67) [‡]	337 (69) [‡]
Work status, n (%)			
Full time	4101 (37)	1077 (55) [‡]	297 (61) [‡]
Part time	897 (8)	166 (8) [‡]	31 (6) [‡]
Disabled	1568 (14)	185 (9) [‡]	66 (13) [‡]
Retired	3628 (33)	416 (21) [‡]	58 (12) [‡]
Symptom duration, years	9.4 (10.9)	11.2 (10.3) [†]	16.7 (12.0) [†]
Disease duration, years	7.6 (9.6)	8.4 (8.8) [†]	9.8 (10.4) [†]
Physician global assessment (VAS 0-100)	27.3 (23.4)	18.6 (19.6) [†]	25.5 (21.8)
Patient pain (VAS 0-100)	39.5 (29.5)	38.9 (29.6)	46.1 (29.6) [†]
Patient fatigue (VAS 0-100)	43.4 (31.3)	41.1 (29.6) [†]	48.3 (29.0) [†]
Patient global assessment (VAS 0-100)	36.9 (27.9)	43.2 (30.5) [†]	50.2 (32.0) [†]
Morning stiffness, n (%)			
< 30 min	4246 (38)	683 (35) [†]	140 (29) [‡]
≥ 30 min	6969 (62)	1244 (65) [‡]	344 (71) [‡]

AxSpA, axial spondyloarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; VAS, visual analog scale.

* All values are presented as mean (SD) unless otherwise stated.

[†] $P < 0.05$ for comparison between patients with RA vs PsA or RA vs axSpA.

[‡] $P < 0.05$ for the overall distribution across categories of patients with RA vs PsA or RA vs axSpA.

Background/Purpose: Rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA) are 3 common inflammatory rheumatic diseases that can lead to deformities and joint destruction; however, more research has been performed to characterize symptom presentation and the impact of disease burden on patients with RA compared with PsA and axSpA. Additionally, few studies have compared disease burden across patients with RA, PsA, and axSpA because there are limited disease measures that are directly comparable across all 3 diseases. The objective of this study was to compare the disease burden of patients diagnosed with RA, PsA, or axSpA enrolled in the US-based Corrona RA and PsA/SpA Registries.

Methods: This study included adult patients with RA enrolled in the Corrona RA Registry and those with PsA or axSpA enrolled in the Corrona PsA/SpA Registry between March 2013 and March 2018. Patient demographics, clinical characteristics, and disease activity measures collected at registry enrollment were compared between patients with RA vs PsA and patients with RA vs axSpA using t tests or Wilcoxon rank-sum tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables.

Results: A total of 11,350 patients with RA, 2003 with PsA, and 495 with axSpA were included. Patients with RA were older than those with PsA or axSpA (58.4 vs 53.6 and 47.6 years, respectively); a higher proportion of patients with RA were female (77% vs 52% and 36%) and a lower proportion were white (86% vs 94% and 93%) compared with patients with PsA or axSpA. Patients with PsA or axSpA had longer symptom duration (11.2 and 16.7 years) and disease duration (8.4 and 9.8 years) compared with those with RA (9.4 and 7.6 years, respectively) (Table). Patients with RA had a mean physician global assessment score comparable to that of patients with axSpA (27.3 vs 25.5) and higher than that of patients

with PsA (18.6) (**Table**). Patients with axSpA had higher mean patient-reported pain, fatigue, and patient global assessment scores than those with RA (46.1 vs 39.5, 48.3 vs 43.4, and 50.2 vs 36.9, respectively), whereas patients with PsA had a comparable pain score (38.9 vs 39.5), lower fatigue score (41.1 vs 43.4), and higher patient global assessment score (43.2 vs 36.9) than those with RA (**Table**). Higher proportions of patients with PsA or axSpA reported experiencing ≥ 30 minutes of morning stiffness compared with those with RA (65% and 71% vs 62%) (**Table**).

Conclusion: The results of this real-world study indicate that, from a patient perspective, patients with PsA and axSpA have a disease burden comparable to or greater than patients with RA; however, the disease burden of PsA and axSpA may not be as well recognized in clinical practice compared with that of RA. These results provide important insights for physicians into the impacts of RA, PsA, and axSpA from a patient perspective and highlight the need to better understand disease burden in patients with PsA and axSpA.

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Abstract Number: 2134

Modifiable Risk Factors and the Development of Psoriatic Arthritis in People with Psoriasis

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Session Information

Session Date: Tuesday, October 23, 2018

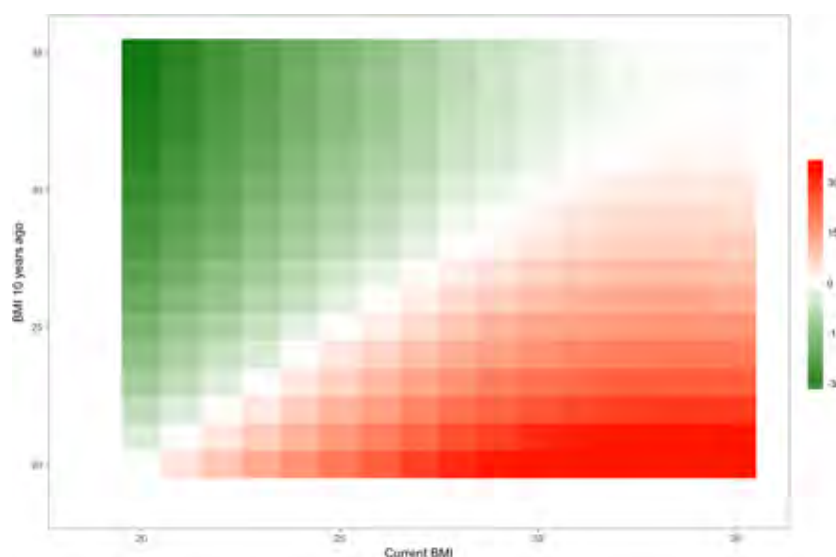
Session Title: Epidemiology and Public Health Poster III: SLE, SSs, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic Arthritis (PsA) is a progressive and often destructive joint disease that causes pain, swelling and joint stiffness, and can lead to an impaired quality of life. As psoriasis commonly precedes PsA, people with psoriasis provide an important population for studying the effect of modifiable risk factors in the development of PsA.

Methods: Incident cases of psoriasis, diagnosed between 1998 and 2014, were identified from the UK Clinical Practice Research Datalink. The association between baseline psoriasis severity, smoking, alcohol consumption and body mass index (BMI), after adjustment for potential confounders, and development of PsA was assessed using generalised additive



models. In addition, the possible non-linear and cumulative/lagged risks associated with change in BMI during follow-up were investigated using distributed lag non-linear models.

Results: The base population consisted of 90,189 incident cases of psoriasis (42% males, mean age 51), of which 1409 developed PsA after the record of their psoriasis diagnosis. Significant increases in the risk of developing PsA were observed for BMIs of 25.0-29.9 (OR_{adj} 1.79 (CI₉₅ 1.46 - 2.19)), 30.0-34.9 (OR_{adj} 2.10 (CI₉₅ 1.67 - 2.63)), and ≥ 35.0 (OR_{adj} 2.68 (CI₉₅ 2.09 - 3.43)) compared to <25.0 . Increased risks of developing PsA were associated with having severe psoriasis: OR_{adj} 3.40 (CI₉₅ 2.83 - 4.08) and alcohol consumption: OR_{adj} 1.13 (CI₉₅ 0.7275 - 1.7047), OR_{adj} 1.46 (CI₉₅ 1.08 - 1.97) and OR_{adj} 0.77 (CI₉₅ 0.46 - 1.29) for ex-, current and heavy drinkers respectively, compared to non-drinkers. Associations with smoking were not significant: OR_{adj} 0.95 (CI₉₅ 0.78 - 1.15) and OR_{adj} 0.87 (CI₉₅ 0.70 - 1.07) for past and current smokers respectively, compared to non-smokers.

A BMI risk calculator was produced to demonstrate the effects of reductions in BMI on (cumulative) risk of developing PsA (Figure 1). For example, reducing BMI over a 10-year period (linearly) was associated with a reduction in the risk of developing PsA when compared to BMI remaining constant over the same period.

Conclusion: The findings from this study add to the growing evidence that severity of psoriasis, alcohol use and increased BMI are associated with an increased risk of PsA in people with psoriasis. Using measurements of BMI over time allowed us to quantify the burden of continuing weight gain on the risk of PsA and, for the first time, we have shown that reducing BMI over time results in a reduction in the risk of PsA. As PsA affects around 20% of people with psoriasis, weight reduction amongst those who are obese may have the potential to greatly reduce their risk of PsA in addition to providing additional health benefits.

Figure 1- Risk calculator for BMI and developing PsA, representing the changes in risk associated with a linear change in BMI vs constant BMI over a 10 year period. Positive changes (shown in red) indicate an increase in risk with negative changes (in green) indicating reduced risk.

Disclosure: A. Green, None; G. Shaddick, None; R. Charlton, None; J. Snowball, None; A. L. Nightingale, None; C. Smith, None; W. Tillet, None; N. McHugh, None.

Abstract Number: 2135

Identification of Psoriatic Arthritis Using an Administrative Claims-Based Algorithm

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Psoriatic arthritis (PsA) is an inflammatory arthritis that can present variably in patients with or without psoriasis. The ability to accurately identify PsA in the large electronic healthcare database is critical for epidemiological studies of this disease. This study aimed to develop and validate a claims-based algorithm to identify patients with PsA.

Methods: We used data from the Partners Healthcare electronic medical record linked to Medicare claims in 2012. We developed 4 claims-based algorithms to identify cases of PsA: 1) ≥ 2 International Classification of Diseases, Ninth Revision (ICD-9) codes for PsA (696.0), at least one by a rheumatologist; 2) ≥ 2 ICD-9 codes for PsA by any physician and ≥ 1 claims for PsA-related medication, including biologic and non-biologic disease modifying anti-rheumatic drugs; 3) ≥ 2 ICD-9 codes for PsA and ≥ 1 ICD-9 codes for psoriasis (696.1) by any physician; and 4) ≥ 2 ICD-9 codes for PsA and no more than one ICD-9 code for rheumatoid arthritis (RA; 714.0). The ICD-9 codes were all separated by ≥ 7 days but < 365 days. In algorithms 1, 3, and 4, the index date was defined as the date of the diagnosis code for PsA that occurred second; in algorithm 2, the index date was defined as whichever event (ICD-9 code or medication claim) occurred third. PsA cases defined by the algorithms were confirmed by medical record review, with diagnosis of PsA documented in the clinical record by the treating physician considered as the gold standard. Positive predictive value (PPV) and 95% confidence intervals (CI) of the algorithms were calculated.

Results: The 4 algorithms identified 281, 261, 224, and 216 records respectively, however around 40% had adequate data (defined below) and were included. The PPV of the algorithms ranged from 86.6-90.5% (Table).

Conclusion: Our records suggest that a claims-based algorithm utilizing two or more diagnosis codes for PsA alone, or in combination with a diagnosis for psoriasis, no more than one diagnosis code for RA, or linked to a PsA-related medication, can accurately identify cases of PsA in the claims database.

Table. Positive predictive value of algorithms.

Algorithm	Records identified n	Records with adequate data* n (%)	Confirmed PsA per treating physician n	PPV of algorithm % (95% CI)
≥2 ICD-9 codes for PsA, at least one by rheumatologist	281	134 (47.6)	116	86.6 (79.6, 91.8)
≥2 ICD-9 codes for PsA AND ≥1 medication claim	261	113 (43.3)	98	86.7 (79.1, 92.4)
≥2 ICD-9 codes for PsA AND ≥1 ICD-9 code for psoriasis	224	95 (42.4)	86	90.5 (82.8, 95.6)
≥2 ICD-9 codes for PsA AND no more than 1 ICD-9 code for RA	216	104 (48.1)	93	89.4 (81.9, 94.6)

* Defined as clinic notes that discuss or address diagnosis of PsA within 6 months of the index date.

Disclosure: J. Ford, None; L. A. MacFarlane, None; A. Tong, None; S. C. Kim, None.

Abstract Number: 2136

Mortality Rates and Causes in Psoriatic Arthritis Patients

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

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Background/Purpose: Psoriatic arthritis (PsA) is an inflammatory musculoskeletal disease that affects about 30% of psoriasis patients, and can lead to significant joint damage and disability. Results from mortality studies are inconsistent. The aims of this study were: 1) to estimate the trends in mortality rates among PsA patients over calendar time 2) to estimate cause-specific mortality rates.

Methods: Patients are evaluated at the initial clinic visit and subsequently every 6-12 months according to a standard protocol. The prospectively collected data are stored in a web-based database and included demographics, personal and family medical history, smoking and alcohol drinking habits, medications, skin and musculoskeletal disease activity, imaging, and laboratory findings. Information on patient deaths and causes of death was collected prospectively and through linkage with the provincial cancer and death registries, through telephone interviews and correspondence with family physicians and patients' relatives, and through daily checks of death notices in the newspaper. Death certificates, and admission letters were used, where possible, to verify patient deaths and to identify the primary cause of death. Standardized mortality ratios (SMRs) were computed with reference to the Ontario population and were calculated overall, by age, and by sex. Causes of death were recorded by ICD9 and ICD10 codes. Cause-specific SMRs were also computed.

Results: Among 1490 patients followed over 14675 patient-years, there were 225 (15%) confirmed deaths among 111 female and 114 male individuals. The overall standardized mortality ratio was 0.92 (95% confidence interval [CI] 0.81-1.05), the sex specific SMRs were 1.08 (95% CI 0.89-1.30) for females and 0.80 (95% CI 0.66-0.97) for males. The age-specific SMRs were of 3.36 (95% CI 1.61-6.18) for those 20-39 years of age, and 0.97 (95% CI 0.68-1.34), 0.88 (95% CI 0.73-1.06) and 0.86 (95% CI 0.66-1.11) for 40-59, 60-79 and above 80 years of age respectively. Major causes of death included malignant neoplasms (n=61; SMR=0.97 [95% CI 0.72-1.28]), acute myocardial infarction (n=32; SMR=1.11 [95% CI 0.74-1.58]), and pneumonia (n=14; SMR=2.46 [95% CI 1.27-4.31]).

Figure 1: Unadjusted standardized mortality ratios. Overall rates in 1490 study patients, as well as sex-specific rates



Table 1: Characteristics of the study patients at first presentation

	Overall (n=1490)	Alive (n=1265)	Deceased (n=225)
Age, mean \pm SD years	44.5 (13.2)	42.8 (12.5)	54.3 (12.8)
Age at Psoriasis onset, mean \pm SD years	28.7 (14.7)	27.5 (13.9)	35.4 (17.2)
Age at PsA onset, mean \pm SD years	38.2 (13.7)	37.1 (13.3)	44.2 (14.5)
PsA duration, mean \pm SD years	6.3 (7.8)	5.6 (7.1)	10.2 (10.6)
Follow up duration, mean \pm SD years	10.4 (9.7)	10.4 (9.7)	8.7 (8.7)
Smoking ever, n(%)	663 (44%)	579 (46%)	84 (37%)
Sex, n (%)			
* Female	660 (44%)	549 (43%)	111 (49%)
Alcohol consumption, n(%)			
* None	510 (41%)	456 (40%)	54 (50%)
* Social	630 (50%)	592 (52%)	38 (36%)
* Daily	109 (9%)	93 (8%)	16 (15%)
Ethnicity, n(%)			
* Caucasian	1281 (87%)	1070 (85%)	211 (84%)
Marital status, n(%)			
* Single	285 (23%)	269 (24%)	16 (14%)
* Married/Common law	824 (68%)	751 (68%)	73 (65%)
* Divorce and other	134 (11%)	111 (10%)	23 (21%)
Decade of entry, n(%)			
* 1975-1987	326 (22%)	186 (18%)	141 (63%)
* 1988-1997	238 (16%)	199 (16%)	39 (17%)
* 1998-2007	427 (29%)	380 (31%)	38 (17%)
* 2008-2018	499 (33%)	482 (39%)	7 (3%)

PsA = Psoriatic arthritis

Conclusion: Although the overall SMR was similar to the general population, higher SMR was found among patients who were younger at presentation. Further analyses are needed to understand the mortality risk, effect of comorbidities, and the effect of therapies.

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Abstract Number: 2137

Primary Antiphospholipid Syndrome with Vascular Manifestations Is a Rare Disease: A Population-Based, Multi-Source Study Assessing the Prevalence and Incidence in Adults

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Session Information

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Background/Purpose: Antiphospholipid Syndrome (APS) is a systemic autoimmune disease characterized by thrombotic and/or obstetrical manifestations mediated by antiphospholipid antibodies (aPL). By now, no population-based study was performed to assess the epidemiology of APS. Incidence and prevalence of primary APS (PAPS) are therefore unknown. The aim of this study was to evaluate the prevalence during the year 2013 and incidence for the period 2011-2015 of vascular PAPS in the adult population in a 40 kilometers long prealpine valley in northern Italy. The population was 101.477 inhabitants in 2013. The only easy access to the valley is from the main city of the area, where the only Rheumatology referral tertiary Center is located. Therefore, this valley is ideal for epidemiological studies by matching different sources for patients' identification. The search for PAPS cases was restricted to adults below the age of 50, since this is supposed to be the age period for the onset of "true" vascular PAPS.

Methods: We identified adult individuals of 18-50 years of age living in the study area. Patients with thrombotic events were identified by three sources: 1) hospital discharge codes using keywords (deep vein thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke); 2) General Practitioners working in the study area; 3) patients with definite diagnosis of vascular PAPS already followed-up in the tertiary Rheumatology Center. Patients were classified as PAPS if aPL positivity was confirmed overtime.

Table 1. Incidence rates of antiphospholipid antibody syndrome per 100,000 inhabitants in younger adult population (18-50 years) between 2011 and 2015. The 95% confidence intervals (CI) are reported in parenthesis.

	INCIDENCE	
	Number of cases	Incidence (95% CI) per 100,000
OVERALL		
Males + Females	5	3.7 (1.7-7.1)
Males	5	4.0 (1.5-9.4)
Females	4	3.4 (0.9-8.6)
VENOUS THROMBOSIS		
Males + Females	4	1.7 (0.5-4.3)
Males	1	0.6 (0.0-4.5)
Females	3	2.6 (0.5-7.3)
CEREBROVASCULAR ACCIDENTS		
Males + Females	4	1.7 (0.5-4.3)
Males	3	2.4 (0.5-7.1)
Females	1	0.9 (0.0-4.0)
MYOCARDIAL INFARCTION		
Males + Females	1	0.6 (0.0-2.3)
Males	1	0.6 (0.0-4.5)
Females	0	—

Results: We identified 47 patients with venous events during the period 2011-2015. Twenty-seven out of 47 (57%) were tested for aPL, 5/27(19%) resulted to be positive. Regarding arterial events, 36 patients had stroke and 33/36 (92%) were tested for aPL, 4/33 (12%) were positive. Sixty-four patients with myocardial infarction (MI) were observed: 14/64 (22%) were tested for aPL, 2/14 (14%) were positive. Prevalence was estimated to be 22,9 (CI 95% 11,4-41,0) per 100.000 inhabitants in 2013. Table 1 shows the incidence figures of vascular PAPS. We also calculated the “historical” incidence of APS in the 10 years before our study period (2001-2010), yielding a value of 1,2 (CI 95% 0,4-2,6) per 100.000 inhabitants. By comparing the two incidence values (1,2 vs 3,7), we can assume a better diagnostic sensitivity over the years and increasing awareness of PAPS as a cause of thrombosis in younger patients.

Conclusion: This is the first population-based epidemiological study assessing the prevalence and incidence of PAPS in adult population below the age of 50. According to the prevalence estimates, PAPS can be classified as a “rare disease”. This study identified a gap in the diagnostic work-up, as nearly 50% and 80% of patients with venous thrombosis and MI were not tested for aPL. We are currently contacting patients who were tested for a PL in order to refine the epidemiological evaluation.

Disclosure: C. Nalli, None; G. Pascariello, None; A. Zentilin, None; E. Raffetti, None; L. Andreoli, None; R. Kumar, None; G. Martini, None; R. Ottaviani, None; C. Gasparotti, None; M. Magoni, None; C. Scarcella, None; F. Donato, None; A. Tincani, Bristol-Myers Squibb, 2, UCB, Inc., 5.

Abstract Number: 2138

Real-World Evaluation of Treatment Patterns of Methotrexate Users in Psoriatic Arthritis

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Session Information

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Session Time: 9:00AM-11:00AM

Background/Purpose: Methotrexate (MTX) is commonly used to treat psoriatic arthritis (PsA), yet data supporting its effectiveness in PsA are limited. This analysis describes real-world dosing, treatment patterns, and administration modifications in PsA patients initiating MTX.

Methods: Adults with PsA were selected if they initiated MTX (index date) between January 1, 2012, and September 30, 2016, had ≥ 12 months pre- and post-index continuous enrollment in the IQVIATM PharMetricsPlus real-world data adjudicated claims database, and had no history of systemic disease-modifying PsA therapies 12 months pre-index. Concomitant drug use with known MTX interactions was captured along with rates of MTX discontinuation, switch, initiation of combination therapy, and changes to dose and/or administration. Concomitant drug use was defined as ≥ 7 days' supply overlap. Discontinuation was defined as a ≥ 60 -day lapse in therapy. Switching was defined as the presence of a new therapy, with a < 60 -day MTX overlap and MTX discontinuation. Combination therapy was defined as the addition of a PsA agent to MTX, with a ≥ 60 -day overlap. Patients were followed for 12 months after their index date.

Results: A total of 2,105 MTX patients were included. Mean (SD) age was 48.0 (10.3) years and 51% were male. Mean follow-up was 30.1 months. During the pre-index period, 48.2%, 54.9%, and 51.5% used topical steroids, systemic steroids, and non-steroidal anti-inflammatory drugs, respectively. Rates of comorbidities that could increase patients' risk of MTX toxicity were hyperlipidemia (33.5%), diabetes (13.3%), and obesity (13.9%). Other comorbidities included osteoarthritis (54.7%), hypertension (33.2%), and fibromyalgia (17.9%). More than half of MTX patients (56.5%) had a concomitant prescription with known MTX interaction. Mean (SD) duration of MTX monotherapy was 186.0 days (129.7). During

12-Month MTX Treatment Patterns in Patients With a Diagnosis of PsA

Treatment Pattern, n (%)	MTX N=2,105
Discontinuation (≥ 60 -day refill gap)	999 (47.5)
Switch	146 (6.9)
Combination	351 (16.7)
No modification	609 (28.9)

follow-up, 57.6% of patients had ≥ 1 increase in dose and 31.6% had ≥ 1 decrease in dose, while 108 (5.1%) patients changed from oral to subcutaneous injection. Discontinuation was the most frequent treatment modification, followed by combination therapy (Table). Mean (SD) time to discontinuation, switch, and combination therapy was 99.8 days (75.5), 112.2 (60.0) days, and 150.8 (84.7) days, respectively.

Conclusion: During follow-up, half of the MTX users discontinued therapy, had concomitant therapy with known MTX interactions, and had at least 1 increase in MTX dose. More research is needed to better understand the impact of treatment patterns on healthcare outcomes among PsA patients initiating treatment with MTX.

Disclosure: B. Ung, Celgene Corporation, 1, 3; D. Hines, IQVIA, 5; S. Mehta, Celgene Corporation, 1, 3; C. Pelletier, Celgene Corporation, 1, 3; X. Wang, IQVIA, 5; R. Wade, IQVIA, 2, 3.

Abstract Number: 2139

Retrospective Study: Association of Hydroxychloroquine Use and Hemolytic Anemia in Patients with Low Levels of Glucose-6-Phosphate Dehydrogenase (G6PD)

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Glucose-6-phosphate dehydrogenase deficiency (G6PD) is linked to hemolytic anemia with certain medications and is the most common enzyme deficiency worldwide. Clinical hemolysis and severity of disease depends on the genotype of G6PD, which also has a different geographic distribution, with the most severe risk of hemolysis in the Mediterranean variant. Although the American College of Rheumatology does not recommend routine testing for G6PD prior to initiation of Hydroxychloroquine (HCQ), the package insert for HCQ does recommend careful use in G6PD deficient patients due to potential for hemolysis. A recent retrospective study from Duke assessed 11 G6PD deficient African American patients exposed to HCQ over 700 months cumulative exposure with no cases of hemolysis during medication exposure. Authors recommended against the routine measure of G6PD levels or withholding therapy with HCQ in African Americans given these results. However, the study population was mainly African American and had minor representation of other ethnicities.

Methods: Eligible subjects in our large, urban medical center were identified using clinical looking glass software from January 1st, 1997 to January 1st, 2018. Data was collected using the institutional EMR. Case records were analyzed for G6PD deficiency, HCQ use, length of exposure to HCQ, demographic characteristics and laboratory evidence of hemolysis.

Results: 5264 patients were prescribed HCQ during the pre specified interval, of which 49.5% (2605 patients) were screened for G6PD deficiency. Of the screened patients, 36 were found to be G6PD deficient. After chart review, 18 G6PD deficient patients were found to be exposed to HCQ. The mean age of the patients was 48 years (SD 14.1, range 18-66), 11 were female, the most common race was African American (n=10) and Hispanic (n=5), and the most common diagnosis was lupus (n=7), followed by rheumatoid arthritis (n=5). The mean exposure time was 32.8 months (SD 30.3, range 2-114 months), with a total cumulative exposure of 591 months. No evidence of hemolysis was found, either by clinical or laboratory criteria.

Conclusion: 5264 patients were prescribed HCQ during the prespecified interval, of which 49.5% (2605 patients) were screened for G6PD deficiency. Of the screened patients, 36 were found to be G6PD deficient. After chart review, 18 G6PD deficient patients were found to be exposed to HCQ. The mean age of the patients was 48 years (SD 14.1, range 18-66), 11 were female, the most common race was African American (n=10) and Hispanic (n=5), and the most common diagnosis was lupus (n=7), followed by rheumatoid arthritis (n=5). The mean exposure time was 32.8 months (SD 30.3, range 2-114 months), with a total cumulative exposure of 591 months. No evidence of hemolysis was found, either by clinical or laboratory criteria.

Disclosure: M. Mejia Saldarriaga, None; I. E. Ramirez de Oleo, None; B. Johnson, None.

Association of Hydroxychloroquine Use and Incident Atrial Fibrillation in Rheumatoid Arthritis: A Retrospective Study

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Session Information

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Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

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Background/Purpose: Hydroxychloroquine (HCQ) is a derivative of quinidine, a class 1 a anti-arrhythmic agent used to prevent ventricular arrhythmias and recurrent atrial fibrillation (AFib). AFib occurs more commonly in patients with rheumatoid arthritis (RA) compared to the general population. HCQ is commonly used to treat mild RA. This study examines the association of HCQ use and AFib or ventricular arrhythmias in RA.

Methods: A retrospective cohort of adult RA (ICD10: M05 and M06) patients at a tertiary academic rheumatology practice from Dec 1,2014 to May 30,2017 excluding patients with prevalent AFib was constructed. Patients were categorized as HCQ users versus nonusers. Primary outcome was incident AFib adjudicated by electronic health record (EHR) review and EKG confirmation. AFib events occurring in the first year of observation were considered prevalent AFib to allow for a run-in period and exclude prevalent cases more reliably. Secondary outcome was incident ventricular arrhythmias- a composite of ventricular tachycardia (VT), ventricular fibrillation (VF), torsades and sudden cardiac death (SCD) adjudicated similarly. Multivariate regression analysis was performed to estimate the association between HCQ exposure and development of incident AFib, after adjusting for relevant confounders, including demographics (age, sex, ethnicity), AFib-related co-morbidities (BMI, smoking, alcohol use, chronic obstructive pulmonary disease, obstructive sleep apnea, hypertension, coronary artery disease, heart failure, diabetes, cerebrovascular accident and transient ischemic attack, peripheral vascular disease, thyroid disorder, chronic kidney disease and liver dysfunction), anti-arrhythmic medication use (beta-blockers, calcium channel blockers, flecainide, digoxin, amiodarone), and autoimmune serologies. Sub-group analysis was performed on patients age >65yrs (given higher risk of AFib).

Results: Our study included 5697 patients with RA, including 1304 HCQ users. During the observation period, 28 incident AFib events occurred in HCQ users and 54 in non-users. Unadjusted odds ratio (OR) was calculated at 1.76 (95% CI 1.11-2.80, p=0.02), and multivariable logistic regression analysis showed an OR of 2.07 (95% CI 1.30-3.30, p=0.002) for incident AFib. Three incident ventricular arrhythmias occurred in HCQ users and 7 in non-users, all were VT, with OR of 1.44 (95% CI 0.37-5.59, p=0.59). In the age>65 yrs sub-group analysis, OR was 1.99 (95% CI 1.18-3.38, p=0.01).

Table 1: Risk of incident AFib according to HCQ use

Variable	HCQ users (N=1304)	HCQ non-users (n=4393)
Age (yrs)	62.4±13.3	65.4±13.7
Female sex	1058 (81%)	3277 (75%)
Caucasian	1164 (89.3%)	3829 (87.2%)
BMI (kg/m2)	29.8±7.3	29.7±7.1
Smoking (ever)	713 (55%)	2220 (51%)
Alcohol user	504 (39%)	1610 (38%)
Anti-arrhythmic medication use	162 (12.4%)	87 (1.9%)
HTN	380 (29%)	1490 (34%)
COPD	2 (0.1%)	2 (0.1%)
OSA	80 (6%)	94 (0.01%)
CAD	52 (4%)	98 (2.2%)
Heart failure	32 (2.4%)	112 (2.5%)
Diabetes	118 (9%)	606 (13.8%)
CVA/TIA	9 (0.6%)	84 (1.9%)
Thyroid disorder	7 (0.5%)	15 (0.3%)
Liver dysfunction	40 (3%)	118 (2.7%)
CKD	44 (3.3%)	210 (4.8%)
PVD	13 (0.9%)	66 (1.5%)
Incident AFib	28 (2.2%)	54 (1.2%)
Unadjusted Odds Ratio	1.76 (95 % CI 1.11-2.80, p=0.02)	
Adjusted Odds Ratio	2.07 (95% CI 1.30-3.30, p=0.002)	

Conclusion: In this exploratory study, HCQ use was associated with a 2 times higher risk of AFib in RA patients. These preliminary results need to be confirmed in larger studies given HCQ's otherwise favorable effect on cardiovascular disease risk profile in multiple previous studies.

Disclosure: A. Gupta, None; A. Joshi, None; O. Saleem, None; M. Chester-Wasko, None; T. S. Sharma, None.

Abstract Number: 2141

Development of a Pediatric Glucocorticoid Toxicity Index

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Session Information

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Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

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Background/Purpose: A Glucocorticoid Toxicity Index app (GTI 2.0) is now used as a clinical trial outcome measure in adults, but glucocorticoid (GC) toxicity issues in children differ from those relevant to adults in a number of respects. We sought to design a pediatric GTI (pGTI) for use as an outcome measure in clinical trials and other settings to assess the impact of treatment interventions on GC toxicity.

Method: Sixteen experts from 7 subspecialties participated. Six were from the U.S. and 10 from Europe, Canada, or New Zealand. Group consensus methods and multi-criteria decision analysis (MCDA) were employed. The pGTI consists of a Composite Index and a Specific List. Toxicities included in the Composite GTI occur commonly and may vary with GC exposure. The Composite GTI reflects GC toxicity with the potential to change over time: to worsen if GC doses increase, or to improve if successful GC sparing is achieved. The Composite pGTI was evaluated by application to paper cases derived from real-life cases. Weights for individual items of the Composite pGTI were assigned through MCDA, facilitated by 1000 Minds software. Similar MCDA approaches were used in the development of the adult GTI and ACR/EULAR Classification Criteria for several rheumatic diseases (RA, SLE, SSc). In contrast, the Specific List describes clinical events that are less common but often severe and typically not reversible by GC reduction. Items of the Specific List are not weighted but rather recorded as a cumulative index of glucocorticoid-related damage.

Results: The complexity of longitudinal GC toxicity assessment in children lends itself well to app technology, which offers significant advantages in ease of calculation. The impact of normally-anticipated growth on several pGTI domains poses particular challenges addressed effectively by app technology. The pGTI Composite Index consists of 10 toxicity domains: body mass index (BMI), growth, glucose tolerance, lipid metabolism, systolic blood pressure, bone mineral density, GC-induced myopathy, skin toxicity, neuropsychiatric impact, and infections. Weighting of items of the Composite GTI permits the calculation of cumulative and aggregate scores. The pGTI weights improvement in GC toxicity within a given domain as highly as worsening: improvements yield negative toxicity scores; worsening, positive scores. As an example, an increase in BMI of >2 but <5 BMI units is associated with an increase in the cumulative GTI of +21 points. In contrast, decline in BMI to a corresponding degree is associated with a reduction in that domain of -21 points. All pGTI scores are calculated based on a change in toxicity between two visits rather than an absolute score at one point in time. The Specific List is designed to capture GC toxicity not included in the Composite GTI. The Specific List includes six additional domains addressing features of GC toxicity such as pubertal delay/sex hormone access interruption, ocular toxicity (cataracts, central serous retinopathy), and bone health (osteonecrosis).

Conclusion: We describe the development and initial evaluation of a comprehensive, weighted index for the assessment of GC toxicity. A pGTI app will be available in the autumn of 2018.

Disclosure: P. Brogan, None; R. P. Naden, None; S. P. Ardoin, None; J. C. Cooper, None; F. De Benedetti, Novartis, Roche, Pfizer, SOBI, AbbVie, Novimmune, BMS, Sanofi, 2; J. F. Dicaire, None; D. Eleftheriou, None; B. M. Feldman, None; J. Goldin, None; S. E. Karol, None; E. Miloslavsky, Genentech, Inc., 2; F. Price-Kuehne, None; D. Skuse, None; C. A. Stratakis, None; N. Webb, None; J. H. Stone, None.

Abstract Number: 2142

Exposure to Disease Modifying Antirheumatic Drugs during Pregnancy in Women with Inflammatory Arthritis and the Risk of Serious Maternal Infection: A Population-Based Cohort Study

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Session Information

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Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

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Background/Purpose: Infection risk is one of the concerns regarding therapy with conventional disease modifying antirheumatic drugs (csDMARDs) and to our knowledge no research has examined this concern in pregnancy. Our objective was to evaluate the association between exposure to csDMARD during pregnancy and risk of serious infections in women with inflammatory arthritis (IA).

Methods: Linking population-based administrative data on all physician visits, hospital admissions, and all dispensed medications to a provincial perinatal registry, we conducted a retrospective cohort study from 01/01/2002 and 12/31/2012. Unique to this registry is detailed information on antenatal, intrapartum, and postpartum maternal and infant outcomes as well as valid information on date of conception. We created a pregnancy cohort of women with IA using a case definition of 2 outpatient physician ICD9 codes within 2 months and less than 2 years apart for rheumatoid arthritis, systemic autoimmune rheumatic diseases, and other IA. We categorized csDMARDs according to accepted compatibility with pregnancy: **Group 1** - antimalarials, cyclosporine, gold, sulfasalazine; and **Group 2** - azathioprine, chlorambucil, cyclophosphamide, leflunomide, methotrexate, minocycline, mycophenolate mofetil, penicillamine. We ascertained exposure during pregnancy as binary use (yes/no) overall and according to the most recent trimester. Serious maternal infection outcomes were those requiring hospitalization during the first 42 days post-partum. We used Poisson regression models to evaluate the association between csDMARD during pregnancy and serious maternal infections, adjusting for baseline covariates.

Results: There were 485 pregnancies in 405 women, and 5,764 pregnancies in 4,168 women in the csDMARDs exposed and unexposed groups, respectively, during the study period (**Table 1**). We identified 3.5%, 3.9%, and 4.0% of mothers with serious infections in unexposed pregnancies and those exposed to Group 1 and 2 csDMARDs, respectively. As shown in **Table 2**, there were no associations with csDMARDs use during pregnancy and serious infections in mothers when considering overall exposure (adjusted odds ratio [OR], 0.96; 95% confidence interval [CI], 0.60 to 1.54) or according to trimester. Findings persisted in sub-analyses according to csDMARD groups.

Conclusion: We found no association with exposure to csDMARDs during pregnancy and serious maternal infections among women with IA. These findings have implications for informing women with IA who are pregnant or planning to become pregnant.

Table 1. Characteristics of pregnant women with inflammatory arthritis exposed and unexposed to csDMARDs preconception and during pregnancy

Characteristics	Exposed to csDMARDs N (%) 405 women 485 pregnancies	Unexposed to csDMARDs N (%) 4,168 women 5,764 pregnancies
Current pregnancy		
Age at delivery (mean (SD))	32.2 (5.0)	31.0 (5.4)
Multiparous	262 (54)	3,429 (59)
Obstetrical history		
Prior preterm delivery	44 (9)	314 (5)

Table . (Cont'd)

Characteristics	Exposed to csDMARDs N (%) 405 women 485 pregnancies	Unexposed to csDMARDs N (%) 4,168 women 5,764 pregnancies
Prior spontaneous abortion	131 (27)	1,454 (25)
Prior neonatal death	<5	35 (1)
Prior stillbirth	17 (4)	62 (1)
Prior low birth weight	26 (5)	162 (3)
Prior congenital anomaly	5 (1)	51 (1)
Inflammatory arthritis type		
Rheumatoid arthritis	239 (49)	1,325 (23)
Systemic autoimmune rheumatic diseases	195 (40)	749 (13)
Other inflammatory arthritides*	51 (11)	3,690 (64)
csDMARD use		
Group 1	360 (74)	
Group 2	125 (26)	
Other medication use#		
Biologics	18 (4)	67 (1)
Glucocorticoids	199 (41)	360 (6)
Traditional NSAIDs	199 (41)	1,120 (19)
COX2 NSAIDs	54 (11)	186 (3)
Antidepressants	87 (18)	853 (15)
Anxiolytics	41 (8)	394 (7)
Comorbidities		
Mood disorders	28 (6)	254 (4)
Anxiety	50 (10)	561 (10)
Asthma	<5	31 (1)

* other includes JIA, AS, and Ps/PsA

other medication use during 90 days preconception and/or during pregnancy

Table 2. Multivariable models showing the association between csDMARD use during pregnancy and risk of serious maternal infections

	Exposure Period	OR (95% CI)
All csDMARDs	overall during pregnancy	0.96 (0.60 to 1.54)
	according to trimester	
	1 st trimester	0.70 (0.26 to 1.89)
	2 nd trimester	0.79 (0.20 to 3.21)
	3 rd trimester	1.12 (0.64 to 1.96)
Group 1 csDMARDs	overall during pregnancy	0.99 (0.58 to 1.70)
	according to trimester	
	1 st trimester	0.71 (0.22 to 2.22)
	2 nd trimester	0.50 (0.07 to 3.57)
	3 rd trimester	1.25 (0.67 to 2.31)
Group 2 csDMARDs	overall during pregnancy	0.84 (0.34 to 2.09)
	according to trimester	
	1 st trimester	0.55 (0.08 to 3.95)
	2 nd trimester	1.46 (0.20 to 10.50)
	3 rd trimester	0.88 (0.27 to 2.82)

* Multivariable models were adjusted for baseline covariates including maternal characteristics, obstetrical history, comorbidities; and use medications (including glucocorticoids, traditional NSAIDs, COX2 NSAIDs, biologic DMARDs)

Disclosure: M. A. De Vera, None; N. W. Tsao, None; E. C. Sayre, None; A. Howren, None.

Abstract Number: 2143

Lymphoproliferative Malignancy in Psoriatic Arthritis and the Role of Systemic Immunosuppressive Therapies

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic arthritis (PsA) is a systemic inflammatory disease that can have musculoskeletal (PsA-MsK) or concurrent MsK and skin (PsA-MsK/skin) manifestations, and the skin disease has the same clinical features as that of psoriasis (PsO). Such autoimmune diseases have been related to increased lymphoproliferative disease risk, which is thought to be due to continual exposure of systemic immunosuppressive therapies and abnormal immune activation. Such risk is well established in PsO, but is unclear in PsA. Also, the use of immunosuppressants has been a conflicting predictor in the development of malignancy. This study was undertaken to investigate the lymphoproliferative risk among patients with PsA-MsK/skin, PsA-MsK, and PsO and in relation to systemic immunosuppressive therapies, including tumor necrosis factor inhibitor (TNFi) and methotrexate (MTX).

Methods: A multicenter retrospective study involving four Veterans (VA) Hospitals in Southern California was performed (n=930,802). Patients with PsA-MsK/skin (n=18,339), PsA-MsK (n=9,437), and PsO (n=15,951) were assembled using the ICD 9 and 10 coding from 2000 to 2017. Each cohort member was linked to ICD-9 and ICD-10 codes for a diagnosis of lymphoma and leukemia. The Odds Ratio (OR) for developing any lymphoproliferative malignancy was calculated and the prevalence for individual lymphoma and leukemia subtypes were compared among the cohorts. A sample of patients with PsA-MsK/skin (n=42), PsA-MsK (n=57), and PsO (n=50) at Long Beach VA Hospital (VALB) and their use of TNFi and MTX therapy were analyzed in relation to their risk for developing malignancy, with the use of therapy defined as being \geq 12 months of exposure.

Results: In the PsA-MsK/skin, PsA-MsK, and PsO groups, the prevalence of lymphoma and leukemia was 0.25%, 0.66%, and 3.70%, respectively. The most common lymphoproliferative malignancy among all three groups was Non-Hodgkin's lymphoma, with diffuse large B-cell lymphoma as the most prevalent subtype. Patients with PsA-MsK/skin have the lowest risk for developing lymphoproliferative cancer (OR 0.15), followed by those with PsA-MsK (OR 0.37) and PsO (OR 2.27; $p < 0.001$ in all groups). In the VALB cohort, twice as many PsA-MsK/skin patients received combination TNFi and MTX therapy compared to PsA-MsK patients, and almost no PsO patients received systemic immunosuppressants (47.6%, 24.6%, 4.0%; $p < 0.001$).

Conclusion: The subtypes of lymphoproliferative cancers were similarly distributed among patients with PsA and PsO. PsA patients have an unexpectedly low prevalence and low risk in developing lymphoproliferative cancers in comparison to PsO patients. One explanation is that aggressive management of PsA with systemic immunosuppression successfully controls autoimmune inflammatory processes and reduces the risk of developing malignancy. These findings also imply that, perhaps, biologics may not induce malignancy as suggested by other studies. Additional studies are needed to elucidate lymphoproliferative cancer risk in relation to disease activity and inflammatory markers in the future.

Disclosure: L. Truong, None; M. Wong, None.

Abstract Number: 2144

Epidemiological Characteristics of Psoriatic Arthritis: A Nationwide Study of Inpatient Hospitalisations in 2014

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Background/Purpose: Psoriatic arthritis is a seronegative inflammatory arthritis associated with Psoriasis. Using the National Inpatient Sample (NIS) we studied the epidemiological characteristics of inpatient admissions using the ICD 9 Code 6460.00 in the year 2014.

Methods: The NIS is a nationally representative sample of 20% of all non-federal hospitals in the USA with information from approximately 1000 hospitals pertaining to records from 7 million inpatient hospital admissions. The epidemiological characteristics we studied were age, gender, payer (Medicare/Medicaid/private insurance/uninsured), patient residence (large central metro, suburbs, medium and small metro and rural areas) and region (northeast, mid-west, southern and west) and associated co-morbidities: hypertension, diabetes, heart failure, chronic kidney disease, osteoarthritis & heart failure. Multiple linear regression was used to analyze factors that were associated with psoriatic arthritis.

Results: For 2014, from a total of nearly 7 million records (7,071,762), there were 775 admissions for psoriatic arthritis as the primary diagnosis (0.16%) which translated to 0.2 admissions per 100,000 persons. The majority of admissions were in the age group of 45 – 64 years (37.4 %) followed by 18-44 age group (30.9%). There was no gender difference males

(52.9%) and females (47.1%) [$p<0.4$]. The total aggregate costs were \$30,851,867 for 2014 amounting to a mean of \$10,728 per admission. Medicare remained the highest payer (36.7%) followed by private insurance (33.5%) and finally Medicaid (21.9%). Patients from a 27.7% patients were from a large central metro and medium and small sized metro and an equal percentage of 27.7% were from a medium sized metro. 26.4% % of patients were from the suburbs and whereas only 18% were from a rural area. The southern region accounted for majority of admissions (34.%) followed by northeast region(25.1%).21.2% were from Midwest and Western region had only 19.3% of all admissions. The mean length of stay (LOS) was 4.4 ± 0.3 days. By multivariate regression the following co-morbidities were noted to be associated with psoriatic arthritis: Hypertension ($p<0.001$), CKD ($p<0.001$), Osteoarthritis ($p<0.001$), Diabetes ($p<0.001$) and Heart failure ($p<0.001$)

Conclusion: While psoriatic arthritis inpatient admissions only account for 0.2 per 100,000 persons, it places a significant burden on cost and length of stay and is independently associated with hypertension, CKD, osteoarthritis, diabetes and heart failure.

Disclosure: V. Murugesan, None; J. Tran, None.

Abstract Number: 2145

Increased Risk of Heart Failure with Prolonged Use of Hydroxychloroquine in Patients with Rheumatoid Arthritis

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Session Information

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Session Time: 9:00AM-11:00AM

Background/Purpose: Hydroxychloroquine(HCQ) is commonly prescribed for patients with rheumatoid arthritis (RA).Cardiotoxicity is a rare but potentially life-threatening side effect of HCQ and may present as a cardiomyopathy resulting in congestive heart failure (HF).The evidence of cardiotoxicity associated with the use of HCQ largely relies on case reports and case series while large cohort studies on the subject are lacking. In this population-based cohort study, we aimed to examine the association between exposure to HCQ and incidence of HF in patients with RA.

Methods: A population-based incidence cohort of RA patients aged ≥ 18 years (1987 ACR criteria first met between 1/1/1980 and 1/1/2008) with no history of HF was followed until onset of HF (defined by Framingham criteria), death, or 1/1/2008. We collected data on RA characteristics, cardiovascular (CV) risk factors including current smoking, obesity, hypertension, antihypertensive use, dyslipidemia, diabetes mellitus, and the presence of coronary heart disease (CHD) defined as any of the following: angina pectoris, coronary artery disease, myocardial infarction (including silent events), and coronary revascularization procedures (i.e., coronary artery bypass graft, percutaneous angioplasty/stenting, and atherectomy).

Results: The study included 795 RA patients [mean age 55.3 years, 69% women, 66% rheumatoid factor (RF)-positive]. During the mean follow-up of 9.7 years, 92 patients developed HF. There was no overall increase in risk of HF in patients who used HCQ at any time during the follow up (HR 0.9, 95%CI 0.6-1.4) or in current users of HCQ vs non-users (HR 1.0, 95%CI 0.5-1.8).However, compared to non-users, patients with RA who used HCQ for>14 years had over 3-fold increase in risk of developing HF (HR 3.61; 95%CI1.23-10.63). The association remained statistically significant when additionally adjusting for corticosteroid use ($p=0.036$), CV risk factors and CHD ($p=0.049$). The association remained significant in the subset of patients without CHD when censoring those who develop CHD during follow-up ($p=0.038$). HCQ users were equally likely to develop HF with preserved or reduced ejection fraction.

Conclusion: Prolonged use of HCQ in RA is associated with increased risk of incident HF. Underlying mechanisms for this association require further elucidation.

Disclosure: E. Myasoedova, None; R. Kurmann, None; C. S. Crowson, None; J. M. Davis III, None; R. Mankad, None.

A Meta-Analysis of the Prevalence and Risk Factors for Retinal Toxicity in Rheumatologic Patients on Hydroxychloroquine Therapy

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSs, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

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Background/Purpose: HCQ is one of the most common DMARD(s) used in treatment of several rheumatologic diseases, including RA and SLE. Although rare, retinal toxicity remains the most feared adverse effect related to HCQ use because it can result in blindness. We conducted a meta-analysis to evaluate the prevalence and risk factors of retinal toxicity in rheumatologic patients on HCQ therapy.

Methods: We searched PubMed, MEDLINE, Scopus, Embase and Cochrane databases (January 1990 to January 2018) supplemented by manual searches of bibliographies of key relevant articles. We selected for all observational studies in which patients were on HCQ therapy for treatment of a rheumatologic disease, and HCQ retinopathy was evaluated. We calculated the pooled prevalence with the corresponding 95% confidence interval (CI) using the fixed effects method and performed a meta-regression to evaluate the variables that could affect the prevalence.

Results: After removal of duplicates, our search strategy found 328 studies. Of the 109 studies reviewed, 7 studies met our eligibility criteria, of which 6 studies had appropriate data for quantitative analysis. Of the studies included, 2 were cohort and 4 were nested case-control, comprising of 4112 evaluable patients. The pooled prevalence of HCQ retinopathy was 6% (95%CI 2-10). We found no statistical association ($p > 0.05$) between the prevalence of retinopathy and the well-known risk factors associated with development of retinopathy, including duration of HCQ use, cumulative dose and daily dose.

Conclusion: Although HCQ use is infrequently associated with retinopathy, the prevalence is higher than previously documented. Larger studies are needed to better power for the meta-regression of risk factors associated with developing HCQ retinopathy. Ophthalmologic screening should continue to be an important part of the evaluation for all rheumatological patients on HCQ therapy.

Figures/Tables:

Forest plot showing prevalence of HCQ retinopathy

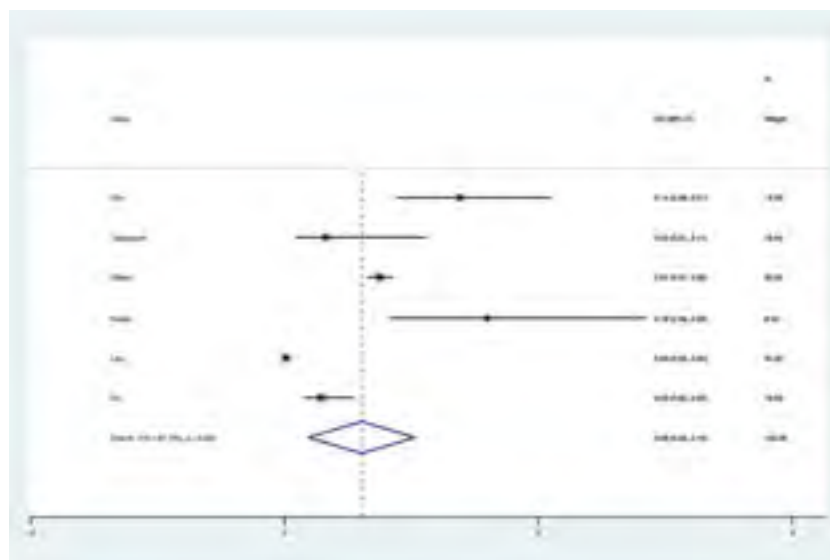


Table showing prevalence data for each study

Author (year)	HCQ users, #	Retinopathy, #	No retinopathy, #	Prevalence, %
Kim et al (2017)	123	17	106	14
Eo et al (2017)	310	9	301	3
Tangtavorn et al (2016)	61	2	59	3
Melles et al (2014)	2361	177	2184	7
Kobak et al (2010)	50	8	42	16
Levy et al (1997)	1207	1	1206	0.08

Table showing meta-regression of risk factors for HCQ retinopathy

	Beta Coefficient	P value	Confidence Interval
Cumulative dose	1.0001	0.14	0.9999 - 1.0004
Daily dose	1.002	0.15	0.998 - 1.005
Duration of use	0.9998	0.38	0.9993 - 1.0003
Age	1.003	0.84	0.965 - 1.288

Disclosure: A. Worme, None; L. Tamariz, None; A. Palacio, None; Z. Nemeth, None; M. Farbman, None.

Abstract Number: 2147

Associations between Current Cigarette Smoking and SLE-Related Cytokine and Chemokine Biomarkers Among U.S. Female Nurses without SLE

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

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Background/Purpose: Current cigarette smoking and recent cessation (within 4 years), compared to no smoking or remote cessation, have been associated with increased anti-dsDNA+ SLE risk among women. SLE-specific cytokines and chemokines have been found to be increased prior to diagnosis. We conducted cross-sectional analyses to investigate whether current smoking was associated with concentrations of SLE-associated cytokines including B lymphocyte stimulator (BLyS), stem cell factor (SCF), interferon-inducible protein-10 (IP-10), and interferon-alpha (IFN α) within a general population of women at risk of SLE.

Methods: The Nurses' Health Study (NHS, n=121,700) and NHSII (n=116,429) cohorts were begun in 1976 and 1989, respectively, and collected detailed exposure and outcome data biennially. In 1988- 1989, ~25% participants donated a blood sample. We identified 1177 women without SLE with banked plasma samples and smoking exposure data prior to the blood draw. We tested for presence of ANA (by Hep2IF), and anti-dsDNA and extractable nuclear antigens (ENAs; anti-Ro, anti-La, anti-Sm and anti-RNP, by ELISAs). Samples were tested by ELISA for BLyS, SCF, IP10, and IFN α . Each passed quality control [QC] using blinded split samples. We adjusted for inter-batch variation using common QC samples. Cytokine/chemokine concentrations were natural log-transformed to improve normality. We assessed relationships between smoking and biomarker concentrations using general linear regression for BLyS and SCF. Tobit regression was employed for IP-10 and IFN α due to a high proportion below the threshold of detection (165[14%] and 754 [64%]).

Results: Mean age at blood draw was 56 (SD 10); 64% of women were White, 36% Black; 15% were current/recent smokers. No association was found between current/recent smoking (vs. never or >4 years past) and ANA/dsDNA/ENA positivity (multivariable-adjusted OR 1.11 [95% CI 0.77, 1.60]). Current/recent smoking was associated with increasing circulating log BLyS (β [SE] = 0.10 [0.03], p<0.0001) and log IFN α (β [SE] = 1.15[0.52], p=0.03), but not SCF or IP-10 compared to never/distant smoking (**Table**). When restricted to the 295 women with ANA+, dsDNA+ or ENA+, the relationship between current/recent smoking and log BLyS was stronger.

Conclusion: Current smoking was associated with elevated BLyS, but not SCF-1 or IP-10, among women without SLE. BLyS is responsible for B-cell survival and maturation and has been reported to be elevated in the lungs of smokers. In stimulating the production of BLyS, smoking may accelerate onset or severity of autoantibody-positive SLE.

	Log BLyS				Log SCF			
	Age-adjusted β (SE)	p	Multivariable- adjusted β (SE)**	p	Age- adjusted β (SE)	p	Multivariable- adjusted β (SE)**	p
A. General Linear Regression Analyses: NHS and NHSII Current Smoking* vs. Past or Never Smoking and Continuous Concentrations of SLE-Associated Biomarkers, Log BLyS and Log SCF-1 among women without SLE								
Current Smoking* among all women (n=1177)	0.09 (0.03)	0.0006	0.10 (0.03)	0.0002	-0.04 (0.02)	0.12	-0.01 (0.02)	0.60
Current Smoking* among ANA/dsDNA/ ENA+ women (n=295)	0.19 (0.05)	0.0003	0.21 (0.05)	< 0.0001	-0.09 (0.08)	0.30	-0.09 (0.10)	0.34
Log IP-10				Log IFNα				
	Age-adjusted β (SE)	p	Multivariable-adjusted β (SE)**	p	Age- adjusted β (SE)	p	Multivariable- adjusted β (SE)**	p
B. Tobit Analyses***: Current Smoking* vs. Past or Never Smoking and Continuous Concentrations of SLE-Associated Biomarkers, IP-10 and Log IFNα								
Current Smoking* among all women (n=1177)	0.12 (0.13)	0.36	0.10 (0.13)	0.43	1.37 (0.52)	0.009	1.15 (0.52)	0.03
Current Smoking* among ANA/dsDNA/ ENA+ women (n=295)	-0.04 (0.24)	0.88	-0.03 (0.25)	0.91	1.98 (1.03)	0.05	1.57 (1.04)	0.13

* Current smoking: includes those who quit within past 4 years of blood draw as risk of SLE continued to be elevated among recent quitters in past analyses.

** Multivariable analyses: adjusted for age, race, body mass index, alcohol intake, history of depression (additional adjustment for oral contraceptive use, menopausal status, postmenopausal hormone use did not affect estimates)

*** Tobit analysis is a method that allows for maximum usage of cytokines/chemokines if there are many undetectable values.

Disclosure: C. Leatherwood, None; X. Liu, None; S. Malspeis, None; A. Roberts, None; J. A. Sparks, None; E. Karlson, None; C. H. Feldman, None; J. A. James, None; L. Kubzansky, None; K. Costenbader, None.

Abstract Number: 2148

Prevalence and Incidence of FMF in Germany – Results of the First Retrospective Analysis of Representative Claims Data

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Familial Mediterranean fever (FMF) is a rare hereditary autoinflammatory disease that predominantly affects, but is not limited to, persons of Middle Eastern ancestry. In Germany, roughly 10% of the general population has Mediterranean roots or migrated from the area of the Silk Road and may therefore be at risk of developing FMF. To our knowledge, epidemiologic data on FMF in Germany remain limited and no analyses of corresponding claims data have been published previously. The aim of this study was to explore the epidemiology of FMF in Germany and to describe demographic characteristics of the affected population.

Methods: We analyzed the database of the Institute for Applied Health Research Berlin (InGef). This database contains a representative subset of anonymized claims based on about 4 million members of the statutory health insurance (SHI) in Germany (overall about 73 million members). Individuals included in this analysis had to be continuously observable between 01-JAN-2012 and 31-DEC-2017. Prevalence and incidence were calculated for two years, 2014 and 2015. FMF patients were identified by ICD codes E85.0 (familial Mediterranean fever) and M14.4 (amyloid arthropathy).

Results: A total of 383 (11.99/100,000) prevalent FMF patients were identified, of whom 111 (28.98%) were < 18 years of age. Adults constituted 71.02% of prevalent cases. Females represented 48.65% of the pediatric population and 49.26% of the adult population. Also, 138 (4.23/100,000) incident cases were observed with a lower number of pediatric patients (47

or 34.06%) than adults (91 or 65.94%) and balanced proportions of males and females. Median age of incident patients was 30 years.

		FMF cases (2014-2015)			
		Prevalent		Incident	
Sex	Age	N	%	N	%
Female	< 18	54	14.10	24	17.39
	≥ 18	134	34.99	41	29.71
Male	< 18	57	14.88	23	16.67
	≥ 18	138	36.03	50	36.23
Total	all	383	100	138	100

Associated rheumatic conditions diagnosed most frequently were juvenile arthritis, rheumatoid arthritis, and spondyloarthritis.

Conclusion: Our analysis provides a broad and current picture of FMF in Germany: We find a 2-year prevalence of about 0.012% for FMF across 2014 and 2015, corresponding to an extrapolated population of about 5,800 affected subjects among SHI members in Germany. The observed 2-year incidence of 0.004% in this population corresponds to approximately 2,100 newly diagnosed patients in 2014 and 2015 (i.e. about 1,050 per year). This high number of newly diagnosed patients in the adult population is unique and surprising, given the predominant onset and diagnosis of FMF during childhood reported in other publications. The cross-sectional design and lack of information on ethnic background constitute methodical limitations of this analysis. Future studies would be needed to assess, if awareness and early diagnosis of FMF improve over time.

Disclosure: **I. Foeldvari**, Novartis, BMF, Bayer, Genentech, Sanofi, Abbvie, Chugai; Medac, BMS, Pfizer, 5, 8; **K. Boehm**, Novartis, 3; **T. Kramps**, Novartis, 3; **L. Mayerhoff**, Elsevier, 3.

Abstract Number: 2149

Assessing the Prevalence of Localized Scleroderma in Childhood Using Administrative Claims Data from the United States

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSs, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Juvenile Localised Scleroderma (jLS) is believed a rare autoimmune disease, which occurs 10 times more often than systemic sclerosis in childhood and is believed to have a prevalence of one per 100 000 children(1). There is no prevalence data published.

Methods: We used Truven MarketScan® commercial insurance claims data from the United States for the years 2010 through 2014, inclusive. MarketScan contains billing records associated with physician office visits, outpatient infusions, and pharmacy claims, among other data, and is intended to be representative of all persons covered by employer-sponsored health insurance in the United States. In each individual calendar year, we identified all persons in the claims data who were less than 16 years old.

Results: The results for each calendar year are shown in the Table. There were approximately 1600-2200 children per year with diagnoses of localized scleroderma and <3% of them had concurrent diagnoses of systemic sclerosis or mixed connective tissue disease. The prevalence estimates in each year ranged from 3.2 to 3.6 per 10,000 children. The proportion of children with localized scleroderma who received methotrexate in each year ranged from 3.2% to 4.4%.

Conclusion: This prevalence data show a higher than expected prevalence compared to the published incidence data with 2.7 per 100 000 to 2.5 children per million per year. We need more prevalence data from other resources to reassure our findings.

Table. The estimated prevalence of juvenile localised Scleroderma in the United States

Year	Total Children (N)	Diagnosis Code for Localized Scleroderma (N)	No Diagnosis Code for Systemic Sclerosis or Mixed Connective Tissue Disease (N)	Use of Methotrexate	Estimated Prevalence per 10,000 Children [95% CI]
2010	5,894,628	2064	2006 / 2064	75 / 2006	3.4 [3.3-3.6]
2011	6,231,475	2269	2222 / 2269	86 / 2222	3.6 [3.4-3.7]
2012	6,278,118	2198	2154 / 2198	68 / 2154	3.4 [3.3-3.6]
2013	4,950,018	1732	1692 / 1732	61 / 1692	3.4 [3.3-3.6]
2014	4,933,523	1620	1588 / 1620	71 / 1588	3.2 [3.1-3.4]

References : 1. Laxer RM, Zulian F. Localized scleroderma. Curr Opin Rheumatol. 2006;18(6):606-13.

Disclosure: T. Beukelman, None; F. Xie, None; I. Foeldvari, Novartis, BMF, Bayer, Genentech, Sanofi, Abbvie, Chugai; Medac, BMS, Pfizer, 5, 8.

Abstract Number: 2150

Association of Poverty Income Ratio with Physical Functioning in a Cohort of Patients with Systemic Lupus Erythematosus

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Session Information

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Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

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Background/Purpose: Lower socioeconomic status (SES) has been shown to be associated with poor physical functioning in systemic lupus erythematosus (SLE) patients; however, previous studies have not used poverty income ratio (PIR), which measures poverty as a ratio of household income to appropriate poverty threshold for household size, as a proxy for SES in this population. Thus, we examined the association of PIR with self-reported physical functioning in a cohort of SLE patients and also whether this association was similar for self-reported physical functioning and a set of complementary measures of physical functioning.

Methods: We used cross-sectional data on 744 participants from the ongoing Georgians Organized Against Lupus (GOAL) cohort, and secondary analyses used data on 56 participants from a GOAL-ancillary pilot study. Primary analyses utilized multivariable linear regression to estimate the association between PIR (categorized as <1.00 (income below the poverty threshold), 1.00-1.99, 2.00-3.99, and ≥4.00 (income 4 times the poverty threshold)) and physical functioning (PF; scaled subscore from Short Form-12 survey; range, 0-100, with higher scores indicating better functioning). Secondary analyses summarized complementary measures of physical functioning as means or percentages by PIR (categorized as <1.00, 1.00-1.99, and ≥2.00).

Results: Overall, the mean age of participants was 48.0 years; 6.7% were male; 80.9% were black; and 37.5%, 21.0%, 29.6% and 12.0% had PIRs of <1.00, 1.00-1.99, 2.00-3.99, and ≥4.00, respectively. The overall mean PF score was 45.8 (36.2, 40.7, 55.5, and 61.2 for PIRs of <1.00, 1.00-1.99, 2.00-3.99, and ≥4.00, respectively). With adjustment, higher PIRs (<1.00, 2.00-3.99, and ≥4.00, respectively, vs. 1.00-1.99) remained associated (β [95% CI]) with higher PF scores (-6.0 [-12.8 to 0.8], 10.9 [3.3 to 18.6], and 16.2 [6.4 to 26.0]). In secondary analyses, higher PIR was consistently associated with better physical functioning across domains, in that participants with higher PIRs, on average, had higher scores for measures of physical performance, were less likely to report difficulty with activities of daily living, and had fewer falls in the prior year. For example, mean Short Physical Performance Battery scores (range, 0-12) were better in those with PIR ≥2.00 compared to those with PIR <1.00 and 1.00-1.99 (10.2 vs. 8.4 and 8.2).

Conclusion: Our results show that higher SES is associated with better physical functioning across multiple domains, warranting further research into multi-component functional assessments to develop individual treatment plans and potentially improve disparities in SLE outcomes.

Disclosure: C. Hoge, None; C. B. Bowling, None; S. S. Lim, None; C. Drenkard, ILAR, 2, PANLAR, 2; L. Plantinga, None.

The Impact of Obesity on SLE Disease Activity

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Session Information

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Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

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Background/Purpose: Obesity is associated with increased disease severity in multiple autoimmune conditions, likely via formation of pro-inflammatory adipokines [1]. However, the role of obesity in systemic lupus erythematosus (SLE) remains controversial. Studies have linked adiposity with a heightened risk of neurocognitive decline, renal impairment, and depressed quality of life – but not disease activity [1-2]. We aimed to reevaluate whether obesity independently associates with higher disease activity in SLE.

Methods: Adult subjects with the diagnosis of SLE according to the Systemic Lupus International Collaborating Clinics criteria were recruited from the longitudinal, multi-ethnic, Southern California Lupus Registry (SCOLR). Sociodemographic and clinical variables were retrospectively collected. Obesity was defined as BMI >30kg/m² and participants were grouped accordingly. Disease activity was ascertained by calculating the SLE Disease Activity Index (SLEDAI). SLEDAI score of <5 and >5 were defined as low and high activity, respectively. Differences in sociodemographic and clinical variables were assessed using t-test and chi-square analyses. Finally, a multivariate regression model was utilized to determine the independent association between obesity and SLEDAI.

Results: 137 patients were included: 48 Caucasian (35%), 49 Hispanic (36%), 17 Asian (12%), and 23 African-American (17%). Mean age was 42.1± 15.4 years and 51 patients (37%) met criteria for obesity. Using univariate analysis (Table 1), increased BMI was significantly associated with SLEDAI ($P = 0.023$), but also sex ($P = 0.040$) and current steroid use ($P = 0.019$). Therefore, a multivariate regression model was utilized. After adjusting for age, sex, current steroid use, disease duration, and presence of nephritis, obesity remained independently associated with lupus activity ($OR\ 1.051$, $P = 0.048$) (Table 2).

Conclusion: In contrast with prior studies, we observed an independent association between obesity and higher disease activity in SLE. This positive data, which is likely attributable to our more heterogeneous population compared to other studies, identifies obesity as a potential treatment target for improving SLE outcomes.

References: [1] Versini M, Jeandel PY, Rosenthal E, Shoenfeld Y. Obesity in autoimmune diseases: not a passive bystander. *Autoimmun Rev.* 2014;13(9):981-1000.

[2] Rizk A, Gheita TA, Nassef S, Abdallah A. The impact of obesity in systemic lupus erythematosus on disease parameters, quality of life, functional capacity and the risk of atherosclerosis. *Int J Rheum Dis.* 2012;15(3):261-7.

Table 1. Relationship between obesity and baseline sociodemographic & clinical variables

	Non Obese (n = 86)	Obese (n = 51)	P-value
Age	42.0 ± 16.9	41.4 ± 13.0	0.079
Male	7 (8.1%)	4 (7.8%)	0.040
Ethnicity			0.236
White, Non-Hispanic	32 (37.2%)	16 (31.4%)	
Hispanic	29 (33.7%)	21 (41.2%)	
Asian	13 (15.1%)	3 (5.9%)	
African American	12 (14.0%)	11 (21.6%)	
SLE Duration	10.5 ± 9.6	7.4 ± 9.3	0.311
Current Steroid Use	29 (33.7%)	27 (52.9%)	0.019
Lupus Nephritis	30 (34.9%)	13 (25.5%)	0.252
SLEDAI			0.023
SLEDAI (<5)	51 (59.3%)	20 (39.2%)	
SLEDAI (>5)	35 (40.7%)	31 (60.8%)	

Table 2. Multivariable analysis against high lupus disease activity index (SLEDAI >5)

	OR	P-Value	95% CI	
			Lower Bound	Upper Bound
Age	1.027	0.057	0.999	1.055
Male	0.469	0.281	0.119	1.858
SLE Duration	0.956	0.046	0.915	0.999
Current Steroid Use	1.621	0.226	0.741	3.546
Lupus Nephritis	2.286	0.060	0.966	5.410
Obesity	1.051*	0.048	1.001	1.103

Disclosure: P. Teh, None; B. Zakhary, None; A. Haghsheenas, None; V. K. Sandhu, None.

Abstract Number: 2152

A Comparison of the American College of Rheumatology (ACR) and Systemic Lupus International Collaborating Clinics Classification (SLICC) Criteria to Detect Patients with Systemic Lupus Erythematosus (SLE) in Electronic Health Record (EHR) Data

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Session Information

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Background/Purpose: Systemic Lupus Erythematosus is a systemic autoimmune disease that has diverse manifestations that can occur over a long period of time. The complexity of the disease and its varied presentation makes identification of patients with SLE difficult. A better understanding of disease presentation based on clinical aspects of disease could support earlier identification of disease, personalized treatment, improve identification of patients for clinical trials, and support research into the genetic and environmental mechanisms of SLE. EHR data presents a rich source of information,

Table 2. Comparison of ACR and SLICC criteria and rate of detection of individual criteria in EHR data as well as overall success of the algorithms in the detection of "definite lupus". (Note that patients were initially on least 4 of 5 criteria for ACR)

Data Types		ACR Criteria	Detected in EHR	SLICC Criteria	Detected in EHR
ICD9/10	Clinical Criteria	Malar Rash	101/255	Acute Cutaneous Lupus	425/435
ICD9/10		Photosensitivity	26/332	Chronic Cutaneous Lupus	141/146
ICD9/10		Discoid Rash	70/97	Oral Ulcers	46/281
ICD9/10		Oral Ulcers	46/281	Synovitis (Arthritis)	161/472
ICD9/10		Arthritis	161/472	Serositis	115/221
ICD9/10		Serositis	115/221	Renal Disorder	118/182
ICD9/10		Renal Disorder	105/166	Neurologic Disorder	59/205
ICD9/10		Neurologic Disorder	11/16	Lymphopenia	369/308
Lab		Hematological Disorders	453/454	Hemolytic Anemia	4/5
Lab				Thrombocytopenia	453/454
ICD9/10	Immunologic Criteria			Alopecia	3/96
Lab				Anti-dsDNA Antibodies	79/109
Lab		Immunological Disorders	327/377	Anti-phospholipid Antibodies	84/131
Lab				Anti-Smith Antibodies	79/109
Lab		Anti-Nuclear Antibodies	259/433	Anti-Nuclear Antibodies	259/433
Lab				Low Complement	368/500
Lab				Direct Coombs' Test	2/12
		Patients Satisfying at least 4 Criteria	308/513	Patients Satisfying at least 4 Criteria	467/513

but no detection algorithms have been developed based on “phenotypic” descriptors of SLE. We examined whether the ACR and SLICC classification criteria could be a foundation for the development of such algorithms to detect patients with SLE in EHR data.

Methods: We identified 513 patients with known SLE in a physician validated registry, the Chicago Lupus Database (CLD), whose medical records were also in the Northwestern Medicine Electronic Data Warehouse (NMEDW). We developed algorithms based on ACR and SLICC classification criteria using diagnosis codes (ICD9/ICD10) and lab results to determine whether patients met the same classification criteria in both the CLD and the NMEDW (see Table 1 for criteria). To be classified with SLE, both ACR and SLICC require patients to meet 4 or more criteria, but SLICC also requires 1 clinical and at least 1 immunologic criteria and 4 or more criteria.

Results: As shown in Table 1, of the 513 patients with physician validated SLE present in the CLD who satisfied both the ACR and SLICC classification criteria, the ACR-based EHR algorithm detected 79% (398/513) as having SLE, while the SLICC-based algorithm detected 91% (467/513).

Conclusion: Both ACR- and SLICC-based EHR algorithms detect a significant proportion of patients in the CLD that were classified as having definite SLE. The SLICC-based algorithm had a higher detection rate, likely due to the inclusion of more laboratory parameters in the criteria set and differences in the skin parameter identification, compared to ACR. Our algorithms were developed using only structured data. Both algorithms will likely be improved by using of natural language processing that can probe free-text physician notes for concepts that align with the classification criteria (such as arthritis or renal biopsy results) that were difficult to detect using only diagnosis codes and lab results.

Disclosure: T. L. Walunas, None; A. S. Ghosh, None; K. L. Jackson, None; A. H. Chun, None; D. L. Erickson, None; K. Mancera-Cuevas, None; A. N. Kho, Health Data Link, Inc, 1; R. Ramsey-Goldman, None.

Abstract Number: 2153

The Effect of Socioeconomic Status on Treatment Outcomes in Lupus Nephritis: Private Versus Public Insurance

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Session Information

Session Date: Tuesday, October 23, 2018

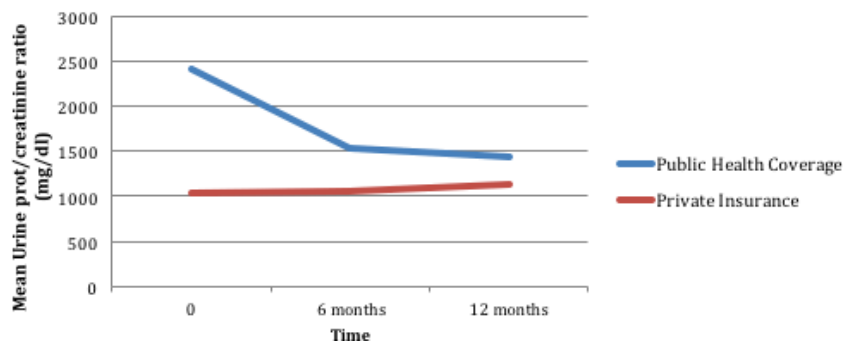
Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Despite therapeutic advancements, lupus nephritis (LN) remains a major cause of mortality among patients with SLE. Loma Linda University Health serves a region in Southern California represented by more individuals below the federal poverty line than the rest of California. As prior studies have demonstrated the impact of socioeconomic status (SES) on long-term outcomes in SLE in their respective counties, we studied the correlation between SES and LN prevalence in our cohort. We further investigated the association between SES, SLE disease activity, and treatment response in a subgroup of LN patients.

Figure1. Correlation between UPC ratio and health coverage



Methods: Adult subjects were recruited from the Southern California Lupus Registry (SCOLR). Sociodemographic data, urine protein to creatinine ratio (UPC), SLEDAI at baseline and 6 months, and insurance type were collected. Using insurance as a surrogate for SES, subjects were divided into 2 groups, public versus private insurance. The prevalence of lupus nephritis was then identified and differences in clinical variables and treatment response in the subgroup were assessed using t-test and chi-square analyses.

Results: 162 SLE patients were recruited. 33% were Caucasian, 36% Hispanic, 11% Asian, and 20% African-American. 42% of patients had public health coverage. After adjusting for age, sex and BMI, SES was independently associated with the prevalence of nephritis ($P = 0.038$) (Table 1).

A subgroup analysis of LN patients demonstrated baseline statistically significant higher UPC in patients with public compared to private insurance ($P = 0.053$) (Figure 1); a similar trend was noted at 6 months. Baseline and 6 month SLEDAI also demonstrated higher numbers among patients with public compared to private insurance (14.91 vs. 11.31; 13.30 vs. 10.42 respectively). No association was detected between medications and insurance type.

Conclusion: SES is associated with greater morbidity in SLE and is a key target for improving outcomes. To our knowledge, this is the first study comparing differences in treatment response to SES in SLE and LN patients in Southern California. In line with prior reports, our findings confirm the association of health insurance with long-term outcomes in SLE and LN. These findings warrant further studies to advocate for change in the healthcare industry to improve long-term outcomes in SLE.

Table 1. Multivariable Analyses Against Prevalence of Lupus Nephritis

	Odds Ratio	P-Value
Age	0.982 (0.955 - 1.009)	0.195
Female	0.993 (0.205 - 4.803)	0.993
BMI	0.968 (0.920 - 1.017)	0.197
Public Health Coverage	2.368 (1.052 - 5.330)	0.038*

Disclosure: A. Haghsheenas, None; P. Teh, None; K. Choi, None; A. Benitez, None; L. Salto, None; M. Firek, None; K. Torralba, None; V. K. Sandhu, None.

Abstract Number: 2154

Biosimilar Infliximab Treated-Patients with Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis in France: Characteristics and Clinical Outcomes

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Session Information

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Session Title: Epidemiology and Public Health Poster III: SLE, SSC, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: CT-P13 was the first monoclonal antibody biosimilar to infliximab (IFX) approved in France. Reflect trial has been set up to evaluate in real life the use of CT-P13 after the introduction of the product in French university hospitals.

Methods: REFLECT is a multicenter, prospective, and observational study. Its objectives are to describe in real-life the patient's (pts) characteristics treated with CT-P13 and the treatment effectiveness. Inclusion criteria were pts (≥ 6 years) with rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), or inflammatory bowel disease treated with CT-P13. IFX naive pts (IFXn) or pts having switched from IFX originator to CT-P13 (IFXs) were enrolled. Preliminary results in pts suffering from rheumatic diseases using descriptive statistical analyses from inclusion were reported here.

Results: On December 28th 2017, 627 pts were included by 35 centres and 339 pts with rheumatic diseases were analyzed: 83 were suffering from RA (22.9% males; mean age: 61.7 ± 10.2 ; median time since diagnosis: 13.4 years), 213 axSpA (59.6%; 48.0 ± 13.3 years; 11.5 years respectively), and 43 PsA (37.2%; 53.4 ± 15.1 years; 8.6 years). The majority of pts have been already treated by CT-P13 before inclusion (64.9%, 69.9%, and 77.1% of RA, axSpA, and PsA pts,

respectively); in these pts, the median treatment duration since the first administration of CT-P13 was 8.5 months for RA, 12.9 months for axSpA and 7.9 months for PsA pts. Previous treatments with other bDMARDs other than IFX were observed in 39.2% of RA, 29.9% of AS and 40.0% of PsA pts. Almost half of pts (41.9% of RA, 49.7% of axSpA, and 42.9% of PsA) switched from the originator IFX to CT-P13. At the baseline, the rate of pts in remission was 19 (26.8%), 27 (23.7%), and 14 (45.2%) of RA, axSpA, and PsA pts respectively.

At the first infusion of CT-P13, the median DAS28 score were 4.9 and 2.5 for RA pts in IFXn and INFs pts, and 3.5 and 2.2 for PsA pts respectively. In axSpA pts, the median BASDAI were 5.5 and 2.1 and the median BASFI was 5.1 and 2.8 in IFXn and IFXs pts, respectively. At 6 month follow-up, 48.5% RA pts, 37.7% axSpA pts, were in remission. The median of disease activity scores decreased from the first administration of CT-P13 to 6 month follow-up in IFXn pts and still stable in IFXs pts for RA and axSpA. The analysis of pts suffering from PsA has not been reported due to the small number of patient who had the follow-up at 6 month (6 IFXn pts and 4 IFXs pts).

The safety data are summarized in Table 1.

Conclusion: Preliminary results from this prospective cohort suggest that the treatment with CT-P13 is safe and efficient in both naïve and switched patients. The safety data did not show any new safety concerns.

Table 1: Safety data

	RA N= 83	AxSpA N=213	PsA N=43
Pts with at least one adverse event (AE)	16 (19.3%)	31 (14.6%)	6 (14%)
Pts with at least one serious AE	4 (4.8%)	5 (2.3%)	-
Pts with at least one allergic infusion reaction†	-	3 (1.4%)	-
Pts with at least one infection‡	-	-	1 (2.3%)

† Including acute and delayed hypersensitivity reactions

‡ Including severe infections, tuberculosis, opportunistic infections, hepatitis.

Disclosure: H. Marotte, Pfizer., 5; N. MAMMAR, Pfizer., 3; B. Fautrel, AbbVie, Biogen, BMS, Celgene, Janssen, Eli Lilly and Company, Medac, MSD, NORDIC Pharma, Novartis, Pfizer, Roche, Sanofi-Aventis, SOBI, UCB, 5, AbbVie, MSD, Pfizer, 2.

Abstract Number: 2155

Diagnosis of Systemic Sclerosis in the United Kingdom: An Observational Study Using the Clinical Practice Research Datalink

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Systemic Sclerosis (SSc) is an autoimmune disease that is characterised by fibroblast dysfunction and excess extracellular matrix deposition that leads to skin thickening and internal organ damage. Patients with SSc often develop interstitial lung disease (ILD) which is currently the leading cause of death. The burden of SSc in the UK is currently unknown. However, it is reported that a high proportion of patients present with advanced disease at diagnosis. The reasons for late diagnosis in SSc are not fully understood, although different routes to diagnosis have been associated with differences in survival. This study aimed to investigate patient characteristics related to first SSc diagnosis in hospital, compared to primary care.

Methods: We carried out a population-based cross-sectional study using data from the Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES). All adult patients with a diagnosis of SSc were identified using International Classification of Diseases-10-Clinical Modification diagnosis codes in hospital records and READ codes in primary care electronic records combined with an adapted version of the EULAR algorithm for defining SSc. Patients were classified into 3 groups: incident SSc, SSc with incident ILD (SSc-ILD), and SSc with other organ involvement (SSc-OOI). Source of diagnosis and patient characteristics were then described.

Results: The study included 606 individuals with incident diagnosis of SSc recorded in either CPRD or HES. Only 1% of patients had a diagnosis code in both primary care and secondary care records. 81% of the cohort were women and the

average age at diagnosis was 61 (SD = 15). 20% of the cohort had SSc-ILD and 63% had SSc-OOI with an overlap of 15%. Patients first diagnosed with SSc in hospital presented higher rates of hospital visits and had a greater proportion of “red-flag” symptoms predictive of SSc (e.g. Raynaud’s or gastrointestinal reflux) prior to SSc diagnosis. Patients with an overlap of SSc-ILD and SSc-OOI tended to be overweight or obese.

Conclusion: Our results provide evidence of differences between patients diagnosed with SSc through UK primary care or secondary/tertiary care routes. These findings should inform the development of initiatives to improve earlier diagnosis of SSc.

Disclosure: A. Gayle, Boehringer Ingelheim, 3; N. Schoof, Boehringer Ingelheim, 3; M. Alves, Boehringer Ingelheim, 3; D. Clarke, Boehringer Ingelheim, 3; C. Poole, Boehringer Ingelheim, 3; C. Raabe, Boehringer Ingelheim, 3; P. Das, Boehringer Ingelheim, 3; T. Maher, GSK, 2, 5, UCB, 2, 5, 6, Boehringer Ingelheim, Astra Zeneca, Roche, Bayer, Biogen Idec, Cipla, Prometic, Samumed, 5, Apellis, 1.

Abstract Number: 2156

Smoking Status Predicts Earlier SLICC Damage Index Progression in a Large SLE Cohort

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

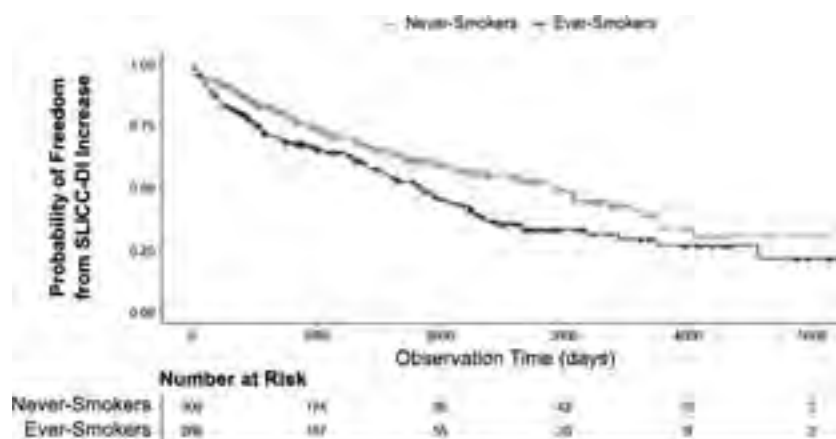
Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Tobacco smoking predisposes to certain specific manifestations of systemic lupus erythematosus (SLE); however, less is known about smoking and cumulative organ damage in SLE. Our study aimed to examine the relationship of smoking history and pack-year exposure on rates of end-organ damage in a cohort of SLE patients.

Methods: Observational study in a cohort of 631 consecutive SLE patients at a single academic institution. Patients with at least one ambulatory rheumatology encounter and an ICD-9 or -10 code for SLE between 2008 and 2016 were identified. Electronic health records (EHR) were manually abstracted and patients meeting either ACR1987 or SLICC 2012 classification criteria for SLE were included in analysis. The primary outcomes examined were median time to SLICC damage index (SLICC-DI) increase or death during the study period. The primary explanatory variable was ever-smoking, defined as current or former smoking as ascertained from the EHR. Covariates examined included age at diagnosis, sex, race, ethnicity, area deprivation index (a marker of neighborhood poverty), number of SLE criteria, and SLICC-DI at time of study entry. Kaplan-Meier survival analysis was used to compare time to DI increase between ever-smokers and never-smokers. Multivariate analysis was performed using a Cox proportional hazards model.

Results: Compared to never-smokers, ever-smokers in the cohort were older at SLE diagnosis and at time of entry into the study (44.7 years vs 44.5, $p < 0.01$; 55.9 years vs. 51.9, $p < 0.01$). There were no significant differences in sex (88% female in



ever-smokers vs 92% in never-smokers, $p=0.41$), race (83% white vs 82%, $p=0.25$) or Hispanic ethnicity (5% vs 3%, $p=0.92$). Among 517 patients with SLICC-DI of 0 at the start of observation, the median time to increase in SLICC-DI was 61.7 months in ever-smokers (95% CI, 50.8 - 75.1) and 97.9 months in never-smokers (95% CI, 74.6 - 121.6), as shown in Figure 1. Age at SLE diagnosis (HR 1.03 per year, 95% CI 1.02 - 1.04) and greater than 10 pack-year smoking history (HR 1.43 compared to never-smokers, 95% CI 1.02 - 2.01) were significant predictors of earlier SLICC-DI increase in an adjusted Cox model.

Conclusion: Current or past smoking predicted earlier progression of cumulative organ damage in this cohort of SLE patients, with ever-smokers first developing organ damage about 3 years earlier than never-smokers. Further work is needed to replicate findings in more diverse cohorts, and to examine the effects of tobacco cessation on damage accrual. Figure 1: Kaplan-Meier survival curve showing probability of freedom from SLICC-DI increase by smoking exposure in patients with no previously accrued damage (SLICC-DI = 0) at time of study entry.

Disclosure: T. McKown, None; R. Unnithan, None; N. Ezech, None; T. Ye, None; C. M. Bartels, Pfizer, Inc., 2.

Abstract Number: 2157

Nationwide Estimated Prevalence of SLE: United States Population-Based Study, 2001-2011

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: In the published literature, the prevalence rates of SLE have widely varied by as much as 12-fold over the years. This is likely due to the variability in study populations (region and race/ethnicity), case definitions (self-report, ICD codes, physician diagnosis, ACR criteria, and SLICC criteria), and case ascertainment sources (case registry, hospital, specialists, laboratory report, US renal database, death certificate, and insurance claims data). Most studies, thus far, covered relatively small population size such as a city, county or state or Medicaid database. To the best of our knowledge, there are no studies on SLE prevalence that cover the total population of the United States (US). Although, elegant reports from 5 CDC registries covering several counties in 5 states provide valuable information on SLE prevalence, there is an important unmet need to estimate the national prevalence of SLE in the US.

Methods: We used ambulatory physician visits in the US derived from the 2001-2011 National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) database to determine encounters that represent SLE, using ICD-9 code 710.0. Using the number of prior visits per patient, we estimated the number of patients with SLE from the visit encounters. STATA was then used to determine the mean proportion and 95% confidence interval.

Results: The overall prevalence rate of SLE is 122/100,000 persons in the US. The annual prevalence of SLE increased from 104.2/100,000 in 2001 to 164.3/100,000 in 2011. The period prevalence of SLE from 2001-2011 is 14-fold higher in females (224/100,000) than males (16/100,000). Non-Hispanic black persons had the highest prevalence of SLE (206/100,000), followed by Hispanics (118/100,000), and non-Hispanic white persons (87/100,000). There were substantial variations in SLE prevalence by geographic regions: persons living in the West had the highest prevalence (143/100,000), followed by South (129/100,000), Northeast (120/100,000), and Midwest (90/100,000).

Conclusion: Analysis of national survey data across the US reveals an increasing trend in the prevalence of SLE over the last decade, which may reflect an increased recognition of SLE, changes in physician's coding practices, or an actual increase in the prevalence. Lack of verification of SLE diagnosis by rheumatologists is a major limitation of this study, especially since there is discordance even among rheumatologists as to what constitutes a diagnosis of lupus. Nevertheless, our data shows regional and demographic differences in SLE prevalence in communities across the US. The female: male ratio of 14:1 in SLE prevalence is higher than in previous studies, which might be due to a lack of recognition of SLE in males by primary care physicians or lack of men visiting clinics that were surveyed by NAMCS or NHAMCS. Like in previous studies, SLE prevalence was higher in black persons than in white persons. Racial/ethnic differences in SLE prevalence may also be due to racial/ethnic differences in individuals who visit clinics that were surveyed or due to lack of entry in the race/ethnicity column by persons of certain race/ethnicity.

Disclosure: K. P. Nguyen, RRF Medical and Graduate Student Preceptorship, 9; E. Yen, None; N. Li, None; R. R. Singh, RRF Medical and Graduate Student Preceptorship Award, 9.

Abstract Number: 2158

Clinical Significance of Anti-Ro52 Antibody in Chinese Patients with Connective Tissue Diseases: A Single-Center Experience

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Session Information

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Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Autoantibody targeting Ro52 has been implied as a unique antibody with distinct clinical properties. However, its relations with anti-Ro60 antibody and various connective tissue diseases (CTDs) remain to be elucidated.

Methods: Anti-Ro52 and anti-Ro60 antibodies were determined by immunoblotting test. All those who had positive records of anti-Ro52 in Drum Tower Hospital between January 1, 2016 and September 30, 2017 were included in the analysis. Clinical data of hospitalized patients were extracted through chart review and compared with the difference between Ro52+ Ro60- group and Ro52+ Ro60+ group by using chi-square test.

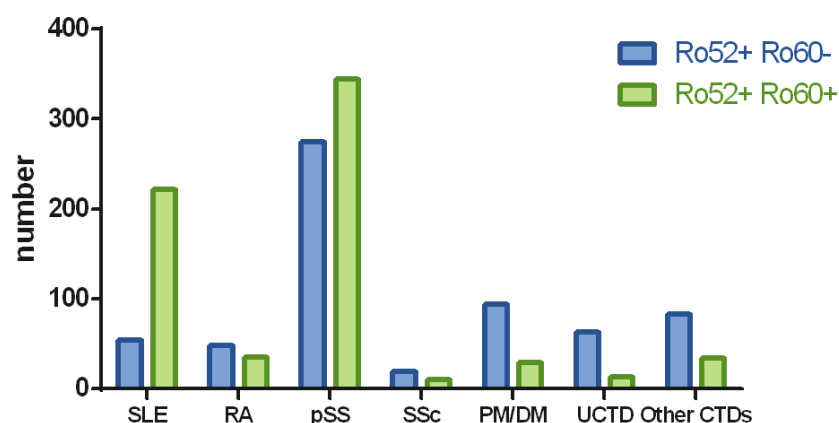


Figure 1. Distribution of Ro52+ Ro60- and Ro52+ Ro60+ in various CTD patients

Results: Totally 4,782 cases were included in this study, among which 3,185 (66.6%) were diagnosis as having CTDs, 1,473 (30.8%) had other diseases and only 124 (2.6%) were healthy. In patients with CTDs, anti-Ro52 was most related to primary Sjögren's syndrome (pSS), systemic lupus erythematosus (SLE), polymyositis/dermatomyositis and rheumatoid arthritis, while in patients with non-CTDs, anti-Ro52 was often seen in those with respiratory, gastrointestinal, neuropsychiatry and urinary diseases. Compared with Ro52+ Ro60+, Ro52+ Ro60- was more frequent in non-CTD patients (42.5% vs. 12.3%, $p < 0.0001$). Distribution of Ro52+ Ro60- and Ro52+ Ro60+ in hospitalized CTD patients was showed in Figure 1. For patients with pSS, Ro52+ Ro60- was associated with a low incidence of mucocutaneous, musculoskeletal, gastrointestinal involvement but a high incidence of cardiopulmonary involvement (all $p < 0.0001$). Meanwhile, SLE patients with Ro52+ Ro60- were found to have less mucocutaneous involvement ($p < 0.001$) but more cardiopulmonary involvement ($p < 0.0001$).

Conclusion: Anti-Ro52 is lack of specific in differentiating CTDs from other diseases, especially when it appears alone. In patients with CTDs, the presence of Ro52+ Ro60- may indicate an increase in cardiopulmonary involvement and a decrease in mucocutaneous involvement.

Disclosure: S. Wu, None; X. Tang, None; X. Feng, None.

Autoimmune Diseases in Catalonia: A Population Based Study Using a Public Big Data Program

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: To analyse the prevalence of autoimmune diseases (ADs) in Catalonia by using a public big data program (Public Data Analysis for Health Research and Innovation Program, PADRIS)

Methods: We used the health insurance database of the Catalan National Health Insurance (CNHI) which includes all catalan insured population in 2016 (7,483,761 inhabitants). ADs were identified according to the corresponding International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. A total of 33

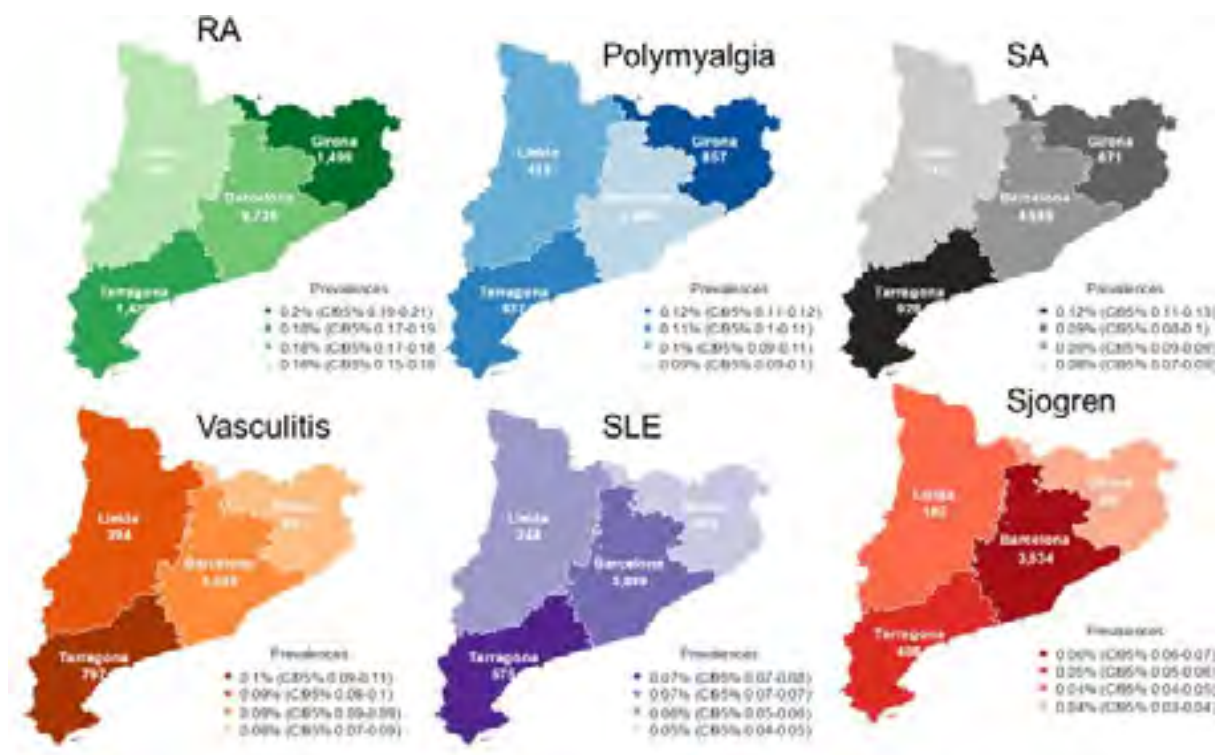


Figure1.

autoimmune diseases were analysed classified in 4 main categories: rheumatic, systemic, organ-specific and immunodeficiency/auto inflammatory. The prevalence of ADs was calculated as the number of ADs patients divided by the total CNHI beneficiaries in the same year (rate per 100,000 persons, 95% confidence intervals -CI-).

Results: In Catalonia, the overall prevalence of ADs was 1,202 per 100,000 persons (95% CI 1,194-1,209); the prevalence was 1,455 (95% CI 1,443-1,467) in women and 939 (95% CI 929-949) in men. ADs were identified as organ-specific (43%), systemic (33%), rheumatic (23%) and immunodeficiency/autoinflammatory (1%) autoimmune diseases. The Top Ten of ADs with the highest prevalence rates included cutaneous psoriasis (282 cases per 100,000), rheumatoid arthritis (178 cases per 100,000), polymyalgia rheumatic (98 cases per 100,000), spondyloarthropathies (92 cases per 100,000), vasculitis (91 cases per 100,000), systemic lupus erythematosus (68 cases per 100,000), Sjögren's syndrome (59 cases per 100,000), celiac disease (58 cases per 100,000), multiple sclerosis (57 cases per 100,000) and psoriatic arthritis (43 cases per 100,000). In 26 (79%) of the 33 ADs, the female:male ratio was higher than 1; the highest ratios were reported for Sjögren's syndrome (10.5), primary biliary cholangitis (5.8), SLE (5.4), systemic sclerosis (3.4) and rheumatoid arthritis (2.6). We found a significant geographical variation in the prevalence of the main diseases (**Figure 1**).

Conclusion: Nearly 90,000 catalans are classified as having an autoimmune disease, representing a prevalence of 1.2% of the total population in Catalonia, a rate that reaches 1.5% in women. We found a different territorial distribution of the main diseases, suggesting a significant influence of geographically-driven determinants in the prevalence of autoimmune diseases.

Disclosure: A. Sisó-Almirall, None; B. Kostov, None; E. Martínez Carbonell, None; S. Retamozo, None; A. Flores-Chavez, None; S. González-Martínez, None; P. Brito-Zerón, None; A. Dedéu Baraldés, None; J. Benavent Àreu, None; M. Ramos-Casals, None.

Abstract Number: 2160

Effect of the Metabolic Syndrome on Incident Vascular Events and Mortality in Four Rheumatic Diseases: An 8-Year Longitudinal Analysis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

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Session Time: 9:00 AM-11:00 AM

Background/Purpose: To study the effect of the metabolic syndrome (MetS) on incident vascular events and mortality in 4 rheumatic diseases over an 8-years' follow-up.

Methods: Consecutive patients who fulfilled the ACR criteria for SLE, EULAR/ACR criteria for RA, ASAS criteria for SpA and CASPAR criteria for psoriatic arthritis (PSA) were recruited in a 2009/2010. At baseline, patients had the following measurements: body weight, height, waist circumference, blood pressure and fasting blood for assay of glucose and lipid (total cholesterol, HDL and LDL cholesterol, triglyceride). The MetS was defined by the updated joint consensus criteria, using the Asian criteria for central obesity, when $\geq 3/5$ components on waist circumference, blood pressure, triglyceride, HDL and glucose. Patients were followed longitudinally for new vascular events and mortality. Comparison was made between those with and without the MetS at baseline. Cox regression analysis was performed to evaluate the impact of MetS on vascular events and mortality.

Results: 1497 patients were studied (693 RA, 577 SLE, 121 SpA and 106 PSA). The age at entry was highest in RA (53.4 ± 12.0 years) and lowest in SpA patients (39.0 ± 11.9 years). The MetS was present in 137 RA (20%), 85 SLE (15%), 13 SpA (11%) and 39 PSA (37%) patients, respectively. Over 94 months' follow-up, new cardiovascular (acute coronary syndrome or angina) and cerebrovascular (ischemic stroke or transient ischemic attack) events developed in 51 and 29 patients, respectively. The incidence of vascular events (per 100 patient-years) was highest in RA patients (0.84), followed by PSA (0.71), SLE (0.67) and SpA (0.62). There were 99 deaths (12 vascular deaths). The mortality rate (per 100 patient-years) was highest in RA patients (1.04), followed by SLE (0.93), PSA (0.24) and SpA (0.21). Patients with MetS had significantly higher rates of vascular events (9.5% vs 4.8%; $p=0.003$), all-cause mortality (11.4% vs 5.6%; $p<0.001$) and vascular mortality (2.2% vs 0.5%; $p=0.004$) than those without. Cox regression showed that MetS was independently associated with new cardiovascular events (HR 1.98[1.08-3.63]; $p=0.03$) or any vascular events (HR 1.64[1.01-2.66]; $p=0.04$), after adjustment for age, sex, duration of underlying disease, ever smoking, LDL and underlying disease (SLE vs

non-SLE). A diagnosis of SLE was independently associated with new cerebrovascular events in a separate Cox regression model (HR 4.66[1.80-12.1]; $p=0.002$). The MetS, however, was not significantly associated with new cerebrovascular events (HR 1.74[0.76-3.97]; $p=0.19$), all-cause mortality (HR 1.33[0.85-2.07]; $p=0.21$) or vascular mortality (HR 2.91[0.89-9.51; $p=0.08$) after adjustment for the same covariates. Factors independently associated with all-cause mortality were age (HR 1.12[1.10-1.14] per year; $p<0.001$), ever smoking (HR 3.26[1.82-5.84]; $p<0.001$) and SLE (HR 3.18[1.88-5.37]; $p<0.001$).

Conclusion: MetS is common in patients with rheumatic diseases. The presence of the MetS increases the risk of new cardiovascular events in these patients over 8 years, which is independent of the underlying rheumatic disease and other risk factors. The MetS is not independently associated with mortality in these four rheumatic diseases.

Disclosure: C. C. Mok, None; C. S. Chu, None; L. Y. Ho, None; K. L. Chan, None; S. M. Tse, None; C. H. To, None.

Abstract Number: 2161

Hemophagocytic Syndrome in Adults and Association with Rheumatologic Diagnoses: US National Inpatient Trend over Nine Years

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Hemophagocytic syndrome (HPS) is a rare fatal condition of excessive immune activation. Association of hemophagocytosis with certain rheumatologic diseases is called macrophage activation syndrome (MAS). We studied the trend of hemophagocytic syndrome and association of rheumatologic conditions over nine years in a large US inpatient database called the Nationwide Inpatient Sample (NIS).

Methods: NIS(2006 – 2014) was used to identify adult hospitalizations ≥ 18 year of age with a listed discharge diagnoses of hemophagocytic syndrome based on ICD-9 diagnosis code 288.4. The code includes multiple white blood cell disorders, including the MAS. Age-and-sex-standardized rates (per 1 million hospitalizations), mortality, mean cost and length of stay (LOS) were calculated for the respective years. Joinpoint regression analysis was used to analyze the yearly trends.

Results: A total of 5679 discharges with the diagnoses of hemophagocytic syndrome were identified among 288.15 million (288,156,693) discharges over nine years (2006-2014).

Hemophagocytic syndrome was more commonly seen in males (57%) vs females (43%) and younger (mean age 45.5 vs 57.1 years). Higher predominance was noted in urban, large and teaching hospital settings. More patients HPS were admitted on emergent basis rather than elective. The trend of hospital discharges for hemophagocytic syndrome was significantly increasing over the years (1.43 per million in 2006 to 44.7 per million in 2014), likely due to increased identification of the entity. Association with rheumatologic conditions as primary diagnoses category was recorded in 3.75% of the total cases of hemophagocytic syndrome. The cost of hospitalization with HPS was \$51,979 vs \$12,340 in those without HPS. Mean LOS remained significantly higher (14.8 days vs 5 days). The mortality and mean cost and LOS with HPS was significantly higher than those without HPS throughout all years (Table 1).

Conclusion: The increasing trend of prevalence and more so in the urban settings may be associated with increasing identification of the condition in inpatient setting. Increased awareness of this rare and fatal condition may help in early identification with an opportunity to better treat with available resources as well as to conduct further studies. The association with specific rheumatologic conditions needs further studies.

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014
Number of cases per million	1.43	4.47	8.56	11.9	11.7	30.1	34.5	33.1	44.7
Mortality percent	10	29.5	28.3	26.5	20.3	27.3	21.9	21.4	22.2
Length of stay (days)	19.1	13.9	18.1	18.3	11	16.5	11.5	14.8	14.9
Mean Cost of hospitalization USD	51,979	78,795	59,762	48,947	43,225	61,148	44,337	53,695	48,489

Table 1: Age and sex standardized results of hemophagocytic syndrome in adults

Abstract Number: 2162

The Prevalence, Incidence, and Determinants of Depression and Anxiety in Less Common Systemic Autoimmune Rheumatic Diseases: A Systematic Review and Meta-Analysis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSs, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Individuals with systemic autoimmune rheumatic diseases (SARDs), including systemic lupus erythematosus (SLE), systemic sclerosis/scleroderma (SSc), Sjogren's syndrome (SjS), dermatomyositis/polymyositis (DM/PM), and systemic vasculitides (SV), experience both physical and psychiatric complications from their disease. Given the high burden of depression and anxiety observed in SLE, the objective of this study was to review the prevalence, incidence, and determinants of depression and anxiety in individuals diagnosed with less common SARDs.

Methods: We conducted a systemic review in MEDLINE, EMBASE, CINAHL, Cochrane Database of Systematic Reviews, and PsycINFO from database inception to March 2018 using terms for all SARDs (SLE, SSs, SjS, DM/PM, SV) combined with terms for "depression" and "anxiety". Inclusion criteria were: 1) observational study design; 2) patients diagnosed with a less common SARD (SSs, SjS, DM/PM, SV); 3) depression and/or anxiety as comorbid outcome; and 4) report relevant estimates (e.g., prevalence proportion, determinants) or sufficient data to allow calculation. Prevalence estimates were pooled using random effects models. Extraction of data on the determinants of depression and anxiety was restricted to studies using multivariate analyses.

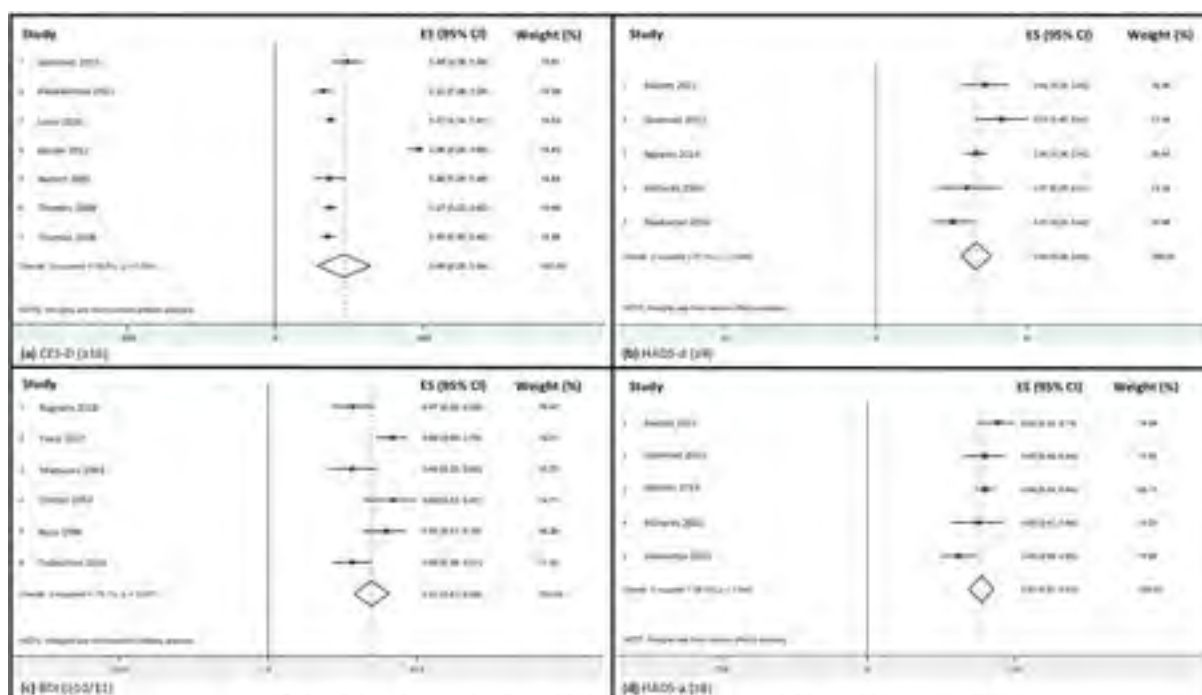


Figure 1. Pooled prevalence estimates (ES) of depression (a-c) and anxiety (d) in systemic sclerosis.

Abb: CI = confidence interval; CES-D = Center for Epidemiologic Studies - Depression scale; HADS-d = Hospital Anxiety and Depression Scale - Depression; BDI = Beck Depression Inventory; HADS-a = Hospital Anxiety and Depression Scale - Anxiety.

Results: Of the 3,059 resultant citations, 65 full-text articles were screened and 42 were included in the final review. Thirty-nine articles reported on the prevalence of depression and estimates ranged from 3-96% in SSc, 7.6-60.9% in SjS, 14.7-26.8% in DM/PM, and 3-64% in SV. The prevalence of anxiety was reported in 17 articles, with estimates ranging from 3-80% in SSc, 4-12.5% in SjS, 39% in DM and 70% in SV. Data available to estimate the pooled prevalence of depression and anxiety according to psychiatric instrument was only available for SSc (Figure 1). The pooled prevalence for depression ranged from 0.40 (95% confidence interval [CI]: 0.34, 0.46) based on the Hospital Anxiety and Depression Scale (HADS) to 0.57 (95% CI: 0.47, 0.66) based on the Beck Depression Inventory and was 0.57 (95% CI: 0.51, 0.63) for anxiety based on the HADS. Two articles evaluated incidence of depression, reporting a 10-year cumulative incidence of 11.1 per 100 in giant cell arteritis ($p < 0.0001$; adjusted hazard ratio [aHR]: 1.37, 95% CI: 1.26, 1.49) and 8.39 per 100 ($p = 0.51$) in granulomatosis with polyangiitis. Significant determinants of depression included disability, pain, tender joints, gastrointestinal symptoms and lung involvement. Determinants of anxiety included disability, pain, and lung involvement.

Conclusion: Our synthesis shows a substantial burden of depression and anxiety in less common SARDs. Findings have implications for raising awareness among health care providers on the importance of these comorbidities among patients with SARDs.

Disclosure: A. Howren, None; E. Z. Zusman, None; J. A. Avina-Zubieta, None; M. A. De Vera, None.

Abstract Number: 2163

Prevalence and Incidence of Idiopathic Inflammatory Myopathies in Korea: a Nationwide Population-Based Study over 10 Years

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Session Information

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Session Time: 9:00 AM-11:00 AM

Prevalence and Incidence of idiopathic Inflammatory Myopathies in Korea: a Nationwide Population-based Study over 10 years

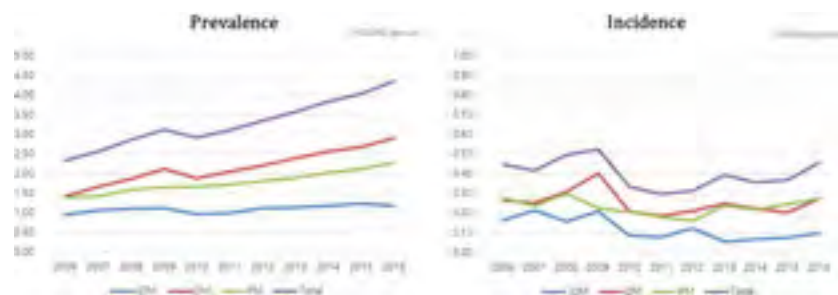
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Background/Purpose: Idiopathic inflammatory myopathies (IIMs) are rare rheumatic diseases, and their incidence vary greatly across studies. The aims of this study were to estimate the prevalence and incidence of IIMs in Korea from 2006 to 2016.

Methods: Using data from the Korean National Health Insurance Service (NHIS) between 2004 and 2016, patients with IIMs were identified based on the diagnostic codes including juvenile dermatomyositis (JDM) of M330, dermatomyositis (DM) of M331 or M339, polymyositis (PM) of M332 and registration code of Individual Copayment Beneficiaries Program (ICBP) for rare and intractable disease. The incident cases were captured for patients with an IIM diagnostic code & ICBP code for at least 1 physician visit with a disease-free period for 24 months before the index date.

Results: In Korea, a total of 1,150 patients with IIMs (117 JDM, 521 DM, 512 PM) were observed in 2006, and the number of IIM patients was increased to 2,281 (122 JDM, 1211 DM, 948 PM) by 2016. Considering that the total population of Korea is about 50 million, the prevalence was estimated at 2.3-4.4 (1.0-1.2 for JDM, 1.4-2.9 for DM, 1.4-2.3 for PM) /100,000PY. We identified 218 incident cases of IIM in 2006 (18 JDM, 98 DM, 102 PM) and 237 patients (9 JDM, 114 DM, 114 PM) in 2016, respectively. The incidence rate was estimated at 2.9-4.9 (0.7-1.8 for JDM, 1.8-3.1 for DM, 1.6-3.0 for PM) /1,000,000PY between 2006 and 2016 and it did not reveal any tendency of variation over 10 years. The mean



age (\pm standard deviation) of incident patients with IIM was 54.8(\pm 17.2) years and the percentage of females was 62.8%. Incidence increased with age and peaked among those aged 51-60 years of age.

Conclusion: We report the prevalence and incidence of IIMs in Korea at the nationwide population level. Although the prevalence seems to be increasing recently, the incidence did not reveal any tendency of variation over 10 years.

Disclosure: Y. K. Sung, None; H. Kim, None; J. Myung, None; E. Nam, None; S. Y. Jung, None; E. J. Jang, None; D. H. Yoo, None; S. K. Cho, None.

Abstract Number: 2164

IMPACT of a Systematic Screening of Multimorbidities in Patients with Chronic Inflammatory Rheumatic Diseases

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: EULAR proposes to screen multimorbidities in chronic inflammatory rheumatic diseases. The aim of the study was to assess i) multimorbidities in patients with chronic inflammatory diseases, ii) how patients follow recommendations given after a systematic standardized multimorbidity screening.

Methods: Exams were performed during a 1-day multimorbidity clinic. Diabetes, hypertension, CVD damage, chronic respiratory diseases, osteoporosis and preventive measures were assessed. Advice, complementary exams and prescriptions were provided to patient and general practitioner after this check-up if needed. Patients were called 3 months later to assess the applications of the given recommendations.

Results: Among the 541 patients screened, hypertension was present in 28.1% patients, dyslipidemia in 19.2%, chronic respiratory tract diseases in 12.8% and diabetes in 9.6%. Screening led to the following recommendations: blood pressure monitoring (22.6% patients), dietary advice (56.8%), cardiologist referral (35.5%), intensification of physical activity (27.0%), cancer screening (50.5%), vaccinations (60.6%) and vitamino-calcium supplementation (30.3%). On the 237 patients called back, 72.3% underwent blood pressure monitoring, 58.6% followed dietary advice, 64.4% took vitamino-calcium supplementation, 55.2% had vaccinations done, 52.1% saw a cardiologist, 42.7% increased physical activity and 31.4% performed cancer screening. No specific gender, age, pathology, or psychological factors were associated with adherence to recommendations.

Conclusion: This study underlines the relevance of a systematic screening of multimorbidities in chronic inflammatory rheumatic diseases, and the good patient's adherence rate to the recommendations. Further information will be found after a follow-up visit provided for all the 1200 patients already screened.

Disclosure: M. Beurai-Weber Jr., None; A. Jaussent, None; G. du Cailar, None; M. C. Picot, None; F. Roubille Sr., None; J. D. Cohen, None; J. Morel, None; J. Bousquet, None; P. Fesler, None; B. Combe, Pfizer, UCB, BMS, Janssen, Lilly, MSD, Roche-Chugai, Abbvie, Novartis, 2, 5, 8; C. Daïen, None.

Abstract Number: 2165

The Trend of Utilization of Therapeutic Plasmapheresis Among Select Rheumatologic Diseases

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSs, APS, PsA, and Other Rheumatic Diseases

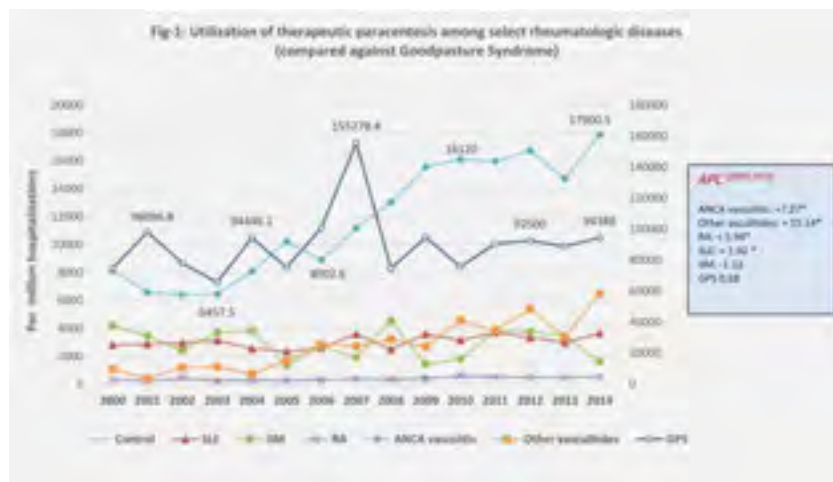
Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Therapeutic plasma exchange (TPE) or plasmapheresis is a process in which plasma containing components, including autoantibodies and immune complexes, can be removed from the circulation. The ability to do so makes TPE an option for the treatment of immune-mediated diseases, including many rheumatologic diseases (RDs). In RDs, TPE can help to rapidly decrease the circulating levels of antibodies, while buying time for the immunosuppressive medications to take effect. The aim of our study was to compare the utilization of plasmapheresis among patients with select RDs and to assess the yearly trends in terms of Annual Percentage Change (APC).

Methods: We used National (Nationwide) Inpatient Sample database from the years 2000-2014 to identify inpatients ≥ 18 years with the diagnosis of autoimmune RDs based on ICD-9 codes. We compared the utilization of therapeutic plasmapheresis in RDs with that in Good pasture's syndrome (a rare autoimmune and a prototypical renal disease in which plasmapheresis remains the treatment of choice). Anti-phospholipid syndrome was not used in the analysis due to unavailability of discrete ICD-9 code for the condition. Joinpoint regression analysis software was used to calculate the APC and to determine if the annual change in trend was statistically significant or not.

Results: Among hospitalized adults, the utilization of TPE was much higher in Goodpasture's syndrome compared to any one of the studied RDs. However, a significantly increasing trend was noted among RDs, most notably the anti-neutrophil cytoplasmic antibody (ANCA)-vasculitis and other Vasculitides. The utilization of TPE in Goodpasture's syndrome was ~74,000 per million hospitalizations on 2000 compared to ~94,000 in 2014. Among various RDs, the highest utilization was noted in ANCA associated vasculitis, and the rate doubled from 8000 per million hospitalizations on 2000 to over



16,000 per million on 2014, with an annual increase of 7.27%. Significant increase in trend was also noted among hospitalizations with other Vasculitides (APC of 15.14) (**Figure 1**).

Conclusion: The steady increase in the utilization of TPE for patients with RDs, mostly the ANCA and non-ANCA associated Vasculitides may be reflective of the mounting data suggesting improved outcomes and decreased progression to end-stage renal disease when TPE is used in addition to immunosuppression. While some case reports and controlled trials have demonstrated treatment benefit from plasmapheresis in patients with SLE and IIM, others have found no improvement in clinical course. While plasmapheresis is relatively safe (mortality rate of ~0.05%), the most common adverse reactions are hypocalcaemia, hypovolemia and rarely anaphylactic reaction. Further studies need to be performed to determine the safety and cost-effectiveness of plasmapheresis as a treatment option for RDs.

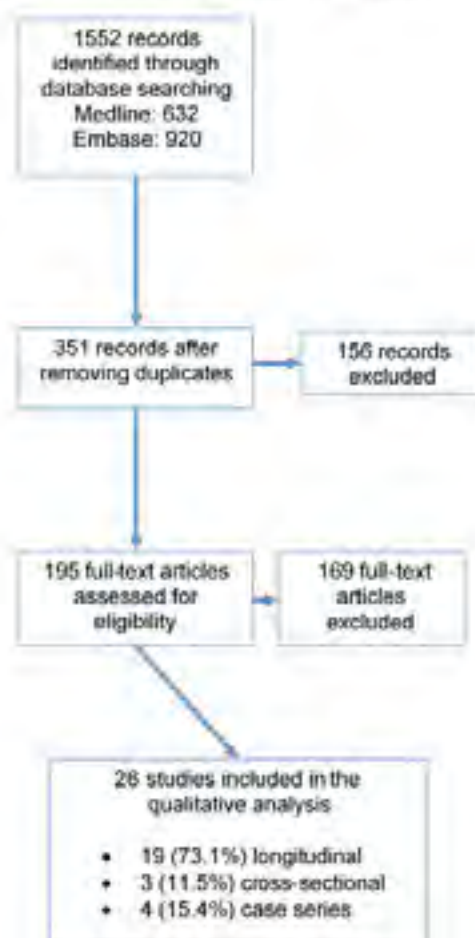
Disclosure: R. Dhital, None; T. Lynn, None; P. Sharma, None; S. Basnet, None; P. Paudel, None; S. Pyakurel, None; D. Poudel, None.

Abstract Number: 2166

Treatment of Venous Thrombotic Events in Behcet Disease: A Systematic Literature Review

Iustina Janta¹, Roberto González², Tania Gudu³ and Indalecio Monteagudo¹, ¹Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain, ²Rheumatology, Hospital general Universitario Gregorio Marañón, Madrid, Spain, ³University of Medicine Carol Davila Bucuresti, Romania, Bucuresti, Romania

Figure 1. Flowchart showing the selection of publications that assessed treatment of venous thrombosis in Behcet disease



Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

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Background/Purpose: Venous thrombosis (VT) is a serious and potentially life-threatening manifestation of Behcet disease (BD). However, there is little evidence of the management of the VT in BD. To review the treatment used in venous thrombotic events in BD.

Methods: A systematic review was performed according to the PICO approach. Several synonyms for the main components (i.e. Behcet, venous thrombosis, treatment) were used. The literature search was performed in Medline and Embase from databases inception to 1st November 2017. Only articles in English and Latin languages were retained. We excluded abstracts, reviews or letters. From the selected studies, data about the VT, treatment and treatment response were retired using a predefined data collection form.

Results: The literature search resulted in 1552 articles (figure 1). The main reason for article exclusion after full-text review was the lack of description of VT and its treatment. Finally, 26 articles were included in the analysis with a total of 1899 patients. Mean age (standard deviation, SD) was 32.8 (5.6) years and most of them were men (77.7%). The mean (SD) duration time between disease onset and VT onset was evaluated in only 16 articles and was 4.67 (2.9) years. Superficial VT was evaluated in 34.6% articles, involving a number of 29 patients, deep VT in 76.9% articles and 291 patients, cerebral VT in 40.7% articles and 140 patients, inferior or superior cava vein VT in 73.1% articles and 270 patients and Budd-Chiari syndrome in 53.8% articles and 73 patients.

Details of the reported treatments are depicted in table 1. Due to the lack of detailed treatment description, no relationship between the type of treatment and the type of VT could be established. Treatment response was evaluated

Table 1. Treatment for venous thrombosis in Behcet disease as reported in the articles included in the systematic review

Treatment	Number of articles reporting the use of treatment	Number of patients receiving the treatment
	N (%)	N *
Anticoagulant	20 (76.9)	481
Antiplatelet	8 (30.8)	36
Fibrinolytic	4 (15.4)	13
Corticosteroids	20 (76.9)	430
Immunosuppressive/immunomodulatory	23 (88.5)	412
Cyclophosphamide	16 (61.5)	264
Azathioprine	17 (65.4)	732
Cyclosporine A	6 (23.1)	28
Mycophenolate mofetil	1 (3.8)	NR
Interferon alpha	4 (15.4)	5
Methotrexate	5 (19.2)	15
Anti-TNF alpha	4 (15.4)	6
Hydroxychloroquine	1 (3.8)	7
Dapsone	1 (3.8)	1
Thalidomide	2 (7.7)	25
Colchicine	11 (42.3)	114
Surgery	9 (34.6)	9

*Number of patients were reported only as frequencies to avoid the underestimation of percentages (some of the studies only mentioned the treatment, without reporting the number of patients that were prescribed the treatment)

NR: not reported

in 23 (88.5%) articles. A good treatment response, i.e., the thromb resolution was reported in 11 articles, corresponding to 161 patients. Death due to VT was reported in 10 articles (38.5%) and 24 patients. Complications and lack of treatment response were also reported: recurrences, extension or progression of the thromb (11 articles, 450 patients), aneurisms (6 articles, 28 patients), new thrombs (3 articles, 20 patients), post thrombotic complications (3 articles, 38 patients). However, data regarding treatment response were inconstantly reported and the outcomes used for assessing it were very heterogeneous. Therefore, correlations and predictive factors of complications or mortality could not be identified.

Conclusion:

Disclosure: I. Janta, None; R. González, None; T. Gudu, None; I. Monteagudo, None.

Abstract Number: 2167

Incidence and Baseline Characteristics of Exacerbation in Patients with Interstitial Pneumonia with Autoimmune Features: A Single Center Large-Scale Cross-Sectional Cohort Study

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Session Information

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Session Time: 9:00 AM-11:00 AM

Background/Purpose: Patients with idiopathic interstitial pneumonia (IIP) may have features of connective tissue diseases (CTDs). The term interstitial pneumonia with autoimmune features (IPAF) has been recently proposed for such patients. A few studies have been reported in prevalence of IPAF which was varied from 7.3% to 34.1% [1, 2]. Factors reported to indicate a poor prognosis in IPAF include age, smoking history, organizing pneumonia pattern in HRCT, anti-RNP antibody positivity, decline in %DLCO and presence of a multi-compartment feature within the morphological domain [2, 3]. To date, however, no study has comprehensively described prevalence of IPAF and factors of exacerbation. The aim of study was to identify of prevalence of IPAF in patients with interstitial lung disease and prognostic factors for exacerbation in patients with IPAF.

Methods: Six hundred and seventy-two patients who visited our department between April 2009 and March 2018 and were evaluated by chest HRCT scan. Then, they were clinically and radiologically diagnosed as having interstitial lung disease (ILD), IIP or connective tissue diseases associated ILD were enrolled. We applied IPAF criteria to these patients. Then, we purified 68 patients. The prognostic factors for exacerbation were prospectively calculated and statistically analyzed using clinical, laboratory and imaging data collected from medical records.

Results: Prevalence of IPAF was 10.1%. Of 68 patients with IPAF, 60% were women and mean age at diagnosis was 64.2 ± 13.8 years old. Mean observation period was 27.1 ± 29.6 months. Exacerbation rate was 25% (n=17). Overall death rate was 5.9% (n=4) and respiratory death rate was 2.9% (n=2). Comparison of characteristics at diagnosis between the exacerbation group and non-exacerbation group showed that the exacerbation group had a significantly elevated rate of smoking, KL-6, and SP-D (P=0.012, 0.0064, and 0.029, respectively).

Conclusion: Our large-scale cross-sectional cohort study identified unique prognostic factors of exacerbation.

Disclosure: O. Murata, None; N. Sasaki, None; M. Maemondo, None.

Seasonal Variation in Incidence of Polymyalgia Rheumatica: A Population-Based

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Session Information

Session Date: Tuesday, October 23, 2018

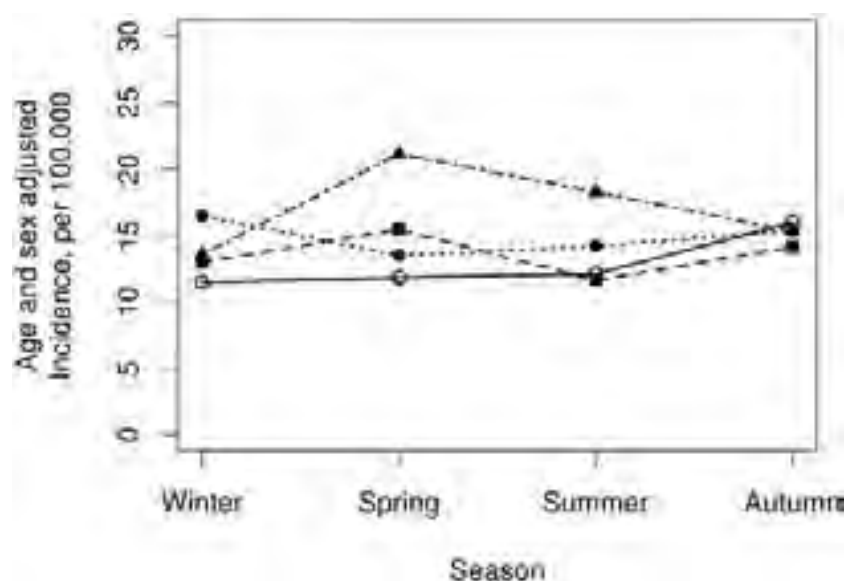
Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: To determine whether there is a seasonal peak onset of polymyalgia rheumatica (PMR). We examined the seasonal variability of PMR in a geographically-defined population.

Methods: In a geographically defined population, we retrospectively identified all incident cases of PMR between January 1, 1970, and December 31, 2014. Detailed review of all individual medical records was performed. All patients fulfilled EULAR/ACR classification criteria for PMR. Incidence rates were age and sex adjusted to the US white 2010 population. Seasonal variation was compared using quasi-Poisson regression models to account for overdispersion.



Results: The cohort included 786 cases of incident PMR (65% female; mean age 73.3 years). Overall, patients in this cohort were more likely to have incident PMR in the spring season with age- and sex-adjusted incidence rates (per 100,000 population) of 17.2 for spring compared with 13.8 for winter, 15.5 for summer and 15.2 for autumn, but this difference did not reach statistical significance ($p=0.21$). However, subgroup analysis by decade revealed that incidence of PMR was significantly higher ($p=0.013$) in the spring season during 2000-2014 with an age-adjusted and sex-adjusted incidence rate per 100,000 of 21.1 compared with winter (13.6), summer (18.3) and autumn (15.3) [Figure]. Figure. PMR incidence rates by season and decade (1970-79 open circles, 1980-89 squares, 1990-99 filled circles, 2000-14 triangles) among Olmsted County, Minnesota residents in 1970-2014

Conclusion: Incident PMR is more common in the spring season. This pattern is more pronounced in recent years. Further study is needed to understand the potential etiological and clinical significance of this finding.

Disclosure: S. Raheel, None; C. S. Crowson, None; E. L. Matteson, None.

Temporal Trends in Mortality in Patients Hospitalized for Cerebrovascular Events with Psoriatic Arthritis: Data from the Healthcare Cost and Utilization Project from 2010-2014

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health Poster III: SLE, SSc, APS, PsA, and Other Rheumatic Diseases

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Cerebrovascular disease risk is increased in patients of Psoriatic arthritis (PsA), as reported in the literature. Epidemiological studies to assess average annual trends are not available in current literature. Majority of studies are from single centers. Our objectives were to describe the demographics and trends of outcomes for PsA patients admitted with cerebrovascular events in United States.

Methods: We analyzed data from the Healthcare Cost and Utilization Project's (HCUP) National Inpatient Sample (NIS). All hospitalized adult (>18 years) patients between 2010 and 2014 hospitalized for cerebrovascular event (stroke or transient ischemic attack) from NIS database were captured, and stratified into two groups based on secondary diagnosis of PsA, using ICD9 codes. Stata version 15 (College Station, TX) was used to perform the statistical analysis. We analyzed the trends in hospitalization, length of stay, total cost per admission and mortality for cerebrovascular events. Chi-Square test, linear regression and multivariate regression models were used for analysis.

Results: Between 2010 and 2014, 2,255,127 were hospitalized with cerebrovascular events including acute stroke and transient ischemic attack (TIA). 1583 patients were found to have a secondary diagnosis of PsA. Patients admitted with cerebrovascular events and underlying PSA had a mean age of 67.5 ± 0.71 years, which was significantly lower in comparison to general population where mean age was 70.86 ± 0.08 years (p value = 0.00). 50.49% patients were females in patients with PsA. There was no significant difference in rates of overall mortality between the two groups from 2010-2014 (2.99% for patients without PsA and 2.71% for patients with PsA, p value=0.769), and this trend was noted in mortality rates from each year (2010 to 2014).

Conclusion: Patients with PsA were admitted with cerebrovascular events at a younger age compared to their counterparts, suggesting higher burden of comorbidities and inflammation. Compared to previously reported data, there wasn't a significance difference in cerebrovascular mortality in patients with PsA. Decreased risk of mortality possibly reflects early recognition and treatment of PsA, with increased awareness of PsA as well as associated cardiovascular risk. Providers should continue to screen patients with PsA for risk factors associated with cardiovascular and cerebrovascular morbidity and mortality, to improve healthcare outcomes.

Disclosure: S. Jatwani, None; K. Chugh, None; K. Jatwani, None; S. Perimbeti, None; V. Modi, None; J. Kaur, None; R. K. Sharma, None.

Relationship between Short- and Long-Term Periods of Self-Reported Physical Activity Patterns in Individuals with SLE

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Session Information

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Session Title: Epidemiology and Public Health Poster III – ARHP

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Physical inactivity is prevalent in Systemic Lupus Erythematosus (SLE). Assessment of physical activity (PA) is vital to manage cardiovascular risk factors in SLE. The aim of this cross-sectional correlational design was to explore the relationship between assessments of PA patterns in individuals with SLE using questionnaires covering short- and long-term periods of PA.

Methods: Individuals with SLE (n=148) according to ACR criteria (52±16 years old; BMI: 24.4±4.3 kg/m²; disease duration 22±15 years) were enrolled. The International Physical Activity Questionnaire Short-Form (IPAQ-SF) covering short-term period (last week) and questions from Physical Activity Questionnaire covering long-term period (last 6-12 months) were used. SLAM-R was used to assess disease activity and SLICC-DI to assess organ damage. Spearman rho analysis and p<0.05 was used.

Results: Median SLAM-R was 5 (IQR 6), SLICC was 1 (IQR 3) and IPAQ-SF PA category was moderate. PA on high exertion (days/week) the last 6-month was moderately correlated with IPAQ-SF vigorous activity days/week (r=0.43) and minutes/day (r=0.47) respectively as well as to IPAQ-SF moderate activity days/week (r=0.44). PA (hours/day) the last year was moderately (r=0.47) correlated with IPAQ-SF walking hours/day. Exercise last year was moderately correlated with IPAQ-SF vigorous activity days/week (r=0.46) and minutes/day (r=0.51) respectively as well as to IPAQ-SF vigorous category (r=0.51) and IPAQ-SF total score (r=0.45). Sitting hours/day last 6-month were strongly (r=-0.63) correlated with IPAQ-SF sitting hours/day.

Conclusion: The results indicate that there are moderate-to-strong relationships between short- and long-term period of PA, exercise and sitting behaviours in SLE with mild disease activity and organ damage. Health professionals in clinical practice, therefore, need different questionnaires to capture different time periods of PA patterns.

Disclosure: G. I. KINIKLI, None; S. Pettersson, None; I. Gunnarsson, None; E. Svenungsson, None; C. Boström, None.

Abstract Number: 2171

A 5-Year National Trend in Acute Myocardial Infarction among Hospitalized Patients with Psoriatic Arthritis: Data from National Inpatient Sample

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Health Services Research Poster III – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Psoriatic arthritis (PsA) is associated with an increased risk of cardiovascular morbidity and mortality. The increase in cardiovascular risk evaluated in a meta-analysis on PsA was around 43% for cardiovascular diseases, independently from traditional cardiovascular risk factors. [1] Higher disease activity has been associated with increased rates of mortality. There is limited data on comprehensive nationwide analysis of inpatient mortality in patients admitted for acute myocardial infarction (AMI) with underlying PsA. Our objectives are to describe the demographics & mortality trends for hospitalized patients with AMI with underlying PsA and understand the factors associated with mortality.

Methods: All adult (>18 years) hospitalized patients between 2010 and 2014 from a nationwide inpatient sample (NIS) database were captured. ICD-9 CM codes were used to identify patients with AMI and PsA. NIS is the largest all-payer inpatient care database in the United States with approximately 8 million hospitalizations each year. Descriptive statistics

were represented as means/medians for continuous and as frequencies and percentages for categorical variables. A survey weighted logistic regression model was used to describe inpatient mortality.

Results: From 2010 to 2014 around 2691 patients were hospitalized for AMI with underlying PsA. Mean age of these patients was 63.788 (significantly lower than those without PsA), and 37.98% were females. Most of patients with PsA and AMI were Caucasian (89.7%) and had private insurances (42.65%). There were 52 inpatient deaths in 5 years. Higher age was associated with significantly higher odds of inpatient mortality. But the odds of mortality in patients admitted with AMI with underlying PsA were found to be lower than their counterparts. (OR = .470 \pm 0.145, p value=0.01)

Conclusion: Patients admitted with AMI and underlying PsA are younger in comparison to their counterparts. This could likely reflect cumulative effect of inflammatory burden as well as cardiovascular risk factors. Decrease in odds of cardiovascular mortality associated with PsA possibly reflects increased awareness of cardiovascular risks in patients with PsA as well increase treatment options to control inflammatory burden. Reinforcing and educating involved stakeholders will continue to improve cardiovascular outcomes in patients with PsA

References: 1. Polachek A et al. Arthritis Care Res (Hoboken). 2017 Jan;69(1):67-74. <https://doi.org/10.1002/acr.22926>. PubMed PMID: 27111228.

Table 1: Baseline Characteristics of patients with Acute Myocardial Infarction and Psoriatic arthritis, National Inpatient Sample 2010-2014

	2010	2011	2012	2013	2014	Total
N (patients with AMI & PsA)	391	421	540	604	735	2691
Age in years (Mean \pm se)	59.742 \pm 1.36	65.3 \pm 1.12	65.5 \pm 0.95	63.19 \pm 1.11	64.27 \pm 0.90	63.79 \pm 0.49
Sex (%)						
Male	60.42	60.33	64.81	58.68	62.59	62.02
Females	39.58	39.67	35.19	41.32	37.41	37.98
Race (%)						
White	75.91	82.69	93	90.09	89.21	89.7
African American	11.22	2.61	0	1.8	2.16	2.06
Hispanic	7.02	6.42	3	5.41	2.16	3.66
Asian/pacific islander	2.29	3.01	3	0.9	0.72	1.49
Native American	0.86	0	0	0	2.16	0.62
Other	2.7	5.28	1	1.8	3.6	2.46
Insurance status (%)						
Medicare	57.74	61.63	60	47.93	51.77	51.27
Medicaid	6.86	1.05	47.6	4.96	3.55	3.22
Private insurance	28.71	34.95	33.33	45.45	39.72	42.65
Self-pay	6.69	2.37	1.9	1.65	4.96	2.86
Median household income for patient's zip code (%)						
0-25th percentile	29.38	22.06	24.3	21.67	19.44	21.42
26th to 50th percentile (median)	27.09	28.05	22.43	27.5	32.64	26.96
51st to 75th percentile	23.87	24.61	20.56	26.67	27.08	25.23
76th to 100th percentile	19.67	25.29	32.71	24.17	20.83	26.39
Hospital location (%)						
Rural	11.71	9.86	6.48	8.26	10.2	8.15
Urban	88.29	90.14	93.52	91.74	89.8	91.85
Hospital size (%)						
Small	10.02	7.86	6.48	13.22	14.29	11.48
Medium	21.09	23.63	23.15	20.66	24.49	23.87
Large	68.9	68.51	70.37	66.12	61.22	64.66
Teaching status of hospital (%)						
Non-teaching	55.21	48.56	50.93	47.11	34.69	45.7
Teaching	44.79	51.54	49.07	52.89	65.31	54.3
Geographical region (%)						
Northeast	19.7	16.62	21.33	23.14	22.45	20.42
Midwest	25.05	29.97	19.44	28.93	19.05	24.23
South	37.58	28.03	33.33	23.97	37.42	30.37
West	17.66	25.38	25.93	23.97	21.09	24.98

Disclosure: S. Jatwani, None; K. Chugh, None; K. Jatwani, None; V. Modi, None; J. Kaur, None.

Overuse of Glucocorticoids in Rheumatoid Arthritis: A National Survey of Primary Care Physicians

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Health Services Research Poster III – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 9:00AM-11:00 AM

Background/Purpose: Most patients with RA receive oral glucocorticoids (GC) such as prednisone, despite concerns about safety. We sought to evaluate how primary care physicians (PCPs) use GC to treat RA patients co-managed by rheumatology, and whether PCP perceptions of GC side effects influences willingness to use GC for established RA patients.

Methods: In 2017, we conducted an online, cross-sectional survey of American College of Physicians members, using its Internal Medicine Insider Research Panel. PCPs without subspecialty training spending $\geq 25\%$ time in direct patient care were invited to participate. We developed a vignette featuring a hypothetical 62-year-old woman with RA co-managed by a

Figure 1: Matrix of GC side effects presented to survey participants (N = 244). Participants rated the degree to which two oral GC regimens increased the risk of the below side effects.

Short-term high-dose: 20mg prednisone daily for 2 weeks.

Mean (SD) score 0.73 (0.4)

71% of participants had mean score <1

Long-term low-dose: 5mg prednisone daily for 4 months

Mean (SD) score 0.83 (0.4)

61% of participants had mean score <1

	Not at all (0)	A little (1)	A lot (2)
Cataracts			
Fractures or osteoporosis			
Minor infections (e.g., URI, complicated UTI)			
Serious infections (e.g., sepsis, pneumonia requiring hospitalization)			
Hypertension			
Death			
Congestive heart failure			
Hyperlipidemia			
Stroke or heart attack			
Adrenal insufficiency			
Venous thromboembolism (e.g., DVT or PE)			
Diabetes			

rheumatologist, at increased risk for several GC side effects, who presents with severe RA flare. Respondents selected management options from a prepopulated list including laboratory tests, imaging studies, and treatments (GC, NSAIDs, and DMARDs). Participants willing to initiate oral GC were asked how long they would be willing to continue treatment. Participants rated the degree to which two different oral GC regimens increased risk of 11 GC side effects (Fig. 1). Response scores for each regimen were averaged; mean score <1 indicated a PCP thought side effects were unlikely with that regimen. We used multivariable linear regression adjusted for provider and practice characteristics to estimate the association between PCP concern about GC side effects and duration of GC prescribed.

Results: 244 of 557 eligible physicians (44%) completed the survey. Mean age was 51 years (SD 10.6), 35% were female, 74% in non-academic practice, and 51% practiced in a suburban area. In the 6 months prior to the survey, 58% had encountered a patient experiencing RA flare. Most reported patients in their panels had no significant difficulties affording medications or accessing a rheumatologist.

205 respondents (84%) were willing to prescribe oral GC for the hypothetical patient in the vignette. 164 (67%) would prescribe ≥ 20 mg burst/taper of prednisone equivalent; 37 (15%) would prescribe Medrol Dosepak. 124 (51%) were willing to continue GC for ≥ 4 weeks; 53 (22%) were willing to continue for ≥ 6 weeks. Most PCPs perceived GC side effects as unlikely, regardless of regimen (Fig 1). PCP perception of GC side effects did not predict duration of GC prescribed ($p=0.2$ overall, 0.5 short-term high-dose, 0.2 long-term low-dose)

Conclusion: In this national sample, 51% of PCPs were willing to prescribe ≥ 1 month of GC to an RA patient at high risk for GC side effects, despite their perception that their patients have good access to rheumatology care and RA medications. The duration of GC they were willing to prescribe was independent of concern about GC side effects. Poor communication between PCPs and rheumatologists, combined with PCP discomfort managing DMARDs, may contribute to GC overprescribing and thus avoidable side effects

Disclosure: B. Wallace, None; A. Waljee, None; A. Weissman, American College of Physicians, 3; T. Caverly, None; S. Saini, None.

Abstract Number: 2173

Budget Impact of Etanercept Versus Adalimumab for Treatment of Rheumatoid Arthritis in Biologic-Naïve Patients in the United Kingdom

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Session Information

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Session Time: 9:00 AM-11:00 AM

Background/Purpose: Etanercept and adalimumab are TNF α inhibitors, both indicated in the UK for the treatment of patients with moderate-to-severe active RA who had inadequate response to DMARDs. The objective of this study was to assess the cost impact of etanercept compared to adalimumab when considering dose escalation.

Methods: A budget impact model was developed to assess the drug cost impact of etanercept versus adalimumab, from the perspective of the UK national healthcare payer over a one-year time horizon. The modelled population represented 79,762 patients with RA who were biologic-naïve (previously failed on DMARDs) and who were treated with either etanercept or adalimumab. Clinical inputs in the model included response to treatment (ACR 20% improvement), with patients who did not respond to the initial dose experiencing dose escalation. Applying Phase III trial data, 65% of patients treated with etanercept and 53% of patients treated with adalimumab responded to their initial dose within 3 months. Based on a published systematic literature review, the model assumed a weighted mean of 14.9% of patients who did not respond to the initial dose of adalimumab and subsequently received dose escalation. Dose escalation was not considered for etanercept as it is not specified in the label. Drug costs were taken from published UK sources. Primary model outcomes were the total costs of etanercept versus adalimumab cohorts and net budget impact over one year. Medical writing assistance was provided by Vojislav Pejović, PhD, of Engage Scientific Services, and was sponsored by Pfizer.

Results: Annual drug costs in the adalimumab and etanercept UK cohorts were £768.4 million and £741.4 million, respectively. Treatment with adalimumab resulted in a £27.0 million increased spend compared to the etanercept cohort. Alternative scenarios around dose escalation were explored and were consistent with base case findings.

Conclusion: Treatment with etanercept may yield cost savings versus adalimumab in the UK for biologic-naïve patients with RA, when considering adalimumab dose escalation.

Disclosure: K. Onishchenko, Consulting at McCann Health, 3, Consulting at McCann Health, 5; M. Tarallo, Pfizer, Inc., 1, Pfizer, Inc., 3; C. Curiale, Pfizer, Inc., 1, Pfizer, Inc., 3; S. T. Alexopoulos, Consulting at McCann Health, 3, Consulting at McCann Health, 5.

Abstract Number: 2174

Self-Report of Fracture History Compared to Fracture Codes from an Electronic Health Record Dataset

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Health Services Research Poster III – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Self-reported fracture (fx) history data is frequently used in epidemiological studies of osteoporosis. Self-reported fx data may differ from fx history coded in electronic health records (EHR) due to imperfect patient recall, incomplete communication with clinicians, or lack of a universal EHR. Because both self-reported fx history and EHR data can define phenotypes for clinical research studies, it is important to understand how these 2 data sources compare. Our objective was to compare self-reported fx history using survey data with fx codes from an available EHR dataset.

Methods: Self-reported fx data was derived from the Activating Patients at Risk for Osteoporosis (APROPOS) trial, which recruited participants from the Global Longitudinal study of Osteoporosis in Women (GLOW) cohort. Prior fx data was collected using a survey deployed June - August 2015. Women were asked if they ever had a fx and for each fx type the date of the most recent one. Data on fx recorded in the EHR September 2011 - June 2015 was obtained from Kaiser Permanente Washington Health Research Institute. We excluded skull, toes and fingers fxs. We defined concordance between the EHR and self-reported data if the location of fx was reported to be the same and if the reported dates were within 1 year of each other. Kappa (κ) statistic described the concordance between the 2 sources of fx history. Descriptive statistics evaluated potential factors associated with discordance between the self-reported and EHR-coded fx history.

Results: A total of 133 fxs from 360 women (91% white, mean [SD]) age 74.5(7.5) years, 82% had some college education) were included. There were 35 fxs reported on the survey but not in the EHR and 39 fxs coded in the EHR but not in the survey. Agreement between self-reported and EHR fxs was κ 0.48. Of the discordant fxs, we were more likely to find claims for fxs in EHR referent to self-report among whites (OR=5.5, 95% CI 1.1-27.9), for major osteoporotic fxs (OR=2.8, 95% CI 1.1-7.1), and for fragility fxs that typically require hospitalization (vertebral, hip, femur, pelvis) (OR=3.8, 95% CI 1.3-10.7). Discordance between EHR codes and self-reported fxs did not vary by age, formal education, or health literacy.

Conclusion: There was only modest correlation between self-reported fx history and EHR fx codes. This discrepancy may have implications for clinical and epidemiological studies of fxs suggesting that combining both types of data may be optimal.

Disclosure: M. I. Danila, None; A. S. Mudano, None; E. J. Rahn, None; A. Z. LaCroix, None; J. R. Curtis, Amgen Inc., 2, 5, AbbVie Inc., 2, 5, BMS, 2, 5, Corrona, LLC, 2, 5, Janssen, 2, 5, Eli Lilly, 2, 5, Myriad, 2, 5, Pfizer, Inc., 2, 5, Roche/Genentech, 2, 5, Radius, 2, 5, UCB, Inc., 2, 5; K. Saag, Amgen Inc., 2, 5, Merck & Co., 2, 5, Lilly, 5, Radius, 5.

Change in Frequency of Arthroplasty Surgery in Rheumatoid Arthritis: A 13-Year Population Health Study

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Background/Purpose: Improvement in the medical management of rheumatoid arthritis (RA) over the past two decades may have reduced the need for arthroplasty surgery but the literature to date has reported inconsistent findings. The objective of our study was to compare the annual frequency of hip, knee and other arthroplasty surgery in a prevalent cohort of RA cases and matched controls over 13 years.

Methods: A retrospective cohort study was performed utilizing administrative healthcare data from approximately 1 million people with access to universal healthcare between 1997 and 2010. RA cases were identified using a previously validated RA case definition in the same dataset (1). Each case was matched by age and sex to 4 randomly selected controls. The annual frequency of arthroplasties in cases and controls was compared. In addition the frequency of coronary artery interventions (bypass grafting, angioplasty and stenting) was used as an additional control. Data included physician billings, hospital discharges and patient registry information using ICD-9 and ICD-10. Statistical analysis used least squares regression t-tests and 2-proportion z-tests.

Results: The number (prevalence) of RA cases per year increased from 3,913 (0.42%) to 4,911 (0.52%) over the study. The mean (SD) age changed from 56.7 (15.9) to 60.1 (14.9) years and the proportion of females from 70.8% to 73.9%. In both the first and last years of the study the frequency of all arthroplasty procedures was higher in cases than controls ($p < 0.001$) (Table). Over time there was a gradual and significant reduction in arthroplasty surgery in RA cases by 51.9% ($p < 0.001$). This was in contrast to controls in whom the frequency of procedures increased by 31.9% ($p = 0.002$) with the exception of hip arthroplasty. For the latter procedure, the frequency decreased by 63% in RA cases ($p < 0.001$) and 35% in controls ($p = 0.617$). In contrast to arthroplasty procedures the frequency of cardiac procedures, which was higher in RA cases in both the first ($p = 0.013$) and final ($p = 0.003$) years of observation, increased in both cases and controls over time although this did not reach statistical significance in either.

Conclusion: There was a striking reduction in arthroplasty surgery in RA cases over 13 years of observation. Lack of similar changes in controls and sustained rates of cardiac procedures over the same time suggests that this was not due to limited surgical access for RA patients. Earlier diagnosis and improved medical treatment of RA are potentially responsible.

Table: Demographics and surgical procedures in RA patients and controls

Demographics	1997		2010	
	RA cases	Controls	RA cases	Controls
Age (SD) in years	56.7 (15.9)	56.7 (15.9)	60.1 (14.9)	60.1 (14.9)
Female (%)	70.8	70.8	73.9	73.9
Surgical procedures	% population undergoing procedure in 1997		% population undergoing procedure in 2010	
	RA cases	Controls	RA cases	Controls
Total arthroplasties	4.78	0.47	2.30	0.62
Hip arthroplasty	1.43	0.20	0.53	0.13
Knee arthroplasty	1.74	0.13	0.81	0.27
Other arthroplasty	1.76	0.13	0.98	0.22
Cardiac procedures	0.36	0.16	0.57	0.29

Reference: 1. JG Hanly, K Thompson, C Skedgel. The use of administrative healthcare databases to identify patients with Rheumatoid Arthritis. *Access Rheumatology: Research and Reviews* 2015;7:69-75.

Disclosure: J. G. Hanly, None; L. Lethbridge, None; C. Skedgel, None.

The Association of Gout with Incident Giant Cell Arteritis in Older Adults

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SESSION INFORMATION

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Session Type: ACR/ARHP Combined Abstract Session

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Giant cell arteritis (GCA) is a vasculitis that affects large and medium sized arteries in people 50 years or older. Gout, the most common inflammatory arthritis in adults, is characterized by the activation of inflammasome and an increased production of pro-inflammatory cytokines, such as IL-1 beta (IL-1 β), IL-6, IL-18 and others, which also play a central role in GCA. Our objective was to assess whether gout in the elderly is associated with a risk of incident GCA.

Methods: We used the 5% Medicare claims data from 2006-2012 for this cohort study. Gout was identified by the presence of two claims for gout at least 4 weeks apart, with International Classification of Diseases, ninth revision, common modification (ICD-9-CM) code of 274.xx. Study outcome was incident GCA, identified by two claims for GCA with an ICD-9-CM code of 446.5, at least 4 weeks apart and an absence of GCA claims in the baseline 365-day period, a valid approach. We used multivariable-adjusted Cox proportional hazard models to assess the association of gout with incident GCA, adjusting for potential confounders/covariates including demographics (age, race, gender), comorbidities (Charlson-Romano comorbidity index), and medications commonly used for cardiac diseases (statins, beta-blockers, diuretics, and angiotensin converting enzyme (ACE)-inhibitors) and gout (allopurinol and febuxostat; Model1).

Results: Among 1,737,027 eligible people in the study cohort, there were 3,004 cases of incident GCA during the follow-up; 2,808 in people without gout and 196 in people with gout. People with gout and incident GCA has a mean duration of gout of 2.2 years prior to the GCA diagnosis (SD, 1.7; median, 1.8; IQR, 0.5, 3.5 years). The crude incidence rate of GCA was 28.0 per 100,000 person-years in people without gout and 63.7 per 100,000 person-years in people with gout. The GCA incidence rate of 28/100,000 in our non-gout population mirrored the incidence rate of 19 to 29/100,000 noted in 50+ year-olds in the three largest population-based studies of GCA. In the main multivariate model, gout was associated with an increased risk of incident GCA, HR was 2.05 (95% CI, 1.82, 2.54; **Table 1**). Women were 2.2-times more likely to have incident GCA compared to men, older age was associated with a higher risk and having 2 or more comorbidities was associated with a 1.7-times HR of incident GCA. Compared to white, black or other race were each associated with 0.6-0.7 times HR of incident GCA (**Table 1**).

Conclusion: Gout was independently associated with 2-fold higher risk of GCA in the older individuals after adjustment for demographics, comorbidity and medications, and the risk could be between 1.4 to 1.9-fold higher risk. Future studies need to confirm this finding and evaluate the underlying mechanism of this novel association.

Table 1. Multivariable-adjusted association of gout and other risk factors with incident GCA

	Multivariable-adjusted (Model 1)*		Multivariable-adjusted (Model 2)*		Multivariable-adjusted (Model 3)*	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (in years)						
65 - <75	Ref		Ref		Ref	
75 - <85	1.70 (1.57, 1.83)	<.0001	1.66 (1.54, 1.80)	<.0001	1.62 (1.50, 1.75)	<.0001
≥85	1.27 (1.11, 1.44)	0.0003	1.24 (1.09, 1.41)	0.001	1.30 (1.14, 1.48)	<.0001
Gender						
Male	Ref		Ref		Ref	
Female	2.19 (2.02, 2.38)	<.0001	2.20 (2.02, 2.39)	<.0001	2.10 (1.93, 2.29)	<.0001
Race						
White	Ref		Ref		Ref	
Black	0.67 (0.58, 0.78)	<.0001	0.67 (0.58, 0.78)	<.0001	0.72 (0.62, 0.83)	<.0001
Other	0.56 (0.46, 0.68)	<.0001	0.56 (0.46, 0.69)	<.0001	0.60 (0.49, 0.73)	<.0001
Charlson-Romano score, per unit change	1.11 (1.11, 1.12)	<0.0001	N/A		N/A	
Charlson-Romano score			And			
0	N/A		Ref		N/A	
1			1.56 (1.39, 1.75)	<.0001		
≥2			1.71 (1.58, 1.85)	<.0001		
Gout	2.05 (1.76, 2.40)	<.0001	2.02 (1.73, 2.35)	<.0001	1.81 (1.55, 2.12)	<.0001

* Model 1 included Charlson-Romano score as a continuous variable; Model 2 replaced it with categorized Charlson-Romano score; and Model 3 replaced it with each of the 17 Charlson-Romano comorbidities. All models were also adjusted for medications for cardiovascular diseases (statins, beta-blockers, diuretics, ACE-inhibitors) and for urate-lowering therapies for gout (allopurinol, febuxostat).

N/A, not applicable; HR, Hazard ratio; CI, confidence interval; Ref, referent category.

Bold represents statistical significance, with a P-value <0.05.

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Abstract Number: 2177

Workforce Requirements in Rheumatology: A Systematic Literature Review informing the Development of a Workforce Prediction Risk of Bias Tool and the EULAR Points to Consider

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Session Information

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Background/Purpose: The projections from existing workforce studies in rheumatology vary by a factor of five, largely due to methodological heterogeneity. The purpose of this study was threefold: 1) to summarise the available information on physician workforce modelling, 2) to develop a rheumatology workforce prediction risk-of-bias tool and 3) to apply it to existing studies in rheumatology.

Methods: A systematic literature review (SLR) was performed in key electronic databases (1946-2017) comprising an update of an SLR in rheumatology and a hierarchical SLR in other medical fields. We extracted data on type of model used, details on need, demand and supply factors considered in the model, and other relevant aspects such as regional heterogeneity or uncertainty analyses. Based on the results, key general as well as specific need/demand, and supply factors for workforce calculation in rheumatology were identified and each factor was assigned a risk of bias level (low, moderate, high). The workforce prediction risk of bias tool was developed and applied to existing workforce studies in rheumatology.

Results: In total, 14 studies in rheumatology and 10 studies in other medical fields were included. Studies used a variety of prediction models based on a heterogeneous set of need/demand and/or supply factors. Only two studies attempted empirical validation of the prediction quality of the model. Based on evidence and consensus, the newly developed risk of bias tool includes 21 factors: general factors (e.g. type of the model, stakeholder involvement), need/demand factors (e.g. scope of diseases covered by rheumatologists, morbidity, demography) and supply factors (e.g. time dedicated to clinical work, entry to profession, demographic composition of workforce). The majority of studies revealed high or moderate risk of bias for most of the factors (Table).

Conclusion: The existing evidence on workforce prediction in rheumatology is scarce, heterogeneous and at moderate or high risk of bias. The new risk of bias tool should enable future evaluation of workforce prediction studies. This review informs the EULAR points to consider for the conduction of workforce requirement studies in rheumatology.

Factor	Risk of bias	N of studies
General factors		
Type of model	High: model that was only based on demand or need or supply factors	n=4
	Medium: integrated model that considered demand, need and supply [supply (s)>demand (d)]	n=6
	Low: integrated model that considered demand, need and supply (s<d)	n=4
Need/demand factors		
Projection of population development	High: not considered or only size of population is included	n=6
	Medium: age and/or sex structure and/or other factors were included but using single data source	n=8
	Low: age and/or sex structure and/or other factors were included using more than one source and relying on statistics or national population projections	n=0
Supply factors		
Time spent on clinical (rheumatologic) care	High: not considered in calculation of supply	n=4
	Medium: % of time dedicated to clinical duties was defined without detailed estimation of number, duration, and type of visit (single or multiple data sources) or	n=10
	Low: % of time dedicated to clinical duties was calculated through estimating the number, duration and type of visits, but using single data source	
	Low: % of time dedicated to clinical duties was calculated through estimating the number, duration and type of visits, using more than one data source	n=0

Table. Example of application of the workforce prediction risk of bias tool to rheumatology workforce studies (in total, 21 factors were evaluated)

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Abstract Number: 2178

Provider Perceptions of Telerheumatology within the Veterans Health Administration: A National Survey Study

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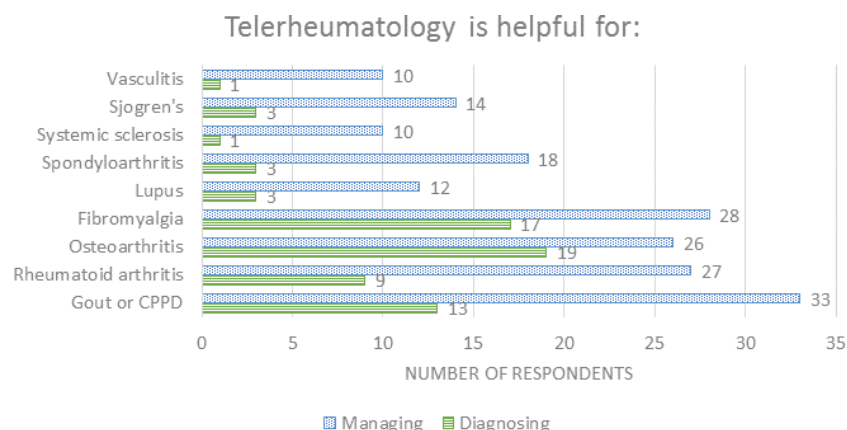
Session Type: ACR/ARHP Combined Abstract Session

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Background/Purpose: Technological advancements and a need to improve access to care due to projected workforce shortages have led to a surge in telehealth use over the last 20 years. Clinical video telehealth application to rheumatology (i.e. telerheumatology) has received limited attention, particularly regarding provider perceptions of clinical usefulness. Our objective was to assess rheumatologists' perceptions of and experiences with telehealth and telerheumatology within the Veterans Health Administration (VA), the largest integrated health care system in the U.S.

Methods: A 38-question survey, modeled after a telehealth providers' satisfaction survey (Becevic et al, 2015), was developed through an iterative process by two VA rheumatologists with expertise in telehealth and a social scientist experienced in survey development. The survey assessed VA provider satisfaction with training and information technology support, as well as barriers to using telehealth systems. The survey additionally evaluated perceptions of clinical video telehealth impact on care and appropriate clinical contexts for telehealth visits. VA REDCap was utilized for survey design and online dissemination to 224 VA rheumatologists through the VA Rheumatology Consortium (VARC). Survey responses were analyzed via descriptive statistics.

Results: Forty-five anonymous responses (20% response rate) were collected. Nearly half of the sample identified as female (47%), 33% were between 45-54 years old, and 71% reported working at an academic center. Physicians comprised



96% all respondents. Only 16 providers reported using clinical video telehealth services (36%) and of those, 13 (29%) had practiced telerheumatology. More than half of all respondents agreed that telerheumatology is vital to increasing access to care (59%), and 40% felt it is vital to increasing quality of care in the VA. The majority of providers felt that the greatest barrier to telerheumatology is the inability to perform a physical exam (97%). Respondents indicated that telerheumatology was more helpful for ongoing management of most rheumatic conditions rather than initial evaluation that included establishing a diagnosis (see graph).

Conclusion: A majority of responding VA rheumatologists believe that telerheumatology is vital to increasing access to care in the VA; however, providers feel the suitability of telerheumatology is dependent on the phase of care. Most respondents have never provided telerheumatology care. As remote care technologies are increasingly adopted, continued attention to provider experience and readiness will need to be addressed in order to maintain high-quality, provider- and patient-centric care systems.

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Abstract Number: 2179

Poor Rates of Screening for Retinal Toxicity in Patients on Antimalarial Medications: A Population-Based Study

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Background/Purpose: Antimalarial drugs (AM) are commonly used to treat rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). AM can be associated with retinal toxicity that may result in vision loss. Current US guidelines recommend annual eye screening for all patients with ≥ 5 years of AM exposure. Our objectives were 1) to identify the pattern of retinal screening in patients with RA and SLE under AM therapy, and 2) to evaluate the association of being seen by a rheumatologist and ophthalmologist retinal screening.

Methods: We conducted a population-based study using an administrative health database including the entire population in the province of British Columbia, Canada (over 5 million individuals). Our data included all outpatient and inpatient visits, investigations, procedure codes, demographics, vital statistics and all dispensed medications. We identified RA and SLE cases using a validated algorithm. We created 2 cohorts of AM users: 1) patients who started AM for ≥ 6 consecutive months after disease onset, and 2) a subset of cohort 1, restricted to patients with continuous AM use for ≥ 5 years, allowing gaps of < 6 months.

The unit of measurement was patient-year (PY) of AM use. The primary outcome was the number of PYs in which individuals had an ophthalmology visit with retinal screening (using billing codes for procedures), defined as either 1)

fluorescein angiography of retina, 2) fundus photography, 3) visual field examination, 4) quantitative perimetry examination, 5) anterior segment gonioscopy, or 6) spectral-domain optical coherence tomography.

For objective 2, we created 18-month windows of AM exposure to assess the odds of a retinal screening visit from a previous rheumatologist visit versus not seen by a rheumatologist. We used a generalized linear model with general estimation equation to estimate the odds ratio (OR) of the events.

Results: In cohort 1, we identified 23,868 patients (RA=20,000, SLE=3,868). Among these, 8,119 (34.0%) patients had a history of ≥ 5 years continuous use of AM (cohort 2). The average age in RA patients was 56.2 (SD=15.7) and the average age in SLE patients was 47.3 (SD=14.9). Seventy-three percent of RA patients and 80.0% of SLE patients were female. For cohort 1, we identified a total of 219,355 PYs. Despite guidelines suggesting eye screening every PY of AM use, only 29.7% (65,106) of PYs were associated with retinal screening. For cohort 2, a total of 44,676 PYs of AM exposure were identified with 43.4% (19,393) PYs associated with retinal screening.

For both cohort 1 and 2, there was a significant association between being seen by a rheumatologist and retinal screening (cohort 1: OR 1.63, 95% CI 1.57-1.69, $P<0.0001$; cohort 2: OR 1.46, 95% CI 1.37-1.56, $P<0.0001$).

Conclusion: Overall, this large population-based study demonstrates that only a small proportion of patients under AM therapy undergo for retinal screening as per current guidelines. Our study shows that visits by rheumatologists improve adherence to screening guidelines, however, a huge gap still remains even in a publically funded healthcare system.

Disclosure: K. Gukova, None; J. M. Esdaile, None; H. Tavakoli, None; J. A. Avina-Zubieta, None.

Abstract Number: 2180

Differences in Longitudinal Disease Activity Measures between Research Cohort and Non-Cohort Participants with Rheumatoid Arthritis Using Electronic Health Record Data

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Session Information

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Background/Purpose: Research using electronic health records (EHR) may offer advantages over traditional observational studies, including lower costs and greater generalizability to a broader patient population; however, EHR data may be more biased as a result of the high prevalence of missing data. Little research is available that directly evaluates the potential benefits and weaknesses of each study design within a single population. We examined differences in baseline demographics and disease outcomes between RA patients enrolled in a cohort study with more standardized data collection and patients whose data comes purely from the EHR within the same health system. We also compared the availability of measures and prevalence of missing data between the two groups and explored differences in longitudinal predictors of RA disease activity.

Methods: We included individuals with an RA diagnosis (ICD-9 code 714.0) and at least 2 rheumatology clinic visits within 12 months between 2013-2017 from the EHR of a public hospital (n=377 patients, n=2,269 visits). Approximately half were also enrolled in an RA cohort study. In order to examine if longitudinal differences in disease activity were present between cohort and non-cohort groups, mixed effects models were used to evaluate the association between sex, race/ethnicity, age, body mass index (BMI), smoking status and medication on Clinical Disease Activity Index (CDAI) score. Interaction between covariates and participant status (cohort vs. non-cohort) was also assessed.

Results: No significant baseline differences between cohort (n=187) and non-cohort (n=190) participants were found with respect to sex, age, race/ethnicity, smoking status, or disease activity measures (Table). Variables with a higher prevalence of missing data in non-cohort individuals compared to cohort individuals included language (14% vs. 0%), BMI (14% vs. 4%), smoking status (18% vs. 6%), and certain disease activity measures (21-22% vs. 3-6%). Black, non-Hispanic race/ethnicity was associated with a higher CDAI score over the study period compared to white, non-Hispanic individuals in non-cohort participants, while no association was found in cohort participants (p-interaction = 0.07).

Conclusion: Non-cohort participants from the EHR were comparable to a research cohort drawn from the same health system across some variables, but demonstrated more severe disease trajectories in racial/ethnic minorities. While challenges remain given the prevalence of missing data for specific variables in the EHR, utilizing EHR data repositories may inform our understanding of disease trajectories for RA patients who are not adequately captured in research cohorts.

Table1. Demographic and disease characteristics of RA cohort and non-cohort participants from the EHR of a public hospital in California, 2013-2017.

	Cohort Participants (n=187)	Non-Cohort Participants (n=190)	P-value
Sex (female)	151 (81)	159 (84)	0.46
Age	57.49 (12.56)	56.74 (11.67)	0.55
Race/Ethnicity			0.93
White, non-Hispanic	16 (9)	13 (7)	
Asian	69 (37)	65 (37)	
Black, non-Hispanic	12 (6)	10 (6)	
Hispanic	89 (48)	90 (50)	
Language			<0.001
English	64 (34)	76 (40)	
Spanish	69 (37)	53 (28)	
Chinese - Cantonese	38 (20)	19 (10)	
Other	16 (9)	15 (8)	
Unknown	0 (0)	27 (14)	
Body Mass Index	27.60 (5.40)	28.95 (7.00)	0.05
Current Smoker	16 (10)	13 (8)	0.48
Biologic/ Small Molecule DMARD	61 (33)	35 (19)	0.002
Synthetic DMARD	142 (76)	132 (70)	0.21
Clinical Disease Activity Score (0-76)	13.94 (11.25)	15.05 (13.06)	0.42
Patient Global Score (0-10)	4.52 (2.47)	4.98 (2.92)	0.11
Physician Global Score (0-10)	2.58 (2.08)	2.71 (2.57)	0.63
Swollen Joint Count (0-28)	4.10 (5.10)	4.39 (5.41)	0.62
Tender Joint Count (0-28)	3.02 (4.58)	3.45 (5.34)	0.43
Number of Visits / Person	5.25 (3.26)	3.75 (2.70)	<0.001

Table values represent: N (%) or Mean (SD).

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Abstract Number: 2181

Development and Feasibility of a Web-Based Data Capture System to Collect Uniform Comprehensive Post-Total Knee Replacement Physical Therapy Intervention Data for Both Clinical and Research Purposes

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Background/Purpose: Total knee replacement surgery (TKR) for osteoarthritis is a highly prevalent treatment with widely variable functional outcomes. Most patients receive physical therapy (PT) following TKR, but PT practice is variable and associations between specific content and dosage of PT interventions and functional outcomes are unknown. Randomized clinical trials demonstrate functional benefits from specific exercise regimens, but what interventions are implemented in clinical practice are unknown. Details of intervention content and dosage are not routinely available in PT clinical documentation. To carry out a pragmatic study of the effectiveness of real-world PT interventions we set out to develop a secure web-based documentation system for physical therapists (PTs) that would meet four goals: 1) capture PT intervention details including content, dosage, intensity and progression; 2) be used easily by practicing clinicians; 3) provide a treatment summary for use as a daily record; and 4) allow data analysis of intervention factors in a multi-site application for health services research. Such a system would provide consistent metrics for future registries and EHRs to assure complete and comprehensive documentation for research and quality measurement.

Methods: We used an iterative process to develop the data capture system and generate an all-inclusive menu of PT interventions used to treat patients post-TKR. The system required a secure user-friendly computer interface allowing clinical access to input data and designed to facilitate aggregation of data for analysis. The intervention menu was generated in four steps: 1) extraction of interventions from 112 patient records from each patient's final episode of post-TKR care; 2) feasibility testing of the compiled list of interventions by 7 PTs and PT interns from 4 clinics in another geographic region to identify interventions not already included in the list; 3) content review and subsequent revision by 4 national PT post-TKR rehabilitation experts; and 4) review and revision by 2 international PT post-TKR rehabilitation experts.

Results: The final intervention menu includes eight intervention categories (strengthening, flexibility and aerobic exercises, balance and functional training, modalities, manual therapy and patient education). Strengthening exercise is the largest category with 62 exercises. All interventions require input of data including intensity and dosage. The system is deployed in 16 practice sites with 59 PTs and 6 PTAs using the system. Input from a treatment session takes less than 5 minutes. PTs deny difficulty with input. Since deployment of the system two interventions have been added to the original list.

Conclusion: Our findings demonstrate the feasibility of a customized web-based data capture system to collect comprehensive intervention data including the content, intensity and dosage of PT treatments for patients post-TKR. We currently use the system in a study to identify intervention factors associated with positive patient outcomes. The system demonstrates a framework to study PT care in other diagnostic categories to identify "best practice" in PT care.

Disclosure: C. A. Oatis, NIH, 2; M. Westby, None; W. Peter, None; C. Lemay, None; N. Taber, None; P. D. Franklin, NIH, AHRQ, PCORI, 2.

Abstract Number: 2182

Defining Alendronate Drug Holidays and Re-Initiation in US Medicare Data

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Session Information

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Background/Purpose: Given alendronate's (ALN) prolonged skeletal retention and emerging safety concerns, the ASBMR task force recommended consideration of a "drug holiday" after 5 years of use. Distinguishing a prolonged gap in intended treatment vs. an intentional drug holiday is often unclear. We sought to estimate the prevalence of potential ALN holidays using two definitions of drug discontinuation, and to evaluate the characteristics of those who restart osteoporosis (OP) therapy after an ALN treatment gap.

Methods: We included only women ALN users (n = 81,287) with a treatment gap in the 2006-2015 US Medicare data, with medical and pharmacy coverage (Medicare parts A, B, and D), and who were at least 80% adherent (MPR) with ALN for ≥ 3 years prior to the gap. We excluded patients with history of cancer, Pagets, Osteogenesis Imperfecta, or systemic hormone therapy. We evaluated the proportion of women with a treatment gap (no prescription claims) for ≥ 6 months and/or ≥ 1 year at which time follow-up began (day 184 and day 366) (index date) until restarting of any OP medication (study end). We used descriptive statistics to characterize women restarting vs. not restarting therapy after a gap of ≥ 1 year.

Results: Using the 6-month gap definition, we identified 35,239 women (43.3% of previously adherent long-term ALN users) who discontinued ALN, of which 6172 (17.5%) restarted on any OP therapy. The median time to restart was 162 days (58, 413.5; 25th and 75th percentile). Half (50%) of the women restarted therapy within a year of stopping, suggesting that a 6-month gap may not truly represent an intended drug holiday. Using a ≥ 1 year gap definition, we identified 27,436 (33.8%) women with a possible drug holiday, of which 2978 (10.9%) restarted OP therapy. The median time to restart was 259 days (92, 512; 25th and 75th percentile). Using the ≥ 1 year definition, restarters and non-restarters differed significantly (p < 0.001) by fracture history (6.9% vs 5.1%), history of previous DXA (21.6% vs. 15.0%), and ≥ 1 rheumatologist or endocrinologist visit (13.8% vs. 8.6%).

Conclusion: Given the large proportion of rapid restarters, a drug holiday gap of only 6-months may not accurately reflect a true drug holiday; a minimum of a 1-year gap appeared more appropriate for defining a likely drug holiday. Increased OP care and history of fractures were associated with OP therapy restart.

Disclosure: A. Jaleel, None; J. R. Curtis, AbbVie, Amgen, BMS, Eli Lilly and Company, Janssen, Pfizer, Roche/Genentech, Corrona, UCB, Myriad, 2, 5; R. Chen, Amgen Inc., 2; H. Yun, None; P. J. Foster, None; N. Wright, Amgen Inc., 2, Pfizer, Inc., 5; T. Arora, Amgen Inc., 2; A. S. Mudano, None; S. Cadarette, None; K. Saag, Amgen Inc., 2, 5, Merck & Co., 2, 5, Lilly, 5, Radius, 5.

Abstract Number: 2183

Access to Prescription Drugs in Canada: Results from an Online Survey

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Health Services Research Poster III – ACR/ARHP

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Prescription medications are an important treatment option for patients living with arthritis. However, patients may often not have access to certain medications they hear about in the news, in part because a medication may not meet regulatory or reimbursement criteria, or may not be included in a person's private health insurance drug coverage. The purpose of this study is to understand knowledge about access to prescription medications in Canada.

Methods: A 20-minute pre- post-survey was conducted using a market research panel. The survey asked questions about prescription drug reimbursement coverage (e.g. are they covered in public drug plans and whether it differs across provinces), the regulatory approval process (e.g. what information is used by Health Canada), who pays for a drug covered by the public drug plan and how it is paid for (e.g. new money versus existing money), and the percentage of the cost that is paid by public drug plans, paid directly by the patient, or not filled by older Canadians due to affordability.

Results: A total of 705 Canadians completed the survey. Most respondents were from Ontario (51%), British Columbia (14%), Alberta (11%), and Quebec (11%). Knowledge on the process of prescription drug approval is low. Most respondents were unaware of the type of information is assessed by Health Canada in the approval process (80%) (many thought that price or cost-effectiveness were considered at this stage). Only 55% of respondents knew that certain prescription drugs paid for by the public drug plan may be covered in some parts of Canada but not others, and only 9% knew that federal recommendation and provincial agreement are required before a Health Canada approved prescription drug is covered by public drug plans (91%). Interestingly, 80% of respondents thought new money is allocated to new drugs that are approved (while current practice often requires money to be diverted from existing spending). Respondents also overestimated how much Canadians pay directly for prescription medications, and how many older Canadians did not fill a prescription because of affordability. Participants were motivated to learn more, particularly about costs and accountability in the Canadian health care system.

Conclusion: The general lack of knowledge about regulatory and reimbursement access to prescription medications limits informed dialogue with patients and the public. This includes changes to the approval process of prescription medications and how decisions are made around allocating budgets to certain prescription drugs. We have developed an educational video that seeks to improve this knowledge and engage patients and the public in these important conversations.

Disclosure: N. Bansback, None; C. L. Koehn, None; J. Chiu, None; M. Mulder, None; L. Li, None.

An Economic Evaluation on the Impact of Earlier Systemic Lupus Erythematosus (SLE) Diagnosis Using Complement C4d Activation Products in a Multivariate Assay Panel (MAP)

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Session Information

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Session Time: 9:00 AM-11:00 AM

Background/Purpose: Diagnosis (dx) of systemic lupus erythematosus (SLE) is made via a combination of clinical and laboratory examinations; the sensitivity and specificity (S&S) of standard diagnostic tests (SDTs) (i.e. ANA and antibodies to dsDNA, Smith, Ro/SSA, La/SSB, centromere, Jo-1, Scl-70, and CCP), are reported to be 83% & 76%, respectively (Putterman et al, 2014). A multivariate assay panel (MAP) combining biomarkers, complement C4d activation products on erythrocytes & B cells, with SDTs, yields improved dx performance with a S&S of 80% & 86%, respectively (Putterman et al, 2014). We evaluated the payer budget impact of SLE dx using MAP compared to SDTs.

Methods: We modeled a health plan of 1 million enrollees, with 0.1% suspected of SLE. SLE dx among suspected SLE patients was 9.2% (Dijkstra et al, 1999). The MAP arm assumed 80% / 20% of suspected SLE patients were tested with MAP/SDTs, compared to 100% SDT testing in SDT arm. Based on improved MAP performance, the hazard ratio for the assumed dx rate compared to SDTs was 1.74, (71, 87, 90, and 91% of the suspected who develop SLE will be diagnosed in years 1 – 4 compared to 53, 75, 84, and 88% with SDTs). Increased MAP performance relative to SDTs should result in earlier dx of SLE, reduction in disease severity at dx, and a longer period of time in less severe disease states (Oglesby et al, 2014) with associated lower costs. Pre-SLE dx claims-based cost data was used to estimate recurring direct costs for

Table 1. Average annual cost per animal year and cost efficiency of SIA

Patient's Language		First Sentence (from Page 100)	Recommendation	Reference
Average First-Sentence score per patient (per year)	U.S. Negative ^a	110,500.00	---	Marshall et al. (2013)
	U.S. Positive	117,400.07	---	Marshall et al. (2013)
Average First-Sentence score per patient (per year)	First sentences as per 2009	110,500.00	---	Garcia et al. (2014)
	First sentences as per 2009 ^b	110,500.00	---	Garcia et al. (2014)
	First sentences as per 2009	\$20,500.42	Remove First-Sentence (merged as a row of Diagnostic) (Average First-Sentence)	Marshall et al. (2013)
	First sentences as per 2009	---	Remove First-Sentence (merged as a row of Diagnostic) (Average First-Sentence)	Garcia et al. (2014)
	First sentences as per 2009	---	Remove First-Sentence (merged as a row of Diagnostic) (Average First-Sentence)	Garcia et al. (2014)

^a *P*-values for full negative parent are based on the adjustment reported by Li et al. (2008).

* Data and presentation of pathway diagrams as true junction and true haplotype as per MAP were sourced from Gerni in 4 (2002–2005) test R.2, 99% as 21.02, accuracy 0.8, 0.9% as 2.02.02, accuracy 0.8, 0.9% as 2.02.02, accuracy 0.8, 0.9% as 2.02.02. Code for all haplotypes is 0.2, and equivalent to those in the 2007 test, accuracy weighted and adjusted: 0.99, 0.2, 0.99, accuracy 0.2, 0.99, accuracy 0.2, 0.99.

Table 3. The dependent variables of ABE vs. BTA, fixed and random effects models for the dependent variables in the

	Pre- and Post-2009 Income before BtAF and BtG							Pre- and Post-2010 Income		Pre- and Post-2010 Savings Effect (only for December Supplement of BtG)			
Look over Year	Pre-2009 Pre-BtAF BtG	Change in Revenue (BtG)	Change in Costs (BtG)	Change in Taxation (Pre-BtAF Pre-BtG)	Change in Life Resources	Change in Production Pre-BtAF	Other Dispositional Factor	BtAF	BtG	Cost Savings between BtAF and BtG	BtAF	BtG	Cost Savings between BtAF and BtG
Year 1	1000,700	111,874	179,838	109,922	129,449	1219,712	1000,690	100,119,120	121,812,447	1000,670	102,499	121,812	179,822
Year 2	1075,000	110,562	168,781	141,824	144,207	1111,090	1074,919	111,209,140	134,342,334	1074,910	113,299	134,342	168,690
Year 3	1115,000	111,395	174,136	141,747	151,294	1109,473	1115,376	114,992,367	134,952,214	1109,470	114,992	134,952	174,136
Year 4	126,562	14,367	111,111	14,344	110,767	126,562	126,562,110	126,562,110	147,275,861	126,562	147,275	147,275	147,275
Year 5	11,715,124	107,161	173,070	144,913	177,396	1711,497	11,864,097	161,104,808	166,275,861	11,864,096	166,275	166,275	166,275

*All 2010 January data for average percent for general medical history, treatment settings, specialty drugs, other risk characteristics, demographics, and other factors based on survey data. Information from Figure 2010. Source: CDC/NCHADS 2010.

undiagnosed patients, and a weighted average of post-dx direct cost data for mild, moderate, and severe SLE were obtained from the literature (Garris, 2014) for SDTs, which was re-weighted to reflect the MAP scenario (Table 1).

Results: Total 4-year pre- and post- dx direct medical cost for suspected SLE patients tested with MAP were \$58,919,462 compared to \$61,174,818 by SDTs (Table 2). Total 4-year average cost savings per suspected SLE patient tested with MAP were \$2,256 (Table 2). Reduced inpatient hospital admissions were the biggest driver of cost savings (\$581,728 in yr 1). In a one-way sensitivity analysis, the percentage of SLE dx among those suspected of SLE and specificity of MAP had the largest impact on average annual cost savings (respective savings of \$16 and \$15 per 1% absolute increase in percentage of SLE among those suspected of SLE and MAP specificity).

Conclusion: Incorporating MAP into SLE dx results in total 4-year direct cost savings of \$2,255,356 (\$2,256 per suspected SLE patient) and year 1 savings of \$711 per suspected SLE patient. Further, by facilitating earlier dx of SLE at a less severe disease state, it is anticipated that MAP will enhance patient outcomes.

Tables and Figures

Disclosure: A. E. Clarke, Exagen Diagnostics, Inc., 5; T. Goss, Exagen Diagnostics, Inc., 5; A. Piscitello, Exagen Diagnostics, Inc., 5; T. Chandra, Exagen Diagnostics, Inc., 5; T. O'Malley, Exagen Diagnostics, Inc., 3; T. Dervieux, Exagen Diagnostics, Inc., 3; T. Powell, Exagen Diagnostics, Inc., 3.

Abstract Number: 2185

Direct Medical Costs for Medicare Patients with Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Health Services Research Poster III – ACR/ARHP

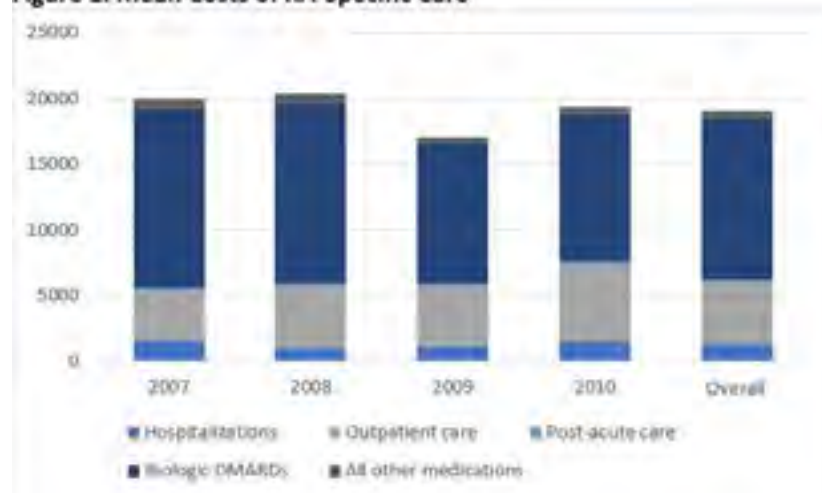
Session Type: ACR/ARHP Combined Abstract Session

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Rheumatoid arthritis (RA) affects over 1 million Medicare enrollees. Despite the size of this population, costs for RA within Medicare remain poorly understood, especially since biologic DMARDs (bDMARDs) have become an important part of care for RA. Greater insight into the detailed cost to Medicare for patients with RA would be valuable to both policy makers and health care providers, supporting planning for the allocation of limited resources.

Methods: Subjects were Medicare beneficiaries enrolled in the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS). Patient inclusion criteria were age greater than 18 years, DAS28-CRP recorded in the BRASS registry in 2006 or later, and at least 18 consecutive months of available Medicare claims data including prescription drug utilization. Cost and utilization data for inpatient admissions, outpatient care, and physician services were acquired from the Medicare Standard Analytics Files for 2006-2010. Prescription drug utilization data was obtained from the Prescription

Figure 1. Mean Costs of RA-Specific Care



Drug Event file, reflecting Medicare Part D claims. Prescription medication costs were calculated by multiplying utilization by a standardized per unit price for each unique National Drug Code, determined using the Centers for Medicare and Medicaid Services' (CMS) National Average Drug Acquisition Cost (NADAC) Tool or from the lowest per unit price listed on the drugs.com website (if no NADAC cost was available). RA-specific costs were determined by isolating claims with an RA-related ICD-9-CM diagnosis code. RA-specific prescription costs were isolated using a comprehensive list of RA-related medications. Each calendar year in which a patient had Medicare utilization was treated as an independent observation, referred to as a patient-year. All costs were converted to 2015 dollars using the consumer price index medical care component.

Results: 197 individual patients met inclusion criteria, contributing a total of 435 patient years. Mean annual direct cost of all medical care was \$36,643 (95% CI 33,603-39,682). RA-specific care accounted for \$19,216, or 52% of total costs. Within RA-specific care, hospitalizations accounted for 6.3% of costs, outpatient care 25.6%, medications 67.3%, and post-acute care 0.9% (see Figure 1). There was no significant difference in distribution of RA-specific costs across years ($p=0.37$). RA-specific costs were dominated by costs of bDMARDs. The mean annual cost for bDMARDs across the total cohort (bDMARD users and non-users) was \$12,167 (95% CI 10,357-13,976), representing 94.6% of RA-related drug costs and 63.6% of total RA-specific costs.

Conclusion: While bDMARDs have expanded treatment options for RA patients, the cost of bDMARDs is the primary driving factor for the cost of RA-specific care.

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Abstract Number: 2186

Process Evaluation of a Culturally-Sensitive, Community Based Self-Management Program for First Nations People with Arthritis and Their Families

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Background/Purpose: First Nation community consultations identified arthritis as a priority health concern and the need for culturally sensitive health services adapted to community needs. In partnership with the communities, a self-management program, the Arthritis Wellness Program (AWP) was developed to improve the health and well-being of people living with arthritis, in collaboration with family members. We report on the process evaluation of the pilot testing.

Methods: Pilot testing of the AWP was performed twice in each of two on-reserve communities (March 2016 - May 2018). Inclusion criteria: i) arthritis (OA, RA, PsA, AS, or SLE) for > 6 months, ii) age > 19, iii) English speaking, iv) residing on-reserve in one of the two communities and v) having an adult family member or close friend willing to participate. Developed based on initial focus group input with people living with arthritis and family members, health professional interviews, and community consultations, the AWP follows principles of self-management and holistic First Nations approaches to health and wellness. Six evening group sessions were attended by people living with arthritis and a family member, focused on improving understanding of arthritis and treatment options (traditional medicines, medications, nutrition, physical activity), supporting behavior change for healthy lifestyle, learning strategies to cope with the physical, emotional, mental, and spiritual impact of arthritis, improving communication, and optimizing social support.

Results: 29 people with arthritis participated in pilot sessions (21 female, mean age: 56.5 years, range: 22 - 75 years). For nine pairs, both participants had arthritis. 28% had multiple forms of arthritis, RA:55.17%, OA: 68.97%, AS: 10.34%, PsA: 3.45%, SLE: 3.45%, FM: 6.90%. 10.34% were unsure of their diagnosis. All participants had high levels of pain, fatigue, and difficulty coping with activities of daily living due to their arthritis. Attendance for the six sessions ranged from 51 - 81%, mean 67.5%. Overall feedback was positive. Mean ratings (scale of 1-5) for the six group sessions of: usefulness of the group meetings ranged from 4.25 to 4.66, satisfaction with group dynamic: 4.07 – 4.63; satisfaction with amount of information: 4.15 – 4.84. In one-on-one interviews post program, participants appreciated learning more about how to live with arthritis, highly valued the group interaction, and the ability to share with and learn from others with arthritis. Suggestions for enhanced interaction and more hands-on activities were noted. Participants in all four pilot groups wished to continue to interact as a group.

Conclusion: Pilot testing of the AWP revealed it is feasible to deliver to people living with arthritis and family members, and participants were very satisfied with the intervention. The AWP offers support and strategies to help First Nations people live well with their arthritis and encourage effective family support to their loved ones. The AWP is an example of community-based research to improve arthritis care that is culturally sensitive and meets the needs of First Nations communities. Once testing is complete, the AWP will be adopted by the communities for ongoing delivery.

Disclosure: D. Lacaille, None; J. Kaminski, None; J. Collison, None; L. Lavender, None; M. Brown, None; K. Roberts, None; D. Da Costa, None; P. Adam, None; L. Li, None; A. Lehman, None.

Abstract Number: 2187

Specialist Link Telephone Advice Cost Effectively Enhances Rheumatology Patient Care in Alberta, Canada

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Session Information

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Background/Purpose: The Calgary zone of Alberta Health Services serves a population of almost 2 million Canadians over a wide geographical area and is underserved in terms of rheumatology specialists. Furthermore, the quality of referral information is variable, and wait times are prolonged, especially for routine appointments. Thus, there is a high rate of inappropriate use of acute services for patients with rheumatic conditions.

The Division of Rheumatology at the University of Calgary chose to partner with the Primary Care Network Specialist Link telephone advice service (operating 8 am to 5 pm Monday to Friday) to provide real time telephone non-urgent advice to improve efficiency and enhance the co-ordination of patient care delivery.

Methods: The rheumatologists were asked to complete a survey after each phone consult in the initial launch period for the first year. Similarly, Primary Care doctors who had used the service were invited for their feedback. Direct costs, and direct savings were calculated based on the fee for service billing schedule, and a conservative cost effective analysis was performed based on the avoidance of relevant and known direct variable costs only.

Results: Data from a period of 13 months were collected. A total of 209 out of a potential 615 (34%) surveys were received from n=12 rheumatologists. Feedback forms from n=49 individual family physicians were also analysed. 68% of the phone calls avoided an emergency room visit and 46% avoided a consult altogether. Further diagnostic imaging and laboratory testing was avoided after 16% and 15% of calls, respectively. Both specialist and family physicians expressed a satisfaction rating of greater than 90% with mutual collegial support (89%), education (87%) and enhanced patient care (77%) identified as subjective benefits on qualitative analysis, while 29% of calls resulted in management being initiated in the primary care setting before seeing the rheumatologist. Opportunity cost analyses revealed an average net savings of CAN\$133 per phone call.

Conclusion: Empowering primary care doctors to provide care for non-urgent rheumatology patients with the specialist support of real time telephone advice is both efficient and cost effective. Furthermore, improved doctor to doctor communication enhances patient care, improves collegiality and prevents unnecessary use of acute services for patients identified as having a real or potential rheumatic disease.

Disclosure: Y. Martens-Vanhilst, None; D. P. Mosher, None; L. Slocombe, None; P. MacMullan, None.

Regional Analysis of Impact of Participation in a Patient Support Program on Clinical Outcomes Among Patients with Rheumatoid Arthritis Receiving Adalimumab (Humira)

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Background/Purpose: Patients (pts) receiving adalimumab for RA or other indications are offered participation in the AbbVie pt support program (PSP). This analysis assessed clinical outcomes across 4 regional areas for pts in the PASSION study according to PSP participation.

Methods: PASSION was a 78-wk postmarketing, global, observational study that include dpts with moderate to severe RA receiving adalimumab in routine clinical care. Clinical outcomes were evaluated in PSP users and non-users in North America, Eastern Europe, Western Europe, and Oceania. Outcome measures included proportion of pts with low disease activity (LDA), defined for this analysis as Clinical Disease Activity Index (CDAI) ≤ 10 , Disease Activity Score 28(CRP) (DAS28[CRP]) < 3.2 , and Simplified Disease Activity Index (SDAI) ≤ 11 ; remission, defined for this analysis as CDAI ≤ 2.8 , DAS28-CRP < 2.6 , and SDAI ≤ 3.3 ; and HAQ Disability Index Minimum Clinically Important Difference (HAQ-DI MCID, ≥ 0.22 decrease from baseline). Differences between PSP users and non-users for demographics and outcome measures were evaluated using a Chi-square test and differences for baseline (BL) disease activity using a 1-way ANOVA.

Results: Of 1025 pts receiving adalimumab, 499 were PSP users and 526 were PSP non-users. Most BL characteristics were similar for PSP users and PSP non-users for each region, although prior biologic DMARD use was higher in PSP non-users (18%–29%) vs PSP users (0–16%) across regions (significantly higher for Western Europe and Oceania, $P < 0.01$). BL mean disease activity was similar in PSP users and non-users from North America and Western Europe, but higher in PSP users vs PSP non-users from Eastern Europe (CDAI, DAS28[CRP], SDAI, all $P < 0.001$) and Oceania (CDAI, $P < 0.05$). Responder data analyzed by region for PSP users and non-users suggested that greater proportions of pts achieved LDA and remission with continued adalimumab treatment (**Table**). Significantly greater proportions of PSP users vs non-users from Eastern Europe and Oceania achieved LDA and/or remission at some time points ($P < 0.05$). The majority of PSP users and PSP non-users achieved HAQ-DI MCID at all assessed time points across all 4 regions (53%–87% PSP users; 59%–73% PSP non-users).

Conclusion: With continued adalimumab therapy, greater proportions of both PSP users and PSP non-users achieved LDA and remission. Participation vs non-participation in the PSP was associated with greater achievement of LDA and remission in the Eastern Europe and Oceania populations at some time points.

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Table. Percentage (95% CI) of Responders by PSP Participation Across Geographic Regions

	North America		Western Europe		Eastern Europe		Oceania	
	PSP User	PSP Non-user	PSP User	PSP Non-user	PSP User	PSP Non-user	PSP User	PSP Non-user
Proportion With Low Disease Activity (Observed)								
CDAI ≤10								
Wk 24	n=66 38 (26, 50)	n=12 33 (7, 60)	n=195 59 (53, 66)	n=170 63 (56, 70)	n=83 57 (46, 67)	n=146 42 (34, 50)	n=30 60 (42, 78)	n=25 64 (45, 83)
Wk 52	n=58 50 (37, 63)	n=6 50 (10, 90)	n=151 67 (59, 74)	n=138 75 (68, 83)	n=80 71 (61, 81)	n=131 49 (40, 57)	n=28 82 (68, 96)	n=19 68 (48, 89)
Wk 78	n=52 60 (46, 73)	n=6 50 (10, 90)	n=150 73 (66, 80)	n=138 78 (71, 85)	n=78 79 (71, 88)	n=111 59 (49, 68)	n=23 87 (73, 100)	n=23 91 (80, 100)
DAS28-CRP <3.2								
Wk 24	n=49 41 (27, 55)	N/A	n=183 62 (55, 69)	n=151 70 (62, 77)	n=81 54 (43, 65)	n=138 47 (39, 55)	n=29 59 (41, 77)	n=23 65 (46, 85)
Wk 52	n=48 56 (42, 70)	n=1 100	n=143 68 (60, 75)*	n=123 80 (73, 87)	n=75 72 (62, 82)*	n=119 55 (46, 64)	n=27 78 (62, 93)	n=18 72 (52, 93)
Wk 78	n=44 57 (42, 71)	n=2 50	n=149 69 (62, 77)*	n=125 80 (73, 87)	n=78 76 (66, 85)	n=100 64 (55, 73)	n=20 85 (69, 100)	n=21 90 (78, 100)
SDAI ≤11								
Wk 24	n=49 41 (27, 55)	N/A	n=180 61 (53, 68)	n=146 63 (55, 71)	n=81 56 (45, 66)	n=137 44 (35, 52)	n=29 59 (41, 77)	n=23 61 (41, 81)
Wk 52	n=48 46 (32, 60)	n=1 100	n=135 68 (60, 76)	n=120 77 (69, 84)	n=75 73 (63, 83)	n=119 52 (43, 61)	n=27 81 (67, 96)	n=18 67 (45, 88)
Wk 78	n=44 50 (35, 65)	n=2 50 (0, 100)	n=138 72 (65, 80)	n=120 80 (73, 87)	n=78 81 (72, 90)†	n=100 58 (48, 68)	n=20 85 (69, 100)	n=21 95 (86, 100)
Proportion With Remission (Observed)								
CDAI ≤2.8								
Wk 24	n=66 12 (4, 20)	n=12 17 (0, 38)	n=195 23 (17, 28)	n=170 25 (18, 31)	n=83 10 (3, 16)	n=146 12 (7, 18)	n=30 27 (11, 42)	n=25 20 (4, 36)
Wk 52	n=58 16 (6, 25)	n=6 33 (0, 71)	n=151 28 (21, 36)	n=138 27 (19, 34)	n=80 21 (12, 30)	n=131 16 (10, 22)	n=28 46 (28, 65)	n=19 32 (11, 52)
Wk 78	n=52 19 (9, 30)	n=6 33 (0, 71)	n=150 37 (29, 44)	n=138 34 (26, 42)	n=78 23 (14, 32)	n=111 20 (12, 27)	n=23 74 (56, 92)†	n=23 35 (15, 54)
DAS28-CRP <2.6								
Wk 24	n=49 29 (16, 41)	N/A	n=183 45 (38, 52)	n=151 50 (42, 58)	n=81 40 (29, 50)	n=138 30 (23, 38)	n=29 48 (30, 66)	n=23 43 (23, 64)
Wk 52	n=48 35 (22, 49)	n=1 100	n=143 48 (40, 56)*	n=123 63 (54, 71)	n=75 57 (46, 69)†	n=119 41 (32, 50)	n=27 74 (58, 91)†	n=18 44 (21, 67)
Wk 78	n=44 43 (29, 58)	n=2 50 (0, 100)	n=149 59 (51, 67)	n=125 70 (62, 78)	n=78 56 (45, 67)	n=100 47 (37, 57)	n=20 80 (62, 98)	n=21 71 (52, 91)
SDAI ≤3.3								
Wk 24	n=49 14 (4, 24)	N/A	n=180 24 (18, 30)	n=146 23 (16, 30)	n=81 10 (3, 16)	n=137 11 (6, 16)	n=29 31 (14, 48)	n=23 22 (5, 39)
Wk 52	n=48 10 (2, 19)	N/A	n=135 27 (20, 35)	n=120 28 (20, 36)	n=75 21 (12, 31)	n=119 18 (12, 25)	n=27 44 (26, 63)	n=18 33 (12, 55)
Wk 78	n=44 18 (7, 30)	N/A	n=138 38 (30, 46)	n=120 38 (29, 46)	n=78 23 (14, 32)	n=100 20 (12, 28)	n=20 65 (44, 86)†	n=21 29 (9, 48)

*Significantly smaller proportion and †significantly greater proportion for PSP users vs non-users ($P < 0.05$) by Chi square test.

Abstract Number: 2189

Use of Smartphones in Collecting Patient Reported Outcomes (PROs): Feasibility of a Study Nested in a US National Cohort

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Session Information

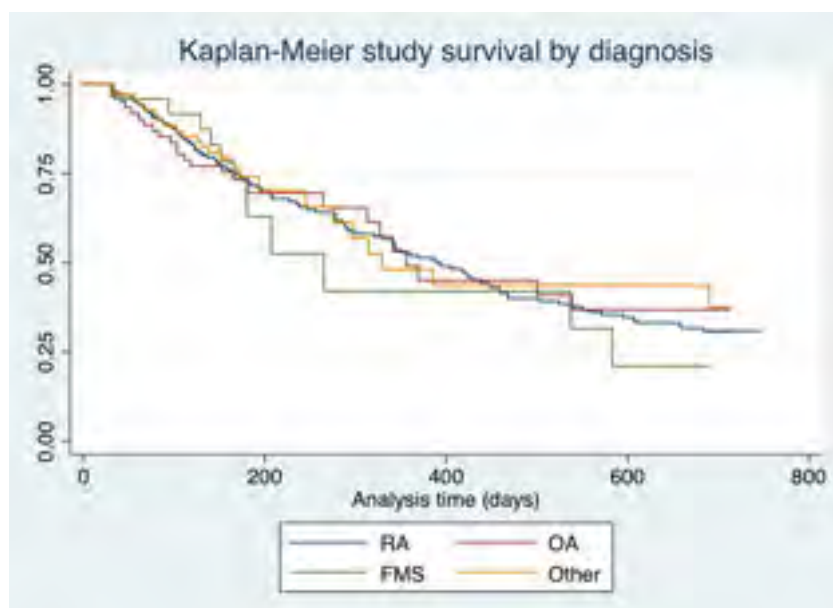
Session Date: Tuesday, October 23, 2018

Session Title: Health Services Research Poster III – ACR/ARHP

Background/Purpose: Multiple small studies have demonstrated that patients with rheumatic disease can and are willing to use smartphones to track disease severity. The objective of this study is to examine the engagement of an app that allows collection of PRO and passive phone data, in terms of adherence, flares, timing and predictors of discontinuation.

Methods: Participants were enrollees in Forward, The National Databank for Rheumatic Diseases; 700 were invited in two phases. In Phase I, 2013-2014, 190 patients enrolled, downloaded the app and agreed to respond to daily PROs (pain and function VAS) for the initial 3 months and weekly PROs for the duration (PAS-II). In Phase I, flare questions were triggered if the daily $\Delta\text{VAS} \geq 2.5$ or weekly $\Delta\text{PAS-II} \geq 1.67$. Phase II had 256 participants in 2014-2015 with identical study design but biweekly flare assessment irrespective of PRO.

Correct adherence was computed daily and weekly over the study period to the point of discontinuation defined as no app use \geq month (implementation). Kaplan Meier estimate was used to analyze time to discontinuation and Cox regression for predictors. Confounders included sociodemographic, clinical, passive phone behavior, and seasonal factors. Kappa statistics between PRO and flares were computed to measure agreement.



Results: Of 446 patients, 66% had RA, 89% were female, and baseline age 53 yrs (SD 11) and HAQ-II 1.0 (0.7). Overall, $62 \pm 28\%$ of patients reported daily measures in the app. Daily and weekly correct implementation was $68 \pm 40\%$ and $90 \pm 40\%$. The probability of discontinuation at 6 months was 0.78 and 1 year, 0.64. No differences were found by diagnosis (P 0.92) (Figure). Younger age, pain, and HAQ were significant predictors of discontinuation. Half of Phase I patients reported having ≥ 1 flare (IQ0-3), and Phase II reported ≥ 3 (0-6) flares. By phase, the agreement between flares and PROs was 55% and 65%.

Conclusion: This study revealed good levels of correct adherence which holds promise for passive behavior use in clinical follow-up and patient self-management. Examining predictors of discontinuation of response to smartphone data collection is also important as additional reminders can encourage continued participation.

Table. HR (95% CI) using both definitions in the overall sample.

	Adherence (90 days)	Implementation	Implementation		Persistence at x days
Stats	Daily	Daily	Weekly	x days	
Mean (SD)	61.5 (28.0)	68.0 (24.0)	89.8 (40.1)	180	77.9%
Median (Q1-Q3)	62.0 (43.0 – 89.0)	69.0 (53.0 – 90.0)	97.0 (80.0 – 100.0)	360	63.9%
Phase 1					
Mean (SD)	44.2 (19.4)	69.3 (25.0)	71.6 (34.0)	180	72.1%
Median (Q1-Q3)	47.8 (32.2 – 60.0)	74.2 (55.8)	84.5 (53.6 – 97.2)	360	50.5%
Phase 2					
Mean (SD)	71.3 (27.8)	73.5 (25.1)	78.5 (50.6)	180	73.7%
Median (Q1-Q3)	80.0 (55.5 – 93.3)	81.1 (57.8 – 93.4)	95.1 (33.5 – 100.0)	360	.

Disclosure: K. Michaud, University of Nebraska Medical Center and FORWARD, The National Databank for Rheumatic Diseases, 3, Rheumatology Research Foundation and Pfizer, 2; S. Pedro, None; M. Grinnell, None; R. Schumacher, FORWARD, The National Databank for Rheumatic Diseases, 3.

Means of Collaboration between Ophthalmologists, Rheumatologists and Internists in the Management of Non-Infectious Uveitis: A Nationwide Study

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Session Information

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Background/Purpose: When uveitis is believed to be part of an underlying systemic disease or when a systemic treatment is required, a multi-disciplinary approach is usually considered for the optimal management of the patients. The objective of this study was to evaluate the means of collaboration between ophthalmologists (OPHS), internal medicine specialists and rheumatologists (RHEUMS) in the care of patients with non-infectious uveitis.

Methods: A multi-disciplinary (rheumatologist, internist, ophthalmologist) scientific committee built a common questionnaire to evaluate if and how French physicians collaborate in daily practice. Questionnaires were sent to all French ophthalmologists from 24th November 2017 to 6th March, 2018. Each OPH designed the Internist/Rheumatologist he usually works with. Questionnaires were also sent to all members of the CMIO ("*club médecine interne et oeil*"), a French group of internists and ophthalmologists involved in the management of uveitis patients. All mandatory regulatory authorizations were obtained.

Results: A total of 88 physicians completed the questionnaires (37 OPHS, 31 internists, 20 RHEUMS). The physicians' mean age was 44 ± 3 years, 53% were males and 84% was hospital-based (68% in university-hospitals, 30% in general hospitals). Among ophthalmology departments 51% had five or more full-time specialists and 45% showed more than 25 uveitis patients per month in their clinic. OPHS collaborated closely with internal medicine specialists in the management of uveitis patients, but not with RHEUMS. This collaboration took place in the same hospital in 83% of cases, but in a shared setting only in 9%. The means of collaboration were as follows: immediately consecutive appointments (7%), face-to-face meetings (23%), or letters (43%). Diagnostic was mainly done by OPHS alone for B27 positive uveitis or by internists for sarcoidosis. OPHS prescribed and managed the follow-up of corticosteroid treatment, but not of corticosteroid-sparing therapies (immunosuppressant). Answers to the questionnaires were globally consistent between OPHS, internists and RHEUMS

Conclusion: The management of patients with uveitis was mostly organized as collaboration between internal medicine specialists and OPHS, rather than with RHEUMS. Heterogeneous patterns of care were observed. This study may help to define goals to optimize a shared multidisciplinary approach for the management of patients with uveitis.

Disclosure: M. Pacanowski Fournier, AbbVie Inc., 1, 3; A. Brezin, None; C. Chiquet Sr., AbbVie Inc., 5; D. Saadoun, Medimmune, Abbvie, Bristol Meyer Squibb, Roche, Servier, Gilead, AstraZeneca and Glaxo Smith Kline, 5; J. Sellam, None; P. Cacoub, Abbvie, Astra Zeneca, Bristol-Myers Squibb, Gilead, Glaxo Smith Kline, Janssen, Merck Sharp Dohme, Roche, Servier and Vifor, 5; P. Sève, Novartis, 5, AbbVie Inc., 5, LFB, 8, Pfizer, Inc., 8, SOBI, 8, AbbVie Inc., 8; B. Bodaghi Sr., allergan, 5, AbbVie Inc., 5, Santen, 5, Optos, 5; L. Kodjikian Sr., AbbVie Inc., 5, allergan, 5, Bayer, 5, Novartis, 5, Krys, 5, Roche, 5, Horus, 5, thea, 5.

Safety of Ultrasound-Guided Injections Using Local Puncture Site Sterility

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Background/Purpose: Ultrasound (US)-guided injections in musculoskeletal medicine typically utilize either local puncture site sterility or conventional surgical sterility. We report on the safety and complications of US-guided injections using local puncture site sterility.

Methods: Local puncture site sterility requires an initial cleansing of the injection site with chlorhexidine antiseptic. The clean, non-sterile US-gel is then placed on the clean, non-sterile US-probe and then both on the skin. Contamination is avoided through use of a longer needle that allows increased distance between the needle puncture site and US-gel-probe (Figure 1A). Under IRB approval, we analyzed 1115 consecutive US-guided corticosteroid injections (in 81.5% females and 18.5% males) to treat predominantly localized osteoarthritis and rheumatoid arthritis. Patient outcomes at 1, 3, 6 and 12 months post-procedure were reviewed for procedural-related complications.

Results: The 1115 US-guided injection procedures consisted of 390 knees (35%), 187 shoulders (17%), 186 carpal tunnels (17%), 120 fingers (interphalangeal and metacarpophalangeal joints, trigger finger) (11%), 47 sacroiliac joints (4.2%), 42 ankles (3.8%), 39 greater trochanteric bursa, (3.5%), 34 wrists (3%), 20 elbows (1.8%), 20 hips (1.8%), 11 popliteal cysts (1%), 11 feet (intertarsal joints) (1%), and 8 toes (interphalangeal and metatarsophalangeal joints (0.7%). Dermal atrophy (Figure 1B) occurred in 51 cases (4.6%), hemorrhage (Figure 2 A) in 1 (0.09%), cellulitis (Figure 2B) in 1 (0.09%), septic joint in 0 (0%), and tendon rupture 0 (0%). All complications resolved with time and proper therapy. The single infection was due to methicillin-sensitive *Staphylococcus aureus* suggesting endogenous contamination from the patient's skin.

Conclusion: US-guided musculoskeletal injections using local puncture site sterility are safe with dermal atrophy being the most common adverse outcome (4.6%). Serious complications, including infection, occur at an incidence less than 0.1% indicating that US-guided injection with local puncture site sterility is an acceptably safe procedural technique.

Figure 1. A. Local puncture site sterility injection. B. Dermal Atrophy after US-guided carpal tunnel injection.

Figure 2. A. Hemarthrosis after US-guided injection. B. Digital cellulitis after US-guided injection.





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Abstract Number: 2192

User Experience with Methotrexate in Managing Inflammatory Arthritis Under the Support of an Interprofessional Arthritis Care Team (UMTX Study)

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Background/Purpose: Methotrexate (MTX) is the cornerstone for the treatment of RA as monotherapy or in combination. While its cost effectiveness in halting the disease is inarguable, many obstacles hinder optimal usage. Myths about MTX, for example, that it is chemotherapy, often lead to fear of side effects and reluctance to accept treatment. While intolerance to MTX has been widely reported, it is known that the subcutaneous administration route is more efficacious than oral and usually better tolerated. Unfortunately, this preferred route is not routinely used based on the belief that self-administration is impractical and unsafe. In our interprofessional arthritis care program, we provide holistic education on disease, medication options and self-management strategies right from the time of diagnosis. Our pharmacists teach subcutaneous self-injection of both MTX and Vitamin B12. In this questionnaire study, we aim to determine patient experience with using MTX with the support of an interprofessional arthritis care team.

Methods: We reviewed and modified, with permission, a survey developed by a national patient advocacy group, adding questions about patient attendance at the interprofessional arthritis care program and whether they have accessed the pharmacist consultation service. The questionnaire, asking for anonymous data only, was administered in hardcopy format to consecutive patients visiting our clinic and the four off-site rheumatologist offices. All patients who have ever used MTX for managing inflammatory arthritis were eligible to participate. Office staff and allied health providers identified eligible participants and provided a study envelope which contained the study participant information letter and the questionnaire. Participants were asked to return the completed questionnaire in a sealed envelope before they left.

Results: Over an 8 week period, a total of 228 completed surveys were received.

Table 1. Study Participants Characteristics (n = 228):

Female	160 (71%)
Age	
< 50 years old	39 (17%)
50 – 70 years old	123 (55%)
> 70 years old	63 (28%)
Diagnosis	
RA	165 (73%)
PsA	30 (13%)
Undifferentiated IA	24 (11%)
Other	7 (3%)
Years since diagnosis	
< 2 years	26 (11%)
2 to 5 years	51 (23%)
5 to 10 years	49 (22%)
> 10 years	99 (44%)
Currently using MTX	162 (75%)
Previously using MTX	54 (25%)
MTX subcutaneous route	163 (73%)
MTX PO route	59 (27%)
MTX dose at least 15mg weekly	84 (49%)
Duration of MTX use	
< 2 years	53 (25%)
2 to 5 years	57 (27%)
5 to 9 years	35 (17%)
> 9 years	65 (31%)
Attended Interprofessional Arthritis Care Program	
Therapeutic education workshop	138 (65%)
Rheumatology clinic/ individual assessment	143 (71%)
Pharmacist consultation	104 (49%)

Over 80% of survey respondents stated they feel MTX helps their arthritis. Only 13% of respondents reported they stopped MTX due to side effects, with nausea and fatigue being most common. It should be noted that 61% of respondents were taking Vitamin B12, with 52% of those using the subcutaneous injection route. Among those using Vitamin B12, 60% believe that it helped reduce the side effects of MTX.

Conclusion: Our survey results suggest long survival of subcutaneous MTX administration. Further study is warranted to explore possible benefits of Vitamin B12 co-prescription and the impact of interprofessional care model on patient experience with MTX use in inflammatory arthritis.

Disclosure: D. Tin, None; M. Craig, None; C. Dittmar, None; C. Thorne, Amgen Inc., 2, 5, 9, Pfizer, Inc., 2, 5, 9, UCB, Inc., 9, AbbVie Inc., 2, 5, 9, Medexus/Medac, 2, 5, 8, Eli Lilly and Co., 9, Merck & Co., 9, Hospira, 5, 9, Janssen, 9, Sanofi Genzyme, 5, 9, Celgene Corporation, 9, CaREBiodam, 9, Centocor, 5, Novartis, 9; N. Samadi, None; E. Ng, None; A. Michael, None.

Abstract Number: 2193

Online Direct-to-Patient Recruitment for Systemic Lupus Erythematosus Results in Rapid Enrollment

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Session Information

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Background/Purpose: For precision medicine to address the dynamic nature of autoimmune diseases, more frequent measurements of disease activity and therapy response are needed. We report on the efficiency of a clinical study with samples sourced directly from participants with Systemic Lupus Erythematosus (SLE), a chronic inflammatory autoimmune disease, recruited entirely through online platforms. Such direct-to-patient recruitment has the added benefit of driving down cost and accelerating the speed at which clinical studies can be conducted.

Methods: We obtained IRB approval to allow for recruitment of SLE participants using online methods (Facebook, 4 bloggers with SLE) and a dedicated webpage (theLIFTstudy.com). Eligible study participants had SLE, were ≥ 18 years of age, lived in the United States, and had access to email and internet. Participants agreed to take online health surveys and self-collect three fingerstick blood samples from home that were returned via US mail for genomic analysis.

Results: Within six weeks, 1,042 SLE participants were recruited, after which time active marketing stopped. In total, over 1,400 participants with SLE (97% women, 3% men) enrolled. Participants with lupus were geographically located across all 50 states, with 17% located in rural areas, similar to the national distribution of 19%.^{1,2} Age Distribution: 0% ≥18-19, 12% ≥20-29; 23% ≥30-39; 30% ≥40-49; 28% ≥50-64; 4% ≥65; 2% unknown. Ethnicity: 72% White, 11% African American, 8% More than One Race, 6% Hispanic/Latino, 1% Native American, 1% Asian.

Channel	Impressions	Click through rate (CTR)	Clicks	Clicks to Email %	# of Emails	Email to Qualified Enrolled %	# Enrolled
Social Platforms	1,423,335	1.4%	19,594,	14%	2,831	38%	1,137
Bloggers			621	70%	436	65%	282
Total							1,419

Study updates allowed for ongoing engagement. A follow-up email sent a year later, requesting an additional fingerstick blood sample, had a 51% open rate, with 88% of the opens agreeing to provide another sample.

Conclusion: An online direct-to-patient process to recruit for an SLE study is an effective model that can help drive down costs in precision medicine. Through the sole use of online platforms, the LIFT study reached its goal of > 1,000 SLE participants enrolled within 6 weeks. The virality of the study enrolled an additional 400 at no additional marketing cost. Online recruitment enabled nationwide participation, with a rural area rate similar to the national distribution, possibly capturing individuals who may normally lack the access and ability to join a traditional SLE study. Bloggers provided an engaged group of patients from which to recruit. Patient engagement to extend participation was also high and may be indicative of the desire for patients to play a more active role in furthering lupus research.

References: Medicare Rural Zipcode.
US census bureau.

Disclosure: J. Fujimoto, DxTerity, 1, 3; L. Borisov, DxTerity, 1, 3; K. Warren, DxTerity, 1, 3; R. Terbrueggen, DxTerity, 1, 3, 4.

Abstract Number: 2194

Develop a New Platform for Post-Marketing Vigilance Though Smart System of Disease Management (SSDM) Mobiles Tools: A Real World Cohort Study of RA Patients from China

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Session Information

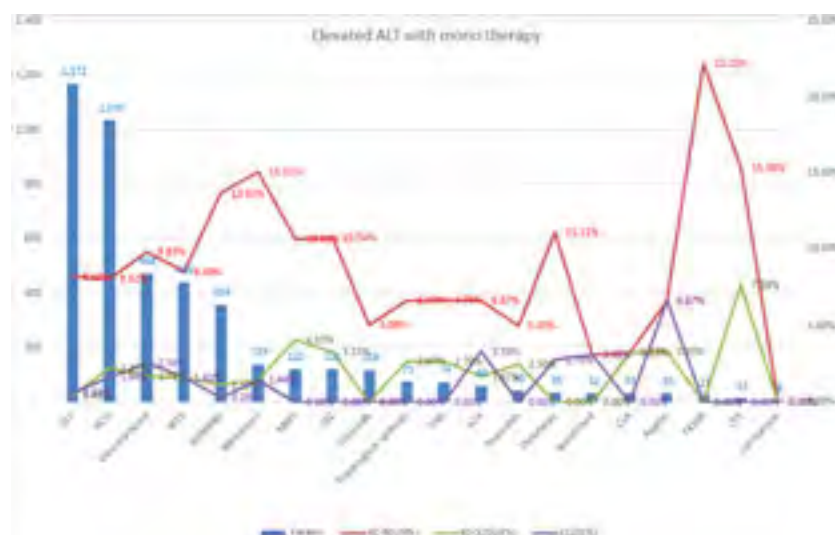
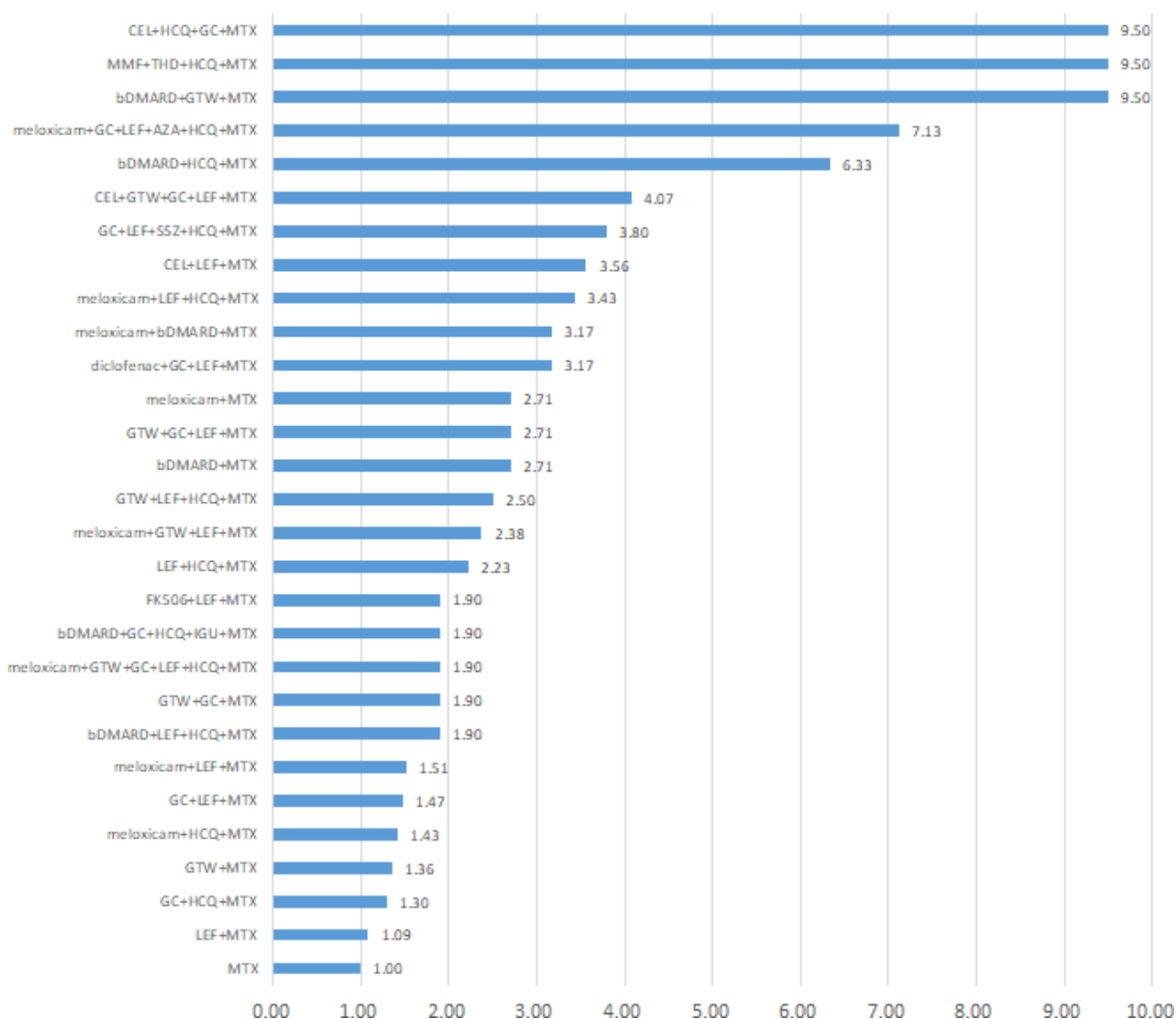
Session Date: Tuesday, October 23, 2018

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The relative risk of MTX based combinations



Background/Purpose: Adverse events (AE) during treatment in RA patients are unavoidable. Monitoring AEs in real time during long-term treatment is critical for AE detection and rational management. The current AE report system in MedWatch can only collect rare AE, but could not support post marketing vigilance and reevaluation for drugs, especially in real world combination therapy.

To develop and validate SSDM as a new platform for post-marketing vigilance through monitoring AEs with common mono- and combination therapies in treatment of rheumatoid arthritis (RA).

Methods: The SSDM is a mobile App which includes two applications for both physicians and patients. Patients were educated to input the data of lab test records and treatment regimens and perform disease activity evaluation once a month. After data entry, patients can synchronize data to the mobile terminal of their authorized rheumatologist and upload onto cloud, which formed a large patient self-management database.

Results: From Aug 2014 to May 2018, a total of 10,903 RA patients from 480 centers in China were entered in the cohort study. These patients contributed more than 18,823 patient-years (PY) follow-up data. The mean age was 49.29 +/- 16.08 (18 to 99) years and the median disease duration was 27.4 months. The treatment regimens include 11 mono and 39 combination therapies. Taken ALT as an example, the profile of AE of ALT elevation for top ten mono therapy regimens is plot (Figure 1). In the database there are thirty-six MTX based combinations treatment regimens. The specifications of elevation of ALT in MTX combination therapy are drafted based on relative risk ratio comparing with rate in MTX mono therapy (Figure 2). Both AE profiles in mono therapy and specification in combination treatment alerted clinicians for unsafe regimens avoidance and timely adjustment.

Conclusion: The findings show that the AEs may be well collected and described via SSDM database through empowering patient. Rheumatologists are able to monitor the real world profile of adverse events in real time. SSDM is able to assist Rheumatologist in making rational clinical decision. SSDM may serve as new platform for post-marketing vigilance.

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Abstract Number: 2195

Predictive Factors of a Positive PET/CT Scan for Vascular Involvement in Patients with Polymyalgia Rheumatica

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Imaging of Rheumatic Diseases Poster III: Other Modalities

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Session Time: 9:00 AM-11:00 AM

Background/Purpose: Polymyalgia rheumatica (PMR) is often the presenting manifestation of giant cell arteritis (GCA). Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) scan often discloses the presence of LVV in PMR patients. We aimed to identify predictive factors of a positive PET/CT scan for LVV in patients classified as having isolated PMR.

Methods: A set of consecutive patients with PMR from a single hospital were assessed. All of them underwent PET/CT scan between January 2010 and February 2018 based on clinical considerations. Patients with PMR associated to other diseases, including those with cranial features of GCA, were excluded. The remaining patients were categorized in classic PMR (if fulfilled the 2012 EULAR/ACR classification criteria at disease diagnosis; n=84) or atypical PMR (who did not fulfill these criteria; n=16). Only information on patients with classic PMR was assessed.

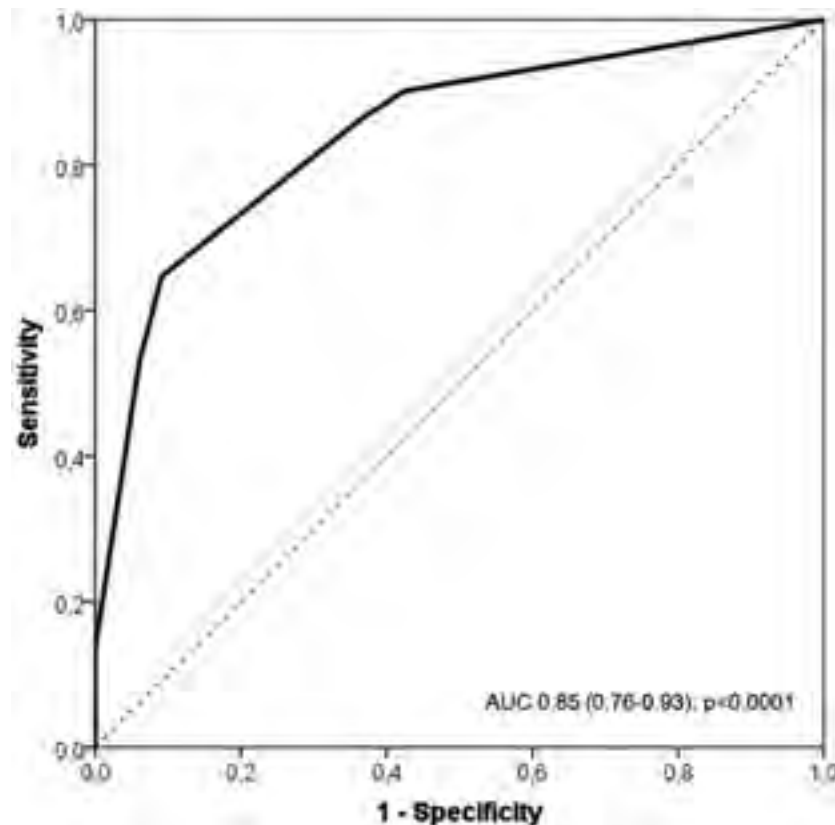
Results: The mean age of the 84 patients (50 women) with classic PMR was 71.4±9.2 years. A PET/CT scan was positive in 51(60.7%). Persistence of classic PMR symptoms was the most common reason to perform a PET/CT scan.

	Classic PMR (N=84)		P
	Positive PET/CT (N= 51)	Negative PET/CT (N=33)	
Sex (women), n (%)	31 (62.7)	19 (57.6)	0.64
Age (years), mean \pm SD	70.0 \pm 9.2	73.7 \pm 9.0	0.08
Cardiovascular risk factors, n (%)			
Hypertension	29 (56.9)	24 (72.7)	0.14
Dyslipidemia	18 (35.3)	16 (48.5)	0.23
Diabetes mellitus	10 (19.6)	12 (36.4)	0.08
Current smokers	5 (9.8)	1 (3.0)	0.40
Polymyalgia symptoms, n (%)			
Neck pain	9 (17.6)	9 (27.3)	0.29
Shoulder girdle pain	33 (64.7)	26 (78.8)	0.17
Pelvic girdle pain	44 (86.3)	12 (36.4)	< 0.01
Morning stiffness	11 (21.8)	10 (30.3)	0.44
Unusual symptoms, n (%)			
Inflammatory low back pain	15 (29.4)	3 (9.1)	0.027
Diffuse lower limb pain	27 (52.9)	2 (6.1)	< 0.01
Constitutional symptoms, n (%)			
Fever	2 (3.9)	2 (6.1)	0.64
Asthenia	15 (29.4)	8 (24.2)	0.60
Hypoxemia	4 (7.8)	7 (21.2)	0.08
Weight loss	9 (17.6)	8 (24.2)	0.46
Laboratory markers.			
Hb (g/dL), mean \pm SD	12.7 \pm 1.3	12.2 \pm 1.6	0.09
Platelet count ($\times 10^9/l$), mean \pm SD	281.4 \pm 84.9	263.7 \pm 100.3	0.19
CRP (mg/dL), median [IQR]	2.0 [0.6-4.4]	2.0 [1.1-5.3]	0.28
ESR (mm/1* h), median [IQR]	33.0 [12.0-65.0]	48.0 [29.5-73.0]	0.15
Treatment.			
Glucocorticoids, n (%)	51 (100.0)	33 (100.0)	0.99
Dose of Prednisone (mg), mean \pm SD	12.0 \pm 5.7	12.3 \pm 7.3	0.88
Months of treatment with Prednisone, median [IQR]	4 [1.0-15.0]	7 [2.5-15.5]	0.31
Methotrexate, n (%)	11 (21.8)	4 (12.1)	0.27

Nevertheless, patients with positive PET/CT scan often had unusual symptoms. The best set of predictors of a positive PET/CT scan were bilateral diffuse lower limb pain (OR=8.8, 95% CI 1.7-46.3; p=0.01), pelvic girdle pain (OR=4.9, 95% CI 1.50-16.53; p=0.01) and inflammatory low back pain (OR=4.7, 95% CI 1.03-21.5; p=0.04).

Conclusion: Inflammatory low back pain, pelvic girdle and diffuse lower limb pain are predictors of positive PET/CT scan for LVV in PMR.

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Abstract Number: 2196

Kinetics of Tissue-Specific Distribution of ^{18}F -Fluorodeoxyglucose in Positron Emission Tomography in Large Vessel Vasculitis

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Session Information

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Session Title: Imaging of Rheumatic Diseases Poster III: Other Modalities

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Background/Purpose: ^{18}F -fluorodeoxyglucose (FDG) PET may be used to quantify vascular inflammation in large-vessel vasculitis (LVV). Quantitative analysis of arterial FDG uptake has not been standardized. Delayed acquisition time may be advantageous for vascular PET imaging but has not been studied in LVV. Arterial FDG uptake is often normalized to uptake in background tissue; however, the factors that influence tissue-specific distribution of FDG in inflammatory diseases are unknown. The study objective was to identify factors associated with FDG uptake in 1) the large arteries and 2) background tissues (liver, blood pool, spleen) at 1 and 2 hour image acquisition times in a cohort of patients with LVV and comparators.

Methods: Patients with LVV and comparators (systemic inflammatory diseases, healthy controls), were recruited into a prospective observational cohort. Participants underwent either whole body PET-MR at 1 hour acquisition time, PET-CT at 2 hour acquisition time, or both. Arterial uptake was quantified as the sum of mean standardized uptake values (SUV_{max}) for 5 segments of the aorta, carotid, and subclavian arteries. SUV_{mean} values were calculated for each background tissue. Multivariate linear regression models were used to identify associations between tissue-specific FDG uptake and atherosclerosis, vasculitis, and FDG clearance- related factors (see **Table**). The same predictor variables were included in each regression model to facilitate comparisons across different tissues. A p value <0.05 was considered significant.

Results: PET scans were performed at 1 hour (n = 175) and 2 hours (n = 194), with most studies performed sequentially at both time points (n = 145). Age, BMI, and CRP were significantly associated with arterial-FDG uptake at both the 1 and 2 hour time points, with increased effect estimates at 2 hours. Additional vasculitis-related factors (diagnosis, treatment) were also significantly associated with arterial uptake at the 2 hour time point. Factors related to FDG clearance (uptake time, glomerular filtration rate) were significantly associated with FDG uptake in liver and blood pool at 1 hour but were weakly or not associated with FDG uptake at 2 hours. Additional factors were associated with liver and blood pool at 2 hours, but with small effects estimate sizes. Vasculitis-related factors were associated with splenic uptake at 1 and 2 hours.

Conclusion: Tissue-specific factors are associated with FDG distribution in a time-dependent manner. Delayed image acquisition demonstrates stronger associations between arterial FDG uptake and atherosclerosis/vasculitis related factors. The impact of factors related to FDG clearance in background tissues is reduced with delayed imaging. Delayed image acquisition and normalization of arterial FDG uptake to liver or vein is preferable in LVV.

Table: Factors significantly associated with tissue distribution of ^{18}f -fluorodeoxyglucose on positron emission tomography in large-vessel vasculitis at 1 and 2 hour imaging acquisition times

		1-hour Positron Emission Tomography	2-hour Positron Emission Tomography
Target Tissue	Artery	Age ($\beta = 0.09$, $p < 0.01$) BMI ($\beta = 0.28$, $p < 0.01$) CRP ($\beta = 0.05$, $p < 0.01$)	Age ($\beta = 0.20$, $p < 0.01$) BMI ($\beta = 0.41$, $p < 0.01$) CRP ($\beta = 0.12$, $p = 0.01$) Diagnosis ($\beta = 2.06$, $p = 0.04$) Immune Meds ($\beta = 1.65$, $p = 0.01$)
			BMI ($\beta = 0.03$, $p < 0.01$) Age ($\beta = 0.004$, $p = 0.02$) Female ($\beta = 0.08$, $p < 0.01$)
Background Tissue	Liver	BMI ($\beta = 0.02$, $p < 0.01$) GFR ($\beta = -0.002$, $p = 0.03$) Uptake time ($\beta = -0.003$, $p = 0.01$)	BMI ($\beta = 0.03$, $p < 0.01$) Age ($\beta = 0.004$, $p = 0.02$) Female ($\beta = 0.08$, $p < 0.01$)
	Blood Pool	BMI ($\beta = 0.01$, $p < 0.01$) Uptake time ($\beta = -0.005$, $p < 0.01$) GFR ($\beta = -0.003$, $p < 0.01$)	BMI ($\beta = 0.02$, $p < 0.01$) Uptake time ($\beta = -0.003$, $p < 0.01$) Age ($\beta = 0.004$, $p < 0.01$) Fasting Glucose ($\beta = 0.003$, $p < 0.01$) Immune Meds ($\beta = -0.003$, $p < 0.01$)
	Spleen	BMI ($\beta = 0.02$, $p < 0.01$) Diagnosis ($\beta = -0.08$, $p = 0.03$) PGA ($\beta = -0.03$, $p = 0.04$) WBC ($\beta = 0.02$, $p < 0.01$)	BMI ($\beta = 0.03$, $p < 0.01$) Immune Meds ($\beta = -0.09$, $p = 0.01$)

* All of the following variables were included in each regression model:

Atherosclerosis-related factors: Gender (male vs female), Body mass index (BMI), Age in years, Fasting glucose (mg/dL).

Vasculitis-related factors: C-reactive protein (CRP, mg/L), Total white blood cell count (WBC, K/uL), Treatment with immunosuppressants (Immune Meds, Yes vs No), Daily prednisone dose (mg), Physician global assessment (PGA, 0-10 scale), Diagnosis (large-vessel vasculitis vs comparator), Hematocrit (%).

FDG clearance factors: Uptake time (minutes from injection of FDG), Glomerular filtration rate (GFR, ml/minute).

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Steroid Bolus Leads to a Negative ^{18}f -FDG PET/CT Scan in Large Vessel Vasculitis. Data from a Multicenter Giant Cell Arteritis Cohort Database

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Imaging of Rheumatic Diseases Poster III: Other Modalities

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are overlapping inflammatory diseases. Large Vessel Vasculitis (LVV) is frequently present in any of the two subsets¹. In some scenarios where complications such as visual loss or stroke are present, treatment with steroids bolus is a common practice. Imaging studies when suspecting LVV are as sensible and more easily available than temporal artery biopsy². ^{18}f -FDG PET/CT is useful to

confirm mural inflammation in extracranial arteries to support diagnosis of LVV. Beside this rationale, some questions still remain unclear regarding the involvement of PET/CT in patients receiving steroids³.

Methods: Multicenter, retrospective, descriptive analysis of 18f-FDG PET/CT in 69 patients who met 2010 ACR criteria for GCA. Demographic data, cumulative GC prior to PET/CT, and vascular territories affected were collected. Patients included were either new diagnosis or those who had previous diagnosis of GCA or PMR, who had a relapse or complicated follow-up. PET/CT scan was reported either positive or negative for LVV for any of 8 major vascular territories: ascending aorta, aortic arch, descending thoracic aorta, abdominal aorta, carotids, subclavian/ brachiocephalic, axillary/humeral and iliac/femoral arteries. Statistic analysis was done with χ^2 with Yates' correction and exact Fischer's test.

Results: Mean age: 72 years \pm 5 yo, 68%, women. Territories mostly affected: thoracic aorta (75%), iliac/femoral arteries (54.2%) and supraaortic vessels (47.9%). In general, GC seemed to be associated with the possibility of a negative PET/CT scan. A subanalysis among patients allowed to classify into 3 groups: (1) no previous steroids (2) previous accumulated GC (3) steroid bolus previous to PET/CT. Group 2, showed a mean accumulated dose of GC 2,908.4 mg \pm 339. A 31.8% of PET/CT scans were negative, interestingly 84% corresponded to the group of patients who had received a steroid bolus prior to the PET/CT (p 0.01) (Table 1).

	Positive PET/CT	Negative PET/CT
Group 1, n= 29	27 (93.1%)	2 (6.9%)
Group 2, n= 27	18(66.7%)	9(33.3%)
Group 3, n=13	2(15.4%)	11(84.6%)

Conclusion: Conclusions: Data from our multicenter cohort of LVV showed that thoracic aorta was the most frequent vessel affected, as expected. When steroid bolus was given, there was a strong association with a negative PET/CT scan, compared with patients who received either a variable dose or any dose of steroids. Our results confirmed something expected beforehand, but not yet described in a large cohort of patients.

<https://doi.org/10.1093/rheumatology/kew273>

2. <https://doi.org/10.1136/annrheumdis-2017-212649>

3. <https://doi.org/10.3899/jrheum.170138>

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Abstract Number: 2198

Evaluation of 18F-Fluorodeoxyglucose PET-CT Score at Baseline on the Therapeutic Response to Prednisone in Polymyalgia Rheumatica: A Retrospective Study

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Session Information

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Background/Purpose: To evaluate the impact of 18F-fluorodeoxyglucose PET-CT (FDG-PET/CT) score at baseline, on the therapeutic response to prednisone, in patients with polymyalgia rheumatica (PMR).

Methods: This is a monocentric retrospective study realized at the university hospital of Besancon. We included patients with a diagnosis of PMR meeting the 2012 ACR/EULAR criteria, who had performed a FDG-PET/CT at baseline, between December 2012 and December 2017. Patients were treated with an initial prednisone dose of 0.3 mg/kg a day, progressively decreased following a standardized tapering dose protocol (10% /month). We excluded patients who received

corticosteroids before the FDG-PET/CT, or without baseline FDG-PET/CT. Seventeen specifics previously described hotspots were visually analyzed (1). We realized a semi-quantitative analysis of FDG uptake (4-point score from 0 to 3), following Goerres scoring system (2). Hotspot with 0 indicating no uptake (same as bone); 1, slight uptake; 2, moderate uptake (same as liver); and 3, uptake higher than the liver. It results in a score of 0 to 51. Then we defined two groups of patients according to their resistance to prednisone at 6 months, defined as the reoccurrence of symptoms and/or an increase of systemic inflammation twice during the prednisone tapering.

Results: 30 patients were included: 12 in the group “resistant” and 18 in the group “sensitive”. There were 60% of women, with a mean age of $67,57 \pm 11,63$ years. The mean CRP at baseline was $45,02 \pm 39,59$ mg/L. The mean FDG-PET/CT score at baseline was 18/51. The FDG-PET/CT score baseline was significantly lower in the resistant group (9 vs 23, $p < 0.009$). Resistant patients were younger (60 years vs 74.5 years, $p < 0.008$), and mostly men (66.5% vs 22%, $p < 0.02$). ROC curve shows a predictive threshold of corticoreistance at 9/51 on the PET/CT score at baseline, with 66.67% of sensibility and 83.37 of specificity [AUC: $0,78 \pm 0,08$] Patients with peripheral synovitis had higher PET/CT score baseline ($p = 0.02$).

However, there was no statistically significant difference of CRP at baseline between the two groups (13.75 vs 15, $p < 0.8$), and no correlation between CRP and PET/CT score at baseline ($p = 0.17$). There was no difference concerning the presence of neoplasia (16.5% vs 11%, $p < 1.00$) in the two groups.

Conclusion: These data suggest that higher baseline FDG-PET/CT score is predictive of a better response to prednisone in patients with PMR, with a predictive threshold of corticoreistance lower than 9/51 on FDG-PET/CT score at baseline. Corticoreistant patients seemed to be mostly men and younger, with no significant difference in CRP at baseline.

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2. Goerres GW, Forster A, Uebelhart D et al. F-18 FDG whole-body PET for the assessment of disease activity in patients with rheumatoid arthritis. Clin Nucl Med 2006;31:386-90.

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Abstract Number: 2199

Active Disease and Follow up 18f-FDG-PET/CT in Patients with Giant Cell Arteritis. Which Treatment Is More Likely to Achieve Remission?

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Session Information

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Session Title: Imaging of Rheumatic Diseases Poster III: Other Modalities

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Background/Purpose: Giant cell arteritis is the most common large vessel vasculitis. ¹⁸F-FDG-PET/CT is known to be a useful imaging technique for diagnosing giant cell arteritis. Only a few ¹⁸F-FDG-PET/CT follow up studies with limited number of patients exist. Especially long term immunosuppressive treatment was so far not analyzed. Withdraw of immunosuppressive treatment is normally guided by clinical symptoms and laboratory testing. Under treatment with tocilizumab laboratory testing is not a helpful guiding tool for clinicians. ¹⁸F-FDG-PET/CT follow up investigations might be a useful diagnostic tool to decide if an immunosuppressive treatment is sufficient.

Methods: 28 patients with an active giant cell arteritis were clinically documented and subjected to ¹⁸F-FDG-PET/CT scanning with a Siemens Biograph™ True Point™ PET/CT. Images were evaluated by specialists at the Departments of Nuclear Medicine and Radiology of the University Clinic of Erlangen via a visual grading system. ¹⁸F-FDG-PET/CT scans were graded as active, questionable active and inactive. The scans were graded active when a vascular uptake of the tracer was higher than liver uptake. Additionally we documented the vascular uptake of the tracer applying the PETVAS score by Grayson et. (0-27). All patients received a follow up investigation to evaluate disease activity under immunosuppressive Treatment.

Results: At time of clinically active disease in 22 patients ^{18}F -FDG-PET/CT scans were graded as active and in 6 patients it was graded as questionable active. The mean CRP level was 52 mg/l and the mean PETVAS score was 17.86. The mean time between the first and second scan was 25.61 months. At the time of follow up only in two patients ^{18}F -FDG-PET/CT scans were graded as active, in 13 patients as questionable active and no activity was seen in 13 patients. The mean CRP level at follow up was 9,7 mg/l and the mean PETVAS score was 8.79. Additionally to glucocorticosteroids 19 patients were treated with MTX (67,9%), 8 patients received Tocilizumab and 1 patient received Azathioprin. We couldn't estimate any statistically significant predictors for a follow up PET-CT with no activity (= PETVAS<10) due to the small patient number. Interestingly all 8 patients (100%) with Tocilizumab treatment between the two scans were graded as no activity at follow up and had a PETVAS score <10. While 31,5% (6 patients) treated with MTX still were questionable or active in their ^{18}F -FDG-PET/CT scan (PETVAS>10).

Conclusion: In this follow up study we could show that ^{18}F -FDG-PET/CT scan is a useful tool to estimate clinical remission additionally to clinical parameters and laboratory tests. Interestingly, all patients that received Tocilizumab had visually graded no activity in their ^{18}F -FDG-PET/CT scans (PETVAS<10), while only 68.5% of the patients treated with MTX could achieve a PETVAS<10 at follow up. Larger studies on follow up ^{18}F -FDG-PET/CT especially under Tocilizumab treatment should be done to confirm this result and the stronger immunosuppressive effect of Tocilizumab in comparison to MTX in patients with giant cell arteritis.

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Abstract Number: 2200

Does an ^{18}F -FDG-PET/CT in Patients with Giant Cell Arteritis in Clinical Remission Make Sense?

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Background/Purpose: Giant cell arteritis is the most common large vessel vasculitis. ^{18}F -FDG-PET/CT is known to be a useful imaging technique for diagnosing giant cell arteritis. Scarce data exists on ^{18}F -FDG-PET/CT in patients with giant cell arteritis in clinical remission. It was shown that ^{18}F -FDG uptake can persist in patients under immunosuppressive treatment. The decision to withdraw immunosuppressive treatment is normally guided by clinical symptoms and laboratory testing. Under treatment with tocilizumab laboratory testing is not helpful. Therefore ^{18}F -FDG-PET/CT might be an additional investigation method to device between subclinical persisting inflammation and true remission.

Methods: 31 patients with giant cell arteritis in clinical remission were clinically documented and subjected to ^{18}F -FDG-PET/CT scanning with a Siemens BiographTM TruePointTM PET/CT. Images were evaluated by specialists at the Departments of Nuclear Medicine and Radiology of the University Clinic of Erlangen via a visual grading system. ^{18}F -FDG-PET/CT scans were graded as active, questionable active and inactive. The scans were graded active when a vascular uptake of the tracer was higher than liver uptake. Additionally, we documented the vascular uptake of the tracer applying the PETVAS score by Grayson et. (0-27).

Results: Of the 31 patients in clinical remission, two patients presented with a visual active vascular uptake of the tracer in the ^{18}F -FDG-PET/CT scan. 11 patients had a questionable active tracer uptake and 18 patients had no visual vascular uptake of the tracer. The mean PEVAS score of patients with visual active vascular uptake was 16, with patients with questionable uptake was 9.27 and with no vascular uptake was 7.44. Interestingly the patients with active disease had no systemic inflammation markers. One patient was treated with MTX 15 mg/week and 5 mg Prednisolone/day, the other was without treatment. 6 patients of the cohort were treated with Tocilizumab, all of them had visually no tracer uptake and their mean PETVAS score was 8.33. On the other hand patients with Methotrexate were found in all three groups equally distributed with a mean PETVAS score of 9.20.

Conclusion: We showed that 11 patients (35,4%) with clinical remission still had visually questionable active ^{18}F -FDG uptake and 2 patients (6.4%) had visually active ^{18}F -FDG uptake in an ^{18}F -FDG-PET/CT scan. It is not clear whether this subclinical ^{18}F -FDG uptake reflects true activity of the large vessel vasculitis or residual effects due to vascular remodeling. Interestingly all patients under Tocilizumab treatment were in the visual not active group (mean PETVAS=8,33) while patients with MTX were equally distributed among all groups. This result indicates a better immunosuppressive effect of Tocilizumab in comparison to MTX and might be a sign for persisting vasculitis activity in patients with significant ^{18}F -FDG uptake despite clinical Remission.

Disclosure: V. Schönau, None; J. Roth, None; M. Englbrecht, None; J. Rech, Bristol-Myers Squibb, 2, 8, Celgene Corporation, 2, 8, AbbVie Inc., 8, Fresenius, 8, Medicap, 8, MSD, 8, Pfizer, Inc., 8, Roche, 8; G. Schett, None.

Abstract Number: 2201

Evaluation of ^{18}F -Fluorodeoxyglucose Positron Emission Tomography/ Magnetic Resonance Imaging (^{18}F -FDG PET/MRI) in C Protein-Induced Myositis Model in Mice

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Imaging of Rheumatic Diseases Poster III: Other Modalities

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Polymyositis is a chronic inflammatory myopathy with proximal muscle weakness due to lymphocyte infiltration, especially CD8 + T cells to the muscle layer. C protein-induced myositis (CIM) is a murine model of polymyositis (PM), muscle injury is mediated by C protein-reactive CD8 + T cells. A recent study reported that the serum levels of muscle-derived enzymes were irrelevant to the severity of CIM. In addition, although the histological scoring is the reliable way to assess the severity of CIM, it has limitation to evaluate the inflammation due to focal involvement. The aim of this study was to evaluate the correlation of skeletal muscle inflammation and ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET)/magnetic resonance imaging (MRI) findings in CIM.

Methods: To induce CIM, 8–10-week-old female mice were immunized intradermally with 200 μg C protein fragments emulsified in 200 μg of Freund's complete adjuvant (CFA). Pertussis toxin (0.2 μg) was injected intraperitoneally at the same time.

FDG (300 mCi) was intravenously injected and simultaneous PET/MRI was obtained 60 minutes later by using a hybrid PET/MRI scanner for small animal. On PET/MRI, FDG uptake was measured in the gluteal and thigh muscle, foot pad, and the soft tissue as a background. Maximal target-to-background ratio (TBR) of the muscles was measured as the index for uptake. To monitor disease progression, ^{18}F -FDG PET/MRI evaluation was performed on day 12, day 14 and day 19 after immunization. The next day after imaging, quadriceps, hamstrings and gastrocnemius muscle specimens were harvested. Each muscle tissues were stained with hematoxylin and eosin (H&E). Myositis was graded on a scale of 1–6 according to the histologic severity.

Results: Histological score showed significantly increased in quadriceps, hamstrings and gastrocnemius muscle compared to control mice on day 14 (mean score =1.83; $p = 0.0037$, mean score =2.42; $p = 0.0027$ and mean score =1.583; $p = 0.009$, respectively). Histological scores were higher but not significant in quadriceps, hamstrings and gastrocnemius muscle of CIM on day 12 (mean score =0.58; $p = 0.37$, mean score =0.58; $p = 0.18$ and mean score =1.17; $p = 0.12$, respectively) and on day 19 (mean score =1.00; $p = 0.16$, mean score =0.33; $p = 0.12$ and mean score =1.67; $p = 0.37$, respectively). Mean of histologic summation score of skeletal muscles was 0.77, 1.94, 0.5 ($p = 0.016$, $p = 0.0014$ and $p = 0.12$, respectively) on day 12, 14, 19 in CIM. On PET/MRI, TBR was 1.67 ± 0.51 in control, whereas it was 4.11 ± 1.34 on day 12, 6.34 ± 1.78 on day 14, and 3.93 ± 0.75 on day 19 in CIM model. TBR was correlated with histologic summation score (Spearman's $\rho = 0.954$, $p < 0.0001$).

Conclusion: The findings of FDG PET/MRI appeared to be correlated with the histologic scoring system in CIM model. FDG PET/MRI could be an effective method for quantitative, repetitive, and serial assessment of inflammatory activity in CIM model

Disclosure: J. Y. Kim, None; J. W. Byun, None; J. H. Shin, None; J. S. Park, None; J. H. Lee, None; S. E. Kang, None; H. J. Yoo, None; E. B. Lee, None; D. W. Hwang, None; Y. S. Lee, None; J. C. Paeng, None; E. Y. Lee, None; Y. W. Song, None.

Abstract Number: 2202

The Relationship between Periodontitis and the Treatment Response to Biologics in Rheumatoid Arthritis Patients; A Post-Hoc Analysis Using [18F] Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Imaging of Rheumatic Diseases Poster III: Other Modalities

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis(RA) and periodontitis have been suggested to be related, and they share many clinical and pathologic features. Both diseases are chronic inflammatory diseases characterized by the accumulation and persistence of inflammatory infiltrates in local lesions. Patients with RA are more likely to have periodontitis, and some reports said the treatment response to RA was less in patients with periodontitis than those without periodontitis. However, there has been no report investigating the relationship between the degree of periodontitis and the treatment response to RA. And it is said that [18F] fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) can evaluate both the degree of synovitis of RA and periodontitis. The aim of this study was to evaluate the relationship between periodontitis and the treatment response to biologics in RA using FDG-PET/CT.

Methods: Sixty RA patients (14 males, 46 females, average age 58.3(17-80) years) treated with biological therapies were assessed. FDG-PET was performed at baseline and six months after the initiation of biological therapy. The maximum standardized uptake value (SUVmax) was used as a representative value for the assessment of the FDG uptake in periodontal tissue (upper posterior gingival tissue). We also evaluated the DAS28-CRP and several clinical parameters (CRP, ESR, anti-cyclic citrullinated peptide antibody [ACPA], rheumatoid factor [RF], matrix metalloproteinase 3 [MMP-3]). Wilcoxon's signed rank sum test and Spearman's rank correlation test were used to assess the correlation between the periodontal SUVmax and the clinical parameters.

Results: Periodontal SUVmax at baseline had relation with patient age ($r=0.302$, $p=0.009$) and ACPA value ($r=0.265$, $p=0.025$).

After biological therapies, the values for DAS28-CRP, CRP, ESR, and MMP-3 were significantly decreased after 6 months. However, the mean periodontal SUVmax increased from 1.83 to 1.88, indicating no significant change in the periodontal SUVmax after treatment. The ACPA and RF values also did not change markedly after treatment. In contrast, we noted a significantly negative correlation between the baseline periodontal SUVmax and the Δ DAS28-CRP ($r=-0.369$, $p=0.004$).

Conclusion: The baseline periodontal SUVmax had a positive correlation with ACPA value. Biological therapies for RA might not cure periodontitis. In addition, concurrent periodontitis might reduce the response to biological therapies in RA patients.

Disclosure: M. Tachibana, None; Y. Yonemoto, None; T. SUTO, None; K. OKAMURA, None; C. OKURA, None; H. SAKANE, None; H. CHIKUDA, None.

Atherosclerotic Inflammation in Rheumatoid Arthritis Patients: A Post-Hoc Study Using Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Imaging of Rheumatic Diseases Poster III: Other Modalities

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) has long been associated with an increased cardiovascular risk, and despite substantial improvements in disease management, its associated mortality remains high. Several reports have suggested that treatment with TNF inhibitors might have a beneficial effect on the cardiovascular risk. However, few studies have quantitatively investigated the relationship between RA and atherosclerotic inflammation. [18F] fluorodeoxyglucose-positron emission tomography (FDG-PET) has been used to assess synovitis in patients with RA and to evaluate the disease activity of RA. In addition, the FDG accumulation has been reported to indicate atherosclerotic inflammation. The aim of this study was to evaluate the relationship between atherosclerotic inflammation and biologics using FDG-PET.

Methods: Sixty RA patients (14 males, 46 females, average age 58.3 [range 17-80] years) treated with biological therapies were assessed. FDG-PET was performed at baseline and six months after the initiation of biological therapy. The carotid FDG uptake was measured by obtaining the standardized uptake values from the carotid of each patient, and the ratio of the carotid to background (blood) activity was determined (TBR). We also evaluated the Disease Activity Score 28 C-reactive protein (DAS28-CRP) and several clinical parameters (CRP, erythrocyte sedimentation rate [ESR], anti-cyclic citrullinated peptide antibody [ACPA], rheumatoid factor [RF], matrix metalloproteinase 3 [MMP-3]). Student's t-test, chi-square test and logistic regression analysis were used to assess the factors influencing the decrease in the TBR.

Results: At six months after starting biological therapies, the values for DAS28-CRP, CRP, ESR, and MMP-3 were significantly decreased. However, the carotid TBR was not significantly improved (1.17 to 1.18). The ACPA and RF values also did not change markedly after treatment. The age, change in the white blood cell count, and carotid TBR at baseline were lower in the decrease TBR group than in increase TBR group. In the logistic regression group, a young age and a low carotid TBR at baseline were factors influencing the decrease in the carotid TBR.

Conclusion: In this study, a young age and a low carotid TBR at baseline were factors influencing the decrease in the carotid TBR. These results suggest that biologics improve not only the disease activity but also atherosclerotic inflammation, especially in young RA patients.

Disclosure: Y. Yonemoto, None; M. Tachibana, None; K. OKAMURA, None; T. SUTO, None; H. SAKANE, None; C. OKURA, None; T. Kaneko, None; H. CHIKUDA, None.

Abstract Number: 2204

Clinical Utility of a Multi-Energy Spectral CT in Crystal Arthritis

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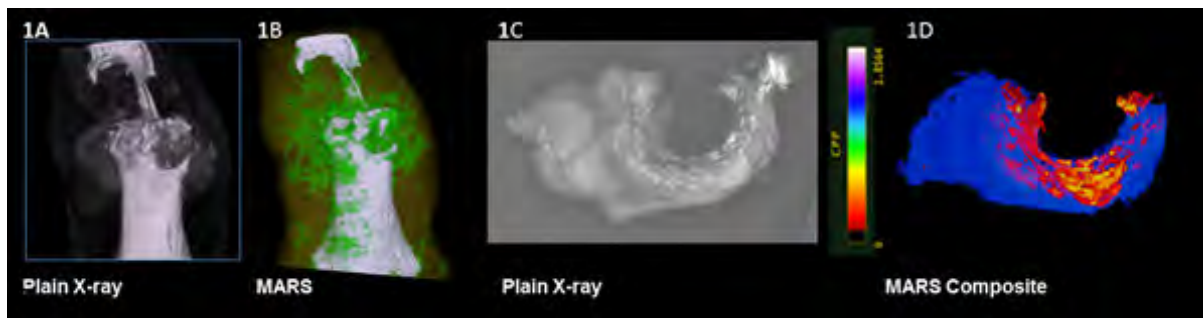
Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Imaging of Rheumatic Diseases Poster III: Other Modalities

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM



Background/Purpose: The gold standard for the diagnosis of crystal-related arthritis requires aspiration and visualization of crystals from synovial fluid or tophus material. However, crystal identification may be suboptimal particularly for crystals other than monosodium urate (MSU) which are associated with gout. New imaging modalities such as ultrasound and dual energy CT are increasingly being used to aid in the diagnosis of gout but their role is less well defined in other crystal deposition diseases. The ability to characterise calcium pyrophosphate (CPP) or hydroxyl apatite (HA) crystals using non-invasive imaging would be an advance. The aim of this study was to determine whether we could detect and differentiate between MSU, CPP and HA crystals using novel multi-energy spectral CT (MARS) imaging.

Methods: A finger with a gouty tophus from the Christchurch Cancer Tissue bank and a calcified medial meniscus excised at the time of joint replacement surgery were obtained. The gouty finger was imaged using plain X-ray, DECT and a preclinical MARS scanner. Images of the whole meniscus using plain X-ray and MARS were obtained. MARS imaging of biological specimens and calibration phantoms containing known concentrations of MSU, CPP and HA crystals was performed using energy thresholds of 20, 30, 40 and 50 keV at 80 kVp. Material decomposition was applied to the imaging data to distinguish MSU, CPP and HA crystals. For validation purposes, samples of the crystals were obtained from the meniscus and tophus and examined by x-ray diffraction (XRD) and polarized microscopy respectively.

Results: Plain X-ray of the gouty finger revealed erosions and changes consistent with a tophus (Figure 1a). DECT and MARS both identified MSU crystals, however, MARS was able to detect finer detail (Figure 1b). Within the meniscus plain X-ray identified chondrocalcinosis consistent with CPP crystals while MARS showed a predominance of CPP crystals in the calcified regions in the excised meniscus and in some parts there was a mixture of HA and CPP (Figure 1d). MARS imaging findings of the meniscus were validated using x-ray diffraction of the crystal scrapings.

Conclusion: MARS spectral CT can not only detect and differentiate MSU crystals in a gouty finger but also specifically detect and identify CPP within an osteoarthritic human knee meniscus and distinguish them from HA crystals. There is potential for MARS to become useful in the diagnosis of crystal-related arthropathies including CPPD, gout and calcific tendonitis.

Figure

Disclosure: L. K. Stamp, Amgen Inc., 8; N. Anderson, None; F. Becce, None; M. Rajeswari, None; M. Polson, None; O. Guyen, None; A. Viry, None; C. Choi, None; T. Kirkbride, None; A. Raja, None.

Abstract Number: 2205

Initial Phase 2 Clinical Data of SEL-212 in Symptomatic Gout Patients: Measurement of Dissolution of Urate Deposits Associated with Monthly Dosing of a Pegylated Uricase (Pegadricase) with Svp-Rapamycin By Dual Energy Computed Tomography

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Imaging of Rheumatic Diseases Poster III: Other Modalities

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Pegylated uricases are therapies for treatment of severe chronic gout, particularly for rapid resolution of tophi. However, uricases are limited by induction of anti-drug antibodies that can compromise efficacy and safety. SEL-212 is a novel combination product consisting of pegadricase (also known as pegsiticase) co-administered with synthetic vaccine particles encapsulating rapamycin (SVP-R). We report initial Phase 2 data on the effect of the intensive lowering of sUA levels by SEL-212 on the dissolution of monosodium urate (MSU) crystals in symptomatic gout patients. Dual-energy computed tomography (DECT) may be used to differentiate urate crystals from calcium by using specific attenuation characteristics, to diagnose gout. DECT uses a computer algorithm to produce color-coded images that render uric acid green, cortical bone blue, and trabecular bone purple. In tophaceous gout patients, DECT may be used for serial volumetric quantification of subclinical tophi to evaluate response to treatment.

Methods: Patients with symptomatic gout (≥ 1 tophus, gout flare within 6 months or gouty arthropathy) and elevated serum uric acid (sUA) ≥ 6 mg/dL were treated with fixed doses of pegadricase (0.2 mg/kg or 0.4 mg/kg) alone or in combination with SVP-Rapamycin (0.05 to 0.15 mg/kg). SEL-212 was infused in 28-day cycles x3 doses followed by challenge with pegadricase alone on 28-day cycles x2 doses, or in 28-day cycles x5 combination doses of SVP-Rapamycin and pegadricase. To investigate changes in uric acid deposits, DECT scans of hand/wrist, feet/ankles, and knees will be performed as an exploratory measure for at least 2 patients in study cohorts which included fixed doses of pegadricase (0.2 mg/kg or 0.4 mg/kg) in combination with SVP-Rapamycin (0.1 to 0.15 mg/kg), during the screening visit, treatment period 3, treatment period 5 or at early termination visit.

DECT images were analyzed by Arthritis Research Canada (ARC) by two DECT Radiologists utilizing a Syngo Via DECT software package.

Results: As of 31 May 2018, an initial DECT scan was performed in 24 patients (143 dosed patients), with 10 patients undergoing a follow-up DECT scan.

The demographics for patients who received a follow-up DECT scan were 44 - 71 years old (mean 57.7 years), male 80%, Black or African American 70%, and Caucasian 30%. Mean BMI at baseline was 31.8 kg/m², with 50% of patients being obese. Mean duration of gout was 6.6 years.

The mean sUA at the screening visit was 8.3 mg/dL. Time between the initial and most recent/follow-up DECT scan ranged from 77 - 147 days (mean 103 days), with a mean change in total urate volume of -1.53 cm³ (range: 0.1 to -11.44 cm³).

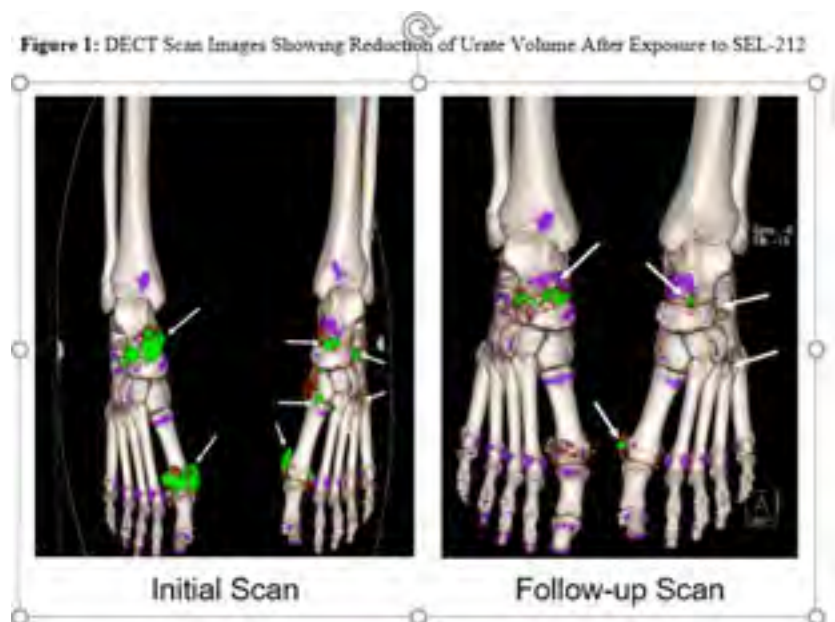


Figure 1: DECT Scan Images Showing Reduction of Urate Volume After Exposure to SEL-212

Conclusion: SEL-212 has a significant impact on the reduction of urate deposits in symptomatic gout patients with hyperuricemia as confirmed by DECT.

Disclosure: R. Azeem, Selecta Biosciences, 1, 3; E. Sands, Selecta Biosciences, 1, 3; L. Johnston, Selecta Biosciences, 1, 3; W. DeHaan Ph.D., Selecta Biosciences, 1, 3; A. J. Kivitz, Novartis, 1, AbbVie, Janssen, Pfizer, UCB, Genzyme, Sanofi, Regeneron, Boehringer-Ingelheim, Sun Pharma, 5, Celgene, Novartis, Genentech, Merck, Horizon, Flexion, Ironwood, Regeneron, Sanofi, Pfizer, 8; T. K. Kishimoto, Selecta Biosciences, 1, 3; J. Park, Selecta Biosciences, Inc, 1, 3; S. Nicolaou, Siemens, 9.

Joint Repair While Initiating Biologic Therapy in Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Imaging of Rheumatic Diseases Poster III: Other Modalities

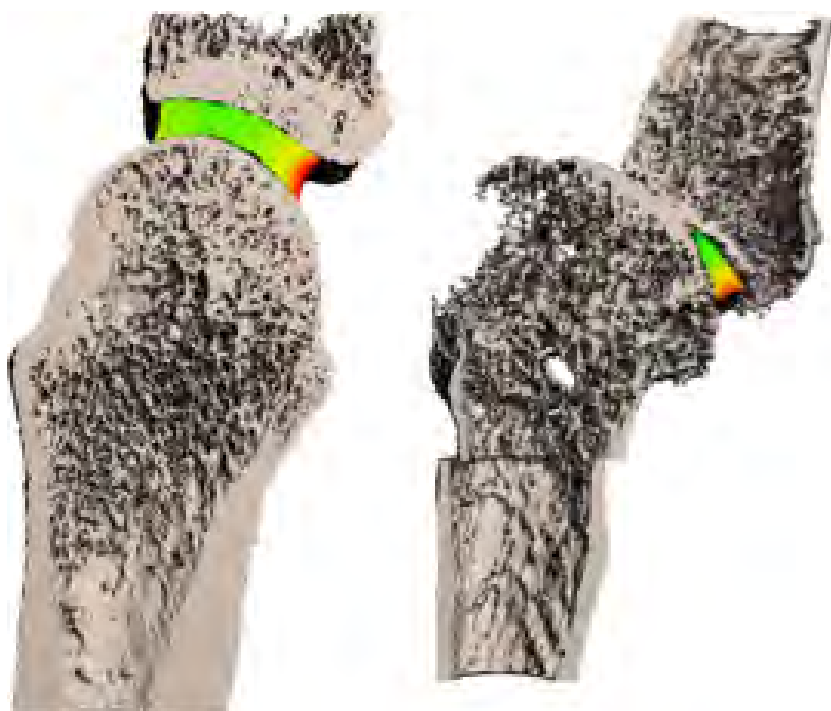
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Functional decline and reduced quality of life for patients with rheumatoid arthritis (RA) results from chronic changes to joints in patients, including bone erosions and joint space narrowing. Advanced biologic therapies can prevent joint damage progression, and it has been suggested that they can repair bone damage^{1,2}. High resolution peripheral quantitative computed tomography (HR-pQCT) provides measurement of joint space and bone microstructure with high sensitivity and precision. The purpose of this study was to investigate whether HR-pQCT can detect joint damage repair in patients initiating biologic therapies, and whether changes in joint damage are associated with changes in clinical outcomes.

Methods: We recruited 88 participants who met the ACR/EULAR2010 Classification Criteria for RA and were starting on a new biologic agent due to moderate or high disease activity. The 2nd and 3rd MCP joints of the dominant hand were scanned with a HR-pQCT scanner (XtremeCTII, Scanco Medical, 61mm) at 3 and 12 months after initiating the new agent. Participants also underwent a rheumatologist examination for disease activity and self-reported measures of physical (Health Assessment Questionnaire) and hand (DASH Questionnaire) function were collected at these visits, along with the Jebsen hand function test. Joint space volume (JSV) was measured in 3D using an algorithm developed by the SPECTRA collaboration³ (Figure 1). Bone erosion quantification will be completed using a 3D segmentation technique using MIAF-Finger⁴. Individual changes in JSV were classified as increased or decreased if the absolute changes were greater than detection limits based on least significant change.

Results: The cohort was 72.7% female with an average disease activity score (DAS28) of 2.58 at baseline and 2.60 at 9 month follow-up. The average DASH score was decreased to 27.6 from 29.3, while the average HAQ score increased to 0.89 from 0.86. There were no statistically significant changes in clinical results. When compared to detection limits, 73 of



the 84 analyzable joints showed no change in joint space volume, 5 showed an increase and 6 showed a decrease. We found no significant relationships between joint space outcome and disease activity, physical function, or hand function.

Conclusion: In most patients there were no significant changes in joint space as they initiate or change biologic therapies. This may be due to a large detection limit making it difficult to detect changes over a 9 month period. Future erosion analysis will provide further insight on the potential benefits of biologic therapy with regards to the reversibility of bone damage as seen on HR-pQCT.

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Figure 1. 3D visualizations of joints with a large JSV (left)and a small JSV (right).

Disclosure: S. Brunet, None; S. Manske, None; K. Engelke, None; S. K. Boyd, None; C. Barnabe, None.

Abstract Number: 2207

Detecting Hand Joint Ankylosis in Radiographic Images Using Deep Learning: A Step in Development of Automatic Radiographic Scoring System for Bone Destruction

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Session Information

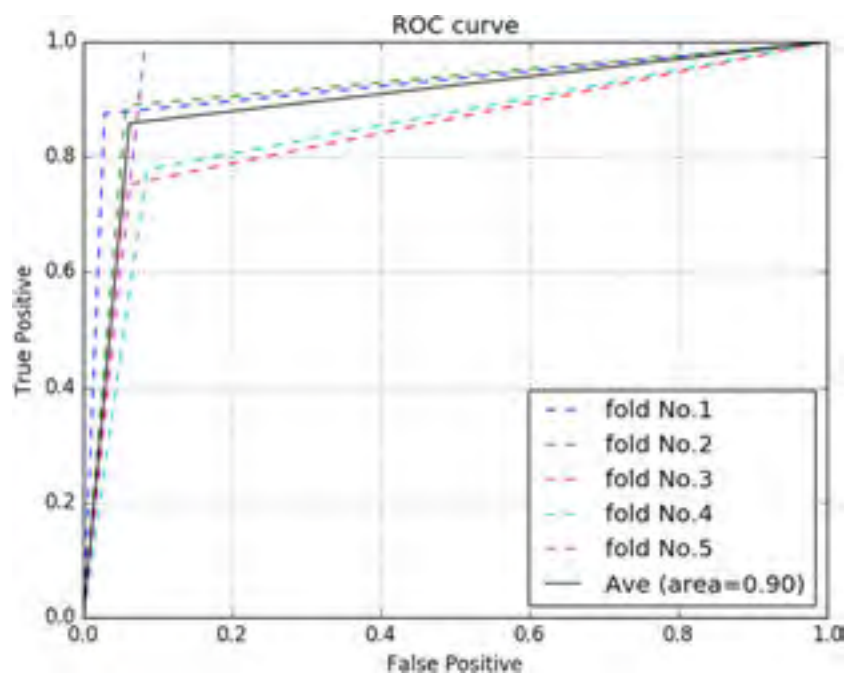
Session Date: Tuesday, October 23, 2018

Session Title: Imaging of Rheumatic Diseases Poster III: Other Modalities

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Artificial intelligence (AI) techniques including deep learning have been rapidly evolving and shown good performance in many fields over recent years. However, there are few cases that apply these techniques to medical field, since it is difficult to collect dataset for training. In our research, to develop an AI-aided automatic radiographic



scoring system for quantitating degree of bone destruction, we aimed to develop a learning-based model to automatically detect hand joint ankyloses in radiographic images.

Methods: Our method consists three parts: (i) collecting dataset with an annotation tool,(ii) predicting hand joint ankyloses using deep learning, and (iii) visualizing where the model focuses in image. First, to collect and annotate dataset for deep learning efficiently, we developed the annotation tool (Fig. 1). A total of 216 radiographic images of hands were randomly obtained from patients who had visited our division at Keio University Hospital in 2015. Forty-three images were identified as having ankyloses in hand joints including wrist joints, MP joints and PIP/IP joints in agreement with a well-trained rheumatologist and radiologist. In learning phase, images were randomly divided into five sets (fold No. 1 to 5) for 5-fold cross validation. We utilized ResNet[1],a deep learning model for classification of images, to predict hand joint ankyloses. In addition, we visualized where the model focuses in image by using Grad-CAM[2]. The ROC analysis was performed to evaluate performance of the model.

Results: As a performance of detecting hand joint ankyloses, our model presented a precision value of 0.78, recall value of 0.86, and F-measure value of 0.82. Mean area under the ROC curve was 0.90 (Fig. 2). When visualizing the result of the model by Grad-CAM, there were some cases where ankylosis in hand joints in the image contributed to the inference results.

Conclusion: A model based on deep learning to automatically detect hand joint ankyloses in radiographic images was developed with relatively small samples, which suggests that the predictive performance may increase by collecting more training dataset. Our developed model needs to be validated in an independent set of images and tested against other experienced doctors. In the next step of development, we are elaborating a plan for a deep learning-based scoring system to evaluate erosion and joint space narrowing.

References: [1]HE, Kaiming, et al. Proceedings of the IEEE conference on computer vision and pattern recognition. 2016.
[2]R. R. Selvaraju, et al. 2017 IEEE International Conference on Computer Vision(ICCV). 2018.

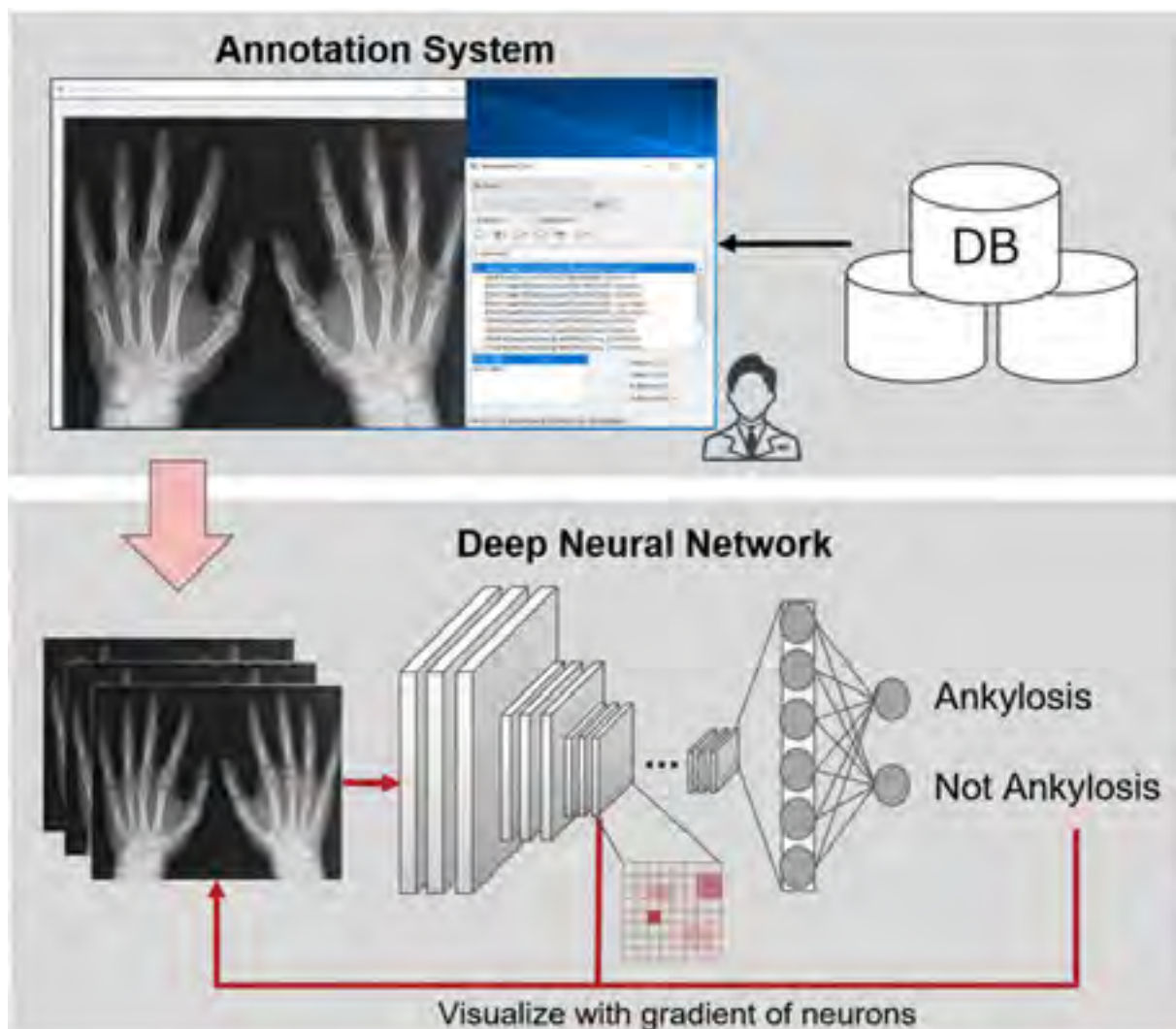


Fig. 1

Fig. 2

Disclosure: K. Izumi, None; M. Hashimoto, None; K. Suzuki, Employee of FUJITSU LABORATORIES LTD., 3; T. Endoh, Employee of FUJITSU LABORATORIES LTD., 3; K. Doi, Employee of FUJITSU LTD., 3; Y. Iwai, Employee of FUJITSU LTD., 3; M. Jinzaki, None; S. Ko, None; T. Takeuchi, None.

Abstract Number: 2208

Novel Fluorescence Optical Imaging Scoring System of Inflammation in the Hand and Wrist Is in Patients with Rheumatoid Arthritis – Agreement with Ultrasonography and Sensitivity to Change

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Imaging of Rheumatic Diseases Poster III: Other Modalities

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Fluorescence optical imaging (FOI) has been used for assessment of inflammation in the hands and has in several cross sectional studies been compared with US and MRI, but no validated scoring systems exist. The aim was in a longitudinal study to validate a new and clinically feasible FOI scoring system for assessments of synovitis in RA hands by comparison with US and determining its sensitivity to change.

Methods: 46 RA patients eligible for initiation or intensification of disease modifying anti-rheumatic drugs and with ≥ 1 clinically swollen joint in the hand, were included and assessed by FOI, US and clinical assessment at baseline and 6 months. FOI image-sets of both wrists and hands were obtained using a Xiralite system unit. The patients received a bolus of i.v. indocyanine green (ICG) 10 seconds after starting the examination, which obtained 1 image/second for 6 minutes. All FOI images were scored by two readers for synovitis at the wrist, MCP and PIP joint levels in both hands. The novel synovitis scoring is based on the assumption that inflamed tissue would demonstrate a more rapid enhancement than surrounding tissues. For each joint, the images were assessed sequentially from start to peak enhancement. Synovitis was defined as a sharply margined enhancement with clear delineation from surrounding tissues and correct anatomical location, lasting ≥ 3 seconds. The width of the pathology fulfilling these criteria was compared to the width of the joint at the 3rd second of enhancement of that particular joint, and scored 0-3 for synovitis (total range 0–66) The readers were blinded to patient data, but not chronology, and had previously showed a high intra- and inter-reader agreement (ICC:0.70-0.92).

For US assessment, a GE Logiq E9 US unit with a high frequency linear 6-15 ML probe and with Doppler settings optimised for slow flow. Synovitis was scored from 0-3 for grey scale (GS) and Doppler using the OMERACT US synovitis

Table 1. Change in synovitis scores, DAS28, and VAS Global, and their standardized response means, during 6 month of follow-up, for all patients.

All sites - imaging modality (n=46)		Baseline	6.5 months		P	SRM	
FOI	Median [25th-75th]	31	[5-39]	-8.9	[-15.1-7]	<0.01	0.85
	Mean \pm SD	52.0	± 7.8	-7.0	± 6.3		
Grey scale US	Median [25th-75th]	9.2	[6-22]	-9	[-15-3.6]	<0.01	0.88
	Mean \pm SD	55.8	± 14.5	-9.1	± 9.3		
Doppler US	Median [25th-75th]	8	[3-24]	-3.5	[-11.0-3.9]	<0.01	0.82
	Mean \pm SD	9.5	± 8.8	-6.6	± 6.0		
DAS28-CRP	Median [25th-75th]	9.0	[4-5.4]	-2.0	[-3.8-0.5]	<0.01	0.95
	Mean \pm SD	4.2	± 3.3	-1.7	± 1.8		
VAS Global	Median [25th-75th]	48.5	[18-81]	-30	[-62-6.5]	<0.01	1.0
	Mean \pm SD	42.7	± 24.8	-30.0	± 31.7		

P, p-value for Wilcoxon's test for change of paired data between 2 time points; N, number of patients; SRM, standardized response mean; FOI, Fluorescence optical imaging; DAS28, Disease Activity Score for 28 joints, using C-reactive protein; VAS Global, patient global visual analogue scale. Values in brackets are values at 25th and 75th percentiles

scoring system by two trained assessors with a previously documented high intra- and inter-reader agreement (wKappa:0.88-0.95).

Agreement for status and change scores was assessed using single measure intraclass correlation coefficients (ICCs) and Spearman correlation coefficients (rho). Responsiveness was assessed using standardized response mean (SRM)

Results: Baseline scores, change scores and their respective SRMs are presented in table. 1. The mean SRM was good for all parameters

ICC and rho between FOI and US total scores were low for both readers at baseline (range 0.3-0.4) ($p<0.05$), and low to moderate (range 0.31-0.54) ($p<0.01$) for change scores.

Conclusion: A moderate correlation with US for change over time, and good responsiveness, were found for a new FOI scoring system. FOI may potentially prove useful for monitoring RA patients in clinical trials and practice.

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Abstract Number: 2209

Fluorescence Optical Imaging Xiralite[®] Is Helpful in the Decision for Rituximab Re-Therapy in Patients with Rheumatoid Arthritis

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Session Information

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Session Title: Imaging of Rheumatic Diseases Poster III: Other Modalities

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Background/Purpose: Rituximab (RTX) is an effective and well-tolerated therapeutic option in rheumatoid arthritis (RA) patients with insufficient response to TNF α inhibitors. However, the exact time point of RTX re-therapy often varies and objective parameters (e.g. imaging, such as MRI and/or musculoskeletal ultrasound [US]) are not yet included in the RA treatment strategy [PMID: 28264816]. The aim of this study was to evaluate the ability of the fluorescence optical imaging Xiralite[®] (FOI) to predict RTX re-therapy in RA patients - in comparison to clinical, laboratory and US.

Methods: In this study, n=31 patients with established RA were included and prospectively followed over one year by DAS28, patient's global VAS (0-100 mm), CRP/ESR, US7 score (for synovitis and tenosynovitis in greyscale and power Doppler of the clinically dominant hand/foot; [PMID: 19714611]), and by FOI (phases 1-3 and PrimaVistaMode [PVM]) at baseline (before RTX), and after 3,6, and 12 months. The need for RTX re-therapy was defined according to DAS28 response criteria by EULAR.

Results: Of the included 31 patients (female 77.4%, mean age 60.1 \pm 11.4, mean disease duration 14.9 \pm 7.1 years), n=14 (45.2%) received RTX re-therapy within 12 months: n=3 after 6 months (mths), n=4 after 7 mths, n=5 after 9 mths, and n=2 after 10 mths. In the group with RTX re-therapy, FOI in PVM mode was the only parameter that presented significant increase (beta 0.40, CI 0.08-0.71; $p=0.013$) – compared to the group without re-therapy. In the prediction model via receiver operating characteristic (ROC) analysis, FOI in PVM reached the highest values of all imaging parameters (phases 1-3, US) at baseline for the prediction of re-therapy over one year with an area under the curve (AUC) of 0.64 (OR 0.9, CI 0.79-1.03), however, without significance ($p=0.117$). Patient's VAS and CRP had similar predictive power with AUC of 0.66 each (each $p=ns$).

Conclusion: The FOI Xiralite[®] in PVM is able to discriminate between groups with and without need for RTX re-therapy better than other included imaging parameters. It is able to predict the need for RTX re-therapy with comparable predictive power to patient's VAS and CRP.

Disclosure: S. Ohrndorf, None; L. Ridha, None; A. M. Glimm, None; G. R. Burmester, None; G. Schmittat, None; M. Backhaus, None; J. Klotsche, None.

Abstract Number: 2210

Effects of Anti-Citrullinated Peptide Antibody (ACPA) on Bone Microstructure in Rheumatoid Arthritis: A HR-pQCT Study

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Session Information

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Background/Purpose: Rheumatoid arthritis (RA) induces systemic osteoporosis as well as osteoporotic change in the bones having arthritis by RA. Recently immune complex and anti-citrullinated peptide antibody (ACPA) in the blood of patients with RA have been reported to promote bone absorption through activating osteoclast directly (Negishi-Koga T. Nat Commun 2015, Harre U. J Clin Invest 2012). Bone absorption by ACPA is mainly observed in the trabecular bone of the cancellous bone (Lundberg K. Ann Rheum Dis 2016). In the present study, we investigated the effects of ACPA on bone microstructure of the distal radius in the patients with RA using high-resolution peripheral quantitative computed tomography (HR-pQCT).

Methods: Subjects were 95 female patients with DMARDs naïve rheumatoid arthritis without bone erosion (N-group) and 14 female patients with primary osteoporosis (OP-group). The N-group was classified into 52 APCA-negative patients (NN-group, 59 ± 2 y.o.) and 43 APCA-positive patients (PN-group, 58 ± 2 y.o.). For subgroup analyses, 29 subjects in NN-group and 14 subjects in PN-group were selected with excluding active synovitis based on the ultrasonographic findings of the wrist and finger joints. All the patients underwent HR-pQCT in Nagoya Rheumatology Clinic. The bone microstructural parameters to be studied were Tt.vBMD (Total volumetric Bone Mineral Density), Ct(Cortical).vBMD, Tb (Trabecular).vBMD, Tb.Meta.vBMD, Tb.Inn (Inner).vBMD, Tb.N (the number of trabecula), Tb.Th (Thickness), Tb.Sp (Separation), Ct.Th (Thickness), Ct.Po (Porosity), and Ct.PoDm (Pore Diameter).

Results: Significant difference ($p < 0.05$) was observed in averaged left and right Ct.Po (cortical porosity) between NN-group (0.006 ± 0.001) and PN-group (0.010 ± 0.001). In NN-group, the parameters negatively correlated with age were Tt.vBMD, Ct.vBMD, Tb.vBMD, Tb.Meta.vBMD, Tb.Inn.vBMD, Tb.N, and Ct.Th, whereas positively correlated parameters were Ct.Po and Ct.PoDm. PN-group differed from NN-group only in that no significant negative correlation was observed in Tb.Inn.vBMD and Tb.N. These results suggested that ACPA affects the number of trabecula beyond the age-related change. The subgroup analyses excluding the effect of active synovitis represented that the difference between left and right Tb.N was significantly larger in PN-group ($0.154 \pm 0.057/\text{mm}$) than in NN-group ($0.070 \pm 0.014/\text{mm}$) and OP-group ($0.056 \pm 0.037/\text{mm}$) ($p < 0.05$). The results mean ACPA have a left-right asymmetrical effect on the trabecular structure in the distal radius without relation to synovitis, while the pathophysiological mechanisms are not clear.

Conclusion: The results suggested that APCA affects trabecular structure in patients with rheumatoid arthritis independent from the activity of synovitis.

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Abstract Number: 2211

Technetium Tc 99m Tilmanocept: A Targeted Immunodiagnostic Radiopharmaceutical for the Assessment of Synovial Macrophage Activity in Rheumatoid Arthritis

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Figure 1. A comparison of Tc 99m tilmanocept imaging in the bilateral hands of a healthy control subject vs. an active RA subject. Imaging was performed at 60 ± 15 minutes and 180 ± 15 minutes post-IV administration of the maximum study dose of 400 μ g tilmanocept radiolabeled with 10 mCi of Tc 99m. No localization was visualized on planar imaging in the healthy control subject. Localization (red circles) to areas of suspected macrophage activity was observed on planar imaging in the bilateral wrists and second MCP of the left hand in the active RA subject. These findings were further observed with greater joint-specific anatomical delineation on SPECT/CT.

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Background/Purpose: Activated macrophages are a critical component of the inflammatory etiology of RA. It is well established that these macrophages perpetuate joint inflammation and destruction through the release of pro-inflammatory cytokines and chemokines, and that a preponderance of these macrophages express the CD206 marker. Tc 99m tilmanocept selectively targets CD206 with high affinity ($K_D = 2.76 \times 10^{-11}$). In this report, we describe planar and SPECT/CT imaging findings from a clinical study examining the safety and efficacy of intravenously (IV) administered Tc99m tilmanocept in subjects with active RA and healthy controls (HC). These results provide significant insight into the longitudinal quantitative immunodiagnostic potential of tilmanocept in the rheumatological space.

Methods: Subjects with active RA were required to have a clinical diagnosis of moderate to severe RA in accordance with the 2010 ACR/EULAR criteria and a DAS28 score of ≥ 3.2 . HC subjects were required to be deemed clinically free of any inflammatory disease. The images in this report were obtained at 60 ± 15 minutes post-IV administration of the maximum study dose of 400 μ g tilmanocept radiolabeled with 10 mCi of Tc99m. Subjects with active RA underwent static planar imaging of the whole body and bilateral hands followed by additional SPECT/CT in areas of increased radiopharmaceutical uptake. HCs underwent static planar imaging of the whole body and bilateral hands only.

Results: Tc 99m tilmanocept was well-tolerated and no drug-related adverse events were observed. Static planar images of joints in active RA subjects demonstrated significant Tc 99m tilmanocept localization to disease-involved joints of the shoulders, knees, hands, and feet. These findings were further interrogated on SPECT/CT, which revealed greater anatomical delineation of localization specifically to the joint space. Whole body and joint-specific static planar imaging in healthy control subjects failed to demonstrate joint-specific localization.

Conclusion: There are currently no FDA-approved functional imaging modalities for the assessment of macrophage-driven arthropathy in patients with clinically diagnosed active RA. The ability to detect synovial macrophage activity from planar and SPECT/CT imaging makes Tc99m tilmanocept a valuable immunodiagnostic agent for the evaluation of joint-specific inflammation, characterization of joint-level pathobiology, and individualization of treatment. Further studies examining the concordance of tilmanocept uptake with CD206-positive synovial macrophages over time may provide valuable, clinically significant insight into the ability to quantitatively monitor treatment response.

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Abstract Number: 2212

Feasibility and Performance of HR-pQCT-Derived Joint Space Width Measurement As Outcome Parameter in Arthropathic Disease – Lessons from Hemochromatosis Arthropathy

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Session Information

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Background/Purpose: High resolution peripheral quantitative computed tomography (HR-pQCT) allows in vivo 3 D imaging of human joint microstructure and joint space width (JSW) at an isotropic resolution of 82µm voxel size. As JSW is regarded a surrogate measure of arthritic disease activity, the HR-pQCT-derived JSW may qualify as an important rheumatologic outcome measure. To date, JSW was reproducibly computed with an ICC of 0.989 in healthy subjects with maintained metacarpophalangeal (MCP) joints. However, data are still lacking on the performance of HR-pQCT-derived JSW measurements in arthropathies with very narrow joint spaces. One of those arthropathies is hemochromatosis arthropathy (HA) which is characterized by excess iron-induced joint destruction and hook-like osteophyte formation. **Objective:** We aimed to determine in patients with HA the 1) feasibility of the HR-pQCT-derived JSW algorithm 2) performance of the JSW-algorithm in this narrow-spaced cohort by assessing failure rates in relation to the corresponding joint space widths 3) JSW cut-off value, below which the JSW algorithm is set to fail and would further require manual re-segmentation.

Methods: MCP of 29 HA patients were imaged on one HR-pQCT system (XtremeCT, Scanco Medical AG). From the images, the mean joint space width (JSW) was semi-automatically computed via an in-house developed and well-validated software as the mean of local 3D widths across the joint space. In case the software failed at the first JSW analysis attempt, each MCP was semi-manually segmented by a trained operator to separate the metacarpal head and phalangeal base and a second JSW-analysis was attempted.

Results: 76.2% of all 84 MCP joint spaces were successfully segmented at the first attempt. 22.6% required semi-manual intervention while in one case the JSW remained undeterminable even after semi-manual correction due to direct contact between the metacarpal and phalangeal bones. MCPs were next subdivided by JSW tertile and failure rates recorded. In MCPs of the lowest tertile software failure rates were highest with 50% failure in MCP2 joints, 44.4% in MCP3 joints, and 22.2% failure rates in MCP4 joints. MCPs ranging in the medium JSW tertile showed 22% (MCP2), 33% (MCP3) and 22% (MCP4) failures rates. Joints with a JSW in highest tertile were all successfully segmentable at the first attempt (0% failure rate). When looking at a JSW-cut-off value, below which the JSW software would fail its segmentation, we observed that in general a mean JSW of <1.4 mm was associated with a high rate of software failure. In MCP 3 and 4 a cut-off of a mean JSW of ≥ 1.41 mm resulted in 100% successfully segmented cases.

Conclusion: Our findings suggest that HR-pQCT-derived JSW quantification in MCP joints is feasible even in arthropathies with known narrow joint spaces such as hemochromatosis arthropathy. Moreover, performance analysis indicated that the software performance seems to be best in the joints belonging to the highest JSW tertile, while joints with a mean JSW of 1.4 mm or smaller seem to fail very likely at the first analysis attempt and do require semi-manual corrections. Further work is needed to assess failure rates in other patient cohorts.

Disclosure: U. Heilmeier, None; A. J. Burghardt, None; P. Kapoor, None; G. Schett, None; R. Voll, None; S. Finzel, None.

Abstract Number: 2213

Usefulness of Shoulder Radiographs to Aid in Determining Need for Advanced Imaging to Detect Operable or Inoperable Full-Thickness Rotator Cuff Tears

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Session Information

Session Date: Tuesday, October 23, 2018

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Table 1

		Type of FTT based on MRI n (% of all FTT)		Type of Surgery Performed		
		rFTT	cFTT	RCR	RTSA	Other
AHI	< 7mm	7 (8%)	19 (22%)	0	6	1
	> 7mm	40 (46%)	21 (24%)	14	5	2
Total n		47 (54%)	40 (46%)	14	11	3

Session Type: ACR Poster Session C

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Background/Purpose: Full-thickness rotator cuff tears (FTT) can be a debilitating cause of shoulder pain and loss of function. Delay in surgical evaluation may result in inoperable changes of the cuff. Advanced imaging involving MRI is often required for diagnosis and provides additional description of the true acuity of the FTT – those with changes of tendon retraction, fatty infiltration, or atrophy are more likely to have a chronic FTT (cFTT) resulting in less successful surgical repair. An acromiohumeral interval (AHI) of < 7mm identified on shoulder x-ray has also been associated with cFTT and less successful surgical treatment. The aim of this study was to determine if x-ray findings of AHI < 7mm was associated with inoperable cFTT in our clinical setting, and could thus be used in place of the more expensive MRI study intriguig initial evaluation of potential FTT into surgical referral vs. medical management.

Methods: Shoulder MRIs performed at the Salt Lake City Veterans Affairs Hospital from March 2017 to March 2018 were identified. Those with a shoulder x-ray within 12 months preceding the MRI were included for review. MRIs were categorized by type of FTT – those potentially repairable without chronic changes (rFTT) and those with changes suggesting inoperability (cFTT). X-rays were then viewed and AHI was calculated. A chi-square analysis was performed on MRI results and AHI > or < 7mm. Finally, charts were reviewed to identify those who received surgical intervention and the type of surgery performed – rotator cuff repair (RCR), reverse total shoulder arthroplasty (RTSA), or other.

Results: 315 shoulder MRIs were identified as having an associated x-ray and included for review. Of those, 87 (28%) had a FTT. Type of FTT and surgery performed are presented in Table 1. There was a significant association between AHI and rFTT or cFTT (chi-square 10.96, p<0.005).

Conclusion: Our findings are consistent with previous reports, where an AHI < 7mm was associated with a FTT that is likely inoperable. Only patients with an AHI > 7mm underwent RCR. We suggest when a FTT is suspected based on clinical exam, the AHI should be measured and if < 7mm, conservative management should be pursued over advanced imaging and surgical referral. This point of triage will hopefully limit unnecessary and expensive imaging where results are unlikely to change initial management, thus improving access to MRI when a delay in care could be detrimental to the patient.

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Abstract Number: 2214

Lung Involvement in Primary Sjögren's Syndrome: Spectrum of Pulmonary Abnormalities and Computed Tomography Findings

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Background/Purpose: Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease that affects exocrine glands. It can generate pulmonary compromise due to dysfunction of the glandular epithelium of the airway. To know the prevalence of pulmonary involvement in patients with pSS in our environment; to detail clinical characteristics associated with pulmonary involvement; to compare demographic, clinical, serological and therapeutic characteristics of patients with and without pulmonary involvement in pSS.

Methods: Retrospective descriptive study. Patients diagnosed with pSS (American-European criteria 2002) were included from 2010 to 2017. Abnormal salivary gland biopsy (SGB) was considered to grades III and IV of the Chisholm and Mason classification. Multivariate analyzes were performed comparing pSS with pulmonary involvement versus pSS without this involvement; $p < 0.05$ value was considered statistically significant. The results were analyzed with the software SPSS 19.0.

Results: 197 patients were included, 180 (90%) were women. The mean age at diagnosis was 54 ± 13.62 years. The most frequent symptoms were xerostomia in 166 (83%) patients and xerophthalmia in 178 (89.0%). In 25 (12.5%) patients, pulmonary involvement was diagnosed by high resolution computed tomography (HRCT), 19 (76%) with interstitial lung disease (ILD) and 6 (24%) with bronchiectasis in the absence of DILD; 21 (10.5%) patients had a history of smoking. The most frequent pattern of ILD was nonspecific interstitial pneumonia (NSIP) in 68.4%, followed by lymphocytic interstitial pneumonia (LIN) and usual interstitial pneumonia (UIP) with 15.78% in both groups. Erythrocyte sedimentation rate (ESR) > 50 mm/h was observed at the time of diagnosis in 26 (13.0%) patients, and elevated C-reactive protein (CRP) in 22 (11.0%), median value of 0.06 (RIQ 0-0.39). Anemia was observed in 14 (7.0%) patients, leukopenia in 16 (8.0%) and hypergammaglobulinemia in 47/81 (58.0%). SGB was abnormal in 179 (89.5%), grade III in 75 (37.5%) and IV in 104 (52.0%). Regarding treatment, 61 (30.5%) received hydroxychloroquine, 56 (28.0%) prednisone < 20 mg / day and only 5 (2.5%) prednisone ≥ 20 mg / day. Three (1.5%) patients died during the 7 years of follow-up. In the univariate analysis, it was observed that patients with pSS and pulmonary involvement were associated with greater age at the time of diagnosis (61 ± 10.75 vs 53 ± 13.7 , $p = 0.004$), smoking history (40% vs 4%, $p < 0.001$); ESR > 50 mm/h at diagnosis (36% vs 9.9%, $p = 0.002$), high CRP (36% vs 7.6%, $p < 0.001$), anemia (20% vs 5.3%; $p = 0.02$), greater use of hydroxychloroquine (60% vs 26.9%, $p = 0.002$) and greater use of prednisone at doses > 20 mg / day (12% vs 1.2%, $p = 0.01$) with respect to patients with pSS without pulmonary involvement. In the multivariate analysis, statistical significance was maintained for smoking (OR: 31, 95% CI: 4.513-212.970, $p < 0.001$) and high CRP (OR: 10.49, 95% CI: 1.609-68.405, $p = 0.014$).

Conclusion: The pulmonary involvement in pSS was mainly associated with a history of smoking and was observed more frequently in older patients, with high inflammatory parameters and anemia.

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Abstract Number: 2215

Evaluation of Left Ventricular Systolic and Diastolic Myocardial Function in Patients with Ankylosing Spondylitis By Speckle-Tracking Echocardiography

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with ankylosing spondylitis (AS) are at increased risk for cardiovascular disease (CVD), although strategies to detect subclinical CVD are poorly characterized. The aim of this study was to assess left ventricular (LV) systolic and diastolic function by speckle tracking echocardiography (STE) to detect subclinical left ventricular

dysfunction in patients with AS without known CVD. We also tested if CVD activity in AS was associated with lower LV systolic function independently of traditional cardiovascular risk factors.

Methods: Two-dimensional, Doppler, tissue Doppler, and STE assessments were performed in 44 patients with AS (Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP) ≥ 1.3), 20 patients with inactive disease (ASDAS-CRP < 1.3), and 26 healthy controls. AS diagnoses fulfilled the modified New York criteria. None of the enrolled patients or healthy individuals had known cardiac disease. LV systolic function was assessed by ejection fraction (EF) and global longitudinal strain (GLS). LV diastolic function was assessed by septal e' , lateral e' , left atrial maximum volume index (LAVI), average E/e' ratio, and peak tricuspid regurgitation velocity.

Results: Mean patient age was 31-35 years with 91-95% males in all groups. The average disease duration for patients with active and inactive AS was 9 years. LV EF was normal in all patients and controls and did not differ between groups ($p \geq 0.43$). GLS was significantly reduced in active AS patients compared with inactive AS patients (21.9 ± 2.02 vs 24.4 ± 2.73 , $p < 0.0001$) and controls (21.9 ± 2.02 vs 24.0 ± 2.00 , $p = 0.0001$). In multivariate analyses, active AS and increasing levels of disease activity by ASDAS-CRP score were associated with lower GLS after adjustment for other covariables that included age, sex, body mass index, systolic blood pressure, and disease duration. Septal e' and lateral e' were decreased in active AS patients compared with controls (9.30 ± 2.08 vs 10.5 ± 1.78 , $p = 0.01$ and 12.9 ± 2.95 vs 14.9 ± 2.91 , $p = 0.007$), respectively, but not inactive AS patients ($p \geq 0.11$). LAVI was not significantly higher in active AS patients versus controls or inactive AS patients ($p \geq 0.10$). The average E/e' ratio was higher in active AS patients compared with controls (8.13 ± 1.97 vs 7.25 ± 1.10 , $p = 0.04$) but not inactive AS patients ($p = 0.27$). GLS, septal e' and lateral e' , LAVI, and average E/e' did not differ between inactive AS and controls ($p \geq 0.49$). Tricuspid regurgitation did not differ among the three groups, and the velocity was far less than 2.8 m/s generally used as the cut-off for diagnosis of LV diastolic dysfunction.

Conclusion: GLS is significant reduced in Active AS patients compared with Inactive AS patients and healthy controls. Active AS is associated with lower LV systolic myocardial function despite normal LV EF. Patients with Active AS may also have impaired left ventricular diastolic function. Speckle tracking echocardiography may be a useful tool for early detection of impaired LV function in patients with AS. Disease activity in AS was associated with lower LV systolic function independently of traditional cardiovascular risk factors.

Disclosure: H. Yang, None; Y. Zhao, None; Y. Liang, None; W. Yan, None; Y. Liu, None; L. Zhang, None; T. Marion, None.

Abstract Number: 2216

Detection of Left Ventricular Regional Function in Primary Sjögren's Syndrome Patients without Cardiac Symptoms, As Assessed By Feature Tracking Cardiac Magnetic Resonance Imaging

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Imaging of Rheumatic Diseases Poster III: Other Modalities

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The risk of major cardiovascular (CV) events and the long-term CV outcome in patients with primary Sjögren's syndrome (pSS) remain unclear. Myocardial disease is typically clinically silent, only manifesting as myocardial dysfunction after an extended preclinical phase. Feature-tracking (FT) cardiac magnetic resonance (CMR) imaging can reliably be used to assess myocardial function in patients with early dysfunction. Left ventricular (LV) global longitudinal peak systolic strain (GLS) is prognostic of adverse cardiovascular outcomes in various patient populations. Global circumferential peak systolic strain (GCS) is a predictor of congestive heart failure. We sought to measure GLS and GCS using FT-CMR in pSS patients without cardiac symptoms. Furthermore, we aimed to evaluate the association of GLS and GCS with pSS status and severity.

Methods: pSS patients without cardiac symptoms were enrolled. Patients and with no history and/or clinical findings of systemic or pulmonary hypertension, coronary artery disease, valvular heart disease, atrial fibrillation, diabetes mellitus, or dyslipidemia underwent non-contrast CMR. Disease activity was assessed using the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI). Minor salivary gland biopsy was documented in 85% of patients. Salivary gland biopsy data were classified using the focus score (FS). All subjects underwent evaluation of LV regional function, as measured by FT-CMR. GLS and GCS were calculated in the 16 segments of the whole LV. Group comparisons were made using the Wilcoxon rank sum test, Fisher's exact test, and t-test where appropriate.

Results: We compared 52 patients with pSS (100% women; mean age, 53.2±9.6 years). A total of 11 patients (21%) had Raynaud's phenomenon (RP). The mean of ESSDAI was 2.5±2.6. The GCS in the RP positive group and FS≥2 group decreased more than that in the RP negative group and FS<2 group (p=0.009, p=0.008, respectively). The GCS tended to decrease in the ESSDAI≥4 group compared to the ESSDAI<4 group (p=0.057). Receiver operating characteristic curve analysis showed that GCS reliably detected RP and FS≥2 (area under the curve, 0.75 and 0.72, respectively). GCS in the pSS group was not associated with CV risk factors or other pSS status. GLS in the pSS group was not associated with CV risk factors or pSS status such as RP, FS, ESSDAI.

Conclusion: To our knowledge, this is the first prospective study of LV regional function in pSS and the only study to explore the associations of pSS characteristics with CMR-assessed GCS and GLS. We suggest that RP, FS≥2 and ESSDAI≥4 may predict LV regional dysfunction observed in patients with pSS without cardiac symptoms. We should consider the possibility of subclinical regional function in patients with pSS, even in those with low scores for FS or ESSDAI.

Disclosure: A. Nishiwaki, None; N. Ikumi, None; H. Kobayashi, None; Y. Kobayashi, None; I. Yokoe, None; Y. Nagasawa, None; K. Sugiyama, None; T. Nozaki, None; M. Iwata, None; N. Kitamura, None; M. Takei, None.

Abstract Number: 2217

Clinical Characteristics of Early Onset Gout in Outpatient Setting

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: There has been an increase in the prevalence of gout over the past two decades, with increasing number of patients presenting at younger age. The clinical characteristics, including comorbidities, concomitant medications, treatment compliance and outcome, have been described in patients with gout, although few studies are available in patients with early onset gout.

Methods: We retrospectively reviewed 327 patients (≥18 years of age) with a diagnosis of gout from 2008 to 2016 using the database of a multispecialty group practice in New England. Patients with ≥ 2 diagnosis of gout per ICD10 code (M10.*) or ICD-9 code (274.xx) recorded on ≥ 2 dates, or 1 diagnosis of gout and ≥ 1 pharmacy prescription of gout-related medications were identified. Patients were classified into age first diagnosed < 30(Group 1), age 30-40 (Group 2) and age >40 (Group 3). All charts of patients with age ≤ 40 by the index date were reviewed, with exclusion of those who did not meet the 2015 ACR/EULAR gout classification criteria or without adequate information. Then, we randomly selected and reviewed 100 out of 7216 patients from Group 3. Clinical characteristics and treatment were compared among the three groups.

Results: We identified 87 patients in Group 1 and 140 patients in Group 2. Patients within Group 1 had significantly higher male/female ratio, body mass index and uric acid level at the time of diagnosis (Table 1). Positive family history of gout was more frequently identified in Group 1. While the prevalence of cardiovascular risk factors was higher in elderly patients, the proportion of patients with hypertension and hyperlipidemia was unexpectedly high within Group 1 (41.4% and 48.3%, respectively). The X-rays of peripheral joints available at the time of gout diagnosis exhibited degenerative changes in 24-47% of patients in different age groups; while erosive changes consistent with gout were found only in few patients. The majority of patients in Group 1 fulfilled the 2012 ACR guidelines for initiating urate lowering therapy (ULT) on the basis of frequency of gout attacks, shown in Table 2. The majority of patients in Group 3 fulfilled the 2012 ACR guidelines for ULT on the basis of chronic kidney disease.

Table 1. Clinical characteristics.

	Group 1 (N=87)	Group 2 (N=140)	Group 3 (N=100)	P ₁ (Group1 vs 3)	P ₂ (Group1 vs 2)	P ₃ (Group2 vs 3)
Male, n (%)	86/87 (98.9)	136/140 (97.1)	71/100 (71.0)	<0.001	0.652	<0.001
Rheumatology consult, n (%)	34/87 (39.1)	44/140 (31.4)	49/100 (49.0)	0.187	0.253	0.007
BMI (baseline)	34.6±7.2	33.6±7.5	31.5±6.1	0.002	0.145	0.042
Age of gout diagnosis, mean±sd	26.1±3.1	34.7±2.5	60.9±11.9	<0.001	<0.001	<0.001
UA at gout diagnosis, mean±sd	9.2±1.5	8.4±1.3	8.4±1.6	0.001	<0.001	0.848
Serum uric acid >8, n (%)	75/87 (86.2)	100/136 (73.5)	73/99 (73.7)	0.045	0.030	1.000
Alcohol use, n (%)	44/87 (50.6)	68/140 (48.6)	48/100 (48.0)	0.770	0.786	1.000
Diuretic use, n (%)	6/87 (6.9)	16/140 (11.4)	64/100 (64.0)	<0.001	0.357	<0.001
Low dose aspirin*, n (%)	2/87 (2.3)	4/140 (3.6)	40/100 (40.0)	<0.001	0.711	<0.001
Family history of gout, n (%)	26/87 (29.9)	20/140 (14.3)	11/100 (11.0)	0.002	0.006	0.559
Baseline X-ray findings, n (%)						
DJD changes	15/48 (31.3)	19/81 (23.5)	30/64 (46.9)	0.120	0.409	0.004
Erosive changes	0/48 (0)	3/81 (3.7)	2/64 (3.1)	0.506	0.294	1.000
Crystal proven gout, n (%)	14/87 (16.1)	15/140 (10.7)	6/100 (6.0)	0.033	0.306	0.250
Comorbidities, n (%)						
CAD	2/87 (2.3)	2/140 (1.4)	35/100 (35.0)	<0.001	0.639	<0.001
Hypertension	36/87 (41.4)	58/140 (41.4)	93/100 (93.0)	<0.001	1.000	<0.001
Hyperlipidemia	42/87 (48.3)	65/140 (46.4)	90/100 (90.0)	<0.001	0.891	<0.001
Diabetes	14/87 (16.1)	14/140 (10.0)	44/100 (44.0)	<0.001	0.214	<0.001

*Aspirin 81mg daily

P₁ results from comparison between Group 1 and Group 3.P₂ results from comparison between Group 1 and Group 2.P₃ results from comparison between Group 2 and Group 3.

BMI, body mass index, UA, uric acid, DJD, degenerative joint diseases, CAD, coronary artery disease

Table 2. Treatment

	Group 1 (N=87)	Group 2 (N=140)	Group 3 (N=100)	P ₁ (Group1 vs 3)	P ₂ (Group1 vs 2)	P ₃ (Group2 vs 3)
Indicated for U.L.T by 2012 ACR guidelines, n (%)	64/87 (73.6)	67/140 (47.9)	76/100 (76.0)	0.497	<0.001	<0.001
Flare >2/year	60/87 (69.0)	51/140 (36.6)	42/100 (42.0)	<0.001	<0.001	0.805
Tuple	9/87 (10.3)	4/140 (2.9)	0/100 (0.0)	0.007	0.035	0.000
CKD (≥ CKD stage 2)	4/87 (4.6)	7/140 (5.0)	88/100 (88.0)	<0.001	1.000	<0.001
Kidney stones	2/87 (2.3)	8/140 (5.7)	8/100 (8.0)	0.308	0.324	0.001
U.L.T prescribed, n (%)	64/87 (73.6)	66/140 (47.3)	66/100 (66.0)	0.271	<0.001	0.012
Prophylaxis prescribed, n (%)	30/80 (37.5)	38/63 (59.6)	88/83 (106.2)	0.275	1.000	0.288
Treat-to-target achieved, n (%)	20/64 (31.3)	23/66 (34.8)	28/65 (43.1)	0.639	0.854	0.066

P₁ results from comparison between Group 1 and Group 3.P₂ results from comparison between Group 1 and Group 2.P₃ results from comparison between Group 2 and Group 3.

U.L.T, urate lowering therapy, CKD, chronic kidney disease

Conclusion: In our population, patients aged ≤ 40 were less likely to achieve target uric acid levels than older patients. In addition, patients with early onset gout frequently have cardiovascular risk factors. Clinicians should be aware that patients with early onset gout may be an undertreated population at increased risk for recurrent gout and cardiovascular diseases.

Disclosure: Y. Li, None; P. Piranavan, None; D. Sundaresan, None; R. A. Yood, None.

Abstract Number: 2218

Use of Anakinra in Hospitalized Patients with Acute Crystalline Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:: Medically complex individuals may have contraindications to standard therapies for acute arthritis secondary to gout or calcium pyrophosphate disease (CPPD). Observational studies have demonstrated the rapid efficacy of the IL-1 receptor antagonist, anakinra, on acute arthritis attacks. In this retrospective observational study, we demonstrate the efficacy and safety of anakinra in medically complex, hospitalized patients with acute gout and CPPD arthritis.

Methods: Adult patients treated with anakinra during their admissions from 2014-2017 at two hospitals were identified for inclusion. Charts were reviewed for demographics, comorbidities, serum uric acid level, joint involvement, prior treatment, anakinra dosing, response, and adverse effects, concurrent infections, and surgical interventions. Response to anakinra treatment was determined from review of provider documentation, as well as recorded pain scores on a numeric scale.

Results: We identified 100 individuals accounting for 115 episodes of arthritis. This population was 82% male, with an average age of 60 years. Comorbidities included renal disease (45%) and history of organ transplantation (14%). Twenty-six episodes of arthritis occurred in the perioperative setting. Concurrent infection was present in 29 episodes. Joint involvement was monoarticular in 43 episodes, oligoarticular in 56, and polyarticular in 15; one episode presented as a systemic inflammatory response alone. The most commonly involved joints were the knee, ankle, wrist, first metatarsal-phalangeal joint, elbow, and fingers. Eighty-four episodes of arthritis had partial or complete response to anakinra within four days of treatment initiation; 66 episodes had partial or complete response within one day of anakinra administration. There was only a partial response in seven episodes and no response in six. There was insufficient information to determine the response in 14 episodes. Side effects included three instances of leukopenia.

Conclusion: This is the largest observational study of anakinra use in the inpatient setting for the acute treatment of gout or CPPD arthritis. We demonstrated a rapid response to anakinra, with 75% of episodes significantly improving or completely resolving within four days of the first dose. Overall, anakinra was well tolerated. This data supports the use of this biologic agent even in individuals with infections, as well as perioperative individuals, and immuno suppressed transplant recipients

Disclosure: J. Liew, None; G. Gardner, None.

Abstract Number: 2219

Safety, Pharmacokinetics and Pharmacodynamics of NC-2500, a Novel Xanthine Oxidoreductase Inhibitor, in Healthy Volunteers

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Session Information

Session Date: Tuesday, October 23, 2018

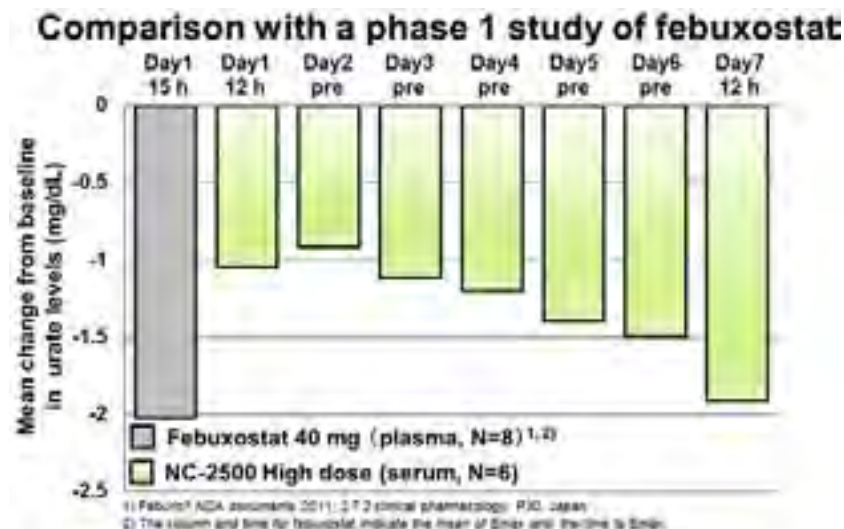
Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Gout flare due to rapid urate reduction after initiating urate-lowering therapy (ULT) is one of the major issues in the therapy. International guidelines recommend anti-inflammatory prophylaxis for gout flares during the initiation of ULT and colchicine is widely used. However, colchicine is potentially toxic and caution is advised. In addition, a recent study in Japan suggests stepwise dose increase of febuxostat from 10 to 20 then 40 mg/day is better than fixed-dose febuxostat 40 mg/day and is comparable with colchicine prophylaxis for the prevention of gout flares¹, though the dosage of febuxostat in the US is 40 and 80 mg/day. NC-2500 is a novel potent XOR inhibitor and preclinical studies have shown that multiple doses increase the plasma concentration and enhance the urate-lowering effect of NC-2500 unlike febuxostat. This study aimed to assess the safety, tolerability, pharmacokinetics and pharmacodynamics (PD) profiles of NC-2500 in healthy volunteers.

Methods: A Phase 1, randomized, single-blind, placebo-controlled, single and multiple ascending dose study was conducted. Each cohort consisted of 8 subjects, with 6 receiving NC-2500 and 2 receiving placebo orally. A total of 5 cohorts were studied in the single-dose study (10 mg to 160 mg, fasted conditions) and 4 cohorts were studied in the



multiple-dose study (10 mg to 80 mg, fed conditions). The levels of NC-2500 and uric acid in plasma/serum and urine were assayed at predetermined time points. Safety and tolerability were assessed by physical examination, vital signs, electrocardiography, clinical laboratory tests and adverse events (AEs).

Results: The maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) increased dose-dependently in the single and multiple dose studies. The time to reach the C_{max} was approximately 2.0–3.0 hours for single dose and 3.0–5.0 hours for repeated doses. Following repeated dose, plasma concentrations of NC-2500 increased (AUC 1.4-fold and C_{max} 1.5-fold at a maximum) in comparison with the first dose. NC-2500 was hardly excreted into the urine. The serum uric acid (sUA) levels were reduced after single and repeated administrations of NC-2500. Moreover, in repeated doses, the sUA levels decreased to a target range gradually over the 7 days. The incidence of AEs was similar between NC-2500 and placebo treatments and all AEs were mild in severity.

Conclusion: NC-2500 is expected to have potential to resolve the issues of current ULT by its unique PD profiles. As for safety, NC-2500 was considered safe and well-tolerated. Furthermore, NC-2500 was hardly excreted through the kidneys, which can be a favorable profile for patients with renal impairment, frequently observed in gout.

References: 1.Yamanaka et al. Ann Rheum Dis 2018.

Disclosure: M. Hirano, Nippon Chemiphar Co., Ltd., 3; S. Kobayashi, Nippon Chemiphar Co., Ltd., 3; E. Miyayama, Nippon Chemiphar Co., Ltd., 3; T. Ohta, Nippon Chemiphar Co., Ltd., 3; M. Yamamoto, Nippon Chemiphar Co., Ltd., 3; T. Yamakawa, Nippon Chemiphar Co., Ltd., 3.

Abstract Number: 2220

Gout, Flares and Allopurinol Use: A Population Based Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Gout flares may often be self-managed, but there is a paucity of population-based data. The aim of this study was to determine the prevalence of self-reported gout and gout flares, the use of urate-lowering therapy, and the association of gout flares with health-related quality of life (HRQoL) in a large community sample.

Flares	Proportion (%)	SF12 PCS	Effect size	p-val
None	58 (50,66)	45 (43,47)	base	
1	17 (12,24)	42 (38,46)	-3 (-7,2)	0.29
>= 2	25 (18,32)	38 (34,42)	-7 (-11,-2)	0.003
Joint p-val				0.012

Methods: The South Australian Health Omnibus Survey is an annual, face-to-face population-based survey. Data collected in the 2017 survey (n = 2977; 65.3% participation rate) included self-reported medically diagnosed gout, allopurinol use (current, previous, never), the number of gout attacks (flares) in the last 12 months, age, gender, body mass index (BMI), relevant comorbidities, socioeconomic status (Index of Relative Socioeconomic Advantage and Disadvantage score, IRSAD) and HRQoL (SF-12). Allopurinol use was used to determine urate-lowering therapy, as this is mandated first line therapy in Australia. Data were weighted to the Australian Bureau of Statistics 2016 census data to reflect the South Australian population. Only participants 25 years and over (n = 2778) were included in the analysis.

Results: The prevalence of self-reported gout was 6.5% (95% CI: 5.5, 7.5), and was more frequent in males, older age, higher BMI, or lower IRSAD groups (p<0.05 in all cases). There was a higher prevalence of ischaemic heart disease (24%), diabetes mellitus (33%), hypertension (54%) and high cholesterol (40%) among participants with gout than amongst those without gout. Only diabetes remained associated after adjustment for sociodemographic variables (p <0.001).

Amongst gout participants, 37.1% (95% CI 29.6, 45.3) reported currently using allopurinol, while 23.2% (95% CI 16.9, 21.0) reported prior use (38% discontinuation rate). Females were less likely to have ever used allopurinol (p = 0.002) and more likely to have discontinued it (p = 0.029).

Frequent flares (defined as >=2 in the last year) were reported by 25% of participants with gout, but only 51% of this group reported current allopurinol use. Frequent gout flares were also more likely with younger age, higher BMI, or current allopurinol use (p<0.05 in all cases). The frequency of gout flares was associated with a lower physical HRQoL (Table 1).

Conclusion: This is the first study to investigate gout flares using a population-based sample. A quarter of gout participants reported frequent gout flares that were associated with reduced physical HRQoL. Current allopurinol use was associated with frequent gout flares, suggesting undertreated disease and suboptimal use of the drug. Determining predictors of flares and ineffective allopurinol use may identify means of improving treatment and reducing flares. Table 1: HRQoL (SF12) physical component score (PCS) by the frequency of flares among participants with gout, adjusted for sociodemographic variables. Brackets enclose 95% confidence intervals.

Disclosure: C. Proudman, None; S. Lester, None; D. Gonzalez-Chica, None; T. Gill, None; N. Dalbeth, Horizon, 5, Kowa, 5, Amgen Inc., 2, AstraZeneca/Ironwood, 2, AbbVie Inc., 8, Pfizer, Inc., 8, Janssen, 8; C. Hill, None.

Abstract Number: 2221

Systematic Genetic Analysis of Early-Onset Gout: ABCG2 141K Is the Strongest Predictor

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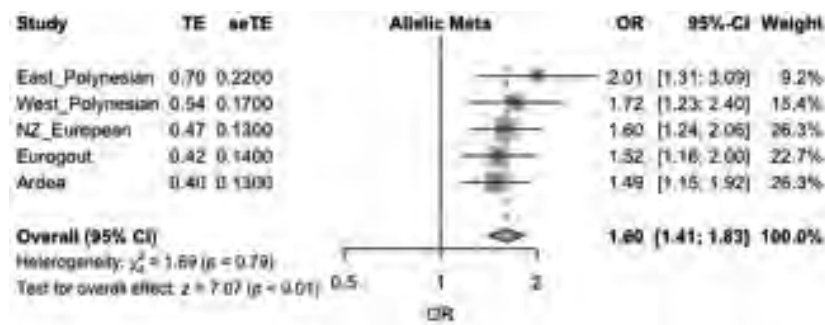
Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM



Background/Purpose: Although increasing age is an important risk factor for development of gout, disease can develop in younger people. The aim of this study was to determine the genetic features of people with early onset gout.

Methods: Participants (n=1,648) with gout according to the 1977 American Rheumatism Association (ARA) classification criteria were recruited from primary and secondary care into the Genetics of Gout in Aotearoa / New Zealand study. All participants had a detailed clinical assessment which included recording of age of onset of first gout presentation. The 10 single nucleotide polymorphisms (SNPs) most strongly associated with serum urate (Köttgen et al, Nature Genetics 2013) were genotyped by the Illumina CoreExome microarray platform. Early onset gout was defined as first presentation before the age of 40 years, consistent with the EULAR gout management guidelines (Richette et al, Ann RheumDis 2017). Genetic associations were also tested in two replication cohorts: Eurogout (n=704) and Ardea clinical trial programme (n=755).

Results:: In the Genetics of Gout in Aotearoa study, there were 712 (43.2%) participants with first gout presentation before 40 years of age. Mean (SD) age of onset was 29 (7) years in the early onset group, and 55 (11) years in the late onset group. In the early onset group, there were significantly more men, higher gout flare frequency, and more tophaceous disease compared with the late onset group. Analysis of the serum urate-associated SNPs, stratified by ancestry, demonstrated no significant associations, with the exception of *ABCG2* rs2231142; the presence of *ABCG2* 141K was associated with early onset gout in participants of Eastern Polynesian ancestry (P=0.002), West Polynesian ancestry (P=0.004) and European ancestry (P<0.001). The association with *ABCG2* 141K persisted after adjustment for sex, highest ever serum urate, tophus, gout flare frequency, serum creatinine and body mass index. Analysis of the replication cohorts confirmed association of early onset gout with *ABCG2*rs2231142 (Figure), but not other serum urate-associated SNPs. Compared with no risk alleles, the meta-analysed odds ratio (95% CI) for *ABCG2* 141K heterozygosity (1 risk allele) was 1.49 (1.27-1.75) and for homozygosity (2 risk alleles) was 2.85 (2.01-4.05).

Conclusion: People with early onset gout have more severe clinical features of disease. In contrast to other serum urate-associated SNPs, *ABCG2* 141K is strongly associated with early onset of gout.

Figure. Forest plot showing association between early onset gout and *ABCG2*. Figure shows meta-analysed allelic odds ratio (95% CI).

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Abstract Number: 2222

Construct Validity of Provisional Remission Criteria for Gout: A Dual Energy CT Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Background/Purpose: Provisional domains and definitions for gout remission criteria have been proposed using consensus methodology (de Lautour et al, Arthritis Care Res 2016). These criteria include 5 domains: serum urate, tophus, flares, pain due to gout, and patient global assessment (Table). Dual energy CT (DECT) is an advanced imaging technique that allows color coding and volumetric measurement of urate crystal deposition. The aim of this study was to test the construct validity of the provisional remission criteria by examining the association of each domain and the full remission criteria with DECT urate crystal deposition.

Methods: Patients with gout on allopurinol ≥ 300 mg daily for at least 3 months were prospectively recruited into a multicenter DECT study, using monitored enrollment to include approximately 25% of patients with subcutaneous tophi and 50% with serum urate < 6.0 mg/dL. Participants all fulfilled the 1977 ARA gout classification criteria, and attended a standardized study visit, which recorded gout flare frequency in the preceding 12 months, physical examination for tophus, serum urate, and patient questionnaires. DECT of both hands/wrists, feet/ankles/Achilles, and knees were performed using the second-generation Siemens 128-slice Definition Dual Source scanner, and urate crystal volume was measured by 2 DECT radiologists. The relationship between the DECT urate crystal volume and deposition with each domain as well as with the full remission criteria set (all 5 domains achieved) was analyzed.

Results: With the exception of the pain domain, participants fulfilling each remission domain had lower DECT urate crystal volume than those who did not fulfil the domain (Table). All 5 remission domains were achieved in 23/152 (15.1%) participants. Of those fulfilling the provisional remission criteria, 10/23 (43.5%) had DECT urate crystal deposition, compared with 95/129 (73.6%) of those not fulfilling their mission criteria ($P < 0.001$). The median (range) DECT urate crystal volume was 0.00 (0.00-0.46) cm^3 for those fulfilling the remission criteria, compared with 0.08 (0.00-19.53) cm^3 for those not fulfilling the criteria ($P = 0.002$). In multivariate linear regression (of ranked DECT crystal volume data) and logistic regression models including all 5 remission domains, the serum urate and tophus domains were independently associated with the DECT urate crystal volume and deposition.

Conclusion: In people with gout taking allopurinol, a state of remission defined by the provisional remission criteria is associated with lower DECT urate crystal deposition. Furthermore, those domains most directly related to monosodium urate crystal pathophysiology (serum urate and tophus) are independently associated with urate crystal deposition measured by DECT. Overall, these findings support the construct validity of the provisional gout remission criteria.

Table. DECT crystal volume (cm^3) according to each remission domain and provisional remission criteria. Data are presented as median (range). Results of Mann-Whitney U test analysis are shown.

Domain (definition)	Fulfilled	Not fulfilled	P
Serum urate (< 0.36 mmol/L)	0.03 (0.00-4.63) n=77	0.09 (0.00-19.53) n=75	0.016
Tophus (absence)	0.05 (0.00-1.23) n=104	0.21 (0.00-19.53) n=48	0.001
Flares (none in the last 12 months)	0.05 (0.00-2.57) n=70	0.11 (0.00-19.53) n=82	0.011
Pain due to gout (< 2)	0.07 (0.00-5.11) n=104	0.08 (0.00-19.53) n=48	0.43
Patient global assessment of gout activity (< 2)	0.05 (0.00-3.34) n=84	0.11 (0.00-19.53) n=68	0.002
Remission criteria (all 5 domains achieved)	0.00 (0.00-0.46) n=23	0.08 (0.00-19.53) n=129	0.002

Disclosure: N. Dalbeth, Horizon, 5, Kowa, 5, Amgen Inc., 2, AstraZeneca/Ironwood, 2, AbbVie Inc., 8, Pfizer, Inc., 8, Janssen, 8; C. Frampton, None; M. Fung, Ardea Biosciences, 3; S. Baumgartner, Ardea Biosciences, 3; S. Nicolaou, Siemens, 9; H. K. Choi, Takeda, Selecta, Kowa, and Horizon, 5, Selecta and Horizon, 2.

Abstract Number: 2223

Proton Pump Inhibitors and Risk of Calcium Pyrophosphate Deposition (CPPD) in a Population-Based Study

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Session Information

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Session Type: ACR Poster Session C

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Background/Purpose: There are no therapies available that specifically target CPPD, with treatment limited to symptomatic management. Hypomagnesemia is a recognized risk factor for CPPD, and its treatment has been advocated for CPPD management. Proton pump inhibitors (PPIs) are an under-appreciated cause of hypomagnesemia, and may therefore be an important risk factor for CPPD. We examined the relation of PPI use to the development of CPPD.

Methods: We conducted a time-stratified propensity score(PS)-matched cohort study in The Health Improvement Network (THIN), a general practitioner (GP) EMR database representative of the UK population. Using greedy matching, we matched incident PPI users to incident H2 blocker users by PS (see table) to reduce confounding by indication in 1-year cohort accrual blocks to account for secular trends. We identified incident cases of individuals diagnosed with pseudo gout or chondrocalcinosis (hereafter labelled CPPD) using READ codes from 1995-2015 among those aged 50-89 who were enrolled in a GP practice for ≥ 1 year prior to study entry. We excluded subjects with a gout diagnosis. We compared the risk of incident CPPD among incident PPI users vs. incident users of H2 blockers using Cox proportional hazard models, censoring at time of drug switch, additionally adjusting for the PS model variables. Because of the small number of cases, we also conducted a nested case-control study within the same cohort, matched 1:4 by age and gender using risk-set sampling, evaluating incident use of PPI vs. non-use and vs. H2-blockers prior to incident CPPD.

Results: We identified 81,011 PPI initiators, who were PS-matched 1:1 to H2 blocker initiators, with mean age 66, mean BMI 26.7, 59% female. Overall, covariates were well-balanced in the two groups (SMDs <0.1). There were 118 and 58 incident cases of CPPD among the PPI and H2 blocker initiators, respectively. Incident PPI use was associated with a HR of 1.19 (95% CI 0.86-1.64) of incident CPPD compared with incident H2 blocker use. In the case-control study, when comparing PPI initiators to non-users, the adjusted OR was 1.58 (95% CI 1.39-1.79). When also considering H2 blocker use, the adjusted ORs were elevated for both PPI and H2 blocker users compared with non-users (ORs 1.79 and 1.52, respectively (see Table)); the ratio of ORs for PPI:H2 blocker initiators was similar to PS-matched study HR (ratio of ORs ~ 1.2 ; HR was ~ 1.2).

Conclusion: In this population-based study of GP-recorded CPPD, compared with incident H2 blocker use, incident use of PPIs was associated with a modest but nonsignificant increased risk of CPPD. We were limited by small number of cases. The elevated risk with H2 blocker use may represent residual confounding (e.g., NSAID with gastroprotective use for undiagnosed CPPD) or potentially a true biologic effect, e.g., due to general gastric acid suppression affecting Mg absorption. Nonetheless, the risk appears higher with PPIs than H2 blockers.

PS-matched cohort study:	PPI initiators		H2 Blockers initiators
Subjects (n)	81011		81011
Incident CPPD	118		58
Total Follow-Up Time (person-years (PY))	528978		327609
Mean Follow-up Time (years)	6.53		4.04
Incidence Rate (per 1000 PY)	0.22		0.18
PS-matched HR	1.21 (95% CI 0.88, 1.67)		
PS-matched HR, additionally adjusting for PS model covariates*	1.19 (95% CI 0.86, 1.64)		
Case-control study** 1:	CPPD cases		Controls
PPI initiators	873		2495
Non-users	1163		5649
Adjusted OR	1.57 (95% CI 1.39, 1.79)		
Case-control study** 2:	CPPD cases	Controls	Adjusted OR (95% CI)
PPI initiators	562	1514	1.79 (1.54, 2.07)
H2 blocker initiators	75	237	1.52 (1.14, 2.03)
PPI and H2 blocker initiators	164	491	1.53 (1.22, 1.93)
Non-users	985	4902	1.0 (referent)

* PS model covariates: age, sex, BMI, CKD, CHF, diabetes, GERD, peptic ulcer disease, hyperparathyroidism, hypertension, osteoarthritis, alcohol use, diuretics (thiazide, loop, K-sparing)

** Case-control studies were adjusted for the same variables as in the PS model, except for age and sex, which were matched. Case-control study #1 was additionally adjusted for H2 blocker use.

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Interactions between Serum Urate-Associated Genetic Variants and Sex on Gout Risk in a European Population

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Session Information

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Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

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Session Time: 9:00AM-11:00AM

Background/Purpose: Sex-specific differences in the effect size of genetic variants on serum urate levels have been described, with *SLC2A9* variants having a greater influence on serum urate in women and *ABCG2* variants exerting a greater effect in men. However, it is unclear whether serum urate-associated genetic variants display sex-specific differences in gout risk. The aim of this study was to systematically examine whether serumurate-associated genetic variants differ in their influence on gout risk in men and women.

Methods: This research was conducted using the UK Biobank Resource. Participants of European ethnicity, aged 40-69 years, and with genome-wide genotypes were included. Exclusions were: self-reported sex mismatch with genetic sex, genotyping quality control failure, and related individuals. Gout was defined using a validated definition (self-report of gout or urate-lowering therapy use). The thirty single nucleotide polymorphisms (SNPs) associated with serum urate reported by Köttgen et al (Nature Genetics 2013) were tested for their association with gout in men and women. Gene-sex interactions on gout risk were analysed using logistic regression models that included an interaction term. Age, body mass index, renal failure and diuretic use were included as variables in all models. A further sensitivity analysis was performed by excluding pre-menopausal women. Data are reported at experiment-wide significance ($P < 0.0017$).

Results: Data were available for 359,876 participants, including 7,342 gout cases (2.0%). Gout was present in 6768 (4.1%) men and 574(0.3%) women; odds ratio (95% CI) for men 13.42 (12.32-14.62) compared to women. In the group overall, association of gout at experiment-wide significance was observed for 22 of the 30 serum urate-associated SNPs tested. In men, experiment-wide association was observed for the same 22 SNPs, and in women for four of the 30 SNPs. Evidence for gene-sex interaction was observed for *ABCG2* (rs2231142) and *PDZK1* (rs1471633), with the interaction at *PDZK1* driven by an absence of effect in women and at *ABCG2* by an amplified effect in men (Table). Similar findings were observed in the sensitivity analysis when excluding pre-menopausal women. For the other SNPs tested, including *SLC2A9* (Table), no significant gene-sex interactions were observed.

Conclusion: In a European population, *ABCG2* and *PDZK1* gene-sex interactions exist for gout risk, with serum urate-raising alleles exerting a greater influence on gout risk in men than in women. In contrast, other serum urate-associated variants including *SLC2A9*, do not demonstrate significant gene-sex interactions for gout risk.

Table: Association and interaction between selected serum urate-associated genetic variants and sex for gout risk according to risk allele presence.

Gene	SNP	Serum urate raising allele	Women		Men		Gene-sex interaction* P
			Risk allele absent Referent OR	Risk allele present OR (95% CI)	Risk allele absent OR (95% CI)	Risk allele present OR (95% CI)	
<i>ABCG2</i>	rs2231142	T	1	1.62 (1.35-1.94)	11.99 (10.81-13.30)	28.65 (25.73-31.90)	4.59×10^{-5}
<i>PDZK1</i>	rs1471633	A	1	0.92 (0.77-1.10)	10.54 (9.00-12.34)	13.61 (11.69-15.85)	3.67×10^{-4}
<i>SLC2A9</i>	rs12498742	A	1	4.13 (2.05-8.30)	18.09 (8.85-36.98)	55.62 (27.78-111.37)	0.42

Abbreviations: CI, confidence interval; OR, odds ratio. * Adjusted for body mass index, age, renal failure, diuretic use.

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Exploring the Relationship between Gout and Diffuse Idiopathic Skeletal Hyperostosis (DISH): An Epidemiologic and Genetic Study

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Session Information

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Session Time: 9:00AM-11:00AM

Background/Purpose: Gout has been reported to be a risk factor for development of diffuse idiopathic skeletal hyperostosis (DISH), a condition characterized by abnormal bone formation of the soft tissues affecting the spine and also peripheral skeleton. However, it is unknown whether gout has a direct effect on development of DISH or whether this association occurs due to shared risk factors, such as raised body mass index or other features of the metabolic syndrome. The aim of this study was to determine whether gout has a direct effect on the development of DISH.

Methods: Participants in the Genetics of Gout in Aotearoa Study with lateral chest or thoracic spine radiographs were included in this analysis. All participants in this analysis were 30 years or older at the time of the imaging test. Each radiograph was scored for the presence of DISH by a trained rheumatologist or musculoskeletal radiologist. For the purposes of this analysis, DISH was defined as definite and probable DISH, according to the criteria of Ustinger et al, 1985. Participants with imaging features of spondyloarthropathy; spondylosis with osteophytes bridging 2 consecutive vertebrae; or features of DISH and another pathology (primarily disc space narrowing) were not included in the analysis. Genotypes were available for the two major gout-associated single nucleotide polymorphisms (SNPs); *ABCG2* rs2231142 and *SLC2A9*rs734553. Genome-wide genotype data generated on the Illumina CoreExome platform were used to estimate the heritability of DISH using the Genome-wide Complex Trait Analysis (GCTA) tool with prevalence estimates of 41% in Māori and Pacific people and 22% in European (Bateman et al 2018). Clinical and genetic associations with DISH were analysed by logistic regression adjusted by age at recruitment, age at the time of the imaging test, sex and, as appropriate, by metabolic co-morbidity.

Results: The analysis included 816 participants, including 535 (65.6%) with gout. DISH was present in 205/816 (25.1%) of all participants, including 138/453 (30.5%) of those of Polynesian ancestry (Māori or Pacific people) and 67/363 (18.5%) participants of European ancestry. DISH was present in 155/535 (29.0%) participants with gout, and 50/281 (17.8%) participants without gout; unadjusted odds ratio (95% CI) 1.85 (1.29-2.65), $P=7.6 \times 10^{-4}$. However, after adjusting for body mass index, DISH was not associated with gout; adjusted odds ratio (95% CI) 1.28 (0.86-1.91), $P=0.22$. Consistent with this, no association was observed between DISH and the gout-associated *ABCG2* and *SLC2A9* SNPs ($P>0.52$ for all comparisons). The heritability (percent variance in phenotype explained by the genome-wide genotype data) was estimated to be 0.37 (se=0.56) in people of Polynesian ancestry and 0.24 (se=2.1) in people of European ancestry.

Conclusion: DISH is more common in people with gout. Although DISH does demonstrate a heritable component, genetic analysis does not support the hypothesis that gout is causal for DISH. The relationship between gout and DISH is likely due to shared risk factors, particularly raised body mass index and other features of the metabolic syndrome.

Disclosure: M. Corkill, None; R. Topless, None; A. Worthington, None; R. Mitchell, None; K. Gregory, None; L. K. Stamp, Amgen Inc., 8; M. Brown, None; T. R. Merriman, None; N. Dalbeth, Horizon, 5, Kowa, 5, Amgen Inc., 2, AstraZeneca/Ironwood, 2, AbbVie Inc., 8, Pfizer, Inc., 8, Janssen, 8.

Gout and the Risk of Incident Dementia in the Elderly: A Medicare Claims Study

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Session Information

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Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The pursuit of a link between gout/hyperuricemia and dementia has led to contradictory results. Most observational studies, including population-based studies, showed that hyperuricemia was associated with a higher risk of dementia and less cognitive dysfunction, while a few studies found hyperuricemia to be associated with a lower risk of dementia. Recently, a large French population-based study in the elderly (65 years or older) showed that hyperuricemia was associated with a higher risk of dementia and with MRI changes of aging in the brain. Our objective was to assess whether gout in the elderly is associated with a risk of incident dementia.

Methods: We used the 5% Medicare claims data for this observational cohort study. We used multivariable-adjusted Cox proportional hazard models to assess the association of gout with incident dementia, adjusting for potential confounders/covariates including demographics (age, race, gender), comorbidities (Charlson-Romano comorbidity index), and medications commonly used for cardiac diseases (statins, beta-blockers, diuretics, and angiotensin converting enzyme (ACE)-inhibitors) and gout (allopurinol and febuxostat).

Results: In our cohort of 1.71 million Medicare beneficiaries, 111,656 had incident dementia. The crude incidence rates in people without and with gout were 10.9 and 17.9 per 1,000 person-years, respectively. In multivariable-adjusted analyses, gout was independently associated with a significantly higher hazard ratio of incident dementia, with a hazard ratio [HR] of 1.15 (95% CI, 1.12,1.18); sensitivity analyses confirmed the main findings. Compared to age 65 to <75 years, older age groups were associated with 3.5 and 7.8-fold higher hazards of dementia; hazards were also higher for females, Black race or people with higher medical comorbidity.

Subgroup analyses indicated that gout was significantly associated with dementia in patients without key comorbidities (CAD, hyperlipidemia, CVD, diabetes, hypertension) with HR ranging 1.19-1.52, but not in patients with each of these comorbidities, except CAD, with HR 0.99-1.04 (**Table 1**).

Table 1. Association of gout with incident dementia, in pre-defined subgroups by the presence/absence of CAD, hyperlipidemia, CVD, diabetes or hypertension

	Multivariable-adjusted (Model 1)		Multivariable-adjusted (Model 1)	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Gout	No CAD 1.19 (1.15, 1.24)	<.0001	CAD 1.04 (0.99, 1.09)	0.14
Gout	No Hyperlipidemia 1.28 (1.23, 1.33)	<.0001	Hyperlipidemia 1.02 (0.98, 1.07)	0.26
Gout	No CVD 1.19 (1.15, 1.22)	<.0001	CVD 1.00 (0.94, 1.07)	0.99
Gout	No Diabetes 1.23 (1.19, 1.27)	<.0001	Diabetes 0.99 (0.95, 1.05)	0.81
Gout	No Hypertension 1.52 (1.43, 1.60)	<.0001	Hypertension 1.01 (0.97, 1.04)	0.68

Gout*CAD p-value <0.0001; Gout*hyperlipidemia p-value <0.0001; Gout*CVD p-value <0.0001;

Gout*diabetes p-value <0.0001; Gout*hypertension p-value <0.0001.

Conclusion: Gout was independently associated with 17-20% higher risk of incident dementia in the elderly. Future studies need to understand the pathogenic pathways involved in this increased risk.

Disclosure: J. A. Singh, Takeda, Savient, 2,Savient, Takeda, Regeneron, Merz, Iroko, Bioiberica, Crealta/Horizon and Allergan pharmaceuticals, WebMD, UBM LLC, Medscape, Fidia pharmaceuticals and the American College of Rheumatology, 5; J. Cleveland, None.

What Should be the Goals of Gout Therapy? a Patient Perspective

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Session Information

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Background/Purpose: In the absence of any available current evidence, our primary objective was to assess the goals of gout treatment from a patient perspective and secondary objective was to examine any differences by sex.

Methods: A convenience sample of consecutive patients with doctor-diagnosed gout seen at a community-based outpatient clinic were invited at the University of Alabama at Birmingham. All groups answered the key question: What should be the goals of gout treatment? Sex-stratified nominal groups were conducted until saturation was achieved. Responses were collected verbatim, discussed and rank-ordered by each participant.

Results: Thirty-six patients with doctor-diagnosed gout participated in 12 nominal groups, six male only, five female only and one group with both. Mean age was 61.9 years (SD,12.3), mean gout duration was 13.3 years (SD, 12.5), 53% were men, 64% African-American, 42% retired, 47% currently married, 87% were using either allopurinol and/or febuxostat, and 40% had had no gout flares in the last 6 months. Nominal group participants brought up several ideas that mapped to 9 key concepts, which are briefly described in the section below (**Table 1**). The top five treatment goals accounted for 91% of all votes and included: (1) Prevent and better manage flare-ups and improve function (25%); (2) Eliminate flare-ups/disease remission(30%); (3) Diet and activity modification/Lifestyle change (13%); (4) Patient education and public awareness (12%); and (5) Medication management and minimization of side effects (11%). When examining the top-rated concern for each nominal group, the first two goals were nominated by four groups each, diet/activity modification and medication management by 1 group each, and patient education by 3 groups. There were no differences evident by sex in top-ranked treatment goal.

Conclusion: People with gout identified and rank-ordered treatment goals relevant to them. Providers of gout care need to be cognizant of these goals. Disease management concordant with these treatment goals might lead to a more satisfied, informed patient. Clinical trialists should consider inclusion of these outcomes in gout domains due to their relevance to patients with gout.

Table 1. Number of nominal groups with relative ranking of each major theme/concept

	Male groups (n=6)	Female groups (n=5)	All groups (n=12*)	Male groups (n=6)	Female groups (n=5)
	Top theme/concept			Among top 3 themes	
A. Prevent and better manage flare-ups and improve function	2	2	4	4	3
B. Eliminate flare-ups/remission	2	2	4	3	3
C. Diet and activity modification/Lifestyle change	1	0	1	4	2
D. Patient education and public awareness	1	1	3*	2	2
E. Medication management and minimization of side effects	1	0	1	2	2
F. Lowering the serum urate/uric acid	0	0	0	2	1
G. Need for additional Healthcare services	0	0	0	1	1
H. Address the emotional burden of flare-ups	0	0	0	1	0
I. Comorbidity management	0	0	0	1	0

* Included one group with mixed population of both men and women.

Total exceeds possible sum, when there was a more than one major theme/concept tied for the top theme or among the top three themes.

Disclosure: J. A. Singh, Takeda, Savient, 2,Savient, Takeda, Regeneron, Merz, Iroko, Bioiberica, Crealta/Horizon and Allergan pharmaceuticals, WebMD, UBM LLC, Medscape, Fidia pharmaceuticals and the American College of Rheumatology, 5;

A Validated Script Concordance Test Demonstrates Interdisciplinary Differences in Clinical Decision-Making When Using Allopurinol to Treat Gout in Chronic Kidney Disease

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Background/Purpose: The safety of allopurinol in the setting of chronic kidney disease (CKD) has been a controversial issue for many years. The perceived increased risk of adverse reactions has made many providers hesitant to use allopurinol in the setting of CKD, leading to inadequate control of this highly prevalent malady. Rheumatologists are generally thought to endorse higher doses of allopurinol in CKD than nephrologists. As there is much overlap between the gout and CKD patient populations, this may lead to conflicting messages regarding allopurinol safety and dosing, which may threaten adherence to urate-lowering therapy. These differences may reflect an educational need or areas where improved communication between providers is important.

A script concordance test (SCT) for gout developed by Siaton et al has demonstrated evidence of validity including high reliability (Cronbach's alpha = 0.93), large effect size (Cohen's d = 0.90), and generalizability for use across multiple institutions and learner groups.^{1,2} This study aimed to use the SCT to explore differences between academic nephrologists and rheumatologists regarding the use of allopurinol in the setting of gout and CKD.

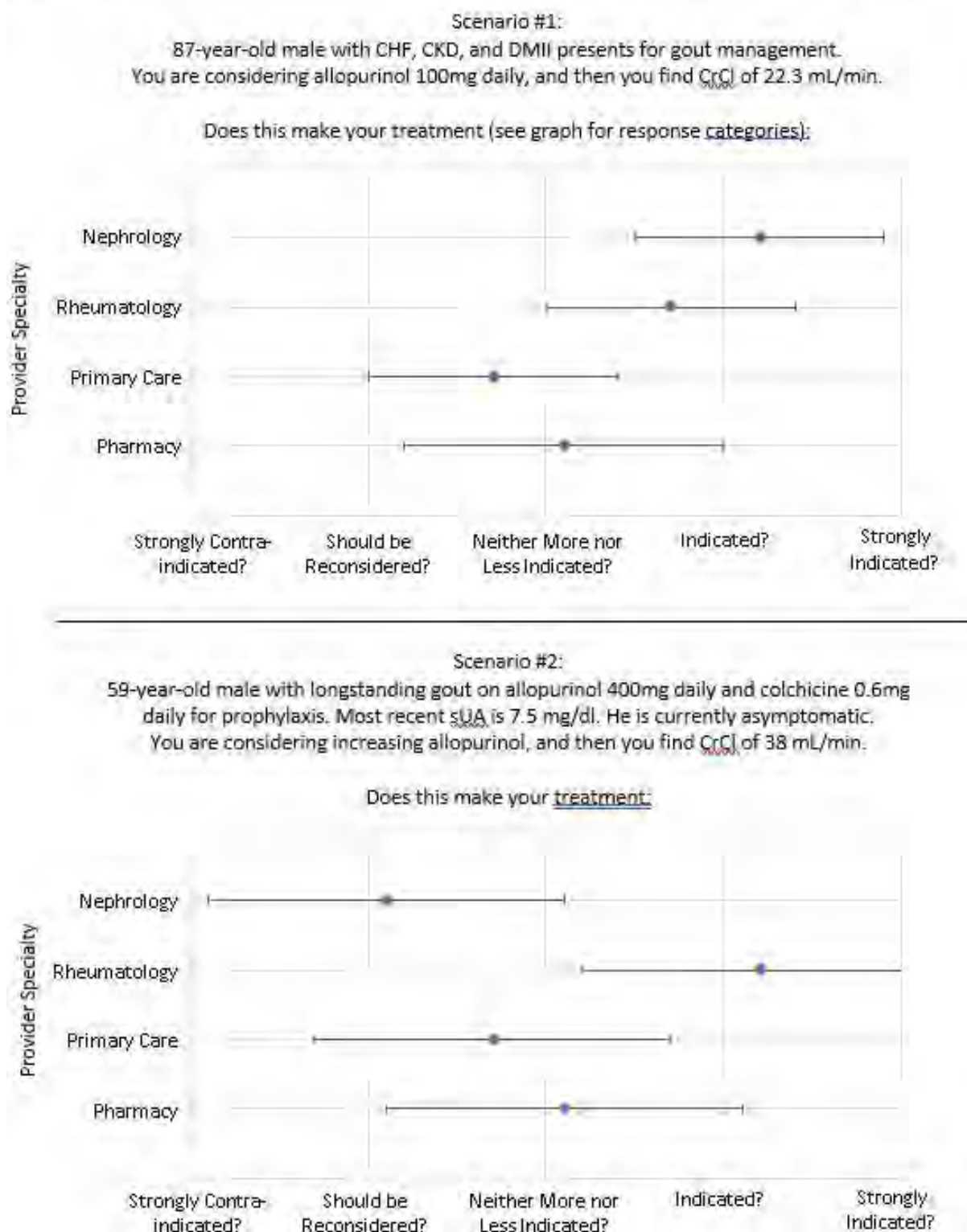
Methods: Using the REDCap online platform, questions from the SCT relevant to the treatment of gout with allopurinol in the setting of CKD were sent via e-mail to attending nephrologists, rheumatologists, primary care providers, and pharmacists associated with training programs of University of Utah. With Excel, response rates were calculated, descriptive statistics were analyzed, and significance of differences in mean responses between specialty groups were examined using 2-tailed Student's t-test.

Results: To date, 38 responses (29%) have been received; details are presented in the Table below:

Specialty	Surveys Sent	Total Responses (Rate)	Rank				
			Instructor	Assistant Professor	Associate Professor	Professor	Other
Nephrology	30	9 (30%)	1	4	1	3	0
Rheumatology	16	10 (63%)	0	3	5	1	1
Primary Care	30	10 (33%)	3	5	1	0	1
Pharmacy	53	9 (17%)	0	0	2	0	7
Total	129	38 (29%)	4	12	9	4	9

Conclusion: Nephrologists were more willing than rheumatologists to start allopurinol at a relatively high dose in CKD (100 mg daily), but were less likely to increase allopurinol to achieve a serum uric acid (sUA) target. This highlights what may be a fundamental disagreement on the mechanism and timing of allopurinol toxicity and the importance of achieving sUA target, where rheumatologists believe it is more dangerous when first being initiated, and nephrologists are less concerned about achieving target sUA in CKD.

Figure 1. Means and Standard Deviations of Responses, Divided for Each Specialty Group



References: 1. SiatonBC, Clayton E, Kueider AM, Rietschel M. *Arthritis Rheumatol.* 2016; 68(suppl 10).
2. SiatonBC, Barker A, Battistone MJ. *Arthritis Rheumatol.* 2017;69(suppl 10)

Disclosure: N. Lebedoff, None; S. Gilligan, None; A. Barker, None; C. L. Koenig, None; K. Starman, None; C. Gallop, None; B. C. Siaton, None; K. L. Raphael, None; M. J. Battistone, ABIM Rheumatology Exam Committee, 9.

Can We Predict Inadequate Response to Allopurinol Dose Escalation? Analysis of a Randomized Controlled Trial

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

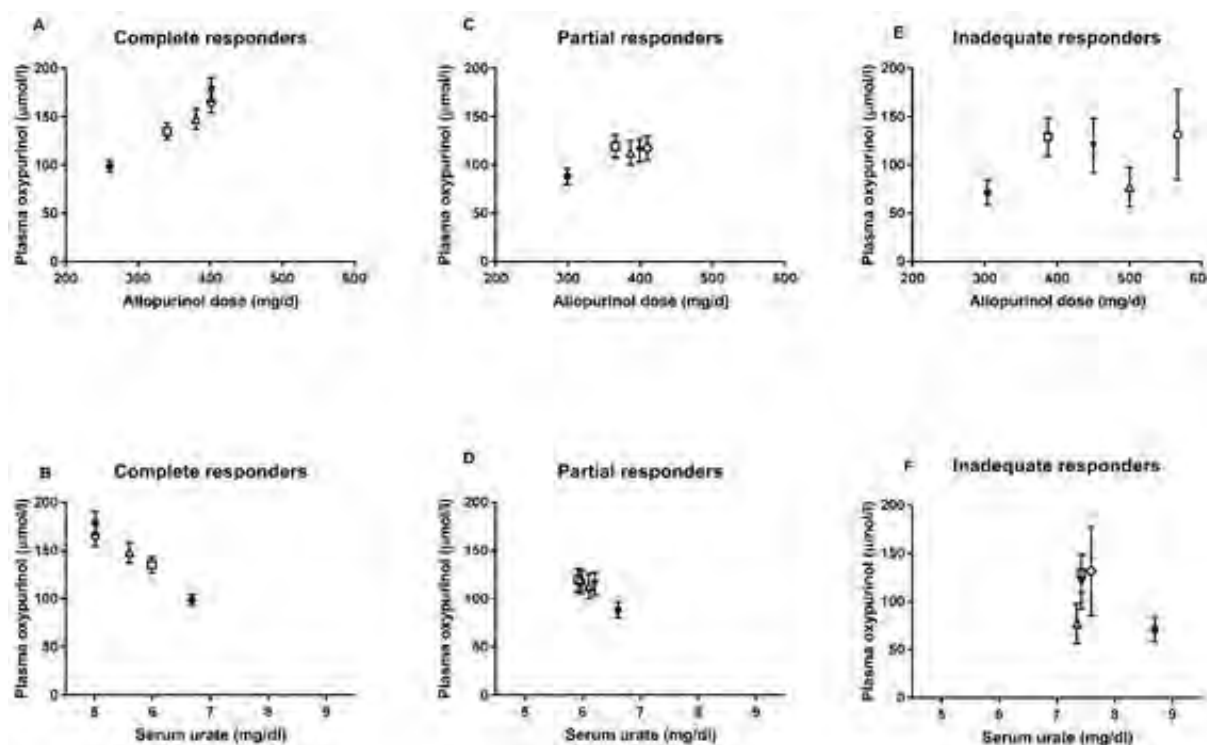
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The two most common causes of inadequate serum urate (SU) lowering with allopurinol are low adherence and under-dosing. Those who are adherent, but do not reach target SU despite allopurinol dose escalation, could be considered to have “inadequate response” to allopurinol. The aim of this study was to investigate the reasons for not reaching target SU and to identify factors that predict response and inadequate response in a randomised controlled trial of allopurinol dose escalation in gout.

Methods: We analysed data from participants in a 24-month open, randomized, controlled, parallel-group, comparative clinical trial. Participants undergoing allopurinol dose escalation were classified as having: *complete response* (CR) –reached target SU at month 9 and 12 of the dose escalation phase **OR** if still dose escalating at month 9 reached target SU by month 12; *partial response* (PR) – reached target at some stage but not fulfilling criteria for CR; or *inadequate response* (IR) – did not reach target SU at anytime. The analysis was designed to minimise the effects of two common causes of inadequate response; low adherence and under-dosing.

Results: Inadequate response was uncommon, occurring in 13/150 (8.7%), compared to 82 (54.7%) CR, and 55 (36.6%) PR. Mean (SEM) SU was higher at the end of the 12-month dose escalation in the IR group compared with both CR and PR groups; 7.6 (0.31) vs. 5.01 (0.06) and 5.97 (0.17) mg/dl respectively ($p<0.001$). There was a relatively linear relationship between increasing allopurinol dose and increasing plasma oxypurinol and between increasing plasma oxypurinol and decreasing SU in the CR group (Figure A and B) over the 12-month dose escalation period. Those with partial response had more static dose and SU levels that were close to the target SU while those with inadequate response had no obvious



relationship between allopurinol dose, plasma oxypurinol and SU (Figure C-E). Using ROC curve analysis, baseline $SU \geq 8\text{mg/dl}$ had a sensitivity of 69.2% and specificity of 85.1% in predicting inadequate response. The OR for an inadequate response if baseline $SU \geq 8\text{mg/dl}$ was 11.7 (95%CI 3.3-41.2). For those with baseline $SU \geq 8\text{mg/dl}$ and baseline allopurinol dose $>200\text{mg/d}$, 7/15 (47%) had an inadequate response.

Conclusion: A minority of people with gout never reach target SU when allopurinol dose is increased in a treat-to-target manner. Approximately half of those with $SU \geq 8\text{mg/dl}$ despite allopurinol $>200\text{mg/d}$ have an inadequate response to dose escalation.

Figure: Relationship between mean allopurinol dose and mean (SEM) plasma oxypurinol and mean serum urate and mean (SEM) plasma oxypurinol in the complete response, partial response, and inadequate response groups at months 0 (●), 3 (□), 6 (Δ), 9 (▼) and 12 (○) of the dose escalation period.

Disclosure: L. K. Stamp, Amgen Inc., 8; P. T. Chapman, None; M. Barclay, None; A. Horne, None; C. Frampton, None; P. Tan, None; J. Drake, None; N. Dalbeth, Horizon, 5, Kowa, 5, Amgen Inc., 2, AstraZeneca/Ironwood, 2, AbbVie Inc., 8, Pfizer, Inc., 8, Janssen, 8.

Abstract Number: 2230

Serum Urate Levels in People with Gout on Dialysis – Are We Achieving Treatment Targets?

Estella Yeo¹, Suetonia Palmer², Peter T. Chapman³, Christopher Frampton⁴ and Lisa K. Stamp⁴, ¹Canterbury District Health Board, Christchurch, New Zealand, ²University of Otago, Christchurch, Christchurch, New Zealand, ³Christchurch Hospital, Christchurch, New Zealand, ⁴University of Otago, Christchurch, New Zealand

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

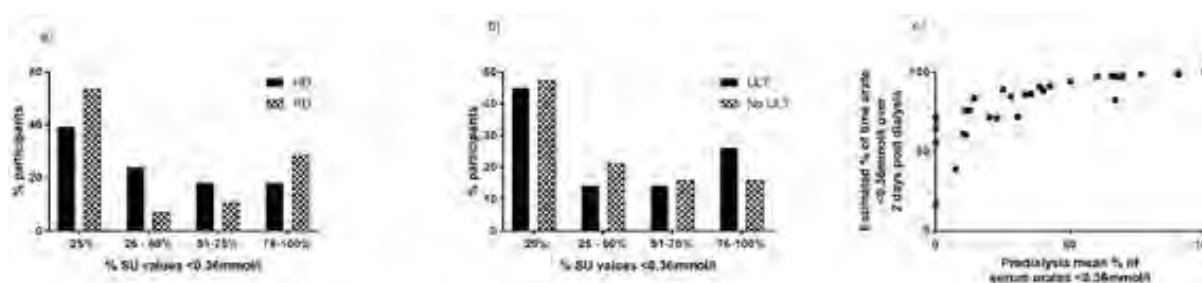
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To explore the number of patients on haemodialysis (HD) or peritoneal dialysis (PD) with gout in Canterbury and to determine how many were receiving urate lowering therapy (ULT) and achieving target serum urate (SU).

Methods: Individuals with gout in Canterbury receiving dialysis for at least 90 days on 1st February 2017, 1st January 2016 and 1st January 2015 were identified. Pre-dialysis SU was recorded and SU levels for two days immediately post dialysis were estimated. These estimates were then used to estimate the percentage time serum urate was $<0.36\text{mmol/l}$ using linear interpolation. Results were compared between those on ULT and not on ULT.

Results: 61/216 (28.8%) dialysis patients had gout. Mean age was 61 years (23-84), 46/61 (75.4%) were male and 37/61 (60.7%) were European. 33/61 (54%) were receiving HD. 42/61 (68.9%) were receiving ULT, all allopurinol with a mean (SD) dose of $116.0 \pm 66.9\text{mg/d}$. A total of 936 pre-dialysis serum urate values were available from the 61 people with gout with a median (range) number of tests per participant of 15 (3-42). 46% of participants had a pre-dialysis $SU <0.36\text{mmol/l}$ on less than 25% of occasions and 23% of participants were below target SU on 76-100% of occasions (Figure). There was no significant differences between those receiving HD and PD (median 35.3% vs. 20.0% $p=0.39$) and between those taking ULT and those not on ULT (median 34.5% vs. 27.8% $p=0.55$) in terms of %pre-dialysis urate below target (figure). The mean reduction in SU 24 and 48 hours post HD were 41% and 12% respectively as calculated from the previous study. The percentage time SU was below target two days post HD was only 41%, with no difference in those on or off ULT (43% vs 36%; $p=0.55$).



Conclusion: Gout is a common disease affecting ¼ dialysis patients in Canterbury. The majority of our study patients were receiving ULT with allopurinol. Dialysis alone is insufficient to lower SU and the use of ULT should be considered in those who remain above target SU using a treat to target SU approach.

Figure1:a) Percentage time at target in a) HD vs PD, b) on and off ULT and c) post HD

Disclosure: E. Yeo, None; S. Palmer, None; P. T. Chapman, None; C. Frampton, None; L. K. Stamp, Amgen Inc., 8.

Abstract Number: 2231

An Ancestral-Specific Interaction of TRIM46 with a Past-History of Smoking May Influence Gout Risk

Niamh Fanning¹, Tony R. Merriman², Amanda Phipps-Green², John Pearson³, Ruth Topless², Murray Cadzow², Douglas White⁴, Nicola Dalbeth⁵ and **Lisa K. Stamp**⁶, ¹Medicine, University of Otago, Christchurch, Christchurch, New Zealand, ²University of Otago, Dunedin, New Zealand, ³University of Otago, Christchurch, Christchurch, New Zealand, ⁴Department of Rheumatology, Waikato Clinical School, Hamilton, New Zealand, ⁵University of Auckland, Auckland, New Zealand, ⁶University of Otago, Christchurch, New Zealand

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Gout is caused by an interplay of genetic and environmental factors. Epidemiological and prospective studies suggest that current-smoking may be protective for developing gout and that smoking cessation may increase risk, although there are conflicting data. The aim of this study was to identify interactions between smoking, genes and the risk of gout.

Methods: New Zealand (NZ) East and West Polynesian and European people with (n=582) or without gout (n=645) genotyped at 10 loci, were compared with 349,748 Europeans from the UK Biobank. The 10 loci were urate-transporter genes (*SLC2A9*, *ABCG2*, *SLC22A11*, *SLC22A12*, *SLC17A1*), gout-associated genes encoding apolipoproteins (*APOA1* and *APOC3*), and loci previously shown to interact with smoking and serum urate (*GCKR*, *TRIM46* and *HNF4G*). Gout was defined by ACR criteria or by self-report and urate-lowering therapy use. Current- and ex-smokers were each compared to never-smokers. The interaction effect on gout between risk allele count and smoking was modelled at each loci and for each population, adjusted for age, gender, alcohol and BMI. Odds ratios (OR) and 95% confidence intervals were calculated. NZ populations were analyzed separately, and combined by meta-analysis, adjusting for genetic admixture using the first 10 principal components generated from genome-wide genotype data. A Bonferroni corrected $p < 0.005$ was used.

Results: An association between ex-smoker status and increased prevalence of gout was observed in NZ [$OR_{meta}=1.61$ (1.21-2.15), $p=0.001$] and UK Biobank [$OR=1.22$ (1.16-1.29), $p=2.2 \times 10^{-14}$] datasets. No association was observed in current-smokers. The only statistically significant interaction between genotype and smoking on gout risk was between ex-smoker status and *rs11264341-TRIM46* C allele in NZ East and West Polynesians [Interaction $OR_{meta}=0.38$ (0.19-0.75), $p=0.0049$], but not in NZ Europeans ($p=0.63$) or the UK Biobank ($p=0.21$). Meta-analysis of *rs11264341-TRIM46* genotype-stratified East and West Polynesian datasets suggests that the risk of gout is higher in ex-smokers without the C allele [$OR_{meta}=4.20$ (1.72-10.26), $p=0.002$] relative to never-smokers without the C allele, but not significantly different in never- or ex-smokers with the C allele [$OR=1.20$ (0.66-2.21), $p=0.55$; and 1.89 [0.92-3.88], $p=0.08$, respectively]. No gout-associated loci interactions were observed for pooled current- and ex-smokers compared to never smokers in the NZ dataset. Interactions influencing gout observed in the UK Biobank dataset were for current smoking with *rs2231142-ABCG2* and *rs670-APOA1* [Interaction $OR=1.17$ (1.00-1.36), $p=0.04$ and 0.79 (0.66-0.95), $p=0.01$, respectively], however these were not significant following Bonferroni correction.

Conclusion: We demonstrate that ex-smokers have higher prevalence of gout than people who have never smoked, and an ancestry-specific interaction between ex-smoker status and *TRIM46* in New Zealanders of Polynesian ancestry. It is unclear how *TRIM46*, a regulator of axonal microtubule organization and neuron polarity, influences risk of gout. There was little evidence of genetic interaction of the loci assessed with smoking and gout.

Disclosure: N. Fanning, None; T. R. Merriman, None; A. Phipps-Green, None; J. Pearson, None; R. Topless, None; M. Cadzow, None; D. White, None; N. Dalbeth, Horizon, 5,Kowa, 5,Amgen Inc., 2,AstraZeneca/Ironwood, 2,AbbVie Inc., 8, Pfizer, Inc., 8,Janssen, 8; L. K. Stamp, Amgen Inc., 8.

Abstract Number: 2232

Prevalence of Gout in the Surviving U.S. Solid Organ Transplant Population

Mark D. Brigham¹, Thilan Tudor¹, Gavin Miyasato¹, Jeffrey D. Kent², Brian LaMoreaux³ and Brian F. Mandell⁴, ¹Trinity Partners, Waltham, MA, ²Medical Affairs, Horizon Pharma USA, Inc, Lake Forest, IL, ³Horizon Pharma USA, Inc, Lake Forest, IL, ⁴Rheumatology, Cleveland Clinic, Cleveland, OH

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Although incidence and survival are frequent topics within the solid organ transplant (SOT) literature, there are no recent publications on the total size of the surviving SOT population. Existing studies of gout in SOT have focused on the incident SOT population. This analysis was performed to characterize the prevalent SOT population and the prevalence of gout within it.

Methods: 2017 U.S. population sizes of kidney, heart, liver, and lung recipients were estimated by combining Organ Procurement and Transplantation Network (OPTN) primary transplant cohort sizes (1988-2017) with previously published survival rates for each annual cohort's time since transplant (0-29 yrs), adjusted for recent improvements in 1-5 yr survival. Gout among prevalent SOT patients was assessed via 2 administrative claims databases: Medicare Fee-For-Service Limited Data Set (5% sample) and a commercial claims sample (IQVIATM Real-World Data Adjudicated Claims – US). Definitions used were – SOT: a claim with an SOT procedure code OR any claim with a history of SOT status code; Gout: ≥ 1 claim with any gout diagnosis code. Total gout prevalence was calculated by weighting Medicare and commercially insured patient estimates by OPTN payer distribution.

Results: 637,231 U.S. patients received a primary kidney (393,953), liver (142,186), heart (66,637), or lung (34,455) transplant between 1988 and 2017. An estimated 355,000 (55.8%) recipients were alive in 2017, comprising 233,000 kidney, 78,700 liver, 29,300 heart, and 14,700 lung recipients. Gout was identified in 11% of prevalent SOT patients in 2016. Higher rates of gout were seen in kidney (13%) and heart (13%) recipients compared to liver (6.4%) and lung (5.3%) recipients ($p < 0.0001$ in both datasets).

Conclusion: Hundreds of thousands of U.S. patients are living with an organ transplant today and these numbers are likely to increase. Within the SOT clinical picture, gout is a frequent co-morbidity of which physicians should be aware. This study suggests a markedly higher rate of gout for the most common SOT types (11%) compared to established rates reported for the general population (e.g. 3.9%). Kidney and heart recipients, with the highest rates of gout, bear much of this disease burden.

Disclosure: M. D. Brigham, Horizon Pharma, 2; T. Tudor, Horizon Pharma, 2; G. Miyasato, Horizon Pharma, 2; J. D. Kent, Horizon Pharma, 3; B. LaMoreaux, Horizon Pharma, 3; B. F. Mandell, Horizon Pharma, 2, 5.

Abstract Number: 2233

Activation and Deficiency of Circulating Mucosal-Associated Invariant T Cells in Patients with Gouty Arthritis

Yong-Wook Park¹, Young-Nan Cho², Hye-Mi Jin¹ and Seung-Jung Kee³, ¹Rheumatology, Chonnam National University Medical School and Hospital, Gwangju, Korea, Republic of (South), ²Rheumatology, Chonnam National University Medical School and Hospital, Gwangju, MN, Korea, Republic of (South), ³Laboratory Medicine, Chonnam National University Medical School and Hospital, Gwangju, Korea, Republic of (South)

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Mucosal-associated invariant T (MAIT) cells contribute to protection against certain microorganism infections and play an important role in mucosal immunity. Upon antigen recognition, MAIT cells rapidly produce Th1/

Th17 cytokines, including interferon (IFN)- γ , tumor necrosis factor (TNF)- α , and interleukin (IL)-17, in an innate-like manner. MAIT cells are known to play important roles in autoimmunity, infectious diseases and cancers. In addition, severe MAIT cell abnormalities are seen in patients with metabolic disorders (e.g., obesity and type 2 diabetes), suggesting a potential role in these disorders. However, little is known about the role of MAIT cells in gouty arthritis. Here, we examined the level and function of MAIT cells in patients with gouty arthritis.

Methods: The study cohort was composed of 60 patients with gouty arthritis (10 acute gout, 25 intercritical gout, and 25 chronic gout), 11 hyperuricemia subjects, and 30 healthy controls. MAIT cell, cytokine, CD69, programmed death-1 (PD-1), and lymphocyte-activation gene 3 (LAG-3) levels were measured by flow cytometry. In addition, peripheral blood mononuclear cells (PBMCs) were cultured *in vitro* with MSU crystals, and CD69, PD-1, and LAG-3 expression was assessed by flow cytometry.

Results: Circulating MAIT cell levels were significantly reduced in patients with acute, intercritical and chronic gout, but their capacities for IFN- γ , IL-17, or TNF- α production were preserved. Notably, expressions of CD69, PD-1, or LAG-3 in MAIT cells were found to be elevated in patients with gouty arthritis as compared with healthy controls. Freshly isolated PBMCs from healthy donor subjects were stimulated with MSU crystals. MSU crystals induced the expressions of CD69, PD-1, and LAG-3 in MAIT cells. In addition, MAIT cell levels were significantly higher in synovial fluid than in peripheral blood of gouty arthritis patients, suggesting accumulation of MAIT cells in the synovial fluid of gouty arthritis patients.

Conclusion: This study demonstrates that circulating MAIT cells are activated, numerically deficient in gouty arthritis patients. In addition, circulating MAIT cell deficiency in gouty arthritis patients is related to accumulation into synovial fluid. These findings suggest that MAIT cells play an important role in gouty arthritis.

Disclosure: Y. W. Park, None; Y. N. Cho, None; H. M. Jin, None; S. J. Kee, None.

Abstract Number: 2234

Liver Safety of Febuxostat Compared with Allopurinol in Gout Patients with Fatty Liver Disease

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Although febuxostat has been widely used for lowering uric acid levels because of its renal safety compared with allopurinol, data on the hepatic safety of febuxostat is limited. Therefore, the purpose of this study was to investigate the hepatotoxicity of febuxostat compared with allopurinol in gout patients with fatty liver disease and the clinical factors associated with hepatotoxicity.

Methods: This study involved gout patients exposed to allopurinol or febuxostat and diagnosed with fatty liver based on liver ultrasonography or CT. Hepatotoxicity was defined as follows: (1) elevation of aspartate transaminase (AST)/alanine transaminase (ALT) at least 3 times the upper normal limit for subjects with normal AST/ALT at baseline and (2) doubling of the baseline AST/ALT for subjects with elevated AST/ALT at baseline. The factors associated with hepatotoxicity were evaluated by Cox regression analysis.

Results: Of 134 gout patients with fatty liver disease, 32 patients (23.9%) received febuxostat, and 102 patients (76.1%) received allopurinol. There was no significant difference in the age, BMI, comorbidity, or fatty liver disease severity between patients taking febuxostat and those taking allopurinol. However, the incidence of hepatotoxicity was significantly lower in the febuxostat group than in the allopurinol group (3/32 (9.4%) vs. 36/102 (35.3%), $p = 0.005$). In multivariate analysis, diabetes (HR: 3.549, 95% CI: 1.374–9.165, $p = 0.009$) and the use of colchicine (HR: 9.122, 95% CI: 4.601–18.084, $p < 0.001$) were associated with hepatotoxicity. In contrast, the use of febuxostat was associated with a lower risk of hepatotoxicity (HR: 0.282, 95% CI: 0.086–0.926, $p = 0.037$).

Conclusion: Febuxostat was well tolerated in gout patients with fatty liver disease in terms of hepatotoxicity. Diabetes and the use of colchicine seem to be important factors related to the risk of hepatotoxicity.

Disclosure: J. S. Lee, None; S. Hong, None; J. Won, None; O. C. Kwon, None; J. S. Oh, None; Y. G. Kim, None; C. K. Lee, None; B. Yoo, None.

Abstract Number: 2235

Monosodium Urate Deposition Distribution in the Knees, Hands, and Feet of Treated Gout Patients: A Dual-Energy CT Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

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Background/Purpose: Prior studies have demonstrated that monosodium urate (MSU) deposits on dual-energy CT (DECT) are commonly found in joints as well as tendons of the feet and ankles of gout patients. However, no study has systematically evaluated the prevalence of MSU deposition in other joints or tendons, particularly in the knee joints. The aim of this study was to determine the prevalence of MSU deposition among multiple sites in the knees, feet/ankles, and hands/wrists among gout patients treated with urate-lowering therapy (ULT).

Methods: Using standardized acquisition protocols, DECT of the bilateral feet/ankles, knees, and hands/wrists were obtained on 153 patients with a known diagnosis of gout and on allopurinol at a dose of at least 300mg daily for at least 3 months. The patients were prospectively recruited as a part of a non-interventional multi-center study conducted in the US and New Zealand. All patients met 1977 ARA gout classification criteria. The presence of MSU deposition was evaluated at 12 sites in the feet/ankles, 4 sites in the knees, and 15 sites in the hands/wrists by two radiologists familiar with DECT interpretation. To account for the larger number of sites in the feet/ankles and hands/wrists, they were then grouped into 4 sub-regions in the feet/ankles (first MTP, other toes, tarsals, tendons) and 3 sub-regions in the hands/wrists (IP joints, MCPs, carpals).

Results: Among 153 gout patients (92% male) with mean duration of allopurinol therapy of 5 years and average allopurinol dose of 333mg daily, mean serum uric acid (SUA) was 6.1mg/dL and 51% of patients had SUA < 6mg/dL. The most commonly involved region was the feet/ankles followed closely by the knees; the hands/wrists had less MSU deposition (61%, 57%, and 23% respectively). The three most commonly affected sub-regions were the lateral tibiofemoral, patellofemoral, and medial tibio femoral compartments of the knees (42%, 39%, and 37% respectively), followed by the first MTP joint (35%) (Table). The prevalence in the cruciate ligaments was similar to that of Achilles tendons (25% and 26%, respectively).

Conclusion: Among patients with gout on ULT, there was a considerable prevalence of MSU deposition in all three compartments and the cruciate ligament of the knee joint. While these findings could reflect the higher frequency of involvement at these sites, they may also reflect larger volume MSU deposits in the knees which takes longer to resolve on ULT. DECT of the knees adds substantial value when assessing MSU burden and response to therapy among treated gout patients.

Table –Prevalence of MSU deposits

Anatomical locations	Prevalence N = 153 patients	Prevalence N = 306 joints
Lateral tibiofemoral compartment	42%	34%
Patellofemoral compartment	39%	32%
Medial tibiofemoral compartment	37%	28%
First MTP	35%	25%
Achilles tendon	26%	19%
Cruciate ligament	25%	17%
Other toes	17%	12%
Tarsals	13%	11%
Carpals	14%	9%
MCPs	7%	5%
Hand IPs	5%	3%

Disclosure: C. Yokose, None; N. Dalbeth, Horizon, 5, Kowa, 5, Amgen Inc., 2, AstraZeneca/Ironwood, 2, AbbVie Inc., 8, Pfizer, Inc., 8, Janssen, 8; S. Nicolaou, Siemens, 9; S. Baumgartner, Ardea Biosciences, 3; J. Hu, Heron Therapeutics, 3; M. Fung, Ardea Biosciences, 3; F. J. Simeone, None; H. K. Choi, Takeda, Selecta, Kowa, and Horizon, 5, Selecta and Horizon, 2.

Abstract Number: 2236

Contemporary Comorbidity Burden of Gout and Hyperuricemia in the US during the Past Decade (National Health And Nutrition Examination Survey [NHANES] 2007-2016)

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Session Information

Session Date: Tuesday, October 23, 2018

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Session Time: 9:00AM-11:00AM

Background/Purpose: Precise estimates of the comorbidity burden of gout and hyperuricemia are critical as their presence has important implications for the treatment of both gout and hyperuricemia. We therefore estimated the decadal US prevalence of cardiovascular-renal-metabolic comorbidities according to gout and hyperuricemia status, based on the National Health and Nutritional Examination Survey (NHANES) 2007-2016.

Methods: Using data from 26,332 participants (12,793 men and 13,539 women) aged ≥ 20 years old from NHANES 2007-2016, we determined the prevalence (%) of cardiovascular-renal-metabolic comorbidities according to gout and hyperuricemia status. Obesity was defined as body mass index ≥ 30 kg/m². Other comorbidities were defined based on an affirmative answer to a question asking if a physician or a health professional had diagnosed the said comorbidity. Hyperuricemia was defined as a serum urate level >7.0 mg/dL in men and >5.7 mg/dL in women. All statistical analyses were conducted using survey commands of Stata (Version 15.1, Stata Corporation, College Station, Texas) to adjust for clusters and strata of the complex sample design as well as incorporate sample weights. Population estimates (in millions) were calculated as per the NHANES analytic guidelines.

Results: Among gout patients, 69.4% (6.0 million) had hypertension, 55.9% (4.8 million) were obese, 26.5% (2.3 million) had type II diabetes mellitus (T2DM), 22.5% (1.9 million) had chronic kidney disease (CKD) stage ≥ 3 , 19.9% (1.7 million) had nephrolithiasis[†], 11.8% (1.0 million) had a myocardial infarction (MI), 11.1% (1.0 million) had heart failure (HF), and 8.7% (0.7 million) had suffered a stroke over 2007-2016. Among the US adults with both gout and hyperuricemia, 73.9% had hypertension, 60.8% were obese, 28.5% had CKD stage ≥ 3 , 25.0% had T2DM, 18.2% had nephrolithiasis[†], 11.9% had HF, 11.6% had a MI, and 9.3% had suffered a stroke (**Table**). These prevalences were substantially higher compared with individuals without gout or hyperuricemia. Hyperuricemia without gout was also associated with higher prevalences of comorbidities (all P-values < 0.005 , **Table**). Among individuals with gout, the presence of hyperuricemia conferred additional risk for hypertension, CKD and obesity (all P-values < 0.05 , **Table**).

Conclusion: The findings from this recent, nationally-representative sample of US adults highlight that both gout patients and those with hyperuricemia continue to carry a substantial burden of cardiovascular-renal-metabolic comorbidities. These add to the overall disease burden of gout and hyperuricemia to society, and provide support for the consideration of these comorbidities in optimizing gout and hyperuricemia care in the US.

Table. Prevalence of Comorbidities According to Gout and Hyperuricemia* in NHANES 2007-2016

Comorbidities**	Gout		No Gout	
	Hyperuricemia	No Hyperuricemia	Hyperuricemia	No Hyperuricemia
Hypertension	73.9 (68.6, 78.6)	65.4 (60.9, 69.6)	47.6 (45.5, 49.7)	26.3 (25.2, 27.4)
Obesity (BMI ≥ 30 kg/m ²)	60.8 (55.6, 65.7)	51.4 (45.0, 57.7)	56.9 (54.8, 59.0)	30.6 (29.4, 31.8)
CKD Stage ≥ 3 (GFR < 60)	28.5 (24.2, 33.2)	17.5 (14.4, 21.1)	15.8 (14.5, 17.2)	3.2 (3.0, 3.5)
Type 2 diabetes mellitus	25.0 (20.3, 30.4)	25.7 (21.5, 30.5)	13.0 (11.8, 14.2)	7.8 (7.2, 8.3)
Nephrolithiasis [†]	18.2 (14.0, 23.4)	22.0 (17.9, 26.8)	10.2 (9.0, 11.4)	8.5 (8.0, 9.1)

Table . (Cont'd)

Comorbidities**	Gout		No Gout	
	Hyperuricemia	No Hyperuricemia	Hyperuricemia	No Hyperuricemia
Heart Failure	11.9 (8.8, 15.8)	9.8 (7.5, 12.7)	5.0 (4.3, 5.8)	1.4 (1.2, 1.6)
Myocardial Infarction	11.6 (8.7, 15.4)	11.6 (8.9, 15.2)	4.3 (3.7, 5.0)	2.6 (2.3, 3.0)
Stroke	9.3 (6.2, 13.6)	8.0 (6.1, 10.5)	4.3 (3.8, 4.9)	2.2 (2.0, 2.4)

* Hyperuricemia defined as serum urate >7.0mg/dL for males and >5.7mg/dL for women

** Comorbidities were ordered by the descending prevalence of comorbidities among all individuals with gout and hyperuricemia

† Data missing from NHANES 2015-16

CKD = chronic kidney disease; GFR = glomerular filtration rate (mL/min per 1.73m²).

Disclosure: M. Chen-Xu, None; C. Yokose, None; M. Pillinger, Horizon Pharmaceuticals, 5,Ironwood, 5,SOBI, 5; H. K. Choi, Takeda, Selecta, Kowa, and Horizon, 5,Selecta and Horizon, 2.

Abstract Number: 2237

Prevalence of Urate-Lowering Therapy Use and Target Urate Level Achievement Among Gout Patients in the United States (National Health And Nutrition Examination Survey [NHANES] 2007-2014)

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To determine the latest national prevalence of urate-lowering therapy (ULT) use and achievement of a therapeutic target serum urate level (SUL) in gout patients, and their predictors in the US (National Health and Nutrition Examination Survey [NHANES] 2007-2014).

Methods: Using data from NHANES 2007-2014, we estimated the prevalence of ULT use and achievement of a therapeutic target SUL in patients with gout. During the home interview of NHANES, all participants were asked about a history of health professional- or physician-diagnosed gout and current prescription medications. We defined ULT as taking allopurinol, febuxostat or probenecid, either alone or in combination, and a therapeutic SUL as <6.0 mg/dL. We conducted logistic regression to examine the potential independent associations with purported factors among gout patients.

Results: The prevalence of ULT usage among US gout patients was 32.8% [95% CI 28.3% to 37.6%] in 2007-2014 (39.0% [95% CI 33.6% to 44.7%] among men and 19.4% [95% CI 15.3 to 44.7%] among women). Allopurinol comprised 95.3% [95% CI 92.2% to 98.4%] of ULT usage. Among gout patients, the mean SULs were 5.8 mg/dL [95%CI 5.5 mg/dL to 6.0 mg/dL] among ULT users and 6.9 mg/dL [95% CI 6.7 mg/dL to 7.1 mg/dL] among non-ULT users (mean difference -1.1 mg/dL [95% CI -1.4 mg/dL to -0.8 mg/dL]). Among gout patients, male sex and chronic kidney disease (CKD) were associated with increased fully-adjusted odds of ULT use (**Table 1**). The prevalence of reaching a therapeutic SUL (<6.0 mg/dL) among gout patients was 38.5% [95% CI 35.3% to 41.7%] in 2007-2014 (32.3% [95% CI 28.3% to 36.5%] among men and 52.0% [95% CI 44.8% to 59.1%] among women). Furthermore, among gout patients, ULT use was associated with a fivefold higher odds for reaching a SUL <6.0 mg/dL. By contrast, male sex, obesity, CKD and thiazide diuretic use were associated with a lower fully-adjusted odds for reaching this target SUL (**Table 2**).

Conclusion: These findings from a nationally-representative samples of US adults indicate that 32.8% of US gout patients are receiving ULT. Among gout patients, males, and those with either obesity or CKD are more often receiving ULT. The benefit of ULT among gout patients in achieving this target SUL appears apparent. Male sex, obesity, CKD and thiazide diuretic use were inversely associated with reaching a therapeutic SUL, suggesting a potential need for more aggressive therapy among these groups.

Table 1. Predictors of ULT Use Among US Gout Patients, NHANES 2007-2014*

ULT Use, % (95% CI)	Unadjusted OR (95% CI)	Age- and sex-adjusted OR (95% CI)	Fully-adjusted OR** (95% CI)
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Table . (Cont'd)

	ULT Use, % (95% CI)	Unadjusted OR (95% CI)	Age- and sex-adjusted OR (95% CI)	Fully-adjusted OR** (95% CI)
Age ≥ 65	38.0 (31.4, 45.0)	1.53 (0.98, 2.39)	1.71 (1.10, 2.64)	1.59 (0.97, 2.62)
Male	38.8 (33.0, 45.0)	2.66 (1.90, 3.72)	2.85 (2.08, 3.91)	3.22 (2.28, 4.54)
African-Americans	28.3 (22.7, 34.5)	0.78 (0.50, 1.21)	0.89 (0.56, 1.41)	0.85 (0.54, 1.36)
Obesity	34.5 (28.3, 41.2)	1.67 (0.92, 3.06)	1.94 (1.04, 3.60)	2.06 (1.18, 3.61)
CKD Stage ≥3	40.5 (34.2, 47.1)	1.55 (1.06, 2.26)	1.54 (1.04, 2.27)	1.59 (1.04, 2.44)
Hypertension	33.7 (28.5, 39.3)	1.15 (0.67, 1.99)	1.15 (0.67, 1.98)	1.07 (0.60, 1.89)
Thiazide diuretic	28.4 (19.8, 38.9)	0.78 (0.46, 1.31)	0.80 (0.47, 1.35)	0.73 (0.42, 1.25)
Alcohol Use	33.7 (27.7, 40.2)	1.18 (0.67, 2.08)	0.81 (0.44, 1.51)	0.86 (0.45, 1.62)

*Data are presented incorporating sample weights and adjusted for clusters and strata of the complex sample design of NHANES 2007-2014.

** Adjusted for all the other covariates in the table.

Table 2. Predictors of SUL <6.0 mg/dL among US Gout Patients, NHANES 2007-2014*

	SUL <6.0 mg/dL, % (95% CI)	Unadjusted OR (95% CI)	Age- and sex-adjusted OR (95% CI)	Fully-adjusted OR** (95% CI)
ULT Use	59.0 (50.7, 66.8)	3.26 (2.25, 4.72)	4.43 (2.75, 7.14)	5.53 (3.36, 9.09)
Age ≥ 65	41.3 (34.4, 48.6)	1.11 (0.68, 1.82)	1.04 (0.63, 1.72)	0.99 (0.60, 1.64)
Male	34.5 (29.2, 40.1)	0.48 (0.30, 0.78)	0.48 (0.29, 0.79)	0.26 (0.14, 0.48)
African-Americans	34.6 (27.9, 42.0)	0.74 (0.53, 1.04)	0.67 (0.47, 0.95)	0.80 (0.55, 1.15)
Obesity	35.0 (29.7, 40.6)	0.55 (0.32, 0.97)	0.53 (0.30, 0.93)	0.36 (0.19, 0.66)
CKD Stage ≥3	33.2 (24.5, 43.3)	0.69 (0.44, 1.09)	0.57 (0.35, 0.93)	0.45 (0.27, 0.75)
Hypertension	37.6 (32.4, 43.1)	0.70 (0.46, 1.07)	0.65 (0.43, 0.99)	0.81 (0.54, 1.22)
Thiazide diuretic	27.1 (18.8, 37.5)	0.50 (0.29, 0.86)	0.45 (0.26, 0.77)	0.49 (0.28, 0.86)
Alcohol Use	38.0 (32.7, 43.5)	0.70 (0.47, 1.04)	0.93 (0.60, 1.45)	0.79 (0.48, 1.31)

* The data were adjusted for clusters and strata of the complex sample design of the National Health and Nutrition Examination Survey (NHANES) 2007–2014, with incorporation of sample weights. 95% CI = 95% confidence interval.

** For all the other covariates in the table.

Disclosure: M. Chen-Xu, None; C. Yokose, None; M. Pillinger, Horizon Pharmaceuticals, 5,Ironwood, 5,SObi, 5; H. K. Choi, Takeda, Selecta, Kowa, and Horizon, 5,Selecta and Horizon, 2.

Abstract Number: 2238

Non-Coding Urate-Associated Variants Function in a Conserved Lincrna Regulatory Domain That Alters MAF transcription

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Genome-wide association studies (GWAS) have revealed that the large majority of disease-associated single nucleotide polymorphisms (SNPs) are located in the non-coding regions of the genome. Genetic variation in the genomic regulatory landscape likely plays a crucial role in the pathology of disease. Non-coding variants associated with disease can influence the expression of long intergenic non-coding RNAs (lincRNAs), which in turn function in the control of protein-coding gene expression. Here, we investigate the function of two independent serum urate-associated signals in the genomic region of *MAF* (musculoaponeurotic fibrosarcoma oncogene homolog) and cis-located lincRNAs. *MAF* encodes a poorly understood transcription factor and is one of >30 loci associated with serum urate levels by GWAS and also associated with the risk of gout.

Methods: Publicly available databases accessed were serum urate GWAS summary statistics from Köttgen et al (2013), the Contextualize Developmental SNPs using 3D Information (CoDeS3D) algorithm, the NepheQTL database and expression quantitative trait loci (eQTL) data from the Genotype Tissue Expression (GTEx) database. Luciferase, siRNA knockdown assays and quantitative PCR were done in HEK293 cells. Chromatin immunoprecipitation was performed in HEPG2 cells with b-globin and *ABCC6* as negative and positive controls, respectively. Enhancer assays were done in zebrafish using the ZED vector and cloning allele-specific fragments.

Results: Serum urate-associated variants *rs4077450* and *rs4077451* lie within an enhancer that forms long-range interactions with loci encoding lincRNAs *LINC01229* and *MAFTRR*. We demonstrate that *rs4077450* and *rs4077451* can differentially regulate enhancer activity. Serum urate associated variants are also associated with expressed quantitative trait loci (eQTL) in *LINC01229* and *MAFTRR*, which are both strongly co-expressed with the closest protein-coding gene *MAF*. We show that the enhancer region marked by *rs4077450* and *rs4077451* drives expression in the zebrafish pronephros, recapitulating endogenous *MAF* expression. Depletion of *MAFTRR* and *LINC01229* in HEK293 cells leads to increased *MAF* expression.

Conclusion: Collectively, our results are consistent with the hypotheses that serum urate associated variants at the *MAF* locus mediate long-range transcriptional regulation of lincRNAs *LINC01229* and *MAFTRR*, which in turn repress the expression of *MAF*.

Disclosure: M. Leask, None; T. R. Merriman, None; A. Dowdle, None; H. Salvesen, None; R. Topless, None; T. Fadason, None; W. Wei, None; W. Schierding, None; J. O'Sullivan, None; J. Horsfield, None.

Abstract Number: 2239

Tenocytes Extracted from Rotator Cuff Tendons Are Able to Induce Mineral Deposition in Vitro and Express Genes Related to a Chondrocyte Differentiation

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

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Background/Purpose: Calcific tendonitis is a frequent cause of shoulder pain. The calcium deposits are composed of carbonated apatite and their origin stays still largely unknown. Our preliminary results showed that calcific deposits are surrounded by chondrocyte-like cells expressing TNAP ((Tissue Nonspecific Alkaline Phosphatase) and ENPP1 (Ectonucleotide pyrophosphatase/phosphodiesterase 1), two key enzymes involved in the mineralization process [1]. The purpose was to study the ability of cells extracted from rotator cuff tendons to produce apatite crystals and to analyze the phenotype of these mineralizing cells.

Methods: Tenocytes were extracted from rotator cuff tendons removed during shoulder total replacement. These cells were first characterized by their gene expression. To evaluate their ability to mineralize, they were cultured in an “osteogenic medium” (OM) containing dexamethasone 10^{-7} M, ascorbic acid 2P (250 μ M) and β -glycerophosphate (10 mM) or in a control medium (DMEM 3%) for 21 days. At 21 days, mineral deposition was assessed by staining with Alizarin red solution. At 21 days, tenocytes total RNA was extracted and quantitative PCRs (qPCRs) were performed after first strand cDNA synthesis. Primers for the following genes were used: Runx2, Sox9, Collagen I, Collagen II, Collagen III, Collagen X, Osteopontin, Osteocalcin, Bone Sialo Protein (BSP), TNAP, ENPP1, Mohawk homeobox (Mkx), Scleraxis (SCX), Tenomodulin (TNMD), Cartilage Oligomeric Matrix Protein (COMP), Aggrecan, Matrix Metalloproteinase 13 (MMP13) and GAPDH. TNAP enzymatic activity was also assessed in the cells at 3, 7, 14 and 21 days.

Results: Tendon samples were obtained from 5 patients (age 69.6 ± 5.13 years). Four were females. Cells extracted from these tendons expressed collagen I, collagen III, Scleraxis and Mkx, as expected for this type of cells. However, TNMD was very weakly expressed and lost after passage 1. These cells were able to mineralize in the OM although no mineralization was observed in the control medium. The mineralized surface was about 15% of surface of the well. qPCR analyses showed a significant increase of TNAP and ENPP1 expression by cells cultured in OM compared to control cells ($p < 0.05$, Mann-Whitney test). Osteoblast markers (Runx2, osteocalcin, osteopontin, BSP) were not increased by the OM. COMP, a chondrocyte marker was significantly increased and there was a trend to an increase of MMP13 and Collagen X suggesting a hypertrophic orientation. In parallel, in the OM, TNAP enzymatic activity started to increase at 7 days and was significantly higher at 14 and 21 days compared to the control medium.

Conclusion: Cells extracted from tendons of the rotator cuff are able to mineralize in an osteogenic medium. The cells expressed genes associated with a chondrocyte phenotype and these results are interesting considering the histological data previously obtained. Further in vitro experiments are necessary to look at the key role of TNAP in the process.

[1] Darrieutort-Laffite C, et al. Rotator Cuff Calcific Tendinopathy: Chondrocyte-like Cells Surrounding Calcific Deposits Express TNAP and ENPP1, Two Key Enzymes of the Mineralization Process. [abstract]. Arthritis Rheumatol. 2017; 69 (suppl 10).

Disclosure: C. Darrieutort-Laffite, None; P. Arnolfo, None; B. Le Goff, None; F. Blanchard, None.

Abstract Number: 2240

Hip Involvement in Patients with Gout: Results of an Ultrasound Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Although considered as uncommon, the hip represents one of the possible targets of gout. To date, hip involvement in patients with gout has been poorly investigated by clinical and/or imaging studies. To the best of our knowledge, this is the first study aimed at assessing the prevalence of monosodium urate (MSU) crystal deposits at the hip in patients with gout. The objective of this study is to investigate the prevalence of the US findings indicative of MSU crystal deposits at the hip in consecutive patients with gout, diagnosed according to the 2015 ACR/EULAR classification criteria.

Methods: Inclusion criteria: synovial fluid analysis positive for MSU crystals or presence of subcutaneous tophi at the physical examination.

Exclusion criteria: prior diagnosis of others crystal related arthropathies, such as CPPD or calcium basic phosphate crystal arthritis, highly suggestive findings of CPPD detected at the knee US exam, previous surgical procedures and/or remarkable injuries of the hip. Each patient underwent a bilateral hip and knee US exam. The US exam was carried out using a My Lab Twice US machine (Esaote S.p.A. Genoa, Italy), working with a linear (3-13 MHz) or, when necessary, a convex probe (2-7 MHz). The US abnormalities indicative of MSU crystals deposition were identified according to the OMERACT definitions. At the hip, the following abnormalities were investigated: intra-articular tophi and/or aggregates, double contour (DC) sign over the hyaline cartilage of the femoral head.

Results: Seventy hips, in 35 patients with gout [age (mean±standard deviation) 69.1±11.2; female/male 1/34, disease duration 10.3±10.8 years], were evaluated. The US examination revealed the presence of one or more US findings indicative of MSU crystal deposits in at least one hip in 15 out of 35 patients (42.8%), in 19 out of the 70 hips (27.1%). Tophi were found in at least one hip in 5 out of 35 patients (14.2%), in 6 of the 70 hips (8.5%). Aggregates were detected in at least one hip in 12 out of 35 patients (34.2%), in 12 out of the 70 hips (17.1%). DC sign was found in at least one hip in 5 out of 35 patients (14.2%), in 6 out of the 70 hips (8.5%). Twenty-eight patients were assessed using a linear probe (3-13 MHz) and the remaining 7 patients were studied using a convex probe (2-7 MHz). Figure 1 shows the US findings indicative of MSU crystal deposits at the hip.

Conclusion: These preliminary results show that the prevalence of hip involvement in patients with gout might be underestimated. Further investigations in a larger cohort of patients are needed to explore the clinical and laboratory features associated with hip involvement in patients with gout.

Reference: Huet T, et al. Hip Gout Arthritis Revealed by Sonography. J Ultrasound Med 2016 Aug;35(8):1828-9

Figure 1. Legend. A: intra-articular tophus (curved arrow). B: intra-capsular aggregate (white arrow). C: double contour over the hyaline cartilage of the femoral head (arrowheads).



Disclosure: A. Di Matteo, None; E. Filippucci, None; E. Cipolletta, None; A. Musca, None; M. V. Martire, None; D. Pierucci, None; E. Di Donato, None; W. Grassi, Grunenthal, 5.

Abstract Number: 2241

What Can Variation in Clinical Practice Teach Us about Treatment Strategies for Patients with Gout?

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To improve quality of care for patients with gout, two hospitals in the Netherlands initiated a protocolized gout clinic. One clinic adopted a patient-centred (PC-) strategy -emphasizing a shared decision based on serum uric acid (sUA) and patient satisfaction with gout control - and the other clinic adopted a strict sUA (≤ 0.30 mmol/L) target (UA-) strategy, with early combination of xanthine oxidation inhibitors (allopurinol) with uricosurics if the target was not reached and fractional uric acid excretion was below 4% (two modes of action (2MoA)).

Methods: Patients newly diagnosed with gout by the rheumatologist and having a follow-up between 9-15 months after the first visit were included. Co-primary outcomes were the proportion of patients reaching a sUA ≤ 0.36 mmol/L, and the proportion of patients free of flares. Secondary outcomes were the proportion of patients with a sUA ≤ 0.30 mmol/L, requiring treatment intensification beyond allopurinol (and especially 2MoA), and experiencing adverse events. Independent t-tests or chi-square were used to test differences in outcomes between strategies, and logistic regressions to adjust the effect of center on outcomes for baseline confounders.

Results: In total, 255 and 142 new patients attended the UA and PC-strategy clinic, respectively, for the first time. Of the initial patients, 29/255 (11%) vs 13/142 (9%) patients stopped prematurely clinical follow-up and 6/255 (2%) vs 11/142 (8%) patients died. Finally, 126 and 86 patients had a follow-up assessment between 9-15 months after inclusion. Diagnosis of gout was further confirmed by ACR/EULAR classification criteria for 122/126 (97%) patients in the UA-strategy vs 51/86 (59%) patients in the PC-strategy ($p < 0.001$), respectively. In the UA-strategy 105/126 (83%) patients compared to 63/86 (74%) patients in the PC-strategy ($p = 0.10$), reached the threshold of ≤ 0.36 mmol/L and 58/126 (46%) vs 31/86 (36%) patients ($p = 0.15$) were free of flares (table 1). In the UA-strategy 76/126 (60%) patients were on allopurinol mono therapy compared to 63/86 (73%) in those receiving the PC-strategy ($p = 0.05$). 2MoA therapy was significantly more frequent in the UA-strategy ($n = 21$ (17%) vs $n = 1$ (1%), $p < 0.001$), yet the number of registered adverse events was not different ($n = 25$ (20%) vs $n = 20$ (23%), $p = 0.55$). After adjustment for baseline confounders, the UA-strategy had a slightly higher but non-significant chance to reach sUA ≤ 0.36 mmol/L and to be free of flares, but required significantly more therapy intensification.

Conclusion: A strict UA-strategy resulted in a non-significant higher proportion of patients reaching the UA target (≤ 0.36 mmol/L) and free of flares. This was accomplished with significant more therapy intensification from allopurinol monotherapy to 2MoA therapy, without a significant difference in adverse events.

Table 1: Uni- and multivariable logistic regression analyses for co-primary and secondary outcomes in patients with gout disease undergoing two different treatment strategies

	UA-strategy (n=126)	PC-strategy (n=86)	Univariate (n=212)		Multivariable (n=207)	
	N (%)	N (%)	Odds ratio	95% CI	Odds ratio	95% CI
Co-primary						
sUA ≤ 0.36 mmol/L	105 (83.3)	63 (74.1)	1.75	0.89-3.43	1.65	0.77-3.56
Free of flares	58 (46.0)	31 (36.0)	1.51	0.86-2.66	1.61	0.83-3.10
Secondary						
sUA ≤ 0.30 mmol/L	83 (65.9)	44 (51.8)	1.80	1.03-3.16	1.97	1.00-3.85
Adverse events	25 (19.8)	20 (23.3)	0.82	0.42-1.59	1.04	0.49-2.21
Allopurinol monotherapy	76 (60.3)	63 (73.3)	0.56	0.31-1.01	0.40	0.20-0.82

Multivariable model includes treatment strategy (center), age, gender, estimated glomerular filtration rate (eGFR), use of diuretics, presence of tophi, and baseline serum uric acid. sUA = serum uric acid, UA-strategy= uric acid strategy, PC-strategy= patient-centred strategy.

Disclosure: R. te Kampe, None; C. van Durme, None; M. Janssen, None; A. Boonen, Celgene and Abbvie, 2, Janssen, Sandoz, Lilly, Novartis and UCB, 9; T. Jansen, AstraZeneca, 2, GRUNENTHAL, 8, ABBVIE, CELGENE, GRUNENTHAL, 5.

Abstract Number: 2242

Cardiovascular Outcomes of Treatment with Febuxostat and Allopurinol in Gout Patients with Kidney Disease

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Comorbidities (CARES) trial demonstrated that major cardiovascular (CV) outcomes on febuxostat versus allopurinol in patients with gout and CV disease were comparable but that rates of CV mortality were higher on febuxostat. We evaluated the CV outcomes in those patients with chronic kidney disease (CKD) according to the need for up-titration of dose aimed at achieving serum urate (sUA) levels < 6 mg/dL.

Methods: Fifty-three percent of the study population in CARES (n = 3267) had moderately impaired kidney function (CKD 3, estimated creatinine clearance (eCRCL) < 60 ml/min and ≥ 30 ml/min). Febuxostat patients received 40 mg daily, increased to 80 mg at Week 4 if the sUA was ≥ 6.0mg/dL at Week 2, regardless of kidney function. Allopurinol patients received 200 mg to 400 mg for CKD 3, or 300 mg to 600 mg when the eCRCL was ≥ 60 ml/min, increased in 100 mg increments each month until the sUA was < 6.0mg/dL. The rates of the primary composite endpoint and its 4 components were analyzed according to final dose requirements in patients with CKD 3.

Results: There were 1636 CKD 3 patients randomized to febuxostat and 1631 to allopurinol in CARES. In these patients, the final dose of febuxostat was 40 mg in 59% and 80 mg in 41% whereas the final dose of allopurinol was 200 mg in 41%, 300 mg in 28%, and 400 mg in 31% of patients. At baseline, CKD 3 patients who required up-titration of dose to achieve serum urate levels < 6 mg/dL for both febuxostat and allopurinol were slightly younger, had greater serum urate levels and higher rates of tophi and higher rates of congestive heart failure compared to those patients not requiring up-titration of dose (p < 0.05) (**Table 1**). In patients with CKD 3, higher proportions of patients in the febuxostat group achieved the targets of < 6 and < 5 mg/dL compared to allopurinol at most time points during the trial and the incidence of gout flares was comparable for the 2 treatment arms (febuxostat, 47.9% and allopurinol 43.9%, overall). The incidence of CV events was greater in the patients who required higher doses and was driven by CV mortality rates; however, these results were similar for both febuxostat and allopurinol (**Table 2**).

Conclusion: CV event rates, driven by CV mortality, were greater in patients with moderately impaired kidney function who required up-titration of both febuxostat and allopurinol. However, these findings occurred in association with greater gout and CV disease burden, particularly heart failure, a comorbidity linked to increases in subsequent CV mortality.

Table 1. Baseline characteristics of CKD 3 patients requiring dose increase versus those who did not

Characteristic	Patients requiring dose increase		Patients not requiring dose increase	
	Febuxostat (n = 687)	Allopurinol (n = 650)	Febuxostat (n = 989)	Allopurinol (n = 681)
Age (years)	64.9 [*]	66.6 [*]	69.5	70.1
N (%) ≥ 65 (years)	413 (60.1) [*]	632 (97.2) [*]	781 (72.5)	580 (75.4)
Serum urate (mg/dL), mean	9.9 [*]	8.3 [*]	8.3	8.0
Tophi present, N (%)	149 (22.3)	331 (51.3) [*]	202 (22.4)	127 (18.6)
≥ 4 gout flares during year prior to randomization	61 (12.1)	134 (23.1)	93 (11.6)	80 (11.7)
History of myocardial infarction	381 (42.1)	394 (44.3)	371 (38.3)	368 (54.2)
History of unstable angina	281 (36.1)	361 (37.3)	250 (23.8)	174 (25.4)
History of heart failure	220 (33.0) [*]	287 (44.2) [*]	188 (19.2)	137 (20.1)

^{*} p < 0.05 versus those not requiring a dose increase

Data are N (%) unless noted.

Abstract Number: 2243

Sex Difference of the Association between Serum Urate and Blood Pressure in Young Adults

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

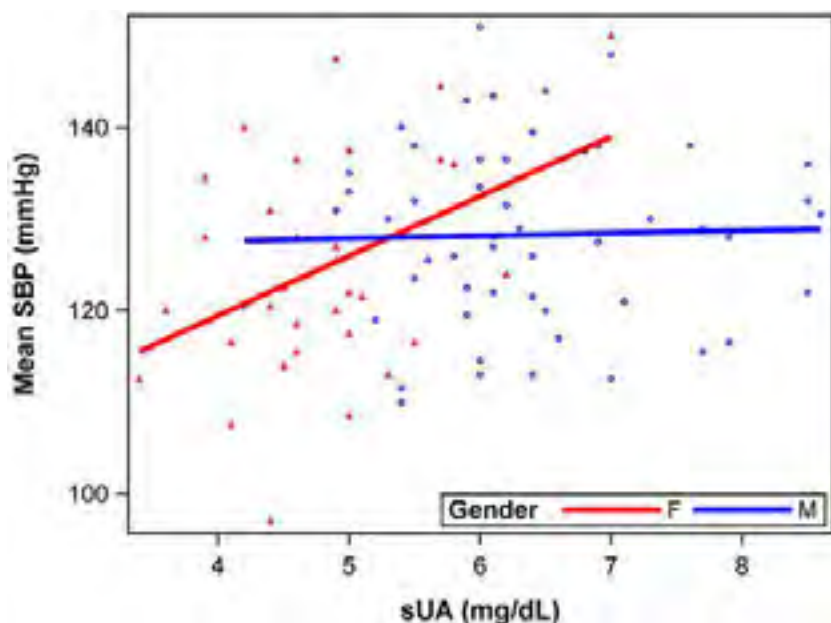
Session Time: 9:00AM-11:00AM

Background/Purpose: Serum urate (sUA) has been associated with blood pressure in most but not all studies. This study aims to test whether there are sex differences in the association between sUA and systolic blood pressure (SBP) in young adults.

Methods: This is a cross sectional analysis using baseline data from young adults with normal renal function participating in a clinical trial. Men and women ages 18-40 years were eligible if they had SBP ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg and sUA > 5.0 mg/dL for men and > 4.0 mg/dL for women. Multiple linear regression analysis was used to evaluate the association between sUA and SBP (measured with in-office sphygmomanometer), controlling for age, sex and race. The potential sex difference was tested with a sex-by-sUA interaction term in the regression model.

Results: The mean age of the 99 participants was 27.6 ± 6.9 years; 37.4% were female, and 40.4% were African American. After controlling for age, sex and race, SBP was significantly associated with sUA ($p=0.019$). The results also suggested a statistically significant sex difference in the association ($p=0.026$). Specifically, a one unit increase in sUA was associated with 6.8 mm Hg higher SBP in women, but only 0.2 mm Hg in men (Figure). No statistically significant race effect was detected.

Conclusion: Higher sUA was associated with higher SBP in women but not in men. This association was present at ranges of sUA below the threshold of hyperuricemia (6.8 mg/dL). Whether an interaction between sUA and hormonal factors can account for this differential effect of sex on SBP in young adults should be explored further.



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Abstract Number: 2244

Comparison of an Interactive Voice Response (IVR) to Smart Phone App to Determine Patient Preference for Reporting Gout Flares

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Gout flares are a major cause of morbidity and are an important outcome in clinical studies. Significant limitations for timely flare ascertainment exist, and while technology has promise to capture flares passively, optimal methods to do so are uncertain. We examined the feasibility, preference, and satisfaction of an interactive voice response [IVR] system versus a smartphone mobile application [RheumPRO; Birmingham, AL] to capture gout flares between study visits.

Methods: Gout patients were randomized to IVR vs. RheumPRO for flare capture and crossed over to the other technology at 3 months. Study inclusion criteria: physician diagnosed gout, hyperuricemia (serum urate level ≥ 6.8 mg/dl), self-report of ≥ 2 flares in the previous 6 months, and smartphone ownership. Participants reported flare status via weekly scheduled RheumPRO interactions or IVR calls. At 3 (crossover) and 6 months (end of study), participants completed satisfaction/feasibility surveys. Feasibility was ascertained via response rate (adherence) to RheumPRO interactions or IVR calls. Satisfaction was assessed using dichotomous preference questions and a Likert scale question on ease of use (range 0 to 10; very easy to very difficult). Descriptive statistics characterized differences between methods.

Results: Of 44 participants enrolled, 38 completed both study arms. Participants were predominantly men (87%), had a mean (\pm SD) age of 50 (± 15) years, and most (87%) were on urate lowering therapy at enrollment. At study completion, 28 (74%) preferred RheumPRO, 3 (8%) preferred IVR and 7 (18%) had no preference. Adherence with both methods did not differ at 80%. Measures of feasibility and satisfaction for each method are shown in Table 1.

Table 1

	IVR	RheumPRO	p-value
<i>Gout Flares</i>			
Weeks with a flare (per pt)	2.6 (± 2.5)	3.4 (± 3.3)	0.27
Mean (\pm SD)			
Total flare weeks (% of study time with flares)	27%	35%	0.02
Feasibility (Adherence) (weekly response to interactions or calls)	80.6% ($\pm 21.3\%$)	80.1% ($\pm 24.6\%$)	0.94
Mean % (\pm SD)			
<i>Technology Satisfaction Measures</i>			
Ease of use (0-10; very easy to very difficult)	1.63 (± 2.5)	0.58 (± 1.12)	0.02
Mean (\pm SD)			
Disrupted activity (i.e. intrusiveness), %	18.4%	2.6%	0.06
Ability to respond to interactions or calls, %	72.8%	94.7%	0.01
Preference of reporting via device/call compared clinic visit, %	86.5%	92.1%	0.48
Satisfaction with frequency of contact, %	89.5%	89.5%	1.00
Willing to use in future, %	89.5%	97.3%	0.36

Conclusion: Both a smartphone App and IVR were found to be equally feasible technologies and reasonably accepted to capture gout flares. More patients preferred the RheumPRO App, which detected more flares, and found it easier to use

and more convenient than an automated call system. Each technology may offer variable benefits for feasible gout flare assessment in future clinical studies.

Disclosure: N. Elmagboul, None; B. W. Coburn, None; K. Saag, Abbott, Amgen, Ironwood/AstraZeneca, Bayer, BMS, Merck, Pfizer, Roche/Genentech, 5; P. J. Foster, None; A. S. Mudano, None; J. A. Melnick, None; D. A. Bergman, None; S. Yang, None; D. T. Redden, None; L. Chen, None; F. Cooper, None; J. R. Curtis, AbbVie, Amgen, BMS, Eli Lilly and Company, Janssen, Pfizer, Roche/Genentech, Corrona, UCB, Myriad, 2, 5; T. R. Mikuls, BMS, Ironwood, Horizon, 2, Pfizer, Inc., 5.

Abstract Number: 2245

Lubricin/Proteoglycan 4 (PRG4) Inhibits NLRP3 Inflammasome Assembly in Monosodium Urate (MSU)-Crystal Induced Arthritis.

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Lubricin/proteoglycan-4 (PRG4) is a mucinous glycoprotein secreted by synovial fibroblast and superficial zone chondrocytes. PRG4 has a multifaceted homeostatic role in the joint including boundary lubrication, friction lowering of apposed cartilage surfaces and prevention of synovial overgrowth. PRG4 is abundant in the synovial fluid (SF) and its levels are reduced in SF from patients with inflammatory arthropathies. Therapeutically, the recombinant and native form of PRG4 has been shown to exhibit a disease-modifying effect in pre-clinical osteoarthritis (OA) models. We recently showed that rhPRG4 reduces phagocytosis of MSU-crystals, activation of chemokines and cytokines, NLRP3 expression, generation of mature IL-1 β , and NF κ B nuclear translocation. The objective of this study was to further evaluate role of Lubricin/PRG4 in NLRP3 inflammasome activation, ASC recruitment and speck formation in MSU-crystal stimulation in THP-1 macrophages and wild-type and Prg4 knock-out macrophages.

Methods: We evaluated the impact of recombinant human PRG4 (rhPRG4) on MSU-induced release, secretion and expression of interleukin-1 beta (IL-1 β), NLRP3 induction, caspase-1 activation by ELISA, immunohistochemistry, and Western-blot analysis in MSU-stimulated THP-1 cell and MSU-stimulated peritoneal macrophages (PEM) and bone marrow derived macrophages (BMDPs) from wildtype and Prg4 knock-out (KO) mice. We also evaluated the role of rhPRG4 in the expression of the NLRP3 inflammasome components using qPCR, immunohistochemistry and western-blot analysis. Immunohistochemistry experiments were performed to evaluate if rhPRG4 inhibited ASC speck formation and oligomerization. Colocalization of rhodamine rhPRG4 and NLRP3, ASC was evaluated in MSU-stimulated THP-1 cells.

Results: rhPRG4 inhibited the expression of NALP3, PYCARD, Caspase-1 and IL-18 in MSU-stimulated THP-1 cell using immunohistochemistry, western blot analysis and qPCR in a dose dependent manner. rhPRG4 inhibited the formation of ASC speck, a critical marker of NLRP3 inflammasome assembly, in MSU-stimulated cells. PEM from Prg4 $-/-$ mice showed increased NLRP3 induction, caspase-1 activation and conversion of pro-IL-1 β to mature IL-1 β compared to wild-type mice. Colocalization of rhodamine rhPRG4 in MSU-stimulated THP-1 cells showed colocalization with NLRP3 but not ASC.

Conclusion: Our findings advance our current understanding of the complex anti-inflammatory mechanisms of PRG4 in gout. One of the rhPRG4's anti-inflammatory mechanism may be due to targeting the NALP3 inflammasome assembly. This work is supported by P20GM104937 (AMR and GDT) and Arthritis Foundation Grant (AMR).

Disclosure: A. M. Reginato, None; C. Sun, None; E. A. Khaled, None; T. A. Schmidt, None; O. D. Liang, None; G. D. Jay, None.

Insulin: Genetic and Physiological Influences on Human Uric Acid Homeostasis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

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Background/Purpose: Insulin plays a key role in the genesis of hyperuricemia. In particular, hyperinsulinemia in metabolic syndrome is inversely correlated with urinary uric acid (UA) excretion and insulin infusion in humans also reduces urinary fractional excretion of UA.

Methods: An existing GWAS cohort was analyzed, testing for association between genetic variants in the insulin and insulin receptor genes with serum UA (SUA). HEK 293T cells, human PTC5 proximal tubule cells, and *Xenopus* oocytes were probed with antibodies to UA transporters, the insulin receptor, downstream kinases, and the relevant phosphokinases. ¹⁴C-UA transport was assayed in these human cell lines and in oocytes expressing individual transporters.

Results: Variants in the human insulin and insulin receptor genes demonstrated significance for association with variation in SUA, at $p < 10^{-4}$ and $p < 10^{-7}$, respectively. HEK293T and PTC5 proximal tubular cells express several endogenous UA transporter proteins, including GLUT9, OAT10, and URAT1. Insulin activates PI3 kinase/Akt and MEK/ERK signaling pathways through the insulin receptor in HEK 293T and PTC5 cells, as detected with phosphokinase antibodies, with activation of endogenous ¹⁴C-UA transport. The stimulatory effect of insulin on UA uptake is abrogated by uricosurics and by inhibition of protein tyrosine kinase (genistein), PI3 kinase (LY295002), and MEK/ERK (PD98059). UA transport mediated by GLUT9a, GLUT9b, OAT10, OAT3, OAT1, NPT1 and ABCG2, when expressed separately in *Xenopus* oocytes, is also activated by insulin, with equivalent activation of signaling pathways and differential effects of signaling inhibitors on insulin-stimulated UA transport. Insulin has no effect on URAT1, OAT4, and the SMCT1/2 nicotinate transporters, when expressed in oocytes. GLUT9a is the basolateral exit pathway in reabsorption of filtered UA by the proximal tubule; given much greater absolute UA transport rates mediated by GLUT9 isoforms in oocytes, much of the anti-uricosuric effect of in vivo insulin infusion is likely due to activation of GLUT9a.

Conclusion: Variation in the human insulin and insulin receptor genes affects SUA. Insulin and associated signaling pathways also activate multiple UA transporters, indicating a pivotal physiological role for insulin in UA homeostasis. We postulate that basolateral GLUT9a in the proximal tubule is the dominant post-translational target of insulin in the regulation of renal UA transport.

Disclosure: D. B. Mount, Astra Zeneca, 2; Kowa Pharmaceuticals, 5; T. R. Merriman, None; A. Mandal, None.

Abstract Number: 2247

Predictors of End-Stage Renal Disease (ESRD) in Gout Patients and General Population (GP) Controls – a Role for Interstitial Nephritis, Urate Nephropathy?

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

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Session Time: 9:00AM-11:00AM

Background/Purpose: Decreased renal excretion of urate is an established risk factor for hyperuricemia, whereas it is less clear if hyperuricemia or gout predict impaired kidney function. Aims were to; 1) Determine if gout predicted ESRD and what the predictors for ESRD were in gout and control subjects separately, 2) describe the underlying kidney diagnoses for ESRD.

Methods: All patients aged ≥ 18 with a visit to physician with a gout diagnosis (ICD-10) between 2002 and 2012 in the Western Sweden Health Care Region (WSHCR) were individually matched with 5 general population controls (GP) by age, sex, county and year of gout diagnosis. In all subjects, for the two years preceding the gout diagnosis, visits to physician with the following diagnoses (ICD10) were identified: atrial fibrillation (AF), diabetes (DM), glomerulonephritis (GN), heart failure (HF), hypertension (HT), ischemic heart disease (IHD), and tubulointerstitial nephritis (TIN). Follow-up started Jan 1st 2002 or at the date of first visit with a gout diagnosis thereafter and ended at the first of ESRD diagnosis, death, or end of study (31st of December 2012). ESRD was defined as first kidney transplantation or start of dialysis during follow-up. Multivariable Cox-regression models with ESRD as outcome were used to examine gout as a predictor and individual predictors in the gout and control cohorts separately. In addition descriptive information on underlying kidney disease diagnoses for ESRD are shown.

Results: We identified 28304 patients with a diagnosis of gout and 135287 GP. In gout patients and GP 0.76% (mean follow-up: 3.92 yrs) and 0.12% (mean follow-up: 4.35 yrs) developed ESRD, respectively. Gout was associated with an increased risk for ESRD (HR 7.2; 95% Confidence Interval (CI) 6.0 to 8.6) compared to GP controls. The HRs for risk factors for ESRD were similar between gout and GP with the exception of male sex and age that decreased the risk in patients with gout (Table 1). Interestingly, when identifying causes to ESRD we found that GN and TIN were significantly more common in gout patients compared to GP controls, 21.6 vs 11.9% ($p=0.005$) and 8.4 vs 3.6% ($p=0.052$) respectively. Diabetic nephropathy was slightly more common in GP controls compared to gout patients, 20.7 vs 18.7% ($p=0.59$).

Conclusion: ESRD is much more common in gout patients compared to GP, with a similar pattern of predictors, with the exception of age and sex. Interestingly, TIN was much more frequent in gout patients both overall and as a cause of ESRD, which may reflect presence of urate nephropathy.

Table 1

	Gout cases, n=28304	Gout hazard ratio (SD)	General population controls, n=135287	General population controls, hazard ratio (SD)
Age at inclusion, year, mean (SD)	68.7(14.9)	0.98 (0.97-0.99)	68.1(14.8)	1.01(0.994-1.02)
Sex, male %	67.2	0.94(0.7-1.27)	66.5	2.72(1.81-4.1)
Atrial fibrillation, %	16.7	0.86(0.56-1.3)	5.8	0.8(0.45-1.4)
Diabetes, %	16.2	2.25(1.67-3.03)	7.5	3.43(2.41-4.89)
Heart failure, %	13.4	2.04 (1.35-3.08)	2.9	2.48(1.45-4.24)
Hypertension, %	49.2	3.68(2.62-5.17)	25.3	3.18(2.26-4.47)
Ischemic heart disease, %	21.0	1.35(0.96-1.89)	9.5	1.59(1.08-2.34)
Non-diabetic glomerular disease, %	0.7	17.34(11.8-25.4)	0.1	47.14(25.4-87.4)
Tubulointerstitial nephritis, %	0.7	6.1(3.56-10.47)	0.3	6.87(2.93-16.14)

Predictors for risk of developing end-stage renal disease, prevalence at baseline and multivariate COX-regression for gout and general population controls, analysis was adjusted for all variables in the table

Disclosure: M. Joelsson, None; L. Jacobsson, None; M. Dehlin, None.

Abstract Number: 2248

Genetic Variants Identify Interleukin 37 As an Important Anti-Inflammatory Cytokine in Gout in Humans

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Session Information

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Background/Purpose: During a gout flare monosodium urate (MSU) crystals induce, in the presence of a secondary stimulus, acute joint inflammation characterized by the recruitment of predominantly neutrophils. These neutrophils release chemokines and inflammatory mediators, further amplifying the inflammation. IL37 emerges as a fundamental inhibitor of the innate immune response and inhibits MSU-crystal induced inflammation in cell lines and murine models of gout. To further elucidate the role of IL37 in gout, we examined DNA of people with gout for genetic variations in *IL37* and assessed the functional consequences of these mutations.

Methods: Exons of the *IL37* gene were sequenced using Molecular Inversion Probes (MIPs) in 677 people with crystal-proven gout. The frequency of rare genetic variants in *IL37* was compared to a cohort of 469 healthy controls and a cluster analysis was performed.

Neutrophils were isolated from healthy Dutch donors, pretreated with IL37, a genetic variant of IL37 or IL37Fc (the tail region of an antibody to IL37) and stimulated with opsonized MSU crystals. Reactive oxygen species (ROS) and IL8 production were measured.

For the validation of genetic variants, a total of 2202 clinically-ascertained gout cases and 2295 controls (further stratified into 424 hyperuricemic ($\geq 0.41\text{mmol/L}$) controls) of European and NZ Māori and Pacific (Polynesian) ancestry were utilized. Taqman[®] genotyping was carried out, followed by multivariate-adjusted association analysis with gout as the outcome.

Results: MIP-sequencing identified 4 non-synonymous rare variants in exon 5 of *IL37* in 6 gout patients, whereas none were detected in the healthy controls (fisher's exact test; $p=0.043$). Two variants (p.H172HX; p.N182S), present in two individuals, were observed in the Exome Aggregation Consortium database; the private variants (p.A144P; p.C181*) were not. Cluster analysis showed the rare variants in *IL37* significantly cluster ($p=5.71 \times 10^{-5}$).

To elucidate the effect of mutations in *IL37*, a recombinant protein was produced based on the p.C181* mutation. *In vitro*, full length IL37(46-218) significantly decreased ROS and IL8 production. The IL37 mutant demonstrated diminished anti-inflammatory effects compared to the full-length protein.

In our validation cohort, the *rs752113534* variant (p.N182S) was monomorphic in people of European ancestry, but the minor G-allele exhibited a frequency of 0.05 in people of Eastern and Western Polynesian ancestry. A meta-analysis of people of Eastern and Western Polynesian ancestry showed a significant association of the G-allele with gout risk using hyperuricemic controls ($\text{OR}=1.81$, $P_{\text{OR}}=0.03$). As a potential therapeutic, IL37Fc was tested *in vitro* and strongly inhibited ROS and IL8 production.

Conclusion: Rare genetic variants in *IL37* clustering in exon 5 were found in people with gout. One of these *IL37* mutants demonstrated a loss of the anti-inflammatory function *in vitro*. Moreover, the association of *IL37* rare variant *rs752113534* in prevalent gout in people of Polynesian ancestry supports a role for IL37 in an inflammatory pathway leading to gout in the presence of hyperuricemia. Furthermore, IL37Fc was identified as a potential new therapeutic in the treatment of gout.

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Abstract Number: 2249

Not Just a Swollen Big Toe: Increasing All-Cause Hospitalizations in Patients with Gout in the United States: 1993–2014

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Session Information

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Background/Purpose: Gout is a disorder of uric acid metabolism and often presents as acute severe joint pain. However, several recent studies have highlighted systemic complications of associated hyperuricemia in patients with gout, including possible increased risk of renal and cardiovascular comorbidities. We studied all-cause hospitalizations in patients with gout in the United States (US) from 1993 to 2014.

Methods: The Nationwide Inpatient Sample (NIS) is a stratified random sample of all US community hospitals. It is the only US national hospital database with information on all patients, regardless of payer, including persons covered by Medicare, Medicaid, private insurance, and the uninsured. We examined all inpatient hospitalizations in NIS from 1993 to 2014 with a primary or secondary diagnosis of gout, and compared them to total all-cause US hospitalizations during the same period. US population estimates and projections for the resident US population were obtained from the US Census Bureau.

Results: There were 789.8 million all-cause hospitalizations in 6.4 billion person-years of observation from 1993 to 2014 (123.4 hospitalizations per 1,000 person-years). During this time-period, 9,741,598 hospitalizations occurred in patients with gout (152.2 per 100,000 person-years). All-cause US hospitalizations increased from 33.7 million in 1993 to 35.4 million in 2014, an increase of 4.8% over 22 years. All-cause hospitalizations in gout patients have increased from 167,441 in 1993 (64.2 per 100,000 person-year) to 854,475 in 2014 (267.9 per 100,000 person-years, a dramatic increase of over 410% ($p<0.0001$)). In 2014, hospitalizations in gout patients accounted for over 4.6 million hospital days at a total national cost of over US \$42.6 billion.

Conclusion: All-cause hospitalizations in patients with gout in the US have significantly increased by 410% in the last 22 years, almost hundred-fold of the 4.8% increase in US population all-cause hospitalization rate in the same time-period. This calls for an increase need for identification and management of serious co-morbid conditions in patients with gout.

Disclosure: G. Singh, Horizon Pharma, 2, 5; A. Mithal, None.

Abstract Number: 2250

Mitigation of Inflammation Induced By Monosodium Urate Crystals in Mice By Treatment with Svp-Rapamycin

Pallavi Kolte, Robert LaMothe, Joseph Ferrari, Sheldon Leung, Wesley DeHaan, Earl Sands and Takashi Kei Kishimoto, Selecta Biosciences, Watertown, MA

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Initiation of urate-lowering therapies is typically associated with an increase in gout flares due to mobilization of pro-inflammatory urate crystals. SEL-212 is a novel combination product consisting of pegadricase (also known as pegsiticase), a pegylated uricase, co-administered with synthetic vaccine particles encapsulating rapamycin (SVP-R) being developed for the treatment of chronic severe gout. Data from the ongoing open-label Phase 2 multidose study of SEL-212 indicate that SVP-R mitigates the formation of anti-drug antibodies (ADAs) against pegadricase, enabling monthly dosing and sustained control of serum uric acid (sUA) levels in most patients. Despite rapid and sustained reduction of sUA, patients treated with SEL-212 experienced a low rate of flares. Here we evaluated in animal studies whether SVP-R might have a beneficial effect on reducing inflammation induced by monosodium urate crystals (MSU) in addition to its effects on mitigating the formation of ADAs.

Methods: MSU-induced inflammation was investigated in an air pouch model in C57Bl/6 mice. An air pouch was generated on the dorsal aspect of a mouse by injecting sterile air on d0 and d3. Mice were treated intravenously with placebo or SVP-R on d7. MSU crystals were injected in the air pouch on d8 and mice were sacrificed 5 hours after MSU injection. Air pouch exudate was analyzed for cellularity and interleukin-1 β (IL-1 β) levels as markers of inflammation.

Results: Injection of MSU crystals into the air pouch of a mouse has been previously shown to induce an acute inflammatory response characterized by expression of IL-1 β and an influx of neutrophils. Intravenous administration of SVP-Rapamycin reduced the generation of IL-1 β in the air pouch exudate by four-fold (from 131.5 pg/ml to 30.5 pg/ml) and the number of Ly6G+CD11b+ neutrophils by five-fold (from 0.5×10^6 cells/ml to 0.1×10^6 cells/ml).

Conclusion: SVP-R has been shown to mitigate the formation of ADAs to biologic therapies by inducing tolerogenic dendritic cells and antigen-specific regulatory T cells. Here we demonstrate that SVP-R also attenuates inflammatory responses induced by MSU crystals and mediated by innate immune cells. These results may explain why gout patients treated with pegadricase in combination with SVP-R experience an unexpectedly low rate of gout flares.

Disclosure: P. Kolte, Selecta Biosciences, 1, 3; R. LaMothe, Roc LMothe, 1, 3; J. Ferrari, Selecta Biosciences, 1, 3; S. Leung, Selecta Biosciences, 1, 3; W. DeHaan Ph.D., Selecta Biosciences, 1, 3; E. Sands, Selecta Biosciences, 1, 3; T. K. Kishimoto, Selecta Biosciences, 1, 3.

Calcific Tendonitis of the Rotator Cuff: Do We Need Steroid Injection after Ultrasound Guided Percutaneous Lavage? Results of a 12-Months Double-Blind Randomized Controlled Study

Christelle Darrieutort-Laffite¹, Stéphane Varin², Guillaume Coiffier³, Jean-David Albert³, Gregoire Cormier² and **Benoit Le Goff**¹, ¹Rheumatology, Nantes University Hospital, Nantes, France, ²Rheumatology, La Roche-Sur-Yon Hospital, La Roche-Sur-Yon, France, ³Rheumatology, Rennes University Hospital, Rennes, France

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

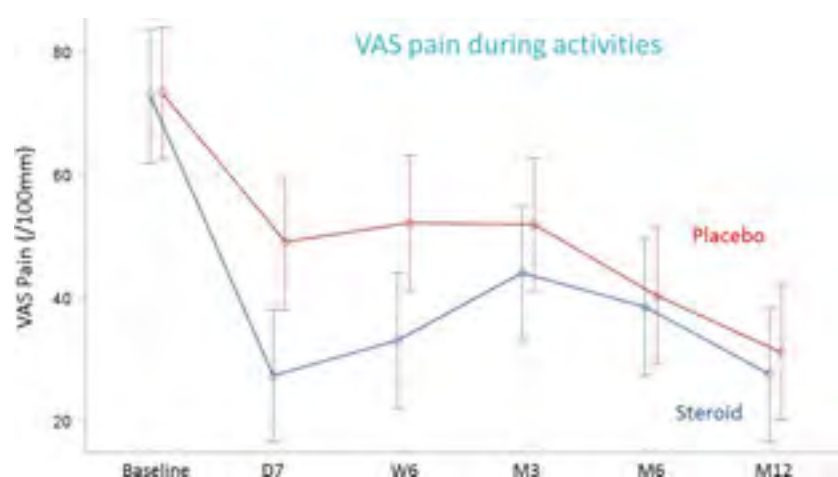
Session Time: 9:00AM-11:00AM

Background/Purpose: Rotator cuff calcific tendinopathy is a common condition causing up to 20% of the painful shoulder. Ultrasound-guided percutaneous lavage (UGPL) is indicated after failure of conservative treatments. Steroids injections in the subacromial bursa (SAB) are usually performed after the lavage to prevent the pain induced by the procedure. However, some suggested that this injection could prevent the inflammatory reaction leading to the disappearance of the calcific deposit. Moreover, its efficacy to prevent post-procedure pain has never been demonstrated. The purpose of the study was to evaluate the effect of a steroid injection in the SAB after UGPL on the pain and the radiographic evolution of the calcification.

Methods: This was a multicentric prospective double-blind randomized controlled study. We included patients with shoulder pain for more than 3 months and a type A or B calcification > 5 mm on X-Ray. Patients were treated with UGPL and, at the end of the procedure, they received a blind injection of either 2 mL of methylprednisolone acetate or 2 mL of serum saline (placebo group). The primary outcome was the maximal VAS pain (0-100) the first week following UGPL. Secondary outcomes were the evolution of VAS pain at 7 days, 6 weeks, 3 months, 6 months and 12 months and the radiographic changes of the calcification during the follow-up.

Results: We included 132 patients: mean age was 49.8 (+/-9.7) years and 89 were females (67.4%). Mean size of the calcification was 1.5 cm (+/- 0.5) and calcifications mainly involved the supraspinatus (86%). Backflow of calcific material was obtained in 107 patients (81.1%). Maximum pain during the first week following UGPL was 71.5 [CI95%:63.9-79.20] in the serum saline group versus 59.8 [CI95%:52.2-67.41] in the steroid group with a mean difference of 11.7 [CI95%:3.7-19.7]. More patients in the placebo group needed to take NSAID (12.1% versus 6.1%) and paracetamol (16.7% versus 9.1%) during the first week. VAS pain during activities decreased significantly more in the steroid group compared to the placebo between the baseline and 3 months while VAS pain was similar at 6 and 12 months (Figure 1). At 12 months, no difference was found in the radiographic evolution: 61.9% of the patients treated with steroid and 65% treated with placebo had more than 50% of resorption of their calcification and complete disappearance of the calcification was obtained in 46% of the steroid group versus 40% of the placebo group.

Conclusion: Our study shows that steroid injection in the SAB leads to a significant decrease of maximal pain during the following week. This treatment also decreases significantly the pain during the 3 first months after UGPL. Importantly, we



found no difference between the 2 groups in the radiographic evolution of the calcification at 12 months. Overall, steroids injections in the SAB can be recommended after UGPL.

Disclosure: C. Darrieutort-Laffite, None; S. Varin, None; G. Coiffier, None; J. D. Albert, None; G. Cormier, None; B. Le Goff, None.

Abstract Number: 2252

Serum Urate Ant Its Clearance in Patients with Chronic Kidney Disease Under Peritoneal Dialysis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Hyperuricemia and gout are common in patients with chronic kidney disease (CKD), some ultimately requiring replacement therapy. Serum urate (SU) levels appear to achieve proper control under hemodialysis [1], making urate-lowering drugs (ULD) unnecessary in this setting. Scant data is available for peritoneal dialysis (PD). The aim of the present study was to assess SU levels and urate clearance in patients with CKD under PD.

Methods: A cross-sectional, monocentric study was performed, enrolling all twenty subjects followed in a PD unit during the study period (2018 Jan-Feb). Treatment modalities employed were continuous ambulatory peritoneal dialysis (CAPD) [n=6]; night intermittent peritoneal dialysis (NIPD) [n=3]; and continuous cyclic peritoneal dialysis (CCPD) [n=11]. Blood, 24h urine and dialysis fluid tests were requested in order to measure SU levels (primary outcome variable) and to estimate urate clearance (total, renal, and peritoneal) and residual kidney function (RKF), according to current guidelines [2]. Hyperuricemia was considered as SU >6.8mg/dl. Demographic, clinical and PD-related variables were also collected to assess factors associated with being on SU target (<6.0 mg/dl). For outcome variables, 95% confidence intervals (95%CI) were estimated, and non-parametric tests (Mann-Whitney U's, Kruskal-Wallis, chi-square, and Fisher's exact) were used to evaluate associations.

Results: Median (IQR) age was 53.5 years (42.3-63.3), being 65% men. Sixty-five percent were on furosemide, and median RKF was 4.7 ml/min/1.73m² (2.1-5.8). Half of subjects were hyperuricemic before initiating PD, only three (15%) reported gout. Urate-lowering drugs (ULD) were currently used in nine patients (45%), mostly allopurinol (n=8, at 100-150 mg/d), febuxostat in one (40 mg/d). In the sample, median SU levels were 5.4 mg/dl [95%CI 4.8-6.0], being 90% <6.8 mg/dl, and 80% <6.0 mg/dl. SU levels did not statistically varied according to the use of ULD (5.6 vs 4.2 mg/dl respectively, p=0.056). Median peritoneal urate clearance was 3.0 ml/min/1.73m² [95%CI 2.5-3.5], that accounted for 71.4% of total urate clearance (4.2 ml/min/1.73m², 95%CI 3.6-4.6). Explanatory variables that significantly associated with a SU on target were peritoneal urate clearance (3.2 vs 2.0 ml/min/1.73m², p=0.006), RKF (4.0 vs 6.4 ml/min/1.73m², p=0.032), and the use of CCPD modality (100% vs 0%, p=0.008). CCPD modality also showed significantly higher peritoneal urate clearance compared to CAPD and NIPD (3.7, 2.7, and 1.3 ml/min/1.73m², respectively, p=0.011).

Conclusion: Most CKD patients under PD showed SU levels on target, suggesting that PD is effective for hyperuricemia management. ULDs appear then unnecessary in this setting. The CCPD modality showed the best results in terms of urate levels and its clearance, finding that may be of interest for CKD patients with gout.

References: [1] *Arthritis Rheumatol.* 2016;68suppl10: abstract #205. [2] Clinical practice guidelines for peritoneal adequacy, update 2006. *Am J Kidney Dis.* 2006;48 Suppl1:S91.

Disclosure: C. Diez, None; J. Pérez-Contreras, None; M. Andrés, None.

Cardiovascular Disease, Other Purported Risk Factors, and Allopurinol-Associated Severe Cutaneous Adverse Reactions: A General Population-Based Cohort Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

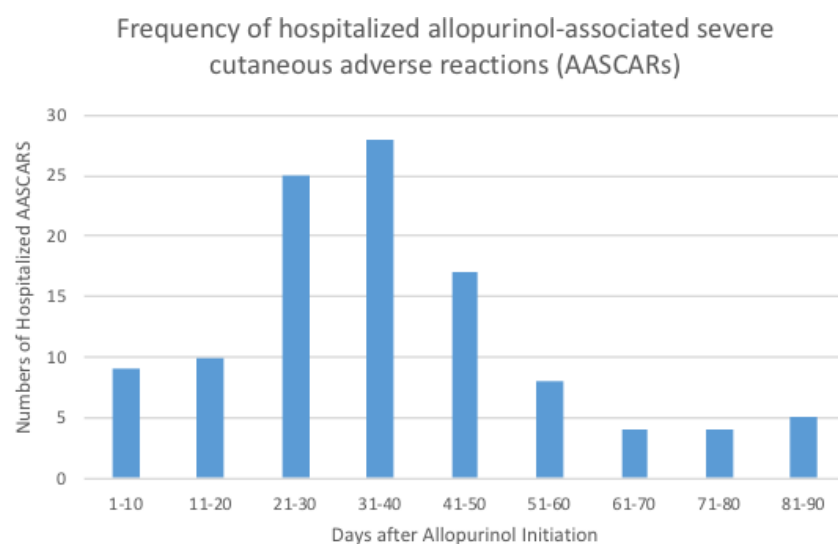
Session Time: 9:00AM-11:00AM

Background/Purpose: A recent US Medicaid study found that in addition to certain races (Asians and Blacks), older age, female sex, chronic kidney disease (CKD), and initial allopurinol dose >100 mg/day are associated with a higher risk of hospitalized allopurinol-associated severe cutaneous adverse reactions (AASCARs) (*Ann Rheum Dis* 2018). We aimed to replicate these findings in a general population database from another country (Canada) and expand our investigation for an independent role of cardiovascular disease (CVD) on the risk of AASCARs.

Methods: We used Population Data BC, a population-based administrative database that covers the entire general population of British Columbia, Canada, to identify incident allopurinol users between 1999 and 2012. We examined the risk of hospitalized AASCARs according to purported key risk factors and used Poisson regression models to calculate relative risks (RR), adjusting for purported risk factors for AASCARs (**Table**).

Results: Among 451,897 allopurinol initiators, we documented 110 hospitalized AASCAR cases (mean age, 62 years; 71% male) during a mean follow-up of 3 months. The risk of hospitalized AASCARs was apparent within 10 days of allopurinol initiation, peaked around one month after initiation, and declined progressively thereafter, reaching its nadir at the end of the third month (**Figure**). Of the 110 cases, 10 (9%) died during hospitalization. The overall risk of hospitalized AASCARs was 1 out of 1185 allopurinol initiators (**Table**). Female sex, older age (>60 years), CKD, and initial allopurinol dose (>100mg/day) were independently associated with a 2.6-, 1.5-, 1.7-, and 2.8-fold higher risk of AASCARs, respectively (**Table**). CVD was associated with a 2.5 higher risk of AASCARs after adjusting for other risk factors (RR, 2.45; 95% CI, 1.59 to 3.77), whereas diuretic use, a previously suspected risk factor, was not (RR, 1.05; 95% CI, 0.69 to 1.60) (**Table**).

Conclusion: This general population-based cohort study confirms the independent role of older age, female sex, CKD, and initial allopurinol dose (>100 mg/day) in predicting a higher risk of AASCARs. Furthermore, having CVD is also strongly



associated with an increased risk of AASCARs, independent of these risk factors. These factors should be considered when initiating allopurinol to help prevent this extremely severe and potentially fatal adverse reaction.

Table 1 Risk of Hospitalized Allopurinol-Associated Severe Cutaneous Adverse Reactions According to Purported Risk Factors

Risk Factor	Allopurinol Initiators, N (%)	Hospitalized SCARs, N	Risk of Hospitalized AASCARs (/1000 persons)	Age-, Sex-Adjusted Relative Risk	Multivariable Relative Risk
All	130441 (100)	110	0.84 (0.69 to 1.02)	-	-
Sex					
Male	93175 (71.4)	49	0.53 (0.39 to 0.70)	1.0	1.0
Female	37266 (28.6)	61	1.64 (1.25 to 2.10)	2.69 (1.84 to 3.95)	2.59 (1.75 to 3.84)
Age					
<60 years	53898 (41.3)	23	0.43 (0.27 to 0.64)	1.0	1.0
≥60 years	76543 (58.7)	87	1.14 (0.91 to 1.40)	2.16 (1.35 to 3.44)	1.54 (0.94 to 2.54)
Chronic Kidney Disease					
Yes	15885 (12.2)	27	1.70 (1.12 to 2.47)	1.87 (1.21 to 2.90)	1.72 (1.08 to 2.74)
No	114556 (87.8)	83	0.72 (0.58 to 0.90)	1.0	1.0
Hypertension					
Yes	80095 (61.4)	85	1.06 (0.85 to 1.31)	1.52 (0.96 to 2.42)	1.23 (0.74 to 2.05)
No	50346 (38.6)	25	0.50 (0.32 to 0.73)	1.0	1.0
Cardiovascular Disease					
Yes	31617 (24.2)	56	1.77 (1.34 to 2.30)	2.58 (1.74 to 3.83)	2.45 (1.59 to 3.77)
No	98824 (75.8)	54	0.55 (0.41 to 0.71)	1.0	1.0
Diabetes					
Yes	32892 (25.2)	36	1.09 (0.77 to 1.52)	1.13 (0.75 to 1.69)	0.87 (0.57 to 1.33)
No	97549 (74.8)	74	0.76 (0.60 to 0.95)	1.0	1.0
Diuretic Use					
Yes	42610 (32.7)	56	1.31 (0.99 to 1.71)	1.42 (0.95 to 2.11)	1.05 (0.69 to 1.60)
No	87831 (67.3)	54	0.61 (0.46 to 0.80)	1.0	1.0
Gout					
Yes	79802 (61.2)	57	0.71 (0.54 to 0.93)	0.80 (0.54 to 1.17)	0.72 (0.49 to 1.06)
No	50369 (38.8)	53	1.05 (0.78 to 1.37)	1.0	1.0
Initial Allopurinol Dose (>100 mg/d)					
Yes	82931 (63.6)	87	1.05 (0.84 to 1.29)	2.48 (1.56 to 3.93)	2.81 (1.76 to 4.48)
No	47510 (36.4)	23	0.48 (0.31 to 0.73)	1.0	1.0

Disclosure: N. Lu, None; C. Yokose, None; H. Xie, None; G. Li, None; S. K. Rai, None; S. C. Kim, None; H. K. Choi, Takeda, Selecta, Kowa, and Horizon, 5, Selecta and Horizon, 2.

Abstract Number: 2254

Update of SEL-212 Phase 2 Clinical Data in Symptomatic Gout Patients: Svp-Rapamycin Combined with Pegadricase Mitigates Immunogenicity and Enables Sustained Reduction of Serum Uric Acid Levels, Low Rate of Gout Flares and Monthly Dosing

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Pegylated uricases are promising therapies for the treatment of severe chronic gout, but are limited by their immunogenicity. We have previously shown that synthetic vaccine particles encapsulating rapamycin (SVP-R) co-administered with pegadricase (also known as pegsiticase) prevented the formation of ADAs in a dose-dependent manner. A Phase 1 study of SEL-212, a novel combination product consisting of pegadricase and SVP-R, demonstrated sustained control of serum uric acid (sUA) for at least 30 days after a single dose. Here we report data on the safety, tolerability, and effects on sUA, ADAs, and gout flares of repeated monthly doses of SEL-212 in symptomatic gout patients treated with 0.125 or 0.15 mg/kg SVP-R in combination with 0.2 or 0.4 mg/kg pegadricase.

Methods: Patients with symptomatic gout (≥1 tophus, gout flare within 6 months, and/or gouty arthropathy) and elevated sUA (sUA≥6 mg/dL) were enrolled in SEL-212 treatment cohorts. Patients reported here received three monthly doses of

SEL-212 (0.2mg/kg or 0.4mg/kg pegadricase combined with 0.125 or 0.15 mg/kg SVP-R) followed by two monthly doses of pegadricase alone. Safety, tolerability, sUA, and ADAs were monitored, and clinical data were collected.

Results: As of 1 June 2018, 143 patients had been dosed in the Phase 2 study. Approximately 81% of evaluable patients receiving 0.125 or 0.15mg/kg SVP-R administered with either 0.2 or 0.4 mg/kg pegadricase maintained serum uric acid levels substantially below 6 mg/dl at week 12 after three monthly doses of SEL-212. The sustained reduction of sUA correlated with low or no ADAs. SEL-212 was generally well tolerated and associated with a low rate of gout flare rates. Thirty-three percent of evaluable patients treated with 0.125-0.15mg/kg SVP-R, and only 27% of all current patients in the SEL-212 Phase 2 trial, experienced gout flares after initiation of first treatment with continued reduction of gout flare rates over months two through five. This low rate of gout flares appears to be in contrast with higher incidence of gout flares reported in clinical trials involving other urate lowering therapies.

Conclusion: SEL-212 has been well-tolerated, showing substantially reduced immunogenicity, sustained control of sUA, and low rate of gout flares with repeated monthly dosing.

Disclosure: E. Sands Selecta Biosciences, 1, 3; A. J. Kivitz, Novartis, 1, AbbVie, Boehringer Ingelheim, Flexion, Genzyme, Janssen, Pfizer Inc, Regeneron, Sanofi, Sun Pharma, UCB, 5, Celgene, Flexion, Genentech, Genzyme, Horizon, Ironwood, Merck, Novartis, Pfizer Inc, Regeneron, Sanofi, 8, Altoona Center for Clinical Research, 9; W. DeHaan Ph.D., Selecta Biosciences, 1, 3; L. Johnston, Selecta Biosciences, 1, 3; T. K. Kishimoto, Selecta Biosciences, 1, 3.

Abstract Number: 2255

Increased Cost Burden in an Early Diagnosed Cohort of Uncontrolled Versus Controlled Gout: Analysis of a Large US Payer Database

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic and Clinical Science Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Gout is a progressive systemic inflammatory disease that is widely prevalent, estimated to effect 3.9% or 8.3 million people of the United State (US) population. The underlying pathogenic feature of gout is hyperuricemia, and appropriate management of gout requires achieving uric acid levels at a minimum of <6 mg/dL to mobilize and clear deposited urate. Uncontrolled gout patients who fail to reach serum uric acid(sUA) level goals do worse in terms of clinical outcomes including gout flares and resolution of visible tophi. Herein, we quantify the cost burden for uncontrolled versus controlled gout patients from a large US payer de-identified database.

Methods: A retrospective review of Humana Healthcare data from 2007 to 2016 in private pay and medicare patients was performed for patients with gout diagnosis codes (ICD9/10) to identify patients with at least 1 gout diagnosis (N=539,802) and 90 days of continuous urate-lowering therapy within 1 year of diagnosis. Two cohorts of patients were categorized according to their sUA levels after at least 90 days of gout therapy: sUA<6.0 mg/dL(controlled) and sUA ≥8 mg/dL (uncontrolled). Patients must have had more than 1 serum uric acid test to be included.

Results: The controlled gout group (sUA<6 mg/dL)included 5,473 patients and the uncontrolled gout group (sUA≥8 mg/dL) had 1,358 patients. The two groups were comparable in terms of demographic features, though the controlled group was slightly younger with an adjusted mean age of 72.5 years compared to mean age of 69.1 in the uncontrolled patients. Costs were higher among the patients in the uncontrolled gout group (**figure 1**). Among total costs, the controlled group mean/patient/year was \$14,892 as compared to the uncontrolled gout patients of \$23,339 (p<0.0001). The cost difference was primarily driven by increased hospital costs within the refractory group, where the cost was \$7,255/patient/year greater than the controlled group (p<0.0001, **figure 1**).

Conclusion: Accepted guidelines for gout management recommend treating to uric acid levels of <6 mg/dL for all patients and <5 mg/dL for tophaceous or symptomatic patients. This analysis sought to quantify costs associated with uncontrolled hyperuricemia (≥8 mg/dL) in early diagnosed gout patients, and found that uncontrolled gout patients had significantly higher per-patient mean total costs and costs from hospitalizations. This disparity may likely be greater in patients with long-standing gout. This finding suggests an increased financial burden associated with uncontrolled gout, and warrants further study.

References: Neogi T. *NEJM*, 2011;364:443-52
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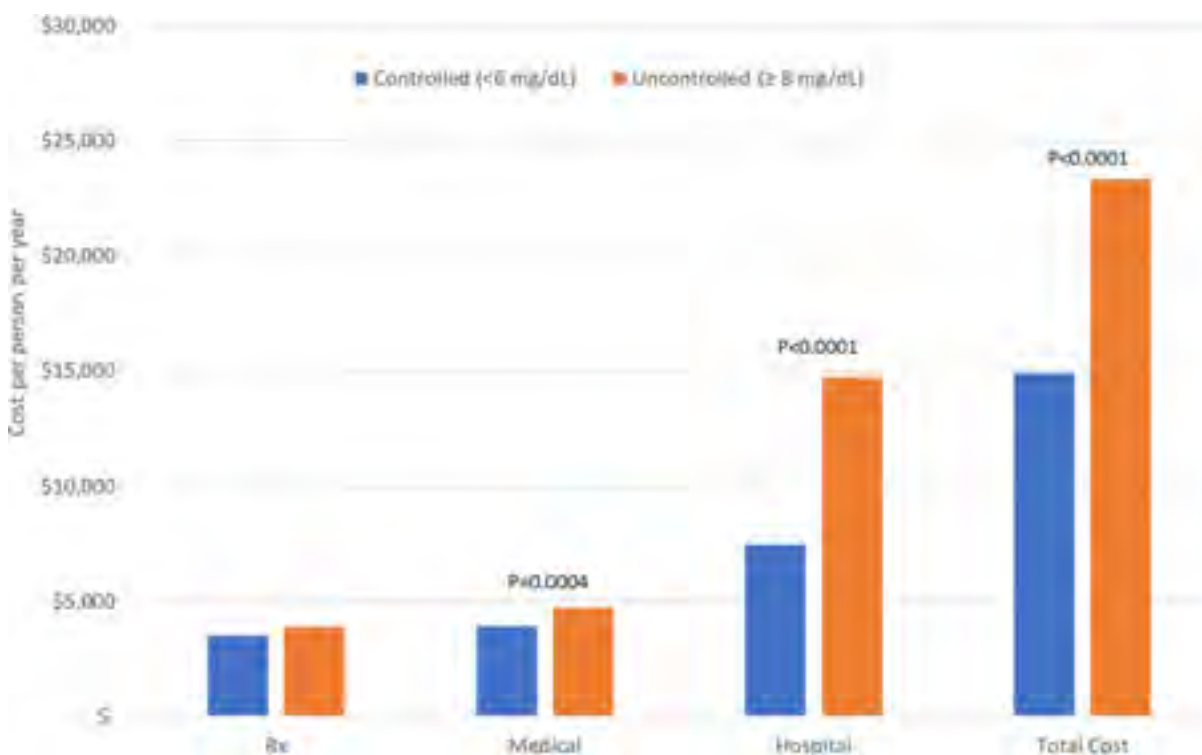


Figure 1:

Disclosure: B. LaMoreaux, Horizon Pharma, 1, 3; M. Francis-Sedlak, Horizon Pharma USA, Inc., 1, 3; R. J. Holt, Horizon Pharma USA, Inc., 1, 3.

Abstract Number: 2256

Rheumatic Diseases Associated with Neuromyelitis Optica Spectrum Disorders (NMOSD): Prevalence, Clinical, Laboratory and Imaging Characteristics

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster III: Sarcoid, Inflammatory Eye Disease, and Autoinflammatory Disease

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: NMOSD are autoimmune disorders characterized by optic neuritis (ON), longitudinal extensive transverse myelitis (LETM), and other clinical features. Aquaporin 4 antibodies (AQP4 Ab) have enhanced diagnostic

accuracy of NMOSD. We aimed to characterize the clinical features, diagnostic laboratory and imaging studies of NMOSD in our Afro-Caribbean patient population to identify associated autoimmune disorders.

Methods: Retrospective chart review of patients ≥ 18 years of age, with a diagnosis of multiple sclerosis, optic neuritis, acute transverse myelitis and NMOSD at 2 urban hospitals from 1/2005 to 4/2017. Demographics, clinical presentation, laboratory, imaging and treatment data were collected to confirm NMOSD as per International Panel for NMOSD Diagnosis. Imaging studies were reviewed for NMOSD details by a Neuro-radiologist.

Results: Of the 1,227 charts reviewed, 39 patients (3.17%) met criteria for NMOSD. Of those 82.1% had positive AQP4 Abs., 87.2% were women, 84.6% were Blacks, and 38.7% had another autoimmune disease, with SLE being the most common (66.7%). ANA and anti-dsDNA were positive in 41.7% and 21.4% of the patients respectively. Motor weakness (55.3%) and visual changes (35.9%) were the most common presenting symptoms. In brain-MRI 62.8% of patients had non-specific white matter lesions, followed by T2 hyperintense lesions in optic nerve (37.1%), spindle like hemispheric lesions (34.3%), and dorsal medulla lesions (34.3%). Spine MRI revealed LETM in 48.6%, and gadolinium enhancement in 68.6% of the cases. Initial therapy included pulse CS in 53.5% followed by pulse CS-plasma exchange(PLEX) (23.1%) and pulse CS-PLEX-IVIG (7.7%). Maintenance therapy included CS in 38.5%, followed by CS-AZA (17.9%) and CS-MMF (10.3%). Four cases received Rituximab after initial therapy. 89.4% of the patients had follow-up imaging. Among the 7 cases of AQP4 negative NMOSD patients, M:F ratio was 2:5, and only 14.3% had other autoimmune diseases, tended to have a lower disability score when compared to AQP4 positive patients, and 50% had optic nerve involvement.

Conclusion: NMOSD prevalence in our population was higher (3.2% vs. 1.5%) than previously reported among patients with suspected inflammatory demyelinating disease. Black middle age women were most frequently affected. SLE was the most prevalent rheumatic disease present prior to NMOSD diagnosis in the majority of the cases. AQP4 seronegative cases had higher male ratio, less association with autoimmune diseases, lower disability scale score and less abnormalities on MRI except for optic nerve involvement.

1227 Neurological Cases identified by ICD codes
Number of NMOSD patients: 39 NMOSD Prevalence 3.2%

No. of women	87.2 % (34/39)
No. of men	12.8 % (5/39)
Women age in years (mean \pm SD)	44.6 \pm 12.2
Men age in years (mean \pm SD)	45 \pm 14.1
Race	
White/Caucasian	0/39
Black	84.6 % (33/39)
Other	15.38 % (6/39)
Ethnicity	
Hispanic	5.1% (2/39)
Family history of Autoimmunity	30.7% (8/26)
Other Autoimmune disease	38.7% (12/31)
Sjögren syndrome	16.7 % (2/12)
SLE	66.7% (8/12)
Graves disease	8.3% (1/12)
Hypothyroidism	8.3 % (1/37)
Presenting features	
Visual changes	35.9 % (14/39)
Expanded Disability Scale Score (EDSS) mean	4.6 \pm 1.2
Acute Myelitis /sensory level	28.6 % (10/35)
Optic neuritis	30.7 % (12/39)
Motor weakness	55.3 % (21/38)
Positive Auto-antibodies	
AQP4 IgG	82.1% (32/39)
ANA	41.7 % (15/36)
ANA w/out other autoimmune disease	28.6 % (8/28)
Anti ds-DNA	21.4% (6/28)
Anti-SSA	40 % (12/30)
Anti-SSA + SSB	23.3 % (7/30)
Anti-Smith	9.7 % (3/31)
Anti-RNP	20 % (5/25)
Anticardiolipin IgM	4.5% (1/22)
Anti- β 2 GPI	9 % (2/22)
Anti-Scl-70	4.5 % (1/17)
Anti-Centromere	0 % (0/21)
MRI Imaging Findings Brain	
Non-specific white matter lesions	62.8 % (22/35)
Spindle like hemispheric lesions	34.3 % (12/35)
Dorsal medulla lesions	34.3 % (12/35)
Area postrema lesions	25.7 % (9/35)
Gadolinium enhancement	31.4 % (11/35)
T2 hyperintense lesions in optic nerve	37.1 % (13/35)
MRI Imaging Findings Spine	

Table . (Cont'd)

1227 Neurological Cases identified by ICD codes Number of NMOSD patients: 39NMOSD Prevalence 3.2%	
Longitudinal Extensive Transverse Myelitis (LETM)	48.6 % (17/35)
Gadolinium enhancement	68.6 % (24/35)
Initial therapy	
No therapy	5.1 % (2/39)
Pulse CS	53.5 % (21/39)
Pulse CS + Plasma Exchange (PLEX)	23.1 % (9/39)
Pulse CS + IVIG	5.1 % (2/39)
Pulse CS + PLEX + Rituximab	5.1 % (2/39)
Pulse CS + PLEX + IVIG	7.7 % (3/39)
MMF	2.6 % (1/39)
CYC	2.6 % (1/39)
Maintenance therapy	
No therapy	12.8 % (5/39)
CS	38.5 % (14/39)
CS + AZA	17.9 % (7/39)
CS + MMF	10.3 % (4/39)
CS + Rituximab	2.6 % (1/39)
Rituximab	5.1 % (2/39)
MMF	5.1 % (2/39)
CS + AZA + IVIG + Rituximab	2.6 % (1/39)

Comparison of AQP4 positive vs. AQP4 negative cases

	Seropositive NMO (32 cases AQP4+)	Seronegative NMO (7 cases AQP4-)
M:F ratio	3:29	2:5
Other autoimmune diseases	11/31	1/7
ANA	13/32	2/7
Anti-dsDNA	5/32	1/6
Anti-SSA	11/23	0/6
Anti SSA+SSB	7/24	0/6
Expanded Disability Scale Score (EDSS)	5.74 ± 2.3	4.07 ± 1.23
MRI findings		
White matter lesions	18/30	2/6
Gadolinium enhancement	21/29	3/6
Optic Nerve involvement	11/29	3/6
Longitudinal extensive transverse myelitis (LETM)	24/29	2/6

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Abstract Number: 2257

Prevalence and Distinct Clinical Phenotype of Concomitant Sarcoidosis in Other Autoimmune Rheumatic Diseases

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster III: Sarcoid, Inflammatory Eye Disease, and Autoinflammatory Disease

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Lung involvement is common in both sarcoidosis (up to 90%) and autoimmune rheumatic diseases (ARDs). Case reports have suggested distinct clinical manifestations when sarcoidosis is diagnosed with other ARDs. However clinical and serological manifestations have not been described in larger cohorts.

Methods: A retrospective medical chart review of patients attending our centre with a diagnosis of sarcoidosis and ARD. ARD was classified as systemic sclerosis (SSc), lupus, myositis or inflammatory arthritis (IA). Organ manifestations were further classified into sarcoid or ARD as the main pathology. Comparison was made between the SSc/sarcoid cohort and other ARD/sarcoid cohort. Statistical analysis of organ involvement was performed using Fisher exact test.

Results: 61 patients (17 males) with overlap sarcoid and ARD were identified, with 5 patients having more than one ARD diagnosis. The mean time lag between sarcoid diagnosis to ARD diagnosis was 51 months (median 71 mths) (range -432 to 372 mths). Sarcoid predates diagnosis of ARD in 68.8% cases.

The majority of patients had an overlap diagnosis of SSc(n=22, 36.1%), of those 77.3% were limited SSc. In the SSc/sarcoid cohort, 92% patients were ANA positive, 35% Scl70 positive, and 21% ACA positive.

In the ARD/sarcoid cohort, the most frequent overlap diagnosis was IA (72%). 23% were ANA positive, 35.8% rheumatoid factor positive, and 30.8% anti-CCP positive.

The frequency of major organ involvement was statistically different for lung disease, arthritis and sarcoid-skin involvement between SSc/sarcoid and ARD/sarcoid cohorts. A trend of increased frequency of pulmonary hypertension in SSc/sarcoid cohort was observed (table 1).

Further evaluation of interstitial lung disease (ILD) highlighted, overall 32% was attributable to sarcoid, and 19% related to ARD. In the SSc/sarcoid cohort, 22% had features of sarcoid ILD (bronchovascular beading or pulmonary nodularity), 45.5% had ILD consistent with SSc (non-specific interstitial pneumonia (NSIP)). In contrast, 38% of the ARD/sarcoid cohort had sarcoid predominant ILD (peribronchovascular beading, pulmonary nodules, and cystic lung disease), and 5% had ARD ILD (NSIP-ILD, and organising pneumonia). Baseline FVC was not different between SSc/sarcoid and ARD/sarcoid ILD cohorts (91.6% and 86.2% respectively).

Conclusion: We report the largest cohort to date of patients with a concomitant diagnosis of sarcoidosis and ARD from a single centre cohort. Our data suggest that lung involvement in overlap SSc/sarcoid is less frequent than expected for each disease in isolation. The significant difference between arthritis between the SSc/sarcoid group and ARD/sarcoid group is likely due to the high proportion of IA in the latter group.

Our results highlight the importance of recognising concurrent sarcoidosis in multisystem ARD, especially as this may affect treatment and outcome.

Table 1 Frequency of key organ involvement for SSc/Sarcoid and ARD/Sarcoid

Organ involvement	SSc/Sarcoid (n)		ARD/Sarcoid (n)		Fisher exact test (p=)
	SSc	Sarcoid	ARD	Sarcoid	
hilar lymph node (LN)	0	14	0	25	1
Lung	10	5	2	15	0.001
Eyes	0	3	0	7	0.735
Cardiac	0	1	1	5	0.616
Muscle	7	0	3	0	0.272
Arthritis	5	2	32	3	p<0.001
Sarcoid skin	0	11	0	7	0.0177
Neurology	0	0	0	2	0.53
Liver	0	1	0	6	0.405
Parotid	0	2	0	7	0.467
Calcium	0	1	0	1	1
Peripheral LNs	0	1	0	8	0.138
Pulmonary hypertension	4	0	1	1	0.052
Renal	1	0	1	0	1
Gastrointestinal	2	0	0	0	0.126
other	0	4	0	7	0.999

Disclosure: K. E. N. Clark, None; H. Beynon, None; C. P. Denton, None; V. H. Ong, None.

Abstract Number: 2258

Defining Characteristics of Patients with Overlap between Sarcoidosis and Connective Tissue Diseases

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Session Information

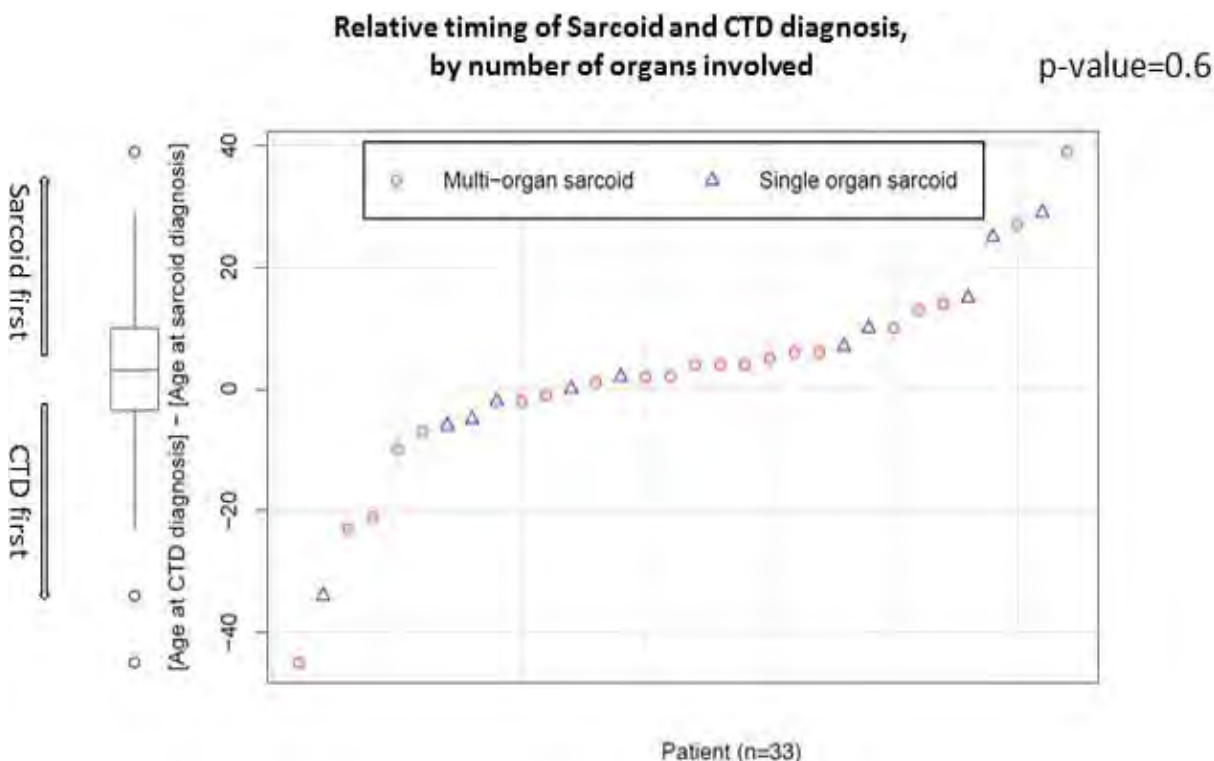
Session Date: Tuesday, October 23, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster III: Sarcoid, Inflammatory Eye Disease, and Autoinflammatory Disease

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Session Time: 9:00AM-11:00AM

Background/Purpose: Sarcoidosis has been suggested to occur with connective tissue diseases (CTDs) more frequently than would be expected by chance, but the types, relative timing, and prognosis of the associated CTDs are not well-described. The objective of this study is to define relative timing of sarcoidosis with CTD to determine whether one could predispose to another. Our secondary objectives are patient demographics, medication triggers, antibody profiles and frequency of overlap with each CTD. We analyzed a large institutional retrospective cohort of patients with overlapping CTD and sarcoidosis, to identify and explore these features.



Methods: For this descriptive study using retrospective chart review we identified patients with a dual diagnosis of sarcoidosis and one of 6 other CTDs (RA, SLE, inflammatory myositis, SpA, SSc or Ss) seen within the Division of Rheumatology from October 2015 to October 2017 in our health system, using ICD-10 codes. These were manually validated by chart review. If patients did not have a diagnosis of CTD and/or sarcoidosis confirmed by Rheumatology or lacked data to validate both of these diagnoses by ACR classification, they were excluded.

Results: 66 charts matched our query and on individual review, 33 patients fulfilled our criteria. 70% of our patients were female and 64% were black. Mean age at diagnosis of CTD was 46 (SD 16.4) years and of sarcoidosis was 44 (14.4) years. There was no predisposition towards development of sarcoidosis or CTD first ($p=0.6$). 58% (19) of patients had RA, 15% (5) had SLE, 15% (5) SSc, 9% (3) SpA, and 3% (1) myositis. 12% (4) of patients had secondary Ss. Lung was the most common organ involved with sarcoidosis (88%); 58% of patients had Scadding stage I disease, and only 1 (3%) had stage IV disease. The odds of single organ sarcoidosis were not different whether the CTD or sarcoidosis was diagnosed first ($p=0.7$); the order of diagnosis did not predict sarcoidosis remission ($p=0.3$). There was a high prevalence of positive ANA throughout the cohort (73% of the 24 with available data). Of 29 patients with data, RF was present in 9 (45%) patients with RA, versus 1 (11%) of patients without RA ($p=0.1$). TNF-alpha inhibitor induced sarcoidosis developed in two patients with RA and one with SpA.

Conclusion: The timing of CTD and sarcoidosis development in this cohort does not argue for a strong effect of CTD predisposing to sarcoidosis or vice versa, and the clinical course of sarcoidosis is similar whether diagnosed before or after the CTD. RA was most commonly associated with sarcoidosis. A High prevalence of Scadding Stage I disease may point to a close link of sarcoidosis with inflammatory disease, as does a high prevalence of ANA and RF across the cohort. Further information from a case control study is needed to draw generalizable conclusions.

Disclosure: M. Agrawal, None; C. Ligon, None.

BONE Sarcoidosis: A French Case Control Study

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Session Information

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Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster III: Sarcoid, Inflammatory Eye Disease, and Autoinflammatory Disease

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Osseous manifestations of sarcoidosis are uncommon. We aimed to characterize clinical presentation, distribution of lesions, treatment, and outcomes of bone sarcoidosis.

Methods: A French retrospective multicenter study of patients with biopsy-proven sarcoidosis and osseous manifestations was analyzed. Inclusion criteria for sarcoidosis with bone involvement were 1) a biopsy-proven granuloma without caseous necrosis and either 2) bone clinical manifestations or 3) abnormal bone imaging. Musculoskeletal involvement with isolated joint or muscular manifestations was excluded. Sarcoidosis patients with bone involvement (patients) were compared to 264 age- and sex-matched patients with a biopsy-proven sarcoidosis and no bone manifestations (controls).

Results: In bone sarcoidosis group (n=88), the median age [IQR] at sarcoidosis diagnosis was 41 [34-51] years, and 44 (50%) patients were women. Forty two out of 88 (48%) patients had bone related symptoms, involving mainly axial (69%) and/or appendicular (58%) skeleton. On imaging, spine was the most commonly affected bone (52%), followed by pelvis (42%), hands (22%) and femur (19%). Bone biopsy showed granuloma without caseous necrosis in 17/25 (68%) patients. Compared to controls, bone sarcoidosis patients had higher rates of mediastinal (93% vs 47%, $P < 0.0001$) and extra-thoracic lymph node (66% vs 21%, $P < 0.0001$), and pulmonary (90% vs 65%, $P < 0.0001$) and cutaneous involvement (44% vs 23%, $P < 0.0001$). Gastro-intestinal involvement was less frequent in bone sarcoidosis group (1% vs 17%, $P < 0.0001$). Hypercalcemia was observed in 8.5% of patients compared to 2% of controls ($P=0.014$). Seven patients did not receive specific treatment for bone sarcoidosis. Glucocorticoid was used in 63/81 (78%) patients, alone in 44 patients, and associated with methotrexate in 13 patients or hydroxychloroquine in 6 patients. Rates of clinical and/or radiological response of bone sarcoidosis were 23/44 (52%), 9/13 (70%) and 4/6 (67%), respectively.

Conclusion: In patients with bone sarcoidosis, spine and pelvis were the most commonly affected bones. Patients with bone sarcoidosis compared to sarcoidosis patients with no bone involvement have higher rates of thoracic and extra-thoracic lymph node, pulmonary, cutaneous involvement and hypercalcemia. Most patients with bone sarcoidosis had a good response to glucocorticoids used alone or in association with methotrexate or hydroxychloroquine.

Disclosure: I. Ben hassine, None; C. Rein, None; C. Comarmond, None; C. Chapelon-Abric, None; N. Saidenberg, None; B. Meunier, None; N. Schleinitz, None; N. Chanson, None; M. Scherlinger, None; C. Richez, None; S. Hirschi, None; M. Groh, None; H. Devilliers, None; D. Saadoun, None; L. Arnaud, None; P. Cacoub, None.

Musculoskeletal Sarcoidosis: A 15-Year Experience from a Tertiary Care Center in the US

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Session Information

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Session Time: 9:00AM-11:00AM

Background/Purpose: Sarcoidosis, a systemic disease characterized by non-caseating granulomas within the affected organs. Less than 10% of cases manifest as musculoskeletal (MSK) involvement of joints, muscles and bone tissue. Common first line therapies for MSK sarcoidosis are NSAIDs and systemic steroids. Due to its rarity, studies assessing clinical presentation and therapeutic efficacy of disease modifying drugs are rare.

We aim to determine prevalence of MSK sarcoidosis at University of Iowa Hospitals and clinics, describe epidemiologic and clinical characteristics of MSK sarcoidosis and describe various therapeutic agents and their outcomes in our cohort.

Methods: We conducted an IRB-approved, retrospective electronic medical records (EMR) search using ICD-9 codes for sarcoidosis followed by review of individual records to identify patients with MSK sarcoidosis between January 1, 2000 and December 31, 2014.

MSK sarcoidosis cases were based on:

a. Lofgren syndrome, or : b. biopsy-proven sarcoidosis and chronic arthritis not attributed to other causes, or

c. biopsy-proven sarcoidosis of MSK tissue (bone, muscle). : Clinical data from the MSK sarcoid cases was then entered into a standardized questionnaire created in REDCap. Statistical analysis was done using REDCap.

Results: Among 1016 patients with sarcoidosis, 58 patients met the inclusion criteria, making the prevalence 5.70%. Epidemiological and clinical characteristics were as follows: Mean age (47.21 years); Female (74.14%); Caucasian (82.76%), African American (10.34%), Lofgren syndrome (46.55%), chronic arthritis (24.14%), osseous sarcoid (25.86%), myopathy (6.90%) (Figure 1). Most commonly involved sites in Lofgren syndrome was ankle (96.30%), in chronic arthritis

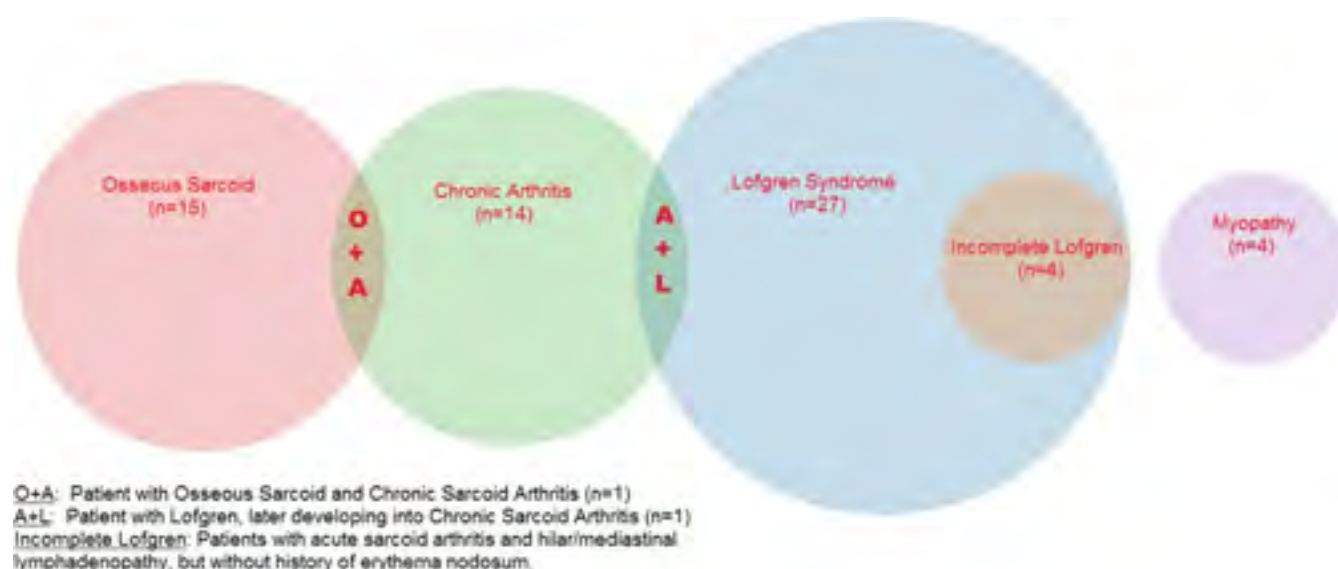


Figure 1. Venn diagram showing distribution of various MSK sarcoidosis manifestations in our cohort.

was finger joints (71.43%), in Osseous sarcoid was pelvis (53.33%), in Myopathy was proximal upper and lower extremity muscles.

Treatment was considered not necessary in 14.81% with Lofgren syndrome and 26.67% with osseous sarcoid. Most commonly used medication was prednisone (59.26% Lofgren, 57.14% chronic arthritis, 60% osseous, 75% myopathy). Methotrexate was the most commonly (25.86%) used DMARD. Biologics (anti-TNF agents) were used for chronic arthritis (n=1), osseous sarcoid (n=1) and myopathy (n=1).

Conclusion: To our knowledge, this is the largest case series describing all forms of MSK sarcoidosis in the US since 1984. MSK sarcoidosis appears to be seen in a small fraction of patients with sarcoidosis, with Lofgren syndrome being the most frequent and myopathy least frequent MSK manifestation. Ankle was most commonly involved in Lofgren and finger joints in chronic arthritis. Osseous sarcoid was seen most commonly in pelvis. Prednisone was most commonly used medication and methotrexate was the most commonly used DMARD across all forms of MSK sarcoidosis. Anti-TNF medications were used in a small minority of patients.

Disclosure: S. Patil, None; M. Arakane, None; S. Jenigiri, None; E. Field, None; N. Singh, None.

Abstract Number: 2261

Long-Term Outcome of Pulmonary Sarcoidosis: A Population-Based Cohort Study from 1976-2013

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Session Information

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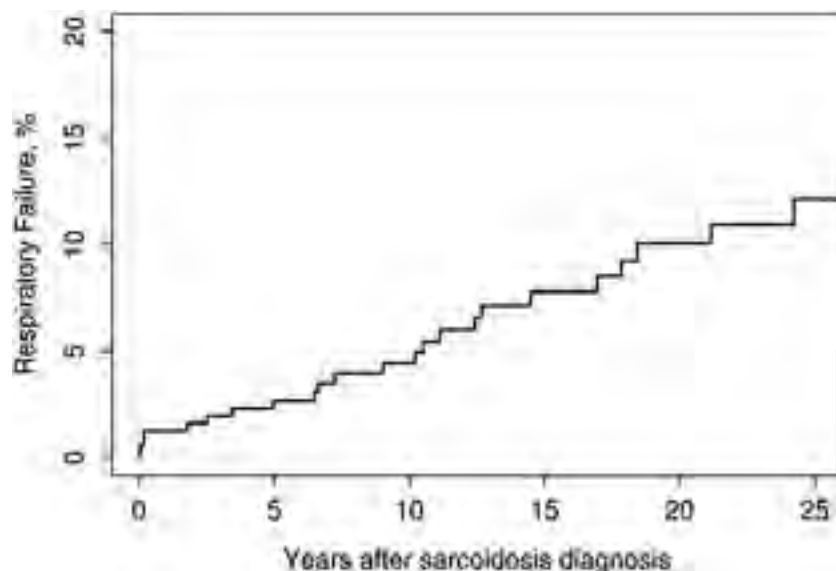
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Long-term Outcome of Pulmonary Sarcoidosis: A Population-Based Cohort Study from 1976-2013

Background/Purpose: A hallmark of sarcoidosis is lung disease, which has variable expression. This study was undertaken to better understand the course of pulmonary sarcoidosis.

Methods: A cohort of 311 incident cases of pulmonary sarcoidosis in a geographically well-defined population from 1976-2013 was identified from the comprehensive medical record-linkage system. Diagnosis of sarcoidosis required physician



diagnosis supported by biopsy showing non-caseating granuloma, radiographic evidence of intrathoracic sarcoidosis and compatible clinical presentations without evidence of other granulomatous diseases. Medical records of the confirmed cases were reviewed from diagnosis to last follow-up. Data on stage of pulmonary sarcoidosis at diagnosis, serial pulmonary function tests (total lung capacity [TLC], forced vital capacity [FVC], forced expiratory volume in 1 second [FEV1] and diffusing capacity for carbon monoxide [DLCO]), requirement of oxygen therapy and treatment were abstracted. The cumulative incidence of chronic respiratory impairment (defined as FVC of <50%, DLCO of <40% or requirement to use oxygen supplementation) adjusted for the competing risk of death was estimated. Cox models were used to assess the association of stage of pulmonary sarcoidosis and treatment on the development of chronic respiratory impairment.

Results: The means of PFT measures at baseline in this cohort were 97.1%, 95.3%, 91.4% and 91.1% of predicted values for TLC, FVC, FEV1 and DLCO, respectively. At 5 years, the mean percentage predicted for TLC, FVC, FEV1 and DLCO declined by 1.6%, 3.5%, 4.3% and 3.1%, respectively. A total of 25 patients developed chronic respiratory impairment which corresponded to 10 year event rate of 4.4% (95% confidence interval [CI], 1.9%–6.9%) as demonstrated in figure 1. Stage of pulmonary sarcoidosis at diagnosis was a strong predictor for chronic respiratory impairment with hazard ratio (HR) compared with stage I of 5.29 (95% CI, 1.65–16.96) for stage II and 8.36 (95% CI, 26.3–26.52) for stage III and IV. Use of glucocorticoids and immunosuppressive agents was associated with a significantly increased risk of chronic respiratory impairment (HR 4.60; 95% CI, 1.94–10.88 and HR 5.13; 95% CI, 1.47–17.86, respectively). However, it is unlikely that treatment with glucocorticoids/immunosuppressive agents had a deteriorative effect on pulmonary function. It is more likely that use of these medications is simply an indicator of more severe disease.

Conclusion: Patients with pulmonary sarcoidosis have a good pulmonary prognosis with a low incidence of chronic respiratory impairment.

Figure 1: Cumulative incidence of chronic respiratory impairment among 311 patients with pulmonary sarcoidosis

Disclosure: P. Ungprasert, None; C. S. Crowson, None; E. M. Carmona Porquera, None; E. L. Matteson, None.

Abstract Number: 2262

Increased Risk of Sarcoidosis Among Patients with Celiac Disease: A Systematic Review and Meta-Analysis

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Session Information

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Session Time: 9:00AM-11:00AM

Increased Risk of Sarcoidosis among Patients with Celiac Disease: A Systematic Review and Meta-Analysis

Abstract:

Background/Purpose: Several epidemiologic studies have suggested that patients with celiac disease may have an increased risk of sarcoidosis but the results were inconsistent. This systematic review and meta-analysis was conducted with the aim to better characterize this risk by summarizing all available data

Methods: A literature review was performed using MEDLINE and EMBASE database from inception to April 2018 using the search strategy that included the terms for sarcoidosis and celiac disease. Cohort studies or case-control studies that compared the risk of sarcoidosis among patients with celiac disease versus individuals without celiac disease were included. For cohort studies, cases must be patients with celiac disease, comparators must be individuals without celiac disease and the outcome of interest must be incident sarcoidosis. For case-control studies, cases must be patients with sarcoidosis, controls must be individuals without sarcoidosis and the exposure of interest must be celiac disease. Point estimates and standard errors of the included studies were extracted and the pooled odds ratio (OR) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method of DerSimonian and Laird.

Results: Of 375 retrieved articles, a total of 4 studies (2 cohort studies and 2 case-control studies) with 693,639 participants met the eligibility criteria and were included into the meta-analysis. The risk of sarcoidosis among patients with celiac disease

was significantly higher than individuals without celiac disease with the pooled OR of 7.16 (95% CI, 1.48 – 34.56). The statistical heterogeneity of this study was high ($I^2=95\%$). The forest plot of this meta-analysis is shown as figure 1.

Conclusion: This systematic review and meta-analysis found a significantly higher risk of sarcoidosis among patients with celiac disease.

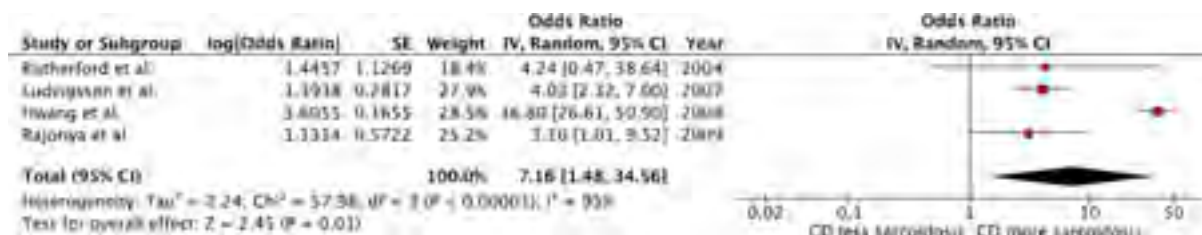


Figure 1: Forest plot :

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Abstract Number: 2263

Differentiated Phenotypes at Diagnosis of Sarcoidosis According to the Scadding Classification: Analysis in 1230 Patients

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Session Information

Session Date: Tuesday, October 23, 2018
Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster III: Sarcoid, Inflammatory Eye Disease, and Autoinflammatory Disease
Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: To analyse the correlation between Scadding radiological stages and the main phenotypic features at diagnosis (epidemiology, clinical patterns at presentation, extrathoracic disease and need for initial systemic therapy) in one of the largest cohorts of patients with sarcoidosis reported from Southern Europe.

Methods: The SARCOGEAS-Study Group was formed in 2015 including a multicenter database of consecutive patients diagnosed with sarcoidosis according to the WASOG 1999 criteria. Extrathoracic disease at diagnosis was defined according to the 2014 WASOG organ assessment instrument and the extrathoracic clusters proposed by Schupp et al.

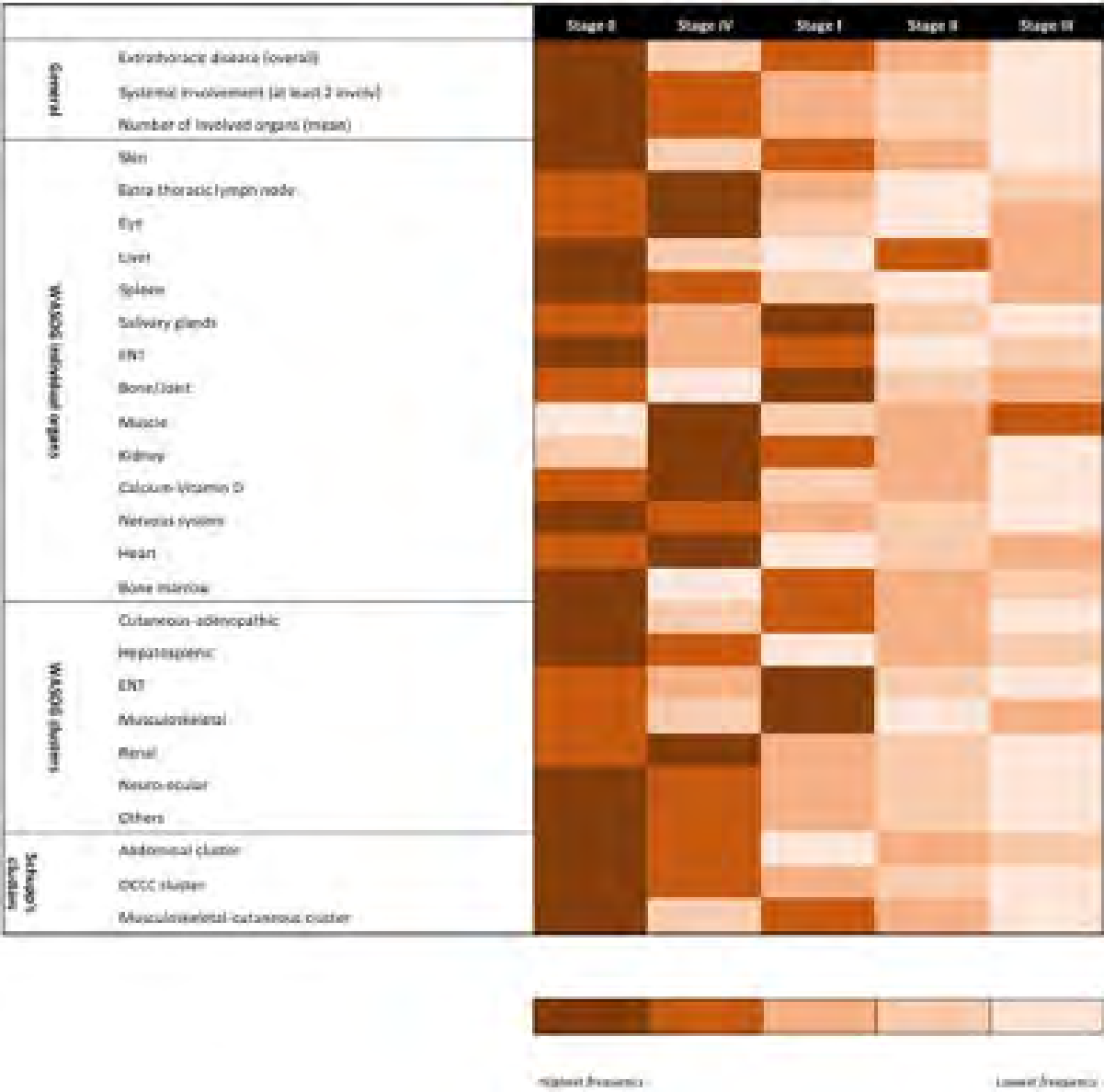


Figure 1.

Results: 1230 patients were finally analysed (712 women, mean age 47.3 yrs). Scadding radiologic stage at diagnosis consisted of stage 0 in 98 (8%) patients, stage I in 395 (32%), stage II in 500 (41%), stage III in 195 (16%) and stage IV in 42 (3%) patients. Epidemiologically, age at diagnosis was clearly linked with the Scadding stage, with younger mean ages being reported for stages I and II ($p=0.001$). With respect to extrathoracic disease, the highest frequencies of the organ-by-organ WASOG involvements are reported in stage 0 (skin, liver, spleen, ENT, nervous system and bone marrow), stage I (salivary glands, bone/joint) and stage IV (extra-thoracic lymph node, eye, kidney, calcium-vitamin D and heart) (**FIGURE 1**). The three SchappOs extrathoracic clusters are overrepresented in stage 0. Patients with stage IV had the highest frequencies of both need of and aggressiveness of therapy, while patients with stage I had the lowest frequencies. Pulmonary fibrosis was related to a higher mean age at diagnosis (55 vs 47 yrs, $p<0.001$), a higher mean number of extrathoracic organs involved (1.5 vs 1.1, $p=0.045$), a higher frequency of calcium/vitamin D WASOG involvement (17% vs 7%, $p=0.047$) and a higher frequency of need for therapy (81% vs 49%, $p<0.001$); no statistically-significant differences were found between the stages II and III.

Conclusion: We found a significant association between Scadding stages and sarcoidosis phenotype at the time of diagnosis, including epidemiological profile, extrathoracic involvement and initial therapeutic management. However, the key determinant in phenotyping the disease at diagnosis was the involvement of each organ more than the classification using the Scadding stages.

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Abstract Number: 2264

Methotrexate in the Treatment of Granulomatous Mastitis: A Retrospective Review of 19 Cases

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Session Information

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Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster III: Sarcoid, Inflammatory Eye Disease, and Autoinflammatory Disease

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Granulomatous Mastitis is a rare, inflammatory disease of the breast. Presenting symptoms in the breast can be unilateral or bilateral pain, masses, skin induration, erythema, discharge, and abscess formation. Few patients experience self-limited disease over 1-2 years, while most have a longer relapsing course. Imaging modalities such as mammography, ultrasonography, and magnetic resonance imaging (MRI) help characterize lesions, but definitive diagnosis requires histologic examination of tissue via biopsy. Frequently used treatment modalities include antibiotics, prednisone, and surgery, which are often ineffective and fraught with recurrence rates of 50%. This study describes the largest granulomatous mastitis cohort to date in the Americas and Europe with an emphasis on the efficacy of methotrexate treatment.

Methods: Institutional Review Board (IRB) approval was obtained from Stanford University. The Stanford Translational Research Integrated Database Environment (STRIDE) was queried using the terms “granulomatous mastitis” and “rheumatology” and “methotrexate” or “prednisone” from 2006-2017. Inclusion criteria included histopathologically-established granulomatous mastitis patients who were evaluated, treated with methotrexate, and had at least one follow up appointment at the Stanford Immunology and Rheumatology Clinic. Retrospective chart review was performed including pertinent demographic, medical, clinical, and treatment information.

Results: Of the 70 patients identified using STRIDE, 19 met the inclusion criteria. All patients were female with an average age of 33.5 years at the time of presentation. Majority were Hispanic (57.9%), followed by Asian (21.1%), African American (10.5%), and Caucasian (10.5%). The average parity at presentation was 2 children with a latency between the last pregnancy and diagnosis of 29.4 months. Presenting symptoms were unilateral in 68.4% of patients and included breast pain/tenderness (68.4%), mass/lump (47.3%), swelling (21.1%), erythema (21.1%) and induration (15.8%). Most patients had prior unsuccessful treatments with antibiotics (84.2%), incision and drainage (42.1%), prednisone (36.8%), and surgical intervention (5.3%). After three and six months of methotrexate treatment, 89.5% and 94.4% of patients noted disease improvement, respectively. In patients who were compliant with prescribed methotrexate treatment for 12-15 months, 71% achieved disease remission and were disease free on follow up ranging from 1-5 years. The average methotrexate dose in the first 12 months of treatment was 18mg PO weekly. The most common reason for termination of treatment was disease remission.

Conclusion: Our center's experience demonstrates that granulomatous mastitis presents predominately in multiparous Hispanic females of childbearing age as unilateral, painful breast masses. Methotrexate is an effective treatment modality resulting in sustained disease remission in most patients who are compliant with therapy for at least one year.

Disclosure: A. Postolova, None; M. C. Genovese, None.

Abstract Number: 2265

Lymphocyte Immunophenotyping and CD4/CD8 Ratio in Cerebrospinal Fluid for the Diagnosis of Sarcoidosis-Related Uveitis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster III: Sarcoid, Inflammatory Eye Disease, and Autoinflammatory Disease

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The diagnostic workup of uveitis is a challenge due to the wide range of diagnoses and the lack of a well-codified diagnostic procedure. Underlying causes are multiple and include 3 major etiological frameworks, i.e. pure ophthalmological entities, infectious diseases, and inflammatory diseases such as sarcoidosis. However, one third of uveitis is considered of undetermined origin or idiopathic. Lumbar puncture with analysis of cerebrospinal fluid (CSF) can be included in the diagnostic workup of uveitis, especially in intermediate and/or posterior uveitis. This study aimed to assess the diagnostic interest of determination of CD4/CD8 ratio in CSF for the etiological diagnosis of intermediate and/or posterior uveitis.

Methods: We prospectively included, from May 2016 to March 2018, patients referred to our department for the diagnostic workup of intermediate and/or posterior uveitis and who underwent lumbar puncture. Patients had a complete ophthalmological examination as well as a clinical and paraclinical examination for diagnostic purposes, and lymphocyte immunophenotyping using Transfix® was also performed on CSF. Etiological diagnoses were established according to international diagnostic criteria, including IWOS criteria for sarcoidosis. Diagnoses were made in a blind manner of Transfix® results.

Results: Fifty-two patients (men 44%, median age 50 years) were included. Features of uveitis were: anterior (60%), intermediate (58%), posterior (67%), and 19 (37%) had panuveitis. The diagnosis of defined, presumed or probable sarcoidosis was made in 29% of patients while 49% of cases remained of undetermined origin. Eleven patients had other diagnoses.

Lumbar puncture was considered contributive in 10 cases (19%). Increased CSF protein (>0.4 g/L) (median 0.68 g/L, range 0.22–1.96 g/L) and lymphocytic meningitis (median 76, range 45–83) were noted in 8 cases each, respectively. The median CD4/CD8 ratio in CSF in patients with definite sarcoidosis, presumed sarcoidosis and in those with uveitis of undetermined origin were 4.50 (1.78–5.94), 4.57 (2.12–5.84) and 2.83 (0.9–8.01) ($P=0.03$), respectively. ROC curve analysis showed that the CD4/CD8 ratio threshold with the best performance was >3.56 for the diagnostic of ocular sarcoidosis with a 66.7% sensitivity, a 76.9% specificity, a 62.6% positive predictive value and a 80% negative predictive value, and an area under the curve of 0.74 (0.56–0.92). A threshold of 1.73 had a 100% sensitivity but a poor specificity of 20%. By analogy with the cut-off used in bronchoalveolar lavage fluid, CD4/CD8 ratio >3.5 had a 66.7% sensitivity, a 73.1% specificity, a 58.8% positive predictive value and a 79.2% negative predictive value for the diagnostic of ocular sarcoidosis.

Conclusion: The determination of CD4/CD8 ratio in CSF can be useful in the etiological workup of patients with intermediate and/or posterior uveitis, since a CD4/CD8 ratio >3.5 in CSF is suggestive of ocular sarcoidosis. These findings need to be confirmed on a larger patient population.

Disclosure: R. Paule, None; L. Denis, None; N. Chapuis, None; J. Rohmer, None; J. London, None; C. Bonnet, None; A. Chauvin, None; L. Mouthon, None; D. Monnet, None; C. Le Jeune, None; A. Brezin, None; B. Terrier, None.

Abstract Number: 2266

Serum 1,25(OH)₂ Vitamin D and 25(OH) Vitamin D Ratio for the Diagnosis of Sarcoidosis-Related Uveitis

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Session Information

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The diagnostic workup of uveitis is challenging, with 30 to 50% of cases remaining of undetermined etiology despite multiple investigations. Sarcoid granuloma-related increase of 1,25(OH)₂D levels could be helpful for the diagnosis of ocular sarcoidosis.

Methods: Monocentric retrospective cohort study of patients for whom serum 25(OH)D and 1,25(OH)₂D levels were measured during the etiologic workup of unexplained uveitis in a tertiary referral center. The diagnoses of uveitis' underlying diseases were established according to international diagnostic criteria.

Results: Fifty-nine patients were included. The diagnosis of defined, presumed or probable sarcoidosis was made in 37% of patients while 41% of cases remained of undetermined origin. The median serum levels of 25(OH)D in patients with ocular sarcoidosis and in those with uveitis due to another cause were 34.50 [21.2–40.8] and 43.20 [32.2–58.3] nmol/L ($P=0.02$), respectively. In the same subgroups of patients, the median serum levels of 1,25(OH)₂D were 132.4 [107.4–163.9] and 108.0 [84.30–130.5] pmol/l ($P=0.02$), and the median 1,25(OH)₂D/25(OH)D ratio was 4.17 [3.11–5.09] and 2.56 [1.54–3.37] ($P=0.0007$) respectively. A 1,25(OH)₂D/25(OH)D ratio >3.5 was associated with the diagnosis of sarcoidosis with a 68% sensitivity and a 78% specificity and, in univariate analysis, was associated with an abnormal chest CT-scan (OR=5.7,

P=0.003), granulomas on bronchial biopsy (OR=14.7, P=0.007) and bronchoalveolar lavage fluid lymphocytosis (OR=12.4, P=0.0006).

Conclusion: The measurement of serum 25(OH)D and 1,25(OH)₂D levels is a useful tool in the etiological workup of patients with unexplained uveitis, since a high 1,25(OH)₂D/25(OH)D ratio is suggestive of ocular sarcoidosis.

Disclosure: J. Rohmer, None; J. Hadjadj, None; A. Bouzerara, None; S. Salah, None; R. Paule, None; M. Groh, None; P. Blanche, None; L. Mouthon, None; D. Monnet, None; C. Le Jeune, None; J. Guibourdenche, None; A. Brezin, None; B. Terrier, None.

Abstract Number: 2267

Ocular and Systemic Features in 262 Patients with Systemic Sarcoidosis and Its Correlation with Iwos Criteria

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Session Information

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Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster III: Sarcoid, Inflammatory Eye Disease, and Autoinflammatory Disease

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Sarcoidosis is a multisystemic inflammatory disease of unknown origin characterized by non-caseating epithelioid granulomas that can affect any organ system. The three most frequency affected organs are lung, skin and eyes. Ocular involvement is the presenting symptom in approximately 20-30% and can involve any part of the eye and its adnexal tissues. Sarcoidosis may cause uveitis, conjunctivitis, episcleritis/scleritis, optical nerve disease and orbital inflammation. The aim of this study was to analyze the prevalence of ocular involvement in systemic sarcoidosis in the population of Cantabria (Spain), the clinical patterns and their correlation with the IWOS criteria.

Methods: Retrospective study of patients admitted to a single reference University Hospital between 2004 and 2017 with diagnosis of sarcoidosis. Clinical findings, demographics features, anatomic location and IWOS intraocular signs were recorded. We also collected serum angiotensin converting enzyme (ACE), liver enzyme test, chest radiography, chest computed tomography scan (CT), treatment and biopsy if it was performed.

Results: We included 262 patients with diagnosis of sarcoidosis. Most of the cases were women (59%) with a median age of 44 years. The most affected organ was lung (79%), followed by skin (25%) and eye (12.2%). Thirty-two patients had ocular symptoms due to sarcoid disease and 29 of them had uveitis. There were 27 patients (84.4%) who met one of the 4 IWOS ocular sarcoidosis diagnostic categories: 15 with definite (46.9%), 9 presumed (28.1%) and 3 with possible (9.4%) sarcoidosis. Five patients did not meet IWOS criteria. The most common ocular signs were bilaterality (55.2%), snowballs or strings of pearls (51.7%), mutton-fat KPs (31%), multiple chorioretinal peripheral lesions (20.7%) and periphlebitis (13.8%). ACE increase was observed in 23% of patients with ocular sarcoidosis with a median value of 75.9. Ninety three percent of patients received oral corticosteroids, 17 a conventional immunosuppressor and 5 a biological treatment.

Conclusion: The eye is the third organ of sarcoidosis involvement. Although there is no gold standard for diagnosing ocular sarcoidosis yet, IWOS signs can help clinicians suspect it. However, there seem to be some limitations.

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Anti-IL6-Receptor Tocilizumab in Graves' Orbitopathy. Multicenter Study of 46 Patients

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Session Information

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Session Type: ACR Poster Session C

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Background/Purpose: To assess the efficacy of Tocilizumab (TCZ) in refractory thyroid associated orbitopathy (TAO) due to Grave's disease.

Methods: Multicenter study of 46 patients with TAO refractory to conventional immunosuppressive therapy.

Results: We studied 46 patients (85 eyes) (37 women/9 men); mean age at diagnosis 49.2 ± 11.8 years. Besides oral corticosteroids and before the onset of TCZ, patients had been treated with pulses of intravenous methylprednisolone (n=42), radioactive iodine (n=4), methotrexate (n=2) and other drugs (methimazole in 8 cases, leflunomide in 1, azathioprine in 1, selenium in 11). Urgent decompressive surgery had to be performed in 7 patients. According to the classification of severity of the EUGOGO group (European Group on Graves' Orbitopathy) using the clinical activity score (CAS), before TCZ onset patients whose data were available had severe (n=27 eyes) or moderate (n=34 eyes) disease. Moreover, patients presented exophthalmos (n=53 eyes), strabismus (n=37 eyes), muscle fibrosis (n=38 eyes) and dysthyroid optic neuropathy (n=10 eyes). TCZ was used in monotherapy (n=43) or combined with methotrexate (n=2) or azathioprine (n=1) at 8 mg/kg/iv/4 weeks (n=41) or 162 mg/sc/week (n=5). TCZ yielded rapid and maintained improvement in all ocular parameters as shown in Table 1. After a mean of 7.42 ± 6.41 months using TCZ and a mean follow-up of 16.47 ± 11.99 months, all patients experienced ocular improvement, with TCZ withdrawal in 28 cases due to complete remission (n=10), improvement (n=12) or stability of ocular inflammation (n=3), inefficacy (n=2) and total thyroidectomy (n=1). Only 5 relevant adverse effects were observed (neutropenia, external otitis, otitis media, costal osteitis and gingival hyperplasia, 1 each).

Conclusion: TCZ appears to be useful in TAO treatment.

Table. Improvement of ocular parameters with TCZ therapy. Data are expressed as mean±SD or median[IQR].

	BASAL	1 WEEK	2 WEEKS	1 MONTH	3 MONTHS	6 MONTHS	1 YEAR
VA	0.9 [0.7-1]	0.8 [0.7-1]	1 [0.8-1]*	1 [0.7-1]*	1 [0.8-1]*	1 [0.7-1]*	1 [0.85-1]*
IOP	19.18±3.94	17.25±1.90	17.60±2.72	18.35±4.49*	17.89±3.85*	17.08±3.62*	16.84±3.56*
CAS	4.63±1.61	4.66±2.61	-	2.97±1.91*	1.91±1.52*	0.97±0.99*	0.77±0.80*

*p<0.05

Abbreviations: VA= visual acuity; IOP= intraocular pressure; CAS= clinical activity score (0/7 at baseline, 0/10 in the rest of time measures).

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Abstract Number: 2269

Infliximab Therapy in Refractory Retinal Vasculitis of Behcet's Disease, Short and Long-Term Follow-up. Multicenter Study of 72 Patients

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Session Information

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Background/Purpose: Retinal vasculitis is a serious complication of uveitis due to Behcet's disease (BD). The treatment is based on corticosteroids, conventional immunosuppressants (IS) and anti-TNF- α drugs in refractory cases. We assess the short and long-term efficacy of Infliximab (IFX) in refractory retinal vasculitis of BD.

Methods: Multicenter study of 72 patients with retinal vasculitis of BD refractory to corticosteroids and at least 1 IS. Diagnosis of retinal vasculitis was realized with fluorescein angiography. We compared the efficacy of IFX between at baseline visit, and the 1st week, 3, 6 months and 1, 2, 3, 4, 5 and 6 years.

Results: We studied 72 patients/129 affected eyes (40 σ /32 φ) with a mean age of 39.65 \pm 9.75 years. HLA-B51 was positive in 63%. Before IFX onset, patients had received: oral prednisone (n=70), methylprednisolone bolus (n=28), CyA (n=56), AZA (n=43), MTX(n=34) and other conventional immunosuppressants (n=22). IFX was administered as monotherapy in 17 patients and in the remaining 55, combined with conventional immunosuppressants.

IFX was administered as follows: 3 mg/kg/4w (n=1), 3mg/kg/8w (n=4), 4 mg/kg/4w (n=1), 5 mg/kg/4w (n=12), 5 mg/kg/6w (n=16), 5mg/kg/8w (n=37) y 5.5 mg/kg/8w (n=1).

Following IFX onset, an improvement in retinal vasculitis was observed, as well as in the rest of the ocular parameters. This enhancement was maintained (**TABLE**).

After a mean follow-up of 26.58 \pm 22.10 months, IFX was discontinued in 44 patients: remission(n=15), insufficient response (n=16), preference of another route of administration (n=8), pregnancy (n=1) and side effects (n=4; 1 miliary tuberculosis, 3 local reactions).

Conclusion: IFX seems an effective and safe short and long-term treatment in retinal vasculitis of BD.

TABLE

	Basal	1 st week	1 st month	3 rd month	6 th month	1 st year	2 nd year	3 rd year	4 th year	5 th year	6 th year
Retinal Vasculitis (n, affected eyes, %)	117 (100%)	93 (79,5%) *	45 (38,5%) *	21 (17,9%) *	13 (11,1%) *	4 (3,1%) *	4 (3,1%) *	3 (2,6%) *	1 (0,9%) *	0 (0%) *	0 (0%) *
BCVA (mean \pm SD)	0,41 \pm 0,31	0,45 \pm 0,32 *	0,57 \pm 0,33 *	0,63 \pm 0,34 *	0,63 \pm 0,34 *	0,63 \pm 0,35 *	0,63 \pm 0,35 *	0,61 \pm 0,33 *	0,63 \pm 0,32 *	0,66 \pm 0,37 *	0,68 \pm 0,37 *
Tyndall (median [IQR])	1 [0-2]	0,5 [0-2] *	0 [0-0] *	0 [0-0] *	0 [0-0] *	0 [0-0] *	0 [0-0] *	0 [0-0] *	0 [0-0] *	0 [0-0] *	0 [0-0] *
Vitritis (median [IQR])	1 [0-2]	1 [0-2] *	0 [0-0,5] *	0 [0-0] *	0 [0-0] *	0 [0-0] *	0 [0-0] *	0 [0-0] *	0 [0-0] *	0 [0-0] *	0 [0-0] *
OCT (mean \pm SD)	346,9 \pm 140,7	339,6 \pm 125,6 *	310,8 \pm 101,4 *	285,4 \pm 74,5 *	264,7 \pm 57,1 *	268,6 \pm 52,7 *	265,2 \pm 43,7 *	253,8 \pm 31,0 *	239,8 \pm 33,8 *	208,0 \pm 26,0 *	184,7 \pm 4,1 *

* p<0,05

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Treatment of Refractory Cystoid Macular Edema to Conventional Immunosuppressive Therapy: Tocilizumab Vs Anti-TNF-Alpha. Multicenter Study of 59 Patients

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Session Information

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Background/Purpose: Cystoid macular edema (CME) is the main cause of irreversible visual loss in patients with uveitis. Our aim objective was to determine the efficacy of Tocilizumab (TCZ) in Immunomediated Inflammatory Diseases (IMIDs) with EMQ and to compare with Anti-TNF drugs in refractory patients to conventional immunosuppressive therapy.

Methods: We set up a multicenter study of patients with refractory CME to traditional treatment with glucocorticoids and at least 1 conventional immunosuppressant. All patients presented OCT> 300μ at the study onset. The main objective was the improvement of macular thickness. Results were expressed as mean±S.D. for variables with a normal distribution, or as median [IQR] [25th, 75th] for those not normally distributed. The Wilcoxon signed-rank test was used to compare continuous variables and Student's t-test was used to compare both groups.

Results: We studied 59 patients (87 affected eyes). Causes of uveitis were: Behcet's disease (n=41), Birdshot's retinochoroidopathy (n=4), Juvenile Idiopathic Arthritis (n=9), Sarcoidosis (n=1) and idiopathic (n=4). 25 patients were treated with TCZ as follows: 8 mg/kg/4 weeks (n=24) and 162 mg s.c./2 weeks (n=1). Anti-TNF-α therapy was used in the remaining 34 as follows: IFX (n=12) (5 mg/kg 0, 2 y 6 weeks and then every 4-8 weeks) y ADA (n=22) (40mg/s.c./2 weeks).

No statistically differences were observed at baseline in both groups (TCZ vs. Anti-TNF-α) in sex (σ/9; 8/17 vs. 15/19; p=0.34), mean age (35.6±18.9 vs. 40.0±9.1; p=0.25), and macular thickness (470.6±159.7 vs. 451.4±128.8; p=0.57). However, we found significant differences in the number of previous biological drugs (1 [1-2] vs. 0 [0]; p<0.01) and in the duration of uveitis before biological therapy onset (112[24-198] vs. 36 [15-82]; p=0.04). Regarding main objective, we observed a rapid and sustained improvement in macular thickness after 1 year of follow-up in both groups, without objectifying significant differences between them (TABLE).

Conclusion: Regardless of the EIIM that causes uveitis, both therapies seem effective in CME refractory to conventional therapy. TCZ is also effective in anti-TNF failure.

TABLE

	TCZ	Anti-TNF	P
Baseline			
OCT	470.6±159.7	451.4±128.8	0.57
Tyndall	1 [0-1]	1 [0-2]	0.13
Vitritis	1 [0-2]	1 [0-3]	0.07
BCVA	0.40±0.31	0.48±0.31	0.98
1st month			

Table . (Cont'd)

	TCZ	Anti-TNF	P
OCT	349.6±108.6	362.6±97.1	0.60
Tyndall	0 [0-0]	0 [0-0]	0.47
Vitritis	0 [0-0,5]	0,5 [0-1]	<0.01
BCVA	0.50±0.30	0.61±0.28	0.58
6th month			
OCT	282.3±78.2	275.6±60.7	0.71
Tyndall	0 [0-0]	0 [0-0]	0.04
Vitritis	0 [0-0,5]	0 [0-0]	<0.01
BCVA	0.56±0.33	0.71±0.31	0.73
1st year			
OCT	265.0±47.9	268.8±54.6	0.79
Tyndall	0 [0-0]	0 [0-0]	<0.01
Vitritis	0 [0-0,5]	0 [0-0]	0.36
BCVA	0.59±0.33	0.72±0.32	0.76

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Abstract Number: 2271

Long-Term Efficacy and Safety of Adalimumab By Immunosuppressant Use in Patients with Non-Infectious Uveitis

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Session Information

Session Date: Tuesday, October 23, 2018

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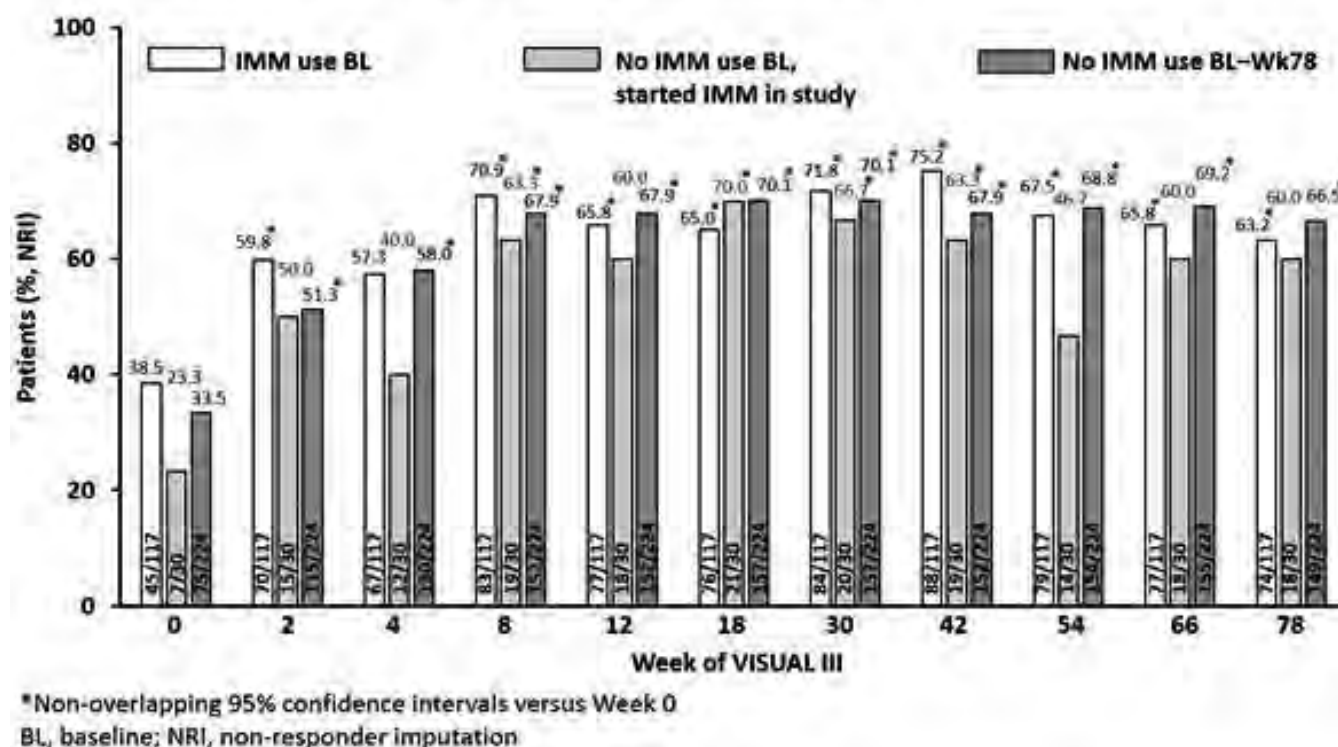
Session Time: 9:00AM-11:00AM

Background/Purpose: To evaluate the long-term safety and efficacy of adalimumab in patients with non-infectious intermediate, posterior, or panuveitis, by immunosuppressant (IMM) use.

Methods: Adult patients who completed or had a treatment failure in the VISUAL I/II trials were eligible to enter the Phase III open-label extension study, VISUAL III. Patients received adalimumab 40 mg every other week in VISUAL III, and interim follow-up data were collected through Weeks 0 to 78. Efficacy measures assessed included proportion of patients with: no active inflammatory lesions in both eyes; anterior chamber (AC) cell grade ≤0.5+ in both eyes; vitreous haze (VH) grade ≤0.5+ in both eyes; quiescence (defined as no active inflammatory lesions AND AC cell grade ≤0.5+ AND VH grade ≤0.5+); and steroid-free quiescence. Mean steroid dose and mean best corrected visual acuity (BCVA) were also assessed. Missing data were imputed using non-responder imputation for categorical endpoints, last observation carried forward for continuous variables, and as-observed for steroid dose. Efficacy was analyzed by IMM (methotrexate, cyclosporine, mycophenolate mofetil, or azathioprine) use. Adverse events (AEs) were reported from first adalimumab dose in VISUAL III through interim cut-off date of Oct 31, 2016, with analysis by IMM use.

Results: Of 371 patients included in the intent-to-treat analysis, 117 (31.5%) were using IMM at VISUAL III baseline (BL) and 30 (8.1%) started IMM during VISUAL III. The proportion of patients with quiescence improved over time irrespective of IMM use; compared with Week 0, 95% confidence intervals were non-overlapping at most time points (Figure). Numeric improvements were achieved in steroid-free quiescence, steroid dose reduction, and BCVA, with no difference by IMM use. No new safety signals were detected through 130 weeks of treatment and AE rates were generally

Figure: Proportion of patients in quiescence by IMM use in VISUAL III



consistent with previous VISUAL trials; some AEs, notably serious infections and malignancies, were slightly higher with concomitant IMM use.

Conclusion: Exploratory analyses from the VISUAL III trial demonstrated that efficacy in adalimumab-treated patients was sustained or improved through 78 weeks of treatment, irrespective of IMM use. AE rates were consistent with previous VISUAL trials, although numerically higher rates for a subset of AEs were observed in patients taking IMM.

Disclosure: Y. Guex-Crosier, AbbVie, Santen, and Novartis, 9; C. S. Foster, Aldeyra, Bausch & Lomb Surgical, EyeGate, Novartis, pSivida, and Xoma, 5; Alcon and Allergan, 8; Alcon, Aldeyra, Bausch & Lomb, Clearside Biomedical, Dompe, Icon, Novartis, Santen, Xoma, Aciont, and pSivida, 2; K. Nakai, None; H. Goto, AbbVie, 9; K. Douglas, AbbVie Inc., 1, 3; S. Pathai, AbbVie Inc., 1, 3; M. Kron, AbbVie Inc., 1, 3; A. P. Song, AbbVie Inc., 1, 3; J. Van Calster, AbbVie, Allergan, Santen, and MSD, 9; AbbVie, Allergan, and MSD, 5; A. Adan, AbbVie, Santen, Allergan, and Novartis, 9.

Abstract Number: 2272

Missed Opportunity? Evaluation for Systemic Autoimmune Diseases in Patients with Uveitis May Not be Optimal: 5-Year Analysis of Patients Being Seen in a Tertiary Medical Center

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Session Time: 9:00AM-11:00AM

Background/Purpose: Uveitis is the most common inflammatory eye disease and is frequently associated with secondary systemic autoimmune diseases (SSAID) excluding infection in 40-55% of cases. This analysis was undertaken to assess the

Table 1. Demographics and Overall Prevalence of Systemic Disorders in Uveitis patients.

Demographics (n=1096)	
Gender	
Female	734 (67%)
Male	362 (33%)
Age	
18-29	133 (12%)
30-39	165 (15%)
40-49	194 (18%)
50-59	222 (20%)
60-69	229 (21%)
≥ 70	153 (14%)
Smoking	
Non-smoker	688 (63%)
Smoker (Current or previous)	408 (37%)
Associated Systemic Diseases (n=434)	
Infectious Causes	238 (22%)
Non-Specific	165 (69%)
Bacterial	10 (4%)
Viral	15 (6%)
Fungal	5 (2%)
Parasitic (Toxoplasmosis)	43 (18%)
Auto-immune Systemic Disorders	184 (17%)
Connective tissue disease	82 (44%)
Sarcoidosis	48 (26%)
Spondyloarthrides	18 (10%)
Reactive Arthritis	6
Ankylosing Spondylitis	3
Psoriatic Arthritis	2
Crohn disease	3
Ulcerative Colitis	4
Systemic Lupus Erythematosus	6 (3%)
Sjogren's syndrome	5 (3%)
Vasculitis	17 (9%)
Behcet syndrome	3 (0.5%)
Multiple Sclerosis	5 (3%)
Malignancy	12 (1%)

diagnostic prevalence of patients of these disorders in patients with uveitis being evaluated by ophthalmology in a tertiary referral center.

Methods: Patients aged 18 years and older with uveitis, diagnosed and followed by ophthalmology from January 2013 to March 2018 were identified. By using the patient cohort explorer, an online visit processing tool, a search for diagnostic codes for uveitis (91 separate ICD-9 and ICD-10 codes) was performed. Individual searches for commonly associated SSAID were further done using ICD-9 and 10 codes to sub-categorize these patients. The search results were cross-referenced by running three additional data searches including medications administration, laboratory and imaging evaluation, and referral to rheumatology. Diagnostic prevalence was calculated and compared to historical data.

Results: There was a total of 1096 patient with uveitis. The majority of patients were female(67%). There was a high prevalence of smoking (37%) and the prevalence of uveitis increased with each decade of life. Only 17% of the cases had a concomitant diagnosis or evaluation for a SSAID, 22% had a diagnosis of an underlying infectious cause and only 1% due to malignancy. Table 1 shows the demographic data and relative frequency of prevalence in these disorders. Non-specific connective tissue disease was the most common diagnosis in SSAID, followed by sarcoidosis and vasculitis. Seronegative spondyloarthritides were only diagnosed in 18 patients (1.6%). HLA-B27 was only checked in 67 patients (6.1%) with 50% being positive.

Conclusion: Evaluation for and prevalence of systemic disease associated with uveitis was significantly lower (17%) than what was expected historically(40-55%). Even though this data is limited by the lack of individual review, the data obtained showed similar results through 4 different algorithmic searches. Smoking, a known risk factor for inflammation, was found at a higher prevalence than the general population, and there was an increase in the prevalence of uveitis with older age till 70 years. These data suggest that, despite overwhelming evidence, patients with uveitis may not be adequately evaluated for these systemic diseases. Strategies to improve education and perhaps targeted diagnostic algorithms may improve the detection of secondary systemic diseases.

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2. Henderly DE, Genstler AJ, Smith RE et al. Changing patterns of uveitis. *Am J Ophthalmol* 1987;103(2):131-6.
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Abstract Number: 2273

High Dose Intravenous Methylprednisolone Induces Rapid Improvement in Severe Non-Infectious Uveitis. a Multicenter Study of 120 Patients

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Background/Purpose: In uveitis rapid and effective remission-inducing therapy is mandatory to avoid irreversible structural and functional damage. Our aim was to evaluate the efficacy and safety of high-dose intravenous methylprednisolone (IVMP) pulse therapy in abroad spectrum of uveitis.

Methods: Multicentre study of 120 patients (190 eyes) with severe ocular inflammation who received IVMP. The underlying diseases were: Idiopathic (n=34), VogtKoyanagy Harada (28), Behcet disease (19), Sarcoidosis (6), Multifocal Choroidopathy (4), Birdshot chorioretinopathy (2), Acute posterior multifocal placoid pigment epitheliopathy (1), Granulomatosis with polyangiitis (2), Aortitis (1), Rheumatoid arthritis (2), Axial Spondylitis (6), Psoriatic arthritis (2), Juvenile Idiopathic Arthritis (1), Eales Disease (1), Sympathetic Ophthalmia (3), Multiple Sclerosis (2), Relapsing Polychondritis (1), Cogan's synd. (1), Sjögren synd. (2), Crohn's disease (1) and Reactive arthritis (1). The inflammatory ocular patterns were: panuveitis (62), posterior uveitis (PU) (29), intermediate uveitis (IU) (3), anterior uveitis (AU) (12), AU and PU (2), AU and IU (1), IU and PU (1), exudative retinal detachment (4), retinal vasculitis (2), pseudotumor (1), scleritis (2) and sclero-uveitis (1). Bilateral ocular involvement was observed in 70 patients. Patients were assessed at basal visit and day 2-5, 7, 15 and 30 after IVMP.

The main outcome variable was best corrected visual acuity (BCVA), the degree of inflammation of the anterior chamber and vitreous, and macular thickness (macular edema defined by OCT >300 µm). The results are expressed as mean ±SD for normally distributed variables, or as median [interquartile range] when are not. Comparison of continuous variables was performed using the Wilcoxon test.

Results: We studied 70 ♀/ 50 ♂; mean age 42 ±14.46 years. IVMP dose ranged from 40-1000mg/day for 3-5 consecutive days. All of them had active intraocular inflammation. Prior to IVMP, cycloplegic and corticosteroid eye drops were used in all cases. Improvement was faster among patients with inflammation in anterior chamber and vitritis than in BCVA, CME, retinitis and retinal vasculitis (TABLE 1). Total remission was achieved in 17.5% of the 120 patients after IVMP. In 118 of the patients continued with oral corticosteroids and 4 received an intraocular dose of corticosteroids. The following conventional immunosuppressive drugs were added: Methotrexate (50), Cyclosporine A (47), Azathioprine (37) and others (5). In a few cases even biological therapy (61) was administered afterwards. In general, acute respiratory infection was the side-effect most frequent.

Conclusion: High-dose IVMP pulse therapy is beneficial in the prompt control of severe uveitis and it is well tolerated. TABLE 1.

	Affected eyes Baseline	Affected eyes after high-dose IVMP (%)			
		Day 2-3	Day 7	Day 15	Day 30
BCVA, mean±SD	0.46±0.35	0.54±0.34*	0.6±0.33*	0.67±0.31*	0.75±0.31*
Anterior chamber cells [median (IQR)]	1 [0-4]	0 [0-4]*	0 [0-4]*	0 [0-3]*	0 [0-2]*
Vitritis [median (IQR)]	0 [0-5]	0 [0-5]*	0 [0-5]*	0 [0-3]*	0 [0-3]*
OCT (microns) mean±SD	411.18±188.4	368.76±161.7*	348.89±153.1*	309.8±122.61*	280.53±109.3*
Choroiditis/ Chorioretinitis n, (%)	52 (21.7%)	47 (19.5%)	31 (13%)	21 (8.7%)	14 (5.8%)
Retinitis n, (%)	84 (35%)	72 (30%)	68 (28%)	48 (20%)	21 (8.75%)
Retinal vasculitis n, (%)	62 (25.8%)	54 (22.5%)	50 (20.8%)	34 (14.1 %)	16 (6.6%)
Synechiae n, (%)	39 (16.2%)	32 (13.3%)	30 (12.5%)	30 (12.5%)	33 (13.75%)
Cystoid macular edema (CME) n, (%)	82 (34%)	67 (28%)	56 (23.3%)	40 (16.6%)	19 (7.9%)

*p <0.05 compared with basal

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Refractory and Severe Uveitic Cystoid Macular Edema Improves with Tocilizumab in Different Immune Mediated Diseases

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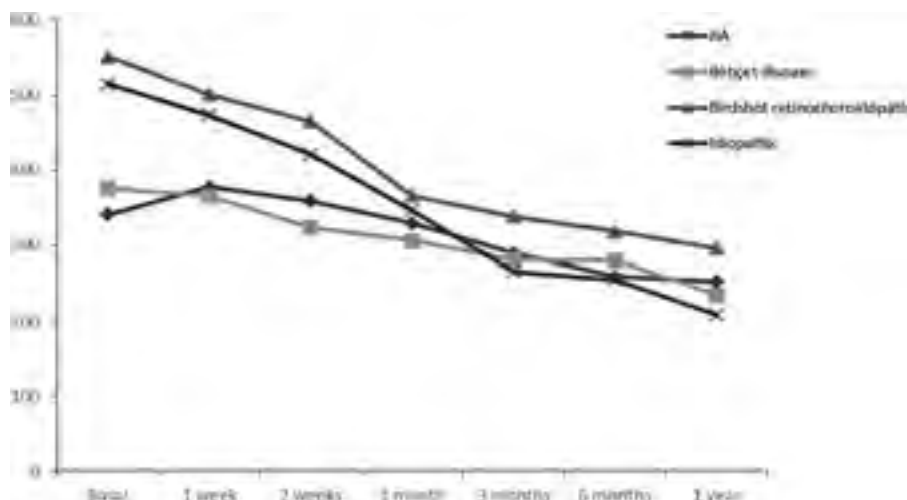
Background/Purpose: Cystoid macular edema (CME) represents the leading cause of blindness in uveitis of different immune mediated diseases (IMD). Our aim was to evaluate the efficacy of Tocilizumab (TCZ) in different IMD with refractory CME to other immunosuppressive drug.

Methods: Multicentre study of 24 patients with CME due to uveitis of different IMD refractory to traditional treatment with systemic corticosteroids and at least one conventional immunosuppressive drug including in most cases biological therapy (n=21). CME was defined by (OCT >300 µm). We studied CME with TCZ in 4 different IMD: juvenile idiopathic arthritis (JiA), Behcet's disease (BD), Birdshot retinochoroidopathy (BR) and idiopathic.

The main outcome was the improvement of macular thickness. Other variables assessed were inflammation of the anterior chamber and vitreous and best corrected visual acuity (BCVA).

Results: We studied 16 ♀/8 ♂, mean age 35.2±19.3 years. The associated diseases were: JiA (n=9), BD (n=7), BR(n=4) and idiopathic (n=4). The ocular patterns were: panuveitis (9), anterior uveitis (6), posterior uveitis (5) and intermediate uveitis (4). Most patients had bilateral involvement (22). The biological therapy used before the administration of TCZ were infliximab (8), adalimumab (18), etanercept (2), golimumab (2), rituximab (2), abatacept (3), anakinra (1) and daclizumab (1). TCZ administration schedule was 8 mg/kg/4 weeks iv. (n=23) or every 2 weeks (n=1). TCZ was used in monotherapy (12) or combined with conventional immunosuppressive drugs (12). OCT values improved considerably in 12 months: in JiA from 340.6 ± 134.1 µm to 252.5 ± 30 µm, in BD from 375.1 ± 117 µm to 235 ± 7.1 µm, in BR from 550.7 ± 214.4 µm to 295.5 ± 43.2 µm and in idiopathic from 515 ± 219.6 µm to 208.3 ± 46.7 µm (**FIGURE**). Inflammation in anterior chamber and vitritis and BCVA also improved in the 4 subtypes. No major side effects were observed, so no patient had to stop treatment.

Conclusion: TCZ seems a rapid effective treatment in severe and refractory uveitic CME, regardless of the underlying IMD.



FIGURE

Disclosure: N. Vegas-Revenge, None; V. Calvo-Río, None; M. Mesquida, None; A. Adan, None; M. V. Hernández, None; E. Beltrán, None; E. Valls Pascual, None; D. Diaz-Valle, None; G. Díaz-Cordovés, None; M. Hernandez Grafella, None; L. Martínez-Costa, None; I. Calvo, None; A. Atanes, None; L. F. Linares, None; C. Modesto, None; E. Aurrecoechea, None; M. Cordero-Coma, None; R. Demetrio-Pablo, None; L. C. Domínguez-Casas, None; J. L. Hernández, None; M. A. González-Gay, None; R. Blanco, None.

Autoimmune Encephalitis with Concomitant Systemic Rheumatologic Auto-Antibodies

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Background/Purpose: Autoimmune encephalitis (AE) is a rapidly progressive encephalopathy presenting with neurologic and psychiatric manifestations and is often associated with antibodies targeting neuronal cell-surface or synaptic proteins. Current diagnostic approaches require exclusion of alternative etiologies, including rheumatologic causes such as SLE, SS or vasculitis. Little is known about presentation or outcomes of patients with AE and concomitant systemic rheumatologic auto-antibodies who do not meet classification criteria for rheumatic disease.

We hypothesize that patients with AE and concomitant systemic rheumatologic auto-antibodies have improved disability and mortality as compared to patients without.

Methods: Patients were retrospectively identified for inclusion into the study if they had been diagnosed with AE by a board-certified neurologist at our institution between 2003 and 2018.

Patients were defined as having positive systemic auto-antibodies if they had positive laboratory results for ANA, SSA, SSB, DsDNA, SCL70, Histone, RNP, centromere, chromatin or ANCA by western blot or ELISA.

Baseline demographics, disease characteristics, neuronal specific autoantibodies, disability measured by modified Rankin scale (MRS) and mortality were compared between groups.

Results: 122 patients were identified for inclusion. 98 patients were negative for systemic rheumatologic auto-antibodies, and 24 were positive. Baseline demographics were similar between groups. Patients presented clinically with symptoms of lethargy or coma, seizures and/or dementia but this was not different between groups. MRI abnormalities were most frequently seen in subcortical or deep regions on T2/FLAIR imaging. Many neuronal specific auto-antibodies were identified, but patients in the positive systemic autoantibody group were more likely to have GAD65abs related to AE as compared to patients without (33.3% vs 9.2% respectively) (Table 1). The most commonly occurring systemic rheumatologic auto-antibody was ANA (15/24 patients), followed by SSA (6/24) and DsDNA (4/24) (Table 2). No patients had or developed a concomitant rheumatic disease over the mean length of follow up of 92 weeks. Treatment did not differ between groups. MRS was not different at baseline or at discharge between groups (Table 1). Kaplan-Meier survival curves for both patient populations revealed no significant difference in the survival rates between groups.

Conclusion: In patients with AE, concomitant systemic antibody positivity does not confer an improved prognosis. No patients developed a systemic rheumatic disease over the length of follow up.

Table 1 Baseline demographics, clinical features, treatment and disability

Factor		Total (N=122)	Negative (N=98)	Positive (N=24)	p-value
Baseline Demographics					
Gender*	Male	47(39.5)	41(43.2)	6(25.0)	0.10 ^c
	Female	72(60.5)	54(56.8)	18(75.0)	
Age at onset		51.6±17.8	52.2±16.7	49.3±22.3	0.46 ^a
Elapsed Time Between AME Onset and Diagnosis (days)*		442.4±783.0	393.4±761.0	633.9±854.3	0.19 ^a
Length of follow up (weeks)				91.9 ± 106.6	
Clinical features at presentation					
Lethargy or Coma		26(21.3)	21(21.4)	5(20.8)	0.95 ^c
Seizures		42(34.4)	36(36.7)	6(25.0)	0.28 ^c
Visual Hallucinations		5(4.1)	4(4.1)	1(4.2)	0.99 ^d
Auditory Hallucinations		4(3.3)	4(4.1)	0(0.0)	0.58 ^d
Ataxia		15(12.3)	11(11.2)	4(16.7)	0.47 ^c
Opsoclonus		2(1.6)	1(1.0)	1(4.2)	0.36 ^d
Dementia		38(31.1)	32(32.7)	6(25.0)	0.47 ^c
Myoclonus		11(9.0)	9(9.2)	2(8.3)	0.90 ^c

Table . (Cont'd)

Factor		Total (N=122)	Negative (N=98)	Positive (N=24)	p-value
MRI findings at presentation	Weakness	14(11.5)	12(12.2)	2(8.3)	0.59 ^c
	Sensory disturbance	15(12.3)	10(10.2)	5(20.8)	0.16 ^c
	Other	45(36.9)	32(32.7)	13(54.2)	0.050 ^c
	DWI Changes Cortex	2(1.6)	1(1.0)	1(4.2)	0.36 ^d
	DWI changes subcortical	1(0.82)	0(0.0)	1(4.2)	0.20 ^d
	DWI changes deep	3(2.5)	3(3.1)	0(0.0)	0.99 ^d
	T2/FLAIR changes cortex	10(8.2)	7(7.1)	3(12.5)	0.39 ^c
Neuronal targeted antibodies	T2/FLAIR changes subcortical	25(20.5)	21(21.4)	4(16.7)	0.60 ^c
	T2/FLAIR changes deep	30(24.6)	26(26.5)	4(16.7)	0.31 ^c
	Temp hippo swelling	24(19.7)	22(22.4)	2(8.3)	0.12 ^c
	Anti NMDA	12(9.8)	11(11.2)	1(4.2)	0.30 ^c
	Anti VGKC	21(17.2)	18(18.4)	3(12.5)	0.49 ^c
	Anti-ganglionic AChR	4(3.3)	2(2.0)	2(8.3)	0.17 ^d
	ANNA-1 Anti Hu	3(2.5)	3(3.1)	0(0.0)	0.99 ^d
	Anti-yo	2(1.6)	2(2.0)	0(0.0)	0.99 ^d
	CRMP-5 IgG	3(2.5)	2(2.0)	1(4.2)	0.48 ^d
	PCA-1	3(2.5)	3(3.1)	0(0.0)	0.99 ^d
	Anti Ma2	3(2.5)	3(3.1)	0(0.0)	0.99 ^d
	Purkinje Cell CytoplasmicAntibodies	1(0.82)	1(1.0)	0(0.0)	0.99 ^d
	GAD65ab	17(13.9)	9(9.2)	8(33.3)	0.002^c
CSF analysis	Gaba B receptor ab	1(0.82)	1(1.0)	0(0.0)	0.99 ^d
	CSF glucose*	70.4±18.4	70.9±18.9	68.4±16.8	0.63 ^a
	CSF protein*	67.3±60.3	71.2±65.0	49.9±26.9	0.20 ^a
Initial Treatment*	CSF WBC*	37.1±110.8	39.8±120.2	25.3±53.3	0.64 ^a
	Intravenous Immunoglobulin	34(35.1)	25(32.5)	9(45.0)	0.65 ^d
	Plasma Exchange	5(5.2)	5(6.5)	0(0.0)	
	Corticosteroids	56(57.7)	45(58.4)	11(55.0)	
	Other	2(2.1)	2(2.6)	0(0.0)	
Disability	Significant improvement with therapy*	57(52.3)	45(52.3)	12(52.2)	0.99 ^c
	MRS Baseline*	2.8±1.3	2.8±1.4	2.5±0.83	0.24 ^a
	MRS Discharge*	2.6±1.4	2.6±1.5	2.4±1.3	0.56 ^a

* Data not available for all subjects

Statistics presented as Mean ± SD, Median [P25, P75], Median (min, max) or N (column %).

p-values: a=ANOVA, b=Kruskal-Wallis test, c=Pearson's chi-square test, d=Fisher's Exact test.

1: Significantly different from Autoimmune

2: Significantly different from Seropositive

A significance level of <0.05 was used for pairwise ad-hoc comparisons.

Table 2 Sub-classification of systemic autoantibodies

Systemic Auto-antibodies	Total (N=24)
ANA	15
SSA	6
SSB	1
DsDNA	4
pANCA	0
cANCA	0
MPO	1
PR3	1
RNP	1
SCL 70	2
Histone	1
Centromere	1
Chromatin	1

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Risk of Hemorrhagic Strokes in Patients with Adenosine Deaminase 2 Deficiency

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Session Information

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Background/Purpose: Deficiency of adenosine deaminase 2 (DADA2) is an autosomal recessive condition characterized by recurrent fevers, early-onset ischemic strokes, livedo racemosa, polyarteritis nodosa, portal hypertension, immune deficiencies, and cytopenias. Additionally, several patients with DADA2 have had hemorrhagic strokes. DADA2 is caused by biallelic loss-of-function mutations in the *ADA2* gene (formerly known as *CECR1*), resulting in very low ADA2 levels in the blood, vasculopathy, and M1 skewing of macrophage differentiation. The use of tumor necrosis factor (TNF) inhibitors has significantly reduced the risk of recurrent stroke. In this abstract, we report two TNF-inhibitor naïve cases who cumulatively developed three spontaneous hemorrhagic strokes on no anticoagulants/antiplatelets. Additionally, we examine the safety of anticoagulants/antiplatelets in patients with DADA2.

Methods: A single center study evaluated 24 patients who had biallelic germline mutations in the *ADA2* gene. Patients were subdivided into those with a history of hemorrhagic stroke versus those without. We then identified the patients with hemorrhagic strokes on no anticoagulant/antiplatelet treatment, ASA alone, and other anticoagulants/antiplatelets versus patients without hemorrhagic stroke on no anticoagulant/antiplatelet treatment, ASA alone, and other anticoagulants/antiplatelets. None of the patients had been on TNF inhibitors at the time of the analysis. The primary outcome measure was to determine occurrence of hemorrhagic strokes in patients with DADA2 and if there is increased risk on anticoagulant/antiplatelet treatment.

Results: Among the 24 patients, 6 (25%) had hemorrhagic strokes and of those 1 was on ASA alone, 3 were on anticoagulants/antiplatelets, and 2 were on no anticoagulants/antiplatelets. The remaining 18 patients did not have a hemorrhagic stroke and of those, 8 were on ASA alone, 3 were on anticoagulants/antiplatelets, and 7 were on no anticoagulants/antiplatelets. The probability of a hemorrhagic stroke following anticoagulant/antiplatelet therapy is 4/13 (31%) while the probability of a hemorrhagic stroke following no such therapy is 2/11 (18%). A Fisher's exact test showed a p-value of 0.6494 (NS). The prevalence of patients with hemorrhagic strokes on ASA alone, no anticoagulant/antiplatelets, and on anticoagulants/antiplatelets were 1:6, 2:6, 3:6 respectively. A Fisher's exact test showed a p-value of 0.263 (NS).

Conclusion: In patients with DADA2, we have shown that there is a strong baseline risk of hemorrhagic strokes as evidenced by the two patients who cumulatively suffered three hemorrhagic strokes on no anticoagulant or antiplatelet treatment. The risk of hemorrhagic stroke was not significantly increased on anticoagulants/antiplatelet agents possibly due to the small sample size. However, given the baseline risk of hemorrhagic stroke in DADA2, and the (non-significant) increase in that risk on anticoagulants and antiplatelet agents, such agents should probably not be used in DADA2 except under extraordinary circumstances.

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Colchicine: An Effective Treatment Option for Unclassified Autoinflammatory Diseases in Children

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Background/Purpose: Interleukin-1 (IL-1) inhibition was found to be an effective, yet very expensive treatment option for children with clinically and genetically defined autoinflammatory diseases (AID). However, patients suffering from unclassified AIDs with mild to moderate disease activity in the absence of a pathogenic mutation commonly have no access to these treatment options. The aim of this study was to explore the efficacy and safety of colchicine monotherapy in children with AIDs without pathogenic mutations.

Methods: A single center prospective cohort study of consecutive AID patients ages <18 years without pathogenic mutations, who were treated with colchicine monotherapy was conducted between January 2009 and February 2018. Patients were included, if they had mild to moderate clinical disease activity and raised inflammatory markers (CRP > 0.5mg/dl, SAA >10 mg/l). Patients were excluded, if they had intolerance to colchicine, elevated liver enzymes > 3x ULN, amyloidosis or other AID related organ damage. Baseline variables included demographics, clinical features, laboratory markers, flare details and overall disease activity. Primary outcome was treatment response at 6 month. Complete response was defined by Physician Global Assessment (PGA) VAS < 2 plus normal inflammatory markers (CRP, SAA), partial response was defined as PGA VAS ≥ 2 - ≤ 5 and low normal inflammatory markers (CRP < 5mg/dl, SAA < 50mg/l). Secondary outcomes included flare characteristics (intervals, duration), toxicity and dose adjustment.

Results: A total of 33 patients were included, 13 girls and 20 boys; median age at start of therapy was 3.8 years (0.8 – 12.6). Clinical diagnoses included PFAPA (14), mutation-negative FMF (9), CAPS with low-penetrance *NLRP3*-variants (8) (2 *V198M*, 6 *Q703K*) and unclassified AID (2). Overall, recurrent fever was the leading symptom, mostly associated with arthralgia and myalgia. On colchicine, the median disease activity decreased from 4 at baseline to 2 at 6 months, median SAA-levels dropped from 74.5 to 4.4 mg/l, CRP from 2.9 to 0.06 mg/dl. Flare frequency was significantly reduced, as was flare duration. Overall, 73% of children responded to Colchicine therapy, complete response was documented in 21%, partial response in 52% at 6 months. The colchicine dose was increased in 79% of children. At last follow-up, 67% had a sustained response to Colchicine. Adverse events included abdominal pain and diarrhea seen in 42%. These appeared to be dose dependent.

Conclusion: Colchicine was an effective and safe treatment option for children with mild to moderately active AIDs. Dose adjustments are frequently required. Gastro-intestinal side effects have to be closely monitored at higher doses.

Disclosure: J. B. Kuemmerle-Deschner, Novartis, 2, Novartis, SOBI, 5; A. L. Schock, None; S. Hansmann, None; S. Benseler, None.

Cryopyrinopathy across Generations: Longterm Disease Outcome

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Background/Purpose: Cryopyrinopathies are autoinflammatory disorders (AID) caused by mutations of NLRP3 gene that lead to interleukin-1 (IL-1) overproduction with the clinical picture of periodic fever. Milder forms as Muckle-Wells syndrome (MWS) can run undiagnosed until adulthood when disease damage (deafness, amyloidosis) may be discovered. We present a observational study of a large family where MWS was diagnosed simultaneously in 4 generations (G). This provides us with the information on the long-term natural disease course followed by systematically documented response to IL-1 blockade.

Methods: Case histories were retrieved from medical records complemented by detailed questioning. Clinical suspicion of MWS was genetically confirmed (c.1322C>T). Patients were followed from the time of diagnosis at 3-monthly intervals by clinical examination, blood and urine tests, patient-reported Auto-Inflammatory Disease Activity Index (AIDAI) and once yearly Autoinflammatory Disease Damage Index (ADDI). Audiometry was performed initially and then in 6-12-monthly intervals. Results of the 2-year follow-up are presented.

Results: Two children in **GIV** (1.5 and 5 yrs old) presented in infancy with urticarial rash. Their inflammatory markers as well as general condition remained normal and they have not yet required therapy. All 5 affected individuals in **GIII** (21-33 yrs old) reported frequent attacks of fever, rash, conjunctivitis and arthralgia since pre-school age. They all had raised inflammatory markers and no organ involvement. All responded briskly to daily anakinra. **GII** has 3 siblings (45, 46, 53 yrs old) all affected (rash, conjunctivitis, arthritis, arthralgia, fever, headaches from pre-school age). Renal amyloidosis was confirmed as a cause of proteinuria and chronic renal failure in patient II/1. Variable degree of sensorineural hearing loss was found in 2 cases. Anakinra led to the rapid improvement of their laboratory activity as well as clinical symptoms. In patient II/1 hearing has remained stable as did his renal function. Audiometry improved by 10-20 dB after 2 years of therapy in patient II/3. Patient I/1 from **GI** died at 52 years from renal failure. The pre-treatment **AIDAI** ranged 20-77 points and normalised within 1-3 months in all patients and have remained so. The disease damage noticed in **GII** expressed by **ADDI** was 6 (II/1) and 1 (II/3) at the first visit and has remained stable within the follow-up.

Conclusion: Although untreated MWS carries high risk of renal and auditory damage, little is known about the timing of their evolution. The cross-sectional view of untreated disease in 11 patients with the same mutation provides valuable information. Absence of impaired hearing in individuals below 40 years has encouraged us to postpone onset of IL-1 blockade in the mildly affected children. On the other hand, renal amyloidosis progressed sub-clinically into significant functional impairment in one patient and was a cause of death in another one both in their early fifties. High level of awareness of AIDs and close collaboration between paediatric and adult specialists are the main pre-requisites to optimal management of these rare diseases.

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Therapeutic Value of Canakinumab in Patients with Yao Syndrome

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Background/Purpose: Yao syndrome (YAOS, OMIM 617321), formerly termed nucleotide-binding, oligomerization domain 2(*NOD2*)-associated autoinflammatory disease, is characterized by periodic fever, dermatitis, arthritis, and swelling of the distal extremities, as well as gastrointestinal and sicca-like symptoms. The disorder is associated with specific *NOD2* variants. YAOS is not uncommon, yet effective drugs remain limited due to its recent identification. This study aimed at examining the therapeutic utility of canakinumab, a monoclonal antibody against interleukin-1 β for the disease.

Methods: In this retrospective analysis of prospectively designed single center study approved by the Institutional Research Board, 6 adult Caucasian patients that were enrolled fulfilled the diagnostic criteria for YAOS as confirmed by molecular analysis. These patients naïve to biologics received subcutaneous injections of canakinumab 150 mg every 4 to 8 weeks for 2 to 12 months. The primary end point was the change of overall clinical response evaluated by patient's global assessment at week 1, 2, 3 and 4. Secondary end points included changes in each of the major signs and symptoms using modified Schnitzler activity score on a scale of 0-4. Inflammation markers and drug adverse reactions were recorded including routine laboratory tests.

Results: All 6 patients receiving canakinumab reported overall clinical improvement with a mean change of 78% as compared with that before the drug administration. Patients noted improvement from day 7 following the injection with peak effect around day 14 to 21, and the improvement generally lasted up to 4 weeks. Patients felt even more symptomatic relief with more drug dosing over time. The results of the constituent signs and symptoms at day 14 after the biologic administrations are summarized in Table 1, and there was 78% improvement in fever and approximately 70% in each of the other major phenotypes, such as rash, arthritis, sicca-like and gastrointestinal symptoms. Three out of the 6 patients had elevated inflammation markers that normalized after canakinumab. Adverse events were minimal, including minimally elevated liver enzymes in one patient.

Table 1 Demographics, Scores and Changes in Major Constituent Manifestations in YAO Syndrome Patients Receiving Canakinumab

Patient	Sex	Age at dx	Age at onset	Caucasian	CAN doses	Fever Score(B/A) Improvement %	Rash Score(B/A) Improvement %	Arthritis Score(B/A) Improvement %	GI Score(B/A) Improvement	Sicca Score(B/A) Improvement %	Overall clinical response Score(B/A) Improvement %
1	F	19	15	Yes	4	(4/0)100	(3/1)67	(4/2)50	(3.5/1)71	(2/0)100	(4/2)50
2	F	40	20	Yes	7	(4/0)100	(3/2)33	(3/1)67	(0/0)	(0/0)	(4/0)100
3	M	34	30	Yes	10	(3/1)67	(4/1)75	(4/1)75	(2/0)100	(3/1)67	(3/1)67
4	M	49	20	Yes	2	(2/0)100	(3/0)100	(3/0)100	(1/0)100	(4/0)100	(4/1)75
5	F	27	7	Yes	6	(3/2)33	(3/1)67	(4/1.5)63	(3/3) 0	(3/1)67	(4/1)75
6	F	49	30	Yes	7	(3/1)67	(1/0)100	(3.5/2.5)29	(3.5/1)71	(4/3)25	(4/2)50
Mean \pm SD						77.8 \pm 27.3	73.7 \pm 25.0	64.0 \pm 23.9	68.4 \pm 40.9	71.8 \pm 30.9	69.5 \pm 18.7

Note: Dx: diagnosis; CAN: Canakinumab; Scores are based upon a scale of 0-4 with 4 being the most severe; B/A: before and after Canakinumab injections; Improvement % is computed based upon the score changes before and after treatment divided by the scores before the treatment; SD: standard deviation.

Conclusion: In this study, canakinumab was effective in patients with YAOS, and thus clinical trial of canakinumab may be warranted as a therapeutic option for this disease.

Disclosure: Q. Yao, Novartis, 5;

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Transcriptomic Analysis of Hidradenitis Suppurativa Skin Demonstrates Dysregulation of Antimicrobial Proteins and Inflammatory Pathways

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Background/Purpose: Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory disease of the apocrine sweat glands. The purpose of the current study was to identify transcripts and upstream regulators that are differentially expressed in HS skin specimens compared to normal skin harvested at abdominoplasty.

Methods: Surgical specimens from operative HS debridement (n=10, IRB 041408) and abdominoplasty (n=11, IRB101419) were collected. Total RNA was extracted, amplified, biotin-labeled, purified and hybridized to Illumina HumanHT-12 v4 Expression BeadChips and scanned using a HiScanSQ system (Illumina Inc., CA). Low-level analysis of raw BeadChip data was performed using the limma and beadarray packages. Differentially expressed genes were detected by fitting gene-wise linear models to the normalized expression data at a false discovery rate (FDR) of <0.05 and an absolute log2-fold change greater than or equal to $\text{abs}(\log_2\text{FC}) \geq 1.00$ (equivalent to 2.0 fold changes). Differentially expressed genes were modelled using Ingenuity Pathway Analysis (IPA, Ingenuity, Qiagen, CA) and upstream regulator analysis was performed.

Results: In the HS to normal control comparison, 436 genes were overexpressed and 363 genes were under-expressed. The top 25 differentially expressed genes are shown in **Figure 1**. Notably, Dermcidin antimicrobial protein normally found in human sweat was significantly downregulated in the HS specimens. Significant differential expression was observed in 30 canonical pathways in the HS samples based on a $-\log(\text{p-value})$ cut off of 1.3 and a Z-score activation prediction cut off of >2 or <-2 , (**Table 1**). Upstream regulator analysis identified interferon alpha (IFN- α), IFN- γ , lipopolysaccharide, tumor necrosis factor and oncostatin-M as the top five upstream regulators in the HS dataset compared to normal skin (**Table 2**).

Conclusion: Production of antimicrobial peptides is dysregulated in HS, and inflammatory pathways, particularly the interferon pathway and pathways of leukocyte activation are upregulated suggesting novel pathways that could be therapeutic targets for the management of this disease.

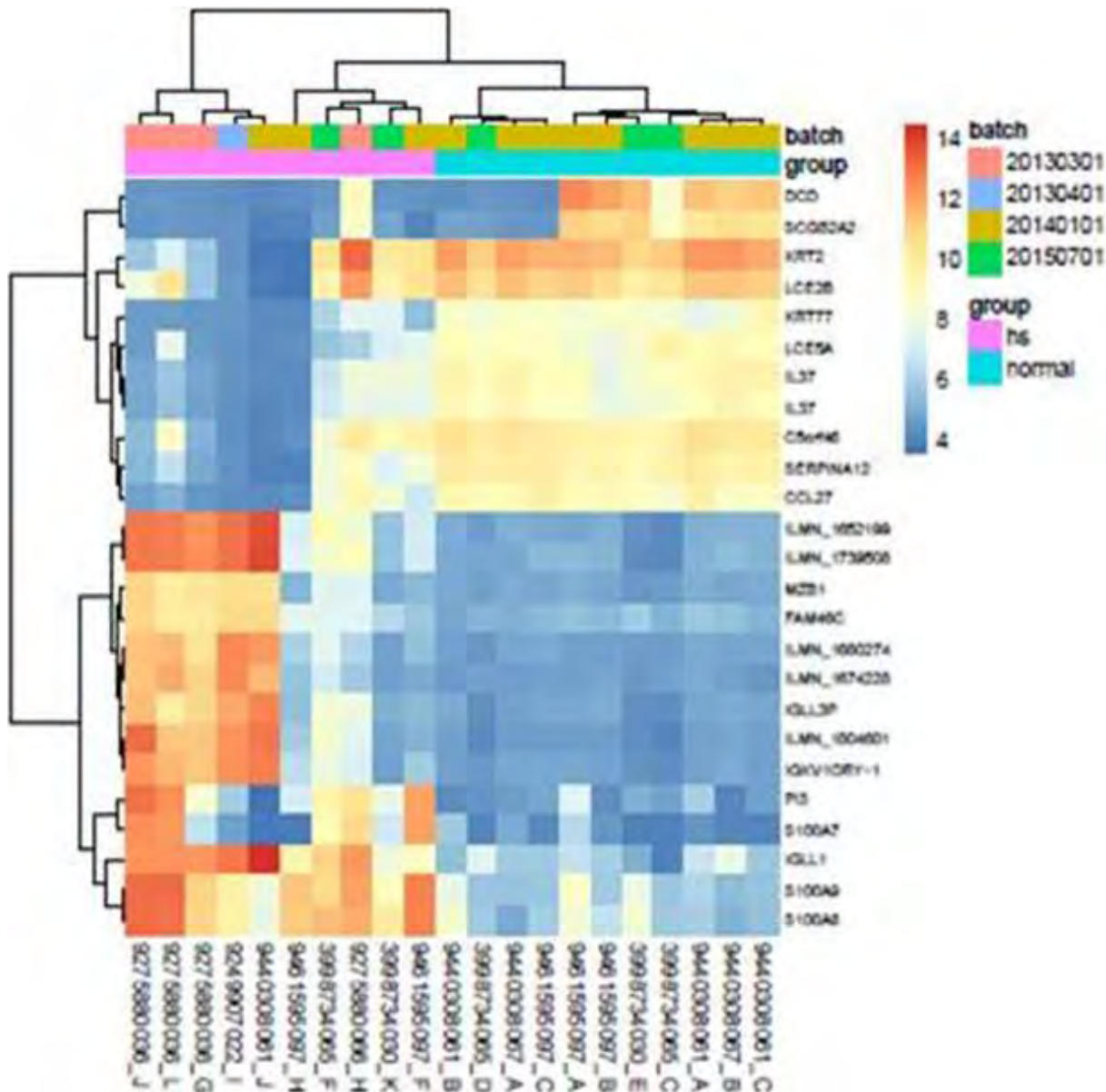


Figure 1. Differential gene expression in HS and normal tissue.

Table 1 Top 30 canonical pathways in HS

	Ingenuity Canonical Pathways	-log(p-value)	Ratio	z-score	Down-regulated	No change	Upregulated
1	Interferon Signaling	7.87	0.528	4.24	2/36 (6%)	0/36 (0%)	17/36 (47%)
2	Leukocyte Extravasation Signaling	7.4	0.27	2.10	19/211 (9%)	0/211 (0%)	38/211 (18%)
3	Th1 Pathway	6.07	0.289	3.77	6/135 (4%)	0/135 (0%)	33/135 (24%)
4	Th2 Pathway	4.86	0.26	2.65	9/150 (6%)	0/150 (0%)	30/150 (20%)
5	Role of NFAT in Regulation of the Immune Response	4.29	0.237	3.68	11/186 (6%)	0/186 (0%)	33/186 (18%)
6	Tec Kinase Signaling	4.24	0.241	2.20	14/170 (8%)	0/170 (0%)	27/170 (16%)
7	Dendritic Cell Maturation	3.59	0.223	3.48	10/193 (5%)	0/193 (0%)	33/193 (17%)
8	Neuroinflammation Signaling Pathway	3.19	0.196	3.71	19/311 (6%)	0/311 (0%)	42/311 (14%)
9	JAK/Stat Signaling	3.13	0.265	2.13	5/83 (6%)	0/83 (0%)	17/83 (20%)
10	Oncostatin M Signaling	3.1	0.353	3.32	0/34 (0%)	0/34 (0%)	12/34 (35%)
11	FcγRIIB Signaling in B Lymphocytes	3.08	0.302	2.00	4/53 (8%)	0/53 (0%)	12/53 (23%)
12	IL-6 Signaling	3.06	0.234	2.04	8/128 (6%)	0/128 (0%)	22/128 (17%)
13	Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	2.96	0.211	3.48	16/194 (8%)	0/194 (0%)	25/194 (13%)
14	TREM1 Signaling	2.54	0.253	3.44	1/75 (1%)	0/75 (0%)	18/75 (24%)
15	p70S6K Signaling	2.52	0.22	2.04	12/132 (9%)	0/132 (0%)	17/132 (13%)
16	iCOS-iCOSL Signaling in T Helper Cells	2.38	0.22	2.40	7/123 (6%)	0/123 (0%)	20/123 (16%)
17	PKCθ Signaling in T Lymphocytes	2.19	0.211	2.75	6/133 (5%)	0/133 (0%)	22/133 (17%)
18	Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	1.76	0.197	2.84	5/137 (4%)	0/137 (0%)	22/137 (16%)
19	Acute Phase Response Signaling	1.7	0.188	3.27	5/170 (3%)	0/170 (0%)	27/170 (16%)
20	LPS/IL-1 Mediated Inhibition of RXR Function	1.69	0.18	2.14	20/222 (9%)	0/222 (0%)	20/222 (9%)
21	GP6 Signaling Pathway	1.63	0.194	2.75	6/134 (4%)	0/134 (0%)	20/134 (15%)
22	Retinoic acid Mediated Apoptosis Signaling	1.58	0.226	2.50	3/62 (5%)	0/62 (0%)	11/62 (18%)
23	Tumoricidal Function of Hepatic Natural Killer Cells	1.53	0.292	2.24	0/24 (0%)	0/24 (0%)	7/24 (29%)
24	B Cell Receptor Signaling	1.45	0.178	2.48	7/191 (4%)	0/191 (0%)	27/191 (14%)
25	PPAR Signaling	1.44	0.2	-2.52	7/95 (7%)	0/95 (0%)	12/95 (13%)
26	Thrombopoietin Signaling	1.42	0.215	2.14	3/65 (5%)	0/65 (0%)	11/65 (17%)
27	Calcium-induced T Lymphocyte Apoptosis	1.37	0.212	2.11	3/66 (5%)	0/66 (0%)	11/66 (17%)
28	SAPK/JNK Signaling	1.33	0.192	2.24	6/104 (6%)	0/104 (0%)	14/104 (13%)
29	PI3K Signaling in B Lymphocytes	1.32	0.185	2.13	8/130 (6%)	0/130 (0%)	16/130 (12%)
30	Telomerase Signaling	1.31	0.189	2.36	8/111 (7%)	0/111 (0%)	13/111 (12%)

Table 2 Top upstream regulators in HS

Upstream Regulator	Predicted Activation State	Activation z-score	p-value of overlap
Interferon alpha	Activated	8.489	1.26E-26
IFNG	Activated	9.593	1.08E-20
lipopolysaccharide	Activated	9.683	2.63E-20
TNF	Activated	7.927	1.52E-19
OSM	Activated	7.511	6.33E-18

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Treatment Choices and Response Rates of SAPHO Syndrome: Single Center Case Series

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Figure 1. Activity parameters at initial and final assessment

Parameter, Mean (SD)	Baseline	Final Assessment	p value
BASDAI	4.6 (2.9)	1.3 (0.6)	0.2
BASFI	5.65 (2.6)	0.65 (0.4)	<0.001
CRP (mg/dl)	2.95 (5.5)	0.60 (0.54)	0.005
ESR (mm/h)	24.8 (22.8)	12.4 (11.9)	0.044
Number of swollen joints	0.20 (0.42)	0	NS
Number of painful joints with palpation	2.6 (3.2)	1.0 (1.7)	0.4

Background/Purpose: SAPHO Syndrome is a chronic disease with bone, joint and skin involvement characterized by synovitis, acne, pustulosis, hyperostosis, osteitis. Treatment decisions of SAPHO syndrome are generally based on experts' opinions. Our aim is to evaluate treatment options and response of patients with SAPHO syndrome in the referral outpatient clinic

Methods: All patients with SAPHO syndrome diagnosed since February 2014 have been registered and monitored prospectively with a standard form. All patients met the Benhamou criteria (1) for SAPHO syndrome. At baseline and follow-up visits, patients were assessed regarding acute phase reactants, BASDAI, BASFI, number of swollen and tender joints (28 joints), patient global assessment (particularly assessed for skin and joint) and overall assessment of patient. Baseline and follow-up treatment choices were decided by expert opinions. There were 25 patients with SAPHO syndrome and 22 patients had complete demographic and treatment data, who were analyzed.

Results: Twenty-two patients (12 (54.5%) female) with SAPHO syndrome were evaluated. Mean age of diagnosis was 40.1 ± 13.2 , the mean follow-up duration was 17.6 ± 24.5 months. The evaluation of the disease activity at initial and final visits were shown in figure 1. Initial and maintenance treatment regimens were given in table 1. At baseline, distribution of each particular treatment choices were pamidronate in 10 patients (45.4%), methotrexate in 9 patients (40.9%), sulphasalazine in 6 patients (27.2%), corticosteroids in 3 patients (13.6%), cyclosporine, anti-TNF and surgery each in 1 particular patient (4.5%). During follow-up period, 3 patients (13.6%) were switched to anti-TNF treatments due to inefficacy of other treatments. At the final visit, all patients achieved remission according to physician assessment. We did not find any treatment-related side effects during follow-up period.

Conclusion: Randomized controlled trials have not been performed to evaluate treatment options for rare rheumatologic disorders such as SAPHO syndrome. In our case series, pamidronate seems to be an effective treatment option against both osteoarthritic and skin manifestations, on the other hand anti-TNF treatments should be kept in mind on the resistant patients.

Reference: 1. Benhamou CL. Rev Rhum Mal Osteoartic. 1984

Table 1 Distribution of drugs administered at baseline and for the maintenance

Treatment regimens	Initial regimen n (%)	Maintenance regimen n (%)
Pamidronate	9 (40.9)	10 (45.4)
Methotrexate	4 (18.1)	2 (9.0)
Methotrexate + sulphasalazine	4 (18.1)	3 (13.6)
Anti-TNF	1 (4.5)	3 (13.6)
Anti-TNF + methotrexate	0 (0)	1 (4.5)
Pamidronate and sulphasalazine	1 (4.5)	1 (4.5)
Sulphasalazine	1 (4.5)	1 (4.5)
Methotrexate + cyclosporine	1 (4.5)	0 (0)
Surgery without concomitant drug	1 (4.5)	1 (4.5)

Disclosure: A. Erden, None; M. Ekici, None; A. Sari, None; B. Armagan, None; L. Kilic, None; S. Apras Bilgen, None; A. Akdogan, None; O. Karadag, None; S. Kiraz, None; I. Ertenli, None.

Measurement of the Pro-Coagulant Activity of Microparticles in Patients with Inflammatory Rheumatic Diseases: Prospective Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster III: Sarcoid, Inflammatory Eye Disease, and Autoinflammatory Disease

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Microparticles (MPs) are small membrane-bound vesicles that arise from activated and dying cells. Although the majority of MPs in the blood originate from platelets, all cells appear to be able to release MPs. Many studies have raised the implication of these MP in various processes: inflammation, thrombosis, angiogenesis. Previous studies reported inconsistent results in inflammatory rheumatic diseases. Studies have shown the correlation between the circulating MPs, platelet MPs and lymphocyte MPs in patients with spondyloarthritis (SpA) compared to control patients. For rheumatoid arthritis (RA), platelet MPs levels were correlated with DAS28. The aim of this study was to search a possible correlation between the disease activity and the pro-coagulant property of microparticles, potential indirect marker of inflammation.

Methods: The test used (STA Procoag PPL®) is a standardised automated test. Results are expressed as coagulation times (in seconds). It is a functional test that provides information on the procoagulant potential of microparticles. The microparticles supply the phospholipids expressed on their membrane surface and the test provides calcium and factor Xa necessary to initiate coagulation : the shorter the coagulation time the greater the procoagulant activity of the phospholipids being studied, suggesting a higher number of MP.

This is a prospective, single-center study, including 39 patients with spondyloarthritis (ASAS criteria), 37 with rheumatoid arthritis (ACR criteria) and 26 control patients (healthy subjects, osteoarthritis). All patients underwent STA Procoag PPL test, and we collected medical data : disease activity (BASDAI, BASFI, DAS28vs and DAS28crp and HAQ), biological inflammation (VS, CRP), duration of disease, and current treatment.

Results: The in vitro clotting time of serum of patients with spondyloarthritis and rheumatoid arthritis compared with controls was not significantly different ($p = 0.23$ and $p = 0.44$, respectively). Regarding the activity scores of inflammatory rheumatic disease: BASDAI and BASFI, DAS28esr, DAS28crp and HAQ for patients with RA, no correlation between these data and coagulation time was found; the same goes for biological inflammation (ESR, CRP), duration and type of treatment (Nonsteroidal anti-inflammatory drugs, DMARDs, biologics).

STA PPL	Controls (n=26)	SpA (n=39)	p	RA (n=37)	p
Mean \pm SD	62,70 \pm 11,58	66,48 \pm 12,77	$p = 0,23$	65,25 \pm 13,54	$P = 0,44$
BASDAI	$r=0,0602$ $p=0,72$		DAS28 esr	$r= 0,230$ $p=0,17$	
BASFI	$r=-0,125$ $p=0,45$		DAS28 crp	$r=0,151$ $p=0,37$	

Conclusion: In this study, there is neither difference in values of procoagulant activity of MPs between inflammatory rheumatic diseases and control subjects, nor correlation with their activity scores or biological inflammation.

Disclosure: C. Mekhail, None; X. Guillot, None; C. Prati, None; P. Saas, None; G. Mourey, None; D. Wendling, None.

Incidental Steroid Use May Worsen Outcomes in Patients with Heparin Induced Thrombocytopenia in the ICU Setting

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster – ARHP

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Heparin induced thrombocytopenia (HIT) is the destruction of platelets in patients exposed to heparin products. While there are two types of HIT, the term is often used without modifier to refer to HIT Type II, which is immune-mediated and severe. Up to 5% of patients on unfractionated heparin and 1-2% of patients on low molecular weight heparin will develop HIT Type II, with 30-80% of them developing thrombotic sequelae. The gold standard for treatment is to stop heparin products and start a different anticoagulant. Although not explicitly indicated, steroids are often incidentally given to suppress the immune-mediated destruction of platelets. However, the impact of steroids on patient outcomes, such as length of stay, mortality, and adverse events like bleeding or thrombosis, is unclear. A literature review of steroid use patients with HIT in the ICU setting did not show any definitive studies looking at this association. We believe that investigating incidental steroid use in this patient population could clarify its role and impact and help us develop better guidelines for treatment.

Methods: We conducted a retrospective analysis using the MIMIC-III Critical Care Database. For our primary endpoint, we selected patients diagnosed with HIT using ICD-9 codes, filtered for earliest admission date and divided them into two groups for comparison: one group who received steroids, and the other group who did not receive steroids. Our sample is composed of 2,205 patients without incidental steroid use and 753 with incidental steroid use, with a total of 2,958. The chart was also abstracted for variables such as length of stay, admit type, mortality, and bleeding, as well as age (stratified by: neonate, 17-29, 30-49, 50-63, 64-75, 76+) and sex (male vs. female). Analysis was performed using chi-square test for categorical variables, Fisher's exact test for the admit type variable, and unpaired 2-sided t-test with unequal variances for the duration of stay variable

Results: Holding all other variables constant, we found that patients who were prescribed steroids had longer hospital stays by 6.5 days on average, when compared to patients who were not prescribed steroids ($p < 0.001$, 95% CI = 5.30 to 7.67). Moreover, patients who were prescribed steroids were almost twice as likely to experience mortality compared to those who were not prescribed steroids ($p < 0.001$, 95% CI = 1.63 to 2.45), and have increased odds of bleeding by 33% compared to those who were not given steroids ($p = 0.004$, 95% CI = 1.10 to 1.62).

Conclusion: This study represents the first attempt to discern the impact of steroid treatment on outcomes in patients with HIT Type II in the ICU setting. Given the results, it seems that steroid use is associated with worsened outcomes, such as longer length of stay, increased mortality, and increased bleeding. Although conventional wisdom has convinced us to give steroids in a large proportion of HIT cases, this study suggests that overall, steroid use in HIT patients may be more harmful than beneficial. We recommend that there be further investigation into the use of steroids in HIT, with demographic stratification, so that we can develop appropriate best practice guidelines for treatment.

Disclosure: R. Souaid, None; C. Lu, None.

Safety and Efficacy of Lenabasum in Refractory Skin-Predominant Dermatomyositis Subjects Treated on an Open-Label Extension of Trial JBT101-DM-001

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster III: Treatment and Classification Criteria

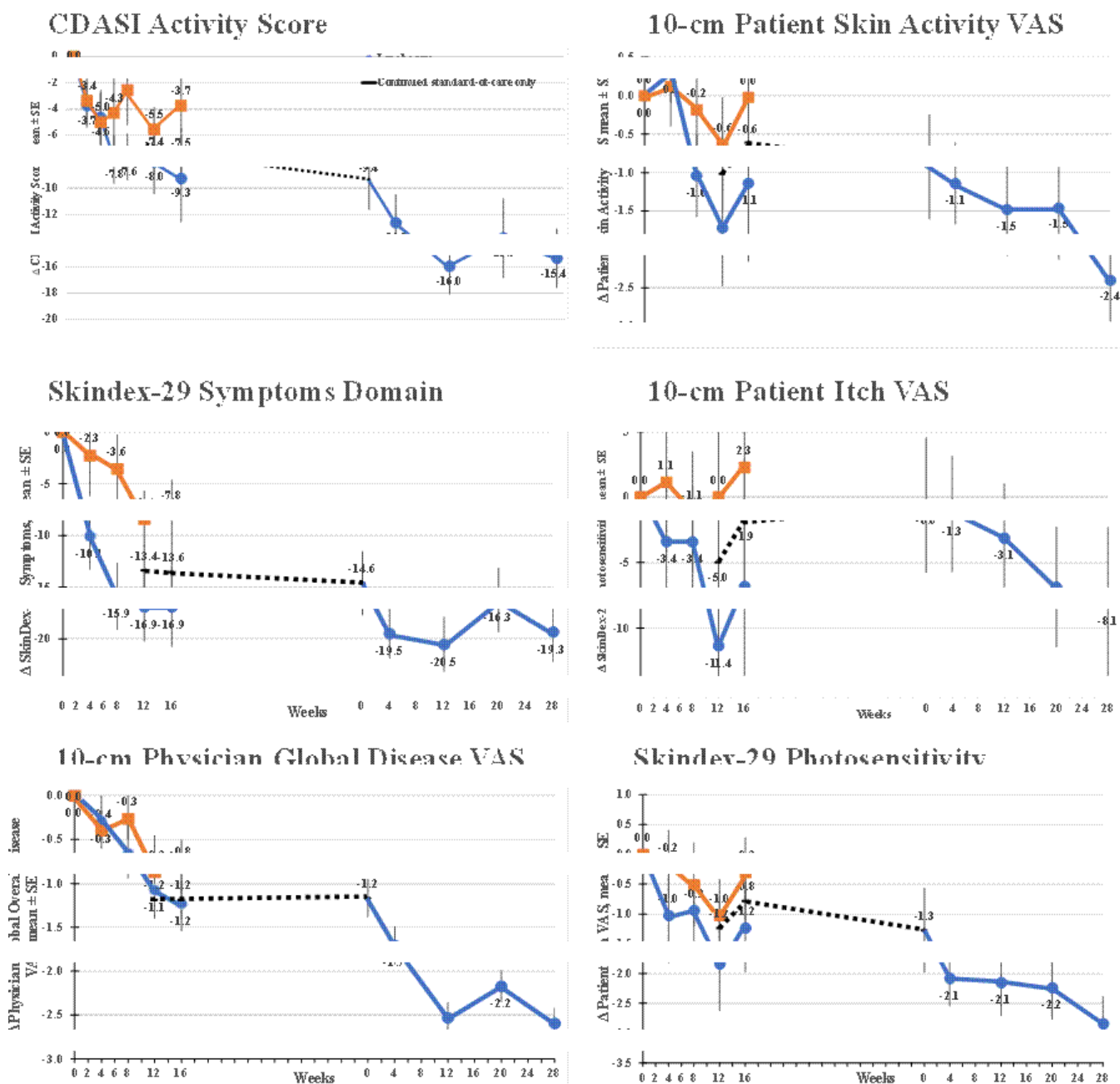
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Lenabasum is a synthetic, non-immunosuppressive, selective cannabinoid receptor type 2 agonist that activates resolution of innate immune responses. Lenabasum had acceptable safety and tolerability and improved efficacy outcomes in the double-blinded, randomized, placebo-controlled (DBPC) part A of Phase 2 trial JBT101-DM-001 (NCT02466243) in dermatomyositis(DM) subjects with refractory, skin-predominant involvement.

Figure 1. Change from Baseline in Selected Efficacy Outcomes in OLE of Phase 2 Trial JBT101-DM-001

Blue circle = lenabasum. Orange square = placebo. Black open circle = maintenance background treatment alone (no investigational product) before start of OLE. n = 21 in lenabasum group, n = 21 in placebo group. Time points are weeks 0, 4, 8, 12, 16, 20, 24, 28.



Objective: To provide long-term safety and efficacy data in DM subjects in study JBT101-DM-001.

Methods: Subjects who completed Part A were eligible to receive oral lenabasum 20 mg BID in an open-label extension (OLE) that assessed safety and efficacy at 4 weeks, then every 8 weeks.

Results: 20/22 (90.9%) eligible subjects received open-label lenabasum, following a mean interval of 31 weeks from end of Part A to start of OLE when they received only standard-of-care. 17/20 (85.0%) subjects were on stable baseline immunosuppressive drugs. At the time of data cut-off, no subjects had discontinued from the OLE, all completed Week 22 and 17 (85%) completed \geq Week 28. Adverse events (AEs, $n = 33$) occurred in 13/20 (65.0%) subjects, with 5/20 (25.0%) subjects having ≥ 1 AE (all mild) related to lenabasum. No subject had a serious or severe AEs. All subjects had AEs with maximum severity of mild (12/20, 60.0%) or moderate (1/20, 5.0%). The only AE that occurred in more than 1 subject was DM flare ($n = 2$, 10%); the last recorded CDASI activity score prior to flare was 14 points lower than baseline in 1 subject and 5 points higher than baseline in 1 subject. Mild dizziness occurred in 1 (5.0%) subject. Improvement was seen in multiple physician- and patient-reported efficacy outcomes including: CDASI activity score; physician VAS assessments of skin activity and extra-muscular disease; physician Likert assessments of global disease, skin disease, and extra-muscular disease; and patient VAS assessments of overall disease, skin disease, itch, pain, and several SkinDEX-29 and PROMIS-29 domain scores. Examples are shown in Figure 1. Mean (SD) changes at Week 28 from study start were: CDASI activity score = -15.4 (9.24) points, with 14/17 (82.3%) subjects achieving ≥ 10 -point improvement and 8/17 (47.1%) subjects achieving low disease activity with CDASI ≤ 14 ; 10-cm Physician Overall Disease VAS = -2.6 (1.90) points, with 14/17 (82.3%) subjects achieving ≥ 1 point and 20% improvement.

Conclusion: Lenabasum continues to have a favorable safety and tolerability profile in the OLE of the Phase 2 trial JBT101-DM-001 with no severe or serious AEs or study discontinuations related to lenabasum. The CDASI activity score and multiple other physician and patient-reported outcomes improved, although limitations of attributing efficacy to lenabasum in the setting of open-label dosing is acknowledged. These data support further testing of lenabasum for the treatment of DM.

Disclosure: V. P. Werth, Corbus Pharmaceuticals, Inc., 5, 9; D. Pearson, None; J. Okawa, None; R. Feng, None; J. Concha, None; B. Patel, None; E. Hejazi, None; C. Cornwall, Corbus Pharmaceuticals, Inc., 3; S. Constantine, Corbus Pharmaceuticals, Inc., 3; B. White, Corbus Pharmaceuticals, Inc., 3.

Abstract Number: 2285

Factors Associated with Corticosteroid Discontinuation, Complete Clinical Response and Remission in Patients with Juvenile Dermatomyositis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster III: Treatment and Classification Criteria

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: We examined patients in a large juvenile dermatomyositis (JDM) registry for frequency of and factors associated with final corticosteroid discontinuation (Steroid DC), complete clinical response (CCR, clinically inactive disease for ≥ 6 continuous months on treatment), and remission (inactive disease for ≥ 6 continuous months off all treatment).

Table: Markov chain Monte Carlo Multivariable Weibull models of time to achieve final steroid discontinuation (DC), complete clinical response (CCR), and remission

Variables	Time to Final steroid DC		Time to CCR		Time to remission	
	Mean	SD	Mean	SD	Mean	SD
Shorter time to outcomes						
Anti-MDA5 autoantibodies	0.81	0.28				
South residential geoclimatic zone	0.71	0.24				
Northwest residential geoclimatic zone			1.35	0.29		
Anti-MJ (NXP2) autoantibodies			0.65	0.25		
Achievement of GS-DC					1.22	0.34
Age at first treatment <7 years old					0.97	0.25
Achievement of CCR					0.81	0.25
Longer time to outcomes						
GI, pulmonary or cardiac signs/symptoms	-0.81	0.17	-0.59	0.24	-0.59	0.23
Anti-p155/140 (TIF1) autoantibodies and any MAA	-0.77	0.35	-1.83	0.50		
Contracture	-0.58	0.19	-0.67	0.22		
Photosensitivity	-0.56	0.19			-0.5	0.22
Dysphonia			-1.21	0.27	-0.92	0.31
Southwest residential geoclimatic zone	-0.67	0.30				
Medication escalation within 18 months after initial treatment			-0.67	0.25		
Infection within 6 months of illness onset					-0.95	0.34
DIC	1401		944		890	

The higher absolute mean value indicates a stronger relative influence in the model. Mean values greater than zero indicate a shorter time to achieve the outcome, and mean values less than zero indicate a longer time to achieve the outcome. Only variables with parameter credible intervals that did not overlap zero were retained in the models. The multivariable models shown have the lowest DIC values. Variables without a mean and standard deviation number indicated were not significant and were not included in the model for that outcome.

Abbreviation: CCR, Complete clinical response; DC, Discontinuation; DIC, Deviance information criterion; GI, gastrointestinal; MAA, Myositis Associated Autoantibodies; MDA5, Melanoma Differentiation-Associated protein 5; NXP2, nuclear matrix protein 2; SD, Standard deviation; TIF1, transcriptional intermediary factor 1.

Methods: A retrospective review of illness outcomes was evaluated in 307 patients with probable or definite JDM with median follow-up duration of 43 months. The probability of achieving steroid DC, CCR, and remission were examined by Weibull time-to-event modeling. Significant univariable predictors were examined in multivariable time-to-event analysis using Markov chain Monte Carlo extension models. The conditional probability of each outcome was also evaluated using Bayesian network models.

Results: One-hundred-ninety-one of the 307 patients (62.2%) achieved at least one of the outcomes. By 60 months from treatment initiation, 57% of patients achieved steroid DC, 44% achieved CCR, and 31% achieved remission. Time to 50% probability of achieving steroid DC, CCR, and remission were 52, 69, and 92 months, respectively. The probability of CCR and remission were conditional. The probability of attaining CCR given steroid DC was 47%; when steroid DC was not attained, the probability of achieving CCR was 19%. When steroid DC and CCR were achieved, the probability of achieving remission was 66%. When steroid DC and CCR were not achieved, the probability of remission was 3.5%. Several factors were associated with longer times to achieve these outcomes in multivariable models. Gastrointestinal, pulmonary or cardiac symptoms were the only factors associated with longer times to achieve all three outcomes. Anti-p155/140 autoantibodies (Abs) with any myositis associated Abs and contractures were associated with longer times to steroid DC and CCR, photosensitivity with longer times to steroid DC and remission, and dysphonia with longer times to CCR and remission. A Southeast residential geoclimatic zone, medication escalation within 18 months of treatment initiation, and an infection within 6 months of illness onset were associated with longer times to achieve a single outcome. Anti-MDA5 Abs and a Southern residential geoclimatic zone were associated with shorter times to steroid DC. A Northwest residential geoclimatic zone and anti-MJ Abs were associated with shorter times to CCR. The achievement of steroid DC and CCR and younger age at first treatment were associated with shorter times to remission.

Conclusion: A large proportion of JDM patients achieve positive treatment responses, including steroid DC, CCR, and remission, although timelines for these important outcomes are relatively long. Factors associated with times to achieve these outcomes include selected clinical features, autoantibodies, and environmental factors.

Disclosure: T. Kishi, Cure JM foundation, The Myositis Association, 2; W. Warren-Hicks, None; N. Bayat, None; I. Targoff, the OMRF Clinical immunology laboratory, 5; T. H. Finkel, None; E. Goldmuntz, None; M. Henrickson, None; B.

Lang, None; A. Mammen, None; L. M. Pachman, None; M. Passo, None; T. P. O'Hanlon, None; F. W. Miller, Hope Pharma, 9; M. Ward, None; L. G. Rider, Hope Pharmaceuticals, Bristol Myers Squibb, Lilly, 2.

Abstract Number: 2286

Myositis and Fasciitis By Magnetic Resonance Imaging in Recent-Onset Polymyalgia Rheumatica and Effect of Tocilizumab Therapy

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster III: Treatment and Classification Criteria

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose : To assess the prevalence of myofascial inflammatory lesions visible by magnetic resonance imaging (MRI) and their changes after tocilizumab therapy in active polymyalgia rheumatica (PMR).

Methods: We conducted a post hoc analysis of data from the TENOR study (Devauchelle-Pensec V, et al Ann Rheum Dis. 2016; 75:1506-10). Inclusion criteria were PMR meeting Chuang's criteria, onset within the past 12 months, active disease defined as PMR-AS>10. 18 patients each received tocilizumab injections at weeks 0, 4, and 8. The shoulder and pelvic girdles were assessed at baseline then at weeks 2 and 12 using an MRI 3T Philips Achieva (Philips, Amsterdam, The Netherlands), with a 32-channel surface antenna. Three sequences were used: axial T1 turbo spin echo (TSE), axial T2 short tau inversion recovery (STIR), and coronal T2 STIR. Radiologists blinded to patient data assessed each muscle group for myositis and fasciitis on baseline, week-2, and week-12 MRIs. Myofascial lesions were defined as a high T2 STIR signal that was either diffuse within the muscle or formed a line surrounding the muscle. Reproducibility was estimated by having two radiologists assess the week-2 MRIs.

Results: For myofascial lesion detection, intraobserver reproducibility was almost perfect ($\kappa = 0.890$) and interobserver reproducibility was substantial ($\kappa = 0.758$). At baseline, all patients had at least one inflammatory myofascial lesion; sites involved were the shoulder in 10 (71.4%) patients, hip in 13 (86.7%), ischial tuberosity in 9 (60.0%), and pubic symphysis in 12 (80.0%). Sites involved at week 12 were the shoulder in 8 (53.3%) patients, hip in 5 (33.3%), ischial tuberosity in 1, and pubic symphysis in 3 (20.0%). At week 12, of 103 muscle groups studied in all, 43 (41.7%) had no inflammatory lesions, compared to 33 at baseline (Mac Nemar; $P < 0.001$) but some areas seemed to be more responsive to tocilizumab compared to other areas. Improvements were noted in 66 (64.1%) muscle groups, worsening in 2 (1.9%), no change in 35 (34.0%).

Conclusion: In addition to synovitis and bursitis, PMR causes myositis and fasciitis of the shoulder and pelvic girdles. Tocilizumab therapy improves the myofascial lesions, in addition to the clinical and laboratory features.

Disclosure: J. P. Laporte, None; F. Garrigues, None; A. Huwart, None; S. Jousse-Joulin, None; T. Marhadour, None; D. Guellec, None; D. Cornec, None; V. Devauchelle-Pensec, Chugai, 2, 5; A. Saraux, Chugai, 2, 5.

Abstract Number: 2287

Interim Results of an Open-Label Study Assessing Efficacy and Safety of Adrenocorticotrophic Hormone Gel for Treatment of Refractory Cutaneous Manifestations of Dermatomyositis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster III: Treatment and Classification Criteria

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Cutaneous dermatomyositis (DM) is often refractory to multiple medications, suggesting better treatments are needed. Adrenocorticotrophic hormone gel is a repository corticotropin injection that is FDA-approved for DM, but little is known about its safety and efficacy for cutaneous DM manifestations. We are conducting an open-label study to assess efficacy and safety of repository corticotropin injection for treatment of refractory cutaneous DM. Here, interim results of this clinical trial are reported.

Methods: DM patients with \geq mild active cutaneous disease despite prior treatment with ≥ 2 systemic agents were eligible for inclusion. Pts were initiated on 80u repository corticotropin injection twice weekly for 24 weeks (6 months (mo)), with clinical evaluations at baseline, 1 mo, 3 mo, and 6 mo. Primary outcomes include decreases in Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity and Physician's Global Assessment (PGA) activity scores.

Results: Nine adults (8 females, 1 male) with DM (8 classic, 1 amyopathic), have been enrolled (average (avg) age 53.6 years (yrs)). On average, patients carried a diagnosis of DM for 5.2 yrs (median (med) 4 yrs) at time of study enrollment. Patients had been treated with an avg of 4.6 systemic medications (med 4) prior to study entry, and were being treated with an avg of 2.3 systemic medications (med 2) at time of study entry. Avg baseline CDASI activity score was 20.8 (med 19) and avg PGA activity score was 6/10 (med 6). In terms of patient assessments, baseline patient global skin (PGS) scores averaged 3.3/10 (med 3) and patient globalitch (PGI) scores averaged 6.4/10 (med 6). Six patients had a positive ANA (titer range= 1:160 to 1:1280, all speckled pattern). Eight patients had detectable myositis-associated autoantibodies (7 anti-transcriptional intermediary factor 1 gamma (TIF1 γ), 1 anti-small ubiquitin-like modifier activating enzyme (SAE) antibodies). All 9 patients completed ≥ 3 mos of treatment and 7 patients completed 6 mos of treatment at time of interim data analysis. At 3 mos, 7/9 patients had improved CDASI activity scores (average 15.3; med=13) and 8/9 had improved PGA activity scores (avg 7.7; med 8) (**Figure 1**). Additionally, 8/9 patients had improved PGS scores (avg 6.33; med 7) and PGI scores (avg 3.22; med 3) at 3 mos. At 6 mos, 7/7 patients had improved CDASI activity scores (avg decrease from baseline = 13.4) and PGA activity scores (avg improvement from baseline of 2.4 points). Furthermore, PGS scores improved in 6/7 patients and PGI scores improved in 5/7 patients at 6 mos. Adverse effects were mild in severity and no patient discontinued medication during the study period.



Conclusion: Our interim results suggest repository corticotropin injection is an effective, safe, and well-tolerated treatment for refractory cutaneous manifestations of dermatomyositis.

Disclosure: A. Fernandez, Mallinckrodt Pharmaceuticals, 2, 8, Pfizer, Inc., 9;

Preexisting Anti-Acetylcholine Receptor Autoantibodies and B Cell Lymphopenia Are Associated with the Development of Myositis in Thymoma Patients Treated with Avelumab, an Immune Checkpoint Inhibitor Targeting Programmed Death-Ligand 1

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster III: Treatment and Classification Criteria

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Immune checkpoint inhibitors (ICIs) enhance the immune response against tumors but may also trigger immune-related adverse events (IRAEs). Myositis following receipt of ICIs is a rare IRAE. In prior studies, creatine kinase (CK) elevations occurred in just 0.2% of patients treated with avelumab, an anti-programmed death-ligand 1 antibody that has been effective against several solid tumor types. Since effective therapies for thymic epithelial tumors are lacking, we included patients with thymic malignancies in a phase I trial of avelumab administered at 10 or 20 mg/kg (NCT01772004).

Methods: Serum and peripheral blood mononuclear cells (PBMCs) were collected before and after avelumab therapy. Serum creatine kinase (CK) levels were monitored during the trial. Laboratory investigations included the assessment of thymoma- and myositis-associated autoantibodies as well as immunophenotyping of PBMCs by flow cytometry.

Results: Seven recurrent thymoma and 1 thymic carcinoma patients were enrolled. No patient had a history of autoimmunity or weakness and each had normal baseline CK levels. Four thymoma patients developed CK elevations (range 762 to 16,037 IU/L) and proximal weakness 7 to 35 days after avelumab administration consistent with ICI-associated myositis. CK levels normalized in all patients within weeks of starting immunosuppressive therapy. One patient with myositis also had myocarditis and a fifth patient without myositis developed enteritis. Four patients had preexisting muscle acetylcholine receptor (mAChR) autoantibodies and each developed CK elevations and weakness. No patient without mAChR autoantibodies developed myositis (100% vs. 0%; $p=0.029$). Electrophysiological studies revealed evidence of myasthenia gravis in just one patient. No patient sera were reactive for any of the 16 myositis autoantigens on EUROLINE Autoimmune Inflammatory Myopathies line blots (EUROIMMUN). Immunophenotyping of PBMCs collected prior to avelumab therapy showed that patients who developed either myositis or enteritis had lower B cell frequencies (0.19%, 0.12-0.73%; median, interquartile range) than those who did not (12.37%, 5.14-16.5%). The median B cell frequencies of 30 patients with non-thymic malignancies and 15 healthy controls were 8.3% (interquartile range 2.4-11.7%) and 16.3% (interquartile range 11.9-17.65%), respectively.

Conclusion: Myositis is a common IRAE in thymoma patients treated with avelumab. Preexisting mAChR autoantibodies may identify thymoma patients most at risk for developing this complication. Since mAChR autoantibodies are known to cause myasthenia but are not associated with myositis, we conclude that they are a marker of preexisting autoimmunity rather than the direct cause of muscle damage. B cell lymphopenia also appeared to be associated with myositis and enteritis in those treated with avelumab. Additional studies are needed to confirm these findings and to determine whether preexisting autoantibodies or immune cell subset dysregulation predicts which non-thymic tumor patients are at increased risk for IRAEs following treatment with avelumab or other immune checkpoint inhibitors.

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Granulomatous Myositis: Heterogeneity and Response to Treatment

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Session Information

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Background/Purpose: Granuloma in the muscle can be found in patients with myopathy. This finding has alternatively been interpreted as either sarcoid myopathy or other myositis subtype associated with granulomatosis. While the response of sarcoid myopathy to immunomodulatory therapy has been purported to be unpredictable, certain myositis subtypes have been linked to specific outcomes. Thus, we aimed at refining the predictive significance of granuloma in patients with myositis.

Methods: A group of 23 patients with myositis and granuloma on muscle biopsy (granuloma-myositis) from 8 centers (7 French and 1 Belgian), was analyzed and compared with a group of 23 patients without identified granuloma (control-myositis) randomly sampled in each centers.

Results: All but two granuloma-myositis patients had extra-muscular involvements, including sarcoid-like signs that were systematically absent in the control-myositis group, such as cutaneous granulomatosis (n=5) or ocular lesion (n=2). In addition, 52% of the granuloma-myositis patients group had biological signs of granulomatosis (i.e. hypercalcemia and/or increased angiotensin converting enzyme) vs. none in the control-myositis group. Hardly half (43%) of the granuloma-myositis patients matched the ENMC 2013 diagnostic criteria for inclusion-body myositis (sIBM, clinico-pathologically defined: n=3, clinically defined n=4 and probable n=3), which was more frequent as compared with the control-myositis group. In accordance with sIBM diagnosis, as compared with remaining granuloma-myositis, these patients were more frequently men, with a longer delay between onset and diagnosis of myositis, suggesting a slow progression of the disease. However, all of them had also extra muscular involvements that were compatible with systemic granulomatosis. All patients were treated with corticosteroids (n=22), methotrexate (n=19), mycophenolate mofetil (n=5), intravenous immunoglobulins (n=3), anti-TNF drug (n=3), hydroxychloroquine (n=2), cyclophosphamide (n=2) because of suspicion of muscle sarcoidosis. Despite a higher number of immunomodulatory treatments as compared with the control-myositis group and the rest of granuloma-myositis group, only 1 granuloma-myositis patients matching ENMC 2013 criteria for sIBM reached muscle improvement (p<0.05 vs. the other myositis groups). Aside one granuloma-myositis patient with anti-PM/Scl positive scleromyositis, the remaining 57% of granuloma-myositis patients did not match the criteria for a well-defined myositis subtype, suggesting pure sarcoidosis. The proportion of patients that reached the definition of muscle improvement at last follow-up in this group (69%) was not significantly different from the patients in the control-myositis group. In multivariate analysis, matching criteria for inclusion-body myositis was the sole feature independently associated with non-response to myopathy treatment in patients with granuloma-myositis (p=0.003).

Conclusion: Granuloma-myositis patients should be carefully screened for inclusion body myositis, which is a very frequent condition in these patients, with important consequences for their care.

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Long Term Follow-up Results of Myositis Patients Treated with H. P. Acthar Gel

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Background/Purpose: Although HP Acthar gel is a purified, injectable formulation of full-length adrenocorticotrophic hormone approved by the FDA for use in myositis, peer-reviewed data is limited. We report long-term outcomes of myositis patients after 6 months of Acthar gel in an open-label pilot study.

Methods: Refractory myositis patients (6 DM, 4 PM) completing 6 months of treatment were included in the study. At the end of trial, 7 of 10 patients met criteria for response at 6 months with a significant reduction in prednisone dose. Post-trial follow-up period was 6 months with assessments at every 2 months which included collection of myositis core set measures (CSM) of disease activity [i.e. extra-muscular global disease activity (Ex-Musc global), physician global disease activity (MD-global), patient global disease activity (Pt-global), health assessment questionnaire (HAQ-DI), manual muscle testing (MMT), and muscle enzymes]. Treatment during the post-trial period was standard of care by the treating physician. ACR-EULAR myositis response criteria as well as the IMACS definition of improvement (DOI) were used to evaluate 12-month outcomes.

Results: 2 of 10 patients were lost to follow-up and 8 patients completed 6 months of post-trial visits. All patients continued their baseline immunosuppressive drugs and were off Acthar gel at the end of trial. Following discontinuation of Acthar gel, all patients had a slow clinical decline with an average time to flare of 4.3 months (median 5, range 0.5-7). Fifty percent of patients (n=4) were restarted on Acthar after an average of 10.3 months (6-13 months) with no other change in medications. The remaining patients who flared were managed by increasing prednisone doses. Patients had an average 41% increase in Ex-Musc global (median 20%, range 0-127%), 79% increase in MD-global (median 107%, range -100%-166%), 7% increase in HAQ-DI (median 0%, range -62% -576%), 0.6% increase in Pt-global (median 0%, range 16%-17%), and 3% decrease in MMT (median: -0.7%, range: -11 -4%) 6 months after Acthar discontinuation. Among 4 patients who restarted Acthar, one was lost to follow-up and 2 showed a partial clinical response in muscle strength and rash after 2 and 3 months and were subsequently treated with IVIG. One patient showed a complete response after restarting Acthar with increased muscle strength and rash resolution. Adverse events with Acthar use included dizziness, facial puffiness and upper respiratory tract infection.

Conclusion: Patients discontinuing Acthar after 6 months of clinical efficacy demonstrated a slow increase in disease activity, disability index, and decrease in muscle strength and had their first flare at 4 months after study drug discontinuation. There is need for a randomized, double-blind, placebo-controlled, clinical trial of Acthar in myositis patients.

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Longitudinal Course of the Disease in Anti-Mi2 Patients: More Intense Muscle Weakness, Good Response to Treatment and Progressive Reduction of Autoantibody Titers

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Background/Purpose: Autoantibodies targeting the Mi-2 (Mi-2a and Mi-2b) nuclear antigen in patients with dermatomyositis (DM) were first described in 1985. However, little is known about the phenotype and evolution of disease over time in these patients compared to anti-Mi2-negative DM patients. The objective of this project was to address the clinical features and the evolution of autoantibody titers over time in DM patients with anti-Mi2 autoantibodies compared to anti-Mi2-negative DM patients and other forms of myositis.

Methods: In this longitudinal cohort study, the prevalence and severity of clinical features at disease onset and during follow-up were compared between anti-Mi2-positive patients and patients with anti-Mi2-negative DM, the antisynthetase syndrome (AS), and immune-mediated necrotizing myopathy (IMNM). The evolution of the anti-Mi2 autoantibody titers were also studied in those patients with available longitudinal sera.

Results: Sixty-two anti-Mi2-positive DM, 160 anti-Mi2-negative DM, 168 AS, and 183 IMNM patients were included in this study. Anti-Mi2-positive patients had more severe proximal muscle weakness and increased muscle enzyme levels both at disease onset and during follow-up compared to anti-Mi2-negative DM (all $p < 0.001$) or AS patients (all $p < 0.01$). Anti-Mi2-positive DM patients were stronger compared to those with IMNM (all $p < 0.01$). Unlike those with IMNM, younger anti-Mi2-positive patients were stronger at disease onset compared to older anti-Mi2-positive patients ($p = 0.005$). Calcinosis and myalgia were less common in anti-Mi2-positive than in anti-Mi2-negative DM patients. Anti-Mi2-positive patients were generally responsive to first-line immunosuppressant treatment; after two years of follow-up, most of them had recovered full strength. Ninety-two percent (11/12) of anti-Mi2-positive patients had decreases in autoantibody titers during the first 3 years of follow-up; 25% (3/12) of them had normalization anti-Mi2 autoantibodies during follow-up.

Conclusion: Although anti-Mi2-positive DM patients are initially weaker than anti-Mi2-negative DM patients, both groups generally respond well to treatment with recovery of muscle strength. With treatment, anti-Mi2 autoantibody titers decrease and may even normalize.

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The Predictive Risk Factors for Opportunistic Infection during Immunosuppressive Therapy for Polymyositis/Dermatomyositis

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Table 1 Comparison between the PMDM patients complicated by CMV antigenemia and those without CMV antigenemia.

PMDM (n=166)		CMV positive n = 52	CMV negative n = 116	p-Value
women n (%)		38 (73%)	82 (71%)	0.210
Type (n)		PM 8, DM 31, CADM 13	PM 34, DM 51, CADM 31	0.099
Age (mean)		58.7 ± 17.2 ^a	55.7 ± 15.7 ^a	0.210
Follow-up time		39.3 [4.10-56.1] ^b	50.2 [20.9-82.7] ^b	0.030*
Smoking n (%)		13/49 (27%)	37/110 (34%)	0.625
Malignancy n (%)		12/49 (25%)	23/115 (20%)	0.521
Interstitial lung disease n (%)		42 (81%)	70 (60%)	0.006*
Death n (%)		13 (25%)	20 (17%)	0.242
Baseline data	CK (U/l)	458 [117-1548] ^a	888 [179-2923] ^a	0.026*
	LDH (U/l)	405 [312-576] ^a	390 [277-579] ^a	0.352
	KL-6 (U/ml)	755 [400-1090] ^a	469 [297-783] ^a	0.034†
	CRP (mg/dl)	0.9 [0.25-1.99] ^a	0.31 [0.11-1.95] ^a	0.015*
	Lymphocyte (/ul)	930 [637-1275] ^a	1075 [739-1460] ^a	0.039*
	Albumin (g/dl)	3.20 ± 0.55 ^a	3.81 ± 0.62 ^a	0.001**
	PaGO2 (mmHg)	35.5 [32.4-38.5] ^b	38.7 [36.1-42.6] ^b	0.004**
	ferritin	613 [245-1321] ^a	291 [134-601] ^a	0.004**
	IgG	1424 [1198-1890] ^b	1456 [1280-1904] ^b	0.082
	Anti Jo-1 Ab	8 (15%)	14/115 (12%)	0.475
Antibodies	Anti ARS Ab	6/27 (22%)	4/31 (13%)	0.489
	Anti MDA5 Ab	5/21 (24%)	4/14 (29%)	1.000
	Anti TIF-1γ Ab	2/3 (67%)	2/3 (67%)	NA
	ANA (>80*)	17/47 (36%)	45/113 (40%)	0.448
	Anti SS-A Ab	9/34 (27%)	17/88 (20%)	0.538
Treatment	PSE (mg/day)	47.3 ± 14.9 ^a	41.9 ± 15.5 ^a	0.042**
	1 month (mg/kg)	24.3 ± 7.4 ^a	21.2 ± 7.1 ^a	0.013**
	2 months (mg/kg)	42.7 ± 13.0 ^a	38.0 ± 13.6 ^a	0.045
	4 months (mg/kg)	67.1 ± 21.6 ^a	62.7 ± 23.0 ^a	0.289
	6 months (mg/kg)	69.4 ± 24.7 ^a	62.2 ± 29.7 ^a	0.201
	mP5L pulse n (%)	39 (75%)	54 (47%)	0.001**
	VCV n (%)	30 (58%)	20 (17%)	<0.001**
	Calcineurin inhibitor n (%)	41 (79%)	45 (40%)	<0.001**
	Combination (n)	27 (52%)	13 (11%)	<0.001**
	IVIg	8 (19%)	3/65 (5%)	0.022†

^aThe data are shown as the mean ± standard deviation^bValues are the median [interquartile range]

*p < 0.05, **p < 0.01

Session Information**Session Date:** Tuesday, October 23, 2018**Session Title:** Muscle Biology, Myositis and Myopathies Poster III: Treatment and Classification Criteria**Session Type:** ACR Poster Session C**Session Time:** 9:00AM-11:00AM

Background/Purpose: Although concomitant infectious diseases are the predominant causes of death in patients with polymyositis (PM)/dermatomyositis (DM), intensive immunosuppressive treatment are necessary for severe cases. We have already reported that high initial dose of glucocorticoid and combination immunosuppressive therapy for induction therapy, and KL-6 levels at the baseline were independent risk factors for infection. Here we investigated the predictive risk factors for opportunistic infection during immunosuppressive treatment for PM/DM by assessing cytomegalovirus (CMV) antigen test as a barometer for immunocompromised status.

Methods: We retrospectively analyzed clinical features, laboratory data at baseline in the patients with PM/DM who had received initial treatment at six hospitals affiliated to Yokohama City University from 2003 to 2016. We also investigated initial therapeutic regimens and clinical outcomes including CMV antigenemia as a complication. We conducted univariate and multivariate analyses to extract risk factors for CMV antigenemia.

Results: One hundred sixty-eight (PM 42, DM 82, and clinically amyopathic DM (CADM) 44) were recruited. The mean age was 56 ± 16 years and 120 (71.4%) were female. As initial therapies, oral prednisolone (PSL) was prescribed in all patients. Methylprednisolone (mPSL) pulse, intravenous cyclophosphamide (IVCY), and oral calcineurin inhibitor therapies were performed in 93 (56%), 50 (30%) and 86 (51%), respectively. Forty patients (24%) received combination therapy with IVCY and a calcineurin inhibitor. Fifty-two patients (31%) had CMV antigenemia within 6 months from initiation of immunosuppressant. An univariate analysis showed complication of ILD, high activity of ILD such as high KL-6 and low PaCO₂ and strong immunosuppressive therapy tended to be positive CMV antigenemia (Table 1). There was no association between the cumulative PSL dose except within one month and CMV antigenemia. A multivariate logistic regression analyses revealed that low PaCO₂ ($p = 0.023$, OR 0.78) and old age ($p = 0.040$, OR 1.07) were independent risk factors for CMV antigenemia. Moreover, the patients with positive CMV antigenemia tended to infected which were needed antibiotic therapy with significant differences (OR 4.52, $p < 0.001$). There were no patients with organ dysfunction as CMV infection.

Conclusion: Although rapid and intensive therapies are required for PM/DM, appropriate monitoring, prophylaxis and early treatment for opportunistic infection are important, especially in patients who receive strong immunosuppressive therapy and who show low PaCO₂ level and old age at baseline.

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Abstract Number: 2293

Subcutaneous Intravenous Immunoglobulins in Idiopathic Inflammatory Myopathies: Analysis of a Monocentric Cohort

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Background/Purpose: Despite the absence of specific guidelines, the treatment with intravenous immunoglobulins (IvIg) is considered effective in patients with refractory idiopathic inflammatory myopathies (IIM). Recently, a new therapeutic approach with subcutaneous immunoglobulins (ScIg) has been proposed. The aim of our study is to evaluate efficacy and safety of ScIg in patients with IIM followed in a rheumatology unit.

Methods: 10 IIM patients (7 Female, mean age 64.4 ± 10.2 years) treated in our rheumatology unit with ScIg were enrolled. Six patients had PM and 3 DM (Bohan and Peter criteria) while 1 had IBM (Griggs criteria). The treatment scheme was 2g/kg/month divided in 4 weekly administrations at home. At baseline and after treatment the following data were

collected: myositis specific/associated autoantibodies; indications to the treatment (skin lesions, dysphagia, lung or muscular involvement) and clinical response according to the manual muscle test 8 (MMT8), creatine kinase (CK), physician and patients' disease activity visual analogue scale (ph-VAS and pt-VAS), and health assessment questionnaires (HAQ).

Results: Nine patients received ScIg after treatment with IvIg (mean 22 months of treatment) while one started ScIg directly for severe skin involvement. Five patients had Ro52 positivity, 1 Tif1 γ , 1 anti-Ku. The indication for the treatment was the presence of refractory disease in 8 patients. All of these patients were treated with high dose steroids and at least 2 immunosuppressant. In 2 patients the treatment was prescribed for recurrent infections during immunosuppressive treatment. In addition, 7 patients had severe dysphagia. Only 1 patient reported an adverse event (vomiting, headache) and stopped the treatment after the first month. In the other nine patients, the duration of the follow-up was 18 months (3-72). At the last evaluation, compared to the switch to ScIg, no statistically significant differences were identified in MMT8, CK, ph-VAS, pt-VAS and HAQ ($p=n.s.$). The mean daily steroid dose was reduced from 6.1 ± 4.2 to 3.7 ± 2.5 mg ($p=n.s.$). Dysphagia improved in 4/7 patients. The patient who started ScIg directly for refractory and severe skin involvement improved after 6 months of treatment. No disease flares were identified during the treatment.

Conclusion: Despite their high cost, ScIg confirmed similar efficacy compared to IvIg for the treatment of refractory IIM patients and may represent an alternative. The treatment may allow an improvement of the quality of life of the patients, reducing the necessity of hospitalization. Furthermore was safe and no serious adverse events were reported during the treatment. Additional data with longer follow-up are necessary to confirm our data in different subset of patients.

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Abstract Number: 2294

Improving EULAR/Acr Classification Criteria for Idiopathic Inflammatory Myopathies

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Background/Purpose: New 2016 EULAR/ACR classification criteria have been established for idiopathic inflammatory myopathies (IIM). The highest weighted score is associated with the presence of anti-Jo-1 antibody and dermatomyositis (DM) classic rashes (Gottron papules/sign and heliotrope rash). The aim of our study was to evaluate if the addition of other myositis specific antibodies (MSAs) and/or other DM rashes would improve the accuracy of the criteria.

Methods: A prospective, longitudinal IIM dataset from a single myositis center was evaluated using the 2016 EULAR/ACR criteria as well as the Bohan & Peter classification criteria. All variables required for both these criteria were ascertained at the patient's first visit and subsequently updated prospectively on follow up visits. Expert physician clinical diagnoses (RA, CVO) were used as the gold standard to evaluate the criteria and proposed modifications. The latter included a) all other MSAs with anti-Jo1, b) all other DM rashes with Gottron papules (i.e. shawl sign, V-neck, holster sign, malar rash not sparing nasolabial fold, mechanics hands, periorbital edema), c) both a& b. This ongoing project thus far only includes data collection for DM. Percent agreement between the criteria and its proposed modifications with expert physician diagnosis were evaluated along with sensitivity and specificity.

Results: 213 DM patients (70% female, 89% Caucasian) have been analyzed to date. 2016 EULAR/ACR and Bohan & Peter showed % agreement of 84.3% and 82.9%, respectively as compared to the expert physician diagnosis, with sensitivity and specificity of 95.3% and 34.2% for EULAR/ACR and 83.8% and 82.9% for Bohan & Peter. The low specificity of EULAR/ACR criteria was partially explained by high false positives, as the current criteria fail to differentiate between DM and amyopathic DM, whereas the expert physician assessment did. The specificity of EULAR/ACR criteria improves to 44.8% without loss of sensitivity, if amyopathic DM is included under DM in the gold standard (Table 1). With the inclusion of other MSAs, there is a small gain in sensitivity to 98.3%, however, there is a marked decrease in specificity and a mild reduction of %agreement (Table 1). Similarly, with modification of inclusion of other

DM rashes, the sensitivity increases to 97.7% at the cost of specificity and %agreement. Applying both other MSA and other rash modifications, the sensitivity increases to almost 99%, with a severe loss of specificity and %agreement.

Conclusion: Contrary to popular belief, addition of other MSAs or other DM rashes or both in the 2016 EULAR/ACR criteria did not improve the criteria. There is a small gain in sensitivity but a marked decrease in % agreement and specificity. Further analysis including PM, IBM and other muscle disease control subjects is required to provide conclusive answers.

Table 1

	Expert Physician Classification Positive	Expert Physician Classification Negative	Sensitivity	Specificity	% Agreement
EULAR/ACR Positive	173	16	95.6%	44.8%	88.5%
EULAR/ACR Negative	8	13			
Bohan & Peter Positive	148	5	84.1%	78.4%	85.3%
Bohan & Peter Negative	28	29			
Modified EULAR/ACR with other MSA Positive	174	28	98.3%	15.2%	85.2%
Modified EULAR/ACR with other MSA Negative	3	5			
Modified EULAR/ACR with other DM Rash Positive	176	26	97.7%	13.3%	85.7%
Modified EULAR/ACR with other DM Rash Negative	4	4			
Modified EULAR/ACR with other DM Rash and other MSA Positive	182	24	98.9%	6.3%	87.6%
Modified EULAR/ACR with other DM Rash and other MSA Negative	2	2			

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Abstract Number: 2295

Classification of Idiopathic Inflammatory Myopathies: Assessment of 123 Patients According to 2017 Acr/EULAR Criteria Followed up By a Single Center from Turkey

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Muscle Biology, Myositis and Myopathies Poster III: Treatment and Classification Criteria

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Session Time: 9:00AM-11:00AM

Background/Purpose: The aim of this study is to evaluate sensitivity, limitations and assessment of 2017 ACR/EULAR IIMs classification criteria (ACR/EULAR2017) in 123 patients with idiopathic inflammatory myopathy (IIM).

Methods: Demographic data, clinical and serological features of 123 patients with a clinical diagnosis of IIM fulfilling Bohan/Peter criteria and followed up between 1994-2018 in our clinic, were collected according to a pre-defined protocol and ACR/EULAR2017 were applied to patients. Muscle biopsy scoring was performed on 70 patients who had biopsy records. Sensitivities and specificity on subset determination of the criteria of were analysed.

Results: The median age of patients was 46±15 and average follow up was 77 months. In 66% of the patients, the diagnosis was dermatomyositis (DM), in 28% polymyositis (PM), in 6% was immune-mediated necrotizing myopathy (IMNM) and inclusion body myositis (ICM). The frequency of arthritis, dysphagia, respiratory muscle involvement, interstitial lung disease and malignancy were detected 25, 35, 12, 29, 24% respectively, and mortality was 19%. ANA positivity was 38% and anti Jo-1 was present in 12% of the patients. Definite or possible IIM according to ACR/EULAR2017 was found in 95% of the patients regardless of muscle biopsy scoring (Possible IIM: 7%; definite IIM: 87%). The classification percentage of DM was 99 (all definite), PM 91 (probable and definite PM: 21 and 70%), IMNM 100 (probable and definite IMNM: 33 and 67), ICM 0 when ACR/EULAR2017 were applied to subsets of IIM without muscle biopsy scoring. On the other hand; in the classification made by including muscle biopsy scoring on the IIM subsets DM

was 100% (probable and definite: 3 and 97%), PM was 93% (probable and definite PM: 30 and 63%), IMNM 83% (all probable), ICM 100% (probable and definite ICM: 50 and 50%).

One of the DM patients and a patient with DM without dermatitis were classified as PM, 4 patients with hypomyopathic DM (HDM) were classified as amyopathic DM (100%) and 6 patients with IMNM was classified as PM (100%).

Conclusion: Without muscle biopsy and EMG, 95% of 123 IIM patients fulfilling Bohan/Peter criteria can be classified with the new ACR/EULAR2017. The sensitivity of the criteria is higher in DM (%99) but lower in PM (91%) and increased when muscle biopsy records are included (98%). On the other hand insufficient biopsy results may cause a slight change from definite to probable PM. ADM patients within the subset of DM were defined 100% correctly. Although ACR/EULAR2017 might have drawbacks in the classification of HDM and IMNM, significant improvement in the classification process with the advantage of weighting towards clinical assessment have been observed.

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Abstract Number: 2296

Novel Classification of Idiopathic Inflammatory Myopathies Based on Distinctive Features and Autoantibodies: Analysis of 67 Korean Patients

Sang Wan Chung¹, Su-Jin Yoo², Seong-Wook Kang³, In-Seol Yoo³, Seung-Cheol Shim³, Mihye Kwon⁴, Chung-Il Joung⁴, Jinhyun Kim⁵, Seung-Jae Hong¹ and Yeon-Ah Lee⁶, ¹Division of Rheumatology, Department of Internal Medicine, Kyung Hee University Hospital, Seoul, Korea, Republic of South, ²Department of Internal medicine, Chungnam National University School of Medicine, Daejeon, Korea, Republic of South, ³Department of Internal Medicine, Chungnam National University School of Medicine, Daejeon, Korea, Republic of South, ⁴Department of Internal Medicine, Konyang University hospital, Daejeon, Korea, Republic of South, ⁵Internal Medicine, Chungnam National University School of Medicine, Daejeon, Korea, Republic of South, ⁶Rheumatology, Kyung Hee University Hospital, Seoul, Korea, Republic of South

Session Information

Session Date: Tuesday, October 23, 2018

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Session Time: 9:00AM-11:00AM

Novel Classification Of Idiopathic Inflammatory Myopathies Based On Distinctive Features And Autoantibodies: Analysis Of 67 Korean Patients

Fig 1. Distribution of 67 patients according to 3 classifications for idiopathic inflammatory myopathies

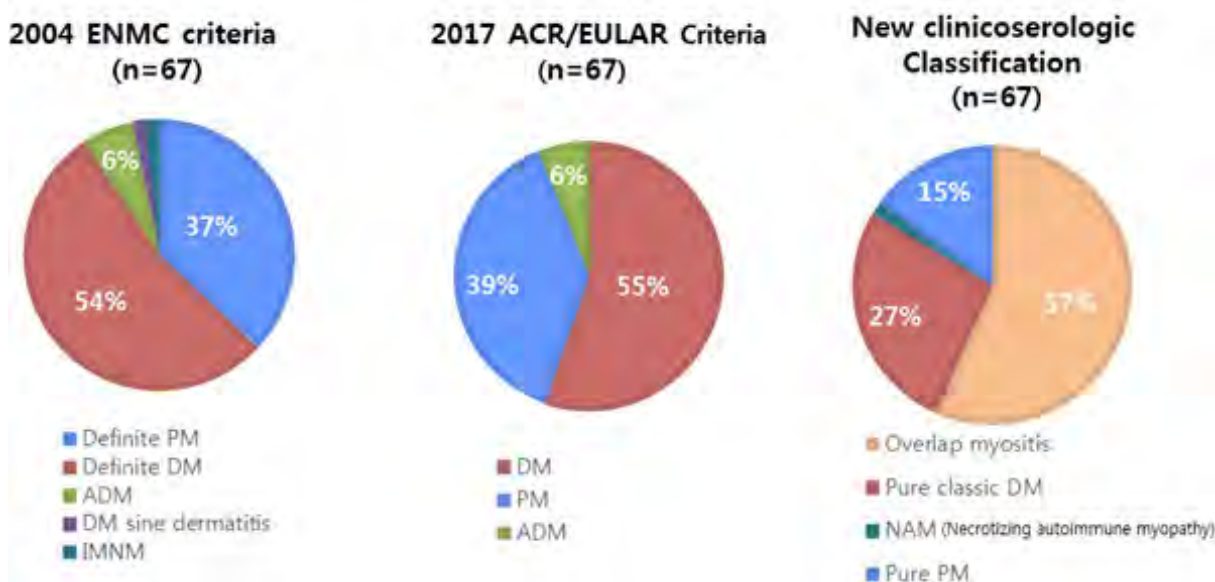


Table 3. Associations between myositis autoantibodies and distinctive clinical features

	Anti-ARS N=21	Anti-SRP N=14	Anti-MDA5 N=14	Anti-TIF1- γ N=9	Anti-Mi2 N=8	Anti-SAE N=3	Total N=67
ILD ^a	20*	5	11*	0	3	1	36
Malignancy	1	3	0	5*	1	0	7
DM specific skin lesion	8†	6	10	9†	5	2	39
Dysphagia	2	2	2	3	2	1	16

†p<0.05 *p<0.01

Background/Purpose: Since Bohan and Peter first described their diagnostic criteria for idiopathic inflammatory myopathies (IIM) in 1975, new discoveries such as myositis-specific and myositis-associated autoantibodies (Abs) have been made.

To investigate correlations between specific myositis Abs and their frequencies and clinical associations across different IIM groups, collectively demonstrating the utility of the new clinicoserologic classification in Korean adult patients with IIM.

Methods: We conducted a multicenter cohort study including 67 adult patients (age, 18 years) who have been diagnosed as IIM by ENMC criteria. Immunoblot assay with Euroline strip (EUROIMMUN, Germany) was performed using the sera of definite dermatomyositis (DM, n=36), definite polymyositis (PM, n=25), amyopathic DM (n=4), DM sine dermatitis (n=1), and immune mediated necrotizing myopathy (IMNM, n=1). Patients were classified based on three classifications: 1) novel clinicoserologic classification suggested by Troyanov et al. in 2017. 2) 2017 EULAR/ACR classification criteria. 3) 2004 European neuromuscular center (ENMC) criteria. Associations of myositis Abs and clinical subsets of IIM were investigated.

Results: The distribution of the various IIM differed strikingly from those using the 3 classifications (Fig 1). According to the 2004 ENMC classification and 2017 EULAR/ACR classification criteria, DM and PM was the most and the second frequent entities (DM: 55.2%, 56.7 %; PM: 35.8%, 37.3%). But, using the new clinicoserologic classification, overlap myositis (OM) is the major type of IIM and the frequency of PM is significantly decreased. Anti-ARS Abs specificity included anti-Jo-1 (16.4%), -OJ (4.6%), -EJ (6.2%), -PL-7 (3.1%), and -PL-12 (4.6%). Interstitial lung disease was closely associated with anti-MDA5, and anti-ARS Abs, while DM-specific skin lesion was frequently observed in patients with anti-TIF1- γ and anti-ARS Abs. Seven patients with cancer-associated DM were identified. They were positive for anti-TIF1- γ (5/7) and anti-SRP (3/7) (Table 1).

Conclusion: Novel classification based on distinctive features and new myositis Abs reflects the clinical phenotype of IIM better. Establishment of a system routinely available to screen myositis Abs is needed. This will be beneficial to provide more precise diagnosis and proper management for patients with IIM.

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Abstract Number: 2297

Performance of the New EULAR/Acr Classification Criteria for Idiopathic Inflammatory Myopathies (IIM) in a Large Monocentric IIM Cohort

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Session Information

Session Date: Tuesday, October 23, 2018

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Background/Purpose: Patients with IIM have been classified mainly according to Bohan and Peter (B&P) criteria, proposed in 1975. In 2017 the new EULAR/ACR criteria were proposed. They are able to classify patients with both adult/juvenile form of IIM and they are applicable also in patients with amyopathic DM (ADM) and in IBM even without the results of muscle biopsy. The objective of this study was to evaluate the performance of the new classification criteria for IIM in a large retrospective cohort of patients.

Methods: Consecutive patients with a clinical diagnosis of IIM, based on physician opinion, referred to a rheumatology unit from 1995 to 2018 were included and assessed according to the B&P and the EULAR/ACR criteria. Data were collected from an existing database and, when missing, additional variables were retrieved from the patient's records when available. Cohen's kappa (K) was used to measure the agreement between physician opinion and the classification criteria; in addition, sensitivity and specificity were calculated.

Results: A total of 424 patients were included in the analysis (M 157, F 269, mean age at the onset 53.5 ± 17.5 years). In 18 patients the onset <18. According to the physician opinion 190 patients had PM, 51 IBM, 146 DM, 11 Juvenile DM (JDM), 4 ADM and 22 incomplete IIM.

Applying the B&P criteria, 406 patients (94.8%) were classifiable as IIM (172 definite, 141 probable, 93 possible): 277 PM (95 def, 106 prob, 76 poss) and 129 DM (77 def, 35 prob, 17 poss). With the EULAR/ACR criteria 351 (82.8%), could be classified as IIM (258 def, 89 prob, 4 poss): 161 PM (83 def, 76 prob, 2 poss), 121 DM (117 def, 4 prob), 44 IBM (41 def, 3 prob, 1 poss), 11 ADM, 13 juvenile IIM (11 DM, 2 PM). The Cohen's K, the sensitivity and the specificity for the criteria are reported in table 1. Eighteen patients were not classifiable according to B&P criteria (11 PM, 1 DM, 1 ADM and 3 incomplete IIM) and 73 according to EULAR/ACR criteria (52 PM, 9 DM, 1 ADM, 1 JDM, 10 incomplete IIM). Missing detailed information on patterns of muscle weakness and muscle biopsy features were explanations for not being able to classify most patients.

Conclusion: The new EULAR/ACR criteria performed well in a retrospective cohort using data from a myositis register and patient records from a myositis clinic, but they depend on muscle strength testing of upper and lower extremities as well as of proximal and distal muscles in the legs.

Criteria	Subtype	Cohen's K	Sensitivity	Specificity
Bohan and Peter	Overall	0.108	0.97	0.16
	PM	0.479	0.97	0.38
	DM	0.705	0.75	0.91
EULAR/ACR	Overall	0.142	0.84	0.45
	PM	0.492	0.72	0.84
	DM	0.755	0.76	0.96
	IBM	0.765	0.93	0.98

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Abstract Number: 2298

Developing a Classification Criteria for Cutaneous Dermatomyositis Utilizing the Delphi Technique

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Session Information

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Background/Purpose: The new European League Against Rheumatism / American College of Rheumatology (EULAR / ACR) classification criteria for inflammatory myopathies are able to identify patients with dermatomyositis (DM). However, approximately 25% of patients with purely cutaneous DM do not meet 2 out of the 3 hallmark skin signs and fail to meet the criteria for myositis. To allow a more inclusive definition of cutaneous DM, we are developing a skin-focused classification criteria based on the consensus of international experts in the Rheum/Derm field. This project specifically aims to distinguish skin findings in DM from potential mimickers.

Methods: An extensive literature review was done. International experts participated in several nominal group discussions to generate items for the Delphi. Items were grouped into categories of distribution, morphology, symptoms, antibodies, histology, and contextual factors. Using REDCap, participants rated these items in terms of their appropriateness and their ability to distinguish DM from other diagnoses. The relevance score ranged from 1 to 100 and the median of each item determined the rank-ordered list. A pre-specified median score cut-off was decided by the steering committee and the participants. There were 2 rounds in this Delphi criteria project.

Results: There were 50 respondents composed of dermatologists and rheumatologists from North America, South America, Europe and Asia. After subjecting the items to a cut-off score of 70 during the first round, 37 out of the 54 items were retained and carried over to the next round. The cut-off was then raised to 80 for the second round, and a list of 22 items (Table 1) was generated for potential inclusion into a set of items that will be used to validate classification criteria in a prospective case-control study.

Conclusion: This project is a key step in the development of prospectively validated criteria that will create well-defined cohorts for clinical research on novel treatments for DM.

Table 1: Potential Cutaneous DM Classification Criteria*

Distribution(median)	Morphology(median)	Symptomatology (median)	Path / Lab(median)	Contextual Factors(median)
Eyelid (85.5) Shawl (83.5) V of Neck (80) Elbow, Knee (80)	Violaceous erythema (90) MCP IP Joints papules (90) MCP, IP joint macules (86) Nailfold Capillary loops (86.5) Nailfold erythema (80) Cuticular Dystrophy (85) Poikiloderma (80) Fissuring of digits (80) Linear extensor erythema (80) Eyelid edema (80) Palmar macules and papules (81)	Pruritus of scalp (80) Photosensitivity (80)	Interface dermatitis (90) Dermal Mucin (80) Presence of myositis antibodies (88.5)	Interstitial lung disease (80) Muscle weakness (85)

* Items generated after 2 rounds of Delphi

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Abstract Number: 2299

Subgroup Analysis of the Effect of Denosumab Compared with Risedronate on Percentage Change in Lumbar Spine Bone Mineral Density at 24 Months in Glucocorticoid-Treated Individuals

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Session Information

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Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

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Background/Purpose: We previously demonstrated that denosumab increased lumbar spine and total hip bone mineral density (BMD) significantly more than risedronate at 12 and 24 months in glucocorticoid (GC)-treated individuals (Saag *ACR*2016; Saag *ECTS* 2018). Prespecified subgroup analyses of lumbar spine BMD at 12 months indicated that denosumab was superior to risedronate across 7 subgroups of GC-treated individuals (Saag *ASBMR* 2017). This analysis explored the effects of denosumab and risedronate on lumbar spine BMD in the same subgroups of GC-treated individuals at 24 months.

Methods: The phase 3, randomized, double-blind, double-dummy, active-controlled study enrolled women and men age ≥ 18 years receiving ≥ 7.5 mg prednisone or equivalent daily for < 3 months (GC-initiating) or ≥ 3 months (GC-continuing) before screening. All subjects age < 50 years were required to have a history of osteoporotic fracture. GC-continuing subjects age ≥ 50 years were required to have lumbar spine, total hip, or femoral neck BMD T-score ≤ -2.0 ; or ≤ -1.0 with a history of osteoporotic fracture. Subjects were randomized 1:1 to denosumab 60 mg SC every 6 months or risedronate 5 mg PO daily for 24 months. All subjects were to receive daily calcium (≥ 1000 mg) and vitamin D (≥ 800 IU). The treatment difference (denosumab – risedronate) for percentage change from baseline in lumbar spine BMD at 24 months was estimated in the GC-initiating and GC-continuing subpopulations, both overall and in 7 prespecified subgroups where treatment effect might differ (sex, race, age, baseline BMD T-score, geographic region, menopausal status, and baseline GC daily dose).

Results: The study enrolled 795 subjects (290 GC-initiating, 505 GC-continuing). Baseline characteristics were balanced between treatment groups within each subpopulation. Denosumab was superior to risedronate for gains in lumbar spine

Table. Treatment Difference [Denosumab [DMAb] – Risedronate [RIS]] in Lumbar Spine BMD Percentage Change From Baseline at Month 24

	GC-initiating Subpopulation (N = 133 RIS / 128 DMAb)				GC-continuing Subpopulation (N = 230 RIS / 228 DMAb)			
			Least Square Mean Estimate of Difference [95% CI]	Interaction P value Quantitative (Qualitative)			Least Square Mean Estimate of Difference [95% CI]	Interaction P value Quantitative
	DMAb (n)	RIS (n)			DMAb (n)	RIS (n)		
Overall subpopulation	107	113	4.5 [3.2, 5.8]*	—	183	174	3.2 [2.0, 4.3]*	—
Sex								
Female	69	72	5.7 [4.0, 7.5]*	0.013 (0.50 ^b)	141	131	3.7 [2.4, 5.0]*	0.13
Male	38	41	2.1 [0.1, 4.1] [†]		42	43	1.4 [-1.1, 4.0]	
Race								
Caucasian	92	97	3.9 [2.4, 5.3]*	0.024 (0.50 ^b)	166	158	3.3 [2.1, 4.5]*	0.63
Not Caucasian	15	16	7.6 [3.8, 11.4]*		17	16	1.9 [-1.6, 5.4]	
Age								
< 60 years	28	41	2.9 [0.1, 5.8] [†]	0.089	79	85	2.9 [1.2, 4.6] [†]	0.72
≥ 60 years	79	72	5.1 [3.6, 6.6]*		104	88	3.4 [1.9, 5.0]*	
Baseline lumbar spine T-score								
≤ -2.5	17	21	4.6 [1.0, 8.1] [†]	0.066	66	68	3.4 [1.1, 5.6] [†]	0.44
> -2.5	90	92	3.9 [2.5, 5.2]*		117	106	2.9 [1.6, 4.2]*	
Baseline lumbar spine T-score								
≤ -1.0	55	60	5.4 [3.6, 7.3]*	0.13	142	141	3.2 [1.8, 4.5]*	0.89
> -1.0	52	53	2.8 [1.0, 4.6] [†]		41	33	2.9 [1.0, 4.8] [†]	
Geographic region								
Europe	65	73	4.0 [2.4, 5.6]*	0.24	135	122	3.2 [1.8, 4.6]*	0.90
Non-Europe	42	40	5.3 [2.9, 7.8]*		48	52	2.6 [0.8, 4.5] [†]	
Menopausal status								
Premenopausal	9	3	11.4 [1.2, 21.7] [†]	0.77	20	20	3.9 [0.2, 7.6] [†]	0.98
Postmenopausal	59	67	5.7 [3.9, 7.6]*		119	109	3.7 [2.3, 5.1]*	
Baseline GC dose[†]								
≥ 7.5 to < 10 mg	20	28	6.3 [2.8, 9.7]*	0.57	61	67	3.4 [1.6, 5.2]*	0.88
≥ 10 mg	85	85	4.3 [2.8, 5.8]*		121	107	3.2 [1.7, 4.7]*	

CI = confidence interval; N = Number of randomized subjects with a baseline measurement and ≥ 1 postbaseline measurement for the lumbar spine BMD; n=number of subjects with observed value. * $p < 0.001$, denosumab vs risedronate. [†] $p < 0.05$, denosumab vs risedronate. [‡]Qualitative p-values > 0.05 support consistent directionality of treatment effect within the subgroups. [§]In prednisone equivalents.

BMD at 24 months in both the GC-initiating and GC-continuing subpopulations. Within each subgroup (Table), denosumab was consistently associated with a greater increase in lumbar spine BMD at 24 months compared with risedronate. Significant quantitative interactions were observed only in the sex and race subgroups in the GC-initiating subpopulation. However, qualitative tests indicated the direction of the denosumab effect did not differ significantly by sex or race in this subpopulation.

Conclusion: Denosumab consistently increased lumbar spine BMD more than risedronate at 24 months in both GC-initiating and GC-continuing subpopulations, with no evidence of directional heterogeneity in treatment effect across 7 prespecified subgroups of GC-treated individuals. Denosumab may be a useful addition to the osteoporosis armamentarium in the common clinical setting of GC use.

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Abstract Number: 2300

Compliance with Screening and Supplementation Guidelines for Glucocorticoid-Induced Osteoporosis, How Bad Did We Do This Time?

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Session Information

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Background/Purpose: Glucocorticoid-induced osteoporosis (GIOP) is a well-established and well-studied phenomenon that is a sequela of the treatment of many inflammatory diseases. Many studies over the years have looked at compliance with guidelines for the prevention and treatment of GIOP. Previous studies have shown compliance with recommendations to be quite poor in regards to DXA screening, as well as calcium and vitamin D supplementation. This study aimed to give a current look at this issue, particularly in light of the most recent release of ACR GIOP guidelines in 2017, to see if compliance has improved over the years.

Methods: Patients who had received a prescription of prednisone between July 2016 to July 2017 from the VA Connecticut Health System were identified. The first 300 patient's charts were reviewed. Patients were excluded if they had received one time tapers of prednisone or if they were receiving prednisone for malignancy and were since deceased. Subsequently 266 patients were included for analysis (on prednisone for ≥ 3 months, dose ≥ 2.5 mg daily, and any indication). Data on age, last dosage of prednisone, duration of treatment, diagnosis, DXA status, DXA results, vitamin D levels, and whether patients were on calcium or vitamin D supplementation were collected.

Results: Of 266 patients included for analysis, mean age was 71 (standard deviation 12 years), mean dosage 7.65mg (range 1-50mg). 120 patients had undergone DXA examination (45.1%), 146 had not. The most frequent diagnoses were RA with 49 patients, COPD 40, PMR 37, transplant 23, and myasthenia gravis 13. Prescriber specialty 114 patients rheumatology, 50 primary care physician, 24 pulmonary, 19 nephrology, 15 each hematology-oncology and neurology, 29 other. Rheumatologists had a rate of DXA scans of 53.5%, primary care physicians 38%, pulmonary 29.2%, renal 42.1%, hematology-oncology 33.3%, and neurology 46.67%. Taking into consideration the 2017 guidelines, with patients ≥ 40 years of age, 45.9% of appropriate patients underwent DXA, 54% did not. Per 2017 guidelines 51.7% were appropriately on calcium supplementation and 57.5% appropriately on vitamin D supplementation.

Conclusion: There have been many studies over the years regarding compliance with guidelines for GIOP. In this particular study, as seen previously, we show poor compliance with only 45.1% of patients appropriately undergoing DXA screening. If accounting for the 2017 guidelines in the cohort of patients ≥ 40 years of age this improves to 45.9%. Patients are still largely not undergoing proper screening and even when they do a large proportion, 48.3% for calcium, 42.4% for vitamin D are not receiving the appropriate calcium and vitamin D supplementation. With each new iteration of guidelines for GIOP it becomes imperative to adjust practice habits appropriately. Unfortunately study after study shows this is not

occurring. Given the continued poor compliance on the part of providers it is worth considering a reduction in frequency of revision of guidelines and better provider education to finally lead to improved compliance.

Disclosure: J. Zawidniak, None; J. Waterman, None.

Abstract Number: 2301

Trend of Osteoporosis and Osteoporotic Fragility Fractures Among Select Autoimmune Rheumatologic Diseases: Results from National Inpatient Sample

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatologic diseases (RDs) have been associated with an increased risk of osteoporosis (OP) and osteoporotic fractures, however, most patients do not receive diagnosis and adequate treatment. The aim of our study was to study the prevalence of OP and osteoporotic fractures in relation to RDs.

Methods: We used National Inpatient Sample (2000-2014) to identify hospitalizations ≥ 18 years of age with OP and osteoporotic fractures and excluded fractures due to other etiologies. We studied the yearly trends of OP and osteoporotic fractures as well as compared the trends among hospitalizations with or without RDs in terms of Annual Percentage Change (APC).

Results: OP was noted to have an increasing trend from 2000 - 2009 (APC=5.81, $p<0.05$) with a decline thereafter (APC=-3.88, $p<0.05$). In contrast, osteoporotic fracture showed an initial downward trend from 2000-2010 (APC=-7.31, $p<0.05$), followed by a slowly rising trend (APC=2.0, $p=NS$) (**Figure 1**). The trends were similar in groups with or without RDs (**Figure 2**). RDs had higher odds of OP [ORs 2.58 (95 % CI 2.55 – 2.60), $p<0.001$] and osteoporotic fractures [OR 1.28 (95% CI 1.25 -1.31), $p<0.001$] (**Table 1**).

Conclusion: RDs were associated with increased OP and osteoporotic fractures; the pathogenesis includes disease-related (chronic inflammation) and treatment-related (glucocorticoid induced) factors. Decreasing trend was noted along with a halt in a previously declining fracture rates. The noted decrease in OP might represent a true decline due to better

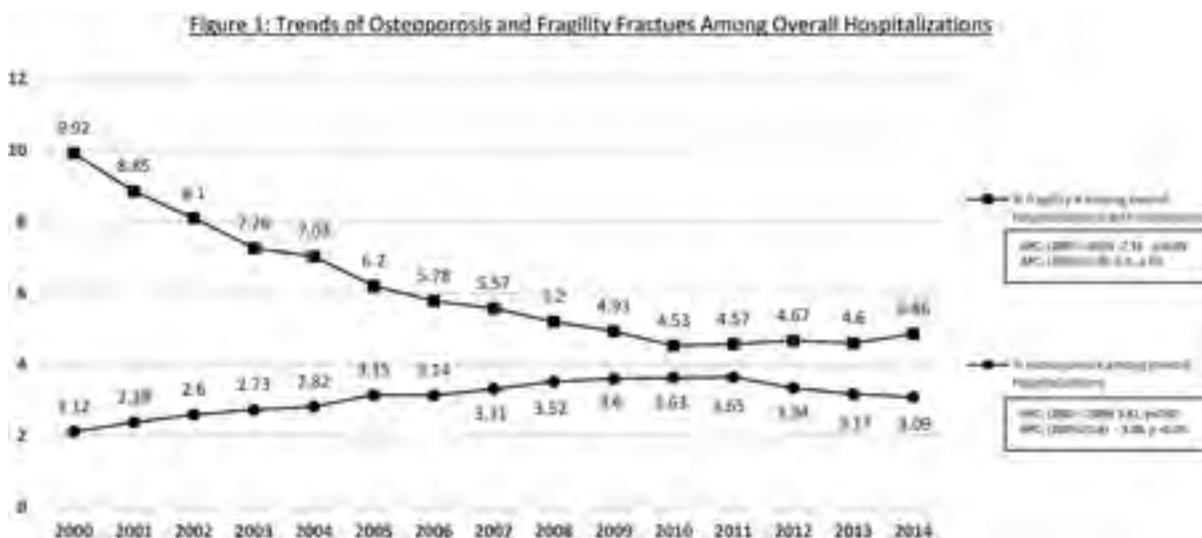
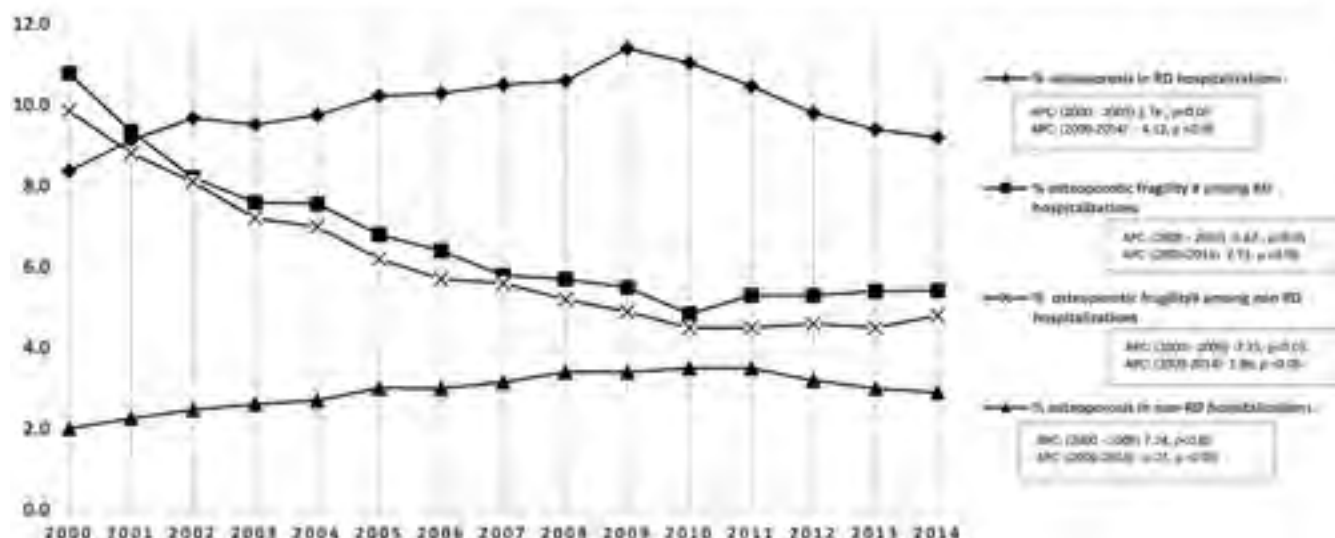


Figure 2: Trends of Osteoporosis and Fragility fractures among hospitalizations with and without Rheumatologic Diseases (RD)



prevention, but may also be due to decreased screening and subsequent detection. Also, if the decreased trend was due to better prevention, one would expect osteoporotic fractures to decrease as well. Potential explanations include inadequate screening per guidelines, suboptimal treatment and decreasing patient compliance, which have also been documented in many prior studies.

In conclusion, primary and secondary prevention measures for OP have been underutilized by both physicians and patients alike, although several possibilities exist. Awareness of this is vital to increase physician prescribing practices and patient compliance.

Table 1: Logistic regression analyses for prevalence of osteoporosis and osteoporotic fragility fracture in hospitalizations with any rheumatologic diseases

	Unadjusted OR	Adjusted* OR
Osteoporosis	3.64 (95% CI 3.60-3.68), $p < 0.001$	2.58 (95% CI 2.55-2.60), $p < 0.001$
Osteoporotic fragility #	1.09 (95% CI 1.06-1.11), $p < 0.001$	1.28 (95% CI 1.25-1.31), $p < 0.001$

* adjusted for age, sex, race, obesity, smoking, obesity, charlson comorbidity index, steroid use

Disclosure: R. Dhital, None; T. Lynn, None; P. Shrestha, None; S. Basnet, None; P. Paudel, None; P. Sharma, None; P. Karmacharya, None; D. Poudel, None.

Abstract Number: 2302

Forearm Bone Mineral Density and Fracture Incidence in Postmenopausal Women with Osteoporosis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

Session Type: ACR Poster Session C

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Background/Purpose: Wrist fractures are the most common fracture of the upper extremity and increase subsequent fracture risk in women with postmenopausal osteoporosis. Most wrist fractures occur at the ultradistal (UD) radius. Abaloparatide (ABL) is a selective activator of the PTH1 receptor signaling pathway that stimulates bone formation. In the ACTIVE phase 3 study, 18 months of ABL significantly increased bone mineral density (BMD) at the UD radius and

maintained BMD at the 1/3 distal radius vs placebo (PBO) and teriparatide (TPTD). BMD effects were associated with a trend for numerically lower wrist fracture incidence for ABL vs TPTD ($P=0.052$). Women receiving ABL or PBO in ACTIVE were offered enrollment in the ACTIVEExtend extension study in which both groups received 24 months of open-label alendronate (ALN) 70 mg/wk for a total of 43 months (18 months ABL or PBO, 1 month for reconsent, 24 months ALN). Our objective was to determine the efficacy of ABL followed by ALN (ABL/ALN) vs PBO/ALN on BMD at the UD radius over 43 months.

Methods: Forearm BMD data (ACTIVE baseline and month 43) were measured for 213 and 233 women in ABL/ALN and PBO/ALN groups, respectively. BMD was centrally analyzed and adjusted for machine differences. DXA scanner and baseline BMD were included as covariates. Wrist fracture event rates were estimated for the ACTIVEExtend ITT population (558 ABL/ALN; 581 PBO/ALN) by KM method.

Results: Over the 18 months of the ACTIVE trial, BMD of the UD radius decreased in the placebo group but increased with ABL; these increases were maintained over the ALN extension (Figure). There were 15 women with wrist fractures in the ABL/ALN group (KM estimate: 2.8%) and 20 in the PBO/ALN group (3.6%). Although the number of wrist fractures was low, these fractures were numerically lower with ABL/ALN vs PBO/ALN (HR=0.77, 95% CI [0.39, 1.50], $P=NS$).

Conclusion: The BMD gains at the UD radius following treatment with ABL were maintained over the subsequent 24 months of treatment with ALN. Wrist fracture risk was numerically lower with ABL/ALN vs PBO/ALN. These results, together with previous ACTIVE analyses, suggest that BMD of the UD radius, which is rich in trabecular bone, may be a better predictor of wrist fracture than the 1/3 distal radius.

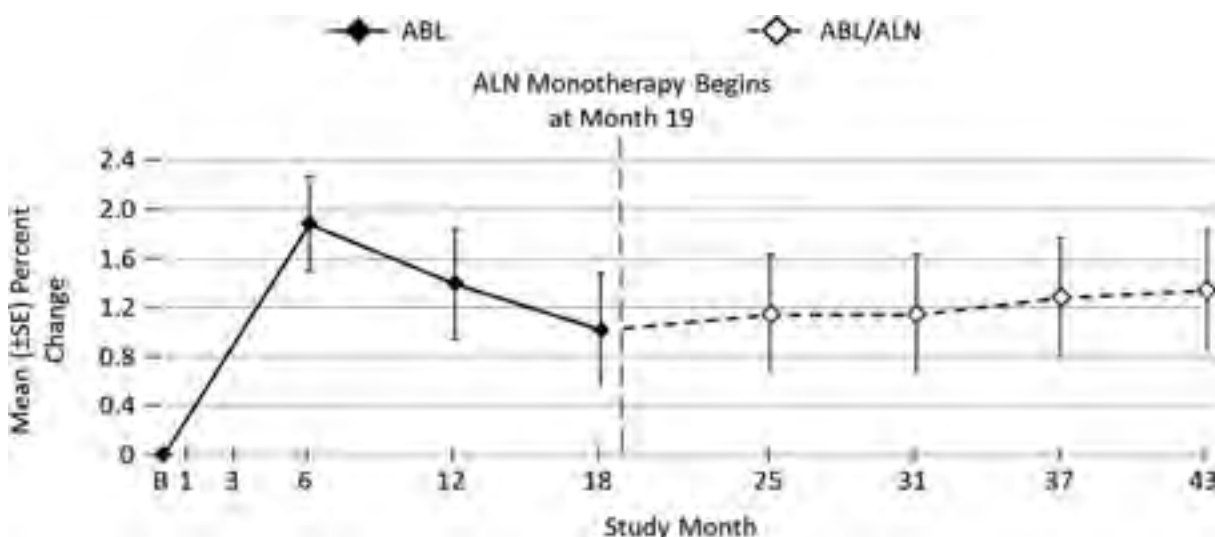


Figure. Mean (\pm SE) Percent Change in Ultradistal Radius BMD from Baseline Through Month 43. Missing BMD data imputed using the method of last observation carried forward. ABL, abaloparatide; ALN, alendronate; SE, standard error.

Disclosure: N. B. Watts, Amgen Inc., 8, Shire Pharmaceutical, 8, AbbVie Inc., 5, Amgen Inc., 5, Janssen, 5, Radius Health, Inc, 5, Sanofi, 5; R. K. Dore, Radius Health, Inc, 8, Eli Lilly and Co., 5, Amgen Inc., 5; S. Baim, None; G. Hattersley, Radius Health, Inc, 3; G. Williams, Radius Health, Inc., 3; Y. Wang, Radius Health, Inc, 3; T. D. Rozenal, None; M. S. LeBoff, NIH/NIAMS, 2, Amgen Inc., 1.

Abstract Number: 2303

Response Rates for Hip, Femoral Neck, and Lumbar Spine Bone Mineral Density in Patients Treated with Abaloparatide Followed By Alendronate

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Abaloparatide (ABL) is a selective activator of the PTH1 receptor signaling pathway that stimulates bone formation. In the ACTIVE Phase 3 study, ABL significantly increased BMD and reduced the risk vertebral, nonvertebral, clinical, and major osteoporotic fractures in women with postmenopausal osteoporosis compared with placebo (PBO). In ACTIVEExtend, the ABL and PBO arms were switched to receive alendronate (ALN) 70 mg weekly for two years. The objective of these analyses was to evaluate bone mineral density (BMD) response rates with ABL/ALN vs PBO/ALN in ACTIVEExtend.

Methods: BMD was measured at the lumbar spine, total hip, and femoral neck from the beginning of ACTIVE to the end of ACTIVEExtend (18 months of ABL or PBO followed by 1 month for reconsent, followed by 24 months of ALN treatment for a total of 43 months). Measurements were collected from 1,139 women enrolled in ACTIVEExtend, and were centrally analyzed. Patients experiencing BMD gains of >0%, >3%, and >6% at the lumbar spine, total hip, and femoral neck were evaluated. A responder was defined as a patient with BMD increases at all three sites. A Chi-square test was used to determine the difference in number of responders between treatment groups.

Results: From ACTIVE baseline through month 43 of ACTIVEExtend, BMD increases of >3% were observed at the lumbar spine in 93.1% (472/507 evaluable patients) and 79.4% (404/509) patients, at the total hip in 80.1% (406/507) and 52.1% (263/505) patients, and at the femoral neck in 67.5% (342/507) and 34.9% (176/505) patients in ABL/ALN and PBO/ALN groups, respectively. A greater percentage of patients in the ABL/ALN group responded with BMD changes from ACTIVE baseline of >0%, >3%, and >6% at all three sites combined compared with the PBO/ALN group ($P<0.0001$ for each comparison). At month 43, 60.7% (307/506) vs 24.0% (121/505) of patients experienced BMD increases of >3% at all three sites in ABL/ALN vs PBO/ALN groups, respectively ($P<0.0001$). Increases of >6% at all three sites were experienced by 33.2% (168/506) vs 4.0% (20/505) of patients in ABL/ALN vs PBO/ALN groups, respectively ($P<0.0001$).

Conclusion: In conclusion, from ACTIVE baseline through the 43 months of ACTIVEExtend, BMD response increased in both ABL/ALN and PBO/ALN groups, with significantly greater response rates in the ABL/ALN group at the total hip, femoral neck, and lumbar spine. Results are consistent with significant BMD response with ABL vs PBO observed in ACTIVE, and continued fracture risk reduction from ACTIVE through ACTIVEExtend with sequential ABL/ALN compared with PBO/ALN treatment.

Disclosure: C. Deal, Amgen Inc., 8, Eli Lilly and Co., 8; B. Mitlak, Radius Health, Inc., 3; Y. Wang, Radius Health, Inc, 3; L. A. Fitzpatrick, Radius Health, Inc., 3; P. D. Miller, Radius Health, Inc., 2, Alexion, 2, Amgen Inc., 2, Boehringer-Ingelheim, 2, Eli Lilly and Co., 2, Novartis, 2, Ultragenyx, 2, Radius Health, Inc., 5, Alexion, 5, Amgen Inc., 5, Eli Lilly and Co., 5, Ultragenyx, 5, Merck & Co., 5.

Abstract Number: 2304

Implication of Bone Turnover Marker Follow-up during Antiresorptive Therapy in Patients with Active Rheumatoid Arthritis on Immunosuppressive Agents

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Changes in bone turnover marker (BTM) are known to offer an information regarding a dynamics of bone remodeling, treatment outcome in primary osteoporosis (OP). However, this has not been robustly investigated in real-world OP patients with rheumatoid arthritis (RA). The aim of this study is to investigate a serial change of BTMs after initiation of antiresorptive therapy in patients with active RA and OP, and compared it with newly diagnosed primary patients.

Methods: By retrospective reviewing of medical records, two groups of study population was designated. Group 1 is patients who newly diagnosed with active RA and OP both, and started antiresorptive therapy (bisphosphonate or selective estrogen receptor modulator) with a concomitant start of disease-modifying immunosuppressive agent and oral

glucocorticoid (above 5mg prednisolone equivalent per day). Group 2 is patients who newly diagnosed with primary OP. Along with demographic parameters, biologic maker of bone formation (osteocalcin) and bone resorption (serum telopeptide of type I collagen (CTX)) was checked on starting and after 3-6 months, 12 months of therapy. BMD by DEXA was checked on starting and after 12 months of treatment. A non-parametric comparison of BTMs, DEXA value between two groups were done. Spearman's correlation and multivariate regression analysis on the effect of followed-up BTM level to good responder after 12 months treatment was investigated.

Results: The mean age of group 1 (34 patients, all female) was 58.5 ± 11.7 years old, which was significantly younger then group 2 (37 patients, all female, 65.8 ± 7.9 years old). The achievement of T-score > -2.5 on lumbar spine or hip (reimbursement guideline of Korean FDA to halt medication for 1 year) was 14 patients (41.2%) in group 1 and 15 patients (40.5%) in group 2. Suppression of BTM after 3-6 months of antiresorptive treatment was sustainable in group 1, 2 and more evident in bisphosphonate group. In group 1, the achievement of T-score > -2.5 was associated with the achievement of low disease activity during treatment of RA and OP. The effect of BTM level at initiation or after 3-6 months antiresorptive treatment on 1 year increment of bone density was not statistically significant in after adjusting demographic parameters and concomitant medication.

Conclusion: BTM suppression and increment of bone density after antiresorptive treatment in RA patients was comparable with response of primary OP. A patient with high RA disease activity during OP medication showed less increment of bone density.

Disclosure: S. Park, None; H. Lee, None; S. K. Kim, None; J. Y. Choe, None.

Abstract Number: 2305

Peripheral Arterial Disease Is Associated with an Increased Risk of Subsequent Hip Fracture: A Systematic Review and Meta-Analysis of Cohort Studies

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Session Information

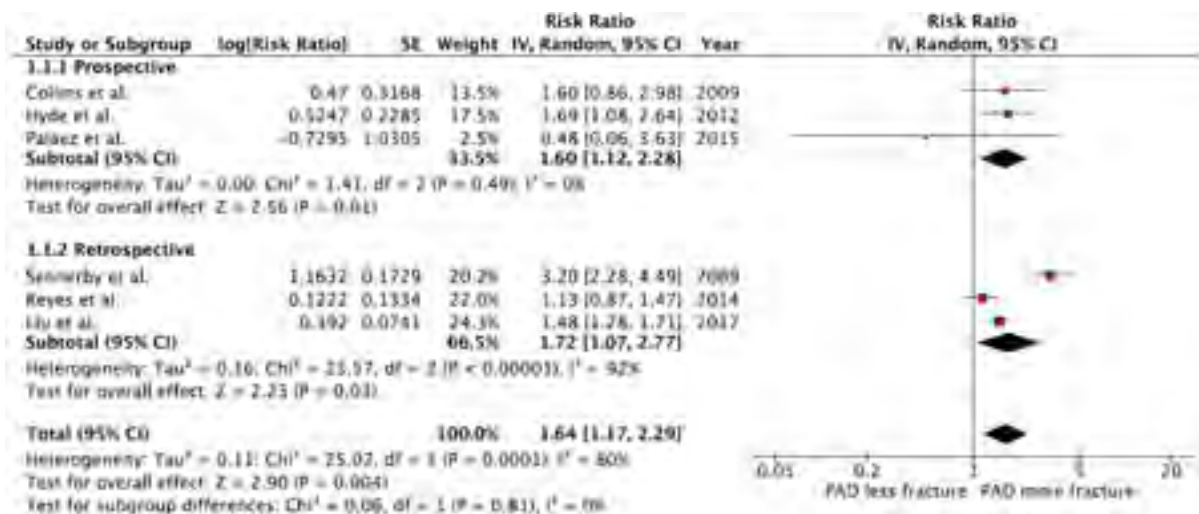
Session Date: Tuesday, October 23, 2018

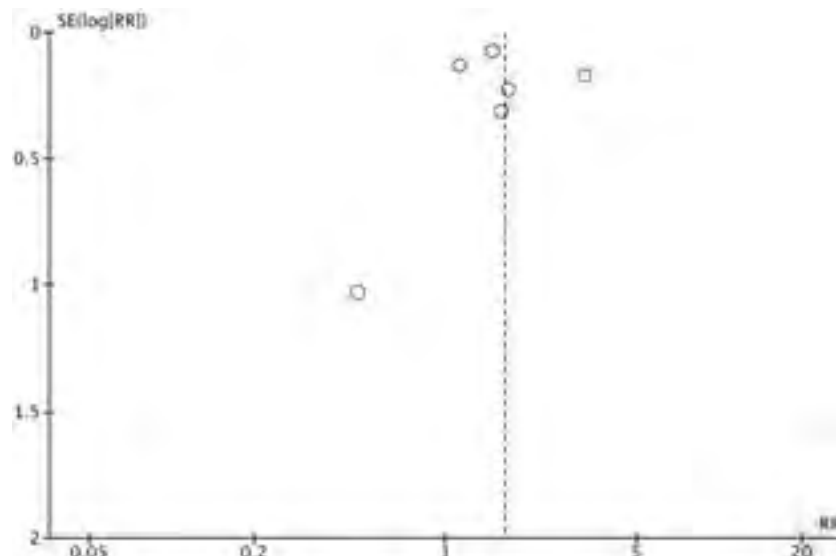
Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Peripheral Arterial Disease is Associated with an Increased Risk of Subsequent Hip Fracture: A Systematic Review and Meta-Analysis of Cohort Studies





Abstract:

Background/Purpose: Studies have suggested an increased risk of hip fracture among patients with peripheral arterial disease (PAD) although the results were inconsistent. This systematic review and meta-analysis was conducted with the aim to comprehensively investigate the risk of hip fracture among patients with PAD by reviewing all available studies.

Methods: A comprehensive literature review was conducted using MEDLINE and EMBASE databases through April 2018 to identify all cohort studies that compared the risk of subsequent hip fracture among patients with PAD with individuals without PAD. Effect estimates and 95% confidence intervals (CI) of the included studies were extracted and combined together using the random-effect, generic inverse variance method of DerSimonian and Laird. Visualization of funnel plot was used for evaluation of publication bias.

Results: The systematic review process yielded 6 eligible cohort studies that comprised of 15,895 patients with PAD. The risk of subsequent hip fracture among patients with PAD was significantly higher than individuals without PAD with the pooled risk ratio (RR) of 1.64 (95% CI, 1.17-2.29; I^2 80%). Subgroup analysis by study design revealed significant results for both prospective studies (pooled RR 1.60; 95% CI, 1.12 – 2.28; I^2 0%) and retrospective studies (pooled RR 1.72; 95% CI, 1.07 – 2.77; I^2 92%). The forest plot of this meta-analysis is shown as figure 1. The funnel plot (figure 2) was relatively symmetric and, thus, was not suggestive of the presence of publication bias in favor of positive studies although interpretation of the funnel plot was limited by the relatively small number of included studies.

Conclusion: This systematic review and meta-analysis demonstrated a significantly increased risk of subsequent hip fracture among patients with PAD compared with individuals without PAD.

Figure 1: Forest plot

Figure 2: Funnel plot

Disclosure: P. Ungprasert, None; K. Wijarnpreecha, None; C. Thongprayoon, None; W. Cheungpasitporn, None.

Abstract Number: 2306

The Association of Dietary Amino Acids with Incident Hip Fracture, BMD and Body Composition. the Cardiovascular Health Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Optimal diet is important for bone health. Low protein intake is prevalent among individuals hospitalized for hip fractures. Studies in the aging mouse model have shown that aromatic amino acids (AAA) (tryptophan, tyrosine, phenylalanine) may help promote bone formation, thus implicating a possible role in the prevention and management of osteoporosis and fragility fractures. The objective of this study was to examine the association of dietary intakes of AAA with incident hip fracture, bone mineral density (BMD) and measures of body composition in the Cardiovascular Health Study (CHS)

Methods: The 5,187 CHS participants who completed food frequency questionnaires in 1989-1990, from which mean daily intakes of AAA were estimated, were included in the hip fracture analysis. Subsequent hip fractures were defined by a hospital discharge International Classification of Diseases, Ninth Revision (ICD-9), code 820.xx. 1,591 of these subjects had a DXA scan from 1994-1995 and were included in analyses on BMD and body composition (percent and total fat mass, percent and total lean mass, and total body mass), all modeled as continuous variables. Cox proportional hazard models were used to estimate the hazard ratio (HR) of incident hip fracture associated with each dietary AAA. In the sub cohort with BMD measurements, linear regression analysis was used to estimate the association between dietary AAA and total hip BMD and body composition measures.

Results: During a median follow-up of 13 years, 725 (14%) of 5,187 subjects had an incident hip fracture (1.09 per 100 person-years). The mean intake of tryptophan was 1.1 g/day; phenylalanine, 4.3 mg/day; and tyrosine, 3.5 mg/day. In multivariable models adjusted for demographics, health history (including lifestyle measures), medication use, cystatin C and diet (calcium, vitamin D, protein, and energy), neither tryptophan, tyrosine, nor phenylalanine were significantly associated with incident hip fractures ((HR=0.14; 95%CI 0.01, 1.89), (HR=0.59; 95%CI 0.27, 1.32), and (HR=0.6; 95%CI 0.23, 1.55), respectively), total hip BMD ($p \geq 0.06$) or any measure of body composition ($p \geq 0.10$).

Conclusion: In this cohort of older community dwelling adults, dietary intake of AAA was not significantly associated with incident hip fracture, hip BMD or body composition.

Disclosure: B. Le, None; P. Buzkova, None; J. Robbins, None; H. Fink, None; M. Raiford, None; C. Isales, None; J. Shikany, None; S. Coughlin, None; L. Carbone, None.

Abstract Number: 2307

In the 21st Century: Is Still Rheumatoid Arthritis a Risk Factor for Osteoporotic Fractures?

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid Arthritis (RA) has been considered an independent osteoporotic risk factor. Nowadays, RA patients have a better disease control and corticosteroid use is less intense. Our objective was to compare incidence of osteoporotic fractures in RA patients diagnosed after year 2000 with matched controls from a university hospital-based health management organization (HMO).

Methods: Consecutive RA patients (n=100) diagnosed after year 2000 (all fulfilling criteria ACR/EULAR 2010 of AR), from the HMO, were matched (age and sex) with controls (1:2). The follow-up period began at the index date, defined as the date of RA diagnosis for RA patients and the date of the first medical claim at the HMO for the non-RA patients. Subjects were then followed until they voluntarily left the HMO, a fracture occurred, the end of study (May 1st 2018), or death. Electronic medical records were reviewed and demographic, clinical and treatment data were collected. Incidence rates per 1000 persons-years (PY) of distinct types of fractures after index dates were calculated and compared between groups. A multivariate cox regression analysis was performed to identify factors associated with fractures.

Results: Patients characteristics are shown in table. RA patients were 97.9% (CI 92.0-99.5) seropositive (Rheumatoid Factor and/or ACPA) and were treated with conventional DMARDs in 94% (CI 87.1-97.3) and biologic DMARDs in 20

% (CI 13.2-29.1). 69% (CI 59.2-77.3) of RA patients used corticosteroids, but only 5% (CI 2.1-11.5) have ever used prednisone > 20 mg/d. No difference was found in the overall fracture incidence rate per 1000 PY between RA and controls (19.5, CI 12.7-28.6 vs 12.1, CI 7.7-18.7, p 0.07). In the Cox regression analysis, only age (HR 1.06, 1.02-1.11, p 0.006) and a prior fracture (HR 9.85, 2.97-32.64, p <0.001) were associated with fractures after the index date. Nor RA diagnosis (HR 0.86, CI 0.24-3.07, p 0.81) not a prolonged use (>3 months) of low dose corticosteroids (HR 1.57, CI 0.39-6.23, p 0.52) were associated with increased fracture risk. When analyzing each type of fracture, only vertebral fractures were more common in RA patients compared with controls (12.9 per 1000 PY, CI 8.9-25.8, versus 3.4, CI 1.4-8.1, p 0.01, respectively) but vertebral fractures were not associated to prolonged use of low dose corticosteroids (HR 3.43, CI 0.74-15.82, p 0.11).

Conclusion: in this cohort of RA patients with diagnosis after year 2000, no overall increased risk of fractures was found in comparison with matched controls. This may be due to a better disease control and rational use of corticosteroids.

	RA patients (n=100)	Controls(n=200)	p
Age at index date, years, media (SD)	62.1 (12.9)	62.4 (13.9)	0.87
Female, n (%), CI)	78 (78, 68.7-85.1)	156 (78, 71.7-83.2)	1
Follow up after index date, years, median (IQR)	9.5 (5.9-13.4)	5.9 (2.4-12.3)	< 0.001
BMI <20, n (%), CI)	5 (5.3, 2.2-12.1)	1 (0.6, 0.1-4.3)	0.02
Ever Smoker, n (%), CI)	33 (33, 24.4-42.9)	31 (15.6, 11.1-21.3)	0.001
Menopause age, years, median (IQR)	47.8 (40.7-51)	48.4 (44.6-51.4)	0.27
Age at first Bone Mineral Density, years, median (RIQ)	62.7 (54.4-74.8)	67.0 (58.9-75.5)	0.09
Osteopenia at first BMD, n (%), CI)	21 (28.4, 19.2-39.8)	31 (35.6, 26.2-46.3)	0.33
Osteoporosis at first BMD, n (%), CI)	23 (31.3, 21.5-42.6)	22 (25, 16.9-35.2)	0.39
Osteoporosis at any Bone Mineral Density, n (%), CI)	27 (36.5, 26.2-48.1)	24 (27.3, 18.9-37.6)	0.21
Corticosteroid use, ever, n (%), CI)	69 (69.0, 59.2-77.3)	5 (2.5, 1.0-5.9)	< 0.001
Prednisone use >= 20 mg/day, ever, n (%), CI)	5 (5.0, 2.1-11.5)	1 (0.5, 0.1-3.5)	0.01
Corticosteroid use >= 3 months, n (%), CI)	63 (63.0, 53.1-71.9)	4 (2.0, 0.7-5.2)	< 0.001
Prior fracture, n (%), CI)	4 (4.0, 1.5-10.2)	3 (1.5, 0.5-4.6)	0.18
Any fracture, incidence rate per 1000 persons-years (CI)	19.5 (12.7-28.6)	12.1 (7.7-18.7)	0.07
Vertebral fracture, incidence rate per 1000 persons-years (CI)	12.9 (8.9-25.8)	3.4 (1.4-8.1)	0.01
Radius fracture, incidence rate per 1000 persons-years (CI)	7.4 (3.6-14.9)	4.7 (2.3-9.8)	0.21
Ulna fracture, incidence rate per 1000 persons-years (CI)	1.0 (0.1-7.1)	0.7 (0.1-4.7)	0.39
Humerus fracture, incidence rate per 1000 persons-years (CI)	1.0 (0.1-7.1)	4.1 (1.8-8.9)	0.09
Rib fracture, incidence rate per 1000 persons-years (CI)	0	0.7 (0.1-4.7)	0.30
Hip fracture, incidence rate per 1000 persons-years (CI)	6.3 (2.8-13.4)	3.4 (1.4-8.0)	0.16
Pelvis fracture, incidence rate per 1000 persons-years, CI)	3.2 (0.9-9.4)	1.4 (0.3-5.3)	0.19

Disclosure: F. Pierini, None; L. F. Lo Giudice, None; M. Scolnik, None; J. Rosa, None; V. Scaglioni, None; E. R. Soriano, AbbVie, Bristol-Myers Squibb, GSK, Janssen, Novartis, Pfizer Inc, Roche, UCB, 2, AbbVie, Bristol-Myers Squibb, Eli Lilly, GSK, Janssen, Novartis, Pfizer Inc, Roche, Sanofi, UCB, 5, AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer Inc, Roche, Sandoz, UCB, 8.

Abstract Number: 2308

Abaloparatide for Risk Reduction of Nonvertebral and Vertebral Fractures in Postmenopausal Women with Osteoporosis: A Network Meta-Analysis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To assess the relative efficacy of abaloparatide compared with other osteoporosis treatment options (alendronate, denosumab, ibandronate, raloxifene, risendronate, romosozumab, strontium ranelate, teriparatide, zoledronic acid).

Methods: PubMed®, Embase® and Cochrane Central Register of Controlled Trials were searched for all randomized controlled trials published prior to December 20, 2017 including postmenopausal osteoporotic women (PMO) with and without prior fractures. Selection of trials for inclusion in the network meta-analysis (NMA) was based on populations (inclusion/exclusion criteria), interventions (dose/frequency), and outcomes (fracture assessment). NMA was conducted by fracture sites with relative risk (RR) of fractures as the main clinical endpoint.

Results: For vertebral fractures (VF) and nonvertebral fractures (NVF), 18 studies informed a network of 11 treatments and 21 studies informed a network of 11 treatments, respectively. For VF, abaloparatide had the greatest effect relative to placebo (RR 0.13; 95% CrI: 0.04-0.34) with estimates ranging from 0.27 for teriparatide to 0.71 for strontium ranelate. For NVF, abaloparatide had a greater risk reduction versus placebo (RR 0.50; 95% CrI: 0.28-0.85) and most effective (with a probability of 0.70) versus teriparatide (RR 0.62; 95% CrI: 0.47-0.82) and romosozumab (RR 0.64; 95% CrI: 0.49-0.81). In a further evaluation of specific fracture sites, 10 studies reporting wrist fractures informed a network of 8 treatments. Abaloparatide was associated with the greatest effect versus placebo (RR 0.39; CrI: 0.15- 0.90) and reduced the risk of fractures versus teriparatide (RR 0.45; CrI: 0.17-1.03) and denosumab (RR 0.47; CrI: 0.18-1.12). The NMA illustrated a good level of agreement with the direct trial evidence and direct pairwise comparisons.

Conclusion: Based on the current NMA, abaloparatide treatment resulted in a greater reduction in RR of both vertebral and nonvertebral fractures in PMO versus placebo in comparison with other treatment options. Generalizability is limited to the trials' population included in the NMA.

Disclosure: J. Y. Reginster, IBSA-Genevri, 5, Mylan, 5, Pierre Fabre, 5, Radius Health, Inc., 5, CNIEL, 8, The Dairy Research Council, 8, IBSA-Genevri, 8, Mylan, 8, CNIEL, 2, IBSA-Genevri, 2, Mylan, 2, Radius Health, Inc., 2; F. Bianic, Radius Health, Inc., 5, InVentiv Health, 3; R. Campbell, Radius Health, Inc., 5, Inventiv health, 3; M. Martin, Inventiv Health, 3, Radius Health, Inc., 5; S. A. Williams, Radius Health, Inc., 3; L. A. Fitzpatrick, Radius Health, Inc., 3.

Abstract Number: 2309

Implementation of a Primary Prevention, Population-Based Virtual Osteoporosis Clinic Dramatically Increases the Number of Rural Veterans Receiving Osteoporosis Screening and Treatment

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The delivery of osteoporosis services is sub-optimal nationally and throughout the Veterans Affairs (VA) healthcare system and particularly poor for rural Veterans. To meet this critical need, we developed a Rural Bone Health Team (BHT), to provide efficient, evidence-based primary prevention osteoporosis services to rural Veterans. We compared the proportion of osteoporosis screening and treatment in Veterans choosing to participate and those who did not participate, both before and after the establishment of the BHT.

Methods: To identify Veterans with osteoporosis risk factors, we operationalized evidence-based screening guidelines into queries to the VHA Corporate Data Warehouse (CDW), a repository of medical and pharmacy records. Captured risk factors included Osteoporosis Self-assessment Tool (OST) score, sex, age, and/or chronic exposure to high risk medications. Veterans at risk were sent enrollment letters, invited to receive care by the BHT, and on acceptance evaluated by clinical nurse educators via standard protocols. As appropriate, enrolled Veterans received DXA scans, education on bone healthy lifestyle, additional fracture risk assessment, and triage for treatment if identified as either osteoporosis or high-risk osteopenia. Advanced practice providers then evaluated Veteran's need for osteoporosis pharmacotherapy, performed laboratory evaluations for secondary causes of bone loss, discussed risks/benefits of pharmacological therapies, and when indicated, therapy initiated and monitored therapy at scheduled intervals. For this study, we included Veterans contacted by the Rural BHT between 12/1/2016 and 02/01/2018. A non-experimental cohort design was utilized to assess pre-specified outcome and process measures, including the number of Veterans contacted, Veterans electing enrollment, DXAs completed, and Veterans receiving pharmacological therapy.

Results: During the first 15 months of implementation, the Rural BHT contacted 3,582 Veterans, with 1,241 (34.6%) Veterans accepting enrollment and 1,132 (91.2%) enrollees completing a DXA scan. Of those participating Veterans, 318 (25.6%) met criteria for and accepted pharmacological therapy. As illustrated in the Table Veterans choosing to participate in the Rural BHT were significantly more likely to complete a DXA scan (91.2% vs. 2.6%, $p < 0.0001$) and to receive pharmacological therapy (25.6% vs. 2.4%, $p < 0.0001$) than those choosing not to participate.

Conclusion: Enrollment in the Rural BHT significantly increases the likelihood that rural Veterans will received appropriate screening and treatment for osteoporosis. This model for the delivery of primary prevention services for

Table 1:			
	Veterans Enrolled (%, 95% CI)	Veterans Not Enrolled (%, 95% CI)	
Veterans	1,241 (34.6%, 33.10-36.22)	2,341 (65.4%, 63.61-67.02)	
Age	74	75.2	
Male Gender (%)	1,177 (94.8%, 93.46-95.95)	2,201 (94.0%, 92.87-94.96)	
OST Score	2.22	1.52	
High Risk Meds	36 (2.9%, 2.09-4.00)	95 (4.1%, 3.33-4.94)	
15 months before BHT:			
DXA completed	22 (1.8%, 1.16-2.68)	78 (3.3%, 2.67-4.14)	<i>p</i> = 0.0074
Pharmacotherapy	13 (1.0%, 0.59-1.80)	67 (2.9%, 2.26-3.62)	<i>p</i> = 0.0003
15 months after BHT:			
DXA completed	1132 (91.2%, 89.51-92.67)	61 (2.6%, 2.03-3.34)	<i>p</i> < 0.0001
Pharmacotherapy	318 (25.6%, 23.27-28.13)	57 (2.4%, 1.88-3.15)	<i>p</i> < 0.0001
Veterans Enrolled:			
DXA completed 15 months before vs. 15 months after BHT			<i>p</i> < 0.0001
Pharmacotherapy started 15 months before vs. 15 months after BHT			<i>p</i> < 0.0001
Veterans Not Enrolled:			
DXA completed 15 months before vs. 15 months after BHT			<i>p</i> = 0.1681
Pharmacotherapy started 15 months before vs. 15 months after BHT			<i>p</i> = 0.4128

osteoporosis provides unique processes and procedures without adding workload to the primary care team and could potentially be adapted to provide other preventative services, as well as instituted in other care settings outside VA.

Disclosure: K. L. Miller, None; S. Patel, None; G. W. Cannon, Amgen Inc., 2; Z. L. Anderson, None.

Abstract Number: 2310

Association of Moderate/Severe Vertebral Fractures with Reduced Trabecular Volumetric Bone Density in Older Women and Reduced Areal Femoral Neck Bone Density in Older Men from Community: A Cross-Sectional Study (SPAHI)

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Session Information

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Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

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Session Time: 9:00AM-11:00AM

Background/Purpose: Many vertebral fractures occur in individuals classified by dual X-ray absorptiometry (DXA) as low risk for fragility fractures. No studies have performed a concomitant evaluation of moderate/severe vertebral fractures, high-resolution peripheral quantitative computed tomography (HR-pQCT), trabecular bone score (TBS) and areal BMD in general elderly population. Thus, we sought to verify the association between moderate/severe vertebral fractures and bone microarchitecture and strength using HR-pQCT, TBS and DXA in older adults.

Methods: 276 older adults from community (176 women and 100 men) were assessed by questionnaire. Lateral scans of spine obtained from Vertebral Fracture Assessment (VFA) by DXA were done to assess vertebral fractures (semiquantitative method). HR-pQCT was performed at the distal radius and tibia and the following parameters were analyzed: volumetric bone mineral density (vBMD) - total (Tt), trabecular (Tb) and cortical (Ct), structural parameters - trabecular number (Tb.N), trabecular thickness (Tb.Th.), trabecular separation (Tb.Sp), cortical thickness (Ct.Th) and strength variables - Stiffness (S), Estimated ultimate failure load (Fult). TBS was performed using DXA iNsight software. Logistic regression was used to identify independent risk factors for fractures.

Results: At least one vertebral fracture was observed in 42.6% of women and 28% of men. At distal tibia, women with moderate/severe vertebral fractures had lower vBMD (Tt.vBMD, $p=0.001$; Tb.vBMD, $p<0.001$; Ct.vBMD, $p=0.017$), lower Tb.N, $p=0.002$, higher Tb.Sp, $p=0.003$ and lower strength parameters (S, $p<0.001$; Fult, $p<0.001$) and men with moderate/severe vertebral fractures had lower Tb.N, $p=0.028$, higher Tb.Sp, $p=0.026$ and lower strength parameter (Fult, $p=0.046$). At distal radius, women with moderate/severe vertebral fractures had lower vBMD (Tt.vBMD, $p=0.003$; Tb.vBMD, $p=0.031$; Ct.vBMD, $p=0.003$), lower structural parameters (Tb.Th, $p=0.026$; Ct.Th, $p=0.003$) and lower bone strength (S, $p=0.005$; Fult, $p=0.003$) and men with moderate/severe vertebral fractures had lower Tb.vBMD, $p=0.031$ and lower strength parameter (S, $p=0.044$; Fult, $p=0.041$). No differences were observed in TBS in female group ($p=0.584$) and male group ($p=0.667$). After adjusting for potential confounding variables, logistic regression model revealed that Tb.vBMD at distal tibia in women (OR 0.980, 95%CI 0.963–0.997, $p=0.022$) and areal femoral neck BMD in men (OR 0.002, 95%CI 0–0.607, $p=0.033$) were independently associated with moderate/severe vertebral fractures.

Conclusion: HR-pQCT images detected marked differences on bone microstructure between older women with moderate/severe vertebral fractures independent of areal BMD and TBS by DXA and could be useful tool to assess fracture risk. Differently, in men, areal BMD at femoral neck was associated with moderate/severe vertebral fractures and DXA continue an important clinical tool for predicting vertebral fracture in male gender.

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Abstract Number: 2311

Effect of TNF Inhibitors on Bone Mineral Density in Rheumatoid Arthritis Patients Receiving Bisphosphonate

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Session Information

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Background/Purpose: This study aimed to investigate whether tumor necrosis factor inhibitors (TNFi) have beneficial effects on bone mineral density (BMD) in rheumatoid arthritis (RA) patients with osteoporosis receiving bisphosphonate (BP).

Methods: A total of 239 RA patients, who were diagnosed with osteoporosis and treated with BP between Jan 2005 and Mar 2017, were reviewed retrospectively. The BMD (g/cm^2) of the lumbar spine, femur neck, trochanter, and total femur was measured by dual-energy X-ray absorptiometry. Changes in the BMD percentage were compared between patients treated with and without TNFi. Multivariate analysis was performed to identify the factors associated with improvement of BMD in RA patients receiving BP.

Results: Among 239 RA patients receiving BP, 35 patients were exposed to TNF inhibitors, and 204 patients were not exposed. The last follow-up BMD was obtained at a median of 2.23 (IQR, 1.13–4.25) years after the initial acquisition of BMD. An improvement in the BMD of the lumbar spine was observed for patients treated with BP; however, there was no significant difference in BMD between patients treated with and without TNFi (4.92% (IQR, 1.6–9.42) vs. 4.99% (IQR, 0.68–10.1), $P = 0.437$). In addition, BMD changes in the femur neck, trochanter, and total hip were not significantly different between the two groups (Table 1). Furthermore, in multivariate analysis, the use of TNFi was not associated with

significant BMD improvement in any sites after adjusting for age, sex, RA duration, cumulative steroid dose, or intake of vitamin D. On the other hand, cumulative steroid dose was significantly associated with a lower improvement in BMD.

Conclusion: In RA patients with osteoporosis receiving BP, TNFi did not provide an additional beneficial effect on BMD improvement.

Table 1 BMD changes in patients treated with and without TNF inhibitors

	With TNFi (n=35)			Without TNFi (n=204)			Intergroup P value
	Baseline	Change, %	P value	Baseline	Change, %	P value	
Lumbar	0.821 (0.11)	4.92	<0.001	0.795 (0.728–0.84)	4.99	<0.001	0.437
Femur neck	0.695 (0.14)	0.26	0.806	0.675 (0.102)	0.89	0.810	0.769
Trochanter	0.549 (0.01)	1.44	0.511	0.546 (0.102)	1.97	0.052	0.725
Femur total	0.765 (0.648–0.798)	0.59	0.512	0.714 (0.106)	0.69	0.549	0.701

Disclosure: J. S. Lee, None; S. Hong, None; D. H. Lim, None; J. Won, None; O. C. Kwon, None; J. S. Oh, None; Y. G. Kim, None; C. K. Lee, None; B. Yoo, None.

Abstract Number: 2312

Spontaneous Vertebral Fractures after Denosumab Discontinuation

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Session Information

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Spontaneous Vertebral Fractures after Denosumab Discontinuation.

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Background/Purpose: Denosumab (Dmab) is an antiresorptive treatment with demonstrated efficacy in osteoporosis. However, discontinuation of Dmab has been associated with rapid bone loss, and recently, the development of vertebral fractures (VF) in some patients. It is essential to identify the risk factors for these adverse events and follow its evolution. The objective of this study is to analyse the clinical characteristics, parameters of bone metabolism and evolution of patients developing VF after Dmab discontinuation.

Methods: Seven women with spontaneous VF after Dmab discontinuation were included (median age 64 years [56-75]). The clinical history, cause of osteoporosis, treatments received, fractures, Dmab treatment duration and discontinuation period were reviewed. Additionally, the clinical and densitometric evolution, and bone mineral parameters were also analysed after Dmab discontinuation.

Results: All the patients had postmenopausal osteoporosis, and two were receiving glucocorticoid treatment; 4/7 patients had previous fractures (2 VF, 1 calcaneus and 1 MTT); 5/7 had previously received antiosteoporotic treatment (hormone replacement therapy, risedronate, alendronate, zoledronate [once or consecutively]) during 6 months - 23 years. All had received Dmab for 24-53 months (median 38). The reasons for treatment discontinuation were: dental indication (2 patients), BMD improvement (T-score -1.2) (1 patient), poor adherence (1), prescription problems and/or delay in administration (3). The median bone mineral density T-scores prior to VF were -2.45 (-1.2/-4) at the lumbar spine and -2.1 (-0.6/-3.1) at the femoral neck. The mean time between the last Dmab dose and VF was 10 months (8-20), with a median of 5 VFs/patient (2-8). No patient showed 25-OH vitamin D <20 ng/ml. After Dmab discontinuation, bone turnover markers increased (median increase +364% in PINP and +287% in NTx); one patient presented hypercalcaemia (calcium 11.3mg/dL); and BMD decreased 1-21% in the lumbar spine and 2-6% in total hip at 8-22 months. After VF, 3 patients restarted Dmab, 1 Dmab+Teriparatide, 1 received zoledronate and 2 alendronate. No new fractures occurred during follow-up.

Conclusion: Discontinuation of Dmab is associated with an increase in bone turnover markers and bone loss which can be associated with the development of spontaneous VF. Previous bisphosphonate therapy does not seem to decrease this risk. Further studies are needed to assess the optimal antiresorptive treatment and its duration after Dmab discontinuation.

Disclosure: H. Florez, None; J. Ramírez, None; A. Monegal, None; N. Guañabens, None; P. Peris, None.

Patients characteristics

Case no	Sex	Age (years)	BMI	Cause OP	Previous Fx (VF)	Site of previous Fx	NV Dmb doses	Dmb Treatment duration (months)	Reason for Dmb discontinuation	Time since last Dmb - Fx (months)	Incident Fx (VF) after Dmb	Site of Incident OP Fx
1	F	67	18,9	Postmen.	0		8	42	Prescription problems / administration delay	8	3 (3)	D8, D9, L1
2	F	72	19,8	Postmen. + GC	1 (0)	Calcaneus	7	36	Lack of adherence	8	8 (7)	D9, D10, L1, L2, L3, L4, L5, sternum
3	F	65	19,6	Postmen.	0		7	38	Dental indication	8	6 (6)	D6, D7, D8, D9, D11, L2
4	F	56	23,7	Postmen.	1 (1)	L5	10	53	BMD improvement	11	5 (5)	D7, D8, D9, D10, D12
5	F	75	24,6	Postmen.	3 (3)	D9, D11, D12	5	24	Prescription problems / administration delay	~20	2 (1)	L1, D1 left costovertebral
6	F	57	25,5	Postmen.	0		6	36	Prescription problems / administration delay	12	7 (6)	D9, D10, D11, L2, L4, L5, rib
7	F	57	24,8	Postmen. + GC	1 (0)	5th MTT	9	48	Dental indication	10	3 (3)	L1, L2, L5
Median (range)		65 (56-75)	23,7 (18,9-25,5)		1 (0-3)		7 (5-10)	38 (24-53)		10 (8-20)	5 (2-8)	

NP: number; F: female; BMI: Body Mass Index; OP: osteoporosis; Postmen.: postmenopausal osteoporosis; GC: glucocorticoids; Fx: fracture; VF: vertebral fracture; Previous Fx: fractures prior to Dmb treatment; MTT: metatarsus; Dmb: denosumab; Time discontinuation Dmb - Fx: time between the last dose of Dmb and VF; Incident Fx: fractures since Dmb discontinuation;

Abstract Number: 2313

The Efficacy of Denosumab for Prevention of Osteoporotic Fractures in Patients with Connective Tissue Diseases Receiving Very High Doses of Glucocorticoid

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Session Information

Session Date: Tuesday, October 23, 2018

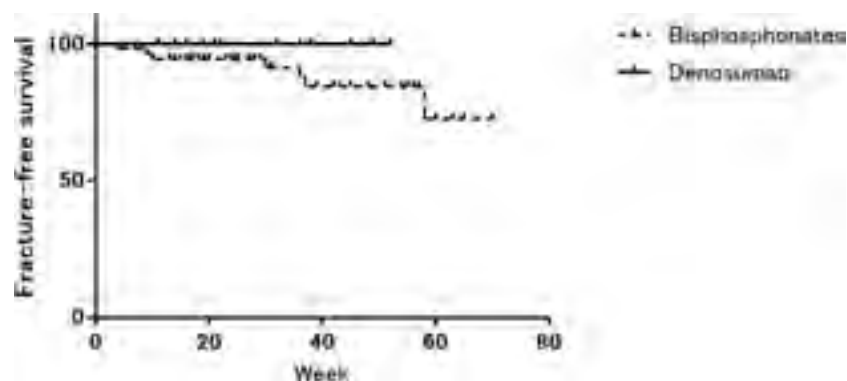
Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoporosis is a common complication of glucocorticoid therapy, contributing to significant morbidity especially in patients receiving very high doses of glucocorticoid (GC). There have been insufficient data supporting the antifracture efficacy of denosumab in glucocorticoid-induced osteoporosis, and its efficacy in patients receiving very high doses of GC has not been demonstrated so far. We aimed to verify the efficacy and safety of denosumab in patients receiving very high doses of GC.

Methods: We retrospectively reviewed the clinical data of patients with connective tissue diseases initiating very high-dose GC treatment (prednisolone ≥ 0.8 mg/kg/day) in our hospital from January 2012 to April 2017. We recruited patients initiating osteoporosis prophylaxis either with denosumab or bisphosphonates within six months after the initiation of GC treatment. We compared the risk of clinical osteoporotic fractures and safety profiles between the denosumab group and the bisphosphonate group.



Results: Among patients initiating very high-dose GC treatment during January 2012 to April 2017, 56 patients (median age: 65 years old) received osteoporosis prophylaxis with bisphosphonates and 16 patients (median age: 69 years old) received osteoporosis prophylaxis with denosumab. The bone mineral density of the femoral neck at baseline was $0.87 \pm 0.23 \text{ g/cm}^2$ in the denosumab group and $0.79 \pm 0.11 \text{ g/cm}^2$ in the bisphosphonate group ($p > 0.05$). No patients suffered clinical osteoporotic fractures in the denosumab group (median observation period: 21.5 months), while seven patients suffered clinical osteoporotic fractures in the bisphosphonate group (median observation period: 30.5 months). The risk of clinical osteoporotic fractures was similar between two groups ($p = 0.21$). Avascular necrosis of the femoral head (AVNFB) occurred in eight patients (14%) in the bisphosphonate group, while no patients suffered AVNFB in the denosumab group. Osteonecrosis of the jaw occurred in one (6%) patient in the denosumab group and one (2%) patient in the bisphosphonate group. Transient hypocalcemia occurred in three (19%) patients in the denosumab group and six (11%) patients in the bisphosphonate group, all of which resolved without any intervention.

Conclusion: Denosumab is a useful option for osteoporosis prophylaxis in patients initiating very high-dose GC treatment, having at least equivalent efficacy and safety with bisphosphonates.

Disclosure: K. Kadoba, None; K. Nishimura, None; H. Mukoyama, None; R. Saito, None; D. Waki, None; T. Yokota, None.

Abstract Number: 2314

Ratio of BMI to BMD at Different Sites and Association with Fragility Fractures

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Session Information

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Background/Purpose: Low body mass index (BMI) is linked to increase risk for osteoporosis, and fragility fractures and is therefore included in most fracture prediction tools. A previous work from our department (Oldroyd et al. Int J Clin Pract. 2014) demonstrated that very high BMI might also be a risk factor for osteoporosis and other authors have recently reported the ratio between lumbar spine BMD and BMI to be strongly correlated with trabecular bone score (TBS) and predictive of fragility fractures in a cohort of obese patients (Watanabe et al. Endocrine Practice. 2018). The aim of our study was to assess the influence of the BMI/BMD ratio on the risk of fractures in an observational cohort of all weight categories.

Methods: All patients referred to our department for having a dual X-ray absorptiometry (DEXA) scan between June 2006 and October 2016 were queried. Results of first scans only were included in our analysis. Risk factors for osteoporosis and fragility fractures were recorded at the time of the scan and included age, gender, comorbidities, medication history, menopause age and fragility fracture history. The ratio of BMI/BMD was obtained and divided into quintiles. Logistic models were fitted unadjusted and adjusted for age and gender comparing those patients who had

presented with a fragility fracture versus those who did not have a fracture. The ratios were calculated for the lumbar spine and both femoral neck and total hip.

Results: 35,759 patients were included in the analysis, 30,095 (84.2%) were female. Mean age was 62.2 years (SD 12.8). 12,186 (34.1%) had sustained a fragility fracture. Mean BMI was 26.8 (SD 5.2). The results of the logistic models are shown in the table below for each site

site	quintile	Unadjusted OR	95%CI	Adjusted OR	95%CI
Lumbar spine N=35,759	1	Ref	Ref	Ref	Ref
	2	1.23	1.15,1.33	1.18	1.09,1.27
	3	1.49	1.38,1.60	1.36	1.26,1.46
	4	1.80	1.67,1.93	1.58	1.47,1.70
	5	2.29	2.14,2.47	1.97	1.83,2.12
Femoral neck N=27,956	1	Ref	Ref	Ref	Ref
	2	1.37	1.27,1.48	1.27	1.17,1.37
	3	1.59	1.47,1.71	1.39	1.29,1.51
	4	1.91	1.77,2.06	1.60	1.49,1.73
	5	2.55	2.37,2.75	2.07	1.87,2.18
Total hip N=27,956	1	Ref	Ref	Ref	Ref
	2	1.51	1.38,1.65	1.39	1.27,1.52
	3	1.97	1.80,2.15	1.73	1.59,1.89
	4	2.31	2.12,2.52	1.94	1.78,2.12
	5	3.33	3.07,3.63	2.61	2.39,2.85

Conclusion: BMI/BMD ratio to BMD appears to be a useful way of predicting fragility fractures in all weight categories in this large observational cohort. Further work looking at site of fracture and the utility of the ratio in a clinical setting will be presented. Particular attention will be given to the role of BMI/BMD ratio at predicting fractures in patient subsets where BMD is known to be less strongly associated with fracture risk (e.g. steroid therapy, diabetes).

Disclosure: M. Massarotti, None; M. Bukhari, None.

Abstract Number: 2315

Opportunistic Screening for Osteoporosis Using Thoraco-Abdomino-Pelvic Computed Tomography Assessing the Vertebral Density in Rheumatoid Arthritis Patients

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Screening for osteoporosis is crucial in rheumatoid arthritis (RA) patients. The aim of this study was to assess the value of thoraco-abdomino-pelvic CT-derived bone mineral density (BMD) results in L1, compared to dual energy X-ray absorptiometry (DXA) results for osteoporosis screening in rheumatoid arthritis patients.

Methods: Consecutive RA patients who underwent a CT-scan and DXA within a two-year period were retrospectively included. The CT sagittal images were then evaluated for vertebral fractures from T4 to L5 using the Genant classification. The CT attenuation values (in Hounsfield units [HU]) of trabecular bone in L1 were measured on axial images and compared to the DXA results.

Results: This study included 105 patients (mean age 61.1 years (\pm 9.5), 78.1% women). There were 28 patients (26.7%) with DXA-defined osteoporosis and 32 (30%) with osteoporotic fractures (vertebral and/or non-vertebral). The CT assessment indicated that the mean (SD) vertebral L1 attenuation was 142.2 HU (\pm 18.5). The diagnostic performance for the vertebral CT-attenuation measurement was acceptable: the AUC was 0.67 for predicting osteoporotic fractures and of 0.69 for predicting vertebral fractures. Among patients with osteoporotic fractures, there were 23 (74%) patients

categorized as osteoporotic with a L1 CT-attenuation of 135 HU or less, whereas there were only 13 patients (42%) identified by DXA.

Conclusion: CT offers a combined opportunistic screening for osteoporosis by assessing both vertebral fractures and bone density on routine CT-scans. This approach may be particularly interesting for RA patients with a high osteoporosis risk.

Disclosure: J. Perrier-Cornet, None; A. Y. OMOUROU, None; M. FAUNY, None; D. Loeuille, None; I. Chary-Valckenaere, None.

Abstract Number: 2316

Errors and Discrepancies in DXA Scans in Imaging Centers in Ecuador

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Session Information

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Background/Purpose: Dual-energy X-ray absorptiometry (DXA) is recognized as the gold standard for measuring bone mineral density (BMD) with acceptable errors, good precision and reproducibility. However, the training of operators in different centers and countries is not standardized and the lack of knowledge can lead to errors both in the acquisition of information, as well as in its analysis and subsequent interpretation. The purpose is to determine the most common errors in the performance of bone densitometry from different imaging centers in Ecuador.

Methods: Cross-sectional descriptive study. We collected DXA scans from different imaging centers in Ecuador. Demographic information from patients included age, sex, height, weight, body mass index (BMI) and main diagnosis. Data from the DXA scan included city of origin, type of specialist that requested it and densitometry diagnosis. The DXA images provided were analyzed double blind by experts in the field from Argentina, according to patient position, presence of artifacts and region of interest correctly placed we.

Results: From a total of 180 patients with a mean age of 63.5 years, 93.6% were women. 78% of the DXA scans came from private imaging centers and 22% from public centers, 95% of all came from the city of Guayaquil. The machines

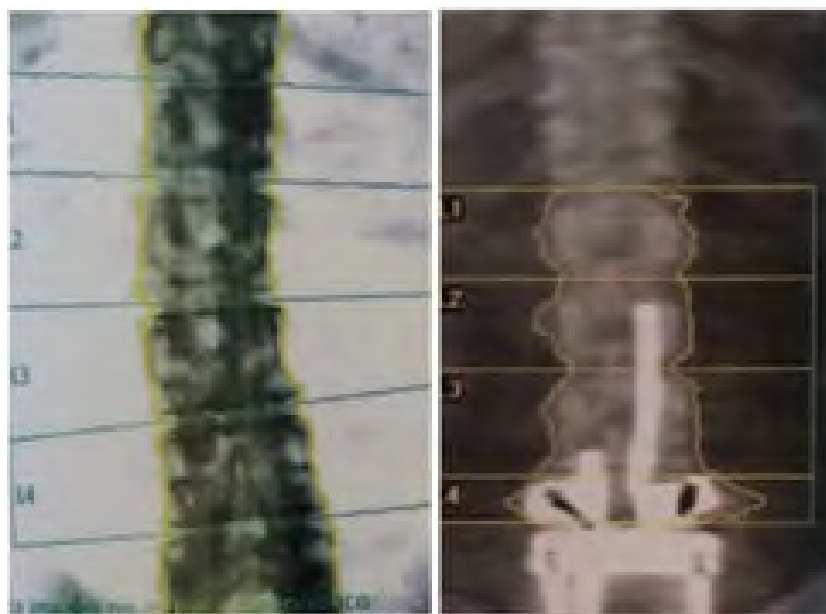


Figure 1: Spine Incorrect alignment and prosthetics

used were Hologic 51.2% and Lunar 48.8%. The densitometric diagnosis was 16.3% normal, 46.1% osteoporosis and 37.6% osteopenia. 112 left hip and 49 right hip scans were analyzed from which 31.1% and 22.4% had errors in patient positioning, respectively, mainly internal or external rotation. 140 lumbar scans were analyzed from which 21.4% had patient positioning errors (not centered or not straight). Also in 38.5% the vertebral area did not correspond to L1-L4. 3.5% had artefacts such as a metal bar or implant. The region of interest was misplaced in 24.1% of the lumbar scans and 19.9% of the femur.

Conclusion: Much of the responsibility of a DXA falls on the operator as he has to review the patient's health history, enter demographic data, perform the acquisition of the image with a correct positioning and analyze it. When studies are performed incorrectly, it can lead to important errors in diagnosis and therapy.



Figure 2. Femur Incorrect vs. correct alignment

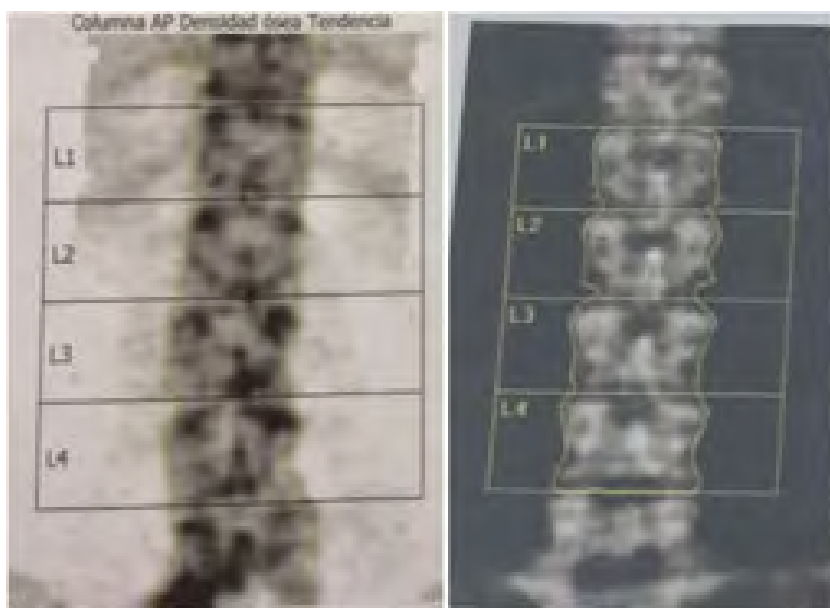


Figure 3. Spine Incorrect vs. correct alignment.

Disclosure: G. Maldonado, None; M. J. Intriago, None; M. Larroude, None; G. Aguilar, None; M. Moreno, None; J. Gonzalez, None; S. Vargas, None; C. Vera, None; R. Guerrero, None; K. Ríos, None; C. Rios, None.

Characterization of Paget's Disease of Bone Patients from the South of Portugal (Algarve and Alentejo) – Clinical and Genetic Aspects

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

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Background/Purpose: Paget's disease of bone (PDB) is a metabolic bone disorder whose prevalence increases with age and affects ~3% of Caucasian individuals older than 55 years (1,2). Recent evidence suggests that may be caused by an accumulation of mutations/variants in different genes. In 15 to 30 % of PDB patients, it appears to have an autosomal dominant mode of inheritance but with incomplete penetrance, which makes it often difficult to determine the familiar history due to the high percentage of asymptomatic individuals carrying the mutations. The first gene mutations associated to PDB were identified in the sequestosome 1 (*SQSTM1*) gene at the PDB3 locus (chromosome 5) (3,4). Later, we and others (5,6) have found that PDB6 locus (chromosome 10) was also linked to PDB, including the Optineurin (*OPTN*) gene, which variant rs1561570 was found to be the most significantly associated with PDB. The aim of this study is to characterize clinically and to investigate the presence of those mutations in PDB patients from the south of Portugal (Algarve and Alentejo).

Methods: This study was approved by the Ethics Committee of University Hospital Center of Algarve, where patients were recruited. In a pilot experiment, the clinical history of 12 patients previously diagnosed with PDB (aged 58 to 81 years old) and 16 healthy controls (aged 47 to 84 years old) was collected and they were also analysed. After DNA extraction from freshly collected biological samples (blood or epithelial swabs), the fragments of interest were amplified by PCR using specific primers for the corresponding loci and the amplified fragments sequenced and compared with the wild type genes.

Results: PDB patient's mean age was 70.8±8.2 years. There was a male predominance (10; 83%). There were more patients with the polyostotic form (10; 83%). Three patients (25%) complained about bone pain and that led to the diagnosis of PDB. The others were identified in routine blood tests where alkaline phosphatase (AF) was included. Treatment consisted mainly of zoledronic acid with excellent results in terms of controlling bone pain and AF levels but it wasn't able to avoid some bony deformities, which occurred in three patients (25%).

The P392L causal mutation of *SQSTM1* was detected in one of the patients (8%) without a familial history of PDB and in none of the healthy controls. Our results also showed that the SNP rs1561570 in the *OPTN* gene had a higher prevalence of allele T in the PDB patients (55%) than in healthy controls (44%) while none of the patients presented the C allele in homozygosity. We have previously shown (7,8) that the presence of the rs1561570 may contribute to PDB since its T allele results in the loss of a methylation site in patients' DNA, higher levels of *OPTN* expression in patients' osteoclasts, higher levels of NF-κB translocation into the nucleus and increasing expression of its target genes, thus contributing to the increased activity of osteoclasts observed in PDB.

Conclusion: The clinical results obtained are in agreement with literature and the genetic study confirm the heterogeneity of PDB and despite the small number of patients so far analyzed the results are in agreement with previous data in terms of type and incidence of mutations in the patients' population.

Disclosure: G. Sequeira, None; P. Carvalho, None; C. Ribeiro, None; A. Alfaia, None; N. Conceição, None; L. Cancela, None.

Fracture Liaison Service in an Open Health System: Outcomes and Challenges

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Session Information

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Background/Purpose: The “osteoporosis care gap” is noted by findings that 80% of patients do not receive treatment after an initial fracture. An initial fracture portends a 60% risk of re-fracture. A Fracture Liaison Service (FLS) is an effective means of addressing secondary fracture prevention. The type of health system model potentially impacts FLS outcomes. A closed model like Kaiser Permanente’s Healthy Bones Program, led by Orthopedic Surgery, resulted in a 40% reduction in hip fractures. Geisinger Health System’s FLS led by Rheumatology, an open-model, has noted 75% treatment rates versus 13.8% for those seen by primary care doctors alone.

Loma Linda University Medical Center (LLUMC) launched a multidisciplinary FLS in 2017. Pre-LLUMC FLS studies (2015-2016) showed that 85% of patients pre-fracture were never screened nor treated for osteoporosis; post-fracture, only 10% of patients were treated, and only 6% had dual x-ray absorptiometry (DXA). Notably, 30% had a prior fracture. LLUMC is the only tertiary medical center in the Inland Empire of Southern California. It has an open health system, historically known for specialty services. The FLS goal was to achieve a 10% improvement in therapy initiation and DXA completion. This study aims to assess the FLS’s effectiveness during the initial eight-month period.

Methods: Data extraction from our Epic® electronic health record (EHR) through the LLUHS Patient Safety and Reliability Office was done to determine the number of inpatient FLS referrals and total eligible fractures from September 2017-April 2018. Outpatient transition to in-network osteoporosis specialist, pharmacotherapy initiation, DXA ordering and completion, vitamin D measurement, number of deaths, transition to dependent living facilities, availability of a primary care provider (PCP) in- or out-of-network were among the metrics determined.

Results: 70 patients were referred to the FLS. 81% and 14.4% had femoral and vertebral fractures, respectively. All had Vitamin D level determination. DXA was set up for 61.5% upon discharge. 13 (18.6%) transitioned to an outpatient LLUHS specialist, while 57 (81.4%) did not. Patients lost to follow-up were characterized by the following traits: lived >30 miles from LLUMC, had no regular PCP or had no in-network PCP, patient/family belief regarding lack of benefit to treatment or non-association of fractures with osteoporosis. Mortality was noted in 6 (10%) patients due to sepsis/other infection. 991 fracture encounters excluding other non-osteoporosis-related causes were admitted during the same time period.

Conclusion: Low recruitment rates in an open-health system FLS require more outreach and coordination with both in and out-of-network primary care providers (PCP) Also increasing PCP, hospital-based provider and patient education regarding the osteoporosis care gap is essential. Since April 2018, an FLS coordinator (nurse practitioner) was hired and community-based education activities for PCPs practicing within 30-60 miles of LLUMC were done. Outcomes in 12 months are to be determined.

Disclosure: D. Jose, None; K. Torralba, None; C. Downey, None; M. Yu, None; L. Salto, None.

Adherence to Guideline Recommendations for Screening and Treatment of Glucocorticoid Induced Osteoporosis in Patients with Rheumatoid Arthritis on Long Term Glucocorticoid Therapy at a Tertiary Care Center

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Session Information

Session Date: Tuesday, October 23, 2018

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Background/Purpose: Glucocorticoid induced osteoporosis (GIOP) is an under-recognized and under-treated condition. Many long-term glucocorticoid (GC) users never receive therapy to prevent bone loss or are only treated after a fracture occurs, despite having known risk factors and available effective therapies to prevent fracture. Our quality improvement study measures 1) osteoporosis (OP) screening rates, and 2) adherence to 2017 ACR guidelines for prevention and treatment of GIOP in the rheumatoid arthritis (RA) patient population at our tertiary care academic rheumatology practice.

Methods: A retrospective review of RA patients (ICD codes M05 and M06) over age of 50 yrs and on long-term GC (≥ 3 months) from 1/1/2015 through 12/31/2017 was performed. The following variables were recorded and validated manually: demographics (age/sex/ethnicity/height/weight), smoking status, GC dose and duration (excluding non-oral formulations and oral tapers), DEXA scans, and left femoral neck T-score (LFNTS). OP screening rates with DEXA scans were measured. A FRAX score was calculated using the online University of Sheffield FRAX calculator. The FRAX score for major osteoporotic fracture risk and hip fracture risk was increased by 15% and 20% respectively for high dose GC use ($>7.5\text{mg/day}$) per ACR guideline recommendations. Patients were risk-stratified as high (LFNTS ≤ -2.5 , or FRAX 10 yr risk of major and hip OP fracture of $\geq 20\%$ and $\geq 3\%$ respectively), moderate (FRAX 10 yr risk of major and hip OP fracture of 10-20% and 1-3% respectively) or low risk (FRAX 10 yr risk of major and hip OP fracture of $<10\%$ and $<1\%$ respectively). We measured the percentage of patients in each category on appropriate OP treatment (defined for high and moderate risk categories as bisphosphonates, and for low risk as calcium/vit D supplementation and/or bisphosphonates).

Results: We identified 1,746 patients with RA over age of 50 yrs during the 3 year study period. Of these, 127 patients were on long term GC (≥ 3 months). Mean age was 65 yrs, 79% were female, 88% were Caucasian, and 54% were current smokers, mean GC dose was 6.5mg/day (prednisone equivalent), and 28% were on high dose GC ($>7.5\text{mg/day}$). Appropriate DEXA screening was performed in 80 (63%) patients. The OP fracture risk stratification of these 80 patients was as follows: 43, 23, and 14 patients were in the high, moderate, and low risk category respectively. The percentage on appropriate treatment in the high, moderate, and low risk categories were 44%, 52%, and 86% (low risk breakdown = 9 calcium/vit D supplementation and 3 bisphosphonates) respectively. Multivariate analysis of predictive risk factors for non-adherence to screening and treatment is ongoing.

Conclusion: In our study on GIOP screening and treatment in RA patients on long term GC therapy, 63% received appropriate OP screening, whereas 44% of the high fracture risk patients and 52% of the moderate risk patients were found to be on appropriate GIOP treatment. A multi-faceted QI initiative to improve GIOP management is underway at our institution- creation of an EHR best practice alert and EHR FRAX calculator along with continued medical education and shared performance metrics. We plan to measure performance closely over time post-intervention.

Disclosure: P. Webster, None; T. S. Sharma, None.

Abstract Number: 2320

Multimorbidity Is Associated with Hip Fractures in Both Women and Men and across Different Races

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Session Information

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Background/Purpose: Multimorbidity, the coexistence of 2 or more chronic conditions, is associated with increased disability and poor functional status, and may serve as an important clinical marker for hip fracture risk. We examined the role of multimorbidity on hip fracture risk and whether this differed between women and men, or by race.

Methods: Using de-identified administrative claims data from a large commercial insurance database, we identified both women and men aged ≥ 50 yrs who had a hip fracture between Jan 1, 2006-Dec 31, 2016, and had at least 1 yr health plan coverage pre-fracture. Subjects without known hip fracture were matched to cases exactly on sex, age, race, year, geographic region, and insurance; they were also required to have at least 1 yr health plan coverage pre-index date.

Diagnostic codes and medications were captured for the year prior to fracture/index date. Using the score from the Elixhauser Comorbidity Index (Elix Index), a set of 31 comorbidities, we categorized subjects into 3 groups (0-1, 2-3, and ≥ 4) and used conditional logistic regression to examine the association with hip fracture. We focused on subjects identified as White, Black or Asian, and examined women and men separately.

Results: We studied 50,136 White/5,770 Black/1,130 Asian women (median age [IQR], yrs: 79[72, 83]/ 78 [71, 83]/ 79 [71, 83], respectively) and 22,329 White/2,419 Black/451 Asian men (median age [IQR], yrs: 77 [66, 82]/ 75 [66, 81]/ 78 [67, 83], respectively) with hip fractures and an equal number of matched controls. Compared to the referent group (Elix Index 0-1), higher Elix Index was associated with increased hip fracture risk with findings similar in women and men and across races studied (Table). In further analyses with a gradient boosting model, a higher Elix Index ranked as the top influence on hip fracture risk over the individual 31 comorbidities (data not shown). In a multivariable penalized logistic regression model, the addition of medication categories to the 31 comorbidities did not contribute additional information on hip fracture risk (data not shown).

Conclusion: Multimorbidity, as assessed using the Elix Index, is associated with an elevated risk for hip fracture, in both women and men, and across races studied. A higher number of co-existing chronic conditions is associated with an even greater risk of hip fracture. Further work is necessary on determining whether specific combinations of comorbidities have a greater impact on risk.

Odds Ratio (OR) and 95% Confidence Interval (95% CI) for Hip Fractures by Elixhauser Comorbidity Index (Elix Index)

	White			Black			Asian		
	Hip Fracture		OR (95% CI)	Hip Fracture		OR (95% CI)	Hip Fracture		OR (95% CI)
	No	Yes		No	Yes		No	Yes	
Women									
N	50,136	50,136		5,770	5,770		1,130	1,130	
Elix Index									
0-1	30.9%	12.2%	referent	25.0%	9.4%	referent	30.4%	15.4%	referent
2-3	34.4%	27.5%	2.2 (2.1-2.3)	35.4%	24.7%	2.0 (1.8-2.3)	38.5%	28.0%	1.7 (1.3-2.2)
≥ 4	34.7%	60.3%	5.1 (4.9-5.3)	39.6%	66.0%	5.1 (4.5-5.8)	31.2%	56.6%	4.5 (3.5-5.9)
Men									
N	22,329	22,329		2,419	2,419		451	451	
0-1	37.0%	14.5%	referent	30.0%	11.3%	referent	37.0%	17.3%	referent
2-3	32.5%	25.0%	2.3 (2.2-2.5)	34.4%	23.2%	2.0 (1.7-2.5)	31.7%	31.9%	2.5 (1.7-3.7)
≥ 4	30.5%	60.5%	6.8 (6.4-7.3)	35.6%	65.4%	5.8 (4.8-7.1)	31.3%	50.8%	4.5 (3.0-6.7)

Disclosure: S. Amin, None; E. J. Atkinson, None; S. Khosla, None.

Abstract Number: 2321

Dickkopf-1 Serum Levels in Patients with Systemic Sclerosis and Correlation with Trabecular Bone Score

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

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Session Time: 9:00AM-11:00AM

Background/Purpose: Dickkopf-1 (DKK1) is a natural inhibitor of Wnt signaling pathway that could be involved in promoting osteoclastogenesis through suppression of osteoprotegerin (1,2). Systemic sclerosis (SSc) patients present an increased risk of low bone mass and of osteoporosis (OP) as a result of different causes (3,4). The aim of this study is to investigate in different nailfold videocapillaroscopic (NVC) patterns (“Early”, “Active”, and “Late”) in SSc patients and to evaluate possible correlations between DKK-1 levels and Trabecular Bone Score (TBS), finally to compare the results with healthy subjects (CNT).

Methods: 60 SSc patients and 60 CNT were enrolled. Dkk-1 serum levels were measured in all 120 subjects by ELISA methods (Quantikine Human DKK-1 Immunoassay R&D System, Minneapolis, USA). Nailfold videocapillaroscopic (NVC) and TBS analysis and Bone Mineral Density (BMD, g/cm²) were also performed.

Results: DKK-1 levels were statistically significantly higher in SSc patients with “Late” NVC pattern than in those both “Active” and “Early” ($p < 0.0001$) and its levels were correlated with Trabecular Bone Score only in patients with “Late” NVC pattern ($p = 0.001$). Serum DKK-1 levels were significantly higher in patients with SSc than in CNT ($p < 0.007$). A negative correlation between Raynaud’s phenomenon duration (years expressed) and DKK-1 levels ($p < 0.01$) was also observed.

Conclusion: Dickkopf-1 values is increased in SSc patients with “Late” nailfold capillaroscopy pattern than in both “Active” and “Early” pattern and in SSc patients than in CNT, furthermore its level correlates with TBS in “Late” NVC pattern.

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Disclosure: B. Ruaro, None; A. Casabella, None; S. Paolino, None; C. Pizzorni, None; V. Smith, None; C. Serio, None; L. Molfetta, None; P. Odetti, None; M. Cutolo, None.

Abstract Number: 2322

Intervals of Bone Mineral Density Measurement during Treatment for Osteoporosis in Patients with Rheumatoid Arthritis

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Background/Purpose: There is controversy about the intervals of retesting bone mineral density (BMD) in patients treated for osteoporosis. The objective of this study is to investigate proper intervals of BMD measurement during treatment of osteoporosis in patients with rheumatoid arthritis (RA).

Methods: We retrospectively studied 297 patients (271 women and 26 men) with RA who were treated for osteoporosis with mean age of 65.7 ± 8.8 years and the mean duration of treatment for osteoporosis of 8.2 ± 3.9 years. BMD had been measured every year for five years. Annual changes of BMD and T-score at lumbar spine (L1-L4), femoral neck and total hip were evaluated. Treatment failure was defined as an occurrence of two or more fractures, or a reduction in BMD more than the least significant change (LSC) despite adequate treatment. The values of the LSC were 5.3% in lumbar spine, 6.9% in femoral neck, and 5.0% in total hip in the 95% confidence interval.

Results: 48 (16.2%) patients stopped treatment for osteoporosis due to improvement of T-score. They had an average treatment duration of 4.3 ± 0.5 years before discontinuation. 227 (76.4%) patients were consistently treated with osteoporosis. 18 (6.1%) patients discontinued treatment due to improvement of T-score and then re-started treatment again with deterioration of T-score on follow-up of BMD test. The number of patients with osteoporotic fracture was 80 (30.3%), and among them 57 (19.2%) patients had sustained fractures before starting treatment and 23 (7.7%) patients had incident fractures during treatment for osteoporosis. Annual changes of BMD were -0.28%, 1.24%, 0.84%, and 2.46% at lumbar spine after the first year to the fourth year of treatment compared to the results of previous year respectively, -1.39%, 1.77%, -0.51%, and 1.78% at femoral neck and -0.56%, -0.49%, 0.97%, and 0.24% at total hip respectively. The changes of BMD from the baseline after one, two, three, and four years of treatment were -0.28%, 1.14%, 1.90%, and 4.31% at lumbar spine, -1.39%, 0.41%, -0.10%, and 2.10% at femoral neck and -0.56%, -0.97%, -0.10%, and 0.28% at total hip respectively (Figure 1). The treatment failure after one year of treatment to the four year compared to the baseline were 11.4%, 7.4%, 5.8% and 3.1% at lumbar spine, 14.7%, 10.1%, 8.4%, and 4.7% at femoral neck and, 13.9%, 12.7%, 9.1%, and 6.3% at total hip respectively.

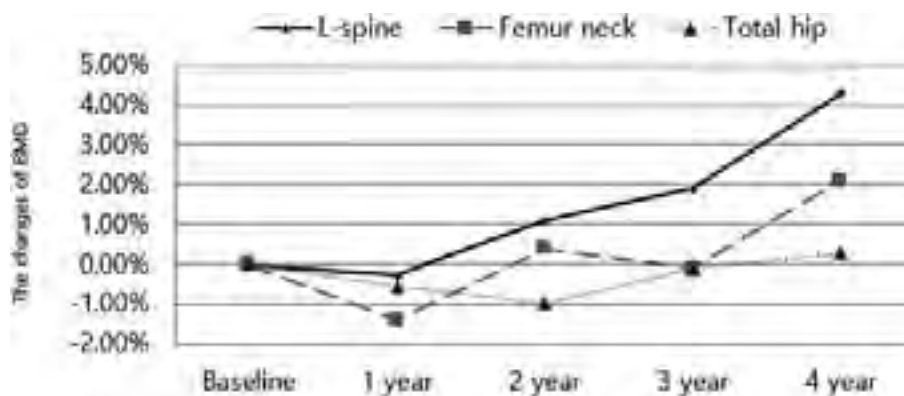


Figure 1. The changes of BMD from the baseline after one, two, three, and four years of treatment.

Conclusion: Despite treatment for osteoporosis, patients with RA did not show significant improvement of BMD by one year. Considering these results, the reasonable interval of BMD measurement would be at least four years during the anti-osteoporotic treatment because the treatment failure is continuously decreasing. Moreover, many patients with RA need continuous treatment for osteoporosis regardless of BMD due to high incidence of fracture.

Disclosure: S. Y. Lee, None; S. R. Kwon, None; M. J. Lim, None; K. H. Jung, None; W. Park, None.

Abstract Number: 2323

Predictors of Mortality in Patients with Hip Fragility Fracture

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

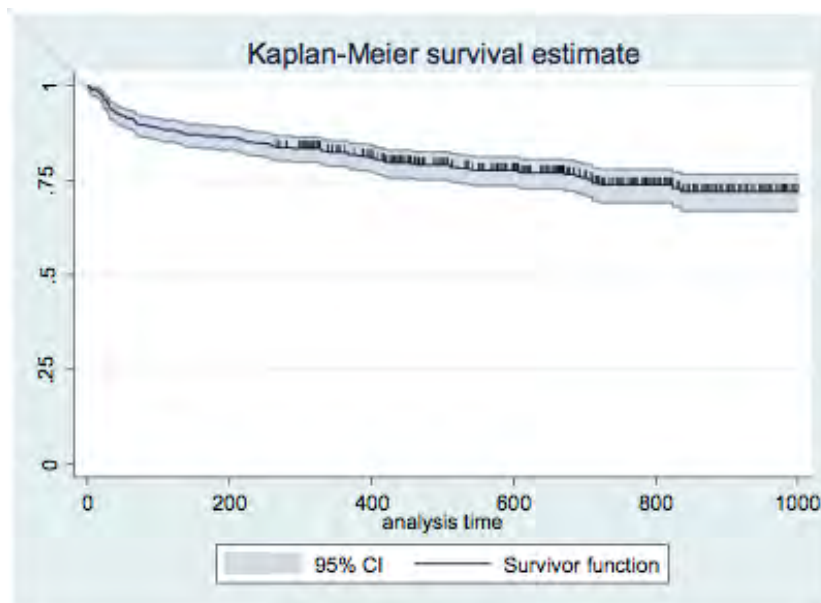
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: In Osteoporosis, hip fractures account for significant disease burden, with increased morbi-mortality and financial load on the patient and healthcare system. This study aimed to assess cumulative survival rate of patients with hip fragility fracture aged ≥ 65 years old, referred to a Rheumatology Department's Fracture Liaison Service (FLS) after admission to the Orthopaedics Inpatient Care Department, and to determine predictors of mortality.

Methods: Longitudinal retrospective study of patients referred to a Rheumatology Department's FLS from March 2015 until March 2017. Demographic and clinical data were collected. Statistical analysis was performed with STATA. Survival cumulative probabilities were calculated through Kaplan-Meier curves and hazard ratios (HR) through cox regression, adjusted to age/degree of care dependency.

Results: 522 patients were referred to the FLS, 79.7% female, with median age of 84 years old (65-103). Table 1 summarizes clinical and demographic characteristics. One hundred and nineteen patients (22.8%) died, 36 still during inpatient care. The cumulative survival probability (image 1) at 1, 3, 6, 12 and 24 months was 94.1% (95%CI 91.7-95.9), 91.1% (95%CI 88.2-93.3), 86.3% (95%CI 82.9-89.0%), 81.7 (95%CI 77.9-84.8) and 73.8% (95%CI 69.2-77.8) respectively. Patients ≥ 80 years old presented lower survival rate (HR 1.64, $p=0.02$), as well as partially dependent and totally dependent patients (HR 1.93, $p=0.047$; HR 5.3, $p=0.000$, respectively). Higher femur BMD (HR 0.01, $p=0.023$) and T-score (HR 0.67, $p=0.038$) were predictors of better survival outcome. Considering laboratory measurements, higher beta-crosslaps serum values predicted worse survival outcome (HR 4.27, $p=0.007$). Gender, fracture classification, type of surgical intervention, presence of vertebral fractures, BMI, serum vitamin D and osteocalcin didn't have impact on survival.



Conclusion: Knowledge of mortality predictors in hip fracture is essential to optimize survival in these patients. In our study, age, autonomy degree, femur BMD/T-score and beta-crosslaps had impact on survival outcome.

Table 1 - Clinical and demographic characteristics of sample

Total (N)	522
Age at admission, y (median, min-max)	84 (65-103)
Sex, female (n, %)	416, 79.7
Deaths (n, %)	119, 22.8
During inpatient care (n, %)	36, 6.9
BMI (N)	218
Underweight (n, %)	80, 36.7
Normal (n, %)	117, 53.7
Overweight (n, %)	20, 9.2
Obesity class I (n, %)	1, 0.5
Degree of care dependency (N)	307
Totally dependent (n,%)	23, 7.5
Partially dependent (n,%)	78, 25.4
Autonomous (n,%)	206, 67.1
Type of fracture	
Transtrochanteric (n,%)	262, 50.2
Femoral neck (n,%)	221, 42.3
Subtrochanteric (n,%)	38, 7.3
Subsequent fracture (n,%)	47, 9.0%
Vertebral fracture (N)	236
0 (n,%)	100, 42.4
1 fracture (n,%)	56, 25.9
>= 2 fractures (n,%)	80, 33.9
Femur BMD, g/cm ² (median, min-max, N)	0.70, 0.36-1.18, 214
Femur T score (median, min-max, N)	-2.6, -7.0-0.7, 214
>2.5 (n,%)	87, 40.7
<=2.5 (n,%)	127, 59.3
Intervention (N)	516
Conservative (n,%)	11, 2.1
Osteosynthesis (n,%)	337, 65.3
Hemiarthroplasty (n,%)	87, 16.9
Total arthroplasty (n,%)	80, 15.5
Girdlestone (n,%)	1, 0.2
25(OH)D, ng/ml (median, min-max, N)	23, 3-54, 219
OC ng/ml (median, min-max, N)	28.2, 6.80-198.60, 215
Beta-crosslaps (median, min-max, N)	0.71, 0.12-3.28, 217

Image 1 - Cumulative survival probability of study sample

Disclosure: M. Guerra, None; S. Ganhão, None; F. Aguiar, None; G. Terroso, None; R. Vieira, None; D. Goncalves, None; T. Meirinhos, None; T. Martins-Rocha, None; A. Águeda, None; R. Ferreira, None; M. Bernardes, Pfizer, Inc., 9, Lilly, 9, Janssen, 9, Merck & Co., 9, GlaxoSmithKline, 9; C. Vaz, None; R. Lucas, None; L. Costa, None.

Predictors of Refracture in Patients with Hip Fragility Fracture

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Hip fractures are associated with substantially elevated morbidity and mortality and thus represent a serious public health problem. The purpose of this study is to assess cumulative refracture free survival probability and possible predictors of refracture in patients older than 65 years admitted by hip fragility fracture.

Methods: Longitudinal retrospective study of patients referred to the Rheumatology department's Fracture Liaison Service (FLS) from march 2015 until march 2017. Demographic and clinical data were collected. Statistical analysis was performed with STATA. Survival cumulative probabilities were calculated with Kaplan-Meier curves. Hazard ratios (HR) were calculated through cox regression, adjusted to age and degree of dependence.

Results: 522 patients were referred to the FLS, with a median age (min-max) of 84 years (65-103); 79,7% (N=416) were female. 47 out of 522 had a subsequent fragility fracture (9%). The cumulative survival probability without refracture at 1, 6, 12 and 24 months was 99,4%, (95%CI [98,2-99,8]), 96% (95%CI [93,8-97,4]), 93%(95%CI [90,2-95,0]) and 89,3% (95% CI [85,8-92,0]), respectively. Neurologic disease and chronic obstructive pulmonary disease (COPD) were both predictors of worst refracture free survival outcome (HR 2,37, 95%CI [1,05-5,37] and HR 3,25, 95%CI [1,09-9,61], respectively). Gender, age, body mass index, degree of dependence, fracture and intervention type, calcium intake, sedative drugs, radiographic vertebral fractures, total femur BMD and T-score, vitamin D, osteocalcin and β crosslaps, discharge to home or institution, supplementation with calcium and vitamin D and anti-osteoporotic treatment didn't have significant impact on survival cumulative probabilities of refracture.

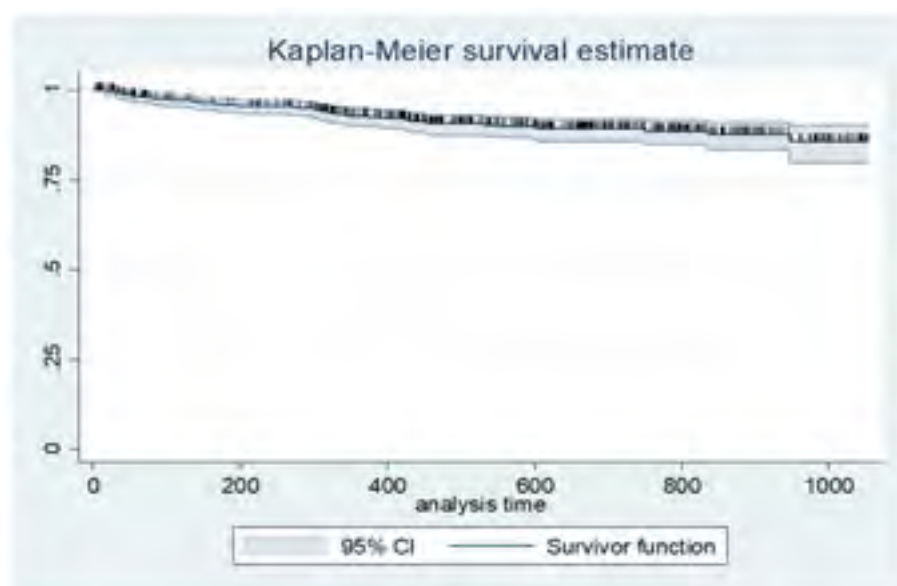


Figure 1: Cumulative refracture free survival probability

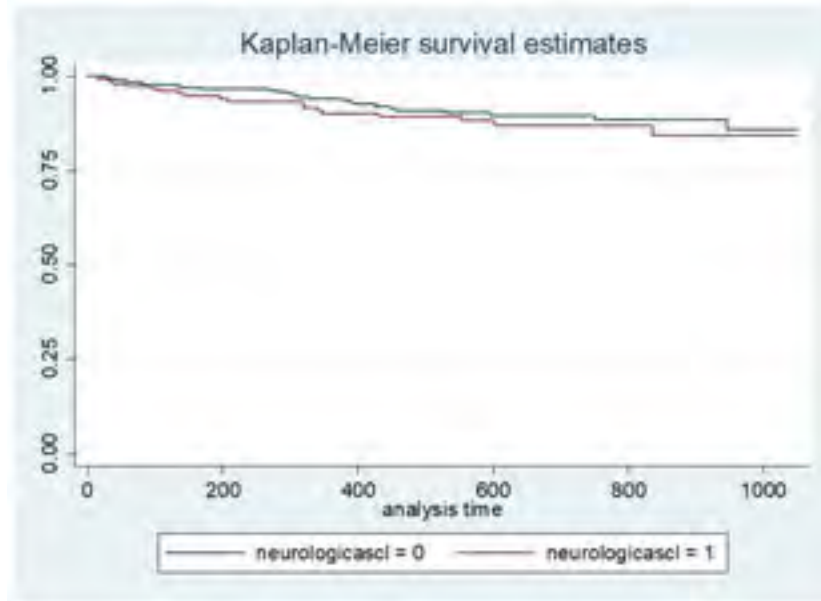


Figure 2: Cumulative refracture free survival probability (with neurologic diseases Vs without neurologic diseases)

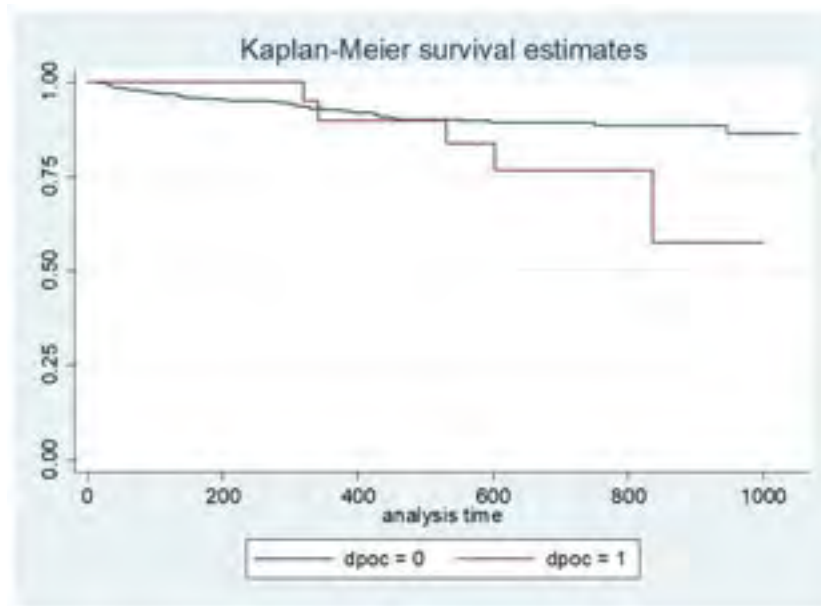


Figure 3: Cumulative refracture free survival probability (with COPD Vs without COPD)

Conclusion: Knowledge of the predictors of refracture is essential for secondary prevention. Our sample suggests that neurologic disease and COPD may increase the risk of subsequent fracture after prior fragility fracture, but further studies are needed.

Disclosure: S. Ganhão, None; M. Guerra, None; F. Aguiar, None; G. Terroso, None; R. Vieira, None; D. Goncalves, None; T. Martins-Rocha, None; R. Ferreira, None; A. Agueda, None; T. Meirinhos, None; E. Mariz, None; R. Lucas, None; M. Bernardes, Pfizer, Inc., 9, Lilly, 9, Janssen, 9, Merck & Co., 9, GlaxoSmithKline, 9; C. Vaz, None; L. Costa, None.

Sex Differences in the Association of Frailty and Bone Mineral Density in Patients with Rheumatoid Arthritis

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Background/Purpose: Frailty in the general population is associated with poor outcomes including osteoporosis (OP), fracture and death. Frailty occurs at a higher rate in RA than in the general population. It is not known, however, if frailty is associated with lower bone mineral density (BMD) in RA. We investigated associations between frailty, RA clinical characteristics, medication use, and body composition and BMD in patients with RA.

Methods: We performed a cross-sectional analysis of a longitudinal RA cohort study from years 2007-2009. All patients met ACR classification criteria for RA. Frailty was evaluated using the Fried Index, categorizing each participant as robust, pre-frail or frail. We used linear regression to evaluate the association between predictors and femoral neck BMD. To

Table 1. Multivariable linear regression of the entire cohort on the outcome of femoral neck BMD (g/cm²) (N=135, r²= 0.37).

Variables	β	95% CI	p-value
Age	-0.003	-0.005 to -0.001	0.002
Male sex	0.027	-0.020 to 0.073	0.258
High Positive Anti-CCP*	-0.052	-0.093 to -0.011	0.013
Disease Duration (years)	-0.001	-0.003 to 0.001	0.333
Fat Mass Index	0.002	-0.003 to 0.007	0.493
Appendicular LMI	0.042	0.021 to 0.063	<0.0001
Prednisone dose	-0.002	-0.003 to 0.001	0.333
Frail Category*:			
Robust	ref	ref	ref
Prefrail	-0.036	-0.095 to 0.022	0.210
Frail	-0.093	-0.176 to -0.008	0.029

*CCP: cyclic citrullinated peptide antibody; LMI: lean mass index.

*High positive anti-CCP >60 units.

*Frail categories based on Fried Index.

*Note: OP medication use had a negative association with BMD suggesting confounding by indication; therefore it was not included in the multivariable model.

Table 2. Multivariable linear regression on the outcome of femoral neck BMD (g/cm²) stratified by sex, Females (N=81, r²=0.31), Males (N=53, r²=0.47).

Variables	Females (N=81)			Males (N=53)		
	β	95% CI	p-value	β	95% CI	p-value
Age	-0.002	-0.004 to 0.001	0.102	-0.005	-0.008 to -0.002	0.003
CCP Positive	-0.047	-0.101 to 0.008	0.095	-0.058	-0.134 to 0.018	0.130
Disease Duration	-0.001	-0.003 to 0.001	0.339	-0.001	-0.005 to 0.005	0.975
Fat Mass Index	0.005	-0.003 to 0.013	0.212	--	--	--
Arm/leg LMI	0.037	0.001 to 0.073	<0.0001	0.042	0.016 to 0.067	0.002
Prednisone dose	-0.005	-0.011 to 0.002	0.168	--	--	--
Frail Category:						
Robust	ref	ref	ref	ref	ref	ref
Prefrail	-0.027	-0.097 to 0.043	0.440	-0.084	-0.197 to 0.030	0.144
Frail	-0.048	-0.177 to 0.079	0.449	-0.160	-0.277 to -0.042	0.009

*CCP: cyclic citrullinated peptide antibody; LMI: lean mass index.

*High positive anti-CCP >60 units.

*Frail categories based on Fried Index.

*Note: OP medication use had a negative association with BMD suggesting confounding by indication; therefore it was not included in the multivariable model. The model for male sex did not include fat mass index and prednisone dose due to the small number of male subjects.

identify independent predictors of BMD, we performed a multivariable linear regression analysis that included variables significant in the univariable analyses at $p < 0.10$. Because sex differences in frailty were noted, we performed additional sex-stratified multivariable analyses.

Results: There were 138 participants (82 females, 56 males) and the mean age was 58.0 ± 10.8 years. 70% were rheumatoid factor positive, and 55% were high anti-cyclic citrullinated peptide (CCP) positive (>60 units). Mean disease duration was 19 ± 10.9 years. 52% had low BMD based on a T or Z score ≤ -1.0 . 44% of participants reported taking prednisone and 27% reported taking OP medications. Males had higher rates of frailty (11% robust, 63% prefrail, 27% frail) compared to females (22% robust, 72% prefrail and 6% frail). In the entire cohort, age, high positive anti-CCP and frailty had independent negative associations with BMD ($\beta = -0.003$, -0.052 and -0.093 respectively, $p < 0.05$) (Table 1). Appendicular lean mass index (ALMI) had a positive linear association with BMD ($\beta = 0.042$, $p < 0.0001$). In females, only ALMI had a significant independent association with BMD ($\beta = 0.037$, $p < 0.0001$). In males, frailty carried the strongest independent association with BMD ($\beta = -0.160$, $p < 0.01$). Age and ALMI also maintained their independent associations with BMD in males ($\beta = -0.005$ and 0.042 respectively, $p < 0.01$).

Conclusion: Frailty, high positive anti-CCP, ALMI and age were independently associated with BMD in patients with RA. Males had higher rates of frailty than females, and in sex-stratified analysis, frailty was independently associated with BMD in males but not in females. Our findings suggest that frailty is an important factor associated with low BMD and that sex may influence the development of frailty in patients with RA.

Disclosure: K. D. Wysham, None; D. M. Shoback, None; J. B. Imboden Jr., None; P. Katz, None.

Abstract Number: 2326

Outcomes One Year after Hip Fracture Repair in the Elderly: Does Social Isolation Matter?

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Hip fractures are a serious public health issue with a significant population burden, especially among those over age 65. Social isolation—how integrated a patient is in their community—is a novel and potentially modifiable risk factor for poor health outcomes after low energy hip fracture. This study evaluates the association of pre-operative social isolation with death, adverse events, and patient-reported outcomes in elderly patients 1 year after surgical repair of low energy hip fracture.

Methods: The Lubben Social Networks Scale-18 (LSNS-18), a validated instrument specifically designed to measure social isolation in the elderly; PROMIS-29, which measures a variety of important patient-reported domains; and the Lower Extremity Activity Scale (LEAS), which measures physical function, were administered to cognitively intact patients \geq age 65 with no active cancer, 2-4 days after surgical repair of hip fracture. Patients were specifically instructed to answer based on their pre-fracture status. Patients were contacted at 4 weeks, 3 months, and 1 year after surgery. The LSNS-18, PROMIS-29, and LEAS were re-administered at 1 year. Data were analyzed using t-tests, chi-square tests, Wilcoxon rank-sum tests and Spearman correlations.

Results: 203 patients enrolled: 71.9% female, 91.6% white, 78.7% college educated, with a median age of 81.8 [74.1, 87.3] years. 36% were socially isolated. Of the 9 known deaths within 1 year, 6/9 (67%) were socially isolated, a much higher percentage than the overall cohort, though not statistically significant ($p = 0.095$).

73/99 (74%) of subjects who were 1-year post-fracture repair completed 1-year questionnaires (20 withdrew consent/were lost to follow-up, and 6 were mentally/physically unable to participate). There was no statistically significant difference in number of adverse events/severe adverse events between socially isolated and non-socially isolated subjects. There was also no difference in LEAS score or any PROMIS-29 domain between isolated and non-isolated subjects 1 year after surgery. However, socially isolated patients were more likely to improve their LSNS-18 score than those who were not socially isolated prior to fracture repair ($\Delta 6.1 \pm 13.3$ vs. $\Delta -1.2 \pm 13.7$; $p = 0.03$).

Conclusion: There is a trend suggesting social isolation may be associated with 1-year mortality in cognitively intact elderly patients undergoing surgical repair of low energy hip fracture. Although there was no association between pre-fracture social isolation and adverse events or self-reported patient reported outcomes, on average socially isolated patients were less isolated 1 year after fracture repair than pre-fracture. Whether the magnitude of improvement in social isolation is associated with improved health status will be evaluated as this study continues to recruit.

Disclosure: L. A. Mandl, None; S. Lian, None; J. Szymonifka, None; K. Grueter, None; A. Hadad, None; J. Lane, None.

Abstract Number: 2327

To Screen or Not to Screen? DEXA Ordering Patterns in SLE Patients Who Take Systemic Glucocorticoids

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Background/Purpose: : High doses of glucocorticoids (GC) are often used in the treatment of Systemic Lupus Erythematosus (SLE), however, studies suggest that SLE patients do not receive adequate screening for glucocorticoid induced osteoporosis (GIOP).

The purpose of our study was to evaluate providers' decisions to order DEXA screening in SLE patients who receive high doses of glucocorticoids for 3 months or longer, in a pragmatic clinical setting

Methods: We conducted a retrospective cohort study using a large healthcare system clinical database from the years 2011 to 2016. SLE cases with long-term prednisone use (≥ 3 months) at doses of at least 7.51 mg daily were identified via database search and manually reviewed by two clinicians for accuracy. Osteoporosis risk factors were assessed retrospectively via chart review. Fracture Risk Assessment (FRAX[®]) score was estimated for patients older than 40 years based on chart review. GIOP screening practices were compared with the 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis as the gold standard. A classification tree was used to identify the key patient-related factors that discriminate screening.

Results: 203 SLE patients met inclusion criteria, with 240 total episodes of high dose glucocorticoid usage for ≥ 3 months. 130 patients were 40 years of age or older. Of the patients younger than 40 years, 69 (95%) were female, their median daily dose of prednisone was 15 [10-20.9] mg/day, and the median duration of prednisone usage was 219 [150-409] days. Among those 40 years and older, 105 (81%) were female, their median daily dose of prednisone was 12.5 [10-18.9] mg/day, and the median duration of prednisone usage was 252 [165-518] days. In the younger age group, 27% of patients had DEXA scans ordered vs 8% deemed appropriate per ACR guidelines. Of patients 40 years and older, 63% underwent DEXA scans, versus 100% recommended by ACR guidelines. In a classification tree analysis, DEXA screening was most likely to be ordered for women, those with an estimated FRAX score greater than 9.95, prednisone use duration of 17 months or longer, and a medication count greater than 10.

Conclusion: Among SLE patients on high dose GC therapy, those younger than 40 had more DEXA scans than deemed appropriate per ACR guidelines, while older patients had fewer. Female sex, higher estimated fracture risk, longer prednisone use, and a higher medication count were key patient-related factors associated with providers' decisions to order DEXA.

Disclosure: S. Baig, None; S. Sapkota, None; A. K. Shmagel, None; P. Fazeli, None; J. Menk, None; A. M. O'Connell, None.

Abstract Number: 2328

Current Factors Associated with Insufficient Vitamin D Status in Patients with Osteoporosis

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Background/Purpose: In 2010, the Canadian Osteoporosis guidelines recommended that patients with osteoporosis be supplemented with vitamin D and to achieve serum levels ≥ 75 nmol/L. Past studies, most of which were completed before these guidelines could be implemented, showed that there is a large proportion of patients whose levels are below this target. For this reason, we aimed to assess the current uptake of these guidelines in osteoporosis patients by: 1) Determining the current prevalence of patients who are vitamin D-sufficient (≥ 75 nmol/L); 2) Assessing factors associated with vitamin D insufficiency; and 3) Identifying groups of patients who are not on vitamin D supplementation.

Methods: We retrospectively reviewed charts of patients referred to a single osteoporosis clinic in Hamilton, Canada, seen between April and October 2017. Inclusion criteria were a lumbar spine or femoral neck T-score ≤ -2.5 or a major fragility fracture, and age above 18 years. Data from the initial consultation appointment was extracted. We also collected absolute vitamin D levels and determined vitamin D insufficiency (< 75 nmol/L) as well as its prevalence. Further, we determined the effects of age, sex, vitamin D intake, BMI, eGFR, fracture history, and PPI use on vitamin D sufficiency and supplementation rates and investigated their role on PTH, calcium levels, fracture prevalence, and BMD. Where appropriate, we completed a Pearson's chi-squared analysis or a Pearson correlation analysis.

Results: Charts were reviewed from 180 patients, mean age 65.8 years (SD 11.9) 78.3% (141/180) female, 82.2% (148/180) reported taking vitamin D supplements. The average vitamin D level was 93.7nmol/L (SD 34.1) and 75% (135/180) were vitamin D-sufficient. We found that patients with vitamin D insufficiency were significantly older (69.2 vs 64.6 years, $r=0.169$, $p=0.023$) with no effect on other bone parameters. We also found that vitamin D-insufficient patients had a significantly lower eGFR (69.6 vs 78.3mmol/L, $r=0.210$, $P=0.005$), which was inversely correlated with PTH level ($r=-0.229$, $p=0.002$). Lastly, we found a difference in sex and vitamin D supplementation rates, as males were less likely to be on vitamin D supplementation (57.9% vs. 91.3%, $X^2=24.86$, $p<0.001$). Other bone parameters were not significantly affected.

Conclusion: In our retrospective analysis, we found that currently, there is strong adherence to the Canadian guidelines for vitamin D status in patients with osteoporosis in Hamilton, Ontario. However, we identified that there continues to be a care gap for patients who are older, male, or have a lower eGFR with regards to their vitamin D status, which are factors that we recommend for practitioners to follow more closely.

Disclosure: S. Dhillon, None; A. Alam, None; M. Wong-Pack, None; A. Lau, AbbVie Inc., 8, 9, Amgen Inc., 8, 9, BMS, 8, 9, Celgene Corporation, 8, 9, Eli Lilly and Co., 8, 9, Merck & Co., 8, 9, Novartis, 8, 9, Janssen, 8, 9, Pfizer, Inc., 8, 9, Roche, 8, 9, Sanofi, 8, 9, Genzyme, 8, 9, UCB, Inc., 8, 9; K. A. Beattie, None; J. D. Adachi, Amgen Inc., 2, 5, 8, McMaster University, 3.

Abstract Number: 2329

Carotid Atherosclerosis Is Associated with Compromised Volumetric Bone Mineral Density and Microarchitecture in Patients with Inflammatory Arthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Inflammatory arthritis patients had increased risk of atherosclerosis and osteoporosis. The association between presence of carotid plaque and volumetric BMD (vBMD)/microarchitecture is yet to be explored. The aim of this study was to explore the relationship between volumetric bone mineral density (vBMD)/microstructural features and presence of carotid plaque (CP) in patients with inflammatory arthritis.

Methods: 175 inflammatory arthritis patients (81 [46%] PsA, 94 [54%] RA; 70 [40%] males; age: 53 ± 12 years) were recruited into an ongoing prospective study assessing the relationship between inflammation, osteoporosis and carotid atherosclerosis. Carotid plaque and intima-media thickness (IMT) were measured by carotid ultrasound. Areal BMD (aBMD) was measured by dual energy X-ray absorptiometry (DXA). Microarchitecture features and vBMD of distal radius were measured using high-resolution peripheral quantitative computed tomography (HR-pQCT).

Results: No patients had established cardiovascular disease (CVD). Data from 172 patients at baseline were analyzed for this cross-sectional study. Patients were sub grouped according to the presence or absence of carotid plaque (CP+ group, n=68 [40%]) and CP- group, n=132 [60%]). CP+ group were older (59 ± 10 vs 49 ± 11 , $p < 0.001$), more likely to be male (54% vs 31%, $p = 0.002$), had higher systolic blood pressure (130 ± 19 vs 124 ± 17 mmHg, $p = 0.034$) and CVD risk (15.7 ± 14.2 vs 7.9 ± 8.6 , $p < 0.001$) according to the Framingham Risk Score (FRS) then the CP- group. aBMD, vBMD and microarchitecture were significantly compromised in the CP+ group. Distal radius aBMD, distal radius total vBMD, trabecular (Tb) vBMD, Tb thickness, cortical (Ct.) vBMD, Ct. thickness and bone volume fraction were 5% ($p = 0.004$), 12% ($p < 0.001$), 8% ($p = 0.007$), 8% ($p = 0.004$), 4% ($p = 0.007$), 10% ($p = 0.001$) and 8% ($p = 0.007$) lower in the CP+ group. The differences remained significant after adjustment for gender, disease type and FRS (Table 1).

Conclusion: Inflammatory arthritis patients with carotid plaque had lower aBMD, vBMD and compromised bone microarchitecture in the distal radius even after adjustment for gender, disease type and FRS, suggesting that inflammation may be the common link for both conditions.

Table – Distal radius vBMD/microarchitecture and presence of plaque

	Carotid plaque						p value	Adjusted p value*
	No (n=104)			Yes (n=68)				
Total radius								
aBMD, g/cm ²	.575	±	.087	.547	±	.091	0.095	0.004
Distal radius								
Total vBMD, mmHA/cm ³	353.8	±	77.8	315.3	±	69.7	0.001	<0.001
Trabecular BMD, mmHA/cm ³	141.5	±	46.2	131.4	±	38.8	0.138	0.007
Bone volume fraction	.118	±	.039	.110	±	.032	0.142	0.007
Trabecular thickness, mm	.077	±	.017	.071	±	.013	0.019	0.004
Cortical vBMD, mmHA/cm ³	902.6	±	58.0	870.0	±	63.5	0.001	0.007
Cortical Thickness, mm	.882	±	.177	.792	±	.211	0.009	0.001

* Adjusted for gender, disease type and Framingham Risk Score

Disclosure: I. T. Cheng, None; Q. Shang, None; E. K. M. Li, None; P. Wong, None; E. W. Kun, None; M. Li, None; T. K. Li, None; T. Y. Zhu, None; P. A. Lee, None; L. Qin, None; L. S. Tam, None.

Abstract Number: 2330

Vitamin D and Bisphosphonate Therapy in SLE Patients Who Receive Glucocorticoids: Are We Offering the Best Care?

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Glucocorticoids(GC) are frequently used for the treatment of systemic lupus erythematosus (SLE), and glucocorticoid induced osteoporosis (GIOP) is a well-known complication of long term glucocorticoid therapy. American College of Rheumatology (ACR) guidelines recommend vitamin D supplementation for all patients on long term GC, and bisphosphonate therapy - for patients with moderate to high risk of osteoporotic fracture. We aimed to evaluate physicians' decisions to prescribe vitamin D and bisphosphonates to SLE patients receiving long-term high dose GC, and compare them with the 2017 ACR GIOP guidelines.

Methods: A retrospective cohort of SLE patients who had received care within a large healthcare system in Minnesota between 2011 to 2016 was identified from electronic medical records. Patients receiving prednisone doses of 7.5 mg or higher for at least 90 days were included in the analysis. Demographic data, duration and dosage of GC use, weight, height, previous history of fracture, family history of osteoporosis, smoking and alcohol use were ascertained from medical records, as well as use of vitamin D supplements and bisphosphonates within 6 months of starting high-dose GC therapy. Contraindications to bisphosphonates were also reviewed. Fracture Risk Assessment (FRAX) score was estimated for patients older than 40 years based on chart review. Two clinicians ascertained indication for bisphosphonate through chart review using the 2017 ACR guidelines as a gold standard. A classification tree was used to identify factors that discriminate prescribing bisphosphonates for those 40 and older.

Results: 203 SLE patients met inclusion criteria. Of those, 130 patients were aged 40 years or older. Vitamin D supplement was prescribed to 83% of patients, however, 8.4% were prescribed less than 800 Units per day. Serum vitamin D levels were checked in 30% of patients during high-dose GC therapy, and on average were vitamin D insufficient (median serum vitamin D level 25 [18.5, 30.0]). Thirty-three patients were prescribed a bisphosphonate within 6 months of starting high-dose GC, 32 of them were older than 40. In the older age group, where recommendations for bisphosphonate therapy are available, 25% were prescribed bisphosphonate therapy, compared with 36% who met indications for bisphosphonates per ACR guidelines. A single node was identified in the classification tree. Patients with FRAX scores (for major osteoporotic fracture) of 23.5 or greater were more likely to be prescribed bisphosphonates.

Conclusion: Both vitamin D supplements and bisphosphonates were under prescribed to SLE patients at risk for osteoporotic fracture. Patients were most likely to receive a bisphosphonate prescription if they had a major osteoporotic fracture risk of over 23.5% in 10 years.

Disclosure: S. Sapkota, None; S. Baig, None; T. Hess, None; A. M. O'Connell, None; J. Menk, None; P. Fazeli, None; A. K. Shmagel, None.

Abstract Number: 2331

Obesity Might Positively Affect TNF Mediated Bone Metabolism in RA Patients

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Session Information

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Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

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Session Time: 9:00AM-11:00AM

Background/Purpose: In this study, we tried to find out the effect of obesity on bone metabolism after one year of anti-TNF agent use.

Methods: Thirty-two seropositive RA patients were enrolled. They had been refractory to antirheumatic drugs and anti TNF therapies including etanercept, adalimumab and infliximab were administrated for one year. Etanercept, adalimumab and infliximab at approved dose were given to 11, 13 and 8 patients, respectively. Body mass index (BMI) was calculated according to patient's weight and height at baseline. BMI 25Kg/m² was considered to be obese. Bone mineral densities (BMD) were measured at baseline and one year after treatment. Blood sampling was done at baseline, 6 months and 1 year after the treatment. Peripheral blood mononuclear cells were cultured and number of osteoclasts was counted. Bone turnover markers including c-terminal telopeptide (CTX), bone specific alkaline phosphatase (BSALP) were measured using enzyme linked immunosorbent assay. In addition, RA disease activity including DAS28 was assessed along with serum level of IL-6.

Results: After 1 year of anti-TNF treatment, bone mineral density (BMD) in non-obese patients worsened although BMD remained still in obese patients (Table 1). Bone resorption pits by cultured osteoclasts from non-obese patients showed marked reduction at 6 months but seemed to increase at 12 months of treatment despite number of the osteoclasts were continuously decreasing. On the contrary, obese patients failed to show significant change in number of osteoclasts after the treatment but resorption pits by the osteoclasts seemed to decrease in trend. DAS28 improved in both non-obese and obese RA patients and significant reduction of serum IL-6 was noted in non-obese patients (Table 2).

Conclusion: One year treatment of anti-TNF agent did not change BMD in obese RA patients although there was a significant reduction in BMD in non-obese patients. Number of osteoclasts from non-obese patients decreased after treatment but the function of osteoclasts reflected as bone resorption pit did not respond to the treatment. Despite no change in number of osteoclasts from obese patients after treatment, function of osteoclasts from obese patients seemed to improve, resulting in no change in BMD. Therefore, we believe obesity might positively affect TNF mediated bone metabolism in RA patients.

Table 1. systemic osteoclastogenesis, bone turnover markers and BMD in RA patients after one year of anti-TNF use

	Non-Obese RA patients (n=24)			Obese RA patients (n=8)		
	at Baseline	at 6 months	at 12 months	at Baseline	at 6 months	at 12 months
BMD at L-spine (g/cm ²)	1.076 ± 0.034	—	1.000 ± 0.025*	1.31 ± 0.057	—	1.32 ± 0.101
BMD at femur (g/cm ²)	0.825 ± 0.092	—	0.787 ± 0.097*	1.014 ± 0.158	—	0.993 ± 0.187
BMD at total hip (g/cm ²)	0.873 ± 0.112	—	0.845 ± 0.125*	1.129 ± 0.175	—	1.105 ± 0.160
CTN (ng/mL)	0.53 ± 0.33	0.50 ± 0.28	0.46 ± 0.2	0.68 ± 0.01	0.9 ± 0.78*	0.43 ± 0.16
BSALP (U/L)	23.38 ± 9.32	28.19 ± 7.83	24.82 ± 7.54*	24.54 ± 8.72	27.56 ± 9.72	27.75 ± 6.97
Number of osteoclasts cultured (/well)	467 ± 292.1	360 ± 143.5*	279 ± 202.5*	409 ± 243.5	392 ± 237.2	454 ± 188.3
Bone resorption pit by osteoclasts cultured (n/well)	173.3 ± 102.35	97 ± 91.88*	165.1 ± 107.04	200.3 ± 83.05	138.1 ± 72.38*	121 ± 104.72

*denotes $p < 0.05$, at Baseline vs. at 6 months or at 12 months.

Table 2. Systemic inflammation and RA disease activity

	Non-Obese RA patients (n=24)			Obese RA patients (n=8)		
	at Baseline	at 6 months	at 12 months	at Baseline	at 6 months	at 12 months
IL-6 (pg/mL)	26.17 ± 31.21	17.13 ± 30.79	4 ± 5.31*	16.68 ± 32.53	3.08 ± 5.49	7.59 ± 11.38
DAS28-ESR	6.69 ± 0.83	4.53 ± 1.44**	3.51 ± 0.91**	6.18 ± 0.79	4.38 ± 1.24*	3.11 ± 1.21*
DAS28-CRP	6.29 ± 0.72	4.13 ± 1.15**	3.23 ± 0.62**	5.77 ± 0.81	3.91 ± 0.93*	3.11 ± 0.57**

*denotes $p < 0.05$, at Baseline vs. at 6 months or at 12 months

**denotes $p < 0.01$, at baseline vs. at 6 months or at 12 months

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Abstract Number: 2332

Rheumatoid Arthritis Effect's on Bone Mass and Muscle

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

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Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is a progressive auto-immune disease characterized by chronic inflammation which leads to joint deformity and disability. However, the bone and muscle are also affected. The aim of this study was to evaluate the total bone mineral density (tBMD) and total lean mass in rheumatoid arthritis patients.

Methods: A total of 50 adult's women with RA and a control group (CG, n=34) matched by sex, age and body mass index (BMI) were included. All patients had more than 18 years and were from Rosario city (32°52'18''S), Argentina. Exclusion criteria: pregnancy, intestinal malabsorption, chronic liver or kidney disease, cancer and drug which could affected the bone mass except glucocorticoids. The whole body composition was performed by Dual X-Ray Absorptiometry (DXA) (Hologic discovery Wi). The muscle strength was evaluated by handgrip strength (Baseline Hydraulic Hand Dynamometer, USA) and the physical performance by sit to stand test and timed up and go test. Data are expressed as mean±SD. Differences between groups were analyzed using the Student t test or Mann-Whitney test as appropriate. Correlations were performed with Pearson or Spearman's correlation test. Contingency tables were evaluated with χ^2 test. The difference was considered significant if $p < 0.05$.

Results: No differences in age (CG: 55.1±12.7 y, RA: 53.5±11.7 y), BMI (CG: 26.0±5.1, RA: 27.8±4.6) and percentage of pre and postmenopausal women were included. According to BMI no differences in total mass by DXA were observed (CG: 66.9±13.1 kg, RA: 68.0±13.1 kg). The total bone mineral content (tBMC) and tBMD were found decreased in RA patients (tBMC= CG: 2111±319 g, RA: 1874±343 g, $p=0.0036$; tBMD= CG: 1.072±0.094 g/cm², RA: 1.016±0.109 g/cm², $p=0.0255$). Furthermore, a tendency to low lean mass in RA patients were observed (CG: 57.3±5.2, RA: 55.7±5.3, $p=0.06$). The muscular involvement was confirmed in muscle strength and physical performance tests. The RA group had significantly lower handgrip strength (CG: 21.4±4.9 kg, RA: 12.3±6.7, $p<0.0001$), lower performance in the sit to stand test (CG: 14.7±4.5 s, RA: 17.9±5.7 s, $p=0.0126$) and timed up and go test (CG: 8.8±1.9 s, RA: 11.6±3.7, $p=0.0003$). A significant correlation between tBMD and total lean mass were found ($r: 0.3$, $p=0.0128$). In addition, significant correlation between regional BMD (left arm, right arm, left leg and right leg) and the lean mass of each region were observed. Therefore the loss of lean mass could explain the loss of bone mass. On the other hand, higher percentage of fat was found in RA patients (CG: 39.4±5.7, RA: 41.9±5.7, $p=0.06$).

Conclusion: the disease activity could affect not only the joint and bone mass, but also the muscle which contributes to bone loss and lead to osteopenia and osteoporosis in RA patients.

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Abstract Number: 2333

High Serum Uric Acid Protects Against Osteoporosis in Postmenopausal Women: Data from the Korean National Health and Nutrition Examination Survey

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Session Information

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Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

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Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoporosis is one of the most common morbidities in postmenopausal women. Although serum uric acid (SUA) accounts for about 50% of extracellular antioxidant activity, the role of hyperuricemia in osteoporosis, a condition characterized by high oxidative stress level, has not been investigated in a Nation-wide scale. The aim of this study is to evaluate an association between SUA and incidence of osteoporosis in postmenopausal women.

Methods: Data of postmenopausal women from the 2016 Korean National Health and Nutrition Examination Survey were included and retrospectively analyzed. Weighted prevalence and logistic regression analysis were used to determine the incidence of osteoporosis and the effect of SUA on osteoporosis in postmenopausal women.

Results: One-thousand three-hundred eighty-two (weighted $n = 7,064,137$) of postmenopausal women were observed. Of these, 401 (29.0 %, weighted $n = 1,880,586$) women developed osteoporosis. Mean age of participants was 63.2 years and mean of SUA was 4.4 mg/dL. The effect of SUA on osteoporosis in postmenopausal women was not statistically significant according to univariable logistic regression (OR 0.977, 95 % CI 0.855-1.116, $p = 0.729$). However, SUA was negatively associated with incidence of osteoporosis in postmenopausal women with statistical significance after adjusting for age, obesity, amount of drink, smoking, intake of calcium, rheumatoid arthritis, thyroid diseases, and loss of activity (OR 0.867, 95 % CI 0.752-0.999, $p = 0.048$).

Conclusion: Our data demonstrated that high SUA is associated with lower incidence of osteoporosis in postmenopausal women. This result suggests a protective role of SUA in metabolic bone diseases.

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Abstract Number: 2334

General Bone Loss in Patients with Erosive and Non-Erosive Hand Osteoarthritis. a Two-Year Longitudinal Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

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Background/Purpose: Hand osteoarthritis (OA) and its more severe subset erosive hand OA are common causes of pain and morbidity. Some metabolic factors were suggested to be implicated in erosive disease. Few studies investigated differences in systemic bone loss between erosive and non-erosive hand OA.

Methods: Consecutive patients with symptomatic HOA fulfilling the American College of Rheumatology (ACR) criteria were included in this study. Erosive hand OA was defined by at least one erosive interphalangeal joint. All patients underwent clinical assessments of joint swelling and radiographs of both hands. DEXA examination of lumbar spine, total femur and femur neck was performed at the baseline and after two years.

Results: Altogether, 144 patients (15 male) with symptomatic nodal HOA were included in this study and followed between April 2012 and January 2018. Out of these patients, 82 had erosive disease after two years. The disease duration ($p < 0.01$) was significantly higher in patients with erosive compared with non-erosive disease at baseline. Osteoporosis (T-score < -2.5 SD) was diagnosed in 12.5% (9/72) of patients with erosive hand OA and in 8.06% (5/57) of patients with non-erosive hand OA. BMD was significantly lowered in patients with erosive compared with non-erosive disease at baseline (lumbar spine: 1.05g/cm² vs. 1.13 g/cm², $p < 0.05$, total femur: 0.90 g/cm² vs. 0.97 g/cm², $p < 0.01$ and femur neck: 0.86 g/cm² vs. 0.91, $p < 0.05$). T-scores of lumbar spine (-0.96 vs. -0.41 SD, $p < 0.05$), total femur (-0.69 vs. -0.33 SD, $p < 0.05$) and femur neck (-1.14 vs. -0.88 SD, $p < 0.05$) were also significantly lowered in patients with erosive compared with non-erosive disease. Furthermore, we found significant decrease in BMD in patients with erosive compared with non-erosive disease over two years (lumbar spine: -3.30% vs. 1.06%, $p < 0.05$, total femur (-1.58% vs. 0.82%, $p < 0.05$) and femur neck (-3.2% vs. 0.02%, $p < 0.05$). The decrease in T-score of lumbar spine (-3.66% vs. 15.52%, $p < 0.01$) and total femur (-4.29% vs. 7.68%, $p < 0.05$) was also significantly higher in erosive compared with non-erosive hand OA.

Conclusion: These results suggest that patients with erosive hand OA are at higher risk for the development of general bone loss.

Disclosure:

O. Ruzickova, None; O. Sleglova, None; K. Pavelka, None; L. Šenolt, None. :

Abstract Number: 2335

Osteoporotic Fracture Trends in a Population of US Managed Care Enrollees: 2007-2017

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Session Information

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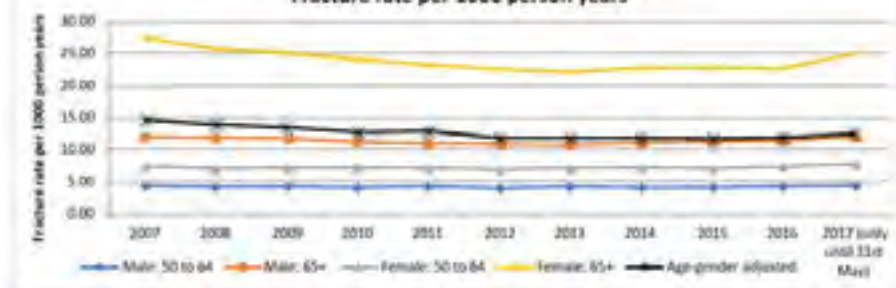
Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoporosis-related fractures (fractures) are a leading cause of morbidity and disability in the US. Epidemiological data on the occurrence of fractures are limited and required to inform healthcare providers, payers, and policymakers on the scope of this disease. The objective of this analysis was to assess the incidence of fractures in a population of managed care enrollees over the past decade.

Methods: The study included commercial and Medicare Advantage health plan members who had evidence of a qualifying fracture between Jan 2007 and May 2017 (identification period). Fractures were considered qualifying if they were either identified during an inpatient stay or were identified in an outpatient setting based on primary or secondary ICD-9 or ICD-10 accompanied by a repair procedure code. Patients ≥ 50 years of age with evidence of a qualifying fracture were included. The denominator population comprised members who were ≥ 50 years of age during the year of interest. The number of days the member was enrolled in the health plan during the year was calculated and was used to determine the total person-years (py) of enrollment for the denominator. Incidence rate is reported as number of events per 1000 py of enrollment during each year from 2007-May 2017. Rates are presented stratified by age category (50-64 vs ≥ 65) and gender (male vs. female). Patients were categorized by 5-year age increments and gender, and an overall age-gender adjusted rate was calculated.

Results: Of 1,841,263 members with fractures in the identification period, 513,176 met the eligibility criteria. The overall age-gender adjusted rate fell from 14.67/1000 py in 2007 to 11.80/1000 py in 2012, and then did not decrease from 2013-May 2017. Among females ≥ 65 years old the incidence of fractures declined from 27.49/1000 py in 2007 to 22.08/1000 py in 2013, and then did not decrease from 2014-May 2017. Similarly, among males ≥ 65 years old incidence decreased from 12.00/1000 py in 2007 to 10.72/1000 py in 2013 and then did not decrease from 2014-May 2017. For males and females ages 50-64 the rates were consistent across years, approximately 4.2 and 7.2 fractures per 1000 py, respectively.

Figure. Incidence of Osteoporotic Fractures Per 1000 Person Years: 2007-May 2017
Fracture rate per 1000 person years



Conclusion: The current study findings suggest fracture incidence has remained the same and potentially rising since 2014. The current study results may reflect insufficient diagnosis and treatment of osteoporosis and support the call to action to increase diagnosis and treatment of osteoporosis especially in older adults.

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Abstract Number: 2336

Identification of Osteoporosis As a Reason for Vertebral Fractures in Patients with Rheumatoid Arthritis and Non-Inflammatory Musculoskeletal Diseases – a Comparison between Trabecular Bone Score (TBS) and Bone Mineral Density (BMD)

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Identification of osteoporosis as a reason for vertebral fractures in patients with rheumatoid arthritis and non-inflammatory musculoskeletal diseases – A comparison between trabecular bone score (TBS) and bone mineral density (BMD)

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Background/Purpose: Osteoporosis-related fractures are common in patients with rheumatoid arthritis (RA). Measurement of bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) alone does not adequately predict fracture risk. Trabecular bone score (TBS) is a surrogate marker for trabecular microarchitecture which independently predicts fracture risk. In this study we assessed the prevalence of low BMD, low TBS and osteoporotic related vertebral fractures in patients with RA in comparison to controls with non-inflammatory musculoskeletal diseases.

Methods: In retrospective study design, we analyzed the data of all patients with available TBS and DXA data presenting to our hospital in the last 5 years. All diagnoses were made by rheumatologists. Comparisons between groups were made by Mann-Whitney-Test and Wilcoxon-Test where appropriate, after adjustment for age, cortisone intake and body mass index.

RA-Patients		TBS	
		low	normal
DXA	low	45 (86,5 %)	2 (3,8 %)
	normal	17 (32,7 %)	2 (3,8 %)

Controls		TBS	
		low	normal
DXA	low	23 (95,8 %)	0 (0,0 %)
	normal	5 (20,8 %)	1 (4,2 %)

Results: There were 143 patients with RA (mean age 72.1 ± 11.1 years, 72% female) and 106 controls (mean age 69.6 ± 12.6 years, 74.5% female). Vertebral fractures were found in 36.4% (n=52) RA patients and in 22.6% (n=24) controls (p=0.02). Overall, there were no differences in the mean DXA BMD (for both, spine and hips) and the mean TBS values in all patients. On the other hand, there were statistically more RA patients with low BMD (n=102; 71.3%) and TBS scores (n=125; 87.4%) than controls (n=61; 57.5% and n=79; 74.5%, respectively, p=0.009). In addition, in patients with a vertebral fracture, a low TBS with a normal DXA was more frequently observed in both groups (numerically higher in RA than in controls), while low BMD with a normal TBS was rare (Table). This was not the case in patients without a vertebral fracture.

Conclusion: Low TBS in the setting of normal BMD was found more frequently in patients with vertebral fractures, especially in patients with RA, whereas the reverse is rare. This suggests TBS might prove to be a useful tool for identification of deteriorated bone microarchitecture and strength in patients with vertebral fracture with normal BMD.

Table: Prevalence of low and normal BMD and TBS results in patients with incident vertebral fractures

Disclosure: B. Buehring, None; X. Baraliakos, AbbVie, BMS, Celgene, Chugai, Merck, Novartis, Pfizer, UCB, and Werfen, 2, AbbVie, BMS, Celgene, Chugai, Merck, Novartis, Pfizer, UCB, and Werfen, 5, AbbVie, BMS, Celgene, Chugai, Merck, Novartis, Pfizer, UCB, and Werfen, 8; J. Thomas, None; J. Braun, Abbvie (Abbott), Amgen, BMS, Boehringer, Celgene, Celltrion, Centocor, Chugai, EBEWE Pharma, Medac, MSD (Schering-Plough), Mundipharma, Novartis, Pfizer (Wyeth), Roche, Sanofi-Aventis and UCB, 2, 5.

Abstract Number: 2337

Vertebral Compression Fractures and Antibodies to Citrullinated Vimentin in Established Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with RA have high rates of osteoporosis and fractures and RA induces articular and extra-articular bone loss. Seropositivity for any CCP antibody is associated with risk of erosions and osteoporosis. In vitro, human antibodies against citrullinated vimentin bind osteoclast cell surfaces, activate their bone resorptive activity and in an animal model, induce bone loss. In humans, it is not known whether these antibodies are a specific risk factor for osteoporosis. The aim of this study was to assess the prevalence of radiographic vertebral compression fractures (VCF), as a marker of skeletal fragility, in an established RA cohort and whether the presence of antibodies to citrullinated vimentin were associated with this.

Methods: Data was obtained from a prospective established RA cohort (ACR/EULAR 2010 or ACR 1987 criteria) undergoing elective arthroplasty. VCF were identified on the lateral pre-operative chest radiograph by two independent readers utilizing the Genant semi-quantitative method. Antibodies to citrullinated vimentin epitopes were measured by mean fluorescence intensity utilizing a custom, bead-based, antigen array comprising CCP and RA-associated citrullinated antigens. To identify risk factors predictive of vertebral compression, univariate logistic regression analysis was performed including known potential risk factors for bone loss in RA.

Table 1: Distribution and grade of vertebral compression fractures as scored by the Genant semi-quantitative method

	No vertebral compression (n=105)	Vertebral compression (n=75)		
		Grade 1 (n=59)	Grade 2 (n=15)	Grade 3 (n=2)
Male	19	13	4	1
Female	86	46	11	1

Table 2: Univariate logistic regression of risk factors for vertebral fracture

Univariate models	Odds ratio (95% CI) for fracture grade 1, 2 or 3	p-value
Age, per 5 years	1.19 (1.04 - 1.38)	0.014
Sex		
Female	0.71 (0.34 - 1.47)	0.389
Male	1.00 (reference)	—
Race		
White	1.32 (0.68 - 2.56)	0.406
Asian	0.92 (0.15 - 5.64)	0.929
Black or African American	0.79 (0.18 - 2.00)	0.396
BMI, per 1 kg/m ²	0.98 (0.93 - 1.03)	0.408
CCP raw value, per 10 units	1.00 (0.99 - 1.01)	0.954
RE raw value, per 10 units	1.00 (0.99 - 1.01)	0.448
DAS28-ESR	0.92 (0.70 - 1.21)	0.566
CDAI	1.01 (0.98 - 1.04)	0.621
Disease duration	0.99 (0.96 - 1.02)	0.419
Symptom duration	0.98 (0.96 - 1.01)	0.243
Current steroid use	0.87 (0.31 - 1.87)	0.808
Prior steroid use	0.80 (0.28 - 1.20)	0.189
Current MTX/DMSARD use	1.15 (0.59 - 2.26)	0.681
Current biologic use	1.25 (0.65 - 2.36)	0.462
Current or former smoker	1.27 (0.66 - 2.44)	0.486
Current alcohol use	1.42 (0.74 - 2.71)	0.289
Prior diagnosis of osteoporosis or current medical therapy for osteoporosis	1.40 (0.17 - 7.12)	0.857
Family history of hip fracture	0.66 (0.26 - 1.77)	0.405
Vimentin 56-77 cit3 cyclic smab-I, IgG	0.82 (0.70 - 1.21)	0.504
Vimentin 56-77 cit3 cyclic smab-I, IgM	0.94 (0.61 - 1.09)	0.417
Vimentin 56-77 cit3 cyclic smab-I, IgE	0.49 (0.22 - 1.08)	0.075

Results: 181 participants had an available chest radiograph. Median age was 65 years [IQR 56, 71] and median disease duration 11 years [IQR 3, 20]. 80% were female, 37% were on current glucocorticoid therapy and 21% had prior exposure. Only 3% self-reported a diagnosis of osteoporosis or use of osteoporosis medications. Despite these numbers, almost half, 76/181 (42%) [58 female] had radiographic VCF (Table 1). Participants with VCF were older [median age 68 years vs. 64 years, $p=0.03$]. In univariate analysis of potential risk factors, only age was associated with VCF (Table 2). No significant differences were seen in antibody levels, including antibody isotypes to citrullinated vimentin.

Conclusion: Vertebral compression fractures were prevalent in patients in this established RA cohort. The strongest risk factor for VCF was age. Antibodies to citrullinated vimentin, implicated in early RA models, were not associated with VCF. Our results highlight the profound detrimental skeletal effects of RA. Further studies are needed to investigate the mechanisms of focal versus generalized bone loss, as well as skeletal changes that occur with RA progression.

Disclosure: J. Cheah, None; J. A. Carrino, None; W. H. Robinson, None; D. Orange, None; J. Szymonifka, None; E. M. Stein, None; S. M. Goodman, Roche, Novartis, 4.

Abstract Number: 2338

Pharmacological and Non-Pharmacological Approaches in a Group of Osteoporotic Patients Referring to a Rehabilitation out-Patient Clinic

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science Poster – ARHP

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Non-pharmacologic treatments are generally kept in the background in management of osteoporosis. The aim of this retrospective study was to evaluate characteristics and frequency of pharmacologic and non-pharmacologic treatments for patients with osteoporosis (OP), in a university hospital, outpatient clinic of Physical Medicine and Rehabilitation, during the last 6 months.

Methods: A hundred and fifty-five OP patients, who were not having any malignancy and/or terminal-term chronic disease, were included to this study. Demographic properties (age, gender, disease duration), clinical characteristics (fracture history, comorbidities, drugs) and treatment approaches for OP (pharmacologic and non-pharmacological) were recorded from files. Descriptive statistics were used for clinical variables and frequency of treatment approaches.

Results: 137 female, 18 male OP patients with a mean age of 66.11 ± 11.21 years, were included to the study. Post-menopausal osteoporosis was present in 130 (83.8%) and secondary OP was determined in 25 (16.2%) of the subjects. The mean duration of OP was 6.95 ± 1.11 years. 24.5% of the patients had at least one porotic fracture. The most frequently causes of secondary OP were drugs (mostly steroids) and comorbid diseases (endocrine diseases, asthma, rheumatic conditions). Pharmacological treatments were prevalent and the most commonly prescribed drugs were denosumab (35.7%), alendronate (22.4%) and ibandronate (10.5%) followed by zoledronic acid (7.7%), teriparatide (2.8%) and risedronate (2.7%). Majority of the patients (68.1%) were concurrently on calcium and/or Vit D therapies. Non-pharmacologic treatments were suggested in 60% of the patients, mostly as exercise (50%), diet (37.5%), lifestyle modifications (28.6%); but only 50% of the subjects were performing regular exercises.

Conclusion: Pharmacologic approaches were common and mostly denosumab and bisphosphonates were the first choices for OP treatment in our study group. Although non-pharmacologic approaches are of great value in OP management (1,2), approximately only half of our patients were prescribed these interventions in our study. We believe that there is an unmet need for non-pharmacologic management in OP. We suggest and emphasize the concurrent recommendations of non-pharmacologic interventions in OP patients, especially in rehabilitation clinics.

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1. Christianson MS, Shen W. Osteoporosis prevention and management: nonpharmacologic and lifestyle options. Clin Obstet Gynecol. 2013 Dec;56(4):703-10
2. Kasturi GC, Adler RA. Osteoporosis: nonpharmacologic management. PM R. 2011 Jun;3(6):562-72.

Disclosure: P. Borman, None; E. G. KOYUNCU, None; A. Yaman, None; M. PARLAK, None.

Abstract Number: 2339

The Patient's Perspective of Glucocorticoid Use: A Systematic Literature Review of Quantitative and Qualitative Studies

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Glucocorticoids (GCs) remain widely used and have well documented adverse effects. However, the impact of these adverse effects from the perspective of the patient, rather than of the clinician, remains relatively unexplored. Additionally, no general patient reported outcome measure has been developed to assess GC adverse effects and impact across rheumatological conditions. The aim of this literature review was to identify the impacts of systemic GC use that are of importance to patients.

Methods: An academic librarian searched OVID EMBASE, OVID MEDLINE, PsycINFO and CINAHL for articles published from inception to October 2017, related to three concepts: GCs, the patient perspective and adverse effects.

Figure: Study selection process

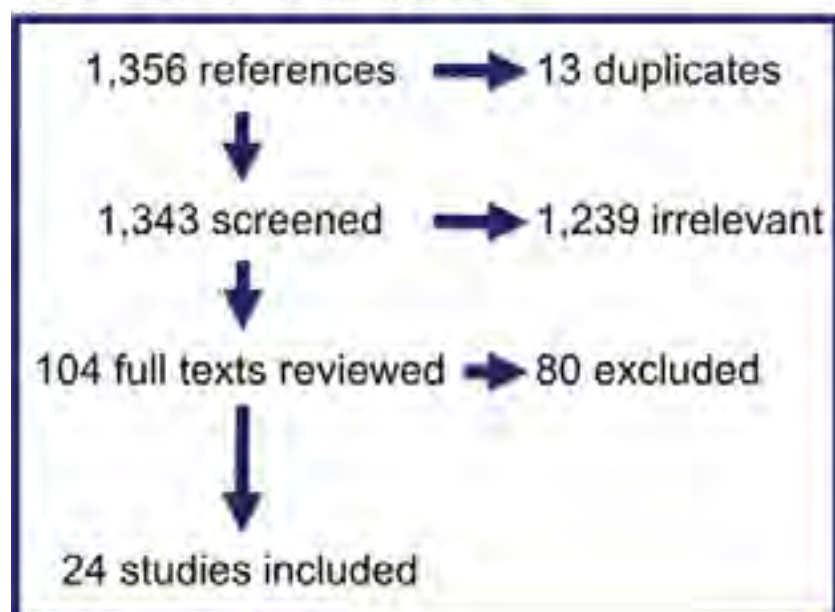


Table: Outcomes with the highest frequency effect size per theme

Theme	Outcome	Frequency effect size (%)
Physical symptoms	Weight gain	74
	Sleep problems	74
	Skin changes	65
	Upper GI problems	65
	Cardiopulmonary	63
Psychological symptoms	Intimacy and mood swings	74
	Depression	43
	Anxiety	35
	Hypersensitivity and asthma	30
	Process of smoking GC use	22
Participation	Impact on sexual relationships	13
	Impact on work	9
	Impact on family	4
Contextual factors	Lack of support of community or media	13
	Self-management and mastery	9
	Lack of support of family and friends	4

Inclusion criteria included systemic GC use for any indication in an adult population and both qualitative and quantitative research methodology. Titles and abstracts were then manually screened by two independent reviewers and subsequent quality assessment and data extraction also completed by two independent reviewers. A meta-synthesis of the qualitative data was performed separately by two independent researchers before qualitative meta-summary was utilized to quantitatively aggregate the findings (combining quantitative and qualitative results), including the derivation of frequency effect sizes to identify those outcomes most prominently featured across all reviewed articles.

Results: The initial search retrieved 1,356 articles, of which 24 (18 quantitative, 6 qualitative) were deemed suitable for quality assessment and data extraction (Figure). Studies included the assessment of GC use across a variety of diseases both rheumatologic (e.g. RA, vasculitis) and non-rheumatologic (including asthma, inflammatory bowel disease and multiple sclerosis). Four major themes emerged amongst the 71 discrete outcomes (Table): physical symptoms (44), psychological symptoms (18), effect on participation (6) and contextual factors (3).

Conclusion: Patients with a broad range of inflammatory diseases and demographic features describe key cross-cutting themes in relation to GCs and their impact on health-related quality of life. This work will inform the development of a core domain set for clinical trials involving GCs and a patient reported outcome to measure the impact of GCs from the patient's perspective.

Disclosure: J. Cheah, None; J. Robson, ChemoCentryx, 5, ABROGATE trial, 6; R. Black, None; S. M. Goodman, Roche, Novartis, 4; S. Lester, None; S. Mackie, PMRGCAuk, 6, PMR and GCA North East, 6, Sanofi, 5, GSK, 5; C. Hill, None.



Table: Description of themes from thematic analysis of interview transcripts

Theme	Key Points with Quotes
Benefits	<p>Pain and swelling</p> <p>'... it does reduce the swelling. And when the swelling is reduced, the joints feel much better.'</p> <p>Return to functional activities</p> <p>'If I can't move my hands, I can't take a shower I can't wash my hair I can't brush my teeth. So how do I get to work? For me that was debilitating... the prednisone allowed me to do that because I would feel the effects within 2-3 days.'</p>
Challenges	<p>Physical (e.g. weight gain and recurrent infections)</p> <p>'I looked like a white whale with a sarpaon in my hip... I looked like Moby Dick.'</p> <p>'I had a respiratory infection a lot I seem subject to those I would get skin infections. I had to be so careful not to break my skin and things.'</p> <p>Emotional (e.g. anger and low mood)</p> <p>'... inside I felt like a terrorist. I really did. I could have killed somebody, I'm not kidding I had a terrible temper.'</p> <p>'My parents... for them to see me unhappy and just not feeling like myself in that way is really hard on them and its hard on me.'</p>
Necessity	<p>Frustration with need</p> <p>'I was angry that I had to take them, I did not want to take them but I had no choice, because they do reduce the inflammation.'</p>
Attribution	<p>Unclear if GCs solely responsible</p> <p>'...when I'm taking all this... it's hard to precisely point to what's working and what's not working what's good what's bad...'</p>

Results: Eleven participants (9 female) were interviewed. All met either the 2010 ACR/EULAR or 1987 ACR classification criteria for RA. Ages ranged from 26-83 years with 8 participants being on GCs at the time of the interview (range 2-20 mg daily of prednisone equivalent). Seven participants had a disease duration >10 years, while 6 had been on chronic GCs for >5 years. The mean RAPID3 score was 9.9 (range 0-19.3). Four themes emerged (Table). Overall, GCs had been beneficial in the control of RA symptoms such as swelling and pain. However, this had 'come at a price', alluding to the unintended impact of GCs, both physical and emotional, such as weight gain and anger. Further important unintended effects included recurrent infections and sweating (Figure). Additionally, there was an acknowledgement of the necessity of GC use in certain contexts due to the need to be able to function for family and work purposes. Finally, there was uncertainty over attribution of potential symptoms solely to GCs or to other DMARDs or to RA itself.

Conclusion: Participants described significant benefits from the use of GCs to control their RA, albeit accompanied by major unintended effects, both physical and emotional, allowing for better understanding of the life impact of chronic GC use in RA. This understanding of the lived experience will be used to design future measurement tools of GC impact in order to better systematically compare GCs to other potential therapeutic options in the research setting.

Disclosure: J. Cheah, None; S. Young, None; S. M. Goodman, Roche, Novartis, 4; C. Hill, None; S. Beard, None; P. Richards, None; S. Mackie, PMRGCAuk, 6, PMR and GCA North East, 6, Sanofi, 5, GSK, 5; J. Robson, ChemoCentryx, 5, ABROGATE trial, 6; I. Navarro-Millán, None.

Abstract Number: 2341

A Link between Quality of Patient–Rheumatologist Communication and Patient Healthcare Needs in Psoriatic Arthritis: An Online Survey of US-Based Patients and Rheumatologists

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Patient (pt)–rheumatologist (rheum) communication may influence symptom reporting and disease control in psoriatic arthritis (PsA). This online survey evaluated pt–rheum communication and assessed PsA symptoms/life impact and satisfaction in pts who reported good/suboptimal communication.

Methods: The survey was conducted in the USA from Nov 2 to Dec 1 2017 (pts) and Dec 11 2017 to Jan 25 2018 (rheums). Eligible pts (≥ 18 years) self-reported having had PsA for >1 year, had visited a rheum or dermatologist in the past year, and reported using ≥ 1 synthetic(s)/biologic(b) DMARD for PsA. Rheums saw ≥ 10 PsA pts/month with $\geq 50\%$ of pts receiving a s/b DMARD. Differences in pt-reported PsA impacts are evaluated by pt–rheum communication status (Table). Analyses are based on descriptive statistics and two-tailed tests for proportions.

Results: In total, 301 pts with PsA responded, mean (SD) age 45 (14.2) years, 61% female, 89% self-reported moderate/severe PsA. 256 pts (85%) were managed by a rheum and are the focus of this analysis. Most pts (93%) and rheums (88%) were satisfied with their current communication. Over 40% of pts reported aspects of suboptimal pt–rheum communication that may impact satisfaction (Table). Overall, 93% of pts were comfortable raising concerns/fears (acknowledged by 94% of rheums) while pts with suboptimal communication were less comfortable doing so (Table). Rheums generally demonstrated good understanding of PsA-related pt worries, and rheums and pts (50% and 52%, respectively) identified ability to perform activities of daily living and/or live independently as a key concern. The negative impact of PsA on physical activity, emotional/mental well-being, work productivity, and romantic relationships/intimacy was considered major/moderate by most rheums (88%, 79%, 75%, 59%, respectively) in alignment with pt reports (80%, 66%, 61%, 55%, respectively). In suboptimal communication pt groups, the impact of PsA on aspects of HRQoL was greater than in good communication groups (Table; $p < 0.05$). Overall, rheums expressed a desire for greater pt understanding of PsA symptoms (86%) and consequences of untreated PsA (88%) and pts expressed a desire to discuss PsA and treatment goals; however, pts with suboptimal communication were less likely to share PsA symptoms with their rheum (Table).

Conclusion: The majority of pts and rheums were satisfied with communication, and rheums were generally aware of pts' worries and impact of PsA on HRQoL. Over 40% of pts reported communication gaps. Pts who reported suboptimal communication were more reluctant to discuss symptoms, ask questions, or share concerns/fears and experienced a greater impact of PsA on HRQoL. Pts reported that rheums did not devote sufficient time to discuss treatment goals. Communication tools may facilitate shared decision-making.

Disclosure: A. M. Orbai, AbbVie, Eli Lilly, Horizon, Janssen, Novartis, 2, Eli Lilly, Novartis, Pfizer Inc, 5; L. C. Coates, AbbVie, Celgene, Janssen, Novartis, Pfizer Inc, 2, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Galapagos, Janssen, MSD, Novartis, Pfizer Inc, Prothena, Sun Pharma, UCB, 5; V. F. Azevedo, AbbVie, Pfizer Inc, 2, AbbVie, Celltrion, Janssen, Novartis, Pfizer Inc, Sandoz, 5, AbbVie, Celltrion, Janssen, Novartis, Pfizer Inc, Sandoz, 8; A. Garg, AbbVie, UCB, 2, AbbVie, Asana Biosciences, Pfizer Inc, UCB, 5; A. Majjhoo, AbbVie, Amgen, Celgene, Crescendo, Eli Lilly, Janssen, Novartis, Pfizer Inc, 5, AbbVie, Amgen, Celgene, Crescendo, Eli Lilly, Janssen, Novartis, Pfizer Inc, 8, Clinical trials work - AbbVie, Amgen, Celgene, Crescendo, Eli Lilly, Janssen, Novartis, Pfizer Inc, 9; C. E. M. Griffiths, AbbVie, Celgene, Eli

	Pts with PsA mostly managed by a rheumatologist (n=256)			
	"I worry that if I ask too many questions my healthcare professional will see me as a difficult pt and it will affect the quality of care I receive"		"I often tell my healthcare professional I am fine when I am really experiencing symptoms"	
	Agree n=105 (41%)	Disagree n=151 (59%)	Agree n=118 (46%)	Disagree n=138 (54%)
Satisfaction with current communication with rheumatologist, n (%)				
Very satisfied	48 (46)	118 (78)*	61 (52)	98 (71)*
Somewhat satisfied	47 (45)*	32 (21)	47 (40)*	32 (23)
Feel comfortable raising concerns/fears with rheumatologist, n (%)				
Strongly agree	39 (37)	110 (73)*	50 (47)	93 (67)*
Somewhat agree	52 (50)*	38 (25)	50 (42)*	40 (29)
Do not always mention PsA symptoms I am still experiencing, even when asked by rheumatologist (strongly/somewhat), n (%)	54 (51)*	17 (11%)	69 (58)*	12 (9)
Do not always proactively mention PsA symptoms I am still experiencing with rheumatologist (strongly/somewhat), n (%)	60 (57)*	17 (11)	61 (52)*	18 (12)
With my rheumatologist and I talked more about PsA and treatment goals (strongly/somewhat), n (%)	80 (82)*	50 (37)	90 (76)*	52 (38)
Reported major/moderate negative impact on:				
Level of physical activity	88 (84)	115 (76)	98 (83)	106 (77)
Emotional well-being	80 (76)*	89 (59)	92 (78)*	77 (56)
Work productivity	72 (69)*	84 (56)	82 (69)*	74 (54)
Romance/intimacy	70 (67)*	72 (48)	78 (66)*	64 (46)
Desires to start family	42 (40)*	36 (24)	49 (42)*	29 (21)
Education	37 (35)*	26 (17)	42 (36)*	21 (15)

*p<0.05 for agree vs disagree.
PsA, psoriatic arthritis

Lilly, Janssen, LEO, Novartis, Pfizer Inc, Sandoz, UCB, 2,AbbVie, Almirall, Bristol-Myers Squibb, Celgene, Janssen, LEO, Novartis, Pfizer Inc, 5; **P. Young**, Pfizer Inc, 1,Pfizer Inc, 3; **J. C. Cappelleri**, Pfizer Inc, 1,Pfizer Inc, 3; **J. Moser**, None; **L. Fallon**, Pfizer Inc, 1,Pfizer Inc, 3.

Abstract Number: 2342

A Pan-Canadian Study of Factors Associated with Perceived Doctor-Patient Communication in Patients with Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with fluctuating levels of disease activity, which may require frequent encounters with the medical system and complex treatment decisions. Doctor-patient communication is an important indicator of health-care quality, with better communication associated with higher health self-management and improved health outcomes. We describe perceptions of doctor-patient communication in lupus patients and the extent to which sociodemographic, disease related and depressive symptoms influence doctor-patient communication.

Methods: Baseline data from patients in the Canadian Network for Improved Outcomes in SLE (CaNIOS) centers participating in the MyLupusGuide™ randomized clinical trial were analyzed. Consenting participants completed on-line questionnaires. Five subscales (eliciting concerns, general clarity, explaining results, decision-making, and compassionate interpersonal style) from the Interpersonal Processes of Care (IPC) instrument measured doctor-patient communication. Each subscale was dichotomized to reflect optimal or suboptimal communication, defined as a score of <4 (range 0 to 4). Self-reported data on demographic (age, sex, ethnicity), disease characteristics and depression were collected using validated measures. Descriptive statistics were performed and univariate logistic regressions estimated with a generalized linear mixed model examined factors associated with each IPC subscale.

Results: Baseline data were available for 532 of 1916 patients, with a mean (SD) age of 50 (14) years, 91% female and 74% self-identified as white. Optimal doctor-patient communication across the subscales ranged between 22.6-35.5%, with shared decision-making receiving the lowest and general clarity the highest ratings. Age (younger) was associated with suboptimal patient perceptions related to eliciting concerns ($p=0.011$) and explanation of test results during patient-doctor interactions ($p=0.035$). Shorter disease duration was associated with suboptimal ratings of general clarity ($p=0.027$) in doctor communication style. More males reported suboptimal communication related to general clarity (83.8%, $p=0.017$) and shared decision making (91.9%, $p=0.042$) compared to females (63.5%, 76.4%, respectively). A greater proportion of participants with depressive symptoms compared to non-depressed reported suboptimal ratings related to their doctor eliciting and responding to their concerns (78.4% vs. 68.2%, respectively; $p=0.01$), explaining test results (72.4% vs. 63.8%, $p=0.04$) and shared decision making (82.4% vs. 73.8%, $p=0.02$). None of the variables examined were associated with the compassionate interpersonal style subscale.

Conclusion: Many lupus patients report suboptimal communication experiences with their doctor, with certain domains being more impacted for patients who are younger, with shorter disease duration, male and depressed. Further research into the factors associated with perceptions of poor communication in the clinical encounter and strategies to improve more patient-centred communication are needed.

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Abstract Number: 2343

Exploring Decision Making Needs about Pain Management Among Adolescents with Juvenile Idiopathic Arthritis and Their Families: Preliminary Results from Interviews

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Adolescents with juvenile idiopathic arthritis (JIA), one of the most common causes of chronic musculoskeletal pain among youth, face many difficult decisions. However, we know little about their decision making needs. Therefore, we sought to explore decision making needs about pain management among adolescents with JIA and their parents/caregivers.

Methods: We have conducted semi-structured individual interviews with adolescents with JIA (13-18 years of age) and one of their parents/caregivers using a qualitative descriptive study design. Using purposive sampling, we recruited adolescents and their parents/caregivers at the Children's Hospital of Eastern Ontario (CHEO) Rheumatology Clinic, and through the Pediatric Rheumatology Care and Outcomes Improvement Network. Eligible participants took part in either face-to-face or online interviews with a research team member. The interview guide was based on a conceptual model developed by the Outcome Measures in Rheumatology (OMERACT) shared decision making working group. Interviews were audiotaped, transcribed verbatim and analyzed using content analysis with NVivo 11 software. We aim to interview fifteen adolescents and their parents, an estimated sample to reach data saturation.

Results: To date, five female adolescents with JIA and five parents have participated in interviews. Most adolescents and parents reported that the disease was not currently active. The median pain value reported by adolescents and their parents was 30 out of 100 mm (range: 3-50 mm) on a visual analogue scale. Adolescents and parents reported having used both medication and non-pharmacological options (e.g., rest, heat, ice, splints, stretching) to manage pain, with the number of treatments ranging from 2 to 6. The most important consideration when choosing pain management options was the effectiveness of treatments. Most adolescents also wanted to avoid injections and splints, while parents wanted to avoid pills, and the short and long term adverse effects of medication. All participants mentioned that adolescents played an active role in choosing pain management options. They also reported discussing their preferences with their healthcare team, but usually in the context of medication to control disease activity. Adolescents and parents wished to know more about a variety of pain management options, potential risks and estimated effectiveness of treatments. Parents preferred receiving this information from an app or website, while adolescents preferred receiving it from their healthcare providers. Adolescents and parents preferred to be involved in the decision making process.

Conclusion: Results of initial interviews suggest an unmet need to receive more information on pain management options and for tools to clarify families' pain management preferences. Adolescents and parents also expressed differences in how they prefer to receive the information. Additional interviews will help inform the development of decision support

interventions to help families make more informed, value-based decisions about pain management options, while simultaneously helping to foster communication within families and with their healthcare providers.

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Treatment Modes in Rheumatoid Arthritis: Moving Toward Shared Decision-Making

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Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

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Table. Most frequent^a reasons for choosing or not choosing each treatment mode as 1st choice

Reasons for choosing OR, n (%) (N=57)		Reasons for not choosing OR, n (%) (N=43)	
Speed of administration	30 (52.6)	Don't want to take another pill	16 (37.2)
Ease of administration	30 (52.6)	Difficulty remembering	15 (34.9)
Portability	23 (40.4)	Possible drug-drug interactions	11 (25.6)
Reasons for choosing SI, n (%) (N=29)		Reasons for not choosing SI, n (%) (N=71)	
Speed/ease of administration	16 (55.2)	Avoidance of pain due to needles	33 (46.5)
Frequency of dosing	12 (41.4)	Avoidance of needles	30 (42.3)
Having a feeling of control	11 (37.9)	Difficulties when traveling	19 (26.8)
		Need to refrigerate	18 (25.4)
Reasons for choosing CI, n (%) (N=2)		Reasons for not choosing CI, n (%) (N=98)	
Wanting someone else to do it	1 (50.0)	Requiring too much time to go to/wait at the clinic/office/hospital; inconvenience	69 (70.4)
Feeling comfortable with experts doing it	1 (50.0)		
Works better	1 (50.0)		
Works faster	1 (50.0)		
Makes me feel safe	1 (50.0)		
Fast to administer	1 (50.0)		
Reasons for choosing INF, n (%) (N=16)		Reasons for not choosing INF, n (%) (N=84)	
Frequency of dosing	13 (81.3)	Requiring too much time to go to/wait at the clinic/office/hospital; inconvenience	56 (66.7)
Feelings of safety and care	5 (31.3)	Long infusion time	23 (27.4)

^aReported by ≥25% of patients

CI, clinic-injection; INF, infusion; OR, oral; SI, self-injection

Session Time: 9:00AM-11:00AM

Background/Purpose: Treatment recommendations in RA emphasize shared decision-making,¹ but little is known about patient(pt) perspectives. Through qualitative research, we aim to understand pt preferences for RA treatment modes of administration and reasons for these preferences, to help guide pt-physician shared decision-making.

Methods: Pt-reported demographic and disease activity information was obtained at screening alongside qualitative interviews conducted using a semi-structured interview guide among adult pts with RA in Brazil, France, Germany, Italy, Spain, Switzerland, UK, and US who were currently taking a DMARD(biologic or non-biologic, including a JAK inhibitor). A 100-point allocation task was used to evaluate the strength of preference (0–100; 100 = strongest) across 4 treatment modes: oral (OR; once daily), self-injection (SI; weekly), clinic-injection (CI; weekly), and infusion (INF; monthly). Transcripts were developed in English; ATLAS.ti software (v7.5) was used for qualitative coding and analysis.

Results: 100 interviews were conducted (female: 75.0%; mean age: 53.9 yrs; mean time since diagnosis: 11.6 yrs). Of the 98 pts who described the severity of their RA, most (70.4%) experienced moderate/severe RA. The most commonly reported symptoms were pain/ache (90.0%), swelling/inflammation (58.0%), and fatigue (54.0%). Current RA medication modes included OR (60.0%), injection (57.0%), and INF (14.0%); 79.0% and 37.0% of pts had experience with injection and INF medications, respectively.

Among the 4 treatment modes, OR was allocated the highest mean (standard deviation) preference points (47.3 [33.1]) and was ranked as 1st choice by the greatest percentage of pts (57.0%), followed by SI (29.7 [27.7]; 29.0%), INF (15.4 [24.6]; 16.0%), and CI (7.5 [14.1]; 2.0%). Notably, the percentage of pts with a 1st choice rank for OR was greater in the US vs Europe (73.3% vs 50.0%; $p < 0.05$). Overall, 56.0% of pts had a 'strong' 1st choice preference (ie, point allocation ≥ 70); the majority of these pts chose OR (62.5%) vs SI (23.2%), INF (10.7%), or CI (3.6%). Speed/ease of administration was the most common reason for pts choosing OR or SI (Table; 52.6%, 55.2%). The most common reason for pts not choosing OR was not wanting to take another pill (37.2%), and for not choosing SI it was to avoid pain due to needles (46.5%).

Conclusion: These data show the most important issues to pts regarding mode of administration of RA medication. Most pts preferred OR as an RA treatment mode, followed by SI. Rationales for preference included ease of use, safety concerns, dosing frequency, feelings of control, and avoidance of pain and needles. While 56.0% of pts had a strong preference for their 1st choice, nearly half did not and may be receptive to, and benefit from, discussions with their healthcare professional and/or pt support groups about RA treatment mode options to guide shared decision-making.

1. Singh JA et al. Arthritis Rheumatol 2016; 68: 1-26.

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Abstract Number: 2345

Systematic Review of Patient Decision Aids for Chronic Musculoskeletal Pain

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Session Information

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Background/Purpose: Chronic musculoskeletal (MSK) pain is common and disabling; it is among the top reasons for doctor's visits in the US. Most treatment decisions for chronic MSK pain are preference-sensitive, meaning that there is more than one reasonable treatment option. Patient decision aids (PDAs) are tools to help patients participate in their healthcare decisions. We performed a systematic review of PDAs for adults deciding about treatment for chronic MSK pain.

Table 1: Characteristics of Included Studies and Selected Outcomes

Reference	Participants	Decision and Condition	Decision Aid and Combination	Selected Outcomes
Allen 2016	N = 159 Mean age: 61.4 years	Joint replacement vs medical management for hip or knee OA	Video and booklet decision aid vs internet based decision aid	Both groups had an increase in knowledge and decrease in decisional conflict but there was no statistically significant difference between groups.
Bock 2011	N = 121 Mean age 63 years	Joint replacement vs medical management for hip or knee OA	Video and booklet decision aid with pre-visit phone call to construct a question list vs educational booklet and appointment reminder phone call	Lower proportion of patients undecided in the intervention group. No statistically significant difference in surgery rates between groups.
de Achaval 2012	N = 208 Mean age 63 years	Joint replacement vs medical management for knee OA	Video and booklet decision aid alone or with computer-based adaptive conjoint analysis tool vs educational booklet	Greater reduction in decisional conflict in the intervention groups. The greatest reduction was in the decision aid alone group.
Graham 2011	N = 658 Mean age 63 years	Joint replacement vs medical management for knee OA	Video decision aid alone or motivational interviewing alone or combined video decision aid and motivational interviewing vs educational booklet	Increase in knowledge with both the decision aid alone and in combination with motivational interviewing. Increased patient-practitioner communication in all intervention groups. No statistically significant difference in number of referrals to orthopedics.
Ibrahim 2017	N = 304 Mean age 59 years	Joint replacement vs medical management for knee OA	Video decision aid vs educational booklet	Higher rate of total knee replacement at 12 months in the intervention group.
Patel 2014	N = 148 Mean age 48 years	Choice among physiotherapy treatments for low back pain	Booklet decision aid with shared decision-making training for physiotherapists vs usual care	No difference in patient satisfaction. Less improvement in the Roland Morris Disability Questionnaire in the intervention group but otherwise no difference in pain, disability, anxiety, depression, pain self-efficacy, or fear avoidance beliefs between the groups.
Rhodes 2001	N = 100 Mean age 50 years	Surgical vs medical management for low back pain	Video and booklet decision aid vs booklet decision aid alone	Greater increase in knowledge score in the combined video and booklet decision aid group. No difference in preference for surgery.
Shen 2011	N = 182 Mean age 63 years	Joint replacement vs medical management for hip or knee OA	Video and booklet decision aid vs booklet decision aid alone	No statistically significant increase in knowledge score in either group. No difference in willingness to participate in the decision process, stage of decision making, or satisfaction between the groups.
Stachy 2014	N = 157 Mean age 67 years	Joint replacement vs medical management for knee OA	Video and booklet decision aid with a patient preference report for the surgeon vs educational booklet and a clinical assessment report for the surgeon	Higher knowledge scores and decision quality in the intervention group. No difference in decisional conflict between the groups. Higher proportion of patients undecided in the intervention group. No statistically significant difference in the percentage of patients choosing surgery or the wait times for surgery between the groups.
Stachy 2016	N = 154 Mean age 66 years	Joint replacement vs medical management for hip or knee OA	Video and booklet decision aid with a patient preference report for the surgeon vs educational booklet and a clinical assessment report for the surgeon	Higher knowledge scores, decision quality, and accuracy of risk perception in the intervention group. No difference in decisional conflict between the groups. No statistically significant difference in the percentage of patients choosing surgery.
Veroff 2011	N = 9925 Mean age 55 years	Surgical vs medical management for knee or hip OA, lower back, or back pain	Video and booklet decision aid alone or in combination with telephone health coaching vs usual care	Higher knowledge scores in both the decision aid alone and decision aid with health coaching groups. No statistically significant difference in decisional conflict between the groups. No statistically significant difference in rates of surgery between the groups.
Vine 2016	N = 490 Mean age 62 years	Joint replacement vs medical management for knee OA	Video decision aid and motivational interviewing vs educational booklet	No statistically significant difference in percentage of patients referred to orthopedic surgery between the groups.

Methods: We searched Ovid MEDLINE, Ovid MEDLINE In-Process and EPubA head of Print, Ovid Embase, Ovid PsycINFO, EBSCO CINAHL, Cochrane CENTRAL, clinicaltrials.gov, and the International Clinical Trials Registry Platform from inception until March 2017. We included randomized controlled trials of adults using PDAs to make treatment decisions for chronic MSK pain in the outpatient setting. We evaluated outcomes related to decision making (knowledge, accurate risk perception, choice congruence with values, decisional conflict, patient-practitioner communication, satisfaction), pain, functional status, and surgery utilization.

Results: We reviewed a total of 342 abstracts, and 12 met our inclusion criteria. Five studies evaluated patients with knee osteoarthritis (OA) alone. Four studies evaluated patients with either hip or knee OA. Two studies evaluated patients with lower back pain. One study evaluated patients with knee pain, back pain, knee or hip OA.

In one study, patients used the PDA to decide between conservative management options for chronic lower back pain. This was the only study that evaluated pain and function outcomes. There was less improvement in one disability score but otherwise no difference with the PDA compared to control.

In the other 11 studies, patients were deciding between surgical and medical management using a video PDA. Seven of eight studies found no difference in the proportion of patients choosing surgery. The effects of the PDAs on decision-related outcomes were mixed. Six of seven studies found improved knowledge scores with use of a PDA. Two of five studies found an improvement in decisional conflict with use of a PDA. The addition of motivational interviewing, an adaptive conjoint analysis tool, or telephone-based health coaching to a PDA did not improve any of the outcomes compared to the use of the PDA alone. Characteristics of included studies and selected outcomes are reported in the table.

Conclusion: PDAs may improve the decision-making process and decision quality for patients deciding between operative and medical management of hip/knee OA and chronic back pain. Additional research is needed to evaluate the effect of PDAs on pain and function. Especially for older adults with multi-morbidity and polypharmacy, who are often not surgical candidates, further research should develop PDAs for non-surgical treatment of chronic MSK pain.

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Abstract Number: 2346

Emerging Ethical Issues in Physical Activity Monitoring of Persons Living with Arthritis: A Qualitative Evidence Synthesis

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Session Information

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Background/Purpose: Although physical activity is a key component of optimal arthritis self-management, levels of physical activity typically fall below expert recommendations among persons with arthritis.[1] Wearable technologies could support persons with arthritis to be physically active; however, questions remain about potential burden that persons with arthritis may experience in the context of their daily lives if wearables are to be integrated into self-management.[2] We aim to broaden understanding of ethical issues in using wearables to support physical activity from the perspectives of persons living with arthritis.

Methods: An exhaustive search of 5 electronic databases (including Medline, CINAHL and Embase) from inception to Jan 2018 was carried out using the SPIDER (Sample, Phenomenon of interest, Design, Evaluation, Research type). We also performed hand-searching of reference lists of included studies. Title/abstract and full-text screening were conducted independently by 4 reviewers. Qualitative studies were eligible if they examined the use of physical activity wearables from the perspectives of persons with arthritis. Eligible articles were appraised using the McMaster Critical Review Form. All relevant data were extracted from eligible articles and coded inductively with thematic analysis.

Results: From a search yield of 4750 records, 63 were read in full and 5 papers from 4 studies met inclusion criteria. Studies were conducted in Canada, Australia, UK and Ireland. Sample included 74 persons with arthritis (62 women, 12 men, aged 43-85). 57 live with osteoarthritis and 17 live with inflammatory arthritis. At least 53 participants have some experience of using a wearable. Across the 4 studies, preliminary themes are: 1) *Becoming more aware*: Participants identified that use of a wearable had made them more aware of their inactivity. While some participants felt motivated to be more active, others highlighted greater awareness alone would not guarantee increased activity; 2) *Seeking appropriate supports*: Participants described seeking appropriate supports (e.g., written instructions) that could guide their early use of wearables, but commonly felt "limited" when these supports were not readily available; 3) *Improving patient-doctor*

communication?: Many participants anticipated that their wearable data would better equip them to improve communication (e.g., by supporting mutual understanding during assessments) with their health professionals.

Conclusion: Themes speak to relational ethics as they direct attention to situations within which autonomy is exercised in daily life.[3] For example, greater awareness of inactivity may empower some persons with arthritis to be more active, and some persons with arthritis may feel a sense of underachievement if their use of wearables is unaccompanied by appropriate supports. Findings also pose questions about how wearables may impact ways of respecting another's autonomy in patient-doctor interactions.

1. Wallis J et al. *Osteoarthritis Cartilage* 2013; (21): 1648-59.
2. Bravata DM et al. *JAMA* 2007; (298): 2296-2304.
3. Austin et al. *Approaches to Ethics* 2003; 45-52.

Disclosure: J. Leese, None; S. Zhu, None; G. Macdonald, None; M. M. Pourrahmat, None; A. F. Townsend, None; C. L. Backman, None; L. Nimmon, None; L. Li, None.

Abstract Number: 2347

Effectiveness of Shared Decision Making in Systemic Lupus Erythematosus Patients at OSU

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Session Information

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Background/Purpose: Patient autonomy is an integral part of the treatment process. For effective shared decision making (SDM) patients must fully understand their disease process, prognosis and treatment. Systemic lupus erythematosus (SLE) patients have significant challenges due to the complex pathophysiology of the disease, multiple treatment regimens, and heterogeneous manifestations including neurocognitive effects. Our prior study demonstrated that one third of the SLE patients did not recognize comorbidities of SLE and medication side effects. The aim of our current study is to use CollaboRATE, a validated SDM tool, to investigate the effectiveness of the SDM process in a subset of SLE patients at OSU.

Methods: Patients >18 years were recruited from The Ohio State University Lupus and Vasculitis Glomerulonephritis Clinic. Patient demographics are described in Table 1. After IRB approval, patients were contacted by phone and administered a 3 item multiple-choice validated CollaboRATE questionnaire that was graded on a 5 point Likert scale (0-4) (Table 1). Data was analyzed as an average score per question and a total sum (max 12 points). A top score was obtained by giving 1 point to individuals who gave the maximum possible response to all 3 questions, and 0 points to everything else.

Results: A total of 52 patients completed the questionnaire. The average score for question 1 was 3.1(+/-1), question 2 was 3.3 (+/- 0.9), and question 3 was 3.1 (+/-1) (Table 2). Sixteen out of 52 patients received a max score of 12, and 30/52 patients scored at least a 10/12 (83%)

Conclusion : The CollaboRATE questionnaire targets the areas of SDM including explanation of the health issues, determination of preferences, and healthcare usage. On average, our SLE cohort feel significant effort is made to help them understand their disease and include their values. Despite this, only about 57% of patients reported a high score (meaning high SDM effectiveness). Based on these results and the prior study by Meara et al, there remains an apparent gap regarding patient knowledge of SLE diagnosis and treatment, putting them at a disadvantage in SDM. This discrepancy may be due to multiple factors. Further studies are needed to investigate the best information delivery methods to improve knowledge in an effort to empower them in the SDM process.

Table 1: Demographic Information

Average age	46.9 +/- 13.5 years			
Ethnicity	48% African American 44% Caucasian 2% Asian 2% Latino/Hispanic 2% Other 2% Refused to answer			
Average duration of disease	12.9 +/- 8.9 years			
Average SLICC	2.7 +/- 1.6			
Average SLEDAI	2.6 +/- 3.4			
CollaboRATE Questions	Scores +/- Standard Deviation (N=52)			
How much effort was made to help you understand your health issues?	3.1 (+/-1)			
0	1	2	3	4
No effort was made	A little effort was made	Some effort was made	A lot of effort was made	Every effort was made
How much effort was made to listen to the things that matter most to you about your health issues?	3.3 (+/- 0.9)			
0	1	2	3	4
No effort was made	A little effort was made	Some effort was made	A lot of effort was made	Every effort was made
How much effort was made to include what matters most to you in choosing what to do next?	3.1 (+/-1)			
0	1	2	3	4
No effort was made	A little effort was made	Some effort was made	A lot of effort was made	Every effort was made

References: Meara A, Yedimenko J, Steigelman H, Ardoin SP, Peters E. "Do You Know What I Mean?" a Tool to Understand What Lupus Patients Comprehend [abstract]. *Arthritis Rheumatol*. 2017; 69 (suppl 10).

Barr PJ¹, Thompson R, Walsh T, Grande SW, Ozanne EM, Elwyn G. The psychometric properties of CollaboRATE: a fast and frugal patient-reported measure of the shared decision-making process. *J Med Internet Res*. 2014 Jan 3;16(1):e2

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Abstract Number: 2348

Prescriber Attitudes and Beliefs about Triple Therapy for Patients with Rheumatoid Arthritis: Knowledge Exchange in Internet Forums and Social Media

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Several forums on the internet serve as repositories of personal experiences and exchange of health information. Online discussions among healthcare providers about management of patients with rheumatoid arthritis occur on a regular basis. Therefore, we explored and characterized the discussions about the use of triple therapy (methotrexate, sulfasalazine, hydroxychloroquine) on Internet forums, as differences in utilization among countries have been reported.

Methods: Online discussions were collected from three "leading edge" forums (ResearchGate, Medscape, and Twitter). Threads of discussion were systematically examined and interpreted to reveal recurring topics and patterns. Each post was coded and arranged into broader categories, which were combined into overarching themes.

Results: Twelve threads with 96 posts were identified. Seventy-nine of the posts were categorized. Seventeen were discarded because they were questions or comments unrelated to the topic discussed in the original thread. Four themes emerged during the analysis: (i) effectiveness (i.e., results from TEAR, Swefot and RACAT trials), (ii) costs, (iii) safety, and (iv) adherence. The first theme dealt primarily with the effectiveness of triple therapy compared with tumor necrosis factor inhibitors [discussion were around being as effective, but not in the first 12 weeks of treatment, or no improvement in radiographic progression]. The second theme focused on the costs. Although the majority agreed that it is a cost-saving

alternative, especially in developing countries, some believed that biosimilars will be as cost-saving and more effective. Some were of the opinion that in the United States patients would have to pay 3 copays for the triple therapy regimen as opposed to 2 with a biologic option. The third theme involved a multitude of safety concerns, such as retinopathy, Stevens-Johnson syndrome, high liver enzymes or low blood cells, or the need for special monitoring in individuals with hepatitis C infection or nonalcoholic steatohepatitis. Tolerance was also a concern when sulphasalazine was not enteric-coated. Some suggested using other combinations such as adding fish oil or replacing sulphasalazine with leflunomide. The last theme covered the use of multiple drugs, which minimizes adherence.

Conclusion: The discussions in online forums showed extensive and cumulative discussions on attitudes and beliefs exchanged about triple therapy. Main concerns included radiographic progression, safety, and adherence which could partially explain low utilization of triple therapy in some countries.

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Abstract Number: 2349

“I Was Prepared for the Other Side Effects; I Wasn’t Prepared for This One.”: A Qualitative Study of the Patients’ Experience of Inflammatory Arthritis Due to Immune Checkpoint Inhibitor Therapy for Cancer

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Session Information

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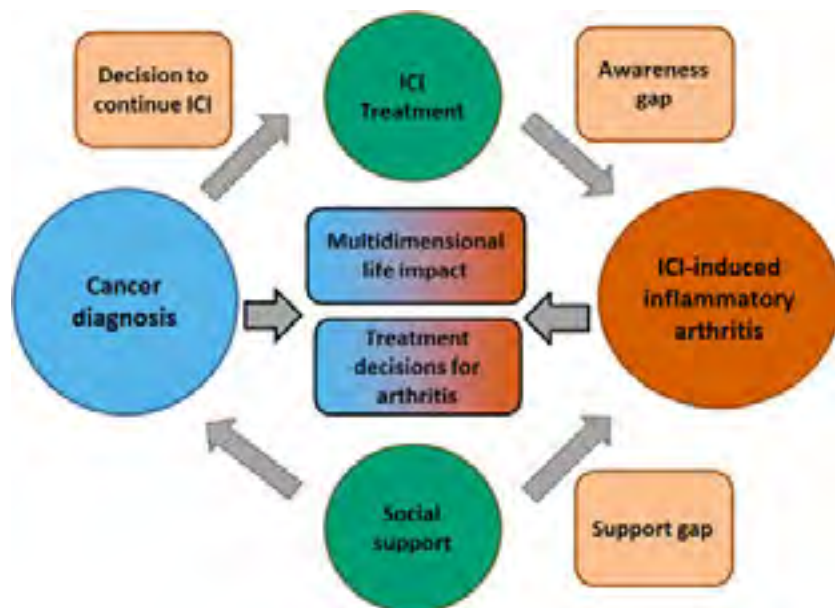
Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

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Background/Purpose: Patients treated for cancer with immune checkpoint inhibitors (ICI) can develop a variety of adverse events. Inflammatory arthritis (IA) is an increasingly recognized event that can persist after cessation of ICI therapy. Patients face a unique clinical experience of having not one, but two functionally consequential illnesses, advanced cancer and IA. We aimed to evaluate the patient experience of ICI-induced IA.

Methods: Participants were identified from a longitudinal cohort of patients with rheumatologist diagnosed ICI-induced IA. We aimed to explore the processes of diagnosis and treatment, symptoms and impacts of ICI-induced IA, coping mechanisms, and the treatment decision-making process through semi-structured one-on-one interviews. Two researchers



performed inductive thematic analysis independently on a subset of transcripts, identified and reconciled codes which were then applied to all subsequent transcripts. The final hierarchical coding structure was developed through data review and discussion among three researchers.

Results: Ten patients with ICI-induced IA participated in one-on-one interviews. The mean (SD) age of participants was 54 (12.1) years, and five were women (50%). Melanoma was the most common underlying cancer (N=5), with hematologic malignancies and other solid tumors also represented. Eight patients (80%) had additional adverse events from ICIs, including colitis, pneumonitis, thyroiditis and hypophysitis. Five main themes were identified: the complex and often delayed process for diagnosis, the significance of IA compared to other side effects, the physical and emotional impacts of IA, complex decision-making processes for treatment and continuing ICI therapy, and differing perceptions of social support for IA versus cancer. From these themes, we propose a conceptual framework for patient experiences with ICI-induced IA that highlights the awareness gap of ICI-induced IA as a potential side effect, the support gap from peers, and the complex decision making for patients (Figure 1).

Conclusion: In this novel qualitative study of cancer immunotherapy patients, ICI-induced IA has a significant impact physically and emotionally, even as compared to other side effects of ICIs. Patients experienced delay in diagnosis that they attributed to lack of awareness of this condition. Fear of their cancer returning influenced the treatment decision-making process.

Figure 1: Conceptual framework for patient experiences with ICI-induced IA

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Abstract Number: 2350

Examining Ethnic Differences in Osteoarthritis (OA) Patients' Knowledge and Attitudes Regarding Prescription Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

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Background/Purpose: NSAIDs are commonly prescribed for the treatment of OA. While there are documented differences between Hispanics and non-Hispanic whites (NHWs) in their treatment preferences for arthroplasty, little is known about ethnic differences in treatment preferences for NSAIDs. The extent to which minority patients convey reluctance to accept proven treatments can contribute to disparities in the utilization of these treatments and in clinical outcomes. The purpose of this study was to determine if there are ethnic differences in OA patients' treatment preferences for, familiarity with, and perceptions of efficacy and risk of prescription NSAIDs.

Methods: Participants with chronic, frequent pain due to knee or hip OA were recruited from a university medical center. Those with cognitive dysfunction, hip/knee arthroplasty, and inflammatory arthritis were excluded. Participants were given a questionnaire to assess their knowledge and attitudes towards OA treatments, including questions regarding their willingness to receive (2 items), familiarity with (3 items, yes/no), and perceptions of benefits (4 items) and risks (3 items) of both prescription oral and topical NSAIDs. Responses to all (except familiarity) question items were based on a five-category ordinal response scale. Fisher's exact or Wilcoxon-Mann-Whitney tests were conducted to determine if individual items of knowledge and perceptions about prescription NSAIDs differed by ethnicity.

Results: In our cohort of patients with knee or hip OA, Hispanics (n=119), in comparison to NHWs (n=186), were younger (mean age 61.5 vs. 65.6) and less likely to have an annual income of \geq \$40,000 (21.6% vs. 55.8%). No differences were found between Hispanics and NHWs in willingness to try prescription oral or topical NSAIDs. Hispanics were less likely to have heard about prescription oral NSAIDs as treatment for OA compared to NHWs (75.22% vs. 85.95%, $p=0.0293$). Hispanics were less likely to believe oral NSAIDs are helpful in OA patients ($p=0.0104$) or for themselves ($p=0.0223$), but they were also less likely to believe oral NSAIDs are risky or dangerous in OA patients ($p=0.0009$) or have concerns about complications from the medication ($p=0.0402$) compared to NHWs (Table 1). Additionally, Hispanics were

Table 1. Perception of Benefits and Risks of Prescription Oral NSAIDs in Hispanic and Non-Hispanic White Osteoarthritis Patients

Perception of Benefits/Risk	Hispanic (n = 119)					Non-Hispanic White (n = 188)					p-value*
	Not at all		Moderate			Not at all		Moderate			
	1	2	3	4	5	1	2	3	4	5	
Helpful in OA Patients	3 (4.42)	24 (21.24)	23 (20.35)	42 (37.17)	18 (15.81)	5 (2.78)	11 (5.11)	41 (22.78)	89 (49.44)	34 (38.89)	0.0104
Helpful for Themselves	10 (8.98)	27 (24.11)	15 (13.38)	43 (38.49)	17 (15.18)	10 (5.52)	18 (9.94)	35 (19.34)	86 (47.51)	32 (17.68)	0.0223
Pain Relief for Themselves	17 (15.74)	27 (25.00)	28 (25.93)	36 (34.67)	10 (9.26)	14 (7.95)	51 (28.98)	48 (27.84)	87 (46.70)	15 (8.52)	0.3972
Functional Improvement for Themselves	19 (17.27)	27 (24.55)	31 (28.18)	35 (32.73)	8 (7.27)	20 (11.38)	48 (27.27)	58 (33.53)	89 (42.16)	10 (5.68)	0.7057
Unpleasant/Risky	Not at all		Moderate			Not at all		Moderate			
	1	2	3	4	5	1	2	3	4	5	
Risky/Dangerous	18 (16.22)	34 (30.63)	38 (34.23)	16 (14.41)	5 (4.50)	7 (3.87)	54 (29.89)	57 (31.48)	53 (29.28)	10 (5.53)	0.0009
Seriousness of Complications	36 (31.86)	29 (25.84)	27 (23.88)	18 (16.15)	5 (4.42)	17 (9.33)	57 (31.32)	38 (20.68)	42 (21.99)	10 (5.49)	0.0594
Concern about Complications	33 (28.32)	40 (35.40)	12 (10.62)	17 (15.04)	12 (10.62)	18 (10.77)	50 (30.08)	26 (14.21)	40 (21.86)	24 (13.11)	0.0492

less likely to believe topical NSAIDs are harmful compared to NHWs ($p=0.0040$). Items pertaining to familiarity with and perceptions of benefits of topical NSAIDs did not significantly differ by ethnicity.

Conclusion: Among patients with knee or hip OA, Hispanics were less familiar with oral NSAIDs, less likely to believe in their efficacy, and less likely to believe that they are harmful, compared to NHWs. Treatment preferences for prescription NSAIDs however did not vary by ethnicity. Improving patient knowledge and attitudes about prescription NSAIDs may reduce ethnic differences in the utilization of this OA treatment.

Disclosure: H. Masood, None; M. J. Hannon, EMD Serono, 5; C. K. Kwok, None; J. Dagnino, None; E. Vina, None.

Abstract Number: 2351

Attitudes Toward Telehealth Video Conferencing Among Patients with Rheumatic Disease

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

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Session Time: 9:00AM-11:00AM

	Interested in VTC Telehealth (n=130)	Not interested in VTC Telehealth (n=137)	P-Value
Male (%)	99 (77%)	115 (84%)	$p = 0.164$
Median Age in Years (IQR)	60.5 (46 - 70)	65.0 (56 - 71)	$p = 0.89$
College Education or Higher	43 (33%)	34 (25%)	$p = 0.18$
Vision or Hearing Problem	24 (18%)	33 (24%)	$p = 0.29$
Median EuroQOL 5D (IQR)	0.71 (0.47 - 0.81)	0.71 (0.44 - 0.81)	$p = 0.98$
Median Time Traveled in Minutes (IQR)	60.0 (30 - 90)	60.0 (30 - 100)	$p = 0.94$
Median Distance Traveled in Miles (IQR)	20.0 (14 - 49)	20.0 (10 - 43)	$p = 0.92$
Travel to Clinic is Convenient	52 (41%)	67 (52%)	$p = 0.10$
Previous VTC Telehealth Usage	18 (14%)	8 (6%)	$p = 0.041$
Comfortable with Skype, Facetime, etc.	93 (74%)	23 (19%)	$p < 0.001$
Concerned about VTC Privacy	25 (21%)	62 (54%)	$p < 0.001$
Number of Internet-Capable Devices (Smartphone, Tablet, Computer)			$p < 0.001$
No Devices	8 (7%)	27 (25%)	
One Device	34 (28%)	61 (55%)	
Two Devices	41 (34%)	36 (33%)	
Three Devices	47 (39%)	13 (12%)	
Perceived Added Convenience of VTC	121 (95%)	61 (50%)	$p < 0.001$

IQR = Interquartile Range

Background/Purpose: Video Teleconferencing (VTC) telehealth is a synchronous medium in which patients may interact with physicians using their own personal electronic device or at a designated remote clinic site. We evaluated the attitudes and interest toward VTC telehealth at two Veteran Affairs (VA) rheumatology clinics.

Methods: Adult rheumatology patients were approached during return clinic visits at the VA Greater Los Angeles Healthcare System to participate in a descriptive survey. The paper survey assessed electronic health literacy, previous VTC and other telehealth use, current barriers to accessing in-person rheumatology care, concerns about VTC telehealth, and perceptions of telehealth. These were rated on a 5-point Likert scale. The validated EuroQOL-5D-3L evaluation was included to assess self-rated quality of life. Patients rated their interest in VTC telehealth as a substitute for some in-person rheumatology clinic follow-up visits on a 7-point Likert scale. Fisher's exact test and Kruskal-Wallis testing was used for univariate analysis for categorical and continuous variables, respectively. Ordered logistic regression was used to analyze variables associated with interest in VTC telehealth.

Results: 337 patients were approached to take the survey and 267 (79%) patients agreed to take it. 130 (49%) respondents expressed interest in VTC (defined as 5+ on a 7-point Likert scale). We found interest in VTC telehealth to be associated with the number of electronic devices owned (OR: 1.38, 95% CI [1.05, 1.81], $p=0.022$), comfort using video chat technology such as Skype or Face time (OR: 5.06, 95% CI [2.84, 9.00], $p<0.001$), and perceived added convenience with adoption of VTC telehealth (OR: 9.70, 95% CI [5.25, 17.95], $p<0.001$). Patients with concerns about privacy were less likely to be interested in VTC telehealth (OR: 0.38, 95% CI [0.22, 0.65], $p<0.001$). We found interest in VTC telehealth not to be associated with age, self-rated quality of life, education, or time/distance traveled to clinic.

Conclusion: VA patient interest in utilizing VTC telehealth as a substitute for some follow-up rheumatology appointments was found to be correlated with the number of electronic devices owned, comfort using video chat, and perceived added convenience. This interest is inversely associated with concerns about potential privacy issues. Interest in VTC telehealth is not associated with distance/time required to travel to clinic nor perceived inconvenience of travelling to clinic, though the study may not be powered to evaluate this.

Disclosure: D. Zhang, None; J. Lu, None; C. Aquino- Beaton, None; N. Harada, None; M. A. Fang, None.

Abstract Number: 2352

Predictors of Patient and Physician Perceptions of Gout Disease Activity

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Background/Purpose: It is unknown what factors contribute to patient and physician perceptions of gout disease activity, and how these perceptions align. The aim of this study was to understand the clinical variables that contribute to the patient and physician perceptions of gout disease activity, and to understand reasons for discordant assessments of gout disease activity.

Methods: Patients (n=223) with gout according to the 1977 ARA gout classification criteria and on allopurinol ≥ 300 mg daily attended a standardized gout assessment visit which recorded gout flare in the preceding 3 and 12 months, physical examination for tophus, laboratory tests and patient questionnaires. Study participants and physicians completed questionnaires rating their global assessment of gout disease activity, (numerical rating scale (NRS); 0=no activity, 10=extremely active). Discordance in the global assessment of gout disease activity was defined as an absolute difference of >2 units between the patient and physician assessments (Desthieux et al, Arthritis Care Res 2016). Data were analysed using linear and logistic regression models.

Results: The mean (SD) patient global assessment of gout disease activity was 2.08 (2.35), and physician global assessment of disease activity was 2.52 (2.58), $P=0.01$. Gout flare in the last 12 months, presence of tophus, gout flare in the last 3 months and serum urate <0.36 mmol/L were independent predictors of patient and physician assessments (Table). Male sex also predicted physician global assessment of gout disease activity, but not patient assessment. Discordant patient and physician scores for gout disease activity were present in 63 (28.3%) participants. In logistic regression models, gout flare in the last 3 months predicted discordant gout disease activity scores >2 (patient assessed gout disease activity as more

severe, n=23); odds ratio 2.8, P=0.021, whereas gout flare in the last 12 months predicted discordant gout disease activity scores <-2 (physician assessed gout disease activity as more severe, n=40); odds ratio 10.4, P<0.001.

Conclusion: For both patients and physicians, gout flares, tophus and serum urate control contribute to assessments of gout disease activity. However, discordance between patients and physicians in their assessment of gout disease activity is not uncommon, with recent gout flares contributing to higher patient global assessments of disease activity, and distant flares contributing to higher physician global assessments of disease activity.

Table. Linear regression models showing predictors of patient and physician global assessments of gout disease activity, ordered by the standardized coefficient, n=223.

Dependent variable	Predictors	B	SE	Standardized coefficient	Sig	Model statistics
Patient global assessment of gout disease activity	Gout flare in the last 12 months	34.69	9.50	0.28	<0.001	Adjusted R ² =0.26, F=16.3, P<0.001
	Gout flare in the last 3 months	26.28	10.11	0.20	0.010	
	Presence of tophus	21.81	8.26	0.15	0.009	
	C-reactive protein	0.82	0.39	0.13	0.035	
	Serum urate <0.36mmol/L	-15.81	7.86	-0.12	0.046	
Physician global assessment of gout disease activity Beliefs about Medicine Questionnaire	Gout flare in the last 12 months	50.53	8.40	0.40	<0.001	Adjusted R ² =0.44, F=30.2, P<0.001
	Presence of tophus	35.56	7.40	0.25	<0.001	
	Gout flare in the last 3 months	27.43	9.02	0.20	<0.001	
	Serum urate <0.36mmol/L	-19.31	6.95	-0.15	0.006	
	Male sex	32.8	12.29	0.14	0.008	
	C-reactive protein	0.74	0.34	0.11	0.032	

Disclosure: N. Dalbeth, Horizon, 5, Kowa, 5, Amgen Inc., 2, AstraZeneca/Ironwood, 2, AbbVie Inc., 8, Pfizer, Inc., 8, Janssen, 8; C. Frampton, None; S. Baumgartner, Ardea Biosciences, 3; M. Fung, Ardea Biosciences, 3; H. K. Choi, Takeda, Selecta, Kowa, and Horizon, 5, Selecta and Horizon, 2.

Abstract Number: 2353

Attitudes and Beliefs Regarding Methotrexate in Patients with Rheumatoid Arthritis: Results from Australian Rheumatology Association Database

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

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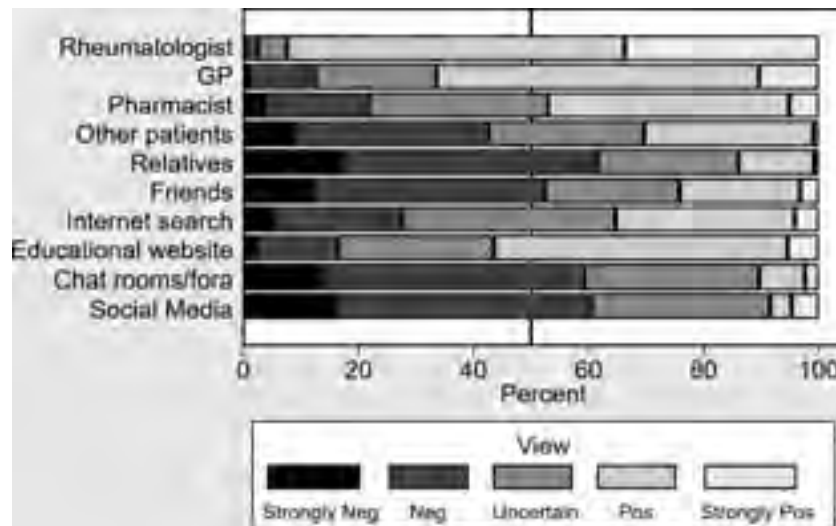
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To determine beliefs about methotrexate (MTX) in patients with Rheumatoid Arthritis (RA) in relation to views obtained from a range of information sources.

Methods: RA patients, who had completed an online questionnaire on a national RA database within the previous 12 months, n=1010, were invited to participate in an additional online questionnaire (Survey Monkey) regarding their use and views of MTX. Participants who had ever-used MTX were asked about sources consulted for MTX information, and whether positive or negative views were obtained. The Beliefs about Medicine Questionnaire (BMQ), consisting of general medication (overuse and harm) and MTX specific (necessity and concerns) was used to measure patient specific beliefs about MTX. Demographic and clinical information of the survey respondents was obtained by linkage to the national database.

BMQ Scale	MTX Current Use (n = 494)	MTX Previous Use (n = 248)	Difference	p-Val
MTX-Specific-Necessity	1.54 (1.47, 1.60)	1.50 (1.42, 1.59)	2.03 (1.92, 2.14)	< 0.001
MTX-Specific-Concerns	2.49 (2.42, 2.56)	2.63 (2.52, 2.74)	-0.14 (-0.23, -0.02)	0.027
General-Overuse	2.62 (2.55, 2.70)	2.71 (2.60, 2.82)	-0.09 (-0.12, 0.04)	0.18
General-Harm	2.18 (2.08, 2.19)	2.16 (2.08, 2.24)	-0.02 (-0.12, 0.07)	0.64



Results: The survey response rate was 804/1010 (80%). MTX survey data was analysed for 742 RA participants (age 59 years, 76% female, disease duration 19 years, 75% rheumatoid factor positive) who had ever-used MTX, with 494/742 (67%) reporting current use.

Current MTX users scored substantially higher on the BMQ MTX specific Necessity scale, and slightly lower on the MTX-specific Concerns scale (Table 1). Table 1. Beliefs about Medicine Questionnaire results by MTX use. Participants consulted multiple information sources (median 3, IQR 1-5), which was associated with younger age, higher education levels, higher MTX-specific concerns and general medication BMQ scores ($p < 0.05$, multiple Poisson regression). Rheumatologists (98%), GPs (55%), internet search engines (39%), educational websites (38%), and Pharmacist (37%) were the most common information sources. When consulted, positive MTX information was most often obtained from rheumatologists (93%), GPs (67%), and educational websites (56%) (Figure 1). Figure 1. Reported MTX Views by Source

Negative MTX information was most often obtained from relatives, social media, internet chat rooms, and friends. Positive information from Rheumatologists ($p < 0.001$) and Educational websites ($p = 0.021$) was influential on favourable MTX-specific necessity and concerns BMQ scores (MANOVA analysis).

Conclusion: RA patients have significant concerns regarding MTX and consult a variety of sources for MTX information. However, the patient perception of this information varies widely. Rheumatologists and educational websites are the most important information sources in terms of utilisation, positive information, and influence on the patient's perception of MTX.

Disclosure: N. Leonardo, None; S. Lester, None; M. Graham, None; S. Whittle, None; D. Rowett, None; R. Buchbinder, None; C. Hill, None.

Abstract Number: 2354

Perspectives of Patients with Inflammatory Arthritis Regarding Cardiovascular Risk: A Qualitative Study

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Background/Purpose: Cardiovascular disease (CVD) is the most common cause of death among patients with inflammatory arthritis (IA) such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) or ankylosing spondylitis (AS). Our

purpose was to elicit perspectives of patients with IA to inform the design of a patient-centered intervention for a CVD risk reduction intervention.

Methods: This was a qualitative study guided by Bandura’s Social Cognitive Theory, placing special emphasis on knowledge about the relationship between arthritis and CVD as well as barriers and facilitators to receiving healthcare related to CVD risk such as screening and management for hyperlipidemia. We recruited patients from a single academic center with either RA, PsA, or AS to participate in focus groups. Data were analyzed thematically.

Results: We conducted three focus groups with a total of 17 participants (5 participants in two and 7 participants in one of the focus groups) of mean age 56 (SD±7.7) years; 15 were women; 3 were on a statin; and 1 previously had a stroke. Five themes emerged (Table):1) Need for more information about IA and its medications; 2) Lack of understanding regarding the association between CVD risk and IA; 3) Holistic approach to CVD risk reduction including lifestyle changes; 4) Possible uses for peer coaches around relevant CVD risk factor mitigation approaches; and 5) Improving doctor-patient communication about IA. In summary, these themes showed that many participants were not aware of the relationship between CVD and IA. They demonstrated interest in learning about IA, IA medication side effects, and prognosis of IA. Participants prioritized learning about IA, its prognosis, and treatment followed by learning about preventive measures for CVD risk within the context of their IA rather than CVD as a separate condition.

Conclusion: Providing a clear understanding about the systemic effects and treatments for IA should be integrated into a CVD risk reduction intervention targeted at patients with IA.

Table Themes and Key Points That Emerged From Focus Groups of Patients with Inflammatory Arthritis

Theme	Quotes from patients
Need for information about IA and medications	<i>“When I was first diagnosed, as far as the medications and the side effects and what I could expect. Like I said, everything I read was bad, and it didn’t—I’m probably going to take it the rest of my life, and you have to get your blood tested every three months to make sure everything’s looking good.”</i>
Lack of understanding regarding the association between CVD risk and IA	<i>“I never even thought about it. Had no idea that it would even affect my heart like that. I’m still in shock [laughter] that that has to do with the arthritis.”</i>
CVD risk reduction as an integrated lifestyle modification	<i>“They (doctors) know about the medicines and everything, so I’ll ask them, ‘Is there something’ I could do or take that would help it?’ We’ve got to do our part, too. We’ve got to exercise. We got to watch what we eat. Stress. I know stress will cause a lot of stuff to come on.”</i>
Possible uses for peer coaches around relevant CVD risk factor mitigation approaches	<i>“It would’ve been helpful if I would talk to somebody who, maybe, was on the medication and could tell me, ‘Well, I haven’t had any problems with it,’ or, ‘Yeah, it does this.’ I’m sure it affects different people differently.”</i> <i>“I guess if it would involve exercising takin’ a walk, it’d be nice to do it with somebody if they’ve got the same (arthritis)—and do it together, that would be motivating.”</i>
Improving doctor-patient communication about IA	<i>“It’s like, first of all, I don’t care for him (doctor). [Laughter] He’s an older doctor and he’s like, ‘I’m only going to see you for one thing.’ I’m like, ‘No, if I have four things wrong with me, you need to see me for four things.’”</i> <i>“The peer coach could go with you to your appointments and to help you to understand. I’ve thought about that, to completely understand and to help communicate.”</i> <i>“If I’m at home, and all of a sudden, I’m like, ‘Why didn’t I ask her that? Let’s write it down. Then when I go to my peer coach, maybe, with those questions, they can also help me to understand that.’”</i>

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Abstract Number: 2355

Assessment of Barriers to Exercise Participation in Patients with RA

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018
Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives
Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: The benefits of exercise for patients with rheumatoid arthritis are widely reported and include sustained improvements in pain, fatigue and self-efficacy.¹ Despite this, the rates of physical activity in patients with arthritis are often lower than is recommended.^{2,3} Assessment of self-reported exercise frequency and of barriers to

participation in exercise can be facilitated by use of the Multidimensional Health Assessment Questionnaire (MDHAQ) and may assist in encouraging appropriate exercise participation in these patients.

Methods: All patients with RA seen at one academic rheumatology centre complete an MDHAQ at all visits. The MDHAQ queries the frequency of physical exercise (>30 minutes with at least some shortness of breath, sweating) with 5 response options: >3 times weekly, 1–2 times weekly, 1–2 times monthly, no exercise and cannot exercise due to disability or handicap. For analysis, the first two categories were grouped into “regular exercise” and the last three into “no regular exercise”. Scores for a range of variables including physical function, pain, patient global estimate (PATGL), fatigue, BMI and dealing with feelings of depression or anxiety were also recorded. Multilevel models were used to analyse the frequency of physical exercise, adjusting for these variables and time.

Results: 194 patients with RA and a total of 1593 clinic visits were included in the analysis (mean 8.2 visits per patient). The mean age (\pm SD) was 56 ± 14.5 years at the first visit. 79.9% were female. Patient reported ethnicity was 52% White, 19% Asian and 29% Other. The average BMI was 28.2 ± 6 kg/m². Only 33.2% reported regular exercise participation. In multivariable modelling, corrected for age, sex, time from first visit and ethnicity, patients whose average physical function score was higher (indicating worse function) demonstrated a significantly increased odds of non-participation in regular exercise (OR 1.43; $p < 0.0002$). In contrast, improved function was associated with exercise participation of at least once per week compared with no regular exercise.

Conclusion: Despite the known safety and benefits of exercise in people with RA, self-reported exercise participation remains low. Poorer physical function reduces the odds of regular exercise participation. Routine assessment of physical function and exercise participation may assist clinicians to address the importance of exercise as part of usual clinical care in patients with RA.

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3. Sokka T, Hakkinen A, Kautiainen H, et al. Physical inactivity in patients with rheumatoid arthritis: data from twenty-one countries in a cross-sectional, international study. *Arthritis Rheum* 2008; 59:42–50.

Disclosure: K. Gibson, None; G. Hassett, None; J. Descallar, None.

Abstract Number: 2356

Perceptions, Incentives, and Barriers to Clinical Trial Participation: Qualitative Evaluation of Lupus Patients, Enriched for Minority Participants

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Although SLE disproportionately affects minority racial groups, they are significantly under-represented in clinical trials. This may lead to false, underpowered conclusions in race-based sub-group analyses. We conducted focus groups to evaluate perceptions of clinical trial participation by diverse lupus patients. The analysis was guided by the Theory of Planned Behavior, a construct that behavior is determined by attitudes (*behavioral beliefs*), the opinions of others (*normative beliefs*), and perceptions about the level of control (*control beliefs*).

Methods: A qualitative research design was employed, using three 90-minute focus groups with 23 patients aged 21-72 years, enriched for minority participants (15/23; 65%). A trained moderator asked open-ended questions about clinical trial participation including: advantages and disadvantages (*behavioral beliefs*), person(s) who would approve or disapprove (*normative beliefs*), and enhancers and barriers (*control beliefs*). Discussions were recorded, transcribed, and analyzed to identify emerging themes.

Characteristics of Focus Group Participants (n=23)	
Female (n, %)	20 (87.0)
Race/Ethnicity (n, %)	
Black/African American	7 (30.4)
Hispanic/Latino	5 (21.7)
White/Caucasian	8 (34.8)
Native American	3 (13.0)
Age (median, IQR)	48.1 [41.5, 57.5]
Duration of SLE in Years (median, IQR)	11.1 [8.0, 16.8]
Healthcare Payor	
Private Insurance	10 (43.5)
Government (e.g. Medicare)	11 (47.8)
Self Pay	2 (8.7)
Employment Status	
Full Time	8 (34.8)
Retired	3 (13.0)
Disabled	6 (26.1)
Unemployed	6 (26.1)
Marital Status (n, %)	
Married	10 (43.5)
Widowed	1 (4.3)
Divorced	2 (8.7)
Separated	3 (13.0)
Single	7 (30.4)
Distance from Clinic in Miles (median, IQR)	10.7 [7.0, 17.6]
Geographic Residence (n, %)	
Urban	11 (47.8)
Suburban	8 (34.8)
Rural	4 (17.4)

Table 1. Patient Characteristics Demographic and socioeconomic information for all SLE focus group participants. Duration of SLE diagnosis ranged from 2 to 26 years and the distance traveled to the clinic ranged from 1 to 88 miles. All participants met the 1997 revised ACR classification criteria for SLE.

Results: Patient characteristics are summarized in Table 1. Initial interrater reliability was high (93%), and the discrepancies were resolved through discussion. Perceived advantages to trial participation included a better understanding of SLE, benefit for current and future patients, and access to otherwise costly or unavailable care and medication. Disadvantages included concerns about unknown aspects (placebo receipt and side effects), information burden (jargon, lengthy and redundant forms that are difficult to process), letdown (exclusion from trials, lack of efficacy, withdrawal of effective therapy), issues with life and health balance (time away and travel), inadequate feedback, and additional procedures in trials. Although some patients engaged in discussions about research participation with approving or disapproving family, friends, or co-workers, self-approval superseded external approval. Comorbidities and costs were identified as barriers. Factors identified that would ease participation in atrial included flexibility in time and scheduling, advanced notice of studies for contemplation and arrangements (childcare, work), streamlined forms with the option of electronic technology, post-study feedback, and the hope of SLE improvement (personal, drug discovery, cure).

Conclusion: Knowledge about potential benefits of trial participation was high, and minority patients appeared to be equally confident as others in making their own informed decisions. Disadvantages and barriers to clinical trial

participation identified by an SLE population enriched for minority patients include the burden of forms, and difficulties with travel, childcare, and work. These suggest a major impact from *behavioral* and *control beliefs* which will need to be considered during trial design and implementation.

Disclosure: C. Arriens, AstraZeneca, 5; F. Carthen, None; D. Grant, None; P. Kamp, None; S. Kamp, None; K. Thanou, None; T. Aberle, None; E. Chakravarty, None; J. A. James, None; J. T. Merrill, BMS, GSK, 2, BMS, GSK, UCB, Questcor, EMD Serono, Amgen, Celgene, Pfizer, RemeGen, Exagen, MedImmune, Lilly, Janssen, Xencor, Sanofi, Neovacs, Immupharma, Astellas, Glenmark, ILToo, 5, Have given talks for BMS but not for Speaker's bureau, 9; M. E. Ogunsanya, None.

Abstract Number: 2357

Reactions to Online Testimonials: A Cluster Analysis of Risk Perception and Decision Making

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SESSION INFORMATION

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Background/Purpose: Testimonials have been shown to have a strong influence on patients' decision-making. Patients are increasingly accessing the Internet as a source of medical information. In this study, we sought to examine whether people differ in the way they react to online treatment testimonials.

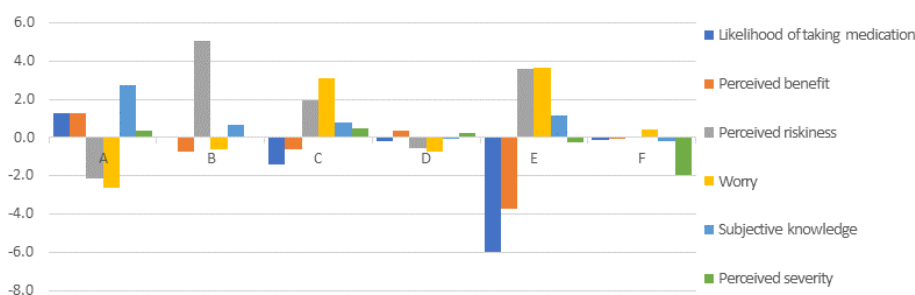
Methods: We administered a survey to Mechanical Turk workers (\bar{x} 50 years old). Participants received information describing outcomes for an osteoporosis medication. Participants' likelihood to take medication, subjective knowledge, perceived benefit, riskiness, and worry related to the medication and perceived severity of osteoporosis were measured on 11-point numeric rating scales before and after reading the description of the medication. We classified participants who accessed at least one online testimonial into different groups using cluster analysis based on the changes in the six listed outcomes. We used ANOVA and Chi-square tests to compare demographic characteristics across the clusters.

Results: 322 participants read one or more online testimonials. The mean (SD) age was 59 (7), and the majority were female (61%), white (73%) and college graduates (67%). Six clusters were identified based on the changes in six outcomes. 64 participants (Cluster A) reacted positively to the testimonials (i.e., more likely to take medication, improved subjective knowledge, the greater perceived benefit of medication, and less perceived riskiness and worry about the medication). Nineteen participants (Cluster E) surprisingly had more misunderstanding of disease then made suboptimal decisions after the intervention. Meanwhile, the intervention changed participants risk perception (Clusters B, D, F) differently, but had a very limited influence on their likelihood to take medication.

We found a statistical difference in ethnicity ($p < 0.01$) and numerical level ($p = 0.02$) across six clusters. Higher numeracy level is positively associated with the better perception of disease and treatment.

Conclusion: Participants reacted drastically different to online testimonials. Only a small proportion of participants benefits significantly from online testimonials, which tend to be high numerates. Table 1. Description of the sample according to the clusters of participants

Figure 1. Changes in each outcome across six clusters



Cluster	A	B	C	D	E	F	p-Value
N	64	14	62	119	19	44	
Age	59.7	60.0	58.8	59.8	60.4	57.5	0.44
Male	45.3%	42.9%	33.9%	36.1%	21.1%	50.0%	0.22
College graduate or higher	71.9%	71.4%	67.7%	67.2%	57.9%	61.4%	0.82
Race-White	79.7%	71.4%	61.3%	83.2%	84.2%	50.0%	<0.01
Numeracy level- High	46.9%	28.6%	30.6%	32.8%	31.6%	13.6%	0.02
Family history of lower bone density/osteoporosis	29.7%	21.4%	30.6%	35.3%	15.8%	34.1%	0.57
Medical history of bone fracture	6.3%	14.3%	9.7%	12.6%	5.3%	20.5%	0.27
Taking Rx medication regularly	53.1%	50.0%	56.5%	51.3%	52.6%	52.3%	0.99
Average rating of accessed reviews	3.4	2.7	3.3	3.3	3.1	3.5	0.05
Number of accessed positive review	10.7	8.1	9.1	8.7	6.0	7.6	0.53
Number of accessed negative review	4.3	3.6	3.8	3.5	4.2	2.6	0.06

Disclosure: C. Jiang, None; L. Fraenkel, None.

Abstract Number: 2358

Risk Factors for Persistent Discordance in Global Assessment of Rheumatoid Arthritis (RA) Disease Activity between RA Patients and Their Physicians: Analysis Based on a Nationwide RA Database (2011 to 2016)

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

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Background/Purpose: Discordance between patient global assessment (PGA) and physician global assessment (PhGA) of RA disease activity may be problematic in clinical practice. Previous studies, including ours (Tago, Int JRheum Dis, 2018), have shown that PGA-PhGA discordance is most strongly associated with pain, followed by functional impairment. The aim of the present study was to investigate the factors responsible for 5-year persistence of PGA-PhGA discordance using a nationwide RA database in Japan (*NinJa*).

Methods: Positive discordance and concordance were defined as PGA minus PhGA (PGA-PhGA) ≥ 3 cm and between -3 cm and 3 cm, respectively. RA patients whose 10-cm visual analog scale (VAS) data were available and who were registered in both *NinJa* 2011 and *NinJa* 2016 (n=4484) were investigated for the association of positive PGA-PhGA discordance in 2016 with clinical manifestations observed in 2011, including age, sex, age at RA onset, disease duration, pain VAS, tender joint counts (TJC), swollen joint counts (SJC), modified Health Assessment Questionnaire (mHAQ), stage, class, disease activity score in 28 joints-C-reactive protein level (DAS28-CRP), and PGA-PhGA discordance status.

Results: The mean PGA-PhGA was significantly higher in 2016 (1.14 ± 1.96) than in 2011 (1.03 ± 1.80) ($p < 0.01$). On reviewing the discordance status in 2011, we found that the mean PGA-PhGA of RA patients who had been classified as showing positive discordance was 2.13 ± 2.13 in 2016, which was significantly higher than those classified as concordance in 2011 (1.12 ± 1.74) ($p < 0.01$). Categorical variable-based analysis also demonstrated that 41.2% of RA patients in the positive discordance group in 2011 remained in the same group in 2016, while only 13.1% in the concordance group shifted to the positive discordance group in 2016; this difference was significant ($p < 0.01$). Stepwise multivariate logistic regression analysis identified high mHAQ values, pain VAS, age, and positive discordance status as significant risk factors for the shift into positive discordance 5 years later (Table 1).

Conclusion: We have demonstrated that PGA-PhGA discordance expanded significantly over the 5-year period, and that this positive discordance can be persistent. Functional impairment, pain, existing discordance, and age are risk factors for persistent discordance. Therefore, RA care providers should focus on ameliorating functional impairment and alleviating pain to circumvent the development of PGA-PhGA discordance.

Table 1 Univariate (unadjusted) and stepwise multivariate (adjusted) logistic regression analysis of predictors of discordance 5 years later regarding PGA-PhGA discordance.

	Unadjusted OR	p-value	Adjusted OR	p-value
Age	1.03 [1.03-1.04]	<0.01	1.02 [1.02-1.03]	<0.01
Female	1.21 [0.98-1.51]	0.08	-	-
Disease duration	1.03 [1.02-1.04]	<0.01	-	-
Stage III-IV	1.62 [1.39-1.90]	<0.01	-	-
Class 3-4	2.08 [1.71-2.52]	<0.01	-	-
Pain VAS	1.33 [1.28-1.37]	<0.01	1.20 [1.13-1.26]	<0.01
TJC	1.03 [1.02-1.05]	<0.01	-	-
SJC	1.01 [0.98-1.03]	0.54	-	-
DAS28-CRP	1.36 [1.27-1.46]	<0.01	0.80 [0.72-0.90]	<0.01
mHAQ	2.54 [2.25-2.88]	<0.01	1.65 [1.41-1.92]	<0.01
PGA-PhGA	1.48 [1.42-1.55]	<0.01	1.25 [1.19-1.32]	<0.01

*OR, Odds ratio.

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Abstract Number: 2359

Systemic Lupus Erythematosus Outcome Concerns: Identifying Pain As the Major Discrepancy between Rheumatologists and Patients

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SESSION INFORMATION

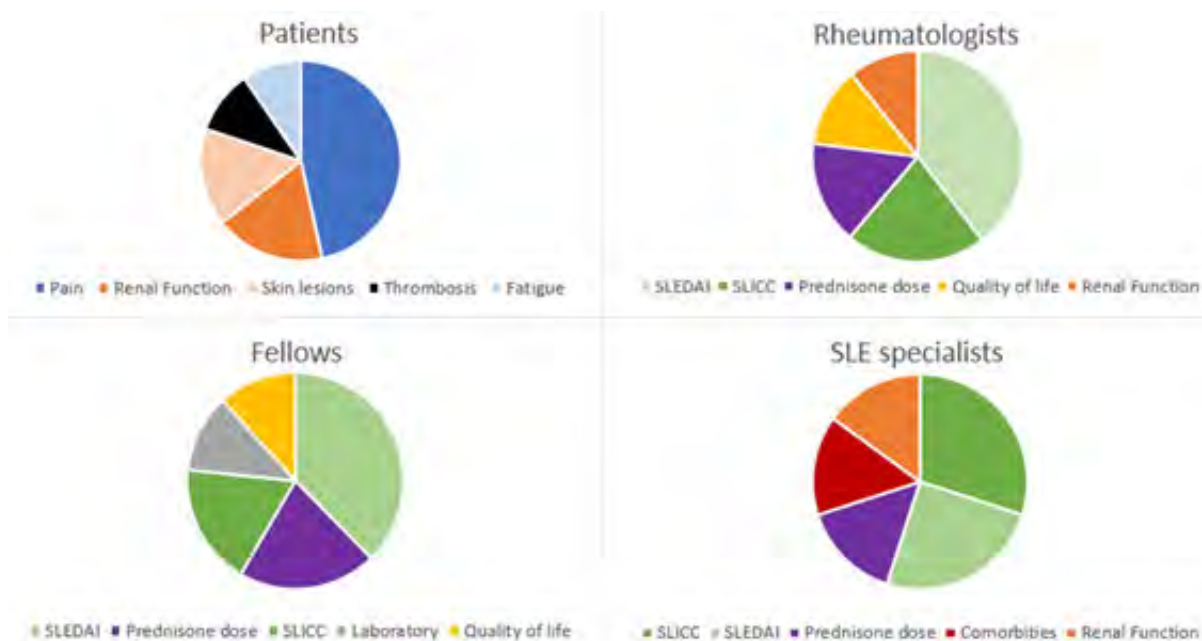
Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Now-a-days there is a growing trend of switching to a more patient-centered healthcare system, with a widespread use of patient-reported outcomes (PROs). However, most of PROs questionnaires are designed by physicians/specialists and patients are underrepresented in this development. This research's purpose was to identify and compare major outcomes that matter for patients and rheumatologist aiming to better address patient's needs.



Methods: 75 consecutive SLE patients (SLICC criteria, 2012) and 53 Rheumatologists from a tertiary center were invited to answer an open questionnaire inquiring their 5 major concerns regarding lupus outcomes. Among the 53 Rheumatologists there were 5 SLE specialists and 20 rheumatology fellows. The top 5 concerns of each group were assessed and frequencies were compared with appropriate tests. The agreement rate was calculated considering the sum of lowest frequency of each concern that appeared in all the analyzed groups.

Results: The top 5 concerns raised by patients were: pain (47%), renal function (18%), skin lesions (16%), thrombosis (10%) and fatigue (10%). The top 5 concerns among rheumatologists were: SLEDAI (40%), SLICC-Damage Index (SDI) (22%), prednisone dose (16%), quality of life (12%) and renal function (11%). The agreement rate between all rheumatologists was 63% (all agreed that SLEDAI, SDI and prednisone dose were major concerns). Fellows pointed laboratory tests (such as anti-DNA and Complement levels) as a major concern not reported by the other rheumatologists ($p=0.002$). SLE specialists pointed comorbidities (such as hypertension and obesity) as main concerns not reported by the other rheumatologists ($p=0.032$). The agreement rate between patients and rheumatologists was 45% (renal function, skin lesions and thrombosis). The main difference between patients and rheumatologists were the pain ($p=0.0001$) and fatigue ($p=0.023$). Fatigue was reported as an outcome concern by 10% of the patients but less than 2% of rheumatologists, however quality of life pointed by rheumatologists may address partially the fatigue concept. Regarding pain, half was related to generalized pain and the other half related solely to arthralgia and therefore the majority would not be scored by SLEDAI (that consider only arthritis as a domains).

Conclusion: We identified that there are different outcome concerns between patients and rheumatologists for lupus treatment. Pain was the most important discrepancy since it is not adequately addressed by the routine SLE indexes reported as the top 5 Rheumatologists outcome concerns. Improving physician's awareness of patient's outcome concerns and of comorbidities, as pointed out by the specialist, may provide a better assistance and ensure treatment adherence in this disease.

Figure 1. Top 5 major outcome concerns among SLE patients and Rheumatologists

Disclosure: I. Bertoglio, None; G. Abrahão, None; E. Bonfa, Fundação de Amparo à Pesquisa do Estado de São Paulo, 2, Conselho Nacional de Desenvolvimento Científico e Tecnológico, 2; M. Lopes, None.

Abstract Number: 2360

Perceptions of Patients with Rheumatoid Arthritis about Self-Assessment of Disease Activity after Watching an Educational Video: Qualitative Pilot Results from the Auto-DAS in Middle Eastern Arab Countries Study

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SESSION INFORMATION

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Background/Purpose: Empowering RA patients through education is linked to improved adherence, treatment decisions and speeding up the assessment process during consultation. The purpose of the study is to evaluate perceptions of patients with RA about self-assessment of their disease activity after watching an educational video about self-assessment using Disease Activity Score 28 (DAS28).

Methods: An educational video was developed to instruct patients with RA on how to assess their disease activity using DAS28 (autoDAS). Consecutive RA patients attending rheumatology clinics during their routine visits (Bahrain, Egypt, Jordan, Lebanon, KSA, UAE) were invited to participate in a structured interview with the study coordinator after the doctor's visit. A purposely-designed video was displayed first, followed by the interview that consisted of a combination of closed and qualitative open-end questions.

Results: 62 patients participated in the study (Fig 1). 95% stated that performing their own assessment was feasible or partially feasible, and 97% said that they felt totally or partially capable of doing it. 59% answered that they felt confident

Question	Answer, n (%)		
	Yes	Partially	No
How feasible it is for you to do your own assessment of your disease activity using auto-DAS?	78	22	2
Do you feel capable in doing your own assessment using auto-DAS?	56	29	3
Do you feel confident in doing your own assessment using auto-DAS?	55	33	9
Do you think that your own evaluation of your disease using auto-DAS can replace the doctor's visit?	1	18	76
Will you continue to do your own self-assessment using auto-DAS on the long term and after the completion of the study?	44	30	8
Do you think that the video was helpful in facilitating your self-assessment using auto-DAS?	91	5	6

in performing auto-DAS all the times. Nevertheless, 76% stated that it will not replace the doctor's visit. The majority (96%) felt that the video was easy and helpful in facilitating their self-assessment (Fig 2).

Open-end questions identified the main advantages: Better understanding of the disease ("makes me aware when disease is active, provides good education about disease, will help me cope better"), Easier communication with physician ("will inform me about the joint I need to tell my doctor about"), Time management ("Less time with physician, less visits meaning less cost"). They also identified some challenges: Calculation was cumbersome (with the calculator being easier than a website), Auto-assessment needs practice.

Conclusion: The majority of patients felt that the video was helpful in many aspects of disease assessment, and felt capable of performing auto-evaluation, with DAS calculation being the hardest part. Most stated that it will not replace the doctor's visit but will help better understanding of the disease and coping, thus better informing the doctor and reducing visit time. Figure 1. Patients Characteristics

Patients, N	62
Age, mean	51.2 yo (SD 13.4)
Female	86%
University education	40%
RA duration, mean	9.3 years (SD 6.6)
Time to diagnosis, mean	1.9 years (SD 6.4)
Rheumatoid Factor +	67%
ACPA +	46%
Bone erosions	48%
Biologic treatment	32%
Targeted Synthetic DMARD	11%
Corticosteroids	24%
Common Comorbidities	Smoking 19%, Hypertension 13%, Osteoporosis 13%, Dyslipidemia 11%, Diabetes 11%, Fibromyalgia 6%

Figure 2. RA patients' responses to some questions of the structured interview.

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Abstract Number: 2361

Needs, Experiences and Views of People with Rheumatic and Musculoskeletal Diseases about Self-Management Mobile Health Apps: Results of a Mixed Methods Approach

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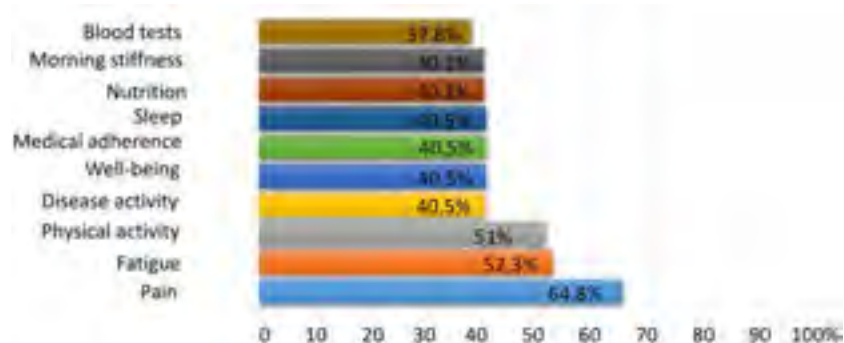


Figure 1. Top 10 aspects to be addressed by the ideal self-management app.

Background/Purpose: While the increasing availability of apps may enable people with rheumatic and musculoskeletal diseases (RMDs) to better self-manage their health, evidence on the development and evaluation of apps for patients that fulfill quality requirements for their implementation as part of routine care is lacking. This work aims to explore the needs, experiences and views of people with RMDs about mHealth apps, seeking to obtain direct patient feedback on preferences for components, content and structure of mHealth apps for self-management of their conditions.

Methods: This was a mixed methods study starting with an initial qualitative phase involving a patient focus group (UK). The latter was followed by a survey based on the key themes emerging from this focus group. The survey validation involved a pre-survey test round based on 5 patients (UK, Slovakia, Germany, The Netherlands, Cyprus). Feedback was collected during the test phase and used to improve the survey. Survey was disseminated through patient associations across EU, USA, Canada and Australia.

Results: The focus group included 6 rheumatoid arthritis (RA) patients. Half of them had used a self-management app at least once. The use of existing apps was reported as time consuming and not always useful due to lack of functionality, with the need for more tailored apps expressed by all patients. Survey participants: 304 patients across European countries, USA, Canada and Australia. Main age category was 45-54 years (25.7%), 78% were women. Patients were diagnosed mostly with RA (n=115, 37.8%), psoriatic arthritis (n=53, 17.4%), ankylosing spondylitis (n=47, 15.5%), fibromyalgia (n=43, 14.1%), osteoarthritis (n=41, 13.5%). Most patients (n=141, 46.7%) had been diagnosed for over 10 years. Most were using a smartphone (n=261, 85.9%); 20.7% (n=63) were using a mHealth Apps. 71% (n=218) agreed that such Apps could make clinic visits more efficient. Patients were mostly interested in an app enabling self-monitoring of health parameters (58.6%), disease activity (51.3%), lifestyle (40.7%); communication with their health care providers (43.4%) and dealing with medication side effects (40.1%). The top ten aspects to be addressed by an ideal App are detailed in Figure 1. Collection of anonymized health data for research purposes is mostly accepted by the patients (57.9%, n=176).

Conclusion: Patients considered that the use of an App tailored for disease self-management and developed in close collaboration with them could benefit their health. The development of such Apps will require standardization and quality check processes. This work will be used as a background for developing future EULAR points to consider for the development, evaluation and implementation of mobile health applications for self-management in patients with rheumatic diseases.

Disclosure: A. Najm, None; E. Nikiphorou, None; H. Lempp, None; L. Gossec, None; F. Berenbaum, None.

Abstract Number: 2362

Understanding Patients' Perceptions of Gout

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Past research has shown that patients' (pts') knowledge of their disease influences health-related behavior. The objective of this study is to explore gout pts' knowledge of the disease, treatment options and chronic management, as well as identify their sources of health information. With only half of gout pts adherent to gout medications, our goal is to guide the development of gout support tools by identifying gaps in pt knowledge.

Methods: We developed an online survey to gather information about pts' knowledge, beliefs and perceptions of gout. Pt members of the Arthritis Power registry or Creaky Joints community were asked to participate if they had a self-reported diagnosis of gout. Pts completed six (Pain Interference, Fatigue, Sleep Disturbance, Physical Function, RAPID3, Gout Flare) pt-reported outcome measures. Pearson's Chi-squared test was used to assess significance. Open-ended questions were analyzed with LIWC 2015, an automated text analysis program.

Results: To date, 103 participants completed the survey; 55% were female, 53% had an annual income \geq \$50,000, 84% white and average age of 56 years (range 32 – 80). 85% believe uric acid causes gout, however, only 50% believe uric acid-controlling medication is the best way to manage the disease. Additionally, 81% believe gout is best managed by diet change. Pts currently experiencing a gout flare were more likely to believe gout is best managed with NSAIDs than those not experiencing a flare (37% vs 16%; $p=0.02$) (Table). The qualitative results showed that non-flaring pts tended to use risk-oriented language while flaring pts used reward-oriented language (Figure). Pts receive information about gout from online health education sites and their PCP at similar rates (60% and 53%, respectively). Non-flaring pts preferred to get information online more than flaring pts (63% vs. 44%; $p=0.06$). Men were more likely to seek information from their rheumatologist than women (28% vs 13%; $p=0.05$).

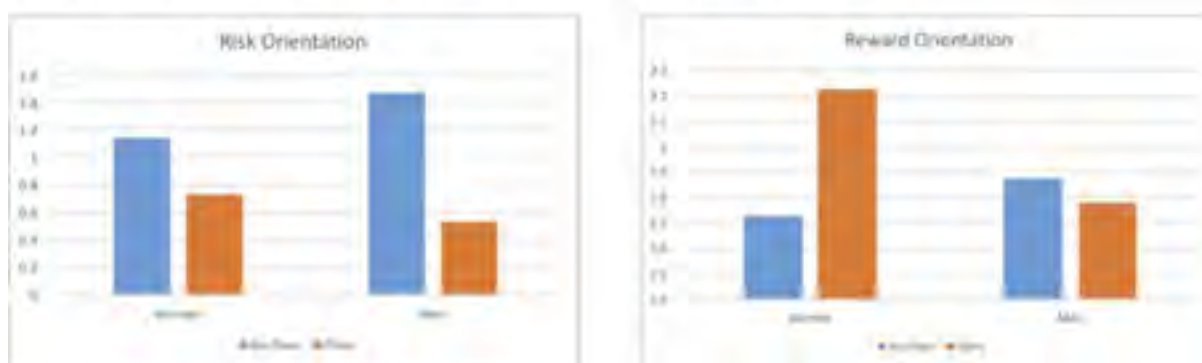
Table: Patients' Perceptions of Causes of Gout

	N (N=103)	Flare (n=41)	No Flare (n=62)	p-value
What do you believe is the main cause of gout?	n (%)	n (%)	n (%)	
Diet	80 (77.7)	25 (61.0)	55 (88.7)	<0.01*
Alcohol consumption	35 (34.0)	10 (24.4)	25 (40.3)	0.09
Obesity	45 (43.7)	17 (41.5)	28 (45.2)	0.71
Medical conditions	47 (45.6)	26 (63.4)	21 (33.9)	<0.01*
Certain medications	22 (21.4)	12 (29.3)	10 (16.1)	0.11
Family history of gout	51 (49.5)	23 (56.1)	28 (45.2)	0.28
Age and sex	23 (22.3)	8 (19.5)	15 (24.2)	0.58
Recent surgery or trauma	6 (5.8)	2 (4.9)	4 (6.5)	0.74
What do you believe causes gout attacks?	n (%)	n (%)	n (%)	
Diet	59 (57.3)	16 (39.0)	43 (69.4)	<0.01*
Alcohol consumption	14 (13.6)	4 (9.8)	10 (16.1)	0.36
Certain medications	11 (10.7)	8 (19.5)	3 (4.8)	0.02*
Uric acid level	87 (84.5)	37 (90.2)	50 (80.7)	0.19
Stress	25 (24.3)	10 (24.4)	15 (24.2)	0.98
How do you believe gout is best managed?	n (%)	n (%)	n (%)	
Diet change	83 (80.6)	29 (70.7)	54 (87.1)	0.04*
Limiting alcoholic beverage intake	34 (33.0)	8 (19.5)	26 (41.9)	0.02*
Exercising regularly and losing weight	50 (48.5)	19 (46.3)	31 (50.0)	0.72
Alternative remedies	27 (26.2)	10 (24.4)	17 (27.4)	0.73
NSAIDs	25 (24.3)	15 (36.6)	10 (16.1)	0.02*
Colchicine	28 (27.2)	14 (34.2)	14 (22.6)	0.20
Corticosteroids	12 (11.7)	9 (22.0)	3 (4.8)	0.01*
Medications that block uric acid production or improve uric acid removal	50 (48.5)	19 (46.3)	31 (50.0)	0.72

*statistically significant at $\alpha=0.05$

Flare status as determined by gout flare assessment (Gaffo et al., 2012)

Figure: Risk-Oriented Language vs. Reward-Oriented Language



Conclusion: The survey shows variation in beliefs about gout and in words used to describe gout by gender, age and gout flare status. Food and lifestyle misconceptions remain a large component of pts' conversations surrounding gout. The majority of pts currently believe gout can be managed through diet rather than prescribed medications, suggesting insufficient pt knowledge about gout. While many pts prefer to access information online, there is still an underutilization of rheumatologists. Developing decisional support tools available at health care offices may help increase knowledge about gout and improve gout health care outcomes.

Disclosure: K. Gavigan, Global Healthy Living Foundation, 3; K. Jordan, None; A. Meara, None; W. B. Nowell, GlaxoSmithKline, 1, Merck & Co., 1, Pfizer, Inc., 1, 2, AbbVie Inc., 1, Bristol-Myers Squibb, 1, 2, Eli Lilly and Co., 1, 2, Janssen, 1, Novartis, 2.

Abstract Number: 2363

Examining Workplace Supports in the Context of RA Disease Activity

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: RA can diminish patients' (pts) work productivity and increase the risk of long-term disability, economic insecurity and worsening health, but limited research informs these issues. The objective was to identify associations between RA and treatment status on pts' productivity and workplace support, using real-world data from the Arthritis Power registry.

Methods: US-resident adult pts with physician-diagnosed RA and a history of or current DMARD use were surveyed from the Arthritis Power registry via smartphone or web app. Pt-reported outcomes included Patient-Reported Outcomes Measurement Information System (PROMIS) pain interference, fatigue, sleep disturbance, physical function, social participation and Routine Assessment of Pt Index Data 3 (RAPID3) score. The Work Productivity and Activity Impairment (WPAI) questionnaire was used to rate how RA affected pt work productivity for past 3 months (scale: 0 [no effect] to 10 [completely prevented from working]).

Results: Of 296 pts, 88% were currently treated with DMARDs (non-biologic and biologic) and 74% had high disease activity (HDA) assessed by RAPID3 (>12). HDA was associated with lower education, lower employment and lower full-time employment, with a higher proportion of pts with HDA reporting being disabled ($p<0.05$ for each). Average self-reported days missed from work due to problems associated with RA in the past 3 months differed between pts with and without HDA (6.1 vs 3.8 days, respectively; $p<0.05$). Pts without HDA missed more work days for medical appointments than pts with HDA (2.6 vs 1.2 days, respectively). Pts with HDA missed more days due to side effects from RA treatment than pts without HDA (mean: 0.5 vs 0.1 days, respectively). RA affected work productivity to a greater extent in pts with HDA than without (WPAI scores 5.3 and 3.3, respectively; $p<0.05$). Unemployed pts had more physically demanding tasks

(e.g. heavy load lifting) in their most recent paid position than currently employed pts (Table 1). Pts who were employed had access to greater workplace flexibility (e.g. changes in start and finish times, working from home) than unemployed pts.

Conclusion: Despite treatment with DMARDs, the majority of HDA pts with RA were more likely to be unemployed or disabled. Physically demanding tasks and less flexible work arrangements were associated with a higher unemployment rate. Attaining lower disease activity and facilitating workplace flexibility (i.e. assign fewer physical tasks, permit flexible hours) may help pts with RA remain employed. Work flexibility policies have been proposed or passed federally in 33 states, yet there is a need for greater visibility, compliance and accessibility to these options for pts with RA. Indirect costs of RA in the workplace should be considered when determining the total cost of RA care.

Medical writing assistance: Carol Keys, PhD (Caudex); funding: Bristol-Myers Squibb.

Table 1 Workplace environment and flexibility by employment status (N=296)

Employment characteristics, n (%)	Currently employed (n=170)	No longer employed (n=126)
Physically demanding tasks		
High physical effort*	14 (8)	40 (32)
Lifting heavy loads*	5 (3)	19 (15)
Stooping, kneeling, crouching*	9 (5)	40 (32)
Standing for majority of time*	15 (9)	28 (22)
Traveling within the community or long distance*	12 (7)	19 (15)
Sedentary tasks		
Good eyesight	108 (64)	85 (67)
Intense concentration or attention*	91 (54)	90 (71)
Use of computers*	124 (73)	72 (57)
Sitting for majority of time*	57 (34)	26 (21)
Altering work hours		
Frequently changing starting and quitting times (e.g. daily basis)*	76 (45)	29 (23)
Vary work schedule from typical work schedule*	71 (42)	27 (21)
Compress work week (i.e. longer hours on fewer days)*	48 (28)	20 (16)
Occasionally changing starting and quitting times*	92 (54)	46 (37)
Input into amount of overtime hours*	66 (39)	33 (26)
Controlling work		
Control breaks*	120 (71)	58 (46)
Work from off-site location for part or all of work week*	59 (35)	18 (14)
Take extra "unpaid" vacation days	44 (26)	25 (20)

All values are n (%).

*p<0.05, differences bolded.

Disclosure: W. B. Nowell, GSK, Merck & Co., AbbVie Inc., Janssen, Pfizer, Bristol-Myers Squibb, Eli Lilly, 1, GSK, Pfizer, Bristol-Myers Squibb, Eli Lilly, Novartis, 2, Global Health Living Foundation, 3; K. Gavigan, Global Healthy Living Foundation (GHLF), 3; G. E. Gonzales, None; S. Venkatachalam, None; J. R. Curtis, AbbVie, Amgen, Bristol-Myers Squibb, Corrona, Janssen, Lilly, Myriad, Pfizer, Radius, Roche/Genentech, UCB, 2, AbbVie, Amgen, Bristol-Myers Squibb, Corrona, Janssen, Lilly, Myriad, Pfizer, Radius, Roche/Genentech, UCB, 5; S. Ghazanfari, Bristol-Myers Squibb, 3; D. Cavazzini, Bristol-Myers Squibb, 3; L. Ferri, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3.

Abstract Number: 2364

Vasculitis Patient Journey: A Scoping Review of Patient Experiences with Vasculitis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Optimal management of vasculitis needs to address disease aspects of significance to patients. Understanding the patients' journey with vasculitis allows clinicians to identify patient goals for treatment. We aimed to review the existing literature regarding patient perceptions of vasculitis' effect on four main domains of health: physical, psychological, social, and financial.

Background/Purpose: Patients' illness perceptions (IP) influence self-management, adherence, and outcomes. Little is known about how cultural background and the lived experiences influence IP among rheumatoid arthritis (RA) patients. We compared IP in people with inflammatory arthritis in men and women, by age of onset (juvenile idiopathic arthritis - JIA vs. RA), and by language/culture (English vs. French Canadian).

Methods: RA patients receiving care at an academic RA Clinic in Montreal, Canada completed the illness perception questionnaire –revised form (IPQ-R) between 2013 and 2015 during a clinic visit. Sociodemographic and RA clinical characteristics were also collected. T-tests and chi-square were used to compare characteristics and mean IPQ-R domain scores between groups by sex, diagnosis and language.

Results: Patients were mostly female, well-educated, spoke English, and had established RA. Over half (56%) were in remission or low disease activity. Mean HAQ ($p<.01$) and pain ($p<.01$) were significantly higher among women. Age, % speaking English, and education were significantly higher, and disease duration and CRP were lower in RA vs. JIA ($p's<.05$). Sociodemographic and RA characteristics were similar by language. Personal and treatment control, timeline-acute/chronic, and disease consequences were similar among groups. As compared to those with RA, JIA patients had significantly higher mean Illness Coherence and Identity scores, and lower emotional representations Table 1. English speaking patients had significantly higher mean Timeline-cyclical scores; a similar trend was seen for women vs. men.

Conclusion: Illness perceptions related to the chronicity of their disease, and confidence that treatment and lifestyle choices could help control their disease were similarly high among all subgroups. As compared to people with RA, those with JIA reported a better understanding of disease-related symptoms, were more likely to identify having JIA as part of who they are, and reported less emotional distress in relation to their disease. English speaking patients and women reported less confidence in their ability to predict their symptoms and disease course. Understanding how patients view themselves, their inflammatory arthritis, and perceptions of timelines and controllability may offer new insight into ways to positively influence treatment expectations, adherence, and self- management.

	Sex	N	Mean	SD	Sig	Diagnosis	N	Mean	SD	Sig	Language	N	Mean	SD	Sig
Timeline - Cyclical	Women	122	14.0	3.3	.071	RA	120	13.7	3.4	.378	English	114	13.4	3.3	.025
	Men	27	12.7	3.1		JIA	29	14.3	3.1		French	35	14.9	3.3	
Illness Coherence	Women	103	18.8	4.6	.350	RA	99	17.5	7.9	.036	English	97	18.2	7.8	.850
	Men	22	15.8	14.4		JIA	26	20.9	3.5		French	28	18.5	5.4	
Emotional Representations	Women	122	16.8	5.4	.203	RA	120	17.3	5.6	.001	English	114	16.5	5.5	.822
	Men	27	15.3	6.2		JIA	29	13.4	4.3		French	35	16.7	6.0	
Identity	Women	107	5.4	2.4	.545	RA	106	5.7	2.5	.005	English	102	5.5	2.5	.757
	Men	25	5.7	2.5		JIA	26	4.3	1.9		French	30	5.3	2.2	

Disclosure: S. J. Bartlett, None; M. Useche, None; M. C. Bazan Bardales, None; E. Hazel, None; I. Colmegna, None.

Table 1. Mean scores on Illness Perception Domains by sex, diagnosis, and language.

	Sex	N	Mean	SD	Sig	Diagnosis	N	Mean	SD	Sig	Language	N	Mean	SD	Sig
Timeline - Cyclical	Women	122	14.0	3.3	.071	RA	120	13.7	3.4	.378	English	114	13.4	3.3	.025
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Identity	Women	107	5.4	2.4	.545	RA	106	5.7	2.5	.005	English	102	5.5	2.5	.757
	Men	25	5.7	2.5		JIA	26	4.3	1.9		French	30	5.3	2.2	

Abstract Number: 2366

Facilitating Shared Decision Making in Psoriatic Arthritis: Factors Influencing Patient Preference for Treatment Mode of Administration

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Table. Most frequently reported reasons ^a for choosing or not choosing each treatment mode as 1st choice			
Reasons for choosing oral, n (%) (N=42)		Reasons for not choosing oral, n (%) (N=43)	
Fast and easy to take/swallow	32 (76.2)	Possible interactions with other pills	22 (51.2)
Familiarity	28 (66.7)	Hard to remember	21 (48.8)
Easier to remember	26 (61.9)	Do not want another pill	15 (34.9)
Portable	22 (52.4)	Frequency of dosing	13 (30.3)
Reasons for choosing SI, n (%) (N=29)		Reasons for not choosing SI, n (%) (N=56)	
Do at home	22 (75.9)	Avoid need/pain/sticking self	31 (55.4)
On it and you're done (easy, fast)	18 (62.1)	Avoid syringe preparation/dispense	17 (30.4)
Frequency of dosing	18 (62.1)		
Having control	16 (55.2)		
Easier to remember	11 (37.9)		
Familiarity	10 (34.5)		
Reasons for choosing CI, n (%) (N=1)		Reasons for not choosing CI, n (%) (N=84)	
Feel comfortable with experts doing it	1 (100)	Avoid trip to doctor's office/clinic	72 (85.7)
Feel safe, well cared for	1 (100)		
Fast results	1 (100)		
Reasons for choosing infusion, n (%) (N=13)		Reasons for not choosing infusion, n (%) (N=72)	
Frequency of dosing	8 (61.5)	Avoid trip to doctor's office/clinic	54 (75.0)
Feel safe, well cared for	5 (38.5)	Long infusion time	36 (50.0)
Feel comfortable with experts doing it	5 (38.5)		
Accountability/can't forget	5 (38.5)		
^a Reported by ≥30% of patients			
CI, clinic injection; N, number of patients analyzed; SI, self-injection			

SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

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Session Time: 9:00AM-11:00AM

Background/Purpose: Shared decision making is key to optimizing management of patients (pts) with psoriatic arthritis (PsA).¹ Few studies have evaluated pt preferences for treatment administration across different countries. Qualitative research allows understanding of pt perspectives to help guide this process. This study aimed to understand PsA pt preferences, with pt justification, for treatment administration modes.

Methods: Pt-reported demographic and disease information was obtained at screening with qualitative interviews conducted using a semi-structured interview guide in adult PsA pts with current DMARD (biologic/non-biologic) experience in the US, UK, France, Germany, Italy, Spain, and Brazil. Choice ranking and 100-point allocation tasks were used to evaluate order and strength of preference (0 to 100 [low to high]) across 4 treatment modes: oral (once daily), self-injection (SI; weekly), clinic injection (CI; weekly), and infusion (monthly). Transcripts were in English. Analyses were descriptive (ATLAS.ti v7.5).

Results: 85 interviews (25 US; 10 in each other country) were conducted (60% female; mean age, 49.6 years; mean age at PsA diagnosis, 39.7 years). Most pts (70.6%) reported moderate/severe PsA with mean joint pain (4.7), fatigue (5.2), and joint/skin severity (5.9) on a 0 to 10 (low to high) numeric rating scale. Most commonly reported symptoms were pain (87.1%), skin plaques (69.4%), stiffness (52.9%), and joint swelling (48.2%). Current PsA treatment mode was oral (62.3%), injection (63.5%), and infusion (5.9%); 80.0% and 29.4% of pts had experience with injections and infusions, respectively. Oral was allocated the highest mean (standard deviation) preference points (43.9[31.9]) and was more frequently ranked 1st choice (49.4%) vs SI (32.4 [24.8];34.1%), infusion (14.5 [20.0]; 15.3%), and CI (9.2 [10.0]; 1.2%). More US than European pts (88.0% vs 38.0%; p<0.001) ranked oral as 1st choice. Overall, 48 (56.5%) pts had a 'strong' 1st choice preference (point allocation ≥60); most chose oral (66.7%) vs SI (27.1%), infusion (6.3%), and CI (0.0%). Speed of administration was the most common reason for choosing oral (76.2%; Table) and for SI was home administration (75.9%). The most common reason for not choosing oral was possible interaction with other pills (51.2%) and for SI was to avoid needle pain (55.4%).

Conclusion: More pts preferred oral as a PsA treatment mode followed by SI, and preference for oral was greater in the US than Europe. Reasons for pt preferences included speed/ease of use, safety concerns, feeling of control, and to avoid pain/needles; 56.5% of pts felt strongly about their 1st choice preference. Discussions with health care professionals and/or pt support groups about PsA treatment mode options may help the shared decision-making process for choosing appropriate treatment. 1. Garrido-Cumbrera et al. Rheumatol Ther 2017; 4: 219-31

Disclosure: D. Aletaha, AbbVie, Bristol-Myers Squibb, MSD, 2, AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Medac, Merck, MSD, Pfizer Inc, Roche, UCB, 5, AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Medac, Merck, MSD, Pfizer Inc, Roche, UCB, 8; M. E. Husni, None; J. F. Merola, AbbVie, Amgen, Biogen Idec, Eli Lilly, Janssen, Kiniksa, Mallinckrodt, Momenta, Novartis, Pfizer Inc, Sumamed, UCB, 5, AbbVie, 8; R. Ranza, AbbVie, Janssen, Novartis, Pfizer Inc, 5, AbbVie, Janssen, Novartis, Pfizer Inc, 8; H. Bertheussen, Pfizer Inc, 5; R. Lippe, Pfizer Inc, 1, 3, Pfizer Inc, 3; P. Young, Pfizer Inc, 1, Pfizer Inc, 3; J. C. Cappelleri, Pfizer Inc, 1, Pfizer Inc, 3; T. M. Brown, None; C. Ervin, RTI Health Solutions (non-profit independent research institute), 3; M. A. Hsu, Pfizer Inc, 1, Pfizer Inc, 3; L. Fallon, Pfizer Inc, 1, Pfizer Inc, 3.

Abstract Number: 2367

Acceptance Rate and Sociological Factors Involved in the Switch from Originator to Biosimilar Etanercept (SB4)

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

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Background/Purpose: Biosimilars represent major potential savings while preserving treatment quality. However, few data are known on how to address the switch from originator to biosimilar in outpatient settings. Our aim was to study acceptance rate and factors influencing acceptance of the switch from originator etanercept (Enbrel®) to biosimilar etanercept (SB4, Bénépali®) in patients with rheumatic disease.

Methods: Patients with a well-controlled rheumatic disease consulting in our rheumatology department were offered the switch for SB4. After oral and written information concerning biosimilar, free choice to accept the switch was left to the patients. The main outcome was primary switch acceptance rate defined by switch acceptance during the initial consult. Real switch adherence, socio-cultural factors and beliefs influencing switch acceptance rate were retrieved during a telephonic interview at distance from the consultation.

Results: Fifty-two patients were eligible for the switch: 32 (62%) with spondyloarthritis and 20 (38%) with rheumatoid arthritis. At the time of the consult, the primary acceptance rate was 92% (48/52). Patients refusing the switch were more likely to report a bad opinion on generic drugs (100% vs 11%, $p < 0.001$). Other patient characteristics were roughly identical except for a statistical trend in the refusal group toward older age (61.4 vs 50.7 years, $p = 0.08$) and longer disease duration (26 vs 12.1 years, $p = 0.05$). Despite initial acceptance, two patients did not begin SB4 after receiving negative information by their regular pharmacist. Real SB4 switch rate (defined as biosimilar use) was 85% (44/52) and 86% (38/44) of patients reported a good experience of the switch.

Conclusion: When presented with positive and reassuring information, most patients agree to the switch from originator to biosimilar etanercept. Patient information, physician and pharmacist knowledge on biosimilars should be addressed in order to improve their diffusion.

Disclosure: M. Scherlinger, None; V. Germain, None; E. Langlois, None; T. Schaeffer, Pfizer, Inc., 2, 5, UCB, Inc., 5, Amgen Inc., 5, AbbVie Inc., 5, Janssen, 5, Roche, 5, BMS, 5, MSD, 5, Novartis, 5.

Abstract Number: 2368

Patient Preferences for Disease Modifying Anti-Rheumatic Drug Treatment in Rheumatoid Arthritis: A Systematic Review

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Treatment choices in rheumatoid arthritis (RA) involve trade-offs in risks, benefits and other considerations such as dosing. Understanding patient preferences for these trade-offs is critical for making patient-centred treatment recommendations. The objective of this study was to summarize patients' preferences for disease modifying anti-rheumatic drug (DMARD) therapy in RA.

Methods: A systematic review was conducted to identify English-language studies in adult RA patients that measured patients' preferences for DMARDs or health states and treatment outcomes relevant to DMARD decisions. We included any study that provided a quantitative assessment of patient preferences, which was defined according to the MeSH definition in the National Library of Medicine as an "individual's expression of desirability or value of one course of action, outcome, or selection in contrast to others". Study quality was assessed using a published quality assessment tool. Data on the importance of treatment attributes and associations with patient characteristics was summarized across studies.

Results: From 7951 abstracts, we included 36 studies, from a variety of countries. Most studies were in patients with established RA and were rated as medium (n=19) or high quality (n=12). The methods to elicit preferences varied, with the most common being discrete choice experiment (DCE) (n=13). Twenty two were focused on decision-making between advanced therapeutics. Despite heterogeneity of attributes in DCE studies, collectively, treatment benefits were usually more important than both serious and non-serious adverse events. Dosing and administration attributes were typically less important than benefits while route and frequency were more important than adverse events. Risk tolerance varied considerably and 3 out of 5 studies showed patients preferred subcutaneous over intravenous therapy. Patient preferences were more commonly associated with sociodemographic variables rather than RA disease characteristics.

Conclusion: Overall, the results support current RA intensive 'treat-to-target' treatment paradigms, but the variability in preferences highlights the need to individualize treatment choices in a shared decision-making context.

Disclosure: C. Durand, None; M. Eldoma, None; D. A. Marshall, None; G. Hazlewood, None.

Abstract Number: 2369

Patients Preference Goes to MTX Autoinjectors over Prefilled Syringes: Results from a Phase III Trial

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The offer of injectable MTX worldwide expanded during past few years with different types of enhanced devices such as prefilled syringes and autoinjector pens. SELF_i trial intended to compare historical MTX prefilled syringes vs a new MTX autoinjector in terms of treatment adherence, functional capacity, and patients' preference at 6 months in RA patients.

Methods: SELF_i was a phase III, randomized open-label trial, conducted in France between Sept. 2015 and March 2017. It included RA patients, treated by oral or injectable MTX for ≥3 months in monotherapy or in association. Patients were randomized in two arms: MTX in prefilled syringes (PS) or MTX in autoinjectors (AI) at the dosage decided by the investigator. Primary co-criteria of the study were non-inferiority of AI vs PS in terms of patients' compliance (measured by the investigator at each visit) and functional capacity (HAQ-DI) at 6 months. Secondary criteria included patients' satisfaction and preference.

Results: Between Sept. 2015 and Sept. 2016, 50 rheumatologists, mostly with private practice, included 271 patients, 197 of which composed the *per protocol* population. Patients baseline characteristics were [mean (\pm SD)]: age: 59.2 (\pm 12.3) yrs; BMI: 26.0 (\pm 4.9) kg/m²; RA duration: 5.35 (\pm 6.70) yrs; DAS28: 3.1 (\pm 1.2); HAQ-DI: 0.6 (\pm 0.6). All patients were treated by MTX (1/3 oral; 2/3 parenteral) at a mean dose of 15.4 (\pm 4.1). There were no significant differences at baseline between PS and AI arms. Proportion of good compliers ($>80\%$) was 89.9% vs 94.9% (AI vs PS): -5% [CI 95% -18.9%; 8.9%]. HAQ decreased by a mean of 0.06 in both groups. Percentage of change was 21.3% vs 22.4% (AI vs PS): -1.1% [-35.0%; 32.7%]. Due to the high data variability, the non-inferiority could not be proved in strict sense, but differences did not appear as relevant.

Patients' reported satisfaction (Likert Scale) secondary criteria	Easy to use AI/PS	Pleasant AI/PS	Satisfying AI/PS	Motivating for further utilization AI/PS	Reassuring AI/PS	Not constraining AI/PS	Not stressful AI/PS	Not painful AI/PS
Strongly agree	60%/21%	7%/0%	63%/21%	61%/35%	30%/14%	51%/36%	55%/41%	51%/38%
Agree	32%/42%	20%/11%	31%/50%	23%/34%	52%/60%	18%/17%	23%/26%	21%/31%
Neither agree nor disagree	4%/23%	32%/26%	2%/19%	9%/17%	9%/15%	19%/24%	14%/17%	25%/24%
Disagree	1%/6%	26%/30%	2%/6%	6%/10%	4%/5%	10%/15%	4%/8%	1%/6%
Strongly disagree	4%/8%	14%/33%	1%/4%	1%/4%	5%/6%	2%/8%	8%/9%	1%/1%
Significance level	p < 0.001	p < 0.001	p < 0.001	p = 0.001	p = 0.02	p = 0.02	p = 0.05	p = 0.15

Patients' reported satisfaction was very significantly higher ($p \leq 0.001$) in AI arm vs PS for the following criteria: easy to use, pleasant, satisfying, willingness for further utilization and significantly higher ($p < 0.05$) for reassuring and not constraining. Of the 132 patients who could try the both devices (during the study or in previous experiences), 127 (96%; $p < 0.001$) preferred the autoinjector over the historical prefilled syringe. No unexpected safety issues were observed during this trial and injection point safety tolerance satisfaction was higher for AI vs PS.

Conclusion: SELFi trial showed that although the non-inferiority of the new MTX autoinjector vs the historical prefilled-syringe was not proved in strict statistical sense, they seem comparable in terms of treatment compliance and functional capacity improvement. Besides the pen is significantly superior in terms of patients' satisfaction and more than 95% of patients who have tried both devices declare preferring it over the syringe.

Disclosure: A. Saraux, Nordic Pharma, 5; C. Hudry, Nordic Pharma, 5; E. Zinovieva, Nordic Pharma, 3; A. Courbeyrette, Nordic Pharma, 3; H. Herman-Demars, Nordic Pharma, 3.

Abstract Number: 2370

Physician and Patient Preferences for Treating SLE: Insights into the Choice of Intravenous Infusion and Subcutaneous Injection

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease characterized by diverse clinical manifestations, chronic inflammation, and significant morbidity that can be fatal¹. Treatment strategies for SLE focus on managing symptoms, reducing flares, preventing organ damage, and improving health-related quality of life^{2,3}. Specific treatment goals should reflect shared decision making between the physician and patient. Currently, patients and physicians have a choice regarding mode of administration for SLE treatments, which range from oral medications, intravenous infusions (IV) and subcutaneous injections (SC). Given these choices, it is important to understand patient and physician characteristics that may drive the choice of selecting a mode of administration. The primary objective of the study was to examine patient and physician characteristics that are associated with the choice of IV or SC for an unspecified SLE treatment.

Methods: An online exploratory stated preference study was conducted with patients and physicians recruited from a web panel in the U.S. among 200 SLE patients and 200 rheumatologists who treat SLE. The survey development was informed by the results of qualitative interviews with physicians who treat SLE and the final surveys were pretested with SLE patients and physicians who treat SLE. The direct elicitation questions described hypothetical SLE treatments with different modes of administration. Pairwise and multivariate analyses were used to estimate the odds ratio (OR) for the likelihood of choosing SC over IV for a variety of respondent characteristics.

Results: Among the respondents, the mean (SD) age was 50.4 (14.0) in patients with SLE (86% female) and 51.4 (10.9) in rheumatologists who treat SLE (>50% in practice for >10 years). Analyses from the patient survey indicated that older respondents were more likely to select SC (OR=4.2); respondents with a fear of needles or self-injection (OR=0.1) and those who never need assistance with household activities (an indicator of higher quality of life) were less likely to choose SC (OR=0.1). Analyses from the physician survey suggested that 15 years or fewer years of training (OR=1.4) and a general preference for SC or IV (OR=2.1) are associated with physician's choice of SC over IV. Treating 21-40 SLE patients each week rather than more (OR=0.6), having two-thirds of treated SLE patients with mild disease rather than more (OR=0.6), having more than 8 infusion chairs in clinic (OR=0.6), and spending more than 80% of the time (OR=0.7) in direct patient care are associated with physician's choice of IV over SC.

Conclusion: This exploratory study is among the first preference studies conducted with SLE patients and physicians who treat SLE. Patient's age, severity of the disease, as well as a range of physician characteristics may play a role in choosing one route of administration over another. These insights may inform shared decision making, which may lead to better alignment between treatment choice and patient preferences, treatment satisfaction, adherence, and improved patient outcomes. The results of this study may inform the development of hypotheses for future studies. (Study funded by GSK HO-16-16706)

Disclosure: M. Lau, GlaxoSmithKline, 1, 3; C. F. Bell, GlaxoSmithKline, 1, 3; C. Poulos, GlaxoSmithKline, 5; A. Benegal, GlaxoSmithKline, 5.

Abstract Number: 2371

Use of Social Media Among Patients with Rheumatic Diseases

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

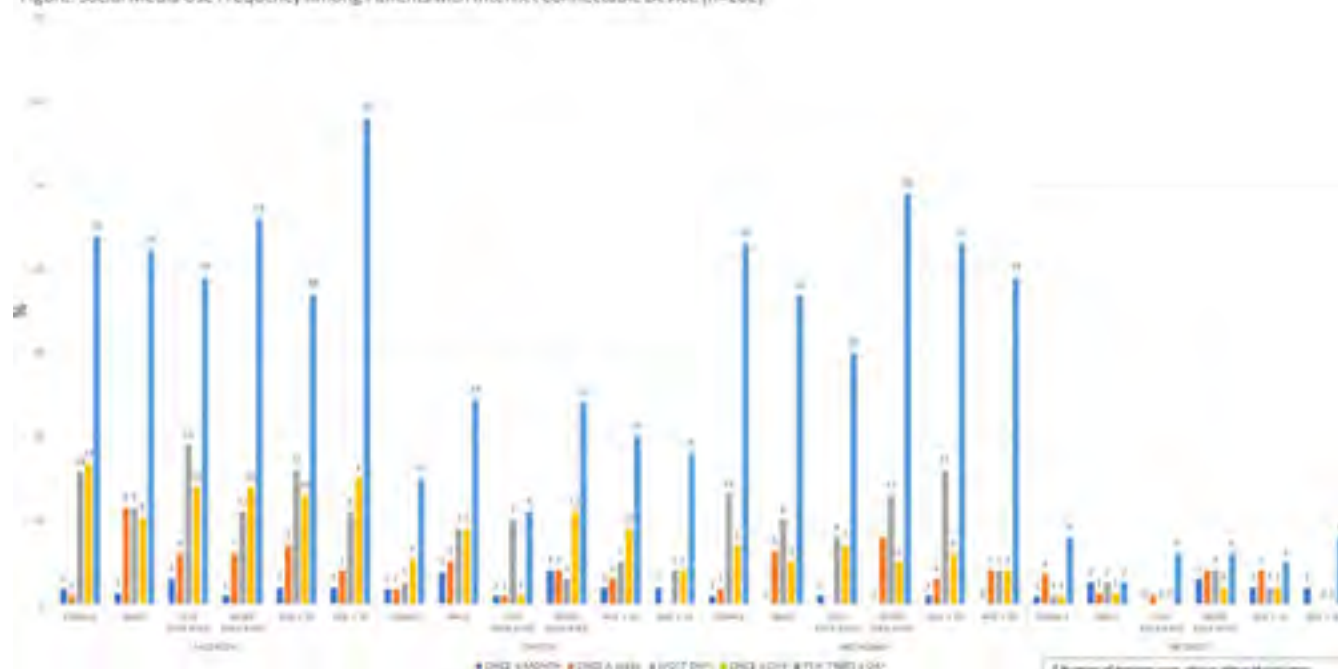
Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The impact of social media on individual or institutional communication and knowledge acquisition is non-negligible. Whether patients (pts) with rheumatic diseases share information about their health on social media is unknown. We aimed to investigate how often and to what extent pts with a rheumatic condition use social media. We also wanted to know whether they communicate with their doctors through social media and what are their expectations.

Figure. Social Media Use Frequency Among Patients with Internet Connectable Device (n=202).



Methods: Consecutive pts with diverse diagnoses attending a rheumatology outpatient clinic were studied. Pts completed a self-administered questionnaire (1) which was modified. Information on demographic features, educational status and diagnosis was also recorded.

Results: We studied 244 (154 F/ 90 M) pts with a median age of 46 years [IQR: 35-55]. Pts were diagnosed as RA (30%), SpA (29%), connective tissue disease (14%), Behcet's syndrome (12%), familial Mediterranean fever (11%) and other diseases (4%). 44% were only elementary school educated. 17% (n=42) did not have any of the communication devices, hence presumed to be social media non-users. Among the remaining 202 pts with devices, 12 (6%) additional pts were defined again as non-users, thus social media users reached 77% (190/244) in total. Smart phone users were in the majority (74%). Facebook was the most preferred social media website (79%), followed by Instagram (70%), Twitter (50%) and Pinterest (13%). While, Facebook users and non-users were similar according to age, gender or educational status, Twitter users were more likely to be male and more educated (Figure). The majority of the pts (78%) thought that social media was a useful information source about health. A total of 77% had no communication connection with their rheumatologist. While 96% were willing to communicate with their doctors through one of the social media source, 75% desired to be friends with their rheumatologist on the Facebook. When we asked "why would you like to communicate with your rheumatologist?"; the majority (39%) responded that it would be easier to understand each other; % 32 thought that they would feel more connected, % 27 thought that their rheumatologist would be more responsible, and 21% thought that their disease will get better.

Conclusion: This survey showed that younger and more educated pts had significantly more communication devices. Facebook was the most preferred social media website. More educated pts prefer using Twitter, Instagram and Pinterest and younger pts Instagram and Pinterest. The majority thought that social media was a useful information source about health. While only 23% had an actual connection with their rheumatologist through social media, 75% desired to be friends with their rheumatologist on the Facebook.

1) Hausman JS et al. "Adolescent and young adult use of social media for health and its implications." *Journal of Adolescent Health* 2017.

Disclosure: M. Erdogan, None; O. Aydin, None; E. Seyahi, None.

Abstract Number: 2372

Social Media Use for Health-Related Purposes By People with Rheumatic and Musculoskeletal Diseases – Results of a Global Survey

Paul Studenic¹, Alessia Alunno², Simon R Stones³, Valentin Ritschl⁴ and Elena Nikiphorou⁵, ¹Division of Rheumatology, Department of Internal Medicine III, Division of Rheumatology, Medical University of Vienna, Vienna, Austria, ²Department of Medicine, Rheumatology Unit, University of Perugia, Perugia, Italy, ³School of Healthcare, University of Leeds, Leeds, United Kingdom, ⁴Center for Medical Statistics, Informatics, and Intelligent Systems, Section for Outcomes Research, Medical University of Vienna, Vienna, Austria, Vienna, Austria, ⁵Academic Rheumatology, Department of Inflammation Biology, King's College London, London, Great Britain

SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

Session Type: ACR Poster Session C

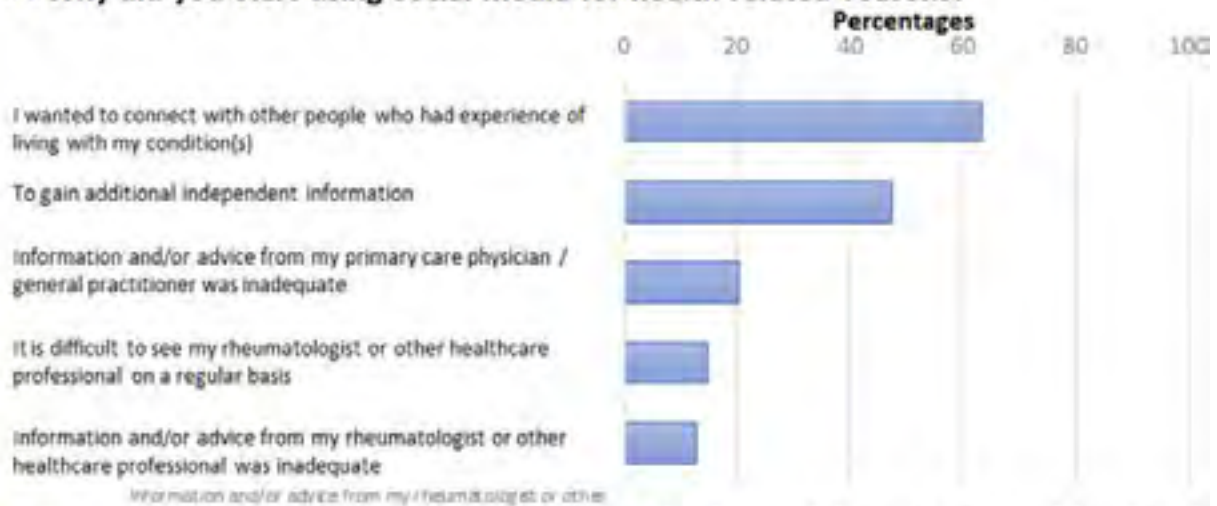
Session Time: 9:00AM-11:00AM

Background/Purpose: Smartphone applications and social media (SM) are increasingly used, transforming the way in which people communicate. Peer interaction, remote information access and community building are just some of the uses of SM, presenting novel opportunities and challenges, especially for people with chronic conditions such as rheumatic and musculoskeletal diseases (RMDs). This study aimed to explore the perspectives of people with RMDs on using social media for health-related purposes.

Methods: A questionnaire-based survey, co-designed in English by rheumatologists and patient research partners and translated into German, Italian, Spanish, Russian and French, was launched at the beginning of May 2018, distributed via patient organizations and SM platforms. We report on interim data analyses after 4 weeks of data collection.

Results: A total of 417 complete responses were received across 44 countries (50% of the UK, Russia, Spain and Italy). 13% of respondents were from non-European countries, with USA and New Zealand being the largest contributors. More than half of respondents were between 35 and 54 years, 87% were female, two thirds had >1 RMD, with inflammatory arthritis and connective tissue diseases being most prevalent. Sixty percent of participants had multimorbidity, with gastrointestinal, thyroid disease and hypertension leading. 38% were involved in patient organizations or as research

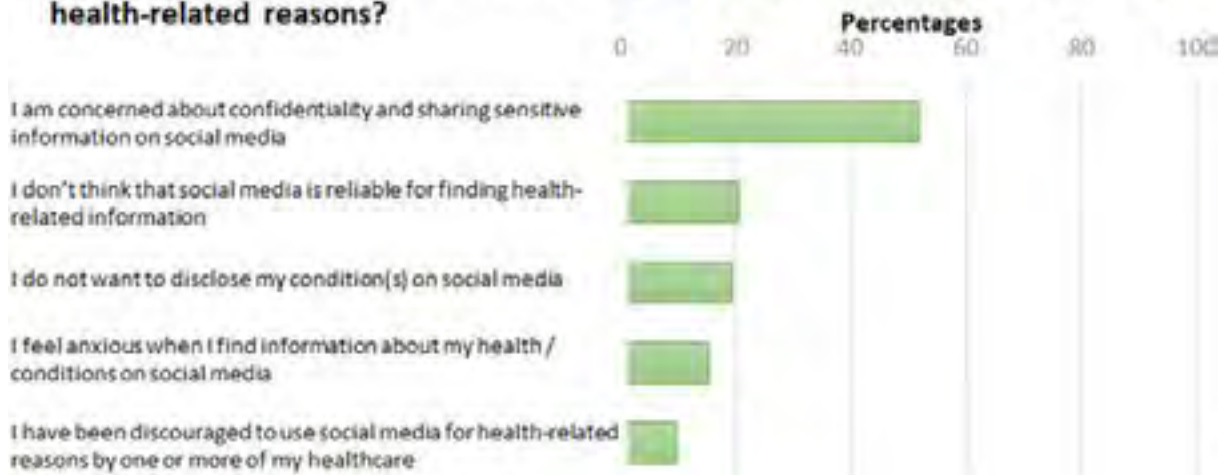
A Why did you start using social media for health-related reasons?



B In your opinion, what are the advantages of using social media for health-related reasons?



C In your opinion, what are the disadvantages or barriers of using social media for health-related reasons?



partners and 65% had a higher education diploma. Practically all (96%) were using SM, half of them more than 6 hours per week. Three quarters reported using SM for health-related purposes, in particular to connect with other people living with the same condition (63%), with Facebook, YouTube and Twitter being the top 3 commonly used platforms (Figure 1A). There was an overall positive perspective for SM, as an easy means to acquire different experiences and exchange knowledge with peers. However, more than half voiced concerns regarding confidentiality (Figure 1B + C). Only 6% had experiences with virtual medical appointments, in most cases for follow-up, with 28% indicating to have more than one RMD. SM use was comparable between groups with different levels of multimorbidity, although general health rating

was poorer than those with ≤ 1 comorbidity ($p=0.002$), they were older and more frequently considered that information provided by primary care physicians was inadequate ($p=0.005$).

Figure:

Conclusion: This study demonstrates that use of SM for health-related purposes is widespread among people with RMDs and is mainly used as a means to connect with peers and exchange knowledge and experience, supporting empowering patients in managing their disease. Despite concerns about confidentiality and the sharing of sensitive data, the considerable use of SM by patients with RMDs is impressive and represents new avenues to explore in health care.

Disclosure: P. Studenic, None; A. Alunno, None; S. R. Stones, None; V. Ritschl, None; E. Nikiphorou, None.

Abstract Number: 2373

How Do Patients Describe Their “New Normal” in Systemic Lupus Erythematosus? Use of Probabilistic Topic Modelling to Characterize Patients’ Experiences Recorded in an Online Health Community

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II: Patient Perspectives

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Patients living with systemic lupus erythematosus (SLE) must typically adapt to altered quality of life and tailor coping mechanisms (e.g. non-pharmacological interventions) to address their personal “new normal”. Patient interactions in online communities provide an opportunity to understand their new way of living with SLE, outside of a clinical setting.

Methods: Topics related to the new normal in SLE were studied by analyzing free text data from patients self-reporting a diagnosis of SLE on PatientsLikeMe, an online community and health network. These data included patients’ brief autobiographies, forum posts and replies, and annotation of their health data. Latent Dirichlet allocation (LDA), a form of probabilistic topic modeling, was used to identify topics from within this corpus. Further analysis of relevant topics, identified by manual review, focused on the language used by patients, effect on their lives and the steps taken to mitigate impact.

Results: 138,409 free-text SLE-related posts from 15,060 users on PatientsLikeMe were analyzed using LDA. 150 unique topics – clusters of related words – were identified, including 12 topics identified as relevant patients’ “new normal” in living with SLE. These 12 topics were then named to reflect their component words and grouped into 3 domains; Emotions (Uncertainty, Isolation, Guilt), Symptoms (Fatigue, Pain, Hair Loss) and Daily Challenges (Inability to work, limited time outdoors, daily variability, managing drugs, hiding symptoms/illness and proving symptoms/illness). Patients reported feeling overwhelmed by pain and fatigue. Patients describe a constant struggle to overcome isolation and communicate their feelings to their family, friends, health care providers (HCPs) and employers. This leads to hiding symptoms, withdrawal and feelings of guilt. In addition, pain management strategies from physicians feel largely ineffective, as do many drug treatments. Patients struggled with the unpredictability of these symptoms and conveyed a sense of resignation and acceptance to this new normal. They accepted that many daily activities (e.g. taking a shower or housework) would never be easy again and adapted their lives accordingly. Patients discussed how they were forced to restrict their social lives and seek support from others for family responsibilities such as childcare. Many patients reduced, changed or stopped employment, negatively impacting finances and self-esteem. However, patients also use the online community to help support each other in their shared experiences with SLE, sharing creative lifestyle modifications, such as using cell phone alarms for limiting sun exposure.

Conclusion: Computational approaches that summarize large volumes of patient-generated free text data in online communities provide direct insight into the ways in which SLE patients live with their condition and how they manage the “new normal” in their lives with its changed lifestyle and expectations. These findings can be used to highlight unmet medical needs from the patient perspective, and help patients and their HCPs create a more complete approach to SLE management.

Disclosure: S. Eaneff, PatientsLikeMe, 3; T. Vaughan, PatientsLikeMe, 3, AstraZeneca, 5; V. Barut, AstraZeneca, 1, 3; J. Havsol, AstraZeneca, 3; B. Nohe, AstraZeneca, 1, 3; C. Emmas, AstraZeneca, 1, 3.

Abstract Number: 2374

Flare Warnings: People with Rheumatoid Arthritis' Perceptions of Their Flares

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II – ARHP

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Flares are exacerbations of rheumatoid arthritis (RA) symptoms of sufficient intensity to require some change in treatment. Even when well-managed, more than half of people with RA experience flares within six months.¹ Despite their common and debilitating nature, there are few studies that examine flare-management. Many people with RA may not know the best methods to control their own flare activity.

We held two 90-minute focus groups with RA patients to discuss their experiences with flares and to identify flare warnings, triggers, and flare-management strategies, both preventative and treatment.

Methods: We recruited 11 people with doctor-diagnosed RA, 9 females and 2 males, 10 white and 1 African American, aged 40 to 78. Their disease duration ranged from 1 to 44 years. Seven reported flare activity within the previous 3 months. We analyzed group transcripts for participant responses and identified common themes about flares.

Results: We found that experiences varied widely, but there were two important commonalities. Flare activity diminished participants' ability to take part in important activities, such as work, family gatherings, playing with grandchildren, and socializing. Flare activity affected simple tasks typically taken for granted. One participant commented, "It's so ridiculous that my feet hurt so bad that I didn't want to go to the bathroom." Group members agreed that coping with RA was challenging without flares, and that the uncertainty of flares made the disorder that much more difficult to manage. As one participant said, "You never know what it's going to be, but it's always something."

Participants reported few concrete signs of imminent flare (Table). They identified multiple flare triggers, many of which related to changes in their lives, such as stressful events, the weather, or overdoing activities. Flare prevention strategies tended to be healthful habits, such as taking prescribed medications, diet, exercise, and sticking to routines. Flare management focused on short-term pain relief, such as increased medication or modalities, and methods to distract and rest the system.

Conclusion: Despite advances in medications for RA, flares are common and triggered by multiple common activities and events. Patients with RA currently have few opportunities to predict flare activity, and are dependent upon their flare management strategies to cope when flares occur. We need more focused research on how to prevent flares, and barring prevention, the most effective methods to manage flares when they occur. ¹Bykerk et al. *J Rheumatol.* 2014;41(2):227-234.

Table: Participant reported flare signs, triggers, prevention and management

Flare Signs	No warning; worsening symptoms; changes in mood
Flare Triggers	Stopping medication; stressful events; changes in barometric pressure (weather, flying); humidity; overdoing it (too much physical activity); fatigue; diet (eating allergens)
Flare Prevention	Appropriate medications; exercise; diet; reduce activity; stick to routines
Flare Management	Additional/increased medications; modalities (heat, cold); distraction (reading, watching tv, playing games); rest; socialize

Disclosure: N. A. Baker, None; L. Person Mecca, None; S. R. Piva, None.

Abstract Number: 2375

When Are People Receptive to Self Management Education Information, and What Information Appeals to Them? : An Analysis of Digital Data

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II – ARHP

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: CDC pilot-tested a marketing campaign to promote self-management education (SME) as a chronic disease management strategy. The campaign targets adults ages 45-75 with any chronic condition, including arthritis. The campaign includes a variety of paid ads (digital, print, radio, billboard, physician office) along with earned media and partner activities. The campaign call to action is to visit www.cdc.gov/LearnMoreFeelBetter to learn more about SME. Digital ads are easily tracked (e.g., Did the receiver click on the ad presented?), which allows us to assess variations in campaign tactics. Web analytics also can track how many visits each page of a website receives. The purpose of this analysis is to compare the productivity of digital SME ads depending on what terms the person was searching when they received the ad, and to explore what web pages attract the most interest on the SME website.

Methods: As part of the pilot-test, campaign ads were presented to people who conducted Google searches for information about a variety of chronic diseases including arthritis, and one of 4 different clusters of search terms (e.g., Arthritis +Signs/Symptoms/Diagnosis, +General information, +Care/Treatment, +Management). The Google ad vendor reported how many times each cluster of search terms was searched so the ad could be presented (i.e., Impressions). Site Catalyst, a web analytics software program, tracked productivity defined in 3 ways: number of times people receiving the ad clicked on it (Clicks), percentage of people who clicked on ad out of all exposed to the ad (Click thru Rate [CTR]), total cost to run ad divided by number of clicks (Cost per Click [CPC]), and average number of minutes spent on the website by those who clicked through the ad to the site (Minutes on Site [MOS]). The campaign website homepage linked to 4 subpages: Site Catalyst was used to track how often these pages were visited from the homepage.

Results: During the campaign pilot-test, Google ad words produced 115,925 Impressions and 5,737 Clicks. The following table reports Impressions and productivity of digital ads by CTR, CPC, and MOS depending on search term used.

Google Ads Runs Time: January 23 – July 23, 2017					
Search Terms	Impressions	Clicks	Avg. CTR	Avg. CPC	Avg. MOS
Signs/Symptoms/ Diagnosis	33,964	3,316	9.76%	\$1.70	1.52
General	60,696	1,878	3.09%	\$2.36	1.94
Care/Treatment	19,903	485	2.44%	\$2.89	3.64
Management	1,362	58	4.26%	\$2.63	0.48
Totals or Averages	115,925	5,737	Avg. 4.9%	Avg. \$1.85	Avg. 1.83

17% of the 26,851 visits to the homepage (from all sources) resulted in visits to at least 1 subpage. SME programs subpage received the most views (1501), followed by What is SME, About the Campaign, and What Others are Saying/Testimonials (811, 330, 293 views respectively).

Conclusion: Although searches for disease General Information many more opportunities to present the SME ads, people searching for Signs/Symptoms/Diagnosis were 3 times as likely to click on the SME ad. Those who received the SME ad while searching Care/Treatment spent the most time on the SME site. People who reached the SME site were most interested in SME Programs, and least interested in Testimonials. This information can help shape SME marketing.

Disclosure: T. Brady, None; M. Lewis, None; C. Cartwright, None.

Abstract Number: 2376

Something for Us: Client Perspectives on Lupus Self-Management Programming Using the 5-a Behavior Change Model

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II – ARHP

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus is the most common and most severe form of lupus involving multiple body systems including the blood, muscles, joints, organs and the nervous system. The Lupus Foundation of America (2012) estimates around 5 million people worldwide have a form of lupus. There is no cure for lupus, so treatment consists of minimizing and managing symptoms. The 5-A model has been shown to be an effective model to facilitate behavior change in those living with chronic disease (Caroll et al., 2012, Glasgow, Emont, Miller, 2006). The purpose of the study was to capture participants voice regarding the value of community based self-management programming based on the 5-A model.

Methods: This retrospective qualitative study was designed to analyze the statements of 48 participants in self-management programming designed based on the 5-A Behavior Change Model. Thirty-eight masters of occupational therapy students (2011-2015) used the 5-A model to design and implement six-week self-management programs as part of their master's project coursework. The students reviewed the literature, designed, and implemented five programs covering the topics of fatigue management, physical activity, stress and pain management. The programs were designed in collaboration with the Lupus Foundation of Minnesota. They were offered free of charge in face to face and online formats. Participants response was assessed through post program assessment of objectives and thematic analysis of participants statements during and following the program.

Results: Forty eight members of the Lupus Foundation of Minnesota participated in the study and were included in the analysis. The majority of participants had SLE (n=42), were female (n=43) and white (n=38). All participants used a four-point scale to indicate if unit objectives were met (1=strongly disagree, 2=disagree, 3=agree and 4=strongly Agree). The average scores per unit ranged from an average of 3.4 to 4 indicating the objectives were met for all programs. Qualitative thematic analysis (Braun & Clark, 2006) of recorded participant statements showed the participants valued the programming and felt it was effective. Thematic analysis uncovered four themes: Learning through understanding, changing routines, adapting life, and gratitude and appreciation.

Conclusion: Qualitative evidence supports use of the 5-A Behavior Change Model as an effective model for self-management education in online and face to face format for those with lupus. Post-program quantitative measures showed those who participated the programming felt the objectives were met. Qualitative analysis revealed evidence-based education increased patients understanding of the rationale for recommendations and promoted behavior c in routines and adaptations that improved quality of life. Those that participated in the program were grateful and appreciative of programming designed specifically for them stating "finally something for us."

Disclosure: B. L. Frie, None;

Abstract Number: 2377

Body Image in Rheumatic Diseases: A Systematic Review

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Patient Outcomes, Preferences, and Attitudes Poster II – ARHP

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: In health conditions that cause changes in appearance, especially in areas of the body that are highly visible and socially salient (e.g., face and hands), there can be alterations in body image, self-esteem, and role-evaluation. Given their chronic and progressive nature and disproportionate impact on women, the rheumatic diseases are an important area for the study of body image in chronic illness. Body image has been explored in various rheumatic conditions, such as systemic sclerosis, rheumatoid arthritis, and systemic lupus erythematosus. To date, no systematic review has summarized the literature on body image in multiple rheumatic diseases.

Methods: PubMed/Medline, PsycINFO, and CINAHL databases were searched on May 13, 2016 and updated on December 19, 2017. Results were limited to English-language studies. Additionally, a manual search was undertaken wherein reference lists of selected articles were screened for inclusion. Grey literature (i.e., conference abstracts and dissertations) was excluded. Studies were screened and evaluated for inclusion by two investigators. Full articles were reviewed to determine eligibility based on the following inclusion criteria: 1) study participants comprised of adult patients with rheumatic diseases that can cause visible differences, and 2) at least one validated measure of body image was used. Studies that focused on surgical outcomes were excluded.

Results: Forty-eight articles were eligible for inclusion in the present review. The majority of studies used disease-specific measures of body image. Eligible studies were identified for lupus, rheumatoid arthritis, scleroderma, and ankylosing spondylitis. No single correlate was found to consistently associate with body image. However, younger age, greater depressive symptomatology, presence of active disease flares, and greater functional deficits were most commonly associated with poorer body image scores.

Conclusion: Rheumatic diseases that cause changes in appearance can have significant impacts on body image. The multidimensional nature of the construct of body image and the use of disease-specific measures complicated the synthesis of the findings across groups or comparisons with non-rheumatic disease samples. However, some disease correlates appeared most commonly associated with poorer body image across disease groups and can be useful in guiding intervention efforts.

Disclosure: S. Gholizadeh, None; A. Meier, None; S. D. Mills, None; V. L. Malcarne, None.

Abstract Number: 2378

Subcutaneous Abatacept in Patients Aged 2–17 Years with Juvenile Idiopathic Arthritis and Inadequate Response to Biologic or Non-Biologic Disease-Modifying Antirheumatic Drugs: Results over 24 Months By Juvenile Idiopathic Arthritis Disease Category

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

Session Type: ACR Poster Session C

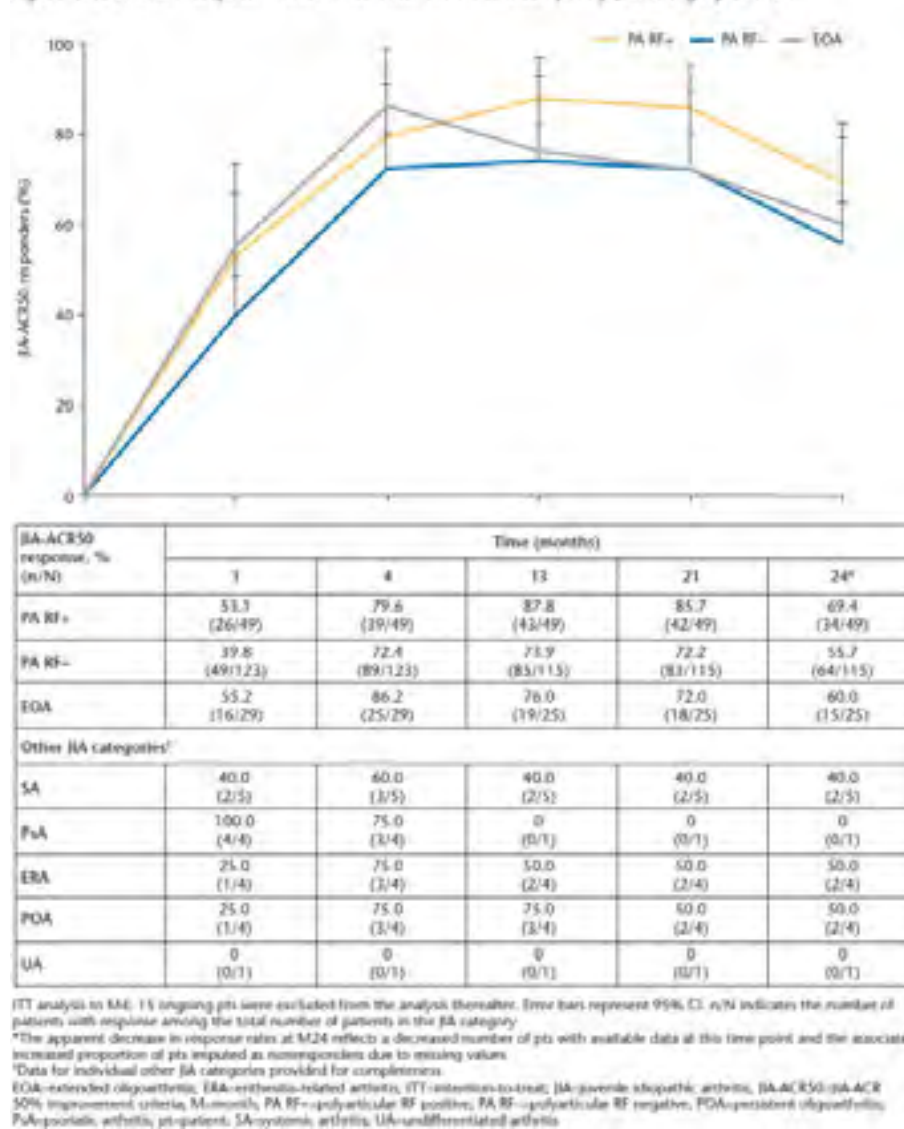
Session Time: 9:00AM-11:00AM

Background/Purpose: The effect of biologic DMARDs on different juvenile idiopathic arthritis (JIA) categories is poorly understood. In patients (pts) with JIA aged 2–17 years (y), SC abatacept (ABA) was effective and well tolerated.¹ Here, effectiveness and HRQoL of SC ABA in pts aged 2–17y by JIA categories over 24 months (M) are presented.

Methods: The design of this single-arm, two-cohort, open-label Phase III study (ClinicalTrials.gov, NCT01844518) has been described.¹ Eligible pts with JIA received SC ABA (50, 87.5 or 125 mg by body-weight tier) weekly for 4M; JIA-ACR criteria 30% improvement (JIA-ACR30) responders at 4M could receive ABA for another 20M. Pre-specified analyses included JIA-ACR30, 50, 70, 90 and 100 responses and inactive disease (modified criteria)² status. *Post hoc* analyses included Juvenile Arthritis Disease Activity Score on 27 joints (JADAS27-CRP) and proportion of pts with minimal clinically important difference (MCID) in Childhood HAQ-DI (CHAQ-DI; MCID –0.188)³ by JIA category (polyarticular [PA] RF positive (+), PA RF negative (–), extended oligoarthritis [EOA], systemic [SA], psoriatic [PsA], enthesitis-related [ERA], persistent oligoarthritis [POA] and undifferentiated[UA] JIA) and overall safety. Due to low pt numbers, separate data for SA, PsA, ERA, POA and UA were not interpreted; data were pooled for JADAS27-CRP.

Results: In 219 treated pts, median (min, max) age was 11.0 (2.0, 17.0) y and disease duration was 1.0 (0.0, 15.0) y. Overall, 19.6% of pts discontinued over 24M with 10.0% discontinuing due to lack of efficacy. Data for SA, PsA, ERA, POA and UA are provided for completeness (Figs 1, 2). In PA RF+, PA RF– and EOA, pts responded early to SC ABA and showed robust JIA-ACR30 responses over time (4M: 80.5–96.6%). More stringent JIA-ACR50 (Fig 1), 70, 90 and 100 responses, inactive disease status and JADAS27-CRP (Fig 2) improved across these categories up to M4 and were sustained to M24; similar results were observed in a JADAS27-CRP pooled analysis of other categories. A trend for

Figure 1. JIA-ACR50 Response Rates Over Time for all Treated pts by JIA Category to M24*



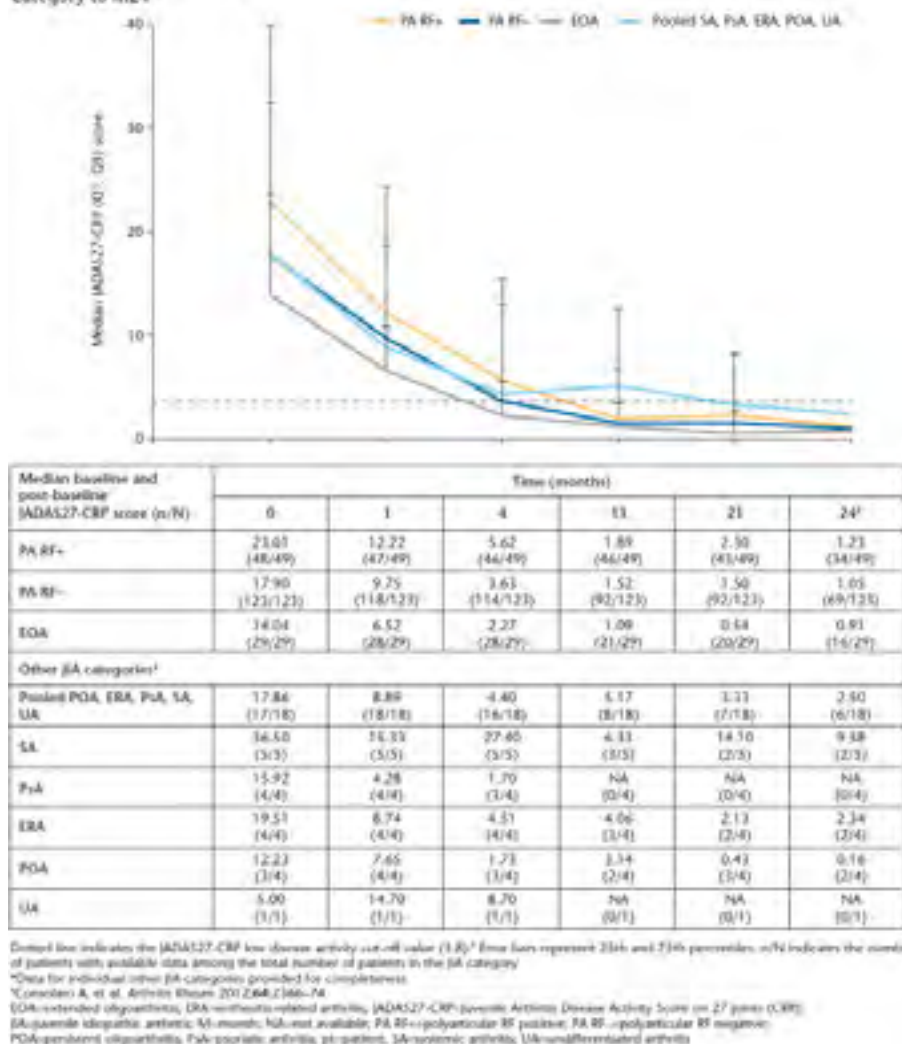
improvement in CHAQ-DI MCID was evident across categories (24M: 50.0–61.2%). None w/unexpected AEs were observed; a safety summary per age cohort over 24M was reported previously.¹

Conclusion: In this analysis of pts aged 2–17 yrs with JIA, SC abatacept was effective and well tolerated and improved HRQoL across JIA categories over 24M.

References: 1. Brunner HI, et al. *Arthritis Rheumatol* 2018; <https://doi.org/10.1002/art.40466>. 2. Wallace CA, et al. *Arthritis Care Res (Hoboken)* 2011;**63**:929–36. 3. Brunner HI, et al. *J Rheumatol* 2005;**32**:150–61. Medical writing assistance provided by Katerina Kumpan, PhD (Caudex), funded by Bristol-Myers Squibb.

Disclosure: N. Ruperto, Abbott, AbbVie, Amgen, Biogenidec, Astellas, Alter, AstraZeneca, Baxalta Biosimilars, Boehringer, Bristol-Myers Squibb, CD-Pharma, Celgene, CrescendoBio, EMD Serono, Hoffman-La Roche, Italfarmaco, Janssen, MedImmune, Medac, Novartis, Novo Nordisk, Pfizer, 8, Abbott, Bristol-Myers Squibb, 2, Rewind Arms, R-Pharma, Sanofi-Aventis, Servier, Sinergie, Takeda, Vertex, UCB Biosciences GmbH, 8; H. I. Brunner, Novartis, Genentech, Pfizer, UCB, Lilly, Janssen, Ablynx, AbbVie, Bristol-Myers Squibb, EMD Serono, Astrazeneca, 5, Genentech and Novartis, 8; G. Vega-Cornejo, None; A. Berman, None; R. J. Cuttica, Abbvie, Bristol-Myers Squibb, Centocor, GSK, Lilly, Novartis, Pfizer, Roche, 5, 8; F. Ávila-Zapata, None; M. Henrikson, None; D. J. Kingsbury, None; J. F. Bohnsack, None; T. Lutz, None; N. E. Rubio-Pérez, None; V. Gerloni, None; X. Li, Bristol-Myers Squibb, 1, 3; M. Nys, Bristol-Myers Squibb, 1, 3; R. Wong, Bristol-Myers Squibb, 1, 3; A. Martini, None; D. J. Lovell, AstraZeneca, Bristol-Myers Squibb, AbbVie, Pfizer, Roche, Novartis, UBC, Forest Research Institute, Takeda, GlaxoSmithKline, Boehringer Ingelheim, Celgene, Janssen, Hoffmann-La Roche, Wyeth Pharma, Amgen, Abbott, 5, Wyeth Pharma, 8.

Figure 2. JADAS27-CRP (Range 0-57) Median Baseline and Post-Baseline Values for all Treated pts by JIA Category to M24



Abstract Number: 2379

Long-Term Safety of Subcutaneous Tocilizumab Administration in Systemic and Polyarticular Juvenile Idiopathic Arthritis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

Background/Purpose: Tocilizumab (TCZ) administered intravenously (IV) was shown to improve the signs and symptoms of polyarticular(p) JIA and systemic (s) JIA.^{1,2} An ongoing 3-year, long-term extension (LTE) of two 52-week, open-label studies in patients (pts) with pJIA/sJIA will evaluate long-term safety and efficacy of subcutaneous (SC) TCZ; 90-day safety results to the clinical cutoffs December 1, 2017 (pJIA) and February 28, 2018 (sJIA) are reported.

Methods: Pts aged 1-17 years received body weight (BW)-based TCZ SC dosing regimens: pJIA pts received TCZ 162 mg every 3 weeks (Q3W) for BW <30 kg or every 2 weeks (Q2W) for BW ≥30 kg; sJIA pts received TCZ 162 mg Q2W for BW <30 kg (every 10 days until week 14) or weekly (QW) for BW ≥30 kg. pJIA pts had failed MTX treatment or could not tolerate MTX and sJIA pts had inadequate response to NSAIDs and glucocorticoids. All pts had to discontinue biologic DMARDs (except TCZ IV, which was switched to SC). After 52 weeks, eligible pts continued TCZ treatment according to BW in the LTE; we report 90-day safety data for pJIA and sJIA as adverse events (AEs), serious AEs (SAEs), and AEs of special interest (AESIs). The safety populations included all pts who received ≥1 dose of TCZ SC and had ≥1 postdose safety assessment.

Results: Of pJIA pts (n = 44), 72.7% were female and 88.6% white. Of sJIA pts (n = 38), 55.3% were female and 84.2% white. Median (range) age in both groups was 9.0 (2-18) years. AE rates (Table [image]) were similar regardless of BW. Most AEs were grade 1 or 2; grade ≥3 AEs were reported by 10/44 (20.8%) pJIA pts and 4/38 (10.5%) sJIA pts. The most common AE was nasopharyngitis in both pJIA (17/44 [38.6%]) and sJIA (11/38 [28.9%]). Other AEs reported in ≥15% of pts were arthralgia, gastroenteritis, cough, vomiting, diarrhea, pyrexia, headache, and oropharyngeal pain in pJIA, and upper respiratory tract infection, cough, pyrexia, arthralgia, and rash in sJIA. AESIs were consistent with the 52-week data, and no opportunistic infections developed. Neutropenia AEs were reported by 6 pJIA pts (13.6%) and 7 sJIA pts (18.4%). Of pJIA pts, 5/44 (11.4%) experienced SAEs (furuncle, appendicitis, pneumonia, eye pain/headache, infectious mononucleosis); only pneumonia was considered treatment related. Of sJIA pts, 2/38 (5.3%) experienced SAEs (pneumonia, craniocerebral injury from a fall); neither was considered treatment related. Neutralizing anti-TCZ antibodies developed in 2 pJIA pts (4.7%) and 0 sJIA pts. No deaths were reported in the LTE to the data cutoff.

	pJIA			sJIA		
	TCZ SC Q3W (<30 kg) n = 24	TCZ SC Q2W (≥30 kg) n = 20	All TCZ SC N = 44	TCZ SC Q10D or Q2W (<30 kg) n = 19	TCZ SC QW (≥30 kg) n = 19	All TCZ SC N = 38
Duration to study, PY	52.3	48.0	100.1	23.4	44.0	67.3
AEs						
Pts, n (%)	24 (100)	20 (100)	44 (100)	17 (89.5)	17 (89.5)	34 (89.5)
n	209	249	518	136	222	358
(rate/100 PY [95% CI])	(514.0 [454.5, 579.3])	(510.7 [449.2, 578.2])	(512.4 [469.2, 558.5])	(582.2 [488.5, 688.7])	(504.8 [440.6, 575.7])	(531.6 [478.0, 580.7])
SAEs						
Pts, n (%)	2 (8.3)	4 (20.0)	5 (11.4)	1 (5.3)	1 (5.3)	2 (5.3)
n	2	4	6	1	3	2
(rate/100 PY [95% CI])	(13.6 [0.5, 33.8])	(16.2 [2.2, 35.0])	(18.9 [2.2, 33.9])	(4.3 [0.1, 23.9])	(7.3 [0.5, 32.7])	(13.0 [0.4, 30.7])
AEs leading to withdrawal						
Pts, n (%)	2 (8.3)	1 (5.0)	3 (6.8)	0	0	0
n	2	1	3	0	0	0
(rate/100 PY [95% CI])	(13.6 [0.5, 33.8])	(2.1 [0.1, 11.4])	(18.0 [0.6, 8.7])	0	0	0
AEs leading to dose interruption						
Pts, n (%)	1 (4.2)	2 (10.0)	3 (6.8)	4 (21.1)	6 (31.6)	10 (26.3)
n	21	3	24	7	14	21
(rate/100 PY [95% CI])	(40.1 [24.8, 61.3])	(6.2 [1.3, 18.0])	(23.7 [15.2, 35.3])	(200.1 [12.0, 61.7])	(31.8 [17.4, 53.4])	(51.2 [19.3, 47.7])

AEs, adverse events; pJIA, polyarticular juvenile idiopathic arthritis; PY, patient-years; Q2W, every 2 weeks; Q3W, every 3 weeks; Q10D, every 10 days; SAEs, serious adverse events; SC, subcutaneous; sJIA, systemic juvenile idiopathic arthritis; TCZ, tocilizumab.

Conclusion: In this long-term extension study of SC TCZ in children with pJIA or sJIA, TCZ continues to have an acceptable tolerability profile with no new safety concerns. *References:* 1. Brunner HI et al. *Ann Rheum Dis.* 2015;74:1110-1117. 2. De Benedetti F et al. *N Engl J Med.* 2012;367:2385-2395. Acknowledgment: PRINTO and PRCSG Investigators. Medical writing: Sally Mitchell, PhD, funded by F. Hoffmann-La Roche Ltd.

Disclosure: H. I. Brunner, Roche, BMS, Novartis, Pfizer, R-Pharm, Celgene, AstraZeneca, Janssen, Ablynx, GSK, Takeda, Sanofi, 5, Roche, Novartis, Pfizer, 8, Roche, Novartis, Pfizer, BMS, 9; N. Ruperto, Abbott, AbbVie, Amgen, Biogenidec, Astellas, Alter, AstraZeneca, Baxalta Biosimilars, Boehringer, BMS, CD-Pharma, Celgene, CrescendoBio, EMD Serono, Hoffmann-La Roche, Italfarmaco, Janssen, MedImmune, Medac, Novartis, NovoNordisk, Pfizer, Rewind Arms, R-Ph, 5, Abbott, BMS, 2; A. Martini, None; A. V. Ramanan, AbbVie, UCB, SOBI, Lilly, 8; R. J. Cuttica, None; J. E. Weiss, None; M. Henrickson, None; H. Schmeling, Roche, 2; J. Anton, None; K. Minden, Pfizer, AbbVie, Roche, 2, AbbVie, Sanofi, Medac, MedCon, 5; G. Horneff, None; M. L. Gámir-Gámir, None; M. Hufnagel, None; W. Douglass, Roche, 1, Roche, 3; C. Wells, Roche, 3; S. Wimalasundera, Roche, 1, Roche, 3; N. L. Mallalieu, Roche, 1, Roche, 3; D. J. Lovell, AstraZeneca, Amgen, Abbott, Pfizer, 5, Wyeth, 8; F. De Benedetti, Abbvie, Sobi, Novimmune, Roche, Novartis, Sanofi, UCB, Pfizer, 2.

The Safety Profile of Adalimumab across Geographic Regions and Dosing Administrations Among Patients with Juvenile Idiopathic Arthritis Enrolled in a Registry

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Adalimumab (ADA) has been approved for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) with long-term use often required to maintain disease control. The purpose of this analysis was to describe the safety of ADA among children with pJIA treated in current clinical practice with fixed-dosing (F-D, by weight category, in the United States [US] and Australia) or body surface area-dosing (BSA-D, in European countries).

Methods: This is a year (yr) 8 interim analysis of an ongoing, multicenter, observational registry of patients (pts) with pJIA with up to 10 yr safety follow-up. Pts included in the registry were treated with ADA, alone or in combination with methotrexate (ADA±MTX), or MTX alone as a comparison arm, according to routine clinical care in PRINTO/PRCSG centres in the US, Australia, and Europe. This analysis included only ADA±MTX-treated pts who were sub-grouped according to enrolling site into two groups: F-D (10 - <15 kg, 10 mg every other week [eow]; 15 - <30 kg, 20 mg eow; ≥30 kg, 40 mg eow) or BSA-D (24 mg/m² [maximum of 40 mg] eow). MedDRA observational adverse events (AEs) were recorded from registry entry through last contact, irrespective of duration of registry treatment with ADA±MTX.

Results: Of the 537 pts enrolled in the ADA±MTX arm, 272 and 263 received F-D and BSA-D, respectively. At registry entry, F-D and BSA-D groups were similar for mean JIA duration (3.5 yrs vs. 3.9 yrs), JADAS27 (CRP) (10.8 vs. 12.2), and CHAQ-DI (0.6 for both). Registry follow-up in the F-D and BSA-D groups were comparable [mean (range) in yrs: 3.96 (0.00–8.92) vs. 3.58 (0.00–7.01)]. Overall, 166 pts (61%) in the F-D and 128 (49%) in the BSA-D group discontinued registry drug. Frequencies and rates of observational AEs per 100 pt years of observation time (from registry entry up to last contact, irrespective of drug treatment duration) were comparable between groups (Table), including rates of serious infection. Two pts from the BSA-D group reported latent TB, although there were no cases of active TB across enrolling sites. One pt (0.2%) from the BSA-D group reported an event of opportunistic infection (fungal oesophagitis). There were no reports of death, malignancy, oral candidiasis, demyelination, or congestive heart failure.

Conclusion: Overall, ADA±MTX was well-tolerated in pts with pJIA where administration has been with a fixed dose, per weight category, or based on BSA, respectively. Table. Overview of the observational adverse events per 100 PYs

	Fixed-dosing ADA±MTX (N=272) PYs=1076 E (E/100 PYs)	BSA-dosing ADA±MTX (N=263) PYs=940.8 E (E/100 PYs)
Any AE	453 (42.1)	358 (38.1)
AE at least “possibly drug related” per the investigator	155 (14.4)	101 (10.7)
Severe AE	47 (4.4)	26 (2.8)
Serious AE	56 (5.2)	92 (9.8)
AE leading to discontinuation of study drug or study	27 (2.5)	34 (3.6)
Infectious AE	160 (14.9)	119 (12.6)
Serious infectious AE	24 (2.2)	20 (2.1)
Injection site-related AE	18 (1.7)	20 (2.1)

E, events; PYs, patient years (Observation time, irrespective of study drug treatment duration).

Disclosure: **H. I. Brunner**, AbbVie Inc., AstraZeneca, Centocor, Bristol-Myers Squibb, Boehringer-Ingelheim, Pfizer, Regeneron, Hoffman La-Roche, Novartis, Takeda, UCB, and Genentech, Lilly, Janssen, Ablynx, R-Pharm, 5, 9, Genentech Pharmaceuticals and Novartis, 8; **N. Ruperto**, full-time employee of the GASLINI Hospital, which has received contributions to support the research activities of the network of PRINTO from AbbVie Inc., AstraZeneca, Bristol-Myers Squibb, Janssen Biologics B.V., Eli Lilly and Co., “Francesco Angelini”, 9, Astellas, AstraZeneca, Bristol-Myers Squibb, Italfarmaco, Janssen Biologics B.V., MedImmune, Roche, and Wyeth/Pfizer, 8; **K. Nanda**, Novartis, 9; **M. Toth**, None; **I. Foeldvari**, AbbVie, Bayer, Chugai, MEDAC, Novartis and Sanofi, 9; **J. F. Bohnsack**, Novartis, 5; **D. Milojevic**, AbbVie Inc., 5; **D. J. Kingsbury**, AbbVie Inc., 9; **K. A. Marzan**, AbbVie Inc., 9; **E. Chalom**, AbbVie Inc., 8; **G. Horneff**, AbbVie, Pfizer, and Roche, 2, AbbVie, BMS, MSD, Novartis, Pfizer, and Roche, 9; **R. M. Kuester**, AbbVie and Wyeth/Pfizer, 9; **J. A. Dare**, AbbVie, AstraZeneca, BMS, Horizon Pharma, Medac, Pfizer, Roche, and UCB, 9; **M. Trachana**, AbbVie, Novartis Hellas, and Pfizer, 2, 9, BMS, Novartis Hellas and Pfizer, 8, 9; **M. Bereswill**, AbbVie Inc., 1, 3; **H. Kupper**, AbbVie Inc., 1, 3; **D. J. Lovell**, CCHMC has received consulting fees from AbbVie Inc., AstraZeneca, Centocor, Bristol-Myers Squibb, Pfizer, Regeneron, Hoffman La-Roche, Novartis, UCB, Xoma, and Genentech, 5, Wyeth Pharmaceuticals, 8, Amgen and Forest Research, 9; **A. Martini**, full-time employee of the GASLINI Hospital, which has received contributions to support the research activities of the network of PRINTO from AbbVie Inc., AstraZeneca, Bristol-Myers Squibb, Janssen Biologics B.V., Eli Lilly and Co., “Francesco Angelini”, 9, Astellas, AstraZeneca, Bristol-Myers Squibb, Italfarmaco, and MedImmune, 8.

Abstract Number: 2381

Long-Term Disease Control Among Patients with Juvenile Idiopathic Arthritis Receiving Adalimumab (Humira) Treatment for up to Six Years

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SESSION INFORMATION

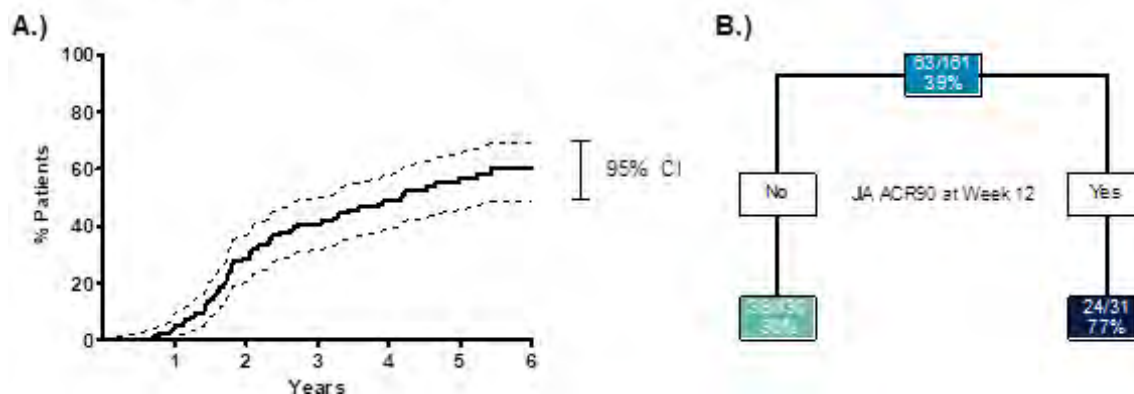
Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Figure. A.) Proportions of patients achieving sustained (≥ 6 continuous months) JADAS27 inactive disease over time; B.) Regression tree analysis selecting JIA ACR90 response at week 12 as significant factor associated with sustained JADAS27 inactive disease.



Background/Purpose: Juvenile idiopathic arthritis (JIA) is a broad term that describes a clinically heterogeneous group of arthritides of unknown cause, which begin before 16 years (yrs) of age and continues into adulthood.¹ The purpose of this analysis was to evaluate the long-term safety and effectiveness, including predictors of sustained disease control, of adalimumab (ADA) among patients (pts) with JIA through 6 yrs of treatment.

Methods: Children aged 4 - 17 yrs with polyarticular JIA were enrolled in a 32-week (wk), phase 3, randomized-withdrawal, double-blind, placebo (PBO)-controlled trial following a 16-wk open-label (OL) lead-in period. Following completion of the double-blind (DB) period, pts were eligible to enter into a long-term extension (LTE) through 360 wks and receive OL ADA based on body surface area (BSA, 24 mg/m², maximum of 40 mg eow) for ≥44 wks and fixed dosing (FD, <30 kg: 20 mg eow; ≥30 kg: 40 mg eow) thereafter. Pts were stratified by baseline (BL) MTX use. Adverse events (AEs) were monitored throughout study duration and 70 days beyond last dose. Effectiveness assessments by visit included JIA ACR30/70/90 responses, and the proportions of pts achieving JADAS27 low disease activity (LDA, 1.1 – 3.8) and inactive disease (ID, ≤1). Pts achieving sustained LDA and ID for ≥6 continuous months were evaluated. Regression tree analysis was used to identify BL and post-BL factors associated with sustained ID. Data were as observed without imputation.

Results: A total of 171 pts were enrolled, and 133 were randomized to PBO or ADA. Of these pts, 128 completed the DB period and entered the LTE. Sixty-two pts completed the LTE (primary reasons for study discontinuation: lost to follow-up [n=14], withdrawal of consent [n=20], other [n=22]). Pts on average were 11 yrs of age, and three-fourths were female with nearly 4yrs of active disease (mean JADAS27, 22.5). Twelve serious infections in 11 pts were reported through >500 pt-yrs of ADA exposure. There were no cases of congestive heart failure-related AEs, demyelinating disease, lupus-like syndrome, malignancies, TB, or deaths reported during any period of the study. At wk 312, 19/28 (68%) and 17/30 (57%) of pts achieved JIA ACR90 and JADAS27 ID, respectively; mean JADAS27 was reduced to 2.5. A total of 63 pts (37%) achieved sustained ID, with a median time of 216 wks to reach sustained ID (Figure). BL factors did not consistently predict sustained ID; however, early JIA ACR responses were associated, with ~75% of pts who achieved JIA ACR90 by wk 12 attaining sustained ID.

Conclusion: ADA appeared well-tolerated among children aged 4-17 with polyarticular JIA through up to nearly 7 yrs of exposure. Significant clinical responses, such as JIA ACR90 and JADAS27 ID, were readily achieved among pts who continued in the study. Early clinical response appeared to predict sustained ID.

Reference:: 1. Giancane, *et al. Rheumatol Ther* 2016(3):187–207.

Disclosure

D. J. Lovell, CCHMC has received consulting fees from AbbVie, AstraZeneca, Centocor, Bristol-Myers Squibb, Pfizer, Regeneron, Hoffman La-Roche, Novartis, UBC, Xoma, and Genentech for the work of DJL, 5, Wyeth Pharmaceuticals, 8, Amgen and Forest Research, 9; **N. Ruperto**, full-time employee of the GASLINI Hospital, which has received contributions to support the research activities of the network of PRINTO from AbbVie Inc., AstraZeneca, Bristol-Myers Squibb, Janssen Biologics B.V., Eli Lilly and Co., “Francesco Angelini”, 9, Astellas, AstraZeneca, Bristol-Myers Squibb, Italfarmaco, Janssen Biologics B.V., MedImmune, Roche, and Wyeth/Pfizer, 8; **A. Reiff**, AbbVie and Amgen, 5, 9; **L. Jung**, OncoImmune and Novartis, 5, AbbVie Inc., 9; **K. Jarosova**, None; **R. Mouy**, AbbVie, BMS and Novartis, 5; **I. Koné-Paut**, AbbVie Inc., 5; **O. Y. Jones**, None; **V. Vargova**, AbbVie and Pfizer, 9; **C. Wouters**, None; **I. Lagunes Galindo**, AbbVie Inc., 1, 3; **C. Mak**, AbbVie Inc., 1, 3; **H. I. Brunner**, AbbVie Inc., AstraZeneca, Centocor, Bristol-Myers Squibb, Boehringer-Ingelheim, Pfizer, Regeneron, Hoffman La-Roche, Novartis, Takeda, UCB, and Genentech, Lilly, Janssen, Ablynx, R-Pharm, 5, 9, Genentech Pharmaceuticals and Novartis, 8; **A. Martini**, full-time employee of the GASLINI Hospital, which has received contributions to support the research activities of the network of PRINTO from AbbVie Inc., AstraZeneca, Bristol-Myers Squibb, Janssen Biologics B.V., Eli Lilly and Co., “Francesco Angelini”, 9, Astellas, AstraZeneca, Bristol-Myers Squibb, Italfarmaco, and MedImmune, 8.

Abstract Number: 2382

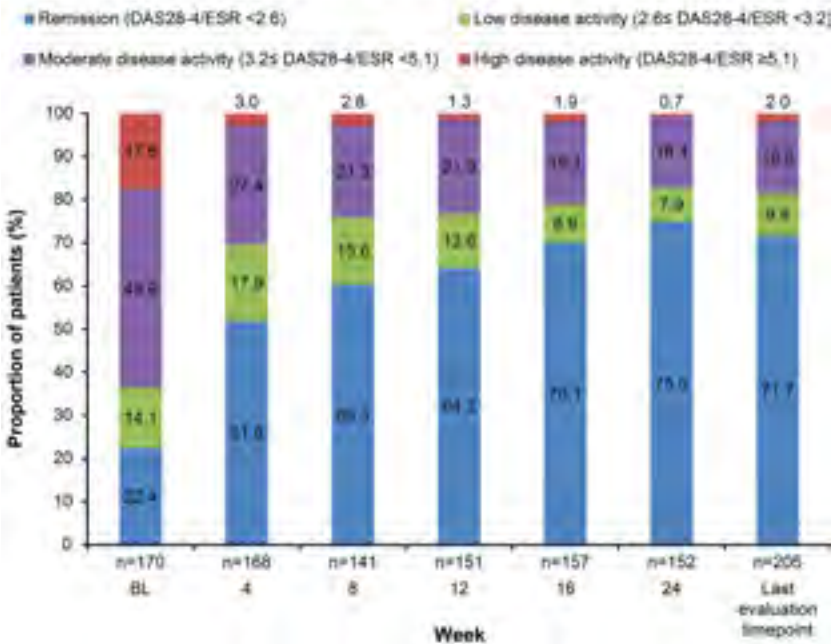
Real-World Safety and Effectiveness of Adalimumab in Patients with Juvenile Idiopathic Arthritis: Results from a Post-Marketing Surveillance in Japan

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Figure 1. Change in DAS28-4/ESR over the study period



DAS28-4/ESR, disease activity score 28-4 erythrocyte sedimentation rate

Table 1. Patient demographics and baseline characteristics

Characteristic	Safety cohort (n=356)
Sex, female, n (%)	241 (67.7)
Age, years, mean (SD) [min-max]	12.8 (4.8) [2-38]
Weight, kg, mean (SD) [min-max]	40.27 (14.44) [12.7-90.5]
JIA type*, n (%)	
Systemic-onset	16 (4.5)
Oligoarticular (persistent)	56 (16.3)
Oligoarticular (extended)	13 (3.7)
Polyarticular (RF negative)	109 (30.8)
Polyarticular (RF positive)	132 (37.1)
Others	37 (10.4)
Comorbidities, present, n (%)	115 (32.3)
Prior treatment for JIA, present, n (%)†	352 (98.8)
Methotrexate	324 (91.0)
Adrenal corticosteroid	200 (56.2)
NSAIDs	241 (67.7)
Other DMARDs	43 (12.1)
Prior treatment with biologics for JIA, n (%)‡	62 (17.4)
Tocilizumab	26 (7.3)
Etanercept	22 (6.2)
Others	14 (3.9)
Concomitant treatment, n (%)‡	352 (98.8)
Methotrexate	327 (91.8)
Corticosteroids	194 (54.5)
NSAIDs	241 (67.7)
Other DMARDs	39 (11.0)
Other drugs	265 (74.4)

*By ILAR (International League Against Rheumatism) classification criteria.

†Data are not mutually exclusive because ≥1 JIA type were possible in a single patient.

‡Data are not mutually exclusive because ≥1 type of treatment were possible in a single patient.

DMARDs, disease-modifying anti-rheumatic drugs; JIA, juvenile idiopathic arthritis; NSAIDs,

non-steroidal anti-inflammatory drugs; RF, rheumatoid factor; SD, standard deviation.

Table 2. Safety profile

Safety cohort (n=356)	ADRs	Serious ADRs
Overall, n (%)	106 (29.8)	12 (3.4)
Number of events	174	16
ADRs of interest,* n (%)		
Infection	44 (11.5)	6 (1.7)
Administration site reactions	14 (3.9)	0
Tuberculosis	1 (0.3)	1 (0.3)

*No cases of other ADRs of interest (malignancy, autoimmune diseases, pancytopenia, demyelinating diseases, congestive heart failure, and intestinal perforation) were reported during the study.
ADR, adverse drug reaction

Background/Purpose: The safety and efficacy of adalimumab (an anti-TNF- α antibody) treatment in patients with JIA have been demonstrated in clinical trials. This study was conducted to investigate the safety and effectiveness of adalimumab in patients with JIA in real-world settings in Japan.

Methods: This all-case post-marketing surveillance (NCT01412021) was conducted at 108 centers in Japan. All patients receiving adalimumab treatment for JIA affecting multiple joints were enrolled between July 1, 2011 and February 26, 2016 and observed for 24 weeks and 1-/2-year follow-ups. The primary endpoint was incidence of adverse drug reactions (ADRs) and secondary endpoint was DAS28-4/ESR remission (<2.6) rate at each study time point.

Results: Of 375 patients enrolled, 356 were included in the safety cohort (Table 1). Adalimumab was administered at a dose of 20 mg every 2 weeks in 65 of 72 patients weighing 15 kg–<30 kg and at a dose of 40 mg in 236 of 240 patients weighing ≥ 30 kg. Mean (standard deviation) treatment duration was 159.0 (31.2) days and number of administration was 11.3 (3.8) times. Treatment was discontinued in 44 (12.4%) patients with the most common reason being ineffectiveness in 28 (7.9%), and the second reason as adverse event in 9 (2.5%) patients. Overall, 174 ADRs were reported in 106 (29.8%) patients (Table 2). No cases of malignancy were reported during the study and at the 1- and 2-year follow-ups. Incidence of ADRs gradually decreased from treatment initiation over time (duration [weeks], %: 0–4, 12.6%; 5–8, 7.1%; 9–12, 4.3%; 13–16, 2.4%; 17–20, 1.9%). Incidence of ADRs was numerically higher in children aged < 15 years (34.6% [79/228]) than in patients aged ≥ 15 years (21.1% [27/128]) and in those weighing 15–<30 kg (47.2% [34/72]) than in those <15 kg (12.5% [1/8]) and ≥ 30 kg (27.5% [66/240]). Self-administration errors were reported in 2 (0.8%) patients. In the effectiveness population (n=205), the DAS28-4/ESR remission rate increased from 22.4% (38/170 patients) at baseline to 75.0% (114/152 patients) at 24 weeks (Figure 1).

Conclusion: In patients with JIA, adalimumab treatment was well tolerated with acceptable safety and effectiveness in real-world settings.

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Abstract Number: 2383

Pharmacovigilance of Biologics for Non-Systemic Juvenile Idiopathic Arthritis By the German Biologics Registry

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Long-term surveillance of biologics is particularly important in pediatric patients (pts) who may require prolonged treatment. Since 2001, the German Biologics JIA Registry (BIKER) allows follow up of an unlimited number of pts in routine clinical care. Long term safety with regard to adverse events of special interest was assessed.

Methods: BIKER was used to identify non-systemic JIA pts on biologics. Safety assessments based on adverse events (AE) reports for 25 predefined AEs of special interest (AESI) including serious and medically important infection, uveitis, chronic inflammatory bowel disease, cytopenia, hepatic event, anaphylaxis, depression, pregnancy, malignancy, and death. Events per 100 patient-years (PY) were calculated using AEs reported after first dose through 70 days after last dose. Rates were compared by Wald test.

Results: 3591 courses of biologics with a total exposure time of 6837 PY were identified with Etanercept (ETA, 5015 PY) as most frequently used followed by Adalimumab (ADA, 1298 PY), Tocilizumab (TOC, 251 PY), Abatacept (ABA, 106 PY), Infliximab (INF, 99 PY), and Golimumab (GOL, 72 PY). Differences in JIA category distribution and concomitant treatment between these cohorts were noted. A total of 5155 AE (rate 75.4/100 years), 461 SAE (5.4) and 611 AESI (8.9) were reported. The most common AESI were uveitis (227) followed by medically important infections (146), cytopenias (44), hepatic events (37), other autoimmuneopathies (27), chronic inflammatory bowel disease (22), depression (22), anaphylaxis (18), pregnancies (10) evolving hypertension (9) and malignancies (7). There were marked differences in the rate of AESI between the biologic-cohorts. Risk Ratios for serious infections were higher with ADA&GOL and lower with ETA. One case of latent tuberculosis infection but no further opportunistic infections were reported. RR for uveitis reports were significantly higher in all TNF-antibody cohorts and lower with ETA or TOC which presumably is biased by indication. RR for hepatic events were significantly higher in the TOC cohort and lower with ETA. RR for cytopenias was significantly higher with TOC. RR for anaphylaxis were significantly higher in the ABA, TOC and INF cohorts probably due to the intravenous route of application. RR for inflammatory bowel disease was higher upon Infliximab which presumably is biased by indication. There was no death in this cohort.

Biologic	ABA	ADA	ETA	GOL	INF	TOC
Pat/exposure years	94/106	827/1298	2336/5015	67/72	66/95	201/251
AESI/rate/100PY	11/10.3	173/13.3	340/6.8	16/22.3	24/25.3	47/18.7
Uveitis	2/1.9 0.6 [0.2-2.6] p=0.678	85/6.5 4.0 [3.1-5.2] p<0.0001	121/2. 0.4 [0.3-0.5] p<0.0001	6/8.4 2.5 [1.1-5.7] P=0.024	10/10.6 3.2 [1.7-6.1] p=0.0003	3/1.2 0.3 [0.1-1.1] P=0.071
Infection	2/1.9 1.0 [0.2-4.0] p=1.0	35/2.7 2.1 [1.4-3.1] p=0.0001	95/1.9 0.7 [0.5-0.9] p=0.025	6/8.4 4.0 [1.8-9.1] P=0.0008	3/3.2 1.5 [0.5-4.7] P=0.495	5/2.0 0.9 [0.4-2.3] P=0.866
Cytopenia		3/0.2 0.5 [0.2-1.6] p=0.566	30/0.6 0.8 [0.4-1.5] P=0.441		1/1.1 1.7 [0.2-12] P= 0.62	10/4.0 7.7 [3.9-16] P<0.0001
Hepatic Event	1/0.9 2.0 [0.3-14] p=0.498	10/0.8 2.5 [1.2-5.1] p=0.014	19/0.4 0.4 [0.2-0.7] P=0.003		1/1.1 2.0 [0.3-14] P=0.503	6/2.4 5.1 [2.1-12] P=0.0002
Autoimmune disease	2/1.9 5.7 [1.4-24] p=0.017	12/0.9 5.3 [2.5-11] p<0.0001	8/0.2 0.2 [0.1-0.3] p<0.0001	1/1.4 3.6 [0.5-26] P=0.207	1/1.1 2.7 [0.4-20] P=0.324	3/1.2 3.3 [1.0-11] P=0.053
IBD		2/0.2 0.7 [0.2-2.9] p=0.709	18/0.4 1.6 [0.6-4.8] p=0.373		2/2.1 7.1 [1.7-30] p=0.008	
Depression	1/0.9 3.4 [0.5-25] p=0.231	5/0.4 2.0 [0.7-5.3] p=0.183	15/0.3 0.8 [0.3-2.0] P=0.586			1/0.4 1.2 [0.2-9.2] P=0.831
Anaphylaxis	2/1.9 8.9 [2.1-38] p=0.003	3/0.2 1.3 [0.4-4.6] p=0.644	3/0.1 0.1 [0.0-0.3] p<0.0001		5/5.3 28 [9.7-76] p<0.0001	5/2.0 10 [3.5-28] P<0.0001
Pregnancy		4/0.3 4.5 [1.3-16] p=0.020	6/0.1 0.5 [0.2-1.9] P=0.348			
Hypertension		4/0.3 5.4 [1.4-20] p=0.012	5/0.1 0.5 [0.1-1.7] P=0.24		1/1.1 12 [1.4-98] P=0.022	
Malignancy			6/0.1 2.2 [0.3-18] P=0.47			

*Data outlined as n (rate/100 years), RR=Risk ratio[95% CI], p-value.

Conclusion: These data provide support for the long-term and comparative safety of biologics in JIA pts. Overall, tolerance is acceptable. Surveillance of pharmacotherapy as provided by BIKER is an import approach especially in the case of long-term treatment of children. Differences between several biologics were noted and should be considered in daily patient care.

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Disclosure: G. Horneff, None; G. Ganser, None; I. Foeldvari, None; F. Weller-Heinemann, None; K. Minden, None; A. Klein, None.

Abstract Number: 2384

Biosimilar Use in Young Adults with Juvenile Idiopathic Arthritis in Germany

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SESSION INFORMATION

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Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The first biosimilars have been approved for the treatment of juvenile idiopathic arthritis (JIA) in the last two years. To date, only a few reports exist about the experience with biosimilars in the treatment of JIA. The objectives of our study was to describe disease characteristics of young adults with JIA at biosimilar treatment start and the onset of adverse events during Treatment.

Methods: We used data collected until May 2018 from the prospective, longitudinal JuMBO (Juvenile arthritis Methotrexate/Biologics long-term Observation) cohort. JIA patients who were originally included in the pediatric register BiKeR (biologics in paediatric rheumatology) with start of a bDMARD or csDMARD will continue to be monitored in the follow-up register JuMBO into adulthood. Details on disease activity, treatment and the onset of adverse events under treatment were half-yearly reported by the treating physician.

Results: Overall, 22 JIA patients started treatment with a biosimilar (SB4: n=20, GP2015: n=1, CT-P13: n=1) in JuMBO until May 2018. The mean age and disease duration at treatment initiation was 23 years (SD=5.2) and 14.9 years (SD=7.4). Three quarters of patients had polyarticular JIA and were female. Etanercept (n=12, 55%) and MTX monotherapy (n=5, 23%) were the most recently used DMARDs before treatment start with the biosimilar. The original DMARD was discontinued due to ineffectiveness (n=7, 32%), economic reasons (n=10, 46%), an adverse event (n=1, 4%) and other reasons (n=4, 18%). The mean cJADAS10 at treatment start was 8.2 (SD=4.5) and the mean physician's global assessment of disease activity on a numerical rating scale was 3.4 (SD=2.2). Patients were treated with the biosimilar in mean for 6 months (SD=6, median=0.5, 13 exposure year). Five patients discontinued SB4 in mean after 4 months (SD=4, median=3) due to ineffectiveness (n=2, 40%), adverse events (n=2, 40%) and after attaining an inactive disease (n=1, 20%). These patients switched to etanercept (n=3, 75%) and golimumab (n=1, 25%) after biosimilar discontinuation. Seven adverse events (rate of 53.8 events per 100 exposure years) at all and 3 serious adverse events (23.1 events per 100 exposure years, hospitalization and two medical procedures) were reported during the observation period.

Conclusion: This study gives a first overview about the use of biosimilars in young adults with JIA in Germany. Economic reasons were the primary reason for switching from the original bDMARD to the biosimilar in Germany. More patients and a longer follow-up are necessary to compare the effectiveness and safety of a biosimilar with its originator in patients with JIA.

Disclosure: J. Klotsche, None; M. Niewerth, None; G. Horneff, None; K. Minden, Pfizer, Abbvie, Roche, 2, Abbvie, Roche, Chugai, Sanofi, MedCon, 5.

The Childhood Arthritis and Rheumatology Research Alliance Start Time Optimization of Biologic Therapy in Polyarticular JIA Study: Updated Report of Baseline Patient Characteristics and Treatment Choices

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: There is significant variation in the timing of when biologic medications are started during initial treatment for polyarticular juvenile idiopathic arthritis (P-JIA) in clinical practice. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) developed three consensus treatment plans (CTPs) that reflect the most commonly-used strategies for when to start biologic treatment. The CARRA Start Time Optimization of Biologic Therapy in Polyarticular JIA (STOP-JIA) study is comparing the effectiveness of the three CARRA-P-JIA CTPs using a prospective, observational study design and aims to enroll 400 children. It is expected that enrollment will be completed in July 2018. This abstract describes interim baseline characteristics and CTP choices for the patients enrolled.

Methods: Untreated P-JIA patients with 5 active joints were enrolled into the CARRA Registry at the time of treatment initiation. Providers and patients together chose one of the CTPs to follow: 1) Step-Up treatment (initial therapy with DMARD and biologic added after 3 months, if needed); 2) Early Combination (initial therapy with both DMARD and biologic); and 3) Biologic First (initial treatment with biologic monotherapy). Providers had the option of prescribing glucocorticoids at baseline per their usual practice. Glucocorticoid tapering suggestions were provided.

Table 1. Baseline Patient Characteristics

	Total Cohort (n= 335)	Step up (n= 218)	Early Combination (n=84)	Biologic First (n=33)
Female N (%)	246 (73)	163 (75)	61 (73)	22 (67)
White N (%)	228 (68)	156 (72)	53 (63)	19 (58)
Age in yrs - mean (range)	10 (1-18)	10 (1-18)	11 (1-17)	11 (1-18)
JIA Category N (%)				
Extended Oligoarticular	9 (3)	9 (4)	--	--
Polyarticular (RF-)	211 (63)	149 (68)	48 (57)	14 (42)
Polyarticular (RF+)	58 (17)	32 (15)	20 (24)	6 (18)
Psoriatic	22 (7)	12 (6)	5 (6)	5 (15)
Enthesitis-related	26 (8)	12 (6)	8 (10)	6 (18)
Undifferentiated	8 (2)	3 (1)	3 (4)	2 (6)
Number of Active joints - mean (range)	13 (5-50)	12 (5-49)	16 (5-50)	11 (5-41)
Physician Global Assessment of Disease Activity - mean (range)	5 (0-10)	5 (0-10)	6 (1-10)	6 (1-10)
Juvenile Arthritis Disease Activity Score - mean (range)	18 (5-29)	17 (5-29)	20 (6-29)	20 (14-28)
CHAQ Score - mean (range)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)
Oral steroids prescribed at baseline - N (%)	85 (25)	57 (26)	23 (27)	5 (15)

Results: Three hundred and fifty-two patients were enrolled at 43 sites in the US and Canada between 1 Nov 15 and 22 May 18. Data for the 335 patients with baseline data available are summarized in Table 1. The most commonly chosen CTP was Step-Up (n=218; 65%). Early Combination CTP was the next most common choice (n=84; 25%). To date, 823 follow up visits have been entered and 152 patients have completed their 12-month endpoint visit. Of the patients with follow-up data available, 31 patients were reported to have changed CTP at least once during STOP-JIA participation. There were 26 Serious Adverse Events (SAE) or non-serious Events of Special Interest (ESI) including 7 cases of new onset uveitis, 8 infections, and 3 episodes of hepatitis.

Conclusion: With > 85% of patients enrolled to date, patients have been enrolled into all 3 CTP choices, with the Step-Up CTP being the most common. Ongoing, prospective data collection from these patients will allow for a comparison of the effectiveness of the strategies.

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Abstract Number: 2386

Secukinumab Is a Promising Treatment for Patients with Juvenile Enthesitis Related Arthritis Nonresponsive to Anti-TNF Treatment

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Secukinumab (SEC) is licensed to treat adults with spondyloarthritis. It is not licensed for pediatric patients with Juvenile Idiopathic Enthesitis related Arthritis (enthJIA) yet. Only anti-TNF is licensed as biologic treatment for enthJIA. Not all patients get into remission with an anti-TNF therapy. We review our first patients, who did not reach remission under anti-TNF and were switched to SEC.

Methods: We conducted a retrospective chart review in our unit of patients with enthJIA, who were treated with SEC.

Results: 14 patients were treated with SEC. 85% of them were female. All patients were diagnosed with enthJIA. The mean age of the patients at the start of the treatment was 18.7 years and the mean weight 61.6 kilograms. The patients received before SEC in average 1.93 different anti-TNF's, where they reached no remission, the JADAS-10 was 8.07 at the time initiation of SEC. SEC was applied according the adult dosing schedule. The mean dose at week 0 was 192 mg/dose and at 12 months 262 mg/dose. At month three already 3 of 14 patients, at month six 6 of 10 patients and at months twelve 6 of 8 patients received 300 mg per application. Mean follow up of the patients under SEC was 6 months. JADAS 10 decreased from 8.07 at timepoint 0 to 6.35 at months 3 (n=14 patients); 5.2 at months 6 (n=10 patients) and 6.00 at months 12 (n=8 patients). The mean number of active enthesitis points decreased from 0.86 at timepoint 0 to 0.25 at months 3, 0.3 at months 6 and 0.25 at months 12. The CHAQ/HAQ score stayed stable around 0.4 during the whole observation period. No patient discontinued the treatment because of AE or SAE.

Conclusion: In this small sample of anti-TNF nonresponder patients SEC showed quite good effectiveness regarding the improvement in JADAS 10 score, at 6 months the JADAS score reached acceptable disease activity (<5.4) and the number of active enthesitis sites decreased. The 150 mg dose seemed to be not sufficient, in over half of the patients the dose had to be increased to 300 mg /dose per application.

Disclosure: I. Foeldvari, Novartis, BMF, Bayer, Genentech, Sanofi, Abbvie, Chugai; Medac, BMS, Pfizer, 5, 8; J. Baer, None.

Resurrecting Triamcinolone Hexacetonide (the Steroid Formerly Known as Aristospan®): Efficacy and Safety of a Compounded Preparation of Triamcinolone Hexacetonide for Intra-Articular Injection in Children with Arthritis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

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Background/Purpose: Intra-articular triamcinolone hexacetonide (TH) historically provided longer-lasting control of chronic arthritis in children than comparator intra-articular glucocorticoid preparations such as triamcinolone acetonide (TA) (J Rheumatol. 2012; 39:374). Prior to 2015, pediatric rheumatologists in the U.S. commonly injected joints with TH to control oligoarticular disease or to provide adjunctive therapy to systemic treatment with methotrexate and/or biologics for polyarticular disease. Since 2015, however, TH is no longer produced or marketed in the U.S. The lack of availability of TH in the past 3 years has required use of the less-effective TA or escalation of systemic therapy. In May 2017, we were able to identify a compounding pharmacist (DB) who could produce compounded TH (cTH). We sought to determine if there was a difference in time to recurrence of swelling in joints injected with cTH versus TA.

Methods: cTH 20mg/ml is prepared with TH, USP powder, sorbitol solution 70% USP, polysorbate 80 NF, benzyl alcohol NF and sterile water for injection, USP. Testing is done as per USP 797 guidelines for sterility, potency and fungal testing. Stability testing done by Compounder's International Analytical Laboratory, and a 90 day beyond use date is established. cTH is ordered as a patient specific prescription and requires lead time for preparation and quality testing. Use of cTH caused some unique barriers. Our Pharmacy had to vet the compounding pharmacy to assure it met FDA rules and USP 797 standards for compounding sterile products. Insurance reimbursement is not consistently approved for compounded products, and reimbursement strategies had to be established. Our pharmacy created a memo to ensure injections of cTH could be performed throughout our organization. We report results of one year of using cTH in children. Demographic information, diagnoses, and prior injection data are summarized. Side effects, including steroid atrophy, are reported.

Results: 82 joints with chronic arthritis were injected with cTH from 5/2017 to 5/2018. 39 joints were injected with TA from 2/2016 to 5/2018. Flares occurred in 16 of 82 cTH joints (20%) versus 28 of 39 TA joints (72%) (p<0.001). There was no difference in time to flare from injection date with either cTH or TA for those individuals who had recurrence of joint swelling. There were no injection site reactions, bleeding, or infections with either cTH or TA. Atrophy was rare in each group.

	# Individuals	# Joints injected	# Knees injected	Recurrence	p-value	Time to flare (months) (#)	p- value
cTH	41	82	67% (55/82)	20% (16/82)	<0.001	4.7 ± 2.8 (16/82)	0.54
TA	18	39	59% (23/39)	72% (28/39)		4.3 ± 2.0 (28/39)	

Conclusion: cTH was effective in managing arthritis in children. Results were similar to that reported in the literature with fewer flares using cTH. We conclude that use of cTH is a viable approach to counter the lack of commercially available TH intra-articular glucocorticoid in the USA for pediatric arthritis patients.

Disclosure: C. A. Bingham, None; L. Scalzi, None; D. Boomsma, Custom Prescriptions of Lancaster, 3; B. Groh, None; N. Gaffney, None; S. Sertial, None; T. Hahn, None; V. Lacroce, None; B. Ostrov, None.

Assessment of Treatment Responses, with Special Reference to Remission Using Juvenile Arthritis Disease Activity Score (JADAS), in the Different Categories of Juvenile Idiopathic Arthritis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Juvenile Idiopathic Arthritis (JIA) is the most common chronic rheumatologic disease in children, which can significantly compromise quality of life. The objective of the study was to assess treatment responses and remission in the different categories of JIA.

Methods: Children with JIA were treated from their first presentation in a tertiary centre according to ACR recommendations for JIA, for a duration of 18 months. Responses to treatment at the end of 18 months were monitored by change in Juvenile Arthritis Disease Activity Score (JADAS) 27 and PedACR30, 70 and 90. Remission was assessed by JADAS27, JADAS10 and cJADAS10 inactive disease state and Wallace remission criteria. Disability was quantified by CHAQ-Disability index at end of follow-up.

Results: Two hundred and twenty children with JIA were included in the study: 80 (36.3%) had Polyarticular JIA, 71 (32.2%) Enthesitis-related, 34 (15.4%) each had Systemic and Oligoarticular and 1 (0.5%) Psoriatic JIA. After 18 months, there was significant drop in mean JADAS27 (from 26.8 to 10). Inactive disease state according to JADAS27 was achieved in 13.9% children overall (13.75% Polyarticular, 15.49% Enthesitis-related, 8.82% Systemic and 17.65% of Oligoarticular JIA; no statistically significant difference between any group). JADAS27 low disease activity was achieved in 29.5% children. JADAS10 and cJADAS10 inactive disease state were achieved by 14.6% and 15.4% children respectively (Table 1). There was strong correlation between JADAS10 and cJADAS10 (Spearman's correlation coefficient at baseline and 18 months, 9.5 and 9.76, respectively). Wallace remission criteria was satisfied by 23.9% children. PedACR 30, 70 and 90 responses were achieved in 81.8%, 50.7% and 26.7% respectively. Mean CHAQ-DI at 18 months was 0.5 (0.31 Polyarticular, 0.23 Enthesitis-related, 1.37 Systemic and 0.08 in Oligoarticular JIA; significantly more in Systemic and Polyarticular JIA versus Oligoarticular). Eighteen percent children required no DMARDs (only NSAIDs and intra-articular corticosteroids), 73% one DMARD and 9% two DMARDs. Systemic steroids was required in 32.4% children overall, being significantly more in Systemic JIA (88.2%). Biologic therapy was given to 28/220 (12.7%) children, being significantly more in Systemic JIA, 15/34 (44.1%) in comparison to 7/71 (9.8%) of Enthesitis related JIA, 5/80 (6.2%) of RF +ve Polyarticular JIA and 1/34 (3%) of Oligoarticular JIA. Tocilizumab was used in Systemic JIA, Rituximab in Polyarticular JIA and anti-TNF in Oligoarticular and Enthesitis-related arthritis. At 6 months after biologics, 19/28 (67.9%) of the children achieved JADAS27 inactive state and 3/28 (10.7%) achieved JADAS27 low disease activity.

Conclusion: Remission according to JADAS27 occurred in only a minority of children with JIA, despite optimum treatment. cJADAS10 may be an effective substitute to JADAS10.

Table 1: Proportions of children inactive or low disease activity according to JADAS and Wallace remission criteria

	Polyarticular JIA	Enthesitis related JIA	Systemic JIA	Oligoarticular JIA	Overall
JADAS27 inactive disease state	13.75% (n=11)	15.49% (n=11)	8.82% (n=3)	17.65% (n=6)	13.9%
JADAS27 low disease activity state	23.8% (n=19)	26.8% (n=19)	23.5% (n=8)	44.1% (n=15)	29.5%
JADAS 10 inactive state	13.75% (n=11)	15.49% (n=11)	11.76% (n=4)	17.64% (n=6)	14.6%
JADAS 10 low disease state	23.75% (n=19)	25.35% (n=18)	20.58% (n=7)	26.47% (n=9)	24%
cJADAS 10 inactive state	13.75% (n=11)	18.31% (n=13)	11.76% (n=4)	17.64% (n=6)	15.4%
cJADAS 10 low disease state	22.5% (n=18)	21.12% (n=15)	23.53% (n=8)	17.65% (n=6)	21.4%
Wallace Remission	15% (n=12)	39.43% (n=28)	14.7% (n=5)	26.47% (n=9)	23.9%

Disclosure: D. Sinha, None; S. Mondal, None; A. Ghosh, None.

Evaluating Disease Activity Outcomes for Juvenile Idiopathic Arthritis across the Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN)

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Table 1. Results reported as frequency (%) or mean (standard deviation).

Variable	All Patients (n = 3806)	Higher CID Rate Centers (n = 2136)	Lower CID Rate Centers (n = 1670)	
Age (years)	12.5 (5.2)	12.7 (5.4)	12.3 (4.9)	p=0.049
Female	2393 (71%)	1219 (71%)	1174 (70%)	p=0.76
Race				p<0.001
White	2749 (85%)	1407 (83%)	1342 (88%)	
Other	164 (5%)	107 (6%)	57 (4%)	
African American	153 (4.8%)	85 (5%)	68 (4.5%)	
Asian	89 (3%)	58 (3%)	31 (2%)	
Multi-race	48 (1.5%)	29 (2%)	19 (1%)	
American Indian/Alaskan Native	10 (0.3%)	7 (1%)	3 (0.2%)	
Native Hawaiian	2 (0.1%)	0	2 (0.1%)	
Insurance Status				p<0.001
Private	2272 (90%)	1280 (92%)	992 (87%)	
Medicaid	139 (5.5%)	39 (3%)	100 (9%)	
More than one	108 (4%)	67 (4.8%)	41 (3.6%)	
Medicare	8 (0.5%)	4 (0.2%)	4 (0.4%)	
Disease Duration (months)	67.0 (53.5)	72.0 (55.7)	61.4 (50.3)	p<0.001
ILAR Subtype				p=0.045
Polyarticular, RF (-)	1041 (31%)	559 (32%)	482 (29%)	
Oligoarticular, persistent	856 (25%)	428 (25%)	428 (26%)	
Enthesitis related arthritis	405 (12%)	183 (11%)	222 (13%)	
Oligoarticular, extended	336 (10%)	179 (10%)	157 (9%)	
Psoriatic arthritis	251 (7%)	114 (7%)	137 (8%)	
Systemic arthritis	220 (6%)	120 (7%)	100 (6%)	
Polyarticular, RF (+)	210 (6%)	105 (6%)	105 (6%)	
Undifferentiated	67 (2%)	32 (2%)	35 (2%)	
ANA Positive	1643 (50%)	868 (50%)	775 (50%)	p=0.996
Patient Global Assessment (0-10)	1.86 (2.4)	1.71 (2.3)	2.04 (2.4)	p=0.001
Pain Score (0-10)	2.15 (2.6)	2.05 (2.5)	2.26 (2.7)	p=0.024
CHAQ	0.28 (0.49)	0.27 (0.49)	0.30 (0.48)	p=0.174
MEDICATIONS				
Non-biologic DMARD				
Total	1233 (32%)	564 (26%)	669 (40%)	p<0.001
Methotrexate	1062 (28%)	478 (22%)	584 (35%)	
Leflunomide	86 (2%)	60 (2.8%)	26 (1.5%)	
Sulfasalazine	54 (1.5%)	18 (0.8%)	36 (2%)	
Hydroxychloroquine	48 (1.2%)	6 (0.3%)	42 (2.5%)	
Other	12 (0.3%)	4 (0.2%)	8 (0.5%)	
Cyclosporine	3 (0.07%)	1 (0.04%)	2 (0.1%)	
Azathioprine	2 (0.05%)	0	2 (0.1%)	

SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: It is widely accepted that the treatment goal for juvenile idiopathic arthritis (JIA) is remission. PR-COIN, a quality improvement collaborative comprised of pediatric rheumatology centers, measures JIA disease activity in patients using the ACR provisional criteria for Clinical Inactive Disease (CID). Significant center-level differences in the percentage of patients in CID have been observed across the network. The objective of the current study was to identify differences between patient-level variables in centers with higher vs lower percentage of patients in CID, although we hypothesize that these differences are primarily driven by center-level factors rather than patient case-mix.

Methods: This study used cross-sectional data provided by PR-COIN that was collected by PR-COIN centers in the ACR Rheumatology Clinical Registry between March 2015 and May 2016. For each patient, variables from the most recent visit were recorded and included age, gender, race, insurance status, duration of diagnosis, ILAR subtype, ANA status, patient global assessment, pain score, Childhood Health Assessment Questionnaire (CHAQ) score, and current medication use. Patients were grouped into two categories based on the percentage of patients in CID at their center (above or below the network average). Statistical analyses were performed using R software, including descriptive analyses and two-group comparisons with chi-square for categorical variables and independent t-tests for continuous variables. Missing data were excluded with each analysis.

Results: There were 3806 patients eligible for analysis from 15 centers. The median center-level rate of CID was estimated at 45.6% with a range from 26.1% to 57.9%. The 7 centers categorized as “higher performing” contained 2136 patients and the 8 centers categorized as “lower performing” contained 1670 patients. Comparing patients from the “higher” vs. patients from the “lower” centers, key significant differences included race, insurance status, disease duration, patient global assessment, pain score, and current use of non-biologic DMARDs, biologic DMARDs, TNF inhibitors, NSAIDs, and glucocorticoids (see Table 1).

Conclusion: By leveraging the framework of a quality improvement learning network such as PR-COIN, we are able to determine predictors of disease activity outcomes using data from clinical practice. This analysis demonstrates preliminary differences in patient characteristics between patients at centers with higher vs lower rates of CID; more advanced modeling is needed to further evaluate these findings. Future directions include development and implementation of interventions to address identified predictors, which can then be tested and spread through the multi-center infrastructure of PR-COIN. This work has the potential to directly impact care delivery and improve outcomes for JIA.

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Abstract Number: 2390

Incidence of and Risk Factors for Adrenal Suppression Following Ultrasound-Guided Intra-Articular Corticosteroid Injection with Triamcinolone Acetonide in Juvenile Idiopathic Arthritis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Intra-articular corticosteroid injection (IACI) is routinely used in juvenile idiopathic arthritis (JIA) with oligoarticular disease and as adjunct therapy for other types of JIA. Adrenal gland suppression following IACI with Triamcinolone Acetonide (TA) has been scantily reported, but its incidence and risk factors are unknown. We studied 23 JIA patients following ultrasound guided IACI with TA to determine the incidence of adrenal gland suppression and risk factors for its development.

Methods: This was a case-control study of patients who satisfied ILAR classification criteria for JIA, received ultrasound-guided IACI with TA between 01/2017-04/2018, had 8AM serum cortisol levels measured 2 weeks after joint injection and had not received systemic steroid therapy for over 3 months. Case subjects were those who developed adrenal gland suppression as defined by 8AM serum cortisol level of <7 micrograms/dL. Control subjects were those who received IACI but did not develop adrenal suppression. Repeat 8AM serum cortisol levels were measured 6 weeks post-IACI in case subjects who had documented adrenal suppression initially. Incidence and risk factors including total dose of TA per body weight, age, number of injected joints and types of JIA were analyzed.

Results: Twenty-three patients, ages 2 to 21 years (mean 11.3 ± 1.09 years), with diagnoses of oligoarticular (9), polyarticular (8), psoriatic (4), and enthesitis-related JIA (2) receiving 0.43-6.8 mg/kg TA were studied. Incidence of adrenal suppression after receiving IACI was 43.5% (10/23); 5 with polyarticular JIA, 4 with oligoarticular JIA, and 1 with enthesitis-related arthritis. Total numbers of injected joints with adrenal suppression were 5 in 3 patients, 4 in 1 patients, 2 in 4 patients and 1 in 2 patients. The means of TA dose and age of patients with and without adrenal suppression were 2.986 mg/kg, 95% CI (2.116, 3.856), 8.9 years, 95% CI (5.1, 12.8) and 2.045 mg/kg, 95% CI (1.119, 2.972), 13.2 years, 95% CI (10.8, 15.7) respectively. Only significant risk factor for adrenal suppression was age ≤ 8 years (odd ratio 8.2, $p = 0.03$), but not TA dose, number of injected joints or types of JIA. Of the 10 patients who developed adrenal gland suppression, only one experienced symptomatic adrenal suppression. All patients with adrenal gland suppression at 2 weeks post-injection had normal 8AM serum cortisol levels by 6 weeks post-injection.

Conclusion: Adrenal gland suppression may be seen in JIA patients 2 weeks post IACI. Children ≤ 8 years are at most risk. The suppression is transient and spontaneously recovers by 6 weeks post-IACI. Unexplained symptoms after IACI may be a manifestation of adrenal insufficiency. Further study of risk factors for adrenal gland suppression following IACI in JIA is warranted.

Disclosure: K. K. Ngo, None; A. Bernier, None; M. E. Elder, None; R. F. Modica, None; A. Thatayatikom, None.

Abstract Number: 2391

Methotrexate Polyglutamates As an Evaluation Tool for Appropriate Dosage of Oral Methotrexate Administration in Pediatric Patients

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SESSION INFORMATION

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Background/Purpose: Since MTX metabolism varies depending on age and dosage, we need to know optimal MTX administration method in children. We performed multi-center prospective study to examine the relationship between MTX dosage and safety using the concentration of MTX polyglutamates in red blood cells (MTX-PG).

Methods: This study is a part of research projects for intractable diseases supported by Health and Welfare Research Expenditure in Japan. Seven hospitals participated and received approval from each ethical review board. Forty-nine JIA patients who had been undergoing the same MTX dosage for 3 months and whose consent had been obtained were included. The total and each fragment of MTX-PG were measured by previously reported methods and calculated as concentration per administration dose per weight. The factors that may influence to MTX-PG were evaluated, such as age, dose per body (mg/m²), dose regimen (split or single), timing of the meal and combination of folic acid. In addition, we examined the presence of gastrointestinal adverse effect, and the above factors were compared in groups with and without that. The values in each group are expressed in median and 25-75% quartile. Fisher's bilateral test and Wilcoxon rank sum test were used for statistical analysis.

Results: The mean age was 10 (6-14) years old and the mean MTX dose was 7.24mg/ m²/W (5.48-8.62). The mean MTX-PG_{total} increased linearly until MTX dose reached to 10mg/ m²/W, and became a plateau. MTX administration

Table. Comparison between group with and without nausea mean (25-75% quartile)			
	With nausea (n=14, 28.6%)	Without nausea (n=35, 71.4%)	P
mean age (year)	11.5 (10-15)	9 (5-14)	0.0597
mean body mass surface (m ²)	1.28 (1.11-1.44)	1.01 (0.76-1.37)	0.0336
Male (%)	5 (35.7%)	12 (34.3%)	1.000
mean MTX (dose) (mg/W/m ²)	7.12 (5.23-8.06)	7.70 (5.48-9.45)	0.45
Single dose regimen (%)	10 (71.4%) *	30 (85.7%)	0.25
post meal regimen (%)	10 (71.4%) **	10 (28.6%)	0.0078
mean MTX-PG _{total} (nmol/L/mg/kg)	358.9 (248.4-444.3)	250.1 (202.1-410.2)	0.1993
mean MTX-PG ₁ (nmol/L/mg/kg)	150.7 (116.3-217.7)	104.3 (64.3-208.8)	0.2851
mean MTX-PG ₂ (nmol/L/mg/kg)	99.1 (80.0-125.0)	69.6 (42.2-108.3)	0.1381
Combination of folic acid (%)	7 (50%)	14 (40%)	0.54
Combination of bDMARD	10 (71.4%)	24 (68.6%)	1.000
mean JADAS 27	3.65 (0-8.3)	0 (0-0)	0.0065
mean ALT (U/L)	15.5 (12-21.5)	15 (11-21)	0.8156
mean MCV (fL)	85.3 (82.2-87.1)	86.7 (83.6-87.2)	0.2032

* Two cases were switched to split dose regimen because of nausea.

** Nine cases were switched to post meal regimen because of nausea.

Fisher's bilateral test

Wilcoxon rank-sum test

of 5 to 10 mg/ m²/W was required for effective and safe range (60 to 100 nmol/L) of MTX- PG_{total} ($y = -1.5446X^2 + 30.989X - 58.527$). The mean MTX- PG_{total} per administration dose per weight gradually increased as age rose, from 224.7 nmol/L/mg/kg in infants to 462.1 nmol/L/mg/kg in adolescents, and that was higher in split regimen group than in single regimen group (344.6 vs. 252.7, $p = 0.0216$) and higher in post meal regimen group than in pre meal regimen group (384.2 vs. 230.6, $p = 0.0043$). As for each fragment, only MTX-PG₁ and MTX-PG₂ were higher in split regimen group ($p = 0.0102$, 0.0332) and post meal regimen group ($p = 0.0072$, 0.0092). The complaint of nausea was seen more in post meal regimen group than in pre meal regimen group (52.6% vs. 13.3%, $p = 0.0078$). The combination of folic acid did not affect MTX- PG_{total}. Compared with the group without nausea, the concentration of MTX- PG_{total} and MTX-PG₁₋₂ tended to be higher in group with nausea (there was no significant difference. see Table). The group with nausea showed significant correlation with higher body surface area, post meal regimen and higher JADAS27.

Conclusion: We recommend that children be administered 5 to 10 mg / m²/W of MTX and take it singly before meal, although it is necessary to consider reduction during puberty when the MTX-PG is prone to increase and nausea is likely to occur. The MTX-PG₁₋₂ increases by post meal administration and may cause nausea.

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Abstract Number: 2392

Are Single Nucleotide Polymorphisms in Methotrexate Transporter Proteins Associated with Methotrexate Intolerance in Juvenile Idiopathic Arthritis?

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Methotrexate (MTX) intolerance is common in juvenile idiopathic arthritis (JIA) and poses the risk of premature termination of an effective treatment. MTX intolerance is a compound concept of stomachache, nausea, vomiting and behavioral symptoms associated with low-dose MTX and covers anticipatory and associative symptoms. Large

inter-individual variation in the level of MTX intolerance exists and genetic factors may play a role. The objective is to investigate if MTX intolerance is associated with selected single nucleotide polymorphisms (SNPs) in MTX transporter proteins in children with JIA treated with low-dose MTX.

Methods: The local research ethics committee approved this observational study. Eligible children were diagnosed with JIA (ILAR criteria), aged ≥ 9 years and treated with low-dose MTX. The enrolment period was December 2013–July 2016. MTX intolerance was assessed by the parents' completion of the MTX intolerance severity score (MISS) (1). A child was categorized MTX intolerant if the MISS score ≥ 6 and min. 1 point in an anticipatory, associative or behavioral symptom. At enrolment a blood sample was drawn for the SNP analysis. DNA was extracted from EDTA blood using salt precipitation. The SNP analysis was performed by PCR amplifying an amplicon containing the selected SNP and then Sanger Sequencing (Eurofins Genomics). Statistic analyses for the SNPs were performed using PLINK 1.9, logistic regression of additive effect of alleles, filtering for Hardy-Weinberg equilibrium and accounting for more than two possible alleles present in the study population for one SNP.

Results: The selected SNPs within genes encoding the MTX transporter proteins were: SLCO1B1 (rs4149056; rs4149081), SLCO1B3 (rs2117032), SLC19A1 (rs1051266), ABCC2 (rs2273697; rs3740066; rs717620), ABCB1 (rs2032582; rs1045642). The study population consisted of 121 JIA patients, 82 girls and 39 boys, with a median age of 13.3 years (IQR: 11.3–15.1). The median MTX dose was 9.7 mg/m²/week (IQR: 9.0–10.9) and the median MTX treatment duration was 340 days (IQR: 142–766). A completed MISS and SNP analysis was available for 118 patients (the MISS: 1 missing; the SNP analysis: 2 missing) and 72 children were categorized as MTX intolerant.

Table 1

	SNP	Alleles Major > minor	MTX _{intolerant} Allel count	MTX _{tolerant} Allel count	OR (95% CI)	p	Gene	Chr.	BP	Consequence
Efflux	Rs2273697	G>A	36	22	1.05 (0.61–1.80)	0.87	ABCC2	10	99804058	Missense
	Rs3740066*	G>A	58	35	1.15 (0.64–2.07)	0.64	ABCC2	10	99844450	Missense
	Rs717620	G>A	29	23	0.77 (0.42–1.41)	0.40	ABCC2	10	99782821	5'UTR variant
	Rs2032582	G>T G>A	61 3	34 2	1.28 (0.73–2.24) 0.96 (0.15–5.96)	0.39 0.96	ABCB1	7	87531302	Missense
	Rs1045642	C>T	62	42	0.88 (0.49–1.57)	0.67	ABCB1	7	87509329	Synonymous
Influx	Rs4149056	T>C	25	13	1.28 (0.62–2.66)	0.51	SLCO1B1	12	21178615	Missense
	Rs4149081	G>A	27	15	1.19 (0.59–2.43)	0.62	SLCO1B1	12	21225087	Intron variant
	Rs2117032	C>T	52	34	0.97 (0.57–1.64)	0.90	SLCO1B3	12	20921188	Downstream 3'UTR
	Rs1051266*	G>A	64	38	1.20 (0.67–2.13)	0.54	SLC19A1	21	45537880	Missense

OR; Odds Ratio. Chr; Chromosome. BP; Base Position.

*SNP variant not available for 1 child

Conclusion: MTX intolerance was not significantly associated with any of the selected SNPs in the MTX transporter proteins. This could indicate that focus in future should be directed at other genetic targets, possibly SNPs in genes encoding other MTX relevant factors.

(1) Bulatovic M, Heijstek MW, Verkaaik M, van Dijkhuizen EH, Armbrust W, Hoppenreijns EP, et al. High prevalence of methotrexate intolerance in juvenile idiopathic arthritis: development and validation of a methotrexate intolerance severity score. *Arthritis Rheum* 2011 Jul;63(7):2007–2013

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Abstract Number: 2393

Is Methotrexate-Induced Nausea in Juvenile Idiopathic Arthritis Influenced By Anxiety or Coping Strategies?

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

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Session Time: 9:00AM-11:00AM

Background/Purpose: Nausea to low-dose methotrexate (MTX) is a significant clinical challenge in the treatment of juvenile idiopathic arthritis (JIA). There exists a large inter-individual variation in the level of MTX-induced nausea. Anxiety and coping strategies have been associated to nausea and vomiting induced by high-dose chemotherapy, but has not been investigated in low-dose MTX treatment of JIA. The objective is to investigate if MTX-induced nausea is associated with anxiety or coping strategies in children with JIA treated with low-dose MTX.

Methods: Children were eligible if diagnosed with JIA (ILAR criteria), aged ³9 years, and treated with low-dose MTX. If children were cognitively impaired or not fluent in Danish they were excluded. Enrolment was from December 2013 - July 2016. The anxiety level was determined using Beck's Youth Inventory – Anxiety (BYI-A) (1). Coping strategies were evaluated by a nausea coping questionnaire (NCQ)[1]. MTX-induced nausea was registered by the children's completion of a nausea diary. The local research ethics committee approved this observational study.

Results: Enrolled were 121 children with JIA (82 girls: 39 boys), the median age (IQR) was 13.3 (11.3-15.1) years. The nausea diary was completed for 1 day by 100 children and for min. 7 days by 77 children. The BYI-A and the NCQ were completed by 119 children. MTX was given orally to 45 patients (MTX_O) and subcutaneously to 76 patients (MTX_{SC}). Fifty-six children had MTX-induced nausea deduced from the diaries (MTX_O:16/27; MTX_{SC}: 40/50; p=0.051). The BYI-A raw score was higher for children with self-reported MTX-induced nausea compared to all others (Table 1). The coping strategy internalizing was used more often by children with MTX-induced nausea compared to all others. No significant associations were found for the remaining coping strategies.

Table 1

	JIA	p
MTX _O : MTX _{SC} , n	45: 76	
MTX dose, median (IQR) mg/m ² /week	9.7 (9.0 – 10.9)	-
MTX _O : MTX _{SC}	9.6 (9.0-10.7) : 9.8 (8.8-11.1)	0.86
MTX treatment duration, median (IQR) days	340 (142-766)	-
MTX _O : MTX _{SC}	261 (143-543) : 417 (134-853)	0.39
BYI-A raw score (total 0 – 60), median (IQR)	26 (22-30)	-
MTX-induced nausea: All others (Diary)	27 (23-32) : 24 (22-27)	0.0164
Coping Strategies, median (IQR)	9 (7-12)	-
Internalizing (range 5-25)	10 (8-13) : 7 (5-8)	<0.0001
MTX-induced nausea: All others (Diary)	5 (5-7)	-
Externalizing (range 5-25)	5 (5-7) : 5 (5-6)	0.29
MTX-induced nausea: All others (Diary)	15 (11-19)	-
Positive Self Statements (range 5-25)	15 (11-18) : 13 (10-19)	0.79
MTX-induced nausea: All others (Diary)	17 (13-21)	-
Information seeking (range 8-40)	17 (14-22) : 16 (14-19)	0.32
MTX-induced nausea: All others (Diary)	13 (10-16)	-
Behavioral Distraction (range 4-20)	13 (10-16) : 12 (10-18)	0.70
MTX-induced nausea: All others (Diary)	21 (18-24)	-
Cognitive Distraction (range 6-30)	21 (18-25) : 22 (20-23)	0.51
MTX-induced nausea: All others (Diary)	15 (12-20)	-
Seeking Social Support (range 6-30)	16 (13-20) : 16 (12-22)	0.50
MTX-induced nausea: All others (Diary)		

Conclusion: MTX-induced nausea was significantly associated with the coping strategy internalizing and anxiety in children with JIA. These psychological factors need attention when children with JIA commence low-dose MTX treatment, in order to intervene when appropriate.

(1) Thastum M, Ravn K, Sommer S, Trillingsgaard A. Reliability, validity and normative data for the Danish Beck Youth Inventories. Scand J Psychol 2009 Feb;50(1):47-54.

[1] Subscales: Information seeking/problem solving, seeking social support, positive self-statements, behavioural distraction, cognitive distraction, externalizing and internalizing/catastrophizing. Frequency of use: 1=never, 2=hardly ever, 3=sometimes, 4 = often, 5 = very often.

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Anti-Adalimumab Antibodies Kinetics: An Early Guide for Juvenile Idiopathic Arthritis (JIA) Switching

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SESSION INFORMATION

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Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

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Background/Purpose: Anti-adalimumab antibody (AAA) production may lead to reduced adalimumab (ADA) serum levels and therapy failure. There are, however, scarce and conflicting data regarding ADA immunogenicity in juvenile idiopathic arthritis (JIA) patients. Importantly, none of these three studies performed AAA production kinetics nor they have evaluated predictors of therapy response. Thereby, our objectives were to assess the longitudinal production of AAA and baseline risk factors for this antibody development in JIA patients initiating ADA.

Methods: From June 2010 to October 2016, 30 consecutive JIA patients under ADA therapy were prospectively followed in the biologic therapy center of Rheumatology Division of a tertiary university hospital. JIA clinical/laboratorial/treatment data and sera for ADA and AAA assays (ELISA and bridging ELISA) were obtained at baseline (BL), 2 months (2M), 3 months (3M), 6 months (6M) and 12 months (12M). Patients with therapy failure requiring ADA withdrawn had their sera evaluated at their last medical visit prior to biologic switch (blinded to ADA and AAA levels).

Results: The mean age at ADA start was 14.5 ± 5.4 years, 67% were females and the mean disease duration until biologic therapy initiation was 8.4 ± 5.8 years. Subtype distribution was 43% polyarticular subtype, 27% systemic, 20% oligoarticular, 7% enthesitis related arthritis and 3% psoriatic arthritis. In 20% patients, active uveitis was the indication for ADA. AAA was absent at BL, first detected at 2M after ADA initiation in 2/30 (7%) patients with a significant increase at 3M [10/29 (34%), $p=0.013$] and no major change in 6M [11/30 (37%)] and 12M [9/26 (35%)]. Of note, at 3M AAA levels correlated negatively with ADA levels ($r=-0.781$, $p=0.0001$). Analysis of BL predictors revealed a significantly higher risk of developing AAA in patients with female gender (odds ratio [OR] 21; 95% confidence interval [CI], 1.08-406.57, $p=0.044$), ESR >30 mm/1st hour (OR 5.44; 95% CI, 1.04-28.53, $p=0.045$) and leflunomide use (OR 9.33; 95% CI, 1.51-57.66, $p=0.016$). In contrast, concomitant use of methotrexate was protective for AAA appearance (OR 0.08; 95% CI, 0.01-0.53, $p=0.009$). At 3M evaluation, AAA positive patients showed higher disease activity parameters: patient VAS [4.5 (0-7) vs. 1 (0-5), $p=0.043$], physician VAS [3 (0-6) vs. 0 (0-5), $p=0.035$] and JADAS-71 [9.8 (0-31.8) vs. 2.7 (0-14.9), $p=0.005$]. After 12M of ADA, 60% of AAA-positive patients required drug switch for drug failure compared to 15% in AAA-negative group ($p=0.03$).

Conclusion: This study provides novel evidence of AAA production kinetics demonstrating a timely significant increase starting at 3M and stable throughout 12M. We also identified female gender, increased ESR and leflunomide use as relevant risk factors for AAA production at BL, whereas methotrexate was protective. Early systematic monitoring of AAA from 3M to 6M may therefore, guide drug switching in these patients.

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Tumor Necrosis Factor- α Inhibitor (TNFi)-Induced Psoriasis: Prevalence and Response to Therapy in Patients with Juvenile Idiopathic Arthritis (JIA) in Two Children's Hospitals

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The development of psoriasis while on TNFi is a paradoxical effect of agents that treat psoriasis and is described in larger cohorts inflammatory bowel disease (IBD) and rheumatoid arthritis. However, there is a paucity of data available on this entity in JIA. The objectives of this study were to determine the prevalence of TNFi-induced psoriasis in patients with JIA at two pediatric centers, and psoriasis response to therapy modifications.

Methods: A retrospective chart review at two pediatric institutions was performed on patients with JIA treated with TNFi (adalimumab, etanercept, infliximab) who developed psoriasis. TNFi-induced psoriasis was defined as any incident diagnosis of psoriasis after starting a TNFi. Patients with a personal history of psoriasis prior to TNFi therapy were excluded. Following diagnosis, improvement or worsening of psoriasis with medication changes were defined based on physician assessments.

Results: Twelve of 169 (7.1%) patients on TNFi for JIA were diagnosed with TNFi-induced psoriasis, including 7.9% and 6.4% at Children's Hospital of Philadelphia and Goryeb Children's Hospital respectively. All 12 cases were female, taken from a mostly female cohort (64%). The median age was 12 (range 2-18) yrs. One patient had a family history of psoriasis. Time from initiation of TNFi agents to onset of psoriasis was a median of 19 (range 7 to 40) mos. All affected patients experienced plaque psoriasis including seven (58%) with moderate to severe scalp involvement. Three (25%) patients achieved significant improvement or complete resolution of rash after switching to a different class of biologic agents while 3 (25%) patients had significant improvement or complete resolution following discontinuation of biologic therapy (and no concomitant changes to other systemic therapy). One of 5 patients who switched to a different TNFi had significant improvement, while 4 had worsening symptoms or partial improvement.

Conclusion: Our findings demonstrate the prevalence of TNFi-induced psoriasis in JIA at two centers. Based on these findings, additional larger cohort studies that adjust for confounding by indication are needed to assess psoriasis response to different treatments.

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Reduction in the Utilization of Prednisone and/or Methotrexate Following the Initiation of Etanercept in Pediatric Patients

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SESSION INFORMATION

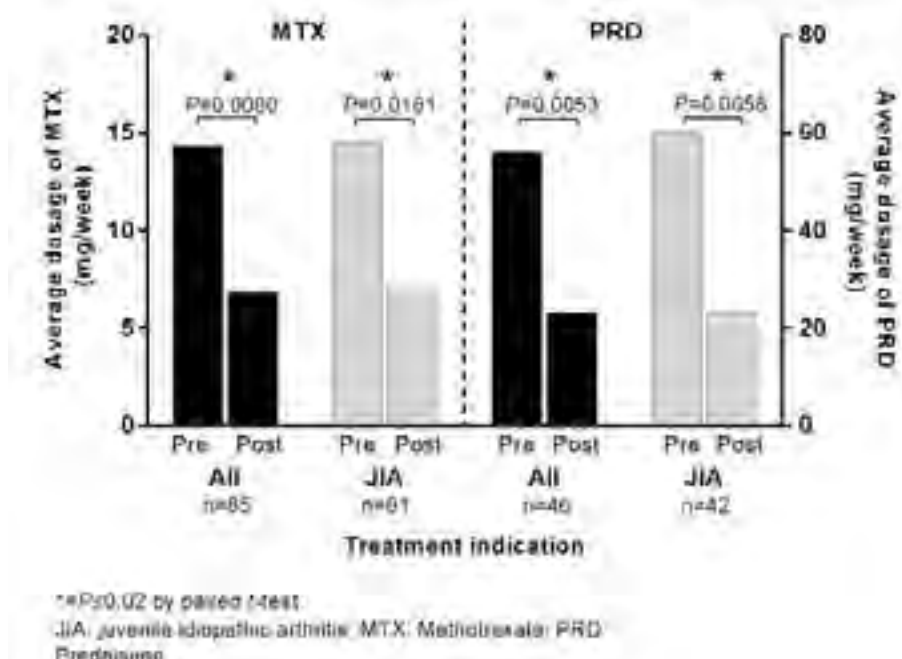
Session Date: Tuesday, October 23, 2018

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Average dose of methotrexate or prednisone pre- and post-initiation of etanercept in pediatric patients with continuing co-treatment



Background/Purpose: In Canada, the pediatric indications of etanercept (ETN) are active ankylosing spondylitis (AS), plaque psoriasis (PsO) and moderate to severely active juvenile idiopathic arthritis (JIA; in those who have had an inadequate response to ≥ 1 DMARDs and are ≥ 4 years of age). A previous analysis of Canadian pediatric claims data showed a 78% yearly retention rate over Year 1 for ETN, which remained high over Years 2-6 (80-90% per year). However, changes in co-medication during ETN treatment in pediatric patients have rarely been evaluated in the real-world setting.

Objective: To evaluate co-treatment utilization and ETN costs in Canadian pediatric patients initiating ETN therapy.

Methods: A retrospective study was conducted using longitudinal prescription drug claims data from the IQVIA Private Drug Plan, Ontario Public Drug Plan, and Quebec Public Drug Plan databases. Biologic-naïve pediatric patients (<18 years, with no biologic treatment in the preceding 12 months) were included if they initiated ETN during the selection period (Jan 2008-Jan 2016). Disease indications were inferred through patient drug history. Analyses of ETN doses and co-treatments were conducted in patients <17 years at index and with no missing data or drug histories indicative of conditions other than JIA, AS, or psoriatic arthritis. Weekly ETN dose was estimated for those who completed 12-month continuous ETN therapy ($7 \times [\text{mg dispensed}/\text{days between claims}]$). Co-treatments were captured for the 6 months preceding and 12 months following index. Drug costs of ETN were estimated for those <18 years who initiated ETN therapy. Editorial support was provided by Jon Edwards, PhD, of Engage Scientific Solutions and was funded by Pfizer.

Results: The study identified 391 patients <18 years old who initiated ETN and had not received a biologic in the preceding 12 months. Of these, 330 provided data for the evaluation of ETN doses, co-treatments, and cost (67% female, 39% aged 10-14 years). Among the 316 patients who completed 12 months of continuous ETN therapy, the average weekly ETN dose was 31 mg (range 14-41 mg), but varied with age. Overall, 31% (n=103) used methotrexate (MTX) before initiating ETN, with 83% (n=85) continuing MTX through the first 12 months of ETN treatment; 28% (n=92) used prednisone (PRD) before initiating ETN, with 50% (n=46) continuing PRD during the first 12 months of ETN treatment. In patients continuing co-treatment, weekly dosages were significantly reduced (Figure). The average yearly cost of ETN was \$13,671 (Canadian \$ per year).

Conclusion: This evaluation of Canadian claims data demonstrated that nearly a third of pediatric patients initiating ETN were co-treated with MTX or PRD. Many patients discontinued their co-therapies, and weekly dosages of MTX or PRD were significantly lower within the first year of initiating ETN treatment for those who continued therapy with these agents. Figure

Disclosure: M. M. M. Khraishi, Pfizer, Inc., 9, Novartis and Roche, 9; B. Millson, IQVIA, 3, Pfizer, Inc., 5, Consultant for clients across the private industry and public sector, 9; J. Woolcott, Pfizer Inc, 1, Pfizer Inc, 3; L. Marshall, Pfizer, Inc., 1, Pfizer, Inc., 3; H. Jones, Pfizer, Inc., 1, Pfizer, Inc., 3.

The Impact of Adalimumab on Growth in Patients with Pediatric Enthesitis-Related Arthritis

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Background/Purpose: Children with one or more subtypes of juvenile idiopathic arthritis, such as enthesitis-related arthritis (ERA), often exhibit growth impairments. The purpose of the analysis was to explore the impact of adalimumab (ADA) on growth in pediatric patients (pts) with ERA.

Methods: Pts aged 6-<18 with ERA were enrolled in a phase 3, multicenter, randomized, double-blind, study. Following 12 weeks of treatment with ADA (24 mg/m² BSA up to 40 mg every other week [eow]) or placebo, pts were eligible to enroll in an open-label extension and receive ADA eow for up to an additional 192 weeks. For this analysis, all pts who received ≥1 dose of ADA were included, and pts were grouped by baseline height percentiles into 2 categories: ≤25th and >25th percentiles based on the World Health Organization (WHO) growth charts. Mean WHO percentile changes in height, weight, and body mass index (BMI) percentiles were calculated through 204 weeks. Per protocol, bone age and familial height were not collected. Growth and efficacy data were analyzed as observed.

Results: Among the 46 pts who received ≥1 dose of ADA in this study, 67% were male with a mean age of 12.9 years; no pts had associated IBD. Eleven pts (24%) were in the ≤25th height percentile, and these pts had a numerically lower baseline height (147.7 cm) and weight (42.5 kg) compared with those pts who were in the >25th height percentile (156.0 cm and 51.5 kg, respectively). Additionally, numerically higher proportions of pts in the ≤25th percentile received concomitant corticosteroids than did the >25th percentile group (54.5% vs 28.6%). Pts in the ≤25th percentile group experienced a larger change in mean height percentile through 204 weeks of ADA treatment (70.3 vs 20.5 for the >25th percentile), a finding that was evident within the first 6 months of treatment. Juvenile males in the ≤25th baseline height percentile demonstrated the numerically highest rates of growth, although similar levels of growth improvement were observed for the lowest quartile of females as well. None of the 11 pts in the ≤25th baseline height percentile remained in this category at their final study visit (Table). Similar percentile increases were observed for BMI percentiles between groups. ACR Pedi90 response rates improved over time in both ≤25th and >25th percentile groups, reaching approximately 80% at the end of 3 years treatment with ADA.

Conclusion: Long-term ADA treatment was associated with growth improvement and maintenance in children with ERA. These improvements among children in the lowest WHO quartiles at baseline may improve their quality of life and psychosocial environment. ADA treatment improved ERA signs and symptoms, regardless of baseline growth status.

Reference: ¹Burgos-Vargas R, *et al. Arthritis Rheumatol* 2016;68(Suppl 10).

Table. Distribution of Height and BMI by WHO Percentile at Baseline and Final Visit

n (%)	WHO Percentile	
	≤25th	>25th
Height, N=46		
Baseline	11 (24)	35 (76)
Final Visit	0	46 (100)
BMI, N=46		
Baseline	10 (22)	36 (78)
Final Visit	3 (7)	43 (93)

Disclosure: R. Burgos-Vargas, AbbVie, BMS, Janssen, Pfizer, and Roche., 5, 8, AbbVie Inc., 2; S. M. L. Tse, AbbVie and Pfizer, 5, AbbVie Inc., 2; K. Minden, AbbVie, Pfizer, and Roche/Chugai, 5, AbbVie and Pfizer, 2, Pfizer, Pharm-Allergan, and Roche/Chugai, 8; P. Quartier, AbbVie, BMS, MedImmune, Novartis, Pfizer, Roche/Chugai, Servier, and Sobi, 5,

AbbVie, Novartis, Pfizer, and Roche/Chugai, 2; **J. K. Anderson**, AbbVie Inc., 1, 3; **K. Unnebrink**, AbbVie Inc., 1, 3; **I. Lagunes Galindo**, AbbVie Inc., 1, 3; **G. Horneff**, AbbVie, Pfizer, and Roche, 2, AbbVie, Novartis, Pfizer, and Roche, 8.

Abstract Number: 2398

Children with Enthesitis Have Worse Quality of Life, Function, and Pain, Irrespective of Their Juvenile Arthritis Category

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To estimate the impact of enthesitis on patient reported outcomes (PROs) in children with juvenile idiopathic arthritis (JIA), irrespective of their JIA category.

Methods: Children with JIA in the Research in Arthritis in Canadian Children emphasizing Outcomes (ReACCh-Out) cohort were studied. Enthesal tenderness by physician examination in 33 defined locations, Juvenile Arthritis Quality of life Questionnaire (JAQQ), Quality of My Life questionnaire (QoML), Childhood Health Assessment Questionnaire (CHAQ), and a pain severity visual analogue scale (VAS) were completed at enrolment, every six months for 2 years, and then yearly for up to 5 years. Analyses consisted of descriptive statistics, multivariate linear mixed models for longitudinal data, and ANCOVA.

Results: Among 1371 patients followed for a median of 35.3 months (IQR 21.1, 49.1), 214 (16%) had enthesitis, of whom 137 (64%) were classified as having enthesitis-related arthritis (ERA). After adjusting for patient characteristics and JIA category, children with enthesitis reported higher JAQQ (0.41 points; 95% CI 0.22, 0.59; 1=no difficulties, 7=difficulties all the time), higher CHAQ (0.14 points; 95% CI 0.07, 0.22; 0 = without any difficulty, 3 = unable to do task), higher pain (0.94 points; 95% CI 0.64, 1.25; 0 = no pain, 10 = maximum pain) and lower QoML (-0.80 points; 95% CI -1.09, -0.51; 0=the worst, 10=the best) scores than children without enthesitis, and these differences persisted during the five years after diagnosis.

Conclusion: Children with enthesitis, regardless of JIA category, report worse PROs than those without enthesitis. Physicians should assess for the presence of enthesitis in all children with JIA. Enthesitis should be considered as a criterion for classification and included in the assessment of treatment response in JIA.

Disclosure: **D. G. Rumsey**, None; **J. Guzman**, None; **A. Rosenberg**, None; **A. Huber**, None; **R. Scuccimarri**, None; **N. J. Shiff**, None; **A. Bruns**, None; **B. M. Feldman**, None; **D. Eurich**, None.

Abstract Number: 2399

Bone Density, Structure and Strength in Canadian Children and Youth with Juvenile Idiopathic Arthritis: The LEAP Study (Linking Exercise, Activity, and Pathophysiology in Canadian Children with Arthritis)

Ciarán M. Duffy¹, Adam Baxter-Jones², Leanne Ward³, Heather Macdonald⁴, Heather McKay⁴, Marta Erlandson², Adam Huber⁵, Susanne Benseler⁶, Michele Gibbon⁷, Jaime Guzman⁸ and Lori Tucker⁸, ¹Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa, ON, Canada, ²University of Saskatchewan, Saskatoon, SK, Canada, ³Department of Paediatrics, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada, ⁴University of British Columbia, Vancouver, BC, Canada, ⁵IWK Health Centre, Halifax, NS, Canada, ⁶Alberta Children's Hospital, Calgary, AB, Canada, ⁷Children's Hospital of Eastern Ontario, Ottawa, ON, Canada, ⁸BC Children's Hospital, Vancouver, BC, Canada

SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM Bone Density, Structure and Strength in Canadian Children and Youth with Juvenile Idiopathic Arthritis: The LEAP Study (Linking Exercise, Activity, and Pathophysiology in Canadian Children with Arthritis)

Authors: CM Duffy, ABaxter-Jones, L Ward, H Macdonald, H McKay, M Erlandson, AM Huber, S Benseler, M Gibbon, J Guzman, LB Tucker and the LEAP Study Investigators.

Background/Purpose: Children and youth with JIA have lower levels of physical activity (PA) than healthy children; lower levels of PA lead to bone mass deficits. The LEAP study is a prospective study, conducted at 12 centres in Canada, of children and youth with JIA, aimed at describing the trajectory of bone development and its relationship to disease factors and physical activity. Here, we compare bone density, structure and strength parameters of children and youth with JIA at study enrollment to reference standards and identify differences between newly and previously diagnosed subjects.

Methods: Inclusion criteria were confirmed diagnosis of JIA, age 10-17 years, and informed consent. Patients had either newly diagnosed JIA (< 6 months since diagnosis) or previously diagnosed JIA (> 6 months after diagnosis). Using a peripheral quantitative computed tomography (pQCT) scanner, a 2.3 mm slice was obtained at the mid-shaft of the tibia (50% site; proximal to the distal tibial end plate). Total bone area (Tt. Ar, mm²), cortical density (Ct.BMD, mg/cm³) and polar strength-strain index (SSI_p, mm³) were calculated. Appropriate reference standards were used to calculate z-scores (ZTt.AR, ZCt.BMD and ZSSI_p) and described as mean z score ± SD.

Results: Data was available on 124 subjects (66.1% female; mean age 13.3 ± 2.2 yrs); 48 newly diagnosed, 76 previously diagnosed. JIA patients, overall, had significantly lower bone area and strain index - ZTt.AR -0.67 ± 0.09, ZSSI_p -0.64 ± 0.09 but significantly greater Ct.BMD; ZCt.BMD 0.30 ± 0.10, than reference children. Bone parameters for the different JIA groups are shown (Table). There were no significant differences in bone area or strain index between the groups; however, the newly diagnosed JIA group had significantly higher cortical density. Numbers are the mean and standard deviation for age, sex and ethnicity adjusted Z-scores.

pQ CT measure (mid-tibia)	All JIA (n=124)	Newly diagnosed JIA (n=48)	Previously diagnosed JIA (n=76)	p-value (new versus previous)
Total bone area	-0.67 ± 0.09	-0.61 ± 1.14	-0.71 ± 1.05	>0.05
Cortical density	0.30 ± 0.10	0.65 ± 1.11	0.08 ± 1.10	<0.05
Strain index	-0.64 ± 0.09	-0.55 ± 1.14	-0.70 ± 1.06	>0.05

Conclusion: Children with JIA had lower tibial bone area and polar strength-strain index than appropriately matched peers but had higher cortical density. While no differences in total area or strain index were found between JIA groups, the newly diagnosed group had greater cortical density. This higher cortical density may reflect lower bone turnover, as this has been observed in other inflammatory diseases of childhood. However, it is also possible that these initial cross-sectional results suggest that cortical density may be compromised by disease over time. Longitudinal analysis of this cohort will provide a better understanding of cortical density and other included measures over time.

Disclosure: C. M. Duffy, None; A. Baxter-Jones, None; L. Ward, None; H. Macdonald, None; H. McKay, None; M. Erlandson, None; A. Huber, None; S. Benseler, Novartis, SOBI, AbbVie, 5; M. Gibbon, None; J. Guzman, None; L. Tucker, None.

Abstract Number: 2400

Validating and Developing a Selected Questionnaire to Predict Early Diagnosis of Juvenile Idiopathic Arthritis in German Population

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory rheumatologic disease in children and adolescents with a prevalence of 1:1000 children in Germany. An early referral of children suspected to have JIA to a pediatric rheumatologist is essential for an early diagnosis and starting treatment to reach a better outcome. An easy-to-use and time efficient questionnaire originally developed by a group led by *Claudio Len* may detect children and adolescent under risk for JIA.

Methods: The questionnaire was translated into German by *I. Foeldvari* and were distributed among patients at the first clinical visit. It includes 12 disease-orientated questions with three possible responses, either: “Yes”, “No” or “I don’t know”. A retrospective evaluation of patients diagnosed with JIA or with a non-inflammatory joint pain (NJP) was performed later on. The sample consisted of patients seen between August 2015 and July 2017. All patients were at least older than 2 years and younger than 17 years at the time of evaluation. Only fully answered questionnaires were evaluated. Subsequently, a weighting scheme of individual questions was applied in order to increase the sensitivity of the tool. Standard statistical techniques were used to find associations between the sum scores and clinical characteristics and to compare the weighted and non-weighted sum scores.

Results: In total 165 of 800 questionnaires could be evaluated for the study. 133 (81%) were diagnosed with JIA and 32 (19%) with NJP. The group of JIA patients consisted of 79 (59%) girls, whereas the control group consisted of 21 (66%) girls. The analysis of the individual questions was performed by comparing the rate of a positive response to the questions (“Yes”) between the two groups. Four questions showed a highly significant difference by comparing answers of the control group with a subgroup of JIA patients having at least one active inflammatory joint. In particular, questions regarding physical constraints ($p=0.020$; AUC= 0.62), joint pain ($p=0.040$; AUC = 0.61), swelling in the joints ($p=0.040$; AUC =0.60) and stamina ($p=0.047$; AUC = 0.60) seem to be relevant in the diagnostic approach. A weight of 3 was assigned to the first and seventh, 2.5 to the fourth and sixth, and 1.5 to the third and fifth item. The diagnostic accuracy of the respective weighted sum score increased from 64% to 68% to discriminate between patients with JIA with at least one active joint and the control group in comparison to the ordinary sum score. An optimal cutoff of 6.0 for referral to a pediatric specialist was calculated. Table 1: ROC-Analysis of the questionnaire in different groups

	Sum Score		Weighted Sum Score	
	AUC	95% CI	AUC	95% CI
JIA vs. musculoskeletal pain	0.59	0.49; 0.70	0.63	0.53; 0.74
JIA with at least one active joint vs. musculoskeletal pain	0.64	0.53; 0.75	0.68	0.57; 0.79

Conclusion: The validation of the questionnaire showed a discriminative difference in patients with clinical diagnosed JIA and a control group diagnosed with NJP. Furthermore, the weighted sum score performed better to differentiate between JIA and NJP patients. The modified questionnaire can be useful to screen for JIA and speed up the referral to a pediatric rheumatologist.

Disclosure: **T. Scheer**, None; **J. Klotsche**, None; **C. A. Len**, None; **I. Foeldvari**, Novartis, BMF, Bayer, Genentech, Sanofi, Abbvie, Chugai; Medac, BMS, Pfizer, 5, 8.

Abstract Number: 2401

The Effects of a Gluten-Free Diet in Juvenile Idiopathic Arthritis – a Pilot Study

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The caregivers of children with juvenile idiopathic arthritis (JIA) frequently ask about the utility of dietary restrictions. Some patients and physicians report a good response to gluten-free diets anecdotally, but the evidence to support a gluten-free diet among children with JIA is limited to 2 small case series, with a total of 8 patients.

Methods: This is a single center pilot study of a gluten-free diet in patients with JIA. Exclusion criteria were diagnoses of systemic JIA, inflammatory bowel disease, or celiac disease. All patients were screened for occult celiac disease and excluded if positive. Outcome measures include disease activity (via JADAS-27), medication changes (escalation or weaning), growth parameter changes (percentile for height, weight, and BMI), and pain. Data collection points are at enrollment, 3 months, and 6 months of the gluten-free diet. Adherence and barriers to adherence were assessed at both follow-up visits. Outcomes were compared using paired t-tests.

Results: 27 patients were enrolled in the trial. 2/27 (7%) screened positive for celiac disease (via tissue transglutaminase IgA) and were excluded from the study. The remainder of the abstract will focus on the remaining 25 patients. 80% are female. Mean age at enrollment is 13.8 years (SD 4.4 years). At baseline, 13 patients (52%) were taking NSAIDs, 11 (44%) were on DMARD therapy, and 8 (32%) were on biologic medications. To date, 12/25 patients have had their 3-month follow-up visit. Five patients (42%) have voluntarily dis-enrolled due to difficulty with the gluten-free diet. At 3 months, adherence to the diet on a 5-point Likert scale (1 = poor, 5 = perfect) was 3.8 (mean) \pm 0.27 (SEM). The majority (83%) cited social situations (such as meals at a restaurant or friend's home) as the main barrier to adherence. The next most common barrier was cost (17%). No patients chose taste or health effects of the gluten-free diet as barriers. There have been no significant differences in the patient global assessment score (GAS), physician GAS, and active joint count from the JADAS-27. There has also been no significant difference in patient pain score. Initiation of a gluten-free diet is associated with significantly lower weight and BMI.

Table 1 Characteristics of patients who have completed 3-month follow-up (n=7).

	At enrollment (mean \pm SEM)	At 3 months (mean \pm SEM)	P-value
Physician GAS	1.86 \pm 0.73	1.64 \pm 0.73	0.65
Active joint count	1.00 \pm 0.38	1.27 \pm 0.90	0.69
Patient GAS	1.79 \pm 0.42	1.50 \pm 0.58	0.73
Pain score	2.96 \pm 0.69	2.29 \pm 0.74	0.23
Height (percentile)	56.40 \pm 6.44	56.00 \pm 6.80	0.82
Weight (percentile)	65.90 \pm 7.08	61.70 \pm 7.93	0.03
BMI (percentile)	65.50 \pm 7.34	59.80 \pm 8.48	0.04

Conclusion: There is no significant difference in disease activity or pain in patients with JIA who trial a gluten-free diet at this interim point. Gluten-free diet might be useful for weight loss; however, pure gluten-free diet is difficult to maintain, as evidenced by our high disenrollment rate. Furthermore, given that 7% of patients screened positive for celiac disease in the absence of any symptoms, there may be utility in screening for celiac disease in patients with newly diagnosed JIA.

Disclosure: A. Sura, None; S. Fogarty-Brown, None; M. Riebschleger, None.

Abstract Number: 2402

Acoustic Emissions Generated By the Temporomandibular Joint of Patients with Juvenile Idiopathic Arthritis and Their Implication on Patient Assessment and Screening: A Pilot Study

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SESSION INFORMATION

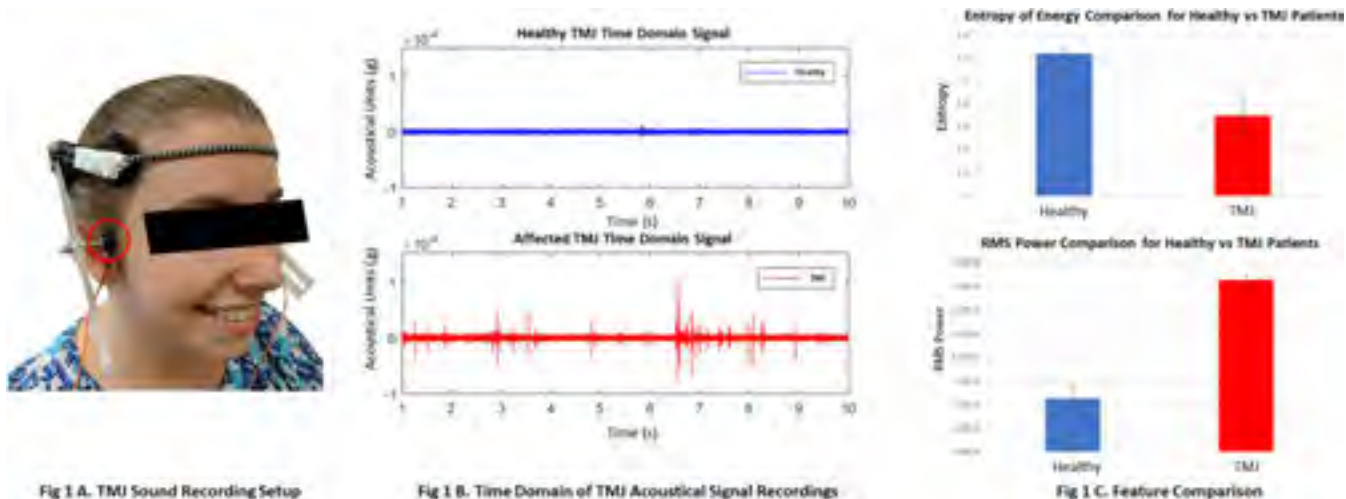
Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

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Session Time: 9:00AM-11:00AM

Background/Purpose: The temporomandibular joint (TMJ) is one of the most commonly affected joints in juvenile idiopathic arthritis (JIA) (up to 45% of cases). There is a discrepancy between clinical signs and presence of arthritis of the TMJ, which makes recognizing TMJ involvement and effective intervention difficult. Currently, combined radiographic and magnetic resonance (MR) imaging studies of the TMJ are necessary for a formal diagnosis. These approaches are time consuming, expensive, restricted to a clinical setting, and may not show involvement until the disease has sufficiently progressed. Thus, the high prevalence and difficulty in identifying the condition justifies the development of a novel



approach for quantitatively and objectively diagnosing and monitoring diseases of the TMJ. The common finding of crepitus in an involved TMJ in patients with JIA inspired the current study. This common, but not well understood sign, led to our development of a novel, inexpensive wearable system for rapid measurement of the acoustic emissions produced during jaw movement. Here, we investigate the use of these sounds as a non-invasively measurable physiological biomarker of TMJ involvement in JIA.

Methods: We built a custom system using contact microphones inside a headset to unobtrusively capture the acoustic emissions generated by the articulation of the TMJ (Fig. 1 A, microphone circled in red). Internal friction between articulating structures of the TMJ during movement produce various frequencies of vibrations that can be detected on the surface of the skin above the joint. To determine the possibility of using these vibrations to classify and diagnose TMJ involvement 6 patients have so far been recruited. 2 of the patients have clinically-diagnosed JIA with TMJ involvement, and 4 served as healthy controls. We recorded the unique audio profile produced by each patient opening and closing their jaw at a rate of 1 cycle / 4 seconds. Several features of the joint sounds were then calculated and compared to determine if they could be used to potentially classify and diagnose the condition.

Results: The time-domain analysis of the signal shows large peaks and a chaotic signal from affected jaws, whereas the healthy jaw produces virtually no sounds with a flat signal (Fig. 1 B). Two of the signal features showing a large difference between the groups are presented (Fig. 1 C).

Conclusion: The signals recorded with our portable TMJ acoustic emission headset may serve as a novel and convenient way to differentiate between patients with affected and unaffected jaws. In this small sample, two signal features were different between patients with affected TMJs and those without. This promising preliminary finding warrants further study, recruitment, and development to determine if this measurement modality can one day serve as a means of screening patients for jaw conditions.

Disclosure: D. Whittingslow, None; H. K. Jeong, None; T. Gergely, None; L. Ponder, None; S. Prahalad, None; O. Inan, None; S. Abramowicz, None.

Abstract Number: 2403

The Therapeutic Alliance Is Associated with a Better Therapeutic Adherence in Children with Juvenile Idiopathic Arthritis: Results of a French Multicenter Study

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Background/Purpose: The therapeutic compliance (TC) is a major issue for the management of Juvenile Idiopathic Arthritis (JIA). The chronic nature of this inflammatory rheumatism requires a strong ability of the child to follow his treatments, where the parental involvement and the link built with the caregiver are essential. The Therapeutic Alliance (TA) measures the multifaceted caregiver-clinician relationship. We hypothesized, that in JIA, TA, that describes the relationship between the child and his (her) therapist, should be a key factor of TC. The aim of this study was to evaluate the link between TA and TC in a large JIA cohort.

Methods: Observational, cross-sectional, multicenter study, in 13 reference centers in France. During a routine consultation, the physicians, rheumatologists or pediatricians, distributed questionnaires to both the children and their parents. Each child, his (her) parents and the physician completed the HAQ-CP TA questionnaire, assessing TA. TC was measured through the Child Adherence Report Questionnaire (CARQ), the Parent Adherence Report Questionnaire (PARQ) and the Morisky questionnaire. Children aged 6 to 18 were included. The treatments, their tolerance, the disease activity and the socio-professional environment of the parents were collected. The univariate relationship between TA and TC, were studied by Pearson correlation coefficient. The multivariate analysis used a multiple linear regression model. 105 patients had to be included to highlight a relationship with a power of 90% at risk alpha 5%.

Results: 119 children (70% girls), age (SD) 12.4 (2.9) were included. The JIAs were oligoarticular (28.6%) or polyarticular (type). The mean disease duration was 73.1 (48.2) months. TA scores were high for parent (86/100), child (84/100) and therapist (80/100). There was a significant correlation between the child's TA and TC ($r=0.31$; $p=0.0009$) and between that of the parent and the child's compliance ($r=0.37$; $p<0.0001$). About factors influencing TC, lifestyle in rural areas was statistically associated to a better adherence ($p=0.0229$) whereas female sex was a factor of poor compliance ($p=0.04$). A poorer child's TA was found when the disease was active ($p=0.048$), when the parents were divorced ($p=0.01$) and in case of sub-urban than in case of rural residence ($p=0.004$). For the parent, TA varied according to the JIA sub-group ($p=0.003$), with lower TA in polyarticular JIA ($p=0.005$). For the therapist, TA varied according to the JIA sub-group with poorer TA in extended polyarticular JIA ($p=0.0326$). A poorer TA was observed when the disease had been evolving for a long time ($p=0.0008$) and the follow-up was long ($p=0.004$).

Conclusion: In JIA, the treatment compliance is highly related to the therapeutic alliance between the child and his (her) therapist. However TA varied widely according to the disease specificities and the child's lifestyle. This must be known by rheumatologists and pediatricians, to improve the adherence to treatment.

Disclosure: V. Devauchelle-Pensec, None; A. Lohse, None; F. Guillemain, None; E. Solau-Gervais, AbbVie Inc., 5, 8, Merck & Co., 5, Celgene Corporation, 5, Novartis, 5; L. Rossi-Semerano, None; A. Duquesne, None; I. Lemelle, None; P. Pillet, None; C. Ballot, None; L. Goumy, None; T. A. Tran, None; L. Sparsa, None; H. Reumaux, None; A. Arbault, None; C. Alleyrat, None.

Abstract Number: 2404

Quality of Life Assessment in Juvenile Idiopathic Arthritis: A Single Center Assessment

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Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with Juvenile Idiopathic Arthritis (JIA) face physical, social, and emotional issues that affect their quality of life. Health-related quality of life (HRQoL) is a multidimensional construct including those issues and other influences of illness on well-being. Previous validation studies found that JIA patients have lower HRQoL compared to healthy peers. We investigated perceptions of HRQoL based on assessments completed by children and their caregivers at a large referral center. We obtained HRQoL data as an initial phase of a larger project striving to educate school nurses and staff at a large urban school district.

Methods: We assessed HRQoL with the PedsQL 4.0 Generic Core Scale (assesses physical activity, emotional, social, and school functioning) and the PedsQL 3.0 Arthritis Module (measures pediatric rheumatology-specific HRQoL: pain and hurt, daily activities, treatment, worry, and communication). Both surveys have age-specific, validated forms (Ages 5-7, 8-12, and 13-18). After IRB approval, we enrolled a 3-month convenience sample of English speaking JIA patients ages 5 to 18, and caregivers who presented to an outpatient clinic. For each survey we calculated subscale and total score means. Higher scores indicated a better HRQoL. We used descriptive and inferential statistics (Pearson correlation, one-way ANOVA and one sample t-tests) to explore HRQoL data in JIA patients. Results were compared to validated healthy control normative values.

Results: Seventy-nine JIA patients and caregivers completed the surveys. Demographic data included patient age (mean 12.05 ± 3.73), gender (female 68%), ethnicity (49% White or Non-Hispanic, 25% Hispanic). Patient JIA classification included: Polyarticular 46.8%, Oligoarticular 30.4%, Psoriatic 8.9%, Systemic 7.6%, and Entesitis-related 6.3%. The cohort mean total score (72.27) was significantly lower than the previously validated total score for of 83.9 for healthy children (95% CI -15.6 to -7.6; $p < .001$). There were modest, mostly negative and at times significant correlations between age and HRQoL domain scores (Table 1). Statistically significant differences in Physical health, Total score (PedsQL 4.0), Daily Activities and Worry (PedsQL 3.0) were driven by lower scores of children with Polyarticular JIA. These differences appeared independent of age and gender.

Table 1: Child PedsQL 4.0 Generic and PedsQL 3.0 Arthritis Module Domain Scores

		Mean (SD)	Correlation with Age	Significance (2-tailed)
Peds QL 4.0-Generic	Physical	72.60 (20.19)	-.386**	<.01
	Emotional	73.45 (22.45)	-.209	NS
	Social	77.41 (22.50)	-.043	NS
	School	64.99 (23.43)	-.221	.05
	Psychosocial	71.95 (19.87)	-.182	NS
	Total	72.27 (17.90)	-.318**	<.01
Peds QL 3.0-Arthritis	Pain and Hurt	64.82 (27.13)	-.234*	.04
	Daily Activities	90.40 (14.98)	-.111	NS
	Treatment	70.19 (20.55)	.246*	.03
	Worry	67.30 (29.50)	.268*	.02
	Communication	68.67 (24.83)	-.137	NS

Bolded values are below total mean score

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

NS: Not significant

Conclusion: As per previous studies, PedsQL scores in JIA patients were significantly lower than healthy norms. These differences may be accentuated in older children and polyarticular subtypes. Disease activity factors will be assessed at the completion of cohort data collection. We will use PedsQL data to train public school nurses about the impact of JIA on HRQoL. QoL interventions may depend on age groups, and may constitute an additional parameter in the management of children with rheumatic diseases.

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Abstract Number: 2405

Health-Related Quality of Life, Functioning, and Mental Health of Children with Chronic Non-Infectious Uveitis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Pediatric chronic non-infectious uveitis can lead to ocular complications and vision loss. The ophthalmic clinical exam is primarily used to assess uveitis outcomes but may be imprecise since it may not reflect changes in quality of vision and effects of vision impairment. Our goal is to provide a comprehensive assessment of the impact of uveitis on health-related quality of life (HRQOL), mental health, visual function, and vision-related QOL in children with JIA-associated uveitis (JIA-U).

Methods: We reviewed records of 79 children (26 JIA alone, 29 JIA-U, 24 other uveitis types). Parents and patients completed questionnaires on general QOL (Pediatric Quality of Life Inventory- PedsQL), depression and anxiety (Revised Children Anxiety and Depression Scale-RCADs), and visual function and vision-related QOL (Effect of Youngsters Eyesight on QOL-EYE-Q). The EYE-Q has items assessing both visual function (i.e. near, far, color, and night vision) and vision-related QOL (i.e. medication use, school absences, and lab draws). We used Wilcoxon Rank-Sum tests to compare disease groups: 1) children with JIA vs. JIA-U, and 2) children with JIA vs. uveitis of all types.

Results: Of 79 children, most were non-Hispanic (88%), Caucasian (66%), females (70%) (Table 1). Among uveitis patients, most had bilateral (70%), anterior (83%) disease with complications (70%). Children with JIA-U had worse EYE-Q total scores compared to those with JIA alone for Parent reports (median 1.25 vs. 1.15, $p=0.007$). (Table 2) However, there were no differences in the scores of the EYE-Q by child report, RCADS, or PedsQL.

Children with all forms of uveitis (JIA-U and other uveitis types) had worse EYE-Q total scores compared to those with JIA alone by Parent (median 1.25 vs. 1.15, $p=0.001$) and Child reports (1.29 vs. 1.17, $p=0.009$). (Table 2) Results were similar when comparing visual function and vision-related QOL sub scores from the EYE-Q. Child reported PedsQL scores in patients with JIA alone were worse than those with uveitis (80.4 vs. 87, $p=0.023$).

Conclusion: This is one of the first assessments of children with JIA-U to incorporate HRQOL, mental health, visual function, and vision-related QOL. We demonstrate the impact of eye disease as children with uveitis had worse vision-related function and QOL compared to children with JIA, but similar general HRQOL and mental health. Uveitis-specific measures like the EYE-Q may reveal disease-related impairments that affect QOL and are not quantified using general measures. An approach that integrates all aspects of disability should be considered.

Table 1 Characteristics of Children with Juvenile Idiopathic Arthritis and Uveitis

N (%), unless indicated	Overall (N = 79)	JIA ^a alone (N = 26)	JIA-U ^b (N = 29)	Other U ^c (N = 24)
Characteristics				
Demographics				
Age, median (25th, 75th)	9 (5, 12)	10 (4, 12)	9 (3, 11)	10 (8, 13)
Race				
White	52 (65.8)	20 (76.9)	23 (79.3)	9 (37.5)
African American	18 (22.8)	5 (19.2)	0 (0.0)	13 (54.2)
American Indian/Alaskan Native	1 (1.3)	0 (0.0)	1 (3.5)	0 (0.0)
Asian	2 (2.5)	0 (0.0)	2 (6.9)	0 (0.0)
Multi-racial	4 (5.1)	0 (0.0)	3 (10.3)	1 (4.2)
Unknown/Declined	2 (2.5)	1 (3.9)	0 (0.0)	1 (4.2)
Ethnicity, Non-Hispanic	68 (88.3)	22 (88.0)	25 (86.2)	21 (91.3)
Gender, female	53 (69.7)	15 (62.5)	21 (72.4)	17 (73.9)
Duration of follow up, years, median (25th, 75th)	9.5 (5.1, 13.0)	10.1 (4.7, 13.0)	8.4 (3.6, 11.2)	10.3 (8.1, 13.7)
JIA Characteristics (N = 55)				
Age at Diagnosis, median (25th, 75th)	4.3 (2.0, 10.6)	8.7 (2.9, 10.6)	3.4 (1.8, 9.6)	
Duration of Disease, years, median (25th, 75th)	5.0 (2.8, 7.3)	5.1 (2.9, 6.1)	4.6 (2.2, 9.0)	
JIA Subtype				
Oligoarticular Persistent	22 (40.0)	6 (23.1)	16 (55.2)	
Oligoarticular Extended	3 (5.5)	0 (0.0)	3 (10.3)	
Polyarticular RF (-)	15 (27.3)	11 (42.3)	4 (13.8)	
Uveitis Characteristics (N = 53)				
Age at Diagnosis, median (25th, 75th)	8.4 (3.8, 10.5)		4.2 (3.4, 9.1)	10.0 (8.7, 12.3)
Duration of Disease, years, median (25th, 75th)	3.7 (2.2, 6.4)		4.2 (2.4, 7.3)	2.7 (1.7, 4.8)
Bilateral Disease	37 (69.8)		21 (72.4)	16 (66.7)
Location				
Anterior	44 (83.0)		28 (96.6)	16 (66.7)
Intermediate	2 (3.8)		0 (0.0)	2 (8.3)
Posterior	5 (9.4)		0 (0.0)	5 (20.8)
Panuveitis	1 (1.9)		0 (0.0)	1 (4.2)
Unknown	1 (1.9)		1 (3.5)	0 (0.0)
Ocular Complications, ever				
Synechiae	26 (49.1)		10 (34.5)	16 (66.7)

Table . (Cont'd)

N (%), unless indicated	Overall (N = 79)	JIA ^a alone (N = 26)	JIA-U ^b (N = 29)	Other U ^c (N = 24)
Cataracts	20 (37.7)		11 (37.9)	9 (37.5)
Cystoid Macular Edema	14 (26.4)		5 (17.2)	9 (37.5)
Band Keratopathy	13 (24.5)		7 (24.1)	6 (25.0)
Glaucoma/ocular hypertension	10 (18.9)		4 (13.8)	6 (25.0)
Other ^d	16 (30.2)		5 (17.2)	11 (45.8)
Treatment, ever				
Steroid drops	48 (60.8)	0 (0.0)	28 (96.6)	20 (83.3)
Pressure lowering drops	13 (16.5)	0 (0.0)	8 (27.6)	5 (20.8)
Dilating drops	18 (22.8)	0 (0.0)	7 (24.1)	11 (45.8)
Methotrexate oral	51 (64.6)	20 (76.9)	21 (72.4)	10 (41.7)
Methotrexate SQ	60 (76.0)	17 (65.4)	23 (79.3)	20 (83.3)
Mycophenolate	3 (3.8)	0 (0.0)	2 (6.9)	1 (4.2)
Etanercept	13 (16.5)	10 (38.5)	2 (6.9)	1 (4.2)
Infliximab	20 (25.3)	1 (3.9)	10 (34.5)	9 (37.5)
Adalimumab	28 (35.4)	6 (23.1)	15 (51.7)	7 (29.2)
Abatacept	5 (6.3)	1 (3.9)	4 (13.8)	0 (0.0)
Tocilizumab	1 (1.3)	1 (3.9)	0 (0.0)	0 (0.0)

^aJIA: juvenile idiopathic arthritis; ^bJIA-U: JIA-associated uveitis; ^cOther U: all other uveitis not associated with JIA; ^dOther complications include: amblyopia, vitreous hemorrhage, optic disc edema, aphakia, choroidal neovascular membranes, chorioretinal scar, retinal neovascularization, retinal detachment, keratic precipitates, peri retinal fibrosis, floaters, blindness, ocular hypertension

Measure	Median (IQR) ^a Range	JIA (N = 26)	JIA-U (N = 29)	All Uveitis JIA-U and other uveitis types (N = 53)	p-value 1 ^b JIA vs. JIA-U	p-value 2 ^c JIA vs. All Uveitis
EYE-Q ^d Parent Total (N = 40)	1.15 (1.04, 1.21) 1.00 – 1.54	1.15 (1.04, 1.21) 1.00 – 1.54	1.25 (1.16, 1.52) 1.07 – 1.91	1.25 (1.17, 1.49) 1.04 – 2.54	0.007*	0.001*
Visual Function	1.00 (1.00, 1.20) 1.00 – 1.60	1.00 (1.00, 1.20) 1.00 – 1.60	1.17 (1.00, 1.48) 1.00 – 2.29	1.27 (1.00, 1.47) 1.00 – 2.80	0.056	0.007*
Vision-related QOL	1.44 (1.00, 1.44) 1.00 – 1.44	1.44 (1.00, 1.44) 1.00 – 1.44	1.44 (1.29, 1.56) 1.13 – 1.67	1.44 (1.29, 1.57) 1.13 – 2.22	0.013*	0.008*
EYE-Q ^d Child Total (N = 29)	1.17 (1.14, 1.25) 1.04 – 1.39	1.17 (1.14, 1.25) 1.04 – 1.39	1.26 (1.14, 1.46) 1.00 – 1.88	1.29 (1.17, 1.54) 1.00 – 2.14	0.092	0.009*
Visual Function	1.07 (1.00, 1.20) 1.00 – 1.46	1.07 (1.00, 1.20) 1.00 – 1.46	1.13 (1.00, 1.27) 1.00 – 2.00	1.27 (1.13, 1.53) 1.00 – 2.38	0.174	0.025*
Vision-related QOL	1.33 (1.00, 1.44) 1.00 – 1.67	1.33 (1.00, 1.44) 1.00 – 1.67	1.44 (1.22, 1.56) 1.00 – 1.78	1.44 (1.33, 1.56) 1.00 – 2.67	0.072	0.028*
RCADS ^e Parent Total (N = 24)	41.9 (36.9, 50.7) 33.1 – 120.0	41.9 (36.9, 50.7) 33.1 – 120.0	38.1 (36.5, 55.6) 33.1 – 78.8	39.0 (36.1, 45.9) 31.8 – 78.8	0.582	0.347
RCADS ^e Child Total (N = 26)	35.1 (29.8, 38.6) 26.8 – 54.4	35.1 (29.8, 38.6) 26.8 – 54.4	34.5 (30.6, 36.8) 28.8 – 71.5	34.5 (30.6, 40.9) 24.2 – 71.5	1.000	0.844
PedsQL ^f Parent Total (N = 43)	84.8 (69.6, 100.0) 51.1 – 100.0	84.8 (69.6, 100.0) 51.1 – 100.0	79.9 (59.8, 91.3) 34.8 – 100.0	83.7 (68.5, 98.9) 34.8 – 100.0	0.518	1.000
PedsQL ^f Child Total (N = 36)	80.4 (63.0, 83.7) 43.5 – 100.0	80.4 (63.0, 83.7) 43.5 – 100.0	84.8 (75.0, 92.4) 45.7 – 100.0	87.0 (78.3, 98.9) 45.7 – 100.0	0.222	0.023*

*p<0.05; ^a IQR: Interquartile Range; ^bp-value 1: comparison of JIA and JIA-U; ^cp-value 2: comparison of JIA and all uveitis; ^dEYE-Q: Effects of Youngsters' Eyesight on Quality of Life, scores range from 0-2, higher scores indicate worse visual function and vision-related QOL; ^eRCADS: Revised Children's Anxiety and Depression Scale, scores ³ 70 indicate clinically significant anxiety and depression; ^fPedsQL: Pediatric Quality of Life Inventory, scores range from 0-100, higher scores indicate better QOL

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Abstract Number: 2406

Clinical Presentation, Management and Long Term Outcome of Pars Planitis (PP), Panuveitis (PU) and Vogt–Koyanagi–Harada Disease (VKH) in Children and Adolescents

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Chronic uveitis is a common manifestation of pediatric rheumatologic conditions and may result in irreversible blindness and long term disability. While chronic anterior uveitis is the most commonly encountered ocular manifestation of rheumatic disease, little is known about the clinical presentation, management and long term outcome of more complex eye conditions such as pars planitis (PP), panuveitis (PU) and Vogt–Koyanagi–Harada disease (VKH).

Methods: We retrospectively reviewed a cohort of 75 children and adolescents with idiopathic PP (50), PU (12) and VKH (14) followed by the Pediatric Rheumatology Core at Children’s Hospital Los Angeles and evaluated referral patterns, clinical presentation, treatment response and long term clinical outcome.

Results: The mean age at disease onset was 10 years and patients were followed for an average of 52 months. The average referral time to a pediatric rheumatologist was 13 months (range 1-96 months). Bilateral eye involvement was seen in 87% of the patients, glaucoma was present in 21% and vision loss (<20/40) was present in 87% of the patients at first presentation. Legal blindness (<20/200 or less in the better-seeing eye) was diagnosed in 18% of the PP, 36% of the PU and 21.5% of the VKH patients at first presentation. Topical steroids were used in all patients, but 98% of the patients required additional DMARDs and 73% required therapy with biologics. After a mean of 52 months, 35% of patients across all disease groups had significant vision loss or were blind, while only 28% were in clinical remission off drug. The worst outcome was observed in children with panuveitis. Earlier referral to a pediatric rheumatologist and earlier initiation of DMARD/biologic therapy clearly correlated with better outcome.

Conclusion: PP, PU and VKH have a high risk of permanent vision loss and should be managed as early and as aggressive as possible by a skilled rheumatologist.

Disclosure: A. Reiff, None;

Abstract Number: 2407

New Onset of Uveitis in Non-Methotrexate Group, Methotrexate Group and Etanercept Group in Juvenile Idiopathic Arthritis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

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Background/Purpose: Uveitis is the most common extra-articular manifestation of juvenile idiopathic arthritis (JIA), often entirely asymptomatic but could be sight-threatening. The most often prescribed biologics in JIA patients without eye involvement is etanercept, which has not effective the uveitis control. Due to known information about new onset of uveitis during etanercept treatment the question about the role of etanercept in new onset of uveitis is still open. The aim of our study was to evaluate the risk of new onset of uveitis in JIA during different types of treatment.

Methods: The clinical charts of all consecutive patients (n=413) who had received a stable management for at least 2 years with or without MTX or etanercept were reviewed. Patients who were given systemic corticosteroids were excluded. Patients with systemic arthritis, rheumatoid factor-positive arthritis, or enthesitis-related arthritis were also excluded. In each patient, the at least 2-year follow-up period after first visit was examined to establish whether uveitis had occurred. All patients according the treatment were divided in 3 groups: i) patients, who received only NSAID and/or intraarticular corticosteroids (IAC) – “no MTX” group; ii) patients who treated with MTX (NSAID and IAC were allowed) – “MTX” group; iii) patients, who treated with etanercept (with or without MTX) – “etanercept” group. For statistical analysis we utilized Cox’s regression models, Log-Rank test, x2 test and Mann-Whitney test. Data are presented by median and interquartile range.

Results: Data of comparison three lines of treatment are presented in the table. In the comparison of treatment curves there was a differences in probability of new onset of uveitis ($p=0.00001$). There were no differences in the time before uveitis in three groups ($p=0.45$). After paired comparison of the treatment arms, there were no difference between “MTX” and “Etanercept” groups $RR=1.47$ (0.54-4.0), $p=0.46$ and were differences between “No MTX” vs “MTX” $RR=4.0$ (2.4;6.7), $p=0.00001$ and “No MTX” vs “Eta” $RR=2.0$ (1.2;3.3), $p=0.002$. After adjustment on ANA status, oligoarticular disease course and JIA onset age <5 years we found out differences. For ANA positive patients $RR=3.2$ (2.0; 5.3), $p=0.000001$, LogRank test $p=0.048$ compare to ANA-negative persons. In the regression models “No MTX” vs “MTX” $RR=3.8$ (2.1; 6.7), $p=0.000006$, “No MTX” vs “Eta” $RR=2.3$ (1.2;4.2), $p=0.01$; “MTX” vs “Eta” $RR=2.2$ (0.6;7.8), $p=0.206$. For patients with oligoarticular disease course $RR=2.9$ (1.9;4.6), $p=0.000002$, LogRank test $p=0.005$. In the regression models “No MTX” vs “MTX” $RR=3.7$ (2.2;6.4), $p=0.000001$, “No MTX” vs “Eta” $RR=1.9$ (1.1;3.2), $p=0.02$; “MTX” vs “Eta” $RR=1.3$ (0.46;3.5), $p=0.65$. For JIA patients less than 5 years $RR = 2.8$ (1.9;4.4); $p=0.000002$, LogRank test, $p=0.18$. In the regression models “No MTX” vs “MTX” $RR=3.6$ (2.1;6.0), $p=0.000002$, “No MTX” vs “Eta” $RR=2.0$ (1.2;3.3), $p=0.006$; “MTX” vs “Eta” $RR=1.4$ (0.5;3.9), $p=0.5$.

Conclusion: The incidence of new onset of uveitis in the etanercept group is the lowest and compare to JIA patients treated with MTX. More likely new onset of uveitis is related to JIA pathogenesis rather etanercept treatment. Further investigation and randomized controlled trials required.

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Abstract Number: 2408

Comparison of the Tear Cytokine and Chemokine Profile of Children with JIA and JIA-Associated Uveitis

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SESSION INFORMATION

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Session Title: Pediatric Rheumatology – Clinical Poster III: Juvenile Idiopathic Arthritis and Uveitis

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Background/Purpose: Children with JIA are at increased risk for uveitis. Known risk factors do not accurately stratify risk. Biomarkers are needed to predict uveitis development in JIA. Aqueous humor (AqH) has been studied, but the clinical application is limited by the invasive nature of collection. Analysis of tears is a non-invasive approach to better identify children with JIA who are most susceptible to uveitis. Our objective is to compare the tear profiles of children with JIA-associated uveitis (JIA-U) to JIA without uveitis (JIA) for the presence of cytokines and chemokines reported in the AqH of adults and children with uveitis.

Methods: Tears were collected from 16 children with JIA-U and 16 with JIA who were ≥ 5 years old using Schirmer strips. Cytokine and chemokines reported in the AqH of children with uveitis (IL-18, IL-8/CXCL8, IP-10/CXCL10, MCP-1, RANTES/CCL5, and sICAM-1) were determined using Milliplex™ Multiplex kits (MilliporeSigma, Darmstadt, Germany). A mixed model approach was used where each cytokine outcome is modeled as a function of diagnosis to compare the tear profile of children with JIA to JIA-U.

Results: There were 29 samples from 16 children with JIA-U, and 32 samples from 16 children with JIA. We did not include the unaffected eye of children with JIA-U in the analysis. Children were primarily Non-Hispanic (93%), White (91%), females (78%) with oligoarticular (72%) or polyarticular rheumatoid factor (RF) negative (28%) JIA. JIA was diagnosed in children with JIA alone at a mean age of 6.7 years (SD 4.2), and in children JIA-U at a mean age of 5.1 years (SD 3.8) (Table 1). Uveitis was diagnosed at a mean age of 6.3 years (SD 4.2). Levels of IL-8, IP-10, and RANTES were significantly increased in JIA compared to JIA-U ($p<0.05$) (Table 2). MCP-1 was significantly increased in JIA-U compared to JIA ($p<0.05$).

Conclusion: In this pilot study, we detected cytokines and chemokines in the tears of children with JIA and JIA-U that were previously identified in AqH. We provide evidence of differences in the tear profile of children with JIA-U and JIA that may differentiate those who develop uveitis. If tears can reflect uveitis activity, similar to AqH, it may be a promising biospecimen for uveitis studies. Use of tears could lead to the discovery of biomarkers for the early detection of uveitis and better prediction models for uveitis onset. Studies in larger cohorts are needed.

Table 1 Characteristics of children with JIA alone and JIA-associated uveitis, N (%) unless indicated

	JIA N = 16	JIA-U N = 16
Female	13 (81)	12 (75)
Caucasian	16 (100)	13 (81)
Non-Hispanic	16 (100)	14 (88)
JIA Category		
Oligoarticular JIA	13 (81)	10 (63)
Polyarticular RF (-) JIA	3 (19)	6 (38)
Age JIA Dx, mean (SD)	6.7 (4.2)	5.1 (3.8)
Duration of JIA, mean (SD)	6.7 (4)	8.0 (4.8)
Active arthritis (yes)	7 (44)	6 (38)
Bilateral	-	13 (81)
Age Uveitis Dx, mean (SD)N = 13	-	6.3 (4.2)
Active uveitis (yes), anterior chamber cells ≥ 0.5 /hpf	-	2 (13)
Topical medications		
Topical steroids	-	12 (75)
Pressure drops	-	1 (6)
Not on systemic treatment	6 (38)	4 (25)
Medications		
Methotrexate	4 (25)	8 (50)
Leflunomide	4 (25)	1 (6)
Etanercept	4 (25)	0 (0)
Infliximab	1 (6)	4 (25)
Adalimumab	1 (6)	3 (19)
Abatacept	2 (13)	1 (6)
Tocilizumab	0 (0)	2 (13)
Age at tear collection, mean (SD)	13.3 (4.2)	11.8 (4.7)

Table 2 Tear cytokine and chemokine profiles of children with JIA alone and JIA-associated uveitis

	JIA N=16	JIA-U N=16	p-value*
IL-8/CXCL8, least square means (SE)	4.0 (0.1)	3.6 (0.1)	0.012
IL-18	3.0 (0.2)	3.4 (0.2)	0.088
IP-10/CXCL10	7.1 (0.1)	6.7 (0.1)	0.005
RANTES/CCL5	2.9 (0.2)	2.1 (0.2)	0.008
MCP-1,	3.1 (0.2)	3.7 (0.2)	0.027
sICAM-1	9.5 (0.1)	9.3 (0.1)	0.228

* Adjusted for potential correlation between a pair of eyes from same child. MCP-1: monocyte chemoattractant protein; IL: interleukin; IP-10/CXCL10: interferon gamma-induced protein/chemokine (C-X-C motif) ligand; RANTES/CCL5: Regulated on activation, normal T expressed, and secreted/chemokine (C-C motif) ligand; sICAM-1: soluble intracellular adhesion molecule 1

Disclosure: S. Angeles-Han, None; V. Miraldi Utz, None; S. Thornton, None; A. Sproles, None; N. Mwase, None; T. Hennard, None; M. Altaye, None; G. Holland, None.

Abstract Number: 2409

Do Children with Juvenile Idiopathic Arthritis Play an Active Role in Their Treatment Adherence? First Results of the Rumaji Study

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II – ARHP

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Adherence to DMARDs such as methotrexate and biologics is critical for patients with Juvenile Idiopathic Arthritis (JIA). Notwithstanding, few studies exist on that topic and we lack information to understand the grounds for adherence.

The RUMAJI study aims, among others, to understand and decipher the parents and children adherence mechanisms and practices.

Methods: Qualitative methods were chosen in order to investigate parents' and children's everyday life with JIA and its treatment. An ethnographic study was designed by a multidisciplinary team including rheumatologists, pediatricians, patient associations members and anthropologists. Parents, children and doctors were interviewed. The study involved 6 doctors (3 paediatricians and 3 rheumatologists) and 15 families (enough to reach saturation), recruited from 5 centers, by diversity of clinical and sociological profiles. The panel included 17 children with JIA, 11 girls and 6 boys, median age 10 [3; 17], median disease duration 2.5 [1; 15]. 4 children were treated with conventional DMARDs in monotherapy, 4 with biologic DMARDs in monotherapy, 5 with cDMARDbDMARD association and 4 with NSAIDs only.

Doctors interviews were conducted first. Parents and children interviews were conducted by anthropologists at family's home using in depth semi directive and biographic methods. 3 fields were explored: organization of everyday life with JIA, treatment practices, impact on school and social activities. Interviews were recorded and transcribed for analysis.

Results: Adherence results from an appropriation process of the JIA and treatment that require both an active role from parents and children, even before the transition. The setting of a partnership-based doctor-children-and-parents relationship has also a positive effect in the family active role. The active role played by children could be either stimulated or inhibited at home according to the family's structure, social background, parents' attitudes toward their child (participation to the decision, explanation of the disease). Children's active role includes in particular: 1) negotiations with parents and physicians, 2) experiments with the treatment (forgetting or involuntary switch from the parents, changing the dosage on their own initiative) and 3) participation to the treatment administration and ritualization.

The manner children consider and manage their DMARDs is the result of an arbitration depending on the positive (a) and side effects (b) they felt in their body and the effects noted by the doctors (c) during the examinations and test results. Dealing with these 3 dimensions requires to link together both a theoretical and practical knowledge of JIA. Thus, children build their own and singular knowledge of their disease and treatment, which is a source of control of their body and their life.

Conclusion: Qualitative methods, through an ethnographic study starting from children, parents and doctors point of view, underline the active role they played by children in their care. Adherence to DMARDs could be improved by supporting children's implication as soon as the beginning of JIA.

Disclosure: G. Montagu, None; E. Mevel, None; W. FAHY, None; L. Rossi-Semerano, None; E. Solau-Gervais, AbbVie Inc., 8, Merck & Co., 8, Celgene Corporation, 8, Novartis, 8; S. Tropé, Nordic Pharma, 6; J. D. Cohen, None.

Abstract Number: 2410

Determining the Need for Fatigue Management Resources for Young Adults with Rheumatic Disease

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical Poster II – ARHP

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Fatigue is a multi-faceted symptom of rheumatic disease that has high priority among patients due to its far-reaching effects on roles and relationships. There is a paucity of resources around the impact of fatigue as experienced by young adults, who are often making decisions around career and family that lay the foundation for their

adult lives. Therefore, the purpose of this study was to determine fatigue impact, gaps in young adult patients' knowledge on fatigue, and preferences for format and content of future fatigue resources.

Methods: Questionnaires and semi-structured interviews were conducted with young adults (18-30 years old) recruited via social media, who self-reported rheumatic diagnoses and had combined fatigue scores of 12+ on the first 3 questions of the Multidimensional Assessment of Fatigue (MAF) Scale. Pregnant women were excluded. The full MAF, PedsQL Multidimensional Fatigue Scale, and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) assessed fatigue impact and experiential components of physical, emotional, and cognitive fatigue. Interviews focused on perceptions of fatigue, strategies to manage fatigue, and preferences for educational resources. Quantitative data were analyzed descriptively; qualitative data were analyzed using constant comparative analysis.

Results: Participants were 10 women (27.0 ± 2.8 years old), had varying diagnoses (e.g. JIA, MCTD, SLE, PsA, Scleroderma), were a majority white (70%), and all employed (100%) with some part-time school enrollment (40%). Participants were significantly impacted by their fatigue, scoring one standard deviation from established patient norms on all surveys (MAF= 38.1 ± 7.0 ; PedsQL= 40.1 ± 13.8 ; FACIT-F Emotional Well-Being= 14.4 ± 4.5). All participants reported the need for additional information about fatigue at diagnosis; participants were not prepared for the chronicity of fatigue and its effects on daily life. Current fatigue management strategies were developed through trial-and-error with limited support from healthcare teams. Participants felt professional recommendations were often non-specific to fatigue, too basic (e.g. take naps), or were un-relatable to their financial situations and high stress environments (e.g. school, work, motherhood). Participants desired more information about the epidemiology and physiology of fatigue and strategies specific to activities of young adults (e.g. having energy to socialize after work). While most participants agreed that information was more helpful from fellow patients rather than providers, there was discussion about how to combine both sets of expertise using innovative online tools.

Conclusion: Young adults reported that fatigue significantly impacted their participation in desired activities. As such, resources should be tailored to developmental concerns especially within contexts of early careers and family life. While non-pharmacological interventions are shown to be efficacious in reducing fatigue for persons with rheumatic disease, future research should assess the relevance of these interventions in addressing specific needs of the young adult population.

Disclosure: K. Carandang, None; J. L. Poole, None.

Abstract Number: 2411

The Ovarian Reserve Measuring the Anti-Müllerian Hormone Is Not Diminished in Patients with Rheumatoid Arthritis Compared to the Healthy Population

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Reproductive Issues in Rheumatic Disorders Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid Arthritis (RA) is the most prevalent chronic inflammatory arthritis, affecting 0.5-1% worldwide population and predominates in females. Altered fertility has been reported due to a decrease in ovarian reserve secondary to sustained inflammation. The anti-Müllerian Hormone (AMH) is currently the most reliable biomarker of ovarian reserve. However, few and contradictory studies have been reported to analyze the relationship between fertility in RA women patients and AMH. The aim of present study is to determine the AMH serum concentrations in a long-standing RA patients and control group. We also sought to determine the correlation between AMH serum levels and disease activity measured by different parameters and the effect of biological DMARDs.

Methods: Serum AMH levels were measured in 60 women with long-standing RA aged 20-50 y.o. and compared to 59 healthy women. AMH was assessed by ELISA (*Gen II Beckman Coulter Inc.*) and a large data set of clinical and molecular data was annotated. Demographic parameters, RA disease activity measured by DAS28 score and inflammatory biomarkers such as ESR, CRP, lymphocyte CD4+, CD8+, NK cells, IL-10 and IL-6 were determined. A comprehensive gynecological self-administered questionnaire was given. Serum AMH levels were age-correlated. Differences between groups were calculated using Student's t-test or Mann-Whitney U test for continuous variables and Fisher's exact test for categorical

variables. Multivariate analysis was conducted by the partial correlation coefficient. Linear regression analysis was performed to study the effect of different variables on proportional AMH change. *P* value <0.005 were considered significant.

Results: The median age was similar in AR and control groups (37.4 ± 6.23 vs 37.3 ± 6.27 $P=0.937$). Mean disease duration was 8.37 ± 5.36 years. The number of previous treatments was <3 in 71.7% of patients and ≥ 3 in 28.3%. Disease activity measured by DAS28 was 2.89 ± 1.54 . The age-adjusted mean serum concentration of HAM was 1.27 ng/ml [IQR 0.42; 2.24] in RA patients and 1.31 ng/ml [IQR 0.46; 3.09] in controls ($P=0.608$). Neither disease activity ($P=0.862$), nor current or previous bDMARDs treatments ($P=0.871$) were associated with HAM levels. However, a negative linear correlation was observed between HAM and IL-10 levels ($P=0.033$).

Conclusion: Our study shows that ovarian reserve determined by HAM serum levels is not reduced in rheumatoid arthritis patients compared with healthy controls. In our series, HAM levels were not affected by disease activity however a significant correlation was observed between HAM and IL-10 levels. These results support the role of cytokines profile in the female reproductive system and will focus further investigations in this critical area, mainly once biological DMARDs have been recommended in RA pregnant patients.

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Abstract Number: 2412

Evaluating Gaps in Reproductive Health Knowledge Among Women with Rheumatic Diseases

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Reproductive Issues in Rheumatic Disorders Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: While women with rheumatic diseases may face considerable reproductive health challenges, few studies have objectively assessed what these women know about their reproductive risks. This study evaluates patients' knowledge across a range of topical domains, including heritability, preconception health, contraception, fertility, pregnancy management, medication risk, and lactation.

Methods: With input from rheumatologists, women's health experts, a pharmacist, and survey methodologist, we created a 10-item test to evaluate patients' knowledge (ReproKnow). Women aged 18-50 years old were recruited to take ReproKnow and a demographic survey immediately after their physician visit at a participating rheumatology clinic. Descriptive statistics were used to summarize sample characteristics. Each question was scored as correct (1) or incorrect (0). Independent sample t-tests were used to evaluate the associations between total knowledge score and age, race, education, family characteristics, and clinical factors. Questions were grouped into domains based on their conceptual relationships, and mean percentages of correct answers were calculated within these domains.

Results: Our sample included 153 women who were 38.3 years old on average (S.D. 8.2) and predominately white (77%). Half (50%) had attained at least a secondary level of education. Patients' mean total knowledge scores were 5.0 (SD 2.2), with a median of 5.0 (range 0-10). Women who were younger, white, had higher education levels, or had experienced pregnancies after rheumatic disease diagnosis, had higher total knowledge scores ($p<0.05$).

When assessed by reproductive health topics, women were least likely to correctly answer questions about the safety of breastfeeding (28.8% correct) or the frequency of birth defects among children born to mothers with rheumatic diseases (30.8% correct). Approximately 50% of women correctly answered questions about fertility, contraception safety and efficacy, preconception planning, and medication risk.

Conclusion: Our study suggests that some women with rheumatic diseases have significant knowledge gaps about aspects of their reproductive health. Future work is needed to assess how knowledge may influence informed reproductive decision-making, behaviors, and outcomes in this high-risk group of women.

	% Correct	% Correct (Down)
Heritability		
1. Moms with autoimmune diseases pass their diseases on to their children (A: Sometimes)	75.8	75.8
Birth Outcomes		
1. If I have an autoimmune disease, my baby's chances of being born with a birth defect are (A: Low)	32.7	38.8
2. If I am pregnant and have a disease flare, my baby may be (A: Born too early)	28.8	
Fertility		
1. Most women with autoimmune diseases can get pregnant as easily as other women (A: Yes)	51.6	51.6
Contraception		
1. Can most women with autoimmune diseases use birth control safely? (A: Yes)	54.7	55.0
2. Which type of birth control is the best at preventing pregnancy? (A: Intrauterine device (IUD))	41.2	
Preconception Planning		
1. When is the best time for a woman with an autoimmune disease to get pregnant? (A: After her disease is controlled on safe meds for a few months)	54.2	54.2
Pregnancy Management		
1. If I find out that I'm pregnant, what should I do next? (A: Continue my meds until I talk with my doctor)	75.2	63.8
2. If I am pregnant and have a flare of my disease (A: I may need to use meds to protect me and my baby)	52.3	
Breastfeeding		
1. Moms with autoimmune diseases who are on safe meds (A: Usually can breastfeed safely. Make breastmilk that is nutritious as other women's)	28.8	28.8
Medication Risk		
1. Can most women with autoimmune diseases use birth control safely? (A: Yes)	54.7	55.0
2. When is the best time for a woman with an autoimmune disease to get pregnant? (A: After her disease is controlled on safe meds for a few months)	54.2	
3. If I find out that I'm pregnant, what should I do next? (A: Continue my meds until I talk with my doctor)	75.2	
4. If I am pregnant and have a flare of my disease (A: I may need to use meds to protect me and my baby)	52.3	
5. Moms with autoimmune diseases who are on safe meds (A: Usually can breastfeed safely. Make breastmilk that is nutritious as other women's)	28.8	

Table 1. Percentage of Correct Answers By Question and By Concept Area (Mean Percentage, %)

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Abstract Number: 2413

Pregnancy Outcomes in Mixed Connective Tissue Disease: Results from a Multicentre Cohort Study

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Reproductive Issues in Rheumatic Disorders Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Mixed connective tissue disease (MCTD) is characterized by signs and symptoms of a combination of disorders, primarily systemic lupus erythematosus (SLE), scleroderma and polymyositis and is characterized by the presence of high titre antibodies to U1-ribonucleoprotein (RNP).

When planning a pregnancy in patients with connective tissue diseases, ENA profiling is suggested but generally refers to testing for maternal antibodies specifically to components of the SSA/Ro-SSB/La ribonucleoprotein complex since these have been associated with foetal cardiac conduction abnormalities and neonatal skin rashes. Nevertheless, little is known about the maternal and foetal pregnancy outcomes in women with the presence of anti-U1RNP antibodies absent reactivity to SSA/Ro-SSB/La.

Methods: Data was retrospectively collected from S. Giovanni Bosco Hospital and Sant' Anna University Hospital, Turin, Italy, the Lupus Unit, Department of Rheumatology at St Thomas' Hospital, London, UK, Hospital das Clínicas da Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil, Hospital Reina Sofia de Córdoba, Spain, ASST Spedali Civili di Brescia, Brescia, Italy.

Patients Characteristics		All (94)	%
Age at data collection, mean (S.D.), years		45,1 (±10,9)	
Ethnicity			
	Caucasian, n	64	68,1
	Black, n	9	9,6
	Asian, n	4	4,3
	Other, n	17	18,1
Diagnosis			
	MCTD	94	100
Disease duration at data collection, mean (S.D.), years		12,3 (±8,5)	
	MCTD and APS	13	13,8
	MCTD and APS	6	6,4
Clinical manifestations			
	Hematological, n	36	38,3
	Skin, n	57	60,6
	Joints, n	65	69,1
	Cardiac, n	10	10,6
	Bone, n	9	9,6
	Muscular, n	31	33
	Raynaud, n	56	59,6
	Pulmonary, n	27	28,7
	Neurological, n	6	6,4
Cardiovascular risk factors			
	History of smoking, n	10	10,6
	Arterial hypertension, n	13	13,8
	Hypolipidemia, n	11	11,7
	Diabetes, n	2	2,1
Laboratory testing			
	Hypocomplementemia (C3), n	28	29,8
	Hypocomplementemia (C4), n	25	26,6
	anti-dsDNA positive, n	12	12,8
	Hypergammaglobulinemia, n	47	50

Inclusion criteria included: Women ever pregnant who fulfilled the established criteria of MCTD with confirmed anti-U1RNP positivity.

Results: This multicentre retrospective cohort study describes the foetal and maternal outcomes of 203 pregnancies in 94 consecutive women ever pregnant (mean age at data collection 45.1 years old, S.D. 10.9; mean disease duration at data collection 12.9 years, S.D. 8.5). Demographic, clinical and laboratory characteristics are summarized in Figure 1. Of the 203 pregnancies analysed the foetal outcomes were as follows: 146 (71.9%) resulted in live births, 38 (18.7%) in miscarriages, 18 (8.9%) in stillbirths (after 20 weeks gestation) and eleven (5.4%) cases showed intrauterine growth restriction (IUGR). Maternal pregnancy outcomes were as follows: eight (3.9%) cases developed pre-eclampsia, two (0.9%) cases developed eclampsia, 31 (15.3%) women developed gestational hypertension and three (1.5%) cases were diagnosed with gestational diabetes. Moreover, we report a case of complete congenital heart block (0.45%) and a case of skin rash in consecutive offspring born to a mother with anti U1RNP antibodies in the absence of anti-Ro/SSA-SSB/La antibodies.

Conclusion: The observed live-birth-rate was as high as 72%, with poorer foetal outcomes observed in MCTD women with anti phospholipid antibodies and pulmonary or muscular involvement. While the true frequency of heart block associated with anti-U1RNP remains to be determined, this study raises the consideration of echocardiographic surveillance in this setting. Women with MCTD should receive a specific counselling when planning a pregnancy, as it is currently done in women with SLE.

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Abstract Number: 2414

The Global Antiphospholipid Syndrome Score in Women with Systemic Lupus Erythematosus and Adverse Pregnancy Outcomes

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

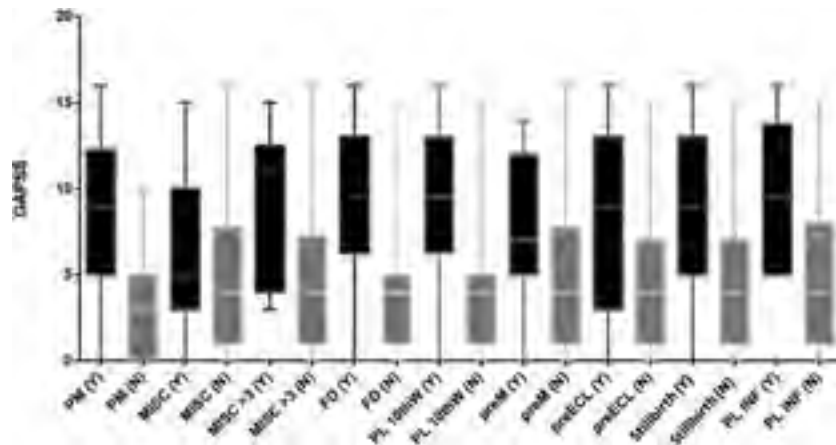
Session Title: Reproductive Issues in Rheumatic Disorders Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) and antiphospholipid antibodies (aPL) are associated with pregnancy complications.

Methods: 143 women ever pregnant with SLE who presented in our outpatient clinic were included. The individual GAPSS was calculated for each patient by calculating the sum of each risk factor score, as follows: three for hyperlipidaemia, one for arterial hypertension, five for aCL IgG/IgM, four for anti-b2 glycoprotein I IgG/IgM, 3 for anti-phosphatidylserine/prothrombin antibodies (aPS/PT) IgG/M and four for lupus anticoagulant (LA).



Results: Significantly higher GAPSS values were seen in patients with the following pregnancy history when compared to those without a history of pregnancy complications: any pregnancy complication (mean GAPSS 8.4, S.D. 4.5) vs. no pregnancy complication (mean GAPSS 3.1, S.D. 2.6, mean difference 5.2, t-test: $p=0.000$, 95% CI 4.0-6.4); three or more consecutive miscarriages of < 10 weeks gestation (mean GAPSS 9.4, S.D. 4.5) vs. no miscarriages <10 weeks gestation (mean GAPSS 4.8, S.D. 4.1, mean difference 4.6; t-test: $p=0.002$, 95% CI 1.7-7.4); any miscarriages (mean GAPSS 6.3, S.D. 4.3) vs. no miscarriages (mean GAPSS 4.7, S.D. 4.3, mean difference 1.6, t-test: $p=0.045$, 95% CI 0.03-3.1); fetal death (mean GAPSS 9.0, S.D. 3.8) vs. no fetal death (mean GAPSS 3.8, S.D. 3.4, mean difference 5.3, t-test: $p=0.000$, 95% CI 3.7-6.8); miscarriage <10 weeks gestation (mean GAPSS 9.1, S.D. 4.2) vs. no miscarriage < 10 weeks (mean GAPSS 3.8, S.D. 3.4, mean difference 5.3, t-test: $p=0.000$, 95% CI 3.9-6.7); premature birth (< 34 weeks) (mean GAPSS 7.8, S.D. 4.7) vs. no premature birth (mean GAPSS 4.8, S.D. 4.1, mean difference 2.9, t-test: $p=0.01$, 95% CI 0.7-5.2); pre-eclampsia (PET) (< 34 weeks) (mean GAPSS 7.8, S.D. 5.1) vs. no PET (mean GAPSS 4.7, S.D. 4.0, mean difference 3.1, t-test: $p=0.002$, 95% CI 1.1-5.2); stillbirth (mean GAPSS 9.1, S.D. 5.1) vs. no stillbirth (mean GAPSS 4.8, S.D. 4.1, mean difference 4.3, t-test: $p=0.002$, 95% CI 1.6-6.9); placental infarction (mean GAPSS 10.6, S.D. 4.2) vs. no placental infarction (mean GAPSS 4.9, S.D. 4.1, mean difference 5.6, t-test: $p=0.004$, 95% CI 1.8-9.4).

Conclusion: Higher GAPSS values are found in women with SLE and aPL with previous pregnancy complications compared to those without pregnancy complications. The clinical utility of the GAPSS score in pregnancy seems promising and should be validated in a prospective cohort.

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Abstract Number: 2415

Increased Sperm DNA Fragmentation in Male Systemic LUPUS Erythematosus Patients

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Reproductive Issues in Rheumatic Disorders Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Gonadal dysfunction may affect male systemic lupus erythematosus (SLE) patients. Recently, sperm DNA integrity analysis has shown better diagnostic and prognostic performance for predicting male reproductive potential. In fact, conventional semen analysis, which focus on sperm concentration, motility and morphology, has been demonstrated to be a poor indicator of fertility and pregnancy outcome. There are, however, no studies assessing sperm DNA fragmentation and in male non-azoospermic SLE patients. Therefore the objective of the present study was to

evaluate sperm DNA fragmentation analysis concomitantly with a global gonadal assessment in non-azoospermic male SLE patients.

Methods: Twenty-eight consecutive male SLE patients (ACR criteria) and 34 healthy controls were evaluated for demographic and exposures data, urologic evaluation and hormone. Semen analysis was performed according to the World Health Organization guidelines and sperm DNA fragmentation by alkaline comet assay in both groups. Clinical features, disease activity/damage scores and treatment were also evaluated in SLE patients.

Results: The median age [33 (20-52) vs. 36.5 (25-54) years, $p=0.329$] and frequency of varicocele (25% vs. 32%, $p=0.183$) were similar in SLE patients and healthy controls. Sperm DNA fragmentation showed significantly higher levels of cells class III [44 (9-88) vs. 16.5 (0-80)%, $p=0.001$] and cell class IV [10.5 (3-86) vs. 7 (0-36)%, $p=0.039$] in SLE patients compared to healthy controls. Sperm DNA fragmentation index was also significantly higher in SLE patients [62 (31-97) vs. 25.5 (0-100)%, $p<0.001$]. Conventional sperm parameters (including sperm count, motility and morphology) were similar in both groups ($p>0.05$). In SLE patients no correlations were observed between sperm DNA fragmentation index and age, disease duration, body mass index, SLEDAI-2K and SLICC/ACR-DI scores, and cumulative dose of prednisone, hydroxychloroquine, methotrexate, azathioprine, mycophenolate mofetil and intravenous cyclophosphamide (IVCYC) ($p>0.05$). Further analysis of SLE patients treated with and without IVCYC showed that total sperm motility was significantly lower in the former group [64 (15-83) vs. 72 (57-86)%, $p=0.024$]. Sperm DNA fragmentation index was alike in both groups [52.5 (31-95) vs. 67.5 (34-97)%, $p=0.185$].

Conclusion: To our knowledge, this was the first report that male non-azoospermic SLE patients have increased sperm DNA fragmentation without evident gonadal dysfunction. IVCYC does not seem to be a major determinant for this abnormality. Future prospective study is necessary to determine the impact of this alteration in these patients' fertility.

Disclosure: B. C. Tiseo, None; C. A. Silva, Fundação de Amparo à Pesquisa do Estado de São Paulo, 2; E. F. Borba, None; G. A. Munhoz, None; M. Srougi, None; E. Bonfa, Fundação de Amparo à Pesquisa do Estado de São Paulo, 2, Conselho Nacional de Desenvolvimento Científico e Tecnológico, 2; M. Cocuzza, None.

Abstract Number: 2416

Good Pregnancy and Neonatal Outcomes in Lupus Nephritis Patients with Complete Remission

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Reproductive Issues in Rheumatic Disorders Poster

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Background/Purpose: To investigate the outcomes of pregnancy and neonatal and the risk factors of lupus flares and pregnancy complications in Chinese patients with lupus nephritis (LN).

Methods: One hundred female patients with LN after complete remission prior to the conception (remission group) were prospectively followed from Jan 2010 to Dec 2016. Twenty-seven LN patients without complete remission prior to conception and unplanned pregnancies were collected concurrently as the control group. Glucocorticoids (GS) or GS plus other applicable immunosuppressant were given during the pregnancy. The rate and risk factors of LN relapse, maternal and neonatal complications, including preeclampsia, abortion, fetal death, intrauterine growth restriction (IUGR) and preterm delivery were analyzed.

Results: In the remission group, 100 LN patients had 104 times of pregnancies and delivered 96 healthy children. During pregnancy, immunosuppressive regimens were GS alone in 74 pregnancies, GS plus other immunosuppressant in 23 pregnancies, no drug in 7 pregnancies. LN relapse developed in 15 (14.42%) pregnancies, logistic regression analysis showed that the duration of complete remission less than 12 months (OR: 200.324 (95% CI 197.967-202.681), $P=0.025$) and positive anti-C1q antibody (OR: 58.159 (95% CI 56.229-60.089), $P=0.035$) before pregnancy were the two independent risk factors for the relapse. Thirty-seven pregnancies (35.85%) developed pregnancy and neonatal complications, including 19 preterm delivery, 5 preeclampsia, 5 IUGR and 8 fetal loss (7 spontaneous abortion, 1 elective abortion due to preeclampsia). Complete remission time less than 6 months before pregnancy (OR: 19.481 (95% CI 18.003-20.959), $P=0.045$) was associated with preterm delivery, while hypocomplementemia (OR: 11.287 (95% CI 10.06-12.514), $P=0.048$) and positive anti phospholipid antibody (OR: 7.118 (95% CI 6.193-8.043), $P=0.034$) before pregnancy were associated with

the fetal loss. In the control group, the rate of lupus relapse (21/27, 77.78%) and pregnancy and neonatal complications (23/27, 85.19%) were significantly higher than that in the remission group ($p < 0.01$).

Conclusion: Complete remission prior to pregnancy and maintaining immunosuppressive treatment during pregnancy showed good pregnancy and neonatal outcomes in patients with lupus nephritis. The duration of complete remission, serum levels of anti-C1q antibody and complement and anti phospholipid antibody were associated with the relapse and pregnant associated complications.

Disclosure: W. HU, None; K. LI, None; Y. CHEN, None; Z. LIU, None; L. YANG, None; D. CHEN, None; H. Zhang, None.

Abstract Number: 2417

Pregnancy Outcomes in Systemic Lupus Erythematosus and Pre-Systemic Lupus Erythematosus: A Population-Based Cohort Study

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SESSION INFORMATION

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Session Title: Reproductive Issues in Rheumatic Disorders Poster

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Background/Purpose: The adverse effects of systemic lupus erythematosus (SLE) on maternal and fetal outcomes in pregnancy have been explored mainly in clinic-based cohorts. However, data comparing maternal and fetal outcomes before and after diagnosis of SLE at the population-based level are scarce. The purpose of our study was to assess fetal and maternal outcomes before and after SLE diagnosis.

Methods: We conducted a population-based, retrospective cohort study from a perinatal registry that included all pregnancies in the province between the 1st of January 2002 and 31st of December 2012. SLE was defined as greater than or equal to 2 ICD-9/ICD-10 codes at least 2 months apart and within a 2-year window. SLE exposure was based on diagnosis before or after date of conception. The groups were defined as post-SLE (pregnancy following SLE diagnosis) or pre-SLE (pregnancy preceding SLE diagnosis). We used logistic, Cox and Poisson regression models to evaluate the effects of SLE on perinatal outcomes (small for gestational age [SGA], congenital anomalies (CA), preterm delivery, major infection in baby) and maternal outcomes (major infections). Infant infections were defined as occurring in the first year of life, while maternal infections were only in the first six weeks following delivery. All models were adjusted for maternal prescription medications, comorbidities, prior pregnancy outcomes, and body mass index.

Results: 405,538 total pregnancies were evaluated, with 608 occurring in SLE patients. Among these, 376 pregnancies were post-SLE, and 232 were pre-SLE. In adjusted analyses, the odds ratios (OR) for the association of SLE with having infants born SGA were 1.91 (95% CI 1.48, 2.46) for post-SLE and 2.28 (95% CI 1.68, 3.09) for pre-SLE when compared to non-SLE pregnancies (See Table 1). The adjusted ORs for CA were also increased in both periods (see Table 1). Furthermore,

Table 1: Association of Systemic Lupus Erythematosus diagnosis before/after conception and risk of fetal and maternal complications

Outcomes	Post-SLE		Pre-SLE	
	OR	(95% CI)	OR	(95% CI)
Small for Gestational Age	1.91	(1.48, 2.46)	2.28	(1.68, 3.09)
Congenital Anomalies	1.59	(1.21, 2.10)	1.45	(1.01, 2.06)
	HR	(95% CI)	HR	(95% CI)
Preterm delivery	1.57	(1.24, 1.98)	1.13	(1.01, 2.62)
	CR	(95% CI)	CR	(95% CI)
Baby infection	0.99	(0.66, 1.49)	1.80	(1.22, 2.67)
Mother infection	1.18	(0.66, 2.03)	0.91	(0.47, 1.80)

the hazard ratios (HR) for the effect of post- and pre-SLE on preterm delivery were also increased. In adjusted analyses, the count ratios (CR) for the association of SLE with a serious newborn infection were increased only in the pre-SLE group, CR = 1.80 (95% CI 1.22, 2.67), when compared to non-SLE pregnancies. No increased risk for serious maternal infection was seen (see Table 1).

Conclusion: We found an increased risk of SGA, CA, preterm delivery, and serious newborn infection in pregnancies of patients with SLE. The risk was increased even in pregnancies before SLE diagnosis. There was no association between SLE and risk of serious maternal infection.

Disclosure: A. N. Wade, None; M. A. De Vera, None; E. C. Sayre, None; J. A. Avina-Zubieta, None.

Abstract Number: 2418

Awareness of Fertility and Contraception Issues Among Women with Rheumatologic Diseases

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose: Because many autoimmune conditions preferentially affect women of childbearing age and both disease and treatment can negatively affect pregnancy outcomes, healthcare providers to women with rheumatologic diseases must be aware of and counsel patients regarding reproductive health issues.

Prior studies have shown that women with lupus of childbearing age are at high risk of unintended pregnancy and pregnancy exposure to teratogenic medication (1, 2). Our academic medical center provides care to a diverse urban population. We designed this study:

1. To assess baseline awareness of reproductive health issues in our patient population.
2. To evaluate the efficacy of an educational intervention, in addition to routine counselling, in improving patients' reproductive health knowledge.

Methods: This descriptive study was performed using a survey instrument. Premenopausal females, between the age of 18 to 45 who were seen at Drexel University College of Medicine Rheumatology clinics, with an underlying diagnosis of rheumatoid arthritis, systemic lupus erythematosus, sero-negative spondyloarthropathy, mixed connective tissue disease, scleroderma, and vasculitis were recruited. Participants were asked to complete a baseline survey and were later randomized 1:1 to receive either pamphlet or audiovisual intervention, followed by a post-intervention survey at routine followup visit.

Results: 74 participants enrolled in the study thus far. All completed the baseline survey. The majority were age 25-30 (34%), African American (44.6%) and at least partially-college educated (74%). 41% were unemployed. 49 participants were randomized to and completed the intervention; 22 respondents completed the post-intervention survey. Pre-intervention, 39% of respondents reported consistent contraceptive use; 47% of women who were sexually active with men reported contraceptive use. Of the 53% of sexually active women not using birth control (at risk of becoming pregnant), 59% were also using teratogenic medications.

Post- intervention, 20% more women felt knowledgeable about medication effects on fertility, 21% more about effects on pregnancy and 14% more about effects on breastfeeding compared to pre-intervention.

Conclusion: Survey respondents report poor baseline knowledge of the impact their diseases and treatments on reproductive health. Preliminary post-intervention data show an increase in knowledge regarding medication effects on reproductive health [in both groups]. With these data, we hope to raise awareness of reproductive health issues and improve counseling of women with autoimmune diseases using the educational interventions to maximize quality of care.

References:

1. Schwarz EB, Manzi S. *Risk of unintended pregnancy among women with systemic lupus erythematosus*. Arthritis Rheum. 2008 Jun 15;59(6):863-6.
2. Yazdany J, Trupin L, et al. *Contraceptive counseling and use among women with systemic lupus erythematosus: a gap in health care quality*. Arthritis Care Res (Hoboken). 2011 Mar;63(3):358-65.

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Abstract Number: 2419

Needs Assessment and Implementation of a Reproductive Health Intention Screen for Women with Systemic Rheumatic Diseases

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Reproductive Issues in Rheumatic Disorders Poster

Session Type: ACR Poster Session C

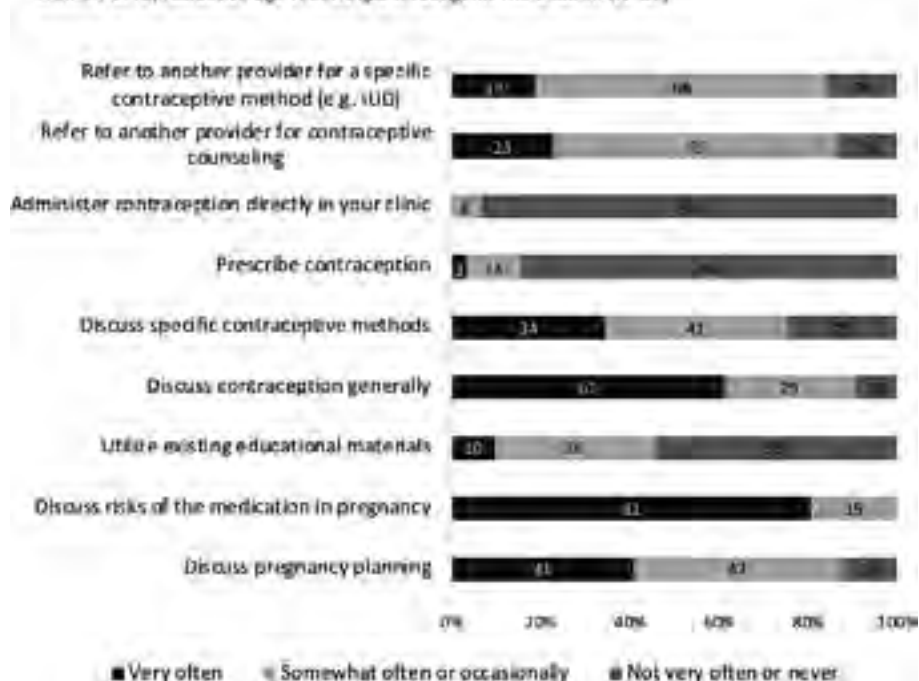
Session Time: 9:00AM-11:00AM

Background/Purpose: Among women with systemic rheumatic diseases (SRD), poor maternal and fetal outcomes may occur if disease activity and medication use are not optimized preconception. We conducted a needs assessment of rheumatologists' potentially modifiable practices around fertility intention screening and contraceptive prescribing. We then implemented an intervention to ameliorate noted gaps in care.

Methods: Using the electronic medical record (EMR) at a large academic medical center, we identified women 18-50 years with SRD and assessed teratogenic medication use, contraceptive use, and obstetrics and gynecology (OB/GYN) care during the year prior to our intervention. We administered a 13-item survey to the rheumatologists to assess fertility intention screening and contraceptive prescribing. We then introduced our intervention, the validated One Key Question[®] (OKQ), "Would you like to become pregnant in the next year?" to rheumatologists during a rheumatology-OB/GYN Grand Rounds lecture, created an EMR template for OKQ documentation, flagged potentially eligible SRD patients each week in the EMR, and introduced a streamlined referral system to facilitate access to OB/GYN care.

Results: We identified 625 women 18-50 with SRD seen by a rheumatologist ≤ 1 year prior to OKQ implementation. Of these, 66% received ≥ 1 medication with known teratogenic risk. Thirty-three percent of these women had any documented

Figure. Rheumatologist-reported frequency of reproductive health care for women of reproductive age receiving a teratogenic medication (N=32)



contraception and 5% had been referred to OB/GYN in the previous year. We received survey responses from 74%(32/43) of the practicing rheumatologists. While many providers frequently discuss contraception when prescribing a teratogen, few utilize educational materials and almost none provide contraception (Figure). When asked about comfort assessing patients' reproductive goals, 31% felt very comfortable, 50% somewhat comfortable, and 19% not very comfortable or unsure (Table). Providers cited multiple potentially modifiable barriers to screening, most notably lack of time (63%), lack of knowledge (31%) or not knowing where to refer patients (41%). Within 2 months of implementation, the OKQ has been documented in 58 charts by 11 providers, and 11 patients (19%) were referred to OB/GYN.

Conclusion: In this large, academic rheumatology practice, physician comfort with reproductive health was highly variable and referrals for OB/GYN care infrequent. Implementation of a single question fertility intention screen (OKQ) may help ensure that an assessment of patients' family planning needs and appropriate follow-up are incorporated into their rheumatologic care.

Table. Reproductive Health in Rheumatology Practice Selected Survey Results (N=32)

	Response - N (%)
Rheumatologists were asked to rate the following:	
Frequency of contraception discussions	
Very often	14 (44)
Somewhat often	7 (22)
Occasionally/ Not very often/Never	11 (34)
Frequency of pregnancy planning discussions	
Very often	13 (41)
Somewhat often	10 (31)
Occasionally/Not very often/Never	9 (28)
Comfort assessing patients' reproductive goals	
Very comfortable	10 (31)
Somewhat comfortable	16 (50)
Not very comfortable/Not comfortable at all/Not sure	6 (19)
Comfort counseling patients about contraceptive options	
Very comfortable	5 (16)
Somewhat comfortable	15 (47)
Not very comfortable/Not comfortable at all/Not sure	12 (38)
Barriers to counseling about reproductive goals and/or contraception*	
Not enough time	20 (63)
Sensitivity of the issue	7 (22)
Topic is out of practice scope	15 (47)
Limited knowledge about contraceptive options	10 (31)
Moral or religious objections	0 (0.0)
Limited knowledge about medication effects in pregnancy	4 (13)
Limited knowledge about disease activity in pregnancy	2 (6)
Inadequate guidelines	6 (19)
Challenges referring patients	13 (41)
Patients' limited knowledge about risks	8 (25)
Patients' limited knowledge/beliefs/myths about contraceptives	10 (31)
Cultural barriers/communication issues with patients	9 (28)
Rheumatologists were asked to rate how influential the following factors are in their decision whether to prescribe methotrexate to a 25 y/o F who declines non-barrier contraceptives	
Patient autonomy	
Not influential at all/slightly influential/somewhat influential	6 (19)
Very influential	17 (55)
Extremely influential	8 (26)
Optimal management of the patient's rheumatic disease	
Not influential at all/slightly influential/somewhat influential	2 (7)
Very influential	20 (65)
Extremely influential	9 (29)
Potential risk to a fetus	
Not influential at all/slightly influential/somewhat influential	4 (13)
Very influential	14 (45)
Extremely influential	13 (42)
Concern for harm to patient related to miscarriage or fetal anomalies	
Not influential at all/slightly influential/somewhat influential	4 (13)
Very influential	15 (48)
Extremely influential	12 (39)
Provider legal/malpractice	
Not influential at all/slightly influential/somewhat influential	12 (39)
Very influential	15 (48)
Extremely influential	4 (13)

*Respondents could choose more than one barrier.

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Abstract Number: 2420

Pregnancy Outcome and Perinatal Complications of Neonate Born to Mothers with Juvenile Idiopathic Arthritis in Asia

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Background/Purpose: Juvenile idiopathic arthritis (JIA) is the leading pediatric rheumatic disease affecting 30 out of a million women. Although spontaneous remission may occur in most patients, physical defects and the associated psychological conditions may impact patients' all aspects of life, including pregnancy. To date, very few studies looked into the maternal and neonatal outcomes among women with JIA, and most of them are focused on the Caucasian population. The aim of this research is to provide proper health counsel for women with Asian descent suffering JIA about the possible complications during pregnancy.

Methods: Using the National Health Insurance database and National Birth Registry, we identified a cohort of all live-births in Taiwan between 2004 and 2014. First child born to mothers with JIA were identified and matched with up to 5 controls by maternal age and birth year. Raw odds ratio (OR) with 95% confidence intervals (CI) and OR with age, infant sex, Charlson comorbidity index, urbanization, income, occupation, birth year, maternal nationality adjustment were used to analyze fetal/neonatal outcomes and maternal outcomes during pregnancies.

Results: Of the 2,100,143 newborn, 0.037% (n=778) were born to JIA mothers. The result for neonatal outcomes suggested that babies born to mothers with JIA were more likely to have low birth body weight, with an adjusted OR of 1.35 (95% CI: 1.02 to 1.79) when compared to babies born to mothers without. No significant differences were found in prematurity, small for gestational age as well as Apgar score <7 at 1 and 5 minutes even after adjustment. In addition, no differences were observed in maternal outcomes between women with and without JIA.

Conclusion: Infants of mother with JIA and women with JIA themselves did not have an increased risk for pregnancy related adverse events. Intensive obstetric and neonatal care may not be necessary for pregnant women with JIA and their infants.

Disclosure: C. Y. Wu, None; S. C. Changchien, None; H. Y. Yang, None; K. W. Yeh, None; J. L. Huang, None.

Abstract Number: 2421

Pregnancy Outcomes in Women with Rheumatic Diseases and Thrombophilia Treated in a Multidisciplinary Unit

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Background/Purpose: To evaluate the efficacy of the treatment on the pregnancy outcomes of women with Rheumatic Diseases and Thrombophilia from a Spanish cohort. Their pregnancies should be considered high obstetric risk and they need close monitoring in a multidisciplinary unit.

Methods: Descriptive, retrospective and open study of 143 patients diagnosed with rheumatic diseases and thrombophilia assisted in a specialized multidisciplinary unit of Rheumatic Diseases and pregnancy (integrated by Gynecologists, Hematologists and Rheumatologists). The following variables were collected: age, maternal pathology, presence of antiphospholipid antibodies (aPL), anti-Ro/La, prior abortions, fetal echocardiograms, treatment during pregnancy, obstetric outcomes births/abortion, pregnancy length and maternal/fetal complications. The statistical analysis was done using the McNemar Test.

Results: 143 pregnant women were included. The baseline characteristics are specified in table 1. Our patients were an average of 33.6 ± 5.44 years old and the 44% were elder than 35 years. 198 pregnancies were developed during the monitoring. Abortions registered are specified in table 2. Before the inclusion in our unit there were 231 abortions with an average of 1.6 ± 1.84 abortions per patient. Only 7 abortions occurred for the patients monitored in our unit. The reduction in the number of abortions was statistically significant ($p < 0.001$). The treatment received is shown in the table 3. 44% pregnant women have higher obstetric risk with an average of 2.48 ± 1.99 abortions per patients. They received treatment with LMWH in combination with ASA and 16 pregnant received also IVIG. The mean gestational age was 38 weeks with an average birth weight of 3058.5 ± 595.6 grams. Only 11% babies were preterm and 34% births were cesarean. 88.4% of our patients did not have complications in the puerperium. All pregnant patients with positive Anti-Ro/La autoantibodies were monitored with periodic fetal echocardiograms from the 16th week of gestation. No Congenital Heart Block or neonatal lupus were registered (100% of newborn were healthy).

Conclusion: The treatment is effective in the decrease in the number of abortions and in a reduction of maternal and fetal morbidity and mortality. The multidisciplinary evaluation is essential in women diagnosed with Rheumatic Diseases and Thrombophilia.

Table 1 The baseline characteristics

	n
<i>Maternal pathology</i>	
Systemic Lupus Erythematosus	49
Antiphospholipid Syndrome	40
Thrombophilia	31
Sjögren's Syndrome	9
Undifferentiated Connective Tissue Disease	7
Rheumatoid Arthritis	6
Spondyloarthropathies	1
<i>Positive Antiphospholipid antibodies (aPL)</i>	
Lupus Anticoagulant	28
Anticardiolipin antibodies IgG	18
Anticardiolipin antibodies IgG	20
Anti-β2-glycoprotein IgG	10
Anti-β2-glycoprotein IgM	15
Triple positive aPL	12
<i>Positive anti-Ro/La</i>	
Anti-Ro 52	31
Anti-Ro 60	10
Anti-La	9

Table 2 Abortions

Abortions before inclusion (n)	231
Abortions after inclusion (n)	7

Table 3 Treatment received during the 198 pregnant

	(n)
Low-molecular-weight heparin (LMWH)	124
Acetylsalicylic Acid (ASA)	111
Hydroxychloroquine	85
Glucocorticoid	30
Intravenous Gammaglobulin (IVIG)	16
Azathioprine	12
Anti-TNF	3
Tacrolimus	1

Disclosure: I. Añón Oñate, None; I. Notario, None; M. Á. Ferrer, None; L. Pérez, None; M. Ramírez, None; R. Cáliz, None.

Abstract Number: 2422

Pregnancy Outcomes in Patients with Interstitial Lung Disease Related to Autoimmune Disease and Sarcoidosis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Reproductive Issues in Rheumatic Disorders Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Currently published data regarding pregnancy outcomes in patients with interstitial lung disease (ILD) related to autoimmune disease and sarcoidosis is limited, with widely variant outcomes reported. Some guidelines even suggest that these patients must avoid or terminate pregnancy. This study aimed to retrospectively analyze the pregnancy outcomes in a cohort of patients with ILD to help inform our ability to counsel patients on decision-making surrounding pregnancy and to help guide our management throughout pregnancy.

Methods: Medical records from 1/1/1996-9/27/2017 were retrospectively searched for encounters at our center for ICD-9/10 codes associated with pregnancy and ILD, including sarcoidosis. Each chart was reviewed to corroborate the diagnosis of lung disease, confirm that it temporally preceded the pregnancy, and ensure availability of delivery outcomes. Patients were categorized into two groups: sarcoidosis and autoimmune-related ILD (AI-ILD). Differences in categorical variables were analyzed using Fisher's Exact Test, and continuous variables were analyzed using ANOVA or Wilcoxon rank-sum test.

Results: Of 631 patient charts reviewed, 62 unique patients with 89 pregnancies (5 twins) met inclusion criteria; 63 pregnancies with sarcoidosis (62% biopsy-proven) and 26 with AI-ILD (11 SLE, 1 RA, 3 SSc, 3 PM, 2 SS, 2 EGPA, 2 UCTD, 2 CTD-ILD). The cohort was predominantly black (84.3%), with mean maternal age of 32 years. In total, there were 62 live births (Table 1), of which 11 were preterm (17.7%). Women in 8 pregnancies (12.9%) required oxygen at the time of delivery; however, only 1 (1.6%) required labor induction for maternal lung disease, and no patients required intubation. Two required ICU stays and no women died. Women with AI-ILD had more preeclampsia, but otherwise had similar pregnancy outcomes to those with sarcoidosis. Minimal differences in pregnancy outcomes and maternal morbidity were found when women with severe lung disease by imaging and/or pulmonary function tests were compared to those mild disease. Women with total lung capacity (TLC) <65% predicted more often required oxygen at delivery and had more C-sections, while women with diffusion capacity (DLCO) <60% predicted had no pregnancy outcome differences compared to women with better levels. The rate of pregnancy termination was similar for women with severe lung disease compared to overall (9.6% and 11.2%, respectively). While black women comprised >90% of the severe subgroups, pregnancy outcomes were similar when compared to non-black women with similar severity.

Conclusion: Pregnancies in women with AI-ILD and especially with sarcoidosis appear to be well tolerated from a pulmonary perspective, even in those with more severe disease by imaging and pulmonary function tests. Our data suggest it is not necessary for these women to avoid or terminate desired pregnancies due to lung disease alone.

Table 1.

	Total	Sarcoidosis	AI-ILD	p value
Pregnancies*, no. (%)	89	63 (70.7%)	26 (20.2%)	
Maternal age, mean \pm sd, y	32.0 \pm 5.9	33.4 \pm 5.7	28.5 \pm 4.9	p=0.0003
Maternal age, range, y	18-42	18-42	19-37	
Severe lung disease, no. (%): fibrosis on imaging, TLC < 65% predicted, AND/OR DLCO < 60% predicted	52/87 (49.8%)	35/61 (57.4%)	17/26 (65.4%)	p=0.6
Race, no. (%)				p=1.0
White	10 (11.2%)	7 (11.1%)	3 (11.5%)	
Black or African American	75 (84.3%)	53 (84.1%)	22 (84.6%)	
Ethnicity, no. (%)				p=1.0
Hispanic	3 (3.4%)	2 (3.2%)	1 (3.9%)	
Co-Morbidities, no. (%)				
Diabetes Mellitus	5 (6.5%)	4 (7.4%)	1 (4.4%)	p=1.0

Table . (Cont'd)

	Total	Sarcoidosis	AI-ILD	p value
Hypertension	10 (12.8%)	6 (10.9%)	4 (17.4%)	p=0.5
Tobacco Use	24 (30.4%)	19 (34.6%)	5 (20.8%)	p=0.3
Alcohol Use	8 (10.5%)	6 (11.5%)	2 (8.3%)	p=1
DMARDs, no. (%)				
Prednisone	24 (27%)	9 (14.2%)	15 (57.7%)	p=0.0001
Hydroxychloroquine	12 (13.5%)	0 (0%)	12 (46.2%)	p<0.0001
Azathioprine	15 (16.9%)	0 (0%)	15 (57.7%)	p<0.0001
Tacrolimus	3 (3.4%)	0 (0%)	3 (11.5%)	p=0.02
Neonatal Outcomes				
Terminations	10 (11.2%)	6 (9.5%)	4 (15.4%)	p=0.6
Live Births	62	46	16	
Gestational Age at Delivery, mean \pm sd, weeks	37.8 \pm 2.6	37.8 \pm 2.6	37.7 \pm 2.7	p=0.8
Small for Gestational Age, no. (%)	14 (22.6%)	12 (25%)	2 (14.3%)	p=0.5
Labor & Delivery Outcomes, no. (%)				
C-section Delivery	37 (59.7%)	27 (58.7%)	10 (62.5%)	p=0.9
Preeclampsia	8 (12.9%)	3 (6.5%)	5 (29.4%)	p=0.02
Oxygen at delivery	8 (12.9%)	4 (8.7%)	4 (26.7%)	p=0.09
ICU Stay	2 (3.2%)	0 (0%)	2 (12.5%)	p=0.06
Intubations	0 (0%)	0 (0%)	0 (0%)	p=1.0

*Analyses performed on individual pregnancies such that one woman could contribute >1 pregnancy.

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Abstract Number: 2423

Births to Women with Systemic Lupus Erythematosus Can be Identified Accurately in the Electronic Health Record

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Reproductive Issues in Rheumatic Disorders Poster

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Background/Purpose: Studying births in women with systemic lupus erythematosus (SLE) is difficult given its rarity and the challenges of randomized trials. While the electronic health record (EHR) serves as a powerful tool that is efficient and cost effective, accurately identifying SLE births is challenging. Our objective was to develop and then externally validate algorithms that use SLE and pregnancy-related ICD-9 and ICD-10 codes, labs, and medications to identify births to SLE patients.

Methods: We used Vanderbilt's Synthetic Derivative, a de-identified EHR with 2.8 million subjects. We selected individuals with at least 1 count of the SLE ICD-9 code (710.0) or ICD-10 codes (M32.1*, M32.8, M32.9) and at least 1 ICD-9 or ICD-10 code for pregnancy-related diagnoses yielding 433 subjects. For a training set, we randomly selected 100 subjects for chart review. A subject was defined as a case if diagnosed with SLE by a rheumatologist, nephrologist, or dermatologist (specialist) and had a birth documented. Positive predictive values (PPVs) and sensitivity were calculated for combinations of counts of the SLE ICD-9 or ICD-10 codes, ever use of antimalarials, a positive antinuclear antibody (ANA) \geq 1:160, and ever checked dsDNA or complements (C3 or C4). We performed external validation of ICD-9 algorithms in Duke's EHR using a set of 100 subjects randomly selected from the Duke Autoimmunity in Pregnancy Registry. ICD-10 algorithms could not be externally validated due to low sample size. Subjects who had an uncertain diagnosis by a specialist (n = 13, Vanderbilt and n = 6, Duke) and subjects with missing notes (n = 5, Vanderbilt and n = 0, Duke) were excluded from the analysis.

Results: PPVs and sensitivities are shown for the algorithms for training and validation sets in Table 1. In the training set, algorithms with ICD-10 codes alone with PPVs from 95 to 100% performed better than algorithms with ICD-9 codes alone with PPVs from 71 to 90%. Adding clinical data improved the PPVs of the algorithms that only used counts of the ICD-9 code.

Clinical data only minimally improved the PPVs of algorithms using ICD-10 codes alone. The algorithm with the highest combined PPV of 100% and sensitivity of 95% was ≥ 1 count of the ICD-10 codes and ever dsDNA, C3, or C4 checked. Algorithms using the ICD-9 code and clinical data in the training set replicated well in the external validation set (Table 1).

Conclusion: We have developed and validated algorithms to detect SLE patients with births in the EHR. Algorithms using ICD-9 codes may require additional clinical data while ICD-10 codes alone can identify SLE patients accurately. Future work is needed to handle subjects with uncertain diagnoses of SLE. Assembling SLE births within the EHR will enable more powerful studies to inform strategies that reduce adverse outcomes.

Table 1.

Algorithm	Positive Predictive Value Training set ^a	Positive Predictive Value Validation set ^b	Sensitivity Training set	Sensitivity Validation set
ICD-9 code only				
≥ 1 count of the ICD-9 code (710.0)	71%	76%	100%	93%
≥ 2 counts	79%	84%	97%	87%
≥ 3 counts	88%	85%	95%	77%
≥ 4 counts	90%	92%	87%	77%
ICD-10 codes only				
≥ 1 count of the ICD-10 codes (M32.1,* M32.8, M32.9)	95%		95%	
≥ 2 counts	100%		91%	
≥ 3 counts	100%		91%	
≥ 4 counts	100%		71%	
ICD-9 code AND ever antimalarial use				
≥ 1 count of the ICD-9 code	85%	72%	87%	54%
≥ 2 counts	87%	80%	85%	50%
≥ 3 counts	89%	86%	82%	50%
≥ 4 counts	91%	92%	77%	50%
ICD-10 codes AND ever antimalarial use				
≥ 1 count of the ICD-10 codes	95%		95%	
≥ 2 counts	100%		91%	
≥ 3 counts	100%		91%	
≥ 4 counts	100%		71%	
ICD-9 code AND ANA positive^c				
≥ 1 count of the ICD-9 code	84%	82%	80%	96%
≥ 2 counts	88%	88%	75%	88%
≥ 3 counts	94%	90%	75%	79%
≥ 4 counts	93%	95%	68%	79%
ICD-10 codes AND ANA positive				
≥ 1 count of the ICD-10 codes	100%		82%	
≥ 2 counts	100%		73%	
≥ 3 counts	100%		73%	
≥ 4 counts	100%		64%	
ICD-9 code AND ever dsDNA or C3 or C4 checked				
≥ 1 count of the ICD-9 code	83%	78%	95%	93%
≥ 2 counts	86%	84%	93%	87%
≥ 3 counts	90%	85%	90%	77%
≥ 4 counts	92%	92%	85%	77%
ICD-10 codes AND ever dsDNA or C3 or C4 checked				
≥ 1 count of the ICD-10 codes	100%		95%	
≥ 2 counts	100%		91%	
≥ 3 counts	100%		91%	
≥ 4 counts	100%		76%	

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Abstract Number: 2424

Bisphosphonates during Pregnancy: A Systematic Review Sayanika Kaur MD Fellow Drexel Rheumatology, Mojdeh Khaamesi MD Resident Internal Medicine Arundathi Jayatilleke MD Program Director Drexel Rheumatology

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SESSION INFORMATION

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Background/Purpose: Recent ACR guidelines on prevention and treatment of CS-induced osteoporosis state that women of childbearing potential who are at moderate-to-high risk of fracture should be given bisphosphonates. However, safety concerns regarding adverse outcomes restrict the prescription of the drugs in women of childbearing potential. Given that relevant human *in vivo* data are limited, we conducted asystematic review of available evidence to assess whether bisphosphonate use in pregnancy and preconception phase (<1 year before pregnancy) increases risk of adverse neonatal and pregnancy outcomes.

Methods:

Results: 24 papers were included in the final analysis, including 15 case reports, 4 case series, 4 cohort studies and covering the impact of 120 preconception or pregnancy exposures to bisphosphonates on pregnancy or neonatal outcome. The majority of exposures were single-dose. Only 4 studies had a comparator group. Indications for bisphosphonate use were malignancy, CS-induced osteoporosis and bone-related disorders like Gaucher.

The quality of evidence in all studies (using the GRADE approach) was “low” or “very low”. Congenital malformations were reported in 7/120 pregnancies including 2 cardiac valvular defects (VSD and PDA), 1 kidney malformation and 3 bony malformative disorders (see Table 1). Rates of congenital malformation and abortion were comparable in bisphosphonate-exposed and controls in studies with a comparator group. Mean birth weight and gestational age were slightly lower than in the general population. Limiting factors include small sample size with varying bisphosphonate formulations and inclusion of case reports and case series. Few studies had a comparator group. Confounding factors include maternal underlying medical condition, concomitant use of corticosteroid, and other immunosuppression.

Conclusion: Our findings suggest that pre-conception and pregnancy exposure to bisphosphonates does not pose major teratogenic risks. These results will be useful when counselling women about risks related to pregnancy and accidental conception. However, further controlled studies are needed to fully establish safety of bisphosphonate use prior to or during pregnancy.

Drug	Duration of exposure/Comments	Pregnancy Outcomes of Interest
Alendronate	56 exposures 1 entire pregnancy 16 first trimester 11 preconception 1 0-5 month of pregnancy	Low birth weight (2900 vs. 3290 gm) Craniotabes Transient hypophosphatemia 6 spontaneous abortions 1 premature birth 1 kidney and cardiac malformation
Diphosphonate	2 exposures in the third trimester	Transient hypocalcemia, Increased uptake on fetal bone scan
Etidronate	8 exposures 2 preconception 1 first trimester	Apert syndrome (before conception to first trimester) patient and baby had FGF gene mutation
Ibandronate	1 exposure in third trimester	No malformation
Pamidronate	20 exposures 6 preconception 2 third trimester 2 lactation	1 Talipes equinovarus 1 Transient hypocalcemia 1 Transient hypocalcemia 1 Low birth weight
Risedronate	18 exposures (exact time of administration not known)	1 prospective study: rate of malformations comparable to general population
Zoledronic acid	exposure through 28 weeks of pregnancy	1 case report: no malformations

Disclosure: S. Kaur, None; M. Khaamesi, None; A. Jayatilleke , None.

Abstract Number: 2425

The Impact of Biologic Treatment for Rheumatoid Arthritis Patients Who Hope to Conceive

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Reproductive Issues in Rheumatic Disorders Poster

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Session Time: 9:00AM-11:00AM

Background/Purpose: Previous reports revealed that it was difficult for rheumatoid arthritis (RA) patients to conceive¹⁾. Age, nulliparity, disease activity, NSAIDs, corticosteroid was known as the risk factors of subfertilities²⁾. On the other hand, anti-TNF inhibitor (adalimumab) combined with or without immunoglobulin was reported to improve the outcome of infertility treatment³⁾. We examine the impact of biologic (bDMARDs) treatment on conception and delivery complicated with rheumatoid arthritis.

Methods: We investigated 25 cases (15 cases which had continued bDMARDs until conceiving; group A, 10 cases which discontinued both bDMARDs and conventional synthetic DMARDs at the time of hope to conceive; group B) retrospectively on the period of conception, the disease activity of RA and perinatal outcomes.

Results: Between two groups, disease activities at the time of planning for pregnancy and conceiving were no significant difference. The average period of conception was 6.14±3.80 months in group A, which was shorter than 11.89±6.21 months in group B ($P=0.024$, figure 1). The average birth weight of the babies in group B was 2446.57±375.73, significantly smaller than 2956.60±506.86 in group A ($P=0.039$, figure 2). However, the average gestational week was 38.58±1.16 in group A, which was not different from 38.00±1.41 in group B. There was no significant difference on the rate of abortion, preterm birth, LFD (light for date), premature rupture of membrane between two groups. In the cases of preterm birth and LFD

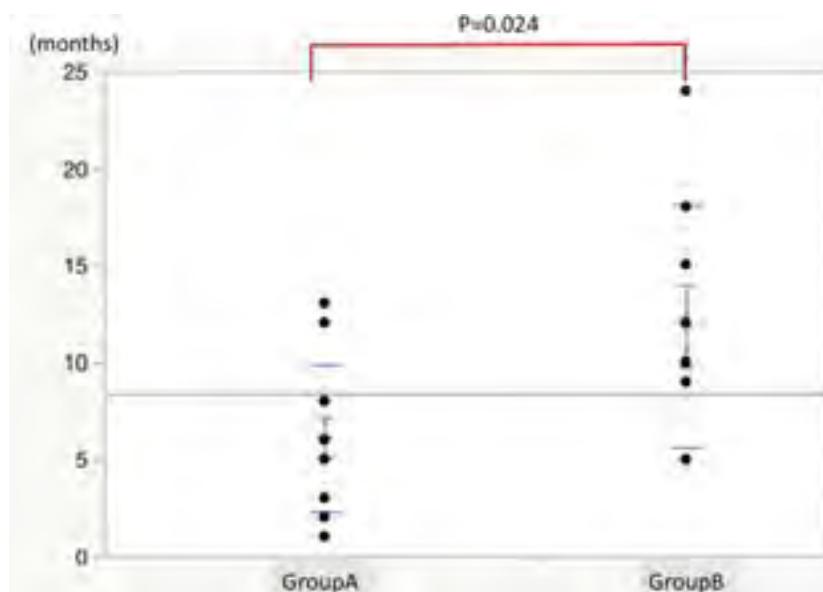


Figure1. Period from planning to getting pregnancy

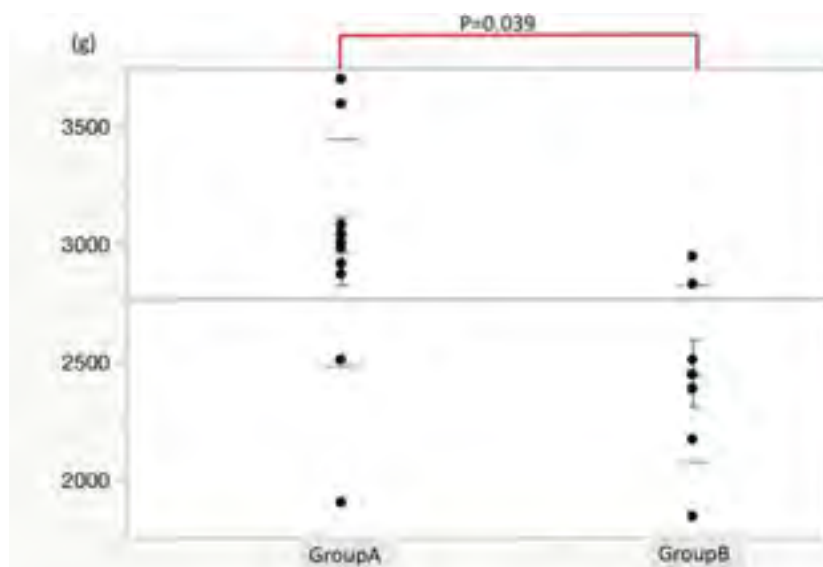


Figure2. birth weight

babies, the average dose of corticosteroid during pregnancy was significantly higher than those of full-term birth and no LFD babies ($P=0.028$, 0.013 respectively).

Conclusion: In RA patients who hope pregnancy, continuing bDMARDs at the time of pregnancy had the advantage in conceiving earlier. Using bDMARDs before pregnancy has an influence on perinatal complications and development of their babies.

Reference: 1) Jawaheer D et al. *Arthritis Rheum.* 2011 Jun;63(6):1517-21
2) Brouwer J et al. *Ann Rheum Dis.* 2015;74:1836-184
3) Winger EE, et al. *Am J Reprod Immunol.* 2009 Feb;61(2):113-20

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Abstract Number: 2426

Defining a Standardized Core Data Set for Pregnancy Registers in Rheumatic Diseases – an European Approach

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Background/Purpose: Robust data on the outcomes of pregnancy and influence of drug exposure in various inflammatory rheumatic diseases (IRD) are needed. Joint analyses of data from different databases could overcome the issue of small study sizes in single databases. A prerequisite for collaborative analyses would be a common core data set, collected by every collaborator. The objective was to develop a core data set for observational research to measure pregnancy course and outcomes of women with IRD.

Methods: The European Network of Pregnancy registers in rheumatology (EuNeP) consists of scientists who run pregnancy registers, namely EGR2 (France), RePreg (Switzerland), REVNATUS (Norway) and Rhekiss (Germany). During a face-to-face meeting involving all principal investigators of the 4 registers, the scope and core areas of the core data set have been developed according to COS-STAD recommendations¹ by consensus. Furthermore, the steps for developing a core data set, the consensus process and cut offs, as well as participants to be invited have been determined.

Results: The scope was defined as follows: 'To develop a standardized core data set for data collection in prospective observational research and clinical care of pregnant women with IRD. All interventions the women receive will be covered. Patients should be enrolled at the earliest possible moment during pregnancy, and data should ideally be collected once every trimester'. Three core areas were described: 'Maternal information' (including demographics, comorbidities and IRD disease characteristics), 'Treatment' (including medications of IRD and other health conditions) and 'Pregnancy' (including prior and actual pregnancy(ies), delivery and infant outcomes).

An initial list of data items possibly relevant for pregnancy registers will be generated based on (I) data items already collected by registers participating in EuNeP, (II) a systematic literature search and (III) results of a survey among patient representatives regarding their needs during pregnancy. Consensus about the importance of each data item to be included in a final core data set will be reached by applying a 2-step Delphi survey. For each item, the importance must be rated on a numeric scale from 1 to 9 (1-3 = low importance, 4-6 = important but not critical, 7-9 = critical importance). Any data item achieving at least 70% of responses as critical will be included in the core data set. Participants involved in the Delphi survey will be (a) the steering committee of EuNeP, (b) a working group of at least 30 experts in the areas of rheumatology, internal medicine, epidemiology and other health professions, and (c) patient representatives.

So far, the protocol has been set up and finalized, the literature search is currently performed. The first step of the Delphi survey will be presumably undertaken in mid-2018, preliminary results are expected to be available at time of the ACR congress.

Conclusion: A core data set which standardizes the data collection of pregnancy registers in rheumatology will facilitate collaborative analyses of different data sources.

¹Kirkham et al., PLoS Med. 2017 Nov 16;14(11):e1002447.

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Abstract Number: 2427

Adequate Vaccine Response According to the Italian Schedule Among the Offspring of Women Affected By Rheumatoid Arthritis and Treated throughout Pregnancy By Certolizumab Pegol: Case Series

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Background/Purpose: Certolizumab pegol (CTZ) is a TNF α inhibitor indicated for the treatment of women affected by rheumatoid arthritis (RA) throughout the whole pregnancy. Some concern, regarding a possible immunosuppression of the newborns, still exists. We aimed to assess the immune response and the presence of infective adverse events among the long-term followed-up offspring of RA mothers, treated by CTZ during pregnancy.

Methods: In a 4-years observational gap, we prospectively enrolled 12 newborns born to RA women that signed an informed consent about children recruitment. The outcomes were a 24-months follow-up of the offspring health status, including infections, and, in case of routine/emergency lab test, assessment of the vaccine response according to the administered ones: equivalent diphtheria, tetanus, acellular pertussis, inactivated poliovirus, Haemophilus influenza type b and Hepatitis B virus combined vaccine (DTaP-IPV/Hib/HBV). Immune response was assessed by the following: anti-PRP antibodies (Abs) to Hib, diphtheria antitoxin and polio virus Abs, by neutralisation assays. Tetanus, pertussis and Anti-HBs Abs by ELISA (Thermo Fisher Scientific, Cleveland, OH, USA). The serology response was compared to the general population by Kruskal-Wallis and reverse regression curves statistical analyses (SAS V.6.12, Chiltern International Limited, Berkshire, UK). The immunogenicity cutoffs were set according to literature references.

Results: Among the 12 children constituting the study population, 2 had to be investigated for suspected infections and one for an episode of foreign body ingestion. According to the protocol, a blood sample taken from the planned lab tests, was sent for the assessment. Hib: the proportion of observed infants with an anti-PRP level >0.15 mg/ml was 93.2% (95% CI 86.6 to 96.7) compared with 100% (95% CI 96.4 to 100) to the reference population. The difference was 6.8% (90% CI 2.8 to 12.1). Regarding diphtheria-tetanus, pertussis, polio and HBV, the protective responses (respectively: >0.01 IU/ml, >0.01 IU/ml, >1:8 and ≥ 10 mIU/mL) were 99% in the study population. As the upper bound of the 90% CI was >10%, this difference confirms the non-inferiority of immune response for these children.

Conclusion: Our data are limited, since an ethical issue rises from proposing a series of blood draws to pediatric population. Regarding the reasons of consultations, to notice that none of them suffered from serious infections requiring hospitalization or parenteral antibiotic administration. The vaccine schedule was reported as well tolerated. Their immune response, finally, was shown to be adequate and superposable to the healthy population, including the administration of an alive vaccine (polio). These results further confirm the long-term overall safety of CTZ administration during pregnancy of RA patients, regarding both the mothers and their offspring.

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Correlation between Antibodies to the Phosphatidylserine/Prothrombin Complex (aPS/PT) and Anti- β 2 glycoprotein-1-Domain 1 (anti- β 2 GP1-D1) and Vascular Thrombosis (VT) and/or Pregnancy Morbidity (PM)

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Background/Purpose: aPS/PT is considered to be a risk factor for vascular thrombosis (VT) and/or pregnancy morbidity (PM). Anti- β 2GP1-D1 is potentially superior to anti- β 2GP1 in predicting VT/PM. We examined the correlation between aPS/PT and anti- β 2GP1-D1 and the laboratory criteria for antiphospholipid antibody syndrome (APS): lupus anticoagulant (LAC), anticardiolipin (aCL), and anti- β 2GP1 and their association with VT/PM.

Methods: Multiple serum samples from patients fulfilling the ACR or Systemic Lupus International Collaborating Clinics (SLICC) Criteria for SLE were analyzed for aPS/PT (IgG/IgM) by ELISA (QUANTA Lite, Inova Diagnostics), anti- β 2GP1-D1 by chemiluminescence immunoassay (QUANTA Flash, Inova), LAC using tissue thromboplastin inhibition test and dRVVT, and aCL (IgG) and anti- β 2GP1 (IgG) by ELISA. VT/PM was based on patient self-report and confirmed by chart review. VT included arterial, venous, or small vessel thrombosis; PM included \geq one fetal death >10 weeks, \geq one premature birth <34 weeks or >3 spontaneous abortions <10 weeks.

The Spearman correlation between aPS/PT and anti- β 2GP1-D1 and the conventional AP autoantibodies and between each autoantibody and VT/PM was calculated. The association between number of autoantibodies and VT/PM was assessed using univariate logistic regression.

Results: 199 patients were included, of which 64 had had VT/PM (Table 1). The percentage of patients ever positive for aPS/PT, anti- β 2GP1-D1, LAC, aCL, and anti- β 2GP1 was significantly higher among those with VT/PM (Table 1). The correlation (95% CI) between IgG aPS/PT and LAC, aCL, anti- β 2GP1, and anti- β 2GP1-D1 was 0.54 (0.43, 0.64), 0.40 (0.27, 0.51), 0.43 (0.30, 0.54) and 0.28 (0.14, 0.42), respectively (Table 2). The correlation between IgM aPS/PT and LAC, aCL, anti- β 2GP1 and anti- β 2GP1-D1 was 0.43 (0.31, 0.54), 0.16 (0.02, 0.30), 0.25 (0.11, 0.38) and 0.24 (0.09, 0.38). The correlation between anti- β 2GP1-D1 and LAC, aCL and anti- β 2GP1 was 0.28 (0.13, 0.42), 0.55 (0.43, 0.64) and 0.61 (0.50, 0.69). The correlation between IgG aPS/PT, IgM aPS/PT, anti- β 2GP1-D1, LAC, aCL, and anti- β 2GP1 and VT/PM was 0.17 (0.03, 0.30), 0.05 (-0.09, 0.19), 0.21 (0.06, 0.35), 0.22 (0.08, 0.35), 0.22 (0.08, 0.35) and 0.24 (0.10, 0.37), respectively. The odds (95% CI) of VT/PM increased incrementally by 46% for each additional autoantibody (1.15, 1.86).

Table 1: Demographics and Clinical Characteristics of Cohort at last Follow-up (n = 199)

	VT/PM +ve (n=64)	VT/PM -ve (n=135)
Age, mean, yrs	51.6	47.5
Disease duration, mean, yrs	16.4	13.2
Female, %	89.1	94.1
Ethnicity, % Caucasian	68.9	55.7
SLEDAI-2K	3.9	3.3
SDI	2.7*	1.0*
Medications, % currently using		
Antimalarials	81.5	83.5
Steroids	41.5	26.2
Immunosuppressants	37.0	33.0
Biologics	1.9	0
Anticoagulants, % ever on	72.4* (for VT only)	5.9*
Autoantibodies, ever +ve %		
ANA, %	90.9	85.4
Anti-dsDNA, %	54.3	40.9
SSA/Ro60	37.8	35.9
SSB/La	13.3	16.3
Sm	28.9	15.2
U1-RNP	28.9	25.0

Table . (Cont'd)

	VT/PM +ve (n=64)	VT/PM -ve (n=135)
LAC	24.6*	8.3*
aCL	21.9*	6.8*
anti-β2GP1	23.4*	6.9*
aPS/PT (IgG)	26.7*	13.0*
aPS/PT (IgM)	33.3	28.2
anti-D1-β2GP1	13.2*	2.6*
≥ 1 Vascular thrombosis, %	90.6	-
≥ 1 Pregnancy morbidity, %	12.5	-

*Significant differences at 95% CI. Table 2: Correlation between aPS/PT and anti-D1- β2GP1 and antiphospholipid antibodies (95% CI)

	aPS/PT (IgG) +ve	aPS/PT (IgM) +ve	anti-D1-β2GP1 +ve
LAC	0.54 (0.43, 0.64)	0.43 (0.31, 0.54)	0.28 (0.13, 0.42)
aCL	0.40 (0.27, 0.51)	0.16 (0.02, 0.30)	0.55 (0.43, 0.64)
anti-β2GP1	0.43 (0.30, 0.54)	0.25 (0.11, 0.38)	0.61 (0.50, 0.69)
anti-D1-β2GP1	0.28 (0.14, 0.42)	0.24 (0.09, 0.38)	-

Conclusion: IgG aPS/PT and anti-β2GP1-D1 are highly correlated with other AP antibodies, which along with the accepted criteria of APS, are all similarly correlated with VT/PM. IgG aPS/PT and anti-β2GP1-D1 should be considered as criteria for APS.

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Abstract Number: 2429

Long-Term Outcome of Children Born to Mothers with Chronic Arthritis and Exposed to TNF-Inhibitors during Pregnancy: A Case-Control Study

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SESSION INFORMATION

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Background/Purpose: Treatment with tumor necrosis factors inhibitors (TNFi) during pregnancy may be required to control maternal disease which can be a threat for maternal-fetal well-being. Information about the follow-up of *in utero* exposed offspring is limited. Aim of this study was to compare health and developmental conditions of children born to mothers with chronic arthritis exposed *in utero* to TNFi with those of unexposed children born to patients with same age and disease.

Methods: Clinical characteristics, pregnancy outcomes were analyzed. An *ad-hoc created* questionnaire was used to collect data on birth and growth parameters, breastfeeding, weaning, developmental milestones, vaccinations and illnesses.

Results: 122 live births in 98 women with chronic arthritis (64 RA, 34 SpA) were observed: 59 pregnancies exposed to TNFi (group A) at conception and 63 pregnancies TNFi-naïve (group B). In 57/59 (group A) pregnancies, TNFi was discontinued at positive pregnancy index as a *general measure* in our Pregnancy Clinic for patients in remission or stable low disease activity. In 2/59 pregnancies TNFi was maintained throughout pregnancy due to active disease at conception.

TNFi was restarted in 16/57 pregnancies (12 etanercept-ETA, 3 certolizumab-CTZ, 1 adalimumab) during the 2nd-3rd trimester due to moderate-severe flare (median exposure 84 days; discontinuation of TNFi between 32-37 gestational weeks). In group B, TNFi (1 ETA, 1CTZ) was introduced in 2/63 pregnancies during the 2nd trimester due to a severe flare. Three flares in 3/63 pregnancies were managed with an increase of prednisone dosage (max 10mg/day). 7 children, exposed to TNFi during 2nd-3rd trimester, were exposed to TNFi (3 CTZ, 3 ETA, 1 golimumab) also during breastfeeding. To investigate the long-term follow-up of children exposed in utero to TNFi, 20 children exposed during 2nd-3rd trimester (median age 29 months) and 20 unexposed children (median age 43 months) were compared (Table 1). No significant differences in growth parameters and developmental milestones were observed. No excess nor particular pattern of congenital defects/malformations were observed. In both groups, vaccinations were performed according to the national schedule (no live vaccines in the first year of life) without relevant complications.

Table 1. Maternal disease characteristics, neonatal outcomes and long-term follow up of children born to patients with chronic arthritis according to the in utero exposure to TNFi.

	Pregnancies exposed to TNFi (n=20)	Pregnancies w/ unexposed to TNFi (n=20)	P value
Maternal characteristics at conception			
Age, yrs	33 (30-36)	32 (30-34)	0.35
Nulliparus, n (%)	11(55)	4(20)	0.02
Previous pregnancy losses, n (%)	7(35)	6(30)	0.74
BMI, median (IQR)	21(20-24)	22(21-25)	0.45
No smokers, n (%)	10(50)	18 (90)	1
Rheumatoid arthritis n (%)	11(55)	11(55)	
Spondylarthritis n (%)	0(45)	0(45)	
Disease duration, mths, median (IQR)	78(34-126)	48(24-89)	0.4
ACPA pos. n (%)	7(35)	7(35)	1
RF pos. n (%)	7(35)	5(25)	0.48
aPL pos. n (%)	3(15)	2(10)	0.63
DAS28, median (IQR)	2.56(2.42-2.67)	2.74(2-2.92)	0.72
CRP, g/L, median (IQR) (n.v. <5)	3(3-4.25)	4(3-6.9)	0.70
ETA	14(70)	-	
ADA	1(5)	-	
CTZ	2(10)	-	
GOL	1(5)	-	
Prednisone dose, median (IQR) n (%)	2.5(0-4.8)	2.5(0-5)	0.85
HCQ, n (%)	12(60)	10(50)	0.52
SSZ, n (%)	4(20)	7(35)	0.28
CyA, n (%)	0	2(10)	0.48
LDA and/or LMWH, n (%)	0	1(5)	1
Breastfeeding, yes, n (%)	7(35)	4(20)	0.28
Duration, mths	7(4-11)	5(2-7)	0.40
Interruption due to drug intake	6(30)	7(35)	0.73
Fetal outcomes			
Delivery			
-gestational week, median (IQR)	37(36-39)	39(38-39)	0.58
-pre-term delivery (<37 w), n (%)	6(30)	3(15)	0.20
-vaginal delivery, n (%)	11(55)	8(40)	0.28
-induced delivery, n (%)	1(5)	2(10)	0.50
-cesarean section, n (%)	4(20)	6(30)	0.44
Birth			
-year (range min-max)	2015(2005-2017)	2014(2006-2017)	
-male sex, n (%)	7(35)	15(75)	0.25
-weight, g, median (IQR)	3160(2750-3370)	3345(1902-3740)	0.68
-length, cm, median (IQR)	48(47-50)	50(49-52)	0.45
-head circumference, cm, median (IQR)	34(34-35)	33(33-35)	0.31
-SGA, n (%)	2(10)	5(25)	0.86
-APGAR score 1 min, median (IQR)	8 (n=2), 9 (n=10), 10 (n=2)	8 (=1), 9 (=10), 10 (=2)	0.99
-APGAR score 5 min, median (IQR)	8 (=1), 9 (=3), 10 (=10)	9 (=1), 10 (=9)	
Disease at birth	2 perinatal infections 1 respiratory distress 1 cryptorchidism	1 Ventricular Septal Defect, Patent Foramen Ovale, lumbar arivertebral fusion 1 Chiari malformation 1 supernumary finger	
Children follow up			
Age at interview, mths, median (IQR)	29(12-52)	43(24-67)	0.41
Breastfeeding duration, mths, median (IQR)	6(3-11)	5(3-7)	0.67
Age at weaning age, mths, median (IQR)	6(5-6)	4(4-6)	0.53
Reactions to vaccinations (performed according to the vaccination schedule for childhood)	1 post MPR (measles, mumps, and rubella); fever, rash and conjunctivitis	0	
Weight			
-at 6 mths, g	7,550(6,912-7,982)	7,800(6,445-8,087)	0.92
-at 12 mths, g	10,025(10,9240-10,950)	9,270(8,890-10,985)	0.49
-at 24 mths, g	10,850(10,700-11,250)	11,560(10,667-12,305)	0.48
Length			
-at 6 mths, cm	66.75(65-75)	66.6(66-64)	0.97
-at 12 mths, cm	75(73-78)	76(71-77)	0.25
-at 24 mths, cm	83(81-83)	85(78-87)	0.11
Head circumference			
-at 6 mths, cm	42(42-44)	42(41-43)	0.92
-at 12 mths, cm	46(44-49)	45(43-46)	0.66
Age at seated position, mths	6(7-6)	6(6-6.25)	0.16
Age at walking, mths	12(14-11)	12(11-14)	0.97
Age at speaking (simple sentences), mths	14(12-24)	20(13-24)	0.96
Pathological conditions during the first year of life	1 oral mucositis 1 hand foot and mouth disease 1 carious molar 1 cryptorchidism surgery 1 anal fissure	1 hydrocephalus and testicular hydrocele 1 alopecic dermatitis 1 inguinal hernia	
Pathological conditions after the first year of life	1 autism spectrum disorder	1 speech delay	

ACPA, anti-citrullinated protein antibodies; ADA, adalimumab; aPL, anti-phospholipid antibodies; BMI, body mass index; CRP, C-reactive protein; CTZ, certolizumab; CyA, Cyclosporine A; DAS28, Disease Activity Score in 28 joints; ETA, etanercept; GOL, golimumab; HCQ, hydroxychloroquine; IQR, interquartile range; LDA, low-dose aspirin.

Conclusion: One third of women with chronic arthritis who discontinued TNFi at positive pregnancy test experienced a moderate-severe flare during pregnancy and resumed TNFi. Thanks to the control of maternal disease, pregnancy outcomes were comparable to those of TNFi-naïve pregnancies in which the frequency of flares was low. Children exposed to TNFi had normal growth parameters and did not have severe infections during the first year. These data suggest that TNFi during pregnancy is effective in controlling maternal disease and ensures a good pregnancy outcome without complications to offsprings.

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Abstract Number: 2430

Pregnancy in Women with Ankylosing Spondylitis Is Not Associated with Poor Obstetric Outcomes: Analysis of Nationwide Inpatient Sample Database 2003-2011

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SESSION INFORMATION

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Background/Purpose: Outcomes of pregnancy are well studied in a number of rheumatic diseases such as Rheumatoid Arthritis (RA) and systemic lupus erythematosus. When compared, there is very limited data in pregnancy outcomes in patients with spondyloarthritis and in particular ankylosing spondylitis (AS). This study was undertaken to determine the frequency of complications occurring during pregnancy for women with AS and to compare these outcomes with the general obstetric population by using the largest inpatient care database.

Methods: By using the 2003-2011 Nationwide Inpatient Sample of Healthcare Cost and Utilization Project, we estimated the number of obstetric hospitalization, deliveries and caesarean deliveries in women between the age group 18-50 years.

Table 1. Obstetric Outcomes for Pregnancy Related Hospitalizations in Ankylosing Spondylitis					
	Total	AS	Controls	OR	p-value
Number of Pregnancies	42317648	2538	41315110	N/A	N/A
Mean Age		29.96	27.32		<0.001
Fetal Death	259227	14(0.6%)	259213(0.6%)	1.126	0.873
Inpatient Mortality	9628	0	9628 (0%)	N/A	0.986
IUGR	774439	54(2.1%)	774385(1.8%)	0.951	0.769
Pre-term delivery	2798720	159(6.3%)	2798561(6.6%)	0.996	0.961
Cesarean-delivery	11857999	696 (27.4%)	11857303(28%)	0.873	0.008
PROM	1456335	93(3.7%)	1456242(3.4%)	0.759	0.047
Hypertensive Diseases	3757992	250(9.9%)	3757742(8.9%)	0.818	0.029
PPH	1106419	34(1.3%)	1106385(2.6%)	0.390	0.000
APH	863232	55(2.2%)	863177 (2%)	1.292	0.061
Abbreviations: AS: Ankylosing Spondylitis, OR: Odds Ratio, IUGR: Intra-uterine Growth Retardation, PROM: Premature Rupture of Membranes, APH: Ante-partum Hemorrhage, PPH: Post-partum Hemorrhage					

Patients hospitalized with AS were identified. Demographic characteristics and in-hospital outcomes were recorded for both AS and control group. Maternal and pregnancy complications for all pregnancy-related admissions for women with and without AS were compared. Multivariate logistic regression analysis was used to obtain adjusted odds ratio (OR).

Results: The total number of obstetric hospitalization was 42.32 million, of which 2538 were women with diagnosis of AS. Mean maternal age of AS population was higher (29.96 years) than the control group (27.32years). After adjusting for potential confounders, the results in this analysis show that maternal AS population had no significant increase of inpatient mortality or fetal death. Prevalence of preterm delivery and intrauterine growth retardation was also similar among the two groups. Interestingly, the odds of hypertensive diseases and premature rupture of membranes, postpartum hemorrhage and cesarean delivery in AS patients were significantly lower. The results do suggest that AS patients may have a higher risk of antepartum hemorrhage, but the results failed to achieve statistical significance. The frequencies of the above outcomes along with Odds Ratio are provided in Table 1.

Conclusion: Based on our study of national cohort, we conclude that pregnancies in women with AS are relatively safe without any increase in maternal or fetal mortality despite having a higher maternal age. These data are further reassuring that AS patients also do not have higher risk of adverse outcomes of pregnancy than women without AS. This is significantly in contrast to the worse outcomes observed in RA patients in the same analysis and available literature. We suggest that in women with AS, close antenatal and post-delivery monitoring pregnancy be performed but these patients are likely to do well. Further studies are needed to examine these findings in a prospective manner.

Disclosure: V. Majithia, None; S. Kishore, None.

Abstract Number: 2431

Birth Outcomes and Disease Activity during Pregnancy in a Prospective Cohort of Women with Psoriatic Arthritis and Ankylosing Spondylitis

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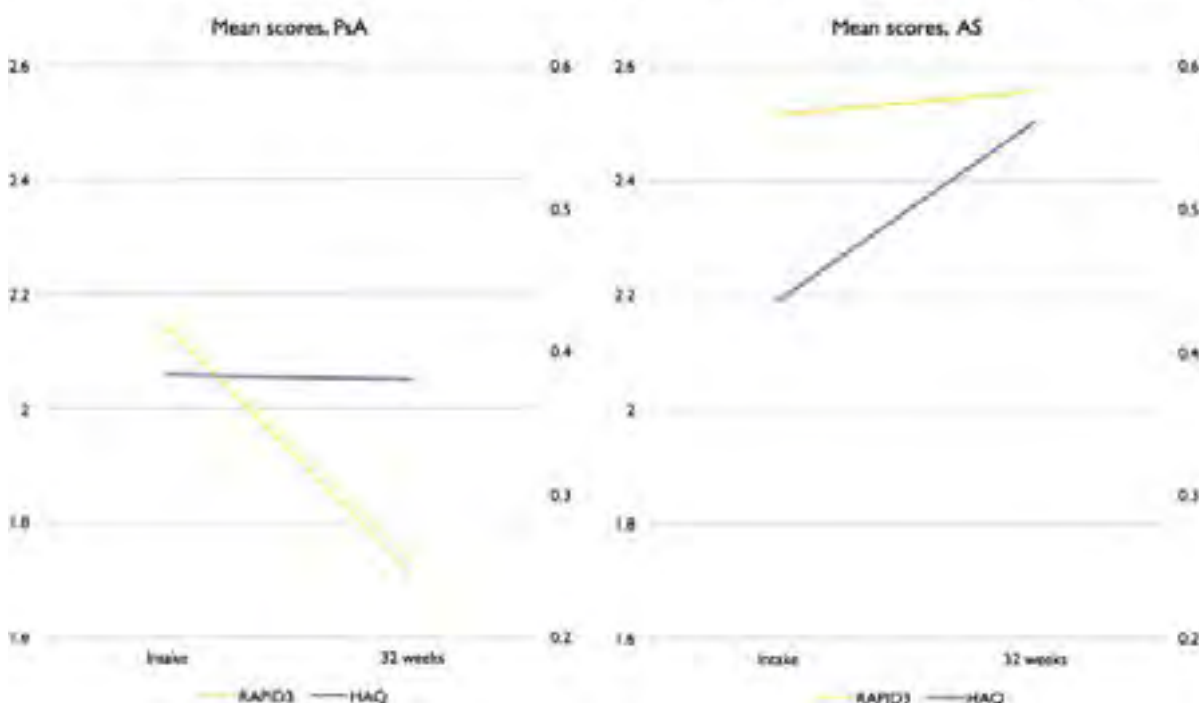
Background/Purpose: The goal of this prospective cohort study is to add to the limited data on birth outcomes in psoriatic arthritis (PsA) and ankylosing spondylitis (AS) and to describe patterns of disease activity during pregnancy in these diseases.

Methods: Women enrolled as part of the Organization of Teratology Information Specialists (OTIS) Autoimmune Disease in Pregnancy Project before 20 weeks gestation from 2004-2018. Delivery of at least one live-born infant was eligibility criteria for analysis. Data on pregnancy events, medications, disease activity, and outcomes were obtained by maternal report and validated by medical records. Disease activity was calculated by the Health Assessment Questionnaire (HAQ) or Routine Assessment of Patient Index Data 3 (RAPID3). Poisson regression with robust standard errors was used to estimate risk ratios (RR), multivariable adjusted risk ratios (aRR) and their 95% Confidence Intervals (CI).

Results: In this large prospective cohort analysis, PsA was associated with an increased risk for moderate preterm delivery (aRR 1.81, 95% CI 1.01-3.26), preterm labor (aRR 2.05, 95% CI 1.21-3.48), oligohydramnios (aRR 3.79, 95% CI 1.34-10.74), and caesarian section (aRR 1.63, 95% CI 1.26-2.12), versus healthier comparison women. The AS group had an increased risk for very preterm delivery (aRR 10.19, 95% CI 2.09-49.78), very low birth weight (aRR 11.02, 95% CI 2.24-54.12), and infant hospitalization in NICU (aRR 1.67, 95% CI 1.05-2.67). Disease activity over the course of pregnancy was either stable (by HAQ) or improved (by RAPID3) in PsA, whereas in AS it slightly worsened with both measures, although changes were small in both disease groups (see Figure 1).

Conclusion: Pregnant women with PsA and AS are at increased risk for some adverse pregnancy outcomes. Disease activity is relatively stable over pregnancy, with slight improvement in PsA and slight worsening in AS, although varying by measure of disease activity used. Further analyses would be useful to tease out the role of disease activity and medications on these outcomes.

Figure 1. Trends in disease activity during pregnancy in PsA and AS



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Abstract Number: 2432

Peripartum Issues in the Inflammatory Arthritis (IA) Patient: A Survey of the Rapport (Rheumatoid Arthritis Pharmacovigilance Program and Outcomes Research in New Therapies) Registry

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Background/Purpose: Multiple issues surround the peripartum period for IA patients including medication use, risk of disease flare and potential impact on neonatal outcomes. We aimed to better understand these issues by surveying childbearing women with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) in a biologic registry.

Methods: A retrospective survey of 440 peripartum females of less than 50 years of age with RA or PsA in the RAPPORT registry was performed using an anonymous electronic-based RedCap survey. Descriptive statistics and Fisher's exact test were used to analyze the results.

Results: 162 patients (133 RA/29 PsA) completed the survey (103 women having 234 pregnancies), 164 pregnancies occurring before and 70 pregnancies occurring after IA diagnosis. Pregnancy outcomes from 103 patients included: 96% live births, 1.9% stillbirths, 23% miscarriages, and 15% therapeutic abortions. A third of patients had fewer children than desired due to IA disease activity, medications and other reasons. For 63 pregnancies after IA diagnosis: (1) 49% of pregnancies received pre-conception counseling; (2) most described good IA disease control during pregnancy but flared in the first 3 months postpartum; (3) 79% of pregnancies discontinued IA medications; (4) 35% of pregnancies occurred on

biologic therapy at or prior to conception. Gestational age at time of delivery was 37-40 weeks in 58% (33/57) post-IA vs 66% (83/126) pre-IA diagnosis pregnancies. No statistically significant differences occurred between pregnancies before or after IA diagnosis for: pregnancy planning, fertility treatment, pregnancy and labour/delivery complications, birth defect frequency or neonatal complications. Neonatal ICU admissions were significantly lower in pre-IA diagnosis pregnancies compared to post-IA diagnosis pregnancies. No pregnancy complications were noted in 24/54 pregnancies on medications compared to 6/9 pregnancies not on medications.

Conclusion: Women with RA and PsA are faced with multiple peripartum issues emphasizing the importance of informed decision-making before, during and after pregnancy. Table 1. Characteristics of RAPPORT Survey Patients

Type of IA # (%)	RA PsA	133 (82.1) 29 (17.8)
Age Range (years)	< 19 20-30 31-40 41-50	1 (0.6) 17 (10.5) 55 (34) 89 (36.4)
Antibodies # (%)	RF+ Anti-CCP + RF & anti-CCP + Do not recall	59 (36.4) 6 (3.7) 13 (8) 84 (51.9)
Pregnancy Outcomes # (%)	Live Births Stillbirths Miscarriages Abortions	99 (96) 2 (1.9) 23 (22.3) 15 (14.5)
Total # pregnancies per patient # (%)	1 2 3 4 5-6	29 (27.2) 40 (38.8) 23 (22.3) 6 (5.8) 6 (5.8)

Table 2. Detailed Pregnancy Outcomes

	All patients with pregnancies Mean +/- SD	Patients with less children than desired (34/103) Mean +/- SD	Patients with expected number of pregnancies (69/103) Mean +/- SD
Total pregnancies	2.27 +/- 1.18	1.97 +/- 1.36	2.42 +/- 1.46
Live pregnancies	1.78 +/- 0.83	1.41 +/- 1.03	1.96 +/- 1.11
Stillbirths	0.03 +/- 0.14	0.03 +/- 0.41	0.02 +/- 0.08
Miscarriages	0.29 +/- 0.64	0.38 +/- 0.56	0.26 +/- 0.45
Therapeutic abortions	0.17 +/- 0.45	0.15 +/- 0.49	0.19 +/- 0.49

Table 3. Pregnancy variables in pre-and post IA pregnancies

	Number (%) of pregnancies prior to IA diagnosis	Number (%) of pregnancies post IA diagnosis	P value
Planned pregnancy	107 (69.9)	46 (73.0)	P=0.74
Time to pregnancy 0-2 months	49 (45.8)	19 (41.3)	P=0.72
Infertility treatment	13 (8.7)	2 (3.2)	P=0.24
37-40 weeks Gestational age at delivery	83 (65.8)	33 (57.9)	P=0.32
No pregnancy complications	86 (56.2)	30 (47.6)	P = 0.29
Labour and delivery complications	28 (22.2)	15 (26.3)	P =0.58
C-section Delivery	27 (21.3)	17 (29.8)	P=0.26
Low birth weight (<2.5kg)	6 (4.8)	4 (7.0)	P=0.50
Breast feeding	96 (76.2)	46 (80.7)	P=0.57
Birth defects	8 (6.3)	3 (5.5)	P=1.00
Neonatal medical complications	19 (15.1)	12 (21.8)	P=0.29
Neonatal ICU admissions	4 (3.2)	8 (14.5)	P=0.0082

Disclosure: T. Dissanayake, None; S. Keeling, None; W. P. Maksymowych, CaRE arthritis, 9.

Abstract Number: 2433

Pregnancy Outcomes in Undifferentiated Connective Tissue Disease- a Single Academic Center's Experience

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Session Type: ACR Poster Session C

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Background/Purpose: SLE patients have poorer pregnancy outcomes than healthy patients, including a lower rate of live birth and higher rates of small for gestational age (SGA) infants, preeclampsia, hypertension, Cesarean delivery (C-section), neonatal intensive care unit (NICU) admissions, and prematurity. In contrast, there are limited data regarding pregnancy outcomes for women with undifferentiated connective tissue disease (UCTD). Most prior studies include pregnant women identified through a screening questionnaire from among healthy women, making these populations different from women with known UCTD who are followed by a rheumatologist.

Methods: Between 2008 and 2017, patients with UCTD and SLE at an academic medical center were recruited to a prospective pregnancy registry. UCTD was defined a positive autoantibody plus symptoms consistent with a connective tissue disease but not meeting criteria for another rheumatic diagnosis. SLE was defined by ACR or SLICC classification criteria. Data were collected prospectively at baseline, during pregnancy, and post-partum. Disease activity was determined by physician global assessment (PGA) score and classified as low, medium, or high. Differences in proportions were estimated by Fisher's exact test. Differences in continuous variables were estimated by t-test or Wilcoxon rank-sum test, depending on the distribution of the data. Data were analyzed using SAS 9.4 (Cary, NC).

Results: We analyzed 51 UCTD pregnancies and 142 SLE pregnancies (Table 1). There were significantly more Caucasian patients with UCTD and significantly more black patients with SLE. Anti-Ro antibodies were the most common autoantibodies in both groups, and anti-RNP antibodies were second most common in the SLE group. Antiphospholipid syndrome was uncommon in both groups. Hydroxychloroquine was prescribed to most patients. A minority of UCTD patients and slightly less than 50% of SLE patients took steroids in any form. Disease activity was low in most patients, but the disease activity of SLE patients was higher. There was no significant difference in the rate of prematurity. More SLE patients had preeclampsia and SGA infants. Nearly 30% of infants born to SLE patients were admitted to the NICU. In models adjusted for race, having SLE was associated with an increased risk of preeclampsia, SGA, and preterm birth. One infant with complete heart block was born to a woman with SLE. Treatment with dexamethasone reversed early stage heart block in 5 cases.

Conclusion: Compared to women with SLE, women with UCTD have a lower rate of preterm delivery and preeclampsia, and their offspring are less frequently small for gestational age or admitted to the NICU. This data suggests that with appropriate screening, treatment, and monitoring, women with UCTD can have pregnancy outcomes comparable to those of healthy women. Table 1. UCTD and SLE Pregnancy Outcomes Data

	UCTD	SLE	p-value
Number of patients	47	127	
Number of pregnancies	51	142	
Demographics			
Age, mean (SD)	31.4 (5.5)	30.0 (5.4)	0.1
Age, range	17-42	20-45	
Race			
Black	10 (20.0%)	72 (50.7%)	0.0002
White	34 (68.0%)	60 (42.3%)	0.002
Antibodies			
Ro positive, n (%)	18/49 (36.7%)	74/141 (52.5%)	0.07
La positive, n (%)	9/48 (18.8%)	23/141 (16.3%)	0.7
RNP positive, n (%)	5/48 (10.4%)	61/140 (43.6%)	<0.0001
Sm positive, (%)	0/48 (0%)	44/139 (31.7%)	<0.0001
Antiphospholipid antibody positive ¹ ever, n (%)	4 (10.5%)	24 (18.8%)	0.3
Antiphospholipid antibody syndrome, n (%)	0/38 (0%)	5/128 (3.5%)	0.3
Medications			
Antihypertensive medicine, n (%)	5 (9.8%)	25 (17.6%)	0.3
Aspirin, n (%)	25 (49.0%)	106 (74.7%)	0.002
Anticoagulation, n (%)	2 (3.9%)	18 (12.7%)	0.1
Steroids (any form), n (%)	9 (17.7%)	68 (47.9%)	0.0001
Dexamethasone for early heart block, n (%)	1 (2.0%)	5 (3.5%)	1
Azathioprine, n (%)	0 (0%)	30 (21.1%)	<0.0001
Hydroxychloroquine, n (%)	33 (64.7%)	119 (83.8%)	0.009
No medications, n (%)	8 (15.7%)	3 (2.1%)	0.001
Disease Activity ²			0.01
High	1 (2.0%)	18 (12.7%)	
Moderate	9 (17.7%)	40 (28.2%)	
Low	41 (80.4%)	84 (59.2%)	
Pregnancy Outcomes			
Pregnancy loss (total), n (%)	4 (7.8%)	19 (13.4%)	0.4
Weeks gestational age at birth, mean (range)	37.7 (27-40)	36.8 (24-40)	0.06
Preterm, n (%)	8 (17.0%)	36 (29.3%)	0.1

Table . (Cont'd)

	UCTD	SLE	p-value
Small for gestational age, n (%)	3/45 (6.7%)	39/118 (33.1%)	0.0005
Preeclampsia or eclampsia, n (%)	2/41 (4.9%)	25/118 (21.2%)	0.02
NICU, n (%) (n=132)	4/36 (11.1%)	27/96 (28.1%)	0.04
Complete heart block, n (%)	0/47 (0.0%)	1/123 (0.8%)	1.0

¹Anticardiolipin or beta-2-glycoprotein I IgG or IgM level >40 is considered positive

²Highest disease activity recorded in pregnancy

Disclosure: K. Kaufman, None; A. M. Eudy, GlaxoSmithKline, 2; N. J. Harris, None; L. Neil, None; M. E. B. Clowse, UCB Pharma, 5, Janssen, Pfizer, 2, 5, AbbVie, Bristol-Myers Squibb, 2, GlaxoSmithKline, 2.

Abstract Number: 2434

Obstetric Outcomes in Women with Takayasu Arteritis: Results from Nationwide Inpatient Sample Database 2003-2011

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Reproductive Issues in Rheumatic Disorders Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Few case reports and series suggest adverse pregnancy outcomes in patients with Takayasu Arteritis (TA). This study was undertaken to determine the frequency of complications occurring during pregnancy for women with TA and to compare these outcomes with the general obstetric population by using the largest inpatient care database.

Methods: By using the 2003-2011 Nationwide Inpatient Sample of Healthcare Cost and Utilization Project, we estimated the number of obstetric hospitalization, deliveries and caesarean deliveries in women between the age group 18-50 years. Patients hospitalized with TA as one of the diagnoses were identified. Demographic characteristics and in-hospital outcomes were recorded for both TA and control group. Then we compared maternal and pregnancy complications for all pregnancy-related admissions for women with and without TA. Multivariate logistic regression analysis was used to obtain adjusted odds ratio (OR).

Results: The total number of obstetric hospitalization was 42.32million of which 348 were women with diagnosis of TA. The maternal age of TA population was higher (28.1 years) than that in the control group (27 years) ($p < 0.001$). After adjusting for potential confounders, maternal TA population had a significantly higher prevalence of hypertensive diseases. The prevalence of intrauterine growth retardation, preterm delivery and antepartum hemorrhage was higher in TA population but did not reach a statistical significance. However, the odds of cesarean delivery, premature rupture of membranes and postpartum hemorrhage was lower in TA population. The frequencies of the above outcomes along with Odds Ratio are provided in Table 1.

Conclusion: Based on our study of national cohort, we conclude that women with TA have a higher risk of adverse outcomes of pregnancy than do pregnant women without TA, especially the hypertensive complications. Thus close antenatal and post-delivery monitoring need to be performed in order to reduce complications. The other outcomes did not reach a statistical significance likely due to small number of TA patients. Further studies with larger number of patients are needed to examine these findings.

References: Healthcare cost and utilization project: overview of the Nationwide Inpatient Sample (NIS). URL:<http://www.hcup-us.ahrq.gov/>

Table 1 Obstetric Outcomes for Pregnancy Related Hospitalizations

Variable	All patients	TA	No TA	OR	P value
No of patients	42317648	348	42317300	NA	
Hypertensive diseases	3757992	182 (52.3%)	3757810 (8.9%)	4.584 (CI 3.352- 6.268)	<0.001
Cesarean Delivery	11857999	78 (22.4%)	11857921 (28%)	0.592 (CI 0.444-0.789)	<0.001

Table . (Cont'd)

Variable	All patients	TA	No TA	OR	P value
IUGR	774439	18 (5.2%)	774421 (1.8%)	1.861 (CI 1.063-3.256)	0.30
Preterm Delivery	2798720	55 (15.8%)	2798665 (6.6%)	1.227 (CI 0.832-1.809)	0.301
PROM	1456334	24 (6.9%)	1456310 (3.4%)	0.434 (CI 0.161-1.167)	0.98
Antepartum hemorrhage	8632232	9 (2.6%)	863223 (2%)	1.479 (CI 0.762-2.871)	0.247
Postpartum Hemorrhage	1106420	10 (2.9%)	1106410 (2.6%)	0.568 (CI 0.226-1.430)	0.230

Abbreviations: TA= Takayasu Arteritis; PROM= Premature Rupture of Membranes; IUGR= Intrauterine Growth Retardation; OR= Odds Ratio (95% Confidence Interval (CI)); NA= Not Applicable

Disclosure: S. Kishore, None; V. Mittal, None; V. Majithia, None.

Abstract Number: 2435

Pregnancy Outcomes Among Women with Rare Autoimmune Diseases

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Reproductive Issues in Rheumatic Disorders Poster

Session Type: ACR Poster Session C

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Background/Purpose: Autoimmune disease in pregnancy creates the potential for increased complications and poor pregnancy outcomes. There is a paucity of outcomes data in less-common autoimmune diseases. We present the rare rheumatologic pregnancies managed over a decade from a university rheumatology pregnancy clinic.

Methods: Data were prospectively collected over a 10-year period in a pregnancy registry for women with autoimmune disease at an academic medical center. Disease activity during pregnancy was measured by physician global assessment (PGA) score and classified as low, medium, or high. Pregnancy outcomes in each group were analyzed with simple statistics.

Results: Data on 37 pregnancies in 28 patients with rare autoimmune diseases were analyzed, with an overall mean age of 30.2 years. Patient diagnoses included myositis (n=11), morphea (n=4), scleroderma (n=7) vasculitis (n=6), and sarcoidosis (n=2). There were 7 patients designated as “other autoimmune disease,” consisting of autoimmune hepatitis (n=2 in the same patient), gout, celiac disease, idiopathic optic neuritis (n=2) and orbital pseudotumor. The myositis group included 9 patients with dermatomyositis and 2 patients with polymyositis. The vasculitis group consisted of Bechet’s (n=1), Buerger’s disease (n=1), eGPA (n=1), cutaneous PAN (2), and thrombotic vasculopathy (n=1).

Disease activity during pregnancy overall was low, with only 1 patient with dermatomyositis and 3 patients in the other autoimmune disease category (n=2 autoimmune hepatitis and n=1 Celiac) having high disease activity. The mean gestational age across all groups was 37.4 weeks, ranging from 26 to 40 weeks, with only 6 total preterm births. There were 3 miscarriages (myositis, scleroderma, autoimmune hepatitis), 1 stillbirth (myositis) and 1 medically-indicated termination (myositis with severe lung disease).

Among the 11 myositis pregnancies, 3 resulted in pregnancy losses (miscarriage, stillbirth, the above termination). The one patient with active disease resulted in a live, term birth. Eight patients (72.7%) in the myositis group took prednisone, and 5 (45.5%) azathioprine.

Among the 6 vasculitis pregnancies, 4/6 (66.7%) patients took corticosteroids during pregnancy. Despite 2 patients having moderate disease activity, there was a 100% live birth rate and only 1 preterm delivery.

Conclusion: Despite having autoimmune diseases with a number of potential complications, patients overall had low disease activity and good pregnancy outcomes. This data suggests that patients with rare autoimmune diseases who are carefully managed by a rheumatologist during pregnancy can have a successful pregnancy.

Table 1 Pregnancy outcomes among women with rare autoimmune diseases (n=37).

	Myositis n=11	Scleroderma n=7	Morphea n=4	Vasculitis n=6	Sarcoidosis n=2	Other Autoimmune Disease n=7
Disease activity during pregnancy						
Low	8 (72.7%)	7 (100%)	4 (100%)	4 (66.7%)	1 (50.0%)	4 (57.1%)
Moderate	2 (18.2%)	0 (0%)	0 (0%)	2 (33.3%)	1 (50.0%)	0 (0%)

Table . (Cont'd)

	Myositis n=11	Scleroderma n=7	Morphea n=4	Vasculitis n=6	Sarcoidosis n=2	Other Autoimmune Disease n=7
High	1 (9.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (42.9%)
Pregnancy Outcome						
Miscarriage	1 (10%)	1 (14.3%)	0 (0%)	0 (0%)	0 (0%)	1 (14.3%)
Stillbirth	1 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Preterm	2 (20%)	1 (14.3%)	0 (0%)	1 (16.7%)	0 (0%)	2 (28.6%)
Term	5 (50%)	5 (71.4%)	4 (100%)	5 (83.3%)	2 (100%)	4 (57.1%)
Termination	1 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Live Birth Outcomes						
Mean gestational age (SD)	36.7 (3.4)	38.0 (3.5)	38.0 (0.8)	38 (2.1)	39 (0)	35.8 (5.0)
Preterm	2 (28.6%)	1 (16.7%)	0 (0%)	1 (16.7%)	0 (0%)	2 (33.3%)
Preeclampsia	1/6 (16.7%)	1/5 (20.0%)	0/4 (0%)	0/6 (0%)	0/2 (0%)	2/4 (50%)
Small for gestational age	1/7 (14.3%)	1/6 (16.7%)	0/4 (0%)	0/5 (0%)	1/2 (50%)	2/5 (40%)
Immunosuppression During Pregnancy						
Azathioprine	5 (45.5%)	1 (14.3%)	1 (25.0%)	1 (16.7%)	0 (0%)	3 (32.9%)
Steroids	8 (72.7%)	1 (14.3%)	0 (0%)	4 (66.7%)	0 (0%)	0 (0%)
HCOQ	2 (18.2%)	5 (71.4%)	0 (0%)	1 (16.7%)	0 (0%)	3 (42.9%)
Antihypertensive	0 (0%)	3 (42.9%)	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)
Aspirin	1 (9.1%)	4 (57.1%)	1 (25.0%)	3 (50%)	1 (50%)	1 (14.3%)
Anticoagulation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)
Topical steroids	1 (9.1%)	0 (0%)	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)
Biologic*	0 (0%)	0 (0%)	1 (25.0%)	1 (16.7%)	0 (0%)	1 (14.3%)
IVIg	1 (9.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (14.3%)
No meds	0 (0%)	1 (14.3%)	3 (75.0%)	0 (0%)	0 (0%)	1 (14.3%)

*Biologics taken during pregnancy included n=1 abatacept (morphea), n=1 etanercept (other autoimmune disease), and n=1 certolizumab and infliximab (vasculitis)

Disclosure: J. Golenbiewski, None; A. M. Eudy, None; M. E. B. Clowse, UCB Pharma, 5, Janssen, Pfizer, 2, 5, AbbVie, Bristol-Myers Squibb, 2.

Abstract Number: 2436

The Impact of Different Classes of Lupus Nephritis on Maternal and Fetal Outcomes

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Reproductive Issues in Rheumatic Disorders Poster

Session Type: ACR Poster Session C

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Background/Purpose: During pregnancy, history of lupus nephritis (LN) has been independently associated with increased risk of adverse maternal and fetal outcomes, which are even more frequent when LN is active at conception. The objective of this study was to analyze the impact of different classes of lupus nephritis (LN) as risk variables for maternal and fetal adverse outcomes in a cohort of pregnant lupus patients.

Methods: 146 pregnancies of 136 SLE patients (ACR criteria) were included. Maternal adverse outcomes observed for each nephritis class among LN patients were compared with those without nephritis. Demographic and clinical features of SLE were recorded, including maternal age at delivery, parity and ethnicity, years since the diagnosis of SLE, activity at conception, association with antiphospholipid syndrome, systemic arterial hypertension and permanent damage defined by SLICC/ACR damage index (SDI). Fischer exact test was used for categorized variables and Student's t test was used for the continuous variables.

Results: 54 patients had proliferative LN (classes III and IV), 12 had mesangial or membranous LN (classes II and V) and 80 did not have LN. SLE patients with proliferative LN but not those with classes II and V had more frequently SLE activity at conception ($p=0.02$), flares ($p=0.04$) or continuous active disease during pregnancy and puerperium ($p=0.006$), hospitalization for any cause ($p=0.003$) and due to SLE ($p=0.02$) and preeclampsia ($p=0.05$) than patients without nephritis. When classes II and V LN were compared to patients without LN, there were no statistically significant

Table 1. Main clinical and demographic features

	All SLE patients n=146	Class II n=6*	Classes III/IV n=54**	Class V n=6***	Without LN n=80
Maternal age at delivery (years)					
mean \pm SD	28.4 \pm 5.1	29.0 \pm 5.1	27.7 \pm 6.8	27.4 \pm 6.2	28.9 \pm 6.1
Ethnicity					
Afrodescendent†	82 (56.1%)	5 (83.3%)	27 (50%)	2 (33.3%)	48 (60%)
Parity					
0	76 (52.1%)	4	30 (55.5%)	5 (83.3%)	37 (46.2%)
≥ 1	70 (47.9%)	2	24 (44.5%)	1 (16.7%)	43 (53.8%)
SLE duration					
mean \pm SD	7.4 \pm 5.3	6.8 \pm 5.6	7.8 \pm 5.0	7.9 \pm 5.0	6.9 \pm 5.6
SLICC/ACR (3) ≥ 1	35 (23.9%)	0	22 (40.7%)	0	13 (16.2%)
Activity at conception	44 (30.1%)	0	22 (40.7%)	2 (33.3%)	20 (25%)
Systemic activity	30 (20.5%)	0	10 (18.5%)	0	20 (25%)
Renal activity	21 (14.3%)	0	19 (35.1%)	2 (33.3%)	0
Antiphospholipid syndrome					
Systemic arterial hypertension	28 (19.1%)	2 (33.3%)	21 (38.8%)	0	5 (6.2%)

SLE=systemic lupus erythematosus, LN=lupus nephritis, SD= Standard deviation, SLICC/ACR-DI= Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. *Class II- mesangial, **Class III- focal proliferative, ***Class IV-diffuse proliferative ****Class V-membranous.

differences in the main outcomes measured. SDI ≥ 1 was more frequent in classes III and IV than among the other patients, even when renal scores were not included. Adverse fetal outcomes such as prematurity, small for gestational age newborns, admission to NICU and perinatal death were more frequent in patients with proliferative LN (61% vs 42.5%; $p=0.01$), but not with mesangial and membranous LN (41.6% vs 42.5%; $p=0.60$) when compared to lupus patients without LN.

Conclusion: SLE patients with proliferative nephritis (classes III and IV), but not with classes II or V, have a higher frequency of adverse maternal and fetal outcomes. This is probably due to the major impact of proliferative forms of nephritis on women global health, which is corroborated by the higher SDI found. These findings suggest that further LN classification beyond the common term nephritis in the context of lupus pregnancy as the impact on maternal and fetal outcomes varies according to histological classes.

Table 2. Comparison of adverse outcomes between SLE patients with nephritis Classes III and IV and without nephritis

Variable	Classes III and IV n=54		Without Nephritis n=80		p value
Active SLE at conception	22	(40.7%)	20	(25%)	0.02
Maintenance of active SLE in pregnancy / puerperium	18	(33.3%)	12	(15%)	0.006
SLE reactivation in pregnancy / puerperium (inactive at conception)	10	(18.5%)	7	(8.7%)	0.04
Hospitalization related to SLE during pregnancy	13	(35.1%)	12	(15%)	0.003
Hospitalization not related to SLE	10	(33.3%)	15	(18.7%)	0.02
Infection	18	(33.3%)	23	(28.7%)	0.28
Preeclampsia	15	(27.7%)	13	(16.2%)	0.05
Cesarean delivery for maternal or fetal compromise	7	(12.9%)	12	(15%)	0.37
Puerperium Hemorrhage	11	(20.3%)	9	(11.2%)	0.07
Adverse fetal outcome	33	(61.1%)	34	(42.5%)	0.01

Categorical data were expressed by frequency (n) and percentage (%) and compared by the χ^2 test. Adverse fetal outcome includes prematurity, small for gestational age newborn, admission to neonatal intensive care unit and perinatal death (fetal or neonatal).

Disclosure: B. Costa Rodrigues, None; M. Ignacchiti Lacerda, None; G. Ramires de Jesus, None; F. C. dos Santos, None; N. Ramires de Jesus, None; R. A. Levy, GlaxoSmithKline, 3; E. M. Klumb, None.

Abstract Number: 2437

Analysis of Occurrence of Small for Gestational Age Infants in Women with Systemic Lupus Erythematosus

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SESSION INFORMATION

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Background/Purpose: Systemic lupus erythematosus (SLE) is associated with a higher risk of fetal growth restriction and birth of small for gestational age (SGA) concepts. Fetuses with growth restriction have 10-fold higher neonatal mortality, higher risk of hypoxia, meconium aspiration, hypoglycemia, delay in neurodevelopment and cerebral palsy. In adulthood, there is a greater risk of hypertension, type 2 diabetes, hypercholesterolemia and cardiovascular disease. The present study aims to analyze the occurrence of SGA (birth weight below 10th percentile) newborns (NB) in pregnant women with SLE accompanied at a tertiary unit. We studied the association of birth of SGA infants with clinical and laboratory characteristics of maternal SLE prior to conception, during gestation and with maternal comorbidities.

Methods: This is a cohort study with retrospective and prospective data collection, with inclusion of patients with ≥ 4 SLE classification criteria (ACR), single pregnancies and deliveries after 22 weeks. Patients with fetuses with congenital malformations or aneuploidy were excluded. Data were obtained by script-oriented chart review. The comparison between groups was done using Student's t-test or Mann-Whitney test for numerical data and chi-square test (χ^2) or Fisher's exact test for categorical data, with significance of 5%.

Results: 151 patients were included, and 28 had SGA NB (18.5%). Of the variables prior to conception, previous history of nephritis (RR = 3.01, 1.28-7.08, $p=0.01$) and presence of anti-RNP antibody (RR = 2.67, 1.11-6.43, $p=0.02$) were more frequent in patients with SGA NB. Among variables that occurred during gestation, active nephritis (RR = 4.11, 1.68-10, $p=0.002$), pulse therapy with methylprednisolone (RR = 20.3, 2.18-190, $p=0.008$) and consumption of C3 complement (RR = 2.70, 1.09-6.67, $p=0.03$) were associated with SGA group. When considering the SGA NB with altered fetal Doppler subgroup, the associated additional variables were the presence of permanent damage by SDI ≥ 1 (RR = 7.43, 1.50-36.7, $p=0.01$), previous history of neurolupus (RR = 5.16, 1.21-21.8, $p=0.03$), presence of lupus anticoagulant (RR = 4.58, 1.07-19.5, $p=0.04$), antiphospholipid syndrome (RR = 5.21, 1.26-21.5, $p=0.04$), activity at conception (RR = 6.27, 1.26-31.1, $p=0.02$) and during gestation (RR = 6.08, 1.22-30.1, $p=0.02$ per clinical judgment and RR = 9.67, 1.97-47.5, $p=0.004$ per SLEPDAI score ≥ 6), extra-renal activity (RR = 6.08, 1.22-30.1, $p=0.02$), presence of anti-DNA (RR = 4.58, 1.07-19.5, $p=0.04$) and SLE-related hospitalization during pregnancy (RR = 8.6, 1.74-42.3, $p=0.006$). Birth weight and gestational age at delivery were lower in the SGA group (1831g \pm 687g vs 2794g \pm 741g, $p<0.0001$; 36.5 vs 38 weeks, $p=0.05$). Fetal death and admission to neonatal ICU were 4.3 ($p=0.03$) and 3.2 ($p<0.0001$) times more frequent among the SGA NB, as were activity in the puerperium (3.9 times, $p=0.02$) and peripartum hemorrhage (2.3 times, $p=0.04$) among women with SGA NB.

Conclusion: These findings reinforce the importance of SLE remission prior to conception, since prior maternal morbidity combined with the presence of disease activity during pregnancy and treatment with high doses of steroids increase the risk of SGA birth.

Disclosure: B. Costa Rodrigues, None; M. Ignacchiti Lacerda, None; G. Ramires de Jesus, None; F. C. dos Santos, None; N. Ramires de Jesus, None; R. A. Levy, GlaxoSmithKline, 3; E. M. Klumb, None.

Abstract Number: 2438

Risk and Severity of Adverse Pregnancy Outcomes in Women with Systemic Sclerosis in Taiwan

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SESSION INFORMATION

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Background/Purpose: Patients with different autoimmune rheumatic diseases are subject to different pregnancy outcomes because of deviant immunity. Systemic sclerosis is known to be associated with higher risk of poor maternal and fetal-neonatal outcomes, such as scleroderma renal crisis and cardiopulmonary complications. The number of pregnancies in patients with systemic sclerosis are relatively lower than other autoimmune diseases such as systemic lupus erythematosus,

ankylosing spondylitis or rheumatoid arthritis in Taiwan. The risks and severity of adverse maternal and neonatal outcomes in systemic sclerosis patients are yet to be documented. This study was designed to analyze the risk of adverse fetal-neonatal and maternal in pregnancies in women with systemic sclerosis in Taiwan.

Methods: We identified 2338180 singleton pregnancies using the birth registry and National Health Insurance Research Database (NHIRD) of Taiwan from 2001 through 2012. 12159 pregnant women suffered from autoimmune rheumatic diseases and 60 were systemic sclerosis. We verified adverse maternal outcomes as death, acute myocardial infarction, acute renal injury, acute respiratory distress syndrome, eclampsia, pulmonary hypertension, sepsis, shock, thrombotic embolism and cerebrovascular disorders. Fetal-neonatal adverse outcomes are verified as stillbirth, low birth weight, low 1 and 5 min APGAR score and fetal distress.

To estimate odds ratios (ORs) and 95% confidence intervals (CIs) for pregnancy outcomes we used an adjusted generalized estimating equation model.

Results: Pregnancy in 60 women with systemic sclerosis were associated with operation on heart and pericardium (OR 24.78 (6.19-99.2)), puerperal cerebrovascular diseases (OR 12.3 (1.73-87.40)), preterm labor (OR 2.43 (1.27-4.68)) and preeclampsia (OR 1.94 (0.62-6.01)). Offspring of women with systemic sclerosis were associated with low birthweight (OR of 2.46 (1.40-4.32)), fetal distress (OR 2.49 (1.25-4.95)), low 1-minute Apgar scores (OR 1.93 (0.62-5.97)) and 5-minute Apgar scores (OR 5.68 (1.45-22.3)). Risks for pregnancy related hypertension (OR 3.06), antepartum hemorrhage (OR 1.52), severe postpartum hemorrhage, and severe postpartum hemorrhage (OR 1.53) were higher in pregnant women with systemic sclerosis. Both maternal and fetal-neonatal outcomes were poor in systemic sclerosis women.

Conclusion: Women with systemic sclerosis were prone to have a higher risk for adverse maternal and neonatal outcomes especially cerebrovascular events and lower APGAR score. Planned pregnancy and rigorous monitoring of renal function, blood pressure and signs and symptoms of cerebrovascular diseases are recommended in women with systemic sclerosis.

Disclosure: C. I. Hsieh, None; S. F. Luo, None; C. F. Kuo, None.

Abstract Number: 2439

A Description of Contraception Practices in the Ohio State University Lupus Cohort

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Reproductive Issues in Rheumatic Disorders Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease, which predominantly affects women and reaches peak incidence during reproductive years. Periods of high disease activity are associated with maternal and fetal morbidity and mortality. Many medications, disease modifying anti-rheumatic drugs (DMARDs), used to treat SLE also have deleterious pregnancy effects. The literature provides clear guidelines for the best approaches to these practices for women with SLE; however, little is known about current practices. Our aim was to determine contraception practices within The Ohio State University (OSU) Lupus/Vasculitis/Glomerulonephritis (LVG) Registry.

Methods: The OSU LVG Registry prospectively collects clinical data of patient reported surveys including information on reproductive health. Per the Registry and chart review, patient reported sexual activity was assessed. An IRB approved retrospective chart review was conducted on female participants within the LVG cohort who received care for SLE between 2013 and 2018. Data collected included: patient demographics, sexual activity, contraceptive method (oral, surgical, devices, condom, or abstinence), and DMARD use.

Results: Within the registry, we had 259 female patients with SLE. Approximately half of the SLE cohort was on medications considered to be potentially teratogenic or non-compatible with pregnancy. Table 1 shows our SLE cohort demographics. 94% of the cohort self-reported as sexually active, with only about 25% reporting the use of prescription

contraceptives (excluding post-menopausal women). An estimated 14% of sexually active patients reported using only condoms or abstinence while almost 27% use no method of contraception.

Conclusion: Within the LVG Cohort, SLE patients are on high risk medications with the potential for high risk pregnancy complications. This further demonstrates the need for assessing pregnancy intention, providing family planning counseling, and birth control methods in rheumatology practice. Further research is need

Table 1: SLE Cohort Demographics per Intake LVG Registry Questionnaire

Characteristics	(%)
Age (years)	
Average age of patients	42.6
Average age at diagnosis	28.6
Sexually active	
Yes – using birth control	31%
No – not using birth control	41%
Not sexually active	6%
Menopausal	22%
Not answered (N = 114)	44%
Race	
Caucasian	57%
African American	36%
Asian	3%
Other	1%
Ethnicity	
Hispanic / Latino	3%
Non-Hispanic	97%
Education	
High school diploma or GED	15.79%
Associate's degree or equivalent	10.39%
Bachelor's degree or equivalent	15.45%
Some post-secondary education	37.39%
Master's degree or higher	10.80%
Question Not Answered	40%
Contraception method	
Abstinence	0.4%
Menopause	21%
None	26.5%
Sterilization	1.6%
Ligation	4.3%
Hysterectomy	14%
Vasectomy	1.9%
IUD	10.5%
Implant	4.7%
Injection	2.7%
Pill-combo	2.3%
Pill-mini	3.9%
Patch	0%
Ring	0.8%
Condoms	13.2%
Diaphragm	0%

ed for the implementation of a sustainable patient and healthcare team education model in this high-risk population.

Disclosure: V. Mruk, None; A. Weaver, None; A. Zofia, None; E. Sullivan, None; K. Morris, None; S. P. Ardoin, None; E. Berlan, None; A. Meara, None.

Abstract Number: 2440

Outcomes of Pregnancy Complicated By ANCA-Associated Vasculitis: A Retrospective Review

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Reproductive Issues in Rheumatic Disorders Poster

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Session Time: 9:00AM-11:00AM

Background/Purpose: ANCA-Associated Vasculitis (AAV) is a small-vessel vasculitis that predominantly affects the kidneys, lungs, and sinuses, among other organs. It has been traditionally associated with older populations, but its occurrence in younger, potentially childbearing, females is increasingly being recognized. In this study, we characterize the outcomes of pregnancy in ANCA-associated vasculitis at a large tertiary care and referral center.

Methods: We performed a retrospective chart review of all patients at the University of Iowa Hospitals and Clinics with a positive PR3 or MPO and a documented diagnosis of vasculitis between 2000 and 2017. Inclusion criteria included female sex and age younger than 45. Charts were reviewed to identify disease activity, clinical manifestations, medication regimens, and pregnancy outcomes.

Results: 24 patients met the inclusion criteria, of which 11 were pregnant at some point, accounting for 29 total pregnancies. Among these, 8 had at least one pregnancy after the diagnosis of AAV and 5 before the diagnosis. Of those who were pregnant after the diagnosis of AAV, all had single pregnancies. They accounted for 16 pregnancies, of which 7 were viable, 2 are currently gravid, and 7 resulted in spontaneous abortions. Among the 8 with a preexisting diagnosis of AAV, the mean age was 29 (age range: 22-34 years). Six patients (75%) were MPO positive while 2 (25%) were PR3 positive. All were in remission at conception. Two patients were on moderate doses of prednisone (15mg – 20mg daily) throughout pregnancy; maintenance immunosuppressive therapy was held for the others. For induction therapy, 5 had cyclophosphamide, 1 had rituximab, and 2 had limited disease not requiring induction therapy. In vitro fertilization was documented in only 1 patient. Four were delivered by Caesarean section. All 7 who have completed pregnancy experienced complications, including premature birth (4), preeclampsia (2), preterm premature rupture of membranes (1), and cholestasis of pregnancy (1). None experienced a relapse in disease activity during pregnancy, although one patient required tracheostomy for preexisting subglottic stenosis at 11 weeks.

Conclusion: Women with AAV should be considered at high risk for pregnancy complications due to the underlying disease and chronic immunosuppressive treatment regimens. With counseling and very close clinical monitoring, women with AAV may be able to conceive and give birth.

Disclosure: J. Strouse, None; M. Swee, None; M. Suneja, None; B. Kumar, None.

Abstract Number: 2441

Needs and Barriers to Pregnancy Counselling in Women with SLE

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Reproductive Issues in Rheumatic Disorders Poster

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Background/Purpose: Existing data suggest that barriers to pregnancy counselling exist and might represent an area of need in order to optimize outcomes for SLE pregnancies. Yet, this issue has not been comprehensively explored, representing an important knowledge gap. Our objectives were to assess pregnancy counselling needs in women with SLE and to identify potential clinical and psychosocial barriers and facilitators to meet their counselling needs.

Methods: Focus groups were conducted with SLE females contemplating pregnancy or trying to conceive, women with SLE who were pregnant or had recently been pregnant (≤ 2 years), and healthcare professionals (e.g. rheumatologists, maternal-fetal medicine specialists, obstetrician-gynecologists, nurses) until thematic saturation was achieved. Participants were recruited through purposive sampling from community-based practices, as well as peripheral and tertiary care centers from the McGill University's health network. Only women meeting ≥ 4 ACR classification criteria for SLE were included. Transcripts were reviewed by 2 independent investigators using the constant comparative method to identify emerging themes and data were analyzed thematically using grounded theory.

Results: Twenty-four SLE patients and 10 healthcare professionals participated in 10 unique focus groups that lasted 60 minutes each. The following themes emerged: 1) Anxiety - Patients feared their disease would affect the health of their offspring, prevent them from breastfeeding and/or care for a newborn. They also worried over the anticipated extra stress and fatigue associated with pregnancy, and expressed concerns that the stress could cause a lupus flare. The systematic categorization of their pregnancy as “high risk” was verbalized as a source of anxiety. Information on the internet was also perceived as “extremely scary”. 2) Confusion - The consensus was that information available on SLE pregnancy was limited and not always clear, particularly on the internet where forums were seen as unreliable. Although patients saw their rheumatologist as the primary source for information, they felt that the information on pregnancy was vague until the moment they voiced that they wanted to conceive. 3) Frustration - Patients were frustrated that their concerns and anxiety were not taken seriously by members of their support system as few of them know what SLE is and what it entails during pregnancy. Having to plan a pregnancy at a time of disease quiescence was also frustrating. This can fall outside of their personal narrative or outside their cultural value system. Not remembering some of their questions or not having time to ask them all during medical encounters was a common source of frustration among patients.

Conclusion: Our qualitative study provides important insight into the needs and barriers to pregnancy counselling in SLE women. Potential strategies to address these might include facilitating access to psychosocial support (e.g. psychologist, social worker) during pregnancy, developing an educational tool, providing a checklist of questions for medical encounters, and designing prenatal classes dedicated to SLE patients and their partners.

Disclosure: A. Neville, None; N. Dayan, None; C. Barnabe, None; S. Elliott, None; L. Proulx, None; D. Da Costa, None; S. Bernatsky, None; E. Vinet, None.

Abstract Number: 2442

Familial Mediterranean Fever Associated Infertility and Underlying Factors with Fertility

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Session Time: 9:00AM-11:00AM

Background/Purpose: Familial Mediterranean Fever (FMF) is the most frequent auto-inflammatory disease caused by MEFV gene mutations. Although disease is characterized by intermittent febrile inflammatory attacks of serositis and arthritis some patients may experience complications of disease. Infertility/subfertility is a complication of auto-inflammatory diseases and data is still unclear about FMF associated infertility. The aim of study is to investigate the frequency and possible underlying factors of FMF associated infertility/subfertility.

Methods: All patients recruited from FMF in Central Anatolia (FiCA) cohort. All patients fulfilled Tel Hashomer criteria and all were using colchicine for at least 1 year. Demographic data, FMF attacks and mutation (if available) characteristics, amyloidosis and treatment features were recorded. For this study data on 403 eligible patients (mean age 41.4±10.7, 68.7% female) who had been willing to have children were used.

Results: Proportions of FMF manifestations were fever 83.1%, peritonitis 89.6%, pleuritis 51.4%, arthritis 43.4% and skin rash 28%. MEFV mutations were available for 317 subjects and 77.9% of subjects harboring M694V mutation (27.4% homozygous for M694V). Among all 42 (10.4%) patients were colchicine non-responders. Infertility was present in 45 (11.2%) of patients. Of these 38 (13.7% of females) were female, 7 (5.6% of males) were male. Female sex (odds ratio, 2.9; 95% confidence interval, 1.07–7.98) and colchicine nonresponse (odds ratio, 4.14; 95% confidence interval, 1.75–9.78) were found to be the independent predictors of infertility.

Conclusion: Colchicine nonresponse and female sex were found to be the independent predictors of infertility and effective therapeutic interventions may help to increase fertility in these patients.

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Abstract Number: 2443

Trends in the Incidence of Lymphomas and Leukemias in Patients with Rheumatoid Arthritis in Spain: An Observational Cohort Study of Hospital Discharges from 1999 to 2015

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Oncohematological diseases have an increased incidence in Rheumatoid Arthritis (RA) patients. In the last years numerous studies have appeared exploring the relationship between these diseases, RA and its treatments. The introduction of biological therapies and new therapeutic strategies have emerged in the last decades implying an important change in the management and evolution of RA. However, the trend of oncohematological diseases in RA in Spain is unknown. Our objective was to analyze the incidence and trend of hospital admissions for lymphomas and leukemias in patients with RA in Spain during the period between 1999 and 2015.

Methods: We performed an observational retrospective population study analyzing the spanish national administrative database that includes a Minimum Basic Data Set (MBDS) of hospital admissions of patients with RA during the period 1999 to 2015. We selected the MBDSs for lymphomas and leukemias. Cases were identified by the presence in primary and secondary diagnosis of ICD 9 codes. The population at risk was estimated through the population census of the National Institute of Statistics, with an estimated prevalence of RA of 0.5% (0.8% in women and 0.2% in men). Crude and adjusted rates of the selected CVDs were calculated, and the trend was analyzed using the Generalized Linear Model (GLM) with the year as the analysis variable. Statistical analysis was made using SPSS statistical package version 20 (SPSS Inc, Chicago, IL).

Results: 338.343 RA hospital admissions were detected in the period, being 3561 (1.1%) due to lymphomas (2190 women and 1371 men, corresponding respectively to 61.5% and 38.5%) and 1664 (0.5%) leukemias (871 women and 793 men, corresponding respectively to 52.3% and 47.7%). Mean age was 68.94 (SD 11.38) in lymphomas and 71.46 (SD 11.24) in leukemias. There were 372 (10.4%) deaths during admission in lymphomas and 257 (15.4%) in leukemias. Age-adjusted rate during the period for lymphoma was 152.19/10⁵ inhabitants per year (92.05 in women and 240.14 in men). Lymphoma age-adjusted rate increased from 52.46/10⁵ inhabitants per year in 1999 to 187.57 in 2015, both women (from 42.74 in 1999 to 142.95 in 2015) and men (from 280.77 in 1999 to 326.63 in 2015). An annual increase in the lymphoma rate of 6.9% is estimated (RRI 1.069; CI 95% 1.054-1.085). Age-adjusted rate during the period for leukemia was 90.87/10⁵ inhabitants per year (37.09 in women and 144.65 in men). Leukemia age-adjusted rate increased from 18.86/10⁵ inhabitants per year in 1999 to 94.05 in 2015, both women (from 13.80 in 1999 to 65.93 in 2015) and men (from 38.70 in 1999 to 204.84 in 2015). An annual increase in the leukemia rate of 8.2% is estimated (RRI 1.083; CI 95% 1.069-1.097).

Conclusion: In Spain, in the period between 1999 to 2015, lymphoma and leukemia hospital admissions in patients with RA increased, with an estimation of 6.9% and 8.2% annual increase respectively.

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Abstract Number: 2444

The Risk of Solid Cancers in Patients with Rheumatoid Arthritis Exposed to Biologic Dmards with/without Prior Cancers

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To compare the risk of solid cancer in patient with rheumatoid arthritis treated with biologic disease modifying antirheumatic drugs (b-DMARDs) to that in patients treated with non-biologic (synthetic) DMARDs (sDMARDs) with/without prior cancers.

Methods: 2190 RA patients were enrolled in our rheumatology clinic. Patients were diagnosed according to ACR/EULAR 2010 classification criteria, and treated with DMARDs. Rate of solid cancers were retrospectively examined.

Results: 2175 RA patients without prior cancers were enrolled to this study. Rates of solid cancers in 1897 patients without prior cancers who received sDMARDs (M/F=1671/226, age=60.5+/-14.2) were compared to those in 278 patients without prior cancers who received bDMARDs (M/F=252/26, age=58.7+/-12.5). 50 patients developed a new solid cancer which include 6 gastric cancers, 6 colon cancers, 3 lung cancers, 14 breast cancers and 21 other cancers. The rates of incident solid cancer were 2.33 events/1000 person-years in sDMARDs cohort, 1.59 events/1000 person-years in bDMARDs cohort and 2.08 events/1000 person-years in TNFi cohort. There was no difference in risk of solid cancer for bDMARDs and TNFi compared to sDMARDs treated patients. There was no difference in the relative risk of cancer for any of the individual TNFi therapy.

Secondary we investigate the recurrence of the solid cancers in 15 patients with RA and a history of solid cancer before start of DMARDs. The 0.7% of patients in the sDMARDs cohort had a recurrence of the same cancer in comparison with the 0.4% and the 0.9% in the bDMARDs and TNFi cohorts, respectively.

Conclusion: The addition of bDMARDs to sDMARDs does not alter the risk of solid cancer in RA patients without prior cancers in this study. Although patient numbers are still low, it seems that RA patients with prior cancer received bDMARDs do not have an increased risk of recurrence of same solid cancers.

Disclosure: M. Yamasaki, None;

Abstract Number: 2445

The Effect of Biologic Agents on Hemoglobin Levels of Patients with Rheumatoid Arthritis

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Background/Purpose: Anemia is not considered a major problem in rheumatoid arthritis. But prevalence data suggest that 30-70% of rheumatoid arthritis (RA) patients have anemia. Inflammatory cytokines such as IL-6 and tumor necrosis factor- α are critically involved in its process. We compare the change of hemoglobin, CRP levels and disease activity index in RA patients who were treated with biological disease-modifying anti-rheumatic drugs (bDMARDs) for 12 months.

Methods: The study population was a prospective, observational, multicenter cohort of Korean patients with RA, who were registered to the Korean College of Rheumatology Biologics (KOBIO) registry and followed up for one year after initiating the biologic agent.

Among the patients using bDMARDs, 692 patients had anemia. Among them, a total of 285 patients who received the same bDMARDs for 1 year were analyzed.

We divided the patients into four groups according to the mechanism of bDMARDs.

Results: The number of each group, group 1 (TNFi users), group 2 (rituximab), group 3 (abatacept), group 4 (tocilizumab) was 162, 8, 37 and 78 respectively. The clinical characteristics of the four groups are summarized in Table 1. There were no significant differences between the four groups for the variables. bDMARDs therapy continually improved the anemic status in four groups. Mean haemoglobin values had increased from 11.0 to 11.9 g/dl in TNFi group, from 11.1 to 12.25 g/dl in rituximab group, from 10.9 to 11.8 in abatacept group, from 10.8 to 12.2 g/dl in tocilizumab group. The mean Hb increase was 1.4 g/dl in the tocilizumab group which was the largest between four groups. bDMARDs therapy resulted in significant reduction in DAS28-CRP and serum CRP levels. Tocilizumab was most effective for reducing DAS28-CRP and serum CRP levels.

Conclusion: The change of hemoglobin level was differed according to bDMARDs. Tocilizumab therapy was the most effective for improving anemia and reduced in DAS28-CRP and serum CRP levels. Table 1. Baseline clinical characteristics of patients.

	Group 1 TNFi	Group 2 rituximab	Group 3 abatacept	Group 4 tocilizumab
No of patients	162	8	37	78
Female, n (%)	139 (85.8%)	8 (100%)	32 (86.49%)	71 (91.03%)
Age	59.1	56.4	57.2	57
Disease duration	8.7	10.8	9.3	8.1
BMI	22.1	21.2	22	22
Hb	11.1	11.1	11.0	10.9
Hct	33.9	34.6	33.9	33.9
SJC	8.8	9.3	5.5	7.3
TJC	11.3	11.6	9.3	8.3
PTGA	6.8	5.9	6.9	7
DAS28 CRP	5.2	5.3	4.8	5.1
RAPID3	16.1	15.4	15.1	15.8
RF	155.9	170.8	113.3	127
CRP	2.7	4	2.5	3.6

Disclosure: H. Lee, None; J. Y. Choe, None; S. K. Kim, None; S. Park, None.

Abstract Number: 2446

The Combined Use of Folic Acid Influenced the Time until the Development of Lymphoproliferative Disorders in Patients with Rheumatoid Arthritis during Treatment with Methotrexate

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Background/Purpose: Lymphoproliferative disorders (LPDs) are a serious complication in patients with rheumatoid arthritis (RA). Methotrexate (MTX) is known to be able to cause a development of LPDs and previous reports have

shown that the cumulative dose of MTX and combination therapy with immunosuppressive agents influence the risk of developing LPDs. However, few reports have focused on the duration from the initiation of MTX to the onset of LPDs. Therefore, the aim of this study is to clarify the factors that influencing the time until the development of LPDs in patients with RA being treated with MTX.

Methods: RA patients who developed LPDs during MTX therapy at Tokai University Hospital between 2001 and 2017 were retrospectively examined. We collected demographic and clinical characteristics and pathological findings from the medical records. The duration from the initiation of MTX to the development of LPDs was calculated. The association between the duration from the initiation of MTX until the development of LPDs and various parameters were analyzed by univariate and multivariate analyses.

Results: A total of 45 patients with RA who developed LPD during MTX therapy were found. Eight patients were excluded from the analysis because of incomplete data and 37 patients (mean 66 years of age) were enrolled. Folic acid (FA), biological disease-modifying anti-rheumatic diseases (bDMARDs), conventional synthetic DMARDs (csDMARDs) and corticosteroid were used in 14, 8 and 16 patients, respectively. The mean duration to the development of LPDs from the first administration of MTX was 6.8 years. In the univariate analysis, the combined use of FA with MTX significantly prolonged the period between the time of MTX initiation and the development of LPDs compared to MTX monotherapy (3.6 years vs. 9.0 years, $p < 0.001$). In addition, we found that the time until the development of LPDs was prolonged in a dose-dependent manner (3.0 years at 0mg; 6.2years at 3mg; 8.7 years at 5mg). In contrast, combination therapy with csDMARDs significantly shortened the time until the development of LPDs compared to without csDMARDs combination therapy (5.1 years vs. 7.9 years, $p = 0.04$). However, no significant association was noted between the time until the development of LPDs and the combined use of bDMARDs or corticosteroids. Complication with Sjögren's syndrome did not influence the time until the development of LPDs. A multiple regression analysis revealed that the combined use of FA was an independent factor that prolonged the time until the development of LPDs ($p < 0.01$).

Conclusion: These results indicated that the combined use of FA with MTX might prolong the time until the development of LPDs during MTX treatment in RA patients.

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Liver Enzyme Abnormalities after Tofacitinib Treatment in Patients with Hepatic Steatosis from the Rheumatoid Arthritis, Psoriatic Arthritis, and Psoriasis Clinical Programs

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

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Background/Purpose: Non-alcoholic fatty liver disease, characterized by hepatic steatosis (HS), is a very common form of chronic liver disease in many countries. Limited data are available on liver enzyme elevation in patients (pts) with HS who are receiving medications for inflammatory conditions, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), and psoriasis (PsO). Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA and PsA, and has also been studied in PsO. The objective of this study was to describe baseline characteristics and liver enzyme abnormalities in pts from the tofacitinib RA, PsA, and PsO clinical programs with/without HS at baseline.

Methods: Pts randomized to the tofacitinib (5 or 10 mg twice daily; doses pooled) and placebo arms of 25 studies in the RA, PsA, and PsO programs were included in this pooled post hoc analysis. Most studies allowed or mandated concomitant treatment with disease-modifying antirheumatic drugs. HS was determined by the investigator and captured per the Medical Dictionary for Regulatory Activities term at baseline. Baseline characteristics, incidence of elevated total bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >1x and >3x the upper limit of normal

Table. Baseline characteristics and liver function up to Month 3, by HS at baseline

	No HS at baseline, all indications (N=10,053) ^a				HS at baseline, all indications (N=159) ^a			
Age, mean (SD), years	49.9 (12.7)				52.5 (11.0)			
Female, n (%)	6,722 (66.9)				91 (57.2)			
BMI, mean (SD), kg/m ²	27.9 (6.6)				32.0 (6.8)			
BMI ≥30 kg/m ² , n (%)	3,171 (31.6)				84 (53.2)			
Alcohol use, n (%)	2,912 (29.7)				52 (33.3)			
Diabetes, n (%)	935 (9.3)				37 (23.3)			
CRP, mean (SD), mg/L	13.2 (21.0)				10.7 (17.1)			
Concomitant NSAID use, n (%)	5,638 (56.1)				92 (57.9)			
Corticosteroid use, n (%)	3,910 (38.9)				54 (34.0)			
LDL, mean (SD), mg/dL	113.7 (33.8)				117.1 (36.1)			
HDL, mean (SD), mg/dL	56.5 (16.8)				52.4 (15.3)			
Triglycerides, mean (SD), mg/dL	131.2 (81.7)				165.8 (96.4)			
AST, mean (SD), IU/L	21.9 (12.1)				27.8 (13.0)			
ALT, mean (SD), IU/L	23.0 (16.9)				34.0 (19.6)			
Gamma-GT, mean (SD), IU/L	31.5 (35.0)				51.0 (57.7)			
MTX use at baseline, n (%)	3,732 (37.1)				67 (42.1)			
Liver function up to Month 3, tofacitinib-treated patients (patients with a post-baseline visit for total bilirubin, AST or ALT)								
	No HS at baseline				HS at baseline			
Indication	RA (N=5,490)	PsA (N=459)	PsO (N=2,166)	All (N=8,115)	RA (N=74)	PsA (N=13)	PsO (N=37)	All (N=124)
ΔCRP, mean (SD), mg/L ^b	-12.54 (23.92) (N=4,747)	-6.69 (21.46) (N=434)	-4.44 (17.79) (N=701)	-11.15 (23.28) (N=5,882)	-9.71 (19.94) (N=67)	-2.40 (9.78) (N=12)	-2.51 (4.75) (N=13)	-7.74 (17.70) (N=92)
Total bilirubin >1x ULN, n (%)	124 (2.3)	12 (2.6)	134 (6.2)	270 (3.3)	4 (5.4)	1 (7.7)	5 (13.5)	10 (8.1)
Total bilirubin >3x ULN, n (%)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST >1x ULN, n (%)	858 (15.6)	86 (18.7)	270 (12.5)	1,214 (15.0)	36 (48.7)	5 (38.5)	13 (35.1)	54 (43.6)
AST >3x ULN, n (%)	36 (0.7)	4 (0.9)	10 (0.5)	50 (0.6)	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.8)
ALT >1x ULN, n (%)	1,070 (19.5)	120 (26.1)	507 (23.4)	1,697 (20.9)	39 (52.7)	9 (69.2)	21 (56.8)	69 (55.7)
ALT >3x ULN, n (%)	73 (1.3)	2 (0.4)	26 (1.2)	101 (1.2)	2 (2.7)	1 (7.7)	0 (0.0)	3 (2.4)
Liver function up to Month 3, placebo-treated patients (patients with a post-baseline visit for total bilirubin, AST or ALT)								
	No HS at baseline				HS at baseline			
Indication	RA (N=1,111)	PsA (N=221)	PsO (N=509)	All (N=1,841)	RA (N=13)	PsA (N=13)	PsO (N=8)	All (N=34)
ΔCRP, mean (SD), mg/L ^b	2.09 (21.17) (N=791)	0.05 (10.93) (N=206)	-1.64 (7.42) (N=151)	1.23 (18.42) (N=1,148)	4.42 (15.81) (N=9)	1.96 (5.29) (N=12)	10.79 (33.52) (N=4)	4.26 (15.70) (N=25)
Total bilirubin >1x ULN, n (%)	13 (1.2)	5 (2.3)	24 (4.7)	42 (2.3)	1 (7.7)	1 (7.7)	1 (12.5)	3 (8.8)
Total bilirubin >3x ULN, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST >1x ULN, n (%)	113 (10.2)	16 (7.2)	48 (9.4)	177 (9.6)	2 (15.4)	2 (15.4)	2 (25.0)	6 (17.7)
AST >3x ULN, n (%)	7 (0.6)	1 (0.5)	1 (0.2)	9 (0.5)	0 (0.0)	1 (7.7)	0 (0.0)	1 (2.9)
ALT >1x ULN, n (%)	165 (14.9)	43 (19.5)	81 (15.9)	289 (15.7)	6 (46.2)	4 (30.8)	3 (37.5)	13 (38.2)
ALT >3x ULN, n (%)	12 (1.1)	1 (0.5)	2 (0.4)	15 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

^aIncludes patients initially randomized to tofacitinib or placebo; ^bPatients with both baseline and Month 3 CRP

A, change from baseline; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; GT, glutamyl transferase; HDL, high-density lipoprotein; HS, hepatic steatosis; LDL, low-density lipoprotein; MTX, methotrexate; N, number of patients analyzed; n, number of patients meeting criteria; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; SD, standard deviation; ULN, upper limit of normal

(ULN) up to Month (M) 3, and change from baseline in C-reactive protein (CRP) at M3 – all by HS at baseline – are reported.

Results: A total of 10,212 pts were included in the analysis. The prevalence of HS was 1.6% across indications (RA: 87/6,729 [1.3%]; PsA: 27/710 [3.8%]; PsO: 45/2,773 [1.6%]). Baseline characteristics were generally similar in pts with or without HS (Table). However, baseline obesity, diabetes, triglycerides, and liver enzymes were numerically higher, and CRP was numerically lower, in pts with HS than in those without HS (Table). In both tofacitinib- and placebo-treated pts, incidence of elevated total bilirubin, AST and ALT >1x ULN up to M3 was higher in pts with HS than in those without HS, across indications (Table). Incidence of elevated total bilirubin, AST and ALT >3x ULN up to M3 was low across indications, irrespective of HS (Table). Among tofacitinib-treated pts, CRP was reduced at M3 in pts with or without HS, but to a lesser extent in those with HS, across indications. Among placebo-treated pts, changes in CRP were small, irrespective of HS (Table).

Conclusion: In this exploratory analysis, prevalence of HS at baseline was 1.6% across the tofacitinib RA, PsA, and PsO programs. After up to 3 months of tofacitinib treatment, incidence of mildly elevated liver enzymes was higher in pts with HS than in those without HS. Incidence of severely elevated liver enzymes was low overall, and similar inputs with or without HS. Further studies are needed to evaluate the effects of tofacitinib on CRP and liver enzymes, and the potential impact on clinical response, in pts with RA, PsA, or PsO who have comorbid HS.

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Correlation between Long-Term Low-Dose Steroid Administration and Reactivation of Hepatitis B Virus in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

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Background/Purpose: It is well known that the use of corticosteroids results in increased viral replication and elevated ALT in patients with hepatitis B virus. The use of high dose corticosteroids for more than 4 weeks usually results in hepatitis worsening after cessation of steroids. However, few studies have investigated the effect of low dose corticosteroids on hepatitis B virus (HBV) reactivation. The aim of this study is to investigate the reactivity of HBV in rheumatoid arthritis patients treated with long-term low dose corticosteroids.

Methods: Patients with HBsAg positive who were diagnosed with rheumatoid arthritis and who received prednisolone of less than 10 mg/day over four weeks were selected at four university hospitals. Medical records and laboratory data were retrospectively analyzed and multivariate analysis was performed.

Results: One hundred forty five patients were included in the study and 26 (17.9%) patients were reactivated with HBV. Mean age was 50.7 years and 104 (71.7%) patients were female. Baseline characteristics including sex, age, past medical history and laboratory findings were not significantly different except the level of aspartate aminotransferase (21 vs. 83 IU/L, p <0.001) and alanine aminotransferase (23 vs. 104 IU/L, p <0.001) in patients with HBV reactivation compared to those without HBV reactivation. The administration of low-dose prednisolone did not affect HBV reactivation, and the duration of prednisolone administration, average daily prednisolone dose, and cumulative prednisolone dose did not affect the reactivation of HBV. However, the administration of leflunomide showed a significant difference in the reactivation of

HBV (adjusted odds ratio 3.81; $p=0.034$), and the administration of hydroxychloroquine tended to cause reactivation of HBV (adjusted odds ratio 3.43; $p=0.06$).

Conclusion: The hepatitis B virus can be exacerbated by spontaneous viral reactivation, so it is difficult to conclude that hepatitis is caused by the administration of steroids. In this study, the administration of low-dose steroids did not affect the reactivation of HBV, suggesting that it could be used safely. Further, prospective studies on the effect of conventional disease-modifying antirheumatic drugs such as leflunomide and hydroxychloroquine on the reactivation are needed.

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Prevalence and Risk Factors of Serious Infections in Rheumatoid Arthritis Patients Receiving the Biologic/Targeted Synthetic Dmards: A Propensity Score Analysis from the Hong Kong Biologics Registry

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

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Session Time: 9:00AM-11:00AM

Background/Purpose: To study the prevalence and risk factors for serious infections (SIs) in rheumatoid arthritis (RA) patients receiving the biologic / target synthetic (b/ts) DMARDs.

Methods: Patients with RA included in the Hong Kong Biologics Registry since 2007 ever treated with b/tsDMARDs were studied. Data on withdrawal of b/tsDMARDs due to serious adverse events (SAEs) and SIs was analyzed. Demographic data, medical comorbidities (eg. diabetes mellitus, chronic lung, kidney and liver diseases) and concomitant use of glucocorticoids (GCs) and csDMARDs were retrieved and their contribution to SIs was evaluated by separate logistic regression. The propensity score for SIs was computed and patients were stratified into 5 quintiles according to the risk. The hazard ratios (HRs) of SIs with respect to individual b/tsDMARDs in each quintile were studied by Cox regression.

Results: 2355 courses of b/tsDMARDs were used in 1355 Chinese patients with RA (83% women; mean age 54.0 ± 12.7 years). The usage of various b/tsDMARDs was: adalimumab (12%), etanercept (24%), infliximab (17%), golimumab (9.4%), certolizumab (0.9%), tocilizumab (19%), rituximab (6.6%), abatacept (7.7%) and tofacitinib (2.7%). After a follow-up of 5056 patient-years, 1433 courses of b/tsDMARDs were discontinued, with major reasons being inefficacy (50%), SAEs (22.4%) and cost (8.4%). Among those b/tsDMARD courses terminated for SAEs, 32% were due to SIs (103 episodes). The rate of SIs was 1.17/100 patient-years. The commonest causes of SIs were pulmonary tuberculosis (TB) (41%), severe pneumonia (33%), soft tissue infection (6.8%), atypical TB (2.9%), urogenital sepsis (2.9%), septic arthritis (2.9%), hepatobiliary / gastrointestinal sepsis (2.9%), central nervous infection (1%), severe viral infections including herpes zoster (5.8%), and opportunistic infections (2.9%). Logistic regression showed that age (OR 1.02[1.001-1.04 per year]), male sex (OR 1.88[1.08-3.26]) and concomitant chronic obstructive pulmonary disease / asthma (OR 2.55[1.05-6.23]) were independent risk factors for SIs. TB infection was most frequent in users of infliximab (2.32/100 patient-years), followed by tofacitinib (1.47), adalimumab (1.27), etanercept (0.62) and tocilizumab (0.36). Non-TB serious infections occurred most frequently with infliximab (2.32/100 patient-years), tofacitinib (1.47) and abatacept (1.15). In the quintile of patients with the highest propensity score for SIs, infliximab had the highest withdrawal rate due to SIs (18%). Cox regression revealed a highest HR for SIs in infliximab users with reference to adalimumab (2.81[0.80-9.88]), followed by tofacitinib (HR 2.12[0.19-23.4]). Concomitant GC was associated with an insignificantly increased risk of SIs.

Conclusion: SIs causing withdrawal of b/tsDMARDs in patients with RA account for one-third of all SAEs. Increasing age, male sex and concomitant chronic chest conditions were independent risk factors for SIs. Infliximab was associated with the highest rates of serious TB and non-TB infection, and this observation was consistent in all quintiles of patients with different propensity to SIs.

Disclosure: C. C. Mok, None; T. H. Wan, None; L. S. Fong, None.

Prosthetic Joint Infection in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

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Background/Purpose: Patients with rheumatoid arthritis (RA) have been shown to have an increased susceptibility to the development of prosthetic joint infection (PJI) after Total Hip or Knee Arthroplasty (THA/TKA). Our aim was to compare the risk of PJI after THA or TKA in patients with RA versus controls.

Methods: All patients with RA (ACR 1987/ACR 2010 criteria) who had undergone joint replacement of the hip or knee in our hospital between 01/01/2008 and 12/31/2016 were included; and compared with patients matched by age and sex (2 to 1), without diagnosis of RA, also subjected to hip or knee joint replacement in the same period. Clinical records were reviewed, collecting demographic data, RA characteristics, treatments and comorbidities. Patients with PJI were identified in cases and controls. Descriptive statistics were performed and risk factors associated with infection were analyzed by logistic regression.

Results: We identified 50 patients with RA who underwent joint replacement surgery in that period, 92% women, mean age at diagnosis of 48.9 years (SD 17.2) and mean age at the time of joint surgery of 60.3 years (DS 15.7) (see table). The cause of joint replacement in control patients was osteoarthritis in 79% of cases. The type of joint surgery in patients with RA was TKA in 27 patients, THA in 20 patients and total hip and knee arthroplasty in 3 patients. At the time of surgery, RA patients were in treatment with: corticosteroids 56%, conventional DMARDs 72% and biologics 34%. DMARD or biological treatment was suspended because of the surgery in 34% of patients. 3 patients with RA (6%, 95% CI: 1.9-17.3) and 2 control patients (2%, 95% CI: 0.5-7.8) had prosthetic infection ($p = 0.2$). All prosthetic infections in patients with RA resolved with prolonged antibiotic treatment, while 1 of the 2 control patients required prosthetic replacement ($p = 0.17$). There was no association between having a PJI with previous comorbidities or with any of the RA treatments.

Conclusion: 6% of the patients with RA undergoing THA/TKA had a prosthetic infection, without difference with the control group.

	Rheumatoid Arthritis (n=50)	Other causes of joint replacement (n=100)	P
Female sex, % (CI 95%)	92 (80-97)	92 (85-96)	1
Age at the time of surgery, years, mean (SD)	60.3 (15.7)	59.9 (13.8)	0.9
Follow-up time in the hospital, years, median (IQR)	9.7 (3.7-14.7)	4.9 (2.2-10.6)	0.001
Type of surgery, n (%)			
Total Knee Arthroplasty (TKA)	27 (54)	26 (26)	0.001
Total Hip Arthroplasty (THA)	20 (40)	72 (72)	<0.001
Total Hip and Knee Arthroplasty	3 (6)	2 (2)	0.2
Time of evolution of RA at the time of THA, years, median (IQR)	10.8 (2.9-15.7)	—	—
Time of evolution of RA at the time of TKA, years, median (IQR)	13.3 (4.7-17.8)	—	—
Preoperative medications, % (CI 95%)			
Glucocorticoids	56 (41.8-69.2)	—	—
csDMARD	72 (57.8-82.8)	—	—
bDMARD	34 (22.1-48.4)	—	—
Treated with glucocorticoids, years, median (IQR)	3 (0-7)	—	—
Suspension of medication prior to surgery	34 (22.1-48.4)	—	—
Comorbidity, % (CI)			
Diabetes mellitus	8 (2.9-19.7)	11 (6.1-18.9)	0.56
Arterial hypertension	50 (36.2-63.7)	47 (37.3-56.9)	0.73
Dyslipidemia	28 (17.2-42.2)	21 (14.1-30.2)	0.34
Active smoker	12 (5.4-24.5)	11 (6.1-18.9)	0.86
Previous articular surgery	18 (9.5-31.4)	11 (6.1-18.9)	0.23
Prosthetic Joint Infection, % (CI)	6 (1.9-17.3)	2 (0.5-7.8)	0.2

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Herpes Zoster in Rheumatoid Arthritis. Prospective Single Center Study of 390 RA Patients for 5 YEARS

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Background/Purpose: Immunosuppressed patients such as Rheumatoid Arthritis (RA) patients have a greater risk (1.5-2 times) of presenting herpes zoster (HZ). Both, the disease itself and the use of immunosuppressive drugs, are involved in this increased risk. Furthermore, in these patients is more frequent disseminated presentation of zoster involving several dermatomes.

In a series of RA patients our aim was analyzed HZ infections and to assess **a)** HZ prevalence and **b)** HZ general features.

Methods: Prospective Single center study of 390 RA patients included in the vaccination program of the Preventive and Rheumatology department of our hospital between October 2011 and October 2016. The follow-up was made until December 2017. HZ vaccination is not included in our program.

RA was diagnosed according to the ACR/EULAR 2010 proposed criteria (Arthritis Rheum 2010; 62: 2569–2581)

The diagnosis of HZ was made according to the clinical manifestations and was confirmed by a dermatologist. These manifestations were characteristic skin rash and blisters, paresthesia and local pain, in one (localized) or more dermatomes (generalized)

Results: We studied 390 patients (307♀/83 ♂), average age 61.28±12.9 years that were included in the vaccination program and followed up.

HZ infection was observed in 12 of 390 (3.07%) in the follow-up (TABLE).

The 12 RA patients (11 women/1 man) with a mean±SD age of 67.5±11.67. More than half of patients, 7 (58.33%) were taking corticosteroids. 8 patients (66.66%) were receiving conventional disease modifying drugs (DMARDs) methotrexate (33.33%), leflunomide (16.66%) and hydroxychloroquine (16.66%). Besides corticosteroids and conventional DMARDs, 7 patients (58.33%) were in treatment with biologic drugs, tocilizumab (n=2), etanercept (n=2), adalimumab (n=2), and rituximab (n=1).

Conclusion: Herpes zoster is a relative frequent viral infection in RA patients non-vaccine for HZ. The female sex, older age, more aggressive RA and treatment with corticosteroids were more frequent. Probably in this group of patients HZ vaccination may be useful. Table General features of 12 RA patients at HZ infection

Case	Sex	Age (years)	Duration of RA (months)	RF+/-	APCA+/-	Erosive RA	HZ Localization	Previous Herpes Viral serology	HZ Treatment	Concomitant treatment for RA
1	♀	74	339	+	+	Yes	Left arm	IgG+ IgM NR	Famciclovir	Corticoids/MTX/TCZ
2	♀	86	142	+	-	Yes	-	IgG+ IgM -	None (topic)	ETN
3	♀	80	90	-	-	Yes	Gluteus (right)	IgG + IgM NR	Brivudina	HCO
4	♀	83	313	+	-	Yes	D9-D10 metamer	IgG + IgM -	Brivudina	Corticoids/MTX/RTX
5	♀	52	222	+	-	Yes	Generalized	IgG + IgM NR	Aciclovir	Corticoids
6	♀	70	171	+	-	No	Left arm	IgG+ IgM NR	Aciclovir	Corticoids/MTX/ADA
7	♀	68	1	+	-	Yes	Intercostal (left)	IgG + IgM -	Brivudina	Corticoids/HCO
8	♀	61	40	-	-	No	-	IgG + IgM NR	-	Corticoids/LFN/TCZ
9	♂	58	34	+	+	No	Intercostal (left)	IgG + IgM NR	Famciclovir	None
10	♀	62	67	+	+	Yes	Intercostal (left)	IgG + IgM NR	Aciclovir	LFN/ETN
11	♀	50	5	-	-	No	Intercostal (left)	IgG + IgM NR	Aciclovir	Corticoids/MTX/ADA
12	♀	66	2	+	+	No	Gluteus (left)	IgG + IgM -	Aciclovir	None

Abbreviations: MTX: methotrexate, LFN: leflunomide, HCQ: hydroxychloroquine, TCZ: tocilizumab, ADA: adalimumab, ETN: etanercept

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Abstract Number: 2452

Incidence Rate and Clinical Characteristics of Herpes Zoster Infection in Korean Patients with Rheumatoid Arthritis Patients

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Herpes zoster (HZ) infection is not uncommon in rheumatoid arthritis (RA) patients, especially in those treated with biologic or targeted synthetic (bts) disease-modifying antirheumatic drugs (DMARDs). Detailed analyses of HZ infection in Korean RA patients are limited, i.e. the relative risk of HZ infection compared with conventional (c) DMARD-treated patients.

Methods: By utilizing the data of the Korean college of Rheumatology Biologics Registry, or KOBIO, we investigated the incidence rate of HZ infection in the registered RA patients. We analyzed 1375 btsDMARD users (group 1), and 617 cDMARD-only users (group 2) registered from 2013 to 2017. The hazard ratio (HR) of HZ infection was adjusted for age, baseline corticosteroid usage, eGFR, and DAS28 (model 1), or age, gender, disease duration, baseline corticosteroid usage, comorbidity, smoking, eGFR, and DAS28 (model 2).

Results: Baseline characteristics of in both populations differed (group 1 vs. group 2) in disease activity (mean DAS28 5.67 vs. 3.33), disease duration (mean 7.7 vs. 6.4 years), dose of corticosteroids, and estimated GFR (eGFR). The overall incidence rate (per 100 patient × years) was 1.49 (95% CI 0.96 - 2.00) in group 1, and 0.90 (95% CI 0.53 - 1.46) in group 2; higher in RA patients treated with btsDMARDs. The unadjusted HR of HZ infection in group 1 in reference to group 2 was 1.562 (95% CI 0.874 - 2.791), and the adjusted HR by model 1 was 1.677 (95% CI 0.698 - 4.027), 1.695 (95% CI 0.707 - 4.063) by model 2.

Conclusion: These results indicate that the incidence rate of HZ infection in btsDMARD users may largely be driven by the baseline characteristics which these RA patients reserve, not only by the augmented immunosuppression they receive.

Disclosure: S. J. Moon, None; M. J. Kim, None; S. K. Lee, None; S. H. Oh, None; H. A. Kim, None; K. Shin, None.

Abstract Number: 2453

Staphylococcus Aureus Carriage Rates Are High in Rheumatoid Arthritis Patients on Biologics

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with rheumatoid arthritis (RA) have a higher risk of surgical site infection than patients with osteoarthritis (OA). Disease modifying therapy is widely used by RA patients, and biologic medications may increase *Staphylococcus aureus* colonization rates. Because *S. aureus* colonization likely increases risk of surgical infection, perioperative assessments and therapies to decrease risk of invasive *S. aureus* infections may be warranted. The objective of this study was to determine if there was a difference in *S. aureus* carriage among patients with RA, OA, and RA on biologics (RA+B).

Methods: An *a priori* power analysis determined 123 participants per group were needed to detect a relative difference of 20% with 80% power. After IRB approval, patients were screened; included patients met ACR classification criteria. Patients were approached between April 2017 and May 2018 and performed a nasal swab using the Center for Disease Control's swabbing protocol; questionnaires pertaining to health status were collected. Swabs were inoculated onto ChromAgar/ChromID MRSA plates for detection of *S. aureus*. Mann-Whitney U and Chi-square tests were used to evaluate baseline differences between groups. Logistic regression evaluated the associations between groups and *S. aureus* carriage. All statistical analyses were performed using SAS Software version 9.3 (SAS Institute, Cary, NC); statistical significance was defined as $p < 0.05$.

Table 1: Patient Characteristics

Variable	All Patients N=369	RA + Biologic N=123	RA N=123	OA N=123	p-value
Age	65.63 ± 13.77	59.15 ± 14.4	65.82 ± 13.85	71.91 ± 9.51	<0.0001
BMI (kg/m ²)	28.17 ± 7.00	27.98 ± 7.12	26.36 ± 6.08	30.19 ± 7.25	<0.0001
Sex					<0.0001
Female	289 (78.32)	108 (87.8)	106 (86.18)	75 (60.96)	
Male	80 (21.68)	15 (12.2)	17 (13.82)	48 (39.02)	
Race					0.002
Asian	17 (4.61)	9 (7.32)	7 (5.65)	1 (0.81)	
White	284 (78.62)	87 (70.73)	87 (70.86)	110 (89.88)	
Black or African American	34 (9.21)	19 (15.45)	7 (5.69)	8 (6.5)	
Other	24 (6.5)	8 (6.5)	12 (9.78)	4 (3.25)	
Smoker (ever)	148 (40.11)	43 (34.96)	42 (34.15)	63 (51.22)	0.009
Smoker (current)	19 (5.15)	10 (8.13)	5 (4.06)	3 (2.44)	0.018
Diabetes	37 (10.03)	6 (4.88)	5 (4.06)	15 (12.2)	0.04
Glucocorticoids	67 (18.16)	32 (26.02)	18 (14.63)	17 (13.82)	0.0211
Antibiotics in past 3 months	164 (44.45)	29 (23.58)	21 (17.07)	54 (43.9)	<0.0001
Hospitalization in past year	89 (24.12)	22 (17.89)	14 (11.38)	53 (43.09)	<0.0001
Years since initial diagnosis	10.72 ± 10.38	13.55 ± 11.00	9.55 ± 10.02	9.04 ± 9.45	
<i>S. aureus</i> growth	59 (16.01)	45 (36.59)	29 (23.58)	25 (20.33)	

*Continuous variables are presented as means & standard deviations.

**Categorical variables are presented as frequency & percent.

Table 2 – Multivariate Analysis of the Relationship between Diagnosis and *S. Aureus* Growth

Risk Factor	OR (95% CI)	p-value
OA vs. RA	0.99 (0.50-2.00)	0.978
RA +biologics vs. RA	1.80 (1.01-3.22)	0.047
Age	0.99 (0.97-1.01)	0.209
BMI	1.01 (0.97-1.04)	0.664
Sex (Male vs. female)	0.80 (0.43-1.50)	0.491
Diabetes (Yes vs. No)	1.29 (0.52-3.19)	0.587
Steroid use (Yes vs. No)	0.79 (0.42-1.48)	0.460
Antibiotics use-last 3 months (Yes vs. No)	0.88 (0.50-1.56)	0.662
Hospitalization in past year (Yes vs. No)	0.82 (0.44-1.53)	0.523

Results: Overall the cohort evaluated had a mean age of 66 (+/-13.7), BMI of 28 (+/-7.0), and were predominantly female (78%) (Table 1). 28% were on antibiotics within three months prior to the swab, 18% were currently on steroids, and 24% had been hospitalized within the last year. We found differences in age ($p<0.001$), BMI ($p<0.001$), sex ($p<0.001$), diabetes ($p=0.04$), steroid use ($p=0.02$), antibiotic use ($p<0.001$), and hospitalizations within the last year ($p<0.001$). *S. aureus* carriage was most prevalent in RA+B (37%), followed by RA (24%), and OA (20%). After multivariate adjustment, RA+B was found to have increased odds of *S. aureus* (OR=1.80, 95% CI 1.00-3.22); $p=0.047$) compared to RA. Use of glucocorticoids, hospitalization, or diabetes did not increase odds of *S. aureus* carriage. The OA group had decreased odds of *S. aureus* compared to the RA group; however this was not statistically significant ($p=0.987$).

Conclusion: RA patients treated with biologics have an increased prevalence of *S. aureus* colonization. Since nasal *S. aureus* carriage may play a role in the pathogenesis of surgical infections, *S. aureus* decolonization should be considered in RA patients on biologics prior to elective surgery.

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Abstract Number: 2454

Virus Reactivation Rate in Rheumatoid Arthritis Using Tofacitinib

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Although the increase in the incidence of Herpes Zoster by tofacitinib (TOF) in rheumatoid arthritis (RA) is well known, the reactivation rate of other viruses is unknown. We clarify the reactivation rate of varicella virus (VZV), hepatitis B virus (HBV), EB virus and cytomegalovirus (CMV) when using TOF for RA patients.

Methods: We measured VZVIgG, VZVIgM, high sensitivity HBs antigen, HBV-DNA, CMVIgG (EIA), CMVIgM (EIA), CMV antigenemer, EBV VCA IgG (EIA, FA) and EBV VCA IgM (EIA, FA) once every 3months. Antigenemia positive, high sensitivity HBs antigen positive, IgG antibody raised by 4 times or more was defined as virus reactivation.

Results: 35 RA patients, 77% of women, 65 years of age, 10 years of disease duration, 74% positive for CCP antibody, SDAI 9.5, corticosteroid (PSL) use rate 14%, mean PSL 2.2 mg / day, MTX usage 23%, mean MTX dose 7.5 mg / week, TOF (average 8 mg / day) was administered on average for 12 months. Each virus reactivation rate was 2.9, 8.6, 25.5 and 0% for CMV, HBV, VZV and EBV, respectively. There were no cases where more than two types of virus reactivation came. As clinical symptoms CMV had fever, VZV showed all cases, eruption. No liver dysfunction was observed in HBV reactivation case. A significant difference (68.8 vs 29.7 $p<0.05$) was observed in the CMV IgG value between the cases of HBV reactivation and no other virus reactivation cases.

Conclusion: Viral reactivation by TOF administration in RA is diverse and its rate is high (37.1%) by highly sensitive virus examination and elaborate observation of body findings, However, it is possible to prevent the seriousness of virus reactivation by TOF by detailed examination and appropriate blood collection, early treatment.

Table 1 Comparison of patient characteristics with or without varicella zoster virus reactivation

	Reactivation (+)	Reactivation (-)	p
n	10	26	
Female (%)	90	73	0.2740
Age (median) (IQR)	66 (59-68)	64 (58-68)	0.5022
Disease duration (month) (mean) (95% CI)	183 (83-284)	153 (110-196)	0.5482
Duration of administration of TOF (month) (mean) (95% CI)	20.8 (9.8-31.8)	12.5 (7.7-17.3)	0.0797
IgMRF positive (%)	80	62	0.2926
CCP positive (%)	80	69	0.5182
SDAI (Base) (median) (IQR)	14.3 (7.6-21.9)	9.1 (4.2-17.0)	0.2659
HAQ-DI (mean) (IQR)	0.7 (0.0-0.9)	0.3 (0.1-1.0)	0.9152
TOF dose (mg/day) (mean) (95% CI)	7.5 (5.6-9.4)	8.3 (7.3-9.2)	0.4030
PSL use (%)	10	15	0.6756

Table . (Cont'd)

	Reactivation (+)	Reactivation (-)	p
PSL dose (mg/day) (mean) (95% CI)	2.0	2.3 (0.2-4.3)	1.0000
MTX use (%)	20	27	0.6674
MTX dose (mg/wk) (mean) (IQR)	5.0 (5.0-10.0)	7.5 (2.5-10.0)	1.0000
CRP (mg/dL) (Last) (mean) (95% CI)	1.5 (0.0-2.9)	1.6 (0.7-2.6)	0.8735
MMP-3 (mean) (95% CI)	203 (95-311)	172 (101-243)	0.4166
IgG (mean) (95% CI)	1371 (1224-1518)	1323 (1157-1489)	0.6236
sIL-2R (U/mL) (mean) (95% CI)	549 (401-696)	590 (430-749)	0.8266
WBC (/mm ³) (mean) (95% CI)	2309 (4676-7980)	3130 (5550-8078)	0.9156
Lymphocyte (/mm ³) (mean) (95% CI)	1480 (1216-1744)	1401 (1149-1653)	0.3227
HBV positive (%)	70	38.5	0.0896
HBsAb positive (%)	40	12	0.0533
HBsAb (median) (IQR)	18 (9.9-122.3)	9 (0.6-61.5)	0.4133
HBcAb positive (%)	40	23	0.3099
HBcAb (median) (IQR)	18 (10-122)	9 (1-62)	0.3991
HBeAb positive (%)	10	12	0.8953
HBeAb (mean) (IQR)	23 (0-75)	61 (0-82)	0.7086
VZV IgM (mean) (95% CI)	0.4 (0.3-0.5)	0.4 (0.3-0.4)	0.7237
VZV IgG (mean) (95% CI)	22.5 (11.0-34.1)	22.6 (16.3-28.9)	0.8589
EB VCA IgM (mean) (95% CI)	2.0 (0.3-3.1)	1.5 (0.5-2.5)	0.4881
EB VCA IgG (mean) (95% CI)	8.2 (6.3-10.1)	7.1 (5.7-8.5)	0.3054
EBNA (mean) (95% CI)	3.7 (3.3-4.1)	3.1 (2.6-3.6)	0.2724
CMV IgM (mean) (95% CI)	0.6 (0.3-1.2)	0.5 (0.4-0.6)	0.6208
CMV IgG (mean) (95% CI)	33.3 (18.5-48.1)	32.2 (22.6-41.8)	0.8737

Table 2 Comparison of patient characteristics with or without HBV reactivation

	Reactivation (+)	Reactivation (-)	p
n	3	14	
Female (%)	33	79	0.1186
Age (median) (IQR)	64 (53-76)	65 (63-67)	0.8997
Disease duration (month) (mean) (95% CI)	237 (101-373)	160 (102-218)	0.1306
Duration of administration of TOF (month) (mean) (95% CI)	18.7 (3.5-33.8)	13.5 (5.3-21.8)	0.6106
IgMRF positive (%)	100	79	0.3770
CCP positive (%)	100	79	0.3770
SDAI (Base) (median) (IQR)	11.9 (-28.9-52.6)	14.4 (8.4-20.4)	0.2659
HAQ-DI (mean) (IQR)	0.8 (0.0-1.0)	0.6 (0.2-0.9)	0.4670
TOF dose (mg/day) (mean) (95% CI)	8.3 (1.2-15.5)	8.2 (6.8-9.7)	0.9394
PSL use (%)	0	14	0.4858
PSL dose (mg/day) (mean) (95% CI)		3.0 (-9.7-15.7)	
MTX use (%)	33	21	0.6594
MTX dose (mg/wk) (mean) (IQR)	5.0	8.8 (4.8-12.7)	0.2207
CRP (mg/dL) (Last) (mean) (95% CI)	2.2 (-6.8-11.1)	1.8 (0.3-2.4)	0.8008
MMP-3 (mean) (95% CI)	166 (-356-688)	230 (92-368)	0.5287
IgG (mean) (95% CI)	1634 (1391-1876)	1402 (1183-1623)	0.0628
sIL-2R (U/mL) (mean) (95% CI)	558 (278-838)	694 (424-962)	0.8997
WBC (/mm ³) (mean) (95% CI)	5373 (3790-6956)	5935 (4440-7431)	1.0000
Lymphocyte (/mm ³) (mean) (95% CI)	1358 (-458-3175)	1257 (1047-1467)	0.8997
HBV positive (%)	100	100	
HBsAb positive (%)	33	43	0.7610
HBsAb (median) (IQR)	2 (0.2-29.6)	17 (8.8-114.5)	0.2207
HBcAb positive (%)	100	50	0.1103
HBcAb (median) (IQR)	9 (7.9-9.8)	8 (4.6-9.8)	0.6831
HBeAb positive (%)	67	14	0.0523
HBeAb (mean) (IQR)	81 (50-86)	12 (0-68)	0.0946
VZV IgM (mean) (95% CI)	0.4 (0.0-0.8)	0.4 (0.3-0.4)	0.5703
VZV IgG (mean) (95% CI)	28.1 (7.1-49.0)	24.0 (15.2-32.9)	0.4497
EB VCA IgM (mean) (95% CI)	2.7 (-3.1-8.4)	2.0 (0.1-3.8)	0.2776
EB VCA IgG (mean) (95% CI)	7.1 (-3.4-17.5)	8.3 (6.9-9.6)	0.8997
EBNA (mean) (95% CI)	3.6 (1.2-6.0)	3.4 (2.9-3.9)	0.8994
CMV IgM (mean) (95% CI)	1.1 (-1.7-3.9)	0.6 (0.5-0.8)	1.0000
CMV IgG (mean) (95% CI)	68.8 (-14.6-152.2)	34.2 (22.6-45.6)	0.0438

Disclosure: Y. Urata, None;

Risk of Venous Thromboembolism in Rheumatoid Arthritis Patients Treated with Biologic and Non-Biologic Dmards

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

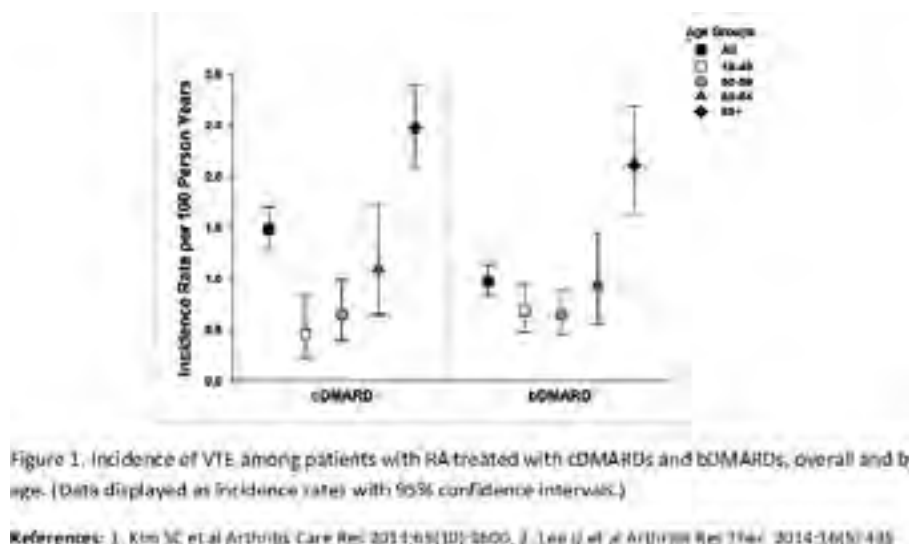
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Individuals with rheumatoid arthritis (RA) have an increased risk of venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), compared with non-RA populations based on several recent studies^{1,2}. However, information is sparse on the risk of VTE among patients receiving treatment with specific disease-modifying antirheumatic drugs (DMARDs) or categories of therapies. The objective was to estimate the incidence of VTE among patients receiving routine clinical care for RA, specifically during treatment with conventional (c) and biologic (b) DMARDs.

Methods: Incidence rates were estimated in a retrospective cohort study of patients with RA (defined as at least 2 International Classification of Disease, Ninth Revision, Clinical Modification [ICD-9-CM] Diagnostic codes) enrolled in US health insurance plans between October 1, 2010 to September 30, 2015 and participating in the Innovation in Medical Evidence Development and Surveillance (IMEDS) program. These data are formatted into the U.S. Food and Drug Administration's Sentinel Common Data Model and Sentinel's publicly available standardized analysis tools were used to estimate the incidence rates of VTE following initiation of cDMARDs or bDMARDs. Patients were required to be new users of the study drug class, with no evidence of use in the 365 days preceding initiation and were not allowed to re-enter the cohort. Patients were required to demonstrate continuous use of the study drug class to be considered at risk for VTE. VTE was defined based on ICD-9-CM codes, but patients diagnosed in outpatient settings were also required to have evidence of oral anticoagulant dispensing within 31 days of the event. PE and DVT ICD-9-CM codes were also disaggregated to produce separate incidence rates.

Results: During treatment with any cDMARDs (methotrexate or leflunomide) or bDMARDs (abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab), patients experienced VTE at a crude incidence rate of 1.49 (95% CI 1.30, 1.71) per 100 person-years (PY) and 0.98 (95% CI 0.83, 1.14) per 100 PY, respectively. For each study drug class, age was an important risk factor for VTE, with increasing age associated with higher rates of VTE; for example, during treatment with bDMARDs incidence rate (IR)_{18-49 years}=0.69, IR_{50-59 years}=0.65, IR_{60-64 years}=0.94, and IR_{65+ years}=2.11 per 100 PY (Figure 1). Men also had higher incidence rates of VTE than women.



In the analyses of PE and DVT, DVT incidence rates were higher than PE incidence rates, and similar incidence rate trends overall and across age strata for cDMARD and bDMARD cohorts were noted.

Conclusion: Venous thromboembolism is an important clinical concern among patients with RA and incidence rates vary by age and sex during routine clinical treatment with DMARDs.

Disclosure: J. Maro, U.S. Food and Drug Administration, 2; T. Menzin, None; K. Hornbuckle, Eli Lilly and Company, 1, 3; J. T. Giles, Eli Lilly and Company, 2, 5; A. Kavanaugh, for Eli Lilly and Company, 5; T. Dörner, Roche/Chugai, Janssen, Sanofi, 2, AbbVie, Celgene, Eli Lilly and Company, Roche, UCB, MSD, Pfizer/Hospira, Novartis, 5, Amgen, Celgene, Biogen, 8; D. Martin, FDA, 3; J. Huang, None; C. A. Salinas, Eli Lilly and Company, 1, 3.

Abstract Number: 2456

Risk of Venous Thromboembolism in Rheumatoid Arthritis Patients in Truven MarketScan Data (Jan 2010–Sept 2015) Treated with Biologic or Conventional Dmards

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with RA have an increased risk of venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT) compared to non-RA populations¹. However, there is limited information available on the risk of VTE among patients receiving treatment with specific DMARDs or categories of therapies. This retrospective cohort study aimed to estimate the incidence of VTE among patients receiving routine clinical care for RA, specifically during treatment with conventional (c) and biologic (b) DMARDs.

Methods: Administrative claims data from TruvenMarketScan, with information on patients enrolled in US commercial or Medicare health plans between January 2010 to September 2015, were used to identify patients diagnosed with RA who had a VTE, PE or DVT during an incident treatment episode. Patients were required to maintain enrollment in the health plan and have drug coverage, with a gap of no more than 45 days, and have at least 2 RA diagnosis codes (International Classification of Diseases, 9th Revision, Clinical Modification [ICD 9-CM]) at least 7 days apart, but within a 365-day period. Medication exposures were based on generic medication names and National Drug Codes and included only incident exposures for the specified medications or medication categories. Incident VTE, PE, and DVT were defined using ICD-9-CM codes and, for events diagnosed in outpatient settings, evidence of dispensing of an anticoagulant within 31 days of the event. All analyses were conducted using SAS v.9.4.

Results: Among 205,785 patients diagnosed with and treated for RA, the crude incidence rate of VTE was 1.05 (95% CI 1.01, 1.09) per 100 person-years (PY). Patients receiving treatment with cDMARDs appeared to have increased risk of

Treatment	Patients (n)	VTE			PE			DVT		
		Events (n)	PY	IR per 100 PY	Events (n)	PY	IR per 100 PY	Events (n)	PY	IR per 100 PY
RA medications, any	205,785	2576	244,940.4	1.05 (1.01, 1.09)	1135	246,199.9	0.46 (0.43, 0.49)	3311	243,903.0	1.36 (1.31, 1.40)
cDMARDs	71,552	719	58,451.5	1.23 (1.14, 1.32)	309	58,710.6	0.53 (0.47, 0.58)	911	58,244.4	1.56 (1.46, 1.67)
bDMARDs	77,086	826	86,827.5	0.95 (0.89, 1.02)	397	86,948.1	0.46 (0.41, 0.50)	1091	86,304.1	1.26 (1.19, 1.34)

bDMARDs=biologic disease-modifying antirheumatic drugs, cDMARD=conventional DMARDs, DVT= deep vein thrombosis, IR=incidence rate, PE= pulmonary embolism, PY=person-years, RA=rheumatoid arthritis, VTE= venous thromboembolism

VTE compared to those treated with bDMARDs (see table), but this difference disappeared when age-stratified incidence rates were examined. For PE and DVT, defined based on diagnostic codes only, the crude incidence rates for patients treated with any DMARD were 0.46 (95% CI 0.43, 0.49) and 1.36 (95% CI 1.31, 1.40) per 100 PY, respectively. Incidence rates of VTE were elevated among those with increased age and rates of DVT were consistently higher than rates of PE.

Conclusion: Patients with RA treated with DMARDs were at risk of VTE. Differences in incidence rates of VTE between patients treated with cDMARDs or bDMARDs were likely due to differences in age distributions between groups, with those in the cDMARD cohort tending to be older than those in the bDMARD cohort.

References: 1. Kim SC et al *Arthritis Care Res.* 2013;65(10):1600

Disclosure: C. A. Salinas, Eli Lilly and Company, 1, 3; L. Mitchell, Eli Lilly and Company, 1, 3; J. T. Giles, Eli Lilly and Company, Genentech, Horizon, 5, Pfizer, Inc., 2; T. Dörner, Roche/Chugai, Janssen, Sanofi, 2, AbbVie, Celgene, Eli Lilly and Company, Roche, UCB, MSD, Pfizer/Hospira, Novartis, 5, Amgen, Celgene, Biogen, 8; S. P. Motsko, Eli Lilly and Company, 1, 3.

Abstract Number: 2457

Association between Biologic Dmards and Weight Change in Patients with Inflammatory Arthritis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

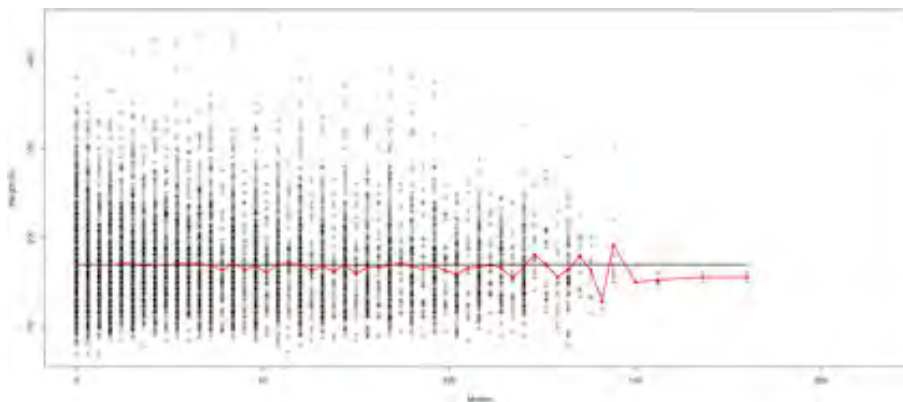
Background/Purpose: Inflammatory arthritis (IA) is a chronic disorder that encompasses rheumatoid and psoriatic arthritis. Rheumatoid cachexia is defined as elevated HDL, increased adiposity, and loss of lean muscle mass and affects up to two thirds of patients with IA. This can result in extremes of weight and is associated with higher disease activity, elevated rate of cardiovascular disease, and increased sedentary behavior.

Conflicting evidence exists around weight change associated with biologic Disease Modifying Antirheumatic Drugs (boDMARDs). This study sought to examine if weight or body mass index is correlated with treatment with a boDMARD in patients with inflammatory arthritis. Secondary objectives examined disease activity as a function of weight change.

Methods: This study was a retrospective analysis of 2228 patients with IA enrolled in the Rheumatoid Arthritis Pharmacovigilance Program and Outcomes Research in Therapeutics (RAPPORT) Database. This database is a cohort of patients with Inflammatory Arthritis in Northern Alberta that captures demographic information including weight at baseline, 1 month, 3 months, 6 months, and subsequently yearly. Weight in pounds, body mass index (BMI), and DAS 28 were tracked over time in months using a mixed effect model with subject specific random effects.

Results: There was a small but statistically significant increase in weight (0.02 lbs, 95% CI 0.018-0.03 p<0.001) and BMI (0.006lbs, p<0.001) over time in months. There was also a negative association between DAS 28 and increased weight (-0.56, p<0.001) as well as BMI (-0.08, p<0.001) suggesting an increase in weight was associated with lower disease activity.

Conclusion: Extremes of weight and BMI have previously been shown to be a risk factor for poor long-term outcomes in patients with IA. This study suggests that patients with inflammatory arthritis on boDMARDs tend to gain weight over time, in keeping with previous studies examining the effects of TNFi on weight. This may be reflective of improved disease control given the negative association between increased weight/BMI and decreased DAS 28. Alternately, it may suggest weight stabilization as by comparison, the average Canadian gains approximately 0.25-0.5lbs/year.



Figures:: Figure 1: Weight(lbs) trend over time after initiation of biologics. Number of patients: 2298. Total visits: 16642.

Disclosure: B. Jones, None; I. Hassan, None; W. P. Maksymowych, CaRE arthritis, 9; E. Yacyshyn, None.

Abstract Number: 2458

Predictors of Hypogammaglobulinemia during Rituximab Maintenance Therapy in Rheumatoid Arthritis: A 12-Year Longitudinal Multi-Center Study

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rituximab (RTX) is an anti-CD20 monoclonal antibody that selectively depletes B-cell population. Thus, it presents a potential risk for the development of hypogammaglobulinemia and related infectious events. Our aim was to identify predictors of hypogammaglobulinemia in RA patients long-term treated with RTX.

Methods: Multicenter longitudinal observational usual care study including RA patients according to ACR 1987 and/or ACR/EULAR 2010 classification criteria followed and treated with RTX. A previous study assessing the safety profile of RTX in patients with RA reported a median follow-up of 30 months (1). Therefore, we decided to include RA patients on RTX maintenance therapy, after a minimal exposition of 30 months. Serum protein electrophoresis was performed one to three days before each RTX infusion. Hypogammaglobulinemia and severe hypogammaglobulinemia were defined as total gammaglobulin <6g/L and <4g/L, respectively. Safety monitoring included the collection of all adverse events (AE) in particular severe infections.

Results: 134 patients met inclusion criteria: 113 female subjects (84.3%); mean age 52.1 ± 11.4 years. Mean follow-up was 79.5 ± 24.6 months and analysis was based on 854.9 patient-years (pt-yrs) of observation. Mean RTX cumulative dose was 12.0 ± 4.9 g. Baseline gammaglobulin levels were significantly lower in subjects aged >65 years as compared to subjects aged <65 years: 10.42 ± 3.05 g/L vs 12.85 ± 3.89 g/L respectively ($p=0.0002$). Hypogammaglobulinemia (<6g/L) occurred during the follow-up period in 23 patients (2.7 events per 100 pt-yrs), leading to an incidence of 17.1%. The mean time to development of hypogammaglobulinemia was 64 ± 23 months. A total of 9.7% of patients had severe infections (1.5 events per 100 pt-yrs). Patients who developed hypogammaglobulinemia were more likely to experience severe infections (26.1% vs. 6.3%, $P=0.033$). Univariate Cox analysis identified age over 65 years (HR 4.28 [95% CI 0.92-19.97], $P<0.001$), low gammaglobulin levels prior the first RTX infusion (<8g/L) (HR 7.35 [95% CI 1.82-29.68], $P<0.001$) as predictors of protective factor (HR 0.26 [95% CI 0.08-0.87], $P=0.03$).

Conclusion: Our results show that gammaglobulin levels of less than 8g/L at baseline is a strong independent risk factor for developing subsequent hypogammaglobulinemia, whereas concomitant MTX therapy seems to be a protective factor in RA patients treated long-term with RTX. Identifying such predictors will raise clinicians' awareness and allow more tailored monitoring of RA patients long-term treated with RTX.

References: (1) Isvy et al, Joint Bone Spine 2012

Disclosure: G. Boleto, None; J. Avouac, None; J. Wipff, None; M. Forien, None; M. Dougados, None; C. Roux, None; A. Kahan, None; P. Dieude, None; Y. Allanore, None.

Abstract Number: 2459

Nivolumab-Induced Synovial Tissue T Cell Infiltration, Sustained PD1 Occupancy and Resolution of Severe Synovitis with Infliximab Therapy

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Checkpoint inhibitors (CI) for cancer therapy are associated with inflammation that can recapitulate features of autoimmunity, including synovitis resembling rheumatoid arthritis (RA). No reports have investigated cellular infiltrates in the synovial tissue (ST) of these patients and no guidelines exist to manage them. Thus, we provide the first report on ST cellular infiltration in PD1 inhibitor-induced rheumatic immune-related adverse-events (irAE).

Methods: ST biopsies, synovial fluid (SF) and PBMCs from a nivolumab-treated small cell lung cancer (SCLC) patient with severe peripheral inflammatory polyarthritis and inadequate response to DMARDs (negative RF and ACPA); 3 DMARD-naïve patients with seropositive early RA were used as comparators.

Serial sections from fresh-frozen ST blocks were stained with H&E, CD3, CD45RO, CD55 and CD68 and semi-quantitatively scored. ST, SF and PBMC single cell suspensions were stained with Zombie UV[®], CD45RO, PD1, CD3, ICOS, CD8, CD4 CD20 prior to flow cytometric acquisition.

Results: CD68+ macrophage, CD20+ B cell and CD3+ T cell and CD45RO+ memory T cell infiltration in irAE was comparable to RA ST on semi-quantitative scoring, while TNF α staining was markedly elevated in irAE compared to RA (irAE-TNF α ; 4, RA-TNF α ; 2) (Figure 1). Flow cytometric analysis identified persistent CD45RO⁺ memory T cell infiltration in the ST and SF compartments (irAE: ST; 27.7, SF; 24.9) compared to RA (RA: ST mean and SEM; 27.5 \pm 3.63; SF; 35.9 \pm 4.85; n=3 for each), driven by continued occupancy of PD1 by nivolumab even 200-days after cessation of treatment (Figure 2). Finally, treatment with infliximab resulted in partial remission of symptoms and reduced synovitis

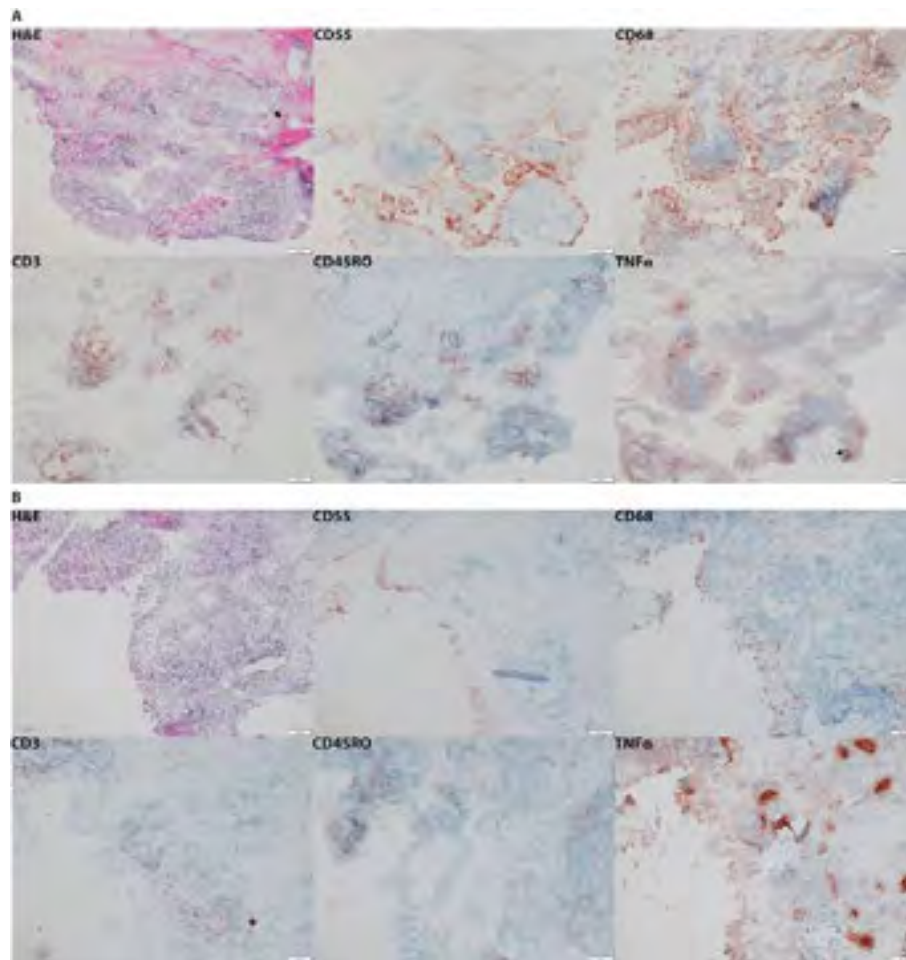


Figure 1. A, RA ST sections (images representative of all 3 RA). B, ICI-irAE SCLC ST sections. Images were captured at x10 magnification.

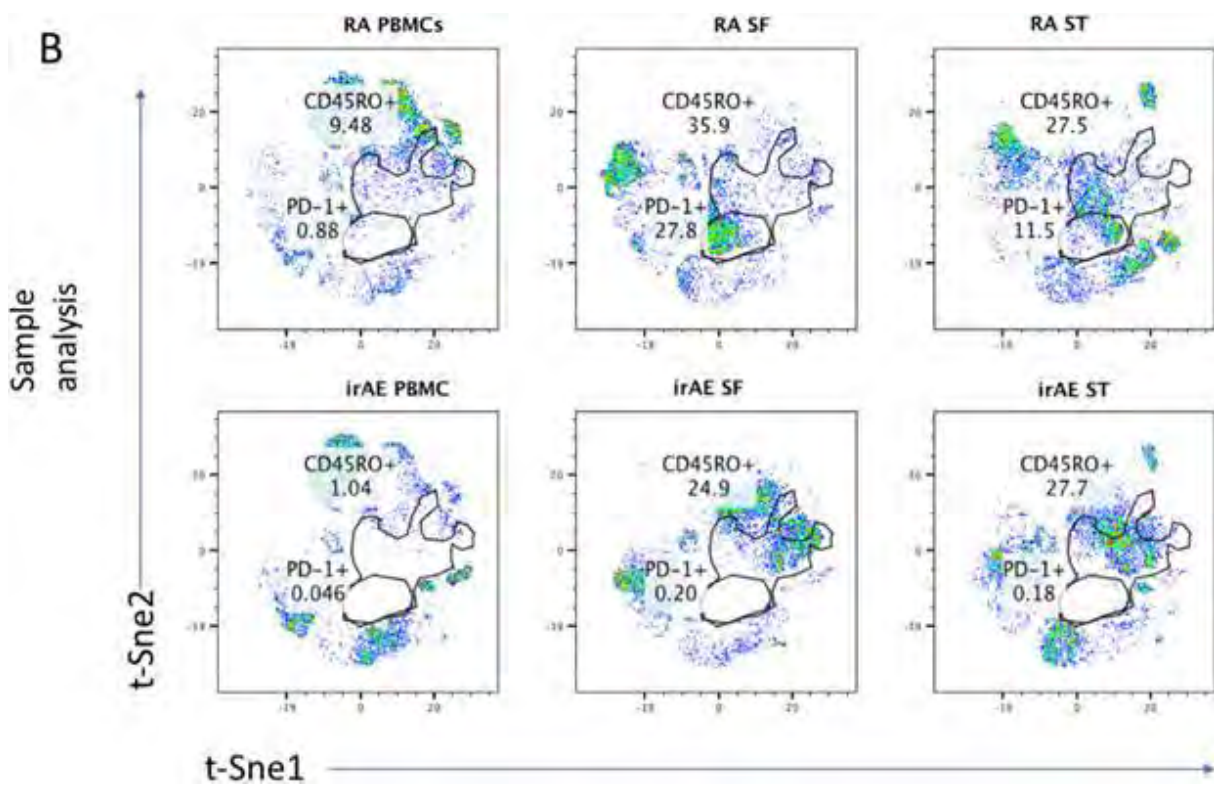


Figure 2. T-Sne global analysis performed on all samples concatenated in a common dimensionally reduced space. Comparable CD45RO+ T cell frequency in ST (irAE; 27.7, RA mean and SEM; 26.5±2.3, n=3) and SF (irAE; 24.9, RA; 36.6±1.79, n=3), flow cytometry revealed a distinct absence of PD1 staining in irAE (ST: irAE: 0.18, SF: 0.20, PBMCs; 0.46) compared to RA (RA: ST; 12.13±1.63; SF; 25.95±2.85; PBMCs; 0.11±0.13, n=3). RA plots representative of all samples.

Conclusion: ST infiltration in irAE SCLC recapitulates many features of RA histopathology. The continued persistence of nivolumab occupancy in rheumatic-irAEs provides a mechanism for exacerbated inflammation. Infliximab treatment was shown to lead to remission in irAE demonstrating high levels of ST TNF α .

Disclosure: W. Murray-Brown, None; H. Weedon, None; T. Wilsdon, None; S. Proudman, None; J. Walker, None; M. D. Smith, None; M. D. Wechalekar, None.

Abstract Number: 2460

Study of Sixteen Cases of Other Iatrogenic Immunodeficiency-Associated Lymphoproliferative Disorders Developed in Rheumatoid Arthritis Patients

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Methotrexate-associated lymphoproliferative disorders (MTX-LPDs) was first reported in 1991. The symptom is known to spontaneously regress after suspending the use of MTX, suggesting its association with LPDs. In recent years, there have been also reports of the disorder's association with biological drugs and immunosuppressive drugs, which are classified as a kind of other iatrogenic immunodeficiency-associated lymphoproliferative disorders (OIIA-LPDs). Regional differences in terms of their frequency, their risk factors, and many other aspects of the disorders still remain unknown.

Methods: The study assessed 16 patients who experienced the onset of OIIA-LPDs during the use of MTX, immunosuppressive drugs, or biological drugs between April 2011 and April 2018. The patients were assessed for their ages, pathological types, MTX dosages, LDH, CRP, lymphocyte counts, sIL-2R, MMP-3, EBER-ISH, EBV-DNA, and DAS28CRP. Also, the study used parameters to analyze the group of patients whose symptoms spontaneously regressed and the other group treated with chemotherapy.

Results: Among the 16 cases, six cases went through spontaneous regression, while two cases terminated in death. Among pathological types, DLBCL accounted for nine cases, followed by four cases with Hodgkin lymphoma. Among the three cases tested with EBER-ISH, two cases were found positive, while one out of four cases tested with EBV-DNA was identified positive. The DAS28CRP level at the onset of LPD was 1.80±0.3 in the spontaneous regression group and 3.8±1.1 in the chemotherapy group, demonstrating a significant decrease ($p=0.01182$) in the spontaneous regression group.

Conclusion: Among the patients with OIIA-LPDs originating in rheumatoid arthritis, the number of EBER-ISH-positive cases was significantly high. Furthermore, the possible association of the active status of rheumatoid arthritis at the onset of LPDs with the necessity of chemotherapy was suggested.

Disclosure: Y. Ikeno, None; Y. Kobayashi, None; I. Akutsu, None; H. Hirata, None; M. Arima, None; K. Kurasawa, None.

Analysis of Severe Adverse Drug Reactions to Disease Modifying Drugs in an Inception Rheumatoid Arthritis Cohort

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: There is a well-known risk of developing adverse drug reactions (ADR) in rheumatic patients due, mainly, to the Disease Modifying Drugs (DMARD) widely used. It is mandatory to increase our knowledge of ADR outside of clinical trials; especially those that put the patient live at risk. The purpose of our study was to describe the incidence and characteristics of severe ADR (SADR) to DMARD in patients with incident RA as well as the factors associated to their development.

Methods: We conducted an observational longitudinal study. Patients: all recent onset RA diagnosed between April 15th 2007 and December 31st 2014 followed in outpatient clinic at Hospital Clinico San Carlos until December 31st 2016, which used any DMARD treatment (synthetic and biologic). Primary outcome: development of a SADR (discontinuation and hospitalization or death due to the ADR). Incidence rates of discontinuation (IR) per 100 patient-years were estimated using survival techniques with their respective 95% confidence interval [CI]. Comparisons between associated factors were run by Cox bivariate and multivariate regression models. Results were expressed by hazard ratio (HR) and [CI].

Results: We included 2388 courses of DMARD treatment in 814 patients (3706.14 patient-years). Of these, 77.52% were women with a mean age at diagnosis of 57.53 ± 15.50 years. 72.85% of patients were diagnosed at first visit and the median value of ESR at diagnose was 35.6 ± 26.9 mm/h. From the courses of DMARD, 13.74% were biologicals (72.04% anti-TNF) and 60% were used in monotherapy. There were 56 SADR in 47 patients (IR: 1.51[1.16-1.96]). Infection was the most frequent cause of SADR (n=31, 55.36%), followed by cancer (n=8, 8.93%); 12 patients died due to an ADR (IR: 0.32 [0.18-0.57]), mostly because of sepsis. IR are shown in table 1. We performed a multivariate analysis (table 2). We repeated the model changing the reference category of DMARD and found a higher risk to develop SADR also for Abatacept (HR: 15.38 [1.93-122.75]) and Gold (HR: 2.31 [1.06-5.03]) compared to the other drugs; the rest of DMARD did not achieve statistical significance in the models performed.

Conclusion: The IR of SADR in our cohort was 1.51% patient-years, being infection the main cause. We found differences in discontinuation rates among DMARD due to SADR, with Abatacept, Tocilizumab and Gold being the drugs with the highest risk. Caution should be taken regarding severe ADR in older patients, male sex, patients living alone or institutionalized, with higher values of ESR at the beginning of DMARD and those using combined therapy or with concomitant corticoids.

Table 1

	Patient-years	n	IR	95%CI
Global	3706.14	56	1.51	1.16-1.96
Women Men	2976.78/29.36	3422	1.14/3.02	0.82-1.60/1.99-4.58
By age category	908.37	7	0.77	0.37-1.62
18-50 years	1963.68	23	1.17	0.78-1.76
51-70 years > 70 years	834.09	26	3.12	2.12-4.58
By therapy regimen	2556.40	32	1.25	0.89-1.77
Monotherapy Combined treatment	1149.74	24	2.09	1.40-3.11
By type of DMARD	3319.50	42	1.27	0.94-1.71
Synthetic	295.10	9	3.05	1.59-5.86
Anti TNF Other biologic DMARD	91.54	5	5.46	2.27-13.12
By treatment course	1666.32	17	1.02	0.63-1.64
First Other	2039.82	39	1.91	1.40-2.62
By drug	12.68	2	15.77	3.95-63.07
Abatacept	23.72	3	12.65	4.08-39.21
Infliximab	14.77	1	6.77	0.95-48.05
Golimumab	16.56	1	6.04	0.85-42.86
Tocilizumab	136.77	8	5.85	2.91-11.70
Gold	62.30	2	3.21	0.80-12.84

Table . (Cont'd)

	Patient-years	n	IR	95%CI
Rituximab	224.45	7	3.12	1.49-6.54
Sulfasalazine	31.36	1	3.09	0.45-22.64
Certolizumab	101.30	3	2.96	0.96-9.18
Etanercept	482.82	11	2.28	1.26-4.11
Leflunomide	242.69	4	1.65	0.62-4.39
Methotrexate sc	626.88	8	1.28	0.64-2.55
Hydroxychloroquine	2234.58	28	1.25	0.87-1.81
Methotrexate oral	684.53	6	0.88	0.39-1.95
Chloroquine	123.95	1	0.81	0.11-5.73
Adalimumab Azathioprine	37.61	0	0	-

Table 2: Multivariate

	Hazard ratio	CI 95%	p
Age at diagnosis	1.04	1.01-1.06	0.009
Male gender	2.43	1.36-4.34	0.003
Living alone	2.95	1.48-5.89	0.002
Institutionalized	6.65	2.40-18.44	0.000
Heart failure	2.29	0.77-6.86	0.138
ESR between 30-59 mm/h at the beginning of DMARD	2.62	1.33-5.19	0.006
ESR > 60 mm/h at the beginning of DMARD	3.58	1.62-7.94	0.002
Combined therapy	2.10	1.20-3.69	0.010
Corticoids dose	1.57	1.04-2.38	0.032
Tocilizumab compared to other DMARD	6.35	1.76-22.96	0.005

Disclosure: Z. Rosales Rosado, None; J. Font Urgelles, None; P. M. Lois, None; C. Vadillo Font, None; D. Freitas Núñez, None; I. Hernández-Rodríguez, None; J. A. Jover Jover, None; L. A. Alcazar, None.

Abstract Number: 2462

Efficacy and Safety in the Middle-LONG Period of Rituximab in the Treatment of Diffuse Interstitial Pulmonary Disease Associated with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To evaluate the efficacy and safety of rituximab (RTX) in the medium- to long-term for the management of progressive rheumatoid arthritis-related interstitial lung disease (RA-ILD).

Methods: We undertook an open observational study in patients with active symptomatic RA-ILD despite treatment with glucocorticoids and disease-modifying antirheumatic drugs or immunosuppressants. The main efficacy variables evaluated at the end of the follow-up period were the evolution of the respiratory functional tests, distance traveled during the 6-minute walk test (6MWT), and changes in high-resolution chest computed tomography scan (HRCT).

Results: Twenty-three patients were included. The median durations of RA and ILD were 48 months (range, 1-273 months) and 21 months (range, 1-144 months), respectively. Twenty-six percent of the cases corresponded to interstitial usual pneumonia. RA was seropositive in 91% of patients. The number of RTX cycles administered (mean \pm SD) was 4 ± 1.9 (range, 2-10), and the median time of follow-up after RTX treatment was 29 months (range, 12-71 months). At the end of follow-up, the mean DAS28-ESR score decreased to 2.6 ± 0.7 ($P = 0.0001$), and there were improvements in mean FVC values (Delta $+0.86$; $P = 0.711$), DLCO values (Delta $+7.93$; $P = 0.007$), and distance covered in the 6MWT (Delta $+21.63$ m; $P = 0.376$).

Considering the total sample, an improvement or stabilization of the FVC values was achieved in 87% of the cases (improvement: 17% of the cases), in 91% of the cases in the DLCO values (improvement: 56% of cases), and in 83% of cases in the ILD radiologic features (improvement: 13% of cases). The median time between the first and the last HRCT was 26 months (range, 12-65 months).

In addition, at the end of the follow-up period, the average dose of prednisone was reduced to 4.5 mg/d, and it could be suspended in 5 patients.

A significant inverse correlation between the ACPA level and baseline DLCO was found in the entire cohort ($r = -0.45$, $P = 0.04$). This correlation was present even after adjusting for tobacco exposure ($P = 0.01$). In some of the patients, a decrease in the ACPA titer was documented with biologic treatment (median Delta [IQR 25th-75th]: $-159 [-875, -83]$), becoming negative in 4 cases, although there was no significant correlation between the decrease in the ACPA titers (Delta ACPA) and the degree of improvement of the parameters in the PFR at the end of the follow-up (FVC: $r = -0.15$, $P = 0.949$; DLCO: $r = -0.20$, $P = 0.385$).

Globally, patients with UIP had globally worse baseline values in PFTs and 6MWT. In addition, the responses obtained with RTX in this group were numerically lower than those in the group with non-UIP patterns, but the differences were only statistically significant in the case of FVC.

The frequencies of adverse effects (mainly respiratory or urinary infections and transient neutropenia) was high, occurring in 43.5% of patients, but they were severe in only 13%, causing withdrawal of treatment. Two (9%) patients died due to progression of ILD, and 2 (9%) ended up requiring a lung transplant. At the end of the follow-up period, 16 of the 23 patients (69%) were still in treatment

Conclusion: According to this preliminary experience, RTX appears to be effective in the treatment of RA-ILD.

Disclosure: F. J. Narváez, None; A. Robles Perez, None; P. Luburich, None; J. Alegre, None; M. Ricse, None; C. Gomez Vaquero, None; J. M. Nolla, None; M. Molina, None.

Abstract Number: 2463

Reducing Time to Treatment in Patients with Early and Uncontrolled RA: Implementation of a Collaborative and Systems-Based Approach to Improve Access to Care

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The first three months following the onset of the first symptoms of rheumatoid arthritis (RA) represent a therapeutic window during which disease-modifying anti-rheumatic drug (DMARD) treatments have been shown to provide disease remission and limit subsequent joint damage. In established RA, the goal of treatment is to achieve minimal disease activity (MDA) as it is associated with less articular and non-articular complications from RA. Delays between symptom onset and the initiation of therapy persist due to multifactorial issues: patient delays in seeking medical advice, primary care physician's (PCP) delays in recognizing symptoms and referring the patient to a rheumatologist, and delays in accessing rheumatology care. While some PCPs are able to recognize early RA (ERA) and start a DMARD, MDA may not be achieved. These factors also delay evaluation by a rheumatologist and potentially cause further damage.

The aim of this study was to decrease the time from first onset of RA symptoms of to rheumatology evaluation and DMARD treatment. If the patient had been prescribed a DMARD by the PCP, the goal was to decrease the time to step-up therapy in those RA patients who were not in the MDA state.

Methods: This 24-month outcomes study using descriptive analysis, focused on improving patient outcomes through enhanced community partnerships, systems-based change and education. Key components of the project's success were the incorporation of a dedicated nurse practitioner, acting as the division's patient case manager, and a medical assistant (MA) who served as a patient navigator to coordinate care. These patients were then prioritized by need and seen by a provider or rheumatology nurse practitioner (NP) who is specifically trained in evaluating and treating patients with RA. Four primary care clinics serving diverse patient populations were selected as partners for this study. A needs assessment was performed in the partner clinics to assess baseline knowledge related to the diagnosis and treatment of RA. Subsequently, targeted education related to ERA treatment and the importance of achieving MDA was created and offered to the partner clinics throughout the duration of the study.

Results: From January, 2017 to May, 2018, 1794 unique patients were referred to our Rheumatology clinic. Of these, 106 were diagnosed with RA while 83 were defined as ERA. Of these RA patients, there were 65 (61%) that were not being treated with DMARD therapy prior to evaluation. The time from referral to evaluation by rheumatology declined significantly from an average of 103 days at baseline to 27 days in the final phase of the study (graph 1). Accordingly, the time between referral to the initiation of DMARD therapy decreased significantly.

Conclusion: This study suggests that the creation of a specific workflow to assess patients with ERA or uncontrolled RA significantly combined with targeted education improved the wait time to a rheumatology evaluation and time to treatment. Our findings are limited by our hospital's status as a tertiary medical center.

Disclosure: I. Amigues, None;

Abstract Number: 2464

Clinimetric and Drug Use Differences in Colombian Patients with Early and Established Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Current guidelines for RA treatment are focused on the importance of defining the duration of symptoms before diagnosis to achieve better outcomes. This concept allows the definition of Early (ERA) and established

Figure 1: Mean Disease Activity measured by DAS-28, during 0, 3, 12, 24, 36 months of follow-up, for patient with Early and Established Rheumatoid Arthritis.

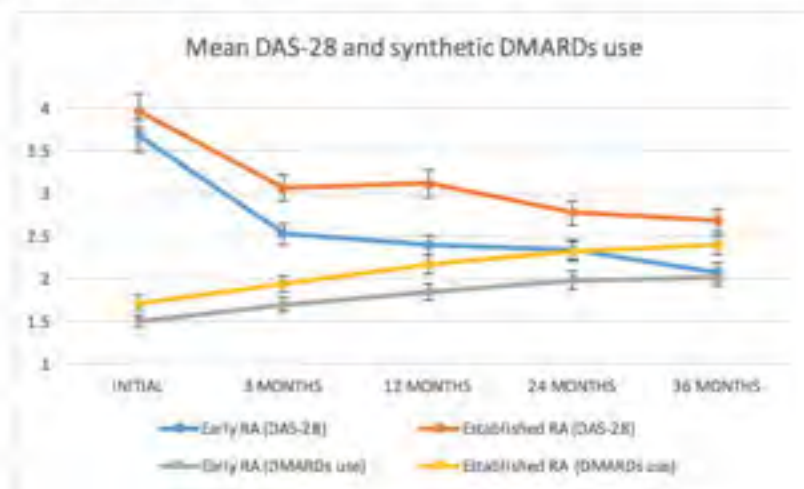


Table 1: Overall mean DMARD dose (MTX, SSZ, LEF), DMARD and biologic use, for patient with Early and Established Rheumatoid Arthritis.

RA classification	Mean DMARD dose														
	INITIAL			3 MONTHS			12 MONTHS			24 MONTHS			36 MONTHS		
	MTX	SSZ	LEF	MTX	SSZ	LEF	MTX	SSZ	LEF	MTX	SSZ	LEF	MTX	SSZ	LEF
Early	16.1	1142.9	120	18.07	1157.9	113.8	18.42	1250	120	21.058	1500	113.8	22.72	1000	112
Established	16.83	1098.4	123.9	18.75	1149.1	120.9	20.49	1151.6	118.6	20.71	1164.4	112.7	20.87	1009.6	112.9

MTX: Methotrexate (mg/week), SSZ: Sulfasalazine (mg/day), LEF: Leflunomide (mg/week).

RA (RA). Evidence suggest that ERA patients achieve better outcomes in terms of disease activity, bone erosions and survival. This study shows the clinimetric and treatment differences between patients with ERA and RA in an excellence clinical care center in Colombia.

Methods: The study used a cohort of Colombian patients with RA (Satisfying ACR/EULAR classification criteria). Data collected from clinical records were: RA classification, disease activity using DAS-28 ESR (DAS-28), number of synthetic and biological DMARDs used, and their respective dose. Data was obtained for 0, 3, 12, 24, and 36 months of follow-up. Patients were classified as ERA or RA. Mean DAS-28, synthetic DMARDs dose, number of synthetic and biologic DMARDs used from each period of time were calculated.

Results: An overall of 805 patients were included; 147 patients with ERA and 658 patients with RA. 82% of patients are seropositive. Both group of patients began with mean DAS-28 corresponding to moderate activity (ERA: 3.67; RA: 3.87). Mean DAS-28 achieve remission since 3 months of follow-up for ERA group. Mean DAS-28 for RA did not achieve remission, but low activity was achieved since 3 months. Mean synthetic and biologic DMARDs use was constantly increasing in both groups, but the number was always greater in RA. About mean DMARD dose for specific drugs, weekly MTX dose stands as it was initially greater in RA, but it achieves an upper limit since 12 months of follow-up. ERA Mean weekly MTX dose constantly increase until 36 months, even surpassing RA mean dose.

Conclusion: Results are consistent with existent evidence of disease behavior in other populations, by showing that Colombian patients with ERA achieve lower disease activity and even remission, and use less medication in comparison to RA patients. DMARD doses were greater in RA group, except for MTX.

Reference: Castañeda S, Navarro F, Fernández-Carballido C, Tornero C, Marced E, Corteguera M. Diferencias en el manejo de la artritis reumatoide precoz y establecida. *Reumatología Clínica*. 2011;7(3):172-178.

Disclosure: J. Florez-Suarez, None; P. Mendez, Novartis, 5, AbbVie Inc., 5; E. Bermudez, None; P. Coral, None; G. Quintana-Lopez, Janssen, 5.

Abstract Number: 2465

Characterizing Palindromic Symptoms in Early Rheumatoid Arthritis: Results from the Canadian Early Arthritis Cohort Study

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Palindromic rheumatism (PR) (transient acute attacks of articular and/or periarticular inflammation) may progress to rheumatoid arthritis (RA). How often early RA (ERA) patients report joint symptoms that come and go prior to diagnosis and how RA presentation may differ in this patient subset is uncharacterized. This study compared ERA patients who did versus did not report a history of transient episodes of joint inflammation preceding RA diagnosis.

Methods: Data were from patients with early classifiable or suspected RA according to their rheumatologist (symptoms <1 year; 83% met 2010 ACR/EULAR criteria) enrolled in the Canadian Early Arthritis Cohort (CATCH) in 2017 to 2018 who completed a new baseline questionnaire on prior inflammatory joint symptoms that “come and go”. Chi-square and t-tests were used to compare baseline sociodemographic and RA characteristics in ERA patients with versus without a reported history of prior palindromic symptoms. Simple, and multivariable logistic regression with backward selection ($p < 0.1$) were used to identify age and sex-adjusted predictors of palindromic symptoms among baseline ERA characteristics.

Table 1: Logistic Regression Examining Associations between RA Baseline Characteristics and History of Transient Joint Episodes Prior to RA diagnosis

Variable	Unadjusted Model		Adjusted Multivariable Model	
	Odds Ratio (OR)	95% Confidence Interval (CI)	OR	95% CI
Age	1.0	1.0, 1.0	1.0	1.0, 1.1
Female sex	2.5	1.2, 5.1	3.3	1.1, 9.5
Income (>\$50,000)	2.0	0.9, 4.2	3.2	1.2, 9.1
Current smoker	2.1	0.9, 4.7	3.2	0.8, 13.7
Depression	3.4	1.2, 9.6	4.3	1.2, 15.8
RF positive	2.5	1.2, 5.0	3.7	1.3, 10.2

Results: 154 ERA patients were included; 66% were female and mean (sd) age was 54 (15) years. 83 (54%) patients reported having any previous joint pain and swelling prior to current episode; 65 (42%) endorsed prior episodic joint pain and swelling, of whom 31 (48%) reported transient joint symptoms for over six months. Patients reporting previous palindromic symptoms were more often female, RF positive, ACPA positive, had more comorbidities, and lower CRP, swollen joints, and baseline DAS28 ($p<0.05$). Univariate predictors of palindromic symptoms included female sex, RF positivity, higher income, comorbid OA, back/spine problems, and depression, higher rheumatic disease comorbidity index, and lower swollen joint count, CRP, DAS28, and physician global assessment of disease activity ($p<0.1$). In multivariable regression, RF positivity, depression, and higher income remained significant predictors of prior palindromic symptoms ($p<0.05$). Smoking was potentially associated with an average 3-fold increase in prior palindromic symptoms, though the relationship was not statistically significant in adjusted models (Table 1).

Conclusion: ERA patients commonly self-reported experiencing transient episodes of inflammatory arthritis prior to being diagnosed with RA; however, whether these symptoms were actual PR cannot be confirmed. ERA patients who endorsed having joint symptoms that come and go prior to RA diagnosis were more likely RF positive with higher income and more comorbidities at ERA cohort entry, but median time to RA onset was not different.

Disclosure: L. Ellingwood, None; O. Schieir, None; S. J. Bartlett, UCB, Inc., 5, Lilly, 5, Pfizer, Inc., 5, Novartis, 5; L. Bessette, Amgen Inc., 2, 5, 8, Bristol-Myers Squibb, 2, 5, 8, Janssen, 2, 5, 8, Roche, 2, 5, 8, UCB, Inc., 2, 5, 8, AbbVie Inc., 2, 5, 8, Pfizer, Inc., 2, 5, 8, Merck & Co., 2, 5, 8, Celgene Corporation, 2, 5, 8, Sanofi, 2, 5, 8, Eli Lilly and Co., 2, 5, 8, Novartis, 2, 5, 8; C. A. Hitchon, Pfizer, Inc., 2, UCB, Inc., 2; G. Boire, Merck & Co., 8, 9, BMS, 8, 9, Pfizer, Inc., 8, 9, Amgen Inc., 9, AbbVie Inc., 9, Novartis, 9, Eli Lilly and Co., 9, Janssen, 9; G. Hazlewood, None; E. C. Keystone, Amgen Inc., 2, 5, 8, Bristol-Myers Squibb, 2, F. Hoffmann-La Roche Inc, 2, Janssen, 2, Lilly Pharmaceuticals, 2, Pfizer Pharmaceuticals, 2, Sanofi-Aventis, 2, AstraZeneca, 5, Biotest, 5, Bristol-Myers Squibb, 5, Crescendo Bioscience, 5, F. Hoffmann-La Roche Inc, 5, Genentech Inc, 5, Janssen Inc, 5, Lilly Pharmaceuticals, 5, Merck & Co., 5, 8, Pfizer Pharmaceuticals, 5, UCB, Inc., 5, Bristol-Myers Squibb, 8, F. Hoffmann-La Roche Inc, 8, Janssen Inc, 8, Pfizer Pharmaceuticals, 8, Sanofi Genzyme, 8, UCB, Inc., 8; D. Tin, None; C. Thorne, AbbVie Inc., 5, 9, Amgen Inc., 9, Celgene Corporation, 9, Centocor, 5, Janssen, 5, Lilly, 5, 9, Medexus/Medac, 5, 8, 9, Merck & Co., 9, Novartis, 9, Pfizer, Inc., 5, 9, Sanofi, 9; V. P. Bykerk, Amgen Inc., 5, Pfizer, Inc., 5, UCB, Inc., 5, Bristol-Myers Squibb, 5, Sanofi-Genzyme/Regeneron, 5; J. E. Pope, Amgen Inc., 5, 9, Pfizer, Inc., 5, 9, UCB, Inc., 5, 9, AbbVie Inc., 5, Bristol-Myers Squibb, 5, 9, Actelion, 5, Eli Lilly and Co., 5, Merck & Co., 5, 9, Bayer, 5, 9, Roche, 5, 9, Novartis, 5, Sanofi, 5, Celtrion, 5, Seagen, 9, Genzyme, 5.

Abstract Number: 2466

Prolonged Delay in Presentation to Rheumatologists for Hispanic Patients with Rheumatoid Arthritis Contributes to Later Diagnosis and Treatment

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Disparities in the initiation of disease modifying anti-rheumatic drugs (DMARDs) in ethnic minorities have been described in rheumatoid arthritis (RA) patients in the US (J Rheumatol 2007;34:2400-7). These disparities are of increased concern, as the early initiation of intensive treatment has become a cornerstone in RA management. Recognizing referral patterns and patient baseline characteristics may help to identify sources of delay. We aimed to evaluate disparities in referral and treatment initiation in RA patients at an academic rheumatology site.

Methods: We conducted a retrospective study of all RA patients (by ICD codes) seen at our rheumatology outpatient clinic between 2011/16. Among 542 RA patients, 152 (28%) received their initial evaluation by a Rheumatologist during this period, and were naive to any DMARD. We determined the duration between initial symptoms and first Rheumatology visit in months. Data extraction included referral source, demographics, and laboratory tests between others. A Multidimensional-Health Assessment Questionnaire, collected routinely in this setting, allowed us to calculate a RAPID3 score for disease activity assessment at baseline. Treatment information also was collected including time to initiate DMARD and prednisone use. Comparison between ethnic groups was performed using ANOVA or Kruskal-Wallis for differences between means or medians and Chi² for proportions.

Results: A total of 152 DMARD naive RA patients were seen; 35% were White, 37% Black, 20% Hispanic, and 8% were others. The median delay to first rheumatology visit ranged from 6 to 8 months for all patients groups, other than Hispanics, for whom delay was 22.7 months (p=0.01) (Table). In the Hispanic group, there was no difference in time to visit between those who selected Spanish as their preferred language and those who selected English. A higher percentage of White and Black patients were referred by PCPs relative to Hispanic patients, who mainly self-referred (p=0.01). Methotrexate was the most prescribed DMARD. No significant differences were seen in time to treatment initiation according to ethnicity. Disease activity by RAPID3 scores (p=0.04) and ESR (p=0.01) was significantly higher in Black and Hispanic groups, but other laboratory tests did not differ between groups.

	ALL N=152	Ethnicity groups			
		White N=53 (35%)	Black N=57 (37%)	Hispanic N=30 (20%)	Other N=12 (8%)
Age, yrs mean (SD)	54.2 (15.5)	57.5 (15.2)	57.2 (15.5)	45.5 (12.6)*	46.8 (14.1)
Female %	81%	74%	86%	83%	83%
Median disease duration, months (IQR)	6.9 (3.0, 24.0)	6.7 (3.5, 23.9)	6.0 (2.1, 22.9)	22.7 (3.0, 47.9)*	8.0 (4.0, 35.9)
Patients treated as early RA (<6m), %	46%	45%	53%	34%	40%
Referral of patients (%):	47%	40%	67%	33%	25%
PCPs	26%	34%	16%	27%	33%
Other physicians self-referral	27%	26%	18%	40%*	42%*
Median time in months to initiate DMARDs (IQR)	0.7 (0.2, 1.4)	0.7 (0.4, 2.0)	0.7 (0.1, 2)	0.7 (0.4, 1.4)	0.5 (0.4, 0.9)
Methotrexate, %	60%	57%	62%	63%	50%
Prednisone dose, %	71%	66%	72%	80%	67%
Mean dose (SD), mg	10.3 (5.0)	10.7 (5.6)	10.7 (5.4)	9.3 (3.4)	9.4 (3.2)
Rheumatoid Factor+, %	60%	46%	66%	72%	56%
Anti-CCP+, %	73%	63%	73%	81%	90%
Abnormal ESR, % (>27mm/h for women and >17mm/h for men)	50%	36%	62%*	59%	33%
Abnormal CRP, % (>8mg/L)	46%	39%	55%	45%	37%
RAPID3, median (IQR)	14.0 (8.3, 19.0)	13.1 (7.4, 16.9)	16.3* (11.2, 19.0)	15.3 (10.0, 21.5)	8.0 (5.4, 13.2)

Statistical significance in bold *p<0.05. ANOVA or Kruskal-Wallis (continuous variables) or Chi² (discrete values)

Conclusion: RA patients are at risk of poorer outcomes as a consequence of delayed presentation to a rheumatologist leading to delay in treatment initiation. This study demonstrates a considerable delay in initial referral to a Rheumatologist, more pronounced among Hispanic patients, although they appear to have higher disease activity at presentation. Once seen in the clinic, initiation of DMARDs occurred within 1-month, regardless of ethnicity. More knowledge concerning delay in referral may help to develop better strategies for equitable access to effective therapies for all RA patients, regardless of ethnicity.

Disclosure: M. Riad, None; D. Dunham, None; J. R. Chua, None; T. Pincus, Medical History Services, LLC., 7, 9; N. Shakoore, Dr. Comfort/DJO, 7; S. Hassan, None; J. A. Block, Gilead, 1, Novartis, 2, Pfizer, Inc., 2, Janssen, 2, GlaxoSmithKline, 5, Zynherba Pharmaceuticals, 5, Agios, Inc, 7, Daiichi Sankyo, Inc., 7, Omeros, Inc., 7; I. Castrejón, None.

Abstract Number: 2467

RAPID3 Is Elevated in 93% of Treatment-Naïve Rheumatoid Arthritis (RA) Patients at Initial Visit Compared to 49% for Erythrocyte Sedimentation Rate (ESR) and 44% for C-Reactive Protein (CRP)

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Quantitative measures to assess and monitor patients with rheumatoid arthritis (RA) traditionally have been laboratory tests, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). However, ESR and CRP values have been found to be normal in about 40% of RA patients^{1, 2}. By contrast, RAPID3 (routine assessment of patient index data) self-report scores are reported elevated in more than 75% of RA patients, and generally are more effective than laboratory tests to distinguish active from control treatment in clinical trials³. Normal initial measures can document worsening of clinical status, but not improvement, at future visits. We analyzed the proportion of treatment-naïve RA patients at an initial visit to an academic rheumatology setting for elevated or normal values for RAPID3, ESR and CRP.

Methods: All patients at one academic setting complete a multi-dimensional health assessment questionnaire (MDHAQ), which includes RAPID3 and other scales, at each visit. RAPID3 is an index of the 3 self-report 0-10 measures, physical function, pain, and patient global assessment, compiled into a 0-30 score. A retrospective analysis of RAPID3, ESR, and CRP data at initial visits of RA patients was conducted. RAPID3 scores were classified as remission (≤ 3), low (3.1-6), moderate (6.1-12), and high (≥ 12) severity⁴. ESR and CRP were classified according to normal values at the study site laboratory as ESR $<$ or >17 mm/hr in men, $<$ or >27 mm/hr in women, and CRP $<$ or >8 mg/dl. ESR data for men and women were merged. Cross-tabulations were performed to compare patients in 4 RAPID3 categories, according to whether ESR or CRP or both ESR and CRP were normal or abnormal; chi-square tests were used to analyze statistical significance.

Results: Overall, 105 patients were studied; 78% female, mean (SD) age 54.2 (15), RAPID3 13.9 (7.2), ESR 33.7 (29.9) and CRP 22.1 (47.9). Among all 105 patients, elevated ESR was seen in 49%, elevated CRP in 44%, both elevated CRP and ESR in 32%, and elevated RAPID3 in 93%, including 82% with moderate, and 65% high severity (Table). Among 86 patients whose RAPID3 indicated moderate or high disease severity, elevated ESR was seen in 38 (44%), elevated CRP in 41 (48%), and both elevated ESR and CRP in 29 (34%). By contrast, 5 of 7 patients with RAPID3 <3 had elevated ESR, and 1 elevated CRP as well as ESR (Table). One limitation of is that comorbidities, which can lead to elevated rapid RAPID3 scores, were not collected systematically.

Table. Number of patients who had elevated ESR or CRP or both ESR and CRP according to 4 RAPID3 categories of remission, low, moderate, and high severity among 105 RA patients on initial visit to an academic rheumatology setting

	RAPID3 Categories					P
	Remission (≤ 3)	Low (3.1-6)	Moderate (6.1-12)	High (≥ 12)		
High ESR M>17 mm/hr. F>27 mm/hr.	51 (49%)	5 (5%)	8 (8%)	6 (6%)	32 (30%)	0.189
High CRP >8 mg/dl.	46 (44%)	1 (1%)	4 (4%)	6 (6%)	35 (33%)	0.142
High CRP+ESR	34 (32%)	1 (1%)	4 (4%)	4 (4%)	25 (24%)	0.476
Total No. of patients	105	7 (7%)	12 (11%)	18 (17%)	68 (65%)	

Conclusion: At the initial visit of treatment naïve RA patients, RAPID3 was substantially more likely to be elevated than ESR or CRP to monitor disease status and document improvement.

References: 1- J Rheumatol. 2009 Jul;36(7):1387-90

2- J Rheumatol. 1994 Jul;21(7):1227-37

3- Bull Hosp Jt Dis (2013). 2013;71(2):117-20

4- Rheum Dis Clin North Am. 2009 Nov;35(4):773-8

Disclosure: M. Riad, None; J. R. Chua, None; I. Castrejón, None; T. Pincus, Medical History Services, LLC, 7, 9.

Window or No Window? Earlier Is Better When Treating Rheumatoid Arthritis

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SESSION INFORMATION

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Background/Purpose: Previous reports on a window of opportunity (WOO) in rheumatoid arthritis (RA) may be related to the use of slow acting csDMARDs. We investigated whether onset of action of therapy might influence whether there is a WOO or whether ‘earlier is better’. Therefore we aimed to investigate the association between symptom duration at treatment onset and the achievement of sustained drug free remission (sDFR) in early RA patients initiating therapy including fast acting prednisone or infliximab, compared to patients initiating csDMARD monotherapy.

Methods: We analysed the shape (non-linear or linear) of the association between symptom duration and achievement of sDFR (DAS<1.6 and no DMARDs for ≥1 year) in 3 cohorts: BeSt, IMPROVED and METEOR. Patients had arthritis symptoms <2 years. In BeSt, RA-patients (1987 criteria) were randomised to 4 targeted treatment strategies aimed at DAS≤2.4: arm 1 and 2 initiated csDMARD monotherapy, arm 3 csDMARDs and tapered high dose prednisone and arm 4 csDMARD and infliximab. In IMPROVED RA patients (2010 criteria) were treated with csDMARD and tapered high dose prednisone. Subsequent treatment adjustments aimed at DFR. METEOR is an international observational cohort including daily practice data from RA patients with a diagnosis and treatment according to the rheumatologist. We selected patients who initiated csDMARD monotherapy or a combination of csDMARD with prednisone or anti-TNF and at least 1.5 year follow-up.

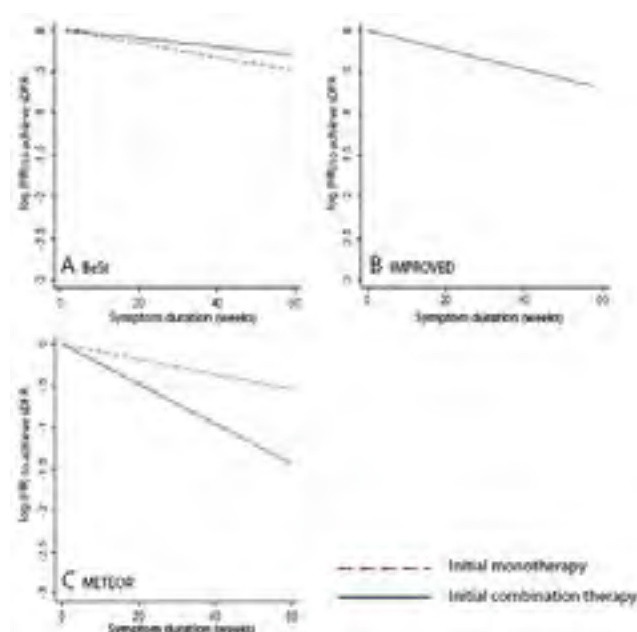


Figure 1. Best fit models to depict the relationship between symptom duration and sDFR in the BeSt (a) and IMPROVED (b) trial and in the METEOR registry (c). Applying natural cubic spline functions (allowing a curved relationship) did not result in a superior fit compared to a linear model.

Table 1. P-values of the likelihood ratio tests to compare the fit of a linear and a non-linear Cox regression model

	BeSt	IMPROVED ^a	METEOR
csDMARD monotherapy	0.609	--	0.678
Fast acting combination therapy ^b	0.743	0.337	0.457

^aNo monotherapy in IMPROVED. ^bIncluding prednisone or infliximab.

We performed Cox regression with as outcome sDFR and as predictor symptom duration and used likelihood ratio tests to compare the fit of a linear model and a model with inclusion of natural cubic spline functions (resulting in a hyperbola).

Results: In BeSt (n=469), IMPROVED (n=421) and METEOR (n=1268) 54, 110 and 10 patients who initiated fast acting combination therapy, and 53 in BeSt and 15 in METEOR who initiated csDMARD monotherapy achieved sDFR. A non-linear model did not show a better fit for the data than a linear model (table 1). Thus, we did not find a curved relationship between time of treatment initiation and achieving sDFR. The best fit models indicate that the earlier treatment is started, the higher the likelihood of achieving sDFR (figure 1).

Conclusion: Our data suggest that there is no evidence for a WOO in early RA in 3 cohorts. This was not related to use of fast acting combination therapy instead of slow acting monotherapy nor was it dependent on strict treat-to-target in clinical trials. Instead, our data reaffirm that earlier is better when treating RA.

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Abstract Number: 2469

Early Referral and Flare's Control Prevent Orthopaedic and Hand Surgery Indication in a Dynamic Cohort of Hispanic Early Rheumatoid Arthritis Patients

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

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Background/Purpose: Rheumatoid arthritis (RA) patients from Latin-America present distinctive characteristics when compared to Caucasians, that are known to impact patient's outcomes. Despite early and more aggressive treatment guidelines recently adopted, some patients require reconstructive joint surgery, considered an indicator of poor prognosis. The objectives of the study were to describe incidence rate of orthopedic and hand surgery indication (OHSI) in a cohort of Mexican Mestizo early RA patients treated with conventional DMARDs according to a T2T strategy and to investigate OHSI predictors.

Methods: Patients enrolled in the cohort had a disease duration of <1 year and complete rheumatic assessments at fixed intervals. Up to February 2018, the cohort comprised 185 RA patients recruited from 2004 onwards, with at least fourteen

months of follow-up; 2.7% were dead, 23.3% lost to follow-up and 74% had active follow-up. Charts were reviewed and incidence rate of OHSI was calculated. A nested within a cohort case-control study was designed to investigate predictors; cases (patients with OHSI) were paired to controls (1:4) according to age (± 5 years), sex, baseline RF and ACCP; cumulative disease activity (summarized as DAS28, first sustained remission [SR], time in SR, number of flares and % of follow-up in remission status), cumulative treatment (N° DMARD/patient, patients with corticosteroids and % of time with corticosteroids), and cumulative persistence (N° of patients persistent and % of follow-up patients were persistent) were compared between cases and controls. Logistic regression's models included baseline and cumulative (up to OHSI or equivalent) variables. Local IRB approved the study.

Results: Patients entering the cohort were predominantly middle-aged (mean \pm SD age of 38.5 \pm 12.9 years) female (87.6%), with (mean \pm SD) 5.4 \pm 2.6 months of disease duration. Up to cut-off, the cohort contributed to 1538 patient-years of follow-up. There were 12 patients with incidental OHSI, at a (mean \pm SD) follow-up of 85 \pm 44.5 months; 9 (75%) received orthopedic surgery indication meanwhile 3 (25%) received hand surgery indication; incident global rate was of 0.8/100 patient-years. Regression models included baseline variables (months of symptom's disease duration) and cumulative variables (N° of flares/patient, % of follow-up in remission status, N° of patients persistent and % of follow-up patients were persistent with therapy). Longer symptom's duration at referral to the cohort (OR: 1.313, 95% CI: 1.02-1.68, $p=0.032$) and higher number of flares (OR: 1.608, 95% CI: 1.05-1.61, $p=0.015$) were predictors of OHSI. ROC showed that the best cut-off for symptom's duration and cumulative number of flares to predict OHSI were 6 months (Sensitivity: 0.833; Specificity: 0.665; AUC: 0.746, 95% CI: 0.593-0.899) and 5 flares/patient (Sensitivity: 0.750; Specificity: 0.625; AUC: 0.702, 95% CI: 0.522-0.882), respectively.

Conclusion: Early referral for appropriated management according to a T2T strategy and flares controls may prevent OHSI in Hispanic early RA patients.

Disclosure: I. Contreras-Yáñez, None; G. Guaracha, None; E. Díaz-Borjón, None; M. Iglesias, None; V. Pascual-Ramos, None.

Abstract Number: 2470

The Impact of Frailty on Changes in Physical Function Among Adults with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

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Background/Purpose: Frailty is a state of excess vulnerability to stressors and is associated with increased risk of poor health outcomes including physical disability. Frailty and reduced physical function are common in rheumatoid arthritis (RA). However, the relationship between frailty and change in physical function over time in RA is unknown. We tested the hypothesis that frailty is a risk factor for worsening patient-reported physical function over time in RA.

Methods: Adults from a longitudinal RA cohort (n=124) participated. Using an established definition of frailty¹, individuals with 3 or more of the following physical deficits were classified as frail: 1) body mass index ≤ 18.5 , 2) low grip strength (adjusted for sex and BMI, measured by handheld dynamometer), 3) severe fatigue (measured by the Fatigue Severity Inventory), 4) slow 4-meter walking speed (adjusted for sex and height), 5) low physical activity (measured by the International Physical Activity Questionnaire). Individuals with 1 or 2 deficits were classified as “pre-frail”, and those with no deficits as “robust¹.” In addition, a frailty score (0-5) was calculated based on an individual's number of deficits. Self-reported physical function was assessed by the Health Assessment Questionnaire (HAQ) at baseline and at follow-up approximately 2 years later. Regression analyses modeled associations of baseline frailty category and frailty score with HAQ score at follow-up with and without controlling for age, sex, disease duration, C-reactive protein, use of oral steroids, and pain. In addition, regression analyses modeled the association of baseline frailty category and frailty score with development of a clinically-meaningful worsening (≥ 0.22) in HAQ score at follow-up with and without controlling for covariates.

Results: Among adults with RA, being frail compared to being robust was associated with a 0.42-point (CI:0.13, 0.71) worse HAQ score at follow-up (Table 1) and 11 times (CI:1.58, 76.60) the odds of developing a meaningfully worse HAQ score at follow-up (Table 2) even when adjusting for covariates. In addition, a 1-point increase in baseline frailty score was associated with a 0.12-point (CI:0.05, 0.21) worse HAQ score at follow-up (Table 1) and nearly twice (CI:1.18, 3.30) the odds of developing a meaningfully-worse HAQ score at follow-up (Table 2).

Conclusion: Frailty may be an important, identifiable, and unique risk factor for the development of physical disability in RA. Future studies should address whether modifying frailty improves physical function in RA.

Table 1: Linear Regression Coefficients (95% CIs) for the Effect of Baseline Frailty Category or Frailty Score on HAQ Scores at Follow-up among Individuals with Rheumatoid Arthritis (n=124)

	Model 1	Model 2	Model 3
Frail	0.87*** (0.45, 1.29)	0.41** (0.13, 0.69)	0.42** (0.13, 0.71)
Pre-frail	0.55*** (0.25, 0.85)	0.22* (0.03, 0.41)	0.20* (0.008, 0.39)
Robust	Reference	Reference	Reference
Frailty Score (per 1 point)	0.29*** (0.18, 0.41)	0.15*** (0.07, 0.23)	0.12** (0.05, 0.21)

Model 1: unadjusted

Model 2: adjusted for baseline HAQ score

Model 3: adjusted for baseline HAQ score, sex, age, baseline disease duration, hsCRP, use of oral steroids, and pain.

Frail= ³ physical deficits, Pre-frail= 1-2 physical deficits, Robust= 0 physical deficits (¹Fried LP et al., J Gerontol A Biol Sci Med Sci, 2001; 56: M146)

HAQ scores are 0-3 with higher scores representing worse physical function.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 2: Odds Ratios (95% CIs) for the Effect of Baseline Frailty Category or Frailty Score on Worsening HAQ Scores at Follow-up among Individuals with Rheumatoid Arthritis (n=124)

	Model 1	Model 2	Model 3
Frail	6.22* (1.20, 32.21)	7.95* (1.40, 45.04)	11.00* (1.58, 76.60)
Pre-frail	2.99 (0.81, 11.04)	3.55 (0.91, 13.77)	3.84 (0.89, 16.50)
Robust	Reference	Reference	Reference
Frailty Score(per 1 point)	1.73* (1.13, 2.66)	1.88** (1.19, 2.96)	1.98** (1.18, 3.30)

Model 1: unadjusted

Model 2: adjusted for baseline HAQ score

Model 3: adjusted for baseline HAQ score, sex, age, baseline disease duration, hsCRP, use of oral steroids, and pain.

Frail= ³ physical deficits, Pre-frail= 1-2 physical deficits, Robust= 0 physical deficits (¹Fried LP et al., J Gerontol A Biol Sci Med Sci, 2001; 56: M146)

HAQ scores are 0-3 with higher scores representing worse physical function. Worsening HAQ score is defined as an increase of at least 0.22, because the minimum clinically significant difference for the HAQ is 0.22.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Disclosure: J. Andrews, None; L. Trupin, None; C. Hough, None; E. H. Yelin, None; P. Katz, None.

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Validation of the Functional Index for Hand Osteoarthritis (FIHOA) in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

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Background/Purpose: There is a high prevalence of upper limbs involvement in Rheumatoid Arthritis (RA), with a lack of useful tools in daily practice assessing the functional capacity of this particular anatomical region. Dreiser et al. developed the Functional Index for Osteoarthritis of hands (FIHOA), aimed to evaluate the functional capacity of patients with hand osteoarthritis (HOA), whose Argentinian version was validated 2016. However, this instrument has not been validated yet in patients with RA. The aim of this study was to validate FIHOA in RA patients.

Methods: Analytical, observational, prospective cross-sectional study including consecutive patients with diagnosis of RA (ACR/EULAR 2010). Demographic and RA characteristics, disease activity measures and treatment were recorded. Patients completed the following self-administered questionnaires: HAQ-A (Health Assessment Questionnaire Argentine Version), HAQUP (Health Assessment Questionnaire-Upper extremity), FIHOA and Quick DASH (Quick Disabilities of the Arm, Shoulder and Hand). For a patient subgroup, an occupational therapist performed an objective evaluation of the functional capacity of the upper limbs using the Sequential Occupational Dexterity Assessment (SODA). To assess reproducibility, 30 patients with similar clinical and therapeutic conditions to their first evaluation completed the questionnaire again 10 to 15 days later. *Statistical analysis:* Patient and disease characteristics were described with means, medians, absolute numbers, proportions, standard deviation (SD) and interquartile ranges (IQR). Reliability was assessed using the Cronbach test. Construct validity was analyzed through the correlation with other functional capacity questionnaires and disease activity parameters using the Spearman coefficient. Reproducibility was estimated using test-retest reliability. A linear regression model was constructed with FIHOA as the outcome variable and those variables that proved significant on bivariate analysis.

Results: We included 100 patients, 83% women, mean age 57.9 years (SD 11.6). Cronbach's alpha test was 0.94. There were no redundant questions by inter-item correlation. FIHOA showed an excellent correlation with HAQ-A ($r = 0.89$); HAQUP ($r = 0.89$); Quick DASH ($r = 0.90$) and SODA ($r = -0.80$). It also showed good correlation with DAS28 ($r = 0.65$) and other composite disease activity measures as well as with other disease parameters [visual analog scale (VAS) for pain, patient and physician global assessment of the disease, tender and swollen joint count]. There was no correlation between FIHOA and age or disease duration. Questionnaire reproducibility was 0.73. A multiple linear regression adjusted for age and sex showed morning stiffness as the main determinant of FIHOA, followed by patient global assessment VAS and glucocorticoid use.

Conclusion: FIHOA was found to be reliable, valid and reproducible in patients with RA, providing a valuable tool for the evaluation of functional capacity of the upper limbs in these patients.

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The Impact of Disease Activity and Patient Reported Outcomes on Grip Force over Time in Early Rheumatoid Arthritis

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Background/Purpose: Although patients with early rheumatoid arthritis (RA) have substantially reduced grip strength compared to the general population, some improvement over time has been demonstrated in many patients. The objective of this study was to identify early predictors of future grip strength in patients with RA.

Methods: An inception cohort of patients with early RA (symptom duration ≤ 12 months), recruited in 1995-2005, was investigated and followed in a structured program (4 examinations over 5 years), including clinical evaluation and grip force measurement. Grip force was measured using the electronic instrument Grip pit (AB Detektor, Gothenburg,

Impact of baseline patient reported outcomes and disease activity on grip force (% of expected value) over time; by quartile

		Intercept (95% CI)	Estimated mean difference (95% CI)	Change/year (95% CI)	Difference in change/year (95% CI)
DAS28	Quartile I (0-3.6)	61.4% (53.4% to 69.4%)	Reference	1.3% (0.02% to 2.6%)	Reference
	Quartile II (3.7-4.7)	48.2% (41.8% to 54.5%)	10.7% (2.0% to 19.4%)	2.6% (1.4% to 3.9%)	1.3% (-0.4% to 3.1%)
	Quartile III (4.8-5.7)	41.3% (34.6% to 47.9%)	16.7% (7.9% to 25.5%)	3.1% (1.9% to 4.4%)	1.8% (0% to 3.6%)
	Quartile IV (5.8-)	29.6% (24.1% to 35.1%)	25.9% (17.2% to 34.6%)	4.4% (3.2% to 5.7%)	3.1% (1.4% to 4.9%)
VAS pain	Quartile I (0-19)	59.4% (52.0% to 66.7%)	Reference	1.8% (0.5% to 3.1%)	Reference
	Quartile II (20-39)	45.2% (37.6% to 52.9%)	11.3% (2.2% to 20.4%)	3.4% (2.0% to 4.7%)	1.5% (0.3% to 3.4%)
	Quartile III (40-63)	34.7% (29.1% to 40.4%)	20.8% (12.2% to 29.5%)	3.9% (2.8% to 5.0%)	2.1% (0.4% to 3.8%)
	Quartile IV (64-100)	41.0% (34.2% to 47.8%)	17.4% (8.6% to 26.3%)	2.3% (0.9% to 3.7%)	0.5% (-1.3% to 2.3%)
VAS Global	Quartile I (0-20)	59.3% (51.3% to 67.2%)	Reference	2.3% (1.0% to 3.6%)	Reference
	Quartile II (21-46)	45.4% (40.0% to 50.9%)	12.6% (3.8% to 21.5%)	2.9% (1.6% to 4.2%)	0.6% (-1.2% to 2.4%)
	Quartile III (47-64)	37.6% (30.5% to 44.7%)	19.2% (10.2% to 28.2%)	3.7% (2.5% to 4.9%)	1.4% (-0.4% to 3.2%)
	Quartile IV (65-100)	38.0% (31.3% to 44.8%)	20.5% (11.5% to 29.5%)	2.7% (1.3% to 4.0%)	0.4% (-1.4% to 2.2%)
HAQ	Quartile I (0-0.38)	62.2% (55.1% to 69.3%)	Reference	2.0% (0.8% to 3.2%)	Reference
	Quartile II (0.39-0.75)	43.2% (36.2% to 50.1%)	17.7% (9.2% to 26.3%)	2.7% (1.4% to 4.0%)	0.7% (-1.1% to 2.5%)
	Quartile III (0.80-1.25)	42.6% (36.8% to 48.4%)	17.0% (8.8% to 25.1%)	3.4% (2.2% to 4.6%)	1.4% (-0.3% to 3.1%)
	Quartile IV (1.30-3.0)	28.8% (22.8% to 34.8%)	30.6% (22.0% to 39.2%)	3.5% (2.0% to 5.0%)	1.5% (-0.3% to 3.4%)

Sweden). Average grip force values of the dominant hand were evaluated at each visit, and compared to the expected, based on age- and sex-specific reference values from the literature. Patients in each of the three higher quartiles of baseline disease activity (DAS28), disability (HAQ), pain (visual analogue scale, VAS) and patient global assessment (VAS global) were compared to the lowest quartile. Differences in percentage of expected grip force values over the study period, and differences in change over time, were estimated using mixed linear effect models.

Results: A total of 233 patients with early RA (70% women, mean age 60.5 years, median symptom duration 7 months) were investigated. The mean value for the average grip force of the dominant hand increased from 40% of expected at baseline to 57% at the 5-year follow-up. Patients with baseline parameters in the three higher quartiles had significantly lower mean grip force values over time, compared to the lowest quartiles (Table). Patients in the highest quartile of DAS28 had significantly greater improvement compared to the lowest quartile (estimated difference in change per year 3.1% of expected; 95% CI 1.4 to 4.9). By contrast, there was no difference in improvement for those in the highest quartiles of VAS pain (estimated difference in change per year 0.5% of expected; 95% CI -1.3 to 2.3) or VAS global (Table), compared to those in the lowest quartiles.

Conclusion: Patients with a severe disease phenotype at baseline had particularly impaired grip force over the first 5 years after RA diagnosis. However, those with high initial disease activity experienced greater improvement in grip force, likely due to successful treatment. By contrast, poor patient reported outcomes at baseline were associated with persistent impairment of grip strength.

Disclosure: M. Rydholm, None; I. Wikström, None; S. Hagel, None; L. Jacobsson, None; C. Turesson, None.

The Relation between Inflammatory Joint Activity and Disability Related to the Lower Extremities in Early Rheumatoid Arthritis

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Background/Purpose: Arthritis in the lower extremities has a major impact in many patients in rheumatoid arthritis (RA), but has not been extensively studied. The objective of this study was to investigate the relation between inflammatory joint involvement and disability related to the lower extremities in early RA.

Methods: An inception cohort of patients with early RA (symptom duration ≤ 12 months), recruited in 1995-2005, was investigated and followed in a structured program. All patients were examined by the same rheumatologist. To estimate disability based on self-reported activity limitations, we used the Health Assessment Questionnaire Disability Index (HAQ-DI). In order to more specifically address disability of the lower extremities, we calculated a sub score, HAQ-DI lower extremities (HAQ-DI-LE), based on the 10 questions that cover activities that are mainly dependent on function of the lower extremities (Ekdahl et al. J Clin Epidemiol 1989;42: 947-54). HAQ-DI LE scores in those with vs without current synovitis of individual joints were compared using the Mann Whitney test.

Results: A total of 233 patients with early RA (70% women, mean age 60.5 years, median symptom duration 7 months) were investigated. The median HAQ-DI LE at inclusion was 0.6 (interquartile range 0.2-1.2). Knee synovitis, ankle synovitis and MTP joint synovitis was present at inclusion in 18%, 26% and 39%, respectively. Proportions with synovitis in the lower extremities declined over time (Table). Knee synovitis was associated with significantly higher HAQ-DI-LE scores at inclusion ($p < 0.001$) and after 6 months ($p = 0.01$), but not at later follow-up visits (Table). Patients with ankle synovitis had higher HAQ-DI-LE at 6 months ($p = 0.02$), 1 year ($p = 0.006$) and 2 years ($p < 0.001$). MTP joint synovitis was also associated higher HAQ-DI-LE, in particular at baseline ($p = 0.045$). However, differences in HAQ-DI-LE for those with vs without synovitis were numerically smaller at 1 year and at 2 years for MTP joint synovitis compared to ankle synovitis (Table).

Conclusion: Knee synovitis was associated with disability related to the lower extremities, in particular in very early RA, whereas ankle synovitis had a greater impact after 1-2 years than at diagnosis. Large joint synovitis maybe more important for lower extremity function compared to synovitis of the MTP joints. These findings underline the importance of assessment of the joints of the lower extremities in patients with RA.

HAQ-DI for the lower extremities at different time points in early RA, by presence of synovitis

	Synovitis status	Inclusion	6 months	1 year	2 years	5 years
Knees	Present	1.2 (0.75-1.6) (n=42) $p < 0.001$	0.7 (0.4-1.2) (n=28) $p = 0.01$	0.8 (0.2-1.2) (n=12) $p = 0.15$	0.7 (0.35-1.6) (n=14) $p = 0.12$	1.0 (0.2-1.4) (n=13) $p = 0.08$
	Absent	0.4 (0.1-1.0) (n=189)	0.4 (0-0.8) (n=184)	0.4 (0-0.8) (n=207)	0.4 (0-1.0) (n=195)	0.6 (0-1.0) (n=102)
Ankles	Present	0.8 (0.2-1.2) (n=61) $p = 0.58$	0.6 (0-1.3) (n=44) $p = 0.02$	0.8 (0-1.2) (n=42) $p = 0.006$	1.0 (0.4-1.6) (n=31) $p < 0.001$	0.8 (0-1.4) (n=20) $p = 0.23$
	Absent	0.6 (0.2-1.2) (n=170)	0.4 (0-0.8) (n=168)	0.4 (0-0.8) (n=178)	0.4 (0-0.8) (n=178)	0.6 (0-1.2) (n=156)
MTP joints	Present	0.8 (0.2-1.2) (n=90) $p = 0.045$	0.5 (0-1.0) (n=52) $p = 0.13$	0.6 (0-1.0) (n=56) $p = 0.10$	0.7 (0.2-1.0) (n=46) $p = 0.04$	1.0 (0.5-1.5) (n=13) $p = 0.09$
	Absent	0.4 (0-1.0) (n=141)	0.4 (0-0.8) (n=160)	0.4 (0-0.8) (n=164)	0.4 (0-1.0) (n=163)	0.6 (0-1.0) (n=163)

Values are Median (IQR); p-values are for present vs absent synovitis.

Disclosure: M. Mellblom Bengtsson, None; S. Hagel, None; L. Jacobsson, None; C. Turesson, None.

Abstract Number: 2474

Development of a Crosswalk for FACIT-10 (Psychometric Work)

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Session Time: 9:00AM-11:00AM

Background/Purpose: Fatigue in patients with rheumatoid arthritis (RA) maybe measured with the 13-item Functional Assessment of Chronic Illness Therapy-Fatigue instrument (FACIT-F). The Patient-Reported Outcomes Measurement Information System (PROMIS) was developed using a population-calibrated T-score metric (mean 50, SD 10). PROMIS Fatigue includes the FACIT-F items, making their scores interchangeable. Crosswalk tables and a pattern scoring system have been developed to link legacy to PROMIS instruments, including fatigue.¹ A subset of 10 FACIT-F items has also been identified as relevant to patients with RA. We assessed treatment response in two phase 3 baricitinib RA trials based on linked FACIT and PROMIS Fatigue scores using both crosswalk tables and the scoring algorithm.

Methods: In RA-BEAM, patients with inadequate response to MTX were randomized 3:3:2 to placebo (PBO) once daily (QD), baricitinib (bari) 4 mg QD, or adalimumab (ADA) 40 mg biweekly.² In RA-BEACON, patients with inadequate response to biological DMARDs were randomized 1:1:1 to receive PBO or bari 2 mg or 4 mg QD.³ Patient-level FACIT-F scores were linked to PROMIS Fatigue scores using validated crosswalk tables¹ (<http://www.prosetastone.org/>) and the scoring algorithm at <http://www.healthmeasures.net/explore-measurement-systems/promis>. Analysis of covariance was conducted on PROMIS score conversions to compare bari to all treatment arms.

Results: At baseline, average PROMIS Fatigue scores across treatment groups and scoring methods ranged from 56.8 to 59.7 in RA-BEAM (FACIT-F range 27.6 to 28.6) and 60.1 to 63.7 in RA-BEACON (FACIT-F range 22.2 to 23.4); they thus reflected severe fatigue compared with the population means (e.g., approaching or exceeding 1 SD above). PROMIS Fatigue scores in RA-BEAM reached normal levels (mean <55) by week 4 for bari and ADA (data not shown). For both studies, at 24 weeks, bari was associated with clinically meaningful improvements from baseline (exceeding 0.5 SD/5 points on the T-score metric) for PROMIS Fatigue scores, and with significant improvements in PROMIS Fatigue for bari 4-mg versus placebo (Table).

Conclusion: These results support the FACIT-F to PROMIS Fatigue crosswalk and scoring algorithm approaches, with similar results shown for the subset of 10 FACIT-F items deemed most relevant to RA. This approach enables comparisons across studies using FACIT-F or PROMIS Fatigue item subsets, and their interpretation relative to US general population norms.

¹LaiJ-S, et al. J Pain Symptom Manage 2014;48: 639–48; ²Taylor PC, et al. N Engl J Med 2017;376:652–62; ³Genovese MC, et al. N Engl J Med 2016;374:1243–52.

Table. FACIT-F and PROMIS^a Fatigue Patient-Reported Outcomes

	FACIT-F standard (raw) score	PROMIS Fatigue score from 13-item FACIT-F and crosswalk table	PROMIS Fatigue score from prorated 10-item FACIT-F and crosswalk table	PROMIS Fatigue score from pattern scoring using 13-item FACIT-F	PROMIS Fatigue score from pattern scoring using 10-item FACIT-F
RA-BEAM					
PBO 24 weeks (BL N=487)	35.3 (10.6)	53.1 (8.5)	53.9 (8.7)	52.7 (7.5)	52.3 (7.2)
Bari 4-mg 24 weeks (BL N=486)	38.5 (9.6)	50.2 (8.7)	51.4 (8.5)	50.3 (7.8)	50.1 (7.5)
Bari 4-mg 52 weeks	38.9 (9.5)	50.1 (8.6)	51.1 (8.5)	49.9 (7.8)	49.7 (7.5)
ADA 24 weeks (BL N=329)	37.6 (10.4)	51.1 (9.0)	52.0 (9.0)	51.0 (7.3)	50.7 (7.1)
ADA 52 weeks	37.5 (10.5)	51.0 (9.2)	51.9 (9.4)	51.0 (7.9)	50.7 (7.5)
RA-BEACON ^b					
PBO 24 weeks (BL N=176)	28.9 (12.1)	58.2 (8.7)	59.1 (9.0)	57.1 (7.7)	56.6 (7.3)
Bari 2-mg 24 weeks (BL N=174)	31.5 (12.3)	56.0 (9.4)	57.5 (9.5)	55.5 (8.2)	55.2 (7.9)
Bari 4-mg 24 weeks (BL N=177)	33.2 (12.7)	54.4 (10.3)	55.5 (9.6)	54.0 (8.8)	53.7 (8.4)

Data are mean (SD). ^aHigher PROMIS scores mean more fatigue ^bNote, BEACON was a 24-week study.
ADA=adalimumab; bari=baricitinib; BL=baseline; PBO=placebo

Disclosure: C. O. Bingham III, Eli Lilly and Company, 5; S. J. Bartlett, – Eli Lilly and Company, 5; D. Cella, Eli Lilly and Company, 5; A. M. DeLozier, Eli Lilly and Company, 1, 3; L. Sun, Eli Lilly and Company, 1, 3; A. Quebe, Eli Lilly and Company, 1, 3; S. Otawa, Eli Lilly and Company, 1, 3; C. L. Gaich, Eli Lilly and Company, 1, 3.

Abstract Number: 2475

Promis Pain Interference 6b and Fatigue 7a Short Forms and Profile-29 in Rheumatoid Arthritis Patients Treated with TNF Inhibitors

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

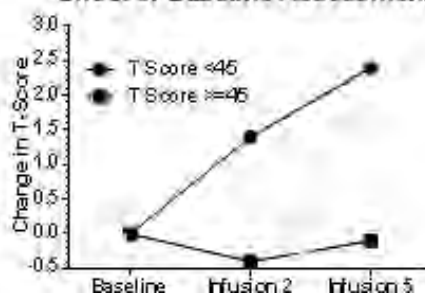
Session Time: 9:00AM-11:00AM

Background/Purpose: PROMIS (Patient Reported Outcomes Measurement Information System) has been used in rheumatoid arthritis (RA) patients (Pts) to assess disease activity across multiple domains (i.e. physical function, fatigue, pain interference). AWARE (Comparative and Pragmatic Study of Golimumab IV Versus Infliximab in Rheumatoid Arthritis) is an ongoing Phase 4 study designed to provide a real-world assessment of intravenous Tumor Necrosis Factor inhibitor (TNFi) medications in RA pts. The study utilizes PROMIS and Clinical Disease Activity Index (CADE) to assess effectiveness. This analysis examined select PROMIS measures to assess (1) relationship between baseline (BL) CADE and PROMIS-scores, (2) responsiveness of PROMIS after initiation of TNFi and (3) relationship between PROMIS T-scores of the 4 item Profile 29v2 Fatigue and Pain Interference domains and respective PROMIS Short Forms (SF).

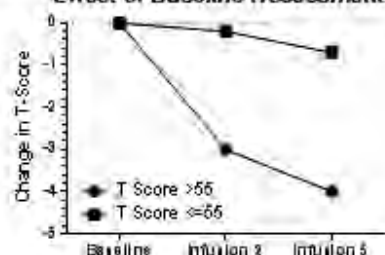
Methods: AWARE is a prospective, noninterventional, 3-year study at 100 US sites. RA pts were enrolled when initiating TNFi treatment. Treatment decisions are at the discretion of the treating rheumatologist. We report on data from Pts' BL PROMIS Pain Interference 6b (PI), Fatigue 7a (F), Profile 29v2 and CDAAI. PROMIS T-scores were compared across CDAAI disease category (high, moderate etc) using ANOVA. We dichotomized pts based on whether their BL T-score was within 0.5 SD of the population mean (i.e. 'normal') or not to evaluate for effect modification in the subsequent change in PROMIS T-scores. Data shown are mean \pm std dev.

Results: Pts (N=1220) were 59.5 ± 13.2 yrs, disease duration 8.2 ± 9.9 yrs, 83.4% female, body weight 85.1 ± 24.2 kg, BMI 31.4 ± 8.51 , BL CDAAI 32.4 ± 15.6 . A significant relationship between PROMIS T-scores (PI, F) and BL CDAAI disease activity category was confirmed. There was minimal change in T-score of pts with BL PI and F T-scores ≤ 45 and ≥ 45 over 5 infusions (approx. 5-7 months). Depending on domain, 14.7-27.3% of pts had initial PROMIS T-scores within 0.5SD of normal. There was a significant ($p < 0.0001$) relationship between PI and F T-scores and the respective 4 questions on the P29v2.

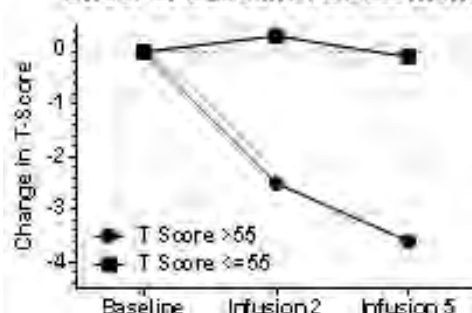
**PROMIS Physical Function T-Score Change:
Effect of Baseline Assessment**



**PROMIS Pain Interference SF6b T-Score Change:
Effect of Baseline Assessment**



**PROMIS Fatigue SF7a T-Score Change:
Effect of Baseline Assessment**



Conclusion: Avoiding floor effects in pts who initiated TNFi therapy with near-normal PROMIS scores, PROMIS instruments demonstrated a robust T-score change in response to initiation of TNFi therapy.

Disclosure: C. O. Bingham III, Janssen Research & Development, LLC, 2; S. Schwartzman, Janssen Research & Development, LLC, 2; S. Kafka, Janssen Scientific Affairs, LLC, 3; D. Parenti, Janssen Scientific Affairs, LLC, 3; S. Black, Janssen Scientific Affairs, LLC, 3; S. Xu, Janssen Research & Development, LLC, 3; W. Langholff, Janssen Research & Development, LLC, 3; J. R. Curtis, Janssen Research & Development, LLC, 2.

Abstract Number: 2476

Analysis of the Disease Activity and Functional Measures of Young Patients with Rheumatoid Arthritis Undergoing Total Joint Arthroplasty By Using the Database of Nation-Wide Observational Cohort

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The aim of this study was to investigate the impact of total joint arthroplasty (TJA) on the disease activity and functional measures of young patients with rheumatoid arthritis (RA).

Methods: Totally 15341 RA patients were registered with NinJa (National Database of Rheumatic Diseases by iR-net in Japan), which is one of the biggest database of nation-wide observational cohort in JAPAN. The data including HAQ-DI (Health Assessment Questionnaire Disability Index), EQ-5D (EuroQol 5 Dimension) as well as SDAI (Simplified disease activity index), CDAI (Clinical Disease Activity Index) and DAS28 (Disease Activity Score 28) was analyzed.

Results: Among them, 1960 patients were under 50 years old, 85 with TJA (group T) and 1875 without TJA (group C). The age at onset of RA was 25.1 years old in group T and 33.5 years old in group C. Methotrexate was used in 54 patients (63.5%) in group T and in 1333 patients (71.5%) in group C, and biologics was used in 49 patients (57.6%) in group T and in 639 patients (34.1%) in group C. In group T, HAQ-DI was 0.97, EQ-5D was 0.68, DAS28 was 2.98, SDAI was 9.06, and CDAI was 8.59. Each score was inferior to that in group C (0.27,0.81,2.51,6.17,5.78, respectively). Moreover, in comparison with 11126 patients over 50 years old without TJA (group O), each score in group T was also inferior to that of group O (0.55,0.77,2.90,6.82,6.28, respectively).

Conclusion: The data demonstrated that patients of group T showed higher disease activity and lower functional ability as well as lower QOL status despite functional reconstruction with TJA, suggesting that the more aggressive therapeutic strategy should be needed for better functional outcome in young patients undergoing TJA.

Disclosure: K. Masuda, None; T. Ikenaka, None; T. Matsui, None; S. Tohma, None.

Abstract Number: 2477

Which Is the Best Measure for Rheumatoid Arthritis Disease Activity? a Head to Head Comparison of the Six American College of Rheumatology Recommended Disease Activity Measures

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Treat-to-target is the recommended strategy for the appropriate management of Rheumatoid arthritis (RA) which involves regular assessment and monitoring of disease activity using a validated measure. Currently 6 measures are recommended by the American College of Rheumatology (ACR) for use in clinical practice.

1. Clinical Disease Activity Index (CDAI)
2. Disease activity Score with 28 Joint Counts (DAS 28)
3. Patient Activity scale (PAS)
4. Patient Activity Scale II (PASII)
5. Routine Assessment of Patient Index Data-3 measures (RAPID-3)
6. Simplified Disease Activity Index (SDAI).

The table lists the key features of each:

Methods: 50 patients diagnosed with RA based on ACR/EULAR 2010 criteria were consented and asked to fill a questionnaire during that visit and follow up visits making a total of 100 encounters. The questionnaire included questions

	CDAI	DAS-28 CRP	PAS	PAS II	RAPID3	SDAI
Methodology:						
Patient health assessment and function questionnaire	No	No	Yes	Yes	Yes	No
Patient Global assessment of disease activity (scale)	Yes	Yes	Yes	Yes	Yes	Yes
Provider Global assessment of disease activity (scale)	Yes	No	No	No	No	Yes
28 Joint count	Yes	Yes	No	No	No	Yes
Laboratory test	No	Yes	No	No	No	Yes
Time:						
Patient time (approximate)	10 sec	10 sec	3.5 min	1.5 min	1.5 min	10 sec
Provider time (approximate)	< 2 min	3-5 min	< 1 min	< 1 min	< 30 sec	< 2 min
Lab time	N/A	Variable	N/A	N/A	N/A	Variable

Age (years) mean \pm SD	51.6 \pm 10.2
Sex (%)	
Female	80
Male	20
Race (%)	
African American	50
Caucasian	46
Hispanic	4
BMI (mean \pm SD)	31.8 \pm 9.23
Tobacco abuse (%)	50
RA Disease characteristics	
Positive RF (%)	88
Positive APCA (%)	90
Median duration of illness (years \pm SD)	5 \pm 5
Number of swollen joints (mean \pm SD)	4 \pm 4
Number of Tender Joints (mean \pm SD)	5 \pm 4
Erosive changes on X ray (%)	76
Treatment	
DMARDs (%)	76
Biologic therapy (%)	26
Steroid therapy (%)	26
Other comorbidities	
Chronic pain/ Fibromyalgia (%)	12
Osteoarthritis (%)	44
Depression (%)	12



for the Health Assessment Questionnaire (HAQ), HAQ II and the Multidimensional Health Assessment Questionnaire (MDHAQ) along with the patient global Assessment. The treating physician filled out the Provider Global Assessment (0 – 10), 28 joint count for swollen and tender joints and documented their clinical impression (1- stable, 2- mild flare, 3- moderate flare or 4- severe flare). The Disease activity measures were calculated using the ACR calculator and recorded (1-remission, 2- Low disease activity, 3- Moderate disease activity and 4- high disease activity). The Pearson correlation coefficient was calculated for each of the six markers compared to the physician's clinical impression.

Results: Patient characteristics

The best correlation was found to be with CDAI (0.84), followed by DAS 28 CRP and SDAI (0.79), then PAS (0.53), PAS II (0.47) and finally RAPID-3 (0.39).

Conclusion: The PAS, PAS II and RAPID-3 which are patient reported are not very well correlated possibly due to over-estimation of symptoms by patients for various reasons. The dependence of SDAI and DAS-28 on CRP value makes them slightly less favorable in practice since the lab value may be reported after the patient encounter has been completed, thus making it less efficient to calculate, document and utilize. CDAI is the best correlated and due to the fact that it does not require any lab evaluation, it is evidently the best measure to adopt.

Disclosure: M. Katikaneni, None; S. Patel, None; A. Garg, None; M. Tariq, None; S. Wilk, None; K. Dahal, None; R. Walter, None; S. Hayat, None.

Do Age and Education Influence the Disease Activity Score? an Explorative Analysis in the Norwegian Register of Dmards

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: While ageing influences auto-immune inflammation and the structure of the joints, knowledge about its influence on appraisal of disease outcomes is more limited.

The purpose of this study was to examine the effect of age and education on the components of the 28-joint Disease Activity Score (DAS28-ESR) in patients with rheumatoid arthritis (RA).

Methods: Baseline data of Disease Modifying Anti-Rheumatic Drug (DMARD)-naive patients with RA from the Norwegian Register of DMARDs (NOR-DMARD) were used. Linear regression models, adjusted for gender and education (low, intermediate and high level), were used to investigate the strength of the association between age (<45, 45-65 and >65 years) and each DAS28-component (Erythrocyte Sedimentation Rate (ESR), 28-tender joint count (28-TJC), 28-swollen joint count (28-SJC), and patient global assessment of disease activity (PGA)). Adjusted scores for components of DAS28 and total DAS28-ESR were computed and relative change across age categories was explored. Interactions between age and gender and age and education were also tested.

Results: Baseline data from 2037 patients (mean (SD) age 55.2 (14.0) years, 68% female) were available. Regression models were stratified for gender (p –interaction <0.05); education was a significant covariate in all regression analyses. Older males (>65 years) with an intermediate level of education would have a 21% higher ESR and 14% higher 28-SJC, as compared to their younger counterparts (<45 years). For females in the intermediate education category, the corresponding differences were 16% and 15%, respectively. Conversely, differences in 28-TJC and the PGA between the highest and lowest age group were negligible in both males and females (Table 1). In absolute effects on DAS28, this means that in male patients the adjusted DAS28 for those >65 years was 4.8 compared to 4.3 in patients <45 years (females 5.0 compared to 4.6). For low and high levels of education, the results were comparable in terms of relative contribution to each DAS28-component.

Conclusion: As expected, DAS28 increases with age. However, the components of DAS28 increase at different rates. The age-related increase in ESR and 28-SJC without a simultaneous increase in 28-TJC and PGA might imply that age-related processes (e.g. osteoarthritis and physiological increase in ESR) drive the DAS28 in older patients. The observed patterns were largely comparable between males and females. The age effect on DAS28 is relevant in a treat-to-target strategy and may be considered when identifying a defined target in individual patients.

Table 1 Effect of age on DAS28 (ESR) for patients with an intermediate educational level.

Component Predicted values	< 45 years (reference) n = 181 (25%)	45 – 65 years n = 419 (58%)	> 65 years n = 123 (17%)	Difference between highest and lowest age group (%)
Males				
28-TJC	1.32	1.33	1.34	2%
28-SJC	0.62	0.66	0.71	14% ^a
PGA	0.57	0.59	0.58	2%
ESR	1.83	2.00	2.22	21% ^a
DAS28-ESR	4.34	4.58	4.83	11%
Females				
28-TJC	1.32	1.39	1.33	1%
28-SJC	0.59	0.63	0.68	15% ^a
PGA	0.67	0.68	0.68	1%
ESR	1.99	2.14	2.31	16% ^a
DAS28-ESR	4.57	4.84	5.00	9%

Abbreviations: TJC, tender joint count; SJC, swollen joint count; PGA, patient global assessment; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score. ^aDifference in scores is significant (p < 0.05).

Disclosure: M. van Onna, None; P. Putrik, None; E. Lie, None; T. Kvien, None; A. Boonen, None; T. Uhlig, None.

Abstract Number: 2479

Pilot Study of Characterizing Rheumatoid Arthritis Related Morning Stiffness

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¹Rheumatology, Hospital For Special Surgery, New York, NY, ²Radiology, Hospital For Special Surgery, New York, NY,
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SESSION INFORMATION

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) related morning stiffness is a cause of early retirement and disability. We hypothesized that circadian variation in hormones or immune cells may contribute to this problem. We compared signs and symptoms of stiffness and disease activity, labs, and hand ultrasounds of RA patients with and without morning stiffness.

Methods: We conducted a prospective feasibility observational study of patients who met ACR2010/EULAR classification criteria for RA and reported stiffness lasting more than one hour or less than 30 minutes. Ten patients were admitted for three days to Rockefeller University hospital. Patients continued standard of care treatment and were matched for steroid use (\pm 2.5 mg prednisone equivalent). The RADAI-5 questionnaire was used to assess symptoms every four hours while awake. CBC, ESR, CRP, and serum cortisol were measured every four hours. Disease activity scores, CDAI and DAS28CRP, and ultrasounds were performed at 8AM and 4PM each day. Ultrasound images of wrists and MCPs 2-5 bilaterally (10 joints) were obtained using a Vevo MD standard 10-22MHz linear probe. A musculoskeletal radiologist used the OMERACT semiquantitative scoring (0-3) system to assess both tendons and synovium and these scores were summed.

Results: The study participants were all seropositive females, with a mean of 57 years of age (Table). Stiffness severity was significantly increased in the morning compared to all other time points in the stiff group ($p < 0.02$). Patients who were stiff had significantly increased tender joint counts, swollen joint counts, patient global assessments of disease activity, CDAI,

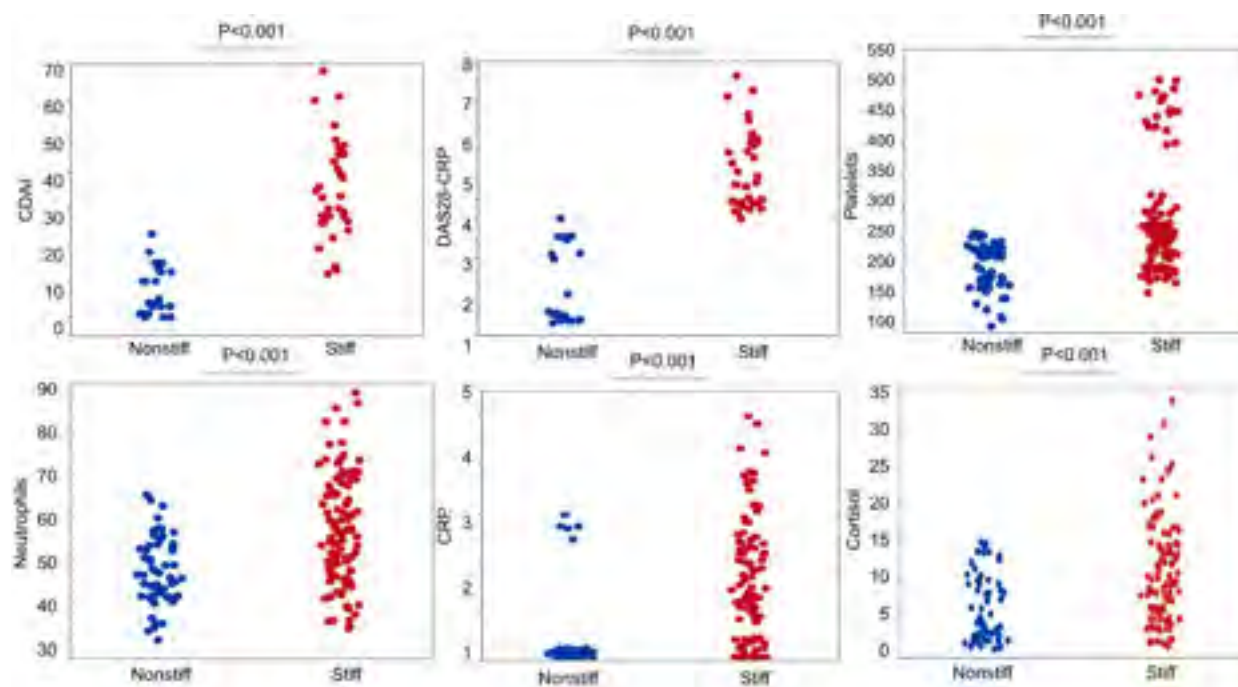


Figure. Comparison of CDAI, DAS28-CRP, platelet count, neutrophils, CRP and Cortisol level between stiff and nonstiff groups. P value: <0.001 is significant in all stiff patients.

Table. Patient Baseline Characteristics			
Variable	Stiff n= 6	Nonstiff n=4	Total n=10
Age (mean)	55.5	60.5	57.5
Female	6 (100)	4 (100)	10 (100)
% Hispanic	0 (0)	1 (25)	1 (10)
Race			
African American	0 (0)	1 (25)	1 (10)
White	6 (100)	3 (75)	9 (90)
BMI (mean)	28.7	27.1	28.1
Current cigarette smoker	2 (34)	0 (0)	2 (20)
years of Symptom duration (mean)	17.8	15.3	16.8
years of Diagnosis duration (mean)	14.2	12.3	13.4
Swollen Joint Count (mean)	11.3	3	8.0
Tender Joint Count (mean)	15.7	0.8	9.7
Seropositive (ACPA or RF)	6 (100)	4 (100)	100 (100)
Erythrocyte sedimentation rate (ESR)	34.8	42	37.7
C-reactive protein (CRP)	0.9	1.0	1.0
Current Medications			
NSAIDs	5 (83)	3 (75)	8 (80)
Glucocorticoids	1 (17)	1 (25)	2 (20)
DMARDs	5 (83)	4 (100)	9 (90)
Biologics	3 (50)	2 (50)	5 (50)

and DAS28-CRP (all $p < 0.001$) compared to nonstiff patients. Platelets, neutrophils, CRP and serum cortisol were all significantly higher in stiff compared to nonstiff patients (all $p < 0.001$) (Figure). Eosinophils demonstrated significant circadian variation in the stiff group ($p < 0.02$). There was significantly increased synovial greyscale scores between stiff and non-stiff patients ($p = 0.03$), and a nonsignificant trend of increased synovial greyscale summary scores between morning and evening time points.

Conclusion: We conclude that stiff patients have increased disease activity, blood levels of platelets, neutrophils, CRP, and cortisol, as well as increased morning eosinophils. This work lays groundwork for follow up studies and suggests that morning stiffness may be reflected in increased synovial gray scale.

Disclosure: N. Mikaberidze, None; O. Nwawka, None; M. A. McNamara, None; A. Hurley, None; V. P. Bykerk, None; D. Orange, None.

Abstract Number: 2480

Patient-Reported Outcome Measures Used in Rheumatoid Arthritis Cohorts and Registries Around the World: An Environmental Scan from the Outcome Measures in Rheumatology Critical Outcomes in Longitudinal Observational Studies Working Group

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Background/Purpose: International registries and cohorts could potentially provide long-term data on patient-centered outcomes. In recent years there has been a concerted effort to define a core set of outcome measures in rheumatoid arthritis (RA) patient registries to reduce the heterogeneity and enhance analysis of data. We conducted an environmental scan in 2016 to identify registries and cohorts (Google, PubMed, patientregistry.ahrq.gov, and clinicaltrials.gov) collecting data on patients with RA. We updated this previous study focusing on patient-reported outcome measures (PROMs). This study will aid in determining the degree of heterogeneity of PROMs worldwide to aid in a systematic effort to define a core set of outcome measures that are truly critical to patients and would probably not be collected in a randomized trial.

Methods: An expert librarian searched Medline and Embase using registries from our previous environmental scan. The name/acronym of each registry or cohort was cross referenced with terms or acronyms to select for RA. We included active registries or cohorts with articles published in the last five years. Two independent reviewers collected data and discrepancies were resolved by consensus or adjudication. Data was summarized using descriptive statistics.

Results: We included 131 registries and cohorts. Registries/cohorts were identified in 46 countries. The majority of these were from Europe (76 [58%]) and the rest from North America (24 [18%]), South America (9 [7%]), and Asia/Oceania (22 [17%]). PROMs measuring a functional impairment domain was frequently measured by the health assessment questionnaire, (HAQ)-HAQ-DI (77 [59%]), MDHAQ (13 [10%]), HAQ-II (5 [4%]), and visual analogue scale function (12 [10%]). Individual PRO domains included pain (44 [34%]), fatigue (16 [12%]), sleep (6 [5%]), quality of life, work productivity and patient-reported disease activity. Quality of life was measured with the medical outcomes Study Short Form with 6 items (2 [2%]), Rheumatoid Arthritis QoL (2 [2%]), Short Form-36 (23 [18%]), and different versions of EuroQoL (EQ) such as EQ-VAS (4 [3%]) and EQ-5D (20 [15%]). Working capacity was measured by the Work Productivity and Activity Impairment Questionnaire in 4 (3%) of the registries and cohorts. Patient-reported disease activity measures included the patient global assessment (49 [37%]), Rheumatoid Arthritis Disease Activity Index (9 [7%]), Rheumatoid Arthritis Impact of Disease (4 [3%]), and the Routine Assessment of Patient Index Data (6 [4%]).

Conclusion: Functional impairment was the most frequently recorded patient-reported outcome. As expected this study reveals a significant heterogeneity and infrequent use of the same PROMs. These data suggests far more effort must be made to include and define a core set of critical outcomes in longitudinal observational studies – outcomes that are critical to patients, and would not be feasible in a randomized trial.

Disclosure: R. Zogala, None; K. Criner, None; M. A. Lopez-Olivo, None; N. Zamora, None; D. Rai, None; G. Pratt, None; J. K. A. des Bordes, None; R. Christensen, None; M. Suarez-Almazor, None.

Abstract Number: 2481

Proposal to Re-Evaluate the Definition of Low Disease Activity in Routine Assessment of Patient Index Data 3 (RAPID3) in Rheumatoid Arthritis Patients

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

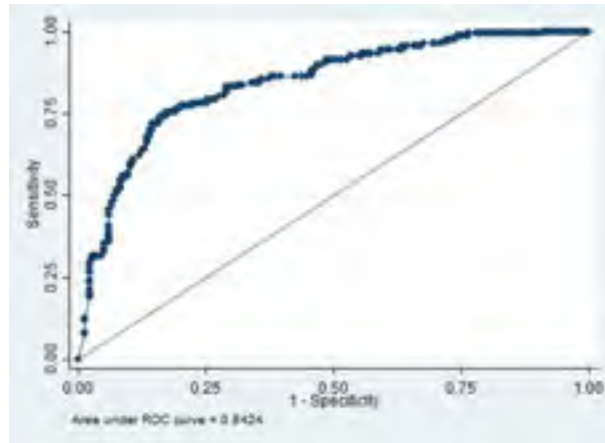
Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: There are multiple instruments to measure rheumatoid arthritis disease activity using various patient, lab or physician parameters. Since the RAPID3 has been published, there have been a few studies re-evaluating the target scores based on clinical experience. We re-evaluated the RAPID3 value for low disease activity and comparing it to two well established instruments approved by ACR, namely CDAI and SDAI.

Methods: A retrospective observational study was done from a single practice database in a community-based rheumatology clinic. Random visits from 345 patients with a diagnosis of rheumatoid arthritis who had documented RAPID3, CDAI and SDAI were studied. Baseline patient demographics, RAPID3, CDAI, SDAI, tender count, swollen count, physician global, pain scale, patient global function was collected. Receiver operator curves (ROC) were created using either low CDAI (CDAI ≤10.0) or low SDAI (SDAI ≤11.0) and a complete sensitivity/specificity report was analyzed using random patient visits.



Results: Study population consisted of 345 patients with documented RAPID3 scores with a mean of 10.19 (0-30) and SD 6.89. The comparison of RAPID 3 with low CDAI, it yielded an area under the curve of 0.84 on the ROC (95% CI 0.80-0.88) (Figure 1) with a sensitivity of 74.21% and specificity of 83.87% for a RAPID3 score of 8.0 (0-30). Similarly, in comparison with low SDAI, it yielded an area under curve of 0.84 on the ROC (95% CI 0.79 – 0.87) with a sensitivity of 74.69% and specificity of 83.06% for a RAPID3 score of 8.2 (0-30). If we reconsider a low disease activity score of 8.0 on the RAPID3, approximately 10% of this patient population were misclassified.

Figure 1. Receiver Operator Curve RAPID3 vs low CDAI

Conclusion: In this cohort, low CDAI and SDAI disease activity were found to be correlated to a higher RAPID3 score cut off. Currently, CDAI low disease activity is defined as >2.8-10, SDAI low disease activity as 3.3-<11 and RAPID3 low disease activity as >3.0-6.0. Using the current low disease activity cut off, our treat to target goal may be misclassifying these patients from low to moderate disease activity thereby overtreating them. We propose that the definition of low disease activity for the RAPID 3 to be <8.0 on a 0-30 scale. Further studies comparing these findings as well as other cut off ranges using larger number of patients are required to substantiate this study.

Disclosure: V. Tiwari, None; A. Maheshwari, None; S. Dheer, None; M. J. Bergman, Merck & Co., 1, 8, AbbVie Inc., 5, 8, BI, 5, Celgene Corporation, 5, 8, Novartis, 5, 8, Pfizer, Inc., 5, Sanofi, 5, 8, Genentech, Inc., 5, Horizon, 5.

Abstract Number: 2482

The Use of Any Conventional Synthetic DMARD Is Associated with Better Indexes of the Physical Component Evaluated By 12-Item Short-Form Health Survey : Analysis of a Cohort of RA Patients

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SESSION INFORMATION

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Background/Purpose: Patients with rheumatoid arthritis (RA) report a reduction in quality of life (QoL) in several aspects when compared to the healthy population. QoL can be evaluated by the 12-Item Short-Form Health Survey (SF-12), a questionnaire that considers the individual's perception of their health in the last 4 weeks and, through a specific algorithm, measures two scores: Physical Component Summary (PCS) and Mental Component Summary (MCS). The score of both ranges from 0 to 100, and higher scores are associated with better QoL indexes. In the present study, we related clinical, laboratory and therapeutic aspects of a large RA cohort with the PCS indexes of SF-12.

Methods: A prospective multicenter cohort study involving 13 centers specialized in the care of patients with RA. All patients underwent at least 3 clinical evaluations over a 12-month period. Only patients older than 18 years and classified as having RA according to the criteria of 1987 (ACR) or 2010 (ACR/EULAR) were evaluated. SF-12 was used to assess QoL, and only the components relevant to the PCS were considered. The comparison between groups was performed using the Mann-Whitney and Kruskal-Wallis tests.

Results: A total of 1,116 patients (89.43% females, mean age 58 ± 11 years) participated in the study. Patients with erosive disease presented lower PCS score ($p = 0.0004$) than those without this characteristic. Regarding medications, the use of at least one conventional synthetic DMARD is associated with a higher score ($p = 0.0004$); the use of at least one biologic or targeted-synthetic DMARD is associated with a lower score ($p = 0.0142$); and the use of abatacept and tocilizumab is associated with a lower score ($p = 0.0276$ and $p = 0.0116$, respectively). In a linear regression model ($p < 0.0001$), it was found that the patient with the highest score of SF-12 physical component is the one using a synthetic DMARD ($p = 0.0016$) and not using tocilizumab ($p = 0.0374$) and abatacept ($p = 0.0151$). The results are summarized in Table 1.

Conclusion: The best QoL indexes observed in patients using any conventional synthetic DMARD reinforce the importance of this class of medications in the treatment of RA. The results obtained with non-anti-TNF biologic DMARDs may reflect the usual choice of these drugs as third-line therapy.

Table 1 – Measures of position and dispersion of the physical component of 12-Item Short-Form Health Survey and result of the comparison between Kruskal-Wallis (K) and Mann-Whitney (M) groups.

Variable	Category	N	p-value
Rheumatoid factor titration	High	598	0.5903 ^K
	Low	242	
	Negative	222	
Anti-CCP titration	High	275	0.7524 ^K
	Low	84	
	Negative	108	
Erosive disease	No	478	0.0004^M
	Yes	584	
Methotrexate	No	366	0.0806 ^M
	Yes	714	
Leflunomide	No	716	0.7090 ^M
	Yes	364	
Hydroxychloroquine	No	961	0.7193 ^M
	Yes	119	
Sulfasalazine	No	1,027	0.1165 ^M
	Yes	53	
Conventional synthetic DMARD	No	113	0.0004^M
	Yes	967	
Adalimumab	No	1,031	0.5650 ^M
	Yes	49	
Infliximab	No	1,034	0.6239 ^M
	Yes	46	
Etanercept	No	1,017	0.6239 ^M
	Yes	63	
Certolizumab	No	1,064	0.4976 ^M
	Yes	16	
Golimumab	No	1,045	0.8640 ^M
	Yes	35	
Tocilizumab	No	1,025	0.0276^M
	Yes	55	
Abatacept	No	1,011	0.0116^M
	Yes	69	
Rituximab	No	1,032	0.9938 ^M
	Yes	48	
Tofacitinib	No	1,071	0.7569 ^M
	Yes	9	
Biologic or targeted-synthetic DMARD	No	690	0.0142^M
	Yes	390	

K: Kruskal-Wallis test; M: Mann-Whitney test; conventional synthetic DMARD: at least one between methotrexate, leflunomide, hydroxychloroquine and sulfasalazine; biologic DMARD: at least one between adalimumab, infliximab, etanercept, certolizumab, golimumab, tocilizumab, abatacept, rituximab and tofacitinib.

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Abstract Number: 2483

Major Secular Trends of Patient Characteristics and Inclusion Criteria in RA Clinical Trials

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SESSION INFORMATION

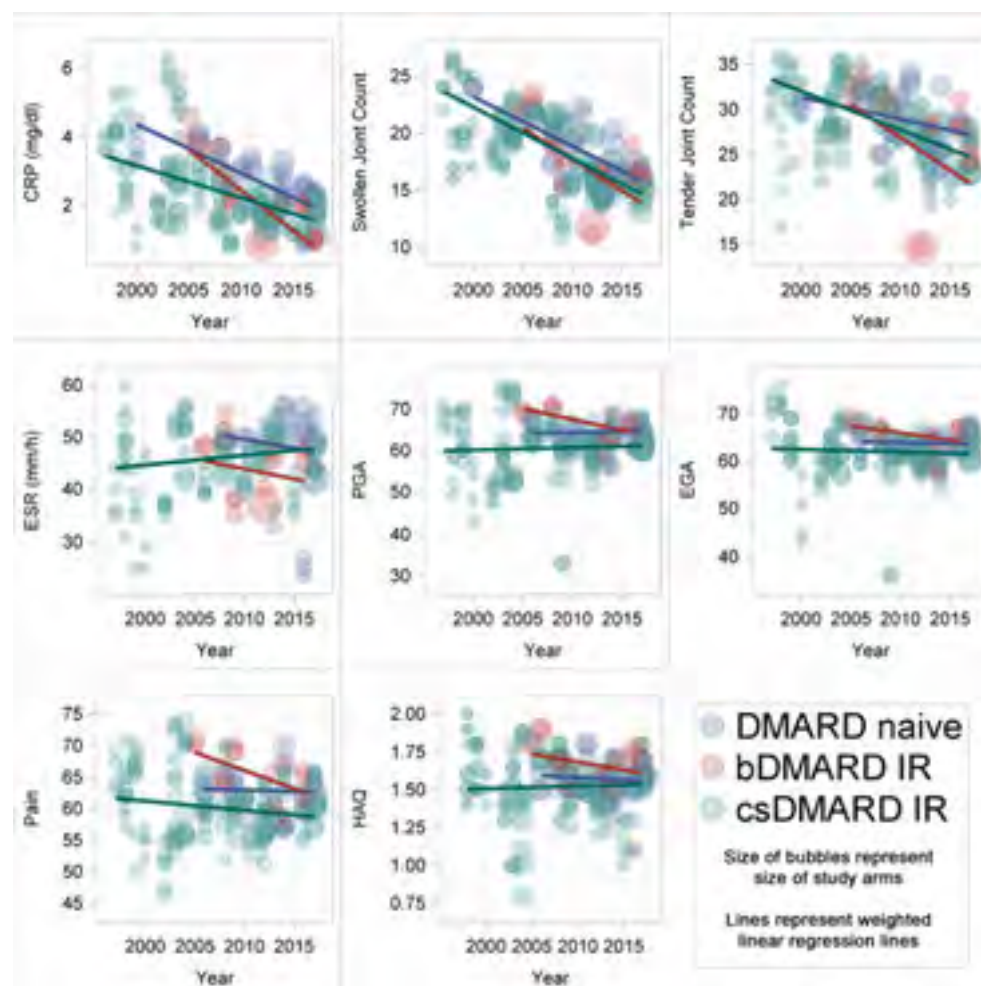
Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is among the most intensively studied chronic inflammatory musculoskeletal diseases. Over the past two decades numerous new compounds have been tested in RA. Although the results from any new clinical trial in RA is usually interpreted in the context of existing data from previous trials, it is not clear whether trial populations are necessarily historically comparable. We investigated secular trends in characteristics of patient populations enrolled in RA clinical trials and inclusion criteria as possible influencing factors.



Methods: We performed a systematic literature review of randomized, controlled, double-blind trials, investigating biological therapies in RA. Reports were identified using PUBMED, EMBASE and the Cochrane Library. Populations were stratified into conventional disease modifying anti-rheumatic drug (DMARD) naïve, DMARD inadequate responders (IR), and biological DMARD IR. The following variables at baseline were extracted from reports: swollen and tender joint counts (SJC, TJC), pain, patient and evaluator global (PGA, EGA), acute phase measures (erythrocyte sedimentation rate, ESR and C-reactive protein, CRP), as well as the Health Assessment Questionnaire Disability Index (HAQ). In addition, we obtained the year of publication and the inclusion criteria (IC) of each trial. We then performed a mixed model meta-regression of year of publication on each of the mentioned variables and IC.

Results: Out of 697 abstracts selected for screening, 73 studies were chosen as relevant; 3 studies with mixed populations were excluded, resulting in 70 studies included for analysis. Table 1 shows the medians and quartiles for the baseline characteristics. Meta-regression showed a significant decrease of SJC ($\beta=-0.415$; $p<.001$), TJC ($\beta=-0.378$; $p<.001$), and CRP ($\beta=-0.123$; $p<.001$) over the years (figure 1); for all other core set measures, there was no trend or significance. IC showed similar trends over time for SJC ($\beta=-0.154$; $p<.001$), TJC ($\beta=-0.243$; $p<.001$), and CRP ($\beta=-0.065$; $p<.001$). Furthermore, there were significant linear associations of IC with SJC ($\beta=1.33$; $p<.001$), TJC ($\beta=1.14$; $p<.001$) and CRP ($\beta=1.16$; $p<.001$) at baseline.

Conclusion: There is a progressive drift towards lower number of swollen and tender joints and lower CRP-levels at trial entry of time, which is at least partly related to a similar trend in inclusion criteria for RA. The constancy of patient-reported outcomes suggests that the baseline activity is still perceived as similarly high. Differences in overall baseline inflammatory activity may pose a challenge for comparing newer with older trial results.

	DMARD NAIVE	bDMARD IR	csDMARD IR
No of trials (n)	13	9	48
No of study arms (n)	39	25	180
No of patients (n)	8894	4584	23752
Year of publication (YYYY)	2014 (2009–2016)	2013 (2008–2016)	2008 (2003–2012)
CRP (mg/dL)	2.59 (2.27–3.26)	2.1 (1.08–3.11)	2.08 (1.67–3)
ESR (mm/h)	49.4 (42–52.8)	46.85 (39.2–48.2)	45.95 (40.2–49.9)
Swollen Joints (0-66)	16.65 (16–20.3)	17.1 (16.2–19)	17.95 (15.59–20.4)
Tender Joints (0-68)	28.05 (25.5–31)	28.75 (25.6–31.2)	28.1 (25.88–31.7)
Patient global assessment (0-100)	63.9 (61.8–66)	66.5 (63–69.7)	61 (58–65)
Evaluator global assessment (0-100)	63.6 (62–65.6)	66.45 (62–67)	62.05 (59.7–65)
Patients pain assessment (0-100)	62.5 (60.9–64.6)	65 (62–69)	60.29 (56.66–65)
Health assessment questionnaire (0-3)	1.54 (1.50–1.63)	1.7 (1.60–1.74)	1.51 (1.41–1.66)

Disclosure: A. Kerschbaumer, Bristol-Myers-Squibb and Pfizer, 9; B. Bierbaumer, None; J. S. Smolen, Abbvie, Astra-Zeneca - to Institution, 2, Abbvie, Chugai, Gilead, ILTOO, Janssen, Lilly, MSD, Novartis-Sandoz, Pfizer, Samsung, Sanofi, 5, Abbvie, Celgene, Chugai, Janssen, Lilly, MSD, Pfizer, Samsung, Sandoz, UCB, 9; D. Aletaha, AbbVie, Merck Sharp and Dohme, Roche, 2, AbbVie, Janssen, Lilly, Novartis, Pfizer, Roche, 5, AbbVie, Janssen, Lilly, Novartis, Pfizer, Roche, Bristol-Myers Squibb, Celgene, Merck, Sharp and Dohme, UCB, 9.

Abstract Number: 2484

Effect of Biologic Agents on Synovial Tissues from Patients with Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

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Background/Purpose: Multiple studies addressing the effects of biologics on the synovial tissue in rheumatoid arthritis (RA) patients have been reported. There are, however, few studies comparing histopathological changes in the synovial tissue in the same RA patients between before and after biologics treatment. We examined the inflammation of synovium before and after biologic agents in the patients with rheumatoid arthritis (RA) and to investigate the association between synovial histopathology and disease activity.

Methods: Synovial tissues were collected from 34 RA joints before and after biologics. The average age and disease duration of the study subjects were 64.0 and 22.5 respectively. Histopathological changes in the synovial tissues were compared based on Rooney's score, and presence or absence of fibrinoid degeneration, proliferation of villi and plasma cell infiltration in the subsynovial tissue. We examined correlation between pathological findings in RA synovium and disease activity under biologics. Disease activity was assessed by CDAI. Etanercept, Infliximab, Tocilizumab, Adalimumab and Abatacept was used as biological drug for 18, 6, 5, 3 and 2 joints respectively.

Results: Rooney score between before and after biological drug usage improved from 28.4 to 12.0 showing significant difference. Significant improvement in Rooney score was observed in all items. Fibrinoid degeneration was observed in 29 cases (85.3%) and 6 cases (17.6%) before and after biologics treatment, respectively, demonstrating a significant reduction with biologics treatment. Proliferation of villi was observed in 32 cases (94.1%) and 11 (32.4%) before and after biologics treatment, respectively, demonstrating a significant reduction with biologics treatment. After the use of biologic agents, Moderate disease activity group had significantly higher in scores of focal aggregates of lymphocytes ($P=0.02$), diffuse infiltrates of lymphocytes ($P=0.019$), and Rooney total scores ($P=0.002$) than Remission and Low disease activity groups.

Conclusion: The study results demonstrated that biologics treatment significantly decreased inflammatory changes in the synovial lining layers and sublining layers. In addition, the results suggested that histopathological findings in the subsynovial tissue reflected disease activity.

Disclosure: A. Kubota, None; T. Suguro, None; A. Nakajima, None; M. Sonobe, None; K. Tsuchiya, None.

Abstract Number: 2485

Comparison of Risk for Infection-Related Hospitalization and Associated Costs of Biologic Experienced Rheumatoid Arthritis Patients Treated with Abatacept Versus Other Targeted Disease Modifying Antirheumatic Drugs

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Background/Purpose: Abatacept is a targeted disease-modifying antirheumatic drug (tDMARD) that has demonstrated a lower risk for infection in comparison with other tDMARDs among rheumatoid arthritis (RA) patients. The potential cost differences associated with the reduced risk of infection among RA patients treated with abatacept vs. other tDMARDs is not well understood. We therefore compared infection-related hospitalization risk and associated costs of RA patients experienced with a tumor necrosis factor- α inhibitor (TNFi) who subsequently received abatacept vs. other tDMARDs, including another TNFi or other non-TNF- α inhibitor (non-TNFi).

Methods: Patients initiating a tDMARD (index drug/date) who had ≥ 1 inpatient diagnosis or ≥ 2 outpatient diagnoses of RA in the 12 months prior to the index date were identified in MarketScan data (1/1/2010-3/31/2016). Patients were required to have been previously treated with a TNFi and have 12 months of insurance coverage prior to the index date (baseline period) and throughout the follow-up period (≥ 12 months; up to 36). Unadjusted and multivariable adjusted regression were used to evaluate the impact of the index drug on infection-related hospitalizations and the per-patient per-month (PPPM) associated costs. Log transformation and gamma distribution were used in the regression analysis of cost data where cost values plus \$1 were used so that after the log transformation the original cost data of \$0 will have the value of $\log(1)=0$.

Results: Of the study population, 308 patients (mean age: 55 years; 86% female) were treated with abatacept, 1,032 with a TNFi (mean age: 52 years; 82% female), and 321 with another non-TNFi (mean age: 55 years; 76% female). Compared to the baseline period, the proportion of patients with infection-related hospitalizations declined in the follow-up period, as did infection-related hospitalization cost among patients treated with abatacept, while increasing in the follow-up period for both the TNFi and non-TNFi cohorts (Table). After adjusting for differences in patient characteristics, Cox regression analysis showed that the risk for an infection-related hospitalization was significantly greater for RA patients treated with a TNFi vs. abatacept (HR: 2.6; 95% CI: 1.2-5.8, $P=0.02$) and numerically higher for those treated with another non-TNFi vs. abatacept (HR: 1.9; CI: 0.7-4.7, $P=0.19$). The change in infection-related hospitalization cost PPPM was significantly higher

Table. Unadjusted Comparison of Infection-related Hospitalizations and Associated Costs PPPM in the Baseline and Follow-up Periods

	Abatacept n=308	TNFi n=1,032	Non-TNFi n=321
Baseline infection-related hospitalization, n (%)	14 (4.6)	21 (2.0)	8 (2.5)
Follow-up infection-related hospitalization, n (%)	7 (2.3)	52 (5.0)	14 (4.4)
Mean baseline infection-related hospitalization cost PPPM	\$120	\$35	\$68
Mean follow-up infection-related hospitalization cost PPPM	\$22	\$68	\$75
Cost change (follow-up — baseline)	-\$98	\$32	\$7

for RA patients treated with a TNFi vs. patients treated with abatacept (\$73; 95% CI: \$16-\$201, $P=0.006$); and was numerically higher but not statistically significant for patients treated with another non-TNFi (\$66; 95% CI: -\$8-\$211, $P=0.08$).

Conclusion: In the real-world setting in the US, patients treated with abatacept vs. a TNFi had a lower risk for infection-related hospitalization and lower associated hospitalization cost.

Disclosure: D. Paul, Bristol-Myers Squibb, 3; L. McDonald, Bristol-Myers Squibb, 3; A. Marshall, Bristol-Myers Squibb, 3; T. Curtice, Bristol-Myers Squibb, 1, 3; M. Lingohr-Smith, Novosys Health, 3; B. Menges, Novosys Health, 3; J. Lin, Novosys Health, 3, Bristol-Myers Squibb, 5.

Abstract Number: 2486

Real-World Outcomes Associated with Triple Therapy Vs. TNFi Combo Therapy: Results from the Corrona Registry

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

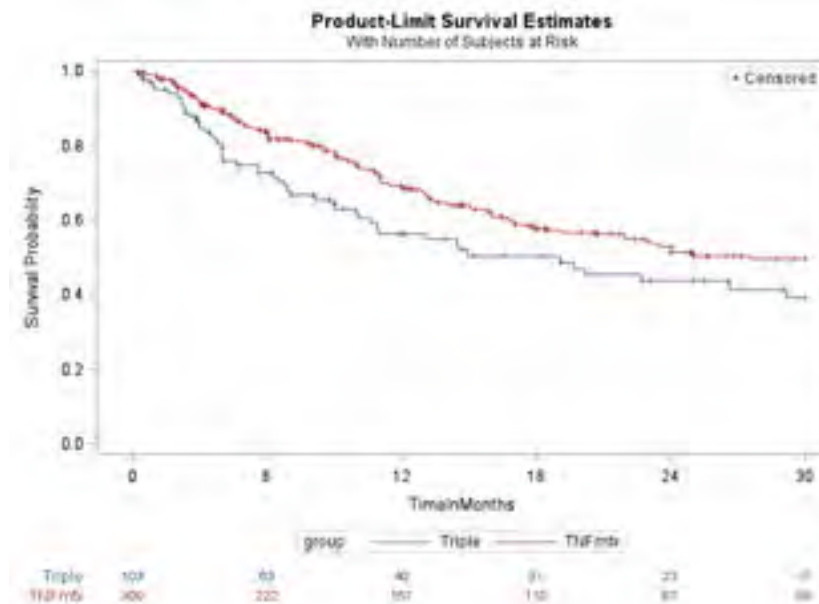
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Despite several randomized controlled trials showing comparable clinical outcomes with triple therapy (Triple; MTX, SSZ, HCQ) versus combination therapy with MTX+TNFi (TNFi Combo), the real-world experience comparing these two strategies may differ.

Methods: We identified new users of Triple vs. TNFiCombo amongst RA patients in the Corrona registry. Initiation of these therapies could have been simultaneous or sequential, but patients had to receive all therapies simultaneously and could not have ever received Triple or TNFi Combo treatment previously. Patients must have had moderate/high disease activity (CDAI >10) at baseline and have ≥1 follow-up visit.

Treatment failure was defined as starting/adding a new biologic/JAKi, csDMARD, or discontinuation of any of the medications in Triple or TNFi Combo exposures. Patients were censored if they attained low disease activity (CDAI < 10). Propensity score (PS) matching (1:3, and 1:1 as part of a sensitivity analysis) was used to balance exposure groups (8-1 digit Greedy Match), with caliper widening if required for higher order matches. Treatment failure was evaluated using KM curves. Cox models were used to control for residual imbalance in baseline factors and account for clustering of the



matched PS pairs. An additional sensitivity analysis evaluated adjusted treatment failure in the entire unmatched sample, controlling for baseline factors and excluding patients in the non-overlapping tails of the PS.

Results: A total of 2156 TNFi Combo and 105 Triple patients were eligible for analysis. Before PS matching, numerous factors were imbalanced between the two groups, with Triple patients being older (mean age: 62 vs. 56 yrs), having longer RA disease duration (9 vs. 6 yrs), and a higher proportion with history of malignancy, diabetes, and serious infections. They also had lower baseline disease activity (mean Triple: 21.2 vs. TNFi Combo: 26.6).

After 1:3 PS matching (n=103 in Triple, n=309 in TNFi Combo in each group), balance was improved but some residual differences remained. Treatment failure was more likely in the Triple group (Figure). After multivariable adjustment, treatment failure was more likely in the Triple group compared to the TNFi combo group (adjusted hazard ratio [aHR] = 1.38, 95% CI 1.02-1.88). Results from both sensitivity analyses (n=2240 patients in entire sample, n=204 in matched sample) were similar (HR=1.45, 95% CI 1.10 to 1.92; aHR=1.64, 95% CI=1.12-2.38 matched, respectively).

Conclusion: Based on real world evidence from a large U.S. RA registry, use of Triple is uncommon, and outcomes associated with Triple are less favorable compared to combination therapy with TNFi+MTX.

Figure: Treatment Failure associated with Triple Therapy (n=103) versus Combination TNFi+MTX (n=309)

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Abstract Number: 2487

Comparison of QOL Evaluation Using EQ-5D-3L and EQ-5D-5L in Japanese RA Patients: A Study Using the IORRA Cohort

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: EQ-5D-3L is frequently used for evaluation of quality of life (QOL). However, there are several problems when using EQ-5L-3L. Evaluation using EQ-5L-3L might not properly reflect the health status of patients since patients can choose from only three levels (no problems, some problems, extreme problems). Another limitation is the ceiling effect, whereby a value of 1 for QOL means “complete health”. Recently, EQ-5D-5L was developed to resolve these problems. Few reports are available which assess both methods for evaluation of QOL in the context of rheumatoid arthritis (RA). This was a comparative study of EQ-5D-3L and EQ-5D-5L in patients with RA conducted using the IORRA cohort to examine the usefulness of the EQ-5D-5L.

Methods: The subjects were Japanese RA patients who participated in the IORRA survey in October 2016. QOL evaluation using EQ-5D-3L and EQ-5D-5L were conducted at the same time, and the following analyses were cross-sectionally examined. The difference in QOL value distribution between EQ-5D-3L and EQ-5D-5L was investigated. The QOL values of EQ-5D-3L and EQ-5D-5L were compared stratified by sex, age, RA disease duration, RA disease activity, dysfunction level, and medications (steroid use, methotrexate [MTX] use and biological DMARD [bsDMARD] use). Among RA patients who evaluated themselves as “complete health” using EQ-5D-3L, the percentage of the patients which did not satisfy “complete health” was investigated.

Results: A total of 5,023 RA patients were included in this study. Baseline clinical features in this cohort were as follows: 94% women; average age of 61 years old; mean RA disease duration: 15.7 years; average DAS28: 2.6; proportions of steroid, MTX and bsDMARD use: 27.2%, 77.0%, and 23.7%, respectively. The average (SD) values of QOL using EQ-5D-3L and EQ-5D-5L were 0.83 (0.18) and 0.85 (0.16), respectively. Although among RA patients who evaluated themselves as “1”, which means “no problems” using EQ-5D-3L in the 4 dimensions (mobility, self-care, usual activities, and anxiety/depression), most of the patients also evaluated themselves as “1” using EQ-5D-5L, while among RA patients who evaluated themselves as “1” using EQ-5D-3L for “pain/discomfort”, most of the patients evaluated themselves as “2” which means “some problems” using EQ-5D-5L. The average QOL value using EQ-5D-3L stratified by each clinical feature was lower than that using EQ-5D-5L regardless of patients’ backgrounds and medications. The percentage of RA patients who evaluated themselves as “complete health” which was scored as “1” in all 5 dimensions using EQ-5D-3L and EQ-5D-5L, were 45.0% and 32.3%, respectively. Among RA patients who evaluated themselves as “complete health” using EQ-5D-3L, 28.2% were omitted from “complete health” using EQ-5D-5L. The dimension of “pain/discomfort” had the most influence on omission from “complete health”.

Conclusion: The problem of ceiling effect was improved by using EQ-5D-5L in RA patients, and was especially influenced by the dimension of “pain/discomfort”, suggesting that the EQ-5D-5L questionnaire might properly reflect the health status of RA patients.

Disclosure: K. Saka, None; E. Tanaka, ET has received lecture fees or consulting fees from Abbvie, Ayumi Pharmaceutical, Bristol Myers Squibb, Chugai Pharmaceutical, Eisai Pharmaceutical, Nippon Kayaku, 8; E. Inoue, None; M. Abe, None; M. kawano, None; N. Sugitani, None; E. Sugano, None; M. Ochiai, None; R. Yamaguchi, None; Y. Shimizu, None; N. Sugimoto, None; K. Ikari, Astellas, AbbVie, Bristol-Meyers, Chugai, Janssen Pharmaceutical, Lilly, Takeda, and Tanabe-Mitsubishi, UCB, 8; A. Nakajima, Eisai, Bristol-Meyers, Novartis, Astellas, Noppon-Shinyaku, Pfizer, Ayumi, Daiichi-Sankyo, Taisyo-Toyama, Tanabe-Mitsubishi, Chugai, janssen, 5; A. Taniguchi, abbVie, Eisai, Jansen, Teijin, Novartis, Eli Lil, 8; H. Yamanaka, AbbVie, Eisai, Bristol-Meyers, Novartis, Behringer, Astellas, Kaken, Noppon-Shinyaku, Pfizer, UCB, Ayumi, Ono, Daoochi-Sankyo, Taisyo-Toyama, Takeda, Tanabe-Mitsubishi, Chugai, Teijin Pharma, Torii, YLbio, 9.

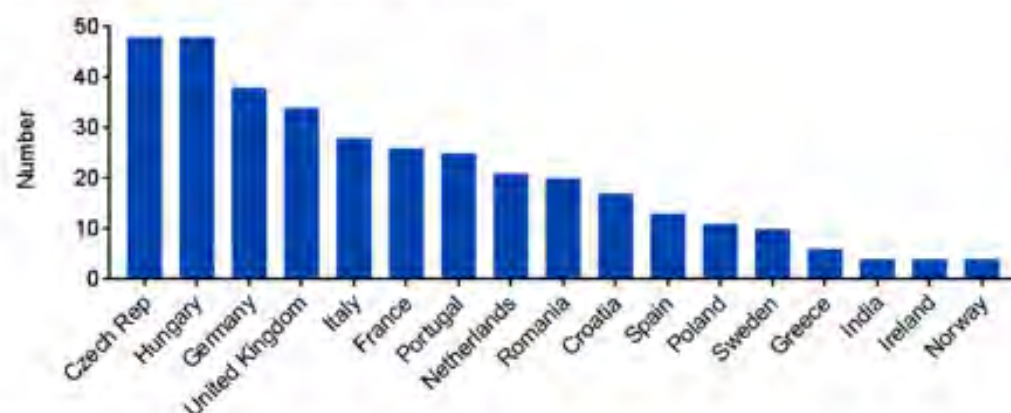
Abstract Number: 2488

Characteristics of Difficult-to-Treat Rheumatoid Arthritis: Results of an International Survey

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France, Paris, France, ⁵Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, ⁶Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK, Glasgow, United Kingdom, ⁷Dept. of Rheumatology and Clinical Immunology, Campus Kerckhoff, Justus-Liebig-University Giessen, Germany, Bad Nauheim, Germany, ⁸First Faculty of Medicine, Charles University, Prague, Czech Republic, Prague, Czech Republic, ⁹Department of Rheumatology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary, Debrecen, Hungary, ¹⁰Department of Genetics, Cell- and Immunobiology & Department of Rheumatology, 3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary, Budapest, Hungary

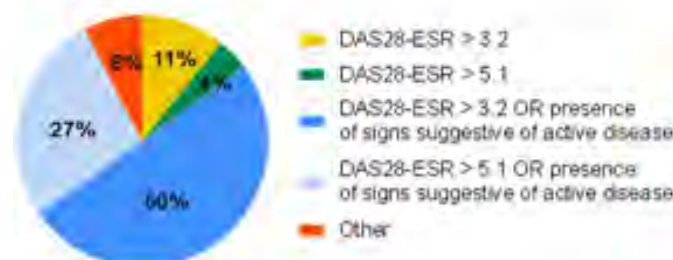
Figure 1a. Number of respondents per country



Less than 4: Austria, Belarus, Bulgaria, Denmark, Egypt, Estonia, Iceland, Israel, Kenya, Pakistan, Russia, Serbia, Slovakia, Slovenia, Tunisia, Turkey

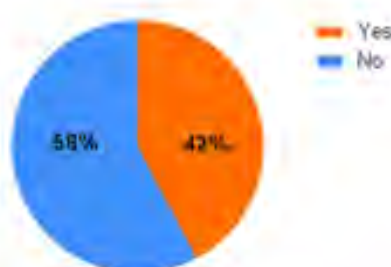
Figure 1b. Characteristics for the concept of difficult-to-treat RA

What should be the definition for not well-controlled disease in the definition of difficult-to-treat RA?



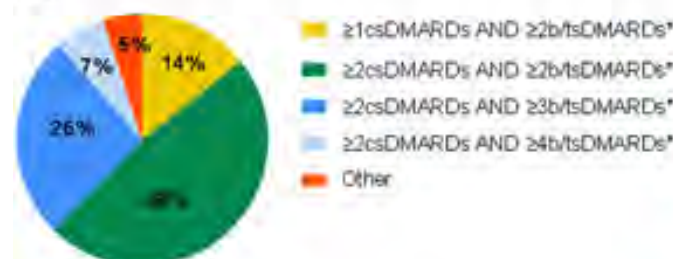
Total responses = 409

Would you include fatigue in the definition of not well-controlled disease?



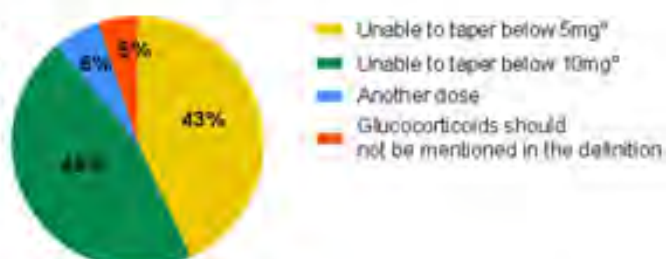
Total responses = 396

Which and how many anti-rheumatic drugs should at least be tried with insufficient effect for the definition of difficult-to-treat RA?



Total responses = 398

Treatment with glucocorticoids should be mentioned in the criteria for difficult-to-treat RA as follows:



Total responses = 397

b/tsDMARDs: biological/targeted synthetic disease-modifying anti-rheumatic drugs; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; DAS28-ESR: disease activity score assessing 28 joints using erythrocyte sedimentation rate; RA: rheumatoid arthritis

* with different mode of action

° or equivalent daily for more than 1 year, irrespective of DMARD treatment

SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

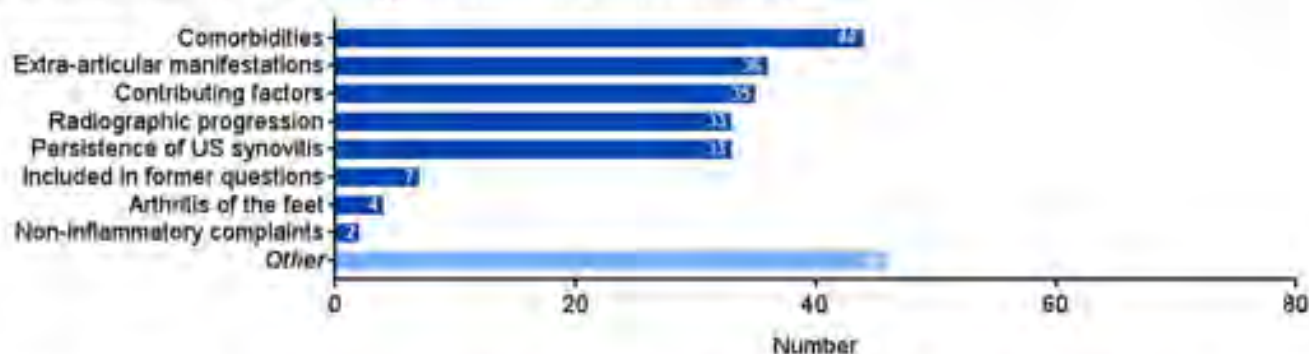
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

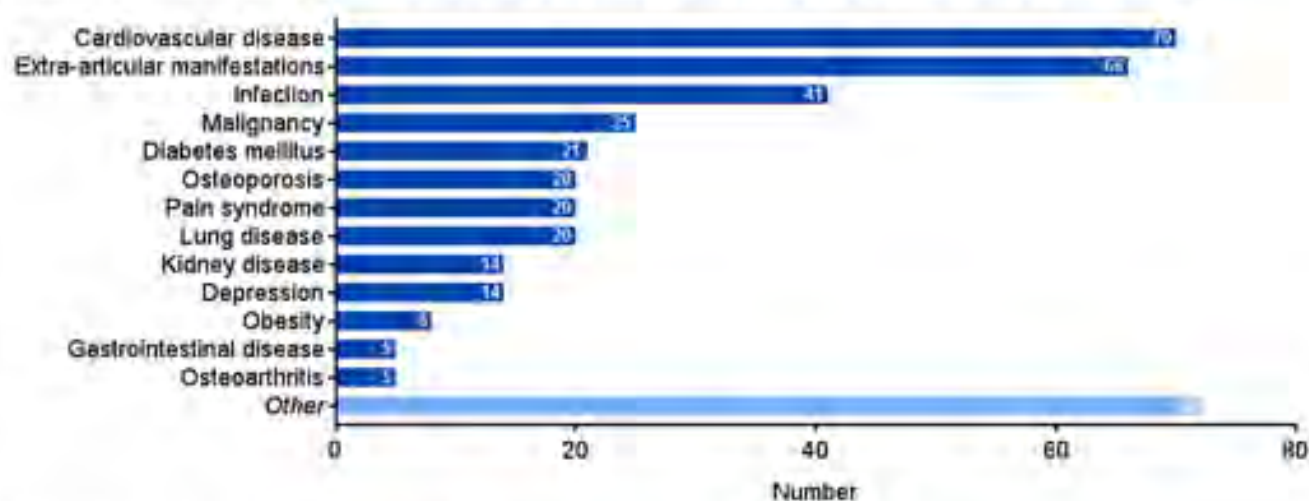
Background/Purpose: EULAR and ACR recommendations on the management of rheumatoid arthritis (RA) mainly focus on early RA and medication.^{1,2} Following these recommendations, several patients nevertheless remain symptomatic, which makes them difficult-to-treat.³ The estimated prevalence of difficult-to-treat RA ranges from 5 to 20%.⁴ A difficult-to-treat RA classification would enable making recommendations on its comprehensive management. We aimed to identify

Figure 2. Additional characteristics of difficult-to-treat RA and clinical issues to be covered in management recommendations

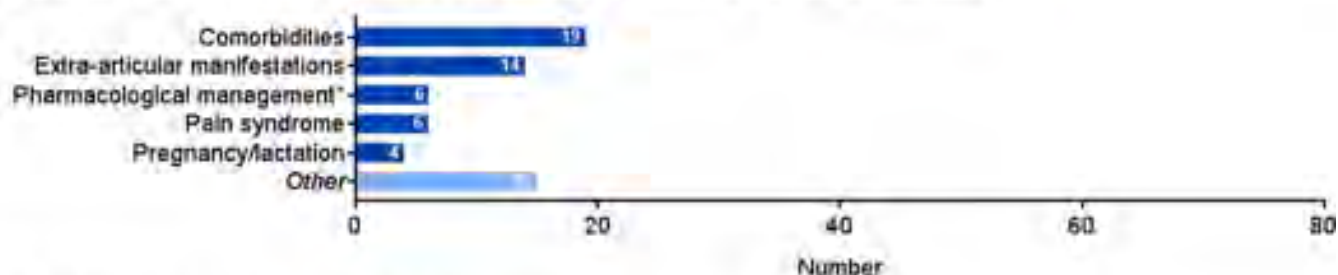
a. Additional characteristics and suggested criteria for difficult-to-treat RA



b. Additional clinical issues or comorbidities to be addressed in the workup and management of these patients



c. Clinically relevant situations which are not covered by the current RA recommendations



RA: rheumatoid arthritis; US: ultrasonography

* e.g. tapering strategies, adverse events, polypharmacy

characteristics of difficult-to-treat RA and issues to be addressed in its comprehensive workup and management that are not covered by the current RA management recommendations.

Methods: Among rheumatologists, an international survey was conducted. It included multiple-choice questions on disease characteristics of difficult-to-treat RA and open questions on additional items to be addressed and items missing in current management recommendations.

Results: 410 rheumatologists (a few of them in training) from 33 countries, mostly in Europe, completed the survey between July 2017 and March 2018 (Figure 1a). For disease characteristics of difficult-to-treat RA, 50% of respondents selected disease activity score assessing 28 joints (DAS28) >3.2 OR signs suggestive of active disease; 42% selected fatigue; 48% selected failure to ³2 conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) AND ³2 biological/targeted synthetic DMARDs; 89% selected inability to taper glucocorticoids below 5 or 10 mg prednisone equivalent daily (Figure 1b). Over 400 responses to the open questions were received (Figure 2). Comorbidities, extra-articular manifestations and polypharmacy were identified as important issues missing in current management recommendations.

Conclusion: Concepts of difficult-to-treat RA vary considerably. Important issues regarding patients with difficult-to-treat RA, such as comorbidities, extra-articular manifestations and polypharmacy, are not addressed by current RA management recommendations.

References: 1 Smolen JS, et al. *Ann Rheum Dis* 2017;76:960-77.

2 Singh JA, et al. *Arthritis Rheum* 2016;68:1-26.

3 de Hair MJH, et al. *Rheumatology (Oxford)* 2017.[Epub]

4 Kearsley-Fleet L, et al. *Ann Rheum Dis* 2017;76:960-77.

Disclosure: N. M. Roodenrijs, None; M. J. de Hair, None; M. C. van der Goes, None; J. W. G. Jacobs, None; P. M. Welsing, None; D. van der Heijde, Imaging Rheumatology BV, 3, AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Daiichi, Eli-Lilly, Galapagos, Gilead, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi and UCB Pharma, 5; D. Aletaha, None; M. Dougados, None; K. L. Hyrich, None; I. B. McInnes, None; U. Müller-Ladner, None; L. Šenolt, AbbVie, BMS, Celgene Corporation, Eli Lilly, Merck Sharp and Dohme, Novartis, Pfizer, Roche, Takeda, UCB, 5; Z. Szekanecz, None; J. van Laar, Arthrogen, MSD, Pfizer, Eli Lilly, BMS, Astra Zeneca, Roche-Genentech, 2, 5; G. Nagy, Amgen, AbbVie, BMS, KRKA, MSD, Pfizer, Roche, UCB, 2.

Abstract Number: 2489

In Clinical Practice a Substantial Group of Rheumatoid Arthritis (RA) Patients on Biologic Therapy (bDMARDs) Has Persistent Moderate Disease Activity Despite Treatment Switches That Correlates with Unfavourable Long-Term Outcome

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Registry data have shown that treatment with bDMARDs induces remission or LDA (RLDA) in up to 50% of RA patients. Approximately 30-50% of patients have moderate disease activity (MDA) after treatment with bDMARDs, nevertheless data for this group are limited. We sought to assess long term outcome and characterize RA patients with persistent MDA (pMDA) on bDMARDs in clinical practice.

Methods: We analyzed data from the University of Crete Rheumatology Clinic. Disease activity, function, treatments of all patients starting a bDMARD are recorded prospectively every 3-6 months. Herein, we included patients with at least 3

Figure 1A.

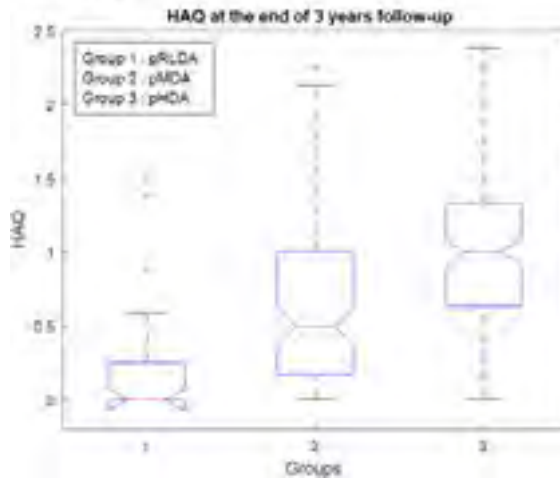


Figure 1B.

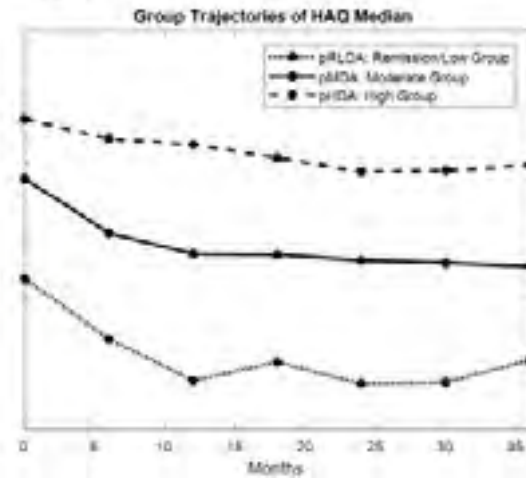


Table 1. Patient characteristics at baseline	Total (n=357)	pRLDA (n=33)	pMDA (n=164)	pHDA (n=160)	P*
Women, N (%)	302 (85)	16 (48.5)	146 (89)	140 (87.5)	<0.001
Age, median (IQR) years	59 (14)	55 (15)	60 (14)	60 (13.5)	0.01
Disease duration, median (IQR) years	5.5 (8.7)	5.4 (8.6)	4.8 (8.5)	6.1 (10.1)	0.58
Anti-CCP or Rheumatoid factor positive, N(%)	124 (47)	14 (56)	56 (45.5)	54 (46.5)	0.33
Previous synthetic DMARDs, median (IQR)	2 (1)	2 (1)*	2 (1)	2 (1)	0.03
Ongoing synthetic DMARDs, N(%)	328 (92)	29 (88)	147 (90)	152 (96)	0.48
Ongoing Methotrexate, N(%)	258 (72)	27 (82)	114 (69.5)	117 (73)	0.15
First bDMARD is TNFi, N(%)	282 (79)	29 (88)	128 (78)	125 (78)	0.20
Number of bDMARDs received during follow-up, median (IQR)	2 (3)	1 (1)	2 (2)	3 (3)	0.01
Tender joint count (0-28), median (IQR)	12 (11)	4 (8)	10 (9)	16 (11)	<0.001
Swollen joint count (0-28), median (IQR)	11 (9)	5 (11)	9 (7)	13 (12)	0.04
Patient VAS global (0-100), median (IQR)	70 (25)	60 (40)	70 (20)	80 (20)	<0.001
Patient VAS pain (0-100), median (IQR)	70 (30)	50 (50)	70 (30)	80 (20)	0.001
ESR, median (IQR)	30 (30)	25 (33)	27 (31)	33 (28)	0.70
CRP (mg/dl), median (IQR)	0.42 (0.78)	0.82 (2.38)	0.37 (0.96)	0.42 (0.58)	0.13
DAS28, median (IQR)	6.1 (1.6)	5.1 (1.8)	5.7 (1.4)	6.5 (1.5)	<0.001
HAQ (0-3), median (IQR)	1 (0.9)	0.5 (0.8)	1.0 (0.9)	1.13 (0.9)	0.003
Physician's VAS global (0-100), median (IQR)	75 (12)	63 (25)	75 (13)	75 (10)	<0.001
Euroqol score (-1 to +1), median (IQR)	0.2 (0.7)	0.6 (0.5)	0.2 (0.75)	0.08 (0.6)	0.02
*p for the comparison of pMDA and pRLDA					

years of follow-up, irrespective of switches. If DAS28-ESR was at the same disease activity range for at least 50% of the follow-up time, patients were assigned to one of 3 groups: persistent RLDA (pRLDA), pMDA and persistent high disease activity (pHDA). HAQ at 3 years was the primary outcome, while baseline characteristics and predictors of pMDA were assessed.

Results: Out of 479 patients with complete data, 357 could be assigned to one of the aforementioned groups; 33,164 and 160 patients in pRLDA, pMDA and pHDA respectively. At baseline, pMDA patients were older, more often women, have received more csDMARDs and had higher DAS28, HAQ and EuroQol status compared to pRLDA group (Table 1).

Table 2. Baseline determinants of achieving persistent moderate disease activity		
Baseline characteristics	Univariable	Multivariable
Gender (female vs. male)	2.04 (1.38-4.2), p=0.002	4.6 (1.93-11.02), p=0.001
Seropositive (yes vs. no)	0.76 (0.51-1.13), p=0.175	
Age	1.00 (0.99-1.02), p=0.735	
Disease duration	0.99 (0.97-1.02), p=0.566	
Nr of previous csDMARDs	1.04 (0.88-1.24), p=0.652	
Monotherapy (yes vs. no)	1.69 (0.86-3.33), p=0.126	
Concomitant MTX (yes vs. no)	0.84 (0.56-1.28), p=0.419	
1 st bDMARD is TNFi (yes vs. no)	0.77 (0.48-1.23), p=0.272	
HAQ	0.82 (0.55-1.21), p=0.316	
CRP	1.02 (0.92-1.15), p=0.684	
Tender joint count (per 1 joint)	0.96 (0.93-0.98), p=0.001	
Swollen joint count (per 1 joint)	0.96 (0.93-0.99), p=0.004	
VAS global	1.01 (1.00-1.01), p=0.189	
VAS pain (per 10 mm)	1.00 (0.99-1.02), p=0.396	
VAS physician (per 10 mm)	1.00 (0.99-1.02), p=0.448	1.02 (1.00-1.04), p=0.028
ESR (per unit increase)	1.00 (0.99-1.00), p=0.321	
DAS28-ESR	0.78 (0.65-0.93), p=0.006	0.62 (0.48-0.80), p<0.001

During follow-up, pMDA had more bDMARDs switches as compared to pRLDA [median (IQR) 1 (2) vs 0 (1), p=0.01]. Notably, although patients in pMDA had significant improvement in HAQ [baseline vs 36 months, median (IQR) HAQ: 1 (0.9) and 0.5 (0.8) respectively, p<0.001], HAQ at 3 years was significantly higher for pMDA compared to pRLDA group [0 (0.25) vs 0.50 (0.83), p<0.001] (Figure 1A). Of note, HAQ trajectories according to DAS28 grouping were clearly defined early at treatment course (6 months) and did not intersect throughout follow-up (Figure 1B). Multivariate analysis indicated that female sex, physician's evaluation and DAS28 were independent predictors for clustering patients in the pMDA group (Table2).

Conclusion: In clinical practice 34% and 33% of RA patients on bDMARDs have persistent MDA or HDA in spite of bDMARDs switches. Although patients on pMDA present early significant improvement in HAQ, they still have worse functional status, compared to patients in pRLDA, after 3 years of follow up.

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Abstract Number: 2490

Real World Evidence Describing Infliximab Utilization Patterns in Rheumatoid Arthritis Patients in Community Rheumatology Practices in the United States: Implications for Cost Efficiencies?

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

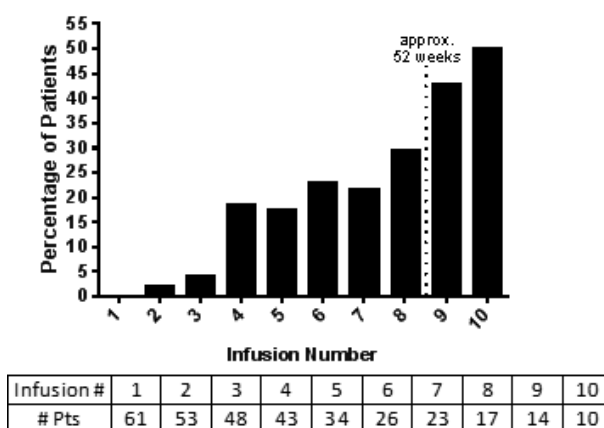
Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: AWARE (Comparative and Pragmatic Study of Golimumab IV Versus Infliximab in Rheumatoid Arthritis) is an ongoing prospective Phase 4 comparator study designed to provide a real-world assessment of intravenous golimumab (GLM) and infliximab (IFX) in patients (pts) with rheumatoid arthritis (RA). The primary endpoint compares the proportion of GLM and IFX pts with an infusion reaction (52wks). Here we report on IFX dose escalation (DE,

Fig A: Percent of Patients With Dose Escalation Above Starting Dose of ≥ 5 mg/kg



defined as at least 1 increase in prescribed dose above baseline) patterns from an interim analysis (IA) of the ongoing AWARE study. The baseline dose was chosen to judiciously evaluate DE by not focusing on pts at 3mg/kg that may be “routinely” moved to 5 mg/kg, but rather to report on the DE pattern of what may be considered more significant IFX DEs.

Methods: AWARE is a noninterventional 3-year study at 100 US sites. All treatment decisions including prescribed dose are made at the discretion of the treating rheumatologist. We report on DE patterns of IFX pts with a starting dose (infusion 1) of ≥ 5 mg/kg. Data shown are mean \pm standard deviation.

Results: Here we report on IFX pts, who’s first prescribed dose was ≥ 5 mg/kg, age = 53.7 ± 13.46 yrs, body weight = 85.1 ± 24.38 kg, BMI = 31.6 ± 10.8 kg/m² and 75.4% were female. Baseline CDAI of DE pts = 32.0 ± 16.17 . Among pts with initial prescribed dose ≥ 5 mg/kg, 26.4% were DE after the first infusion, and 38.2% of pts had two or more consecutive infusion intervals < 7 weeks duration (37.7% had both a DE and contraction of dosing interval). Among this cohort of pts who had ≥ 3 infusions, 16.7% had at least one dose ≥ 8 mg/kg. The pattern of DE is shown in the figure below, and in the table the % of pts prescribed ≥ 8 mg/kg at each infusion visit is shown.

Infusion #	# Pts Treated	# of Pts with Prescribed Initial Dose ≥ 8 mg/kg IFX	% of Pts with Prescribed Initial Dose of ≥ 8 mg/kg IFX
1	61	9	14.80
2	53	7	13.20
3	48	5	10.40
4	43	6	14.00
5	34	5	14.70
6	26	3	11.50
7	23	2	8.70
8	17	2	11.80
9	14	1	7.10
10	10	2	20.00

Conclusion: Of this subset of IFX pts, close to 20% were DE by infusion 4, with 10-14% dosed ≥ 8 mg/kg. Dose interval shortening could further affect the impact of DE. The AWARE study will utilize these data to assess the impact on IFX utilization in a real-world rheumatology practice setting.

Disclosure: S. Schwartzman, Janssen Research & Development, LLC, 2; D. Parenti, Janssen Scientific Affairs, LLC, 3; S. Black, Janssen Scientific Affairs, LLC, 3; S. Xu, Janssen Research & Development, LLC, 3; W. Langholff, Janssen Research & Development, LLC, 3; S. Kafka, Janssen Scientific Affairs, LLC, 3.

Treat-to-Target (T2T) Is Not Enough: Identify Factors Leading to a Mismatch between T2T and HAQ Among RA Patients through Data Mining from Smart System of Disease Management (SSDM)

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

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Background/Purpose: T2T, achieving a DAS28 score lower than 3.2 is the main management strategy recommended by ACR and EULAR. HAQ is the most widely used in evaluation of physical function in RA. However, T2T may not always associate with good HAQ. Our purpose is to quantify phenomenon of mismatch between T2T and HAQ in RA patients, identify influential factors from real world data mining in smart system of disease management (SSDM).

Table 1. The mean scores for each functioning category in HAQ and the top 3 target joints.

	Mean score	The top 3 target joints
1 Dress yourself including shoelaces and buttons	0.43	Wrist, shoulder, middle finger
2 Get in and out of bed	0.3	Knee, wrist, shoulder
3 Lift a full glass to your mouth	0.32	Wrist, shoulder, middle finger
4 Walk outdoors on flat ground	0.38	Knee, wrist, shoulder
5 Wash and dry your body	0.48	Wrist, shoulder, elbow
6 Bend down to pick up clothing from the floor *	0.81*	Knee, wrist, shoulder
7 Turn faucets (or corks) on and off	0.47	Wrist, middle finger, index finger
8 Get in and out of a car	0.48	Knee, wrist, shoulder

* P < 0.001.

Methods: SSDM is a novel mobile tool of disease management. The patients were trained to master SSDM by health professionals and conducted DAS28 and HAQ self-evaluations once a month. The data were synchronized with their physicians and uploaded onto cloud for analysis.

Results: From June 2014 to June 2018, 31,230 RA patients from 587 hospitals in China used SSDM, of which 22,862 patients made 42,498 DAS28 and HAQ self-evaluations. The T2T rates were 29% at baseline (n=22,862) and 58% after 6 months (n=4,783).

Inpatients who achieved T2T, 76% had normal physical function (HAQ = 0), but 24% were with HAQ score higher than 0 with mean score 0.46, indicating physical dysfunction. The “Bend down to pick up clothing from the floor” was the move being affected most, with a mean score of 0.81, significantly higher than other dysfunctions, $P < 0.001$. The mean numbers of tender and swollen joints among T2T patients were 1.53 and 1.32 respectively. The analysis of correlation between physical dysfunction and the affected joints showed the knees were the top targets. Table 1 showed the mean scores for each functioning category in HAQ and the top 3 target joints.

Inpatients who did not achieve T2T, 32% had HAQ scores of 0, showing that these patients had normal physical function despite failure in achieving T2T. The mean number of tender and swollen joints in these patients was 4.31 and 2.85, respectively. The affected joints were mainly hand joints.

According to the cluster weights for the impact of impact joints on physical function, the weighted coefficient of affected joints impacting on physical function was obtained. The highest score was for knee (0.46), followed by wrist (0.35), middle finger (0.19), index finger (0.18), shoulder (0.15), ring finger (0.13), elbow (0.09) and little finger (0.07).

Conclusion: 1/4 RA patients suffer physical dysfunctions even though T2T are achieved. Diseased knees, wrists and middle fingers are the top 3 joints critically impacting on corresponding physical dysfunctions and contribute to a mismatch between T2T and HAQ. Conversely, diseased shoulder, elbow and other small hand joints are less likely resulting in physical dysfunction. Therefore, not all joints are equal, and joints of knees, wrists and middle fingers deserve higher weighing coefficient in evaluation of disease activity. T2T guided by DAS28 is not good enough and may misleading. A modified DAS28 should be considered for overcome the mismatch with HAQ and a special attention should be paid on these top three joints for rehabilitations.

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Pattern Shift and Influential Factors in Promoting Treat-to-Target (T2T) for Follow-up RA Patients with a Rheumatologist-Patient Interactive Smart System of Disease Management (SSDM): A Cohort Study from China

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SESSION INFORMATION

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Methods: Patients were registered through downloading the SSDM application, then were trained to master SSDM by health professionals in clinics. The first assessment for DAS28 were performed as baseline. The patients were required to perform repeated assessments once a month after leaving clinic.

<=““ while=“while” 721)of=“21.4%(147/721)of” 21.4%(147=““ than=“than” higher=“higher” score=“score” 79.6%=“79.6%”
haq=“HAQ” 0.=“0.” 732)performed=“>98.5%(721/732)performed” >98.5%(721=““ at=“at” 0=“0” of=“of” baseline,
=“baseline,” 721)=“(574/721)” (574=““>
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haq=“HAQ” 0.=“0.” 732)performed=“>98.5%(721/732)performed” >98.5%(721=““ at=“at” 0=“0” of=“of” baseline,
=“baseline,” 721)=“(574/721)” (574=““>

Conclusion: After proactive disease management via SSDM for more than 6 months, the rate of T2T in RA patients increased significantly. The patients who bear better HAQ scores and perform more self-evaluations through SSDM had lower probability of relapse and higher T2T maintaining and achievement. SSDM is a valuable tool for long term RA

	Baseline Total (2,666)	Achiever of T2T (1,638, 39%)		Failure of T2T (1,028, 61%)	
	Final follow-up (≥6 months)	Maintenance of T2T 732 (70.3 %)	Relapse 306 (29.3%)	Maintaining failure of T2T 946 (59.1%)	Achieve of T2T 682 (41.9%)
Age (years): mean ± SD		49.21 ± 13.38	48.82 ± 13.70	50.99 ± 14.02	48.45 ± 13.82
Disease duration (months): mean ± SD		61.33 ± 36.11	63.98 ± 34.11	61.96 ± 72.48	63.87 ± 85.42
Time of patient self-evaluation and data entry: mean ± SD		5.47 ± 1.39	2.92 ± 1.20*	2.81 ± 1.44	3.43 ± 1.43*
DAS28: mean ± SD	Baseline	2.29 ± 0.61	2.48 ± 0.58	4.87 ± 1.16	4.33 ± 0.94
	Final follow-up	2.11 ± 0.63	3.14 ± 0.84	4.51 ± 0.98	2.34 ± 0.60
Morning stiffness duration (minutes): median (IQR), mean ± SD	Baseline	0(0-6)	0(0-10)	20(16-34.26)	15.28 ± 20.25**
	Final follow-up	0(0-2)	18(11-32.14)	11(01-22.16)	0(0-3)
HAQ dysfunction (HAQ score > 0)	Baseline	347 (26.3%)	83 (36.3%)	678(71.8%)	406(39.3%)
	Final follow-up	135 (18.4%)	17(13.9%)	642(67.9%)	192(27.7%)

†††. $P < 0.001$; One-way analysis of variance was used for comparisons in the same group between baseline and final follow up.

follow-up through empowering patients. Future RCT of improving T2T outcome through intervention of above influential factors with SSDM is warranted

<=““ while=“while” 721)of=“21.4%(147/721)of” 21.4%(147=““ than=“than” higher=“higher” score=“score” 79.6%=“79.6%” haq=“HAQ” 0.=“0.” 732)performed=“>98.5%(721/732)performed” >98.5%(721=““ at=“at” 0=“0” of=“of” baseline, =“baseline,” 721)=“(574/721)” (574=““>

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Abstract Number: 2493

Features of Disease Severity Associated with Patient Satisfaction with Biologic Treatment: Results from the Abatacept Best Care Real-World Study

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

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Background/Purpose: Patients satisfaction with their treatment is important for adherence to medications, particularly for chronic conditions such as rheumatoid arthritis (RA). The aim of this analysis was to explore the relationship between patient satisfaction with treatment and features of disease activity as well as to identify thresholds of disease severity optimally associated with satisfaction of RA patients treated in routine clinical care.

Methods: Abatacept Best Care (ABC) is a prospective, multicenter, observational study of patients with RA starting subcutaneous abatacept. Patient expectations in regard to RA activity, pain, function, and fatigue were assessed at baseline using a VAS mm scale (0=no expectation, 100=highest expectation), and patient satisfaction with treatment for each aspect during treatment was assessed in a similar fashion. The correlation of patient satisfaction at 6 and 12 months and TJC28, SJC28, physician global (MDGA), patient global (PtGA), DAS28, CDAI, RAPID3, HAQ, pain, and fatigue (and changes from baseline in these variables) was assessed with the Pearson's correlation coefficient (r). ROC analysis was used to identify thresholds of CDAI, pain, HAQ, and fatigue optimally associated with patient satisfaction (>50mm).

Results: 275 patients (74.8% females) were included with a mean (SD) age of 59.7 (11.7) years and disease duration of 7.4 (8.7) years. At baseline, mean (SD) parameters were: CDAI (30.0 [10.7]), pain (64.6 [23.4]), HAQ (1.5 [0.6]), and fatigue (63.3 [23.4]); patient expectations were: RA activity (70.3% [23.9]), pain (72.1% [24.4]), function (71.1% [23.8]), and fatigue (69.1% [25.7]).

At 6 months, weak-to-moderate negative correlations ($0.2 < r < 0.6$) were observed between patient satisfaction with treatment and all parameters studied, the strongest being with MDGA, DAS28, CDAI, PtGA, and pain. Similar results were observed at 12 months, however patient satisfaction with treatment in terms of function was only correlated (moderately) with DAS28. Regarding the correlation of patient satisfaction with changes from baseline in disease parameters, again, weak-to-moderate negative correlations were observed which were lower at 12 months compared to 6 months. No correlation between patients with high expectations of treatment outcome and satisfaction was observed at any time.

In ROC analysis, optimal thresholds of disease severity were identified for all aspects of patient satisfaction which showed statistically significant ($p < 0.001$) fair precision ($\text{ROC} \approx 0.7$; Table 1).

Conclusion: Weak-to-moderate correlation was observed between patient satisfaction with treatment and various outcomes. Specific thresholds corresponding to moderate disease activity, moderate and mild pain at 6 and 12 months, respectively, and mild functional disability and fatigue were identified which could be targeted in routine clinical care.

Table 1 ROC Analysis for Detection of Optimal Thresholds Associated with Patient Satisfaction with Treatment

	Patient Satisfaction with Treatment in Terms of:							
	RA Activity		Pain		Functional		Fatigue	
	6m	12m	6m	12m	6m	12m	6m	12m
CDAI*	13.5 / 0.76	11.8 / 0.73						
Pain (VAS)*			54.0 / 0.75	32.0 / 0.69				
HAQ*					0.88 / 0.70	1.00 / 0.67		
Fatigue (VAS)*							42.9 / 0.68	40.0 / 0.67

*Optimal threshold/AUC

Disclosure: **B. Haraoui**, AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Merck, Pfizer, Roche, and UCB, 6, AbbVie, Amgen, BMS, Janssen, Pfizer, Roche, and UCB, 2, Amgen, BMS, Janssen, Pfizer, and UCB, 8; **J. E. Pope**, AbbVie, Amgen, BMS, GSK, Eli Lilly, Merck, Novartis, Pfizer, Roche, Sandoz, Sanofi, and UCB, 5, 9; **E. Rampakakis**, JSS Medical Research, 3; **J. Vaillancourt**, JSS Medical Research, 3; **M. Maoui**, BMS, 3; **L. Bessette**, Amgen, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Celgene, Eli Lilly, and Novartis, 5, Amgen, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Sanofi, Eli Lilly, and Novartis, 9, Amgen, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Eli Lilly, and Novartis, 8.

Abstract Number: 2494

Relationship between Specific Joint Involvement and Work/Activity Impairment in Rheumatoid Arthritis Patients: Implications for Clinical Practice

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Background/Purpose: Swelling or tenderness of specific joints may differentially impact the ability of rheumatoid arthritis (RA) patients to perform daily activities and work. The aim of this analysis was to explore the relationship between specific joint involvement and work or activity impairment due to RA.

Methods: The Abatacept Best Care Study (ABC) is a prospective, multicenter, observational study evaluating the usefulness and adherence to a T2T approach vs. standard of care in real-life management of patients with active RA starting subcutaneous (SC) abatacept 125 mg once weekly. Interim data were used. Based on joint involvement evaluated with the 28-joint count, five groups were created: shoulder(s), elbow(s), wrist(s), hand(s), and knee(s). The impact of specific joints on % activity impairment (AI) and overall work impairment (WI) due to health at baseline as well as their change from baseline to 12 months, as measured with the Work Productivity and Activity Impairment (WPAI) questionnaire were assessed with general linear regression adjusting for age, gender, and total swollen and tender joint counts.

Results: 255 patients (74.8% females) were included with a mean (SD) age of 59.5 (11.6) years, 7.9 (4.7) swollen joints, and 9.7 (6.2) tender joints at baseline. Of these, 86 (33.7%) had information on WI at BL. At 12 months, 182 (71.4) and 58 (22.7%) had information on AI and WI, respectively. At baseline, increased number of tender, but not swollen, joints was associated with significantly increased AI (increase by 1.3 percentile units for each additional tender joint, $p<0.001$) and WI (increase by 1.9 percentile units for each additional tender joint, $p=0.002$). For specific joints, swollen shoulder(s) and knee(s), and tender shoulder(s) and elbow(s) were associated with increased, but not statistically significant, AI. Swollen shoulder(s) and elbow(s), and tender shoulder(s) and elbow(s), were associated with numerically, but not statistically, higher WI. For hand(s), nearly all patients had swollen and tender MCPs and/or PIPs so a baseline association was not performed.

At 12 months, swollen/tender wrist(s) ($p=0.015/p=0.003$) and hands ($p<0.001/p<0.001$) were associated with significantly lower improvement from baseline in AI (Table 1). Similarly, swollen/tender wrist(s) ($p=0.002/p<0.001$) and hands ($p<0.001/p<0.001$), as well as tender elbows ($p=0.032$) were associated with significantly lower improvement in WI.

Conclusion: Swelling and tenderness at specific joints has differential impact on the ability to work and perform daily activities. Residual involvement of upper limb joints after 12 months of treatment was associated with persistent activity and work impairment.

Table 1 Relationship Between Specific Joint Involvement at 12 Months and Improvement in AI/WI from Baseline

Swelling in:	Difference in Δ AI*	Difference in Δ WI*	Tenderness in:	Difference in Δ AI*	Difference in Δ WI*
Shoulder(s)	13.2 / $p=0.14$	-12.3 / $p=0.57$	Shoulder(s)	11.4 / $p=0.06$	4.6 / $p=0.80$
Elbow(s)	10.3 / $p=0.36$	36.0 / $p=0.09$	Elbow(s)	13.8 / $p=0.08$	36.8 / $p=0.032$
Wrist(s)	11.9 / $p=0.015$	28.1 / $p=0.002$	Wrist(s)	14.3 / $p=0.003$	30.9 / $p<0.001$
Hand(s)	17.7 / $p<0.001$	26.1 / $p<0.001$	Hand(s)	18.9 / $p<0.001$	28.5 / $p<0.001$
Knee(s)	11.0 / $p=0.16$	36.0 / $p=0.09$	Knee(s)	10.1 / $p=0.08$	19.2 / $p=0.08$

*Adjusted difference in improvement (from baseline to 12 months) in % impairment when joint is affected vs. not affected at 12 months. More positive values indicate lower improvement over time.

Disclosure: B. Haraoui, AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Merck, Pfizer, Roche, and UCB, 6, AbbVie, Amgen, BMS, Janssen, Pfizer, Roche, and UCB, 2, Amgen, BMS, Janssen, Pfizer, and UCB, 8; J. E. Pope, AbbVie, Amgen, BMS, GSK, Eli Lilly, Merck, Novartis, Pfizer, Roche, Sandoz, Sanofi, and UCB, 5, 9; E. Rampakakis, JSS Medical Research, 3; J. Vaillancourt, JSS Medical Research, 3; M. Maoui, BMS, 3; L. Bessette, Amgen, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Celgene, Eli Lilly, and Novartis, 5, Amgen, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Sanofi, Eli Lilly, and Novartis, 9, Amgen, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Eli Lilly, and Novartis, 8.

Abstract Number: 2495

Sex Differences in the Achievement of Remission in Rheumatoid Arthritis – Choice of Disease Activity Measure Matters

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Background/Purpose: In rheumatoid arthritis (RA), women may be less likely to achieve clinical remission. These sex differences remain incompletely understood and might relate to differences in performance of disease activity measures, rather than biological sex differences. We evaluated sex differences in remission and low disease activity in patients with RA, comparing composite disease activity measures and definitions.

Methods: This longitudinal cohort study utilized data from the Veterans Affairs Rheumatoid Arthritis registry. Participants fulfilled ACR criteria for RA. Remission and low disease activity were defined based on composite scores (DAS 28 joints with ESR [DAS28-ESR], DAS 28 joints with CRP [DAS28-CRP], clinical disease activity index [CDAI], routine assessment of patient index data 3 [RAPID3]). We also studied achievement of low disease activity based on individual measures applying Boolean and other published criteria (tender joint count 28 joints [TJC28], swollen joint count 28 joints [SJC28], ESR, CRP, physician global assessment [PhGA], patient global assessment [PtGA]). We assessed 1) the likelihood of point remission at any time and 2) the time to sustained remission (2 consecutive visits) among those not in remission at enrollment. Logistic regression models incorporated generalized estimating equations to account for repeated disease

activity measures and adjusted for age, race, smoking, and disease duration. Multivariable Cox proportional hazard models assessed differences in the time to sustained remission.

Results: At enrollment, women (n=252, 10.2%) were younger, less likely to be smokers, used less prednisone, and had fewer comorbidities. Considering all points in time, the odds of remission for women were lower only for DAS28-ESR [OR 0.71, (95% CI 0.55, 0.91), p<0.01] (Table 1). In contrast, women were more likely to attain CDAI low disease activity [OR 1.36, (95% CI 1.08, 1.73), p=0.01]. Women were more likely to achieve favorable individual measures- low SJC 28, CRP, and PhGA, except for having an ESR <30 mm/hour [OR 0.72, (95% CI 0.57, 0.90), p<0.01]. Using an age-, sex-specific definition, women were more likely to achieve a low ESR [OR 1.32, (95% CI 1.05, 1.64), p=0.02]. In Cox models, women were less likely to reach sustained remission only by DAS28-ESR [HR 0.53, (95% CI 0.35 - 0.80), p<0.01]. There were no significant differences in sustained remission rates using DAS28-CRP, CDAI, or RAPID3.

Conclusion: The comparison of remission rates between men and women varied greatly based on the composite disease activity measure selected. Sex- specific differences in the ESR bias towards lower rates of remission among women using DAS28-ESR. This study suggests selection of disease activity measure may have influenced prior research suggesting low remission rates in women and illustrates the need for sex-specific treatment targets for the DAS28-ESR.

Table 1 Odds Ratio of being in remission or low activity for women versus men at any observation adjusted for age, race, smoking, and disease duration.

	Observations	Total n (women)	OR (95% CI)	p-value
Remission				
DAS28-ESR (<2.6)	26148	2398 (238)	0.71 (0.55 – 0.91)	<0.01
DAS28-CRP (<2.6)	24875	2330 (233)	1.14 (0.91 – 1.42)	0.25
CDAI (≤2.8)	20261	2227 (221)	1.28 (0.96 – 1.71)	0.09
RAPID3 (≤3)	26261	2348 (231)	0.97 (0.67 – 1.39)	0.85
Low Disease Activity				
DAS28-ESR (≤3.2)	26148	2398 (238)	0.87 (0.71 – 1.08)	0.21
DAS28-CRP (≤3.2)	24875	2330 (233)	1.19 (0.96 – 1.48)	0.12
CDAI (≤10)	20261	2227 (221)	1.36 (1.08 – 1.73)	0.01
RAPID3 (≤6)	26261	2348 (231)	1.04 (0.80 – 1.35)	0.76
Component Measures				
TJC28 (≤1)	28991	2475 (249)	1.07 (0.88 – 1.31)	0.48
SJC28 (≤1)	28999	2476 (249)	1.51 (1.22 – 1.88)	<0.001
ESR (<30 mm/hour)	26714	2442 (249)	0.72 (0.57 – 0.90)	<0.01
ESR (age-, sex- specific)	26714	2442 (249)	1.32 (1.05 – 1.64)	0.02
CRP (≤1.0 mg/dL)	25196	2366 (243)	1.26 (1.01 – 1.59)	0.04
PhGA (≤1, 0 to 10 scale)	20363	2238 (222)	1.54 (1.23 – 1.93)	<0.001
PtGA (≤1, 0 to 10 scale)	28705	2457 (245)	1.22 (0.95 – 1.56)	0.11

Abbreviations: OR= Odds Ratio; DAS28= Disease Activity Score in 28 joints; ESR= Erythrocyte Sedimentation Rate; CRP= C-Reactive Protein; CDAI= Clinical Disease Activity Index; RAPID3= Routine Assessment of Patient Index Data; TJC28= Tender Joint Count in 28 joints; SJC28= Swollen Joint Count in 28 joints; PhGA=Physician Global Assessment; PtGA= Patient Global Assessment

Disclosure: C. Maynard, None; T. R. Mikuls, BMS, Ironwood, Horizon, 2, Pfizer, Inc., 5; G. W. Cannon, Amgen Inc., 2; B. R. England, None; G. S. Kerr, Novartis, 2; J. Barton, None; J. F. Baker, Corrona, Bristol Myers Squibb, 5.

Abstract Number: 2496

Determination of the Minimally Important Difference for Interpreting the RA Multi-Biomarker Disease Activity Test Score: Impact of Diurnal and Daily Biomarker Variation on Scores Adjusted for Age, Sex and Adiposity

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Previous studies have demonstrated the efficacy of a treat-to-target approach to optimize therapeutic outcomes for patients with RA using measures of clinical disease activity to monitor patient response. The Multi-Biomarker Disease Activity (MBDA) test is an objective molecular measure of 12 serum biomarkers that has been validated as a measure of disease activity and predictor of radiographic progression. A recent study has also demonstrated that adjusting the MBDA score for age, sex and adiposity improves its ability to predict radiographic progression relative to the unadjusted MBDA score and clinical measures of disease activity (i.e. DAS28). Short-term variation in test biomarkers can be observed as day-to-day (daily) or within-day (diurnal) fluctuations. Establishing a minimally important difference (MID) in the MBDA score – the smallest score change that exceeds inherent variability – accounts for such fluctuations and provides a reference point for interpreting MBDA score changes over time. This study evaluated daily and diurnal variation in MBDA scores adjusted for age, sex and adiposity. The data were used to determine the MID and establish a cut point for meaningful change in the MBDA score.

Methods: 28 adult, seropositive RA patients with clinically stable disease were enrolled from a single US rheumatology research center. MBDA testing was performed for each patient on 9 non-fasting serum samples obtained over 4 consecutive days: 6 samples during the first 24 hours (8 AM, 12 PM, 4 PM, 8 PM, 12 AM, and 8 AM), 1 sample at 12 PM in the next 24-hour period, 1 sample at 8 AM on each of the two following days. Patients were stratified by MBDA disease activity category (high, >44; moderate, 30-44; low, <30). MBDA scores were also adjusted for age, sex and adiposity, using serum leptin as a proxy for adiposity. MBDA score variation was assessed for daily and diurnal timeframes. The standard deviation (SD) of MBDA scores was calculated using a linear mixed model that included random effects for patient, day, and time of day. The MID was calculated as $z_{0.95} \sqrt{2 \times \text{total variance of MBDA scores}}$, where $z_{0.95}$ is the standard normal deviate corresponding to the 95th percentile. The MID was assessed for the unadjusted and adjusted MBDA scores for all patients as well as for those with clinically active disease (moderate/high).

Results: In a combined daily-diurnal variation analysis including all patients, the SD of MBDA score change was 4.7, and the MID was 11. In a subset analysis of moderate/high disease activity categories (n=22), the total SD of MBDA scores was 3.6, and the MID was 8 MBDA units. When the MBDA was adjusted for age, sex and adiposity, the MID for patients with moderate/high disease activity was unchanged at 8 units.

Conclusion: For individuals with moderate or high disease activity based on the adjusted or unadjusted MBDA score, the MID was determined to be 8 MBDA score units. A change in MBDA score greater than or equal to the MID represents a change in RA disease activity that clinicians can use as a benchmark for therapeutic drug efficacy and can be incorporated in a treat-to-target strategy that combines both clinical and molecular metrics.

Disclosure: D. Chernoff, Crescendo Bioscience Inc., 3, Myriad Genetics, Inc., 1; P. S. Eastman, Crescendo Bioscience Inc., 3, Myriad Genetics, Inc., 1; D. D. Flake II, Myriad Genetics, Inc., 1, 3; A. J. Kivitz, Genentech, Pfizer, UCB, Janssen, 5; J. R. Curtis, AbbVie, Amgen, BMS, Eli Lilly and Company, Janssen, Pfizer, Roche/Genentech, Corrona, UCB, Myriad, 2, 5.

Abstract Number: 2497

The Relationship between Difficulty Affording Arthritis Medications and Illness Intrusiveness in Rheumatoid Arthritis Patients: A Longitudinal Study

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: We examined the relationship between the difficulty rheumatoid arthritis (RA) patients have being able to afford their arthritis medications and illness intrusiveness. Illness intrusiveness reflects the extent to which an illness interferes with daily activities, including both instrumental activities and interpersonal relationships.

Methods: Participants (n=300) with physician-diagnosed RA and moderate/severe disease activity were recruited to participate in a longitudinal study. Data were collected via online questionnaires. At baseline, participants were asked if they had difficulty affording their RA medications (no trouble, a little trouble, a lot of trouble) and illness intrusiveness and self-efficacy were assessed using standardized questionnaires. The illness intrusiveness and self-efficacy measures were re-administered at a 6-month follow-up. We used a 13-item illness intrusiveness scale; participants were asked how their illness and/or its treatment interfere with different aspects of their lives ranging from 0 (not very much) to 100 (very much). To measure self-efficacy participants were asked how certain they were that they can manage their disease independently. Responses are scored from 0 (very uncertain) to 100 (very certain). Data were analyzed using linear regression.

Results: At baseline, controlling for education, race, and gender, participants who reported no trouble being able to afford the medications they need to control their RA, reported less illness intrusion than participants who reported having either a little or a lot of trouble (adjusted means=44.1, 51.8, and 57.7, $p < 0.0001$). At the 6-month follow-up, controlling for illness intrusion at baseline, education, race and gender, participants who had reported no trouble being able to afford their RA medications at baseline, reported less illness intrusion than participants who had reported having a lot of trouble (adjusted means=46.8 and 55.9, respectively, $p=0.02$). Participants who had reported having a little trouble fell between the other two groups (adjusted mean=48.5) and differed only from those who had reported having a lot of trouble ($p=0.06$). In exploratory analyses, we found that the relationship between trouble affording one's medications and illness intrusiveness appears to be mediated by self-efficacy. At the 6-month follow-up, controlling for self-efficacy at baseline, education, race, and gender, participants who reported no trouble being able to afford their RA medications had greater self-efficacy than participants who had reported having either a little or a lot of trouble (adjusted means=53.7, 43.7, 35.1, $p < 0.0001$). After controlling for self-efficacy at the 6-month follow-up, the relationship between trouble affording ones medications and illness intrusiveness was no longer statistically significant ($p=0.36$).

Conclusion: Financial barriers that limit access to the medications needed to control one's disease may have a deleterious effect on patient self-efficacy and contribute to lifestyle disruptions experienced by people with RA.

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Abstract Number: 2498

The Association of Vitamin D with the Lipid Profile in Rheumatoid Arthritis: An Interplay Among Genetic Polymorphisms, DHCR7 Levels and Seasonality

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Vitamin D deficiency is a common hallmark of rheumatic diseases, and some controversy exists about its effect on rheumatoid arthritis (RA), in particular about the association between vitamin D levels and lipid profiles. Several factors influence this cross-talk, including polymorphisms in vitamin D bioactivating enzymes (CYP27A1 and CYP2R1) and signaling (vitamin D receptor), and 7-dehydrocholesterol reductase (7DHCR7), an enzyme using a common metabolite to vitamin D and cholesterol syntheses. The contribution of these factors to the association between vitamin D and lipid profiles in RA is unknown. The main aim of this study was to evaluate the impact of vitamin D-related polymorphisms and DHCR7 serum levels on the association between vitamin D and lipid profile in RA.

Methods: Serum 25 (OH)-vitamin D and DHCR7 levels were measured in a cross-sectional group of 211 RA patients (EULAR/ACR 2010 criteria) and 94 healthy controls (HC). An additional group of 13 RA patients undergoing anti-TNF α treatment was prospectively followed for 3 months and samples were taken before and after TNF α -blockade. VDR-

rs2228570, CYP27A1-rs933994, CYP2R1-rs10741657 and DHCR7-rs12785878 polymorphisms were genotyped with TaqMan Assays.

Results: RA patients exhibited decreased vitamin D levels ($p<0.001$), but no associations with disease activity, duration, HAQ or treatments were found. Vitamin D levels were correlated with HDL-cholesterol ($r=0.217$, $p<0.001$) and total-/HDL-cholesterol ratio ($r=-0.227$, $p=0.004$). This correlation was restricted to patients harboring the VDR-rs2228570 AG/AA genotype, and vitamin D levels remained the only predictor of HDL-cholesterol in these patients in a multivariate regression analysis adjusted for age, gender, seasonality, disease activity and treatments (B[95% CI], p : 0.246 [0.036, 0.455], $p=0.022$). Vitamin D deficiency (<20 ng/ml) was associated with lower HDL-cholesterol ($p=0.028$), higher tender ($p=0.005$) and swollen ($p=0.002$) joint counts, higher DAS28 ($p=0.018$) and HAQ ($p=0.024$) in AG/AA-patients but not in their GG-counterparts (all $p>0.050$). No differences in the distribution of any of the polymorphisms was found between patients and controls none of them showed any effect on HDL-cholesterol. On the other hand, decreased DHCR7 serum levels were observed in RA compared to HC in individuals sampled in winter/spring ($p=0.012$) but not in summer/autumn ($p=0.354$). RA patients with a previous history of CV disease exhibited decreased DHCR7 levels than their CV-free counterparts ($p=0.024$). The associations among DHCR7, vitamin D and lipid profile followed a seasonal pattern, decreased DHCR7 ($p=0.008$) and vitamin D ($p<0.001$) together with increased total-cholesterol ($p=0.025$) being found in winter/spring. Finally, increasing vitamin D upon TNF α -blockade was positively correlated to the change in DHCR7 levels ($r=0.766$, $p=0.002$).

Conclusion: The adverse impact of vitamin D deficiency on the lipid profile and clinical features in RA is influenced by the VDR-rs2228570 polymorphism and DHCR7 levels. DHCR7 may be a missing link to better understand the connections between vitamin D, lipid profiles and seasonality in RA.

Disclosure: J. Rodríguez-Carrio, None; M. Alperi-López, None; M. Naves-Díaz, None; A. Dusso, None; P. López, None; F. J. Ballina-García, None; J. B. Cannata-Andía, None; A. Suárez, None.

Abstract Number: 2499

Predictors of Rheumatoid Arthritis Development in Patients with Early Undifferentiated Arthritis: A 2-Years Follow-up Study

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

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Background/Purpose: Early treatment of RA improves longterm outcomes. However, at the beginning of the disease, some patients with RA fall within undifferentiated arthritis (UA) patients. Almost half of patients with UA may experience spontaneous remission. So, in order to prevent overtreatment and poor outcomes, the identification of predictors of RA development is desirable. The objective of this research is to determine the frequency of patients with UA evolving into RA after 2 years of follow-up and the factors contributing to predict this outcome.

Methods: A prospective analysis of an early arthritis cohort of 1377 patients from 1993 to 2017 was undertaken. For this study, 2-years follow-up data of patients who presented with UA were analyzed. A detailed baseline assessment was completed including clinical features, physical examination and laboratory tests. Patients were stratified in two groups based on progression to RA (according to physician's diagnosis) or to another disease (non-RA). First, differences between groups were tested using chi-squared and Student-t tests in the univariate analysis. Second, multivariate logistic regression models were employed to investigate the association between possible predictive factors and RA development.

Results: A total of 471 UA patients were included for analysis. Mean age was 48.7 ± 17.5 years, 352 (74.9%) were females, and mean symptoms duration was 13.9 ± 13.9 weeks. After 2 years of follow-up, 93 (19.7%) of UA patients evolved into RA. Meanwhile, 175 (37.2%) remained undifferentiated and 203 (43.1%) developed into other musculoskeletal diseases. Baseline characteristics between both groups are compared in Table 1. In the univariate analysis, the presence of rheumatoid factor (RF) and anti-citrullinated peptides antibodies (ACPA), tender and swollen joint count, duration of morning stiffness, smoking, symmetry and ESR values were significantly associated with RA development. In the

multivariate analysis, RF (OR= 5,899; 95% CI 1,795-19,382), ACPA (OR= 123,238; 95% CI 29,353-517,410) and swollen joint count (OR=1,233; 95% CI 1,048-1,450), remained significantly associated with RA development (Table 2).

Conclusion: Approximately, 1 out of 5 patients with UA evolves into RA after 2-years of follow-up. Swollen joint count, and the presence of rheumatoid factor (RF) and anti-citrullinated peptides antibodies (ACPA) are independent predictors for the development of RA, supporting the early DMARDs initiation in such patients.

Table 1. Baseline characteristics of patients with UA

		Total n= 471	RA n=93 (19.7%)	Non RA n=378 (80.3%)	p
Age		48.7 ± 17.5	48.5 ± 15.7	48.7 ± 18	0.8
Sex	Female	352 (74.9%)	77 (82.8%)	275 (72.9%)	0.1
Race	Caucasian	274 (82.5%)	65 (83.3%)	209 (82.3%)	0.01
n= 332	Arabian	1 (0.3%)	0 (0%)	1 (0.4%)	
	Asiatic	2 (0.6%)	0 (0%)	2 (0.8%)	
	Hispanic	52 (15.7%)	11 (14.1%)	41 (16.1%)	
	Black	3 (0.9%)	2 (2.6%)	1 (0.4%)	
Smoking	Non smoker	238 (54%)	36 (39.1%)	202 (57.9%)	0.001
n= 441	Smoker	113 (25.6%)	30 (32.6%)	83 (23.8%)	
	Former smoker	90 (20.4%)	26 (28.3%)	64 (18.3%)	
Extension	Monoarticular	59 (12.7%)	6 (6.5%)	53 (14.2%)	0.1
	Oligoarticular	209 (44.8%)	38 (40.9%)	171 (45.8%)	
	Polyarticular	198 (42.5%)	49 (52.7%)	149 (39.9%)	
Affectation	Acute	142 (30.4%)	14 (15.1%)	128 (34.2%)	0.001
	Subacute	325 (69.6%)	79 (84.9%)	246 (65.8%)	
Time (weeks) from symptoms onset n=401		13.9 ± 13.9	18 ± 12.4	12.9 ± 14	0.03
Morning stiffness (minutes) n=445		72.5 ± 187.3	84.3 ± 164.3	69.6 ± 192.6	0.5
Pain (VAS 0-100) n=430		44.8 ± 27.6	47.8 ± 27.3	44 ± 27.7	0.2
Patient Global Assessment (0-100) n=439		42.7 ± 27.5	46.2 ± 26	41.8 ± 27.9	0.1
Physician Global Assessment (0-100) n=361		28.7 ± 21	34.2 ± 22.3	27.1 ± 20.4	<0.001
HAQ n=421		7.41 ± 5.8	8.2 ± 5.5	7.2 ± 5.9	0.1
28 Tender Joint Count		4.7 ± 5.5	6.42 ± 6.1	4.3 ± 5.3	0.001
28 Swollen Joint Count		3.2 ± 4.2	4.6 ± 5.4	2.8 ± 3.7	<0.001
ESR (mm/h) n=449		26.6 ± 21.9	31.8 ± 21.2	25.2 ± 21.9	0.010
CRP (mg/L) n=438		2.8 ± 8.2	1.9 ± 2.8	3.08 ± 9	0.2
RF (IU/mL)		40.7 ± 144.7	133.5 ± 243.1	17.5 ± 94.1	<0.001
ACPA (IU/mL) n=454		129.7 ± 425.6	579.5 ± 762.9	15.41 ± 126.2	<0.001

Table 2 Independent predictors of RA development based on logistic regression model

	Odds ratio	95% CI	
		Lower	Upper
Physician Global Assessment (0-100)	1,016	983	1,051
28 Tender Joint Count	949	852	1,057
28 Swollen Joint Count	1,233	1,048	1,450
ESR (mm/h)	1,018	992	1,044
Race	633	021	19,250
Smoking	851	223	3,245
Symmetry	568	145	2,225
RF (IU/mL)	5,899	1,795	19,382
ACPA (IU/mL)	123,238	29,353	517,410

Disclosure: J. Molina, None; M. G. Gonzalez Álvarez, None; V. Navarro-Compán, None; L. Nuño, None; A. Villalba, None; D. Peiteado, None; P. Bogas, None; A. Balsa, None.

Abstract Number: 2500

Association between Anti-Citrullinated Protein Antibody Status, Erosive Disease and Healthcare Resource Utilization in Patients with RA

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

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Background/Purpose: Anti-citrullinated protein antibody (ACPA) is a highly specific biomarker for RA¹ and ACPA-seropositive patients have a tendency toward severe erosive disease and more rapid disease progression.²⁻⁴ Little is known regarding the impact of poor prognostic factors, such as ACPA and erosive disease, on healthcare resource utilization (HCRU). The purpose of this analysis was to characterize the rate of HCRU between anti-cyclic citrullinated peptide (anti-CCP; a surrogate of ACPA) positive (+) patients with or without erosions who initiated biologic (b) DMARD treatment.

Methods: This analysis included patients aged ≥ 18 years who were enrolled in a large sequential RA registry (October 2001–August 2017) and who had known erosions, as measured by radiography, and anti-CCP+ status at or prior to bDMARD initiation visit and a 12-month (± 3 months) follow-up visit. Anti-CCP+ was defined as ≥ 20 U/mL. Rates of HCRU, including all-cause hospitalizations, all joint surgeries (total and partial; all sites), radiographic procedures and use of assistive devices, were estimated over 12 months of follow-up from the bDMARD initiation visit in anti-CCP+ patients with or without erosions. Rates of HCRU per 100 patient-years and risk ratios, adjusted by baseline age, were estimated with 95% CI using a Poisson regression model.

Results: A total of 2047 anti-CCP+ patients were included in this analysis, 868 with and 1179 without erosions. At biologic initiation visit, mean (SD) age was 58.9 (12.5) and 55.9 (12.5) years and disease duration was 11.7 (10.1) and 6.4 (7.5) years, respectively, in anti-CCP+ patients with and without erosions. Over 12 months of follow-up, the rates of HCRU were higher among anti-CCP+ patients with versus without erosions at baseline bDMARD initiation visit (Table).

Conclusion: ACPA seropositivity with erosive disease predicts high utilization of healthcare resources, suggesting that early therapeutic intervention may be warranted in anti-CCP+ patients to achieve better disease control and reduce complications from RA.

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Table. Age-Adjusted Rates (95% CI) of HCRU and Adjusted Risk Ratios in Anti-CCP+ Patients With RA With and Without Erosions

	Age-adjusted rate (95% CI)*†		Adjusted risk ratio (95% CI)*† Anti-CCP+ with erosions vs anti-CCP+ without erosions‡
	Anti-CCP+ without erosions (n=1179)	Anti-CCP+ with erosions (n=868)	
Hospitalization, all cause	9.44 (7.77, 11.37)	15.21 (12.72, 18.05)	1.47 (1.14, 1.90)
Joint surgery visits, all sites	3.74 (2.72, 5.02)	5.34 (3.91, 7.12)	1.31 (0.86, 1.98)
Radiography, all cause	18.12 (15.77, 20.72)	22.18 (19.14, 25.56)	1.25 (1.03, 1.53)
Assistive devices	60.65 (56.28, 65.27)	73.03 (67.44, 78.97)	1.12 (1.00, 1.25)

*Rates per 100 patient-years with 95% CI based on Poisson distributed counts

†Adjusted for baseline age

‡Reference group: anti-CCP+ and erosions

Anti-CCP+=anti-cyclic citrullinated peptide positive; HCRU=healthcare resource utilization

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Disease Activity Is the Major Discriminator When Defining Refractory Rheumatoid Arthritis

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Session Information

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Session Time: 9:00AM-11:00AM **Disease Activity is the Major Discriminator When Defining Refractory Rheumatoid Arthritis**

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Background/Purpose: Rheumatoid arthritis (RA) is characterised by the presence of a progressively destructive joint inflammation. Even in times of modern therapeutics, a subgroup of patients continues to be refractory to numerous consecutive therapeutic interventions with regards to control of inflammation, joint damage. To date, there exists no definition for refractory RA.

Methods: To explore different modifications of a definition for refractory RA, we defined the base case of refractory RA as patients who had experienced ≥ 3 treatment courses (with at least one biological failure) over a minimum of 18 months since first treatment initiation (to avoid counting treatment courses that were given for a too short period), and the lack of reaching the treatment goal of low disease activity or remission (defined by a Clinical Disease Activity Index, CDAI, >10). We then modified our working definition based on these four variables (disease duration: 12/18/24 months; disease activity: moderate/high; number of treatment courses: $\geq 3/\geq 4$; different biologic agents: $\geq 1/\geq 2$).

Results: From our clinic's ongoing longitudinal data set we identified 68 refractory patients out of 688 RA outpatients. There was virtually no difference based on modifying disease duration, so we kept our working definition of a minimum disease duration of at least 18 months (n=464; 12 months: n=466; 24 months: n=453). Changing the disease activity component of the definition had a great impact on the identified refractory RA population, by requiring high instead of moderate disease activity (MDA: CDAI >10 , n=129 vs. HDA: CDAI >22 , n=31). In both, the MDA and the HDA group of patients, we could observe $\geq 60\%$ of patients, who already experienced at least three treatment courses (MDA, n=82/129; HDA, n=21/31). Above a half in each group qualified as refractory also with the criterion of an addition fourth failed treatment course (MDA, n=64/129; HDA, n=15/31). When further stratifying patients based on the number of failed different biologic DMARDs, we could observe that regardless of the level of disease activity and number of failed treatment courses, most patients experienced at least one or even a second biologic agent (table).

Conclusion: The level of disease activity is the major discriminator when defining a population of refractory RA. The duration of treatment does not significantly impact the identification of refractory RA. The number of failed treatment courses and insufficient responses to biologic DMARDs further helps characterizing patients with refractory RA. Considerations of the impact of these different characteristics of refractory disease may well inform future criteria for refractory RA.

Last clinical visit ≤ 6 months ago + Disease duration ≥ 18 months n=464	Moderate disease activity (CDAI >10) n=129	≥ 3 failed treatment courses n=82	≥ 1 failed bDMARD n=68 ≥ 2 failed bDMARDs n=49
		≥ 4 failed treatment courses n=64	≥ 1 failed bDMARD n=58 ≥ 2 failed bDMARDs n=46
	High disease activity (CDAI >22) n=31	≥ 3 failed treatment courses n=21	≥ 1 failed bDMARD n=17 ≥ 2 failed bDMARDs n=11
		≥ 4 failed treatment courses n=15	≥ 1 failed bDMARD n=13 ≥ 2 failed bDMARDs n=10

Abstract Number: 2502

Influence of the Treatment with Biologic Agents in the Viremia By the Endogenous Anellovirus Torque Teno Virus in Patients with Chronic Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Torque teno virus (TTV) is an endogenous anellovirus that is highly prevalent in adult healthy subjects (up to 90%) without known pathogenicity. Increased replication has been associated to immunosuppression, leading to higher viral loads in patients with HIV infection or in transplanted patients on immunosuppression. Therefore, it has been proposed as an indirect marker of immunosuppression with potential predictive value of infectious complications.

The aim of our study was to analyze whether the biologic agents used in the treatment of chronic arthritis induce an increase in TTV viremia, compared to healthy controls and to patients with arthritis on conventional DMARD.

Methods: A cross-sectional study was performed in 79 patients with chronic arthritis on biologic therapy (58 rheumatoid arthritis and 21 spondyloarthritis). In a single visit, clinical and analytical data were collected, and a plasma sample was obtained for the analysis of viremia (TTV DNA load assessed by quantitative PCR). A group of 54 healthy individuals sex and age matched, and a group of 23 patients with chronic arthritis treated with conventional DMARDs (leflunomide and/or methotrexate) were used as control groups. In another group of 29 patients with chronic arthritis starting biologic therapy, a longitudinal study was performed, comparing baseline and follow-up (after 4 months on biologic) samples. Mean TTV viremia in the different groups was compared using ANOVA with Dunnett's multiple comparison test. Correlation between different quantitative variables and viremia was analyzed by the Spearman or Pearson test where appropriate. Mean viremia in groups stratified by different qualitative variables was compared using the Student's t-test, defining $p < 0.05$ as statistically significant.

Results: In the cross-sectional sample of 79 patients, TTV load was significantly higher in abatacept, infliximab and tocilizumab groups compared to healthy and to arthritic DMARD groups (ANOVA $p < 0.0001$). Healthy and arthritic patients treated with DMARD showed similar TTV loads. Patients on rituximab did not show an increased TTV load compared to the control groups. In the group of patients longitudinally analyzed, there was a significant increase in the TTV load after 4 months of biologic compared to the baseline (pre-biologic) sample ($p = 0.042$). Significant correlations between the TTV load and the clinical or analytical variables analyzed (age, disease duration, concomitant glucocorticoid or DMARD therapy, diabetes, CRP, ESR, lymphocytes, disease activity) were not found. Patients with previous history of severe infection did not have higher levels of TTV viremia.

Conclusion: Patients with chronic arthritis on therapy with abatacept, tocilizumab or anti-TNF have an increased TTV viremia compared to arthritic on conventional DMARD or to healthy control groups, while it was similar in patients treated with rituximab. TTV viremia was similar in patients with arthritis on DMARD compared to healthy controls. In this population, no correlation between TTV viremia and other clinical or analytical factors was found.

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Impact of Tobacco Smoking on 1-Year Mortality Following Total Hip and Total Knee Arthroplasty Among Rheumatoid Arthritis Patients – a Danish Cohort Study Using Nationwide Health Care Registers

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Background/Purpose: Tobacco smoking and rheumatoid arthritis (RA) are independent risk factors for short-term complications following total hip and total knee arthroplasty (THA/TKA). We aimed to investigate the impact of smoking on 1-year post-operative mortality in RA patients undergoing THA/TKA.

Methods: Nationwide register-based cohort study from Denmark from 2000-14. The study population was RA patients (diagnosed according to either ACR 1987 or ACR/EULAR 2010 criteria) registered in the Danish rheumatology register (DANBIO) and in the linked Danish Hip or Knee Arthroplasty Registers with a first elective THA/TKA surgery. Information on smoking status (exposure), DAS28, HAQ-DI, biological and conventional synthetic DMARD (bDMARD and csDMARD) and glucocorticoid treatment within 90 days preceding surgery (confounders) was gathered from DANBIO. Information on pre-existing comorbidities and mortality data (outcome) was obtained by linkage to the Danish National Patient Register and the Civil Registration System. Using multivariable Cox proportional hazards models, we calculated hazard ratios (HR) for death during the first year following surgery among patients who at the time of surgery were active and previous smokers, respectively, compared with never-smokers. We used multiple imputation for missing information on smoking, DAS28 and HAQ-DI.

Results: We identified 1,946 RA patients undergoing an elective THA/TKA with available smoking status for 1,092 patients: 255 (24 %) current, 417 (39 %) ex- and 420 (37 %) never smokers (Table). Compared with never smokers, current smokers were more likely to be males, treated with glucocorticoids, have COPD and ischemic heart disease. During the first year post-operatively, 24 patients died. Current smokers had increased HRs for death in uni- and multivariable analyses: adjusted HR 3.33 (95% CI 0.84-13.20) compared with never smokers. Similar results were observed in complete case and imputed analyses.

Conclusion: We found a 3-fold borderline significant increased 1-year mortality risk among RA patients who were active tobacco smokers at the time of elective THA/TKA surgery. Considering the increased risk of death associated with RA by itself, these results emphasize the importance of smoking abstinence/ cessation prior to major surgery in this vulnerable group of patients.

Table. Number of patients, demographics, pre-surgical characteristics and results of regression analyses on 1-year mortality risk in current, previous and never smoking rheumatoid arthritis (RA) patients with elective total hip or total knee arthroplasty.

	Current smoker	Previous smoker	Never smoker	p-value*
Number of patients before imputation, % of cohort	257 (24)	423 (39)	402 (37)	
Mean % of patients after multiple imputation	24	40	36	
Female (%)	173 (67)	285 (67)	333 (83)	<0.001
Age at surgery (mean (sd))	61.4 (11.1)	65.7 (9.8)	62.1 (12.5)	<0.001
Age at RA diagnosis (mean (sd))	51.9 (13.2)	55.9 (13.4)	50.8 (15.4)	<0.001
Seropositive RA (%)	226 (88)	384 (91)	351 (87)	0.109
DAS28-CRP (mean (sd))	3.7 (1.3)	3.6 (1.4)	3.7 (1.4)	0.235

Table . (Cont'd)

	Current smoker	Previous smoker	Never smoker	p-value*
HAQ-DI (mean (sd))	1.20 (0.77)	1.12 (0.76)	1.23 (0.74)	0.001
Treated with bDMARD (%)	68 (27)	72 (17)	94 (23)	<0.001
Treated with csDMARD (%)	105 (41)	156 (37)	159 (40)	0.276
Treated with MTX (%)	71 (28)	114 (27.0)	120 (29.9)	0.526
Treated with glucocorticoids (%)	46 (18)	58 (14)	47 (12)	0.005
History of hospitalization due to infection (%)	70 (27)	117 (28)	102 (25)	0.559
Diabetes mellitus (%)	13 (5)	30 (7)	27 (7)	0.796
Chronic obstructive pulmonary disease (%)	22 (9)	35 (8)	20 (5)	0.008
Ischemic heart disease (%)	12 (5)	30 (7)	9 (2)	0.001
Hazard ratio for death by smoking status (complete case analysis, non-imputed data)				
Number of deaths	5	4	2	
Univariate non-imputed, HR (95% CI)	3.93 (0.76-20.26)	1.88 (0.34-10.27)	1 (Ref)	
Multivariable model 1 □, HR (95% CI)	3.87 (0.73-20.35)	1.54 (0.28-8.49)	1 (Ref)	
Multivariable model 2 □□, HR (95% CI)	4.05 (0.67-24.35)	2.22 (0.38-13.07)	1 (Ref)	
Hazard ratio for death by smoking status (complete cohort, imputed data)				
Number of deaths	12	7	5	
Univariate analysis, HR (95% CI)	3.45 (0.88-13.49)	1.93 (0.43-8.62)	1 (Ref)	
Multivariable model 1 □, HR (95% CI)	3.46 (0.87-13.74)	1.53 (0.34-6.94)	1 (Ref)	
Multivariable model 2 □□, HR (95% CI)	3.33 (0.84-13.20)	1.70 (0.36-7.95)	1 (Ref)	

* Using t-test and chi-square as appropriate.

□ : Adjusted for age at surgery, sex, biological DMARD, conventional synthetic DMARD and glucocorticoid treatment (yes/no) within 90 days prior to surgery.

□□ : Adjusted for age at surgery, sex, biological DMARD, conventional synthetic DMARD and glucocorticoid treatment (yes/no) within 90 days prior to surgery, DAS28 and HAQ-DI. Abbreviations: 95% CI, 95 % confidence intervals; bDMARD, biological DMARD, csDMARD, conventional synthetic DMARD; DAS28-CRP, disease activity score using the 28 joint-count and C-reactive protein; HAQ-DI, health assessment questionnaire disability index; HR, hazard ratio; MTX, methotrexate; sd, standard deviation.

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Abstract Number: 2504

A More Time Under Remission Impacts in a Better Health-Related Quality of Life in Rheumatoid Arthritis Mestizo Population

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Session Information

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

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Session Time: 9:00AM-11:00AM

Background/Purpose: In Rheumatoid Arthritis (RA), sustained remission is associated with less disability ^(1,2), and this outcome should be the goal in the RA treatment; however, there are scarce of data about the impact of prolonged remission in health-related quality of life (HRQoL) in RA patients in our region. The aim of this study is to determine the impact of time under remission in to achieve a better HRQoL status in RA

Methods: Prospective study in a RA cohort from a single center. Subjects with at least two visits performed, were included. Visits were performed every six months; socio-demographic, clinical data (including disease activity status) and HRQoL measured by the *36-Item Short Form Health Survey questionnaire* (SF36), were recorded in each visit. Remission and low disease activity (LDA) statuses were defined as *Clinical Disease Activity Index* (CDAI) definition (<2.8 and 2.9-10, respectively) and time in remission was categorized in percentiles of time (>50, >25% and ≤50%, and ≤25%) in remission. The outcome was the value of each SF36 component and domain at the final visit. Univariable and multivariable lineal regression models, adjusted by age at diagnosis, disease duration, treatment [use of corticosteroid, synthetic(s) and biologic (b) Disease Modifying Rheumatic Drugs (DMARDs)], time of follow up and each baseline SF36 component or domain were performed in order to determine the associations.

Results: Four hundred nine patients were included; 369 (90.2%) were female, age at diagnosis was 44.49 (13.84) years and disease duration at baseline was 16.57 (11.50) years. sDMARDs and bDMARDs were used at baseline by 58.7% and 9.5% respectively. The mean follow-up was 1.39 (0.49) years. Percentage of time under remission and LDA status during the follow up were 13.33(26.39) and 49.61(39.16) respectively. In the multivariable analyses the better percentile under remission (>50%) predicted a better HRQoL performance in the Physical Component Summary(PCS): $B=0.170(0.705-1.635)$; $P<0.001$, and in the following components: physical functioning [$B=0.078$; (0.033; 0.122); $p<0.001$], role physical [$B=0.215$ (0.163-0.267); $p<0.001$], body image [$B=0.293$; (0.251-0.335); $p<0.001$], global health [$B=0.127$ (0.083-0.171); $p=0.001$], role emotional [$B=0.184$ (0.126-0.242); $p<0.001$]; mental health [$B=0.051$; (0.011-0.091); $p=0.012$]. There were not statistically significant associations with the other component and domains.

Conclusion: A more prolonged time under remission predicted a better HRQoL status in our RA patients. Prolonged remission in addition with sustained remission could be a treatment goal to avoid disability.

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Abstract Number: 2505

Sociodemographic Factors Are Predictors of Poorer Clinical Outcome Trajectories in Early Rheumatoid Arthritis: Results from the Singapore Early Arthritis Cohort

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Session Information

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Background/Purpose: Variable outcomes in early rheumatoid arthritis (ERA) may be explained by heterogeneous latent disease activity trajectories, the predictors of which are not well defined. Hence, the study aims to characterise distinct disease activity trajectories and describe the relationship between disease, disability and health-related quality of life (HRQoL) trajectories.

Methods: Data were collected prospectively from patients in the Singapore Early Arthritis Cohort over 3 years. Disease activity, disability and HRQoL were assessed using the Disease Activity Score in 28 Joints with ESR (DAS28ESR), modified Health Assessment Questionnaire (mHAQ) and EuroQol-5D Index (EQ5D Index) respectively. Group-based trajectory modelling (GBTM) was used to identify latent disease activity trajectories. Multi-trajectory modelling was used to describe the relationship between disease, disability and HRQoL trajectories. Multinomial logistic regression was used to identify predictors of trajectory membership.

Results: 213 ERA patients (73.2% female, 58.2% Chinese, age 51.3 ± 12.6 years, symptom duration 21.8 ± 15.3 weeks) were included. Three disease activity trajectories were identified [T1: moderate disease activity to remission (57.8%); T2: high to low disease activity/remission (30.1%); T3: high to moderate/low disease activity (12.1%)]. Non-Chinese patients were more likely to belong to T2 and T3 as compared to T1 [RRR (95% CI) 2.29 (1.09, 4.84) and 2.03 (1.07, 5.84) respectively]. Patients with higher body mass index (BMI) were more likely while patients with tertiary education were less likely to belong to T3 compared to T1 [RRR (95% CI) 1.13(1.02, 1.28) and 0.13 (0.02, 0.75) respectively]. Seropositivity and radiographic erosions were not significant predictors of trajectory membership. A higher proportion of patients in T3 were treated with combination disease modifying anti-rheumatic drugs (DMARDs). Trajectories of disability and HRQoL were closely associated with disease activity trajectories.

Conclusion: In this Asian cohort of ERA patients, sociodemographic factors, rather than seropositivity and radiographic erosions, predicted poorer outcomes (trajectory 3) in spite of more aggressive treatment. Efforts to improve health-literacy may be the key to improving outcomes in these patients.

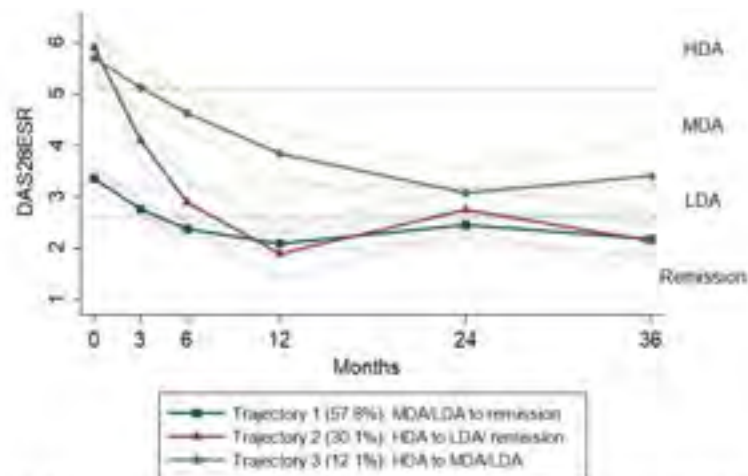


Figure 1 Disease activity trajectories based on DAS28ESR score. Dotted lines represent the 95% confidence intervals. Estimated probabilities of each trajectory are labelled in the legend. The estimated probabilities may differ from the number of patients assigned to each group based on the maximum probability assignment rule. LDA, Low Disease Activity; MDA, Moderate Disease Activity; HDA, High Disease Activity; DAS28ESR, Disease Activity Score in 28 Joints with ESR.

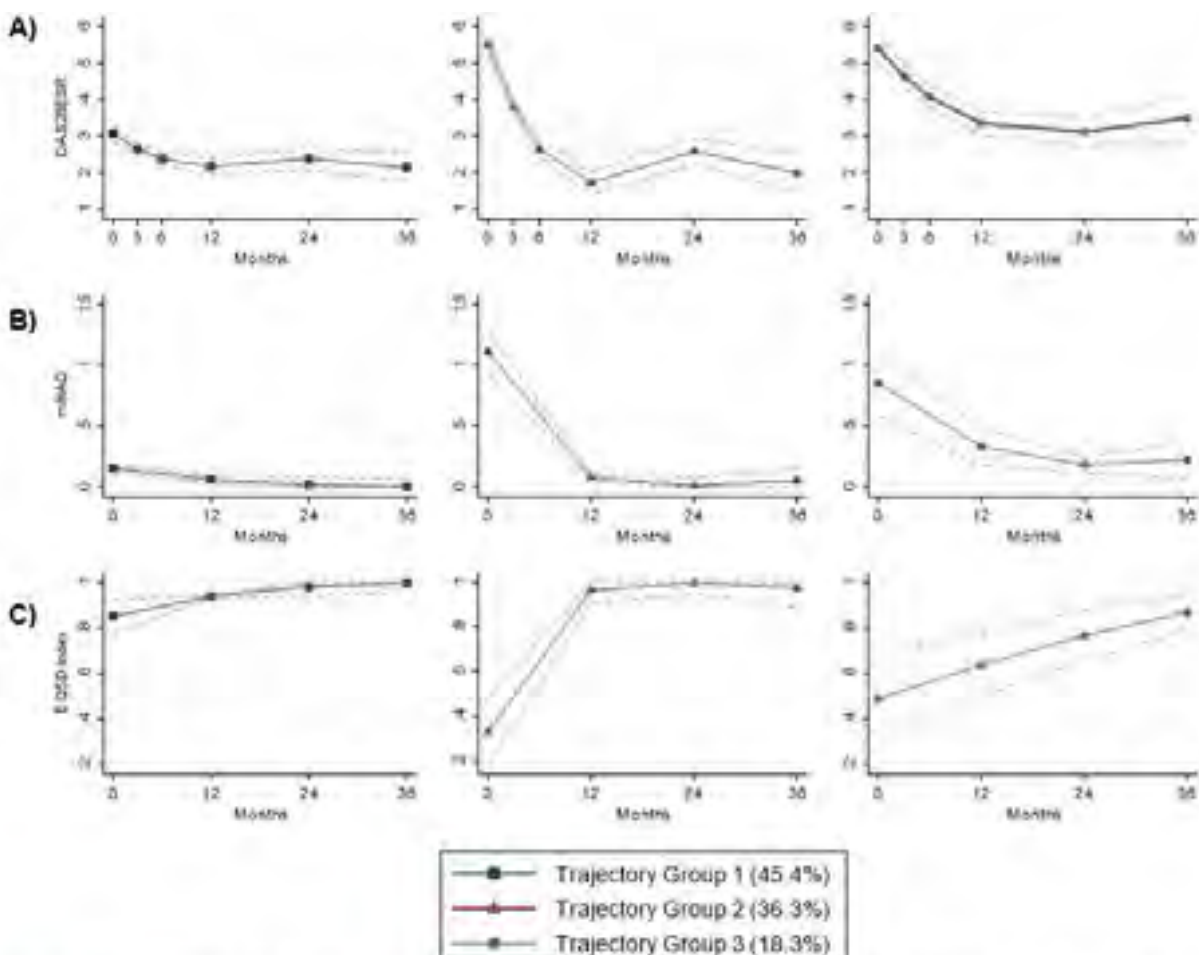


Figure 2 Multi-trajectory modelling of DAS28ESR, mHAQ and EQ5D index: A) DAS28ESR trajectories B) mHAQ trajectories C) EQ5D index trajectories. Dotted lines represent the 95% confidence intervals. Estimated probabilities of each trajectory group are labelled in the legend. The estimated probabilities may differ from the number of patients assigned to each group based on the maximum probability assignment rule.

Table 1 Baseline Determinants of Disease Activity Trajectory (Multinomial Logistic Regression)

	Univariable		Multivariable	
	RRR	95% CI	RRR	95% CI
Age (per unit increase)				
• Trajectory 1	(Ref)		(Ref)	
• Trajectory 2	1.01	0.99, 1.04	1.00	0.97, 1.03
• Trajectory 3	1.01	0.97, 1.05	0.99	0.94, 1.04
Female (vs. male)				
• Trajectory 1	(Ref)		(Ref)	
• Trajectory 2	0.79	0.41, 1.54	0.71	0.30, 1.69
• Trajectory 3	1.40	0.44, 4.49	1.95	0.43, 5.20
Non-Chinese (vs. Chinese)				
• Trajectory 1	(Ref)		(Ref)	
• Trajectory 2	1.73	0.94, 3.20	2.29	1.09, 4.84
• Trajectory 3	3.43	1.27, 6.24	2.03	1.07, 5.04
BMI (per unit increase)				
• Trajectory 1	(Ref)		(Ref)	
• Trajectory 2	0.99	0.93, 1.07	0.97	0.90, 1.05
• Trajectory 3	1.10	1.07, 1.30	1.13	1.02, 1.28
Ever smoker (vs. never smoker)				
• Trajectory 1	(Ref)			
• Trajectory 2	0.84	0.40, 1.74		
• Trajectory 3	1.35	0.48, 3.82		
Symptom duration (weeks)*				
• Trajectory 1	(Ref)		(Ref)	
• Trajectory 2	1.00	0.99, 1.02	1.00	0.96, 1.02
• Trajectory 3	0.99	0.97, 1.02	1.00	0.97, 1.03
Seropositivity [‡]				
• Trajectory 1	(Ref)			
• Trajectory 2	0.75	0.40, 1.40		
• Trajectory 3	1.00	0.37, 2.70		
Radiographic erosions				
• Trajectory 1	(Ref)			
• Trajectory 2	1.44	0.66, 3.18		
• Trajectory 3	1.92	0.61, 4.03		
Non-MTX DMARD (vs. MTX monotherapy) [†]				
• Trajectory 1	(Ref)		(Ref)	
• Trajectory 2	1.60	0.65, 3.94	2.20	0.87, 5.92
• Trajectory 3	1.52	0.36, 5.05	1.75	0.26, 5.90
Combination DMARD (vs. MTX monotherapy) [†]				
• Trajectory 1	(Ref)		(Ref)	
• Trajectory 2	1.35	0.70, 2.64	1.31	0.65, 2.67
• Trajectory 3	3.32	1.03, 6.70	2.92	0.02, 6.45
Tertiary education (vs. none, primary or secondary education)				
• Trajectory 1	(Ref)		(Ref)	
• Trajectory 2	0.54	0.28, 1.07	0.61	0.27, 1.40
• Trajectory 3	0.17	0.04, 0.70	0.13	0.02, 0.75
Private housing (vs. government housing)				
• Trajectory 1	(Ref)			
• Trajectory 2	0.47	0.18, 1.24		
• Trajectory 3	0.79	0.21, 2.90		

Variables with *P* value < 0.2 in the univariable models were brought forward into the multivariable models.

* Weeks from symptom onset to first rheumatologist review.

‡ Either RF or ACPA positivity.

† DMARD treatment at 3 month visit.

BMI, Body Mass Index; RF, Rheumatoid Factor; ACPA, Anti-Citrullinated Protein Antibody; MTX, Methotrexate; DMARD, Disease-Modifying Antirheumatic Drug.

The Joint Disease Burden in Patients with Secondary Sjögren's Syndrome and RA Compared to Patients with RA Only

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Session Information

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Background/Purpose: Secondary Sjögren's syndrome (sSS) is considered a poor prognostic factor in RA and is a common extra-articular manifestation of RA. We estimated prevalence of sSS and joint disease burden in patients (pts) with RA with sSS based on physician diagnosis or Ro-antibody positive (SSa), plus presence of dry eyes or dry mouth.

Methods: Data from adult pts with RA enrolled in a longitudinal RA registry were analyzed. Pts in the registry were evaluated by a rheumatologist annually for disease activity and treatments and semi-annually for multiple clinical pt-reported outcomes (PROs) and resource utilization parameters. For this analysis, pts with RA were categorized into two cohorts: pts with sSS and pts with RA only. Prevalence estimates of pts with sSS were based on clinician diagnosis or meeting ACR/EULAR 2016 classification of primary Sjögren's syndrome. Baseline characteristics between the two cohorts were compared using the Kruskal-Wallis test for continuous variables and chi-square test for categorical variables, with a significance level of 0.05. Mean change from baseline to 12 months in disease activity measures and PROs of fatigue were assessed for pts with data available at baseline and follow-up.

Results: A total of 1471 pts with RA were included in the analysis. The prevalence of sSS was 28.2% (n=415); the remaining 71.8% (n=1056) were included in the RA only cohort. Physician diagnosis comprised ~10% of pts with sSS; the remainder was based on SSa positivity and symptoms of dry eyes or dry mouth. Compared with the RA only cohort, pts with RA with sSS were more likely to be female, have early onset of RA, longer RA disease duration, greater seropositivity, higher antibody titers, higher disease activity levels (Rheumatoid Arthritis Disease Activity Index, CDAI and DAS28 [CRP]), higher fatigue and more likely to have comorbidities of vasculitis, neuropathy and pulmonary nodules (Table 1). In addition, a greater proportion of pts with RA with sSS had prior biologic (b)DMARD exposure (n [%] 248 [59.8] vs 463 [43.8]; p<0.0001), with a higher proportion currently taking bDMARDs (195 [47] vs 382 [36.2]; p=0.0001). Pts with RA with sSS continued to experience higher disease activity and fatigue at 12 months, with a significantly lower reduction in disease activity versus pts in the RA only cohort (Table 2).

Conclusion: The prevalence of sSS was 28% in pts with RA. Although the majority of pts with RA with sSS compared with pts with RA without sSS had exposure to bDMARDs, they continued to experience higher autoantibody burden (RF and ACPA), joint disease activity and fatigue.

Table 1. Baseline Characteristics in Patients With sSS Compared With Patients With RA Only

	Pts with sSS		Pts with RA only		p value*
	N	Mean (SD)	N	Mean (SD)	
Age, years	415	57.8 (13.4)	1056	56.0 (14.7)	0.044
Age at RA diagnosis, years	414	42.4 (14.5)	1054	44.1 (15.7)	0.060
Age at onset of RA symptoms, years	411	39.6 (14.7)	1049	41.9 (15.9)	0.016
Duration of RA symptoms, years	411	18.0 (13.4)	1049	14.1 (12.5)	<0.0001
Female, n (%)	415	378 (91.1)	1056	828 (78.4)	<0.0001
BMI	370	26.9 (6.1)	980	26.9 (5.6)	0.754
RF titer, IU/mL	381	168.0 (401.3)	906	117.8 (300.8)	0.002
RF+, n (%)	381	255 (66.9)	906	546 (60.3)	0.024
ACPA titer, IU/mL	383	154.1 (173.0)	928	121.8 (149.0)	0.0005
ACPA+, n (%)	383	259 (67.6)	928	551 (59.4)	0.005
RADAI	388	3.6 (2.2)	938	3.2 (2.3)	0.002
DAS28 (CRP)	355	3.9 (1.7)	923	3.6 (1.6)	0.033
CDAI score	356	21.8 (17.9)	927	18.7 (15.7)	0.009
Number of swollen joints	393	6.6 (7.5)	1055	6.0 (6.8)	0.364
Number of painful joints	393	7.8 (8.6)	1055	6.5 (7.2)	0.084
MDHAQ fatigue scale	387	49.4 (30.5)	942	38.5 (28.5)	<0.0001

Table . (Cont'd)

	Pts with sSS		Pts with RA only		p value*
	N	Mean (SD)	N	Mean (SD)	
Comorbidities, n (%)					
Vasculitis, cutaneous	415	13 (3.1)	1056	4 (0.4)	<0.0001
Vasculitis, other	415	3 (0.7)	1056	0 (0.0)	0.022
Lymphoma	415	2 (0.5)	1056	10 (0.9)	0.527
Neuropathy	415	15 (3.6)	1056	9 (0.9)	0.001
Lung cancer	415	2 (0.5)	1050	5 (0.5)	1.000
Pulmonary fibrosis	415	13 (3.1)	1056	28 (2.7)	0.601
Pulmonary nodules	415	17 (4.1)	1056	12 (1.1)	0.001

Data are expressed as mean (SD) unless otherwise indicated

* Significant at p<0.05

ACPA=anti-citrullinated protein antibody; MDHAQ=Multidimensional Health Assessment Questionnaire; pts=patients; RADAI=Rheumatoid Arthritis Disease Activity Index; sSS=secondary Sjögren's syndrome

Table 2. Disease Activity Measures and Fatigue at 12 Months and Change From Baseline

	12 months		Change from baseline		p value
	Pts with sSS (n=372)	Pts with RA only (n=925)	Pts with sSS (n=372)	Pts with RA only (n=925)	
RADAI	3.3 (2.1)	2.6 (2.0)	-0.2 (1.7)	-0.6 (1.9)	0.006
N	344	840	344	840	
DAS28 (CRP)	3.5 (1.7)	3.1 (1.5)	-0.3 (1.4)	-0.5 (1.3)	0.037
N	250	628	250	628	
CDAI score	18.5 (17.3)	14.0 (13.9)	-2.6 (14.3)	-4.7 (13.0)	0.029
N	249	642	249	642	
Number of swollen joints	4.8 (6.7)	3.9 (5.8)	-1.6 (6.3)	-2.1 (5.8)	0.361
N	307	766	307	766	
Number of painful joints	5.9 (7.9)	4.9 (6.8)	-1.4 (7.3)	-1.4 (6.1)	0.424
N	307	766	307	766	
MDHAQ fatigue scale	46.1 (27.7)	36.5 (26.5)	-2.8 (22.8)	-1.5 (22.7)	0.503
N	342	841	342	841	

Data are expressed as mean (SD) N

MDHAQ=Multidimensional Health Assessment Questionnaire; pts=patients; RADAI=Rheumatoid Arthritis Disease Activity Index; sSS=secondary Sjögren's syndrome

Disclosure: E. Alemao, Bristol-Myers Squibb, 1, 3; Y. Saini, Mu-sigma, 5; Y. Bao, Bristol-Myers Squibb, 1, 3; A. Rao, Mu Sigma for Bristol-Myers Squibb, 5; C. K. Iannaccone, None; M. E. Weinblatt, Amgen, Crescendo Bioscience, Bristol-Myers Squibb, Sanofi/Regeneron, 2, AbbVie, Ablynx, Amgen, Bristol-Myers Squibb, Canfite, Corrona, Crescendo, GSK, Gilead, Lilly, Lycera, Merck, Momenta, Novartis, Pfizer, Roche, Samsung, Set Point, UCB, Vertex, 5; N. A. Shadick, Amgen, Mallinckrodt, Bristol-Myers Squibb, Sanofi-Regeneron, 2, Bristol-Myers Squibb, 5.

Abstract Number: 2507

Healthcare Resource Utilization in Patients with Secondary Sjögren's Syndrome Associated with RA Compared with Patients with RA in an Insured Population

Evo Alemao¹, Aarti Rao², Chidananda Samal² and Robert Wong¹, ¹Bristol-Myers Squibb, Princeton, NJ, ²Mu Sigma, Bangalore, India

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Secondary Sjögren's syndrome (sSS) is a rheumatic disease that may coexist with RA. Joint disease is more severe in patients (pts) with RA with versus without sSS.¹ There are limited data on healthcare resource use (HCRU) of pts with RA with sSS.

Methods: Pts (≥ 18 years) from the Optum™ Clinformatics™ Data Mart administrative claims database with incident RA (≥ 2 claims for RA with International Classification of Diseases [ICD]-9 [714.0] or ICD-10 [M05.xxx/M06.0xx/M06.8xx/M06.9] and ≥ 1 claim for a conventional DMARD) from Jan 2010 to Jun 2016 were included. Two mutually exclusive RA cohorts were created: one with incident sSS (≥ 2 claims for SS with ICD-9 [710.2] or ICD-10 [M35.0x]) and one without sSS. The index date was the first diagnosis date of sSS (RA with sSS) or RA (RA without sSS). All-cause HCRU was captured during a 12-month period from (and including) the index date (post-index period). Statistical differences in HCRU between cohorts were assessed using chi-square and Kruskal-Wallis tests. For RA with sSS, HCRU during the 12 months pre- and post-index period was compared using McNemar and Wilcoxon sign rank tests.

Results: Overall, 1858 pts with RA with sSS and 21,264 with RA without sSS met inclusion criteria and were analyzed. Of pts with RA with sSS, first sSS diagnosis occurred before RA in 630 (33.9%), after RA in 978 (52.6%) and on the same date in 250 (13.5%). Pts with RA with (vs without) sSS were younger, more likely to be female and had higher incidences (standardized difference $>10\%$) of fibromyalgia, gastrointestinal reflux, hypothyroidism, osteoporosis, systemic sclerosis/scleroderma and systemic lupus erythematosus (Table 1). After sSS diagnosis, proportionally more pts with RA with sSS had inpatient admissions (vs the pre-index period, Table 2). Mean length of stay and number of inpatient visits, outpatient visits and prescriptions were higher in the post-index period (Table 2). Pts with RA with sSS had more outpatient visits and prescriptions than pts with RA without sSS (Table 3).

Conclusion: Pts with RA with sSS (vs pts with RA without sSS) had more comorbidities at baseline. Also, pts with RA with sSS had an increased HCRU post-sSS diagnosis. Further research is needed to understand if HCRU use is associated with clinical manifestation of sSS.

Reference:

1. Brown LE, et al. *Rheumatology (Oxford)* 2015;**54**:816–20.

Table 1. Baseline Characteristics and Comorbidities by Cohort

	Pts with RA with sSS (n=1858)	Pts with RA without sSS (n=21,264)	p value	Standardized difference
Age, years, mean (SD)	58.7 (13.9)	61.3 (14.5)	<0.0001	–
Female sex, n (%)	1665 (89.6)	15,503 (72.9)	<0.0001	–
CCI, mean (SD)	1.6 (1.6)	1.0 (1.4)	<0.0001	–
Comorbidities, n (%)				
Avascular necrosis	8 (0.4)	72 (0.3)	0.517	–0.015
Bronchiolitis	12 (0.6)	51 (0.2)	0.001	–0.061
Celiac disease	14 (0.8)	72 (0.3)	0.005	–0.056
Chronic/recurrent cystitis	18 (1.0)	148 (0.7)	0.182	–0.030
COPD/asthma	51 (2.7)	633 (3.0)	0.571	0.014
Dyslipidemia	623 (33.5)	7733 (36.4)	0.015	0.060
Fibromyalgia	491 (26.4)	3669 (17.3)	<0.0001	–0.223
Gastrointestinal reflux	478 (25.7)	3922 (18.4)	<0.0001	–0.176
Hypertension	932 (50.2)	11,595 (54.5)	0.0003	0.088
Hypothyroidism	520 (28.0)	4402 (20.7)	<0.0001	–0.170
Ischemic heart disease	199 (10.7)	2783 (13.1)	0.003	0.074
Myocardial infarction	28 (1.5)	434 (2.0)	0.115	0.041
Peripheral vascular disease	223 (12.0)	2353 (11.1)	0.219	–0.029
Peptic ulcer disease	15 (0.8)	147 (0.7)	0.565	–0.014
Primary biliary cirrhosis	10 (0.5)	24 (0.1)	<0.0001	–0.075
Osteoporosis	280 (15.1)	2250 (10.6)	<0.0001	–0.135
Osteoarthritis	739 (39.8)	8738 (41.1)	0.268	0.027
Pulmonary nodule	108 (5.8)	793 (3.7)	<0.0001	–0.098
Renal disease	178 (9.6)	2018 (9.5)	0.899	–0.003
Systemic sclerosis/scleroderma	54 (2.9)	157 (0.7)	<0.0001	–0.163
SLE	343 (18.5)	1259 (5.9)	<0.0001	–0.391
Transient ischemic attack	32 (1.7)	366 (1.7)	0.997	–0.0001
Vasculitis, retinal	2 (0.1)	11 (0.1)	0.281	–0.020
Vasculitis, other	33 (1.8)	278 (1.3)	0.093	–0.038

CCI=Charlson Comorbidity Index; COPD=chronic obstructive pulmonary disease; pt=patient; sSS=secondary Sjögren's syndrome; SLE=systemic lupus erythematosus

Table 2. Healthcare Resource Utilization During the 12-Month Pre-Index Period and 12-Month Post-Index Period for the sSS Cohort

	RA with sSS in pre-index period (n=1858)	RA with sSS in post-index period (n=1858)	p value
Number of patients utilizing healthcare services, n (%)			
Inpatient admissions	371 (20.0)	439 (23.6)	0.003
Outpatient services	1645 (88.5)	1652 (88.9)	0.442
Emergency visits	408 (22.0)	401 (21.6)	0.716

Table . (Cont'd)

	RA with sSS in pre-index period (n=1858)	RA with sSS in post-index period (n=1858)	p value
Urgent care visits	49 (2.6)	51 (2.7)	0.819
Pharmacy prescriptions	1821 (98.0)	1849 (99.5)	<0.0001
Number of healthcare services utilized, mean (SD)			
Inpatient admissions	2.2 (3.4)	2.4 (4.0)	0.001
Length of stay, days	8.8 (14.1)	11.3 (20.0)	0.001
Outpatient visits	30.6 (28.5)	36.6 (30.6)	<0.0001
Emergency visits	5.0 (5.7)	5.9 (7.8)	0.249
Urgent care visits	1.7 (1.3)	1.6 (0.9)	0.724
Pharmacy prescriptions	44.1 (35.3)	53.5 (37)	<0.0001

sSS=secondary Sjögren's syndrome

Table 3. Healthcare Resource Utilization During the 12-Month Post-Index Period

	Pts with RA with sSS (n=1858)	Pts with RA without sSS (n=21,264)	p value
Number of patients utilizing healthcare services, n (%)			
Inpatient admissions	439 (23.6)	5143 (24.2)	0.589
Outpatient services	1652 (88.9)	19,008 (89.4)	0.522
Emergency visits	401 (21.6)	4683 (22.0)	0.660
Urgent care visits	51 (2.7)	543 (2.6)	0.617
Pharmacy prescriptions	1849 (99.5)	21,098 (99.2)	0.158
Number of healthcare services utilized, mean (SD)			
Inpatient admissions	2.4 (4.0)	2.6 (4.6)	0.459
Length of stay, days	11.3 (20.0)	13.0 (23.0)	0.389
Outpatient visits	36.6 (30.6)	33.1 (30.8)	<0.0001
Emergency visits	5.9 (7.8)	5.5 (6.7)	0.655
Urgent care visits	1.6 (0.9)	1.8 (1.7)	0.613
Pharmacy prescriptions	53.5 (37)	49.6 (35.3)	<0.0001

sSS=secondary Sjögren's syndrome

Disclosure: E. Alemao, Bristol-Myers Squibb, 1, 3; A. Rao, Mu Sigma for Bristol-Myers Squibb, 5; C. Samal, Mu-sigma, 5; R. Wong, Bristol-Myers Squibb, 1, 3.

Abstract Number: 2508

A First-in-Man Bioelectronic Therapy for Biologic-Refractory Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

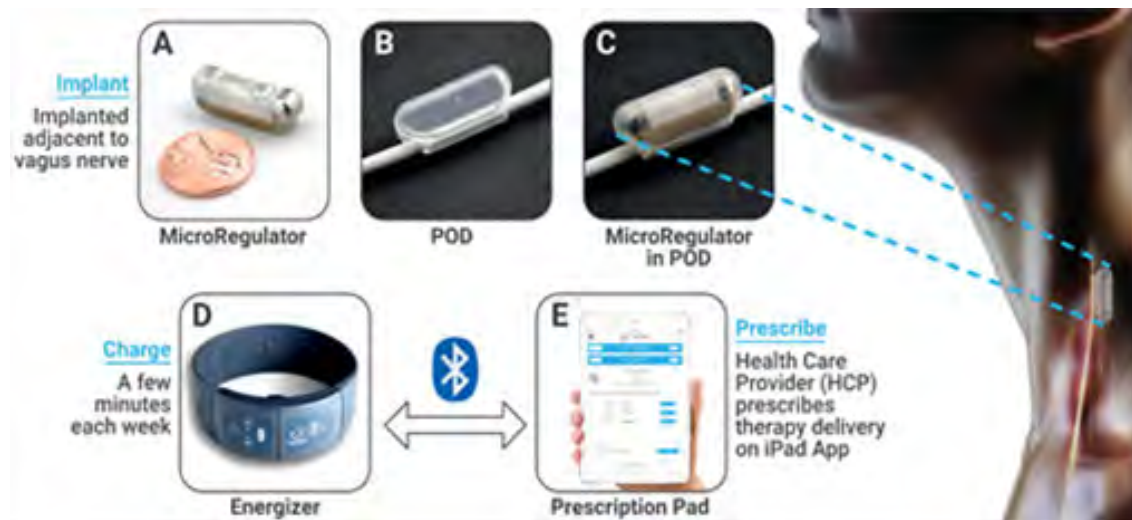
Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes Poster III: Complications of Therapy, Outcomes, and Measures

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is a debilitating chronic disease with an unmet need for additional therapeutic approaches. Bioelectronic therapy (BET), such as electrical neurostimulation of the vagus nerve to activate innate protective neuro-immune reflexes, represents a novel means of treating diseases characterized by systemic inflammation. We performed a proof-of-concept study in RA patients using a marketed vagus nerve stimulation device at very low duty cycles (1-4 min/day), showing reduction of clinical disease activity, concomitant with reductions in TNF- α and IL-6 (PNAS 2016;113:8284). We have developed a novel advanced generation neurostimulation device, the MicroRegulator System, which is being evaluated in a first-in-man clinical study.

Methods: The MicroRegulator System is unique in that it is implanted directly on the vagus nerve as a single unit that contains an application specific integrated circuit (ASIC), pulse generator with a wireless rechargeable battery, as well as a self-contained nerve-encapsulating cuff and electrodes that function without vagus nerve lead wires (Figure 1). Low power requirements allow for miniaturization of the device (< 2 cc). External components include an intermittently worn flexible collar that generates a radio frequency field for recharging and telemetry, as well as an iPad-based control device programming application.



Results: The first-in-man study is a USA-based multi-centered double-blind trial, designed to look at safety and efficacy of the implanted MR system in refractory RA patients that have insufficient response to ≥ 2 biologic or targeted synthetic DMARDs of ≥ 2 modes of action. This study is unique in its use of a neurosurgical sub-investigator paired with the rheumatologist to manage the first weeks of the study period. Implanted subjects, washed off biologics and on stable background of methotrexate, are randomized to 1 min of sham, QD, or QID stimulations for 12 weeks. Efficacy outcomes include standard RA clinical disease measures as well as quantitative MRI joint scoring, validated RA-specific biomarker panels, autonomic balance measurements and immune cell bioassays.

Conclusion: A novel neurostimulation device has been developed and deployed in a first-in-man clinical study. BET, a non-pharmacological intervention, will potentially give rheumatologists a novel alternative means to treat RA, including those patients who have failed conventional treatments.

Figure 1. Schematic Representation of MicroRegulator System

Disclosure: D. Chernoff, SetPoint Medical, Inc., 1, 3, Adamas Pharmaceuticals, 1, 5, OLLY Nutrition, 1, 5, NAIA Pharma, 1, 5, Aquinox Pharma, 1, 5, Crescendo BioScience, 5; Y. Levine, SetPoint Medical, Inc., 1, 3; C. Peterfy, Spire Sciences, Inc., 3, 4, SPIRE Registry, LLC, 4, Amgen Inc., 8, Bristol-Myers Squibb, 8; M. C. Genovese, SetPoint Medical, Inc., 2, SetPoint Medical, 5, Galvani, 5, GlaxoSmithKline, 5, Vorsos, 5.

Abstract Number: 2509

Long-Term Treatment with Sarilumab Plus Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs): Pooled Safety and Efficacy with over 4 Years' Treatment

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: EXTEND (NCT01146652) is an ongoing open-label extension study enrolling patients completing five sarilumab originator studies (MOBILITY [NCT01061736]; TARGET [NCT01709578]; ASCERTAIN [NCT01768572]; ACT11575 [NCT01217814]; ONE [NCT02121210]) in adults with rheumatoid arthritis (RA). This analysis assessed safety and efficacy of sarilumab+csDMARDs after 4 years' treatment.

Methods: Patients received open-label sarilumab 200 mg q2w SC (reduced to 150 mg q2w if indicated). Primary outcome was treatment-emergent (TE) adverse events (AEs), and secondary outcomes comprised efficacy endpoints. This analysis included only patients receiving sarilumab+csDMARDs enrolling into EXTEND. Data are presented as observed.

Results: Patients (mean age 52 years; 81% female) originally enrolled in MOBILITY (n=1283), TARGET (n=454), ASCERTAIN (n=168) and ACT11575 (n=7) were included. Median drug survival time was 312 weeks. At baseline, mean (range) duration of RA was 9.74 (0.3-54) years and 47.9% of patients had received prior bDMARDs. After 6007.1 patient-years' follow-up, overall incidences of TEAEs, serious AEs and TEAEs leading to discontinuations were 186.0, 13.3, and 7.3 /100 patient-years, respectively. Infections were the most common AE of special interest (AESI; Table); incidences of serious infections and opportunistic infections were 3.7 and 0.9/100 patient-years, respectively. There were 24 deaths over the study period (11 due to infection). Incidences of AST/ALT>3x the upper limit of normal and Grade 3/4 neutropenia were 3.5%/8.6% and 10.4%/1.1%, respectively. Neutropenia was not associated with increased risk of infection. Confirmed GI perforations (0.1/100 patient-years) and thrombotic events were rare. Efficacy (DAS28-CRP, CDAI, SDAI and HAQ-DI) was sustained over the study period (Figure). By Week 216, over 60% of continuing patients had achieved DAS28-CRP <2.6. In patients switched to sarilumab 200 mg q2w from placebo or lower doses, efficacy quickly (over the first 12–24 weeks) reached that of sarilumab 200 mg q2w and was sustained.

Conclusion: Through 4 years' follow-up, the safety profile of sarilumab 200 mg q2w was consistent with anticipated class effects and no new safety signals were identified. The rate of serious infection remained consistent over the treatment period. Efficacy was sustained over time.

Acknowledgements: Study funding and medical writing support (Sarah Feeny, Adelphi Communications) provided by Sanofi and Regeneron Pharmaceuticals, Inc.

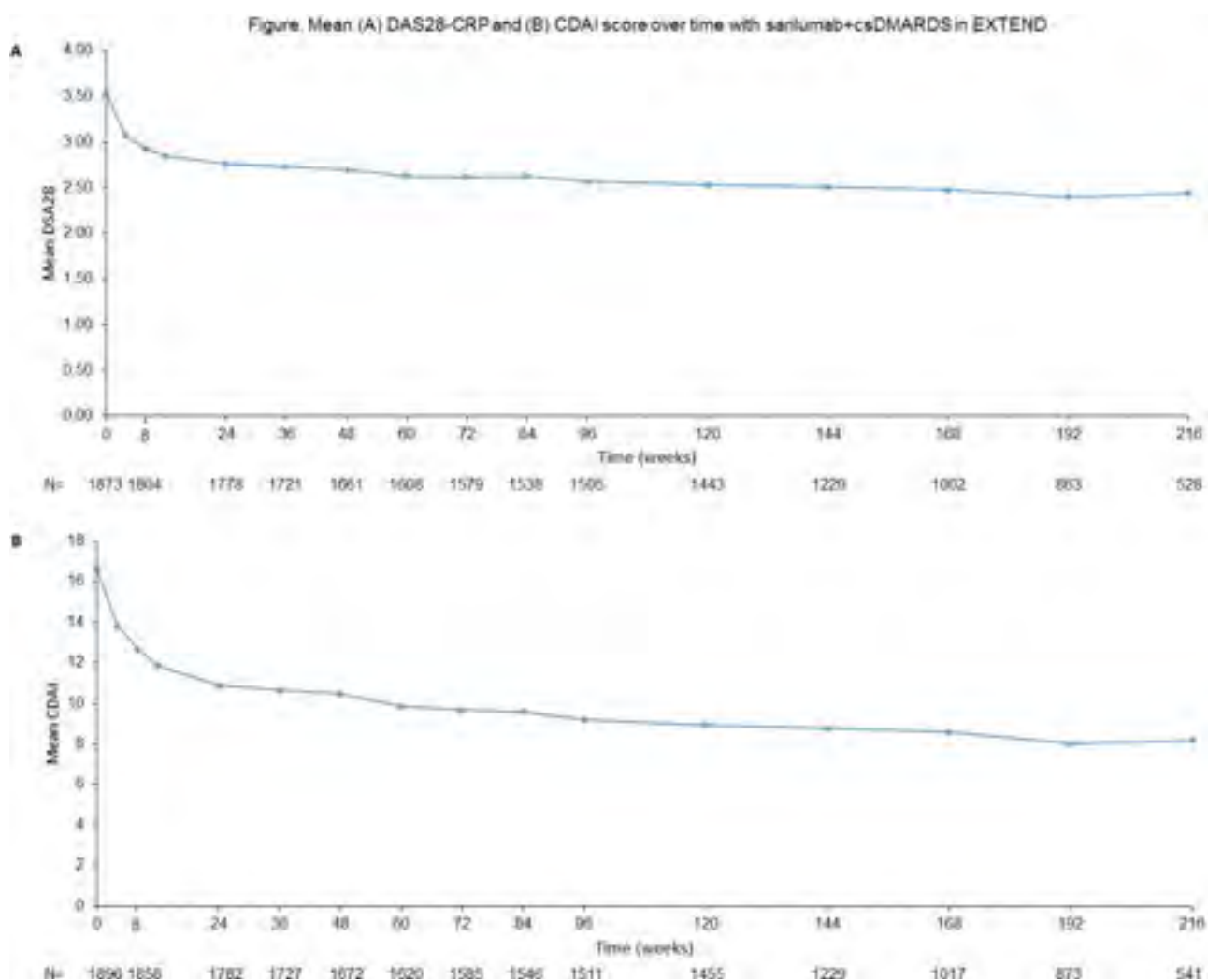


Table. AE and AESI summary with sarilumab+csDMARDS in EXTEND (safety population)

	MOBILITY (N=1281)	TARGET (N=454)	ASCERTAIN (N= 168)	ACT11575 (N=7)	Total (N=1910)
Patient-years	4480.6	1075.7	431.2	19.6	6007.1
Safety overview, n (patients/100 patient-years)^a					
TEAEs	7668 (171.1)	2520 (234.3)	949 (220.1)	37 (188.5)	11174 (186.0)
TE serious AEs	572 (12.8)	168 (15.6)	57 (13.2)	3 (15.3)	800 (13.3)
TEAEs leading to death	21 (0.5)	4 (0.4)	3 (0.7)	0	28 (0.5)
TEAEs leading to discontinuation	327 (7.3)	82 (7.6)	24 (5.6)	4 (20.4)	437 (7.3)
AESI, n (events/100 patient-years)^b					
Infections	2079 (46.4)	615 (57.2)	218 (50.6)	11 (56.0)	2923 (48.7)
Serious Infections	169 (3.8)	40 (3.7)	10 (2.3)	2 (10.2)	221 (3.7)
Opportunistic infectionsc	41 (0.9)	11 (1.0)	3 (0.7)	1 (5.1)	56 (0.9)
Herpes zosterc	25 (0.6)	13 (1.2)	2 (0.5)	1 (5.1)	41 (0.7)
Tuberculosisc	3 (0.1)	1 (0.1)	0	0	4 (0.1)
Leukopeniad	584 (13.0)	171 (15.9)	81 (18.8)	2 (10.2)	838 (14.0)
Thrombocytopeniad	61 (1.4)	32 (3.0)	9 (2.1)	1 (5.1)	103 (1.7)
Hepatic disorders	327 (7.3)	78 (7.3)	26 (6.0)	1 (5.1)	432 (7.2)
Confirmed GI perforations	10 (0.2)	0	0	0	10 (0.2)
Elevation in lipidsd	241 (5.4)	66 (6.1)	26 (6.0)	0	333 (5.5)
Hypersensitivity	159 (3.5)	60 (5.6)	18 (4.2)	0	237 (3.9)
Anaphylaxis	0	0	0	0	0
Injection site reactions	770 (17.2)	234 (21.8)	125 (29.0)	0	1129 (18.8)
Malignancy	23 (0.5)	6 (0.6)	6 (1.4)	0	35 (0.6)
Malignancy excluding NMSC	16 (0.4)	3 (0.3)	3 (0.7)	0	22 (0.4)
Lupus-like syndrome	3 (0.1)	1 (0.1)	0	0	4 (0.1)
Demyelinating disorders	0	0	0	0	0

GI, gastrointestinal; NMSC, non-melanoma skin cancer; ^aexposure period is cumulative time at risk of first event; ^bexposure period is cumulative total TEAE period; ^call cases of herpes zoster reported to date were localized; herpes zoster and tuberculosis were reported as opportunistic infections per protocol (not per clinical judgment); ^dindividual events were reported and laboratory abnormalities were not necessarily persistent.

Disclosure: M. C. Genovese, Sanofi/Genzyme, Genentech/Roche, RPharm, 2, 5; H. van Hoogstraten, Sanofi, Novartis, 1, Sanofi, 3; G. St. John, Regeneron Pharmaceuticals Inc., 1, 3; Q. Dong, Sanofi Genzyme, 1, 3; J. J. Gómez-Reino, Biogen, Gilead, Eli Lilly, Merck Sharp & Dohme, Pfizer and Roche, 2, 5; J. A. Maldonado-Cocco, Pfizer, Merck Sharp Dohme, Sanofi – Aventis, Novartis, Bristol Myers Squibb, Roche, Boehringer Ingelheim, Schering – Plough, Abbott, UCB, Eli Lilly, Gilead, 5, 8; J. Carlos Salazar, Abbvie, GlaxoSmithKline, Janssen, Pfizer, Roche and UCB, 2, 5, 8; T. W. J. Huizinga, Ablynx, Roche and Sanofi, 2, 5; G. R. Burmester, AbbVie, Pfizer, UCB, Roche, 2, AbbVie, Lilly, MSD, Pfizer, Sanofi, Roche, UCB, 5, 8.

Abstract Number: 2510

A Phase IIa Mechanistic Study of Anti-GM-CSF (GSK3196165) with Methotrexate Treatment in Patients with Rheumatoid Arthritis (RA) and an Inadequate Response to Methotrexate

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: GSK3196165 is a high-affinity anti-GM-CSF cytokine IgG mAb currently in development for RA, with reported efficacy using IV dosing. This study evaluated the effects of GSK3196165 in RA.

Methods: 39 adult subjects with RA per ACR 2010 criteria, ≥ 4 each of swollen and tender joints, DAS28(CRP) ≥ 3.2 , CRP ≥ 3.0 mg/L, were randomized (1:3) to placebo or GSK3196165 180 mg SC weekly for 5 injections, then every other week for 3 further injections. Primary outcome was change from baseline (CFB) in exploratory serum biomarkers, effects on circulating cells, assessment of inflammatory joint damage in the hand/wrist using DCE-MRI, and clinical outcomes.

Results: A total of 7/11 (64%) subjects in the placebo group and 23/28 (82%) in the GSK3196165 group completed the study. Patients characteristics were well balanced. Observed PK exposures were lower than anticipated from previous studies. During the 5 weekly doses, maximum pre-dose concentrations were observed at Week 4 with geometric mean of 2,790 ng/mL (CV_b 65.3%), however concentrations dropped unexpectedly after reducing dosing frequency. At Week 12, pre-dose geometric mean concentration was 991 ng/mL (CV_b 86.5%). GM-CSF-mAb Complex (target engagement) in the GSK3196165 group increased during weekly dosing, to peak at 138 ng/L (CV_b 151%) at Week 4. Consistent with the PK profile, the Complex declined from Week 6 to Week 12 and was undetectable after cessation of treatment.

CCL17 declined in only the GSK3196165 group, with a 35% CFB at Week 2. Consistent with the PK profile, after Week 8 CCL17 then increased back towards baseline. Week 12 results are in the Table below. No observable differences between placebo and GSK3196165 groups were noted for most biomarkers.

All imaging measures of synovial inflammation showed a reduction at Week 12 (see Table). No structural changes were observed.

The onset of clinical effect across most endpoints was seen at Week 1, but appeared to plateau from Week 6 onwards. The difference of active over placebo at Week 12 was reflected in other clinical endpoints with or without acute-phase reactants (see Table).

GSK3196165 was well-tolerated, AEs were similar across both arms. No SAEs, significant infections and/or pulmonary events were observed.

Conclusion: Clinical efficacy with consistent improvement in MRI synovitis score was observed in this study. Lower than predicted exposure following dosing every two weeks was reflected in lower concentration of GM-CSF-mAb complex and less suppression of CCL17. Further studies are required to confirm the additional clinical benefit expected with increased exposure from weekly dosing of GSK3196165 in patients with RA.

Study NCT02799472 was funded by GSK.

Endpoint at Week 12	Placebo (N=11)	180mg (N=28)	
Biomarker	LS geometric mean ratio to baseline (CV_b, %)		Ratio to placebo (95% CI)
CCL17	1.71 (25.0%)	0.89 (13.9%)	0.52 (0.29, 0.92)
MRI synovitis	LS mean change from baseline (SE)		Difference from placebo (95% CI)
RAMRIS	0.8 (1.2)	-1.3 (0.60)	-2.2 (-4.9, 0.5)
RAMRIQ	-912 (1406)	-1,417 (672)	-505 (-3730, 2721)
Clinical			
DAS28(CRP)	-0.04 (0.56)	-1.29 (0.30)	-1.26 (-2.54, 0.03)
CDAI	-2.44 (7.35)	-16.71 (3.70)	-14.26 (-30.98, 2.45)
Pain	1.3 (9.7)	-14.7 (5.1)	-16.0 (-38.2, 6.3)
HAQ-DI	0.094 (0.214)	-0.301 (0.117)	-0.395 (-0.892, 0.102)
Patient's Global Assessment of Arthritis	-1.5 (9.4)	-14.3 (5.0)	-12.9 (-34.4, 8.7)
Responders n (%)			
ACR20	1 (9%)	9 (32%)	23.1% (-1.2, 47.3)
ACR50	0	6 (21%)	21.4% (6.2, 36.6)
Good/moderate EULAR	2 (18%)	13 (46%)	28.2% (-1.1, 57.6)

Disclosure: M. C. Genovese, GlaxoSmithKline, 5; M. Berkowitz, None; P. G. Conaghan, AbbVie Inc., 5, Bristol-Myers Squibb, 8, 9, GlaxoSmithKline, 5, Novartis, 5, 8, Pfizer, Inc., 5, 8, Roche, 8; K. Davy, GlaxoSmithKline, 1, 3; D. Inman, GlaxoSmithKline, 1, 3; E. Fischeleva, GlaxoSmithKline, 1; A. Gupta, GlaxoSmithKline, 1, 3; R. Janiczek, GlaxoSmithKline, 1, 3; M. Layton, GlaxoSmithKline, 1, 3; N. Mitchell, GlaxoSmithKline, 3; J. Patel, GlaxoSmithKline, 1, 3; J. E. Smith, GlaxoSmithKline PLC, 3; R. Williamson, GlaxoSmithKline, 1, 3; P. P. Tak, GlaxoSmithKline, 1, 3.

Abstract Number: 2511

Benepali Switches in Clinical Practice – a Positive Single Centre Experience

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Benepali (SB4), an etanercept (ETN) biosimilar, has demonstrated comparable efficacy in randomised controlled trials. Switching patients to biosimilars has cost benefits to the national health systems (NHS). However, there is reluctance to switch patients, due to lack of real world data about its efficacy and safety. The impetus for this study was to determine the real data trends of efficacy and safety in SB4 switching during treatment of patients with inflammatory arthritis.

Methods: Inflammatory arthritis patients, (rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (AS)) switching from ETN to SB4, between Mar/17 and Oct/17, were included in this prospective observational single centre study. Disease activity scores and CRP before, and 3-6 months after switch, were calculated. Factors associated with SB4 withdrawal were recorded. DAS28, spinal VAS, BASDAI, and 66/68 swollen joint (SJ) and tender joint (TJ) counts were captured to measure efficacy. Flares were defined as a change of 1.2 points in DAS28, whilst a change of 22.55% in BASDAI was considered clinically significant.

Results: A total of 158 inflammatory arthritis SB4 switch patients were identified (87 RA, 30 PsA and 41 AS). Patients switched from ETN after a median time of 67 (RA), 110 (PsA) and 51 (AS) months. Demographics are shown in Table 1. Disease activity measurements before, and 3-6 months after switch, are shown in Table 2. In RA, no statistical difference was found in mean DAS28 scores ($p=0.344$). In PsA, no significant difference was found in 68 TJ counts ($p=0.565$) and 66 SJ counts ($p=0.475$). In AS, there was no difference in mean BASDAI ($p=0.893$) or VAS scores ($p=0.108$). Median CRP level was comparable in the three groups ($p=0.363$). 144 (91.14%) patients continued to receive SB4 at six months. In total, 14 patients (8.9%) switched back to ETN from SB4: 4 AS (2.5%) patients had disease flare. 7 patients (4.4%) had mild adverse reaction (pruritus (2), rash (1), dizziness (1), bruising (2) and blurred vision (1)), and 3 RA patients (1.9%) had a subjective deterioration with unchanged DAS 28. All 14 patients achieved improvement after switching back to ETN.

Table 1. Baseline demographics of Barts patient cohort

	RA (n=87)	PsA (n=30)	AS (n=41)
Age (mean \pm SD)	61.68 \pm 13.61	54.77 \pm 13.54	41.90 \pm 9.80
Female gender, n (%)	70 (80.5%)	12 (29.3%)	7 (23.3%)
Duration of ETN (months), median [IQR]	67 [38.75-115]	110 [85-115]	51 [20.5-86.0]
Other biologic drug prior to ETN, n (%)	6 (6.9%)	1 (2.4%)	3 (10%)

ETN indicates etanercept; RA, rheumatoid arthritis; PsA, psoriatic arthritis; AS, axial spondyloarthritis

Table 2. Disease activity scores before and 3-6 months after switch

	ETN (mean \pm SD)	SB4 (mean \pm SD)	p-value
DAS28	2.82 \pm 1.49	3.03 \pm 1.47	0.344
BASDAI	3.27 \pm 2.59	3.32 \pm 2.24	0.893
Spinal VAS	3.22 \pm 2.95	4.12 \pm 2.99	0.108
68 TJC	4.26 \pm 10.55	3.81 \pm 9.76	0.565
66 SJC	0.78 \pm 1.97	0.93 \pm 1.64	0.475

ETN indicates etanercept; SB4, benepali

Conclusion: In this real-life observational study, biosimilar switch of SB4 was successful in over 90% of cases. The efficacy of SB4 seemed comparable to ETN and was well tolerated. In this cohort, the switch to SB4 resulted in an approximate cost saving of £370,000/yr to the NHS. It is hoped these results will encourage other centers to switch their patients from originator ETN to biosimilar SB4.

Disclosure: H. Alkoky, None; A. Pakozdi, None; H. Tahir, None.

Abstract Number: 2512

Treatment Continuation on the Etanercept Original in Comparison with a Biosimilar

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

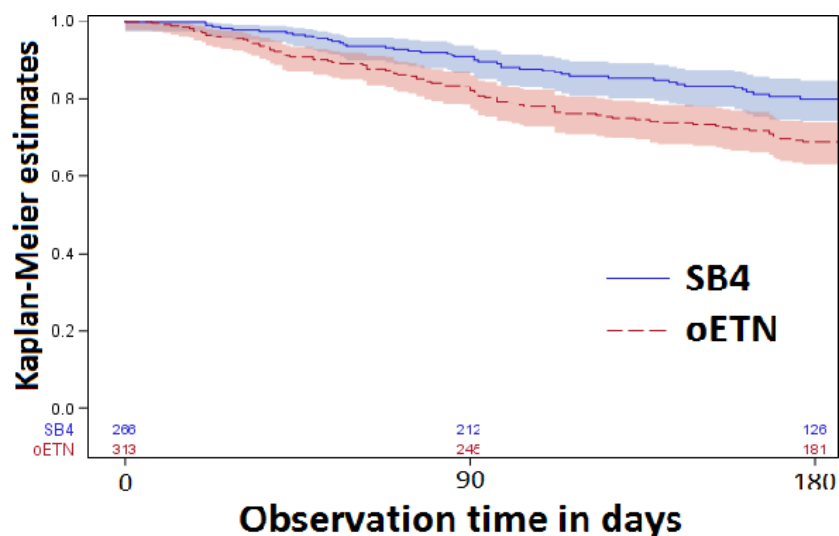


Figure. Treatment continuation in bionaive patients enrolled with a start of treatment with either SB4 or oETN .

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The number of biosimilars approved for the treatment of rheumatoid arthritis (RA) is constantly increasing. Until now, there are just a few analyses investigating retention rates of biosimilars and the respective originators. We compared treatment survival on SB4 to the originator etanercept (oETN) using real-world data.

Methods: We used data gathered until April 2018 from the prospective, longitudinal RABBIT (*R*heumatoid *A*rrthritis: *O*bservation of *b*iologic *t*herapy) cohort. RA patients are enrolled in RABBIT when they start a biologic, biosimilar or new csDMARD treatment. Bionaive patients enrolled since 2015 starting a treatment with either SB4 or oETN who had at least one follow-up visit were compared. The drug survival rates during the first six months were analyzed using Kaplan-Meier curves.

Results: Overall, 266 patients treated with SB4 and 313 with oETN fulfilled the inclusion criteria. Compared to oETN patients, those enrolled with SB4 had lower disease duration (7.5 vs. 8.7 years), were younger (58 vs. 59 years) and significantly fewer patients had three or more comorbidities (39% vs. 47%). Kaplan-Meier curves show higher retention rates over 6 months for SB4 than oETN (figure). Patients switching from oETN to SB4 or vice versa were censored and not counted as discontinuations (oETN to SB4: n=7, SB4 to oETN: n=1). Adjusting for disease duration and comorbidities had no significant influence on the results. 9% (n=25) of SB4 patients and 18% (n=55) of oETN patients stopped treatment during the first 90 days. Additional 8% (n=21, SB4) / 12% (n=37, oETN) stopped the treatment within 180 days after enrolment. The most frequent reasons for discontinuation of both treatments were adverse events (AE) in 48% (21 of 44, SB4) / 54% (49 of 91, oETN) and ineffectiveness in 36% (16 of 44, SB4) / 36% (33 of 91, oETN) of patients. The most frequent AE leading to discontinuation was 'flare' in SB4 patients (12%, 4 of 33 AEs), and 'skin reactions at the injection site' in oETN patients (26%, 18 of 68 AEs). Overall, injection site reactions occurred in 7% (n=23) of oETN patients and 3% (n=7) of SB4 patients (leading to discontinuation in only one patient).

Conclusion: We found higher retention rates for bionaive patients starting the biosimilar SB4 compared to those starting the originator oETN. Whereas both treatments were equally effective, patients treated with oETN had more injection site reactions. We cannot rule out selection bias since there is practice variation in the usage of biosimilars in Germany (regional quota systems). In addition, patients receiving either oETN or SB4 were not entirely comparable (e.g. more comorbidities on oETN).

Disclosure: L. Baganz, None; Y. Meißner, Pfizer, Inc., 8; P. Herzer, Pfizer, Inc., 8; J. Braun, None; A. Gräßler, None; A. Strangfeld, AbbVie, BMS, Lilly, MSD, Pfizer, Roche and UCB, 8; A. Zink, BMS, Lilly, Pfizer, Roche, UCB, 8.

Change in Disease Activity after Switching Etanercept (originator) to Biosimilar (Benepali) Is Associated with Active Disease at Baseline

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Session Information

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Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

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Background/Purpose: Biosimilar contains a version of active substance similar of an already approved biological agent in terms of quality, characteristic, biological activity, safety and efficacy. The price of biosimilars is often less than their original biologic agents. Many healthcare providers have the option of switching patients from original biologic agents to biosimilars to reduce cost. The Purpose of this study was to compare the effectiveness and safety of the Etanercept Biosimilar (Benepali) with Originator (Enbrel) after switching in patients with rheumatoid arthritis (RA) in Wales, United Kingdom

Methods: A retrospective study was conducted across all hospitals within Wales in the United Kingdom as a national audit. Patients switched from Enbrel to Benepali were identified. Efficacy was assessed by change in DAS28CRP disease activity status before and after switching. We included both biologic naïve and experienced patients.

Results: ± 9.2 yrs. Enbrel was used as first line biologic treatment in 105 patients, second line in 14 and third line in 1 patient. Rheumatoid Factor and ACPA were positive in 72% and 63% of patients respectively. Most patients were taking concomitant DMARDs (96/120). Only 24 patients were not taking any conventional DMARDs, however, 8 patients were treated with prednisolone. Methotrexate was the most commonly used DMARD. After switching to biosimilar, 47 (39.1%) patients out of 120 patients had increase in their DAS28CRP score of which 27 patients (22.5%) moved from a lower disease state to a higher disease state (Table). Out of 102 patients who were in remission at the time of switching, 17 (17%) patients developed low, moderate or high diseases activity. At baseline, 18 patients were in low or moderate disease activity, 10 (56%) moved to moderate or high disease activity. Amongst 47 patients who had increase in DAS28CRP, 18 reported disease flares. Most flares occurred within the first 4 months of switching (16 out of 18 flares). Half of these patients (9 out of 18) were switched back to Enbrel. 13 adverse reactions were noted after switching to on Benepali, which included 5 infections (chest and urinary), 4 others (shortness of breath, oral ulcerations, eczema, neutropenia 1 patient each) and 4 unspecified.

Table

Baseline N=120	After Switching			
	Remission	LDA	MDA	HAD
Remission (n=102)	85	8	8	1
LDA (n=7)	0	0	6	1
MDA (n=11)	0	0	8	3
HAD (n=0)	0	0	0	0

LDA –low diseases activity MDA-Moderate diseases activity HDA-High diseases activity

Conclusion: After switching from Enbrel to biosimilar Benepali, many patients experience increase in disease activity, this is more likely if patients are not in disease remission at the time of switching suggesting that these may be due to natural fluctuation or spontaneous disease flares in patients with unstable disease. Only 18 (15%) patients reported disease flare and 9 (8%) patients had to switch back to Enbrel.

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Development of a Subcutaneous Formulation of CT-P13 (Infliximab): Maintenance Subcutaneous Administration May Elicit Lower Immunogenicity Compared to Intravenous Treatment

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

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Background/Purpose: Intravenous (IV) use of CT-P13, an infliximab (INX) biosimilar, has resulted in comparable efficacy, safety and immunogenicity as innovator INX in various indications including rheumatoid arthritis (RA)¹ and Crohn's disease (CD)². A subcutaneous (SC) formulation of CT-P13 is developed to provide patients with opportunities for self-injection, thereby enhancing convenience and flexibility in treatment. This work aimed to investigate immunogenicity by post-hoc analysis of two randomized controlled trials comparing pharmacokinetics of CT-P13 IV and CT-P13 SC.

Methods: Patients with RA (6 or more swollen and tender joints and serum C-reactive protein [CRP] concentration >0.6 mg/dL) and active CD (Crohn's Disease Activity Index [CDAI] score of 220 – 450) were treated with CT-P13 IV at Weeks 0 and 2. At Week 6, patients were randomized for continuation with IV or SC administration. The IV cohorts received CT-P13 IV (3 mg/kg for RA and 5 mg/kg for CD) every 8 weeks and the SC cohorts were treated with CT-P13 SC (90, 120, 180 mg for RA and 120, 180 and 240 mg for CD) every 2 weeks up to Week 30. Trough serum concentrations (C_{trough}) were assessed at Weeks 6, 14 and 22 for IV and Weeks 6, 8, 10, 14, 22, 24, 26 and 28 for SC. Target exposure level was considered as 1 µg/mL for RA^{3, 4} and 5 µg/mL for CD^{5, 6}. Anti-drug antibody (ADA) was assessed before study drug administration at Weeks 0, 6, 14, 22 and 30 by a drug-sensitive, enzyme-linked immunosorbent assay.

Results: In total, 92 patients were randomized at Week 6 to IV (RA: n=13, CD: n=13) or SC (RA: n=35, CD: n=31). All RA patients used methotrexate as concomitant medication throughout the study. Among CD patients, immunomodulators were used at Week 6 by 9 (69.2%) and 15 (48.4%) patients in IV and SC cohorts, respectively. Efficacy results (EULAR [CRP] responder rate for RA and CDAI-70 responder rate for CD) were comparable between the IV and SC. Systemic safety profiles observed from CT-P13 SC after randomization were also comparable to those of IV. A sub-therapeutic C_{trough} level below target exposure was detected at least once in 23 (92.0%) and 9 (14.1%) patients in IV and SC cohorts, respectively. ADA were detected at least once in 16 (64.0%) versus 11 (18.1%) of patients in the IV and SC cohorts ($p<0.0001$), respectively.

Table. Efficacy, C_{trough} and immunogenicity among RA and CD patients

Efficacy	IV cohort	SC cohort	p value a
EULAR (CRP) responder rate at Week 30 in RA patients	12/13 (92.3%)	32/32 (100%)	0.2889
CDAI-70 responder rate at Week 30 in CD patients	8/10 (80.0%)	24/26 (92.3%)	0.3048
C_{trough}	IV cohort (N=25)	SC cohort (N=64)	p value a
$C_{trough}<$ target exposure at least once	23 (92.0%)	9 (14.1%)	<0.0001
$C_{trough}\geq$ target exposure throughout the study	2 (8.0%)	55 (85.9%)	
Immunogenicity	IV cohort	SC cohort	p value a
Anti-drug antibody positive at least once	16/25 b (64.0%)	11/61 b (18.1%)	<0.0001
RA patients	9/13 (69.2%)	8/33 b (24.2%)	0.0071
CD patients	7/12 b (58.3%)	3/28 b (10.7%)	0.0033

Note: ^a p value was derived from Fisher's exact test.

^b Patients who reported ADA positive at Week 0 or 6 (before randomization) were excluded.

Conclusion: After initial loading two doses of CT-P13 IV, patients subsequently receiving biweekly maintenance treatment with CT-P13 SC achieve more stable steady state therapeutic blood levels of INX and have lower rate of ADA compared

with patients receiving continued IV treatment. Further work to corroborate these findings is ongoing through a confirmatory efficacy trial.

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Abstract Number: 2515

Joint Damage Progression According to Disease Activity States in Patients with Rheumatoid Arthritis Treated with CT-P10 and Reference Rituximab: Up to 48 Weeks Results from Phase III Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

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Session Time: 9:00AM-11:00AM

Background/Purpose: CT-P10 is a biosimilar of the reference rituximab (RTX) and has been approved by several regulatory agencies including EMA. Pharmacokinetic and therapeutic equivalence from phase III study (NCT02149121) in rheumatoid arthritis has been reported previously^{1,2}. The objective of this report is to evaluate radiographic joint damage progression and its association with disease activity states in terms of disease activity score by 28 joint counts (DAS28)

Table 1 Comparison of Disease Activity States between CT-P10 and RTX

Week	Disease activity state	DAS28-CRP		DAS28-ESR		CDAI		SDAI	
		CT-P10	RTX	CT-P10	RTX	CT-P10	RTX	CT-P10	RTX
24	Remission	35 (25.2%)	50 (25.9%)	16 (11.5%)	27 (14.0%)	20 (14.4%)	33 (17.1%)	18 (12.9%)	31 (16.1%)
	LDA	27 (19.4%)	35 (18.1%)	19 (13.7%)	22 (11.4%)	43 (30.9%)	54 (28.0%)	45 (32.4%)	56 (29.0%)
	Remission/LDA	62 (44.6%)	85 (44.0%)	35 (25.2%)	49 (25.4%)	63 (45.3%)	87 (45.1%)	63 (45.3%)	87 (45.1%)
	MDA	60 (43.2%)	82 (42.5%)	65 (46.3%)	90 (46.6%)	47 (33.8%)	63 (32.6%)	53 (38.1%)	73 (37.3%)
	HDA	13 (9.4%)	26 (13.3%)	36 (25.9%)	34 (28.0%)	26 (18.7%)	43 (22.3%)	19 (13.7%)	33 (17.1%)
	MDA/HDA	73 (52.5%)	108 (55.8%)	101 (72.7%)	144 (74.6%)	73 (52.5%)	106 (54.9%)	72 (51.8%)	106 (54.9%)
48	Remission	45 (32.4%)	65 (33.7%)	24 (17.3%)	44 (22.8%)	28 (18.0%)	43 (22.3%)	26 (18.7%)	41 (21.2%)
	LDA	24 (17.3%)	29 (15.0%)	24 (17.3%)	22 (11.4%)	49 (35.4%)	55 (28.5%)	47 (33.2%)	56 (29.0%)
	Remission/LDA	69 (49.6%)	94 (48.7%)	48 (34.5%)	66 (34.2%)	74 (53.2%)	98 (50.8%)	73 (51.8%)	97 (50.3%)
	MDA	56 (40.3%)	73 (37.8%)	63 (45.3%)	81 (42.0%)	38 (27.3%)	60 (31.1%)	45 (32.4%)	64 (33.2%)
	HDA	6 (4.2%)	15 (7.8%)	21 (15.1%)	36 (18.7%)	20 (14.4%)	25 (13.0%)	13 (9.4%)	21 (10.9%)
	MDA/HDA	62 (44.6%)	88 (45.6%)	84 (60.4%)	117 (60.6%)	58 (41.7%)	85 (44.0%)	58 (41.7%)	85 (44.0%)

Note: Data was shown in the number (%) of patients with each disease activity state. Percentages were calculated using the number of subjects who received two treatment courses as denominator.

Table 2 The Proportion of Radiographic Non-Progressor between CT-P10 and RTX depending on Disease Activity States

Activity States		Radiographic non-progressor (n/N)	
Week	Disease activity state	SvdH ≤ 2.76 (SDD)	
DAS28-CRP		CT-P10	RTX
24	Remission/LDA	48/50 (96.0%)	60/66 (90.9%)
	MDA/HDA	55/59 (93.2%)	76/86 (88.4%)
48	Remission/LDA	64/65 (98.5%)	71/77 (92.2%)
	MDA/HDA	39/44 (88.6%)	64/74 (86.5%)
DAS28-ESR		CT-P10	RTX
24	Remission/LDA	29/30 (96.7%)	37/39 (94.9%)
	MDA/HDA	75/80 (93.8%)	99/113 (87.6%)
48	Remission/LDA	45/46 (97.8%)	51/54 (94.4%)
	MDA/HDA	59/64 (92.2%)	85/98 (86.7%)
CDAI		CT-P10	RTX
24	Remission/LDA	48/50 (96.0%)	60/66 (90.9%)
	MDA/HDA	56/60 (93.3%)	76/86 (88.4%)
48	Remission/LDA	66/67 (98.5%)	71/80 (88.8%)
	MDA/HDA	38/43 (88.4%)	65/72 (90.3%)
SDAI		CT-P10	RTX
24	Remission/LDA	48/50 (96.0%)	60/66 (90.9%)
	MDA/HDA	55/59 (93.2%)	76/86 (88.4%)
48	Remission/LDA	65/66 (98.5%)	72/80 (90.0%)
	MDA/HDA	36/43 (83.7%)	63/71 (88.7%)

Note: n = Patients with changes from baseline of SvdH \leq 2.76 (SDD) at week 48 by each disease activity state. N = Patients who received two treatment courses and had SvdH score at both baseline and week 48 by each disease activity state.

based on C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), clinical disease activity index (CDAI) and simplified disease activity index (SDAI) for 48 weeks.

Methods: Patients with RA were randomized to CT-P10 or RTX (US or EU sourced rituximab) groups and received 2 courses of either CT-P10 or RTX at weeks 0 and 24. Radiographic progression was evaluated using the van der Heijde modified Sharp Scoring system (SvdH). The smallest detectable difference (SDD) was calculated to define radiographic non-progressor (defined as change in SvdH lesser than or equal to SDD at Week 48)³. The proportions of patients achieving remission or low disease activity (LDA) and, moderate disease activity (MDA) or high disease activity (HDA) in terms of DAS28, CDAI, and SDAI were compared at weeks 24 and 48.

Results: The mean (standard deviation) increase from baseline in SvdH score was similar between CT-P10 and RTX (1.85 [9.03] vs 1.24 [2.98]) at Week 48. Comparable proportion of radiographic non-progression was observed between CT-P10 and RTX; 94.5% vs. 89.5% based on calculated SDD (SvdH equal to 2.76). The proportion of patients with remission or LDA and, MDA or HDA was generally comparable between CT-P10 and RTX at weeks 24 and 48 for various disease activity indices (DAS28-CRP, DAS28-ESR, CDAI, SDAI) (Table 1). The proportion of radiographic non-progressors was comparable between two groups within each disease activity state with an increasing trend as disease activity improved (Table 2).

Conclusion: Comparable disease activity and effect of inhibition for joint damage progression were shown between CT-P10 and RTX groups. The evaluation of radiographic progression with disease activity states by DAS28, CDAI and SDAI showed a trend of higher proportion of radiographic non-progressors in Remission or LDA than that of MDA or HDA.

Reference :

1. Yoo *et al.* (2016), Arthritis Rheumatol 68(Suppl 10): 2037-9.
2. Shim *et al.* (2017), Arthritis Rheumatol 69(Suppl 10): 3447-9.
3. Bruynesteyn *et al.* (2005), Ann Rheum Dis 64:179-182.

Disclosure: C. H. Suh, CELLTRION, Inc., 5; D. H. Yoo, None; W. Park, CELLTRION, Inc., 5; S. C. Shim, CELLTRION, Inc., 5; S. J. Lee, employee, 3; Y. J. Bae, employee, 3; S. E. Han, employee, 3; S. M. Lee, employee, 3.

Long-Term Maintenance of Response in Patients with Rheumatoid Arthritis Treated with Certolizumab Pegol

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The safety and efficacy of certolizumab pegol (CZP) for treating patients (pts) with rheumatoid arthritis (RA) are well-established in a clinical trial setting.^{1,2} However, data describing these outcomes in routine clinical practice are needed.

Methods: This was a prospective, observational, multicenter study conducted in France. Data are reported from 2014–2017. Eligible pts were adults with moderate-to-severe, active RA starting treatment with CZP following inadequate response to DMARDs (incl. MTX). Safety outcomes were measured in the safety set (SS; all pts who received ≥ 1 dose CZP); efficacy in the full analysis set (FAS; SS pts with no protocol deviations).

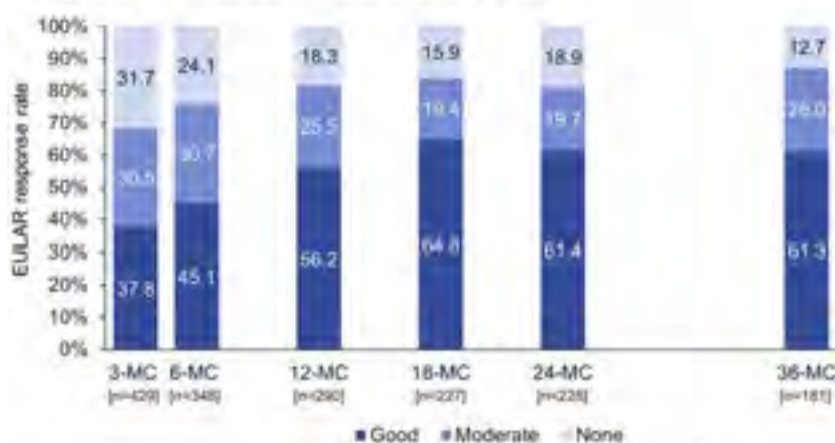
The primary endpoint was EULAR response at the 12-month(mo) visit, and has been reported previously.³ Other measures included clinical disease activity index (CDAI), fatigue assessment scale, health assessment questionnaire-disability index (HAQ-DI), patient's assessment of arthritis pain (PtAAP), and patient/physician global assessment of disease activity (Pt/PhGADA). Adverse drug reactions (ADRs) and serious ADRs (SADRs) included events with known relationship to CZP, or for which causality was not determined. Data were collected at baseline and routine clinical visits at ~3, 6, 12, 18, 24 and 36mo. Here we report final observed data from 36mo follow-up.

Results: 792 pts were included: 776 (98.0%) in the SS, 733 (92.6%) in the FAS. In the FAS, most pts were female (78.0%), and the mean age at baseline was 55.1 years. Most pts had moderate (n=320, 49.5%) or high (n=265, 41.0%) baseline disease activity based on DAS28(ESR).

The proportion of pts with a EULAR response increased up to the 12mo visit and was sustained to 36mo (**Figure**); the proportion of non-responders also remained stable from 12mo. These improvements were reflected in other measures of clinical effectiveness (**Table A**). Overall, 776 ADRs were reported in 350 (45.1%) pts, including 242 SADRs in 151 (19.5%) pts (**Table B**). The most frequent ADRs by System Order Class were infections and infestations (268 events in 179 [23.1%] pts). ADRs were consistent with the known safety profile for CZP, with no new safety signals identified.

Conclusion: RA pts treated with CZP in French clinical practice experienced improvements in disease outcomes after 12mo that were sustained up to 36mo in pts still receiving CZP, with a safety profile that reflects trial data.

Figure: EULAR response over 36 months of follow-up (FAS)



Observed data from patients who completed CZP treatment at each timepoint. EULAR, European League Against Rheumatism; FAS, Full Analysis Set; MC, month completers.

Table A: Clinical effectiveness of CZP over 36 months of follow-up (FAS)

Mean (SD) [n]	Baseline	12-month completers	36-month completers
CDAI	25.74 (12.34) [n=700]	8.22 (7.93) [n=357]	5.87 (7.51) [n=214]
Fatigue [a]	6.13 (2.22) [n=707]	4.38 (2.47) [n=344]	4.13 (2.60) [n=196]
HAQ-DI	1.28 (0.69) [n=707]	0.71 (0.65) [n=345]	0.63 (0.66) [n=199]
PtAAP [b]	52.92 (23.63) [n=706]	25.41 (23.14) [n=361]	20.01 (21.21) [n=223]
PhGADA [c]	56.02 (18.73) [n=727]	20.64 (19.24) [n=372]	13.83 (15.84) [n=228]
PtGADA [c]	56.06 (22.25) [n=715]	27.07 (22.76) [n=362]	20.73 (20.49) [n=224]

Observed data from patients who completed CZP treatment at each timepoint. [a] Measured using the fatigue assessment scale, which ranges from 0 (no fatigue) to 10 (worst fatigue); [b] Measured using a 100 mm visual analog scale, where 0=no pain and 100=severe pain; [c] Measured using a 100 mm visual analog scale, where 0=very good, asymptomatic and no limitation of normal activities and 100=very poor, very severe symptoms, which are intolerable, and inability to carry out all normal activities. CDAI: Clinical Disease Activity Index; CZP: certolizumab pegol; FAS: Full Analysis Set; HAQ-DI: Health Assessment Questionnaire-Disability Index; PtAAP: Patient's Assessment of Arthritis Pain; PhGADA: Physician's Global Assessment of Disease Activity; PtGADA: Patient's Global Assessment of Disease Activity.

	n (%) [NE] IR
Total serious ADRs	151 (19.5) [242] 10.2
Serious infections	67 (8.6) [83] 4.2
Herpes zoster	8 (1.0) [8] 0.5
Bronchitis	7 (0.9) [7] 0.4
Lung infection	7 (0.9) [7] 0.4
Pyelonephritis	7 (0.9) [7] 0.4
Malignancies	20 (2.6) [21] 1.2
Serious adverse cardiovascular events	9 (1.2) [12] 0.5

Table B: Serious adverse drug reactions (SS; N=776)

All percentages are reported out of the total SS (N=776). ADR: adverse drug reaction; IR: incidence rate per 100 patient years; NE: number of events; SS: Safety Set.

References:

1. Keystone E. Arthritis Rheum 2008;58:3319–29;
2. Smolen J. Ann Rheum Dis 2009;68:797-804;
3. Saraux A. Ann Rheum Dis 2017;76:786–7.

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Disclosure: A. Saraux, UCB Pharma, 5; R. M. Flipo, UCB Pharma, 5; F. Fagnani, UCB Pharma, 5; G. Cukierman, UCB Pharma, 3; I. Bru, UCB Pharma, 3; J. M. Joubert, UCB Pharma, 3; J. C. Schuller, UCB Pharma, 3; J. Massol, None; B. Combe, Merck, Pfizer, Roche-Chugai, 2, 5, 8, Bristol-Myers Squibb, Celgene, Eli Lilly, Novartis, UCB Pharma, 5, 8.

The JAK1-Selective Inhibitor Filgotinib Reverses the Disease-Associated Transcriptional Profile Found in the Blood of Patients with Active Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Filgotinib (FIL), an oral JAK1- selective inhibitor, has shown good safety and efficacy in active rheumatoid arthritis (RA) patients with inadequate response to MTX in two phase 2b studies: with methotrexate (DARWIN 1) and as monotherapy (DARWIN 2). To better understand and define the differences in molecular pathways in these RA patients, their correlation to disease severity, and the impact of FIL on these pathways, a large-scale RNA sequencing study was conducted.

Methods: PAX gene blood samples from 150 RA patients in DARWIN 1 (D1) on either a stable dose of MTX and placebo (PBO) or FIL 200mg once daily (QD); and 92 RA patients in DARWIN 2 (D2) on either PBO or FIL monotherapy 100mg or 200mg QD, were collected and analyzed at baseline, week 1 and/or week 12. RNA in whole blood was sequenced (Illumina HiSeq 2500) after globin depletion. Differential gene expression analysis was performed on all time-paired subject data after subtracting gene expression changes in the PBO group. Pathway analysis was performed using GSEA and GO enrichment. Spearman's rank correlation of gene expression to disease activity score (DAS28-CRP or VectraDA) was calculated on samples without missing values to define disease-associated molecular pathways. A false-discovery rate (FDR) of 10% was applied for all analyses.

Results: Of the 14,984 genes evaluated, 6,413 genes correlated with DAS28-CRP or VectraDA baseline disease activity and defined a Transcriptional Disease Profile (TDP). FIL treatment reversed the expression of 70% of the TDP genes in D1 and 74% in D2, with 3,801 (59%) reversed in both D1 and D2. Of the 607 genes differentially expressed in D1 or 2, FIL significantly reversed 337 genes in the TDP, suggesting an impact on disease biology with or without MTX. DAS28-CRP or VectraDA-associated genes reversed by FIL were enriched in processes for neutrophil and granulocyte activation, blood coagulation and inflammatory responses. Genes associated with innate immune responses and c-Jun N-terminal kinase signaling correlated with the TDP but were not significantly impacted by FIL. Following FIL treatment, disease-correlated gene set enrichment scores were also significantly reversed for PD1 signaling, JAK/STAT signaling via IL-6, epithelial-mesenchymal transition, and extracellular matrix regulation. Patients with increased expression of a RA-associated interferon gene set showed a reduced clinical response (median ACR-N) at 12 weeks with PBO (D1 p=0.15, D2 p=0.35) but trended toward an increased clinical response with FIL (D1 p=0.049, D2 p=0.33). Patients receiving FIL showed a reduced interferon profile at 12 weeks (D1 p =0.032, D2 p < 0.001), while no significant change was observed for patients on PBO.

Conclusion: Disease-associated molecular pathways relevant to DAS28-CRP and VectraDA were shown to be significantly improved at 12 weeks after FIL therapy. This work helps elucidate the molecular correlates of RA disease activity as well as the selective impact of FIL on key relevant pathways. Consistent with previous data, a blood based RA interferon signatures was prognostic for reduced clinical response with PBO and here predicted and showed an improved response with FIL.

Disclosure: P. C. Taylor, Celgene, Eli Lilly, Galapagos, UCB, 2, AbbVie, Eli Lilly, Galapagos, GlaxoSmithKline, Pfizer Inc, UCB, Biogen, Sandoz, Novartis, Janssen, Gilead Sciences Inc, 5; B. Downie, Gilead Sciences Inc, 1, 3; L. Zhuo, Gilead Sciences Inc, 1, 3; Y. Gindin, Gilead Sciences Inc, 1, 3; J. Tarrant, Gilead Sciences Inc, 1, 3; J. Liu, Gilead Sciences Inc, 1, 3; R. Galien, Galapagos, 3; A. M. Mirza, Gilead Sciences Inc, 1, 3.

GS-9876, a Novel, Highly Selective, SYK Inhibitor in Patients with Active Rheumatoid Arthritis: Safety, Tolerability and Efficacy Results of a Phase 2 Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Spleen tyrosine kinase (SYK) mediates immunoreceptor signaling and is essential in activation of cells including B lymphocytes, monocytes, macrophages, dendritic cells, and osteoclasts. SYK may play an important role in the initiation and progression of autoimmune diseases, including rheumatoid arthritis (RA) and lupus. GS-9876 is a novel, potent, highly selective, oral inhibitor of SYK in phase 2 trials for autoimmune diseases.

Methods: Patients with active RA with prior inadequate response to methotrexate (MTX) or a biologic anti-rheumatic drug were randomized 1:1:1:1 to receive GS-9876 30 mg, GS-9876 10 mg, selective JAK inhibitor filgotinib (FIL) 200 mg or matching placebo once daily for 12 weeks on a stable background of oral MTX. The primary endpoint for GS-9876 was the change in DAS28(CRP) at week 12. Pharmacokinetics (PK) and various biomarkers were evaluated at several time points, including VectraDA and stimulation of whole blood in TruCulture (Myriad RBM) tubes.

Results: A total of 83 patients received study drug and 79 completed the study. Fourteen patients (16.9%) were male and 69 (83.1%) were female. The majority were white (77 patients, 92.8%). The mean (SD) age at baseline was 55 (11.5) years (range 18 to 73). The primary and secondary endpoints are reported in Table 1. For DAS28(CRP), the mean (SD) at baseline was 5.75 (0.961) with a median of 5.69; a statistically significant reduction at week 12 was observed only in patients receiving FIL as compared to placebo (Table 1). Adverse events (AE) were reported across all groups (37.5% in the combined GS-9876 arms, 38.1% in FIL, 40.9% in placebo). No deaths or serious AE were reported. Plasma exposures of all study drugs were comparable to those observed in healthy subjects and historical data. *Ex vivo* stimulated whole blood identified differential responses between GS-9876 and placebo.

Conclusion: Clinical efficacy of GS-9876 in RA was not observed, but GS-9876 was safe and well-tolerated over a 12 week period in patients with active RA on MTX. FIL showed favorable safety and clinical efficacy consistent with prior data, validating the study concept and design. Additionally, biomarker changes with GS-9876 support the continuation of studies in lupus-related diseases.

Table 1. Key endpoints at week 12; *p (compared to placebo)

	DAS28(CRP) Primary endpoint (mean change from baseline to week 12)	ACR20/50/70 Secondary endpoints (% achieving at week 12)	HAQ-DI Secondary endpoint (mean change from baseline to week 12)
Placebo	-1.36 (1.044)	40.9 / 22.7 / 13.6	-0.39 (0.389)
GS-9876 10 mg	-0.78 (1.119)	25.0 / 20.0 / 15.0	-0.18 (0.800)
GS-9876 30 mg	-1.26 (1.276)	35.0 / 20.0 / 5.0	-0.46 (0.480)
Filgotinib 200 mg	-2.46 (1.242); *p=0.002	81.0 / 47.6 / 38.1	-0.70 (0.649)

Disclosure: A. J. Kivitz, Novartis, 1, AbbVie, Janssen, Pfizer, UCB, Genzyme, Sanofi, Regeneron, Boehringer-Ingelheim, Sun Pharma, 5, Celgene, Novartis, Genentech, Merck, Horizon, Flexion, Ironwood, Regeneron, Sanofi, Pfizer, 8; D. P. Mehta, None; F. Matzkies, Gilead Sciences, Inc., 1, 3; A. Mozaffarian, Gilead Sciences, Inc., 1, 3; R. Kunder, Gilead Science, Inc, 1, 3; J. Di Paolo, Gilead Sciences, 1, 3; N. Mozaffarian, Gilead Science Inc, 1, 3; S. Hsueh, Gilead Sciences, Inc., 1, 3; J. Kim, Gilead Sciences, Inc., 1, 3; W. Jiang, Gilead Sciences, Inc., 1, 3; L. Liu, Gilead Sciences, Inc., 1, 3; J. S. Sundry, Gilead Sciences, Inc., 1, 3; M. C. Genovese, Gilead, Galapagos, Abbvie, Lilly, Pfizer, 2, Gilead, Galapagos, Abbvie, Lilly, Pfizer, 5.

Exposure-Efficacy Analysis in DMARD Inadequate Response Rheumatoid Arthritis Patients Treated with GSK3196165 Along with Methotrexate

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: GSK3196165 is an anti-GM-CSF mAb being developed for RA. In a phase IIb dose-finding study (NCT02504671), RA patients with inadequate response to methotrexate were administered placebo or GSK3196165 (22.5, 45, 90, 135 and 180 mg SC 5 weekly doses followed by administration every other week for 50 weeks) with background methotrexate therapy. The study results are reported in a separate abstract. This analysis aimed to characterize exposure-efficacy relationship for DAS28(CRP), ACR20 and ACR50, and describe the time course of change in DAS28(CRP).

Methods: All available PK data from 222 randomized patients and PK data from previous studies were used to develop a population PK model. ACR data at Week 12 and time-course DAS28(CRP) were used for exposure-response analyses and analysed using both graphically and model-based approaches.

Change from baseline in DAS28(CRP) and proportion of ACR20/50 responders were plotted for placebo group and quartiles of GSK3196165 steady-state trough concentrations. Longitudinal data for DAS28(CRP) was modelled using an indirect response model to describe the treatment effect, placebo effect was described by an exponential decline. Exposure-efficacy relationship for ACR20 and ACR50 at Week 12 was analysed using logistic regression analysis. PK/PD models for DAS28(CRP) and ACR20/50 were utilized to inform optimal dose and regimen for subsequent clinical trials.

Results: GSK3196165 exhibited linear PK over the tested dose range with a mean systemic clearance (CL) of 0.93 L/day and bioavailability (F) of 0.35 in healthy volunteers which is significantly higher CL and lower F than a typical monoclonal antibody. The apparent clearance in RA patients (CL/F) was 2.5 times faster than predicted, resulting in significantly lower trough levels at steady-state. The elimination half-life in RA population was estimated to be 10 days.

At Week 12, higher response for both DAS28(CRP) and ACR20/50 was associated with higher exposures of GSK3196165. The highest quartile showed a median change from baseline of 1.63 points over placebo for DAS28(CRP), while ACR20 and ACR50 showed 59% and 34% response, respectively (12% and 9% in the placebo group). Using population PK and PK/PD models, a dose of 150 mg weekly is predicted to achieve a steady state trough concentration of 2,500 ng/mL, DAS28(CRP) change from baseline of 1.67 over placebo, and ACR50 response rate of 44%.

Conclusion: GSK3196165 has high CL/F compared to typical monoclonal antibody against soluble cytokines. A clear exposure-response relationship was observed with a greater efficacy achieved at higher trough concentration. The predictions suggest that weekly SC administration of 150 mg GSK3196165 can be associated with the clinically-meaningfully higher response rate in both DAS28(CRP) and ACR50 compared with the observed data in study NCT02504671. Further studies are now required to confirm the expected clinical benefit of increased exposure with weekly dosing of GSK3196165 in patients with RA.

Disclosure: A. Gupta, GlaxoSmithKline, 1, 3; C. Zecchin, GlaxoSmithKline, 1, 3; E. Fischeleva, GlaxoSmithKline, 1; M. Layton, GlaxoSmithKline, 1, 3; S. Zamuner, GlaxoSmithKline, 1, 3.

Efficacy of the Reference Biologic Agents in Two Different Types of Randomized Clinical Trials: 1/ the Ones Comparing Their Efficacy Vs. Placebo and 2/ the Ones Comparing Their Efficacy Vs. Biosimilar in Rheumatoid Arthritis: A Systematic Review of Literature and Meta-Analysis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

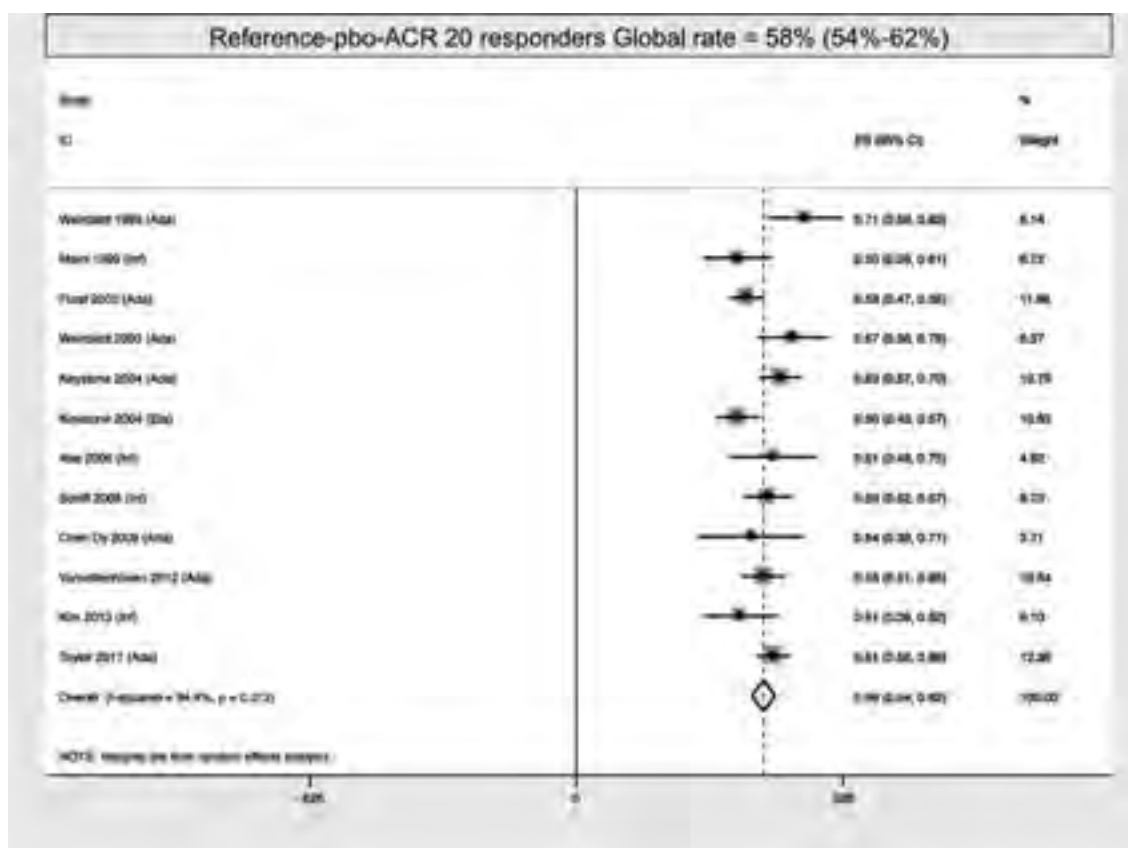
Session Type: ACR Poster Session C

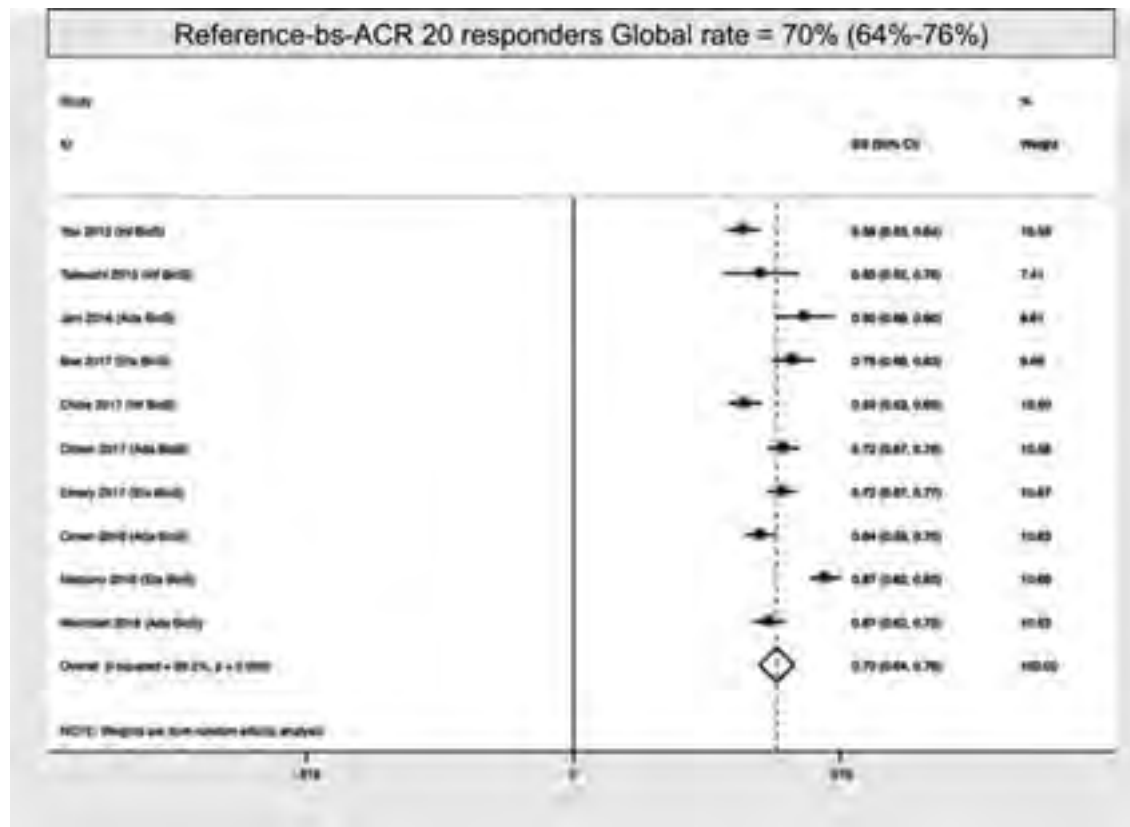
Session Time: 9:00AM-11:00AM

Background/Purpose: Recent randomized clinical trials (RCTs) have shown similar efficacy of biosimilar agents compared to reference agents. Is the efficacy of reference biologic agents different in pivotal RCTs and in recent RCTs comparing these agents vs biosimilar?

To compare the reference agent efficacy (infliximab, etanercept, adalimumab, rituximab) in pivotal RCTs (reference agent vs. placebo), with their efficacy in non-inferiority RCTs (reference agent vs. biosimilar), in rheumatoid arthritis (RA).

Methods: We searched in MEDLINE and EMBASE (until March 2018) for randomized, double-blind, placebo-controlled (Reference-pbo group) or biosimilar controlled trials (Reference-bs group) in rheumatoid arthritis. We included the RCTs in methotrexate/disease-modifying anti-rheumatic drug incomplete or inadequate responders (MTX/DMARD-IR). RCTs in monotherapy, in MTX-naïve patients, and biologics incomplete or inadequate responders (bDMARD-IR) were excluded. The primary endpoint was the American College of rheumatology 20% response criteria (ACR 20) of reference agents. We calculated the global rate of ACR 20 responders in Reference-pbo group and in Reference-bs group by performing a





meta-analysis using the inverse variance approach with fixed or random effect model according to heterogeneity estimation.

Results: We included 22 articles within the 783 found: 12 in Reference-pbo group, 10 in Reference-bs group. We excluded Rituximab because Rituximab-bs trials (3) were only in bDMARD-IR patients. Global rate of ACR 20 response of the reference biologic agents is 58% (54%-62%) in Reference-pbo group and 70% (64%-76%) in Reference-bs group. Global rate of ACR 50 response of the reference biologic agents is 34% (30%-39%) and 44% (37%-51%) in Reference-pbo and Reference-bs groups, respectively. The time frame was comparable in the two groups: mostly 24 weeks. The inclusion criteria in both groups were similar. The characteristics of the population (disease duration, disease activity, seropositivity % and MTX dose) in both groups were similar.

Conclusion: The efficacy of reference agents is better in recent non-inferiority RCTs where all patients were treated with the reference agents or its biosimilar, than in pivotal RCTs where the patients could potentially be treated with the biologic agents or a placebo. Inclusion criteria or characteristics of the population in these different trials seem comparable. We believe that a nocebo effect could explain this difference.

Disclosure: L. Lopez, None; C. Richez, None; M. E. Truchetet, None; B. Bannwarth, None; T. Barnette, None; T. Schaefferbeke, None.

Abstract Number: 2521

A Randomized, Double-Blind Phase III Study Comparing the Efficacy, Safety and Immunogenicity of PF-06438179/GP1111 (Ixifi™), an Infliximab Biosimilar, and Infliximab Reference Product (Remicade®) in Patients with Moderate to Severe Active RA: Results from Week 54 to Week 78

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: PF-06438179/GP1111 (IFX-PF) is an infliximab (IFX) biosimilar for the treatment of immune-mediated inflammatory diseases, including RA. This randomized, double-blind, comparative clinical study evaluated the efficacy, safety and immunogenicity of IFX-PF and IFX reference product sourced from the European Union (IFX-EU) in patients (pts) with moderate to severe active RA with inadequate response to MTX and ≤ 2 doses of 1 non-depleting, non-IFX biologic (NCT02222493). We report results from Week (Wk) 54 to Wk 78.

Methods: Pts (N=650), stratified by geographic region, were initially randomized (1:1) in treatment period 1 (TP1) to IFX-PF or IFX-EU (3 mg/kg IV at Wks 0, 2, 6, and then every 8 wks), both given with MTX (10–25 mg/wk). The primary endpoint was ACR20 at Wk 14. Secondary efficacy endpoints included ACR20 (other than at Wk 14), DAS28-CRP and other measures of clinical response or remission. At Wk 30 (beginning of TP2), patients receiving IFX-EU were blindly re-randomized (1:1) to remain on IFX-EU or transition to IFX-PF for 24 wks. During TP3 (beginning at Wk 54), all pts received open-label treatment with IFX-PF; 3 groups were evaluated in TP3 corresponding to the treatment sequence (TP1/TP2/TP3) during the study: IFX-PF/IFX-PF/IFX-PF; IFX-EU/IFX-EU/IFX-PF; IFX-EU/IFX-PF/IFX-PF.

Results: Of the pts initially randomized (TP1) (IFX-PF, n=324; IFX-EU, n=326), 566 pts entered TP2 at Wk 30. At Wk 54, all pts remaining on IFX-EU were switched to IFX-PF; 505 pts continued to participate in TP3. The majority of TP3 pts were female (79.2%) and White (78.6%). ACR20 response rates and DAS28-CRP scores were sustained and comparable across the 3 groups during TP3 (Table). IFX-PF was well tolerated during TP3; the safety profile was comparable across all 3 groups. Incidence of treatment-emergent adverse events during TP3 was 29.3% overall and 28.9% (IFX-PF/IFX-PF/IFX-PF), 30.2% (IFX-EU/IFX-EU/IFX-PF), and 29.4% (IFX-EU/IFX-PF/IFX-PF); the incidence of infusion-related reactions was 2.0% overall and 1.2%, 3.2% and 2.4% in the 3 groups, respectively. Pre-dose (TP3) anti-drug antibody (ADA) rates at Wk 54 were 44.3%, 47.6% and 53.2% for the IFX-PF/IFX-PF/IFX-PF, IFX-EU/IFX-EU/IFX-PF and IFX-EU/IFX-PF/IFX-PF groups, respectively. The incidences of pts with a first positive ADA result occurring during TP3 (6.0%, 8.0% and 6.4% for the IFX-PF/IFX-PF/IFX-PF, IFX-EU/IFX-EU/IFX-PF and IFX-EU/IFX-PF/IFX-PF groups, respectively) and overall, post-dose ADA rates in TP3 (56.9%, 63.5%, and 65.1%, respectively) were comparable among groups.

Conclusion: In line with earlier findings from this study, results from TP3 (Wks 54–78) show the absence of clinically meaningful differences in efficacy, safety and immunogenicity between treatment groups, independent of a single treatment transition from IFX-EU to IFX-PF at Wk 30 or Wk 54.

Table

ACR20 Response by Visit (TP3 ITT Population), n (%)				
Week	IFX-PF/IFX-PF/IFX-PF (N = 253)	IFX-EU/IFX-EU/IFX-PF (N = 126)	IFX-EU/IFX-PF/IFX-PF (N = 126)	Total (N = 505)
54	197 (77.9)	90 (71.4)	99 (78.6)	386 (76.4)
78	192 (75.9)	86 (68.3)	98 (77.8)	376 (74.5)
DAS28-CRP Score by Visit (TP3 ITT Population), mean (SD)				
Week	IFX-PF/IFX-PF/IFX-PF (N = 251)	IFX-EU/IFX-EU/IFX-PF (N = 125)	IFX-EU/IFX-PF/IFX-PF (N = 125)	Total (N = 501)
54	3.4 (1.32)	3.6 (1.35)	3.6 (1.26)	3.5 (1.32)
78	3.1 (1.28)	3.3 (1.30)	3.3 (1.23)	3.2 (1.27)

Abbreviations: DAS28-CRP, Disease Activity Score-28; 4 components based on high-sensitivity C-reactive protein; IFX-EU, infliximab reference product sourced from the European Union; ITT, intent to treat; N, number of subjects in the TP3 ITT population; n, number of subjects; IFX-PF, PF-06438179/GP1111; SD, standard deviation; TP3, treatment period 3.

Disclosure: S. Cohen, AbbVie Inc., Amgen; Pfizer, Genentech, Lilly, Roche, Sanofi, 2, 5; A. J. Kivitz, Novartis, 1, AbbVie, Boehringer Ingelheim, Flexion, Genzyme, Janssen, Pfizer Inc, Regeneron, Sanofi, Sun Pharma, UCB, 5, Celgene, Flexion, Genentech, Genzyme, Horizon, Ironwood, Merck, Novartis, Pfizer Inc, Regeneron, Sanofi, 8, Altoona Center for Clinical Research, 9; M. Tee, None; C. Cronenberg, Pfizer, Inc., 1, 3; M. Zhang, Pfizer, Inc., 1, 3; S. Hackley, Pfizer, Inc., 1, 3; K. Schumacher, Sandoz, 3, Novartis, 1; M. I. Rehman, Pfizer, Inc., 1, 3.

Biosimilar BI 695501 and Adalimumab Reference Product (RP) Have Similar Efficacy and Safety in Patients (pts) with Moderately-to-Severely Active Rheumatoid Arthritis (RA): Long-Term Results from a Phase IIIb Extension Study (VOLTAIRE®-RAext)

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Clinical equivalence of BI 695501 to the adalimumab RP has been shown in pts with moderately-to-severely active RA in the Phase III VOLTAIRE®-RA study (NCT02137226), through similar American College of Rheumatology 20% (ACR20) responses at Weeks (wks) 12, 24 and 48 (Cohen et al 2018. ARD <https://doi.org/10.1136/annrheumdis-2017-212245>). Here we present long-term safety, efficacy and immunogenicity data.

Methods: This 48-wk, open-label, multicenter, Phase IIIb extension study (VOLTAIRE®-RAext, NCT02640612) included 430 adults with moderately-to-severely active RA who wished to continue, and could benefit from continuing (per investigator's assessment), treatment with BI 695501 following participation in the VOLTAIRE®-RA study. All pts received 40 mg BI 695501 self-administered via pre-filled syringe every 2 wks. The primary endpoint was proportion of pts with drug-related adverse events (AEs) from the start of VOLTAIRE®-RAext to end of 10 wks' follow-up. Secondary efficacy endpoints included change from baseline in Disease Activity Score 28 (DAS28)-erythrocyte sedimentation rate (ESR), and proportion of pts achieving EULAR response, ACR/EULAR remission and ACR20 response at Wk 48 (using VOLTAIRE®-RA baseline as reference). Further endpoints included ACR50/70.

Results: All 430 pts in this study received BI 695501; 225 from the BI 695501 continuous (BI 695501-CONT), 102 from the adalimumab RP to BI 695501 switch at 24 wks (SWITCH), and 103 from the adalimumab RP continuous (RP-CONT) arms of VOLTAIRE®-RA. Baseline demographics were balanced across treatments arms in the parent study. A total of 87 (20.2%) pts experienced ≥1 drug-related AE, with a slightly lower proportion in the SWITCH arm (n=18; 17.6%) compared with BI 695501-CONT (n=48; 21.3%) and RP-CONT (n=21; 20.4%) arms (Table 1). 26 (6.0%) pts experienced ≥1 serious AE and 1 pt (BI 695501-CONT arm) experienced AEs leading to death (investigator assessed as not drug-related). Anti-drug antibody (ADA) and neutralizing antibody (nAb) data were similar between treatment arms. At Wk 48, clinical efficacy was similar irrespective of treatment arm in the parent study (Table 2). 42 (9.8%) and 36 (8.4%) pts prematurely discontinued the trial and treatment, respectively.

Conclusion: No new safety or immunogenicity findings were identified in this extension study. The clinical efficacy observed at wk 48 in VOLTAIRE®-RA (Cohen et al 2018. ARD <https://doi.org/10.1136/annrheumdis-2017-212245>) was sustained for up to 2 years in pts in the BI 695501-CONT arm, 72 wks in pts in the SWITCH arm, and 1 year in pts who switched to BI 695501 when entering VOLTAIRE®-RAext.

Table 1. Overview of treatment-emergent AEs* during VOLTAIRE®-RAext (SAF)

Pts, n (%)	BI 695501-CONT (n = 225)	SWITCH (n = 102)	RP-CONT (n = 103)	Total (n=430)
≥1 AE	116 (51.6)	34 (33.3)	43 (41.7)	193 (44.9)
≥1 drug-related AE	48 (21.3)	18 (17.6)	21 (20.4)	87 (20.2)
≥1 serious AE	14 (6.2)	4 (3.9)	8 (7.8)	26 (6.0)
AE leading to study drug discontinuation	7 (3.1)	2 (2.0)	7 (6.8)	16 (3.7)

AE = treatment-emergent adverse event.

SAF = safety analysis set.

* All AEs occurring between the start of treatment (VOLTAIRE®-RAext baseline) and 10 wks after the last dose of trial drug.

Table 2. Clinical efficacy at Wk 48 (FAS)

	BI 695501-CONT (n = 225)	SWITCH (n = 101†)	RP-CONT (n = 103)	Total (n=429)
Mean change in DAS28-ESR, from baseline*	-3.01	-2.98	-2.91	-2.98
EULAR response, n (%)	85 (37.8)	42 (41.6)	39 (37.9)	166 (38.7)
Good	112 (49.8)	52 (51.5)	56 (54.4)	220 (51.3)
Moderate No response	21 (9.3)	3 (3.0)	6 (5.8)	30 (7.0)
ACR/EULAR remission, n (%)	19 (8.4)	7 (6.9)	10 (9.7)	36 (8.4)
ACR20 response, n (%)	174 (77.3)	75 (74.3)	80 (77.7)	329 (76.7)
ACR50 response, n (%)	126 (56.0)	52 (51.5)	56 (54.4)	234 (54.5)
ACR70 response, n (%)	72 (32.0)	30 (29.7)	35 (34.0)	137 (31.9)

FAS = full analysis set.

* VOLTAIRE®-RA baseline used as the baseline reference point† One pt from the SWITCH arm was excluded from the FAS due to not having ≥ 1 DAS28 or ACR20 measurement during the trial.

Disclosure: S. Cohen, Boehringer Ingelheim, 2; N. Czeloth, Boehringer Ingelheim, 3; E. Lee, None; P. A. Klimiuk, None; N. Peter, Boehringer Ingelheim, 3; G. Jayadeva, Boehringer Ingelheim, 3.

Abstract Number: 2523

Rapid Response with Upadacitinib Treatment in Patients with Rheumatoid Arthritis and an Inadequate Response to csDMARDs or bDMARDs

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Upadacitinib (UPA), an oral JAK inhibitor selective for JAK1, demonstrated efficacy in patients (pts) with moderate to severe rheumatoid arthritis (RA) with an inadequate response (IR) to csDMARDs or bDMARDs in the SELECT-NEXT¹ and SELECT-BEYOND² trials, respectively. The purpose of the analysis was to investigate the speed of response to UPA across disease measures in csDMARD- and bDMARD-IR pts.

Methods: 661 pts in NEXT and 498 in BEYOND received UPA 15mg or UPA 30mg once daily (QD) or placebo (PBO) for 12 weeks (wks)^{1,2}. Time to first achievement of clinically meaningful outcomes, including ACR20/50, DAS28-CRP ≤ 3.2 and Low Disease Activity (LDA) measures of CDAI (≤ 10) and SDAI (≤ 11) was evaluated. The cumulative incidences of ACR20/50, DAS28-CRP ≤ 3.2 and LDA by CDAI and SDAI over 12 wks were estimated. Hazard ratios between UPA and PBO were obtained using Cox proportional hazards model with treatment group, corresponding baseline values and main stratification factors, without control for multiple comparisons. All analyses were based on observed data without imputation.

Results: Pts had a disease duration of 7 and 13 years in NEXT and BEYOND respectively.^{1,2} In BEYOND, pts were treatment-refractory as evidenced by 53% having received ≥ 2 prior bDMARDs². Median times to achieve ACR20 were similar, irrespective of pt population, being 4 wks for UPA 15mg QD and 2-3 wks for UPA 30mg QD vs 12 wks on PBO ($p < .001$). In general, the median times to achieve ACR50 and DAS28-CRP ≤ 3.2 for UPA 15mg and 30mg QD were -12 wks and -8 wks for both csDMARD-IR and bDMARD-IR pts, whereas the median was not reached for pts on PBO during the first 12 wks ($p < 0.001$, Table 1). The median time to LDA by CDAI and SDAI was -12 wks across UPA doses and populations, but was not reached for pts receiving PBO within that time. Pts receiving UPA were 2-4 times more likely to achieve clinical responses vs pts receiving PBO. In general, both UPA doses performed similarly across pt populations, with numerically quicker responses observed in pts receiving UPA 30mg vs UPA 15mg QD. Median times to achieve 20% and 50% improvements in tender and swollen joint counts were 1-2 wks and 2-4 wks respectively, for both UPA doses, irrespective of pt population. Median times to achieve 20% improvements in morning stiffness duration and severity were approximately 2 wks in each of the UPA arms vs 4 wks on PBO ($p < 0.001$).

Conclusion: Pts receiving UPA at either 15mg or 30mg QD were more likely to achieve clinical responses at significantly earlier time points when compared with pts receiving PBO. Irrespective of being csDMARD-IR or bDMARD-IR, times to achieve various clinical responses were consistent between pt populations.

References:

1. Burmester et al; Arthritis Rheumatol 2017;69 S10
2. Genovese et al; Arthritis Rheumatol 2017;69 S1

Table 1. Summary of Median Time (in Weeks) to Achieve First Response Over 12 Weeks							
		csDMARD-IR			bDMARD-IR		
		N	Median (Q1, Q3)	HR	N	Median (Q1, Q3)	HR
ACR20	PBO	221	12.1 (3.9, NE)		169	11.9 (2.3, NE)	
	UPA 15	219	4.1 (2, 12.1)	2.1***	164	4.1 (1.3, 12.1)	2.0***
	UPA 30	216	2.4 (1.3, 8.1)	2.5***	164	2.7 (1.6, 12.1)	2.0***
ACR50	PBO	221	12.9 (12.4, NE)		169	NE (NE, NE)	
	UPA 15	219	12.3 (4.3, NE)	2.4***	164	12.7 (8, NE)	2.8***
	UPA 30	216	8.6 (4.1, 13.4)	3.4***	165	12.1 (4.1, NE)	3.6***
DAS28-CRP ≤3.2	PBO	221	NE (12.1, NE)		166	NE (12.2, NE)	
	UPA 15	214	12.1 (4.1, 13)	2.9***	163	12.2 (4.1, NE)	2.8***
	UPA 30	215	8.1 (2.6, 12.7)	3.9***	163	8.7 (4.1, 13)	3.2***
CDAI LDA	PBO	210	NE (12.1, NE)		159	NE (NE, NE)	
	UPA 15	206	12.3 (8, 13)	2.2***	156	13.1 (8.1, NE)	2.1***
	UPA 30	209	12.1 (4.1, 13.3)	2.6***	156	12.3 (4.3, NE)	2.5***
SDAI LDA	PBO	210	NE (12.1, NE)		160	NE (12.3, NE)	
	UPA 15	206	12.3 (4.1, 13)	2.6***	156	12.4 (7.7, NE)	2.2***
	UPA 30	209	12 (4.1, 13.4)	3.2***	156	12.1 (4.1, NE)	2.7***
TK68.50% Improvement	PBO	221	8.1 (2.3, NE)		169	8.1 (2.1, 12.4)	
	UPA 15	220	4.1 (2.0, 12.1)	1.6***	164	4.1 (1.3, 12.1)	1.5**
	UPA 30	216	4.1 (2.1, 8.6)	1.7***	165	4.1 (2.0, 8.4)	1.5**
SK66.50% Improvement	PBO	221	4.4 (2.1, 12.9)		169	4.1 (2.1, 12.3)	
	UPA 15	220	4.0 (1.4, 8.1)	1.5***	164	2.3 (1.3, 8.4)	1.4**
	UPA 30	216	2.2 (1.3, 8.1)	1.6***	165	3.9 (1.4, 8.1)	1.4**
HR, hazard ratio; NE (not estimatable) indicates that the response was not reached within the 12-week period. ***p<0.001							

Disclosure: O. FitzGerald, Pfizer, Abbvie, Lilly, Celgene, Novartis, BMS and Janssen, 2; Pfizer, Abbvie, Lilly, Celgene, Novartis, BMS and Janssen, 8; A. Rubbert-Roth, Abbvie, BMS, Chugai, Pfizer, Roche, Janssen, Lilly, Sanofi, Amgen,

Novartis, 5, Abbvie, BMS, Chugai, Pfizer, Roche, Janssen, Lilly, Sanofi, Amgen, Novartis, 8; **K. Chen**, AbbVie, 1, 3; **S. Meerwein**, AbbVie, 1, 3; **J. J. Enejosa**, AbbVie, 1, 3; **T. Shaw**, AbbVie Inc., 1, 3; **A. F. Wells**, AbbVie, 2, 5.

Abstract Number: 2524

Effect of Upadacitinib on Pain and Morning Stiffness in Patients with Rheumatoid Arthritis and Inadequate Response to Conventional Synthetic or Biologic Disease-Modifying Anti-Rheumatic Drugs

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

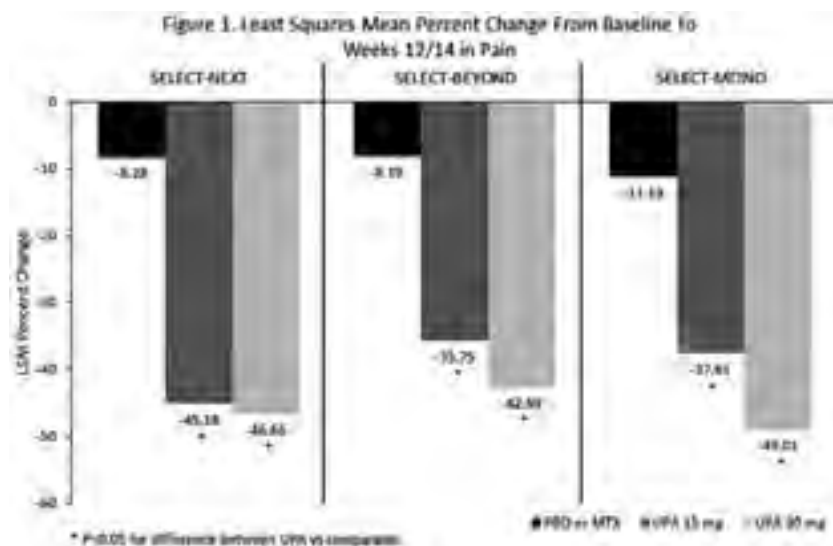
Session Type: ACR Poster Session C

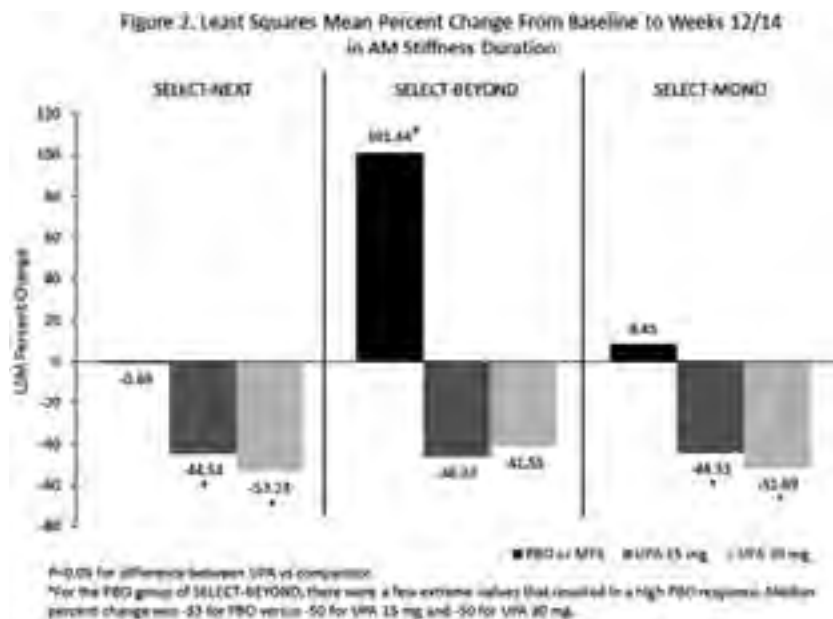
Session Time: 9:00AM-11:00AM

Background/Purpose: Although treatment with csDMARDs and bDMARDs can lead to remission in patients with RA, many patients still experience pain and morning (AM) stiffness, which have a meaningful negative impact on quality of life. We assessed the effect of upadacitinib (UPA), a selective JAK-1 inhibitor, alone or in combination with csDMARDs vs background therapy on pain and AM stiffness in patients with active RA who had an inadequate response (IR) to csDMARDs or bDMARDs.

Methods: Data from the SELECT-NEXT (NCT02675426), SELECT-BEYOND (NCT02706847), and SELECT-MONO (NCT02706951) randomized controlled trials were analyzed. Patients in NEXT (csDMARD-IR) and BEYOND (bDMARD-IR) received UPA (15 mg or 30 mg daily) or PBO with csDMARDs for 12 weeks (wks), and those in the MONO trial (csDMARD-IR) received UPA monotherapy (15 mg or 30 mg daily) or MTX (mean dose: 17 mg/wk) for 14 wks. Pain and duration of AM stiffness were assessed through 12/14 wks. Least squares mean (LSM) percent changes from baseline (BL) to wk 12/14 were based on mixed effect repeated measures models. Percentages of patients reporting $\geq 50\%$ improvement in pain, those reporting no pain or mild pain (absolute pain score < 20), and those reporting AM stiffness < 15 minutes were determined at each time point for UPA (both doses), PBO, or MTX; comparisons between groups used Cochran-Mantel-Haenszel tests with prior bDMARDs use as stratification factor.

Results: Across all 3 trials, statistically significant LSM percent changes from BL to wks 12/14 in pain and duration of AM stiffness were reported in both UPA dose groups (except AM stiffness duration in BEYOND) compared with PBO or MTX groups (**Figures 1 and 2**). Across trials, significantly ($p < 0.05$) more UPA-treated patients (15 mg: 41–51%, 30 mg: 42–56%) reported $\geq 50\%$ improvement in pain at wks 12/14 compared with PBO or MTX (19–25%). Significantly ($p < 0.05$) more UPA-treated patients (15 mg: 30–36%, 30 mg: 36–44%) reported no pain or mild pain at wks 12/14 compared with PBO or MTX (14–15%). The percentage of UPA-treated patients (15 mg: 26–42%, 30 mg: 29–43%) reporting AM





stiffness duration <15 minutes at wks 12/14 was approximately twice that in PBO or MTX (15–23%) groups. Across all measures, improvements in UPA-treated patients were evident as early as wk 2.

Conclusion: Treatment with UPA in combination with csDMARDs vs PBO resulted in significant and rapid improvements in pain and AM stiffness across different RA patient populations including csDMARD-IR and bDMARD-IR. Similar improvements vs MTX were reported when UPA was administered as monotherapy.

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Disclosure: A. F. Wells, AbbVie Inc., 2, 5, AbbVie Inc., 2; Y. C. Lee, Pfizer, Inc., 2, Eli Lilly and Co., 6; N. Tundia, AbbVie Inc., 3, AbbVie Inc., 1; J. Suboticki, AbbVie Inc., 3, AbbVie Inc., 1; K. Chen, AbbVie Inc., 3, AbbVie Inc., 1; A. Friedman, AbbVie Inc., 3, AbbVie Inc., 1; V. Strand, AbbVie, Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Celltrion, EMD Serono, Genentech/Roche, GSK, Janssen, Lilly, Novartis, Pfizer, Regeneron, Sanofi, and UCB, 5.

Abstract Number: 2525

Correlation Analysis between Sirukumab Exposure and Selected Safety Events Following Subcutaneous Administration Using Pooled Phase 3 Data in Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To characterize the exposure-response (ER) relationship between systemic exposure to sirukumab (an anti-interleukin-6 [IL-6] human monoclonal antibody) and the occurrence of selected safety events in patients with active rheumatoid arthritis (RA). The safety events of interests include serious infection, clinical laboratory abnormalities (neutropenia, thrombocytopenia, elevations of alanine aminotransferase [ALT], triglyceride, total cholesterol, low-density lipoprotein (LDL) or bilirubin, and abnormal high-density lipoprotein [HDL]), major adverse cardiovascular events (MACE), malignancy, and death.

Methods: Serious infection and laboratory abnormalities were assessed based on pooled data from 4 phase 3 trials of sirukumab (ie, data through Week 52 from SIRROUND-D and -M, and data through Week 24 from SIRROUND-T and -H). MACE, malignancy, and death were assessed through the BLA safety data cut (September 2016) to leverage as much

data available as possible due to lower incidence of events. Established population PK model of sirukumab was used to generate empirical Bayesian estimates of exposure metrics for individual patients using actual dosing records, including cumulative area under the curve (AUC), maximum (C_{max}), minimum (C_{min}) and average (C_{ave}) concentrations at steady-state. For serious infection and laboratory abnormalities, two analyses were performed, quartile analysis where the proportion of patients with events were assessed by 4 PK quartile subgroups and the distribution of PK exposure versus the occurrence of events or laboratory abnormality toxicity grade reached (worst grade experienced over the assessment period). For MACE, malignancy and death, distribution plots of PK exposure versus events were generated.

Results: Based on the distribution plots and/or the quantile analysis of pooled data, there was no trend of increasing occurrence of events with higher sirukumab exposures for MACE, malignancy, death, serious infection, triglyceride elevation or thrombocytopenia. Weak correlations were observed between sirukumab exposure and neutropenia, ALT elevation, LDL elevation, total cholesterol elevation, abnormal HDL or bilirubin elevation, where patients who had higher exposure to sirukumab tended to have more abnormal laboratory measures.

Conclusion: No apparent correlation was identified between sirukumab exposure and MACE, malignancy, and death in RA patients receiving up to 5 years of SC sirukumab treatment. Small ER trends were observed for neutropenia, ALT elevation and abnormal lipid parameters, which were consistent with the known modulation effects of anti-IL6 agents as reported for other anti-IL-6 biologics in patients with RA.

Disclosure: Y. Xu, Janssen Research & Development, LLC., 1, 3; Y. Zhuang, Janssen Research & Development, LLC., 1, 3; C. Hu, Janssen Research & Development, LLC., 1, 3; B. Hsu, Janssen Research & Development, LLC., 1, 3; Z. Xu, Janssen Research & Development, LLC., 1, 3; A. Sharma, Janssen Research & Development, LLC., 1, 3; H. Zhou, Janssen Research & Development, LLC., 1, 3.

Abstract Number: 2526

Revealing and Addressing Knowledge Gaps Regarding Biosimilars in Rheumatology Practice with Targeted Continuing Education and Patient Surveys

Katie Robinson and Robert Esgro, Vindico Medical Education, Thorofare, NJ

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: With the recent introduction of biosimilars in the US market, providers lack knowledge of how these agents compare to reference biologics and the implications for clinical practice. Targeted continuing education (CE) is a suitable platform to assess knowledge of and attitudes towards biosimilars among providers of patients with rheumatic disease as well as to address persisting gaps towards enhanced patient care.

Methods: Vindico Medical Education partnered with Kynectiv, Inc. to provide an interactive CE activity targeted to rheumatologists, internists, and pharmacists who care for patients with rheumatoid arthritis (RA). A survey of 17 patient influencers representative of over 650,000 patients with RA was also sent to gauge alignment of patient/provider views of biosimilars. Data was collected from October 2016 through October 2017.

Results: Overall, 49% of providers (n=598) indicated that their knowledge regarding the differences between biosimilars and reference biologics was fair or poor; the gap was more striking among pharmacists (n=186) versus rheumatologists (n=161). Similarly, 66% lacked knowledge of the regulatory pathway for biosimilars, though there was minimal difference across disciplines. Despite these knowledge gaps, nearly 78% of rheumatologists report willingness to prescribe biosimilars. Regarding pharmacy-level substitution of biosimilars, 57% of pharmacists agree that it should be allowed without restriction if deemed interchangeable by the FDA, though only 16% of rheumatologists agreed. Instead, most rheumatologists felt that a biosimilar should be substituted only if the prescriber was informed. Regarding patient concerns about biosimilars, physicians and pharmacists over-estimated concerns regarding decreased efficacy and under-estimated concerns regarding side effects. The greatest concern among patients was being forced to switch from a reference biologic to a biosimilar due to payor restrictions. Importantly, following completion of the activity, there was an 84% relative increase in knowledge regarding biosimilars, and 87% had begun talking to patients about biosimilars.

Conclusion: Physicians and pharmacists lack knowledge regarding the approval and regulation of biosimilars as well as how these agents differ from reference biologics. In addition, they do not recognize patient concerns regarding biosimilars.

These knowledge and practice gaps were closed via participation in this targeted CE activity, demonstrating the continued need for CE to activate learning and ensure the proper use of biosimilars.

Disclosure: K. Robinson, None; R. Esgro, None.

Abstract Number: 2527

Long-Term Safety with Sarilumab Plus Conventional Synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs) and Sarilumab Monotherapy in Rheumatoid Arthritis (RA): An Integrated Analysis with 9,000 Patient-Years (Pt-Yrs) of Follow-up

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Sarilumab has shown efficacy in RA both as monotherapy and in combination with csDMARDs in Phase 3 trials. We assessed long-term safety from the sarilumab clinical development program in adult pts with RA who received sarilumab+csDMARD or sarilumab monotherapy from: MOBILITY (NCT01061736); TARGET (NCT01709578); ASCERTAIN (NCT01768572); MONARCH (NCT02332590); ACT11575 (NCT01217814); ONE (NCT02121210); COMPARE (NCT01764997); EASY (NCT02057250); and an ongoing open-label extension EXTEND (NCT01146652), which enrolled pts completing originator studies.

Methods: Data (cut-off Jan 30, 2018) were pooled from pts on sarilumab+csDMARD (N=2887) or sarilumab monotherapy (N=471). Pts had received sarilumab 200 mg or 150 mg q2w SC, except 151 pts from MOBILITY Part A who received 100 mg qw, 150 mg qw, or 100 mg q2w. Treatment-emergent (TE) adverse events (AEs), AEs of special interest (AESI), and discontinuations were assessed.

Results: Baseline characteristics were similar between sarilumab+csDMARD and monotherapy pools (mean age 52 yrs; 81–83% female). At baseline, mean RA duration was 9.4 vs 8.3 yrs in combination and monotherapy pools, respectively, with 38.7% vs 8.5% of pts having received prior bDMARDs. Cumulative drug exposure was 7,985.5 vs 798.7 pt-yrs, with maximum duration 7.3 vs 3.5 yrs for sarilumab+csDMARD vs monotherapy, respectively. Exposure-adjusted rates of TEAEs, serious AEs, and TEAEs leading to discontinuations were similar between pools (Table). Infections were the most common AESI. Serious infection event rates were 3.7 vs 1.0/100 pt-yrs for combination vs monotherapy, respectively, and not associated with decreased absolute neutrophil counts (ANC). Incidences of ALT >3x upper limit of normal were 10.3% and 5.5% for sarilumab+csDMARD and monotherapy, and ANC <1.0 Giga/L were 12.7% and 14.9%, respectively. Rates of confirmed GI perforation for combination vs monotherapy were 0.1 vs 0/100 pt-yrs. Analyzing data by 6-month intervals showed no increase in rate over time for serious infections, malignancy, major adverse cardiac events, or ANC <1.0 Giga/L (Figure).

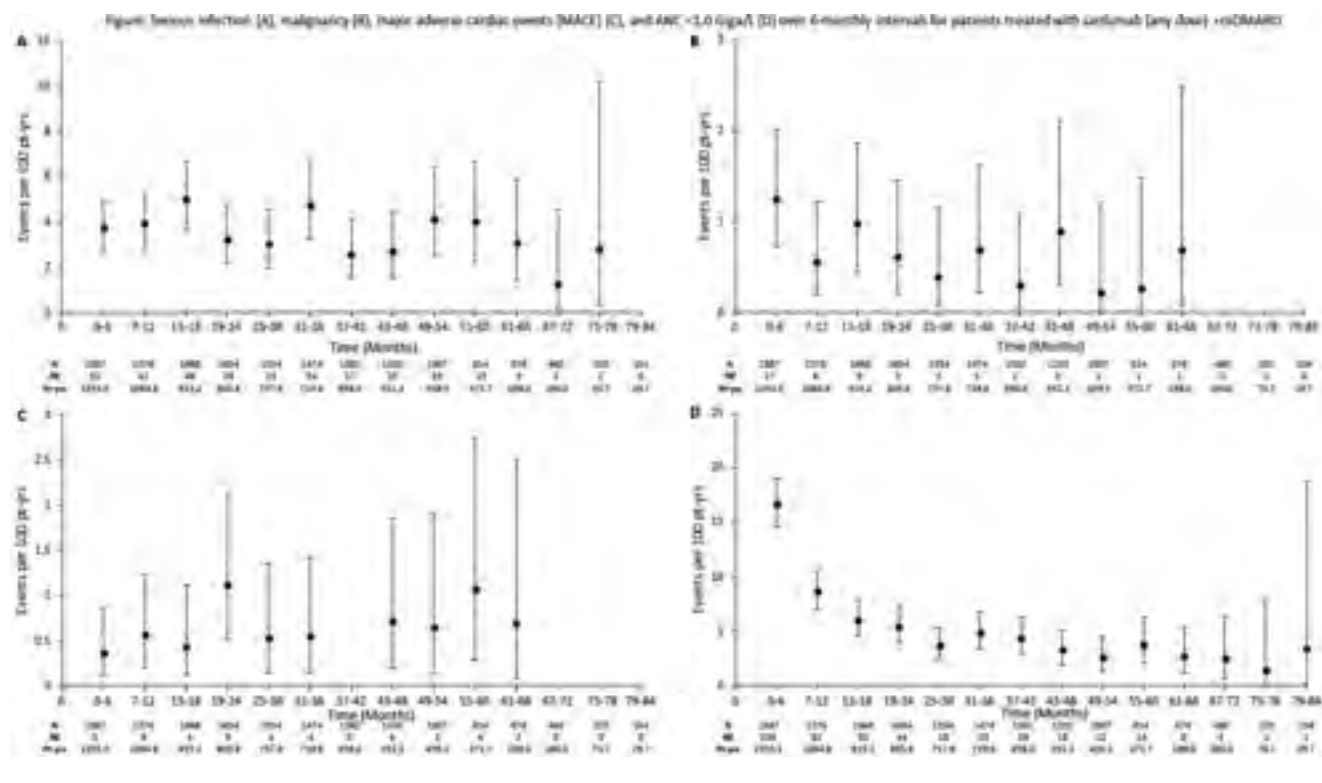
Conclusion: The long-term safety profile of sarilumab (a human IL-6R blocker recently approved for the treatment of RA), either as monotherapy (observed for >3.5 yrs) or with csDMARD, (observed for >7 yrs) remains stable and consistent with the anticipated profile of an IL-6R α blocker.

Acknowledgements: Study funding and medical writing support (Julie Gray, Adelphi Communications) provided by Sanofi and Regeneron Pharmaceuticals, Inc.

Table. Overview of safety analysis from the two pooled data sets sarilumab (any dose) +csDMARD and sarilumab monotherapy (any dose)

	Sarilumab+csDMARD (N=2887)	Sarilumab monotherapy (N=471)
Safety overview: (patients/100 pt-yrs)a		
TEAEs	2489/1726 (144.2)	386/254.3 (151.8)
Serious TEAEs	685/7270 (9.4)	52/770.4 (6.7)
TEAEs leading to death	31/8187 (0.4)	5/812.3 (0.6)
TEAEs leading to discontinuation	705/8061 (8.7)	53/804.9 (6.6)
AESI: (events/100 pt-yrs)b		
	Pt-yrs=8187.7	Pt-yrs =812.4
Infections	4451 (54.4)	446 (54.9)
Serious Infections	301 (3.7)	8 (1.0)
Opportunistic Infections	76 (0.9)	6 (0.7)
Herpes zoster	60 (0.7)	8 (1.0)
Tuberculosis	4 (0.0)	1 (0.1)
Leukopenia	1482 (18.1)	244 (30.0)
Thrombocytopenia	147 (1.8)	8 (1.0)
Hepatic disorders	726 (8.9)	58 (7.1)
Confirmed GI perforations	9 (0.1)	0
Elevation in lipids	498 (6.1)	18 (2.2)
Major adverse cardiovascular event	45 (0.5)	2 (0.2)
Hypersensitivity	444 (5.4)	48 (5.9)
Anaphylaxis	0	0
Injection site reactions	1934 (23.6)	279 (34.3)
Malignancy	56 (0.7)	5 (0.6)
Malignancy excluding NMSC	38 (0.5)	4 (0.5)
Lupus-like syndrome	5 (0.1)	0
Demyelinating disorders	0	1 (0.1)

GI, gastrointestinal; NMSC, non-melanoma skin cancer; ^aexposure period is cumulative time at risk of first event; ^bAESI were investigator reported; exposure period is cumulative total TEAE period; ^call cases of herpes zoster reported to date were localized; herpes zoster and tuberculosis were reported as opportunistic infections per protocol (not per clinical judgment); ^dindividual events were reported and laboratory abnormalities were not necessarily persistent; ^eMACE includes cardiovascular death, myocardial infarction, stroke, hospitalization for either unstable angina and/or transient ischemic attack.



Disclosure: R. Fleischmann, AbbVie, Amgen, AstraZeneca, BMS, Celgene, EMD-Serano, Eli Lilly, Merck, Novartis, Pfizer, Roche, Sanofi-Genzyme, UCB, 2, AbbVie, ACEA, Amgen, BMS, GSK, Eli Lilly, Novartis, Pfizer, Sanofi-Genzyme, UCB, 5; Y. Lin, Sanofi Genzyme, 1, 3; G. St. John, Regeneron Pharmaceuticals Inc., 1, 3; D. van der Heijde, AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Daiichi, Eli-Lilly, Galapagos, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, UCB, 5; C. Qiu, Sanofi Genzyme, 1, 3; J. J. Gómez-Reino, Biogen, Gilead, Eli Lilly, Merck Sharp & Dohme, Pfizer, Roche, 2, 5; J. A. Maldonado-Cocco, Pfizer, Merck Sharp and Dohme, Sanofi – Aventis, Novartis, Bristol-Myers Squibb, Roche, Boehringer Ingelheim, Schering

– Plough, Abbott, UCB, Eli Lilly, Gilead, 5, 8; **M. Stanislav**, R-Pharm, 5; **B. Seriola**, None; **G. R. Burmester**, AbbVie, Pfizer, UCB, Roche, 2, AbbVie, Eli Lilly, Merck Sharp & Dohme, Pfizer, Sanofi, Roche, UCB, 5, 8.

Abstract Number: 2528

A Multicenter Study Assessing the Efficacy and Safety of Repository Corticotropin Injection in Patients with Rheumatoid Arthritis: Preliminary Interim Data from the Open-Label Treatment Period

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disorder associated with chronic inflammation and commonly treated with disease-modifying anti-rheumatic drugs (DMARDs) and corticosteroids. Repository corticotropin injection (RCI) is approved in the United States as adjunctive therapy for short-term administration (during an acute episode or exacerbation) in RA (selected cases may require low-dose maintenance therapy). Here, we present interim data from the initial 12-week open-label phase of an ongoing phase 4, multicenter, 2-part study evaluating the efficacy, safety, and appropriate duration of RCI therapy in patients with persistently active RA despite receiving 1 or 2 conventional synthetic or biologic DMARDs (cs/bDMARDs) and corticosteroids.

Methods: In the open-label period (Part 1, Weeks 0–12), all enrolled patients received RCI 1 mL (80 U) subcutaneously (SC) twice per week for 12 weeks. After the initial 12 weeks, patients who achieved low disease activity (LDA; DAS28-ESR score <3.2) at Week 12 continued in the double-blind maintenance phase of the trial (Part 2), during which they were randomized 1:1 to receive either RCI 1 mL (80 U) SC or matching placebo 1 mL SC twice per week for an additional 12 weeks. The primary endpoint was the proportion of patients who achieved LDA at Week 12. Secondary endpoints included assessment of the safety and tolerability of RCI. Disease activity was also assessed by the proportion of patients who achieved 20%, 50%, and 70% improvement in American College of Rheumatology (ACR) response criteria (ACR20, ACR50, and ACR70, respectively) at Week 12.

Results: As of 10 May, 2018, 116 patients had enrolled, 100 had completed, 2 were ongoing, and 14 had discontinued the 12-week open-label period of the study. Among patients who completed the open-label period, 84% were female, and the mean age of patients was 54 years. Twelve weeks of RCI treatment resulted in >60% of patients achieving LDA; patient baseline characteristics and the results of the primary and select secondary endpoints for this interim analysis are presented in Table 1. Forty six adverse events (AEs) were reported among the 116 patients enrolled in the study, and 2 patients reported serious AEs (chest pain and pneumonia). The most common AEs were headache (n=10), urinary tract infection (n=4), hyperglycemia (n=3), and pharyngitis (n=3).

Table 1. Interim Results at Baseline and at Week 12 for Patients Who Completed the Open-label Period (N=100)

Endpoints	Baseline	Week 12
LDA (DAS28-ESR <3.2)	1%	61%
DAS28-ESR score, mean	6.3	3.5
Tender joint count,* mean	14.8	3.5
Swollen joint count,* mean	11.1	2.6
ACR20		85%
ACR50		66%
ACR70		34%

* Sub-components of the 28-joint count, a measure used to determine the DAS28-ESR score and ACR criteria scale.

Conclusion: In this ongoing study, RCI was a potentially safe and effective treatment option in patients with persistently active RA who were nonresponsive to corticosteroids and cs/bDMARD treatment, as demonstrated by improvement in multiple measures of disease activity during a 12-week open-label period.

Disclosure: **R. Fleischmann**, None; **D. E. Furst**, BMS and Genentech/Roche, 2, Amgen, UCB, and Pfizer, 9; **R. Brasington**, Pfizer, Novartis, Amgen, Mallinckrodt, Sanofi-Genzyme, 9, Boehringer-Ingelheim, 9; **E. Connolly-Strong**, Mallinckrodt ARD, Inc., 1, 3; **J. Liu**, Mallinckrodt ARD, Inc., 1, 3; **M. E. Barton**, Mallinckrodt ARD, Inc., 1, 3.

Liver Function Test Levels with Sarilumab Treatment in Phase 3 Trials: Analysis By Baseline Liver Function Test (LFT) Level

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Sarilumab showed efficacy in RA and superiority to placebo and adalimumab in Phase 3 trials. This post hoc analysis investigated LFT levels in three sarilumab Phase 3 trials.

Methods: The adalimumab-controlled MONARCH (NCT02332590) and placebo-controlled TARGET (NCT01709578) and MOBILITY (NCT01061736) studies allowed alanine- (ALT) or aspartate aminotransferase (AST) levels $\leq 1.5\times$ upper limit of normal (ULN) at entry. Patients who received ≥ 1 dose of sarilumab and had ≥ 1 post-baseline measurement of ALT or AST were categorized by baseline and maximum on-study ALT, AST, total bilirubin, and alkaline phosphatase (AP).

Results: In MOBILITY (MTX-IR), among patients with normal ALT at baseline (n=1085), maximum on-study ALT $>3\times$ ULN was seen in 8.0% (n=29) and 7.8% (n=28) of patients in sarilumab 150 and 200 mg + MTX groups, respectively, versus 2.2% (n=8) with placebo + MTX (Table 1). Among patients with ALT $>ULN$ at baseline (n=106), maximum on-study ALT $>3\times$ ULN was seen in 23% (n=9) and 16% (n=6) in sarilumab 150 and 200 mg + MTX groups, respectively, versus 3.6% (n=1) with placebo + MTX. In the monotherapy MONARCH study, the proportion of patients with maximum on-study ALT $>3\times$ ULN was 2.4% (n=4) in patients with normal baseline ALT and 15% (n=2) in patients with baseline ALT $>ULN$ in the sarilumab group, and 1.7% (n=3) and 20% (n=2), respectively, in the adalimumab group (Table 2). ALT elevations in TARGET (TNF-IR; Table 3) were less frequent compared with MOBILITY. There were no cases of Hy's Law attributable to sarilumab treatment. Laboratory investigations (including LFT elevations) led to treatment discontinuation in 0.2–0.6% of placebo- and 0.5–2.8% of sarilumab-treated patients.

Conclusion: LFT elevations with sarilumab, an IL-6R blocker recently approved for the treatment of RA, were more likely in combination with csDMARDs than with monotherapy, and more likely in patients with baseline elevations. Incidence of ALT $>3\times$ ULN was similar between monotherapy sarilumab and adalimumab. Importantly, LFT elevations rarely necessitated treatment discontinuation

Acknowledgements: Study funding and medical writing support (Matt Lewis, Adelphi Communications) provided by Sanofi and Regeneron Pharmaceuticals, Inc.

Table 1. Maximum on-treatment LFTs in 52-week MOBILITY study of sarilumab+csDMARDs in patients with RA and inadequate response to MTX (MTX-IR)

	Placebo (N=397)		Sarilumab 150 mg (N=401)		Sarilumab 200 mg (N=396)	
	Baseline		Baseline		Baseline	
ALT	LLN–ULN n=367 (92%)a	>ULN n=28 (7.1%)a	LLN–ULN n=361 (90%)a	>ULN n=40 (10%)a	LLN–ULN n=357 (90%)a	>ULN n=38 (9.6%)a
Maximum on-treatment value, n (%)b						
LLN–ULN	251 (68)	3 (11)	177 (49)	4 (10)	147 (41)	4 (11)
>ULN–3x ULN	108 (29)	24 (86)	155 (43)	27 (68)	182 (51)	28 (74)
>3x ULN–5x ULN	7 (1.9)	1 (3.6)	19 (5.3)	6 (15)	20 (5.6)	4 (11)
>5x ULN	1 (0.3)	–	10 (2.8)	3 (7.5)	8 (2.2)	2 (5.3)
AST	LLN–ULN n=381 (96%)a	>ULN n=14 (3.5%)a	LLN–ULN n=374 (93%)a	>ULN n=26 (6.5%)a	LLN–ULN n=374 (94%)a	>ULN n=20 (5.1%)a
Maximum on-treatment value, n (%)b						
LLN–ULN	307 (81)	4 (29)	216 (58)	4 (15)	209 (56)	8 (40)
>ULN–3x ULN	71 (19)	10 (71)	145 (39)	18 (69)	157 (42)	10 (50)

Table . (Cont'd)

	Placebo (N=397)		Sarilumab 150 mg (N=401)		Sarilumab 200 mg (N=396)	
	Baseline		Baseline		Baseline	
>3x ULN–5x ULN	3 (0.8)	–	7 (1.9)	3 (12)	6 (1.6)	1 (5.0)
>5x ULN	–	–	6 (1.6)	1 (3.8)	2 (0.5)	1 (5.0)
Total bilirubin	LLN–ULN	>ULN	LLN–ULN	>ULN	LLN–ULN	>ULN
	n=370 (93%)a	n=0	n=370 (92%)a	n=2 (0.5%)a	n=370 (93%)a	n=1 (0.3%)a
Maximum on-treatment value, n (%)b						
LLN–ULN	361 (98)	–	342 (92)	–	335 (91)	–
>ULN–1.5x ULN	9 (2.4)	–	17 (4.6)	–	23 (6.2)	1 (100)
>1.5x ULN–2x ULN	–	–	8 (2.2)	2 (100)	9 (2.4)	–
>2x ULN	–	–	3 (0.8)	–	3 (0.8)	–
AP	LLN–ULN	>ULN	LLN–ULN	>ULN	LLN–ULN	>ULN
	n=359 (90%)a	n=38 (9.6%)a	n=366 (91%)a	n=34 (8.5%)a	n=350 (88%)a	n=45 (11%)a
Maximum on-treatment value, n (%)b						
<LLN	–	–	–	–	1 (0.3)	–
LLN–ULN	321 (89)	–	338 (92)	12 (35)	326 (93)	21 (47)
>ULN–1.5x ULN	36 (10)	29 (76)	22 (6.0)	14 (41)	19 (5.4)	19 (42)
>1.5x ULN	2 (0.6)	9 (24)	6 (1.6)	8 (24)	4 (1.1)	5 (11)

Patients with baseline value <LLN (all LFTs) or missing (total bilirubin or AP) are not shown; ^apercentage of treatment group; ^bpercentage of baseline category within treatment group. LLN, lower limit of normal

Table 2. Maximum on-treatment LFTs in 24-week MONARCH study of sarilumab monotherapy in patients with active RA

	Adalimumab 40 mg q2w (N=184)		Sarilumab 200 mg q2w (N=184)	
	Baseline		Baseline	
ALT	LLN–ULN	>ULN	LLN–ULN	>ULN
	n=174 (95%)a	n=10 (5.4%)a	n=169 (92%)a	n=13 (7.1%)a
Maximum on-treatment value, n (%)b				
LLN–ULN	137 (79)	2 (20)	112 (66)	2 (15)
>ULN–3x ULN	33 (19)	6 (60)	53 (31)	9 (69)
>3x ULN–5x ULN	3 (1.7)	–	3 (1.8)	2 (15)
>5x ULN	–	2 (20)	1 (0.6)	–
Missing	1 (0.6)	–	–	–
AST	LLN–ULN	>ULN	LLN–ULN	>ULN
	n=176 (96%)a	n=8 (4.3%)a	n=175 (95%)a	n=7 (3.8%)a
Maximum on-treatment value, n (%)b				
LLN–ULN	153 (87)	3 (38)	144 (82)	1 (14)
>ULN–3x ULN	19 (11)	4 (50)	29 (17)	6 (86)
>3x ULN–5x ULN	3 (1.7)	–	2 (1.1)	–
>5x ULN	–	1 (13)	–	–
Missing	1 (0.6)	–	–	–
Total bilirubin	LLN–ULN	>ULN	LLN–ULN	>ULN
	n=170 (92%)a	n=1 (0.5%)a	n=164 (89%)a	n=1 (0.5%)a
Maximum on-treatment value, n (%)b				
LLN–ULN	165 (97)	–	150 (91)	1 (100)
>ULN–1.5x ULN	4 (2.4)	–	7 (4.3)	–
>1.5x ULN–2x ULN	–	1 (100)	5 (3.0)	–
>2x ULN	–	–	2 (1.2)	–
Missing	1 (0.6)	–	–	–
AP	LLN–ULN	>ULN	LLN–ULN	>ULN
	n=168 (91%)a	n=15 (8.2%)a	n=170 (92%)a	n=14 (7.6%)a
Maximum on-treatment value, n (%)b				
<LLN	1 (0.6)	–	1 (0.6)	–
LLN–ULN	149 (89)	3 (20)	158 (93)	7 (50)
>ULN–1.5x ULN	14 (8.3)	9 (60)	9 (5.3)	7 (50)
>1.5x ULN	3 (1.8)	3 (20)	2 (1.2)	–
Missing	1 (0.6)	–	–	–

Patients with baseline value <LLN (all LFTs) or missing (total bilirubin or AP) are not shown; ^apercentage of treatment group; ^bpercentage of baseline category within treatment group. LLN, lower limit of normal

Table 3. Maximum on-treatment LFTs in 24-week TARGET study of sarilumab+csDMARDs in patients with RA and inadequate response or intolerance to >1 TNF inhibitor

	Placebo (N=181)		Sarilumab 150 mg (N=181)		Sarilumab 200 mg (N=184)	
	Baseline		Baseline		Baseline	
ALT	LLN-ULN n=164 (91%)a	>ULN n=17 (9.4%)a	LLN-ULN n=163 (90%)a	>ULN n=18 (10%)a	LLN-ULN n=176 (96%)a	>ULN n=7 (3.8%)a
Maximum on-treatment value, n (%)^b						
LLN-ULN	129 (79)	4 (24)	98 (60)	2 (11)	92 (52)	1 (14)
>ULN-3x ULN	34 (21)	12 (71)	61 (37)	15 (83)	75 (43)	5 (71)
>3x ULN-5x ULN	1 (0.6)	1 (5.9)	3 (1.8)	1 (5.6)	6 (3.4)	1 (14)
>5x ULN	–	–	–	–	1 (0.6)	–
Missing	–	–	1 (0.6)	–	2 (1.1)	–
AST	LLN-ULN n=171 (94%)a	>ULN n=8 (4.4%)a	LLN-ULN n=177 (98%)a	>ULN n=4 (2.2%)a	LLN-ULN n=173 (94%)a	>ULN n=9 (4.9%)a
Maximum on-treatment value, n (%)^b						
LLN-ULN	147 (86)	2 (25)	132 (75)	1 (25)	125 (72)	1 (11)
>ULN-3x ULN	24 (14)	6 (75)	42 (24)	3 (75)	39 (23)	7 (78)
>3x ULN-5x ULN	–	–	2 (1.1)	–	6 (3.5)	1 (11)
>5x ULN	–	–	–	–	1 (0.6)	–
Missing	–	–	1 (0.6)	–	2 (1.2)	–
Total bilirubin	LLN-ULN n=169 (93%)a	>ULN n=0	LLN-ULN n=175 (97%)a	>ULN n=0	LLN-ULN n=170 (92%)a	>ULN n=1 (0.5%)a
Maximum on-treatment value, n (%)^b						
LLN-ULN	164 (97)	–	163 (93)	–	150 (88)	–
>ULN-1.5x ULN	4 (2.4)	–	9 (5.1)	–	13 (7.6)	–
>1.5x ULN-2x ULN	–	–	2 (1.1)	–	4 (2.4)	–
>2x ULN	1 (0.6)	–	–	–	2 (1.2)	–
Missing	–	n/a	1 (0.6)	n/a	1 (0.6)	1 (100)
AP	LLN-ULN n=167 (92%)a	>ULN n=14 (7.7%)a	LLN-ULN n=158 (87%)a	>ULN n=23 (13%)a	LLN-ULN n=155 (84%)a	>ULN n=29 (16%)a
Maximum on-treatment value, n (%)^b						
LLN-ULN	146 (87)	–	149 (94)	9 (39)	141 (91)	12 (41)
>ULN-1.5x ULN	18 (11)	12 (86)	6 (3.8)	11 (48)	11 (7.1)	12 (41)
>1.5x ULN	3 (1.8)	2 (14)	2 (1.3)	3 (13)	1 (0.6)	5 (17)
Missing	–	–	1 (0.6)	–	2 (1.3)	–

Patients with baseline value <LLN (all LFTs) or missing (total bilirubin or AP) are not shown; ^apercentage of treatment group; ^bpercentage of baseline category within treatment group; n/a, not applicable. LLN, lower limit of normal

Disclosure: J. Tesser, Sanofi Genzyme/Regeneron, Abbvie, 2, 8, Sanofi Genzyme/Regeneron, 5; G. St. John, Regeneron Pharmaceuticals Inc., 1, 3; T. Kimura, Regeneron Pharmaceuticals Inc., 1, 3; S. Fiore, Sanofi Genzyme, 1, 3; M. Rischmueller, Member of the Australian sarilumab advisory board, 9, Investigator on the TARGET and MOBILITY trials, 9; J. A. Maldonado-Cocco, Pfizer, Merck Sharp Dohme, Sanofi – Aventis, Novartis, Bristol Myers Squibb, Roche, Boehringer Ingelheim, Schering – Plough, Abbott, UCB, Eli Lilly, Gilead, 5, 8; J. Braun, None; J. Kaine, Sanofi Genzyme, Regeneron Pharmaceuticals Inc., 2, 5, 8.

Abstract Number: 2530

Uncovering Clinicians' Gaps and Attitudes Toward Biosimilars: Impact of a 2-Phase Educational Program

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Biosimilar agents have changed the clinical landscape in rheumatology, gastroenterology, and dermatology. We sought to measure clinicians' competence and knowledge of biosimilars and to address identified educational gaps related to their clinical application.

Table. Pain relief response for all patients and by subgroups at Week 12

	n/N (%)	All patients	Baseline Pain		TNF history		bDMARD history	
			< median (68 mm)	≥ median (68 mm)	1 TNF	>1 TNF	<3 bDMARDs	≥3 bDMARDs
≥30% pain relief	Placebo	54/172 (31.4)	27/85 (31.8)	27/87 (31.0)	35/103 (34.0)	19/66 (28.8)	47/128 (36.7)	7/44 (15.9)
	Bari 2mg	74/171 (43.3)	39/93 (41.9)	35/78 (44.9)	45/100 (45.0)	29/71 (40.8)	57/121 (47.1)	17/50 (34.0)
	Bari 4mg	101/173 (58.4)	38/74 (51.4)	63/99 (63.6)	63/102 (61.8)	38/68 (55.9)	76/128 (59.4)	25/45 (55.6)
≥50% pain relief	Placebo	30/172 (17.4)	18/85 (21.2)	12/87 (13.8)	22/103 (21.4)	8/66 (12.1)	27/128 (21.1)	3/44 (6.8)
	Bari 2mg	53/171 (31.0)	31/93 (33.3)	22/78 (28.2)	32/100 (32)	21/71 (29.6)	43/121 (35.5)	10/50 (20.0)
	Bari 4mg	61/173 (35.3)	27/74 (36.5)	34/99 (34.3)	39/102 (38.2)	22/68 (32.4)	46/128 (35.9)	15/45 (33.3)
≥70% pain relief	Placebo	12/172 (7.0)	5/85 (5.9)	7/87 (8.0)	8/103 (7.8)	4/66 (6.1)	10/128 (7.8)	2/44 (4.5)
	Bari 2mg	32/171 (18.7)	15/93 (16.1)	17/78 (21.8)	21/100 (21.0)	11/71 (15.5)	27/121 (22.3)	5/50 (10.0)
	Bari 4mg	32/173 (18.5)	13/74 (17.6)	19/99 (19.2)	24/102 (23.5)	8/68 (11.8)	26/128 (20.3)	6/45 (13.3)

Session Time: 9:00AM-11:00AM

Background/Purpose: Baricitinib (BARI) 2 mg and 4 mg once daily demonstrated significant clinical improvements compared to placebo in the phase 3 study of RA patients on 1 or 2 csDMARDs with an inadequate response or intolerance to ≥1 tumor necrosis factor (TNF) inhibitors (bDMARD-IR)(RA-BEACON).¹ In this RA population, patients often experience pain, a key factor influencing quality of life. The objective of this *post hoc* analysis was to characterize the effects of BARI on pain relief by baseline pain and RA treatment history.

Methods: 527 patients were randomized to placebo (n=176), BARI 2 mg (n=174), or 4 mg (n=177) once daily for 24 weeks. The time of the primary endpoint was Week 12. Pain was assessed using a visual analog scale (VAS, 0-100 mm) at each study visit. The proportion of patients achieving ≥30%, ≥50%, and ≥70% pain relief at Week 12 was compared between BARI 2 mg or 4 mg vs placebo using logistic models. The treatment comparisons within each subgroup category (pain < median [68] vs ≥median, number of prior TNF inhibitors [1 vs >1] and prior bDMARDs [<3 vs ≥3]) on pain relief were performed. Missing pain values were imputed using modified last observation-carried-forward (mLOCF).

Results: Mean baseline pain scores were 65, 62, and 66 mm for placebo, BARI 2 mg, and BARI 4 mg, respectively. Approximately 40% of patients had received >1 TNF inhibitor and a quarter of patients had received ≥3 bDMARDs, representing patients with highly refractory disease. At Week 12, significantly more patients achieved ≥30%, ≥50%, and ≥70% pain relief with BARI 2 mg or 4 mg vs placebo (P<0.05, for all comparisons).² Consistent results were observed regardless of baseline pain (Table). Prior TNF inhibitor history appeared to influence the achievement of ≥70% pain relief, but had limited effect on the ≥30% and ≥50% pain thresholds. Variability in response for the 3 treatment groups was observed at the different pain relief thresholds for patients with <3 vs ≥3 bDMARDs. Regardless of treatment history, patients receiving BARI 2 mg or 4 mg were more likely to reach all pain relief thresholds than placebo.

Conclusion: BARI 2 mg or 4 mg provided greater pain relief in bDMARD-IR patients with RA compared with placebo in all patients and inpatients with different baseline pain severity and prior treatment history.

References: ¹Genovese MC, et al., N Engl JMed 2016;374:1243-52; ²Taylor PC, et al., Ann Rheum Dis. 2017;76:788

Disclosure: J. E. Pope, AbbVie Inc., 5, Amgen Inc., 5, Bristol-Myers Squibb, 5, Lilly, 5, Merck & Co., 5, Novartis, 5, Pfizer, Inc., 5, Roche, 5, Sanofi, 5, Sandoz, 5, Celltrion, 5, United Chemicals Belgium, 2; A. Quebe, Eli Lilly and Company, 1, 3; B. Zhu, Eli Lilly and Company, 1, 3; L. Sun, Eli Lilly and Company, 1, 3; C. L. Gaich, Eli Lilly and Company, 1, 3; F. de Leonardis, Eli Lilly and Company, 1, 3; A. Cardoso, Eli Lilly and Company, 1, 3; M. C. Genovese, Sanofi/Genzyme, Genentech/Roche, RPharm, 2, 5.

The Efficacy and Drug Survival of the Biosimilar Infliximab (CT-P13) Compared to the Original Reference Infliximab in Inflammatory Rheumatic Diseases; Results from the Turkbio Registry

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Biosimilar infliximab (CT-P13) has been used to treat patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) in Turkey since 2013. The aim of this study was to examine its efficacy and drug survival and compare it to the original reference infliximab (inf) in patients with inflammatory rheumatic diseases based on the database from the Turkish TURKBIO registry.

Methods: All patients with RA, SpA, PsA, and other diseases receiving CT-P13 and original infliximab registered in the TURKBIO database between the dates of June 2013 and January 2017 were included in the study. Demographic information, laboratory parameters and disease indices were collected (at baseline, and months 6 and 12). We used Kaplan Meier survival curves to examine drug survival patterns.

Results: Data collected from a total number of 614 patients were analyzed (Table 1). The analysis of each treatment group was made according to gender, age, and diagnosis. In both groups most of the patients were diagnosed as having axial SpA, followed by RA, PsA and other diseases. CT-P13 group had female predominance. In patients with RA and PsA, baseline DAS28 scores were found to be higher in CT-P13 group. Baseline values of ASDAS-CRP in SpA patients and CRP in all patients were similar for both groups (Table 2). Mean CRP levels at month 6 and ASDAS scores at month 12 were found to be higher in inf group. The ratio of males was higher in axial SpA patients receiving inf, but did not statistically affect the 12th month ASDAS results. The results of the database analysis showed that the drug survival rate of CT P13 (78,4%) is higher than inf (63,6%) at year 4 (Figure 1). At 4-year follow-up, drug withdrawal was observed in both groups due to ineffectiveness (CT-P13; n=13 54,16%, inf; n=89 41,58%) and side effects (CT-P13; n=8 33,33%, inf; n=43 20,09%). In CT-P13 group, six patients had switched from inf to biosimilar and other 20 had used ≥ 1 previous biologicals. Of the 503 patients who used inf, 164 had used ≥ 1 biologicals previously.

Conclusion: The results of this study demonstrated long term higher drug survival rate of biosimilar CT-P13. The study also suggested that efficacy of CT-P13 on disease activity was similar to original infliximab in patients with inflammatory rheumatic diseases.

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Switching Patients with Arthritis from Etanercept (Enbrel) to the Biosimilar Drug, Benepali: A Single- Center Retrospective Observational Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Background/Purpose: Benepali, the etanercept biosimilar, is licenced in the UK for the same indications as the reference product, Enbrel.

In 2016, the Rheumatology Department at Blackpool Teaching Hospitals, after informing all the patients on Enbrel about Benepali, switched the patients that gave consent.

A proportion of these patients requested a switch back to Enbrel and therefore we aimed to investigate the reasons for Benepali withdrawal and if the loss of effect (LOE) is reflected in change of disease activity measures.

Figure 1: Kaplan-Meier survival curve of biosimilar infliximab and original reference infliximab ($p < 0.05$)

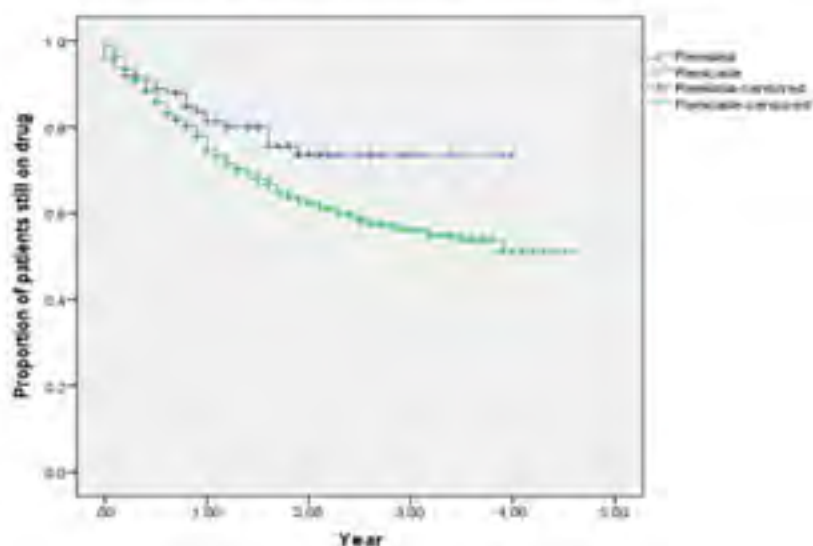


Table 2. Disease activity at baseline and months 6 and 12

	CT-P13	Infliximab	P value
DAS28, mean			
Baseline	3.95	3.47	0.007
Month 6	2.54	2.27	0.385
Month 12	2.18	2.17	0.959
CRP, (mg/L)			
Baseline	21.00	21.82	0.818
Month 6	4.06	13.09	<0.001
Month 12	10.52	9.97	0.889
ASDAS, mean			
Baseline	3.47	3.31	0.280
Month 6	1.57	1.90	0.093
Month 12	1.23	1.87	0.008

Methods: We included all the patients switched to Benepali from July 2016 to April 2018, identified from the departmental biologics database. Data were collected from patients' records.

Baseline characteristics associated with Benepali withdrawal were explored by multivariate logistic regression analysis stratified by diagnosis (RA, SpA, PsA) and included age, gender, duration of disease, co-treatment with DMARDs, concomitant Methotrexate, number of biological DMARDs (bDMARDs) before Enbrel, duration on Enbrel, number of swollen and tender joints, baseline ESR and CRP; only for RA: seropositivity for RF and/or ACPA, DAS-28 before any bDMARD, baseline DAS-28 and Patient Global Score (PGS); only for SpA: HLA-B27 status, BASDI before any bDMARD, baseline BASDI and pain Visual Analogue Score (VAS) and only for PsA: Baseline Patient (PtGA) and Physician Global Assessment (PGA).

Wilcoxon signed-rank test was performed to compare the various expressions of disease activity (DAS-28 and PGS for RA, BASDI and pain VAS for SpA, PtGA and PGA for PsA, ESR, CRP) before switching to Benepali and before Benepali withdrawal in patients with LOE.

Results: A total of 72 patients on Enbrel were switched to Benepali, of which 19 (26,4%) switched back to Enbrel after 6 months [interquartile range (IQR) 3.5- 10] on the biosimilar product (Table). All the 19 patients had remained on Enbrel until the time of data analysis [follow-up period: 12 months (IQR 7.5- 15.5)].

The reasons of withdrawal were LOE (58%), adverse events (32%), infection (5%) and difficulty using the pen device (5%). In RA, the duration on Enbrel was associated with Benepali withdrawal [OR 1.43 (95% CI 1.02, 2.00)] and no statistically significant factors were found in SpA and PsA.

For RA, LOE is reflected in the DAS-28 increase (2.99), PGS increase (40 mm), increase in tender joints (3.5) and CRP increase (2 mg/dl) (all $p < 0.05$), whereas for SpA and PsA there was no statistically significant change in disease activity measures.

Conclusion: The majority (73,6%) had a good response to Benepali, which is in keeping with the current evidence. In RA, LOE is reflected only in the subjective measures, except for CRP. Interestingly, all the patients switching back to Enbrel, stayed on this treatment, which may indicate other contributing factors in withdrawal not identified by this study, due to the limitation of the small sample size.

Table: Baseline characteristics of patients switched to Benepali

	Rheumatoid arthritis	Axial Spondyloarthritis	Psoriatic arthritis
Number, n	36	23	13
Female, n (%)	27 (75%)	7 (30%)	6 (46%)
Age, years	62 (56- 77)	56 (46- 66)	54 (51.5- 67.5)
Duration on Etanercept (Enbrel) before switching to Benepali, years	3.8 (2.3- 7.5)	5.2 (3.1- 7.5)	2.8 (2.3- 6.6)
Duration of disease before switching to Benepali, years	15 (8.2- 21)	29 (17.3- 38)	17 (12.5- 26.5)
Co-treatment with DMARDs, n (%)	32 (89%)	2 (8,7%)	9 (69,2%)
Concomitant Methotrexate, n (%)	26 (72%)	1 (4,3%)	6 (46,2%)
On other bDMARDs before Enbrel, n (%)	8 (22,2%)	4 (17,4%)	2 (15,4%)
DAS- 28 before any bDMARD	6.18 (5.72- 6.71)	NA	NA
DAS- 28 before switching to Benepali	2.87 (1.89- 3.73)	NA	NA
BASDI before any bDMARD	NA	7.01 (6.25- 8.68)	NA
BASDI before switching to Benepali	NA	2.95 (1.94- 4.85)	NA
ESR before switching to Benepali, mm/hr	12.50 (6.00- 19.75)	6.00 (2.00- 9.00)	7.00 (5.00- 26.50)
CRP before switching to Benepali, mg/dl	2.00 (1.00- 5.00)	4.00 (1.00- 7.90)	2.00 (1.00- 9.50)

Numbers are medians (interquartile ranges) unless otherwise stated
bDMARDs= biological DMARDs, NA= Not Applicable

Disclosure: A. V. Madenidou, None; A. Jeffries, Pfizer, Inc., 9; S. Varughese, None; S. Jones, None; H. Veevers, None; H. Sari- Kouzel, None; C. Rao, Pfizer, Inc., 9.

Abstract Number: 2534

Impact of Block Switch to Biosimilar Etanercept in Practice, Across Different Rheumatic Diseases

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Biosimilars of biotechnological agents represent an important opportunity to increase accessibility to these medications. Clinicians still maintain reservations regarding the similarity of their efficacy and safety in practice. Our purpose was to evaluate the clinical consequences of a block switch of etanercept (ETN) original to biosimilar in a clinical practice setting.

Methods: The study included all patients aged 18+ treated in a Tertiary Rheumatology Department with original ETN who were switched to his biosimilar following a decision by the hospital administration, accepted by rheumatologists. Disease activity and adverse events were evaluated at baseline (time of switch) and 3 months after and were compared using Paired samples T-test and Wilcoxon test, as appropriate. A $p < 0.05$ was considered statistically significant. Adaptation to the drug delivery instrument was also evaluated. Continuous variables are presented as means and categorical variables as proportions.

Results: From 98 patients treated with original ETN in our department, 89 were switched to his biosimilar. The remaining ones maintained the treatment with the reference biological product for several reasons. Twelve patients were excluded from this analysis: poor adherence to treatment ($n=3$), early interruption of treatment [$n=3$, due to surgery ($n=1$), respiratory infection ($n=1$) and suspected allergic reaction to biosimilar ($n=1$)] and 3 months observations still to be performed ($n=6$). Of the remaining 77 patients (58.4% female, mean age 55.3 ± 11.7 years), 39% had RA, 37.7% SpA, 20.8% PsA and 2.6% JIA. Disease activity was stable over the followup in patients with RA, PsA and SpA, as no statistically significant differences were observed in acute phase reactants, patient or physician global assessment between the two time points. Minor adverse events were reported by 2 patients (pain and local cutaneous reaction) and another 2 report impression of disease exacerbation that was not confirmed by clinical and analytical evaluation. Two patients reported minor infections. Good adaptation to the drug delivery instrument was reported by 93% of patients.

Table 1. Acute phase reactants, disease activity, joint count and patient and physician global assessment through follow-up

	Baseline	3 Months after switch
ESR (mm/h)f	8.50(9.80)	8.00(11.00)
CRP (mg/dL) f	0.21(0.56)	0.31(0.59)
DAS-28-ESR §*	2.08(0.97)	2.23(1.01)
Tender joint-28§	0.24(0.09)	0.45(0.10)
Swollen joint-28§	0.49 (0.12)	0.54(0.12)
PtGA (0-100)f	40.00(40.00)	40.00(33.00)
PhGA (0-100)f	7.50(11.00)	5.00(20.00)

IQR – Interquartile range; PhGA physician global assessment; PtGA- patient global assessment; SD - standard deviation; f median(IQR); § mean (SD). *Only for RA and PsA patients ($n=46$). None of the differences was statistically significant by paired tests.

Conclusion: The non-medical switch from ETN to his biosimilar in this group of patients followed in routine care did not affect the overall efficacy and safety of treatment. However, these observations only cover 3 months of follow up. A longer observational period is necessary to assess the long-term response.

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Abstract Number: 2535

Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of CKD-506, a Novel, Histone Deacetylase 6 (HDAC6) Inhibitor, in Healthy Volunteers

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Session Information

Session Date: Tuesday, October 23, 2018

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: HDAC6 is a pleiotropic enzyme which removes of acetyl groups from non-histone proteins. HDAC6 inhibition represses inflammatory responses such as cytokines, chemokines and cell adhesion molecules by repressing NADPH Oxidase activity in macrophage as well as enhance Treg function by enhancing transcriptional activity of FOXP3 which induces several immunomodulatory proteins such as CTLA4. Thus, HDAC6 was proposed as a therapeutic target to provide significant therapeutic benefit to patients with severe immune disorders. CKD-506 is an oral hydroxamate HDAC6 selective inhibitor without genotoxicity. CKD-506 has shown strong therapeutic efficacy in adjuvant-induced arthritis (AIA) rheumatoid arthritis model. Furthermore, CKD-506 showed strong synergistic therapeutic efficacy in combination with methotrexate (MTX). In RA patients' PBMC and fibroblast like synoviocytes (FLS), CKD-506 suppressed inflammatory cytokines such as TNF α , CXCL10 and CCL2 and induced the anti-inflammatory cytokines such as IL-10, strongly implying that CKD-506 may be efficacious in RA patients.

Objective: To evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of CKD-506 in single ascending dose (SAD) and multiple ascending dose (MAD) in healthy volunteers.

Methods: This first-in-human study consisted of two randomized, double-blind, placebo-controlled parts: Part A, 7 SAD cohorts (50 – 1000 mg) and in Part B, 5 MAD cohorts with 14 days treatment (200, 400, 600 mg and 800 mg QD and 400 mg BID). Adverse events (AEs), clinical labs, vital signs and electrocardiogram (ECGs) were evaluated. Plasma PK concentration were assessed by LC-MS/MS. PD was assessed by measuring the acetylated α -tubulin and histone H3 using flow cytometry.

Results: CKD-506 was safe and well-tolerated following single and multiple doses for 14 days without significant changes in vital sign, ECG and laboratory measurements. All treatment-emergent adverse events (TEAEs) were mild in severity and the most common AEs were headache, hot flush, rash, pruritus and abdominal discomfort. Following single doses of CKD-506, CKD-506 was rapidly absorbed with median time to maximum observed concentration (t_{max}) between 0.5-1 hour. Following multiple doses of CKD-506, exposure reached steady state on day 6 for all QD dosing and day 12 for the 400 mg BID dosing. A minimal accumulation was observed with mean accumulation ratio (R_{ac}) ranged from 1.05 to 1.30. The mean changes-from-baseline for acetylated α -tubulin and histone H3 generally displayed a dose-dependent increase in CD3⁺ T cells and monocytes on day 1 and day 14. The maximum levels of acetylated α -tubulin was observed between 1-4 hours post-dose on day 1 and 14 with returned to near basal levels by 24 hours.

Conclusion: CKD-506 was generally safe and well-tolerated following single and multiple doses in healthy volunteers. Plasma exposure was relatively dose proportional. The levels of acetylated α -tubulin increased dose dependently. These results support further clinical development of CKD-506 with once daily dosing regimen for the treatment of RA and other inflammatory and autoimmune diseases.

Disclosure: Y. Shim, None; S. Kim, None; M. Velinova, None; G. Arold, None; S. Kim, None; Y. I. Choi, None; K. M. Park, None.

Abstract Number: 2536

Vagus Nerve Stimulation in Patients with Rheumatoid Arthritis: 24 Month Safety and Efficacy

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: RA is a debilitating chronic disease with an unmet need for additional therapeutic approaches. Modulating innate neuro-immune reflex pathways by stimulation of the vagus nerve (VNS) could represent a novel means of treating RA (van Maanen MA et al. NatRev Rheumatol. 2009; 5:229-32). We recently reported a 12-week proof of concept study using a VNS device, approved for drug-resistant epilepsy, showing reductions in the DAS28-CRP and in TNF- α and IL-6 levels (Koopman FA et al. PNAS 2016;113:8284). To understand the long term safety and efficacy of this

novel treatment approach, we followed the patients in a 24 months long-term extension study and report on the safety and clinical efficacy data.

Methods: In the primary study, VNS devices were implanted into 17 RA patients, mostly with insufficient response to multiple conventional and biologic DMARDs, on stable background of methotrexate (≤ 25 mg weekly) therapy. The devices electrically stimulated the vagus nerve, 1-4 min/day, over a 12 week open label period. On completion, subjects were offered to enroll into a follow-up study, where the study physicians were given flexibility to alter VNS dosing parameters and/or to add a biologic DMARD to the treatment regimen. DAS28-CRP and Health Assessment Questionnaire-Disability Index (HAQ-DI) were collected over 2 years.

Results: All subjects electively continued on VNS treatment through 24 months of the long term follow-up study. Biologic DMARDs were started in 1 and restarted in 8 of 17 subjects; of these, 4 were non-responders to VNS in the primary study, and 5 had stable improvement but had not yet achieved disease remission on VNS alone (Table 1). At the start of the follow-up study, the mean DAS28-28 and HAQ-DI were significantly reduced compared to the pre-implant baseline (mean difference \pm SE in DAS28-CRP = -1.60 ± 0.37 , $p < 0.0001$; mean difference \pm SE in HAQ-DI = -0.44 ± 0.21 , $p < 0.037$), and the depth of effect was retained through 24 months. No association between DAS28-CRP and stimulation frequency (Range = 1X-8X/day) was observed. At 24 months, both the subjects using VNS monotherapy and those using a combination of VNS and biologic DMARDs exhibited stable improvements in DAS28-CRP and HAQ-DI. No difference in the adverse events profile between the two groups was observed.

Conclusion: The data presented here demonstrate that VNS in subjects with RA is associated with a substantial reduction in disease activity that is sustained for 24 months without untoward safety signals. Further, the data suggest that biological DMARDs may be initiated safely in combination with VNS treatment, though this requires validation in larger cohorts. These results support additional development of VNS devices as an alternative therapeutic approach for RA treatment, which potentially can safely be combined with biologic DMARDs.

Table 1. Two Year Efficacy of VNS Treatment. Mean DAS28-CRP at primary study baseline (month -3.5) and at visits over 2 years of long term follow up (months 0-24).

Study Month	All subjects (n=17)			VNS as Monotherapy (n=8)			VNS + Re-initiated Biologic (n=9)			VNS Monotherapy Survival
	Mean	STD	P-value vs -3.5	Mean	STD	P-value vs -3.5	Mean	STD	P-value vs -3.5	
-3.5	6.05	0.75		6.33	0.72		5.79	0.73		
0	4.44	1.32	0.0002	4.15	1.35	0.0012	4.70	1.32	0.07	1.00
3	3.96	1.45	< 0.0001	3.52	1.20	< 0.0001	4.35	1.61	0.017	1.00
6	3.69	1.41	< 0.0001	3.6	1.59	0.0001	3.76	1.35	0.0011	0.82
12	3.49	1.08	< 0.0001	3.63	1.10	< 0.0001	3.37	1.10	0.0001	0.65
18	3.35	0.90	< 0.0001	3.3	1.03	< 0.0001	3.38	0.85	0.0002	0.59
24	3.41	1.52	< 0.0001	3.76	1.77	0.0008	3.21	1.44	< 0.0001	0.47

Disclosure: F. A. Koopman, None; A. Musters, None; M. M. J. Backer, None; D. Gerlag, GlaxoSmithKline, 1, 3; S. Miljko, None; S. Grazio, None; S. Sokolovic, None; Y. Levine, SetPoint Medical, Inc., 1, 3; D. Chernoff, SetPoint Medical, Inc., 1, 3, Adamas Pharmaceuticals, 1, 5, OLLY Nutrition, 1, 5, NAIA Pharma, 1, 5, Aquinox Pharma, 1, 5, Crescendo BioScience, 5; N. de Vries, AbbVie Inc., 2, Janssen, 2, Ergomed Clinical Research, 2, GlaxoSmithKline, 2, Pfizer, Inc., 2, Boehringer Ingelheim, 2, Roche, 2, MSD, 5, Pfizer, Inc., 5; P. P. Tak, GlaxoSmithKline, 1, 3.

Abstract Number: 2537

Benefit Study: Results of Interim Analysis of a Pan-European Observational Study to Evaluate Real-World Effectiveness of SB4 Following Transition from Originator Etanercept (ETN) in Patients with Rheumatoid Arthritis (RA) or Axial Spondyloarthritis (AxSpA)

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: SB4, a biosimilar to the reference ETN, received EU marketing authorisation in January 2016, based on the totality of evidence from pre-clinical and clinical Phase I and III studies that demonstrated similar efficacy, bioequivalence, and comparable safety and immunogenicity to ETN. There are few published data on outcomes of transition from originator to biosimilar outside the controlled setting of randomised clinical trials.

Objectives: Provide real world evidence on the outcomes of transition from ETN to SB4 in routine clinical practice.

Methods: This ongoing observational study is designed to enrol 600 subjects with RA or axSpA, who initiated SB4 as part of routine clinical practice following a minimum of 6 months treatment with a stable dose of originator ETN, at clinics in France, Germany, Italy and Spain. Data are captured from clinic records, retrospectively for 6 months prior to switch and prospectively and/or retrospectively for 6 months following switch. Outcome measures include disease score (DAS-28 for RA, BASDAI for axSpA) over time, clinical characteristics and management, and adverse events. This interim analysis (IA) describes baseline characteristics and clinical outcome 3 months post-initiation of SB4.

Results: In this interim analysis, 255 subjects have been included: 163 with RA and 92 with axSpA, both groups possibly representing longer-standing established disease; neither group experienced a clinically significant difference in disease score from baseline to 3 months post-transition, with mean individual change of 0.0 (95% CI -0.1, 0.2) and 0.4 (95% CI 0.0, 0.9) in RA and axSpA subjects respectively.

Table 1: Baseline characteristics of subjects at transition, and 3-month disease score outcomes

	RA (N=163)		AxSpA (N=92)	
	Mean (SD)	Q1, Q3	Mean (SD)	Q1, Q3
Age in years	60.8 (11.09)	54.0, 69.0	50.7 (12.49)	40.0, 61.0
Women n (%)	112 (68.7)	–	28 (30.4)	–
Duration of disease, years	14.3 (9.49)	7.4, 21.0	12.8 (11.44)	5.0, 16.3
Current/Ex-smoker n (%)	37 (23.6)	–	32 (34.8)	–
Currently unemployed n (%)	96 (58.9*)	–	24 (26.1*)	–
csDMARD** concomitant to SB4 n %	83 (76.1***)	–	20 (47.6***)	–
	Mean (SD)	95% CI	Mean (SD)	95% CI
DAS-28 in 6 months prior to transition to SB4 (n = 146)	2.0 (0.92)	1.8, 2.1	–	–
DAS-28 at 3 months post-transition to SB4 (n = 85)	2.2 (1.87)	2.0, 2.4	–	–
Individual change in DAS-28 from baseline to 3 months post-transition to SB4 (n= 79)	0.0 (0.84)	-0.1, 0.2	–	–
BASDAI in 6 months prior to transition to SB4 (n = 76)	–	–	3.0 (2.02)	2.5, 3.4
BASDAI at 3 months post-transition to SB4 (n = 42)	–	–	3.4 (2.29)	2.7, 4.1
Individual change in BASDAI at 3 months post-transition to SB4 (n = 37)	–	–	0.4 (1.35)	0.0, 0.9

DAS-28, Disease Activity Score 28; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; SD, standard deviation.

*Data available for 157 and 86 subjects respectively. **Conventional synthetic disease-modifying antirheumatic drug. ***Data available for 109 and 42 subjects respectively.

Conclusion: This IA provides a first insight into clinical outcomes in a contemporary cohort of EU patients with established RA and axSpA, transitioned from originator to biosimilar ETN in a study of clinical practice: data do not indicate loss of treatment effectiveness in the 3 months following transition. Subsequent to these preliminary data, the study will provide ongoing, pertinent information about 3- and 6-month outcomes in these populations, helping to inform evidence-based treatment decisions.

Disclosure: K. Krüger, None; C. Selmi, AbbVie, Janssen, MSD, Novartis, Pfizer, 2, AbbVie, Alfa-Sigma, Biogen, Bristol-Myers Squibb, Celgene, Eli-Lilly, GlaxoSmithKline, Janssen, Merck Sharp and Dohme, Novartis, Pfizer, Roche, Sanofi-Genzyme, UCB, 5, 8; A. Cantagrel, AbbVie Inc., 2, 8, Chugai, 2, 5, 8, MSD, 2, Pfizer, Inc., 2, 5, 8, UCB, Inc., 2, 5, 8, Bristol-Myers Squibb, 5, 8, Janssen, 5, 8, Lilly France, 5, 8, Médac, 5, MSD France, 5, 8, Novartis, 5, 8, Roche, 5, 8, Sandoz, 5, Sanofi Aventis, 5, Biogen, 8, Celgene Corporation, 8, Nordic-Pharma, 8; M. A. Abad, None; U. Freudensprung, Biogen, 1, 3; M. F. Rezk, Biogen, 1, 3; J. Addison, Biogen Idec Ltd, 1, 3.

Abstract Number: 2538

Rapamycin Induces Remission in Patients with Newly Diagnosed Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation of the joints. We found that there was an imbalance between Th17 and Treg cells in the patients with active refractory RA, reduced absolute number of Treg cells was found in these patients. To observe the medium-term curative effect of rapamycin in the treatment of 25 cases newly diagnosed rheumatoid arthritis.

Methods: Collecting 25 patients of newly diagnosed rheumatoid arthritis, which accorded with RA diagnosis standard of ACR in 1987. The patients were treated with rapamycin at a dose of 0.5 mg every 2 days for 24 weeks, then we observed the change of clinical improvement and immunological assessments after 24 weeks.

Results: There was 25 patients were enrolled. After rapamycin treatment for 24 weeks, the mean DAS28 of them was decreased from 5.36[1.42] to 3.45[1.29] (P=0.001). The absolute number of Treg^{CD4+CD25+Foxp3+} cells significantly higher than baseline (30.24 [14.44], 46.64 [27.54], P=0.025). The absolute number of Th17 cells was not significantly different (6.40 [4.46], 7.03 [5.60], P>0.05), and the same as the ratio of Th17/Treg cells (0.25 [0.18], 0.19 [0.16]), P>0.05). Meanwhile, the mean dose of prednisone was decreased from 11.25 mg/d to 9.6 mg/d.

Conclusion: Rapamycin could induce the balance of Th17 cells and Treg cells, especially up-regulate the absolute number of Treg cells, thus induce remission in patients with newly diagnosed RA.

Disclosure: M. Chen, None; X. F. Li, None; C. Gao, None; C. H. Wang, None.

Abstract Number: 2539

SB4 Shows Comparable Short-Term Effectiveness to Its Etanercept Originator As First-Line Biologic Treatment for Patients with Rheumatoid Arthritis in Routine Clinical Care

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: In the United Kingdom (UK) since 2016, etanercept biosimilars (SB4) are since 2016 a first-line treatment option for the management of severe rheumatoid arthritis (RA) defined as non-response to ≥ 2 csDMARDs. However, real world data, including how it compares with the etanercept originator (ETN) are lacking. This study aims to compare the short-term effectiveness of etanercept originator with its biosimilar in patients with RA when used as a first biologic following csDMARDs.

Methods: This study included patients with RA registered with the British Society for Rheumatology Biologics Registers for RA (BSRBR-RA) at the point of starting either ETN or an SB4 since 2016 as their first biologic. Baseline information is collected at drug start and includes demographic and clinical data. Follow-up (FU) data are captured every 6 months and include details on therapy changes, current disease activity, and development of any adverse events. The primary outcome of this study is effectiveness as calculated by change in the 28 joint count disease activity score (DAS28). Only patients with a complete DAS28 at baseline and their first FU were included in the final analysis of this study. Hazard ratios (HR) comparing drug survival and risk of first serious adverse event (SAE) between ETN and SB4 patients were calculated using adjusted Cox regression.

Results: Between January 2016 and 27 March 2018, 322 and 855 patients starting ETN or SB4 respectively as first biologic were recruited to the BSRBR-RA. Complete DAS28 data at baseline and first FU were available for 192 ETN patients and 301 SB4 patients. Patient characteristics were similar between the 2 cohorts (Table). Only the baseline DAS28 was slightly higher in the ETN patients compared with the SB4 patients ($p=0.02$). After adjusting for baseline patient and clinical characteristics, no difference between groups was observed in DAS28 ($p=0.1$) or remission status ($p=0.5$) at first FU.

Thirteen (7%) and 11 (3%) ETN and SB4 patients stopped their respective treatments by the first FU. The adjusted hazard ratio for stopping ETN versus SB4 over this time period was similar (HR=1.0 (95% CI 0.4-2.5); $p=0.9$). Risk of SAEs over the first 6 months was also similar between groups (HR (SB4 versus ETN) =0.5 (95% CI 0.3-1.1); $p=0.1$), with 13 (14%) and 19 (6%) SAEs reported in ETN and SB4 patients respectively until first FU.

Conclusion: In the UK, etanercept biosimilars are now frequently used as first-line biologics in RA patients. These short-term follow-up data demonstrate in routine clinical care that SB4 appears to have comparable short-term effectiveness to ETN in terms of drug response, drug survival and safety profile.

Table

	ETN	SB4	p-value
Number	192	301	
Female, n (%)	129 (67%)	226 (75%)	0.1
Age (years)	59 (50; 67)	59 (51; 68)	0.7
Disease Duration (years)	5 (2; 13)	5 (2; 13)	0.3
Smoking			0.5
Current	26 (14%)	79 (18%)	
Former	80 (43%)	117 (40%)	
Never	80 (43%)	125 (42%)	
Comorbidities			0.2
0	100 (52%)	178 (59%)	
1	63 (33%)	72 (24%)	
2	18 (9%)	33 (11%)	
3+	11 (6%)	18 (6%)	
Baseline MTX use (%)	101 (54%)	181 (61%)	0.1
HAQ (0-3)	1.6 (0.8; 2.0)	1.5 (1.0; 2.1)	0.3
DAS28 at baseline	6.0 (5.4; 6.8)	5.9 (5.2; 6.4)	0.02
DAS28 at 6 months	3.2 (2.3; 4.4)	3.1 (2.1; 4.4)	0.2
DAS28 change at 6 months	2.6 (1.4; 3.9)	2.9 (1.7; 3.8)	0.5
DAS28 remission	65 (34%)	118 (39%)	0.2
DAS28 low disease activity	96 (50%)	159 (53%)	0.5
EULAR Good response	95 (49%)	159 (53%)	0.5
Linear regression DAS28* RR (95% CI)	Ref.	-0.3 (-0.6; 0.0)	0.1
Logistic regression DAS28* remission HR (95% CI)	Ref.	0.2 (-0.3; 0.7)	0.5

Disclosure: D. De Cock, None; L. Kearsley-Fleet, None; R. Davies, None; K. Watson, None; K. L. Hyrich, None.

Abstract Number: 2540

Effect of Buccal Hygiene on the Systemic Activity of Patients with Rheumatoid Arthritis: A Randomized Clinical Trial

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Good evidence suggests a relationship between rheumatoid arthritis (RA) and periodontitis. We aimed to investigate if a good oral hygiene could improve activity of RA.

Methods: BHYRRA (Buccal HYgiene and Reduction of activity of RA) is a randomized trial nested in the French early arthritis ESPOIR cohort. The patients with RA according to ACR/EULAR 2010 criteria and included in the ESPOIR cohort were randomized into 2 groups:

- Group A: treated according to a periodontal care program of good oral hygiene proposed to the general population, which included: (1) tooth brushing twice a day with a Triclosan polymer dentifrice (Colgate Total®); (2) mouth rinse once a day with an antiseptic mouthwash including essential oils (Listerine®); (3) scaling by a periodontist twice a year.
- Group B: no specific intervention and no specific information was given to the patients.

In both groups the treatment of RA was conducted according to the decision of the physician.

The primary endpoint was the delta between M12 and M0 DAS28-VS in both groups. The ability of the intervention to decrease the gingiva bacterial load was also analyzed.

Given the fact that it was expected that numbers of patients in whom the intervention will be proposed will not accept it, the primary analysis was a complier average causal effect (CACE) analysis, restricted to patients having their first visit to the dentist planned in group A. Two approaches were used for CACE analyses; 1) weighting and 2) instrumental variable (IV).

PCR analysis of nine periodontal pathogens was performed at M0 and M12.

Results: 472 patients from the ESPOIR cohort were randomized, 238 in the intervention group (A) and 234 in the control group (B). 92/238 from group A accepted the procedure but only 81/92 had a first visit to the dentist. Duration of RA was 9.7 +/- 1.1 years. Baseline DAS28-VS was 2.65 +/- 1.31 and 2.72 +/- 1.26 in group A and B, respectively. Delta DAS was -0.19 +/- 1.37 and -0.02 +/- 1.18 in group A and B respectively (weighted difference: -0.02 (95 %CI -0.38; 0.33), p =0.90; IV: -0.37 (CI 95% -1.12; 0.37) p = 0.33). In anti-CCP positive patients, the delta DAS28-VS was -0.20 +/- 1.51 and 0.03 +/- 1.26 in group A and B respectively (weighted difference: -0.03 (95% CI -0.55; 0.49), p =0.92; IV: -0.43 (CI 95% -1.37; 0.51), p = 0.37). For the patients becoming negative to the red complex, there was a decrease of DAS albeit not significant (-0.30 (95% CI -1.12; 0.51), p=0.47)

Microbiological analysis of the periodontal bacteria indicated a significant decrease in the red complex involved in the pathogenesis of periodontitis; i.e. *Porphyromonas gingivalis* (p = 0.002), *Tannerella forsythia* (p = 0.002) and *Treponema denticola* (p = 0.019).

Conclusion: Following in RA patients the recommendations to the general population for a good oral hygiene decreased the bacterial load of bacteria involved in periodontal disease but did not improve RA activity. In the present study, the lack of clinical effect on RA may be due (1) to the relatively long duration of the disease in the patients enrolled (10 years), and (2) to the very good control of the disease at baseline (DAS28-VS around 2.7). The efficacy of oral prevention, through the above simple approach should be tested in patients with earlier RA and more active disease.

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Abstract Number: 2541

Impact of 12-Weeks of Upadacitinib Treatment on Individual and Composite Disease Measures in Patients with Rheumatoid Arthritis and Inadequate Response to Conventional Synthetic or Biologic DMARDs

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Background/Purpose: Upadacitinib (UPA), an oral, JAK1-selective inhibitor, demonstrated efficacy through 12 and 24 weeks (wks) in phase 3 trials of patients (pts) with active rheumatoid arthritis (RA) and inadequate response (IR) to csDMARDs and bDMARDs, respectively.^{1,2} Efficacy evaluations at Wk 12 are an important assessment point according to T2T recommendations.³ The purpose of this analysis was to assess the impact of UPA at 12 wks on individual and composite measures of RA disease activity.

Methods: Pts received UPA 15mg or 30mg once daily (QD) or PBO for 12 wks in two phase 3 trials. SELECT NEXT¹ and SELECT BEYOND² enrolled csDMARD- and bDMARD-IR pts, respectively. For this investigation, responses at Wk 12, were defined as $\geq 50\%$ improvement in ACR components. Among ACR50 responders, the proportions of pts achieving $\geq 50\%$ improvement in all 7 components of the ACR response criteria [Tender Joint Count (TJC68), Swollen Joint Count (SJC66), Pt Global Assessment (PtGA), Physician Global Assessment (PhGA), Pt Pain, Health Assessment Questionnaire-Disability Index (HAQ-DI), and high sensitive C-reactive protein (hsCRP)] were assessed. Differences in the cumulative distributions of CDAI, DAS28-CRP, and SDAI between baseline (BL) and Wk 12 were assessed. All analyses were based on observed data without imputation.

Results: Pts in both studies, on average, had established, moderate to severe RA at BL, with (mean) disease durations of 7.3 and 13.2 years, CDAI of 38.2 and 40.9, in csDMARD-IR and bDMARD-IR, respectively; 53% of bDMARD-IR pts had exposure to ≥ 2 bDMARDs.^{1,2} In both populations, significantly more pts on UPA vs PBO achieved $\geq 50\%$ improvements in each ACR component at Wk 12 (Table). Among pts who achieved ACR50 at Wk 12, approximately one-half of the csDMARD-IR and one-third of the bDMARD-IR pts achieved $\geq 50\%$ improvement in all 7 ACR components. While there were no differences at BL, cumulative distributions of CDAI, DAS28-CRP, and SDAI separated by treatment at Wk 12 ($p < 0.001$); for the lowest quartiles for UPA 15mg and 30mg vs PBO, CDAI levels dropped to 6.2 and 5.1 vs 12.5 in csDMARD-IR; and 7.2 and 8.2 vs 13.1 in bDMARD-IR.

Conclusion: In pts with an insufficient response to either csDMARDs or bDMARDs, treatment responses at 12 wks were observed in significantly higher proportions with UPA vs PBO. Favorable effects with UPA were seen in the composite scores and the individual parameters, including PROs and acute-phase reactants.

References:

1. Burmester et al; 2017, Arthritis Rheumatol; 69 S10
2. Genovese et al; 2017, Arthritis Rheumatol; 69 S10
3. Smolen et al; 2015; <https://doi.org/10.1136/annrheumdis-2015-207524>

Proportions of Patients Achieving 50% Improvements in Core Components of the ACR Score at Week 12

		SELECT-NEXT (csDMARD-IR)			SELECT-BEYOND (bDMARD-IR)		
		N	n (%)	Δ from PBO	N	n (%)	Δ from PBO
TJC $\geq 50\%$ Improvement	PBO	207	95 (45.9)	-	147	68 (46.3)	-
	UPA 15 mg	210	140 (66.7)***	20.8***	157	116 (73.9)***	27.6***
	UPA 30 mg	201	143 (71.1)***	25.2***	149	105 (70.5)***	24.2***
SJC $\geq 50\%$ Improvement	PBO	207	114 (55.1)	-	147	81 (55.1)	-
	UPA 15 mg	210	153 (72.9)***	17.8***	157	123 (78.3)***	23.2***
	UPA 30 mg	201	158 (78.6)***	23.5***	149	109 (73.2)***	18.1***
Pain $\geq 50\%$ Improvement	PBO	206	42 (20.4)	-	145	34 (23.4)	-
	UPA 15 mg	207	112 (54.1)***	33.7***	156	67 (42.9)***	19.5***
	UPA 30 mg	200	111 (55.5)***	35.1***	146	70 (47.9)***	24.5***
PtGA $\geq 50\%$ Improvement	PBO	206	49 (23.8)	-	145	33 (22.8)	-
	UPA 15 mg	207	108 (52.2)***	28.4***	156	73 (46.8)***	24***
	UPA 30 mg	200	109 (54.5)***	30.7***	147	74 (50.3)***	27.5***
PhGA $\geq 50\%$ Improvement	PBO	192	74 (38.5)	-	137	56 (40.9)	-
	UPA 15 mg	193	129 (66.8)***	28.3***	150	97 (64.7)***	23.8***
	UPA 30 mg	187	140 (74.9)***	36.4***	137	94 (68.6)***	27.7***
HAQ-DI $\geq 50\%$ Improvement	PBO	206	48 (23.3)	-	145	22 (15.2)	-
	UPA 15 mg	206	91 (44.2)***	20.9***	156	41 (26.3)*	11.1*
	UPA 30 mg	200	83 (41.5)***	18.2***	146	41 (28.1)**	12.9**
hsCRP $\geq 50\%$ Improvement	PBO	207	38 (18.4)	-	146	39 (26.7)	-
	UPA 15 mg	209	159 (76.1)***	57.7***	155	114 (73.5)***	46.8***
	UPA 30 mg	201	145 (72.1)***	53.7***	146	100 (68.5)***	41.8***
$\geq 50\%$ Improvement in all 7 ACR components for ACR50 responders	PBO	32	2 (6.3)	-	20	2 (10)	-
	UPA 15 mg	84	38 (45.2)***	38.9***	56	19 (33.9)	23.9
	UPA 30 mg	94	39 (41.5)***	35.2***	58	19 (32.8)	22.8

*, **, *** $p < .05$, .01 and .001 respectively for comparisons of UPA vs PBO; delta (Δ)= difference between response rate on placebo and upadacitinib 15 or 30 mg.

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Abstract Number: 2542

Integrated Exposure-Response Analyses for Upadacitinib Efficacy and Effects on Laboratory Parameters in Rheumatoid Arthritis – Analyses of Phase 2b Studies

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

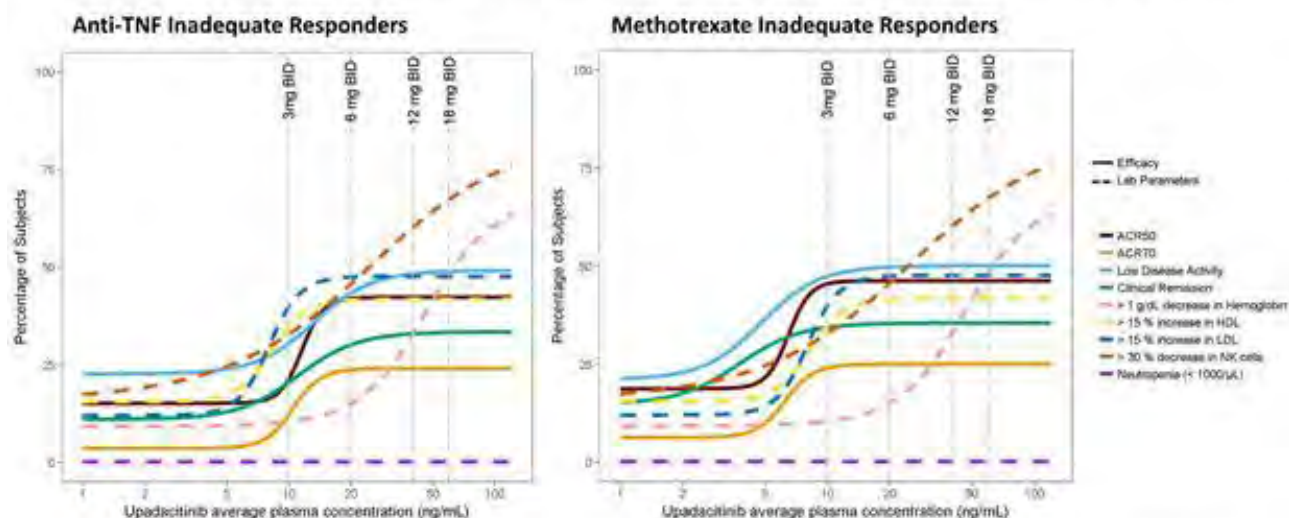
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Upadacitinib is an oral, selective inhibitor of Janus kinase 1 (JAK1) which is currently being evaluated for the treatment of several autoimmune disorders, including rheumatoid arthritis (RA). Upadacitinib demonstrated favorable efficacy and acceptable safety in two Phase 2b studies in subjects with moderate to severely active RA who had inadequate response to anti-TNF therapies (BALANCE I) or to methotrexate (BALANCE II). The presented analyses were conducted to characterize the relationships between upadacitinib plasma exposures and various efficacy endpoints, as well as effects on select laboratory parameters of interest to support the selection of doses to evaluate in Phase 3.

Methods: The analyses included data from 574 patients who had completed BALANCE I and II studies. Logistic regression analyses were conducted for the relationship between upadacitinib average plasma concentration during a dosing interval (C_{ave}) and the probability of achieving various efficacy endpoints (ACR50, ACR70, low disease activity and clinical remission based on DAS28CRP) or experiencing a certain degree of change in select laboratory parameters (hemoglobin, NK cells, LDL-C, HDL-C, neutrophils). Data from BALANCE I and II were analyzed separately for efficacy, and data from both studies were pooled for the laboratory parameters analyses.

Figure 1. Model-Predicted Percentage of Subjects with RA who Achieve the Different Efficacy Endpoints or Experience Specific Changes in Laboratory Parameters Based on Exposure-Response Analyses of Phase 2b Studies



Colored lines represent the median predicted percentage of subjects meeting the different efficacy endpoints or changes in laboratory parameters.

Vertical gray lines represent the median C_{ave} for different BID immediate-release doses evaluated in BALANCE I and BALANCE II studies.

Results: The percentage of subjects achieving ACR50, ACR70, low disease activity, and clinical remission increased with increasing upadacitinib plasma exposures. With increasing upadacitinib plasma exposures, there was also an increase in the percentage of subjects experiencing decreases in hemoglobin and NK cells and increases in HDL-C and LDL-C from baseline to Week 12. There was no relationship between upadacitinib plasma exposures and neutropenia (< 1000 cells/L). The model-predicted percentage of subjects who achieve various efficacy endpoints or experience specific changes in laboratory parameters is shown in Figure 1.

Conclusion: Upadacitinib plasma exposures associated with 6 mg BID to 12 mg BID using the immediate-release formulation (equivalent to 15 mg QD to 30 mg QD using the extended-release formulation, respectively) are predicted to achieve near maximum efficacy in RA patients while having limited effects on NK cells, hemoglobin, LDL-C, and HDL-C. Exposures higher than 12 mg BID are not predicted to result in additional efficacy benefits in subjects with RA, but they have the potential for greater effects on laboratory parameters. Results from these analyses supported the evaluation of extended-release formulation 15 mg and 30mg QD in Phase 3 trials in RA.

Disclosure: M. E. Mohamed, AbbVie Inc., 1, 3; I. Winzenborg, AbbVie Inc., 1, 3; E. Doelger, AbbVie Inc., 1, 3; P. Noertersheuser, AbbVie Inc., 1, 3; H. S. Camp, AbbVie Inc., 1, 3; S. Meerwein, AbbVie, 1, 3; A. A. Othman, AbbVie Inc., 1, 3.

Abstract Number: 2543

Retention Rate and Safety Data of Biosimilar CT-P13 in Patients with Rheumatoid Arthritis: Data from the Korean College of Rheumatology Biologics Registry

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: CT-P13 is a biosimilar prescribed in a number of countries for indications approved for the reference infliximab (RINF) including rheumatoid arthritis (RA), ankylosing spondylitis (AS), and inflammatory bowel diseases. Clinical data of CT-P13 have been analyzed in previous clinical trials, demonstrating non-inferiority of efficacy and equivalence pharmacokinetic profile to RINF. However, there are few studies showing long-term data of its drug survival or safety. This study is to investigate the drug retention rate and safety data of biosimilar CT-P13 in Korean RA patients.

Methods: Subjects were RA patients enrolled in the Korean College of Rheumatology biologics registry (KOBIO). Data from patients who received RINF and CT-P13 were included in the analysis (Dec 2012 ~ Dec 2017). Discontinuation was defined as switching or stopping the biologic agent. Kaplan-Meier curve were used for further analysis. Reason for RINF or CT-P13 discontinuation was also assessed.

Results: Data from 199 RA patients (CT-P13; 147, RINF; 52) were analyzed. The mean age of patients was 51.3 years in the CT-P13 group, and 12% were males. The mean disease duration was 7.7 years. Eighty four percent of CT-P13 treated patients were first-time biologic users. The overall drug retention rate of CT-P13 versus RINF was comparable ($p = 0.8382$), as well as the retention rates of first-line ($p = 0.6609$) and second or more (≥ 2)-line users ($p = 0.9552$) of agents. The reasons for discontinuing were inefficacy (31.8% in CT-P13, 34.8% in RINF), adverse events (20.0% in CT-P13, 23.9% in RINF), clinical improvement (3.0% in CT-P13, 4.3% in RINF), and others (10.4% in CT-P13, 4.3% in RINF). The incidence of adverse events in CT-P13 treated patients leading to discontinuation was comparable to that of RINF; infusion reaction (10.2%), skin eruption (2.0%), and herpes zoster (0.68%).

Conclusion: Our study demonstrates that the drug retention rate of CT-P13 was similar to RINF, and CT-P13 showed a reasonable long-term safety profile comparable to RINF in Korean RA patients.

Disclosure: H. A. Kim, None; E. Y. Lee, None; S. K. Lee, None; Y. B. Park, None; Y. N. Lee, Celltrion Healthcare Co. Ltd, 3; H. Kang, Celltrion Healthcare Co. Ltd, 3; K. Shin, None.

Abstract Number: 2544

Changes of CD4-(CD8+) Regulatory T Cells in Rheumatoid Arthritis Patients and during Interleukin-2 Therapy

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Recent studies have showed that quantitative and/or functional abnormalities of the regulatory T cells (Tregs) may play a vital role in the development of rheumatoid arthritis (RA). It is reported that CD25⁺FOXP3⁺ T cells include CD4⁺CD25⁺FOXP3⁺ T (CD4⁺Tregs) and CD8⁺CD25⁺FOXP3⁺ T cells (CD8⁺ Tregs). CD8⁺ Tregs also have been showed even stronger immunosuppressive function and more sensitive to IL-2 than CD4⁺Tregs in vivo. Our study was designed to clarify the level of peripheral CD8⁺ T cell subsets in RA patients, especially CD4⁺(CD8⁺) CD25⁺FOXP3⁺ T cells, and to investigate the role of recombinant human interleukin-2 (IL-2) in the regulation of CD4⁺(CD8⁺)CD25⁺FOXP3⁺ T cells in RA patients to provide a basis to IL-2 therapy.

Methods: Total 231 Patients with RA were enrolled, including 75 new-onset RA and 156 treated with low dose IL-2 (50 WIU/day for 5 days, subcutaneous injection), and 90 healthy adults were included as controls. The clinical data of RA patients were collected, including gender, age, joint swelling, tenderness and so on. And laboratory parameters were erythrocyte sedimentation rate (ESR), C reactive protein (CRP), rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (Anti-CCP). At the same time, the DAS28 score of RA group was calculated. The absolute number of CD4⁺CD25⁺FOXP3⁺ T cells in peripheral blood were detected by flow cytometry. We assume that CD4⁺ T cells with CD25⁺ and FOXP3⁺ were mostly CD8⁺CD25⁺FOXP3⁺ T cells, i.e. 8⁺ Tregs.

Results: As compared with the healthy controls, the absolute number of CD8⁺ Treg cells decreased significantly in the new-onset RA patients [0.92(0.42,1.39) vs 1.31(0.72,2.52), $P < 0.001$]. The absolute number of CD8⁺ Treg cells was significantly negative correlated with tenderness joints, DAS28 score and RF, ($r = -0.249$, $P = 0.032$; $r = -0.294$, $P = 0.010$; $r = -0.365$, $P = 0.001$); The absolute number of CD8⁺ Treg cells was no significantly correlated the swelling of the joints, ESR, CRP, Anti-CCP antibody ($r = -0.199$, $P = 0.087$; $r = -0.202$, $P = 0.082$; $r = 0.008$, $P = 0.947$; $r = -0.083$, $P = 0.480$). After treatment with IL-2, the absolute number of CD8⁺ Treg cells increased significantly as compared with that before treatment [0.88 (0.42,1.51) vs 1.98(0.91,3.37), $P < 0.001$].

Conclusion: The absolute number of CD8⁺ Treg cells in initial diagnosed patients was lower than that of healthy controls, implying that the immunosuppressive function was attenuated by disease itself, rather than immunosuppression therapy, which may be an important factor in the pathogenesis of RA. Low dose IL-2 can expand CD8⁺ Treg cells in peripheral blood, and thereby improve the immune function, so that RA patients were relieved. We are about to detect CD8⁺ Treg cells using more accurate technique to verify this theory.

Disclosure: X. Jia, None; F. Li, None; J. Luo, None; C. Gao, None; X. F. Li, None.

Use of Oral Complementary Medicine in Inflammatory Arthritis: Data from the Australian Rheumatology Association Database (ARAD)

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To describe the use of oral complementary medicine (CM) in people with inflammatory arthritis.

Methods: The Australian Rheumatology Association Database (ARAD), an observational database, collects outcome data from people with rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and juvenile idiopathic arthritis (JIA). Participants complete semi-annual then annual questionnaires. CM use from baseline questionnaire for participants recruited between 2006 and 2016 was categorised into fatty acids (eg. fish oil, evening primrose oil), herbs (eg. ginger, turmeric) or supplements (eg. glucosamine, vitamins). Changes in CM use over time were also determined.

Results: Of 4,425 ARAD participants 43.4% were taking CM at enrolment (RA: 1,324 (45.7%), AS: 261 (40.7%), PsA 307 (43.2%), JIA: 31 (17.7%)). Use was more prevalent in women (OR 1.37; 95% CI 1.25-1.59), those with tertiary education (OR 1.26; 95% CI 1.10-1.44), private health insurance (OR 1.30; 95% CI 1.01-1.52), drinking alcohol sometimes compared to never (OR 1.24; 95% CI 1.06-1.44), and less prevalent in current smokers (OR 0.75; 95% CI 0.62-0.91). Levels of pain in the last week were not different between CM users and non-users (OR 1.00; 95% CI 1.00-1.00). Overall, 35% were taking fatty acids, 7% herbs and 19% supplements. The most common CMs were fish oils (1,489 (34%)) followed by glucosamine (605 (14%)), although both have declined in use over the last decade (fish oil 2006-2016: 31%-28%, $p=0.85$; glucosamine 20%-9%, $p<0.001$). Over time, there has been increased use of supplements, particularly vitamin D (2006-2016: 1.6%-3.3%, $p<0.001$) and magnesium (2006-2016: 0.4%-2.7%, $p=0.02$), turmeric has also increased (2006-2016: 0%-1.2%, $p<0.001$), while the use of krill oil has declined (2012-2016: 3.9%-0.3%, $p<0.001$) and calcium has remained level (2006-2016: 3.0%-2.4%, $p=0.71$).

Conclusion: Just under half of ARAD participants were taking CM at ARAD entry. Types of CM used by people with inflammatory arthritis appear to change over time but appear to have no influence on levels of pain. Further research could investigate what prompts use of these products.

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The Association between Patient Reported Outcomes and Clinical Measures Among Rheumatoid Arthritis Patients: Analyses Using Phase 3 Clinical Trials of Upadacitinib

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Patient-reported outcomes (PROs) in RA are important to evaluate total disease impact, although treatment decisions may often be guided by traditional physician-derived measures of disease activity. The purpose of this analysis was to determine the association between PROs and composite outcomes in RA patients receiving the JAK1-selective inhibitor, upadacitinib (UPA), with prior inadequate responses (IR) to conventional synthetic (cs) or biologic (b) DMARD(s).

Methods: Data were analyzed from two 12-week (wk), phase 3, RCTs in csDMARD-IR (SELECT-NEXT) and bDMARD-IR (SELECT-BEYOND) patients receiving UPA 15 or 30 mg daily (QD) or placebo and background csDMARD therapy; as well as from a third trial (SELECT-MONOTHERAPY), in which MTX-IR patients received UPA monotherapy or MTX (blinded) for 14 wks. Moderate and substantial improvements in pain ($\geq 30\%$ and $\geq 50\%$ improvement from baseline [Δ BL], respectively), and normative values in HAQ-DI (≤ 0.25) and functional assessment of chronic illness therapy-fatigue (FACIT-F: ≥ 43.6 , SELECT-NEXT only) were evaluated. Associations between clinical outcomes (total and swollen joint counts [TJC, SJC], physician global assessment [MDGA], CRP and composite measures [ACR, DAS28-CRP, CDAI]), and PROs (pain [VAS], HAQ-DI, patient global assessment [PtGA], morning stiffness, FACIT-F) were evaluated through Pearson correlations and a univariate logistic model, controlling for treatment group and BL value.

Results: Patients enrolled in the SELECT-NEXT and SELECT-BEYOND trials had moderate to severely active RA (mean DAS28-CRP: 5.6 and 5.8, respectively), with disease durations of 7 and 12 years, respectively. In general, Δ BL in pain and HAQ-DI scores were marginally correlated with individual physician-derived measures (SELECT-NEXT: pain, 0.161-0.537, HAQ-DI, 0.081-0.425; SELECT-BEYOND: pain, 0.131-0.511, HAQ-DI, 0.052-0.409); moreover, moderate to high correlations were observed between pain, HAQ-DI and PtGA in both RCTs (SELECT-NEXT: pain, 0.835-0.851, HAQ-DI, 0.418-0.518; SELECT-BEYOND: pain, 0.828-0.871, HAQ-DI, 0.479-0.520). In regression analyses, improvements in individual disease assessments were associated with significant improvements in pain at Wk12 across RCTs (**Table**). In addition, patients with improvement in composite measures were more likely to report substantial improvements in pain. Similar associations were evident for HAQ-DI scores at Wk12 across RCTs (including SELECT-MONOTHERAPY), as well as for FACIT-F in SELECT-NEXT.

Conclusion: Achieving substantial improvements in pain, physical function, and fatigue was associated both with individual physician-derived measures and with composite disease outcomes. These data support the use of PROs in RCTs and also imply that, although PROs may be included in composite endpoints, they are distinct parameters that provide additional insights into the true impact of RA.

Table. Association between PROs and clinical outcomes

	SELECT-NEXT (csDMARD-IR)			SELECT-BEYOND (bDMARD-IR)	
	Substantial improvement in pain ($\geq 50\%$)	Normative HAQ-DI (≤ 0.25)	Normative FACIT-fatigue (≥ 43.6)	Substantial improvement in pain ($\geq 50\%$)	Normative HAQ-DI (≤ 0.25)
Improvement from baseline to wk 12, Odds ratio (95% CI)					
TJC68	1.04 (1.03–1.06)***	1.05 (1.03–1.07)***	1.04 (1.02–1.05)***	1.04 (1.02–1.06)***	1.04 (1.02–1.06)***
SJC66	1.04 (1.02–1.06)***	1.05 (1.02–1.07)***	1.04 (1.01–1.06)**	1.04 (1.02–1.07)***	1.05 (1.02–1.08)**
MDGA	1.04 (1.03–1.05)***	1.03 (1.02–1.04)***	1.04 (1.02–1.05)***	1.03 (1.02–1.04)***	1.05 (1.03–1.07)***
hsCRP	1.02 (1.01–1.03)***	1.02 (1.01–1.04)***	1.02 (1.01–1.03)**	1.01 (1.00–1.02)*	1.02 (1.01–1.04)**
HAQ-DI	6.98 (4.63–10.53)***	NE	6.56 (4.12–10.45)***	8.76 (5.30–14.50)***	NE
PtGA	1.11 (1.09–1.14)***	1.04 (1.03–1.05)***	1.04 (1.03–1.05)***	1.10 (1.08–1.12)***	1.04 (1.03–1.06)***

Table . (Cont'd)

	SELECT-NEXT (csDMARD-IR)			SELECT-BEYOND (bDMARD-IR)	
	Substantial improvement in pain ($\geq 50\%$)	Normative HAQ-DI (≤ 0.25)	Normative FACIT-fatigue (≥ 43.6)	Substantial improvement in pain ($\geq 50\%$)	Normative HAQ-DI (≤ 0.25)
AM stiffness duration	1.00 (1.00–1.00)**	1.00 (1.00–1.00)**	1.00 (1.00–1.00)	1.00 (1.00–1.01)***	1.00 (1.00–1.00)*
AM stiffness severity	1.56 (1.43–1.70)***	1.34 (1.22–1.48)***	1.36 (1.24–1.48)***	1.66 (1.50–1.84)***	1.69 (1.45–1.97)***
Response at wk 12, odds ratio (95% CI)					
ACR20	12.67 (8.18–19.64)***	8.81 (4.88–15.91)***	4.98 (3.06–8.11)***	13.30 (7.95–22.25)***	7.84 (3.39–18.12)***
ACR50	38.57 (22.94–64.86)***	8.52 (5.02–14.46)***	5.22 (3.31–8.23)***	60.15 (30.64–118.06)***	12.18 (5.79–25.65)***
ACR70	62.59 (22.49–174.16)***	14.35 (7.84–26.29)***	7.31 (4.31–12.40)***	96.16 (22.97–402.56)***	14.47 (6.73–31.14)***
DAS28-CRP ≤ 3.2	11.27 (7.56–16.78)***	6.75 (4.07–11.18)***	3.95 (2.53–6.15)***	9.43 (5.90–15.07)***	7.09 (3.52–14.30)***
DAS28-CRP < 2.6	11.07 (6.85–17.90)***	4.75 (2.93–7.71)***	3.99 (2.53–6.32)***	12.11 (6.91–21.23)***	7.39 (3.85–14.18)***
CDAI ≤ 10	12.36 (8.09–18.87)***	4.75 (2.97–7.58)***	3.61 (2.34–5.57)***	12.99 (7.83–21.53)***	8.76 (4.44–17.29)***
CDAI ≤ 2.8	27.90 (8.43–92.30)***	6.18 (3.07–12.45)***	9.14 (4.44–18.82)***	NE	6.76 (3.01–15.20)***

Odds ratio, 95% CI, and *P*-values were calculated using univariate logistic regression model with treatment group, baseline value, and corresponding clinical outcome. ***, **, and * statistically significant at <0.001 , <0.01 , and <0.05 levels, respectively. NE, estimate not possible.

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Abstract Number: 2547

Upadacitinib Monotherapy Improves Patient-Reported Outcomes in Patients with Rheumatoid Arthritis and Inadequate Response to Methotrexate

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Upadacitinib (UPA) is a selective JAK-1 inhibitor with demonstrated patient-reported benefits in the treatment of active rheumatoid arthritis (RA).^{1,2} The objective of this analysis was to evaluate the effect of UPA compared to MTX on PROs in the SELECT-MONOTHERAPY randomized controlled trial (RCT).

Methods: SELECT-MONOTHERAPY (NCT02706951) is a Phase 3 RCT conducted in patients with active RA with inadequate responses to MTX (MTX-IR) that were switched to UPA monotherapy (15mg or 30 mg once daily) or continued on MTX. The following PROs were included: Patient Global Assessment of Disease Activity (PtGA) by visual analog scale (VAS), pain by VAS, Health Assessment Questionnaire Disability Index (HAQ-DI), and health-related quality of life (HRQOL) by 36-Item Short Form Health Survey (SF-36). Least squares mean (LSM) changes from baseline to Week 14 were based on mixed effect repeated measures models. The percentage of patients reporting improvements \geq minimum clinically important differences (MCID) in PROs from baseline to Week 14 and scores \geq normative values were determined; comparisons between groups used chi-square tests, statistical significance at the 5% level.

Results: Data from 648 patients (215, 217, and 216 in the UPA 30 mg, UPA 15mg, and MTX group [mean dose: 17 mg/week], respectively) were analyzed. Mean age was 54.3 years, 80.7% were female, and 42.3% had RA for ≥ 5 years. At Week 14, both UPA doses resulted in statistically significant LSM changes from baseline vs MTX in PtGA, pain, HAQ-DI, SF-36 Physical (PCS) and Mental Component Summary (MCS), and all SF-36 domain scores (Table). Compared with MTX, statistically more patients reported improvements \geq MCID across all PROs in UPA 30 mg and all but SF-36 MCS and SF domain scores in UPA 15 mg (Table). Scores \geq normative values were reported across all PROs in UPA 30mg and all but SF-36 MCS and RP, GH, RE, and MH SF-36 domains in UPA 15 mg.

Conclusion: Treatment with UPA 15 mg or 30 mg as monotherapy for 14 weeks resulted in statistically significant and clinically meaningful improvements in PROs compared with MTX, including disease activity, pain, physical function, and HRQOL among MTX-IR patients.

References: 1. Strand et al. Poster SAT0254, European League Against Rheumatism (EULAR) 2018; 2. Strand et al. Poster SAT0255, European League Against Rheumatism (EULAR), 2018.

LSM Changes From Baseline and Percentage of Responders at Week 14 After UPA Initiation

PRO	Baseline Mean (n=647)	LSM Changes From Baseline			Patients Reporting Improvements ≥MCID, n (%)		
		MTX (n=216)	UPA 15 mg (n=217)	UPA 30 mg (n=215)	MTX (n=216)	UPA 15 mg (n=217)	UPA 30 mg (n=215)
PtGA	60.4	-11.18	-23.40*	-29.89*	102 (47.2)	132 (61.1)*	158 (73.5)*
Pain VAS	62.3	-13.88	-26.15*	-33.18*	100 (46.3)	139 (64.4)*	162 (75.3)*
HAQ-DI	1.5	-0.32	-0.65*	-0.73*	98 (45.4)	140 (64.8)*	148 (68.8)*
SF-36 PCS	33.5	4.32	8.28*	10.19*	103 (47.7)	141 (65.0)*	157 (73.4)*
SF-36 MCS	44.6	1.88	4.55*	4.68*	91 (42.1)	109 (50.2)	124 (57.9)*
SF-36 PF	32.9	4.11	8.47*	10.27*	124 (57.4)	161 (74.2)*	162 (75.3)*
SF-36 RP	35.3	3.58	7.02*	8.26*	101 (46.8)	150 (69.1)*	154 (71.6)*
SF-36 BP	35.2	4.67	8.89*	11.02*	114 (52.8)	148 (68.2)*	159 (74.0)*
SF-36 GH	38.6	2.81	5.57*	7.05*	115 (53.2)	146 (67.3)*	146 (67.9)*
SF-36 VT	41.6	3.13	8.06*	8.36*	107 (49.5)	152 (70.0)*	151 (70.2)*
SF-36 SF	39.9	3.56	6.26*	7.01*	103 (47.7)	121 (55.8)	129 (60.0)*
SF-36 RE	40.3	2.05	4.82*	6.08*	82 (38.0)	118 (54.4)*	123 (57.2)*
SF-36 MH	42.0	2.46	5.35*	5.67*	108 (50.0)	133 (61.3)*	132 (61.4)*

* $P < 0.05$ for UPA vs MTX. LSM change from baseline P values represent statistical significance between groups.

BP, bodily pain; GH, general health; HAQ-DI, Health Assessment Questionnaire Disability Index; LSM, least squares mean; MCID, minimum clinically important difference; MCS, Mental Component Summary; MH, mental health; MTX, methotrexate; PCS, Physical Component Summary; PF, physical function; PRO, patient-reported outcome; PtGA, Patient's Global Assessment of Disease Activity; RE, role emotional; RP, role physical; SF, social function; SF-36, 36-Item Short Form Health Survey; UPA, upadacitinib; VAS, visual analog scale; VT, vitality. Medical writing services provided by Hannah Greenwood (Fishawack Communications) and funded by AbbVie.

Disclosure: V. Strand, AbbVie, Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Celltrion, EMD Serono, Genentech/Roche, GSK, Janssen, Lilly, Novartis, Pfizer, Regeneron, Sanofi, and UCB, 5; M. Buch, Pfizer Ltd, Roche, and UCB, 2, Abbvie, BMS, Eli Lilly, Roche, Pfizer, and Sandoz, 5; N. Tundia, AbbVie Inc., 1, 3; H. S. Camp, AbbVie Inc., 1, 3; J. Suboticki, AbbVie Inc., 3, AbbVie Inc., 1; D. Goldschmidt, Analysis Group, which received research funding from AbbVie for this study, 3; A. F. Wells, AbbVie Inc., 2, 5, AbbVie Inc., 2.

Abstract Number: 2548

The Impact of Rheumatoid Arthritis on Patient-Reported Outcomes: Comparison between Sarilumab Clinical Trials and Real-World Patient Data

Vibeke Strand¹, Colleen M. Carpinella², Lulu K. Lee², Susan Boklage³ and Matthew Reaney⁴, ¹Stanford University School of Medicine, Palo Alto, CA, ²Kantar Health, San Mateo, CA, ³Regeneron Pharmaceuticals, Inc., Tarrytown, NY, ⁴Sanofi, Guildford, United Kingdom

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

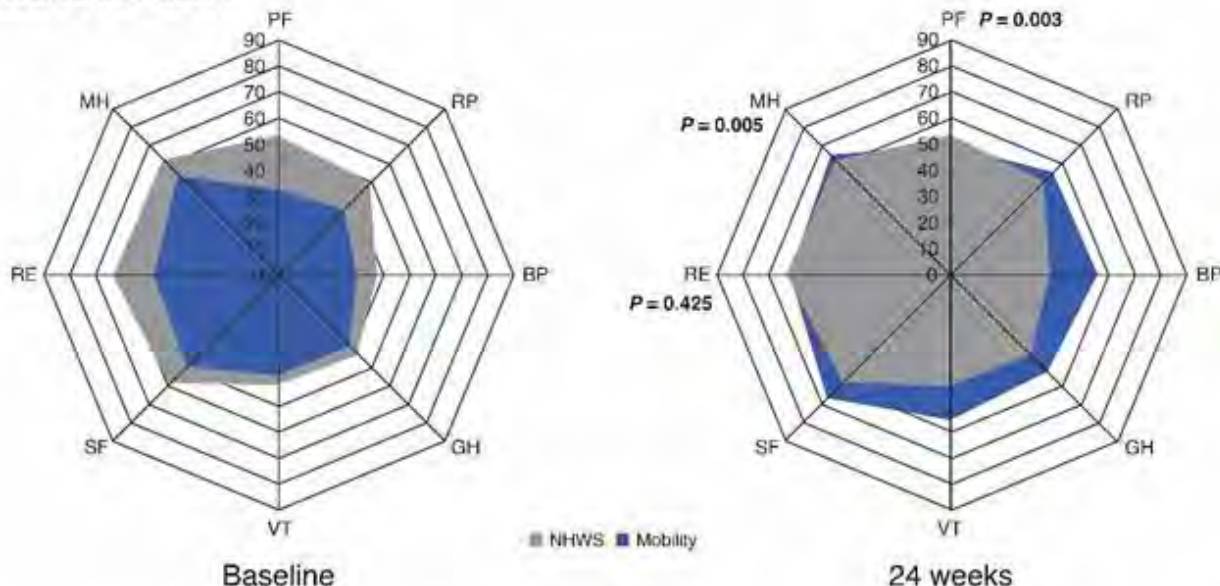
Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) and its treatment have significant impacts on health-related quality of life (HRQoL), work productivity (WP) and activity participation. Data are limited comparing the magnitude of impacts observed in routine clinical practice and randomized controlled trials (RCTs). This study evaluated the impact of RA on HRQoL, WP and activity participation among adult RA patients in the US general population compared with patients from two sarilumab pivotal phase 3 RCTs. Sarilumab is a human anti-IL-6R α monoclonal antibody for treatment of moderate-to-severely active RA.

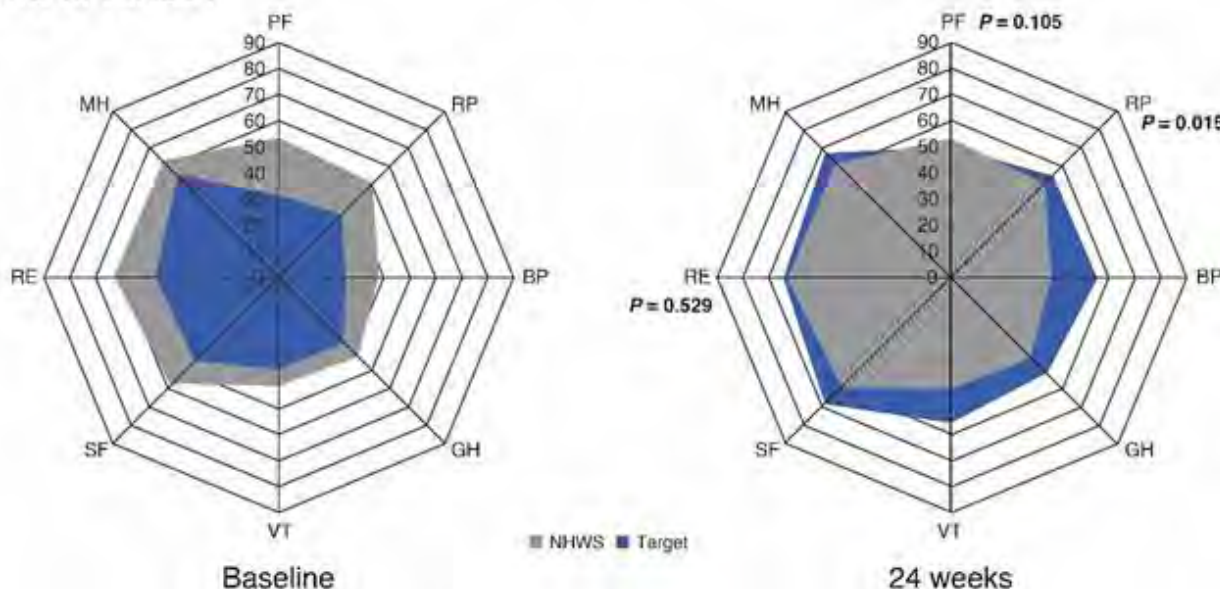
Methods: “Real world” data were from adult participants of the cross-sectional 2015 US National Health and Wellness Survey (NHWS) with a patient-reported diagnosis of RA, moderate/severe disease activity and administered disease-modifying anti-rheumatic drugs (DMARDs) at the point of survey. RCT data were from MOBILITY – Part B and TARGET trials comparing the efficacy and safety of sarilumab subcutaneous (SC) 150 mg and 200 mg every 2 weeks

Figure. SF-36 individual domain scores for NHWS versus MOBILITY and TARGET, respectively

NHWS vs MOBILITY



NHWS vs TARGET



(q2w)plus methotrexate in MOBILITY or conventional DMARDs in TARGET versus placebo in patients with moderate-to-severely active RA and inadequate responses to methotrexate (MTX-IR, MOBILITY) or tumor necrosis factors inhibitors (TNF-IR, TARGET). HRQoL was measured using the Short Form-36v2 (SF-36v2) in the NHWS, and both RCTs at baseline and Week 24; WP impairment (WPI) and activity impairment (AI) were measured via the WPAI scale in the NHWS and MOBILITY. Bivariate analyses evaluated between-group differences in SF-36v2 physical (PCS) and mental (MCS) component summary and domain scores and WPAI absenteeism, presenteeism (%work time missed), overall WPI and AI.

Results: Mean ages of the analyzed cohorts were 54, 51 and 53 years; 61%, 82%, and 80% were female, respectively in NHWS (n=2016), MOBILITY (n=799) and TARGET (n=365). At baseline, versus NHWS patients, those enrolled in MOBILITY reported greater presenteeism (47.25 vs 37.50; $P < 0.001$), overall WPI (51.29 vs 43.11; $P = 0.001$) and AI (62.42 vs 50.96; $P < 0.001$). Patients in MOBILITY and TARGET reported significantly lower baseline scores versus NHWS in SF-36v2 PCS (31.27, 29.42 vs 38.54) MCS (38.86, 38.73 vs 43.97), and all domain scores ($P < 0.001$; Figure) indicating greater HRQoL impairment. At Week 24 both trial cohorts reported improved HRQoL (Figure) and AI in MOBILITY (34.08 vs 39.76, respectively; $P < 0.05$) following treatment with sarilumab than the NHWS cohort scores.

Conclusion: Patients in both sarilumab RCTs reported worse baseline HRQoL, and in MOBILITY greater WPI and AI than NHWS RA patients. After 24 weeks treatment with sarilumab, both RCT cohorts reported improvements exceeding NHWS scores, with few exceptions. These data offer perspective on the benefits of sarilumab treatment on HRQOL, **WP** and **AI**.

Keywords: Rheumatoid arthritis, sarilumab, anti-IL-6R α , health-related quality of life

Disclosure: V. Strand, None; C. M. Carpinella, Sanofi and Regeneron Pharmaceuticals, Inc., 9; L. K. Lee, Sanofi and Regeneron Pharmaceuticals, Inc., 9; S. Boklage, Regeneron Pharmaceuticals, Inc., 1, 3; M. Reaney, Sanofi, 1, 3.

Abstract Number: 2549

Patient-Reported Benefits of Sarilumab Monotherapy in Adult Patients with Active Rheumatoid Arthritis: Results from an Open-Label Extension Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Sarilumab is a human monoclonal antibody that binds to membrane and soluble IL-6R, which is approved for the treatment of moderate to severe rheumatoid arthritis (RA) in adult patients. In MONARCH (NCT02332590), sarilumab 200 mg monotherapy administered every 2 weeks (q2w) was superior to adalimumab monotherapy 40 mg q2w, among patients with RA intolerant of, inappropriate candidates for, or inadequate responders to methotrexate (MTX-IR).¹ Safety profiles of both therapies were consistent with previously reported data with this class.¹ Patients completing MONARCH could enter the open-label extension (OLE [maximum duration 276 weeks]), where all patients received sarilumab 200mg q2w. The objective of the study was to compare patient-reported outcomes (PROs) among patients remaining on sarilumab (continuation group) vs patients switching from adalimumab to sarilumab (switch group) in the OLE.

Methods: PROs assessed at entry into the OLE and at week 24 of the OLE are shown in the Table. Patient global assessment of disease activity (PtGA) by visual analog scale (VAS), pain VAS and Health Assessment Questionnaire Disability Index (HAQ-DI) were also assessed at week 48 of the OLE. *P*-values for all PROs in the OLE were considered nominal. Available safety data were reported for all patients who reached week 52 of the OLE as of March 2017.

Table. Mean scores for PROs at week 24 of the double-blind MONARCH study (week 0 of OLE, week 0E) and at week 24 of the OLE (week 24E) of MONARCH

PRO	Week 0E score ^a Mean (SD)		<i>P</i> -value ^b	Week 24E score ^a Mean (SD)		<i>P</i> -value ^b
	ADA	SAR		ADA/SAR	SAR/SAR	
Patient Global VAS ^c	42.57 (22.20)	34.58 (23.93)	0.0012	28.94 (20.80)	27.44 (20.94)	0.3020
Pain VAS ^c	42.49 (23.87)	34.44 (22.52)	0.0011	27.85 (20.32)	26.40 (21.70)	0.7014
HAQ-DI ^c	1.21 (0.67)	1.20 (0.64)	0.9014	0.87 (0.62)	0.86 (0.61)	0.2000
SP-36 component summary ^d						
PCS	37.14 (7.70)	38.36 (7.85)	0.0000	38.37 (7.80)	41.82 (8.20)	0.0000
MCS	43.89 (11.88)	44.89 (10.51)	0.5029	40.28 (10.90)	44.58 (10.97)	0.0019
SP-36 individual domain ^e						
Physical functioning	36.63 (23.70)	35.68 (23.48)	0.0340	34.47 (20.81)	36.28 (22.86)	0.0019
Role-physical	50.44 (22.43)	50.22 (21.32)	0.0000	37.12 (19.88)	40.30 (21.40)	0.1000
Bodily pain	47.45 (19.02)	52.54 (19.11)	0.0001	33.06 (17.38)	35.80 (21.10)	0.0000
General health	46.35 (19.29)	47.04 (19.04)	0.0703	33.48 (17.38)	32.48 (19.08)	0.2004
Vitality	40.63 (19.20)	41.94 (19.27)	0.1986	30.30 (17.34)	30.79 (19.01)	0.5204
Social functioning	40.50 (20.36)	47.04 (23.37)	0.0002	30.29 (20.23)	33.63 (22.89)	0.0472
Role emotional	41.83 (20.36)	46.54 (24.52)	0.0001	30.88 (22.07)	36.15 (22.11)	0.0004
Mental health	38.42 (19.60)	38.15 (17.52)	0.8443	30.18 (17.88)	37.47 (17.23)	0.0000
FACT-G ^f	32.51 (10.26)	30.67 (9.43)	0.0040	30.20 (9.84)	30.01 (9.10)	0.9001
Morning stiffness VAS ^g	39.62 (20.45)	34.08 (20.80)	0.0001	28.84 (20.20)	28.35 (24.70)	0.8520
EQ-5D VAS ^h	58.68 (21.72)	54.80 (21.70)	0.0486	70.20 (18.30)	71.74 (19.08)	0.0000
EQ-5D Single Index Utility ⁱ	0.58 (0.20)	0.60 (0.20)	0.0000	0.84 (0.20)	0.87 (0.20)	0.0004
SAIDI ^j	4.14 (2.14)	3.44 (2.14)	0.0000	2.88 (1.77)	2.88 (1.80)	0.8801
WPI-BA ^k						
Work days missed due to RA	1.62 (0.63)	1.54 (0.73)	0.0009	0.62 (0.20)	0.40 (0.20)	0.0002
Days with work productivity reduced by 50% due to RA	1.21 (0.60)	1.70 (0.70)	0.0004	1.10 (0.74)	0.30 (0.24)	0.0004
Rate of RA interference with work productivity	23.04 (30.11)	20.47 (27.93)	0.0002	16.57 (24.40)	19.31 (27.08)	0.2007
House work days missed due to RA	3.27 (0.63)	2.72 (0.60)	0.0000	2.96 (0.67)	0.70 (0.31)	0.1400
Days with household work productivity reduced by 50% due to arthritis	4.67 (0.40)	3.36 (0.40)	0.0003	3.24 (0.10)	3.40 (0.24)	0.3000
Days with family, social, or leisure activities missed due to RA	2.00 (0.60)	1.40 (0.40)	0.1404	1.00 (0.20)	1.04 (0.42)	0.0004
Days with outside help hired due to RA	2.00 (0.70)	1.88 (0.42)	0.1700	1.10 (0.10)	1.47 (0.70)	0.0002
Rate of RA interference with household work productivity	17.65 (27.20)	7.34 (20.00)	0.0004	26.72 (20.24)	24.58 (24.40)	0.0000

^aWeek 0E: baseline (end of the double-blind period) and the start of the OLE; week 24E: maximum duration of the OLE (week 276).

^bQ2: baseline week 24 in the OLE; activity: patients from the ADA/IT comparison (continued) vs SAR (continued) vs SAR/SAR (continued).

^cSP-36 component summary: SF-36.

^dPCS: physical component summary.

^eMCS: mental component summary.

^fFACT-G: Functional Assessment of Cancer Therapy - General.

^gEQ-5D VAS: EuroQol Visual Analog Scale.

^hEQ-5D Single Index Utility: EuroQol Single Index Utility.

ⁱSAIDI: Simple Arthritis Index.

^jWPI-BA: Work Productivity Index - Baseline.

Results: Of 321 patients who completed MONARCH, 320 entered the OLE; 155 in the switch and 165 in the continuation groups. From entry to the OLE through week 24 of the OLE, when all patients received sarilumab, the switch and continuation groups reported further improvements in PROs, including FACIT-F and RAID. Patients in the continuation group reported better SF-36 physical component summary (PCS), physical and social functioning domain scores, and less work days missed due to RA ($P \leq 0.05$) (Table). PtGA VAS, pain VAS, and HAQ-DI were stable in both groups from week 24 of the OLE through week 48 of the OLE (data not shown). Available safety data showed 76.1% vs 70.9% treatment-emergent adverse events (TEAEs), 11.0% vs 3.6% serious adverse events, and 6.5% vs 7.3% TEAEs leading to treatment discontinuation in the switch and continuation groups, respectively. Two deaths occurred in the switch and one in the continuation groups.

Conclusion: Sarilumab was superior to adalimumab in many PROs at the end of MONARCH. In the OLE, where all patients received sarilumab, patients in the switch group reported similar improvements in PROs as the continuation group, with the two groups reporting similar outcomes by weeks 24 and 48 of the OLE, except in SF-36 PCS, physical function and social function domains, and work days missed due to RA, where patients in the switch group reported better scores.

Reference: 1. Burmester GR et al. *Ann Rheum Dis*. 2017;76:840–847.

Disclosure: V. Strand, Abbvie, Amgen Corporation, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Celltrion, CORRONA, Crescendo/Myriad, EMD Serono, Genentech/Roche Janssen, Lilly, Merck, Novartis, Pfizer, Samsung, Sandoz, UCB, 5; M. Reaney, Sanofi, 1, 3; E. Mangan, Regeneron Pharmaceuticals Inc., 1, 3; H. van Hoogstraten, Sanofi, Novartis, 1, Sanofi, 3; S. Boklage, Regeneron Pharmaceuticals, Inc., 1, 3; C. C. Hu, Sanofi, 1, 3.

Abstract Number: 2550

Phase 3 Equira 48 Week Study Results Demonstrated No Impact on Efficacy and Safety When Patients with Moderate-to-Severe Rheumatoid Arthritis Were Switched between Reference Etanercept (ETN) and GP2015, an Etanercept Biosimilar

Arthur Kavanaugh¹, Marco Matucci-Cerinic², Hendrik Schulze-Koops³, Maya Buch⁴, Yannick Allanore⁵, Eugeniusz J. Kucharz⁶ and Goran Babic⁷, ¹UC San Diego School of Medicine, La Jolla, California, La Jolla, CA, ²Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy, ³Ludwig-Maximilians-University, Munich, Germany, Munich, Germany, ⁴University of Leeds, United Kingdom, Leeds, United Kingdom, ⁵Cochin Hospital, Paris Descartes University, Paris, France, Paris, France, ⁶Department of Internal Medicine and Rheumatology, Medical University of Silesia, Katowice, Poland, Katowice, Poland, ⁷Hexal AG, a Sandoz company, Holzkirchen, Germany, Holzkirchen, Germany

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

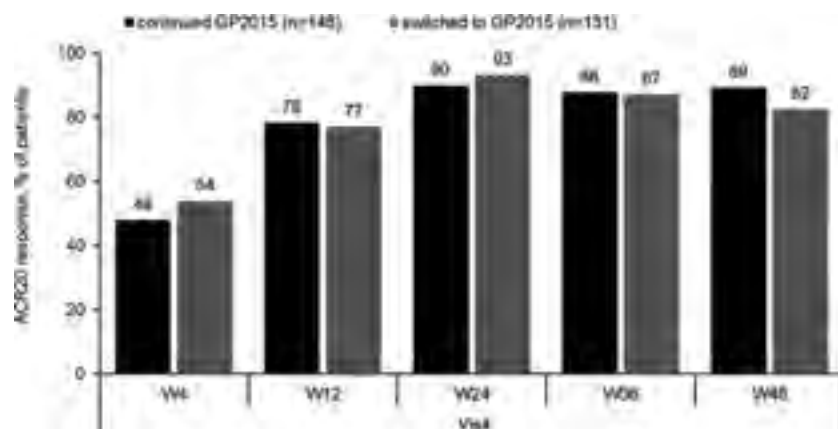
Session Time: 9:00AM-11:00AM

Background/Purpose: Compared to ETN, GP2015 has equivalent efficacy, and comparable safety and immunogenicity in patients with chronic plaque-type psoriasis.¹ The purpose of this study is to compare the efficacy and safety of GP2015 and ETN and evaluate the effects of switching from ETN to GP2015 in patients with moderate-to-severe rheumatoid arthritis (RA).

Methods: EQUIRA was a 48-week, randomized, double-blind, Phase 3, two treatment period confirmatory study. The primary endpoint was equivalent change from baseline (BL) in DAS28-CRP at week 24. Patients ≥ 18 years with active RA (ACR 1987 or ACR/EULAR 2010 criteria for ≥ 6 months before BL and active disease defined as DAS28-CRP ≥ 3.2 and CRP > 5 mg/L or ESR ≥ 28 mm/h) and inadequate response to methotrexate (MTX) were randomized 1:1 to 50 mg GP2015 or ETN subcutaneously once weekly for 24 weeks (Treatment period 1 [TP1]). Patients with at least moderate EULAR response at Week 24 either continued GP2015 treatment or, in the ETN group, were switched to receive 50 mg GP2015 up to 48 weeks (Treatment period 2 [TP2]). All patients continued to receive concomitant MTX (10–25 mg/week) at a stable dose and folic acid. Efficacy outcome measures included change in DAS28-CRP, EULAR and ACR20/50/70 responses.

Results: Baseline characteristics were comparable between the GP2015 (n=186) and ETN (n=190) groups. The primary endpoint for equivalence during TP1 was met and previously presented.² At Week 48, the ACR 20 response rates were

comparable between patients who continued on or switched to GP2015 (Figure 1). In TP2, treatment-emergent adverse events (AEs) (Figure 2) occurred in 42.9% vs 38.0% patients with only 13.1% vs. 11.4% considered drug related in the continued GP2015 (n=175) vs the switched (n=166) groups; serious AEs occurred in 2.3% vs 2.4% patients (TP2 safety set). Injection site reactions occurred in 6 (3.6%) patients in the switched group but none in the continued GP2015 group. In TP2, four (2.4%) patients in the continued GP2015 group had single-event, very low titer, non-neutralizing antidrug antibodies detected.



Conclusion: The efficacy of GP2015 over 48 weeks was comparable to that of ETN. In addition, the switch from ETN to GP2015 did not impact efficacy and safety of etanercept in patients with moderate-to-severe RA.

References: 1. Griffiths CEM, et al. *Br J Dermatol.* 2017;176:928–38; 2. Kavanaugh A, et al. [abstract]. *Arthritis Rheumatol.* 2017; 69 (suppl 10).

Figure 1. ACR20 Response Rates from Baseline through Week 48

Figure 2. Safety Overview (TP2)

Disclosure: A. Kavanaugh, Sandoz, 5, Merck & Co., 5, Boehringer-Ingelheim, 5; M. Matucci-Cerinic, Actelion, 2, Beyer, 2, Bristol-Myers Squibb, 2, Chemomab, 2, Inventiva, 2, Pfizer, Inc., 2, Sandoz, 5; H. Schulze-Koops, None; M. Buch, Pfizer, Eli Lilly, Roche, AbbVie, Astra Zeneca, Sandoz, UCB, 2, Abbvie, Astra Zeneca, Eli Lilly, Roche, Pfizer, and Sandoz, 5; Y. Allamore, Pfizer, Inc., 2, Sandoz, 2; E. J. Kucharz, AbbVie Inc., 5, Berlin Chemie, 5, Biogen, 5, Celgene Corporation, 5, Egis, 5, Eli Lilly and Co., 5, Merck & Co., 5, Novartis, 5, Pfizer, Inc., 5, Polpharma, 5, Roche, 5, Sandoz, 5, UCB, Inc., 5; G. Babic, Hexal AG, a Sandoz company, 3.

Abstract Number: 2551

Rheumatoid Arthritis Treatment with Filgotinib: Week 132 Safety Data from a Phase 2b Open-Label Extension Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The orally administered, selective inhibitor of Janus Kinase 1 (JAK1), filgotinib (FIL), is currently being investigated for the treatment of rheumatoid arthritis (RA) in Phase 3 studies and in other inflammatory diseases. The long-term safety and efficacy of FIL in patients (pts) with RA is being evaluated in the DARWIN 3 (Phase 2b) open-label extension (OLE).

Methods: Two 24-week Phase 2b studies, DARWIN 1 and 2 (Ref 1, 2) evaluated the safety and efficacy of FIL in pts with moderately to severely active RA. Eligible pts from these studies could enroll in DARWIN 3. In this OLE study, pts received FIL 200 mg QD or 100 mg BID or 100 mg QD (US males only). Here we present cumulative safety data (from the first dose of FIL in the DARWIN program through 20 Feb 2018) and efficacy data (from DARWIN 3 Day 1 to Week 132).

Results: Of 877 pts from DARWIN 1 and 2, 790 (90%) completed the study, and 739 (84%) enrolled in DARWIN 3; 603 (82%) were female, mean age was 53 years. At analysis, 469/739 (64%) remained in the OLE. Cumulative patient years of exposure (PYE) was 2081, median time on study drug was 1197 days. Key safety data are summarized in Table 1; laboratory abnormalities are shown in Table 2. No new trends or safety signals were identified. Efficacy data revealed that 89%, 70%, and 49% of pts had ACR20/50/70 responses, respectively, and 69% achieved DAS28-CRP ≤ 3.2 (observed case analysis).

Conclusion: Filgotinib continues to demonstrate a favorable safety and tolerability profile in pts with RA over a 2.5-year period, with maintenance of therapeutic response in the long-term.

Table 1: Key Safety Events Per 100 PYE

	Filgotinib (200mg daily) + MTX PYE=1443	Filgotinib (200mg daily) Monotherapy PYE=599	Total* PYE=2042
Treatment-emergent AEs (TEAEs)	144.1	151.5	146.3
Serious TEAEs	5.1	6.8	5.6
TEAEs for Infections	41.6	36	40
Serious TEAEs for Infections	0.8	1.7	1
Malignancy (excluding NMSC†)	0.6	0.7	0.6
Herpes Zoster	1.5	1.5	1.5
Deep Vein Thrombosis ‡	0.07	0	0.05
Pulmonary Embolism‡	0.07	0	0.05
Active Tuberculosis	0	0	0
Deaths	0.1	0.5	0.2

* Treatment groups with fewer than 10 subjects were omitted for clarity; †Non-melanoma skin cancer; ‡Single patient DVT leading to PE.

Table 2. Key Treatment-Emergent Laboratory Abnormalities

	Filgotinib (200mg daily) + MTX N=500†	Filgotinib (200mg daily) Monotherapy N=224	Total* N=724
Grade 1 or 2 (% of patients‡)			
Hemoglobin Decrease	22.8%	28.6%	24.6%
Lymphocytes Decrease	21.6%	16.1%	19.9%
Neutrophils Decrease	11.0%	12.5%	11.5%
Platelets Decrease	3.8%	2.2%	3.3%
ALT Increase	26.5%	18.8%	24.1%
Creatinine Increase	3.8%	8.0%	5.1%
Grade 3 or 4 (% of patients‡)			
Hemoglobin Decrease	1.0%	0.9%	1.0%
Lymphocytes Decrease	3.6%	1.8%	3.1%
Neutrophils Decrease	1.0%	1.3%	1.1%
Platelets Decrease	0.4%	0	0.2%
ALT Increase	0.4%	0.9%	0.6%
Creatinine Increase	0.2%	0	0.1%

*Treatment groups with fewer than 10 subjects were omitted for clarity; †One patient in this group did not have post-baseline data due to withdrawal from the study; ‡Percent of patients who had at least one measured laboratory parameter of the listed grades.

References:

1. Westhovens R, et al. *Ann Rheum Dis* 2017;76:998-1008; 2. Kavanaugh A, et al. *Ann Rheum Dis* 2017;76:1009-1019.

Disclosure: A. Kavanaugh, Gilead Science Inc, 5; M. C. Genovese, Gilead, Galapagos, Abbvie, Lilly, Pfizer, 2, Gilead, Galapagos, Abbvie, Lilly, Pfizer, 5; K. Winthrop, Pfizer, Lilly, Galapagos, Gilead, Abbvie, 5; M. Greenwald, Celgene, Bristol Myers Squibb, Gilead, Lilly, Pfizer, Abbvie, Fuji, and Novartis, 2, Novartis, 5; L. Ponce, None; F. Enriquez Sosa, None; M. Stanislavchuk, None; M. Mazur, None; A. Spindler, None; R. Cseuz, None; N. Nikulenkova, None; M. Glowacka-Kulesz, None; I. Szombati, None; A. Dudek, None; N. Mozaffarian, Gilead Science Inc, 1, 3; J. Greer, Gilead Science, Inc, 1, 3; R. Kunder, Gilead Science, Inc, 1, 3; D. An, Gilead Science Inc, 1, 3; L. Meuleners, Galapagos, 3; R. Besuyen, Galapagos, 3, 5; R. Alten, Gilead Science Inc, Galapagos, 2; R. Westhovens, Celltrion, Galapagos, Gilead, 5, Bristol Myers Squibb, Roche, 2.

Fatigue in Psoriatic Arthritis Patients Treated with Intravenous Golimumab: Early Improvement Is Associated with Week 24 Outcomes in Acr 20, 50, and Health-Related Quality of Life

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To investigate improvement in fatigue in adult patients with active psoriatic arthritis (PsA) treated with intravenously administered (IV) golimumab, an anti-TNF α monoclonal antibody, and to evaluate improvement in fatigue at Week 8 in predicting ACR 20, 50, minimal disease activity (MDA), and health-related quality of life (HRQoL) outcomes at Week 24.

Methods: GO-VIBRANT is a Phase 3, multicenter, randomized, double-blinded, placebo-controlled trial. Adults with active PsA who were biologic-naïve (n=480; aged ≥ 18 years) were randomized to IV golimumab 2 mg/kg at Weeks 0 and 4 and every 8 weeks thereafter (n=241), or placebo at Weeks 0, 4, 12, and 20 with crossover to IV golimumab at Week 24 (n=239). Fatigue was measured using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and HRQoL and physical function were measured by the Short-Form 36 (SF-36) and Health Assessment Questionnaire Disability Index (HAQ-DI). ANCOVA, T-test, CMH test, and Chi-square test were used for various analyses.

Results: There was greater mean improvement in the FACIT-F score from baseline with IV golimumab than placebo at Weeks 8, 14, and 24 (7.9 vs 2.0; 8.4 vs 2.2; 9.2 vs 2.3, respectively, all $p < 0.0001$) (Table 1a). A larger proportion of golimumab-treated patients achieved a ≥ 4 -point improvement in FACIT-F as early as Week 8 vs placebo ($p < 0.0001$) (Table 1b). Similar results were found after adjusting for ACR 20 and 50 response. General linear models suggested patients with clinically meaningful improvement in fatigue (≥ 4 points) at Week 8 (on average) achieved improvements in HAQ-DI and (SF-36) Mental Component Summary (MCS) and Physical Component Summary (PCS) at Week 24 (Table 2b). Logistic regressions suggested that clinically meaningful improvement in fatigue at Week 8 was associated with ACR 20 and ACR 50 responses, as well as clinically meaningful improvements in SF-36 MCS, PCS (≥ 5 points), and HAQ-DI (≥ 30) at Week 24, but not MDA responses (OR 1.54 [95% CI 0.89-2.67, p -value 0.1184) (Table 2a). Fatigue improvements at Week 8 did not predict normal SF-36 MCS and PCS scores (≥ 50) at Week 24.

Conclusion: Adult patients with active PsA treated with IV golimumab showed larger mean improvement in fatigue vs placebo. Early improvement in fatigue is associated with 24-week outcomes in ACR 20, 50, and HRQoL.

Table 1a. Summary of Change from Baseline in FACIT-Fatigue Through Week 24 Without ACR 20 and 50 adjustments

Mean \pm SD change from baseline in FACIT-F score	Time point	Golimumab (N is between 231 - 233)	Placebo (N=between 221-225)	P-value*
	Week 8	7.9 \pm 9.53 (n=232)	2.0 \pm 7.89 (n=225)	<0.0001
	Week 14	8.4 \pm 9.86 (n=233)	2.2 \pm 7.60 (n=222)	<0.0001
	Week 24	9.2 \pm 9.77 (n=231)	2.3 \pm 7.80 (n=221)	<0.0001
*p-value is based on ANCOVA controlling for baseline MTX usage (Yes, No) and baseline FACIT-fatigue score.				
1b. Number of Subjects Who Achieved at Least a 4-Unit Improvement from Baseline in FACIT-Fatigue Through Week 24				
Number (%) of patients who achieved ≥ 4 -unit improvement from baseline in FACIT-F score	Week 8	161 (69.4) (n=232)	91 (40.4) (n=225)	<0.0001**
	Week 14	159 (68.2) (n=233)	92 (41.4) (n=222)	<0.0001**
	Week 24	162 (70.1) (n=231)	95 (43.0) (n=221)	<0.0001**
**p-value is based on CMH test controlling for baseline MTX usage (Yes, No)				

Table 2a. Logistic regression of ACR 20, 50, Minimal Disease Activity, and HRQoL at Week 24 (dependent variable) on FACIT-fatigue improvement of ≥ 4 at Week 8 (independent variable)

	Odds ratio	95% CI	P-value*
Week 24			
ACR 20 (N=457)	1.98	1.28-3.07	0.0022
ACR 50 (N=457)	2.19	1.33-3.60	0.0020
HAQ-DI (≥ 30) (N=449)	2.31	1.53-3.51	<.0001
Minimal Disease Activity (N=449)	1.54	0.89-2.67	0.1184
SF-36 MCS (≥ 50) (N=457)	0.94	0.63-1.41	0.7615
SF-36 PCS (≥ 50) (N=457)	1.14	0.63-2.07	0.6634
SF-36 MCS improvement (≥ 5 points) (N=457)	2.22	1.48-3.34	0.0001
SF-36 PCS improvement (≥ 5 points) (N=457)	2.20	1.45-3.33	0.0002

*p-value is based on Chi-Square test controlling for treatment

2b. General linear model of quality of life parameters at Week 24 (dependent variable) on FACIT-fatigue improvement of ≥ 4 at Week 8 (independent variable)

	Estimate**	P-value*
Week 24		
HAQ-DI (N=449)	0.229	<.0001
SF-36 MCS (N=457)	-2.842	0.0003
SF-36 PCS (N=457)	-3.340	<.0001

*p-value is based on t-test controlling for baseline value of quality of life parameters.

All variables are based on observed score, **estimate represents the average impact of having a 4-point FACIT-F improvement (compared to not having a 4-point FACIT-F improvement) on the quality of life parameters

Disclosure: A. Kavanaugh, Janssen Research & Development, LLC, 2; M. E. Husni, Janssen Research and Development, LLC, 2; E. K. H. Chan, Janssen Global Services, LLC, 3; D. D. Harrison, Janssen Research & Development, LLC, 3; L. Kim, Janssen Research & Development, LLC, 3; K. H. Lo, Janssen Research and Development, LLC, 3; E. C. Hsia, Janssen Research & Development, LLC, 3; C. Han, Janssen Research & Development, LLC, 3.

Abstract Number: 2553

Secukinumab Provides Early and Sustained Improvements in Health-Related Quality of Life in Patients with Psoriatic Arthritis: Pooled Results from the Secukinumab Phase 3 Trial Program

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Session Information

Session Date: Tuesday, October 23, 2018

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Session Time: 9:00AM-11:00AM

Background/Purpose: Improving health-related quality of life (HRQoL) is a key goal of psoriatic arthritis (PsA) therapy. Secukinumab, a fully-human IL-17A inhibitor, has been shown to rapidly and sustainably improve multiple clinical domains of PsA. This comprehensive pooled analysis assessed the impact of secukinumab on HRQoL, assessed by the Short Form-36 Health Survey (SF-36), in TNF inhibitor (TNF)-naïve and TNF inhibitor inadequate responder/intolerant (TNF-IR) patients (pts) with PsA in FUTURE 2, 3, 4 and 5 (NCT01752634; NCT01989468; NCT02294227; NCT02404350).

Methods: Pts with active PsA, stratified by TNF status, were randomized to subcutaneous placebo (PBO) or secukinumab 75 mg (FUTURE 2), 150 mg (FUTURE 2, 3, 4, 5), 150 mg no load (FUTURE 4, 5) or 300 mg (FUTURE 2, 3, 5) administered at baseline (BL) and Wks 1, 2, 3 and 4, followed by every 4 wks (or every 4 wks from BL in no load arms). At Wk 16 or 24, pts on PBO were re-randomized to secukinumab. Mixed-model for repeated measures was used to assess change in SF-36 from BL to Wk 16; observed data are presented at Wk 52. The proportion of pts reporting improvements meeting or exceeding the minimal clinically important differences for SF-36 physical (PCS responders), mental component

summary (MCS responders) and individual SF-36 domains was assessed. Non-responder imputation was used, and the proportion of SF-36 responders was compared using Fisher's exact test. Pooled data for pts receiving licensed doses of secukinumab (300 or 150 mg) or PBO are shown.

Results: Of 2049 pts overall, 461, 572, 335 and 681 were in the secukinumab 300 mg, 150 mg, 150 mg (no load) and PBO groups, respectively, of whom approx. 30% were TNF-IR. Least squares mean changes from BL in PCS and MCS at Wk 16 were significantly improved vs PBO for all secukinumab doses, overall and in both TNF-naïve and TNF-IR pts (Table 1). All individual domain scores were also significantly improved with secukinumab vs PBO, except role-emotional in TNF-IR pts with secukinumab 150 mg. There was a significantly higher proportion of SF-36 responders (PCS, MCS and individual domains) in the secukinumab groups at Wk 16 vs PBO in the overall sample (Table 2), except for role-emotional with secukinumab 150 mg. There were consistent trends for higher SF-36 response rates with secukinumab vs PBO regardless of TNF status, with higher SF-36 response rates in TNF-naïve pts. Improvements in PCS, MCS, individual domain scores and response rates were sustained to Wk 52.

Conclusion: Secukinumab 300 mg and 150 mg offered significant and sustained improvements in HRQoL (SF-36) up to 52 wks in pts with PsA, regardless of TNF status.

Table 1. Least squares mean changes from baseline to Week 16 in SF-36 scores in TNF-naïve and TNF-IR patients in a pooled analysis of FUTURE 2, FUTURE 3, FUTURE 4, and FUTURE 5 RCTs.

LS mean change from baseline	Secukinumab 300 mg			Secukinumab 150 mg			Secukinumab 150 mg (no load)			Placebo		
	(N = 461)			(N = 572)			(N = 335)			(N = 681)		
	Overall group	TNF-naïve	TNF-IR	Overall group	TNF-naïve	TNF-IR	Overall group	TNF-naïve	TNF-IR	Overall group	TNF-naïve	TNF-IR
PCS	6.74*	7.32*	6.49*	5.10*	5.78*	4.65*	4.88*	5.50*	4.48**	1.58	2.14	1.24
MCS	3.68*	3.97*	3.55**	3.31*	3.80*	2.73***	3.30**	3.60**	3.09***	1.02	1.46	0.45
Physical functioning	17.58*	19.31*	16.70*	12.68*	14.75*	11.01*	13.15*	14.98*	11.78**	3.64	5.97	0.80
Role-physical	16.93*	17.97*	17.68*	13.33*	15.60*	11.10***	12.66*	14.61*	10.81	5.42	6.49	5.88
Bodily pain	18.50*	20.13*	17.93*	15.29*	16.84*	14.89*	14.89*	16.80*	13.13**	5.05	6.46	4.69
General health	10.09*	11.58*	8.80*	7.02*	8.53*	5.46**	6.20*	6.73*	7.11**	1.04	2.33	-0.07
Vitality	13.06*	14.36*	12.43*	10.61*	12.35*	8.93**	10.33*	11.18*	10.82**	2.90	3.95	2.97
Social functioning	13.42*	14.01*	14.40*	12.27*	13.55*	11.74**	11.28*	12.65*	10.35**	3.30	4.78	1.94
Role-emotional	10.33*	10.84*	11.14**	7.43**	9.14**	5.55	8.57**	9.86**	7.38	3.50	4.60	2.74
Mental health	8.15*	9.33*	6.69**	7.21*	8.20*	6.29**	6.98*	7.79**	6.31**	1.82	3.14	-0.11

* p < 0.0001; ** p < 0.01, *** p < 0.05 versus placebo.

LS = least squares; MCS = mental component summary; MMRM = Mixed model for repeated measures; PCS = physical component summary; RCT, randomized controlled trial; TNF-IR, tumor necrosis factor inhibitor inadequate responder/intolerant; TNF-naïve, tumor necrosis factor inhibitor naïve.

MMRM was used to assess change in SF-36 from baseline to Week 16.

Table 2. Proportion of SF-36 responders (improvements \geq MCID) at Weeks 16 and 52 in a pooled analysis of FUTURE 2, FUTURE 3, FUTURE 4, and FUTURE 5 RCTs.

SF-36 Responder rates (%)	Secukinumab 300 mg		Secukinumab 150 mg		Secukinumab 150 mg (no load)		Placebo
	(N = 461)		(N = 572)		(N = 335)		(N = 681)
	Week 16	Week 52	Week 16	Week 52	Week 16	Week 52	Week 16
PCS	65.9*	65.7	59.4*	55.1	61.8*	52.2	42.0
MCS	48.4**	49.4	50.0**	44.9	49.9**	45.1	40.4
Physical functioning	70.9*	66.1	65.2*	59.1	65.1**	54.0	50.2
Role-physical	65.5*	62.8	63.8*	56.0	63.0**	52.2	48.5
Bodily pain	66.8*	68.2	65.2*	59.1	64.2*	61.1	45.4
General health	62.0*	60.3	57.9*	49.4	53.7**	50.4	42.9
Vitality	63.8*	59.0	63.1*	54.8	62.4*	62.8	44.1
Social functioning	56.2*	52.3	55.9*	49.7	54.3*	45.1	39.4
Role-emotional	51.0**	50.6	48.3	43.8	45.4	37.2	40.7
Mental health	58.8**	57.7	59.8*	50.3	55.8**	61.1	45.1

* p < 0.0001; ** p < 0.01, *** p < 0.05 versus placebo.

MCID = minimal clinically important difference; MCS = mental component summary; PCS = physical component summary; RCT = randomized controlled trial.

PCS and MCS response: patients with ≥ 2.5 point increase in component summary score.

SF-36 Individual domain response: patients with ≥ 5.0 point increase in SF-36 individual domain score.

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Abstract Number: 2554

Abatacept without Methotrexate in Patients with Active Psoriatic Arthritis: A Post Hoc Analysis of a Phase III, Randomized Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: In the randomized, placebo (pbo)-controlled Phase III ASTRAEA study (ClinicalTrials.gov, NCT01860976) patients (pts) with active psoriatic arthritis (PsA) were randomized to abatacept (ABA) or pbo; ABA significantly improved ACR20 responses at 24 weeks (wks).¹ MTX was permitted but not required; randomization was by concurrent MTX resulting in a subgroup of pts receiving ABA or pbo without MTX. This *post hoc* analysis evaluates the efficacy of ABA in pts not receiving MTX.

Methods: Pts with PsA and inadequate response/intolerance to conventional synthetic (cs)DMARDs were randomized (1:1) to SC ABA 125 mg or pbo weekly for 24 wks. At Wk 16, pts without $\geq 20\%$ improvement in joint counts escaped to open-label ABA.¹ MTX, other csDMARDs and corticosteroids (≤ 10 mg prednisone equivalent) at enrollment could be continued at a stable dose. Baseline pt characteristics were analyzed descriptively by concomitant MTX use. Outcomes including ACR20 responses (95% CI) and adjusted mean changes in DAS28 (CRP) from baseline were evaluated in pts not receiving MTX.

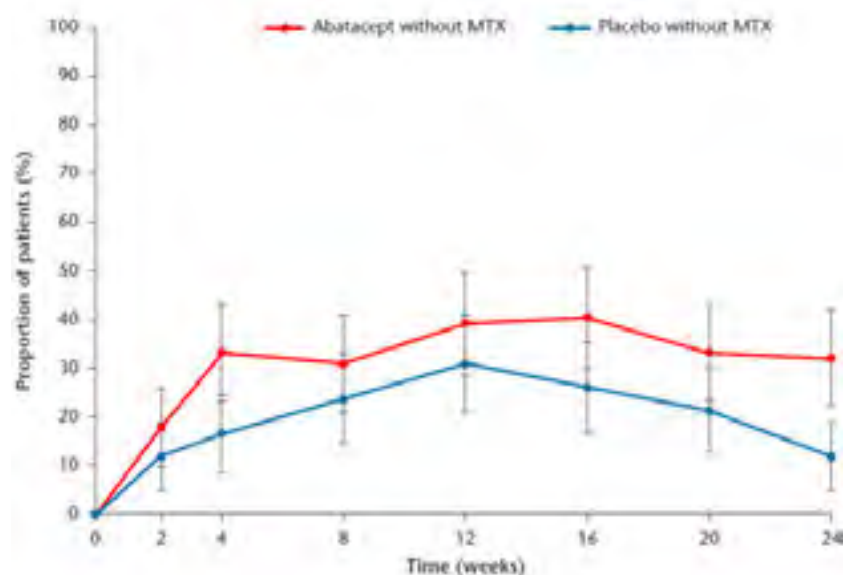
Results: Of 424 randomized pts, 168 were not receiving concomitant MTX (ABA [n=84], pbo [n=84]). Pts not receiving MTX vs pts receiving MTX were more likely to be from N America, less likely to be from S America, had longer disease duration, and higher rates of TNF inhibitor or experience with ≥ 2 prior csDMARDs (Table 1). In pts not receiving MTX, the percentage of female pts and baseline structural damage were greater in the ABA vs pbo group. At Wk 24, ABA without MTX significantly increased ACR20 responses (95% CI) vs pbo (32.1% [22.2,42.1] vs 11.9% [5.0, 18.8]; Figure 1) and improved adjusted mean changes in DAS28 (CRP) from baseline to Wk 24 (95% CI) vs pbo (−1.49 [−1.87, −1.12] vs −0.68 [−1.11, −0.26]; adjusted difference −0.81 [−1.34, −0.28]; Figure 2).

Conclusion: In this *post hoc* analysis of ASTRAEA, abatacept without MTX significantly improved ACR20 responses and DAS28 (CRP) in pts with PsA. Improvements in outcomes in the pbo group help characterize the true pbo response and the variable nature of PsA symptoms. These data suggest that abatacept without MTX may be successfully used in pts with PsA and inadequate response/intolerance to MTX.

Reference:

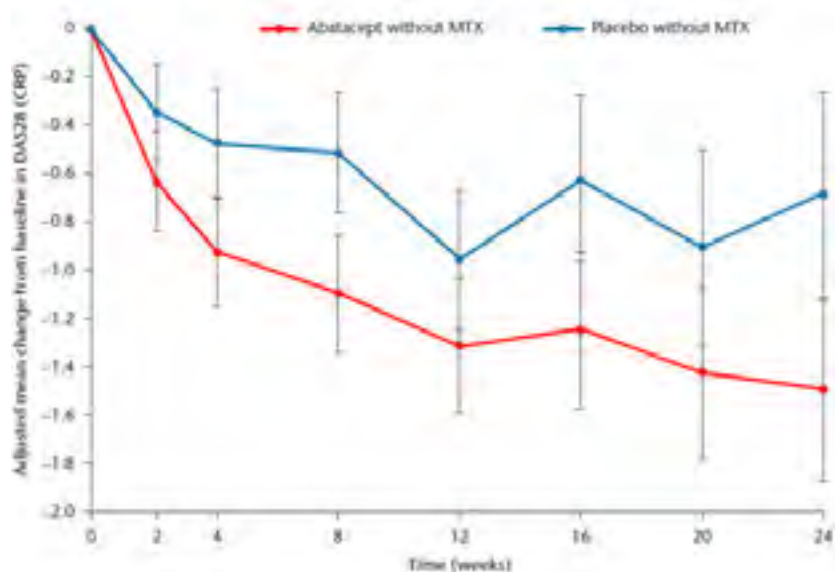
1. Mease PJ, et al. *Ann Rheum Dis* 2017;**76**:1550–8. Medical writing assistance provided by Katerina Kumpan, PhD (Caudex), funded by Bristol-Myers Squibb.

Figure 1. ACR20 Response Over Time in Patients Receiving Abatacept or Placebo, Both Without MTX



Error bars represent 95% CIs
Patients who escaped to open-label abatacept at Week 16 were imputed as non-responders at Weeks 20 and 24

Figure 2. Adjusted Mean Change From Baseline in DAS28 (CRP) Over Time in Patients Receiving Abatacept or Placebo, Both Without MTX



Error bars represent 95% CIs
Patients who escaped to open-label abatacept at Week 16 were imputed as missing at Weeks 20 and 24

Table 1. Selected Baseline Demographic and Clinical Characteristics at Baseline by Concomitant MTX

Characteristic	With MTX		Without MTX*	
	Abatacept (n=129)	Placebo (n=127)	Abatacept (n=84)	Placebo (n=84)
Region				
North America	22 (17.1)	13 (10.2)	22 (26.2)	27 (32.1)
South America	63 (48.8)	58 (45.7)	32 (38.1)	22 (26.2)
Female	65 (50.4)	65 (51.2)	56 (66.7)	47 (56.0)

Table . (Cont'd)

Characteristic	With MTX		Without MTX*	
	Abatacept (n=129)	Placebo (n=127)	Abatacept (n=84)	Placebo (n=84)
Disease duration, mean (SD), years	7.5 (7.8)	8.6 (8.2)	9.4 (8.5)	9.1 (8.5)
mTSS, mean (SD)	18.0 (43.5)	22.3 (44.3)	28.5 (54.7)	16.2 (36.9)
Joint space narrowing score, mean (SD)	7.1 (18.3)	10.1 (21.8)	12.7 (25.9)	7.4 (19.1)
Erosion score, mean (SD)	10.9 (25.6)	12.2 (23.4)	15.8 (29.3)	8.9 (19.0)
Pt assessment of pain (VAS), mean (SD)	61.7 (23.6)	64.7 (20.6)	67.9 (23.1)	63.9 (23.6)
Prior csDMARDs	129 (100)	127 (100)	81 (96.4)	80 (95.2)
1	99 (76.7)	100 (78.7)	42 (50.0)	50 (59.5)
2	24 (18.6)	19 (15.0)	34 (40.5)	21 (25.0)
≥3	6 (4.7)	8 (6.3)	5 (6.0)	9 (10.7)
Prior TNFi	71 (55.0)	69 (54.3)	58 (69.0)	61 (72.6)

Data are n (%) unless specified otherwise Data in bold are overall *Other csDMARDs and corticosteroids at a stable dose were permitted
csDMARD=conventional synthetic DMARD; pt=patient; mTSS, modified Total Sharp Score; TNFi=TNF inhibitor; VAS=Visual Analog Score (0–100 mm)

Disclosure: V. Strand, AbbVie, Amgen Corporation, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Celltrion, Corrona, Crescendo/Myriad, EMD Serono, Genentech/Roche, Janssen, Lilly, Merck, Novartis, Pfizer, Samsung, Sandoz, UCB, 5; T. Lehman, Bristol-Myers Squibb, 1, 3; H. A. Ahmad, Bristol-Myers Squibb, 1, 3; A. Johnsen, Bristol-Myers Squibb, 1, 3; S. Balachandar, Rutgers, The State University of New Jersey, 3, Bristol-Myers Squibb, 5; P. J. Mease, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Lilly, Novartis, Pfizer, Sun, UCB, 2, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Corrona, Janssen, Lilly, Novartis, Pfizer, Sun, UCB, Zynerva, 5, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Genentech, Janssen, Novartis, Pfizer, UCB, 8.

Abstract Number: 2555

Ixekizumab Treatment Results in Rapid and Sustained Improvements in the Disease Activity Index for Psoriatic Arthritis (DAPSA) in Patients Naïve to Biologic DMARDs or with Previous Inadequate Response to TNF Inhibitors

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

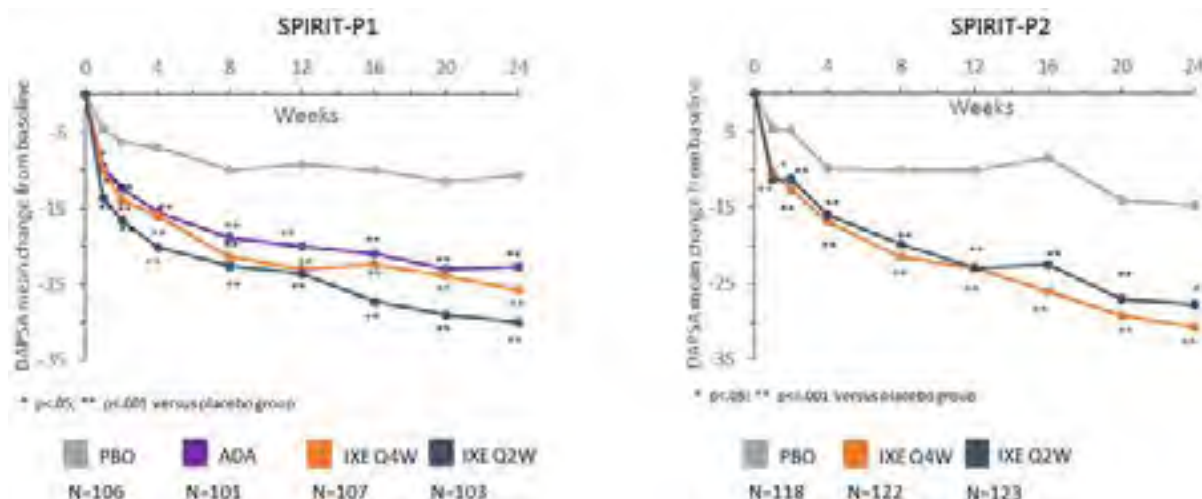
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The DAPSA is a composite tool that assesses several domains of psoriatic arthritis (PsA) manifestations and was developed as a disease activity measure for clinical trials and clinical practice. Ixekizumab is a high affinity mAb against IL-17A recently approved for the treatment of PsA, and in this analysis, we evaluated the impact of ixekizumab treatment on disease activity assessed with the DAPSA through 52 weeks in patients who are biologic DMARD (bDMARD)-naïve or TNF- inadequate responders (TNF-IR).

Methods: Data from the 24-week, randomized, double-blind, placebo-controlled periods from 2 Phase 3 clinical trials (SPIRIT-P1, NCT01695239; SPIRIT-P2, NCT02349295) and their extension periods were analyzed. Patients from SPIRIT-P1 were bDMARD-naïve (N=417) and patients from SPIRIT-P2 had inadequate response or intolerance to TNF inhibitors (N=363). Patients were randomized to receive subcutaneous placebo (PBO), adalimumab (ADA, SPIRIT P1 only) or 80 mg ixekizumab every 2 (IXE Q2W) or 4 wks (IXE Q4W), after a 160 mg starting dose. The components of the DAPSA (68 tender joint counts, 66 swollen joint counts, patient assessment of pain, patient global assessment and CRP) were assessed at each visit. Comparisons versus placebo were made on changes in each component of DAPSA and the composite DAPSA score through week 24 using mixed effects model for repeated measures. Mean change values were reported through week 52 for patients initially randomized to ixekizumab treatment arms for the intent-to-treat population using last observation carried forward for imputing the missing values.

Results: Baseline DAPSA was 44.7 for bDMARD- naïve and 50.4 for TNF-IR patients. After 24 weeks of treatment in bDMARD-naïve patients, the mean change from baseline in DAPSA was -25.7 (IXE Q4W), -30.0 (IXE Q2W), -22.6



(ADA) versus -10.7 (PBO; $p<0.001$ vs PBO for all comparisons; FIGURE). Similarly, in TNF-IR patients, mean change from baseline in DAPSA was -30.6 (IXE Q4W), -27.7 (IXE Q2W) vs -14.7 (PBO; $p<0.001$ vs PBO for all comparisons; FIGURE). In both populations, significant differences versus PBO were observed as early as Week 1. Furthermore, improvements persisted through 52 weeks with changes of -31.0 (IXE Q4W) and -33.8 (IXE Q2W) in the bDMARD-naïve population and -31.7 (IXE Q4W) and -32.1 (IXE Q2W) in the TNF-IR population from baseline to week 52. Consistent, rapid and sustained improvements were observed with each component of the DAPSA.

Conclusion: Ixekizumab treatment resulted in significant and rapid improvements in DAPSA and its components from week 1 to week 24 which persisted through 52 weeks in 2 independent trials, SPIRIT-P1 (bDMARD-naïve patients) and SPIRIT-P2 (TNF-IR patients).

Disclosure: P. Sunkureddi, Eli Lilly and Co, 2, 8; B. Zhu, Eli Lilly and Company, 1, 3; A. Ogdie, Novartis, Pfizer Inc, 2, AbbVie, Bristol-Myers Squibb, Celgene, Corrona, Eli Lilly, Novartis, Pfizer Inc, Takeda, 5; A. Spraberry, Eli Lilly and Co., 1, 3; J. Lisse, Eli Lilly and Co., 1, 3; C. Y. Lin, Eli Lilly and Company, 1, 3; D. Shrom, Eli Lilly and Co., 1, 3.

Abstract Number: 2556

Secukinumab 150 mg Provides Sustained Improvements in the Signs and Symptoms of Active Ankylosing Spondylitis with Consistent Safety Profile and High Retention Rate: 4-Year Results from a Phase III Trial

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Secukinumab, a fully human monoclonal IgG1 antibody that neutralizes IL-17A, has shown significant and sustained improvement in the signs and symptoms of active ankylosing spondylitis (AS) through 3 years in the MEASURE 2 study (NCT01649375).¹ Here, we report the longer-term (4-year) efficacy and safety of subcutaneous (s.c.) secukinumab 150 mg in the MEASURE 2 study.

Methods: AS patients (pts; N = 219) were randomized to receive s.c. secukinumab 150 mg, 75 mg or placebo at baseline, Weeks (Wks) 1, 2 and 3 and every 4 wks from Wk 4. At Wk 16, placebo-treated pts were re-randomized to receive secukinumab 150/75 mg. Efficacy results are reported for pts initially randomized to secukinumab 150 mg and those who switched from placebo to secukinumab 150 mg at Wk 16 (N = 106). Outcome measures at Wk 208 included ASAS20 and 40, BASDAI, SF-36 PCS, and ASAS partial remission. Analyses stratified by anti-TNF status (anti-TNF-naïve and anti-

TNF inadequate response [IR]) were pre-specified. Safety analysis included all pts who received ≥ 1 dose of secukinumab. Results are reported as observed.

Results: The retention rate from Wk 16 to 208 was 85% (85/100) for secukinumab 150 mg. Sustained improvements were observed with secukinumab 150 mg across all endpoints through 4 years (Table). These improvements were maintained regardless of prior exposure to anti-TNF therapy; greater responses were demonstrated in anti-TNF-naïve pts. Over the entire study period, the mean exposure (\pm SD) to secukinumab was 1189.3 ± 452.9 days. Exposure-adjusted incidence rates (per 100 pt-years) with any secukinumab dose for selected adverse events were: serious infections/infestations (1.5), *Candida* infections (1.2), Crohn's disease (0.6), major adverse cardiovascular events (0.6), uveitis (0.6), and malignant/unspecified tumours (0.4).

Conclusion: Secukinumab 150 mg provided sustained improvement in the signs, symptoms, and physical function in pts with AS through 4 years of treatment with 85% retention rate. The safety profile of secukinumab remained favorable and was consistent with previous reports.¹⁻³ References: 1. Marzo-Ortega, et al. RMD Open. 2017;3:e000592; 2. Marzo-Ortega et al. Ann Rheum Dis. 2016;75:812-3; 3. Baraliakos X, et al. Clin Exp Rheumatol 2017.

Table. Clinical improvements with secukinumab 150 mg at Weeks 52 and 208

Variable	Week	Secukinumab 150 mga		
		Total	Anti-TNF-naïve	Anti-TNF-IR
ASAS20, % responders (n)	52	74.2 (93)	80.0 (60)	63.6 (33)
	208	73.3 (86)	74.6 (59)	70.4 (27)
ASAS40, % responders (n)	52	57.0 (93)	63.3 (60)	45.5 (33)
	208	60.5 (86)	62.7 (59)	55.6 (27)
BASDAI, mean change \pm SD (n)	52	-3.2 \pm 2.3 (93)	-3.3 \pm 2.3 (60)	-3.0 \pm 2.1 (33)
	208	-3.2 \pm 2.3 (86)	-3.5 \pm 2.4 (59)	-2.7 \pm 2.0 (27)
SF-36 PCS, mean change \pm SD (n)	52	7.6 \pm 7.7 (94)	8.0 \pm 7.5 (61)	6.9 \pm 8.1 (33)
	208	8.3 \pm 8.3 (85)	9.4 \pm 8.5 (58)	6.2 \pm 7.8 (27)
ASAS partial remission, % responders (n)	52	24.7 (93)	28.3 (60)	18.2 (33)
	208	27.9 (86)	32.2 (59)	18.5 (27)

^a Includes placebo switchers. Data are reported as observed.

ASAS; Assessment in SpondyloArthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; IR, inadequate response; SD, standard deviation; SF-36 PCS, Short Form (36) Health Survey Physical Component Summary; TNF, tumor necrosis factor

Disclosure: H. Marzo-Ortega, Janssen and Pfizer, 2, Abbvie, Celgene, Janssen and UCB, 8, Abbvie, Celgene, Janssen, Novartis and UCB, 5; J. Sieper, AbbVie, Pfizer and Merck, 2; AbbVie, Pfizer, Merck, UCB and Novartis, 5, AbbVie, Pfizer, Merck and UCB, 8; A. J. Kivitz, AbbVie, Pfizer, Genentech, UCB, Sanofi/Regeneron and Celgene, 5, Celgene, Pfizer, Sanofi/Regeneron, Horizon and Merck, 8; R. Blanco, None; M. Cohen, Abbvie, Amgen, BMS, Celgene, Hospira, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, Sanofi and UCB, 5, Abbvie, Amgen, BMS, Celgene, Hospira, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, Sanofi and UCB, 8; E. M. Delicha, Novartis, 1, 3; S. Rohrer, Novartis, 1, 3; H. Richards, Novartis, 1, 3.

Abstract Number: 2557

Efficacy of Ustekinumab on Spondylitis-Associated Endpoints in TNF-Naïve Active Psoriatic Arthritis Patients with Physician-Reported Spondylitis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: In PSUMMIT 1&2, Phase 3 trials of ustekinumab (UST) in adults w/ active psoriatic arthritis (PsA), 30.1% & 22.4% of patients (pts) had peripheral arthritis w/ physician-reported spondylitis (PA-PRS), respectively. To evaluate the proportion of anti-tumor necrosis factor (TNF)-naïve pts w/ PA-PRS from pooled data in PSUMMIT 1&2

treated w/UST achieving Ankylosing Spondylitis Disease Activity Score (ASDAS) responses and other axial disease response measures.

Methods: Pts had active PsA (≥ 5 swollen & tender joints, CRP ≥ 3.0 mg/L) for ≥ 6 mo despite treatment w/ csDMARDs &/or NSAIDs (PSUMMIT 1&2) &/or anti-TNF agents (PSUMMIT 2). In both studies, pts were randomized to SC injections of placebo (PBO) or UST 45mg or 90mg at wks 0, 4 & every 12 wks. PBO pts crossed over to UST 45mg at wk 24. At wk 16, early escape (PBO, UST 45mg; UST 45mg, UST 90mg; UST 90mg, UST 90mg) was possible. The proportion of pts achieving ASDAS responses of inactive disease (<1.3), major improvement (decrease ≥ 2.0), & clinically important improvement (decrease ≥ 1.1) at wks 12 & 24 were calculated. Modified Bath Ankylosing Spondylitis Disease Activity Index (mBASDAI) scores were calculated at wks 12 & 24 (based upon BASDAI w/o Q#3).

Results: Of 747 TNF-naïve pooled pts, 223 had PsAw/ PA-PRS. For the PA-PRS subset, baseline mean scores included BASDAI 6.57 (UST 45mg), 6.60 (UST 90mg), and 6.37 (PBO); ASDAS 3.86 (UST 45mg), 3.90 (UST 90mg), 3.68 (PBO); BASDAI Q#2 6.62 (UST 45mg), 6.84 (UST 90mg), 6.14 (PBO); and mBASDAI 6.52 (UST 45mg), 6.56 (UST 90mg), 6.27 (PBO). A numerically greater change from baseline in mBASDAI was achieved in both UST 45mg & 90mg groups vs PBO at both wks 12 and 24 (Table 1). Additionally, significantly greater proportions of pts in both UST 45mg & 90mg groups vs PBO achieved ASDAS inactive disease by wk 24 (Table 2). Similarly, by wk 24, significantly greater proportions of pts in both 45mg & 90mg UST groups vs PBO achieved ASDAS major improvement and clinically important improvement.

Conclusion: Approximately half of UST-treated PA-PRS pts attained meaningful improvements in ASDAS by wk 24, and similar numerically greater changes from baseline were observed in mBASDAI. These results are limited and should be interpreted with caution as this was a heterogenous patient group in the absence of definitive imaging, and improvements in extra-axial domains, such as peripheral arthritis and enthesitis, may have contributed to the changes in ASDAS and mBASDAI scores. Further research is needed to examine the efficacy of UST in treatment of spondylitis in PsA patients.

Table 1. Mean change from baseline in mBASDAIa in PA-PRS subset at wk 12 & 24 in PSUMMIT 1&2

	PBO	UST 45mg	UST 90mg	UST Combined
PA-PRS Subset, n	84	66	73	139
Wk 12, n	77	61	70	131
Mean change (SD)	-0.52 (1.47)	-1.81 (1.84)	-1.78 (2.11)	-1.79 (1.98)
Wk 24, n	71	63	69	132
Mean change (SD)	-0.59 (1.58)	-1.73 (2.13)	-2.41 (2.20)	-2.09 (2.18)

BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; mBASDAI=modified BASDAI; PA-PRS=peripheral arthritis with physician-reported spondylitis; PBO=placebo; SD=standard deviation; UST=ustekinumab

a mBASDAI scores were calculated based on the BASDAI with question #3 removed ($0.25[F+S+E+0.5 \times \text{DURATION}]$).

Table 2. PA-PRS subset achieving ASDAS responses at wk 12&24 in PSUMMIT 1&2

	PBO	UST 45mg	UST 90mg	UST Combined
PA-PRS Subset, n	84	66	73	139
Wk 12, ASDAS, n	78	61	70	131
ASDAS <1.3 , inactive disease, n (%)	2 (2.6)	4 (6.6)	5 (7.1)	9 (6.9)
ASDAS improvement, n	77	60	70	130
Major improvement, decrease ≥ 2.0 , n (%)	2 (2.6)	8 (13.3)	10 (14.3)	18 (13.8)
Clinically important improvement, decrease ≥ 1.1 , n (%)	9 (11.7)	25 (41.7)	29 (41.4)	54 (41.5)
Wk 24, ASDAS, n	72	64	69	133
ASDAS <1.3 , inactive disease, n (%)	0 (0)	4 (6.3)**	8 (11.6)**	12 (9.0)**
ASDAS improvement, n	71	62	69	131
Major improvement, decrease ≥ 2.0 , n (%)	1 (1.4)	9 (14.5)**	19 (27.5)*	28 (21.4)*
Clinically important improvement, decrease ≥ 1.1 , n (%)	9 (12.7)	27 (43.5)*	38 (55.1)*	65 (49.6)*

ASDAS=Ankylosing Spondylitis Disease Activity Score; PA-PRS=peripheral arthritis with physician-reported spondylitis; PBO=placebo; UST=ustekinumab

*p<0.001; **p<0.01; ***p<0.05

Disclosure: P. Helliwell, Janssen Research & Development, LLC., 2; D. D. Gladman, Janssen Research and Development, LLC, 2; S. D. Chakravarty, Janssen Scientific Affairs, LLC, 3; S. Kafka, Janssen Scientific Affairs, LLC, 3; C. S. Karyekar, Janssen Research & Development, LLC, 3; Y. You, Janssen Scientific Affairs, LLC, 3; A. Kavanaugh, Janssen Research & Development, LLC, 2; L. S. Gensler, Janssen Research and Development, LLC, 2.

Efficacy and Safety Outcomes in Patients with Axial Spondyloarthritis Treated with Certolizumab Pegol: Results from the 48-Week Run-in Part of a Withdrawal Study (NCT02505542)

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: C-OPTIMISE is the first trial to evaluate whether certolizumab pegol (CZP) can be reduced/discontinued in patients with radiographic (r)-axSpA/ankylosing spondylitis (AS) and non-radiographic (nr)-axSpA achieving sustained remission after 48 weeks' (wks') treatment. Here, we report interim efficacy and safety data for both subpopulations from the ongoing trial.

Methods: Up to wk 48, C-OPTIMISE (NCT02505542) was open-label (Part A), followed by 48-wk parallel-group, double-blind, placebo-controlled treatment (full dose and half dose) to wk 96 (Part B). Patients with adult-onset axSpA of <5 years' duration, fulfilling ASAS classification criteria, were recruited. Part A: patients received CZP (400mg at wks 0/2/4, then 200mg Q2W); patients achieving sustained remission (ASDAS<1.3 at wk 32 and <2.1 at wk 36 [or vice versa], and <1.3 at wk48) were eligible for Part B (secondary outcome). Primary outcome (not reported): percentage of patients in Part B not experiencing a flare. Missing values were imputed using non-responder imputation (NRI) and last observation carried forward (LOCF).

Results: Part A: Of 736 patients (**Table 1**), 43.9% achieved sustained remission (r-axSpA/AS: 42.8%; nr-axSpA: 45.3%; NRI). At baseline, 98.5% patients had high/very high disease activity (ASDAS≥2.1); at Wk48, 52.7% (r-axSpA/AS: 52.6%; nr-axSpA: 52.9%) had inactive disease (ASDAS<1.3; LOCF; **Table 2**). The treatment-emergent adverse event (TEAE) rate/100 patient-years' exposure was 224.2; 3.9% patients discontinued CZP due to TEAEs. No new safety signal was identified.

Conclusion: The run-in phase of C-OPTIMISE shows that similar and substantial proportions of patients with r-axSpA/AS and nr-axSpA achieved sustained remission during 48 wks' CZP treatment. No new safety signal was identified. The study was funded by UCB Pharma, medical writing by Hinal Tanna, Costello Medical, UK. We thank the patients who contributed.

Disclosure: **R. B. M. Landewé**, Abbott, Amgen, Centocor, Pfizer, Roche, Schering-Plough, UCB Pharma, Wyeth, 2, 5, 8, Ablynx, AstraZeneca, GlaxoSmithKline, 5, Novartis, 2, 5, Merck, Bristol Myers Squibb, 5, 8; **D. van der Heijde**, Imaging Rheumatology BV, 3, AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Daiichi, Eli-Lilly, Galapagos, Gilead, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi and UCB Pharma, 5; **M. Dougados**, AbbVie, Eli Lilly, Merck, Novartis, Pfizer, UCB Pharma, 2, 5; **X. Baraliakos**, AbbVie, Bristol-Myers Squibb, Celgene, Chugai, Janssen, MSD, Novartis, Pfizer and UCB Pharma, 2, 5, 8; **F. van Den Bosch**, AbbVie, Bristol Myers-Squibb,

Table 1: Baseline characteristics

	Part A (CZP 200 mg Q2W): Open Label Set		
	axSpA (n=736) [a]	r-axSpA/AS (n=407) [b]	nr-axSpA (n=329) [c]
Age (years), mean (SD)	32.9 (7.0)	33.7 (6.8)	32.1 (7.1)
Male, n (%)	513 (69.7)	318 (78.1)	195 (59.3)
Symptom duration (years), mean (SD) [c]	2.2 (1.7)	2.5 (1.8)	1.8 (1.8)
HLA-B27 positive, n (%)	597 (81.1)	354 (87.0)	243 (73.9)
Sacroiliitis on imaging, n (%) [d]	681 (93.9)	401 (98.5)	290 (88.1)
Prior anti-TNF treatment, n (%)	31 (4.2)	20 (4.9)	11 (3.3)

Table 2: Clinical outcomes

Part A (CZP 200 mg Q2W): Open Label Set						
	axSpA (n=738)		r-axSpA/AS (n=407)		nr-axSpA (n=329)	
%	BL	Wk48 (NRI)	BL	Wk48 (NRI)	BL	Wk48 (NRI)
ASAS20	–	79.6	–	79.9	–	79.3
ASAS40	–	72.0	–	71.3	–	72.9
ASAS PR	–	57.3	–	55.8	–	59.3
BASDAI 50	–	71.7	–	71.3	–	72.3
Mean [e]	BL	Wk48 (LOCF [e])	BL	Wk48 (LOCF [e])	BL	Wk48 (LOCF [e])
ASDAS	3.7	1.6	3.8	1.6	3.6	1.5
ID, %	–	52.7†	–	52.6	–	52.9†
CII, % [f]	–	76.5	–	78.6	–	73.9
MI, % [f]	–	56.3	–	58.7	–	53.2
BASDAI	6.7	2.1	6.7	2.1	6.7	2.2
BASFI	5.3	1.7	5.4	1.7	5.1	1.6
BASMI	3.1	2.3	3.5	2.6	2.7	1.9
Nocturnal back pain	6.9	1.8	7.0	1.8	6.8	1.8
Fatigue	7.1	2.6	7.1	2.5	7.1	2.6
CRP (mg/L), median [g]	7.8	2.0	10.7	2.0	4.5	2.0

[a] Patients with prior exposure to >1 anti-TNF were excluded. [b] A central reading of patients' sacroiliac joint x-rays was used to confirm their stratification into nr-axSpA and r-axSpA/AS subpopulations. [c] Time since diagnosis of disease. [d] MRI or X-ray. [e] Unless stated otherwise, [f] NRI. [g] Values below the limit of quantification were set to half of the limit of quantification. †n=734. ‡n=327. AS: ankylosing spondylitis; ASAS20/40: ≥20% or ≥40% improvement in Assessment of SpondyloArthritis international Society response criteria; ASAS PR: ASAS Partial Remission; ASDAS: Ankylosing Spondylitis Disease Activity Score; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASDAI 50: ≥50% improvement in BASDAI; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BL: baseline; CII: ASDAS Clinically Important Improvement (RFB ≥1.1); CRP: C-reactive protein; CZP: certolizumab pegol; ID: ASDAS Inactive Disease (ASDAS <1.3); LOCF: last observation carried forward; MI: ASDAS Major Improvement (RFB ≥2.0); MRI: magnetic resonance imaging; nr-axSpA: non-radiographic axSpA; NRI: non-responder imputation; Q2W: every 2 weeks; r-axSpA: radiographic axSpA; RFB: reduction from baseline; Wk: week.

Celgene, Janssen, Merck, Novartis, Pfizer and UCB Pharma, 5, 8; **B. Hoepken**, UCB Pharma, 3; **K. Thomas**, UCB Pharma, 3; Karen Thomas Statistics Limited, 4; **L. S. Gensler**, UCB Pharma, 2.

Abstract Number: 2559

Efficacy and Safety of Ixekizumab in Patients with Active Psoriatic Arthritis and Previous Inadequate Response to TNF Inhibitors: Two-Year Follow-up from a Phase 3 Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Ixekizumab (IXE), a high-affinity monoclonal antibody that selectively targets IL-17A, was superior to placebo(PBO) at Week (Wk) 24 for treating PsA signs and symptoms in patients (pts) with active PsA and prior inadequate response or intolerance to TNF inhibitors (TNFi)(Nash et al. Lancet, 2017). We report efficacy and safety results of IXE following 2 years of treatment in SPIRIT-P2.

Methods: Adult subjects (N=363) who met Classification for PsA (CASPAR) criteria with active PsA and inadequate response or intolerance to TNFi were randomized 1:1:1 to 80 mg IXE every 4 wks (Q4W, N=122) or 2 wks (Q2W, N=123) following a 160-mg starting dose of IXE at Wk 0 or PBO (N=118). Pts randomized to PBO were re-randomized 1:1 to IXE Q2W or Q4W at either Wk 16 if inadequate responders (<20% improvement in both tender joint count [TJC] and swollen joint count [SJC]) or Wk 24. From Wk 32, pts were discontinued from the study if they had <20% improvement in both TJC and SJC. Efficacy outcomes were ACR20/50/70 response, Psoriasis Area and Severity Index (PASI) 75/90/100 response, Leeds Enthesitis Index (LEI), Leeds Dactylitis Index-Basic (LDI-B), Minimal Disease Activity (MDA), and HAQ-Disability Index (DI). Ad-hoc efficacy analysis for the combined treatment periods from Wk 0-108 included pts initially randomized to IXE. Missing values were imputed by modified nonresponder imputation (mNRI) for categorical data or modified baseline observation carried forward (mBOCF) for continuous data. Safety analyses included all available safety data at the time of Wk 108 database lock for pts receiving ≥ 1 dose of IXE and was summarized as incidence rates (IR) per 100 pt-years.

Results: Overall, 54.2% of randomized pts completed 108 wks of treatment. Wk 108 responses (mNRI) for pts initially randomized to IXE Q4W or IXE Q2W, respectively, were 59.6% and 47.9% for ACR20, 33.2% and 27.8% for MDA, 65.1% and 48.3% for PASI 75, 45.5% and 37.5% for LEI=0, and 63.0% and 60.0% for LDI-B=0; mean (SD) change from baseline (mBOCF) in HAQ-DI was -0.4 (0.5) for IXE Q4W and -0.4 (0.6) for IXE Q2W. IRs of treatment-emergent adverse event (AE) are provided in the table below; most were mild or moderate in severity. Serious AE IRs were 5.8 (IXE Q4W) and 7.7 (IXE Q2W). Three deaths occurred; causes of death were myocardial infarction (IXE Q2W/IXE Q2W), metastatic renal cell carcinoma (IXE Q4W/IXE Q4W), and cardiopulmonary arrest (PBO/IXE Q2W).

Conclusion: IXE provided clinically meaningful and sustained improvement in PsA signs and symptoms for up to 2 years of treatment among pts with prior inadequate response or intolerance to TNFi, consistent with responses during earlier treatment periods of SPIRIT-P2. No unexpected safety outcomes were reported and the safety profile was consistent with the IXE Phase 3 program in pts with active PsA and with moderate-to-severe plaque psoriasis.

Table. Efficacy and Safety Outcomes at Week 108 of SPIRIT-P2

Efficacy (Intent-to-Treat—Patients Randomized to IXE at Week 0)	IXE Q4W N=122	IXE Q2W N=123
<i>Response rate (mNRI), n/Nx (%)</i>		
ACR20	73/122 (59.6)	59/123 (47.9)
ACR50	56/121 (46.2)	40/123 (32.5)
ACR70	28/122 (23.2)	27/121 (22.6)
MDAa	41/122 (33.2)	34/123 (27.8)
LEI=0b	31/68 (45.5)	32/84 (37.5)
LDI-B=0c	17/27 (63.0)	12/20 (60.0)
PASI 75d	44/68 (65.1)	33/68 (48.3)
PASI 90d	38/68 (55.3)	27/68 (40.3)
PASI 100d	27/68 (39.0)	24/68 (35.3)
<i>Change from baseline (mBOCF), mean (SD)</i>		
Baseline HAQ-DI total score	1.2 (0.6)	1.2 (0.6)
HAQ-DI, change from baseline	Nx=101 -0.4 (0.5)	Nx=103 -0.4 (0.6)
Safetye		
(All Patients Receiving ≥ 1 Dose of IXE)	Total IXE Q4W N=168	Total IXE Q2W N=169
<i>Number of Events, n (IR)</i>		
Total patient-years	308.7	271.5
Treatment-emergent adverse eventsf	150 (48.6)	150 (55.3)
Mild	92 (29.8)	81 (29.8)
Moderate	93 (30.1)	89 (32.8)
Severe	14 (4.5)	28 (10.3)
Discontinuations due to adverse event	15 (4.9)	20 (7.4)
Serious adverse events	18 (5.8)	21 (7.7)
Death	1 (0.3)	2 (0.7)
Adverse events of special interest		
Serious infections	5 (1.6)	4 (1.5)
Allergic reactions/hypersensitivities	16 (5.2)	15 (5.5)
Anaphylaxis	0	0
Injection site reactions	28 (9.1)	43 (15.8)
Malignancies	6 (1.9)	1 (0.4)
Inflammatory bowel disease	1 (0.3)	0

^aMDA response is defined as fulfilling at least 5 of 7 MDA criteria: TJC ≤ 1 , SJC ≤ 1 , PASI ≤ 1 (or body surface area $\leq 3\%$), Patient pain VAS ≤ 15 , patient global disease activity VAS ≤ 20 , HAQ-DI ≤ 0.5 , and tender entheses points ≤ 1 . ^bPatients with baseline enthesitis (LEI >0). ^cPatients with baseline dactylitis (LDI-B >0). ^dPatients with baseline psoriasis body surface area involvement $\geq 3\%$. ^eIncludes all available safety data at the time

of Week 108 database lock; baseline for safety analysis was defined as the time of first IXE injection. [†]Patients with multiple occurrences of the same event were counted under the highest severity category.
Abbreviations: IR, incidence rate per 100 total patient-years; IXE Q2W, ixekizumab 80 mg every 2 weeks; IXE Q4W, ixekizumab 80 mg every 4 weeks; LDI-B, Leeds Dactylitis Index-Basic; LEI, Leeds Enthesitis Index; mBOCF, modified baseline observation carried forward; MDA, Minimal Disease Activity; mNRI, modified nonresponder imputation; n, number of patients who met criteria; Nx, number of patients in the specified analysis population; PASI, Psoriasis Area and Severity Index; SJC, swollen joint count; TJC, tender joint count; VAS, visual analog scale.

Disclosure: A. M. Orbai, Abbvie, Celgene, Eli Lilly and Company, Horizon, Janssen, Novartis, Pfizer, 2, Eli Lilly and Company, Janssen, Novartis, Pfizer, UCB, 5; A. M. Gellett, Eli Lilly and Company, 1, 3; L. Kerr, Eli Lilly and Company, 1, 3; A. Constantin, Abbvie, BMS, Janssen, Eli Lilly and Co., Medac, MSD, Nordic Pharma, Novartis, Pfizer, Sanofi, UCB, 5, 6.

Abstract Number: 2560

Efficacy of Guselkumab in Psoriasis Patients with Self-Reported Psoriatic Arthritis with Involvement of the Scalp, Nails, Hands, and Feet: A Pooled Analysis from 2 Pivotal Phase 3 Psoriasis Studies

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: VOYAGE1 & 2 were the pivotal Ph3 GUS trials for plaque PsO.^{1,2} Here we compare efficacy of GUS vs PBO & adalimumab (ADA) on PsO involving scalp, nail & palmoplantar (palmoplantar pustular PsO excluded per protocol) PsO in subgroup of pts w/ self-reported PsA, given the association between these distinct PsO phenotypes & PsA.

Methods: VOYAGE 1(n=837) & VOYAGE 2(n=992) enrolled adult pts who had plaque PsO for ≥6 months, an Investigator Global Assessment (IGA) score ≥3, PASI score ≥12, ≥10% BSA involvement at baseline (BL), & were candidates for phototherapy or systemic treatment for PsO. Pts were randomized to GUS, PBO or ADA at BL, w/ PBO crossover to GUS at wk16. This post-hoc analysis used observed pooled efficacy data for scalp-specific (ss-IGA), Physician's Global Assessment (PGA) of Hands &/or Feet (hf-PGA), fingernail PGA (f-PGA), & Nail Psoriasis Area & Severity Index (NAPSI) in subset of pts self-reporting PsA.

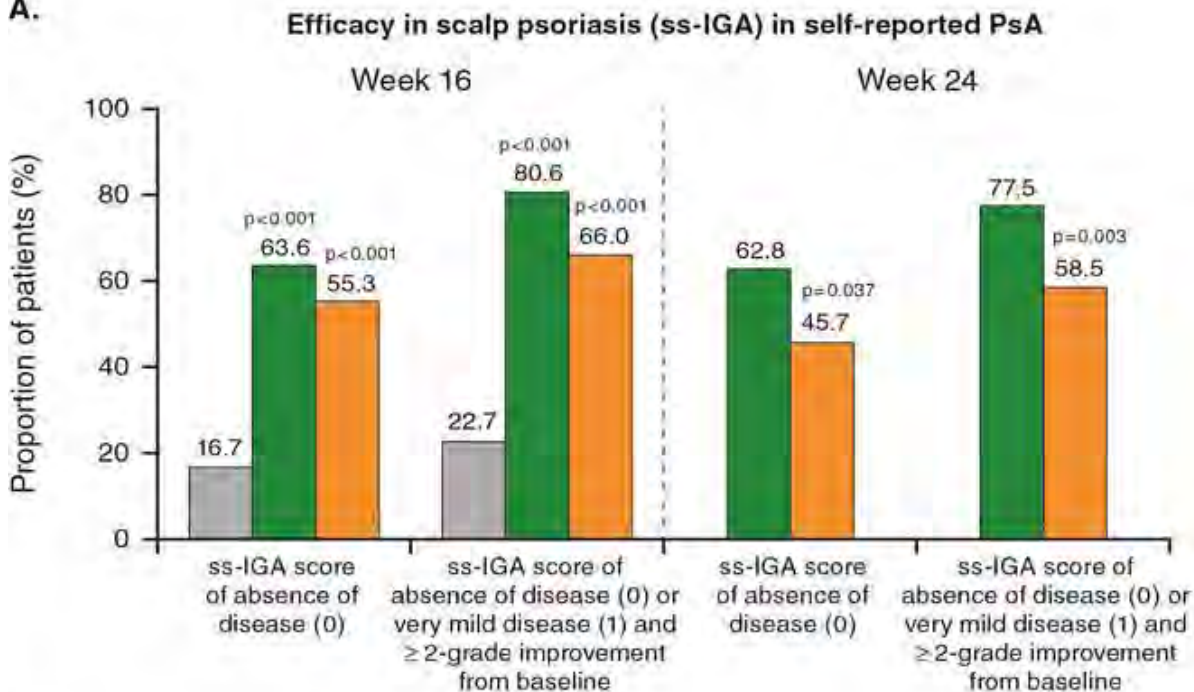
Results: In VOYAGE 1 & 2 combined, 335 (18.3%) PsO pts self-reported PsA (PBO 76, GUS 153, ADA 106). Baseline demographics were generally comparable across all 3 treatment groups, w/ history of methotrexate use: PBO 64.5%, GUS 70.6%, ADA 61.3%. A significantly greater proportion of GUS-treated pts achieved a ss-IGA score of 0/1 (absent/very mild) at wk16 vs PBO, & at wk24 vs ADA (Figure A). Significantly higher proportions of GUS-treated pts achieved a hf-PGA score of 0/1 (clear/almost clear) vs PBO at wk16 w/ numerically greater differences at wk24 vs ADA (Figure B). At wk16, proportions of pts achieving a f-PGA score of 0/1 (clear/minimal) were 47.6% for GUS vs 17.0% for PBO (p<0.001). The proportions of pts achieving a f-PGA score of 0/1 for GUS vs ADA were comparable at wk16 (47.6% vs 46.4%) & wk24 (67.0% vs 60.9%), but were higher for GUS by wk48 (82.5% vs 57.5%, Table). Mean (SD) % improvement from BL in NAPSI score was significantly higher for GUS vs PBO [39.5 (48.9) vs 6.5(47.5), p<0.001] at wk16 & was comparable for GUS vs ADA at wk24 [58.0 (51.3) vs 59.9(40.4)]. By wk48, mean % improvement from BL in NAPSI score was higher for GUS vs ADA (70.8% vs 61.3%, Table).

Conclusion: GUS-treated PsO pts w/self-reported PsA showed clinically meaningful improvements vs ADA in ss-IGA & hf-PGA scores at wks 16 & 24. Although improvements in f-PGA & NAPSI were similar in pts treated w/ GUS vs. ADA at earlier time points, numerically greater differences were observed w/ GUS by wk48, likely requiring the additional duration to discriminate between treatments in this slow-growing cutaneous appendage.

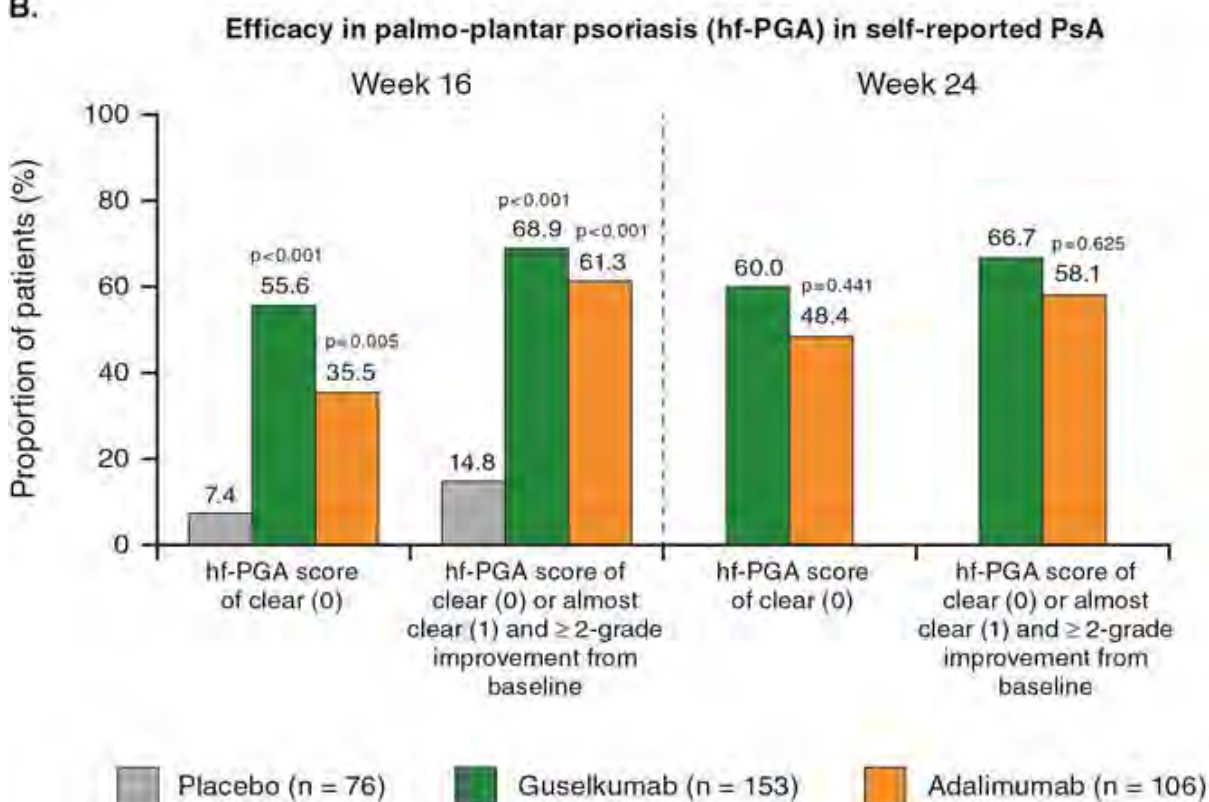
¹Blauvelt A, et al. J Am Acad Dermatol. 2017 Mar;76(3):405-417

²Reich K, et al J Am Acad Dermatol. 2017 June;76(6): 1226

A.



B.



p-values based on the Cochran-Mantel-Haenszel chi-square test stratified by study and represent the comparison vs. placebo at wk 16 and guselkumab vs. adalimumab at wk 24.

Table. Fingernail (f)-PGA score of clear (0) or minimal (1) in Psoriasis Patients with Self-Reported PsA at Wk 48*

	Guselkumab	Adalimumab
PsO Patients randomized at Week 0, n	329	334
PsO Patients with Self-reported PsA, n	64	62
Patients with f-PGA score >2 at baseline	40	40
f-PGA score of clear (0)	20 (50.0%)	16 (40.0%)
f-PGA score of clear (0) or minimal (1)	33 (82.5%)	23 (57.5%)
Percent improvement from baseline in NAPS I Scores in Psoriasis Patients with Self-Reported PsA at Wk 48*		
	Guselkumab	Adalimumab
PsO Patients randomized at Week 0, n	825	582
PsO Patients with Self-reported PsA, n	153	106
NAPS I (N)	111	74
Mean (SD)	70.84 (40.49)	61.25 (42.43)
Median	100.00	70.85
Range	(-100.0; 100.0)	(-50.0; 100.0)
IQ range	50.00; 100.00)	(33.30; 100.00)

* --Post-hoc analyses based on Voyage 1 only

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Abstract Number: 2561

Rapid and Sustained Improvements in Patient-Reported Signs and Symptoms with Ixekizumab in Biologic-Naive and TNF-Inadequate Responder Patients with Psoriatic Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Ixekizumab (IXE), a high-affinity mAb that selectively targets IL-17A, has shown improvements up to Week (Wk) 24 across several domains of PsA (including ACR20) compared to placebo in 2 Phase 3 trials in PsA patients (SPIRIT-P1 and SPIRIT-P2).^{1,2} We analyzed the onset and duration of patient-reported improvements in symptoms of PsA, including patient-reported pain and fatigue, following treatment with IXE up to Wk 52.

Methods: The SPIRIT-P1 and -P2 study designs have been reported previously.^{1,2} Patients with active PsA either naive to biologic DMARDs (bDMARD-naive; SPIRIT-P1) or with inadequate response to or intolerance to prior TNF-inhibitors (TNFi-IR; SPIRIT-P2) were randomized to placebo (PBO; Wk 0-24 only) or 80 mg IXE every 4 (IXE Q4W) or 2 wks (IXE Q2W) after a 160-mg starting dose. We analyzed change from baseline for the joint pain visual analog scale (VAS; 0-100 scale), patient global assessment (PatGA VAS; 0-100 scale), fatigue Numerical Rating Scale (NRS; 0 [no fatigue] to 10 [worst imaginable]), and Health Assessment Questionnaire-Disability Index (HAQ-DI) up to Wk 52 (double-blind treatment period, Wk 0-24; and extension period, Wk 24-52). Continuous data were analyzed using a mixed-effects model for repeated measures (MMRM) from baseline to Wk 24. From Wk24 onward, all missing data were imputed using the multiple imputation (MI) method.

Results: Patients treated with both IXE doses reported rapid and statistically significant reductions compared to PBO in pain VAS, PatGA, and HAQ-DI scores as early as Wk 1, which persisted or improved through Wk 52. Improvements were consistent in bDMARD-naive (SPIRIT-P1) and TNFi-IR (SPIRIT-P2) patients (Table). Fatigue scores improved in the IXE dose groups compared to PBO in both the studies at the earliest time point measured (Wk 4 in SPIRIT-P1; Wk 2 in SPIRIT-P2); results were statistically significant at Wk 24 in SPIRIT-P2, but not SPIRIT-P1 (Table).

Conclusion: Patients treated with IXE achieved significantly greater improvements compared to PBO as early as Wk1 in joint pain, HAQ-DI, and PatGA. Fatigue also improved significantly, at the earliest time point measured (Wk 4). Improvements for pain, PatGA, and physical function persisted up to Wk 52, and were generally consistent in the bDMARD-naive (SPIRIT-P1) and TNFi-IR (SPIRIT-P2) populations.

Table: Summary of Change from Baseline in Individual Clinical Responses over Time up to Week 52

Outcomes	Visits	SPIRIT-P1			SPIRIT-P2		
		PBO (N = 106)	IXE80 Q4W (N = 107)	IXE80 Q2W (N = 103)	PBO (N = 118)	IXE80 Q4W (N = 122)	IXE80 Q2W (N = 123)
Joint Pain (VAS)	Baseline, mean (SD)	-58.5 (23.0)	-60.1 (19.4)	-59.8 (21.7)	-53.9 (20.1)	-53.9 (21.4)	-52.7 (20.4)
	LSM change from baseline at Wk 1 (SE)	-6.1 (1.9)	-14.5 (1.9)	-12.5 (2.0)*	-8.4 (2.1)	-18.1 (2.7)*	-15.1 (2.6)*
	LSM change from baseline at Wk 24 (SE)	-14.0 (2.7)	-35.0 (2.5)*	-31.0 (2.8)*	-21.4 (4.0)	-38.0 (3.7)*	-33.5 (3.6)*
	Mean change from baseline at Wk 52 (SE)	NA	-28.7 (2.8)	-34.6 (2.9)	NA	-31.8 (2.5)	-29.5 (2.7)
PainGA (VAS)	Baseline, mean (SD)	-61.1 (22.7)	-62.7 (19.1)	-62.5 (19.9)	-64.1 (21.5)	-66.4 (20.5)	-66.0 (20.5)
	LSM change from baseline at Wk 1 (SE)	-8.2 (2.0)	-16.8 (2.0)	-15.2 (2.1)*	-9.0 (2.9)	-22.0 (2.9)*	-22.7 (2.6)*
	LSM change from baseline at Wk 24 (SE)	-14.8 (2.7)	-33.8 (2.5)*	-35.8 (2.5)*	-19.0 (3.0)	-40.7 (3.7)*	-37.5 (3.5)*
	Mean change from baseline at Wk 52 (SE)	NA	-33.0 (2.5)	-38.8 (2.1)	NA	-36.7 (2.8)	-34.1 (2.5)
HAQ-DI	Baseline, mean (SD)	-1.2 (0.8)	-1.2 (0.8)	-1.2 (0.8)	-1.2 (0.7)	-1.2 (0.8)	-1.2 (0.6)
	LSM change from baseline at Wk 1 (SE)	-0.1 (0.0)	-0.2 (0.0)	-0.2 (0.0)*	-0.1 (0.1)	-0.3 (0.1)*	-0.2 (0.1)
	LSM change from baseline at Wk 24 (SE)	-0.2 (0.1)	-0.4 (0.1)*	-0.5 (0.1)*	-0.2 (0.1)	-0.6 (0.1)*	-0.4 (0.1)*
	Mean change from baseline at Wk 52 (SE)	NA	-0.5 (0.1)	-0.6 (0.1)	NA	-0.6 (0.1)	-0.4 (0.0)
Fatigue NRS	Baseline, mean (SD)	5.4 (2.2)	5.8 (2.3)	5.5 (2.4)	5.8 (2.3)	5.9 (2.5)	6.0 (2.5)
	LSM change from baseline at Wk 1 (SE)	-0.8 (0.2)	-1.5 (0.2)**	-1.6 (0.2)**	-0.8 (0.3)	-1.6 (0.3)*	-1.4 (0.3)*
	LSM change from baseline at Wk 24 (SE)	-1.3 (0.3)	-1.8 (0.2)	-1.9 (0.2)	-1.7 (0.3)	-2.0 (0.4)*	-2.1 (0.3)*
	Mean change from baseline at Wk 52 (SE)	NA	-2.2 (0.3)	-2.3 (0.3)	NA	-2.3 (0.2)	-2.2 (0.3)

Abbreviations: HAQ-DI=Health Assessment Questionnaire-Disability Index; IXE=ixekizumab; Q4W=ixekizumab 80 mg every 4 weeks; Q2W=ixekizumab 80 mg every 2 weeks; LSM=least squares mean; NA=not applicable; N=number of patients in the analysis population; (SE)=standard error; NRS=numeric rating scale; PainGA=patient global assessment; PBO=placebo; SE=standard error; VAS=visual analog scale; Wk=week.

Mean models repeated measures (MMRM) analysis was used to calculate LSM change from baseline up to Week 24. Multiple imputation (MI) was used to impute missing data up to Week 52.

*P<0.05 vs PBO.

**P<0.002 vs PBO.

- References:** 1. Mease PJ, et al. *Ann Rheum Dis*. 2017;76(1):79-87.
2. Nash P, et al. *Lancet*. 2017;389(10086):2317-2327.

Disclosure: A. M. Orbai, Abbvie, Celgene, Eli Lilly and Company, Horizon, Janssen, Novartis, Pfizer, 2, Novartis, and Pfizer, 5; D. D. Gladman, Abbvie, Amgen, BMS, Celgene, Eli Lilly and Company, Janssen, Novartis, Pfizer, UCB, 5, Abbvie, Amgen, Celgene, Janssen, Novartis, Pfizer and UCB, 2; J. Birt, Eli Lilly and Company, 1, Eli Lilly and Company, 3; A. M. Gellett, Eli Lilly and Company, 1, Eli Lilly and Company, 3; C. Y. Lin, Eli Lilly and Company, 1, Eli Lilly and Co., 3; T. Kvien, AbbVie, Biogen, BMS, Boehringer Ingelheim, Celgene, Celltrion, Eli Lilly and Company, Epirus, Hospira, Merck-Serono, MSD, Mundipharma, Novartis, Oktal, Orion Pharma, Hospira/Pfizer, Roche, Sandoz, UCB, 5, Diakonhjemmet Hospital, AbbVie, BMS, MSD, Pfizer, Roche, UCB, 2.

Abstract Number: 2562

Secukinumab Improves Grappa-Omeract Core Domains of Psoriatic Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Secukinumab, a fully human monoclonal antibody that selectively neutralizes IL-17A, has demonstrated efficacy for patients with psoriatic arthritis (PsA) in multiple phase 3 clinical trials.¹⁻⁴ To improve and standardize the assessment of PsA outcomes, the PsA core domain set, initially implemented in 2006,⁵ has been updated by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and endorsed by Outcome Measures in Rheumatology (OMERACT)⁶ in 2016. The updated PsA core domains are: musculoskeletal disease activity (arthritis, enthesitis, dactylitis, and spine symptoms), skin disease activity (psoriasis and nail psoriasis), pain, patient global assessment, physical function, fatigue, health-related quality of life, and systemic inflammation; structural damage assessment is recommended at least once in the development program of PsA medications. Here we report the efficacy of secukinumab vs placebo across individual PsA core domains, using pooled data from 4 phase 3 FUTURE studies.

Methods: Patients with active PsA participated in the phase 3 clinical trials FUTURE 2, 3, 4, and 5 (397, 414, 341, and 996 patients, respectively).¹⁻⁴ Data were pooled from the studies using secukinumab dosed at 150 mg (load vs no load), 300 mg, or placebo at the end of the 16-week double-blind period, and efficacy evaluated according to the updated GRAPPA-OMERACT PsA core domains. Core domains were assessed using multiple instruments (Table 1) with improvement defined as percentage of patients achieving $\geq 50\%$ improvement (joints), complete resolution (arthritis, enthesitis, dactylitis), or minimal clinically important difference in PsA where known and/or least squares mean change from baseline (patient-reported outcomes). Axial data are from MEASURE 2 (not assessed in FUTURE studies).

Results: 2049 patients were included, of whom 461 received secukinumab 300mg, 572 received secukinumab 150 mg, 335 received secukinumab 150 mg no load, and 681 received placebo. Baseline demographics and disease characteristics were broadly similar in all treatment groups. Efficacy results for each core domain are provided in Table 1.

Conclusion: Secukinumab demonstrated efficacy across GRAPPA-OMERACT PsA core domains in the phase 3 clinical trials program using multiple instruments and thresholds to measure improvement. Secukinumab 300 mg had the greatest efficacy across domains vs placebo. Our results indicate that secukinumab improves both the disease manifestations and life impact of PsA as demonstrated using the PsA core domain set.

References: 1. McInnes IB, et al. *Rheumatology*. 2017;56:1993-2003; 2. Nash P, et al. *Arthritis Res Ther*. 2018;20: 47; 3. Kivitz A, et al. PANLAR 2018 [abstract 364]; 4. Mease PJ, et al. ACR 2017 [abstract 17L]; 5. Gladman DD, et al. *J Rheumatol*. 2007;34:1167-70; 6. Orbai AM, et al. *Ann Rheum Dis*. 2017;76:673-80.

Table 1. Pooled efficacy results across GRAPPA-OMERACT PsA core domains.

Improvement in Patients With PsA at Week 16 in FUTURE Trials ^a					
PsA Core Domains	Measures and Improvement Definitions, n/M (%)	Secukinumab 300 mg n = 461	Secukinumab 150 mg n = 572	Secukinumab 150 mg, no load n = 335	Placebo n = 681
Inner circle domains (should be measured in all PsA clinical trials)					
Musculoskeletal disease activity	SJC76, $\geq 50\%$ improvement	314/444 (70.7)	353/551 (64.1)	201/323 (62.2)	258/626 (41.2)
	SJC76 resolution	158/444 (35.6)	151/551 (27.4)	77/323 (23.8) ^b	104/626 (16.6)
	- Arthritis	289/444 (65.1)	316/551 (57.4)	183/323 (56.7)	204/626 (32.6)
	- Enthesitis	89/444 (20.0)	80/551 (14.5)	32/323 (9.9) ^c	35/626 (5.6)
	- Dactylitis	151/284 (53.2)	166/374 (44.4)	80/195 (41.0) ^d	125/431 (29.0)
Skin disease activity	LDI resolution	107/174 (61.5)	98/188 (52.1)	74/141 (52.5) ^e	76/231 (32.9)
	PASI75	151/214 (70.6)	175/306 (57.2)	95/171 (55.6)	34/326 (10.4)
	IGA 0/1	112/214 (52.3)	125/306 (40.8)	55/171 (32.2)	25/326 (7.7)
Pain	PsA pain, mean change from BLfg	-19.75 (n = 440)	-15.94 (n = 545)	-15.44 (n = 320)	-4.46 (n = 616)
	PsA pain VAS, ≥ 3 points improvement ^g	313/440 (71.1)	403/545 (73.9)	229/319 (71.8)	331/617 (53.6)
Patient global	PGA, mean change from BLfg	-20.04 (n = 440)	-15.92 (n = 545)	-14.60 (n = 320)	-5.31 (n = 616)
Physical function	HAQ-DI, MCID = 0.3	262/459 (57.1)	281/571 (49.2)	172/335 (51.3)	226/680 (33.2)
	HAQ-DI, mean change from BLf	-0.48 (n = 438)	-0.36 (n = 544)	-0.40 (n = 320)	-0.16 (n = 615)
	SF-36 PCS, MCID ≥ 2.5 , %	65.9	59.4	61.8	42.0
HRQOL	SF-36 MCS, MCID ≥ 2.5 , %	48.4 ^h	50.0 ^h	49.9 ^h	40.4
	PsAQOL, mean change from BLf	-3.65 (n = 443)	-3.26 (n = 548)	-3.16 (n = 319)	-1.20 (n = 622)
	FACIT-Fatigue, mean change from BLfg	1.13 (n = 442) ⁱ	0.63 (n = 546) ^j	-0.29 (n = 319) ^k	1.18 (n = 621)
Fatigue					
Systemic inflammation	Elevated CRP (> 10 mg/L) resolution	83/111 (74.8)	86/134 (64.2)	52/ 75 (69.3)	55/154 (35.7)
Middle circle domains (important but not required in all PsA clinical trials)					
Participation	WPAI-GH, mean change from BLf	-13.98 (n = 283)	-10.85 (n = 392)	-13.39 (n = 186)	-4.62 (n = 417)
Structural damage	No structural progression at week 24l	191/217 (88.0)	170/213 (79.8) ^m	176/210 (83.8) ⁿ	218/296 (73.6)
Improvement in Patients With Ankylosing Spondylitis at Week 16 in MEASURE 2a'o					
		Secukinumab 150 mg n = 72	Placebo n = 74		
Spine symptoms	BASDAI, mean change from BL	-2.19 ^p	-0.85		

^a All *P* values vs placebo were *P* < .0001 except where indicated. All *P* values were for hypothesis generation. No adjustment was made for multiple comparisons. ^b *P* = .0073. ^c *P* = .0139. ^d *P* = .0066. ^e *P* = .0003. ^f Least squares mean change from BL; n is the number of patients with measures at both baseline and week 16 visit. ^g No MCID has been defined in PsA. ^h *P* < .01. ⁱ *P* = .9213. ^j *P* = .2581. ^k *P* = .0136. ^l Defined as a

change from baseline vdH-mTSS of ≤ 0.5 . Data shown are from the FUTURE 5 study. ^m $P = .1027$. ⁿ $P = .0053$. ^o Baeten D, et al. *N Engl J Med*. 2015;373:2534-2548. ^p $P < .001$.

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BL, baseline; CRP, C-reactive protein; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; HRQOL, health-related quality of life; IGA, Investigator's Global Assessment; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; MCID, minimal clinically important difference; MCS, mental component summary; PASI75/90, 75%/90% reduction in the Psoriasis Area and Severity Index; PCS, physical component summary; PGA, patient global assessment; PsA, psoriatic arthritis; PsAQOL, psoriatic arthritis-specific quality of life; SJC76, swollen joint count based on 76 joints; TJC78, tender joint count based on 78 joints; VAS, 100-mm visual analogue scale; vdH-mTSS, van der Heijde-modified Total Sharp Score; WPAI-GH, Work Productivity and Activity Impairment Questionnaire: General Health.

Disclosure: A. M. Orbai, AbbVie, Eli Lilly, Horizon, Janssen, Novartis, 2, Eli Lilly, Novartis, Pfizer Inc, 5; I. B. McInnes, Novartis, Janssen, Abbvie, Celgene, Lilly, Pfizer, Leo, UCB, BMS, 5, Janssen, Celgene, UCB, BMS, 2; L. C. Coates, Abbvie, Celgene, Novartis, Pfizer, 2, Abbvie, Amgen, BMS, Celgene, Galapagos, Janssen, Lilly, MSD, Novartis, Pfizer, Prothena, Sun Pharma, UCB, 5, Abbvie, Celgene, Janssen, Lilly, Novartis, UCB, 8; M. E. Husni, Janssen Research and Development, LLC, 2; D. D. Gladman, Abbvie, Amgen, BMS, Celgene, Galapagos, Gilead, Janssen, Eli Lilly, Novartis, Pfizer, UCB, 5, Abbvie, Amgen, Celgene, Eli Lilly, Novartis, Pfizer, UCB, 2; L. Gossec, Pfizer, UCB, Lilly, Bristol-Myers Squibb, 2, AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Novartis, Pfizer, Roche, UCB, 5; L. Pricop, Novartis, 1, 3; O. Chambenoit, Novartis, 1, Novartis, 3; X. Meng, Novartis, 3, Novartis, 1; P. J. Mease, AbbVie, Amgen, BMS, Celgene, Janssen, Eli Lilly, Novartis, Pfizer, Sun, UCB, 2, AbbVie, Amgen, BMS, Celgene, Janssen, Eli Lilly, Novartis, Pfizer, Sun, UCB, 5, AbbVie, Amgen, BMS, Celgene, Genentech, Janssen, Novartis, Pfizer, UCB, 8.

Abstract Number: 2563

Efficacy and Safety of a Potent and Highly Selective Oral Tyrosine Kinase 2 Inhibitor, BMS-986165, in Patients with Moderate-to-Severe Plaque Psoriasis: A Phase II, Randomized, Placebo-Controlled Trial

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Session Information

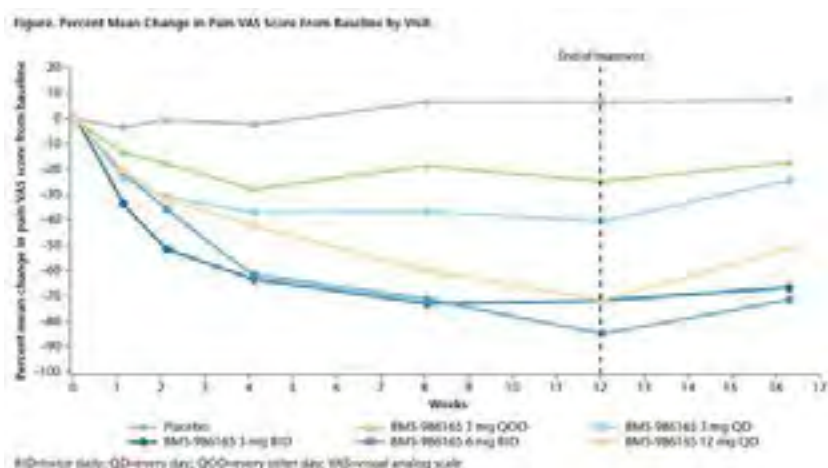
Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: BMS-986165, a potent and highly selective oral tyrosine kinase 2 inhibitor, inhibits signal transducer and activator of transcription (STAT)-dependent signalling pathways of interleukin-23 and type I interferons involved in the pathology of immune-mediated diseases. A 12-week (wk), placebo (pbo)-controlled, Phase II, dose-ranging study



(ClinicalTrials.gov, NCT02931838) investigated the efficacy and safety of BMS-986165 in patients (pts) with moderate-to-severe plaque psoriasis (PsO).

Methods: Adults with PsO for ≥ 6 months and moderate-to-severe disease (body surface area [BSA] $\geq 10\%$, Psoriasis Area and Severity Index [PASI] ≥ 12 , static Physician Global Assessment [sPGA] ≥ 3) were randomized to pbo or BMS-986165 (3 mg every other day [QOD], 3mg every day [QD], 3 mg twice daily [BID], 6 mg BID, 12 mg QD). Primary endpoint was PASI 75 at Wk 12. Pain was assessed by ACR pain visual analog scale (VAS).

Results: For the 267 pts randomized and treated, baseline characteristics (mean age 45 years, male 73%, median disease duration 15 years, prior biologic experience 43%, mean BSA 23%, mean PASI score 18.0) were generally balanced among treatment arms. At Wk 12, a significantly greater proportion of pts achieved PASI 75, PASI 90 and sPGA 0/1 at doses ≥ 3 mg QD vs pbo ($p < 0.05$), with dose response observed across all efficacy measures (Table 1). Efficacy was observed in both biologic-naïve and biologic-experienced pts, with rapid onset of response by Day 15. Pain VAS score showed a dose-dependent decrease, with the three top dose groups reaching $\sim 70\%$ decrease at Wk 12 (Figure). None of the five serious AEs were considered drug-related: two events in one pbo pt (hemorrhagic anemia, hemorrhoidal hemorrhage) and three events with BMS-986165 (3 mg QOD: gastroenteritis rotavirus; 3 mg QD: eye injury; 3 mg BID: dizziness). AEs were reported in 51% (pbo), 59% (3 mg QOD), 55% (3 mg QD), 64% (3 mg BID), 80% (6 mg BID) and 77% (12 mg QD) of pts. The most common AEs reported by pts across treatment arms (ranges) included nasopharyngitis (2–16%), headache (4–9%), and diarrhea (2–9%). AEs were generally mild to moderate and resulted in drug discontinuation in 4% of pbo pts and 2–7% of pts across the active doses. There were no significant changes in liver enzymes, blood counts or lipid levels.

Conclusion: In pts with moderate-to-severe PsO, BMS-986165 demonstrated statistically greater efficacy on skin measures vs pbo at doses ≥ 3 mg QD and a dose-dependent decrease in pain. BMS-986165 was generally well tolerated. Further evaluation in PsO and psoriatic arthritis is warranted. Medical writing assistance provided by Bu Reinen, PhD (Caudex), funded by Bristol-Myers Squibb.

Table 1. Response Rates (%) at Week 12

	Placebo n=45	3 mg QOD n=44	3 mg QD n=44	3 mg BID n=45	6 mg BID n=45	12 mg QD n=44
PASI 75	7	9	39*	69**	67**	75**
PASI 90	2	7	16*	44**	44**	43**
PASI 100	0	2	0	9	18*	25*
sPGA 0/1	7	21	39*	76**	64**	75**
DLQI 0/1	6	18	17	44*	68**	65**

* $p < 0.05$ vs placebo ** $p < 0.0001$ vs placebo BID=twice daily; DLQI=Dermatology Life Quality Index; PASI=Psoriasis Area and Severity Index; QD=every day; QOD=every other day; sPGA=static Physician Global Assessment

Disclosure: **K. A. Papp**, AbbVie, Akros, Amgen, Arcutis, Astellas, AstraZeneca, Baxalta, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, CanFite, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Forward Pharma, Galderma, Genentech, Janssen, Kyowa Hakko Kirin, Leo, 5, AbbVie, Amgen, Astellas, Celgene, Eli Lilly, Galderma, Janssen, Kyowa Hakko Kirin, Leo, Merck (MSD), Novartis, Pfizer, Valeant, 8, AbbVie, Akros, Allergan, Amgen, Anacor, Arcutis, AstraZeneca, Baxalta, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Galderma, Genentech, GSK, Janssen, Kyowa, Hakko Kirin, Leo, MedImmune, Meiji Seika Pharma, 2, AbbVie, Akros, Amgen, Baxter, Boehringer Ingelheim, Celgene, Coherus, Eli Lilly, Forward Pharma, Galderma, GSK, Janssen, Kyowa Hakko Kirin, Merck (MSD), Merck Serono, Novartis, Pfizer, Takeda, UCB, Valeant, 9, AbbVie, Akros, Amgen, Anacor, Astellas, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dow Pharma, Eli Lilly, Galderma, Janssen, Kyowa Hakko Kirin, Merck (MSD), Merck Serono, Novartis, Pfizer, Regeneron, Sanofi-Aventis/Genzyme, Valeant, 9, Meiji Seika Pharma, Merck (MSD), Merck Serono, Mitsubishi Pharma, Novartis, Pfizer, Regeneron, Roche, Sanofi-Aventis/Genzyme, Takeda, UCB, Valeant, 5, Merck Serono, Novartis, Pfizer, Regeneron, Roche, Sanofi-Aventis/Genzyme, Takeda, UCB, Valeant, 2; **K. B. Gordon**, AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermira, Eli Lilly, Janssen, Novartis, Pfizer, Sun, UCB, 2, 5; **D. Thaci**, AbbVie, Almirall, Amgen, Biogen-Idec, Bio Skin, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Chugai, Dermira, Dignity, Eli Lilly, Forward Pharma, GlaxoSmithKline, Leo Pharma, Janssen Cilag, Maruho, MSD, Mitsubishi Pharma, Novartis, Pfizer, 2, AbbVie, Almirall, Biogen-Idec, Bio Skin, Bristol-Myers Squibb, Celgene, Dignity, Galapagos, Leo Pharma, Maruho, Mitsubishi, Novartis, Pfizer, XenoPort, 5, AbbVie, Almirall, Amgen, Biogen-Idec, Bio Skin, Celgene, Dignity, Janssen, Leo Pharma, Pfizer, Roche-Posay, Novartis, Mundipharma, MSD, USB, Sanofi, Sandoz-Hexal, 9, AbbVie, Amgen, Biogen-Idec, Bio Skin, Bristol-Myers Squibb, Celgene, Dignity, Eli Lilly, GSK, Galapagos, Leo Pharma, Janssen Cilag, Morphosis, Novartis, Pfizer, Mundipharma, MSD, Sandoz, Sanofi, UCB, 9, Regeneron, Roche, Sanofi, Sandoz-Hexal, UCB, 2, AbbVie, Almirall, Biogen-Idec, Bio Skin, Bristol-Myers Squibb, Celgene, Dignity, Galapagos, Leo Pharma, Maruho, Mitsubishi, Novartis, Pfizer, XenoPort, 5; **A. Morita**, AbbVie, Eli Lilly, Janssen, Kyowa Hakko Kirin, Leo Pharma, Maruho, Mitsubishi-Tanabe, Novartis, 2, 5, 8; **M. Gooderham**, AbbVie, Akros, Amgen, Arcutis, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermira, Eli Lilly, Galderma, GSK, Incyte, Janssen, Kyowa Kirin, Leo Pharma, Merck, MedImmune, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Takeda, UCB, Valeant, 2, 5, 8; **P. Foley**, Galderma, LEO/Peplin, Janssen, Eli Lilly, 3M/iNova/Valeant, GSK/Stiefel, Abbott/AbbVie, Biogen Idec, Schering-Plough/MSD, Wyeth/Pfizer, Amgen, Novartis, Celgene, Dermira, Boehringer Ingelheim, Cutanea, Celtaxsys, Regeneron, Sanofi Genzyme, Sun Pharma, UCB, 2, 5, 8, 9, Bristol-Myers

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Abstract Number: 2564

Secukinumab Efficacy in Psoriatic Arthritis: Individual Patient Meta-Analysis of Four Phase 3 Trials in 2049 Patients

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Session Information

Session Date: Tuesday, October 23, 2018

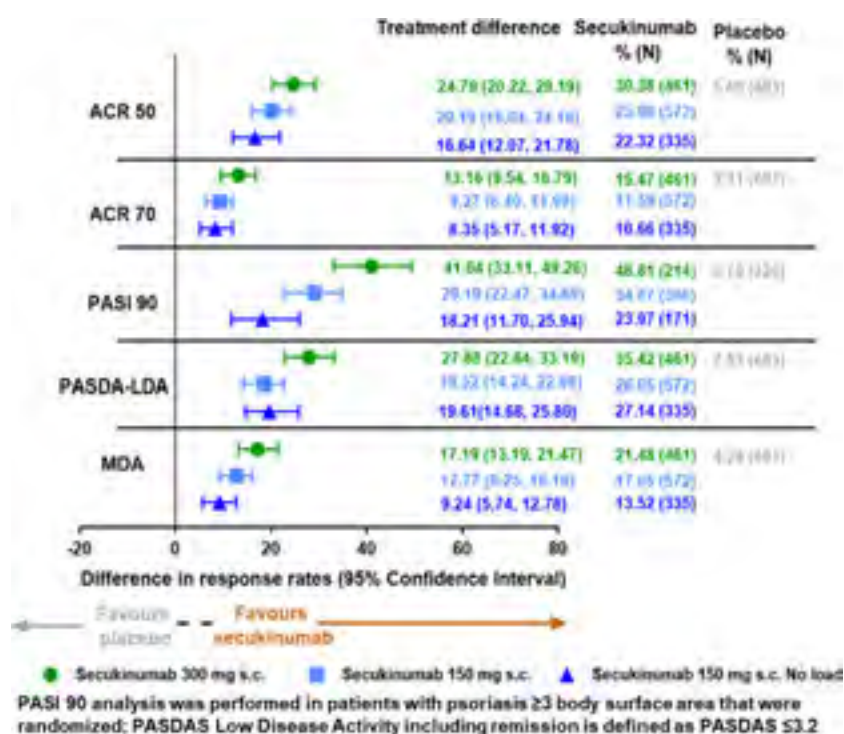
Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Secukinumab provided rapid, significant and sustained improvement in the signs and symptoms of psoriatic arthritis (PsA) in multiple Phase 3 studies.¹⁻⁴ Herein, we report individual patient meta-analysis data for secukinumab on achievement of high hurdle efficacy endpoints versus placebo (PBO) at Week (Wk) 16 in patients (pts) with PsA from four Phase 3 studies: FUTURE 2, 3, 4 and 5. Analyses in subgroups by baseline (BL) disease activity, BL psoriasis, prior Anti-TNF and concomitant Methotrexate (MTX) use were also evaluated.

Methods: Overall, 397, 414, 341, and 996 pts with active PsA were randomized in FUTURE 2, 3, 4, and 5 studies, respectively. Secukinumab doses included subcutaneous 300 mg and 150 mg administered at BL with loading doses (LD) at Wks 1, 2, and 3, followed by maintenance dose every 4 wks (q4w) starting at Wk 4. Data collected up to Wk 16 were pooled. Assessments included: ACR 50/70/PASI90 responses, PASDAS-Low Disease Activity (PASDAS-LDA), and Minimal Disease Activity (MDA) in overall population. ACR 50/70 and PASI 90 responses by BL Disease Activity Score (DAS) 28- C-Reactive Protein (CRP) (≤ 5.1 and > 5.1), BL CRP (≤ 10 mg/L and > 10 mg/L), BL Body Surface Area (BSA) ($\geq 3\%$ - $<10\%$, and $\geq 10\%$) with psoriasis and prior Anti-TNF and concomitant MTX use were also assessed. Results are reported after application of non-responder imputation.



Results: A total of 2049 pts were included in the meta-analysis, of which 461, 572, 335, and 681 pts received secukinumab 300mg, 150mg, 150mg without LD and PBO, respectively. Improvements were observed with secukinumab (300 mg, 150 mg, and 150mg without LD) vs PBO for all endpoints at Wk 16 in the overall population (Figure 1) and in all subgroups (data not shown). Secukinumab 300 mg was associated with greater improvements compared to the 150 mg dose for all endpoints in overall population and in subgroups.

Conclusion: Secukinumab provided improvements in high hurdle efficacy endpoints in patients with active PsA in the overall population and in subgroups with various levels of baseline disease activity and psoriasis. Secukinumab 300 mg was associated with higher responses compared to secukinumab 150 mg across all endpoints and in all groups.

References:

1. McInnes IB, et al. *Rheumatology* (Oxford) 2017; 56: 1993-2003.
2. Nash P, et al. *Arthritis Res Ther*. 2018; 20: 47.
3. Kivitz A, et al. *J Clinical Rheumatol*. 2018; 24 (suppl 3).
4. Mease P, et al. *Arthritis Rheumatol*. 2017; 69 (suppl 10).

Figure 1. Responses of High Hurdle Endpoints at Week 16 in Overall Population

Disclosure: A. B. Gottlieb, Janssen, Incyte, UCB, Novartis, and Eli Lilly and Company, 2, Janssen, Celgene, Bristol-Myers Squibb, Beiersdorf, Inc., AbbVie, UCB, Novartis, Incyte, Eli Lilly, Reddy Labs, Valeant, Dermira, Allergan, and Sun Pharmaceutical Industries, 5, 8, 9; P. J. Mease, AbbVie Inc., 2, 5, 8, Amgen Inc., 2, 5, 8, Bristol-Myers Squibb, 2, 5, 8, Celgene Corporation, 2, 5, 8, Crescendo Bioscience, 2, 5, 8, Genentech, Inc., 2, 5, 8, Janssen, 2, 5, 8, Lilly, 2, 5, 8, Merck & Co., 2, 5, 8, Novartis, 2, 5, 8, Pfizer, Inc., 2, 5, 8, UCB, Inc., 2, 5, 8; B. Kirkham, AbbVie Inc., 2, 5, 9, Bristol-Myers Squibb, 2, 5, 9, Celgene Corporation, 2, 5, 9, Janssen, 2, 5, 8, 9, Lilly, 2, 5, 9, MSD, 2, 5, 8, 9, Novartis, 2, 5, 9, Roche, 2, 5, 9, UCB, Inc., 2, 5, 9; P. Nash, Novartis, 2, 9, AbbVie Inc., 2, 9, Roche, 2, 9, Pfizer, Inc., 2, 9, Bristol-Myers Squibb, 2, 9, Celgene Corporation, 2, 9, Janssen, 2, 9; A. Balsa, AbbVie Inc., 2, 5, 9, Bristol-Myers Squibb, 2, 5, 9, Lilly, 2, 5, 9, Pfizer, Inc., 2, 5, 9, MSD, 9, Novartis, 2, 5, 9, Roche, 2, 5, 9, UCB, 9, Sanofi, 2, 5, 9, Nordic, 2, 5, 9, Celltrion, 2, 5, 9; B. Combe, Pfizer, MSD, Roche-Chugai, 2, Pfizer, UCB, Bristol-Myers Squibb, Janssen, Eli Lilly and Company, MSD, Roche-Chugai, AbbVie, Novartis, 5, Pfizer, Bristol-Myers Squibb, Eli Lilly and Company, MSD, 8; J. Rech, Bristol-Myers Squibb, 2, 8, Celgene Corporation, 2, 8, AbbVie Inc., 8, Fresenius, 8, Medicap, 8, MSD, 8, Pfizer, Inc., 8, Roche, 8; R. Martin, Novartis, 1, 3; G. Ligozio, Novartis, 1, 3; K. Abrams, Novartis, 1, 3; L. Pricop, Novartis, 1, 3.

Abstract Number: 2565

Safety and Efficacy of Tofacitinib, an Oral Janus Kinase Inhibitor, up to 36 Months in Patients with Active Psoriatic Arthritis: Data from the Third Interim Analysis of OPAL Balance, an Open-Label, Long-Term Extension Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of psoriatic arthritis (PsA). We report the safety, tolerability, and efficacy of tofacitinib in patients (pts) with active PsA from an ongoing, open-label, long-term extension (LTE) study (OPAL Balance, NCT01976364; August 31, 2017 data-cut; study ongoing, database not locked; some values may change in final, locked database).

Methods: Eligible pts from 2 Phase (P) 3 tofacitinib PsA studies (OPAL Broaden, NCT01877668; OPAL Beyond, NCT01882439) entered a 3-year LTE \leq 3 months after completing the P3 study or discontinuing for reasons other than treatment-related adverse events (AEs). Pts received tofacitinib 5 mg twice daily (BID) to Month (M) 1, after which dose adjustments between 5 and 10 mg BID were permitted to improve efficacy, or for safety reasons. Pts receiving a conventional synthetic disease-modifying antirheumatic drug (csDMARD) at P3 study entry continued the same

csDMARD in the LTE. Primary endpoints were incidence and severity of AEs, incidence of clinical abnormalities, and changes from baseline (Δ) in laboratory values. Safety data are reported up to M36. Efficacy was evaluated up to M30 (when N>60) as a secondary endpoint.

Results: 686 pts were treated in OPAL Balance; 468 (68.2%) remained in the study at data cut-off. Mean (range) LTE tofacitinib treatment duration was 614 (1–1,032) days. On Day 1, 675 pts (98.4%) received a csDMARD, which was discontinued in 86 pts (12.7%). To M36, 2,189 AEs were reported in 546 pts (79.6%), 95 pts (13.8%) had serious AEs, and 59 pts (8.6%) discontinued due to AEs. Serious infections occurred in 12 pts (1.7%), herpes zoster in 20 pts (2.9%; 1 serious event), major adverse cardiovascular events in 5 pts (0.7%), malignancies in 24 pts (3.5%; including 12 pts with non-melanoma skin cancer), and uveitis in 2 pts (0.3%). No AEs of gastrointestinal perforation or inflammatory bowel disease were reported. There were 5 deaths (not attributed to treatment, as assessed by the investigator) due to metastatic pancreatic carcinoma, acute cardiac failure/hypertensive heart disease, chronic obstructive pulmonary disease, pulmonary embolism, and cardiovascular insufficiency. Four AEs of latent tuberculosis were reported in pts whose previously negative QuantiFERON response became positive. Alanineaminotransferase was elevated $\geq 3\times$ the upper limit of normal (ULN) in 27 pts (4.0%), and aspartate aminotransferase $\geq 3\times$ ULN in 15 pts (2.2%). Changes in laboratory values observed in P3 studies were generally stable in the LTE, except for a modest decrease in absolute lymphocyte count over time. Eight pts (1.2%) discontinued (protocol-mandated) due to laboratory value changes. ACR responses, Δ Health Assessment Questionnaire-Disability Index, Psoriasis Area and Severity Index $\geq 75\%$ improvement response, Δ Leeds Enthesitis Index, Δ Dactylitis Severity Score, and Δ Pain were maintained up to M30.

Conclusion: Over 36 months in the LTE, the safety profile of tofacitinib in active PsA pts was generally similar to that of the P3 studies. No new safety risks were identified. Efficacy across various PsA disease domains was maintained over time.

Disclosure: P. Nash, AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer Inc, Roche, Sanofi, UCB, 2, AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer Inc, Roche, Sanofi, UCB, 5, AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer Inc, Roche, Sanofi, UCB, 8; L. C. Coates, AbbVie, Celgene, Janssen, Novartis, Pfizer Inc, 2, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Galapagos, Janssen, MSD, Novartis, Pfizer Inc, Prothena, Sun Pharma, UCB, 5; A. J. Kivitz, Novartis, 1, AbbVie, Boehringer Ingelheim, Flexion, Genzyme, Janssen, Pfizer Inc, Regeneron, Sanofi, Sun Pharma, UCB, 5, Celgene, Flexion, Genentech, Genzyme, Horizon, Ironwood, Merck, Novartis, Pfizer Inc, Regeneron, Sanofi, 8, Altoona Center for Clinical Research, 9; P. J. Mease, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis, Pfizer Inc, Sun Pharma, UCB, 2, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis, Pfizer Inc, Sun Pharma, UCB, 5, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Genentech, Janssen, Novartis, Pfizer Inc, UCB, 8; D. D. Gladman, AbbVie, Amgen, Celgene, Eli Lilly, Novartis, Pfizer Inc, UCB, 2, AbbVie, Amgen, Celgene, Eli Lilly, Galapagos, Janssen, Novartis, Pfizer Inc, UCB, 5; J. A. Covarrubias-Cobos, None; D. Fleishaker, Pfizer Inc, 1, 3; C. Wang, Pfizer Inc, 1, Pfizer Inc, 3; E. Kudlacz, Pfizer Inc, 1, Pfizer Inc, 3; S. Menon, Pfizer Inc, 1, 3; L. Fallon, Pfizer Inc, 1, Pfizer Inc, 3; T. Hendriks, Pfizer Inc, 1, Pfizer Inc, 3; K. S. Kanik, Pfizer Inc, 1, 3.

Abstract Number: 2566

Impact of Guselkumab Versus Placebo and Adalimumab on Patient Reported Outcomes in Patients with and without Psoriatic Arthritis in a Phase 3 Pivotal Psoriasis Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: VOYAGE 2 is a phase 3 double-blind, placebo/active comparator-controlled trial comparing guselkumab (GUS) with placebo (PBO) and adalimumab (ADA) in patients (pts) with moderate-to-severe PsO. The impact of treatment on patient-reported outcomes (PROs) was evaluated.

Methods: Pts were randomized to GUS 100mg (wks 0 & 4, then q8 wks), ADA (80 mg wk 0, 40 mg wk 1, then 40 mg q2 wks), or PBO (wks 0, 4, & 12, then GUS 100mg wks 16 & 20). We evaluated PROs using the Work Limitations Questionnaire [WLQ; work productivity], the Hospital Anxiety & Depression Scale [HADS], and the Medical Outcomes

Study 36-Item Short Form (SF-36; health related quality of life) at wk16 (GUS vs PBO) and wk24 (GUS vs ADA) in pts with and without PsA.

Results: In all, 18% of pts reported a history of PsA. At wk16, GUS pts had numerically greater improvements vs PBO in work productivity, anxiety and depression, and SF-36 PCS & MCS scores regardless of PsA status. The least square (LS) mean differences (95% CI; adjusted for baseline value) for GUS vs PBO for all PROs were generally similar between pts with and without PsA. At wk24, GUS pts had numerically greater improvements vs ADA in all PROs regardless of PsA status. The LS mean differences for GUS vs ADA were generally greater for pts with PsA vs pts without PsA (Table).

Conclusion: GUS showed better improvements in all PROs vs PBO at wk16 and vs ADA at wk24. Improvements vs PBO were similar regardless of PsA status, while improvements vs ADA were greater for pts with PsA.

Table: Summary of Change from Baseline in WLQ, HADS and SF-36 Scores from VOYAGE 2

	Week 16 GUS vs PBO				Week 24 GUS vs ADA			
	w/ PSA		w/out PSA		w/ PSA		w/out PSA	
	N, LS Mean Diff (95% CI)	p-value	N, LS Mean Diff (95% CI)	p-value	N, LS Mean Diff (95% CI)	p-value	N, LS Mean Diff (95% CI)	p-value
WLQ Physical Demands	86, -7.1 (-13.21, -0.92)	0.0249	446, -7.7 (-10.56, -4.88)	<0.0001	79, -1.6 (-10.58, 7.29)	0.7152	445, -2.6 (-5.39, 0.28)	0.0769
WLQ Time Management	85, -6.6 (-15.35, 2.06)	0.1326	419, -7.0 (-10.31, -3.79)	<0.0001	79, -4.3 (-14.40, 5.81)	0.3996	420, -0.6 (-3.46, 2.30)	0.6931
WLQ Mental-Interpersonal	83, -3.8 (-11.03, 3.35)	0.2913	439, -4.9 (-7.54, -2.35)	0.0002	78, -11.4 (-19.37, -3.34)	0.0061	436, -1.5 (-4.16, 1.11)	0.2569
WLQ Output Demands	84, -7.9 (-14.51, -1.21)	0.0211	440, -3.5 (-6.11, -0.88)	0.0089	79, -14.7 (-24.29, -5.17)	0.0030	437, -1.2 (-3.94, 1.62)	0.4136
Anxiety Score	135, -1.2 (-2.45, 0.04)	0.0584	608, -1.6 (-2.05, -1.07)	<0.0001	133, -2.1 (-3.33, -0.83)	0.0012	608, -0.8 (-1.29, -0.28)	0.0025
Depression Score	135, -1.2 (-2.55, 0.06)	0.0611	608, -1.5 (-1.96, -0.98)	<0.0001	133, -1.5 (-2.85, -0.09)	0.0374	608, -0.4 (-0.91, 0.10)	0.1158
SF-36 Physical Score	135, 5.7 (2.94, 8.43)	<0.0001	607, 4.4 (3.31, 5.39)	<0.0001	132, 2.9 (0.21, 5.57)	0.0346	608, 1.0 (-0.10, 2.04)	0.0753
SF-36 Mental Score	135, 4.5 (1.61, 7.48)	0.0026	607, 4.8 (3.53, 6.15)	<0.0001	132, 3.2 (-0.12, 6.53)	0.0591	608, 1.8 (0.45, 3.15)	0.0092

N is the sample size across two groups

Disclosure: **L. Puig**, Janssen Research & Development, LLC, 2; **C. Han**, Janssen Research & Development, LLC, 3; **R. Vender**, Janssen Research & Development, LLC, 2; **M. Song**, Janssen Research & Development, LLC, 3; **Y. You**, Janssen Research & Development, LLC, 3; **Y. K. Shen**, Janssen Research & Development, LLC, 3; **P. Foley**, Janssen Research & Development, LLC, 2.

Abstract Number: 2567

Clinically Meaningful Improvement in Skin and Nail Psoriasis in Bio-Naïve Active Psoriatic Arthritis Patients Treated with Intravenous Golumumab: Results through Week 24 from a Phase 3 Study

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Session Information

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: GO-VIBRANT was a Phase 3 trial of intravenous (IV) golumumab (GLM) in adult patients (pts) w/ active psoriatic arthritis (PsA). To evaluate improvement in skin, nail psoriasis & Dermatology Life Quality Index (DLQI) w/ IV GLM.

Methods: Adult bio-naïve PsA pts w/ active disease (≥5 swollen & tender joints, CRP ≥0.6mg/dl, active plaque psoriasis or documented history, & despite treatment w/csDMARDs&/or NSAIDs) were randomized to IV GLM 2mg/kg at wks 0, 4, & every 8 wks thereafter or PBO at wks 0, 4, 12, & 20 w/ crossover to GLM at wk24. Pts w/≥3% body surface area (BSA)

psoriasis at baseline (BL) were assessed using Psoriasis Area and Severity Index (PASI, 0-72) 75/90/100% & modified Nail Psoriasis Severity Index (mNAPSI, 0-130) at BL, wks 14 & 24 (in pts w/mNAPSI >0 at BL). DLQI was assessed at BL, wks 8, 14 & 24.

Results: 394 pts (PBO: n=198; GLM: n=196) had $\geq 3\%$ BSA psoriasis at BL; 76.5% had mNAPSI>0 at BL (mean 18.6). Pts on GLM achieved a greater PASI 75 response vs PBO (59.2% vs 13.6%, $p<0.001$) at wk14 & at wk24 (64.8% vs 13.1%, $p<0.001$). At wk14, pts on GLM achieved greater PASI 90/100 responses vs PBO (39.3/16.8% vs 6.6/4.5%; $p<0.001$ for all) & at wk24 (42.9/25.5% vs 7.6/5.6%; $p<0.001$ for all) (Table 1). At wk14, similar proportions of pts in the GLM groups, regardless of BL MTX use, achieved PASI 90/100 responses. At wk24, greater proportions of pts on GLM +MTX & GLM only achieved PASI 100 vs PBO (+MTX: 30.5% vs 7%, $p<0.001$; -MTX: 15.4% vs 1.8%, $p<0.010$) (Table 1). The mean decrease (improvement) from BL in the mNAPSI score was greater in GLM vs PBO (-9.6 vs -1.9, $p<0.001$) at wk14 & at wk24 (-11.4 vs -3.7, $p<0.001$). At wk8, the mean decrease (improvement) from BL in DLQI was greater in GLM vs PBO (-7.2 vs -1.7, $p<0.001$), at wk14 (-7.7 vs -1.8, $p<0.001$) & wk24 (-8.1 vs -1.9, $p<0.001$). At wk14, 55.1% of pts treated w/ GLM achieved a PASI 50 response & improvement in DLQI ≥ 5 vs 7.1% treated w/ PBO ($p<0.001$) & at wk24, 59.2% vs 8.1% ($p<0.001$).

Conclusion: As early as wk14, IV GLM demonstrated clinically meaningful improvements in skin psoriasis irrespective of MTX use & nail psoriasis. Improvement in DLQI was seen as early as wk8, w/ continued improvement at wks 14 & 24.

Table 1. Change from Baseline in PASI 90/100 Through Wk24

	Wk14		Wk24	
	PBO	GLM	PBO	GLM
Pts evaluable for improvement fr/ BL in PASI, n	198	196	198	196
PASI 90 (%)	6.6	39.3	7.6	42.9
% Diff (95% CI)		32.7 (25.10, 40.40)*		35.3 (27.52, 43.16)*
PASI 100 (%)	4.5	16.8	5.6	25.5
% Diff (95% CI)		12.3 (6.34, 18.30)*		20.0 (13.22, 26.85)*
+ BL MTX, n	142	131	142	131
PASI 90 (%)	m	41.2	9.2	45.8
% Diff (95% CI)		33.5 (23.97, 42.98)*		36.6 (26.88, 46.41)*
PASI 100 (%)	5.6	17.6	7.0	30.5
% Diff (95% CI)		11.9 (4.39, 19.46)**		23.5 (14.55, 32.43)*
- BL MTX, n	56	65	56	65
PASI 90 (%)	3.6	35.4	3.6	36.9
% Diff (95% CI)		31.8 (19.21, 44.41)*		33.4 (20.65, 46.05)*
PASI 100 (%)	1.8	15.4	1.8	15.4
% Diff (95% CI)		13.6 (4.17, 23.03)***		13.6 (4.17, 23.03)***

* $p<0.001$; ** $p=0.002$; *** $p=0.010$

Table 2. Change from Baseline in mNAPSI Through Wk24

	Wk14		Wk24	
	PBO	GLM	PBO	GLM
Pts (mNAPSI >0) evaluable for change fr/ BL, n	170	197	170	197
Mean (SD)	-1.9 (13.05)	-9.6 (15.71)	-3.7 (14.45)	-11.4 (16.38)
LS Mean diff (95% CI)				
		-8.4 (-10.71, -6.05)*		
		-8.4 (-10.82, -6.01)*		

* $p<0.001$

Disclosure: M. E. Husni, Janssen Research & Development, LLC, 2; P. J. Mease, Janssen Research & Development, LLC, 2; S. D. Chakravarty, Janssen Scientific Affairs, LLC, 3; S. Kafka, Janssen Scientific Affairs, LLC, 3; D. D. Harrison, Janssen Research & Development, LLC, 3; D. Parenti, Janssen Scientific Affairs, LLC, 3; L. Kim, Janssen Research & Development, LLC, 3; K. H. Lo, Janssen Research & Development, LLC, 3; E. C. Hsia, Janssen Research & Development, LLC, 2; A. Kavanaugh, Janssen Research & Development, LLC, 2.

Secukinumab Provides Sustained Improvements in the Signs and Symptoms in Psoriatic Arthritis: Final 5 Year Efficacy and Safety Results from a Phase 3 Trial

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Summary of Efficacy Results at Week 260			
Efficacy endpoints (n/M unless otherwise stated)		Secukinumab IV→150 mg Group (N = 161)*	Secukinumab IV→75 mg Group (N = 147)*
ACR20		89/131 (67.9)	98/127 (77.2)
ACR50		69/131 (52.7)	65/127 (51.2)
ACR70		49/131 (37.4)	43/127 (33.9)
^a PASI 90		48/72 (66.7)	47/71 (66.2)
HAQ-DI, mean change from baseline (SD)		n = 131, -0.4 (0.58)	n = 126, -0.5 (0.61)
SF-36 PCS, mean change from baseline (SD)		n = 131, 6.6 (8.33)	n = 123, 5.9 (9.36)
^b Resolution of enthesitis		67/81 (82.7)	60/77 (77.9)
^c Resolution of dactylitis		63/67 (94.0)	63/70 (90.0)
ACR Response before and after dose escalation (based on patients with complete data up to 56 weeks after the escalation)			
		Responses post-escalation (150 mg to 300 mg) M = 126	
Variables	Pre-escalation (150 mg), %	12 to 32 weeks	36 to 56 weeks
ACR < 20 (non-responder)	42.9	31.7	27.8
20 ≤ ACR < 50	25.4	24.6	21.4
50 ≤ ACR < 70	16.7	18.3	24.6
ACR ≥ 70	15.1	25.4	26.2
N total number of randomized patients; M is number of evaluable patients; n, number of responders ^a Secukinumab 150 and 75mg arms include 60 and 121 patients, respectively, who were dose escalated at Wk 156 or later; ^b Patients with psoriasis affecting ≥3% body surface area at baseline (150 mg: N = 89; 75 mg: N = 82) ^c Patients (N = 99 [150 mg], and 91 [75 mg]) with enthesitis at baseline ^d Patients (N = 83 [150 mg], and 77 [75 mg]) with dactylitis at baseline			
Pre-escalation is defined as the last assessment done on or before the patient administered the escalated dose; 126 patients (including placebo switchers) with both pre and all post-dose escalation assessments data available are included in the analysis			

Background/Purpose: Secukinumab (SEC), a fully human monoclonal IgG1 antibody, provided rapid and significant improvements in all key clinical domains of psoriatic arthritis (PsA) in the FUTURE 1 study (NCT01392326) with improvements sustained through 3 years.¹ Here, we present the final 5 year efficacy and safety results of the study, including efficacy results in patients who had a dose escalation during the study.

Methods: Overall, 606 adults with active PsA were originally randomized to receive SEC IV→150 mg, IV→75 mg, or placebo) and then re-randomized to SEC 150 mg or 75 mg. The study design has been previously described.¹ At Wk 104, 460 patients entered the 3-year extension study. As per the protocol amendment, patients could have SEC dose escalated from 150 to 300mg and from 75 mg to 150/300mg from Wk 156, based on physician's judgement. Assessments at Wk 260 included ACR20/50/70, PASI 90, HAQ-DI, SF-36 PCS, and resolution of dactylitis and enthesitis and are reported for patients originally randomized to the SEC 150 mg and 75 mg groups (observed data). Dose escalation results are reported for all patients who entered the extension study (i.e. including placebo-switchers). Safety is reported as exposure adjusted incidence rate/100 patient-years (EAIR) for all patients (n =587) who received ≥1 dose of study treatment.

Results: Overall, 132/161 (82%) and 124/147 (84.4%) patients entered the extension study who were originally randomized to SEC 150mg/75 mg, respectively, completed 260 Wks of treatment. Clinical responses were sustained or further improved through 5 years treatment (Table 1). A total of 86/236 (36.4%) patients on SEC 150 mg dose in extension were escalated to 300mg, while 180/221 (81.4%) patients on SEC 75mg dose were escalated to 150/300mg. Post-escalation, the proportion of patients with non/low level ACR responses improved with corresponding increases in the proportion of patients achieving moderate/high ACR responses (Table 1). Over the entire study period (SEC mean exposure of 2320 patient-years), the safety profile of SEC was consistent with previous reports.¹ EAIR of selected adverse events for SEC were serious infections (1.8), ulcerative colitis (0.04), Crohn's disease (0.1), and MACE (0.5). Six deaths (3 in each dose group) were reported in any SEC group through 5 years.

Conclusion: Over 80% of patients who entered the extension study completed 5 years of treatment. Secukinumab provided sustained improvements in the signs and symptoms in the major clinical domains of PsA through 5 years. Efficacy improved with dose escalation to secukinumab 150 mg or 300 mg during the study. Secukinumab was well tolerated with no new safety signals identified and safety profile was consistent with that previously reported.

Reference:

1. Mease PJ, et al. *Ann. Rheum. Dis.* 2017; 76 (suppl 2): 952.

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Association of Enthesitis with Achievement of Normal Quality of Life and Clinical Response in Patients with Non-Radiographic Axial Spondyloarthritis Treated with Adalimumab

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Session Information

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Enthesitis, a key pathology in non-radiographic axial spondyloarthritis (nr-axSpA), has been difficult to treat with conventional therapies and may take longer to resolve than other disease manifestations. It is unknown if failure to attain resolution of enthesitis affects achievement of normal quality of life (QoL) and clinical response. This analysis aimed to assess if enthesitis at baseline (BL) and after 12 wks of adalimumab (ADA) treatment in the ABILITY-3 study associates with achieving normal QoL and clinical response in patients (pts) with nr-axSpA.

Methods: ABILITY-3 enrolled adult pts with nr-axSpA with objective evidence of inflammation (MRI positive or elevated hsCRP), active disease at BL (ASDAS ≥ 2.1 , BASDAI ≥ 4 , and Patient's Assessment of Total Back Pain score ≥ 4), and an inadequate response to ≥ 2 NSAIDs. Pts received ADA 40 mg every other wk during a 28-wk open-label lead-in. Pearson's correlation coefficients were used to assess the relationship between total enthesitis count (sum of Maastricht Ankylosing Spondylitis Enthesitis Score [MASES] and plantar fascia enthesitis score) and QoL and disease activity at BL. Multivariable stepwise logistic regression was used to evaluate the relationship between total enthesitis count/location and normal QoL (EQ-5D ≥ 0.898 or SF36 MCS/PCS ≥ 50) and clinical response (ASDAS-ID [ASDAS < 1.3], ASAS40, or BASDAI50) at wk 12.

Results: At BL, 74% (501/673) of pts had enthesitis, and mean (95% CI) total enthesitis count was 3.7 (3.42, 3.98). Enthesitis resolved in 39% (196/501) of pts, and total enthesitis count was 1.9 (1.68, 2.12) at wk 12 of ADA treatment. At BL, total enthesitis count significantly correlated with all QoL and disease activity measures (**Table**). Each 1-unit increase in BL total enthesitis count was associated with 7% lower odds of ASDAS-ID (OR [95% CI]: 0.93 [0.88, 0.99], $P=0.018$) and 6% lower odds of BASDAI50 (0.94 [0.89, 0.99], $P=0.024$) at wk 12 and was not associated with normal QoL or ASAS40 at wk 12. Total enthesitis count at wk 12 was associated with lower odds of normal QoL and clinical response at wk 12 (**Table**). Achievement of normal QoL at wk 12 was less likely if pts had BL enthesitis at the posterior (EQ-5D ≥ 0.898) or anterior superior iliac spine (SF36 PCS ≥ 50), and pts with BL enthesitis at the 7th costochondral joint were less likely to achieve clinical response at wk 12 (**Table**).

Conclusion: 39% of pts achieved complete resolution of enthesitis after 12 wks of ADA treatment. Total enthesitis count at BL was not associated with normal QoL and inversely associated with clinical response at wk 12. Total enthesitis count at wk 12 was negatively associated with normal QoL and clinical response. Our exploratory analysis suggested possible inverse associations of specific BL enthesitis sites with achievement of normal QoL and clinical response; additional research is needed to further define these relationships.

Table. Association of Total Enthesitis Count With QoL and Diseases Activity at BL and Clinical Response at Wk 12

Baseline			
Measure	n		Pearson Correlation Coefficient
EQ-5D	672		-0.23*
SF-36 PCS	672		-0.18*
SF-36 MCS	672		-0.15*
BASDAI50	673		0.27*
ASDAS	673		0.18†
Patient Global Assessment	673		0.14*
Physician Global Assessment	671		0.17*
Wk 12			
Measure	n		Odds Ratio (95% CI)
EQ-5D ≥ 0.898	658		0.62 (0.48, 0.78)*
SF-36 PCS ≥ 50	658		0.70 (0.61, 0.81)*
SF-36 MCS ≥ 50	658		0.85 (0.80, 0.91)*
ASDAS-ID	628		0.82 (0.75, 0.91)*
ASAS40	632		0.82 (0.76, 0.88)*
BASDAI50	632		0.74 (0.69, 0.81)*
Enthesitis Location at baseline			
Measure at wk 12	n	Location	Odds Ratio (95% CI)
EQ-5D ≥ 0.898	660	Posterior superior iliac spine L/R	0.58 (0.34, 0.99)‡
SF-36 PCS ≥ 50	660	Anterior superior iliac spine L/R	0.60 (0.37, 0.96)‡
SF-36 MCS ≥ 50	663	—	—
ASDAS-ID	630	7th costochondral joint L/R	0.57 (0.36, 0.91)‡
ASAS40	637	7th costochondral joint L/R	0.62 (0.42, 0.91)‡
BASDAI50	634	7th costochondral joint L/R	0.60 (0.40, 0.91)‡

Locations evaluated included 1st costochondral joint L/R, 7th costochondral joint L/R, anterior superior iliac spine L/R, posterior superior iliac spine L/R, iliac crest L/R, 5th lumbar spinous process, proximal insertion of Achilles tendon L/R, and plantar fascia L/R. ASAS40, Assessment of SpondyloArthritis international Society 40% improvement; ASDAS-ID, Assessment of SpondyloArthritis international Society inactive disease; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; EQ-5D, EuroQol 5 dimension; MCS, mental component summary; PCS, physical component summary; QoL, quality of life; SF-36, short form health survey.

* $P < 0.001$; † $P < 0.01$; ‡ $P < 0.05$.

Disclosure: P. J. Mease, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Lilly, Novartis, Pfizer, Sun Pharma, and UCB, 2; AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Lilly, Novartis, Pfizer, Sun Pharma, and UCB, 5; AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Genentech, Janssen, Novartis, Pfizer, and UCB, 8; F. van Den Bosch, AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Lilly, Merck, Novartis, Pfizer, and UCB, 2, 5, 8; U. Kiltz, Pfizer, Inc., 2; AbbVie, Grünenthal, Novartis, and UCB, 5; AbbVie, Chugai, Janssen, Lilly, MSD, Novartis, Pfizer, and Roche, 8; P. Zueger, AbbVie Inc., 1, 3; K. Chen, AbbVie Inc., 1, 3; M. Wu, AbbVie Inc., 1, 3; J. K. Anderson, AbbVie Inc., 1, 3.

Probability of Achieving Low Disease Activity or Remission in Subjects with Active PsA Treated with Apremilast

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Session Information

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Background/Purpose: The ability to predict responses to apremilast (APR) could impact treatment decisions. This post-hoc analysis was conducted to (1) assess the predictive values of baseline (BL) clinical disease status on achieving long-term Clinical Disease Activity for Psoriatic Arthritis (cDAPSA) targets at Week 52 and (2) examine the association between early response to APR at Week 16 and the achievement of cDAPSA targets at Week 52.

Methods: Pooled analyses of 3 phase III trials (PALACE 1-3) were performed among subjects assigned to receive APR 30 mg BID at BL. Data were analyzed using multiple imputation to account for subjects who discontinued or had missing values, using all available cDAPSA scores. Probability of shifting across different cDAPSA categories from BL to Week 52 was calculated within these subjects. Binary logistic regression was also performed to confirm the results. To determine the extent of changes (from BL to Week 16) associated with achieving treatment targets at Week 52, we analyzed mean cDAPSA over time (from BL to Week 52) by cDAPSA category at Week 52.




Results: A total of 496 subjects who received APR were included in the analyses. The estimated probabilities of achieving either cDAPSA low disease activity (LDA) or remission (REM) at Week 52 were 47.6% in subjects with BL moderate disease activity (cDAPSA >13 to ≤27) and 72.1% in subjects with BL LDA (cDAPSA >4 to ≤13) (Table). In subjects with BL high disease activity (cDAPSA >27), the probability of achieving LDA or REM by Week 52 was 25.1%. Binary logistic regression provided similar results. In subjects with moderate or low disease activity at BL, mean cDAPSA scores ranged from 21.0 to 22.4. Among these subjects, those who further achieved Week 52 LDA and REM had a mean cDAPSA at Week 16 of 14.9 and 8.2, respectively, suggesting that a reduction of ≥30% in cDAPSA by Week 16 predicts achievement of LDA or REM at Week 52.

Conclusion: Subjects with low or moderate disease activity at BL exhibited the highest likelihood of achieving and maintaining an improvement in LDA or REM with continued APR treatment to Week 52. Early response, based on changes in mean cDAPSA level from BL to Week 16, was associated with the achievement or maintenance of cDAPSA LDA or REM by Week 52.

**Probability of Achieving cDAPSA Disease Status at Week 52
(APR 30 mg BID From BL)**

Baseline cDAPSA	Chance of Achieving Target Scores at Week 52				
	High	Moderate	Low	REM	Low/REM
Low	2.7%	25.1%	54.1%	18.0%	72.1%
Moderate	12.6%	39.8%	36.6%	10.8%	47.6%
High	36.3%	38.6%	20.9%	4.2%	25.1%

Multiple imputation.
cDAPSA=Clinical Disease Activity for Psoriatic Arthritis; REM=remission (cDAPSA ≤4); Low=low disease activity (cDAPSA >4 to ≤13); Moderate=moderate disease activity (cDAPSA >13 to ≤27); High=high disease activity (cDAPSA >27).

 Subjects with ≥1 disease activity category improvement
 Subjects with ≥1 disease activity category decline
 Subjects with no change in disease activity target score

Disclosure: P. J. Mease, Janssen Research & Development, LLC, 2; F. Behrens, Abbvie, Pfizer, Roche, Chugai, Janssen, 2, Abbvie, Pfizer, Roche, Chugai, UCB, BMS, Celgene, MSD, Novartis, Biotest, Janssen, Genzyme, Lilly, Sandoz, 8, Abbvie, Pfizer, Roche, Chugai, UCB, Celgene, Novartis, Biotest, Janssen, Genzyme, Lilly, Boehringer, 5; D. D. Gladman, AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, 2, 5; A. Kavanaugh, Abbott, Amgen, AstraZeneca, BMS, Celgene Corporation, Centocor-Janssen, Pfizer, Roche, UCB, 2; M. Brunori, Celgene Corporation, 3; L. Teng, Celgene Corporation, 3; B. Guerette, Celgene Corporation, 3; R. Queiro, None; A. Ogdie, Pfizer, Novartis, 2, Abbvie, BMS, Lilly, Pfizer, Novartis, Takeda, 5.

Abstract Number: 2571

Adalimumab Serum Concentration Fails to Predict Achievement of Sustained Remission or Absence of Flare for Patients with Non-Radiographic Axial Spondyloarthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: In patients (pts) with active non-radiographic axial spondyloarthritis (nr-axSpA) in the ABILITY-3 study who achieved sustained remission with adalimumab (ADA), continued ADA therapy was associated with significantly fewer pts flaring than treatment withdrawal. Sustained remission is an important treatment goal in pts with nr-axSpA, but factors predicting sustained remission and absence of flare are unknown. The purpose of this analysis was to determine whether an ADA concentration threshold is predictive of achievement of sustained remission and absence of flare in pts with nr-axSpA.

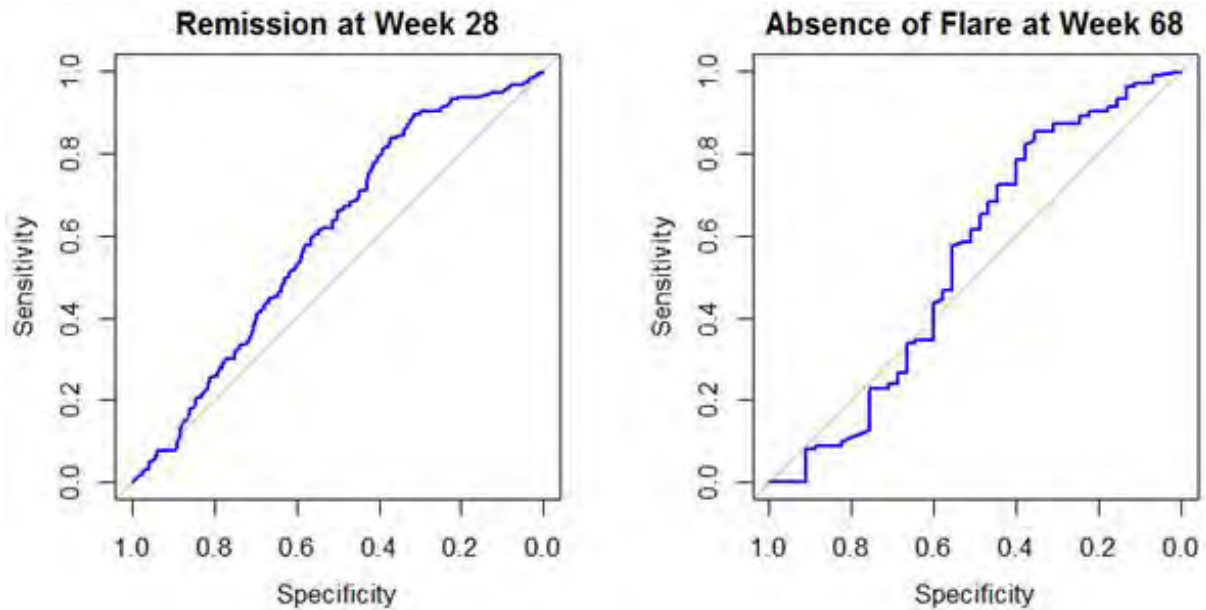
Methods: ABILITY-3 included a 28-wk open-label (OL) ADA (40 mg every other wk) lead-in in which pts who achieved sustained remission (ASDAS <1.3 at wks 16, 20, 24, and 28) were randomized to double-blind (DB) placebo (PBO) or continued ADA for 40 wks (68 wks total). Pts not achieving remission were discontinued at wks 20, 24, or 28. The primary efficacy variable was the proportion of pts who did not experience a flare (ASDAS ≥2.1 at 2 consecutive visits) by wk 68. Pts who flared received OL ADA rescue. ADA trough concentrations at wks 12 or 28 were used to predict achieving sustained remission by wk 28 (all OL patients, N=673) and absence of flare at wk 68 (patients randomized to DB ADA, n=152). Threshold analysis was conducted by constructing receiver operating characteristic (ROC) curves (R Ver 3.3.3) to assess predictive ADA trough concentration thresholds based on specificity and sensitivity values.

Results: Of 673 pts enrolled in the OL phase, 305 met criteria for remission at wk 28 and were randomized to DB treatment. Mean ± SD ADA trough concentrations were 6.68±5.23 µg/mL at wk 12 and 8.36±5.27 µg/mL at wk 28. During the DB phase, 81 and 45 pts flared and 68 and 36 pts received ≥12 wks of OL ADA rescue in PBO (n=153) and ADA (n=152) arms, respectively. ADA mean ± SD trough concentration at wk 68 for pts randomized to DB ADA with flare (7.64±5.22 µg/mL) was slightly lower than for DB ADA pts without flare (8.12±4.35 µg/mL). ROC curves showed AUC values ≤0.6 for achieving sustained remission by wk 28 and absence of flare at wk 68, with no concentration threshold meeting sensitivity and specificity criteria for reliable prediction of such endpoints (**Figure**).

Conclusion: ROC analyses did not identify an ADA trough concentration threshold that reliably predicted whether a pt with nr-axSpA would achieve sustained remission (by wk 28) or absence of flare (at wk 68).

Figure. Receiver Operating Characteristic Curves to Predict Sustained Remission by Week 28 and Absence of Flare at Week 68 by Adalimumab Serum Concentration

Disclosure: N. Kwantra, AbbVie Inc., 1, 3; M. Magrey, Amgen, AbbVie, and UCB Pharma, 2, UCB and Janssen, 5; P. J. Mease, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Lilly, Novartis, Pfizer, Sun Pharma, and UCB, 2, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Lilly, Novartis, Pfizer, Sun Pharma, and UCB, 5, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Genentech, Janssen, Novartis, Pfizer, and UCB, 8; J. Sieper, AbbVie, Janssen, Lilly, Merck, Novartis, Pfizer, Sun Pharma, and UCB, 5, AbbVie, Janssen, Lilly, Merck, Novartis, Pfizer, and UCB., 8; R. B. M. Landewé, Abbott/AbbVie, Ablynx, Amgen, Astra-Zeneca, Bristol Myers Squibb, Celgene, Janssen (formerly Centocor),



Galapagos, GlaxoSmithKline, Novartis, Novo-Nordisk, Merck, Pfizer, Roche, Schering-Plough, TiGenix, UCB, and Wyeth, 5, 9, Abbott, Amgen, Centocor, Novartis, Pfizer, Roche, Schering-Plough, UCB, and Wyeth, 2, Abbott/AbbVie, Amgen, Bristol Myers Squibb, Janssen (formerly Centocor), Merck, Pfizer, Roche, Schering-Plough, UCB, and Wyeth., 8; **X. Wang**, AbbVie Inc., 1, 3; **A. Lertratanakul**, AbbVie Inc., 1, 3; **J. K. Anderson**, AbbVie Inc., 1, 3; **N. Mostafa**, AbbVie Inc., 1, 3.

Abstract Number: 2572

Predictors for Use of Secukinumab 300mg over 150mg in Psoriatic Arthritis: A Meta-Analysis of Four Phase 3 Trials By Machine Learning

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Session Information

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

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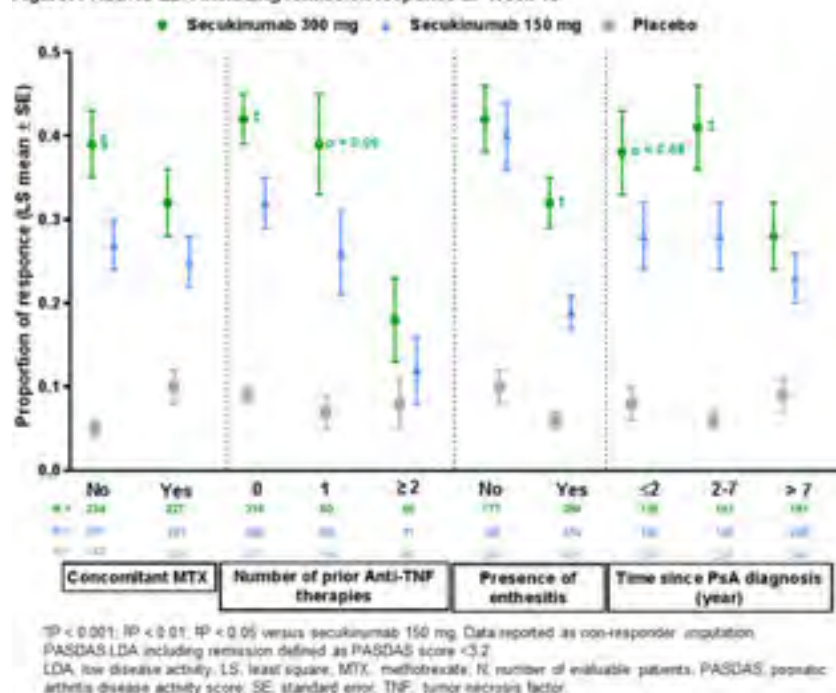
Session Time: 9:00AM-11:00AM

Background/Purpose: Subcutaneous secukinumab 150mg and 300mg are approved doses for the treatment of psoriatic arthritis (PsA) with the higher dose recommended for patients with anti-TNF inadequate response or moderate-to-severe psoriasis. Although multivariate logistic regression analysis can predict if a specific group of patients can benefit from the higher dose, machine learning surpasses these traditional estimation-focused analyses with a higher area under the Receiver Operating Characteristic curve. The objective is to investigate if specific baseline clinical characteristics can be used to predict which patients gain additional benefit from the 300mg dose using pooled data from the secukinumab phase 3 studies.

Methods: Bayesian Elastic net was used to analyze 4 studies (FUTURE 2-5) with 2148 patients investigating a total of 275 predictors (baseline demographic, disease characteristics in both main effects and interaction effects). Eleven endpoints were analyzed at Week 16 including ACR50, PASI90, and psoriatic arthritis disease activity score (PASDAS). Heatmaps were used to identify common predictors across endpoints at Week 16. PASDAS low disease activity (LDA), including remission (REM) (PASDAS LDA+REM; PASDAS score < 3.2)¹, is reported as a recommended disease activity target using meta-analytic techniques. Missing responses are imputed as non-responders.

Results: There was no single predictor which alone could adequately predict which patients would achieve PASDAS LDA+REM with 300mg compared to 150mg. However, several predictors jointly produced adequate predictions: no prior use of biologic, 1 previous anti-TNF therapy, no use of concomitant methotrexate (MTX), presence of enthesitis at baseline and earlier time since PsA diagnosis (**Figure**).

Figure: PASDAS LDA including remission response at Week 16



Conclusion: Machine learning on this pooled dataset confirmed previous clinical findings for the additional benefit of secukinumab 300mg over 150mg in patients with moderate to severe psoriasis in PsA², and in PsA patients with previous exposure to anti-TNF and in patients without concomitant MTX³. In addition, early PsA, and presence of enthesitis were identified as predictors of PASDAS LDA+REM that warrant further investigation.

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Disclosure: L. Pricop, Novartis, 1, 3; C. Gaillez, Novartis, BMS, 1, Novartis, 3; G. Ligozio, Novartis, 1, 3; X. Zhu, Novartis, 3; D. James, Novartis, 1, 3.

Abstract Number: 2573

The Effect of Biologic Disease-Modifying Antirheumatic Drugs in Targeting Disease Remission in Axial Spondyloarthritis: A Systematic Literature Review

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Table 1: bDMARD trials addressing ASAS-PR or ASDAS-ID as outcomes

Reference	Phenotype	Placebo-controlled phase duration	Drug (number of patients enrolled)	Type of Outcome	Results
Sieper, 2014	r-axSpA/ nr-axSpA	28 weeks	NPX+IFX vs NPX+PBO (105)	Primary	ASAS-PR in 61.9% NPX+IFX vs 35.3% NPX+PBO ($p=0.002$) at w.28
Van der Heijde, 2005	r-axSpA	24 weeks	IFX vs PBO (279)	Secondary	ASAS-PR in 22.4% IFX vs 1.3% PBO ($p<0.001$) at w.24
Barkham, 2009	r-axSpA/ nr-axSpA	16 weeks	IFX vs PBO (40)	Secondary	ASAS-PR in 55.6% IFX vs 12.5% PBO ($p=0.009$) at w.16
Brandt, 2003	r-axSpA	6 weeks	ETN vs PBO (33)	Secondary	ASAS-PR in none patient at w.6
Davis, 2003	r-axSpA	24 weeks	ETN vs PBO (277)	Secondary	ASAS-PR in 17% ETN vs 4% PBO ($p=0.005$) at w.24
van der Heijde, 2006	r-axSpA	12 weeks	ETN 50mg once weekly/25mg twice weekly vs PBO (361)	Secondary	ASAS-PR in 31.6% ETN 50mg once weekly/21.3% twice weekly vs 5.9% PBO ($p<0.05$) at w.12
Dougados, 2011	r-axSpA	12 weeks	ETN vs PBO (62)	Secondary	ASAS-PR in 18% ETN vs 5% PBO ($p=0.073$) at w.12
Song, 2011	r-axSpA/ nr-axSpA	48 weeks	ETN vs SSZ (78)	Secondary	ASAS-PR in 50% ETN vs 10% SSZ ($p=0.006$) at w.48
Dougados, 2014	nr-axSpA	12 weeks	ETN vs PBO (215)	Secondary	ASDAS-ID in 40% vs 17.4% PBO ($p<0.001$) at w.12
van der Heijde, 2006	r-axSpA	24 weeks	ADA vs PBO (315)	Secondary	ASAS-PR in 20.7% ADA vs 3.7% PBO ($p<0.001$) at w.12 ASAS-PR in 22.1% ADA vs 5.6% PBO ($p<0.001$) at w.24
Halbes, 2008	nr-axSpA	12 weeks	ADA vs PBO (46)	Secondary	ASAS-PR in 22.7% ADA vs 0% PBO ($p=0.019$) at w.12
Huang, 2013	r-axSpA	12 weeks	ADA vs PBO (344)	Secondary	ASAS-PR in 21.8% ADA vs 3.5% PBO ($p<0.001$) at w.12 ASDAS-ID in 40.2% ADA vs 5.2% PBO ($p<0.001$) at w.12
Sieper, 2013	nr-axSpA	12 weeks	ADA vs PBO (192)	Secondary	ASAS-PR in 16% ADA vs 5% PBO ($p<0.001$) at w.12 ASDAS-ID in 24% ADA vs 4% PBO ($p<0.001$) at w.12
Landewe, 2013	r-axSpA/ nr-axSpA	24 weeks	CZP 200mgQ2W/400mgQ4W vs PBO (325)	Secondary	ASAS-PR in 23.4% CZP 200mgQ2W/ 24.3% CZP 400mgQ4W vs 3.7% PBO ($p<0.001$) at w.12
Sieper, 2015	nr-axSpA	16 weeks	GOL vs PBO (196)	Secondary	ASAS-PR in 33%GOL vs 18% PBO ($p=0.0136$) at w.16
Baeten, 2013 (MEASURE 1)	r-axSpA	16 weeks	SEC 75/150mg vs PBO (371)	Secondary	ASAS-PR in 16% 75mg/ 15% 150mg vs 3% PBO ($p<0.01$) at w.16
Baeten, 2015 (MEASURE 2)	r-axSpA	16 weeks	SEC 75/150mg vs PBO (219)	Secondary	ASAS-PR in 15% 75mg/ 14% 150mg vs 4% PBO ($p>0.05$) at w.16
Sieper, 2016 (MEASURE 2, stratification by prior TNFi)	r-axSpA	16 weeks	SEC 75mg/150mg vs PBO (219)	Secondary	TNFi naïve: ASAS-PR in 20% 75mg / 18.2% 150mg vs 6.7% PBO ($p>0.05$ for both dose regimens) at w.16 TNFi IR: ASAS-PR in 7.1% 75mg/ 7.1% 150mg vs 0% PBO ($p>0.05$) at w.16
Sieper, 2014	r-axSpA	12 weeks	Sarilumab (5 dose regimens) vs PBO (301)	Secondary	ASAS-PR between 1.9%-8.2% Sarilumab vs 2% PBO ($p>0.05$ for all dose regimens) at w.12

Legend: ADA: adalimumab; ASAS-PR: ASAS- Partial Remission; ASDAS-ID: ASDAS Inactive Disease; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IFX: infliximab; NPX: naproxen; nr-axSpA: non-radiographic axial spondyloarthritis; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks; r-axSpA: radiographic spondyloarthritis; SEC: secukinumab; SSZ: sulfasalazine; TNFi: tumor necrosis factor inhibitor; TNFi- IR: inadequate response/intolerance to one TNFi; vs - versus

Background/Purpose: The treat-to-target concept is currently recommended in Axial Spondyloarthritis (axSpA) and remission is the main objective of treatment. Although consensual definitions of remission are lacking, ASAS-Partial Remission (ASAS-PR) and ASDAS-Inactive Disease (ASDAS-ID) have gained wide acceptance as clinical remission-like definitions in current practice.

Methods: In this review we assessed the efficacy of different biologic disease-modifying anti-rheumatic drugs (bDMARD) in achieving ASAS-PR or/and ASDAS-ID, as remission-like outcomes. Data from placebo-controlled phases of randomised controlled trials (RCTs) were included. A systematic literature review was performed using the MEDLINE database (May 1 2018) with the filters “published since the year 2000” and “humans”. The PICO (P, population; I, intervention; C, comparison; O, outcome) concept was used to perform the analysis according to: Patients- adults (>18 years old) with radiographic axSpA (r-axSpA) or non-radiographic axSpA (nr-axSpA); Intervention - any bDMARD regardless of formulation or duration; Comparison - placebo and/or any different drug; Outcomes: ASAS-PR and ASDAS-ID. For each outcome, we assessed whether the treatment group was superior, equal or inferior to the comparator group regarding the achievement of the ASAS-PR or ASDAS-ID, as primary outcomes.

Results: After screening 152 references, 19 RCTs fulfilled the inclusion criteria – 15 concerning tumor necrosis factor inhibitors (TNFi), 3 secukinumab (anti-IL17A) and 1 sarilumab (anti-IL6R). Eleven studies were conducted in r-axSpA, four in nr-axSpA and four in both populations. ASAS-PR was the dominant remission-like definition, used in 18 of the trials. Only 1 RCT used these remission-like endpoints as primary outcomes, in the remaining 18 trials, ASAS-PR or ASDAS-ID were just focused as secondary measures (Table 1). Concerning TNFi bDMARDs, 14 of the 15 trials provide evidence of efficacy in achieving remission, with the proportion of patients achieving ASAS-PR and ASDAS-ID varying between 16-61.9% and 24-40.2% respectively with a minimum and maximum of placebo-controlled phase duration of 12 to 48 weeks. Secukinumab was effective in achieving ASAS-PR when an initial intravenous loading dose was applied (MEASURE 1), while sarilumab was not able to induce remission in axSpA.

Conclusion: Clinical trials addressing remission-like concepts as outcomes are limited. Most studies were conducted in r-axSpA and ASAS-PR score was the preferred remission outcome. Considering nowadays-aimed treatment targets, these data raise the unmet need for improved treatment options favoring optimized remissions rates in axSpA patients.

Disclosure: A. R. Machado, None; S. Rodrigues Manica, None; J. Leite Silva, None; F. Pimentel-Santos, None; J. Tavares Costa, None; E. Vieira-Sousa, None.

Abstract Number: 2574

Tapering TNF Inhibitors in Axial Spondyloarthritis: Systematic analysis of the literature and meta-Analysis

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Session Information

Session Date: Tuesday, October 23, 2018

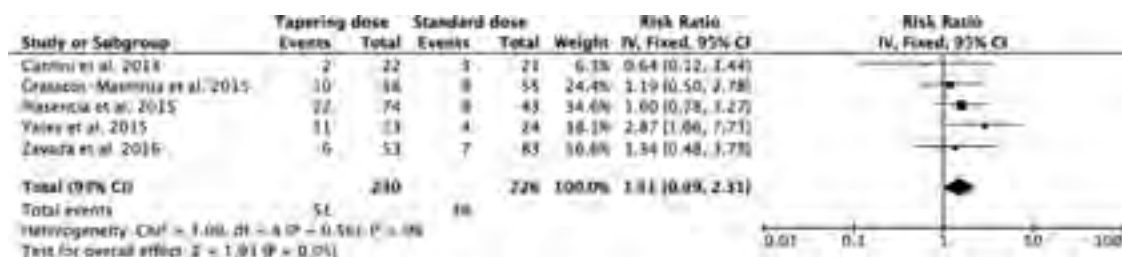
Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Tumor necrosis factor inhibitors (TNFi) are effective in treating patients with axial spondyloarthritis (axSpA), but they are associated with adverse effects and high costs. According to the ASAS-EULAR recommendations, if patients are in sustained remission or low disease activity, tapering of TNFi can be considered. We aimed to assess the risk of relapse after TNFi tapering strategies compared to standard dose continuation in patients with axSpA.

Methods: We conducted a systematic search of the literature using Medline, Embase and Cochrane databases up to 27 February 2018. All randomized controlled trials (RCTs) and controlled cohort studies (CCTs) comparing the rate of relapse in patients with tapering dose versus standard dose of TNFi after achieving remission or low disease activity were selected. For the meta-analysis, the estimated event was the number of patients who had relapsed or not maintained remission or low disease activity in each treatment group (tapering versus standard dose). Data were extracted independently by two investigators. A global risk ratio (RR) was estimated using an inverse variance approach with fixed or random effect model, according to the level of heterogeneity (I², Cochran's Q-test). All these computations were performed using RevMan 5.3 software with a p-value threshold of 0.05.



Results: Among the 544 publications screened, 5 studies (3 RCTs including one available only as abstract and 2 CCTs) were included, involving 230 patients who tapered TNFi dose and 226 treated with standard dose. Clinical heterogeneity between the trials was low: mean age between 46.0 and 46.7 years, male: 72.6% - 87.2%, ankylosing spondylitis according to modified New York criteria: 74% - 100%, HLA-B27 positive: 91.0% - 93.0%. Methodological heterogeneity between the trials was high: all tapering modalities, relapse definitions, duration of the follow-up and evaluation times were different. None of tapering strategies were disease activity guided.

Tapering TNFi dose was not associated with a statistically significant increase of relapse (RR [95% CI] = 1.51 [0.99 to 2.31], $p = 0.05$ in comparison with standard dose continuation [Figure]. A relapse was observed in 22.2% of patients who tapered TNFi versus 13.3% in patients with standard doses.

Conclusion: Tapering doses of TNFi does not seem to increase the risk of relapse compared to TNFi standard dose continuation. However, data are scarce and heterogeneous, a need exists for additional, well designed, randomized controlled trials on this topic.

Disclosure: L. Couvaras, None; T. Barnetche, Roche SAS, 5, Chugai Pharma France, 5; A. Constantin, MSD Avenir, 2; T. Pham, AbbVie Inc., 2, 5, Pfizer, Inc., 2, 5, MSD, 5, Roche, 5, Janssen, 5, UCB, Inc., 5, Novartis, 5, Lilly, 5, Sanofi, 5, BMS, 2, 5, Chugai, 5.

Abstract Number: 2575

Long-Term Effects of TNF-Alpha Inhibitors on Bone Mineral Density and the Incidence of Vertebral Fractures in Patients with Ankylosing Spondylitis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Ankylosing Spondylitis (AS) is not only characterized by pathological bone formation leading to ankylosis, but also by bone loss which may lead to vertebral fractures (VFX). TNF-alpha inhibitors (TNFi) have proven to be effective in blocking the inflammation process. A few studies also showed an increase of Bone Mineral Density (BMD) in AS patients treated with TNFi¹⁻³ but the incidence of VFX after two years of treatment was increased.³⁻⁴ To evaluate the long-term effect of TNFi on BMD and the incidence of VFX in patients with AS.

Methods: Consecutive TNFi naive patients diagnosed with AS according to the Modified New York criteria were included. Patients were recruited from the VUmc and the Amsterdam Outpatient clinic Reade and were treated with TNFi for 4 years. BMD at hip and lumbar spine (LS) were measured at baseline and after 4 years. T-scores were categorized as 'normal BMD', 'osteopenia' and 'osteoporosis', based on the WHO osteoporosis criteria.⁵ The incidence of VFX was determined by two observers using the Genant method.⁶

Results: In total, 107 AS patients with complete datasets (68.2% male) were included. The mean age was 42.6 years and the disease duration (time since diagnosis) was 11.0 years. At baseline 40.1% of the patients had a decreased BMD of the hip and 40.2% of the spine, of whom 27 patients (26%) had both a decreased hip BMD as well as a decreased lumbar

BMD. The BMD of spine and hip improved after 4 years of TNFi treatment (Table 1). In 13 patients (12.1%), 14 VFx were observed both at baseline. After 4 years of TNFi-treatment 26 VFx were observed in 21 patients. After 4 years, 4 out of 21 patients with ≥ 1 VFx had a decreased BMD at hip and lumbar spine whereas the other 17 patients had a normal BMD. The majority of VFx was localized in the mid or lower thoracic spine.

Table 1: BMD measurement in spine and hip of 107 AS patients treated with TNFi.

	Baseline*	After 4 years of TNFi**	p-value
Osteopenia LS	34 (31.8)	25 (23.4)	<0.001
Osteoporosis LS	9 (8.4)	2 (1.9)	
Abnormal BMD LS	43 (40.2)	27 (25.3)	
Osteopenia total hip	39 (36.4)	31 (29.0)	
Osteoporosis total hip	4 (3.7)	3 (2.8)	
Abnormal BMD total hip	43 (40.1)	34 (31.8)	0.03
Patients with VFx	13 (12.1)	21 (19.6)	0.004
Total number of VFx	14	26	

*1 patient with spondylodesis; 4 patients with a total hip replacement

** 2 patients with spondylodesis; 5 patients with a total hip replacement

LS: lumbar spine, Abnormal BMD = osteopenia and/or osteoporosis according to WHO guideline⁶

Vertebral fractures (VFx) are presented in number of patients with a VFx and the actual prevalence of VFx. Outcomes are presented in n (%)

Conclusion: The percentage of relatively young AS patients with a decreased BMD at baseline of the hip and lumbar spine was high (40%). After 4 years of TNFi-treatment the BMD of the lumbar spine improved in 14.9% of the patients and of the hip in 8.3% of the patients. At baseline, several vertebral fractures were found and a few additional vertebral fractures were observed after 4 years of treatment.

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Abstract Number: 2576

Anti-Drug Antibodies, Efficacy, and Impact of Concomitant Methotrexate in Ixekizumab-Treated Patients with Psoriatic Arthritis

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Session Information

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Session Time: 9:00AM-11:00AM

Background/Purpose: Anti-drug antibody (ADA) development can potentially affect the efficacy of biologics; concomitant MTX decreases the development of ADA for some biologics.¹ Ixekizumab (IXE), a mAb that selectively targets IL-17A, may be used with or without MTX. In IXE-treated patients (pts) with active PsA, we evaluated whether ADA development was affected by concomitant MTX or had an effect on long-term efficacy.

Methods: Two Phase 3 randomized, double-blind, placebo-controlled clinical trials evaluated IXE treatment in adult pts with PsA who were biologic-naïve (SPIRIT-P1; NCT01695239) or inadequate responders/intolerant to TNF inhibitors (SPIRIT-P2; NCT02349295). Study details were published^{2,3}; all pts met the Classification Criteria for PsA. Pts received placebo or 80 mg IXE every 2 weeks (Wks; Q2W) or 4 Wks (Q4W) after a 160- mg loading dose. Pts continued stable concomitant conventional DMARDs through Wk 24 (except inadequate responders at Wk 16 who received rescue therapy). Analyses included ADA evaluable pts initially randomized to IXE. ADA, titer, and neutralizing antibody (NAb)

status were stratified by MTX use (Integrated data). ACR20 responses stratified by ADA and NAb status were analyzed for SPIRIT-P1 and -P2, separately. Missing values were imputed by non-responder imputation for ACR20 and last observation carried forward for ADA titer.

Results: Of 223 pts treated with concomitant MTX, 96 (89.7%) of IXE Q4W and 110 (94.8%) of IXE Q2W were ADA negative (-); 11 (10.3%) of IXE Q4W and 6 (5.2%) of IXE Q2W were ADA positive (+). Similarly, of 222 pts without concomitant MTX, 103 (88%) of IXE Q4W and 96 (91.4%) of IXE Q2W were ADA-; 14 (12.0%) of IXE Q4W and 9 (8.6%) of IXE Q2W were ADA+. The majority of ADA+ pts had low titer ADA. The table shows ADA, titer, and NAb status stratified by MTX use. The proportion of SPIRIT-P1 pts achieving ACR20 at Wk 52 when ADA- was 63.8% (n=60) of IXE Q4W and 66.7% (n=60) of IXE Q2W, and when ADA+ was 50.0% (n=6) of IXE Q4W and 54.5% (n=6) of IXE Q2W. The proportion of SPIRIT-P2 pts achieving ACR20 response at Wk 52 when ADA- was 57.1% (n=60) of IXE Q4W and 50.9% (n=59) of IXE Q2W, and when ADA+ was 92.3% (n=12) of IXE Q4W and 50.0% (n=2) of IXE Q2W (Figure).

Conclusion: The absolute number of ADA+ pts with IXE was relatively small and the majority were low titer. The presence of ADA did not affect the long-term efficacy of IXE in PsA pts. Concomitant MTX did not appear to have a meaningful effect on ADA development.

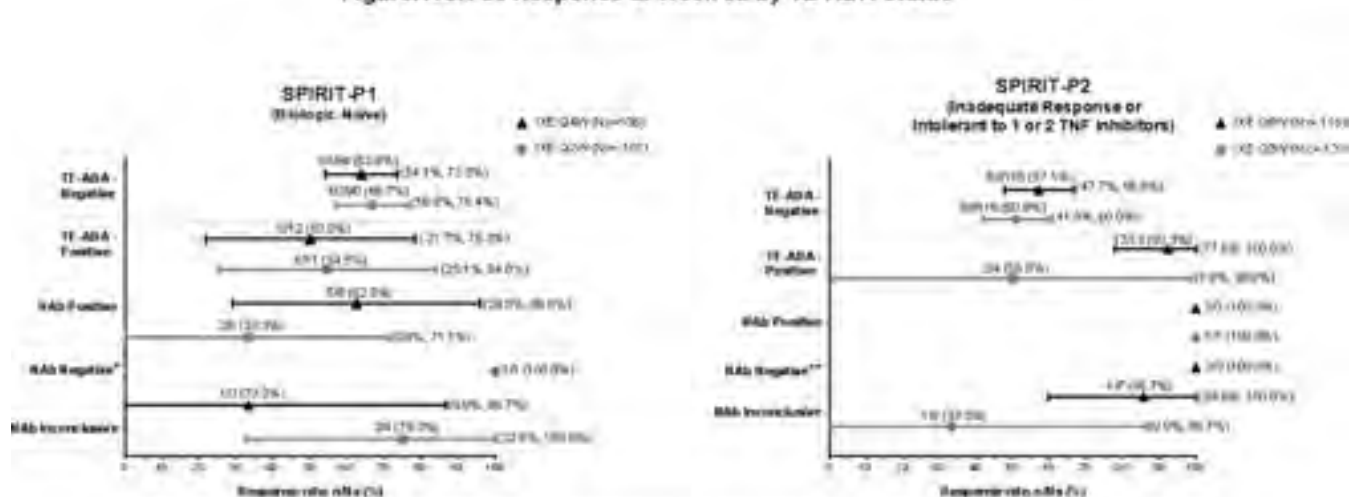
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1. Lecluse LLA et al. *Arch Dermatol.* 2010;146(2):127–132.
2. Mease PJ et al. *Ann Rheum Dis.* 2016;0:1-9.
3. Nash P et al. *Lancet.* 2017;76:79-87.

Table. Immunogenicity Incidence in SPIRIT-P1 and -P2 (Integrated) by TE-ADA Status and by Presence of Concomitant Methotrexate (Weeks 0-52)

	Yes: Concomitant MTX		No: Concomitant MTX	
	IXE Q4W (N=110)	IXE Q2W (N=118)	IXE Q4W (N=119)	IXE Q2W (N=107)
ADA evaluable, Nx	107	116	117	105
TE-ADA negative, n (%)	96 (89.7%)	110 (94.8%)	103 (88.0%)	96 (91.4%)
TE-ADA positive, n (%)	11 (10.3%)	6 (5.2%)	14 (12.0%)	9 (8.6%)
TE-ADA positive titer status, n (%)				
Low titer	10 (9.3)	6 (5.2%)	12 (10.3%)	8 (7.6)
Moderate titer	0	0	2 (1.7%)	1 (1.0%)
High titer	1 (0.9%)	0	0	0
TE-ADA positive NAb Status, n (%)				
NAb positive	5 (4.7%)	3 (2.6%)	6 (5.1%)	4 (3.8%)
NAb negative	3 (2.8%)	0	1 (0.9%)	1 (1.0%)
NAb inconclusive	3 (2.8%)	3 (2.6%)	7 (6.0%)	4 (3.8%)

Figure. ACR 20 Response at Week 52 by TE-ADA Status



[†] There was only one patient in IXE Q4W arm who was NAb Negative and did not achieve ACR20.

^{**} There were no patients in the IXE Q2W arm who were NAb Negative.

Abbreviations: IXE Q4W = ixekizumab 80 mg every 4 weeks; IXE Q2W = ixekizumab 80 mg every 2 weeks; NAb = Neutralizing antibody; Nx = number of ADA-evaluable patients (patients with baseline ADA sample and at least 1 evaluable post-baseline sample or no baseline ADA sample but all post-baseline samples are negative); Ns = number of patients in the subgroup who were ADA positive/negative; R = number of patients who achieved ACR20 (values are shown as n/Ns, (%), 95% Confidence Interval); TE-ADA = treatment emergent anti drug antibody.

Abbreviations: ADA=anti-drug antibody; IXE Q4W = ixekizumab 80 mg Q4W; IXE Q2W = ixekizumab 80 mg Q2W; IXE = ixekizumab; N = number of patients in the subgroup of the PsA safety population; Nx = number of ADA- evaluable patients (patients with baseline ADA sample and ≥ 1 evaluable post-baseline sample or no baseline ADA sample but all post-baseline samples are negative); n = number of patients within the specific category who were ADA Positive/Negative; TE-ADA = treatment-emergent anti-drug antibody

Disclosure: C. T. Ritchlin, UCB, Inc.; Janssen; Abbvie; Amgen, 9, Amgen Inc.; Abbvie; Janssen; Lilly; Novartis; Pfizer, 5; J. F. Merola, Merck Research Laboratories, AbbVie, Eli Lilly and Company, Novartis, Janssen, UCB, Samumed, Celgene, Sanofi Regeneron, GSK, 5, Biogen IDEC, Novartis, Pfizer, Sanofi Regeneron, Incyte, 9, AbbVie Inc., 8; A. M. Gellett, Eli Lilly and Company, 1, 3; C. Y. Lin, Eli Lilly and Company, 1, 3; T. Muram, Eli Lilly and Company, 1, 3.

Abstract Number: 2577

Long-Term Effect of Ixekizumab on Patient-Reported Outcomes in Patients with PsA and Inadequate Response to TNF Inhibitors: 2-Year Follow-up from a Phase 3 Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: PsA is a chronic and complex inflammatory disease with both articular and extra-articular symptoms, including joint pain, enthesitis, dactylitis, fatigue, and skin and nail manifestations. Improvements in signs and symptoms of PsA have been demonstrated with ixekizumab treatment in patients experienced with biological DMARDs. Here we provide patient-reported outcomes through 2 years of ixekizumab treatment in patients with an inadequate response or intolerance to TNF inhibitors (TNFi).

Methods: In a Phase 3 study, patients who met CASPAR Classification Criteria for PsA and had an inadequate response or intolerance to 1 or 2 TNFi received subcutaneous ixekizumab 80 mg every 2 weeks (IXEQ2W) or every 4 weeks (IXEQ4W), after a 160 mg starting dose, or placebo (PBO) for up to 24 weeks. At Week 16, patients not meeting predefined criteria received rescue therapy. At Week 24, PBO patients were rerandomized to IXEQ2W or IXEQ4W. The ensuing ad hoc analyses are derived from patients in the intent-to-treat population initially randomized to ixekizumab. Patients self-rated multiple areas of health and quality of life on various scales, including the Fatigue Severity Numeric Rating Scale (Fatigue NRS[not yet validated]; 0 [none] to 10 [worst imaginable]), the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36; 0 [no improvement] to 100 [better function or health]), the European Quality of Life-5 Dimension visual analog scale (EQ-5D VAS; 0 [worst imaginable] to 100 [best imaginable]), and the Work Productivity and Activity Impairment-Specific Health Problem (WPAI-SHP). Missing values were imputed by a modified baseline observation carried forward approach.

Results: At 108 weeks of treatment, patients receiving either dose of ixekizumab showed sustained improvements in their level of fatigue, mental and physical component scores on the SF-36, quality of life on the EQ-5D, percentage of presenteeism, overall work impairment, and percentage of activities outside of work. Patients receiving IXEQ4W also showed sustained improvement in percentage of absenteeism, whereas those receiving IXEQ2W did not.

	Baseline		Change from Baseline at Week 108	
	IXEQ4W N=122 n=120	IXEQ2W N=123 n=119	IXEQ4W N=122 n=109	IXEQ2W N=123 n=105
Fatigue NRS	5.9±2.5	6.0±2.5	-1.8±2.8	-2.3±2.9
SF-36, mental component score	48.5±12.1	47.9±12.3	3.7±11.6	3.0±9.9
SF-36, physical component score	32.7±9.2	32.2±9.5	6.8±10.2	6.9±10.5
EQ-5D VAS	53.9±22.4	53.9±19.7	12.2±22.5	10.7±22.5
WPAI-SHP, percentage of absenteeism	11.6±26.6	8.8±23.2	-0.13±19.8	4.2±31.1

Table . (Cont'd)

	Baseline		Change from Baseline at Week 108	
WPAI-SHP, percentage of presenteeism	n=60 45.0±25.7	n=59 37.0±25.0	n=56 -21.1±28.1	n=53 -20.0±26.8
WPAI-SHP, overall work impairment score	n=60 46.9±26.7	n=59 38.8±26.6	n=56 -20.5±29.8	n=53 -18.5±28.6
WPAI-SHP, percentage of impaired activities outside of work	n=118 53.9±24.9	n=119 49.3±26.5	n=107 -23.6±28.8	n=105 -19.6±28.6

Data are mean±standard deviation.

Modified baseline observation carried forward method was used to impute missing data.

EQ-5DVAS=European Quality of Life-5 Dimension visual analog scale; IXEQ2W=ixekizumab 80 mg every 2 weeks; IXEQ4W=ixekizumab 80 mg every 4 weeks; N=number of patients in the analysis population; n=number of patients with non-missing data; NRS=Numeric Rating Scale; SF-36=Medical Outcomes Study 36-Item Short Form Health Survey; WPAI-SHP=Work Productivity and Activity Impairment-Specific Health Problem.

Conclusion: In patients with PsA and inadequate response or intolerance to TNFi, improvements in patient-reported outcomes were sustained through 2 years of ixekizumab treatment.

Disclosure: A. Turkiewicz, Eli Lilly and Company, 2, 5, 8, Janssen, 2, 5, 8, Pfizer, Inc., 2, 5, 8, Novartis, 2, 5, 8, AbbVie Inc., 2, 5, 8; A. M. Gellett, Eli Lilly and Company, 1, 3; L. Kerr, Eli Lilly and Company, 1, 3; J. Birt, Eli Lilly and Company, 1, 3; J. Gratacos, None.

Abstract Number: 2578

Exposure Response Analyses to Describe the Relationship between Ixekizumab Concentrations and ACR Responses in Psoriatic Arthritis Patients

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Ixekizumab is a high-affinity monoclonal antibody that selectively targets interleukin (IL)-17A. It has been approved to treat adult patients with moderate-to-severe plaque psoriasis and adult patients with active psoriatic arthritis (PsA). Exposure-response relationships nowadays provide important information to help determine the optimal dose/regimens.¹ The analyses described herein characterized the exposure-efficacy relationships for 20, 50, and 70% improvement in the American College of Rheumatology criteria (ACR 20, 50, and 70, respectively) at Week 24, using data from 2 Ph3 PsA studies.

Methods: In both Ph3 studies, Ixekizumab was administered subcutaneously as a 160mg starting dose followed by repeated 80mg doses given every 2 weeks (Q2W) or every 4 weeks (Q4W). An ordered categorical model was used to describe the relationship between observed ixekizumab serum concentrations and the likelihood of ACR response at Week 24. Data from placebo patients were also included in the model fitting to allow estimation of the placebo effect. Using this model, ACR20/50/70 responses were fit simultaneously, and patient specific factors affecting the ACR response rates were explored.

Results: The models adequately characterized the ACR20/50/70 responses at Week 24. The ACR model results suggested similar efficacy between the 80mg Q2W and Q4W dosing regimens, consistent with the trial observations, and a relatively flat exposure - ACR response relationship in the ixekizumab serum concentration range observed in the trials. Age and sex were found to be significant covariates for the drug effect on ACR responses, which however do not affect the selection of optimal regimen for PsA treatment.

Conclusion: In patients with active PsA, the exposure response analyses suggest that increasing the dosing frequency from Q4W to Q2W would not offer additional clinically important ACR improvement. The analyses support the approved ixekizumab regimen for PsA patients, i.e., 160mg at week 0, followed by 80mg given Q4W as the recommended dose.

REFERENCES: [1] FDA. Guidance for industry: exposure-response relationships – study design, data analysis, and regulatory applications. (2003)

Disclosure: C. S. Ernest II, Eli Lilly and Company, 1, 3; N. Velez de Mendizabal, Eli Lilly and Company, 1, 3; L. Hu, Eli Lilly and Company, 1, 3.

Abstract Number: 2579

Ixekizumab Treatment Significantly Improves Enthesitis and Dactylitis in Patients with Active Psoriatic Arthritis: Results from Two Phase 3 Trials

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Ixekizumab (IXE), an IL-17A antagonist, is approved in the USA for the treatment of PsA including patients (pts) with pre-existing enthesitis or dactylitis. Previous results have shown significantly higher resolution of enthesitis (SPIRIT-P1) and dactylitis (SPIRIT-P1 and -P2) after 24 wks.^{1,2} The purpose of the study was to investigate the impact of IXE treatment on the resolution of enthesitis or dactylitis and whether such improvements were associated with improved function and health-related quality of life (HRQoL).

Methods: Pts with active PsA who were biologic-naïve (SPIRIT-P1)¹ or with prior inadequate response to tumor necrosis factor inhibitor(s) (SPIRIT-P2)² were randomized to placebo (PBO) or 80-mg IXE every 4 (IXEQ4W) or 2 weeks (wks; IXEQ2W), after a 160-mg starting dose. At Wk 16, all inadequate responders received rescue therapy (changes in background therapy). Leeds Enthesitis Index (LEI), Leeds Dactylitis Index-Basic (LDI-B), HAQ Disability Index (HAQ-DI), and EuroQoL-5D Visual Analog Scale (EQ-5D VAS) were measured at Wk 24. Missing data or data from inadequate responders were considered non-response or imputed with last observation carried forward for categorical and continuous measures, respectively. Statistical comparisons between PBO and IXE treatment groups were performed with a logistic regression model using Wald's test with treatment and study as factors. In post hoc-analyses, associations between enthesitis and dactylitis with HAQ-DI and EQ-5D VAS are based on an ANCOVA model adjusting for study and Disease Activity of PsA (DAPSA).

Results: In the integrated SPIRIT-P1 and -P2 dataset (N=679), 403 pts (59% of total) had baseline enthesitis (LEI>0) with a mean 2.9 LEI score, and 155 pts (23% of total) had baseline dactylitis (LDI-B>0) with a mean 56.4 LDI-B score. Both IXEQ4W and IXEQ2W had significantly higher enthesitis and dactylitis resolution than PBO at Wk 24 (Table). In ad-hoc analysis, IXE treatment had significantly higher resolution of enthesitis compared to PBO at the enthesal points comprising the LEI score (Table). For all PBO- and IXE-treated pts at Wk 24, least squares mean (SE) HAQ-DI

Table: Enthesitis and Dactylitis Resolution from the Integrated SPIRIT-P1 and SPIRIT-P2 Dataset (Wk 24)

	PBO	IXEQ4W	IXEQ2W
LEI=0	26/126 (21%)	53/136 (39%)*	49/141 (35%)*
Lateral epicondyle=0	24/79 (30%)	39/85 (46%)*	39/86 (45%)
Medial femoral condyle=0	23/79 (29%)	41/92 (45%)*	45/100 (45%)*
Achilles tendon insertion=0	19/64 (30%)	37/75 (49%)*	38/74 (51%)*
LDI-B=0	10/42 (24%)	52/67 (78%)**	30/46 (65%)**

Data presented as n/N (%). IXEQ4W/IXEQ2W=80-mg ixekizumab every 4 or 2 weeks; LDI-B=Leeds Dactylitis Index-Basic; LEI=Leeds Enthesitis Index. N=patients with baseline enthesitis (LEI>0), depicted enthesal points, or dactylitis (LDI-B>0); n=responding patients; PBO=placebo.

*p<0.05; **p<0.01

improvement from baseline were -0.44 (0.05) and -0.25 (0.03; $p<0.01$) for pts who did and did not resolve enthesitis, and -0.41 (0.06) and -0.31 (0.07; $p=0.34$) for pts who did and did not resolve dactylitis. Corresponding EQ-5D VAS improvements were 12.3 (2.2) and 5.8 (1.5; $p=0.02$) for pts who did and did not resolve enthesitis, and 10.8 (2.8) and 9.8 (3.5; $p=0.83$) for pts who did and did not resolve dactylitis.

Conclusion: Treatment with IXE resulted in significant improvement in enthesitis and dactylitis in pts with pre-existing enthesitis or dactylitis. Resolution of enthesitis symptoms was associated with improvements in pts' function and HRQoL.

References:

1. Mease et al. 2017 ARD 76(1):79
2. Nash et al. 2017 Lancet 389(10085):2317

Disclosure: D. D. Gladman, Abbvie, Amgen, Celgene, Janssen, Novartis, Pfizer, UCB, 2, Abbvie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, UCB, 5; A. M. Orbai, Abbvie, Celgene, Eli Lilly, Horizon, Janssen, Novartis, 2, Eli Lilly, Janssen, Novartis, Pfizer, 5; G. Gallo, Eli Lilly and Company, 1, 3; J. Birt, Eli Lilly and Company, 1, 3; S. Rathmann, Eli Lilly and Company, 1, 3; H. Marzo-Ortega, Janssen, 2, Abbvie, Celgene, Janssen, Lilly, Novartis, UCB, 5, Abbvie, Celgene, Lilly, Novartis, UCB, 6.

Abstract Number: 2580

Predicting Treatment Persistence and Non-Persistence of Newly Initiated TNF Inhibitor Therapy in Ankylosing Spondylitis Patients: A Gender Comparison

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The purpose of this study was to compare treatment patterns in the 2 years following the initiation of TNF inhibitor (TNFi) in AS patients.

Methods: Adult patients with ≥ 2 AS diagnostic codes (ICD-9: 720.0 and ICD-10:M45.x) were included in this retrospective analysis of data from the Truven MarketScan Commercial Claims database. Patients who newly initiated a TNFi from 01/01/2009-12/31/2013 were indexed on their first TNFi. Patients were required to have a 1-year pre-index clean period of TNFi and continuous enrollment 1-year pre-index and 2-years post-index. Patients were excluded if they had ≥ 2 diagnostic codes for the following conditions: RA, juvenile idiopathic arthritis, PsA, Crohn's disease, ulcerative colitis, plaque psoriasis, hidradenitis suppurativa, or uveitis. Demographic, clinical, and treatment patterns were analyzed. Treatment patterns included switching to a new TNFi, discontinuation (≥ 90 -day gap in therapy), or persistence (no gaps in therapy ≥ 90 -days) during the 2-year follow-up period. Logistic regression analyses predicting persistent vs. non-persistent and switching vs. discontinuation were conducted.

Results: 1,372 AS patients (846 M/ 526 F) met the inclusion criteria for this study. Males (M) had a mean age of 44.29 years, while females (F) had a mean age of 42.31 years. Adalimumab was the first biologic for the majority of patients (44.6% M/ 43.3% F), followed by etanercept (40.4% M/ 41.6% F), infliximab (10.4% M/ 10.8% F), golimumab (4.6% M/ 3.8% F), and certolizumab pegol (0.0% M/ 0.4% F). During the follow-up period, 32.6% of males were persistent on their first TNFi, while only 22.8% of females were persistent. The majority of male (67.4%) and female patients (77.2%) discontinued their first TNFi during the 2-year follow-up period. Patients prescribed cDMARDs were more likely to be persistent, while females and opioid users were less likely to be persistent on their first TNFi (Table 1). Among those that discontinued their first TNFi, 32.8% ($n=187$) of males and 43.6% ($n=177$) of females switched to a 2nd TNFi. Females, cDMARD users, and non-opioid analgesic users were more likely to switch to a 2nd TNFi (Table 2).

Conclusion: This study suggests that approximately 67% of male AS patients and 77% of female AS patients newly initiating a TNFi do not remain on the index therapy 2 years post initiation. In this AS population, the proportion of female patients switching to a second TNFi is higher than the proportion of male patients.

Table 1. Logistic regression analyses predicting persistent vs. non-persistent to first TNFi

	Regression Coefficient	Standard Error	Chi-Square	Odd Ratio (95% CI)	P-value
Intercept	-0.9700	0.2470	15.4200		<0.0001
Gender (Female vs. Male)	-0.4563	0.1311	12.1186	0.634 (0.49-0.81)	0.0005
Age	0.00974	0.0053	3.3297	1.010 (0.99-1.02)	0.0680
Medicaid	-0.7560	0.4170	3.2873	0.470 (0.20-1.06)	0.0698
Medicare	-0.2249	0.3030	0.5510	0.799 (0.44-1.44)	0.4579
Use of cDMARDs	0.2633	0.1333	3.9043	1.301 (1.00-1.69)	0.0482
Use of Opioids	-0.4637	0.1226	14.3172	0.629 (0.49-0.80)	0.0002

Table 2. Logistic regression analysis predicting switching TNFi vs. discontinuing TNFi

	Regression Coefficient	Standard Error	Chi-Square	Odds Ratio (95% CI)	P-value
Intercept	-1.2949	0.1837	49.6609		<.0001
Gender (Female)	0.3455	0.1390	6.1792	1.413 (1.076-1.855)	0.0129
Medicaid	-0.8016	0.3670	4.7699	0.449 (0.218-0.921)	0.0290
Medicare	-1.2866	0.4241	9.2061	0.276 (0.120-0.634)	0.0024
Use of cDMARDs	0.3034	0.1505	4.0631	1.354 (1.008-1.819)	0.0438
Use of Non-opioid Analgesics	0.6615	0.1785	13.7264	1.938 (1.366-2.749)	0.0002

Disclosure: T. Hunter, Eli Lilly and Company, 3; A. A. Deodhar, AbbVie Inc., 2, Eli Lilly and Co., 2, 5, Janssen, 2, 5, Novartis, 2, 5, Pfizer, Inc., 2, 5, UCB, Inc., 2, 5, Sun pharma, 2; R. Bolce, Eli Lilly and Company, 1, 3; K. Schroeder, Eli Lilly and Company, 1, 3; D. S. Calderon, Eli Lilly and Company, 1, 3.

Abstract Number: 2581

Comparing Treatment Patterns of Non-Radiographic Axial Spondyloarthritis Patients in the United States and Europe

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

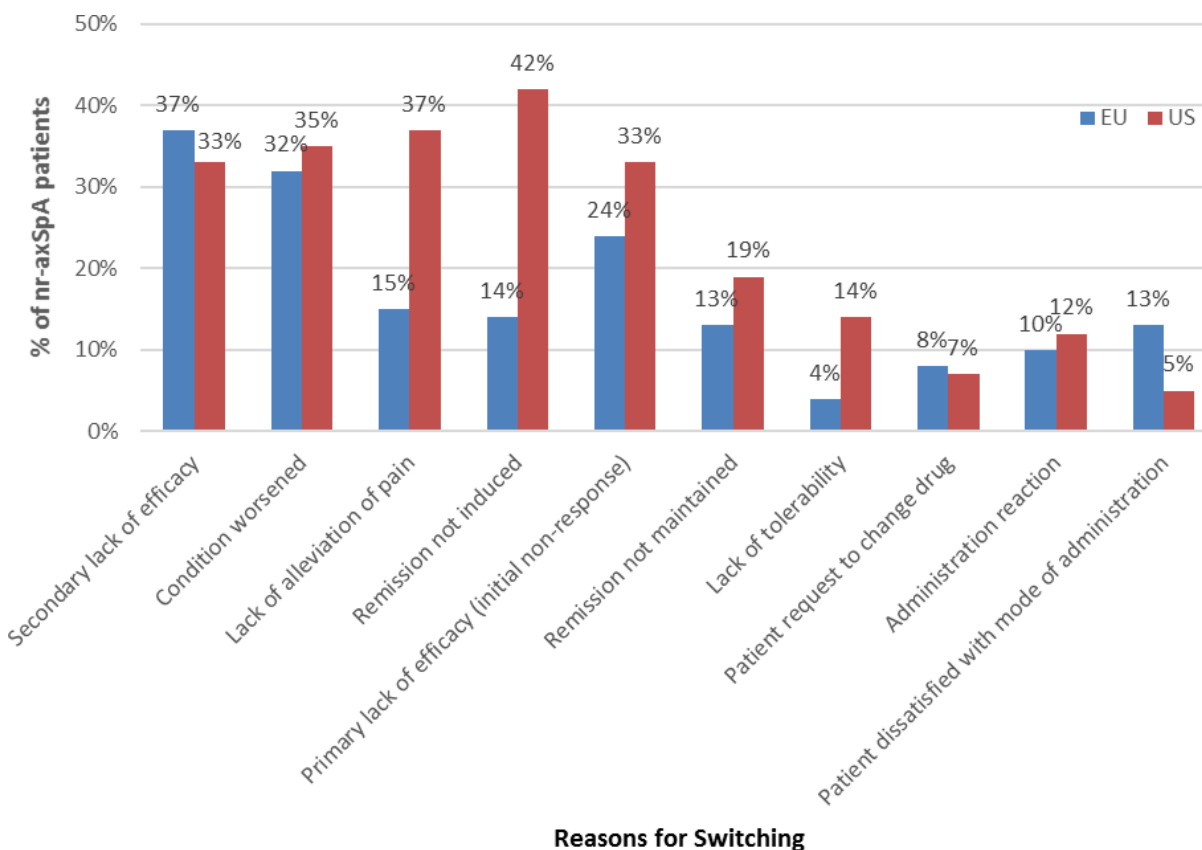
Background/Purpose: To compare TNF inhibitor (TNFi) use and switching patterns among patients with nr-axSpA in the United States (US) and Europe (EU).

Methods: Data from a cross-sectional, multi-national survey of rheumatologists and their consulting axSpA patients conducted in France, Germany, Italy, Spain, United Kingdom, and the US were analyzed. Rheumatologists and patients completed forms containing information on current treatment and reasons for switching therapies.

Results: Data from 391 rheumatologists (299 EU/92 US) and 1,995 patients with nr-axSpA (1513 EU/482 US) were included in this analysis. In the US, 43.8% of patients were female, with a mean age of 42.6 years, while in the EU, 46.6% of patients were female, with a mean age of 41.0 years. In the US, 30.9% were in remission (as reported by their rheumatologist) compared to 41.3% patients in the EU. In the US sample, 57.7% of patients were receiving a TNFi, 35.1% were receiving a cDMARD and 46.3% were receiving a NSAID. In the EU sample, 54.1% were receiving a TNFi, 30.4% were receiving a cDMARD, and 48.3% were receiving a NSAID (Table 1).

US and EU patients that received TNFi (n=1079) had significantly higher physician-reported severity (p<0.0001) and higher levels of pain (p<0.0001) immediately prior to initiation of the current treatment regimen than those patients not receiving biologic therapy (n=916). Of the US patients prescribed a TNFi, 83.6% were receiving their first, 12.2% their second and 4.2% their third or more. Of the EU patients that were prescribed a TNFi, 91.1% were receiving their first, 6.9% their second, and 2.0% their third or more. Lack of remission, poor pain control, and worsening of condition were the main reasons that US patients switched to their current TNFi. Loss of response over time, worsening of condition, and lack of remission were the main reasons that EU patients switched to their current TNFi (Figure 1).

Conclusion: Even though over half of the patients in this survey were prescribed either a TNFi, cDMARDs, and/or NSAIDs, less than one-third of US patients and less than half of EU patients were in remission. While there was minimal



switching of TNFi, when it was done, it was usually due to lack of efficacy, lack of pain relief, and inability to induce or maintain remission. New therapies such as IL-17 inhibitors were not included in this analysis. Additional research needs to be conducted to better understand how IL-17s can be utilized to help nr-axSpA patients achieve better outcomes.

Table 1. Medication use of nr-axSpA patients in the US and EU

	EU (n=1,513)	US (n=482)
TNF inhibitors	818 (54.1%)	277 (57.4%)
Adalimumab	321 (21.2%)	116 (24.1%)
Etanercept	208 (13.7%)	90 (18.7%)
Infliximab	107 (7.1%)	48 (10.0%)
Certolizumab Pegol	60 (4.0%)	17 (3.5%)
Golimumab	122 (8.1%)	8 (1.7%)
cDMARDs	460 (30.4%)	169 (35.1%)
Methotrexate	284 (18.7%)	90 (18.7%)
Sulfasalazine	145 (9.6%)	61 (12.7%)
Leflunomide	16 (1.1%)	6 (1.3%)
Hydroxychloroquine	4 (0.3%)	7 (1.5%)
Azathioprine	11 (0.7%)	5 (1.0%)
NSAIDs	731 (48.3%)	223 (46.3%)
Cox inhibitors	167 (11.0%)	21 (4.4%)
Non-opioid analgesics	150 (9.9%)	12 (2.5%)
Opioids	50 (3.3%)	23 (4.8%)
Oral Steroids	104 (6.9%)	23 (4.8%)
Injection Steroids	17 (1.1%)	12 (2.5%)

Figure 1. Reasons that US and EU nr-axSpA patients switched to their current TNFi

Disclosure: T. Hunter, Eli Lilly and Company, 1, 3; D. S. Calderon, Eli Lilly and Company, 1, 3; S. Lobosco, Adelphi Real World, 3; R. Moon, Adelphi Real World, 3; G. Milligan, Adelphi Real World, 3; R. Bolce, Eli Lilly and Company, 1, 3.

Post-Marketing Safety of Secukinumab in Adult Patients with Psoriasis, Psoriatic Arthritis and Ankylosing Spondylitis: Cumulative Analysis across >96,000 Patient-Treatment Years Exposure

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Secukinumab, a fully human monoclonal IgG1 antibody that selectively neutralizes IL-17A, is currently approved in >75 countries for use in psoriasis /psoriatic arthritis and ankylosing spondylitis with over 150,000 patients treated. Pooled safety data for secukinumab from clinical trials in >7350 patients representing >16,000 patient-treatment years (PY) exposure demonstrated a consistent safety profile.^{1,2} Post-marketing data is considered complementary to data from randomized clinical trials (RCTs); here we report cumulative post-authorization safety data for secukinumab from ongoing periodic safety update reports (PSUR).

Methods: We report the cumulative number of cases along with patient-treatment exposure and exposure-adjusted reporting rates (EARR) across 5 successive PSUR periods covering Dec 26, 2014 to June 25, 2017 for the following adverse events: infections, neutropenia, hypersensitivity, malignant and unspecified tumors, major adverse cardiac events (MACE), inflammatory bowel disease (IBD), immunogenicity, hepatitis B reactivation and interactions with live vaccines.

Results: The cumulative post-marketing exposure to secukinumab was estimated to be ~96,054 PY across the approved indications. Overall EARRs are summarized in the Table. EARR for infections and serious infections were 4.7 and 1.8 per 100 PY, respectively. Neutropenia was reported at the rate of 0.07 per 100 PY. Hypersensitivity reporting rate was 2.4 per 100 PY. EARR for malignancies and MACE were both 0.2 per 100 PY with most assessable cases having multiple confounders, risk factors, or alternative explanations for the events. Total IBD was reported at the rate of 0.2 per 100 PY. There was one case of immunogenicity, and no cases of either hepatitis B reactivation or interactions with live vaccines reported. The safety profile from the PSUR was consistent to that reported in RCTs with secukinumab.^{1,2}

Conclusion: Secukinumab was associated with a consistent safety profile in the post-marketing setting across the approved psoriasis, psoriatic arthritis and ankylosing spondylitis indications. There were no new or changing safety signals reported in successive PSUR periods.

References:

1. Deodhar, et al. *Arthritis Rheumatol.* 2017; 69 (S10). [Abstract Number: 1529]
2. Mease, et al. *Arthritis Rheumatol.* 2017; 69 (S10). [Abstract Number: 606]

Table. Summary of secukinumab post-marketing safety: Cumulative and across 5 PSUR periods

Reporting period	26 Dec 14 – 25 June 15	26 June 15 – 25 Dec 15	26 Dec 15 – 25 June 16	26 June 16 – 25 Dec 16	26 Dec 16 – 25 June 17	Cumulative rate
Exposure (PY)	1,838	7,450	16,871	28,549	41,346	96,054
Infections and infestations/Serious infections						
Cases (n)	178/89	495/149	712/232	1136/475	1730/573	4,483/1,688
EARR (per 100 PY)	9.7/4.8	6.6/2.0	4.2/1.4	4.0/1.7	4.2/1.4	4.7/1.8
Neutropenia						
Cases (n)	0	11	12	22	24	66
EARR (per 100 PY)	0	0.2	0.07	0.08	0.06	0.07
Hypersensitivity						
Cases (n)	82	293	425	573	752	2,293
EARR (per 100 PY)	4.5	3.9	2.5	2.0	1.8	2.4

Table . (Cont'd)

Reporting period	26 Dec 14 – 25 June 15	26 June 15 – 25 Dec 15	26 Dec 15 – 25 June 16	26 June 16 – 25 Dec 16	26 Dec 16 – 25 June 17	Cumulative rate
Malignant or unspecified tumors						
Cases (n)	2	15	21	50	76	173
EARR (per 100 PY)	0.1	0.2	0.1	0.2	0.2	0.2
Total IBD						
Cases (n)	4	12	37	46	93	195
EARR (per 100 PY)	0.2	0.2	0.2	0.2	0.2	0.2
MACE						
Cases (n)	6	15	16	39	58	148
EARR (per 100 PY)	0.3	0.2	0.09	0.1	0.1	0.2

Approximation was not done if EARR is less than 0.1

EARR, exposure-adjusted reporting rates; IBD, inflammatory bowel disease; MACE, major adverse cardiac events; PSUR, periodic safety update report; PY, patient-treatment years

Disclosure: **A. A. Deodhar**, AbbVie Inc., Eli Lilly, GSK, Janssen, Novartis, Pfizer Inc., and UCB, 2, AbbVie, Eli Lilly, Janssen, Novartis, Pfizer, and UCB, 5; **D. D. Gladman**, Amgen, AbbVie, Celgene, Eli Lilly, Janssen, Novartis, Pfizer and UCB, 2, Amgen, AbbVie, BMS, Celgene, Eli Lilly, Janssen, Novartis, Pfizer and UCB, 5; **I. B. McInnes**, Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, and UCB, 2, Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, and UCB, 5, Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, and UCB, 8; **F. van Den Bosch**, AbbVie, BMS, Celgene, Galapagos, Janssen, Lilly, Merck, Novartis, Pfizer and UCB, 2, 5, 8; **A. Shete**, Novartis, 1, 3; **R. You**, Novartis, 3; **S. Hussain**, Novartis, 3; **J. Safi**, Novartis, 1, Novartis, 3.

Abstract Number: 2583

Secukinumab Provides Early and Sustained Improvements in Health-Related Quality of Life in Patients with Ankylosing Spondylitis: A Pooled Analysis from the Secukinumab Phase 3 Trial Program

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

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Background/Purpose: Secukinumab has demonstrated rapid and sustained improvements in the signs and symptoms of ankylosing spondylitis (AS) across multiple randomized controlled trials. Using pooled data from MEASURE 1,2 and 4 (NCT01358175; NCT01649375; NCT02159053), this comprehensive analysis investigated the effect of secukinumab on health-related quality of life (HRQoL), assessed by the Short Form-36 Health Survey (SF-36), in TNF inhibitor (TNF)-naïve and TNF inhibitor-inadequate responder/intolerant(TNF-IR) patients (pts) with AS.

Methods: Pts with active AS were randomized to secukinumab (10 mg/kg intravenously followed by 150 or 75 mg subcutaneously [SC] in MEASURE 1; 150 or 75 mg SC in MEASURE 2; and 150 mg SC with/without loading in MEASURE 4) or placebo (PBO) for 16 wks, stratified by prior TNF inhibitor therapy. At Wk 16 (or Wk 24 in MEASURE 1 depending on ASAS20 response), pts on PBO were switched to secukinumab. Mixed-model for repeated measures was used to assess change in SF-36 from baseline (BL) up to Wk 16; observed data are presented at Wk 52. The proportion of pts reporting improvements meeting or exceeding the minimal clinically important differences (MCID) for SF-36 physical (PCS responders), mental component summary (MCS responders) and individual SF-36 domains was assessed. Missing data were imputed as non-response, and the proportion of responders at Wk16 were compared between treatment groups using Fisher's exact test. Pooled data for pts receiving the licensed dose of secukinumab (150 mg) or PBO are shown.

Results: A total of 743 pts were included: 430 and 313 in the secukinumab 150 mg and PBO groups, respectively, of whom approximately 30% were TNF-IR. The least squares mean changes from BL to Wk 16 in SF-36 were significantly greater

with secukinumab 150 mg vs PBO for PCS (6.09 vs 2.75; $p < 0.0001$), MCS (4.40 vs 2.45; $p < 0.01$), and all individual domain scores. Similar improvements were reported with secukinumab 150 mg vs PBO in TNF-naïve pts at Wk 16 (PCS: 7.23 vs 3.40, $p < 0.0001$; MCS: 5.22 vs 2.92, $p < 0.01$). In TNF-IR pts, PCS score was significantly improved with secukinumab 150 mg vs PBO at Wk16 (4.79 vs 2.44; $p < 0.05$). There was a significantly higher proportion of PCS responders in the secukinumab 150 mg group at Wk 16 vs PBO, regardless of TNF status (Table). Similar results were reported for all individual domains in the overall population. Consistent trends for higher response rates in favour of secukinumab 150 mg were observed in both TNF subgroups, with the TNF-naïve subgroup reaching statistical significance across all individual domains except mental health. Improved PCS, MCS, individual domain scores and responder rates were sustained to Wk 52 with secukinumab 150 mg.

Conclusion: Secukinumab 150 mg resulted in significant, clinically meaningful, and sustained improvements in HRQoL (SF-36) up to Wk 52 in both TNF-naïve and TNF-IR pts with AS.

Table. Proportion of SF-36 responders (≥ 2.5 point improvements in PCS and MCS; ≥ 5 points for individual domains) at Wks 16 and 52 in the overall, TNF-naïve, and TNF-IR groups in a pooled analysis from MEASURE 1, MEASURE 2, and MEASURE 4 RCTs.

Responder rates (%)	Secukinumab 150 mg						Placebo		
	Week 16			Week 52			Week 16		
	Overall	TNF-naïve	TNF-IR	Overall	TNF-naïve	TNF-IR	Overall	TNF-naïve	TNF-IR
PCS	71.4*	75.8*	60.5**	68.6	74.2	54.8	46.6	50.2	38.5
MCS	53.7	55.2	50.0	52.8	54.6	48.4	47.9	51.2	40.6
Physical functioning	73.3**	76.8**	64.5	71.6	74.8	63.7	58.5	61.3	52.1
Role-physical	68.1**	73.2**	55.6	67.9	72.5	56.5	52.4	56.2	43.8
Bodily pain	73.3*	76.1*	66.1	71.9	75.8	62.1	55.0	57.1	50.0
General health	62.8*	67.0*	52.4	60.2	64.4	50.0	45.0	46.5	41.7
Vitality	66.5***	70.3**	57.3	65.8	69.3	57.3	55.3	57.1	51.0
Social functioning	61.9**	66.0**	51.6	60.0	62.7	53.2	49.5	50.7	46.9
Role-emotional	54.7***	56.9***	49.2	52.6	55.6	45.2	43.8	44.2	42.7
Mental health	60.9***	62.7	56.5	61.2	63.7	54.8	50.8	53.9	43.8

* $p < 0.0001$; ** $p < 0.01$, *** $p < 0.05$ versus placebo.

MCS, mental component summary; PBO, placebo; PCS, physical component summary; RCT, randomized controlled trial; TNF-IR, tumor necrosis factor inhibitor-inadequate responder; TNF-naïve, tumor necrosis factor inhibitor-naïve.

PCS and MCS response: patients with ≥ 2.5 point increase in SF-36 component summary score (PCS and MCS)

Individual domain response: patients with ≥ 5.0 point increase in SF-36 individual domain score

Disclosure: A. A. Deodhar, Amgen, Abbvie, GSK, Eli Lilly, Janssen, Novartis, Pfizer, UCB, 2; Eli Lilly, Janssen, Novartis, Pfizer, UCB, 9; A. Boonen, Merck, Pfizer, Abbvie and Amgen, 2, Sandoz, Janssen, Lilly, 8; G. Ferraccioli, BMS, Roche, MSD, 2, AbbVie, Pfizer, UCB, Roche, MSD, Eli Lilly, GSK, Novartis, 9; F. van Den Bosch, Abbvie, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Merck, Novartis, Pfizer, UCB, 8; D. Martinez, RTI Health Solutions, which received funding for this work from Novartis, 3; B. Porter, Novartis, 1, 3; A. Shete, Novartis, 1, 3; N. Scheuer, Novartis, 1, 3; I. Gilloteau, Novartis, 1, 3; V. Strand, AbbVie, Amgen, BMS, Celgene, Celltrion, CORRONA, Genentech/Roche, GSK, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Samsung, Sanofi, and UCB, 5.

Abstract Number: 2584

Low Incidence of Both New-Onset and Flares of Uveitis in Secukinumab-Treated Patients with Ankylosing Spondylitis: Clinical Trial and Post-Marketing Safety Analysis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

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Background/Purpose: Uveitis, a common extra-articular manifestation of spondyloarthritis (SpA), has an estimated prevalence of 33.2% in patients with ankylosing spondylitis (AS), which increases with duration of disease and positive HLA-B27 status.¹ The exposure-adjusted incidence rates (EAIR) of uveitis (combined new-onset and flares) reported in AS patients treated with TNF inhibitors is 2.6–3.5 per 100 patient-years.^{2–5} Here we report the incidence of uveitis in secukinumab-treated AS patients in long-term pooled clinical data from three Phase 3 trials (MEASURE 1–3 [NCT01358175, NCT01649375, NCT02008916]) and from post-marketing analyses.

Methods: Analysis included pooled patient-level data from all patients (N=794) who received any dose (≥ 1) of secukinumab up to the last patient attending Week 156 study visit in MEASURE 1, and up to visit Week 156 in MEASURE 2 and visit Week 104 in MEASURE 3 for each patient, respectively. Post-marketing data were from the most recent periodic safety surveillance report. Incidence of uveitis is reported as EAIR per 100 patient-years of secukinumab exposure.

Results: In the three Phase 3 clinical trials of AS patients, 135 (17%) reported pre-existing (but not active or ongoing) uveitis at baseline and 589 (74.2%) were HLA-B27 positive. The EAIR for uveitis was 1.4 per 100 patient-years over the entire treatment period (N=794; **Table**). Among all cases of uveitis (n=26), 14 (54%) were flares in patients with a history of uveitis at baseline. The EAIR of uveitis in the post-marketing data (based on cumulative secukinumab exposure of 96,054 patient-years) was 0.03 per 100 patient-years.

Conclusion: In secukinumab-treated patients with active AS, a low incidence of uveitis was observed, including new-onset cases and flares, in both clinical trials and post-marketing analyses.

References:

1. Zeboulon, et al. *Ann Rheum Dis*. 2008;67:955–59;
2. Wendling, et al. *Curr Med Res Opin*. 2014;30:2515–21;
3. Van der Heijde, et al. *Rheumatology (Oxford)* 2017;56:1498–509;
4. Sieper, et al. *Arthritis Rheum*. 2014;66:S242; 5. Heldmann, et al. *Clin Exp Rheumatol*. 2011;29:672–80.

Table. Safety Analysis for Uveitis with Secukinumab in AS

Data from Clinical Studies	
Number of clinical studies/patients included	3/794
Uveitis cases reported, n (%)	
Total	26 (3.3%)
New onset cases	12 (1.5%)
Treatment discontinuation	2 (0.3%)
Treatment interruption	1 (0.1%)
EAIR (95% confidence interval) per 100 patient-years ^a	1.4 (0.9, 2.0)
Post-Marketing Datab	
Cumulative estimated market experience (patient-treatment years) ^c	96,054
Cumulative number of cases reported	29
Crude incidence rate per 100 patient-years	0.03

^a Rates for uveitis using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PT)

^b Data from the periodic safety update report (PSUR) dated 10th August 2017-includes all indications

^c Estimated based on cumulative worldwide sales volume and the average maintenance dose

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Secukinumab Immunogenicity in Patients with Psoriatic Arthritis and Ankylosing Spondylitis during a 52-Week Treatment Period

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Session Information

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Background/Purpose: Secukinumab, a fully human monoclonal IgG1 antibody (mAb) that selectively targets IL-17A, is efficacious for the treatment of psoriasis, psoriatic arthritis (PsA) and ankylosing spondylitis (AS). mAb therapies may be associated with immunogenicity and the production of anti-drug antibodies (ADAb) that may cause adverse events (AEs) and/or affect drug pharmacokinetics and clinical response. Secukinumab immunogenicity occurred in 0.4% of patients with plaque psoriasis and not associated with loss of efficacy or issues of clinical concern.¹ Here we report the immunogenicity of secukinumab in PsA and AS patients treated with secukinumab for up to 52 weeks (Wks).

Methods: Immunogenicity in patients with PsA (FUTURE 1–3 studies) and AS (MEASURE 1–4 studies) exposed to secukinumab was evaluated at baseline (BL) and Wks 16 (AS only), 24, and 52. ADAb were defined as a positive ADAb (ADAb⁺) signal in ≥1 post-secukinumab treatment sample in patients negative at BL. ADAb positive samples were analyzed for drug-neutralizing potential, immunogenicity-related AEs and ADAb impact on secukinumab pharmacokinetics and efficacy through Wk 52.

Results: Of 1414 treated PsA and 1163 treated AS patients with samples for immunogenicity evaluation, 5 (0.35%) and 8 (0.68%) developed ADAb, respectively, over 52-wks (Table). All but 1 ADAb⁺ PsA patients were biologic-naïve; 2/5 PsA and 1/8 AS ADAb⁺ patients received concomitant methotrexate, and 2/8 AS ADAb⁺ patients received concomitant sulfasalazine. Associations between ADAb and secukinumab dose, frequency or mode of administration were not observed. ADAb were neutralizing in only 1 patient (with PsA), and none were associated with any immunogenicity-related AE. All ADAb were associated with normal secukinumab pharmacokinetics and none were associated with loss of secukinumab efficacy over 52 wks (Table). In the pharmacokinetics samples from patients with PsA or AS at the time points that immunogenicity was measured, 96% had secukinumab serum concentration below the drug tolerance level of 53.8 µg/ml, confirming sufficient immunogenicity sensitivity during treatment with secukinumab.

Conclusion: Secukinumab treatment was associated with a low incidence of immunogenicity in PsA and AS patients, as shown by ADAb detection in only 0.35% PsA patients and 0.68% AS patients over 52 wks in a database of >2500 patients, which is consistent with the low incidence of immunogenicity (0.4%) seen with secukinumab in patients with plaque psoriasis.¹

References:

1. Reich et al, *Br J Dermatol*. 2017;176:752

Table. Overview of patients with ADAb¹

	Study	Secukinumab dose	Prior biologics	ADAbs (titer)/ Neut-Ab	Immunogenicity- related AE	Impact on efficacy ²	Pharmacokinetics behavior ³
PsA trials	F2306	PBO- 75 mg	0	Wk24 (no titer)/Y	N	None	Normal
	F2312	PBO-150 mg	0	Wk52 (2.99)/N	N	None	Normal
	F2318	150 mg	Infliximab	Wk52 (2.14)/N	N	None	Normal
		150 mg	0	Wk24 (1.00)/N	N	None	Normal
		150 mg	0	Wk52 (2.59)/N	N	None	Normal

Table . (Cont'd)

	Study	Secukinumab dose	Prior biologics	ADABs (titer)/ Neut-Ab	Immunogenicity- related AE	Impact on efficacy ²	Pharmacokinetics behavior ³
AS trials	F2305	10mg/kg–150 mg	0	Wk52 (2.39)/N	N	None	Normal
		PBO–150 mg	0	Wk52 (10.61)/N	N	None	Normal
	F2310	PBO–75 mg	0	Wk52 (39.39)/N	N	None	Normal
	F2314	PBO–300 mg	0	Wk52 (1.02)/N	N	None	Normal
	F2320	150 mg	0	Wk16 (6.35)/N W52/(2.96)/N	N	None	Normal
		150 mg No Load	0	Wk16 (2.70)/N	N	None	Normal
		150 mg	0	Wk24/(2.80)/N	N	None	Normal
		PBO–150 mg	0	Wk52/(2.89)/N	N	None	Normal

Neut-Ab=neutralizing antibodies; N, No; PBO, placebo; Y, yes; Wk, week. ¹Only positive ADAB results at the respective study wk are shown;

²Impact on efficacy is defined as: PsA, failure to achieve >20% reduction, compared to baseline, in both tender and swollen joint counts; AS, failure to achieve ASAS20, after previously achieving such improvement for at least 2 consecutive visits prior to the first detection of ADAB;

³Normal PK: Concentrations in ADAB-positive patients within observed range for all patients without ADAB

Disclosure: A. A. Deodhar, AbbVie Inc., Eli Lilly, GSK, Janssen, Novartis, Pfizer Inc., and UCB, 2, AbbVie, Eli Lilly, Janssen, Novartis, Pfizer, and UCB, 5; D. D. Gladman, Amgen, AbbVie, Celgene, Eli Lilly, Janssen, Novartis, Pfizer and UCB, 2, Amgen, AbbVie, BMS, Celgene, Eli Lilly, Janssen, Novartis, Pfizer and UCB, 5; I. B. McInnes, Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, and UCB, 2, Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, and UCB, 5, Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, and UCB, 8; V. Strand, AbbVie, Amgen, BMS, Celgene, Celltrion, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, Sandoz and UCB., 5, AbbVie, Amgen, BMS, Celgene, Celltrion, Genentech, Janssen, Merck, Novartis, Pfizer, Sandoz and UCB., 9; M. Ren, Novartis, 3; S. Spindeldreher, Novartis, 1, Novartis, 3; L. Pricop, Novartis, 1, 3; B. Porter, Novartis, 1, 3; J. Safi, Novartis, 1, Novartis, 3; A. Shete, Novartis, 1, 3; G. Bruin, Novartis, 1, Novartis, 3.

Abstract Number: 2586

Changes in Lymphocytes and Lymphocyte Subsets in Tofacitinib-Treated Patients with Psoriatic Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of psoriatic arthritis (PsA). Cytokines involved in lymphocyte development, function, and homeostasis signal through JAKs, and reductions in mean lymphocyte count overtime have been reported in tofacitinib-treated patients (pts) with rheumatoid arthritis.¹

Methods: Data were pooled from 2 placebo (PBO)-controlled, double-blind, Phase (P) 3 studies (OPAL Broaden [12 months; NCT01877668]; OPAL Beyond [6 months; NCT01882439]). Pts had active PsA and inadequate response to ≥ 1 conventional synthetic DMARD (OPAL Broaden) or to ≥ 1 tumor necrosis factor inhibitor (OPAL Beyond). Pts were randomized to tofacitinib 5mg twice daily (BID), tofacitinib 10 mg BID, adalimumab 40 mg subcutaneous injection once every 2 weeks (active control; OPAL Broaden only), or PBO. PBO pts advanced in a blinded manner to tofacitinib 5 or 10 mg BID at Month (M) 3. Absolute lymphocyte counts (ALCs) and lymphocyte subset counts (LSCs) were assessed every 3 months as part of safety monitoring procedures in the P3 studies (any abnormalities were confirmed by retesting). Median ALCs and LSCs are reported up to M6. Incidence rates (pts with event/100 pt-years) for serious infections (SIs) were assessed by confirmed (2 sequential measurements) ALC categories (≥ 2.0 , <2.0 – 1.5 , <1.5 – 1.0 , and <1.0 – $0.5 \times 10^3/\text{mm}^3$) up to M12.

Results: The analysis included 816 pts: tofacitinib 5 mg BID, n=238; tofacitinib 10 mg BID, n=236; adalimumab, n=106; PBO, n=236. Up to M6, minimal decreases in median ALC were observed in pts who received tofacitinib 5 mg BID, tofacitinib 10 mg BID, and no change observed in PBO (up to M3 only) (Table). LSCs, including total T cells (CD3+), cytotoxic T cells (CD8+), and NK cells (CD16+56+), showed a similar trend to ALC for both tofacitinib doses (Table), with minimal decreases observed over 6 months. B cells (CD19+) showed numerical increases across treatments. Percentage

changes from baseline in LSCs at M6 showed a generally similar pattern to absolute values. In adalimumab-treated pts, ALCs and all LSCs increased over 6 months. Up to M6, no pts receiving tofacitinib or adalimumab had confirmed ALC $<0.5 \times 10^3/\text{mm}^3$; 1 pt receiving PBO had a confirmed ALC $<0.5 \times 10^3/\text{mm}^3$ over 3 months, resulting in discontinuation from

Table. Median (range) absolute lymphocyte counts and lymphocyte subset counts up to Month 6, pooled across OPAL Broaden and OPAL Beyond

	Tofacitinib 5 mg BID N=238	Tofacitinib 10 mg BID N=236	Adalimumab 40 mg SC Q2W^a N=106	Placebo^b N=236
<i>ALC ($\times 10^3/\text{mm}^3$)</i>				
Baseline	1.74 (0.78–5.24)	1.71 (0.72–4.20)	1.62 (0.79–3.20)	1.69 (0.60–3.78)
Month 3	1.71 (0.60–4.38)	1.75 (0.47–4.74)	1.96 (1.11–3.80)	1.69 (0.65–3.45)
Month 6	1.68 (0.22–4.42)	1.68 (0.55–4.51)	1.88 (0.87–4.69)	—
<i>Total T cells: CD3+ ($\times 10^3/\text{mm}^3$)</i>				
Baseline	1.32 (0.48–3.88)	1.35 (0.44–3.60)	1.27 (0.43–2.73)	1.28 (0.26–3.04)
Month 3	1.30 (0.41–4.45)	1.33 (0.49–3.18)	1.44 (0.62–3.04)	1.35 (0.34–2.69)
Month 6	1.25 (0.28–3.66)	1.33 (0.26–3.30)	1.47 (0.71–4.08)	—
<i>T-helper cells: CD4+ ($\times 10^3/\text{mm}^3$)</i>				
Baseline	0.88 (0.32–3.24)	0.87 (0.26–2.68)	0.78 (0.32–2.04)	0.84 (0.08–2.54)
Month 3	0.88 (0.29–3.77)	0.90 (0.32–2.30)	0.93 (0.28–2.15)	0.87 (0.22–2.15)
Month 6	0.84 (0.22–2.64)	0.91 (0.20–2.58)	0.91 (0.44–2.60)	—
<i>Cytotoxic T cells: CD8+ ($\times 10^3/\text{mm}^3$)</i>				
Baseline	0.41 (0.10–1.40)	0.40 (0.08–1.03)	0.39 (0.07–1.16)	0.41 (0.06–1.32)
Month 3	0.38 (0.08–1.43)	0.38 (0.09–1.08)	0.44 (0.09–1.17)	0.43 (0.07–1.18)
Month 6	0.37 (0.05–1.20)	0.36 (0.04–1.32)	0.50 (0.12–1.57)	—
<i>B cells: CD19+ ($\times 10^3/\text{mm}^3$)</i>				
Baseline	0.21 (0.00–1.48)	0.20 (0.00–1.30)	0.18 (0.01–0.62)	0.21 (0.00–1.15)
Month 3	0.27 (0.01–1.08)	0.30 (0.01–1.42)	0.27 (0.02–0.99)	0.22 (0.01–0.93)
Month 6	0.26 (0.01–1.32)	0.28 (0.00–1.22)	0.26 (0.02–0.95)	—
<i>NK cells: CD16+56+ ($\times 10^3/\text{mm}^3$)</i>				
Baseline	0.23 (0.06–1.39)	0.22 (0.06–0.94)	0.22 (0.03–0.60)	0.20 (0.04–0.75)
Month 3	0.20 (0.04–0.79)	0.18 (0.03–0.75)	0.22 (0.05–0.66)	0.22 (0.03–0.71)
Month 6	0.19 (0.04–0.83)	0.19 (0.04–1.09)	0.25 (0.05–0.75)	—

^aOPAL Broaden only; ^bPlacebo-controlled period was 3 months

ALC, absolute lymphocyte count; BID, twice daily; N, number of patients with observations at baseline; NK, natural killer; Q2W, once every 2 weeks; SC, subcutaneous

the study before advancing to active treatment. Up to M12, SIs were reported in 7 tofacitinib- (including 2 pts who advanced from PBO) and 1 adalimumab-treated pt; only 1 SI (PBO advanced to tofacitinib) occurred >6 months after treatment initiation. There was no trend that suggested an increased risk of SIs in any ALC category (data not shown).

Conclusion: Minimal changes in ALCs and LSCs were observed up to M6 in tofacitinib-treated pts with active PsA. Incidence of SIs did not appear to be related to ALC in this clinical trial setting.

1. van Vollenhoven R et al. Ann Rheum Dis 2016; 75: 258, abs

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Abstract Number: 2587

The Impact of Tumor Necrosis Factor Inhibitors on Diabetes Mellitus Among Patients with Inflammatory Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

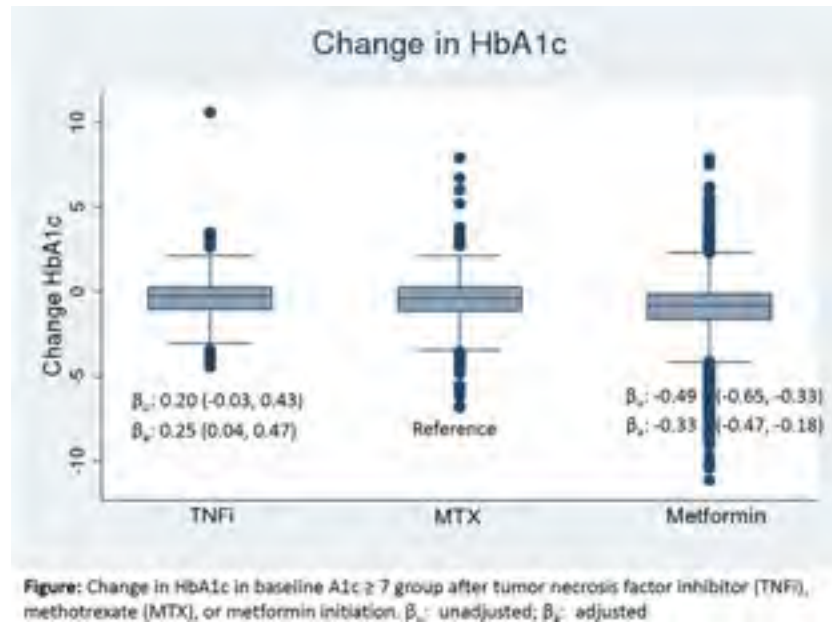
Session Time: 9:00AM-11:00AM

Background/Purpose: Tumor necrosis factor (TNF) is a key inflammatory cytokine in the pathogenesis of psoriatic arthritis (PsA), RA, ankylosing spondylitis (AS), and diabetes mellitus (DM). TNF inhibitors (TNFi) have been shown to be associated with a decreased incidence of DM, but it is unknown whether treatment of PsA, RA, or AS with TNFi has off-target therapy benefits for patients with DM. The objective of this study is to determine whether initiation of a TNFi, compared to initiation of MTX or metformin, results in a decrease in Hemoglobin A1c (HbA1c) in patients PsA, RA, or AS with DM and elevated HbA1c.

Methods: A retrospective cohort study was conducted in OptumInsight from 2000-2014, a de-identified administrative claims database that includes laboratory values for approximately 10% of patients. We identified patients with PsA, RA, or AS, and DM (defined by ICD-9-CM codes), with an HbA1c ≥ 7 and examined change in HbA1c among new initiators of a TNFi (etanercept, adalimumab, certolizumab, golimumab, or infliximab), MTX, or metformin (positive control). A baseline period of 12 months prior to the index date was required to capture potential confounders. All patients were required to have one HbA1c in the six months prior to and one HbA1c in the 6 months after drug initiation. We compared median HbA1c change in each treatment group using Wilcoxon Rank Sum (unadjusted). Linear regression models were used to compare change in HbA1c between treatment using MTX as the reference with adjustment for age, sex, baseline A1c, DM medications, and comorbidities in the baseline period, with clustering to account for multiple new drug initiations per patient.

Results: Among 13,135 drug initiations in 12,689 patients with PsA, RA, or AS, diabetes and available HbA1c values, HbA1c was ≥ 7 before 255 (35%) of TNFi initiations, 411 (37%) of MTX initiations, and 5894 (52%) of metformin initiations. The average time between baseline and follow-up HbA1c values was 227 days. Median HbA1c change was -0.30 (IQR -1.10, 0.30) after TNFi initiation, -0.40 (IQR -1.20, 0.30) after MTX initiation, and -0.80 (IQR -1.70, -0.10) after metformin initiation. In adjusted analyses, TNFi initiators had a significantly smaller decrease in HbA1c compared to MTX initiators, β 0.25 (95% CI: 0.04, 0.47), while Metformin initiators had a significantly greater change in HbA1c than MTX patients, β -0.33 (95% CI: -0.47, -0.18).

Conclusion: TNFi and MTX initiation lead to a decline in HbA1c by approximately half as much as metformin.



Disclosure: S. Mantravadi, Janssen, 3; M. D. George, Bristol Myers Squibb, 2; A. Ogdie, Pfizer, Inc.; Novartis, 2, Abbvie, Amgen, BMS, Corrona, Lilly, Novartis, Pfizer, Takeda, 5.

Abstract Number: 2588

Baseline Pain Severity As a Predictor of Pain Improvement Following Treatment with Tofacitinib in Psoriatic Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Pain is a core domain of psoriatic arthritis (PsA), and it is recommended that all randomized controlled trials (RCTs) in patients (pts) with PsA include an assessment of pain.¹ Tofacitinib is an oral Janus kinase inhibitor for the treatment of PsA. The objective of this post hoc analysis was to determine the impact of pain severity at baseline as a predictor of time to pain improvement in pts with active PsA following treatment with tofacitinib for up to 12 months.

Methods: Data from pts randomized to tofacitinib 5 mg twice daily (BID) in 2 Phase 3 RCTs were included in this analysis. Pts had active PsA and an inadequate response to ≥ 1 conventional synthetic DMARD (csDMARD) (OPAL Broaden; NCT01877668), or to ≥ 1 tumor necrosis factor inhibitor (OPAL Beyond; NCT01882439). All pts continued on a stable dose of a single csDMARD. Current arthritis pain severity was reported by pts using a 100 mm visual analog scale, where higher scores indicated greater severity of pain. Pain improvement was defined as the first post-baseline pain improvement of $\geq 30\%$ (meaningful change), $\geq 50\%$ (substantial change), and $\geq 70\%$ relative to baseline.² Median time to pain improvement was assessed using a parametric model. The model was fitted to examine the relationship between baseline pain severity and time to pain improvement.

Results: Overall, 236 pts who received tofacitinib 5 mg BID were included in this analysis. The Table and Figure present an estimated relationship between baseline pain score and the median time to response. It was shown that, for pts with a baseline pain level of 90 mm, the predicted median time to achieve $\geq 30\%$ pain improvement was 39.3 days, meaning that 50% of pts with baseline pain of 90 mm were estimated to achieve $\geq 30\%$ pain improvement during the first 39.3 days. For a baseline pain level of 50 mm, the predicted median time to achieve $\geq 30\%$ pain improvement was 56.7 days (Table; Figure).

Figure. Predicted median time (days) to pain improvement ($\geq 30\%$, $\geq 50\%$, and $\geq 70\%$ improvement) as a function of baseline pain severity in pts with PsA receiving tofacitinib 5 mg BID

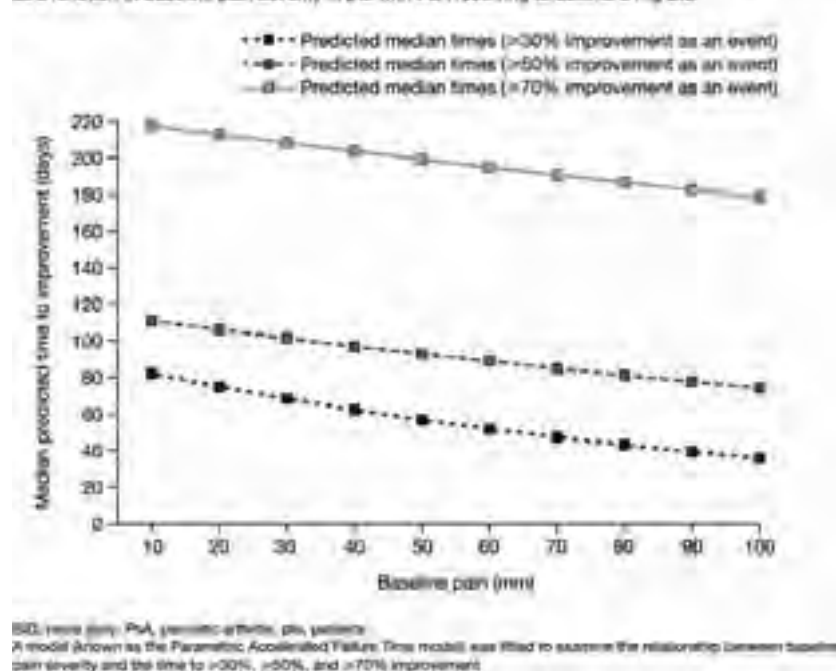


Table. Predicted median time (days) to pain improvement ($\geq 30\%$, $\geq 50\%$, and $\geq 70\%$ improvement) as a function of baseline pain severity in pts with PsA receiving tofacitinib 5 mg BID

Baseline pain, mm (VAS)	Predicted median time to improvement, days (95% CI)		
	$\geq 30\%$ improvement	$\geq 50\%$ improvement	$\geq 70\%$ improvement
10	82.0 (57.2, 117.5)	110.8 (73.9, 166.1)	210.8 (132.2, 357.9)
20	74.8 (55.4, 100.9)	106.0 (75.6, 148.5)	206.0 (140.0, 323.4)
30	68.2 (53.4, 87.1)	101.3 (76.9, 133.5)	203.6 (147.3, 294.2)
40	62.2 (51.0, 75.8)	96.9 (77.5, 121.2)	203.6 (153.0, 271.0)
50	56.7 (48.0, 67.1)	92.7 (76.7, 112.1)	199.2 (155.4, 255.2)
60	51.7 (44.0, 60.9)	88.7 (73.7, 106.6)	194.8 (152.9, 248.2)
70	47.2 (39.2, 56.8)	84.8 (68.7, 104.6)	190.6 (145.4, 249.9)
80	43.0 (34.3, 54.3)	81.1 (62.7, 104.9)	186.5 (134.7, 258.1)
90	39.3 (29.6, 52.0)	77.5 (56.5, 106.4)	182.4 (123.0, 270.5)
100	35.8 (25.5, 50.3)	74.2 (50.6, 108.7)	178.4 (114.3, 280.0)

BID, twice daily; CI, confidence interval; PsA, psoriatic arthritis; pts, patients; VAS, visual analog scale.

Conclusion: In pts with active PsA treated with tofacitinib 5 mg BID, the time to pain improvement was dependent upon baseline pain severity, with lower pain scores at baseline associated with longer time to improvement than higher pain scores. Pts with higher pain severity at baseline achieved clinically meaningful pain improvements faster than pts with lower severity of pain. It is important to consider the non-linearity of change in pain, and the decreased ability to assess change in pain among pts with lower pain scores at baseline, when interpreting these findings.

1. Orbai AM et al. Ann Rheum Dis 2017; 76: 673-80.
2. Dworkin RH et al. J Pain 2008;9: 105-21.

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Abstract Number: 2589

Clinical Characteristics and Treatment Profile of Patients with Psoriatic Arthritis Who Initiated Secukinumab and Other Biologics: Results from the Corrona Psoriatic Arthritis/Spondyloarthritis (PsA/SpA) Registry

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Table 1. Demographics, Clinical Characteristics, and Treatment Profiles Among Patients With PsA Who Initiated Secukinumab or Other Biologics*

Characteristic [†]	Secukinumab Initiators (n = 64)	Other Biologic Initiators (n = 132)
Age, years	52.0 (13.8)	52.4 (12.7)
Female, n (%)	31 (48.4)	70 (53.4)
White, n (%)	58 (92.1)	116 (88.5)
Patient-reported work status, n (%) [‡]		
Full time	29 (45.3)	82 (62.6)
Part time	10 (15.6)	11 (8.4)
Disabled	11 (17.2)	6 (4.6)
Retired	9 (14.1)	23 (17.6)
Other	5 (7.8)	9 (6.9)
BMI, kg/m ²	32.1 (7.8)	31.2 (6.7)
Symptom duration, years [‡]	12.3 (10.5)	7.9 (10.6)
Disease duration, years [‡]	8.4 (8.5)	5.2 (8.3)
Physician-reported history of comorbid conditions, n (%)		
Psoriasis	39 (60.9)	84 (63.6)
Hypertension	20 (31.3)	53 (40.2)
Hyperlipidemia	11 (17.2)	29 (22.0)
Depression [‡]	15 (23.4)	16 (12.1)
Nail psoriasis	10 (15.6)	20 (15.2)
Fibromyalgia	5 (7.8)	8 (6.1)
History of prior biologic use, n (%) [‡]	60 (93.8)	61 (46.2)
No. of prior biologics, n (%) [‡]		
0	4 (6.3)	71 (53.8)
1	22 (34.4)	39 (29.5)
≥ 2	38 (59.4)	22 (16.7)
History of prior csDMARD use, n (%) [‡]	40 (62.5)	39 (29.5)
History of prior prednisone use, n (%)	14 (21.9)	39 (29.5)

BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; PsA, psoriatic arthritis.

* Other biologics included abatacept, adalimumab, etanercept, certolizumab, infliximab, golimumab, and ustekinumab.

[†] All values are presented as mean (SD) unless otherwise stated.

[‡] P < 0.05 for comparisons between secukinumab and other biologic initiators.

Background/Purpose: Few real-world studies have characterized patients with psoriatic arthritis (PsA) who initiate secukinumab. This study described characteristics of patients who initiated secukinumab and other biologics for the treatment of PsA in the US Corrona PsA/SpA Registry.

Methods: This study included adult patients with PsA enrolled in the Corrona PsA/SpA Registry who initiated secukinumab or other biologics (abatacept, adalimumab, etanercept, certolizumab, infliximab, golimumab, and ustekinumab) at a Corrona visit between April 2017 and March 2018. Patient demographics, clinical characteristics, treatment profile, disease activity, quality of life, and work productivity were assessed at the time of biologic initiation (baseline) and compared between patients who initiated secukinumab and other biologics using *t* tests or χ^2 tests.

Results: Of the 196 patients with PsA who initiated a biologic, 64 (32.7%) initiated secukinumab and 132 (67.3%) initiated other biologics. Secukinumab initiators were less likely to work full time (45.3% vs 62.6%) and more likely to be disabled from working (17.2% vs 4.6%), had longer mean symptom (12.3 vs 7.9 years) and disease duration (8.4 vs 5.2 years), and were more likely to have depression (23.4% vs 12.1%) vs those who initiated other biologics (**Table 1**; all *P* < 0.05); secukinumab initiators were also twice as likely to have prior biologic (93.8% vs 46.2%) and csDMARD use (62.5% vs 29.5%) (**Table 1**; both *P* < 0.05). Secukinumab initiators had significantly higher mean SPARCC Enthesitis Index scores (4.0 vs 2.4), were less likely to have dactylitis (14.1% vs 26.5%), and had a worse health state (mean EQ VAS, 59.4 vs 66.3) compared with other biologic initiators (**Table 2**; all *P* < 0.05). Although no significant differences were noted for other measures of disease activity, quality of life, and work productivity, secukinumab initiators on average had higher tender joint counts (8.3 vs 6.6) and worse pain (54.5 vs 49.4), fatigue (51.2 vs 48.1), and patient global skin assessment scores (48.0 vs 41.3) compared with other biologic initiators.

Conclusion: In this real-world study of US patients with PsA, secukinumab initiators had more established disease, were less likely to be working full-time, and had increased prior biologic use compared with other biologic initiators. Although there were few significant differences across several disease activity, quality of life, and work productivity measures (eg,

Table 2. Disease Activity, Quality of Life, and Work Productivity Among Patients With PsA Who Initiated Secukinumab or Other Biologics*

Characteristic†	Secukinumab Initiators (n = 64)	Other Biologic Initiators (n = 132)
MDA, n (%)	12 (19.0)	24 (19.0)
Tender joint count (0-68)	8.3 (10.7)	6.6 (8.1)
Swollen joint count (0-66)	3.8 (4.9)	4.3 (5.8)
Enthesitis, n (%)	22 (34.4)	38 (28.8)
SPARCC Enthesitis Index (1-16)‡	4.0 (2.9)	2.4 (1.6)
Dactylitis, n (%)‡	9 (14.1)	35 (26.5)
Dactylitis count (1-20)	2.6 (1.7)	2.7 (2.3)
CDAI	15.8 (10.5)	15.8 (11.6)
BSA, % affected	7.1 (13.9)	8.8 (17.3)
DAPSA	28.9 (21.7)	24.0 (17.0)
cDAPSA	22.2 (16.5)	20.3 (15.3)
Modified DAS28	4.0 (1.3)	4.0 (1.3)
Physician global assessment (VAS 0-100)	34.9 (23.0)	32.6 (20.9)
BASFI (0-10)	5.0 (2.8)	3.9 (2.9)
Patient pain (VAS 0-100)	54.5 (30.7)	49.4 (30.3)
Patient-reported fatigue (VAS 0-100)	51.2 (33.1)	48.1 (28.9)
Patient global skin assessment (VAS 0-100)	48.0 (24.9)	41.3 (27.3)
HAQ (0-3)	0.9 (0.7)	0.8 (0.6)
EQ VAS (0-100)‡	59.4 (22.1)	66.3 (22.0)
WPAI domains		
% Work time missed	8.2 (17.2)	8.5 (17.8)
% Impairment while working	29.4 (27.8)	29.1 (25.0)
% Overall work impairment	33.3 (30.9)	34.9 (27.1)
% Activity impairment	45.4 (33.5)	35.4 (29.2)
Current employment, n (%)	40 (62.5)	91 (69.5)

BASFI, Bath Ankylosing Spondylitis Functional Index; BSA, body surface area; CDAI, Clinical Disease Activity Index; cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; DAPSA, Disease Activity Index for Psoriatic Arthritis; DAS28, Disease Activity Score using 28 joints; EQ, EuroQol; HAQ, Health Assessment Questionnaire; MDA, minimal disease activity; PsA, psoriatic arthritis; SPARCC, Spondyloarthritis Research Consortium of Canada; VAS, visual analog scale; WPAI, Work Productivity and Activity Impairment questionnaire.

* Other biologics included abatacept, adalimumab, etanercept, certolizumab, infliximab, golimumab, and ustekinumab.

† All values are presented as mean (SD) unless otherwise stated.

‡ *P* < 0.05 for comparisons between secukinumab and other biologic initiators.

enthesitis counts and overall health state), secukinumab initiators generally had higher tender joint counts and worse quality of life measures than other biologic initiators.

Disclosure: A. Ogdie, Amgen, AbbVie, BMS, Celgene, Lilly, Novartis, Pfizer, and Takeda, 5, National Institutes of Health/ National Institute of Arthritis and Musculoskeletal and Skin Diseases, Rheumatology Research Foundation, Pfizer, and Novartis, 2; M. Liu, Corrona, LLC, 3; S. Rebello, Corrona, LLC, 3; M. Glynn, Corrona, LLC, 3; P. Hur, Novartis Pharmaceuticals Corporation, 3; P. J. Mease, Celgene, Novartis, AbbVie, Amgen, Bristol-Myers Squibb, Lilly, Pfizer, and UCB, 2, Celgene, Corrona, Novartis, AbbVie, Amgen, Bristol-Myers Squibb, Crescendo, Genentech, Janssen, Lilly, Merck, Pfizer, and UCB, 5, AbbVie, Amgen, Bristol-Myers Squibb, Crescendo, Celgene, Genentech, Janssen, Pfizer, and UCB, 8.

Abstract Number: 2590

Descriptive Comparisons of the Impact of Apremilast and Methotrexate Monotherapy in Patients with Oligoarticular Psoriatic Arthritis in the Corrona Psoriatic Arthritis/Spondyloarthritis Registry

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Table 1. Baseline Demographic and Clinical Characteristics of Patients With Oligoarthritis

Demographic and Disease Characteristics	APR n=34	MTX n=15	bDMARD n=101
Age, years Mean (SD)	n=33 55.7 (12.6)	n=15 61.5 (16.6)	n=99 52.9 (11.5)
Body mass index, kg/m ² Mean (SD)	n=34 34.4 (9.3)	n=14 30.6 (8.1)	n=96 32.7 (6.8)
Obese* n (%)	n=34 22 (64.7)	n=14 8 (57.1)	n=96 58 (60.4)
Years since PsA diagnosis Mean (SD)	n=33 8.0 (6.7)	n=14 5.4 (7.8)	n=96 9.7 (9.4)
Prior biologic use (≥1) n (%)	n=34 27 (79.5)	n=15 3 (20.0)	n=101 76 (75.2)
Body surface area Mean % (SD)	n=30 7.1 (17.6)	n=14 4.8 (9.4)	n=97 4.1 (7.8)
Swollen joint count (0-66) Mean (SD)	n=34 1.5 (1.5)	n=15 1.0 (1.1)	n=101 0.8 (1.3)
cDAPSA (0-154) Mean (SD)	n=34 14.0 (8.5)	n=11 11.5 (4.9)	n=98 12.3 (9.1)
cDAPSA category	n=34	n=11	n=98
Remission (≤4), n (%)	5 (14.7)	1 (9.1)	17 (17.3)
Low disease activity (>4-≤13), n (%)	12 (35.3)	7 (63.6)	45 (45.9)
Moderate disease activity (>13-≤27), n (%)	14 (41.2)	3 (27.3)	30 (30.6)
High disease activity (>27), n (%)	3 (8.8)	0 (0.0)	6 (6.1)
PtGA-PsO (VAS 0-100 mm) Mean (SD)	n=34 47.1 (29.4)	n=12 28.4 (16.6)	n=99 41.2 (26.8)
PtGA-PsA (VAS 0-100 mm) Mean (SD)	n=34 47.1 (29.8)	n=13 32.5 (26.3)	n=99 42.9 (27.7)
Patient-reported fatigue (VAS 0-100 mm) Mean (SD)	n=34 55.9 (30.0)	n=15 37.8 (31.9)	n=101 41.2 (29.0)
Patient-reported overall pain (VAS 0-100 mm) Mean (SD)	n=34 50.5 (31.1)	n=14 46.7 (26.5)	n=99 42.7 (29.6)
HAQ Mean (SD)	n=34 1.0 (0.7)	n=14 0.5 (0.4)	n=100 0.7 (0.6)

*Body mass index ≥30 kg/m². PtGA-PsO=Patient's Global Assessment of Disease Activity–Psoriasis; PtGA-PsA=Patient's Global Assessment of Disease Activity–Psoriatic Arthritis; VAS=visual analog scale.

Table 2. Clinical Disease Assessments of PsA/SpA Patients with Oligoarthritis at the 6-Month Visit

Disease Characteristics	APR n=34	MTX n=15	bDMARD n=101
Swollen joint count (0-66) Mean (SD) change	n=34 -0.4 (1.2)	n=15 0.1 (0.4)	n=101 0.2 (1.4)
Achieved swollen joint count (0-66) $\leq 1^*$ n (%)	n=17 7 (41.2)	n=4 0 (0.0)	n=26 4 (15.4)
cDAPSA (0-154) Mean (SD) change	n=32 -1.5 (5.8)	n=11 -0.2 (1.9)	n=96 -0.1 (6.8)
cDAPSA category [§] , n (%)	n=17	n=3	n=36
Remission (≤ 4)	1 (5.9)	0 (0.0)	2 (5.6)
Low disease activity ($>4-\leq 13$)	4 (23.5)	0 (0.0)	6 (16.7)
PtGA-PsO (VAS 0-100 mm) Mean (SD) change	n=34 -2.3 (22.1)	n=11 1.7 (10.1)	n=97 -2.0 (27.4)
PtGA-PsA (VAS 0-100 mm) Mean (SD) change	n=34 -0.2 (23.8)	n=13 2.5 (13.9)	n=97 0.4 (25.0)
Patient-reported fatigue (VAS 0-100 mm) Mean (SD) change	n=33 -1.4 (15.7)	n=15 0.3 (30.2)	n=100 -0.3 (20.1)
Patient-reported overall pain (VAS 0-100 mm) Mean (SD) change	n=32 0.2 (26.3)	n=14 -0.1 (15.6)	n=99 0.1 (20.4)
Achieved HAQ MCID (≥ 0.35 point decrease) n (%)	n=34 4 (11.8)	n=14 1 (7.1)	n=100 8 (8.0)

*Assessed among patients with swollen joint count > 1 at initiation.

§Assessed in patients who did not meet criteria for either cDAPSA remission or low disease activity at the time of treatment initiation. Change at 6 months was calculated as the 6-month visit value minus the baseline value.

MCID=minimal clinically important difference.

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The effectiveness of therapies has rarely been studied in the subpopulation of patients with oligoarticular psoriatic arthritis (PsA). The objective of this study was to examine the baseline characteristics and 6-month clinical assessments of patients with PsA who had oligoarthritis (≤ 4 swollen joints) and initiated treatment with apremilast (APR) or methotrexate (MTX) monotherapy in the Corrona Psoriatic Arthritis/Spondyloarthritis (PsA/SpA) Registry, a prospective, US-based observational cohort study. Patients initiating biologic disease-modifying anti-rheumatic drug (bDMARD) monotherapy were also examined as a point of reference.

Methods: Patients ≥ 18 years of age with PsA and oligoarthritis in the registry who initiated monotherapy with APR, MTX, or a bDMARD and had a 6-month follow-up visit between June 2014 and March 2018 were included in the analysis. Descriptive statistics were calculated for patients' clinical characteristics and disease assessments at treatment initiation and at the 6-month follow-up visit.

Results: The analysis included 150 patients initiating therapy (APR: n=34; MTX: n=15; bDMARD: n=101). Among APR and MTX initiators, 80% and 20% received at least 1 prior bDMARD, respectively (Table 1). APR was associated with higher levels of disease activity at baseline, including higher swollen joint count, Clinical Disease Activity for Psoriatic Arthritis (cDAPSA) (moderate and high: 50% [APR] vs. 27% [MTX]) and disease impairments represented by numerically higher scores of patient-reported outcome (PRO) measures, including the HAQ. Taken together, results suggest that APR initiators had more refractory oligoarthritis compared with MTX initiators. Clinical assessments at the 6-month follow-up indicate that patients who initiated APR experienced numerically higher improvements in disease activity and various PRO measures compared with MTX, as well as achievement of ≤ 1 swollen joint, HAQ minimal clinically important difference, and cDAPSA remission or low disease activity (Table 2). Of note, results associated with bDMARDs were more comparable to that of APR.

Conclusion: In this analysis of the Corrona PsA/SpA Registry, APR monotherapy was more often used in patients with refractory oligoarthritis compared with MTX monotherapy. Despite this, the APR group experienced numerically greater improvements in disease activity measures. Improvements observed with APR in patients with long-standing disease and refractory oligoarthritis were modest and comparable to that of bDMARDs.

Disclosure: A. Ogdie, Pfizer, Novartis, 2, Abbvie, BMS, Lilly, Pfizer, Novartis, Takeda, 5; M. Liu, Corrona, LLC, 3; M. Glynn, Corrona, LLC, 3; K. Emeanuru, Corrona, LLC, 3; L. R. Harrold, Corrona, LLC, 1, Pfizer, Inc., 2, Roche, Bristol-Myers Squibb, 5, Corrona, LLC, University of Massachusetts Medical School, 3; S. Richter, Sven Richter, 3; B. Guerette, Celgene Corporation, 3; P. J. Mease, Janssen Research & Development, LLC, 2.

Abstract Number: 2591

Real-World Use of Secukinumab in Axial Spondyloarthritis: First Year Data from the Czech National Registry

Herman F Mann¹, Jakub Zavada², Lucie Nekvindová³, Zlatuse Kristkova³, Pavel Horák⁴, Jiri Vencovsky¹ and Karel Pavelka², ¹Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Czech Republic, Prague 2, Czech Republic, ²Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, ³Institute of Biostatistics and Analyses, Ltd., spinoff company of Masaryk University, Brno, Czech Republic, ⁴IIIrd Department of internal Medicine, Faculty of Medicine and Dentistry, Palacký University, Olomouc, Czech Republic

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Until recently, inhibitors of TNF (TNFi) had been the only bDMARD treatment option for patients with axial spondyloarthritis (AxSpA). This situation changed when anti-interleukin-17A monoclonal antibody secukinumab (SEC) became available in March 2017. We aimed to characterize and compare patient populations starting treatment with SEC versus TNFi during the first year of SEC availability in Czech Republic.

Methods: All adult patients with AxSpA who either started biological therapy or switched to a new drug during the period of March 1st 2017 and March 1st 2018 were considered. Baseline characteristics of patients were described and compared between the two treatments. Mean \pm SD and absolute/relative frequencies were used to describe continuous and categorical variables, respectively. P-value of Fisher's exact test and Mann-Whitney test is given when assessing difference between groups in categorical and continuous variables. Odds for the prescription of SEC versus TNFi were assessed using logistic regression. ATTRA is a computerized registry of patients receiving bDMARD therapy in the Czech Republic. Both TNFi and SEC is indicated for patients with AxSpA who have failed treatment with NSAIDs, have CRP \geq 1 mg/dl and BASDAI score \geq 4. The choice of drug is left to the discretion of treating rheumatologist.

Results: A total of 500 bDMARD treatments were initiated or changed during the study period, 460 were included in the analysis (77 SEC, 383 TNFi). SEC was initiated as first line therapy in 48.1%, TNFi in 49.9% (P=0.804). Significant differences between SEC and TNFi were observed for some baseline patient characteristics (Table 1). Overall, patients starting SEC tended to have higher disease activity and worse measures of physical functioning. Patients after failure of \geq 3 bDMARDs are 4.2 times more likely to receive SEC compared to patients starting their first line bDMARD (P <0.001). Odds of receiving SEC increase with increasing values of CRP (P = 0.027), BASDAI (P = 0.004), ASDAS (P = 0.024), BASFI (P = 0.004) and decrease with higher scores of SF36 physical role functioning (P = 0.008), physical functioning (P = 0.004) and bodily pain (P = 0.005) domains. Baseline disease activity and physical functioning measures were not significantly different between SEC and TNFi among a subgroup of 228 patients (37 SEC, 191 TNFi) receiving first line bDMARD.

Conclusion: Our data suggest that in real-life SEC is used as a first line bDMARD just as often as TNFi, however after failure of at least three bDMARDs patients are more likely to receive SEC. Overall patients starting SEC tend to have higher disease activity compared to patients starting TNFi.

Table 1: Selected baseline characteristics of patients starting SEC or TNFi treatment for AxSpA

Parameter	SEC	TNFi	P-value
Female gender, N (%)	23 (29.9%)	125 (32.6%)	0.690
Age in years, mean (\pm SD)	32.7 (8.5)	33.8 (9.4)	0.491
Disease duration in years, mean (\pm SD)	11.5 (9.3)	9.7 (8.1)	0.067
BMI, mean (\pm SD)	27.5 (5.2)	27.8 (5.0)	0.965
CRP mg/dL, mean (\pm SD)	2.61 (3.47)	1.93 (1.95)	0.478
BASDAI, mean (\pm SD)	6.0 (1.9)	5.1 (2.7)	0.012
BASFI, mean (\pm SD)	5.4 (2.4)	4.4 (2.7)	0.004
HAQ, mean (\pm SD)	1.3 (0.6)	1.0 (0.6)	<0.001
EUROQOL, mean (\pm SD)	0.4 (0.3)	0.4 (0.3)	0.090
SF-36 physical role functioning, mean (\pm SD)	45.7 (21.9)	54.3 (25.8)	0.006
SF-36 physical functioning, mean (\pm SD)	17.2 (27.4)	30.7 (36.9)	0.006
SF-36 bodily pain, mean (\pm SD)	30.5 (16.2)	38.8 (24.0)	0.023
1st line bDMARD, N (%)	37 (48.1%)	191 (49.9%)	0.804

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Disclosure: H. F. Mann, None; J. Zavada, None; L. Nekvindová, None; Z. Kristkova, None; P. Horák, None; J. Vencovsky, None; K. Pavelka, None.

Abstract Number: 2592

Real-World Use of Secukinumab in Psoriatic Arthritis: First Year Data from the Czech National Registry

Herman F Mann¹, Jakub Zavada², Lucie Nekvindová³, Zlatuse Kristkova³, Pavel Horák⁴, Jiri Vencovsky¹ and Karel Pavelka², ¹Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Czech Republic, Prague 2, Czech Republic, ²Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, ³Institute of Biostatistics and Analyses, Ltd., spinoff company of Masaryk University, Brno, Czech Republic, ⁴IIIrd Department of internal Medicine, Faculty of Medicine and Dentistry, Palacký University, Olomouc, Czech Republic

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Until recently, inhibitors of TNF (TNFi) had been the only bDMARD treatment option for patients with psoriatic arthritis (PsA). This situation changed when anti-interleukin-17A monoclonal antibody secukinumab (SEC) became available in March 2017. We aimed to characterize and compare patient populations starting treatment with SEC versus TNFi during the first year of SEC availability in Czech Republic.

Methods: All adult patients with PsA who either started biological therapy or switched to a new drug during the period of March 1st 2017 and March 1st 2018 were considered. Baseline characteristics of patients were described and compared between the two treatments. Mean \pm SD and absolute/relative frequencies were used to describe continuous and categorical variables, respectively. P-value of Fisher's exact test and Mann-Whitney test is given when assessing difference between groups in categorical and continuous variables. Odds for the prescription of SEC versus TNFi were assessed using logistic regression. ATTRA is a computerized registry of patients receiving bDMARD therapy in the Czech Republic. Both TNFi and SEC is indicated for patients with PsA who have previously failed treatment with csDMARD. The choice of drug is left to the discretion of treating rheumatologist.

Results: A total of 243 bDMARD treatments were initiated or changed during the study period, 222 were included in the analysis (59 SEC, 163 TNFi). SEC was initiated as first line therapy in 47.5%, TNFi in 55.2% (P=0.361). Significant differences between SEC and TNFi were observed for some baseline patient characteristics (Table 1). Overall, patients starting SEC tended to have higher disease activity and worse measures of physical functioning. Patients after failure of 2 bDMARDs are 2.5 times more likely and after failure of ≥ 3 bDMARDs are 6.5 times more likely to receive SEC compared to patients starting their first line bDMARD (P<0.05). Odds of receiving SEC increase with increasing values of DAS28 (P = 0.003), SDAI (P = 0.014), and HAQ (P = 0.003) and decrease with higher scores of EUROQOL (p=0.002) and SF36 physical role functioning (P = 0.046), bodily pain (P = 0.004) and social role functioning (P = 0.040) domains. Baseline disease activity and physical functioning measures were not significantly different between SEC and TNFi among a subgroup of 118 patients (28 SEC, 90 TNFi,) receiving first line bDMARD.

Conclusion: Our data suggest that in real-life SEC is used as a first line bDMARD just as often as TNFi, however after failure of two or more bDMARDs patients are more likely to receive SEC. Overall patients starting SEC tend to have higher disease activity compared to patients starting TNFi.

Table 1: Selected baseline characteristics of patients starting SEC or TNFi treatment for PsA

Parameter	SEC	TNFi	P-value
Female gender, N (%)	31 (52.5%)	86 (52.8%)	1.000
Age in years, mean (±SD)	48.8 (9.0)	51.6 (11.6)	0.081
Disease duration in years, mean (±SD)	12.6 (9.0)	11.2 (7.9)	0.464
BMI, mean (±SD)	30.1 (6.5)	28.8 (5.2)	0.248
CRP in mg/dL, mean (±SD)	2.18 (2.38)	1.80 (2.55)	0.187
Presence of psoriasis, N (%)	36 (92.3%)	133 (91.1)	1.000
DAS28, mean (±SD)	5.0 (1.2)	4.2 (1.6)	0.004
SDAI, mean (±SD)	29.2 (13.3)	23.3 (15.1)	0.015
HAQ, mean (±SD)	1.4 (0.6)	1.1 (0.7)	0.005
EUROQOL, mean (±SD)	0.2 (0.3)	0.4 (0.4)	0.004
SF-36 social role functioning, mean (±SD)	43.4 (22.5)	50.9 (23.3)	0.039
SF-36 bodily pain, mean (±SD)	29.9 (15.4)	40.8 (24.9)	0.020
1st line bDMARD, N (%)	28 (47.5%)	90 (55.2%)	0.361

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Disclosure: H. F. Mann, None; J. Zavada, None; L. Nekvindová, None; Z. Kristkova, None; P. Horák, None; J. Vencovsky, None; K. Pavelka, None.

Abstract Number: 2593

Similar Efficacy and Safety of Biosimilar Candidate IBI303 and Reference Products of Adalimumab in Patients with Ankylosing Spondylitis: Results from a Randomized, Double-Blind, Phase III Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: IBI303, an injection of recombinant human anti-tumor necrosis factor- α monoclonal antibody, is adalimumab biosimilar candidate. Physicochemical properties assessment and non-clinical studies showed the structure, pharmacodynamics and pharmacokinetics of IBI303 were similar to adalimumab. This study compared the efficacy and safety of IBI303 with adalimumab in patients with ankylosing spondylitis (AS).

Methods: This was a randomized, double-blind, and adalimumab-controlled phase III clinical study. Patients met the classification criteria of the 1984 modified New York criteria for AS and in active disease were enrolled, and assigned to IBI303 or adalimumab groups in 1:1 ratio. The primary endpoint was the percentage of patients achieving the Assessment of SpondyloArthritis International Society (ASAS) 20 response criteria at week 24. Patients without data at week 24 were treated as non-responders. The safety and immunogenicity of the two groups were also compared.

Results: A total of 438 patients were randomized (IBI303, n=220; adalimumab, n=218). Baseline demographics were generally similar between the two groups. At week 24, there were 75.0%(165/220) and 72.5%(158/218) patients achieved ASAS20 response in IBI303 and adalimumab group, respectively, and 95% confidence interval (CI) of differences between the two groups was -5.7% to 10.8%, indicating the IBI303 was equivalence to that of adalimumab in efficacy. Results of other efficacy endpoints were comparable between the two groups (Table 1). The overall incidence of adverse events (AEs) was 79.1% for IBI303 group and 81.7% for adalimumab group, respectively (Table 2). The most common AEs in IBI303 group were upper respiratory tract infection (24.5%), alanine aminotransferase increased (12.7%) and hyperuricaemia (10.5%), while in adalimumab group were upper respiratory tract infection (20.6%), alanine aminotransferase increased (19.3%) and Aspartate aminotransferase increased (10.6%). The positive rate of antidrug antibodies was 58.6% and 61.9%, and the positive rate of neutralizing antibodies was 46.5% and 51.1% in IBI303 and adalimumab group, but had no observable impact on ASAS20 response.

Conclusion: This study demonstrated IBI303 is similar to adalimumab in clinical efficacy, safety and immunogenicity in patients with moderate to severe AS.

Table 1. ASAS response rates at week 24 (Full analysis set)

	IBI303 N=220 n (%)	Adalimumab N=218 n (%)	difference (95% CI)	P value
ASAS20	165(75.0)	158(72.5)	2.5% (-5.7%, 10.8%)	0.5732
ASAS40	137(62.3)	134(61.5)	0.8% (-8.3%, 9.9%)	0.8636
ASAS partial remission	65(29.5)	74(33.9)	-4.4% (-13.1%, 4.3%)	0.3724

Table 2. Summary of AEs

	IBI303 N=220 n (%)	Adalimumab N=218 n (%)
Treatment-emergent adverse events	174 (79.1)	178 (81.7)
Significant AEs	119 (54.1)	113 (51.8)
Serious adverse events	7 (3.2)	8 (3.7)
AEs leading to study discontinuation	6 (2.7)	5 (2.3)

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Abstract Number: 2594

Median Time to Pain Improvement in Patients with Psoriatic Arthritis Treated with Tofacitinib

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Session Information

Session Date: Tuesday, October 23, 2018

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Session Time: 9:00AM-11:00AM

Background/Purpose: Pain is a core domain of psoriatic arthritis (PsA).¹ Rapid, sustained pain reduction is a priority for patients (pts) and physicians when choosing treatment. Tofacitinib is an oral Janus kinase inhibitor for the treatment of PsA. This post hoc analysis aimed to estimate time to clinically meaningful pain improvement with tofacitinib.

Methods: Data were analyzed from 2 Phase 3 studies of tofacitinib in pts with active PsA and an inadequate response to ≥1 conventional synthetic DMARD (OPAL Broaden; NCT01877668; 12-month study) or to ≥1 tumor necrosis factor inhibitor (OPAL Beyond; NCT01882439; 6-month study). Pts treated with tofacitinib 5 mg twice daily (BID) and placebo (PBO) advanced to tofacitinib 5 mg BID at Month 3 (PBO-tofacitinib), in combination with csDMARDs, were included in

this analysis. Current arthritis pain severity was reported by pts using a 100 mm visual analog scale, where higher scores indicated greater severity of pain. Pain improvement was defined as the first post-baseline improvement of $\geq 30\%$ (meaningful change), $\geq 50\%$ (substantial change), or $\geq 70\%$ relative to baseline.² Time-to-event analyses were performed using a Kaplan-Meier (KM) method on pooled data. Descriptive analyses of the rate of improvements by study were performed.

Results: Overall, 354 pts were available for analysis. Rates of pain improvement overtime with tofacitinib 5 mg BID were approximately the same in both studies (Figure). By Month 1, $\geq 40\%$ of pts experienced $\geq 30\%$ pain improvement, and by Month 2, approximately 55% of pts experienced $\geq 30\%$ pain improvement (Figure). KM analyses showed that pts receiving tofacitinib 5 mg BID achieved improvements in pain severity of 30–70% significantly faster compared with pts in the PBO-tofacitinib group (Table). The median time to $\geq 30\%$ pain improvement was 55 days in the tofacitinib 5 mg BID group and

Figure. Proportion of pts receiving tofacitinib 5 mg BID with $\geq 30\%$ improvement in pain, by study

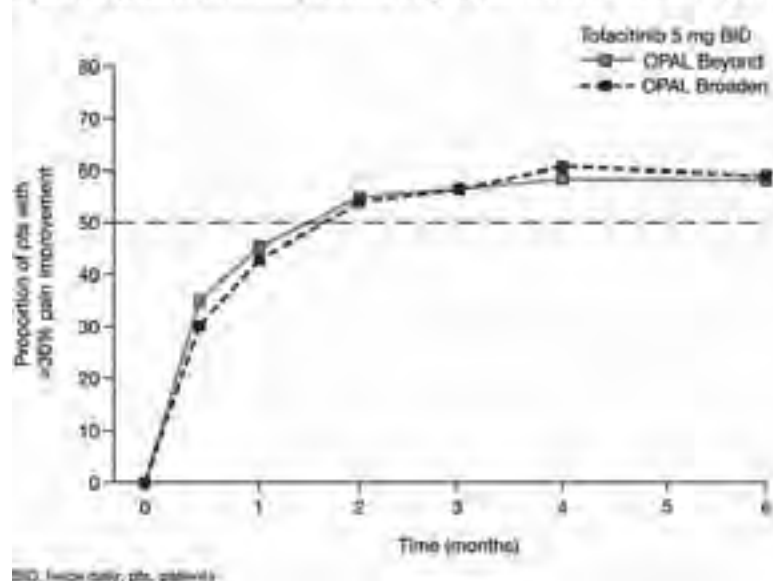


Table. Median time (days) to clinically meaningful pain improvement by improvement threshold in pts with PsA

VAS pain improvement threshold	Median time (days) to pain improvement		Test of equality between groups Log-rank test, p value
	Tofacitinib 5 mg BID	PBO switching to tofacitinib 5 mg BID at Month 3	
$\geq 30\%$	55	106	0.0132
$\geq 50\%$	85	169	0.0068
$\geq 70\%$	184	337	0.0033

Derived using non-parametric KM models for time to event

BID, twice daily; KM, Kaplan-Meier; pts, patients; PBO, placebo; PsA, psoriatic arthritis; VAS, visual analog scale

106 days in the PBO-tofacitinib group (pts switched to tofacitinib 5 mg BID at Month 3; $p=0.0132$). Similar trends between treatment groups were observed across other pain improvement thresholds.

Conclusion: In pts with active PsA, faster, clinically meaningful pain improvements were reported in pts receiving tofacitinib 5 mg BID vs pts receiving PBO who switched to tofacitinib 5 mg BID at Month 3. After switch from PBO to active treatment, pain improvement was observed in line with pts receiving active treatment from Day 0. To achieve pain improvement at greater thresholds, longer duration of active treatment was required.

1. Orbai AM et al. Ann Rheum Dis 2017; 76: 673-80.
2. Dworkin RH et al. J Pain 2008;9: 105-21.

Disclosure: K. de Vlam, Pfizer Inc, 8; A. Ogdie, Novartis, Pfizer Inc, 2, AbbVie, Bristol-Myers Squibb, Celgene, Corrona, Eli Lilly, Novartis, Pfizer Inc, Takeda, 5; A. G. Bushmakina, Pfizer Inc, 1, Pfizer Inc, 3; J. C. Cappelleri, Pfizer Inc, 1, Pfizer Inc, 3; R. Fleischmann, Pfizer Inc, 2, Pfizer Inc, 5, Pfizer Inc, 8; P. C. Taylor, Eli Lilly, Galapagos, UCB, 2, AbbVie, Eli Lilly, Galapagos, Pfizer Inc, 5; V. F. Azevedo, AbbVie, Pfizer Inc, 2, AbbVie, Celltrion, Janssen, Novartis, Pfizer Inc, Sandoz, 5, AbbVie, Celltrion, Janssen, Novartis, Pfizer Inc, Sandoz, 8; L. Fallon, Pfizer Inc, 1, Pfizer Inc, 3; A. Maniccia, Pfizer Inc, 1, Pfizer Inc, 3; J. Woolcott, Pfizer Inc, 1, Pfizer Inc, 3; P. J. Mease, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis, Pfizer Inc, Sun, UCB, 2, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis, Pfizer Inc, Sun, UCB, 5, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Genentech, Janssen, Novartis, Pfizer Inc, UCB, 8.

Abstract Number: 2595

Golimumab Improves Socio- and Health Economic Parameters in Patients with RA, PsA and AS: Real World-Data from a Non-Interventional Clinical Study in Germany

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Golimumab (GLM) has shown its efficacy and safety in various clinical trials. Data from socio- and health economic parameters and costs in daily clinical practice in Germany are rare.

Methods: Descriptive post-hoc analysis of socio- and health-economic parameters of the non-interventional, multicenter, prospective GO-NICE study ($n=1,458$), compared baseline (BL) to the situation at 24 months (M24) ($n=664$, 45.5%). To explore the impact of GLM days of sick leave / absenteeism, days of impaired capability / presenteeism, as well as the work productivity, quality of work and normal course of life (in the past 30 days and 6 months) were analyzed. Further, the number of consultations, ambulatory treatments, days of hospitalizations and rehabilitation measures in the previous 6 months. Socioeconomic costs were calculated based on administrative charges and rates or on official statistics.

Results: The mean number of sick leave days in the previous 30 days decreased from baseline (BL) 4.0 to 0.9, and in the past 6 months from BL 13.7 to 3.3 at M24. The improvement was greatest in patients (pts.) with RA. The mean number of days with impaired capability in the previous 30 days decreased from BL 14.9 to 4.5, in the previous 6 months from BL 65.8 to 19.8 at M24. The improvement was greatest in pts. with AS. On a numeric rating scale (range: 0=no limitation to 10=very strong limitation), the pts' mean ratings on the impact of disease during the previous 6 months on work productivity decreased from BL 5.5 to 2.5 points, on quality of work from 4.8 to 2.2 points, and on the normal course of life from 5.3 to 2.4 points at M24, respectively. The decrease in the mean scores BL to M24 was comparable in pts. with RA, PsA and AS. Intersubject variability was high. On retrospective evaluation for the past 6 months, the percentage of pts. with physician consultations declined from BL to M24: with general practitioners in pts. with PsA -19.7%, AS -17.8%, RA -6.8%. A marked decline was also observed in the percentage of pts. with PsA having dermatologist consultations (-15.0%). The percentage of patients receiving physiotherapy, massages, occupational therapy and packs declined from BL to M24, primarily the application of physiotherapy (-16.9%, -10.9% and -9.1%) in pts. with AS, PsA and RA. The

frequency of hospitalizations decreased from 10.4 / 7.6 / 14.0% at BL to 1.7 / 2.2 / 0.8%, and the frequency of rehabilitation decreased from 3.3 / 3.7 / 7.5% at BL to 0.6 / 1.8 / 2.1% at M24 in pts. with RA, PsA, and AS. Applying a standard cost model, treatment with GLM may generate savings of 2,400 from a public perspective (including costs for absenteeism) and 1,350 from the German health insurance perspective per patient and year.

Conclusion: This evaluation showed remarkable improvements in socio- and health-economic parameters. On GLM treatment, there was a reduction in the days of absenteeism from work, impaired capability / presentism and the days with limited productivity, while the quality of work increased, in a very similar manner across the three indications. The proportion of pts. requiring physician consultations, days of hospitalization and furthermore the need for rehabilitation measures decreased on GLM 50mg treatment, and savings can be generated.

Disclosure: K. Krüger, MSD Sharp Dohme GmbH, 9, AbbVie Inc., 9, BMS, 9, Celgene Corporation, 9, Janssen, 9, Lilly, 9, Pfizer, Inc., 9, Sanofi-Aventis, 9, UCB, Inc., 9; G. R. Burmester, AbbVie, BMS, Lilly, MSD, Pfizer, Roche, 5; S. Wassenberg, AbbVie, Chugai, Janssen Biologics, MSD, Novartis, Pfizer, Roche, and UCB, 5; V. Biermann, None; M. H. Thomas, MSD Sharp & Dohme GmbH Germany, 3.

Abstract Number: 2596

Real-World Long-Term Effectiveness of Switching between Tumor Necrosis Factor Inhibitors in Psoriatic Arthritis Patients from the Rheumatic Diseases Portuguese Register

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

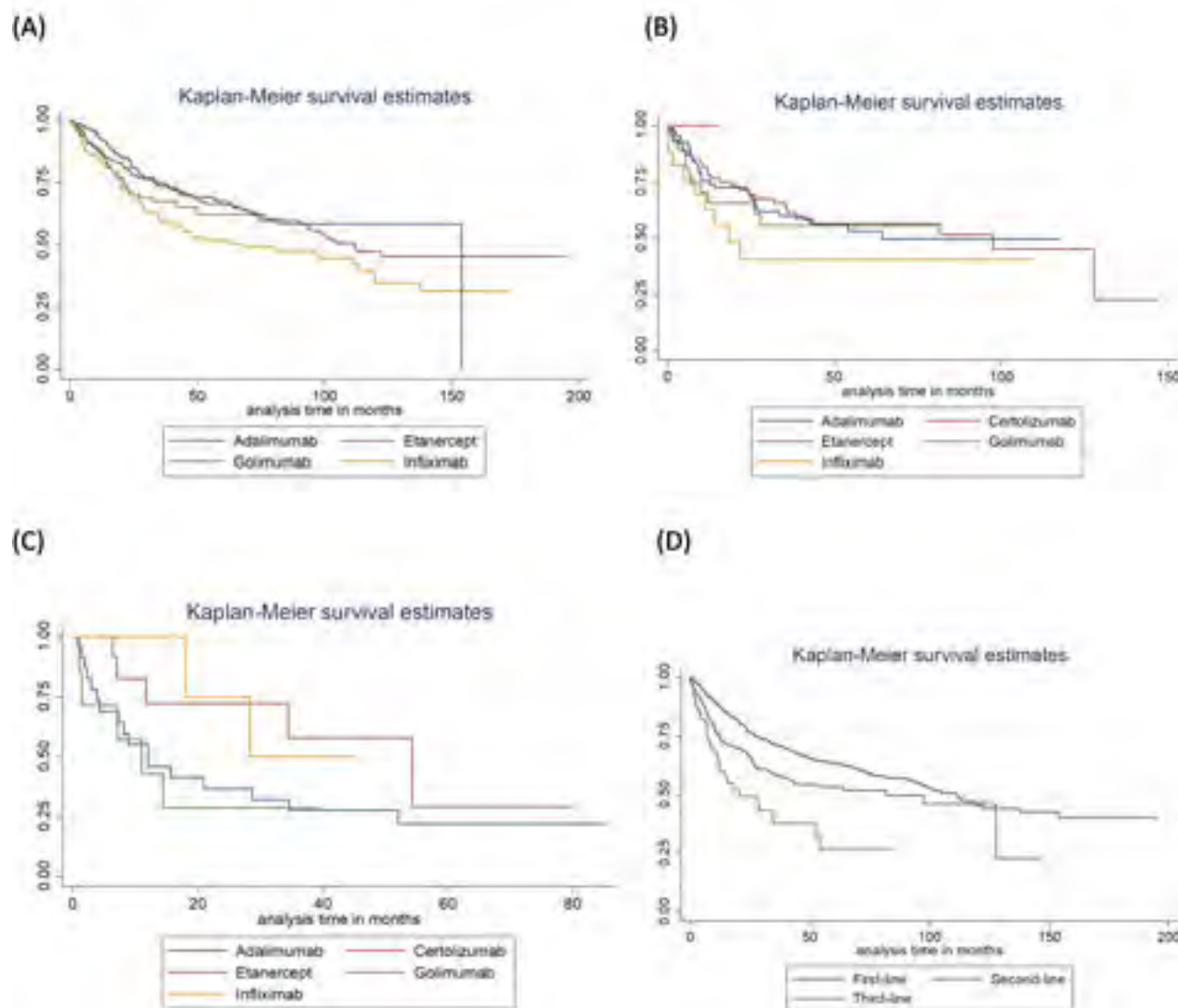
Session Time: 9:00AM-11:00AM

Background/Purpose: Tumor necrosis factor inhibitors (TNFi) lead to a dramatic improvement in the management of psoriatic arthritis (PsA). Nevertheless, a significant proportion of patients do not respond or are intolerant to TNFis, requiring treatment switch for an adequate control of disease activity. The aim of this study is to assess long-term TNFis drug retention and predictors for TNFi discontinuation in PsA patients registered at Rheumatic Diseases Portuguese Registry (Reuma.pt).

Methods: All PsA patients registered at Reuma.pt, with at least one TNFi prescription were included. Drug retention for a 1st, 2nd and 3rd-line TNFi was assessed by Kaplan-Meier survival analysis. Comparative analysis of survival curves was performed using the Wilcoxon (Breslow) for the equality of survival functions. The reasons for TNFis discontinuation were described as frequencies. Predictors of discontinuation, were studied using a Cox model considering discontinuation of the first TNFi, independently of the indication.

Results: 750 PsA patients were identified, with a mean age of 47.6 years; 50.3% female. 185 patients (26.2%) were treated with adalimumab, 322 (45.7%) etanercept, 100 (14.2%) golimumab and 98 (13.9%) with infliximab as first TNFi. The overall retention of TNFi was 49±40 months when treated with a 1st TNFi, decreasing to 36±33 months for the 2nd TNFi, and 23±23 months for the 3rd TNFi. After being treated with a 1st TNFi, 35.8% discontinued therapy, 53.5% due to lack or loss of effectiveness and 24.4% due to adverse events. The rates of discontinuation for the 2nd and 3rd TNFi were of

Figure 1. Drug retention in psoriatic arthritis patients treated with a first (A), second (B) and third-line (C) tumor necrosis factor inhibitor (TNFi) and overall TNFi survival (D).



39% and 54%, respectively, with similar proportions for lack/loss of effectiveness and adverse events for the 2nd (62.3%; 21.6%) and 3rd TNFi (63.0%; 22.2%). When considering predictors of discontinuation for the first TNFi, independently of the indication, being female increased by 2.1 times the risk of discontinuation (HR=2.1, p-value=0.003). In addition, each increase of one unit in DA28 at baseline, increased the risk of discontinuation by 18% (HR=1.18, p-value=0.039). Finally, being treated with infliximab in comparison with etanercept, increased by 2.0 times the risk of discontinuation, assuming the other variables as constant (HR=2.0, p-value=0.007, global p-value=0.012).

Conclusion: The overall persistence of a 1st TNFi was high in PsA patients registered at Reuma.pt, decreasing on average 13 months, in those who switched to a 2nd TNFi or a 3rd TNFi. Lack or loss of response were the main reasons for TNFi discontinuation, independently of TNFi position. Female gender and higher peripheral disease activity (DAS28) at baseline, were associated with an increased risk of discontinuation of TNFis. Likewise, Infliximab doubled the risk of discontinuation when compared with etanercept.

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Disclosure: E. Vieira-Sousa, None; M. Eusébio, None; P. Ávila-Ribeiro, None; N. Khmelinskii, None; A. R. Machado, None; T. Martins-Rocha, None; M. Bernardes, Pfizer, Inc., Lilly, Janssen-Cilag, MSD, GSK, 9; D. Santos Faria, None; J. Leite Silva, None; H. Santos, None; C. Miguel, None; P. Carvalho, None; T. Costa, None; L. Teixeira, None; T. Meirinhos, None; P. Nero, None; M. J. Santos, None.

The Effect of Biologic Disease-Modifying Antirheumatic Drugs in Patient Reported Outcomes in Axial Spondyloarthritis; A Systematic Literature Review and a Call for Action

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Patient reported outcomes (PROs) have gained relevance in the evaluation of axial SpA (axSpA), as they convey a more objective patient perspective. The concept of minimally clinical important difference (MCID) informs if a numerical difference on a given outcome measure (*ie*, PRO) over time is related to a relevant clinical effect (1). This review assessed the efficacy of different biologic DMARDs (bDMARDs) on several PROs in randomised controlled trials (RCT) in axSpA.

Methods: A systematic literature review (SLR) was performed using the MEDLINE (May 1st, 2018) with the filters “published in the last 10 years” and “humans”. The PICO(P, population; I, intervention; C, comparison; O, outcome) concept was used according to: P: adults (>18 years old) with radiographic axSpA (r-axSpA) or non-radiographic axSpA (nr-axSpA); I: any bDMARD regardless of formulation or duration; C: placebo (PBO) and/or any different drug; O: BASDAI, BASFI, the Ankylosing Spondylitis Quality of Life (ASQoL), the EuroQol-5D (EQ-5D), the Short Form 36 Health Survey physical component summary (SF36-PCS), the Short Form 36 Health Survey mental component summary (SF36-MCS), and the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F). The efficacy of bDMARDs on PROs was evaluated through MCID concept or differences between baseline and a later time point.

Results: After screening 84 initial references and manually adding other 9, 17 RCTs fulfilled the inclusion criteria (11r-axSpA, 4 nr-SpA and 2 with both phenotypes), corresponding to 27 publications (table 1). All of them assessed TNF inhibitors (TNFi) or IL17 inhibitors (IL17i).

Only 6 RCTs reported quantitative differences in MCID achievement between treatment arms (table 2). Most of the RCTs reported the mean difference of a given PRO between baseline and a later time point (as absolute values or percentage of variation), providing a statistical test (confidence interval and/or p-value) to express the magnitude of the difference between the treatment and PBO arm. A significant high proportion of MCID achievement is recorded using bDMARDs (table 2).

Conclusion: PROs are reported in an unstandardized way, and there is scarce information regarding clinical implications of the differences achieved (*ie* MCID). Our results launch a call for reporting PROs in a clinically relevant and standardized way and to define cut-offs that may reflect remission. However, bDMARDs seems to contribute to MCID achievement in a high proportion of patients.

References: 1 – *Deodhar. Arthritis Rheumatol. 2016 Dec;68(12):2901-10*

Disclosure: S. Rodrigues Manica, Merck Sharp & Dohme; Novartis Pharmaceuticals, 2, 5; J. Leite Silva, Novartis Pharmaceuticals, 5; A. R. Machado, Novartis Pharmaceuticals, 5; C. Coelho, None; J. Duarte, Novartis Pharmaceuticals, 3; E. Vieira-Sousa, Novartis Pharmaceuticals, 5; J. Tavares Costa, Novartis Pharmaceuticals, 5; F. Pimentel-Santos, Novartis Pharmaceuticals, 5.

Treatment arms at the primary endpoint (number of participants)/Trial registration number(NCT)/Trial acronym if any/Time to primary endpoint	Phenotype	Reference	PROs – Timepoint of report (when inside the RCT phase)	MCID presented
ADA (208) vs PBO (107)/NCT0005644/ATLAS/12 weeks	r-axSpA	van der Heijde 2006	BASDAI; BASFI 12,24 weeks	NO
		Davis JR 2007	SF36-PCS; SF36-MCS; ASQoL 12,24 weeks	YES SF36-PCS;SF36-MCS;ASQoL
		van der Heijde 2009	BASDAI; BASFI; SF36-PCS; SF36-MCS; ASQoL SF36 8 domains; 24 weeks	YES BASFI;ASQoL;SF36-PCS
ADA (26) vs PBO (20)/ X/12 weeks	r-axSpA	Hu 2012	BASDAI; BASFI 12 weeks	NO
ETN (42) vs PBO (48)/ NCT01298531/ SPARSE/ 12 weeks	r-axSpA	Dougados 2014	BASDAI; BASFI 8 weeks	NO
ETN (34) vs PBO (16)/ X/6 weeks	r-axSpA	Brandt 2003	BASDAI; BASFI 6 weeks	NO
ETN 25 weekly (155) vs ETN 50 twice week (150) vs PBO (51)/ NCT00418548 / 12 weeks	r-axSpA	van der Heijde - 2006	(BASDAI – Data on figure) 12 weeks	NO
		Braun 2007	BASFI, SF36-8 comp EQSD VAS, EQSD utility (data on figures) 12 weeks	YES EQSD;BASFI;SF36-data for the 8 components
GOL100(140) vs GOL50(138) vs PBO(78) /NCT00265083/ GO-RAISE/ 14 weeks	r-axSpA	Inman 2008	BASDAI (data on figure); BASFI; SF36-PCS;SF36-MCS 14,24 weeks	NO
		van der Heijde 2015	SF36-MCS;SF36-PCS 14,24 weeks	YES SF36-PCS;SF36-MCS
GOL (105) vs PBO (103)/ NCT02186873/GO-ALIVE/16 weeks	r-axSpA	Dendhar 2017	BASFI;SF36-PCS;SF36-MCS;ASQoL 16 weeks	NO
IFX (201) vs PBO (78) NCT00237419/ASSERT/ 24 weeks	r-axSpA	van der Heijde 2005	BASDAI; BASFI; SF36-PCS; SF36-MCS 24 Weeks	NO
IFX (34) vs PBO (33) / X/12 weeks	r-axSpA	Braun 2002	BASDAI;BASFI; SF36-PCS; SF36-MCS 12 weeks	NO
SECU150 (125) vs SECU75 (124) vs PBO (122) NCT01358175/ MEASURE 1/ 16 weeks	r-axSpA	Derocha 2016	BASDAI; BASFI; SF36-PCS; SF36-MCS; FACIT-F; EQ-5D health state 16 weeks	YES for all outcomes (numerical data not shown)
SECU150 (72) vs SECU75 (73) vs PBO (74) - NCT01649375/MEASURE2/ 16 weeks	r-axSpA	Sieper 2017	BASDAI; SF36-PCS; ASQoL 16 weeks	NO
		Marzo-Ortega 2017	BASDAI;SF36-PCS;EQSD;FACIT-F 16 weeks	NO
SECU – (Data from MEASURE1 + MEASURE2)	r-axSpA	Barten 2017	BASDAI; SF36-PCS; ASQoL 16 weeks	NO
SECU(46)E vs PBO(23) – (Data from Measure 1 and 2 Asia - Subanalysis in Asian patients)	r-axSpA	Wu 2017	BASDAI; SF36-PCS; ASQoL; 16 weeks	NO
ETN(106) vs PBO(109)/ NCT01258738/EMBARC 12 weeks	nr-axSpA	Dougados 2014	BASDAI; BASFI 12 weeks	NO
		Dougados 2015	EQSD VAS, EQSD utility, SF36-PCS, SF36-MCS, ASQoL 12 weeks	YES EQ-5D utility
		Dougados 2017	BASDAI;BASFI 12 weeks	NO
GOL(98) vs PBO(100)/NCT01453725/GO-AHEAD 16 weeks	nr-axSpA	Sieper 2015	BASDAI; BASFI; SF36-PCS;SF36-MCS;ASQoL;EQSD index 16 weeks	NO
ADA(91) vs PBO(94)/ NCT00939003/ABILITY-1/ 12 weeks	nr-axSpA	Sieper 2013	BASDAI;BASFI;SF36-PCS 12 weeks	NO
ADA(22) vs PBO(24)/NCT00235105 12 weeks	nr-axSpA	Haibel 2008	BASDAI;BASFI;SF36-PCS;SF36-MCS;EQSD 12weeks	NO
CZP200(111) vs CZP400(107) vs PBO(107) /NCT01087762/RAPID 12 weeks	axSpA (r-axSpA + nr-axSpA)	Landewe -2014	BASDAI; BASFI 12 weeks	NO
		Sieper 2015	ASQoL 1,24 weeks	YES ASQoL; SF-36-PCS;SF36-MCS
IFX (20) vs PBO (20) /X/16 weeks	axSpA (r-axSpA + nr-axSpA)	Barkham 2009	BASDAI; BASFI, ASQoL 16w weeks	NO

Table 1 – RCT on bDMARDs in axSpA approaching PROs (BASDAI;BASFI;SF36-PCS;SF36-MCS;ASQoL;EQ-5D;FACIT)

r-axSpA: Radiographic axSpA; nr-axSpA: non-radiographic axSpA; NCT: Mandatory Reporting of National Clinical Trial Identifier; ADA: Adalimumab; ETN: Etenimcept; GOL: Golimumab; IFX: Infliximab; SECU: Secukinumab; PBO: Placebo; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: the Ankylosing Spondylitis Quality of Life; EQ-5D: the EuroQoL-5D; SF36-PCS: the Short Form 36 Health Survey physical component summary; SF36-MCS: the Short Form 36 Health Survey mental component summary; FACIT-F: the Functional Assessment of Chronic Illness Therapy – Fatigue; X: No NCT number; E: The pooled Secukinumab arm includes patients under 150mg and 50mg from MEASURE1 and 150mg from MEASURE2 (data for the 75mg arm of MEASURE2 was excluded)

Phenotype	Reference	Weeks	PRO	MCID - Treatment vs PBO
r-axSpA	Braun 2007 - NCT00418548	12 weeks	BASFI	ETN50(155):78%+
				ETN25(150):74%+
				PBO(51):49%
		12 weeks	EQ-5D utility	ETN50 (155):66%+
				ETN25(150)#
				PBO(109):50%
r-axSpA	Davis JR 2007 - NCT0085644	12 weeks	ASQoL	ADA(208):80%+
		(24 weeks)		PBO(107):42%
		12 weeks	SF36-PCS	ADA(208):65%+
		(24 weeks)		PBO(107):38%
		12;24 weeks	SF36-MCS	No difference*
r-axSpA	van der Heijde 2009 NCT0085644	24 weeks	ASQoL	ADA(208):65%+
				PBO(107):43%
		24 weeks	SF36-PCS	ADA(208):67%+
				PBO(107): 40%
		24 weeks	BASFI	ADA(208):69%+
				PBO(107): 36%
r-axSpA	van der Heijde 2015 NCT00265083	12 weeks	SF36-PCS	GOLcom(278):62%+
				GOL100(140): 63%+
				GOL50(138):62%+
				PBO(78):33%
		12 weeks	SF36-MCS	GOLcom(278):42%+
				GOL100(140):46%+
				GOL50(138):38%
				PBO(78):27%
		24 weeks	SF36-PCS	GOLcom(278):64%+
				GOL100(140):62%+
				GOL50(138):67%+
				PBO(78):36%
		24 weeks	SF36-MCS	GOLcom(278):42%
				GOL100(140):51%+
				GOL50(138):32%
				PBO(78):29%
nr-axSpA	Dougados 2015 - NCT01258738	12 weeks	EQ-5D utility	ETN(106):60%+
				PBO(109):43%
Both axSpA	Sieper 2015 - NCT01087762	24 weeks	ASQoL	CZP200(111):77%+
				CZP400(107):70%+
				PBO(106):27%
		24 weeks	SF36-PCS	CZP200(111):69%+
				CZP400(107):89%+
				PBO(106):28%
		24 weeks	SF36-MCS	CZP200(111):53%+
				CZP400(107):61%+
				PBO(106):24%

Table 2 – MCID of PROs (BASDAI/BASFI,SF36-PCS,SF36-MCS,ASQoL,EQ-5D,FACIT) reported in RCT in axSpA

MCID: Minimally Clinically Important Difference, r-axSpA: Radiographic r-axSpA, nr-axSpA: non-radiographic r-axSpA, NCT: Ministry Reporting of National Clinical Trial Identifier, BASFI: Bath Ankylosing Spondylitis Functional Index, ASQoL: the Ankylosing Spondylitis Quality of Life, EQ-5D: the EuroQol-5D, SF36-PCS: the Short Form-36 (v2) health Survey physical component summary, SF 36-MCS: the Short Form-36 (v2) health Survey mental component summary, PBO: Placebo, ADA: Rituximab, ETN: Etanercept, GOL: Golimumab, CZP: Certolizumab, # P=0.08 for difference between treatment arm and PBO, *MCID values not included in this study, #MCID not achieved (scored) out of the 100 enrolled.

Efficacy of Anti-Tumor Necrosis Factor (TNF) Alpha Therapy, in Patients with Spondylarthritis in the University Center of Rouen in France, Divided to the Berlin Algorithm Modified By the Assessment Spondylarthritis Group: A Ten Years Retrospective Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Treatments and diagnosis of SpA is a public health problem. The efficacy of anti-TNF alpha treatment is different from one patient to another. In 2013, the ASAS society modified the Berlin algorithm, allowing us to define different subgroups of patients. The aim of the study was to compare the anti-TNF alpha response in the eight phenotypes of patients defined by the ASAS modified Berlin algorithm.

Methods: This French retrospective study was performed using the active file of patients suffering of SpA, in the University Hospital of Rouen, since 2005 from 2015, and using an anti-TNF alpha treatment. Patients diagnosed as having SpA by the rheumatologists of the hospital were included. The ASDAS-CRP and BASDAI score were calculated for all the patients at the initiation of the treatment (M0) and one year later (M12). The primary endpoint was the improvement of the ASDAS-CRP score after one year of treatment.

Results: 331 patients were included and distributed according to the modified algorithm (figure 1). 69(%) had radiographic sacroiliitis, 117 (35%) had positive MRI, and 149(45%) had positive HLA-B27. All the groups were similar for their average age at the start of the treatment. The duration of the disease was lower in the group 7 (7.2 ± 3 years), higher in group 1 (14.7 ± 11.3 years). The male and female distribution was similar only in the first three groups, the proportion of female were higher in groups 4 to 8 (Table 1). The ASDAS-CRP and BASDAI scores were significantly improved in all groups except in the group 6. Nevertheless, the magnitude of this improvement is greater in the groups 1, 2 and 3. In group 1: ASDAS-CRP at M0 was 3.41 and 2.04 at M12 ($p < 0.0001$). In group 2 ASDAS-CRP M0 was 3.12 and 2.15 at M12 ($p < 0.0001$). In group 3 ASDAS-CRP M0 was 3.1 and 1.9 at M12 ($p < 0.0001$) (figure 2).

Conclusion: This study demonstrates the heterogeneous response in patients with SpA, distributed according to the modified algorithm of Berlin, after one year of treatment with anti-TNF alpha. This algorithm which is basically a diagnostic tool, can help us to define the populations of patients for which anti TNF alpha treatment would be more relevant.

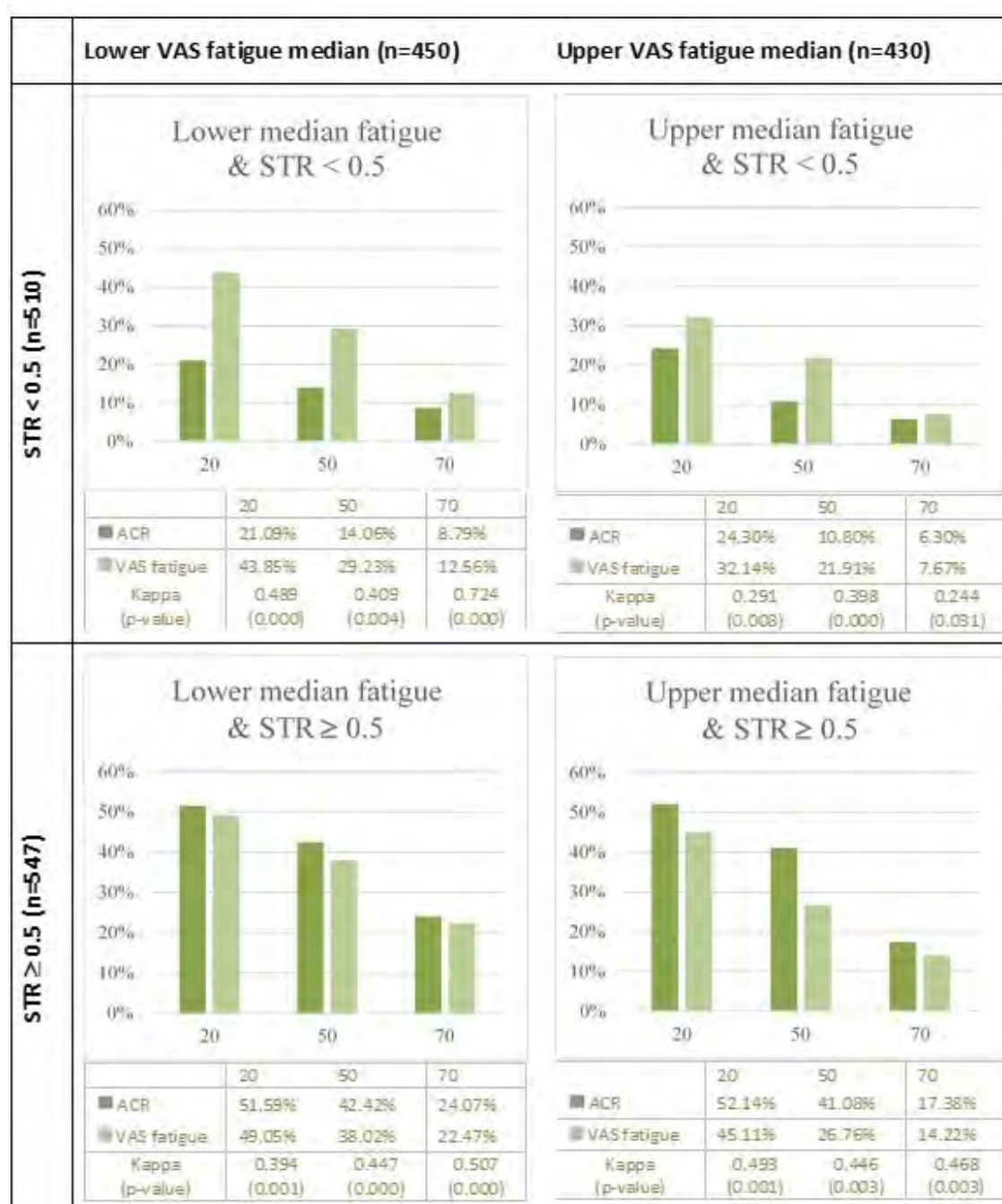
Disclosure: C. Princivil, None; T. Lequerre, None; D. Alcaix, None; O. Vittecoq, None.

The Agreement between TNFi Treatment Responses and Fatigue Responses Is Weak to Moderate Suggesting Heterogeneity between Experienced Fatigue and Joint Inflammation: A Danish Population-Based Cohort Study

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Session Information

Session Date: Tuesday, October 23, 2018



Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Despite better control of inflammation, e.g. with biological treatments, some patients with psoriatic arthritis (PsA) continue to cite fatigue as one of the most challenging aspects of their disease as it decreases their health-related quality of life. The aim of this study was to investigate the associations between fatigue and disease activity. A second aim was to explore the agreement between VAS fatigue responses and ACR treatment responses in Danish patients with PsA.

Methods: All PsA patients registered in DANBIO during the period from 2000 to 2015 and in treatment with their first TNFi were identified and considered eligible for participation in the study. For the assessment of associations between fatigue and disease activity patients were stratified based on number of swollen joint / tender joint ratio (STR) either being <0.5 or ≥ 0.5 . Kappa statistics were used to assess agreement between fatigue and ACR20/ACR50/ACR70 responses, respectively at 6-month follow-up.

Results: From 2000 to 2015, 880 patients were identified eligible for analyses. 14.22% of patients in the upper median fatigue group with $STR \geq 0.5$ showed 70% improvement in fatigue when treated with TNFi, compared to the $STR < 0.5$ group where only 7.67% showed 70% fatigue improvement. The same applied for patients in the lower median fatigue group where 22.47% of patients with $STR \geq 0.5$ showed 70% improvement in VAS fatigue, compared to 12.56% for $STR < 0.5$ (Figure). The kappa values between ACR20, 50, 70 and VAS fatigue responses in the upper median fatigue group with $STR \geq 0.5$ were 0.49, 0.45 and 0.47 ($p < 0.005$), respectively (Figure). Whereas the kappa value in the lower median fatigue group with $STR < 0.5$ were 0.29, 0.40 and 0.24 ($p < 0.05$), respectively (Figure).

Conclusion: Fatigue remains a dominating symptom after TNFi treatment. More patients with relatively more swollen joints ($STR \geq 0.5$) reached improvement in both VAS fatigue and ACR responses compared to patients with relatively more tender joints ($STR < 0.5$) showing less effect of TNFi treatment on fatigue. The agreement between ACR treatment responses and VAS fatigue responses was weak to moderate suggesting heterogeneity between experienced fatigue and joint inflammation. Our results suggest that fatigue is a clinical domain with some independence from pure disease activity, using ACR response as a surrogate for disease activity response to treatment. This observation contributes to our understanding of why it is important to have fatigue as a separate item in the PsA Core Domain set (OMERACT) and why a measure of fatigue should ultimately be in the PsA Core Measurement set.

Disclosure: T. S. Jørgensen, Abbvie, Roche, UCB, Novartis, Pfizer, Biogen and Eli Lilly, 8; M. Skougaard, None; R. L. Hansen, None; C. Ballegaard, Janssen Pharmaceuticals, 8; P. J. Mease, Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, SUN, UCB, 5, Abbvie, Amgen, BMS, Celgene, Janssen, Novartis, Pfizer, UCB, 8; V. Strand, Abbvie, Amgen, BMS, Boehringer Ingelheim, Celltrion, Janssen, Lilly, Merck, Novartis, Pfizer, Samsung, Sandoz, UCB, 5; L. Dreyer, UCB, MSD, Janssen, 8; L. E. Kristensen, Pfizer, AbbVie, Amgen, UCB, Celgene, BMS, MSD, Novartis, Eli Lilly, Janssen Pharmaceuticals, 8.

Abstract Number: 2600

Clinically Meaningful Improvement in Health-Related Quality of Life and the Association with Disease Activity in Psoriatic Arthritis after Treatment with Guselkumab: Results from a Randomized Placebo-Controlled Phase II Clinical Trial

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To evaluate the effect of guselkumab (GUS) on Health-Related Quality of Life (HRQOL) and correlate changes of HRQOL and disease activity in patients with psoriatic arthritis (PsA).

Methods: Patients from the Phase 2a, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of guselkumab in the treatment of patients with active PsA were analyzed. Patients with active PsA and $\geq 3\%$ body surface area (BSA) of plaque psoriasis despite current or previous treatment with standard-of-care therapies, including those previously exposed to anti-TNF α agents, were randomized 2:1 to receive GUS 100mg subcutaneously or placebo (PBO) at wks 0, 4, and every 8 wks (q8w) thereafter through wk44. At wk16, pts from either group with $< 5\%$ improvement from baseline in both swollen and tender joint counts were eligible for early escape to open-label ustekinumab. At wk24, all remaining PBO pts crossed-over to receive GUS 100 mg, and then received GUS at wk28, and q8w thereafter through wk44. HRQOL was assessed using 36-Item Short Form Health Survey (SF-36) which assesses general health from 8 functional areas. A physical and mental component summary scores (PCS and MCS) were derived from 8 scale scores. A change of ≥ 5 points from the baseline in PCS or MCS was defined as clinically meaningful. Correlations of changes in SF-36 PCS and MCS with changes in Disease Activity in Psoriatic Arthritis (DAPSA) were evaluated using Spearman correlation at Week 24.

Results: The mean (SD) of SF-36 PCS and MCS at the baseline was 33.8 (7.4), 44.2 (11.9), respectively, which were significant below the US population norm (50 +/-10). At wk24, patients in the GUS group achieved statistically greater mean improvement in SF-36 PCS (6.6) and MCS (4.7) than PBO group (0.5 in PCS, -0.1 in MCS) (all $p < 0.01$); and greater proportions of patients in GUS group achieved a clinically meaningful improvement in PCS (55%) and MCS (47%) than patients in PBO group (22.5% in PCS, $p < 0.001$; 26.5% in MCS, $p = 0.017$). Additionally, greater mean improvements in all SF-36 scales score in GUS group than PBO group were observed. At wk44, patients randomized to PBO at the baseline and crossed over to GUS at wk24 achieved improvements in SF-36 PCS (8.0) or MCS (5.5). The magnitude of these changes was similar to patients randomized to GUS at baseline (8.3 in PCS, 5.6 in MCS). Change in DAPSA score at wk24 was significantly correlated with change in PCS ($r = -0.57$, $p < 0.001$) and MCS ($r = -0.45$, $p < 0.001$).

Conclusion: GUS-treated PsA patients demonstrated significant improvement in HRQOL and in all subscales of SF-36, indicating patient-perceived improvements in health status. Improvement in SF-36 was highly correlated with reduction in PsA disease activity.

Disclosure: L. Gossec, Janssen Research Development, LLC, 2; B. Kirkham, Janssen Research Development, LLC, 2; P. Rahman, Janssen Research Development, LLC, 2; P. Helliwell, Janssen Research & Development, LLC., 2; A. B. Gottlieb, Janssen Research & Development, LLC., 2; W. H. Boehncke, Janssen Research & Development, LLC, 2; C. Han, Janssen Research & Development, LLC, 3.

Abstract Number: 2601

Nonsteroidal Anti-Inflammatory Drugs Attenuate Active Inflammatory Sacroiliac Joint Lesions in Patients with Early Axial Spondyloarthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The purpose of the present study was to examine the therapeutic effect of NSAIDs on active inflammatory lesions (bone marrow oedema [BMO]) in the sacroiliac (SI) joint in early axial spondyloarthritis (SpA). The aim was to propose optimal duration of treatment in initially diagnosed axial SpA patients with a good response to NSAIDs.

Methods: We enrolled 19 patients with axial SpA who were initially diagnosed in our hospital, and prescribed full-dose NSAIDs for 12 weeks. Twelve patients completed the 12-week protocol. We collected demographic, clinical, laboratory, and radiologic data at the time of enrolment and after 6 and 12 weeks of NSAID treatment. Baseline, 6-week, and 12-week data were compared using the Friedman test.

Results: The total SPondyloArthritis Research Consortium of Canada (SPARCC) score decreased significantly at 6 and 12 weeks (*P* value for 6 weeks and 12 weeks, 0.001, 0.025, respectively). The SPARCC score was significantly correlated with the ESR and CRP (*P* value for ESR and CRP, 0.041, 0.001, respectively). Univariate and multivariate regression analyses showed that the body mass index was significantly associated with changes in the SPARCC score.

Conclusion: Active inflammation in the SIJ was significantly attenuated by 6 weeks of full-dose NSAIDs. The SPARCC score was well-correlated with CRP and ESR. Therefore, at least 6 weeks of full-dose NSAIDs can decrease active SIJ lesions, and initial full-dose NSAIDs may prevent further structural damage as shown by reverting early radiologic change (BMO).

Disclosure: H. K. Min, None; H. Cho, None; S. H. Park, None.

Abstract Number: 2602

Evolution of Patient Characteristics in the Era of Biological Treatment of Psoriatic Arthritis: 18-Year Belgian Experience from Leuven Spondyloarthritis Biologics Cohort (BioSPAR)

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Biologicals revolutionized the management of PsA. Since the introduction of the first TNF inhibitor (TNFi) in the early 2000s, therapeutic options for PsA are increasing steadily and a new generation of biologicals allows distinct targeted approaches.

Purpose: To investigate whether PsA patient population (demographic and clinical characteristics), selected for biological treatment in daily practice, changed over time.

Methods: PsA patients (CASPAR criteria) were included in the KU Leuven BioSPAR register, a prospective cohort treated with biologicals and apremilast. Demographics, prior drug use, disease characteristics and activity parameters were recorded at the initiation of biological treatment.

Tree treatment periods were defined: First period: from the date the 1st patient started TNFi therapy (infliximab, etanercept or adalimumab) until the “second generation” of anti-TNF (golimumab and certolizumab) were available: 09/15/2000-06/03/2006. Second period: end of period 1 until the “third generation” of biologicals (ustekinumab, secukinumab) or apremilast were available: 06/04/2006- 03/22/2016. Third period: after period 2: 03/23/2016-02/28/2018. Statistical analysis was performed using SPSS statistical software, version 24.0 with descriptive statistics, one-way ANOVA, Kruskal-Wallis or Chi-square tests as appropriate.

Results: The PsA cohort includes 185 Caucasian patients. We found no difference in the age of patients, mean weight or BMI at the time of biological initiation in 3 time groups. Proportion of male/female patients was also similar. Disease duration was significantly longer in the 1st, compared to the 2nd (*p*=0.006) and 3rd (*p*=0.017) time periods. However, there was no difference in disease duration between period 2 and 3 (*p*=0.19). Further, patients in period 1 had more tender joints than patients in period 3 (*p*=0.012). But the difference in TJC68 was not significant between period 1 and 3 or period 2 and 3. Number of swollen joints in the period 1 was significantly higher than in patients in the second and third time periods (*p*=0.0001). Skin and nail psoriasis were more frequent in earlier compared to the later treatment periods (*p*<0.0001 for both). In our study population, the proportion of patients with dactylitis or enthesitis was similar in tree time periods.

CRP levels, but not ESR, significantly differed between the groups, being higher in period 1 compared 2 (*p*=0.006) and 3 (*p*= 0.023). Clinical scores for psoriasis, enthesitis and disease activity did not reach statistical difference between the three time periods.

Conclusion: The population of patients, selected for treatment escalation, changed significantly over time since the introduction of biologicals. Although patient characteristics were similar in all time periods, disease duration and objective disease activity characteristics (swollen and tender joints, psoriatic nail and skin involvement, CRP) were lower in the later

time periods. Our results suggest that with years of experience, PsA patients might be considered earlier and with less active disease for therapy intensification, to obtain a tight disease control and to prevent long term damage.

Disclosure: A. Ishchenko, None; R. Lories, AbbVie Inc., Boehringer-Ingelheim, Celgene, Eli-Lilly, Galapagos, Janssen, MSD, Novartis, Pfizer, Samumed and UCB., 2, 5, 9; K. de Vlam, None.

Abstract Number: 2603

Efficacy of Tildrakizumab in Etanercept Partial Responders or Nonresponders

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¹Bakersfield Dermatology, Bakersfield, CA, ²Probit Medical Research, Waterloo, ON, Canada, ³University of British Columbia, Department of Dermatology and Skin Science and Probit Medical Research, Surrey, BC, Canada, ⁴Sun Pharmaceutical Industries, Inc., Princeton, NJ, ⁵Merck & Co., Inc., Kenilworth, NJ

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Etanercept (ETN), an anti-TNF medication, was among the first biologics approved for psoriasis. Additional psoriasis medications that have been developed, or are in development, may benefit patients (pts) who do not adequately respond to ETN. The efficacy of tildrakizumab (TIL), a high-affinity, humanized, anti-interleukin-23p19 monoclonal antibody, was evaluated in pts with moderate to severe chronic plaque psoriasis who were partial responders (Psoriasis Area and Severity Index [PASI] ≥ 50 – <75) or nonresponders (PASI <50) to ETN and were subsequently rerandomized to TIL in a phase 3 trial.

Methods: Pts with psoriasis ($\geq 10\%$ body surface area, Physician's Global Assessment [PGA] ≥ 3 , and PASI ≥ 12) participated in a 3-part, 52-week, randomized controlled trial (reSURFACE 2; NCT01729754). In Part 1 (Week [W]0–W12), pts were randomized to subcutaneous placebo (PBO), TIL 100 mg, or TIL 200 mg administered at W0 and W4, or ETN 50 mg administered 2x/wk. In Part 2 (W12–W28), TIL and ETN pts remained on the same treatment (TIL administered at W16; ETN 1x/wk), whereas PBO pts were rerandomized to TIL 100 or 200 mg. In Part 3 (W28–W52), ETN responders (PASI ≥ 75) were discontinued; partial and nonresponders were switched to TIL 200 mg (administered at W32, W36, W48). For this post hoc analysis, the proportions of pts (\pm SD) with PASI responses and PGA response (score of 0 [“clear”] or 1 [“minimal”] with at least a 2-grade score reduction from baseline) were determined at W52.

Results: In all, 1090 pts were randomized. Of the 313 pts randomized to ETN, by W28 there were 83 partial responders and 39 nonresponders. At W52 (after 20 weeks of TIL treatment) for ETN partial responders, $75\% \pm 5\%$, $34\% \pm 5\%$, $15\% \pm 4\%$, and $58\% \pm 5\%$ had achieved PASI 75, 90, 100, and PGA responses, respectively, with TIL 200-mg treatment. At W52 for ETN nonresponders, $54\% \pm 6\%$, $31\% \pm 5\%$, $10\% \pm 3\%$, and $56\% \pm 5\%$ had achieved PASI 75, 90, 100, and PGA responses, respectively, with TIL 200-mg treatment. Adverse events were similar in pts switched from ETN to TIL at W28 compared with the pts who were maintained on TIL through W52.

Conclusion: A substantial portion of patients with moderate to severe chronic plaque psoriasis who are partial responders or nonresponders to ETN may respond after switching to treatment with TIL 200 mg. TIL may be a reasonable option for those with inadequate response to ETN.

Analyses presented at the American Academy of Dermatology Annual Meeting, February 16–20, 2018, San Diego, CA, USA.

Disclosure: J. Crowley, AbbVie, Amgen, Boehringer Ingelheim, Janssen, Lilly, MC2 Therapeutics, Merck & Co, Novartis, Pfizer, Regeneron, Sandoz, Sanofi, Sun Pharmaceuticals Industries Inc, UCB, and Verrica Pharmaceuticals, 2, AbbVie, Amgen, Celgene, Dermira, Lilly, Novartis, Sun Pharmaceutical Industries, Inc and UCB, 5, AbbVie, Amgen, Janssen, Lilly, Novartis, Regeneron, and Sanofi, 8; K. A. Papp, AbbVie, Akros, Allergan, Amgen, Anacor, Arcutis, Astellas, Baxalta, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Galderma, Genentech, GSK, Janssen, Kyowa Hakko Kirin, Leo, Medimmune, Merck Sharp & Dohme, Me, 2, AbbVie, Akros, Amgen, Arcutis, Astellas, Astra Zeneca, Baxalta, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, CanFite, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Forward Pharma, Galderma, Genentech, Janssen, Kyowa Hakko Kirin, Leo, Meiji Seika, 5, AbbVie, Amgen, Astellas, Celgene, Eli Lilly, Galderma, Janssen, Kyowa Hakko Kirin, Leo, Merck Sharp & Dohme, Novartis, Pfizer, Valeant, 8; C. H. Hong, Amgen, AbbVie, Eli Lilly, Janssen, Merck, Novartis, GlaxoSmithKline, Celgene, UCB, 2, Amgen, AbbVie, Eli Lilly, Janssen, Novartis, GlaxoSmithKline, Celgene, Sun Pharmaceutical Industries, Inc, 5,

Amgen, AbbVie, Eli Lilly, Janssen, Novartis, Celgene, 8; **J. Parno**, Sun Pharmaceutical Industries, Inc., Kyowa Kirin Pharmaceutical Development, Inc., 5; **A. M. Mendelsohn**, Sun Pharmaceutical Industries Inc, 3; **Q. Li**, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, 3; **N. Cichanowitz**, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, 1, 3.

Abstract Number: 2604

Incidence of Serious Gastrointestinal Events and Inflammatory Bowel Disease Among Tildrakizumab-Treated Patients with Moderate to Severe Plaque Psoriasis: Data from 3 Large Randomized Clinical Trials

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Tildrakizumab (TIL), a high-affinity, humanized, immunoglobulin G1κ, anti-interleukin-23p19 monoclonal antibody, has demonstrated efficacy in the treatment of chronic plaque psoriasis.^{1,2} Here, we evaluate the incidence of gastrointestinal (GI) adverse events (AE), specifically cases of inflammatory bowel disease (IBD), reported during the TIL clinical development program.

Methods: Patients with moderate to severe plaque psoriasis were randomized in 3 large clinical trials: P05495 (phase 2; NCT01225731),¹ reSURFACE 1 (phase 3; NCT01722331),² and reSURFACE 2 (phase 3; NCT01729754).² In this post hoc analysis, we identified serious GI AEs and new onset or exacerbation of preexisting IBD from a pooled dataset of patients receiving TIL in these 3 studies, which followed patients up to 52 (P05495 and reSURFACE 2) or 64 (reSURFACE 1) weeks. TIL doses were 5 mg, 25 mg, 100 mg, and 200 mg in P05495, and 100 mg and 200 mg in the reSURFACE studies.

Results: In this analysis, we pooled 1911 patients from the 3 trials who received either TIL 100 mg or 200 mg. There were no new cases of IBD reported; among 6 patients with a history of IBD randomized to TIL, none experienced an exacerbation. The number (rate per 100 patient-years) of patients in the pooled dataset who experienced serious GI AEs was 8 (0.80) for TIL 100 mg and 4 (0.43) for TIL 200 mg. These serious GI AEs included abdominal pain, constipation, diverticulum, dyspepsia, gastritis, thrombosed hemorrhoids, esophageal polyp, and pancreatitis (1 patient each) among patients receiving TIL 100 mg and abdominal hernia, upper abdominal pain, acute pancreatitis, and salivary gland enlargement (1 patient each) among patients receiving TIL 200 mg.

Conclusion: Serious GI AEs were found to be infrequent in this post hoc analysis of patients with chronic plaque psoriasis receiving TIL in 3 large randomized clinical trials. No new cases of IBD or exacerbations of preexisting IBD were observed during treatment with TIL.

References:

1. Papp K, et al. *Br J Dermatol*. 2015;173:930–939.
2. Reich K, et al. *Lancet*. 2017;390:276–288.

Analyses were presented at the 2018 American Academy of Dermatology Annual Meeting, February 16–20, 2018, San Diego, CA, USA.

Disclosure: **M. Gooderham**, AbbVie, Actelion Pharmaceuticals, Akros Pharma Inc, Amgen, Arcutis Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb Co, Celgene, Dermira, Eli Lilly and Co., Galderma, GSK, Glenmark, Janssen, LEO Pharma, Medimmune, Merck & Co, Novartis, Pfizer, 5, AbbVie, Actelion Pharmaceuticals, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly and Co., Galderma, Janssen, LEO Pharma, Merck & Co., Novartis, Pfizer Inc., Regeneron, Sanofi Genzyme, and Valeant Pharmaceuticals Inc., 5; **B. E. Elewski**, AbbVie, Boehringer Ingelheim, Celgene, Incyte, Leo, Lilly, Merck, Novartis, Pfizer, Regeneron, Sun Pharmaceuticals Inc., Valeant (Ortho dermatology), 2, Boehringer Ingelheim, Celgene, Leo, Lilly, Novartis, Pfizer, Sun Pharmaceuticals Inc., Valeant (Ortho dermatology), 5; **D. M. Pariser**, Abbott Laboratories, Amgen, Asana Biosciences, Bickel Biotechnology, Celgene, Dermavant Sciences, Eli Lilly, LEO Pharma US, Merck & Co., Novartis, Novo Nordisk, Ortho Dermatologics, Peplin Inc., Pfizer Inc., Photocure ASA, Promius Pharmaceuticals, 2, Bickel Biotechnology, Biofrontera AG, Celgene Corporation, Dermira, DUSA

Pharmaceuticals Inc., LEO Pharma US, Novartis, Promius Pharmaceuticals, Regeneron, Sanofi, TheraVida, and Valeant Pharmaceuticals, 5, Pfizer, Inc., 5; **H. Sofen**, Amgen, Boehringer Ingelheim, Janssen, Lilly, Merck & Co., Novartis, Pfizer, 5, Janssen, Lilly, Novartis, 5, Janssen, Lilly, Novartis, 8; **A. M. Mendelsohn**, Sun Pharmaceutical Industries Inc, 3; **N. Cichanowitz**, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, 1, 3; **Q. Li**, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, 3.

Abstract Number: 2605

Drug Retention and Response Rates of TNFi Treatment in 13,170 Patients with Psoriatic Arthritis Treated in Routine Care – Pooled Data from the EuroSpA Research Network Collaboration

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Session Information

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Drug retention and response rates of TNFi treatment in 13,170 patients with psoriatic arthritis treated in routine care – pooled data from the EuroSpA Research Network Collaboration

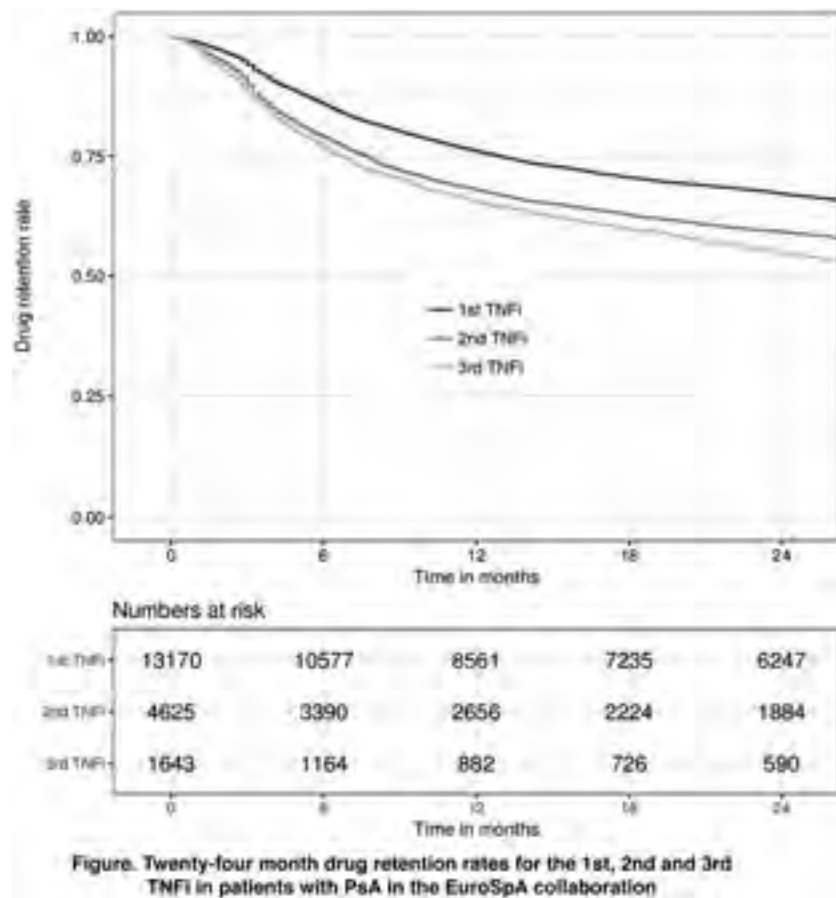
Background/Purpose: A research network collaboration of 15 European registries sharing data on patients with spondyloarthritis (SpA), “EuroSpA”, has recently been created to strengthen research capabilities in the real world setting¹. We aimed to investigate Tumour Necrosis Factor inhibitor (TNFi) retention and response rates at 6, 12 and 24 months in patients with psoriatic arthritis (PsA) treated with their 1st, 2nd or 3rd TNFi in clinical practice across Europe.

Methods: A common data model was agreed upon by the EuroSpA Scientific Committee. Registry data managers clarified data availability and uploaded anonymized data through the secure Virtual Private Network pipelines to the EuroSpA server. Baseline characteristics, drug retention and response rates were investigated with non-parametric descriptive statistics. Kaplan-Meier estimation was used to investigate TNFi retention rates. Both crude and Lundex adjusted² response rates were calculated for DAS28 remission (DAS28≤2.6) after 6,12 and 24 months and ACR20/50/70 after 6 months.

Results: In May 2018, 10 of the 15 registries participating in EuroSpA had completed data upload to the EuroSpA server, including 13,170 patients with PsA. Baseline characteristics of the pooled population are shown in Table.

For the 1st TNFi, 6 and 24 months’ retention rates were 86% and 67%, respectively. Corresponding retention rates for the 2nd TNFi were 79% and 59%, and for the 3rd TNFi 77% and 55%, respectively (Table and Figure). For the 1st TNFi, 6 and 24 months Lundex adjusted DAS28 remission rates were 44% and 30%. Corresponding remission rates for the 2nd TNFi were 34% and 22%, and for the 3rd TNFi, 26% and 16%. For the 1st TNFi, 6 months Lundex adjusted ACR 20/50/70 response rates were 40%, 27% and 15%, respectively. Corresponding ACR 20/50/70 response rates for the 2nd TNFi were 21%, 13% and 6% and for the 3rd TNFi, 20%, 10% and 5%, respectively.

Conclusion: These initial analyses demonstrate that the creation of a large European database of PsA patients treated in routine care based on a common data model is feasible, offering important opportunities for future research. In this



pooled dataset from 10 European registries, we found decreasing retention rates and response rates with increasing number of previous TNFi.

References: 1) Ann Rheum Dis, 2017, suppl. 2, p. 65

References: 2) Arthritis Rheum, 2006, 54(2), p. 600-6.

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Table 1: Baseline characteristics, retention and response rates in patients with psoriatic arthritis. Pooled data from ten registries participating in the EuroSpA Research Network Collaboration.

	1 st treatment series		2 nd treatment series		3 rd treatment series	
	No. of patients with available data, n	Median(IQR) or percentage	No. of patients with available data, n	Median(IQR) or percentage	No. of patients with available data, n	Median(IQR) or percentage
Age, years	13164	49 (39-57)	4623	50 (41-58)	1643	51 (42-58)
Male, pct	13189	48.5	4624	41	1642	38
BMI, kg/m ²	4255	27 (24-31)	1566	28 (25-32)	587	28 (24-32)
csDMARD, pct	13049	58.5	4616	53	1642	52
Disease duration years	6610	4 (1-9)	2269	5 (2-11)	806	7 (4-12)
Smoking status, current, pct	11883	16.9	4259	16	1552	19
First TNFi drug, pct						
Infliximab, pct	2911	22	564	12	292	16
Etanercept, pct	4478	34	1761	39	468	29
Adalimumab, pct	3885	30	1554	34	478	28
Certolizumab, pct	500	4	176	4	82	5
Golimumab, pct	1396	11	550	12	323	20
Start before 2009	3437	26	800	17	200	12
Start 2009-2011	2975	23	1073	23	371	23
Start 2012-2014	3372	26	1429	31	583	34
Start 2015-2017	3385	26	1323	29	509	31
DAS28-CRP	8686	4 (3-5)	2943	4 (3-5)	1002	4 (3-5)
CRP, mg/L	10275	7 (3-16)	3533	5 (2-13)	1216	5 (2-14)
SJC (0-28)	9978	2 (0-5)	3382	2 (0-6)	1189	2 (0-4)
TJC (0-28)	9965	4 (2-9)	3384	4 (1-9)	1193	4 (1-9)
SJC (0-66)	3823	4 (1-7)	1328	2 (0-6)	515	2 (0-6)
TJC (0-66)	3886	7 (3-13)	1370	6 (2-12)	533	6 (2-12)
Pain, (0-100 mm)	9893	51 (41-75)	3435	63 (40-78)	1183	66 (42-80)
Fatigue, (0-100 mm)	5032	64 (40-80)	2016	68 (45-81)	759	71 (49-85)
	Retention rates		Retention rates		Retention rates	
6/12/24 months, pct	88 (85-88) / 76 (75-77) / 67 (66-65)		79 (78-80) / 68 (67-69) / 59 (58-61)		77 (75-79) / 66 (63-68) / 55 (52-58)	
	Response rates		Response rates		Response rates	
	Crude*	Lundex adjusted **	Crude*	Lundex adjusted **	Crude*	Lundex adjusted **
DAS28 remission, at 6/12/24 months, pct	55 / 50 / 64	44 / 39 / 30	46 / 50 / 54	34 / 29 / 22	37 / 39 / 46	26 / 21 / 16
ACR 20/50/70, at 6 months, pct	47 / 33 / 19	40 / 27 / 15	29 / 17 / 9	21 / 13 / 6	28 / 14 / 6	20 / 10 / 5

Data are as observed: median (IQR) or percentage. BMI: Body Mass Index; csDMARD: conventional synthetic Disease Modifying Anti Rheumatic Drug; TNFi: tumor necrosis factor inhibitor; INF: infliximab; ETA: etanercept; ADA: adalimumab; CER: certolizumab pegol; GOL: golimumab; SJC: swollen joint count; TJC: tender joint count; PGL: Patient Global; PhGL: Physician Global; VAS: visual analogue scale; DAS28: Disease Activity Score 28 joints; ACR: American College of Rheumatology. *Crude value: The fraction responding of those still on drug at 6, 12 and 24 months, respectively. **Lundex adjusted: crude value adjusted for drug retention.

Long-Term Inhibition of Radiographic Progression with Originator Adalimumab in Patients with Moderate to Severe Psoriatic Arthritis with or without Radiographic Damage at Baseline

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Session Information

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Adalimumab (ADA) inhibited radiographic progression in patients (pts) with moderate to severe PsA in the ADEPT study and its open label extension (OLE). These post-hoc analyses evaluated long-term inhibition of radiographic progression and impact on quality of life (QoL) in ADA treated pts with respect to the presence or absence of baseline (BL) radiographic damage.

Methods: Pts who completed the ADEPT study (phase 3, double-blind, placebo [PBO]-controlled, 24-week [wk] study in TNF inhibitor naive PsA pts) were eligible to enroll in the 120-wk OLE with ADA 40 mg every other wk (eow). Only pts who continued into the OLE were included in these analyses of observed data. Radiographic damage at BL (BLrd) was defined as a modified Total Sharp Score (mTSS) >0.5; radiographic progression was defined as a change (Δ) from BL in mTSS by >0.5. Radiographic progression and changes in general health (SF-36), fatigue (FACIT-F) and physical function (HAQ-DI) were evaluated until Wk 144 in pts grouped by presence or absence of BLrd and treatment (PBO/ADA or ADA/ADA in the ADEPT/OLE studies, respectively).

Results: BLrd was observed in 81% (n=231/285) of the enrolled pts. At Wk 144, 49.8% (n=115/231) of those with BLrd and 51.9% (28/54) of those without BLrd, did not progress radiographically. Radiographic progression by Wk144 was significantly smaller in pts without than with BLrd (mean Δ mTSS from BL: 0.85 vs. 2.91, $p<0.01$). Further, in pts without BLrd who initially received ADA, fewer progressed (Wk 144: 12% vs. 24%), with significantly less mean radiographic progression up to Wk 144 (mean Δ mTSS from BL: 0.49 vs. 1.12, $p<0.05$). Mean radiographic progression through Wk 144 did not significantly differ between pts initially receiving ADA or PBO who had BLrd (mean Δ mTSS from BL: 3.41 vs. 2.43, NS). At Wk 144, there were no statistically significant differences in the mean changes from BL in HAQ-DI, FACIT-F, and SF-36 (PCS and MCS) in pts with or without BLrd (-0.40 vs. -0.33, 6.11 vs. 6.45, 7.50 vs. 7.98, and 2.88 vs. 3.44, NS). However, pts who received ADA compared with PBO exhibited significantly greater improvement in physical function (both SF-36 PCS and HAQ-DI, $p<0.01$) by wk 24 regardless of BLrd (**Table**).

Conclusion: Moderate to severe PsA pts with BLrd experienced more long-term radiographic progression than those without. Interestingly, among pts without BLrd, initial treatment with ADA compared with PBO resulted in 50% fewer pts with radiographic progression and significantly lower mean radiographic progression through 144 weeks, whereas no long-term difference has been observed for physical function and QoL parameters.

Table: Summary of change from baseline in the Quality of Life (QoL) parameters of SF-36, FACIT-F and HAQ-DI

Change from BL in SF-36 (PCS) [†]				Without BL radiographic damage (N=54)			
With BL radiographic damage (N=231)				Visits	PBO/ADA	ADA/ADA	p value
Visits	PBO/ADA	ADA/ADA	p value	Visits	PBO/ADA	ADA/ADA	p value
	(N=116)	(N=115)			(N=31)	(N=23)	
Wk 24	1.94±9.6	8.64±9.1	<0.001	Wk 24	-0.49±8.7	11.42±11.9	<0.001
Wk 144	7.13±11.2	7.88±11.4	NS	Wk 144	8.6±10.2	7.06±13.1	NS
Change from BL in SF-36 (MCS) [†]				Without BL radiographic damage (N=54)			
With BL radiographic damage (N=231)				Visits	PBO/ADA	ADA/ADA	p value
Visits	PBO/ADA	ADA/ADA	p value	Visits	PBO/ADA	ADA/ADA	p value
	(N=116)	(N=115)			(N=31)	(N=23)	
Wk 24	-0.29±11.2	2.26±9.8	NS	Wk 24	1.86±9.1	0.87±7.9	NS
Wk 144	3.43±11.5	2.32±10.7	NS	Wk 144	4.77±10.7	1.57±8.6	NS
Change from BL in FACIT-F ^{††}				Without BL radiographic damage (N=54)			
With BL radiographic damage (N=231)				Visits	PBO/ADA	ADA/ADA	p value
Visits	PBO/ADA	ADA/ADA	p value	Visits	PBO/ADA	ADA/ADA	p value
	(N=115)	(N=115)			(N=31)	(N=22)	

Wk 24	-0.08±10.1	7.08±9.6	<0.001	Wk 24	0.90±8.1	6.86±12.7	NS
Wk 144	5.41±10.1	6.81±11.1	NS	Wk 144	7.19±10.2	5.41±11.9	NS
Change from BL in HAQ-DI ^{†††}							
With BL radiographic damage (N=231)				Without BL radiographic damage (N=54)			
Visits	PBO/ADA (N=115)	ADA/ADA (N=115)	p value	Visits	PBO/ADA (N=31)	ADA/ADA (N=22)	p value
Wk 24	-0.11±0.4	-0.41±0.5	<0.001	Wk 24	-0.04±0.4	-0.37±0.4	<0.01
Wk 144	-0.4±0.6	-0.40±0.5	NS	Wk 144	-0.36±0.6	-0.29±0.4	NS

† higher SF-36 scores indicate better overall health; †† higher FACIT-F scores indicate lower fatigue; ††† lower HAQ-DI scores indicate lower disability or better function. *P* values are from comparison of means between PBO/ADA and ADA/ADA using T-test.

ADA: originator adalimumab; BL: Baseline; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue scale; HAQ-DI: Health Assessment Questionnaire-Disability Index; MCS: Mental Component Summary; N: number of patients; PCS: Physical Component Summary; PBO: placebo; SF-36: Short Form Health Survey comprising of 36 questions; Wk: week

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Early Achievement of ASDAS-Major Improvement in Patients with Ankylosing Spondylitis Treated with TNF- α Blockers Is Associated with a Prominent Long term Improvement in Metrologic Indices

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Session Information

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Background/Purpose: Limited spinal mobility is a cardinal sign of ankylosing spondylitis (AS) and shows a close relationship with functional disability which leads to high individual socioeconomic consequences and lifetime costs. To measure the metrologic outcomes which may be critical in daily clinical practice, BASMI is used in conjunction with chest expansion which is for more accurate assessment of thoracic spinal mobility. ASDAS, a composite index score, was developed for assessment of disease activity and efficacy of treatment. Recently, ASDAS is known to be related with spinal mobility and radiographic spinal progression. In this study, we investigated whether early ASDAS changes is related with the longitudinal improvements of spinal mobility in patients treated with TNF- α blockers.

Methods: This was an observational study in 126 adult AS patients who were treated with TNF- α blockers up to 33 months. All outcome measures, including disease activity and metrologic outcomes, were performed at baseline and month 3, and then every six month up to month 33. Clinical efficacy was presented by ASAS and ASDAS response criteria, such as ASDAS major improvement (ASDAS-MI). Cumulative probability plots were used for association between ASDAS changes and metrologic improvements. Differences in BASMI₁₀ and chest expansion at any time point between responder and non-responder groups were examined with a mixed linear model.

Results: The BASMI₁₀ showed a rapid and significant improvement to month 3 ($p<0.001$), a further response to month 9 ($p=0.003$), and then maintained to month 33. The chest expansion considerably increased to month 3 ($p=0.011$) and then slowly improved up to month 33. ASDAS-CRP improved prominently at month 3 ($p<0.001$), a further significantly at months 9 ($p<0.001$) and mildly up to month 33. The cumulative probability plots, in which scatter plots of the individual 3-month ASDAS-CRP changes in cumulative order versus the 33-month BASMI₁₀ and chest expansion changes, demonstrated a significant tendency toward 33-month BASMI₁₀ improvements with 3-month ASDAS-CRP changes ($r=0.383$, $p<0.001$). The 33-month chest expansion changes showed a weak, but significant, tendency to increase with respect to 3-month ASDAS-CRP changes ($r=-0.245$, $p=0.031$). ASDAS-MI responders at month 3 had a significant improvement in 33-month BASMI₁₀ ($p=0.011$) and chest expansion changes ($p=0.015$), compared to non-responders, while baseline BASMI₁₀ and chest expansion were not significantly different. The mixed linear model revealed that a significant difference between two groups were detected in both BASMI₁₀ ($p=0.0099$) and chest expansion ($p=0.0189$). On the contrary, ASAS20 responders at month 3 did not show a significant difference in 33-month BASMI₁₀ and chest expansion

improvements. On the analysis using a mixed linear model, BASMI₁₀ showed a significant difference between two groups ($p=0.00375$), while chest expansion scores were not different.

Conclusion: These results suggested that ASDAS-MI responsiveness at month 3, not ASAS20 responsiveness at month 3, may be related with an outstanding improvement in metrologic outcomes of long-term TNF- α blocker treatment in AS.

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Secukinumab Provides Sustained Improvements in the Signs and Symptoms of Active Psoriatic Arthritis: Long-Term (4-Year) Data from a Phase 3 Study

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Background/Purpose: Secukinumab (SEC), a fully human monoclonal IgG1 antibody that selectively neutralizes IL-17A, provided sustained improvement in the signs and symptoms of active psoriatic arthritis (PsA) over 2 years (yrs) in the FUTURE 2 study.¹ Herein, long-term (4-yr) efficacy and safety results in patients (pts) from FUTURE 2 study, including results of dose-escalation, are reported.

Methods: Overall, 397 pts with active PsA were randomized to either SEC (300, 150, or 75mg) or placebo weekly followed by every 4 weeks (wks) starting at Wk 8.¹ Of the overall randomized pts, approximately 1/3 had inadequate response [IR] to prior anti-TNF use. Pts were escalated from 150 to 300mg and from 75 to 150/300mg starting at Wk 128, if active signs of disease were observed based on physician's judgement; the escalated dose was maintained thereafter. Assessments at Wk 208 included ACR20/50/70, PASI 75/90, HAQ-DI, SF-36 PCS, and resolution of dactylitis and enthesitis. Analyses by prior anti-TNF use (naïve/IR) and with/without concomitant methotrexate (MTX) were also assessed. ACR responses for dose-escalated pts included placebo-switchers. Data are reported as observed. Safety analysis included all pts who received ≥ 1 dose of SEC.

Results: Overall, 69/100 (69%), 70/100 (70%), and 62/99 (63%) pts originally randomized to SEC 300, 150, and 75mg, respectively, completed 208 wks of treatment. A total of 46/100 (46%) pts in the 150mg group were escalated to 300mg and 56/99 (57%) pts in the 75mg group escalated to 150/300mg. Clinical responses were sustained through Wk 208 with 300mg and sustained/further improved following dose-escalation to 300/150mg in the 150 and 75mg groups (Table). ACR20 response rates at Wk 208 in anti-TNF-naïve pts were 75.5%, 76.5%, and 71% in the 300, 150, and 75mg groups, respectively; corresponding rates in anti-TNF-IR pts were 60%, 71%, and 64%. ACR20 response rates in pts with concomitant MTX were 67.6%, 77.1%, and 78.8% in the 300, 150, and 75mg groups, respectively; corresponding rates in pts without concomitant MTX were 74.4%, 73%, and 58.6%. After dose-escalation, the proportion of pts with non/low level ACR responses improved, with corresponding increases in the proportion of pts achieving moderate/high ACR responses (Table). Over the study (SEC exposure of 238.6 pt-yrs), the type, incidence, and severity of adverse events were consistent with previous report.¹ Treatment-emergent anti-drug antibody was reported in 3 pts, with no neutralizing antibody or loss of efficacy. In the entire study, one death (due to sepsis) was reported in the 150mg group over 4 yrs.

Conclusion: SEC 300 and 150mg provided sustained improvement in the signs and symptoms of PsA over 4 yrs. Efficacy was sustained/further improved following dose-escalation. SEC was well tolerated, with no new/unexpected safety signals. Reference: 1. McInnes IB, et al. *Rheumatology* (Oxford) 2017;56:1993–2003.

Table

Efficacy Results at Wk 208				
Endpoints, n/M (%), unless stated	Secukinumab 300mg (N = 100)	Secukinumab 150mg group (N = 100)*		Secukinumab 75mg group (N = 99)*
ACR20	52/73 (71.2)	54/72 (75.0)		43/ 62 (69.4)
ACR50	34/73 (46.6)	37/72 (51.4)		23/62 (37.1)
ACR70	26/73 (35.6)	18/72 (25.0)		8/62 (12.9)
aPASI 75	25/31 (80.6)	35/43 (81.4)		24/36 (66.7)
aPASI 90	18/31 (58.1)	30/43 (69.8)		15/36 (41.7)
HAQ-DI, mean change (SD)	n = 72 -0.59 (0.63)	n = 72 -0.51 (0.54)		n = 62 -0.33 (0.61)
SF-36 PCS, mean change (SD)	n = 73 6.9 (8.73)	n = 72 7.5 (7.35)		n = 62 5.3 (8.89)
bResolution of enthesitis	29/41 (70.7)	33/46 (71.7)		29/45 (64.4)
cResolution of dactylitis	29/34 (85.3)	22/25 (88.0)		24/26 (92.3)
ACR response rates before and after dose-escalation				
ACR response, %	150mg to 300mg (M = 90) ^d		75mg to 150mg (M = 45) ^d	
	Before dose-escalation	After dose-escalation	Before dose-escalation	After dose-escalation
ACR <20 (non-responder)	46.7	33.3	42.2	33.3
20 ≤ ACR <50	30.0	18.9	33.3	33.3
50 ≤ ACR <70	13.3	30.0	17.8	26.7
ACR ≥70	10.0	17.8	6.7	6.7

* Secukinumab 150 and 75mg arms include 46 and 56 pts, respectively, who were escalated at Wk 128

^a PASI responses assessed in pts with psoriasis affecting ≥3% body surface area at BL (300mg: N = 42; 150mg: N = 58, and 75mg: N = 50)

^b Assessed in pts (N = 56 [300mg], 64 [150mg], and 68 [75mg]) with this symptom at BL

^c Assessed in pts (N = 46 [300mg], 32 [150mg], and 33 [75mg]) with this symptom at BL

^d All pts (including placebo-switchers) with non-missing assessment values at all time points are included

^e Before dose-escalation is defined as the last assessment done on or before pt started on the higher dose

BL, baseline; HAQ-DI, Health Assessment Questionnaire-Disability Index; PASI, Psoriasis Area and Severity Index; M, number of evaluable pts; N, total number of pts; n, number of responders; SF-36 PCS, Short Form 36 Physical Component Summary

Disclosure: **I. B. McInnes**, Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, and UCB, 2, Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, and UCB, 5, Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, and UCB, 8; **A. J. Kivitz**, Celgene, Janssen, Pfizer, Genentech, Novartis, and Sanofi, 5, Celgene, Pfizer, Sanofi-Regeneron, and Novartis, 8; **P. Nash**, Novartis, Abbvie, Roche, Pfizer, BMS, Janssen, and Celgene, 2, Novartis, Abbvie, Roche, Pfizer, BMS, Janssen, and Celgene, 9; **P. Rahman**, Abbott, Abbvie, Amgen, BMS, Celgene, Janssen, Novartis, Pfizer and Roche, 5; **J. Rech**, BMS and Celgene, 2, Abbvie, BMS, Celgene, Fresenius, Medcap, MSD, Novartis, Pfizer, and Roche, 8; **B. Kirkham**, Abbvie, BMS, Celgene, Janssen, Lilly, MSD, Novartis, Roche, and UCB, 2, Abbvie, BMS, Celgene, Janssen, Lilly, MSD, Novartis, Roche, and UCB, 5, Abbvie, BMS, Celgene, Janssen, Lilly, MSD, Novartis, Roche, and UCB, 8; **S. V. Navarra**, Pfizer, Novartis, AstraZeneca, Janssen, Astellas, Roche, 5, 8; **K. Ding**, Novartis, 1, Novartis, 3; **E. Ilesley**, Novartis, 1, Novartis, 3; **L. Pricop**, Novartis, 1, 3.

Abstract Number: 2609

Survival of Disease-Modifying Drugs in Patients with Recent Diagnosis of Psoriatic Arthritis in Daily Clinical Practice

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic arthritis (PsA) is a chronic inflammatory disease that benefits from DMARDs, in this regard knowing more about these therapies is a great step forward in the management of these patients in daily clinical practice. Objectives: To evaluate the survival of DMARDs used in recent diagnose PsA patients as well as the causes of discontinuation and to analyze the possible associated factors

Methods: Retrospective longitudinal observational study. **Subjects:** Inception cohort of patients from January 2010 to December 2014, and followed up to December 2016, diagnosed with PsA according to ICD-10 code. **Main outcome:** discontinuation of conventional DMARDs (cDMARDs) and biological DMARDs (bDMARDs) due to: Adverse drug reactions (ADRs); Improvement or remission; Inefficacy; Patient's decision and Physician's decision. **Covariables:** sociodemographic and clinical. **Statistical analysis:** To estimate DMARDs discontinuation rates, survival techniques were used, expressing the incidence rate (IR) per 100 patients*year with their respective CI at 95%. Multivariate Cox regression models were performed to analyze the factors associated with DMARDs discontinuation and the results were expressed in Hazard ratio(HR) and 95% CI.

Results: 191 patients with recent diagnosis of PsA were included, with a 379.7 Patients*year follow-up. 50.3% were male, the mean age at diagnosis was 50±14.6 years old. 46.6% of the patients had a history of cutaneous psoriasis. HLA-B27 was positive in 20% of patients. 50% of the patients started a DMARD at the first visit. Throughout the follow-up, all patients received cDMARDs and 23 used bDMARDs. The median DMARD per patient was 2[1-3]. Methotrexate (MTX) was the most used drug 69.7%. According to the treatment regimen, 30% were on combination therapy, the most frequent was antiTNF+MTX (33%). 103 discontinuations were recorded with a IR 27.1[22.3-32.9] within these, 44 were related with ADRs (IR 11.5[8.6-15.5]), 24 (IR 6.3[3.5-11.1]) were due to inefficiency, 9 (IR 2.3[1.2-4.5]) were registered after remission, 12 (IR 3.1[1.7-5.5]) by decision of the patient and 12 (IR 3.1[1.7-5.5]) by doctor's decision. The DMARDs median survival was 1.8 years [1.4-2.7]. Table 1 shows the discontinuation rates for each type of DMARDs and the multivariate analysis for the factors associated with DMARDs discontinuation is in Table 2.

Conclusion: In our study, the DMARD discontinuation rate was 27.1, mainly related with ADRs. We have also found some clinical and therapy regimen factors that can modify the DMARDs survival on PsA. We observed that MTX, presented the longest survival independent of the rest of the factors.

Table 1.

	Patients*years	Events(n)	IR	95% CI
MTX orally	243.46	53	21.77	16.63-28.49
Sc MTX	49.90	18	36.07	22.73-57.25
Salazopyrin	84.80	30	35.37	24.73-50.59
Leflunomide	21.83	10	45.80	24.64-85.13
Antimalarials	25.34	8	31.56	15.78-63.12
bDMARDs	57.56	25	43.43	29.35-64.28

Table 2.

	HR	95% CI
Women	1.51	0.61-3.09
Age at diagnosis	0.97	0.97-1.01
Distress level	1.87	1.00-3.48
CRP ≥ 1.05gr/dL	1.85	0.99-3.48
Combination therapy	2.36	1.46-3.80
bDMARDs	1.05	0.52-2.11
MTX vs rest DMARDs	0.53	0.31-0.91

Disclosure: D. Freites Núñez, None; Z. Rosales Rosado, None; J. Font Urgelles, None; I. Hernández-Rodríguez, None; L. Leon, None; G. Candelas Rodriguez, None; L. Rodriguez-Rodriguez, None; B. Fernández-Gutiérrez, None; J. A. Jover Jover, None; L. A. Alcazar, None.

Abstract Number: 2610

Certolizumab Pegol Serum Levels ≥20 Mg/L Are Associated with Treatment Response in Patients with Axial Spondyloarthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Measurement of serum drug levels can help clinicians tailor treatment with TNF-inhibitors.

An association between certolizumab pegol (CP) serum levels and response has previously been found in patients (pts) with rheumatoid arthritis (1). Data for pts with axial spondyloarthritis (axSpA) are lacking. Here, we examine the association between serum CP levels and treatment response in pts with axSpA and tentatively identify a therapeutic target level.

Methods: Patients with a clinical diagnosis of axSpA starting standard treatment with CP included in the NOR-DMARD study with biobank sample at 3 months follow-up, were included in the present analyses. Serum drug levels (non-trough) were analysed with an in-house immunofluorometric assay automated on the AutoDELFIA immunoassay platform.

Associations between CP level and improvement in ASDAS-CRP and response (defined as ASDAS clinically important improvement (CII)) were assessed by multivariable linear and logistic regression (adjusting for age, sex and prior bDMARD (Y/N)), respectively.

Results: Median serum drug level at 3 month follow up was 35.0 mg/L (IQR 21.3-45.3) in 116 pts. Response data were available in 110/116 patients.

Serum CP level ≥ 20 mg/L was associated with improvement in ASDAS at 3 months ($\beta=0.55$, (95% CI 0.12-1.98), $P=0.01$).

Serum CP level ≥ 20 mg/L was associated with ASDAS CII at 3 months (OR 3.4 (95% CI 1.0-11.1, $P=0.045$)).

Only 18.2 % of pts with CP level <20 mg/L achieved ASDAS CII at 3 months, while 53.2% of pts with CP level 20-40 mg/L and 36.6 % with ≥ 40 mg/L were responders.

Conclusion: Serum CP level was associated with clinical response after 3 months of treatment in pts with axSpA. We suggest 20 mg/L as a lower target level for non-trough samples. No additional benefit of having a certolizumab level over 40 mg/L was observed. These results suggest that a therapeutic level of 20-40 mg/L can be implemented in clinical practice for non-trough serum samples in pts with axSpA.

1. Jani M et al. Ann Rheum Dis 2017;76(1):208-13.

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Abstract Number: 2611

Multidrug Resistant AxSpA: No Advantage of Switching Class in Patients with Inadequate Response to Two Prior TNFi Agents

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Lack of efficacy (LOE) to TNF inhibitor (TNFi) treatments is an important issue and can be seen in up to 40% of the patients with axial Spondyloarthritis (axSpA). In patients with LOE, further treatment responses have been reported to be lower: 6 month BASDAI 50% response rates of 37% for a 2nd TNFi and 30% for a 3rd TNFi.

Secukinumab, an IL-17 inhibitor (IL-17i) is a relatively new treatment option for patients with active axSpA. However, there are currently limited data regarding the treatment responses in inadequate responders to ≥ 2 prior TNFi agents.

We aimed to compare the treatment outcomes of patients switching to TNFi or IL-17i following LOE to ≥ 2 TNFi.

Methods: Patients who fulfilled ASAS classification criteria for axSpA and who were on the 3rd or 4th biologic because of LOE to prior biologic treatments were identified. Patients who discontinued prior biologics because of intolerance or financial reasons were excluded. Patients were stratified into two groups based on the class of most recent biologic: TNFi or IL-17i. Demographic and clinical data including disease activity scores were collected from the database. Treatment responses at 6 months were compared between the groups. Good response was defined as ≥ 2 unit or $\geq 50\%$ decrease in BASDAI. Other outcome measures assessed include clinically important improvement (CII; $\Delta \geq 1.1$) and major improvement (ASDAS-MI; $\Delta \geq 2.0$) in ASDAS-CRP.

Results: There were 106 patients (89 AS, 17 nr-axSpA) on a 3rd or 4th course of biologic medication following LOE to former biologic agents. Overall, 34 patients were on IL-17i and 72 on TNFi. Baseline demographics and clinical parameters are presented in **Table 1**. In the IL-17i group there were more patients with psoriasis and only one with IBD. There was no significant difference in other parameters between groups. The response rates were similar in IL-17i and TNFi treated patients (**Table 2**). BASDAI ≥ 2 response rates were 15.2% for IL-17i and 14.8% for TNFi. ASDAS-CII was seen in 3.0% for IL-17i and 11.7% for TNFi. No patients achieved ASDAS-MI and there was no significant difference between sexes in the analysis.

Table 1: Baseline demographics and clinical parameters of 3rd and 4th biologic users

	TNFi group (n: 72)	IL-17i group (n: 34)	p value
Sex, male, n (%)	48 (66.7%)	21 (61.8%)	0.67
Age (mean \pm SD)	39.2 \pm 13.6	40.0 \pm 11.3	0.79
Dis. Duration (mean \pm SD)	16.2 \pm 11.6	19.3 \pm 10.3	0.21
Baseline ESR (mean \pm SD)	13.2 \pm 18.2	17.1 \pm 16.3	0.32
AS, n (%)	60 (83.3)	29 (85.3)	0.52
Nr-axSpA, n (%)	12 (16.7)	5 (14.7)	0.52
HLA B27 +, n (%)	50 (69.4)	25 (73.5)	0.43
Baseline CRP (mean \pm SD)	10.3 \pm 18.9	10.65 \pm 21.7	0.93
Baseline BASDAI (mean \pm SD)	6.04 \pm 1.7	6.3 \pm 1.5	0.47
Baseline TBP (mean \pm SD)	6.3 \pm 2.1	6.9 \pm 1.8	0.12
Baseline PGA (mean \pm SD)	6.3 \pm 2.2	6.7 \pm 1.8	0.37
Baseline BASDAI	6.0 \pm 1.7	6.3 \pm 1.5	0.47
Baseline ASDAS ESR	3.0 \pm 0.9	3.3 \pm 0.8	0.07
Baseline ASDAS CRP	3.3 \pm 0.9	3.5 \pm 0.8	0.30
Arthritis, n (%)	63 (87.5)	32 (94.1)	0.24
IBD, n (%)	14 (19.4)	1 (2.9)	0.017
Psoriasis, n (%)	11 (15.3)	11 (32.4)	0.04
Enthesitis n (%)	35 (48.6)	20 (58.8)	0.40
Uveitis, n (%)	27 (37.5)	13 (38.2)	0.56
F. History of SpA, n (%)	17 (23.6)	6 (17.6)	0.34
Smoking History, n (%)	32 (44.4)	13 (38.2)	0.35

Table 2: Clinical response rates of 3rd and 4th biologic users

	TNFi group (n: 60)	IL-17i group (n: 33)	p value
BASDAI ≥ 2 unit, n (%)	9 (14.8)	5 (15.2)	0.59
BASDAI 50 n (%)	3 (4.9)	2 (6.1)	0.58
CII ASDAS CRP, n (%)	7 (11.7)	1 (3.0)	0.25

CII: Clinically Important Improvement; $\Delta \geq 1.1$ in ASDAS CRP.
There were no patients with major improvement.

Conclusion: Clinical response rates to a 3rd or 4th biologic, regardless of class, were low in AxSpA patients.

Disclosure: S. E. Tunc, None; I. Sari, None; R. D. Inman, None; N. Haroon, None.

Abstract Number: 2612

Utility of Infiltration with Steroids in Dactylitis. Is the Infiltration Guided By Ecography Better THAN Conventional?

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Session Information**Session Date:** Tuesday, October 23, 2018**Session Title:** Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment**Session Type:** ACR Poster Session C**Session Time:** 9:00AM-11:00AM

Background/Purpose: Dactylitis, also called “sausage fingers”, is considered one of the differential signs characteristic of Spondyloarthritis (SpA). The absence of knowledge of its pathophysiology make it a clear manifestation of a difficult clinical treatment. The use of imaging techniques, such as resonance or ultrasound, have demonstrated that there is more inflammation at the level of the tendons than synovitis, with soft edema parts, and that the target organ in these cases is the enthesis. The standardized treatment is the use of NSAIDs, steroids and local infiltration. Different biological treatments have shown good results (secukinumab, antiTNFs). Our objective is to evaluate how local infiltration with steroids modifies both expression clinical, and echographic changes typical of dactylitis. As well as evaluate if there is a difference between the guided ultrasound Vs infiltration.

Methods: Clinical trial, randomized, with blind and unicentric radiological evaluation. They were included patients with clinical dactylitis who presented echographic signs that confirmed the diagnosis. All of them tributaries of local infiltration with steroids. Simple patients’ randomization was done, according to the order of assignment in the study. Paired patients with conventional infiltration and odd patients with guided ultrasound infiltration. The response to the treatment using ultrasound (tenosynovitis, synovitis and Doppler) and clinical criteria were evaluated at 2 and 6 months of infiltration. The assessment of the clinical remission of dactylitis was made under the yes or no dichotomous variable. The assessment of clinical remission of dactylitis was assessed when the Flexor tenosynovitis and Doppler scored 0.

Results: A total of 28 patients were collected, with a total of 50 fingers, the average age was 47.57 ± 10.99 , with an average of fingers per patient of 1.78 ± 0.56 . 42.9% were diagnosed of psoriatic arthritis, the rest still to be affiliated. All the patients presented clinical and ultrasonographic dactylitis, 100% ecográfica tenosynovitis with positive PWD signal, 54% (27) grade 1 and 46% (23) grade 2. Of the 28 patients, 16 had MCF arthritis and 12 of them MCF and IFP. They underwent conventional infiltration to 28 Vs 22 patients who were echoguided. Two months after the infiltration, clinical and sonographic remission was achieved in 68% (34) maintained after 6 months of follow-up. From the 34 fingers that achieved remission, 21 performed ultrasound-guided infiltration and 13 conventional (p 0.002). Only arthritis was resolved associated in 2 of the patients.

Conclusion: We can conclude that steroid infiltration guided by ultrasound is a good option treatment in patients with dactylitis. Conventional infiltration should not be done given the low efficiency.

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Abstract Number: 2613

Patterns of Medication Use in a Validated Cohort of Psoriatic Arthritis (PsA) Patients

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Session Information**Session Date:** Tuesday, October 23, 2018**Session Title:** Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment**Session Type:** ACR Poster Session C**Session Time:** 9:00AM-11:00AM

Background/Purpose: There is currently a lack of consensus among experts on the optimal therapeutic management of psoriatic arthritis (PsA). EULAR and GRAPPA recommendations support initial treatment with classic synthetic (cs) DMARDs. Recently the American College of Rheumatology /National Psoriasis foundation have presented draft recommendations suggesting that treatment naïve patients with active PsA be treated with anti-TNF agents first. In clinical practice it is assumed that treatment with a csDMARD, usually methotrexate (MTX), precedes therapy with biologic agents. In this analysis we evaluated whether the current pattern of PsA treatment in a validated academic cohort of PsA patients begins with MTX.

Methods: All patients with ICD-9 or -10 codes for PsA seen at a single academic center between January 1, 2013 and December 31, 2016 were identified. Patients who met CASPAR classification criteria and consented were enrolled. Patients were sent a survey eliciting date of PsA diagnosis, medication use, efficacy of therapy and reason for stopping medications.

Results: 161/336 (47.9%) of patients completed the survey: mean age 58.3 years (range 22-100), 50.3% female, 88.2% white, 3.4% Hispanic. 64.6% had been on MTX at some point in time and of these, 32.4% were currently using MTX. 35.4% had never been on MTX. 88.2% of patients who took MTX received it without ever being prescribed a biologic or prior to starting a biologic; of these 36.6% were never prescribed a biologic. Of the patients still on MTX, 84.4% took MTX orally and 15.6% via injection, with a mean oral MTX dose of 15.3mg weekly (range 2.5-25). 83.9% of patients who were currently taking MTX believed it helped their PsA, and 43.1% of patients who stopped MTX believed it had helped their PsA. Overall 77.6% of patients who were once on MTX discontinued; 46.4% because MTX was ineffective and 40.6% because of side effects, fatigue being the most frequent (See Table 2). 26.1% of patients had at some point been on a non-MTX csDMARD. 65.2% of patients had been on a biologic agent at some point in time, and of these 56.2% have taken ≥ 2 biologic agents. 48.4% of patients were currently taking a biologic agent.

Table 1. Penetrance of drugs in CASPAR criteria validated cohort of PsA patients (N=161).

Drug	n (%)
Biologics	105 (65.2%)
adalimumab	81 (50.3%)
etanercept	63 (39.1%)
secukinumab	20 (12.4%)
infliximab	18 (11.2%)
ustekinumab	16 (9.9%)
certolizumab	12 (7.5%)
golimumab	9 (5.6%)
abatacept	6 (3.7%)
ixekizumab	4 (2.5%)
rituximab	3 (1.9%)
Targeted synthetic	
apremilast	26 (16.1%)
tofacitinib	4 (2.5%)
Synthetic DMARDS	117 (72.7%)
methotrexate	104 (64.6%)
leflunomide	12 (7.5%)
hydroxychloroquine	10 (6.2%)
azithioprine	3 (1.9%)
Other drugs	115 (71.4%)
NSAIDs	91 (56.5%)
prednisone	51 (31.7%)
methylprednisolone	18 (11.2%)
minocycline	1 (0.6%)

Table 2. Self-reported reasons PsA patients stopped methotrexate (MTX).

Reason for stopping MTX	n (%) (n=69 stopped)
Ineffective	32 (46.4%)
Side effects	28 (40.6%)
Fatigue	14 (20.3%)
GI problems	12 (17.4%)
Abnormal liver tests	11 (15.9%)
Hair loss	8 (11.6%)
Ulcers in mouth	5 (7.2%)
Infections	4 (5.8%)
Rash	3 (4.3%)
Abnormal blood counts	1 (1.4%)
Other side effects	7 (10.1%)
Patient Preference	9 (13.0%)
Symptoms improved	5 (7.2%)
Other reason	11 (15.9%)

Conclusion: Nearly 9 out of 10 patients in an academic PsA Registry received MTX prior to a biologic, and 32.4% of MTX users remained on it. Interestingly, among those who discontinued, 43.1% believed it helped their PsA. These patterns suggest a benefit from MTX, and that even in a center where patients and physicians have access to biologics, MTX remains standard of care as initial therapy. Given the lower cost and patient self-report of benefit, in selected patients MTX should remain a first-line treatment.

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Abstract Number: 2614

The Effect of Secukinumab on the Immunogenicity of Influenza Vaccine in Patients with Psoriatic Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The humoral response to vaccination may be affected by the use of immunosuppressive drugs. The effect of secukinumab on the humoral response of vaccines is unknown. We aimed to assess the immunogenicity and safety of vaccination against seasonal influenza in psoriatic arthritis (PsA) patients treated with secukinumab in comparison with healthy controls

Methods: Patients with PsA fulfilling the CASPAR criteria treated with secukinumab for at least 3 months and healthy controls were vaccinated with the Sanofi Pasteur vaccine recommended by the WHO in 2017 composed of 3 antigens (H3N3, H1N1 and B/Victoria). Clinical and laboratory assessments were performed on the day of the vaccination and 4-6 weeks later. The immunogenicity of the vaccine was evaluated by haemagglutination inhibition assay against the 3 antigens included in the vaccine. Responders to each antigen were defined as patients who had a 4- fold increase in the titer of the antigen or if they seroconverted in cases where the baseline level was below 1/40.

Results: The study included 32 consecutive PsA patients treated with secukinumab for more than 3 months with a median age of 52 years, 18(56%) females, 10 (31%) treated with concomitant conventional synthetic DMARDs, mostly methotrexate and 17 age/gender matched healthy controls (median age=48.5, females=6 (35%), males=11 (65%)). A significant increase in the geometric mean titers of each antigen was observed in both groups. The number of responders in each group was similar for H3N2, H1N1 and significantly higher in the PsA group for B /Victoria. The proportion of patients with a seroprotective level defined as a titer above 1/40 was high and similar in both groups. No correlation was found between the rate of response and factors such as age, gender and parameters of disease activity. No increase was found in the different parameters of disease activity which included tender and swollen joint counts, Leeds enthesitis index, physician and patient global assessment, PASI and CRP.

Conclusion: Treatment with secukinumab does not affect the humoral response to influenza vaccine in patients with PsA.

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Abstract Number: 2615

The Effect of Smoking on Response to Tumour Necrosis Factor-Alpha Inhibitor Treatment in Psoriatic Arthritis Patients: Results from the TURKBIO Registry

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The aim of the study was to investigate the impact of smoking on disease activity, treatment adherence and treatment response in psoriatic arthritis (PsA) patients on tumour necrosis factor-alpha inhibitor (TNFi) therapy in a real-life cohort.

Methods: PsA patients treated with their first TNFi therapy (including adalimumab, certolizumab, etanercept, golimumab and infliximab) in TURKBIO registry were included in the study. Demographic and clinical features of current smokers were compared with never smokers and previous smokers.

Treatment response was evaluated as achievement of EULAR-good-response (yes/no) at the 3-months' and 6-months' visits. We classified patients as 'responders' if they achieved clinical response at the both 3-months' and 6 months' visits.

DAS28-CRP, CDAI and HAQ measurements and also ESH and serum CRP levels were compared between the study groups at baseline. After 3 months and 6 months, changes in these parameters were measured again and recompared between the groups.

Results: Among 102 PsA patients analysed (62 % women; mean age: 41.5) in the study, 97 (95%) had known smoking status. The median follow-up time was 1.3 years (IQR: 0.2-2.3) and disease duration was 3 years (0.6-7.7). No significant difference was found in these parameters between current, never and previous smokers.

At baseline, current smokers were younger and had higher methotrexate use rate ($p=0.009$) compared with previous smokers. Never smokers had female predominance and higher erythrocyte sedimentation rate (ESR) compared with current smokers. Disease duration, body mass index, CRP and baseline disease indexes (DAS28CRP, CDAI, HAQ) were not found to be different between current and never smokers and also previous smokers. Treatment adherence for TNFi showed no difference between the groups (Table 1). The use of concomitant DMARDs was also similar.

Treatment response (EULAR good response) was found to be similar between current, never and previous smokers. The changes in the measurements of DAS28-CRP, CDAI and HAQ at the month 3 and 6 revealed also no difference.

In multivariate analysis, patients with high CRP (OR: 2.8; 95% CI (0.91-8.55), $p=0.07$) and longer biologic follow up time (>1 year) (OR: 15.47; 95% CI (5.52-43.35), $p<0.01$) were found to be associated with EULAR-good responses.

The treatment adherence was better in patients having high ESR (HR: 1.87; 95% CI (1.08-3.25), $p=0.03$) and high clinical disease activity (CDAI >22) (HR: 2.5; 95% CI (1.27-5.10), $p=0.009$). However, smoking status was neither associated with treatment response (EULAR-good response) nor treatment adherence in the patients.

Conclusion: This study suggested that smoking might not be associated with disease activity, treatment adherence and treatment response in PsA patients treated with TNFi in clinical practice.

Table 1. Baseline demographic and clinical features; and treatment adherence and responses in study groups

	Smoking status			P*	P**
	Current	Never	Previous	Current vs Never	Current vs Previous
Number, n (%)	21 (20)	62 (61)	14 (14)		
Age, median (IQR), years	36 (31.5-43.5)	41 (33.7-50.2)	49 (38.2-56.3)	0.15	0.01
Women, n (%)	10 (15.9)	47 (74.6)	3 (4.8)	0.02	0.12
Disease duration, median (IQR), years	0.87 (0.3-6.5)	3.4 (0.7-7.8)	3.3 (1.9-11.1)	0.11	0.06
Follow up time, median (IQR) years	1.8 (0.3-2.5)	1.3 (0.2-2.4)	1.1 (0.4-1.5)	0.31	0.21
Body Mass Index, kg/m ² median (IQR)	27.8 (25.3-31.8)	28.7 (26.9-31.2)	29.5 (24.8- 35.6)	0.68	0.76
CRP, mg/L, median (IQR)	15 (3-33)	12 (5-18.5)	12 (4-26.5)	0.83	0.87
ESR, mm/h, median (IQR)	20 (7-40.5)	34 (22-49)	29.5 (18.5-58.5)	0.05	0.37
DAS28CRP, median (IQR)	4.4 (3.5-4.7)	4.2 (3.6-4.9)	4.5 (3.3-4.9)	0.87	0.60
CDAI, median (IQR)	19 (12.7-24)	17.6 (11.9-23.2)	14.5 (8.9-21.3)	0.77	0.23
HAQ, median (IQR)	0.75 (0.6-0.9)	0.7 (0.7-1)	0.75 (0.75-0.9)	0.40	0.68
Treatment adherence, median (IQR), years	1.1 (0.3-2.3)	1.1 (0.2-1.9)	0.8 (0.4-1.2)	0.57	0.52
Discontinue reason n, (%)					
Adverse events	1 (17)	1 (6)	0 (0)	0.70	0.70
Lack of efficacy	2 (33)	6 (38)	2 (50)		
Other	3 (50)	9 (56)	2 (50)		
EULAR- good response, n, (%)	10 (23,3)	26 (60,5)	7 (16,3)	0.6	0.90

Disclosure: H. Yarkan, None; G. Kenar, None; S. Capar, None; G. Can, None; B. Zengin, None; S. Akar, None; E. Dalkilic, None; S. Senel, None; S. S. Koca, None; A. Tufan, None; A. Yazici, None; N. Inanc, None; H. Ellidokuz, None; N. Akkoc, None; F. Onen, None.

Abstract Number: 2616

The Effect of Smoking on Response to Tumor Necrosis Factor-Alpha Inhibitor Treatment in Ankylosing Spondylitis Patients: Results from the TURKBIO Registry

Handan Yarkan¹, Gercek Can¹, Sedat Capar², Berrin Zengin¹, Gokce Kenar¹, Servet Akar³, Ediz Dalkilic⁴, Soner Senel⁵, Suleyman Serdar Koca⁶, Abdurrahman Tufan⁷, Ayten Yazici⁸, Nevsun Inanc⁹, Hülya Ellidokuz¹⁰, Nurullah Akkoc¹¹ and Fatos Onen¹, ¹Rheumatology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey, ²Statistics, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey, ³Rheumatology, İzmir Katip Celebi University, School of Medicine, Rheumatology, İzmir, Turkey, ⁴Department of Internal Medicine, Division of Rheumatology, Uludağ University Faculty of Medicine, Bursa, Turkey, ⁵Rheumatology, Kayseri Erciyes University, Faculty of Medicine, Kayseri, Turkey, ⁶Rheumatology, Firat University Faculty of Medicine, Elazığ, Turkey, ⁷Internal Medicine-Rheumatology, Gazi University Faculty of Medicine, Ankara, Turkey, ⁸Rheumatology, Kocaeli University, Faculty of Medicine, Kocaeli, Turkey, ⁹Rheumatology, Marmara University faculty of Medicine, İstanbul, Turkey, ¹⁰Statistics, Dokuz Eylül University Faculty of Medicine, İZMİR, Turkey, ¹¹Rheumatology, İzmir, Turkey, İzmir, Turkey

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Although there is good evidence that smoking has a dose-dependent impact on structural damage progression in ankylosing spondylitis (AS) the evidence is poor for its impact on disease activity, physical mobility, life quality and treatment response.

Therefore we aimed to investigate the impact of smoking on disease activity, treatment adherence and treatment response in Turkish patients with AS treated with their first tumour necrosis factor-alpha inhibitor (TNFi) therapy in a real-life cohort.

Methods: 561 patients fulfilling the modified New York criteria for AS and treated with their first TNFi therapy (including adalimumab, certolizumab, etanercept, golimumab and infliximab) since 2009 from 9 centers in Turkey were included in the analysis.

Treatment response was evaluated as achievement of 'BASDAI50' or 'ASDAS Clinically important improvement (CII)' at the 3-months' and 6 months' visits. We classified patients as 'responders' if they achieved clinical response at the both 3-months' and 6 months' visits.

Clinical and demographic parameters were compared between current/never and current/previous smoker groups.

Demographic and descriptive data are presented by medians/interquartile ranges (IQRs). Groups were compared by non-parametric tests (χ^2 , Kruskal Wallis and Mann Whitney tests).

Results: Among 561 AS patients analysed (40 % women, mean age: 37.9 ± 11), 506 (90 %) had known smoking status. The median follow-up time was 1.9 years (IQR 0.85-3.5) and disease duration was 3.1 years(0,6-7,7).

At baseline, current smokers were younger compared with never and previous smokers. Current smokers had male predominance; lower erythrocyte sedimentation rate and higher change in BASMI at 3 months compared with never smokers. HLA status, body mass index, CRP, baseline disease indexes (BASDAI, BASFI, BASMI, ASDAS) and treatment response was not found to be different between current and never smoker patients in our population. (Table 1).

Treatment adherence was better in previous smokers compared with current smokers but no difference was found between current and never smoker patients(Table 1).

In multivariate analysis, male (OR: 1,98; 95% CI (1,39-2,82), $p < 0,01$), HLA positive (OR: 1,54; 95% CI (1,08-2,18), $p = 0,016$) and active DMARD user (OR: 1,84; (95% CI 1,12-3,01) $p = 0,015$) patients had better treatment response and treatment adherence ((HR: 1,93; 95% CI (1,36- 2,73); HR: 1,60; 95% CI (1,13-2,27); HR: 1,80; 95% CI (1,10-2,95) all $p < 0,005$) but smoking status were not significant ($p > 0,05$).

Conclusion: This study suggested that smoking might not be associated with disease activity, treatment adherence and treatment response in AS patients treated with TNFi in clinical practice.

Table 1. Baseline demographic and clinical features; and treatment adherence and responses in study groups

	Smoking status			P*	P**	Smoking status unknown
	Current	Never	Previous	Current never	Current previous	
Number, n (%)	209 (37)	199 (35,5)	98 (17,5)			55 (10)
Age, median (IQR), years	34 (29-41)	38 (30-46)	42 (34-49)	0,007	<0,001	38 (29-48)
Women, n (%)	61 (27,2)	114 (50,9)	22 (9,8)	<0,001	0,37	27 (12,1)
HLA positivity, n (%)	84 (37,0)	77 (33,9)	54 (23,8)	0,23	0,4	12 (5,3)
Disease duration, median (IQR), years	3,5 (0,7-9,2)	3,5 (1-7,1)	3,5 (0,6-8,7)	0,1	0,5	0,1 (0-4,6)
Follow up time , median (IQR), years	2,3 (0,8-3,5)	1,7 (0,8-2,9)	3,4 (1,6-5,1)	0,13	<0,001	0,9 (0,4-1,6)
Treatment response n, (%)	133 (39,9)	120 (36)	59 (17,7)	0,53	0,37	21 (6,3)
DMARD use, n(%)	12 (21,1)	22 (38,6)	13 (22,8)	0,05	0,08	10 (17,5)
CRP, mg/L, median (IQR)	11 (4-25)	14 (5-29)	13 (6-30)	0,37	0,25	9 (5-19)
ESR, mm/h, median (IQR)	28 (13-42)	34 (20-49)	24,5 (12-44,2)	0,003	0,63	30 (14-43)
BASDAI, median (IQR)	45 (34-60)	46 (36-57)	52 (37-62)	0,9	0,1	60 (44-71)
BASFI, median (IQR)	25,5 (17-43)	25,5 (16-38)	25 (13-39,5)	0,5	0,5	48,5 (23,7-63)
BASMI, median (IQR)	30 (9,5-50)	15 (4-30)	25 (6,2-50)	0,11	0,8	30 (20-57,5)
ASDAS	3,4 (2,6-4)	3,3 (2,2-3,9)	3,4 (2,7-3,9)	0,3	0,99	3,5 (2,4-4,1)
Stop reason n(%)						
Adverse events	7 (30,4)	7 (30,4)	4 (17,4)	0,3	0,3	5 (21,7)
Lack of efficacy	17 (24,2)	24 (34,2)	16 (22,8)			14 (20)
Other	33 (41,3)	25 (31,3)	15 (18,8)			7 (8,8)
Changes at 3 months						
BASDAI, median (IQR)	37 (25-50)	37 (24-50)	40 (26,7-53)	0,82	0,68	45 (27,5-62)
BASFI, median (IQR)	22 (12,5-35)	19 (13-32)	19,5 (11-30)	0,44	0,2	29 (15-51)
BASMI, median (IQR)	40 (10-57,5)	10 (4-30)	30 (10-50)	0,04	0,58	30 (20-60)
ASDAS, median (IQR)	2,2 (1,4-3,1)	2,2 (1,2-3,3)	2,4 (1,7-3,3)	0,97	0,24	2,4 (1,3-3,5)

Disclosure: H. Yarkan, None; G. Can, None; S. Capar, None; B. Zengin, None; G. Kenar, None; S. Akar, None; E. Dalkilic, None; S. Senel, None; S. S. Koca, None; A. Tufan, None; A. Yazici, None; N. İnanc, None; H. Ellidokuz, None; N. Akkoc, None; E. Onen, None.

Abstract Number: 2617

Prolonged Effectiveness of a 12 Week Regimen of Biosimilar Adalimumab in Indian (Asian) Patients Suffering from Symptomatic Acute-Chronic Ankylosing Spondylitis (AS)

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

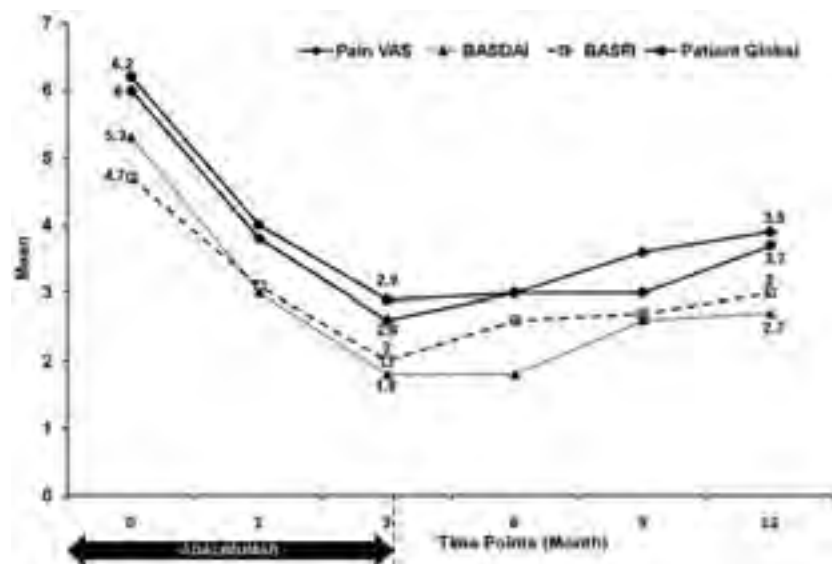
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: On regulatory approval in India, challenging socioeconomics and infection prone scenario compelled us to seek prolonged effectiveness of short term anti-TNF therapeutic regimen (Chopra et al. APLAR Congress 2005). However, there was very little professional and industrial support to research this approach. With the advent of 'Biosimilars', we decided to evaluate the effectiveness of a shorter therapeutic regimen of a Biosimilar Adalimumab in AS

Methods: 62 consenting severely symptomatic patients (86% B27+) with failed NSAID response were screened; 12 were suspected latent TB and offered INH prophylaxis. 50 patients (42 males, mean age 31.2 years, mean duration 98.8 months) were enrolled into an observational design study in a community practice setting; mean of AS-DAS 4.6, ESR 88mm, CRP 64 mg/dl (nephelometry, cut off 5 mg/dl). 40 mg Biosimilar Adalimumab (Bsmr-ADL) (Exemptia™) was administered subcutaneous every fortnight for 12 weeks as per protocol and standard (ACR) clinical and laboratory monitoring performed. Cytokines assay Standard intention-treat analysis was performed (Student T and matched sign rank); significant p <0.05.

Results: Improvement was rapid (week 4- mean ESR 29.1 mm), significant and sustained (Figure). The Tables shows the proportion of patients showing index improvement and ASDAS change. 10 patients failed ASAS 20 at week 12 and despite additional Bsmr-ADL (2 injections, 2 week apart) did not show ASAS based improvement at later time points (data not shown). 12 patients withdrew (1 drug fear, 4 logistics, 5 poor response, 2 unknown). None had active TB/severe AE. Cytokine assay (IL-6, TNF α and IL-17) at baseline and a-priori endpoints will be presented. We continue to monitor patients and have completed 18 months post ADA. We lacked active control and did not study structure modification.



Conclusion: This investigator initiated study demonstrated prolonged benefit of a 12 week regimen with Biosimilar ADA in several patients of severe AS. This is a promising way forward in our setting. But validation studies are required..

Acknowledgment: Zydus Cadila India provided a generous research grant and substantial free of cost Biosimilar ADL injections.

Table shows the proportion of patients with severe AS showing response at study end points

Index	12-14 weeks	22-26 weeks	46-52 weeks
ASAS 20 (%)	80	72	52
ASAS 40(%)	68	60	38
ASDAS (mean)	2.4	2.9	3.5
ASAS partial remission (%)	34	22	12

Figure shows the mean Efficacy Measures in severe AS treated with Biosimilar Adalimumab

Disclosure: A. Chopra, None; N. Khadke, None; M. Saluja, None; T. Kainifard, None; A. Venugopalan, None.

Abstract Number: 2618

Drug Survival of Non TNF Inhibitors bDMARDs in Psoriatic Arthritis (Ustekinumab/Secukinumab) : A Real-World Multicentric Cohort of 161 Patients

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

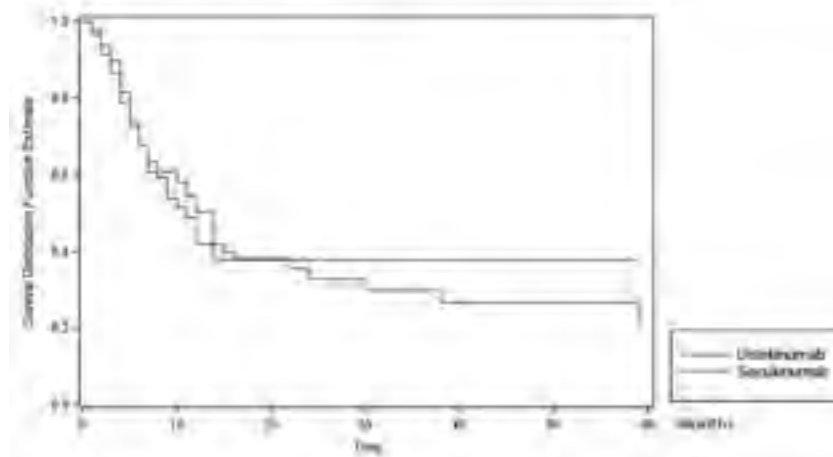
Session Time: 9:00AM-11:00AM

Background/Purpose: Ustekinumab and secukinumab are two new Biologic Disease-modifying Antirheumatic Drugs (bDMARDs) in severe psoriatic arthritis (PsA), targeting respectively IL12-23 and IL 17. Data in real-world are missing for these treatments. For ustekinumab, there is only one study with a large number of patients (160). For secukinumab, there are only the data from clinical trials. The objective was to assess drug survival, efficacy and remission of ustekinumab (UST) and secukinumab (SEK) in a retrospective multicentric cohort of 161 PsA.

Methods: This is a multicentric retrospective study of patients suffering from PsA (CASPAR criteria) from July 2011 to April 2018. Drug survival is defined as the time from initiation to discontinuation (stop/switch) of biologic therapy on the registry. Using Kaplan-Meier survival curves and Cox-regression analyses [hazard ratios (HR) and 95% confidence intervals (CIs)], time to discontinuation was compared across the cohort. For peripheral forms, treatment was considered to be effective for patients with a favourable expert opinion or > 30% clinical improvement of swollen and tender joint counts (SJC and TJC). For axial forms, efficacy criteria were: improvement of BASDAI by at least 2 points on a scale from 0 to 10 or 50% improvement (BASDAI 50) or expert opinion. Remission was considered if TJC ≤ 1, SJC ≤ 1, PASI ≤ 1, patient Visual Analogue Scale (VAS) ≤ 15, Patient global activity VAS ≤ 20 and Tender enthesal points ≤ 1 (Very Low Disease Activity (VLDA) criteria except HAQ).

Results: 161 were included with a mean follow up greater than or equal to 6 months. The sex ratio was balanced with 54.7% of women. The mean age was 50.2 years old and the body mass index(BMI) was 27.6 kg/m². The disease duration was 9.6 years. 47.7% of patients did not smoke. The patients presented axial PsA in 59.0%, peripheral PsA in 94.9% and

Fig. 1 Drug survival of secukinumab and ustekinumab in ustekinumab and secukinumab-naïve patients



enthesitis in 31.4%. Patients were bDMARD-naïve in 13.0%. The median drug survivals for UST AND SEK were respectively 11 and 12 months. There was no impact of the age, the sex, the disease duration, smoking status or the BMI on the drug survival. The drug survival was similar in UST and SEK-naïve patients (HR, 1.07 (0.67 to 1.70), $p=0.77$) (Fig 1) as efficacy for both treatments ($p=0.15$) whereas remission was higher in SEK group (36.2% vs 18.2%, $p=0.012$).

Conclusion: This is the first real-world study which compares these two new treatments in psoriatic arthritis. Ustekinumab and secukinumab in psoriatic arthritis have similar drug survival and efficacy in our study. However, remission based on VLDA criteria was achieved more often with secukinumab.

Disclosure: J. G. Letarouilly, None; J. Sellam, Janssen, 5, Novartis, 5; P. Richette, Novartis, 5, Janssen, 5; P. Dieude, None; P. Claudepierre, Novartis, 5, Janssen, 5; T. Pascart, None; E. Houvenagel, Janssen, 5, Novartis, 5; M. H. Guyot, None; N. Segaud, None; P. Coquerelle, None; F. Maury, None; L. Marguerie, None; X. Deprez, Novartis, 5, Janssen, 5; J. H. Salmon, Novartis, 5, Janssen, 5; G. Baudens, None; E. Gervais, Novartis, 5; M. Kyheng, None; J. Paccou, Janssen, 2; R. M. Flipo, Janssen, 5, Novartis, 5.

Abstract Number: 2619

Effect of Statins on CRP Elevation in Patients with Psoriatic Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: It is well established that psoriatic arthritis is associated with increased cardiovascular disease risk. The use of statins may impart anti-inflammatory effects, possibly through blocking mevalonate production, thereby preventing induction of trained immunity. Mevalonate activates mammalian target of rapamycin (mTOR) and other mediators, subsequently modifying inflammatory pathways. Several studies confirm beneficial effects of statins on C-reactive protein (CRP) in patients with rheumatoid arthritis and lupus. CRP enhances mTOR signaling. Therefore, we aimed to evaluate whether statin therapy affects psoriatic arthritis disease activity by evaluating the degree of systemic inflammation, using CRP elevation as a marker, in an outpatient population at a hospital based clinic.

Methods: A retrospective analysis was performed on the University of Tennessee Knoxville Patient Database for all patients with an ICD-10 code corresponding to psoriatic arthritis that had a CRP checked in the last 10 years. From the selected patients, we divided them into two separate groups: the first group of 54 patients were on statin therapy, and the second group of 152 were not on a statin. We also recorded the most recent CRP concentration, as well as other

parameters including ESR, BMI, and specific treatments for psoriatic arthritis including any DMARD, biologic, or steroid use in each of these patients. Non-parametric Mann-Whitney *U* tests were used for between-subject comparisons using CRP concentration and other parameters with either the presence or absence of statin therapy. The association between CRP level and patient's BMI was tested using Spearman's rho correlation.

Results: Out of a total of 220 patients with an ICD-10 code corresponding to psoriatic arthritis in our system over the last 10 years, 206 had CRP levels on record. In this group of 206, significant beneficial role of statin medication on CRP level was found when prescribed with or without conventional DMARDs or biologic agents. CRP level was found to be significantly lower in the patients on adjunct statin medication compared to the non-statin group ($p = 0.003$), with the statin group of 54 patients demonstrating lower median CRP level of 0.2 (IQR = 0.4) compared to non-statin group of 152 patients with median CRP of 0.4 (IQR = 0.6). ESR elevation was not significantly different between the groups though there was a trend, with lower levels seen in the statin group compared to the non-statin group ($p = 0.07$). The statin group demonstrated lower median ESR level of 5 (IQR = 8.0) compared to the non-statin group median ESR of 7 (IQR = 13.0). There was a statistically significant positive correlation between CRP and BMI with $r_s = 0.35$, $p < 0.001$.

Conclusion: These results suggest a potentially beneficial role of statin therapy in patients with psoriatic arthritis. Statins produced significant biochemical improvement based on CRP level. More studies are needed to further characterize the effect of statins on clinical outcomes. These results also suggest that the pathogenesis of psoriatic arthritis may involve alterations in trained immunity.

Disclosure: L. Jackson, None; J. Bieber, None; R. E. Heidel, None.

Abstract Number: 2620

The Treatment Choices and Response for a Psoriatic Arthritis Inception Cohort

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: There had been a lot of new therapeutic agents for the treatment of Psoriatic Arthritis (PsA) in the last decade. In this study we aimed to assess the treatment choices of rheumatologists in real life in the era of new options, focusing on new diagnosis of PsA.

Methods: The Psoriatic Arthritis Registry of Turkey (PsART) is a multicenter web-based PsA registry (1). At the time of the analysis, 283 out of 1353 patients for the registry had new diagnosis and were given treatment for PsA for the 1st time. Within these 283 patients, 174 also had at least one follow up visit where the changes in the medications and response rates were documented. Fourteen of 174 patients who had used synthetic DMARDs because of psoriasis, were not assessed for treatment strategies. Psoriatic arthritis minimal disease activity (MDA) parameters were collected at baseline and during follow-up period.

Results: Overall, 160 patients (56.9% female), with a mean (SD) age of 44.9±12.6 were assessed. Polyarticular, mono-oligoarticular, and axial disease were 27.6%, 48.2%, and 34.5%, respectively. Baseline minimal disease activity parameters were followed; tender and swollen joint counts 4.8 (4.7) and 2.3 (3.5), body surface area 13.0 (16.6), Leeds enthesitis index 0.08 (0.36), patients global assessment of disease activity-VAS 60 (21), pain-VAS 58 (25) and HAQ-DI 0.89 (0.60). Baseline and last control visit treatments were given at table 1. Mean (SD) and median (range) follow-up duration was 16 (13) months and 14 (min-max 3-43) months. The retention rates of methotrexate, sulphasalazine, leflunomide were 90.3%, 91.5%, and 100%, respectively. Twenty-one (13.1%) patients were switched synthetic DMARDs to anti-TNF treatments during follow up period. The baseline characteristics of patients who remained on synthetic DMARDs versus who were switched to biologics did not differ. Only 40% of patients achieved to minimal disease activity in the last visit.

Table 1. Baseline and follow-up treatment choices in psoriatic arthritis

	Baseline n=160	Last control visit N=160
Only NSAID drugs, n (%)	20 (12.5)	0 (0)
Methotrexate, n (%)	120 (75.0)	124 (77.5)
Sulphasalazine, n (%)	42 (26.3)	47 (29.4)
Leflunomide, n (%)	3 (1.9)	19 (11.9)
Glucocorticoids, n (%)	62 (38.7)	37 (23.1)
Anti-TNF, n (%)	0 (0)	21 (13.1)
Combination synthetic DMARDs treatment, n (%)	32 (20.0)	55 (34.4)

Conclusion: Methotrexate is the most commonly used drug for newly diagnosed PsA patients in real life. Sulphasalazine was chosen either in combination or as monotherapy for a subgroup of patients although not being a part of the EULAR or GRAPPA recommendations. Leflunomide seems to be a second line treatment option. The cross-sectional assessment of PsART cohort, almost 31% of patients used biological DMARDs (1). Moreover within 16 months, 13% of new diagnosed PsA patients were switched from synthetic DMARDs to anti-TNF treatments. Glucocorticoid usage decreased during follow-up period.

Reference:

1. Kalyoncu U et al. The Psoriatic Arthritis Registry of Turkey: results of a multicenter registry on 1081 patients. *Rheumatology*. 2017;56:279-286.

Disclosure: U. Kalyoncu, None; A. Erden, None; G. Kimyon, None; T. Kasifoglu, None; A. Dogru, None; O. Bayindir, None; E. Dalkilic, None; C. Ozisler, None; A. Balkarli, None; G. Cetin, None; R. Mercan, None; O. Kucuksahin, None; A. Omma, None; S. Ergullu Esmen, None; L. Kilic, None; D. Solmaz, None; M. Cinar, None; S. Pehlevan, None; S. Yilmaz, None; T. Duruoz, None; S. Bakirci, None; S. Z. Aydın, None.

Abstract Number: 2621

Predictors of Survival of Adalimumab Treatment in the Management of Ankylosing Spondylitis and Psoriatic Arthritis in Canadian Routine Care

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

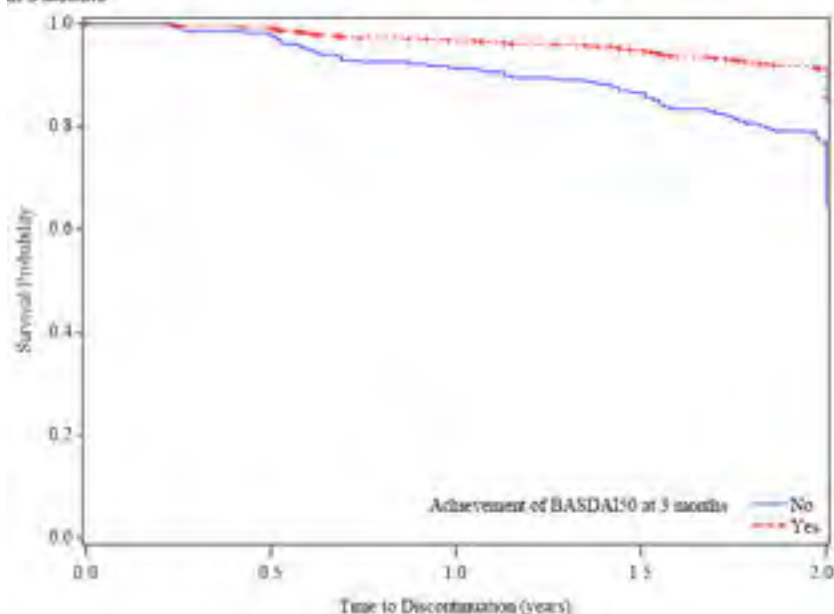
Session Time: 9:00AM-11:00AM

Background/Purpose: Biologics therapy survival is often used as a proxy for treatment effectiveness and safety. However, it may be influenced by patient characteristics, utilization patterns, and available treatment alternatives, which tend to change over time. The objective of this analysis was to assess in Canadian routine clinical practice the survival of treatment with adalimumab (ADA) in AS and PsA, and the determinants of ADA survival.

Methods: COMPLETE-AS is an ongoing Canadian observational study of anti-TNF α naïve adults with active AS or PsA who require, per the judgment of the treating physician, change in current treatment. Patients are followed for up to 2 years. In the current analysis, patients initiating ADA were included. Kaplan Meier (KM) estimates and Cox proportional models were used in the analysis. Potential predictors evaluated were age, gender, enrollment period, combination treatment with non-biologic DMARD(s) (nbDMARDs) vs. monotherapy, baseline disease activity (AS: BASDAI; PsA: DAS28), and baseline functional activity (AS: BASFI; PsA: HAQ). In a secondary analysis, the achievement of BASDAI 50 (AS) and Δ DAS28 ≥ 1.2 (PsA) at 3 months were also considered.

Results: A total of 459 AS and 278 PsA patients were included in the analysis. Mean age of the AS and PsA patient cohorts was 43.9 and 52.0 years, respectively. Mean BASDAI and DAS28 scores in AS and PsA patients were 6.4 and 4.8,

Figure 1. Adjusted Survival Curve for Time to ADA Discontinuation by Achievement of BASDAI 50 at 3 Months



respectively. KM-based mean (95% CI) time to ADA discontinuation was 1.77 (1.72-1.82) years and 1.83 (1.77-1.88) years for AS and PsA patients, respectively.

Among AS patients, BASFI score at baseline was identified as the only significant predictor of ADA survival, (HR [95% CI]: 1.17 [1.08-1.28]). In the secondary analysis considering response to treatment at 3 months, achievement of BASDAI 50 was associated with significantly lower hazard for discontinuation (0.36[0.20-0.65]; Figure 1); in this analysis, age (0.98 [0.97-1.00]) and baseline BASFI score (1.24 [1.11-1.39]) were also significant predictors of ADA retention.

Among PsA patients, male gender was identified as the only significant (positive) predictor of ADA survival, both in the primary (0.50 [0.29-0.85]) and secondary (0.39 [0.18-0.85]) analysis.

Conclusion: The results of this analysis have shown that early achievement of BASDAI 50 is associated with improved long-term retention of ADA treatment among AS patients. Furthermore, gender differences may exist in the real-world survival of ADA treatment in PsA.

Disclosure: L. Bessette, Amgen, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Lilly, Novartis, 2, 5, 8; M. Khraishi, AbbVie Inc., 2, 5, 8; J. Stewart, Pfizer, AbbVie, Merck, Amgen, Celgene, Roche, Novartis, Bristol Myer Squibb, Janssen, 2, 5; A. Chow, AbbVie, BMS, Janssen, Pfizer, Takeda, 8, AbbVie, Amgen, BMS, Celgene, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, Sanofi, UCB, 5; V. Pavlova, Amgen, Abbvie, BMS, Janssen, Lilly, Merck, Novartis, Roche, UCB, Pfizer, 8, Amgen, Abbvie, BMS, Janssen, Lilly, Merck, Novartis, Roche, UCB, Pfizer, 5, UCB, 2; B. Florica, Janssen, Merck, Abbvie, Roche, BMS, Novartis, Pfizer, Celgene, UCB, 2, 5, 8; V. P. Remple, AbbVie Inc., 1.

Abstract Number: 2622

Regional and Temporal Variation in the Baseline Profile of Ankylosing Spondylitis Patients Initiating Adalimumab Following Failure of Non-Biologic Treatment in Canadian Routine Care

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Treatment selection in Canadian routine clinical care is based on the judgment of the treating physician but is also affected by treatment guidelines and regional reimbursement which may vary over time. The objective of this analysis was to describe the regional and temporal variability of the profile of anti-TNF naïve patients with ankylosing spondylitis (AS) at initiation of adalimumab (ADA) following failure of initial non-biologic treatment.

Methods: COMPLETE-AS is an ongoing Canadian observational study of anti-TNF α naïve adults with active AS who require, per the judgment of the treating physician, change in current treatment. Patients are followed for up to 2 years. Regional variation between the following regions was assessed: Alberta/British Columbia/Manitoba (AB/BC/MB) vs. New Brunswick/Newfoundland/Nova Scotia (NB/NL/NS) vs. Ontario (ON) vs. Quebec (QC). In a sensitivity analysis, patients from AB and MB were excluded due to low numbers. Temporal variation over the following periods was assessed: 2011-2012 vs. 2013-2014 vs. 2015-2017. To evaluate the independent impact of region and time period on disease activity (BASDAI) and function (BASFI) multivariate linear regression was used.

Results: A total of 459 patients were included of whom 95 (20.7%) were from AB/BC/MB, 39 (8.5%) from NB/NL/NS, 202 (44%) from ON and 123 (26.8%) from QC. By period, 133 (29%) were enrolled in 2011-2012, 133 (29%) in 2013-2014, and 193 (42%) in 2015-2017.

In univariate analysis, significant regional variation was observed in mean age (range from 41.1 to 48.4; $p=0.013$), gender (males from 46.3% to 64.2%; $p=0.036$), tobacco use (current smoking: 15.4% to 30.7%; $p=0.003$), alcohol use (non-drinker 17.9% to 52.6%; $p=0.007$), disease duration (4.2 to 9.7 years; $p<0.001$), and use of ADA monotherapy (71.6% to 87.2%; $p=0.033$). No differences in BASDAI and BASFI were observed. Similar results were observed in the sensitivity analysis. In terms of temporal variation, more recent years (2015-2017) were associated with lower BASDAI (6.4 vs. 6.7 vs. 6.2; $p=0.040$) and BASFI (5.6 vs. 5.9 vs. 5.1; $p=0.013$) scores without any other differences. In multivariate analysis adjusting for age and gender, enrollment period but not region was associated with BASDAI ($p=0.034$) and BASFI ($p=0.006$) levels, with patients in more recent years having less severe disease when initiating ADA.

Conclusion: The results of this analysis have shown that significant regional and temporal variation exists in the profile patients selected for ADA treatment in Canadian routine care. Furthermore, a significant independent association was identified between more recent years and lower BASDAI and BASFI scores at ADA initiation.

Disclosure: L. Bessette, Amgen, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Lilly, Novartis, 2, 5, 8; M. Khraishi, AbbVie Inc., 2, 5, 8; V. Pavlova, Amgen, Abbvie, BMS, Janssen, Lilly, Merck, Novartis, Roche, UCB, Pfizer, 8, Amgen, Abbvie, BMS, Janssen, Lilly, Merck, Novartis, Roche, UCB, Pfizer, 5, UCB, 2; B. Florica, Janssen, Merck, Abbvie, Roche, BMS, Novartis, Pfizer, Celgene, UCB, 2, 5, 8; V. P. Remple, AbbVie Inc., 1.

Abstract Number: 2623

Efficacy of TNF Inhibitors and Predictive Factors of Clinical Presentation in Patients with Psoriatic Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic arthritis (PsA) is a heterogeneous disease. Patients with PsA may have predominant axial (axPsA) or peripheral (pPsA) manifestations but the factors influencing on this are unknown. Recently, the recommended disease activity indexes have been updated, being these ASDAS for axial manifestations and DAPSA for peripheral manifestations. However, the impact of these changes in the outcomes of patients treated with biological therapies is unclear. Our objective is to analyse the efficacy of treatment in patients with axPsA and pPsA starting TNFi and the predictive factors of clinical presentation in clinical practice.

Methods: An observational study analysing data from a prospective cohort including 93 patients (pts) with axPsA or pPsA treated with TNFi from 2002-2018 was conducted. Demographic information, disease activity indexes (ASDAS for axPsA and DAPSA for pPsA) and laboratory tests were collected before starting TNFi (baseline visit) and 6 months later (6 m visit). At 6 m, the percentage of pts achieving inactive disease (ASDAS <1.3) and low disease activity (LDA)

	Total n=93		p-value
	axPsA n=45	pPsA n=48	
Male, n (%)	28 (62%)	20 (42%)	0.04
BMI, Mean (SD)	27.4 (5.5)	26.4 (5.5)	0.01
Age at diagnosis (years), mean (SD)	37 (15.3)	42 (12.7)	0.02
Age at start biologic (years), mean (SD)	43 (14.1)	51 (13.1)	0.03
Smokers, n (%)	25 (55%)	8 (17%)	0.2
Disease duration (years), mean (SD)	19 (10.8)	18 (8.4)	0.8
Biologic use time (years), mean (SD)	5.8 (8.1)	6.8 (5.3)	0.3
HLA B27, n/N (%)	8/22 (36%)	—	
RF, n/N (%)	—	3/44 (6.8%)	
ACPA, n/N (%)	—	0/45	
αDMArDA, n (%)	28 (69.7%)	35 (74.5%)	0.5
ASDAS, mean (SD)	5.1 (1.2)	—	
hASAS, mean (SD)	—	4.7 (1.3)	
CRP mg/L, mean (SD)	12.9 (14.8)	10.1 (14.7)	0.3
ESR, mean (SD)	29.4 (28.4)	28.8 (20.1)	0.3

(ASDAS 1.3-2.1) for axPsA, or remission (DAPSA < 4) and LDA (DAPSA 4.1-15) for pPsA as well as the percentage of pts achieving clinical improvement (defined as ASDAS-clinically important improvement = delta-ASDAS > 1.1- or delta-DAPSA50) was determined. Baseline predictor factors for developing axial or peripheral manifestations were identified using a univariable and multivariable binary regression models adjusted for confounder factors.

Results: Out of 93 included pts, 45 pts had predominant axPsA and 48 pPsA. Administered TNFi were etanercept for most pts (42%), infliximab in 29%, adalimumab in 22% and golimumab in 7%. Baseline characteristics are shown in Table 1. In axPsA, 49% clinically improved, 56 % pts reached LDA and 35% reached inactive disease. In pPsA, 56% pts clinically improved, 67% pts reached LDA and 25% pts were on remission at 6 m. The univariate analysis demonstrated in our cohort of patients with PsA that patients with younger age at diagnosis (OR, p=3.5; p=0.03), younger age at starting the biologic (OR, p=4.9; p=0.03), obesity (OR, p=6.4; p=0.03), and male gender (OR, p=3.0; p=0.03) had more risk to present axPsA. After multivariable analysis, only the obesity reached significance (p=0.01) for risk of presenting axPsA.

Conclusion: According to newly recommended disease activity indexes (ASDAS and DAPSA) 1 out of 3 pts with axPsA and 1 out of 4 in pPsA is on remission 6 m later after initiating a TNFi in clinical practice. Additionally, around 1 out of 2 clinically improve in both groups. The presence of obesity, male gender and younger age at diagnosis or when initiating TNFi are associated with developing axial predominant manifestations in PsA.

Table 1

Disclosure: D. Benavent, None; C. Plasencia, None; V. Navarro-Compán, None; B. Hernández-Breijo, None; A. Villalba, None; D. Peiteado, None; E. Fernández, None; P. Bogas, None; M. de Diego, None; A. Balsa, None.

Abstract Number: 2624

Cost-Effectiveness of Swapping Strategy for Established Psoriatic Arthritis and Immediate Versus Standard Swapping Strategy for Early Psoriatic Arthritis

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Session Information

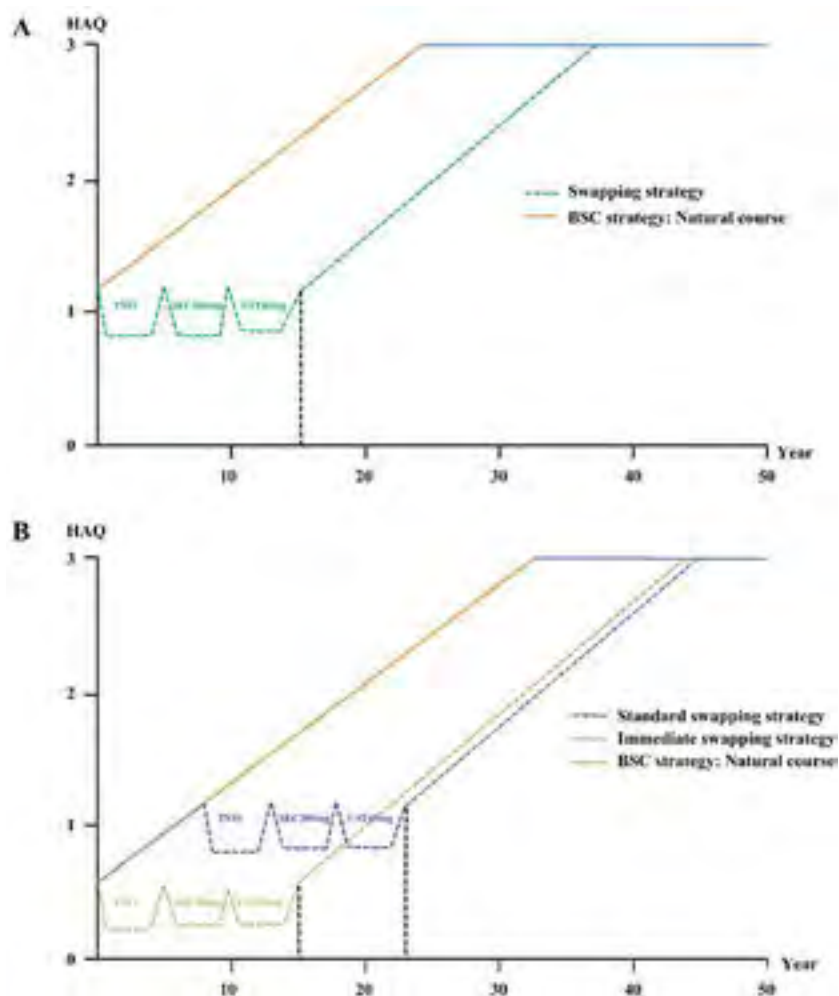
Session Date: Tuesday, October 23, 2018

Background/Purpose: For patients with psoriatic arthritis (PsA) failing the first TNF-inhibitor, switching to biologic DMARDs [bDMARDs] with different mechanism of actions (swapping strategy) may be superior than switching to another anti-TNF (cycling strategy) ^[1,2].

The aims of the study were to evaluate the cost-effectiveness of 1) swapping strategy for established PsA and 2) immediate versus standard swapping strategy for early PsA from the Hong Kong (HK) societal perspective

Methods: A swapping York model with life time horizon was developed for two hypothetical subpopulations: 1) established PsA (age=47, HAQ=1.22, Figure A) received five swapping strategies and 2) early PsA (age=40, HAQ=0.71, Figure B) received immediate (start bDMARDs after diagnosis) or standard (initially given BSC and then start bDMARDs when HAQ increase to 1.22) use of the most cost-effective swapping strategy. Both subpopulations were further classified into mild to moderate psoriasis (MMP, PASI=0.73) and moderate to severe psoriasis (MSP, PASI=12.5). All five swapping strategies started with an anti-TNF, followed by secukinumab 300mg and then ustekinumab 45mg. The cost-effectiveness of each strategy was determined using a willingness-to-pay (WTP) threshold of £32,356/quality-adjusted life-year (QALY) (HK Gross Domestic Product per capita).

Results: For the base-case scenario, all five swapping strategies are cost-effective versus BSC strategy for established PsA, which are associated with greater QALY gain and lower treatment related direct costs, psoriasis cost and productivity loss. In established PsA with MMP and MSP, etanercept swapping strategy is likely to be the most cost-effective strategy with an incremental cost £9,518.93 and £9,084.58 per QALY gained over BSC strategy respectively. For early PsA with MMP and MSP, the base-case results indicated that standard etanercept swapping strategy was cost-saving (£-50,635.74 and £-67,843.32) and more effective (1.20 and 1.32 QALYs); while immediate etanercept swapping strategy was costlier (£13294.95 and £8986.16), more effective (3.82 and 3.27 QALY), and had relative low ICER (£3482.36 and £2745.35 per QALY gained) relative to BSC strategy.



Conclusion: Swapping strategy showed favorable cost-effectiveness for established PsA as well as early PsA. The increased costs of biologic agents are offset by the gain in benefits from long-term HAQ reduction.

Reference: ^[1]Merola JF, et al. Semin Arthritis Rheum 2017;47:29-37

^[2]Cantini F, et al. Semin Arthritis Rheum 2017;47:183-192

^[3]Kane D, et al. Rheumatology (Oxford) 2003; 42:1460-8

Disclosures: This study has been partly presented at EULAR 2018.

Disclosure: D. Wu, None; T. Xu, None; I. T. Cheng, None; S. H. M. Lam, None; J. Yue, None; P. Wong, None; E. Li, None; T. K. Li, None; L. S. Tam, None.

Abstract Number: 2625

TNF Inhibitor Reduces ASDAS Faster and More Stable in Ankylosing Spondylitis Patients: Results from a Real World Prospective Cohort Managed By Smart Phone System

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

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Session Time: 9:00AM-11:00AM

Background/Purpose: The Smart-phone Spondyloarthritis Management System (SpAMS) is a mobile health tool, specifically designed to conduct prospective clinical studies on SpA/AS in China, using real-world clinical workflows. The aim of this study was to explore the effectiveness of tumor necrosis factor inhibitors (TNFi) in controlling disease activity in a real-world setting.

Methods: The Chinese Ankylosing Spondylitis Prospective Imaging Cohort (CASPIC) is a nation-wide, ongoing, prospective, and state-funded cohort study, launched in conjunction with SpAMS. All patients fulfilled the 1984 modified NY criteria. Patients on medication and with full medication records were enrolled in this study. Generalized additive mixed models were used to study the relationship between TNF inhibitor(TNFi) treatment (users or non-users) and AS Disease Activity Score (ASDAS)during the follow-up period. The model adjusted for gender, symptom duration, HLA-B27, BMI, smoking status, peripheral arthritis, and treatment with NSAIDs and DMARDs.

Results: A total of 1201 AS patients were recruited in CASPIC from April 2016 to April 2018. Sixty-eight patients (5.7%) with no medication records or withdrawals were removed (Figure 1).The characteristics of 332 TNFi user and 801 nonuser were summarized in Table 1. Mean (SD) followed-up duration were 12.3 (5.9) months. Mean (SD) duration of TNFi use were 9.3 (5.9) months. TNFi user were slightly younger, more likely to present with peripheral arthritis, had higher baseline disease activity scores, higher baseline inflammation marker levels, and were less likely to be prescribed NSAIDs and DMARDs. TNFi user had a higher ASDAS at baseline which subsequently declined rapidly, and then remained at a

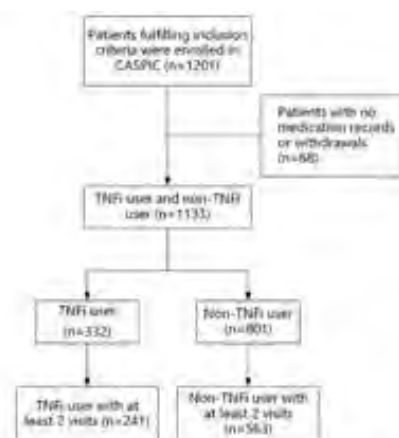


Figure 1. Flow chart of the participants enrolled in this study

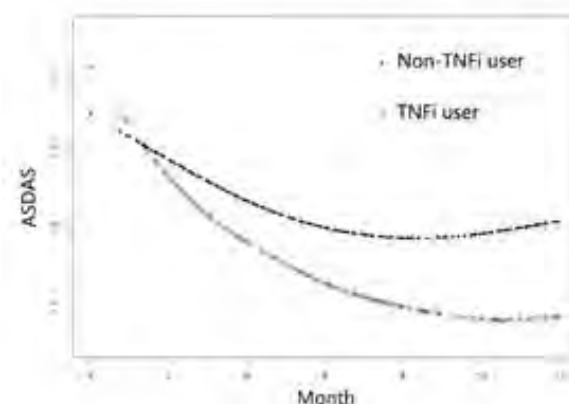


Figure 2. Smoothing analysis curves pertaining to ASDAS and follow-up duration stratified by TNFi treatment status

consistently lower level throughout the first 12 months than did nonuser (Figure 2). ASDAS decline were significantly more in TNFi user than they were in those of nonuser in the first 3 months (0.62 units, 95% CI 0.13 to 1.10, P=0.017).

Conclusion: The use of TNFi in AS patients may reduce disease activity in a faster and more stable fashion.

Table

Characteristic	Non-TNFi user N=801	TNFi user N=332	P value
Male sex, %	84.0	81.3	0.269
Age, year, mean(SD)	31.1 (8.9)	29.2 (7.9)	<0.001*
Symptom duration, year, mean(SD)	8.4 (6.3)	8.7 (5.7)	0.533
BMI, kg/m ² , mean(SD)	23.6 (4.1)	23.3 (4.4)	0.250
HLA-B27 positive, %	88.6	90.7	0.326
PhGA, mean(SD)	2.1 (1.3)	2.5 (1.4)	<0.001*
BASFI, mean(SD)	1.5 (1.6)	1.9 (1.8)	<0.001*
ESR, mean(SD)mm/hour	14.3 (15.5)	23.5 (23.4)	<0.001*
CRP, mean(SD) mg/L	11.7 (22.9)	21.6 (32.0)	<0.001*
ASDAS, mean(SD)	2.0 (0.9)	2.4 (1.1)	<0.001*
Enthesitis, %	21.8	32.5	<0.001*
Peripheral arthritis, %	9.3	22.2	<0.001*
NSAIDs, %	99.0	94.0	<0.001*
DMARDs, %	71.2	54.5	<0.001*

Disclosure: X. Ji, None; J. Zhu, None; J. Zhang, None; F. Huang, None.

Abstract Number: 2626

Normalization of CRP Levels and Clinical Response to Ixekizumab in Patients with Psoriatic Arthritis: Results from the Spirit Studies

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: It is important to understand the association between early changes in inflammatory biomarkers and treatment response at later times after initiation of a biologic DMARD. In the SPIRIT-P1 (NCT01695239) and SPIRIT-P2 (NCT02349295) phase 3, multicenter, double-blind studies of patients with active PsA, high-sensitivity CRP (hs-CRP) levels declined rapidly during the first 4 weeks (wks) of treatment with ixekizumab (IXE), a high affinity monoclonal antibody against IL-17A. This post-hoc analysis used data from the 2 studies to describe and compare efficacy outcomes at wk 24 according to change in hs-CRP levels from baseline (wk 0) to wk 4.

Methods: In SPIRIT-P1, biologic naïve patients received subcutaneous IXE 80 mg every 4 (Q4W; N=107) or 2 wks (Q2W; N=103) after a starting dose of 160 mg at wk 0, or adalimumab 40 mg every 2 wks (N=101), or placebo (PBO; N=106).¹ In SPIRIT-P2, patients with an inadequate response/intolerance to TNF inhibitors received IXE Q4W (N=122) or Q2W (N=123), or PBO (N=118).² For this analysis, the 2 IXE dose groups were combined and 3 patient hs-CRP subgroups were defined: normal (<6.0 mg/L) hs-CRP levels at wks 0 and 4; hs-CRP levels that normalized during treatment (elevated ≥6.0 mg/L at wk 0, normal at wk 4); and elevated hs-CRP levels (normal/elevated at wk 0, elevated at wk 4). Between-treatment differences (combined IXE vs. PBO) across hs-CRP subgroups in efficacy outcomes were evaluated using the Cochran-Mantel-Haenszel general association test.

Results: Baseline patient characteristics, including BMI, was generally similar between the 3 hs-CRP subgroups, but with a numerically higher disease activity in those with elevated hs-CRP. Across the 3 subgroups, responses to active treatment were rapid and sustained at wk 24. In both studies, differences between IXE and PBO for clinical outcomes (ACR20/50/70, minimal disease activity, DAPSA low disease activity/remission) differed statistically significantly across hs-CRP subgroups as early as wk 4 or 8 (Tables 1 and 2). Numerically greater differences in the normalized hs-CRP subgroup was

observed. Although performed on a smaller sample size, efficacy results across the 3 subgroups were generally consistent with those previously reported at wk 24 for the overall population in both studies.

Conclusion: In PsA, a response can be achieved after 24 wks of treatment with IXE regardless of prior biologic use, even when hs-CRP is still elevated at wk 4.

References:

1. Mease PJ et al. *Ann Rheum Dis*. 2017;**76**:79–87.
2. Nash P et al. *Lancet*. 2017;**389**:2317–27.

Table 1. Response rates according to hs-CRP levels in patients with active PsA from the SPIRIT-P1 study. Results are expressed as proportions of patients in the ITT population calculated using NRI.

	Stable, normal hs-CRP		Normalized hs-CRP		Persistently elevated (increased) hs-CRP	
Response	PBO (N=34)	IXE (N=77)	PBO (N=10)	IXE (N=68)	PBO (N=59)	IXE (N=55)
ACR20						
Week 4***	17.7%	41.6%	10.0%	54.4%	18.6%	38.2%
Week 8***	41.2%	58.4%	40.0%	60.3%	28.8%	61.8%
Week 12***	41.2%	54.5%	40.0%	66.2%	25.4%	60.0%
Week 24*	47.1%	58.4%	50.0%	86.8%	40.7%	65.5%
ACR50						
Week 4***	0.0%	18.2%	0.0%	27.9%	1.7%	18.2%
Week 8***	14.7%	27.3%	10.0%	35.3%	6.8%	32.7%
Week 12***	5.9%	37.7%	0.0%	41.2%	5.1%	30.9%
Week 24**	17.6%	42.9%	30.0%	57.4%	18.6%	34.5%
ACR70						
Week 4ns	0.0%	2.6%	0.0%	10.3%	1.7%	1.8%
Week 8*	5.9%	14.3%	10.0%	16.2%	0.0%	7.3%
Week 12***	0.0%	14.3%	0.0%	23.5%	0.0%	9.1%
Week 24**	5.9%	28.6%	0.0%	36.8%	10.2%	18.2%
MDA_{PASI}						
Week 4**	2.9%	10.4%	10.0%	13.2%	1.7%	14.6%
Week 8***	5.9%	26.0%	10.0%	26.5%	3.4%	18.2%
Week 12***	11.8%	28.6%	10.0%	30.9%	0.0%	20.0%
Week 24ns	20.6%	37.7%	50.0%	42.6%	11.9%	27.3%
DAPSA LDA						
Week 4*	12.1%	19.5%	10.0%	33.8%	6.8%	18.2%
Week 8**	14.7%	37.7%	30.0%	29.4%	8.5%	23.6%
Week 12*	26.5%	39.0%	30.0%	32.4%	8.5%	20.0%
Week 24ns	23.5%	37.7%	40.0%	38.2%	22.0%	27.3%
DAPSA remission						
Week 4ns	0.0%	2.6%	0.0%	1.5%	0.0%	1.8%
Week 8ns	2.9%	6.5%	10.0%	11.8%	0.0%	3.6%
Week 12*	2.9%	11.7%	0.0%	13.2%	0.0%	3.6%
Week 24*	8.8%	22.1%	20.0%	23.5%	1.7%	14.5%

^{ns} not significant, *p<0.05, **p<0.01, ***p<0.001 for differences between IXE and PBO across the 3 hs-CRP groups (Cochran-Mantel-Haenszel general association test).

Abbreviations: ACR20/50/70=20/50/70% improvement from baseline in ACR criteria; ACR=American College of Rheumatology; DAPSA=Disease Activity Index for PsA; hs-CRP=high sensitivity C-reactive protein; ITT=intent-to-treat; IXE=ixekizumab; LDA=low disease activity; MDA_{PASI}=minimal disease activity according to the Psoriasis Area and Severity Index; NRI=non-responder imputation; PBO=placebo; PsA=psoriatic arthritis

Table 2. Response rates according to hs-CRP levels in patients with active PsA from the SPIRIT-P2 study. Results are expressed as proportions of patients in the ITT population calculated using NRI.

	Stable, normal hs-CRP		Normalized hs-CRP		Persistently elevated (increased) hs-CRP	
Response	PBO (N=49)	IXE (N=116)	PBO (N=11)	IXE (N=53)	PBO (N=55)	IXE (N=66)
ACR20						
Week 4***	22.4%	36.2%	27.3%	67.9%	9.1%	25.8%
Week 8***	20.4%	42.2%	18.2%	62.3%	10.9%	34.8%
Week 12***	32.7%	48.3%	18.2%	66.0%	14.5%	37.9%
Week 24**	34.7%	50.0%	36.4%	75.5%	27.3%	43.9%
ACR50						
Week 4**	6.1%	17.2%	9.1%	22.6%	0.0%	4.5%
Week 8***	2.0%	17.2%	0.0%	35.8%	0.0%	16.7%
Week 12***	4.1%	32.8%	9.1%	39.6%	1.8%	25.8%
Week 24***	12.2%	30.2%	9.1%	52.8%	10.9%	28.8%
ACR70						

Table . (Cont'd)

Response	Stable, normal hs-CRP		Normalized hs-CRP		Persistently elevated (increased) hs-CRP	
	PBO (N=49)	IXE (N=116)	PBO (N=11)	IXE (N=53)	PBO (N=55)	IXE (N=66)
Week 4 ^{ns}	6.1%	4.3%	0.0%	11.3%	0.0%	0.0%
Week 8 ^{**}	2.0%	7.8%	0.0%	18.9%	0.0%	6.1%
Week 12 ^{**}	2.0%	11.2%	0.0%	17.0%	1.8%	12.1%
Week 24 ^{***}	0.0%	12.1%	9.1%	32.1%	1.8%	15.2%
MDA_{PASI}						
Week 4 ^{ns}	8.2%	11.2%	0.0%	11.3%	1.8%	7.6%
Week 8 ^{**}	8.2%	21.6%	0.0%	13.2%	1.8%	15.2%
Week 12 ^{***}	10.2%	23.3%	0.0%	24.5%	1.8%	18.2%
Week 24 ^{***}	10.2%	25.0%	0.0%	34.0%	1.8%	24.2%
DAPSA LDA						
Week 4 ^{ns}	30.6%	21.6%	0.0%	20.8%	3.6%	13.6%
Week 8 ^{**}	22.4%	30.2%	0.0%	32.1%	7.3%	22.7%
Week 12 ^{***}	22.4%	38.8%	18.2%	34.0%	1.8%	28.8%
Week 24 ^{**}	22.4%	37.1%	27.3%	49.1%	16.4%	31.8%
DAPSA remission						
Week 4 ^{ns}	6.1%	5.2%	0.0%	7.6%	0.0%	1.5%
Week 8 [*]	2.0%	7.8%	0.0%	7.5%	0.0%	3.0%
Week 12 ^{**}	2.0%	6.0%	0.0%	7.5%	0.0%	10.6%
Week 24 ^{**}	2.0%	11.2%	0.0%	13.2%	1.8%	10.6%

^{ns}not significant, *p<0.05, **p<0.01, ***p<0.001 for differences between IXE and PBO across the 3 hs-CRP groups (Cochran-Mantel-Haenszel general association test).

Abbreviations: ACR20/50/70=20/50/70% improvement from baseline in ACR criteria; ACR=American College of Rheumatology; DAPSA=Disease Activity Index for PsA; hs-CRP=high sensitivity C-reactive protein; ITT=intent-to-treat; IXE=ixekizumab; LDA=low disease activity; MDA_{PASI}=minimal disease activity according to the Psoriasis Area and Severity Index; NRI=non-responder imputation; PBO=placebo; PsA=psoriatic arthritis

Disclosure: B. Combe, Pfizer, MSD, and Roche-Chugai; Consultant: Pfizer, UCB, Bristol-Myers Squibb, Janssen, Eli Lilly and Company, MSD, Roche-Chugai, AbbVie, Novartis, 2, Pfizer, Bristol-Myers Squibb, Eli Lilly and Company, MSD, 8; P. Emery, Consulting; Eli Lilly and Company, Abbvie, BMS, MSD, Novartis, Pfizer, Roche, Samsung, Sandoz, UCB, 5; A. Boonen, Lilly, Novartis, Sandoz, Janssen, 5, Lilly, Novartis, Sandoz, Janssen, 9, Abbvie, Celgene, 2; S. Liu Leage, Eli Lilly and Company, 1, 3; C. Sapin, Eli Lilly and Company, 1, 3; N. Bello, Eli Lilly and Company, 1, 3; M. Dougados, Abbvie, Pfizer, Eli Lilly and Company, Novartis, UCB, Merck, Roche, BMS, UCB, 2, 5.

Abstract Number: 2627

Not All Clinical Responders in SLE Are Equal: Comparison of Subcutaneous Belimumab + Standard of Care Responders to Placebo + Standard of Care Responders

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To determine whether degree of response among responders to subcutaneous (SC) belimumab (BEL) + standard of care (SoC) is greater than that for responders to placebo (PBO) + SoC.

Methods: Patients with SELENA-SLEDAI (SS) ≥8 on stable SoC ≥30 days were randomized (2:1) to weekly SC BEL 200 mg + SoC or PBO + SoC in BLISS-SC (NCT01484496). Primary endpoint was SLE Responder Index 4 (SRI4) at week (Wk) 52 (≥4-point SS reduction, <0.3 increase in Physician's Global Assessment [PGA], and 0 new BILAG A or ≤1 new BILAG B organ domain scores, all vs baseline [BL]). SRI4 responders were compared based on treatment (BEL vs PBO) for changes in clinical and laboratory parameters. SRI4 non-responders were also evaluated.

Results: 61.4% of BEL + SoC and 48.4% of PBO + SoC were SRI4 responders¹. BEL + SoC responders had better outcomes than PBO + SoC responders at Wk 52 (Table 1) and during the trial: greater % reductions in SS (Wk 20-52, $p \leq 0.0199$) and PGA scores (Wk 20-52, $p \leq 0.0304$); organ system improvement (SS Wk 52 immunologic [$p = 0.0064$] and vascular [$p = 0.0199$] and BILAG vasculitis [Wk 16-52, $p \leq 0.0301$]); 65% reduced risk of severe flare (HR=0.35 [95% CI: 0.13, 0.94], $p = 0.0367$); normalized complement levels (Wk 16-20,28-36, 44, 52: C3 $p \leq 0.0232$ and Wk 16-24, 36-52: C4 $p \leq 0.0303$). Percent of patients with ≥ 5 , 6, 7, or 8 point reductions in SS excluding serology (anti-dsDNA, complement) were numerically greater for BEL + SoC responders from Wk 8-52, with significant differences at earlier time points (Table 2). Among patients receiving BL prednisone >7.5 mg/day, more BEL + SoC responders reduced their CS dose $\geq 25\%$ to ≤ 7.5 mg/day during Wks 40-52 vs PBO + SoC responders but did not reach statistical significance (23.8% vs 14.6%, OR 1.79 [95% CI: 0.89, 3.59], $p = 0.1008$). Anti-dsDNA shifts and FACIT-fatigue score improvements were similar between groups. Non-responders had no significant differences, irrespective of treatment, in changes in SS (\pm serology) or PGA, organ system involvement, flares, steroid use, complement, anti-dsDNA, or FACIT-fatigue scores. BL BAFF levels (range 1.574-1.769 ng/mL) and SoC medications were similar across treatment groups regardless of SRI4 response. No gender differences were noted.

Conclusion: SRI4 responders with BEL + SoC had greater degree of response compared to PBO + SoC based on clinical and serological measures. Earlier SS reductions (\pm serology) for BEL + SoC responders points to more rapid clinical improvement. These observations add robustness to existing knowledge that treatment with BEL could add therapeutic benefit to SoC alone.

Reference:

1. *Arth Rheum* 2017;69:1016-27.

Table 1 – Comparison of changes from BL to Wk 52 in clinical and laboratory parameters between BEL + SoC SRI4 Responders and PBO + SoC SRI4 Responders (based upon intent-to-treat population)

	BEL + SoC	PBO + SoC	p-value
Patients, n	340	135	
SELENA-SLEDAI reduction, n (%)			
≥ 5 point reduction	283 (83.2%)	95 (70.4%)	0.0024
≥ 6 point reduction	274 (80.6%)	94 (69.6%)	0.0145
≥ 7 point reduction	178 (52.4%)	53 (39.3%)	0.0110
≥ 8 point reduction	174 (51.2%)	50 (37.0%)	0.0059
Number of organ domains improved			
SELENA-SLEDAI, mean \pm SE	2.1 \pm 0.04	1.9 \pm 0.06	0.0233
BILAG, mean \pm SE	1.6 \pm 0.04	1.6 \pm 0.07	0.1230
% change in PGA from BL in patients, mean \pm SE	-67.1 \pm 1.5	-58.2 \pm 2.9	0.0054
Prednisone reduction by $\geq 25\%$ from	49/206 (23.8%)	12/82 (14.6%)	0.1008
BL to ≤ 7.5 mg/day during Wks 40-52 in patients with BL prednisone >7.5 mg/d, n/N (%)			
Patients with flares by SFI (SLE Fare Index), n (%)			
Severe	8 (2.4%)	8 (5.9%)	0.0367
Mild-Moderate	189 (55.6%)	83 (61.5%)	0.2061
C3 complement shifts - Low to Normal/High, n/N (%)	74/150 (49.3%)	13/55 (23.6%)	0.0013
C4 complement shifts - Low to Normal/High, n/N (%)	52/91 (57.1%)	7/29 (24.1%)	0.0026
Anti-dsDNA shifts - Positive to Negative, n/N (%)	50/242 (20.7%)	21/94 (22.3%)	0.7666
FACIT-Fatigue Scale Score	191/340 (56.2%)	65/135 (48.1%)	0.2868
exceeding ≥ 4 (minimal clinically important difference), n/N (%)			

Table 2 – SELENA SLEDAI reductions ≥ 5 , 6, 7, or 8 points excluding serology (complement, anti-dsDNA) – Study weeks with significant differences ($p < 0.05$) for BEL + SoC SRI4 Responders vs PBO + SoC SRI4 Responders (based upon intent-to-treat population)

	BEL + SoC	PBO + SoC	p-value
Patients, n	340	135	
SELENA-SLEDAI reduction, n (%)			
Wk 8			
≥ 8 point reduction	48 (14.1%)	10 (7.4%)	0.0444
Wk 12			
≥ 7 point reduction	81 (23.8%)	20 (14.8%)	0.0344
≥ 8 point reduction	78 (22.9%)	19 (14.1%)	0.0321
Wk 16			
≥ 7 point reduction	101 (29.7%)	26 (19.3%)	0.0216
≥ 8 point reduction	96 (28.2%)	24 (17.8%)	0.0192
Wk 20			
≥ 5 point reduction	194 (57.1%)	62 (45.9%)	0.0321
≥ 7 point reduction	113 (33.2%)	28 (20.7%)	0.0075
≥ 8 point reduction	108 (31.8%)	27 (20.0%)	0.0128
Wk 24			

Table . (Cont'd)

	BEL + SoC	PBO + SoC	p-value
≥ 7 point reduction	126 (37.1%)	31 (23.0%)	0.003
≥ 8 point reduction	120 (35.3%)	28 (20.7%)	0.0020
Wk 44			
≥ 5 point reduction	249 (73.2%)	85 (63.0%)	0.0341
Wk 48			
≥ 5 point reduction	249 (73.2%)	86 (63.7%)	0.0448

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Abstract Number: 2628

Hydroxychloroquine and Prednisone Have Different Effects on Antiphospholipid Antibodies in SLE, with Hydroxychloroquine Not Reducing IgA Anticardiolipin

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Antiphospholipid antibodies in SLE may be changed by treatment, but past studies have been conflicting. We examined the impact of starting or stopping two treatments (hydroxychloroquine and prednisone) on levels of antiphospholipid antibodies.

Methods: 943 SLE patients, who had at least 10 quarterly visits for testing for each anticardiolipin isotype (IgG, IgM and IgA) and dRVVT (lupus anticoagulant; LA), were included in the study. Treatment was recorded at every visit. Visits during which a patient was treated were compared to visits when the same patient was not treated with respect to levels of each antibody using conditional logistic regression.

Results: Hydroxychloroquine treatment reduced the levels of all antibodies, except for IgA aCL (Table 1).

Table 1 – Hydroxychloroquine Reduces All Antiphospholipid Antibodies EXCEPT for aCL IgA.

Definition of aPL	Number of patients informative for the analysis ¹	Odds ratio of having the antiphospholipid antibody on visits with HCQ compared to visits without HCQ	P-value
aCL IgG>20	149	0.56 (0.43, 0.72)	<0.0001
aCL IgG> 40	56	0.35 (0.22, 0.55)	<0.0001
aCL IgM>20	169	0.51 (0.39, 0.67)	0.0002
aCL IgM> 40	80	0.56 (0.36, 0.87)	0.010
aCL IgA>20	56	1.08 (0.62, 1.87)	0.80
aCL IgA> 40	25	2.28 (0.99, 5.26)	0.053
dRVVT>45	268	0.65 (0.53, 0.80)	<0.0001
Any of the above	377	0.64 (0.55, 0.75)	<0.0001

¹ In each cell, individuals are informative if they have at least one visit with antiphospholipid positivity, at least one visit without antiphospholipid antibody, at least one visit with when treated with HCQ, and at least one visit when not treated with HCQ. Prednisone reduced aCL IgG and aCL IgA, but not aCL IgM or dRVVT (seconds prolongation) (Table 2).

Table 2 – Prednisone Reduces aCL IgG and IgA but not lupus anticoagulant (by dRVVT).

Definition of Antiphospholipid	Number of informative strata	Current Prednisone Dose	Odds ratio of having aPL at visits by Prednisone exposure	P-value
aCL IgG>20	2207	No Prednisone	1.0 (Ref)	<0.0001
		Some but less than 10mg/d	0.54 (0.40, 0.72)	
		10+mg/day	0.35 (0.25, 0.49)	
aCL IgG>40	83	No Prednisone	1.0 (Ref)	0.16
		Some but less than 10mg/d	0.68 (0.40, 1.16)	
		10+mg/day	0.57 (0.32, 1.03)	
aCL IgM>20	231	No Prednisone	1.0 (Ref)	0.19
		Some but less than 10mg/d	1.23 (0.90, 1.67)	
		10+mg/day	0.88 (0.62, 1.23)	
aCL IgM>40	110	No Prednisone	1.0 (Ref)	0.059
		Some but less than 10mg/d	1.65 (0.98, 2.78)	
		10+mg/day	1.03 (0.59, 1.80)	
aCL IgA>20	80	No Prednisone	1.0 (Ref)	0.058
		Some but less than 10mg/d	0.57 (0.32, 1.02)	
		10+mg/day	0.49 (0.24, 0.97)	
aCL IgA>40	32	No Prednisone	1.0 (Ref)	0.57
		Some but less than 10mg/d	1.38 (0.46, 4.10)	
		10+mg/day	2.69 (0.78, 9.34)	
dRVVT <45	338	No Prednisone	1.0 (Ref)	0.64
		Some but less than 10mg/d	1.07 (0.82, 1.39)	
		10+mg/day	1.17 (0.88, 1.56)	
Any of the above	511	No Prednisone	1.0 (Ref)	0.90
		Some but less than 10mg/d	0.99 (0.81, 1.20)	
		10+mg/day	0.86 (0.69, 1.07)	

Conclusion: Hydroxychloroquine use was associated with reduced lupus anticoagulant (by seconds of prolongation) and reduced titers for most of the isotypes of anticardiolipin, except for IgA. Prednisone did not reduce the seconds of dRVVT prolongation. Anticardiolipin IgA seemed the most resistant to therapy. These data will help clinicians pick prophylactic therapy, which needs to be based on the antiphospholipid subtype.

Disclosure: M. Petri, EMD Serono, 5, Exagen, 2, Janssen, 5, GSK, 5, AstraZeneca, 2, Inova Diagnostic, 5, Novartis, 5, Amgen Inc., 5, Decision Resources, 5, Medscape, 5, Eli Lilly and Co., 5, Quintiles, 5; M. Avci, None; L. S. Magder, None.

Abstract Number: 2629

Longitudinal Analysis of Persistent Positivity of Antiphospholipid Antibodies in Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: ‘Persistent positivity’ has been a part of laboratory criteria for antiphospholipid syndrome classification criteria and requires two positive tests. We investigated the clinical utility of multiple measures of lupus anticoagulant and anticardiolipin antibodies in SLE patients over the course of clinical care.

Methods: We studied 943 SLE patients in a large single-center cohort who were assessed for lupus anticoagulant (by dRVVT) and anticardiolipin (aCL) IgG, IgM and IgA at at least 10 clinic visits. For each patient, we determined the percent of follow-up time positive for antiphospholipid antibodies and assessed the relationship between this percent and lifetime history of thrombosis.

Results: Among those ever positive for antiphospholipid antibodies, the large majority of SLE patients were positive less than 25% of time followed (Table 1).

Table 1. Most SLE Patients are Positive for aCL or dRVVT Less Than 25% of time followed

aPL definition	Proportion of time during follow-up in which aPL were positive				
	0	>0-0.25	>0.25-0.5	>0.5-0.75	>0.75
aCL IgG \geq 20	728 (77%)	149 (16%)	33 (4%)	15 (2%)	18 (2%)
aCL IgG \geq 40	856 (91%)	66 (7%)	11 (1%)	5 (1%)	5 (1%)
aCL IgM \geq 20	693 (73%)	185 (20%)	26 (3%)	14 (1%)	25 (3%)
aCL IgM \geq 40	829 (88%)	85 (9%)	14 (1%)	7 (1%)	8 (1%)
aCL IgA \geq 20	861 (91%)	69 (7%)	9 (1%)	0 (0%)	4 (<1%)
aCL IgA \geq 40	909 (96%)	29 (3%)	2 (<1%)	1 (<1%)	2 (<1%)
dRVVT>45	564 (60%)	273 (29%)	49 (5%)	22 (2%)	35 (4%)
Any of above	378 (40%)	369 (39%)	90 (10%)	35 (4%)	71 (8%)

For the lupus anticoagulant, there was a progressively increasing association of history of thrombosis with greater proportion of time positive (Table 2). For anticardiolipin antibodies or lupus anticoagulant, even those with relatively infrequent positive measures had a greater likelihood of a history of thrombosis than those who were never positive.

Table 2: Associations of aCL and dRVVT with Thrombosis.

aPL Definition	Proportion of time with aPL	Any Thrombosis			
		N	Number (%) with Thrombosis	RR1 (95% CI)	P-value
aCL IgG>20	0	728	138 (19%)	1.0 (Ref)	
	>0-0.25	149	46 (31%)	1.7 (1.2, 2.3)	0.0034
	>0.25-0.5	33	9 (27%)	1.5 (0.9, 2.5) ²	0.13
	>0.5-.75	15	1 (7%)		
	>0.75	18	7 (39%)		
aCL IgG>40	0	856	175 (20%)	1.0 (Ref)	
	>0-0.25	66	20 (30%)	1.5 (0.9, 2.3)	0.11
	>0.25-0.5	11	2 (18%)	1.8 (0.8, 4.0) ²	0.16
	>0.5-.75	5	2 (40%)		
	>0.75	5	2 (40%)		
aCL IgM>20	0	693	138 (20%)	1.0 (Ref)	
	>0-0.25	185	41 (22%)	1.2 (0.9, 1.8)	0.24
	>0.25-0.5	26	8 (31%)	1.7 (1.1, 2.7) ²	0.020
	>0.5-.75	14	3 (21%)		
	>0.75	25	11 (44%)		
aCL IgM>40	0	829	166 (20%)	1.0 (Ref)	
	>0-0.25	85	24 (28%)	1.4 (0.9, 2.2)	0.099
	>0.25-0.5	14	4 (29%)	2.2 (1.2, 4.0) ²	0.012
	>0.5-.75	7	3 (43%)		
	>0.75	8	4 (50%)		
aCL IgA>20	0	861	177 (21%)	1.0 (Ref)	
	>0-0.25	69	18 (26%)	1.1 (0.7, 1.9)	0.59
	>0.25-0.5	9	4 (44%)	2.1 (0.9, 4.7) ²	0.079
	>0.5-.75	0			
	>0.75	4	2 (50%)		
aCL IgA>40	0	909	190 (21%)	1.0 (Ref)	
	>0-0.25	29	9 (31%)	1.3 (0.7, 2.5)	0.45
	>0.25-0.5	2	1 (50%)	1.7 (0.4, 6.8) ²	0.46
	>0.5-.75	1	0 (0%)		
	>0.75	2	1 (50%)		
dRVVT>45	0	564	91 (16%)	1.0 (Ref)	
	>0-0.25	273	68 (25%)	1.5 (1.1, 2.0)	0.018
	>0.25-0.5	49	19 (39%)	2.7 (1.6, 4.43)	0.0001
	>0.5-.75	22	8 (36%)	2.2 (1.1, 4.5)	0.033
	>0.75	35	15 (43%)	3.4 (2.0, 5.9)	<0.0001
Any of the above	0	378	60 (16%)	1.0 (Ref)	
	>0-0.25	369	81 (22%)	1.3 (1.0, 1.9)	0.095
	>0.25-0.5	90	25 (28%)	1.8 (1.1, 2.8)	0.016
	>0.5-.75	35	8 (23%)	1.5 (0.7, 3.1)	0.31
	>0.75	71	27 (38%)	2.6 (1.6, 4.1)	<0.0001

¹ Based on a Cox Model. ² RR and p-value are for >0.25-0.5, >0.5-0.75, and >0.75 groups combined compared to Reference.

Conclusion: In SLE, antiphospholipid antibody positivity tends to be at a minority of visits. Yet, even those with sporadic positive findings are at increased risk of thrombosis. This contrasts with the natural history of primary antiphospholipid antibodies/syndrome. These data strongly support prophylactic therapy in those who are sporadically positive.

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Complement C4d Split Products in Combination with Lupus Anticoagulant and Low Complement Associate with Thrombosis in Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

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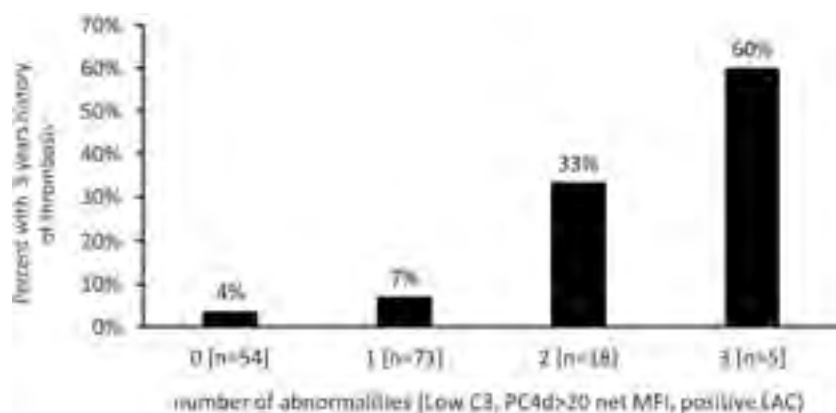
Background/Purpose: Lupus anticoagulant (LAC) is an established risk factor for thrombosis in systemic Lupus erythematosus (SLE). Emerging data suggest that activation of the complement system is also involved in the pathogenesis of thrombosis. Our objective was to evaluate the relationships between complement C4d split products deposited on erythrocytes (EC4d), Platelets (PC4d) and thrombosis in SLE.

Methods: This was a cross sectional analysis of 148 consented SLE patients (by ACR or SLICC criteria; 82% ANA positive [$>1:80$] by indirect immunofluorescence; mean age: 47 ± 1 years, 32% taking prednisone; mean SELENA-SLEDAI: 2.5 ± 0.2 points). SLE were classified with ($n=16$, 11%) or without ($n=132$, 89%) a history of thrombotic events (venous or arterial) in the past 5 years. EC4d and PC4d levels were measured using quantitative flow cytometry, and expressed as mean fluorescence intensity (MFI) (abnormal EC4d >14 net MFI, PC4d >20 net MFI, each corresponding to the 99th percentile of normal healthy group). Complement C3, C4 and LAC were measured using immunochemistry (low C3 <81 mg/dl, low C4 <12.9 mg/dl) and Dilute Russell Viper Venom Time (positive DRVVT >37 seconds), respectively. Statistical analysis consisted of Mann Whitney test and logistic regression.

Results: SLE with a history of thrombosis in the past 5 years presented with 5.5 and 2.2-fold higher median PC4d (27 [IQR: 8-79 net MFI] vs 5 [IQR: 2-14 net MFI] net MFI) and EC4d (19 [IQR: 9-59 net MFI] vs 9 [IQR: 6-19] net MFI) levels, respectively, than SLE without thrombotic events ($p<0.001$; $n=148$). Low C3 (OR=10.5 [CI 95%: 2.6-42.0]), low C4 (OR=3.5 [CI 95%: 1.1-11.1]), abnormal PC4d (OR=19.0 [CI 95%: 3.7-96.4; $n=148$]), EC4d (OR=4.0 [CI 95%: 1.3-11.8]), and LAC (OR=5.3 [CI 95%: 1.1-24.5; $n=144$]) were all significantly associated with thrombosis ($p<0.035$). Prednisone was also associated with thrombosis (OR=3.2 [CI 95%: 1.1-8.9]) ($p=0.037$). Multivariate analysis revealed that low C3, abnormal PC4d and LAC were all independently and significantly associated with thrombosis ($p<0.027$) and the cumulative presence of these abnormalities resulted in higher likelihood of thrombosis (OR range: 81.9 CI 95%: 9.7-688.5; $n=144$) ($p<0.001$) (Figure). These results remained significant after adjusting for prednisone.

Conclusion: Complement C4d split products associate with thrombotic events in SLE, independent of other risk factors. A composite score of risk factors performed better than single risk factors alone, and should be studied prospectively.

Disclosure: M. Petri, Exagen Diagnostics, Inc., 2; J. Conklin, Exagen Diagnostics Inc., 3; R. Apilado, Exagen Diagnostics, 3; T. O'Malley, Exagen Diagnostics, 3; J. Ligayon, Exagen Diagnostics, Inc, 3; L. Wolover, Exagen Diagnostics, Inc., 3; T. Dervieux, Exagen, 3.



Hydroxychloroquine Blood Levels Are Significantly Associated with Cardiovascular Risk Factors

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Background/Purpose: In studies of SLE patients, the benefits of hydroxychloroquine (HCQ) extend beyond control of disease activity. In particular, HCQ use has decreased multiple cardiovascular risk factors (cholesterol and risk of diabetes) and reduced thrombosis in those with antiphospholipid antibodies. However, the amount of HCQ needed to obtain these benefits has not been ascertained. We asked whether blood HCQ levels were associated with cardiovascular risk benefit.

Methods: HCQ blood levels were measured by liquid chromatography-tandem mass spectrometry as described by Füzéry, et al (Clin Chim Acta 2013;421:79-84). We looked at the within-person relationship between HCQ blood concentration and three cardiovascular risk factors (systolic or diastolic blood pressure, cholesterol and glucose). To perform this analysis we calculated the mean HCQ blood level across each person. For each visit, we calculated the difference between the HCQ blood level at that particular visit and the patient's mean. We then assessed whether there was a relationship between these differences and the patient's cardiovascular risk factor level at a particular visit. The results indicate whether changes in HCQ blood concentration correspond to changes in cardiovascular risk factors.

Results: The association between changes in HCQ blood concentration and changes in cardiovascular risk factors is shown in Table 1.

Table 1. Association between changes in HCQ blood concentration and changes in cardiovascular risk factors.

Cardiovascular Risk Factor	Expected change in cardiovascular risk factor per 500 ng/ml increase in HCQ blood concentration (95% CI)	P-value
Systolic Blood Pressure (mmHg)	-0.9 (-1.2, -0.6)	<0.0001
Diastolic Blood Pressure (mmHg)	-0.4 (-0.6, -0.2)	0.0005
Cholesterol mg/dl	-1.0 (-1.6, -0.3)	0.0039
Glucose	-0.75 (-1.16, -0.34)	0.0003

We next looked to see whether increases in HCQ blood concentration among those with low levels (<500 ng/ml) had more of an effect than changes in the therapeutic range (500-1999 ng/ml). We also looked at changes in the super-therapeutic range (>2000 ng/ml). The results are in Table 2 below.

Table 2. Association between changes in HCQ concentration by ranges and changes in cardiovascular risk factors.

Cardiovascular Risk Factor	Expected change in cardiovascular risk factor per 500 ng/ml increase in HCQ concentration (95% CI)		
	Changes < 500 ng/ml	Changes between 500 and 1999 ng/ml	Changes over 2000 ng/ml
Systolic Blood Pressure (mmHg)	-1.2 (-2.6, 0.2) p=0.087	-0.7 (-1.2, -0.3) p=0.003	-1.1 (-1.9, -0.2) p=0.012
Diastolic Blood Pressure (mmHg)	-0.6 (-1.5, 0.4) p=NS	-0.4 (-0.7, -0.1) p=0.023	-0.2 (-0.8, 0.3) p=NS
Cholesterol mg/dl	-5.2 (-8.2, -2.2) p=0.0006	-0.3 (-1.4, 0.7) p=NS	-0.3 (-2.1, 1.4) p=NS
Glucose	-2.4 (-4.3, -0.6) p=0.0097	-0.36 (-0.99, 0.3) p=NS	-0.95 (-2.1, 0.2) p=0.098

For cholesterol, a change of HCQ of 500 ng/ml in the sub-therapeutic range (i.e. an increase from 0 to 500 ng/ml) was associated with a relatively larger improvement in cholesterol (decline of 5.2 mg/dl). However changes in cholesterol in the HCQ therapeutic or super-therapeutic range were not associated with a decrease in cholesterol.

Conclusion: HCQ blood levels are statistically associated with blood pressure, cholesterol and glucose (proven for the first time). For cholesterol, the association is also meaningful clinically. The benefit is achieved when the HCQ blood level moves from 0 to 500 (low end of therapeutic range).

Disclosure: M. Petri, EMD Serono, 5, Exagen, 2, Janssen, 5, GSK, 5, AstraZeneca, 2, Inova Diagnostic, 5, Novartis, 5, Amgen Inc., 5, Decision Resources, 5, Medscape, 5, Eli Lilly and Co., 5, Quintiles, 5; D. Goldman, Merck & Co., Pfizer, 1; L. S. Magder, None.

Abstract Number: 2632

Rates and Predictors of Thirty-Day Readmission Among Patients Hospitalized for Systemic Lupus Erythematosus at a Single Tertiary Care Center

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Background/Purpose: Systemic lupus erythematosus (SLE) has a 27.2% all-cause 30 day readmission rate, the 6th highest principle diagnosis among all medical conditions. The primary objective of the current study was to determine the 30-day all-cause readmission rate for adults with SLE at Wake Forest Baptist Medical Center (WFBMC). The secondary objective was to determine risk factors associated with 30-day readmission.

Methods: Using the electronic medical record, we conducted a retrospective chart review of patients who met the following criteria: ICD 9 code for SLE, age >18, and had at least one hospital admission within a 2-year study period (8/1/2012-7/31/2014). Individual charts were manually reviewed to validate the diagnosis of SLE. Planned hospitalizations were excluded. The primary outcome was all cause-readmission within 30 days of initial hospital discharge. We recorded demographics, health care system-related variables and clinical data including comorbidity illness burden using the Charlson Comorbidity Index (CCI).

Results: Over a 24 month period there were a total of 74 unique patients with SLE who had a total of 233 admissions. Of these 233 admissions, 82 (35.2%) were 30-day readmissions. The mean age of the cohort was 43.8 (SD 14.22), 85.1% female, 67.6% African Americans and 23.0 % on Medicaid/self-pay. Of these 74 patients, 27 (36.5%) had at least one 30-day readmission and contributed to 70% of total admissions. On bivariate analysis, serositis, higher CCI, estimated GFR <60, greater number of ER visits and less frequent rheumatology clinic visits were significant predictors of 30-day readmission. On multivariate analyses, significant predictors of 30-day readmission included estimated GFR < 60 (OR 3.34; p=.0224), presence of serositis as a prior criterion for lupus diagnosis (OR 11.87; p=.0071), and more frequent ER visits (OR 1.04; p=0.0010). More frequent rheumatology clinic visits (OR 0.74; p=<.0001) was associated with less readmission during the 2-year study period.

Conclusion: We found a 35.2% 30-day readmission rate that was substantially higher than the previously cited 27.2% readmission rate. Serositis (as a criterion in SLE diagnosis), EGFR < 60, and more frequent ED visits were associated with increased rate of 30-day readmissions. On the other hand, higher number of completed rheumatology visits was associated

Table 1: Odds of 30-day readmission among adults with SLE

	OR (95% CI)	P for 95% CI
Demographic and Socioeconomic Characteristics		
Age	1.01 (0.98, 1.04)	.4954
Female (reference group: male)	1.31 (0.49, 3.47)	.5900
African Americans (reference group: others)	1.41 (0.66, 2.99)	.3720
Median household income (based on zip code)	1.00 (1.00, 1.00)	.9086
Medicaid/Self Pay vs. Other	0.86 (0.40, 1.81)	.6870
Clinical Characteristics		
Smoking status		
Former (reference group: never smoke)	1.40 (0.52, 3.79)	.5082
Current (reference group: never smoke)	2.13 (0.99, 4.58)	.0533
Serositis as lupus manifestation	2.51 (1.24, 5.05)	.0102*
Charlson Comorbidity Index	1.14 (1.02, 1.27)	.0218*
History of MI	1.69 (0.52, 5.46)	.3832
Chronic pulmonary disease	1.89 (0.92, 3.88)	.0837
Moderate/Severe renal disease	2.44 (1.07, 5.58)	.0341*
Hospitalization level characteristics		
Length of stay (# of days)	0.99 (0.93, 1.05)	.7112
Primary Discharge Diagnosis		
Non-SLE (reference group: SLE)	0.97 (0.38, 2.48)	.9412
Resident admitting service	1.20 (0.59, 2.42)	.6144
Plaquenil on medication list	0.49 (0.18, 1.33)	.1612
Immune-suppressant use	0.70 (0.34, 1.44)	.3285
Prednisone dose (mg) on admission	1.00 (0.98, 1.01)	.6109
Prednisone dose (mg) on discharge	1.00 (0.98, 1.02)	.6612
General medicine service vs other	1.16 (0.62, 2.17)	.6455
Rheumatology consult index	0.95 (0.36, 2.52)	.9244
EGFR < 60 (reference group: EGFR ≥60)	2.55 (1.14, 5.74)	.0233*
Index admission hemoglobin	0.96 (0.81, 1.13)	.6194
Index admission platelet count	1.00 (1.00, 1.00)	.7405
Index admission white blood cell count	0.96 (0.90, 1.02)	.2289
Health care system level characteristics		
Length of time to follow-up	1.00 (1.00, 1.00)	.9569
Hospital follow up with rheum attended if scheduled	0.43 (0.11, 1.68)	.2254
Number of ED visits	1.03 (1.01, 1.05)	.0025*
Number of Completed Rheumatology visits	0.82 (0.67, 0.99)	.0429*
Number of No shows to Rheumatology visits	1.05 (0.97, 1.14)	.2564

Table 2: Multivariable Analysis for Odds of 30-day readmission among adults with SLE

	OR (95% CI)	P for 95% CI
Plaquenil on medication list	1.09 (0.40, 2.93)	.3670
EGFR < 60 (reference group: EGFR ≥60)	3.34 (1.25, 9.42)	.0224*
Smoking status		
Former (reference group: never smoke)	2.43 (0.92, 6.41)	.0733
Current (reference group: never smoke)	1.67 (0.62, 4.50)	.3142
Number of ED visits	1.04 (1.02, 1.07)	.0016*
Number of Completed Rheumatology visits	0.74 (0.66, 0.84)	<.0001*
Charlson Comorbidity Index	0.98 (0.80, 1.21)	.8616

with less frequent 30-day readmissions. Surprisingly, demographics, median household income, insurance payer status, and lupus disease activity including the use of immune-suppressant at index admission were not significant predictors of readmission.

Disclosure: S. Mullis, None; D. Ang, None.

Abstract Number: 2633

Disease Activity, Organ Damage and Patient-Reported Outcome Measures in Swedish Patients with Recent-Onset SLE

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Session Information

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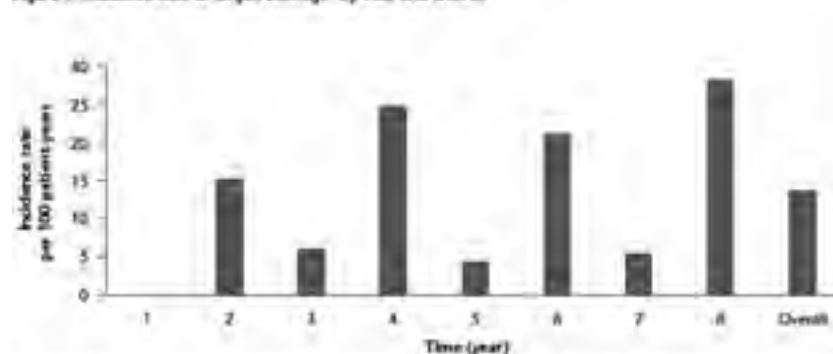
Background/Purpose: Patient (pt)-reported outcome measures (PROMs) are important to inform shared decision-making between pts with SLE and physicians.¹ Established measures of disease activity and organ damage are predictors of disease progression, prognosis and survival.^{2,3} However, there is no established correlation with PROMs. We used registry data from well-characterized Swedish pts with recent-onset SLE to identify potential correlations of disease activity and organ damage with PROMs.

Methods: Consecutive and newly diagnosed pts of the Clinical Lupus Register in Northeast Gothenburg who met the 1982 ACR⁴ and/or the 2012 Systemic Lupus International Collaborating Clinics (SLICC)⁵ SLE classification criteria with no prior organ damage were followed prospectively after diagnosis. Pts were seen by a rheumatologist at Months 0 (inclusion), 6, 12, 24, 36, 48 and 60, with collection of SLE Disease Activity Index-2000 (SLEDAI), SLICC/ACR organ damage index score and PROMs (quality of life [QoL]: EuroQoL-5 Dimensions [EQ-5D]; pain and fatigue: visual analog scale [VAS] 0–100 mm) at each visit. The incidence rate (IR) of organ damage and Pearson correlations of SLEDAI and organ damage with PROMs were calculated.

Results: Of the 41 pts in the study at baseline: median age 39 years, 80% female, 85% white, 88% met ACR-82 criteria and 37% had lupus nephritis. Organ damage occurred at an overall IR of 13.6 per 100 pt-years (Figure 1), with neuropsychiatric, ocular and cardiovascular damage as most common (Figure 2). SLEDAI significantly correlated with pain at Months 6, 36 and 48 ($p<0.03$; Figure 3). SLICC/ACR damage index score significantly correlated with EQ-5D ($p=0.003$) and fatigue ($p=0.009$) at Month 24.

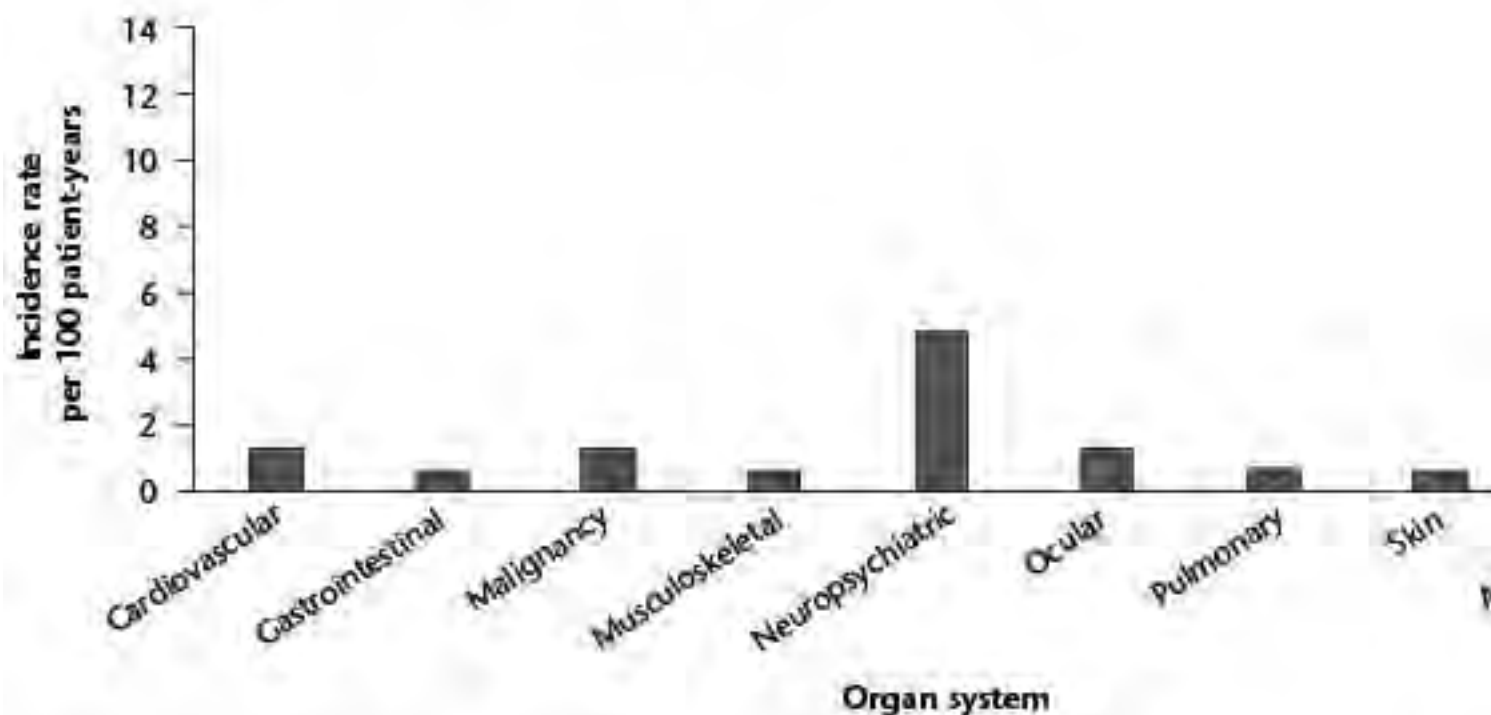
Conclusion: Our findings illustrate the importance of the interplay between the physician's and pts' perception of SLE, which may affect compliance and adherence to therapy, and play a role in achieving successful outcomes in SLE management.

Figure 1: Incidence Rate of Organ Damage* by Year and Overall



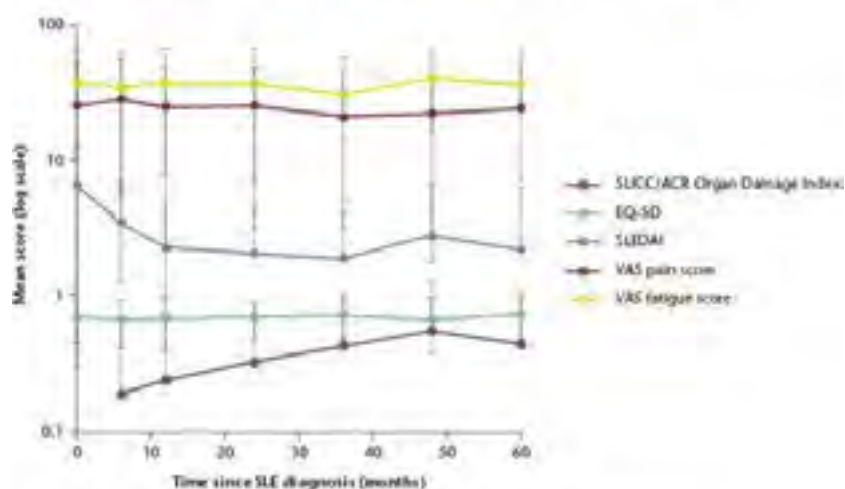
*Incidence rates were calculated as the number of incident cases of organ damage in the study period over the person-time at risk. Person-time at risk was calculated as the time a patient remained in the database without organ damage.

Figure 2. Incidence Rate of Organ Damage* by Organ System and Overall



*Incidence rates were calculated as the number of incident cases of organ damage in the study period over the person-time at risk. Person-time at risk was calculated as the time a patient remained in the database without organ damage

Figure 3. Mean SLICC/ACR Organ Damage Index, SLEDAI Assessment, EQ-5D, VAS Pain Score and VAS Fatigue Score



Error bars represent standard deviations
SLICC/ACR damage index score at each visit
EQ-5D=EuroQol-5 Dimensional; SLE=systemic lupus erythematosus; SLEDAI=SLE Disease Activity Index;
SLICC=Systemic Lupus International Collaborating Clinics; VAS=visual analog scale

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Abstract Number: 2634

The Risk of Hydroxychloroquine Retinopathy in an SLE Cohort: Screening and Prevention in Clinical Practice

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Background/Purpose: Hydroxychloroquine (HCQ) is a commonly used medication for SLE because of its highly favorable risk-benefit ratio. Drug-induced retinopathy is one of very few serious toxicities associated with long-term use. Studies have reported varied prevalence of HCQ retinopathy ranging from 0.5% to 7.5%. In 2016, the American Academy of Ophthalmology published revised guidelines for drug-induced retinopathy prevention. Despite the guidelines, there is some degree of expected variability in clinical practice. We reviewed a large, diverse cohort of SLE patients at an academic center in order to characterize physician practices and patient behaviors with regard to HCQ retinopathy screening and prevention.

Methods: A retrospective chart review was conducted of patients in our SLE cohort. There were 301 SLE patients reviewed, all of whom were seen at academic rheumatology practices between 2004 and 2018. Patients were categorized according to HCQ use at the time of most recent clinic visit. For patients who had been on HCQ, we determined timing of last retinopathy screening exam. We reviewed patients with documented eye-related concerns to determine specific findings and next steps taken.

Results: Of the 301 patients reviewed, 65% were taking HCQ as of the most recent visit and 91% had been on HCQ at some time. There were 205 patients with available rheumatology records for whom HCQ retinopathy screening was indicated. Based on the documentation, 46.8% were up to date on retinopathy screening, 10.2% were overdue, 7.8% had discussed screening with a rheumatologist but follow-up was unclear, and 35.1% had unknown screening status. Among 274 active or former HCQ users, 11.7% had eye-related concerns while on HCQ. These included 1.8% with true drug-induced retinopathy, 5.1% with nonspecific retinal findings leading to HCQ discontinuation, and 4.7% with retinal pathology not attributed to HCQ who continued the drug. Six patients with eye-related concerns had been tested for antiretinal antibodies and 100% were positive. HCQ was discontinued in four of these cases: one had confirmed drug-induced retinopathy and three had nonspecific retinal abnormalities. In the remaining two cases, HCQ was continued with close monitoring.

Conclusion: Our data suggest that there may be inconsistent compliance with ophthalmology guidelines for HCQ retinopathy screening. In addition, only a small subset of patients in our cohort with retinal abnormalities detected by screening was found to have confirmed HCQ retinopathy. Lastly, a select group of patients on HCQ with nonspecific

retinal pathology had positive antiretinal antibodies. Further research is needed to determine the incidence of antiretinal antibodies in HCQ users without retinal pathology in order to understand the implications of this finding.

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Combined Panel of Nine Tests Has the Greatest Sensitivity but the Lowest Specificity to Detect Antiphospholipid Antibody Syndrome in Patients with Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Antiphospholipid antibody syndrome (APS) is an autoimmune hypercoagulable state caused by antiphospholipid antibodies (aPL) which represent a diagnostic criterion and underlie significant comorbidities in patients with and without systemic lupus erythematosus (SLE). Although several tests exist for APS diagnosis, their utilization has been highly variable among laboratories and physicians. Therefore, we have evaluated a panel of nine tests and conducted a retrospective study to determine their sensitivity and specificity for supporting the diagnosis of APS in SLE at our Institution between 2010 and 2018.

Methods: 1633 SLE patients, who satisfied the ACR criteria for a definitive diagnosis (*Arthritis Rheum.* **25**,1271, 1982; *Arthritis Rheum.* **40**, 1725, 1997), were evaluated for the presence of APS as earlier described (*J. Thromb. Haemost.* **4**, 295 (2006). Lupus anticoagulants were assessed by Sta clot LA hexagonal phase phospholipid neutralization assay (HPPNA; delta <8 seconds), Sta clot diluted Russell viper venom test (dRVVT; <1.2 normalized ratio) obtained from Stago (Parsippany, NJ, USA). Platelet neutralization procedure (PNP; delta < 1 second) has been performed using a STA-R Evolution instrument by Stago, as earlier described (*Am. J. Clin. Pathol.* **79**, 678, 1983; *Am. J. Clin. Pathol.* **124**, 586, 2005). IgG and IgM antibodies against β 2-glycoprotein 1 (a β 2-IgG, a β 2-IgM) and cardiolipin (aCL-IgG, aCL-IgM) were measured in house while IgA isotypes (a β 2-IgA, aCL-IgA) were tested by LabCorp Diagnostics (Burlington, NC).

Table 1. Sensitivity and Specificity of Nine Tests for Detection of APS in SLE Patients										
TEST	HPPNA	PNP	dRVVT	a β 2-IgG	a β 2-IgM	a β 2-IgA	aCL-IgG	aCL-IgM	aCL-IgA	All 9 tests
APS+ TEST+	102	35	36	15	14	13	21	28	8	73
APS+ TEST-	96	77	155	191	192	173	195	185	181	26
APS- TEST+	395	78	96	43	57	47	81	123	41	215
APS- TEST-	777	536	1179	1285	1271	1110	1298	1245	1089	236
p value	<0.0001	<0.0001	<0.0001	0.0046	NS	NS	0.0316	NS	NS	<0.0001
Sensitivity (%)	52	31	19	7	7	7	10	13	4	74
p value vs HPPNA		0.0006	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0003
PPV (%)	21	31	27	26	20	22	21	19	16	25
Specificity (%)	66	87	92	97	96	96	94	91	96	52
p value vs HPPNA		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
NPV (%)	89	87	88	87	87	86	87	87	86	90
Number of Patients Tested	1370	726	1466	1534	1534	1345	1595	1581	1119	550

Sensitivities, specificities, and positive (PPV) and negative predictive values (NPV) for detection of APS were calculated and compared by 2-tailed chi-square tests using GraphPad software.

Results: 222/1633 SLE patients had APS when using a combination of nine tests. Table 1 shows the frequency of positive and negative test results and p value for each assay. The greatest sensitivity was seen when all nine tests were performed together for detecting APS in SLE patients (74%; χ^2 p=0.0003). In contrast, combining all tests had the lowest specificity (52%; p<0.0001). Importantly, the 2nd most sensitive test for detection of APS was the HPPNA at 52%, this test also had the second lowest specificity (66%). Similar trends were seen when individual APS comorbidities, such as deep venous thrombosis (DVT), pulmonary embolism (PE), and stroke, were separately analyzed. Among the charts reviewed, the complete 9-test panel was only performed in 550 of 1633 patients (Table 1).

Conclusion: This study demonstrates that utilizing a combined 9-test panel has the greatest sensitivity but lowest specificity for detecting APS in SLE subjects. Thus, a failure to employ the complete panel may lead to exclusion of patients who may meet criteria for identifying patients with APS who need long-term anticoagulation for preventing life-threatening thrombotic events.

Disclosure: S. Sharmeen, None; K. Banki, None; A. Perl, None.

Abstract Number: 2636

Investigating Lupus Nephritis Patient Outcomes Receiving Belatacept Post Renal Transplant Using the UNOS Database

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Session Information

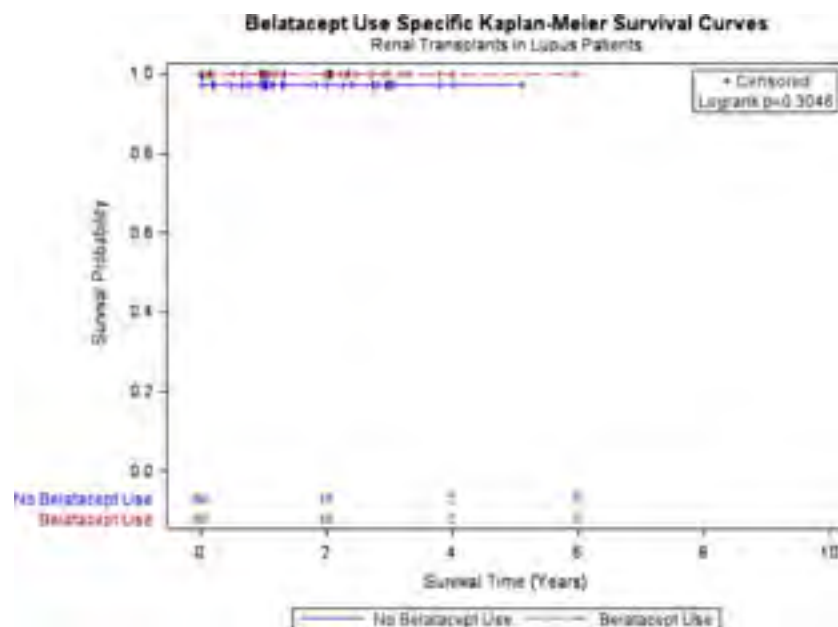
Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Twenty to sixty percent of patients with systemic lupus erythematosus (SLE) can progress to lupus nephritis (LN) and those that do can develop end stage renal disease 15% of the time. Belatacept is a new immunosuppressive agent with 7 year post transplant outcomes showing patient/graft survival and mean estimated



glomerular filtration rate (eGFR) to be significantly higher than cyclosporine [1]. These effects have not been confirmed in LN patients who can benefit from improving strategies.

Methods: LN patients who underwent renal transplants were identified within the United Network for Organ Sharing (UNOS) database from 2008 to 2014 and a cohort was established based on the use of tacrolimus or cyclosporin, mycophenolate mofetil (MMF) and steroid maintenance medications. This cohort was stratified by use of Belatacept and propensity score matching was used to match non-Belatacept patients to 39 Belatacept patients based on age, gender, race, history of diabetes, status of a living donor, and year of transplant. Pre- and post-match Belatacept use was cross classified by each categorical variable and was examined with the chi-square test; the Mann-Whitney test was used to compare continuous variables. The Kaplan-Meier method was used to examine unadjusted graft failure and survival. A linear mixed model with a heterogeneous autoregressive covariance structure was used to examine follow up creatinine and eGFR values over time of the matched patients.

Results: There were no graft failures or deaths within the Belatacept group and a single patient who experienced graft failure and death within the matched non-Belatacept group. Results of the linear mixed models for creatinine and GFR provided evidence of no difference between groups. For every year there was a significant increase in creatinine (0.22 mg/dL; $p = 0.009$) and decrease in GFR ($-7.20\text{mL/min/1.73 m}^2$; $p < 0.001$).

Conclusion: Belatacept has been used in a limited number of patients requiring renal transplants with LN since 2008. In our study, no significant difference in graft survival, death or renal function in cohorts using standard therapy versus Belatacept was noted. No improvement in mean eGFR was seen in the Belatacept group as seen in prior work [1]. Future studies are needed to evaluate the impact of Belatacept based regimens in LN patients post-transplant.

1. Vincenti, F., Rostaing, L., Grinyo, J., Rice, K., Steinberg, S., & Gaite, L. et al. (2016). Belatacept and Long-Term Outcomes in Kidney Transplantation. *New England Journal Of Medicine*, 374(4), 333-343. <https://doi.org/10.1056/nejmoa1506027>

Disclosure: O. Bhatt, None; S. Aurit, None; R. Sen, None; J. Nahas, None; S. Jagadesh, None.

Hydroxychloroquine Improves Disease Activity and Allows Reduction of Corticosteroid Dose Regardless of Background Treatment in Japanese Patients with Systemic Lupus Erythematosus

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Session Information

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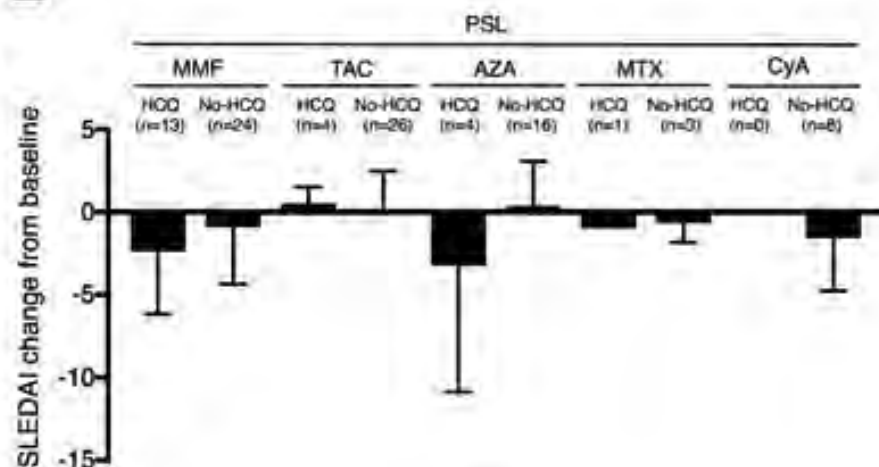
Background/Purpose: Hydroxychloroquine (HCQ) was not approved in Japan until 2015 and its therapeutic potential remains poorly understood in the population. In this study, we evaluated the additional therapeutic effect of HCQ in Japanese patients with systemic lupus erythematosus (SLE) on maintenance therapy.

Methods: Patients with SLE who visited our hospital from 2015 to 2016 and were taking prednisolone (PSL) at < 20 mg/day were retrospectively evaluated. All patients were divided into 3 groups according to their maintenance treatment regimen: PSL plus immunosuppressant (IS), PSL alone, and no treatment. We compared changes in the SLE disease activity index (SLEDAI), PSL dose, and cumulative flare rate between patients who were and were not treated with HCQ.

Results: Among the 165 patients evaluated, 35 (21.2%) were treated with HCQ. The mean period of observation did not differ between patients who did and did not receive HCQ ($p = 0.3$). The SLEDAI (Figure 1A) and PSL dose (Figure 1B) were significantly reduced in patients who received HCQ regardless of their background treatment regimen. We next

Figure 2

(A)



(B)

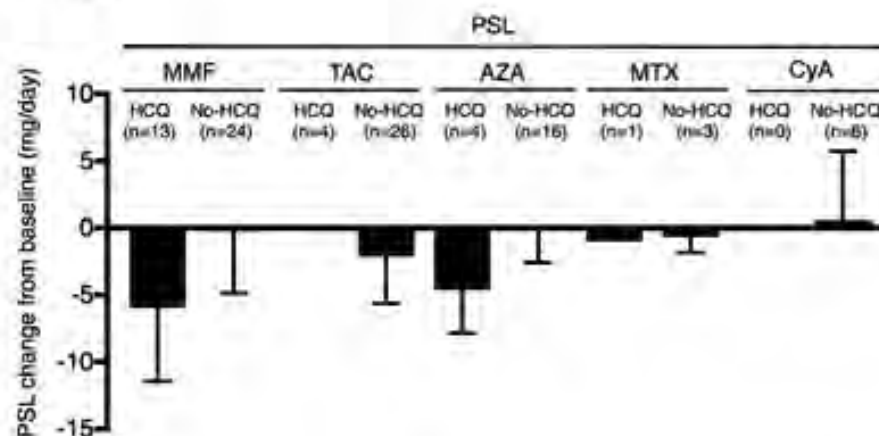
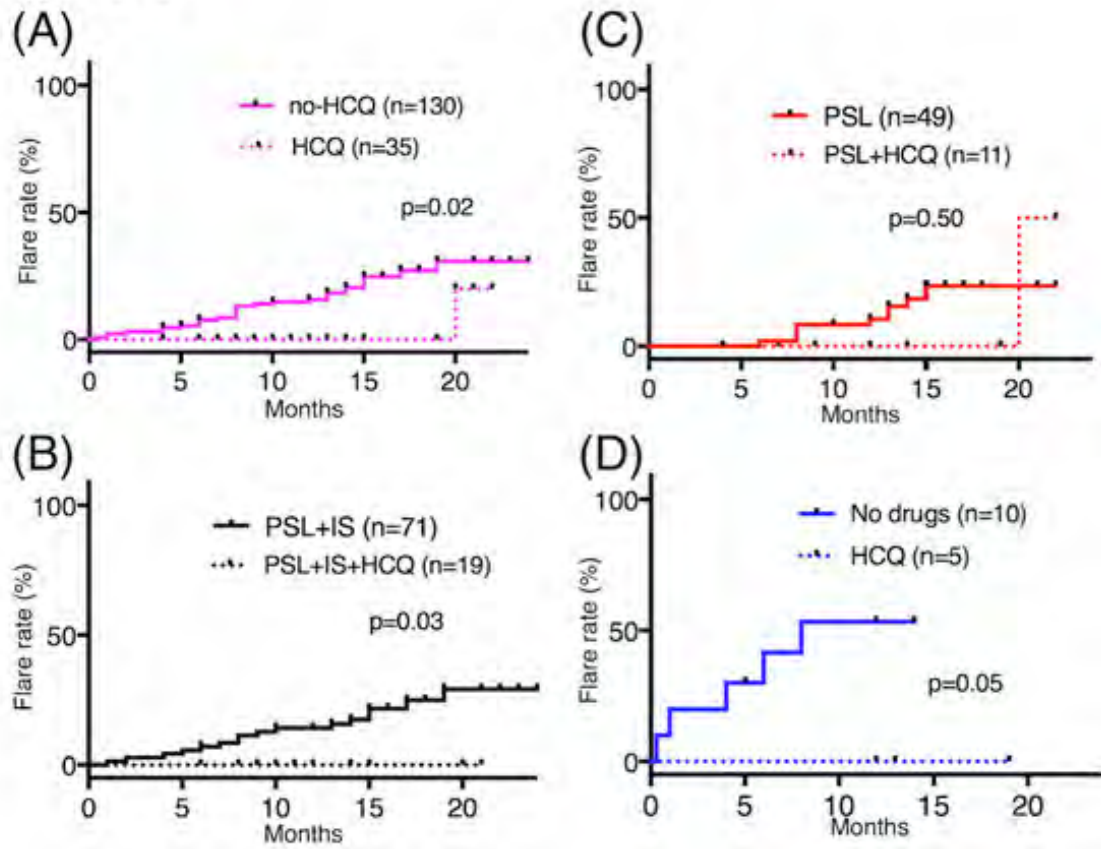


Figure 3



focused on the change in SLEDAI and PSL dose depending IS use (Figure 2). Addition of HCQ on mycophenolate mofetil and azathioprine might have superior efficacy to other combinations and we found less additional therapeutic effect on tacrolimus (TAC) users. The cumulative flare rate was lower in patients who received HCQ compared to those who did not in the PSL plus immunosuppressant and no maintenance treatment groups ($p = 0.03$ and $p = 0.05$, respectively) (Figure 3).

Conclusion: The addition of HCQ reduced disease activity and permitted PSL dose reduction regardless of background treatment in Japanese patients with SLE. In the view of combination with IS, however, our results suggested addition of HCQ on TAC might have less additional clinical efficacy than other IS combination.

Disclosure: H. Hanaoka, None; H. Iida, None; T. Kiyokawa, None; Y. Takakuwa, None; K. Kawahata, None.

Abstract Number: 2638

Tacrolimus Use in Hispanic Patients with Refractory Lupus Nephritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

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Background/Purpose: Lupus nephritis is one of the most common and severe manifestations of patients with SLE. Studies assessing the use of Tacrolimus (TAC) in lupus nephritis are promising, however results are primarily based on patients of Asian ethnicity and limited by significant heterogeneity. The Los Angeles County + University of Southern California Medical Center (LAC+USC) serves a largely Hispanic, underinsured, indigent population. The purpose of this study is to evaluate the use and effectiveness of TAC in LAC+USC Rheumatology clinic.

Methods: This is a retrospective analysis of adult patients with SLE, satisfying the 1997 ACR criteria, from LAC+USC medical center seen from January 2010 to January 2018. Patients with biopsy proven lupus GN were identified and screened for previous or current use of TAC. Patient demographics, 2003 International Society of Nephrology (ISN)/Renal Pathology Society (RPS) Classification of lupus nephritis, treatment history, laboratory features, and SLEDAI were noted. Renal response as defined by the 2006 ACR response criteria for proliferative and membranous renal disease was calculated for each patient.

Results: Ten patients were included (100% female, mean age 32.3 ± 8.8 years, mean disease duration 8.2 ± 5.2 years). Ninety percent were Hispanic and 10% were African American. Hypertension was present in 70% of patients and diabetes mellitus in 10%. Eighty percent of patients were on an angiotensin converting enzyme inhibitor/angiotensin II receptor blocker. According to ISN/RPS class, patients were Class V (50%), III/V (40%), IV/V (10%). The most common indication of TAC was refractory or resistant lupus nephritis therapy as determined by physician judgment, persistent proteinuria, persistent active sediment, hypocomplementemia or elevated dsDNA. Median daily dose of TAC was 4mg. Mean duration of therapy 1.2 ± 0.8 years. Previous medications included GC (70%; mean daily dose 7.5mg), CYC (70%), MMF (100%), AZA (60%), RTX (80%), CSA (10%), Belimumab (30%), HCQ (70%). According to ACR response criteria, 60% of patients had no change, 10% worsened, 10% had partial response, 20% achieved complete response, 0% improved. Median urine protein creatinine ratio increased from 2.0 at baseline to 2.3 ($p=0.99$). Median SLEDAI decreased from 16.5 at baseline to 16.0 ($p=0.97$). Median creatinine did not change from baseline 0.7mg/dL ($p=0.16$). TAC was discontinued in 8 patients due to inefficacy.

Conclusion: The study demonstrates the use of TAC in a primarily Hispanic population with refractory lupus nephritis. Although small and uncontrolled, the data proposes that TAC may not be as effective in Hispanics with refractory lupus nephritis in achieving a partial or complete response. This is in contrast to results from previous studies performed in Asian patients. Larger prospective studies are needed to better understand the potential role of TAC in the treatment of lupus nephritis.

	Pre TAC			Post TAC			p-value ¹
	Median	Mean	Standard deviation	Median	Mean	Standard deviation	
Creatinine (mg/dL)	0.7	0.7	0.2	0.7	1.1	0.8	0.16
Urine Protein Creatinine Ratio	2.0	3.3	2.8	2.3	3.4	3.5	0.99

Table . (Cont'd)

	Pre TAC			Post TAC			p-value ¹
	Median	Mean	Standard deviation	Median	Mean	Standard deviation	
C3 (mg/dL)	75.5	80.3	41.1	70.5	75.1	33.9	0.37
C4 (mg/dL)	10.4	12.8	9.1	9.9	11.6	7.7	0.59
Albumin (g/dL)	3.3	3.2	0.7	3.2	3.2	0.8	0.87
SLEDAI	16.5	15.4	5.7	16.0	15.7	6.9	0.97

Disclosure: P. Aleksiejuk, None; E. Ortiz, None.

Abstract Number: 2639

Bone Mineral Density Is Not Associated with Osteoporotic Fractures in Premenopausal Women and Men < 50 Years Old with Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoporosis is common in patients with systemic lupus erythematosus (SLE). Guidelines for the treatment and prevention of glucocorticoid induced osteoporosis (GIOP) are detailed for postmenopausal women and older men. However, there are less data on risk factors for osteoporotic fracture in premenopausal women and men <50 years old with SLE resulting in conditional recommendations in the 2017 American College of Rheumatology GIOP guidelines. The goal of this project is to identify risk factors for osteoporotic fracture in premenopausal women and men < 50 with SLE.

Methods: In this retrospective chart review of SLE patients at an academic medical center, 218 premenopausal women (defined as age < 45 or age at menopause) and men (age <50) with bone mineral density (BMD) results were identified. All patients fulfilled the 1997 ACR criteria for the classification of SLE. Variables collected included BMD, osteoporotic fracture (rib, sacrum, hip, spine, wrist, forearm, humerus, ankle, tibia/fibula fractures¹), smoking, BMI, gender, SLE disease duration, bisphosphonate and oral contraceptive (OCPs) use, ethnicity, age, vitamin D, and lifetime cumulative prednisone dose categorized as <10, 10-20, and >20 grams. Variables were collected at the time of BMD or fracture. The fracture and non-fracture groups were compared using Student's *t*-test for continuous variables and chi-squared test for categorical variables. Multivariate analysis was used to examine potential variables associated with fracture.

Results: This study included 202 women and 16 men who had a mean age of 34.5 years. Out of the 218 subjects, 15 (2 men, 13 women) had an osteoporotic fracture. One subject had 2 fractures. Fractures included 2 tibia, 2 forearm, 1 ankle, 2 rib, 1 hip, and 8 vertebral. No difference was found in BMD of the lumbar spine, hip, or femoral neck between those with fracture vs no fracture. Lifetime cumulative prednisone dose, BMI, smoking, vitamin D level, use of bisphosphonates or OCPs, gender, ethnicity, and SLE disease duration were not associated with increased risk of fracture. In those with fracture, 9 had used >20g of cumulative lifetime prednisone use, 3 had used 10-20g, and 3 <10g; however, these findings did not reach statistical significance. There were no associations between fracture and age, lumbar BMD, cumulative prednisone dose, ethnicity, or BMI on multivariate analysis.

Conclusion: Osteoporotic fractures were infrequent (6.9%) in premenopausal women and men < 50 with SLE, but higher than would be expected in a healthy population. There was no significant association between fracture risk and BMD nor cumulative prednisone dose highlighting a need for further studies to determine risk factors to identify patients most likely to benefit from preventive osteoporotic medications.

1. Warriner AH, Patkar NM, Curtis JR et al. Which fractures are most attributable to osteoporosis? *J Clin Epidemiol.* Jan 2011;64(1):46-53.

Disclosure: T. Driver, None; M. A. McMahon, None; B. Tsao, None; J. M. Grossman, None.

Abstract Number: 2640

Table 1

Variable	Patients with Fracture (n = 15)	Patients without Fracture (n = 203)	P value
Age at DEXA (years)	36.9	34.1	ns
Gender			ns
Female	13	189	
Male	2	14	
Ethnicity (no. of patients)			
Caucasian	5 (33.3%)	93 (45.8%)	ns
Asian	4 (26.7%)	36 (17.7%)	ns
Hispanic	6 (40.0%)	43 (21.2%)	ns
African American	0 (0%)	22 (10.8%)	ns
Pacific Islander	0 (0%)	2 (1.0%)	ns
Unknown	0 (0%)	7 (3.4%)	ns
Total hip BMD (g/cm ²)	0.872	0.887	ns
Femoral neck BMD (g/cm ²)	0.747	0.775	ns
Lumbar spine BMD (g/cm ²)	0.922	0.969	ns
SLE disease duration* (years)	12.2	9.9	ns
BMI (kg/m ²)	23.8	25.8	ns
Vitamin D** (ng/mL)	32.1	28.4	ns
Smoking (no. of patients)			ns
Current	0 (0%)	8 (4.0%)	
Prior	3 (23.1%)	311 (15.3%)	
Never	10 (76.9%)	163 (80.7%)	
Bisphosphonates (no. of patients)			ns
Yes	4 (30.8%)	36 (18.9%)	
No	9 (69.2%)	154 (81.1%)	
Oral contraceptives (no. of patients)			ns
Yes	2 (15.4%)	33 (17.4%)	
No	11 (84.6%)	157 (82.6%)	
Cumulative prednisone dose (no. of patients)			ns
<10 grams	3 (20.0%)	67 (33.0%)	
10-20 grams	3 (20.0%)	46 (22.7%)	
>20 grams	9 (60.0%)	90 (44.3%)	

*SLE disease duration until most recent DEXA

**Vitamin D level within one year prior to DEXA

Hematologic Activity in Systemic Lupus Erythematosus: Is Splenectomy Our Best Choice?

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Session Information

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Hematologic manifestations are found in up to 30% of SLE patients. Although splenectomy is considered an acceptable therapeutic option for both refractory thrombocytopenia and autoimmune hemolytic anemia in different primary hematologic disorders, its role in SLE has been controversial, mainly because of its potential surgical complications and possible association with SLE flares. The aim of this study was to determine safety and efficacy of splenectomy in a cohort of SLE patients when compared to patients with hematologic activity who only received medical treatment.

Methods: We included all patients with SLE who fulfilled ≥ 4 ACR criteria and underwent splenectomy because of refractory hematologic activity between 2000 and 2016 in a tertiary care center in Mexico City. We also included SLE patients who were hospitalized during that same period because of hematologic activity, but who did not undergo surgical treatment. Patients with other rheumatic diseases (except for APS) were excluded. We recorded demographic, clinical and serologic characteristics at baseline and during follow-up.

Results: We included 30 patients in whom splenectomy was performed and 32 patients with hematological activity without splenectomy. Most patients were female (87%) and mean age was 31 years. Patients who underwent surgery had lower platelet levels at baseline (23,500 vs 73,000/ μ l, $p < 0.01$) and had a higher cumulative prednisone dose in the previous year (8.77 ± 5.93 vs 2.25 ± 1.08 grams, $p < 0.001$). Regarding splenectomy, 83% were laparoscopic and there were surgical complications in 4 patients (13%), all of which resolved.

Mean follow-up time was 63 months in patients with splenectomy and 66 months in those without it. Patients who underwent surgery achieved remission in a shorter time (2.4 ± 1.2 vs 4.8 ± 3.8 months, $p < 0.01$). However, after 12 months, there was no difference in the remission rates between both groups (78 vs 86%, $p = 0.44$). Although the cumulative prednisone dose after one year of surgery/hospitalization was similar between groups (5.41 ± 3.54 vs 5.24 ± 3.71 gr, $p = 0.86$), the prednisone dose in patients with splenectomy was lower than the previous year (5.41 ± 3.54 vs 8.77 ± 5.93 gr, $p = 0.02$) whereas in patients without surgery it was higher (5.24 ± 3.71 vs 2.25 ± 1.08 gr, $p < 0.01$). There were no differences in SLEDAI or SLICC damage index scores at one year or at the end of follow-up.

Major infections were more frequent in patients who underwent splenectomy (43 vs 9%, $p < 0.01$). Among patients with infectious complications, 69% had a complete immunization schedule. After multivariate analysis, considering factors such as vaccination, splenectomy remained as an independent risk factor for infection during follow-up (RR 5.15, 95% CI 1.05-25.11, $p = 0.043$).

Conclusion: Splenectomy may seem like an attractive alternative for SLE patients with refractory hematologic activity, since it is associated with shorter time to remission and the possibility of lowering glucocorticoid doses. However, it represents a significant risk factor for major infections, regardless of the patients' immunosuppressive treatment and vaccination status.

Disclosure: M. F. Zavala-Miranda, None; S. Govea-Peláez, None; R. Vázquez-Rodríguez, None; R. Reyna, None; S. Morales, None; D. Gómez-Martín, None; J. Alcocer-Varela, None; J. Merayo-Chalico, None; A. Barrera-Vargas, None.

Abstract Number: 2641

Hydroxychloroquine Could Modulate S100 Proteins Expression, Which Reflect the Activity of Lupus Nephritis or Skin Lesion, in Systemic Lupus Erythematosus Patients with Low Disease Activity

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To find the effect of HCQ treatment on expression of S100 proteins which were reported to reflect the activity of SLE including lupus nephritis or skin lesion.

Methods: We enrolled 51 SLE patients treated without additional immunosuppressive therapy more than 3 months before HCQ treatment in our institute from Jan 2016 to Dec 2017. Serum levels of S100A8 and S100A9 proteins were measured by ELISA (CircuLex ELISA Kit, MBL) at the screening, 3 months and 6 months after HCQ administration. Disease activity of SLE was measured using the SLENA-SLEDAI 2011. Cutaneous disease activity was evaluated by Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI). Immunological activity of SLE was also evaluated by the measurement of serum complement level(C3, C4, CH50), anti-dsDNA anti-body titer and blood cell count.

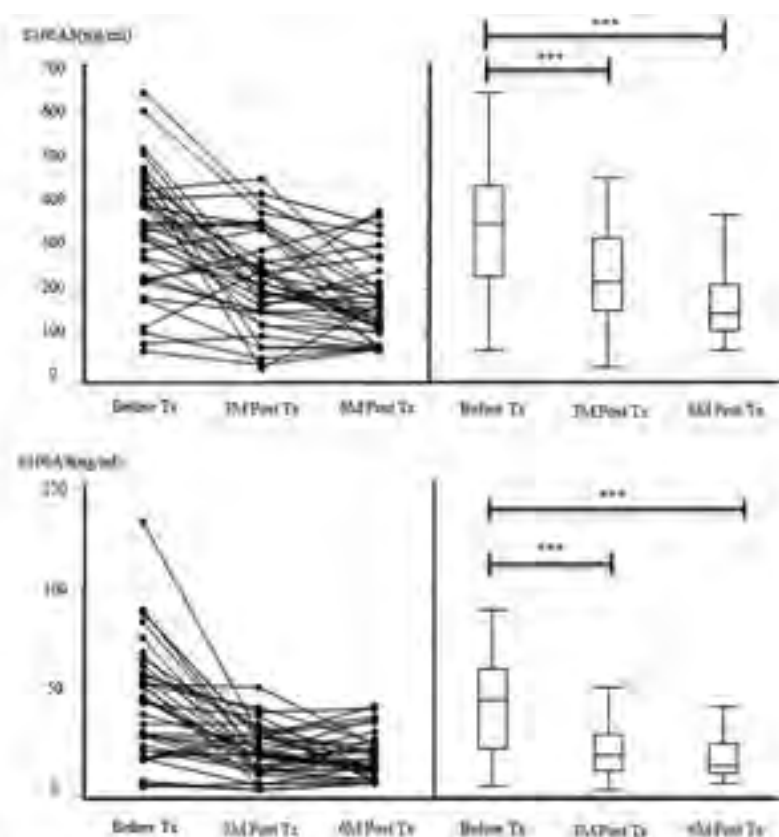


Figure.1 The change of serum level S100 proteins by HCQ treatment

Serum S100A8 and S100A9 levels at baseline were compared to the level after 3 and 6 months of HCQ treatment. Serum S100A8 and S100A9 levels significantly decreased by HCQ treatment in SLE patients. For statistical analyses: *** $p < 0.0001$

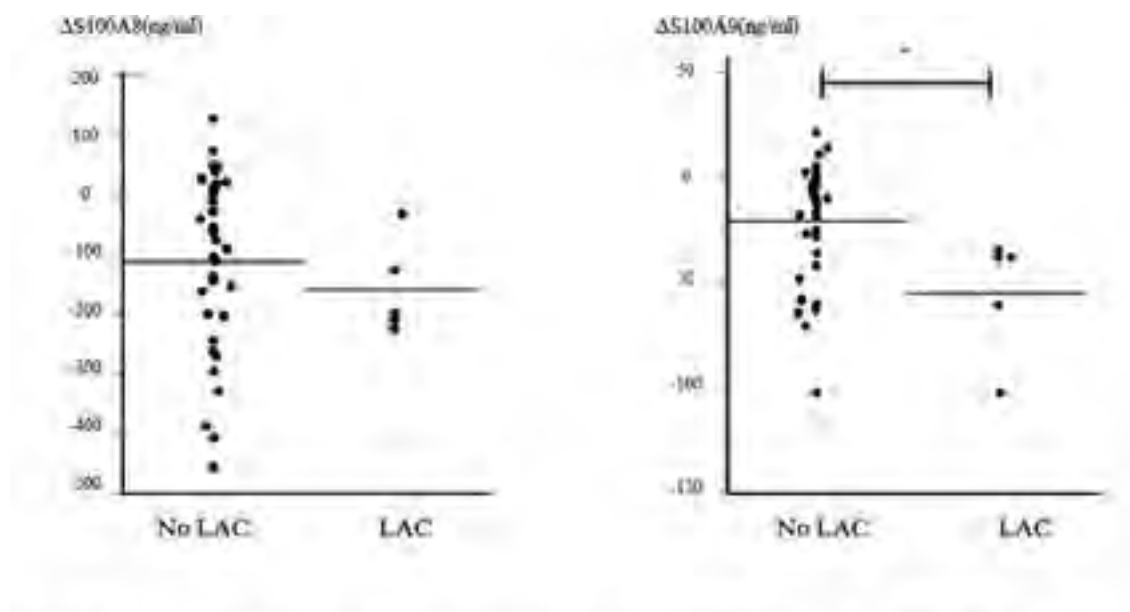


Figure.2 The changes amount of serum S100 proteins expression compared with presence($n=5$) or absence($n=35$) of lupus anticoagulant(LAC).
The changes amount of serum S100A9 levels in LAC-positive SLE patients are significantly lower than in LAC-negative SLE patients.
For statistical analyses: * $p<0.05$, p value: t test
lupus anticoagulant: LAC.

Results: 43 patients were enrolled in this study (M:F; 3:40, average age; 38.5±11.5) (Table 1).

At the screening before HCQ administration, serum levels of S100A8 and S100A9 proteins were significantly elevated in SLE patients with the history of renal involvement. These S100 proteins expression were decreased significantly after 3 and 6 months of HCQ treatment (Figure 1).

Additionally, this effect of HCQ treatment on serum S100A8 and S100A9 expression was observed in SLE patients with or without the history of renal involvement. As for the correlation with skin involvement, serum S100A8 and S100A9 expressions decreased by HCQ treatment in only SLE patients with improvement of CLASI activity score significantly. The changes of serum S100A9 levels in SLE patients with lupus anti-coagulant (LAC) are lower compared than those without LAC significantly (Figure 2).

We considered these effects on S100 proteins expression were induced by HCQ treatment mainly.

Conclusion: S100 proteins were reported to correlate with the pathogenesis of organ involvements in SLE patients. Our findings could suggest that HCQ affect the improvement of organ improvements in SLE through the modulation of S100 proteins expression especially in renal or skin involvement. Further investigation is needed to clarify the mechanism of these modulations by HCQ use.

Disclosure: R. Wakiya, None; T. Kameda, None; S. Nakashima, None; H. Shimada, None; M. Kato, None; T. Miyagi, None; K. Ueda, None; H. Dobashi, None.

Age, years	38.5 ± 11.5
Disease duration, years	12.3 ± 10.3
Past involvement	
Skin involvement	40 (95)
Renal involvement	19 (44)
NPSLE	2 (5)
Photosensitivity	33(77)
Raynaud phenomenon	13(30)
Complicated autoimmune disorder	
Sjogren's syndrome	7 (16)
Antiphospholipid syndrome	3 (7)
mixed connective tissue disease	1 (2)
Concomitant immunosuppressant	
Prednisone	
No.(%)	37 (89)
Median Dosage, mg/day (range)	5 (1-20)
Tacrolimus	16 (37)
Mycophenolate mofetil	9 (21)
Cyclosporine A	3 (7)
Mizoribine	3 (7)
Methotrexate	2 (5)
Azathioprine	1 (2)
Positive rate of autoantibody	
Anti-Sm, no.(%)	9 (21)
Anti-RNP, no.(%)	17 (40)
Anti-SS-A, no.(%)	22 (51)
Anti-SS-B, no.(%)	8 (19)
Lupus anticoagulant, no.(%)	6 (14)
Anti-cardiolipin, no.(%)	19 (44)
Anti-β2GPI, no.(%)	3 (7)
Disease activity	
SLEDAI score	3.6 ± 2.0
CLASI activity	3.7 ± 3.3 (n=30)
CLASI damage	0.7 ± 1.8(n=30)
anti-dsDNA, IU/ml	13.4 ± 13.3
C3, mg/dl	77.8 ± 21.8
C4, mg/dl	15.3 ± 7.4
CH50, U/ml	33.8 ± 9.4
White Blood Cell, /μl	5161.2 ± 1899.2
Lymphocytes, /μl	1129.3 ± 653.3
Platelet, × 10 ⁴ /μl	22.0 ± 6.9

Atacept Dose Rationale for a Phase 3 Study in Patients with High Disease Activity and Auto-Antibody Positive SLE

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Atacept targets the B-cell-stimulators BLyS and APRIL, and is in development for the treatment of patients (pts) with SLE. Here, we integrated non-clinical and clinical data to determine an appropriate atacept dose for a Phase 3 (P3) study in auto-antibody positive SLE pts with high disease activity (HDA).

Methods: Non-clinical data for atacept were obtained from two murine models: a spontaneous SLE model (given control or mouse TACI-Fc 5 mg/kg intraperitoneally [IP] 3 times per week [wk]) and a 4-hydroxy-3-nitrophenylacetyl-Keyhole Limpet Haemocyanin (NP-KLH) vaccinated model to assess immunomodulation (given control or atacept 1, 3 or 10 mg/kg IP every third day). Clinical data were obtained from a P1 pharmacokinetic (PK) study in healthy participants (Study 022; single-dose atacept 25, 75 or 150 mg) and two P2 studies in pts with autoantibody-positive SLE (APRIL-SLE [NCT00624338]; ADDRESS II [NCT01972568]). In both P2 studies, pts were randomized (1:1:1) to once-wkly (QW; initial 4 wks of twice-weekly dosing in APRIL-SLE) subcutaneous atacept (75 or 150 mg) or placebo (PBO). Primary endpoints: APRIL-SLE, proportion of pts with BILAG A/B flare over 52 wks; ADDRESS II, SRI-4 response at Wk 24. An analysis of SRI-6 response at Wk 24 was performed in ADDRESS II pts with Screening HDA (SLEDAI-2K \geq 10). A population PK model was developed and population PK model-derived exposure vs probability of clinical response (BILAG A/B flare, SRI-4, SRI-6) evaluated. An exploratory analysis of the impact of atacept exposure on safety was also performed.

Results: In the spontaneous SLE model, TACI-Fc 5 mg/kg prevented proteinuria development and glomerular damage. In atacept-treated NP-KLH vaccinated mice, anti-KLH IgG decreased markedly (>50% reduction vs control at all doses), with mean atacept serum trough concentrations (C_{min}) of ~2.3 μ g/mL (1 mg/kg), ~5 μ g/mL (3 mg/kg) and ~8.5 μ g/mL (10 mg/kg). Atacept 150 mg QW resulted in greater clinical responses than PBO (APRIL-SLE: BILAG A/B flare, time to flare; ADDRESS II: SRI-4 [modified intention-to-treat] and SRI-6 response [HDA]). In both studies, atacept exposure-response (E-R) relationships were identified. For maximal flare reduction, atacept AUC τ (area under the concentration curve over one dosing interval, i.e. 1 wk) \geq 1 mg \cdot hr/mL was identified and was more achievable with 150 than 75 mg (60% vs 15% probability); AUC τ was the exposure metric that contributed to the P3 dose selection. Atacept exposure for maximal flare reduction corresponded to a C_{min} of 5 μ g/mL which was similar to that observed in the murine models. SRI-4 and SRI-6 (HDA) response rates increased with increasing atacept AUC within the exposure range observed in ADDRESS II. Atacept 150 and 75 mg had acceptable safety profiles in SLE pts; there was no apparent E-R relationship for serious infections.

Conclusion: Integrated non-clinical, clinical and E-R data demonstrate an acceptable benefit-risk profile for atacept in SLE pts with HDA and support the selection of 150 mg QW for P3 studies.

Disclosure: J. Shen, EMD Serono Research & Development Institute, Inc. (a business of Merck KGaA, Darmstadt, Germany), 3; O. Papasouliotis, Merck Institute for Pharmacometrics, Lausanne, Switzerland (an affiliate of Merck KGaA, Darmstadt, Germany), 3; E. Samy, EMD Serono Research & Development Institute, Inc. (a business of Merck KGaA, Darmstadt, Germany), 3; P. Haselmayer, Merck KGaA, Darmstadt, Germany, 3; P. Chang, EMD Serono Research & Development Institute, Inc. (a business of Merck KGaA, Darmstadt, Germany), 3; V. Ona, EMD Serono Research & Development Institute, Inc. (a business of Merck KGaA, Darmstadt, Germany), 3; A. H. Kao, EMD Serono Research & Development Institute, Inc. (a business of Merck KGaA, Darmstadt, Germany), 3.

SLEDAI-2K Responder Index-50 Is Effective in Demonstrating Partial Response in a Phase 2, Randomized Placebo-Controlled Study of Ustekinumab in Patients with Active Systemic Lupus Erythematosus

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Background/Purpose: Ustekinumab(UST), a monoclonal antibody that targets the shared p40 subunit of the cytokines IL-12 & IL-23, is being investigated in patients (pts) w/ active systemic lupus erythematosus (SLE). While traditional SLE Disease Activity Index 2000 (SLEDAI-2K) scoring assesses complete SLE response for individual disease manifestations, the SLEDAI-2K Responder Index-50 (S2K RI-50) can be used to evaluate SLE responses using partial improvement ($\geq 50\%$) in each domain. To evaluate SLEDAI-2K vs S2K RI-50 response in a randomized, placebo (PBO) controlled trial of UST in pts w/ active SLE.

Methods: We conducted a phase 2, PBO-controlled study in adults w/ active disease (SLEDAI score ≥ 6 with ≥ 1 BILAG A &/or ≥ 2 BILAG B scores) despite standard-of-care therapy. Pts (n=102) were randomized (3:2) to receive UST IV ~6 mg/kg or PBO at week (wk) 0, followed by SC injections of UST 90mg q8w or PBO beginning at wk8, both added to standard of care. We calculated S2K RI-50 response at wk24 using various thresholds to define response including a decrease of at least 1, 2, 3, 4, 5, or 6 points from baseline in the S2K RI-50 score. We also compared the proportion of patients w/ SLEDAI-2K response vs S2K RI-50 response in pts receiving UST (n=62) vs PBO (n=40) at wk24.

Results: Change from baseline SLEDAI-2K & S2K RI-50 scores were strongly correlated ($R=0.92$, $p<0.0001$) at wk24. A greater proportion of UST vs PBO pts achieved S2K RI-50 response at wk24, regardless of threshold used to define response (Table). The greatest differences in S2K RI-50 response rates between UST vs PBO were observed for a 4-point decrease (23.3%, $p=0.010$), a 5-point decrease (22.8%, $p=0.023$), & a 6-point decrease (26.5%, $p=0.014$) from baseline. S2K RI-50 captured more responders than SLEDAI-2K at wk24, however, the difference in SLEDAI-2K 4-point response in UST vs PBO was $\square 27\%$ ($p=0.005$) while S2K RI-50 was $\square 23\%$ ($p=0.010$).

Conclusion: S2K RI-50 is an instrument that can capture partial clinically important improvement of $\geq 50\%$ in SLE disease manifestations. The data suggests cut points for defining S2K RI-50 response in clinical trials of patients with moderate-to-severe SLE disease activity.

Table 1. S2K RI-50 response rates at Wk24 for various thresholds to define response

Decrease from Baseline	UST (%) ^{a,b}	PBO (%) ^{a,b}	Difference between UST & PBO	p-value ^c
1 Point Decrease	95.3	88.6	6.7	0.1334
2 Point Decrease	93.5	79.3	14.2	0.0337
3 Point Decrease	84.1	70.9	13.2	0.0820
4 Point Decrease	84.0	60.7	23.3	0.0104
5 Point Decrease	73.5	50.7	22.8	0.0234
6 Point Decrease	70.5	44.0	26.5	0.0138

Note: S2K RI-50 response is defined differently in each row using different cutoffs.

S2K RI-50 uses partial response definition of $\geq 50\%$ improvement for each individual SLEDAI-2K descriptor.

^a Values for subjects meeting treatment failure criteria are set to missing from point of treatment failure forward.

^b Response based upon multiple imputations for missing data from Wk16 to Wk24, where Markov chain Monte Carlo method is used to make missing pattern monotone & serial logistic regression is used to impute monotone missing. The imputation model includes treatment group & baseline SLEDAI-2K covariate.

^c Test for greater treatment effect in UST over PBO (alternative hypothesis) is based upon logistic regression w/ treatment group, baseline SLEDAI-2K, baseline medication use for SLE & race as covariates.

Disclosure: Z. Touma, Janssen Research & Development, LLC, 2; M. Urowitz, Janssen Research & Development, LLC, 2; D. D. Gladman, Janssen Research & Development, LLC, 2; C. Wagner, Janssen Research & Development, LLC, 3; B. Zhou, Janssen Research & Development, LLC, 3; R. Gordon, Janssen Research & Development, LLC, 3; B. Hsu, Janssen Research & Development, LLC, 3; M. Chevrier, Janssen Research & Development, LLC, 3; S. Rose, Janssen Research & Development, LLC, 3.

Identifying Response for the Systemic Lupus Erythematosus Disease Activity Glucocorticoid Index (SLEDAI-2KG)

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Background/Purpose: Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) Glucocorticoid Index (SLEDAI-2KG) is a valid index able to measure disease activity while accounting for glucocorticoid (GC)dose SLEDAI-2KG has the same descriptors as SLEDAI-2K in addition to a new descriptor “GCs” with different weight scores based on the dose of GCs. We aimed to: 1) determine the best cut-off for SLEDAI-2KG in identifying responders, 2) compare the performance of SLEDAI-2K and SLEDAI-2KG in identifying responders.

Methods: Patients seen between January 1995 – April 2018, at a single lupus centre, with SLEDAI-2K ≥ 6 and on GC ≥ 5 mg/day at baseline, and follow-up visits at 3, 6 and 9 months were studied.

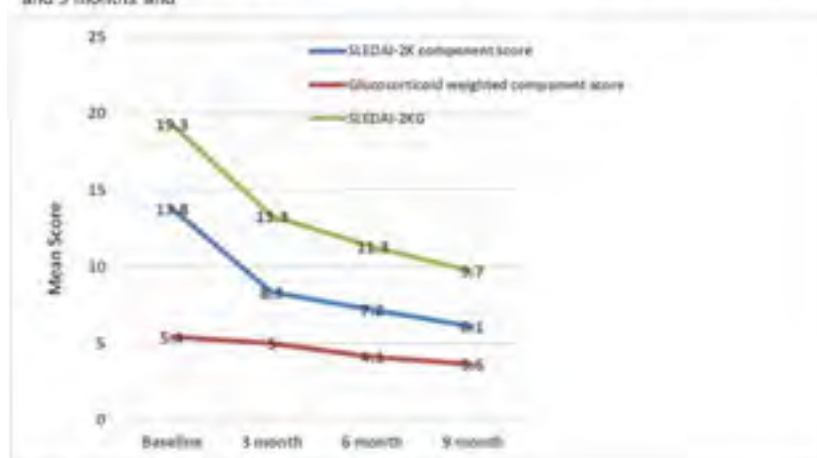
Response to SoC therapy, at follow up visits were assessed by SLEDAI-2K and SLEDAI-2KG. The weighted GC score is as follows: <5 mg/day = 0; 5 mg/day = 1; 7.5 mg/day = 2; 10-12.5 mg/day = 3; 15-17.5 mg/day = 4; 20-22.5mg/day = 5; 25-30 mg/day = 6; 32.5-42.5 mg/day =7; ≥ 45 mg/day=8. The performances of SLEDAI-2K and SLEDAI-2KG were compared using different cut-off points; 4, 5 and 6. Descriptive statistics and McNemar’s tests for paired responses at the same time point and level were performed in the analysis. A sensitivity analysis was conducted for patients on GC ≥ 10 mg/day. To gain insight on the decrease of SLEDAI-2KG scores, we evaluated SLEDAI-2K scores and GCs weighted scores change on follow up visits.

Results: Of the 247 patients, 86.2% female, 47.9% Caucasian, 19.7% Black, 15.4% Asian, 17.0% other. The mean age at SLE diagnosis was 31.0 ± 13.0 and mean age at baseline was 35.7 ± 13.4 years. SLE duration was 9.02 ± 7.74 years. Mean SLEDAI-2K and SLEDAI-2KG at baseline was 13.8 ± 6.9 and 19.3 ± 7.8 respectively. The mean GC dose at baseline was 28.6 ± 19.7 mg/day.

The results confirmed that a **cut-off of 5** is the best for SLEDAI-2KG in identifying responders and SLEDAI-2KG identified more responders at 3, 6 and 9 months in patients taking ≥ 5 mg and ≥ 10 mg/day of GCs (table 1).

The decrease in SLEDAI-2KG scores on follow-up is the result of decrease in the scores of its components SLEDAI-2K and GCs weighted scores. Figure 1 illustrates the mean SLEDAI-2KG scores and its component scores including both the SLEDAI-2K component and the weighted GC dose at baseline, 3, 6 and 9 months follow-up.

Figure 1. Mean SLEDAI-2KG and components scores: SLEDAI-2K and weighted GC score at 3, 6 and 9 months and



Conclusion: The cut-off 5 is the most appropriate to identify responders by SLEDAI-2KG. Also, SLEDAI-2KG, is superior to SLEDAI-2K in identifying responders at 3, 6 and 9 months in patients taking ≥ 5 and ≥ 10 mg/day of GCs. The decrease of SLEDAI-2KG scores resulted from the decrease of its components-SLEDAI-2K scores and the weighted scores of GC.

Table 1. Responders by SLEDAI-2K and SLEDAI-2KG at 3, 6 and 9 months after baseline using different cut-offs

Index Point Reduction	Baseline GC dose ≥ 5 mg/day (N=188)		
	SLEDAI-2K (%)	SLEDAI-2KG (%)	McNemar's Agreement test(p values)
3 MONTHS			
4 Point Reduction	113 (60.1)	110 (58.5)	-
5 Point Reduction	87 (46.3)	99 (52.7)	0.0143
6 Point Reduction	85 (45.2)	90 (47.9)	-
6 MONTHS			
4 Point Reduction	126 (67.0)	125 (66.5)	-
5 Point Reduction	103 (54.8)	113 (60.1)	0.025
6 Point Reduction	101 (53.7)	105 (55.9)	-
9 MONTHS			
4 Point Reduction	143 (76.1)	149 (79.3)	-
5 Point Reduction	112 (59.6)	133 (70.7)	<0.001
6 Point Reduction	108 (57.5)	122 (64.9)	0.004

Disclosure: Z. Touma, GlaxoSmithKline, 2; D. D. Gladman, Amgen, AbbVie, Celgene, Eli Lilly, Janssen, Novartis, Pfizer and UCB, 2, Amgen, AbbVie, BMS, Celgene, Eli Lilly, Janssen, Novartis, Pfizer and UCB, 5; J. Su, None; N. Anderson, None; M. Urowitz, GlaxoSmithKline, 2.

Abstract Number: 2645

The Impact of Metformin on Disease Activity in Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

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Background/Purpose: Metformin is a mainstay of therapy for type 2 diabetes mellitus. Newer evidence suggests that metformin may reduce lupus flares. An entity called neutrophil extracellular traps (NETs) has been found to be important in the pathogenesis of lupus, as they promote plasmacytoid dendritic cells (PDCs) to differentiate and activate. These PDCs, when activated, release interferon α (IFN α), which plays a pivotal role in the pathogenesis of lupus. The formation of NETs is reactive oxygen species (ROS) dependent. Metformin can selectively inhibit mitochondrial respiratory chain complex I and decrease NADPH oxidase activity leading to a reduction in ROS production. A November 2015 article by Wang H, et al in Arthritis and Rheumatology designed a randomized, proof-of-concept trial to evaluate the efficacy and safety of metformin on a background of corticosteroids and conventional immunosuppressive agents in patients with mild or moderate lupus. That study demonstrated that add-on metformin reduced the risk of disease flares by 51% compared with conventional treatment only. Prednisone exposure was also lower in the metformin add-on group than in the conventional treatment group. The objective of our study is to compare the disease activity of lupus patients on metformin versus those not on metformin.

Methods: We conducted a retrospective review of lupus patients followed in our Rheumatology clinic over one year. The primary outcome was to determine if lupus patients on metformin had lower disease activity compared to those not taking metformin. The population for review included those from the Lupus Initiative. We compared the mean Systemic Lupus Erythematosus Activity Index (SLEDAI) scores which measures disease activity between the two groups.

Results: In total, 15 patients out of 1446 patients with lupus were taking metformin. Using a Wilcoxon rank sum test, there was a statistically significant difference in patients SLEDAI scores between the lupus patients taking metformin versus the lupus patients not taking metformin (SLEDAI $z=-2.7$, $p=0.0061$). We found that the average SLEDAI score in those patients taking metformin was lower compared to those who were not on metformin. This is likely due to the mechanism of metformin which selectively inhibits mitochondrial respiratory chain complex I and decreases NADPH oxidase activity leading to decreased production of ROS. Reduced ROS production thus leads to fewer NETs forming, thus fewer PDCs differentiate and there is reduced release of IFN α which is a pivotal player in the pathogenesis of lupus. Further study comparing the mean prednisone dose between the two groups is currently underway.

Conclusion: We identified that lupus patients taking metformin had a lower median SLEDAI score compared to the patients not taking metformin. Metformin may play an important role in decreasing lupus flares by targeting NET activity and further research into this association should be done, as this may be one of the new approaches to treating lupus.

Disclosure: C. McLeod, None; G. Olayemi, None; N. Bhatia, None; F. Migliore, None; R. Quinet, None.

Abstract Number: 2646

Disparities in Antimalarial Prescribing for Systemic Lupus Erythematosus Nephritis Using a Real-World, Electronic Health Record

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Session Information

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Background/Purpose: Antimalarials (AMs) improve survival in patients with systemic lupus erythematosus (SLE). Current guidelines suggest AMs for all SLE nephritis patients. Studies using patient-reported data showed AMs are not universally prescribed. Using a real-world electronic health record (EHR) cohort, SLE nephritis vs. non-nephritis patients were less likely to be prescribed AMs. We examined if patient or prescriber characteristics impact AM prescribing patterns.

Methods: Potential SLE cases were from a de-identified EHR with 2.8 million subjects using a previously validated algorithm of 4 or more counts of the SLE ICD-9 code(710.0) and antinuclear antibody (ANA) positive (titer $\geq 1:160$) while excluding dermatomyositis and systemic sclerosis ICD-9 codes. A subject was a case if diagnosed with SLE by a specialist (rheumatologist or nephrologist). SLE nephritis was defined as positive renal biopsy or clinical diagnosis by a specialist. We assessed for current use of AMs as documented by a specialist's note closest to October 1, 2015 (end of ICD-9 coding). We collected age at time of analysis, sex, race/ethnicity, specialist prescribing AM, and whether patients underwent dialysis or kidney transplant. The kidney function and blood counts closest to the specialist's note date were recorded. We evaluated for differences in SLE cases currently prescribed AMs vs. those not using the Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables.

Results: Our validated algorithm identified 1147 potential SLE subjects with 977 chart-confirmed SLE cases and 244 SLE nephritis cases. Of the SLE nephritis cases, mean age was 43 ± 16 years with 89% female, 47% Caucasian, 44% African American, 6% Asian, and 3% Hispanic. Among cases, 81% were followed by a rheumatologist with 38% ever on dialysis and 21% receiving kidney transplant. Only 63% ($n = 153$) of SLE nephritis cases were current AM users. No retinopathy was noted in cases not prescribed AMs. There were no differences in sex or race between current vs. non-current users (Table 1). Current users were significantly younger than non-current users ($p < 0.001$). Patients were more likely to be prescribed AMs when followed by a rheumatologist vs. a nephrologist (76% vs. 37%, $p < 0.001$). Current vs. non-current users were less likely to be on dialysis ($p < 0.001$) and less likely to have had a kidney transplant ($p < 0.001$). Current vs. non-current users had significantly lower creatinine ($p < 0.001$), lower urine protein/creatinine ratio ($p = 0.04$), and higher hemoglobin ($p < 0.01$).

Conclusion: Using a large EHR cohort, only 63% of SLE nephritis cases are currently prescribed AMs. As AMs reduce renal damage in SLE nephritis, our results demonstrate an opportunity to target future efforts to improving adherence to guidelines for AM prescribing.

Table 1.

SLE nephritis cases (n = 244)	Currently Prescribed Antimalarials (n = 153)	Not Currently Prescribed Antimalarials (n = 88)	p value ^a
Current age, mean \pm SD (years)	39 \pm 14	50 \pm 17	< 0.001
Sex, n (%)			0.68
Female	134 (63%)	79 (37%)	
Male	19 (68%)	9 (32%)	
Race/ethnicity, n (%)			0.46
Caucasian	73 (66%)	37 (34%)	
African American	60 (59%)	42 (41%)	
Hispanic	5 (63%)	3 (37%)	
Asian	11 (79%)	3 (21%)	
Prescribing specialistb, n (%)			< 0.001
Rheumatology	142 (76%)	46 (24%)	
Nephrology	10 (37%)	17 (63%)	
Both	0 (0%)	14 (100%)	
Dialysis, n (%)	35 (38%)	56 (62%)	< 0.001
Renal transplant, n (%)	13 (26%)	37 (74%)	< 0.001
Serum creatinine, mean \pm SD	1.8 \pm 2.7	3.0 \pm 3.2	< 0.001
Urine protein/creatinine ratio, mean \pm SD	1.4 \pm 2.6	3.0 \pm 6.3	0.04
WBC count, mean \pm SD	7.4 \pm 5.4	8.0 \pm 4.9	0.07
Hemoglobin, mean \pm SD	12.1 \pm 2.1	11.2 \pm 2.3	< 0.01
Platelet count, mean \pm SD	240 \pm 91	224 \pm 93	0.23

^a Chi-square, Fisher's exact test, or Mann-Whitney U test

^b Both indicates followed by rheumatologist and nephrologist

Disclosure: W. Xiong, None; J. B. Boone, None; C. P. Chung, None; L. Crofford, None; A. Barnado, None.

Abstract Number: 2647

Comparison of Low-Dose Intravenous Cyclophosphamide with Oral Mycophenolate Mofetil in the Treatment of Lupus Nephritis: Long Term Follow-up Data

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Background/Purpose: We present the long-term follow-up of patients with lupus nephritis who completed the randomized controlled trial on comparison of low-dose intravenous cyclophosphamide (IV CYC) with oral mycophenolate mofetil (MMF) as the induction therapy.

Methods: Prospective data on kidney function and survival in 83 out of 100 patients, who completed the initial trial, were collected over at least 36 months. Response, number of relapses, and time to first relapse were compared between the low dose IV CYC and oral MMF group on follow-up. Response, complete remission (CR) and partial remission (PR) and relapse (mild, moderate and severe) were defined according to Kidney Disease Initiative Global Outcomes (KDIGO) criteria.

Results: Of the initial 100 patients randomized to two groups, 83 patients (42 in IV CYC arm and 41 in oral MMF arm) completed 24 weeks study period. Of these, 67 patients had achieved treatment response, while 16 patients did not achieve response. All the 67 responders were started on azathioprine as the maintenance agent. On follow-up, 15 relapses occurred in the MMF group (13 patients had 1 relapse each and 2 had more than 1 relapse) and 12 relapses were seen in the IV CYC group (12 patients had 1 relapse each) on a follow-up of 36 months ($p > 0.05$). Of the 15 relapses in the MMF group, 9 were mild, 5 were moderate and 1 was severe relapse, respectively. The patient with severe relapse died due to disease activity at 36th month of follow-up. Of the 12 relapses in the IV CYC group, 8 were mild and 4 were moderate relapses, respectively.

Of the 16 non-responders, 11 were started on azathioprine, 4 were started on alternate induction agent and one patient was continued on the same induction agent. Of the 11 patients on azathioprine, the mean time to achieve response was 9.38 months in all, except in 3 lost to follow-up and 3 had mild relapse on follow-up. Of the 4 patients on alternate induction therapy, 2 required further change in therapy, 1 responded at 18 months and 1 died at 12 months due to disease activity. The patient on the same induction agent achieved response at 30 months. Overall, the mean time to first relapse was 23.95 months in the IV CYC group and 23.22 months in the oral MMF group ($p=0.807$).

Conclusion: Long term follow-up data shows that both low dose IV CYC and oral MMF induction therapy followed by azathioprine maintenance are equally effective in maintaining response in patients with lupus nephritis.

Disclosure: M. Rathi, None; A. Sharma, None; J. Sharma, None; K. L. Gupta, None.

Abstract Number: 2648

Relationship between Damage and Mortality in Juvenile-Onset Systemic Lupus Erythematosus: Cluster Analyses in a Large Cohort from the Spanish Society of Rheumatology Lupus Registry

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To identify patterns (clusters) of damage manifestation within a large cohort of juvenile SLE (jSLE) patients and evaluate their possible association with mortality.

Methods: This is a multicentre, descriptive, cross-sectional study of a cohort of 345 jSLE patients from the Spanish Society of Rheumatology Lupus Registry (RELESSER). Organ damage was ascertained using the Systemic Lupus International Collaborating Clinics Damage Index. Using cluster analysis, groups of patients with similar patterns of damage manifestation were identified and compared.

Results: Mean age (years) \pm S.D. at diagnosis was 14.2 ± 2.89 ; 88.7% were female and 93.4% were Caucasian. Mean SLICC/ACR DI \pm S.D. was 1.27 ± 1.63 . A total of 12 (3.5%) patients died. Three damage clusters were identified: Cluster 1 (72.7% of patients) presented a lower number of individuals with damage (22.3% vs. 100% in Clusters 2 and 3, $P<0.001$); Cluster 2 (14.5% of patients) was characterized by renal damage in 60% of patients, significantly more than Clusters 1 and 3 ($P<0.001$), in addition to increased more ocular, cardiovascular and gonadal damage; Cluster 3 (12.7%)

was practically the only group with musculoskeletal damage (100%), significantly higher than in Clusters 1 and 2 ($P<0.001$). The overall mortality rate in Cluster 2 was 2.2 times higher than that in Cluster 3 and 5 times higher than that in Cluster 1 ($p<0.017$ for both comparisons).

Conclusion: In a large cohort of jSLE patients, renal and musculoskeletal damage manifestations were the two dominant forms of damage by which patients were sorted into clinically meaningful clusters. We found two clusters of jSLE with important clinical damage that were associated with higher rates of mortality, especially for the cluster of patients with predominant renal damage. Physicians should be particularly vigilant to the early prevention of damage in this subset of jSLE patients with kidney involvement.

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Prevalence of Cancer in Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

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Background/Purpose: Cancer is one of the main causes of morbidity and mortality worldwide. The overall risk of cancer in SLE is higher than in the general population (SIR 1.14). Objectives: To determine the incidence and prevalence of cancer in patients with SLE. To identify prevalent types of cancer and associated risk factors. To estimate mortality of patients with SLE due to neoplastic etiology.

Methods: A cohort study was conducted, all medical charts of patients diagnosed with SLE (ACR 1982/97 classification criteria) by different Rheumatology Services from January 2000 to June 2016 were reviewed. We studied sociodemographic variables and those related to SLE and to cancer. Statistical analysis: Descriptive, Prevalence, Incidence, Chi²-exact test, T Test and Mann Whitney, ANOVA, Multiple Linear Regression, Kaplan-Meier curves.

Results: We included 303 SLE patients, 88.4% women. Twenty-two cancers were diagnosed in 18 patients, determining a prevalence of 5.9% [IC 95% 3.3-8.6] and an annual incidence rate of 5.2 / 1000 inhabitants, both rates being higher compared to the general population ($p=0.0001$, $p=0.02$ respectively), and a risk of cancer of 2.4. The mean age at diagnosis of cancer was 46 ± 12.9 years, 94.4% were women and 16.6% (3/18) had a family history of cancer. Five types of cancers were observed: 8 cervical, 3 breast, 3 ovarian, 3 thyroid, 1 non-Hodgkin's lymphoma. All patients received treatment (14 surgeries, 1 chemotherapy and 3 combined), 15 remitted and 2 developed metastases. Three patients had 2 cancers and 1 patient had 3. There was no association between the presence of cancer and smoking, alcoholism, obesity or immunosuppressive treatment. Patients with cancer had more comorbidities such as arterial hypertension (55.5% vs 44.5%, $p=0.031$) and diabetes (22.2% vs 3.9%, $p=0.009$) compared with those who did not have cancer. In the regression analysis, greater cumulative damage, older age at diagnosis of SLE, longer disease duration and HPV infection were significantly associated with cancer. The mean survival time in patients with SLE who had cancer was 10.8 years. Thirty six patients died, 33 due to other causes and 3 due to cancer. The cancer mortality rate per year was 3.9%.

Conclusion: The prevalence of cancer in patients with SLE was 5.9%, with an annual incidence of 5.2 / 1000 inhabitants. The most frequent types of cancer were: cervix, breast, ovarian, thyroid and lymphoma. The risk factors that were associated with cancer were HPV infection, higher SLICC/SDI, older age at diagnosis of SLE and longer time of evolution of SLE. The death rate due to cancer was 3.9%.

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Abstract Number: 2650

Efficacy, Safety, and Predictor of Response to Belimumab in a Large Nationwide Cohort Study of Patients with Active Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To investigate effectiveness, safety, and predictors of response to belimumab in patients with active SLE in clinical practice setting.

Methods: Four hundred and one active SLE patients (ACR criteria) with positive anti-dsDNA antibody and low C3 and/or C4, from 22 Italian Centers, were treated with belimumab (10 mg/kg day 0, 14, 28 and then every 28 days), as add-on therapy. They were 366 (91.27%) females, mean age 43.51±11.20 years; mean disease duration 12.79±8.74 years. SLEDAI-2K, anti-dsDNA, C3, C4, prednisone daily dose, DAS-28, 24-hours proteinuria, CLASIa (Cutaneous LE Disease Area and Severity Index Activity), PGA, Fatigue (VAS 0-10) were recorded at baseline and every 6 months. SLICC-DI was evaluated 5-years before belimumab initiation, at baseline and every year after belimumab initiation. Response was evaluated according to SLE Responder Index-4 (SRI-4) at 12, 24, 36 and 48 months. Adverse events (AEs) were subdivided in noninfectious or infectious AE, and infusion reactions. AE was defined as severe (SAE) when hospitalization was required and/or death and/or life-threatening manifestations occurred. Statistics were performed by pairs T-test, chi-square test and multiple logistic regression analysis using SPSS package (version 22.0).

Table. Variation of clinical and serologic disease activity variables in patients with active lupus treated with belimumab

	N° pts*	Baseline	6 months	12 months	18 months	24 months	36 months	48 months	60 months	p
SLEDAI-2K	401	8.03±3.36	4.96±3.23	3.81±2.70	3.81±3.15	3.52±2.77	2.64±2.31	2.82±2.42	2.67±2.03	<0.0001
Prednisone daily dose (mg/day)	401	10.44±8.05	6.65±4.58	3.32±4.71	4.31±4.03	3.76±3.66	3.46±2.88	3.39±4.30	3.44±4.48	<0.0001
DAS-28	389	3.35±1.69	2.48±1.54	2.18±1.55	1.94±1.35	1.70±1.25	1.61±1.46	1.44±1.39	1.43±1.41	<0.0001
CLASI-a	234	3.29±4.66	1.88±3.30	1.00±2.18	0.35±2.12	0.60±1.78	0.38±1.39	0.56±1.39	0.22±0.73	<0.0001
PGA	356	1.79±0.59	1.15±0.71	0.84±0.62	0.81±0.71	0.75±0.63	0.66±0.59	0.67±0.56	0.72±0.63	<0.0001
Fatigue (VAS 0-10)	197	5.21±2.99	4.26±2.80	3.31±2.58	2.84±2.66	2.80±2.60	2.53±2.91	2.33±2.73	2.42±2.95	<0.0001
Anti-dsDNA (ELISA, KU/L)	131	230±354	144±217	118±179	107±164	99.2±162	71.5±104	74.4±145	23.0±56.2	<0.006
Anti-dsDNA (CLIA)	63	148±185	128±177	112±167	83.5±147	67.5±125	54.1±15.6	36.7±86.9	18.2±41.5	<0.015
C3 (mg/dl)	401	70.1±38.8	57.5±41.8	61.2±41.8	59.8±43.1	62.1±41.8	59.2±43.2	64.9±42.6	73.3±43.3	<0.001
C4 (mg/dl)	401	7.74±7.72	10.4±8.54	11.2±9.29	11.2±9.44	11.9±9.32	11.8±9.32	13.8±10.1	13.8±9.73	<0.006
24-h proteinuria (g/die)	77	1.28±1.1	0.83±0.85	0.39±0.39	0.58±0.68	0.58±0.59	0.58±0.76	0.44±0.495	0.64±0.33	0.012

*Number of patients at baseline.

p calculated using univariate analysis

SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2000; CLASI-a: Calcutta Lupus erythematosus Activity and Severity Index-

activity; DAS-28: disease activity score-28 joints; anti-dsDNA: anti-double stranded DNA ELISA; Enzyme-Linked Immunosorbent Assay; pts:

patients; CLIA: chemiluminescent immunoassay

Results: Mean follow-up was 21.07±15.34 months (range 3-60). Active manifestations requiring the use of belimumab were articular in 40.82%, mucocutaneous in 21.84%, renal in 14.56%, hematologic in 16.32% and serositis in 6.24% of cases. SRI-4 was achieved by 68.2%, 73.3%, 74.7% and 68.3% of patients at 12, 24, 36 and 48 months, respectively. The improvement in clinical and serological variables during the follow-up are reported in the Table.

We observed a decrease in the mean number of flare during belimumab treatment compared with the corresponding period before belimumab initiation (p<0.0001).

SLEDAI-2K ≥10 resulted as an independent predictor of response by logistic regression at month 12 and 24 (p=0.003 and p=0.025).

Mean SLICC-DI was 0.71±1.07 five years before belimumab initiation, 0.96±1.31 at baseline and 1.00±1.52, 1.09±1.70, 1.27±1.91 at 24, 36 and 48 months of follow-up, respectively. We observed a significant increase in mean SLICC-DI between 5 years before belimumab initiation and baseline (p<0.01), but not between baseline and 2-year follow-up.

A total of 8,831 infusions were analyzed. A total of 681 AEs were observed in 298 patients, SAEs were 32 in 29 patients. No severe infusion reactions were observed; 15 patients had infective SAEs, and 18 non infective SAEs.

Conclusion: Belimumab reduces global and organ specific disease activity, frequency of flares and prednisone daily dosage. SLEDAI-2K ≥10 at baseline was the best predictor of response in our cohort of patients with active SLE. Belimumab was well tolerated.

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Patients Characteristics and Patters of Treatment in Refractory Systemic Lupus Erythematosus Patients in the Pre-Biologic Period: Data from a Multiethnic, Multinational Latin American Lupus Cohort

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Session Information

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Background/Purpose: Over the last few years, the importance of treating patients with systemic lupus erythematosus (SLE) towards achieving Remission or Low Disease Activity State has become the goal. Nevertheless, some patients remain with active disease despite full immunosuppressive drugs, and are usually called active refractory lupus. The present study was conducted to describe the clinical characteristics and treatment patterns for refractory lupus patients from a multi-ethnic, multicenter lupus cohort (GLADEL for Latin American Group for the Study of Lupus).

Methods: Between 1997 and 2005, GLADEL established an observational inception cohort constituted by more than 1400 SLE patients. This cohort comprises 34 centers with experience in SLE (tertiary referral centers with a lupus clinic, an academic profile and a rheumatology training program). Sociodemographic, clinical, immunological, treatment characteristics, disease activity and damage data were obtained at all visits. For the purpose of this study, refractory SLE was defined as patients with SLE Disease Activity Index (SLEDAI)–2K ≥ 6 points and a stable treatment regimen with fixed doses of prednisone ≥ 7.5 mg/day, or immunosuppressive drugs for at least 30 days at any point during follow up. The renal and CNS items of the SLEDAI–2K were not considered for scoring the SLEDAI-2K. Sociodemographic, clinical, immunological, treatment characteristics and disease activity are described as median (interquartile range, IR) and number (percentages); All analyses were performed using the SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results: The cohort consisted of 1432 patients; 262 (18.3%) of them had refractory SLE. Of them, 229 (87.4%) were women and their median ages (diagnosis, refractory) were 27.0 and 28.8 years; 137 (52.3%) patients were Mestizos, 87 (33.2%) Caucasians and 29 (11.1%) were African-Latin Americans. Table 1 depicts these patients' sociodemographic and SLEDAI–2K clinical and immunological characteristics, while Table 2 shows their patterns of treatment at time of being refractory.

Conclusion: In this pre-biologic period, refractory Latin American lupus patients presented most frequently with arthritis and new rash while they were treated with glucocorticoids, azathioprine and cyclophosphamide.

Table 1. Sociodemographic and SLEDAI clinical and immunological characteristics of GLADEL patients with refractory disease.

Variable, (n, %)	Refractory lupus (n=262)
Age at diagnosis, years, median	27.0 (20.0-36.0)
Age at refractory, years, median	28.8 (21.5-36.6)
Female	229 (87.4)
Ethnicity,	
Mestizo	137 (52.3)
Caucasian	87 (33.2)
African-Latin American	29 (11.1)
Socioeconomic status	
Low	159 (60.9)
Middle	72 (27.6)
High	30 (11.5)
Education	
0-7 years	159 (60.9)
8-12 years	131 (51.8)
>12 years	49 (19.4)
SLEDAI at refractory, median	11 (8-19)
SLEDAI items	
Vasculitis	41 (15.7)
Arthritis	202 (77.1)
Myositis	5 (1.9)
New rash	114 (43.5)
Alopecia	98 (37.4)
Mucosal ulcers	60 (22.9)
Pleurisy	37 (14.1)
Pericarditis	29 (11.1)
Low complement	120 (45.8)
Increased DNA binding	113 (43.1)
Fever	58 (22.1)

Table 2. Patterns of treatment in refractory patients from GLADEL.

Variable, (n, %)	Refractory lupus (n=262)
Antimalarials	
Added or increased	22 (8.4)
Stay on	155 (59.2)
Glucocorticoids (Prednisone dose or equivalent) any dose	
Added or increased	22 (8.4)
Stay on	237 (90.5)
Glucocorticoids (Prednisone dose or equivalent) > 20 mg/d	145 (55.3)
Azathioprine	
Added or increased	68 (26.0)
Stay on	39 (14.9)
Cyclophosphamide use	
Added or increased	61 (23.3)
Stay on	29 (11.1)
Cyclosporine	
Added or increased	8 (3.1)
Stay on	4 (1.5)
Methotrexate	
Added or increased	19 (7.2)
Stay on	24 (9.2)

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Engaging the Cholinergic Anti-Inflammatory Pathway By Stimulating the Vagus Nerve Reduces Pain and Fatigue in Patients with SLE

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Musculoskeletal (MS) pain is a common symptom of patients with Systemic Lupus Erythematosus (SLE) affecting up to 95% of patients and contributing to a reduced quality of life. Safe and efficacious treatment remains an unmet need for this disease feature. The cholinergic anti-inflammatory pathway is a physiologic mechanism diminishing inflammation. Stimulation of the vagus nerve results in reduction of inflammatory mediators with beneficial effects in both human inflammation and animal models of disease. We proposed to evaluate transcutaneous, noninvasive stimulation of the vagus nerve through its auricular branch in SLE patients with MS pain.

Methods: 18 SLE patients with MS pain ≥ 4 on an anchored 10cm Visual Analog Scale for pain and MS activity defined by SLEDAI-2K arthritis or a BILAG MS score $\geq C$, were randomized (2:1) in this double-blind study to receive 5 minutes of transcutaneous auricular vagus nerve or sham stimulation (taVNS or SS) for 4 consecutive days. Patients with a diagnosis of fibromyalgia were excluded. For sham stimulation, electrodes were placed on the earlobe and no current was delivered. Evaluations at baseline, day 5 and day 12 included patient assessments of pain, disease activity (PtGA) and fatigue. Tender and swollen joints, SLEDAI-2K and the Physician Global Assessment (PGA) were completed by a blinded

Change of clinical parameters and biomarkers from Day 1/Baseline

	Day 5			Day 12		
	taVNS median (IQR)	SS median (IQR)	P ¹	taVNS median (IQR)	SS median (IQR)	P ¹
Δ VAS pain (0-10mm)	-5.00 (-5.80, -3.10)	0.10 (-10.0, 1.00)	0.049	-5.35 (-5.80, -1.45)	0.15 (-0.60, 0.70)	0.079
Δ FACIT-F ²	11.00 (4.50, 16.00)	0.00 (-2.00, 1.00)	0.003	0.00 (0.0, 0.0)	-0.12 (-0.12, 1.10)	0.003
%Tender joint reduction	100.0 (100.0, 100.0)	5.27 (-11.1, 80.0)	0.005	98.49 (50.0, 100.0)	10.00 (0.00, 34.61)	0.050
%Swollen joint reduction ³	100.0 (100.0, 100.0)	9.09 (-8.33, 57.15)	0.019	100.0 (80.0, 100.0)	14.29 (-100.0, 59.09)	0.056
Δ PtGA (0-100mm)	-22.50 (-46.50, 2.50)	4.00 (-2.00, 9.00)	0.125	18.50 (-64.00, -7.00)	-0.52 (-18.00, 9.00)	0.301
Δ PGA (0-3)	-0.51 (-0.99, -0.30)	0.04 (-0.06, 0.12)	0.053	-0.50 (-0.84, -0.08)	0.03 (0.03, 0.12)	0.107
Δ CRP (mg/dL)	0.00 (-0.15, 0.00)	-0.05 (0.00, 0.10)	0.165	0.00 (-0.20, 0.00)	-0.05 (-0.20, 0.20)	1.00
Serum cytokine						
IL-1 α ng/mL	0.00 (0.00, 0.00)	0.12 (-0.12, 1.10)	0.87	0.00 (-0.01, 0.00)	0.25 (0.00, 1.00)	0.080
IL-1 β pg/mL	-0.01 (0.40, 0.20)	-0.01 (-0.02, 0.02)	0.82	-0.01 (-0.04, 0.00)	-0.04 (-0.05, 0.04)	0.87
IL-6 pg/mL	-0.11 (-2.25, -0.01)	0.77 (-1.10, 1.80)	0.14	-0.17 (-2.54, 0.45)	-0.20 (-2.80, 0.10)	0.96
IL-10 pg/mL	0.05 (-0.10, 1.10)	-0.08 (-0.16, 0.30)	0.6	0.12 (-0.17, 0.23)	0.04 (-0.10, 0.40)	0.569
TNF pg/mL	-0.05 (-0.25, 0.12)	0.00 (-0.80, 0.20)	0.94	-0.05 (-0.25, 0.12)	-0.05 (-0.20, 0.20)	0.848

¹ Mann-Whitney Exact test

² Higher FACIT-F scores correspond to lower fatigue

³ Data shown for 7 taVNS and 5 SS subjects with swollen joints at baseline

physician. Potential biomarkers were also determined at these times and included serum levels of acute phase reactants, inflammatory cytokines as well as cytokine levels following whole blood stimulation (WBS) with TLR 4, 7 or 9 agonists.

Results: taVNS and SS were well tolerated with no significant adverse events in 19 enrolled subjects. Per protocol, 1 subject who withdrew after day 3 with a flu-like winter illness was replaced. Baseline characteristics of subjects receiving VNS or SS were similar. Following 4 consecutive days of stimulation, at day 5, subjects receiving VNS had a significant decrease in pain and fatigue compared to SS (Table 1), were more likely (OR =25 p=.02) to experience a minimal clinical significant reduction (1.58) in pain and were more likely to report improvement on a Likert scale. PtGA, joint counts and PGA were improved at day 5 in taVNS compared to SS subjects.. Pain reduction and improvement of fatigue correlated (R=0.49 p=.04, R=.83 p=.003 respectfully) with the average stimulation level. In general, response was maintained through day 12. Examination of serum and WBS biomarkers showed no significant differences at days 5 or 12 compared to baseline.

Conclusion: In a pilot study, VNS resulted in a significant reduction of pain, fatigue and joint scores in SLE patients with MS pain. Additional studies evaluating this promising intervention and its potential mechanisms are warranted.

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Abstract Number: 2653

Contraceptive Documentation in Systemic Lupus Erythematosus Patients at a Safety Net Hospital

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Session Information

Session Date: Tuesday, October 23, 2018

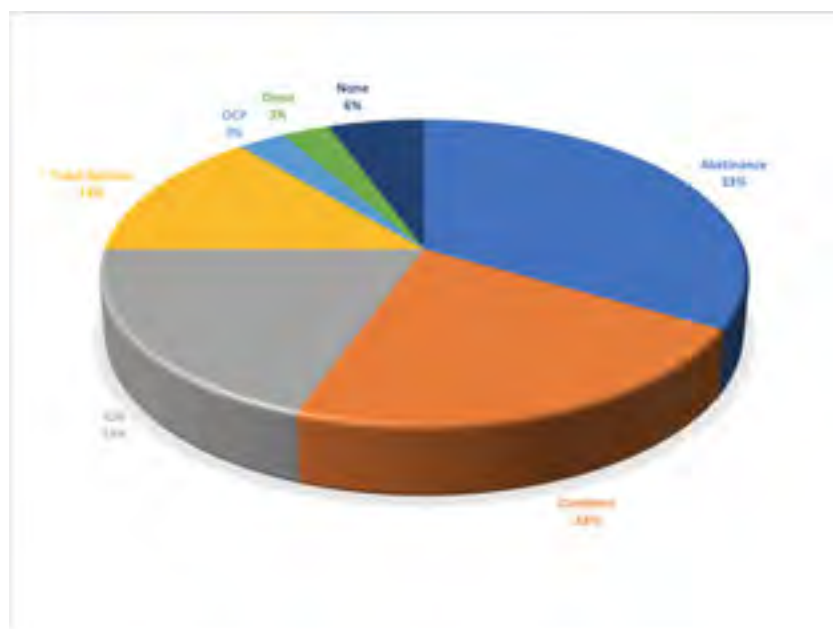
Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic Lupus Erythematosus (SLE) predominately affects reproductive aged women. Contraceptive counseling is an important quality indicator in SLE patient care. Here we evaluate current practice in the documentation of contraceptive use amongst reproductive aged women with SLE cared for at a large safety net hospital.

Methods: Using ICD10 codes for SLE (M32, M320, M321, M328, M329), we identified reproductive aged (ages 16-50) female SLE patients, who presented to the outpatient rheumatology clinic at Parkland Hospital between 07/01/17 and 11/



30/17. We performed a retrospective chart review for contraceptive use documentation. Medication use including potential teratogenic medications was also assessed.

Results: Among 131 clinic encounters, contraceptive use was documented in 61% of encounters. Amongst those women prescribed a potentially teratogenic medication, mycophenolate mofetil was the most common followed by methotrexate. Amongst those on teratogenic medication, documentation of contraception was present in 67% of clinic notes. The average age of women who were on potentially teratogenic medicine and had documented contraception was younger (mean 30, SD 7) than those in whom contraception was not documented (mean 37, SD 10). Greater than 50 % of those patients on potentially teratogenic medicine used less reliable contraceptive methods: abstinence or condoms. Providers rarely documented other information in regard to reproductive health such as pregnancy planning and the desire to have children.

Fig 1. Contraceptive methods used among SLE patients who are on potentially teratogenic medications.

Conclusion: Contraceptive use documentation amongst reproductive aged women with SLE in a safety net hospital is often lacking even amongst those on potentially teratogenic medication. Documentation of contraception is more common in younger women. Identifying barriers to contraceptive use documentation and implementing interventions to facilitate documentation is a future goal.

Disclosure: O. Azzouqah, None; B. L. Bermas, UptoDate, 7.

Abstract Number: 2654

Exposure to Air Pollution and the Onset and Progression of Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Air pollution may contribute to many autoimmune diseases including systemic lupus erythematosus (SLE), but limited information is available on its role in the onset and progression of SLE. The objective of the current study was to determine the relationship between air pollution exposure and characteristics associated with expression and severity of SLE.

Methods: In this retrospective cohort study, we identified patients with childhood onset SLE (cSLE) residing in the greater Cincinnati, OH region at the time of their SLE diagnosis and being followed for their care at Cincinnati Children's Hospital Medical Center (CCHMC). Demographic and clinical information at the time of diagnosis were extracted from our cSLE cohort, and included phenotypic information on SLE (1997 American College of Rheumatology classification criteria) and SLE disease activity index (SLEDAI). Patients' home address at the time of diagnosis was geocoded. Exposure to traffic-related pollutants was estimated for each participant by calculating the distance to the nearest major road. In addition, a previously developed and validated land-use regression model for the study region was applied to estimate the concentrations of elemental carbon attributable to traffic (ECAT), a surrogate marker for traffic related air pollution and specifically attributable to diesel exhaust. SLEDAI scores were categorized as high (> 8) or low to moderate activity (≤8). ECAT concentrations were log transformed and logistic regression was used to estimate the association between air pollution exposures and SLEDAI (high/low) and ACR classification criteria for phenotypic expression of disease.

Results: The cSLE patients' (n = 158) mean age at diagnosis was 16.9 (SD 4.2) years. The majority (76.7%) were female with nearly equal representation of Caucasians and African Americans (42.1% and 41.5%, respectively). ECAT exposures were not associated with overall disease activity (SLEDAI) (Odds Ratio (OR) 1.4 (95% CI 0.3 – 7.1). However, as shown in Table 1 with higher ECAT exposures there was a significantly increased risk for renal involvement (OR = 3 (95% CI 1.0-8.7)) also a trend towards experience more commonly serositis (OR = 3.8 (95% CI 0.8 – 18.2)).

Conclusion: Our preliminary study suggests that environmental exposure to air pollution is associated with increased risk for certain manifestations of cSLE. Further work is needed to establish longitudinal effect of air pollution on the disease activity and cumulative damage and cSLE phenotypes over time.

TABLE 1: Logistic Regression Analysis of log (ECAT) values versus presence of phenotypic features of cSLE at disease onset

Dependent Variable (ACR classification Criteria)	log (ECAT)		P value
	OR	95% CI	
Malar rash	0.631	0.223 – 1.784	0.3852
Discoid rash	1.972	0.485 – 8.019	0.3425
Photosensitivity	1.184	0.419 – 3.347	0.7505
Mucosal ulcers	0.540	0.185 – 1.578	0.2602
Arthritis	0.785	0.241 – 2.556	0.6880
Serositis	3.806	0.795 – 18.224	0.0944
Renal	2.991	1.026 – 8.720	0.0448
Neurologic	1.159	0.290 – 4.631	0.8341
Hematologic	1.082	0.348 – 3.366	0.8920
Immunologic	0.653	0.198 – 2.154	0.4837
ANA	1.071	0.127 – 9.070	0.9495

ECAT = elemental carbon attributable to traffic; ACR = American College of Rheumatology; ANA = Antinuclear antibody

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Abstract Number: 2655

SLE-Key® RuleOut Testing in Support of Patient Triage in the Clinical Rheumatology Setting

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

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Session Time: 9:00AM-11:00AM

Background/Purpose: SLE diagnosis and classification can be challenging. The low incidence of SLE limits primary care physician experience with the disease, but the impact of early diagnosis & treatment on long term outcome makes a compelling case for early referral for rheumatology consultation upon suspicion of SLE. ANA testing, currently used for screening of suspected SLE patients, is characterized by high false positive rates increasing the likelihood of misplaced suspicion of SLE. The diagnostic workup for referred patients is long, costly and often inconclusive, with a high rate of misdiagnosis. Misdiagnosis can lead to use of medications with potential side effects and even irreversible damage as well as significant psychological distress, anxiety and/or depression for the patient as well as family members. Access to a simple serological test to rule out a diagnosis of SLE would contribute to all the stakeholders involved in lupus diagnosis; patients, physicians and payers. The SLE-key® test may represent such a test. The SLE-key® Rule Out test was developed and validated to rule out a diagnosis of SLE with 94% sensitivity and 75% specificity (Putterman C, J Imm Meth 2016). The goal of the current study was to monitor the clinical and financial impact of the test in clinical practice.

Methods: 245 patients were referred from five busy, geographically independent rheumatology clinics. Serum samples and clinical information were collected from both patient and physician with informed consent in a HIPAA compliant manner. Sera along with clinical data were sent to ImmunArray's CLIA-certified laboratory, Veracis (Richmond, VA) for SLE-key® RuleOut testing and evaluation using ImmunArray's iCHIP® platform.

Results: The SLE-key® test effectively ruled out a diagnosis of SLE in >54% of patients referred, including patients with personal or family history of autoimmune disease. Over 300 ANA tests were recorded for this cohort and almost 90% of the patients had at least one positive ANA test result sometime during their clinical evaluation. 55% of these were Ruled Out using the SLE-key test. These included patients referred with multiple symptoms including joint pain, mouth sores and rashes in addition to their ANA positive test. Clinical data from at least one visit post SLE-key® testing was available for

98/134 patients where SLE was ruled out. Clinical diagnosis in 5 (5%) of these cases was SLE. For an additional 8 (8%) cases, SLE remained under consideration as part of the differential diagnosis.

Conclusion: The SLE-key® test can be used to enhance the efficiency of triage of patients referred into the rheumatology practice. More than half of patients referred with symptoms leading to a suspicion of systemic autoimmune rheumatic disease (SARD) may have a diagnosis of SLE quickly eliminated from the diagnostic algorithm. Thus, the SLE-key Rule Out test, can significantly reduce unnecessary costs and diagnostic time and increase the efficiency of healthcare delivery.

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Abstract Number: 2656

Apremilast As Treatment of Refractory Skin Lupus Lesions

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Session Information

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Background/Purpose: Skin lesions of lupus may be refractory to standard therapy. Apremilast is an orally small molecule which inhibits phosphodiesterase-4 (PDE-4) that modulates some inflammatory pathways. Our aim was to assess the efficacy of apremilast in lupus rashes refractory to conventional treatment.

Methods: We set up a retrospective study on 6 lupus patients treated with apremilast at standard dose of 30 mg twice daily, with the initial 5-day titration schedule. The outcome was improvement of lupus rashes.

Results: We studied 6 patients (5 women/1 male); mean age, 40.6±11.5 years with extensive skin lesions due to lupus. Three patients had a discoid lupus and other three patients had systemic lupus erythematosus (SLE) (one with panniculitis, one with polycyclic ring lupus and the other one with psoriasiform lupus). The cutaneous lupus was confirmed in all patients by skin biopsy.

Prior to apremilast all patients had received conventional treatment: topical corticosteroids (n=6), antimalarials (n=6), topical tacrolimus (n=3), oral corticosteroids (n=3), thalidomide (n=1), belimumab (n=2) and rituximab (n=2).

The duration of the cutaneous lesions until Apremilast onset was 148±90.6 months. After a mean follow-up of 6.2±2.9 months, all the patients experienced improvement of the skin lesions (in two patients was complete). In one patient it was necessary to reduce the dose of apremilast to 30 mg/day because of digestive symptoms (diarrhoea and vomiting) (TABLE).

Conclusion: Apremilast can be useful in the treatment of refractory skin lesions of lupus.

TABLE

Patient	Age/Sex	Skin lesions	Previous treatments	Months from diagnosis to Apremilast onset	Apremilast onset		Apremilast follow-up			
					Antinuclear Antibody (ANA)	Simultaneous treatment	Months from Apremilast onset	Adverse effects	Discontinued	Response
1	46 / Female	Polycyclic ring lupus	Prednisone Hydroxychloroquine Thalidomide Belimumab, RTX	300	ANA 1/1280	Prednisone	2	diarrhoea	No	Partial
2	45 / Female	Lupus panniculitis	Prednisone Hydroxychloroquine	156	ANA 1/1280	Prednisone Hydroxychloroquine	7	No	No	Complete
3	36 / Male	Discoid lupus	Prednisone Hydroxychloroquine	ND	ANA (-)	Prednisone Hydroxychloroquine	6	Diarrhoea vomiting	No. 30 mg/24 h	Complete

Table . (Cont'd)

Patient	Age/Sex	Skin lesions	Previous treatments	Months from diagnosis to Apremilast onset	Apremilast onset		Apremilast follow-up			
					Antinuclear Antibody (ANA)	Simultaneous treatment	Months from Apremilast onset	Adverse effects	Discontinued	Response
4	57 / Female	Discoid lupus	Prednisone Hydroxychloroquine	72	ANA (-)	Prednisone Hydroxychloroquine	6	No	No	Complete
5	37 / Female	Discoid lupus	Prednisone Hydroxychloroquine	120	ANA (-)	Prednisone Hydroxychloroquine	10	No	No	Complete
6	23 / Female	Psoriasiform lupus	Prednisone Topical Tacrolimus Hydroxychloroquine Belimumab, RTX	92	ANA 1/160	Prednisone Hydroxychloroquine	4	No	No	Partial

+ RTX =Rituximab; ANA: Antinuclear antibody.

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Abstract Number: 2657

Assessment of Habitual Physical Activity and Performance during Maximal Exercise Test in Systemic Lupus Erythematosus Patients

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Session Information

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Background/Purpose: Patients with systemic lupus erythematosus (SLE) present low physical capacity when compared to healthy controls. In addition to chronotropic incompetence during exercise, slow recovery of post-exertion heart rate and lower values of maximal strength and muscle function are found in SLE when compared with healthy controls. The aim of this study was to evaluate the habitual physical activity measured by the Baecke questionnaire and evaluate performance during maximal exercise in SLE patients and healthy controls.

Methods: Thirty one women with SLE, who met the ACR criteria of 1997 and the Systemic Lupus International Collaborating Clinics criteria of 2012, and 24 healthy women, who were matched by sex, age and body mass index, participated in this study. All participants answered the Habitual Physical Activity Questionnaire (Baecke). This questionnaire is a reminder instrument of the last 12 months, comprising 16 questions and addressing magnitudes such as occupational physical activity (8 questions), physical exercise in leisure (4 questions) and physical leisure and locomotor physical activity (4 questions). The participants were submitted to a maximal exercise test on a motorized treadmill, with increases in velocity every minute until exhaustion in order to assess velocity (km/h), heart rate, Borg scale (6-20) and the reason to interrupting the test (fatigue and/or dyspnea). The test was considered maximal if it reached at least 90% of the maximum heart rate (by the formula 220-age) or reached values of 19 to 20 in the Borg scale.

Results: The evaluation of the habitual physical activity by Baecke questionnaire revealed no significant differences between groups regarding to occupational (p=0.506), sports activity (p=0.945) and physical leisure domains (p=0.904). Half of the controls walked 16 to 30 min/day, while only 22.6% of SLE patients walked the same time. In the maximal exercise test, the control group presented a higher mean maximum heart rate (p=0.001) and maximum velocity (p=0.002). The main reason for discontinuing the test was the occurrence of dyspnea in both, controls and SLE patients (66.67% vs 46.43%).

Conclusion: During the exercise test, the maximum heart rate and maximum velocity reached during the test was lower in SLE patients than the controls. These results suggest cardiorespiratory capacity impairment and low tolerance to physical effort in SLE patients.

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Real World Medication Use in Incident Systemic Lupus Erythematosus and Lupus Nephritis Patients

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease that causes inflammation in connective tissues and can involve multiple organs systems. Lupus nephritis (LN) is an inflammatory kidney disease caused by SLE. There is a gap in the literature regarding the standard of care in SLE and LN patients. This study generated real world medication use among SLE and LN patients.

Methods: This retrospective study used data from two large administrative databases in the US: Truven Health MarketScan[®] and Optum[®] databases to identify adult patients (≥18 years of age) with ≥2 medical claims on different dates for SLE or LN diagnoses from 01 JAN 2013-31 DEC 2015. SLE was identified using the International Classification of Diseases, 9th and 10th Revision, Clinical Modification [ICD-9-CM] codes (710.0) OR ICD-10-CM (M32.10-M32.19, 32.8, 32.9). LN was captured as a subset of SLE using [ICD-9-CM: 710.0 AND (581.81 or 582.81 or 583.81); OR (ICD-10-CM: M32.14)]. The first SLE or LN diagnosis was designated as the index date. Patients were required to have continuous health plan enrollment for 1 year pre-index date (baseline period) and 1 year post-index date (follow-up period) and no prior SLE/LN diagnosis claims or belimumab medical/prescription claim during the baseline period to ensure incident patients were captured. The Truven Health MarketScan[®] and Optum[®] databases were pooled together and duplicates were identified and retained in MarketScan[®] only. Patient demographics and clinical characteristics during the baseline period were assessed. SLE treatment used during the follow-up period was evaluated and the proportion of patients that used SLE medications and average number of medical/prescription claims (#Rx)for each medication were provided.

Results: A total of 31,345 patients were identified including 30,086 SLE and 1,259 LN patients. Key results are shown in Table 1. The mean age was 52.7 years for SLE and 48.3 years for LN patients. Over 80% of the patients were female, with a mean Charlson Comorbidity Index (CCI) score of 1.1 and 1.8 for SLE and LN patients respectively. The most common comorbidities at baseline were hypertension and infections. Corticosteroids (SLE= 58.3%, #Rx=4.5; LN=66.2%, #Rx=6.5) and hydroxychloroquine (SLE=43.4%, #Rx=5.8; LN=40.7% #Rx=6.2) were most commonly used SLE medications during 1-year follow up period. Approximately 2% of patients used biologics including belimumab (SLE=1.1%, #Rx=8.8; LN=1.4%, #Rx=8.3)and rituximab (SLE=0.9%, #Rx=4.2; LN=2.1%, #Rx=4.0).

Conclusion: Our findings indicate a nominal use of biologics (~2%) among SLE and LN patients. Corticosteroids and hydroxychloroquine were most commonly used SLE treatment. These data reveal an unmet need for availability of advanced therapy to treat SLE and LN. Future studies are warranted to understand the underlying causes.

Table 1. SLE Medications during 1 year of follow-up period

	Systemic Lupus Erythematosus (N=30,086)	Lupus Nephritis (N=1,259)
SLE Medications, N (%)		
Corticosteroids ^a	17533 (58.3%)	834 (66.2%)
Number of prescriptions, Mean (SD)	4.5 (5.0)	6.5 (6.0)
Hydroxychloroquine	13061 (43.4%)	513 (40.7%)
Number of prescriptions, Mean (SD)	5.8 (3.6)	6.2 (3.7)
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) ^b	11342(37.7%)	271 (21.5%)
Number of prescriptions, Mean (SD)	3.6 (4.0)	3.0 (3.9)
Angiotensin Converting Enzyme Inhibitor (ACE) ^c	3827 (12.7%)	409 (32.5%)
Number of prescriptions, Mean (SD)	5.4 (3.7)	5.4 (3.7)
Angiotensin II Receptor Blockers (ARB) ^d	3376 (11.2%)	318 (25.3%)
Number of prescriptions, Mean (SD)	5.8 (3.7)	5.6 (4.0)
Methotrexate	2884 (9.6%)	62 (4.9%)
Number of prescriptions, Mean (SD)	5.5 (4.1)	4.9 (3.3)
Immunosuppressante	1239 (4.1%)	83 (6.6%)
Number of prescriptions, Mean (SD)	4.8 (3.8)	4.1 (2.9)
Cyclosporine	1090 (3.6%)	40 (3.2%)
Number of prescriptions, Mean (SD)	2.7 (2.6)	3.8 (3.9)

Table . (Cont'd)

	Systemic Lupus Erythematosus (N=30,086)	Lupus Nephritis (N=1,259)
Mycophenolate Mofetil	985 (3.3%)	397 (31.5%)
Number of prescriptions, Mean (SD)	5.2 (3.7)	6.0 (4.0)
Leflunomide	523 (1.7%)	15 (1.2%)
Number of prescriptions, Mean (SD)	4.3 (3.3)	4.7 (4.0)
Belimumab	306 (1.0%)	17 (1.4%)
Number of medical/prescription claims, Mean (SD)	8.8 (6.5)	8.3 (6.7)
Rituximab	275 (0.9%)	26 (2.1%)
Number of medical/prescription claims, Mean (SD)	4.2 (4.0)	4.0 (4.5)
Cyclophosphamide	98 (0.3%)	67 (5.3%)
Number of prescriptions, Mean (SD)	5.0 (5.0)	4.4 (2.7)

SD: Standard Deviation

^a **Corticosteroids:** Prednisone, Betamethasone, Budesonide, Cortisone, Desoxycorticosterone, Dexamethasone, Fludrocortisone, Hydrocortisone, Methylprednisolone, Paramethasone, Prednisolone, Triamcinolone^b **NSAIDs:** Diclofenac, Bromfenac, Choline and Magnesium salicylate, Methenamine and sodium salicylate, Fenoprofen, Flurbiprofen, Ketoprofen, Naproxen, Oxaprozin, Sulindac, Piroxicam, Etodolac, Meloxicam, Nabumetone, Celecoxib/Celebrex, Indomethacin, Mefenamic acid, Meclofenamate, Diflunisal, Tolmetin, Salsalate, Aspirin, Ibuprofen, Ketorolac^c **ACE:** Captopril, Enalapril/ Enalaprilat, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Trandolapril, Benazepril^d **ARB:** Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan, Azilsartan^e **Immunosuppressant:** Azathioprine, 6 mercaptopurine

Disclosure: L. Xie, Janssen Scientific Affairs, LLC, 5; F. Kariburyo, Janssen Scientific Affairs, LLC, 5; J. Sah, Janssen Scientific Affairs, LLC, 5; J. Lofland, Janssen Scientific Affairs, LLC, 3; N. Li, Janssen Scientific Affairs, LLC, 3.

Abstract Number: 2659

Clinical Features, Damage Accrual and Survival in Patients with Familial Systemic Lupus Erythematosus (SLE): Data from a Multiethnic, Multinational Latin American Lupus Cohort

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: GLADEL (Grupo Latino Americano De Estudio de Lupus) has previously shown that a 14.1% of its patients have relatives with an autoimmune disease (1). The present study was conducted to contrast the clinical features, damage accrual and survival of GLADEL patients with familial and sporadic SLE.

Methods: Familial SLE was defined as patients with a first degree relative with SLE (parents, siblings and offspring); these relatives were interviewed in person or by telephone and examined, if warranted. Patients with second and third degrees relatives with SLE were excluded from these analyses. All other patients were considered as having sporadic lupus. The sociodemographic, clinical, immunological, treatment characteristics plus disease activity, damage and mortality, were compared between the two patient groups using Wilcoxon test and Chi-square tests for continuous and categorical variables, respectively. Odds ratios (OR) and 95% confidence intervals (CI) were estimated. Time-to-damage and mortality were examined with Cox multivariable regressions [Hazard ratios (HR) and 95% CI] in which variables previously found to be associated were also included. Statistical significance was set at $p \leq 0.05$; All analyses were performed using the SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results: The cohort consisted of 1176 patients; 66 (5.6%) of them had familial and 1110, sporadic lupus. The majority of patients in both groups were women, of comparable age and all ethnic groups were represented. None of the sociodemographic variables examined were significantly associated with familial SLE. As shown in Table 1, there were some differences in terms of the clinical variables with discoid lupus [22.7% versus 12.9%; $p = 0.024$; OR 1.97 (1.08- 3.60)] and neurologic disorder [(45.4% versus 33.5%; $p = 0.047$; OR 1.65 (1.00- 2.73)] being significantly associated with familial SLE. In contrast, pericarditis was negatively associated with familial SLE [7.6% versus 19.1%; $p = 0.01$; OR 0.35 (0.14- 0.87)]. The SLEDAI and SDI were similar in both groups; in the Cox analyses, familial lupus was not significantly associated with damage accrual (HR=1.00; 0.53– 1.89; $p = 0.99$) or higher mortality (HR 1.01; 0.24– 4.31; $p = 0.99$).

Conclusion: Familial SLE was associated with the presence of neurologic manifestations and of discoid lupus and with the absence of pericarditis, which has not been previously reported; however, no differences in hard endpoints such as disease activity, damage accrual and/or mortality were observed when compared with sporadic SLE.

1. Alarcon-Segovia D, et al. Familial aggregation of systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases in 1,177 lupus patients from the GLADEL cohort. *Arthritis Rheum.* 2005;52(4):1138-47.

Table 1. Characteristics of GLADEL patients associated with familial lupus versus all other GLADEL patients

Variable, (n, %)	Familial lupus (n=66)	Sporadic lupus (n=1110)	p-value	OR (CI _{95%})
Malar rash	44 (66.6%)	714 (64.3%)	0.699	
Discoid lupus	15 (22.7%)	144 (12.9%)	0.024	1.97 (1.08- 3.60)
Photosensitivity	38 (57.6%)	666 (60.0%)	0.696	
Oral ulcers	30 (45.4%)	494 (44.5%)	0.880	
Arthritis	53 (80.3%)	920 (82.9%)	0.590	
Pleuritis	16 (24.2%)	288 (25.9%)	0.759	
Pericarditis	5 (7.6%)	212 (19.1%)	0.019	0.35 (0.14- 0.87)
Neurological disorder	30 (45.4%)	372 (33.5%)	0.047	1.65 (1.00- 2.73)
Renal disorder	40 (60.6%)	641 (57.7%)	0.648	
Haematological disorder	52 (78.8%)	873 (78.6%)	0.979	
Immunological disorder (*135)	50 (83.3%)	795 (81.0%)	0.659	
ANA	62 (93.9%)	1061 (95.7%)	0.531	
Raynaud's phenomenon	21 (31.8%)	347 (31.3%)	0.924	
Anti-dsDNA antibodies (*7)	44 (66.7%)	650 (58.5%)	0.193	
Anti-SSA/Ro (*110)	15 (22.7%)	274 (24.7%)	0.719	
Anti-SSB/La (*117)	11 (16.7%)	155 (13.9%)	0.5401	
Antiphospholipid antibodies (*74)	26 (39.4%)	383 (34.5%)	0.4178	
Hypocomplementemia (*30)	39 (59.1%)	642 (57.84%)	0.8412	
Mortality in the follow-up (n, %)	4 (6.0%)	73 (6.58%)	0.8692	
SLEDAI at cohort entry (*147) (median, IQR)	9 (13.0)	8 (11.0)	0.692	
SDI accrual (median, IQR)	1.0 (2.0)	1.0 (2.0)	0.859	

* Missing data; OR (odd ratio); IQR (Interquartile range); ANA (Anti-nuclear antibodies); SLEDAI (Systemic Lupus Erythematosus Disease Activity Index); SDI (SLICC/ACR Damage Index)

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None; **E. Borba**, None; **E. Bonfa**, Fundação de Amparo à Pesquisa do Estado de São Paulo, 2, Conselho Nacional de Desenvolvimento Científico e Tecnológico, 2; **R. M. Xavier**, None; **A. C. de Oliveira e Silva**, None; **J. Molina**, None; **A. Iglesias-Gamarra**, None; **M. Guibert-Toledano**, None; **G. A. Reyes**, None; **L. Massardo**, None; **O. J. Neira**, None; **M. H. Cardiel**, Gilead, Pfizer Inc, Roche, 2, Eli Lilly, Pfizer Inc, 5, Eli Lilly, Pfizer Inc, 8; **L. Barile**, None; **M. C. Amigo**, None; **L. H. Silveira**, None; **I. Garcia de la Torre**, None; **E. Acevedo-Vasquez**, None; **M. Ugarte-Gil**, None; **J. Alfaro-Lozano**, None; **I. Segami**, None; **R. Chacón-Díaz**, None; **M. H. Esteva Spinetti**, None; **J. A. Gómez-Puerta**, None; **G. S. Alarcón**, None; **B. A. Pons-Estel**, None.

Abstract Number: 2660

Low-Dose Interleukin-2 Treatment of Refractory Lupus Nephritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Lupus nephritis (LN) is a common and serious organ manifestation of SLE and is associated with substantial patient morbidity and mortality. The production of interleukin-2 (IL-2), a key cytokine that regulates the differentiation and activation of CD4⁺ T cell subsets, is impaired in LN patients. Previous studies have shown IL-2 can expand Treg cell numbers and reduce Tfh and Th17 effector CD4⁺ T cell subsets in SLE. However, the efficacy of low-dose IL-2 to refractory LN is still unclear.

Methods: We conducted a prospective, open-label study to evaluate the effects of low-dose rhIL-2 (recombinant human IL-2^{Ser125}, Beijing SL Pharma) in patients with refractory LN. Three cycles of rhIL-2 were administered subcutaneously at a dose of 1 million IU every other day for 2 weeks (a total of 7 doses), followed by a 2-week break. After the initiation of IL-2, no increase in any other treatments for SLE was permitted. Clinical and laboratory data were measured at baseline and every 4 weeks thereafter until week 12. Refractory disease was defined as no or incomplete response to conventional 2-drug immunosuppressive therapy. Ten patients with refractory LN were eligible in IL-2 group and 10 in Placebo Group.

Results: Significant reductions of 24 h proteinuria and urine erythrocyte ($p < 0.05$) in IL-2 group compared with placebo group. Serum albumin also demonstrated improvement. Both C3 and C4 increased significantly at week 12 ($P < 0.01$). In addition, anti-dsDNA and Anti-Nuclear Ab titer decreased significantly ($P < 0.01$). Immunological analysis revealed that low-dose rhIL-2 administration was associated with selective expansion of Treg cells and conversely with reductions of Tfh and Th17 cells.

Conclusion: Low-dose IL-2 therapy was effective in refractory LN.

Disclosure: X. Zhang, None; J. He, None.

Abstract Number: 2661

Metformin Combined with Conventional Therapy Increases Absolute Number of Regulatory T Cells in Patients with Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Table 1 changes of Th17/Treg cell expression after metformin treatment

组别	Th17 细胞 (个/ml)	Treg 细胞 (个/ml)	Th17/Treg
MET 治疗 0 周	5.96 (7.52)	25.41 (19.13)	0.25 (0.31)
MET 治疗 6 周	5.60 (5.87)	25.78 (25.89) *	0.24 (0.24)
MET 治疗 12 周	4.56 (5.38)	21.09 (13.25)	0.22 (0.23)

Note that: * means $p < 0.05$.

Table 2 changes of ESR(mm/h), SLEDAI Score after metformin treatment

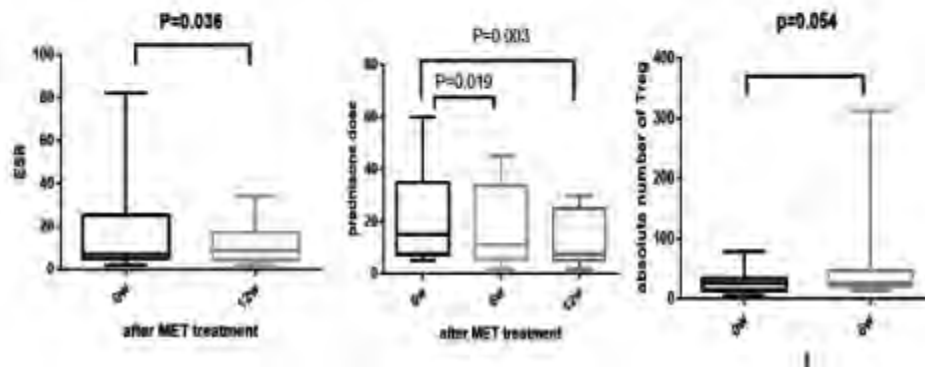
组别	ESR (mm/h)	SLEDAI 评分
MET 治疗 0 周	7 (20.25)	2 (1)
MET 治疗 6 周	6 (9.75)	1 (0)
MET 治疗 12 周	9 (12.5) *	0 (0.25)

Note that: * means $p < 0.05$.

Table 3 Changes of drugs after metformin treatment

组别	Pre(mg/d)	HCQ(g/d)
MET 治疗 0 周	16(28.0)	0.4(0.15)
MET 治疗 6 周	11.15(28.10)*	0.4(0.05)
MET 治疗 12 周	6.5(19.5)**	0.4(0.10)

Note that: * means $p < 0.05$, ** means $p < 0.001$.



Background/Purpose: To observe the clinical efficacy of metformin in the treatment of SLE and regulation of CD4⁺ Treg and Th17 cells.

Methods: Thirty-one patients with SLE, fulfilled the ACR 1997 standard, were enrolled in this study. Their average age was 37.21 ± 15.65 years, and disease duration was 58.33 ± 56.48 months. They were administered with metformin (MET) 250mg Bid combined with conventional therapy for 12 weeks. At week 0, week 6 and week 12, the absolute numbers of Th17 and Treg cells were assayed by flow cytometry and SLEDAI score and drug doses were collected.

Results: At week 0, 6 or 12 after metformin treatment combined with conventional therapy, the absolute number of Treg cells in 31 patients was 25.41 ± 7.52 , 25.78 ± 25.89 ($P=0.054$), or 21.09, while that of Th17 cells was 5.96 ± 7.52 , 5.60 ± 5.87 , or 4.56 ± 5.38 . The dosage of prednisone in SLE patients was decreased from 16(28.0) mg/d to 11.15(28.10) mg/d ($P=0.019$) or 6.5 (19.5) mg/d ($P=0.003$).

Conclusion: Our findings suggest that metformin can effectively up-regulate Treg cells as well as increase Th17 cells in a short time and can reduce the usage of prednisone.

Disclosure: M. Hao, None; Z. Liang, None; X. Jing, None; C. Gao, None; X. F. Li, None; J. Chen, None.

Abstract Number: 2662

Changes in Blood Pressure and Proteinuria at One Year in Two Lupus Nephritis Clinical Trials

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

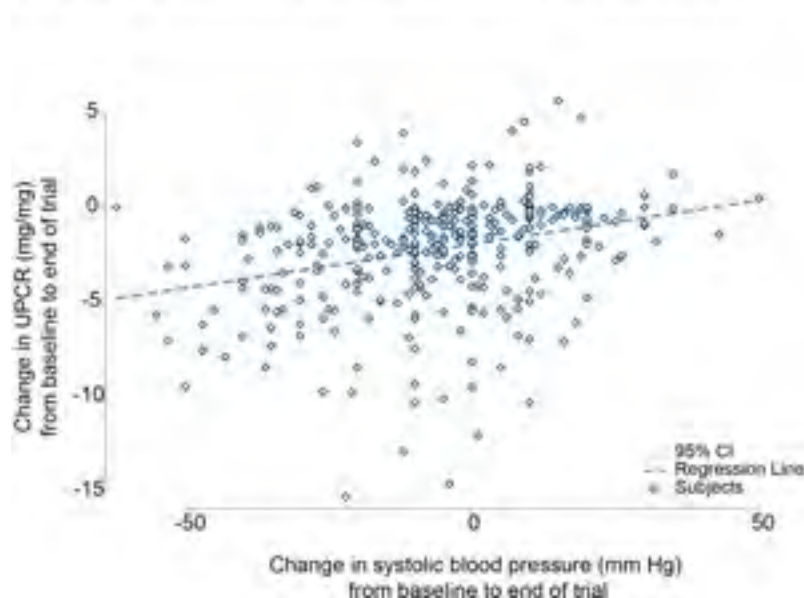
Session Time: 9:00AM-11:00AM

Background/Purpose: Hypertension predicts poor long-term renal outcomes for patients with lupus nephritis (LN) [1, 2]. We sought to characterize relationships between blood pressure and proteinuria using data from randomized clinical trials.

Methods: We analyzed patient-level data from LUNAR (NCT00282347) [3] and BELONG (NCT00626197) [4], which compared rituximab [3] or ocrelizumab [4] vs. placebo in addition to background therapy for the treatment of LN. Complete renal response (CRR) was defined for LUNAR as urine protein/creatinine (UPCR) levels below 0.5, creatinine levels $\leq 115\%$ of baseline, and inactive urinary sediment. CRR for BELONG was defined as UPCR < 0.5 and creatinine $\leq 125\%$ of baseline. Data from baseline and 1 year visits were analyzed. Logistic regression was used to estimate the association between change in BP and CRR while adjusting for baseline proteinuria and estimated glomerular filtration rate (eGFR). Linear regression was used to estimate the association between change in BP and change in proteinuria while adjusting for race, treatment received, and baseline eGFR.

Results: Each 10 mmHg increase in baseline systolic BP had an odds ratio (OR) of 0.8 for CRR at 1 year (95% CI 0.74, 0.97). This association did not remain significant after adjusting for baseline proteinuria and eGFR (OR 0.9, 95% CI 0.79, 1.05). Baseline systolic and diastolic BP had a weak correlation with baseline UPCR ($r=0.2$, $p<0.01$ for both). Change in systolic and diastolic BP from baseline to 1 year was associated with improvement in proteinuria at 1 year in adjusted regression: each 10 mmHg decrease in systolic BP was associated with a 0.45 g/g (CI 0.3, 0.6, $p<0.01$) improvement in

Figure 1. Change in systolic blood pressure versus change in proteinuria from baseline to one year after adjustment for race, treatment received, and baseline eGFR



proteinuria at 1 year; each 10 mmHg decrease in diastolic BP was associated with a 0.44 g/g (CI 0.2, 0.65, $p<0.01$) improvement in proteinuria. These results were consistent when studies were analyzed separately.

Conclusion: Baseline systolic BP was associated with the probability of CRR at 1 year in univariate analysis. However, this association was explained by baseline proteinuria and eGFR. Changes in systolic or diastolic BP were significantly associated with decreases in proteinuria at 1 year. Further characterization of the relative contributions of BP, disease severity, and immunosuppression are warranted.

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Abstract Number: 2663

Comparison of Clinical and Laboratory Profiles in 3575 Systemic Lupus Erythematosus Patients with and without Sjögren's Syndrome: Data from the Spanish Society for Rheumatology Lupus Registry

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The clinical coexistence of Systemic Lupus Erythematosus (SLE) and Sjögren's Syndrome (SS) was recognized in 1959. The prevalence of SS among patients with SLE varies considerably among the published studies (10-30%). There is still controversy as to whether or not SLE patients with overlapping SS have a distinct and significantly milder lupus. To address the clinical and serologic features of SLE and differences from SLE that occurs in overlap with SS.

Methods: This is a multicenter, descriptive, cross-sectional study of 3575 patients from the Spanish Society for Rheumatology Lupus Registry (RELESSER). Unselected SLE patients from 45 Rheumatology Departments across Spain were evaluated for the presence of overlapping SS using the American-European consensus criteria. Cumulative clinical data were collected at the moment of the last assessment. Clinical and laboratory parameters in SLE patients with SS (SLEwSS) were compared with those in SLE patients without SS (SLEwoSS).

Results: SS was identified in 516 SLE patients (14.4%). Compared with the SLEwoSS group, patients with SLEwSS were significantly older, had a higher frequency of mucocutaneous manifestations, Raynaud's phenomenon, peripheral neuropathy, anti-Ro/SSA, anti-La/SSB, neoplasia, and older age at death, but had a significantly lower frequency of renal involvement, thrombocytopenia, anti-DNA, anti-β2-GPI IgM and complement consumption. Both groups displayed a clinically similar presentation of lymphadenopathy, systemic vasculitis, serositis, damage accrual, mortality, musculoskeletal and CNS manifestations.

Conclusion: SLEwSS appears to constitute a subgroup of SLE patients with distinct clinical and serologic features, in whom SS is expressed as an overlapping entity. A particular cluster of clinical variables, namely, mucocutaneous manifestations, Raynaud's phenomenon, peripheral neuropathy, renal involvement and thrombocytopenia, was found to be

FEATURES	SLEwSS N=516	SLEwoSS N=3059	p
Age, years \pm SD	54.2 \pm 14.9	45.6 \pm 14.5	<0.001
Age at SLE onset, years \pm SD	38.6 \pm 15	32.1 \pm 14	<0.001
Female	97.5	89.1	<0.001
Lymphadenopathy	11.8	10.0	0.233
Photosensitivity	65.0	57.2	0.002
Oral ulcers	55.8	42.7	<0.001
Alopecia	36.3	32.0	0.069
Raynaud's Phenomenon	39.9	32.7	0.001
Systemic vasculitis	9.6	8.4	0.352
Arthritis	75.0	76.5	0.467
Myositis	4.0	3.4	0.515
Fibromyalgia	13.9	5.1	<0.001
Pleurisy	22.7	22.4	0.893
Pulmonary fibrosis	2.3	1.9	0.563
Renal manifestations	18.3	32.7	<0.001
Seizures	6.3	6.6	0.805
Peripheral neuropathy	5.4	2.9	0.004
Hemolytic anemia	7.1	8.6	0.272
Leucopenia	55.6	53.5	0.428
Thrombocytopenia	15.5	20.8	0.007
Anti-Ro/SSA	69.2	34.4	<0.001
Anti-La/SSB	48.1	14.4	<0.001
Anti-Sm	19.8	21.2	0.495
Anti-RNP	23.2	25.2	0.317
Anti-DNA	55.9	65.1	<0.001
Anti- β 2-GPI IgM	8.6	14.5	0.006
Antiphospholipid syndrome	13.0	14.0	0.520
Hypocomplementemia	62.3	69.0	0.012
SLICC-ACR DI	1.19 \pm 1.8	1.03 \pm 1.7	0.062
Neoplasia	7.8	5.5	0.042
Exitus	7.2	6.0	0.324
Age at death, years \pm SD	67.3 \pm 14.4	54.2 \pm 18.0	<0.001
SLEwSS: Systemic lupus erythematosus with Sjögren's syndrome. SLEwoSS: Systemic lupus erythematosus without Sjögren's syndrome. SLICC-ACR DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. Except where indicated otherwise, values are the percentage.			

important overall for discriminating SLE patients with or without SS. SLEwSS patients constitute a subgroup of patients with SLE characterized by milder lupus: older age at death, similar rates of mortality and SLICC-ACR damage index, less renal and immunological manifestations.

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Abstract Number: 2664

Long-Term Clinical Outcomes in a Cohort of Adults with Childhood-Onset Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

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Session Time: 9:00AM-11:00AM

Background/Purpose: Childhood-onset SLE (cSLE) is a severe lifelong multisystem autoimmune disease. Long-term outcome data are limited. Here, we report for the first time on the development of disease manifestations and damage over time in adults with cSLE and their health-related quality of life (HRQOL).

Methods: All patients underwent a single study visit comprising a structured history and physical examination. Disease activity (SLEDAI-2K), damage (SLICC-Damage Index (SDI)) and HRQOL (SF-36) were determined. Medical records were retrieved.

Results: In total, 111 cSLE patients were included, median disease duration 20 years, 91% female and 72% white. Disease activity was low (median SLEDAI 4), with 68% of patients using prednisone and/or disease-modifying anti-rheumatic drugs. The vast majority of new cSLE-related manifestations developed within 2 years of diagnosis. Damage like myocardial infarctions started occurring after 5 years. Most patients (62%) had damage, predominantly in the musculoskeletal, neuropsychiatric and renal systems. Cerebrovascular accidents, renal transplants, replacement arthroplasties and myocardial infarctions, developed at young age (median age 20, 24, 34 and 39 years respectively). Multivariate logistic regression showed that damage accrual was associated with disease duration (OR=1.15; p<0.001), antiphospholipid-antibody positivity (OR=0.56; p=0.026), and hypertension (OR=3.21; p=0.043). Current HCQ-monotherapy was associated with an SDI-score of 0 (OR=0.16; p=0.009). HRQOL was impaired compared to the Dutch population. Presence of damage reduced HRQOL in only one domain. High disease activity (SLEDAI ≥8) and changes in physical appearance strongly reduced HRQOL (4/8 and 7/8 domains).

Conclusion: The majority of adults with cSLE in this large cohort developed significant damage at young age and have impaired HRQOL without achieving drug free remission, illustrating the great impact of cSLE on future life.

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Abstract Number: 2665

Treatment Trends of Systemic Lupus Erythematosus during Early-Years of the Disease

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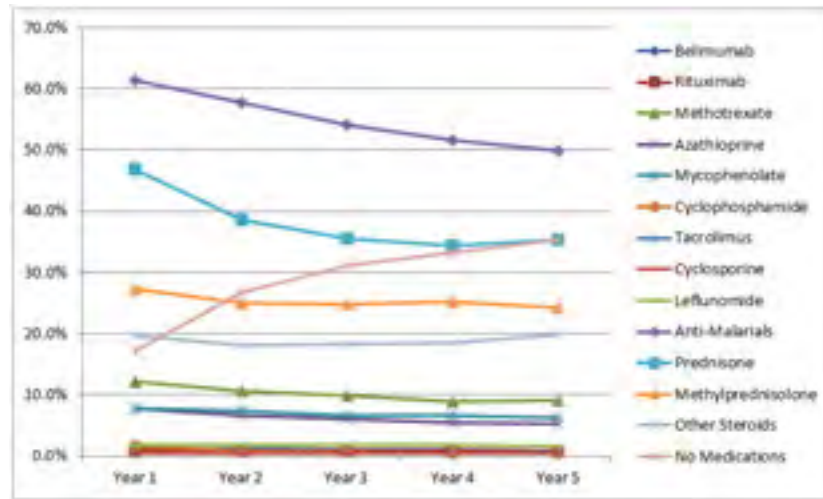


Figure 1 Proportion of patients on the drugs of interest per year after diagnosis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is treated with glucocorticoids, anti-malarials, immunosuppressive medications, and, more recently, biologics (specifically, belimumab and rituximab). While belimumab had positive results in trials, the rituximab trials were negative. With expanding therapeutic options, it is important to understand the current utilization patterns among patients with SLE, as this knowledge can inform policy, formulary planning and future needs. Little is known about the population level trends in the use of these agents, particularly during the early-years of the disease. We described the trends in medication use during the first five years after SLE diagnosis.

Methods: Using a large administrative database of commercially insured and Medicare Advantage beneficiaries across the U.S. (OptumLabs Data Warehouse) from 2006-2016, we identified newly diagnosed patients with SLE (ascertained using three ICD-9/10 codes separated by ≥ 30 days). Patients had at least two years of enrollment prior to SLE diagnosis and were followed for a maximum of five years after diagnosis or until disenrollment, whichever happened first. Follow up was calculated using the person-years method. For every year after diagnosis, we estimated the proportion of patients who filled prescriptions for the drugs of interest (figure).

Results: We identified 10,274 patients with newly diagnosed SLE, of whom 4227 had ≥ 5 years of follow up. Mean age at diagnosis (SD) was 45.7 (12.1) years, 89% were female, 62% were White, 17% Black, 12% Hispanic, 4% Asian, and 5% other/unknown race. Anti-malarials were the most frequently used drugs, filled at least once by 61% of patients during the first year after diagnosis, and decreased to 50% at five years after diagnosis. Prednisone was the second most frequently used drug, used by 47% of patients during the first year of the disease and 35% at 5 years after diagnosis. Methylprednisolone and other steroids were used by 20% or more patients consistently during the 5 years of follow up. Methotrexate was used by 12% of the patients during the first year, and was most common immunosuppressive drug prescribed. Azathioprine and mycophenolate mofetil were each used by 8% of the patients. Rituximab was used by 1% and belimumab by 2% of patients consistently during the five years of follow up. Overall there was a progressive decline in the use of most medications. By year five, 35% of the SLE patients did not fill prescriptions for any of the drugs of interest.

Conclusion: During the first five years after SLE diagnosis, there was a progressive decline in the use of all immunosuppressive medications. Five years after diagnosis, a high proportion of patients with SLE continue receiving glucocorticoids. Is unclear if these observations are due to lower disease activity over time, medication intolerance, increased noncompliance or combination thereof.

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Abstract Number: 2666

Trends in Treatment of Systemic Lupus Erythematosus and Lupus Nephritis: 2006-2016

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Table. Proportion of patients with SLE and LN receiving any of the drugs of interest (%)

SLE	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Prednisone	40.0	35.9	33.6	32.9	32.0	34.4	33.4	33.5	32.0	32.6	34.7
Methylprednisolone	18.7	19.4	18.7	21.3	21.7	19.7	21.2	22.0	22.0	22.9	24.4
Other Steroids	13.7	14.1	13.9	14.3	15.7	15.6	16.1	16.6	16.8	17.1	19.7
Anti-Malarials	50.1	46.4	44.7	44.8	45.4	46.4	46.8	47.2	46.1	45.1	47.5
Methotrexate	9.1	8.1	8.1	7.5	8.1	7.9	7.9	8.1	8.1	7.7	8.1
Leflunomide	1.4	1.4	1.5	1.4	1.3	1.3	1.4	1.6	1.6	1.6	1.9
Azathioprine	6.6	5.6	4.9	4.8	4.5	4.5	4.2	4.3	4.3	4.3	4.8
Mycophenolate	6.3	4.9	4.6	4.5	4.5	4.5	4.5	4.8	4.4	4.6	5.0
Cyclophosphamide	1.2	1.0	0.9	0.9	0.8	0.5	0.5	0.6	0.4	0.3	0.3
Tacrolimus	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.4	0.4	0.5	0.6
Cyclosporine	0.7	0.5	0.4	0.4	0.4	0.3	0.3	0.3	0.2	0.2	0.2
Belimumab	0.0	0.0	0.0	0.0	0.0	0.3	0.8	1.0	1.1	1.2	1.4
Rituximab	0.6	0.7	0.7	0.7	0.7	0.7	0.7	0.8	0.8	0.8	1.0
No Medication	23.7	26.9	29.6	28.3	28.2	28.0	27.6	26.7	27.9	28.3	24.7

LN	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Prednisone	49.4	44.6	44.9	44.6	41.5	44.1	44.0	42.9	39.6	40.7	41.9
Methylprednisolone	13.1	15.3	16.0	19.6	17.9	18.2	19.7	20.6	20.7	20.7	22.2
Other Steroids	10.0	11.1	11.6	14.9	15.8	14.7	14.1	17.1	16.3	16.6	17.9
Anti-Malarials	38.8	39.3	41.2	41.3	41.7	43.9	44.7	46.2	42.5	42.7	45.1
Methotrexate	2.7	3.9	4.6	5.2	6.5	5.2	5.7	6.4	6.0	5.6	5.4
Leflunomide	1.5	1.6	1.9	1.9	1.6	1.6	1.7	1.7	1.6	1.3	1.9
Azathioprine	6.4	6.2	6.1	6.2	6.0	6.1	6.0	5.7	5.5	5.4	5.4
Mycophenolate	19.1	15.2	14.7	14.2	14.5	13.9	14.1	14.5	13.4	14.0	14.8
Cyclophosphamide	4.2	2.3	2.2	2.1	2.6	1.6	2.0	2.3	1.6	1.1	1.3
Tacrolimus	2.5	2.2	2.2	2.3	2.2	2.2	2.3	2.0	1.6	1.9	2.3
Cyclosporine	2.6	1.8	1.9	2.0	1.7	1.6	1.2	1.1	0.7	0.7	0.6
Belimumab	0.0	0.0	0.0	0.0	0.0	0.4	1.1	1.3	1.2	1.1	1.4
Rituximab	0.8	1.1	0.6	1.1	1.0	1.0	1.0	1.3	1.2	1.2	1.6
No Medication	24.0	25.9	24.0	22.7	24.9	25.2	22.1	22.8	25.4	25.0	24.2

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Glucocorticoids, anti-malarials and conventional immunosuppressive agents have been the mainstay of therapy for systemic lupus erythematosus (SLE) and lupus nephritis (LN); more recently biologic agents have been introduced for their treatment. We evaluated utilization trends in SLE and LN therapy over the past decade.

Methods: Using 2006-2016 data from a large administrative database of commercially insured and Medicare Advantage beneficiaries, we identified patients with SLE and a subset of patients with LN based on validated claims-based algorithms. Included patients had at least one year of enrollment in the cohort. We estimated the annual age- and sex- standardized proportion of patients who filled prescriptions for at least one of the drugs of interest (Table).

Results: A total of 30,787 patients with prevalent SLE were identified, of whom 5,267 had LN. Mean age (SD) was 49.3 (14.1) years for SLE and 51.9 (17.2) years for LN. Ninety percent were female, 61.0% White, 17.4% Black, 11.2% Hispanic, 3.0% Asian and 7.0% other/unknown. Use and time trends of therapeutic agents for 2006-2016 are included in the table. Anti-malarials were the most frequently used drug class for both SLE and LN, with some temporal change over the course of the study; 50.1% in 2006 to 47.5% in 2016 for SLE, and 38.8% in 2006 to 45.1% in 2016 for LN. Prednisone was the second most frequently used drug, decreasing from 40.0% in 2006 to 34.7% in 2016; use of methylprednisolone and other systemic glucocorticoids increased during that time period. Methotrexate was the most commonly used nonbiologic immunosuppressive drug in SLE (8.0%), while MMF was most frequently prescribed in LN (15.0%), both of which remained stable during the study period. Cyclophosphamide use declined over the last decade for both SLE (1.2% to 0.3% in 2016) and LN (4.2% to 1.3% in 2016). Belimumab was the most commonly used biologic for SLE with a slight uptrend since approval. Rituximab use increased in SLE and was the most commonly used biologic for LN. At any point in time ~24% of the patients were not receiving any of the medications of interest.

Conclusion: Over the past decade, a substantial proportion of patients with SLE and LN continued to receive glucocorticoids. Although the use of prednisone declined, the use of methylprednisolone and other glucocorticoids increased concurrently. The proportion of patients receiving nonbiologic immunosuppressants remained relatively stable for both SLE and LN, however there was a progressive decline in the use of cyclophosphamide. Since 2011 the proportion of patients receiving rituximab is higher than for cyclophosphamide. The increasing use of biologics for SLE and LN, particularly rituximab, which is not currently approved for SLE, highlights the need to clarify their therapeutic role in these diseases.

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Abstract Number: 2667

Sledai and Mex-Sledai Glucocorticoid Indices As Predictors of Damage and Mortality in Multinational Multiethnic Latin American Cohort

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Disease activity is one of the major predictors of damage accrual and mortality in systemic lupus erythematosus (SLE). Glucocorticoid use, especially in high dose, could underestimate the inflammatory status in SLE patients. Based on that, a modification of the SLEDAI accounting for glucocorticoid dose has been proposed, the SLEDAI glucocorticoid index (SGI)¹. The aim of this study is to evaluate the impact of SGI and Mex-SLEDAI GI (M-SGI) as predictors of damage and mortality.

Methods: Patients from a multinational, multiethnic Latin American cohort were included in these analyses. SGI was calculated based on the impact of glucocorticoids proposed by the Toronto Cohort¹. The same value for the impact of glucocorticoid was used for developing an M-SGI. Damage accrual was evaluated using the SLICC/ACR damage index (SDI). To evaluate the impact of SGI and M-SGI on the first increase on damage and on mortality, Cox regression models were performed, adjusting for gender, age at diagnosis, ethnicity, medical coverage, place of residence, educational level, SDI at baseline and antimalarial, glucocorticoid and immunosuppressive drugs use before baseline. Similar models were applied for the SLEDAI and the Mex-SLEDAI. All confounders were evaluated at or before baseline, and disease activity indices were evaluated as a time-dependent variable.

Results: One thousand three-hundred and twenty-one patients were included, median (25th-75th) age at diagnosis was 27.0 (20.0-37.0) years, 582 (44.1%) were Mestizo, 532(40.3%) Caucasian, and 207 (15.7%) other. Median SLEDAI was 4 (0-12), Mex-SLEDAI was 3 (0-6), SGI was 7 (4-12) and M-SGI was 5 (2-9). Median follow-up was 4.3 (2.1-5.9) years. During follow up, sixty-nine patients (5.2%) died and 323 (24.5%) accrued new damage. The median values for the disease activity indices as a function of damage and mortality are depicted in Table 1. The corresponding hazard ratios are depicted in Table 2.

Conclusion: SGI and M-SGI predicted new damage and mortality in SLE patients independently of other well-known risk factors. However, their impact seems to be similar to those of the original versions of these instruments.

References :

1. Touma Z, Gladman D, Su J, Urowitz M. 11 Development and initial validation of a novel lupus disease activity index to account for glucocorticoids: SLEDAI-2K glucocorticoids index(SGI). *Lupus Sci Med* 2017;4 :doi: 10.1136/lupus-2017-000215.11

Disclosure: M. Ugarte-Gil, None; I. Segami, None; G. Harvey, None; G. J. Pons-Estel, None; R. Quintana, None; C. Reategui-Sokolova, None; J. Cieza, None; L. J. Catoggio, None; M. Garcia, None; V. Saurit, None; F. Caeiro, None; C. Drenkard, ILAR, 2, PANLAR, 2; G. Berbotto, None; E. Sato, None; L. Costallat, None; E. Bonfa, Fundação de Amparo à Pesquisa do Estado de São Paulo, 2, Conselho Nacional de Desenvolvimento Científico e Tecnológico, 2; J. C. Tavares Brenol, None; N. A. Da Silva, None; F. Cavalcanti, None; A. Iglesias-Gamarra, None; M. Guibert-Toledano, None; G. A. Reyes, None; L. Massardo, None; O. J. Neira, None; M. H. Cardiel, Gilead, Pfizer Inc, Roche, 2, Eli Lilly, Pfizer Inc, 5,

Table 1: Median (25th-75th) values of different disease activity indexes according to increased damage and mortality status on follow up

	Increase in damage accrual			Mortality		
	No	Yes	p value	No	Yes	p value
SGI	7 (3-12)	8 (5-12)	0.0033	7 (3-12)	12 (8-20)	<0.0001
SLEDAI	4 (0-10)	5 (2-9)	0.2997	4 (0-9)	10 (4-16)	<0.0001
M-SGI	5 (2-9)	7 (4-11)	<0.0001	5 (2-9)	10 (6-14)	<0.0001
Mex-SLEDAI	3 (0-6)	4 (1-7)	0.0004	3 (0-6)	6 (2-11)	<0.0001

Eli Lilly, Pfizer Inc, 8; L. Barile, None; M. C. Amigo, None; L. H. Silveira, None; I. Garcia de la Torre, None; E. Acevedo-Vasquez, None; R. Chacón-Díaz, None; M. H. Esteva Spinetti, None; G. S. Alarcón, None; B. A. Pons-Estel, None.

Abstract Number: 2668

Hydroxychloroquine and the Risk of Thrombotic Events in Systemic Lupus Erythematosus Patients: A Systematic Review and Meta-Analysis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM **Hydroxychloroquine and Risk of Thrombosis in Patients with Systemic Lupus Erythematosus: A Systematic Review and Meta-analysis**

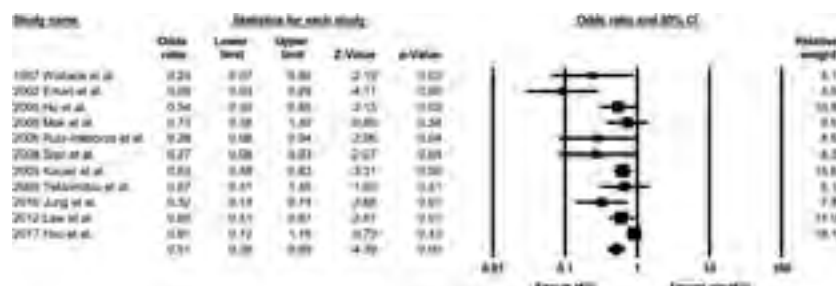
Authors: Sankhyan P, Boonpheng B, Cook CT

Background/Purpose: Over the course of the past few years hydroxychloroquine (HCQ) has been demonstrated to have a significant role in the symptom management of systemic lupus erythematosus (SLE) especially in milder forms of the disease. Several studies have also shown its benefit in prevention of thrombosis in SLE patients, yet the evidence remains unclear. We undertook this meta-analysis to assess the risk of vascular thrombosis on SLE patients on hydroxychloroquine.

Methods: A systematic review was performed on the studies obtained from the databases of MEDLINE, EMBASE and Cochrane, from inception through January 2018 to extract studies that demonstrated an odds ratio of thrombosis in SLE patients (with or without anti-phospholipid antibodies) who were treated with HCQ compared to those not treated with HCQ. Effect estimates from the individual study were extracted and combined using random-effect, generic inverse variance method of DerSimonian and Laird.

Results: 11 observational studies with a total of 14,066 SLE patients were enrolled. Compared with the patients not on HCQ, HCQ exposure was associated with significantly decreased risk of vascular thrombosis with a pooled odds ratio of 0.51 (95% CI 0.38-0.69, $p < 0.001$). However, the result may be limited by publication bias as assessed by funnel plot.

Conclusion: HCQ use is associated with 49% lower risk of vascular thrombosis compared to non-HCQ use in patients with SLE, as derived from our meta-analysis.



Disclosure: P. Sankhyan, None; B. Boonpheng, None; C. Cook, None.

Abstract Number: 2669

Assessing the Need for Pneumocystis Jiroveci Pneumonia (PCP) Prophylaxis in SLE Patients on Immunosuppression

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The risk-benefit of *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis in systemic lupus erythematosus (SLE) is not well defined and there are no SLE-specific guidelines. On the one hand, the risk of PCP is relatively low.^{1,2} On the other hand, high frequency of trimethoprim-sulfamethoxazole (TMP-SMX) related adverse effects have been reported.³ Prophylaxis initiation is highly variable among providers, based on 2008 survey data.⁴ As a result, it is unknown whether the decision to initiate PCP prophylaxis is guided by patient-specific characteristics. Therefore, the objective of this study was to ascertain the rates of PCP prophylaxis and factors associated with prophylaxis initiation among SLE patients receiving immunosuppression.

Methods: Using electronic medical record, we identified new SLE as having: 1) ≥ 2 SLE ICD codes within 1-6 months of each other between 1/1/2006 and 12/31/2017, 2) no visits with SLE codes or SLE-related prescriptions within one year prior, and 3) ≥ 1 immunosuppressive prescriptions after the first SLE visit. Records of patients with the word “pneumocystis” were reviewed to identify PCP cases. Patient-specific characteristics were compared between patients who had received a prescription for PCP prophylaxis (TMP-SMX, atovaquone, or dapsone) within 14 days of starting immunosuppression (besides corticosteroids), and those who did not.

Results: Of the 693 patients who met inclusion criteria, there was 1 confirmed (by quantitative PCR in bronchoalveolar lavage) and 1 probable PCP case; 111(16%) were started on PCP prophylaxis (Table). Compared to patients not on prophylaxis, patients on PCP prophylaxis had a higher frequency of renal disease (15% vs. 7%, $p=0.002$) and congestive heart failure (5% vs. 2%, $p=0.04$). They were more likely to be on hydroxychloroquine (70% vs. 48%, $p<0.001$), and had a longer median duration between the first SLE visit and initiation of immunosuppression (3.5 vs. 11.5 months, $p<0.001$). There were no differences between groups in patient demographics, comorbidities, or cell counts at SLE onset.

Conclusion: Over a 12-year period at our tertiary care center, the use of PCP prophylaxis in SLE patients on immunosuppression was relatively low (16%), and the incidence of PCP among patients not on prophylaxis was rare (0.34%). Prophylaxis was significantly more likely to be initiated in SLE patients with cardiac or renal disease. Additional secondary analyses of duration and choice of PCP prophylaxis, as well as compliance and adverse effects that could have affected the number of patients on prophylaxis are ongoing. These results will guide establishment of evidence-based guidelines on the use of PCP prophylaxis for SLE patients.

References:

1. Feldman CH et al., A&R 2015; 67: 1577–1585.
2. Kapoor TM, et al Lupus. 2017 Dec;26(14):1473-1482.
3. Petri M et al., J Rheum 1992; 19: 265–269.
4. Gupta D et al, J Clin Rheum 2008; 14: 267–272.

Baseline characteristics of SLE patients on immunosuppression*

	No PCP prophylaxis (N=582)	Yes PCP prophylaxis** (N=111)	p-value
Age, median (IQR)	36 (22, 51)	34 (22, 45)	0.21
Women, n(%)	519 (89)	96 (86)	0.41
Black Race, n(%)	237 (41)	50 (45)	0.17
Hispanic ethnicity, n(%)	215 (37)	35 (32)	0.15
Hydroxychloroquine, n(%)	282 (48)	78 (70)	<0.001
Prednisone, n(%)	512 (89)	81 (95)	0.08
WBC, median (IQR)	5.8 (4.1, 7.8)	6.6 (4.0, 8.6)	0.11
ANC, median (IQR)	3.6 (2.4, 5.4)	4.5 (2.6, 6.0)	0.14
Lymph, median (IQR)	1.3 (0.80, 1.8)	1.3 (1.0, 1.8)	0.49
Diabetes Mellitus, n(%)	26 (5)	8 (7)	0.22
Cancer, n(%)	13 (2)	5 (5)	0.17
HIV, n(%)	4 (0.6)	1 (0.9)	0.81
CHF, n(%)	12 (2)	6 (5)	0.04
Renal Disease, n(%)	38 (7)	17 (15)	0.002
Lung Disease, n(%)	93 (16)	15 (14)	0.51
PCP cases, n(%)	2 (0.34)	0	
Time between first SLE visit and initiation of immunosuppression, months, median (IQR)	3.5 (0.7, 11)	11.5 (2.4, 33)	<0.001

* Immunosuppression defined as the earliest prescription of: methotrexate, leflunomide, azathioprine, mycophenolate, cyclophosphamide, cyclosporine, tacrolimus, rituximab or belimumab.

** Initiation of PCP prophylaxis defined as a prescription for trimethoprim-sulfamethoxazole, atovaquone, or dapsone written within 14 days of the first immunosuppressive prescription date.

Disclosure: K. A. Lynch, None; M. Salgado Guerrero, None; A. Londono Jimenez, None; I. Gendlina, None; W. B. Mowrey, None; M. H. Mokrzycki, None; A. R. Broder, None.

Abstract Number: 2670

Association of Hydroxychloroquine Use and Incident Atrial Fibrillation in Systemic Lupus Erythematosus: A Retrospective Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Hydroxychloroquine (HCQ) is a derivative of quinidine, a class 1a anti-arrhythmic agent used to prevent ventricular arrhythmias and recurrent atrial fibrillation (AFib). AFib occurs more commonly in patients with systemic lupus erythematosus (SLE) compared to the general population. HCQ is a cornerstone treatment in SLE. This study examines the association of HCQ use and AFib or ventricular arrhythmias in SLE.

Methods: A retrospective cohort of adult SLE (ICD 10: M32) patients at a tertiary academic rheumatology practice from Dec 1,2014 to May 30,2017 excluding patients with prevalent AFib was constructed. Patients were categorized as HCQ users versus non-users. Primary outcome was incident AFib adjudicated by electronic health record (EHR) review and EKG confirmation. AFib events occurring in the first year of observation were considered prevalent AFib to allow for a run-in period and exclude prevalent cases more reliably. Secondary outcome was incident ventricular arrhythmias- a composite of ventricular tachycardia (VT), ventricular fibrillation (VF), torsades, and sudden cardiac death (SCD) adjudicated similarly. Multivariate regression analysis was performed to estimate the association between HCQ exposure and development of incident AFib, after adjusting for relevant confounders, including demographics (age, sex, ethnicity), AFib-related co-morbidities (BMI, smoking, alcohol use, chronic obstructive pulmonary disease, obstructive sleep apnea, hypertension, coronary artery disease, heart failure, diabetes, cerebrovascular accident and transient ischemic attack, peripheral vascular disease, thyroid disorder, chronic kidney disease and liver dysfunction), anti-arrhythmic medication use (beta-blockers, calcium channel blockers, flecainide, digoxin, amiodarone), and autoimmune serologies. Sub-group analysis was performed on patients age >65yrs (given higher risk of AFib).

Results: Our study included 1646 patients with SLE including 754 HCQ users. During the observation period, 5 AFib events occurred in HCQ users and 18 in non-users. Unadjusted odds ratio (OR) was calculated at 0.22 (95% CI 0.08-0.60, p=0.003), and multivariable logistic regression analysis showed an OR of 0.33 (95% CI 0.12-0.91, p=0.03) for incident AFib. Six incident ventricular arrhythmia events (2 VT, 3 torsades, 1 SCD) occurred in HCQ users and 3 (2 VT, 1 SCD) occurred in non-users with OR of 2.49 (95% CI 0.62-9.9, p=0.2). In the age>65 yrs sub-group analysis, OR was 0.4 (95% CI 0.13-1.25, p=0.11).

Table 1: Risk of incident atrial fibrillation according to hydroxychloroquine use in systemic lupus erythematosus

Variable	HCQ users (N=934)	HCQ non- users (n=754)
Age (yrs)	52.2±14.0	56.3±14.7
Female sex	867 (93%)	693 (92%)
Caucasian	777 (83.1%)	615 (81.6%)
BMI (kg/m2)	28.8±7.6	29.5±8.2
Smoking (ever)	372 (39.8%)	336 (44.6%)
Alcohol user	402 (43%)	302 (40%)
Anti-arrhythmic medication use	121 (12.9%)	129 (17.1%)
HTN	244 (26%)	265 (35.1%)
COPD	2 (0.2%)	3 (0.4%)
OSA	19 (2%)	37 (4.9%)
CAD	44 (4.7%)	65 (8.6%)
Heart failure	45 (4.8%)	70 (9.3%)
Diabetes	60 (6.4%)	105 (13.9%)
CVA/TIA	10 (1.1%)	19 (2.5%)
Thyroid disorder	5 (0.5%)	6 (0.8%)
Liver dysfunction	31 (3.3%)	25 (3.3%)
CKD	62 (6.6%)	77 (10.2%)
PVD	20 (2.1%)	32 (4.2%)

Table . (Cont'd)

Variable	HCQ users (N=934)	HCQ non- users (n=754)
AFib	5 (0.5%)	18 (2.4%)
Unadjusted Odds Ratio	0.22 (95% CI 0.08-0.60, p=0.003)	
Adjusted Odds Ratio	0.33 (95% CI 0.12-0.91, p=0.03)	

Conclusion: In this exploratory study, HCQ use was associated with a 67% reduced risk of incident AFib in SLE. In light of the cardiovascular risk benefits of HCQ and its close relation to anti-arrhythmic medication quinidine, if our preliminary results are confirmed in larger studies, our findings may be used as rationale for a randomized study of HCQ's protective role against AFib in high-risk patients with SLE.

Disclosure: A. Gupta, None; A. Joshi, None; M. Chester-Wasko, None; T. S. Sharma, None.

Abstract Number: 2671

Development and First-in-Human Characterization of an ICOSL and BAFF Bispecific Inhibitor AMG 570 for SLE Treatment

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Autoimmune diseases, including systemic lupus erythematosus (SLE), are associated with dysregulated T cell and B cell responses. AMG 570 is a bispecific molecule targeting T cell and B cell activity through inhibition of the inducible costimulator ligand (ICOSL) and the B cell activating factor (BAFF). We hypothesize that targeting both ICOSL and BAFF will be more effective than single target inhibition in SLE and other autoimmune diseases.

We investigated if targeting ICOSL and BAFF has superior efficacy to single target inhibition in mouse arthritis and lupus models. We also investigated the safety, tolerability, pharmacokinetics, and pharmacodynamics of AMG 570 in healthy subjects after single subcutaneous doses.

Methods: A murine surrogate ICOSL/BAFF bispecific along with single or combination inhibition was evaluated in the mouse collagen induced arthritis (CIA) and NZB/NZW lupus models. AMG 570 binding affinity to human and cyno ICOSL/BAFF was tested by Kinexa A. An ongoing, first-in-human study has enrolled healthy adult subjects into 6 escalating single-dose cohorts. Eight participants were enrolled into each cohort and randomized 3:1 to receive AMG 570 or placebo. The primary endpoint of the study was treatment-emergent adverse events (AEs). Secondary endpoints included pharmacokinetics and pharmacodynamics.

Results: ICOSL and BAFF dual inhibition was more effective than single inhibition in ameliorating arthritis incidence and severity in the mouse CIA model as well as reducing anti-dsDNA IgG, delaying proteinuria and improving survival in the NZB/NZW lupus model. Based on high affinity to ICOSL and BAFF, AMG 570 was selected for investigation in a single ascending dose study in healthy subjects. As of an ad hoc interim analysis following six cohorts, 48 healthy participants received one dose of investigational product (AMG 570 or placebo). Overall, 73 mild to moderate AEs were reported. The most common AEs were upper respiratory tract infection and injection site erythema. No drug-related serious AEs or fatal AEs were reported thus far. AMG 570 demonstrated nonlinear pharmacokinetics consistent with cell surface ICOSL binding. At the highest dose tested, AMG 570 achieved >90% mean ICOSL receptor occupancy on circulating B cells 8 days after dosing. AMG 570 led to a reduction in circulating naïve B cells and an increase in circulating memory B cells.

Conclusion: Dual inhibition of ICOSL and BAFF is more efficacious than single target inhibition in mouse disease models. In healthy subjects to date, single doses of AMG 570 have been safe, well-tolerated and demonstrated pharmacodynamic activity consistent with inhibition of both ICOSL and BAFF.

Disclosure: L. E. Cheng, Amgen Inc., 1, 3; H. Hsu, Amgen Inc., 1, 3; M. Kankam, None; N. Siebers, None; R. Stoltz, None; L. Abuqayyas, Amgen Inc., 1, 3; B. Ertik, Amgen Inc., 1, 3; B. Sullivan, Amgen Inc., 1, 3; L. Zhou, Amgen Inc., 1, 3; J. R. Parnes, Amgen Inc., 1, 3.

Abstract Number: 2672

Serum Vitamin D Levels and Its Effect on Disease Activity and Fatigue in Systemic Lupus Erythematosus Patients

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease involving many organs and systems. Evidences show that vitamin D plays an important role in the pathogenesis and progression of SLE. Vitamin D deficiency is highly prevalent in SLE patients due to photoprotection, renal insufficiency and use of different medication. But a causal relationship between vitamin D serum concentration and disease activity in SLE patient could not be established.

To evaluate the prevalence of vitamin D deficiency in patient with SLE and to investigate the association between vitamin D serum concentrations and disease activity, fatigue and quality of life and autoantibodies levels in SLE patients.

Methods: We included a total number of 92 patients diagnosed with SLE according to the American College of Rheumatology (ACR) classification criteria. We assessed disease activity according to SLEDAI and organs damage according to SLICC criteria. All patients completed the quality of life questionnaires Health Assessment Questionnaire (HAQ) and EuroQol. Serum vitamin D levels were measured by standardized immunochemical assay from blood samples.

Results: We analyzed 92 patients, 85 (92,4%) women and 7 (7,6%) men. 43 (46,7%) patients had lower level of vitamin D than the standard given by the laboratory (< 50 nmol/l), the mean was $38,3 \pm 11,2$ nmol/l.

On contrary to some recent studies we did not find any statistically significant differences in the quality of life, fatigue, and disease activity between two groups with low and normal vitamin D levels. Conversely, in low vitamin D group, milder fatigue, better quality of life and lower anti-dsDNA antibody levels were found. Only when we compared a group of 35 patients with an initially low level of vitamin D ($39,7 \pm 9,8$) after supplementing it to standardize its level ($67,3 \pm 15,7$), we found improvements in quality of life, functional ability of patients, fatigue reduction, and decreased SLE activity in these patients according to SLEDAI.

Conclusion: We demonstrated a very high frequency of vitamin D deficiency and insufficiency among patients with SLE. But we didn't establish a causal relationship between vitamin D serum concentration and disease activity in SLE patients. On the other hand, we demonstrated a trend of fatigue and disease activity reduction with vitamin D supplementation in these patients. The limitation of our observation was mainly small sample size of patients and although we included patients with established diagnosis of SLE who are on the long treatment including glucocorticoids and other immunosuppressive drugs.

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Disclosure: R. Moravcova, None; H. Ciferska, None; M. Olejarova, None; D. Tegzova, None; J. Zavada, None; M. Lösterova, None.

Different Risk Profiles for Development of Steroid-Related and Steroid-Unrelated Damage in Early Diagnosed SLE: Results from the Italian Multicenter Early Lupus Project Inception Cohort

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Preventing organ damage is a major challenge in Systemic Lupus Erythematosus (SLE). To evaluate factors associated with development of steroid-related and unrelated damage in an inception cohort of early diagnosed SLE patients.

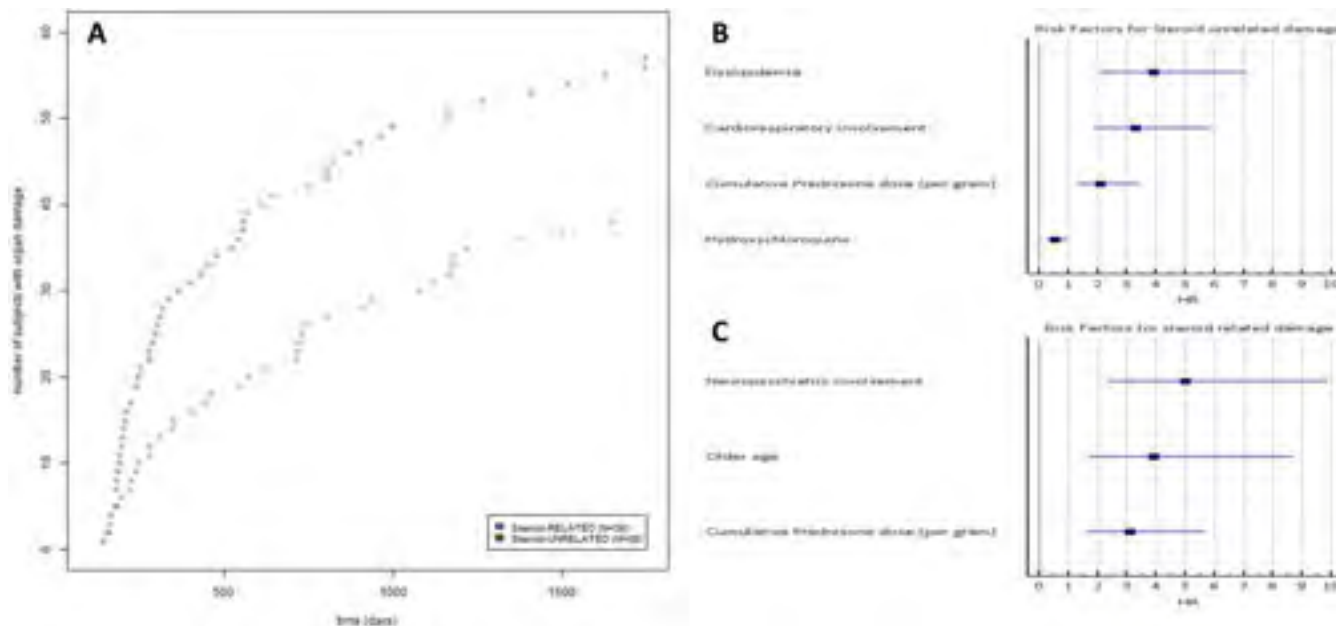
Methods: The Early Lupus Project encompasses 9 Italian centers recruiting consecutive patients diagnosed within 12 months of SLE (1). At enrolment and then every 6 months a panel of data (including demographic, comorbidities, serologic, clinic by BILAG2004 domains, ECLAM, HRQoL by visual analogic scale and treatment) was recorded. Using univariate analysis, we assessed the contribution of covariates collected at baseline in development of steroid-related and not-related damage categorized according to previous definition (2) and assessed by the SLICC/ACR Damage Index (SDI from 0 to ≥ 1). Forward-Backward Cox-regression models were fitted with covariates with $p < 0.05$ to identify factors independently associated with increased risk of damage development.

Results: Overall, 279 patients were enrolled in the Early Lupus Project inception cohort up to the 31st of December 2017; 230 patients (89.6% Caucasians, 13.4% males) were eligible for this study having SDI=0 at enrolment and at least 6 months of follow-up. Age (mean \pm SD) at diagnosis was 36.5 ± 14.4 years, the median interval between diagnosis and recruitment was 1.1 months (interquartile range 0.0-4.8) and median follow-up was 27.4 months (interquartile range 7.2-48.0).

At last follow-up visit 84 patients (36.5%) had an SDI score ≥ 1 (median = 0; interquartile range 0-1); 38 of them (16.5%) developed steroid-related damage and 58 (25.2%) developed steroid-unrelated damage. Figure A shows the kinetics of damage development.

Factors independently associated with increased risk of developing steroid-related damage were baseline neuropsychiatric involvement ($p < 0.001$; HR 5.0 95% CI 2.3-10.6), older age ($p = 0.001$; HR 3.9 95% CI 1.8- 8.7) and cumulative prednisone dose ($p < 0.001$; HR 3.1 per 10 grams; 95% CI 1.6-5.7) were (Figure B). Factors independently associated with increased risk of steroid-unrelated damage accrual were baseline dyslipidemia ($p < 0.001$; HR 3.9 95% CI 2.1-7.1), cardiorespiratory involvement ($p < 0.001$; HR 3.3 95% CI 1.9-5.9), and cumulative prednisone dose ($p < 0.001$; HR 1.0001 per 10 grams; 95% CI 2.1-3.4), whereas hydroxychloroquine reduced the risk of steroid-unrelated damage ($p = 0.041$; HR 0.53; 95% CI 0.29-0.98) (Figure C).

Conclusion: The risk profile for damage development in this early SLE cohort differs for steroid-related and unrelated damage. Addressing modifiable risk factors, adding hydroxychloroquine since the very early stages and treating disease activity to target remission or minimal disease activity, may reduce damage and improve patients outcome.



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2. Gladman D, et al. J Rheumatol 2003;30:1955-1959

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Abstract Number: 2674

Identifying Phenotype Clusters in Systemic Lupus Erythematosus By Damage Cluster

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Session Information

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Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

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Background/Purpose: Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease with complex genetic background. Recently, subphenotype in SLE has influenced dialogue on discussing the genetic background, disease course, outcomes and treatment. The objective of this study is to identify phenotype clusters within a SLE cohort patients, and compare the genetic risk score (GRS), clinical manifestations and mortality between clusters.

Methods: This is a single center, descriptive study of from Hanyang BAE lupus Cohort. Patients whose disease duration is less than 5 years were excluded to minimize potential confounding effects of disease duration. Mortality data were derived in connection with data from the Korean National Statistics Office. Patients were grouped into 3 clusters based on SLICC Damage Index (SDI) using K-mean cluster analysis. Clinical characteristics were compared using ANOVA and Tukey's test.

Results: In 1130 analyzed patients, musculoskeletal damage was the most prevalent (20.2%), followed by ocular (11.4%), renal (10.5%) and neuropsychiatric damage (10.2%). Three separate damage clusters were identified, each with significantly different damage manifestations. Cluster 1 (n=824) showed the least damage profile. Cluster 2 (n=195) was represented by the predominance of renal damage (55.4%), with prevalent ocular (58.0%), musculoskeletal (29.2%) damage and diabetes

Table 1. Cluster analysis of 1130 SLE patients

Variable	Damage Cluster			P
	Cluster 1 (n=824)	Cluster 2 (n=195)	Cluster 3 (n=111)	
Female sex	774 (93.9)	169 (86.7)	102 (91.9)	<0.01
Disease duration, years	12.1 ± 5.4	15.0 ± 6.1	14.1 ± 5.8	<0.01
Age at SLE diagnosis	27.9 ± 10.5	27.2 ± 11.3	26.6 ± 10.4	0.40
Adjusted mean SLEDAI	4.0 ± 2.2	5.4 ± 2.9	4.2 ± 2.9	<0.01
SDI score at enrollment	0.2 ± 0.6	0.9 ± 1.2	1.3 ± 1.5	<0.01
SDI score at last follow up	0.5 ± 0.9	2.8 ± 2.1	2.8 ± 1.8	<0.01
Ocular	0	113 (58.0)	16 (14.4)	<0.01
Neuropsychiatric	0	4 (2.1)	111 (100.0)	<0.01
Renal	0	108 (55.4)	11 (9.9)	<0.01
Pulmonary	60 (7.3)	20 (10.3)	19 (17.1)	0.02
Cardiovascular	26 (3.2)	13 (6.7)	3 (2.7)	0.15
Peripheral vascular	27 (3.3)	8 (4.1)	5 (4.5)	0.76
Gastrointestinal	8 (1.0)	3 (1.5)	3 (2.7)	0.45
Musculoskeletal	132 (16.0)	57 (29.2)	39 (35.1)	<0.01
Skin	31 (3.8)	10 (5.1)	7 (6.3)	0.46
Premature gonadal failure	0	5 (2.6)	4 (3.6)	<0.01
Diabetes Mellitus	22 (2.7)	16 (8.2)	6 (5.4)	<0.01
Malignancy	47 (5.7)	7 (3.6)	3 (2.7)	0.13
Weighted GRS	1.56 ± 1.09	1.78 ± 1.00	1.43 ± 1.12	0.04*
Mortality	20 (2.4)	11 (5.6)	16 (14.4)	<0.01

Data were given as mean ± SD or number (%).

SLE, Systemic Lupus Erythematosus, SLEDAI, Systemic Lupus Erythematosus Disease Activity Index, SDI, Systemic Lupus International Collaborating Clinic/American College of Rheumatology Damage Index; GRS, Genetic Risk Score

*Tukey's test showed no differences

mellitus (8.2%). Cluster 3 (n=111) was characterized by neuropsychiatric damage (100%) with musculoskeletal (35.1%) and pulmonary damage (17.1%). Age of onset of SLE and autoantibody positivity were similar among clusters. Cluster 2, represented by prevalent renal and glucocorticoid associated damages, showed higher adjusted mean SLEDAI score (AMS) (Mean ± SD, 6.7 ± 4.8) than other two clusters. Cluster 3 distinguished by neuropsychiatric damage showed the highest mortality among three clusters. However, GRS showed no difference between 3 clusters after Tukey's test.

Conclusion: We identified different patterns of damage manifestations in a large cohort of SLE patients. Renal and neuropsychiatric damage were the two distinct domain of damage that classified patients into 3 clinically meaningful clusters. Patients in cluster 2 (prevalent renal and glucocorticoid associated damage) had the highest AMS. The highest mortality was recognized in cluster with prevalent neuropsychiatric damage. However, GRS showed no difference between clusters. Further studies assessing comprehensive subphenotypes are needed.

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Age-Related Metabolic Changes Underlie Pro-Inflammatory Lineage Specification and Contribute to Therapeutic Responsiveness to Mechanistic Target of Rapamycin Blockade in SLE

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Session Information

Session Date: Tuesday, October 23, 2018

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Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) patients exhibit T-cell dysfunction which can be reversed by blockade of the mechanistic target of rapamycin (mTOR) with therapeutic efficacy (Nat. Rev. Rheumatol. 12:169-182, 2016; Lancet, 391:1186-1196, 2018). Since mTOR is a key controller of mammalian lifespan (Nature 460:392-395, 2009; Science 326:140-144, 2009), we examined the relationship of immune senescence to rapamycin-responsive pro-inflammatory lineage skewing in SLE.

Methods: 838 immunometabolic parameters were assessed by flow cytometry (Lancet, 391:1186-1196, 2018) in 84 SLE patients (44.3 ± 1.4 years of age; mean \pm SE; range 18-71) having active disease and unresponsive or intolerant to conventional medications, but unexposed to treatment with rapamycin. Disease activity was characterized by SLEDAI (10.1 ± 0.7), BILAG (27.8 ± 1.3), and prednisone use (5.3 ± 1.4). Control samples for biomarker studies were obtained from 84 healthy controls (HC) and matched for patients' age (45.0 ± 1.4 years of age; range 20-63), gender, and ethnicity for each visit. Rapamycin (sirolimus) was started at 2 mg/day with dosage adjusted to tolerance and 6-15 ng/ml through levels in 40 of these SLE patients over 12 months (ClinicalTrials.gov number NCT00779194). The number (n) of patients available for each assay is indicated. Statistical analyses were performed with GraphPad (San Diego, CA); changes at 2-tailed $p < 0.05$ were considered significant for hypothesis testing.

Results: Patients' age did not correlate with SLEDAI, BILAG, or prednisone dosage. Aging occurred with increased mitochondrial transmembrane potential or mitochondrial hyperpolarization (MHP) and increased mitochondrial mass in all T cells, increased CD4/CD8 ratio, depletion of CD45RA⁺ naïve and expansion of CD45RO⁺ memory CD8⁺ T cells both in SLE and HC subjects. Expression of CD98 and activation of mTOR complex 1 (mTORC1) in CD4⁺ T cells was enhanced and CD4⁺CD25⁺FoxP3⁺ Tregs were expanded of HCs only, while mTORC1 activity was selectively increased in CD8 T cells and CD4⁺CD8⁻CD3⁺ double-negative (DN) CD27⁺CD197⁻ T cells and CD8⁺CD62L⁻CD197⁻ effector-memory T cells were only expanded in SLE patients with aging. Rapamycin expanded CD4⁺CD45RO⁺ memory T cells, CD8⁺CD62L⁻CD197⁻ effector-memory T cells, and CD8⁺FoxP3⁺ Tregs irrespective of age, while it preferentially reduced nitric oxide production, MHP, and mitochondrial mass in DN T cells, expanded CD4⁺FoxP3⁺ Tregs, IFN γ -producing CD4⁺ and CD8⁺ T cells, and CD19⁺ B cells in younger SLE patients (37.0 ± 2.7 years of age; n=14). Rapamycin preferentially reduced the production of IL-4 and IL-17 by DN and CD8⁺ T cells in older SLE patients (57.6 ± 1.5 years of age; n=14).

Conclusion: Age-related metabolic changes underlie pro-inflammatory lineage specification and may contribute to clinical efficacy of mTOR blockade in SLE.

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Abstract Number: 2676

SLE Patients with No Organ Damage Might Benefit More from Belimumab Treatment

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Session Information

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Session Time: 9:00AM-11:00AM

Background/Purpose: In systemic lupus erythematosus (SLE), organ damage is associated with unfavourable disease courses and premature mortality. We aimed at investigating the impact of organ damage on belimumab treatment efficacy.

Methods: We included 1684 patients with SLE from the BLISS-52 (n=865) and BLISS-76 (n=819) trials. Data were accessed through a data sharing agreement with GSK. Organ damage was assessed using the SLICC/ACR Damage Index (SDI). Disease activity was assessed using the SLEDAI-2K. We evaluated baseline SDI scores as predictors of treatment outcome using logistic regression with SLE responder index (SRI) response at week 52 as the dependent variable. Adjustments for potential confounding factors were performed as appropriate.

Results: When all patients were considered, high baseline SDI scores were associated with a lower chance of attaining SRI response (OR: 0.88, 95% CI: 0.81-0.95; P=0.002). In multivariate analysis, a high baseline SDI score was an independent predictor of non-response, as was long disease duration, whereas high baseline disease activity and high baseline prednisone dose independently predicted SRI response (Figure). We observed the same association between high baseline SDI scores and non-response at week 52 in patients who received belimumab (1 mg/kg or 10 mg/kg; n=1122) (OR: 0.88, 95% CI: 0.79-0.97; P=0.007). High SDI scores independently reduced the probability of response, and high baseline disease activity and prednisone dose independently predicted SRI attainment. Interestingly, disease duration was no longer an independent predictor of treatment outcome (Figure). In patients who received standard of care therapy only (n=562), baseline SDI score were not found to impact the treatment outcome (OR: 0.88; 95% CI: 0.76-1.02; P=0.091).

Conclusion: Previous observations of baseline organ damage reducing belimumab efficacy (1) were corroborated. This impact of organ damage on treatment efficacy was not seen in the placebo group, lending support for a treatment-specific effect. The data suggest that belimumab may be expected to be more efficacious in SLE patients with no organ damage established prior to treatment initiation, irrespective of disease duration and activity grade.

References:

1. Parodis I, et al. *Autoimmun Rev.* 2017; 16: 343-51.

Disclosure: I. Parodis, None; S. Emamikia, None; A. Gomez, None; K. Chatzidionysiou, None.

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A Systematic Review Examining the Association between Organ Damage and Health-Related Quality of Life in Systemic Lupus Erythematosus

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Session Information

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Background/Purpose: SLE-related organ damage is associated with increased morbidity. The comorbidity burden of SLE can involve various organ systems and may include pain, fatigue, difficulty in performing daily life activities, and reduced physical and emotional well-being, all of which contribute to high rates of disability. We conducted a systematic literature review to assess the association between SLE-related organ damage and health-related quality of life (HRQOL).

Methods: Systematic search of PubMed, EMBASE, Cochrane Library, and Latin American and Caribbean Health Sciences Literature bibliography (Jan 2000–Feb 2017) to identify studies in which the association between organ damage (measured by SLICC/ACR Damage Index [SDI]) and HRQOL was evaluated in adults with SLE.

Results: Of 10,420 articles screened, 20 studies (3 prospective cohort and 17 cross-sectional) were included in the analysis. For HRQOL, the 36-item Short-Form Health Survey (SF-36: Physical and Mental Component Summaries [PCS and MCS]) was used in 15 studies; the Fatigue Severity Scale (FSS) in 2 studies; the EuroQOL 5D in 2 studies; and the LupusQOL, Multidimensional Fatigue Inventory, Quality of Life Questionnaire of the European Foundation for Osteoporosis, and WHO Quality of Life Scale (WHOQOL-BREF) in 1 study each. HRQOL was assessed using the SF-36 in the 3 prospective studies; in 2 of these, SDI was modeled as a binary variable. For patients without baseline organ damage, any damage accrued over 2 years was associated with a 5.5-fold increased risk of reduced HRQOL (SF-36 overall relative risk [RR]: 5.5 [95% CI: 1.1–26.6; $p=0.03$]). Similar trends were observed for PCS (RR: 2.5 [95% CI: 0.6–10.0; $p=0.19$]) and MCS (RR: 4.6 [95% CI: 0.9–22.8; $p=0.06$]). Any damage at baseline was associated with 67% reduced odds of achieving minimum clinically important improvement in SF-36 PCS (odds ratio: 0.33 [95% CI: 0.13–0.85; $p=0.02$]; no association was noted for MCS. When SDI was modeled as a continuous variable, increasing organ damage was associated with reduced SF-36 PCS compared with no damage [regression coefficients: (SDI=0); SDI 1: -2.64, $p<0.001$; SDI 2: -2.86, $p=0.003$; SDI 3: -5.94, $p<0.001$; SDI 4: -6.35, $p<0.001$; and SDI 5+: -8.11, $p<0.001$]. In cross-sectional evaluations, increasing organ damage correlated modestly with reduced HRQOL (SF-36 correlation coefficient: -0.12 to -0.30; SF-36 regression coefficient: -0.011 to -4.65; LupusQOL correlation coefficient: -0.31, $p<0.01$; and WHOQOL-BREF regression coefficient: -0.06, $p=0.57$). Increasing fatigue was weakly correlated with organ damage (FSS correlation coefficient: 0.04 to 0.15).

Conclusion: In most studies analyzed, organ damage was associated with reduced HRQOL. Heterogeneity in HRQOL instruments and methodology was observed across studies. Improving construct validity of instruments and consistent evaluation will enable a more accurate estimation of the burden of SLE and enhance efforts to improve HRQOL in SLE.

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Abstract Number: 2678

Integrated Safety Profile of Atacicept from All Clinical Studies to Date

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Session Information

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Background/Purpose: We conducted an integrated analysis of pooled safety data from all 17 atacicept clinical studies to date, across multiple indications, to further define atacicept's safety profile.

Methods: Analyses were based on 3 pooled datasets: Double-blind placebo (PBO)-controlled set (DBPC-S n=1,568; key endpoint: treatment-emergent AEs [TEAEs]); SLE set (SLE-S n=761; key endpoint: IgG change and serious infection rates); full analysis set (FA-S n=1,845; key endpoint: exposure-adjusted mortality).

Results: Of 1,568 patients in the DBPC-S, 30.8% received PBO, and 8.2%, 24.5% and 36.5% received atacicept 25, 75 and 150 mg, respectively. Overall, baseline characteristics were balanced across treatment arms. Treatment exposure was similar with PBO and atacicept 75 mg and 150 mg (278.3, 225.0 and 286.7 patient-years, respectively), but was lower with atacicept 25 mg (51.5 patient-years). Exposure-adjusted TEAE rates were generally higher with atacicept vs placebo, with no consistent association between atacicept dose and cardiac arrhythmias, serious and severe infections or injection site reactions (Table). Serious infection and serious TEAE rates were similar between atacicept and PBO. TEAE-related discontinuation rates were higher with atacicept versus placebo (16.1 vs 10.9/100 patient-years). In the SLE-S, there was no association between reduced IgG levels and increased infection rates. Across all studies (FA-S), 11 patients died during treatment (10 atacicept [0.5%], 1 PBO [0.1%]; see Table for infection-related deaths in the DBPC-S). Exposure-adjusted mortality rates/100 patient-years (95% CI) were 3.60 (0.90–14.38), 0.34 (0.05–2.43), 1.18 (0.49–2.82) for atacicept 25, 75 and 150 mg, and 0.44 (0.06–3.12) with PBO.

Conclusion: Results from this pooled analysis clarify the benefit-risk relationship for atacicept, which is being further evaluated in additional clinical studies in IgA nephropathy and SLE.

Table. Exposure-adjusted TEAE rates by dose (DBPC-S)

	PBO n=483	Atacicept				Total, n=1,568
		25 mg, n=129	75 mg, n=384	150 mg, n=572	All, n=1,085	
Total number of patient-years	278.3	51.5	225.0	286.7	563.2	841.4
TEAE, n (per patient-years)						
Hypersensitivity*	37 (13.9)	8 (15.7)	40 (19.1)	55 (20.4)	103 (19.4)	140 (17.6)
Infections	211 (107.8)	43 (104.4)	180 (118.7)	281 (141.3)	504 (128.7)	715 (121.7)
Herpes zoster	13 (4.7)	2 (3.9)	10 (4.5)	17 (6.1)	29 (5.2)	42 (5.1)
Serious infection	20 (7.3)	1 (1.9)	23 (10.5)	22 (7.7)	46 (8.3)	66 (7.9)
Severe infection	9 (3.2)	0	11 (4.9)	16 (5.6)	27 (4.8)	36 (4.3)
Injection-site reactions	54 (20.9)	27 (64.8)	109 (63.0)	156 (72.4)	292 (67.9)	346 (50.2)
Severe hypogammaglobulinemia (IgG <3 g/L)	0	0	2 (0.9)	4 (1.4)	6 (1.1)	6 (0.7)
Cardiac arrhythmias [all]*	18 (6.6)	11 (22.4)	23 (10.6)	25 (8.9)	59 (10.8)	77 (9.4)
Ventricular arrhythmias	5 (1.8)	0	4 (1.8)	6 (2.1)	10 (1.8)	15 (1.8)
Ischaemic heart disorders*	11 (4.0)	3 (5.9)	13 (5.9)	11 (3.9)	27 (4.9)	38 (4.6)
Embolic and thromboembolic events*	11 (4.0)	1 (2.0)	6 (2.7)	9 (3.2)	16 (2.9)	27 (3.2)
Vestibular disorders*	19 (7.0)	5 (9.9)	18 (8.3)	26 (9.3)	49 (8.9)	68 (8.3)
Demyelination*	1 (0.4)	1 (1.9)	0	5 (1.7)	6 (1.1)	7 (0.8)
Depression*	14 (5.1)	3 (5.8)	8 (3.6)	11 (3.9)	22 (3.9)	36 (4.3)
Malignant tumour*	0	1 (1.9)	1 (0.4)	3 (1.1)	5 (0.9)	5 (0.6)
Serious TEAE	51 (18.9)	15 (30.0)	51 (23.9)	61 (21.8)	127 (23.4)	178 (21.9)
Severe TEAE	28 (10.2)	10 (19.6)	45 (20.9)	56 (20.0)	111 (20.3)	139 (17.0)
Discontinuation of treatment due to TEAE	30 (10.9)	14 (27.6)	30 (13.4)	46 (16.1)	90 (16.1)	120 (14.3)
Deaths related to infections, n (%)						
Deaths	0	0	0	2 (0.3)†	0	0

* Programmatically determined (crude results of the search) from a predefined list of MedDRA preferred terms according to the Standardized MedDRA Query (SMQ) or Customized MedDRA Query (CMQ) classification of the corresponding MedDRA version

† Acute respiratory failure and probably leptospirosis (n=1); pneumonia and pulmonary alveolar haemorrhage (n=1)

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Glucocorticoids Withdrawal in Systemic Lupus Erythematosus: Are Remission and Low Disease Activity Reliable Starting Points for Stopping Therapy? a Real-Life Experience

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Session Information

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Background/Purpose: Glucocorticoids (GC) are a cornerstone of the treatment of Systemic Lupus Erythematosus (SLE); however, a significant organ damage is associated with long-term GC use in SLE. GC withdrawal is therefore a target in SLE management.

The aims of our study were to evaluate the proportion of patients GC-free in a prospective cohort over a period of 6 years, to evaluate the main characteristics of patients at GC withdrawal with respect to the available definitions of remission and low disease activity (LDAS), to evaluate the occurrence of flares after GC withdrawal.

Methods: This is a retrospective study of prospectively collected data from a monocentric longitudinal cohort of patients with SLE (revised ACR criteria) followed from 2012 to 2017. Patients GC-free at last visit in 2017 were identified and compared with patients on GC at last visit. Patients GC free at the cohort entry (n= 35) or patients with incomplete follow-up (n=45) were excluded from this analysis. Disease activity was evaluated with the SELENA-SLEDAI index, while organ damage with the SLICC/DI. Definitions of remission according to the European consensus criteria (DORIS) and of LDAS according to the Asian Pacific Lupus Consortium definition and LDAS were applied at GC withdrawal.

Results: A total of 188 patients were included; characteristics of GC-free (n=69) and on GC patients (n=119) at last observation are reported in table 1.

Among GC-free patients, disease activity at the moment of GC discontinuation was low (median SLEDAI: 1.2, IQR 0-2) and 12.2% of patients were serologically active; 77,8% had at least one organ damage. 49.2 % of patients were in complete remission on treatment (cRONT), 42.9% in clinical remission on treatment (clRONT) and 6.35% were in LLDAS.

Nine disease flares (14%) were recorded after GC withdrawal (6 cutaneous \pm articular, 3 renal) after a median time of 1 year (min 6 months- max 3 years). By comparing the pre-GC stopping and the post GC stopping periods for each patients we didn't observed a significant increase in the number of flares (p=n.s.); the patients who flared didn't show a significant difference neither of SLEDAI, nor complement values at the stop of GC. Being in remission or in LDAS was not associated with a different risk in disease flare (OR: 0.6; p=n.s)

	GC free (n=69)	on GC (n=119)	p
Age (IQR)	46 (36,53)	44 (35,45)	0.97
Disease duration	15,5 (7-23)	15 (9-22)	0.8
SLICC LAST median (IQR)	0 (0-1)	1 (0-2)	0.007
SLEDAI LAST median (IQR)	2 (0-2)	2 (0-4)	0.01
Therapy with HCQ	56/69 (%)	96/120 (%)	0.8
Therapy with immunosuppressants	30/69 (%)	56/120 (%)	0.6

Conclusion: This analysis shows that GC withdrawal is feasible in a significant proportion of patients on remission or low disease activity; in these patients GC withdrawal is not associated with an increased risk of disease flare and probably it would spare damage accrual.

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Activation Towards Health Self-Management in Patients with Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with fluctuating levels of disease activity. Control of disease activity is associated with better outcomes and the ability to self-manage one's health is an important skill towards this goal. We describe patient's activation towards health self-management in a population of lupus patients and the factors associated with lower health self-management.

Methods: Patients from the Canadian Network for Improved Outcomes in SLE (CaNIOS) centers participating in the MyLupusGuide™ randomized clinical trial were studied at baseline for their health self-management skills. The study is conducted online after patients receive a written invitation to participate, provide consent, and register online. The Patient Activation Measure (PAM) is a validated self-reported tool designed to measure an individual's level of confidence, beliefs, knowledge, and skills about managing one's health. PAM can be used as a continuous score or be divided into four levels with the first two levels indicating insufficient or low activation. We used the PAM as our outcome of interest and compared it to other self-reported data on demographics and psychosocial variables using several validated self-reported instruments (Table 1). Descriptive statistics were performed and univariate linear regressions using mixed model with random effect for site were used for continuous and categorical variables.

Results: Baseline data collection for MyLupusGuide™ trial was available for analysis on 539 patients from ten centers. Their baseline characteristics are reported in Table 1 with mean (sd) age = 50 (14), female = 91%, Caucasian = 74%. The mean PAM score was moderate at 61.2 (13.5) with a proportion of 16, 20, 42 and 22% in PAM levels 1 to 4 respectively, indicating insufficient and low activation towards health self-management in 36% of patients. Variables associated with lower PAM scores (Table 1) included shorter disease duration, higher disease activity, lower physical and mental health status, depressive symptoms, less distraction and instrumental coping and more emotional coping, lower lupus self-efficacy and less social support. Categorical variables associated with lower PAM were being work disabled and less medication adherence.

Table 1: Baseline demographic, disease and psychosocial characteristics of 539 SLE patients and their association with activation towards health self-management.

Variable	Descriptive statistics				Univariate analyses with PAM		
	n	Mean	SD	95% CI	Regression coefficient	Standard error	P value
Demographic							
Age	502	49.64	13.95	(48.42; 50.87)	0.033	0.043	0.44
Computer use (hrs/wk)	521	14.44	13.71	(13.26; 15.62)	-0.069	0.043	0.11
Disease characteristics							
Disease duration (years)	532	16.94	11.92	(15.92; 17.95)	0.124	0.049	0.01
SLAQ - activity	539	13.98	7.98	(13.30; 14.65)	-0.319	0.073	<.0001
LDIQ - damage	539	3.53	3.06	(3.27; 3.79)	-0.036	0.193	0.85

Table . (Cont'd)

Variable	Descriptive statistics				Univariate analyses with PAM		
	n	Mean	SD	95% CI	Regression coefficient	Standard error	P value
SF36-PCS – health status	539	38.92	11.94	(37.91; 39.93)	0.298	0.048	<.0001
SF36-MCS –health status	539	43.97	11.26	(43.02; 44.92)	0.217	0.051	<.0001
Psychosocial variables							
CESD - depression	537	15.61	10.69	(14.71; 16.52)	-0.316	0.053	<.0001
CHIP# - Distraction*	538	24.70	6.16	(24.18; 25.22)	0.562	0.091	<.0001
CHIP – Instrumental*	538	29.27	5.27	(28.82; 29.71)	0.778	0.105	<.0001
CHIP – Emotional*	538	19.84	7.60	(19.20; 20.49)	-0.453	0.074	<.0001
Lupus self-efficacy	538	69.00	23.61	(67.00; 71.00)	0.258	0.022	<.0001
MOS social support	538	20.16	6.68	(19.59; 20.72)	0.455	0.084	<.0001
PAM score	539	61.18	13.53	(60.03; 62.32)	na	na	na

CHIP=Coping with Health Injuries and Problems. *Higher values are associated with greater use of each coping related strategy.

Conclusion: More than one third of lupus patients showed low health self-management activation which is a common barrier to improvement of outcomes and health status for patients with lupus. Reversible factors associated with poor health self-management include lupus disease activity, health status, depression and coping strategies.

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Abstract Number: 2681

Lupus Primary Care Management Practices

Karin Tse and R. Paola Daly, Lupus Foundation of America, Washington, DC

Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Due to the systemic nature of lupus, individuals may interact with a diverse healthcare team when experiencing lupus symptoms and before receiving a diagnosis. This study describes the management practices of various physicians who may care for patients presenting with lupus with a focus on primary care physicians (PCPs) to highlight areas of opportunity to reduce time to diagnosis and care.

Methods: An online survey was administered to 910 physicians in September 2016 using a provider list from the Lupus Foundation of America and a commercial web panel of physicians. Data collection included physicians' perceptions, attitudes and reported behaviors related to the path to diagnosis and treatment of people with lupus. Descriptive analyses were conducted using chi-square and Kruskal Wallis tests for post-hoc comparisons.

Results: Respondent characteristics are described in Figure 1. Figure 2 summarizes referral and management practices among different provider types, notably with higher proportions of dermatologists and PCPs often diagnosing or treating lupus patients. Rheumatologists were excluded from analyses as they are the primary healthcare providers for people with lupus. All provider groups differed significantly from one another in management practice, with PCPs being more likely than pediatricians and OB/GYNs to manage lupus patients on their own before referring patients out. Providers classified as having minimal or no experience with lupus were also asked to identify earliest actions they would take during an appointment if a patient presented with lupus symptoms. 86.2% of PCPs with minimal experience (n=119) would order bloodwork as their first action, which was a higher percentage than all other provider types. Only 13.8% of these PCPs reported that referring to a specialist would be their first action, ranking last after ordering bloodwork, asking a patient to track symptoms and following up, or directly treating the symptoms.

Conclusion: PCPs frequently care for patients presenting with lupus who may or may not yet be diagnosed. These analyses highlight the tendency of PCPs to delay referrals when caring for these patients. Further studies should be conducted to examine whether this management preference exists among larger groups of PCPs and explore potential barriers for referring to specialists.

Disclosure: The Lupus Foundation of America received funding from UCB Pharma to support study data collection.

Respondent characteristics (n=910)		
	Characteristic	n (%)
Provider type	PCP	350 (38.5)
	Pediatrician	130 (14.3)
	OB/GYN	130 (14.3)
	Rheumatologist	170 (18.7)
	Dermatologist	130 (14.3)
Practice setting	Independent/private	511 (56.2)
	Public health clinic (non-academic)	61 (6.7)
	Part of a network of physicians at a hospital, health system, or university	298 (32.7)
	Other	40 (4.4)
Medicaid/Medicare acceptance	Accept Medicare	221 (24.3)
	Accept Medicaid	92 (10.1)
	Accept both Medicare and Medicaid	525 (57.7)
	Do not accept Medicare or Medicaid patients	57 (6.3)
	Not sure	15 (1.6)
Geographic location	(Sub)urban	821 (90.2)
	Rural	89 (9.8)

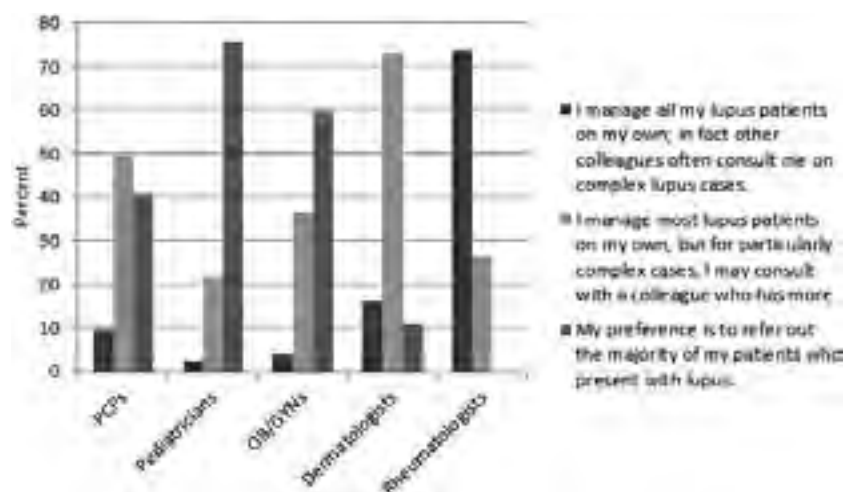


Figure 1. Respondent Characteristics

Figure 2. Management practices of patients presenting with lupus among physician groups(n=910)

Disclosure: K. Tse, Lupus Foundation of America, 3; R. P. Daly, Lupus Foundation of America, 3.

Abstract Number: 2682

Novel Antibody Against Commensal Bacterial Antigen in Prediction of the Response of Rituximab in Systemic Lupus Erythematosus

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Session Information

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Background/Purpose: Streptococcal infections can cause rheumatic fever sharing clinical presentations similar to SLE. Whether oral commensal streptococci could induce cross-reactive and pathogenic antibodies remained unknown. So we aimed to search for novel biomarkers in SLE through cross-reactive antibody repertoire screening, and we investigated to find specific antibodies presented in the serum of lupus patients.

Methods: The streptococcal L7/L12 ribosomal protein(RP-L7/L12) was identified through serum antibody-screening assay in SLE patient with higher disease activity followed by a proteomic approach. Recombinant RP-L7/L12 was purified and serum antibody levels were detected by ELISA quantitatively. The biomarkers of kidney impairment associated with SLE such as UPCR(urine protein to creatinine ratio), serum complement component 3(C3) and Anti-dsDNA were test serially too.

Results: A total of 25 lupus patients were enrolled from Jan, 2016 to May, 2018, with diagnosis of systemic lupus erythematosus according to The Systemic Lupus International Collaborating Clinics (SLICC) 2012 criteria, were to receive rituximab (500 mg) on days 1, 15, 168 (Week 24), and 182. The primary end point was UPCR result at day 336 (Week 48). Patients (N=14/25, 56%) respond to rituximab therapy (decrease of UPCR compared to baseline UPCR (baseline mean: 1.97 ± 2.84 mg/mg; Day 336 (Week 48) Mean: 0.44 ± 0.58), and the overall improvement of UPCR is significant ($p=0.01$ (Wilcoxon signed-rank test)); The concomitant increase of C3 (70.9 ± 28.1 mg/dL; Week 48: 85.19 ± 23.54 mg/dL, $p=0.004$), decreasing Anti-dsDNA (192.11 ± 203.48 ; Week 48: 107.30 ± 101.19 WHO units/mL, $p=0.0025$), and steroid sparing effect (prednisolone equivalent: 15.70 ± 9.47 mg/day; Week 48 mean: 10.20 ± 6.08 , $p=0.0032$) were also noted. The mean SELENA-SLEDAI scores (systemic lupus erythematosus disease activity index SELENA modification) was higher in the response group. Higher anti-RP L7/L12 antibody titres (0.72 ± 0.35 (SLE-glomerulonephritis (GN)) vs 0.52 ± 0.33 ($p=0.09$)) in patients with SLE is associated with higher rate of GN (proteinuria ≥ 0.5 gm/day.) An average 76.0% decrease of anti-RP-L7/L12 titre after a 24-week interval were detected in patients of SLE (N=15) receiving rituximab. Another three patients with SLE had two-fold increase in anti-RP-L7/L12 after rituximab, probably indicative of disease flare. The Pearson correlation coefficient was calculated between the dynamics of anti-RP-L7/L12(baseline/12/24-week) and the dynamics of UPCR change, a moderate positive correlation was observed ($R^2=0.3367$.)

Conclusion: Higher streptococcal anti-RP L7/L12 antibody in SLE is associated with higher rate of glomerulonephritis. The novel antibody against commensal bacterial antigen is predictive of the response of rituximab in SLE. Further identification of human cross-reactive antigens were underway.

Disclosure: Y. M. Kuo, None; J. Chen, None; J. S. Chia, None; C. J. Jung, None; S. C. Hsieh, None.

Abstract Number: 2683

Selective Expansion and Targeting of FoxP3+CD127^{lo} Regulatory T Cells By Low-Dose IL-2 Therapy in Active SLE

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Session Information

Session Date: Tuesday, October 23, 2018

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Session Time: 9:00AM-11:00AM

Background/Purpose: Interleukin-2 (IL-2) is crucial for the growth and survival of regulatory T cells (Treg), and thus for the control of autoimmunity. In previous studies we revealed the significance of an acquired IL-2 deficiency and related Treg defects in the pathogenesis of systemic lupus erythematosus (SLE). Here, we report the cellular responses to low-dose IL-2 therapy observed during an open-label, uncontrolled, dose escalation, phase 1/2a single-center clinical trial in patients with active SLE (EudraCT-Number: 2013-001599-40; DRKS-ID: DRKS00004858).

Methods: Twelve patients with active and refractory SLE (SLEDAI ≥ 6) were treated at our site with a low-dose IL-2 regimen consisting of four separate treatment cycles each with daily subcutaneous injections of recombinant human IL-2 (aldesleukin) at single daily doses of 0.75, 1.5 or 3.0 million IU for five consecutive days. Cells from peripheral blood were analyzed by flow cytometry at every study visit before and one day after each treatment cycle.

Results: All 12 treated patients showed highly significant cycle- and dose-dependent increases in the percentage of FoxP3+CD127^{lo} Treg, of CD25^{hi} cells among Treg and in the mean fluorescence intensity (MFI) of CD25 in Treg. In parallel, absolute numbers of CD25^{hi} Treg and of FoxP3+CD127^{lo} Treg in the peripheral blood increased significantly in a cycle-dependent fashion. By contrast, we observed only minor increases in the proportions and absolute numbers of CD25^{hi} cells among CD3+CD4+FoxP3⁻ conventional T cells (Tcon) and in the MFI of CD25 in Tcon. Moreover, there were no relevant changes in the absolute numbers of CD3+CD8⁺ T cells, of CD3+CD56⁺ NK T cells and of CD3-CD56⁺ NK cells. In addition, we noted robust and dose-dependent increases in the frequencies of Treg expressing the proliferation marker Ki67. Although significant increases in the proportions of Ki67⁺ Tcon were also apparent at the end of each treatment cycle, the calculated ratio between Ki67⁺Treg and Ki67⁺ Tcon continuously increased and was significantly higher at the end of the treatment phase, indicating a partial restoration of the homeostatic Treg/Tcon balance and suggesting a preferential targeting of the Treg population by low-dose IL-2 therapy.

Conclusion: Low-dose IL-2 therapy is capable to selectively expand and target the Treg population in patients with active SLE. This study also provides novel insights into the pharmacodynamics and immunological effects of low-dose IL-2 therapy.

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Abstract Number: 2684

Type I IFN, TLR7, MHC Class I, B Cell and OX40 Pathways Suppressed By Anifrolumab (anti-type I IFN receptor) in Moderate to Severe SLE Patients

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose : Type I interferon has been identified as one of the central mediators in the pathogenesis of SLE, such that patients are characterized by activation of this pathway with an elevated signature of type I IFN-inducible genes in the blood. Anifrolumab, an IFNAR1-specific human monoclonal antibody developed to block the type I interferon pathway, is under evaluation in Ph3 clinical trials of patients with moderate-to-severe SLE. To understand how anifrolumab modifies disease-relevant biological pathways, we explored gene expression changes in blood in SLE patients enrolled in a Ph2 trial of anifrolumab.

Methods: Gene expression was profiled on blood samples from moderate-to-severe adult SLE patients a Phase 2b clinical study at baseline, 169, and 365 days post-treatment (NCT01438489; n=301) with Affymetrix HGU133+2 arrays. The ratios of day 169 levels to baseline and day 365 to baseline were calculated for 70 cell type- and cytokine pathway-specific gene signatures. Then the 300 and 1000 mg doses were compared independently with placebo with a t-test. Statistical tests were adjusted for multiplicity using false discovery rate.

Results: Type I IFN ($p<0.0001$, FC>2.5), TLR7 ($p<0.0001$, FC>1.6), and MHC class I ($p<0.05$, FC>1.4) gene expression pathways were most suppressed at day 169 post treatment with anifrolumab compared to placebo in both the 300 and 1000 mg patient cohorts. At day 365 post treatment, type I IFN ($p<0.0001$, FC>2.5) and OX40 ($p<0.0001$, FC>1.8) gene expression pathways were most suppressed by anifrolumab compared to placebo. The suppression due to 1000 mg dose was no different from the 300 mg dose. The median suppression level of the type I IFN pathway was >75% at both time points and both dose levels compared to >15%, >20%, and >8% for TLR7, MHC class I, and OX40 gene expression pathways, respectively. Following anifrolumab treatment, expression of PECAM-1, which can reduce both T cell

and B cell activation, was significantly increased at days 169 and 365 (FC=1.51, $p < 0.0001$ and FC=1.47, $p < 0.0001$, respectively).

Conclusion: Type I IFN, TLR7, MHC class I and OX40 gene expression pathways were suppressed with anifrolumab. Both TLR7 and OX40 induce type I IFN signaling and HLA class I is known to be upregulated by IFNs. These results help to explain the efficacy of anifrolumab in SLE, support selection of the 300 mg dose in Ph3 trials, and highlight the potential of anifrolumab to impact autoimmune diseases more broadly.

Disclosure: K. Streicher, AstraZeneca, 1, 3; J. Wang, AstraZeneca, 1, 3; P. Z. Brohawn, AstraZeneca, 1, 3; B. W. Higgs, MedImmune LLC, 3; R. Tummala, AstraZeneca, 1, 3; K. Ranade, MedImmune LLC, 3.

Abstract Number: 2685

Interferon-Inducible Gene Expression Kit As a Potential Diagnostic Test for Anifrolumab: Analytical Validation for Use in Clinical Trials

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Anifrolumab is a fully human monoclonal antibody that binds to the type I interferon (IFN) receptor. Its efficacy and safety in the treatment of patients with moderate-to-severe systemic lupus erythematosus (SLE) is being evaluated in Phase III clinical trials. Patients with a high IFN-inducible gene signature (IFNGS) respond better to anifrolumab than those with a low IFNGS.¹ AstraZeneca and QIAGEN have developed an *in vitro*, reverse transcriptase polymerase chain reaction (RT-PCR)-based diagnostic test for type I IFN-inducible gene expression (IFIGx) that enables the detection of expression of 4 IFN-inducible genes (*IF127*, *IF114*, *IF114L*, and *RSAD2*) relative to 3 housekeeping genes. The efficacy of anifrolumab will be evaluated in patients with high and low IFNGS. In the present study, we conducted analytical validation of the *therascreen*[®] IFIGx RGQ RT-PCR kit (IFIGx kit) for use in clinical trials, as well as to potentially support future regulatory submissions.

Methods: Measurements were performed on mRNA extracted from whole blood from adults with SLE. Patients were identified as “type I IFNGS test-high” or “type I IFNGS test-low” based on a generated score. Analytical validation comprised 6 studies that measured lot interchangeability, linearity, repeatability, reproducibility, cross contamination, and system verification.

Results: Reproducibility and repeatability were >96% and 100%, respectively, with linearity of score observed at $\pm 10\%$ defined input concentration. No cross contamination in reverse transcription or PCR steps was observed. Results of all studies validated the IFIGx kit (Table).

Conclusion: The analytical validation of the *therascreen*[®] IFIGx RGQ RT-PCR kit demonstrates this is a robust, reproducible diagnostic test for type I IFNGS. The IFIGx kit was shown to be valuable in a prior anifrolumab study,¹ and clinical utility is being further established in the anifrolumab Phase III study to potentially support regulatory filings.

Reference:

1. Furie et al. *Arthritis Rheumatol*. 2017;69:376-86.

Table: Summary of Analytical Validation of Anifrolumab IFIGx Test

Study	Description	Results
Lot interchangeability	<ul style="list-style-type: none"> Verification that scores and assay Ct values were robust when different lots of kit components were used Acceptance criterion: <0.58 Ct 	<u>Lot interchangeability verified</u> Largest observed change=0.16 Ct
Linearity	Verification—using linear and quadratic regression analyses—that mRNA input concentration (10 ng/μL) is in the assay's linear range	<u>Linearity verified</u> No change in score over the concentration range on either side of 10 ng/μL=0.0043 Ct
Repeatability	Verification of Dx result repeatability when the same operator tested 60 random samples using the same kit lot and instrument	<u>Repeatability verified</u> Observed repeatability=100%
Reproducibility	<ul style="list-style-type: none"> Verification of Dx result reproducibility when multiple operators tested 48 random samples using multiple kit lots and instruments at different sites For verification, overall rate of correct calls must be ≥95% 	<u>Reproducibility verified</u> Overall rate=99.7% After 6 samples with values close to the cut-off were added for further confirmation, overall rate=96.5%
Cross contamination	Investigation of inter- and intra-run cross contamination	<u>No cross contamination</u> No cross contamination found in reverse transcription or PCR steps
System verification	Verification of functionality and utility of the IFIGx software and IFIGx assay package	<u>System verification confirmed</u> Software flags produced as expected

Ct, cycle threshold (PCR cycle at which fluorescence rises above background level); Dx, diagnostic; IFIGx, interferon-inducible gene expression; PCR, polymerase chain reaction; mRNA, messenger ribonucleic acid.

Disclosure: P. Z. Brohawn, MedImmune LLC, 3; B. W. Higgs, MedImmune LLC, 3; S. Patel, AstraZeneca, 3; A. Moody, QIAGEN Manchester Ltd, 3; P. Cooper, QIAGEN Manchester Ltd, 3; K. Ranade, MedImmune LLC, 3.

Abstract Number: 2686

Podocyte Foot Process Width Is a Prediction Marker for Complete Renal Remission at 6 and 12 Months after Induction Therapy in Lupus Nephritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical Poster III: Treatment

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Session Time: 9:00AM-11:00AM

Background/Purpose: Lupus nephritis (LN) is a most important predictor of morbidity and mortality in patients with systemic lupus erythematosus (SLE). Histopathology samples from patients with LN can demonstrate injury to nearly any cell type, including the mesangial, endothelial, podocyte, tubulointerstitial and vascular involvement associated with different pathogeneses, clinical presentations, therapeutic responses, and outcomes in LN patients. Podocytes are epithelial cells that provide the glomerular filtration barrier with foot processes and slit diaphragms. The morphological change with diffuse effacement of the foot processes is correlated with proteinuria in patients with LN. It has also been shown that in patients with nephrotic LN, foot process effacement estimated by the foot process width (FPW) was more extensive than in patients with non-nephrotic LN. We evaluated the possible association between podocyte injury and clinical features in LN.

Methods: We studied 73 patients with LN who underwent a renal biopsy at our hospital or a community hospital in 1993–2016. We collected the data of clinico-pathological parameters and assessed the FPW for evaluating podocyte effacement. We retrospectively analyzed the complete renal remission (CR) rate at 6 and 12 months after induction therapy and determined the predictive factors for CR. Univariate and multivariable competing risks regression analyses were used to determine the predictive factors of CR. Decision tree models predicting CR were built with the Classification and Regression Trees (CART) algorithm.

Results: At 6 and 12 months after induction therapy, 34 patients (46.6%) and 47 patients (64.3%) achieved CR, respectively. The multivariate analysis revealed that female gender (OR 5.288, 95% CI: 1.197–37.29, $p=0.0267$) and FPW (OR 0.999, 95% CI: 0.997–0.999, $p=0.0150$) for predicting CR at 6 months and lymphocyte counts (OR 1.002, 95% CI: 1.001–1.003, $p=0.0028$) and FPW (OR 0.998, 95% CI: 0.996–0.999, $p=0.0027$) for predicting CR at 12 months were significant. The median FPW was 1088 nm (IQR 895–1465 nm) in the total group of 73 patients. The degree of foot process effacement was significantly different among the various types of LN ($p=0.0007$): 701 nm (IQR 546–902 nm) in class I, 817 nm (IQR 685–1056 nm) in class II, 921 nm (IQR 711–1145 nm) in pure class III, 1294 nm (IQR 1086–1804 nm) in pure class IV, 1283 nm (IQR 899–1484 nm) in pure class V, and 1421 nm (IQR 887–1976 nm) in the combined group (class III + V and IV + V). We found that there was a moderate correlation between the individual FPW value and the amount of proteinuria ($r=0.3554$, $p=0.00022$). There was also a significant correlation between the individual FPW and serum albumin ($r= -0.4757$, $p<0.0001$) and between the individual FPW and the index of activity (0–24) ($r=0.4908$, $p<0.0001$). The cut-off point determined by the CART algorithm showed that FPW <908.3 nm provide the best performance to predict patients who achieve CR at 12 months.

Conclusion: We found that the lymphocyte count and/or the foot process width are prognostic markers for the achievement of a CR at 6 and 12 months after induction therapy for lupus nephritis. The pathological role of the FPW is still unknown, but it may reflect the degree of podocyte function.

Disclosure: K. Ichinose, None; M. Kitamura, None; S. Sato, None; K. Fujikawa, None; Y. Horai, None; N. Matsuoka, None; M. Tsuboi, None; F. Nonaka, None; M. Umeda, None; T. Koga, None; T. Igawa, None; T. Nishino, None; A. Kawakami, None.

Abstract Number: 2687

Patient-Level Evaluation of Components of the American College of Rheumatology Combined Response Index in Systemic Sclerosis (CRISS) Using Patient-Reported Anchors

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Treatment benefit is demonstrated by evidence that interventions have positive impacts on how patients feel, function, and/or survive (FDA Guidance, 21CFR314.510). The ACR CRISS, a composite endpoint for trials in systemic sclerosis (SSc), uses a weighted score combining outcome assessments that directly measure how patients feel and function [HAQ-DI and patient (PGA) global assessment] with outcome assessments that are indirect measures of patient symptoms/function [FVC, modified Rodnan skin score (mRSS), and physician global assessments (MDGA)]. Understanding the relationship and magnitude of effects on these indirect assessments would provide confidence that each component of CRISS would reliably predict an effect on direct measures of patient benefit. Our objective was to provide data to support evaluation of CRISS using patient-reported outcome (PRO) anchors - HAQ-DI and PGA.

Methods: We evaluated 2 cohorts: an early diffuse cutaneous SSc (dcSSc) cohort that was used for development of ACR CRISS (1) and a phase 2 trial of TCZ vs. placebo in dcSSc [faSScinate trial (2)]. Using the early dcSSc cohort, we assessed the effect size (ES) at the patient-level for non-PRO variables (mRSS, MDGA, and FVC%) in those we defined as “responders” who met minimal clinically important differences (MCID) estimates for HAQ-DI (defined as an improvement of ≥ 0.22) and PGA improvement of ≥ 1.0 (range 0-10). We interpreted ES using Cohen’s criteria: < 0.20 = negligible, 0.20 - 0.49 = small, 0.50 - 0.79 = medium, >0.80 = large (3). We assessed whether ES in patients who met the responder criteria in HAQ-DI and PGA in the faSScinate trial was associated with larger improvements in the ACR CRISS scores at week 24 and 48.

Results: In the dcSSc cohort, the ES was of greater magnitude for responders vs. non-responders (Table), except for HAQ-DI and FVC% when using PGA as an anchor. In the faSScinate trial, statistically significant improvements in the median ACR CRISS scores were seen in those who attained MCID vs. patients who did not (Table).

Conclusion: In a dcSSc cohort, generally patients who achieved MCID in HAQ-DI and PGA are associated with larger magnitude of improvement in ACR CRISS non-PRO variables. Limitations of the analysis are: 1. HAQ-DI and PGA are part of the ACR CRISS score, and 2. Assessing the relationships in an observational cohort. Ongoing trials should confirm the relationships between non-PRO variables (mRSS, MDGA, and FVC%) vs. PRO anchors.

References:

1. Khanna, D. *Arthritis & Rheumatology*
2. Khanna D. *Lancet*. 2016
3. *Psychol Bull*. 1992

Role of the study sponsor: F Hoffmann-La Roche Ltd funded the study and was involved in writing the abstract.

Table: Change in the CRISS variables in improvers and non-improvers based on HAQ-DI and PGA MCID estimates

	Patients with HAQ-DI \geq 0.22 (MCID) Responders	Patients with HAQ-DI <0.22 Non-responders	P value	Patients with PGA \geq 1 (MCID)	Patients with PGA<1	P value
Early diffuse SSc cohort						
MRSS, ES	- 0.70, N= 27	- 0.30, N= 84	0.06	- 0.65, N= 37	- 0.25, N=74	0.03
FVC%, ES	0.20, N= 24	- 0.07, N= 87	0.002	0.11, N= 32	- 0.07, N=79	0.04
PGA, ES	- 0.29, N= 28	0.03, N= 69	0.13	NA	NA	
MDGA, ES	- 0.43, N= 23	- 0.06, N= 72	0.30	- 0.31, N=31	-0.06, N=64	0.40
HAQ-DI, ES	NA	NA		- 0.14, N=37	0.10, N=62	0.16
Data from faSScinate trial						
CRISS Score at 24 week, median	0.381, N=18	0.002, N=49	0.045	0.229, N=21	0.018, N=46	0.02
CRISS Score at 48 week, median	0.947, N=15	0.011, N=43	<0.001	0.705, N=22	0.018, N=36	0.01

Disclosure: V. Nagaraja, None; J. Powers, Corbus Pharmaceuticals Holdings, 5; C. J. F. Lin, Genentech, Inc., 1, 3; B. Brennan, None; V. J. Berrocal, None; D. Khanna, Eicos Sciences, 1, Pfizer, Inc., 2, Horizon, 2, BMS, 2, Actelion, 5, Bayer, 5, Bayer, 2, Corbus, 5, Cytari, 5, EMD Serono, 5, Genentech, Inc., 5, Sanofi-Aventis, 5, GSK, 5, Boehringer Ingelheim, 5, Civi BioPharma, 3.

Abstract Number: 2688

Increased Serum Uric Acid Levels Are Associated with a Higher Risk of Digital Ulcers in Patients with Systemic Sclerosis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Endothelial cell dysfunction and/or injury are considered critical early events in the pathogenesis of vasculopathy in patients with systemic sclerosis (SSc). Hyperuricemia is known to induce endothelial dysfunction and vascular inflammation; however, the link between uric acid and SSc vasculopathy has not been well established. We investigated whether increased serum uric acid levels (SUA) are associated with the digital ulcers (DUs) in patients with SSc.

Methods: In this cross-sectional study, we consecutively recruited 71 women with SSc and 103 age- and sex-matched healthy subjects at a university-affiliated rheumatology center, and SUA levels were measured in all study subjects. All patients with SSc fulfilled the preliminary classification criteria established by the American College of Rheumatology for SSc. Active DUs were defined as a loss of epithelialization and tissues involving the epidermis, dermis, subcutaneous tissue, and bone. DUs included both, active and healed lesions.

Results : The mean (\pm standard deviation) SUA levels in patients with SSc were significantly higher than those in controls (4.5 ± 1 vs. 4.2 ± 0.9 mg/dL, respectively, $p=0.027$). Patients with SSc showed a significantly lower body mass index (BMI) than healthy subjects (21.8 ± 2.8 vs. 23.3 ± 3.5 kg/m², respectively, $p=0.005$) whereas no statistically significant intergroup difference was observed in the estimated glomerular filtration rate (eGFR). Among patients with SSc, 22 (31%) had DUs (active DUs: 8, healed DUs: 14). Patients with SSc presenting with DUs showed significantly higher SUA levels than those

without DUs (5 ± 1 vs. 4.3 ± 0.9 mg/dL, respectively, $p=0.008$). In multivariable logistic regression models adjusting for confounders including BMI and eGFR, increased SUA levels were observed to be independently associated with a higher risk for the presence of DUs as shown in Table 1 (OR 2.3, 95% CI 1.16–4.57, $p=0.018$). Additionally, the modified Rodnan skin score and the disease duration showed a significant association with DUs (OR 1.14, 95% CI 1.03–1.27, $p=0.013$; and OR 1.01, 95% CI 1–1.02, $p=0.023$, respectively).

Table 1. Association between serum uric acid level and digital ulcers ever in patients with systemic sclerosis evaluated by logistic regression models

Variables	Univariable model		Multivariable model	
	Crude OR (95% CI)	p-value	*Adjusted OR (95% CI)	p-value
SUA level, mg/dL	2.19 (1.23-3.92)	0.008	2.3 (1.16-4.57)	0.018
MRSS	1.14 (1.04-1.25)	0.004	1.14 (1.03-1.27)	0.013
Disease duration, months	1.01 (1-1.02)	0.02	1.01 (1-1.02)	0.023
ILD	3.27 (1.1-9.78)	0.034	-	-
eGFR, mL/min/1.73m ²	1.01(0.98-1.03)	0.508	-	-
BMI, kg/m ²	0.97 (0.81-1.16)	0.72	-	-
PAH	0.51 (0.1-2.6)	0.424		
Anti-centromere antibody	0.38 (0.1-1.51)	0.169		
Anti-Scl70 antibody	0.65 (0.21-1.95)	0.437		
Diffuse SSc (ref. limited SSc)	1.33 (0.49-3.66)	0.576		

* Estimated using backward multivariable logistic regression models including SUA levels, MRSS, disease duration, ILD, eGFR and BMI.

Conclusion: Our data revealed that elevated SUA levels are associated with a higher risk for DUs in patients with SSc regardless of confounding factors, thereby suggesting the potential role of hyperuricemia in the pathogenesis of SSc vasculopathy.

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Abstract Number: 2689

Association between Small Vessel Disease and Arterial Stiffness in Systemic Sclerosis

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Session Information

Session Date: Tuesday, October 23, 2018

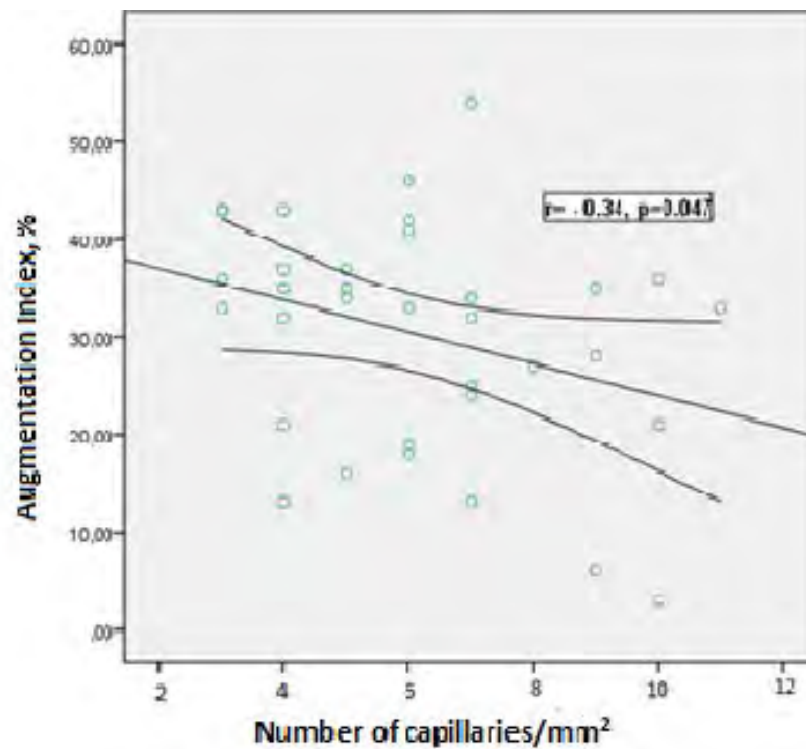
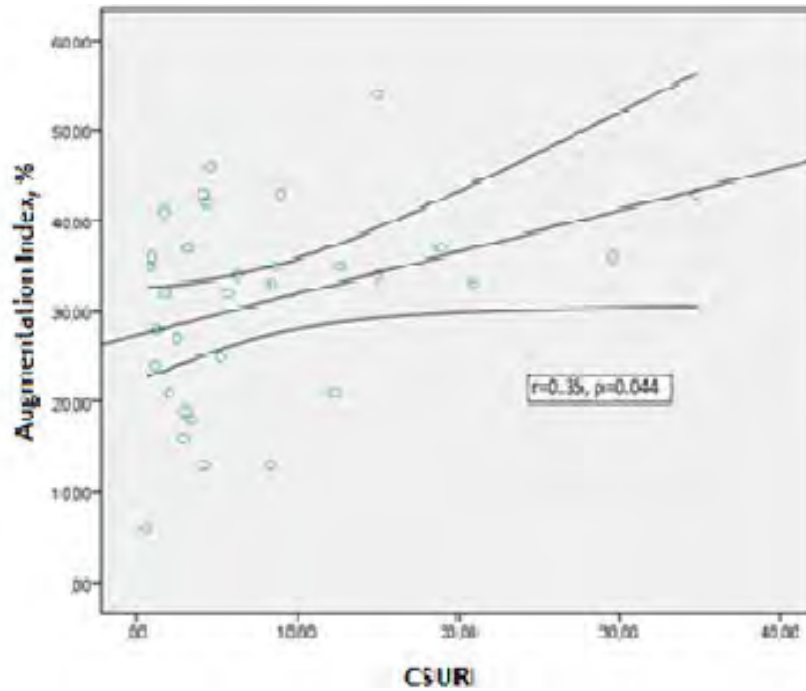
Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Microangiopathy predominates in the pathophysiology of Systemic Sclerosis (SSc). However, large vessel involvement leading to higher risk for cardiovascular disease in SSc remains unclear. Nailfold videocapillaroscopy (NVC) is an established method for the assessment of the microvasculature, aiding in distinguishing different types of structural vascular abnormalities. Until recently, NVC was used in the diagnosis of SSc as well as in the assessment and follow-up of peripheral digital vasculopathy however recent data indicates a possible association with macrovascular involvement namely atherosclerosis and coronary artery disease. The aim of this study was the investigation of the relation between microvascular and macrovascular involvement in the setting of SSc.

Methods: Consecutive patients with established SSc treated in the Scleroderma Clinic of State Hospital Unit from September 2016 until June 2017 were enrolled in our study. We conducted NVC to evaluate microcirculation. The number of capillaries/mm² and capillaroscopic index CSURI were measured. Findings were also classified to the three scleroderma patterns (early, active, and late). Cardiovascular risk was assessed using the European SCORE, while the following vascular markers were measured: carotid intima-media thickness (IMT), Augmentation Index (AIx) of the aorta, aortic pulse wave velocity (PWV) and central systolic and diastolic blood pressure. The correlation between microvascular and macro-vascular parameters was examined.



Results: Thirty-seven (1 man) SSc individuals were studied. Among the atherosclerotic morphological and functional parameters assessed, a significant correlation was observed between aortic AIx and the average number of capillaries/mm² ($r = -0.34, p = 0.047$) and between AIx and the capillary index CSURI ($r = 0.35, p = 0.044$). In addition, lower AIx values were recorded in the “early” scleroderma pattern compared to the “active” and “late” pattern [20.5 ± 11.4 vs $34.1 \pm 11.5\%$, $p = 0.02$ (early vs. active) and 20.5 ± 11.4 vs $33.4 \pm 8.8\%$, $p = 0.05$ (early vs late)]. No statistically significant associations were demonstrated between abnormalities of nailfold capillaries and IMT, PWV or SCORE in our population.

Conclusion: The extent of microangiopathy is related to the degree of arterial stiffness assessed by AIx suggesting a potential link between micro- and macrovascular disease in SSc.

Disclosure: S. Soulaïdopoulos, None; E. Pagkopoulou, None; E. Triantafyllidou, None; N. Katsiki, None; G. D. Kitas, None; A. Karagiannis, None; A. Garyfallos, None; T. Dimitroulas, None.

Abstract Number: 2690

Potential Markers of Skin Involvement in Systemic Sclerosis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Skin fibrosis is a hallmark of systemic sclerosis (SSc). There are no widely accepted biomarkers of skin involvement in this condition. Several serum or plasma markers have been studied in patients with SSc - monocyte chemoattractant protein-1 (MCP-1), chemokine (C-X-C motif) ligand 8 (CXCL8), interleukin-13 (IL-13), and some more recognized such as - platelet derived growth factor (PDGF), transforming growth factor-beta 1 (TGF-beta 1), epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF). The aim of this study was to assess several circulating biomarkers which may be relevant to the fibrosing process and further to correlate the obtained data with clinical indicators specific for SSc skin involvement.

Methods: 59 SSc patients (M/F 9/50; mean age 52.1 years, mean disease duration 6.7 years, 36 patients with limited cutaneous SSc and 23 with diffuse cutaneous SSc. As a control group 36 healthy individuals matched to sex and age were examined. Serum concentrations of bFGF, granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage-colony stimulating factor (GM-CSF), MCP-1, PDGF, IL-8 and IL-13 were analysed using commercial multiplex kit. The following clinical examinations were performed: modified Rodnan skin score (mRSS), Hand Mobility in Scleroderma Test (assessing hand function) (HAMIS), Cochin Hand Function Scale (hand function) (CHFS), Delta Finger-to-Palm Distance (extension-flexion) (dFTP), Inter-lip Distance (inter-lip), Inter-incisor Distance (inter-incisor), and Mouth Handicap in Systemic Sclerosis Scale (mouth opening) (MHISS). For statistical evaluation Spearman's correlation coefficient was used.

Results: When compared with healthy controls serum concentrations of bFGF ($p<0.001$), G-CSF ($p<0.0001$), GM-CSF ($p<0.0001$), MCP-1 ($p<0.0001$), IL-8 ($p<0.0001$), and IL-13 ($p<0.001$) were significantly elevated in SSc cohort. PDGF levels were increased in SSc patients with only a lower significance ($p<0.01$). bFGF, G-CSF, MCP-1 and IL-8 levels correlated significantly ($p<0.05$) with mRSS and HAMIS. GM-CSF levels correlated with mRSS and HAMIS and there was only a trend for negative correlation with inter-incisor. There was no correlation of IL-13 and PDGF levels with the evaluated clinical data.

Conclusion: Our results have shown that G-CSF, GM-CSF and IL-8 play a substantial role in SSc fibrosing process. Potential biomarkers as bFGF, G-CSF, MCP-1 and IL-8 correlated with a few clinical indices of SSc skin involvement.

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Disclosure: R. Becvar, None; H. Storkanova, None; B. Sumova, None; M. Spiritovic, None; S. Oreska, None; L. Šenolt, None; M. Tomcik, None.

Abstract Number: 2691

Increased Plasma Angiopoietin-2 in Systemic Sclerosis: Potential for Use As a Biomarker of Vasculopathy and Fibrosis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Angiogenic pathways are likely to contribute to pathogenesis of both vasculopathy and fibrosis in Systemic sclerosis (SSc). The angiogenic actions of Angiopoietins (pro-angiogenic Ang1 and divergent Ang2) through competitive Tie2 binding could be attractive biomarkers in SSc. We report the association between Ang1, Ang2 and Tie2 with objective assessments of peripheral vasculopathy and cutaneous fibrosis in SSc.

Methods: Fifty-one SSc patients (2013 ACR/EULAR criteria) and fifteen healthy controls (HC) underwent functional assessment of post-occlusive digital vascular responses using Laser Speckle Contrast Imaging (LSCI), morphological

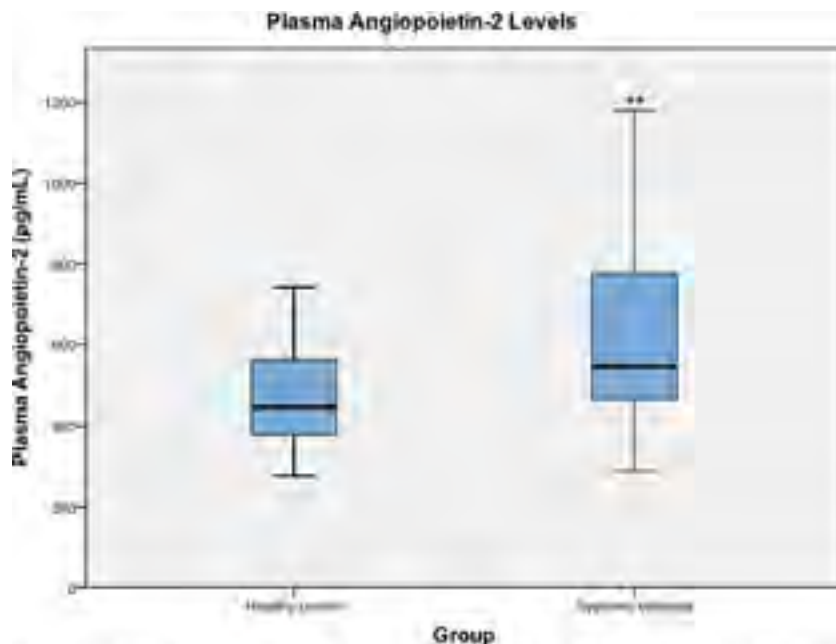


Figure 1. Plasma Angiopoietin-2 levels are significantly higher in SSc than controls. Box plots demonstrate inter-quartile ranges and median (horizontal line). Whiskers demonstrate minimum and maximum values. Significance $p < 0.01$. Illustrated by ** (Mann-Whitney U).

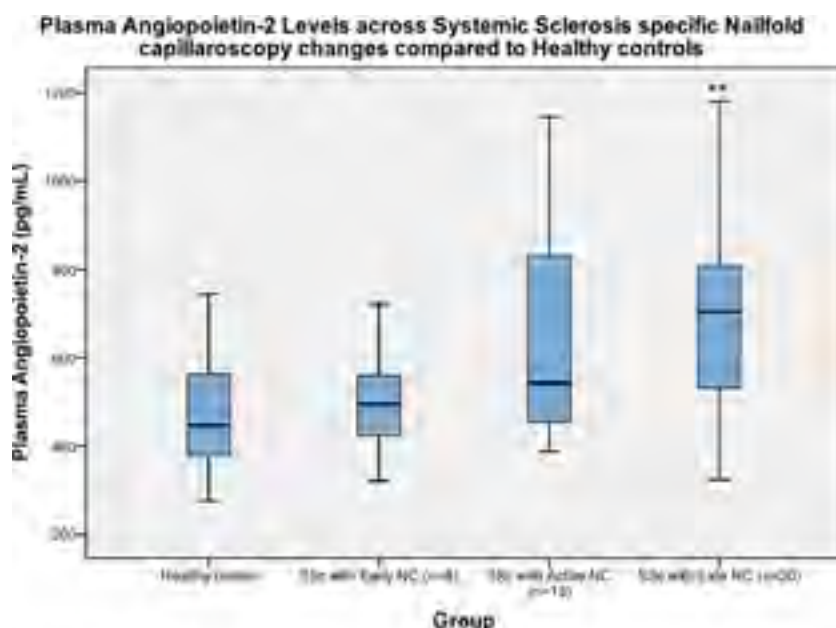


Figure 2. Plasma Angiopoietin-2 levels progressively increase with progressive nailfold capillaroscopy (NC) classification. Box plots demonstrate interquartile ranges and median levels (horizontal line). Whiskers show minimum and maximum values. Significance $p < 0.01$ compared to Healthy controls illustrated by ** (Kruskal-Wallis).

Biomarker (n)	Raynaud's Condition Score	LSCI Post Occlusive Reperfusion Gradient	HFUS Vascularity Index	NC Inter-capillary distance	mRSS	HFUS Dermal thickness	HFUS Echogenicity	HFUS SWE
(n)	42	47	51	51	51	51	51	51
Ang-1	+0.153	+0.150	-0.083	-0.040	-0.129	-0.035	+0.181 **	+0.069
(n)	39	44	48	48	48	48	48	48
Ang-2	+0.169	-0.368 **	-0.021	+0.284	+0.255	-0.235	+0.330 *	+0.348 **

Table 1. Spearman's Rank correlation coefficient (r_s) for plasma biomarkers with subjective and objective measures of vasculopathy and fibrosis in the Systemic Sclerosis group. Significance $p < 0.05$ illustrated by *, $p < 0.01$ illustrated by **. Functional assessment by Laser Speckle Contrast Imaging (LSCI) is reflected in a reperfusion gradient of the distal fingers following an occlusive challenge. High Frequency Ultrasound (HFUS) Vascularity index was assessed over the distal phalanx of the middle finger. Inter-capillary distance was manually calculated from Nailfold capillaroscopy (NC) images. HFUS assessment of dermal thickness, Echogenicity and Shear wave Elastography (SWE) were recorded over the proximal phalanx of the middle finger. In SSc, Ang2 demonstrated a negative correlation with the post-occlusive reperfusion gradient on LSCI and positively with inter-capillary distance (the latter of borderline significance ($p = 0.05$)). Ang2 also positively correlated with Echogenicity and SWE. Ang1 demonstrated a weak positive correlation with Echogenicity.

capillary assessment using nailfold capillaroscopy (NC) and High Frequency Ultrasound (HFUS) assessment of cutaneous fibrosis and digital vasculopathy. Modified Rodnan Skin Score (mRSS) and Raynaud's Condition Score were assessed in SSc. Plasma Ang 1, Ang 2 and Tie2 levels were measured using ELISA.

Results: Ang2 was significantly increased in SSc compared to HC (Figure 1). There was no significant difference in Ang1 or soluble Tie2, however Ang1/2 ratio was significantly reduced in SSc compared to HC (median 4.4 versus 6.2, $p = 0.018$). In SSc, Ang2 demonstrated a weak negative correlation with the post-occlusive reperfusion gradient on LSCI and a weak positive correlation with inter-capillary distance (Table 1), suggesting an association between impaired functional and structural microangiopathy and increased Ang2. Ang2 progressively increased with progressive NC qualitative classification (early, active and late, Figure 2). Interestingly, Ang2 also correlated weakly with Echogenicity and Shear wave Elastography on HFUS, suggesting an association with skin fibrosis. Ang1 had a weak positive correlation with Echogenicity only suggesting that as the oedematous phase of SSc skin disease resolves, Ang1 increases. The lack of significant correlation between Ang1 and Elastography suggests there is no clear association with fibrosis (Table 1).

Conclusion: Our findings suggest that Ang2 may reflect anti-angiogenic and pro-fibrotic mechanisms in SSc. Further study is warranted to explore the relative expression of Angiopoietins in well phenotyped SSc patients and evaluate their role as novel biomarkers.

Disclosure: V. Flower, None; S. Barratt, None; D. Hart, None; A. MacKenzie, None; J. Shipley, None; S. Ward, None; J. Pauling, None.

Abstract Number: 2692

High Frequency Ultrasound As a Novel Approach to Quantifying the Digital Microangiopathy of Systemic Sclerosis

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Session Information

Session Date: Tuesday, October 23, 2018

Background/Purpose: Structural and functional vascular abnormalities occur in Systemic Sclerosis (SSc). We report on the use of High Frequency Ultrasound (HFUS) with Superb Microvascular Imaging (cSMI) as a novel approach to assessing digital vasculopathy in SSc.

Methods: Fifty-three SSc (2013 ACR/EULAR criteria) and fifteen healthy controls (HC) underwent assessment of the distal middle finger using a novel Doppler cSMI modality, able to detect low velocity microvascular flow and simultaneously minimise motion artefact. HFUS cSMI was used to measure Vascularity Indices (VIs) at 3 regions of interest (Dorsovascular [DVVI], Nailfold [NVI] and Fingertip [FVI]). Morphological assessment of capillaries was undertaken using nailfold capillaroscopy (NC). Functional post-occlusive microvascular responses were assessed using Laser Speckle

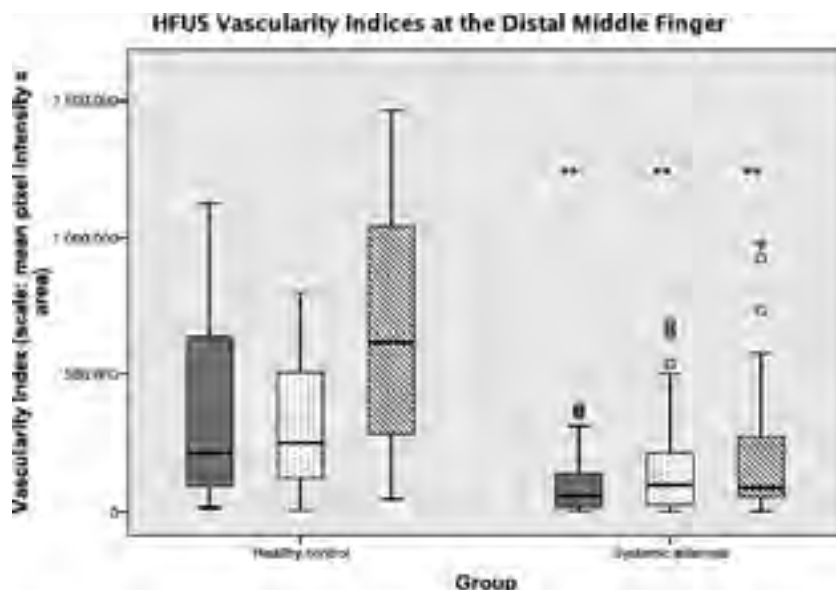


Figure 1. Vascularity Indices (VIs) on High Frequency Ultrasound (HFUS) at the distal middle finger are significantly reduced in SSc compared to healthy controls (Mann-Whitney U). Box plots demonstrate inter-quartile range and median (horizontal line). Whiskers demonstrate minimum and maximum values. Order from left-right: Dorsovascular VI (grey), Nailfold VI (spot) and Fingertip VI (striped). Significance $p < 0.01$ illustrated by ** compared to healthy controls.

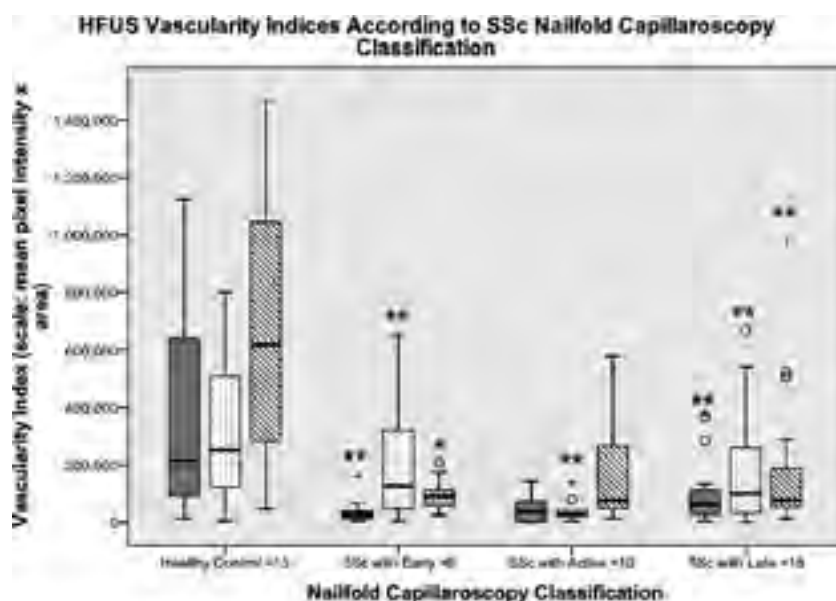


Figure 2. High Frequency Ultrasound (HFUS) Vascularity Indices (VIs) at the distal middle finger are reduced in SSc with Early, Active and Late NC changes. Significance $p < 0.05$ illustrated by *, $p < 0.01$ by ** (Kruskal-Wallis). Box plots demonstrate inter-quartile range and median (horizontal line). Whiskers demonstrate minimum and maximum values. Order from left-right: Dorsovascular VI (grey), Nailfold VI (spot) and Fingertip VI (striped).

Laser Speckle Contrast Imaging Parameter	Dorsovolar VI	Nailfold VI	Fingertip VI
Median Baseline Fingertip Perfusion (Mean of Digits 2-5, n=52)	+0.376 **	+0.393 **	+0.638 **
Percentage change in Post-Occlusive Fingertip Flux (n=40)	-0.339 *	-0.266	-0.465 **

Table 1. Spearman's Rank Correlation Coefficient (r_s) demonstrating weak-moderate correlations between Vascularity Indices (VIs) and LSCI parameters in SSc group with the exception of Nailfold VI and percentage change in post-occlusive fingertip flux, which approached significance ($p=0.065$). Significance $p<0.05$ illustrated by*, $p<0.01$ by**

Contrast Imaging (LSCI). The Raynaud's Condition Score (RCS) diary was collected as a patient-reported measure of Raynaud's phenomenon severity.

Results: All 3 VIs were significantly reduced in SSc compared to HC (Figure 1). The DVVI and FVI were also significantly reduced in SSc with a history of digital ulcers (DU) versus without, (40120 versus 110443, $p=0.015$ and 51955 versus 195408, $p=0.006$ respectively). All 3 VIs in the SSc group correlated with baseline fingertip perfusion on LSCI (strongest association seen with FVI, Table 1). The association was particularly strong in limited SSc (Spearman's r_s +0.703, $p<0.001$). There was a significant reduction in DVVI and FVI of SSc patients with each of early, active and late NC patterns compared to HC, as well as NVI with an active pattern (Figure 2). No significant differences were identified between SSc NC classifications. No correlations were seen with RCS.

Conclusion: Our findings suggest a role for HFUS in the assessment of digital vascular abnormalities in SSc with the advantages of quick quantifiable data capture over broad regions of interest. The relationship with DU history suggests a potential future role as a vascular biomarker and prognostic factor in SSc.

Disclosure: V. Flower, None; S. Barratt, None; D. Hart, None; A. MacKenzie, None; J. Shipley, None; S. Ward, None; J. Pauling, None.

Abstract Number: 2693

What Is the Effect of Cyclophosphamide Iv Pulse Therapy in Patients with Diffuse Cutaneous Systemic Sclerosis on Skin Involvement: An Observational Study

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Session Information

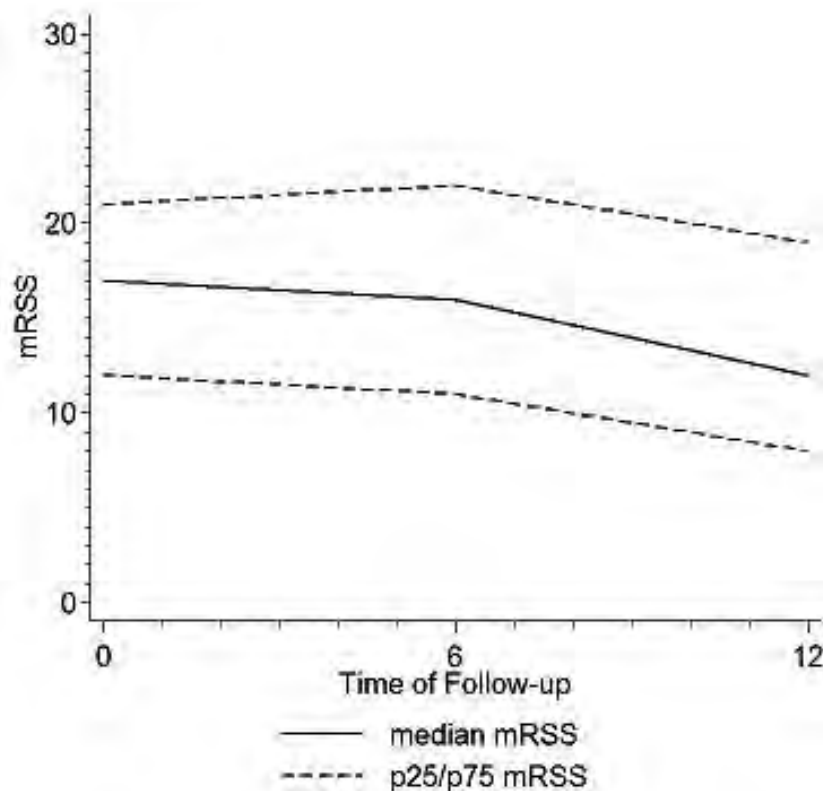
Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with systemic sclerosis who have proximal skin involvement are classified as diffuse cutaneous systemic sclerosis (DcSSc). Patients with progressive skin involvement have worse prognosis. Treatment options consist among others of cyclophosphamide iv pulse therapy (iv CYC). Recent studies show significant improvement of skin thickening in patients treated with cyclophosphamide orally, but the effect of iv CYC on skin involvement remains unclear. Our aim is to examine the extent of skin involvement during 12 monthly iv CYC in DcSSc and to identify factors that predict response to therapy.



Methods: Patients with DcSSc receiving iv CYC between 2004 and 2016 were included. Skin involvement was assessed with the modified Rodnan Skin score (mRSS) at baseline, six, 12, 24 and 36 months by the same rheumatologist. Data of baseline and at least one follow-up measurement were included. Missing mRSS data were imputed using multiple imputation by chained equation. Patients were classified as responders if the mRSS decreased at least 5 points and 25% from baseline at month 12. A prediction model for response at 12 months was created using backwards logistic regression considering baseline variables and response at six months as possible predictors.

Results: A total of 91 patients were included (Table 1). The mean improvement of mRSS over time was -4.05 (95% CI - 5.53 to -2.55) (Figure 1). 43% of patients had a response according to the criteria. In univariate prediction models, baseline mRSS (OR 1.06, $p=0.024$), response at six months (OR: 37.45, $P<0.001$) and completed treatment (yes/no) (OR: 4.108, $p=0.033$), were significant predictors of response at 12 months. For the last variable it should be mentioned that some patients who did not achieve a response at month 6 did not continue iv CYC for that reason.

Figure 1. mRSS course of all patients during iv CYC

Conclusion: This study shows that only 43% of treated DcSSc patients experienced clinically important improvement of skin involvement following iv CYC. Response at month six is the best predictor for response on month 12. This could imply that at this time point, counseling about other available treatment options, should be considered in those patients.

Disclosure: B. Kersten, None; N. den Broeder, None; F. van den Hoogen, None; E. van den Ende, None; M. Vonk, None.

Abstract Number: 2694

Performance of Anti-Scl-70 Antibody Testing By Multiple-Bead, Enzyme-Linked Immunosorbent Assay, and Immunodiffusion in a University Setting

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The gold standard for anti-Scl-70 antibody testing in systemic sclerosis (SSc) uses immunodiffusion (ID) techniques, but enzyme-linked immunosorbent assay (ELISA) and multi-bead technology are often used to save time and cost. There is concern that using this methodology results in an increase in false positive results. Our aim was to assess the performance of the multi-bead, ELISA, and ID testing methods.

Methods: We conducted a retrospective study of patients whose extractable nuclear antigen-10 (ENA-10) autoantibody panel tested positive for the anti-Scl-70 antibody by multi-bead technology during a one-year period. All samples positive by multi-bead were sent to a reference laboratory to be reflexed for ELISA, and all anti-Scl-70 antibodies positive by ELISA were further tested by ID. Clinical data was reviewed by a rheumatologist and assessed for presence of SSc, internal organ involvement, and other connective tissue disease (CTD).

Results: Approximately 9500 extractable nuclear antigen-10 (ENA-10) panels were ordered by physicians at our institution between August 2016 and August 2017. Of these, 129 patients were positive for the anti-Scl-70 antibody by multi-bead assay, 51 were positive by ELISA, and 21 were positive by ID. On chart review of the patients who were positive by multi-bead assay, 33 (25.6%) had SSc and 9 (7.0%) had diffuse cutaneous SSc (dcSSc). Twenty-four (18.6%) had other CTDs, with 72 (55.8%) presenting with no evidence of CTD (Table). Of the 51 patients who were positive by multi-bead and ELISA, 23 (45.1%) had a diagnosis of SSc and 8 (15.7%) had dcSSc. Eight (15.7%) were diagnosed with other CTDs. For the 21 patients who were positive by multi-bead, ELISA and ID, 19 (90.5%) were diagnosed with SSc and 8 (38.1%) had dcSSc. We found that 25.6% of patients positive by multi-bead, 45.1% positive by ELISA, and 90.5% positive by ELISA and ID had SSc.

Conclusion: Multi-bead assays have a high rate of false positive results for the anti-Scl-70 antibody in patients without clinical evidence of SSc. A stepwise approach of confirmation of positive multi-bead results using both ELISA and ID greatly improves the predictive value of antibody testing for the diagnosis of SSc.

Table: Relative frequency of anti-Scl-70 antibody in patients diagnosed with systemic sclerosis, diffuse cutaneous systemic sclerosis and other connective tissue diseases

	Total n (%)	SSc n (%)	Diffuse Cutaneous SSc n (%)	Other CTDs n (%)
Anti-Scl-70 positive by multi-bead	129 (100)	33 (25.6)	9 (7.0)	24 (18.6)
Anti-Scl-70 Negative by ELISA	78 (60.5)	10 (12.8)	1 (1.3)	16 (20.5)
Anti-Scl-70 Positive by multi-bead + ELISA	51 (39.5)	23 (45.1)	8 (15.7)	8 (15.7)
Anti-Scl-70 Negative by ID (positive by multi-bead + ELISA)	30 (58.8)	4 (13.3)	0 (0)	6 (20.0)
Anti-Scl-70 Positive by multi-bead, ELISA and ID	21 (41.2)	19 (90.5)	8 (38.1)	1 (4.8)

Disclosure: K. Homer, None; J. Warren, None; D. Karayev, RDL Reference Laboratory, 3; P. P. Khanna, AstraZeneca, 2, SOBI, 2, Ironwood, 2; A. Young, T32-AR007080-38, 2; V. Nagaraja, None; A. L. Metzger, RDL Reference Laboratory, 4; D. Khanna, Eicos Sciences, 1, Pfizer, Inc., 2, Horizon, 2, BMS, 2, Actelion, 5, Bayer, 5, Bayer, 2, Corbus, 5, Cytos, 5, EMD Serono, 5, Genentech, Inc., 5, Sanofi-Aventis, 5, GSK, 5, Boehringer Ingelheim, 5.

Abstract Number: 2695

Progressive Skin Fibrosis, Internal Organ Involvement and All-Cause Mortality in an Early Diffuse Cutaneous Systemic Sclerosis United States Multicenter Registry

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Session Information

Session Date: Tuesday, October 23, 2018

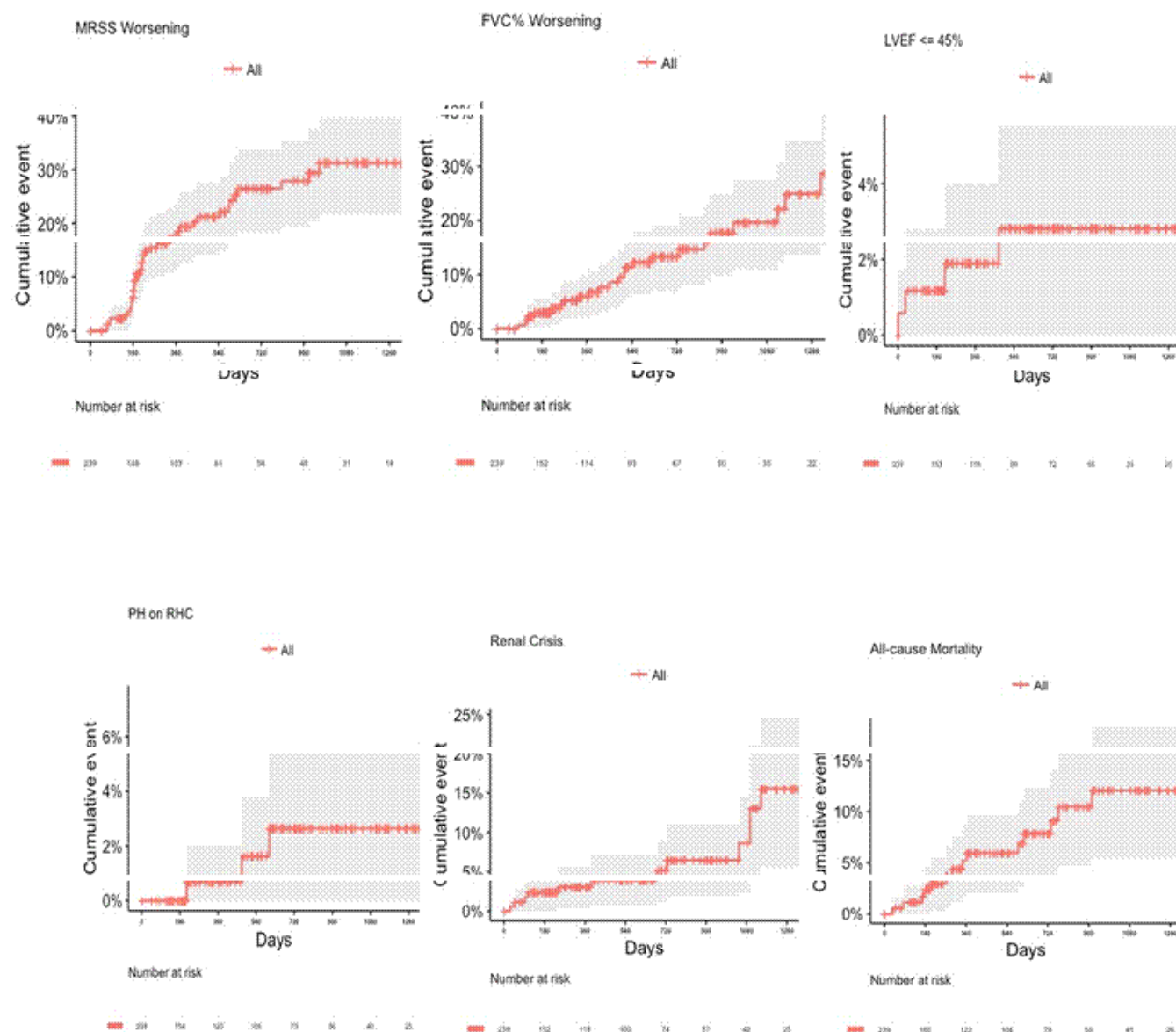
Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

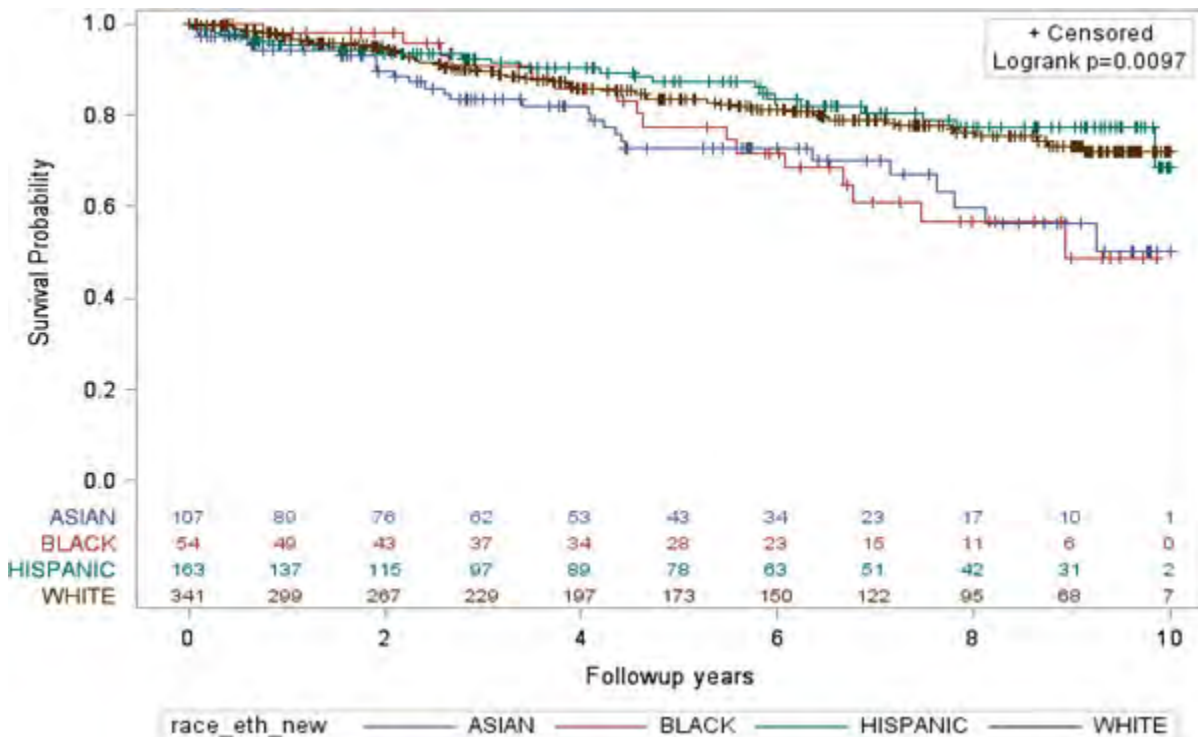
Session Time: 9:00AM-11:00AM

Background/Purpose: Early diffuse cutaneous systemic sclerosis (dcSSc) carries a high morbidity and mortality, predominantly due to internal organ involvement. The purpose of this study was to investigate the time to event of new

Figure: Cumulative Progressive Skin Fibrosis, Internal Organ Involvement and All-Cause Mortality Event Percentages with Confidence Intervals*



*Shading represents confidence intervals.



onset of visceral organ involvement and all-cause mortality in early dcSSc participants in an ongoing US multicenter registry(Prospective Registry of Early Systemic Sclerosis [PRESS]).

Methods: Inclusion criteria include a diagnosis of dcSSc and a disease duration of ≤ 2 years calculated from the date of onset of first non-Raynaud's phenomenon symptom. Organ involvement was defined as new involvement or worsening during follow up visits— 1) absolute increase in mRSS of ≥ 4 units or 20%, 2) an absolute decline of FVC % of $\geq 10\%$; 3) PH on RHC; 4) LVEF of $\leq 45\%$ on echo; 5) scleroderma renal crisis; or 6) all-cause mortality. We reported number of participants experiencing organ involvement during the course of the study via frequency tables and characterized the distribution of events through plots of the cumulative proportion of participants experiencing each event by time. Confidence intervals in the cumulative proportion plots were derived via bootstrap method.

Results: The cohort consisted of 239 participants from 11 US SSc centers at baseline with median follow-up of 414 days (IQR=112-922 days). The baseline mean age for the cohort was 50.1 years, disease duration was 1.3 years, HAQ-DI score was 0.82, 71.1% were female, and 76.2% were white. In this cohort, 199 (83.3%) were treated with immunomodulatory therapies during the course of the study (82.0% during the first year) including 63.2% on mycophenolate mofetil, 20.9% on methotrexate, 5.0% on cyclophosphamide, 3.3% on D-penicillamine, 16.3% on hydroxychloroquine, and 2.1% on azathioprine(percentage is greater than 82.0% as some participants were on multiple therapies at a single time-point and/or during the study). Survival function plots showed that 75 of 231 (32.5%) participants showed progressive skin fibrosis, 27 of 192 (14.1%) showed $\geq 10\%$ worsening of FVC%, 4 of 199(2.0%) showed LVEF of $\leq 45\%$, 12 of 239 (5.0%) had new onset scleroderma renal crisis, 5 of 239 (2.1 %) had PH on RHC, and 14 of 239 (5.9%) died during the course of the study (Figure); 11 of the 14 deaths were considered to be related to SSc.

Conclusion: Despite immunomodulatory therapy, a high proportion of early dcSSc patients experience worsening of mRSS and lung function and mortality within 2 years of dcSSc diagnosis. There are ongoing vascular-predominant complications over the course of the disease, consistent with published literature [1]. This data supports an ongoing need to identify novel therapies for dcSSc.

1. Nihtyanova SI. *Arthritis & rheumatology*. 2014.
ADDINEN.REFLIST

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Increased Mortality in Black and Asian Patients with Systemic Sclerosis in Northern California

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

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Background/Purpose: Studies indicate that black patients with systemic sclerosis (SSc) demonstrate a distinct phenotypic profile, with more severe disease, heightened mortality, and poorer prognosis compared to whites. Limited studies have evaluated disease severity and mortality in Asian Americans. Our aim was to compare disease manifestations and survival across race/ethnicity in SSc patients from Northern California, with a focus on Asians.

Methods: A retrospective study was conducted among Kaiser Permanente Northern California adults with a diagnosis of SSc by a rheumatologist from 2007-2017, confirmed by chart review to fulfill 2013 ACR-EULAR classification criteria. Self-reported race/ethnicity was categorized as: white, Asian, Hispanic, and black. Other racial subgroups were excluded from this study. Disease manifestations and all-cause mortality were compared between the race/ethnic groups with whites as the reference. Chi-square, Fisher exact tests, and multest were used for categorical variables. Kaplan-Meier and multivariate Cox regression analyses were used to estimate the probability of survival by race/ethnicity for incident cases, and to assess if race/ethnicity was a significant factor associated with death correcting for age. $P < 0.05$ was considered statistically significant.

Results: 1055 SSc patients were included with 665 incident and 390 prevalent cases. Most patients had limited cutaneous SSc ($n=937$, 89%) with only 11% categorized as diffuse ($n=118$). 89% were female, with mean age 56.5 ± 14.6 years, and mean disease duration 5.0 ± 3.2 years from date of diagnosis. The racial/ethnic distribution was 54% white ($n=569$), 23% Hispanic ($n=241$), 14% Asian ($n=152$), and 9% black ($n=93$). Although Hispanics did not display any significant differences in clinical features from whites, Asians had a lower frequency of calcinosis (32% vs. 16%, $p < 0.001$) and telangiectasias (75% vs. 53%, $p < 0.001$); blacks had a higher frequency of interstitial lung disease (38% vs. 57%, $p = 0.016$), but a lower frequency of telangiectasias (75% vs. 53%, $p < 0.001$) and Raynaud phenomenon (98% vs. 91%, $p = 0.036$). 9-year overall survival rates for whites, Hispanics, Asians, and blacks were 72.0%, 68.6%, 50.1%, and 48.6%, respectively (log-rank $p < 0.01$) (Figure 1). Pairwise comparisons demonstrated increased mortality in Asians compared to non-Asians ($p = 0.008$). On multivariate analysis, Asians and blacks had increased mortality compared to whites even after controlling for age (HR 2.2, CI 1.4-3.5, $p < 0.001$; HR 2.3, CI 1.3-4.0, $p < 0.001$, respectively), but not Hispanics (HR 1.1, CI 0.7-1.8, $p = 0.6$).

Conclusion: Survival in patients with SSc from Northern California differs by race. Asians and blacks had more than 2-fold increased risk of death compared with whites.

Table 1: Kaplan-Meier survival estimate by race/ethnicity

Disclosure: M. Chung, None; M. Dontsi, None; D. Postlethwaite, Bayer Global, 2; S. Kesh, None; L. Zaba, None; L. Chung, Third Rock Ventures; Incyte, 5.

Elevated Serum Interleukin-34 Levels Are Correlated with Interstitial Lung Disease in Systemic Sclerosis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

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Background/Purpose: Interleukin (IL)-34 is a hematopoietic cytokine, which promotes survival, proliferation, and differentiation of monocytes and macrophages. We investigated serum IL-34 levels in patients with systemic sclerosis (SSc).

Methods: The numbers of subjects enrolled in this study were as follows; 43 diffuse cutaneous SSc (dcSSc) patients, 15 limited cutaneous SSc (lcSSc) patients, and 20 healthy controls.

Results: Serum IL-34 levels in dcSSc patients were 10.97 ± 1.42 pg/mL (mean \pm s.e.m), which was significantly higher than lcSSc (5.16 ± 1.16 pg/mL) and healthy controls (3.81 ± 0.77 pg/mL). SSc patients with increased serum IL-34 levels suffered from interstitial lung disease (ILD) more frequently than those with normal levels. When we checked the correlations between serum IL-34 levels and ILD markers, serum IL-34 levels negatively correlated with the percentage of predicted vital capacity ($r = -0.32$, $P < 0.01$), while they positively correlated with ground-glass opacity score ($r = 0.49$, $P < 0.01$) and fibrosis score ($r = 0.31$, $P < 0.05$) on chest computed tomography. Serum IL-34 levels also positively correlated with serum KL-6 levels ($r = 0.33$, $P < 0.01$) and surfactant protein D levels ($r = 0.46$, $P < 0.01$). There was no association between serum IL-34 levels and the presence of anti-topoisomerase I, anti-centromere, or anti-polymerase III antibody.

Conclusion: Increased serum IL-34 levels were associated with greater frequency and severity of ILD in SSc patients, suggesting that serum IL-34 levels could be a useful serologic marker for SSc-associated ILD.

Disclosure: H. Suga, None; A. Kuzumi, None; Y. Asano, None; A. Yoshizaki, None; S. Sato, None.

Abstract Number: 2698

Renal Involvement in Mixed Connective Tissue Disease: A Single Center Experience

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Session Information

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Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

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Background/Purpose: Kidney injury in mixed connective tissue disease (MCTD) is an uncommon manifestation. Prevalence has been reported to be <4% in some cohorts. The frequency of renal involvement in Hispanic patients with MCTD is not known. We aimed to describe the prevalence, clinical characteristics and outcomes of renal involvement in Mexican patients with MCTD.

Methods: We conducted a retrospective single-center study. We included patients with a diagnosis of MCTD according to the Alarcón-Segovia criteria who regularly attended to a referral center in Mexico City (2003-2017) and we identified those with renal involvement defined as proteinuria >500 mg/d with or without active sediment, creatinine elevation 50% above baseline or development of glomerular filtration rate (GFR) <60 ml/min, with no other known cause. We collected demographics, clinical manifestations, follow-up time, treatment, outcomes and damage (SLICC/ACR-DI), renal function, serological and histological variables.

Results: One hundred and thirty one patients with MCTD were followed at our center. We identified 14 patients with renal involvement with a prevalence of 10.7%. Among those patients, 13 were women (92.8%); mean age at onset of renal involvement was 44 ± 8 years. Most frequent manifestations were Raynaud's phenomenon in 13 (92.8%) patients, arthritis in 12 (85.7%), puffy hands in 12 (85.7%), sclerodactyly in 8 (77.1%), sicca syndrome in 8 (77.1%) and myositis in 7 (50%). Median time elapsed from MCTD diagnosis to renal involvement was 83 (2-365) months. In 3 patients, renal involvement was present at MCTD onset. Seven (50%) patients had other signs of MCTD activity at the time of renal involvement onset. Four (28.5%) patients presented with sub-nephrotic proteinuria, 3 (21.4%) with nephrotic range proteinuria and kidney injury, 2 (14.3%) with sub-nephrotic proteinuria and kidney injury, 2 (14.3%) with nephrotic range proteinuria, 1 only with nephrotic range proteinuria and 1 (7.1%) with end-stage renal disease. Microscopic hematuria was present in 9

(64.3%) patients and leukocyturia in 6 (42.8%). Renal biopsy was performed in 8 (57%) patients; pathological diagnoses were: crescentic and necrotizing glomerulonephritis (GN) (2 patients; one of these patients developed positive ANCA antibodies), membranous GN (2), GN ISN/RPS 2003 class III + V (1), GN ISN/RPS 2003 class IV and vasculopathy (1), minimal mesangial GN (1) and chronic tubulointerstitial nephritis with vasculopathy (1). Ten (71.4%) patients achieved either total or partial remission at a median follow up of 82 (1-367) months. Only one patients required dialysis. At last follow up the median SLICC/ACR-DI was 1.5 (0-4) points. Two patients died.

Conclusion: In our cohort of MCTD patients, prevalence of renal involvement was low, although higher than the one reported in other populations. Clinical presentation and pathological diagnoses were diverse. Renal biopsy was helpful, since glomerulonephritis, vasculopathy and overlap with ANCA associated vasculitis were found in several patients; these options should be considered in the differential diagnoses of MCTD patients with renal involvement.

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Abstract Number: 2699

Using ICD-10 Codes to Identify Patients with Systemic Sclerosis in the Electronic Health Record

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

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Session Time: 9:00AM-11:00AM

Background/Purpose: Pragmatic research in rare diseases is difficult, largely limited by small sample size and single center cohort studies. The electronic health record (EHR) can serve as a powerful tool to study rare diseases, such as systemic sclerosis (SSc), allowing researchers to collect a large cohort of patients across the healthcare system. To assemble these patients, algorithms are needed to identify these patients accurately. We have previously developed and validated algorithms to identify SSc subjects in the EHR using ICD-9 billing codes, laboratory data, and keywords. With the widespread implementation of ICD-10 billing codes, we sought to develop algorithms using ICD-10 codes, as well as other clinical data to identify SSc patients in the EHR.

Methods: We analyzed data from a de-identified version of Vanderbilt's EHR that contains over 2.8 million subjects with longitudinal clinical data. We identified 1899 potential SSc patients with at least one count of the SSc ICD-9 (710.1) or ICD-10 (M34*) codes. Of these potential subjects, we randomly selected 200 as a training set for chart review to identify true case status. A subject was defined as a case if diagnosed with SSc by a Vanderbilt or external rheumatologist, dermatologist, or pulmonologist (specialist). We selected the following algorithm components based on clinical knowledge and available data: SSc ICD-10 codes, positive anti-nuclear antibody (ANA) (titer $\geq 1:80$), and a keyword of Raynaud's phenomenon (RP) in notes. Positive predictive values (PPVs) and sensitivities were calculated for ICD-10 codes, as well as combinations of the above algorithm components. Subjects with an unclear diagnosis by a specialist (n = 24) or missing clinic notes (n = 20) were excluded from the analysis.

Results: Table 1 provides the PPVs and sensitivities of the algorithms. PPVs were higher for algorithms using ICD-10 codes compared to those using the ICD-9 code. Algorithms that used only ICD-10 codes without other clinical data performed well, with PPVs ranging from 94 to 96%. When adding a positive ANA or RP keyword to ICD-10 codes, PPVs increased to 100%. The algorithm with the highest combined PPV of 100% and sensitivity of 78% was ≥ 2 counts of the SSc ICD-10 codes and a positive ANA or RP keyword.

Conclusion: Overall, the PPVs for algorithms using ICD-10 codes were higher compared to PPVs for ICD-9 codes. While adding clinical data to algorithms only using ICD-9 codes was needed to improve those algorithms' PPVs, this was not needed for algorithms using ICD-10 codes. Therefore, using only ICD-10 codes without the addition of clinical data can serve as an efficient and effective way to identify SSc subjects accurately in the EHR.

Table 1.

Algorithm	Positive Predictive Value	Sensitivity
ICD-9 codes only		
≥ 1 count of the ICD-9 code (710.1)	50%	N/A
≥ 2 counts	68%	85%
≥ 3 counts	82%	77%
≥ 4 counts	90%	67%
ICD-10 codes only^a		
≥ 1 count of the ICD-10 codes	88%	85%
≥ 2 counts	96%	76%
≥ 3 counts	95%	53%
≥ 4 counts	94%	44%
ICD-10 codes AND ANA positive^b		
≥ 1 count of the ICD-10 codes AND ANA	94%	67%
≥ 2 counts AND ANA	100%	75%
≥ 3 counts AND ANA	100%	55%
≥ 4 counts AND ANA	100%	45%
ICD-10 codes AND Raynaud's (RP) keyword		
≥ 1 count of the ICD-10 codes AND RP	96%	83%
≥ 2 counts AND RP	100%	77%
≥ 3 counts AND RP	100%	57%
≥ 4 counts AND RP	100%	47%
ICD-10 codes, RP, ANA positive		
≥ 1 count of the ICD-10 codes AND ANA OR RP	95%	83%
≥ 2 counts AND ANA OR RP	100%	78%
≥ 3 counts AND ANA OR RP	100%	57%
≥ 4 counts AND ANA OR RP	100%	43%
≥ 1 count AND ANA AND RP	94%	68%
≥ 2 counts AND ANA AND RP	100%	61%
≥ 3 counts AND ANA AND RP	100%	43%
≥ 4 counts AND ANA AND RP	100%	35%

^a ICD-10 codes used included M34 grouping.

^b Anti-nuclear antibody (ANA) positive was defined as $\geq 1:80$.

Disclosure: L. Jamian, None; L. Crofford, None; A. Barnado, None.

Abstract Number: 2700

Rescuing Standard Analyses of Immunosuppressive Rescue Therapy in Randomized Controlled Trials: Alternative Approaches in a Scleroderma Clinical Trial

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Placebo-controlled clinical trials are the gold standard to provide the highest-quality evidence of treatment efficacy; however, in early SSc, requiring participants to take long-term placebo raises feasibility and ethical concerns. Studies may allow immunosuppressive rescue therapy when a participant's condition worsens. Statistically, adjusting for rescue therapy to derive appropriate conclusions about treatment efficacy is complicated. We applied several analytic approaches to address rescue therapy in a recently-completed trial.

Methods: ASSET was a multicenter double-blind, randomized placebo (PBO)-controlled trial of abatacept (ABA; NCT02161406). Eligible participants were randomized 1:1 to 12 months ABA or matching PBO, stratified by duration of dcSSc (≤ 18 vs >18 to ≤ 36 months). After 6 months of treatment, investigators were given a choice to add rescue therapy for worsening signs or symptoms.

Our primary analytic strategy for treatment comparisons for the primary (change from baseline to month 12 in mRSS) and secondary endpoints was based on the ITT principle for inclusion of participants, but to eliminate data after the onset of rescue therapy using linear mixed models. We also applied the “standard” approach of performing a strict ITT analysis and including all observations (i.e., including post-rescue therapy values). In addition to censoring, we used two models to

Table: Least Square Means (Standard Error) and P-values from Linear Mixed Model Analyses of Change from Baseline to Month 12 in Modified Rodan Skin Score (mRSS) for Various Approaches to Rescue Therapy

Model 4: Method to Address Rescue Therapy	Abatacept (N=44)	Placebo (N=44)	Treatment Difference (ABA-PBO)	p-value
#1: Values Censored after Initiation of Rescue Therapy – No Rescue Therapy Covariate [1]	-6.24 (1.143)	-4.49 (1.144)	-1.75 (1.611)	0.2794
#2: No Values Censored after Initiation of Rescue Therapy – No Rescue Therapy Covariate [1]	-6.64 (1.098)	-4.22 (1.039)	-2.42 (1.502)	0.1088
#3: Values Censored after Initiation of Rescue Therapy – Rescue Therapy Covariates [2]	-5.58 (1.317)	-3.48 (1.003)	-2.11 (1.634)	0.1983

mRSS scores have a range from 0 to 51, with higher score indicating greater severity of SSc.

[1] Estimates and p-values are from a linear mixed model with treatment group, month (3, 6, 9 and 12), treatment group x month interaction, duration of dSSC (≤18 vs >18 to ≤36 months), and baseline mRSS as fixed effects and participant as a random effect.

[2] Estimates and p-values are from a linear mixed model with treatment group, month (3, 6, 9 and 12), treatment group x month interaction, escape therapy, treatment group x escape therapy interaction, duration of dSSC (≤18 vs >18 to ≤36 months), baseline mRSS as fixed effects except for escape therapy and participant as random effect(s).

deal with rescue therapy – inclusion and exclusion of terms for rescue therapy and treatment group X rescue therapy interaction.

Results: 44 ABA and 44 PBO were randomized. 7 (16%) ABA and 16 (36%) PBO participants began rescue therapy (p=0.03). By eliminating observations after the start of rescue therapy and not incorporating rescue therapy into the model, the smallest mean treatment difference occurred (see Table, #1). As might be expected with twice as many PBO participants starting rescue therapy, the largest mean treatment difference occurred when all observations were included in the analysis and rescue therapy was not incorporated into the model (See Table, #2). Censoring observations after the start of rescue therapy and incorporating rescue therapy as a covariate resulted in an intermediate estimate. No statistically significant treatment differences were observed from any model.

Conclusion: Although there was differential use of rescue therapy in our study, several simple approaches to handling rescue therapy resulted in comparable conclusions, providing confidence in our results. More sophisticated analytic methods, such as jointly modeling the primary endpoint and the probability of rescue therapy, may be useful, as well as consideration of the choice of estimand during the design of the trial which will help focus analytic efforts.

Disclosure: C. Spino, EICOS Sciences, 5; R. A. Parker, None; D. Khanna, Eicos Sciences, 1, Pfizer, Inc., 2, Horizon, 2, BMS, 2, Actelion, 5, Bayer, 5, Bayer, 2, Corbus, 5, Cytos, 5, EMD Serono, 5, Genentech, Inc., 5, Sanofi-Aventis, 5, GSK, 5, Boehringer Ingelheim, 5.

Abstract Number: 2701

Botulinum Toxin in the Management of Raynaud's Phenomenon

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The objectives of this study were to evaluate the effectiveness and safety of botulinum toxin injection in Raynaud's phenomenon.

Methods: Medline and Embase databases were search to identify eligible studies. Studies reporting use of botulinum toxin, effectiveness measures and safety outcomes were included.

Results: A total of 421 patients with Raynaud's were identified of which 324 (77%) were determined to have a secondary cause. A total of 202 subjects had systemic sclerosis (SSc) (33% limited SSc, 22% diffuse SSc, and 45% unknown subtype). Botulinum toxin A doses ranged from 10-200 units, administered with similar frequency to the palm (n=272) and digits

(n=253). The mean duration of benefit was 6.28 months with a range of 1 month to 8.6 years. There were no attributable deaths reported with botulinum toxin use. The most common adverse event was intrinsic muscle weakness (32 total events, frequency of 7.6%), and pain in 2 subjects. Only a single subject experienced persistent muscle weakness and atrophy. Benefit was consistently demonstrated across a heterogeneous group of objective and subjective outcomes.

Conclusion: Botulinum toxin injection for the management of refractory primary and secondary Raynaud's phenomenon, using various doses and injection techniques, was demonstrated to be generally safe. Effectiveness of this treatment is suggested by the consistently positive, although heterogeneous, objective and subjective outcomes. These findings support the ongoing study of botulinum toxin for the management of refractory Raynaud's phenomenon.

Disclosure: D. Ennis, None; Z. Ahmad, None; K. Devakandan, None; M. A. Anderson, None; S. Johnson, Roche, Bayer, Boehringer, BMS, NIH, Merck, 9.

Abstract Number: 2702

Incidence, Prevalence, Mortality and Comparison of the ACR/EULAR 2013 Classification Criteria with 1980 Criteria in Physician Diagnosed Systemic Sclerosis: Results from a Population Based Cohort (1980-2016)

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Session Information

Session Date: Tuesday, October 23, 2018

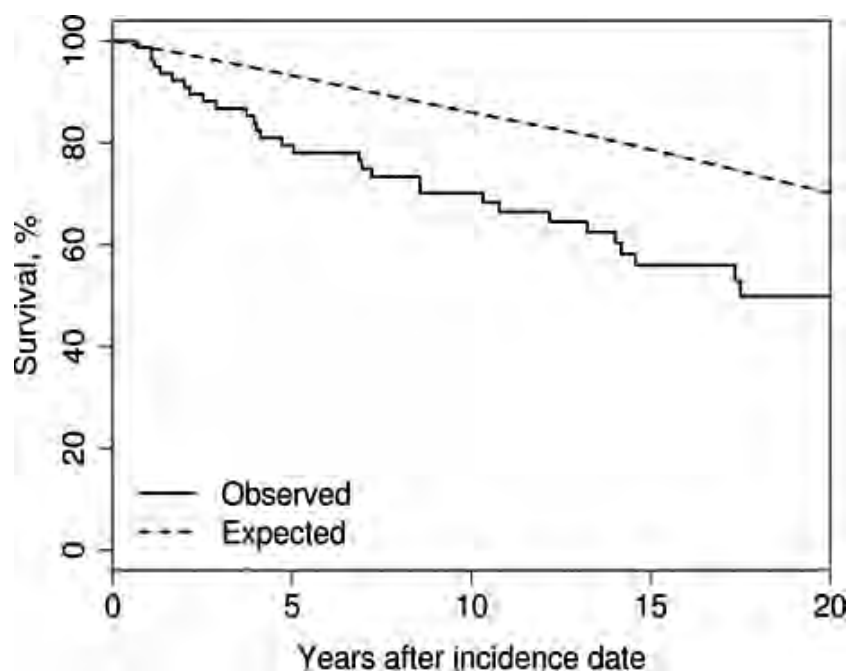
Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic Sclerosis (SSc) is a complex and heterogeneous chronic inflammatory disease characterized by widespread fibrosis of the skin and visceral organs, microvascular injury and evidence of immune system activation. We aimed to determine the incidence, prevalence and mortality of physician diagnosed SSc in a population-based cohort and to evaluate the performance of the ACR/EULAR 2013 Classification criteria vs. 1980 ACR criteria in classifying patients with SSc.

Methods: Medical records of patients with a diagnosis or suspicion of SSc in a geographically well-defined area from Jan 1, 1980 to Dec 31, 2016 were reviewed to identify incident cases of SSc (defined by physician diagnosis). Prevalent cases of



SSc on Jan 1, 2015 were also identified. Incidence and prevalence rates were age and sex adjusted to the 2010 US white population. Survival rates were compared with expected rates in the general population. Fulfillment of the 1980 and 2013 classification criteria was ascertained.

Results: 79 incident cases of SSc (90% female, 87% Caucasians, mean age at diagnosis 55.8 +/- 16 y) from 1980-2016 and 49 prevalent cases on Jan 1, 2015 were identified. . The overall age- and sex-adjusted annual incidence for 1980-2016 was 2.7 (95% C.I. 2.1- 3.3) per 100,000 population (age-adjusted incidence was 4.6 (95% CI: 3.5-5.7) per 100,000 for females and 0.6 (95% CI: 0.2-1.1) per 100,000 for males), with no change in incidence over time. The age-and sex-adjusted prevalence on January 1, 2015 was 47.4 (95% CI: 34.1 -60.7) per 100,000 population. 64 of 79 (81%) patients fulfilled the 2013 classification criteria, while only 48% fulfilled the 1980 criteria. All but 1 patient that fulfilled the 1980 criteria also fulfilled the 2013 criteria. At SSc diagnosis, 74 (94%) patients had Raynaud's, 13/44 (30%) had abnormal nail fold capillaries, 16/33 (48%) had digital ulcers/pitting scars, 43 (54%) had sclerodactyly, 39 (49%) had telangiectasias, 8 (10%) had pulmonary hypertension, and 7 (9%) had interstitial lung disease. 66 patients had limited cutaneous SSc, 11 had diffuse cutaneous SSc and only 2 had Sine scleroderma. 39 patients had a positive autoantibody for SSc : ACA in 29, anti-Scl-70 in 8 and anti RNA-polymerase III in 2. Mortality among SSc patients was significantly higher in comparison to the general population (standardized mortality ratio, 2.24; 95% C.I., 1.52-3.18; Figure).

Conclusion: The average incidence of SSc in this population-based cohort was 2.7 per 100,000 population with no evidence of a change in incidence over the 36 year period of study. The new 2013 classification criteria perform significantly better than the 1980 criteria, but failed to classify 19% of patients in this cohort. Overall survival of patients with SSc is worse than the general population with no evidence of improved survival over time, indicating an unmet need for early diagnosis and more aggressive management.

Disclosure: A. S. Sandhu, None; C. S. Crowson, None; P. R. Bauer, None; E. L. Matteson, None; A. Makol, None.

Abstract Number: 2703

Delay in Initiation of Therapy Predicts Worse Outcomes in Scleroderma Renal Crisis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Scleroderma renal crisis (SRC) is a rare complication of patients with systemic sclerosis (SSc). ACE inhibitors (ACEI) favorably alter the natural history of this condition. However, clinicians are wary of initiating this therapy because of a rising serum creatinine. There is paucity of data on the association between the time of initiation of therapy and long-term outcomes. We evaluated the effect and timing of treatment on long term outcomes in patients with SRC.

Methods: We screened 393 adult patients with SSc (fulfilling 2013 ACR/EULAR criteria) in our institution from 2004 to 2/2018 of which 25 satisfied the diagnosis of SRC, as defined by Steen et al¹. Data on patient demographics, clinical presentation, serology, time to initiation of therapy, and type of therapy were evaluated. We evaluated the following outcomes: mortality, need for dialysis and partial or complete renal recovery. Follow up was censored on May 11th, 2018. Continuous variables were expressed as mean \pm SD. Discrete variables were expressed as mean (%) and compared with chi-squared tests. Kaplan-Meier curves were used to describe long term survival estimates. A two-tailed p-value of less than 0.05 was considered significant for all statistical testing.

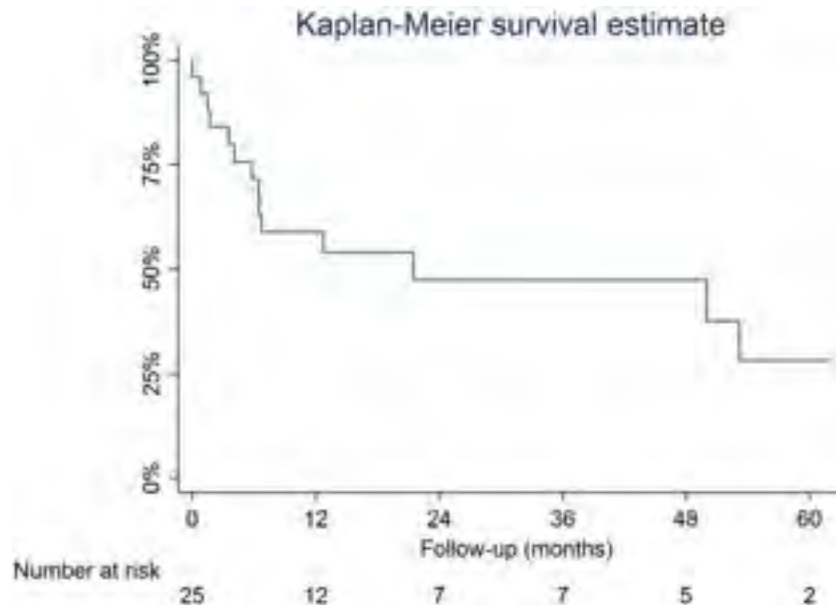
Results: Our cohort included 25 patients with SRC of which one patient was normotensive; 63% were females and mean ages at diagnoses of SSc and SRC were 54 \pm 14.1 years and 58 \pm 11.2 years respectively; 96% of the patients were treated with ACEI including 16% who were already on one. Baseline characteristics, clinical features, and disease course of patients with SRC are shown in Table 1. At one year, mortality was 41.2%; 52% (13/25) required dialysis. Of which one patient was able to discontinue dialysis after 25 days. Dialysis requirement was significantly higher in those who were started on ACEI > 48 hours after onset of clinical manifestations (78.6% vs 16.7%, p= 0.018). Kaplan-Meier survival estimates at 5 years follow up are shown in Figure 1.

Table 1: Baseline characteristics, clinical features, laboratory abnormalities, and disease course of patients with SRC.

Age at diagnosis of SSC, in years	54.0 ± 14.1
Age at diagnosis of SRC, in years	58.48 ± 11.2
Gender	
<i>Female</i>	16 (64%)
<i>Male</i>	9 (36%)
Race	
<i>Caucasian</i>	20 (80%)
<i>African American</i>	5 (20%)
Serology	
<i>Anti-RNA polymerase III Ab</i>	13 (52%)
<i>Anti-Scl 70</i>	6 (24%)
<i>None of the above</i>	6 (24%)
Symptoms	
<i>Headaches</i>	10 (40%)
<i>Seizures</i>	0 (0%)
<i>Oliguria</i>	14 (56%)
Manifestations	
<i>Hypertension</i>	24 (96%)
<i>Acute kidney injury</i>	25 (100%)
<i>MAHA</i>	11 (44%)
<i>Thrombocytopenia</i>	9 (36%)
<i>Pericardial effusion</i>	8 (32%)
<i>Myocarditis</i>	1 (4%)
<i>Encephalopathy</i>	2 (8%)
Urine Microscopy	
<i>RBC's in urine microscopy</i>	19 (76%)
<i>Proteinuria</i>	22 (88%)
<i>Clear</i>	2 (8%)
Peak Creatinine	5.73±2.81
Number of antihypertensive meds	
<i>ACEI</i>	24 (96%)
<i>ARB</i>	4 (16%)
<i>CCBs</i>	19 (76%)
<i>Beta-blockers</i>	10 (40%)
<i>Vasodilators</i>	5 (20%)
Choice of ACE inhibitor	
<i>Lisinopril</i>	23 (92%)
<i>Enalapril</i>	5 (20%)
<i>Captopril</i>	1 (4%)
Approved maximum dose of ACEI received	13 (52%)
Pre-existing ACEI use	4 (16%)
Use of preceding or concomitant glucocorticoids	8 (32%)
TMA features on renal biopsy	8 (88%, n=9)

Data presented as Mean ± SD or N (column %). ARB, Angiotensin receptor blocker,

CCB, Calcium channel blocker. MAHA, Microangiopathic hemolytic anemia. TMA, Thrombotic microangiopathy



Conclusion: Early (≤ 48 hours) initiation of ACEI in patients with SRC significantly reduces need for dialysis. However, irrespective of the timing of initiation of therapy, the long-term mortality of patients with SRC remains high.

Reference :

1. Steen VD, Medsger TA. Long-Term Outcomes of Scleroderma Renal Crisis. *Ann Intern Med.* 2000;133:600–603.

Figure 1: Kaplan-Meier survival estimates at 5 years follow up

Disclosure: A. Patel, None; K. Banerjee, None; S. Chatterjee, None.

Abstract Number: 2704

Pregnancy in Systemic Sclerosis (SSc): A Systematic Review and Meta-Analysis

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Session Information

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Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: In a systematic literature review and meta-analysis, to determine maternal and fetal outcomes in pregnant SSc women and to analyse the effect of pregnancy on SSc disease activity.

Methods: A systematic literature search was performed in four different databases: PubMed, Cochran, EMBASE and Web of Science for articles published between 1950 and 1st February 2018. All articles reporting on SSc and pregnancy were analysed. Review articles were examined for further references. Reviewers double extracted articles (with a third reviewer resolving differences) to: (1) obtain agreement on > 95% of pre-defined critical outcomes (eg pregnancy outcome, fetal death etc) and >90% of the other variables; (2) maintain quality assurance; (3) screen and extract data. Descriptive analysis described the results. Comparisons of SSc pregnancies to healthy controls used a Chi-square test.

Results: 458 publications were identified. 16 studies met the inclusion criteria and were included in the meta-analysis 1,403 pregnancies in the SSc group were compared to 12,196,221 healthy control pregnancies. In SSc pregnancies, there were

significantly more miscarriages (15.7% vs 11.3%, $p=0.007$), stillbirths, (4.5% vs 0.3%, $p<0.001$), preterm births (12.9% vs 3.9%, $p<0.001$) and fetuses with intra-uterine growth retardation (IUGR) (5.5% vs 1.7%, $p<0.001$), compared to controls. There were no differences (all $p<0.05$) in the percent infant deaths (2.5% vs 1.9%), infant malformations (2.2% vs 1.7%) and low birth weight neonates (11.8% vs 9.4%) between the two groups. In SSc, pre-eclampsia (4.4% vs 1.1, $p<0.00$) and gestational hypertension (17.8% vs 8.4%, <0.001) occurred more frequently, compared to controls. In additions, there were significantly more Caesarean deliveries in SSc pregnancies (39% vs 31%, $p<0.001$). No increases in maternal mortality or eclampsia rates were observed in SSc patients versus controls. Regarding the effect of pregnancy on SSc disease activity, one or more disease manifestations worsened or appeared during pregnancy in 44/307 (14.3%). In additional in 32/306 (10.5%) pregnancies, SSc manifestations worsened or appeared during the 6-months post-partum period. In two cases this worsening led to maternal death.

Conclusion: Despite our rigorous inclusion/exclusion criteria resulting in selecting only 16 articles out of 458 publications, and despite the limited data available, our SLR and meta-analysis in SSc pregnancies demonstrated an increased frequency of miscarriages, stillbirths, IUGR and pre-term labour versus healthy control pregnancies. SSc patients were more prone to develop pre-eclampsia and gestational hypertension, but not eclampsia. Notably, maternal mortality was not increased in SSc pregnancies, nor did pregnancy lead to worsening disease in most cases. Further analysis is planned to identify the predictors for adverse fetal and maternal outcomes and for disease progression in SSc pregnancies.

Disclosure: J. Blagojevic, None; K. A. AlOdhaibi, None; A. M. Aly, None; M. Matucci-Cerinic, None; D. E. Furst, None.

Abstract Number: 2705

Optimized Protocol for Extracorporeal Shock Wave Therapy on Digital Ulcers in Systemic Sclerosis

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Session Information

Session Date: Tuesday, October 23, 2018

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Extracorporeal shock wave therapy (ESWT) at low energy has been shown to be effective for digital ulcers in systemic sclerosis (SSc) in our study reported at ACR last year. However, studies to confirm treatment protocols with the most therapeutic effect have not been satisfactorily performed. We aimed to determine the optimal treatment period by comparing the number of cutaneous ulcers before and after treatment.

Methods: The study enrolled 60 patients with SSc and refractory digital ulcers. Of these, 30 were treated with ESWT and 30 received conventional treatment. ESWT treatment was performed once a week for 8 weeks and the results were observed for 4 additional weeks. The total number of ulcers and the number of large ulcers (defined as having a diameter ≥ 5 mm) were evaluated. During the treatment period, outcomes were assessed every week for 8 weeks and then evaluated during a 4-week observation period, after treatment completion. The visual analog scale (VAS) for pain as a patient-reported outcome (PRO) was also evaluated.

Results: The ulcers decreased by 78.34% in the ESWT group and 20.94% in the conventional treatment group at 8 weeks, and the difference was significant ($p=0.0001$). However, the ulcers decreased by 71.85% in the ESWT group and 53.75% in the conventional treatment group at 12 weeks (observation period). No further improvement was seen following the

treatment period in the ESWT group, and the difference in efficacy from the conventional treatment group decreased during the observation period. Large ulcers alone decreased by 84.21% in the ESWT group and 52.78% in the conventional treatment group at 8 weeks, and the difference was not significant. However, the improvement in VAS pain scores at 8 weeks was 43.96% in the ESWT group and -16.60% in the conventional treatment group ($p=0.0817$). The pain VAS scores did not decrease significantly probably because of insufficient improvement in large ulcers.

Conclusion: ESWT treatment was discontinued at 8 weeks, but some ulcers remained. Persistence of large ulcers had a significant influence on VAS pain scores. Treatment protocols may require continued ESWT until ulcer disappearance, especially for large ulcers.

Disclosure: T. Ishii, ONO PHARMACEUTICAL, 8, Janssen Pharmaceutical, 8, Astellas Pharma, 8, Sanofi KK, 8; Y. Kawaguchi, None; O. Ishikawa, None; H. Takemori, None; N. Takasawa, None; H. Kobayashi, None; Y. Takahashi, None; H. Yasuoka, None; T. Koderu, None; O. Takai, None; I. Nakaya, None; T. Izumiyama, None; H. Fujii, None; Y. Kamogawa, None; Y. Shirota, None; T. Shirai, None; Y. Fujita, None; S. Saito, None; H. Shimokawa, None; H. Harigae, None.

Abstract Number: 2706

Discriminant Validity and Reliability of World Scleroderma Foundation (WSF) Definition of Skin Ulcers in Systemic Sclerosis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To date, there is lack of a uniform definition of systemic sclerosis related skin ulcer (SSc-skin ulcer) for use in clinical trials. Our group previously published a consensus driven definition of SSc-skin ulcer under the patronage of WSF(1) . The definition was based on a systematic literature review followed by a nominal group technique to establish consensus among SSc experts. Face validity and feasibility were demonstrated. However, further validation of the WSF skin ulcer definition is needed.

Aim: to establish the sensitivity and specificity of the proposed WSF clinical definition of SSc-skin ulcers and evaluate Its reliability among investigators.

Step I: To determine the ability to discriminate between SSc-Skin ulcers, SSc non-ulcer lesions and non SSc lesions.

Step II: To examine the inter-rater and Intra-rater reliability of the WSF definition among investigators.

Methods: Four hundred images {200 SSc skin lesions (ulcers and non-ulcers), 200 non-SSc skin lesions} were evaluated by two highly qualified SSc experts and their scoring were considered the gold standard scores.

Step I: 10 investigators with different levels of expertise in SSc were included to utilize the definition indiscrimination between SSc-skin ulcers from other lesions (SSc non-ulcers and non-SSc lesions) as compared to gold standard. Each investigator scored 40 images.

Step II: A total of 45 images were sent to each of the 10 investigators. Twenty (20) images per investigator evaluated in step I, were examined again for intra-investigator reliability. Twenty-five (25) images (the same images examined across the 10 investigators) were used to examine inter-investigator reliability.

Results: Step I:

- For discriminating SSc-skin ulcers from SSc non-ulcer lesions: sensitivity was 78% and specificity was 94 %
- For discriminating SSc-ulcers from non SSc-ulcer lesions: sensitivity was 78% and specificity was 100%

Step II:

Intra-rater reliability using ICC was 0.99, with kappa agreement of 0.89 (excellent)

Inter-rater reliability using Fleiss Kappa was 0.346 (only fair, given a range of 0-1.0).

Discussion: As is the case for mRSS, repeated training sessions prior to starting a clinical trial may decrease variability among investigators .

Conclusion: Discrimination among a group of rheumatologists with varying SSc experience for differentiating between SS-ulcers, SSc-non-ulcers and non-SSc lesions was very good(sensitivity) to excellent (specificity)

As for other clinical SSc measures (e.g. mRSS), it will be necessary in clinical trials to have the same investigator examining a given patient over time, as inter-rater reliability is not sufficient.

Ref: Y Suliman et al., Defining Skin Ulcers in Systemic Sclerosis: Systematic Literature Review and Proposed World Scleroderma Foundation (WSF) Definition. *JSRD* Vol 2, Issue 2.

World Scleroderma Foundation(WSF) skin ulcer definition:

1. Loss of epidermal covering with a break in the basement membrane (which separates dermis from the epidermis). It appears clinically as visible blood vessels, fibrin, granulation tissue and/or underlying deeper structures (e.g. muscle, ligament, fat), or as it would appear on debridement.
 2. This excludes: Scar, Abrasion, Incision, Laceration, Fissure, Infected ulcer, ulcer with underlying calcinosis, and gangrenous ulcers
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Abstract Number: 2707

Scleroderma Renal Crisis: The Association of High-Dose Steroids and Poor Outcome

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Scleroderma renal crisis (SRC) is the most acute and life-threatening complication of scleroderma characterized by sudden increase in blood pressure and worsening kidney function. Historically, development of SRC was almost always fatal. With the use of angiotensin-converting enzyme inhibitors (ACEI), one-year survival has improved up to 76%; however, SRC remains a poor prognostic marker for long-term survival. Dialysis dependency after an episode of SRC portends a worse long-term prognosis. Here we report on our 15 years of experience with SRC at our institution with a focus on identifying characteristics that predicted initiation of dialysis or death.

Methods: We undertook a retrospective single-center chart review of patients aged 18-80 years old that developed SRC between the years 2002-2016. Baseline characteristics such as age, gender, race, comorbidities and exposures were noted. Outcome data was collected at time of admission, 6 months and 12 months. Patients with the diagnosis of scleroderma and acute kidney injury for any other reason other than SRC were excluded.

Results: In the 15-year period, we identified 34 patients with an episode of SRC (table 1). Of these patients, 16 developed poor outcome (death or dialysis) during their hospital admission. Exposure to steroids within one month of admission was

similar in both groups; however, poor outcome was more common in those with exposure to ≥ 40 mg prednisone ($p=0.007$). This trend continued at the 6 and 12-month follow-up.

Conclusion: Exposure to steroids is known to be a risk factor for the development of SRC. Use of higher dosages of steroids may also be associated with worse outcomes in patients with SRC.

Table 1. Results are reported as proportions or means \pm standard deviation or ranges

	Death or Dialysis (n=16)	Recovered (n=18)	p-value
Age, mean \pm SD, years	47.7 \pm 14.6	53.9 \pm 12.5	0.19
Female, n%	11 (68.8)	17 (94.4)	0.05
Systolic blood pressure, mmHg	161.7 \pm 46.4	161.7 \pm 46.4	0.05
Diastolic blood pressure, mmHg	89.0 \pm 20.5	99.9 \pm 21.7	0.14
Duration of disease, years	0.6-2.3	0.5-2.0	0.37
RNA Polymerase III +	10 (71.4)	11 (64.7)	0.69
ACEI exposure	10 (62.5)	10 (55.6)	0.68
Steroid exposure	10 (62.5)	12 (66.7)	0.80
Dose of prednisone, mg	40.0-1000.0	5.0-30.0	0.007
Thrombotic Microangiopathy (TMA)	7 (58.3)	3 (37.5)	0.36
Related to stem-cell transplant	5 (31.3)	1 (5.6)	0.05

Disclosure: N. Ghosh, None; X. Cai, None; C. Ghossein, None.

Abstract Number: 2708

Current Management of Early Diffuse Cutaneous Systemic Sclerosis in US Scleroderma Centers

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Session Information

Session Date: Tuesday, October 23, 2018

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Standard treatment for the diverse aspects of diffuse cutaneous systemic sclerosis (dcSSc) is not yet well defined although experts have described therapeutic algorithms. The Prospective Registry of Early Systemic Sclerosis (PRESS) is longitudinal cohort of patients with early dcSSc at 11 US centers enrolling since 2012. In this study we describe the medical treatments utilized by PRESS investigators throughout the duration of the study and their changes over time.

Methods: Adult patients with a diagnosis of dcSSc and early disease as defined as <2 years since the onset of the first non-Raynaud's symptom are included. Associations of treatment choices with demographic factors and organ involvement were assessed using logistic regression and Fisher's exact test.

Results: As of May 2018, baseline data were available on 239 patients with characteristics listed in table 1. Follow-up data was available on 168 (70.3%). The median follow-up time was 12 months.

During the study period, 68.4% were noted to have Interstitial lung disease (ILD). At baseline, 60.3% of patients were on an immunosuppressive agent, the majority of whom were taking MMF (37.2%). During follow-up, MMF was the most commonly prescribed immunosuppressive and was taken by 151 patients (63.2%) followed by MTX by 50 (20.9%), and HCQ by 39 (16.3%). Seventy-four (31.1%) of patients used prednisone at baseline but its use waned over time. Forty

(16.7%) patients remained off immunosuppressive therapy throughout the course of follow-up. The use of these drugs over time is shown in table 2.

Immunosuppressive choice was noted to be associated with specific demographic factors. Patients disabled due to scleroderma at the baseline visit were less likely to have previously received MMF, odds ratio (OR) 0.27 (0.07 - 0.96), $p = 0.044$, and patients with RA overlap were more likely to have received MMF, OR 3.26 (1.06 - 10.06), $p = 0.040$. Use of MMF at baseline was not associated with more severe Modified Rodnan Skin Score (MRSS). MTX use at baseline was more common in patients with higher MRSS scores, but this trend lost significance when looked at over the first year. Looking at medication use through one year of follow up, patients were more likely to be prescribed MMF if they had ILD defined at baseline ($p=0.043$) and less likely to receive MTX ($p=0.034$). Prednisone use was more common in those patients with overlapping RA or polymyositis.

Conclusion: Most patients enrolled in the PRESS registry are treated with immunosuppressive agents, most commonly MMF or MTX. Treatment choice varies with disease manifestations and severity.

Baseline characteristic	N=239 patients
Swollen hands or sclerodactyly, n (%)	239 (100.0%)
Anti-Scl 70 or anti-RNA polymerase	146 (61.1%)
Skin thickening involving upper arms, thighs or torso	196 (82.0%)
Tendon friction rubs	75 (31.4%)
Age, years, mean±SD	50.1±14.0
Sex, n (%)	
Female	170 (71.1%)
Race, n (%)	
African/African-American/Black	40 (16.7%)
Asian/Asian-American	8 (3.4%)
Caucasian/White	182 (76.2%)
Native American/Alaskan Native	1 (0.4%)
Ethnicity, n (%)	
Hispanic	23 (9.6%)
Employment status, n (%)	
Full-time	126 (58.9%)
Part-time	11 (5.1%)
Retired	31 (14.5%)
Early retirement	6 (2.8%)
Disability/disabled	10 (4.7%)
Disabled due to scleroderma	19 (8.9%)
Overlapping rheumatic diseases, n (%)	
Rheumatoid arthritis	14 (5.9%)
Systemic lupus erythematosus (SLE)	2 (0.8%)
Sjogren's syndrome	5 (2.1%)
Polymyositis	9 (3.8%)
Dermatomyositis	0 (0.0%)
Smoking status, n (%)	
Never	147 (61.5%)
Former	76 (31.8%)
Current	16 (6.7%)
Disease duration, months, mean ± SD	
First symptoms	25.3±48.0
Non-Raynaud's phenomenon	15.0±11.0
Raynaud's phenomenon	34.1±63.3
Interstitial Lung Disease (ILD)	
Abnormal HRCT at baseline	76/142 (53.5%)
FVC < 80% at baseline	100/203 (49.3%)
One or more of the above at baseline	132/216 (61.1%)
Abnormal HRCT throughout study	96/164 (58.5%)
FVC < 80% throughout study	121/217 (55.8%)
One or more of the above throughout study	154/225 (68.4%)

Medication	Baseline, n (%) (N=239)	6m, n (%) (n=156)	12m, n (%) (n=127)	18m, n (%) (n=94)	24m, n (%) (n=78)	30m, n (%) (n=46)	36m, n (%) (n=36)
Immunosuppressives	144 (60.3%)	128 (82.1%)	103 (81.1%)	78 (83.0%)	57 (73.1%)	28 (60.9%)	28 (77.8%)
Cyclophosphamide	6 (2.5%)	7 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
Mycophenolate mofetil	89 (37.2%)	100 (64.1%)	91 (71.7%)	64 (68.1%)	52 (66.7%)	25 (54.4%)	19 (52.8%)
D-penicillamine	5 (2.1%)	7 (4.5%)	5 (3.9%)	2 (2.1%)	1 (1.3%)	0 (0.0%)	0 (0.0%)
Methotrexate	33 (13.8%)	22 (14.1%)	13 (10.2%)	12 (12.8%)	9 (11.5%)	4 (8.7%)	8 (22.2%)
Hydroxychloroquine	30 (12.6%)	8 (5.1%)	4 (3.2%)	8 (8.5%)	5 (6.4%)	1 (2.2%)	2 (5.6%)
Azathioprine	4 (1.7%)	1 (0.6%)	1 (0.8%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Prednisone (^a 1 week)	74 (31.1%)	43 (27.6%)	34 (26.8%)	21 (22.3%)	17 (21.8%)	8 (17.4%)	10 (27.8%)

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Abstract Number: 2709

Conversion of Normal Mean Pulmonary Arterial Pressure to Pulmonary Hypertension in Systemic Sclerosis – a Longitudinal Observational Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Pulmonary hypertension (PH) is one of the leading causes of mortality in patients with systemic sclerosis (SSc). Active screening detects PH earlier and may improve survival in SSc patients. Our objective was to evaluate the development of PH in high risk SSc patients over time who initially had a negative right heart catheterization (RHC).

Methods: Subjects with a diagnosis of SSc based on the 2013 ACR/EULAR criteria who did not have a prior diagnosis of PH who underwent a resting RHC due to increased risk based on 2013 recommendations for screening and detection of connective tissue disease-PAH¹, which includes DETECT, were included in this prospective observational cohort. Those subjects who did not have a diagnosis of PH according to resting baseline RHC with mean pulmonary artery pressure (mPAP) < 25mmHg underwent subsequent screening resting RHC approximately 24 months later, or earlier if they developed new symptoms and/or change in non-invasive testing parameters.

Results: Sixty-seven subjects with SSc who underwent baseline resting RHC were included. Ninety-percent of subjects were female, 82% were Caucasian, 12% were African American, 66% had limited cutaneous SSc, and 34% had diffuse cutaneous SSc. Mean (SD) age was 61.4 (9.6) years, SSc disease duration was 13.2 (11.4) years, FVC% predicted was 79.9 (20.3), DLCO% predicted was 57.7 (18.4), and FVC/DLCO was 1.5 (0.6). At baseline RHC, 24% had normal mPAP (\leq 20mmHg), 34% had borderline mPAP (BoPAP, 21-24 mmHg), and 42% had PH (\geq 25mmHg) (Figure 1). No patients with normal mPAP or BoPAP were treated with PAH specific therapies. Eleven subjects, 2 with normal mPAP and 9 with BoPAP, underwent repeat RHC; 3 subjects with BoPAP progressed to PH, 3 subjects with BoPAP decreased to normal mPAP, 3 subjects remained BoPAP, 1 subject with normal mPAP progressed to BoPAP and 1 subject with normal mPAP remained at normal mPAP (Figure 2).

Conclusion: Use of 2013 recommendations resulted in identification of a high proportion of subjects with normal mPAP or BoPAP. Approximately 1/3 of patients with BoPAP progress to PH after 2 years, which is different than previously reported^{2,3}. This may be due to universal PAH screening of SSc patients at our center on annual basis.

References:

1. Khanna et al. Arthritis Rheum. 2013.
2. Bae et al. Ann Rheum Dis. 2012.
3. Valerio et al. Arthritis Rheum. 2013.

Disclosure: A. Young, None; S. H. Visovatti, None; T. Cascino, None; N. Vasilottos, None; V. McLaughlin, Consultancies Bayer, Arena, Medtronic, Merck, SteadyMed, United Therapeutics, St. Jude Medical, Actelion., 5, Grant / Research Support: Actelion, Eiger, Sonovie, Arena, Bayer., 2; D. Khanna, Eicos Sciences, 1, Pfizer, Inc., 2, Horizon, 2, BMS, 2, Actelion, 5, Bayer, 5, Bayer, 2, Corbus, 5, Cytori, 5, EMD Serono, 5, Genentech, Inc., 5, Sanofi-Aventis, 5, GSK, 5, Boehringer Ingelheim, 5, CiVi BioPharma, 3.

Figure 1. Baseline RHC Results

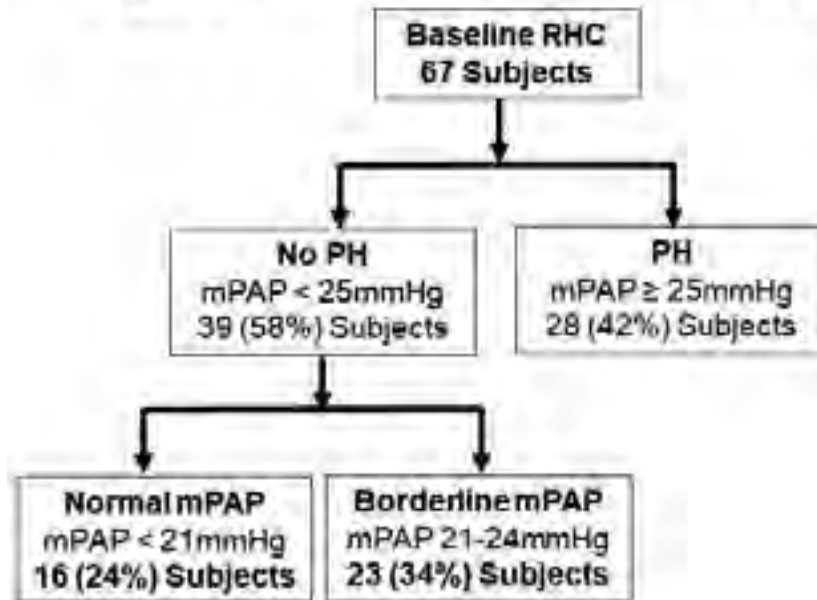


Figure 2. RHC mPAP Changes Over Time in SSc Subjects without PH



Abstract Number: 2710

Physical Activity Trackers Work Well As a Monitor of Physical Activity in Systemic Sclerosis

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Session Information

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Background/Purpose: Systemic sclerosis (SSc) patients have reduced physical function, exercise capacity and health related quality of life (HRQOL). The objective of this study was to assess the feasibility and test-retest reliability of physical activity trackers as a measure of physical activity in patients with SSc.

Methods: SSc subjects, based on 2013 ACR/EULAR classification criteria, 18 to 79 years old without large joint contractures or use of mobility devices, and with access to a smartphone or computer were eligible; if subjects had pulmonary hypertension (PH) and/or interstitial lung disease (ILD), medications were stable for 3 months prior to enrollment. Subjects received a Fitbit Zip® physical activity tracker to wear daily during awake hours and performed their

Figure 1. Average Weekly Step Counts

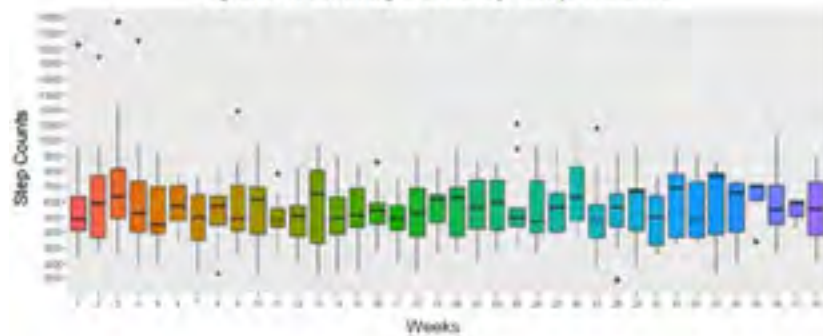
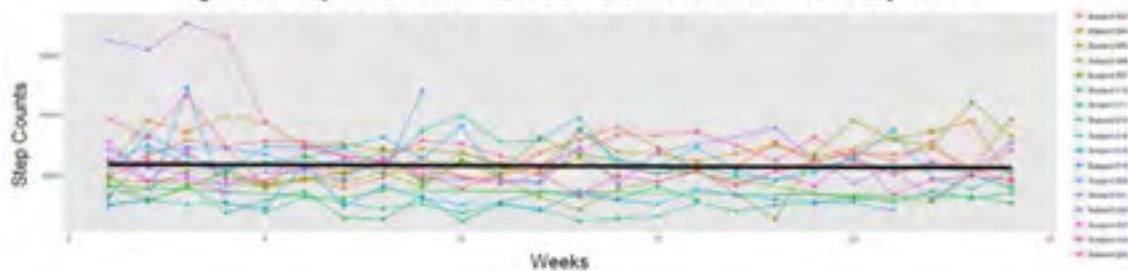


Figure 2. Step Counts are Stable Over Time for Individual Subjects



everyday activities; no step goals were provided. Patient reported outcomes (PROs) were provided at baseline and follow up visit.

Results: Twenty subjects have been recruited; 75% were female, 90% were Caucasian, 50% had diffuse cutaneous SSc, 40% had limited cutaneous systemic sclerosis, 10% had sine scleroderma, 35% had ILD, 10% had PH, mean (SD) age was 49 (11.7) years old and SSc disease duration was 5.3 (3.6) years. PROMIS-29 mean (SD) values at baseline (N=19) were as follows: physical function 47.2 (7.9), social roles 53.3 (8.4), anxiety 49.5 (9.7), depression, 47.3 (8.8), fatigue 50.0 (9.4), sleep disturbance 49.7 (7.3), pain interference 51.7 (7.7), and pain intensity 2.6 (2.4). Two subjects withdrew after enrollment and did not use the tracker. Mean (SD) study duration for the remaining 18 subjects was 177.7 (89.2) days and mean (SD) daily step counts during the first week were 5710.8(3212.4) steps (Figure 1). Mixed effects model to assess test-retest reliability of weekly step counts for each subject indicated step counts were stable over time (Figure 2). PROMIS-29, UCSD SOBQ, SHAQ, and mMRC PROs did not indicate a statistically significant difference from baseline to follow up (data not shown, $p > 0.05$). On comparison of subjects without ILD and/or PH (N=13) to those with ILD and/or PH (N=7), mean (SD) daily steps counts were numerically higher in those without ILD and/or PH (6523 vs 4925, $p = 0.29$) but there were statistically significant differences for PROMIS-29 physical function (50.18 vs 41.5, $p = 0.047$), mMRC grade (0.33 vs 1.33, $p = 0.018$), and VAS breathing problems (0.5 vs 2.17, $p = 0.035$).

Conclusion: Physical activity trackers show acceptable feasibility and test-retest reliability for use in SSc. Future studies will evaluate change in HRQOL with use of step count goal interventions.

Disclosure: A. Young, None; E. A. Jackson, None; D. Khanna, Eicos Sciences, 1, Pfizer, Inc., 2, Horizon, 2, BMS, 2, Actelion, 5, Bayer, 5, Bayer, 2, Corbus, 5, Cytos, 5, EMD Serono, 5, Genentech, Inc., 5, Sanofi-Aventis, 5, GSK, 5, Boehringer Ingelheim, 5, Civi BioPharma, 3.

Abstract Number: 2711

Comparison of Gastric Antral Vascular Ectasia Associated with Systemic Sclerosis with That Associated with Other Diseases: Are There Differences?

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Session Information

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Background/Purpose: Gastric antral vascular ectasia (GAVE) is a pathologic angioectasia with a characteristic endoscopic appearance. Rugal folds with dilated blood vessels radiate from the antrum and converge at the pylorus resembling watermelon stripes, supporting the name watermelon stomach. It can cause anemia and significant morbidity, hence needs surveillance. GAVE has been associated with cirrhosis of liver, autoimmune diseases (e.g. systemic sclerosis (SSc), rheumatoid arthritis, primary biliary cholangitis), ESRD, hypertension, heart failure, hypothyroidism, chronic pulmonary disease and hematopoietic stem cell transplantation. Prevalence of SSc associated GAVE is highly variable ranging from 1% to 76%. Prevalence of GAVE in other associated diseases and its long term outcomes are still unknown. We aimed to compare the differences in GAVE in SSc with that in other diseases.

Methods: We conducted a retrospective chart review of patients with GAVE at a single referral center. We evaluated patients diagnosed with GAVE between 2012 - 2017; 145 GAVE patients were initially identified. We selected 37 consecutive SSc and 37 consecutive non SSc patients from the GAVE database. Outcomes were defined by number of transfusions, number of recurrences of GAVE bleeding diagnosed endoscopically (low <5 or high ≥ 5), and death. Groups were compared using ANOVA and Kruskal Wallis tests for continuous variables and Pearson's chi square tests or Fisher's exact tests for categorical variables. Also, comparisons were made using linear regression to adjust for covariates.

Results:

Table 1.

Factor	Total (N=74)	Non- scleroderma (N=37)	Scleroderma (N=37)	p-value
Age of onset	62.4±12.6	66.8±12.6	57.9±11.0	0.002^a
Gender				0.006^c
Male	23(31.1)	17(45.9)	6(16.2)	
Female	51(68.9)	20(54.1)	31(83.8)	
Ethnicity				0.99 ^d
African American	2(2.7)	2(5.4)	0(0.0)	
Caucasians	71(95.9)	35(94.6)	36(97.3)	
Asian	1(1.4)	0(0.0)	1(2.7)	
Disease Frequency				
Limited SSc		-	23 (31.5)	
Diffuse SSc		-	14 (19.2)	
Chronic pulmonary disease		20(27.4)	-	
ESRD		7(9.6)	-	
Hypertension		36(49.3)	-	
Heart failure		19(26.0)	-	
Cirrhosis of liver		19(26.0)	-	
Primary biliary cholangitis		0(0.0)	-	
Rheumatoid arthritis		2(2.70)	-	
Hypothyroidism		19(26.0)	-	
HSCT		1(1.4)	-	

Statistics presented as Mean ± SD or N (column %).

p-values: a = ANOVA, c = Pearson's chi-square test, d = Fisher's Exact test.

HSCT = hematopoietic stem cell transplantation

ESRD = end stage renal disease

Table 2. Outcome of GAVE

Factor	Total (N=74)	Non-scleroderma (N=37)	Scleroderma (N=37)	p-value
Number of transfusions ^a	2.0 (0.00,25.0)	5.0 (0.00,25.0)	0.00 (0.00, 18.0)	<0.001^b
Number of recurrences of GAVE/GI bleed*				0.43 ^c
Low (<5)	49(70.0)	23(65.7)	26(74.3)	
High (>=5)	21(30.0)	12(34.3)	9(25.7)	

^aβ= Number of transfusions was not significant when adjusted for hemoglobin before transfusion, using multiple regression model

*Data not available for all subjects. Missing values: Number of recurrences of GAVE/GI bleed = 4. Statistics presented as Median (min, max) or N (column %).

P-values: b=Kruskal-Wallis test, c=Pearson's chi-square test

Clinical manifestations associated with GAVE in SSc and non-SSc groups respectively, were telangiectasias (29.7% vs 0%), melena (37.8% vs 86.5%), hematemesis (5.4% vs 8.1%), fatigue (86.5% vs 81.1%), dyspnea (19.4% vs 24.3%) and lightheadedness (2.8% vs 8.1%).

Patients were followed for a median of 5 years. When adjusted for pre-transfusion hemoglobin, difference in transfusion requirements was not statistically significant between the two groups. There was no difference in use of NSAIDs and anticoagulants between the two groups. There was also no difference in number of recurrences of GAVE. Two patients with cirrhosis of liver died.

Conclusion: Our study demonstrates that SSc patients with GAVE were significantly younger than those with non-SSc GAVE, and were mostly females. There was little difference in the presentation, severity and outcome of GAVE between the two groups. In future, further studies with larger cohorts of GAVE patients may be helpful in understanding its natural history and outcomes in specific diseases with which it is associated.

Disclosure: R. Mirza, None; Y. Jin, None; D. F. Kirby, None; S. Chatterjee, None.

Abstract Number: 2712

Evaluation of Longitudinal Outcomes in Scleroderma Patients with Negative Immunofluorescent Anti-Nuclear Antibodies

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Session Information

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Background/Purpose: Systemic Sclerosis (SSc) is an autoimmune disease characterized by inflammation, fibrosis, and vasculopathy. Historical data indicates approximately 90% of patients with SSc test positive for anti-nuclear antibodies using immunofluorescence (IF-ANA) as well as for scleroderma specific extractable nuclear antibodies such as topoisomerase (Scl-70), centromere, THTO, U3RNP, U1RNP and RNA Polymerase III. However, a small subset of scleroderma patients test negative for anti-nuclear antibodies. The purpose of this study was to investigate whether scleroderma patients with negative IF-ANA had different characteristics when compared to scleroderma patients with positive IF-ANA.

Methods: This study was IRB approved and all patients consented to be included in the study. At the time of data lock, 68 patients fulfilled diagnostic criteria for systemic sclerosis. Data was collected on patient demographics, autoantibody profile, clinical findings, internal organ involvement, modified Rodnan Skin Score (mRSS) and Medsger Severity Scale. IF-

ANA testing was performed using the Hep-2 cell line through Laboratory Corporation of America (LabCorp, Burlington, NC).

Results: Of the 68 patients, 54 had positive IF-ANA and 14 had negative IF-ANA. There was no significant difference in age, sex, race or scleroderma subtype (sine, limited, diffuse, or localized) between the IF-ANA positive and negative groups. There was no significant difference in mRSS at baseline between the IF-ANA positive and negative groups. However, patients in the IF-ANA negative group had a significantly lower mRSS at follow-up ($p=0.02$). This significant improvement was driven both by patients treated with immunosuppression and a small number of patients who were found to have underlying malignancy and whose scleroderma went into remission with treatment of the malignancy. Notably however, the IF-ANA negative group was also more likely to have positive U3RNP ($p=0.009$) indicating that this antibody may be missed using IF-ANA.

Conclusion: Scleroderma patients with negative IF-ANA testing appeared to have milder progression of mRSS with therapy at follow-up indicating that this subgroup of patients may have a relatively better prognosis. Additionally, this study found that U3RNP antibody was more commonly seen in the IF-ANA negative subgroup indicating that this antibody subtype may be missed using commercially available IF-ANA testing. This is an important finding since scleroderma patients with U3RNP are at higher risk for life threatening complications of scleroderma, including pulmonary hypertension and pulmonary fibrosis.

Disclosure: M. Haj-Ali, None; D. Jones, None; S. McNish, None; S. Stupp, None; M. Mangini, None; V. Shanmugam, None.

Abstract Number: 2713

Is Effectiveness of Immunosuppression for Interstitial Lung Disease in Systemic Sclerosis (SSc) Modified By Lung Disease Severity or SSc Duration?

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Interstitial lung disease (ILD) is a leading cause of mortality in SSc. Immunosuppression is used to treat ILD, but little is known about its benefits in mild ILD or late SSc, as these patients were excluded from randomized trials. Our aim was to determine if, in SSc patients with incident ILD, the effectiveness of immunosuppression was differential according to ILD severity and SSc duration.

Methods: We studied all SSc patients with incident ILD, using data from the Canadian Scleroderma Research Group registry (> 98% met 2013 ACR/EULAR classification criteria for SSc). The primary exposure was time dependent ever/never exposure to methotrexate, cyclophosphamide, mycophenolate, azathioprine and/or cyclosporin A. The primary outcome was progression-free survival, with clinically meaningful progression defined as >10% decline in forced vital capacity (FVC), or >5% to <10% decline in FVC and >15% decline in diffusion capacity of lung for carbon monoxide (DLCO) (OMERACT CTD-ILD 2015). Using ILD diagnosis as time zero, time to progression or death was compared between exposed and unexposed subjects. A marginal structural Cox model with inverse probability of treatment weights and multiple imputation was used to account for potential confounding and for missing data, respectively. Weights were constructed using age at baseline, sex, race, disease subtype (diffuse vs limited), and autoantibodies. Mild ILD was defined as FVC>80% predicted, and late SSc duration was defined as >7 years since first non-Raynaud. Our final model also adjusted for age, sex, race, disease subtype, and autoantibodies. Interaction terms were examined to determine if immunosuppression effectiveness differed in mild vs moderate/severe ILD, or in late vs early SSc. Subjects were censored at the visit when the outcome (death or progression) was first recorded, lost to follow-up or at last study visit.

Results: There were 204 SSc patients with incident ILD; 67 were exposed to immunosuppression at time zero or during follow up and 134 remained unexposed throughout follow-up (Table 1). In our models, subjects exposed to immunosuppression tended to have a lower estimated risk of progression or death versus unexposed subjects: weighted

hazard ratio(HR) 0.65 (95% CI 0.34, 1.25). We were unable to detect a differential effect of immunosuppression according to ILD severity or SSc duration (p=0.24 and p=0.85 for interaction terms, respectively).

Conclusion: We were unable to detect a differential effect of immunosuppression according to ILD severity or SSc duration; this may be due to lack of power. A larger sample would be required to resolve this uncertainty and answer the important clinical question of whether SSc patients perceived to be at increased risk of progressive ILD, even if mild or later in the disease course, benefit from immunosuppression.

Table 1. Baseline characteristics of the cohort, stratified by exposure status

	Never-exposed to treatments (N=134)		Ever-exposed to treatments (N=67)	
	Mean (SD) or N (%)	Missing (%)	Mean (SD) or N (%)	Missing (%)
Age, years	60.5 (10.7)	-	53.6 (12.6)	-
Female	122 (89.1%)	-	56 (83.6%)	-
White	97 (73.5%)	4	44 (67.7%)	3
Smoking (ever vs. never)	75 (59.1%)	7	39 (63.9%)	9
Disease duration from 1 st non-RP	14.2 (10.0)	-	9.2 (7.8)	-
Diffuse subtype (vs. limited)	62 (45.3%)	-	49 (73.1%)	-
Modified Rodnan skin score (0-51)	9.5 (8.5)	2	13.8 (11.4)	1
Anti-centromere	50 (39.7%)	8	10 (15.6%)	4
Anti-topoisomerase 1	20 (15.9%)	8	15 (23.4%)	4
Anti-RNA polymerase III	19 (15.1%)	8	18 (28.1%)	4
Anti-Ro52/TRIM21	35 (27.8%)	8	14 (21.9%)	4
FVC, % predicted	90.8 (17.4)	16	84.8 (17.8)	19
TLC, % predicted	95.5 (16.6)	23	88.9 (14.4)	28
DLCO, % predicted	65.5 (19.4)	23	63.9 (22.8)	31

Disclosure: S. Hoa, None; S. Bernatsky, None; R. Steele, None; M. Hudson, None.

Abstract Number: 2714

Significance of Anti-Neutrophil Cytoplasmic Antibodies in Systemic Sclerosis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

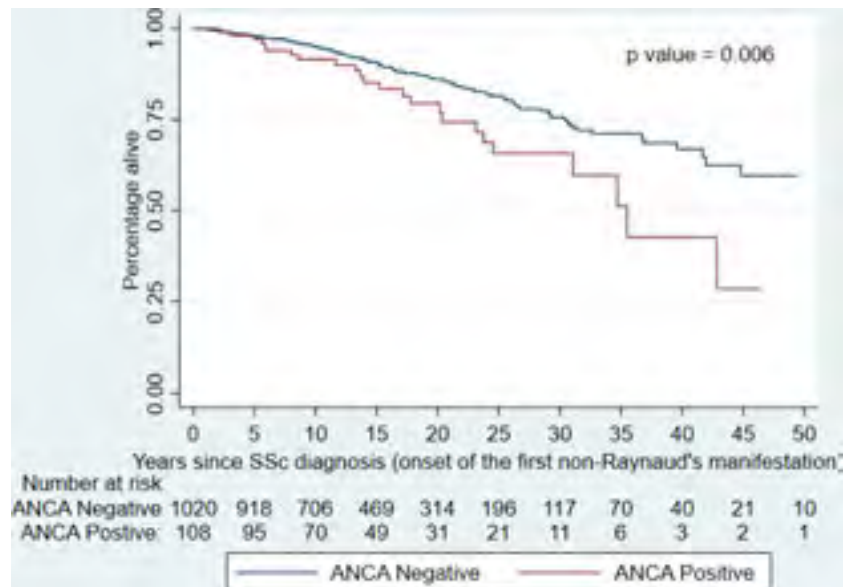
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: ANCA are detected in 0-11.7% (1) of patients with systemic sclerosis (SSc) and only a minority of these patients will develop an overlap syndrome with ANCA associated vasculitis (AAV). The clinical significance of ANCA in SSc patients without AAV is unknown. The aim of this study was to determine the prevalence of ANCA in a large SSc cohort and the association between ANCA positivity and SSc clinical characteristics, autoantibodies and mortality.

Methods: The cohort comprised patients who fulfilled 2013 ACR/EULAR criteria for SSc, enrolled in a multicentre prospective cohort study across 13 centres. ANCA positive (ANCA+) was defined as the presence of at least one of p-ANCA, c-ANCA, atypical ANCA, MPO or PR3. Univariable and multivariable associations of ANCA were determined using Chi-square and logistic regression. The effect of ANCA status on mortality was studied using Kaplan Meier survival analysis.

Results: Of 1303 patients who fulfilled inclusion criteria, 116 (8.9%) were ANCA+. Median follow-up was 3.5 years (IQR 2.7). Mean \pm SD age at recruitment was 57.7 \pm 12.5 years and 25.2% had diffuse SSc. Of the ANCA+ group, 2 (1.7%) had AAV, 13 (11.2%) were MPO+ and 18 (15.5%) were PR3+. Gender and disease subtype did not significantly differ between the ANCA+ and ANCA- groups. The ANCA+ group had a higher prevalence of Asian patients (12.9% vs 3.7%, p=0.001), interstitial lung disease (ILD) (44.8% vs 21.8%, p<0.001), malignancy (26.7% vs 18.6%, p=0.04), synovitis (54.3% vs 38.2%, p=0.001), overlap syndrome with Sjogren's (4.3% vs 1.6%, p=0.04), and overlap features with another connective tissue disease (12.1% vs 5.2%, p=0.003). Pulmonary embolism (PE) was more common among ANCA+ patients (8.6% vs



3.0%, $p=0.002$) even after adjusting for antiphospholipid antibodies. ANCA+ patients had a higher prevalence of anti-Scl70 (25.0% vs 12.8%, $p<0.001$) and anti-Ro (11.2% vs 6.2%, $p=0.04$). ILD remained significantly associated with ANCA in multivariable analysis adjusting for anti-Scl70 (OR 2.6, 95% CI 1.7-4.0, $p<0.001$). Use of azathioprine (13.8% vs 7.5%, $p=0.017$) and calcium channel antagonists (75% vs 64%, $p=0.018$) was more common in the ANCA+ group. The PR3+ group was more likely than PR3- to have anti-Scl70 (44.4% vs 13.4%, $p<0.001$), ILD (50% vs 23.4%, $p=0.009$), PE (16.7% vs 3.3%, $p=0.022$) and to use mycophenolate (22.2% vs 7.6%, $p=0.046$). The MPO+ group was more likely than MPO- to have anti-Scl70 (38.5% vs 13.6% $p=0.006$), overlap syndrome with rheumatoid arthritis (15.4% vs 1.9%, $p=0.028$) and to use cyclophosphamide (30.8% vs 8.8%, $p=0.023$). ANCA+ patients had higher mortality than ANCA- patients ($p=0.006$).

Conclusion: In SSc, ANCA identifies a high risk group, with greater prevalence of ILD and PE, and poorer overall survival. ANCA+ SSc patients require close monitoring for complications.

1. Quéméneur T, et al. Systemic Vasculitis During the Course of Systemic Sclerosis. *Medicine (Baltimore)* 2013;92.

Disclosure: J. Moxey, None; M. Huq, None; S. Proudman, Actelion Australia, 2, Actelion Australia, 8, GlaxoSmithKline, 2; J. Sahhar, None; G. S. Ngian, None; J. Walker, None; G. Strickland, None; M. Wilson, None; L. Ross, None; G. Major, None; J. Roddy, None; W. Stevens, None; M. Nikpour, Actelion, GSK, Pfizer, BMS, Eli Lilly, UCB, Astra Zeneca, Janssen, 2, 5.

Abstract Number: 2715

The Effect of an Intensive Controlled 6-Month Physical-Occupational Therapy Program with Subsequent 6-Month Follow-up Period in Patients with Systemic Sclerosis – Preliminary Data

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Background/Purpose: Involvement of the skin and musculoskeletal system is associated with impaired quality of life in patients with systemic sclerosis (SSc). Data on efficacy of non-pharmacological care in SSc is limited due to the heterogeneity in studied interventions/outcomes. The aim of our study was to minimize the limitations of available studies and to determine the effect of intensive physical-occupational therapy on hand/face function and on the quality of life in cohorts with a substantial number of SSc patients.

Methods: All patients were non-selectively consecutively recruited into an intervention (IG) and control (CG) group. They fulfilled the ACR/EULAR 2013 criteria for SSc, and had skin involvement of the hands and face. Patients from both groups received educational material for home exercises, but only the IG underwent a six-month intervention with a subsequent six-month follow-up period. All patients were evaluated by a physician and physiotherapist blinded to intervention at 0, 3, 6 and 12 months. Patients also filled out patient reported outcomes/questionnaires and provided blood for routine laboratory analysis and biobanking. Data analysis was performed between groups and within the group.

Results: In total 25 patients were included in the IG and 30 into the CG. Compared to the observed statistically significant deterioration in CG, we found a statistically significant improvement in IG in objectively assessed function and strength of hand, distance between incisors and lips and also subjectively assessed functional ability (SHAQ). During the follow-up period there was a significant deterioration or stagnation of the achieved results in the IG. Only numerical improvements in IG compared to numerical deterioration in CG, but not statistically significant, were observed, during the intervention period, in subjectively evaluated parameters (hand/face function (CHFS/MHISS), functional ability (HAQ), and some domains of (SF-36).

Conclusion: Our program led to a significant improvement in the observed parameters that were clinically relevant in a substantial proportion of patients with SSc (in the IG) and prevented the natural course of progressive deterioration in hand/face function (observed in the CG).

Acknowledgments: The project was supported by AZV-16-33574A, MHCR 023728 and SVV for FTVS UK 2019-260466.

Parameter (unit)	Intervention group Mean ± SEM	Control group Mean ± SEM	Intra-group analysis (Friedman+Dunn)		
			Intervention gr.	Control group	Inter-group analysis (2WA)
dFTP, dominant hand (cm)	m0: 5.7 ± 0.5 m3: 6.2 ± 0.5 m6: 6.8 ± 0.6 m12: 6.0 ± 0.6	m0: 6.8 ± 0.5 m3: 6.2 ± 0.4 m6: 5.9 ± 0.4 m12: 5.6 ± 0.4	m0-3: p<0.01 m3-6: p<0.05 m0-6: p<0.0001 m6-12: p<0.0001	m0-3: NS m3-6: NS m0-6: p<0.0001 m6-12: NS	p<0.0001
Hand grip strength, dominant hand (kg)	m0: 17.2 ± 1.8 m3: 19.2 ± 1.9 m6: 19.7 ± 1.9 m12: 17.5 ± 2.0	m0: 16.5 ± 1.2 m3: 14.9 ± 1.3 m6: 13.8 ± 1.2 m12: 14.2 ± 1.3	m0-3: p<0.05 m3-6: NS m0-6: p<0.001 m6-12: p<0.05	m0-3: NS m3-6: NS m0-6: p<0.01 m6-12: NS	p<0.0001
HAMIS, dominant hand	m0: 9.8 ± 1.3 m3: 7.1 ± 1.3 m6: 4.1 ± 0.9 m12: 7.2 ± 1.2	m0: 3.9 ± 1.1 m3: 6.3 ± 1.2 m6: 8.9 ± 1.1 m12: 9.8 ± 1.2	m0-3: p<0.01 m3-6: p<0.001 m0-6: p<0.0001 m6-12: p<0.001	m0-3: NS m3-6: p<0.001 m0-6: p<0.0001 m6-12: NS	p<0.0001
Inter-lip distance (cm)	m0: 3.92 ± 0.16 m3: 4.24 ± 0.17 m6: 4.46 ± 0.18 m12: 4.25 ± 0.20	m0: 4.18 ± 0.11 m3: 4.03 ± 0.12 m6: 4.02 ± 0.13 m12: 3.88 ± 0.13	m0-3: p<0.01 m3-6: NS m0-6: p<0.0001 m6-12: NS	m0-3: NS m3-6: NS m0-6: NS m6-12: NS	p<0.0001
Inter-incisor distance (cm)	m0: 2.9 ± 0.2 m3: 3.2 ± 0.2 m6: 3.5 ± 0.2 m12: 3.2 ± 0.2	m0: 3.3 ± 0.1 m3: 3.1 ± 0.1 m6: 3.0 ± 0.1 m12: 3.0 ± 0.1	m0-3: p<0.01 m3-6: NS m0-6: p<0.0001 m6-12: p<0.01	m0-3: p<0.01 m3-6: NS m0-6: p<0.001 m6-12: NS	p<0.0001
SHAQ (mm)	m0: 28.8 ± 3.9 m3: 21.5 ± 3.4 m6: 22.0 ± 3.5 m12: 23.4 ± 3.7	m0: 21.5 ± 2.1 m3: 24.6 ± 2.6 m6: 24.9 ± 2.9 m12: 27.5 ± 3.3	m0-3: NS m3-6: NS m0-6: p<0.05 m6-12: NS	m0-3: NS m3-6: NS m0-6: NS m6-12: NS	p=0.0015

Acronyms: SEM, standard error of the mean; Friedman, Friedman's test; Dunn, Dunn's post hoc test; 2WA, two way ANOVA, dFTP, delta finger to palm; HAMIS, Hand Mobility in Scleroderma; m0, month 0 (= at the baseline); m3, month (= in the middle of the intervention period); m6, month 6 (= at the end of intervention); m12, month 12 (= at the end of the 6-month follow up period); p, p-value; NS, not significant

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A New Score to Predict Digital Ulcers Combining Clinical Data, Imaging and Patient History in Systemic Sclerosis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Ischemic complications such as digital ulcers (DU) are a common complication in systemic sclerosis (SSc) patients. The aim of this study was to combine clinical characteristics and imaging methods to a composite predictive score.

Methods: Seventy-nine SSc patients received clinical examination and their patient history was taken. Furthermore, we performed nailfold capillaroscopy (NC), colour Doppler ultrasonography (CDUS) and fluorescence optical imaging (FOI) of the hands at baseline. Newly developed digital ulcers over a period of approximately 12 months were registered. We used criteria with significant ($p < 0.5$) OR values above 3.5 in regard to the development of these new DU to create the score (CIP-DUS, clinical features, imaging, patient history – digital ulcer score).

Results: Twenty-nine percent of the patients developed new DU during follow-up (48.1% diffuse SSc, 18.4% limited SSc). The following criteria were used: SSc diffuse subtype (OR 4.127, $p = 0.0087$), modified Rodnan skin score > 8 (OR 9.429 [95% CI: 3.0-29.2], $p < 0.0001$), pulmonary arterial hypertension (OR 6.854 [95% CI: 1.6-9.7], $p = 0.0088$), present digital ulcers or pitting scars at baseline (OR 15.71 [95% CI: 3.3-74.3], $p < 0.0001$), history of digital ulcer or pitting scars (OR 36.15 [95% CI: 2.1-626.9], $p < 0.0001$), NC pattern (OR 18.6 [95% CI: 1.1-326.4], $p = 0.0035$), reduced capillary density ($< 7/\text{mm}$) in digit III of the right hand in NC (OR 9.0 [95% CI: 1.1-73.6], $p = 0.0266$), missing initial enhancement in FOI in digit III of the right hand (OR 3.857 [95% CI: 1.2-12.8], $p = 0.0323$), percentage of pathologic (i.e. narrowed or occluded) vessels $> 35\%$ in CDUS (OR 4.286 [95% CI: 1.5-12.4], $p = 0.0099$). Criteria with greater OR should impact the score to a higher degree so we appointed three points to dichotomous criteria with OR > 10 , two points for criteria with OR between 5-10, and one point for criteria with OR < 5 . Regarding the NC pattern, 3 points were given to patients with late pattern, 2 points for active and 1 point for early pattern. Best results were found for a cut-off of > 10 points with obtained sensitivity levels of 95% and specificity levels of 74% in regard to new DU (AUC = 0.8687, $p < 0.0001$). In the absence of CDUS and FOI data, specificity levels dropped slightly to 72% with unchanged sensitivity values of 95%.

Conclusion: A new score was introduced with the aim to predict digital ulcers. If applied correctly and with the new imaging techniques proposed, 95% of patients at risk of digital ulcers throughout 12 months could be identified.

Disclosure: S. Friedrich, None; S. Lueders, None; G. R. Burmester, None; G. Riemekasten, None; S. Ohrndorf, None.

Factors Predicting Severe Infections in Patients with Systemic Necrotizing Vasculitides Based on Data from 733 Patients Enrolled in Randomized–Controlled Trials

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis – ANCA-Associated Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Although overall survival of patients with systemic necrotizing vasculitides (SNVs) has improved markedly over the last 20 years, infectious complications remain a major cause of morbidity and mortality. This study aimed to identify factors predicting severe infections in SNV patients and assess the impact of the different therapeutic regimens.

Methods: Data were pooled from 5 randomized-controlled trials conducted by the FVSG—CHUSPAN1, CHUSPAN2, WEGENT, CORTAGE, MAINRITSAN—that enrolled 733 patients between 1993 and 2012. Those trials evaluated therapeutic strategies to treat polyarteritis nodosa (PAN), granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and/or eosinophilic granulomatosis with polyangiitis (EGPA). The primary endpoint of this study was the occurrence of severe infection, defined as a severe adverse event, requiring hospitalization, intravenous antibiotics and/or resulting in death. Univariate and multivariate analyses were computed to identify associations between baseline characteristics and 2- and 5-year severe infection rates.

Results: SNV diagnoses were: 238 (32.5%) MPA, 224 (30.6%) GPA, 186 (25.4%) EGPA and 85 (11.6%) PAN. Baseline characteristics were: mean \pm SD age 58 ± 12 years, 55% men, 61% with pulmonary involvement, 55% with nervous system involvement, Five Factor Score = 0 for 59%, glomerular filtration rate <60 ml/min in 35%. Induction therapies were glucocorticoids alone (15%), glucocorticoids & azathioprine (16%) or glucocorticoids & cyclophosphamide (69%). Maintenance regimens were azathioprine for 28% of the patients, methotrexate for 9%, rituximab for 8% or none for 55%. After median follow-up of 5.2 (IQR 3–9.7) years, 148 (20.2%) patients experienced ≥ 1 severe infection(s). Median inclusion-to-severe-infection interval was 14.9 (4.3–51.7) months. Among all severe infections 48% were bronchopulmonary and 57% were bacterial. Patients with ≥ 1 severe infection(s) had a higher risk of death (22% vs 8%; $P<0.001$). At 2 years, patients with ≥ 1 severe infection(s) were older, had more frequent pulmonary involvement, nervous system involvement and FFS >0 , and were more likely to have received cyclophosphamide for induction. Multivariate analyses retained pulmonary [OR 2.11 (1.18–3.77); $P=0.01$] and nervous system involvements [OR 1.82 (1.01–3.30), $P=0.048$] as independent predictors of severe infection. At 5-years, baseline characteristics were the same for patients with ≥ 1 severe infection(s) but they had more likely received rituximab for maintenance therapy. Multivariate analyses retained pulmonary involvement [OR 1.71 (1.10–2.65); $P=0.02$] and age [OR 1.19 (1.02–1.38) per 10 years, $P=0.02$] as independent predictors of severe infection.

Conclusion: Severe infections, frequent adverse events in SNV patients, mostly occurred >1 year post-inclusion, and substantially impacted mortality. Age and pulmonary involvement were independent predictors of severe infection. Patients who had taken cyclophosphamide or rituximab had more severe infections than other regimens.

Disclosure: L. Antoine, None; C. Pagnoux, None; X. Puéchal, None; M. Samson, None; M. Hamidou, None; A. Karras, None; T. Quémeneur, None; M. Groh, None; L. Mouthon, None; L. Guillevin, None; B. Terrier, None.

Abstract Number: 2718

Comparison of Various ANCA Detection Methods in Predominantly MPO ANCA-Associated Vasculitis Cohort

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis – ANCA-Associated Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: In 2017, the multicenter European Vasculitis Study Group (EUVAS) evaluated the diagnostic accuracy of a wide spectrum of detection tests of MPO and PR3-ANCA (*Ann Rheum Dis* 2017;76:647). The study reported a high diagnostic performance of PR3-ANCA and MPO-ANCA by antigen-specific immunoassay to discriminate ANCA-associated vasculitis (AAV) from disease controls. They concluded that dual indirect immunofluorescence (IIF) / antigen-specific immunoassay testing of each sample is not necessary for maximal diagnostic accuracy and proposed that the current international consensus on ANCA testing for AAV needs revision. However, the AAV patients of the EUVAS study were predominantly PR3-ANCA positive. The epidemiological manifestations of AAV differ geographically. We aimed to compare various ANCA detection methods in predominantly MPO ANCA-associated vasculitis cohort.

Methods: Stored sera (obtained at the time of diagnosis) from 162 patients with newly diagnosed and untreated AAV, including microscopic polyangiitis (MPA; $n = 115$), granulomatosis with polyangiitis (GPA; $n = 32$), and eosinophilic granulomatosis with polyangiitis (EGPA; $n = 7$), from 124 disease controls, and from 50 unmatched healthy controls were tested for the presence of perinuclear and cytoplasmic pattern ANCA (P-ANCA and C-ANCA, respectively) by standard IIF, and for the presence of MPO-ANCA and PR3-ANCA by 4 different antigen-specific immunoassays: an enzyme-linked immunosorbent assay (ELISA), a chemiluminescent enzyme immunoassay (CLEIA), a third-generation fluorescent enzyme immunoassay (FEIA), and a latex agglutination turbidimetry (LA). Patients with AAV were defined and classified according to the European Medicines Agency algorithm. Patients in whom inflammatory bowel disease and/or autoimmune liver disease was considered were excluded. Sensitivities and specificities for AAV diagnoses and concordance of each AAV tests were evaluated.

Results: P-ANCA and MPO-ANCA was detected in 82% and 61–82% of the AAV patients, respectively. C-ANCA and PR3-ANCA was detected in 8% and 6–11% of the AAV patients, respectively. When P and C-ANCA or MPO and PR3-ANCA were combined, the sensitivities and specificities for AAV diagnoses were 90% and 94% with the IIF, 82% and 98% with the ELISA, 89% and 95% with the CLIA, 88% and 97% with the FEIA, and 65% and 91% with the LA, respectively. K coefficients between P-ANCA and MPO-ANCA (by the ELISA, CLIA, FEIA, and LA) were 0.87, 0.96, 0.93, and 0.64, respectively. K coefficients between C-ANCA and PR3-ANCA (by the ELISA, CLIA, FEIA, and LA) were 0.54, 0.59, 0.58, and 0.48, respectively. Screening for ANCA with the CLIA and FEIA and confirming by IIF strategy increased the diagnostic accuracy only minimally (from 0.92 to 0.93 with CLIA/IIF and from 0.93 to 0.94 with FEIA/IIF).

Conclusion: The present study demonstrated a high diagnostic performance by antigen-specific immunoassays to discriminate AAV from controls in predominantly MPO-ANCA-associated vasculitis cohort. Consequently, increase in overall performance by dual IIF/antigen-specific immunoassay testing of each sample in such cohort is minimal.

Disclosure: Y. Katsumata, None; K. E. Sada, None; T. Kameda, None; H. Dobashi, None; H. Yamanaka, None; M. Harigai, None.

Abstract Number: 2719

Tracking the Risk of Infections in ANCA-Associated Vasculitis: Results from a Scottish Matched-Cohort Study

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Session Information

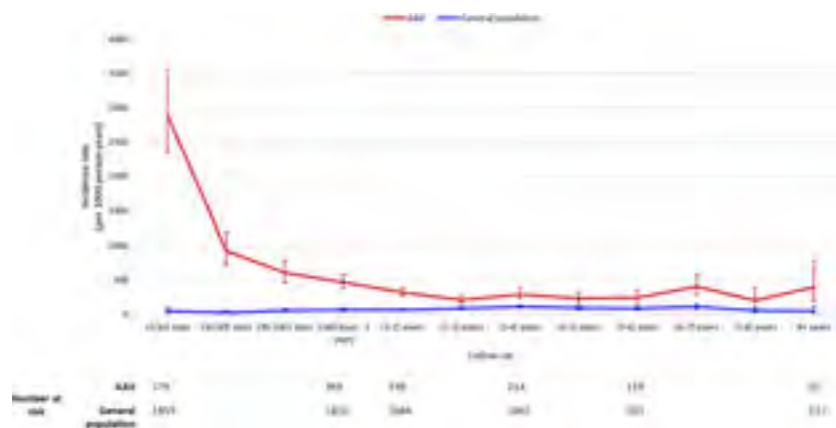
Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis – ANCA-Associated Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Evaluation of infection risk in ANCA-associated vasculitis (AAV) has been limited to small, selected populations and/or serious episodes. In this large study, we aimed to track the risk of all infections in AAV and compare it to the general population.



Methods: A longitudinal matched-cohort study was developed using Scottish administrative health-data registries. Uniquely, these resources provide over 97% population coverage and offer the capacity to link microbiological laboratory data from all levels of health care in Scotland. AAV patients fulfilling European Medicines Agency criteria were identified by clinicians across Scotland. Each was matched with up to 5 general population controls by age (± 2 years), sex and geography. Both cohorts were followed from the date of AAV diagnosis (same day assigned for matched controls) until death or 02/28/17, whichever came first. Data on all infections were retrieved from the Electronic Communication of Surveillance in Scotland Database. Descriptive statistics were used to compare infection types in both cohorts. Incidence rate ratios (IRR) and 95% confidence intervals (CI) were computed using multilevel Poisson regression.

Results: A total of 379 AAV patients (51.7% male; median age: 61.6 years) and 1859 general population controls were followed for a median of 3.5 years. During follow-up, AAV patients and controls developed 1127 and 1256 infections, respectively (55.7% of AAV, 15.8% of controls; IRR 6.7, 95% CI 5.2-8.6, $p < 0.0001$). Over 60 infection types were identified in AAV patients in whom *Escherichia coli* was the most commonly observed infection (15.8% vs 5.2%, $p < 0.001$). However, compared to the general population, AAV patients were at greatest risk of contracting Rhinovirus (IRR 9.5, 95% CI 3.5-25.8, $p < 0.0001$), Mycobacterium (IRR 9.5, 95% CI 2.5-34.1, $p < 0.0001$), Enterobacter (IRR 8.8, 95% CI 3.0-25.7, $p < 0.0001$), and Citrobacter (IRR 6.4, 95% CI 2.0-20.4, $p < 0.0001$), respectively. Interestingly, the highest rates of infections in AAV were observed during the first two years of AAV diagnosis ($p < 0.0001$, Figure 1). Although this risk decreased over time, AAV patients continued to be at a higher risk of infection than controls.

Conclusion: To our knowledge, this is the first and the most comprehensive study to analyse both the risk and type of infections using laboratory records and to track infection risk over time in AAV. Our findings indicate that AAV patients face a high risk of infections, especially in the first two years after AAV diagnosis. This risk reduces with time, but remains significantly greater than that in the general population even after eight years of follow-up.

Figure 1. Comparison of the rate of infections in ANCA-associated vasculitis and the general population

Disclosure: S. Sarica, None; N. Dhaun, None; J. Sznajd, None; J. Harvie, None; N. Joss, None; J. McLaren, None; L. McGeoch, None; N. Amft, None; V. Kumar, None; A. Marks, None; C. Black, None; N. Basu, None.

Abstract Number: 2720

30-Day Hospital Readmission for Granulomatosis with Polyangiitis: Analysis from National Readmission Database

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis – ANCA-Associated Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Granulomatosis with polyangiitis (GPA) is a systemic vasculitis with multi-organ involvement which can lead to frequent hospitalizations. Our study is to investigate characteristics and predictors of 30-day hospital readmission in GPA

Methods: We used data from the National Readmission Database (NRD) for the year 2014. Diagnoses were identified by ICD-9 diagnosis code. Non-elective hospital admissions from January to November with a diagnosis of GPA (ICD-9 code 446.4) were included. Readmission was defined as hospital admissions within 30 days of discharge of a prior hospitalization. We studied characteristics of readmissions and non-readmissions. Mixed-effects multivariable logistic regression controlling for clustering of hospitals was performed to investigate the independent predictors for readmissions. To represent the national hospitalization data, analyses were accounted for the complex survey design and stratification of the data per NRD database sets.

Results: A total of 9,119 hospital admissions with a diagnosis of GPA were identified in the year 2014. There were 2,173 readmissions within 30 days (23.8%). The top five primary diagnoses for readmissions were GPA (10.2%), sepsis (8.3%), pneumonia (5.8%), acute respiratory failure (2.6%) and acute kidney injury (AKI, 2.5%). Compared with non-readmissions, GPA readmissions were less likely to have private insurance (19% vs 26%, $p < 0.001$), more likely to have acute in-hospital events including acute respiratory failure (20% vs 18%, $p = 0.021$), sepsis (17% vs 15%, $p = 0.009$) and acute decompensated heart failure (10% vs 6%, $p < 0.001$), more likely to have chronic comorbidities including congestive heart failure (28% vs 20%, $p < 0.001$) and chronic kidney disease (62% vs 48%, $p < 0.001$), more likely to have higher hospital length of stay (8.0 vs 7.2 days, $p = 0.019$) and less likely to discharge home (50% vs 61%, $p < 0.001$) (Table 1). For GPA admissions, those who were readmitted within 30 days after discharge were more likely to be younger (OR = 0.99, $p < 0.001$), with higher Charlson Comorbidity Index (OR = 1.12, $p = 0.044$), have congestive heart failure (OR = 1.75, $p = 0.001$), develop AKI in the hospital (OR = 1.39, $p = 0.006$) and discharge to home health care (OR = 1.29, $p = 0.041$), and less likely to have private insurance (OR = 0.50, $p < 0.001$) (Table 2).

Conclusion: There is a major burden of 30-day readmission among GPA patients. Predictors of readmissions include younger age, public insurance status, higher Charlson Comorbidity Index, heart and kidney complications and unfavorable discharge dispositions.

Table 1

	Readmission	Not a readmission	P value
Demographic characteristics			
Age	61	62	0.844
Gender (female)	51%	53%	0.113
Primary payer			
Medicare	68%	62%	0.001
Medicaid	10%	8%	0.493
Private	19%	26%	< 0.001
Other	3%	4%	0.291
Median income of patient ZIP code, state quartiles			
First (lowest)	23%	20%	0.112
Second	25%	27%	0.358
Third	26%	25%	0.52
Fourth	26%	28%	0.283
Clinical characteristics of hospitalizations			
Charlson Comorbidity Index	2.67	2.25	< 0.001
Acute in-hospital events			
Acute respiratory failure	20%	18%	0.021
Pneumonia	22%	24%	0.178
Sepsis	17%	15%	0.009
Acute myocardial infarction	2%	3%	0.208
Acute decompensated heart failure	10%	6%	< 0.001
Acute kidney injury	30%	28%	0.563
Chronic comorbidities			
Hypertension	19%	25%	< 0.001
Diabetes mellitus	25%	23%	0.645
Coronary artery disease	23%	21%	0.132
Congestive heart failure	28%	20%	< 0.001
Obstructive lung disease*	32%	35%	0.479
Interstitial lung disease	5%	5%	0.606
Chronic kidney disease	62%	48%	< 0.001
Chronic liver disease	4%	3%	0.711
Cerebrovascular disease	6%	7%	0.55
Mortality	5%	6%	0.213
Length of stay	8.0	7.2	0.019
Hospital cost	19583	18478	0.289
Discharge disposition			
Home	50%	61%	< 0.001
Home health care	22%	17%	< 0.001
Skilled nursing facility	20%	15%	< 0.001
Other	8%	7%	0.092
Hospital characteristics			
Hospital location			
Urban	99%	98%	0.342
Rural	1%	2%	

Table . (Cont'd)

	Readmission	Not a readmission	P value
Hospital teaching status			
Teaching	71%	69%	0.286
Non-teaching	29%	31%	

* Obstructive lung disease includes asthma, chronic obstructive pulmonary disease and bronchiectasis

Table 2

	Adjusted odds ratio	P value
Demographic characteristics		
Age	0.99	0.011
Gender (female)	1.01	0.947
Primary payer		
Medicare	reference	
Medicaid	0.95	0.810
Private	0.50	<0.001
Self-pay	0.59	0.207
No charge	0.70	0.565
Other	1.01	0.980
Median income of patient ZIP code, state quartiles		
First (lowest)	reference	
Second	0.81	0.163
Third	0.73	0.052
Fourth	0.79	0.158
Clinical characteristics of hospitalizations		
Charlson Comorbidity Index	1.12	0.044
Acute in-hospital events		
Acute respiratory failure	1.10	0.514
Pneumonia	0.86	0.243
Sepsis	0.94	0.665
Acute myocardial infraction	1.17	0.626
Acute decompensated heart failure	0.76	0.212
Acute kidney injury	1.39	0.006
Chronic comorbidities		
Hypertension	1.21	0.192
Diabetes mellitus	0.99	0.954
Coronary artery disease	0.84	0.270
Congestive heart failure	1.75	0.001
Obstructive lung disease*	0.81	0.091
Interstitial lung disease	1.65	0.062
Chronic kidney disease	0.99	0.965
Chronic liver disease	1.12	0.629
Cerebrovascular disease	0.61	0.069
Discharge disposition		
Home	reference	
Home health care	1.29	0.041
Skilled nursing facility	1.03	0.852
Left against medical advice	1.63	0.317
Other	1.18	0.683
Hospital characteristics		
Hospital location		
Urban	reference	
Rural	0.35	0.143
Hospital teaching status		
Teaching	reference	
Non-teaching	0.82	0.091

* Obstructive lung disease includes asthma, chronic obstructive pulmonary disease and bronchiectasis

Disclosure: Y. Luo, None; C. Jiang, None; A. B. Arevalo Molina, None; S. Murray, None; M. Salgado, None; J. Xu, None.

Venous Thromboembolism in ANCA Associated Vasculitis. a Population-Based Cohort Study from Southern Sweden

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis – ANCA-Associated Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To estimate the rate and predictors of venous thromboembolic events (VTEs) in a population-based cohort of patients with ANCA- associated vasculitis (AAV).

Methods: 322 patients (47% women) diagnosed with AAV between 1997 and 2016 from a well-defined population in southern Sweden, were included in this study. The diagnosis of AAV and VTEs were ascertained by review of medical records. Radiological investigations, clinical notes, laboratory results and prescriptions of anticoagulation therapies were reviewed to identify patients with VTEs. Demographics, clinical and laboratory data were collected from time of AAV diagnosis until death or end of follow-up, September 2017. Birmingham Vasculitis Activity Score (BVAS) was used to assess AAV disease activity. Organ damage was assessed by vasculitis damage index (VDI). VTEs occurred within 3 months prior to AAV diagnosis and any time after that were considered as AAV-related VTEs.

Results: 55 patients (17%) developed a total of 63 VTEs of which 31 cases were deep vein thrombosis, 21 pulmonary embolisms and 11 other VTEs (5 retinal vein thrombosis, 1 sinus thrombosis, 1 subclavian vein thrombosis, 2 cases of jugular vein thrombosis, 1 right ventricle thrombosis, 1 olecranon bursa vein thrombosis). Of all patients with VTEs, 45 (82%) developed AAV-related VTE resulting in an incidence rate of 2.4/100 person-years (95% CI 1.7-3.1) during 1906 person-year of follow-up. The incidence rate of AAV-related VTEs during first year from diagnosis of AAV was estimated to 10.9/100 person-year (95% CI 6.8-14.9), decreased to 6.2 at 2-years ($p=0.07$), 3.9 at 5-years ($p<0.001$) and 2.8 at 10 years from diagnosis of AAV ($p<0.001$). The incidence rate of VTEs /100 person-year in patients with positive MPO-ANCA was 3.3 (95% CI 2-4.7) vs. 2.1 (95% CI 1.2-3.0) in patients with PR3-ANCA, $p=0.1$. Patients who developed any VTE were older at diagnosis and had higher BVAS score, were more likely to be MPO-ANCA positive and had higher VDI at 12 months after diagnosis of AAV (Table 1).

Conclusion: Higher age at diagnosis of the vasculitis, MPO positivity and high disease activity were associated with VTEs. The incidence rate of AAV-related VTEs was higher early at disease onset compared to the whole period of follow-up.

Table 1. VTEs in 322 patients with ANCA Associated Vasculitis

	All patients (n=322)	VTEs (n=55)	No VTEs (n=267)	P-value
Age at diagnosis, mean \pm SD, years.	64.4 \pm 16.4	68.8 \pm 13.9	63.5 \pm 16.8	0.03
Sex, Female, n (%)	150 (47)	23 (42)	127 (48)	0.4
Diagnosis: GPA: MPA: EGPA	166: 134: 22	26: 27: 2	140: 107: 20	
PR3-ANCA +, n (%)	156 (51)	21 (41)	135 (54)	0.1
MPO-ANCA +, n (%)	138 (45)	32 (62)	106 (42)	0.01
BVAS at diagnosis, mean \pm SD	15.3 \pm 6.2	17.1 \pm 7	14.6 \pm 6	0.009
Laboratory data at diagnosis				
S-creatinine, μ mol/l, median (IQR)	136 (74-308)	190 (76-355)	128 (73-283)	0.1
Haemoglobin, g/l mean \pm SD	110 \pm 20	110 \pm 17	110 \pm 20	0.8
White blood cell count, mean \pm SD	12 \pm 4.9	12 \pm 5.4	12 \pm 4.8	0.7
Platelet count mean \pm SD	370 \pm 144	343 \pm 144	375 \pm 144	0.1
CRP, mg/l, median (IQR)	77 (23-134)	53 (11-121)	83 (26-143)	0.2
ESR, mm/hr, mean \pm SD	64 \pm 33	62 \pm 30	64 \pm 34	0.8
eGFR ml/min/1.7m ² , median (IQR)	44 (18-86)	30 (15-82)	47 (17-87)	0.3
Deaths, n (%)	144 (45)	28 (51)	116 (43)	0.3
ESRD, n (%)	51 (16)	9 (16)	42 (16)	0.9
BVAS at 12 months, mean \pm SD	0.8 \pm 2.5	0.7 \pm 2.1	0.9 \pm 2.4	0.7
VDI, at 12 months, median (IQR)	1 (0-2)	2 (1-3)	1 (0-2)	0.1

GPA: granulomatosis with polyangiitis, MPA: microscopic polyangiitis, EGPA: eosinophil granulomatosis with polyangiitis, PR3: proteinase-3, MPO: myeloperoxidase, BVAS: Birmingham Vasculitis Activity Score, IQR: interquartile range, CRP: c-reactive protein, ESR: erythrocyte sedimentation rate eGFR: estimated glomerular filtration rate at disease onset, ESRD: end-stage renal disease, VDI: vasculitis damage index.

Disclosure: M. Liapi, None; D. Jayne, None; M. Segelmark, None; A. Mohammad, None.

Abstract Number: 2722

Incidence and Predictors of Severe Infections in ANCA Associated Vasculitis in a Population-Based Cohort – Preliminary Results

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis – ANCA-Associated Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To determine the incidence rates, predictors and outcome of severe infections in ANCA associated vasculitis (AAV).

Methods: We conducted a population-based cohort study in Southern Sweden with 326 incident cases of AAV diagnosed between 1997 and 2016. Clinical diagnosis of vasculitis was confirmed by case record review and patients were classified according to the European Medicine Agency algorithm. Demographics, clinical, laboratory and treatment data was collected from time of diagnosis and follow-up. All events of severe infection (required hospitalization or treated by intravenous antibiotics) were identified. Vasculitis disease activity was evaluated using the Birmingham Vasculitis Activity Score (BVAS) and the extent of organ damage was assessed using the vasculitis damage index (VDI). Estimated glomerular filtration rate (eGFR) was calculated using the MDRD formula. Patients were followed from time of diagnosis of AAV to death or end of study, December 2017

Results: Data on 221 patients (96 women) was collated and are presented in this report. In total 89 (40%) patients experienced at least one severe infection during the follow-up, 25 (11%) suffered two infections and 10 (5%) suffered 3 severe infections or more. Table 1 summarizes demographics, clinical and laboratory data in this study. Compared to those who did not suffer severe infection, patients with severe infection were older at diagnosis, had higher serum creatinine, lower eGFR, were more likely to have MPO-ANCA positivity, had higher BVAS at disease onset and higher VDI after 12 months (Table 1). Age and BVAS at diagnosis were the only factors that independently predicted severe infection. The incidence rate of severe infection was higher during the first year after diagnosis compared to that during the whole follow-up time (38.6/100 year vs. 10.4/100, $p<0.001$). An association between steroid exposure and serious infection could not be demonstrated. Severe infection was associated with worse prognosis in terms of renal and patient's survival (Table 1)

Conclusion: In this cohort the incidence rate of severe infection is comparable to earlier published data in AAV. Severe infection in ANCA associated vasculitis is still a major clinical problem and is associated with high age, increased disease activity at diagnosis, renal disease and MPO-ANCA positivity. The rate of severe infection is higher early in the disease course. Severe infection is associated with a worse prognosis.

Table 1. Severe infections in 221 patients with ANCA associated vasculitis

	All patients (n=221)	Severe infection (n=89)	No severe infection (n=132)	P-value
Age at diagnosis, mean \pm SD, years.	64,5 \pm 17,1	70,2 \pm 14	60,8 \pm 18	<0.001
Sex, Female: Male	98: 123	35: 54	63: 69	0.1
Diagnosis: GPA/MPA/EGPA	122/83/16	43/38/5	75/45/11	0.2
PR3-ANCA +: MPO-ANCA +	103: 96	33: 46	70: 50	0.02
BVAS at diagnosis, mean, SD	15 \pm 5.7	16 \pm 5	13.8 \pm 5.4	0.001
Laboratory data at diagnosis				
S-creatinine, μ mol/l , median (IQR)	132 (73-275)	181 (80-370)	103 (71-202)	0.016
Haemoglobin g/l, mean, SD	110 \pm 20.1	107.7 \pm 20.3	112.6 \pm 19.9	0.66
White blood cell count, mean, SD	12.4 \pm 4.99	12.2 \pm 4.3	12.5 \pm 5.4	0.74
Platelet count, mean, SD	366.7 \pm 148	339 \pm 141.7	385 \pm 151	0.03
CRP, mg/l, median (IQR)	73 (23-130)	66 (19-128)	79 (26-130)	0.6
GFR ml/min, median (IQR)	47.1 (17-87)	30 (12-77)	67 (25-96)	0.01
Deaths, n (%)	89 (40)	47 (53)	37 (28)	<0.001

Table . (Cont'd)

	All patients (n=221)	Severe infection (n=89)	No severe infection (n=132)	P-value
ESRD, n (%)	27 (12)	16 (18)	11 (8)	0.03
BVAS at 12 months, mean (SD)	0.9 ±3	0.59 ±1.6	0 ±2.8	0.1
VDI, at 12 months, mean (SD)	1.65 ±1.4	2.14±1.6	1.3±1.2	0.04
Induction treatment CYC, N (%)	174 (78)	73 (82)	101 (76)	0.2
Induction treatment RTX, N (%)	35 (15)	17 (19)	18 (13)	0.8
Daily corticosteroid dosages (mg)				
0 months (onset), mean, SD	57 ±18	58 ±16	56 ±18	0.4
3 months, median (IQR)	15 (12.5-20)	15 (11-20)	15 (12.5-20)	0.8
6 months	10 (7.5-15)	10 (7.5-15)	10 (7.5-12.5)	0.6
9 months	7.5 (7.5-10)	7.5 (5-10)	7.5 (7.5-10)	0.7
12 months	7.5 (5-10)	6.25 (5-10)	7.5 (5-10)	0.6

GPA: granulomatosis with polyangiitis, MPA: microscopic polyangiitis, EGPA: eosinophil granulomatosis with polyangiitis, PR3: proteinase-3, MPO: myeloperoxidase, BVAS: Birmingham Vasculitis Activity Score, IQR: interquartile range, CRP: C - reactive protein, eGFR: estimated glomerular filtration rate at disease onset, ESRD: end-stage renal disease, VDI: vasculitis damage index.

Disclosure: J. Rathmann, None; D. Jayne, None; G. Jönsson, None; M. Segelmark, None; J. A. Nilsson, None; A. Mohammad, None.

Abstract Number: 2723

Patient Experience in ANCA-Associated Vasculitis Evolves over Time from Diagnosis and Both Benefits and Adverse Impacts Are Felt with Current Therapy

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis – ANCA-Associated Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: ANCA-associated vasculitis (AAV) leads to both acute illness and a long-term condition in which the disease remits and relapses. Therapy is often complex and associated with toxicity in its own right. Relatively little is known about the patient experience in AAV and how that evolves over time, but it is important when considering new therapeutic options. This study aimed to examine patient experiences and views around AAV and its treatment.

Methods: Qualitative research was performed using one-on-one interviews with 33 AAV patients (11 male) from 4 European countries. 20 patients had granulomatosis with polyangiitis, 12 had microscopic polyangiitis, and 1 had eosinophilic granulomatosis with polyangiitis. AAV duration (median 3.5 years, range 1-32) and patient age (3 under 40 years old, 25 aged 40-80 years, and 5 over 70 years) allowed rich insight into the patient journey from diagnosis through follow up.

Results: Thematic analysis of the interview transcripts by a single experienced researcher was performed to examine issues along the patient journey from diagnosis to treatment. Key findings were: (1) Suboptimal referral – patients report a long journey to diagnosis leading to long lasting psychological damage, worsened with treatment burden following diagnosis. (2) Recognition - patient experience is worse with sudden onset or misdiagnosis. Patients express concern over low empathy and understanding of their needs by professionals. (3) Knowledge gaps – patients want to understand their future, duration of therapy, and when they can expect to return to normality. (4) Measuring response –patients have a low awareness of how their response is assessed clinically and categories of response or scales used by clinicians. Patients refer to “feeling better” and going home as being important to them. (5) Decision making – they had a low involvement in treatment decisions particularly over glucocorticoids (GCs) and immunosuppression. (6) Unmet needs – while they are grateful for the efficiency of GCs, they feel major side effects which impair their quality of life, satisfaction and functional status with evolving symptomatic problems over their journey as GC dose changes. These findings were consistent across the 4 countries with only minor differences driven by variations in healthcare system and organization.

Conclusion: Patient experience in AAV is challenging both before and after diagnosis, and once treatment begins with evolution over time. Physicians need to consider AAV patients’ needs at diagnosis, when assessing response to treatment,

and when changing treatment. GCs are a particular problem for patients and there is a need for new therapies which reduce the significant treatment burden.

Disclosure: P. Rutherford, Vifor Pharma, 3; D. Goette, Vifor Pharma, 3; J. O'Donoghue, Elma Research, 3; X. Liu, Elma Research, 3.

Abstract Number: 2724

Variable Response to Induction Therapy and Significant Burden of Treatment Adverse Events over the First 12 Months in Incident ANCA-Associated Vasculitis (AAV) Patients – a Study of Routine Clinical Practice in the EU

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis – ANCA-Associated Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Aims of therapy in incident AAV patients include ensuring rapid diagnosis, assessment of comorbidity, disease activity, and vasculitis damage before commencing treatment with a combination of high dose glucocorticoids (GC) with rituximab (RTX) or cyclophosphamide (CYC). It is believed to be important to achieve control of the vasculitis as soon as possible but also to avoid acute treatment-related morbidity as well as prevention of long term GC damage. This study aimed to examine clinical outcomes and adverse events in incident AAV patients in routine clinical practice in the EU.

Methods: This was a retrospective clinical review of 929 incident AAV (granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)) patients from 4 European countries (399 physicians) who were diagnosed between 2014-17. Clinical data were reviewed at baseline, and at 1, 3, 6 and 12 months following commencement of induction therapy.

Results: 54% of patients had GPA, 46% MPA and mean age was 56.8 years (SD 14.2) with 53.7% male. Birmingham vasculitis activity score (BVAS) was used in only 12% of cases, but physicians reported 12% as mild/localized, 54% as moderate systemic and 34% as severe, life threatening. Comorbidities were common, with hypertension (44.9%), diabetes (18.1%), COPD/asthma (15.1%) and coronary arterial disease (10%) among the most frequently reported. Only 32.2% reported no comorbidities. Induction therapy varied with 59% receiving CYC, 24% RTX whilst 83% received GCs. As BVAS was not assessed in routine practice, clinical response was assessed as full (no vasculitis activity and GC taper on track), partial (reduction in vasculitis activity and major organ damage arrested) and no response (no improvement in vasculitis). Response rate varied and therapy-related adverse events were common.

	1 month	3 months	6 months	12 months
Full response %	18	43	61	59
At least one AE %	45	42	35	30
Infection %	27	28	23	20
Still receiving GC %	82	79	67	53

Full response at 1 month was associated with good 12-month outcomes (81% full response) whereas a partial response at 1 month (56%) was associated with less favourable outcomes (58% full response at 12 months). Over the first 12 months of therapy, 6% of patients relapsed and required additional Treatment.

Conclusion: Incident AAV patients frequently have comorbidity at diagnosis and vasculitis was rarely assessed using BVAS. Response to remission therapy was variable but early response is associated with a better response rate at 12 months. Therapy-related adverse events and infections are common, especially in the first 3 months. There is an unmet medical need for better response rates and reduction in toxicity of existing therapy.

Disclosure: P. Rutherford, Vifor Pharma, 3; D. Goette, Vifor Pharma, 3; M. Stamm, Elma Research, 3; X. Liu, Elma Research, 3.

Clinical Characteristics and Long-Term Follow-up of 382 Microscopic Polyangiitis Patients

Yann Nguyen¹, Christian Pagnoux², Alexandre Karras³, Thomas Quémeneur⁴, Francois Maurier⁵, Mohamed Hamidou⁶, Alain Le Quellec⁷, Noémie Jourde-Chiche⁸, Pascal Cohen¹, Alexis Régent¹, Francois Lifermann⁹, Arsène Mékinian¹⁰, Chahéra Khouatra¹¹, Eric Hachulla¹², Jacques Ninet¹³, Jacques Pourrat¹⁴, Marc Ruivard¹⁵, Pascal Godmer¹⁶, Jean-Francois Viallard¹⁷, Benjamin Terrier¹, Luc Mouthon¹, Loïc Guillevin¹ and Xavier Puéchal¹, ¹Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP-HP, Université Paris Descartes, Paris, France, Paris, France, ²Division of Rheumatology, Division of Rheumatology, Mount Sinai Hospital, Toronto, ON, Canada, ³Department of Nephrology, Hôpital Européen Georges Pompidou, APHP, Paris, France, Paris, France, ⁴Department of Internal Medicine, CH of Valenciennes, France, Valenciennes, France, ⁵Médecine interne, Hôpitaux Privés de Metz, Metz, France, ⁶Department of Internal Medicine, CHU de Nantes, France, Nantes, France, ⁷Department of Internal Medicine, Hôpital Saint-Eloi, CHU de Montpellier, France, Montpellier, France, ⁸Nephrology, Department of Nephrology, AP-HM, CHU Conception, Marseille, France, Marseille, France, ⁹Dax, Dax, France, ¹⁰Department of Internal Medicine, Hôpital Saint-Antoine, APHP, Paris, France, Paris, France, ¹¹Department of Respiratory Medicine, National Reference Center for Rare Pulmonary Diseases, Hospices civils de Lyon, Hôpital Louis Pradel, Lyon, France, Lyon, France, ¹²Department of Internal Medicine, National Reference Center for Systemic Sclerosis, Hôpital Claude Huriez, CHRU Lille, France, Lille, France, ¹³Department of Internal Medicine, Hôpital Edouard Herriot HCL, CHU de Lyon, France, Lyon, France, ¹⁴Department of Nephrology, Hôpital de Rangueil, CHU Toulouse, France, Toulouse, France, ¹⁵Department of Internal Medicine, CHU Estang, Clermont-Ferrand, France, Clermont-ferrand, France, ¹⁶Department of Internal Medicine, CH Vannes, France, Vannes, France, ¹⁷Department of Internal Medicine, Hôpital Haut-Lévêque, Bordeaux, France, CHU Bordeaux, France

Session Information

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Session Title: Vasculitis – ANCA-Associated Poster II

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Background/Purpose: Microscopic polyangiitis (MPA) is a systemic ANCA-associated small-vessel necrotizing vasculitis characterized by general symptoms, and visceral manifestations, including rapidly progressive glomerulonephritis and alveolar hemorrhage. The main characteristics and long-term outcomes of a nationwide patient cohort are described.

Methods: French Vasculitis Study Group's cohort patients with MPA, satisfying Chapel Hill criteria, were studied retrospectively. Their characteristics at diagnosis, 2009 Five Factor Score (FFS) and Birmingham Vasculitis Activity Score (BVAS) were collected. For the earliest recruits, ANCA tests were not available. MPA diagnoses were reassessed, taking follow-up into account. Patients' overall (OS) and relapse-free survival (RFS) were analyzed using log-rank tests and multivariable Cox proportional hazards models.

Results: Patients (n=382) were diagnosed between 1966 and 2017 (30 [8%] before 1990, 101 [26%] 1990–2000, 152 [40%] 2000–2010 and 99 [26%] after 2010), and followed-up for (mean \pm SD) 5.5 ± 4.6 yr. At diagnosis, mean \pm SD age was 61.1 ± 15.1 yr, with 182 (48%) >65 yr old. Main clinical manifestations included fever >38°C (45%); weight loss (57%); arthralgias (45%); myalgias (40%); purpura (19%); mononeuritis multiplex (33%). Creatinine levels rose >30% in 154 (40%) patients, with mean \pm SD creatininemia at 215 ± 223 μ mol/L, and creatininemia >150 μ mol/L for 158 (41%) patients. Alveolar hemorrhage occurred in 59 (16%; with massive hemorrhage and/or hemoglobin <9 g/dL in 17 (4.5%)) patients, cardiomyopathy in 22 (6%) and severe gastrointestinal signs (bleeding, perforation, pancreatitis) in 15 (4%). IF ANCA test results were available for 350 patients and ELISA for 345; 276 (80%) patients were anti-MPO-ANCA+ and 13 (3.7%) anti-PR3+. FFSs were 0 for 110 (29%) patients, 1 for 181 (47%), ≥ 2 for 91 (24%). Median BVAS was 17.3. Glucocorticoids alone were induction for 92 patients (24%); 280 also took an immunosuppressant, including rituximab for 43 (11%). After a mean \pm SD of 3.0 ± 2.9 yr, 133 (35%) patients had relapsed. Respective 5-year OS and RFS were 86.9% and 60.5%. Over the last 40 yr, OS increased from 63% before 1990 to 94% after 2010 (P for trend <0.001), but not RFS. FFS ≥ 1 and an increased BVAS were associated with death ($P < 0.0001$ and <0.0001, respectively). Multivariable analyses (hazard ratio; 95% confidence interval) retained age >65 yr (4.6; 2.7–7.8), the need for assisted ventilation (3.9; 1.3–11.5), creatininemia >150 μ mol/L (2.6; 1.6–4.2) and mononeuritis multiplex (1.9; 1.1–3.2) as independent risk factors for death; and cardiomyopathy (1.8; 1.0–3.0), severe gastrointestinal manifestations (2.1; 1.1–3.8) and mononeuritis multiplex (1.7; 1.3–2.3) as factors associated with poor relapse-free survival. Immunosuppressant use for induction therapy did not modify those results.

Conclusion: This retrospective study provides useful information on the characteristics and outcomes of a large cohort of MPA patients. OS improved over decades. However, data collection before ANCA discovery and evolution of therapeutic strategies may represent a study limitation.

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Abstract Number: 2726

Severe Infections in Systemic Necrotizing Vasculitis: Incidence and Risk Factors

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Session Information

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Background/Purpose: Infections in patients with systemic necrotizing vasculitis represent one of the main causes of mortality. Risk factors of infection such as corticosteroid use, intensity of immunosuppressive therapy, age, presence of leucopenia, lymphopenia, associated organic involvement, and dialysis dependence have been identified. Objective: To determine the incidence of infection in patients diagnosed with: Polyangiitis with Granulomatosis (GPA), Eosinophilic Polyangiitis with Granulomatosis (EGPA), Microscopic Polyangiitis (PAM) and Panarteritis Nodosa (PAN), b) clinical characteristics and associated risks factors

Methods: Retrospective study. Data source: clinical records of patients diagnosed with ANCA associated vasculitis and PAN, evaluated in a center of rheumatology (2000-2016). Variables: Demographic data, clinical manifestations, laboratory data, infectious events serious (requiring hospitalization or prolonged antibiotic/antiviral treatment, recurrences of herpes zoster virus or opportunistic infections), sites of infection, isolated microorganisms, mortality related to the infectious event.

Results: 80 patients, 61.25% women. Mean age at diagnosis: 49.2 years (range 18-77). Types of vasculitis: 41.2% GPA, 18.7% EPGA, 26.25% PAM, 3.73% PAN not associated with HBV and 10% ANCA-associated vasculitis that did not met classification criteria. Systemic involvement (68%), pulmonary (59%), renal (58%) and otorhinolaryngology (43.6%) were the most frequent. 36 infectious events were recorded in 28 patients. Follow-up time: Median 22 m (IQR 6-64). Incidence of infection: 38.4%, with a median of 3 m (IQR 1-18 m) from diagnosis of vasculitis. Low respiratory infections (40.7%), sepsis (39.3%), and urinary tract infections (15%) were the most common. 25% of these patients presented a second infectious event, being low respiratory tract the most frequent site (47%). Two patients had a 3rd event (soft tissue infection, septic shock). Bacterial etiology was the most prevalent (45%), being the microorganisms most frequently isolated: *Klebsiella pneumoniae* (25%), *Acinetobacter* spp (19%), *E. coli* and polymicrobial (12.5% respectively). Overall mortality was 17.5% (14/80) and related infectious event: 50% (n=7). 71.4% of patients were in the induction phase of treatment. Immunosuppressants used prior to infectious event: cyclophosphamide (48.1%), azathioprine (11.1%), methotrexate (7.4%), mofetil mycophenolate (3.7%), none (22.2%). Corticosteroids ≥ 30 mg/d were observed in 35.7% patients, ranging from 7.5-30 mg/d (10.7%), and ≤ 7.5 mg/d in 35.7%. Presence of leukopenia (26%), lymphopenia (44%), hypoalbuminemia (24%), renal insufficiency (63%) and dialysis dependency (37%) were identified in patients with infectious events. Renal involvement (p 0.01) and dialysis dependence (p 0.001) were significantly associated with infection.

Conclusion: The incidence of infection was 38.4%. Lower airway infections, septicemia and urinary tract infections were the most commonly implicated sites. Most infections occurred in the induction phases of the disease. Dialysis dependence and presence of renal involvement were significantly associated with this complication.

Disclosure: C. E. Pena, None; A. C. Costi, None; L. Garcia, None; M. Pera, None; M. Garcia, None.

Prevalence of Clinical and Subclinical Ophthalmologic Manifestations in Association with Systemic Symptoms, Disease Activity and Damage in Patients with Granulomatosis with Polyangiitis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis – ANCA-Associated Poster II

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Background/Purpose: Ophthalmologic involvement in Granulomatosis with Polyangiitis (GPA) is present in 50-60% of the patients and can affect any part of the ocular globe and the orbit. We aimed to describe clinical and subclinical ophthalmologic manifestations, association with systemic symptoms, disease activity and damage in patients with GPA.

Methods: Cross-sectional study including patients with GPA diagnosis (ACR 1990 classification criteria and/or 2012 Chapel Hill Consensus definitions). All patients underwent rheumatologic and ophthalmologic evaluation. Information regarding demographics, comorbidities, clinical variables, ophthalmologic symptoms, serologic markers, radiographic studies, disease activity and damage was retrieved. Descriptive statistics, correlation and univariable logistic regression analyses, Student t, Mann-Whitney U, chi square and Fisher's exact tests were performed.

Results: Fifty patients were included, 60% female, age 56 years (24-82), disease duration 72.5 months (0-469). Nineteen patients (38%) had ophthalmic manifestations at GPA diagnosis; being scleritis/episcleritis the most frequent (18%), while 27 (54%) presented them during follow-up, with repeated scleritis/episcleritis and lacrimal gland involvement being the most frequent. Concomitant ophthalmic and sinus involvement was present in 12 (24%). Radiologic abnormalities were observed in 35 (76%), being sinusitis the most frequent (Table 1). BVAS/GPA was 1 (0-17) and VDI 5.5 (0-11), with ocular and ENT damage being present in 58% and 70%, respectively. Forty three patients (86%) presented at least one ophthalmologic symptom, being epiphora and blurred vision the most frequent (40%). At least one clinical abnormality was found in 31 (62%). Scleromalacia (27%) and conjunctival hyperemia (26%) were the most frequent findings (Table 2). Association between radiographic granulomas and clinical proptosis ($r=0.69$, $p=0.001$), and between extraconal fat herniation and episcleritis ($r=0.69$, $p=0.0001$) was found. Ophthalmic involvement at diagnosis was associated with concomitant ophthalmic and sinus involvement at follow-up (OR 4.72, 95% CI 1.17-19.01, $p=0.01$). Ophthalmic involvement at follow-up was associated with age at GPA diagnosis (OR 0.94, 95% CI 0.90-0.99, $p=0.03$), VDI (OR 1.29, 95% CI 1.03-1.61, $p=0.02$), and ENT damage (OR 5.27, 95% CI 1.37-20.13, $p=0.01$).

Conclusion: In GPA, clinical and subclinical ophthalmic involvement is frequent at diagnosis and follow-up, it is associated with concomitant sinus involvement and has impact on ocular and ENT damage.

Table 1.

Variable	n (%)
Ophthalmic manifestations at diagnosis	19 (38)
Scleritis/Episcleritis	9 (18)
Lacrimal gland involvement	2 (4)
Optic nerve involvement	3 (6)
Retinal artery occlusion	2 (4)
Ulcerative keratitis	3 (6)
Uveitis	2 (4)
Pseudotumor	1 (2)
Ophthalmic manifestations at follow-up	27 (54)
Scleritis/Episcleritis	6 (12)
Repeated scleritis/episcleritis	8 (16)
Lacrimal gland involvement	8 (16)
Chronic dacryocystitis	4 (8)
Retinal involvement	2 (4)
Uveitis	3 (6)
Optic nerve involvement	4 (8)
Other	7 (14)

Table . (Cont'd)

Variable	n (%)
Concomitant ophthalmic and sinus involvement	12 (24)
Radiologic findings (n=46)	n (%)
Radiologic abnormalities	35 (76)
Sinusitis	25 (54)
Granulomas	4 (9)
Pseudotumor	2 (4)
Bone erosions	10 (22)
Pachymeningitis	2 (4)
Mastoiditis	5 (11)
Otomastoiditis	4 (9)
Lateral cartilage collapse	17 (37)
Septal perforation	19 (41)
Exophthalmos	7 (15)
Lacrimal gland enlargement	6 (13)
Extraconal fat herniation	2 (4)

Table 2.

Sign	Either eye n (%)
Blindness	12 (24)
Extraocular muscular involvement	2 (4)
Exophthalmos	10 (20)
Orbital granuloma	2 (4)
Palpebral edema/inflammation	3 (6)
Proptosis	2 (4)
Ptosis	3 (6)
Dacryocystitis	9 (18)
Nasal conjunctive fistulas	2 (4)
Optic neuropathy	3 (6)
Diplopia	1 (2)
Epiphora	10 (20)
Conjunctival inflammation/hyperemia	13 (26)
Episcleritis	1 (2)
Necrotizing scleritis	1 (2)
Ulcerative peripheral keratitis	2 (4)
Keratoconjunctivitis sicca	4 (8)
Scleromalacia	13 (27)
Retinal vasculitis	1 (2)
Retinal exudates	1 (2)

Disclosure:

A. Hinojosa-Azaola, None; A. García-Castro, None; A. Juárez-Flores, None. :

Abstract Number: 2728

Validation of the Draft Classification Criteria of Granulomatosis with Polyangiitis (GPA) Amongst Indian Patients with ANCA Associated Vasculitis

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Session Information

Session Date: Tuesday, October 23, 2018

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Background/Purpose: A draft classification criteria of GPA was proposed at ACR meeting in San Diego in 2017. The present criteria is a modification of ACR/EULAR provisional 2017 classification criteria for GPA presented at ACR Washington meeting in 2016. This has been a result of data driven DCVAS study. The purpose of the present study was to validate the recently proposed draft classification criteria of GPA in a real life cohort of ANCA associated vasculitis (AAV).

Methods: The draft GPA criteria was applied to patients diagnosed to have AAV according to European Medicines Agency (EMA) algorithm. The level of agreement between the draft GPA criteria and EMA algorithm was assessed using Cohen's kappa. The level of agreement between the ACR/EULAR provisional 2017 classification criteria for GPA and EMA algorithm was also assessed using Cohen's kappa. Sensitivity and specificity of the draft GPA criteria and the ACR/EULAR provisional 2017 classification criteria for GPA was calculated taking EMA algorithm as gold standard.

Results: 224 patients with mean age of 41.7 ± 15.0 years were included. Female: male ratio was 1.3:1. ANCA by IIF was done in all patients and was positive in 171 (cANCA -125, pANCA -46). PR3/MPO ELISA was available in 125 patients (PR3-93, MPO- 32). Using EMA algorithm EGPA was diagnosed in 6, GPA in 187 and MPA in 31. With ACR 1990 criteria, GPA was diagnosed in 137 patients while with draft GPA criteria 136 were classified as GPA. Draft GPA criteria had fair agreement with EMA (kappa-0.23, sensitivity-66% and specificity-70%) than ACR criteria (kappa 0.1, sensitivity -64% and specificity-45%). ACR/EULAR provisional 2017 classification criteria for GPA also had a fair agreement with EMA (kappa 0.26, sensitivity -69.5% and specificity-70.2%). Eleven of thirty one MPA patients were reclassified as GPA by draft GPA criteria. 5 patients who were classified as GPA by EMA and ACR/EULAR provisional 2017 classification criteria for GPA were excluded by the new criteria. All of them were MPO positive and had pulmonary nodules and paranasal sinus involvement.

Conclusion: Within the limits of a retrospective design, the study showed fair agreement of draft GPA criteria with EMA algorithm. The specificity of the new criteria compared to EMA algorithm is low, likely due to the stress given to PR3/cANCA positivity.

Table 1. Reclassification of various AAV patients (EMA and ACR 1990) by draft GPA criteria

ANCA associated vasculitis	No. of patients (n=224, %)	Reclassified as GPA by ACR/EULAR 2018 criteria
ACR 1990 GPA	137(61.1)	89
EMA GPA	187(83.4)	125
EMA MPA	31(13.8)	11
EMA EGPA	6(2.6)	0

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Increased Risk of Cerebrovascular Accident Among Patients with Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis: A Systematic Review and Meta-Analysis of Cohort Studies

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Session Information

Session Date: Tuesday, October 23, 2018

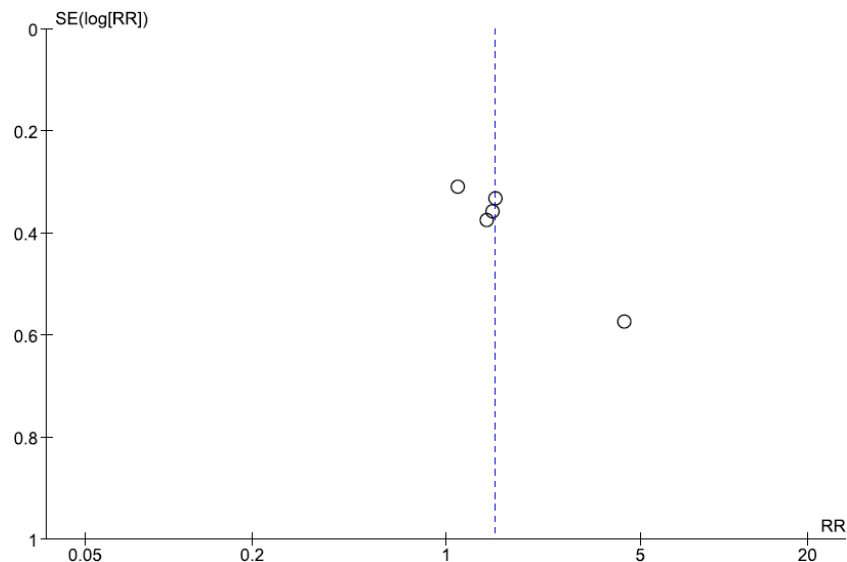
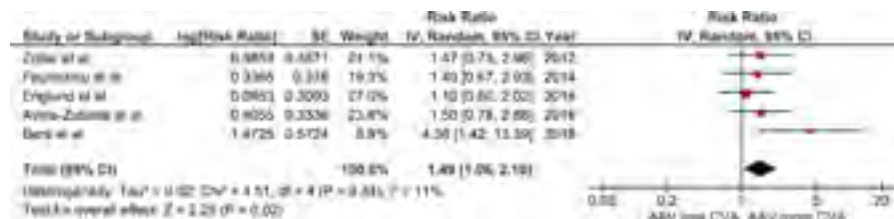
Session Title: Vasculitis – ANCA-Associated Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM **Increased Risk of Cerebrovascular Accident among Patients with Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis: A Systematic Review and Meta-analysis of Cohort Studies**

Abstract

Background/Purpose: An increased risk of cardiovascular disease, including cerebrovascular accident (CVA), among patients with chronic inflammatory immune-mediated disorders is well-recognized, especially among patients with rheumatoid arthritis and systemic lupus erythematosus. Patients with anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) may be at an increased risk of CVA as well although the data are still inconclusive as most studies addressing this association were small in size. The current systematic review and meta-analysis was conducted with the aims to identify all relevant studies and summarize their results together.



Methods: Two investigators independently searched for published studies indexed in MEDLINE and EMBASE database from inception to April 2018 using the search strategy that included the terms for anti-neutrophil cytoplasmic antibody-associated vasculitis and cerebrovascular accident. Eligible studies were cohort studies (either retrospective or prospective) that compared the risk of incident CVA between patients with AAV and individuals without AAV. They must also report the relative risk or hazard ratio with 95% confidence intervals (CI) of this comparison. Point estimates and standard errors from each study were extracted and combined together using the random effect, generic inverse variance technique of DerSimonian and Laird. Evaluation for publication bias was conducted using funnel plot.

Results: Of 1,132 retrieved articles, a total of 5 studies fulfilled the inclusion criteria and were included in this meta-analysis. The risk of incident CVA among patients with AAV was significantly higher than individuals without AAV with the pooled risk ratio of 1.49 (95% CI, 1.06–2.10). The statistical heterogeneity was insignificant with an I^2 of 11%. The forest plot of this meta-analysis is shown as figure 1. The funnel plot (figure 2) of this study was relatively symmetric and did not suggest the presence of publication although the interpretation was limited by the relatively low number of included studies.

Conclusion:: A significantly increased risk of cerebrovascular accident among patients with anti-neutrophil cytoplasmic antibody-associated vasculitis was observed in this study.

Figure 1: Forest plot of this meta-analysis

Figure 2: Funnel plot of this meta-analysis

Disclosure: P. Ungprasert, None; K. Wijarnpreecha, None; W. Cheungpasitporn, None.

Handgrip Strength Predicts the Risk of Bone Fracture and Severe Adverse Events in Patients with Systemic Necrotizing Vasculitis

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Session Information

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Sarcopenia, characterized by progressive loss of both muscle mass and muscle strength, has been associated with poor outcomes in various diseases. Muscle weakness is a major public health concern because it predicts future all-cause mortality and is associated with falls, disability, cardiovascular mortality and morbidity. However, its impact on systemic necrotizing vasculitides (SNVs) had never been characterized. We aimed to assess the frequency, associated factors and prognostic impact of sarcopenia in SNVs.

Methods: Patients with ANCA-associated vasculitides (AAVs) or polyarteritis nodosa (PAN) seen in our department were successively included in a longitudinal study assessing musculoskeletal parameters, cardiovascular complications and other sequelae (OSTEOVAS cohort). At inclusion, dual x-ray absorptiometry assessment skeletal muscle mass index (SMI) was obtained, and muscle strength was evaluated by handgrip strength measured with a handheld dynamometer. Handgrip strength is a simple method to assess muscle function in routine practice. Patients were prospectively followed and outcomes were recorded. Cumulative relapse, bone fracture, cardiovascular event, adverse event and mortality rates were analyzed.

Results: One hundred and twenty SNV patients were included (54 men, mean±SD age 53 ± 18 years, median SNV duration 54 months). Median follow-up was 42 months. At inclusion, 28 (23%) patients had low handgrip strength (<30 kg for men and <20 kg for women), but none exhibited low skeletal muscle mass index (<7.23 kg/m² for men and <5.67 kg/m² for women). At that time, low handgrip strength was significantly associated with: age ($P<0.0001$), type of vasculitis ($P=0.011$), Vasculitis Damage Index ($P=0.01$), prior falls ($P=0.0002$), osteoporosis ($P=0.036$), low serum albumin ($P=0.003$) and prealbumin ($P=0.0007$), high C-reactive protein ($P=0.001$), and low femoral neck bone-mineral density ($P=0.0002$), as were high Framingham risk score ($P=0.008$) and high fracture risk ($P=0.002$). During follow-up, 12 (10%) patients suffered bone fractures and 31 (26%) had vasculitis treatment-related severe adverse events. Low handgrip strength was associated (hazard ratio [95% CI]) with higher cumulative incident bone fracture rate (4.25 [1.37–13.2]; $P=0.012$) and severe adverse events (2.80 [1.35–5.81]); $P=0.006$) but not relapses or cardiovascular events.

Conclusion: Handgrip strength assessed in patients with AAVs and PAN was associated with nutritional status and comorbidities, eg bone disease, and predicted the risk of bone fracture and serious adverse events during follow-up. In contrast, the utility of skeletal muscle mass index assessment in this population remains uncertain.

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Clinical Characteristics and Outcomes of ANCA-Vasculitides Associated Renal Disease in a Multi-Ethnic Population from a County Hospital

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis – ANCA-Associated Poster II

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Session Time: 9:00AM-11:00AM

Background/Purpose: Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and renal-limited vasculitis (RLV). We aimed to study the clinical features and renal outcomes of ANCA vasculitides patients in a county hospital.

Methods: 37 consecutive patients with biopsy proven glomerulonephritis related to ANCA vasculitides were included to participate in the study. IRB approval was taken. Patients with minimum follow up of 6 months were considered to be eligible. Data was collected through retrospective medical chart reviews including on demographics, ANCA type and titers, other organ involvement, kidney biopsy findings, treatment received, baseline and follow up at creatinine at 6 months, and outcomes with respect to renal function, and death. Chi-square and t-tests were done to study correlates of crescentic glomerulonephritis, progression to ESRD and mortality.

Results: Mean (SD) age was 54 years (14) with 21 female and 16 male patients. Almost half of the patients (17/37; 46%) were of Hispanic origin (Table 1). Clinical diagnosis was MPA in 16/37 (43%) patients while 10/37 (27%) had GPA, and rest 11/37 (30%) had RLV. Serology was positive for pANCA in 22/37 (59.5%) patients and rest were cANCA positive (12/37; 32.4%). 36/37 (97.3%) patients had hematuria on their urinalysis with 12/37 (32%) having nephrotic range proteinuria (>3.5 g). 27/37 (73%) patients had crescents on kidney biopsy. Pulmonary involvement was seen in over 50% patients (19/37) with diffuse alveolar hemorrhage in 8/37 (21%). Most patients were treated with cyclophosphamide (35/37; 94.6%) with only 8/37 (21%) and 6/37 (16%) being treated with plasmapheresis and rituximab, respectively. Mean (95% CI) baseline and 6 month follow up creatinine were 4.93 (3.65 – 6.22) and 2.82 (1.95 – 3.69), respectively. Median (IQR) follow up was 22 (12-53) months. 10 out of 37 patients (27%) progressed to ESRD and needed dialysis. Mean time (SD) to progression to ESRD was 9.05 (5.08) months. Gender, ethnicity, ANCA type and titers did not predict crescentic glomerulonephritis on kidney biopsy. Crescentic glomerulonephritis did not predict progression to ESRD but correlated with mortality (P value 0.002). Degree of fibrosis on renal biopsy also did not correlate with progression to ESRD but predicted mortality (P value 0.03).

Conclusion: Crescentic glomerulonephritis was more common in this multi-ethnic population. Crescentic glomerulonephritis and degree of fibrosis on kidney biopsy did not predict progression to ESRD but correlated with mortality.

Table 1: Clinical characteristics and outcomes of ANCA related vasculitides associated renal disease

Age	54.40 ± 14.22 (Mean ± SD)
Gender	
Female	21/37 (56.8%)
Male	16/37 (43.2%)
Ethnicity	
Caucasian	6/37 (16.2%)
African American	7/37 (18.9%)
Hispanic	17/37 (45.9%)
Asian	4/37 (10.8%)
Other	3/37 (8.1%)
Diagnosis	
GPA	10/37 (27%)
MPA	16/37 (43%)
Isolated renal AAV	11/37 (29.7%)
Serology	
pANCA	22/37 (59.5%)
cANCA	12/37 (32.4%)
ANCA titer	104.07 ± 34.14 (Mean ± SD)
Urinalysis findings	
Hematuria	36/37 (97.3%)
Nephrotic range proteinuria	12/37 (32.4%)
Renal biopsy findings	

Crescentic glomerulonephritis	27/37 (73.0%)
Fibrosis	50%, 40-75% (Median, IQR)
Lung involvement	19/37 (51.4%)
Diffuse alveolar hemorrhage	8/37 (21.6%)
Treatment	
Plasmapheresis	8/37 (21.6%)
Cyclophosphamide	35/37 (94.6%)
Rituximab	6/37 (16.2%)
Renal outcomes	
Baseline creatinine	4.93 (3.65-6.22) (Mean, 95% CI)
Follow up creatinine (at 6 months)	2.82 (1.95-3.69) (Mean, 95% CI)
Progression to ESRD	10/37 (27.0%)
Mortality	3/37 (8.1%)

Disclosure: S. Arora, None; A. Athavale, None; P. Hart, None.

Abstract Number: 2732

Peripheral Neuropathy Is More Common in Microscopic Polyangiitis Than in Granulomatosis with Polyangiitis: Data from a Single Tertiary Referral Center

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis – ANCA-Associated Poster II

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Background/Purpose: Among many other organs and systems, ANCA-associated vasculitis (AAV) may also affect nervous system in up to more than half of patients, resulting in various central nervous system (CNS) disturbances and/or involvement of cranial or peripheral nerves. In the present study, we focused on pure peripheral neuropathy and aimed to compare the frequency of this problem between patients having microscopic polyangiitis (MPA) with those having granulomatosis with polyangiitis (GPA).

Methods: Medical charts of 48 patients with MPA and 58 patients with GPA, fulfilling relevant European Medicines Agency (EMA) classification algorithm, and being followed up by Ege University Hospital Rheumatology Department between 1997 and 2017 were retrospectively analyzed. Presence or absence of symptoms suggesting peripheral sensorial and/or motor neuropathy and electromyography (EMG) results were noted. Additional co-morbidities which may cause neuropathy such as diabetes mellitus were also noted. Patients with CNS problems and/or cranial nerve(s) involvement were

Table: Demographic and disease characteristics of patients with GPA and MPA

	GPA (n=58)	MPA (n=48)	P
Age at disease onset (years, mean ± SD)	46±12	63±10.8	0.001
Gender			
• Female (n, %)	73; 39.7	30; 62.5	0.019
• Male (n, %)	35; 60.3	18; 37.5	
Diabetes mellitus (n, %)	7; 12	18; 20.8	0.22
Mean follow up duration (months, mean ± SD)	61.5±48.9	42.5±39.6	0.045
Types of involvement			
• Renal involvement (n, %)	30; 65.5	36; 75	0.29
• Pulmonary involvement (n, %)	41; 71.7	38; 81.3	0.20
• Cutaneous findings (n, %)	15; 26.3	7; 14.6	0.14
• Musculoskeletal (n, %)	23; 39.7	21; 43.8	0.67
• Peripheral neuropathy (n, %)	7; 12.1	18; 37.5	0.002
ANCA positivity			
• c-ANCA (n, %)	45; 77.6	3; 6.3	<0.001
• p-ANCA (n, %)	9; 15.5	40; 96.8	<0.001

excluded. Descriptive analyses were given using mean \pm standard deviation (SD) for continuous variables and numbers (percentages) for categorical variables. Chi-square test was used to analyze differences between categorical data, while Mann-Whitney U tests were applied to test statistical differences between continuous data.

Results: Demographic features, mean follow up durations, types of clinical involvements, and ANCA status of the patients are given in Table. Patients with MPA were notable with being more frequently women and having older age of disease onset. Frequency of peripheral neuropathy in MPA (37.5%) was significantly higher than in GPA (12.1%). Peripheral neuropathy was in the form of axonal sensorimotor type in all patients, except for two cases with MPA having pure motor neuropathy. The frequency of diabetes in both groups was not statistically different. On the other hand, comparison of all patients with and without peripheral neuropathy showed that peripheral neuropathy group had older age of disease onset (60.88 ± 13.6 versus 51.7 ± 13.73 years, $p: 0.04$) and had more frequent musculoskeletal symptoms (39.7% versus 33.3%, $p: 0.02$).

Conclusion: Our data show that peripheral neuropathy is more frequent in patients with MPA compared to GPA. In literature, there are controversial reports about whether neuropathy is more frequent in GPA or in MPA. This may be due to genetic differences, as well as inclusion or exclusion of cases with central nervous system involvement and/or cranial neuropathy. Future studies with larger series will probably clarify this issue.

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Abstract Number: 2733

From a Myth to a Menace: Increased Disease Severity and Poor Outcomes in an Urban Cohort of African-American Patients with ANCA-Associated Vasculitis

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Background/Purpose: Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) is a systemic inflammatory disorder frequently associated with significant disability and morbidity, which may lead to end-stage renal disease (ESRD) or death. The purpose of our study was to examine disease characteristics and outcomes in an urban African-American (AA) cohort with AAV and compare them with a matched Caucasian (CA) cohort with AAV.

Methods: A detailed electronic chart review of patients with positive anti-neutrophil cytoplasmic antibody testing was performed to identify patients with AAV using the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Patients with isolated renal disease were included if they demonstrated biopsy evidence of necrotizing pauci-immune glomerulonephritis with P-ANCA/MPO or C-ANCA/PR-3 positivity at the time of diagnosis. African-American AAV patients were matched 1:2 to CA patients with AAV by gender and age within 5 years.

Results: 21 AA patients with AAV were identified, of which fourteen (66.7%) were female, with a mean age at diagnosis of 61 years. Microscopic polyangiitis occurred more commonly in AA patients than CA patients (38% vs. 14%), while granulomatosis with polyangiitis was more common in CA patients (76% vs. 47%). AA patients had more severe disease at the time of diagnosis, with increased need on admission for ICU care (50% vs. 23%, $p=0.04$), mechanical ventilation (40% vs. 10%, $p=0.007$), hemodialysis (52% vs. 19% $p=0.007$), with lower hemoglobin (mean 7.0 vs. 10.0, $p=0.001$), and higher serum creatinine (mean 6.1 vs. 2.7, $p=0.001$). Although the likelihood of receiving high dose pulse steroid therapy at diagnosis was not significantly different between groups, the mean dose of prednisone initiated at disease diagnosis in AA patients was significantly lower (143 mg vs. 455 mg, $p=0.004$), while the concomitant use of steroid-sparing immunosuppressive agents for induction therapy did not differ significantly between groups. There was a significant increase in the incidence of ESRD in AA patients when compared to CA patients (62% vs. 19%, $p=0.001$) without significant differences in the prevalence or severity of hypertension and diabetes at the time of diagnosis between groups. Death occurred in 33% of the AA patients and 21% of CA patients during follow up.

Conclusion: In an urban cohort, AA patients with AAV were more likely to present with severe disease requiring ICU care, mechanical ventilation, and hemodialysis compared to Caucasian patients with AAV. Despite similar rates and severity of diabetes and hypertension in these populations, African-American patients were significantly more likely to develop ESRD. There are many factors that could influence these outcomes, including other comorbid conditions, genetics, differences in treatment and response to immunosuppressive therapies, environmental factors, and limited access to care because of socioeconomic factors. Further study is needed to better understand factors that influence AAV severity and course in this population in order to improve long-term outcomes and survival.

Disclosure: K. Maksimowicz-McKinnon, None; P. McCarthy, None; S. Soman, None; J. McKinnon, None.

Abstract Number: 2734

The Effect of Age at Diagnosis on Mortality in ANCA-Associated Vasculitides

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Background/Purpose: Elderly patients with ANCA associated vasculitides (AAV) seem to have clinical differences compared to younger patients. The aim of this study is to compare clinical and laboratory characteristics, survival and mortality rates of patients with AAV with respect to age at diagnosis.

Methods: Medical records of patients with microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) or eosinophilic granulomatosis with polyangiitis (EGPA), classified according to the European Medicine Agency classification algorithm and followed up by Ege University Hospital Rheumatology Department between 1997 and 2017 were retrospectively analyzed. Patients were divided into two groups based upon age at disease onset: <65 years (Group 1) and ≥65 years (Group 2). Gender, age at diagnosis, time to diagnosis, follow up time, involved organs/systems, pattern of ANCA positivity, type of AAV and number of deaths were noted. Chi-square test, two-way t test, Cox regression analysis and Kaplan-Meier method were used to compare the groups.

Results: In our cohort, 87 patients <65 years and 30 patients ≥65 years were enrolled. Demographic, clinical and laboratory characteristics of those patients are given in Table. There were no differences in gender and smoking status

Table. Demographic, clinical and laboratory characteristics of patients with AAV

	Group 1 AAV <65 years (n=87)	Group 2 AAV ≥65 years (n=30)	p value
Female, n (%)	46 (52.9)	13 (43.3)	0.36
Age at diagnosis onset, mean±SD	53.46±11.5	73.37±5.59	<0.001
Follow-up, months, mean±SD	64.6±49.1	22.9±23.6	<0.001
Diagnostic delay, months, mean±SD	9.97±14.5	14.3±19.6	0.2
Type of AAV, n (%)			
MPA	24 (27.6)	24 (80)	<0.001
GPA	57 (65.5)	1 (3.3)	
EGPA	6 (6.9)	5 (16.7)	
ANCA positivity, n (%)			
p-ANCA	34 (39.5)	26 (86.7)	<0.001
c-ANCA	45 (52.3)	5 (16.7)	0.002
Initial involvement			
Constitutional	64 (73.6)	23 (76.7)	0.73
Renal	59 (67.8)	17 (56.7)	0.27
Pulmonary	62 (71.3)	25 (83.3)	0.19
Upper airway	33 (37.9)	1 (3.3)	<0.001
Skin	20 (23)	6 (20)	0.71
Neuropathy	17 (19.5)	14 (46.7)	0.004
Joint	33 (37.9)	17 (56.7)	0.04
Mortality, n (%)	6 (6.9)	7 (23.3)	0.01

between the groups, but the rates of malignancy, hypertension and hyperlipidemia were higher in Group 2. Upper airway involvement was more frequent in Group 1, peripheral neuropathy was more frequent in Group 2. These findings were probably due to more frequent occurrence of GPA in Group 1 and MPA in Group 2.

As expected, mortality rate was higher in Group 2 (Table). The mean survival time was 221 ± 7.47 months for Group 1, and 65 ± 8.14 months for Group 2. One-year, 2-years, 5-years and 10-years survival rates were 96%, 96%, 91%, and 91% in Group 1, respectively. On the other hand, one-year, 2-years and 5-years survival rates were 81%, 70% and 70% for group 2, respectively. Ten-years survival rates could not be calculated for Group 2. One death(1/6) in Group 1 and six deaths (6/7) in Group 2 were due to opportunistic infections.

Being diagnosed at the age of 65 years or over increased the mortality by 48.7 times compared to being diagnosed before the age of 65 years (%95 CI: 6.37-372.09, $p < 0.001$). We also found out that each increase of one year at the age of diagnosis resulted in an increment in the mortality 1.1 times (%95 CI: 1.03-1.18, $p: 0.003$). When age factor is removed, type of AAV, basal serum creatinine level and having GFR < 50 ml/min per 1.73 m^2 did not affect the mortality significantly.

Conclusion: In our study, the age at diagnosis was established to be the most significant factor on mortality of AAV. We found out that basal serum creatinine level and GFR did not affect the mortality critically, when adjusted by age. Because of the high mortality rate, more attention should be paid to the management of AAV patients diagnosed at advanced age.

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Abstract Number: 2735

Identifying ANCA-Associated Vasculitis Cases in Electronic Health Records Using Natural Language Processing

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Session Information

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Background/Purpose: Epidemiologic studies of ANCA-associated vasculitis (AAV) using large data sets are often limited by the lack of validated definitions of AAV cases that can be applied on a large scale. A prior study developed algorithms using billing codes, prescription records, and ANCA pattern (not antigen specificity) to classify patients into traditional clinical phenotypes (e.g., granulomatosis with polyangiitis, GPA) with PPV ranging from 81% to 100%. We sought to determine whether a user-friendly natural language processing (NLP) tool could improve the performance of AAV case-finding algorithms in an electronic health record (EHR) database.

Methods: Using EHR data on 2 million patients from a large, multi-center healthcare system that includes Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH), we evaluated the performance of algorithms that incorporated billing codes, ANCA antigen specificity test results, and/or NLP to identify patients with AAV. Unstructured data (e.g., pathology reports, clinical notes) were searched using NLP for key words and phrases suggestive of AAV. The NLP program eliminates reports where the search phrase is near a term that may negate a diagnosis of AAV (e.g., "the patient does not have ANCA-associated vasculitis"). To assess the performance (Positive Predictive Value, PPV) of each algorithm, a cohort of patients with and without AAV was identified from a population of 35,623 patients. We then evaluated the performance of each algorithm in randomly assembled cohorts of patients evaluated in rheumatology and nephrology clinics.

Results: The general AAV cohort used for primary validation was established from the entire population and included 207 patients, the majority of whom had AAV (N=161, 78%). This cohort included 25 patients (12.1%) with positive ANCA test results but without AAV. An algorithm solely using billing codes had a PPV of 79% (73%-84%), 18% (5%-40%), and 4% (0%-14%) for identifying cases of AAV in the entire EHR, a rheumatology clinic cohort, and nephrology clinic cohort, respectively (Table 1). An algorithm that required an NLP reference to AAV, a billing code associated with AAV, and a positive PR3- or MPO-ANCA test result led to a PPV of 95% (88%-98%), 100%, and 100%, respectively.

Conclusion: In our study, the use of NLP substantially improved the PPV of algorithms meant to identify cases of AAV. In the context of increasingly large data sources that include both structured (e.g., billing codes, test results) and unstructured data (e.g., clinical notes), NLP can improve the ability to accurately (PPV > 90%) classify patients with AAV. Furthermore, as ANCA type is increasingly viewed as a superior approach to differentiating AAV subtypes compared with clinical phenotypes (e.g., GPA), an algorithm such as ours that incorporate ANCA types can be useful for future epidemiologic studies in AAV using EHRs.

Table 1: Algorithm Performance in 207 Patients Selected based on ICD-9 Codes for ANCA-Associated Vasculitis

	Total Possible AAV Cases Identified by Algorithm in EHR	Positive Predictive Value (95% CI)
1. ICD-9 code	20,557	79% (73%-84%)
2. ICD-9 and ANCA-positive	1,951	88% (82%-92%)
3. NLP and ANCA-positive	898	92% (87%-98%)
4. NLP or ICD-9 and ANCA-positive	2,065	87% (80%-91%)
5. NLP and ICD-9 and ANCA-positive	775	95% (88%-98%)

Disclosure: Z. Wallace, None; J. H. Stone, Roche, 2, Roche, 5; H. K. Choi, Takeda, Selecta, Kowa, and Horizon, 5, Selecta and Horizon, 2.

Abstract Number: 2736

Value of Histology for Diagnosis and Classification in ANCA Associated Vasculitis

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Background/Purpose: Diagnosis of ANCA-associated vasculitis (AAV) and the classification of granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) is based on clinical and histologic characteristics. The value of renal and non-renal biopsies for classification of AAV is of great interest for the diagnostic work-up. We aimed to evaluate specific histopathologic features of organ biopsies and their contribution to the diagnosis of vasculitis and to the classification of specific AAV subgroups according to ACR criteria and to the preliminary 2017 DCVAS criteria.

Methods: Retrospective, single-center cohort study in patients with GPA, EGPA and MPA, who have received at least one organ biopsy. Characteristic histopathologic features were analyzed. Diagnosis of vasculitis and classification to subgroups were analyzed with and without consideration of histologic features.

Results: 306 patients (GPA 154, MPA 58, EGPA 94, mean age at diagnosis 55.2±16.5 years, 48% males) diagnosed between 1990-2017, were included. 451 biopsies (168 renal biopsies, 283 non-renal biopsies) were taken at active stage of AAV at initial diagnosis (n=415) or during disease-flair (n=36). 222 patients (72.5%) were ANCA positive (150 cANCA+, 72 pANCA+). In kidney biopsies, glomerulonephritis was described in 78.6%, unspecific inflammation in 26.8% and normal tissue in 1.2%. In non-renal biopsies, vasculitis, granuloma, tissue eosinophilia, unspecific inflammation or normal tissue were reported in GPA 32.9 / 29.4 / 21.2 / 71.8 / 9.4%, MPA 27.3 / 9.1 / 27.3 / 90.9 / 9.1% and EGPA 20.2 / 10.1 / 67.4 / 73.0 / 20.2%; p<0.0001. According to the ANCA status, the distribution was 31.1 / 25.2 / 28.3 / 68.9 / 10.7% in ANCA+ patients and 20.8 / 11.1 / 62.5 / 79.2 / 19.4% in ANCA- patients (p<0.0001). Biopsy results were decisive for diagnosis of vasculitis in 2% of GPA, none of MPA and 8% of EGPA patients. Fulfillment of 1990 ACR criteria depended on inclusion of histology in 6.6% of GPA and 35.5% of EGPA. For the preliminary 2017 DCVAS criteria, histology was decisive in 2% of GPA, 0% of MPA and 21% of EGPA.

Conclusion: Histologic proof of vasculitis contributes to diagnosis of AAV. The diagnostic value is most prominent for renal biopsies. While classification to EGPA according ACR criteria depends on histology in almost one third of patients,

it is critical for GPA in only a few patients. The relevance of biopsy for the preliminary 2017 DCVAS criteria is clearly diminished, remaining most prominent for EGPA.

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Abstract Number: 2737

Opportunistic Infections in Medium and Small-Sized Vessel Vasculitis: Based on a Retrospective study on 108 Patients

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Session Information

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Session Title: Vasculitis – ANCA-Associated Poster II

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Background/Purpose: Overall survival has been markedly improved during the last decades in systemic vasculitis. In contrast, the use of immunosuppressive agents led to an increased risk of infectious complications, ranging from common to opportunistic infections (OI). While the former have been well described, data on the latter are scarce. This study aimed to describe characteristics of patients having OI during systemic vasculitis.

Methods: We conducted a retrospective, observational, multicenter study, including patients with medium and small-sized vessel vasculitis according to Chapel Hill definitions and presenting with OI. Clinico-biological findings and therapies were recorded at diagnosis and follow-up of vasculitis and diagnosis of OI.

Results: A total of 108 patients (men 51%, mean age at infection 59.3±15.4 years), experiencing 132 OI between 1985 and 2018, were included. Twenty-five (19%) patients had multiple OI. Vasculitis diagnoses were: ANCA-associated vasculitis (AAV) in 86 (80%) patients, i.e. granulomatosis with polyangiitis in 51, microscopic polyangiitis in 18 and eosinophilic granulomatosis with polyangiitis in 17, polyarteritis nodosa in 10 (9%), and immune complex vasculitis in 12 (11%). Comorbidities included chronic kidney failure with eGFR <60 ml/min/1.73m² in 33 (31%), chronic respiratory disease in 22 (20%) and diabetes in 14 (13%). Before OI, 30 (28%) patients experienced 31 common infections. Treatments received before OI were glucocorticoids in 106 (99%) patients, cyclophosphamide in 75 (73%) with a median cumulative dose of 7.2 g (IQR 3.6-18), rituximab in 31 (32%), and both drugs in 14 (13%). Median interval from diagnosis of vasculitis to OI was 11 (3-62) months.

Opportunistic infections were: invasive fungal infections in 75 (including pneumocystis in 40, invasive aspergillosis in 19, severe candidiasis in 12, cryptococcosis in 4, mucormycosis in 1), viral infections in 30 (including cytomegalovirus in 24), bacterial infections in 24 (including tuberculosis in 12, atypical mycobacteria in 5, nocardiosis in 7), and parasitic infections in 3. OI were disseminated in 24 (18%) cases, and organ-limited in 108 (82%), the latter involving the lungs in 87 (81%).

At diagnosis of OI, patients were under glucocorticoids in 75%, at a median dose of 20 mg/day (5-50). Lymphopenia <1000/mm³ was noted in 34%, with a median CD4 T cell count of 226/mm³(143-578), respectively, and hypogammaglobulinemia <6 g/L in 31%. Only 5 patients with pneumocystis infection had prophylaxis.

OI required hospitalization in intensive care unit in 24 (18%) and led to death in 19 (14%). Among all death (n=37), OI were the leading cause of death (51%).

Twelve OI (9%) were diagnosed concomitantly to a vasculitis flare, and OI led to a modification of immunosuppressive therapy in 42% of cases, mainly through a decrease of immunosuppression.

Conclusion: Opportunistic infections mainly occur during AAV, especially granulomatosis with polyangiitis receiving high doses of glucocorticoids. Pneumocystis was the most frequent infection, followed by cytomegalovirus infection and invasive aspergillus. Prognosis was severe, with high number of patients requiring ICU and/or dying.

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Abstract Number: 2738

A Randomized Phase 3 Trial Evaluating the Safety and Efficacy of Avacopan in Patients with New or Relapsing Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

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Session Information

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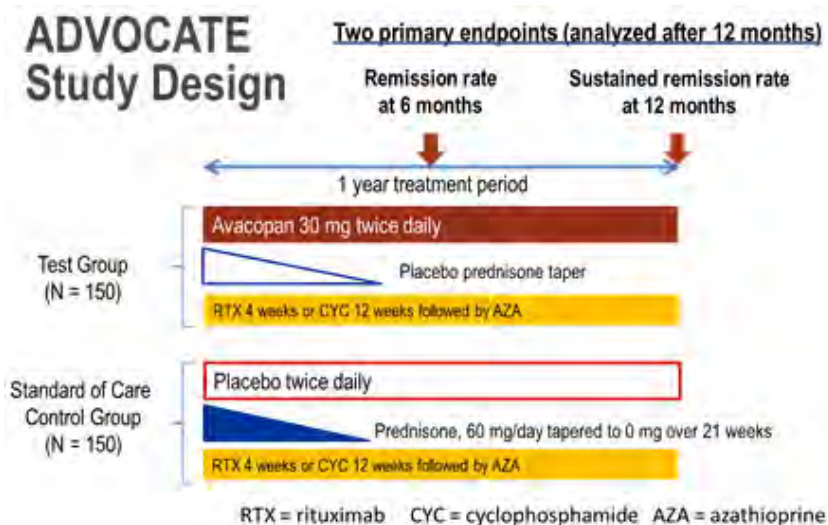
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM **A Randomized Phase 3 Trial Evaluating the Safety and Efficacy of Avacopan in Patients with New or Relapsing Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis**

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Background/Purpose: Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) is a potentially life-threatening systemic autoimmune disease characterized by relapses and remissions. Treatment to induce remission usually includes high-dose glucocorticoids in combination with rituximab (RTX) or cyclophosphamide (CYC), followed by less intensive treatment to prevent relapse. The overall burden of disease remains high, with progressive organ system damage and morbidity attributable to therapy. High-dose glucocorticoids are associated with increased risk of infection, metabolic syndrome, bone loss, and an overall negative impact on health-related quality of life (HRQoL). There is a need for less toxic treatment alternatives for AAV. Avacopan (previously CCX168) is a novel, orally bioavailable, highly-selective



antagonist of the human C5a receptor that has demonstrated promising efficacy and a favorable safety profile when administered for 12 weeks in Phase 2 studies of patients with active AAV (NCT0136388 and NCT0222155).

Methods: The ongoing ADVOCATE trial (NCT02994927) is a double-blind, parallel-arm, active-comparator randomized trial comparing avacopan vs. high-dose glucocorticoids in patients (age ≥ 12 years) with AAV, when co-administered with either 1) RTX OR 2) CYC followed by azathioprine or mycophenolate mofetil, for up to 1 year (**Figure**). The choice of RTX vs CYC is based on investigator judgement. Patients are stratified by: i) intended use of RTX vs CYC, ii) ANCA type (PR3-ANCA vs MPO-ANCA), and iii) newly-diagnosed vs relapsing disease.

The primary trial endpoints are 1) the proportion of patients in remission at week 26 based on BVAS=0 (Birmingham Vasculitis Activity Score) and not taking glucocorticoids; and 2) the proportion of patients who sustain remission from week 26 through week 52. HRQoL will also be assessed in patients through 52 weeks which will add to the understanding of the patient experience in AAV. Other endpoints include adverse events, requirement for rescue medication, markers of renal disease, the Glucocorticoid Toxicity Index, and the Vasculitis Damage Index.

Results: Planned enrollment is ~300 patients from 230 sites in 20 countries, and is expected to be completed in mid-2018. Details of the study design, outcome measures, and baseline patient data will be presented.

Conclusion: The ADVOCATE trial is unique in seeking to advance a nearly glucocorticoid-free induction regimen for AAV and has the potential to have a substantial impact on the approach to treatment of this rare disease.

Disclosure: P. A. Merkel, Bristol-Myers Squibb, 2, ChemoCentryx, 2, 5, Genentech, Inc., 2, 5, InnfaRx, 5, Inmed, 5, AbbVie Inc., 5, CaridianBCT, 2, 5, GlaxoSmithKline, 2, 5, Kypha, 2, Kiniksa, 5, Boehringer-Ingelheim, 2, 5; D. Jayne, ChemoCentryx, GlaxoSmithKline, Sanofi, Roche, 2, Boehringer-Ingelheim, Astra-Zeneca, AbbVie, CSL, InflaRx, Bristol-Myers Squibb, Takeda, 5, Aurinia, 6; T. J. Schall, ChemoCentryx, 1, 3, 4; P. Bekker, ChemoCentryx, 1, 3; J. Hillson, ChemoCentryx, 1, 3, Bristol-Myers Squibb, 1.

Abstract Number: 2739

Systemic Vasculitis: Incidence of Glucocorticoid Related Adverse Events

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Background/Purpose: The glucocorticoid toxicity index (GTI) (Miloslavsky et al. Ann Rheum Dis 2017) is useful to assess impact on morbidity associated with these drugs. It consists of two components, a compound and a specific index. This last includes serious clinical adverse effects.

Our objective was to assess the incidence of the items included in the specific index of the GTI in patients with Giant Cell Arteritis (GCA), Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA).

Methods: Clinical records of incident cases of GCA, GPA, MPA were scanned for serious adverse effects associated with GC treatment defined in the specific index of GTI over the first two years of treatment. The GC cumulative dose was calculated at 6 months, 1 year, and 2 years of treatment.

Incidence density of serious adverse effects was compared in patients with GCA (all fulfilling ACR criteria) and ANCA associated vasculitis (GPA and MPA, all fulfilling Chapel Hill criteria). Logistic regression multivariate analysis was performed to evaluate the association between total cumulative GC dose and severe adverse effects, adjusted by confounders.

Results: 130 patients were included (92 ACG, 18 GPA, 20 MPA), 80% of whom were women, with a median age at diagnosis of 77 years (ICR 72-81).

Cumulative GC doses at 6 months, 1 and 2 years of treatment were significantly higher in ANCA vasculitis. 97,4 % (IC 95% 82,9-99,6) of patients with ANCA vasculitis used immunosuppressors associated with GC at treatment start vs 14,1% (IC 95 8,3-22,9) of patients with GCA ($p<0,001$). Immunosuppressors usage in patients with GCA did not conduct to a lower cumulative GC dose at 2 years of treatment. 15 patients with ANCA vasculitis (39,5%, IC 95%: 25,1-55,9) and 36 with GCA (39,1%, IC 95%29,6-49,6) presented some serious adverse effect included in the GTI ($p=0,97$).

The adverse effect incidence density was 22,2/100 patients-year for ANCA and 19,9/100 patients-year for GCA (p=0,73). Severe infections were more frequent in patients with ANCA vasculitis than in GCA [13,2% (IC 95%: 5,4-28,4) vs 2,2% (IC 95%: 0,5-8,4), p=0,01]. Mortality was 28,9 % (IC 95%: 16,6-45,5) for ANCA vasculitis vs 3,3% (IC 95%: 1-9,8) for GCA (p<0,001). Having a severe adverse effect or a serious infection was not associated with the GC cumulative dose, the initial GC dose, GC pulses, cyclophosphamide use, and diagnosis in the multivariate analysis. The greater cumulative GC dose was associated with having ANCA vasculitis diagnosis (p=0,019) and having received GC pulses (p<0,001) in the linear regression analysis.

Conclusion: Incidence of GC related adverse effects at 2 years of treatment was similar in ANCA associated vasculitis and GCA. Presenting a serious adverse effect was not associated with the total cumulative or initial GC dose, or having received GC pulses. Serious infection rate was greater in ANCA vasculitis with no relation to the GC dose.

	GCA (n=92)	GPA and MPA (n=38)	p
Age, years, median (RIC)	77 (73-80)	75 (65-82)	0.15
Female sex, % (IC 95)	81,5 (72,1-88,3)	76,3 (59,9-87,4)	0.5
Follow up time, years, median (ICR)	12,4 (8,3-15,2)	10 (7,4-12,9)	0.08
Initial meprednisone oral dose, mg/day, median (ICR)	40 (30-40)	40 (40-60)	0.07
GC pulses, %, (IC 95%)	18,5 (11,7-27,9)	78,9 (62,8-89,3)	<0.001
Cumulative meprednisone dose, mg, median (RIC):			
● At 6 months	5010 (3660-6315)	6952(5280-8730)	<0.001
● At 1 year	6510 (5040-8325)	7790 (6975-9930)	0.01
● At 2 years	7440 (6240-10260)	9482 (8025-11200)	0.02
Initial associated immunosuppressor at baseline, % (IC 95%)	14,1 (8,3-22,9)	97,4 (82,9-99,6)	<0.001
Severe GC related adverse effects, % (IC 95%):			
Hypertensive emergency	0 (0)	2,6 (0,3-17,1)	0.12
Reversible posterior encephalopathy	0	0	---
Pathological fractures/avascular osteonecrosis	5,43 (2,3-12,5)	0	0.14
Severe reduction in BMD	9,9 (5,2-18,1)	2,6 (0,3-17,1)	0.16
Diabetic retinopathy /Diabetic Neuropathy/Diabetic Nephropathy	0	0	---
Severe cutaneous toxicity	0	0	---
Severe Myopathy	1,1 (0,1-7,5)	0	0.52
Psychosis	2,2 (0,5-8,4)	2,6 (0,3-17,1)	0.87
Severe Infection	2,2 (0,5-8,4)	13,2 (5,4-28,4)	0.01
Adrenal Insufficiency	1,1 (0,1-7,5)	0	0.52
Gastrointestinal Perforation	0	0	---
Gastrointestinal ulcers	0	0	---
Tendon ruptures	0	0	---
Cataracts	21,7 (14,4-31,5)	23,7 (12,6-40)	0.81
Retinopathy	1,1 (0,1-7,5)	0	0.52
Glaucoma	2,2 (0,5-8,4)	0	0.36
Obesity	1,1 (0,1-7,5)	5,3 (1,3-19,3)	0.15
Some severe adverse effect, % (IC 95%)	39,1 (29,6-49,6)	39,5 (25,1-55,9)	0.97
Mortality, % (IC 95%)	3,3 (1-9,8)	28,9 (16,6-45,5)	<0.001
Severe adverse effect incidence density at 2 years, in 100 person-year	19,9	22,2	0.73

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Abstract Number: 2740

Clinical and Laboratory Characteristics of ANCA-Associated Vasculitis in Pediatric and Young Adult Patients: A Retrospective Review

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Background/Purpose: ANCA-associated vasculitis (AAV) is a heterogeneous group of small-vessel vasculitides that typically affects the kidneys, respiratory tract, and other organ systems. The onset of AAV may occur at any age, although literature suggests that this is more common in older populations. We aim to characterize the clinical and laboratory

	Age < 18		18 < Age < 35		35 ≤ Age < 65		Age ≥ 65	
	MPO	PR3	MPO	PR3	MPO	PR3	MPO	PR3
Total Number	7	6	4	14	36	31	26	17
Female	6	4	3	6	20	14	18	7
White	7	6	3	12	34	30	25	16
Renal Involvement	6	5	3	11	26	25	24	10
Hematuria	6	5	2	8	25	21	22	8
Proteinuria	4	3	3	9	21	20	19	9
Glomerulonephritis by renal biopsy	2	1	3	3	14	5	12	2
ANA	2	2	3	2	12	8	14	5
Ear, Nose, and Throat	0	0	0	3	5	5	2	2
Respiratory	2	3	1	4	15	14	11	4
Arthritis	3	0	0	1	1	3	1	0

manifestations of AAV based on age of onset in pediatric and adult patients younger than 35 years, compared to other age groups.

Methods: We performed a retrospective chart review of all patients with positive MPO or PR3 lab results by ELISA and a diagnosis of vasculitis from 2000 to 2017. Patients were classified into four groups according to age and divided into two groups each depending on MPO or PR3 serotypes. These features were compared to one another through descriptive statistics, as noted in the included table.

Results: 141 patients were identified based on the inclusion criteria, of which 31 were below the age of 35. The majority of patients were white females. Upper respiratory tract involvement and arthritis were much more common in the pediatric and adults younger than 35. PR3 was also more frequent in this group as well. Renal and lower respiratory involvement were comparable between the age groups.

Conclusion: Onset of AAV in young adulthood has distinct characteristics that more closely resemble pediatric AAV than compared to their older counterparts. Prior literature demonstrates a much higher percentage of extrarenal, extra-respiratory involvement in the pediatric population, which is consistent in our sample as well. Further analysis on clinical presentation, prognosis and treatment outcomes are forthcoming.

Disclosure: M. Swee, None; M. Suneja, None; M. Gill, None; B. Kumar, None.

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Candidate Biomarkers in ANCA-Associated Vasculitis Identified Using a Proteomic Approach

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Background/Purpose: Concentrations of many circulating proteins are elevated during severe, active ANCA-associated vasculitis (AAV). Finding biomarkers associated with milder disease, a more clinically relevant need, has proved challenging. In addition, some biomarkers may be directly affected by glucocorticoids.

Methods: 30 patients with AAV participating in a longitudinal cohort were studied. Serum samples from 2 visits were used for this study: i) a visit during active disease and when off prednisone; and ii) a visit approximately 3 months later when in clinical remission and on prednisone. A proteomic approach (SOMAscan, SomaLogic, Boulder, CO, USA) was used to assess more than 1000 circulating proteins simultaneously. Using Wilcoxon signed rank tests, a randomly selected sub-cohort of 15 patients was analyzed first, and markers significant at $p < 0.01$ were then analyzed in the remaining sub-cohort of 15 patients, with $p < 0.05$ regarded as validation. WebGestalt was used to test for enrichment in components of functional pathways.

Results: The cohort included 23 patients with GPA, 5 with EGPA, and 2 with MPA. Mean age was 52, and 18 were female. Thirteen were taking a non-steroid immunosuppressive drug at the time of flare, and 21 afterward. Disease activity was relatively low: physician global assessment of severity on a 0-10 scale had a mean of 3.2 (median 3, range 1-7), and only 7 patients had a “major” manifestation by BVAS/WG. Fourteen proteins were validated as associated with active disease (**Table 1**). Few of these markers have been previously identified in vasculitis, and only one (thrombospondin, TSP) in AAV. Four markers (CCL3/Mip-1a, CCL15/Mip-5, TNFRSF9/4-1BB, prolactin) are associated with the KEGG pathway Cytokine-cytokine receptor interaction.

Conclusion: In a cohort of patients with active but relatively mild AAV, 14 serum proteins were associated with significant change after successful treatment with prednisone. Thirteen of these markers have not been reported in AAV. These proteins, all of which are measurable by commercial immunoassays, are candidates for further study in real-world cohorts of partially-treated patients with AAV with mildly active disease.

Table 1. Protein biomarkers in active ANCA-associated vasculitis

Protein	Discovery (n=15)		Validation (n=15)	
	Fold-change*	p-value	Fold-change*	p-value
Prolactin	1.17	0.002	1.12	<0.01
CCL15/MIP-5	1.26	<0.001	1.20	<0.01
RET	0.77	0.004	0.77	0.02
PAPP-A	0.58	0.007	0.70	0.02
SERPINA7	0.91	0.005	0.92	0.02
TSP4	0.69	<0.001	0.74	0.02
FAP/Seprase	0.87	0.002	0.87	0.02
Siglec-9	0.89	0.007	0.87	0.02
TNFRSF9/4-1BB	0.89	0.002	0.96	0.03
Factor B	0.85	0.002	0.88	0.04
REG4	1.2	0.004	1.12	0.04
CD200R1	0.86	<0.001	0.93	0.04
ADAM12	0.91	0.002	0.94	0.04
CCL3/MIP1a	0.83	0.003	0.92	0.05

* Fold change (mean) calculated by dividing post-treatment by pre-treatment values; values <1 indicate higher concentrations in active disease.

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Rituximab Versus Cyclophosphamide for Vasculitic Neuropathy: A Patient Reported Outcomes Study

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Background/Purpose: Vasculitic neuropathy (VN) is a major complication of systemic vasculitis and contributes to morbidity, functional limitation, and health care utilization in affected patients. Patient reported outcomes (PRO) in patients with VN is limited. Our aim was to compare long term PRO for neuropathic symptoms in patients with VN undergoing induction treatment with rituximab(RTX) or cyclophosphamide (CYC).

Methods: The medical record was screened by keywords for patient charts that included vasculitis and neuropathy. Diagnosis of granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, or isolated VN was confirmed per ACR classification criteria or 2012 Revised International Chapel Hill Consensus Nomenclature. VN diagnosis was confirmed independently by a neurologist reviewing clinical presentation, EMG findings,

Table 1. Baseline patient characteristics and clinical features of patients with vasculitic neuropathy treated with rituximab or cyclophosphamide.

	Total N=41	Rituximab N=10	Cyclophosphamide N=31	p-value
Gender				0.12 ^a
Male	20(48.8)	7(70.0)	13(41.9)	
Female	21(51.2)	3(30.0)	18(58.1)	
Diagnosis				0.14 ^b
GPA	16(39.0)	6(60.0)	10(32.3)	
MPA	4(9.8)	2(20.0)	2(6.5)	
EGPA	16(39.0)	2(20.0)	14(45.2)	
Neuropathy only	5(12.2)	0(0.0)	5(16.1)	
BVAS	8.0[6.0,10.0]	7.5[4.0,9.0]	8.0[7.0,10.0]	0.50 ^c
Age at diagnosis, years	56.9±11.7	58.8±16.2	56.2±10.1	0.55 ^d
Neurologic presentation				0.75 ^b
Motor	1(2.4)	0(0.0)	1(3.2)	
Sensory	9(22.0)	3(30.0)	6(19.4)	
Motor and sensory	31(75.6)	7(70.0)	24(77.4)	
Affected limb				
UE	1(2.4)	0(0.0)	1(3.2)	0.99 ^b
LE	24(58.5)	7(70.0)	17(54.8)	0.40 ^a
UE and LE	16(39.0)	3(30.0)	13(41.9)	0.50 ^a
Duration from onset to follow-up, months	68.0[41.0,105.0]	39.5[30.0,56.0]	90.0[60.0,123.0]	0.002^c

Data presented as Mean ± SD, Median [interquartile range], or N (column %).

p-values. a=Pearson's chi-square test, b=Fisher's Exact test, c=Kruskal-Wallis test, d=ANOVA

GPA, granulomatosis with polyangiitis, MPA, microscopic polyangiitis, EGPA, eosinophilic granulomatosis with polyangiitis, BVAS, Birmingham Vasculitis Activity Score; UE, upper extremity; LE, lower extremity

Table 2: Patient reported outcomes and adverse events in patients with vasculitic neuropathy treated with rituximab or cyclophosphamide

	Total N=41	Rituximab N=10	Cyclophosphamide N=31	p-value
Outcome Measures				
CAP-PRI Total Score	7.9±5.7	10.1±5.3	7.1±5.8	0.16 ^a
VAS of self-perceived improvement in symptoms	76.0[25.0,90.0]	30.0[0.0,80.0]	80.0[49.0,90.0]	0.13 ^b
ODSS				
UL and LL	2.0[1.00,3.5]	5.0[3.0,7.0] [†]	2.0[1.00,3.0] [‡]	0.039 ^c
LL only	1.0[0.50,2.0]	1.0[0,1.0] [†]	1.0[1.0,2.0] [‡]	0.17 ^c
Adverse events				
Serious infection	10(24.4)	1(10.0)	9(29.0)	0.22 ^c
Malignancy	0(0.0)	0(0.0)	0(0.0)	
Serious infusion related	0(0.0)	0(0.0)	0(0.0)	

Data presented as mean ± SD, Median [interquartile range] or frequency (column %).

p-values: a=ANOVA, b=Kruskal-Wallis test, c=Pearson's chi-square test.

†p<0.05, ‡p<0.05.

CAP-PRI, chronic acquired polyneuropathy patient reported index, VAS, visual analog scale, ODSS, Overall Disability Sum Score, UL, upper extremity, LL, lower extremity.

and nerve biopsy. Patient with neuropathy secondary to other etiologies were excluded. Data including treatment regimen, affected limb, Birmingham Vasculitis Activity Score (BVAS), and duration of follow up was collected. Patients were invited to participate in a survey utilizing validated, neuropathy-specific PRO. Outcomes of interest were Chronic Acquired Polyneuropathy-Patient Reported Index score (CAP-PRI), a visual analog scale of self-perceived improvement in symptoms (VAS), and Overall Disability Sum Score (ODSS). Comparisons between treatment groups were performed with ANOVA, Kruskal-Wallis test, Pearson's chi-square test, or Fisher's exact test as appropriate. Multiple regressions were performed to control for disease duration, BVAS, and affected limb.

Results: Sixty-four patients with VN were sent PRO surveys. Survey response rate was 64% (n=41, 25% RTX, 75% CYC). Baseline patient characteristics, clinical features, and specific vasculitis diagnoses are listed in Table 1. No significant differences between treatment groups were seen in CAP-PRI (p=0.16) or VAS (p=0.13) (Table 2). There was no difference between treatment groups for ODSS (p=0.17) in patients with only lower extremity involvement. In patients with both upper and lower extremity involvement, patients treated with RTX had higher disability by ODSS at follow up (p=0.039), though small sample size limits interpretability. Multivariable analyses did not reveal significant differences in CAP-PRI, VAS, or ODSS in the two treatment groups after adjustment.

Conclusion: Overall, no significant differences in PRO were found in patients with VN treated with RTX compared to CYC. Prospective studies could help validate these findings.

Disclosure: A. Patel, None; K. Byram, None; Y. Jin, None; A. Wu, None; Y. Li, None; L. H. Calabrese, Bristol-Myers Squibb, 5, 8, Genentech, Inc., 5, 8; R. A. Hajj-Ali, None.

Abstract Number: 2743

Favorable Efficacy of Rituximab in ANCA-Associated Vasculitis Patients with Excessive B Cell Differentiation

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis – ANCA-Associated Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: B cell depletion by rituximab (RTX) is effective treatment for ANCA-associated vasculitis (AAV). However, the phenotype of peripheral B cells and the selection criteria for RTX in AAV remain unclear. We assessed the correlation between B cell phenotype and clinical outcome of RTX therapy in AAV patients.

Methods: All AAV patients who were introduced to remission induction therapy were registered for immunophenotyping-analysis using multi-colour flow cytometry. Phenotypic characterization of the circulating T cells and B cells were defined by 8-color flow cytometric analysis for “Human Immunology Project” termed by NIH/FOCIS in 58 AAV patients (18 GPA and 40 MPA). Based on the judgement by physicians who do not know the result of immunophenotyping-analysis, the patients were considered suitable to receive immunosuppressive drugs (conventional immune suppressants group; n=28) or RTX (RTX group; n=30). All patients also received high dose glucocorticoids (GC). We assessed the phenotype of circulating T cells and B cells, the correlation between these lymphocytes and clinical findings in active AAV and evaluated the efficacy and safety outcomes at 6 months after treatment. Definition of clinical improvement was a reduction of 50% or more in BVAS in vital organs without relapse.

Results: The proportions of naïve CD4⁺ T cells was higher, while that of central memory CD4⁺ T cells was lower, in AAV patients than healthy control (HC). Higher proportions of IgD⁺CD27⁺ B cells and lower proportions of IgM memory B cells, were found in AAV patients compared with HC. The proportion of IgD⁺CD27⁺ or class-switched memory B cells was increased in 23 out of 58 patients (40%) compared with HC. The rate of improvement in BVAS negatively correlated with the proportion of naïve B cells and positively correlated with that of IgD⁺CD27⁺ B cells. There was no correlation between the proportion of CD4⁺ T cell-phenotype and the rate of improvement. Twenty nine out of 30 patients (97%) in RTX group achieved clinical improvement. Among 28 patients in conventional immune suppressants group (including 20 intravenous cyclophosphamide and 8 azathioprine), 23 patients (82%) achieved clinical improvement. There was no significant difference in the rate of improvement, relapses, serious adverse events between the two treatment groups. The rate of clinical improvement in patients with excessive B cell differentiation was significantly lower than in patients without excessive B cell differentiation. In the patients with excessive B cell differentiation, the rates of survival, improvement in BVAS and GC reduction were significantly higher in RTX group than in conventional immune suppressants group at 6 months after treatment.

Conclusion: The presence of excessive B cell differentiation was associated with treatment resistance. However, in the patients with excessive B cell differentiation, RTX was effective and showed rapid effect of GC tapering and higher survival rate compared to conventional immune suppressants. The results suggested that multi-color flow cytometry might be useful for the selection of RTX therapy in AAV patients.

Disclosure: Y. Miyazaki, None; S. Nakayamada, Bristol-Myers, UCB, Astellas, Abbvie, Eisai, Pfizer, Takeda, 8, Mitsubishi-Tanabe, Novartis and MSD, 2; S. Kubo, Bristol-Myers, Pfizer, and Takeda, 8; K. Nakano, UCB, Astellas, Mitsubishi-Tanabe, 8, Mitsubishi-Tanabe and Eisai, 2; S. Iwata, None; S. Fukuyo, None; A. Kawabe, None; Y. Tanaka, Daiichi-Sankyo, Astellas, Pfizer, Mitsubishi-Tanabe, Bristol-Myers, Chugai, YL Biologics, Eli Lilly, Sanofi, Janssen, UCB, 8, Mitsubishi-Tanabe, Takeda, Bristol-Myers, Chugai, Astellas, Abbvie, MSD, Daiichi-Sankyo, Pfizer, Kyowa-Kirin, Eisai, Ono, 2.

Abstract Number: 2744

Giant-Cell Arteritis: Is Glucocorticoid-Sparing Treatment Still Relevant? a Retrospective Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Giant-cell arteritis (GCA) is the most common primary large-vessel vasculitis affecting patients over 50 yr. Despite frequent and severe adverse events (AEs), glucocorticoids (GCs) are the reference treatment.¹ In 2003, Proven et al reported GC-related AEs in 86% of their patients.² Efficacy of immunosuppressants, specifically methotrexate, is modest. Although tocilizumab is emerging as an alternative agent, the long-term benefit of IL6 blockade is unknown. Moreover, application of the most recent recommendations on GC-induced osteoporosis or vaccinations might change the GC-associated risks and, thus, the risk/benefit balance needs to be updated. We evaluated the GC-induced frequencies of AEs in a French cohort of GCA patients.

Methods: This retrospective study was conducted in 2 French hospitals. GCA was diagnosed between May 2009 and March 2018, based on ACR criteria or the diagnostic criteria used in the GIACTA trial. GC-associated AEs and prophylaxis against infection, osteoporosis and gastrointestinal bleeding were recorded at each outpatient consultation.

Results: The cohort comprised 89 women and 27 men; median age 73 [IQR 67–79] years. The median number of ACR criteria met/patient was 3 [IQR 3–4]. Temporal artery biopsies were positive for 63% and 34% had imaging-revealed aortitis. All took GCs for a median duration of 22 [IQR 18–32] months, with tapering to 5 mg/day achieved after 10 [IQR 8–14] months. At the end of follow-up, 36 patients (31%) were still taking GCs. Among the other 69% who had stopped GCs after 21.5 [IQR 18–28] months, 13 relapsed. Median follow-up was 29 [IQR 19.5–47] months (369 patient/years). Patients were also taking bisphosphonates (79%), calcium (79%), vitamin D (87%) and/or proton-pump inhibitors (51%) and 36% had been vaccinated against pneumococci and/or flu. AEs occurred in 66 (57%) patients, including bone fractures in 22%, diabetes mellitus onset in 1%, gastrointestinal bleeding in 1%, hypertension in 10%, infections in 10%, and cataract(s) in 7%. Thirty-seven (32%) patients received GC-sparing therapy: methotrexate for 32, tocilizumab for 10 and azathioprine for 1; those agents were mainly initiated at the time of relapses/flares (49%).

Conclusion: GC-related AEs were less frequent in this cohort of GCA patients than Proven's cohort, perhaps explained by measures taken to prevent them or our study's retrospective design. Although alternative options to GC are important, the exact place of new therapies should also take into account better prevention of GC-related AEs.

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2. Proven A et al. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. *Arthritis Rheum* 2003;49:703–8.

Disclosure: S. Perrineau, None; R. Paule, None; P. Charles, None; M. GAYRAUD, None; B. Terrier, None; L. Guillemin, None; L. Mouthon, None; A. Régent, None.

Abstract Number: 2745

Clinical and Serological Outcomes of Patients with Giant Cell Arteritis Treated with Tocilizumab or Abatacept As Steroid-Sparing Agents

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: At least 2 biological therapies [tocilizumab (TCZ) and abatacept (ABA)] have been proven to be effective in the management of Giant cell arteritis (GCA) in randomized controlled trials. Nevertheless, their use as steroid sparing agents might need further investigation.

Methods: We included GCA patients who were treated with TCZ, both intravenous (IV) and subcutaneous (SC), and/or ABA SC (8 mg/kg/month, 162mg/week, and 125 mg/week respectively). Complete response to the treatment was defined as

a clinical and serological remission after 12 months of therapy; partial response as clinical or serological remission after 12 months.

Results: This study included 33 GCA patients [mean age 74, females 63%, mean follow-up 44±34 months]. *Figure 1* resumes the characteristics of the GCA patients included in the study. Twenty-eight patients out of 33 (85%) received one biologic agent. Five patients (15%) needed a therapeutic switch (one patient from TCZ to ABA, and 4 patients from ABA to TCZ). Patients were treated as follow: 9 with TCZ IV, 11 with TCZ SC, and 18 with ABA. Among the TCZ IV group, all patients experienced a response (57% complete response, and 43% partial response). Among the TCZ SC group, 83% experienced a response (67% complete response, and 16% partial response). Among the ABA group, 86% experienced a response (36% complete response and 50% partial response). After 12 months of therapy, 100% of patients in TCZ groups, both IV and SC, and 64% of ABA group were treated with low doses of oral prednisone (≤ 7.5 mg/day) as maintenance. We noticed a significant reduction of inflammatory parameters [C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)] after 12 months of therapy with TCZ [TCZ IV group: mean baseline CRP (mg/dl) 1.9 ± 2.3 , mean CRP after 12 months of therapy 0.3 ± 0.2 ; mean baseline ESR (mm/h) 58.1 ± 25.6 , mean ESR after 12 months 9.5 ± 4.2 ; TCZ SC group: mean baseline CRP 4.5 ± 3.8 , mean CRP after 12 months 0.2 ± 0.2 ; mean baseline ESR 51.9 ± 27 , mean ESR after 12 months 6.5 ± 6]. When compared to standard GC regimen, in patients treated with TCZ, both IV and SC, we estimated a median steroid-sparing effect quantifiable in 30 mg/daily in the first month and an overall steroid-sparing effect of 15 mg/daily when assessed in 12 months.

Characteristics of patients included in the study

	Total number of patients (33)	%
Demographic characteristics		
Female/Male	21/12	
Age (years) (mean, SD)	73.6 ± 8.7	
Clinical characteristics at the onset of GCA		
Fever (n)	12	36.4
Fatigue (n)	18	54.5
Headache (n)	28	84.8
Scalp tenderness (n)	8	24.2
Jaw claudication (n)	15	45.4
Vision loss (n)	16	48.5
PMR (n)	11	33.3
Diagnosis		
Biopsy proven	27/32	84.4
PET positivity	12/29	41.4
Eco-color-doppler positivity	30/31	97
GC therapy		
Previous methylprednisolone pulses (n)	7	21.2
Oral prednisone (n)	33	100
Dose of oral prednisone (mg/day) (mean, SD)	49.7 ± 15.1	
Previous immunosuppressive therapies		
Methotrexate (n)	11	33.3
Mean dose (mg/week) (mean, SD)	15.6 ± 1.7	
Mycophenolate (n)	6	18.1
Mean dose (g/day) (mean, SD)	2.2 ± 0.4	

Conclusion: This study confirms the efficacy of biological therapies in the management of CGA. Besides, in our experience TCZ allowed a significant reduction of GCs use, especially in the first month of therapy, when compared to standard GCs-based regimens.

Disclosure: D. Rossi, None; I. Cecchi, None; E. Rubini, None; M. Radin, None; S. Sciascia, None; D. Roccatello, None.

Abstract Number: 2746

Tocilizumab Monotherapy for Large Vessel Vasculitis: Results of 104-Week Treatment of a Prospective, Single-Center, Open Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

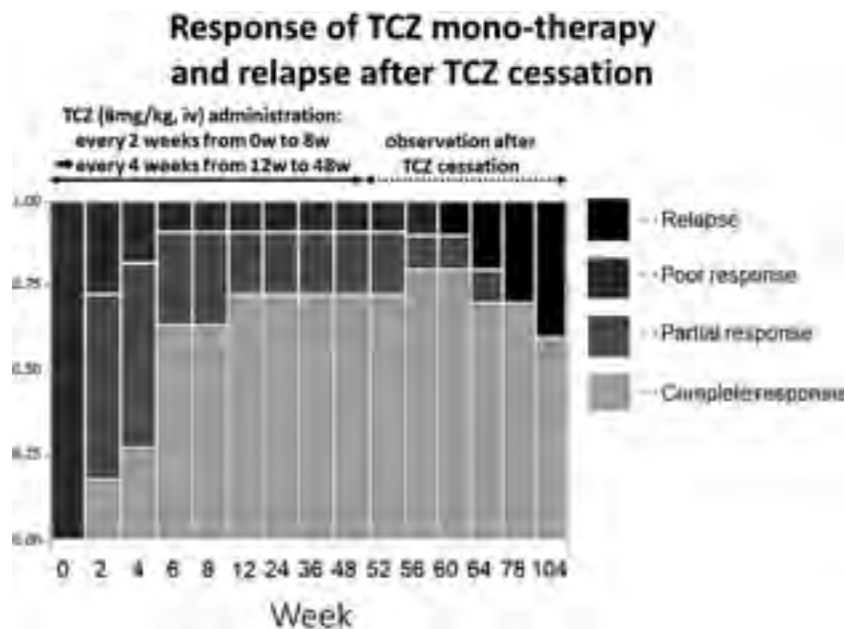
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To evaluate the efficacy and safety of tocilizumab (TCZ) monotherapy for Large Vessel Vasculitis (LVV), including Takayasu arteritis (TAK) and Giant cell arteritis (GCA).

Methods: Twelve LVV patients (4 TAK patients and 8 GCA patients) who had been newly diagnosed at our hospital from January 2013 to May 2016 were enrolled in a prospective, open-label study. TCZ (8mg/kg) was administered intravenously every 2 weeks for the first 2 months and every 4 weeks for the next 10 months (total 15 times) without any corticosteroid (CS) or immunosuppressants (IS). Patients were followed for another 1 year after last TCZ administration without any treatment. The efficacy was assessed by clinical symptoms (fever, headache, fatigue, etc.) and CRP level. Complete and partial response (CR and PR) was defined as disappearance or improvement of all clinical symptoms due to vasculitis and normalization of CRP ($<0.3\text{mg/dl}$). Poor clinical response was defined as patients who did not satisfy the criteria of CR/PR. Relapse of the disease was defined as the worsening or recurrence of clinical symptoms, increase of CRP attributable to activity of vasculitis, or initiation of CS and/or IS.

Results: The mean age was 58.9 y/o, the mean disease duration was 3.4 months, mean CRP was 6.0 mg/dl at the diagnosis of the LVV. Efficacy of the TCZ monotherapy in active LVV was assessed in 11 patients, since 1 TAK patient chose not to participate in the study at week 2. Although 1 GCA patient had TCZ withdrawal due to heart failure at week 24, there were no other serious adverse events. LOCF (Last Observation Carried Forward) method was utilized to fill the missing data. Relapse after TCZ cessation was assessed in 10 patients who completed week 52. CR and PR rate were 73%/18% at



week 24, and were maintained at week 52. Relapse occurred in 4 out of 10 patients (40%), although 60% completed week 104 after TCZ cessation. Response and relapses at each visit are summarized in figure 1.

Conclusion: This is the first study to show the effectiveness of merely IL-6 signal blockade in LVV patients, which could help us to understand the crucial role of IL-6 in the pathogenesis of LVV. TCZ monotherapy showed high response rate as an induction therapy for newly diagnosed LVV patients, and some of the patients did not require maintenance therapy after TCZ cessation. TCZ monotherapy might be an acceptable strategy as induction therapy for active LVV patients.
<Figure 1>

Disclosure: S. Saito, None; A. Okuyama, None; Y. Okada, None; A. Shibata, None; R. Sakai, None; K. Chino, None; T. Kurasawa, None; T. Kondo, None; H. Takei, None; K. Amano, None.

Abstract Number: 2747

Leflunomide and Methotrexate in Treatment of Giant Cell Arteritis: Comparison of Efficacy, Safety and Drug Survival

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Methotrexate (MTX) and leflunomide (LEF) are used as adjunct immunosuppressants and corticosteroid sparing agents in treatment of Giant Cell Arteritis (GCA), but the efficacy is poorly investigated. The aim of this study was to compare efficacy, safety and drug survival between MTX and LEF in the treatment of GCA.

Methods: During 2007-2017 all patients diagnosed with GCA at the Department of Rheumatology were included in a hospital-based retrospective study. All patients receiving MTX and/or LEF due to insufficiency and/or adverse effects of treatment with Prednisolone were identified. Duration of treatment, causes of discontinuation and changes in Prednisolone dose, Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were registered. Concomitant myalgia and/or polymyalgia rheumatica (PMR) and large vessel involvement (LVI) (involvement of aorta and its primary and secondary branches) were noted. Remission was defined as doctor's opinion of clinical remission and a Prednisolone dose ≤ 5 mg/day. Baseline Prednisolone dose and CRP values were unevenly distributed between the groups. Therefore the effect in patients with a Prednisolone dose >7.5 mg at start of treatment were analyzed separately, interpreted as a group of patients with higher disease activity. Student-t test was used to compare means and Chi-square test to compare categorical variables. All statistical analyses were performed using the SPSS statistical package version 23.

Results: 216 patients (70.4% women) were included (mean age 72.9 at time of diagnosis). Twenty-seven and 24 patients started treatment with LEF and MTX, respectively. During the treatment-period, the observed mean reduction in Prednisolone dose, ESR and CRP did not differ significantly. No significant difference between LEF and MTX in treatment duration to achieve remission/still on treatment was found ($p=0.19$). For patients with higher disease activity (Prednisolone >7.5 mg), this difference was significant favoring LEF ($p=0.02$). In the same group, a non-significant difference was found in the time to discontinuation due to adverse effects ($p=0.13$). There were no differences in the number of adverse effects in the treatment groups, most of them mild and well known.

Conclusion: To our knowledge this is the first study to compare LEF and MTX in the treatment of GCA. Patients treated with LEF achieved remission earlier than MTX, and this difference was significant in patients with higher disease activity ($p=0.02$). We found no difference in tolerability and reduction in ESR and CRP after 6 months of treatment between the groups.

Disclosure: S. Tengesdal, None; G. Myklebust, None.

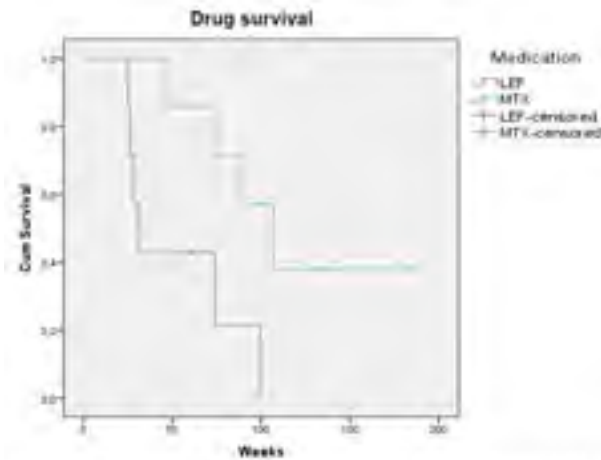


FIGURE 1: Patients with Prednisolone dose >7.5mg at start of treatment of LEF (n=7) or MTX (n=7). Treatment duration in weeks (mean, 95%CI) for achieving remission or still on treatment (censored). LEF: 48.4 (22.4 – 76.4); MTX: 104.9 (64.0 – 145.7).

TABLE 1

	Lefturamide	Methotrexate	P values
Basic characteristics			
Cases	27	34	
Mean age (95% CI)	70.6 (66.5 – 75.0)	68.9 (60.6 – 77.1)	p=0.23
Myalgia and/or PMR (n)	11 (40.7%)	12 (50.0%)	p=0.51
Large vessel involvement (n)	17 (63.0%)	13 (54.2%)	p=0.52
Time from diagnosis to start* (weeks) (95% CI)	65.6 (43.8 – 87.4)	48.2 (24.9 – 71.6)	p=0.27
Initial drug dose (of LEF or MTX respectively)	10.7 mg/day	10.7 mg/week	
Mean prednisolone dose at start* (mg) (95% CI)	12.3 (8.3 – 16.3)	16.9 (11.2 – 22.7)	p=0.17
Mean baseline CRP value* (mg/L) (95% CI)	14.6 (8.7 – 20.5)	20.0 (11.1 – 28.9)	p=0.29
Mean baseline ESR value* (mm/h) (95% CI)	23.8 (17.6 – 30.1)	31.0 (21.7 – 40.2)	p=0.16
Results:			
	Mean (95% CI)	Mean (95% CI)	
TD (weeks) before achieving remission/still on treatment*	56.4 (28.4 – 84.4) (n=8)	66.4 (45.7 – 127.1) (n=9)	p=0.19
TD (weeks) before discontinuation due to adverse effects	30.4 (14.1 – 46.6) (n=14)	40.4 (2.0 – 78.9) (n=10)	p=0.56
Prednisolone >7.5mg*:			
TD (weeks) before achieving remission/still on treatment	48.4 (22.4 – 76.4) (n=7)	104.9 (64.0 – 145.7) (n=7)	p=0.02
TD (weeks) before discontinuation due to remission	47.5 (14.4 – 80.6) (n=6)	79.3 (38.8 – 119.7) (n=4)	p=0.13
TD (weeks) before discontinuation due to adverse effects	32.8 (8.6 – 37.0) (n=12)	53.3 (-2.4 – 106.9) (n=7)	p=0.13
Reduction in dose of Prednisolone (mg) **	6.3 (2.0 – 10.6)	10.4 (5.0 – 15.8)	p=0.22
ESR decrease after 6 months (mm/h)	0.7 (-8.6 – 10.1)	7.4 (-9.5 – 24.4)	p=0.47
CRP decrease after 6 months (mg/L)	10.4 (3.4 – 17.5)	10.6 (-1.8 – 22.9)	p=0.96

TD: Treatment duration

*at time starting treatment with LEF or MTX

** From start to discontinuation of LEF or MTX.

Abstract Number: 2748

Giant Cell Arteritis in Treatment with Tocilizumab. Evolution of Vascular FDG Uptake on PET/CT

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Session Information

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Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

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Background/Purpose: Giant cell arteritis (GCA) is a large-vessel vasculitis which can involve the aorta and/or its major branches. Tocilizumab (TCZ) seems to be effective in giant cell arteritis (GCA) (1-4). Our aim was to assess if the clinical and analytical improvement yielded in patients with GCA treated with TCZ is accompanied by a reduction of the vascular inflammation evaluated by PET/CT.

Methods: Study of 36 patients who had a baseline and follow-up PET/CT from a multicenter series of 134 patients with GCA in treatment with TCZ. The evolution of the vascular involvement objectified by PET/CT was assessed. In addition, clinical efficacy, analytical improvement (acute phase reactants) and the reduction of corticosteroid dose was studied.

Results: The 36 patients (28 women and 8 men) had a mean age of 69.8±8.6 years. After TCZ onset, a rapid and maintained clinical improvement was observed (TABLE). In addition, during the first twenty-four months of follow-up, C-reactive protein decreased from 2.4 [0.9-6.8] to 0.1 [0.0-0.5] mg / dL and the erythrocyte sedimentation rate from 41.5 [16.7-58.5] to 4 [2-12.5] mm/1st hour. On the other hand, the levels of haemoglobin experienced an increase from 12.3 [11.3-13.0] to 13.3 [13.0-13.9] g/dL. The median dose of prednisone decreased from 12.5 [9.4-26.2] to 0.0 [0.0-0.0] mg/day. However, the decrease in F18-fluorodeoxyglucose uptake in the PET/CT study was not as evident, reaching a complete improvement in PET/CT uptake in 7 (20%) patients at 24 months of follow-up.

Conclusion: Although TCZ seems to be an important therapeutic agent in the treatment of GCA, achieving a rapid and sustained clinical and analytical improvement, the decrease in vessel inflammation assessed by F18-fluorodeoxyglucose uptake seems to take a slower course.

	Baseline	Month 6	Month 12	Month 18	Month 24
Clinical improvement n, (%)					
Complete		28/35 (80)	24/27 (88.9)	21/22 (95.4)	17/18 (94.4)
Partial		5/35 (14.3)	3/27 (11.1)	1/22 (4.5)	1/18 (5.5)
No improvement		2/35 (5.7)	0 (0)	0 (0)	0 (0)
Laboratory markers, median [IQR]					
ESR	41.5 [16.7-58.5] (36)	4 [2-8] (35)	4.5 [2-12] (28)	5 [2.5-11] (23)	4 [2-12.5] (19)
CRP	2.4 [0.9-6.8] (36)	0.1 [0.0-0.7] (33)	0.3 [0.1-0.6] (27)	0.1 [0.1-0.5] (23)	0.1 [0.0-0.5] (18)
Dose of corticosteroids (mg/day), median [IQR]	12.5 [9.4-26.2] (36)	5 [1.2-5.0] (33)	0.0 [0.0-2] (28)	0.0 [0.0-2.5] (21)	0.0 [0.0-0.0] (19)
Improvement in PET/CT					
Complete		0/8 (0)	3/21 (14.3)	6/32 (18.75)	7/36 (19.4)
Partial		6/8 (75)	12/21 (54.3)	19/32 (59.4)	21/36 (58.3)
No improvement		2/8 (25)	6/21 (28.6)	7/32 (21.9)	8/36 (22.2)

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Clinical and Anatomical Correlation in Patients with Polymyalgia Rheumatica By 18F-FDG PET/TC. Study of 75 Patients from a Single Referral Center

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Background/Purpose: Polymyalgia rheumatica (PMR) is an inflammatory disease characterized by pain and stiffness of the neck, shoulder and pelvic girdles. It can also be accompanied by other non-specific symptoms such as inflammatory low back pain, diffuse lower limb pain and constitutional syndrome. ¹⁸F-FDG PET /CT has been proposed as a promising tool for characterizing the anatomical affection of PMR but it remains unknown if there is a correlation between clinical symptoms and ¹⁸F-FDG uptake.

Objectives: Our aim was to assess if the localization of pain of patients with PMR correlates with ¹⁸F-FDG uptake in the corresponding region.

Methods: Study of 75 patients with PMR and their respective PET/CT scans from a referral center. PMR was diagnosed according to 2012 EULAR/ACR criteria. All PET/CT images were evaluated qualitatively by two experienced nuclear medicine physician.

TABLE

Clinical manifestation/location of FDG uptake	F FDG uptake		P
	Positive, n/N (%)	Negative, n/N (%)	
Shoulder girdle pain (n=40)			
Shoulder	27/45 (60.0)	13/30 (43.3)	0.16
Sternoclavicular joints	22/33 (66.7)	18/42 (42.9)	0.04
Cervical interspinous bursae	6/9 (66.7)	34/66(51.5)	0.49
Neck pain (n=12)			
Shoulder	8/45 (17.8)	4/30 (13.3)	0.61
Cervical interspinous bursae	2/9 (22.2)	10/66 (15.5)	0.63
Pelvic girdle pain (n=42)			
Hips	23/32 (71.8)	19/43 (44.2)	0.02
Lumbar interspinous bursae	18/29 (62.1)	24/30 (80.0)	0.40
Subtrochanteric bursae	11/20 (55.0)	31/55 (56.4)	0.92
Isochial tuberosities	10/19 (52.6)	32/58 (55.2)	0.73
Pubic symphysis	3/4 (75.0)	32/71 (45.1)	0.63
Inflammatory low back pain (n=20)			
Hips	10/32 (31.3)	10/43 (23.3)	0.44
Lumbar interspinous bursae	10/29 (34.5)	10/46 (21.7)	0.22
Isochial tuberosities	3/19 (15.8)	17/56 (30.4)	0.26
Subtrochanteric bursae	7/20 (35.0)	13/55 (23.6)	0.33
Pubic symphysis	3/4 (75.0)	17/71 (23.9)	0.06
Diffuse lower limb pain (n=35)			
Knees	16/33 (48.5)	19/42 (45.2)	0.78
Subtrochanteric bursae	8/20 (40.0)	27/55 (49.1)	0.49
Isochial tuberosities	9/19 (47.4)	26/56 (46.4)	0.94
Hips	15/32 (46.9)	20/43 (46.5)	0.98

Results: We evaluated 75 patients (27 men/48 women); mean age \pm SD of 68.2 \pm 0.7 years. A PET/CT was performed in all of them. Pattern of F-FDG uptake in patients with different clinical manifestations are summarized in the **TABLE**. Twenty-two out of thirty-three patients (66.7%) with ^{18}F -FDG uptake in sternoclavicular joints had shoulder girdle pain. Twenty-three patients of thirty-two patients (71.8%) with ^{18}F -FDG uptake in hips had pelvic girdle pain. The remaining localizations of ^{18}F -FDG uptake in PET/CT scans did not show significant correlations with clinical symptoms.

Conclusion: In patients with PMR, clinical manifestations do not always correlate with the anatomic allocation of ^{18}F -FDG uptake. Only, the presence of shoulder girdle pain seems to correlate with ^{18}F -FDG uptake in sternoclavicular joints and pelvic girdle pain with ^{18}F -FDG uptake in hips.

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Utility of Methotrexate in Polymyalgia Rheumatica

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Session Information

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Polymyalgia rheumatica (PMR) is a frequent inflammatory condition in patients over 50 years old. Nearly 60% of patients experience relapses of the symptoms during steroids tapering and steroids dependency is frequent. There is a need to find other therapeutic options to avoid the risks of long term steroid treatment. Methotrexate (MTX) use in PMR has been studied with contradictory results regarding reduction of relapses. Our objective was to evaluate the efficacy of MTX to reduce relapses and recurrences in patients with PMR.

Methods: This is an observational longitudinal cohort study. We included 94 consecutive patients with PMR fulfilling EULAR/ACR 2012 criteria. Clinical symptoms, laboratory results, treatment received and disease course information were extracted from the medical records.

Patients were assigned to 3 groups according to the treatment prescribed by the treating physician. Group 1: treated with steroids alone, group 2: treated with steroids initially and MTX following a relapse or recurrence and group 3: treated with steroids and MTX from diagnosis.

Definitions:

- Relapse: recurrence of symptoms and an increase of erythrocyte sedimentation rate (ESR) or C reactive protein (CRP) in patients still receiving steroids.
 - Remission: time of discontinuing prednisone.
 - Recurrence: recurrence of the original symptoms and an increase of ESR or CRP after discontinuing prednisone.
- We studied predictors of relapse in the total population. To evaluate MTX effect, patients from group 2 were analyzed comparing outcomes during the first period with corticosteroids alone with the second period with steroids and MTX.

Results: Ninety four patients were included, 77.6% women, mean age 75.6 years old (SD 8.1). The median time of follow up was 21.3 months (IQR 11.7-56.2).

Patients were assigned to one of 3 groups according to their treatment: 53 (56.4%) were treated only with steroids (group 1), 33 (35.1%) received initially steroids and later on MTX (group 2) and 8 (8.5 %) had steroids and MTX from diagnosis (group 3). Table 1 shows a comparison between groups.

We found a tendency of ESR to predict relapses (p 0.07) in the total population.

In group 2, we identified 35 relapses during the period of treatment with steroids alone and only 8 relapses during the period of combined treatment (p 0.0001). MTX reduced the dose of corticosteroids used and reduced the time to remission in this group of patients (Table 2).

Table 1

	GROUP 1	GROUP 2	GROUP 3
N	53	33	8
One relapse, n (%)	12 (22.6)	28 (84.8)	4 (50)
More than 1 relapse, n (%)	3 (5.6)	11 (33.3)	2 (25)
Time to the first relapse, months, median (IQR)	9.2 (6.7-10.7)	8.6 (6-14.9)	21.5 (9.6-92.8)
Remission, n (%)	20 (37.7)	14 (42.4)	3 (37.5)
Time to remission, m (IQR)	12.9 (11.8-21.6)	21.2 (15-25.2)	13.3 (12.4-99.8)
Duration of remission, m (SD)	1.8 (0-15.2)	6.6 (2.8-17.6)	19.5 (4.4-40.5)
Recurrence, n (%)	4 (7.5)	11 (33.3)	0 (0)
Total dose of steroids, g, mean (SD)	3.7 (4.8)	5.6 (3.3)	12 (14.6)

Table 2

	pre MTX	post MTX	p
Relapses, n	35	8	0.0001
Time to first relapse, months, median (ICR)	13.2 (6.4-16.8)	9.2 (6.2-17.4)	0.12
Time free of relapse, months, median (ICR)	8.6 (5.3-14.9)	7.5 (4.6-17.4)	0.25
Dose of steroids at first relapse, mg/day, mean (SD)	5.1 (2.3)	3 (1.5)	0.02
Remission, n	7	9	0.73
Time to remission, months, median (ICR)	22.9 (18.1-30.1)	8.7 (7-12.2)	0.01
Duration of remission, months, mean (SD)	14.7 (17.4)	13.9(20.9)	0.53
Recurrences, n	7	4	0.36

Conclusion: The use of MTX in PMR patients who already had a relapse reduces the number of future relapses and reduced the time to achieve remission. Starting MTX allowed a reduction of corticosteroids dose.

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Effects of Baseline Prednisone Dose on Remission and Disease Flare in Patients with Giant Cell Arteritis Treated with Tocilizumab in a Phase 3 Randomized Controlled Trial

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Session Information

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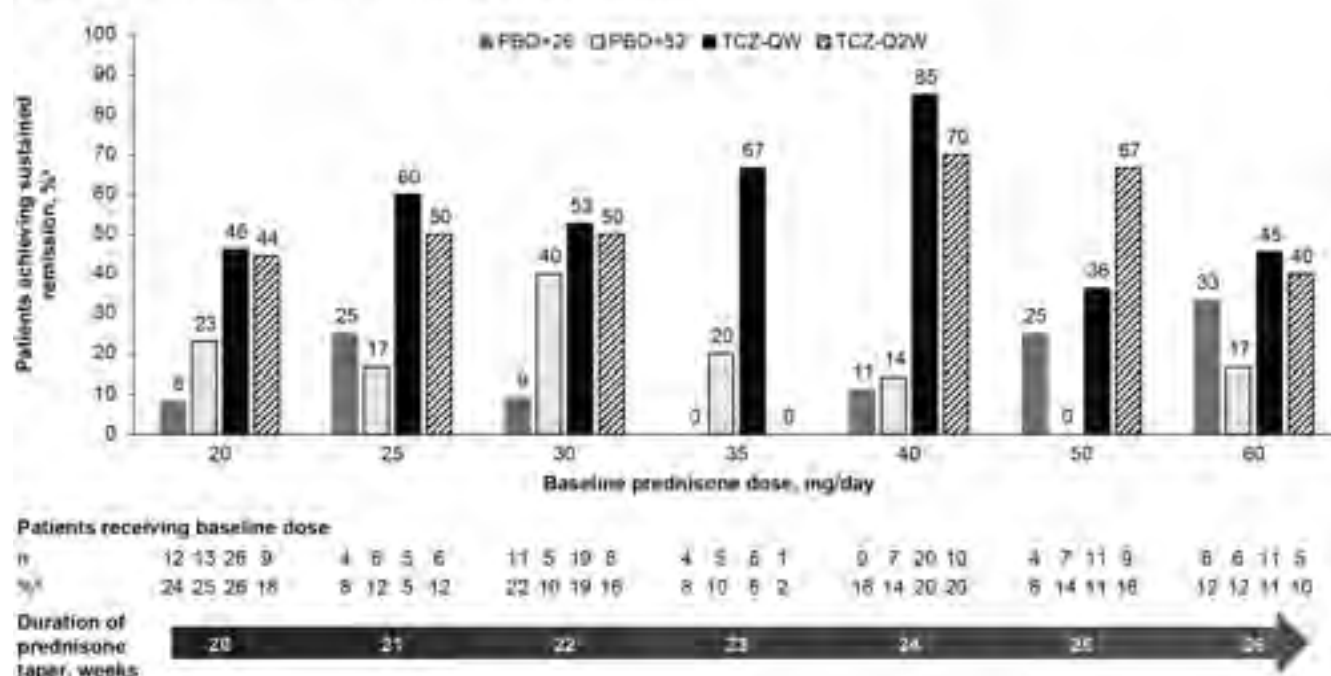
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Adding tocilizumab (TCZ) to tapered prednisone treatment for patients (pts) with giant cell arteritis (GCA) leads to improved rates of sustained glucocorticoid-free remission.¹ It is not known, however, whether the glucocorticoid dose at initiation of TCZ affects disease control. We investigated sustained remission and disease flare according to baseline (BL) prednisone doses in pts with GCA treated with TCZ or placebo (PBO) and scheduled prednisone tapering in the GiACTA trial.¹

Methods: Pts received TCZ-weekly or-every-other-week + 26-week prednisone taper (TCZ-QW [n=100] or TCZ-Q2W [n=49]) or placebo + 26-week or 52-week prednisone taper (PBO+26 [n=50] or PBO+52[n=51]) for 52 weeks.¹ Flare was defined as recurrence of GCA signs/symptoms and/or ESR ≥ 30 mm/h attributable to GCA requiring increased prednisone

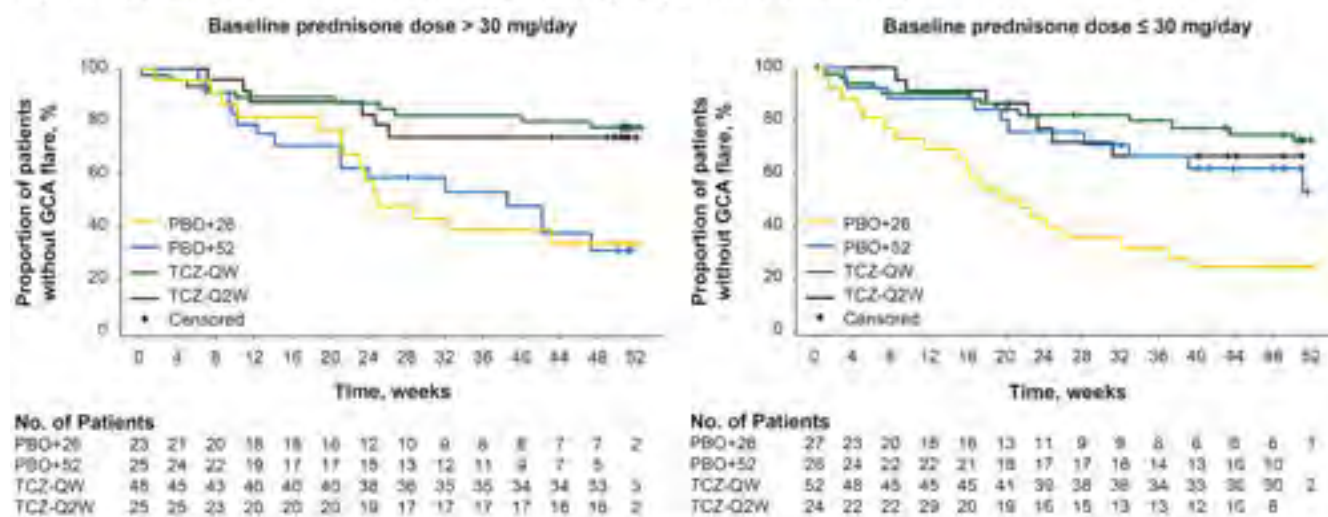
Figure 1. Sustained remission at week 52 according to BL prednisone dose



¹Percentages based on number of patients receiving BL dose

²Percentages based on total number of patients in each treatment group at BL

Figure 2. Kaplan-Meier analysis of time to first GCA flare according to high or low BL prednisone dose.



Randomization was stratified by baseline prednisone dose (>30 mg/day and ≤30 mg/day).

Patients never in remission were censored at day 1 and patients who withdrew from the study before week 52 were censored from the time of withdrawal.

	Baseline dose >30 mg/day				Baseline dose ≤30 mg/day			
	PBO+26	PBO+52	TCZ-QW	TCZ-Q2W	PBO+26	PBO+52	TCZ-QW	TCZ-Q2W
Pts who flared, n (%)	14 (60.9)	15 (60.0)	10 (20.8)	6 (24.0)	20 (74.1)	10 (38.5)	13 (26.0)	7 (29.2)

dose. Sustained remission was defined as absence of flare, normalization of CRP (<1 mg/dL), and adherence to the protocol-defined prednisone taper to week 52. All pts received prednisone during screening at a dose selected by the investigator before entry to the trial at BL. In this post hoc analysis, sustained remission rates were assessed according to BL prednisone dose and time to first flare was assessed according to protocol-defined BL prednisone dose stratification factors (>30 mg/day or ≤30 mg/day). All analyses are descriptive.

Results: Sustained remission was achieved by higher proportions of pts in the TCZ groups than the PBO groups across the range of BL prednisone doses (Figure 1). Figure 2 shows Kaplan-Meier analysis of time to flare. Among pts with high BL prednisone doses (>30 mg/day), TCZ-treated pts had longer time to flare than pts in the PBO groups. Pts with low BL prednisone doses (≤30 mg/day) had separation between the TCZ groups and the PBO+26 group from week 12, with longer time to flare in the TCZ and PBO+52 groups than in the PBO+26 group. In the PBO+26 group, pts with low BL prednisone doses flared earlier than pts with high BL doses, but there was no apparent difference in time to flare between high and low BL prednisone dose for the TCZ groups.

Conclusion: Pts with GCA treated with TCZ and prednisone tapering could achieve sustained remission across a range of BL prednisone doses. Fewer pts in the TCZ groups than the PBO groups had GCA flares. Time to flare was similar for pts treated with TCZ regardless of starting prednisone dose. *Reference:* 1. Stone JH et al. *N Engl J Med.* 2017;377: 317-328. *Acknowledgment:* GfACTA investigators. Medical writing: Sara Duggan, PhD, funded by F. Hoffmann La-Roche Ltd.

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Tocilizumab in Giant Cell Arteritis. National Multicenter Study of 134 Patients of Clinical Practice

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

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Background/Purpose: Tocilizumab (TCZ) has showed efficacy in randomized clinical trials in Giant cell arteritis (GCA).Data were of selected patients including many GCA of recent onset. In addition, TCZ route (IV or SC) and

concomitant corticosteroid dose were not established. To assess the efficacy and safety of TCZ in an unselected largest series of GCA in clinical practice.

Methods: Retrospective, open label multicenter study on 134 patients from 40 national referral centers with GCA in treatment with TCZ due to lack of efficacy and/or unacceptable adverse events of previous therapy.

Results: 134 (101 women) patients; mean age, 73.0±8.8 years. Before TCZ and besides steroids, 98 (73.1%) patients also received immunosuppressive agents. The median [IQR] time from GCA diagnosis was 13.5 [5.0-33.5] months. After 1 month of TCZ, 93.9% showed clinical improvement. It was observed a decrease in: a) CRP from 1.7 [0.4-3.2] to 0.11 [0.05-0.5] mg/dL ($p<0.0001$), b) ESR from 33[14.5-61] to 6 [2-12] mm/1st hour ($p<0.0001$), c) anemia from 16.4% to 3.8% ($p<0.0001$). This improvement was maintained reaching prolonged remission at 55.5%, 70.4%, 69.2% and 90% at 6, 12, 18 and 24 months respectively. Improvement in ^{18}F -FDG uptake in PET-TAC occurred slower, and complete resolution was observed in 0%, 14.3%, 18.7% and 19.5% cases at 6, 12, 18 and 24 months respectively. The most relevant side-effects were serious infections (10.6/100 patients-year), associated to higher doses of prednisone during the first three months of TCZ.

Conclusion: TCZ leads to a rapid and maintained improvement in refractory GCA, regardless TCZ route, GCA duration and prednisone dose. Serious infections were higher than in clinical trials. With TCZ a maximum dose of prednisone of 15 mg with rapid reduction is advisable.

	Baseline n= 134	Month 1 n= 132	Month 3 n= 122	Month 6 n= 99	Month 12 n= 71	Month 24 n= 39	Month 48 n= 10
Clinical improvement, % (n/n available cases)		93.9% (124/132)	94.2% (119/122)	90.9% (97/99)	92.9% (66/71)	100% (39/39)	100% (10/10)
Laboratory improvement							
CRP (mg/dL), median [IQR] (n/n available cases)	1.7 [0.4-3.2] (131/134)	0.11 [0.05-0.5]* (98/132)	0.09 [0.02-0.3]* (110/122)	0.09 [0.03-0.2]* (92/99)	0.09 [0.02-0.19]* (67/71)	0.1 [0.02-0.34]* (39/39)	0.13 [0.09-0.47]* (10/10)
ESR (mm/1 st /h), median [IQR] (n/n available cases)	33 [14.5-61] (129/134)	6 [2-12]* (102/132)	4 [2-7.5]* (116/122)	4 [2-8]* (93/99)	4 [2-8]* (71/71)	6 [2-16]* (39/39)	9 [3-22]* (10/10)
Hemoglobin (g/dL), mean (SD) (n/n available cases)	12.3±1.5 (125/134)	13.1±1.3* (104/132)	13.3±1.3* (107/122)	13.4±1.4* (88/99)	13.3±1.4 * (64/71)	13.1±1.3* (36/39)	13.3±1.1* (9/10)
Anemia (<11.0 g/dL), % (n/n available cases)	16.4% (22/134)	3.8% (5/132)	4.9% (6/122)	3.0% (3/99)	4.2% (3/71)	5.1% (2/39)	0% (0/10)
Prolonged remission †%, (n/n available cases)	-	-	-	55.5% (55/99)	70.4% (50/71)	69.2% (27/39)	90% (9/10)
Relapses ‡%, (n/n available cases)	-	3.0% (4/132)	5.8% (7/122)	5.1% (5/99)	14.1% (10/71)	17.9% (7/39)	10% (1/10)
Prednisone dose, median [IQR] (n/n available cases)	15 [10-30] (134/134)	13.75 [7.5-20]* (115/132)	8.1 [5-12.5]* (120/122)	5 [2.5-7.5]* (97/99)	2.5 [0.0-5]* (71/71)	0.0 [0.0-5]* (39/39)	2.5 [1.3-7.5]* (10/10)

* $p<0.01$ vs. baseline (Wilcoxon test).

† Prolonged remission.

Absence of clinical symptoms and signs and normalization of the acute phase reactants (CRP and ESR) for at least 6 months. ESR <20 or 25 mm/h (in men and women, respectively) and/or CRP<0.5 mg/dL were considered normal.

‡ At least one relapse during follow-up.

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Extension of Extracranial Vessel Involvement in Patients with Giant Cell Arteritis

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Session Information

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Background/Purpose: Giant cell arteritis (GCA) is a large vessel vasculitis with a predisposition for the cranial branches of the external carotid artery. However, aorta and / or its main branches may also be involved (1-4). In a series of patients with GCA who presented extracranial vessel involvement, our aim was to assess a) the vascular territories most frequently affected and b) correlation of a major extension of extracranial vascular involvement with a more severe clinical and analytical features.

Methods: Multicenter study of 68 patients with GCA who presented a compromise of extracranial vessels confirmed by PET/CT. Visual analysis of vascular uptake was performed on supra-aortic trunks (SAT), aortic arch (AA), thoracic aorta (TA), abdominal aorta (AA), iliac arteries (IA), lower limb arteries (LLA), and upper limb arteries (ULA).

Results: We evaluated 68 patients with GCA (51w/17m) with a mean age of 68.0±8.3 years. The vascular territories affected were: TA (n=58, 85.29%), SAT (n=38, 55.88%), AA (n=28, 41.18%), AA (n=18, 26.47%), LLA (n=17, 25%), IA (n=13, 19.12%) and ULA (n=6, 8.82%). We considered 3 groups according to the number of vascular territories affected: a) 1 or 2 territories, b) 3 or 4 territories and c) 5 or more territories and made a comparative study between these groups. In patients with 35 vascular territories affected, we observed a higher baseline ESR, and the most frequent systemic manifestations were polymyalgia rheumatica and constitutional symptoms with statistical significance (TABLE). Distribution of categorical variables was compared by the Pearson Chi-squared test. Quantitative variables were analyzed using the ANOVA test.

Conclusion: In patients with GCA the involvement of TA is very frequent, followed by the SAT and the AA. Regarding the laboratory findings, patients with higher levels of ESR presented a major extension of extracranial vascular involvement, as well as presenting PMR and/or constitutional symptoms was also related to more affection of extracranial territories.

	Number of vascular territories affected			p
ACUTE PHASE REACTANTS	1-2	3-4	≥5	
CRP, mg/dL mean (SD)	3.1 ± 1.0	5.4 ± 1.8	7.3 ± 3.2	0.315
ESR, mm/1 st hour, mean (SD)	36.8 ± 5.3	44.4 ± 6.2	74.5 ± 13.0	0.031
Hemoglobin, g/dL, mean (SD)	12.4 ± 0.2	12.0 ± 0.4	11.6 ± 0.5	0.438
SYSTEMIC MANIFESTATIONS				
Constitutional syndrome, n (%)	6 (17.1)	6 (22.2)	5 (83.3)	0.002
PMR, n (%)	28 (52.9)	23 (85.2)	4 (66.7)	0.03
ISCHEMIC MANIFESTATIONS				
Headache, n (%)	11 (31.4)	10 (37)	2 (33.3)	0.898
Jaw claudication, n (%)	1 (2.9)	3 (11.1)	1 (16.7)	0.307
Visual involvement, n (%)	2 (5.7)	2 (7.4)	-	0.783

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Comparison between Tocilizumab Prescribed As Monotherapy Versus Combined with Conventional Immunosuppressant Agents in Giant Cell Arteritis Patients

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Session Information

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Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

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Background/Purpose:: Giant cell arteritis (GCA) can be refractory to corticosteroid therapy (1-3). Tocilizumab (TCZ) has been approved in the treatment of GCA. There are no studies comparing the efficacy and safety when using TCZ as monotherapy or in combination with conventional immunosuppressive drugs in GCA. Our aim was to compare efficacy and safety of TCZ combined or in monotherapy in GCA.

Methods: Multicenter study on 134 patients with refractory GCA who received TCZ therapy as monotherapy or combined with conventional immunosuppressants. Large vessel involvement was considered when the aorta and/or its major branches were involved and when disclosed by imaging techniques such as ¹⁸F-FDG PET-CT scan, MRI-A, CT-A, or helical CT-scan. Prolonged remission was defined by the absence of clinical symptoms and signs and normalization of the acute phase reactants for at least 6 months. Relapse was defined as the recurrence of signs or symptoms of GCA and/or ESR>20 mm/h in men or >25 mm/h in women, and/or serum CRP >0.5 mg/dL related to GCA, both before and after starting TCZ therapy. A serious infection was considered to be present when a life-threatening, fatal, or required hospitalization infection occurred, intravenous antibiotics were necessary, or the process lead to persistent or significant disability. We also compared a subgroup of 36 patients, that had a baseline and follow-up PET/CT, to evaluate evolution of the vascular involvement.

Results: We evaluated 134 patients (101 w/33m); mean age, 73.0±8.8 years. TCZ was prescribed as monotherapy in 82 (62.2%) and combined with conventional immunosuppressants in 52 (38.8%) patients: MTX(n=48), AZA (n=3), and LFN (n=1). A comparative study between both groups is summarized in **TABLE**. Patients who received combined TCZ were younger and had a higher C-reactive protein (CRP) and a higher presence of aortitis in imaging techniques. When TCZ was started, prolonged remission was reached with combined therapy (statistical significance at 12 and 24 months). The corticosteroids sparing effect was similar in both groups. Side effects were similar in both groups too. There were no statistical significance regarding aortitis evolution.

Conclusion: Patients receiving combined conventional immunosuppressants with TCZ in the clinical practice study showed a higher prolonged remission. The incidence of serious infections and/or relevant adverse events was not affected according to the treatment. As well as the corticoid-sparing effect was achieved in the same way in both groups.

TABLE 1

	TCZ IN MONOTHERAPY (n=82)	TCZ COMBINED (n=52)	p
BASAL FEATURES AT TCZ ONSET			
GENERAL FEATURES			
Age, years, mean± SD	71.2 ± 9.0	68.8 ± 8.0	0.04
Sex, female/male n (%)	62/20	39/13	0.93
Time from GCA diagnosis to TCZ onset (months), median [IQR]	13.0 [7.75-33.5]	18.5 [6.25-34.0]	0.333
SYSTEMIC MANIFESTATIONS			
Fever, n (%)	6 (7.3%)	3 (5.8%)	0.72
Constitutional syndrome, n (%)	18 (22.0%)	13 (25.0%)	0.68
PMR, n (%)	40 (48.8%)	33 (63.5%)	0.096
ISCHEMIC MANIFESTATIONS			
Visual involvement, n (%)	20 (24.4%)	8 (15.4%)	0.21
Headache, n (%)	42 (51.2%)	28 (53.8%)	0.76
Jaw claudication, n (%)	7 (8.5%)	7 (13.5%)	0.36
AORTITIS AND ANOTHER LVV involvement, n (%)	28 (34.1%)	30 (57.7%)	0.007
ACUTE PHASE REACTANTS			
ESR, mm/1 st hour, mean (SD)	39.4 ± 32.5	42.3 ± 29.6	0.6
CRP, mg/dL mean (SD)	2.1 ± 3.0	4.4 ± 7.5	0.014
Hemoglobin, g/dL, mean (SD)	12.2 ± 1.5	12.4 ± 1.4	0.41

Table . (Cont'd)

	TCZ IN MONOTHERAPY (n=82)	TCZ COMBINED (n=52)	p
CORTICOSTEROIDS AT TCZ ONSET			
Prednisone dose, mg/d	23.9±17.3	19.4 ±14.0	0.11
EFFICACY AND SAFETY AFTER TCZ			
Prolonged remission n (%)			
Month 6	31 (50.8)	27 (69.2)	0.160
Month 12	18 (51.4)	28 (82.4)	0.006
Month 24	10 (50)	17 (85)	0.018
Relapses n (%)			
Month 1	3 (3.8)	1 (2)	0.579
Month 3	4 (5.4)	3 (6.3)	0.845
Month 6	3 (4.9)	2 (5.1)	0.962
Month 12	6 (17.1)	3 (8.8)	0.305
Month 24	6 (30)	1 (5)	0.037
AORTITIS AND ANOTHER LVV improvement n (%)			
Month 6	3 (20)	3 (14.3)	0.650
Month 12	6 (40)	10 (47.6)	0.650
Month 24	11 (73.3)	17 (81)	0.588
CORTICOSTEROIDS SPARING EFFECTS, median [IQR]			
Month 1	15 [7.5-21.25]	10 [7.5-20]	0.457
Month 3	10 [5-15]	7.5 [5-10]	0.179
Month 6	5 [2.5-10]	5 [2.5-7.5]	0.146
Month 12	5 [0-5]	2.5 [0-5]	0.064
Month 24	1.3 [0-5]	0 [0-1.25]	0.095
SIDE EFFECTS, n (%)			
Relevant adverse events	23 (28)	9 (17.3)	0.155
Serious infections	12 (14.6)	4 (7.7)	0.227

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Utility of Tocilizumab in Visual Affection of Patients with Giant Cell Arteritis

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Background/Purpose: Giant cell arteritis (GCA) is a large vessel vasculitis with a special predilection for extracranial branches of the external carotid artery. Among its most fearsome complications is visual affection. Tocilizumab (TCZ) is a monoclonal antibody directed against the interleukin 6 receptor that has shown utility in the treatment of GCA. Our aim was to assess the evolution of visual clinic in patients with GCA treated with TCZ.

Methods: Retrospective multicenter study on 20 GCA patients with visual involvement in treatment with TCZ. The efficacy of this drug on visual symptoms was evaluated.

Results: We assessed 20 patients (14 women and 6 men) with a mean age \pm SD of 73.7 ± 10.1 years with GCA and visual symptoms. In total there were 23 affected eyes. The symptoms reported were: unilateral blindness (n = 6), unilateral blurred vision (n = 6), unilateral amaurosis fugax (n = 3), unilateral hemianopsia (n = 2), bilateral blindness (n = 1), bilateral blurred vision (n = 1), bilateral hemianopsia (n = 1). Before starting treatment with TCZ, all patients had received high doses of prednisone, with a mean \pm SD dose of 54.2 ± 13.8 mg / day (range of doses: 40-80 mg / day). In addition, 9 of them also received intravenous corticosteroid boluses. In addition, 13 patients received traditional immunosuppressants: methotrexate (MTX) (n= 12), cyclophosphamide (n = 2), leflunomide (n = 1) and azathioprine (n = 1). Regardless of corticosteroids, TCZ was administered as monotherapy in 14 patients, while in 6 it was administered in combination with MTX. The TABLE shows the evolution of the visual affection of these patients. Throughout a median follow-up [RIC] of 9 [4-18] months, none of the 7 patients who had a blindness regained vision. The 2 patients who presented unilateral hemianopsia recovered vision. The patient with bilateral hemianopsia and the patient with bilateral blurred vision experienced a partial improvement. The remaining patients achieved a complete recovery.

Conclusion: Although TCZ seems to be also useful in the treatment of visual manifestations of ACG, once blindness is established, it does not seem to be effective.

	Month 1 n=20	Month 3 n=14	Month 6 n=10	Month 12 n=5
Visual improvement after starting TCZ, n (%)				
Complete improvement	6 (30)	5 (35.7)	5 (50)	1 (25)
Partial improvement	2 (10)	3 (21.4)	0 (0)	0 (0)
No improvement	12 (60)	6 (42.8)	5 (50)	5 (50)

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A Multicenter Series of Giant Cell Arteritis Patients from Clinical Practice in Treatment with Tocilizumab Compared with Giacta Trial

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Background/Purpose: GiACTA study is a randomized, phase III controlled clinical trial of tocilizumab (TCZ) in giant cell arteritis (GCA) (1,2). Our aim was to compare GiACTA trial data from those of a national multicenter series of 134 patients with GCA from the clinical practice.

Methods: In the GiACTA study the diagnosis of GCA was established by the ACR modified criteria, in our clinical practice series it was established by ACR criteria, positive biopsy of temporal artery and/or presence of imaging techniques consistent with LVV in patients with cranial symptoms of GCA. In the GiACTA trial TCZ was given subcutaneously (162 mg every 1 or 2 weeks) while in the clinical practice study TCZ was used at standard IV dose (8 mg/kg/month) and subcutaneously (162 mg/week). Quantitative variables were expressed as mean±SD and they were compared by the Student's t-test. Dichotomous variables were expressed as percentages and compared using the chi-square test.

Results: We did a comparative study between GiACTA trial (overall n=251 and only relapsing n=132) and our clinical practice series (overall n=134). At TCZ onset, in the clinical practice series (n=134) there were a significantly greater (TABLE): a) mean age at ACG diagnosis, b) polymyalgia rheumatica and visual affection frequency, c) ESR and CRP, and d) previous conventional immunosuppressants (mainly MTX). There was also a non-statistically significant difference, in terms of achieving sustained remission and developing severe infections. The mean dose of prednisone at the TCZ onset was lower in patients from the clinical practice.

Conclusion: Patients receiving TCZ in the clinical practice study have several baseline clinical and laboratory differences when compared to those included in the GiACTA trial. Patients of clinical practice were older, with a longer evolution time of disease. At TCZ onset were more symptomatic and had elevated levels of ESR and CRP, as well as, they had received more previous immunosuppressant agents.

TABLE 1

	GiACTA overall (n=251)	GiACTA (only relapsing; n=132)	Clinical Practice Overall (n=134)	GiACTA overall vs Clinical Practice overall	GiACTA relapsing vs Clinical Practice overall
Inclusion criteria	ACR 1990 modified	ACR 1990 modified	ACR 1990, biopsy proven GCA, cranial symptoms plus LVV*		
Women / men, n (%)	188 (74.9)/63 (25.1)	99 (75)/33 (25)	101 (75.4)/ 33 (24.6)	0.98	0.94
Age, mean (SD)	69 (8.2)	69.1 (8)	73 (8.8)	<0.0001	0.0002
Newly diagnosed GCA/ recurrent GCA	119/132	0/132	0/134	-	-
Time (months) from GCA diagnosis, mean (SD)	9.1 (16.8)	16.9 (20.3)	13.5 [5.0-33.5]	-	-
Signs/symptoms of GCA at TCZ onset	98 (39)	59 (44.7)	74 (55.2)	0.003	0.11
PMR, n (%)	49 (19.5)	40 (30.3)	73 (54)	<0.0001	0.0001
Visual affection, n (%)	4 (1.6)	4 (3)	28 (20.9)	<0.0001	<0.0001
ESR, mean (SD)	24 (19.4)	26.8 (19.6)	40.5 (31.2)	<0.0001	<0.0001
CRP, mean (SD)	7.5 (13.4)	8.4 (15.4)	3 (5.3)	<0.0001	0.0002
Positive TAB, n (%)	156 (62.1)	82 (62.1)	72 (53.7)	0.14	0.21
Imaging techniques, n (%)	138 (55)	70 (53)	75 (56)	0.93	0.72
Positive MRA, n (%)	8 (3.2)	4 (3)	16 (11.9)	0.002	0.01
Positive CT scan, n (%)	13 (5.2)	7 (5.3)	4 (44.4)	0.46	0.52
Positive PET/CT scan, n (%)	97 (38.7)	42 (31.8)	52 (38.8)	0.93	0.29
Patients on corticosteroids at study onset, n (%)	251 (100)	132 (100)	134 (100)	-	-
Prednisone at TCZ onset, mean (SD)	40 (13.1)	30.2 (12)	21.7(16.1)	<0.0001	<0.0001
Previous immunosuppressant agents, n (%)	27 (10.8)	23 (17)	98 (73.1)	<0.0001	<0.0001
Previous biologic therapy, n (%)	-	-	3 (2.2)	-	-
TCZ route	SC	SC	IV (106) SC (28)	-	-
Sustained remission, n (%) §	82 (54.6)	-	50 (70.4)	0.42	-
Severe infection, n (%)§	9/150 (6)	-	16 (11.9)	0.12	-

*Large vessel vasculitis (LVV) by imaging techniques.

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Abstract Number: 2757

A Comparison of Pharmacokinetic and Pharmacodynamic Outcomes of Tocilizumab Treatment in Giant Cell Arteritis after Subcutaneous and Intravenous Dosing

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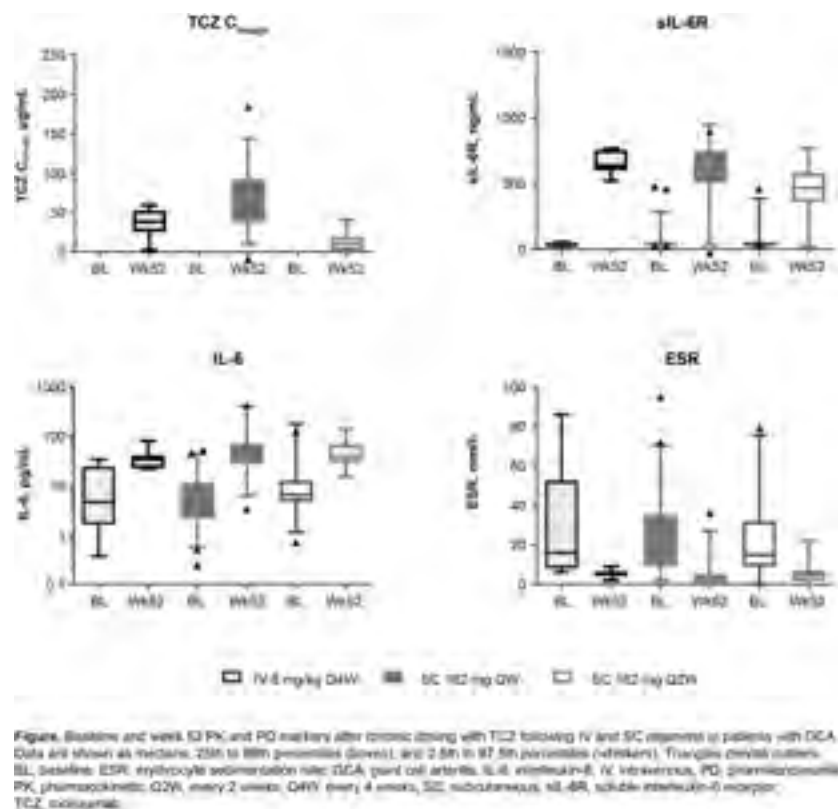
Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM



Background/Purpose: Tocilizumab (TCZ), an anti-interleukin-6 receptor (IL-6R) monoclonal antibody, was recently approved for the treatment of patients with giant cell arteritis (GCA) based on results of a double-blind randomized controlled trial (RCT) in GCA patients given 162 mg TCZ every week (QW) or every other week (Q2W) by subcutaneous (SC) route (GiACTA trial¹). Another RCT of 8 mg/kg TCZ given intravenously (IV) every 4 weeks (Q4W) also showed positive outcomes in GCA patients.² The double-blind part of each study lasted approximately 1 year. All 3 regimens (SC 162 mg QW, SC 162 mg Q2W, IV 8 mg/kg Q4W) yielded positive outcomes for sustained remission of GCA. However, a higher benefit was noted in some key secondary efficacy outcomes with the QW versus the Q2W SC regimen.¹ The present analysis investigated the pharmacokinetics (PK) of TCZ in GCA patients and assessed the impact of the exposure differential from the 3 regimens on pharmacodynamic (PD) markers.

Methods: TCZ levels and PD biomarkers (soluble IL-6R [sIL-6R], IL-6, erythrocyte sedimentation rate [ESR], and C-reactive protein [CRP]) were measured using validated assays at regular intervals throughout the dosing period from all patients in each trial. PK and PD outcomes were compared to facilitate understanding of the dose exposure-response relationships.

Results: At week 52, mean trough steady state exposure (C_{trough}), a key PK driver of TCZ efficacy, was highest for SC 162 mg QW, then IV 8 mg/kg Q4W, and finally SC Q2W (Figure). At week 52, sIL-6R levels were similar for the SC QW and IV regimens but lower for the SC Q2W regimen (Figure), possibly demonstrating a higher level of target engagement from the SC QW and IV regimens compared with the Q2W regimen. IL-6 levels increased versus baseline after TCZ administration for all 3 regimens, reflecting displacement of bound, endogenous IL-6 from its receptor, consistent with the mechanism of action of TCZ. ESR levels decreased to a similar extent in response to TCZ administration with all 3 regimens. Change from baseline in CRP was comparable between both SC regimens (~79-93% reduction from baseline from the QW and Q2W regimens, respectively). Quantitative changes in CRP values are not available for the IV study.

Conclusion: Comparison of C_{trough} after 52 weeks of dosing with TCZ from the 8 mg/kg IV regimen with that obtained from 2 SC regimens showed that exposures from the IV regimen were within the range of exposures of the SC QW and Q2W regimens. Comparison of PD outcomes showed that all 3 regimens had comparable results, except for lower levels of sIL-6R (a mechanistic marker reflecting serum concentration and target engagement) from the SC Q2W regimen. Comparability of PD results is consistent with similar efficacy outcomes in the SC and IV trials. *References:* 1. Stone JH et al. *N Engl J Med* 2017;377:317-328. 2. Villiger PM et al. *Lancet* 2016;387:1921-1927.

Disclosure: N. L. Mallalieu, Roche, 1, Roche, 3; J. H. Stone, Roche, 2, Roche, 5; P. M. Villiger, None; M. Klearman, Genentech/Roche, 1, Genentech/Roche, 5; L. Brockwell, Roche, 3; S. Dimonaco, Roche, 1, Roche, 3; J. E. Charoin, None.

Tocilizumab Interruption in Patients with Giant Cell Arteritis Achieving the Clinical Remission: Interim Analysis of an Open-Label, 18-Month, Pilot Study

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Session Information

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Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

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Session Time: 9:00AM-11:00AM

Background/Purpose: The efficacy of tocilizumab (TCZ), an anti-IL-6 targeted monoclonal antibody, in patients with refractory GCA has been demonstrated. The purpose of this study was to investigate the persistence of clinical remission after TCZ interruption. We also evaluated the role of acute-phase reactants and ¹⁸F-Fluorodeoxyglucose Positron Emission Tomography (¹⁸F-FDG –PET) in predicting the relapse and remission, and the occurrence of adverse event (AEs).

Methods: All refractory GCA patients with involvement of aorta and its thoracic branches received prednisone (PDN) 50 mg/day and intravenous TCZ (TCZiv) 8 mg/Kg/monthly or subcutaneous TCZ (TCZsc) 162 mg/weekly. PDN was tapered and withdrawn at month 2.

At month 6, in patients achieving a stable remission, TCZ was bimonthly tapered as follows: TCZiv 2 mg/Kg, and TCZsc 1 injection every 2, 3 and 4 weeks until month 12. In responders both treatments were interrupted at month 12.

Remission was assessed at months 6, 12, and 18 by the evaluation of GCA symptoms and signs, patient global health assessment by visual analogue scale 1 to 10 (VAS), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP). ¹⁸F-FDG –PET was performed at baseline, month 6, and 2 months after TCZ withdrawn. A Standardized Uptake Value normalized for liver uptake (nSUVmax) ≤ 1 was assumed as normal.

Anova test and Person test were used to measure the difference between groups and for correlations respectively. :

Results: 15 patients were enrolled, 12 females and 3 males, mean age at diagnosis was 69.8 years (± 7.70 SD). Seven patients were treated with TCZiv and 8 patients with TCZsc. After 2 months of TCZ therapy all patients stopped CS, and after 6 months of TCZ treatment all patients were in clinical (VAS mean value 2.01 ± 0.76 SD), laboratory (ESR $9 \text{ mm/h} \pm 6.66$ SD; CRP $0.29 \text{ mg/dl} \pm 0.27$ SD) remission. 11 patients completed the 12-month scheduled follow-up. Of these, 7 maintained the drug-free remission that persisted over a median follow up of 12 months afterward. After 2 months from TCZ discontinuation, in the 7 remitting patients SUVmax and nSUVmax were significantly reduced as compared with baseline, while no differences resulted with ¹⁸F-FDG –PET values at month 6. (table 1). A correlation between nSUVmax and VAS and CRP was found (Pearson 0.9: $p = 0.0005$ and 0.59 $p = 0.006$, respectively). Four patients reactivated after two months of TCZ discontinuation with median VAS 7.9, median ESR 50, median CRP 1.66. Two patients had stable disease with every other week TCZsc and 2 patients with monthly TCZsc. None of the patients required CS. No AEs were recorded. The remaining 4 patients with incomplete follow up, were in remission with no flares after 8,10, and 12 months of treatment.

	Baseline	Month 6	P value	Pre TCZ	After 2 months from TCZ discont.	P value	Month 6	After 2 months of TCZ discont.	P Value
SUVmax mean (\pm SD)	3.3 (0.36)	2.13 (0.42)	0.0005	3.3 (0.36)	1.9 (0.24)	0.0005	2.13 (0.42)	1.9 (0.24)	0.43
nSUVmax mean (\pm SD)	1.49 (0.26)	0.85 (0.19)	0.0005	1.49 (0.26)	0.77 (0.15)	0.0005	0.85 (0.19)	0.77 (0.15)	0.76

Conclusion: Drug-free remission maintenance after TCZ discontinuation seems to be a proposable strategy in GCA.

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Effect of Specific Treatments on Clinical, Serologic, and Imaging Assessments of Disease Activity in Large-Vessel Vasculitis

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Session Information

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Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Disease activity in large vessel vasculitis (LVV) is traditionally assessed by clinical and serologic (ESR, CRP) parameters. Imaging assessment, including ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET), may be useful to monitor LVV. The study objective was to determine the impact of tocilizumab, infliximab and methotrexate (MTX) on disease activity in LVV as assessed by clinical, serologic, and imaging-based parameters.

Methods: Patients with GCA or TAK were recruited into a prospective, observational cohort involving ≥ 2 FDG-PET/CT scans at 6-month intervals. Clinical assessment [physician global assessment (PGA, range 0-10)], serologic assessment (CRP-mg/L, ESR-mm/hr), and imaging assessment [PET Vascular Activity Score (PETVAS)] was determined at each visit. PETVAS is a global summary score of arterial FDG uptake assessed qualitatively relative to liver activity in 9 vascular beds, ranging from 0 to 27 with higher scores indicating more vascular inflammation. Clinical and imaging assessments were performed blinded to each other. Wilcoxon signed rank test was used to compare changes in PGA, CRP, ESR, and PETVAS between interval visits in response to treatments.

Results: Fourteen subjects with GCA were treated with tocilizumab. Prior to treatment, every patient had clinical and PET scan activity. There was significant reduction in PGA (2.5 vs 0, $p < 0.01$), CRP (6.8 vs 0.5, $p < 0.01$), ESR (22.5 vs 4.5, $p < 0.01$), and PETVAS (25.0 vs 22.0, $p = 0.01$). PETVAS improved in 5 of 7 patients with GCA treated with tocilizumab. Despite significant improvement in PETVAS, only 2 of 14 patients (14%) had normalization of PET activity after treatment with tocilizumab. In contrast, clinical remission after tocilizumab occurred in most of these patients ($n = 10$; 71%). Most of the subjects were on glucocorticoids (GCs) and there was significant reduction the daily GC dose ($p = 0.01$) at follow up.

Six subjects with TAK were treated with infliximab. All of them had clinically active disease and active PET scan at baseline. There was significant improvement in PGA (5.5 vs 2, $p = 0.03$); however, four of six patients (67%) continued to have clinically active disease at follow up. All six patients had an improvement in PETVAS (21.0 vs 14.5, $p = 0.03$). However, four of the six patients continued to have active vasculitis by PET at follow-up despite treatment and there was no significant change in CRP (24.9 vs 4.9, $p = 0.31$) or ESR (32.5 vs 18.5, $p = 0.13$). Daily GC dose was similar at baseline and follow up ($p = 0.5$).

Treatment with MTX was studied in 12 patients (TAK=3, GCA=9). Variable response to MTX was observed without significant change in PGA (3 vs 0, $p = 0.09$), CPR (5.8 vs 3.5, $p = 0.18$), ESR (31 vs 19.5, $p = 0.33$), or PETVAS (24 vs 18, $p = 0.31$).

Conclusion: Imaging and clinical assessment of disease activity significantly improved but rarely normalized in response to tocilizumab in GCA and TNF inhibitors in TAK. In contrast, methotrexate did not consistently improve clinical or imaging-based assessments of disease activity in LVV. These findings support a need to study the value of FDG-PET as a surrogate outcome measure of vascular activity in randomized clinical trials in LVV.

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Clinical Outcomes of Patients with Giant Cell Arteritis Treated with Tocilizumab in Real-World Clinical Practice

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Previously, the GiACTA study demonstrated the superiority of subcutaneous (SC) tocilizumab (TCZ) plus prednisone vs prednisone alone in achieving sustained glucocorticoid (GC)-free remission in patients with giant cell arteritis (GCA)¹. We aimed to evaluate the effectiveness and safety of SC and intravenous TCZ in real-world clinical practice.

Methods: We performed a retrospective analysis of GCA patients treated with TCZ at a single center (MGH) between 2010-2018. Time to disease relapse, number of relapses, prednisone use, and adverse events (AE) before and after TCZ

Figure 1. Time to disease relapse before (A) and after (B) TCZ initiation

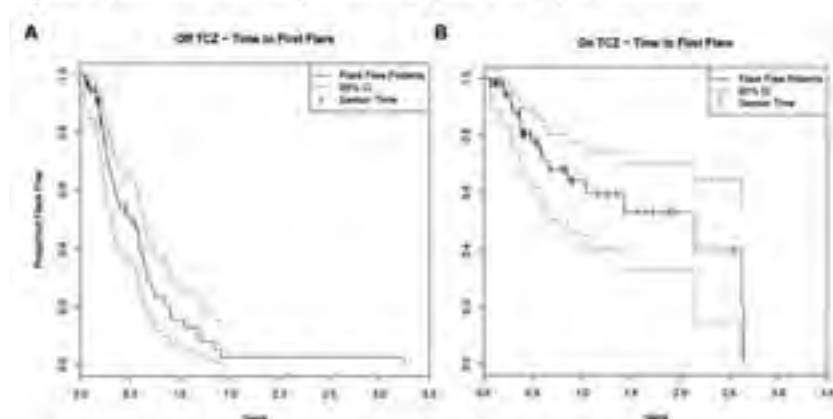


Table 1. Patient baseline characteristics and treatments

Age, mean (SD)	69.4 (8.4)
Female sex, n (%)	43 (71.7)
Caucasian ethnicity, n (%)	53 (88.3)
Clinical manifestations at disease onset	
Headache, n (%)	47 (78.3)
Scalp tenderness, n (%)	28 (46.3)
Joint claudication, n (%)	31 (51.7)
Amblyopia/tears, n (%)	11 (18.3)
Transient blurry vision, n (%)	18 (30.0)
Permanent vision loss, n (%)	9 (15.0)
Isotopia, n (%)	2 (3.3)
PMR symptoms, n (%)	32 (53.3)
ESR (mm/hr), mean (SD)	72.8 (33.6)
CRP (mg/L), mean (SD)	78.9 (72.6)
Positive FA biopsy, n (%)	30 (49.3)
Prednisone dose (mg/day) at disease onset, mean (SD)	54 (18.6)
Use of other immunosuppressants before TCZ initiation, n (%) ^a	15 (25)
Duration of disease before TCZ initiation (years), median (IQR)	0.6 (0.2-1.8)
Prednisone dose (mg/day) at TCZ initiation, mean (SD)	30 (18.3)
Received TCZ IV, n (%) ^b	22 (37.3)
Received TCZ SC, n (%) ^b	43 (72.6)
Duration of TCZ treatment (years), median (SD)	0.9 (1.0)
Duration of TCZ treatment (years), median (IQR)	0.5 (0.3-1.4)

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IV = intravenous; PMR = polymyalgia rheumatica; SC = subcutaneous; SD = standard deviation; TCZ = tocilizumab.

^a Other immunosuppressants include methotrexate, cyclophosphamide, azathioprine, mycophenolate mofetil, sirolimus, tacrolimus, cyclosporine, and rituximab.

^b No patients received both IV and SC.

Table 2. Clinical outcomes and adverse events

	Off TCZ (N = 60)	On TCZ (N = 60)
Patients with ≥ 1 relapse	47 (78.3)	10 (16.7)
1 relapse	21 (35.0)	6 (10.0)
2 relapses	10 (16.7)	2 (3.3)
3 relapses	8 (10.0)	2 (3.3)
≥ 4 relapses	10 (16.7)	0
Time to relapse (years), median (IQR)	0.51 (0.26-0.75)	2.14 (0.56-2.63)
Patients with ≥ 1 AE, n (%)	34 (56.7)	33 (55.0)
AEs attributed to GC*	50 / 66 (75.8%)	42 / 78 (53.8%)
AEs attributed to TCZ*	NA	28 / 78 (35.9%)
Patients with ≥ 1 SAE, n (%)	9 (15.0)	7 (11.7)
SAEs attributed to GC	5 / 11 (45.5%)	4 / 9 (44.4%)
SAEs attributed to TCZ	NA	3 / 9 (33.3%)

AE = adverse event; GC = glucocorticoids; IQR = interquartile range; NA = not applicable; SAE = serious AE; TCZ = tocilizumab.
* Multiple occurrences of AEs are included. Denominators are all AEs or SAEs.

initiation were assessed. Disease relapse was defined as the re-appearance of clinical manifestations of GCA (e.g., cranial symptoms) that required treatment modification.

Results: A total of 60 GCA patients were included in the analysis. **Table 1** depicts the baseline characteristics and the treatments received by this cohort. The median (IQR) disease duration before TCZ use was 0.6 (0.2-1.6) years. Fifty-eight patients (96.7%) received concomitant prednisone (mean [SD] dose: 30 [18.3] mg daily) at the time of TCZ initiation. Patients received TCZ for a median (IQR) period of 0.5(0.3-1.4) years. While not on TCZ treatment, 47 patients (78.3%) had ≥1 relapse (median [IQR] time to flare 0.5 [0.3-0.8] years). On TCZ, 10 patients (16.7%) had ≥1 relapse (median [IQR] time to flare 2.1 [0.6-2.3] years) (**Table 2, Figure 1**). Twenty-four patients (41.4%) successfully tapered off prednisone during TCZ treatment. The incidence of AEs and serious AEs (SAE) was similar before and after TCZ initiation (**Table 2**). During TCZ treatment, however, 42 out of 78 AEs were considered related or possibly related to prednisone. An AE led to TCZ discontinuation in 5 patients. No deaths occurred during the study period.

Conclusion: In this retrospective analysis, TCZ improved clinical outcomes in patients with GCA as indicated by a reduced incidence of relapses and by the ability to discontinue prednisone. The occurrence of AEs and SAEs (many due to GC) did not differ substantially while patients were on or off TCZ. These real-world findings support the previously reported efficacy and safety profile of TCZ in patients with GCA.

References: Stone JH, et al. *NEngl J Med*. 2017;377(4):317-328.

Disclosure: S. H. Unizony, None; J. Pei, Genentech, Inc., 3; P. N. Sidiropoulos, Genentech, Inc., 3; J. H. Best, Genentech, Inc., 3; C. Birchwood, Genentech, Inc., 3; J. H. Stone, Roche, 2, Roche, 5.

Abstract Number: 2761

High-Dose Prednisone Use up to 42 Days Prior to Temporal Artery Biopsy (TAB) Did Not Reduce Yield of Positive Biopsy in the Veterans Health Administration (VHA) Database Cohort

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Session Information

Session Date: Tuesday, October 23, 2018

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Background/Purpose: Temporal artery biopsy (TAB) currently remains the gold-standard confirmatory test for the diagnosis of giant cell arteritis (GCA); positive TAB justifies long-term steroid use and/or immunosuppression. High-dose glucocorticoids are often briskly initiated when GCA is clinically suspected, even before TAB is obtained, to avoid ischemic complications. Historically, this has raised concern over the effect of glucocorticoids on TAB yield. This study aimed to determine if the duration of prednisone use, dosed at 30 mg or more daily, prior to TAB influenced TAB result in subjects with suspected GCA.

Methods: Subjects with a procedure code for TAB between 1999-2017 were queried through the VHA national database. TAB result (positive or negative, presence of granuloma/giant cells) was reviewed manually; indeterminate results (i.e. inconclusive, healed arteritis) were categorized as negative. Prescription data regarding prednisone dosage and dispense date were also extracted for each subject. Days of prednisone use (≥ 30 mg daily) before TAB were categorized as follows: 0-14, >14-28, >28-42, >42, and prednisone started after TAB. Abnormal ESR and CRP values within 180 days before TAB to 14 days after TAB, as well as age, gender, TAB laterality, and TAB length were also extracted. Logistic regression models were run using Stata.

Results: 3,057 biopsies were reviewed, 306 (10%) of which were deemed positive per pathology report. Prednisone use ≥ 30 mg daily was identified among 2,012 subjects. Of these, 1,474 (73.3%) initiated prednisone within 14 days prior to TAB. The duration of prednisone use before TAB, as a continuous variable, was not influenced by age, TAB length, TAB laterality, or abnormal ESR or CRP values by linear regression. Male gender had a significant negative correlation with prednisone initiation prior to TAB (coefficient -2.97, CI -5.6 to -0.4, $p < 0.05$). After adjustment for gender, there was no association between positive TAB and time of prednisone initiation up to 42 days prior to TAB. Furthermore, prednisone administration up to 42 days prior to TAB did not influence the presence of granulomatous inflammation. Interestingly, positive TAB was significantly associated with prednisone dosed after TAB date, suggesting that a positive TAB prompted the provider to initiate treatment. Additionally, there was no significant correlation between a positive TAB and abnormal ESR or CRP values within 180 days pre- and 14 days post-TAB after correcting for pre-TAB prednisone exposure.

Conclusion: This is the largest retrospective study to date showing that prednisone ≥ 30 mg daily initiated up to 42 days prior to a TAB did not influence biopsy yield. This study also demonstrated that abnormal ESR or CRP values prior to TAB were not associated with positive TAB even after corrections for pre-TAB prednisone usage, suggesting that these inflammatory markers may not be independently helpful in the diagnosis of GCA.

Disclosure: S. H. Chung, None; M. B. Morcos, None; B. Ng, None.

Abstract Number: 2762

A Longer or Bilateral Temporal Artery Biopsy (TAB) Is More Likely to Yield a Positive Result for Giant Cell Arteritis (GCA) in the Veterans Health Administration (VHA) Database Cohort

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: TAB is currently considered the gold standard for the diagnosis of GCA. However, it is suspected that the sensitivity of TAB is limited by the segmental nature of the artery involvement in this condition. Expert opinion for obtaining TAB recommends an initial unilateral approach with an attempt to obtain at least 10-20 mm of artery, followed by the pursuit of the contralateral side if initial biopsy is negative and clinical suspicion remains high. Several smaller retrospective studies have not reached a consensus with regards to the optimal length of TAB. This study aimed to determine if length of TAB or initial bilateral TAB impacted the yield of positive TAB result in the national VHA cohort.

Methods: Subjects with a procedure code for TAB between 1999-2017 were queried through the VHA national database. TAB reports (positive, negative) were reviewed manually; indeterminate results (i.e. inconclusive, healed arteritis) were categorized as negative. The following data was extracted: 1) post-fixation TAB length 2) whether bilateral TAB was performed in one sitting 3) age at TAB 4) gender. TAB length categories were organized as follows: ≤ 10 mm, 10 to ≤ 15 mm, 15 to ≤ 20 mm, 20 to ≤ 25 mm, 25 to ≤ 30 mm, and ≥ 30 mm. Multivariate analyses and logistic regression models were run using Stata.

Results: A total of 3,057 biopsies were reviewed; 306 (10%) were deemed positive per pathology report. The likelihood of a positive TAB significantly correlated with TAB length greater than 30 mm (OR 1.65, CI 1.06-2.57, $p < 0.05$ when compared to a reference category ≤ 10 mm) as well as with bilateral biopsy in one sitting (OR 2.05, CI 1.43-2.94, $p < 0.01$), suggesting higher yield with longer or initial bilateral biopsies. The likelihood of a positive TAB was incrementally higher with longer biopsies. Positive TAB also significantly correlated with age greater than 70 years (OR 1.9 in the age 61-70 group, CI 1.0-3.7, $p = 0.07$; OR 4.2 in the age 71-80 group, CI 2.2-8.3, $p < 0.01$; OR 6.0 in the age ≥ 80 group, CI 3.1-11.6,

p<0.01 when compared to a reference category aged 51-60 years). Neither gender or age influenced TAB length or the likelihood that bilateral TAB was performed.

Conclusion: This is the largest retrospective study to date examining the relationship between TAB length and yield. Longer length of biopsy (≥ 30 mm) was more likely to yield a positive TAB. Additionally, initial bilateral TAB was twice as likely to yield a positive result compared with unilateral TAB. These observations may be explained by “skip lesions” that can lead to false-negative results with shorter TAB. Overall, these findings suggest that higher yield of TAB might be achieved with longer or initial bilateral biopsies.

Disclosure: S. H. Chung, None; M. B. Morcos, None; B. Ng, None.

Abstract Number: 2763

Utility of Serum Free Light Chains, Antiphospholipid Antibodies, and Cytokines in Giant Cell Arteritis

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Session Information

Session Date: Tuesday, October 23, 2018

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Session Time: 9:00AM-11:00AM

Background/Purpose: To investigate the utility of serum free light chains (FLC), antiphospholipid antibodies (APL), and cytokines in the evaluation of patients with biopsy-proven giant cell arteritis (GCA).

Methods: We conducted a cross-sectional study of 75 patients with biopsy-proven GCA. Sera were evaluated for the presence and quantity of the following biomarkers: serum FLC [kappa, lambda], anticardiolipin antibodies (ACL; IgM/IgG), beta-2 glycoprotein antibodies (β 2GP; IgM/IgG), *antiphosphatidylserine*-prothrombin antibodies (PS-PT; IgM/IgG), and 20 circulating cytokines (GCSF, GMCSF, IFN γ , IL-1b, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p40, IL-12p70, IL-13, IL-17, MCP-1, TNF α , TNF β and VEGF). Quantification of serum FLC was obtained by nephelometric assay. ACL, β 2GP, and PS-PT antibody levels were determined via enzyme-linked immunosorbent assay. Cytokines were measured with a fluorescent microsphere-based assay. Rank sum test was used to compare biomarker levels between patients with active and inactive GCA, patients with and without large vessel vasculitis (LVV), patients with and without visual ischemia. Associations between biomarker levels and ESR/CRP were examined using Spearman correlation methods.

Results: The study included 60 (80%) women and 15 (20%) men. Mean age at inclusion was 75.0 ± 7.3 years. Clinically active disease was present in 28 (37%) and 47 (63%) were clinically inactive at time of sera collection. LVV was identified radiographically in 29 (39%) and visual ischemia occurred in 19 (25%). At time of sera collection, no significant difference in prednisone dose was observed between the evaluated groups. APL were infrequently detected: 13 ACL IgM weak(+); 1 ACL IgM(+); 6 ACL IgG weak(+); 1 β 2GP IgM(+); 3 β 2GP IgG weak(+); 5 PS-PT IgM(+); 2 PS-PT IgG(+). No significant differences between the presence and the level of APL were observed between the evaluated groups. Elevated kappa FLC levels were present in 35 (74%), elevated lambda in 4 (5%), and elevated kappa/lambda ratios in 14 (19%). There was no difference between serum FLC or kappa/lambda ratios between comparison groups. Serum FLC and APL had weak to moderate correlation with ESR/CRP.

Cytokine levels of IL-6, IL-8, and VEGF were significantly higher in active patients compared to inactive patients (p<0.05). No differences between APL, serum FLC, or cytokines were observed between patients with and without LVV. Patients with visual ischemia had significantly higher cytokine levels of GCSF, GMCSF, IFN γ , IL-10, IL-12p70, IL-13, IL-1b, IL-2, IL-4, IL-5, IL-6, TNF α compared to those without visual ischemia. The highest correlations (r_s) among individual cytokines with ESR/CRP were observed with IL-6 (0.42), IL-7 (0.42), IL-8 (0.46), and IL-17 (0.43).

Conclusion: In this study, APL and serum FLC were not useful in determining the level of disease activity or differentiating between patients with or without LVV or visual ischemia. A distinct cytokine profile was observed in patients with visual ischemia compared to those without. Prospective studies are needed to determine the role of these cytokines as biomarkers of visual ischemic complications in patients with GCA.

Disclosure: M. J. Koster, None; M. Snyder, None; M. Villatoro-Villar, None; C. S. Crowson, None; T. A. Kermani, None; K. J. Warrington, GlaxoSmithKline, 2, Eli Lilly and Co., 2, Sanofi, 5.

Incidence, Characteristics and Management of Giant Cell Arteritis in France: A Study Based on National Health Insurance Claims Data

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Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

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Background/Purpose: Giant cell arteritis (GCA) is an immune-mediated, primary systemic vasculitis that affects large and medium-sized arteries. GCA may cause vision loss in up to 20% and requires long term glucocorticoids (GCs). There are currently few data available in France on the epidemiology, patients' (pts) characteristics, diagnosis and management of GCA in a real-world setting. The objectives of this study were to address these questions using Health insurance claims data.

Methods: This retrospective cohort study used the EGB (*Echantillon Généraliste des Bénéficiaires*) database, a 1% random and representative sample of the French national Health insurance system. The EGB database contains anonymous demographic and comprehensive medical data on conditions with long-term disease (LTD) status, hospitalizations and reimbursement claims for medications dispensed in the community. The study used data collected between Jan 1, 2007 and Dec 31, 2015. Inclusion criteria were: 1) age ≥ 50 years; 2) hospitalization for GCA or LTD status for GCA (ICD-10 codes: M31.5/6); and 3) ≥ 4 drug dispensing of oral GCs within 6 months around the index date. The index date was defined as the date of 1st occurrence of GCA code and cases were considered as incident if the GCA code first occurred after ≥ 2 years of follow-up. Demographics, co-morbidities, diagnostic tests and therapies were analysed. A treatment sequence was defined as the start of a new drug or the resumption of the same drug after a stop ≥ 3 months. Prevalence and annual incidence were calculated by using the people recorded in the database as denominator.

Results: Among the 752717 people recorded in the EGB, 241 pts fulfilled our criteria. Prevalence was 150/100000 people ≥ 50 years-old. Around 24 pts were newly diagnosed/year with an annual incidence of 7-10/100000 people ≥ 50 years-old. 72% of the 241 pts were females, mean age was 77.5 (± 8.9) and mean follow-up 3.7 (± 2.6) years. In the 12 months before index date, 74.3% of the pts had ≥ 1 proxy for hypertension, 39.4% for depression/insomnia and 33.6% for osteoporosis. After index date, temporal artery biopsy (TAB) was performed in 43.2%, high-resolution Doppler ultrasound of the temporal arteries in 35.3% and 18FDG-PET in 11.6%. Among the 235 pts (97.5%) who had ≥ 1 drug dispensing of oral GCs, 198 pts (84.3%) used only GCs while 37 (15.7%) also received 1 to 3 adjunctive agents. Mean 1st GCs sequence duration was 17.2 months (± 16.5) in 96.6%. 95 pts (40.4%) had a 2nd sequence, i.e. resume GCs and or start a new drug for a duration of 6.7 months (± 8.1) for GCS alone or 12.2 months (± 8.8) for GCs + adjunctive drug. The most commonly prescribed adjunctive agent was MTX (12.0%). Use of other adjunctive drugs was marginal: hydroxychloroquine 7 pts, azathioprine 4, cyclophosphamide 1, infliximab 1, adalimumab 2 and etanercept 1 pt.

Conclusion: These real-world data indicate an incidence of GCA in France of 7-10/100,000 people ≥ 50 years-old and underline that most patients with GCA are treated with GCs alone whereas adjunctive agents, mainly methotrexate, are given to 15% of patients. The utilization of TAB in only half of the patients might reflect a shift towards increasing use of imaging techniques to diagnose GCA.

Disclosure: V. Devauchelle-Pensec, Roche SAS, 5, Chugai Pharma France, 5; E. Hachulla, Roche SAS, 5, Chugai Pharma France, 5; M. Paccalin, Roche SAS, 5, Chugai Pharma France, 5; S. Gandon, Roche SAS, 3; I. Idier, Chugai Pharma France, 3; M. Nolin, None; M. Belhassen, None; A. Mahr, Roche SAS, 5, Chugai Pharma France, 5.

Thyroid Artery Involvement Detected By Colour-Doppler Ultrasonography in an Incipient, Single Centre Giant Cell Arteritis Cohort

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The inflammation of thyroid arteries (ThA) is not commonly considered and investigated in giant cell arteritis (GCA). We aimed to estimate the frequency of ThA involvement as detected by Colour Doppler Sonography (CDS).

Methods: We conducted a prospective single center study between 1 October 2013 and 30 March 2018. The CDS of superior and inferior ThA was performed in all newly diagnosed, treatment naive GCA patients, in addition to the routinely evaluated temporal, facial, occipital and large supra-aortic arteries. The superior and inferior ThA were identified at their respective anatomical locations in close proximity to the thyroid gland and examined using the standard Doppler settings for temporal arteries. Arteries were evaluated in two planes for the highly specific *halo* sign. Laboratory thyroid function tests consisted of TSH, T3 and T4 measurements at the time of GCA diagnosis (prior to any steroid therapy). Characteristics of GCA cases with inflamed ThA were explored and compared to the GCA group without ThA involvement.

Results: During the 54 months we performed the CDS of the multiple arteries in 153 consecutive GCA patients (median age 75.2 (IQR 66.5–80.0) years, 63% female). We observed the halo sign on either superior or inferior ThA in 16 (10.5%) cases. All patients but one (15/16) with ThA involvement also had CDS signs of temporal artery involvement and 2/16 patients (12.5%) had CDS signs of large supra-aortic artery involvement.

Constitutional symptoms were reported significantly more often by the patients with ThA involvement (100% vs. 73%, $p=0.013$); specifically, fever was significantly more frequent (44% vs. 19%, $p=0.047$). No significant correlation was found between ThA involvement and other clinical or demographic characteristics, including headache, jaw claudication and visual disturbances.

Local symptoms consistent with thyroid gland pathology were reported by 4/16 patients (25%) with ThA involvement. Laboratory signs of thyroid dysfunction were found in 3/16 patients (19%) with ThA involvement (2 latent hyperthyroidism, 1 latent hypothyroidism); none of these patients had any previous history of thyroid disease. Previous history of thyroid disease was noted in 19 (12%) out of all GCA patients (13 hypothyroidism, 1 hyperthyroidism, 2 euthyrotic goiter; 3 patients had thyroid surgery because of either goiter or suspected malignancy). Two of those patients also had CDS signs of ThA involvement, yet their thyroid function tests were normal at the time of GCA diagnosis.

Conclusion: In our incipient GCA cohort, a tenth of all patients had ultrasonographic signs of ThA involvement. GCA patients with ThA involvement had a higher prevalence of constitutional symptoms than those without ThA inflammation.

Disclosure: R. Jese, None; Z. Rotar, None; M. Tomsic, None; A. Hočevar, None.

Seasonal Variation in Incidence of Giant Cell Arteritis: A Population-Based Cohort Study

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Session Information

Session Date: Tuesday, October 23, 2018

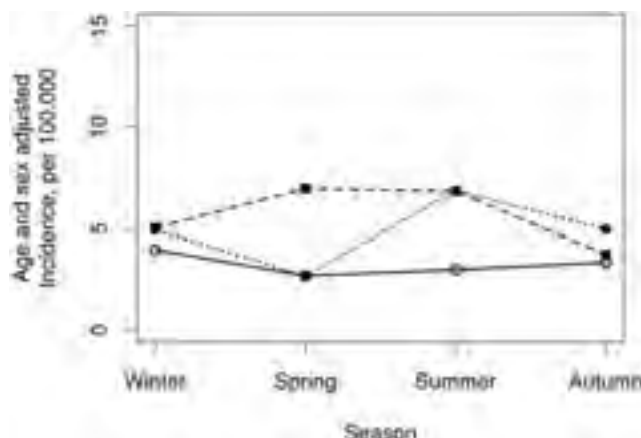
Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To determine whether there is a seasonal peak onset of giant cell arteritis (GCA). We examined the seasonal variability of GCA in a geographically-defined population.

Methods: In a geographically defined population, we retrospectively identified all incident cases of GCA between January 1, 1950, and December 31, 2009. Detailed review of all individual medical records was performed. All included patients met the 1990 ACR criteria for classification of GCA. Seasonal variation was compared using quasi-Poisson regression models to account for overdispersion.



Results: The cohort included 248 cases of incident GCA (79% female; mean age 75.6 years). Overall, patients in this cohort were more likely to have incident GCA in the summer season with age- and sex-adjusted incidence rates (per 100,000 population) of 5.5 for summer compared with 4.7 for winter, 3.9 for spring and 4.3 for autumn, but this difference did not reach statistical significance ($p=0.19$). However, subgroup analysis by decade revealed that incidence of GCA was significantly highest ($p=0.018$) in the summer season and lowest in the spring during 1995-2009 with an age-adjusted and sex-adjusted incidence rate per year 100,000 of 6.8 compared with winter (4.9), spring (2.7) and autumn (5.0) [Figure].

Figure. GCA incidence rates by season and decade (1950-79 open circles, 1980-94 squares, 1995-09 filled circles) among Olmsted County, Minnesota residents in 1950-2009

Conclusion: Incident GCA is more common in the summer season and least common in the spring. This pattern is more pronounced in recent years. Further research needs to be done in order to understand whether these findings provide insights regarding the etiology of GCA.

Disclosure: S. Raheel, None; C. S. Crowson, None; E. L. Matteson, None.

Abstract Number: 2767

Herpes Zoster As a Risk Factor for Polymyalgia Rheumatica: A Population-Based Study

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Session Information

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Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The presence of varicella zoster virus (VZV) signal in the temporal arteries of patients with giant cell arteritis has suggested a possible role of VZV in triggering the immunopathology of GCA. This calls into question whether VZV may also play a role in the development of polymyalgia rheumatic (PMR). We aimed to determine whether herpes zoster (HZ) infection is a risk factor for PMR.

Methods: All incident cases of PMR in a geographically-defined area diagnosed between 1990 and 2014 were identified. For each patient with PMR, a non-PMR control subject matched on age and sex was randomly selected from the same underlying population. Each control was assigned an index date corresponding to the PMR incident date of the matched case. The medical records of all patients with codes for HZ were reviewed to confirm the incident date and diagnosis.

Results: The study included 541 patients with PMR and 541 subjects without PMR. The average age at PMR incidence (index date for the non-PMR cohort) was 74 years, and 349 (65%) subjects were female in each cohort. Prior to index date, 61 (11%) patients with PMR and 62 (11%) non-PMR patients had HZ infection ($p=0.92$).

Conclusion: Herpes zoster infection was not associated with an increased risk of PMR. Further work is needed to determine the etiology of PMR.

Disclosure: S. Raheel, None; C. S. Crowson, None; E. L. Matteson, None.

Abstract Number: 2768

Comorbidity Accrual and Mortality in an Inception Cohort of Patients with Giant Cell Arteritis and Polymyalgia Rheumatica: A Single-Center, Observational Long-Term Study

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Session Time: 9:00 AM-11:00 AM

Background/Purpose: Patients with giant-cell arteritis (GCA) and polymyalgia rheumatica (PMR) are treated with high cumulative glucocorticoid (GC) dose during their disease course. We sought to determine the accrual of comorbidity as well as survival in patients with GCA and PMR.

Methods: We conducted a retrospective follow-up study of an inception cohort of patients diagnosed with GCA and PMR according to ACR criteria and persistently followed at our rheumatology clinic from January 1990 until March 2018. Disease manifestations, time duration of GC dose tapering and discontinuation as well as calculated cumulative GC dose were determined. Baseline and last encounter age-adjusted Charlson Comorbidity Index (CCI) and Rheumatic Disease Comorbidity Index (RDCI) as well as the increment (Δ) of CCI and RDCI at the last study encounter were scored. Mortality rate and cause were recorded.

Results: The cohort consisted of 69 patients (24 GCA and 45 PMR, 68.1% female). Mean age at diagnosis was 71.38 ± 5.58 years and 74.53 ± 9.67 for GCA and PMR, respectively. The mean daily initial prednisone dose for GCA was 61.25 ± 11.91 mg and for PMR 18.11 ± 7.85 mg ($p < 0.001$), and prednisone cumulative dose was $13,382.19 \pm 6189.21$ mg and $6,610.36 \pm 4,755.55$ mg for GCA and PMR, respectively ($p < 0.001$). Systemic symptoms such as fever and weight loss as well as ESR at diagnosis were comparable in GCA and PMR. Time duration until achieving 50% and 25% of the initial prednisone dose was longer for patients with PMR vs. GCA (3.87 ± 2.22 months vs. 3.02 ± 1.15 months, $p = 0.049$ and $p = 0.03$, respectively), however, the disease duration until achieving daily prednisone dose of 7.5 mg and 5 mg was longer in the GCA group (9.88 ± 3.08 months vs. 4.4 ± 2.4 months, $p < 0.001$, and 12.85 ± 6.35 months vs. 7.28 ± 7.48 months, $p = 0.005$, respectively). Nevertheless, the time duration to discontinuation of prednisone and prednisone-free survival did not differ among GCA and PMR patients, as well as the time duration to the first disease flare. Disease remission rate for the entire cohort was 28.9% for a follow-up period of 7.5 ± 3.9 years (range: 2.4 – 16.9 years). The CCI and RDCI scores for GCA at diagnosis and at the last study encounter did not differ between GCA and PMR groups. Interestingly, initial prednisone dose, time to achieving 50% and 25% of initial prednisone dose, time to daily prednisone dose of 7.5mg and 5mg as well as time to prednisone discontinuation and prednisone-free survival did not differ when comparing $\Delta CCI \geq 1$ and $RDCI \geq 1$ with $\Delta CCI = 0$ and $RDCI = 0$, respectively. Mortality rate did not differ between GCA and PMR groups: 5-, 10-, and 15-years survival were 62.5% and 71.1%, 25% and 24.4%, and 8.33% and 4.44%, respectively. Comorbidity was associated with higher mortality rate: CCI and RDCI at diagnosis (HR 1.9, CI 95% 1.3-2.6, $p = 0.0002$ and HR 1.7, CI 95% 1.2-2.2, $p = 0.004$, respectively) and at last study encounter (HR 1.4, CI 95% 1.3-2.6, $p = 0.0002$ and HR 1.5, CI 95% 1.04-2.1, $p = 0.03$, respectively).

Conclusion: Despite significant higher cumulative dose of prednisone for patients with GCA compared to patients with PMR, comorbidity scores and mortality rate are comparable. Our results emphasize the unmet need for novel steroid-sparing drugs in PMR as well as in GCA.

Disclosure: E. Pokroy-Shapira, None; A. Dortort-Lazar, None; Y. Molad, None.

Abstract Number: 2769

A Single Center Experience of Temporal Artery Biopsies Performed in 30 African American Patients

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

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Session Time: 9:00AM-11:00AM

Background/Purpose: Giant cell arteritis (GCA) is a systemic vasculitis of large and medium-sized arteries mostly reported in Caucasians (CCs) over 50y.o. There is limited data in the literature on the incidence of GCA in patients of African descent. Here, we view the incidence of GCA based on temporal artery (TA) biopsies in a comparatively large cohort of African-American (AA) patients.

Methods: This is a retrospective chart review of patients (pts) who underwent TA biopsies (TABs) for suspicion of GCA between 1/1/1997 and 1/31/2018 at a tertiary medical center in USA. Cases were identified by searching the pathology database at our institution. Terms used in the search included temporal artery, temporal arteritis, giant cell arteritis, and borderline arteritis. Self-reported demographics were obtained from the charts. Glass slides from 2 AA pts with a positive pathology report for GCA were reviewed by a pathologist to confirm positivity based on histopathologic features for GCA. Comparisons were made with Fisher Exact Test, using two-tailed test with < 0.05 considered significant.

Results: 200 pts with TABs were identified (Table 1). Of these 30/200 (15%) were AA with a total of 33 TABs (3 bilateral). The median age of diagnosis was 66.5 (range 45-90), and 23/30 (75.66%) were female. Although 2/30 (6.7%) were originally reported as positive for GCA, upon review by the pathologist, one was consistent with small vessel vasculitis with fibrinoid necrosis, and the other did not have histopathologic features of GCA. In contrast, 25/155 (16%) CC pts had positive TABs with a median age of 76 (range 56 - 87) and 98/155 (63.22%) were female. The remaining 15/200 pts were of other ethnicities of whom 2 had positive TABs. GCA was less frequent in AAs than CCs based on TAB ($P=0.0163$). Only 3 AAs were seen by a rheumatologist before biopsy as most of the biopsies of AA pts were requested by ophthalmologists, neurologists and primary care physicians. Reasons for biopsy referral among AAs were headache; 24/26 (92%), Scalp tenderness; 9/17 (53%), jaw claudication; 3/13 (23%), and vision loss; 6/21 (28.6%). 14/25 (56%) AA pts had ESR > 50 mm/hr, and 19/22 (86.4%) met 3/5 ACR classification criteria for GCA.

Conclusion: This is one of the largest reported case series in the literature of TA biopsies (TABs) performed in patients of African descent in a single institution in North America. Pathological features of GCA were not present in any TABs in this cohort of 30 African-American (AA) pts. Our data correlates with the clinical observation that GCA usually presents in Caucasians and is rare in AAs. The suspicion and diagnosis of GCA should be made with caution in AA pts. Awareness of this among other specialists and primary care physicians may reduce the need for performing unnecessary TABs.

TABLE 1

Ethnicity	Number of patients with Temporal artery biopsy (total 200)	Median Age at biopsy (range)	Female Gender (F)/total (%)	Biopsy consistent with GCA N/(%)	P-Value by Fisher Test (compared to Caucasians)
Caucasians	155	76 (56 - 87)	98/155 (63.22%)	25/155 (16%)	REF
African-Americans	30	66.5 (45 - 90)	23/30 (75.66%)	0/30 (0%)	0.0163
Hispanics	9	68 (54 - 79)	6/9 (66.66%)	0/9 (0%)	0.3573
Asians	3	63 (59 - 68)	3/3 (100%)	1/3 (33.33%)	0.4191

Table . (Cont'd)

Ethnicity	Number of patients with Temporal artery biopsy (total 200)	Median Age at biopsy (range)	Female Gender (F)/total (%)	Biopsy consistent with GCA N/(%)	P-Value by Fisher Test (compared to Caucasians)
Native-American	1	70	1/1 (100%)	0/1 (0%)	--
Unidentified	2	83.5 (72 - 95)	0/2 (0%)	1/2 (50%)	--

Disclosure: A. Haikal, None; G. Fraga, None; J. Springer, None; M. Maz, None.

Abstract Number: 2770

The Effect of Metabolic Syndrome on Giant Cell Arteritis Treatment

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The effects of metabolic syndrome on vasculature are complex, and studies exploring the role of metabolic syndrome (including diabetes mellitus, obesity, hypertension, and hyperlipidemia) in the development and progression of giant cell arteritis (GCA) have been inconclusive. The objective of this retrospective study was to investigate how preexisting metabolic syndrome disorders impact the disease course, and if those with one or more disorders would require higher total cumulative steroid dose to achieve remission.

Methods: We identified GCA patients based on electronic medical record review using appropriate ICD-10 diagnosis codes. 51% of patients met ACR criteria for GCA. Selection criteria included time frame of 2008 – 2018, and actively being followed at our rheumatology clinics. We collected demographic, clinical, laboratory, imaging and histopathologic data for patients at the time of diagnosis through chart review. We used descriptive statistics for patient characteristics, and used regression analysis to investigate potential associations between metabolic syndrome disorders and total cumulative steroid treatment. Stepwise regression was used to determine the optimal regression model. We evaluated for potential confounding factors including age, gender, race and methotrexate (MTX) use.

Results: Our study population (n =35) was predominantly Caucasian (67%) and female (74%) with mean age at diagnosis of 62.4 ± 12.8 years. Metabolic syndrome was prevalent at or prior to the time of diagnosis in our group: 60% had hypertension, 23% had diabetes, 43% had hyperlipidemia and 43% were obese. Only two patients did not have any metabolic syndrome disorders. All patients received prednisone since their diagnosis, and 40% received MTX during their disease course. The mean total prednisone dose was 6780 ± 6457 mg. Regression analysis of individual metabolic disorders showed only significant association between hypertension and prednisone dosage, where on average, those with hypertension received 5986 mg less total prednisone ($t = -2.249$, $p = 0.033$). This result was not altered when accounting for age of onset, gender and race ($t = -2.180$, $p = 0.040$). However, when accounting for MTX use in subgroup analysis, the association between hypertension and total prednisone was no longer significant ($t = -1.380$, $p = 0.217$ with MTX; and $t = -1.198$, $p = 0.256$ without MTX). Stepwise regression of hypertension, age, gender, race and MTX use yielded a model including only hypertension and MTX. Stepwise regression including all metabolic syndrome diseases and potential confounders yielded a model including diabetes, obesity, hyperlipidemia, hypertension and MTX, where hypertension was the only variable significantly associated with prednisone dose ($t = -2.550$, $p = 0.021$).

Conclusion: Although a small cohort, our study population was similar in distribution when compared to larger cohorts studied previously. Contrary to our hypothesis, there were no metabolic disorders that were associated with significantly higher doses of cumulative prednisone dose. Further studies with larger study populations are needed to elucidate the complex interactions between metabolic syndrome and GCA.

Disclosure: W. Guo, None; R. Jandarov, None; G. Gulati, None.

Current Practice of Cardiovascular Risk Assessment in Giant Cell Arteritis: A Single Center Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Giant cell arteritis (GCA) is a large vessel vasculitis affecting individuals over 50 years of age. Multiple epidemiological studies have determined increased risk of cardiovascular diseases (CVD) in GCA. There are no guidelines to assess CV risk in GCA. The study objective was to review current practice of monitoring CV risk in GCA by rheumatologists in a single center academic rheumatology practice.

Methods: Retrospective chart review of patients diagnosed with GCA was conducted. Data included demographics, comorbid conditions including CVD, obesity, diabetes mellitus (DM), hypertension (HTN), hyperlipidemia (HLD), tobacco use, and physician intervention for CV risk reduction which was defined as measuring lipid profile (LP), use of antiplatelet agent, smoking cessation counseling, lifestyle modification counseling defined as education on healthy diet, exercise, and weight loss. LP measurement was either done at rheumatologists' office or documented as done outside by primary care physician or cardiologist. We used backward elimination logistic regression to assess associations between the likelihood of physician intervention for CV risk reduction, with respect to age, gender, presence or absence of CV risk factors (BMI, tobacco use, DM, HTN, HLD), and prior CVD. HLD was defined as per American College of Cardiology 2013 guidelines.

Results: 148 patients with GCA were seen from 2008 - 2017. The majority of patients were female (111, 75%) with median age of 75 (range 51-93) years. Prevalence of HTN, HLD, CVD, and DM was 72% (n=106), 53% (n=79), 34% (n=50), and 21% (N=31), respectively. Few patients were active smokers (13, 9%) but many were overweight/obese (93, 64%). LP was assessed at least once in only 18% (n=26) patients, and 43% (n=63) were taking a statin. 67% (n=99) patients were on antiplatelet or anticoagulation (AC) therapy. Lifestyle modification counseling was documented in 45% (n=67) patients. Smoking cessation was discussed in 31% smokers. Among the patients with prior CVD, 82% (n=41) were on antiplatelet/AC; 14% (n=7) had LP assessed; and lifestyle modification counseling was documented in 36% (n=18). Male gender and high BMI were associated with higher likelihood of lifestyle modification counseling, (OR 3.4; 95% CI 1.2-10.2) and (OR 1.16; CI 1.1-1.3), respectively. Measuring LP was more common in men (OR 5.2; 95% CI 1.4-19.5) and in subjects with HLD (OR 32.1; 95% CI 6.0-172.1).

Conclusion: This single center study identified potential areas of improvement in the monitoring of CV risk in patients with GCA. Assessment of lipid profile, lifestyle modification counseling, and smoking cessation were infrequently performed or documented in patients with GCA. The likelihood of physician intervention for CV risk reduction was associated with presence of traditional CV risk factors rather than consideration of GCA as a strong independent risk for CVD. Developing guidelines to monitor CV risk in GCA will be useful for clinicians and may help to reduce CV morbidity and mortality in this population.

Disclosure: M. Bari, None; A. Ocon, None; M. Tageldin, None; M. Mumtaz, None; M. Saad Shaukat, None; P. Feustel, None; R. Peredo, None; P. C. Grayson, None; S. Banerjee, None.

Incidence of Cardiovascular Events in Giant Cell Arteritis: A Matched-Control Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Cardiovascular risk in systemic vasculitis may be higher than in normal population, but there is scarce data. Ethnic component plays a role on certain components of the disease and prevalence data on cardiovascular events vary worldwide. Our objective was to compare incidence rates of cardiovascular events (CVE) in patients with giant cell arteritis (GCA) with matched controls from a university hospital-based health management organization (HMO).

Methods: All GCA patients (fulfilling ACR 1990 criteria) diagnosed after the year 2000 from the HMO and age and sex matched controls (1:2) were included. The follow-up period began at the index date, defined as the date of GCA diagnosis for GCA patients and the date of the first medical claim at the HMO for the non-GCA patients. Patients with history of cardiovascular events before diagnosis of GCA and controls with CVE before its correspondent case date of diagnosis were excluded. Subjects were then followed until they voluntarily left the HMO, a CVE occurred, the end of study (May 1st 2018), or death. Electronic medical records were manually reviewed and demographic, clinical and treatment data were collected. Incidence rates per 1000 person-years (PY) of each CVE after index dates were calculated and compared between groups. A multivariate cox regression analysis was performed to identify factors associated with CVE.

Results: 105 GCA patients and 210 controls were included and contributed 1276.9 and 1735.3 PY of follow up respectively. Patients' characteristics are shown in table 1. Use of aspirin and diabetes were more frequent in GCA than in controls. Overall CVE incidence rate was similar between groups: 18.0 per 1000 PY in GCA patients (95% CI 12.3-25.4) and 14.4 per 1000 PY in controls (95% CI 9.9-20.6), $p=0.22$. Development of a thoracic aneurism was significantly more common in GCA patients (6.6 per 1000 PY, 95% CI 3.3-12.7, versus 2.3 per 1000 PY, 95% CI 0.9-6.1, $p=0.04$). Other CVE occurred at similar rates in both groups. In the multivariate cox regression analysis, after adjusting for traditional risk factors, a diagnosis of GCA was not associated with more cardiovascular events and only male sex was associated with an increased CV risk (OR 2.04, 95% CI 1.06-3.95, $p=0.03$). Treatment with statins was protective (OR 0.38, 95% CI 0.18-0.80, $p=0.01$).

Conclusion: As previously described, we found an increased risk of thoracic aneurism in GCA patients in comparison with matched controls. Other CVE were similar across groups.

	GCA patients(n=105)	Controls(n=210)	p
Age, years, media (SD)	75.5 (11.4)	73.4 (8.9)	0.08
Female, n (%), 95% CI)	88 (83.8, 75.4-89.7)	182 (85.8, 80.4-89.9)	0.63
Arterial hypertension, n (%), 95% CI)	72 (68.6, 59.0-76.8)	148 (69.8, 63.3-75.6)	0.82
Diabetes, n (%), 95% CI)	10 (9.5, 5.2-16.9)	5 (2.4, 0.9-5.6)	0.005
Ever Smoker, n (%), 95% CI)	22 (20.9, 14.2-29.9)	44 (20.8, 15.8-26.8)	0.97
Dyslipidemia, n (%), 95% CI)	45 (43.3, 34.0-53.0)	68 (32.1, 26.1-38.7)	0.06
Obesity, n (%), 95% CI)	11 (10.5, 5.9-18.0)	24 (11.3, 7.7-16.4)	0.82
Aspirin user, n (%), 95% CI)	26 (24.8, 17.4-33.9)	18 (8.5, 5.4-13.1)	<0.001
Thoracic aneurism, n (%), 95% CI)	8 (7.6, 3.8-14.6)	4 (1.9, 0.7-4.9)	0.01
Thoracic aneurism, incidence rate, per 1000 patient-years (95% CI)	6.6 (3.3-12.7)	2.3 (0.9-6.1)	0.04
Abdominal aneurism, n (%), 95% CI)	1 (0.9, 0.1-6.5)	2 (0.9, 0.2-3.7)	0.99
Abdominal aneurism, incidence rate, per 1000 patient-years (95% CI)	0.8 (0.1- 5.9)	1.2 (0.2-4.8)	0.41
Stroke, n (%), 95% CI)	6 (5.7, 2.6-12.2)	9 (4.2, 2.2-7.9)	0.56
Stroke, incidence rate, per 1000 patient-years (95% CI)	4.1 (2.2-10.5)	4.7 (2.7-9.9)	0.42
Coronary event, n (%), 95% CI)	5 (4.8, 1.9-11.0)	8 (3.8, 1.9-7.4)	0.68
Coronary event, incidence rate, per 1000 patient-years (95% CI)	4.8 (2.2-10.3)	5.3 (2.8-10.0)	0.43
Peripheral arteriopathy, n (%), 95% CI)	5 (4.8, 1.9 -11.0)	3 (1.4, 0.4-4.3)	0.08
Peripheral arteriopathy, incidence rate, per 1000 patient-years (95% CI)	4.1 (1.6-9.3)	1.7 (0.5-5.3)	0.13
Any cardiovascular event, n (%), 95% CI)	23 (21.9, 14.9-30.9)	25 (11.8, 8.1-16.9)	0.02
Any cardiovascular event, incidence rate, per 1000 patient-years (95% CI)	18.0 (12.3-25.4)	14.4 (9.9-20.6)	0.22
Death, n (%), 95% CI)	7 (6.7, 3.2-13.4)	26 (12.3, 8.5-17.4)	0.12
Cardiovascular death, n (%), 95% CI)	0	5 (20.0, 0.8-41.4)	0.19
Follow up time, years, median (IQR)	11.3 (7.5-15.9)	7.8 (4.3-11.9)	<0.001

Disclosure: F. B. Mollerach, None; M. Scolnik, None; N. M. Marin Zucaro, None; J. M. Martinez P, None; E. R. Soriano, AbbVie, Bristol-Myers Squibb, GSK, Janssen, Novartis, Pfizer Inc, Roche, UCB, 2, AbbVie, Bristol-Myers Squibb, Eli Lilly, GSK, Janssen, Novartis, Pfizer Inc, Roche, Sanofi, UCB, 5, AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer Inc, Roche, Sandoz, UCB, 8.

Diagnostic and Therapeutic Management of a Suspected Case of GCA: An Opinion Survey

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Giant-cell arteritis (GCA) is the most common vasculitis. Specialists have formulated recommendations on how to manage a patient with a possible diagnosis of GCA. However, general practitioners' (GPs) and internal medicine or rheumatology specialists' practices may differ from those recommendations.

Methods: We conducted an opinion survey to determine how they would hypothetically diagnose and manage a suspected case of GCA in France, based on 2 very short "case-vignette" clinical case descriptions, each representing a situation more-or-less typical of GCA, followed by multiple- or single-choice questions. Questionnaires were emailed via the French doctors' Medical Association, and French societies of internal medicine (SNFMI) and rheumatology (SFR).

Results: Between November 2016 and March 2018, 967 GPs and 485 specialists returned their completed questionnaires. Respectively, >46% and 96%, reported having had a confirmed GCA case in consultation. Hypothetical responses, expressed as the % of cases, are how these doctors think they would react to the described cases. Among GPs, 49.1% would systematically refer the patient to a specialist. GPs would initially diagnose 32.1% and prescribe glucocorticoids (GCs), for the most typical GCA case ($P<0.05$), without any visual complications ($P<0.05$). GPs with a prior suspected-GCA case would start GCs more often ($P<0.05$). GPs would start GCs for 40.6%, at 1 mg/kg/day for 66.4% of them, and set up a temporal artery biopsy (TAB), within a mean of 7–15 days for 78.8%, and imaging studies for 10.2%, mainly TA-color duplex ultrasonography (TA-CDU) for 77.5%. GPs would prescribe antiplatelet drugs for 17.8%. Internal medicine and rheumatology specialists would order a TAB for 80.6%, within a mean of 4–7 days, and imaging investigations for 16.2%, mainly TA-CDU (68.8%) or PET scan (43.9%). Among specialists starting GCs, the preferred dose would be 0.7 mg/kg/day for 46.9%. Specialists would prescribe antiplatelet drugs to 51.7%. Among GPs and specialists who would start GCs, TABs would be ordered for similar percentages of cases, but specialists did so earlier ($P<0.05$). GPs and specialists prescribed GCs based only on clinical findings for 14.1% and 8.7%, respectively. GPs would not order a TAB, considering it too complicated to set up, for 67%. Specialists used imaging more often to diagnose GCA ($P<0.05$). Finally, GPs would prescribe significantly higher GC doses ($P<0.05$).

Conclusion: Based on survey findings for 2 hypothetical cases, nearly a third of GCA cases would be managed by GPs alone. GPs and specialists would prefer TAB as the diagnostic test and TA-CDU as the imaging modality, and neither group would seek confirmation for 14.1% or 8.7%, respectively. Daily GC doses and antiplatelet-drug prescriptions would differ between GPs and specialists.

Disclosure: H. Guillet, None; R. Porcher, None; A. Saraux, None; L. Guillevin, None; L. Mouthon, None; A. Régent, None.

Treatment with Methotrexate and Risk of Ischemic Relapses in Patients with Giant Cell Arteritis in Clinical Practice

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Clinical trials have shown the efficacy of Methotrexate (MTX) in giant cell arteritis (GCA) but it is necessary to corroborate these results in real life. The purpose of our study was to assess the incidence and the risk of ischemic relapses in GCA patients treated with and without MTX in clinical practice.

Methods: We performed a retrospective longitudinal observational study. Patients: all GCA patients diagnosed between January 1991 and September 2013 and followed at the Rheumatology department of Hospital Clínico San Carlos until loss of follow up or September 2014. Main outcome: relapses by ischemic event (RIE) defined by the presence of this three circumstances after having achieved an improvement: 1) *clinically:* mandibular claudication, visual manifestations (blurred vision, diplopia, transient or permanent loss of vision), cerebrovascular accident, ischemic heart disease or claudication of limbs, 2) *laboratory test:* increase in the erythrocyte sedimentation rate (ESR) and 3) *treatment:* need to increase corticosteroids (at least 10 mg over the previous dose). Independent variable: exposure to MTX over time. Secondary variables: sociodemographic, clinical and treatment. Statistical analysis: RIE rates were assessed by survival techniques, expressing the incidence per 100 patients-year with their 95% confidence interval [CI]. The influence of MTX on the REI was analysed by multivariate Cox regression models. Results were expressed as Hazard ratios (HR) with their respective CI.

Results: 168 patients were included with a follow-up of 675.6 patients-year. 80.4% were women (mean age: 76.8±7 years). The most prevalent comorbidities were arterial hypertension (64%), dyslipidaemia (34%) and cardiovascular disease (30%). The most common clinical GCA symptoms at diagnosis were headache (87.4%), systemic involvement (55%) and polymyalgia rheumatica (49.7%). At baseline, ESR was 78 ± 30.9 mmHg and the haemoglobin level was 12.06 ± 1.58 mg/dL. 46.4% patients had a positive biopsy and 64% received MTX (mean dose: 10 mg) during follow-up. The mean initial dose of corticosteroids was 50.7 ± 15.5 mg. There were 21 RIE in 20 patients with a frequency of 12.5% and the median time to first RIE was 1.1 [0.4-5.1] years. The main cause of RIE was visual manifestations (61.9%). The incidence of RIE was 3.1 [2.0-4.8], being 1.92 [0.8-4.6] in patients exposed to MTX and 3.8 [2.4-6.3] in those without MTX. The incidence of REI in women was 3.4 [2.2-5.5] and in men was 1.9 [0.6-6]. In the multivariate analysis after adjusting by age, sex, disease activity and calendar time, exposure to MTX (HR 0.3 [0.1-0.9]; p = 0.048) had less risk of RIE compared to no exposure to MTX.

Conclusion: In our cohort, the frequency of REI was 12.5% and the incidence 3.1 per 100 patients-year with a median time to first REI of 1.1 years. The main cause of REI was visual manifestations. In patients with MTX, the incidence of REI was half that of patients without MTX (1.92 vs 3.84). With the results observed in this study, we can consider that the use of MTX decreases the risk of developing REI.

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Abstract Number: 2775

Neutrophil to Lymphocyte Ratio Predicts Glucocorticoid Resistance in Polymyalgia Rheumatica

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Session Information

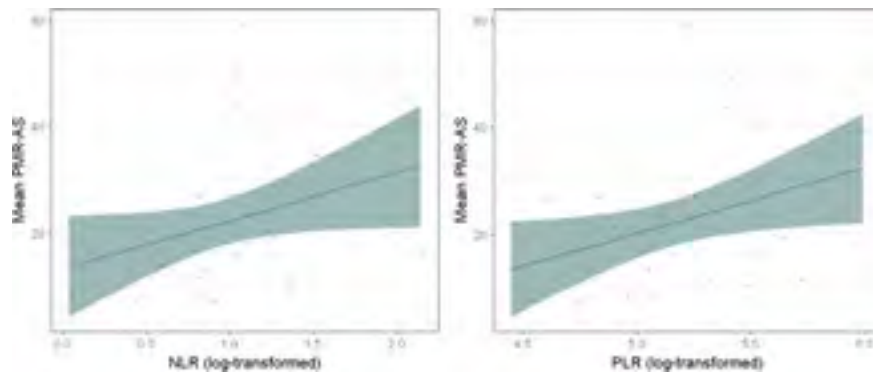
Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been demonstrated to correlate with disease activity and predict treatment response in rheumatic diseases including rheumatoid arthritis and SLE. Are liable and readily accessible biomarker that fulfils these roles has not been identified in polymyalgia



rheumatica (PMR). This study evaluated the relationship between NLR and PLR, and disease activity and glucocorticoid resistance in PMR.

Methods: Data for disease activity (as measured by the PMR-Activity Score [PMR-AS]), prednisolone dose and full blood count was obtained from the Melbourne Predictors of Relapse in PMR (MPR-PMR) study: a prospective observational cohort comprising 37 patients (35 steroid naïve) with newly diagnosed PMR (2012 EULAR/ACR Classification Criteria) treated with a standardised weaning course of prednisolone (British Society of Rheumatology Guideline) for the duration of follow-up (46 weeks) or until the addition of a steroid-sparing agent was indicated. Prior ethics approval was received from Austin Health Research Ethics Committee and the trial registered with the Australian and New Zealand Clinical Trials Registry (trial identification ACTRN1261400696695). Glucocorticoid resistance was defined as non-response to initial prednisolone dose (15mg/day) or initial response followed by flare (as defined by PMR-AS ≥ 9.35 or $\Delta \geq 6.6$) upon weaning prednisolone to 5mg/day. Univariable linear regression analysis of the relationship between PMR-AS (baseline and mean) and NLR and PLR was performed, with comparison of glucocorticoid-resistant patients to glucocorticoid-responders undertaken using logistic regression on baseline NLR. All statistical analysis was performed using R version 3.5.0.

Results: Complete data was available for 33/37 patients (89.2%). Mean age was 69.2 ± 7.53 years, 54% were male and 97% Caucasian. Median ESR was 46 (29 – 65) and CRP 40.2 (19 – 64.4) at diagnosis, whilst median PMR-AS was high at 68.7 (49.7 – 98). A statistically significant relationship was identified between PMR-AS and both NLR ($p = 0.025$) and PLR ($p = 0.005$) at baseline. PLR correlated with mean PMR-AS during follow-up ($p = 0.033$), whilst there was a trend towards significance in the relationship between NLR and mean PMR-AS ($p = 0.054$). In evaluating treatment response, baseline NLR was found to predict glucocorticoid resistance ($p = 0.042$).

Figure 1: Relationship between PMR-AS and NLR and PLR.

Conclusion: Baseline NLR can predict glucocorticoid resistance in newly diagnosed patients with PMR. Both NLR and PLR may also be useful biomarkers of disease activity in PMR.

Disclosure: C. Owen, None; C. McMaster, None; D. Liew, None; J. Leung, None; A. Scott, None; R. Buchanan, None.

Abstract Number: 2776

Interleukin-6 Expression in Inflamed and Non-Inflamed Temporal Arteries from Patients with Giant Cell Arteritis

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Session Time: 9:00 AM-11:00 AM

Background/Purpose: To evaluate if interleukin-6 (IL-6) expression in the temporal artery biopsy (TAB) specimens may differentiate patients with giant cell arteritis (GCA) from those without.

Methods: 63 consecutive formalin-fixed, paraffin-embedded (FFPE) TABs performed between 2009 and 2012 from 32 patients with transmural biopsy-proven GCA, 8 patients with biopsy-negative GCA and 23 controls were retrieved. Demographic, clinical, and laboratory data at presentation and at each follow-up visit were collected. A pathologist reviewed all TABs. Immunohistochemistry was performed on 4µm FFPE tissue sections with a 1:400 dilution of rabbit polyclonal anti-human IL-6 antibody (NOVUS Biologicals Littleton, Co.) for 60' at 37°. Slides of TAB specimens were independently assessed by five readers. IL-6 expression was graded as 0 (absent), 1 (mild), 2 (moderate) and 3 (marked). Inter-reader differences were resolved by consensus. Anti-IL6 staining was considered positive if staining was grade 2 or 3, since grade 1 was faint, sometimes difficult to differentiate from background, and showed the least degree of agreement between Readers.

Results: TAB specimens from patients with biopsy-proven GCA, biopsy-negative GCA and controls were positive for anti-IL-6 staining in 59%, 13% and 48% of cases, respectively, the difference between biopsy-proven and biopsy-negative GCA patients being significant ($p = 0.04$). In non-inflamed TABs, IL-6 was mainly expressed by mesenchymal cells in media and intima layers, while in inflamed TABs IL-6 was mainly expressed by mononuclear inflammatory infiltrating cells. IL-6 grade 2-3 expression was observed in all 6 patients with visual loss compared to 25 (43.9%) of 57 patients without ($p = 0.011$). Blindness was recorded in 2 patients with biopsy-proven GCA and 4 controls (all with a final diagnosis of non-arteritic ischemic optic neuropathy). No associations were found between IL-6 expression and demographic characteristics, GCA signs/symptoms, laboratory and histopathological TAB findings. However, there was a statistical trend ($p = 0.055$) of increased frequency of the halo sign at temporal artery CDS in patients with IL-6 expression grade 2-3 compared to those with IL-6 expression grade 0-1. No significant differences for the expression of IL-6 were observed between patients with and without PMR (5/8 - 62.5% - versus 6/15 - 40% -, $p = 0.400$) and between patients with isolated PMR and those with TAB positive GCA (62.5% vs 59%, $p = 1.000$).

Conclusion: Our study provides evidence that IL-6 expression does not increase the sensitivity of TAB in patients with morphologically uninflamed arteries. A search for further markers that may increase the sensitivity of TAB is warranted.

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Abstract Number: 2777

Dynamics in Peripheral Blood Cell Counts in Giant Cell Arteritis before Treatment, during Treatment and in Treatment-Free Remission

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Session Information

Session Date: Tuesday, October 23, 2018

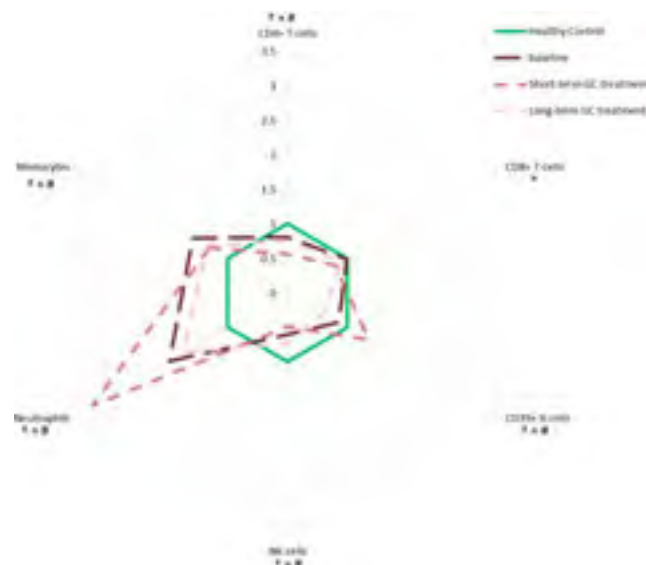
Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Giant cell arteritis (GCA) is an inflammatory disease of large vessels requiring long-term treatment with glucocorticoids. The immunopathology is characterized by vessel infiltrating innate and adaptive immune cells. In GCA, only limited data on dynamics in blood cell populations before, during and after treatment are available. Moreover, it is unknown whether patients that reached treatment-free remission are truly cured or are still suffering from ongoing subclinical vasculitis. This analysis aims to document effects of short and long-term glucocorticoid treatment on leukocyte subsets in this elderly population and may provide clues on the immunopathology of GCA.

Methods: Newly-diagnosed GCA patients (not yet on treatment, $n=41$) were prospectively studied for a median of 914 days. Absolute numbers of leukocyte subpopulations and other standard lab parameters were measured at fixed time points. Values were compared with age-matched healthy controls ($n=52$). Treatment free remission was defined as absence of symptoms without immunomodulatory treatment for at least 6 months.



Results: Platelet counts and inflammatory markers CRP and ESR were significantly increased in newly-diagnosed GCA patients compared to healthy controls. Monocyte and neutrophil counts were, while NK-cells were decreased. CRP and ESR, correlated with monocyte counts, only.

During short-term treatment (up to 3 months), most cell populations decreased but neutrophils and B-cells increased compared to baseline GCA.

After 12 months of treatment, T-cells, NK-cells and neutrophils returned to baseline GCA levels, while B-cells and monocytes were decreased. When compared to healthy controls monocytes and neutrophils were significantly increased after 12 months of treatment while B-cells, CD4+ T-cells and NK-cells were decreased.

In samples of GCA patients in treatment-free remission, innate immune cells did not normalize to healthy control levels. Monocytes and neutrophils remained significantly increased, whereas NK-cells remained decreased.

Conclusion: In GCA, innate rather than adaptive immune cells show major fluctuations before and during treatment. These fluctuations in innate immune cells persisted even in treatment-free remission. Whether this reflects development of a new immune balance or an ongoing subclinical vasculitis remains to be investigated.

Figure 1. Changes in cell populations counts in GCA patients. Counts at baseline (n=41), during short-term (n=69) and long-term treatment (n=100) were expressed as median fold-change compared to healthy controls (n=52). †: significant differences between healthy controls and baseline, ×: significant differences between healthy controls and short-term treatment samples, #: significant differences between healthy controls and long-term treatment samples (Mann-Whitney U test $P < 0.05$).

Disclosure: J. C. Graver, None; Y. van Sleen, None; W. H. Abdulahad, None; A. M. H. Boots, None; M. Sandovici, None; E. Brouwer, None.

Abstract Number: 2778

High Prevalence of Vascular Surgery and Autoimmune Comorbidity in Takayasu Arteritis

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Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

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Background/Purpose: Large vessel vasculitis (LVV) is the arteritis in aorta and its major branches, and classified into Takayasu arteritis (TAK) and giant cell arteritis (GCA). Some patients with aortic valve regurgitation (AR) or aortic

aneurism need vascular surgery, and TAK patients sometimes manifest comorbidities including ulcerative colitis and other autoimmune diseases. However, their prevalence and clinical characteristics are poorly identified. The aim of this study is to determine the prevalence and clinical characteristics of patients who possessed complications or comorbidities of LVV.

Methods: 144 patients who were diagnosed as either TAK (n=132) or GCA (n=12) according to JCS or ACR classification criteria in Tohoku University during 2008-2017 were enrolled to this study. The prevalence and clinical characteristics of patients who received surgery or were complicated by other autoimmune disorders were retrospectively evaluated.

Results: Vascular surgeries were performed in 38 TAK patients (28.8 %) (Aortic valve replacement (AVR), 15; aortic root substitution, 8; other valve replacement, 4; coronary artery graft, 6; percutaneous transluminal angioplasty of renal artery, 5). The proportion of type V lesion was higher in patients who received surgery (43 %) compared to total population (31 %). Difference in vascular type was more evident in patients with AR and AVR. Type IIa accounted for 36 % of patients with AR and 52% of patients who received AVR, while it accounted 25 % in total population. 46.8 % of vascular surgeries were performed within a year after diagnosis (Figure 1), and the age was negatively correlated with C-reactive protein levels in such patients ($p=0.008$, $r=0.35$). These data revealed that there existed a group in which patients manifested rapidly progressive course. Surprisingly, autoimmune comorbidities were observed in 38.6 % of TAK patients and included inflammatory bowel diseases (IBD, 12 cases), thyroid diseases (9), hearing loss (5), rheumatoid arthritis (4), interstitial pneumonia (3), sternoclavicular joint arthritis (3), osteomyelitis (2), uveitis (2), and spondyloarthropathy (SpA, 2). More than half of comorbidities were diseases in which tumor necrosis factor (TNF)-inhibitor was effective. Most of these comorbidities preceded TAK for about a few years.

Conclusion: 28.8 % of TAK patients received vascular surgeries, and half of them manifested rapidly progressive course. Particularly, type V lesion in young, type IIa lesion with AR, male, and complication of AR in the older are at high risk for vascular surgery. 38.6 % of TAK patients possessed autoimmune comorbidities, half of which can be complicated in SpA as well. This suggests similar pathomechanisms among TAK and SpA-related diseases and effectiveness of TNF inhibitors.

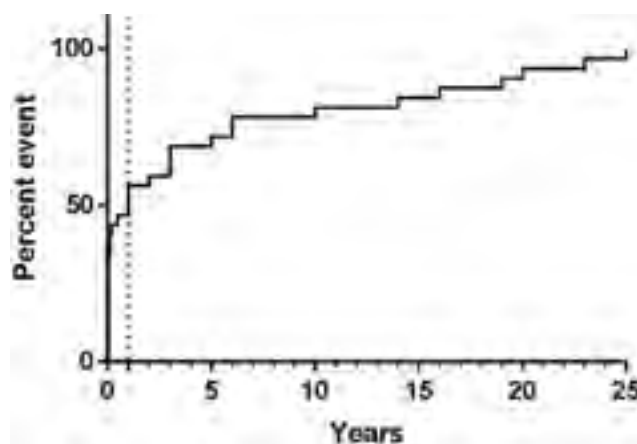


Figure 1. Years from diagnosis to surgery

Disclosure: T. Shirai, None; T. Muto, None; Y. Shirota, None; H. Fujii, None; T. Ishii, None; H. Harigae, None.

Abstract Number: 2779

Long-Term Outcome and Prognostic Factors after Aortic Valve Surgery Due to Aortic Valve Regurgitation in Patients with Takayasu Arteritis

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Session Information

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Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

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Background/Purpose: Aortic valve (AV) surgery is often performed for aortic regurgitation (AR) in patients with Takayasu arteritis (TA). However, data on the long-term outcomes, including survival and cardiac and cerebrovascular outcome, are lacking. This study aimed to characterize the long-term outcomes and prognostic factors of TA patients who underwent surgery for AR.

Methods: Medical records of patients with TA who underwent surgery for moderate to severe AR between January 1995 and December 2015 were reviewed. Poor outcomes were defined as all-cause death and major adverse cardiac and cerebrovascular events (MACCE) including life-threatening aortic aneurysm. Overall survival (OS) was presented with the Kaplan-Meier method and risk factors for poor outcome were analyzed with multivariate Cox analysis.

Results: Total 35 patients with TA with AR underwent AV surgery. The mean age of the patients (male 5, female 30) was 47.2 ± 13 years and the mean follow-up duration was 107.9 ± 85.7 months (median, 97 months; interquartile range, 44-150). Inflammatory values (ESR 36.9 ± 30.6 mm/h, CRP 3.4 ± 4.9 mg/dL) were elevated and 25 of total 35 patients (71%) received perioperative steroid therapy. The 5-year OS rate of the patients was 85.4% and the 5-year MACCE free survival rate was 73.9% (OS rate; 68.1%, MACCE free survival; 46.6% at 10-year). Eighteen of 35 patients (51.4%) had a poor outcome during follow-up. Re-operation was needed in eleven patients (11/35, 31.4%) and stroke occurred in three patients (3/35, 8.6%). Hata angiographic classification type V (6/17 [35.3%] vs 10/18 [55.6%], $p = 0.036$) and coronary disease (0/17 [0%] vs 4/18 [22.2%], $p = 0.030$) were significantly more frequent in patients with poor outcome. Multivariate analysis revealed that coronary disease (hazard ratio [HR], 4.665; 95% confidence interval [CI], 1.252-17.385; $p = 0.022$), diagnosis of TA before the age of 40 (HR, 3.909; 95% CI, 1.221-12.517; $p = 0.022$) were significantly associated with development of poor outcomes (Table 1).

Conclusion: In patients with TA with surgery for AR, poor cardiovascular outcome was frequently observed during follow-up period. It was associated with concomitant coronary artery disease, and TA diagnosis before the age of 40.

Table 1. Multivariate analysis of predictive factors of poor outcomes in patients with Takayasu arteritis with surgery for aortic regurgitation.

Variables	HR	95% CI	p-value
Coronary disease¶	4.665	1.252-17.385	0.022
Age at diagnosis of TA < 40 years	3.909	1.221-12.517	0.022

CI: confidence interval; HR: hazard ratio; TA: Takayasu arteritis

¶ coronary disease: severity is more than moderate stenosis (minimal: 1-24%, mild: 25-49% moderate: 50-69%, severe > 70%)

Disclosure: S. H. Nam, None; D. H. Kim, None; D. H. Lim, None; J. S. Oh, None; S. Hong, None; Y. G. Kim, None; C. K. Lee, None; B. Yoo, None.

Abstract Number: 2780

Insufficient Use of Corticosteroids Results in Higher Relapse in Takayasu Arteritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Takayasu arteritis (TAK) is the chronic granulomatous inflammation of the aorta, its major branches. Although Corticosteroids, such as prednisolone (PSL), and immunosuppressants are key drugs for the treatment of TAK, relapse is frequent when treatment is tapered and there is limited evidence concerning optimal dose for PSL as initial treatment. The aim of this study is to reveal the correlation between PSL dose and relapse in TAK.

Methods: One hundred and five patients with TAK satisfying the criteria of Japanese Circulation Society and American College of Rheumatology in our institution during 1990 to 2015 were enrolled. Clinical characteristics and outcome of

patients with TAK were retrospectively evaluated. The relapse free period was assessed according to the difference in initial treatments.

Results: Among 105 patients with TAK, relapse was observed in 58 patients (55.2 %) during a median 56 months follow-up. Male gender and younger age of onset were significantly associated with relapse. Although PSL \leq 30 mg/day was preferably prescribed for patients with lower inflammatory markers as monotherapy compared to PSL \geq 40 mg/day (87.2 % vs 51.8 %), a significantly higher relapse rate was observed in PSL \leq 30 mg/day group (hazard ratio 1.69, $p=0.048$). Furthermore, the relapse free period was improved in patients treated with a PSL dose \geq 50 mg/day compared to those with a PSL dose 40 mg /day. In addition, combination therapy with immunosuppressants improved the relapse free period compared with PSL monotherapy in the short term (relapse free rate; 82.4 vs 55.6 % at 12 months).

Conclusion: The lower-dose PSL monotherapy resulted in a higher relapse rate compared to the higher-dose PSL, even when disease activity was low. Furthermore, combination therapy could improve the relapse free period at least in the short term. These results indicate that higher doses of PSL or combination therapy with immunosuppressive drugs are desirable strategies for remission induction in TAK, because it has the potential to decrease the relapse rate and suppress further vascular damage in patients with TAK.

Disclosure: T. Muto, None; T. Shirai, None; H. Fujii, None; T. Ishii, None; H. Harigae, None.

Abstract Number: 2781

Long Term Follow-up Results of Takayasu Arteritis Cohort: A Tertiary-Single Center Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

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Background/Purpose: To assess the clinical characteristics and long term follow-up outcomes of patients with Takayasu's arteritis (TAK) in a tertiary referral center.

Methods: In this retrospective study, 107 (F/M: 96/11) patients fulfilling ACR 1990 criteria for Takayasu Arteritis and referred to our center between 2004 and 2017 were investigated. All clinical and demographic data during first diagnosis and longitudinal followup were abstracted from medical records. Relapse was defined according to the physician's global assessment (PGA).

Results: The median age was 30 (14-67) years at symptom onset and 33(14-68) years at diagnosis. Median follow-up duration was 72 (6-264) months. According to Hata Angiographic Classification, Type 5 (51.8%) and Type 1(38.8%) were the most common patterns with the most frequently affected vessel subclavian artery (82.2%) . At diagnosis 0.5-1 mg/kg/day corticosteroid treatment was started in 94.6% patients and a steroid-sparing immunosuppressive(IS) agent in 96.3% of the patients. An initial pulse steroid (1 g/day) therapy was chosen for 8 patients. Before diagnosis 24% patients had a history of are vascularization procedure. After IS treatments, 24% of the patients were undergone a new revascularization procedure. During follow-up, biologic agents were chosen for 13.8% of the patients (5 infliximab and certolizumab each, 2 adalimumab and 2 tocilizumab). Remission was observed in 84% of the patients. At least one relapse was occurred in 43% and > 1 relapse in %14 patients. At the last visit 26% were determined to have an active disease. A > 4 mg of methylprednisolone dose was required in only 8.4% (Image 1) . Mortality rate was 3.7% (4 patients).

Table 1- Baseline characteristics and outcomes of patients

Gender (F)	56 (89.8%)
TAK Type	
1	32 (38.8%)
2	6 (7.4%)
3	0 (0%)
4	2 (1.5%)
5	15 (53.8%)
Age at symptom onset	30 (14.6)
Age at diagnosis	32 (14.6)
Time to diagnosis delay (months)	12 (0-180)
Follow-up time (months)	72 (6-254)
Cardiovascular risk factors (Baseline)	
Hypertension	41 (43.3)
Diabetes	6 (7.6)
Dyslipidemia	25 (23.4)
Coronary artery disease	13 (12.3)
Congestive heart failure	4 (3.7%)
Stroke	10 (9.3%)
Smoking	
Current	10 (28%)
Former	6 (5.8%)
Family history of atherosclerosis	28 (26.2%)
Laboratory findings (baseline)	
ESR (mm/h)	43.8±27.9
CRP (mg/L)	18.2±22.6
Cardiovascular surgery at (%)	
Angioplasty at (%)	13 (7.4)
Bypass at (%)	18 (16.8)
Stent at (%)	28 (24.2)
Treatment at first visit at (%)	
Immunosuppressives	100 (93.4%)
Methotrexate	16 (15%)
Azathioprine	49 (45.3)
Leflunomide	20 (18.7%)
Infliximab	2 (1.9%)
Adalimumab	1 (0.9%)
Certolizumab	2 (2.8%)
Tocilizumab	2 (1.8%)
Certolizumab+Azathioprine	1 (0.9%)
Certolizumab+methotrexate	1 (0.9%)
Infliximab+azathioprine	1 (2.8%)
Adalimumab+Leflunomide	1 (0.9%)
Glucocorticoids*	51 (47.7%)
<4 mg	42 (89.2%)
>4 mg	9 (8.6%)
Cumulative glucocorticoid dose (g)	7.5 (0-21.9)
Damage Scores	
VDI	1.6±2.3
TADS	3.2±3.1

*methylprednisolone **Vasculitis damage index ***Takayasu arteritis damage score

Conclusion: We have defined the long-term follow-up results of our Takayasu's arteritis cohort. Comparing with European and Asia series published recently, requirement for a surgical intervention was lower under immunosuppressive treatments in our series. However, disease activity and relapse rate were still high under conventional ISs, suggesting a need for better therapeutic options.

Image 1- Baseline characteristics and outcomes of patients

Disclosure: S. Kaymaz Tahra, None; F. Alibaz-Oner, None; H. Direskeneli, None.

Abstract Number: 2782

Is It Necessary to Hold Anticoagulation Prior to Temporal Artery Biopsy?

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Session Information

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Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Giant cell arteritis (GCA) and Temporal arteritis (TA) is characterized by chronic granulomatous inflammation in medium and large-sized vessels. It affects 20 in 100,000 people aged 50 and older in the United States. Temporal artery biopsy (TAB) is a common diagnostic tool. Patients are often on anticoagulation (AC) therapy for other comorbidities. In current clinical practice, there are no guidelines on AC use perioperatively for TAB. Our study aimed at examining whether AC therapy was held prior to TAB as well as potential complications post-biopsy in our hospital.

Methods: The study is a retrospective chart review and was approved by the Stony Brook University Institutional Review Board. Electronic Medical Records (EMRs) were searched using ICD 9 and 10 codes for GCA among hospitalized patients between January 2013 and December 2016. Relevant data was collected, including demographics, AC usage and potential TAB related complications, such as ecchymosis, hematoma, infection, wound dehiscence, and facial nerve injury. TAB was performed by General or Vascular Surgeons in our hospital and documented by standard procedure in the EMRs. In most cases, ultrasound was used to map out temporal artery, lidocaine was administered locally, and a segment of temporal artery was obtained. Descriptive statistics and chi-square/Fisher exact tests were used for the data analysis.

Results: Forty-six patients were included in this study due to high clinical suspicion for GCA. The mean age of the patients was 72.8 years, females accounted for 67.4% of patients, and 76.7% were Caucasian. Twenty-seven of 46 patients underwent TAB, of whom 20 patients were on AC therapy prior to procedure. All but one patient continued AC prior to TAB. Of the 20 patients with TAB, surgical data was available in 16 patients. Thirteen patients did not experience complications and only 3 patients reported incision site pain, minor bleeding, or small ecchymosis. There was no significant difference in TAB-associated complications between the two groups. Aspirin dosing was 81 mg, except one patient on 325 mg, and clopidogrel dosing was 75 mg daily. Perioperative use of AC medications and TAB-associated complications are shown in Table 1 and 2.

Conclusion: This study indicates that patients who continued AC prior to TAB developed minimal TAB-associated complications. Our data seems to support the view that there may be inadequate evidence to recommend holding anticoagulation prior to TAB. A prospective study of a large sample size is needed to confirm the results.

Table 1: Perioperative Use of Anticoagulation Medications

N=41	TAB completed		P-value
	No (N=17)	Yes (N=24)	
Ac prior to Biopsy (5 missing)			
No	7 (41.18)	4 (16.67)	0.1509
Yes	10 (58.82)	20 (83.33)	
Was AC held			
No, continued	10 (100.0)	19 (95.00)	1.0000
Yes, Held	0 (0.0)	1 (5.00)	
AC started after TAB (5 missing)			
No	7 (41.18)	5 (20.83)	0.1838
Yes	10 (58.82)	19 (79.17)	

Table 2: Anticoagulation Medications and TAB Complications

N=16	TAB complications		P-Value
	No (N=13)	Yes (N=3)	
AC medication type			
ASA	8 (61.54)	2 (66.7)	0.3582
Plavix	2 (15.38)	0 (0.0)	
ASA & Plavix	1 (7.69)	0 (0.0)	
Warfarin	1 (7.69)	0 (0.0)	
Rivaroxaban	1 (7.69)	0 (0.0)	
ASA & Warfarin	0 (0.0)	0 (0.0)	
Apixaban	0 (0.0)	1 (3.3)	
AC Medication Use			
Yes	13 (81.25)	3 (100.0)	1.0000
No	3 (18.75)	0 (0.0)	

Disclosure: M. Haq, None; D. Schwartz, None; M. Weinberg, None; J. Cepeda, None; E. Taub, None; A. Patniak, None; Q. Yao, Novartis, 5.

Abstract Number: 2783

EULAR Task Force Recommendations for a Minimum Core Set of Parameters to be Collected in Giant Cell Arteritis Registries and Databases

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Table 1: Minimum core set of parameters to be collected in giant cell arteritis registries and databases

Item	Instrument	Baseline	Follow-up
General			
patient identifier		X	X
visit date	date	X	X
Demographics			
age	date of birth (convert to year of birth for questionnaire)	X	
sex			
GCA-related signs & symptoms			
cranial			
ocular involvement	yn (interview)	X	X
ocular symptoms: diplopia, blurring, transient visual loss, persistent fugate	yn (interview); if yes, AION/CRAD/other	X	X
permanent partial visual loss / field defect / blindness / RAPD	yn (interview)	X	X
headache	yn (interview)	X	X
temp arteritis	yn (interview)	X	X
jaw claudication	yn (interview)	X	X
Other medical events or conditions			
death	if yes, cause		X
cardiovascular	date ¹ , <input type="checkbox"/> evidence of vascular change of supplying arteries	X	X
TIA	date ¹ , <input type="checkbox"/> evidence of vascular change of supplying arteries	X	X
stroke	date ¹ , <input type="checkbox"/> evidence of vascular change of supplying arteries	X	X
ischemic	date ¹ , <input type="checkbox"/> evidence of vascular change of supplying arteries	X	X
transient	date ¹ , <input type="checkbox"/> evidence of vascular change of supplying arteries	X	X
Treatment			
glucocorticoids			
current use	mg per day in prednisone equivalent, route of administration	X	X
recent dose	yn (interview)	X	X
continuous (> 3 months) intake			
immunosuppressant/ modulators			
conventional synthetic DMARDs	current medication ² historical treatment ^{3,4}	X	X
biological DMARDs	current medication ² historical treatment ^{3,4}	X	X
important systemic DMARDs	current medication ² historical treatment ^{3,4}	X	X
emipilates agents	current medication ² historical APT ⁵	X	X

¹ report with date if it occurs; ² record every 3-6 months; acute changes need to be recorded whenever they occur (e.g. new medication, imaging finding, osteoporotic fracture); ³ record every 6-12 months; acute changes need to be recorded whenever they occur (e.g. new medication, imaging finding, osteoporotic fracture); ⁴⁻¹⁰ other detailed information given (not specified in this abstract)

Background/Purpose: Giant cell arteritis (GCA) represents the most common form of primary systemic vasculitis, and is frequently associated with comorbidities related either to the disease itself or induced by its treatment. Systematically collected data on disease course, treatment and outcomes of GCA remain scarce. This EULAR Task Force therefore established a core set of data items which can easily be collected by clinicians, in order to facilitate collaborative research into the course and outcomes of GCA.

Methods: A multidisciplinary EULAR task force group of 20 experts including rheumatologists, internists, epidemiologists and patient representatives was assembled. A compilation of items describing GCA status and disease course was compiled to be discussed by three breakout groups during a one-day meeting. The results were presented to all members of the task force and further discussed. Final consensus was achieved by means of several rounds of email discussions after the meeting.

Results: Out of the original compilation, 95 parameters were considered relevant. Potential items were subdivided into the following categories: General, demographics, GCA-related signs and symptoms, other medical conditions, and treatment. Suitable instruments and assessment intervals were proposed for documentation of each item. In the next round of discussions the selection was reduced to a minimum core set of 70 parameters to facilitate implementation of the recommendations in both clinical care and clinical research. The following table represents an excerpt of the set of selected items. This is still a tentative listing since the final voting process on the choice of items is currently ongoing.

Conclusion: The recommended core set of parameters is intended to guarantee comparability of relevant items from different GCA registries and databases for the dual purposes of facilitating clinical research and improving clinical care.

Disclosure: L. Ehlers, None; J. Askling, AbbVie Inc., BMS, MSD, Pfizer, Roche, Astra-Zeneca, Eli Lilly, Samsung Bioepis, UCB, 9, Pfizer, Eli Lilly, 5; J. W. J. Bijlsma, Roche, SUN, 5; M. C. Cid, Roche, 5; M. Cutolo, Mundipharma, Horizon, 5; B. Dasgupta, Roche, Servier, GSK, Mundipharma, Pfizer, Merck, Sobi, UCB, 5, Napp, Roche, 2; C. Dejaco, MSD, Pfizer, UCB, AbbVie, Roche, Novartis, Lilly, Celgene, Merck, Sandoz, GSK, 5, Pfizer, MSD, 2; W. G. Dixon, Bayer, 5; N. Feltelius, Swedish Medical Products agency MPA, 3; A. Finckh, AbbVie, AB2BIO, BMS, Eli-Lilly, MSD, Pfizer, Roche, 5; K. Gilbert, PMRGCAuk, 5; S. Mackie, Roche, GSK, Sanofi, Chugai, 5, PMRGCAuk, PMR and GCA North East patient support group, 6; A. Mahr, Roche-Chugai, 5; E. L. Matteson, Novartis, GSK, Endocyte, BMS, Hoffman-La Roche, Genentech, 5, UpToDate, Paradigm, 9; L. Neill, PMR-GCA Scotland, 6; C. Salvarani, Roche, 5; W. A. Schmidt, Roche, GSK, Sanofi, 5; A. Strangfeld, AbbVie, BMS, Lilly, MSD, Pfizer, Roche, Sanofi-Aventis, UCB, 5; R. van Vollenhoven, AbbVie, BMS, GSK, Pfizer, UCB, 2, AbbVie, AstraZeneca, Biotest, BMS, Celgene, Crescendo, GSK, Janssen, Lilly, Merck, Novartis, Roche, UCB, 5; F. Buttgereit, Horizon, Mundipharma, Roche, Galapagos, 5.

Abstract Number: 2784

Multi Modal Imaging Algorithm to Improve the Accuracy for the Diagnosis of Giant Cell Arteritis

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Session Information

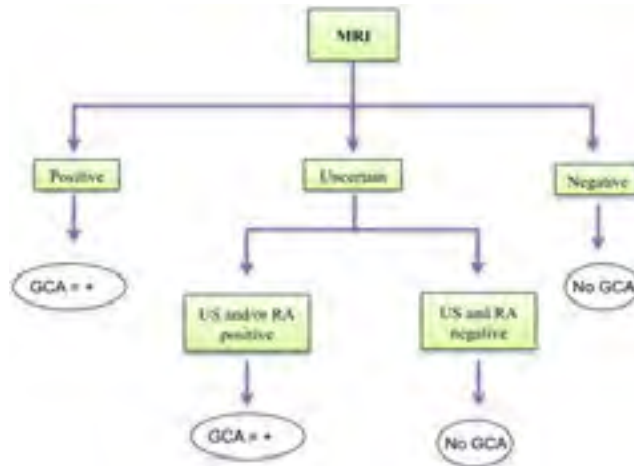
Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis Poster III: Immunosuppressive Therapy in Giant Cell Arteritis and Polymyalgia Rheumatica

Session Type: ACR Poster Session C

Session Time: 9:00 AM-11:00 AM

Background/Purpose: Giant Cell Arteritis (GCA) is the most common systemic vasculitis in patient over 50 years of age. It is a medical emergency as it may lead to ischemic complications, including permanent visual loss in 20 % of untreated patients. Early diagnosis enabling a rapid initiation of treatment is of critical importance. Positive Temporal Artery Biopsy (TAB) is still the gold standard test. However, a negative TAB does not rule out the disease. Encephalic high-field MRI, temporal arteries ultrasonography (US) or fluorescein and indocyanine green angiogram (FA) have been widely studied as diagnostic tests. However, there is currently no consensus nor clearly identified algorithm for their use in a current practice, either alone or in combination. Our objective was to develop a new multimodal imaging algorithm based on a combination of encephalic high-field (3T) MRI, ultrasonography (US) and retinal angiogram (fluorescein (FA) and indocyaninegreen (ICGA)) , to improve the diagnosis of GCA



Methods: All patients referred for suspected GCA at our center from December 2014 to October 2017 were prospectively included in this study. The study was approved by an official external Ethical Review Board. Patient's informed consent was obtained upon inclusion.

For each patient, encephalic 3T MRI, cervical and temporal arteries US and retinal angiogram (RA) were performed. Subsequently, a TAB was performed.

TAB-positive patients were considered cases of GCA ; TAB-negative patients files were reviewed by two experts in internal medicine to determine whether they were or not cases of GCA based on ACR criteria.

Diagnostic accuracy of the combination of MRI, US and RA was statistically evaluated, first separately for each imaging modality, then using a multimodal classification tree.

Results: Forty five patients were included. GCA was diagnosed in 25 patients, TAB was positive in 19 patients. Thirty one patients presented a partial vision loss. MRI was positive in 24/44 patients, negative in 16/44 patients and uncertain in 4/44 cases. No patients with negative MRI had GCA. When MRI was positive, 23/24 patients had GCA. If MRI was uncertain and both US and RA were negative, final diagnosis was no GCA ; if either US and/or RA was positive, final diagnosis was GCA. We propose the following algorithm, with a positive predictive value of 96.2 % and a negative predictive value of 100%.

Conclusion: We propose an algorithm that is highly predictive for GCA diagnosis and can be a valuable tool in suspected cases of GCA.

When GCA is suspected, we suggest to perform 3T encephalic MRI first and if uncertain, to add US and RA.

Disclosure: A. Lecler, None; T. Sené, None; H. Picard, None; T. Leturcq, None; K. Zuber, None; F. Charbonneau, None; C. Vignal-Clermont, None; G. Clavel, None.

Abstract Number: 2785

Efficacy and Safety of Ustekinumab, an Interleukin-12/23 Inhibitor, in Patients with Active Systemic Lupus Erythematosus: 1-Year Results of a Phase 2, Randomized Placebo-Controlled, Crossover Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: ACR Abstract: Plenary Session III

Session Type: ACR Plenary Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: Both the IL-12 and IL-23 pathways have been linked to SLE pathogenesis. The anti-IL-12/23p40 monoclonal antibody ustekinumab (UST), which is approved for psoriasis, PsA, and Crohn's disease, was evaluated in patients with active SLE. We previously reported greater improvement with UST vs PBO in several SLE disease measures through wk24.¹ Results through 1 year are reported here.

Methods: We conducted a phase 2, PBO-controlled study in 102 patients with seropositive SLE, defined by SLICC criteria and active disease (SLEDAI score ≥ 6 and ≥ 1 BILAG A and/or ≥ 2 BILAG B scores). Patients were randomized (3:2) to UST (6 mg/kg single IV loading dose, then 90 mg SC q8w beginning at wk8) or PBO, added to standard care. At wk24, PBO patients crossed over to UST (90 mg SCq8w). The primary endpoint was the proportion of patients achieving SLE response index (SRI)-4 response at wk24. Modified intention-to-treat (mITT) analyses across SLE disease activity measures were performed to evaluate for maintenance of response with UST between wk24 and wk48. Safety was assessed through wk56.

Results: SRI-4 response rate was significantly greater ($p=0.0057$) in the UST group (61.7%) vs PBO group (33.3%) in the wk24 primary endpoint analysis and was sustained at 1 year (63.3%) in the UST group (Table 1). Rates of SLEDAI-2K (65% at wk24 vs 66.7% at 1 year), PGA (67.9% at wk24 vs 75% at 1 year), and active joint (86.5% at wk24 vs 86.5% at 1 year) responses were also sustained from wk24 to 1 year in the UST group (Table 1). CLASI response rate plateaued by wk28 (53.1% at wk24 vs 67.7% at wk28) and was maintained through 1 year in the UST group (68.6%) (Table 1). Among PBO patients who crossed over to UST at wk24 ($n=33$), 54.5% achieved an SRI-4 response at 1 year. Of UST-exposed patients, 81.7% had ≥ 1 TEAE, 15.1% had ≥ 1 SAE, and 7.5% had ≥ 1 serious infection through 1 year (Table 2). No deaths, malignancies, opportunistic infections, or tuberculosis cases were observed. Safety events were consistent with the known UST safety profile.

Conclusion: UST provided sustained clinical benefit in global and organ-specific SLE activity measures through 1 year, with a safety profile consistent with other indications. Thus, UST may be an effective therapy for SLE.

Reference: vanVollenhoven R, Hahn BH, Tsokos GC, et al. Efficacy and safety of ustekinumab, an interleukin 12/23 inhibitor, in patients with active systemic lupus erythematosus: results of a phase 2, randomized, placebo-controlled study [abstract]. *Arthritis Rheumatol.* 2017 ; 69 (Suppl 10).

Table 1. Efficacy results at 24 weeks and 1 year in patients initially randomized to UST

	UST	
	Week 24	Week 48
Randomized patients (mITT)	60	60
SRI-4 response ^a , n/randomized (%)	37/60 (61.7)	38/60 (63.3)
Improvement from baseline in SLEDAI-2K score ^b , n/randomized (%)	39/60 (65.0)	40/60 (66.7)
$\geq 30\%$ improvement from baseline in PGA, n/evaluable ^c (%)	38/56 (67.9)	39/52 (75.0)
$\geq 50\%$ improvement from baseline in the number of joints with pain and signs of inflammation, n/evaluable ^d (%)	32/37 (86.5)	32/37 (86.5)
$\geq 50\%$ improvement from baseline CLASI activity score, n/evaluable ^e (%)	17/32 (53.1)	24/35 (68.6)

a SRI-4 response was defined as a ≥ 4 -point reduction in SLEDAI-2K total score, no new BILAG A and no more than 1 new BILAG B domain score, and no worsening ($<10\%$ increase) from baseline in the PGA of disease activity score

b SLEDAI-2K response defined as ≥ 4 -point improvement from baseline score

c Values for patients meeting treatment failure criteria are set to missing from the point of treatment failure forward

d Patient subpopulation (67% of total population) with ≥ 4 joints with pain and signs of inflammation at baseline

e Patient subpopulation (60% of total population) with CLASI activity score of ≥ 4 at baseline

CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; mITT, modified intention-to-treat; PBO, placebo; PGA, Physician Global Assessment; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI-4, SLE Responder Index-4; UST, ustekinumab; wk, week.

Table 2. Safety results at 24 weeks and 1 year

	Placebo-controlled period through Week 24		Exposed to UST through 1 year	
	PBO	UST	Randomized to UST	All UST (UST + PBO-UST)
Treated patients	42	60	60	93
Patients with ≥ 1 TEAE	29 (69.0)	47 (78.3)	54 (90.0)	76 (81.7)
Patients with ≥ 1 SAE	4 (9.5)	5 (8.3)	10 (16.7)	14 (15.1)
Patients with ≥ 1 infection ^a	21 (50.0)	29 (48.3)	40 (66.7)	56 (60.2)
Patients with ≥ 1 serious infection ^a	0 (0)	2 (3.3)	6 (10.0)	7 (7.5)
Patients with ≥ 1 DCAE	4 (9.5)	4 (6.7)	5 (8.3)	6 (6.5)

All data are presented as n (%).

a Based on infection system organ class

DCAE, adverse event leading to discontinuation; PBO, placebo; PBO-UST, patients who crossed over from PBO to UST at wk24; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UST, ustekinumab; wk, week.

Disclosure: R. van Vollenhoven, Janssen Research & Development, LLC, 2; B. H. Hahn, Janssen Research & Development, LLC, 2; G. C. Tsokos, Janssen Research & Development, LLC, 2; C. Wagner, Janssen Research & Development, LLC, 3; P. Lipsky, Janssen Research & Development, LLC, 2; B. Hsu, Janssen Research & Development, LLC, 3; M. Chevrier, Janssen Research & Development, LLC, 3; R. Gordon, Janssen Research & Development, LLC, 3; K. H. Lo, Janssen Research & Development, LLC, 3; M. Triebel, Janssen Research & Development, LLC, 3; K. Fei, Janssen Research & Development, LLC, 3; S. Rose, Janssen Research & Development, LLC, 3.

Prospective Multicenter Validation Study of the Lupus Low Disease Activity State – a Treatment Target for Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: ACR Abstract: Plenary Session III

Session Type: ACR Plenary Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: The adoption of treat to target approaches for Systemic Lupus Erythematosus (SLE) requires the definition of a target state validated for improved patient outcomes. The Lupus Low Disease Activity State (LLDAS) has been shown in multiple retrospective and cross-sectional studies to have face, content, construct and criterion validity and be associated with better quality of life. We report on a multinational prospective study undertaken to determine whether LLDAS attainment is associated with protection from flare and damage accrual.

Methods: A prospective multicenter cohort study was undertaken in 13 centres between 2013-2017. Patients with SLE (ACR or SLICC criteria) were recruited, SLEDAI-2k, SELENA flare index, PGA, and medication data collected at every visit, and damage (SLICC-ACR damage index (SDI)) collected annually. Time-dependent Cox proportional hazards models were used to assess the association of LLDAS at any time point, as well as the effect of the proportion of time spent in LLDAS, with disease flare and damage accrual (increase in SDI).

Results: 1735 patients (93% female, 77.7% anti-dsDNA positive, mean baseline SLEDAI-2k 4.3 ± 4.4) were followed for (mean \pm SD) 2.2 ± 0.9 years, totalling 12,534 visits (mean interval 0.34 ± 0.17 y). LLDAS was achieved in 54.6% of observed visits. Attainment of LLDAS at any timepoint was highly significantly protective against subsequent flare and damage accrual (Table 1).

Table 1. Association of LLDAS with subsequent flare and damage accrual

Outcome	Time-dependent proportional hazards model (independent variable: in LLDAS (Yes/No))		
	HR	95% CI	p value
Flare (any) at subsequent visits	0.65	0.56 – 0.76	<0.001
Flare (mild-moderate) at subsequent visits	0.74	0.63 – 0.87	<0.001
Flare (severe) at subsequent visits	0.41	0.34 – 0.51	<0.001
Damage accrual (Increase in SDI ≥ 1)	0.55	0.43 – 0.70	<0.001

Similarly, patients who spent $\geq 50\%$ of their observed time in LLDAS had a two-fold reduction in risk of flare and damage accrual (flare: HR 0.49, 95% CI 0.42-0.58, $p < 0.001$; damage accrual HR 0.53, 95% CI 0.41-0.68, $p < 0.001$), compared to those with $< 50\%$ of observed time in LLDAS.

Conclusion: In this large prospective multicenter study, we demonstrate that LLDAS attainment provides significant protection against disease flares and damage accrual. Our findings support the use of LLDAS as a treatment target for SLE, and as an outcome measure for clinical trials and treat-to-target strategies.

Disclosure: V. Golder, None; R. Kandane-Rathnayake, None; M. Huq, None; W. Louthrenoo, None; S. F. Luo, None; Y. J. Wu, None; A. Lateef, None; S. Sockalingam, None; S. Morton, None; S. V. Navarra, None; L. Zamora, None; L. Hamijoyo, None; Y. Katsumata, None; M. Harigai, None; M. Chan, None; S. O'Neill, None; F. Goldblatt, None; C. S. Lau, None; Z. G. Li, None; A. Y. Hoi, None; M. Nikpour, Actelion, GSK, Pfizer, BMS, Eli Lilly, UCB, Astra Zeneca, Janssen, 2, 5; E. Morand, None.

Abstract Number: 2787

–21 HLA-Class I Dimorphism Differentiates Psoriatic Arthritis (PsA) from Psoriasis without Psoriatic Arthritis (PsC)

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: ACR Abstract: Plenary Session III

Session Type: ACR Plenary Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: The association between human leukocyte antigen (HLA) class I alleles and psoriatic disease indicates a potential role for the innate immune system in disease pathogenesis. HLA class I educates NK cells through interactions with killer cell Immunoglobulin receptors (KIRs) and by supplying peptides that bind HLA-E to form ligands for the more conserved CD94/NKG2A NK receptors. The peptides corresponding to residues –22 to –14 of the leader sequence of HLA-A, HLA-B, and HLA-C specifically bind to the binding site of HLA-E. In ~80% of HLA-B allotypes, methionine at position –21M (21M) is replaced by threonine. Methionine –21 delivers functional peptides, whereas threonine at this position (–21T) does not. This functional dimorphism divides the human population into three groups: –21M/M, M/T, and T/T, with decreased order of potency of the NK CD94/NKG2A+ receptor. We aimed to determine whether the distribution of the M and T haplotypes differed between patients with PsA, PsC and healthy controls.

Methods: Two sets of cohorts were included in this study: (a) A discovery cohort of 664 PsA patients, 1155 PsC patients and 3118 controls. Class I HLA alleles were imputed using SNP2HLA. Logistic regressions were used to obtain the association p values by PLINK. We performed three association analyses between HLA B -21 amino acid polymorphisms and different phenotypes: 1) PsC vs. controls; 2) PsA vs. controls; 3) PsA vs. PsC. Population stratification and sex were controlled by including the top seven principal components and sex as covariates in logistic regression. (b) A replication cohort of 1177 PsA patients, 659 PsC patients and 1096 controls with self reported European ethnicity from a large well-phenotyped single centre cohort. HLA typing was done by sequence specific oligonucleotide (SSO) probes using the reverse line blot technique with ambiguous results resolved using sequence specific primers (PCR-SSP). Association analyses as with the Discovery cohort were repeated. All analyses were conditioned on HLA-B*27.

Results: PsC patients within our discovery cohort had a significantly lower prevalence of -21M compared to controls as well as those with PsA (Table 1). The results of the replication study showed similar results (Table 2).

Conclusion: The study provides indications for a potential role of NK cells in PsA pathogenesis, as well as provides a genetic marker that differentiates PsA from PsC.

Table 1. Results of the association study in the discovery cohort.

Comparisons	Freq of -21M in affected	Freq -21M in controls	OR (95% CI)	P value	P value (adjusted)
PsC vs. Controls	0.285	0.331	0.78 (0.70, 0.87)	4.262e-05	4.411e-06
PsA vs. Controls	0.337	0.331	1.04 (0.92, 1.18)	0.671	0.546
PsA vs. PsC	0.337	0.285	1.36 (1.17, 1.58)	0.001	6.692e-05

Table 2. Results of the association study in the replication cohort.

Comparisons	Freq of -21M in affected	Freq -21M in controls	OR (95% CI)	P value	P value (adjusted)
PsC vs. Control	0.276	0.309	0.82 (0.70, 0.96)	0.042	0.015
PsA vs. Control	0.326	0.309	1.13 (0.99, 1.29)	0.203	0.069
PsA vs. PsC	0.326	0.276	1.40 (1.20, 1.63)	0.002	2.268e-05

Disclosure: V. Chandran, AbbVie Inc., 2, AbbVie Inc., amgen, celgene, eli lilly, Janssen, Novartis, Pfizer and UCB, 5, Eli Lilly and Co., 9; Q. Li, None; R. Machhar, None; F. Abji, None; J. Y. Ye, None; R. Nair, None; P. Stuart, None; K. Oikonomopoulou, None; J. T. Elder, None; D. D. Gladman, Amgen, AbbVie, Celgene, Eli Lilly, Janssen, Novartis, Pfizer and UCB, 2, Amgen, AbbVie, BMS, Celgene, Eli Lilly, Janssen, Novartis, Pfizer and UCB, 5; P. Rahman, AbbVie, Amgen, BMS, Celgene, Eli-Lilly, Janssen, Pfizer, Novartis, Merck, UCB, 5, Janssen, 2, AbbVie, Amgen, BMS, Celgene, Eli-Lilly, Janssen, Pfizer, Novartis, Merck, UCB, 8.

Abstract Number: 2788

The Effects of Plasma Exchange and Reduced-Dose Glucocorticoids during Remission-Induction for Treatment of Severe ANCA-Associated Vasculitis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: ACR Abstract: Plenary Session III

Session Type: ACR Plenary Session

Session Time: 11:00AM-12:30PM

Background/Purpose: It is uncertain whether plasma exchange improves clinical outcomes in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Also uncertain is whether, compared to standard therapy with high-dose oral glucocorticoids, a lower-dose glucocorticoid regimen reduces the risk of infection without increasing the risk of end-stage renal disease or death. The PEXIVAS clinical trial addressed both of these questions.

Methods: PEXIVAS was a 2-by-2 factorial, randomized, controlled trial to separately evaluate plasma exchange and two different regimens of oral glucocorticoids in patients with new or relapsing severe ANCA-associated vasculitis, including lung hemorrhage and/or glomerulonephritis (eGFR <50 ml/min/1.73 m²). Participants were randomly assigned to 7 treatments of plasma exchange or no plasma exchange. Participants were also randomly assigned to either a standard-dose oral glucocorticoid regimen or a reduced-dose oral glucocorticoid regimen (<60% of the standard regimen by 6 months). All patients received immunosuppression with either cyclophosphamide or rituximab. Patients were followed for up to 7 years for the primary composite outcome of death from any cause or end-stage renal disease.

Results: The trial recruited 704 participants from 98 sites in 15 countries: 397 (56%) men; 289 (41%) PR3-ANCA, 209 (59%) MPO-ANCA; 691 (98%) with renal involvement; 191 (27%) with alveolar hemorrhage. 109 (15%) patients received rituximab and 595 (85%) received cyclophosphamide.

Among 704 participants, the primary outcome occurred in 28% of patients allocated to plasma exchange compared to 31% in the no plasma exchange group (hazard ratio 0.86, 95% confidence interval [CI] 0.65 to 1.13; p=0.27). The primary outcome occurred in 28% of patients in the reduced glucocorticoid group and 26% in the standard glucocorticoid group (absolute risk difference 2.3%, 90% CI -3.4% to 8.0%; met non-inferiority hypothesis). Serious infections in the first year occurred less often in the reduced glucocorticoid group compared to the standard group (incidence rate ratio 0.70, 95% CI 0.52 to 0.94; p=0.02). The results were similar for both the plasma exchange and glucocorticoid interventions when the individual outcomes of end-stage renal disease or death were analyzed separately.

Conclusion: Plasma exchange does not reduce the risk of end-stage renal disease or death in patients with ANCA-associated vasculitis. Compared to a standard dose, reduced glucocorticoids did not substantially increase the risk of death or end-stage renal disease and resulted in fewer serious infections. The primary results of PEXIVAS, regarding both the use of plasma exchange and dosing of glucocorticoids, will have immediate and substantial impact on the standard of care for patients with ANCA-associated vasculitis.

Disclosure: M. Walsh, None; P. A. Merkel, Bristol-Myers Squibb, 2, ChemoCentryx, 2, 5, Genentech, Inc., 2, 5, InnfaRx, 5, Inmed, 5, AbbVie Inc., 5, CaridianBCT, 2, 5, GlaxoSmithKline, 2, 5, Kypha, 2, Kiniksa, 5, Boehringer-Ingelheim, 2, 5; D. Jayne, Chemocentryx, GlaxoSmithKline, Sanofi, Roche, 2, Boehringer-Ingelheim, Astra-Zeneca, AbbVie, CSL, InflaRx, Bristol-Myers Squibb, Takeda, 5, Aurinia, 6.

Efficacy of Apremilast for Oral Ulcers Associated with Active Behcet's Syndrome over 28 Weeks: Results from a Phase III Study

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Session Information

Session Date: Tuesday, October 23, 2018

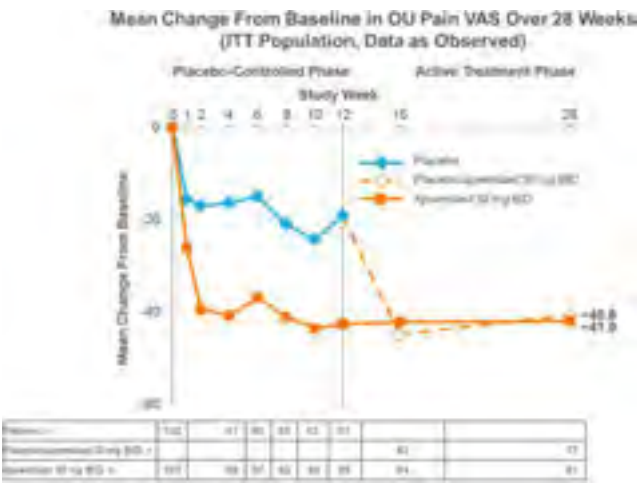
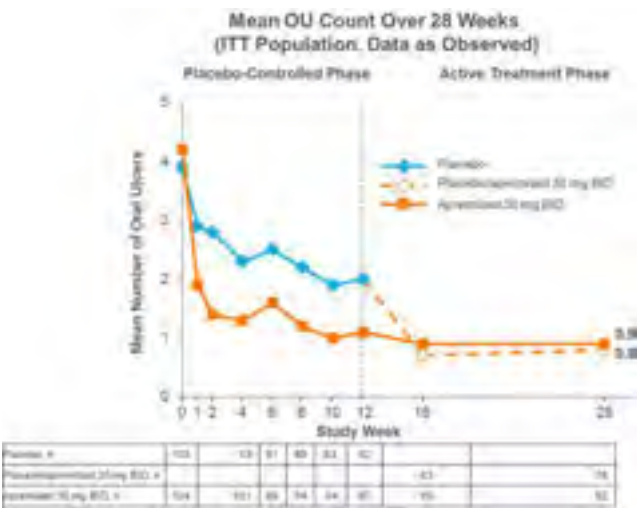
Session Title: ACR Abstract: Plenary Session III

Session Type: ACR Plenary Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: Behcet's syndrome is a chronic, relapsing, multi-system inflammatory disorder characterized by recurrent oral ulcers (OU), which can be disabling and substantially impact quality of life. In a phase III study (RELIEF), apremilast (APR) reduced the number and pain of OU in patients with active Behcet's syndrome over 12 weeks.

Methods: In this phase III, multicenter, placebo (PBO)-controlled study, adult patients with active Behcet's syndrome (defined by ≥ 3 OU at randomization or ≥ 2 OU at screening and at randomization without active major organ involvement) were randomized (1:1) to PBO or APR 30 mg BID for 12 weeks. All patients then received APR treatment through Week 64. The primary endpoint was area under the curve (AUC_{Wk0-12}) for total number of OU over 12 weeks, which reflects the



number of OU over time and accounts for the recurring-remitting course of OU. The current analysis assessed APR efficacy in the treatment of OU for up to 28 weeks.

Results: A total of 207 patients were randomized and received ≥ 1 dose of study medication (PBO: n=103; APR: n=104). At baseline (BL), mean OU counts were 4.2 (APR) and 3.9 (PBO) and mean visual analog scale pain scores were 61.2 (APR) and 60.8 (PBO). The primary endpoint of AUC_{Wk0-12} was achieved; a statistically significantly lower AUC_{Wk0-12} was observed for APR vs. PBO (129.54 vs. 222.14; $P < 0.0001$, multiple imputation). APR treatment resulted in a significantly lower number of OU ($P \leq 0.0015$, multiple imputation) and reduction in OU pain ($P \leq 0.0035$, mixed-effects model for repeated measures) compared with PBO at every visit from Week 1 through Week 12. APR efficacy was sustained with continued treatment through 28 weeks. At Week 28, 62% of patients achieved complete response of OU, with a 70% relative reduction in OU pain from BL. Patients initially randomized to PBO and switched to APR at Week 12 showed comparable benefits (Figures). At Week 28, 59.0% of patients achieved complete remission of OU, with a 68% relative reduction in OU pain from BL. The incidence of any adverse event (AE) was comparable between APR and PBO during the PBO-controlled period (78.8% and 71.8%, respectively). The most common AEs were diarrhea, nausea, headache, and upper respiratory tract infection; most AEs were mild or moderate in severity. No new safety concerns were identified with up to 28 weeks of APR treatment.

Conclusion: APR demonstrated efficacy in the treatment of OU in patients with active Behcet's syndrome. Benefits were sustained for up to 28 weeks with continued treatment. APR was generally well tolerated and safety was consistent with the known safety profile of apremilast.

Disclosure: G. Hatemi, Celgene Corporation, 2; A. Mahr, None; Y. Ishigatsubo, None; Y. W. Song, None; M. Melikoglu, None; S. Cheng, Celgene Corporation, 3; S. McCue, Celgene Corporation, 3; M. Paris, Celgene Corporation, 3; M. Chen, Celgene Corporation, 3; Y. Yazici, Celgene Corporation, 2.

Abstract Number: 2790

Screening of Patients with Adult-Onset Idiopathic Polyarteritis Nodosa for Deficiency of Adenosine Deaminase 2

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: ACR Abstract: Plenary Session III

Session Type: ACR Plenary Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Deficiency of adenosine deaminase 2 (DADA2) is the first described type of monogenic vasculitis. Patients usually present in childhood, but age of onset, disease severity, and organ involvement of DADA2-associated vasculitis is highly variable and clinical features overlap with the typical features of polyarteritis nodosa (PAN). This study aimed to test the prevalence of DADA2 in patients with presumed idiopathic PAN.

Methods: Patients (n=117) with idiopathic PAN, all of whom tested negative for hepatitis B virus infection, were screened for mutations in *ADA2* (formerly known as *CECRI*). DNA was extracted from whole blood by standard methods. Standard PCR amplification and Sanger sequencing was performed for the 9 coding exons of the *ADA2* gene. To further assess the pathogenicity of identified variants on a functional level, *ADA2* activity was determined using the adenosine deaminase assay kit from Diazyme.

Results: Eight of 117 patients (6.8%) were identified as having rare missense variants in *ADA2* with a minor allele frequency of < 0.005. Four patients (3.4%) were homozygous or compound heterozygous for variants in *ADA2*. Of the 7 distinct variants present in these 4 patients, G47A, G47W, R169Q, E328K, F355L, and G383S had previously been reported as causative for DADA2. The remaining variant, P106S, is a rare variant predicted to be damaging to protein function by the PROVEAN algorithm. Four additional patients were carriers for the monoallelic variants R34W, T65M, M309I, and V349I. R34W was reported in DADA2 before, while the 3 remaining variants are of unknown clinical significance.

Serum samples were available on patients with the G383S/G383S and E328K/F355L genotypes and measurements showed markedly reduced *ADA2* enzyme activity, comparable to levels seen in patients with DADA2. *ADA2* activity in the serum of 2 of the monoallelic carriers was not reduced, confirming the non-pathogenicity of T65M and V349I. The median age at diagnosis for the 4 patients with biallelic *ADA2* mutations was considerably younger (median 23.0 years, range 17.4-24.4) than for the 4 patients with heterozygous *ADA2* variants (median 42.0 years, range 16.5-59.0) or the other 109 patients in the cohort (median 47.0 years, range 33.3-56.7) (p=0.04). There were no marked differences in the types of clinical manifestations between patients with or without *ADA2* mutations, including neurologic disease.

Conclusion: This is the first study to report biallelic pathogenic variants in *ADA2* in patients with adult-onset, HBV-negative PAN, and demonstrates that DADA2 accounts for a subset of patients with idiopathic PAN. Given the potential efficacy of TNF-inhibitors in DADA2, that anti-TNF treatment is not the conventional therapy in PAN, and the consequences for other family members, these findings suggest that *ADA2* testing should be considered in patients with HBV-negative idiopathic PAN, especially in patients with an early onset of this potentially life-threatening disease.

Disclosure: O. Schnappauf, None; M. Stoffels, None; I. Aksentijevich, None; D. L. Kastner, None; P. C. Grayson, None; D. Cuthbertson, None; S. Carette, None; S. A. Chung, None; L. J. Forbess, None; N. A. Khalidi, None; C. L. Koenig, None; C. Langford, None; C. A. McAlear, None; P. A. Monach, None; L. W. Moreland, None; C. Pagnoux, None; P. Seo, None; J. Springer, None; A. G. Sreih, None; K. J. Warrington, GlaxoSmithKline, 2, Eli Lilly and Co., 2, Sanofi, 5; S. R. Ytterberg, None; P. A. Merkel, None.

Abstract Number: 2791

Characterization of Monoclonal Anti-PAD4 Autoantibodies from Rheumatoid Arthritis Patients: Functional Implications for Citrullination and Disease Progression

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Anti-citrullinated protein antibodies (ACPA) are present in two-thirds of patients with rheumatoid arthritis (RA), and target proteins that have been post-translationally modified by the calcium-dependent peptidylarginine deiminase (PAD) family of enzymes. In addition, anti-PAD4 autoantibodies are found in about 30% of RA patients and are correlated with disease severity. Anti-PAD4 autoantibodies are thought to enhance the calcium (Ca^{++}) sensitivity of PAD4, thereby increasing its activity at sub-optimal Ca^{++} concentrations present in the synovial tissues. In this study, we aim to identify, isolate, and functionally characterize anti-PAD4 monoclonal antibodies (mAbs) derived from RA patients' plasmablasts to investigate their pathophysiological role in disease.

Methods: We sequenced the paired heavy and light chain immunoglobulin genes of individual plasma blasts from RA patients' blood using DNA cell barcode-enabled sequencing. We recombinantly expressed 72 mAbs representing clonal families identified in the plasmablast antibody repertoires of 6 RA patients, and evaluated their capacity to bind PAD4 by ELISA and immunoprecipitation/Western blotting (IP/WB) assays. We further evaluated the effects of anti-PAD4 mAbs and Ca^{++} concentration on PAD4 enzymatic activity by co-incubating each mAb with recombinant PAD4 and the substrate histone H3. We extended these experiments to assays using freshly isolated human neutrophils.

Results: 7/72 (9.7%) recombinant mAbs recognized PAD4 by ELISA and/or IP/WB. Most of the anti-PAD4 mAbs (5 of 7) belonged to clonal families that included additional ACPA members, and 2 anti-PAD4 mAbs were polyreactive against multiple citrullinated antigens. When the anti-PAD4 mAbs and related clonal family members were tested for their effects on PAD4 activity, we found that the majority enhanced enzymatic activity, resulting in increased citrullination of H3 (citH3), both in the recombinant PAD4 and neutrophil *in vitro* assays. Interestingly, in the latter assay, increased citrullinated H3 was observed both at 0.5 (suboptimal) and 2 (optimal) mM Ca⁺⁺. We also observed that combinations of anti-PAD4 mAbs were more effective at enhancing enzyme activity, suggesting additive or synergistic effects of anti-PAD4 mAbs on potentiating PAD4 activity.

Conclusion: We identified affinity-matured and class-switched RA blood plasmablast clonal families that encode PAD4-reactive antibodies, suggesting that they arise from antigen- and T-cell-driven mechanisms. Most of the anti-PAD4 mAbs identified enhanced PAD4 activity *in vitro*, particularly at sub-optimal Ca⁺⁺ concentrations. Experiments to characterize the specific binding epitopes of anti-PAD4 mAbs and to evaluate their pathogenic effects *in vivo* are ongoing.

Disclosure: A. Gomez, None; S. Kongpachith, None; N. Lingampalli, None; C. Cisar, None; W. H. Robinson, Atreca Inc., 1, 5, 6.

Abstract Number: 2792

The Effect of B Cell Targeted Therapies on Autoantibodies and Excessive Neutrophil Extracellular Trap Formation in Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Systemic lupus erythematosus (SLE) is a severe systemic autoimmune disease characterized by immune-complexes (ICx) which cause inflammation and damage. Effective targeting of autoantibody secreting cells could be key to reset autoimmunity. Functionally, SLE-specific ICx are important triggers of neutrophil extracellular trap (NET) formation. A consortium was formed to study B-cell targeted therapies, including RTX, Bortezomib (BTZ) or combination of RTX + Belimumab (BLM). The present study aimed to investigate the effects of these therapies on relevant autoantibody levels and excessive NET formation.

Methods: This study involved three cohorts of severe SLE patients that were eligible to experimental treatment with RTX (n=16), BTZ (n=12) or RTX+BLM (n=16). A cross-sectional cohort of 35 SLE patients served as a control cohort. A panel of SLE relevant autoantibodies against dsDNA, histones, nucleosomes and C1q were measured by ELISA. NET formation was quantified by a novel highly-sensitive assay using 3D confocal microscopy (Kraaij et al. 2016).

Results: Comparing three regimens, RTX+BLM resulted in the strongest significant reduction on anti-dsDNA, anti-Histone and anti-Nucleosomes antibodies compared to a smaller decrease by RTX and BTZ. Interestingly, RTX+BLM specifically decreased anti-C1q antibodies, which were not targeted by RTX or BTZ. ICx-mediated NET formation was only significantly decreased with a median of 75% [53 – 85%] after RTX+BLM (p=0.0002). Successful seroconversion of autoantibodies associated with decreased NET formation (p=0.02). The latter phenomenon was further corroborated in an independent cohort of SLE patients, where excessive NET formation associated with the presence of three or more autoantibody specificities (p=0.02), and specifically with the presence of anti-C1q antibodies (p=0.03).

Conclusion: In this reverse, translational study of B-cell targeted therapies, we demonstrate that anti-C1q autoantibodies were derived from Blys-dependent proliferating plasma blasts because they were only susceptible to RTX+BLM therapy. Moreover, therapeutically narrowing of the autoantibody repertoire decreased immune-complex mediated NET formation.

Disclosure: L. van Dam, None; Z. Osmani, None; T. Kraaij, None; S. W. A. Kamerling, None; J. A. Bakker, None; H. U. Scherer, None; T. Rabelink, None; R. Voll, None; D. A. Isenberg, None; C. van Kooten, None; Y. K. O. Teng, None.

Molecular Mimicry and Autoimmunity: Anti-*P. Gingivalis* antibody Response in ACPA-Positive Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: The presence of anti-citrullinated protein antibodies (ACPA) is a hallmark of rheumatoid arthritis (RA). ACPAs specifically recognize citrullinated epitopes, a result of a post-translational modification catalyzed by peptidyl arginine deiminases (PAD). Based on the unique feature of the periodontal bacteria *Porphyromonas gingivalis* (*Pg*) to express *P*-PAD it has been suggested that ACPA-positive RA may be precipitated in the gum mucosa. To address this hypothesis, we have investigated the antibody response against a citrullinated peptide derived from *P*-PAD (CPP3) in patients with RA, patients with chronic periodontitis (PD), and in controls. In addition, we have cloned B cells from gingival tissue of a patient suffering from both PD and RA and generated monoclonal antibodies (mAbs) with an aim to demonstrate that citrulline-specific B cells, previously detected only in RA joints and circulation, may also reside in gingival tissue.

Methods: Gingival tissue-derived single CD19+B cells from an ACPA-positive RA patient with PD were sorted by flow cytometry. Immunoglobulin variable region genes were sequenced and expressed to generate recombinant mAbs. CPP3-reactivity was analysed by ELISA in serum samples from 66 PD patients, 63 periodontally healthy controls (non-PD), 200 RA patients, and 120 systemically healthy controls (non-RA), as well as in 55 mAbs. Differences in antibody levels were examined using Mann-Whitney *U* test for independent groups.

Results: Anti-CPP3 antibody levels were low in non-PD controls, while 65% of PD patients showed elevated levels ($p<0.0001$). Significantly increased antibody levels were also detected in 50% of ACPA-positive RA, 20% of ACPA-negative RA, and in 37% of non-RA controls ($p<0.0001$). Notably, this antibody response was citrulline-specific, as the antibody response against the arginine-containing control peptide RPP3 was significantly lower in all subsets ($p<0.0001$). Among 55 mAbs from gingival tissue, 14 (25%) unique clones were CPP3-reactive, of which 4 showed cross-reactivity with RPP3. Interestingly, 4 out of 14 (29%) CPP3-reactive clones also bound citrullinated peptides derived from human α -enolase, filaggrin and histone4, demonstrating cross-reactivity between a bacterial epitope and human epitopes on a monoclonal level.

Conclusion: This study shows that a substantial proportion of systemically healthy individuals possess ACPAs directed against *Pg*, and these ACPAs also bind epitopes on human proteins. Based on our data, we propose that the ACPA response may be triggered by *Pg*, via an antibody response against CPP3, which cross-reacts with human citrullinated proteins by mechanisms of molecular mimicry.

Disclosure: N. Sherina, None; N. Sippl, None; L. Israelsson, None; E. Le Maitre, None; N. Kharlamova, None; M. Hansson, None; K. Eriksson, None; T. Yucel-Lindberg, None; K. Amara, None; K. Lundberg, None.

Peptidylarginine Deiminases Are Required for Normal Immunoglobulin G Half-Life

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Antibodies are a cornerstone of immunity and pathologic in autoimmunity. Immunoglobulin G (IgG) can undergo multiple different post-translation modifications, some of which can alter IgG half-life, but citrullination has not been evaluated in this context. Citrullination, the post-translational conversion of arginines to citrullines, as well as the citrullinating enzymes peptidylarginine deiminase (PAD) 2 and 4, are increased in inflammation and rheumatoid arthritis. Further, citrullinated IgG has been detected in human rheumatoid arthritis and both PAD2 and PAD4 are required for normal IgG levels in a murine model of rheumatoid arthritis. However, the role of these PADs in a normal antibody response and IgG half-life is unknown. The purpose of this study is to determine if PAD2 or PAD4 is required for a normal IgG response to a T cell dependent immunization and normal IgG half-life.

Methods: Wild-type mice, PAD2^{-/-} mice, PAD4^{-/-} mice, wild-type mice treated daily with the pan-PAD inhibitor Cl-amidine, and wild-type mice treated with vehicle control were immunized and then boosted at day 42 with 4-hydroxy-3-nitrophenylacetyl conjugated to keyhole limpet hemocyanin (NP-KLH) precipitated in alum to generate a T cell dependent immune response against NP. Serum from multiple time points was subjected to enzyme-linked immunosorbent assay (ELISA) to detect anti-NP IgG. To assess IgG half-life, serum from NP-KLH immunized mice was transferred to naïve mice. Serum was collected from recipients and the loss of NP-specific IgG quantified by ELISA over time. Similar studies were performed with transferred purified IgG from NP-KLH immunized PAD2^{-/-} and PAD2^{+/-} mice after *in vitro* citrullination with PAD2. The Fc portion of IgG was purified and citrullination assessed by anti-modified citrulline (AMC) western blot.

Results: PAD2^{-/-}, PAD4^{-/-}, and Cl-amidine treated wild-type mice have reduced IgG titers in response to NP-KLH compared to untreated or vehicle control-treated wild-type mice. NP-specific IgG titers fall faster in recipients of serum from PAD2^{-/-}, PAD4^{-/-}, and Cl-amidine treated mice than recipients of serum from untreated or vehicle control-treated wild-type mice, with a more pronounced effect with serum from PAD2^{-/-} donors compared to wild-type than PAD4^{-/-} donors compared to wild-type. IgG is citrullinated in healthy mice and citrullination of the Fc portion of IgG is reduced as detected by AMC blot in PAD2^{-/-}, but not PAD4^{-/-} mice. *In vitro* citrullination rescues the half-life of IgG from PAD2^{-/-} mice.

Conclusion: IgG is citrullinated and PAD enzymes, especially PAD2, are required for normal IgG levels in response to immunization as well as normal IgG half-life in mice. These findings have implications for immunity, for monoclonal antibody based therapies in rheumatoid arthritis, and for both the longevity and specificity of rheumatoid autoimmune antibodies, which bind to citrullinated proteins and IgG.

Disclosure: M. Bawadekar, None; M. A. Shelef, None.

Abstract Number: 2795

IL-23 Acts through IL-23R⁺ Tfh cells to Promote Pathogenic IgG Autoantibody Formation in Lupus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: B Cell Biology and Targets in Autoimmune and Inflammatory Disease

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: IL-23 is currently a target for several forms of autoimmune diseases, yet its role in promoting pathogenic autoantibody development is less clear. IL-23 was required for pathogenic autoantibody production in Fas

deficient B6-Fas^{lpr/lpr} mice. In contrast, in the type II collagen immunized DBA/1 mice, IL-23 did not promote germinal center (GC) formation and IgG anti-CII autoantibody generation. The purposes of this study are to: (i) determine if IL-23 is required for GC and pathogenic autoantibody development; and (ii) determine if IL-23 acts on follicular T-helper cells (Tfh) or GC B cells to induce autoantibody formation in BXD2 mice.

Methods: Sera autoantibody levels were assessed by ELISA in B6, BXD2, and BXD2-*p19*^{-/-} mice. GC development was determined by FACS (GL-7⁺ Fas⁺) and immunostaining and confocal imaging (PNA⁺). IL-23R expression was measured by FACS and quantitative real-time PCR. GC program genes and plasma cell program genes expression were measured by quantitative real-time PCR. Exogenous IL-23 was administered to mice using an IL-23 expressing adenovirus (AdIL-23, 2x10⁹ pfu).

Results: There was significantly increased total IgM and IgM anti-DNA and RF but decreased total IgG autoantibodies in BXD2-*p19*^{-/-} mice compared to BXD2 mice. Surprisingly, the size and number of GC were increased in BXD2-*p19*^{-/-} mice, compared to IL-23 competent BXD2 mice. *Il23r* expression was higher in Tfh cells compared to non Tfh cells and *Il23r* was undetectable in GC B cells. Moreover, administration of AdIL-23 into B6 mice induced significantly increased expression of IL-23R in Tfh cells but not in GC B cells. Despite the lack of IL-23R expression in GC B cells, the low titers of autoantibodies in BXD2-*p19*^{-/-} mice was associated with a significantly diminished expression of activation-induced cytidine deaminase (AID or *Aicda*) in GC B cells of BXD2-*p19*^{-/-} mice compared to BXD2 mice. However, *p19* deficiency did not suppress the expression of other canonical GC program genes, *Bach2* and *Pax5*.

Conclusion: Our data suggest that IL-23 is required for GC B-cell AID induction and thereby pathogenic autoantibody class-switch recombination. Furthermore, IL-23 acts through a novel population of IL-23R⁺ responding Tfh cells to promote IgG pathogenic autoantibody production in the BXD2 mouse model of lupus.

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Abstract Number: 2796

Sex-Based Differences Control ABC Function in SWEF-Deficient Mice

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Session Information

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Age-associated B cells (ABCs) are a novel B cell subset, which expands with age in non-autoimmune mice but accumulates prematurely in autoimmune-prone strains. ABCs exhibit unique phenotypic and functional characteristics. In addition to classical B cell markers ABCs also express markers such as CD11c and CD11b. ABC differentiation depends on the transcription factor T-bet and is promoted by TLR7 stimulation. While ABCs have been proposed to play a key role in the development of autoimmune diseases and in the sex bias observed in these disorders the molecular mechanisms driving ABC formation and function are poorly understood. The SWEF proteins constitute a small family of proteins that includes SWAP-70 and its homolog DEF6, a recently identified risk variant for human SLE. The lack of SWEF proteins leads to the spontaneous development of a lupus-like syndrome, which, similarly to human SLE, preferentially occurs in female mice. We have recently shown that ABC formation is enhanced in SWEF-deficient mice (double knock-out, DKO mice) and is controlled by IL-21 and IRF5. Here we have investigated whether sex-specific differences control the accumulation and/or function of ABCs in SWEF-deficient mice.

Methods: We have evaluated the accumulation of ABCs and their ability to produce autoantibodies in male and female DKO mice. We have also generated male Yaa-DKO mice, which carry a duplication of the TLR7 gene on the Y chromosome, to assess the effects of TLR7 dysregulation on the sex-bias observed in SWEF-deficient mice. T_{FH} cells, ABCs, Germinal center B cells (GCBs), and plasma cells (PCs), were analyzed in the spleens of WT females, WT males, DKO females, DKO males, Yaa-B6 males and Yaa-DKO male mice by FACS. To monitor the severity of the lupus phenotype,

autoantibody levels were tested by ELISAs. Finally, ABCs from all genotypes were FACS-sorted and stimulated *in vitro* with a TLR7 ligand and autoantibody production in the culture supernatant was tested by ELISA.

Results: As compared to WT mice, ABCs accumulate to a similar extent in male and female SWEF-deficient mice. FACS-sorted ABCs from male mice, however, produced much lower titers of anti-dsDNA IgG_{2c} compared to ABCs from DKO female mice upon TLR7 stimulation. Yaa-DKO male mice exhibited a greater expansion of ABCs than male or female DKOs and a marked accumulation of other immune cells including T_{FH} cells, GCBs, and PCs. Yaa-DKO mice had significantly higher autoantibody titers and a shortened lifespan. Interestingly, *in vitro* stimulation of ABCs from Yaa-DKO male mice with a TLR7 ligand resulted in greatly increased autoantibody production compared to male DKOs.

Conclusion: While ABCs accumulate in a similar manner in female and male SWEF-deficient mice, they exhibit a differential ability to produce autoantibodies upon TLR7 stimulation. The functional capability of the SWEF-deficient ABCs is affected by the Yaa translocation. The enhanced autoantibody producing capability of ABCs from Yaa-DKO male mice is accompanied by increased titers of autoantibodies and a shortened lifespan. Thus TLR7 dysregulation alters the sex-bias exhibited by SWEF-deficient ABCs.

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Abstract Number: 2797

Regulation of Autoimmune T Cells By the Co-Receptors CD28 and PD-1

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: T cells play a major role in the pathogenesis of Rheumatoid Arthritis (RA). These cells are regulated by signals provided via the T cell receptor (TCR) complex as well as by a set of co-receptors, which can propagate either stimulatory or inhibitory signals. CD28, a co-stimulatory receptor, and PD-1, a co-inhibitory receptor, are two essential T cell co-receptors whose ligands belong to the B7 family, but have opposing functions. Interestingly, both co-receptors play a role in the pathogenesis of RA and recent studies have shown that CD28 is targeted directly by PD-1. Accordingly, understanding the interplay between CD28 and PD-1 in the context of RA may provide novel approaches to better understand or treat autoimmunity. We hypothesize that PD-1 regulates CD28 function by dephosphorylating specific motifs in the tail of CD28 resulting in impaired downstream T cell function.

Methods: Genetically modified T cell lines were used to study the contribution of different versions of CD28 to TCR signaling. Western blotting and cytokine levels were used to measure the role of CD28 on T cell function. The inhibitory effect of the PD-1 was examined by plating T cells on PD-1 ligand coated surfaces. Mass spectrometry was used to uncover additional proteins that regulate the interaction between PD-1 and CD28. To translate our finding to RA, blood and synovial fluid were collected from active RA patients (disease activity score (DAS)>5.1) to analyze expression of PD-1, CD28 and other signaling mediators. Peripheral blood mononuclear cells (PBMCs) and synovial fluid mononuclear cells (SFMCs) were analyzed by flow cytometry.

Results: We discovered that signaling downstream of PD-1 dephosphorylates tyrosine 173 of CD28 and that this event was absolutely required for the ability of PD-1 to inhibit interleukin 2 (IL-2) secretion. Mass spectrometry results identified SAP, a hematopoietic-restricted adaptor protein found to be associated with autoimmunity, as a regulator of the functional interaction between PD-1 and CD28. SAP co-localized and physically interacted with CD28 to counter PD-1 mediated dephosphorylation. More specifically, SAP bound to tyrosine 173, but not to tyrosine 190 of the cytoplasmic tail CD28, and by doing so blocked the ability of PD-1 to dephosphorylate this site. Additionally, serine at position 171 of CD28 was required to stabilize the interaction between SAP and CD28. Finally, we also learned that SAP levels were elevated in synovial fluid and peripheral blood RA T cells, concordant with PD-1 levels and DAS.

Conclusion: Our results demonstrate that SAP binds to phosphorylated CD28 at tyrosine 173 to interfere with PD-1 activity. It has been suggested that RA T cells are in a state of dysfunction with limited ability to regulate IL-2 production. Our finding of elevated SAP levels in these cells provides a mechanistic explanation for these observations whereby SAP interferes with PD-1 signaling by shielding phosphorylated CD28 and leading to persistent activation in acute disease

followed by dysfunction in chronic disease. Therefore, SAP has potential to be utilized as a biomarker for RA disease activity. Manipulation of the PD-1/CD28 axis may prove to be a promising therapeutic target in autoimmunity.

Disclosure: S. Sandigursky, None; A. Mor, None.

Abstract Number: 2798

Expanded T-Cell Clones Are Present in the Synovium before the Clinical Onset of Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: In healthy individuals with arthralgia and RA-specific autoantibodies (so called *at-risk* individuals) the presence of expanded B-cell receptor (BCR) clones in peripheral blood (PB) accurately predicts who will develop arthritis in the short term¹. Following up on these observations, we investigated in the same cohort of *at-risk* individuals whether the T-cell receptor beta (TCR β) repertoire characteristics in PB and synovial tissue (ST) might also predict imminent onset of arthritis.

Methods: Next-Generation Sequencing of the TCR β repertoire was performed on 20 randomly selected individuals with elevated IgM-RF and/or ACPA levels. Ten individuals did not develop RA during at least 3 years of follow-up, and 10 individuals did. Peripheral blood and synovial tissue samples were analysed during the *at-risk* phase and, for individuals that developed RA, again after RA onset. T-cell clones were identified by their unique TCR β sequence².

Results: In the *at-risk* phase, the synovium is already characterized by expanded TCR β clones, both in *at-risk* individuals that will and will not develop arthritis later. These clones persist in the tissue during onset of arthritis. A higher impact of the dominant TCR β clones in the synovial tissue in the *at-risk* phase was associated with longer time to arthritis ($p=0.02$).

Conclusion: Expanded T-cell clones are present in the synovium of *at-risk* individuals regardless of future development of RA. The expanded clones are maintained after onset of clinical disease. Combined with literature data, these observations show that T cell clones are already expanded in ST very early in disease, and suggest an overall regulatory role. Further studies are needed to characterize these clones.

References:

¹Tak PP et al. Ann Rheum Dis. 2017.

²Klarenbeek PL et al. Immunol Lett. 2010.

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Sjogren's Syndrome Minor Salivary Gland CD4⁺ T Cells Associate with Oral Disease Features and Have a T Follicular Helper-like Transcriptional Profile

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: The predominant salivary gland (SG) T cell types contributing to disease in Sjögren's syndrome (SS) are unclear. This study assessed the frequency and number of SG CD3⁺ T cell subtypes for association with SS disease features and compared the SG CD4⁺ T cell transcriptome of primary SS subjects to that of sicca controls not meeting criteria for SS.

Methods: CD3⁺ T cells from SG biopsy tissue of subjects with primary SS and non-SS sicca were evaluated for proportion (n=51 SS, n=69 non-SS) and number/mg biopsy tissue (n=34 SS, n=56 non-SS) of T cell subsets defined by CD3, CD4, CD8 and CD45RA using flow cytometry. Proportions of memory CD4⁺ T cells were evaluated for correlation with clinical and oral disease parameters. Sorted salivary gland memory CD4⁺ T cells from a subset of focus score positive SS cases (n=17) and focus score negative non-SS subjects (n=15) were evaluated for global gene expression by microarray. Differentially expressed genes were assessed using the limma R package, and bioinformatics analyses were performed using Ingenuity Pathways Analysis and Gene Set Enrichment Analysis.

Results: Proportions of CD4⁺CD45RA⁺ T cells (mean \pm SEM pSS: 33.2% \pm 2.0, non-SS: 21.9% \pm 1.2, p<0.0001) but not those of other CD3⁺ T cell subsets were increased in SS cases compared to non-SS sicca subjects. Proportions of SG CD4⁺ memory T cells positively correlated with SG focus score (r=0.47, p<0.0001), morphologic area of SG fibrosis (r=0.35, p=0.006), and van Bijsterveld corneal damage score (r=0.37, p<0.0001), with relationships remaining after age correction. Differentially expressed (DE) genes in SS cases versus non-SS sicca subjects were enriched for T follicular helper (Tfh), interferon, T cell homeostasis, resistance to apoptosis, atypical lymphoid trafficking and elevated inflammatory response pathways, but not Th17 profile. Predicted upstream drivers of the DE genes included CXCL13, CD40/CD40 ligand and Bcl6, while predicted decreased effects included FoxP3, Fas, STAT6 and mTOR.

Conclusion: Proportion and number of SG memory CD4⁺ T cells selectively associate with key SS disease features, and SG memory CD4⁺ T cells are enriched for a predominant Tfh-like cell profile.

Disclosure: M. L. Joachims, None; K. M. Leehan, None; M. Dozmorov, None; Z. Pan, None; A. Rasmussen, None; L. Radfar, None; D. M. Lewis, None; D. U. Stone, None; K. Grundahl, None; R. H. Scofield, NIH, ept Veran Affirs, Lupus earch Institute, 2, Dept of Veterans Affairs, University of Oklahoma, 3, Boston Pharmaceuticals, 5; C. J. Lessard, None; J. Wren, None; L. F. Thompson, None; K. L. Sivils, None; J. Maier-Moore, None; A. D. Farris, None.

Adenosine 2a Receptor Signals Act to Limit Autoimmune Arthritis By Inhibiting Pathogenic Germinal Center T Follicular Helper (GC-Tfh) Cells

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease

Session Type: ACR Concurrent Abstract Session

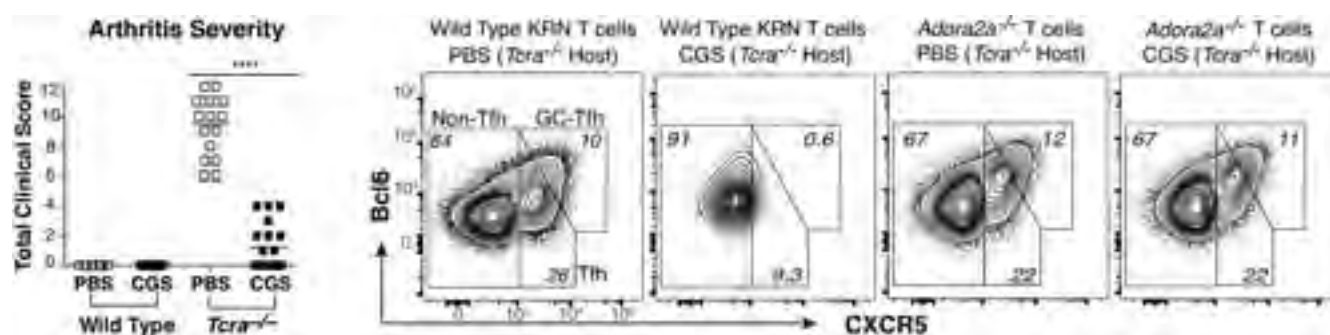
Session Time: 2:30PM-4:00PM

Background/Purpose: CD4 germinal center (GC)-T follicular helper (Tfh) cells are important in the pathogenesis of autoimmune arthritis. Previous studies have shown that adenosine 2a receptor (A2aR, *Adora2a*) signaling can divert CD4 T cells away from the GC-Tfh cell lineage during the primary response to foreign antigens. Therefore, we examined the effects of A2aR signaling on CD4 T cells during the recognition of a self-antigen using a mouse model of autoimmune arthritis.

Methods: Wildtype and *Adora2a*-deficient KRN TCR-transgenic CD4 T cells specific for glucose-6-phosphate isomerase (GPI)/I-A^{g7} self-peptide were transferred into immunodeficient *Tcr α ^{-/-}* I-A^{g7}-expressing mice to induce arthritis, and then recipients were treated with either the selective A2aR agonist CGS-21680 (CGS) or PBS vehicle alone. Severity of disease, autoantibody titers, KRN T cell numbers and phenotype, and GPI-specific isotype class-switched plasmablasts were tracked.

Results: CGS treatment inhibited arthritis development and KRN Bcl6^{hi} CXCR5^{hi} GC-Tfh cell differentiation, blocked the appearance of high affinity GPI-specific and IgG1 isotype class-switched polyclonal plasmablasts, and led to a reduction in anti-GPI IgG1 titers. Additionally, therapeutic administration of CGS after the onset of arthritis blocked further disease progression in association with reduced KRN GC-Tfh cell numbers and anti-GPI IgG1 titers. The therapeutic effects of CGS treatment were lost when the *Adora2a* gene was deleted only from the KRNT cells.

Conclusion: Strong A2aR signaling diverts autoreactive CD4 T cell differentiation away from the GC-Tfh lineage, thus reducing help for the differentiation of dangerous autoreactive B cells that promote arthritis. Therefore, our data suggest that the A2aR and its downstream signaling pathways in CD4 T cells may be promising therapeutic targets to interfere with autoreactive GC-Tfh cell differentiation.



Disclosure: S. Schmiel, None; D. L. Mueller, None.

A Novel B-Cell-Helper IL-21-Producing CD8⁺ T Cell Subset Involved in the Pathogenesis of Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: T Cell Biology and Targets in Autoimmune and Inflammatory Disease

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: A plethora of evidence from genome-wide association studies and relevant animal models implicates a pivotal role of T cells in the pathogenesis of rheumatoid arthritis (RA). CD8⁺ T cells comprise ~40% of all T cells infiltrating the rheumatoid synovium, and the number of activated CD8⁺ T cells in synovial fluids (SF) and peripheral blood (PB) of RA is associated with disease activity. Production of cytotoxic molecules such as granzyme B and perforin in CD8⁺ T cells is more pronounced in patients with RA than in healthy controls (HC).

Apart from their cytotoxicity, CD8⁺ T cells have recently gained attention as an IL-21-producing cell population. In mice a novel subset of IL-21-producing CD8⁺ T cells, like follicular helper CD4⁺ T cells (Tfh), is induced by IL-6 from naïve CD8⁺ T cells and capable of supporting B cell differentiation into Ab-producing cells. However, little is known about a role of human IL-21-producing CD8⁺ T cells, particularly in autoimmune diseases. Here, we have investigated a generation mechanism of IL-21-producing CD8⁺ T cells in humans, and also determined a role of this novel subset in patients with RA.

Methods: CD8⁺ T cells in PB and SF from HC and patients with RA with or without CD3/28 stimulation were subject to the analysis of IL-21 expression at both mRNA and protein levels. To clarify a generation mechanism of IL-21-producing CD8⁺ T cells in humans, naïve (CD45RA+CCR7+) CD8⁺ T cells were highly purified using a flow cytometry and tested for their differentiation into IL-21-producing CD8⁺ T cells in the presence of multiple combination of cytokines along with CD3/28 stimulation. Moreover, using a flow cytometry we thoroughly analyzed the phenotype of a IL-21-producing CD8⁺ T cell subset in HCPB and RAPB as well as RASF. To determine whether IL-21-producing CD8⁺ T cells exert B-cell-helper functions, these cells were co-cultured with memory B cells.

Results: CD3/28 stimulation induced IL-21 production in whole CD8⁺ T cells from HC, and central memory (CD45RA-CCR7+), but not naïve and terminal effector, CD8⁺ T cells were a main producer of IL-21. Among several cytokines extrapolated from studies of CD4⁺ T cell subsets, IL-12 was the most potent cytokine to generate IL-21-producing CD8⁺ T cells from naïve CD8⁺ T cells. IFN- γ , IL-6 and IL-21 were also able to do so, albeit to a lesser extent. The surface phenotype of IL-21-producing CD8⁺ T cells was CD28+CD69+CD95+PD-1+, and these cells also had potential to produce IFN- γ , but not IL-17. Central memory CD8⁺ T cells stimulated with CD3/28 facilitated the differentiation from memory B cells (CD27+CD38-) to plasmablasts (CD27^{high}CD38^{high}) via up-regulation of expression of blimp-1 transcription factors. Compared with HCPB, central memory CD8⁺ T cells were pronounced in RAPB, and this trend was further prominent in RASF. Moreover, RASF enriched CD69+, CD95+ and PD-1+ CD8⁺ T cells than PB from HC and RA. Central memory CD8⁺ T cells in PB and SF from RA most significantly produced IL-21 among CD8⁺ T cell subsets.

Conclusion: Together, these findings suggest that IL-21-producing central memory CD8⁺ T cells are a novel subset that plays a pivotal role in the pathogenesis of RA by exerting B-cell-helper functions.

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Risk of Ischemic Stroke in Veterans with Systemic Sclerosis: A Nationwide Cohort Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health III: SLE and Scleroderma, Big Data and Large Cohorts

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Previously thought to involve primarily the microvasculature, systemic sclerosis (SSc) has been increasingly linked to macrovascular disease. Cardiovascular and cerebrovascular disease are responsible for 20-30% of mortality in SSc, but few studies have shown an independent association between SSc and stroke. In this study, we assessed whether SSc was an independent risk factor for ischemic stroke.

Methods: Using national VA (Veterans Affairs) electronic health record data, we conducted a retrospective cohort study comparing veterans with SSc (defined as ≥ 1 ICD-9 code) to a matched cohort without SSc. We matched subjects 2:1 on date of birth, sex, race, VA facility, observable time, and baseline smoking status. We collected data from October 1999 to September 2014. Follow-up began after the first ICD code for SSc (710.1) among cases, and a matched index date among controls. We excluded subjects with prior ischemic stroke. Subjects were censored after their first diagnosis of ischemic stroke, death, or last encounter, whichever came first.

Baseline comorbidities (hypertension, diabetes, atrial fibrillation, non-cerebrovascular atherosclerotic disease) were assessed prior to the index date using ICD codes. Use of oral glucocorticoids, aspirin and NSAIDs was identified by a filled prescription or provider-recorded non-VA medication in the 12 months before the index date. Medicare enrollment was used as a proxy for non-VA care, defined as enrollment for ≥ 1 year during follow-up. We generated a Kaplan-Meier plot to compare stroke-free survival between groups. We used an adjusted Cox regression model accounting for matching to generate hazard ratios (HRs) for ischemic stroke.

Results: SSc patients had more cardiovascular risk factors, medication use, and Medicare enrollment (Table). Mean follow-up time was 5.1 years for SSc subjects and 5.2 years for non-SSc subjects. We found a significantly increased risk of stroke among SSc patients (12.0/1000 patient-years vs. 8.8/1000 patient-years, unadjusted HR 1.40 (95% CI 1.20 to 1.64); see Figure). After adjustment for baseline cardiovascular risk factors, medications and Medicare enrollment, the HR remained significant (1.29 (95% CI 1.09 to 1.53)).

Conclusion: SSc is associated with a higher risk of ischemic stroke compared to non-SSc patients in the US veteran population, independent of traditional cardiovascular comorbidities and baseline medications. This is the largest study to date of cerebrovascular disease in SSc. Patients with SSc represent a population likely to benefit from targeted stroke screening or prevention therapies.

Figure: Kaplan-Meier estimates of cumulative incidence of ischemic stroke in veterans with SSc compared to matched controls

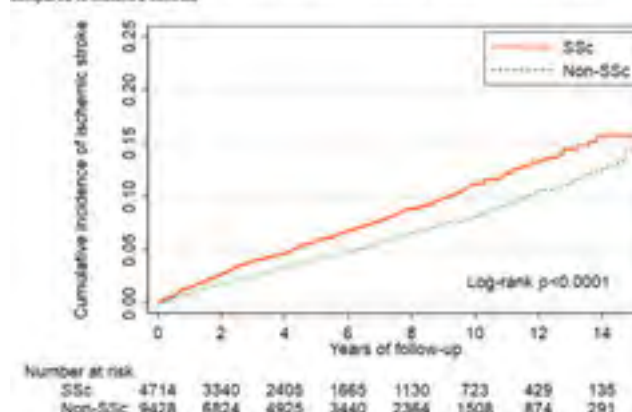


Table: Baseline characteristics of individuals with SSc and matched controls in a national Veterans Affairs population

Variable	SSc N=4714	Non-SSc N=9428	p-value
Age (mean years \pm SD)	61.1 \pm 12.9	61.2 \pm 13.1	0.48
Female	802 (17.0%)	1604 (17.0%)	1.00
Race			1.00
Caucasian	2823 (59.9%)	5646 (59.9%)	
African-American	821 (17.4%)	1642 (17.4%)	
Other	1070 (22.7%)	2140 (22.7%)	
Smoking status			1.00
Never	1334 (28.3%)	2668 (28.3%)	
Ever	2333 (49.5%)	4666 (49.5%)	
Unknown	1047 (22.2%)	2094 (22.2%)	
Atrial fibrillation	368 (7.8%)	467 (5.0%)	<0.001
Hypertension	2863 (60.7%)	5090 (54.0%)	<0.001
Diabetes	1231 (26.1%)	2062 (21.9%)	<0.001
Non-cerebrovascular atherosclerotic disease	1574 (33.4%)	2269 (24.1%)	<0.001
Oral glucocorticoid use†	726 (15.4%)	452 (4.8%)	<0.001
Aspirin use†	837 (17.8%)	1229 (13.0%)	<0.001
Nonsteroidal anti-inflammatory drug use†	1415 (30.0%)	2071 (22.0%)	<0.001
Medicare enrollment‡	3561 (75.5%)	6456 (68.5%)	<0.001

†Filled prescription or provider-reported non-VA medication in the 12 months prior to cohort entry

‡Enrollment in Medicare for at least 1 year during follow-up period

Disclosure: D. Ying, None; M. Gianfrancesco, None; L. Trupin, None; J. Yazdany, None; E. Greidinger, None; G. Schmajuk, None.

Abstract Number: 2803

48-Year Trends in Systemic Sclerosis Mortality in the United States, 1968-2015: Steady Decrease for 15 Years after 33 Years of Continuous Increase

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health III: SLE and Scleroderma, Big Data and Large Cohorts

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: A comprehensive evaluation of long-term trends in systemic sclerosis (SSc) mortality is important to understand the influence of recent advances in SSc management and to identify groups at the highest risk of death. Our objective is to identify secular trends in SSc mortality, and trends in SSc mortality relative to mortality from all other causes (non-SSc).

Methods: We used national mortality and census database to calculate age-standardized mortality rate (ASMR) for SSc and non-SSc causes, ratio of SSc-ASMR to non-SSc-ASMR, and proportions of SSc and non-SSc deaths by age groups for each year from 1968 through 2015. We performed joinpoint trend analysis to estimate annual percent change (APC) and average APC (AAPC) for the above measures for the total population and by sex, race, and age.

Results: From 1968 to 2015, there were 46,798 SSc deaths and 106,058,839 non-SSc deaths. The ASMR for SSc was 2.7 (95% CI, 2.4-2.9) per million persons in 1968 and 3.2 (95% CI, 3.0-3.4) per million persons in 2015. Joinpoint trend

analysis showed that SSc-ASMR increased at an APC of 1.0% between 1968 and 1987, and continued to increase at a higher APC (2.2%) from 1987 to 2001, before decreasing starting in 2001 (APC, -2.6%; 95% CI, -2.2% to -3.1%; 2001-2015). In contrast to this rise-and-decline trend in SSc-ASMR, the non-SSc-ASMR continuously decreased throughout the study period. The resulting SSc-ASMR:non-SSc-ASMR ratio was 111.6% higher in 2015 than in 1968. Men with SSc died at younger ages than did women with SSc. However, women had greater annual increases in SSc-ASMR than did men from 1968 to 2000. Black persons had higher SSc-ASMRs and died at younger ages than did white persons. However, over the entire study period, the SSc-ASMR decreased in black persons (AAPC, -0.4%, 95% CI, -0.7% to -0.0%) while it increased in white persons (AAPC, 0.4%, 95% CI, 0.1% to 0.6%). Persons aged ≥ 65 years had the steepest increases in SSc-ASMRs (AAPC, 2.0%; 95% CI, 1.8% to 2.2%; cumulative, 187.0%), whereas those aged ≤ 44 years had the largest decrease (AAPC, -1.9%; 95% CI, -0.2.5% to -1.2%; cumulative -60.0%) over the 48-year period. Consistently, the proportions of SSc deaths significantly decreased in ≤ 44 and 45-54 year age groups, but increased at a higher APC in ≥ 65 year old decedents.

Conclusion: After continuously increasing for 33-years (1968-2000), SSc mortality decreased during 2001-2015. The most improvement in SSc mortality was seen in younger age groups. However, the improvement in SSc mortality has not kept up with the improvement in non-SSc mortality. Racial and sex disparities persist in SSc mortality. Men and black persons with SSc die at younger ages.

Disclosure: E. Yen, None; D. Singh, None; R. R. Singh, None.

Abstract Number: 2804

Identifying Lupus Patients in Electronic Health Records: Development and Validation of Machine Learning Algorithms and Application of Rule-Based Algorithms

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Epidemiology and Public Health III: SLE and Scleroderma, Big Data and Large Cohorts

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: To utilize electronic health records (EHR) to study SLE, phenotypic algorithms are needed to accurately identify these patients. We aimed to generate an EHR algorithm for SLE using machine learning, which allows the data to inform algorithmic features, with the primary goal of optimizing the positive predictive value (PPV). We also aimed to compare this algorithm with the performance of published rule-based algorithms (Barnado et al. *Arthritis Care Res* 2017) that pre-specify combinations of ICD-9 codes, medications and laboratory tests in our EHR.

Methods: We randomly selected 400 subjects with ≥ 1 SLE ICD-9 code (710.0) from a large, academic medical system EHR, and two rheumatologists identified gold standard cases of definite and probable SLE. Subjects meeting 1997 ACR or 2012 SLICC Classification Criteria for SLE were classified as definite SLE; those with partial, usually 3 criteria, considered to have likely SLE by the treating rheumatologist and reviewers were defined as probable SLE. We divided subjects into a training set (N=200) and validation set (N=200). We extracted codified and narrative concepts using natural language processing (NLP) from the training set and generated algorithms using penalized logistic regression (LASSO) to classify subjects with definite or definite/probable SLE. Algorithms were applied to the validation set using the original case definition and validated externally at the institution where the rule-based algorithms were developed (N=175) using a more liberal definition of specialist-reported SLE diagnosis. We also applied published rule-based algorithms to our training set to assess portability.

Results: In the combined training and validation cohorts (N=200 each), 29% had definite SLE and 41% had definite/probable SLE. Using machine learning methods, our codified data algorithm had a PPV of 90% for definite SLE at 97% specificity and 64% sensitivity (**Table 1**). For definite/probable SLE, the PPV was 92% at 97% specificity and 47% sensitivity. Models with NLP data performed similarly. In the external cohort validation, the codified definite/probable SLE

algorithm had 95% PPV, 98% specificity, and 13% sensitivity. The PPVs of rule-based algorithms were <50% for definite SLE and ≤65% for definite/probable SLE in our EHR (Table 1).

Conclusion: Our final machine learning SLE phenotype algorithms performed well in our EHR and had high PPV but lower sensitivity when externally validated in a cohort that did not require ACR/SLICC criteria to define cases. Rule-based SLE phenotype algorithms did not perform as well in our EHR likely because of these differences in case definitions and variations in clinical practice, medication use, laboratory tests, billing and documentation across EHRs. Unique EHR characteristics, case definitions, and research goals must be considered when applying algorithms to identify SLE patients in EHRs.

Table 1: Algorithm performance characteristics

	Definite SLE*			Definite/Probable SLE		
	Sensitivity (%)	Specificity (%)	PPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)
Machine-learning codified algorithms**	64	97	90	47	97	92
Machine learning codified/ natural language processing algorithms	46	97	87	41	97	90
Top-performing rule-based algorithm 1*** ≥3 ICD-9 codes for SLE, ANA ≥1:40, ever DMARD use, and ever steroid use	58	72	47	53	75	63
Top-performing rule-based algorithm 2*** ≥3 ICD-9 codes for SLE and ever antimalarial use	86	60	46	84	69	65

* In the definite SLE algorithms, probable cases were considered non-SLE.

** Definite SLE algorithm includes the coded variables chronic renal failure, rheumatoid arthritis, sicca syndrome, SLE, unspecified connective tissue disease, anti-dsDNA laboratory test, complement laboratory test, and anti-TNF/biologic DMARDs (etanercept, adalimumab, infliximab, abatacept, tofacitinib, tocilizumab, certolizumab, golimumab, secukinumab, and ustekinumab). Definite/probable SLE algorithm includes the coded variables chronic renal failure, SLE, anti-dsDNA, complement, and antimalarial medication.

*** Barnado, A. et al, *Arthritis Care Res*, 2017

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Abstract Number: 2805

Association of Dietary Quality Scores and Incident SLE in the Nurses' Health Studies

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Session Information

Session Date: Tuesday, October 23, 2018

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Background/Purpose: High intake of antioxidants, fruits/vegetables, nuts and legumes and low intake of sodium, sweetened beverages, and red/processed meats may reduce inflammatory biomarkers and decrease risk of chronic inflammatory diseases. Current knowledge remains scarce regarding the association of diet and SLE risk. We prospectively evaluated four dietary quality scores and risk of SLE and its subtypes, dsDNA positive (+) versus negative (-) SLE. We hypothesized that SLE risk would be inversely associated with adherence to healthier dietary quality scores (including the Alternative Healthy Eating Index [AHEI-2010], Alternative Mediterranean Diet Score [aMed], and Dietary Approach to Hypertension [DASH]) and positively associated with an inflammatory dietary pattern, measured by the validated Empirical Dietary Inflammatory Pattern [EDIP]).

Methods: We included 79,569 female nurses in NHS (1984-2012) and 93,553 in NHSII (1991-2013). Lifestyle, environmental, and medical data were collected on baseline and biennial questionnaires. Incident SLE was confirmed by medical record review. Dietary data were obtained from validated food frequency questionnaires at baseline and approximately every 4 years in follow-up. Four dietary scores, (AHEI-2010, aMed, DASH, and EDIP), were calculated and women were classified according to dietary score use in tertiles. Time-varying Cox regression models estimated

Table. Hazard Ratios for Risk of Incident SLE according to Four Dietary Quality Scores (in Tertiles) among Women in Nurses' Health Study (NHS, 1984-2012) and Nurses' Health Study II (NHSII, 1991-2012)								
Overall SLE			dsDNA-Positive SLE			dsDNA-Negative SLE		
Cases/ person-years	MV HR (95%CI) ¹	p- trend ²	Cases/ person-years	MV HR (95%CI) ¹	p- trend ²	Cases/ person-years	MV HR (95%CI) ¹	p- trend ²
Alternate Healthy Eating Index (AHEI-2010)								
Tertile 1	66/132640	1.00 (ref)	30/132112	1.00 (ref)		30/132680	1.00 (ref)	
Tertile 2	64/133176	1.01 (0.71-1.42)	32/132438	1.08 (0.65-1.78)		32/133180	0.95 (0.55-1.53)	
Tertile 3	54/132538	0.90 (0.62-1.31)	27/132530	0.83 (0.54-1.29)	0.79	28/133182	0.91 (0.55-1.52)	0.73
Alternative Mediterranean Diet Score (aMed)								
Tertile 1	70/134322	1.00 (ref)	30/132650	1.00 (ref)		31/134270	1.00 (ref)	
Tertile 2	59/125806	0.88 (0.60-1.29)	34/134868	0.83 (0.43-1.43)		30/125670	0.92 (0.55-1.50)	
Tertile 3	61/129252	0.89 (0.61-1.29)	32/134712	1.00 (0.53-1.79)	0.99	29/128214	0.79 (0.47-1.34)	0.35
Dietary Approach to Hypertension (DASH) diet								
Tertile 1	64/133103	1.00 (ref)	32/132888	1.00 (ref)		32/133617	1.00 (ref)	
Tertile 2	59/134345	0.93 (0.65-1.33)	33/133972	0.77 (0.45-1.33)		33/134278	1.08 (0.65-1.78)	
Tertile 3	64/131854	1.20 (0.84-1.72)	34/131680	1.29 (0.78-2.12)	0.33	31/131508	1.15 (0.69-1.88)	0.62
Empirical Dietary Inflammatory Pattern (EDIP)								
Tertile 1	61/133180	1.00 (ref)	29/132781	1.00 (ref)		33/132978	1.00 (ref)	
Tertile 2	64/133765	1.02 (0.71-1.45)	31/132808	1.08 (0.65-1.81)		33/133044	0.83 (0.57-1.21)	
Tertile 3	59/133107	0.88 (0.59-1.31)	29/134303	0.98 (0.57-1.67)	0.97	30/133177	0.74 (0.44-1.24)	0.20
Alternate Healthy Eating Index (AHEI-2010): 11 food/nutrients: vegetables, fruits, whole grains, nuts/legumes, sugar-sweetened beverages, red/processed meat, trans-fat % of energy, long-chain omega-3 fats, polyunsaturated fat, sodium and alcohol (each scored 1 to 10). Higher tertiles = healthier.								
Alternative Mediterranean Diet Score (aMed): 9 components: vegetables (excluding potatoes), fruits, nuts, red/legumes, legume, fish, ratio of monounsaturated to saturated fat, red and processed meats, and alcohol. Higher tertiles = healthier.								
Dietary Approach to Hypertension (DASH): 8 components: high intake of fruits, vegetables, nuts and legumes; low-fat dairy products; and whole grains and low intake of sodium, sweetened beverages, and red and processed meats. Higher tertiles = healthier.								
Empirical Dietary Inflammatory Pattern (EDIP): weighted scores including pro- or anti-inflammatory food groups associated with plasma inflammatory biomarker levels (CRP, IL-6, and sTNF-R2). Higher tertiles = increased inflammation = less healthy.								
¹ Multivariable (MV)-adjusted hazard ratios (HR) from time-varying Cox proportional hazards model, adjusted for age, cohort, total energy intake, race, education, household income, smoking, body mass index, oral contraceptive use, age at menarche, menopausal status and postmenopausal hormone use. ² p for trend linear trend across categories of dietary scores, testing median value of each category as contrast.								

multivariable-adjusted hazard ratios (HRs [95% confidence intervals]) of SLE risk, adjusting for potential confounders, overall and by dsDNA subtype, in association with cumulative average dietary scores in tertiles through the 2-year cycle prior to diagnosis.

Results: We identified 184 incident SLE cases (89 dsDNA+ and 95 dsDNA-) from 1984 to 2013. SLE risk was not significantly different among women with dietary patterns in the highest tertile of each dietary score (vs. lowest tertile; AHEI-2010: HR 0.90 [95% CI 0.62-1.31], aMed:HR 0.89 [95% CI 0.61-1.29], DASH: HR 1.20 [95% CI 0.84-1.72], EDIP: HR 0.86[95% CI 0.59-1.25]). No significant trends across tertiles of dietary patterns were observed and no risk was demonstrated for dsDNA+ or dsDNA- SLE subtype with any dietary score (Table).

Conclusion: No association was demonstrated between long-term adherence to the AHEI-2010, aMed, DASH, or EDIP scores with SLE risk overall or by dsDNA subtype among women. These studies make a large effect of dietary pattern upon the risk of developing SLE among women unlikely.

Disclosure: M. Barbhaya, RRF, 2; B. Lu, None; S. K. Tedeschi, None; C. Leatherwood, None; J. A. Sparks, None; E. Karlson, None; K. Costenbader, None.

Abstract Number: 2806

Childhood Physical and Sexual Abuse and Risk of Systemic Lupus Erythematosus Among African American Women

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Session Information

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Session Time: 2:30 PM-4:00 PM

Background/Purpose: We and others have previously reported that post-traumatic stress disorder (PTSD) is associated with increased risk of developing SLE. We aimed to investigate the relationship between physical and sexual abuse as a child and future risk of developing SLE among African American women.

Methods: We examined whether there was an association between self-reported physical and sexual abuse in childhood and SLE risk in a large nationwide prospective cohort of African American women, the Black Women's Health Study (59,000 women enrolled in 1995 and followed through 2017). Nine childhood abuse questions (from Conflict Tactics Scale, Straus MA, 1979 and Pregnancy Abuse Assessment Screen, McFarlane J, 1992) were asked on the 2005 questionnaire. Types of physical and sexual child abuse were described and response categories were, never, 1-3 times or ≥ 4 times (for questions not answered, we considered responses to be 'never'). Covariate data, mainly concerning childhood exposures, were obtained from baseline and biennial questionnaires. Incident SLE was identified by self-report and verified by medical record review for 1997 Updated ACR Criteria. We used Cox regression models to estimate HRs and 95% CIs for SLE risk related to several types of past physical and sexual abuse, adjusting for potential confounders.

Table. Hazard Ratios for SLE in Relation to Childhood Physical and Sexual Abuse among 36,153 Participants in the Black Women's Health Study without SLE at Cohort Enrollment in 1995								
			Age- and Questionnaire Period- Adjusted			Multivariable-Adjusted*		
	Cases	Person-years	HR	95% CI		HR	95% CI	
Pushed me								
Never	43	263462	Ref.			Ref.		
1-3 times	33	259421	0.76	0.49	1.21	0.77	0.49	1.21
≥4 times	26	147958	1.03	0.63	1.68	1.04	0.64	1.70
Threw something at me								
Never	65	445478	Ref.			Ref.		
1-3 times	24	169723	0.94	0.59	1.51	0.94	0.58	1.50
≥ 4 times	13	55640	1.52	0.84	2.76	1.52	0.83	2.76
Kicked or punched me								
Never	54	393869	Ref.			Ref.		
1-3 times	31	203088	1.06	0.68	1.66	1.06	0.68	1.66
≥4 times	17	73884	1.56	0.90	2.70	1.57	0.91	2.72
Hit me with something								
Never	41	265413	Ref.			Ref.		
1-3 times	28	228714	0.76	0.47	1.24	0.76	0.47	1.23
≥4 times	33	176714	1.13	0.71	1.80	1.14	0.72	1.81
Choked or burned me								
Never	95	642857	Ref.			Ref.		
1-3 times	4	23042	1.12	0.41	3.05	1.14	0.42	3.10
≥4 times	3	4942	3.71	1.17	11.7	3.88	1.22	12.3
Physically attacked me								
Never	76	544228	Ref.			Ref.		
1-3 times	13	88087	1.04	0.58	1.88	1.04	0.58	1.88
≥4 times	13	38526	2.32	1.29	4.19	2.35	1.30	4.25
Exposed their genitals								
Never	74	548856	Ref.			Ref.		
1-3 times	17	89646	1.35	0.79	2.28	1.34	0.79	2.28
≥4 times	11	32339	2.35	1.24	4.44	2.36	1.24	4.46
Was sexual with me								
Never	78	551049	Ref.			Ref.		
1-3 times	10	80396	0.84	0.43	1.62	0.84	0.43	1.63
≥4 times	14	39396	2.36	1.33	4.17	2.37	1.33	4.21
Seriously harmed a loved one								
Never	82	569741	Ref.			Ref.		
1-3 times	12	65883	1.24	0.67	2.27	1.23	0.67	2.26
≥4 times	8	35217	1.51	0.73	3.12	1.53	0.74	3.19
Frequency of sexual abuse								
Never	78	548145	Ref.			Ref.		
1-3 times	10	83300	0.80	0.42	1.56	0.81	0.42	1.56
≥4 times	14	39396	2.34	1.32	4.15	2.36	1.32	4.19
*Adjusting for started alcohol consumption age ≤ 14, passive smoking exposure at ages 0-10, BMI at age 18, area-level socioeconomic status, first oral contraceptive use at age ≤14 years, parental education level, age at menarche.								

Results: Of the 36,153 women who answered the child abuse questions, mean age at study baseline was 39.2 years (10.6 SD), 14% were current smokers, and mean BMI was 27.9 (6.6 SD). During 670,841 person-years of follow-up, we identified 102 incident SLE cases with self-reported data on childhood physical and sexual abuse. Compared to women who denied any abuse, those who reported frequent severe abuse, including being choked, burned, physically attacked, having genitals exposed to them or having sexual relations, all occurring ≥ 4 times, experienced increased risk of SLE as an adult (HRs 2.3-3.7)(Table).

Conclusion: Childhood physical and sexual abuse, in particular severe and frequent abuse, were associated with increased risk of developing SLE among adult African American women. While these results are based on small numbers and there is a potential for recall bias, they are thought-provoking and need to be pursued and verified. The biologic mechanisms underlying this association are not well understood, but could involve dysregulation of the hypothalamic-pituitary axis and stress hormones in PTSD, or stimulation of inflammatory cytokines.

Disclosure: M. Barbhaya, RRF, 2; Y. Cozier, None; N. Castro-Webb, None; S. K. Tedeschi, None; C. Leatherwood, None; L. Rosenberg, None; K. Costenbader, None.

Association of Exposure to Childhood Abuse with Incident Systemic Lupus Erythematosus in a Longitudinal Cohort of Women

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Background/Purpose: Prior studies demonstrated associations between post-traumatic stress disorder and increased risk of incident SLE and between childhood trauma and increased risk of hospitalization for autoimmune disease during adulthood. Severe stressors may alter immune function and result in increased inflammation and cytokine release, thereby increasing risk of SLE. We examined if childhood abuse is associated with increased risk of incident SLE.

Methods: Data are from the Nurses' Health Study II, a longitudinal cohort of female U.S.-based nurses enrolled in 1989 followed with biennial questionnaires. To measure childhood physical and emotional maltreatment, we used the Physical and Emotional Abuse Subscale of the Childhood Trauma Questionnaire (CTQ), for sexual abuse, the Sexual Maltreatment Scale of the Parent-Child Conflict Tactics Scales (CTS-SA), and for childhood physical assault, the Physical Assault Scale of the Conflict Tactics Scales (CTS-PA), all administered in 2001 with 75% response rate (68,505/91,268). Higher scores indicate more frequent abuse. We defined incident SLE through 2015 by self-report, confirmed by medical record review with ≥ 4 SLE ACR criteria. We excluded 1,071 women with missing childhood abuse exposure data or with self-reported, unconfirmed connective tissue disease. Multivariable Cox regression models evaluated the association (hazard ratio [HR] and 95% CI) between childhood abuse and incident SLE. We examined whether biennially assessed risk factors (e.g. smoking, BMI, alcohol use, oral contraceptive use) and potential confounders (e.g. age, race, median household income, parental education) accounted for increased SLE risk among those with vs. without childhood abuse exposure.

Results: Among 67,434 women, with a mean age of 34.6 (SD 4.8) in 1989, with >24 years of follow-up, there were 93 incident SLE cases. In age and race-adjusted models, exposure to the highest vs. lowest physical and emotional maltreatment was associated with >2-fold greater risk of SLE (HR 2.21 (95% CI 1.29-3.80)). Exposure to moderate and high levels of physical assault was associated with 1.70 (95% CI 1.08-2.68) times higher risk of SLE vs. no exposure. We did not find statistically significant associations between sexual abuse and SLE risk. After additionally accounting for potential lifestyle, reproductive and socioeconomic factors in separate models, HRs were only slightly attenuated (**Table**).

Conclusion: In this longitudinal cohort, we observed significantly increased risk of incident SLE among women who experienced childhood physical and emotional abuse compared with women who had not. Our findings suggest that exposure to extreme childhood stress and adversity may contribute to SLE development. Further studies are needed to investigate the role of timing and of the socioenvironmental context of abuse exposures and potential underlying mechanisms.

Table. Association of childhood trauma exposure with risk of incident SLE in multivariable-adjusted models (N=67,434)

Scale	SLE Cases/ Person-years	Age and race-adjusted models Hazard ratio (95% CI)	Lifestyle factor-adjusted models* Hazard ratio (95% CI)	Reproductive factor-adjusted models** Hazard ratio (95% CI)	Socioeconomic factor- adjusted models+ Hazard ratio (95% CI)
Childhood Physical and Emotional Maltreatment (CTQ)					
None	22/577,387	Ref.	Ref.	Ref.	Ref.
Low	24/356,531	1.81 (1.01-3.24)	1.78 (1.00-3.19)	1.80 (1.01-3.22)	1.80 (1.01-3.23)
Medium	14/327,027	1.12 (0.57-2.19)	1.07 (0.55-2.10)	1.09 (0.56-2.13)	1.11 (0.57-2.18)
High	33/385,090	2.21 (1.29-3.80)	2.05 (1.18-3.53)	2.12 (1.23-3.65)	2.19 (1.27-3.77)
p for trend		p=0.01	p=0.03	p=0.02	p=0.02
Childhood Physical Assault (CTS-PA)					
None	34/769,049	Ref.	Ref.	Ref.	Ref.
Low	17/333,044	1.14 (0.63-2.04)	1.11 (0.62-1.99)	1.11 (0.62-2.00)	1.14 (0.62-2.04)
Med/High	42/544,762	1.70 (1.08-2.68)	1.60 (1.01-2.53)	1.63 (1.03-2.57)	1.69 (1.07-2.66)
p for trend		p=0.02	p=0.04	p=0.03	p=0.02

Table . (Cont'd)

Scale	SLE Cases/ Person-years	Age and race-adjusted models Hazard ratio (95% CI)	Lifestyle factor-adjusted models* Hazard ratio (95% CI)	Reproductive factor-adjusted models** Hazard ratio (95% CI)	Socioeconomic factor- adjusted models+ Hazard ratio (95% CI)
Childhood Sexual Abuse (CTS-SA)					
None	60/1,097,828	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>
Low	25/388,509	1.15 (0.72-1.84)	1.10 (0.69-1.76)	1.12 (0.79-1.79)	1.14 (0.71-1.82)
Med/High	8/160,518	0.89 (0.42-1.86)	0.79 (0.38-1.67)	0.82 (0.39-1.73)	0.87 (0.41-1.82)
p for trend		p=0.84	p=0.60	p=0.68	p=0.80

Adjusted for age, race/ethnicity, smoking status (never, past, current), BMI (18.5-<25, 25-<30, 30+), cumulative alcohol use (0-<5g/day, \geq 5g/day), exercise (0-9 mets/week, \geq 10 mets/week)

** Adjusted for age, race/ethnicity, ever/never oral contraceptive use, menopausal status, age at menarche (<10, \geq 10)

+ Adjusted for age, race/ethnicity, parental education (\leq high school, some college, college+), median household income (<40K, \geq 40K)

Disclosure: C. H. Feldman, None; S. Malspeis, None; C. Leatherwood, None; L. Kubzansky, None; K. Costenbader, None; A. Roberts, None.

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T-Score As an Indicator of Fracture Risk on Therapy: Evidence from Romosozumab Vs Alendronate Treatment in the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk Trial

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Session Information

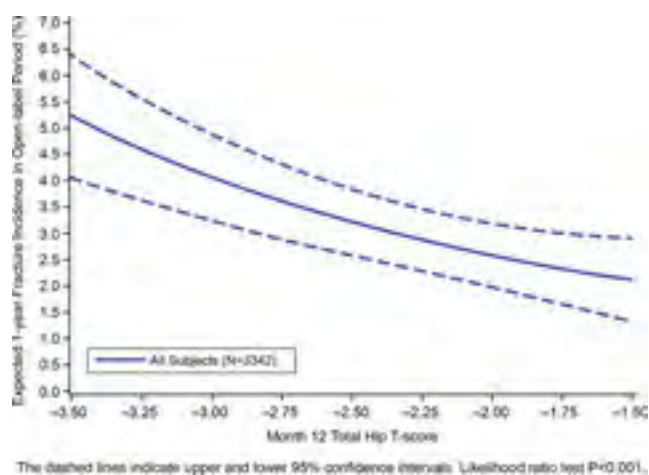
Session Date: Tuesday, October 23, 2018

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Background/Purpose: BMD is a strong predictor of fracture risk in untreated patients. Recent evidence suggests that BMD achieved during treatment also reflects fracture risk; thus, T-scores are being considered as a target to guide osteoporosis treatment. In the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk trial (ARCH [NCT01631214]), romosozumab (Romo), an investigational bone-forming agent with a dual effect of increasing bone formation and decreasing bone resorption, followed by alendronate (ALN) had greater efficacy in fracture risk reduction and BMD gains vs ALN alone (Saag NEJM 2017). Of note, a cardiovascular imbalance was observed with Romo in ARCH and a comprehensive assessment of these data is ongoing. Here we explored the relationship between T-scores achieved on-study after 1 year with Romo or ALN and subsequent fracture risk.



Methods: Postmenopausal women with osteoporosis and prior fragility fracture were randomized 1:1 to receive Romo 210mg SC QM or ALN 70mg PO QW for 12 months, followed by open-label (OL) ALN 70mg PO QW for ≥ 12 months, with an event-driven primary analysis. We examined change from baseline in BMD and T-scores at 12 months and the relationship between total hip T-scores at month 12 and subsequent nonvertebral (NVT) fracture rates. We also compared fractures in the OL period, including new vertebral (VT) fractures in year 2 (based on month 24 spine radiographs) and clinical, NVT, and hip fractures between arms in the full OL period.

Results: ARCH enrolled 4093 patients (2046 Romo, 2047 ALN); mean baseline T-scores were -2.96 at the lumbar spine and -2.80 at the total hip. 3465 patients (1739 Romo, 1726 ALN) received ≥ 1 OL ALN dose in the OL period (median 1.9 years follow-up). Mean total hip BMD increased by 6.2% for Romo and 2.8% for ALN in the first year, with increases in T-score of 0.31 and 0.15, respectively. At month 12, the achieved total hip T-score was associated with the 1-year NVT fracture rate observed in the OL period (Figure) and the relationship was independent of the drug received in the first year. During the OL period, when all patients were on ALN, patients who received Romo first had a 75% lower relative risk of new VT fracture ($P < 0.001$), and had reductions in clinical (32%, $P = 0.001$), NVT (19%, $P = 0.120$), and hip (40%, $P = 0.041$) fractures vs patients who received ALN first.

Conclusion: Higher absolute total hip T-scores achieved on therapy at month 12 resulted in subsequent lower fracture risk regardless of the treatment received, with ongoing benefits from building a BMD foundation. These data support the concept of a T-score target to improve outcomes in osteoporosis treatment.

Figure: Month 12 total hip T-score and nonvertebral fracture rate during the open-label period

Disclosure: F. Cosman, Amgen, Eli Lilly, 2, Eli Lilly, Merck, Radius, Tarsa, 5, Amgen, Eli Lilly, Radius, 8, Amgen Eli Lilly, Merck, Radius, 9; E. M. Lewiecki, Amgen, Radius, 2, 5, Radius, 8; P. R. Ebeling, Amgen, Eli Lilly, Novartis, 2, Amgen, Alexion, 5, Amgen, Eli Lilly, Gilead, 9; E. Hesse, AgNovos, 5, Amgen, Eli Lilly, 9; N. Napoli, Amgen, Lilly, 5; D. B. Crittenden, Amgen Inc., 1, 3; M. Rojeski, Amgen Inc., 1, 3; W. Yang, Amgen Inc., 1, 3; C. Libanati, UCB Pharma, 1, 3; S. Ferrari, Amgen, UCB, AgNovos, 5, UCB, MSD, Amgen, 2.

Abstract Number: 2809

Skeletal Benefit/Risk of Long-Term Denosumab Therapy: A Virtual Twin Analysis of Fractures Prevented to Skeletal Safety Events Observed

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science

Table. Ratio of Fractures Prevented per Bone Safety Event Observed in Long-term FREEDOM Extension Subjects Using the Virtual Twin Method

	Exposure-adjusted subject incidence per 100,000 subject-years				
	Clinical fractures N = 2343 Exp = 16295	Major osteoporotic fractures ^a N = 2343 Exp = 15772	Vertebral fractures N = 2416 ^a Exp = 18385	Non-vertebral fractures N = 2343 Exp = 16451	Hip fractures N = 2343 Exp = 19742
Long-term	1777	1525	981	1520	148
Ratio ^b	3160	2689	1874	2904	281
Ratio ^c	0.86	0.57	0.48	0.53	0.58
Fractures prevented	1603	1174	478	1388	148
Ratio of fractures prevented per AE observed ^d	AFF (5) ^e ONJ (35) ^f	280.8 33.5	186.8 21.8	274.2 38.9	19.6 4.2

Based on long-term denosumab subjects. All results are based on 5000 bootstrap samples.

N = number of long-term subjects who had fracture-outcome data. Exp = a exposure time in subject-years (estimated the time from FREEDOM baseline to the onset of first event) (for subjects who had a fracture event) or end of study or last assessment date, whichever was greater (for subjects who did not have a fracture event).

^a Major osteoporotic fractures were defined as clinical spine, forearm, hip, or shoulder fracture.

^b 227 long-term subjects had missing vertebral fracture outcome data during FREEDOM and/or its Extension.

^c Calculated as (long-term rate) / (virtual twin rate).

^d Calculated as (virtual twin rate – long-term rate) / AE rate.

^e The number in parenthesis indicates the AE-related incidence rate per 100,000 subject-years in long-term subjects.

^f There were 2 mild, 5 moderate, and no severe cases of ONJ in the long-term group.

AE, Adverse event; AFF, atypical femoral fracture; ONJ, osteonecrosis of the jaw.

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Osteoporosis is a chronic disease, yet skeletal safety events—atypical femoral fracture (AFF) and osteonecrosis of the jaw (ONJ)—remain a concern with long-term treatment. Ten years of denosumab therapy in postmenopausal women with osteoporosis has demonstrated sustained and low vertebral and non vertebral fracture rates, with low adverse event rates (*Bone Lancet Diabetes Endocrinol* 2017). Here, we generated a denosumab skeletal benefit/risk ratio derived from observed data and model-based estimates from the FREEDOM trial and its Extension.

Methods: Exposure-adjusted subject incidence per 100,000 subject-years of clinical, major osteoporotic, vertebral, nonvertebral, and hip fractures was calculated for long-term subjects randomized to denosumab in the 3-year FREEDOM trial and enrolled in the 7-year Extension (follow-up time on denosumab 3 to 10 years). Due to the lack of a long-term placebo group, fracture rates in a hypothetical cohort of 10-year placebo controls (virtual twins; Vittinghoff *Stat Med* 2010) were estimated: A regression model was generated using data from subjects randomized to PBO during FREEDOM and then enrolled in the Extension; a virtual twin with identical baseline characteristics to each long-term subject was derived; and fracture rates were then predicted for the untreated virtual twin group using the regression model. The number of fractures prevented per 100,000 subject-years was calculated as (virtual twin rate – long-term rate). AFF and ONJ incidences on denosumab were based on observed cases in the long-term group during the Extension; the virtual twin group was assumed to have no AFF or ONJ in the absence of treatment. A skeletal benefit/risk ratio was calculated from fractures prevented per AFF or ONJ observed.

Results: This analysis included 2343 subjects. The estimated number of clinical fractures prevented was 1403 per 100,000 subject-years (Table). There was 1 case of AFF and 7 ONJ (mild and moderate), corresponding to rates of 5 (AFF) and 35 (ONJ) per 100,000 subject-years. Hence, there were 281 and 40 clinical fractures prevented per AFF and ONJ observed, respectively. The skeletal benefit/risk ratio for other fracture endpoints is shown below (Table).

Conclusion: As long-term placebo-controlled fracture outcome studies in postmenopausal osteoporosis are not ethical, the virtual twin model provides a reasonable estimate of untreated fracture rates. Using this model, long-term denosumab therapy has a highly favorable benefit/risk profile when comparing fractures prevented per skeletal adverse event observed.

Disclosure: S. Ferrari, Amgen, UCB, AgNovos, 5, UCB, MSD, Amgen, 2; E. M. Lewiecki, Amgen, Radius, 2, 5, Radius, 8; P. W. Butler, Amgen Inc., 1, 3; D. L. Kendler, Eli Lilly, Amgen, AstraZeneca, 2, Eli Lilly, Amgen, Pfizer, 5, Eli Lilly, Amgen, 8; N. Napoli, Amgen, Lilly, 5; S. Huang, Amgen Inc., 1, 3; D. B. Crittenden, Amgen Inc., 1, 3; N. Pannacciulli, Amgen Inc., 1, 3; E. S. Siris, None; N. Binkley, Novartis, Viking, Radius, 2, Radius, Viking, 5.

Abstract Number: 2810

Fracture and Bone Mineral Density Response By Baseline Risk in Patients Treated with Abaloparatide Followed By Alendronate

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Abaloparatide (ABL) is an anabolic PTHrP analog approved to treat postmenopausal women with osteoporosis at high risk of fracture. In the ACTIVE Phase 3 study of postmenopausal osteoporotic women, 18 months of ABL significantly increased bone mineral density (BMD) and reduced the risk of vertebral, nonvertebral, clinical, and major osteoporotic fractures versus placebo (PBO) irrespective of baseline risk factors. In ACTIVEExtend, women assigned to receive ABL or PBO in ACTIVE were offered enrollment in an extension study during which both groups received open-label alendronate (ALN) 70 mg weekly for 24 months. In this analysis, we assess whether fracture risk reduction and BMD gains were consistent across multiple subgroups categorized by baseline risk.

Methods: A total of 1,139 patients (558, ABL/ALN and 581, PBO/ALN) were enrolled in ACTIVEExtend (18 months of ABL or PBO followed by 1 month for re-consent, followed by 24 months of ALN treatment for a total of 43 months). Risk factor subgroups were prospectively defined by BMD T-score of the lumbar spine, total hip, and femoral neck (≤ -2.5 vs > -2.5 ; ≤ -3.0 vs > -3.0); nonvertebral fracture history (yes/no); prevalent vertebral fracture at baseline of ACTIVE (yes/no); and age (< 65 vs 65 to < 75 vs ≥ 75 years) at baseline. Treatment effects in subgroups were assessed by forest plots

and statistical tests for interactions using relative risk ratios for new vertebral fractures (Breslow-Day test), hazard ratios for nonvertebral fractures (Cox proportional hazards model), and least-squares mean differences in percent change for BMD (ANCOVA).

Results: Patients in ACTIVEExtend were well balanced for baseline characteristics including age, lumbar spine BMD, total hip BMD, femoral neck BMD, vertebral fracture, and prior nonvertebral fracture. The relative risk reductions for new vertebral, non-vertebral, clinical, and major osteoporotic fractures were greater in the ABL/ALN group compared with the PBO/ALN group for all subgroups analyzed. There was no evidence of meaningful interaction between treatment assignment and any baseline risk variable. Additionally, BMD gains at 43 months for total hip, femoral neck, and lumbar spine were greater in the ABL/ALN group versus the PBO/ALN group among all subgroups analyzed without any meaningful interaction between treatment assignment and any baseline risk variable.

Conclusion: These results suggest that the improved efficacy of 18 months of ABL followed by 24 months of ALN versus 18 months of PBO followed by 24 months of ALN is unaffected by baseline risk. Fracture risk reductions and BMD increases were consistent among all prespecified patient risk subgroups.

Disclosure: B. Leder, Amgen Inc., 5, Eli Lilly and Co., 5, Radius Health, Inc., 5, Amgen Inc., 2, Eli Lilly and Co., 2; C. Zapalowski, Radius Health, Inc., 3; M. Y. Hu, Radius Health, Inc., 3; G. Hattersley, Radius Health, Inc., 3.

Abstract Number: 2811

Abaloparatide Effect on Bone Mineral Density and Fracture Incidence in Postmenopausal Women with Osteoporosis Aged 80 Years or Older

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: The risk of fracture increases with increasing age. Thus, it is important to understand efficacy and safety of osteoporosis treatments in elderly patients. In the ACTIVE phase 3 study, 18 months (M) of abaloparatide (ABL) treatment significantly increased bone mineral density (BMD) and reduced the risk of new vertebral, nonvertebral, clinical, and major osteoporotic fractures vs placebo (PBO). Women receiving ABL or PBO in ACTIVE were offered enrollment in the ACTIVEExtend extension study in which both groups received 24M open-label alendronate (ALN) 70 mg weekly for a total of 43M (18M ABL or PBO, 1M for reconsent, and 24M ALN). The objective of this post hoc analysis was to evaluate efficacy and safety of ABL followed by ALN (ABL/ALN) vs PBO/ALN in the subgroup of patients aged ≥ 80 years in ACTIVEExtend.

Methods: ACTIVEExtend enrolled postmenopausal women with osteoporosis between the ages of 50 and 85; 558 were from the original ABL group and 581 from the PBO group of the ACTIVE study. Pre-specified endpoints, including BMD, new vertebral, nonvertebral, clinical, and major osteoporotic fractures, were assessed over the 43M period. Nonvertebral fracture endpoints were assessed using the Kaplan-Meier (KM) method, proportional hazard model, and logrank test.

Results: A total of 56 ACTIVEExtend patients (29 ABL/ALN; 27 PBO/ALN) were aged ≥ 80 years at ACTIVE baseline. Mean age was 81.8 years in both groups. Mean percent changes from baseline in total hip, femoral neck, and lumbar spine BMD were all significantly greater with ABL/ALN vs PBO/ALN at all timepoints assessed, except for total hip at M6. At M43, BMD mean percent change from baseline was 5.3% ABL/ALN vs 3.1% PBO/ALN ($P=0.024$) at the total hip, 4.6% ABL/ALN vs 3.1% PBO/ALN ($P=0.044$) at the femoral neck, and 17.2% ABL/ALN vs 8.6% PBO/ALN ($P<0.0001$) at the lumbar spine. Fracture rates were very low in both groups in this small subset of women (new vertebral: 0 ABL/ALN, 1 PBO/ALN; nonvertebral: 1 ABL/ALN, 2 PBO/ALN). Adverse event rates were similar between treatment arms with 78.6% and 81.5% of patients in the ABL/ALN and PBO/ALN groups, respectively reporting ≥ 1 treatment-emergent adverse event.

Conclusion: In conclusion, significant BMD gains were maintained through 43M with ABL/ALN vs PBO/ALN. This post hoc analysis suggests that an ABL/ALN treatment was effective in an elderly subgroup of ACTIVEExtend, with a safety profile similar across treatment arms.

Disclosure: S. L. Greenspan, NIH, 2, PCORI, 2, Amgen Inc., 2, Eli Lilly and Co., 2; L. A. Fitzpatrick, Radius Health, Inc., 3; B. Mitlak, Radius Health, Inc., 3; Y. Wang, Radius Health, Inc, 3; N. C. Harvey, None; C. Deal, Amgen Inc., 8, Eli Lilly and Co., 8; F. Cosman, Radius Health, Inc., 5, Amgen Inc., 5, Amgen Inc., 2, Amgen Inc., 8, Eli Lilly and Co., 5, Eli Lilly and Co., 2, Eli Lilly and Co., 8, Tarsa, 5; M. McClung, Radius Health, Inc, 5, Amgen Inc., 5.

Abstract Number: 2812

Evaluation of Cortical Microarchitecture, Bone Stiffness and Bone Remodeling in Patients with Atypical Femoral Fracture

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Atypical femoral fractures (AFF) are low energy femoral fractures and subtrochanteric/diaphyseal localization that have been related to long-term bisphosphonate therapy. Patients with AFF exhibit cortical thickening in femoral shaft, suggesting that AFF may occur due to cortical stress. Analysis of cortical bone microarchitecture, biomechanical properties of bone and bone remodeling in AFF are poorly explored in the literature. Our aim is to evaluate patients with AFF including: 1) cortical bone microarchitecture and bone stiffness by high resolution peripheral quantitative computed tomography (HR-pQCT) and 2) cortical microarchitecture and parameters of bone remodeling by bone histomorphometry of iliac crest.

Methods: Eighteen patients with AFF by the American Society of Bone Mineral Research. Cortical bone parameters (cortical volumetric bone mineral density: Ct.vBMD, mgHA/cm³; and cortical thickness: Ct.Th, mm) and bone stiffness (S, kN/mm) were studied at tibia and distal radius by HR-pQCT and compared to healthy controls matched for sex and age. Cortical thickness (Ct.Th, µm) and bone remodeling (bone formation rate: BFR/BS, µm³/µm²/day) were assessment (Osteomeasure software®) and compared with healthy individuals matched for sex and age.

Results: The mean age of the patients was 64.9±13.3 years old, 94.4% women and 72.2% Caucasian. Seventeen used bisphosphonates (5.8±2.7 years) and 83.3% alendronate at the time of fracture. One patient was on denosumab, but had received bisphosphonate for 6 years. Presence of rheumatic disease was observed in 50% of the patients, most of them with rheumatoid arthritis and 44.4% of the patients used oral glucocorticoid. All fractures were diaphyseal, of which 16 (88.8%) were complete and 4 (22.2%) were bilateral. HR-pQCT (n=12) at tibia showed decreased/normal Ct.vBMD in 83.3% and decreased/normal Ct.Th in 91.6% of the patients. Similar findings were observed at distal radius. Seventy-five percent of the patients had decreased S at tibia and 58.3% at radius. At tibia, S was positively correlated with Ct.Th (r = 0.783, p = 0.001) and Ct.vBMD (r = 0.573, p = 0.004). At radio, S was positively correlated with Ct.Th (r = 0.720, p = 0.007). Bone histomorphometry (n=6) exhibited Ct.Th decreased in 66.6% and normal in 33.3% of the cases. All patients had suppressed bone remodeling.

Conclusion: Our data suggest that AFF patients maintain bone fragility observed in peripheral sites (tibia and radius) and in the iliac crest. Impairment of cortical microarchitecture associated with decreased bone stiffness and suppression of bone remodeling would explain bone fragility in these patients. Our data warn that the cortical bone should be contemplated in the treatment of AFF.

Disclosure: M. O. Perez, None; D. S. Domiciano, None; L. M. Reis, None; V. Jorgetti, None; R. M. R. Pereira, None, 2.

Risk of Venous Thromboembolism with Selective Estrogen Receptor Modulators for Postmenopausal Osteoporosis: A Meta-Analysis of Randomized Trials

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Osteoporosis and Metabolic Bone Disease – Basic and Clinical Science

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Selective Estrogen Receptor Modulators (SERMs) are one of the available treatment options for postmenopausal osteoporosis. Since Raloxifene was first introduced on 1997 for post-menopausal osteoporosis, studies have shown increased risk of venous thromboembolism (VTE). However, some more recent studies have reported no significant increase in risk. Lasofoxifene and Bazedoxifene (approved for postmenopausal osteoporosis in the US by FDA on 2005 and 2013, respectively) are relatively newer SERMs that are generally well-tolerated and have similar efficacy while also reducing coronary heart disease and stroke risk, making them desirable options for postmenopausal women. However, studies have variable results when it comes to VTE risk with these novel SERMs. The aim of this study was to perform a quantitative meta-analysis of randomized controlled trials(RCTs) to assess the risk of VTE with SERMs.

Methods: Relevant trials were identified through electronic searches of PubMed, EMBASE, Cochrane library and Google Scholar as well as from references of the included studies. Only RCTs comparing SERMs with placebo were included. Data from the trials pertinent to VTE as an adverse event were extracted. A subgroup analyses was performed to identify if any difference existed between Raloxifene and other newer SERMs.

Results: In 11 RCTs involving 39,920, the risk of VTE with any SERM was significantly increased [odds ratio (OR) 1.7, 95 % CI 1.37-2.12, $p < 0.001$, $I^2 = 0\%$] compared to placebo (Fig-1). On a subgroup analysis, this risk was even higher with newer SERMs [OR 2.0, 95 % CI 1.33-2.98, $p < 0.001$, $I^2 = 0\%$](Fig-2). The risk of VTE with Raloxifene was higher than placebo but lower compared to other SERMs [OR 1.58, 95 % CI 1.22-2.05, $p < 0.001$, $I^2 = 0\%$](Fig-2).

Conclusion: The risk of VTE seems to be elevated with any of the SERMs. Even though the newer SERMs have been reported to have better cardiovascular risk profiles (reduction in heart disease and stroke) compared to Raloxifene, the risk of VTE seems to be similar or may be even higher in these agents.



Figure 1. Meta-analysis of VTE risk in postmenopausal women using SERMs

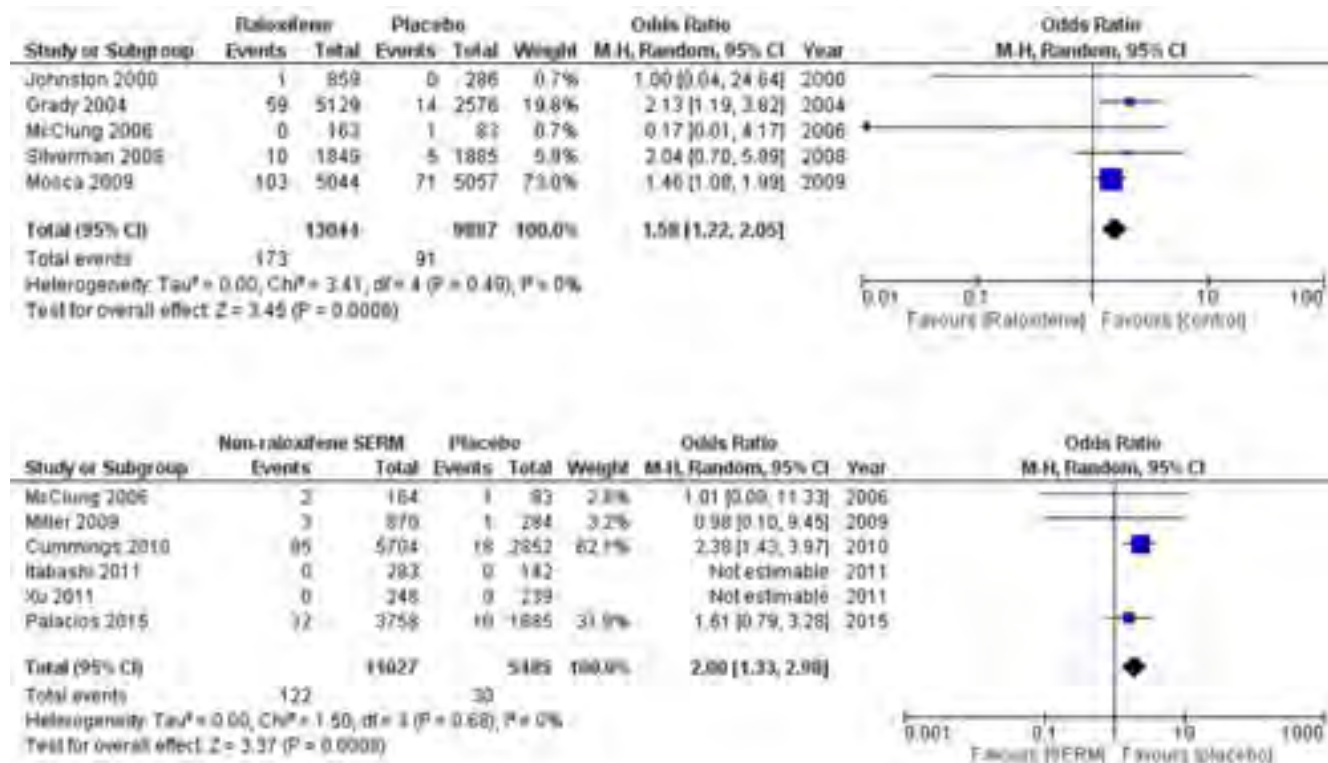


Figure 1. Subgroup analysis (Raloxifene and novel SERMs) of VTE risk in postmenopausal women using SERMs

Disclosure: R. Dhital, None; D. Poudel, None; B. Timilsina, None; T. Lynn, None; C. Peters, None; O. Oladiran, None; P. Parajuli, None; P. Paudel, None; A. Donato, None.

Abstract Number: 2814

Methotrexate Use and the Risk for Cardiovascular Disease Among Rheumatoid Patients Initiating Biologic Disease-Modifying Anti-Rheumatic Drugs

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Session Information

Session Date: Tuesday, October 23, 2018

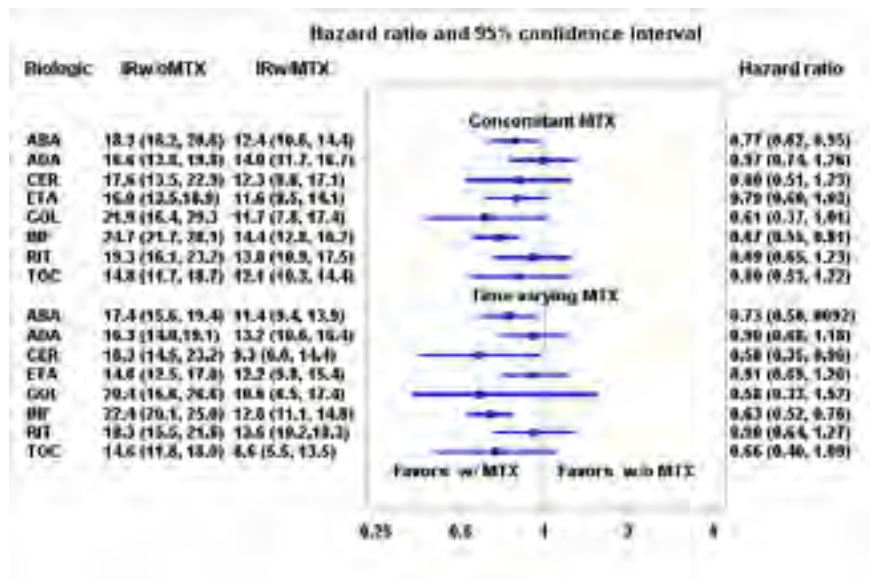
Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes IV: Cardiovascular Co-Morbidities

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Methotrexate(MTX) has been associated with reduced risk for cardiovascular disease (CVD) in several studies conducted among rheumatoid arthritis (RA) patients never exposed to biologic disease-modifying antirheumatic drugs (bDMARDs). Effect of concomitant MTX use on CVD risk among RA patients initiating bDMARDs remains unknown.

Methods: A retrospective cohort study was conducted using 2006-2015 Medicare claims data for RA patients. Follow up started at initiation (index date) and ended at earliest of 1) end of exposure of the specific bDMARDs agent (days of supply + 90 day extension), 2) switched to other bDMARDs or tofacitinib, 3) CVD event, 4) death date, 5) loss of Medicare coverage, 6) end of study (September 30, 2015). MTX use was defined as 1) concomitant MTX use, with prescription for MTX within 120 days after index date and 2) time varying MTX, defined as prescription date to prescription date plus days of supply without extension. For sensitivity analysis, a 90-day extension was added to days of supply. The primary outcome was



composite of incident MI, incident stroke and fatal CVD. Fatal CVD were identified by a claims based algorithm with PPV $\geq 80\%$. Incidence rates (IR) and 95% confidence intervals (CI) were calculated using Poisson regression. Overall association between MTX use and risk of CVD were assessed using Cox regression. Given that the interactions between MTX and background bDMARDs was significant, we performed contrast (MTX Yes vs. No) to examine the association between MTX and risk for CVD for each underlying bDMARDs in one model. A subgroup analysis limited the cohort to RA patients with previous exposure to MTX was conducted to ensure consistency of findings.

Results: A total of 88,255 DMARDs initiations (64,218 patients) were included in this study. The average age at initiation was 64.6 (12.3) years, 84.0% were female, 68.2% were non-Hispanic white. The crude IRs for CVD were 13.1 (95% CI: 12.2-14.0) and 18.7 (95% CI: 17.6-19.9) events per 1,000 person years (PY) for RA patients with and without concomitant MTX respectively. The crude IRs for CVD were 12.1 (95% CI: 11.1-13.2) and 17.9 (95% CI: 16.9-18.8) events per 1,000 PY for RA patients with and without time varying MTX respectively. IRs for individual bDMARDs are shown in figure. P-value for interaction between concomitant MTX and background bDMARDs was 0.0189 and p-value for interaction between time varying MTX and background bDMARDs was 0.0030. The contrast HRs for concomitant MTX ranged from 0.61 (0.37, 1.01) for golimumab initiators to 0.97 (0.74, 1.26) for adalimumab initiators (Figure). The contrast HRs for time varying MTX ranged from 0.58 (0.35, 0.96) for certolizumab initiators to 0.90 (0.68, 1.18) for adalimumab initiators. Results were robust in sensitivity and subgroup analyses.

Conclusion: Our observational study suggests an overall 23% reduction of CVD risk associated with concomitant MTX use. The effect sizes vary among background bDMARDs.

Disclosure: F. Xie, None; L. Chen, None; E. Levitan, Amgen Inc., 2, 5, Novartis, 5; P. M. Muntner, None; J. R. Curtis, Amgen Inc., 2, 5, AbbVie Inc., 2, 5, BMS, 2, 5, Corrona, LLC, 2, 5, Janssen, 2, 5, Eli Lilly, 2, 5, Myriad, 2, 5, Pfizer, Inc., 2, 5, Roche/Genentech, 2, 5, Radius, 2, 5, UCB, Inc., 2, 5.

Abstract Number: 2815

Cardiovascular Safety – Update from up to 6 Years of Treatment with Baricitinib in Rheumatoid Arthritis Clinical Trials

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes IV: Cardiovascular Co-Morbidities

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

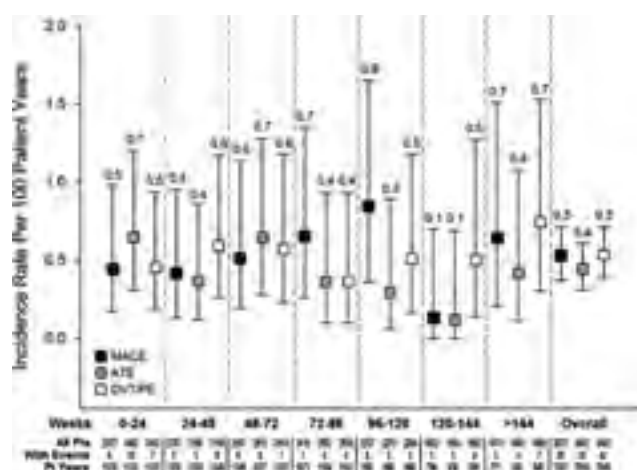


Fig. 1 MACE, ATE, and DVT/PE incidence rates over time in the All BARI RA dataset (Phase 1-2). ATE and MACE include only positively adjudicated events; ATE, arterial thrombotic event; BARI, budesonide; DVT/PE, deep vein thrombosis and/or pulmonary embolism; MACE, major adverse cardiovascular event (composite of myocardial infarction, stroke, and cardiovascular death); PE, patient.

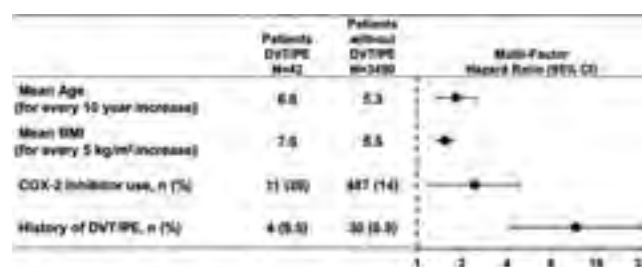


Fig. 2 Multi-Factor Hazard Ratio (95% CI) for DVT/PE incidence rates. DVT/PE, deep vein thrombosis and/or pulmonary embolism; BMI, body mass index; COX-2, cyclooxygenase-2; CI, confidence interval; DVT/PE, deep vein thrombosis and/or pulmonary embolism; HR, hazard ratio; PE, patient; PE, patient.

Table 1. Cardiovascular event rates by analysis dataset

	PBO-Controlled		Extended BARI 2-mg vs 4-mg		All BARI RA
	PBO N=1070	BARI 4-mg N=997	BARI 2-mg N=473	BARI 4-mg N=473	All BARI RA N=3492
MACE					
n (%)	2 (0.2)	3 (0.3)	1 (0.2)	2 (0.5)	38 (1.1)
IR [95% CI]	0.5 [0.1, 2.0]	0.8 [0.2, 2.2]	0.17 [0.00, 0.95]	0.37 [0.04, 1.32]	0.48 [0.34, 0.66]
ATE					
n (%)	2 (0.2)	2 (0.2)	3 (0.6)	3 (0.6)	35 (1.0)
IR [95% CI]	0.49 [0.06, 1.76]	0.48 [0.06, 1.72]	0.49 [0.10, 1.42]	0.46 [0.09, 1.34]	0.45 [0.31, 0.62]
DVT/PE					
n (%)	0 (0.0)	6 (0.6)	3 (0.6)	4 (0.8)	42 (1.2)
IR [95% CI]	0.0 [NA, 0.91]	1.4 [0.53, 3.12]	0.49 [0.10, 1.43]	0.61 [0.17, 1.56]	0.53 [0.39, 0.72]
DVT					
n (%)	0 (0.0)	3 (0.3)	3 (0.6)	2 (0.4)	30 (0.9)
IR [95% CI]	0.0 [NA, 0.91]	0.7 [0.15, 2.68]	0.48 [0.10, 1.43]	0.30 [0.04, 1.10]	0.38 [0.26, 0.54]
PE					
n (%)	0 (0.0)	3 (0.3)	1 (0.2)	2 (0.4)	19 (0.5)
IR [95% CI]	0.0 [NA, 0.91]	0.7 [0.15, 2.08]	0.16 [0.00, 0.99]	0.30 [0.04, 1.10]	0.24 [0.15, 0.38]
Serious DVT/PE					
n (%)	0 (0.0)	3 (0.3)	3 (0.6)	2 (0.4)	28 (0.8)
IR [95% CI]	0.0 [NA, 0.91]	0.7 [0.15, 2.09]	0.49 [0.10, 1.43]	0.46 [0.09, 1.33]	0.36 [0.24, 0.51]
Serious DVT					
n (%)	0 (0.0)	1 (0.1)	3 (0.6)	1 (0.2)	17 (0.5)
IR [95% CI]	0.0 [NA, 0.91]	0.2 [0.01, 1.33]	0.49 [0.10, 1.43]	0.15 [0.00, 0.65]	0.22 [0.13, 0.35]
Serious PE					
n (%)	0 (0.0)	2 (0.2)	1 (0.2)	2 (0.4)	17 (0.5)
IR [95% CI]	0.0 [NA, 0.91]	0.5 [0.06, 1.72]	0.16 [0.00, 0.99]	0.30 [0.04, 1.10]	0.22 [0.13, 0.35]

IRs are per 100 patient-years of exposure. ATE, arterial thrombotic event; BARI, budesonide; CI, confidence interval; DVT/PE, deep vein thrombosis and/or pulmonary embolism; IR, incidence rate; MACE, major adverse cardiovascular event (composite of myocardial infarction, stroke, and cardiovascular death); PBO, placebo; NA, pneumotest arthritis, vs, versus.

Background/Purpose: Baricitinib (BARI), a selective inhibitor of Janus kinases, is approved in >40 countries for the treatment of active rheumatoid arthritis (RA) in adults. Patients (pts) with RA have increased cardiovascular (CV) risk, including for arterial and venous occlusive events. This analysis provides an update to CV safety in pts treated with BARI for up to 6 years.

Methods: Data were pooled from 8 Phase 1-3 studies, including a long-term extension study (LTE) up to April 1, 2017, and analyzed in 3 sets: 1) All BARI RA (all pts exposed to any BARI dose); 2) Placebo (PBO)-controlled (6 studies comparing BARI 4-mg once daily [QD] to PBO, 0-24 weeks); and 3) Extended 2- vs 4-mg (4 studies with BARI 2- and 4-mg QD, including LTE data). Major adverse cardiovascular events (MACE) were adjudicated in Phase 3 by a blinded, independent panel. Study database preferred term searches identified arterial thrombotic events (ATE; adjudicated where applicable) and events of deep vein thrombosis and/or pulmonary embolism (DVT/PE; analyzed without adjudication). Risk factors were analyzed between pts with and without events in the All BARI RA set using Cox regression. Incidence rates (IRs) are per 100 pt-years (PY) of exposure.

Results: 3492 pts were exposed to BARI (7860 PY; median 933 days; max 2230 days), 2723 (78.0%) for ≥ 1 year; 1788 (51.2%) for ≥ 2.5 years. For ATE and MACE, the frequency of reported events and IR were low, comparable across treatments and analysis sets, and did not increase with prolonged exposure (Table 1). For DVT/PE, events (n=6) were reported for BARI 4-mg but not PBO during the 24-week PBO-controlled period. This imbalance was not replicated during 24 weeks after switch to BARI 4-mg from PBO (N=928, 1 event) or active comparator (N=451, 0 events). At longer exposure, DVT/PEIRs were comparable between BARI 2- and 4-mg doses (Table 1). Within the All BARI RA set, IRs were stable over time (Fig 1; overall IR 0.53), the frequency of permanent discontinuation following a DVT/PE event was low (n=5; 0.1%; IR=0.06), and factors (age, BMI, COX-2 inhibitor use, and prior history of DVT/PE) were identified that may contribute to increased risk of DVT/PE (Fig 2).

Conclusion: MACE and ATE IRs were low and did not increase with prolonged exposure. For DVT/PE, IRs were similar between BARI doses and in line with published rates in RA.

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Abstract Number: 2816

Development of a microRNA Panel for Predicting Coronary Atherosclerosis in Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes IV: Cardiovascular Co-Morbidities

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Small noncoding RNAs (sRNAs), such as microRNAs (miRNAs), regulate gene expression and can be used as biomarkers of disease. Patients with rheumatoid arthritis (RA) have accelerated atherosclerosis leading to excess cardiovascular morbidity and mortality. Traditional risk factors used in the general population for risk stratification are inadequate in RA. Our objective was to develop a microRNA panel which predicts presence of coronary artery atherosclerosis in patients with RA.

Methods: Plasma sRNA sequencing was performed on samples from 161 patients with RA whose Agatston scores for coronary artery calcium were previously assessed by electron beam computed tomography. The TIGER pipeline was used

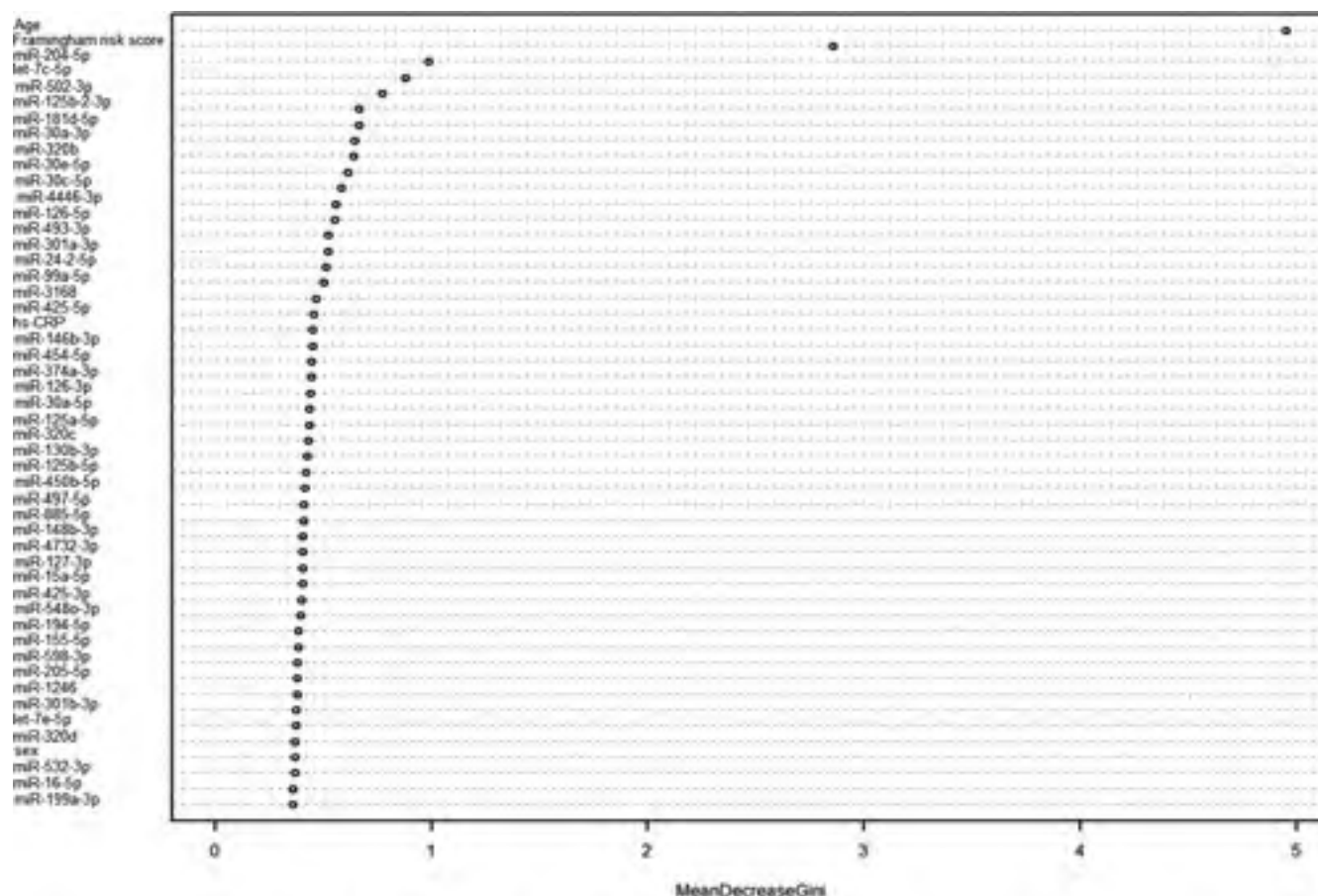


Figure 1. Random forest analysis for predictors of coronary atherosclerosis in patients with RA.

to quantify miRNAs. Random forest analysis including plasma miRNA expression by sRNA sequencing, age, race, sex, Framingham risk score, and high-sensitivity CRP was used to determine which covariates best differentiated between those with and without coronary calcium. The top 15 miRNAs based on random forest analysis were chosen. Logistic regression and area under the receiver operating characteristic curve analyses were used to assess the miRNA panel for prediction of the presence of coronary calcium.

Results: Age and Framingham risk score were the strongest predictors of coronary atherosclerosis (Figure 1); however, the AUC for predicting atherosclerosis was the same for age alone and for age plus Framingham risk score (AUC=0.80 (95% CI 0.73, 0.87), $P<0.001$). The addition of the top 15 miRNAs based on random forest analysis resulted in an improved ability to predict atherosclerosis (AUC=0.85 (95% CI 0.79, 0.91), $P<0.001$)(Figure 2).

Conclusion: A set of 15 plasma miRNAs improved coronary atherosclerosis prediction capacity beyond use of traditional risk factors. Further validation is necessary to confirm these findings and the use of the panel for prediction of coronary events in RA.

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Abstract Number: 2817

Cardiovascular Disease Risk with Biologics and Tofacitinib Compared to Conventional Synthetic Dmards in Patients with Rheumatoid Arthritis

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Session Information

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes IV: Cardiovascular Co-Morbidities

Background/Purpose: Cardiovascular disease (CVD) represents the leading cause of death in RA, accounting for ~50% of excess mortality. Disease activity, strongly linked to CVD, has been significantly improved by biologic (b) and targeted-synthetic DMARDs in RA. However, the influence of these agents targeting different inflammatory pathways on the CVD risk in RA is not yet clear. We examined the comparative effects of bDMARDs and tofacitinib against conventional synthetic (cs) DMARDs on incident CVD in RA patients.

Methods: RA patients with ≥ 1 year participation in FORWARD, The National Databank for Rheumatic Diseases, from 1998 through 2017 were assessed for incident CVD (myocardial infarction, stroke and heart failure validated from hospital/death records). DMARDs were categorized into 7 mutually exclusive groups: (1) csDMARDs-referent (2) TNFi(3) Abatacept (4) Rituximab (5) Tocilizumab (6) Anakinra (7) Tofacitinib. For glucocorticoids (GC), a weighted cumulative exposure (WCE) model which combines information about duration, intensity, and timing of exposure into a summary measure was used. Event rates were calculated and compared across bDMARDs using Cox proportional hazards with adjustment for sociodemographics, comorbidities, and RA severity measures.

Results: 1,561 CV events were identified in 17,363 RA patients (mean [SD] age 63[13] years, disease duration 18[13] years) during a median (IQR) 4.1(1.8-8.2) years of followup. TNFi and non-TNFi bDMARDs users had significantly higher disease activity, disability, and comorbidity scores than csDMARD users. The incidence rate (95% CI) of CVD for the entire cohort was 1.78 (1.69-1.87)per 1,000 patient-years. Incidence rates in each DMARD group are shown in the *Table*. The adjusted model showed a significant CVD risk reduction with TNFi (HR 0.79 [0.69-0.92])and abatacept (HR 0.53 [0.30-0.92]) compared to csDMARDs whereas GC as WCE was associated with significant risk increase (HR 1.15 [1.11-1.20]). Other bDMARDs and tofacitinib were not significant (Figure). In analysis of individual TNFi, although all TNFi tended to be associated with decreased CV risk, only the risk with infliximab(HR 0.81 [0.67-0.98]) and etanercept (HR 0.78 [0.64-.95]) reached statistical significance.

Conclusion: TNFi, notably infliximab and etanercept, and abatacept were associated with decreased risk of CVD and GC with increased risk. Despite reported similar efficacies of bDMARDs in RA, the difference in CV benefits may be due to drug-specific mechanisms directly influencing the atherosclerosis or metabolic changes.

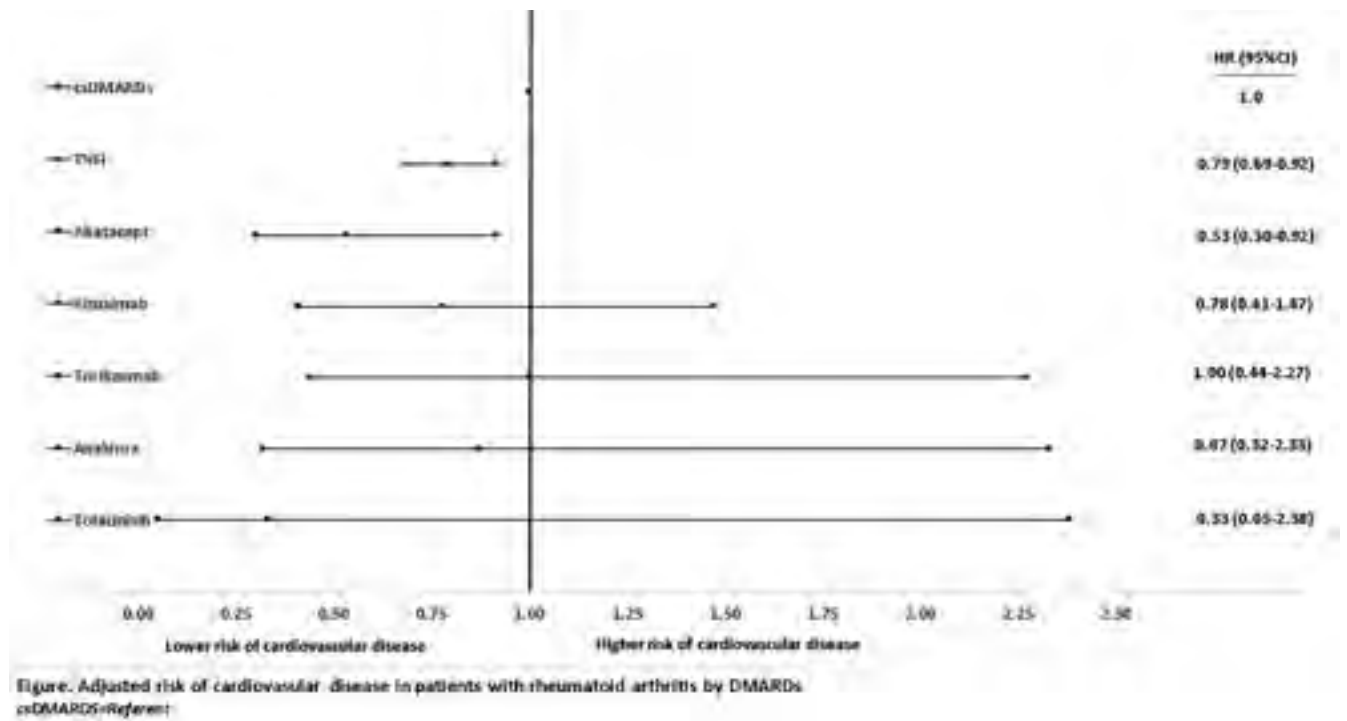


Table. Crude incidence rates and risk of cardiovascular disease in rheumatoid arthritis by treatment

	No. of events/exposure	Patient-years	Incidence rate (95% CI)*	Unadjusted HR (95% CI)	Adjusted HR _l (95% CI)
All patients	1,561/17,363	87,723	1.78 (1.69-1.87)	-	-
Glucocorticoids	646/8,914	29,930	2.16 (2.00-2.33)	1.18 (1.15-1.21)	1.15 (1.11-1.20)
DMARD Category					
csDMARDs (referent)	1,184/14,418	64,265	1.84 (1.74-1.95)	Referent	Referent

Table . (Cont'd)

	No. of events/exposure	Patient-years	Incidence rate (95% CI)*	Unadjusted HR (95% CI)	Adjusted HR [‡] (95% CI)
TNFi	340/7,178	20,260	1.68 (1.51-1.87)	0.57 (0.50-0.64)	0.79 (0.69-0.92)
Abatacept	15/1,048	18,913	0.79 (0.48-1.32)	0.21 (0.13-0.35)	0.53 (0.30-0.92)
Rituximab	11/509	5,467	2.01 (1.11-3.63)	0.47 (0.26-0.85)	0.78 (0.41-1.47)
Tocilizumab	6/390	4,411	1.36 (0.61-3.03)	0.31 (0.14-0.69)	1.00 (0.44-2.27)
Anakinra	4/137	1,419	2.82 (1.06-7.51)	1.08 (0.41-2.90)	0.87 (0.32-2.33)
Tofacitinib	1/275	1,769	0.57 (0.10-4.01)	0.10 (0.01-0.72)	0.33 (0.05-2.38)

* Per 1,000 patient-years

‡ Adjusted for age, sex, disease duration, socioeconomic status (employment and education level, insurance, location of residency), ethnicity, smoking, hypertension, diabetes, comorbidity index, BMI, HAQ, NSAIDs, statins, prior count of csDMARDs and bDMARDs, prior CVD history and year of entry

Disclosure: G. Ozen, None; S. Pedro, None; K. Michaud, None.

Abstract Number: 2818

Galectin-3 As a Marker of Subclinical Atherosclerosis, Arterial Stiffness and Myocardial Performance in Patients with Rheumatoid Arthritis

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Session Information

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes IV: Cardiovascular Co-Morbidities

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Background/Purpose: Galectin-3 has emerged as a promising novel biomarker of cardiovascular fibrosis, that can improve cardiovascular risk stratification in high-risk populations. Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by excess cardiovascular risk. We investigated for the first time whether galectin-3 correlates with robust markers of subclinical atherosclerosis, arterial stiffness and myocardial function in patients with RA.

Methods: Serum levels of galectin-3 were determined by enzyme-linked immunosorbent assay (ELISA) in RA and non-RA individuals. Carotid-femoral pulse wave velocity (PWV) was estimated as the gold-standard measure of arterial stiffness with applanation tonometry. Subclinical atherosclerosis was evaluated by measurement of carotid intima-media thickness (cIMT) from carotid ultrasound. Indices of myocardial blood flow (cardiac output, stroke volume), contractility (acceleration index, velocity index) and afterload (systemic vascular resistance) were non-invasively assessed with impedance cardiography, which offers continuous, beat-by-beat measurements of central hemodynamics. Cardiovascular risk was estimated from the Framingham Heart Study.

Results: A total of 124 participants with a mean age of 59.6±11.6 years were studied, of whom 85 were RA patients and 39 controls. Mean DAS score was 3.6±1.2, median disease duration was 10 (5–18) years, and median erythrocyte sedimentation rate was 20 (10–30) mm/hr. Serum galectin-3 was significantly higher in RA patients, compared to the control group [17.7 (9.8 – 33.5) vs 9.1 (6.0 – 12.0) ng/dl, p<0.001]. However, galectin-3 did not significantly differ when the subgroup of patients without cardiovascular comorbidities (n=38) were separately compared to controls [10.7 (6.4–20.3) vs 9.1 (6.0–12.0) ng/dl, p=ns].

In the univariate analysis, galectin-3 significantly correlated with both PWV (r=0.341, p=0.002) and cIMT (r=0.312, p=0.004) among RA patients. An inverse association was found between galectin-3 and stroke volume (r=–0.279, p=0.010), which was even stronger with cardiac output (r=–0.409, p<0.001). Galectin-3 strongly correlated with systemic vascular resistance (r=0.364, p=0.001) and both acceleration index (r=–0.317, p=0.003) and velocity index (r=–0.395, p<0.001). A positive association was observed between galectin-3 and the estimated 10-year cardiovascular risk from the Framingham Heart Study (r=0.379, p=0.001). On the contrary, no associations were found between galectin-3 and disease-related parameters, including inflammation and disease activity. Multivariate analysis revealed an independent association between galectin-3 and cardiac output (beta=–0.274, p=0.039).

Conclusion: In a relatively well-controlled cohort of RA patients presenting with low-grade systemic inflammation and long-standing disease, serum galectin-3 strongly correlated with markers of cardiac performance and the estimated 10-year cardiovascular risk. By contrast, galectin-3 was not related to inflammation and disease activity in these patients.

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Abstract Number: 2819

Alcohol Consumption and the Risk of Coronary Heart Disease and Mortality in Patients with Rheumatoid Arthritis

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Session Information

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes IV: Cardiovascular Co-Morbidities

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Rheumatoid arthritis (RA) is associated with an increased risk of premature cardiovascular events and mortality. Prospective general population studies have shown moderate alcohol consumption is associated with a 25-40% reduced risk of all-cause mortality and coronary heart disease (CHD). Alcohol use has been discouraged in RA patients taking methotrexate (MTX) due to potential liver toxicity. However, a recent population-based study found moderate alcohol consumption (0-14 UK units or 0-8US drinks per week) was not associated with a higher risk of hepatotoxicity. The aim of this study is to examine the effect of alcohol intake on all-cause mortality and CHD events among RA patients taking disease-modifying anti-rheumatic drugs (DMARDs), including those taking MTX.

Methods: A prospective cohort study (1995-2017) was conducted using electronic medical records from The Health Improvement Network (THIN) database, representative of the general United Kingdom (UK) population. Our study population consisted of RA patients taking MTX or other DMARDs. Alcohol exposure was defined as first recorded alcohol use following RA diagnosis and divided into 5 categories: non-drinkers, 1-7 units/week (mild), 8-14 units/week (moderate), 15-21 units/week (moderate-high) and >21 units/week (high), where 1 UK unit = 8g alcohol. We created Cox-proportional hazard models using age as the time-scale and calculated hazard ratios (HR) for the relation of alcohol consumption to all-cause mortality and CHD events, adjusting for age, sex, body mass index (BMI), smoking status, and Townsend deprivation index.

Results: Of 43214 patients with RA (women: 70%, mean age: 60.2 years), 9102 deaths and 2013 CHD events occurred over 350612 person-years (mean follow-up = 8 years). Alcohol use was associated with a decreased risk of all-cause mortality in RA patients taking MTX, particularly with mild to moderate use. When the analysis was restricted to other DMARDs, the results did not change materially (Table). Alcohol consumption was also associated with a decreased risk of CHD events in both groups, most prominently with moderate-high to high use (Table).

Conclusion: In this prospective cohort study, mild to moderate alcohol use is associated with decreased risk of all-cause mortality among RA patients taking MTX and patients taking other DMARDs. Alcohol consumption is also associated with a decreased risk of CHD events in both groups. Given these results, the prior recommendation for avoiding alcohol use in RA patients taking MTX warrants reconsideration.

Table. Relation of Alcohol Consumption to All-Cause Mortality and CHD Events in Patients with RA

Alcohol Intake (Units/Week)†	N	Events	Event Rate (Per 1000 Person-Years)	Unadjusted HR (95% CI)	Adjusted HR‡ (95% CI)
Mortality in RA Patients Taking MTX					
0	13157	2283	25.39	1.00 (Reference)	1.00 (Reference)
1-7	5244	797	19.44	0.88 (0.82 — 0.96)	0.90 (0.82 — 0.99)
8-14	1747	202	17.18	0.80 (0.69 — 0.92)	0.69 (0.58 — 0.82)
15-21	633	82	18.93	0.92 (0.74 — 1.15)	0.80 (0.62 — 1.03)
>21	586	94	22.20	1.35 (1.10 — 1.66)	1.03 (0.81 — 1.32)
Mortality in RA Patients Taking Other DMARDs					
0	18361	3785	25.39	1.00 (Reference)	1.00 (Reference)
1-7	7198	1219	19.44	0.83 (0.77 — 0.88)	0.82 (0.76 — 0.89)
8-14	2441	343	17.18	0.83 (0.74 — 0.93)	0.67 (0.59 — 0.77)

Table . (Cont'd)

Alcohol Intake (Units/Week)†	N	Events	Event Rate (Per 1000 Person-Years)	Unadjusted HR (95% CI)	Adjusted HR‡ (95% CI)
15-21	938	145	18.93	0.93 (0.79 — 1.10)	0.77 (0.63 — 0.94)
>21	893	152	22.20	1.28 (1.09 — 1.50)	0.95 (0.78 — 1.15)
CHD Events in RA Patients Taking MTX					
0	12625	516	5.03	1.00 (Reference)	1.00 (Reference)
1-7	5045	196	4.46	0.91 (0.77 — 1.08)	0.89 (0.73 — 1.09)
8-14	1669	74	5.55	1.19 (0.93 — 1.52)	0.98 (0.74 — 1.31)
15-21	602	22	4.55	0.96 (0.62 — 1.46)	0.48 (0.28 — 0.85)
>21	566	21	4.76	1.06 (0.68 — 1.64)	0.48 (0.28 — 0.85)
CHD Events in RA Patients Taking Other DMARDs					
0	17572	752	5.37	1.00 (Reference)	1.00 (Reference)
1-7	6913	265	4.46	0.86 (0.75 — 0.99)	0.80 (0.68 — 0.95)
8-14	2337	96	5.14	1.05 (0.85 — 1.30)	0.85 (0.67 — 1.09)
15-21	895	35	4.91	0.99 (0.70 — 1.39)	0.51 (0.33 — 0.80)
>21	864	36	5.56	1.18 (0.84 — 1.64)	0.57 (0.37 — 0.87)

† Units based on standard UK measures where 1 unit = 8g alcohol. By US standards, 4 drinks = 7 UK units

‡ Adjusted for age, sex, BMI, smoking status, and Townsend deprivation index

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Abstract Number: 2820

Sustained Clinical Remission after Discontinuation of Infliximab with a Raising Dose Strategy in Patients with Rheumatoid Arthritis (RRRR study): A Randomized Controlled Trial

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Background/Purpose: Infliximab (IFX), a TNF inhibitor, is one of the most widely used biological disease-modifying antirheumatic drugs. Recent studies indicated that baseline levels of serum TNF- α could be considered as a key indicator for optimal dosing of IFX for treatment of rheumatoid arthritis (RA) to achieve the clinical response and its sustained remission. The Remission induction by Raising the dose of Remicade in RA (RRRR) study (trial registry no; UMIN000005113) was designed to evaluate the clinical remission after 54 weeks of “programmed” treatment, whose dose

of IFX for each patient was determined by the baseline serum TNF- α . The sustained remission rate after 1-year discontinuation of IFX was compared to standard treatment of IFX at week 106.

Methods: RRRR study was a randomized, active controlled, multicenter phase 4 study. IFX-naïve RA patients who showed an inadequate response to MTX were randomized 1:1 to the programmed treatment strategy (programmed group) and the standard treatment strategy (standard group).

Patients in programmed group received 3 mg/kg IFX at week 0, 2, and 6. After 14 weeks, a dose of IFX was kept or raised based on baseline levels of serum TNF- α (3 mg/kg for TNF- α < 0.55 pg/mL; 6 mg/kg for 0.55 pg/mL- <1.65 pg/mL; 10mg/kg for 1.65 pg/mL or greater) every 8 weeks until week 54 after enrollment. Patients in standard group received 3mg/kg of IFX from week 0 to 54. If patients showed a simplified disease activity index (SDAI) \leq 3.3 at week 54, they discontinued IFX. The primary endpoint was the proportion of patients who kept discontinuation of IFX at week 106 (1-year sustained discontinuation rate).

Results: From April 2011 to September 2013, 405 patients were enrolled and 337 patients who completed IFX treatment at week 0, 2, and 6 were randomized to the programmed group (n = 170) and the standard group (n = 167). The patient characteristics in intention-to treat population were similar between groups (Table 1). One hundred and seventeen patients (68.8%) in the programmed group and 112 patients (67.1%) in the standard group completed the 54 weeks IFX treatment after enrollment. At week 54, 39.4% (67/170) in the programmed group and 32.3% (54/167) in the standard group could attain the remission defined by SDAI ($p = 0.176$) and withdrew IFX treatment.

At week 106, the 1-year sustained discontinuation rate of the programmed group and standard group was 23.5% (40/170) and 21.6% (36/167), respectively (2.2% difference, 95% confidence interval = -6.6 to 11.0%; $p = 0.631$). No difference was observed in severe infections and other severe adverse events between groups.

Conclusion: Programmed treatment strategy using different dose of IFX based on the baseline levels of serum TNF- α tended to increase the remission rate at week 54, but did not increase the sustained remission rate after 1-year discontinuation of IFX treatment at week 106.

Table 1. Patients characteristics

	Standard group (N = 167)	Programmed group (N = 170)
Age, years, median (range)	59 (20 to 83)	58 (20 to 81)
Female, n (%)	136 (81.4)	129 (75.9)
Duration of disease, > 3 years, n (%)	69 (41.3)	71 (41.8)
Baseline SDAI, mean (SD)	27.0 (13.1)	28.2 (14.1)
Tender/painful joint count, mean (SD)	7.7 (6.4)	8.7 (6.4)
Swollen joint count, mean (SD)	7.4 (5.2)	7.4 (4.9)
Patients' global assessment VAS, mean (SD)	49.8 (19.1)	50.7 (25.1)
Physicians' global assessment VAS, mean (SD)	49.0 (19.1)	48.6 (22.4)
CRP, mg/dL, median (range)	0.91 (0.0 to 15.1)	1.0 (0.0 to 20.7)
Baseline DAS28 CRP, mean (SD)	4.1 (1.0)	4.2 (1.0)
Baseline TNF- α , < 0.55 pg/dL, n (%)	55 (32.9)	51 (30.0)
Baseline TNF- α , 0.55 to < 1.65 pg/dL, n (%)	61 (36.5)	68 (40.0)
Baseline TNF- α , > 1.65 pg/dL, n (%)	51 (30.5)	51 (30.0)
HAQ-DI score, mean (SD)	1.0 (0.8)	1.0 (0.8)
mTSS, median (range)	8.25 (0 to 318)	8 (0 to 403)
RF, IU/ml, median (range)	45.2 (0 to 2301)	59 (0 to 2050)
Dose of MTX, mg/w, mean (SD)	10.8 (3.2)	11.5 (3.3)

SD, standard deviation; SDAI, simplified disease activity index; VAS, visual analog scale; CRP, C-reactive protein; DAS28, disease activity score 28; HAQ-DI, health assessment questionnaire disability index; mTSS, modified total sharp score; RF, rheumatoid factor;

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Dose Tapering and Discontinuation of Biological Therapy in Rheumatoid Arthritis Patients in Routine Care – 2-Year Outcomes and Predictors

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Dose tapering and discontinuation of biological therapy in rheumatoid arthritis patients in routine care – 2-year outcomes and predictors

Background/Purpose: A cohort of routine care rheumatoid arthritis (RA) patients in sustained remission had biological disease-modifying anti-rheumatic drugs (bDMARDs) tapered according to a treatment guideline. We studied: 1) the proportion of patients whose bDMARD could be successfully tapered or discontinued; 2) unwanted consequences of tapering/discontinuation; 3) potential baseline predictors of successful tapering and discontinuation.

Methods: One-hundred-and-forty-three patients with sustained disease activity score (DAS28-CRP) ≤ 2.6 and no radiographic progression the previous year were included. bDMARD was reduced to 2/3 of standard dose at baseline, 1/2 after 16 weeks, and discontinued after 32 weeks. Patients who flared (defined as either DAS28-CRP ≥ 2.6 and Δ DAS28-CRP ≥ 1.2 from baseline, or erosive progression on X-ray and/or MRI) stopped tapering and were escalated to the previous dose level.

Results: One-hundred-and-forty-one patients completed 2-year follow-up. At 2 years, 87 patients (62%) had successfully tapered bDMARDs, with 26(18%) receiving 2/3 of standard dose, 39(28%) 1/2 dose and 22(16%) having discontinued; and 54 patients (38%) were receiving full dose. Δ DAS28-CRP_{0-2yrs} was 0.1 ((-0.2)-0.4) (median(interquartile range)) and mean Δ Total-Sharp-Score_{0-2yrs} was 0.01(1.15)(mean(SD)). Radiographic progression was observed in 9 patients (7%). Successful tapering was independently predicted by: ≤ 1 previous bDMARD, male gender, low baseline MRI combined inflammation score or combined damage score (Figure). Negative IgM-rheumatoid factor predicted successful discontinuation. The “heat-map” for predicted probabilities for successful tapering based on logistic regression model including the 4 baseline variables are shown in Figure 2.

Conclusion: By implementing a clinical guideline, 62% of RA patients in sustained remission in routine care were successfully tapered, including 16% successfully discontinued at 2-years. Radiographic progression was rare. Maximum one bDMARDs, male gender, and low baseline MRI combined inflammation and combined damage scores were independent predictors for successful tapering.

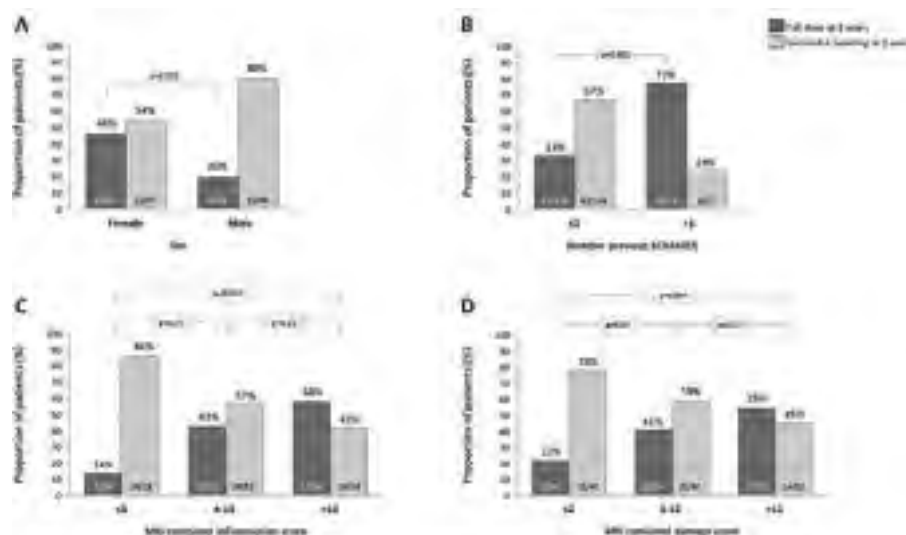


Figure 1: Observed association between potential predictors and the proportion of patients with successful tapering (i.e. less than full dose) versus full dose at year 2

A (male gender):

MRI combined inflammation score	≤ 1 bDMARD	> 1 bDMARD	MRI combined damage score
≤ 3	86 %	64 %	≤ 2
	74 %	73 %	3-12
	64 %	66 %	≥ 13
4-12	74 %	57 %	≤ 2
	71 %	60 %	3-12
	67 %	52 %	≥ 13
≥ 13	83 %	55 %	≤ 2
	71 %	47 %	3-12
	65 %	54 %	≥ 13

B (female gender):

MRI combined inflammation score	≤ 1 bDMARD	> 1 bDMARD	MRI combined damage score
≤ 3	86 %	64 %	≤ 2
	78 %	46 %	3-12
	73 %	40 %	≥ 13
4-12	64 %	71 %	≤ 2
	47 %	71 %	3-12
	41 %	71 %	≥ 13
≥ 13	63 %	59 %	≤ 2
	45 %	71 %	3-12
	30 %	71 %	≥ 13

Figure 2: Predicted probability (%) for successful tapering of bDMARDs for male gender (A) and female gender (B). Red, yellow and green shows probabilities of 0-39%, 40-69% and 70-100%, respectively.

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Should We Prefer Leflunomide to Methotrexate in Combination with Biologics? a Systematic Review and a Meta-Analysis

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Background/Purpose: In rheumatoid arthritis (RA), biologics are more efficient in combination with methotrexate (MTX) than in monotherapy. When MTX cannot be used, others csDMARD can be proposed in combination with biologics. However, the effectiveness of other csDMARD compared to MTX in combination with bDMARD is not clear. The aim of our study was to assess currently available literature on the association of csDMARD with biologics, compared with MTX.

Methods: We systematically searched literature (via Pubmed, Embase and abstracts from ACR and EULAR congresses) for studies that compare effectiveness, retention rate and safety of MTX versus other csDMARD (leflunomide [LEF] or all non-MTX csDMARD) as concomitant therapy with rituximab (RTX), TNF inhibitors (TNFi), abatacept, tocilizumab and JAK inhibitor (JAKi). A meta-analysis was performed with RevMan software using an inverse variance approach with fixed or random effects models, depending on the presence of heterogeneity. Data were extracted by one investigator and independently checked by another.

Results: From 3842 articles, the literature search revealed 144 articles and abstracts of potential interest, and further examination resulted in 8 studies fulfilling required criteria for RTX and 10 for TNFi. All of these studies were cohort studies. For tocilizumab, JAKi and abatacept, there were not enough studies to conduct meta-analysis. For patients receiving RTX, who had similar baseline characteristics in the two groups, those treated with LEF had a higher EULAR good response rate than those treated with MTX (n=3250, 5 studies, RR=1.46 (95% confidence interval [95% CI] 1.25;1.70), $P=0\%$, $p<0.001$). The variation of DAS28 at 6 months also tended to be higher in patients treated with LEF (-0.18 [-0.38;0.01], n=1449, 2 studies, $P=0\%$, $p=0.07$). The risk of adverse events also tended to be lower in patients treated with LEF (n=2718, 4 studies, RR=0.73 [0.52;1.03]; $P=0\%$, $p=0.07$).

Regarding patients receiving TNFi, those receiving MTX had a higher EULAR good or moderate response rate than those treated with other csDMARDs (n=1859, 3 studies, RR=0.88 [0.81;0.96]; $P=0\%$, $p=0.004$). The change in DAS28 at 6 months was also higher in patients treated by MTX than other csDMARD (-0.28 [-0.51;-0.05]; $P=0\%$, $p=0.02$). The risk ratio of discontinuing therapy due to adverse events at 6 months and the risk ratio of serious adverse events were similar between MTX and other csDMARD.

Conclusion: LEF or other csDMARD are safe and efficient for people who are intolerant to MTX to combine with biologics. Whereas MTX appears to be superior than other csDMARD in combination with TNFi, LEF might be superior than MTX in combination with RTX. Randomized controlled trials should be conducted to confirm this result.

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Comparative Long-Term Effectiveness of Switching to Another Tumour Necrosis Factor Antagonists, Tocilizumab or Rituximab in Patients with Rheumatoid Arthritis and Inadequate Response to a First-Line TNF Inhibitor

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Background/Purpose: Tumour necrosis factor inhibitors (TNFi) are highly effective treatments for active Rheumatoid Arthritis (RA). However, up to 40% of patients either fail to respond adequately to TNFi or lose response over time. Options available include treatment with a 2nd TNFi or switching to a biological therapy with a different target such as Tocilizumab (TCZ) or Rituximab (RTX).

Objectives: To compare the effectiveness of a 2nd TNFi, TCZ or RTX, measured by stratified persistency rates, in RA patients with previous discontinuation of their 1st TNFi; to compare the response rates of TNFi, TCZ or RTX at 6 months, 1 and 2 years; to clarify the frequency and reasons for treatment discontinuation.

Methods: Non-interventional prospective study of RA patients exposed to a 2nd TNFi, TCZ or RTX treatment after previous TNFi discontinuation using real-world data from the Reuma.pt database. Patient and disease baseline characteristics, disease activity at follow-up (6 and 12 months and every year thereafter), discontinuation date and reason were collected and compared according to biologic class. Persistency of RTX, TCZ and TNFi were estimated using Kaplan-Meier analysis, from initiation of each therapy until discontinuation/ switch or last follow-up visit.

Results: 643 patients were included, 88.8% females, with a mean age of 59.4 (\pm 12.8) years. After 1st TNFi discontinuation, 390 (60.7%) patients initiated a 2nd TNFi, 147 (22.9%) TCZ and 106 (16.5%) RTX. There were no significant differences in patient and disease characteristics among the 3 groups, except for extra-articular manifestations, higher in RTX group ($p=0.013$), education ($p=0.002$) and current full-time employment ($p<0.001$), both lower in RTX patients. At baseline, TNFi group included more patients treated with concomitant methotrexate ($p=0.002$) and a higher swollen joint count-28 ($p=0.010$). However, the disease activity according to DAS28, CDAI and SDAI were similar between the different therapy groups. The persistency rates according to Kaplan-Meier survival curve were significantly greater (log rank test, $p<0.001$) among patients who initiated TCZ or RTX. The multivariate analysis showed a lower risk of discontinuation for TCZ (HR 0.39, 95% CI 0.23-0.64, $p<0.001$) and RTX (HR 0.42, 95% CI 0.25-0.72, $p=0.001$) and a significant risk for discontinuation for smoking (HR 2.43, 95% CI 1.50-3.95, $p<0.001$) and higher HAQ at baseline (HR 1.51, 95% CI 1.14-2.00, $p=0.004$), adjusted for gender, disease duration and comorbidities. The proportion of patients with a EULAR good response at 6 months ($p<0.001$), 1 ($p<0.001$) and 2 years ($p=0.021$) were, respectively, 23.7%, 28.0%, 31.4% for TNFi, 51.7%, 54.4%, 55.9% for TCZ and 27.5%, 23.1%, 25.6% for RTX. The main reason for discontinuation was inefficacy for TNFi and RTX and adverse events for TCZ ($p<0.001$).

Conclusion: Our findings showed a significantly higher drug persistence for RTX and TCZ compared with 2nd TNFi and a similar persistence among RTX and TCZ, in patients with previous TNFi discontinuation. These data corroborate the notion that switching to a biologic with a different mechanism of action might be more effective after TNFi discontinuation.

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Order*	Drug	Baseline Dose	Taper 1	Taper 2	Taper 3	Taper 4	Taper 5
1	Hydroxychloroquine	200mg bd	200mg od	stop	-	-	-
2	Sulfasalazine	1.5g bd	1g bd	1.5g od	500mg bd	500mg od	stop
3	Methotrexate	25mg/week	15mg/week	7.5mg/week	no change	stop	-
N/A	Etanercept	50mg/week	25mg/week	25mg/every 2 weeks	25mg/every 4 weeks	stop	-
N/A	Adalimumab	40mg/every 2 weeks	40mg/every 4 weeks	40mg/every 8 weeks	40mg/every 16 weeks	stop	-
N/A	Infliximab	Variable	Halve dose	Halve dose	Double time interval	stop	-
N/A	Certrolizumab	200mg/every 2 weeks	200mg/every 4 weeks	200mg/every 8 weeks	200mg/every 16 weeks	stop	-
N/A	Golimumab	Variable	Every month	Every 2 months	Every 4 months	stop	-

NB: Patients were seen 3-monthly. If they remain in remission, they proceed to the next taper unless there is a significant clinical reason not to taper at the time of assessment (as per standard care).

* Order of cs-DMARD therapy tapered if on dual/triple therapy

Flare Definition	csDMARD (n=66) Hydroxychloroquine n=13, Sulfasalazine n=8, Methotrexate n=45, (On monotherapy n=41, Combination therapy n=23)	bDMARD (n=32) Etanercept n=17, Adalimumab /Infliximab/ Certolizumab/Golimumab n=15
Physician Judgement (Increase in therapy +/- prescription of corticosteroid):	47% flare Higher total PD (p=0.005) RF positive (p=0.010) Higher total GS (p=0.012) ACPA positive (p=0.041)	50% flare Reduced Treg (p<0.0001)
DAS28 flare (increase in 3vDAS28 >1.2)	24% flare RF positive (p=0.007) Higher total PD (p=0.018)	29% flare Reduced Treg (p=0.001)
Loss of remission (3vDAS28 >2.6)	38% flare Higher TJC28 (p<0.0001) Higher total PD (p=0.003) Higher CRP (p=0.006) RF positive (p=0.009)	44% flare Reduced Treg (p=0.001) Increased IRC (p=0.008)
Loss of LDA (3vDAS28 >3.2)	27% flare Higher TJC28 (p<0.0001) Higher CRP (p=0.01)	37% flare Reduced Treg (0.004) Increased IRC (p=0.006) RF positive (p=0.014)
Loss of Boolean remission* (TJC, SJC & CRP all >1)	52% flare Longer disease duration (p=0.005) Higher CRP (p=0.002)	70% flare No associations
* Considering only patients who were in Boolean remission at baseline: 46 for csDMARDs and 10 for bDMARDs. Patient global health assessment omitted due to missing data. Abbreviations: Rheumatoid Factor (RF), Anti-citrullinated protein antibodies (ACPA), Power Doppler Synovitis (PDS), Grey Scale Synovial Hypertrophy (GS), Tender/Swollen Joint Counts (TJC28/SJC28), Age-corrected T-regulatory cells (Treg), Inflammatory Related Cells (IRC).		

heterogeneity in terms of flare rate according to the definitions used (Table 1). Tapering of b-DMARDs was associated with higher flare rate (29-70%) compared to cs-DMARDs (24-52%). Demographics were not associated with flare by any definition (except longer disease duration for cs-DMARD patients who lost Boolean remission status). Clinical (notably seropositivity) and US measures were associated with flare for cs-DMARDs. Reduced Treg and higher IRCs at baseline were associated with flare in patients tapering b-DMARDs.

Conclusion: The flare rate varied with the definition used and was more common when tapering b-DMARDs compared to cs-DMARDs. Flare was predicted in the latter patients by clinical and US (including seropositivity) findings, whereas T-cell abnormalities predicted flare in b-DMARD patients. These results will help formulate further tapering strategies.

Table 1. Rate of flare according to different definitions and associations with baseline characteristics

Figure 1. Tapering Protocol

Disclosure: H. Gul, None; F. Ponchel, None; P. Emery, None.

Abstract Number: 2825

Reduction of Antidrug Antibody Levels after Switching to Rituximab in Patients with Rheumatoid Arthritis with Previous Failure to Infliximab or Adalimumab

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments IV: Strategy

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Rituximab (Rtx) induces transient depletion of B cells. Previous data showed that Rtx is particularly effective on autoimmune diseases in which auto-antibodies (auto-Ab) are produced, such as rheumatoid arthritis (RA). It is hypothesized that plasma cells expressing CD20 could be targets of Rtx. Therefore, the immunogenicity related to the use of Infliximab (Ifx) or Adalimumab (Ada) could be cleared by Rtx.

The study aims were i) to analyze the persistence of anti-drug antibodies (ADA) after switching to a 2nd drug (TNFi, Rtx or Tocilizumab-Tcz-) after 24 months of follow-up and ii) to evaluate whether the reduction of ADA level is influenced by the mechanism of action of the second biological therapy (BT).

Methods: Dataset from a prospective cohort including all patients with RA starting BT in a tertiary hospital was used. For this study, data from 40 patients who failed to Infliximab (Ifx) (68%) or Adalimumab (Ada) (32%) related to ADA detection and then switched to a 2nd TNFi (Ifx, Ada, Etanercept or Certolizumab) or to Rtx or to Tcz were analyzed. Additionally, patients should have two determinations of ADA levels: one at the end of the first BT and at least another one at 6, 12 or 24 months after switching BT. ADA levels were determined by bridging ELISA. The proportion of patients with ADA negative levels at 6, 12 and 24 months was determined. Median ADA survival time (mst) performed by Kaplan-Meier curves was determined. The relative reduction (in median) of ADA levels at 6, 12 and 24 months respect to baseline was compared between the switching to different BT.

Results: Out of 40 ADA positive patients with RA, 26 (65%) switched to a 2nd TNFi, 9 (23%) to Rtx and 5 (13%) to Tcz. Patients' characteristics are shown in Table 1.

The percentage of patients with undetectable ADA levels was higher in the group of patients switching to Rtx or Tcz compared with patients switching to a 2nd TNFi (29% and 33% vs 8% at 12 months; 33% and 25% vs 8% at 24 months, respectively).

Moreover, undetectable ADA levels appears earlier in patients switching to Rtx (mst=12) than in patients switching to TNFi or Tcz (mst=24 in both BT).

The relative ADA reduction was higher in patients switching to Rtx than in patients switching to TNFi or Tcz. Reduction of median ADA levels at 6, 12 and 24 months were as follows: 80%, 75% and 92%, respectively for TNFi; 97%, 98% and 98% for Rtx and 25%, 84% and 67% for Tcz.

Conclusion: Despite discontinuing TNFi, ADA titers remain positive in a high proportion of patients with RA after 24 months of treatment with a second biologic. However, in patients receiving Rtx, ADA levels appear to decrease earlier and more patients became ADA negative than patients receiving TNFi or Tcz. This effect could be explained by the intrinsic action mechanism of Rtx on plasmatic CD20+ cells.

Table I: Demographics characteristics of the 40 patients according to the second biologic.

Switch to:	TNFi (n=26)	Rtx (n=9)	Tcz (n=5)	p
Women, n(%)	24 (92%)	6 (67%)	5 (100%)	0.08
Age, years, median (IQR)	44 (33.5-53.2)	51 (42.5-63.5)	52 (44-67.5)	0.09
Smokers, n (%)	10 (38%)	3 (33%)	1 (20%)	0.7
BMI, Kg/m ² , median(IQR)	24,7 (22.1-27)	31 (26.3-34.6)	25.9 (23-33.1)	0.05
MTX, n (%)	20 (77%)	6 (67%)	2 (40%)	0.2
Duration in previous biologic, median (IQR)	4.3 (1.3-7.84)	1.4 (1.1-3.6)	1.3(0.15-4.7)	0.08
Duration in second biologic, median (IQR)	2.3 (0.7-3)	1.75 (1-2)	1.96 (1-2,6)	0.2

Disclosure: A. Martínez, None; C. Plasencia, None; V. Navarro-Compán, None; B. Hernández-Breijo, None; D. Pascual-Salcedo, None; P. Nozal, None; C. Diego, None; I. Monjo, None; L. Nuño, None; A. Balsa, None.

Abstract Number: 2826

Emergence of Severe Spondyloarthropathy Related Enthesal Pathology Following Successful Vedolizumab Therapy for Inflammatory Bowel Disease

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical IV: Comorbid or Related Conditions

Session Type: ACR Concurrent Abstract Session

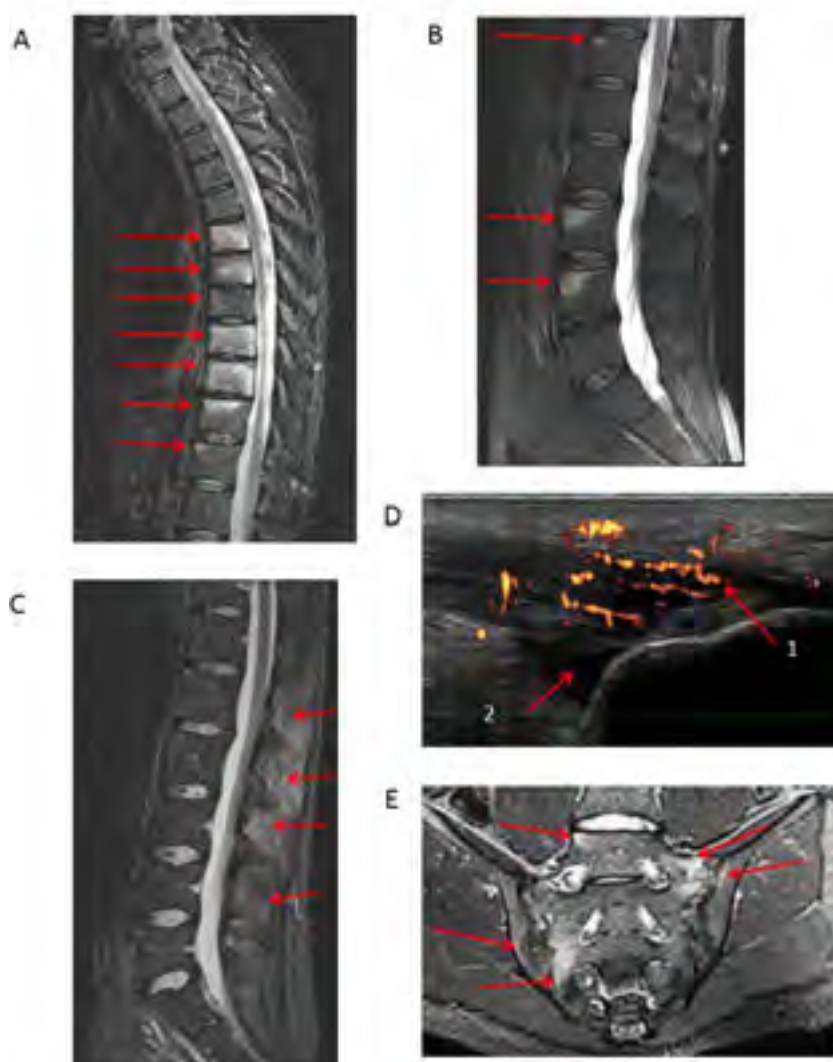
Session Time: 2:30 PM-4:00 PM

Background/Purpose: Vedolizumab therapy for inflammatory bowel disease (IBD) has been associated with mild spondyloarthritis (SpA) related features including sacroiliitis and synovitis. Herein, we report a series of cases demonstrating the emergence of severe SpA associated enthesitis/osteitis following successful IBD therapy with vedolizumab.

Methods: We evaluated 11 vedolizumab treated patients with IBD across 7 centres that developed severe active SpA and/or enthesopathy with the aim of characterising the vedolizumab associated SpA or enthesal flares. Imaging features demonstrating particularly severe disease were recorded.

Results: De novo SpA developed in 9 of 11 patients and flare of known SpA in 2 patients with 4 cases requiring hospitalisation due to disease severity. Available data showed that 1/7 cases were HLA-B27 positive. The median time from vedolizumab initiation to flare was 12 weeks with IBD well controlled in 7/10 (no data 1 case) at flare. Severe SpA

Figure 1



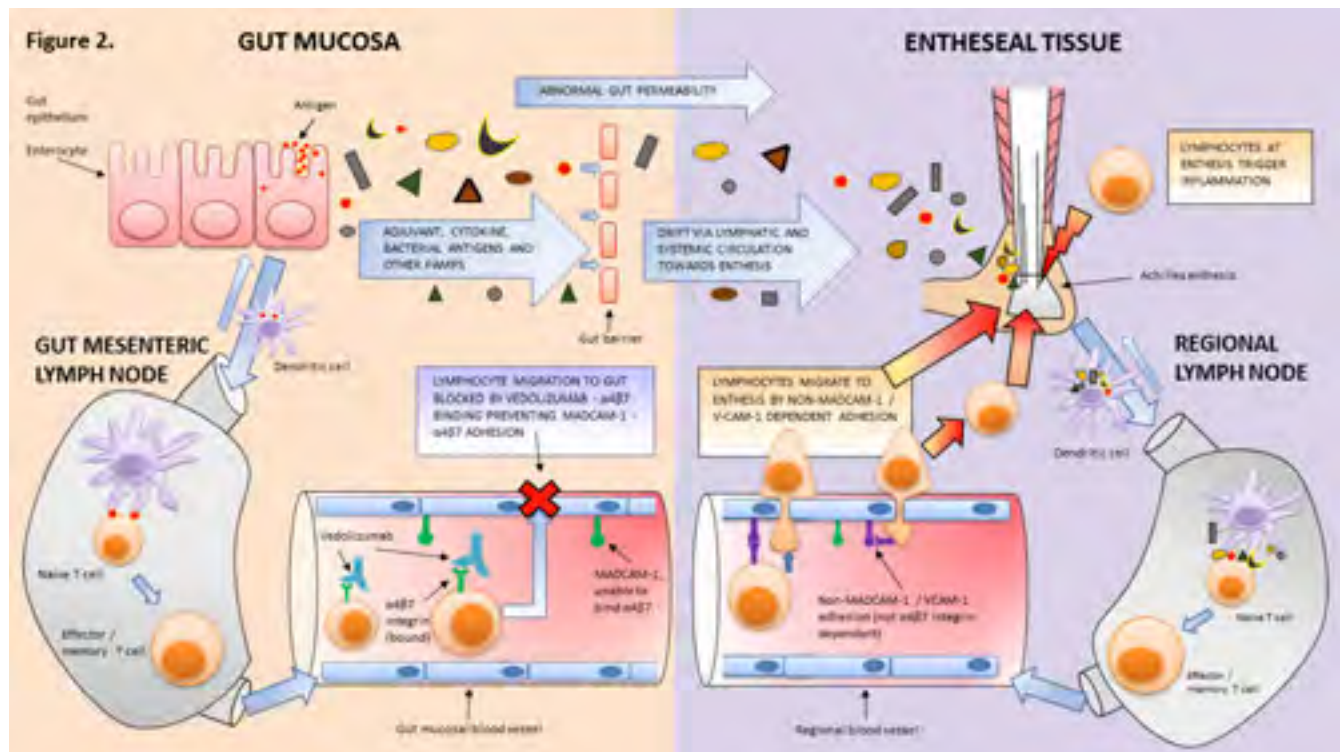


Table 1.

Patient number	1	2	3	4	5	6	7	8	9	10	11
Age, M/F	28, M	48, M	55, F	50, M	35, F	40, F	32, F	32, M	45, F	44, F	72, M
Postulated	Y	N	N	N	Y	Y	N	N	Y	N	N
Vedolizumab exposure (weeks)	34	20	20	8	8	28	8	4	4	52	20
Pre-existing SpA	Y	N	N	N	N	N	N	N	Y	N	N
psoriatic	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y
psoriatic	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Crohn's/Colitis	Y	N	N	N	N	N	N	N	N	N	N
MRI/USI imaging feature	MR: Iliac bone marrow oedema, sacroiliitis, vertebral oedema	MR: Iliac bone marrow oedema, sacroiliitis	MR: Iliac bone marrow oedema, sacroiliitis	MR: Iliac bone marrow oedema, sacroiliitis, vertebral oedema, sacroiliitis, and ribs	MR: Iliac bone marrow oedema, sacroiliitis, vertebral oedema, sacroiliitis, and ribs	MR: Iliac bone marrow oedema, sacroiliitis, vertebral oedema, sacroiliitis, and ribs	MR: Iliac bone marrow oedema, sacroiliitis, vertebral oedema, sacroiliitis, and ribs	MR: Iliac bone marrow oedema, sacroiliitis, vertebral oedema, sacroiliitis, and ribs	MR: Iliac bone marrow oedema, sacroiliitis, vertebral oedema, sacroiliitis, and ribs	MR: Iliac bone marrow oedema, sacroiliitis, vertebral oedema, sacroiliitis, and ribs	MR: Iliac bone marrow oedema, sacroiliitis, vertebral oedema, sacroiliitis, and ribs
HLA-B27	N	NA	NA	N	Y	NA	N	N	N	N	NA
Smoker (cigs)	15	NA	NA	25	N	N	N	N	N	N	N
BDs (active, PaC)	N	N	N	N	N	N	N	N	N	N	N
BD type/active	CC/Low/controlled	CC/Low/controlled	CC/NA	CC/Active (High)	CC/Low/controlled	CC/Low/controlled	CC/Low/controlled	CC/Low/controlled	CC/Low/controlled	CC/Low/controlled	CC/Low/controlled
CAP (active/ing)	118	45	45	24	24	28	55	52	55	50	55
Concomitant DMARD	MTX 2.5mg/wk	ADA 15mg/wk	MTX 2.5mg/wk	None	None	None	None	None	None	None	None
TNF failure	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Previous TNF (DMARD)	IFX	ADA	ADA	IFX	ADA	ADA	ADA	ADA	ADA	ADA	ADA
ADA	ADA	ADA	ADA	ADA	ADA	ADA	ADA	ADA	ADA	ADA	ADA
CDP	CDP	CDP	CDP	CDP	CDP	CDP	CDP	CDP	CDP	CDP	CDP
Vedolizumab discontinued	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Treatment change	GLM	Tacrolimus	Tacrolimus	Tacrolimus	Tacrolimus	Tacrolimus	Tacrolimus	Tacrolimus	Tacrolimus	Tacrolimus	Tacrolimus
Outcome	Remission IBD and SpA activity at 8 months, CDP 25, BASDAI 0.9 (previously 3.5)	Remission IBD and SpA activity at 8 months, CDP 25, BASDAI 0.9 (previously 3.5)	Remission IBD and SpA activity at 8 months, CDP 25, BASDAI 0.9 (previously 3.5)	Remission IBD and SpA activity at 8 months, CDP 25, BASDAI 0.9 (previously 3.5)	Remission IBD and SpA activity at 8 months, CDP 25, BASDAI 0.9 (previously 3.5)	Remission IBD and SpA activity at 8 months, CDP 25, BASDAI 0.9 (previously 3.5)	Remission IBD and SpA activity at 8 months, CDP 25, BASDAI 0.9 (previously 3.5)	Remission IBD and SpA activity at 8 months, CDP 25, BASDAI 0.9 (previously 3.5)	Remission IBD and SpA activity at 8 months, CDP 25, BASDAI 0.9 (previously 3.5)	Remission IBD and SpA activity at 8 months, CDP 25, BASDAI 0.9 (previously 3.5)	Remission IBD and SpA activity at 8 months, CDP 25, BASDAI 0.9 (previously 3.5)

Legend:
 Y= yes, N= no, NA= not available, cpg= cigarettes per day, EAMs= extra-articular manifestations, Y= non-radiographic, Y= positive, N= negative, o= once daily, w= once weekly, PaC= psoriasis, BASDAI= Bath Ankylosing Spondylitis Disease Activity Index, CD= Crohn's disease, UC= ulcerative colitis, CC= Crohn's disease, MR= magnetic resonance imaging, ILL= inflammatory bowel disease, BM= bone marrow oedema, PO= Power Doppler, XR= X-ray, TNF= tumour necrosis factor inhibitor, ADA= adalimumab, CDP= certolizumab pegol, CYS= cyclosporine, GLM= golimumab, IFX= infliximab, MZ= mesalazine, MTX= methotrexate, Tac= tacrolimus, TDP= tofacitinib, VED= vedolizumab, ZOL= zoledronic acid.

enthesitis/osteitis was evident on magnetic resonance imaging (MRI) or ultrasound (figure 1) including acute sacroiliitis (n=5), extensive vertebral osteitis (n=1), peri-facetal oedema (n=1), and isolated peripheral enthesitis (n=3). Due to arthritis severity, vedolizumab was discontinued in 9 of 11 cases and a change in therapy including alternative anti-TNF was initiated. Patient characteristics and outcomes are outlined in table 1.

Conclusion: Severe SpA, predominantly HLA-B27 negative, with osteitis/enthesitis, may occur under successful vedolizumab treatment for IBD. These cases pose the question why in the face of quiescent gut disease do patients develop a severe SpA/ enthesitis? The binding of α 4 β 7 to adhesion molecules to MADCAM-1/ VCAM-1 for T cell transportation into mucosal vascular tissue, may not be dependent for disease at enthesal or joint tissue and would

therefore not hinder adaptive T cell responses at these locations. This proposed model of pathogenesis offers an explanation for these severe SpA flares (figure 2). As we anticipate increasing use of $\alpha 4\beta 7$ inhibition, awareness of this paradoxical reaction and specific phenotype amongst rheumatologists and gastroenterologists alike, can facilitate combined management decisions for effective treatment of IBD and SpA or enthesitis.

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Abstract Number: 2827

Remission Targets and Prevention of Subclinical Atherosclerosis in Psoriatic Arthritis- Which Target Should We Choose?

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical IV: Comorbid or Related Conditions

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Systemic inflammation contributes to the excess risk of cardiovascular disease (CVD) in PsA. We had demonstrated that achieving sustained minimal disease activity (sMDA) was associated with protective effect on subclinical atherosclerosis and arterial stiffness¹. Yet, it is unclear if remission or stable low disease activity over time is sufficient to diminish the CV harmful effects of systemic inflammation.

Methods: We conducted a post hoc analysis of the PsA MDA vascular study¹. 101 PsA patients without overt CVD were recruited in this 2-year prospective study. All patients received protocolized treatment aiming at MDA. High-resolution ultrasound for subclinical atherosclerosis and arterial stiffness were assessed annually. Carotid plaque progression was defined as increased number or region harboring plaque. 4 definitions of remission/inactive disease were used: MDA and very low disease activity (VLDA)² defined as 5 & 7 MDA cut points are met. Disease Activity Index for Psoriatic Arthritis remission (DAPSA-rem) and low disease activity (DAPSA-LDA) were defined as DAPSA \leq 4 and \leq 14. Sustained disease control was defined as achieving these targets at each consecutive visit from month 12 till month 24.

Results: 90 PsA patients [male: 52 (58%); age: 50 \pm 11] who completed follow up were included in this analysis. Significant improvement in disease activity was observed (MDA: 15 [17%] at baseline vs 62[69%] at 2-year, $p<0.001$; DAPSA 19 [13,32] at baseline: vs 7 [4,14] at 2 year, $p<0.001$). 46%, 4%, 44% and 4% of subjects achieved sMDA) sustained VLDA (sVLDA), sustained DAPSA-LDA and sustained DAPSA-rem respectively. 34 (38%) had plaque progression. The rate of plaque progression was significantly lower in sMDA group when compared to those who did not. Achieving MDA was also associated with less progression in mean intima-media thickness (IMT) and augmentation index (AIx) (Fig 1). Using multivariate analysis, achieving sMDA had protective effect on plaque progression, less increase in total plaque area (TPA), mean IMT and AIX after adjusting baseline covariates (Table 1). No significant association between progression of vascular parameters and other treatment targets was observed.

Conclusion: Achievement of sMDA was associated with protective effect in subclinical atherosclerosis and arterial stiffness progression but not sDAPSA-LDA. Multidimensional domain of disease control is preferable for minimizing CV risk in PsA.

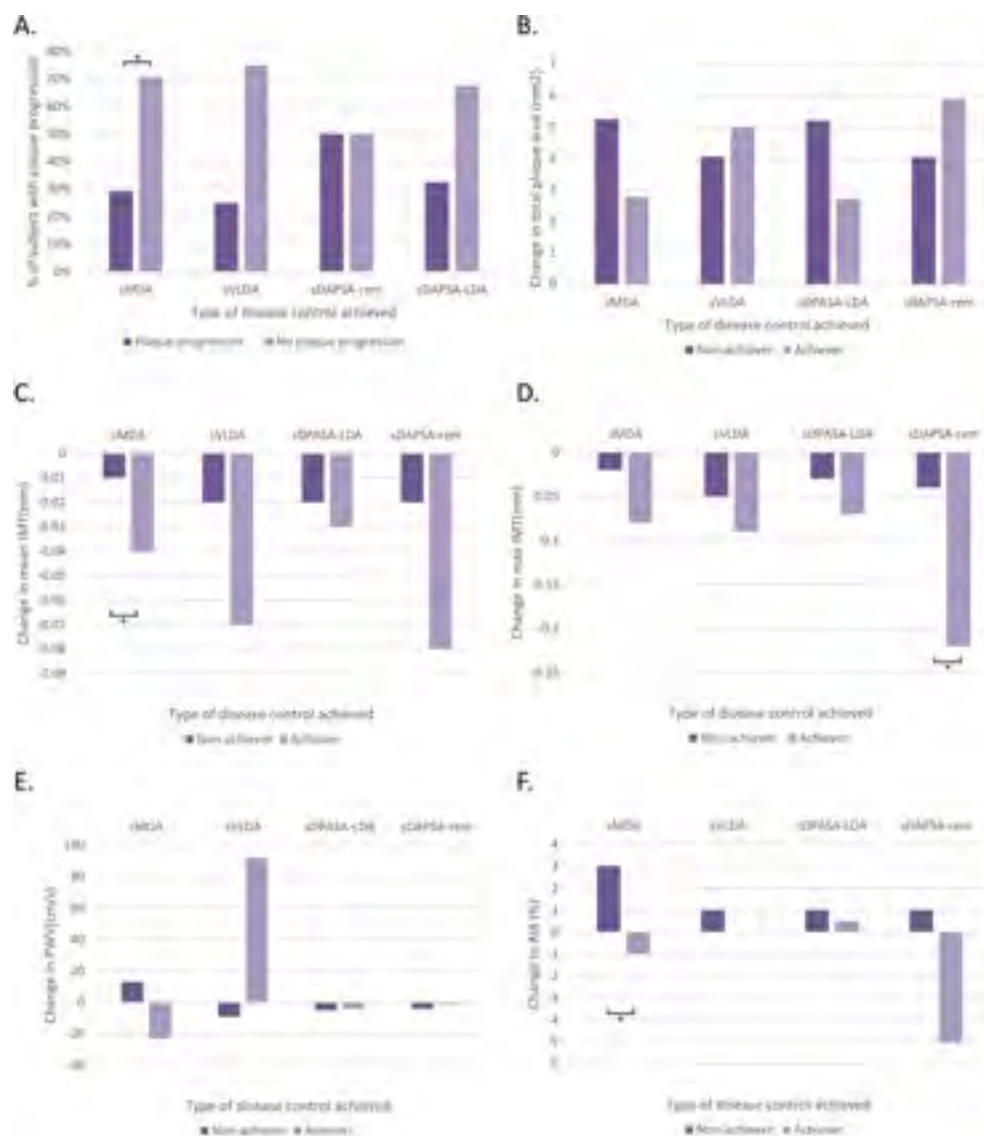


Figure 1

Figure legend

Figure 1. Vascular outcomes between subjects achieving various sustained disease control target. A. Percentage of subjects having plaque progression; B. change in total plaque area (TPA); C. change in mean IMT; D. change in maximum IMT; E. change in PWV; F. change in AIX.

Table 1 - Multivariate analysis on the change in mean/max IMT, AIX, PWV, any plaque progression and change TPA

	Multi-variate analysis		
	OR	95% CI	p-value
<i>Plaque progression¹</i>			
Age	1.069	1.009 to 1.131	0.023
Physicians' global assessment, baseline	0.964	0.936 to 0.993	0.016
Plasma LDL-C, baseline	2.628	1.310 to 5.493	0.007
bDMARDs use at baseline	0.110	0.018 to 0.652	0.015
Achieved sustained MDA	0.273	0.088 to 0.846	0.024
Multi-variate analysis			
	β	95% CI	p-value
<i>Change in total plaque area²</i>			
BMI, kg/m ² , baseline	-0.428	-0.760 to -0.096	0.012
Plasma LDL-C, baseline	2.828	0.723 to 4.932	0.009
Achieved sustained MDA	-3.919	-7.181 to -0.657	0.019
<i>Change in mean IMT³</i>			
bDMARDs use throughout the year	-0.034	-0.065 to -0.004	0.028
Achieved sustained MDA	-0.037	-0.066 to -0.007	0.014

Table . (Cont'd)

	Multi-variate analysis		
	OR	95% CI	p-value
<i>Change in max IMT⁴</i>			
Age	0.003	0.000 to 0.005	0.038
CRP, baseline	0.002	0.000 to 0.005	0.036
NSAIDs use, baseline	0.122	0.045 to 0.199	0.003
Maximum IMT, baseline	-0.455	-0.646 to -0.264	<0.001
<i>Change in PWV⁵</i>			
Age	4.953	0.919 to 8.986	0.017
PWV, baseline	-0.483	-0.676 to -0.289	<0.001
Achieved sustained MDA	-71.4	-143.2 to 0.2	0.051
<i>Change in AIX⁶</i>			
Male gender	3.332	0.105 to 6.560	0.043
Achieved sustained MDA	-3.059	-6.067 to -0.051	0.046

1 Adjusted for age, gender, baseline deformed joint count, physicians' global assessment score, plasma total triglyceride, total cholesterol, LDL-C, use of bDMARDs and presence of carotid plaque at baseline; ²Adjusted for age, gender, baseline BMI, VAS pain score, patient's global assessment score, plasma total triglyceride, total cholesterol, LDL-C level and use of csDMARDs; ³Adjusted for disease duration, baseline CRP, Framingham risk score, use of NSAIDs and use of bDMARDs throughout the year; ⁴ Adjusted age, gender, baseline CRP, waist-to-hip ratio, plasma total cholesterol, LDL-C level, NSAIDs use and maximum IMT; ⁵ Adjusted for age, gender, baseline abdominal obesity and PWV; ⁶ adjusted with age, gender, baseline AIX and csDMARDs use throughout the year; IMT-intima media thickness; AIX-augmentation index; PWV-pulse wave velocity; TPA-total plaque area; LDL-C- low density lipoprotein cholesterol; BMI-body mass index; csDMARDs- conventional synthetic disease modifying anti-rheumatic drugs; bDMARDs-biologic disease modifying anti-rheumatic drugs; VAS-visual analogue scale; CRP-C-reactive protein; NSAIDs-non-steroidal anti-inflammatory drug

Reference:

1. Isaac T et al, Can achieving sustained Minimal Disease Activity (MDA) prevent progression of subclinical atherosclerosis? A two-year prospective cohort study in Psoriatic Arthritis. 19th Asia Pacific League of Associations for Rheumatology Congress (APLAR); Dubai: International Journal of Rheumatic Diseases; 2017
2. Coates LC et al, Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. Ann Rheum Dis. 2010;69:48-53.

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Abstract Number: 2828

Utility of Fecal Calprotectin Levels for the Diagnosis of Inflammatory Bowel Disease in Patients with Spondyloarthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical IV: Comorbid or Related Conditions

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: It is estimated that between 5 and 10% of patients with spondyloarthritis (SpA) are associated with inflammatory bowel disease (IBD).

The **purpose** of our study was to assess the usefulness of the determination of FC for the diagnosis of IBD in patients diagnosed with SpA without suggestive manifestations or previous diagnosis of IBD.

Methods: Unicentric, observational cross-sectional study with prospective clinical data collection. We included patients consecutively selected in a Rheumatology Clinic diagnosed of SpA who fulfilled ASAS criteria and who did not present digestive symptoms suggestive of IBD (chronic diarrhea, rectal bleeding, perianal disease, chronic abdominal pain - persistent or recurrent-). Demographic, clinical and analytical data of SpA (uveitis, HLAB27, acute phase reactants), treatments and FC were collected, establishing as a pathological FC cut-off point >50 mg/Kg. For patients on NSAIDs, suspension was recommended two weeks prior to collection of stool samples. Patients with a positive FC test underwent ileocolonoscopy. Biopsies (between 4 and 12) of colon and terminal ileum were taken for pathological study. A descriptive analysis of the collected variables and a comparative analysis of the baseline characteristics for the groups

(CF>50mg/Kg and <50mg/KG) were carried out. Qualitative data were compared using the chi-square test and Fisher's exact test, for quantitative data between two groups, a Student's t test was used for independent data as a parametric test and the Mann-Whitney U test as a non-parametric test. The statistical significance considered was $p<0.05$.

Results: Ninety nine patients were included. 50% men, average age 46+11 years. BASDAI of 3.7+2.5. 79% were HLAB27 positive, 31% had high ESR levels (>20mm/h) and 9% had elevated CRP (>10mg/L). 49 patients (49.5%) had high FC levels, with mean levels of 276mg/kg (range 52-3,038). Ileocolonoscopy was performed in 47 of these patients, with alterations in 12 (25.5%), of which 4 (8.5%) were classified histologically as IBD type Crohn's disease. Among patients with FC >50 mg/kg, a greater number of cases of IBD were identified (28.6%) in the subgroup of patients with high CRP, as compared with patients with normal CRP (5.9%) ($p=0.045$). The subgroup of patients with high ESR also presented a prevalence higher (14.3%) than patients with normal ESR (6.9%) ($p=0.393$). Patients with a history of uveitis also had a higher prevalence of IBD (25% vs 5.7%; $p=0.090$). There were no significant differences in relation to HLAB27 nor in relation to the history of psoriasis. No statistically significant differences were found in the mean FC levels between patients with high FC who were diagnosed with IBD and those who did not (328mg/kg vs 296mg/kg).

Conclusion: In our study, the group of patients with FC>50 mg/Kg presented an IBD prevalence of 8.5%, suggesting the usefulness of this biomarker in the screening of IBD among patients with SpA. The diagnosis of IBD was found to be associated with high FC levels, CRP>10 mg/L, high ESR or a history of uveitis.

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Abstract Number: 2829

The Response to TNF-Blockers Treatment of SpA Patients Is Influenced By the Interplay between HLA-B27 and Gut Microbiota Composition at Baseline

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical IV: Comorbid or Related Conditions

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: The response to TNF-blockers in axial spondyloarthritis (AxSpA) is at least partially influenced by HLA-B27 through a still poorly understood mechanism. Given that HLA-B27 regulates the gut microbiota composition in rats, we seek to evaluate the predictive value of the gut microbiota composition in AxSpA patients at baseline on their subsequent responsiveness to TNF-blockers.

Methods: 58 patients were recruited according to the following criteria: active disease despite NSAIDs intake; no history of inflammatory bowel disease; no antibiotics intake within 3 months prior recruitment. Bacterial 16S rRNA gene sequencing region was performed on stools samples before and after TNF-blocker treatment. Diversity metrics and custom LefSe were used to explore the relationship between the composition of the intestinal microbiota and the efficacy of TNF-blockers.

Results: A lower alpha diversity at baseline was unexpectedly associated with better treatment response, HLA-B27 genotype and smoking behavior. Meanwhile, beta diversity was associated with smoking behavior and HLA-B27 genotype before and after treatment. Beta diversity at baseline was associated with the BASDAI index after treatment, and the response to the treatment. These results indicate a potential regulatory role for the gut microbiota on the underlying mechanisms involved in the response to TNF-blockers. Moreover, a LefSe-like approach identified 6 bacterial species as potential biomarkers for the treatment response, despite the absence of global changes (beta diversity) in the microbiota composition following a 3-month TNF-blocker intake.

Conclusion: The baseline composition of the gut microbiota from AxSpA patients could be associated with treatment efficacy. Further functional studies will be conducted to assess which of the aforementioned bacteria could be used as predictors of the treatment efficacy and potentially as probiotics promoting treatment efficacy among non-responders patients.

Disclosure: M. Vallier, None; M. Dougados, Abbvie, Pfizer, Eli Lilly and Company, Novartis, UCB, Merck, Roche, BMS, UCB, 2, 5; S. Ferreira, None; S. Menegatti, None; E. Bianchi, None; L. Rogge, None; M. Chamillard, None; C. Miceli-Richard, Janssen, 5, Novartis, 2, 5, Pfizer, Inc., 2, 5, AbbVie Inc., 5, Roche, 2.

Abstract Number: 2830

Synovitis in Psoriatic Arthritis and Seronegative Rheumatoid Arthritis: Differential Histological Features

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical IV: Comorbid or Related Conditions

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: To identify synovial tissue (ST) biomarkers differentially expressed in Psoriatic Arthritis (PsA) and seronegative Rheumatoid Arthritis (Ab^{neg} RA) and test their predictive value of therapeutic response.

Methods: 34 PsA patients [12 DMARDs naive and 22 no-responder to Methotrexate (MTX-IR)] with peripheral joint involvement and 55 Ab^{neg} RA (27 DMARDs naive and 28 MTX-IR) underwent US-guided ST biopsy and immunohistochemistry (IHC) for CD68⁺, CD3⁺, CD20⁺, CD21⁺, CD117⁺ and CD138⁺ cells. After study entry, each DMARD naive patient started MTX therapy and was followed in an outpatient setting for at least 6 months to define the achievement of Minimal Disease Activity (PsA) and DAS-remission (Ab^{neg} RA) status respectively. Each IR-MTX patient was treated according to EULAR recommendations.

Results: At study entry, there were no significant differences in terms of demographic and clinical characteristics of enrolled PsA and Ab^{neg} RA cohorts. IHC analysis revealed that naive PsA patients had lower IHC scores of lining and sublining CD20⁺ than Ab^{neg} RA patients (p=0.002 and p=0.05 respectively), whereas no significant differences were found in terms of lining and sublining CD68⁺, CD21⁺ and CD3⁺ cells among the two cohorts. Moreover, regardless to the therapeutic scheme, PsA patients showed higher IHC score of lining and sublining CD117⁺ cells (p<0.001 for both) compared to Ab^{neg} RA patients. Conversely, Ab^{neg} RA patients showed higher IHC score of lining and sublining CD138⁺ cells, despite the therapeutic scheme (p=0.04 and p=0.01 for naive and MTX-IR respectively). Analysing the response rate to the therapeutic scheme, naive PsA patients reaching MDA status at 6 months follow-up, showed, at study entry, lower IHC score of sublining CD3⁺ cells compared to PsA patients not reaching this outcome (p=0.03), conversely, naive Ab^{neg} RA patients reaching DAS-remission status at 6 months follow-up, showed, at study entry, lower IHC score of sublining CD68⁺ cells compared to Ab^{neg} RA patients not reaching this outcome (p<0.001).

Conclusion: CD117⁺ and CD138⁺ cells are differentially distributed among PsA and Ab^{neg} RA. Histological analysis of ST may help to solve the clinical overlap between the two diseases and provides prognostic data about the therapy success.

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Abstract Number: 2831

High Need for Anti-TNF Therapy after Withdrawal Strategy in Early Peripheral Spondyloarthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical IV: Comorbid or Related Conditions

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Treatment with TNFi in early stages of peripheral Spondyloarthritis (pSpA) results in higher rates of clinical remission, compared to treatment in more longstanding disease. When remission is reached, the recently updated T2T-recommendations suggest tapering of treatment. In the CRESPA-trial pSpA patients were treated with golimumab monotherapy; we demonstrated that – after reaching sustained remission – discontinuation of golimumab led to biological-free remission in 53% of patients; conversely 47% experienced a disease flare. It is currently unknown if concomitant administration of DMARDs could lead to higher rates of biological-free remission. The objective is to explore - in pSpA patients in clinical remission - the possibility that co-medication with methotrexate would allow discontinuation of the TNFi.

Methods: The CRESPA-trial included patients with active pSpA and symptom duration <12 weeks; the primary study results have been reported previously (reference). In the CRESPA-Extension protocol, patients were included that either did not reach remission (but had substantial improvement with golimumab treatment), or that experienced recurrence of arthritis, enthesitis or dactylitis within 1 year after discontinuation of golimumab. These patients received additional open-label golimumab 50 mg SC every 4 weeks for 2 years. At week 104, patients were offered an additional 12 weeks of golimumab treatment, but now in combination with methotrexate 15mg weekly. At week 116, patients in clinical remission continued methotrexate, but discontinued golimumab. Patients were prospectively followed to assess the rate of sustained biological-free clinical remission. In case of relapse of arthritis, enthesitis or dactylitis under methotrexate monotherapy, golimumab was restarted.

Results: Currently, twenty three of the original 60 pSpA patients included in the CRESPA-trial, completed the 2-year CRESPA-Extension protocol; of these, 21 (91%) were in clinical remission at week 104 when methotrexate was added. The mean follow-up period after completion of the extension part, was 80 ± 28 w. 5 patients (24%) are still in sustained remission (n=5) under methotrexate monotherapy whereas in 16 patients (76%), golimumab needed to be re-installed because of relapse of disease activity (n=14) or development of adverse events related to methotrexate (n=2). Recurrence of disease was characterized by development of arthritis in all patients with a median of 4 tender and 3 swollen joints. In 50% (n=7) of the cases, concomitant dactylitis was present. 64% (9/14) were having concomitant psoriasis which was mild since all had a BSA < 5%. The mean time for recurrence was 28,6 weeks. Restarting golimumab treatment promptly restored clinical remission in all patients within 12 weeks.

Conclusion: In patients with pSpA in clinical remission after 2 years of golimumab monotherapy, concomitant administration of methotrexate before discontinuation of the TNFi, did not significantly raise the percentage of patients in biological-free remission. In 76% of patients, golimumab had to be restarted, underscoring the overall weak efficacy of methotrexate in pSpA.

Disclosure: P. Carron, None; G. Varkas, None; T. Renson, None; R. Colman, None; D. Elewaut, None; F. van Den Bosch, None.

Abstract Number: 2832

Multiple Subpopulations of Peripheral Lymphocytes Were Absolutely Decreased in SLE Patients with Infection and Restored By Low-Dose IL-2

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical III: Translational Aspects

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disorder characterized by disturbed cellular and humoral immune responses. Dysregulations of intrinsic or adaptive immune system as well as

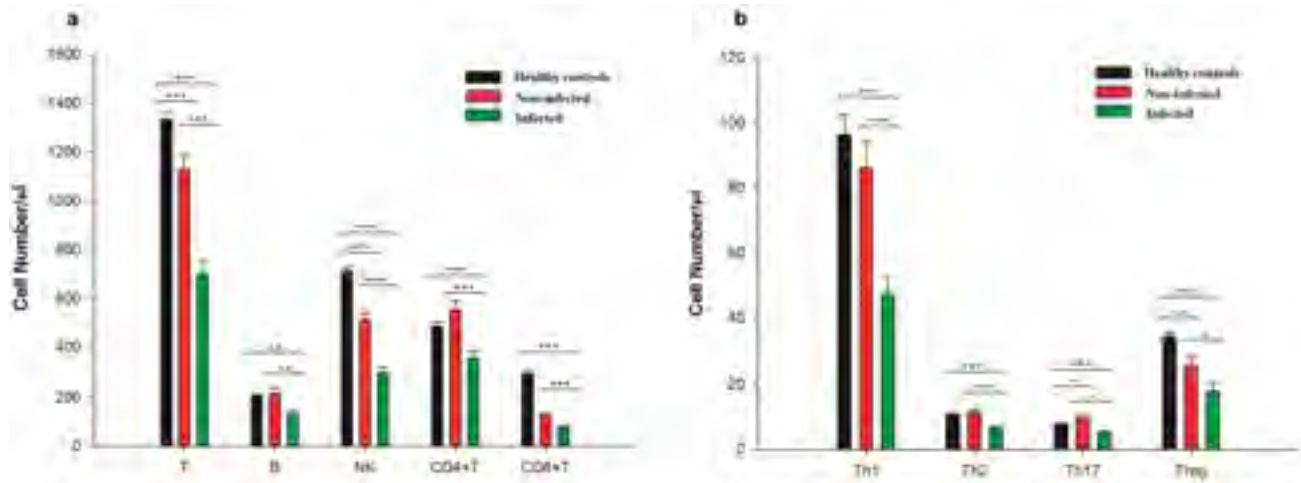


Figure 1: Multiple subpopulations of lymphocytes decreased in peripheral blood of SLE patients with infection. Absolute numbers of peripheral lymphocytes subpopulations were analyzed by flow cytometry. Data were presented as mean \pm SD and statistical analysis was determined by one-way ANOVA. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. (a) shows that SLE patients ($n = 495$) have lower levels of T, B, NK, CD4+T and CD8+T cells in PB compared with that of health controls. The numbers of PB lymphocytes in the infected groups ($n = 162$) was also much lower than those in non-infected patients ($n = 333$). (b) show the comparison of numbers of CD4+T cell subsets among different groups. Patients with SLE has lower levels of Th1 cells, Th2 cells, Th17 cells as well as Treg cells compared with those in health donors ($n = 132$), especially the infected groups.

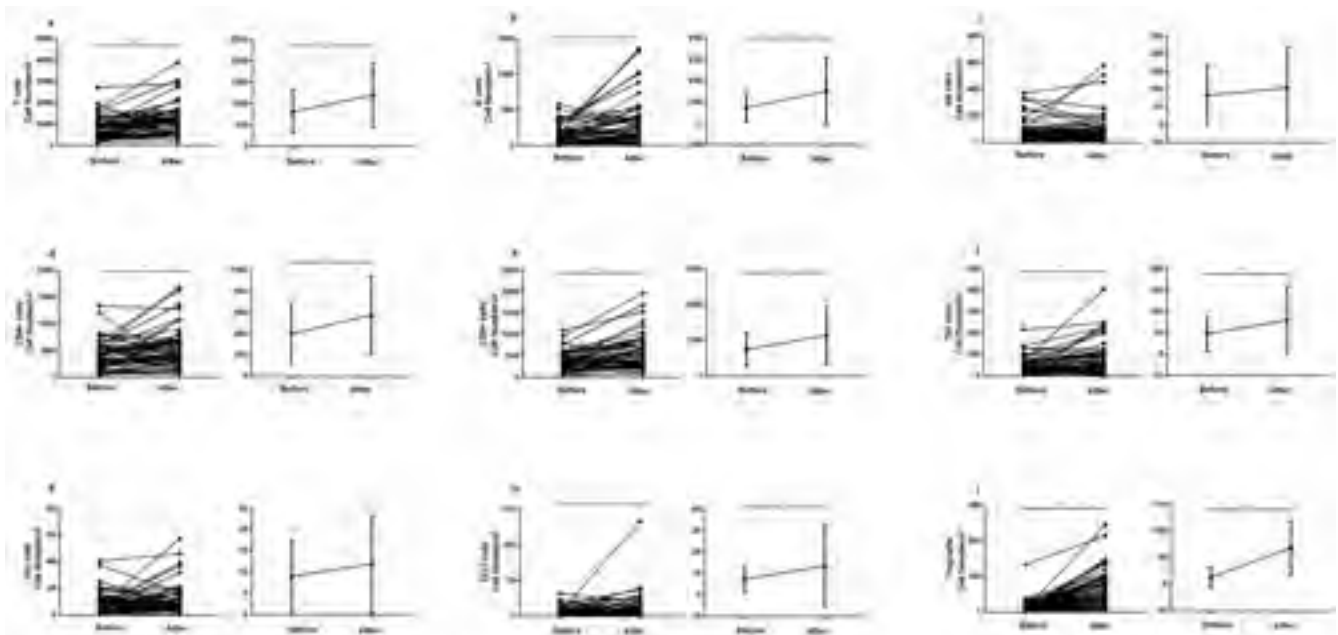


Figure 2: Multiple subpopulations of peripheral lymphocytes of SLE patients were significantly upregulated after low-dose IL-2 treatment ($n = 54$). Absolute numbers of lymphocyte subpopulations in peripheral blood were analyzed by flow cytometry. (a-f) Changes in the numbers of T, B, NK, CD4+T, CD8+T, Th1, Th2, Th17 and Treg cells. Comparison between amounts of cells at baseline and after the treatment. Data were presented as mean \pm SD. And data were calculated and compared by paired-sample t -test. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

immunosuppressive medications predispose SLE patients to infection. This study aimed to investigate the alterations and their clinical significance of the absolute numbers of lymphocyte subpopulations in SLE patients with different infection and to restore the immunologic balances by low-dose IL-2.

Methods: Total 333 patients with SLE without recent infection, 163 patients suffering infection, and age- and sex-matched 132 healthy individuals were recruited. Of these patients, 54 were received a five-day course of low-dose IL-2 administration at a dose of 0.5 million IU per day. Lymphocyte subpopulations were analyzed by flow cytometry before and after the treatment.

Results: Patients with SLE had a lower level of lymphocyte subpopulations in peripheral blood such as T, B, NK, CD4+T, CD8+ T, Th1, Th2, Th17 and Treg cells, and the reduction in these cells was more obvious in SLE patients with infection

($P < 0.05$ to $P < 0.01$). Low-dose IL-2 effectively expanded T ($P < 0.001$), B ($P < 0.001$), CD4+T ($P < 0.01$), CD8+T ($P < 0.001$), Th1 ($P < 0.01$), Th17 ($P < 0.1$) and Treg cells ($P < 0.01$) of SLE patients, these cells were comparable to that of health controls after the IL-2 treatment.

Conclusion: Patients with SLE had fewer cells in various lymphocyte subsets than healthy controls. The absolute cell numbers in these subsets were reduced more dramatically in SLE patients with infection than those without infection, suggesting that the low absolute numbers of these cells may be used as indicators of high infection risk in SLE patients and low-dose IL-2 may enhance the ability to resistant infection in SLE patients by restoring the decreased number of lymphocyte subpopulations.

Disclosure: S. X. Zhang, None; X. Y. Wu, None; J. Luo, None; G. Y. Liu, None; C. Gao, None; C. H. Wang, None; X. F. Li, None.

Abstract Number: 2833

Complement Activation Is a Feature of Diseases in the Lupus Spectrum

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical III: Translational Aspects

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: We showed previously that complement activation - cell-bound complement activation products (CB-CAPS) or multi-analyte assay panel (MAP) - is a sensitive and specific biomarker for the diagnosis of systemic lupus erythematosus (SLE). We report here the frequency of positive CB-CAPS and MAP in subjects with diseases in the lupus

Figure. Frequency of positive of CB-CAPS (elevated EC4d and/or BC4d), MAP, anti-dsDNA antibody (measured by ELISA and confirmed by immunofluorescence with the Crithidia lucillae assay), and low complement (low C3 and/or C4), in SLE, pSLE (all patients and divided based on whether they fulfilled or not SLICC criteria), SjS, and other diseases.

CB-CAPS values were not available for 3 patients (2 SLE and 1 SjS) and MAP scores could not be calculated for 3 patients (1 SLE, 1 pSLE, and 1 SjS).

* Difference between elevated CB-CAPS and low complement and in all pSLE (n=92), pSLE SLICC (n=35), pSLE non SLICC (n=57) were statistically significant ($p < 0.0001$, $p < 0.05$, $p < 0.05$, respectively).

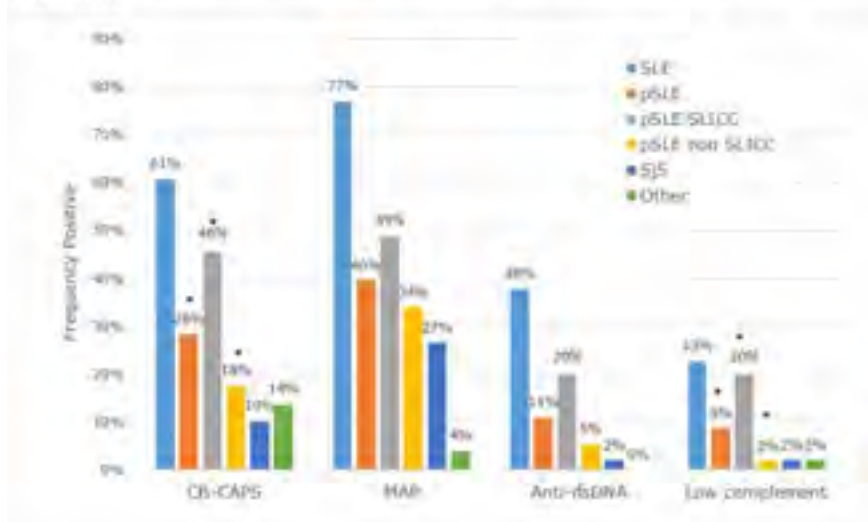
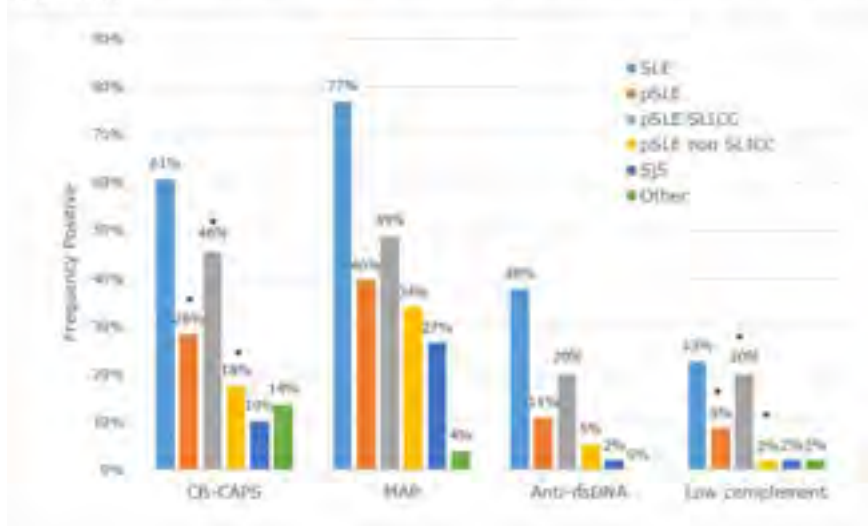


Figure. Frequency of positive of CB-CAPS (elevated EC4d and/or BC4d), MAP, anti-dsDNA antibody (measured by ELISA and confirmed by immunofluorescence with the *Crithidia Luciliae* assay), and low complement (low C3 and/or C4), in SLE, pSLE (all patients and divided based on whether they fulfilled or not SLICC criteria), SjS, and other diseases. CB-CAPS values were not available for 3 patients (2 SLE and 1 SjS) and MAP scores could not be calculated for 3 patients (1 SLE, 1 pSLE, and 1 SjS). * Difference between elevated CB-CAPS and low complement and in all pSLE (n=92), pSLE SLICC (n=35), pSLE non SLICC (n=57) were statistically significant ($p<0.0001$, $p<0.05$, $p<0.05$, respectively).



Demographic characteristics of patients enrolled in the study.

pSLE SLICC: pSLE patients fulfilling SLICC criteria; pSLE not SLICC: pSLE patients not fulfilling SLICC criteria; n: number of patients in each group; yr: year; ANA positivity rate (by immunofluorescence [IFA] and/or ELISA) on the day of the visit

	Male (n)	Female (%)	Years since Dx	Comorbidity (%)	African American (%)	Asian (%)	Hispanic (%)	ANA (IFA or ELISA) (%)
SLE	53	38	9.6	24%	38%	8%	21%	98%
pSLE	92	43	8.5	41%	16%	2%	27%	92%
pSLE SLICC	35	42	8.8	54%	28%	2%	27%	97%
pSLE non SLICC	57	43	8.4	35%	14%	7%	24%	90%
SjS	50	54	8.5	38%	28%	14%	13%	98%
Other	51	11	10.5	62%	18%	0%	22%	78%

spectrum (SLE, probable SLE [pSLE], primary Sjogren's syndrome [SjS]) and other rheumatic diseases compared to low plasma complement levels and anti-dsDNA positivity.

Methods: SLE patients fulfilled ACR and SLICC classification criteria. pSLE were enrolled if the investigator had a high suspicion of lupus and fulfilled only 3 ACR criteria (including anti-nuclear antibodies [ANA]); fulfillment of SLICC criteria was not required. Diagnosis of SjS was based on modified ACR criteria and on expert opinion for other diseases. CB-CAPS (complement split product C4d bound to erythrocytes [EC4d] and B-cells [BC4d]) were measured by quantitative flow cytometry. Serum complement proteins (C3 and C4) and autoantibodies were measured by turbidimetry and ELISA, respectively. Anti-dsDNA positivity was confirmed by immunofluorescence with *Crithidia Luciliae*. MAP was evaluated as previously described (Putterman et al., Lupus Science & Medicine, 2014). Statistical comparisons were done by Chi-square analysis.

Results: The study included 53 SLE; 92 pSLE, 35 (38%) of whom fulfilled SLICC criteria; 50 SjS; and 51 other diseases including rheumatoid arthritis (n=31), juvenile idiopathic arthritis (n=3), psoriatic arthritis (n=10), ankylosing spondylitis (n=1), dermatomyositis (n=4), and scleroderma (n=2). Patient characteristics are reported in the Table. A higher percentage of pSLE (fulfilling or not SLICC criteria) were CB-CAPS and MAP positive compared to anti-dsDNA positive or having low plasma complement levels, indicating higher sensitivity of CB-CAPS and MAP than standard markers, not only in SLE, but also in pSLE. Frequency of positive MAP was 27% in SjS, supporting other studies that suggest that complement may be activated in some SjS patients. Positive CB-CAPS or MAP were infrequent in other rheumatic diseases (Figure).

Conclusion: This study demonstrates that CB-CAPS and MAP are positive more frequently than standard immunological markers (eg, soluble complement proteins and anti-dsDNA antibodies) to better identify patients with definite SLE and probable SLE. CB-CAPS were statistically significantly better than low C3/C4 as markers of complement activation and represent new biomarkers for the diagnosis of lupus spectrum disorders.

Disclosure: R. Ramsey-Goldman, Exagen Diagnostics, Inc, 2; R. Alexander, Exagen Diagnostics, Inc., 3; E. Massarotti, Exagen Diagnostics, Inc, 2; D. J. Wallace, Exagen Diagnostics, Inc, 2; S. Narain, Exagen Diagnostics, Inc, 2; C. Arriens, Exagen Diagnostics, Inc, 2; C. E. Collins, Exagen Diagnostics, Inc, 2; A. Saxena, Exagen Diagnostics, Inc, 2; C. Putterman, Exagen Diagnostics, Inc, 2; K. C. Kalunian, Exagen Diagnostics, Inc, 2; A. Sace, None; R. Lafon, None; T. O'Malley, Exagen Diagnostics, 3; J. Ligayon, Exagen Diagnostics, Inc, 3; C. Ibarra, Exagen Diagnostics, 1, 3; J. Conklin, Exagen Diagnostics Inc., 3; T. Dervieux, exagen, 3; A. Weinstein, Exagen Diagnostics, Inc, 5.

Abstract Number: 2834

The Presence of Anti-Rituximab Antibodies Predicts Infusion-Related Reactions in Patients with Systemic Lupus Erythematosus

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Session Information

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Session Time: 2:30 PM-4:00 PM

Background/Purpose: Rituximab is a genetically engineered chimeric anti-CD20 monoclonal antibody that is commonly used in the treatment of severe and refractory SLE. Although generally well tolerated, infusion-related reactions do occur and can be severe / life threatening. At present it is not possible to predict which patients are at risk of developing these reactions. A major limitation to biologic therapy is the formation of anti-drug antibodies (ADA). To date, ADA to rituximab have not previously been studied in detail.

In this study, we assessed the prevalence of ADA to rituximab in patients receiving treatment for SLE and how this related to therapeutic efficacy and prediction of infusion reactions.

Methods: We assessed for the presence of rituximab ADA using a Meso Scale Discovery Platform in 57 patients with SLE attending University College London Hospital (UCLH), UK. A subgroup of 42 patients were followed up longitudinally for up to 8 years following the first dose of rituximab. Clinical parameters including BILAG, complement C3 levels, dsDNA titres, lymphocyte count and CD19 positive B-cells were recorded. A retrospective review of patient records was undertaken to assess for the occurrence of infusion-related reactions. Mann Whitney U test was used to compare differences between ADA positive (+ve) and ADA negative (-ve) groups. Paired t-tests were used to assess for changes in variables both immediately before and six months after treatment. P-value of <0.05 was considered statistically significant.

Results: Of the 57 patients recruited, 88% were female (50/57) with a mean age of 38.9 years old. Mean disease duration was 102 months. ADA to rituximab were detected in 37% of patients (21/57). Those who developed ADA were significantly younger than ADA -ve patients (mean age 31.9; $p<0.001$) although no difference in disease duration between the two groups was observed ($p=0.37$). Males were also more likely to develop ADA than females ($p=0.04$). Patients receiving rituximab for the treatment of nephritis were more prone to develop ADA ($p=0.03$).

Following retreatment with rituximab, all ADA +ve patients developed infusion-related reactions. No reactions were seen in those who were ADA -ve. There was no difference in the efficacy of B cell-depletion between ADA +ve and ADA -ve patients (as measured by CD19 +ve B-cell count at six months; $p=0.93$). C3 levels showed statistically significant improvements in both groups six months post-treatment. A significant improvement in dsDNA titres was seen in those who were ADA -ve ($p=0.008$). However, there was no statistically significant improved in dsDNA titres in those who were ADA +ve at six months ($p=0.96$).

Conclusion: We have detailed ADA to rituximab in a cohort of SLE patients who have undergone B-cell depletion therapy for the first time. Younger patients, males and those receiving treatment for nephritis were at increased risk of developing ADA. In patients who were ADA +ve there was no significant improvement in dsDNA levels at six months post-treatment. We found that the presence of these antibodies prior to retreatment predicted infusion-related reactions in all cases. In future, routine screening for rituximab ADA will help predict those at risk of subsequent infusion-related reactions.

Disclosure: C. Wincup, None; M. Menon, None; E. Smith, None; D. A. Isenberg, None; E. Jury, None; C. Mauri, None.

Association between Changes in Gene Signature Expression and Disease Activity in Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical III: Translational Aspects

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Session Time: 2:30 PM-4:00 PM

Background/Purpose: We assessed the stability of BAFF, interferon, plasma cell and LDG neutrophil gene expression signatures over time, and whether changes in gene expression coincided with changes in SLE disease activity.

Methods: 243 patients with SLE were evaluated for disease activity, serological parameters and peripheral blood gene signatures in clinic visits that occurred between 2009 and 2012. 143 SLE patients contributed two visits, 40 patients contributed three visits and 60 patients contributed four or more visits. Levels of the BAFF gene transcript, plasma cell signature, Interferon (IFN) signature and the low density granulocytes (LDG)-associated neutrophil gene signature were assessed in PAX-gene-preserved peripheral blood by global microarray. For multi-gene signatures, the geometric mean of component expression was calculated. The stability of repeated measures of gene expression was quantified using intra-class correlation coefficients (ICC). SLE disease activity was measured using the Physicians Global Assessment (PGA) and the SELENA-SLEDAI index and its components. Using a mixed effects regression model we assessed: 1) the association between a patient's average gene signature expression over time and disease activity, and 2) the association between a patient's changes in gene expression over time and changes in disease activity.

Results: Gene expression signatures showed more within-person stability than systolic blood pressure. The IFN signature exhibited the most stability. Patients with high levels of BAFF and IFN transcripts tended to have significantly higher levels of musculoskeletal disease, skin disease, anti-dsDNA, and ESR, and lower levels of complement. However, changes in BAFF or IFN gene signatures were not associated with changes in disease activity. The same associations were seen between the LDG gene signature and disease activity. However, when LDG increased, complement tended to increase. Patients with high levels of plasma cell gene signature tended to have higher levels of anti-dsDNA and lower levels of complement. However, unlike the other gene signatures, changes in plasma cell gene signature significantly coincided with changes in anti-dsDNA and complement.

Conclusion: The gene expression signatures were relatively stable within patients over time. BAFF and IFN gene expression were markers of patients with generally higher disease activity, but changes in these gene signatures did not coincide with changes in disease activity. The plasma cell gene signature expression tracked with the traditional SLE serologic markers of anti-dsDNA and complement.

Disclosure: M. Petri, EMD Serono, 5, Exagen, 2, Janssen, 5, GSK, 5, AstraZeneca, 2, Inova Diagnostic, 5, Novartis, 5, Amgen Inc., 5, Decision Resources, 5, Medscape, 5, Eli Lilly and Co., 5, Quintiles, 5; W. Fu, None; A. Ranger, Biogen Idec, 3; N. Allaire, Biogen Idec, 3; P. Cullen, Biogen Idec, 1, 3; L. S. Magder, None.

Measurement of Interferon Alpha Expression Using Multiple Methodologies Identifies a Signature in a Subgroup of Connective Tissue Disease Patients with Haematological Abnormalities

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical III: Translational Aspects

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Interferon alpha ($IFN\alpha$) is an inflammatory cytokine implicated in the development and persistence of autoimmunity. Although $IFN\alpha$ expression is increased in a subgroup of SLE patients its role in other connective tissue diseases (CTDs) is less clear. We aimed to characterise the $IFN\alpha$ signature across CTDs using 3 methods and determine whether in this mixed cohort we could identify common associations with clinical and laboratory features.

Methods: Patients with at least 1 CTD clinical feature and at least 1 autoantibody were recruited. Detailed clinical assessment was conducted and whole blood collected for RNA analysis and plasma for $IFN\alpha$ protein measurement by single molecule assay (SIMOA).

Interferon-stimulated gene (ISG) and nucleic acid receptors (NAR) expression was measured in whole blood using RT-qPCR. The ISG score was calculated as the mean expression of 6 ISGs (IFI27, IFI44L, IFIT1, ISG15, RSAD2, SIGLEC1) relative to HPRT1 and 18s. The ISG score was classed as positive (ISG+) or negative (ISG-) using the mean +2 SD of healthy controls. 6 NARs were measured: DDX58, MB21D1, TMEM173, TLR3, TLR7 and TLR9. Expression of 30 ISGs was also explored using the NanoString customer designed code sets in a subgroup of patients.

Results: We recruited 164 patients covering 6 diseases; SLE, Sjogren's syndrome (SS), undifferentiated and mixed CTD (UCTD, MCTD), inflammatory myopathy (IIM) and systemic sclerosis (SSc). 63/164 (38%) of patients were ISG+ (figure). NanoString (27 patients) and was strongly correlated with the IFN score ($r=0.96$). Similarly 39/93 (41%) had plasma $IFN\alpha$ protein levels $<10\text{fg/ml}$ (correlation for the 2 methods, $r=0.83$, $p<0.001$).

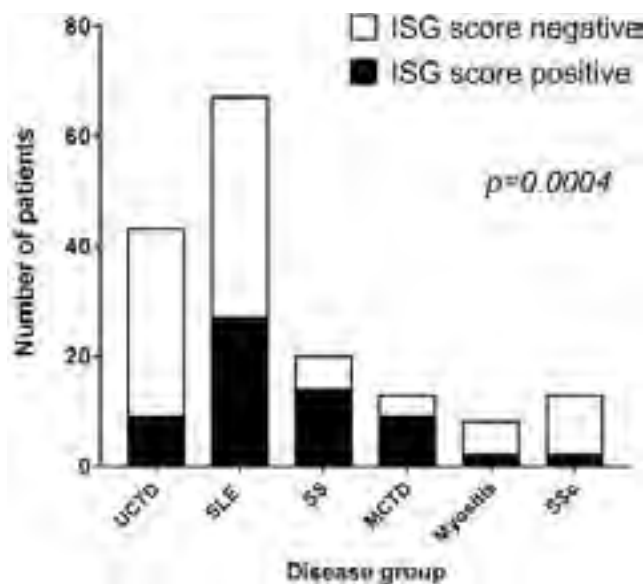
There were no differences in mucocutaneous or internal organ involvement between ISG+ and ISG- patients. ISG+ patients had increased prevalence of rheumatoid factor, anti-Sm and -chromatin antibodies after adjusting for disease type.

ISG+ patients had increased frequency of ever having a haematological disorder (as per the ACR SLE criteria) and in models adjusted for disease type, lower lymphocyte and neutrophil counts.

Expression of TLR7, TLR9, DDX58, MB21D1 and TMEM173 (but not TLR3) was increased in CTD compared to HC (all $p<0.001$). Only DDX58 was positively associated with the ISG score ($r=0.6556$) and was increased in patients who were anti-ENA or anti-chromatin positive. Anti-Ro was associated with reduced expression of all NARs (except DDX58); this association remained after adjustment for age, gender, disease group and ISG score.

Conclusion: $IFN\alpha$ is increased in a subgroup of CTD patients but more strongly associates with haematological abnormalities than any disease subtype. Increased NAR expression does not correlate with increased $IFN\alpha$ suggesting that the drivers of $IFN\alpha$ may be multifactorial. The identification of this high- IFN subset of patients within a CTD cohort supports a pathology-based approach to treatment.

Figure



Disclosure: J. A. Reynolds, None; T. A. Briggs, None; G. Rice, None; E. Bruce, None; S. Haque, None; E. McCarthy, None; A. L. Herrick, Actelion, 2, Medical Research Council (MRC), 2; H. Chinoy, None; D. Duffy, None; Y. J. Crow, None; B. Parker, None; I. N. Bruce, Sanofi Genzyme, 2.

Abstract Number: 2837

Diminished STAT-3 Phosphorylation and Associated Cell Pathways Characterize MMF-Treated Systemic Lupus Erythematosus Patients

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical III: Translational Aspects

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Mycophenolate mofetil (MMF) is a commonly used medication to treat major organ involvement in SLE, specifically in patients with lupus nephritis. The safety and effectiveness of MMF therapy in SLE is well-known and determined by clinical response, but the systemic impact of MMF treatment on immune cellular subsets, cell activation and soluble mediator pathways in SLE remain ill-defined.

Methods: PBMCs and plasma samples from SLE patients not taking MMF (n=10) and SLE patients taking MMF (n=5) were studied. Subjects were matched by gender, ethnicity, age \pm 5 years, medication use, and disease activity by SELENA-SLEDAI, and fulfilled the American College of Rheumatology (ACR) criteria for SLE classification. Using single cell proteomics by mass cytometry, PBMCs were clustered using 33 markers and cell heterogeneity was visualized using viSNE in Cytobank. Plasma cytokine levels were assessed by 51-plex xMAP assays and ELISAs. Flow cytometry was utilized to assess STAT3 phosphorylation and apoptosis of healthy control PBMCs(n=6) following treatment with IL-6 and MMF *in vitro*.

Results: Patients taking MMF had significant reductions in total numbers of transitional B cells (p=0.0077), plasmablasts (p=0.0480) and T cells (p=0.0486), specifically CD4⁺ Th17-type cells (p=0.0260) and CD4⁺ Treg-type cells (p=0.0469), compared to SLE patients not taking this medication. In addition, activation both of dendritic cells(p=0.0080) and B cells (p=0.04), specifically naïve (p=0.0127) and memory B cells (p=0.04), were reduced in patients taking MMF compared to non-MMF patients. MMF patients also had reduced levels of activated CD4⁺ T cells(p=0.0483). Plasma soluble mediators were decreased in MMF treated SLE patients including chemokines (MIG/CXCL9 and SDF-1a/CXCL12)and growth

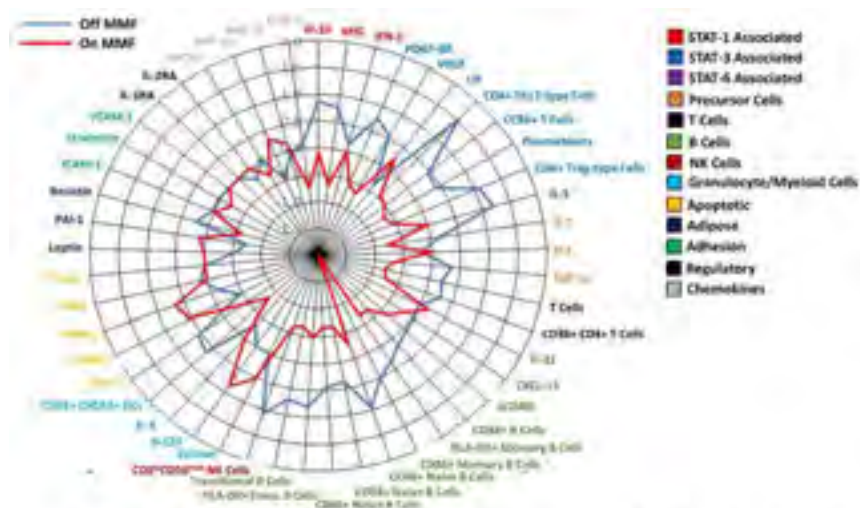


Figure 1. Downregulation of STAT-3 associated and B cell pathways distinguish MMF-treated SLE patients from non-MMF treated patients. A radar plot using the group median of the variable converted to Z-scores show significant differences between off-MMF SLE patients (blue) and On-MMF SLE patients (red). Cytokines, chemokines, and significant cell numbers and frequencies were grouped according to STAT-associated pathways, cell lineage or functional properties.

Table 1. Primary immunodeficiencies associated with vasculitis in USIDNET database. N=76

PID Diagnosis	
Common variable immune deficiency	29 (38)
Wiskott-Aldrich Syndrome	20 (26)
Combined Immune Deficiency	4 (5)
Hypogammaglobulinemia	4 (5)
Immunodeficiency with myelodysplasia (GATA2 and others)	4 (5)
Immune Dysregulation	3 (4)
Chronic Granulomatous Disease	3 (4)
Agammaglobulinemia	2 (3)
Specific antibody deficiency with normal Ig and B cell concentrations	2 (3)
Autoimmune Lymphoproliferative Syndrome (ALPS)	1 (1)
Complement Deficiency	1 (1)
DiGeorge syndrome	1 (1)
Hyper IgE Syndrome	1 (1)
Hyper IgM Syndrome	1 (1)

Reported as frequency (%).

Table 2. Characteristics of patients with primary immunodeficiency (PID), common variable immune deficiency (CVID), and Wiskott-Aldrich syndrome (WAS) and associated vasculitis in USIDNET database.

	PID (n=76)	CVID (n=29)	WAS (n=26)
Demographics			
Age at diagnosis PID, mean (range)	22.0 (0-72.5)	41 (0.5-72.5)	1.7 (0-3.3)
Age over 18 years old at diagnosis	30 (38)	23 (29)	0 (0)
Sex, female	35 (46)	21 (72)	0 (0)
Ethnicity, Caucasian	58 (76)	23 (79)	17 (65)
Vasculitis Diagnosis			
Central nervous system vasculitis	11 (14)	5 (17)	1 (4)
Henoch-Schönlein Purpura	9 (12)	1 (3)	6 (23)
Cutaneous Vasculitis	5 (7)	2 (7)	0 (0)
Behcet's Disease	4 (5)	2 (7)	0 (0)
Granulomatosis with Polyangiitis	3 (4)	3 (10)	0 (0)
Cryoglobulinemic Vasculitis	2 (3)	1 (3)	0 (0)
Kawasaki's Disease	2 (3)	0 (0)	0 (0)
Microscopic Polyangiitis	1 (1)	0 (0)	0 (0)
Polyarteritis Nodosa	1 (1)	0 (0)	0 (0)
Giant Cell Arteritis	1 (1)	1 (3)	0 (0)
Takayasu's Arteritis	1 (1)	0 (0)	1 (4)
Hypocomplementemic Urticarial Vasculitis	1 (1)	1 (3)	0 (0)
Vasculitis, unspecified	35 (46)	13 (45)	12 (60)
Immunomodulatory Therapy			
Glucocorticoids	45 (59)	20 (69)	12 (60)
Azathioprine	5 (7)	1 (3)	0 (0)
Cyclophosphamide	5 (7)	2 (7)	1 (4)
Rituximab	4 (5)	1 (3)	0 (0)
Mycophenolate mofetil	4 (5)	1 (3)	1 (4)
Methotrexate	4 (5)	4 (14)	0 (0)
Hydroxychloroquine	3 (4)	2 (7)	0 (0)
Cyclosporine	2 (3)	0 (0)	1 (4)

Reported as frequency (%) unless otherwise noted.

factors (VEGF-A and PDGF-BB) compared to non-MMF patients ($P < 0.05$). Cytokines, chemokines and significant cell populations grouped by STAT-pathways, cell lineage and functional properties revealed significant modifications associated with the STAT3 and B cell pathways (Figure 1). Healthy PBMCs treated with IL-6 and MMF identified a significant downregulation of pSTAT3 following MMF addition ($p = 0.0313$), but no alterations in pSTAT5 or caspase3/7 levels were observed following a 3 hour incubation.

Conclusion: Our results indicate that MMF suppressed STAT3 phosphorylation in response to IL-6 with associated decreases in antigen presentation, lymphocyte activation, and pro-inflammatory soluble mediators of SLE patients. Together these data suggest immunologic changes in the STAT3 pathway are critical for driving MMF disease remission in SLE patients.

Disclosure: S. Slight-Webb, None; J. M. Guthridge, None; E. Chakravarty, None; H. Chen, None; R. Lu, None; K. M. Bean, None; H. T. Maecker, None; P. J. Utz, None; J. A. James, None.

Comorbid Vasculitis Among Patients in a National Primary Immunodeficiency Database

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis II: Novel Diagnostics and Therapeutics

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Vasculitis has been reported in patients with various forms of primary immunodeficiency (PID) in case reports in the literature. The goal of this study is to evaluate the frequency of vasculitis in a large national database of patients with primary immunodeficiency.

Methods: The United States Immunodeficiency Network(USIDNET) is a large national consortium organized to collect registry data on patients with primary immune deficiencies. The USIDNET database was queried for patient records with a documented history of vasculitis. Data regarding demographics, type of vasculitis diagnosis, specific PID diagnosis, immunologic laboratory results and immunomodulatory treatment was abstracted from the records and descriptive statistics are presented. Focused analyses were also performed for patients with common variable immune deficiency (CVID) and Wiskott-Aldrich syndrome (WAS).

Results: As of March 12, 2018 data were available on 4,888 patients and 76 patients (1.6%) with vasculitis were identified. CVID (n=29, [38%]) and WAS (n=20, [26%]) were the most common PID associated with vasculitis (Table 1). Table 2 describes the results for the total PID cohort, as well as CVID and WAS sub-populations. Overall, 76% of patients were Caucasian, and 46% of patients were female. Central nervous system (CNS) vasculitis was the most common specific vasculitis syndrome identified among patients with PID in the USIDNet Registry (n=11, [14 %]). Glucocorticoids were the most frequent immunomodulatory therapy reported in all populations studied and occurred in more than half of cases (59-69%). In the CVID cohort, 29 cases of vasculitis were identified, with CNS vasculitis being the most common (n=5, [17%]). About half of cases of vasculitis were reported to be present before or at the diagnosis of the PID (n=37, [49%]) and CVID (n=14, [48%]). Henoch-Schonlein Purpura was the most common vasculitis (n=6, [30]) associated with WAS, with most cases (75%) being present before or at diagnosis of WAS.

Conclusion: Vasculitis is an uncommon complication of PID but can be encountered in a variety of syndromes, and was most frequently associated with CVID and WAS in the USIDNet Registry. Vasculitis complicating PID can represent a challenging confounder and mimic of serious infections. Clinicians caring for patients with PID need to be aware that vasculitis may be a rare autoimmune manifestation associated with PID especially those with CNS involvement.

Disclosure: K. Byram, None; L. H. Calabrese, Bristol-Myers Squibb, 5, 8, Genentech, Inc., 5, 8; J. Fernandez, None.

MicroRNA Expression in the Vasculitic Skin Lesions of Adult Patients with IgA Vasculitis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis II: Novel Diagnostics and Therapeutics

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: IgA vasculitis (IgAV) represents a common systemic vasculitis in paediatric and adult population. Our current knowledge of disease pathogenesis is still very limited and information on miRNAs expression in IgAV is lacking. The aim of our study was to determine the expression of five miRNAs (miRNA-146a-5p, miRNA-148-3p, miRNA-155-5p, miRNA-223-3p and let-7b) in the affected skin of adult IgAV patients.

Methods: The study included 65 skin samples from consecutive, untreated IgAV patients (61.5% male, median age 67.6 years, range 29–91), and 20 samples of normal skin from healthy volunteers. Total RNA was isolated from tissue sections of formalin-fixed, paraffin-embedded samples. Expression of miRNAs was measured using qRT-PCR. To present relative miRNA expression, the $\Delta\Delta CT$ method was used. Skin miRNAs expression was correlated to clinical characteristics of adult IgAV patients.

Results: We found significantly higher levels of miRNA-155-5p, miRNA-223-3p and let-7b in the affected skin compared to controls (18.6-fold, 6.4-fold and 7.9-fold higher respectively). Contrary, the miRNA 148-3p expression was significantly lower (2.2-fold). The expression of the miRNA-146-5p was near normal levels. Patients with necrotic skin lesions had significantly higher miRNA-223 tissue expression than those with non-necrotic purpura ($p=0.029$). Gastrointestinal tract involvement inversely correlated with the expression of miRNA-155-5p ($p=0.004$) and/or miRNA-146a-5p ($p=0.041$) in affected skin. No significant association between renal involvement or its severity, and skin expression of the investigated miRNAs was found. Patients with elevated serum IgA had a borderline upregulated skin expression of miRNA 223-3p ($p=0.053$).

Conclusion: An altered expression of miRNA-148b-3p, miRNA-155-5p, miRNA-223-3p and let-7b was found in vasculitic skin lesions in IgAV. The study revealed potential associations between the selected miRNA expression patterns and specific disease manifestations. Aberrantly expressed miRNAs could represent a biomarker in adult IgAV.

Disclosure: A. Hočevar, None; M. Tomšič, None; J. Pižem, None; L. Bolha, None; S. Sodin Semrl, None; D. Glavač, None.

Abstract Number: 2840

miR-125-b Is a Promising Biomarker for Giant Cell Arteritis in Patients with Negative Temporal Artery Biopsy Examination

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis II: Novel Diagnostics and Therapeutics

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Giant cell arteritis (GCA) is a systemic vasculitis of large- and medium-sized arteries, diagnosed either with a temporal artery biopsy (TAB) histology or by imaging techniques. MicroRNAs (miRNAs), the small non-coding RNAs, regulate gene expression post-transcriptionally and contribute to the pathogenesis of autoimmune diseases, including GCA (1). We aimed to explore whether miRNA expression in TABs of treatment-naïve GCA patients is deregulated and could separate TAB-positive GCA from TAB-negative or non-GCA patients.

Methods: Total RNA was isolated from TABs of 24 patients, suspected of having GCA at disease presentation. These patients comprised 3 groups: GCA patients with transmural artery inflammation (TAB-positive; $n=12$), GCA patients without inflammation (TAB-negative, $n=6$), and patients in whom GCA was finally refuted (non-GCA, $n=6$). Occlusion of lumen of temporal arteries in GCA patients was also recorded. The expression of selected miRNAs (based on literature search), including miR-155, -146-a, -146-b, -299, -17-3p, -181-b, -125-b and -29-b was measured with TaqMan qPCR using specific single TaqMan miRNA assays and normalization to the levels of the small nucleolar RNA (RNU48).

Results: While confirming significantly higher median (IQR) of miR-155 expression in TAB-positive GCA patients (0.118 (0.096)) as compared to TAB-negative GCA patients (0.017 (0.051); $p<0.01$) and non-GCA patients (0.029 (0.083); $p<0.05$) (1), our study also shows significantly lower miR-17-3p expression in TAB-positive (0.002 (0.001)) vs. TAB-negative (0.003 (0.001); $p<0.05$) GCA patients. MiR-125-b expression was significantly up-regulated in TAB-positive (0.410 (0.358); $p<0.05$)

and TAB-negative (0.910 (0.573); $p<0.001$) GCA patients as compared to non-GCA patients (0.029 (0.024)). There was no difference observed between the three groups of patients for miR-146-a, -146-b, -299, -181-b and -29-b. GCA patients with occlusion of lumen of temporal arteries had significantly higher expression of miR-155 (0.113 (0.102) vs 0.036 (0.09); $p<0.05$), -146-b (1.029 (0.1) vs 0.305 (0.574); $p<0.01$) and -299 (0.004 (0.006) vs 0.001 (0.002); $p<0.01$) as compared to patients without lumen occlusion.

Conclusion: Our study reports for the first time that miR-125-b could be useful as a biomarker for distinguishing non-GCA patients from TAB-negative GCA patients. MiR-125-b could potentially be involved in tissue remodelling, since it was found to regulate matrix metalloproteinases-2 and -9. This could aid, in the future, to identify patients with atypical GCA presentation, without signs of inflammation in TABs.

References: 1. Crocchi S, et al. MicroRNA markers of inflammation and remodelling in temporal arteries from patients with giant cell arteritis. *Ann Rheum Dis.* 2016;75(8): 1527-33.

Disclosure: T. Kuret, None; M. Frank Bertonecelj, None; K. Lakota, None; S. Sodin Semrl, None; S. Čučnik, None; M. Tomšič, None; A. Hočvar, None.

Abstract Number: 2841

Apremilast for Behcet's Syndrome: Results from a Phase III, Randomized, Double-Blind, Placebo-Controlled Study in a Japanese Subgroup

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis II: Novel Diagnostics and Therapeutics

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Apremilast, an oral phosphodiesterase 4 inhibitor, demonstrated efficacy in a global, phase III, multicenter, randomized, double-blind, placebo-controlled study in patients with Behcet's syndrome and active oral ulcers previously treated with ≥ 1 non-biologic therapy. A subgroup analysis was performed for Japanese patients in this study. We

Outcomes at Week 12 in the Japanese Subgroup			
	Adjusted Treatment Difference (or 95% CI)	APR vs. PBO (LS Mean, Median Time or %)	P Value
AUC for the number of OU from baseline through Week 12	-137.5	115.9 vs. 253.3	0.0166
Proportion of patients achieving complete response	32.8%	57.9% vs. 25.0%	0.0426
Maintenance of complete response*	47.4%	47.4% vs. 0.0%	0.0066
Time to OU resolution	160.3 (d)	Median time in weeks: 2.1 vs. NA†	0.0081
BSAS	-10.9	-10.5 vs. 0.5	0.0316
OU pain VAS (0-100 mm), change from baseline	-17.0	-30.3 vs. -13.3	0.1273
BDCAF, change from baseline			
BDCAI	-0.8	-0.8 vs. 0.0	0.3507
Patient's Perception of Disease Activity	-1.2	-1.4 vs. -0.2	0.0210
Discian's Dyedol Perception of Disease Activity	-1.2	-1.5 vs. -0.3	0.0248
BDQOL, change from baseline	-1.8	-1.2 vs. 0.6	0.1545

*Patients achieving OU resolution by Week 6 who remained OU-free for 46 additional weeks.

†NA, as $\geq 50\%$ of patients with complete OU resolution (median) was not achieved in the placebo group.

BDCAF=Behcet's Disease Current Activity Index; BDQOL=Behcet's Disease Quality of Life.

assessed the efficacy and safety of apremilast compared with placebo over 12 weeks in the subgroup of Japanese patients with Behcet's syndrome in the study.

Methods: In the global study, 207 patients with Behcet's syndrome were randomized (1:1) to apremilast 30 mg BID (n=104) or placebo (n=103) for 12 weeks, followed by a 52-week active-treatment phase. Patients were stratified by region (Japan and "Other"). Patients had active Behcet's syndrome, with ≥ 3 oral ulcers at randomization or ≥ 2 oral ulcers at screening and randomization without major organ involvement. The primary endpoint was the area under the curve (AUC_{Wk0-12}) for the total number of oral ulcers over 12 weeks. Additional endpoints included the assessments of oral ulcers, including pain, overall disease activity (Behcet's Syndrome Activity Score [BSAS] and Behcet's Disease Current Activity Form [BDCAF]), and quality of life (QoL) at Week 12. The primary and secondary variables in the Japanese subset analysis were pre-specified without adjustment for multiplicity. Nominal *P* values are presented.

Results: A total of 39 patients were included in the Japanese subgroup (placebo: n=20; apremilast: n=19). The subgroup analysis showed that the AUC_{Wk0-12} for oral ulcers was significantly lower in the apremilast group compared with the placebo group over 12 weeks (Table), which is consistent with the findings of the overall study population (129.5 vs. 222.1; $P<0.0001$). Similarly, as observed in the overall population, significantly greater improvements were shown in complete response rate of oral ulcers and maintenance of complete response of oral ulcers, time to oral ulcer resolution, and BSAS at Week 12 in the apremilast group. Numerical improvements were observed in oral ulcer pain, BDCAF, and QoL at Week 12 in the apremilast group; unlike the overall population, significance was not achieved, likely due to the limitation of the small sample size. Treatment-emergent adverse events (AEs) were comparable between the apremilast (73.7%) and placebo (75.0%) treatment groups. One serious AE (migraine) was reported with apremilast treatment. No AEs led to discontinuation.

Conclusion: The Japanese subgroup analysis showed that apremilast reduced the number of oral ulcers and overall disease activity and had favorable effects on oral ulcer pain and QoL in patients with Behcet's syndrome and active oral ulcers over 12 weeks. The safety profile was consistent with the known safety profile of apremilast, and results were consistent with findings in the overall study population.

Disclosure: M. Takeno, Celgene Corporation, 2; Y. Tanaka, Daiichi-Sankyo, Astellas, Pfizer, Mitsubishi-Tanabe, Bristol-Myers, Chugai, YL Biologics, Eli Lilly, Sanofi, Janssen, UCB, 8, Mitsubishi-Tanabe, Takeda, Bristol-Myers, Chugai, Astellas, Abbvie, MSD, Daiichi-Sankyo, Pfizer, Kyowa- Kirin, Eisai, Ono, 2; H. Kono, Celgene Corporation, 2; S. Sugii, Bristol-Meyers Squibb, Tanabe Mitsubishi Pharma, Chugai Pharmaceutical Co., Takeda Pharmaceutical Co., Pfizer, AYUMI Pharmaceutical Co, 8; M. Kishimoto, None; S. Cheng, Celgene Corporation, 3; S. McCue, Celgene Corporation, 3; M. Paris, Celgene Corporation, 3; H. Dobashi, None.

Abstract Number: 2842

Does Leflunomide Have a Role in Giant Cell Arteritis?

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Vasculitis II: Novel Diagnostics and Therapeutics

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: Glucocorticoids have been the mainstay treatment of giant cell arteritis (GCA) for decades. Recently, tocilizumab has been proven to be an effective alternative to glucocorticoid. However, not all GCA patients are eligible for biologics. We aimed to evaluate the role of leflunomide as a steroid sparing agent in GCA.

Methods: This open label study included newly diagnosed GCA patients followed at least 48 weeks at a single secondary/tertiary rheumatology centre. At the time of diagnosis patients received glucocorticoid, in line with the EULAR recommendations. At week 12 of follow up (FU), leflunomide 10 mg qd was recommended as an adjunctive therapy to all patients without known contraindications. The final decision to start the leflunomide was patient dependent. At week 48 we planned to stop glucocorticoid in leflunomide group. The number of relapses, a cumulative glucocorticoid dose during follow-up and treatment related adverse events (AE) were recorded and compared between glucocorticoid-only and leflunomide groups.

Results: Seventy-six patients (65.8% female, median (IQR) age 73.7 (66.1–78.8) years) were followed for a median (IQR) 96 (86–96) weeks. Thirty out of 76 patients (39.5%) received leflunomide at week 12 (leflunomide group), the others continued treatment with glucocorticoid (glucocorticoid-only group). During the first 48 weeks of FU, 22 patients relapsed,

4 in leflunomide group (13.3%) and 18 (39.1%) in glucocorticoid-only group. The difference was statistically significant ($p=0.02$; NNT 3.9 (95% CI 2.2-17.4)). Furthermore, 17/30 patients (56.7%) in the leflunomide group managed to stop glucocorticoid at week 48 (with one relapse (5.9%) shortly afterwards). The cumulative glucocorticoid dose at the last visit was lower in the leflunomide group than in the glucocorticoid only group (4,390 (4,132–5,558) mg, vs. 5,340 (4,652–5,792) mg, $p=0.01$). The patients tolerated leflunomide relatively well. Eight out of 30 patients (26.7%) discontinued leflunomide (one due to ineffectiveness and seven due to AE).

Conclusion: Our findings indicate the steroid sparing effect of leflunomide in GCA.

Disclosure: A. Hočevár, None; R. Jese, None; Z. Rotar, None; M. Tomšič, None.

Abstract Number: 2843

Leflunomide in Giant Cell Arteritis and Polymyalgia Rheumatica: A Real World Single Centre Experience

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Session Information

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Session Title: Vasculitis II: Novel Diagnostics and Therapeutics

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: LEF could be the favourable DMARD for PMR/GCA due to inhibitory activity on dendritic cells and IL-6. Previous case series have shown efficacy of LEF in PMR and GCA(1). Higher risk of adverse events due to CS use and disease activity is most associated in patients with relapsing/refractory disease. In current biologic era, LEF could be an efficacious and cost-effective treatment alongside with low dose of CS(2).

Methods: We conducted a retrospective cohort study to evaluate the efficacy and safety profile of LEF in 40 patients with GCA and 23 with PMR. Information was collected from our database of all patients with known GCA and PMR.

	GCA group	PMR Group
Sample size	40	23
Mean age (years)	75.7	67
F:M ratio	28:12	19:4
Investigations for Diagnosis		
US Only	9	N/A
Temporal artery biopsy only	4	N/A
PET only	10	7
Temporal artery biopsy & US	2	N/A
Temporal artery biopsy & PET	4	N/A
US & PET	9	N/A
US & PET & Temporal artery biopsy	2	N/A
Median CRP at diagnosis (mg/dL and interquartile range)	52.5 (19.5-85.5)	25 (12.5-37.5)
Pre LEF treatment		
Median prednisolone dose(mg/day and interquartile range)	16.5 (7.875-24.875)	10 (5-15)
Median CRP values (mg/dL and interquartile range)	10 (4-16)	18 (15-21)
Post LEF treatment		
Median prednisolone dose(mg/day and interquartile range)	5 (0.5-9.5)	N/A
Median CRP values (mg/dL and interquartile range)	4 (2.25-5.75)	4 (2-6)
Reason for LEF		
Relapsing disease	17	16
Steroid sparing agent	33	20
Maintain remission post biologic treatment	2	N/A
Median leflunomide treatment (months)		
	36 (30-42)	33 (21-45)
No of patients used other DMARD before LEF		
	3	2

Demographics, baseline characteristics, prednisolone dose, CRP values, disease and treatment duration with LEF and side effects were reviewed.

Results: Baseline characteristics, investigations, CRP, median treatment duration of CS and LEF are summarised in Image 001. A Wilcoxon signed rank test was used. For 30 GCA and 16 PMR patients (10 and 7 CRP missing respectively, excluded from analysis), median decrease of CRP on initiation and 6 months post LEF treatment was statistically significant ($z=48.5$, $p<0.01$ and $z=7.5$, $p=0.13$ respectively). The median reduction in prednisolone dose from initiation to 6 months was also statistically significant ($z=44.5$, $p<0.000$). Median time to reduce Prednisolone to $<5\text{mg/day}$ was 5.5 months (achieved in 17/23) in the PMR group and 6.5 months for the GCA group (achieved in 9/16) since starting on LEF. Hypertension, hair thinning, rash, gastrointestinal disturbances, liver function test abnormalities and infections were reported in 15 patients in the GCA group. Rash, nausea, weight loss and gastrointestinal disturbances were reported in 7 patients in the PMR group. LEF was discontinued in 7/40 patients in GCA group; 3 due to side effects, 1 due to diagnosis of lymphoma, 1 due to pneumonia which required short admission to the hospital, 2 due to flare which required steroids dose increase despite leflunomide and 1 due to peripheral neuropathy. LEF was discontinued in 7/23 in PMR group due to side effects. One death reported in a patient who was started on LEF 3 months earlier; cause is unknown. In 3/63 patients LEF was discontinued as they sustained remission.

Conclusion: LEF seems to be effective as a CS sparing agent in patients with GCA and PMR. Randomized controlled trials are warranted to confirm the usefulness of leflunomide in the therapy of GCA/PMR.

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2. Strehl C, et al. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force. *Ann Rheum Dis.* 2016 Jun;75(6):952–7.

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A Mixed-Methods Feasibility Study Exploring the Cultural Adaptation of Walk with Ease to the United Kingdom

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Session Information

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Session Title: ARHP II: Clinical Aspects and Outcomes Research

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Background/Purpose: The Arthritis Foundation's Walk With Ease (WWE) is an evidence-based 6 week community-based walking program for adults with arthritis delivered in instructor-led or self-directed format. It has been shown to improve physical function, pain, stiffness and fatigue. WWE is also a Centers for Disease Control and Prevention-recommended physical activity (PA) program. In recent years, WWE has been scaled-up and expanded to communities across the United States (US), yet is little known outside North America. This study aimed to examine the relevance, acceptability and feasibility of WWE in a United Kingdom (UK) context, where walking for pleasure and transport is culturally embedded.

Methods: This 4 phase study was carried out in collaboration with community and patient partners: 1) Cultural adaptation; 2) WWE program; 3) Qualitative enquiry; 4) Future planning. Recruitment was primarily via invitation letter to persons registered in selected Aberdeen primary care practices. Eligible (≥ 18 years, doctor diagnosed arthritis (confirmed or self-report), and self-reported joint symptoms in last 30 days, $\text{BMI} \geq 25 \text{ kg/m}^2$, and $<150 \text{ min/week}$ of moderate/vigorous PA) and consented participants were randomised into 2 groups: WWE program or usual care. Descriptive statistics explored physical performance measures (PPM), symptoms and beliefs using physical performance assessment and survey data

Outcome Measures	Baseline Mean (SD)	6-Week follow-up Mean (SD)	Change (95% CI)	N
Lower extremity strength – chair stand, seconds				
Instructor-led	17.89 (7.02)	14.53 (5.29)	-3.36 (-1.74, -4.98) ^{***}	31
Self-directed	14.65 (4.67)	13.07 (4.18)	-1.48 (-0.57, -2.59) ^{**}	32
360° turn ability, seconds				
Instructor-led	3.70 (1.73)	3.26 (1.24)	-0.44 (-0.98, 0.10)	33
Self-directed	3.27 (1.80)	2.94 (1.48)	-0.33 (-0.84, -0.03) [*]	34
Single Leg Stance, seconds				
Instructor-led	10.88 (13.63)	14.09 (14.38)	3.21 (-0.19, 6.61) [†]	29
Self-directed	17.39 (19.37)	18.58 (15.28)	1.19 (-3.75, 6.12) [†]	34
Walking speed, meters/second				
Instructor-led	0.80 (0.28)	0.89 (0.26)	0.09 (0.01, 0.16) [*]	33
Self-directed	0.87 (0.23)	0.94 (0.24)	0.06 (-0.02, 0.15)	34
Endurance = 2 minute step test, count				
Instructor-led	56.29 (25.79)	64.61 (26.61)	8.32 (0.10, 16.55) [*]	31
Self-directed	54.42 (19.22)	61.52 (19.82)	7.09 (1.24, 12.95) [*]	33
VNRS – Pain				
Instructor-led	4.92 (2.55)	4.50 (2.59)	-0.42 (-1.03, 0.18)	38
Self-directed	5.89 (2.43)	5.13 (2.30)	-0.76 (-1.38, -0.14) [*]	36
VNRS – Fatigue				
Instructor-led	4.74 (3.23)	3.79 (2.90)	-0.95 (-1.60, -0.30) ^{†*}	38
Self-directed	4.84 (2.84)	4.32 (2.57)	-0.53 (-1.25, 0.19)	36
VNRS – Stiffness				
Instructor-led	5.34 (2.43)	4.53 (2.59)	-0.82 (-1.55, -0.07) [†]	38
Self-directed	5.79 (2.55)	5.03 (2.24)	-0.76 (-1.51, -0.02) [*]	36
Arthritis Self Efficacy – Pain				
Instructor-led	5.04 (2.26)	5.96 (2.33)	0.08 (-0.71, 0.87)	39
Self-directed	5.02 (1.67)	5.77 (1.91)	0.76 (0.09, 1.43) [*]	38
Arthritis Self Efficacy – Symptoms				
Instructor-led	6.13 (2.17)	6.73 (2.26)	0.59 (0.08, 1.27) [†]	37
Self-directed	5.84 (1.88)	6.49 (1.85)	0.65 (0.02, 1.28) [*]	39
Rheumatology Attitudes Index (range 1-5)				
Instructor-led	2.78 (0.88)	2.44 (0.84)	-0.34 (-0.54, -0.14) ^{†*}	38
Self-directed	2.56 (0.75)	2.29 (0.72)	-0.27 (-0.44, -0.11) ^{†*}	39

CI=confidence intervals; SD=standard deviation; VNRS = visual numerical rating scale; ^{*}p<0.10, [†]p<0.05, ^{†*}p<0.05, ^{***}p<0.001

collected at baseline and post-6 week program. Participants' experiences of WWE were explored via video ethnography and narrative interviews, and analysed thematically.

Results: Of 149 participants, the majority were women (70%) aged 60 years (76%). OA was most prevalent (66%), followed by back pain (54%) and RA (13%); most also had at least 1 non-arthritis condition (79%). Among participants, 97 received the WWE program: 52 chose instructor-led; 45 chose self-directed. Follow-up was 80.4% at 6-weeks; 82.5% at 18-weeks. Average walk attendance across 5 walking groups was 63% (11.5/18 walks). Nearly all (99%) would recommend WWE to family or friends and 81% reported they were satisfied with the program. At 6 weeks, about half reported being at least moderately better in physical health (47%) and emotional well-being (53%). Within both WWE formats, statistically significant differences representing improvement were observed at 6 weeks from baseline for PPM, symptoms and beliefs (table). Qualitatively, participants described liking and using the WWE guidebook but wanted a foldable exercise leaflet and expanded online resources. Positive experiences were reported, with emergent themes of improved motivation, mental health and social well-being.

Conclusion: Findings indicate that WWE is a relevant and acceptable walking program in a UK context. Wider implementation of this evidence-based program may benefit the physical health and well-being of people with arthritis.

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Abstract Number: 2845

A Close Relationship between a Novel Visceral Adiposity Index and Bone Microstructure in Female Early Rheumatoid Arthritis Patients: A 1-Year Follow-up Study By HR-pQCT

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Session Information

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Session Title: ARHP II: Clinical Aspects and Outcomes Research

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Session Time: 2:30 PM-4:00 PM

Background/Purpose: Background

Obesity has been traditionally considered to protect the skeleton against osteoporosis and fracture. Recently, body fat, specifically visceral adipose tissue (VAT), has been associated with lower bone mineral density (BMD) and increased risk for some types of fractures. Chinese visceral adiposity index (CVAI) is a validated index for the evaluation of visceral fat dysfunction in Asians and strongly correlated with insulin resistance (IR) and was found to predict metabolic syndrome (MS), hypertension and diabetes better than body mass index (BMI) and waist circumference (WC). Spinal cortical and trabecular bone mineral density (BMD) were found to be inversely correlated with visceral adipose area measured by computed tomography even after adjusting for BMI. Whether CVAI correlates with bone microstructure in early rheumatoid arthritis (ERA) has not been assessed.

Purpose: 1) To compare CVAI between ERA patients and controls; 2) To assess the relationship between CVAI and the bone microstructure detected by high-resolution peripheral quantitative computed tomography (HR-pQCT) in patients with ERA.

Methods: In this study, 104 female ERA patients treated with a tight-control protocol using csDMARDs were prospectively followed for 1 year. 30 female healthy controls were also recruited. All the 104 female ERA patients were scanned by HR-pQCT of the distal radius and tibia at baseline and one-year. CVAI was calculated by the following formula: $CVAI = -187.32 + 1.71 \times \text{age} + 4.23 \times \text{BMI} + 1.12 \times \text{WC (cm)} + 39.76 \times \text{Log10 TG} - 11.66 \times \text{HDL-C}$. The female ERA patients were sub-grouped according to the median CVAI value (65.73) (low CVAI and high CVAI groups).

Results: After adjusting for age and BMI, the CVAI in the ERA group was significantly higher than the control group (55.10 ± 32.02 versus 41.11 ± 20.89 , $p=0.010$). ESR level at baseline in the high CVAI group was statistically higher than the low CVAI group (73.63 ± 34.49 versus 55.52 ± 27.52 , $p=0.038$). Cortical volumetric BMD (vBMD) in the distal radius and tibia at baseline were significantly lower in the high CVAI group compared to the low CVAI group (all $p<0.01$). Linear regression models indicated that CVAI at baseline was an independent negative predictor of distal radius cortical vBMD at Month 12 ($B=-1.033$, $p=0.022$, 95% CI: $-1.914 \sim -0.153$) and tibia cortical vBMD at Month 12 ($B=-0.828$, $p=0.003$, 95% CI: $-1.366 \sim -0.290$). In addition, CVAI at baseline was an independent predictor of the decreased trabecular vBMD in tibia ($B=0.040$, $p=0.001$, 95% CI: $0.018 \sim 0.063$) and decreased trabecular vBMD in distal radius ($B=0.233$, $p=0.008$, 95% CI: $0.063 \sim 0.403$).

Conclusion: CVAI is an independent predictor of bone loss in female patients with ERA. CVAI may have an important role in the changed trabecular density. These associations may be mediated by a chronic inflammatory state.

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Abstract Number: 2846

Foot and Lower Limb Characteristics in People with SLE: A Comparison with Age- and Sex-Matched Healthy Control Participants

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Background/Purpose: People with SLE report joint pain and swelling, impaired circulation, cutaneous lesions and foot deformity. Foot- and lower-limb-related functional impairment has also been described in SLE. However, objectively assessed measures of foot function, including muscle strength and gait characteristics have not been evaluated in people with SLE. This study aimed to identify foot and lower limb characteristics in people with SLE compared to age- and sex-matched controls.

Methods: The study included 54 people with SLE (all fulfilling the 1997 ACR classification criteria) and 56 age- and sex-matched healthy control participants (mean (SD) age: 52 (14) SLE vs 48 (14) controls, 93% females in both groups), who attended a study visit designed to comprehensively assess foot function. Assessment of patient-reported foot and lower limb pain and disability was measured using: Manchester Foot Pain & Disability Index; Lower Limb Task Questionnaire; and 100 mm foot pain VAS. Isometric muscle force for ankle plantar flexion, dorsiflexion, inversion and eversion was assessed using dynamometry; foot joint motion was assessed using goniometry; foot type was assessed using the Foot Posture Index (FPI); foot problems were assessed using the Foot Problem Score (FPS); neurological evaluation included vibration perception thresholds (VPT) and presence of protective sensation. Temperature and Ankle Brachial Index (ABI) were also assessed. Dynamic function was assessed using plantar pressure and spatiotemporal gait analysis. Data were analysed using regression models.

Results: Participants with SLE had a mean (SD) disease duration of 15 (12) years and a SLEDAI-2K score of 13 (10). Differences in foot characteristics are presented in the Table. Participants with SLE reported greater foot and lower limb pain and disability in all questionnaires. Compared to control participants, those with SLE had significantly reduced muscle strength for ankle plantar flexion, dorsiflexion, inversion, and eversion. Participants with SLE had higher FPI (3.6 vs 5.4, $P = 0.007$) and FPS (11 vs 16, $P = 0.001$), VPT (8.9 vs 13.2, $P = 0.001$) and prevalence of abnormal ABI (odds ratio (95% CI) 3.13 (1.03, 9.49), $P = 0.044$). No differences were observed between groups for joint motion, protective sensation, or temperature. Participants with SLE exhibited higher pressure time integrals for all regions of the plantar foot and walked significantly slower with reduced step length and greater swing and stance times compared to control participants.

Conclusion: People with SLE report a wide-range of foot complaints related to pain, disability and activity limitation. People with SLE also exhibit objective evidence of foot and ankle disease, including reduced foot and ankle muscle strength, and altered plantar pressure and gait patterns when compared to matched controls.

Table. Difference in foot and lower limb characteristics between controls and SLE

	Mean (SD)		P
	Control	SLE	
Foot pain VAS, mm	4.5 (24.3)	25.7 (23.9)	<0.001
MFPDI, total	1.3 (2.6)	11.6 (8.4)	<0.001
LLTQ activities of daily living	39.2 (1.4)	34.7 (5.6)	<0.001
LLTQ recreational activities	35.7 (11.0)	24.9 (6.2)	<0.001
Plantar flexion force, N	231.1 (67.5)	188.5 (63.3)	<0.001
Dorsiflexion force, N	178.8 (49.7)	144.8 (49.8)	<0.001
Inversion force, N	103.0 (38.6)	79.3 (38.3)	<0.001
Eversion force, N	88.1 (30.7)	65.6 (31.3)	<0.001
1MTP dorsiflexion ROM, °	82.5 (22.2)	80.2 (21.6)	0.44
STJ inversion ROM, °	35.3 (12.5)	35.1 (12.4)	0.89
STJ eversion ROM, °	14.1 (7.9)	13.8 (7.9)	0.76
Ankle lunge, °	43.0 (9.4)	40.8 (9.3)	0.08
Temperature, °C	24.9 (3.0)	25.2 (2.9)	0.44
Pressure time integral, kPa*s ^a			
Heel	48.7 (40.3)	151.6 (40.3)	<0.001
Midfoot	29.4 (25.3)	66.7 (25.3)	<0.001
First metatarsal	51.6 (46.1)	117.7 (46.3)	<0.001
Second metatarsal	73.7 (45.1)	170.9 (45.3)	<0.001
Third to fifth metatarsals	59.8 (41.2)	147.0 (41.4)	<0.001
Hallux	35.9 (37.3)	126.0 (37.1)	<0.001
Toes	22.2 (25.6)	60.4 (25.7)	<0.001
Spatiotemporal gait parameters ^b			
Step length, cm	63.5 (9.4)	57.0 (9.4)	<0.001
Swing time, s	0.39 (0.04)	0.42 (0.04)	<0.001
Stance time, s	0.64 (0.11)	0.73 (0.12)	<0.001
Velocity, cm/s	123.4 (18.5)	101.2 (18.5)	<0.001
Cadence, steps/min	116.6 (10.2)	105.6 (10.2)	<0.001

VAS = Visual Analogue Scale; MFPDI = Manchester Foot Pain and Disability Index; LLTQ = Lower Limb Task Questionnaire; 1MTP = first metatarsophalangeal joint; STJ = subtalar joint; ROM = range of motion; Diff. = difference between controls and SLE; CI = Confidence Interval.

^aAdjusted for BMI and gait velocity. ^bAdjusted for BMI. Bolded P values indicate significant difference at $P < 0.05$.

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Associations between Serum Uric Acid Level and Coronary Artery Disease

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Title:

Association between Serum Uric Acid Level and Coronary Artery Disease :

Background/Purpose: Previous studies have shown an unclear relationship between serum uric acid (SUA) and coronary artery disease (CAD). We attempt to clarify this relationship using the largest public US dataset available; the National Health and Nutrition Examination Survey (NHANES).

Methods: NHANES data from 2003 to 2014 was selected based on an affirmative response to the questions: 1. "Ever told you had angina/angina pectoris", 2. "Ever told you had heart attack", and 3. "Ever told you had coronary heart disease". The resulting data set was analyzed for uric acid levels (cut-off >6.0 mg/dL in females and >7.0 mg/dL in males), and CAD risk factors. Proportional analyses as well as univariate and multiple logistic regression models were used to evaluate the associations between SUA levels and CAD.

Results: 36,267 survey participants (Mean age 49.35 yrs.) from 2003 to 2014 were included in the study. There were 20,201 (51.7%) females and 18,863 (48.3%) males. A total of 2,797 (7.2%) had CAD; 39% of these were female and 61% were male. Univariate analyses showed a significant association between high SUA levels (OR 1.4; 95% CI 1.3 - 1.6), hypertension (OR 1.1; 95% CI 1 - 1.2), and renal dysfunction (OR 2.0; 95% CI 1.8 - 2.3). The relationship between SUA and CAD was reaffirmed in our multiple regression models (p-value <0.001) after adjusting for age, sex, race, smoking, diabetes, blood pressure and cholesterol.

Conclusion: Our study showed that there is a significant association between SUA levels and CAD in the NHANES population. This suggests that including SUA in risk models may improve risk stratification for CAD. Further prospective studies are needed to confirm this association and clarify the mechanisms behind it.

Disclosure: P. Kachur, None; S. Tadepalli, None; S. Kachur, None; P. Cheriya, None.

Racial Disparities in Utilization of Knee Replacement: Data from the Osteoarthritis Initiative

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: ARHP II: Clinical Aspects and Outcomes Research

Session Type: ARHP Concurrent Abstract Session

Session Time: 2:30 PM-4:00 PM

Background/Purpose: While risk of knee osteoarthritis (OA) is higher among black than white individuals, the rate of knee replacement—an effective treatment for end-stage OA among blacks is lower than among whites. Identifying mechanisms of racial disparity in utilization of knee replacement would help toward development of innovative programs or

interventions to reduce disparities and improve OA care in blacks. We compared the risk of knee replacement between black and white individuals and assessed the extent of which the difference in risk of knee replacement was accounted for by several potential mediators.

Methods: Data on race, age, sex, education, family income, and health insurance at baseline examination as well as incident knee replacement during the follow-up were obtained among participants in the Osteoarthritis Initiative, which is a multicenter prospective cohort study of participants with or at high risk of knee OA. First, we compared the risk of knee replacement between blacks and whites using generalized estimating equations, adjusting for age and sex. Then, we estimated the indirect effect of race on the risk of knee replacement mediated through education, income and health insurance using marginal structural model.

Results: Of 4,057 participants (8,114 knees) in the OAI, 3,368 (83.0%) were white (mean age: 61.5 years; women: 54.9%, \geq college education: 87.6%, income < \$50,000/year: 33.3%, and health insurance coverage: 89.6%) and 689 (17.0%) were black (mean age: 58.9 years; women: 68.5%, \geq college education: 73.4%, income < \$50,000/year: 61.8%, and health insurance coverage: 85.5%). During the follow-up period, 341 (10.1%) whites and 43 (6.2%) blacks have knee replacement therapy. Compared with whites an age-sex-adjusted odds ratio (OR) of knee replacement for blacks was 0.63 (95% Confidence Interval [CI]: 0.45-0.88). In the multiple mediation analysis, the natural direct effect of race on knee replacement was 0.71 (95% CI: 0.49-1.04), and the natural indirect effect through income and health insurance were 0.93 (95% CI: 0.87-1.00) and 0.97 (95% CI: 0.95-0.99), with each of these mediators explaining 20.6% and 9.6% of risk of knee replacement between two racial groups, respectively. (see **Table 1**).

Conclusion: Blacks were less likely to have knee replacement than whites, indicating racial disparities in the utilization of knee replacement. Such a disparity was partially attributed to the difference in income and health insurance between two racial groups. Future studies evaluating how perception and willingness on knee replacement mediate the effect of race on knee replacement are warranted.

Table 1 Results of Multiple Mediation-analysis of the Association between Race (black versus white) and Utilization of Knee Replacement

Black versus white	OR* (95% CI)	Proportion Mediated (%)	P value
Total Effect	0.63 (0.45, 0.88)	-	<0.01
Direct Effect	0.71 (0.49, 1.04)	-	0.09
Indirect Effect through Education	1.00 (0.95, 1.06)	0	1.00
Indirect Effect through Income	0.93 (0.87, 1.00)	20.6	<0.05
Indirect Effect through Health Insurance	0.97 (0.95, 0.99)	9.6	<0.01

OR, Odds Ratio; 95% CI, 95% Confidence Interval

*OR was adjusted for age and sex

Disclosure: J. Wei, None; C. Zeng, None; U. S. D. T. Nguyen, None; H. K. Choi, Takeda, Selecta, Kowa, and Horizon, 5, Selecta and Horizon, 2; Y. Zhang, None.

Abstract Number: 2849

Risk of Obstructive Sleep Apnea in Rheumatoid Arthritis

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Session Information

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Session Title: ARHP II: Clinical Aspects and Outcomes Research

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Background/Purpose: Self-reported sleep disturbances (SDs) are common in RA. Most studies of sleep in RA have focused on SDs in general. Obstructive sleep apnea (OSA) is one specific type of SD, which has well characterized negative health effects and for which treatment is available. We examined the frequency OSA symptoms, risk, diagnosis, and treatment, and factors associated with OSA risk.

Methods: Data were from Forward – The National Data bank for Rheumatic Diseases, for which participants complete questionnaires every 6 months. RA diagnoses were physician-reported. In one questionnaire, items about the presence of symptoms, physician diagnoses (MD-DX), and treatment of OSA were included. Risk of OSA was assessed using a validated questionnaire with positive predictive value of ~85%¹. Items included snoring, daytime sleepiness, observations of

apnea episodes by others, presence/treatment of hypertension (Table 1). Presence of ≥ 2 of these symptoms plus age > 50 or BMI > 35 indicates high risk for OSA. Use of continuous positive air pressure (CPAP) devices were also assessed. Frequencies of OSA symptoms, risk, diagnosis, and treatment were tabulated. Multivariate logistic regression analyses identified independent predictors of high risk of OSA. Potential predictors included age, sex, smoking, low income, chronic obstructive pulmonary disease (COPD), other comorbid conditions, obesity, disease duration, self-reported RA disease activity (RA Disease Activity Index, RADAI), medications, and pain.

Results: Subject characteristics and prevalence of OSA symptoms are shown in Table 1 (n = 2623). 16% reported MD-DX OSA and an additional 8% were at high risk of OSA, compared to OSA prevalence of $\sim 2\text{--}4\%$ in the general population. 9% used CPAP (58% of MD-DXOSA; 34% of those at high risk for OSA). Independent predictors of OSA risk were obesity, smoking, more comorbid conditions, and RADAI (Table 2).

Conclusion: OSA was more common in RA than in the population, with only 2/3 of those at high risk reporting an OSA diagnosis. Half of those with a diagnosis reported treatment. Some predictors of OSA were similar to predictors in the population (age, obesity), but disease activity was also associated with OSA. Self-reported sleep problems are associated with poor RA disease outcomes. In other conditions, OSA is linked to heightened inflammation, so it could be a cause of increased RA disease activity. Further research is needed to tease out disease-specific causes and effects of OSA and other sleep disturbances in RA.

¹ Chung F et al: Anesthesiol 2008;108:812; J Clin SleepMed 2014;10:951

Table 1. Subject characteristics (n = 2639)

	Mean +/- SD or % (n)		Mean +/- SD or % (n)
<u>Sociodemographic</u>			
Age, years	67.2 +/- 11.4	Female	82.7 (2168)
White	93.4 (2465)	Low income	25.4 (687)
<u>General health</u>			
Current smoker	3.6 (94)	Obese (BMI ≥ 30)	32.1 (861)
Rheumatic Disease Comorbidity Index ²	2.1 +/- 1.7	Morbid obesity (BMI ≥ 35)	15.3 (402)
COPD	7.9 (208)		
<u>RA characteristics</u>			
RA duration, years	23.0 +/- 12.8	Prednisone use	25.2 (657)
Pain rating (0 – 10)	3.2 +/- 2.5	Biologic use	51.5 (1349)
RA Disease Activity Index (RADAI)	2.2 +/- 1.5	Function (HAQ; Health Assessment Questionnaire)	0.98 +/- 0.73
<u>Obstructive sleep apnea risk factors¹</u>			
Snoring: do you snore loudly (loud enough to be heard through closed doors)?			12.0 (311)
Daytime sleepiness: do you often feel sleepy during the daytime (such as falling asleep during driving or while talking to someone)?			11.9 (310)
Observed apnea episodes: Has anyone observed you stop breathing or choking/gasping during your sleep?			13.1 (341)
Hypertension: do you have or are you being treated for high blood pressure?			31.3 (821)

² England BR. *Arthritis Care Res* 2015; 6: 865

Table 2. Significant predictors of Obstructive Sleep Apnea (OSA)*

	High risk OSA	
	Bivariate	Multivariate
Age	0.99 (0.98, 1.00)	ns
Female	0.6 (0.5, 0.8)	0.6 (0.4, 0.8)
RDCI	1.3 (1.3, 1.4)	1.2 (1.1, 1.3)
COPD	2.4 (1.7, 3.3)	ns
Obese	3.3 (2.7, 4.2)	2.6 (2.1, 3.4)
Current smoking	2.2 (1.3, 3.5)	1.7 (1.0, 2.8)
Low income	1.3 (1.0, 1.7)	ns
RA duration	0.99 (0.98, 1.0)	ns
RADAI	1.5 (1.4, 1.6)	1.4 (1.2, 1.6)
Pain rating	1.2 (1.2, 1.3)	ns
Biologic use	1.0 (0.8, 1.2)	ns
Prednisone use	1.3 (1.0, 1.7)	ns

* Tabled values are odds ratio (95% CI) from multiple logistic regression analyses.

Disclosure: P. Katz, Bristol-Myers Squibb, 2; S. Pedro, None; K. Michaud, None.

Human Toll-like Receptor 8 Adversely Affects Placental Development and Pregnancy Outcomes in a Mouse Model of Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Innate Immunity

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Systemic Lupus Erythematosus (SLE) predominantly affects women of childbearing age and is associated with adverse pregnancy outcomes including pre-eclampsia, intrauterine fetal growth restriction (IUGR), placental abnormalities and maternal and fetal mortality, particularly during active disease or in the presence of antiphospholipid antibodies (aPL). Pro-inflammatory factors rather than thrombosis are now thought to be the main contributor to placental and fetal damage in women with APS. Pathogenic mechanisms that damage the fetal-maternal unit and cause abnormal placental development, however, remain poorly understood. The endosomal RNA sensor Toll-like receptor 8 (TLR8) that is predominantly expressed in macrophages and neutrophils was recently hypothesized to play a role in antiphospholipid syndrome (APS) and aPL antibody-induced placental and fetal damage. The role of TLR8 in systemic autoimmunity remains elusive as TLR8 function differs from mouse to man with respect to recognition of RNA. We are currently studying the functional consequences of one or two copies of human (huTLR8) in murine SLE, and hypothesize that the presence of huTLR8 and aPLs will adversely affect pregnancy outcomes in SLE.

Methods: Sle1 mice expressing huTLR8 as a BAC transgene (huTLR8tg) were generated and followed clinically. HuTLR8 DNA copy number and mRNA expression was confirmed by qDigital and qRT-PCR respectively. Pregnancies were closely followed and terminal C-sections were performed in pregnant females with dead pups or exhibiting signs of dystocia or prolonged end-stage pregnancy. Pup and placental weight was assessed. Placental tissues were histologically characterized by H&E and immunohistochemical staining for neutrophil GR1-Ly6 and the granular protein Myeloperoxidase (MPO) to distinguish intact from netting neutrophils. Additionally, placental tissue was stored for further mRNA and microRNA analysis. Auto-antibody status in serum from pregnant females was assessed.

Results: Female huTLR8tg Sle1 mice manifested splenomegaly [mean 0.323g, n=16] compared to their non-huTLR8 counterparts [mean 0.123g, n=18] (p=0.0013) and developed anti-cardiolipin antibodies at a younger age than their wild type controls. We observed 26/55=47% loss of litters due to fetal resorption/dystocia resulting in fetal and maternal death, compared with 0% in n=20 Sle1 controls. Pup weights were significantly lower (p<0.0001) for stuck/dead pups [median 1.212g, n=31] compared to normal pups [median 1.649g, n=55]. Abnormal placental morphology was observed, with dense tissue structure, defective vasculature and increased GR1-Ly6 neutrophil infiltration. An increase in netting neutrophils was identified by MPO as decondensed non-intact nuclei.

Conclusion: We observed 47% loss of litters in huTLR8tg Sle1 pregnancies due to fetal resorption/dystocia resulting in both fetal and maternal death. This was due to placental developmental abnormalities, including vascular remodeling and inflammation in the presence of aPLs. Here we identify a potential new model to study adverse pregnancy complications in SLE and APS and further define the mechanistic role of TLR8 in promoting pregnancy loss.

Disclosure: N. I. Maria, None; S. Martinez, None; A. Davidson, None.

NF-Kappa b Signaling in the Myeloid Cell Lineage Drives the Pathogenesis of Immune-Mediated Nephritis

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Session Information**Session Date:** Tuesday, October 23, 2018**Session Title:** Innate Immunity**Session Type:** ACR Concurrent Abstract Session**Session Time:** 4:30 PM-6:00 PM

Background/Purpose: Immune-mediated glomerulonephritis is a serious end organ pathology that commonly affects patients with systemic lupus erythematosus (SLE). Nephrotoxic serum nephritis, induced by passive transfer of preformed nephrotoxic antibodies, is a mouse model commonly used to study lupus nephritis (LN). We and others have previously shown that macrophages are important in the pathogenesis of LN. To further delineate critical nephritis-associated pathways, in this study we assessed the importance of NF- κ B signaling in the myeloid cell lineage in the pathogenesis of LN.

Methods: Using flox-cre technology, we created a novel B6 mouse strain with genetic deficiency in RelA (aka p65) restricted to myeloid cells (RelA *flox/flox* LyzM *cre/cre* B6; KO mice), thus facilitating the study of the role of classical NF- κ B signaling in myeloid cells in the context of immune mediated nephritis. Lupus like nephritis was induced at 9-10 weeks of age in both the KO mice and age-matched wildtype control B6 mice (WT mice). Mice were immunized on day 0 with rabbit IgG emulsified in complete Freund's adjuvant, and 5 days later were given the nephrotoxic serum (containing rabbit antibodies which target murine glomerular antigens) by intravenous injection. Mice were then serially assessed for the development of nephritis.

Results: By day 13, myeloid cell RelA KO mice (n=14) injected with nephrotoxic serum had significantly attenuated proteinuria (mean protein: creatinine ratio KO=3.1 \pm 2.2 vs. WT=29.0 \pm 9.0, p<0.05) and lower serum BUN levels (mean KO= 46.0 \pm 5.7 mg/dL vs. WT 69.9 \pm 6.2 mg/dL, p<0.01) compared to control injected WT mice (n=16). Inhibiting myeloid NF- κ B signaling also decreased inflammatory modulators within the kidneys. We found significant decreases in expression of IL-1 α , IFN γ , and IL-6 in kidneys from KO mice, but higher IL-10 expression. We also found a significant reduction of macrophages accumulating in the kidney by immunofluorescent staining, a finding confirmed by flow cytometry. Specifically, flow cytometric analysis revealed decreased numbers of classically activated macrophages infiltrating the kidneys of KO mice. Kidney IgG and C3 deposition, however, was not different between KO and WT mice. Additionally, the two strains had no differences in their antibody response to the initial immunization (in both total IgG concentration and concentrations of different isotypes), indicating that any differences in disease severity were not because deficient myeloid NF- κ B signaling interfered with disease induction. Analysis of renal histopathology is pending.

Conclusion: Our studies indicate that macrophage NF- κ B signaling is instrumental in the contribution of this cell type to the pathogenesis of nephritis induced by pathogenic antibodies. These results suggest that while approaches which decrease macrophage numbers can be effective in LN, more targeted treatments directed at modulating macrophage signaling and/or function could be beneficial, at least in early stages of the disease.

Disclosure: S. Chalmers, None; S. Garcia, None; J. Shum, None; L. Herlitz, None; C. Putterman, None.

Abstract Number: 2852

Excessive Formation of Neutrophil Extracellular Traps: Different Role in the Pathogenesis of ANCA-Associated Vasculitis and Systemic Lupus Erythematosus

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Session Information**Session Date:** Tuesday, October 23, 2018**Session Title:** Innate Immunity**Session Type:** ACR Concurrent Abstract Session**Session Time:** 4:30 PM-6:00 PM

Background/Purpose: ANCA-associated vasculitis (AAV) and systemic lupus erythematosus (SLE) both cause glomerulonephritis with pauci-immune and full-house immunofluorescence patterns, respectively. Although AAV and SLE are clinically divergent autoimmune diseases, neutrophil extracellular traps (NETs) are postulated to be involved in both diseases. NETs are immunogenic, extracellular DNA structures harbouring relevant AAV- and SLE-autoantigens. The aim of this study was to dissect AAV- and SLE-induced NET formation and study their pathogenic role in the pathophysiology of these autoimmune diseases.

Methods: Ex vivo NET formation was quantified by a novel, highly-sensitive NET-quantification assay using 3D-confocal microscopy for 82 AAV patients, 56 SLE patients and 10 healthy controls (HC). Morphology and kinetics of AAV- and SLE-induced NET formation was studied through live-cell imaging. Qualitative characteristics of NETs were investigated by immunofluorescence microscopy that detected co-localisation of NET-related proteins, including citrullinated histone-3 (CitH3) and high mobility group box-1 (HMGB1). Also, the presence of IgG, IgM or IgA autoantibodies on AAV- and SLE-induced NETs was studied through immunofluorescence. Autoantibodies as trigger of NET formation were investigated by depleting serum from IgG and NET inhibition assays were performed using peptidylarginine deiminase-4 (PAD4) and NADPH inhibitors.

Results: Ex vivo NET formation was higher for AAV compared to SLE, which was triggered by immune complexes (ICx) in SLE but not in AAV. In AAV, lytic NET formation was induced involving NADPH oxidase and PAD enzymes resulting in a lytic expulsion of citrullinated NETs within a timeframe of hours. In SLE, non-lytic NET formation with clustering of NET-ting neutrophils is induced within minutes. SLE-induced NETs have immunogenic properties including enrichment for HMGB1, oxidized mtDNA and immune complex formation which was not the case for AAV-induced NETs.

Conclusion: This study demonstrates that excessive NET formation in AAV is intrinsically different to NET formation in SLE, identifying suicidal NET formation and vital NET formation, respectively, which closely associated with the respective, typical features of “pauci-immune”, histone-mediated crescentic glomerulonephritis in AAV and immune-complex mediated “full-house” lupus nephritis in SLE.

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Abstract Number: 2853

A Protective Langerhans Cell-Keratinocyte Axis That Is Dysfunctional in Photosensitivity

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Background/Purpose: Photosensitivity, or skin sensitivity to ultraviolet radiation (UVR), is a feature of lupus erythematosus (LE) and other autoimmune conditions. Photosensitive lesions can be disfiguring and photosensitivity can be associated with flares of systemic disease. Increased UVR-induced keratinocyte apoptosis is thought to play a role in the pathogenesis, but factors that regulate keratinocyte apoptosis in photosensitivity are poorly understood. Langerhans cells (LCs), mononuclear phagocytes positioned primarily in the epidermis, can have regulatory roles. As LCs are closely associated with keratinocytes, we hypothesized that LCs can limit UVR-induced keratinocyte apoptosis and skin injury.

Methods: We exposed mice to UVR at a minimal erythema dosage and 24 hours and 5 days later, harvested ear skin for immunohistochemistry to measure activated caspase 3, for flow cytometry to enumerate monocyte infiltration, for histology to measure epidermal thickness, and for toluidine blue dye assays to measure epidermal permeability. Primary mouse and

human keratinocyte cultures were exposed to UVR in the presence or absence of LCs and keratinocyte apoptosis was measured. Skin sections from healthy controls and SLE patients were stained for immunofluorescence analysis of LC numbers and epidermal markers.

Results: Here, we identify a Langerhans cell (LC)-keratinocyte axis that limits UVR-induced keratinocyte apoptosis and skin injury via keratinocyte epidermal growth factor receptor (EGFR) stimulation. We show that absence of LCs in Langerin-DTA mice leads to photosensitivity and that, in vitro, mouse and human LCs can directly protect keratinocytes from UVR-induced apoptosis. LCs express EGFR ligands and ADAM17, the metalloprotease that activates EGFR ligands. Deletion of ADAM17 from LCs leads to photosensitivity and UVR induces LC ADAM17 activation and generation of soluble active EGFR ligands, suggesting that LCs protect by providing activated EGFR ligands to keratinocytes. Photosensitive systemic LE (SLE) models and human SLE skin show reduced epidermal EGFR phosphorylation and LC defects, and topical EGFR ligand reduces photosensitivity.

Conclusion: Together, our data establish a direct tissue-protective function for LCs, reveal a mechanistic basis for photosensitivity, and suggest EGFR stimulation as a treatment for photosensitivity in LE and potentially other autoimmune conditions.

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Abstract Number: 2854

Majeed Syndrome Causing LPIN2 mutations May Prevent Bone “Healing” By Rendering M2 Macrophage Proinflammatory

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Background/Purpose: To study the mechanism that leads to bone inflammation in a 4-year old patient of mixed Puerto Rican and African-American background who presented with sterile osteomyelitis (Majeed syndrome), that is caused by two novel compound heterozygous *LPIN2* mutations.

Methods: Targeted genetic analysis for known autoinflammatory genes was performed that revealed Majeed syndrome and functional studies (stimulation assays and immune-histochemistry) on patient's monocytes, monocyte-derived M1 (MDM1) and M2 (MDM2) macrophages (culture with GM-CSF or M-CSF respectively for 5 days) from the Majeed patient, patients with NOMID (n=3) and DIRA (n=4), and healthy controls (n=4) were conducted to assess IL-1 production and the production of other inflammatory cytokines and chemokines.

Results: The patient has a novel splice site mutation on one allele of *LPIN2*, that leads to a loss of exon 10 and 11, and a novel 16.0 Kb deletion on the other allele deleting exons 7-18 including a conserved residue that confers phosphatase activity. Treatment with IL-1 blocking treatment led to complete clinical remission. Functional studies from monocytes and MDM1 macrophages show increased LPS+ATP induced IL-1 production and increased upregulation of gasdermin D with increased cell death in MDM1s from the Majeed pt. similar to NOMID patients but higher than controls. In contrast, the Majeed pt's MDM2 produced lower amounts of IL-10 than MDM2 from HC, NOMID and DIRA patients. However, unstimulated Majeed pt's MDM2 spontaneously produced high levels of IL-8 and CCL2/MCP1 and LPS and ATP stimulated MDM2 macrophages from the Majeed pt. produced significantly higher levels of IL-6, TNF, IL-8 and other chemokines compared to MDM2s from healthy controls and NOMID patients. MDM2 from DIRA patients were more inflammatory than NOMID and HC but less than the Majeed pt's MDM2s. Studies evaluating the effect of the *LPIN2* mutations on osteoclast function are ongoing.

Conclusion: We report two novel loss-of-function mutations in *LPIN2*, in an American pt. of mixed racial background. The increase in caspase-1 activity and gasdermin D levels in the Majeed pt. are consistent with increased inflammasome activation in monocytes and MDM1s. However, the differentiation of Majeed monocytes into inflammatory MDM2 macrophages that express high levels of TNF, IL-6, IL-8 and chemokines known to activate osteoclasts distinguish the Majeed syndrome pt. from pts with GOF mutations in *NLRP3* (causing cryopyrinopathies) and suggest a possible mechanism of sterile osteomyelitis by causing an inflammatory local bone environment that may prevent bone healing.

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Abstract Number: 2855

Expanding the Phenotype: New Variant in the *IL1RN*-Gene Associated with Late Onset and Atypical Presentation of DIRA

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Innate Immunity

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Deficiency of the Interleukin-1 receptor antagonist (DIRA) is an autoinflammatory disease of infancy characterized by severe systemic inflammation with bone and skin involvement. This is a report of a novel variant in the *IL1RN*-gene associated with late onset and atypical phenotype of DIRA.

Methods: A 3 year-old Caucasian boy presented with recurrent monthly episodes of fever and fatigue, associated with lymphadenopathy, pericarditis, pleuritis, pancreatitis, and arthritis involving sacroiliac, hip, knee and ankle joints in the absence of skin involvement. Symptoms had started at age one and progressed over time to life-threatening episodes requiring intensive care. Throughout, ESR, CRP, SAA, S100A8/9, leukocytes, and platelets were highly elevated. Treatment with colchicine and steroids improved symptoms; however, did not prevent flares. Genetic testing did not identify known pathogenic variants of immune deficiencies and AIDs including DITRA.

Results: Whole exome sequencing detected a novel homozygous stop variant c.62C>G; p.Ser21* in the *ILRN* gene (NM_173842.2). Mother, father and brother were heterozygous for the same variant. In addition, three variants of unknown significance were identified in the patient's *PCGF5*, *CPA1* and *SPTA1* genes. Functional studies revealed marginally low secretion of IL-1RA from unstimulated leucocytes and after stimulation with IL-1 β and LPS, confirming the disease-causing nature of the variant. IL-1 inhibition with anakinra at 2 mg/kg/d was started resulting in complete resolution of clinical symptoms, inflammatory markers and signs of inflammation on MRI. Intolerance to daily sc injections prompted a switch to canakinumab at 4 mg/kg/4 weeks. However, canakinumab did not prevent significant disease flares including new bone inflammation. Re-start of anakinra resulted in recapture of disease control.

Conclusion: This is the first report of the novel c.62C>G; p.Ser21* variant in the *IL1RN*-gene resulting in late onset DIRA with prominent systemic and bone/joint inflammation. DIRA should be considered in older children even in the absence of skin disease.

Disclosure: J. B. Kuemmerle-Deschner, Novartis, 2, Novartis, SOBI, 5; K. Hoertnagel, None; S. Schlipf, None; S. Hansmann, None; T. Hospach, None; I. Tsiflikas, None; X. Liu, None; S. Benseler, None; A. Weber, None.

Do Patients with Moderate or High Disease Activity Escalate RA Therapy According to Treat-to-Target Principles? Results from the Acr's RISE Registry

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Measures and Measurement of Healthcare Quality I: Quality Improvement in Rheumatoid Arthritis

Session Type: ACR Concurrent Abstract Session

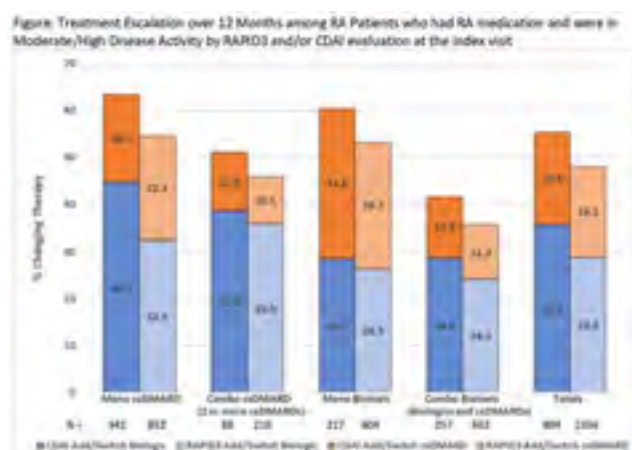
Session Time: 4:30 PM-6:00 PM

Background/Purpose: Routine measurement of RA disease activity and adjustment of drug therapy to attain remission or low disease activity is recommended by the ACR and EULAR. However, it is unclear whether this occurs in real-world settings. We identified longitudinal RA treatment changes stratified by disease activity categories and the methods used to measure it.

Methods: Using the ACR's national EHR-based RISE registry, we identified adult RA patients who had ≥ 1 rheumatologist visit (indexvisit) with a disease activity measure available (e.g. RAPID3, CDAI) in 2016. We assessed disease activity measurement(s) used for each patient and calculated the proportion of patients with moderate/high disease activity (M/HDA) at the index visit. We evaluated treatment and disease activity changes at the follow-up visit occurring month 7-12 after index. Results were stratified based on available measurement tool and patients' baseline RA medications. Subgroup analyses were conducted for patients with 'persistent' M/HDA (at both the index visit and the visit immediately prior), for patients with past (ever) biologic use, for patients with seropositive RA, and for those with past methotrexate use.

Results: Among 457,950 patients included in the 2016 RISE registry, we identified 50,996 eligible RA patients. Mean age was 62.4 (SD:13.7); 76.7% were women; 52.8% had Medicare insurance and 25.3% had concurrent glucocorticoid use. Most (85%) were evaluated with only one RA measurement at the index visit. RAPID3 was most commonly used (79%), followed by CDAI (34%) and DAS 28 ESR/CRP (3%). A total of 7,467 (14.6%) patients had both RAPID3 and CDAI measured at the index visit. For patients with M/HDA and RA medication at the index visit and who had a follow-up visit occurring 7-12 months after index (n=2,336 for RAPID3, n=904 for CDAI), changes in treatment is shown (Figure). Irrespective of baseline RA medication, RA treatment change did not exceed 65% of the patients. For the subgroup of patients with persistent M/HDA by RAPID3 (n=1,241) or CDAI (n=497), the proportion of treatment switching was consistent with the main analysis. Patients with any history of biologic exposure had a similar pattern in therapy change (<10% different). The treatment pattern for seropositive patients and with a history of methotrexate was also similar to the main analysis.

Conclusion: Irrespective of the measurement tool used (RAPID3 or CDAI), past biologic use, or persistent M/HDA, almost half of RA patients in the ACR RISE registry with M/HDA did not change their current therapy over the next year. To optimize RA therapies in accordance with treat-to-target principles, more effective intervention is needed to encourage treatment change and improve patient outcomes.



Disclaimer: *his data was supported by the ACR's RISE Registry. However, the views expressed represent those of the authors, not necessarily those of the ACR.*

Disclosure: H. Yun, Bristol Myers Squibb, 2; L. Chen, None; F. Xie, None; H. Patel, Lilly, 3; N. Boytsov, Lilly, 3; X. Zhang, Lilly, 3; J. R. Curtis, Amgen Inc., 2, 5, AbbVie Inc., 2, 5, BMS, 2, 5, Corrona, LLC, 2, 5, Janssen, 2, 5, Eli Lilly, 2, 5, Myriad, 2, 5, Pfizer, Inc., 2, 5, Roche/Genentech, 2, 5, Radius, 2, 5, UCB, Inc., 2, 5.

Abstract Number: 2857

An Electronic Audit, Reporting, and Data Correction System Improves the Quantity and Quality of Observational Data Collected for US Veterans Enrolled in the Veterans Affairs Rheumatoid Arthritis Registry

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Measures and Measurement of Healthcare Quality I: Quality Improvement in Rheumatoid Arthritis

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: The Veterans Affairs (VA) Rheumatoid Arthritis (RA) (VARA) registry is an observational cohort study of US Veterans with RA at 11 VA Medical Centers. VARA investigators capture clinical and laboratory disease activity measures (DAMs) during clinic visits via standardized templates in the electronic health record (EHR). Six clinical (tender/swollen joints, patient/provider global, MD-HAQ, pain) and 2 laboratory (ESR, CRP) DAMs are extracted post-visit using natural language processing (NLP). An audit and reporting system was developed to identify and report incomplete DAM collection and provide a method for entering missing data, when available. We report the impact of this system on the quantity and quality of DAMs collected.

Changes in Collection of Disease Activity Measures (DAMs) before and after the Implementation (IMP) of an Audit, Reporting, and Feedback System in the VARA Registry.

Patients and Notes	Pre-IMP	Post-IMP		Increase (%)
Unique patients	861	1,017		156 (18.1%)
Total Notes	1,182	1,423		241 (20.3%)
Disease Activity Measure (DAMs)		Feedback and Correction		
		Before	After	
Total DAMs	5,882	7,283	7,585	1,903 (33.5%)
Number Clinical DAMs per note	4.8	5.1	5.4	0.6 (11.7%)
Notes with 6 Clinical DAMs	865 (56.3%)*	1,000 (70.8%)‡	1,051 (75.1%)‡	396 (33.5%)
Notes with 4 DAMs for DAS28	806 (68.1%)*	944 (66.8%)‡	984 (69.7%)‡	138 (22.2%)
Notes with 6 clinical and 2 lab DAMs	595 (50.4%)*	778 (55.1%)‡	820 (58%)‡	225 (37.8%)

* Percent of total notes during the pre-implementation period.

‡ Percent of total notes during the post-implementation period.

‡ Percent change from pre-implementation baseline to post-implementation after corrective.

VARA registry goal is to collect the following Disease Activity Measures (DAMs) at each visit.

Six Clinical DAMs

Joint Tender Count of 28 joints
Joint Swelling Count of 28 joints
Patient Global Assessment of Disease Activity
Physician Global Assessment of Disease Activity
Medical Health Assessment Questionnaire
Patient Pain Score

Two Laboratory DAMs

Westergren Erythrocyte Sedimentation Rate
C-Reactive Protein

Composite DAM

Disease Activity Score for 28 joint count (DAS28)

Methods: After March 2017, VARA site investigators were provided monthly reports of incomplete / missing DAMs for the prior month. Review of clinic notes was used to identify data that was not captured by NLP because of modification of EHR templates or data entry errors. Updated and/or corrected data were entered into the EHR via note addendums and then automatically re-extracted by NLP to complete the capture of DAM data. DAMs collection from October 1, 2016 to March 31, 2017 (pre-implementation – Pre-IMP) was compared to collection from October 1, 2017 to March 31, 2018 (post-implementation –Post-IMP) before and after investigators received monthly reports.

Results: During the pre-IMP period, there were 1,182 notes with DAMs collected on 861 unique patients compared to 1,423 notes on 1,017 unique patients in the post-IMP period--an increase of 156 (18%) unique patients and 241 (20%) notes. The quantity of DAMs collected increased from 5,682 to 7,585, a 34% increase. During this timeframe enrollment in the VARA registry increased by only 4%. The quality of DAMs collected was measured by completeness of notes containing DAMs which also increased with corrections, as demonstrated by an increase in the average number of DAMs collected per note rising from 4.8 to 5.4 and proportion of notes achieving the goal of 6 clinical DAMs increasing from 56% to 75%. There were 170 notes identified with deficiencies and with monthly feedback 302 DAMs that were original missing added to the database. Similar quantity and quality/completeness improvements were seen in notes with all clinical and laboratory DAMs and the ability to calculate DAS28 (see Table).

Conclusion: An audit, reporting, and efficient data collection system improved both the quantity and quality of DAMs collected in this national observational study. The improvement in the collection of DAMs in RA patients will further enhance the feasibility of conducting epidemiologic and outcomes studies of RA and provide higher quality longitudinal data to enhance the care of RA patients via expanded use of HER.

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Abstract Number: 2858

Gaps in Patient Safety Performance before Treatment with Biologic Disease-Modifying Antirheumatic Drugs or Tofacitinib in a Large Academic Healthcare System

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Measures and Measurement of Healthcare Quality I: Quality Improvement in Rheumatoid Arthritis

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Treatment with biologic disease-modifying antirheumatic drugs (DMARDs) and tofacitinib confer increased risk of life-threatening infections, including reactivation of latent tuberculosis infection (LTBI), hepatitis B virus (HBV), and hepatitis C virus(HCV). We aimed to assess gaps in patient safety measures such as LTBI and hepatitis screening prior to drug initiation among patients treated with biologic DMARDs or tofacitinib in a large health system across multiple specialties.

Methods: We analyzed electronic health record (EHR) data from a university center, including diagnosis codes, problem lists, medications, laboratories, procedures, clinical notes, and scanned documents. Patients included all new users of a biologic DMARD (abatacept, adalimumab, anakinra, canakinumab, certolizumab, etanercept, golimumab, infliximab, secukinumab, tocilizumab, or ustekinumab) or tofacitinib between 7/1/13 and 10/1/17. We assessed screening for each infection: LTBI (fulfilled via tuberculin skin test, interferon gamma release assay, or prior treatment for TB); HBV (hepatitis B surface antigen); and HCV (Hepatitis C antibody) from 12 months preceding through 60 days after medication initiation. Next, we calculated performance on a composite safety measure that required screening for all 3 infections. We then liberalized the screening window to include any time prior to medication initiation. Multivariable logistic regression was used to assess differences in screening across prescribing specialties, adjusting for race, sex, age, and comorbidities.

Results: We included 1,029 patients; mean age was 39.5(SD 19.5), mean Charlson score 1.1 (SD 2.1), and 64% were White, 13% Hispanic, 12% Asian, 4% African American, and 22% other/not reported. Rheumatology was the most common prescribing specialty (Table) and the most common drugs prescribed were adalimumab (32%), etanercept (24%), infliximab (19%), and ustekinumab (9%). Overall, 62% of patients were screened for LTBI, 42% for HBV, 33% for HCV, and only 26% for all 3 infections within 12 months preceding through 60 days after initiation of an eligible drug. When we assessed screening at any time before drug initiation, the proportions screened were: 68% for LTBI, 55% for HBV, 46% for HCV, and 36% for all 3. Screening patterns differed by treating specialty (p<0.0001) (Table).

Conclusion: Screening for LTBI and hepatitis B and C among patients initiating biologic DMARDs or tofacitinib in a large health system is suboptimal. More robust safety protocols are needed across specialties to ensure adequate screening and prevent adverse drug events in this high-risk population.

Performance on Composite Patient Safety Measure (Screening for LTBI, Hepatitis B, and Hepatitis C), by Treating Specialty			
	N (%)	Unadjusted Performance*	Adjusted Performance** (95% CI)
All clinics	1,029	26.0%	n/a
Rheumatology	265 (25.8%)	32.8%	31.7% (25.9, 37.5)
Dermatology	277 (22.1%)	35.2%	35.8% (29.2, 42.3)
Gastroenterology	211 (20.5%)	21.3%	21.9% (16.2, 27.6)
Pediatrics subspecialties	160 (15.6%)	1.3%	1.5% (0.0, 3.6)
Oncology	10 (1.0%)	20.0%	14.8% (0.0, 34.9)
Other specialties	156 (15.2%)	33.3%	30.7% (23.1, 38.4)

* Proportion of patients who completed screening for LTBI, HBV, and HCV within 12 months before or 60 days after starting a new biologic DMARD or tofacitinib.

** Adjusted proportions calculated based on multivariate logistic regression adjusted for age, race, sex, and Charlson comorbidity score.

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Abstract Number: 2859

Do Preventive Cardiology Consults Versus Usual Care Improve Cardiovascular Risk Factor Assessment and Management in Patients with Rheumatoid Arthritis?

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Measures and Measurement of Healthcare Quality I: Quality Improvement in Rheumatoid Arthritis

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Session Time: 4:30 PM-6:00 PM

Background/Purpose: Rheumatoid arthritis (RA) patients have around 50% increased risk of cardiovascular disease (CVD). Both traditional and RA-specific cardiovascular(CV) risk factors contribute to the excess risk. Although RA is an independent risk factor for CVD, management of traditional CV risk factors is inadequate in this population. In order to improve risk factor management, we implemented a best practice alert (BPA) in the electronic health record (EHR) to prompt referral to preventive cardiology. We then investigated the impact of preventive cardiology on CV risk factor assessment and management in RA patients compared to usual care.

Methods: This retrospective cohort included adult RA subjects without CVD who were seen by a board-certified rheumatologist from 2009-2015 and exposed to the BPA, which prompted referral to preventive cardiology. The date that the BPA triggered was the baseline date. The main analysis included intervention subjects (referred and attended cardiology) and primary control subjects (referred but did not attend). A secondary analysis combined additional control subjects (not referred at all) with the primary control group. The primary outcome was CV risk factor assessment, defined as 4 of 5 traditional risk factors measured within one year. The secondary outcome was risk factor management, including starting or adjusting cardiac medications and providing lifestyle management counseling.

Results: 1,979 RA subjects (mean \pm standard deviation age: 56 \pm 14 years, 80% female, 74% white) were included. Overall, 266 (13%) subjects were referred to preventive cardiology; 145 (55%) subjects attended at least one preventive cardiology appointment (intervention), and 121 (45%) subjects were referred but did not attend (primary control). The

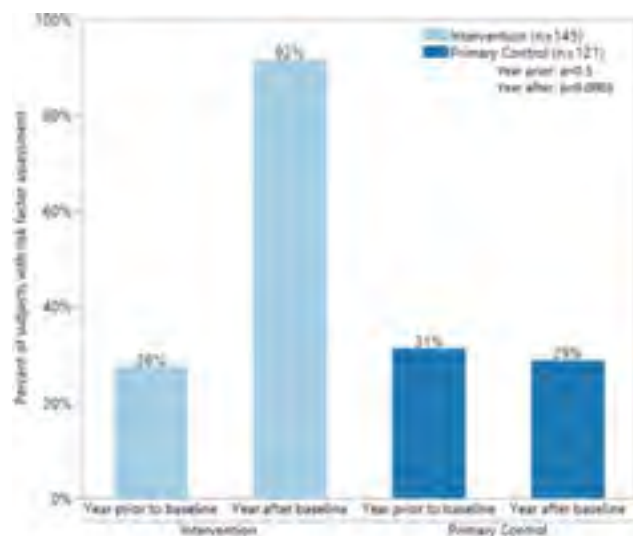


Figure 1. CV risk factor assessment one year prior to and one year after referral to preventive cardiology. Risk factor assessment is defined as at least 4 of 5 risk factors measured, including blood pressure, lipid panel, glucose, BMI, and smoking status.

remaining 1,713 subjects (not referred at all) were included in the combined control group (n=1834). One-third of subjects had risk factor assessment in the year prior to baseline. In the year after baseline, risk factor assessment occurred in 133 (92%) intervention vs. 35 (29%) primary control subjects ($p < 0.0001$; Figure 1). The intervention group had higher frequency of lipid-lowering medication management (intervention 36% vs. primary control 12%, $p < 0.0001$) and lifestyle management counseling (intervention 46% vs. 3% primary control, $p < 0.0001$). Additionally, the intervention group experienced significant decreases in total cholesterol (-14.6 ± 32.2 mg/dl, $p = 0.03$) and low-density lipoprotein (-13.8 ± 23.8 mg/dl, $p = 0.002$) at one year. Results were similar using the combined control group.

Conclusion: RA patients who attended preventive cardiology visits prompted by an EMR-based technology had increased CV risk factor assessment, pharmacologic and lifestyle management, and improved lipid profiles compared to usual care.

Disclosure: E. Romich, None; H. Ahmed, None; A. Nowacki, None; M. E. Husni, None.

Abstract Number: 2860

Disease Activity and Its Measurement in Patients with RA across the U.S.: Data from the Rheumatology Informatics System for Effectiveness (RISE) Registry

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Session Information

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Background/Purpose: Although national quality measures promote the measurement of disease activity (DA) in RA, the burden of DA in a population-based sample of RA patients is unknown. We used the ACR's RISE registry to assess variation in DA and methods of DA measurement nationwide.

Figure 1. Proportion of RA patients in RISE with disease activity in the remission or low categories on their most recent assessment, by practice, between July 2016 - June 2017

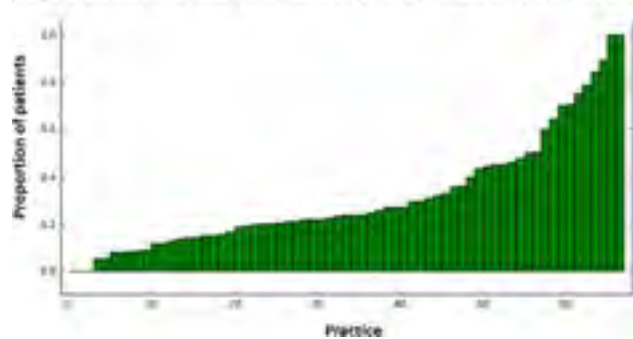


Figure 2. Proportion of RA patients in RISE with disease activity in remission or low categories, by state, between July 2016 - June 2017. Colors reflect adjusted proportions from a logistic regression model that controlled for measurement tool only. States in white did not have any patients included in this analysis.



Methods: RISE is a national, EHR-enabled registry that passively collects data on all patients seen by participating practices, reducing the selection bias present in single-insurer claims databases. As of June 2017, RISE held validated data from 663 providers in 110 practices, representing ~19% of the U.S. clinical rheumatology workforce. Patients in this study had 2 RA codes ≥ 30 days apart and ≥ 1 RA DA score recorded from July 2016- June 2017 by a practice with ≥ 20 RA patients. DA scores from validated instruments (CDAI, DAS, PASII, or RAPID3) were categorized using accepted cut-points. We calculated 1) the proportion of patients in remission, low, moderate, or high DA on their most recent assessment, overall and aggregated by practice or state; and 2) proportion with ≥ 2 DA scores ≥ 90 days apart with all assessments in remission/low DA. We then tested whether DA was associated with the measurement tool used using a chi square test and generated adjusted state-level proportions of patients in remission/low DA on the most recent assessment using logistic regression.

Results: We included 56,850 patients from 71 practices; 77% were female, 65% white, with mean age 61 ± 13 . Overall, 21% of patients were in remission and 24%, 29%, and 26% had low, moderate, and high DA, respectively. The proportion of patients in a given practice in remission/low DA ranged from 0-99% (Figure 1). Of the 35,573 patients with ≥ 2 DA scores, 27% were consistently in remission/low DA. RAPID3 was the most used tool (54%), followed by CDAI (42%), DAS (2%), and PASII (2%); RAPID3 scores were more likely to be moderate/high DA compared to CDAI scores ($p < 0.001$). State-level variation was significant, even after adjusting for measurement tool ($p < 0.001$, Figure 2).

Conclusion: Less than half of RA patients across the U.S. have DA in remission or low categories on their most recent assessment, with large differences across practices and states. Although some of this variation can be explained by the tool used to assess DA, additional factors such as underlying patient characteristics or preferences, availability and affordability of medications, or differences in treatments or treatment intensity should also be explored.

Disclaimer: This data was supported by the ACR's RISE Registry. However, the views expressed represent those of the authors, not necessarily those of the ACR.

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Clinical Laboratory Telephone Communication Outreach to Rheumatology Patients Improves Guideline-Concordant Timeliness of Monitoring of Conventional and Biologic Disease-Modifying Anti-Rheumatic Drugs (DMARDs)

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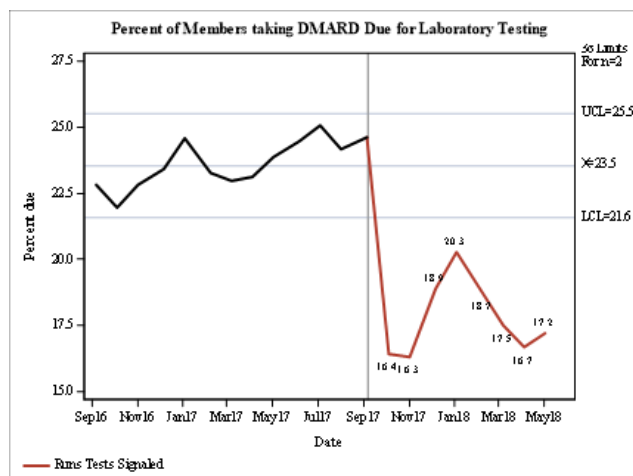
Session Type: ACR Concurrent Abstract Session

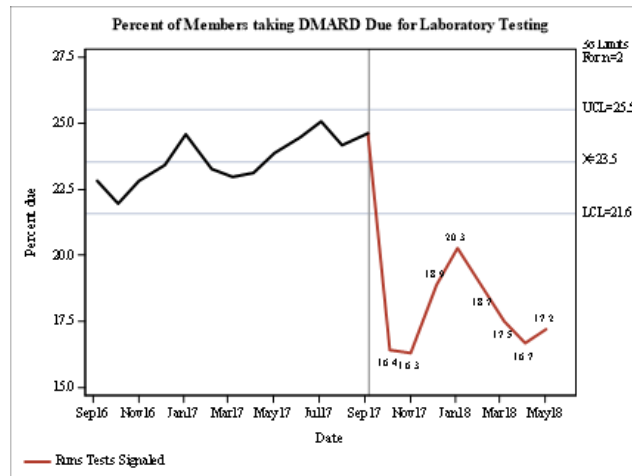
Session Time: 4:30 PM-6:00 PM

Background/Purpose: The American College of Rheumatology has published guidelines for laboratory monitoring of conventional DMARDs (cDMARDs). At Kaiser Permanente Colorado (KPCO), although most patients eventually complete recommended monitoring, we found a test utilization gap in timeliness to monitoring. The purpose of this work was to develop a laboratory-led intervention to improve timeliness of test completion. Here we describe the direct-to-patient interactive voice response (IVR) outreach we developed and present healthcare system results of this work.

Methods: KPCO is an integrated healthcare delivery system with about 600,000 members in the Denver-Boulder area. The KPCO Virtual Data Warehouse (VDW) was used to identify patients and to extract all data. cDMARDs included were: methotrexate (MTX), leflunomide (LEF), sulfasalazine (SZA), and azathioprine (AZA). Biologic DMARDs(bDMARDs) included were: tocilizumab (TCZ), tofacitinib (TOF), adalimumab (ADA), certolizumab pegol (CER), etanercept (ETN), golimumab (GOL), infliximab (IFX) and rituximab (RTX). We identified members aged ≥ 18 receiving cDMARD/bDMARD therapy from a rheumatologist. Patients were eligible for outreach if they were due (within 3 days) or overdue for testing based on their most recent dates of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr), and/or complete blood count (CBC) testing. Whether patients were due/overdue was defined as: 1) MTX, LEF, SZA, AZA: ALT, AST, Cr and CBC every 4 weeks if < 3 months therapy; every 12 weeks if ≥ 3 months therapy. 2) TCZ, TOF: ALT, AST, Cr, and CBC every 6 weeks if < 3 months therapy; every 12 weeks if ≥ 3 months therapy. 3) ADA, CER, ETN, GOL, IFX: CBC every 6 months. 4) RTX: CBC every 3 months. An interactive voice response (IVR) system was employed in outreach. This system sends texts to text-enabled phones and calls to phones that are not text-enabled. The messages state in part: "You are due for a lab test to continue taking your medicine safely. Go to any Kaiser lab within the next week. No appt is needed..." System outcomes analysis was descriptive.

Results: The cohort included 3737 patients, 2365 (63.3%) of whom were taking MTX. Overall, the % of patients due for testing dropped after the intervention began and remained below baseline (Figure). For example, among patients taking MTX during the baseline period, 37% had ≥ 1 ALT testing gap > 100 days (12 weeks + 16 days "grace" period). Comparable proportions of patients had AST, CBC, or Cr testing gaps. During the intervention period, 27% of patients





taking MTX had ≥ 1 ALT testing gap >100 days. Patient and clinician feedback is positive. The outreach requires minimal maintenance.

Conclusion: Automated telephone communication outreach to remind rheumatology patients to obtain ordered laboratory testing improves the timeliness of cDMARD and bDMARD monitoring, is liked by patients, and is efficient.

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Abstract Number: 2862

Magnitude of Response to TNF Inhibitors in Children with Spondyloarthritis and Sacroiliitis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical II: Treatment Update

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: We aimed to quantify the magnitude of biologic effect on sacroiliitis in juvenile SpA by comparing the change in the Spondyloarthritis Research Consortium of Canada (SPARCC) sacroiliac joint inflammation score (SIS) over time in TNF inhibitor (TNFi)-exposed versus TNFi-naïve patients.

Methods: This retrospective multi-center cohort study included 34 children with SpA. Children were included if they met ESSG SpA or ILAR juvenile arthritis criteria for enthesitis-related arthritis and had at least 2 pelvic MRI studies separated by at least 12 weeks between 2005 and 2018. Images were de-identified, randomized and reviewed independently by 3 radiologists and assigned a SPARCC SIS, with mean score used for analysis. The SIS divides the joint into quadrants and scores presence, depth, and intensity of bone marrow edema on STIR MRI (total score 0-72). We used a recency-weighted cumulative exposure model to quantify TNFi exposure in which higher weights were given to more recent exposure relative to the imaging date. The cumulative exposure scores were applied to a linear mixed-effects regression to test the association of TNFi exposure and change in SIS over time, adjusted for baseline SIS score. Kruskal-Wallis and chi-squared tests were used to assess relationships between clinical findings and SIS scores, as appropriate. Spearman's correlation was used to test association of change in clinical factors with the outcome.

Results: Baseline clinical features are in Table 1. The median time between images was 22 months (IQR 13-34.1). Ten (29%) children received a TNFi prior to baseline imaging, with a median exposure of 10 mos (IQR 3.9-24.4). Of the 26 patients (76%) with TNFi exposure between images, median exposure was 15.6 months (IQR 9-25.8). The mean SIS change score was 6.9 (SD 16.4; range -36 to 47). Patients with baseline SIS >1 had higher physician global assessments

Table 1: Subject characteristics at baseline imaging	All subjects (n=34)	TNFi exposure (n=26)	TNFi naïve (n=8)
	N (%)		
Age, years (median, IQR)	13.1 (10.2-15.3)	13.1 (10.2-15.3)	13.6 (10.8-15.2)
Sex, male	18 (52.94)	13 (50.0)	5 (62.5)
Race, Caucasian	27 (79.41)	21 (80.77)	6 (75.0)
HLA-B27 positive	17 (50)	15 (57.69)	2 (25.0)
Hip arthritis	6 (17.65)	5 (19.23)	1 (12.5)
Lower back pain	23 (67.65)	16 (61.54)	7 (87.5)
Morning stiffness (>15 minutes)	14 (42.42)	10 (40.0)	4 (50.0)
Disease duration, months (median, IQR)	13.8 (5.1-34.6)	14.7 (5.1-32.7)	12.4 (4.9-47.9)
Active joint count (mean, SD)	0.79 (1.98)	0.5 (1.65)	1.63 (2.77)
Tender entheses (mean, SD)	2.5 (3.23)	2.31 (3.28)	3.13 (3.18)
Physician global (0-10; mean, SD)	2.60 (1.82)	2.7 (1.57)	2.29 (2.61)
Patient global (0-10; mean, SD)	4.13 (2.81)	4.26 (2.72)	3.67 (3.33)
SIS baseline (median, IQR)	0 (0-19)	0.5 (0-21)	0 (0-7)
SIS baseline* (median, IQR)	15 (1-28)	19 (1-28)	7 (0-24.5)

*Excludes patients who experienced no change

($p=0.02$), fewer tender entheses ($p=0.02$), and shorter disease duration ($p=0.05$). Cumulative TNFi exposure was significantly associated with a decrease in SIS over time ($b=-0.02$, $p=0.01$). Of those with progression in SIS from 0 to >0 ($n=4$), two were exposed to a TNFi, but were off therapy for at least six months preceding the second MRI. There was no significant correlation between change in pain score and SIS ($p=0.09$).

Conclusion: Biologics have a quantifiable effect in reducing inflammation at the sacroiliac joints in children with SpA. Future studies should evaluate the rate of change in SIS in response to biologics to help guide appropriate timing for follow-up imaging in both clinical practice and efficacy studies.

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Abstract Number: 2863

Long-Term Efficacy and Safety of Canakinumab in Patients with Colchicine-Resistant FMF (crFMF), Hids/Mkd and TRAPS: Results from the Pivotal Phase 3 Cluster Trial

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Session Information

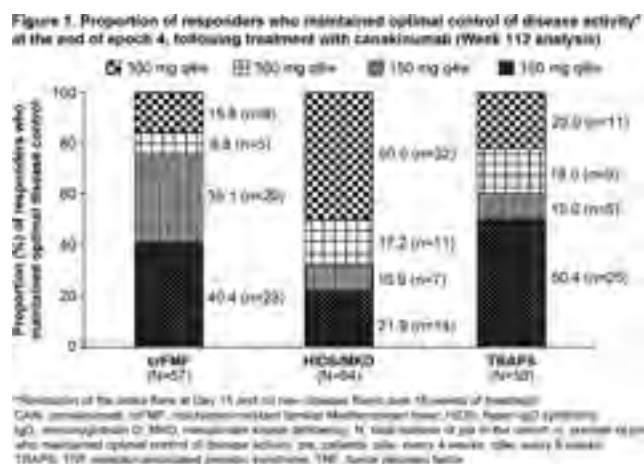
Session Date: Tuesday, October 23, 2018

Session Title: Pediatric Rheumatology – Clinical II: Treatment Update

Background/Purpose: Canakinumab (CAN), a selective, human anti-interleukin (IL)-1 β has demonstrated efficacy and safety in patients (pts) with colchicine-resistant familial Mediterranean fever(crFMF), hyper-IgD syndrome (HIDS)/ mevalonate kinase deficiency (MKD), and tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) in epochs 2 and 3 (E2 and E3) of the CLUSTER study(NCT02059291).^{1,2}Here, we evaluated the long-term maintenance of optimal control of disease activity (median of no or 1 flare and no up-titration) on every 4 weeks (q4w) and every 8 weeks (q8w) regimens of CAN and safety in pts with crFMF, HIDS/MKD and TRAPS through epoch 4 (E4) of the CLUSTER study.

Methods: The study comprised 4 epochs (E1–E4). The study design for E2 and E3 have been reported previously.¹ After lead-in E1, E2, a 16-weeks (wk) randomized, double-blind, placebo (PBO)-controlled epoch, assessed the ability of CAN 150/300mg q4w to induce complete response (absence of flares). E3, a 24 wk open-label randomized withdrawal epoch, assessed whether responders to either doses in E2 could maintain clinical efficacy on PBO or a prolonged dosing interval (150/300mg q8w). Pts who did not maintain clinical response on PBO or q8w were up-titrated to 150/300mgq4w. E4, a 72-wk, open-label epoch, assessed the long-term maintenance of efficacy and safety in pts on q4w and q8w dose regimens. Safety assessments included adverse events (AEs) and serious AEs.

Results: At the end of E4 (Wk 112), the proportion of pts who maintained optimal control of disease activity following treatment with 150/300mg q4w or q8w in all 3 cohorts are shown in Figure 1. More HIDS/MKD pts required up-titration to maximum dose (300mg q4w). The majority of pts in all 3 cohorts had Physician Global Assessment <2 (no or minimal disease activity) and a median of 1 or no new flare (crFMF: 96.6%, HIDS/MKD:83.3%, TRAPS: 94.3%). In all 3 cohorts, the median SAA levels decreased rapidly from baseline and remained suppressed through E4 (crFMF: 618 to 21 mg/L, HIDS/MKD: 2061 to 16mg/L and TRAPS: 243 to 12 mg/L). The most frequent AEs in E4, were infections and infestations (crFMF, 70.0%; HIDS/MKD, 86.4%; TRAPS, 81.1%) followed by gastrointestinal disorders (crFMF, 40.0%; HIDS/MKD, 65.2%; TRAPS, 50.9%). No deaths were reported in this study. No new or unexpected safety issues were reported over 112 weeks (E1-E4) of CAN treatment.



Conclusion: CLUSTER study demonstrated that long-term treatment (up to Week 112) with canakinumab 150/300 mg, with up-titrations to q4 w was necessary maintained optimal control of disease activity in crFMF, HIDS/MKD, and TRAPS patients. Majority of patients particularly in the HIDS/MKD cohort remained on the 150/300mg q4w at the end of Epoch 4. No new or unexpected safety issues were reported over 112 weeks of CAN treatment.

References: De Benedetti F, et al. *ArthritisRheumatol.* 2016;68 (suppl 10). ²De Benedetti F, et al. *NEJM* 2018;378:1908-19.

Disclosure: F. De Benedetti, Novartis, Roche, Pfizer, SOBI, AbbVie, Novimmune, BMS, Sanofi, 2; J. Frenkel, Novartis and SOBI, 2; A. Simon, Novartis, Xoma/Servier, CSL Behring, 2, Novartis, Takeda, SOBI, Xoma, 5; J. Anton, None; H. J. Lachmann, Novartis, SOBI, Takeda, GSK, 5, Novartis, SOBI, 8; M. Gattorno, Novartis and SOBI, 2, Novartis and SOBI, 5; S. Ozen, None; I. Koné-Paut, None; E. Ben-Chetrit, Novartis, 5; M. Wozniak, Novartis, 3; X. Wei, Novartis, 3; E. Vrizali, Novartis, 3.

Identification of Optimal Subcutaneous Doses of Tocilizumab in Children with Systemic Juvenile Idiopathic Arthritis

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Session Information

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Session Title: Pediatric Rheumatology – Clinical II: Treatment Update

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Background/Purpose: Efficacy and safety of intravenous (IV) tocilizumab (TCZ) were shown in patients (pts) with systemic JIA (sJIA) in the phase 3 TENDER study.¹ This multicenter, open-label, phase 1b study investigated dosing regimens of subcutaneous (SC) TCZ in pts with sJIA relative to data from TENDER to identify the optimal SC regimen and ensure that C_{trough} from SC regimens was equivalent to or higher than that from the IV regimen.

Methods: Pharmacokinetics (PK), pharmacodynamics (PD), and safety of TCZ SC were investigated in pts aged 1-17 years with sJIA and inadequate response to glucocorticoids; efficacy was an exploratory objective. Pts could be TCZ naive or could switch from TCZ IV to TCZ SC. Interim analysis was conducted after 24 pts had received TCZ SC for 14 weeks. TCZ SC was administered for 52 weeks according to body weight (BW): <30 kg received 162 mg every 10 days (Q10D) before interim analysis or 162 mg every 2 weeks (Q2W) after interim analysis; ≥30 kg received 162 mg every week (QW).

Results: In total, 51 pts were enrolled; 25 weighed <30 kg and 26 weighed ≥30 kg. Twenty-six pts (51%) were TCZ naive and 25 (49%) switched from TCZ IV. Interim analysis revealed higher than desired exposure in the <30 kg group, so dosing frequency was reduced from Q10D to Q2W. Median and range steady state C_{min} were similar in both BW groups (Table). More than 95% (49/51) of pts treated with TCZ SC had model-computed steady state C_{min} higher than the 5th percentile achieved with TCZ IV. Median and range AUC_{2weeks} were similar in both BW groups (Table). Changes in IL-6, CRP, and ESR were similar for both BW groups. Almost all pts had ≥1 adverse event (AE; n = 50; 98.0%). Injection site reactions (ISRs) occurred in 21 pts (41.2%); most were mild, and none led to treatment interruption or withdrawal. The AE rate was 1200.3/100 pt-years (PY) (909.3/100 PY, excluding ISRs). The most common AEs were viral upper respiratory tract infection (13; 25.5%), neutropenia (13; 25.5%), and cough (12; 23.5%). Nine serious AEs occurred in 7 pts (13.7%; 19.3/100 PY); 5 were infections, all in the <30 kg group. Two deaths occurred, both in the <30 kg group. Median Juvenile Arthritis Disease Activity Score-71 improved from baseline to week 52 for TCZ-naive pts (<30 kg, -13.9; ≥30 kg, -12.4) and was maintained or improved further for pts who switched from TCZ IV (<30 kg, -0.7; ≥30 kg -0.2). At week 52, 29/43 pts (67.4%) had inactive disease (JADAS-71 <1.0).

Table

	TCZ SC		TCZ IV	
	<30 kg TCZ 162 mg Q2W n = 25	≥30 kg TCZ 162 mg QW n = 26	<30 kg TCZ 12 mg/kg Q2W n = 46	≥30 kg TCZ 8 mg/kg Q2W n = 43
Model-computed steady state PK parameters, median (range)				
$C_{min,ss}$ µg/mL	64.2 (16.6-135.9)	72.4 (19.5-157.8)	65.9 (19.0-135.5)	70.7 (5.3-126.6)
$C_{max,ss}$ µg/mL	126.6 (51.7-265.8)	89.8 (26.4-190.2)	274.4 (148.8-444.0)	253.0 (119.6-404.3)
$AUC_{2weeks,ss}$ µg/mL×day	1298 (539-2792)	1154 (334-2370)	1734 (840-2712)	1631 (526-2779)

Conclusion: A PK-based strategy was successful in bridging TCZ SC to TCZ IV in pts with sJIA. Dosing regimens of 162 mg Q2W in pts <30 kg and 162 mg QW in pts ≥30 kg provided adequate exposure to support efficacy comparable to that of TCZ IV. Except for ISRs, safety results were consistent with the known safety profile of TCZ in sJIA. *Reference:* 1. De Benedetti F et al. *N Engl J Med.* 2012;367:2385-2395. Acknowledgment: The PRINTO and PRCSG Investigators. Medical writing: Sara Duggan, PhD, funded by F. Hoffmann-La Roche Ltd.

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Abstract Number: 2865

Canakinumab, on a Reduced Dose or a Prolonged Dose Interval without Concomitant Corticosteroids and Methotrexate, Maintains Efficacy in Systemic Juvenile Idiopathic Arthritis Patients in Clinical Remission

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Session Information

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Session Title: Pediatric Rheumatology – Clinical II: Treatment Update

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Background/Purpose: Treatment with canakinumab (CAN), a selective, human anti-IL-1 β monoclonal antibody, has shown sustained therapeutic effect along with corticosteroid dose reduction/discontinuation in patients with systemic juvenile idiopathic arthritis (SJIA), in a long-term extension study (NCT00891046).¹ Herein, we report the efficacy and safety results from a study evaluating 2 different CAN tapering regimens in SJIA patients who were in clinical remission (NCT02296424).

Methods: This Phase 3b/4 study had two parts. In Part I, 182 patients with inactive disease from the extension study¹ (cohort 1) and CAN-naïve patients (cohort 2) with active disease were administered subcutaneous CAN 4 mg/kg q4w. Per protocol titration off corticosteroids and/or methotrexate was attempted during Part I. Eligible patients (inactive disease for 24 consecutive weeks and being corticosteroid- and methotrexate-free for at least 4 weeks) advanced to Part II. Patients were randomized to either a 3-step CAN dose reduction regimen (2mg/kg/q4w, followed by tapering to 1 mg/kg/q4w and then discontinuation) or dose interval prolongation regimen (4mg/kg q8w, followed by tapering to 4 mg/kg/q12w and then discontinuation); patients advanced to the next tapering step if inactive disease was maintained for 24 weeks. The primary objective was to evaluate if at least 40% of patients were able to maintain inactive disease status for at least 24 consecutive weeks on either 2mg/kg q4w or 4mg/kg q8w.

Results: In Part II, a total of 75 patients were randomized to a dose reduction (n=38) or dose interval prolongation (n=37) CAN tapering regimen. The proportion of patients who maintained inactive disease for 24 consecutive weeks exceeded the predefined threshold of 40% for Step 1 of: the reduced CAN dose (71%; 2 mg/kg q4w) and prolonged dose interval (84%; 4 mg/kg q8w) treatment arms. A total of 68% (26/38) and 79% (30/37) of the dose reduction and interval prolongation arms, respectively were successful in Step 2, while only 33% (25/75) of patients successfully discontinued CAN and maintained inactive disease for 24 consecutive weeks. Adverse events (AEs) and serious AEs observed within the 2 treatment cohorts and across Parts I and II were similar without any specific pattern or relationship to patients' disease status at baseline or treatment regimen. The most frequent AEs were common infections such as nasopharyngitis, upper respiratory tract infection, and pharyngitis followed by SJIA-related events such as rash, pyrexia and arthralgia. Clinical laboratory abnormalities were consistent with expected findings in patients with active SJIA and the known safety profile of CAN.

Conclusion: SJIA patients who are able to maintain inactive disease status on CAN monotherapy can successfully taper CAN by either reducing the dose or prolonging the dosing interval. However, only a minority of patients successfully

discontinued CAN treatment for 24 weeks. The safety profile for both CAN titration regimens was similar and consistent with other CAN SJIA studies; no new signals were identified.

Reference: 1. Brunner et al. *Arthritis Rheumatol.*2016; 68 (S10).

Disclosure: P. Quartier, Novartis and SOBI, 5, AbbVie, Lilly, Novartis and SOBI, 8, AbbVie, BMS, Novartis, Pfizer, Sanofi, 9, AbbVie, Novartis, Pfizer, SOBI, 9; E. Alexeeva, Roche, Abbott, Pfizer, Bristol-Myers Squibb, Centocor, Novartis, 2; C. Wouters, GSK, Roche, Pfizer, 9; I. Calvo, None; T. Kallinich, Novartis, 8; B. Magnusson, None; N. Wulffraat, Novartis, 5; X. Wei, Novartis, 3; A. Slade, Novartis Pharmaceuticals Corporation, 1, Novartis Pharmaceuticals Corporation, 3; K. Abrams, Novartis Pharmaceuticals Corporation, 3, Novartis Pharmaceuticals Corporation, 1; A. Martini, None.

Abstract Number: 2866

Biologic Refractory Disease in a Cohort Study of Children and Young People with Juvenile Idiopathic Arthritis from the United Kingdom

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Session Information

Session Date: Tuesday, October 23, 2018

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Session Time: 4:30 PM-6:00 PM

Background/Purpose: Biologics are a main treatment option for children and young people with juvenile idiopathic arthritis (JIA) who do not respond or are intolerant to methotrexate. Unfortunately, for some children on biologics, disease control will remain elusive and they will continue to have active disease despite usage of multiple biologics; biologic refractory disease. The aim of this analysis was to quantify biologic refractory JIA and identify clinical characteristics, measured at start of first biologic, associated with biologic refractory disease.

Methods: Patients with JIA starting a first biologic, from 1st January 2010 to 31st January 2016, in two UK cohort studies were included; the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN) and the Biologics for Children with Rheumatic Diseases (BCRD) study. Data were collected at baseline, six months, one year, then annually on patient characteristics and anti-rheumatic therapy. The total number of unique biologics a patient had received was calculated. Patients were classified as refractory on the date they commenced their third biologic. Follow-up was censored at last study follow-up, 31st January 2018, or death, whichever came first. Switching patterns for biologics were described in the biologic refractory patients. Cox-regression analysis identified baseline clinical factors associated with biologic refractory disease. Multiple imputation of missing baseline data was used.

Results: There were 620 patients starting a first biologic, the majority starting tumour necrosis factor inhibitor (TNFi; 88%); 67% female, median age 11 years, median disease duration 2 years, across all ILAR categories, with a majority of patients having either polyarticular rheumatoid factor (RF) negative (32%), or extended oligoarticular JIA (20%). Overall, 39 (6.3%) patients became biologic refractory over a median of 2.9 years of follow-up; median time to third biologic was 2.5 years. The most common treatment pathways for these patients were three TNFi (26%), or two TNFi followed by either tocilizumab (28%) rituximab (12%) or abatacept (8%). The reasons given for discontinuing first and second biologic among biologic refractory patients included: 33% repeated ineffectiveness, 3% repeated adverse events, 15% ineffectiveness followed by an adverse event, 10% an adverse event followed by ineffectiveness, whilst 28% a mixture of other reasons. In the univariable analysis, patients with worse pain at the start of their first biologic were at increased risk of biologic refractory disease.

Conclusion: In this real-world cohort of children and young people with JIA, approximately 6% had received at least three different biologic therapies, here defined as biologic refractory JIA. Higher pain scores at the start of first biologic predicted refractory disease. Further understanding of why some patients are refractory to biologic therapies is vital to enable patient specific treatment pathways, accurate prognosis discussions and cost effectiveness analysis for service provisions.

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Abstract Number: 2867

Efficacy and Safety of Intravenous Belimumab in Children with Systemic Lupus Erythematosus

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Session Information

Session Date: Tuesday, October 23, 2018

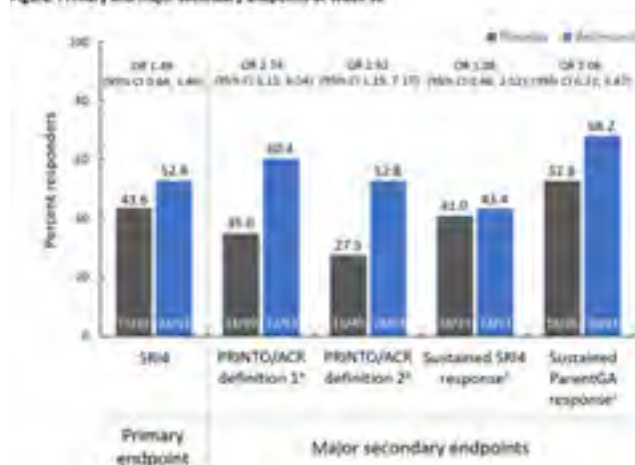
Session Title: Pediatric Rheumatology – Clinical II: Treatment Update

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Belimumab (BEL) is approved in adults with active systemic lupus erythematosus (SLE). There are no approved biologic therapies for pediatric patients with childhood-onset SLE (cSLE). This Phase 2, multicenter, randomized, double-blind trial (NCT01649765) evaluated the efficacy, safety, and pharmacokinetics (PK) of intravenous (IV) BEL vs placebo (PBO), plus standard therapy (SoC), in cSLE. <

Figure. Primary and major secondary endpoints at Week 52



*At least 50% improvement in 2 of 5 core response variables, with no more than 1 of the remaining worsening by more than 30%; †At least 30% improvement in 3 of 5 core response variables, with no more than 1 of the remaining worsening by more than 30%; *Weeks 44-52

CI, confidence interval; OR, odds ratio

Table. Change from baseline cSLE core response variables at Week 52

	Placebo (N=40)	Belimumab (N=53)
Median [range] % change ParentGA	-21.61 (-95, 800)	-53.85 (-100, 900)
n	38	47
Mean \pm SE % change PGA	-48.80 \pm 8.648	-56.53 \pm 6.089
n	40	53
Mean \pm SE % change SELENA-SLEDAI	-38.0 \pm 6.33	-43.3 \pm 6.05
n	39	53
Median [range] % change Pediatric (physical functioning)	12.5 (-53, 575)	10.3 (-100, 280)
n	40	53
Median [range] % change 24-hour proteinuria	7.092 (-91.548, 570.149)	-2.128 (-85.073, 1681.884)
n	40	53

Pediatric quality of life; PGA, physician global; SE, standard error; SELENA-SLEDAI, Safety of Estrogens in Lupus National Assessment of Disease Activity Index

Methods: Patients with cSLE aged 5–17 years were randomized to BEL 10mg/kg IV or PBO every 4 weeks, plus SoC. The primary endpoint was SLE Responder Index 4 (SRI4) at Week (Wk) 52. Major secondary endpoints were: proportion of patients achieving the Pediatric Rheumatology International Trials Organization/ACR (PRINTO/ACR) cSLE Evaluation criteria for improvement using two definitions at Wk 52; cSLE core response variables at Wk 52 (Table); and sustained SRI4 and Parent Global Assessment (ParentGA) responses (Wks 44–52). Other secondary endpoints included time to first severe flare (modified SELENA-SLEDAI Flare Index). Safety and PK were assessed. The study was not powered for statistical testing.

Results: 93 patients comprised the intent-to-treat population (BEL, 53; PBO, 40). Mean (SD) baseline SELENA-SLEDAI was 10.4 (3.63) for PBO and 10.3 (3.34) for BEL; 17 (42.5%) PBO and 22 (41.5%) BEL patients were anti-dsDNA positive and had low complement. At Wk 52 there were numerically more SRI4 and PRINTO/ACR responders in BEL vs PBO (Figure). Numerically more BEL patients had sustained SRI4 and ParentGA responses at Wks 44–52 vs PBO (Figure). Changes in cSLE core response variables are shown in the Table. Severe flares were 62% less frequent with BEL vs PBO (hazard ratio 0.38 [95% CI 0.18, 0.82]); median (IQR) time to first severe flare was 159.5 (47.5, 314.5) vs 82.0 (57.0, 228.0) days for BEL vs PBO. Overall incidence of adverse events (AEs) was similar between groups. 9/53 (17%) BEL patients experienced ≥ 1 SAE vs 14/40 (35%) PBO patients. 1/53 [1.9%] BEL patients experienced depression/suicide/self-injury vs 4/40 [10%] PBO patients. One PBO patient died of acute pancreatitis. At Wk 52 the geometric mean (95% CI) BEL trough concentration was 44.96 (27.52, 73.43) $\mu\text{g/mL}$ for patients aged 5–11 years, and 59.71 (46.41, 76.81) $\mu\text{g/mL}$ for patients aged 12–17 years.

Conclusion: The benefit/risk profile and PK of BEL IV plus SoC in cSLE are generally consistent with those in adult BEL study populations. The 10 mg/kg IV dose used in adults may be an appropriate dose in cSLE.

Disclosure: H. I. Brunner, GlaxoSmithKline (GSK), F. Hoffman-La Roche, Novartis, Pfizer, Sanofi Aventis, Merck Serono, 5, AbbVie, Amgen, Biogenidec, Alter, AstraZeneca, Baxalta Biosimilars, Biogenidec, Boehringer, BMS, Celgene, Crescendo Bio, EMD Serono, F. Hoffman-La Roche, Janssen, MedImmune, Novartis, Pfizer, Sanofi Aventis, Takeda, and UCB Biosciences GmbH, 5; C. Abud-Mendoza, None; D. I. Viola, None; I. Calvo, None; D. M. Levy, None; J. Calderon Gallegos, None; M. Ferrandiz, None; V. Chasnyk, None; V. Keltsev, None; J. Anton, None; M. Paz, None; M. Shishov, None; A. L. Boteanu, None; M. Henrickson, None; D. Bass, GSK, 1, 3; K. Clark, GSK, 1, 3; A. Hammer, GSK, 1, 3; B. Ji, GSK, 1, 3; D. Roth, GSK, 1, 3; H. Struemper, GSK, 1, 3; M. L. Wang, GSK, 1, 3; A. Martini, Abbvie, Biogen, Boehringer, Bristol Myers and Squibb, EMD Serono, Janssen, Novartis, Pfizer, R-Pharm on behalf of the Gaslini Institute, 5; D. J. Lovell, AstraZeneca, Amgen, Abbott, Pfizer, 5, Wyeth Pharma, 8; N. Ruperto, Abbott, AbbVie, Amgen, Biogenidec, Astellas, Alter, AstraZeneca, Baxalta Biosimilars, Boehringer, BMS, CD-Pharma, Celgene, Crescendo Bio, EMD Serono, Hoffman-La Roche, Italfarmaco, Janssen, MedImmune, Medac, Novartis, Novo Nordisk, Pfizer, Rewind Arms, 5, 6, 7, 8, R-Pharma, Sanofi Aventis, Servier, Sinergie, Takeda, Vertex, UCB Biosciences GmbH, 5, 6, 7, 8, BMS, “Francesco Angelini”, GlaxoSmithKline (GSK), Hoffman-La Roche, Italfarmaco, Janssen, Novartis, Pfizer, Sanofi Aventis, Schwarz Biosciences, Sobi, Xoma, Wyeth, 2.

Tender Joint Count May Not Reflect Inflammatory Activity in Established Rheumatoid Arthritis Patients; Results from a Longitudinal Study of Tocilizumab

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes V: Outcomes Measures

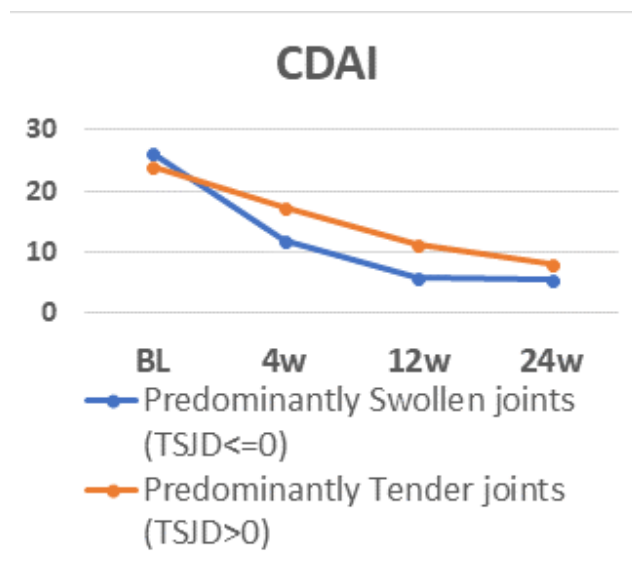
Session Type: ACR Concurrent Abstract Session

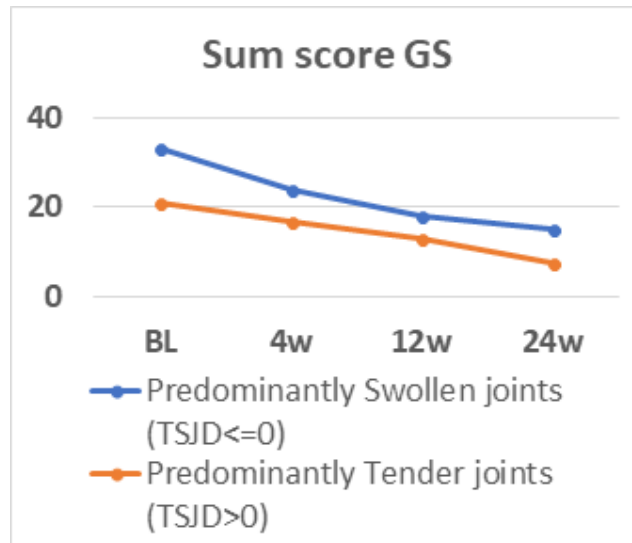
Session Time: 4:30 PM-6:00 PM

Background/Purpose: Tender joints may be caused by non-inflammatory pathologies but are still included in composite scores like CDAI. The present objective was to explore the impact of tender joints by use of Tender-Swollen Joint Difference(TSJD) assessing patients with predominantly tender (TSJD>0) in comparison to predominantly swollen (TSJD≤0) joints.

Methods: Rheumatoid arthritis (RA) patients assessed by US in a Nordic study of tocilizumab sc to csDMARDs non-responders (1) were included. Clinical(28 tender/swollen joint count (TJC/SJC)), patient reported outcomes, laboratory tests and US examination (36 joints and 4 tendons, scored according to the Norwegian US atlas (2)) were performed at baseline (BL), 4, 12 and 24 weeks. CDAI and EULAR/ACR Boolean remission and sum score grey scale (GS) and power Doppler(PD) were calculated, with PD sum score=0 as US remission. Associations were explored by Spearman's rank correlation and differences between TSJD>0 vs ≤0 by Mann-Whitney test.

Results: 110 patients (83% female, mean (SD) age 55.6 (12.1) years and RA duration 8.7 (9.5) years, 81% anti-CCP positive) were assessed. All variables decreased significantly ($p<0.001$) (table). Number of patients with TSJD>0 decreased during follow-up (64% to 39%). During the study, TJC had low correlation coefficients (range) with SJC (0.24-0.47), examiner's assessment (0.19-0.48) and sum score GS (0.13-0.25)/PD (0.00-0.22). There were no differences in CDAI for patients with TSJD>0 vs ≤0 at BL, but at 4,12 and 24 weeks patients with TSJD>0 had higher CDAI levels ($p\leq 0.002$), but lower GS sum scores at BL, 4 and 26 weeks($p=0.026-0.002$) and lower PD scores at BL and 24 weeks ($p\leq 0.009$). The figure illustrates mean levels of CDAI and GS levels during follow-up dependent on TSJD group. CDAI/Boolean remission in patients with TSJD>0 vs ≤0 was 0%/0% vs 45.2%/33.3% at 12 weeks and 8.1%/5.4% vs 50.8%/40.7% at 24 weeks, while PD remission at 12 and 24 weeks was found in 41.8-70.7% independent of TSJD.





Conclusion: In patients with established RA, TJC had low association with objective signs of inflammation, and patients with predominantly tender joints seldom reached composite score remission despite PD remission. These findings question the dominant role of tender joints in assessment of inflammatory activity.

References: 1. EULAR 2017 Abstract SAT0199. 2. Hammer HB et al, ARD, 2011

	Baseline Median (IQR) n=110	4 weeks Median (IQR) n=102	12 weeks Median (IQR) n=95	24 weeks Median (IQR) n=91
Sum score GS	21 (13-36)	16 (8-30)	12 (5-21)	9 (3-19)
Sum score PD	8 (2-20)	4 (1-10)	1 (0-4)	0 (0-2)
Tender joint count	8 (5-12)	4 (1-9)	2 (0-5)	1 (0-3)
Swollen joint count	6 (2-10)	2 (0.5-6)	1 (0-2.5)	0 (0-2)
Patient's global VAS (0-100)	55 (36-70)	32 (18-49)	16 (7-31)	12 (4-28)
Assessor's global VAS (0-100)	35 (25-49)	17 (11-31)	10 (5-18)	5 (2-11)
CRP (mg/L)	5.5 (2.6-13.1)	0.2 (0.2-0.4)	0.2 (0.2-0.6)	0.2 (0.2-0.4)
ESR (mm/h)	21 (12-34)	4 (2-7)	3 (2-5)	3 (2-5)
CDAI	23.8 (17.1-31.2)	12.9 (7.3-21.9)	7.2 (3.6-11.4)	4.3 (1.8-9.8)

Disclosure: H. B. Hammer, AbbVie Inc., Novartis, 8; I. M. J. Hansen, None; P. Järvinen, None; M. Leirisalo-Repo, None; M. Ziegelsch, AbbVie Inc., 8; B. Agular, Roche, 3; L. Terslev, Novartis, AbbVie, Pfizer, UCB, Roche and MSD, 8.

Abstract Number: 2869

Incorporation of Patient Reported Outcomes Data in the Care of US Veterans with Rheumatoid Arthritis: A Randomized, Controlled Trial

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Session Information

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes V: Outcomes Measures

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Quantitative disease activity measures are required to implement a treat-to-target algorithm for the treatment of rheumatoid arthritis (RA). Available measures based on patient-derived data have the advantage of ease of use and have been shown to correlate with physician-derived data. While data support the conclusion that the concept of treat-to-target is beneficial to patient outcomes, there is a paucity of data that show that the utilization of any specific disease activity measure improves outcomes. The purpose of this study was to test the hypothesis of whether the addition of the RAPID3 (Routine Assessment Of Patient Index Data 3) patient-reported outcome (PRO) data improves outcomes in RA. Disease activity as measured by DAS28 as well as patient-centric outcomes, including patient reported well-being, patient satisfaction and medication compliance, were measured.

Methods: The intervention design was a single blind, randomized controlled trial of US Veterans with RA. The intervention was to provide PRO data to rheumatologists treating patients in an outpatient setting. PRO data were not provided to physicians for control subjects. All participating physicians attended a lecture series providing education about treat-to-target strategies in RA. Baseline inclusion criteria were patients older than 18 who have had rheumatoid arthritis according to the 1987 ACR revised criteria for RA, and had been seen at least one time previously with diagnosis of RA. Subjects had at least moderate disease activity (DAS28-CRP > 3.2). Trial duration was 12 months. The primary outcome was a change in DAS28. Secondary outcomes included patient satisfaction, percent with minimal clinically important improvement (MCII) in patient global, medication compliance, DAS28, and frequency of achievement of remission criteria (DAS28-CRP < 2.3).

Results: The study enrolled 141 subjects with PRO data provided to the treating physician for 71 subjects. Average subject age was 57, 88% were male, and average DAS28 score at entry was 4.01. The average duration of disease was 4.8 years. There were no significant differences in these measures between intervention and control subjects. Data for the primary outcome was available for 108 patients. The DAS28 score decreased to 3.63 ± 0.41 in the intervention group and 3.60 ± 0.43 in the control group. DAS28 remission criteria were met in 4 or 5.6% of intervention subjects and 6 or 8.6% of control subjects. There was a trend to improvement in the MCII for patient global scores in the intervention group.

Conclusion: In this population of US Veterans with relatively advanced RA, the provision of RAPID3 data to rheumatologists who were well-versed in the treat-to-target approach to RA did not significantly improve outcomes.

Disclosure: M. R. Bubb, None; R. Judd, None; A. D. Chauffe, None.

Abstract Number: 2870

Thresholds for Disease Activity Measures DAS28, CDAI, and RAPID3 Do Not Align with Clinical Practice Patterns of Rheumatoid Arthritis (RA) Disease Management Decisions

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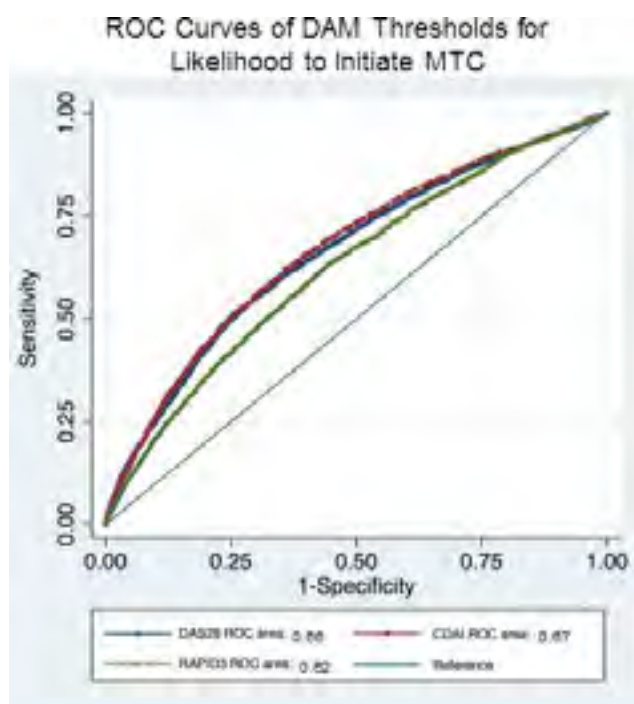
Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes V: Outcomes Measures

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM



Background/Purpose: Treatment guidelines recommend using disease activity measures (DAMs) to guide RA therapy, but DAM use in real-world treatment decisions is not defined. We compared frequency of major therapeutic change (MTC) across disease activity categories for 3 DAMs (Disease Activity Score with 28 joints [DAS28], Clinical Disease Activity Index [CDAI], Routine Assessment of Patient Index Data 3 [RAPID3]); explored ability of DAMs to discriminate between patients with/without MTC; and identified DAM thresholds to optimize discriminant ability.

Methods: US Veterans enrolled in Veterans Administration RA registry (VARA) had: visit with complete set of DAMs (index date); 2 additional visits ≥ 60 days apart during 18-month pre-index period; clinical data available 18 months before through 30 days after index date were eligible. MTC was assessed 1 week before through 30 days after index, defined as: initiation of synthetic or biologic disease-modifying antirheumatic drug (sDMARD, bDMARD); DMARD dose escalation $\geq 25\%$; prednisone use (new agent or after 90-day gap); prednisone dose increased 25%; and/or corticosteroid injection in ≥ 2 joints. Sensitivity and specificity for disease category to predict MTC was calculated for each DAM. Youden's Index (sensitivity + specificity – 1) was used to determine thresholds at which providers were likely to initiate MTC. Receiver operating characteristic (ROC) curves were used to assess discrimination thresholds.

Results: For 1,776 patients (12,094 visits), 89% were male, mean RA disease duration was 13.4 years (95% confidence interval[CI]: 12.8, 13.9), and mean age of 63.4 years (95% CI 62.9, 63.9). Positive associations between disease activity level and MTC proportion were observed (Table 1). Most MTCs occurred with sDMARDs (Table 2). Empiric thresholds (highest Youden Indices)(95% CI) were DAS28: 4.02 (3.70, 4.36); CDAI: 12.9 (10.6, 15.1); RAPID3: 3.81(3.32, 4.30) (Figure).

Conclusion: Decision points for MTC per Youden Index thresholds were higher than moderate disease activity definitions, suggesting disease activity stratification is not aligned with physician practice. MTC based on DAS28 and CDAI were driven by changes in sDMARDs. Physician-driven DAMs (DAS28, CDAI) had better discriminant abilities than patient-driven RAPID3.

Table 1 Frequency of MTC Stratified by DAM Category

	Visits with MTC, n/N (%)		
	DAS28	CDAI	RAPID3
High disease activity	890/1,986 (44.8%)	1,115/2,504 (44.5%)	1,849/5,596 (33.1%)
Moderate disease activity	1,342/4,853 (27.7%)	1,094/3,998 (27.4%)	792/3,802 (20.8%)
Low disease activity	381/2,059 (18.5%)	664/4,141 (16.0%)	258/1,513 (17.1%)
Remission	464/3,196 (14.5%)	204/1,451 (14.1%)	178/1,184 (15.0%)

n, number of visits with MTC; N, number of visits with DAM recorded

Table 2 Type of MTC Stratified by DAM Category

DAM and disease activity level		Visits with MTC, n (%)			
		N	Initiated, changed, or escalated dose of sDMARD	Initiated, changed, or escalated dose of bDMARD	Initiated, changed, or escalated dose of prednisone joint injections
DAS28					
High	1,986	498 (25.1%)	276 (13.9%)	173 (8.7%)	21 (1.1%)
Moderate	4,853	758 (15.6%)	309 (6.4%)	219 (4.5%)	33 (0.7%)
Low	2,059	221 (10.7%)	58 (2.8%)	66 (3.2%)	5 (0.3%)
Remission	3,196	212 (6.6%)	90 (2.8%)	114 (3.6%)	5 (0.2%)
CDAI					
High	2,504	632 (25.2%)	346 (13.8%)	197 (7.9%)	27 (1.1%)
Moderate	3,998	616 (15.4%)	226 (5.7%)	202 (5.1%)	25 (0.6%)
Low	4,141	352 (8.5%)	113 (2.7%)	123 (3.0%)	12 (0.3%)
Remission	1,451	89 (6.1%)	48 (3.3%)	50 (3.5%)	0
RAPID3					
High	5,595	981 (17.6%)	491 (8.8%)	351 (6.3%)	51 (0.9%)
Moderate	3,802	472 (12.4%)	150 (4.0%)	141 (3.7%)	10 (0.3%)
Low	1,513	146 (9.6%)	56 (3.7%)	40 (2.6%)	2 (0.1%)
Remission	1,184	90 (7.6%)	36 (3.0%)	40 (3.4%)	1 (0.1%)

n, number of visits with MTC; N, number of visits with disease activity recorded

Disclosure: B. C. Sauer, Amgen Inc., 2; C. C. Teng, MS, Amgen Inc., 2; N. A. Accortt, Amgen Inc., 1, Amgen Inc., 3; D. H. Collier, Amgen Inc., 1, Amgen Inc., 3; T. C. Lin, Amgen Inc., 1, Amgen Inc., 3; G. W. Cannon, Amgen Inc., 2.

Comprehensive Provider Judgement Is a Significant Determinant of Major Therapeutic Change in Patients with Moderate to Severe Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes V: Outcomes Measures

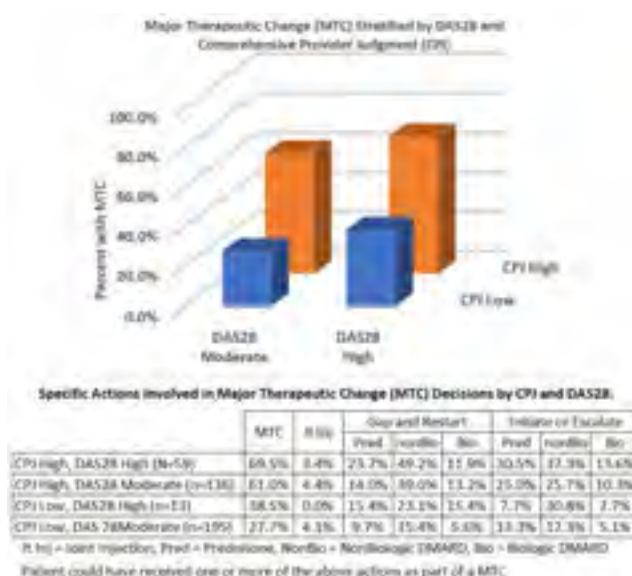
Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: We have previously reported an evaluation of 941 US Veterans in the Veterans Affairs (VA) Rheumatoid Arthritis (RA) (VARA) registry that 559 (59%) did not have a major therapeutic change (MTC) in RA therapy despite elevated DAS28>3.2. Medical chart notes found that a comprehensive provider judgment (CPJ) of acceptable/low disease activity was a leading factor in the decision to not change therapy despite elevated disease activity by DAS28. This study investigates the utility of CPJ and DAS28 to predict MTC in patients with moderate (DAS28=3.2 to 5.1) and severe (DAS28>5.1)RA and compares types of MTC to determine whether specific changes varied according to the DAS28 and/or CPJ.

Methods: US Veterans in the VARA registry with 1) moderate/severe disease activity (DAS28≥3.2) on index day 2) 18 months of VA data prior to the index date and 3) 90 day observation after index date were eligible for review. A MTC was defined as 1) re-initiation of prior DMARD and/or prednisone (Pred) after ≥90 day gap in therapy, 2) initiation of new DMARD and/or Pred, 3) escalation of current DMARDs and/or Pred and/or 4) 2 joint injections within either 7 days before to 90 days after the index date. There were 403 patients from 9 VARA registry sites meeting the above criteria randomly selected for chart review. A CPJ was made by the chart reviewer (JS) blinded to DAS28 who categorized CPJ as mild or moderate/severe on the basis of text notes by the provider using these terms or similar comments on disease state. The MTC decisions were then stratified by the corresponding CPJ and DAS28 levels to investigate their association with MTC. Specific MTC actions were classified as joint injection, gaps in therapy with re-initiation of same DMARD for Pred, or initiation new DMARD or Pred/escalation of current DMARD or Pred.

Results: The 403 patients evaluated were age 65±10 years, RA disease duration 14±11 years, 85% male, 81% seropositive for rheumatoid factor, and 64% positive for a CCP. The proportion of patients with high CPJ with MTC was 124/195 (63.5%) and similar to MTC in patients with high DAS28 46/72 (64.8%) The interaction of CPJ and DAS28 on MTC suggests CPJ may have a higher association with MTC than DAS 28 (Figure). When evaluating the specific types of MTC that occurred in the groups stratified by both CPJ and DAS28 there were no evident differences in the types of changes that were instituted (Table).



Conclusion: Less than half of patients (45.5%) studied received a MTC despite having moderate to severe RA by DAS28. High disease activity by either CPJ or DAS28 were associated with MTC. In patients with moderate DAS28, a high CPJ was associated with a greater tendency to have a MTC. The specific actions involved in the MTC did not vary significantly with CPJ or DAS28 levels. Both CPJ and the DAS28 appear to be important in the decision to make a MTC in RA patients with moderate/severe disease activity by DAS28.

Disclosure: J. R. Stever, None; B. C. Sauer, Amgen Inc., 2; G. W. Cannon, Amgen Inc., 2.

Abstract Number: 2872

Variation in Predictors of Patient and Physician Defined Flares in Rheumatoid Arthritis

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Session Information

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Session Type: ACR Concurrent Abstract Session

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Background/Purpose: The identification of risk factors associated with flares in RA is challenging because of the use of different composite disease activity scores and a lack of consistency in the definition of a flare. The Clinical Disease Activity Index (CDAI) is a composite disease activity score that incorporates both a patient and evaluator global assessment (PGA and EGA, respectively). We hypothesized that predictors of flares would vary based on the contribution of clinically important worsening of PGA or EGA to the CDAI and identified predictors of RA flare.

Methods: We utilized data from the Veterans Affairs RA (VARA) registry- a longitudinal multicenter cohort of US veterans who fulfill the 1987 American College of Rheumatology (ACR) criteria for the classification of RA. Only patients with low disease activity (LDA) defined by CDAI score (≤ 10) were included in analyses. A CDAI flare was defined as an increase in CDAI to ≥ 10 and change in CDAI of ≥ 2 . PGA and EGA LDA flares were defined as an increase to >10 and a change ≥ 10 mm in the PGA or EGA. We used multivariable logistic regression incorporating generalized estimating equations to evaluate for independent predictors of flare by the next visit. Covariates tested included age, sex, race, disease duration, smoking status, common comorbidities, sustained low activity, serostatus, current medications, recent medication changes, inflammatory markers, function status (MD-HAQ), and length of interval between visits.

Results: Data from 1,582 observations with LDA were included [mean age 63 (± 11), 90% male, 82% Caucasian, 81% rheumatoid factor (RF) positive]. Predictors of subsequent CDAI flare, EGA flare and PGA flare are outlined in Table 1. Factors associated with subsequent CDAI flare (N=437) included higher tender joint count, swollen joint, and MD-HAQ score. CDAI flare was less likely among those with sustained CDAI LDA at the prior visit. EGA flare (N=505) was associated with the presence of RF, black ethnicity, elevated CRP, and greater TJC. EGA flare was less likely among patients using methotrexate, a sustained LDA by CDAI and higher patient global score. The strongest predictors of PGA flare (N=542) were a greater MD-HAQ score, black ethnicity, and RF positivity.

Conclusion: Sustained LDA is a strongly associated with a reduced risk of subsequent CDAI flare and EGA flare but not PGA flare. Predictors of increase in both PGA and EGA included black ethnicity and RF positivity. However, while the TJC and CRP predicted EGA flare, the MD-HAQ was the strongest predictor of PGA flare. Understanding the factors that influence evaluator and patient perception of disease flare is important, as this may have implications for treatment decisions.

Table 1: Factors associated with subsequent CDAI, EGA or PGA flare from low disease activity.*p<0.05, **p<0.01, ***p<0.001, ns – non-significant

	CDAI flare (N=437)		Evaluator Global Flare (N=505)		Patient Global Flare (N=542)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.00 (0.98-1.01)	NS	1.01 (0.99-1.02)	NS	0.99 (0.98-1.00)	NS
Female sex	0.79 (0.48-1.30)	NS	0.90 (0.56-1.44)	NS	0.60 (0.35-1.03)	NS
Black ethnicity	1.02 (0.73-1.42)	NS	1.45 (1.07-1.96)	*	1.79 (1.25-2.55)	**
Current smoker	1.08 (0.80-1.46)	NS	1.20 (0.91-1.58)	NS	1.07 (0.78-1.49)	NS
RF positive	1.42 (0.97-2.07)	NS	1.62 (1.11-2.35)	*	1.52 (1.05-2.20)	*
CCP positive	0.81 (0.58-1.12)	NS	0.90 (0.65-1.26)	NS	0.57 (0.39-0.82)	**
Nodules	1.40 (0.99-1.96)	NS	1.09 (0.79-1.51)	NS	0.94 (0.66-1.33)	NS
Disease duration	1.01 (1.00-1.02)	NS	1.00 (0.99-1.01)	NS	1.01 (1.00-1.02)	*
Sustained CDAI LDA	0.55 (0.44-0.69)	***	0.64 (0.51-0.81)	***	0.87 (0.69-1.08)	NS
Tender joint count (0-28)	1.23 (1.11-1.35)	***	1.12 (1.02-1.23)	*	1.09 (1.00-1.19)	NS
Swollen joint count (0-28)	1.14 (1.04-1.25)	**	1.04 (0.96-1.13)	NS	0.97 (0.89-1.06)	NS
MD-HAQ	1.68 (1.21-2.34)	**	1.55 (1.13-2.12)	**	2.20 (1.59-3.03)	***
Patient global (0-100mm)	1.01 (1.00-1.02)	**	1.00 (1.00-1.01)	NS	0.96 (0.95-0.97)	***
Physician global score (0-100mm)	1.02 (1.00-1.03)	**	0.96 (0.95-0.97)	***	1.03 (1.00-1.04)	***
CRP	1.10 (0.96-1.25)	NS	1.16 (1.02-1.32)	*	1.10 (0.96-1.25)	NS
Medications (at flare)						
Methotrexate	0.85 (0.66-1.09)	NS	0.75 (0.59-0.95)	*	0.97 (0.76-1.23)	NS
Prednisone	1.27 (0.94-1.71)	NS	1.19 (0.88-1.62)	NS	1.12 (0.84-1.49)	NS
TNFi	0.88 (0.66-1.16)	NS	0.89 (0.67-1.17)	NS	1.02 (0.76-1.38)	NS
Comorbidities						
Depression	1.03 (0.71-1.50)	NS	0.98 (0.72-1.33)	NS	1.47 (1.00-2.16)	NS
Anxiety	1.23 (0.74-2.03)	NS	1.38 (0.86-2.21)	NS	0.80 (0.48-1.34)	NS
Diabetes	1.21 (0.89-1.64)	NS	0.98 (0.72-1.33)	NS	1.18 (0.85-1.62)	NS
COPD	1.12 (0.85-1.47)	NS	1.12 (0.86-1.33)	NS	1.40 (1.07-1.85)	*
Non-obese (BMI 18.0-24.9)	1.37 (0.65-2.89)	NS	1.38 (0.72-2.64)	NS	1.26 (0.58-2.76)	NS
Obesity(BMI 30.0-34.9)	0.76 (0.56-1.02)	NS	1.03 (0.76-1.40)	NS	0.80 (0.59-1.09)	NS
Obesity(BMI 30.0-34.9)	0.76 (0.54-1.06)	NS	1.10 (0.79-1.53)	NS	0.98 (0.69-1.39)	NS

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Abstract Number: 2873

Remaining Pain and Widespread, Non-Inflammatory Pain Distribution during the First 12 Months after RA Diagnosis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes V: Outcomes Measures

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: The incidence of fibromyalgia is highest in the first 12 months after RA diagnosis, ¹indicating that this period may represent a critical window during which acute inflammatory pain transitions to chronic non-inflammatory pain. With this study we aimed to describe the evolution of pain characteristics during the first 12 months after RA diagnosis and to identify predictors of remaining pain and widespread pain distribution (“fibromyalgic RA”) at 12 months.

Methods: Data were obtained from early RA patients in the Canadian Early Arthritis Cohort (CATCH), a prospective inception cohort. The primary outcomes were: 1) remaining pain above the Patient Acceptable Symptom State (PASS), defined as a score >4 on a pain intensity numerical rating scale (NRS, range 0-10), and 2) widespread pain distribution (or “fibromyalgic RA”), defined by tender joint count (TJC28) – swollen joint count (SJC28) ≥ 7.^{2,3} Descriptive statistics were

used to summarize distributions of remaining pain and widespread pain over 12 months. Univariate and multivariable logistic regression models were used to identify predictors of remaining pain and widespread pain distribution at 12 months.

Results: 1,270 patients were included, with mean (SD) age of 53.9 (14.5), symptom duration of 5.8 (3.0) months and baseline DAS28 of 5.0 (1.4). The percentage of patients with remaining pain decreased from 64% at baseline to 24% at 12 months, and the percentage of patients with a wide spread pain distribution decreased from 9% to 5%. The strongest predictors of 12-month remaining pain were sleep problems (highest quartile OR 2.2, 95% CI 1.2-3.9), pain intensity > 4/10 (OR 2.1, 95% CI 1.3-3.4), and higher HAQ-Disability Index (DI) score (OR 1.5, 95% CI 1.1-2.0). The strongest predictors of 12-month adjusted pain distribution were higher HAQ-DI score (OR 1.8, 95% CI 1.1-3.1) and higher number of comorbidities (OR 1.2, 95% CI 1.0-1.5). Baseline non-MTX, conventional synthetic DMARD (csDMARD) was associated with lower likelihood of widespread pain (OR 0.5, 95% CI 0.3-0.8).

Conclusion: Despite improvements in pain during the first year after RA diagnosis, 24% continued to report remaining pain above the PASS, and 5% reported widespread pain at 12 months. Baseline measures of sleep, pain intensity and disability were the strongest predictors of 12-month remaining pain. Disability and comorbidities were the strongest predictors of widespread pain distribution. Inflammatory markers were not associated with 12-month remaining pain or pain distribution.

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Table. Multivariable logistic regression models for the association between baseline characteristics and a) remaining pain (pain NRS > 4), and b) widespread pain distribution (TJC28-SJC28 > 7).

Baseline characteristics	Remaining Pain ¹ OR, 95% CI	Widespread pain ² OR, 95% CI
Age (for change of 10 yrs)	0.8 (0.7, 1.0)	0.7 (0.6, 0.9)
Baseline pain intensity > 4/10	2.1 (1.3, 3.4)	2.1 (0.8, 5.4)
Sleep problems, quartiles		
≤0 and ≤2	REF	REF
>2 and ≤5	1.8 (1.1, 3.1)	0.7 (0.3, 1.9)
>5 and ≤8	1.8 (1.1, 3.0)	0.9 (0.4, 2.2)
>8 and ≤10	2.2 (1.2, 3.9)	1.0 (0.3, 2.7)
Missing	0.6 (0.1, 5.6)	2.2 (0.2, 24.3)
HAQ-DI	1.5 (1.1, 2.0)	1.8 (1.1, 3.1)
Number of comorbidities	1.1 (1.0, 1.3)	1.2 (1.0, 1.5)
Non-MTX csDMARD use	0.8 (0.6, 1.1)	0.5 (0.3, 0.8)

¹ Adjusted for sex, education, income, SJC28, ESR, depression, back pain, osteoarthritis, MTX use, NSAID use

² Adjusted for sex, SJC28, ESR, depression, back pain, osteoarthritis, MTX use, NSAID use, baseline pain distribution

Disclosure: Y. C. Lee, Multiple, 2; O. Schieir, Other, 2; M. F. Valois, Other, 2; S. J. Bartlett, Multiple, 2, 5; G. Boire, Multiple, 2, 6; B. Haraoui, Multiple, 2, 6; C. A. Hitchon, Multiple, 2; E. C. Keystone, Multiple, 2; D. Tin, Multiple, 2; C. Thorne, Multiple, 2; J. E. Pope, Multiple, 2; V. P. Bykerk, Multiple, 2.

Abstract Number: 2874

Comparison of Missing Data Reporting and Handling in Randomized Controlled Trials of Rheumatoid Arthritis Drug Therapy: A Snapshot Ten Years Apart

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments V: Beyond Individual Compounds

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Intention-to-treat (ITT) principle is recommended to analyze randomized controlled trials (RCTs). It entails analyzing all subjects per the assigned group at randomization to avoid treatment effect estimation bias. Missing outcome data in RCTs can compromise results¹ and its wrong handling may cause bias. Single imputation methods e.g.

“last observation carried forward (LOCF)” have unrealistic assumptions and discount the uncertainty of imputation². Sensitivity analyses are recommended to assess robustness of such assumptions². We studied RCTs of rheumatoid arthritis (RA) for ITT use, missing outcome data handling, and sensitivity analysis usage. Trends between 2006 and 2016 were analyzed.

Methods: MEDLINE and Cochrane Central Register of Controlled Trials database were searched to identify parallel-design, non-phase-1, English language, original RA RCTs of drug therapy with clinical primary outcome(s) published in 2006 and 2016. The study RCTs were assessed by two reviewers. ITT analysis was defined when all randomized subjects were included in the final analysis for the primary outcome(s). A modified ITT (mITT) allowed exclusion of one or more of the following: those found non-eligible after randomization, those who never received study intervention, and those without baseline or any post-baseline assessment³. All other exclusions were classified as inadequate.

Results: 80 RCTs, 36 from 2006 and 44 from 2016, were eligible (Table 1). 48/69 (69.5%) RCTs had > 10% and 17/69 (24.6) had >20% missing data. RCTs doing ITT or mITT analyses enrolled more subjects ($p < .001$) but had similar completion rates ($p = .734$). Missing data of >10% was more in comparator arm vs. experimental intervention arm [16 (25.4%) vs. 3 (4.8%)]. RCTs performing ITT analyzed 100% subjects. Median (IQR) % analyzed for mITT RCTs was 98.8 (97.5-99.5) and inadequate analysis RCTs was 88.6 (81.7-92.1). LOCF was the most used imputation method. Utilization of ITT or mITT analysis from 2006 to 2016 was similar [23/34 (67.6%) vs 25/42 (59.5%), $p = .465$]. Only 42.9% and 57.1% RCTs reporting ITT analysis actually performed one in 2006 and 2016 respectively. Sensitivity analysis use between 2006 and 2016 was similarly low [6/36 (16.7%) vs 9/44 (20.5%), $p = .666$]. Only one 2006 RCT used the preferred imputation methods. Missing mechanisms and comparison of completers and dropouts were given by one RCT each.

Table 1. Comparison of 2006 and 2016 RCTs

Characteristics	All (n = 80)	Study year		P
		2006 (n = 36)	2016 (n = 44)	
Funding source				
Non-profit	21 (26.3)	8 (22.2)	13 (29.5)	.623
Industry	40 (50)	20 (55.6)	20 (45.5)	
Both non-profit & industry	5 (6.3)	3 (8.3)	2 (4.5)	
Unspecified	14 (17.5)	5 (13.9)	9 (20.5)	
Experimental intervention				
Biologic	42 (52.5)	19 (52.8)	23 (52.3)	.123
Traditional DMARD	8 (10)	5 (13.9)	3 (6.8)	
Small molecule	4 (9.1)	0 (0)	4 (9.1)	
Other	26 (32.5)	12 (33.3)	14 (31.8)	
Efficacy*				
Positive	59 (80.8)	28 (84.8)	31 (77.5)	.427
Negative	14 (19.2)	5 (15.2)	9 (22.5)	
Study phase				
Phase 2	13 (16.3)	3 (8.3)	10 (22.7)	.074
Non-phase 2/unspecified	67 (83.8)	33 (91.7)	34 (77.3)	
Total patient	(n = 76)	(n = 34)	(n = 42)	.913
Median (IQR)	162 (74-326)	163 (53-367)	159 (79-311)	
Patient percent completing study	(n = 69)	(n = 31)	(n = 38)	.201
Median (IQR)	86.7 (79.8-91.4)	85.1 (71.5-92.3)	87.4 (81.5-91.3)	
Patient percent analyzed for primary* outcome	(n = 73)	(n = 32)	(n = 41)	.879
Median (IQR)	99.7 (97.1-100)	99.6 (97.3-100)	99.7 (96.9-100)	
Analysis**				
ITT	28 (36.8)	12 (35.3)	16 (38.1)	.217
Modified ITT	20 (26.3)	11 (32.4)	9 (21.4)	
Completer/inadequate	16 (21.1)	4 (11.8)	12 (28.6)	
Unclear	12 (15.8)	7 (20.6)	5 (11.9)	
Amount of missing outcome data	(n = 69)	(n = 31)	(n = 38)	.116
<5%, N (%)	8 (11.6)	1 (3.2)	7 (18.4)	
5.1-10%, N (%)	13 (18.8)	8 (25.8)	5 (13.2)	
10.1-20%, N (%)	31 (44.9)	13 (41.9)	18 (47.4)	
>20%, N (%)	17 (24.6)	9 (29.0)	8 (21.1)	.275
Missing data handling method given***	(n = 79)	(n = 36)	(n = 43)	
N (%)	43 (54.4)	22 (61.1)	21 (48.8)	
Stated using ITT or mITT**	(n = 76)	(n = 34)	(n = 42)	
N (%)	48 (63.1)	23 (67.6)	25 (59.5)	.465
Common methods to impute missing data,	(n = 80)	(n = 36)	(n = 44)	.069 .818 .535
LOCF, N (%)	25 (31.3)	15 (41.7)	10 (22.7)	
Non-responder imputation, N (%)	21 (26.3)	9 (25.0)	12 (27.3)	
Baseline observation carried forward, N (%)	4 (5.0)	2 (5.6)	2 (4.5)	
Performed sensitivity analysis	(n = 80)	(n = 36)	(n = 44)	.666
N (%)	15 (18.8)	6 (16.7)	9 (20.5)	

* N = 73, 4 RCTs excluded as safety was primary outcome and 3 as strategy trials with no a priori declared experimental intervention; **N = 76, 4 RCTs excluded as safety was primary outcome; ***One RCT had no missing data. **Conclusion**

Missing data is common and most RCTs have >10 % missing data. While most patients are in the final analysis, many RCTs apply ITT principle incorrectly, utilize inappropriate single imputation methods and do not specify missing data handling methods. Sensitivity analyses and mechanism of missingness reporting is very low. No significant changes were seen from 2006 to 2016.

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2. Little RJ. N Engl J Med 2012;367:1355-60
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Disclosure: F. Aslam, None; K. Torralba, GlaxoSmithKline, Pfizer, Exagen, 5; N. A. Khan, None.

Abstract Number: 2875

Identifying Trends in Lines of Therapy Following Initial Biologic Disease-Modifying Antirheumatic Drug in Patients with Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments V: Beyond Individual Compounds

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Among patients with rheumatoid arthritis (RA) who have an inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), the addition of a biologic DMARD (bDMARD), is recommended. If treatment with a first bDMARD fails, patients may move to subsequent bDMARD lines of therapy (LOT), either cycling to a bDMARD with the same mode of action (MOA) or switching to a targeted therapy (bDMARD or janus kinase inhibitor) with a different MOA. The objective of this study was to evaluate LOT among RA patients receiving bDMARDs in the US.

Methods: Data were taken from the MarketScan Commercial claims database between Jan 01, 2011 and Sep 30, 2015. Patients were included if they had: ≥ 1 inpatient or ≥ 2 outpatient claims at least 30 days apart for RA; ≥ 1 bDMARD (tumor necrosis factor inhibitor [TNFi] or non-TNFi [date of first bDMARD initiation was the index date]); and 12 months continuous medical and prescription insurance coverage prior to the index date. The bDMARD at the index date was defined as LOT1 and could be used as either monotherapy or in combination with a csDMARD. Patients were considered to have a new LOT (e.g. LOT2, LOT3) when a prescription or administration for a different RA therapy was filled, or the patient resumed the same therapy after a gap of >90 days. Counts and percentages were reported for categorical variables. Means (SD) were reported for continuous variables. Kaplan-Meier (KM) analysis was used to analyze time to discontinuation of each LOT.

Results: 17,525 RA patients were included in the analysis: mean (SD) age 50.9 (9.6) years; 79.0% women; mean (SD) number of LOT 1.8 (1.1); and median follow-up 27 months. The most commonly used medications for LOT1 were etanercept (36.6%) and adalimumab (31.4%). Across all LOT and individual medications, the mean proportion of days covered in the 12 months post-index was 0.63. Approximately half of patients (54.5%) had 1 LOT; 25.8% had 2 LOT; 11.7% had 3 LOT; 8% had ≥ 4 LOT. In patients who started with a TNFi on the index date, 20.6% had ≥ 3 LOT, and in patients who had a non-TNFi on the index date, 15.2% had ≥ 3 LOT. Among patients who had a non-TNFi on the index date, 75.6% and 75.6% of patients who moved to LOT 2 and 3, respectively, had subsequent non-TNFi's. Among patients who had a TNFi on the index date, 76.0% and 51.5% of patients who moved to LOT2 and 3, respectively, had subsequent TNFi's. Overall, the use of concomitant methotrexate was greater (47.8%) in LOT1 than in LOT2 (38.4%) or LOT3 (35.4%). KM estimates showed that patients spent the longest time on LOT1 (mean: 726.9 days), followed by LOT2 and LOT3 (mean: 567.6 days and 487.2 days, respectively).

Conclusion: In this study, the longest duration of treatment occurred for LOT1, and shortened with each subsequent LOT. These results suggest frequent cycling occurs within the non-TNFi and TNFi categories. Future research is needed to understand the duration of LOT by non-TNFi and TNFi agents and the impact on patient outcomes.

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Torque Teno Virus Quantification for Functional Monitoring of Immunomodulation with Biological Compounds in the Treatment of Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments V: Beyond Individual Compounds

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Rheumatoid arthritis (RA) patients who fail to respond to methotrexate (MTX) can be subjected to an addition of biologic disease-modifying antirheumatic drug(bDMARD). Currently there are 4 modes of action of bDMARDs: inhibitors of tumor-necrosis-factor alpha (TNFi), of interleukin-6 (anti-IL-6), lymphocyte co-stimulation (anti-CTLA4) and B-cell directed therapy (anti-CD20). All bDMARDs show similar response rates at 6 months treatment, while differences in response between patients may relate to variable level of immunomodulation by each drug.

The a pathogenic and highly prevalent Torque Teno Virus (TTV) is a potential novel candidate for functional monitoring of immune response. TTV in peripheral blood has been shown to mirror the immunocompetence of its host in patients with HIV, malignancies and solid organ transplantation.

Here we explore levels of TTV replication in patients receiving bDMARDs, and their association with clinical response to therapy.

Methods: The BIOBIO Study is a multicenter randomized open-label trial, including RA patients with insufficient response to MTX. Patients were randomized to either TNFi (infliximab, INF); anti-IL-6 (tocilizumab, TCZ); CTLA4-Ig (abatacept, ABA) or anti-CD20 (rituximab, RTX) in addition to MTX. Serum samples were collected at baseline and 3 months. RT-PCR was used to quantify TTV within these serum samples.

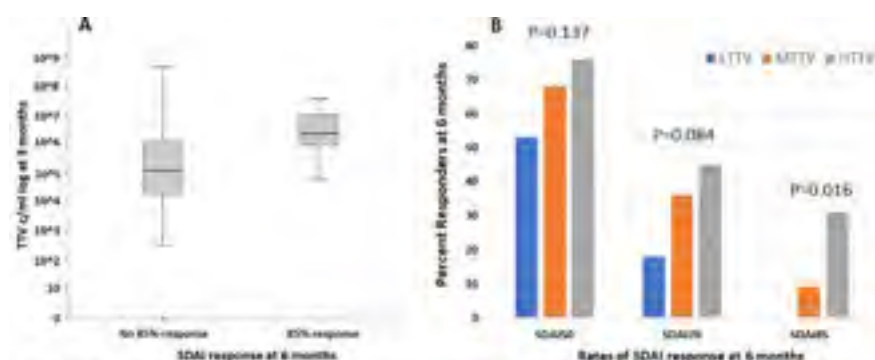


Figure: A: Boxplots of TTV levels at 3 months, shown separately for SDAIS responders and non-responders. B: Rates of SDAI response at 6 months separately shown by tertiles of TTV at 3 months (JTV: lowest TTV tertile; MTTV: middle TTV tertile; HTTV: highest TTV tertile)

Results: TTV was measured in 95 RA patients randomized to INF (n=23), TCZ (n=22), ABA (n=27) or RTX (n=23); 77% were female, 72% were ACPA and 51% RF positive and 2/3 showed high disease activity. Median TTV at baseline was 4.3×10^4 c/ml (IQR: 7.4×10^3 , 1.3×10^5) with no difference between the 4 treatment groups. After 3 months of treatment patients showed increase in TTV levels compared to baseline (INF: p=0.018; ABA: p=0.071; RTX: p≤0.001). There was no change in TTV for TCZ, and therefore omitted from further analyses on the association between TTV and treatment response.

TTV at 3 months after treatment was higher in patients achieving a SDAI85 response at month 6 (p=0.007; Figure 1A). Receiver operating characteristics outlined an area under the curve of 0.756 for prediction of SDAI85 at month 6 after treatment by TTV at month 3 (p≤0.001). A TTV level of 5.6×10^5 c/ml at month 3 shows a 67% specificity, 81% sensitivity, relating to a +likelihood ratio of 2.6 (95% CI: 1.6-4.1) for SDAI85 prediction at month 6. Patients in the top tertiles of month 3 TTV had greater changes in SDAI (p=0.043), CDAI (p=0.022) and DAS28 (p=0.022) and higher SDAI85 response rates at month 6 (OR=5.85, CI: 1.4-24.5; p=0.016; Figure 1B). No patient below a TTV value of 2.7×10^4 c/ml showed SDAI85 treatment response.

Conclusion: Our data suggest that TTV level in the peripheral blood corresponds to and predicts clinical response to bDMARDs for RA, except for TCZ. Future prospective trials have to clarify the potential of TTV tailored bDMARD dosing.

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Abstract Number: 2877

The Comparative Effectiveness of First-Line Tumor Necrosis Factor Inhibitor (TNFi) Compared with Non-TNFi Agents in Patients with Rheumatoid Arthritis: Results from the Corrona Registry

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments V: Beyond Individual Compounds

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: RA patients who are intolerant or have an inadequate response to conventional synthetic DMARDs (csDMARDs) can be treated with a biologic DMARD (bDMARD). Tumor necrosis factor inhibitors (TNFi) are often used first-line but non-TNFi bDMARDs are also used. Data comparing the effectiveness of TNFi and non-TNFi following csDMARDs are limited; we therefore sought to compare the real-world effectiveness of TNFi and non-TNFi agents in bDMARD-naïve patients.

Methods: Demographic, clinical, disease characteristic, and patient-reported outcomes (PROs) were collected for patients enrolled in a large US registry (Corrona) from Jan 1, 2001 to Jan 20, 2018 with diagnosis of RA, ≥18 years at diagnosis, initiating (mono- or combination therapy) with a TNFi or non-TNFi bDMARD, and with follow-up 6–15 months after initiation. Non-TNFi and TNFi patients were propensity score matched (PSM) on a 1:4 basis by age, RA duration, cardiovascular and hypertension history, prior cancer, private insurance, Medicare, marital status, smoking status, work status, ACR functional class, and concomitant csDMARDs; variables with >10% missing data were omitted. The PSM used no replacement matching. Baseline characteristics after PSM were compared using two-sample *t*-tests (continuous) and Chi-squared tests (categorical). Outcomes were assessed after 12 months of therapy; for patients switching therapy last-visit outcomes were carried forward. Random effect linear (continuous) and random effect logistic (binary) regression were used to compare outcomes at 12 months between matched populations further adjusted by baseline value, concomitant csDMARD, and prednisone use. A number of outcome covariates were assessed as potential effect modifiers using interaction terms in multivariable mixed models.

Results: Of the bDMARD-naïve patients, 4186 initiated a TNFi and 630 a non-TNFi. After PSM, 2372 TNFi and 593 non-TNFi patients were included. Respectively, mean (SD) age was 61.0 (12.9) vs 62.3 (12.8) years (*P* = 0.03); 76.8% vs 79.8% female (*P* = 0.12); mean (SD) duration of RA 8.2 (9.3) vs 8.7 (9.5) years (*P* = 0.24); RF positive 70.2% vs 70.4% (*P* = 0.95);

Table 1. Comparison of efficacy and PRO outcomes at 12 months follow-up in the PSM TNFi and non-TNFi initiators

	TNFi patients (n = 2372)	Non-TNFi patients (n = 593)	Comparison (TNFi vs non-TNFi) ²	P-value
<i>Binary outcomes</i>		<i>Response rate (%)</i>	<i>Odds ratio (95% CI)</i>	
Low disease activity (CDAI ≤10)¹	597/1498 (39.9)	154/370 (41.6)	1.00 (0.94, 1.05)	0.87
Remission (CDAI ≤2.8)¹	363/2066 (17.6)	82/504 (16.3)	1.02 (0.98, 1.06)	0.26
MCID in CDAI¹	940/2066 (45.5)	227/504 (45.0)	1.01 (0.97, 1.07)	0.55
Remission (mDAS28)	449/1835 (24.5)	118/447 (26.4)	0.99 (0.95, 1.04)	0.65
Patient reported				
Problems with sleeping	588/2363 (24.9)	136/591 (23.0)	1.02 (0.98, 1.06)	0.35
Anxiety	308/2363 (13.0)	73/591 (12.4)	1.01 (0.98, 1.04)	0.70
<i>Change in continuous outcomes¹</i>		<i>n, mean (SD)</i>	<i>β (95% CI)</i>	
CDAI	2065 -6.8 (14.0)	504 -6.5 (13.8)	-0.78 (-1.07, 0.31)	0.16
HAQ	1732 -0.1 (0.6)	373 -0.1 (0.5)	-0.05 (-0.11, 0.00)	0.07
EQ-5D	1097 0.0 (0.2)	357 0.0 (0.2)	-0.01 (-0.03, 0.01)	0.48
Patient reported				
Morning stiffness (hours)	1599 -0.3 (2.5)	396 -0.2 (2.9)	-0.15 (-0.41, 0.12)	0.29
Fatigue	1119 -4.7 (30.1)	263 -6.3 (26.2)	1.27 (-1.84, 4.38)	0.42

CI, confidence interval; HAQ, Health Assessment Questionnaire; MCID, minimal clinically important difference; mDAS28, modified Disease Activity Score 28

¹Estimates from multivariable models. ²Among those with moderate or high disease activity at baseline; ³Among those with low, moderate, or high disease activity at baseline; ⁴MCID: change over 12 months dependent on baseline score, for CDAI 2.8–10.0, a decrease of ≥2; CDAI 10.1–22.0, ≥6; CDAI >22.0, ≥11. 112-month outcome minus baseline measurement.

mean (SD) BMI 30.0 (7.1) vs 29.8 (7.3) ($P = 0.41$); concomitant csDMARD 78.0% vs 76.7% ($P = 0.83$); prednisone use 31.7% vs 31.2% ($P = 0.81$); mean (SD) clinical disease activity index (CDAI) 19.8 (13.2) vs 20.1 (13.1) ($P = 0.72$); and mean (SD) HAQ 1.1 (0.6) vs 1.1 (0.6) ($P = 0.96$). No significant differences were observed in 12-month outcomes for TNFi and non-TNFi initiators (Table). No significant effect modification was observed between cohorts for outcomes including achievement of low CDAI and remission, PROs (sleep, anxiety, fatigue, and morning stiffness) and change in CDAI, HAQ, and EuroQoL-5 dimensions (EQ-5D) (data not shown).

Conclusion: No differences in clinical responses were observed in patients with RA initiating a TNFi or non-TNFi as their first bDMARD in this large real-world US cohort.

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Abstract Number: 2878

Phase II Clinical Trials Systematically Overestimate Treatment Effects of Subsequent Phase III Trials in Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments V: Beyond Individual Compounds

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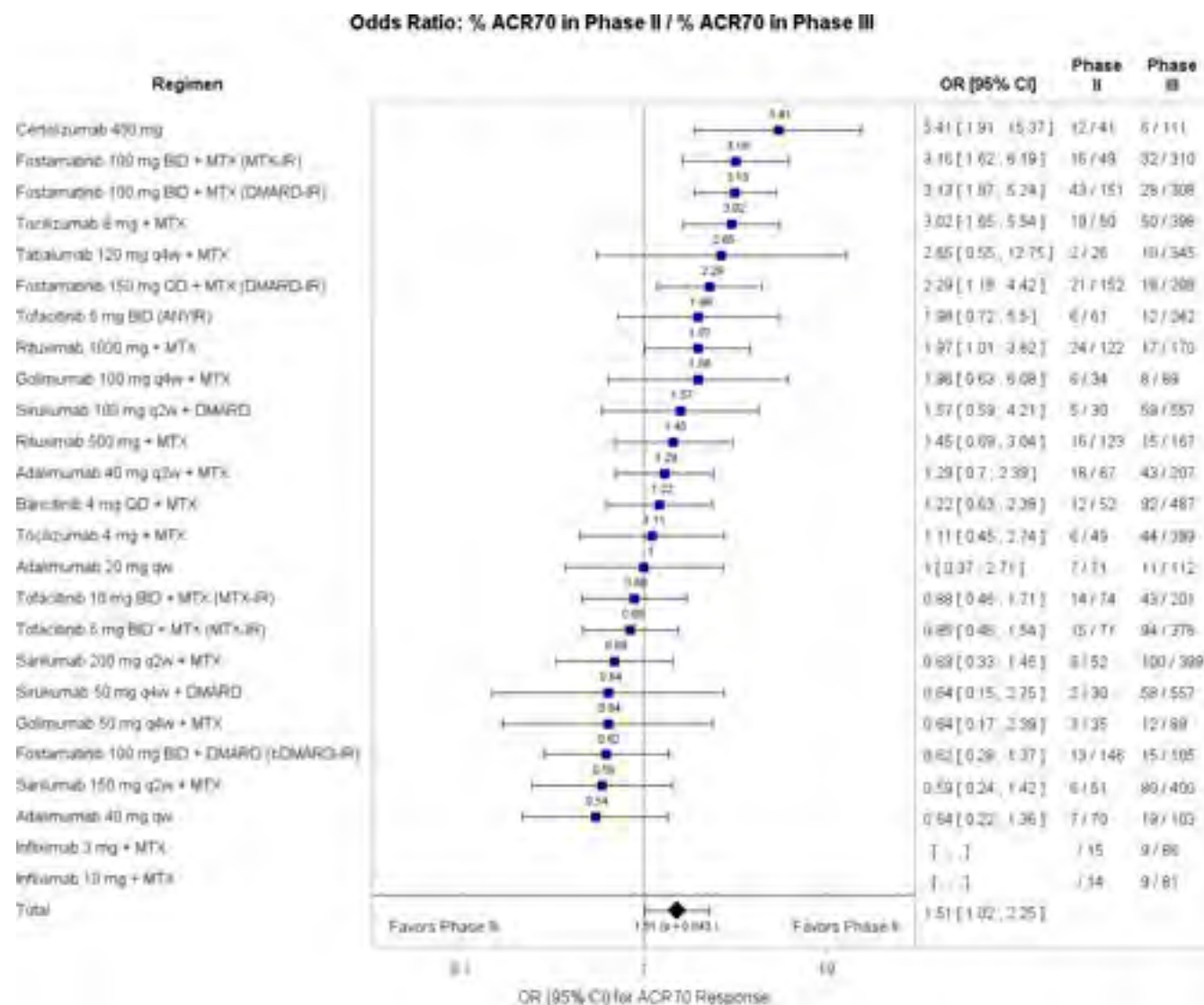
Session Time: 4:30 PM-6:00 PM

Background/Purpose: Phase 3 (P3) clinical trials are the mainstay of drug development in all areas of medicine, including rheumatology, allowing to determine safety and efficacy of new drugs on their way to approval. Historically, efficacy results of P3 trials have often been disappointing with respect to the expectations set by phase 2 (P2) trials. It is unclear whether these observations are reflection of a true bias or merely a play of chance. We therefore systematically compared efficacy of P2 versus P3 trials in RA.

Methods: We performed a systematic review of all disease modifying anti-rheumatic drugs (DMARDs) tested in P2 trials in rheumatoid arthritis (RA) over the last 20 years for which also P3 trials exist. We searched Medline, EMBASE, and the Cochrane Library to identify all randomized controlled double-blind trials investigating biological (b) and targeted synthetic DMARDs in RA. The criteria for inclusion in the analyses were defined as follows: (i) treatment arms in P2 and P3 used the same treatment regimen; (ii) the same RA population was studied (DMARD naïve; conventional DMARD insufficient responders (IR); bDMARD IR). The treatment regimen was regarded the same when a DMARD was used at the same dose, interval and route in P2 and P3. Multilevel mixed model logistic regression was used to determine a summary estimate for comparison of P2 versus P3 results on the outcomes of American College of Rheumatology (ACR) 20, ACR50, and ACR70 responses (in separate models). Results are expressed as Odds Ratio (OR) and 95% confidence intervals (95% CI).

Results: In total 1290 abstracts were screened of which 133 were regarded as potentially relevant, with 34 trials (16 agents, 25 regimens, 8855 patients) finally included in the analysis. Summary estimates revealed that outcomes of P2 trials were systematically over estimating the subsequent P3 results for ACR20 (OR: 1.45; 95% CI: 1.12-1.88; p=0.010), ACR50 (OR: 1.45; 95% CI: 1.09-1.93; p=0.017) and ACR70 (OR: 1.51; 95% CI: 1.02-2.25; p=0.043). Figure 1 shows ORs (95% CI) for ACR70 responses, which represent the most relevant clinical outcome in RA.

Conclusion: Our results reveal that Phase 2 clinical trials over estimate the treatment effects when compared with subsequent Phase 3 trials in RA. The identification of this systematic bias towards overestimation of efficacy by Phase 2



studies has implications for considerations of clinical investigators, sponsors, and regulatory agencies during the development and licencing process of new compounds, as well as potential ethical implications. Investigation of determinants of Phase 2 overestimation is currently ongoing.

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Abstract Number: 2879

Plasma IL-23 and IL-25 Predict Response to Anti-TNF- α Therapy in Rheumatoid Arthritis

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Rheumatoid Arthritis – Treatments V: Beyond Individual Compounds

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: TNF- α inhibitors are among the most widely used biological-DMARDs in rheumatoid arthritis (RA). Means to predict response would allow for a more effective, targeted approach to therapy. Th17-related cytokines synergise with TNF- α to intensify joint inflammation. Evidence suggests poor response to TNF- α inhibitors reflects a TNF- α -independent, Th17-driven process. Our aim was to assess plasma concentrations of a panel of Th17-related cytokines to identify predictors of response to TNF- α inhibitors.

Methods: Ninety-three patients with RA as defined by ACR criteria were seen prior to and 4-6 months after commencing etanercept or adalimumab. Plasma concentrations of Th17-related cytokines (IL-1 β , IL-4, IL-6, IL-10, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-25, IL-31, IL-33, sCD40L, IFN- γ , TNF- α) were measured at baseline. DAS28-CRP with 4 variables (DAS28) was calculated and EULAR cut-off for low disease activity was used to group patients into poor (DAS28 >3.2) and good (DAS28 \leq 3.2) responders at follow up. IL17-IL23-pathway cytokines (IL-17A, IL-17F, IL-22, IL-23, IL-1b and IFN- γ) were grouped to form a pro-inflammatory cumulative score (presence of 0 to 6 cytokines), while anti-inflammatory cytokines, IL-4, IL-10 and IL-25, were grouped to form an anti-inflammatory cumulative score (presence of 0 to 3 cytokines). Multivariate logistic regression was used to identify predictors of response, and odds ratios (OR) and 95% confidence intervals (CI) were calculated.

Results: Patients with IL-23 present at baseline were more likely to be poor-responders [14/20 (70%) of IL-23⁺ patients versus 31/73 (42.5%) of IL-23⁻ patients; p<0.05]. Multivariate analysis suggests that presence of IL-23 predicts poor response following treatment with anti-TNF- α [OR (95% CI) for 6.55 (1.82-23.63), p<0.01], while presence of IL-25 predicts good response [OR (95% CI) = 4.50 (1.53-13.19), p<0.01]. These associations were independent of baseline DAS28. The remaining individual cytokines tested were not associated with response to anti-TNF- α therapy. Pro-inflammatory and anti-inflammatory cumulative scores were not associated with response to anti-TNF- α therapy in univariate analysis. However the anti-inflammatory score was associated with reduced risk of poor response in a multivariate model, including baseline DAS28 and the pro-inflammatory score [OR (95% CI) = 0.54 (0.30-0.97), p<0.05], suggesting the association was dependent on confounding effects of these variables.

Conclusion: IL-23, which promotes pathogenic activity of Th17 cells, may be a useful predictor of poor outcome following anti-TNF- α therapy. IL-25 which downregulates pathogenic activity of Th17 cells may be useful alongside IL-23 to predict a favourable outcome. A cytokine expression profile including IL-25 and additional anti-inflammatory cytokines, IL-4 and IL-10, may indicate increased likelihood of response.

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Serum Levels of Thymic Stromal Lymphopoietin: A Possible Novel Biomarker in Primary Sjögren's Syndrome and Related Lymphoproliferation

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Thymic stromal lymphopoietin (TSLP) has been demonstrated to be involved in B-cell lymphoproliferation and lymphoma mainly by tissue studies on salivary glands (SG) biopsies of patients with primary Sjögren's syndrome (pSS) (1). The aim of this work is to study serum TSLP as a possible novel biomarker in pSS.

Methods: Ninety-one antiSSA-positive pSS patients (females n=86, 94.5%; mean age 57.2 years, range 25-80), fulfilling the 2016 ACR-EULAR classification criteria, were studied by ELISA for the expression of serum TSLP, in comparison with 80 matched healthy blood donors (HBDs) and with 21 patients with non-autoimmune sicca syndrome (nSS). pSS patients were then stratified according to the degree of lympho proliferation (2) in available SG biopsies as follows: fully benign (fbSS), myoepithelial sialadenitis (MESA) and B-cell MALT lymphoma (NHL), and the difference in serum TSLP levels was evaluated between these three subgroups.

In addition, prospective serum samples, collected at the time of MESA diagnosis and also later at the time of NHL development, were studied in 3 pSS cases.

All the pSS patients were naïve to immunosuppressants, biotechnological drugs, chemotherapies and were not receiving steroids at the time of sample collection.

The most relevant clinical features of pSS linked to lymphoproliferation (i.e. persistent parotid swelling and mixed cryoglobulinemia), the presence of ectopic germinal centres (GCs) in SG, and the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) were also collected.

Results: Serum TSLP resulted significantly increased in pSS (mean 47.19 pg/mL, range 0-324.89) compared to nSS (mean 2.74 pg/mL, range 0-15.9) ($p<0.0001$) and to HBDs controls (mean 0.59 pg/mL, range 0-11.09: very low detectable levels only in 4/80) ($p<0.0001$). The significance was the same ($p<0.0001$) also after excluding NHL pSS patients.

Serum TSLP showed a progressive, significant increase from fbSS (n=65; mean 26.54 pg/mL; range 0-75.11) to MESA (n=14; mean 69.72 pg/mL; range 20.62-140.8) (MESA vs fbSS $p<0.0001$) and finally to NHL (n=12; mean 151.96 pg/mL; range 58.16-324.89) (NHL vs fbSS $p<0.0001$; NHL vs MESA $p=0.009$).

In prospective sera, TSLP levels increased in all the 3 pSS patients from MESA to NHL, from 3.76 times to 70.46 times (mean of serum TSLP increase: 30 times).

Benign pSS patients with persistent parotid swelling, mixed cryoglobulinemia and with GCs in SG biopsy showed significantly ($p<0.05$) higher TSLP serum levels compared to pSS patients without these features.

A significant correlation between higher TSLP serum levels and increasing ESSDAI was finally found ($R^2=0.51$; $p<0.0001$).

Conclusion: Serum TSLP could represent a novel biomarker of pSS-related lymphoproliferation. The validation of present results is currently ongoing in independent pSS cohorts belonging to the EU Project Harmonic SS consortium (3).

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How Immunological Profile Drives Clinical Phenotype of Primary Sjögren's Syndrome at Diagnosis: Analysis of 10.500 Patients (Sjögren Big Data Project)

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: To evaluate the influence of the main immunological markers on the disease phenotype at diagnosis in a large international cohort of patients with primary Sjögren's syndrome (SjS).

Methods: The Big Data Sjögren Project Consortium is an international, multicentre registry created in 2014. As a first step, baseline clinical information from leading centres on clinical research in SjS of the 5 continents was collected. The centres shared a harmonized data architecture and conducted cooperative online efforts in order to refine collected data under the coordination of a big data statistical team. Inclusion criteria were the fulfilment of the 2002 classification criteria. Immunological tests were carried out using standard commercial assays.

Results: By January 2018, the participant centres had included 10,500 valid patients from 23 countries. The cohort included 9,806 (93%) women and 694 (7%) men, with a mean age at diagnosis of primary SjS of 53 years, mainly White (78%) and included from European countries (71%). The frequency of positive immunological markers at diagnosis was 79.3% for ANA, 73.2% for anti-Ro, 48.6% for RF, 45.1% for anti-La, 13.4% for low C3 levels, 14.5% for low C4 levels and 7.3% for cryoglobulins. Positive autoantibodies (ANA, Ro, La) correlated with a positive result in salivary gland biopsy, while hypocomplementemia and especially cryoglobulinaemia correlated with systemic activity (mean ESSDAI score of 17.7 for cryoglobulins, 11.3 for low C3 and 9.2 for low C4, in comparison with 3.8 for negative markers). The immunological markers with a great number of statistically-significant associations ($p < 0.001$) in the organ-by-organ ESSDAI evaluation were cryoglobulins (9 domains), low C3 (8 domains), anti-La (7 domains) and low C4 (6 domains).

Conclusion: we confirm the strong influence of immunological markers on the phenotype of primary SjS at diagnosis in the largest multi-ethnic international cohort ever analysed, with a greater influence for cryoglobulinaemic-related markers in comparison with Ro/La autoantibodies and ANA. Immunological patterns play a central role in the phenotypic expression of the disease already at the time of diagnosis, and may guide physicians to design a specific personalized management during the follow-up of patients with primary SjS.

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Abstract Number: 2882

Minimal Progression of Disease Manifestation in Patients with Sjögren's Syndrome Re-Evaluated Multiple Years after Initial Disease Classification

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Classical connective tissue diseases, such as SLE and RA have well documented progression of disease and damage accrual. However, the natural history of Sjögren's syndrome (SS) has been less well documented, particularly in research settings where comprehensive multidisciplinary assessments can be performed at more than one time point. The objective of the present study was to re-evaluate past participants in the OMRF Sjögren's research clinic (SRC) with the same protocol that was used for their initial research classification with the goal of documenting changes in their disease.

Methods: Questionnaires assessing health changes and willingness to be re-evaluated were mailed to 800 SRC participants. Twenty respondents (17 SS and 3 incomplete SS [iSS] both by AECG and ACR-EULAR criteria) participated in this pilot study in which all procedures performed in their initial evaluation were repeated.

Results: 356 (45%) questionnaires were answered (161 SS and 195 iSS). Subjectively, respondents reported equal or better status of ocular and oral symptoms but significantly worse fatigue and arthralgias ($p < 0.001$) with no differences between SS and iSS. The 20 re-evaluated patients returned after an average of 5.4 years (range 2-9). Thirteen (65%) retained the initial disease classification, but 6 subjects (30%) went from SS to iSS and 1 (5.0%) from iSS to SS. It is noteworthy that this subject only met SS criteria by AECG and not by ACR-EULAR because his serology was anti-La (+) only with negative biopsy. Furthermore, only 2 subjects had a net increase in the number of criteria, while 18 had the same number ($n=8$) or fewer ($n=10$). There were no consistent patterns of change in the objective measures of lacrimal and salivary gland function: 5 subjects became Schirmer's (+) and 1 reversed to (-); the opposite was the case for the ocular staining, with 5 becoming (-) and 1 becoming (+). The only unchanged results in all the recalls were the anti-Ro/anti-La status. The most intriguing results were the changes in the minor salivary gland biopsy; 4 (20%) subjects went from positive to negative biopsy resulting in a change in classification from SS to iSS in 3 cases. Moreover, the focus score was lower in the second biopsy of 10 (50%) cases, 4 (20%) had a higher score and the remaining 6 (30%) were unchanged. The morphology of the salivary gland tissue of these reversed cases showed extensive fibrosis, fatty infiltration and atrophy of the gland, precluding the lymphocytic infiltrates from meeting the definition of being surrounded by normal tissue. Further supporting the notion of worsening gland architecture, final focus score trended to inversely correlate with WUSF ($r = -0.4$; $p = 0.089$). Complement levels and hypergammaglobulinemia did not predict stability or worsening of SS.

Conclusion: Re-evaluated patients showed little disease progression but steady presence of autoantibodies. Detrimental changes in salivary gland morphology were observed in later biopsies, even when classified as "negative" using current criteria. These results suggest that significant tissue destruction in long standing disease may lead to false negative biopsy results in spite of progressive glandular dysfunction.

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Abstract Number: 2883

Testing for Anti-Microbial Antibodies with Cross-Reactivity to Human Tissue in Autoimmune Diseases

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science

Session Type: ACR Concurrent Abstract Session

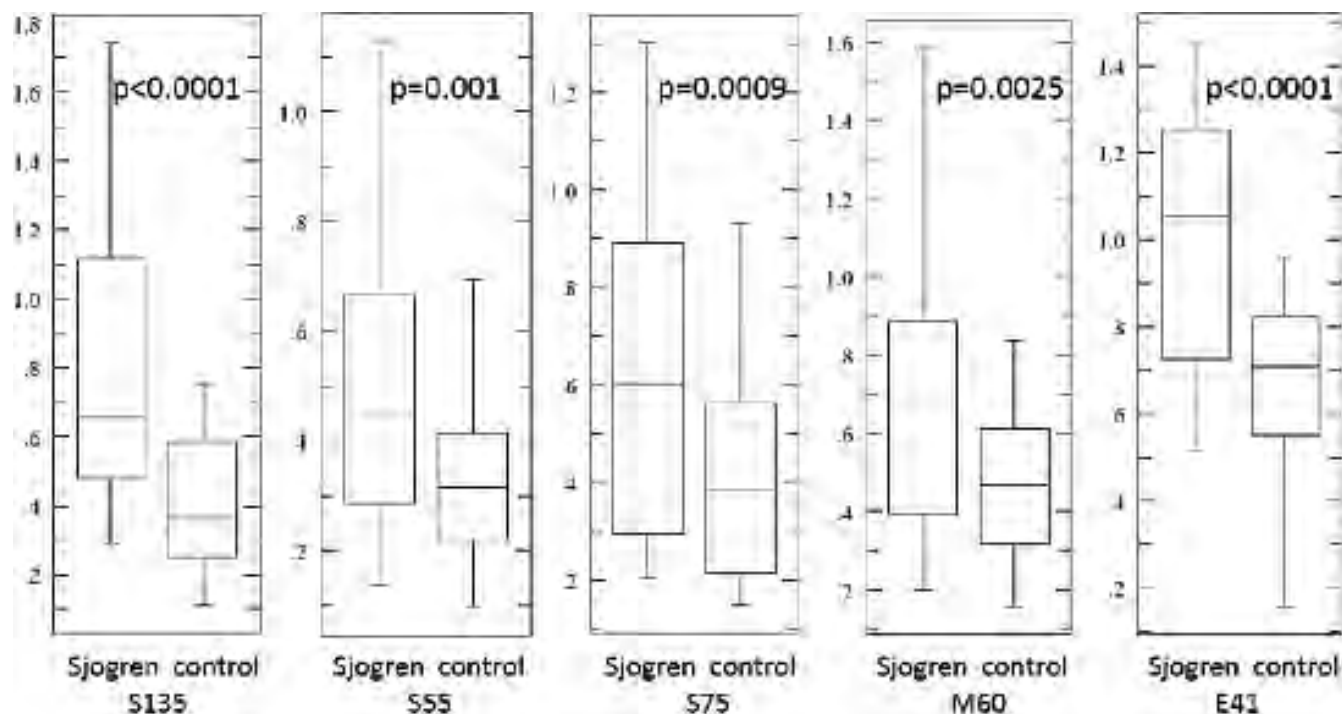
Session Time: 4:30 PM-6:00 PM

Background/Purpose: Autoantibodies are defining features of autoimmune diseases. How and why the autoantibodies are produced and how these autoantibodies relate to pathogenesis is poorly understood. Current study is to examine the role of anti-microbial antibodies in patients with Sjögren's syndrome and Crohn's disease.

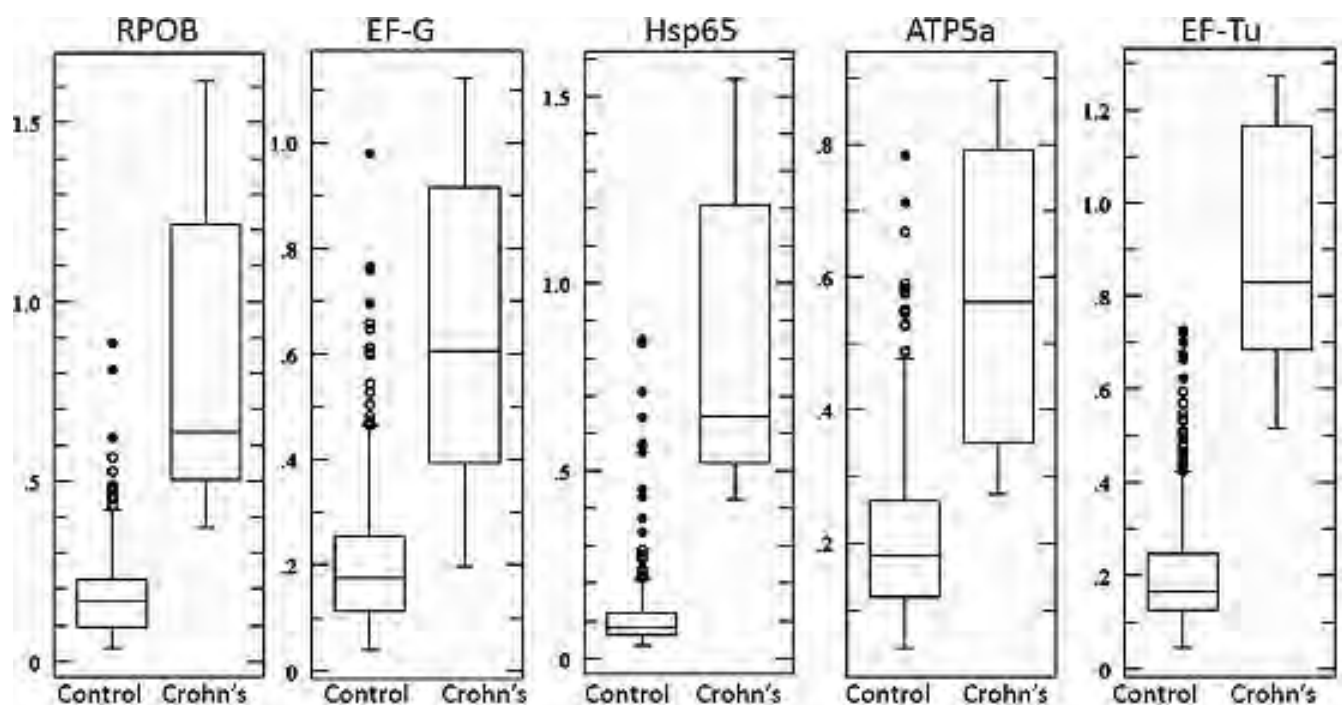
Methods: We have discovered a panel of serology biomarkers against microbial antigens through Western blot analysis, mass spectrometry, immunohistochemistry and ELISA assays.

Results: We have discovered a novel panel of anti-microbial antibodies from the blood of patients with Sjögren's syndrome and Crohn's disease, and these antimicrobial antibodies are significantly elevated in the patients in comparison to the

healthy controls. The anti-microbial antibodies are directed to RPOB (S135) from *S. aureus*, EF-G (S75) from *S. aureus/pseudintermedius*, Hsp65 (M60) from *Mycobacterium*, ATP5a (S55) from *S. aureus* and EF-Tu (E41) from *E. coli*. These bacteria are commensal commonly present on the surface of human body, in the gut, and environment. Specific monoclonal and polyclonal antibodies against these microbial proteins can cross-react to the normal human tissues by immunohistochemistry. We have tested 23 patients with Sjogren's and 45 patients with Crohn's disease for the blood levels



Patients N=23, All negative 4, one or more positive 19, positive predictive value 83%
Control N=31, All positive 0, one or more positive 6, negative predictive value 81%



Normal blood donor samples (n=288)
Crohn's (n=45) $p < 0.0001$ (t-test)

of these anti-microbial antibodies below in comparison to 288 normal controls. We also found these anti-microbial antibodies are elevated in patients with systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis and Lyme disease.

Conclusion: The defining features of autoantibodies in autoimmune diseases may in fact be anti-microbial antibodies with cross-reactivity to human tissues. The presence of anti-microbial antibodies with cross-reactivity to human tissue may provide a basis of pathogenesis in autoimmune disease through molecular mimicry and offer new direction of research in disease mechanisms and therapeutics for a spectrum of autoimmune diseases.

Disclosure: P. Zhang, Owner of the company, 4; L. Minardi, PZM Diagnostics, LLC, 4; J. T. Kuenstner, PZM Diagnostics, LLC, 4; S. Zekan, PZM Diagnostics, LLC, 4.

Abstract Number: 2884

Correlation between Salivary Gland Ultrasonography, Minor Salivary Gland Histopathology and Sialometry: Towards a Composite Assessment of Salivary Gland Involvement in Primary Sjögren's Syndrome

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science

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Session Time: 4:30 PM-6:00 PM

Background/Purpose: Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease that specifically involves salivary glands. Several complementary tools including salivary gland ultrasonography (SGUS), histology and saliva collection have been proposed to estimate glandular inflammation and dysfunction. Few studies have explored the association between SGUS, salivary gland histology and saliva production. Moreover, it has to be elucidated whether an integrated composite evaluation of salivary gland involvement, based on the combination of these different tools, may improve patients' stratification and management. Aims of this study were: 1) to analyze the correlation between SGUS, saliva production and gland histology, and 2) to assess the prevalence of different subsets of glandular involvement in pSS defined on the basis of the combination of SGUS, histology and sialometry.

Methods: Newly diagnosed pSS patients were consecutively enrolled. Subjects underwent a complete rheumatologic evaluation, SGUS, minor salivary gland biopsy and sialometry (USFR). SGUS was performed by the same operator who graded the echostructure of each gland on a 5-point scale (0–4), defining as pathological a SGUS score ≥ 2 . Histology evaluation included the assessment of the focus score (FS) and the reporting of the number of germinal centre (GC)-like structures.

Results: We included 90 newly diagnosed pSS patients. Out of them: 51 presented abnormal findings at SGUS and 39 had a normal SGUS. SGUS score correlated better with FS ($r=0.642$, $p=0.001$) and GCs ($r=0.492$, $p=0.001$) than with USFR ($r=-0.361$, $p=0.003$). When SGUS findings were combined with histology and USFR we distinguished four major patterns of salivary involvement. The most common subset was represented by patients (26/90 (29%)) with abnormal SGUS, preserved USFR and a high FS. In addition, 21/90 (23%) pSS patients presented abnormal SGUS findings, reduced USFR and a high FS; 17/90 (19%) patients had normal SGUS, preserved USFR and a low FS, and 17/90 (19%) had normal SGUS, preserved USFR and a high FS. Nine patients presented characteristics intermediate between the mentioned subsets. Patients included in the first two groups presented a higher frequency of anti-Ro/SSA, Rheumatoid factor, hypergammaglobulinemia and salivary gland swelling. Patients with lower USFR presented a reduced size in their submandibular glands at SGUS examination.

Conclusion: This study suggest that an integrated evaluation of salivary gland involvement may allow to better define the relationship between tissue inflammation/damage and functional dysfunction. This composite approach may be useful in pSS phenotyping as a prerequisite towards personalized interventions.

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Expansion of Activated PD-1⁺ ICOS⁺ T Follicular and Peripheral Helper Cells in Primary Sjögren's Syndrome Associates with Abnormalities in B Cell Compartment

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Sjögren's Syndrome – Basic and Clinical Science

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Session Time: 4:30 PM-6:00 PM

Background/Purpose: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by immune cell infiltration in the salivary glands resulting in ocular and oral dryness. Abnormalities in both B and T follicular helper (Tfh) cells associated with ectopic germinal center formation in the salivary gland has been described in pSS. However, the diversity of Tfh cells and relationship between B and T cell subsets has not been fully elucidated. In this study, we examined the expression of ICOS and PD-1, two critical immune co-regulatory molecules for T follicular helper function, on memory T cells in both CXCR5⁺ (Tfh) and CXCR5⁻ (Tph) populations in pSS compared to HC, SLE and RA. We evaluated changes in peripheral blood B and T cell populations in pSS compared to other diseases and healthy controls.

Methods: pSS, SLE and RA patients, along with age and gender matched HC were recruited at University of Rochester. pSS (n=40), SLE (n=19) and RA (n=20) were classified based on ACR criteria. PBMCs were isolated by Ficoll-Hypaque and the frequencies of B and T subpopulations measured by multi-parameter flow cytometry. The mean \pm SEM was calculated for each cell population and statistical analysis was done by t-test. Correlation analysis was done by Pearson method, $p < 0.05$ was considered significant.

Results: pSS and SLE had significantly higher frequency of both CXCR5⁺PD-1⁺ICOS⁺ (PD-1⁺ICOS⁺ Tfh) and CXCR5⁺PD-1^{hi}ICOS⁺ (ICOS⁺ Tph) than HC, while RA and SLE had higher percent of CXCR5⁺PD-1^{hi} (Tph) than HC. Further evaluation of Tfh subsets (based on CXCR3 and CCR6), revealed higher frequency of PD-1⁺ICOS⁺ Tfh1 and PD-1⁺ICOS⁺ Tfh2 in pSS and SLE compared to HC. In addition, we evaluated PD-1⁺ICOS⁻ Tfh populations that have been shown to have B cell helper functions. PD-1⁺ICOS⁻ Tfh1 and PD-1⁺ICOS⁻ Tfh2 were expanded in pSS and RA compared to HC, while RA patients also showed expansion of PD-1⁺ICOS⁻ Tfh17. Characterization of B cells in pSS patients revealed significant contractions of switched memory (SM), un-switched memory (USM) and double negative memory (DN) B cell compared to HC. In contrast, the fraction of activated memory B cells (CD95⁺ or CD21⁺) was significantly higher in pSS compared to HC. Additionally, the frequency of activated CD27⁺ memory B cell were positively correlated with frequency of PD-1⁺ICOS⁺ Tfh and ICOS⁺ Tph. The frequency of ICOSL⁺ B cells was positively associated with the frequency of PD-1⁺ICOS⁻ Tfh17 ($r=0.362$, $p=0.024$), a putative B cell helper Tfh subset. We are currently evaluating transcriptomic and proteomic data from these patients to correlate with flow cytometry data and to further elucidate the interaction between the B cell and T cell compartment in pSS.

Conclusion: Our data highlight the significant abnormalities in the peripheral Tfh and B cell compartment in pSS and the critical role of Tfh-B cell interactions. The association between ICOSL⁺ memory B cells and ICOS⁺ T cells suggests their potential interaction in germinal center-like structures in salivary glands.

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Secukinumab Provides Rapid and Sustained Resolution of Enthesitis in Psoriatic Arthritis Patients: Pooled Analysis of Two Phase 3 Studies

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical V: Treatment of PsA and Peripheral SpA

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Secukinumab (SEC), a fully human monoclonal antibody that selectively neutralizes IL-17A, provided significant and sustained improvement in the signs and symptoms of active PsA, with sustained resolution of enthesitis in Phase 3 FUTURE 2 and FUTURE 3 studies.^{1,2} This *post-hoc* analysis evaluated the effect of SEC on resolution of enthesitis count (EC; defined by Leeds Enthesitis Index) in PsA patients (pts) using pooled data from FUTURE 2 and FUTURE 3 studies.

Methods: Study designs have been reported previously.^{1,2} The results are reported only for SEC 300 and 150 mg (approved doses). Pts with baseline (BL) enthesitis (BLE) or without BLE (No BLE) were included. Evaluation through Week (Wk) 104 included: time to first resolution of enthesitis (i.e. EC = 0); shift analysis of BL EC (1 or 2 or 3–6) to full resolution (FR) and partial resolution (PR; reduction of EC) at Wks 24 and 104; and number of new enthesitis sites developed in pts with No BLE. Individual status over time with respect to resolution of EC was also determined by heat map analysis using last observation carried forward. Data are as observed in the overall population; time to first resolution of enthesitis was analyzed in the overall population and by prior use of tumor necrosis factor inhibitor (TNFi-naïve and – inadequate responders [IR]).

Results: A total of 466 pts had BLE with a mean EC of 3.1±1.6, and 246 pts had no BLE. Median days to resolution of EC in BLE pts for SEC 300, 150 mg and PBO groups were 57, 85 and 167 in overall population; 57, 85 and 120 in TNFi-naïve pts; and 92, 82 and 169 in TNFi-IR pts, respectively. In pts with BL EC = 1 or 2, 72%/61% (SEC 300 mg), 71%/66% (SEC 150 mg) and 45%/44% (PBO), respectively, achieved FR at Wk 24, with FR in SEC groups sustained or increased to 77%/81% (SEC300 mg) and 75%/88% (SEC 150 mg) at Wk 104. In BL EC = 3–6, 81% (SEC 300mg), 73% (SEC 150 mg) and 71% (PBO) of pts achieved FR and PR at Wk 24, with an increase of FR and PR to 88% (in both SEC 300 and 150 mg) at Wk 104 (Figure). A total of 89% of pts with No BLE did not develop enthesitis by Wk 104. Heat map analysis showed that SEC-treated pts at individual level had more resolution of EC than PBO pts at Wk 24.

Conclusion: Time to resolution of enthesitis was earlier with SEC than PBO in the overall population, with faster resolution observed in TNFi-naïve than TNFi-IR pts. Majority of SEC-treated pts with BL EC = 1 or 2 had FR by Wk 24, with further improvement by Wk 104. In pts with BL EC = 3–6, greater improvement was observed with SEC 300 mg vs PBO in the proportion of pts with FR and PR of enthesitis at Wk 24; further improvements were observed in both SEC groups at Wk 104.

References: 1. McInnes IB, et al. *Lancet* 2015;386:1137–2. Nash P, et al. *Arthritis Res Ther* 2018;20:47.

Disclosure: L. C. Coates, AbbVie, Janssen, Novartis, Pfizer, 2, AbbVie, Amgen, BMS, Celgene, Pfizer, UCB, MSD, Boehringer Ingelheim, Novartis, Lilly, Janssen, Sun Pharma, Prothena, 5; D. McGonagle, Novartis, Janssen, Pfizer, AbbVie, 2, Novartis, Janssen, Pfizer, AbbVie, 8; G. Schett, BMS, Celgene, GSK, Lilly, Novartis, 2, AbbVie, BMS, Celgene, Janssen, Lilly, Novartis, UCB, 5, AbbVie, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, 8; P. J. Mease, AbbVie, Amgen, Biogen Idec, BMS, Celgene, Crescendo, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, 2, AbbVie, Amgen, Biogen Idec, BMS, Celgene, Covagen, Crescendo, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, 5, AbbVie, Amgen, Biogen Idec, BMS, Crescendo, Janssen, Lilly, Pfizer, UCB, 8; E. Quebe-Fehling, Novartis, 1, Novartis, 3; D. L. Asquith, Novartis, 1, Novartis, 3; L. Rasouliyan, Novartis, 5, RTI Health Solutions, 3; S. Mpofu, Novartis, 1, Novartis, 3; C. Gaillez, Novartis, 1, Novartis, 3.

Chronic Pain and Assessment of Pain Sensitivity in Patients with Established Axial Spondyloarthritis – a Cross-Sectional Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical V: Treatment of PsA and Peripheral SpA

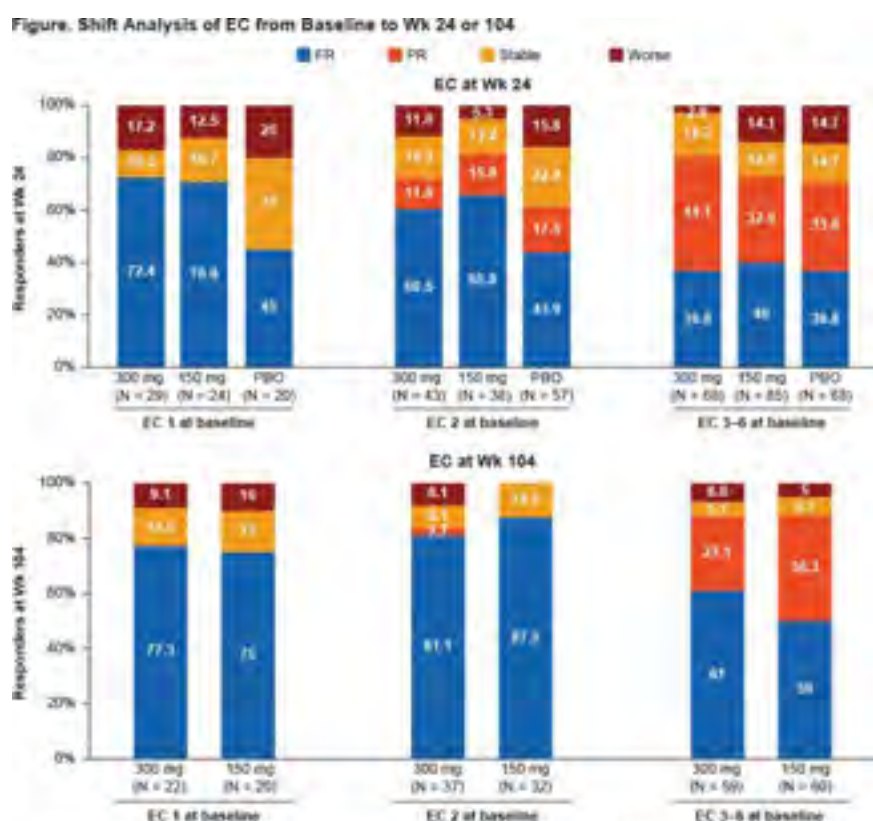
Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Pain remains a common and debilitating symptom in arthritis, despite good options to treat inflammation. In axial spondyloarthritis (axSpA), data on chronic pain remain scarce.

Objective: To assess self-reported and observed aspects of pain in subgroups of axial spondyloarthritis (axSpA), and to investigate associations between these pain aspects and different health outcome measures.

Methods: A cross-sectional study of patients with axSpA (ankylosing spondylitis (AS) and undifferentiated spondyloarthritis (USpA, based on ICD 10 codes)), consecutively enrolled in the SPARTAKUS cohort (n=226). Of 197 patients, for whom all relevant information was available, 173 patients fulfilled the ASAS axSpA criteria, and 115 the modified New York criteria. We investigated self-reported pain (intensity, duration, and distribution) and categorized patients into chronic widespread pain, chronic regional pain and no chronic pain. In addition, pain sensitivity (pain threshold, pain tolerance



and temporal summation of pain), was assessed by computerized cuff pressure algometry (CPA). Comparisons between AS and USpA and between women and men were performed using Student's t-test or Chi-squared test. Associations of pain sensitivity measures and different health outcome measures, adjusted for age and sex, were analyzed by multivariate linear regression.

Results: All assessed pain measures, except for number of pain regions, were similar in AS and USpA. Almost 50% of the axSpA patients, reported chronic widespread pain (AS 42%, USpA 53%), which was more pronounced in women (60% vs. 34% for men, $p<0.001$). For pain sensitivity measures, women had lower pain tolerance as compared to men (AS ($p=0.03$), USpA ($p=0.01$)), while pain threshold was lower only for women with USpA ($p<0.01$) (Table). Furthermore, irrespective of diagnosis subgroup, lower pain tolerance was associated with higher disease activity, more fatigue and less spinal mobility.

Conclusion: In this population-based, cross-sectional study of established axial spondyloarthritis, chronic widespread pain was common, affecting 50% of the patients. A clear sex difference was found, with women reporting worse measures for both self-reported pain and pain sensitivity. Overall, lower pain tolerance was associated with worse disease activity, fatigue and spinal mobility. CPA shows promising results regarding assessment of pain sensitivity and provides additional information in pain evaluation in AxSpA.

Table Comparisons of clinical characteristics and pain variables for AS and USpA and by women and men

Variables	AS				USpA				AS vs. USpA p-value
	All n = 110	Women n = 36	Men n = 74	p-value	All n = 116	Women n = 79	Men n = 37	p-value	
Age, years	56 (13)	56 (12)	55 (13)	0.681	48 (13)	46 (12)	51 (14)	0.082	≤ 0.001
Symptom duration, years	30 (14)	31 (14)	29 (14)	0.477	21 (13)	19 (12)	24 (15)	0.048	≤ 0.001
HLA-B27 pos, n = 218, n (%)	89 (82)	25 (69)	64 (86)	0.012	64 (58)	37 (47)	27 (73)	0.002	≤ 0.001
ASDAS-CRP	1.9 (1.0)	2.3 (0.9)	1.8 (1.0)	0.016	2.0 (0.9)	2.1 (0.9)	1.7 (1.0)	0.029	0.756
Pain group, n (%) NCP	27 (25)	2 (6)	25 (35)	$\leq 0.001^*$	20 (17)	10 (13)	10 (27)	0.161*	0.212*
CRP	35 (32)	9 (25)	26 (37)		35 (30)	25 (32)	10 (27)		
CWP	45 (42)	25 (69)	20 (28)		61 (53)	44 (56)	17 (46)		
Pain regions, no	4.4 (4.0)	7.1 (3.9)	3.1 (3.5)	≤ 0.001	5.6 (4.3)	6.1 (4.2)	4.4 (4.3)	0.044	0.039
Pain threshold	32.0 (16.6)	27.9 (15.3)	34.1 (17.0)	0.101	29.5 (12.2)	27.3 (11.5)	34.8 (12.4)	0.007	0.247
Pain tolerance	64.6 (28.2)	55.3 (28.0)	69.3 (27.3)	0.028	60.4 (24.3)	56.4 (22.1)	70.2 (26.8)	0.012	0.293
TSI	0.72 (0.52)	0.78 (0.52)	0.68 (0.52)	0.431	0.60 (0.52)	0.58 (0.56)	0.65 (0.42)	0.565	0.148
Pain, 0-100	33 (27)	49 (26)	26 (25)	≤ 0.001	39 (27)	42 (27)	32 (27)	0.069	0.138
Pain > 40 mm, n (%)	40 (37)	22 (61)	18 (24)	≤ 0.001	55 (48)	40 (51)	15 (41)	0.372	0.104
Fatigue, 0-100	36 (27)	54 (24)	28 (24)	≤ 0.001	42 (30)	44 (30)	38 (30)	0.268	0.127
Global health	34 (26)	46 (26)	28 (24)	0.001	38 (26)	41 (26)	31 (27)	0.069	0.241
EQ-5D	0.72 (0.23)	0.62 (0.28)	0.77 (0.19)	0.001	0.65 (0.29)	0.63 (0.29)	0.71 (0.29)	0.192	0.069
HADS anxiety	5.3 (3.8)	5.4 (4.3)	5.2 (3.5)	0.843	6.2 (3.9)	6.3 (4.1)	5.9 (3.5)	0.600	0.083
depression	4.2 (3.1)	4.5 (3.8)	4.0 (2.8)	0.465	4.5 (3.4)	4.2 (3.3)	4.9 (3.6)	0.300	0.491
BASDAI	3.1 (2.3)	4.5 (2.0)	2.4 (2.2)	≤ 0.001	3.8 (2.3)	4.1 (2.2)	3.1 (2.3)	0.043	0.032
BASFI	2.4 (2.4)	3.2 (2.3)	2.0 (2.4)	0.016	2.5 (2.3)	2.8 (2.4)	1.9 (2.1)	0.054	0.704
BASMI	3.6 (1.8)	3.0 (1.2)	3.9 (1.9)	0.014	2.5 (1.1)	2.5 (1.1)	2.4 (1.2)	0.903	≤ 0.001
MASES	4.0 (3.8)	6.2 (3.6)	3.0 (3.4)	≤ 0.001	6.1 (3.8)	7.2 (3.6)	3.7 (3.1)	≤ 0.001	≤ 0.001
Smoking, n (%) ever	51 (47)	14 (39)	37 (50)	0.220*	45 (39)	29 (37)	16 (43)	0.501*	0.203*
never	57 (53)	22 (61)	35 (47)		71 (61)	50 (63)	21 (49)		
BMI, n (%) 18.5-24.9	40 (37)	16 (44)	24 (32)	0.197*	48 (44)	35 (44)	13 (35)	0.367	0.503*
25-29.9	41 (38)	9 (25)	32 (43)		34 (31)	20 (25)	14 (38)		
>30	28 (26)	10 (28)	18 (24)		28 (26)	20 (25)	8 (22)		
Ongoing treatment, csDMARDs, n (%)	23 (21)	12 (33)	11 (15)	0.025	27 (23)	22 (28)	5 (14)	0.089	0.668
bDMARDs, n (%)	48 (44)	15 (42)	33 (45)	0.771	53 (46)	35 (44)	18 (49)	0.662	0.756
Glucocorticoids, n (%)	9 (8)	1 (3)	8 (11)	0.144	14 (12)	10 (13)	4 (11)	0.776	0.346

Presented with mean and standard deviation (SD) unless otherwise indicated,

* for all

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Concomitant Csdmards Influence Clinical Response to TNF Inhibitors Only in Overweight Patients with Axial Spondyloarthritis

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Session Information

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Background/Purpose: In patients with axial spondyloarthritis (axSpA), the use of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), such as methotrexate (MTX) and sulfasalazine (SSZ), as well as the body mass index (BMI) have been associated with circulating TNFi levels. Recently, BMI has also been associated with TNFi clinical response but csDMARDs have not shown any significant clinical improvement for axial manifestations [1]. However, no study has assessed in the same population the influence of both factors -csDMARDs and BMI- on drug serum levels and clinical response.

To investigate the influence of csDMARD and BMI on circulating drug levels and clinical response to TNFi therapy in axSpA patients

Methods: A 1-year follow-up prospective observational study with two cohorts (Madrid and Amsterdam) including 180 axSpA patients treated with standard doses of infliximab (41%) or adalimumab (59%). Laboratory and clinical parameters were collected every 6 months. Patients were stratified by BMI: normal-weight (18.5-24.9 kg/m²) and overweight-obesity (>25.0 kg/m²). TNFi trough levels were measured by capture ELISA [2]. Clinical response to TNFi was defined as ΔBASDAI≥2. The association between concomitant csDMARDs and BMI with drug levels and clinical response to TNFi at 1 year was analysed through multivariate log-regression models (odds ratio and 95% CI). The presence of significant interactions between covariates was tested and all models were adjusted for age, gender, HLA-B27, disease duration, TNFi-type (for drug levels) and baseline BASDAI and CRP (for clinical response)

Results: Seventy-nine out of 180 patients (44%) received concomitant csDMARDs (MTX 14%, SSZ 20% and MTX+SSZ 10%), 78 (43%) patients were normal-weight and 102 (57%) overweight-obese. Mean (SD) age and disease duration was 47 (13) and 11 (9) years respectively, 59% were males, 73% HLA-B27+ and 78% had r-axSpA. Concomitant csDMARDs (OR: 3.82; IC 95%: 1.06-13.84) and being overweight-obese (OR: 18.38; IC 95%: 2.24-150.63) were independently associated with serum TNFi drug presence. Furthermore, a significant interaction between csDMARDs and BMI with clinical response was found. While the use of concomitant csDMARD contributed positively to achieve clinical response in overweight-obese patients (OR: 7.86; IC 95%: 2.39-25.78), no association was found for normal-weight patients (OR: 1.10; 0.33-3.58). Additionally, sensitivity analysis using remission status and ASDAS were performed and showed results along the same line

Conclusion: In patients with axSpA, TNFi drug persistence is positively influenced by the use of concomitant csDMARDs and especially by being normal-weight. However, TNFi clinical response is associated with the use of concomitant csDMARDs only in overweight-obese, but not in normal-weight patients. Based on this, the use of concomitant csDMARDs in patients with axSpA could be beneficial in overweight patients

References: [1] van der Heijde D, et al. *Ann Rheum Dis*. 2017;76(6):978-991; [2] Pascual-Salcedo D, et al. *Rheumatology (Oxford)*. 2011;50(8):1445-52

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Inhibition of Radiographic Progression and Correlation with Changes in Composite Indices of Disease Activity in Patients with Active Psoriatic Arthritis Treated with Intravenous Golimumab, As Measured in a Phase III Trial

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Background/Purpose: GO-VIBRANT is a Phase 3 trial of intravenous (IV) golimumab (GLM), an anti-tumor necrosis factor alpha (TNF α) monoclonal antibody, in adult patients (pts) w/ active psoriatic arthritis (PsA). To assess whether changes in Clinical Disease Activity Index (CDAI), Disease Activity in Psoriatic Arthritis (DAPSA) score, Minimal Disease Activity (MDA), & Very Low Disease Activity (VLDA) disease activity measures correlate w/ X-ray progression.

Methods: In this multicenter, randomized, double-blind, placebo (PBO)-controlled trial, 480-bonaïve PsA pts w/ active disease (≥ 5 swollen & ≥ 5 tender joints, C-reactive protein ≥ 0.6 mg/dL, active plaque psoriasis or documented history, & despite treatment w/ csDMARDs &/or NSAIDs) received IV GLM 2 mg/kg (N=241) at Wks 0 & 4 then q8 wks or PBO (N=239) at Wks 0, 4, 12, & 20 w/ crossover to GLM at Wk24. In this post-hoc analysis, disease activity measures CDAI, DAPSA score, MDA, & VLDA were associated w/ X-ray progression from baseline to Wk24 & baseline to Wk52. Total modified van der Heijde-Sharp (vdH-S) score was used to assess X-rays at Wks 0, 24, & 52. Imputation rules were applied for all variables using last observation carried forward for partially missing data & non-responder imputation for completely missing data.

Results: Changes in all disease activity measures appeared to be correlated w/ X-ray progression (Table). GLM-treated pts had less X-ray progression regardless of disease activity measure used. GLM-treated pts in remission or in low disease activity (LDA) tended to have less X-ray progression at Wk52 vs pts in moderate or high disease activity categories (mean change in CDAI: remission -1.06, low activity -0.81, moderate activity 0.20, high activity 1.11). Irrespective of level of disease activity, GLM-treated pts from Wk0-52 tended to have less X-ray progression vs PBO-treated pts who switched to GLM at Wk24 (mean change in CDAI 0-52 wk GLM vs PBO: remission -1.06 vs 1.52, low activity -0.81 vs 1.21, moderate activity 0.20 vs 1.32, high activity 1.11 vs 1.75). GLM-treated pts w/ DAPSA scores ≤ 28 at Wk0-52 tended to have less X-ray progression (mean change -0.74) vs pts w/ scores > 28 (mean change 0.41). Pts treated w/ GLM who despite not achieving MDA or VLDA by Wk52 also tended to have far less X-ray progression vs PBO pts (mean change MDA PBO 1.50 vs GLM 0.03; $p < 0.0011$ & mean change VLDA PBO 1.45 vs. -0.30; $p < 0.0001$).

Conclusion: In this analysis, all disease activity measures generally correlated w/ X-ray progression from baseline to Wk24 & baseline to Wk52. Higher disease activity was associated w/ increased X-ray progression. GLM-treated pts not achieving MDA & VLDA at Wk52 tended to have less X-ray progression vs PBO \rightarrow GLM pts. GLM's ability to inhibit X-ray progression, despite pts not being in clinical remission or LDA, illustrates an example of "disconnect" between clinical outcomes & X-ray findings seen in other studies.

Table. Mean change from baseline (SD) in total modified vdH-S score stratified by CDAI, DAPSA, MDA, & VLDA in PsA pts from GO-VIBRANT

	Baseline to Wk24		Baseline to Wk52	
	PBO	GLM 2 mg/kg	PBOa	GLM 2 mg/kg
CDAI at Wk24 or Wk52				
Remission (≤ 2.8), n	5	43	58	63
Mean change (SD)	-0.60 \pm 1.34	-0.80 \pm 1.76	1.52 \pm 5.55	-1.06 \pm 2.41
Median	0	-0.5	0	0
Range	-3.00, 0.00	-5.00, 2.00	-6.50, 33.23	-8.50, 6.00

Table . (Cont'd)

	Baseline to Wk24		Baseline to Wk52	
	PBO	GLM 2 mg/kg	PBOa	GLM 2 mg/kg
p-value ^b		0.917		0.0003
Low disease activity (>2.8 & £10), n	28	98	78	92
Mean change (SD)	0.77±2.01	-0.41±1.43	1.21±3.59	-0.81±2.12
Median	0.5	0	0	0
Range	-4.50, 5.50	-5.00, 2.50	-7.00, 15.50	-7.90, 3.00
p-value		0.0011		<0.0001
Moderate disease activity (>10 & £22), n	67	66	64	69
Mean change (SD)	0.88±2.73	-0.10±2.04	1.32±4.25	0.20±2.82
Median	0	0	0	0
Range	-4.50, 12.92	-7.50, 7.50	-5.77, 21.71	-7.29, 15.96
p-value		0.0429		0.0905
High disease activity (>22), n	137	30	37	13
Mean change (SD)	1.96±3.79	0.30±1.95	1.75±5.34	1.11±2.65
Median	0.5	0	0	0
Range	-3.50, 19.00	-3.50, 8.00	-1.50, 29.61	-2.50, 7.50
p-value		0.0079		0.8144
DAPSA at Wk24 or Wk52				
£28, n	47	166	171	183
Mean change (SD)	0.22±1.87	-0.53±1.62	1.45±4.66	-0.74±2.17
Median	0	0	0	0
Range	-4.50, 5.50	-5.50, 3.36	-7.00, 33.23	-8.50, 6.00
p-value		0.0046		<0.0001
>28, n	190	71	66	54
Mean change (SD)	1.77±3.56	0.21±1.97	1.27±4.36	0.41±3.30
Median	0.5	0	0	0
Range	-3.50, 19.00	-7.50, 8.00	-3.50, 29.61	-7.29, 15.96
p-value		0.0007		0.2598
MDA at Wk24 or Wk52				
Yes, n	11	78	80	101
Mean change (SD)	0.91±2.49	-0.83±1.78	1.19±3.86	-1.16±2.46
Median	0	0	0	0
Range	-3.00, 5.50	-7.50, 1.50	-7.00, 16.65	-8.50, 6.00
p-value		0.0232		<0.0001
No, n	226	159	157	136
Mean change (SD)	1.49±3.39	-0.05±1.70	1.50±4.90	0.03±2.44
Median	0.5	0	0	0
Range	-4.50, 19.00	-5.00, 8.00	-5.77, 33.23	-7.29, 15.96
p-value		<0.0001		0.0011
VLDA at Wk24 or Wk52				
Yes, n	1	16	24	35
Mean change (SD)	0±NA	-0.91±1.04	0.91±3.32	-1.49±2.22
Median	0	-1	0	-0.5
Range	0.00, 0.00	-3.00, 1.00	-4.00, 8.76	-8.00, 1.50
p-value		0.3749		0.0041
No, n	236	221	213	202
Mean change (SD)	1.47±3.36	-0.26±1.80	1.45±4.69	-0.30±2.52
Median	0.5	0	0	0
Range	-4.50, 19.00	-7.50, 8.00	-7.00, 33.23	-8.50, 15.96
p-value		<0.0001		<0.0001

CDAI=Clinical Disease Activity Index; DAPSA=Disease Activity in Psoriatic Arthritis score; GLM=golimumab; MDA=Minimal Disease Activity; NA=not available; PBO=placebo; PsA=active psoriatic arthritis; SD=standard deviation; VLDA=Very Low Disease Activity

a PBO pts crossed over to IV GLM at Wk24.

b P-value is based on ANOVA w/ Van der Waerden rank test

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Effect of Tapering of Tumor Necrosis Factor Inhibitor on Achieving Inactive Disease in Axial Spondyloarthritis Based on the 'Treat-to-Target' Strategy: A Nationwide Prospective Cohort Study

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Background/Purpose: Although recent treatment guideline of axial spondyloarthritis (axSpA) by the European League Against Rheumatism (EULAR) recommended that tapering of tumor necrosis factor inhibitor (TNFi) can be considered if a patient is in sustained remission, its efficacy compared to standard TNFi treatment has not been thoroughly investigated. Furthermore, whether the tapering strategy would affect the probability of achieving the optimal treatment target as recommended by 'Treat-to-Target' strategy is also unknown.

Methods: This was a nationwide, prospective cohort study including 776 axSpA patients in South Korea who had been receiving TNFi for at least 1 year with a 3-year follow-up. The effect of the tapering strategy on longitudinal disease activity was analyzed) by comparison of two groups according to patient's mean dose quotient (DQ) of TNFi during the observation (individual level) and 2) by comparison of 1-year intervals stratified by corresponding DQ (time level). The primary outcome was achieving Ankylosing Spondylitis Disease Activity Score (ASDAS) in active disease (ASDAS-CRP less than 1.3) in 1-year interval. The relationship between the dosing strategy and the primary outcome was analyzed using generalized estimating equations (GEE).

Results: A total of 776 patients, with an observation period of 1576 person-years were analyzed. Patients' mean (SD) age was 37.8 (12.5) years and 605 (78.0%) of them were male. HLA-B27 was positive in 644 (92.0%) patients. Overall, 454 patients had maintained the standard dose of TNFi during the follow up (control group), and 322 patients were exposed to at least one episode of tapering (tapering group).

Mean (SD) ASDAS-CRP at baseline in the control and tapering groups were 3.6 (1.0) and 3.6 (1.1), respectively. ASDAS inactive disease was achieved in 665 (42.3%) intervals and the probability of achieving the target was not changed according to the follow-up periods. At the individual level, longitudinal changes in ASDAS-CRP in both groups were comparable during the observation period (beta = 0.05 [95% confidence interval-0.11 to 0.20]). This result was consistent at the time level; a 1-year interval with reduced DQ showed comparable odds for achieving the treatment target in corresponding intervals (adjusted OR 1.09 [0.89 to 1.33]). However, after further stratification of reduced DQs based on

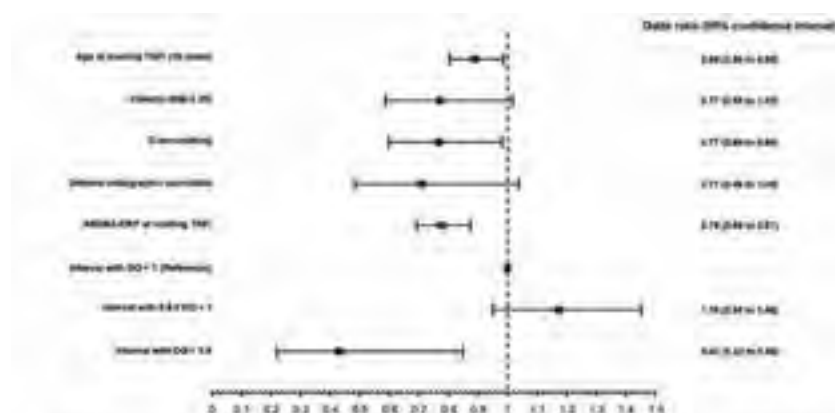


Figure. Forest plot indicating the probability for achieving the inactive disease (ASDAS < 1.3) analyzed using multivariable generalized estimating equation (GEE). DQ, Dose quotient of TNFi (maximum 1).

the intervals with DQ less than 0.5, those with DQ less than 0.5 were associated with decreased odds for achieving the optimal target (adjusted OR 0.43 [0.22 to 0.85]) (Figure). Meanwhile, drug survival between the two groups was comparable.

Conclusion: Tapering (but not by less than 0.5 of DQ) of TNFi showed a comparable efficacy to standard-dose TNFi treatment in achieving the optimal target in axSpA patients who had received TNFi for more than a year.

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Abstract Number: 2891

Eligibility Criteria for TNFi Therapy in Axial Spa: Going Beyond Basdai

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical V: Treatment of PsA and Peripheral SpA

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: ABASDAI ≥ 4 has often been required to start TNF inhibitors (TNFi) therapy in patients with axial SpA (axSpA). However, this cut-off of high disease activity (HDA) is largely arbitrary. Unlike BASDAI, the Ankylosing Spondylitis Disease Activity Score (ASDAS) incorporates objective measures (e.g. CRP) and has a validated definition of HDA (≥ 2.1). It has thus been suggested that ASDAS could also be used to guide treatment decisions, but evidence to support this is still scarce.

Our objective was to compare the impact of applying the ASDAS and BASDAI definitions of HDA in selecting patients for TNFi-treatment in daily clinical practice.

Table 1. TNFi response criteria across subgroups according to BASDAI/ASDAS category ('efficacy population')

Variables	Overall (N= 296) *	ASDAS ≥ 2.1		ASDAS < 2.1		p-value **
		BASDAI ≥ 4 (N=256)	BASDAI < 4 (N=34)	BASDAI ≥ 4 (N=1)	BASDAI < 4 (N=5)	
Outcomes - 3 months, n (%)						
ASAS20	159 (59)	142 (60)	15 (56)	0 (0)	7 (40)	0.48
ASAS40	127 (47)	111 (46)	14 (52)	0 (0)	2 (40)	0.74
ASAS PR	73 (24)	56 (33)	14 (50)	0 (0)	3 (60)	<0.01
BASDAI50	184 (62)	160 (62)	21 (62)	0 (0)	3 (60)	0.04
ASDAS CR	207 (70)	179 (70)	26 (77)	0 (0)	2 (40)	0.16
ASDAS MI	128 (42)	111 (41)	12 (35)	0 (0)	0 (0)	0.16
ASDAS ID	90 (30)	68 (26)	20 (59)	0 (0)	4 (80)	<0.01
Outcomes - 6 months, n (%)						
ASAS20	160 (61)	159 (61)	1 (6)	0 (0)	3 (60)	0.67
ASAS40	124 (46)	104 (45)	17 (57)	0 (0)	3 (60)	0.43
ASAS PR	74 (27)	57 (24)	13 (48)	0 (0)	4 (80)	<0.01
BASDAI50	188 (64)	167 (65)	18 (51)	0 (0)	3 (60)	0.29
ASDAS CR	216 (73)	190 (74)	25 (74)	0 (0)	1 (20)	0.02
ASDAS MI	128 (43)	117 (46)	11 (32)	0 (0)	0 (0)	0.08
ASDAS ID	84 (28)	68 (25)	17 (50)	0 (0)	4 (80)	<0.01

* AxSpA patients treated with TNFi, with complete 6 months of follow-up and data for BASDAI/ASDAS at every time point. ** Comparison between subgroups according to BASDAI/ASDAS category for disease activity (NCR) for categorical variables and Fisher's exact test for categorical variables. ASDAS: Assessment of Spondyloarthritis International Society; BASDAI: Bath ankylosing spondylitis disease activity index; ASAS: Ankylosing Spondylitis Disease Activity Score; ASAS20: ASAS clinical remission; ASAS40: ASAS clinical remission; ASAS PR: ASAS partial remission; BASDAI50: BASDAI clinical remission; ASDAS CR: ASDAS clinical remission; ASDAS MI: ASDAS moderate improvement; ASDAS ID: ASDAS severe improvement.

Methods: Patients from Reuma.pt (Rheumatic Diseases Portuguese Register), with diagnosis of axSpA according to their rheumatologists (both treated and not treated with their first TNFi), with complete baseline BASDAI and ASDAS data and complete 6-month of follow-up (i.e. baseline, 3 and 6 months visits available) were included. Four subgroups [cross-tabulation between ASDAS (≥ 2.1) and BASDAI (≥ 4) definitions of HDA], were compared according to baseline demographic and clinical characteristics in the 'eligible population' (i.e. irrespective of TNFi-treatment). In addition, for patients starting TNFi and with complete follow-up BASDAI/ASDAS data ('efficacy population'), the subgroups were also compared according to different response criteria (Table 1), at 3 and 6 months.

Results: In total, 466 patients were included (59% males and 66% HLA-B27 positive). The large majority (n=382; 82%) fulfilled the definition of HDA according to both BASDAI and ASDAS at baseline (i.e. ASDAS ≥ 2.1 and BASDAI ≥ 4). The frequency of ASDAS ≥ 2.1 , if BASDAI < 4 , was much higher than the opposite condition (i.e. ASDAS < 2.1 , if BASDAI ≥ 4) (70% vs 0.5%). Compared to patients fulfilling both definitions, those who were ASDAS ≥ 2.1 only were more likely to be male (82.5% vs 54%), HLA-B27 positive (79% vs 54%), to show higher levels of CRP (2.6 (SD 2.5) vs 2.2 (2.8) mg/dL) and lower BASFI (3.1 (2.6) vs 5.6 (2.3)). In the 'efficacy population' (n=296), better responses were observed among patients with ASDAS ≥ 2.1 only, especially for the most 'stringent' outcomes [e.g. ASDAS inactive disease (ASDAS ID): 59% and 50%, at 3 and 6 months, respectively], compared to patients fulfilling both definitions (ASDAS ID: 26% and 25% at 3 and 6 months, respectively) (Table 1).

Conclusion: Our results show that the ASDAS-HDA definition (ASDAS ≥ 2.1) is more inclusive than the BASDAI-HDA definition (≥ 4) in selecting axSpA patients for TNFi treatment. Importantly, the additionally 'captured' patients respond better and have higher likelihood of predictors thereof. These results support the use of ASDAS ≥ 2.1 as a selection criterion for treatment decisions.

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Abstract Number: 2892

Safety and Immune Response of a Live Attenuated Herpes Zoster Vaccine in Patients with Systemic Lupus Erythematosus (SLE): A Randomized Placebo-Controlled Trial

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical IV: Clinical Outcomes

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: To evaluate the safety and immune response of a live attenuated herpes zoster (HZ) vaccine in patients with SLE by a randomized placebo-control trial (RCT).

Methods: Adult patients (age > 18 years) who fulfilled ≥ 4 ACR criteria for SLE and had a SLEDAI score < 6 with stable immunosuppressive treatment in the preceding 6 months were recruited. Exclusion criteria were: active infection, lymphocyte count $< 500/\text{mm}^3$, reduced IgG/A/M level, a history of malignancies, and current treatment with high-dose immunosuppression (eg. prednisone $> 15\text{mg/day}$, azathioprine $> 100\text{mg/day}$, mycophenolate mofetil $> 500\text{mg/day}$, cyclophosphamide and biological agents etc.). Participants were randomly assigned to either HZ vaccine (@Zostavax) or placebo given subcutaneously. Anti-VZV IgG reactivity was measured by a two-step enzyme linked fluorescence assay (VIDAS [Biomérieux]). An index value was computed and higher values reflect increased anti-VZV titers. Cell-mediated response to HZ was assessed by a specific VZV-stimulated IFN γ release ELISPOT assay. Disease activity of SLE was assessed by the SLEDAI. Unsolicited adverse events (AEs) at week 6 were compared between the two groups.

Results: 90 SLE patients were recruited (age 45.6 ± 14.1 years; 93% women): 45 assigned to vaccine and 45 to placebo. Baseline clinical characteristics and SLEDAI scores (1.58 ± 1.8 vs 1.64 ± 1.7 ; $p=0.86$) of the vaccine and placebo groups of

patients were similar. Proportion of patients who were using various immunosuppressive agents, and the baseline lymphocyte count, serum creatinine and IgG/A/M levels were also similar in the two groups. The baseline VZV IgG index value was 3.28 ± 1.19 and 3.45 ± 1.07 in the vaccine and control group of patients, respectively ($p=0.48$). The paired VZV IgG titer at week 6 was significantly higher in the vaccine than control group, even after adjustment for baseline value (4.16 ± 1.26 vs 3.32 ± 1.01 ; $p<0.001$), clinical characteristics, SLEDAI and other risk factors for HZ infection. The increase in VZV IgG antibody was significantly higher in the vaccinated than control patients ($+59.8\%$ vs -2.1% ; $p=0.01$). In 10 patients (5 vaccine; 5 placebo) who had undergone ELISPOT assay so far (the work is ongoing), the number of IFN γ -secreting CD4+ T cell colonies dropped from 32.8 ± 17 to 28.4 ± 12 in the placebo-treated patients but increased from 29.6 ± 4.5 to 55.0 ± 11.4 in vaccinated patients from week 0 to week 6. Twenty-one and 6 unsolicited AEs were reported in the vaccinated and control patients, respectively. Significantly more vaccinated patients reported pain and erythema at the injection site than controls (31% vs 7% ; $P<0.01$), and in all cases, symptoms were mild and self-limiting. Other AEs were minor and did not differ between the two groups. Two vaccinated patients (4.4%) had mild flare of skin/joint disease, and one control patients (2.2%) had mildly increase in proteinuria between week 0 and 6. No patients had evidence of HZ infection 6 weeks after vaccination.

Conclusion: In patients with stable SLE who were not receiving intensive immunosuppression, vaccination with the live attenuated HZ vaccine provoked an expected cell-mediated and humoral response. The HZ vaccine was well tolerated.

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Clinical Outcomes and Response to Anti-Thrombotic Treatment Among Patients with Concomitant Lupus Nephritis and Thrombotic Microangiopathy: A Multicenter Cohort Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical IV: Clinical Outcomes

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Session Time: 4:30 PM-6:00 PM

Background/Purpose: Renal vascular involvement is an important prognostic marker of lupus nephritis (LN). Among patients with various vascular changes, individuals with thrombotic micro angiopathy (TMA) present with severe clinical manifestations and have a high mortality.

We sought to assess renal outcomes and response to anti-thrombotic treatments in addition to conventional immunosuppression in patients with biopsy proven LN and TMA.

Methods: Clinical and renal histopathological data for 97 patients with biopsy-proven LN and TMA were retrospectively analysed. Antibody profiles, induction and maintenance therapies for LN, and anti-thrombotic treatments were collected. TMA lesions were classified into acute and chronic (Figure 1). A complete renal response (CR) was defined as proteinuria <0.5 g/24h and normal or near-normal (within 10% of normal GFR if previously abnormal) GFR. Partial Response (PR)

Acute TMA features	Chronic TMA features
•Endothelial swelling with partial or complete occlusion of lumina;	•Capillary wall thickening with double contours;
• Microthrombi, focal or global;	•Organizing capillary thrombi;
fragmented RBC on glomerular subendothelial space and/or mesangial areas;	•Glomerular ischemic collapse with afferent arteriolar occlusion;
•Mesangiolysis, focal, segmental/global;	•Segmental/global glomerulosclerosis
•Glomerular congestion with efferent arteriolar occlusion	

was defined as a $\geq 50\%$ reduction in proteinuria to subnephrotic levels and normal or near-normal GFR. Renal outcomes were assed at one year post biopsy.

Results: The mean age was 38.9 ± 15.2 years (range, 13–69 years). The study included 85 females (87.6%) and 12 males (12.4%). The clinical presentations were nephrotic syndrome, nephritic syndrome, and asymptomatic urinary abnormalities in 38(39.2%), 20 (20.6%), 39 (40.2%) patients, respectively. Nine patients were classified Class III (9.3%, including 2 as Class III + V), 82 as Class IV(84.5%, 10 as Class IV-segmental(IV-S) (10.3%) and 72 as Class IV-global (IV-G)(74.2%), including 4 as Class IV-G + V) and 6 as Class V (6.2%). Forty-two(43%)patients presented with acute and 55 (57%) with features of chronic TMA. All patients had received treatment with standard immunosuppressants (55% mycophenolate, 39% cyclophosphamide, 6% other regimen) and steroids.

At 12 months, CR was observed in 37 patients (38.1%), PR in 22 (22.6%) and no response in 38 (39.1%). Sixty-one patients (62.9%) were antiphospholipid positive (aPL) and 37 (38.1%) received anticoagulation with vitamin-K antagonist (VKA) and/or heparins. Presence of aPLs(OR, 2.4; 95% confidence interval-CI-, 1.2–7.3; $p = 0.03$), anti-DNA positivity (OR, 12.8; 95% CI 3.0–71.3; $p = 0.002$), and chronic features of TMA (OR, 3.0; 95% CI 1.2–17.5; $p = 0.04$) were all found to be associated with no response. When limiting the analysis to a PL positive patients, after adjusting for type of immunosuppressant therapy and LN class on biopsy, variables that were significantly associated with CR+PR were features of acute TMA rather than chronic (OR, 8.62;95% CI 1.4–97.1; $p = 0.03$) and the use of VKA/heparins(OR, 2.1; 95% CI, 1.02–16.2; $P = 0.046$)

Conclusion: In patients with concomitant LN and TMA, the presence of aPL and chronic features of TMA were associated with poorer renal outcomes. In patients with aPL, the use of anticoagulation appeared protective and warrants further investigation as a therapeutic tool, especially in the setting of acute TMA.

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Abstract Number: 2894

Psychosis in Systemic Lupus Erythematosus: Results from an International, Inception Cohort Study

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical IV: Clinical Outcomes

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Background/Purpose: Psychosis, one of the rarer neuropsychiatric (NP) events in lupus patients, features in both the ACR and Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE. Our objective was to determine, in a multi-ethnic/racial, prospective SLE inception cohort, the frequency, attribution, clinical and autoantibody associations with lupus psychosis and the outcome as assessed by physicians and patients.

Methods: A prospective study of new onset SLE patients was performed by an international network of 32 academic centers in 11 countries. Patients were evaluated at enrollment and annually for up to 17 years. Data were collected at each assessment on 19 NP events including psychosis, as per the ACR case definitions for NPSLE. Pre-defined decision rules were used to attribute the events to SLE and non-SLE causes. Demographic features, medications, SLE disease activity index-2000 (SLEDAI-2K), SLICC/ACR damage index (SDI) and SF-36 mental (MCS) and physical (PCS) component summary scores were also recorded. Plasma lupus anticoagulant (LAC), serum IgG anti-cardiolipin, anti- β_2 glycoprotein-I, anti-ribosomal P (anti-P) and anti-NR2 glutamate receptor antibodies were measured. Descriptive statistics, time to event analysis and linear regressions were used as appropriate and multivariable models included demographic, clinical and serological variables.

Results: Of 1,826 SLE patients, 88.8% were female, 48.8% Caucasian. The mean \pm SD age was 35.1 \pm 13.3 years, disease duration 5.6 \pm 4.2 months and follow-up 7.4 \pm 4.5 years. There were 31 psychotic events in 28/1,826(1.53%) patients and most patients [(26/28; 93%)] had a single event. In the majority of patients [25/28; (89%)] and events [28/31; (90%)] psychosis was attributed to SLE, usually within 3 years of SLE diagnosis. Concurrent therapies included corticosteroids 23/28 (82.1%) with a mean (SD) prednisone dose of 21.9 (14.9) mg/day, immunosuppressants 17/28 (60.7%), biologics 1/28 (3.6%), antipsychotic drugs 19/28 (67.9%) and antidepressants 11/28 (39.3%). In multivariable analyses, positive associations [hazard ratio and 95% confidence interval [HR (95% CI)] with lupus psychosis were prior SLE NP events [3.59,(1.16, 11.14), male sex [3.0, (1.20, 7.50)], younger age at SLE diagnosis [(per 10 years younger), 1.45 (1.01, 2.07)] and

African ancestry [4.59 (1.79,11.76)]. There was no association with SLE disease activity, organ damage or autoantibodies. Patients with psychosis had significantly lower concurrent SF-36 summary scores compared to patients without NP events (MCS: 38.9±13.3vs. 48.9±10.7;PCS: 38.9±11.0 vs. 44.1±10.9; p<0.001).By physician assessment 80% of psychotic events resolved by the second annual assessment following onset. For these patients there was a concurrent clinically significant improvement in both MCS (45.5±14.1) and PCS scores (43.2±10.9).

Conclusion: Psychosis is an infrequent but important manifestation of NPSLE. It occurs early after SLE onset, is usually mono-phasic and has a significant negative impact on health status. As determined by patient and physician report, the outcome is favorable for most patients.

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Abstract Number: 2895

Effect of Vitamin D on Serum Markers of Bone Turnover in SLE in a Randomized Controlled Trial

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Session Information

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Background/Purpose: Bone health in SLE is adversely affected by vitamin D deficiency, inflammatory cytokines including interferon (IFN)- α , and glucocorticoid use. We tested the hypothesis that vitamin D supplementation would increase bone formation and decrease bone resorption in an SLE clinical trial.

Methods: Vitamin D-deficient SLE subjects had completed a randomized controlled trial (NCT00710021) testing the effect of 2000 IU/d or 4000 IU/d vitamin D supplementation vs. placebo for 12 weeks upon the IFN gene signature. For this analysis, low- and high-dose vitamin D groups were analyzed together. All subjects met 1997 ACR SLE Classification Criteria, had inactive disease (SELENA-SLEDAI ≤ 4), and were taking <20 mg of prednisone daily at baseline. Serum 25 (OH) vitamin D and bone turnover markers (N-terminal propeptide of type 1 collagen [P1NP], a marker of bone formation, and C-telopeptide [CTX], a marker of bone resorption), were assayed in baseline and week 12 blood samples. Change in (Δ) P1NP, CTX, and 25(OH)D were calculated as week 12 minus baseline. Spearman rho estimated the correlation between Δ 25(OH)D and Δ bone turnover markers. We tested the effect of vitamin D supplementation vs. placebo on Δ P1NP and Δ CTX using Wilcoxon rank-sum tests in an intention-to-treat analysis. Subgroup analyses tested the effect of vitamin D among subjects with current glucocorticoid use and with a detectable IFN signature. Secondary analyses excluded bisphosphonate users and tested the effect of achieving vitamin D repletion (≥ 30 ng/mL).

Results: We analyzed 28 subjects randomized to vitamin D and 15 randomized to placebo. Baseline characteristics including P1NP and CTX were similar between groups. Mean age was 39.0 (SD 11.5) years, 93.0% were female, 48.8% Black, 41.8% White, and 39.5% used glucocorticoids at baseline. IFN signature was present in 83.7% at baseline. Sixty-five percent of subjects in the vitamin D group achieved repletion compared to none in the placebo group. Mean increase in 25(OH)D was 17.7 (SD 8.2) ng/mL in the vitamin D group vs. 2.9 (SD 4.9) ng/mL in the placebo group (p <0.01). Changes in 25(OH)D were not significantly correlated with Δ P1NP or Δ CTX. Changes in bone turnover markers were not significantly different in the vitamin D group vs. placebo group in the primary analysis (**Table**). The effect of vitamin D vs. placebo did not differ by glucocorticoid use. An increase in P1NP, suggesting bone formation, was observed in subjects without baseline IFN signature assigned to vitamin D, but this was not significantly different from placebo (p 0.16). Results

from the primary analysis were similar after excluding bisphosphonate users (n=4). Changes in bone turnover markers were not significantly different in those who did vs. did not achieve vitamin D repletion.

Conclusion: Vitamin D supplementation did not affect the 12-week change in bone turnover markers among SLE subjects in this trial.

Table. Effect of vitamin D vs. placebo on 12-week change in bone turnover markers

	ΔP1NP, ng/mL	p value	ΔCTX, ng/mL	p value
Primary analysis (n=43)				
Vitamin D (n=28)	-0.2 (-6.2, 4.7)	0.83	0.01 (-0.04, 0.02)	0.50
Placebo (n=15)	-1.1 (-6.8, 13.0)		-0.04 (-0.07, 0.03)	
Subgroup analyses				
Glucocorticoid use at baseline				
Yes (n=17)				
Vitamin D (n=12)	-0.4 (-5.1, 7.1)	0.96	0.01 (-0.04, 0.02)	0.33
Placebo (n=5)	-1.2 (-6.8, 3.8)		-0.04 (-0.05, -0.01)	
No (n=26)				
Vitamin D (n=16)	0.6 (-8.6, 3.8)	0.74	-0.01 (-0.06, 0.04)	0.90
Placebo (n=10)	0.3 (-4.9, 13.0)		-0.01 (-0.07, 0.05)	
Interferon signature at baseline				
Present(n=36)				
Vitamin D (n=25)	-0.5 (-8.3, 2.2)	0.51	0.01 (-0.05, 0.01)	0.22
Placebo (n=11)	-1.2 (-6.8, 13.2)		-0.04 (-0.08, 0.03)	
Absent (n=7)				
Vitamin D (n=3)	15.8 (10.8, 16.1)	0.16	0.03 (-0.04, 0.36)	0.87
Placebo (n=4)	0.3 (-5.0, 7.4)		0.02 (-0.03, 0.49)	

Presented as median (25th, 75th)

p values from Wilcoxon rank-sum tests

Disclosure: S. K. Tedeschi, None; C. Aranow, GlaxoSmithKline, 5, GlaxoSmithKline, 2, EMD Serrono, 2, Xencor, 2, UCB, Inc., 2, Takeda, 2, Janssen, 2; D. L. Kamen, None; M. S. LeBoff, NIH/NIAMS, 2, Amgen Inc., 1; B. Diamond, None; K. Costenbader, None.

Abstract Number: 2896

Increased Mortality Among Patients with Systemic Lupus Erythematosus after Hydroxychloroquine Discontinuation

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Session Information

Session Date: Tuesday, October 23, 2018

Session Title: Systemic Lupus Erythematosus – Clinical IV: Clinical Outcomes

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30 PM-6:00 PM

Background/Purpose: Hydroxychloroquine (HCQ) is near-universally recommended for patients with SLE. Use of this medication has previously been associated with a substantial survival benefit among SLE patients. We aimed to determine the potential temporal association between HCQ discontinuation and all-cause and cardiovascular disease (CVD) mortality.

Methods: We conducted a population-based case-control study using an administrative health database including the entire population in the province of British Columbia, Canada (over 5 million individuals). We identified cases with SLE who died, and for each case we identified up to three living controls with SLE matched on age, sex, and SLE disease duration. We used conditional logistic regression to assess the association between current use of HCQ or recent discontinuation of HCQ and the risk of all-cause and cause-specific mortality relative to remote HCQ users. Remote users were defined by a duration greater than 365 days between the last HCQ prescription and the index date (i.e., death date). Recent users had

Table 1. Risk of Death with Current Usage, Non-Usage, and Recent Discontinuation Compared with Remote Usage of Hydroxychloroquine Among Patients with Systemic Lupus Erythematosus

All-Cause Mortality	Cases, N	Controls, N	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Remote HCQ Users	72	106	1.0 (reference)	1.0 (reference)
Recent HCQ Discontinuers	65	34	3.03 (1.77-5.17)	3.78 (2.07-6.91)
Current HCQ users	32	156	0.30 (0.18-0.49)	0.35 (0.20-0.59)
HCQ Non-users	121	206	0.83 (0.55-1.24)	0.93 (0.59-1.44)
Cardiovascular Disease Mortality				
Remote HCQ Users	17	28	1.0 (reference)	1.0 (reference)
Recent HCQ Discontinuers	17	11	2.57 (0.96-6.92)	4.63 (1.31-16.42)
Current HCQ users	9	44	0.32 (0.12-0.87)	0.37 (0.11-1.27)
HCQ Non-users	40	59	1.11 (0.51-2.44)	1.15 (0.45-2.99)
Other Cause Mortality				
Remote HCQ Users	35	52	1.0 (reference)	1.0 (reference)
Recent HCQ Discontinuers	33	18	3.17 (1.45-6.93)	3.90 (1.56-9.75)
Current HCQ users	13	72	0.28 (0.14-0.58)	0.32 (0.14-0.71)
HCQ Non-users	37	95	0.89 (0.49-1.64)	1.18 (0.29-2.37)

a duration less than 365 days since the last HCQ prescription and index date. Current users had active HCQ prescriptions spanning the index date. Fully adjusted models included chronic kidney disease, Charlson comorbidity index, glucocorticoids, and cardiovascular medication use assessed at the time of SLE diagnosis.

Results: We identified 290 SLE cases who died and 502 matched controls among 792 individuals with SLE. The mean age at index date was 65.6 years for cases and 64.7 years for controls. The majority were female (87.9% of cases and 91.4% of controls). The mean SLE disease duration was 5.3 years for both groups. Adjusted odd ratios (ORs) for all-cause mortality relative to the remote users were 0.35 (95% CI: 0.20, 0.59) for current users and 3.78 (95% CI: 2.07, 6.91) for subjects who recently discontinued HCQ (**Table 1**). HCQ non-users had the same risk of death as remote users (OR 0.93 [95% CI: 0.59, 1.44]). Similar trends were seen for the risk of mortality due to CVD.

Conclusion: In this general population-based case-control study of SLE mortality, we found a nearly four-fold increased risk of death associated with recent HCQ discontinuation and a substantially increased risk of CVD death. The cause of this association is unknown. This could be partially explained by a direct protective effect of HCQ that is rapidly lost following discontinuation. However, there may also be an indirect association due to selective provider discontinuation or patient non-adherence with HCQ when patients become acutely ill. We also demonstrated a 65% reduced risk of death among current HCQ users compared with remote users. By leveraging remote users as the comparison group, we reduced the potential for confounding by indication. Further studies are needed to explain the temporal relationship between HCQ discontinuation and SLE mortality.

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Abstract Number: 2897

Hydroxychloroquine Blood Levels Show Significant Trend Test for Risk of Retinopathy

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Session Information

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Session Title: Systemic Lupus Erythematosus – Clinical IV: Clinical Outcomes

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Session Time: 4:30 PM-6:00 PM

Background/Purpose: Hydroxychloroquine (HCQ) retinopathy after 10 years or more of use is more frequent than previously appreciated. This led to new ophthalmology guidelines that changed the recommended dosing from 6.5 mg/kg to 5 mg/kg. However, it is not clear that the lower dose of hydroxychloroquine will have the same efficacy for SLE activity or

the same protective role against cardiovascular risk factors and thrombosis. We asked whether hydroxychloroquine blood levels could help identify those at greater future risk of retinopathy.

Methods: We analyzed data on 477 SLE patients from a clinical cohort who had repeated assessments of HCQ blood concentrations, and were evaluated one or more times for retinopathy (306 single retinopathy exam, 115 two and 58 three or more assessments). The patients were 93% female and 42% Caucasian. Hydroxychloroquine blood levels were performed as previously described. In our analysis, HCQ toxicity was defined dichotomously by a retina expert: all those with a value of “No” or “Possible” were categorized as not having HCQ toxicity, and those who had a “Yes” were categorized as having it. Mean and maximum HCQ blood concentration over all cohort visits prior to the final retinopathy assessment were calculated. Risk of HCQ toxicity was then assessed in tertiles defined by these variables. The duration of hydroxychloroquine use (years in tertiles by distribution) and its association with HCQ toxicity were also examined.

Results: The risk of HCQ toxicity is shown in Table 1.

Table 1. Risk of HCQ retinal toxicity by variable.

Characteristic	No n (%)	Yes n (%)	p	P for Trend
Sex			0.0479	
Female	423 (96.1)	17 (3.9)		
Male	33 (89.2)	4 (10.8)		
Ethnicity			0.3165	
White	210 (94.2)	13 (5.8)		
Black	193 (96.5)	7 (3.5)		
Other	53 (98.2)	1 (1.8)		
Age			0.0001	<0.0001
<45	189 (99.5)	1 (0.5)		
45-59	157 (95.7)	7 (4.3)		
60+	110 (89.4)	13 (10.6)		
HCQ max			0.0923	0.045
1 (0 to 1194)	145 (98.6)	2 (1.4)		
2 (1195 to 1732)	137 (94.5)	8 (5.5)		
3 (1733 to 5873)	138 (93.9)	9 (6.1)		
HCQ duration			0.0003	
1 (0 to 8yrs)	145 (99.3)	1 (0.7)		
2 (9 to 15yrs)	148 (97.4)	4 (2.6)		
3 (16 to 52yrs)	139 (90.3)	15 (9.7)		
BMI	-	-	0.3025	0.034
<20	43 (97.7)	1 (2.3)		
20-25	151 (97.4)	4 (2.6)		
25-30	144 (95.4))	7 (4.6)		
30-35	66 (94.3)	4 (5.7)		
35+	50 (90.9)	5 (9.1)		

Patients had a variety of retinal testing done, with optical coherence testing most frequent. Table 2 shows the concordance of a test abnormality with the retina expert opinion.

Table 2. Performance of retinal imaging modalities relative to expert diagnosis

Test	Retinopathy N (%)	No Retinopathy N (%)
Ocular Coherence Tomography (OCT)		
Abnormal	23 (92%)	106 (15%)
Normal	2 (8%)	605 (85%)
Total	25	711
Electroretinogram (ERG)		
Abnormal	14 (100%)	142 (40%)
Normal	0 (0%)	210 (60%)
Total	14	352
Microperimetry (MP1)		
Abnormal	14 (100%)	98 (24%)
Normal	0 (0%)	307 (76%)
Total	14	405
Fundal Autofluorescence (FAF)		
Abnormal	16 (76%)	144 (24%)
Normal	5 (24%)	462 (76%)
Total	21	606

OCT Sensitivity = 85%, Specificity = 92%

ERG Sensitivity = 100%; Specificity = 60%

MP1 Sensitivity = 100%; Specificity = 76%

FAF Sensitivity = 76%; Specificity = 76%

Conclusion: Our data show that the risk of HCQ retinopathy increases in men, Caucasians, older patients and with duration (but the frequency was less than in other publications). For the first time, our data show the utility of HCQ blood levels in predicting retinopathy. This would allow clinicians to either decrease dose or increase monitoring in those with high blood levels. Our data also show the need for ophthalmologists with retinopathy expertise to interpret retina testing, as screening tests can be abnormal due to causes other than HCQ retinopathy. Stopping HCQ based on an abnormal test without confirmation from a retinopathy expert could needlessly deprive an SLE patient of an important medication.

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Increased Frequency of Circulating CD4+CXCR5-PD1hi Peripheral Helper T (cTph) Cells in Patients with Seropositive Early Rheumatoid Arthritis (RA)

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis II

Session Type: ACR Concurrent Abstract Session

Session Time: 9:00 AM-10:30 AM

Background/Purpose: A novel population of CD4+ T cells with B cell helping capacity has been described in the synovial tissues and peripheral blood of seropositive RA patients with an established disease, and termed ‘peripheral helper’ (Tph) cells (Rao DA et al, Nature 2017). Tph cells are characterized by the lack of CXCR5 together with a bright expression of PD-1 (CD4+CXCR5-PD-1hi T cells). As opposed to CD4+CXCR5+PD-1hi follicular helper T cells (Tfh), Tph cells are not located in lymphoid organs but accumulate in inflamed tissues. Tph cell numbers have not been previously examined in early RA (eRA). Therefore, our objective was to study the frequency of circulating CD3+CD4+CXCR5-PD-1hi Tph cells (cTph), in patients with eRA.

Methods: Peripheral blood was drawn from DMARD-naïve early RA patients (eRA) (2010 ACR criteria) with a disease duration <24 weeks (n=42), and healthy controls (HC) matched for age and gender (n=42). For comparison, blood was also drawn from 66 patients with established RA (disease duration > 2 years), 45 patients with Spondyloarthritis (SpA), and their age and gender-matched HC (one HC per patient). In addition, synovial fluid from 7 patients with established RA and 3 patients with SpA was examined. Established RA patients were receiving low-dose oral methotrexate and were naïve for biological agents. SpA patients were receiving NSAIDs, low-dose oral methotrexate and/or sulphasalazine and were naïve for biologicals. After isolation by Ficoll-Hypaque gradient, PBMCs were stained with antibodies to CD3, CD4, CXCR5, ICOS and PD-1, and examined by flow cytometry.

Results: The frequency of circulating CXCR5- cells gated for CD4+ T cells was not different among the studied groups. In contrast, eRA patients demonstrated an increased frequency of circulating CD4+CXCR5-PD-1hi Tph and CD4+CXCR5-PD-1hiICOS+ T cells. When examining seropositive (RF+ and/or ACPA+, n=25) and seronegative eRA patients (RF- and ACPA-, n=17) separately, it was evident that the above described alterations were only apparent in seropositive eRA. Likewise, increased cTph numbers were observed in seropositive (n= 47) but not seronegative (n=19) established RA, and not in SpA patients (n=45), which is consistent with data reported by Rao et al. Interestingly, this increased cTph cell frequency was observed only in seropositive RA patients with an active disease (DAS28>2.6, n=24), whereas the numbers of cTph cells in established RA patients who had achieved remission (DAS28<2.6, n=23) were not different from HC. Furthermore, Tph cells were present in the synovial fluid of seropositive RA (n= 4) but not of seronegative RA (n= 3) or SpA (n=3).

Conclusion: Tph cells may play an important role in the pathogenesis of seropositive but not seronegative RA. An increased cTph cell frequency is a marker of active, seropositive RA.

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Sustained Drug-Free Remission in Early RA Following Methotrexate-Based Strategy: Role of the JAK-STAT Pathway

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Session Information

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Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis II

Session Type: ACR Concurrent Abstract Session

Session Time: 9:00 AM-10:30 AM

Background/Purpose: We previously identified several co-expressed genes associated with achieving sustained drug-free remission (sDFR) following a methotrexate (MTX)-based strategy in early rheumatoid arthritis (RA).¹ The aim of the present analyses was to identify, within the same patients, inflammatory proteins associated with achieving sDFR and to study associated biological pathways and compare these with those previously found in the transcriptomic analyses.

Methods: Data was used from patients participating in the U-Act-Early trial who achieved sDFR (i.e. being drug-free for ≥ 3 months) after therapy with a treat-to-target MTX-based strategy ($n=10$).² When the treatment target, sustained remission (disease activity scores assessing 28 joints (DAS28) < 2.6 and ≤ 4 swollen joints for ≥ 24 weeks), was achieved, therapy was tapered and thereafter discontinued. Controls were patients without a drug-free period during the study ($n=7$). In baseline serum samples, 85 proteins were measured and analysed using multi-analyte profiling. Partial least square discriminant analysis (PLSDA) was used to identify relevant proteins, which were subsequently used for pathway analyses in the Genes Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases.

Results: Table 1 shows baseline clinical characteristics; no significant differences were found between those achieving sDFR vs. controls ($p > 0.14$). PLSDA identified 13 proteins, of which pathway analyses yielded 117 significant GO terms and 14 KEGG pathways (Fig. 1). Comparison of the significantly enriched pathways found in the transcriptomic analyses and those in the present study yielded 33 corresponding GO terms, including “janus kinase signal transducer and activator of transcription (JAK-STAT) cascade” ($p \leq 8.97 \times 10^{-3}$) and “positive regulation of tyrosine phosphorylation of STAT protein” ($p \leq 8.37 \times 10^{-3}$), which is important for signal transduction in the JAK-STAT pathway. Additionally, one KEGG pathway (“JAK-STAT signalling pathway”) was also found to be significantly enriched in both transcriptional and proteomic analyses ($p \leq 2.22 \times 10^{-4}$).

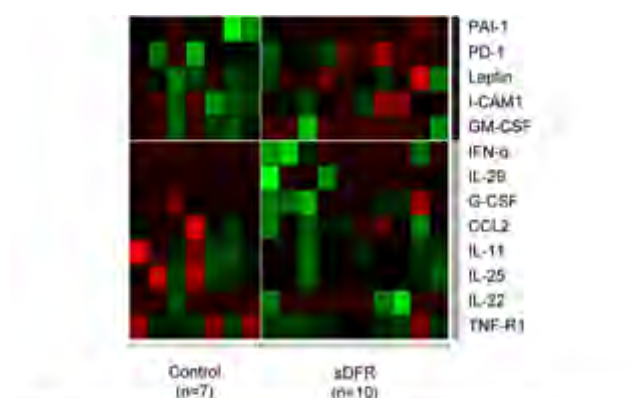


Figure 1: Clustered heatmap of the identified proteins. Red colour depicts a negative z-score (i.e. lower concentration) and green colour depicts a positive z-score (i.e. higher concentration). Proteins in the black cluster have on average a lower concentration (i.e. effect estimate ≤ 0) in the sDFR group and those in the grey cluster a higher concentration (i.e. effect estimate > 0).

Table 1: Baseline clinical characteristics		
	sDFR (n=10)	Controls (n=7)
Female gender	8 (80%)	6 (86%)
Age (yrs.)	50 (14)	46 (17)
BMI (kg/m ²)	29 (4)	26 (3)
Caucasian	10 (100%)	7 (100%)
Current smokers	1 (10%)	1 (14%)
Symptom duration (days)	30 (13-40)	31 (20-46)
Seropositive for RF	9 (90%)	5 (71%)
Seropositive for anti-CCP	7 (70%)	6 (86%)
CRP (mg/L)	11 (5-18)	5 (4-12)
ESR (mm/h)	25 (13-47)	16 (13-25)
DAS28 ^a	4.6 (1.2)	4.8 (0.9)
HAQ ^b	0.9 (0.6)	1.0 (0.5)
Sharp/van der Heijde score ^c	0 (0-1)	0 (0-0)
Data presented as mean (standard deviation), median (interquartile range), or n (%). ^a range 0-9.4; 9.4=maximum, ^b range 0-3; 3=maximum, ^c range 0-448; 448=maximum. Anti-CCP=anti-cyclic citrullinated peptide, BMI=body mass index, CRP=c-reactive protein, DAS28=disease activity score assessing 28 joints, ESR=erythrocyte sedimentation rate, HAQ=health assessment questionnaire, RF=rheumatoid factor.		

Conclusion: Biological processes important for effectively reducing inflammation in new-onset RA, treated to target with a MTX-based strategy, were found to be associated with activity of JAK-STAT signalling components. Involvement of this pathway was found both in the analyses of the transcriptome and proteome, demonstrating a specific JAK-STAT profile at baseline affects the immunosuppressive efficacy of MTX.

References:

1. Teitsma XM, *et al. Arthritis Res Ther* 2017;19:170.
2. Bijlsma JW, *et al. Lancet* 2016;388:343-55.

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Abstract Number: 2900

Impaired TCR Signaling Paves the Way for Cytokine Hyper-Responsiveness in Arthritogenic T Cells

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Session Information

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Background/Purpose: The inability to identify relevant arthritogenic CD4 T cells in patients and in murine disease models has limited our understanding of disease initiating events in rheumatoid arthritis (RA). To overcome this limitation, we took advantage of the dynamic expression pattern of Nur77 (*Nr4a1*)—a sensitive and specific marker of TCR signaling that is insensitive to cytokine stimulation—to identify antigen-activated CD4T cells in human RA and the SKG mouse model of autoimmune arthritis.

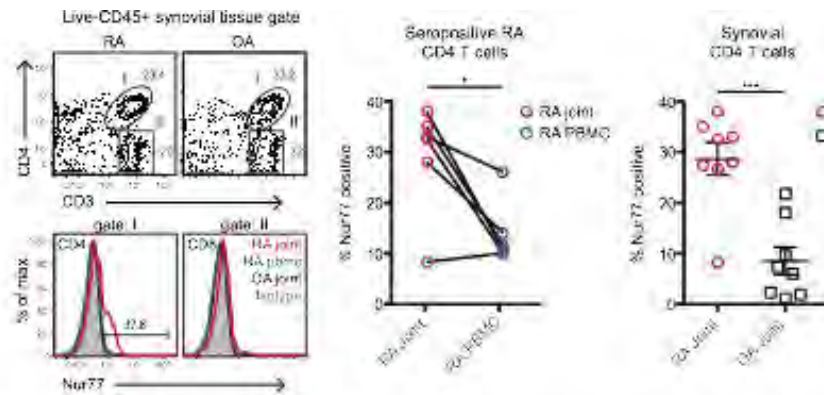


Figure 1. Frequency of Nur77⁺ antigen-activated CD4 T cells in seropositive RA synovium (left, middle, right) compared to matched RA PBMC (left, middle) and OA synovium (left, right).

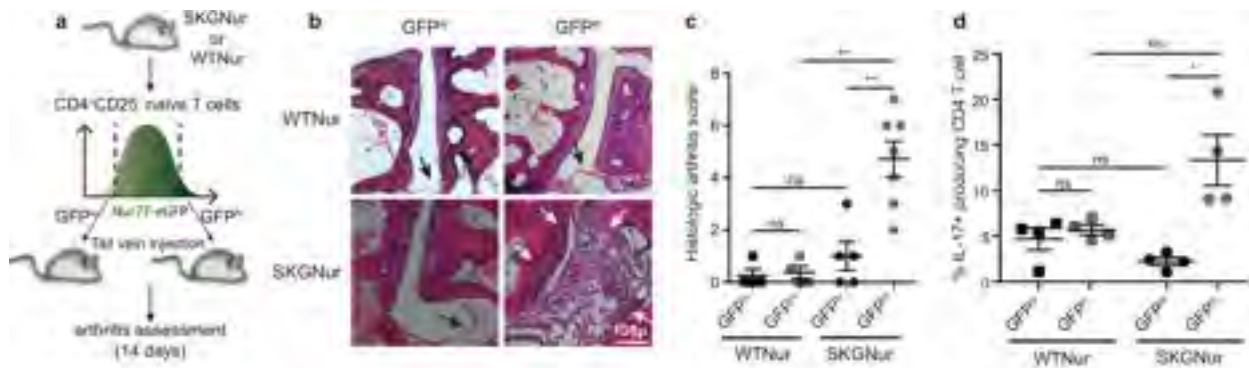


Figure 2. Nur77-eGFP marks arthritogenicity of CD4 T cells in SKGNur mice. (a) The 5% highest and 5% lowest Nur77-eGFP sorted CD4⁺CD25⁻ naive T cells were adoptively transferred into SCID recipients. (b) Joint histopathology by H&E. Black arrows indicate normal synovial lining and white arrows indicate synovial proliferation and early joint destruction. (c) Dot plot of blinded histology scores. (d) Frequency of IL-17 producing CD4 T cells from SCID recipient splenocytes.

Methods: We used intracellular flow cytometry to identify T cells that express Nur77 protein in synovial tissue and blood from patients with seropositive RA or osteoarthritis (OA), as well as in the SKG arthritis model. A fluorescent reporter (eGFP) of Nur77 expression was backcrossed into SKG mice (SKGNur) to identify and study arthritogenic T cells in this model. Functional and signaling differences between CD4 T cells that expressed the highest and lowest amounts of eGFP (GFP^{hi} and GFP^{lo}, respectively) were compared using *in vitro* assays, adoptive transfer, and gene expression assays. We searched general public repository databases for available transcriptome data from human RA synovium (13 studies met inclusion criteria comprising over 300 synovial samples) to examine candidate gene expression profiles.

Results: Nur77 expression was specifically enriched in a subset of synovial CD4 T cells from patients with RA (Fig 1). This suggested the presence of antigen-activated T cells in RA synovial tissue. This was confirmed in the SKG mouse. Higher levels of Nur77-eGFP (GFP^{hi}) in SKGNur CD4 T cells marked their autoreactivity and arthritogenic potential and their ability to more readily differentiate into IL-17 producing cells (Fig 2). T cells exhibiting this heightened auto reactivity still had diminished TCR signaling, perhaps due to upregulation of inhibitory receptors. Moreover, the enhanced autoreactivity was associated with upregulation of IL-6 cytokine signaling machinery, but a reduced amount of expression of suppressor of cytokine signaling 3 (SOCS3)—a key negative regulator of IL-6 signaling. As a result, the more autoreactive GFP^{hi} CD4T cell population from SKGNur mice was uniquely hyper-responsive to IL-6. Consistent with findings from SKGNur mice, *SOCS3* expression was similarly downregulated in RA synovium.

Conclusion: This suggests that, despite impaired TCR signaling, autoreactive T cells exposed to chronic antigen stimulation exhibit heightened sensitivity to IL-6 receptor signaling which contributes to their arthritogenicity in SKG mice, and perhaps in patients with RA.

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Sputum Neutrophils from Individuals at-Risk for RA Demonstrate Increased Citrullinated Histone H3 Containing Neutrophil Extracellular Traps That Correlate with Sputum Anti-Cyclic Citrullinated Peptide Antibody Levels

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Session Type: ACR Concurrent Abstract Session

Session Time: 9:00 AM-10:30 AM

Background/Purpose: Our group previously demonstrated that anti-citrullinated (cit) protein antibodies (ACPA) in the sputum correlate with remnants of neutrophil extracellular traps (NETs) in RA-free subjects At-Risk for future RA. Sputum neutrophils from these subjects also had increased ex vivo NET formation (NETosis) (*Okamoto ACR 2017*). However, it is unknown what specific features these sputum NETs contain and how they relate to inflammation and ACPA production in the lung. Of note, NETs variably contain cit proteins that can be targets of ACPA. Herein, we explored associations between ACPA and cit-histone H3 (cit-H3) in sputum NETs and local cytokines in the lung.

Methods: In 32 At-Risk subjects without synovitis yet At-Risk for RA because they were first-degree relatives (FDR) of RA patients (N=29) or serum ACPA(+) [N=13, 5/13 also FDRs] and in 16 serum ACPA(-) non-FDR healthy controls, we tested serum and induced sputum for ACPA using anti-cyclic cit peptide (CCP) ELISA (CCP3.1IgG/IgA, Inova). After incubation of sputum plugs for 1 hour without stimulation followed by staining with Hoechst 33342, anti-myeloperoxidase (MPO) and anti-cit-H3, we determined sputum neutrophils that had formed NETs ex vivo by microscopy. Separately, in sputum cell-free supernatant, the level of NET remnants was quantified by sandwich ELISA for the NET-specific protein complex DNA-cit-H3, and the levels of IL-1 β , IL-4, IL-6, IL-8, IL-10, TNF α and IFN γ were measured by Meso Scale Discovery assay.

Results: The% of sputum neutrophils that formed NETs was higher in serum CCP(+) At-Risk but not serum CCP(-) At-Risk subjects compared to controls (Figure 1A). However, the% of sputum neutrophils that formed NETs specifically expressing cit-H3 was higher in all At-Risk subjects (Figure 1B). In all At-Risk subjects, sputum anti-CCP levels significantly correlated with formation of cit-H3 containing NETs (Figure 1C) but not overall sputum NETosis. NET remnants containing DNA-Cit-H3 complexes also significantly correlated with sputum anti-CCP level ($r=0.80$, $p<0.001$). After accounting for multiple comparisons, sputum anti-CCP and DNA-cit-H3 levels significantly correlated with sputum levels of IL-6, IL-8, IL-10 and TNF α (Figure 2).

Conclusion: Sputum neutrophils in At-Risk subjects demonstrate increased cit-H3 expressing NETs that strongly correlate with sputum anti-CCP and multiple cytokines. These findings suggest that cit-H3-expressing NETosis in the lung may play a

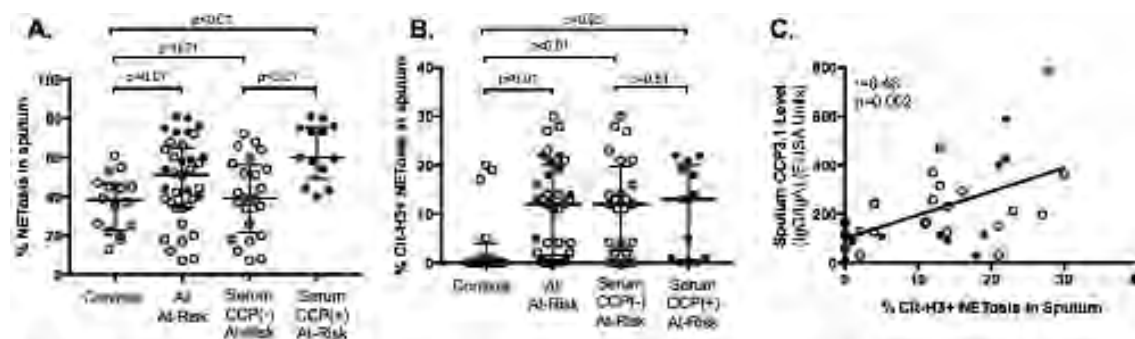


Figure 1. Sputum Cit-H3 expressing NETs are elevated in At-Risk subjects and correlate with sputum anti-CCP3.1 levels. The figure depicts the % NETosis in sputum in At-Risk subjects defined as the # of sputum neutrophils that formed NETs ex vivo at 1 hour without stimulation divided by the total # of sputum neutrophils (200 neutrophils counted per subject). Panel B depicts the % NETosis in sputum of At-Risk subjects but is limited to NETs staining positive for citrullinated histone H3 (Cit-H3+). Panel C depicts the correlation between sputum anti-CCP3.1 levels (y-axis) and the % of sputum neutrophils that underwent NETosis expressing Cit-H3 (x-axis) in At-Risk subjects. P-values were calculated using Mann-Whitney U testing (Panels A and B) and Spearman's correlation (Panel C). In all panels, * = Serum CCP3.1(+) At-Risk and ○ = Serum CCP3.1(-) At-Risk

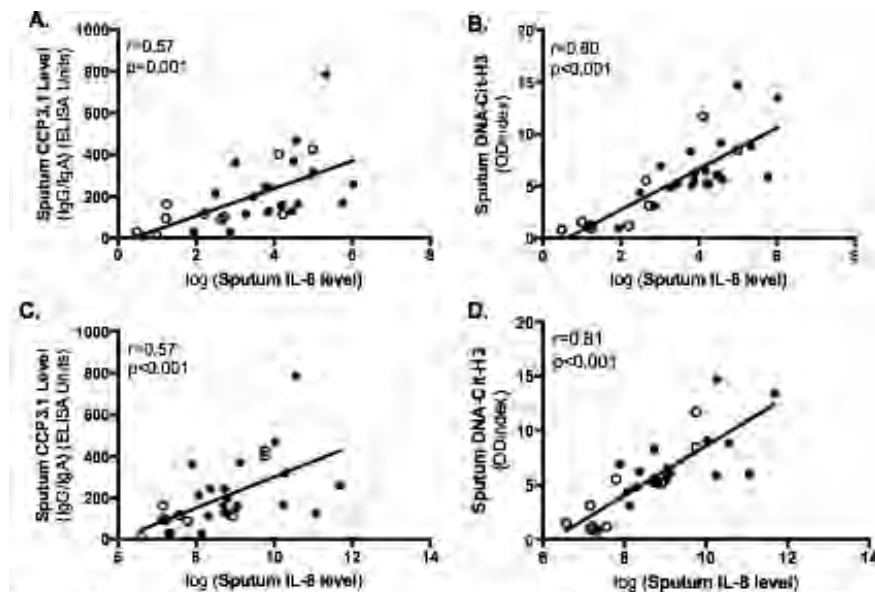


Figure 2. Sputum cytokine levels correlate with sputum anti-CCP3.1 and cit-H3 containing NET remnants in At-Risk subjects. The figure depicts the correlation between sputum anti-CCP3.1 levels and log transformed sputum cytokine levels (IL-6 in Panel A and IL-8 in Panel C) in At-Risk subjects. Similar correlations were demonstrated for TNF α ($r=0.72$, $p<0.001$) and IL-10 ($r=0.52$, $p=0.003$). The figure also depicts the correlation between sputum levels of NET remnants measured by the NET-specific protein complex DNA-citrullinated histone H3 (DNA-Cit-H3) and log transformed sputum cytokine levels (IL-6 in Panel B and IL-8 in Panel D) in At-Risk subjects. Similar correlations were demonstrated for TNF α ($r=0.70$, $p<0.001$) and IL-10 ($r=0.65$, $p<0.001$). R and p values based on Pearson's correlation coefficient. In all panels, \bullet = Serum CCP3.1(+) At-Risk and \circ = Serum CCP3.1(-) At-Risk.

role in the development of ACPA. Additional studies are needed to determine associations with transitions to systemic ACPA and classified RA.

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Abstract Number: 2902

Antibodies to PAD4 Drive Monocyte Activation and Differentiation into Osteoclast-like Cells

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis II

Session Type: ACR Concurrent Abstract Session

Session Time: 9:00 AM-10:30 AM

Background/Purpose: Agonistic antibodies to Peptidylarginine Deiminase 4 (PAD4) are hallmarks of a severe form of rheumatoid arthritis (RA) characterized by the most erosive joint damage and lung disease. PAD4 activation and the production of citrullinated autoantigens targeted in RA is likely a major mechanism by which these antibodies may worsen the disease. However, whether anti-PAD4 antibodies may have other effector functions in RA is unknown. The recent discovery that PAD4 is found on the surface of monocytes drove our interest to define the consequences that anti-PAD4 binding may have on the function of these cells.

Methods: We investigated the consequences of PAD4-activating antibody binding to monocytes using a well-characterized panel of human anti-PAD4 and control monoclonal antibodies (mAbs). Extracellular citrullination of fibrinogen was used to study antibody-mediated PAD4 activation on surface of monocytes. We measured anti-PAD4 antibody surface binding and monocyte activation using flow cytometry, and release of pro-inflammatory cytokines using ELISA at 24 hours. We

assessed differentiation of monocytes into osteoclasts using tartrate resistant acid phosphatase (TRAP) staining and quantitative estimation of acid phosphatase (AP) activity in the presence of a sub-optimal dose of RANKL at 14 days.

Results: PAD4 is expressed on the monocyte surface in an enzymatically active state that can be hyperactivated twofold upon binding by PAD4 antibodies. Flow cytometry studies revealed preferentially binding of PAD4 mAbs to PAD4 present on surface of monocytes where 63% monocytes bound with PAD4 mAbs versus 1.9% binding with control mAbs ($p=0.0087$). Moreover, PAD4 mAbs but not control mAbs induced monocyte activation with upregulation of surface markers such as CD40, CD11c and PDL-1 after 24 hours. Other activation markers such as CD80, CD86 and HLA-DR remained unchanged. Interestingly, monocytes treated with PAD4 mAbs released 100-fold more RA-associated pro-inflammatory cytokines, including IL-6 (1440 pg/ml) and TNF-alpha (94pg/ml), compare to monocytes incubated with control mAbs (14 pg/ml and 0 pg/ml, respectively). At 14 days, we observed larger osteoclast-like cells that were positively stained for TRAP in the presence of PAD4 mAbs compared to control mAbs. This corresponded to a three-fold increase in the amount of AP released by cells cultured with PAD4 mAbs over control mAbs.

Conclusion: Anti-PAD4 autoantibodies can directly interact with monocytes and influence their pathophysiological functions. The pro-inflammatory activation and differentiation into osteoclast-like cells may contribute to the erosive joint disease observed in this severe RA subset.

Disclosure: P. Naik, None; J. Shi, None; F. Andrade, Medimmune; BMS; Pfizer, 2, 5, 7; E. Darrah, Padlock Therapeutics; Medimmune; Pfizer, 2, 5, 7.

Abstract Number: 2903

Single Cell Association Testing Identifies an Expanded Th1-Skewed Cytotoxic Effector CD4+ T Cell Subset in Rheumatoid Arthritis

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Rheumatoid Arthritis – Etiology and Pathogenesis II

Session Type: ACR Concurrent Abstract Session

Session Time: 9:00 AM-10:30 AM

Background/Purpose: Defining the precise CD4+ T cell subsets that are dysregulated in RA patients is critical to deciphering pathogenesis. Here we present Mixed effects modeling of Associations of Single Cells (MASC), a novel reverse single cell association strategy to determine if a cellular subpopulation is associated with case-control status while controlling for technical confounders and biological covariates. We applied MASC to identify T cell populations expanded in rheumatoid arthritis(RA).

Methods: Cryopreserved PBMCs from 26 RA and 26 osteoarthritis patients were analyzed by a 32-marker mass cytometry panel. All RA patients met ACR 2010 Rheumatoid Arthritis classification criteria. We identified 19 CD4+ T cell populations and tested for case-control associations using our novel association testing method, MASC. MASC uses a logistic regression mixed effects model where the cluster membership of each single cell is the dependent variable. The model estimates fixed effects for donor age, sex, and case-control status, and random effects for each donor and technical batch.

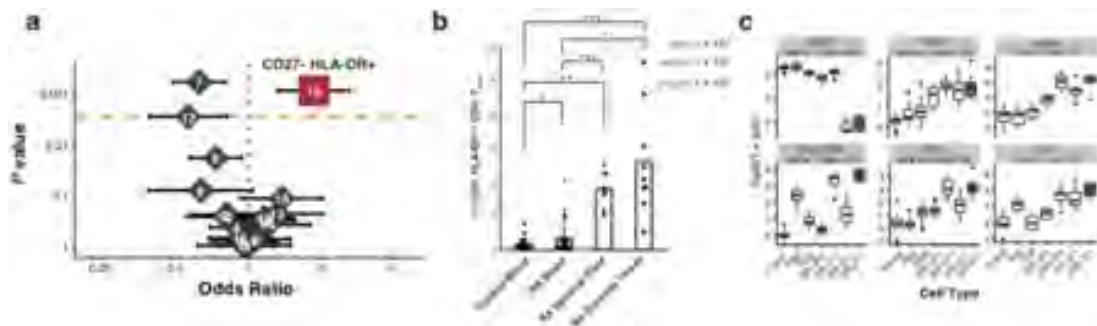


Figure 1. MASC identifies an expanded CD27- HLA-DR+ T_{EM} population in RA. (a) MASC odds ratios and association p-values were calculated for each cluster identified by DensVM. Cluster 18 was significantly expanded in RA and was CD27- HLA-DR+. (b) Flow cytometric quantification of the percentage of memory CD4+ T cells with a CD27- HLA-DR+ phenotype in cells from seropositive RA synovial fluid (n=8) and synovial tissue (n=9), compared to blood samples from RA patients and controls. Significance was assessed using one-tailed t-tests and applying a Bonferroni correction for multiple testing. (c) RNA-seq characterization of the expression of key genes in CD27- HLA-DR+ (DR+27-) cells and 6 related CD4+ T cell populations: naive T cells (T_{naive}), regulatory T cells (T_{reg}), central memory T cells (T_{CM}), and three populations of effector memory T cells, CD27+ HLA-DR- (DR-27+), CD27+ HLA-DR+ (DR+27+), and CD27- HLA-DR- (DR-27-). P values are adjusted for multiple testing using the Benjamini-Hochberg procedure.

Results: MASC revealed a significantly expanded population of CD4+ T cells, identified as CD27- HLA-DR+ effector memory cells, in RA patients (OR = 1.7; $p = 1.1 \times 10^{-3}$, **Figure 1A**). These cells comprised ~2% of CD4+ memory T cells in RA samples compared to 0.8% in OA controls. Compared to peripheral blood, synovial fluid and synovial tissue samples from RA patients were significantly enriched for CD27-HLA-DR+ cells, which comprised ~10-15% of synovial CD4+ T cells ($p < 1 \times 10^{-3}$, **Figure 1B**). The abundance of CD4+ CD27^D HLA-DR+ cells decreased in RA patients who responded to immunosuppressive therapy ($p = 0.006$). Considered together, mass cytometry and flow cytometry analyses indicated that CD27- HLA-DR+ cells were significantly associated with RA (meta-analysis $p = 4.8 \times 10^{-5}$). CD27- HLA-DR+ cells express a distinctive effector memory transcriptomic program with Th1- and cytotoxicity-associated features and produce abundant IFN- γ and granzyme A upon stimulation (**Figure 1C**).

Conclusion: MASC is a sensitive and well-calibrated statistical method for analyzing high-dimensional mass cytometry data. We used it in an RA case-control study to identify a novel disease-associated CD4+ T cell population. The expansion of a unique CD27- HLA-DR+ effector memory population in RA periphery may represent disease-driving cells and could be ideal for defining the antigenic repertoire in RA. We propose that MASC is a broadly applicable method to perform association testing with single cell data and can help identify other cellular populations that are critical to rheumatic disease pathogenesis.

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Abstract Number: 2904

Serum, Cellular and Imaging Markers of Arthritis in Psoriasis Patients and Healthy Controls

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Imaging of Rheumatic Diseases II: Ultrasound

Session Type: ACR Concurrent Abstract Session

Session Time: 9:00 AM-10:30 AM

Background/Purpose: The events that underlie the transition from psoriasis (Ps) to psoriatic arthritis (PsA) are not well understood, although up to 30% of Ps patients develop PsA within 8 to 10 years. A biomarker for subclinical joint inflammation in Ps patients would provide a tool allowing earlier intervention. Ultrasound (US) findings of PsA have been reported in Ps patients without MSK symptoms, but the prevalence of these findings varies in different studies, many without healthy controls. One cellular marker, circulating osteoclast precursors (OCP), is significantly higher in Ps than healthy controls (HC). The purpose of study is to analyze and correlate serum, cellular and imaging biomarkers of arthritis in Ps patients and controls to facilitate early interventions and improve outcomes.

Methods: US studies and serologic assessment for OCP and OCP subsets were performed on Ps patients (dermatologist confirmed) and HC. All US studies were performed on a GE LOGIQ E9 unit, and read by a rheumatologist certified in MSK US (RT). A modification of the PsASon system was used including the four domains: I. Joint: gray scale (GS) synovitis, power Doppler (PD) signal, erosion and osteophytes; II. Tenosynovitis: GS and PD; III. Peritendinitis: GS and PD; IV. Enthesitis: tendon structure, thickness, enthesitis associated bursitis, erosion, calcification or PD signal. US assessment included the bilateral radiocarpal and midcarpal joints, MCP joints, IP joints and PIP joints; 4th and 6th extensor compartments, flexor tendons 2-5 for tenosynovitis, extensor tendons 1-6 for peritendinitis; and bilateral elbow, knee, dorsal and plantar calcaneal entheses. Serum 14-3-3 η levels were assayed by ELISA and blood samples were drawn for OCP quantification from purified monocytes after 8-day cell culture. The OCP were quantitated as #TRAP positive cells per 100,000 monocytes.

Results: 150 patients were screened at the University of Rochester and regional dermatology practices. 78 Ps patients (mean age 49.5; mean BMI 31.9; mean disease duration 20 years; f, n=42; m, n=36) and 25 HC (mean age 43; mean BMI 27.3; f, n=17; m, n=8) were enrolled. No subject had symptoms or physical findings of PsA. Complete OCP data were available for 74 Ps and 20 HC subjects. US assessments were obtained in all HC and 75 Ps subjects. The frequency of OCP in the healthy; PDUS- and PDUS+ groups was 649.4 +/- 947.5; 843.6 +/-1545 and 1514.2. Levels of 14-3-3 η were not elevated in patients or controls.

Ultrasound Scores in Psoriasis and Healthy Controls

	Psoriasis n=75	Control n=25
Total modified PsASon score	9.0 \pm 7.7	2.8 \pm 2.3
Joint synovitis sub score	1.9 \pm 1.1	0.0
Joint PD sub score	2.6 \pm 1.9	0.0
Joint PD + GS sub score	4.5 \pm 1.5	0.0
Enthesis PD sub score	4.2 \pm 2.7	0.24 \pm 0.5
Enthesis erosions sub score	4.0 \pm 1.7	0.0

Conclusion: Imaging abnormalities were noted in almost 50% of Ps patients without MSK symptoms. This was significantly higher than in HC. Findings included synovitis, enthesitis and increased PD signals. The frequency of OCP was significantly higher in Ps patients than controls, and most elevated in patients with US findings. Serum levels of 14-3-3 η were not increased in patients or controls. The combination of US findings and elevated OCP has potential to identify Ps patients at risk for developing PsA.

Disclosure: R. G. Thiele, AbbVie Inc., 8, Amgen Inc., 8; Y. G. Chiu, None; N. Huertas, None; D. Li, None; C. Feng, None; S. Moorehead, None; C. Bell, None; C. T. Ritchlin, AbbVie, Amgen, UCB, 2, AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer Inc, 5.

Ultrasound Diagnosis of Large Vessel Inflammation in New-Onset Treatment-Naïve GCA Patients Using Fluorine-18-Fluorodeoxyglucose PET/CT As the Reference Standard – a Prospective Study of 86 Patients Suspected of GCA

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Imaging of Rheumatic Diseases II: Ultrasound

Session Type: ACR Concurrent Abstract Session

Session Time: 9:00 AM-10:30 AM

Background/Purpose: EULAR recommendations suggest diagnostic imaging in all GCA suspects. Vascular ultrasound (US) is cheap, readily available and the recommended first line examination in cranial GCA (c-GCA). Hence, US is an attractive first line examination also in large vessel GCA (LV-GCA). However, lower incidence of LV involvement is reported in US studies than in PET studies indicating a lower diagnostic sensitivity of US.

In a prospective study of glucocorticoid-naïve patients suspected of new-onset GCA, we evaluated the diagnostic accuracy of axillary artery US in the diagnosis of LV-GCA using 18F-FDG PET/CT as reference standard.

Methods: Patients suspected of GCA were consecutively considered for inclusion. Inclusion criteria were: 1) age ≥ 50 years; 2) CRP > 15 mg/L or ESR > 40 mm/h; 3) either a) cranial symptoms, b) new-onset claudication c) protracted constitutional symptoms d) polymyalgia rheumatica (PMR) symptoms. Main exclusion criteria were: 1) recent or ongoing glucocorticoid or DMARD treatment; 5) previous diagnosis of GCA or PMR ; 6) large vessel inflammation mimicking LV-GCA. Clinical evaluation and imaging was performed before treatment initiation. The reference diagnosis for LV-GCA was a clinical diagnosis of GCA and a 18F-FDG PET/CT revealing aortic and/or subclavian/axillary artery FDG uptake $>$ liver uptake. Patients not diagnosed with GCA were considered controls. US was performed by experienced sonographers, blinded to PET results. Axillary arteries were assessed for the presence or absence of the 'halo sign' and intima media thickness (IMT) was measured. Sensitivity and specificity of the halo sign in axillary arteries was evaluated. ROC curve analysis was performed to estimate axillary IMT cut off.

Results: 86 patients were included (97 screened). 45 were diagnosed with LV-GCA (with or without concomitant c-GCA), 10 with isolated c-GCA, 21 with PMR and 10 with other diseases. Baseline characteristics of LV-GCA and controls are shown in table 1.

None of the controls had a positive axillary US, whereas 36/45 LV-GCA patients were axillary US positive yielding a specificity of 100% (95% CI: 89-100%) and a sensitivity of 80% (95%CI: 65-90%). Of the 73 PET positive axillary arteries in LV-GCA patients, 53 were axillary US positive (sensitivity 72% (95%CI: 61-83%)). Four PET negative axillary arteries were US positive (specificity 95% (95%CI: 87-99%)). An AUC of 0.86 (95%CI: 0.79-0.92) was obtained by ROC curve analysis of axillary IMT with axillary PET diagnosis as a reference. An IMT cut off value of 0.9 mm revealed a sensitivity of 74% and a specificity of 92%.

Conclusion: In the hands of experienced sonographers, axillary arteries US shows high sensitivity and specificity for the diagnosis of LV-GCA which clearly suggests US as a first line imaging test in LV-GCA suspected patients. Suggested IMT cut off confirms findings of previous studies using different reference standards.

Table 1. Baseline characteristics of the cohort

	LV-GCA	Controls (PMR+others)	PMR	others	LV-GCA vs controls*
Total number	45	31	21	10	
Women, no.	28	15	13	2	p=0.25
Age, years (mean, range)	67 (51- 83)	69 (51-84)	70 (55-85)	66 (51-76)	p=0.29
Temporal artery biopsy positive, no/performed	30/45	0/21	0/18	0/3	
Fulfillment of ACR criteria, no. (%)	41 (91%)	11 (35%)	3 (14%)	8 (80%)	p=0.000
Disease duration, weeks (median, range)	13 (2-72)	6 (1-36)	8 (4-36)	3.5 (1-7)	p=0.0001

Table . (Cont'd)

	LV-GCA	Controls (PMR+others)	PMR	others	LV-GCA vs controls*
CRP, mg/ml? Median, 95% CI	72 (60-86)	46 (35-59)	35 (34-47)	70 (37-132)	p=0.0037
Concomitant AT-GCA*, no. (%)	34 (76%)	nr	nr	nr	
Concomitant PMR, no. (%)	8 (18%)	nr	nr	nr	

Controls are PMR patients and other diseases. *p-values on difference between LV-GCA and control group. Nr, not relevant.

Disclosure: B. D. Nielsen, Roche, 9; I. Tønder Hansen, None; K. K. Keller, Pfizer, Inc., 9; P. Therkildsen, None; L. C. Gormsen, None; E. M. Hauge, Roche and Novartis, 2, MSD, AbbVie, UCB and Sobi, 9.

Abstract Number: 2906

Synovitis Focused Ultrasound in Rheumatoid Arthritis: A Joint Reduction Strategy

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Imaging of Rheumatic Diseases II: Ultrasound

Session Type: ACR Concurrent Abstract Session

Session Time: 9:00 AM-10:30 AM

Background/Purpose: Musculoskeletal ultrasound is increasingly being used as a tool to assess inflammatory burden in rheumatoid arthritis (RA). Ultrasound-based outcome measures include power Doppler (PD) and grey scale synovial hypertrophy and have been assessed on fixed sets of between 5 to 78 joints. Although scanning large numbers of joints maybe feasible in clinical trials, it may not be practical in clinical practice. We therefore evaluated a novel patient-specific method for constructing a longitudinal ultrasound outcome measure in RA patients.

Methods: This was a 24 week, phase IV double blind open label clinical trial of 54 patients at 2 clinical centers with RA by 1987 ACR criteria and moderate to severe disease, treated with IV tocilizumab at initial dose of 4mg/kg. Patients not achieving DAS28-ESR_{3.2} at 12 weeks dose escalated to 8mg/kg. Baseline patient characteristics pluslabs, clinical exam of swollen and tender joints, and PD of 34 joints (bilateral MCP 1-5, PIP 1-5, midline and radioulnar wrist, knee, MTP 2-5) at baseline and at 4, 12, 16, and 24 weeks were collected.

Table 1. Correlation between changes in PDUS / rPDUS scores and changes in DAS score from baseline to 4, 12, 16, and 24 weeks.

	DAS28 Δ0-4wks	DAS28 Δ0-12wks	DAS28 Δ0-16wks	DAS28 Δ0-24wks
PDUS/rPDUS Δ0-4wks	0.32* / 0.16			
PDUS/rPDUS Δ0-12wks		0.55* / 0.46*		
PDUS/rPDUS Δ0-16wks			0.32* / 0.28	
PDUS/rPDUS Δ0-24wks				0.42* / 0.37*

* denotes p < 0.05

Table 2. Proportion of joints that flip from having no PD signal at baseline to having PD signal by follow-up at 4, 12, and 24 weeks.

	4 weeks	12 weeks	24 weeks
All Joints	10.0% (123/1235)	8.1% (95/1171)	5.6% (57/1011)
MCP	13.4% (46/343)	10.0% (33/327)	7.1% (20/283)
PIP	7.9% (33/418)	6.6% (26/396)	5.3% (18/340)
Midline Wrist	25% (4/16)	18.8% (3/16)	14.3% (2/14)
Radioulnar	6.8% (3/44)	12.2% (5/41)	8.3% (3/36)
Knee	8.8% (5/57)	13.0% (7/54)	8.3% (4/48)
MTP	9.0% (32/357)	6.2% (21/337)	3.4% (10/290)

Results: At each visit, PD score (PDUS) was computed as the sum of semi-quantitative PD signal for all joints (0-3 per joint, max 102). A novel patient-specific PD score was calculated from the reduced subset of joints with PD \geq 1 at baseline (rPDUS). Pearson correlation coefficients between 1) changes in PDUS and rPDUS versus changes in DAS, and 2) changes in PDUS versus changes in rPDUS were used to assess each outcome measure's response to therapy from baseline to follow-up periods. The proportion of joints without PD signal at baseline that later developed PD signal ("flipped") was estimated.

54 RA patients with mean age 51.9 ± 15.2 years, 91% female, 61.5% Caucasian, 85% seropositive, mean disease duration 10.0 ± 10 years, 72% on background DMARD at baseline were enrolled. At baseline, 1236 of 1829 joints scanned (67.5%) did not have PD signal. Changes in PDUS and changes in DAS were moderately correlated over intervals 0-4 weeks, 0-12 weeks, 0-16 weeks, and 0-24 weeks. Changes in rPDUS also correlated with changes in DAS, though slightly less so than with PDUS (Table 1). PDUS and rPDUS scores were highly correlated with $r = 0.91$ to 0.97 . The overall proportion of "flipped" joints was 8.1% at 12 weeks and 5.6% at 24 weeks, with greatest variability seen in the midline wrist and MTP (Table 2).

Conclusion: In RA patients starting a biologic, scanning only joints with baseline power Doppler synovitis can substantially reduce the number of joints needing to be scanned at follow-up visits. This gain in feasibility comes at a cost of a small reduction in correlation with validated disease activity measures.

Disclosure: D. Kuo, None; G. Kaeley, None; A. Ben-Artzi, None; J. Brook, None; A. Floegel-Shetty, None; D. Elashoff, Genentech, Inc., 2, Pfizer, Inc., 2, mallinckrodt, 2, Amgen Inc., 5; V. K. Ranganath, Genentech, Inc., 2, Pfizer, Inc., 2, mallinckrodt, 2, Amgen Inc., 5.

Abstract Number: 2907

Comparison of the Joints Ultrasonography in the Patients with Rheumatoid Arthritis Treated By Biological Agents and the Corresponding Synovial Histological Findings

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Imaging of Rheumatic Diseases II: Ultrasound

Session Type: ACR Concurrent Abstract Session

Session Time: 9:00 AM-10:30 AM

Comparison of the joints ultrasonography in the patients with rheumatoid arthritis treated by biological agents and the corresponding synovial histological findings

Background/Purpose: In the treatment of Rheumatoid arthritis (RA), early diagnosis and early treatment with tight control have become increasingly important with the advent of biological therapy. Ultrasonography (US) of the various joints enables the real-time evaluation of synovial hypertrophy, effusion and bone erosion, Power Doppler (PD) ultrasound is able to identify both subclinical synovitis and early erosive disease. The objectives of this study were to investigate whether the image of US at the operated joint reflect synovium histopathology or clinical indicators, and to compare the results in the patient treated by non-biological agent (NonBio) and biological agent (Bio)..

Methods: RA related orthopaedic surgery was performed at 1191 joints including 17 shoulders, 144 knees, 92 elbows, 352 wrists, 333 fingers, 34 ankles and 218 toes during the period between January 2011 and May 2018 at our rheumatic center. Preoperatively, ultrasound evaluations were performed and grade of PD signal was determined at the part with the highest signal. PD signal consists 4 grades from grade 0 to 3. The operations were performed within one week after the ultrasound evaluations. Rooney score of the synovium pathology, DAS28-ESR(4), MMP-3, CRP were investigated. Rooney score represents the histologic features in the synovium of RA. It includes 6 features i.e. synoviocytes hyperplasia, fibrosis, proliferating blood vessels, perivascular infiltrates of lymphocytes, focal aggregates of lymphocytes, diffuse infiltrates of lymphocytes. They were scored separately on a scale of 1-10. The treatments that the patients received included: biological agents (Bio) (n=351 29%), etanercept (ETN) (n= 96), tocilizumab(TCZ) (n=99), infliximab (IFX) (n=25), adalimumab (ADA)(n=26), certolizumab pegol (CZP)(n=8), golimumab (GLM) (n=49), and abatacept (ABT) (n=47), tofacitinib(TOF) (n=1).

Results: PD signal (0.75}{0.89), DAS28(2.77}{1.13), CRP(0.10}{1.22 mg/dL), MMP-3 (104.6}{108.4 ng/mL) and Rooney score (22.1}{7.7) in the patients treated by Bio were significantly lower than those (1.41}{0.96, 3.67}{1.11, 0.79}{1.32 mg/dL, 145.0}{138.2 ng/dL, 28.5}{9.24) in the patients using NonBio. Rooney score fibrosis (9.57}{1.51) in patients using Bio was

significantly higher than those (8.55}2.45) in patients treated by NonBio. Rooney score synoviocyte hyperplasia (0.91}1.27), three items of lymphocyte (1.59}2.91, 1.38}2.49, 0.86}2.27) in patients treated Bio were lower than those (1.73}1.30, 3.84}3.56, 3.70}3.48, 2.47}2.93) in patients treated by NonBio. TCZ, ADA, ABT and IFX had some significant differences for Rooney score and Rooney item score between the patients treated NonBio.

Conclusion: The activity of RA synovitis at operated site was suppressed in patients treated by Bio. There were some differences in clinical data, histopathological score, PD signal and DAS among Bio.

Disclosure: A. Abe, None; H. Ishikawa, None; K. Wakaki, None.

Abstract Number: 2908

Agreement between Ultrasound and Whole Body Magnetic Resonance Imaging Assessment of Joint Inflammation and Enthesitis in Rheumatoid Arthritis Patients

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Imaging of Rheumatic Diseases II: Ultrasound

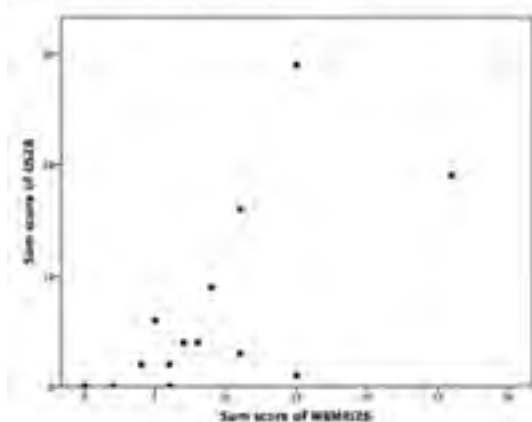
Session Type: ACR Concurrent Abstract Session

Session Time: 9:00 AM-10:30 AM

Background/Purpose: To evaluate the agreement between ultrasound (US), whole body magnetic resonance imaging (WBMRI) and clinical assessment of joint inflammation and enthesitis in rheumatoid arthritis (RA) patients, by comparison on joint/entheses level and by evaluating the correlation between composite scores at patient level.

Methods: US, WBMRI and clinical assessment for tender joints (TJ) and swollen joints (SwJ) were performed in 19 RA patients (90% Women, median (range) age 55 (26-73), diseases duration 5.5 (1-42), SwJ(28) 5 (1-13), TJ(28) 7 (2-24) and DAS28-CRP 4.66 (3.48 -6.66))) fulfilling ACR 1987 criteria for RA. The 28 conventional joints, bilateral ankles and MTP 1-5, and the entheses of supraspinatus, gluteus muscles, quadriceps and Achilles tendon were assessed by WBMRI and US.

Figure 1. Correlation between US score (for 28 joints (US28)) & whole body MRI score (for 28 joints (WBMRI28)) for assessing joint inflammation.
* Range of score score=US28 (0-14) and WBMRI28 (0-32)



Spearman correlation=0.72, p=0.003

Joint inflammation by US was graded 0-3 on B-mode and colour Doppler (CD), respectively, and subsequently converted to +/- for both components by defining US synovitis as B mode ≥ 2 or CD ≥ 1 . US finding of enthesitis was defined by presence of CD activity $< 2\text{mm}$ from the cortical insertion, with or without erosions, or enthesophytes/calcifications. For WBMRI, joint inflammation was defined as presence of synovitis and/or osteitis, and enthesitis as presence of soft tissue inflammation and/or osteitis. For both modalities, the max score was 2 for a joint and 1 for an enthesis. To assess the total inflammatory burden, a composite score was established as sum scores for the 28 conventional joints for US (US28) and for 26 joints (WBMRI26) for WBMRI - same 28 joints except elbows (due to poor image quality). The agreement between the clinical joint assessment, US and WBMRI for joint inflammation and enthesitis was calculated with Cohen's kappa (κ). The correlations between US28, WBMRI26 and DAS28-CRP were calculated by Spearman correlation coefficient (ρ).

Results: US28 and WBMRI26 sum scores showed good correlation $\rho = 0.72$ ($p = 0.003$) (Fig. 1), whereas US28 and WBMRI26 did not correlate with DAS28 CRP ($\rho = -0.26$, $p = 0.28$; $\rho = 0.20$, $p = 0.47$ respectively). Moderate-good agreement was found between US and WBMRI in wrists and MCP 1, 2 and 5 ($\kappa = 0.42-0.62$) but poor in other joints ($\kappa \leq 0.37$). Agreement between US and clinical joint tenderness was poor (all $\kappa < 0.31$; except $\kappa = 0.42$ for wrist), but better between US and clinical swelling for shoulders, elbows, MCP1 and PIP5 ($\kappa = 0.42-0.66$) while ≤ 0.36 for other joints. Agreement between WBMRI and clinical joint swelling or tenderness showed $\kappa < 0.35$ in all joints. Enthesitis was rare in RA patients, when defined by positive Doppler signal on US (only 3 cases were detected) and hence poor agreement ($\kappa < 0.1$ at all entheses) was found between US and WBMRI.

Conclusion: WBMRI and US sum scores of joint inflammation showed good correlation in RA patients but the agreement at joint level was variable. The agreement on enthesitis between MRI and US was low, but findings were minimal. No correlation with DAS28 was found for either modality.

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Abstract Number: 2909

Diagnostic and Prognostic Value of Ultrasound Compared with Plain Radiography in Knee Osteoarthritis

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Session Time: 9:00 AM-10:30 AM

Background/Purpose: Plain radiography of knee osteoarthritis (OA) has inherent diagnostic and prognostic limitations, especially in early disease. Ultrasound (US) examination sheds light on disease activity and inflammatory changes in OA, but there is no uniformity or standard for its routine use in evaluation of OA. Our aim is to identify sonographic features that consistently assess burden of disease and predict future OA progression.

Methods: Knee US was performed on OA patients who were enrolled in a study of biomarkers for radiographic progression. We recorded US images of the more painful knee at baseline and both knees at 24 months. Each set of US images was scored semiquantitatively (0-3) for osteophyte size, degree of damage to the femoral articular cartilage (FAC), severity of synovitis/effusions, and popliteal cyst size, and these scores were combined to calculate a composite score (0-12). Weight-bearing knee radiographs taken at baseline and 24 months were scored for Kellgren-Lawrence (KL) grade. Linear regression of each set of the 5 US scores and the corresponding KL scores (with 0 and 24 month readings combined) were run to assess how well each of the US measures trended with KL readings. A second analysis compared the 5 mean *baseline* ultrasound scores for two groups of patients, those with and without KL worsening at 24 months, to identify sonographic predictors of radiographic progression.

Results: US images were obtained on 591 knees from 199 patients at the two time points. There was a significant association between the KL grades and each of the 5 US scores by regression, most significant for osteophytes ($R^2 = 0.396$) and the composite score ($R^2 = 0.334$), all with p -values < 0.001 (see **Figure 1**). In separate t-test analyses of the radiographic

Figure 1. Four different sonographic features and the composite score correlate with radiographic KL grades in knee OA.

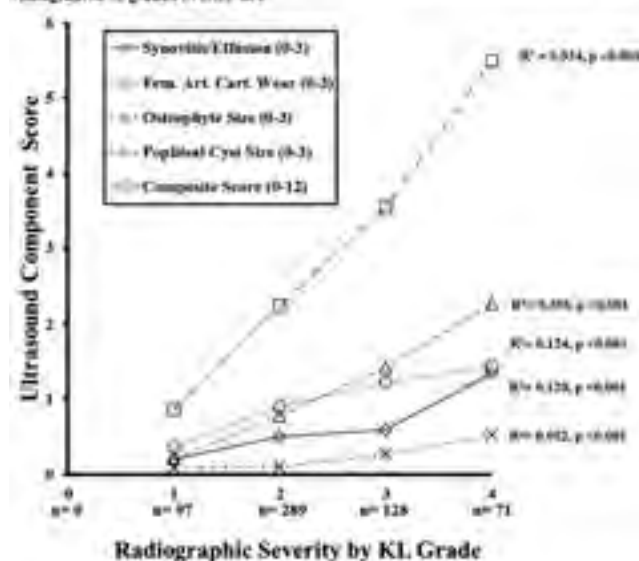


Table 1. Ultrasound predictors of radiographic progression in knee OA

Ultrasound Measure (mean score at baseline)	No Progression Δ KL=0 (n=175)	Progressed Δ KL>0 (n=24)	p-value
Synovitis/effusion (0-3)	0.75	1.77	0.072
Femoral Articular Cartilage Wear (0-3)	1.13	1.33	0.513
Osteophyte Size (0-3)	1.08	1.27	0.542
Popliteal Cyst Size (0-3)	0.27	0.75	0.178
Composite Score (0-12)	3.16	4.25	0.049*

progression over 24 months of the more painful knee, the 24 patients whose KL grade worsened (Δ KL>0) had a higher mean baseline US composite score than those whose KL grade didn't change (Δ KL=0) (4.25 vs. 3.16, $p=0.049$). The 4 sonographic subscores were also higher at baseline in patients who later progressed radiographically, but none reached significance (see **Table 1**).

Conclusion: US can be used to reliably identify structural and inflammatory changes in knee OA – often earlier or better than plain radiography. Our cohort also demonstrates that more robust sonographic pathology predicts which patients' knee OA may be more likely to progress overtime. This may be helpful in selecting patients for trials of disease-modifying medications.

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Abstract Number: 2910

Development of a Rheumatoid Arthritis Global Outcome Measure to Enable Comparisons of Patient Experiences across Treatment Arms in Randomized Clinical Trials

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Session Information

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Session Title: Patient Outcomes, Preferences, and Attitudes II: Patient-Reported Outcomes

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Background/Purpose: Randomized controlled trials currently report benefits and adverse events (AEs) separately, and therefore do not permit comparisons of patients’ overall experiences on one treatment versus another. The purpose of this study is to develop a Global Patient-Reported Outcome Measure (G-PROM) to quantify and compare the distribution of patients’ overall experiences on medications.

Methods: We invited rheumatoid arthritis (RA) patients who were part of an online community to complete a survey, based on Trajectory Mapping (TM) to generate a hierarchy of AEs. The TM survey establishes a hierarchy by enabling patients to indicate whether an AE is worse, better, or no better or worse than a referent AE. TM allows the construction of “equivalence classes” i.e., groups of AEs judged by patients as having a comparable impact on quality of life. We subsequently conducted a second survey in which participants (who did not participate in the initial TM survey) were asked to indicate their preference for pairs of outcomes, where each outcome include both a specified level of benefit [little or no improvement (ACR20 or less), some improvement (between ACR20 and 50), and major improvement (ACR50 and greater)]and an AE (see Figure 1).

Results: 195 participants completed the initial TM survey. The mean age was 53.5 (11.6), 89% were female, and 56% were college graduates. The initial TM survey generated 11 hierarchies of AEs. The final hierarchy (9 levels of AEs ranging from no AEs to serious AEs resulting in irreversible harm) was chosen based on goodness of fit parameters (see Figure 2). 426 participants with similar demographic characteristics completed the second survey. Ratings revealed that when paired with benefits, AEs clustered into 3 main groups: no, mild or manageable AEs (Levels 1-4), moderate AEs (Levels 5-6), and serious AEs (Levels 7-9). Participants’ ratings generated a 5-level hierarchy of global outcomes illustrated in Figure 3.

Conclusion: After validation, G-PROM will enable randomized controlled trials to report the percentage of patients classified into each level; thus, providing patients and their rheumatologists with a much clearer understanding of the range and likelihood of the total effects of competing treatment options on their quality of life.

Figure 1. Example of Paired Comparison Question

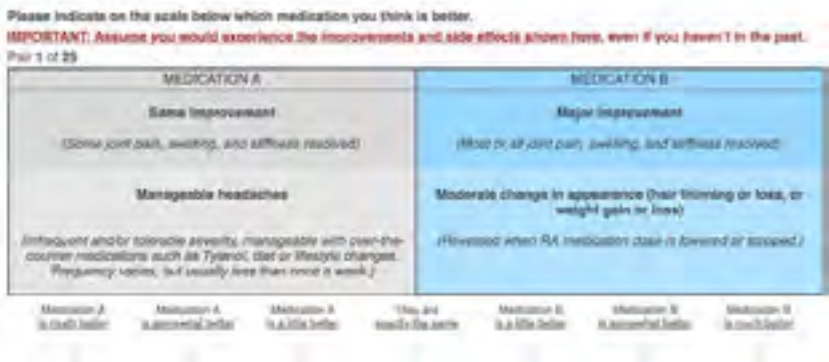


Figure 2. Adverse Events Hierarchy

LEVEL	ADVERSE EVENTS							
1	No AEs							
2	Mild injection site skin reaction or rash							
3	Manageable headaches	Manageable mouth ulcers	Mild infection	Reversible blood test abnormalities	Manageable fatigue	Manageable brainfog/light headedness	Diet-controlled high BP ¹ , DM ² , cholesterol	Mild weight gain, hair loss
4	Manageable depression, anxiety	Manageable stomach pain, diarrhea	Manageable nausea, vomiting	Medication-controlled high BP, DM, cholesterol	Moderate weight gain, hair loss			
5	Cataracts	Curable skin cancer	Severe fatigue	Severe brainfog/light headedness				
6	Severe headaches	Stingies						
7	Serious infection							
8	Serious complication (full recovery)							
9	Serious complication with damage or requiring ongoing treatment							

1. BP = Blood pressure
2. DM = Diabetes mellitus

Figure 3. Global Outcome Hierarchy

LEVEL	GLOBAL OUTCOME		
1 (Best)	Major improvement + No, mild, or manageable AEs		
2	Major improvement + Moderate AEs	Some improvement + No, mild, or manageable AEs	
3	Major improvement + Serious AEs	Some improvement + Moderate AEs	Little or no improvement + No, mild, or manageable AEs
4	Some improvement + Serious AEs	Little or no improvement + Moderate AEs	
5 (Worst)	Little or no improvement + Serious AEs		

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Abstract Number: 2911

Patient-Reported Outcomes Measurement Information System (PROMIS®) Global Health Short Form Is Responsive to Patient Reported Changes in SLE Health Status

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Background/Purpose: The accurate and efficient serial measurement of patient centered outcomes is a priority in the clinical care of SLE. Patient-Reported Outcomes Measurement Information Systems (PROMIS®) Global Health Short Form (PROMIS10) is a 10-item universal patient reported outcome measure of global physical and mental health with construct validity in SLE. The longitudinal responsiveness (sensitivity to change) of PROMIS10 in SLE patients is unknown. We aimed to evaluate the responsiveness of PROMIS10 in SLE outpatients using patient and physician-derived anchors.

Methods: Adults meeting ACR SLE classification criteria were recruited from an SLE Center of Excellence. Subjects completed PROMIS10 at two visits a minimum of one month apart. SLE disease activity was measured with a patient global assessment of change, a physician global assessment and the physician-derived SELENA-SLEDAI. Responsiveness over time of PROMIS10 scores was evaluated using known-groups validity. Effect sizes of changes in PROMIS global physical health and global mental health scores from baseline to follow up were compared across groups of patients who differed in their patient global assessment of change, physician global assessment, and SELENA-SLEDAI using Kruskal-Wallis tests.

Results: A diverse cohort of 228 SLE patients completed baseline surveys (Table 1), with 190 (83%) completing a follow up survey. Using the patient-based anchor, PROMIS10 demonstrated mild to moderate responsiveness to improvement (effect size 0.29) and worsening (effect sizes -0.27 and -0.54) of health status for both global physical health and global mental health (Table 2). Using the physician global assessment and SELENA-SLEDAI as anchors, there were no statistically significant differences in effect sizes across groups.

Conclusion: PROMIS10 showed responsiveness over time to patient-reported, but not physician-derived changes in lupus health status. These data suggest that PROMIS10 can be used to efficiently measure and monitor important aspects of the patient experience of lupus not captured by physician-derived metrics. Further studies are needed to evaluate the role of PROMIS in optimizing longitudinal disease management in SLE.

Table 1. Baseline Characteristics of Participants (n= 228)

Table . (Cont'd)

Characteristic	Value
Characteristic	Value
Age, median [IQR] years	37 [29, 49]
Disease duration, median [IQR] years	10.6 [5.8, 16.4]
Sex, n (%)	
Male	20 (8.8)
Female	208 (91.2)
Race, n (%)	
White	87 (38.2)
Black or African-American	64 (28.1)
Asian	26 (11.4)
Other	38 (16.7)
Not Reported	13 (5.7)
Ethnicity, n (%)	
Hispanic or Latino	65 (28.5)
Not Hispanic or Latino	155 (68.0)
Not Reported	8 (3.5)
Insurance, n (%)	
Medicaid	82 (36.0)
Medicare	22 (9.7)
Third party/private	124 (54.4)
Physician Global Assessment, median [IQR] (Possible range 0 – 3)	0.5 [0.3, 1.0]
SELENA-SLEDAI, median [IQR] (Possible range 0 – 105)	4 [2, 6]
SELENA-SLEDAI Flare, n (%)	32 (17.3)
SLICC-ACR Damage Index, median [IQR] (Possible range 0 – 46)	1 [0, 2]

Table 2. Responsiveness of PROMIS10: Median Effect Sizes [Number of Contributing Participants] by Anchor Type

Patient Global Rating of Change	Better	Same	Worse	p-value
Global Physical Health	0.29 [72]	0.0 [76]	-0.27 [31]	<0.01
Global Mental Health	0.29 [59]	0.0 [72]	-0.54 [25]	<0.01
Physician Global Assessment	Better:	Same:	Worse:	p-value
	≥ 0.5 point decrease	< 0.5 point change	≥ 0.5 point increase	
Global Physical Health	0.0 [41]	0.0 [108]	-0.27 [29]	0.22
Global Mental Health	-0.26 [39]	0.26 [90]	-0.29 [26]	0.23
SELENA-SLEDAI	Better:	Same:	Worse:	p-value
	≥ 3 point decrease	< 3 point change	≥ 3 point increase	
Global Physical Health	0.0 [36]	0.0 [122]	-0.27 [20]	0.19
Global Mental Health	0.26 [33]	0.0 [105]	-0.31 [17]	0.10

Disclosure: S. Kasturi, None; J. Szymonifka, None; J. R. Berman, None; K. A. Kirou, None; A. B. Levine, None; L. R. Sammaritano, None; L. A. Mandl, None.

Abstract Number: 2912

Lupus Flare Activity from the Patient Perspective

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Session Information

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Background/Purpose: Lupus patients may experience flares in disease activity that require rapid management. This study describes the experience, identification, and management of a flare from the patient perspective.

Methods: An online survey was administered to persons with lupus who responded to outreach from the Lupus Foundation of America or the Research Now survey research service. Data collection included sociodemographic characteristics, flare profile, the Lupus Impact Tracker (LIT), and hospital admissions. The results were summarized with descriptive statistics.

Results: 1503 individuals with self-reported lupus completed the survey from May to October 2017. 77% were Caucasian, 89% were female, mean age was 45 yrs, mean duration of illness was 12 yrs, and 19% reside rurally. 78% had flare activity in the past year. Of these, half reported 4 or more flares, and 66.9% perceived their flares as moderate to severe. The most common flare symptoms (**Figure 1**) were extreme fatigue/exhaustion (87%), aching/increased swelling of the joints (80%), and muscle weakness/pain (73%). Respondents who suffered more flares had worse LIT scores and more hospital admissions during the past year (**Figure 2**). Many respondents (48%) could not predict when a flare would occur but noted that flare triggers were events such as emotional stress, overdoing it, lack of rest, and sunlight exposure. 40.5% engaged the healthcare system, such as doctor, ER, or hospital, when suffering a flare. 54% self-treated flares, most frequently with over-the-counter products and prescription drugs kept on hand. For the most recent flare 34.8% delayed seeking care for 3

Figure 1: Flare symptom frequency among respondents with flare activity in the past 12 months (n=1174)

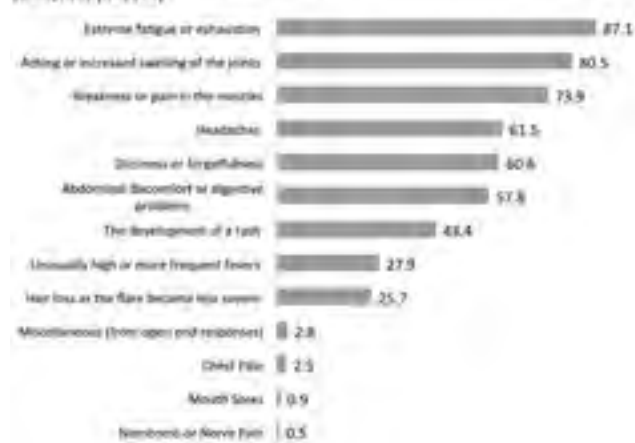


Figure 2: Flare frequency stratification and corresponding mean results for LIT and number of past year hospital admissions for lupus among respondents with flare activity in the past 12 months (n=1174)

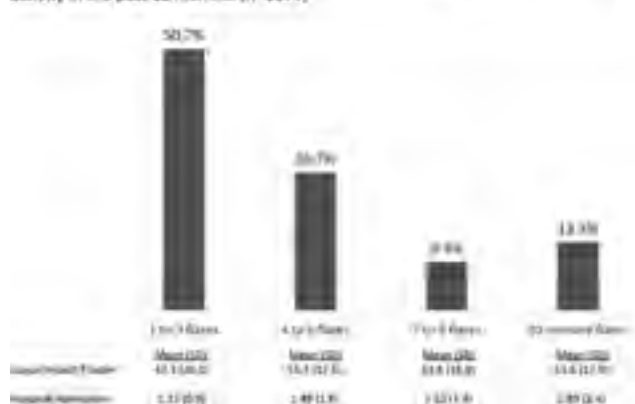
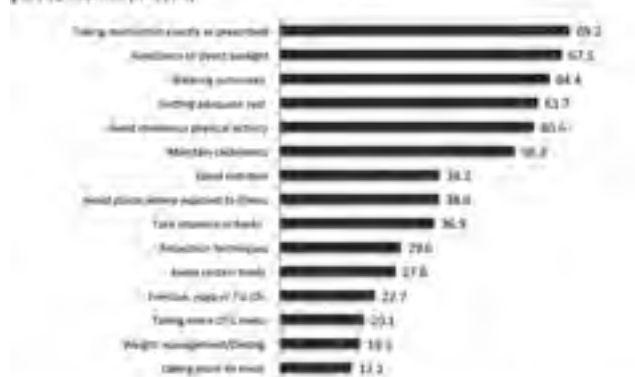


Figure 3: Flare management strategies among respondents with flare activity in the past 12 months (n=1174)



Legends (Stress 7.4%, Acupuncture 5.8%, Diet/Herbs 3.1%, Acupuncture 2.8%, Massage 2.9%, Diet/Herbs 2.8%)

days or longer (24.3% of urban residents, 41.9% of rural); more than half did not receive care within 24 hours (46.1% of urban, 62.2% of rural). **Figure 3** shows various tactics used to manage flares.

Conclusion: Lupus flare burden is high, and flares often resulted in healthcare encounters and medication use. The most common flare symptoms may not be congruent with how clinicians define flares, leading to communication challenges. Patients appear to be receptive to self-treatment, presenting an opportunity to enhance their self-care skills. Findings provide insight into how clinicians and patients can work together to identify and manage flares more effectively.

Disclosure: W. Nelson, Mallinckrodt Pharmaceuticals, 1, 3; P. Katz, Mallinckrodt Pharmaceuticals, 5; R. P. Daly, Mallinckrodt Pharmaceuticals, 2; L. Topf, Mallinckrodt Pharmaceuticals, 2; E. Connolly-Strong, Mallinckrodt Pharmaceuticals, 1, 3; M. Reed, Mallinckrodt Pharmaceuticals, 5.

Abstract Number: 2913

A Draft Modified Core Domain Set for Patient-Reported Outcomes (PRO) in Patients with Idiopathic Inflammatory Myopathies (IIM): An Omeract Report

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Session Information

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Session Title: Patient Outcomes, Preferences, and Attitudes II: Patient-Reported Outcomes

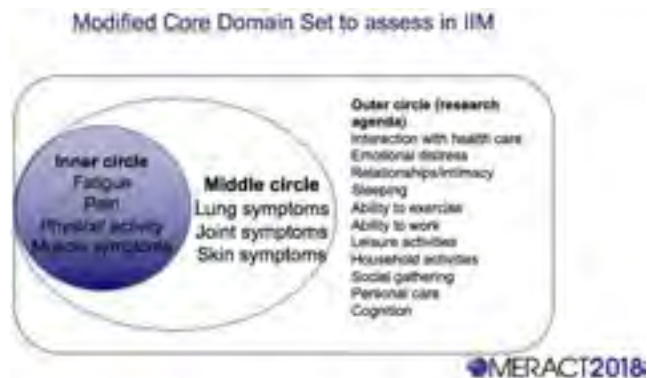
Session Type: ACR Concurrent Abstract Session

Session Time: 9:00 AM-10:30 AM

A Draft Modified Core Domain Set for Patient-Reported Outcomes (PRO) in Patients with Idiopathic Inflammatory Myopathies (IIM): An OMERACT Report

Background/Purpose: The OMERACT Myositis special interest group (SIG) represents clinicians, patients, and researchers from four continents. Focus groups were conducted including 61 patients on three countries resulting in a list of 26 domains (1). In collaboration with International Myositis Assessment Clinical Study Group (IMACS), our goal was to identify a set of core patient-reported outcomes (PRO) in regards to life impact important to assess in clinical trials and clinical practice in myositis.

Methods: Patients with adult polymyositis, dermatomyositis, antisynthetase syndrome, or immune-mediated necrotizing myopathy (IMNM) in South Korea, Sweden and USA (N=638) responded to the first online modified Delphi in 2016. The second modified Delphi included patients (N=563), healthcare providers (HCP) (N=101), care givers (N=27) and



regulatory agencies (n=xx) from multiple countries in 2017. A third modified Delphi was administered in 2018 including 410 patients, 109 HCP, 22 caregivers.

Results: From this work, four domains were deemed mandatory to measure in all clinical trials for IIM: fatigue, pain, levels of physical activity, and muscle symptoms (Figure 1). Additional optional domains include skin symptoms, lung symptoms, and joint symptoms. Several other domains were deemed important to study with further research efforts including sleeping difficulty, cognitive distress, ability to work, and emotional distress.

Conclusion: A draft set of core PRO has been developed through validated methods based on OMERACT guidelines. Fatigue, pain, levels of physical activity and muscle symptoms were included in the inner circle and should always be used in clinical trials in IIM. We next seek to develop corresponding instruments with each of these domains with future efforts. Reference: Regardt M et al. Patients' experience of myositis and further validation of a patient-reported outcome measure – establishing core domains and expanding patient input on clinical assessment in myositis. Report from OMERACT 12. J Rheumatol 2015;42:2492-5.

Figure 1: Draft Modified Core Domain Set for PROs in IIM Patients

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Abstract Number: 2914

Examination of Psychometric Properties of the Patient-Reported Outcomes Measurement Information System Fatigue 4-Item Short Form in Psoriatic Arthritis

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Session Information

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Session Title: Patient Outcomes, Preferences, and Attitudes II: Patient-Reported Outcomes

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Background/Purpose: PROMIS (Patient-Reported Outcomes Measurement Information System) measures have not been tested in psoriatic arthritis (PsA). We examined the reliability, validity and responsiveness of the PROMIS Fatigue (PR-FAT) 4-item short form in PsA and developed estimates of the minimally important difference (MID).

Methods: Data were from Forward/National Data Bank for Rheumatic Diseases. Participants complete questionnaires every 6 months. PR-FAT was included in five administrations. Changes were calculated for consecutive questionnaire administrations, yielding four change periods. Cronbach's α tested internal consistency. Construct validity was assessed by examining correlations of PR-FAT with other measures of fatigue and other patient-reported outcomes. Responsiveness was examined using changes in self-rated fatigue, self-rated health and satisfaction with health as anchors, and

standardized response means (SRMs) were calculated. MIDs were estimated using both anchor- and distribution-based methods.¹ Anchor-based analyses used comparisons of overall health to 6 months ago (rated as much better, somewhat better, neither better nor worse, somewhat worse, much worse).² Four sets of analyses were conducted: physician-confirmed PsA only without concomitant osteoarthritis (OA) or rheumatoid arthritis (RA) (n ranged from 60–78 in the 5 administrations) and with RA/OA (n: 102–129), and physician-confirmed PsA plus self-reported PsA without RA/OA (n: 111–148) and with RA/OA (ALL_PsA; n: 192–245).

Results: Findings were similar for all groups, so only results for ALL_PsA are shown. Table 1 shows characteristics of respondents. Cronbach's α was ≥ 0.94 for each administration. Concurrent validity analyses showed high correlations with self-rated fatigue (≥ 0.72), moderate correlations with pain (r: 0.45–0.66) and function (r: 0.34–0.58) and significant differences among self-rated health groups ($p < 0.0001$). In responsiveness analyses, all SRMs were > 0.3 . Estimates of MID are shown in Table 2.

Conclusion: PR-FAT appeared to be reliable and valid in this sample with PsA. SRMs in responsiveness analyses met the criterion generally accepted as adequate (0.3).³ The MID appears to be similar to those reported for other PROMIS scales. This information supports the use PR-FAT in PsA and provides important information to facilitate interpretation of scores.

References:

1. Revicki D, et al. *J Clin Epidemiol* 2008;**61**:102–9.
2. Bellamy N, et al. *Arthritis Care Res* 2015;**67**:972–80.
3. Revicki D, et al. *Health Qual Life Outcomes* 2006;**4**:70.

Table 1. Characteristics of Respondents to July 2017 Questionnaire (N=192)

Age, years	62.2±10.7
Male, %	73.3
White, %	93.5
PsA duration, years	20.8±12.3
Comorbid OA, %	14.1
Comorbid RA, %	27.2
HAQ score	0.83±0.68
Fatigue*	4.0 ± 3.1
PROMIS® Fatigue	53.3±12.7

Data are mean ±SD unless otherwise indicated

*Numeric rating scale: 0 (no problem) to 10 (severe problem)

OA=osteoarthritis; PROMIS®=Patient-Reported Outcomes Measurement Information System; PsA=psoriatic arthritis

Table 2. MID Estimates for PROMIS® Fatigue Short-Form in PsA

	Anchor-based analysis		Distribution-based analysis				MID best estimate	
	ΔPROMIS		Standard error of measurement		0.20 SD			
	Better*	Worse*	Mean	Range	Mean	Range		
Health compared with 6 months prior [†]	−3.0	1.8	2.26	2.09–2.48	2.39	2.24–2.54	−3	+2

Disclosure: P. Katz, Bristol-Myers Squibb, 2; A. Ogdie, Novartis, Pfizer, 2, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Corrona, Lilly, Novartis, Pfizer, Takeda, 5; E. Alemao, Bristol-Myers Squibb, 1, 3; J. Mukherjee, Bristol-Myers Squibb, 1, 3; K. Michaud, University of Nebraska Medical Center and FORWARD, The National Databank for Rheumatic Diseases, 3, Rheumatology Research Foundation and Pfizer, 2.

Abstract Number: 2915

Can Passively-Collected Phone Behavior Determine Rheumatic Disease Activity?

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Session Information

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Background/Purpose: Advances in reality mining combined with the pervasive use of smart phones have shown measurable changes in phone behavior due to changes in health. We sought to determine if passively collected digital measures could predict patient-reported outcome (PRO) measures in patients with rheumatic diseases.

Methods: Participants were a subset of adult smart phone users enrolled in Forward, The National Databank for Rheumatic Diseases during 2013-2015. They used a custom smart phone app that collected daily passive digital measures including GPS-tracked mobility (single path) and mobility radius (circle that included all daily mobility). Users with Android OS phones also provided number and duration of calls and texts. PROs included daily pain and global assessment and weekly HAQ-II and PAS-II. Disease flares were regularly self-reported. Statistics included linear mixed effect models (MRM) with random slope for days for PROs and logistic GEE (for flares). Best models were selected using stepwise. Moving averages (MA) of the prior week were applied to the log-transformed passive data. Possible confounders accounted for included patient demographics, clinic measures, and seasonal factors.

Results: Of the 446 participants, 292 (66%) had rheumatoid arthritis (RA). They were mostly female (91%), of middle age (54 ± 12 yrs) with moderate disability (HAQ-II 0.8 ± 0.6) and comorbid illness (RDCI 2.3 ± 1.7); 44% were treated with biologics. The MA of text length was most strongly and inversely associated with PROs including weekly pain ($\beta = -0.15$, 95%CI -0.26, -0.05). MA of mobility measures were significantly associated with global, HAQ-II, and PAS-II, but not pain. Table 1 shows estimates in RA from the MRM model for passive phone data keeping other variables at mean values. Flare incidence was significantly associated with the MA of mobility radius (OR = 0.92, 95%CI 0.86, 0.98).

Conclusion: Digital measures collected via smart phone may be a less intrusive means to identify worsening in patients with RA and other rheumatic diseases. Additional studies should confirm and expand these findings.

Table 1. Predictions of weekly PRO for ranges of passive data in RA patients

Passive variable	Estimated*: Pain	Global	HAQ-II	PAS-II
SMS length				
20 characters	3.46 (2.86 - 4.07)	3.50 (2.98 - 4.02)	0.98 (0.82 - 1.13)	2.61 (2.18 - 3.04)
50	3.32 (2.73 - 3.91)	3.38 (2.88 - 3.88)	0.96 (0.80 - 1.11)	2.51 (2.09 - 2.93)
100	3.21 (2.62 - 3.81)	3.29 (2.78 - 3.79)	0.94 (0.79 - 1.10)	2.43 (2.01 - 2.85)
150	3.14 (2.54 - 3.74)	3.23 (2.71 - 3.74)	0.93 (0.78 - 1.09)	2.38 (1.95 - 2.81)
500	2.96 (2.33 - 3.60)	3.08 (2.52 - 3.63)	0.91 (0.75 - 1.07)	2.26 (1.81 - 2.70)
Interaction diversity				
0	1.88 (0.40 - 3.37)	2.40 (0.92 - 3.88)	0.69 (0.39 - 0.99)	1.46 (0.51 - 2.41)
1 person	3.14 (2.54 - 3.75)	3.25 (2.74 - 3.77)	0.93 (0.77 - 1.08)	2.38 (1.95 - 2.81)
3	3.26 (2.67 - 3.85)	3.33 (2.83 - 3.84)	0.95 (0.79 - 1.10)	2.46 (2.04 - 2.89)
5	3.31 (2.72 - 3.91)	3.37 (2.87 - 3.87)	0.96 (0.80 - 1.11)	2.50 (2.08 - 2.93)
15	3.43 (2.82 - 4.04)	3.45 (2.92 - 3.97)	0.98 (0.82 - 1.14)	2.59 (2.16 - 3.02)
30	3.50 (2.87 - 4.13)	3.49 (2.95 - 4.95)	0.99 (0.83 - 1.15)	2.64 (2.20 - 3.08)
Reaction time				
0.5 hour	3.27 (2.67 - 3.86)	3.34 (2.84 - 3.84)		2.47 (2.05 - 2.89)
2.5	3.30 (2.71 - 3.89)	3.36 (2.86 - 3.86)		2.49 (2.07 - 2.92)
7	3.32 (2.73 - 3.92)	3.37 (2.87 - 3.88)		2.51 (2.09 - 2.93)
12	3.33 (2.74 - 3.93)	3.38 (2.88 - 3.88)		2.52 (2.10 - 2.94)
Mobility				
0.5 mile		3.31 (2.81 - 3.81)	0.95 (0.79 - 1.10)	2.47 (2.04 - 2.89)
5		3.47 (2.96 - 3.97)	0.97 (0.82 - 1.13)	2.53 (2.11 - 2.95)
10		3.51 (3.00 - 4.02)	0.98 (0.83 - 1.14)	2.55 (2.12 - 2.97)
20		3.56 (3.04 - 4.08)	0.99 (0.84 - 1.15)	2.57 (2.14 - 3.00)
Mobility radius				
1 mile		3.31 (2.80 - 3.81)	0.96 (0.81 - 1.12)	
5		3.34 (2.84 - 3.84)	0.96 (0.80 - 1.11)	
10		3.36 (2.85 - 3.86)	0.95 (0.80 - 1.11)	
50		3.39 (2.88 - 3.89)	0.95 (0.79 - 1.10)	
250		3.42 (2.91 - 3.93)	0.94 (0.78 - 1.09)	

* Adjusted for sex, ethnicity, total income, baseline pain, education, number of persons in household, rheumatic disease comorbidity index (RDCI), sleep scale, self-reported joint count, prior biologic and DMARD exposures, Medicare status, calendar year, season, region and season/region interaction.

Disclosure: K. Michaud, University of Nebraska Medical Center and FORWARD, The National Databank for Rheumatic Diseases, 3, Rheumatology Research Foundation and Pfizer, 2; S. Pedro, None; R. Schumacher, FORWARD, The National Databank for Rheumatic Diseases, 3.

New JADAS10- and cJADAS10-Based Cutoffs for Juvenile Idiopathic Arthritis Disease Activity States: Validation in a Multinational Dataset of 4830 Patients

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Session Information

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Session Title: Pediatric Rheumatology – Clinical III: Assessment Tools and Biomarkers

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Background/Purpose: The Juvenile Arthritis Disease Activity Score (JADAS) and its clinical version excluding the acute phase reactant (cJADAS) were developed for measuring disease activity in children with juvenile idiopathic arthritis (JIA). Cutoffs for the state of remission, low disease activity (LDA), moderate disease activity (MDA) and high disease activity (HDA) are necessary to interpret the scores. Aiming to obtain cutoffs suitable for any clinical setting, new values were recently developed for JADAS10 and cJADAS10 in oligoarthritis and polyarthritis, based on a large multinational dataset (Consolaro A, et al. *Arthritis Rheumatol.* 2017; 69s10). Aim of the study is to externally validate the new cutoffs for JADAS10 and cJADAS10 disease activity states.

Methods: Four JIA patients dataset were considered: 1) 4397 oligoarthritis and polyarthritis patients from the EPOCA study; 2) 148 oligoarthritis patients from the TRIMECA trial; 3) 172 polyarthritis patients from the Abatacept trial, 4) 113 patients first starting methotrexate from a monocentric retrospective cohort (Swart et al, *Ann Rheum Dis.* 2018;77:336-342). Face validity was assessed in dataset 1) by plotting the proportion of patients in remission and LDA against the values of the 6 parameters in the ACR JIA core set. Discriminative ability was assessed in datasets 2) and 3) by comparing the percentage of patients below the cutoff values in the different ACR pediatric categories of response. In dataset 1) we compared in each disease activity state, the level of pain (0-10 VAS), functional ability impairment, and number of restricted joints and the frequency of patients satisfied with disease outcome, starting a new medication for JIA, and having morning stiffness. Predictive ability was assessed in dataset 4) by calculating sensitivity and specificity of the cutoffs for remission and LDA after 3 months for treatment response after 12 months.

Results: Only most relevant results are described. JADAS10 and cJADAS10 cutoffs for remission allowed up to 1 active joint for polyarthritis and 0 for oligoarthritis. In dataset 2), 42% and 63% of patients achieving an ACRp70 response met the JADAS10 cutoffs for remission and LDA, respectively. In dataset 3), these percentages were 48% and 82%, respectively. In dataset 1), the median level of pain was 0, 1.5, 3, and 5.5 for polyarthritis patients in cJADAS10 remission, LDA, MDA, and HDA, respectively (Kruskal-Wallis $p < 0.001$). The frequency of satisfaction with disease outcome was 94%, 76%, 56%, and 24% for oligoarthritis patients in cJADAS10 remission, LDA, MDA, and HDA, respectively (Chi2 test $p < 0.001$). In dataset 4), 100% and 71% of patients with oligoarthritis classified as non-responders after 12 months had JADAS levels after 3 months above the cutoffs for remission and LDA, respectively. For polyarthritis, 90% and 80% of non-responders had JADAS levels after 3 months above the cutoffs for remission and LDA, respectively.

Conclusion: New JADAS cutoffs showed good face and content validity; achievement of remission and LDA defined by the cutoffs predicted the response to therapy. Cutoffs were developed and validated in a large multinational dataset and they are ready for use in clinical trials and routine practice.

Disclosure: A. Consolaro, None; C. Trincianti, None; P. van Dijkhuizen, None; G. Januskeviciute, None; G. Giancane, None; A. Alongi, None; J. Swart, None; N. Ruperto, full-time employee of the GASLINI Hospital, which has received contributions to support the research activities of the network of PRINTO from AbbVie Inc., AstraZeneca, Bristol-Myers Squibb, Janssen Biologics B.V., Eli Lilly and Co., "Francesco Angelini", 9, Astellas, AstraZeneca, Bristol-Myers Squibb, Italfarmaco, Janssen Biologics B.V., MedImmune, Roche, and Wyeth/Pfizer, 8; A. Ravelli, Abbvie, Bristol Myers Squibb, Novartis, Pfizer, Roche and Johnson & Johnson, 5, 8.

Multiplex Serum Biomarker Analysis before and during Therapy with Canakinumab in Patients with Systemic Juvenile Idiopathic Arthritis

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Background/Purpose: Canakinumab (CAN), a monoclonal anti-interleukin (IL)-1 β antibody, is approved for the treatment of systemic juvenile idiopathic arthritis (SJIA). CAN-treated patients with SJIA showed a high treatment response rate in an open-label long-term extension study. However, little is known about the correlation of various serum biomarkers in patients with different treatment outcomes.

Methods: Serum samples from 54 patients treated with CAN in the open-label long-term extension study were studied in a 14-plex bead array assay (Luminex) at different time points during the clinical trial, including days 1 (prior to first administration of CAN), 3 and 15, and months 1, 3, 6, 12, 18 and 24. Treatment outcomes included (1) a modified pediatric American College of Rheumatology (pACR) 90 response within 15 days of treatment with CAN and (2) an pACR100 response or clinical inactive disease within 15 days plus no disease flare or macrophage activation syndrome (MAS) during the study (=sustained complete response). Biomarker data, multiple clinical parameters and treatment outcomes were analysed using rank correlation, two-group comparisons via non-parametric testing (Mann-Whitney U test), receiver operating characteristic (ROC) analysis and hierarchical clustering.

Results: Twenty-six of 54 patients (49%) reached a modified pACR90 response within 15 days. Within a median follow-up of 23 months (range 0.5-32 months), 12 of 54 (22%) patients had a sustained complete response and 5 (9%) had developed MAS. Several biomarkers were moderately to strongly associated with each other prior to initiation of CAN therapy (Spearman rank correlation coefficient highest for interferon (IFN)- γ and IL-18: 0.90). Biomarkers did not correlate significantly with age, duration of disease or active joint count. Several biomarkers (IL-1 β , IL-18, IL-6 and S100A12) were markedly elevated when compared to healthy controls and decreased during CAN therapy. There were significant differences in day 1 CXCL9 levels between patients exhibiting an pACR90 response by day 15 (responders: median 296 pg/ml, non-responders: 709 pg/ml, $p < 0.01$). Further, day 1 levels of CXCL9, IL-7 and IL-18 as well as the CXCL9:IFN- γ ratio differed between sustained complete responders and those without sustained complete response (CXCL9 median: 278 pg/ml vs. 566 pg/ml; IL-7: 12.3 pg/ml vs. 7.4 pg/ml; IL-18: 1700 pg/ml vs. 556 pg/ml; CXCL9:IFN- γ ratio: 0.12 vs. 0.50). As determined via ROC analysis, these markers had moderate accuracy in predicting a sustained complete response (area under the curve: for CXCL9 0.72, CXCL9:IFN- γ ratio 0.79, IL-18 0.73, IL-7 0.83). Several clusters were apparent but not clearly related to clinical outcomes.

Conclusion: Several serum biomarkers measured prior to and shortly after initiation of CAN therapy in patients with SJIA showed an association with treatment response. Lower CXCL9 serum concentrations, a lower CXCL9:IFN- γ ratio, and higher IL-18 and IL-7 serum concentrations measured before CAN therapy were moderately associated with a better treatment response.

Disclosure: T. Hinze, Novartis, 5; C. Kessel, Novartis, 2; C. Hinze, Novartis, 5; J. Seibert, Novartis, 3; H. Gram, Novartis, 3; D. Foell, Novartis, 2.

Physical Activity in Canadian Children with Juvenile Idiopathic Arthritis: The LEAP Study (Linking Exercise, Activity, and Pathophysiology in Canadian Children with Arthritis)

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Background/Purpose: Physical activity (PA) is an important component of health, and is essential for optimal growth and development. Children with juvenile idiopathic arthritis (JIA) are reported to have lower PA levels than healthy peers, but most reported studies are cross-sectional and have included small patient numbers. The LEAP study is a large prospective study of children and youth with JIA, conducted at 12 centres in Canada, that aims to describe the trajectory of PA and its relationship to disease factors, quality of life, inflammation, and bone and muscle function. Here we report baseline PA at the time of LEAP study entry, and its association with these factors in children with JIA compared to healthy peers.

Methods: All patients with definite JIA (ILAR criteria) enrolled in the LEAP study between 2012-2015 who completed baseline visits were included. Patients had either newly diagnosed JIA (enrolled within 6 months of diagnosis), or previously diagnosed JIA (enrolled > 2yrs after diagnosis). The Physical Activity Questionnaire (PAQ) was the primary outcome. This 7 day self report tool is scored from 1 (very low PA) to 5 (high PA). We compared the PAQ for JIA patients to standard population normative values. The clinician completed demographic and clinical data, including a physician global assessment of disease activity (PGDA; VAS 0-100), while patient/parent-report outcomes included the Juvenile Arthritis Quality of Life Questionnaire (JAQQ), and the Childhood Health Assessment Questionnaire (CHAQ). Descriptive statistics and tests of association were performed using STATA.

Results: Of the 573 patients included (69% female, mean age 12.1 \pm 2.6 yr), 166 had newly diagnosed JIA and 407 had previously diagnosed JIA (median disease duration 0.3 and 5.8 yr respectively). The mean PAQ score was lower overall for children with JIA (mean 2.61, SD 0.75) compared to a healthy population (mean 2.75, SD 0.6) ($p < 0.001$). Newly diagnosed JIA patients had a lower PAQ score (median 2.54, IQR 2.4, 2.6) than those with longer disease duration (median 2.64, IQR 2.5, 2.7) ($p = 0.003$). PAQ score varied significantly ($p = 0.0059$) by JIA disease subtype, with lowest scores in patients with RF + polyarthritis (PAQ 2.15, IQR 1.9, 2.39) and enthesitis related arthritis (PAQ 2.48, IQR 2.29, 2.67); children with systemic JIA, oligoarticular persistent, psoriatic and undifferentiated subtypes had mean PAQ scores higher than 2.65. Variables associated with lower PAQ score included older age, higher number of active joints, and worse PGDA, JAQQ and CHAQ scores. Self-reported pain and gender were not associated with the PAQ score.

Conclusion: This large pan-Canadian study confirms that children with JIA have lower PA levels than healthy peers. PA is lower at diagnosis and in early disease compared to later in disease, and children with RF+ polyarthritis and ERA have lower PA levels. Children and youth with higher disease activity report lower PA, lower functional status and lower health related quality of life.

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An Epidemic: Severe Lung Disease in Patients with Systemic Juvenile Idiopathic Arthritis, Risk Factors and Predictors

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Session Information

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Session Title: Pediatric Rheumatology – Clinical III: Assessment Tools and Biomarkers

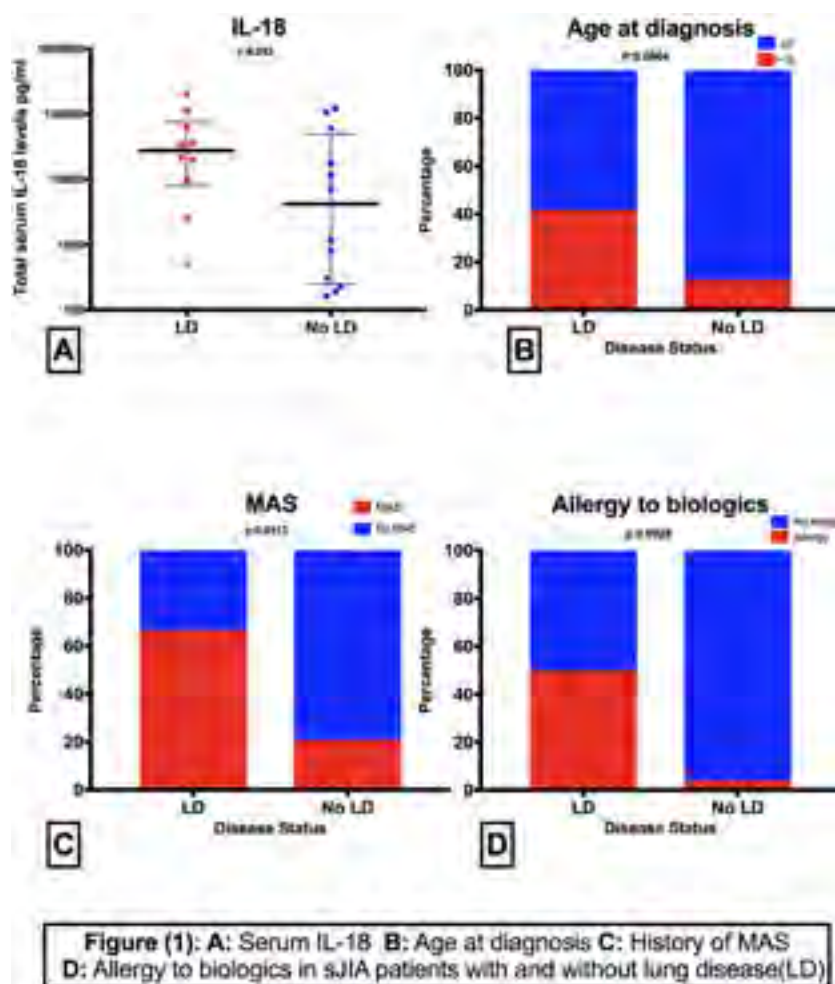
Session Type: ACR Concurrent Abstract Session

Session Time: 9:00 AM-10:30 AM

Background/Purpose: There is growing awareness of severe and often fatal chronic lung disease in patients with systemic juvenile idiopathic arthritis(sJIA). However, clinical features and risk factors for sJIA- associated lung disease are poorly characterized.

Objectives: 1- Describe clinical characteristics and immunological findings in patients with sJIA- associated lung disease.
2- Determine risk factors and predictors of lung disease in sJIA patients.

Methods: This study was approved by CCHMC Institutional Review Board, and informed consent was obtained from all patients. Clinical data was abstracted from medical records. We matched 12 sJIA patients with chronic with lung disease to



24 controls without lung disease using current age and gender (1:2) in a case-control design. We used Fischer exact and T-test for comparisons.

Results: Since 2010, we evaluated 12 patients (including second opinion) with sJIA-associated lung disease. Nearly half (5/12) were evaluated over the last year. In the last 5 years 74 patients with sJIA have had their primary rheumatology care at CCHMC. Of those patients, 6 developed lung disease, indicating both increased detection and an incidence as high as 8%.

In our cohort, 83% of patients with lung disease (10/12) were diagnosed with sJIA before age 5 (42% before age 2). Median age at diagnosis was 2.5 years (IQR: 0.75-4.25). When compared to controls, lung disease patients were diagnosed with sJIA at younger age, many before age 2 (OR: 5, $p=0.08$) (Figure 1-B). In the majority (75%) lung disease symptoms started within 1 year of diagnosis with mean time from sJIA onset to lung disease diagnosis of (1.65 ± 1.26). Interestingly, all patients with lung disease presented with prominent systemic features and two-thirds (66.6%) have history of macrophage activation syndrome (MAS). Compared to controls, lung disease patients were significantly more likely to have had MAS with OR of 7.6 ($p=0.0113$) (Figure 1-C). They also had markedly elevated IL-18 levels (Median 27,612.0, IQR: 9746-63,417). IL-18 levels were higher than those in patients with active sJIA without lung disease (Median 7194 IQR: 907-60,260 ($p:0.032$)), but when compared to age-matched controls it did not achieve significance ($P:0.093$) (Figure 1-A).

Moreover, significantly more patients with lung disease (6 patients) developed allergic/anaphylactic reaction to one of the cytokine-targeted biologics (mostly tocilizumab) with an OR of 23 ($p:0.0028$) (Figure 1-D).

Conclusion: Severe lung disease is increasingly recognized in children with sJIA, particularly in those presenting at younger age, with prominent systemic features, history of MAS, or allergy to biologics. These patients also tend to have ongoing chronic inflammation with highly elevated IL-18 levels. Early screening and expedited work up of this fatal complication is prudent especially in patients with before mentioned risk factors.

Disclosure: S. Yasin, None; C. Towe, None; N. Fall, None; A. Grom, Novartis, NovImmune and AB2Bio, 9; G. Schulert, None.

Abstract Number: 2920

Correlations of Type I Interferon Score and Interferon Induced Chemokines CXCL10 and CXCL9 with Cutaneous and Muscular Disease Activity in Juvenile Dermatomyositis

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Session Information

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Session Time: 9:00 AM-10:30 AM

Background/Purpose: Interferons (IFNs) seem to play an important role in the pathogenesis of juvenile dermatomyositis (JDM). We previously reported that expression of both type I and type II IFN related genes is increased in muscle biopsies of JDM patients and correlates with histological and clinical features of the disease. Interferon regulated genes (IRGs) have also been reported to be upregulated in peripheral blood of JDM patients and could represent valuable biomarkers of disease activity. The aim of this study was to investigate expression of IRGs (measured as type I IFN score), as well as serum levels of two type I and type II IFN induced chemokines (CXCL9, CXCL10) in peripheral blood of JDM patients and to assess their correlations with clinical and laboratory findings.

Methods: We collected 125 blood samples from 28 JDM patients at different time points during follow-up. We measured expression of IRGs (IFI27, IFI44L, IFIT1, ISG15, RSAD2, SIGLEC1) by quantitative PCR (qPCR) and calculated the type I IFN score; serum levels of CXCL9 and CXCL10 were analyzed by ELISA. At each visit, the following clinical data were recorded: physician's global assessment of disease activity VAS (Visual Analogue Scale), cutaneous VAS, Cutaneous Assessment Tool (CAT) activity score, Childhood Myositis Assessment Score (CMAS), serum levels of creatine phosphokinase (CK, IU/l), antinuclear antibody (ANA) status, presence of myositis specific or myositis associated antibodies (MSA/MAA), prednisone (or equivalent) dose (mg/kg/daily) ongoing immunosuppressive medications.

Results: Type I IFN score was significantly higher in patients with features of active disease (physician's global VAS >0.2, CAT activity score ≥ 1 , CK >150 IU/l). CXCL10 levels were significantly higher in patients with features of active muscle disease (CMAS <46, CK >150 IU/l) whereas CXCL9 levels were significantly higher only in patients with abnormal CK levels. In a multilevel mixed effect approach, type I IFN score was significantly associated with physician's global VAS, cutaneous VAS, CAT activity score, CMAS and CK levels; CXCL9 showed no significant association with the evaluated clinical features; CXCL10 levels were significantly associated with CK levels and CMAS. Including time from disease onset to sampling did not change the results. Immunosuppressive medications negatively modulated expression of IRGs and IFN induced chemokines.

Conclusion: Our findings indicate that expression of IRGs, measured as type I IFN score, and serum levels of CXCL10 reflect specific features of disease activity in JDM, further supporting their role as valuable disease biomarkers.

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Abstract Number: 2921

The Performance of the Newly Proposed EULAR/Acr Classification Criteria in Juvenile-Onset Systemic Lupus Erythematosus

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Session Information

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Session Time: 9:00 AM-10:30 AM

Background/Purpose: To avoid misclassifications, a new set of classification criteria have been developed by the collaboration of the EULAR/ACR and the draft was presented at the 2017 ACR/ARHP Annual Meeting. To compare the sensitivity and specificity of the new EULAR/ACR criteria with those of the 1997 ACR criteria and 2012 SLICC criteria in juvenile-onset SLE patients.

Methods: Juvenile SLE patients initially were evaluated by ACR-1997, SLICC-2012 and EULAR/ACR classification criteria at baseline. The diagnostic sensitivity of the three sets of classification criteria were further tested within 1 year of diagnosis and at last patient visit, longitudinally. Subjects with a clinical diagnosis other than SLE for at least 1 year-period, consecutively enrolled as controls.

Results: A total of 104 juvenile-onset SLE patients were enrolled for the sensitivity performance of classification criteria at diagnosis and 104 controls (69 juvenile idiopathic arthritis, 9 juvenile systemic sclerosis, 5 juvenile dermatomyositis, 1 mixed connective tissue disease, 15 vasculitis and 5 other diseases) for specificity at their last visit. Since the follow-up period was less than 1 year, 12 SLE subjects excluded after baseline evaluation. Finally, 92 SLE subjects were eligible for sensitivity evaluation within 1 year of diagnosis and at last visit. The median age of the SLE patients at diagnosis of clinician was 13.0 years (range 3.1–17.9 years, interquartile range (IQR) 11.1–16.5 years) with median disease duration of 5.0 years (IQR 3.0-8.0 years). The female-to-male ratio was 4.7:1. The newly developed EULAR/ACR classification criteria were more sensitive than SLICC-2012 and ACR-1997 at diagnosis (93.3% versus 91.3% and 85.6%, respectively), and at first year (95.7% versus 94.6% and 90.2%, respectively ($p > 0.05$)). At last visit the sensitivity of the new set of criteria and SLICC-2012 were same (97.8 %), but higher compared to ACR-1997 criteria (95.7%). Specificity of the EULAR/ACR criteria (86.5%, $n=90$) were found to be higher than SLICC-2012 (81.7%, $n=85$). Compared to SLICC-2012, an additional 5 subjects among 104 controls without SLE succeeded to get rid of misclassification as SLE by the newly developed criteria. However, the performance of the new EULAR/ACR criteria in diagnostic specificity (86.5%), could not reach the level of ACR-1997 criteria (89.4%).

Conclusion: Juvenile-onset systemic lupus erythematosus was classified by the newly proposed EULAR/ACR criteria with higher sensitivity compared with SLICC-2012 and ACR-1997 at disease onset and within one year of diagnosis. However, last visit assessment demonstrated equal sensitivity between new EULAR/ACR criteria and SLICC-2012. Although the difference was not significant, the new set of criteria seems to be capable of recruiting more children with juvenile SLE to clinical trials. The performance of the newly developed criteria seems more successful in specificity compared to the

SLICC-2012. Application of the newly developed EULAR/ACR criteria to the juvenile-onset SLE patients resulted in higher sensitivity and specificity compared to SLICC-2012.

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Abstract Number: 2922

Magnetic Resonance Imaging of Sacroiliac Joints in Patients with Osteitis Condensans Ilii Reveals a Typical Pattern of Lesions Relevant for Differential Diagnosis with Axial Spondyloarthritis

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical VI: Imaging of Axial SpA

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Session Time: 9:00 AM-10:30 AM

Background/Purpose: Osteitis condensans ilii (OCI) is regarded to as a non-inflammatory disorder induced by mechanical stress and mechanical instability of the sacroiliac joints (SIJ). OCI is being increasingly recognized as an important differential diagnosis for axial spondyloarthritis (axSpA), due to onset at young age, possible inflammatory character of back pain and recently described presence of subchondral bone marrow edema on magnetic resonance imaging (MRI) of the SIJ. The objective of the study was to compare active and chronic inflammatory lesions of the SIJ as detected by MRI in patients with OCI and axSpA.

Methods: Using medical database search we identified n=103 patients aged ≥ 18 years who were diagnosed with OCI upon presentation with chronic back pain and suspicion of axSpA. A total of 27 patients had evaluable MRIs of the SIJ in STIR and T1-weighted sequences that were used for the current study. These patients were matched according to the back pain duration to 27 patients with definite axSpA. MRIs were scored in a blinded fashion according to the Berlin scoring system for osteitis, fatty metaplasia, erosions, sclerosis and ankylosis independently by 3 trained and calibrated readers. In addition, the preferential localization of lesions (ventral, mid, or dorsal part of the SIJ) was recorded.

Results: There were no differences either in the osteitis score or in the proportion of patients with presence of osteitis on MRI of the SIJ between OCI and axSpA patients (table). The fatty metaplasia score was significantly lower in OCI as compared to axSpA, although the difference in the prevalence of the fatty lesions did not reach the level of statistical significance. There was a non-significant trend towards a higher sclerosis score in OCI patients. Importantly, there was a highly significant difference in the erosion score and in the prevalence of erosions: only 2 (7.4%) OCI vs. 18 (66.7%)

Table 1. MRI findings in the sacroiliac joints in patients with osteitis condensans ilii (OCI) and with axial spondyloarthritis (axSpA).

MRI findings		OCI	axSpA	p-value ^{***}
		N=27	N=27	
Osteitis	Osteitis score (0-24), mean \pm SD	3.8 \pm 2.3	4.4 \pm 4.1	0.89
	Osteitis present*, n (%)	25 (90.2%)	23 (85.2%)	0.351
Fatty metaplasia	Fatty metaplasia score (0-24), mean \pm SD	2.0 \pm 2.3	4.5 \pm 6.7	0.001
	Fatty metaplasia present*, n (%)	14 (51.9%)	20 (74.1%)	0.158
Erosions	Erosions score (0-6), mean \pm SD	0.2 \pm 0.4	3.0 \pm 2.3	<0.001
	Erosions present*, n (%)	2 (7.4%)	18 (66.7%)	<0.001
Ankylosis	Ankylosis score (0-2), mean \pm SD	0	0.3 \pm 0.7	0.040
	Ankylosis present*, n (%)	0 (0%)	4 (14.8%)	0.111
Sclerosis	Sclerosis score (0-2), mean \pm SD	1.4 \pm 0.6	1.0 \pm 0.8	0.055
	Sclerosis present*, n (%)	24 (88.9%)	19 (70.4%)	0.175

The absolute lesion scores represent mean values of 3 readers.

* Score ≥ 1 in the opinion of at least two readers.

** Mann-Whitney U-test for the scale variable or Fisher's exact test for the categorical variables.

axSpA patients had at least one erosion (table 1). Importantly, none of the OCI patients had high-grade (>5 erosions) erosive changes.

There were substantial differences concerning localization of the lesions: in OCI, ventral localization was recorded in 96% of the cases for osteitis, in 100% for fatty metaplasia, and in 96% for sclerosis, while in axSpA, osteitis was preferentially localized in the ventral part only in 29% of the cases, fatty metaplasia in 25%, sclerosis in 29% ($p<0.001$ for all comparisons vs. OCI). Ankylosis and erosions were localized in the mid part in almost all cases.

Conclusion: MRI of sacroiliac joints in OCI is characterized by preferential ventral localization of lesions (osteitis, fatty metaplasia, and sclerosis), absence of ankylosis and absence of extended erosive changes. Such a findings constellation should be taken into account as suggestive of OCI for the differential diagnosis of axSpA in clinical practice.

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Abstract Number: 2923

Is All MRI-SIJ Inflammation the Same? Gradient of Structural Damage with Increasing Cumulative Inflammation at the SIJ Quadrant Level in Axial Spondyloarthritis – 5-Year Data from the DESIR Cohort

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical VI: Imaging of Axial SpA

Session Type: ACR Concurrent Abstract Session

Session Time: 9:00 AM-10:30 AM

Background/Purpose: Axial inflammation is a key feature in axial spondyloarthritis(axSpA). An (overall) definition of bone marrow oedema (BMO) on the MRI of the SIJ(MRI-SIJ) has been proposed by ASAS (i.e. considering all 8 anatomical quadrants (Q) of both SIJ together). This study aims to investigate how BMO evolves over time at the quadrant level by comparing several patterns of inflammation and their possible impact on clinical and structural outcomes.

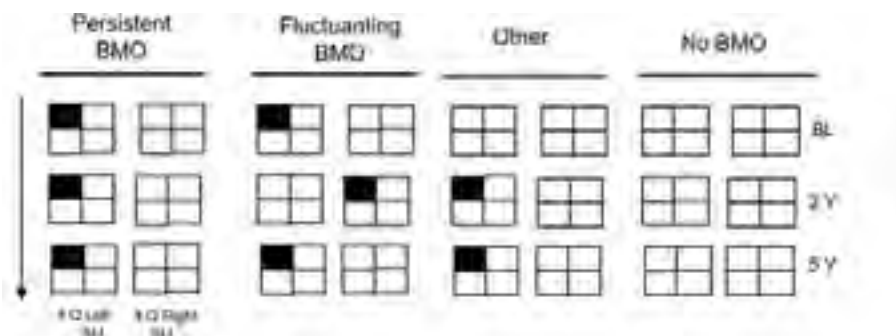


Figure. Graphical representation of examples (of the multiple possible combinations) of presentation of BMO throughout time (baseline, 2 and 5 years) across 8 SIJ quadrants and combined into four patterns. **Persistent BMO:** Constant BMO, in at least one quadrant (e.g. 1-1-1, and no fluctuating pattern in the remaining quadrants). **Fluctuating BMO:** Fluctuating BMO at any of the 8 quadrants (e.g. 1-0-1 or 0-1-0 across observations), regardless of the pattern of BMO in the remaining quadrants; **Other:** Other pattern of BMO (not included in the previous) (e.g. 1-1-0 in one quadrant); **No BMO:** No BMO at any observation (0-0-0, in all quadrants).

Table. Clinical and imaging features at 5 years comparing the different BMO change patterns* (n=136)

	Persistent BMO (n= 14; 10.3%)	Fluctuating BMO (n=17; 12.5%)	Other pattern of BMO (n=42; 30.9%)	No BMO (n= 63;46.3%)	p-value§
ASDAS-CRP	2.0 (0.9)	1.5 (0.9)	2.0 (0.9)	2.0 (0.9)	0.18
CRP mg/L	6.4 (6.0)	4.6 (5.7)	3.8 (4.7)	3.2 (2.6)	0.03
BASFI (0-10)	2.0 (1.6)	1.2 (1.7)	1.9 (2.0)	2.3 (2.2)	0.27
BASMI (0-10)	2.5 (1.4)	1.9 (0.5)	2.3 (0.9)	2.4 (0.8)	0.31
ASQoL (0-18)	6 (4.6)	4.4 (4.5)	6.3 (5.3)	7.4 (5.2)	0.17
mNYC (%)	6 (46)	6 (35)	10 (24)	5 (9)	<0.05
mNYC continuous (0-8)	3.4 (2.6)	2.4 (2.0)	1.9 (1.9)	1.0 (1.4)	<0.01
mSASSS (0-72)	4.9 (11.5)	0.2 (0.5)	1.0 (2.5)	1.0 (3.1)	0.33
N Syndesmophytes	1.7 (3.8)	0 (0)	0.2 (1.0)	0.3 (1.0)	0.05
SPARCC SU (0-72)	8.5 (5.8)	6.3 (7.5)	2.4 (4.1)	0.1 (0.3)	<0.01
MRI-SIJ ≥ 5 fatty lesions or erosions (%)	7 (50)	8 (47)	12 (29)	3 (5)	<0.01

*Detailed in Figure. Mean (SD) or n (%). §For categorical variables chi2 was used; for continuous Kruskal-Wallis H test was used.

Methods: Patients from the DESIR cohort (early axSpA according to the rheumatologist) with MRI-SIJ available at baseline, 2 and 5 years were included. Each image was scored by 3 trained central readers blinded to chronological order. BMO was considered positive if detected (by $\geq 2/3$ readers) in $\geq 1/6$ slices in each of the 8 quadrants and per timepoint. Four different patterns of BMO throughout time were defined (persistent same Q BMO, persistent fluctuating Q BMO, other pattern of BMO and no BMO) considering all 8 quadrants (Figure). The four groups were compared in terms of clinical and imaging outcomes at 5 years.

Results: In total 136 patients were included (age 34 (SD 9) years, 50% male, and 63% HLA-B27 positive). The ‘No BMO’ pattern was the most frequent (n=63; 46%). The fluctuating pattern was seen in 17 patients (13%) and the ‘persistent BMO’ in 14 patients (10%). ‘Other patterns of BMO’ (not fitting any of the previous) were seen in 42 patients (31%). Considering the increasing sequence of local inflammation as ‘no BMO’, ‘other patterns of BMO’, ‘fluctuating BMO’ and ‘persistent BMO’, a gradient could be found in several outcomes, namely: higher likelihood to be mNYC positive (9%, 24%, 35% and 46%, respectively); higher CRP (3.2, 3.8, 4.6 and 6.4 mg/L), higher SPARCC-SIJ scores (0.1, 2.4, 6.3 and 8.5), and a higher frequency of SIJ structural changes (≥ 5 fatty lesions or erosions: 5%, 29%, 47% and 50%) at 5 years (Table). Bone formation was especially observed in the persistent BMO group. No differences in treatment were found across the groups.

Conclusion: Only 10% of the patients showed persistent inflammation in the same Q over a 5-year period and 12.5% fluctuating inflammation in different Qs. A gradient of higher structural damage and systemic inflammation was found in patients with increasing cumulative local inflammation at the quadrant level of the SIJ.

Disclosure: S. Rodrigues Manica, None; A. Sepriano, None; S. Ramiro, None; R. B. M. Landewé, None; P. Claudepierre, None; A. Moltó, None; M. Dougados, None; M. van Lunteren, None; D. van der Heijde, None.

Abstract Number: 2924

Spinal Radiographic Progression in Early Axial Spondyloarthritis: 5-Year Data from the DESIR Cohort

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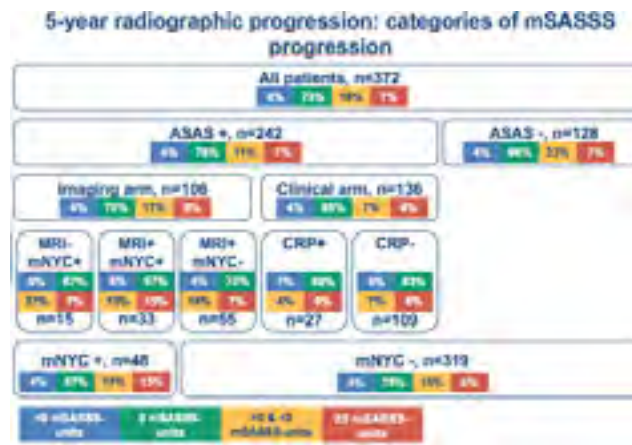
Session Information

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Background/Purpose: Spinal radiographic progression has been investigated in patients with r-axSpA, but not yet as thoroughly in early axSpA. We aimed to analyse the progression of spinal radiographic damage in patients with early axSpA.

Methods: Five-year spinal radiographs from patients with early axSpA from the DESIR cohort were scored by 3 readers (average) according to the mSASSS (0-72). Change scores for all available intervals were calculated. The development of new syndesmophytes (2 out of 3 readers) was calculated as a net change: number of patients with positive change minus number of patients with negative change divided by total number of patients. Two- and 5-year mSASSS progression and development of new syndesmophytes were assessed in subgroups defined at baseline according to the ASAS axSpA criteria and its arms, mNYC and also to the presence of syndesmophytes.

Results: In total, 549 patients (mean age 34 (SD 9) years, 46% males, 63% fulfilling ASAS axSpA criteria, baseline mSASSS0.5(1.5)) were included. Thirty-eight patients (7%) showed syndesmophytes at baseline, 42% of which were ASAS axSpA criteria negative. Mean mSASSS progression was 0.2(0.9) at 2 years and 0.4(1.8) at 5 years. 18% of the patients fulfilling the ASAS axSpA criteria showed a 5-year positive mSASSS change (>0), compared to 30% in those not fulfilling the criteria (Figure). 26% of the patients fulfilling the imaging arm had a positive change: highest positive change in MRI-mNYC+ (34%), followed by MRI+mNYC+ (27%) and lastly MRI+mNYC- (23%). Mean mSASSS progression was highest in the mNYC+MRI+ group (1.3(4.0)). Eleven percent of the patients fulfilling only the clinical arm of the ASAS criteria had a positive change in mSASSS at 5 years, mean change of 0.1(0.7). Patients with baseline syndesmophytes (across all subgroups) had the highest progression: 2.7(5.0) mSASSS-units. At 5 years, 7% of all patients had a net change of any new syndesmophyte; this was 6% for ASAS+, 9% for ASAS-, 10% for the imaging arm (18% for mNYC+MRI+) and 3% for patients fulfilling the clinical arm only. Seventeen percent of the mNYC+ patients had a net change in new syndesmophytes as well as 42% of the patients with baseline syndesmophytes.

Conclusion: Spinal radiographic progression, though limited in early axSpA, can be captured already at 2 years of follow-up. Inflammation and damage in the SIJ are associated with a higher radiographic progression. The presence of baseline syndesmophytes strongly predicts the development of further structural damage already early in the disease.

Figure: Five-year mSASSS radiographic progression categories according to the subgroups of the ASAS criteria, arms of the ASAS criteria and fulfillment of mNYC at baseline.

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Abstract Number: 2925

Fatty Lesions Detected on MRI Scans in Patients with Ankylosing Spondylitis Are Based on the Deposition of Fat in the Vertebral Bone Marrow

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical VI: Imaging of Axial SpA

Session Type: ACR Concurrent Abstract Session

Session Time: 9:00 AM-10:30 AM

Background/Purpose: Fatty lesions (FL), similar to bone marrow edema (BME) and sclerosis (SCL), are characteristic findings in MRI examinations of patients with ankylosing spondylitis (AS) and degenerative disc disease (DDD). It has recently been shown that FL are associated with syndesmophyte formation in AS. The anatomic correlate of FL has not been studied to date. Current assumptions are solely based on non-invasive data. Here we examine the cellular composition of FL in the edges of vertebral bodies of patients with AS or DDD by histology.

Methods: Patients with AS or DDD undergoing planned kyphosis correction surgery by spinal osteotomy (in AS) or surgery to correct spinal stenosis (in DDD) were included into this biopsy study. The spinal surgeon (HB) took all biopsies mainly in the area close to the vertebral edge in many of which FL had been seen by MRI (Fig. 1a for AS and 1b for DDD). Biopsies were decalcified, embedded in paraffin, cut and stained by hematoxylin and eosin. The marrow composition was analyzed and the cellularity graded (%surface area) by two different investigators blinded to patients' diagnosis. Four different marrow compositions could be differentiated: (i) fat, (ii) fibrosis, (iii) inflammation and (iv) hematopoiesis (normal).

Results: A total of 60 biopsies mostly obtained from the lower thoracic spine and the lumbar spine of 21 AS patients (mean age 51.7 years, mean disease duration 24.6 years) and of the lumbar spine in 18 DDD patients (mean age 60.1 years) were available. On the patient level, the histological appearance of MRI-FL was different between the groups: fat marrow was present in biopsies of 19 AS (90%) but in only 5 DDD (28%) patients. Inflammatory marrow changes, resembling mononuclear infiltrates, were found in 8 AS (38.1%) and 14 DDD (77.8%) patients at areas with concomitant FL and BME on MRI, while marrow fibrosis was seen in 6 AS (28.6%) and 4 DDD (22.2%) patients at areas with concomitant FL and SCL on MRI.

In the semiquantitative histopathological analysis, the mean distribution (\pm standard deviation) of the various bone marrow tissue types in the biopsies differed between the AS vs. DD in a similar way, with 43% (\pm 26.3%) vs. 16% (\pm 30.3%) for fatty marrow, 11% (\pm 15.5%) vs. 55% (\pm 42%) for inflammatory marrow and 9% (\pm 16.1%) vs. 13% (\pm 27.8%) for fibrotic marrow, respectively.

Conclusion: The presence of FL on MRI corresponds to fat deposition in the bone marrow of patients with advanced AS. These data show that the MRI change termed “fatty lesion” is indeed based on the deposition of fat in the vertebral bone marrow in AS. Since vertebral bone marrow is physiologically harboring hematopoiesis, AS seems to lead to a change in the bone marrow microenvironment with local disruption of hematopoiesis and replacement by fat. The link between fat and new bone formation should be studied in earlier disease stages.

Disclosure: X. Baraliakos, None; H. Boehm, None; A. Samir, None; G. Schett, None; J. Braun, None; A. Ramming, None.

Which MRI Lesions in the Sacroiliac Joint Are Associated with the Diagnosis of Axial Spondyloarthritis after 2 Years Follow up in the Echography in Spondyloarthritis Cohort?

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Session Information

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Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical VI: Imaging of Axial SpA

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Session Time: 9:00 AM-10:30 AM

Background/Purpose: MRI of the sacroiliac joint (SIJ) is emerging as an important prognostic tool for assessment of patients presenting with axSpA. A major challenge in the evaluation of early SpA is establishing the diagnosis and this requires prospective follow up to determine which cases have developed axSpA with more certainty. We aimed to assess the baseline distribution and prognostic capacity of MRI lesions in the SIJ of patients diagnosed with axSpA after 2 years follow up in the ECHOSPA cohort.

Methods: Consecutive outpatients with age <50 years and symptoms >3 months suggestive of SpA (inflammatory back pain [IBP], peripheral arthritis or inflammatory arthralgia (IA), enthesitis or dactylitis, uveitis with HLA-B27 positivity, a family history of SpA) were enrolled. The diagnosis of SpA was ascertained by an expert committee, blind to MRI evaluation, after at least 2 years of follow-up. MRI scans from 223 cases were available for evaluation by 2 readers and an adjudicator who assessed MRI lesions in the SIJ according to updated consensus definitions from the ASAS-MRI group. These were recorded in an ASAS consensus-derived eCRF that comprises global assessment (active and/or structural lesion typical of axSpA present/absent) and detailed scoring of individual lesions (SPARCC SIJ inflammation, SPARCC SIJ structural). Clinical, lab, and imaging variables associated with the diagnosis of axSpA at 2 years were first identified by univariate regression. A base model of all clinical/lab variables associated with axSpA was included as a group in multivariate logistic regression models that tested the independent association with MRI lesions.

Results: Mean age of the 223 cases was 39.6 (10.5) years, mean symptom duration was 2.5 (4.1) years, 49.5% were HLA-B27+ and 63.7% were female. Primary inclusion criterion was IBP in 53%, IA in 27%, ED in 9%, B27+U in 8% and Fam in 4%. At 2 years follow up, 165(74%) were deemed to have axSpA. In group comparisons (Table) and univariate regression, both active and structural MRI lesions were associated with diagnosis of axSpA at 2 years ($p=0.03$, $p=0.01$, respectively). Age, B27, and psoriasis were the clinical variables associated with diagnosis of axSpA at 2 years in univariate analysis (all $p<0.0001$) and were included together with gender in multivariate analyses. Active and structural lesions typical of axSpA and SPARCC BME score ≥ 2 were each independently associated with diagnosis of axSpA at 2 years (OR (95%CI)- 6.8(1.4-34.1)($p=0.02$); 17.9(2.2-146.6) ($p=0.007$); 4.9(1.3-18.4) ($p=0.02$). With all variables simultaneously added to the model, only structural lesions were significantly associated.

Conclusion: Assessment of both active and structural lesions on MRI may help determine which patients have axSpA with higher diagnostic certainty over time.

Table. Distribution of MRI lesions at baseline according to diagnosis of axSpA after 2 years.

MRI Lesion	AxSpA n=165 (74.0%)	NOT SpA n=58 (26.0%)	P value
Active lesion typical for axSpA	26 (16.0%)	2 (3.6%)	0.019
Active lesion typical for axSpA (confidence ≥ 3 , 0-4 scale)	18 (11.9%)	1 (1.8%)	0.027
ASAS MRI positivity	24 (14.6%)	1 (1.7%)	0.006
ASAS MRI positivity (confidence ≥ 3 , 0-4 scale)	17 (10.8%)	1 (1.7%)	0.048
Structural lesion typical for axSpA	32 (19.6%)	1 (1.8%)	0.0004
Structural lesions typical for axSpA (confidence ≥ 3 , 0-4 scale)	27 (17.3%)	0 (0%)	0.0002
Active AND structural lesion typical for axSpA	19 (11.7%)	0 (0%)	0.004
Active OR structural lesion typical for axSpA	39 (23.9%)	3 (5.4%)	0.001
Only active lesion typical of axSpA	7 (4.3%)	2 (3.6%)	1.0
Only structural lesion typical of axSpA	13 (8.0%)	1 (1.8%)	0.12

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Abstract Number: 2927

What Are the Optimal MRI Lesion Cut-Offs That Define Active and Structural Lesions in the Sacroiliac Joint As Being Typical of Axial Spondyloarthritis By Expert Readers?

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical VI: Imaging of Axial SpA

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Session Time: 9:00 AM-10:30 AM

Background/Purpose: Defining what constitutes a definite MRI lesion in the SIJ typical of axSpA has been hampered by lack of international consensus for standardized lesion descriptions and definitions. The ASAS MRI group has generated updated consensus lesion definitions (ASAS_MRI_defⁿ) for the spectrum of MRI lesions in the SIJ and these have been applied to the assessment of MRI images from the ASAS Classification Cohort (ASAS-CC) by 7 experts in MRI interpretation from the ASAS-MRI group. We aimed to determine optimal quantitative SPARCC cut-offs for specific MRI lesions for a definite MRI lesion typical of axSpA, the external reference being majority reader decision as to the presence of an active or structural lesion typical of axSpA.

Methods: ASAS_MRI_defⁿ were recorded in an eCRF that comprises global assessment (active or structural lesion typical of axSpA present/absent), links to reference images, and detailed scoring of lesions per SIJ quadrant (SPARCC SIJ inflammation, SPARCC SIJ structural). MRI images were available from 278 of the 495 cases that had MRI performed in the ASAS-CC. Detailed SPARCC scoring data was based only on assessment of images in DICOM format (n=175). We calculated sensitivity and specificity for varying numbers of SIJ quadrants with bone marrow edema (BME), erosion, and fatty lesions where a majority of readers ($\geq 4/7$) agreed as to the presence of an active or structural lesion typical of axSpA.

Results: BME was the most frequent lesion (SPARCCBME score, mean (SD) =14.4(15.5) in cases where a majority of readers agreed there was an active lesion typical of axSpA. For majority agreement as to the presence of a structural lesion typical of axSpA, the most frequent lesions were fatty lesion, and erosion (mean (SD) SPARCC score per case of 8.6(9.1) and 8.2(5.7), respectively). Other structural lesions were much less frequent. Optimal SPARCC cut-offs that focus on specificity ($\geq 95\%$) were BME ≥ 3 for defining an active lesion, and fatty lesion ≥ 3 and erosion ≥ 2 for defining a structural lesion (Table).

Conclusion: The ASAS MRI specific lesion definitions perform well when judged against the expert opinion of ASAS-MRI readers. In particular, the optimal cut-off for an erosion lesion, as defined by ASAS, has similar performance to the optimal cut-off for BME.

Table. Sensitivities and specificities of cut-offs for SIJ lesion scores (number of SIJ quadrants) according to presence of definite active or structural lesion typical for axSpA ($\geq 4/7$ readers in agreement)

	Sensitivity (95% CI)	Specificity (95% CI)
Majority agree active lesions indicative of axSpA present		
BME Score ≥ 2	80.0 (65.4 - 90.4)	93.9 (88.2 - 97.3)
BME Score ≥ 3	77.8 (62.9 - 88.8)	99.2 (95.8 - 100.0)
Majority agree structural lesions indicative of axSpA present		
Fatty lesion (any) ≥ 2	63.2 (46.0 - 78.2)	90.5 (83.7 - 95.2)
Fatty lesion (any) ≥ 3	55.3 (38.3 - 71.4)	94.8 (89.1 - 98.1)
Erosion Score ≥ 2	84.2 (68.7 - 94.0)	96.6 (91.4 - 99.1)
Erosion Score ≥ 3	79.0 (62.7 - 90.4)	99.1 (95.3 - 100.0)
Majority agree active OR structural lesions indicative of axSpA present		
BME Score ≥ 2	70.4 (56.4 - 82.0)	95.0 (89.5 - 98.2)
BME Score ≥ 3	66.7 (52.5 - 78.9)	100.0 (97.0 - 100.0)
Fatty lesion ≥ 2	50.0 (36.1 - 63.9)	93.4 (87.4 - 97.1)

Table . (Cont'd)

	Sensitivity (95% CI)	Specificity (95% CI)
Fatty lesion ≥ 3	40.7 (27.6 - 55.0)	95.9 (90.6 - 98.6)
Erosion Score ≥ 2	63.0 (48.7 - 75.7)	98.4 (94.2 - 99.8)
Erosion Score ≥ 3	57.4 (43.2 - 70.8)	100.0 (97.0 - 100)

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Validation of New Systemic Lupus Erythematosus Classification Criteria

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Systemic Lupus Erythematosus – Clinical V: Biomarkers, Criteria, and Outcomes

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Background/Purpose: Correct classification of patients with systemic lupus erythematosus (SLE) is critical for clinical trials and clinical and translational science. The ACR 1997 criteria were criticized for their suboptimal sensitivity. The Systemic Lupus International Cooperating Clinics (SLICC) 2012 criteria increased sensitivity, but at the price of reduced specificity. This and further advances in the field led to the current four phase SLE criteria project. Following an item generation phase and item reduction via a Delphi and a nominal group exercise (1), the provisional criteria were derived from a multicriteria decision analysis exercise (2). These criteria were hence simplified and validated in a large international cohort.

Methods: A large international cohort of 2,321 patients was collected from 23 SLE expert centers, contributing up to 100 patients with SLE and with non-SLE, each. Diagnoses were verified by 3 independent reviewers for 1,193 SLE and 1,059 non-SLE patients. 501 randomly selected SLE and 500 non-SLE patients formed the derivation cohort. All other patients with confirmed SLE or non-SLE diagnosis formed the validation cohort. Sensitivity and specificity were compared to the ACR 1997 and the SLICC 2012 criteria.

Results: The criteria were fine-tuned and simplified, using ANA of $\geq 1:80$ as entry criterion and a classification threshold of 10. Items can only be counted for classification if there is no more likely cause, and at least one clinical item must be present.

Renal	Class III/IV nephritis	10	Class II/V nephritis	8	Proteinuria ≥ 0.5 g/day	4
Specific antibodies	Anti-Sm or Anti-dsDNA	6				
Muco-cutaneous	ACLE	6	SCLE or DLE	4	Alopecia or oral ulcers	2
Serosa	Acute pericarditis	6	Effusion	5		
Musculo-skeletal	Arthritis	6				
CNS	Seizures	5	Psychosis	3	Delirium	2
Blood	Autoimmune hemolysis or thrombocytopenia	4	Leukopenia	3		
Complement	Low C3 and C4	4	Low C3 or C4	3		
Anti-phospholipid	Anti-Cardiolipin or anti- $\beta 2$ -GPI or lupus anticoagulant	2				
Constitutional	Fever	2				

Sensitivity was close to the SLICC 2012 criteria, specificity maintained at the level of the ACR 1997 criteria. This performance was independently confirmed in the validation cohort.

	ACR 1997 criteria	SLICC criteria	New criteria
Derivation			
Sensitivity	84.63	96.81	98.00
Specificity	95.20	90.00	96.40
Validation			
Sensitivity	82.76	96.70	96.12
Specificity	93.38	83.62	93.38

Conclusion: The novel set of criteria reached the goal of improved sensitivity close to the SLICC 2012 criteria, while maintaining the specificity of the ACR criteria.

Funding note: This project is jointly supported by the ACR and EULAR, but the final criteria have not yet been reviewed or approved by either organization.

References: (1) Aringer et al. Ann Rheum Dis 2017;76 (S2):4; (2) Tedeschi et al. Arthritis Rheumatol 2017; 69 (S10): #1589

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Validation of Remission and Lupus Low Disease Activity State As Predictors of Organ Damage in SLE

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Session Information

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Session Title: Systemic Lupus Erythematosus – Clinical V: Biomarkers, Criteria, and Outcomes

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Background/Purpose: Outcome measures that combine control of SLE activity and prednisone reduction are clinically relevant. A clinical goal in SLE is to reduce risk of long-term organ damage. We assessed whether two recently proposed disease activity outcomes were predictive of future damage.

Methods: For each month of follow-up in a large SLE cohort, we determined whether the patient was in Clinical Remission (as defined by the DORIS working group) or lupus low disease activity state (LLDAS) (as defined by Franklyn et al). Clinical Remission was defined as a PGA<0.5, clinical SLEDAI=0 and no prednisone or immunosuppressants. Clinical Remission on Treatment allowed for prednisone≤5mg/day and immunosuppressant use. LLDAS was defined as a SLEDAI ≤4, PGA ≤1.0, no major organ activity, and no new activity. LLDAS on treatment allowed for prednisone use ≤7.5 mg/d and immunosuppressants. Damage was defined using the SLICC/ACR Damage index.

Results: There were 81,118 person-months observed among 2,026 patients (92% female, 53% Caucasian, 39% African-American). Table 1 shows the rates of damage, per person month, in subgroups defined by Remission or LLDAS.

Table 1. Rates of new damage, in subgroups defined by past levels of disease activity

Percentage of Prior Months in:	Number of person-months observed	Number of months with an increase in SLICC/ACR Damage Index	Rate of damage per 100 person months	Rate Ratios	P-values
Clinical Remission	-	-	-	-	-
None	35,772	406	1.13	1.0 (Ref)	-
Not none, but < 25%	14,358	102	0.71	0.60 (0.48,0.75)	<0.0001
25% to 50%	6573	50	0.76	0.66 (0.46,0.94)	0.023
50% to 75%	3845	27	0.7	0.63 (0.42,0.97)	0.035
75%+	1,641	10	0.61	0.58 (0.30,1.15)	0.12
Clinical Remission on Treatment	-	-	-	-	-
None	16,491	250	1.52	1.0 (Ref)	-
Not none, but < 25%	20,169	170	0.84	0.54 (0.44,0.67)	<0.0001
25% to 50%	14,344	103	0.72	0.46 (0.36,0.60)	<0.0001
50% to 75%	8396	54	0.64	0.43 (0.30,0.60)	<0.0001
75%+	2,789	18	0.65	0.45 (0.27,0.75)	0.0019
LLDAS	-	-	-	-	-
None	30,366	343	1.13	1.0 (Ref)	-
Not none, but < 25%	10,880	106	0.97	0.86 (0.69,1.07)	0.18
25% to 50%	5012	40	0.8	0.70 (0.51,0.98)	0.037
50% to 75%	8494	60	0.71	0.63 (0.48,0.83)	0.001
75%+	7,527	46	0.61	0.54 (0.40,0.73)	<0.0001
LLDAS on Treatment	-	-	-	-	-
None	7,656	117	1.53	1.0 (Ref)	-
Not none, but < 25%	10,555	134	1.27	0.83 (0.65,1.06)	0.14
25% to 50%	12,686	129	1.02	0.66 (0.51,0.85)	0.0013
50% to 75%	18,151	133	0.73	0.48 (0.37,0.61)	0.001
75%+	13,141	82	0.62	0.40 (0.30,0.54)	<0.0001

Damage rates were relatively low when LLDAS was achieved at least 50% of the time. These rates were similar to those experienced by patients who met a more stringent treatment restriction with Remission on Treatment at least 50% of the time.

Conclusion: Percent time in LLDAS had a clear dose response for rate ratios of organ damage. The equivalence of LLDAS and DORIS remission on treatment is welcome news, as LLDAS on treatment > 50% of the time is an easier goal to achieve (3 times more person-months observed in our cohort) and more realistic as a clinical trial outcome.

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Prospective Comparison of Remission and Lupus Low Disease Activity State – Effect on Disease Outcomes in Systemic Lupus Erythematosus

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Systemic Lupus Erythematosus – Clinical V: Biomarkers, Criteria, and Outcomes

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Background/Purpose: The Definitions of Remission in SLE (DORIS) group has proposed multiple definitions of remission, but these are infrequently attained and have not previously been evaluated in relation to protection from damage accrual in a prospective study. In contrast, the Lupus Low Disease Activity State (LLDAS) is potentially more attainable, and has been shown to be associated with improved patient outcomes. The objective of this study was to compare the attainability and effect of LLDAS and remission on outcomes in a prospective multicenter study.

Methods: A prospective multinational cohort study was undertaken in 13 centres between 2013-2017. Time dependent Cox proportional hazards models were used to compare LLDAS and DORIS definitions of remission in terms of impact on disease flares and damage accrual. All eight DORIS remission definitions include a clinical SLEDAI-2K of 0, and PGA (0-3) <0.5, whilst varying in allowing for serological activity, prednisolone and immunosuppressants.

Results: 1735 SLE patients (meeting ACR or SLICC criteria) were recruited, and followed for (mean \pm SD) 2.2 ± 0.9 years, totalling 12,534 visits. LLDAS was achieved in 6922 visits (54.6%). In contrast, remission was achieved in 140 (1.1%) to 1952 (15.4%) visits depending on definition. LLDAS attainment at any visit was associated with significantly reduced subsequent flare (HR 0.65, 95%CI 0.56-0.76, $p < 0.001$) and damage accrual (HR 0.55, 95%CI 0.43-0.70, $p < 0.001$). In contrast, considering every visit, only the least stringent remission definition (allowing serology, prednisolone ≤ 5 mg, and immunosuppression) could be demonstrated to be associated with significantly reduced subsequent damage accrual (HR 0.58, 95%CI 0.39-0.88, $p 0.01$). Only remission definitions including serological remission were significantly associated with reduction in subsequent flares. Using a cut off of $\geq 50\%$ of observed time meeting a given definition, LLDAS resulted in a two-fold reduction in risk of flare and damage accrual (HR 0.49, 95%CI 0.42-0.58, $p < 0.001$; HR 0.53, 95% CI 0.41-0.68, $p < 0.001$, respectively), while only the least stringent remission definition, or the related definition excluding serology (13.6% visits), were significantly protective against damage (HR 0.59, 95% CI 0.42-0.83, $p 0.003$; HR 0.69, 95% CI 0.48-0.99, $p 0.05$, respectively). When attained for $\geq 50\%$ of observed time, all but one remission definition was significantly associated with reduced flares.

Conclusion: In this first-ever prospective study, LLDAS was markedly more attainable than any remission definition, whilst still conferring significant protection against flares and damage accrual. Among the remission definitions only the least stringent could be shown to be associated with significant reduction in damage accrual, likely reflecting a low frequency of remission attainment overall, and normal serology was required for protection from subsequent flare. LLDAS is a valid treatment target for SLE which is more achievable than remission.

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Abstract Number: 2931

Missing Outcomes in SLE Clinical Trials: Impact on Estimating Treatment Effects

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Session Information

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Background/Purpose: Missing data due to drop-out and loss to follow-up is a common problem in SLE trials. The usual approaches for handling this issue include analyzing only subjects with complete data (complete case analysis; CC), last observation carried forward (LOCF), or imputing non-responses for missing outcomes (non-responder imputation; NRI). However, the validity of these methods depends on strong assumptions about the missing data mechanism. Multiple imputation (MI) is a flexible model-based technique that accounts for uncertainty in the imputation process by generating several possible values for the missing data, resulting in multiple complete data sets. These are analyzed separately and results are combined. MI is being used more widely in different disease settings but has not been applied to analyze the primary outcome in a SLE trial. We explored the use of MI to address missing data in the composite outcome, SLE Responder Index (SRI)-5, using data from patients assigned to standard of care (SoC) in a 52-week trial.

Methods: Data on 279 SLE patients randomized to SoC for 52 weeks who were receiving mycophenolate mofetil (MMF), azathioprine, or methotrexate at entry were obtained from the Lupus Foundation of America-Collective Data Analysis Initiative database. Multiple imputation using chained equations was applied to handle missing data in an analysis to evaluate differences in SRI-5 response rates at 52-weeks between patients treated with MMF versus other immunosuppressants (non-MMF). Three different imputation models were considered that included various combinations of longitudinal measures of disease activity (both composite and individual measures) and patient characteristics to impute the missing outcomes. Results were compared to estimates from the CC, LOCF, and NRI methods.

Results: Missing data rates were 32% in the MMF and 23% in the non-MMF groups. As expected, the NRI missing data approach yielded the lowest response rates (Table 1). The smallest and least significant estimates of between group differences were observed with LOCF. The precision of the estimated difference, as measured by the width of the confidence interval, was lowest with the CC method because of the reduced sample size. Group differences were magnified with all three MI models compared to results of other methods. Imputing SRI-5 directly (MI-1) versus the individual components (MI-2) yielded nearly identical results.

Conclusion: Given the limitations of conventional approaches for handling missing data, the MI method should also be considered in SLE trials. However, results can vary depending on the imputation model that is used, and the assumptions required for validity of this and other missing data methods must be justified. Sensitivity analysis using different approaches is important to demonstrate robustness of results especially when missing data rates are non-negligible.

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Table 1. SRI-5 Response Rates on SoC at 52 weeks by Immunosuppressant Use

Missing Data Approach	Non-MMF	MMF	Difference	95% CI	P-value
CC	46.8%	29.3%	17.5%	1.7% to 33.3%	0.043
LOCF	40.6%	30.0%	10.6%	-2.7% to 23.9%	0.13
NRI	36.1%	20.0%	16.1%	4.1% to 28.0%	0.019
MI-1	47.6%	28.5%	19.1%	4.6% to 33.5%	0.010
MI-2*	46.0%	27.0%	19.0%	4.3% to 33.6%	0.011
MI-3	47.6%	29.7%	17.9%	3.1% to 32.7%	0.018

*MI-2: Imputed data sets: MI-1: Imputation model includes MMF status, race, baseline values of SLEDAI, PGA, BILAG score, protein/creatinine ratio, anti-dsDNA, SRI-5 at 12, 24, 36, 44, 52 weeks; MI-2: Imputation model same as MI-1 but separately imputing components of SRI-5 (SLEDAI, BILAG, PGA); MI-3: Imputation model includes MMF, SRI-5 at all time points.

Systemic Lupus Erythematosus Biomarkers Identified Using Multi-Omic and Artificial Intelligence Analysis through Interrogative Biology

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Background/Purpose: Biomarkers for use in developing treatments and diagnostics for Systemic Lupus Erythematosus (SLE) are a large unmet need. The wide differential in patient progression and outcome for SLE calls for the identification of informative biomarkers for use in patient stratification and determining course of treatment. In this study we used Berg Interrogative Biology®, a platform technology integrating multi-omic (metabolomics, lipidomics and proteomics) and artificial intelligence (bAIcis®) technologies to discover serum and urine based candidate markers of lupus.

Methods: This study was conducted using retrospectively collected and clinically annotated serum and urine samples from 166 patients (90 African American and 71 Caucasian). Medical data included demographic data, ACR classification criteria, SLICC-damage index, SLEDAI disease activity scores, lab data, and medication information. Omics data for Mass Spectrometry included serum proteomics, metabolomics and lipidomics, and urine proteomics and metabolomics. As part of Berg Interrogative Biology® technology, all clinical and omics datasets were processed and fully integrated in a harmonized dataset. The multi-omic/clinic dataset was analyzed by Berg Artificial Intelligence technology (bAIcis®) that uses data-driven methods to identify panels of Lupus candidate biomarkers, each with a target area under the ROC curve (AUC) of 0.8 with the minimal combination of up to 6 biomarkers. Biomarker panels were analyzed separately for each biomatrix. bAIcis® provided (1) a summary table with individual AUC, panel AUC, panel power, and number of samples participated; (2) a panel ROC curve; and (3) a diagnostic table with statistics: sensitivity, specificity, positive predicted value (PPV), negative predicted value (NPV), and odds ratio.

Results: Biomarker panels in serum and urine were discovered for lupus vs non-lupus (2 biomarkers in serum with AUC 0.836 and 5 in urine with AUC 0.805), renal disease vs no renal disease (2 biomarkers in serum with AUC 0.848 and 2 in urine with AUC 0.844), scleroderma vs. non-scleroderma (2 biomarkers in serum with AUC 0.826 and 2 in urine with AUC 0.705), scleroderma vs. lupus (5 biomarkers in serum with AUC 0.831 and 3 in urine with AUC 0.771), SLICC stage <2 vs >=2 (4 biomarkers in serum with AUC 0.829 and 2 in urine with AUC 0.77), SLEDAI score <6 vs >=6 (2 biomarkers in serum with AUC 0.809 and 2 in urine with AUC 0.641), ANA (1 biomarkers in serum with AUC 0.604 and 2 in urine with AUC 0.73), and drug efficacy for Mycophenolate (2 biomarkers in serum with AUC 0.847 and 1 in urine with AUC 0.933).

Conclusion: Biomarker panels with AUC > 0.8 and power > 0.8 will be pursued in further prospective clinical study with a larger subject number. The urine and serum biomarker panels for lupus vs no lupus, renal disease vs no renal disease, scleroderma vs no scleroderma, scleroderma vs lupus, SLICC stage, and drug efficacy for Mycophenolate are fit for further validation. Integrating multi-omic analysis with artificial intelligence identified several biomarker panels that meet numerous unmet needs for the identification and clinical stratification of Systemic Lupus Erythematosus.

Disclosure: E. Grund, BERG, LLC, 1, 3; L. Zhang, BERG, LLC, 1, 3; L. Rodrigues, BERG, LLC, 1, 3; V. Akmaev, BERG, LLC, 1, 3; R. Sarangarajan, BERG, LLC, 1, 3, 4; M. Kiebish, BERG, LLC, 1, 3; N. Narain, BERG, LLC, 1, 3, 4; G. S. Gilkeson, None.

Non-Invasive Tape Sampling Reveals RNA Gene Clusters in Cutaneous Lupus Erythematosus That Discriminate Affected from Unaffected and Healthy Volunteer Skin

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Session Information

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Background/Purpose: Punch biopsy, the standard diagnostic and monitoring procedure for patients with cutaneous lupus erythematosus (CLE), impedes patient recruitment and follow up due to risk of infection, discomfort and cosmetic scarring. This study assessed the feasibility of an adhesive tape device from Dermtech, Inc to collect RNA from affected and unaffected skin and its potential to detect gene expression differences between groups.

Methods: Subjects with active discoid lupus erythematosus (DLE; n=9), subacute CLE (SCLE; n=1), atopic dermatitis (AD; n=3) and healthy volunteers (HV; n=10) were enrolled. Skin tape samples from affected (A) and unaffected (U) skin were collected from all subjects. Gene expression was quantified by qPCR on the OpenArray platform. Candidate genes (n=94) were grouped by differential expression using consensus K-means and hierarchical clustering. Distinct gene clusters were assigned to canonical pathways using tools in Ingenuity Pathway Analysis (Invitrogen) software.

Results: Using an unbiased clustering algorithm, genes amplified from skin RNA collected by tape were segregated into 6 clusters. Two of 6 clusters resulted in differential expression between both CLE-A vs HV, and CLE-A vs CLE-U, as follows: (Cluster 1) composed largely of type I interferon (IFN-I) signaling genes (n=18 genes, fold change 23 and 7, p<0.001 and p=0.002, respectively) and (Cluster 2) containing genes involved in cytotoxic T lymphocyte and natural killer (NK) cell-mediated apoptosis, communication between innate and adaptive immune cells, and cytokines and chemokines in viral infection (n=22 genes, fold change 5 and 3, p<0.001 and p=0.007).

Conclusion: RNA from the skin surface distinguishes CLE-A from HV skin and CLE-A from CLE-U skin with robust fold changes in genes implicated in CLE pathogenesis including IFN-I signaling and cytotoxic T lymphocyte and NK cell-mediated apoptosis. This non-invasive technique offers promise for the diagnosis, stratification and follow up of patients with CLE.

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Abstract Number: 2934

Myocardial Microscopic Fibrosis Assessed By T1 Mapping Sequences on Cardiac Magnetic Resonance Imaging Predicts Cardiac Events in Systemic Sclerosis: Data from a Prospective Cohort Study on 40 Patients

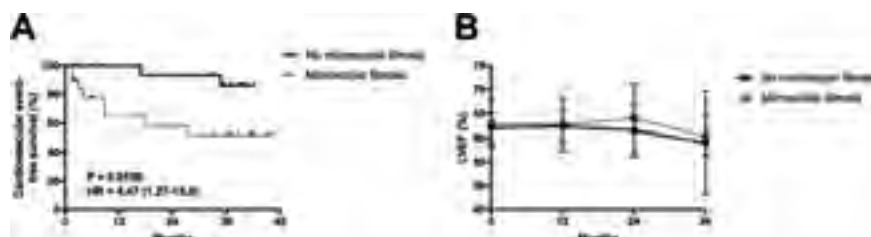
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Session Information

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Background/Purpose: Studies have shown that myocardial involvement may occur in systemic sclerosis (SSc) and lead to cardiac failure. We showed previously that cardiac magnetic resonance imaging (CMRI) with T1 mapping sequences could detect myocardial microscopic fibrosis in 50% of SSc patients, especially in those with diffuse cutaneous forms. However, no prospective data is yet available to analyze the prognostic impact of MMF on cardiac outcome in SSc patients.

Methods: We conducted a single-center prospective study of consecutive patients with SSc fulfilling the ACR/EULAR criteria. CMRI with T1 mapping and multi-b value diffusion-weighted sequences were performed in all patients. T1 mapping sequences assess collagen myocardial infiltration, defining microscopic fibrosis. Myocardial microscopic fibrosis was defined on T1 mapping sequences by a value greater than 1250 ms. Patients were prospectively followed-up for the occurrence of cardiovascular (CV) events and decline in left ventricular ejection fraction (LVEF) assessed by cardiac ultrasonography.



Results: Forty patients, 35 women and 5 men, mean age 54.7 ± 14.6 years, were included. At inclusion, patients had diffuse cutaneous forms in 19 cases, limited cutaneous forms in 16 cases, and SSc sine scleroderma in 5 cases. Median time from disease diagnosis to CMRI was 77 months (1-302). Myocardial microscopic fibrosis was found in 21(53%) SSc patients.

After a median follow-up of 38.2 months (IQR 19.4-41.0), 10 (25%) patients experienced CV events: hospitalization for heart rhythm disorder in 7 cases, for heart failure in 2 cases (leading to death in one case) and unstable angina in one case.

Presence of myocardial microscopic fibrosis on CMRI at inclusion was significantly associated with a poorer CV event-free survival ($P=0.02$). Hazard ratio (95% confidence interval) for incident CV events in patients with myocardial microscopic fibrosis compared to those without was 4.47 (1.27-15.8) (Fig. A).

In contrast, no difference in the decline of LVEF over time was noted between patients with and without myocardial microscopic fibrosis (from 62.0 ± 3.2 and $62.9 \pm 4.7\%$ at inclusion to 59.0 ± 10.8 and $59.4 \pm 5.3\%$ at 36 months, respectively) (Fig. B).

Conclusion: This study shows a significant association between myocardial microscopic fibrosis assessed by T1 mapping sequences on cardiac MRI and cardiovascular events in systemic sclerosis, but no impact on LVEF decline over time. The prognostic impact of myocardial microscopic fibrosis should be evaluated in larger studies, especially in patients with diffuse cutaneous forms.

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Abstract Number: 2935

A Practical Classification of Systemic Sclerosis Using Subset and Autoantibodies for the Purpose of Early Risk Stratification

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Background/Purpose: The Le Roy *et al.* classification of SSc into limited and diffuse cutaneous subtype remains the most commonly used. Nevertheless, autoantibodies are much better predictors of organ involvement. Although more sophisticated approaches exist, a simple classification, using antibodies and skin subset is relevant to clinical practice and could help risk stratification.

Methods: Initially subjects were divided into 12 groups, based on skin subset and autoantibodies - ACA, anti-Scl-70 antibodies, anti-RNA polymerase antibodies (ARA), anti-U3RNP antibodies, anti-PmScl antibodies and a group with other antibodies, including rarer specificities, ANA+ ENA- and ANA negative patients.

Kaplan-Meier (KM) estimation of survival and cumulative incidence of organ complications were calculated for each subgroup. Subgroups were ranked in terms of endpoint estimates and those showing similar ranking in multiple endpoints, were merged.

Results: The cohort consisted of 1025 SSc patients. Mean age at disease onset was 47 years and 16% were male. Diffuse cutaneous (dc)SSc was diagnosed in 35% of the subjects. Antibody characteristics included ACA in 31%, Scl-70 in 22%, ARA in 11%, U3RNP in 5% and PmScl in 4% of the subjects. For the whole cohort, at 20 years from onset, estimated survival was 60%, incidence of significant pulmonary fibrosis (PF) was 44%, pulmonary hypertension (PH) 25%, scleroderma renal crisis (SRC) 7% and cardiac SSc 6%.

The final classification included 7 subgroups. Group 1 (29%) consisted of ACA+ lcSSc patients. This was the subgroup with the highest survival (72%), the lowest incidence of PF (13%) and SRC (no cases) at 20 years from onset. The incidence of PH was similar to the average for the whole cohort.

Group 2 (11%) consisted of all ARA+ subjects and it had the highest incidence of SRC (32% at 20 years), while other organ complications and survival were similar to the cohort average.

Group 3 (11%) included Scl-70+ lcSSc patients and although incidence of PF in this group was the second highest (69% at 20 years), other complications were rare. The group had the lowest incidence of PH (6%) and the second lowest incidence of SRC (3%) at 20 years.

On the other hand, Scl-70+ dcSSc patients (group 4, 11%), had a very poor prognosis with the highest incidence of PF (91%), cardiac scleroderma (14%) and the worst survival (41%) at 20 years.

Group 5 included all U3RNP+ patients (5%). Although survival in this group was not bad (70% at 20 years), this group had the highest PH incidence (40%) and the second highest incidence of cardiac SSc (11%) at 20 years.

Groups 6 and 7 (22% and 11% respectively) included lcSSc and dcSSc patients with other antibody specificities. Group 6 had low overall risk of SRC and cardiac SSc, while other outcomes were similar to the cohort average. Conversely, group 7 had poor prognosis, with the second lowest survival (42% at 20 years) and above average rates of organ disease, particularly PF and SRC.

Conclusion: We propose a simple classification scheme, combining autoantibody specificity and extent of skin involvement, which is easy to apply in a clinical setting and distinguishes well between patient groups at risk of serious complications.

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Abstract Number: 2936

Esophageal Erosion Predicts Progression of Lung Disease in Patients with Systemic Sclerosis

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Background/Purpose: Interstitial lung disease (ILD) is the leading cause of death in Systemic Sclerosis (SSc) but its pathogenesis is not fully understood. Esophageal disease is common in SSc and micro-aspiration of both acid and non-acid gastroesophageal reflux could be involved in the pathogenesis of ILD. Esophagogastroduodenoscopy (EGD) is an essential tool to evaluate disease severity of upper gastrointestinal tract involvement in SSc. The objective of the present study is to assess the role of EGD in predicting pulmonary functional deterioration in SSc patients.

Methods: One hundred and fifty patients with SSc and suspected esophageal involvement underwent EGD. Pulmonary function tests were performed at baseline and after a 36-months follow-up. Patients were characterized for disease phenotype, BMI, smoking exposure and medication history. A significant ILD progression was defined as a relative decline $\geq 10\%$ of FVC or a concomitant decline $\geq 5\%$ of FVC and $\geq 15\%$ of DLCO.

Results: One hundred and thirty-six patients (90.5%) were female with a mean age of 55.6 ± 13.8 years and 12.1% were active smokers. Fifty patients (33.3%) had a diffuse cutaneous disease; 37.4% and 40.8% were positive for anti-centromere and anti-Scl70 antibodies respectively. The mean disease duration from the first non-Raynaud symptom was 5.9 ± 6.7 years. Sixty-one patients (40.8%) showed EGD signs of reflux esophagitis. Among them, 31.3% had an erosive form (9.5% grade A, 15.6% grade B, 4.8% grade C and 1.4% grade D according to Los Angeles classification). At the baseline, 23.1% of the patients had a $FVC \leq 80\%$ and 45.6% had a $DLCO \leq 50\%$. Patients with erosive esophagitis did not differ in terms of sex, age, duration and disease variant, positivity for anti-centromere, skin score values, FVC and DLCO at baseline compared to patients without erosions, but had a lower prevalence of anti-Scl70 (28.3 vs 52.5%, $p=0.005$) and active smoking (20.0 vs 8.4%, $p=0.05$). At follow-up, patients with esophageal erosions showed a greater relative decrease in FVC ($3.4\% \pm 9.3\%$ vs $1.7\% \pm 12.0\%$; $p=0.013$) without significant differences in the DLCO change. Overall, 11.0% of patients presented pulmonary disease progression. The presence of esophageal erosions was associated with a significantly greater risk of lung disease progression (OR 5.3, 95% CI 1.7-16.8, $p=0.004$) after paired correction for sex, age, duration of disease, auto-antibodies, skin involvement variant, baseline FVC and DLCO, smoke exposure and therapy with immunosuppressants, proton pump inhibitors, prokinetics, antiplatelet agents and prostanoids.

Conclusion: SSc patients with erosive esophagitis present a higher risk of progression of interstitial lung disease. This evidence supports a role of micro-aspiration of gastric contents in the development of inflammation and fibrosis of the airways.

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Abstract Number: 2937

Anti-Vinculin Antibodies in Systemic Sclerosis (SSc): A Potential Biomarker Linking Vascular and Gastrointestinal System Involvement in Two Phenotypically Distinctive SSc Groups

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Systemic Sclerosis and Related Disorders – Clinical III: Cohort Studies, Biomarkers, & Response

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Background/Purpose: Vinculin is a cytoskeletal protein that plays a major role in cell-cell and cell-extracellular matrix adhesion thus regulating cell growth, migration and function of enteric nerves, smooth muscles as well as endothelial cells. Antibodies directed against vinculin protein have been identified as biomarker in irritable bowel syndrome (IBS). Recently, vinculin was identified as one of the targets of anti-endothelial antibodies in serum of SSc patients.

Aim: To evaluate serum anti-vinculin antibodies (aVin-abs) in two phenotypically different SSc patient cohorts (vascular and gastrointestinal-enriched groups).

Methods: Controls and SSc subjects recruited from two SSc centers (University of California, Los Angeles [UCLA], USA and the University of Leeds, UK. Subjects were assessed as two groups:

Group I (gastrointestinal [GI] enriched group) included 83 SSc patients (pts), where 55 pts were noted to have a gastrointestinal (GI) Visual analogue scale [GI-VAS] > 40/ 100 whereby GI-VAS was a component of SSc Health Assessment Questionnaire. Group II (vascular-enriched group) included 72 SSc pts, of whom n=17 had digital ulcers, and n=23 had known pulmonary artery hypertension. SSc serum samples as well as 50 age and sex matched controls were evaluated in one laboratory, where aVin-abs were tested by ELISA and results reported as OD. Clinical data were obtained by chart review for statistical correlations.

Results: Features and demographics of recruited SSc subjects supported the group assignments (Table 1). Among all SSc patients, aVin-abs were significantly higher in SSc groups than in controls (1.4 ± 0.9 compared to 0.6 ± 0.6 in control [p-value=0.002] in Group I) and, (1.0 ± 1.0 in SSc versus 0.6 ± 0.6 in control [p-value =0.01] in Group II). Group I (GI-enriched) patients were then dichotomized based on aVin-abs cutoff level (used in IBS study [high>1.7 or low< 1.7]). Using this cutoff, BMI was significantly lower in SSc pts with high levels of abs ($19.9 \pm 4.1 \text{ kg/m}^2$) versus low levels (21.9 ± 4.7) (p=0.05). Significantly higher GI-VAS was recorded in SSc pts with high aVin-abs (6 [range 2-9]) in comparison to SSc pts with low (2 [range 1-9]) (p-value=0.0001). In group II, we examined predictors of higher aVin-abs in group II (vascular -enriched): BMI and PAH were significant predictors of higher anti-vinculin (p<0.005 and 0.04, respectively

Conclusion: This is one of the first studies to report an association between autoimmunity to vinculin in patients with SSc-GI involvement. This suggests that higher aVin-abs are associated with greater severity of GI involvement with consequent decreased BMI. In addition, we report that aVin-abs also appear associated with vasculopathy such as pulmonary artery hypertension.

	Group I	Group II
Age mean (SD)	57.4 (12.64)	56.36 (13.83)
Sex: females	69 (83%)	58(82.85%)
Diffuse subtype	24 (29%)	(32) 48.48%
BMI Mean (SD)	26.16 (5.71)	24.3 (4.25)
GI-VAS	3 (1-9)	2.2 (0-9)
PAH	5(6%)	23 (31%)
Current skin ulcers	30(36%),	17 (25%)
FVC mean (\pm SD)	98.3 ± 25.2	79.8 ± 26.1

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Abstract Number: 2938

Evaluation of American College of Rheumatology Provisional Composite Response Index in Systemic Sclerosis (ACR CRISS) in a Phase 3 Randomized Controlled Trial

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Session Information

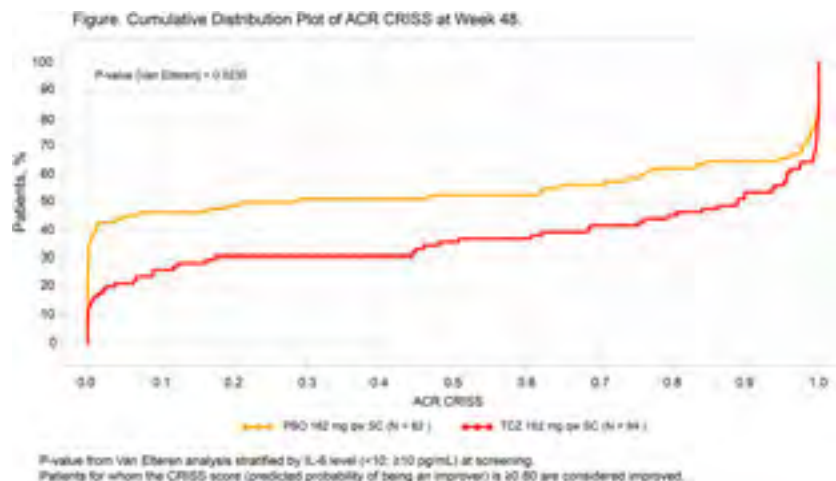
Session Date: Wednesday, October 24, 2018

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Background/Purpose: Treatment with the IL-6 receptor inhibitor tocilizumab (TCZ) in early progressive systemic sclerosis (SSc; focuSSc trial; NCT02453256) resulted in numeric improvements in skin sclerosis and clinically meaningful forced vital capacity(FVC) results at week 48 (data on file). The combined response index for SSc (ACRCRISS), a composite



outcome measure for trials in SSc,¹ is a 2-step process that assigns a probability of improvement for each patient (pt) ranging from 0 [no improvement] to 1 [marked improvement]. Step 1 assesses clinically meaningful decline in cardio-pulmonary-renal involvement with a probability of 0. For remaining pts, the probability of improvement examines change from baseline in 5 variables: modified Rodnan skin score, FVC%, pt and physician global assessments (PtGA, MDGA), and HAQ-DI. CRIS distinguished between TCZ and placebo (PBO) in the faSScinate trial.² We prospectively assessed the performance of ACR CRIS, an exploratory outcome in focuSSced, at week 48; this is the first time ACR CRIS has been prospectively evaluated in a phase 3 trial in SSc.

Methods: Pts ≥18 years of age with active SSc were randomly assigned 1:1 to TCZ 162 mg or PBO subcutaneously every week for 48 weeks. Step 1 for ACR CRIS was captured prospectively with blinded review of adverse events (AEs) and serious AEs between medical monitors and the lead investigator. Step 2 was calculated as defined.¹ The van Elteren test was used to assess whether differences existed between TCZ and PBO groups in the ACR CRIS score in its continuous form. The analysis included all pts who received study treatment, stratified by baseline IL-6 levels (<10; ≥10 pg/mL) with no imputation for missing data.

Results: In total, 210 pts (104 TCZ, 106 PBO) received study treatment; 13 pts in the PBO group and 6 in the TCZ group met the predefined definition of worsening cardio-pulmonary-renal involvement (step 1) and were given a score of 0. Using the ACR CRIS as a continuous measure, scores favored TCZ over PBO at week 48: median(IQR), 0.89 (0.09-1.00) vs 0.25 (0.00-0.99) ($p = 0.023$; Figure). In the binary form of CRIS, 51% of pts in the TCZ group vs 37% in the PBO group achieved the cutoff of ≥0.60 at week 48 (difference, 13.9; 95% CI, 1.0-26.8; $p = 0.035$).

Conclusion: In analysis of patient-level data from the focuSSced trial, more pts had cardio-pulmonary-renal involvement in the PBO group than in the TCZ group (captured by step 1). Additionally, step 2 CRIS score distinguished TCZ from PBO. The focuSSced study validates the ACR CRIS end point for the first time in an independent prospective clinical trial and highlights the importance of step 1 as an indicator of reduced organ progression during 48 weeks of treatment. **References:** 1. Khanna D et al. *Arthritis Rheumatol.* 2016; 299-311. 2. Khanna D et al. *Arthritis Rheumatol.* 2017;69(suppl 10). Abstract 2981. Acknowledgment: focuSSced clinical trial investigators.

Disclosure: D. Khanna, None; C. J. F. Lin, Genentech, Inc., 3; H. Spotswood, Roche, 1, Roche, 3; J. Siegel, Genentech, Inc., 1, Genentech, Inc., 3; A. Jahreis, Roche, 1, Genentech, Inc., 3; C. P. Denton, GSK, CSF Behring, Inventiva, 2, Roche/Genentech, Actelion, GSK, Sanofi, Inventiva, CSL Behring, Boehringer Ingelheim, Bayer, 5; D. E. Furst, Roche/Genentech, 2.

Abstract Number: 2939

Clinical Features Associated with Severe Lower Bowel Involvement in Systemic Sclerosis

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Background/Purpose: Although up to 90% of scleroderma (SSc) patients are affected by gastrointestinal (GI) dysmotility, clinical features of patients with severe lower gastrointestinal involvement are not well-defined. We sought to identify such features by studying a large cohort of SSc patients.

Methods: We performed a retrospective analysis of patients seen during a 15-year period between 2002-2017 at The Johns Hopkins Scleroderma Center. All patients had data prospectively collected in a longitudinal database if they met 2013 ACR/EULAR criteria for systemic sclerosis, 1980 American College of Rheumatology (ACR) criteria or had at least three of five features of CREST syndrome. Lower gastrointestinal involvement was defined as ever having a Medsger's GI severity score of a 3, which is characterized by malabsorption syndrome and/or recurrent episodes of pseudo-obstruction. Clinical and serologic characteristics of these patients were compared to those who received grades of 0, 1, or 2 throughout follow-up.

Results: There were 193 patients with SSc who received a grade of 3 in GI severity during follow-up, and 3,577 patients who did not. In univariable analyses, lower GI involvement was significantly associated with older age at the time of severe bowel disease onset (58 vs. 53 years, $p < 0.001$), diffuse cutaneous disease (47% vs. 37%; $p = 0.006$), history of tendon friction rubs (24% vs. 16%; $p = 0.003$), myopathy (31% vs. 17%; $p < 0.001$), cancer (22% vs. 16%; $p = 0.027$), and death (44% vs. 34%; $p = 0.006$). Such patients were also more likely to have ever had a lower FVC (66% vs. 70%, $p = 0.01$) and DLCO (56 vs. 61%, $p = 0.02$) and to have received opioids (44% vs. 27%; $p < 0.001$), and prednisone (42% vs. 32%; $p = 0.005$). A positive association with anti-U3RNP antibodies trended towards significance (7% vs. 4%; $p = 0.06$). Autoantibodies to RNA polymerase 3 (RNAPol3) were inversely associated with severe lower bowel involvement (11% vs. 18%; $p = 0.02$). In multivariable analyses (adjusted for significant variables from the univariable analysis) age (OR 1.03; 95%CI 1.02-1.05), diffuse cutaneous disease (OR 1.76; 95%CI 1.16-2.67), myopathy (OR 1.56; 95%CI 1.06-2.30), and opioid use (OR 2.31; 95%CI 1.64-3.25) remained significantly associated with severe lower bowel disease in SSc. Anti-RNA pol3 antibodies were protective of this complication (OR 0.39; 95%CI 0.22-0.68).

Conclusion: We report extra-intestinal clinical features of SSc patients with lower GI involvement in a large cohort. Our results demonstrate that older age, diffuse skin disease, and myopathy are associated with developing lower GI involvement. The prescription of opioids may be a modifiable risk factor for the development of severe lower GI involvement in patients with SSc.

Disclosure: E. Dein, None; L. K. Hummers, None; C. A. Mecoli, None; Z. McMahan, None.

Abstract Number: 2940

Complementary Practices As Alternatives to Pain: Effectiveness of a Pain Management Program for Patients in an Orthopedic Clinic

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: ARHP III: Interventions and Self-Management

Session Type: ARHP Concurrent Abstract Session

Session Time: 9:00 AM-10:30 AM

Background/Purpose: In 2018, according to the National Institute of Health, opioid misuse and addiction is a major public health issue. Approximately 70% of individuals who use opioids on a long-term basis have musculoskeletal disorders, such as low back pain, spondylosis and osteoarthritis. Additionally, one-third of patients with Rheumatoid Arthritis are prescribed an opioid to treat their condition, while one in ten use opioids chronically during their disease course. Over the last 25 years, there has been an increase in physicians prescribing opioids for chronic pain, while there is limited availability of alternatives for identifying, managing, and treating pain. To address this epidemic, Hospital for Special Surgery (HSS) implemented a Pain and Stress Management (PSM) program to improve knowledge and implementation of complementary practices as alternatives to medications.

Methods: In 2017, the PSM program was piloted to patients at the HSS Ambulatory Care Center (ACC), a low income, diverse community living with chronic musculoskeletal conditions. Reaching 122 participants, this included weekly

meditation conference calls and monthly workshops with a social work-led debrief session. Participants engaged in mindful breathing techniques and meditation practices to cope with chronic pain and stress. Knowledge, self-management and program acceptability were evaluated using post surveys. As a follow-up to the survey, qualitative data was collected to obtain additional information on program effectiveness (i.e., how often participants use the learned techniques and how the techniques have helped participants cope with their pain and stress).

Results: The program was highly rated by 98% of participants. Most participants showed increase in knowledge of complementary alternative treatments (95%) and ability to apply the techniques learned to manage their pain and stress (95%). One out of three participants reported using the mindful breathing techniques 5 or more times a week in place of medication. Debrief sessions revealed that after using the techniques, participants experienced improved daily function, calmness, improved self-efficacy and state of mind, reduced pain and stress, and were less reliant on pain medication to manage their condition.

Conclusion: Results indicate that alternative approaches are effective in reducing pain and stress, and improving self-management and general well-being. Based on the success of the PSM program in the orthopedic clinic, we are expanding the program to patients of the HSS rheumatology clinic, who also rely on opioid use to cope with chronic pain, to help this population increase their knowledge and awareness of alternative approaches to manage their debilitating condition.

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Abstract Number: 2941

Reach and Effectiveness of a Health Communications Campaign Promoting Self Management Education: Results of a Pilot Test of the Learn More. Feel Better. Campaign

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Background/Purpose: *Learn More. Feel Better.* (LMFB) is a multi-modal marketing campaign to promote self-management education (SME) as a chronic disease management strategy. The campaign targets adults ages 45-75 with chronic conditions including arthritis. Campaign strategies include paid and earned media, and local partner activity; all promote the same call-to-action to visit www.cdc.gov/LearnMoreFeelBetter to learn more about SME.

CDC pilot-tested the LMFB campaign in January-August, 2017, in one designated market area (DMA) (a midwestern five county area including a midsize urban area). Implementation included paid ads (print, radio, billboard, digital, and physician waiting/exam rooms), earned media (news stories/blog posts resulting from media outreach), and local partner promotion (in-person events, web and social media). Two campaign tactics (digital advertising via Google ads, and physician waiting/exam rooms ads) ran continuously. The remaining strategies and tactics were conducted intermittently (e.g., the magazine ad ran in February, June, and July; billboards ran 4 weeks in March-April).

The purposes of this observational study are to assess: 1) effectiveness of LMFB in motivating people to visit the LMFB website, 2) effectiveness of the website in retaining visitors' interest, and 3) lessons learned to guide future campaign implementation.

Methods: Campaign effectiveness was defined as the number of visits to the LMFB website homepage, as calculated by Site Catalyst, a web analytics software program. To put this into perspective, this number was compared to number of visits to select CDC webpages from the target DMA for the same time period.

Effectiveness of the website in retaining interest was assessed by examining the number of people who left the homepage without visiting additional pages, also calculated by Site Catalyst. Patterns of impressions and website visits were examined to identify lessons learned.

Results: The 7 month LMFB pilot-test resulted in more than 31 million impressions; with approximately 80% from paid media, 11% from earned media, and 9% from partners' promotion.

The pilot-test generated 26,851 visits to the LMFB homepage; 58% from the targeted DMA, a total of 85% from the state. Other CDC websites had less than 1% of their visits from the target DMA during the pilot-test period. Visits to the

homepage peaked in periods where ads were running in multiple channels; the impact of digital ads is easiest to track, but ads in traditional media (print, radio, billboard) contribute to impressions and message repetition that leads to action.

Only 17% of homepage visits resulted in visitors viewing another page on the website. :

Conclusion: LMFB pilot-test was successful in driving traffic to the LMFB website; nearly 60% came from the targeted DMA. The additional visits from the state are likely due to spread of LMFB materials since the only 15% of visits were from outside the state. Paid media was an essential part of this pilot-test and use of multiple channels increased effectiveness. However, the LMFB homepage was less successful in enticing visitors to visit additional pages on the site, suggesting further improvements to the homepage are necessary.

Disclosure: T. Brady, None; M. Lewis, None; C. Cartwright, None; A. Hvizdak, None; S. Lasker, None.

Abstract Number: 2942

Dyadic Study of Partner Social Support for Physical Activity and Its Role in the Initiation and Maintenance of Increased Physical Activity Among Insufficiently Active People with Hip/Knee Osteoarthritis

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Background/Purpose: People who increase their physical activity (PA) (e.g., in an intervention) typically return to a less active lifestyle within 3-6 months. Yet, the health benefits of a more active lifestyle require lasting behavior change. In people with osteoarthritis (PWOA), increasing PA can reduce chronic joint pain. The present study examined social support for PA from a committed romantic partner as a facilitator of lasting PA change. We sought to clarify types of partner support associated with short- and long-term PA increases in insufficiently active PWOA.

Methods: Participants included people with hip/knee OA who self-reported <120 minutes of moderate-to-vigorous PA (MVPA) per week and their partner (N=116 couples). Couples attended a group class on OA, PA, and working together to help PWOA become more active. After class they were instructed to complete the Active Living Everyday Workbook (12 chapters, 1 per week) and to read a study booklet on social support for PA. Partners could try to increase their PA, but that was not a focus of the study. Participants independently completed a pre-class baseline assessment and follow-up assessments at 3-, 6-, and 12-months post-class. At each assessment, they wore an accelerometer and completed questionnaires, including 2 validated measures of partner support for PA. Partners reported support they provided to their PWOA, and PWOAs reported support they received from their partner. PWOAs' accelerometer-assessed MVPA at each assessment was categorized as: 0=minimal (<45 min/week), 1=insufficient (45 to <60 min/week), 2=borderline (60 to <150 min/week), or 3=exceeding recommendations (≥150 min/week).

Results: Factor analysis of our data suggested 2 main ways partners could support PA: (1) enacted informational, instrumental, and emotional support for PA (general support) and (2) doing PA with the PWOA (collaborative support). We conducted ordinal logistic regressions predicting PWOAs' level of MVPA at 3-, 6-, and 12-months, adjusting for their baseline MVPA and demographic and medical characteristics. Support variables evaluated in the models included PWOA-reported general and collaborative support received and partner-reported general and collaborative support provided. In models predicting MVPA at all assessments, PWOAs' baseline MVPA significantly predicted their MVPA at follow-up assessments (p 's <.001). At 3 months, there were no associations between the support variables and PWOAs' level of MVPA. PWOAs with a higher level of MVPA at 6 months had partners who reported providing more collaborative support at baseline (p =.04). PWOAs with a higher level of MVPA at 12 months reported receiving greater general partner support for PA at the 6- and 12-month follow-ups (p 's=.03-.04) and they tended to have more partner-reported collaborative support for PA at baseline and at the 12-month follow-up (p 's .07-.09).

Conclusion: Findings suggest that partner support for PA may play a more critical role in maintenance than in initiation of PA over the course of a year, especially with respect to PWOAs' reports that partners had recently provided them with general support for PA. We will discuss implications for interventions.

Disclosure: C. Rini, None; D. Hales, None; S. Bahorski, None; M. Altpeter, None; D. Carthron, None; A. Phillips, None; J. Upchurch, None; I. Griesemer, None; H. Wasser, None; S. Soto, None; S. Rimmler, None; B. Patel, None; K. Ellis, None; L. F. Callahan, Lilly, 5.

Abstract Number: 2943

Helping a Non-Urban Community Walk with Ease: A Feasibility Pilot Study of an Arthritis Activity Intervention

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Background/Purpose: An estimated 54 million US adults have arthritis, and more than half are not receiving the recommended physical activity (MMWR, 2018). Walk With Ease (WWE) is one of five evidence-based programs shown to improve physical activity and self-management in patients with arthritis (Callahan, 2011). However, WWE is not widely used in non-urban communities. The objectives of this study were to 1) implement WWE in a community YMCA fitness center, 2) examine physical function and self-reported health outcomes in patients with arthritis, and 3) examine the feasibility and sustainability of implementing WWE.

Methods: Brochures, flyers, and electronic health record referrals from a YMCA and one health system were used to recruit adults who self-identified with arthritis and met the program requirements of being able to stay on their feet for 10 minutes. A physical therapist and two Arthritis Foundation trained YMCA staff members conducted a total of six, 6-week sessions, meeting 3 days/wk between Aug 2016 and Dec 2018. Walking speed measurements and 2-minute step counts were performed at baseline and 6-week follow-up. Pre/post-surveys were distributed to all registered participants, including those who did not complete the program. Survey items (n=25) included a 10-point visual analogue scale for arthritis pain, mood, fatigue, and global health, a validated multi-dimensional health assessment questionnaire (MD-HAQ) and a weekly exercise plan. Results were compared using paired t-tests.

Results: Of 35 registered participants, 31 attended WWE (range 2-10 participants per session). Participants were predominately 65 years or older (78%), female (77%) and Caucasian (100%). All had pre- or post-data, while only 21 (67%) had paired data. In paired data, normal and fast walking speed increased an average of 0.53 ft/s (p=0.02) and 0.67 ft/s (p=0.01), respectively. 2-minute step count increased an average of 48.5 steps (p<0.01). MD-HAQ and pain scores improved an average of 2.84 (p<0.01) and 1.43 (p=0.01). Global health scores improved an average of 1.43 (p<0.01). Most participants (87%) reported plans to continue to exercise 2-3x/wk. Average program costs to YMCA (\$208/participant) were comparable to a comprehensive physical therapy visit. Limitations include a small, single-center cohort with low diversity and inconsistent completion among participants.

Conclusion: Our pilot study showed that WWE improves physical function and self-reported health outcomes in patients with arthritis. In addition, WWE appears to be a feasible, sustainable, and cost effective program within non-urban community partners. Given observed improvements, health professionals should continue to emphasize the importance of physical activity, including community referrals. Future studies should examine how to increase provider referral of patients with arthritis to improve patient outcomes.

Table 1. Results of pre- and post-outcome measures

Outcomes	Pre, mean	Post, mean	Significance, p value
Normal walk speed (ft/s)	3.84	4.55	0.02
Fast walk speed (ft/s)	4.88	5.76	0.01
2-minute step count	137.44	190.70	<0.01
MD-HAQ*	5.82	3.32	<0.01

Table . (Cont'd)

Outcomes	Pre, mean	Post, mean	Significance, p value
Patient global health impact*	3.82	2.45	<0.01
Pain*	4.95	3.32	0.01
Fatigue*	4.07	2.89	0.14
Mood*	3.09	2.96	0.32
Baseline exercise (times/wk)	1.37	2.43	0.02

* Measured on a 10-point visual analogue scale (0-10 worst)

Disclosure: A. Perez, None; B. Polnaszek, None; D. White, Pfizer, Inc., 2; L. Walraven, None; C. Barnes, None; C. M. Bartels, Pfizer, Inc., 2.

Abstract Number: 2944

Longitudinal Outcomes and Predictors of E-Learning Effectiveness in Patients with Axial Spondyloarthritis: A Randomized Controlled Trial

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: ARHP III: Interventions and Self-Management

Session Type: ARHP Concurrent Abstract Session

Session Time: 9:00 AM-10:30 AM

Background/Purpose: There is evidence that education programs are effective (e.g. improved disease activity and quality of life) for patients with arthritis, but little is known about the impact of education interventions in axial spondyloarthritis (axSpA). The purpose of this study was to determine the impact of an e-Learning education program on patients' disease knowledge and self-efficacy, as well as to determine the predictors associated with better self-management.

Methods: The Toronto Western Hospital Spondyloarthritis Program developed an interactive, e-Learning education program for axSpA^{1,2}. Patients were randomly allocated to either the intervention (e-Learning with usual care) or control (usual care) group. All patients completed the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Knowledge (AS-Q) questionnaire, and the Stanford Exercise and Chronic Disease Self-Efficacy (CDSE) scales at baseline, first follow-up (FU1), and at second follow-up (FU2) 6-12 months after FU1. A linear-based generalized estimating equation for continuous data was used to explore the associations between covariates including group, baseline sociodemographic characteristics (including risk factors for poor disease outcomes) and a main effect for time.

Results: 44 AS and 10 non-radiographic axSpA patients (n = 54) were included in the analyses. Of these, 23 received the intervention and 31 proceeded with usual care. 85.2% had completed college or university and the median number of education sources (i.e. # sources accessed such as internet, pamphlets, physician) prior to the study was 3 (IQR = [2,3]). The mean age was 41.9 years (12.9 SD) and 81.5% were HLA-B27+ with a mean of 17.8 (10.8 SD) years of symptoms. There was a significant increase in disease knowledge over time (p = 0.043) but no group differences for the above outcomes. Three or more education sources were significant (p = 0.014) predictors for an increase in AS-Q in the control group. Allocation to the e-Learning group was a predictor of more confidence in getting help (p = 0.015) from family and friends as per the CDSE. Female gender (p = 0.05) was a predictor of greater confidence in managing disease overall, and symptoms >10 years predicted more confidence in managing both disease (p = 0.018) and depression (p = 0.014).

Conclusion: The e-Learning module shows promising efficacy in improving knowledge, health literacy behaviours, and also serves to benefit individuals with limited access to specialized, tertiary care. There is a need for trials to assess more effective education outcomes and future studies should include characteristics and risk factors (e.g. gender, previous education sources, symptom duration) that were shown to be meaningful in this analysis.

Cited:

1. We Got Your Back! Education Module for People with Ankylosing Spondylitis. 2016. Spondylitis Program, University Health Network. [ONLINE] Available at: https://www.uhnmodules.ca/Modules/Ankylosing-Spondylitis/story_html5.html
2. Kang, R., et al. (2014). Utilization of an informational needs assessment to develop an education program for patients with ankylosing spondylitis and related axial spondyloarthritis. *Ann Rheum Dis* 72(Suppl 3): A1037-A1038.

Disclosure: D. O. Lawson, None; A. Omar, None; R. Kang, None; N. Haroon, None; R. D. Inman, None; L. Passalent, None.

Abstract Number: 2945

Culturally Enhanced Pain Coping Skills Training for African Americans with Osteoarthritis

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: ARHP III: Interventions and Self-Management

Session Type: ARHP Concurrent Abstract Session

Session Time: 9:00 AM-10:30 AM

Background/Purpose: African Americans (AAs) bear a disproportionate burden of osteoarthritis (OA), with greater pain and disability compared with Non-Hispanic Whites. Pain coping skills training (PCST) is a promising intervention to reduce racial disparities in OA-related pain and other outcomes, but there has been little study of PCST among AAs. This project engaged AAs with OA and other stakeholders (caregivers, clinicians) to culturally tailor a PCST program for AAs, then evaluated the PCST program in a multi-site randomized controlled trial.

Methods: 248 AAs (51% male, mean age = 29 years) with knee OA were randomized with equal allocation to PCST and wait list (WL) control groups. The PCST program involved 11 telephone-based sessions over 12 weeks, delivered by a counselor. Outcomes were assessed at baseline, 12 weeks and 36 weeks and included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (primary outcome), WOMAC total score (pain, stiffness and function), Coping Strategies Questionnaire (CSQ) – Total Coping Attempts, Pain Catastrophizing Scale (PCS), PROMIS Pain Interference Scale, Patient Health Questionnaire (PHQ-8, depressive symptoms), and Arthritis Self-Efficacy Scale. Linear mixed models were fit for all outcomes with unstructured covariance to account for repeated measurements. All models included stratification variables (enrollment site and gender).

Results: At 12-week follow-up, the PCST group improved (decreased) in WOMAC pain score more than the WL group, but the difference was not statistically significant (Table 1). At 12-week follow-up there were significant differences, in favor of the PCST group, for CSQ Total Coping Attempts, PCS, and Arthritis Self Efficacy ($p < 0.01$). At 36 weeks, WOMAC pain scores were significantly improved in the PCST group compared with the WL group ($p < 0.05$, Table 1). CSQ Total Coping Attempts and Arthritis Self Efficacy scores were also significantly improved at 36 weeks in the PCST group, compared with the WL group ($p < 0.01$).

Conclusion: The culturally tailored PCST program resulted in improved pain severity, particularly at longer-term follow-up, and pain coping among AAs with knee OA. Other studies also suggest that effects of PCST interventions may be more robust after patients have had more opportunity to practice and incorporate skills. Dissemination of this PCST program may help to reduce racial disparities in pain.

Table 1 Mean Differences in Study Outcomes Between PCST and WL Control Groups

Outcome	Time Point	WL Control (N=124) Mean (95% CI)	PCST (N=124) Mean (95% CI)	Treatment Difference: PCST-WL Mean (95% CI)	p-value
WOMAC Pain Score	Baseline	11.01 (10.53,11.49)		N/A	N/A
	12 weeks	10.05 (9.43,10.68)	9.39 (8.75,10.03)	-0.66 (-1.48,0.16)	0.1122
	36 weeks	9.6 (8.91,10.3)	8.69 (7.96,9.42)	-0.91 (-1.82,-0.01)	0.0476
WOMAC Total Score	Baseline	53.01 (50.8,55.21)		N/A	N/A
	12 weeks	49.02 (46.17,51.87)	46.33 (43.43,49.23)	-2.69 (-6.09,0.7)	0.1194
	36 weeks	47.49 (44.36,50.61)	43.71 (40.48,46.95)	-3.77 (-7.57,0.03)	0.0516

Table . (Cont'd)

Outcome	Time Point	WL Control (N=124) Mean (95% CI)	PCST (N=124) Mean (95% CI)	Treatment Difference: PCST-WL Mean (95% CI)	p-value
CSQ Total Coping Attempts	Baseline	105.28 (100.52,110.04)		N/A	N/A
	12 weeks	106.43 (101.19,111.68)	121.64 (116.29,126.99)	15.2 (8.99,21.42)	0.001
	36 weeks	102.87 (97.33,108.42)	114.27 (108.53,120.01)	11.4 (4.82,17.98)	0.0008
PCS	Baseline	19.73 (18.18,21.27)		19.73 (18.18,21.27)	
	12 weeks	20.83 (18.86,22.8)	17.8 (15.8,19.8)	-3.03 (-5.25,-0.8)	0.0078
	36 weeks	18.35 (16.32,20.37)	16.97 (14.85,19.08)	-1.38 (-3.85,1.09)	0.2728
PROMIS Pain Interference	Baseline	63.76 (62.89,64.62)		N/A	N/A
	12 weeks	61.96 (60.91,63.02)	61.09 (60.01,62.17)	-0.87 (-2.21,0.47)	0.203
	36 weeks	62.14 (60.93,63.35)	60.91 (59.65,62.17)	-1.23 (-2.69,0.24)	0.1009
PHQ-8	Baseline	6.2 (5.54,6.86)	6.2 (5.54,6.86)	N/A	N/A
	12 weeks	6.38 (5.53,7.24)	5.88 (5.6,76)	-0.5 (-1.57,0.57)	0.356
	36 weeks	6.33 (5.44,7.21)	5.31 (4.37,6.25)	-1.02 (-2.19,0.15)	0.0866
Arthritis Self-Efficacy Scale	Baseline	5.87 (5.62,6.11)		N/A	N/A
	12 weeks	5.66 (5.35,5.98)	6.67 (6.35,6.99)	1.01 (0.61,1.41)	<0.001
	36 weeks	5.66 (5.33,5.99)	6.33 (5.99,6.67)	0.67 (0.24,1.09)	0.0021

Disclosure: K. Allen, None; T. Somers, None; L. Campbell, None; C. Coffman, None; L. Arbeevea, None; C. Cene, None; E. Oddone, None; F. Keefe, None.

Abstract Number: 2946

T Peripheral Helper Cells Are Expanded in the Circulation of Active SLE Patients and Correlate with CD21low B Cells

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis II

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: Pathologic T cell-B cell interactions and production of autoantibodies are hallmark features of SLE. T follicular helper (Tfh) cells are generally considered the principal T cell population capable of helping B cells. However, distinct T cell populations can augment B cell responses in chronically inflamed peripheral tissues. We recently described a dramatically expanded population of T peripheral helper (Tph) cells that promotes B cell responses in synovium of patients with seropositive RA. Here we evaluate the frequency, phenotype, and clinical associations of Tph cells in the circulation of patients with lupus.

Methods: Mass cytometry data from the Accelerating Medicines Partnership RA/SLE Network were used to quantify cell populations in PBMCs from 27 lupus nephritis patients, 27RA patients, and 25 non-inflammatory controls. Frequencies of Tph cells (PD-1^{hi}CXCR5⁻ CD4⁺ T cells), Tfh cells (PD-1^{hi} CXCR5⁺CD4⁺ T cells), and CD21^{low} CD19⁺ B cells were quantified by standardized gating, and associations with SLEDAI and dsDNA titers were assessed. For *in vitro* T cell-B cell co-cultures, sorted Tph cells, Tfh cells, or control T cell populations from SLE patients were co-cultured with memory B cells and stimulated with SEB + LPS, and CD38^{hi} CD27⁺ plasmablasts were quantified at day 5.

Results: We first confirmed that Tph cells (PD-1^{hi} CXCR5⁻ CD4⁺ T cells) from SLE patients possess B cell helper function, as we previously observed in RA. Tph cells sorted from blood from 5 different lupus patients strongly induced B cell differentiation into CD38^{hi} CD27⁺ plasmablasts *in vitro* (Figure 1A). By mass cytometry, Tph cells are markedly expanded in the circulation of SLE patients compared to non-inflammatory controls (4.3-fold increase, p<0.0001, Figure 1B). Tfh cells are also increased in the SLE patients compared to controls (1.9-fold); however, the magnitude of the increase in Tph cells in SLE patients well exceeds that of Tfh cells. Tph cell frequency is higher in lupus nephritis

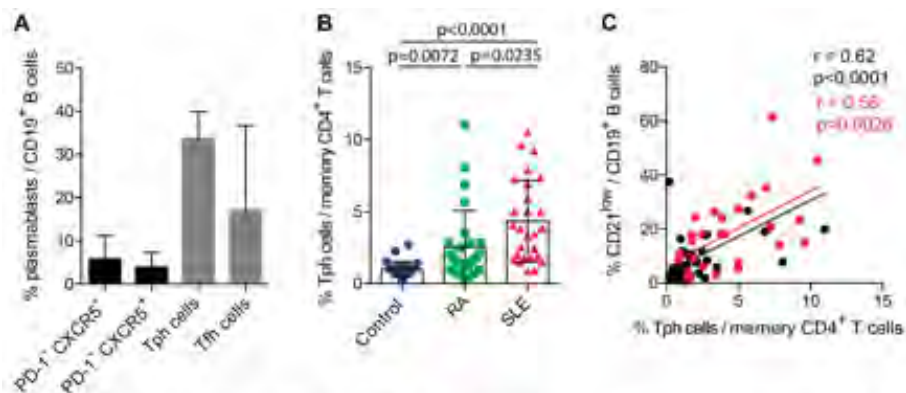


Figure 1: Expanded Tph cells in SLE patients. A) Plasmablast differentiation induced *in vitro* by PD-1-high CXCR5-neg Tph cells or other T cell populations sorted from PBMCs of SLE patients (n=5 donors). B) Proportion of Tph cells among memory CD4+ T cells in PBMC from SLE, RA, and control patients by mass cytometry. C) Correlation between circulating Tph cells and CD21-low B cells in SLE patients (red) or including all patients (black). Spearman statistics.

patients with dsDNA titers >50 ($p=0.017$) and with SELENA-SLEDAI > 10 ($p=0.046$) compared to patients with lower disease activity measures. Similar associations with disease activity were not observed for Tfh cells. Expression of surface receptors on Tph cells from SLE and RA patients was similar. A strong positive correlation emerged between the frequencies of Tph cells and CD21^{low} B cells, an activated B cell population highly expanded in SLE (Spearman $r=0.56$, $p=0.0026$, Figure 1C). In contrast, no correlation was seen between Tfh cells and CD21^{low} B cells in SLE patients.

Conclusion: Tph cells are markedly expanded in the circulation of patients with SLE and demonstrate robust B cell helper function. The strong and specific positive correlation between Tph cell and CD21^{low} B cell frequencies suggests that these cells may act coordinately in the pathologic autoimmune response in SLE.

Disclosure: D. Rao, Amgen Inc., 5, Merck & Co., 2; A. Bocharnikov, None; C. Fonseka, None; J. Keegan, None; B. Diamond, None; J. Anolik, None; P. Nigrovic, Novartis, AbbVie, Sobi, 2, Novartis, AbbVie, Sobi, UCB, Pfizer, 5, UpToDate, American Academy of Pediatrics, 7; S. Raychaudhuri, None; J. A. Lederer, None; M. Brenner, None.

Abstract Number: 2947

Peripheral Helper T Cells in Systemic Lupus Erythematosus

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis II

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Autoreactive T-B cell interactions in lymphoid tissue have been thought to play a crucial role in the autoantibody production in systemic lupus erythematosus (SLE). These CD4⁺ T cells are known as follicular helper (T_{FH}) cells expressing CXCR5, a chemokine receptor promoting cell migration to B cell follicles. Recently, a new population of ‘peripheral helper’ T (T_{PH}) cells that help B cell responses has been discovered in synovium of patients with rheumatoid arthritis. Like T_{FH} cells, T_{PH} cells express ICOS and PD-1, but these cells lack CXCR5. Here we assessed whether T_{PH} cells are involved in the pathogenesis of SLE.

Methods: Peripheral blood mononuclear cells (PBMCs) were obtained from SLE patients and age- and sex-matched healthy individuals as controls. The patients fulfilled the 1997 ACR criteria. A total of 65 patients provided blood samples (57 women and 8 men). The median age of patients was 41 years (range, 21-52), and the median SLEDAI score was 4 (range 0-31). The majority of patients (n=54) were taking medications such as glucocorticoids, hydroxychloroquine, tacrolimus, cyclosporine, azathioprine, mizoribine, and mycophenolate mofetil. Isolated PBMCs were stained with antibodies against CD3, CD4, CD45RA, CXCR5, PD-1, ICOS, CD19, CD20, CD27, CD38, CD180, IgD, and HLA-DR,

and were analyzed by flow cytometry. T_{PH} were defined as PD-1^{hi}CXCR5⁺CD45RA⁺CD4⁺CD3⁺ cells. Frequency and activated status of T_{PH} cells were compared with those of other immune cells including B cell subsets, clinical data (anti-DNA antibody titers, serum complement levels, and lymphocyte counts) and SLEDAI. IL-21-producing capacity of T_{PH} upon stimulation with phorbol 12-myristate 13-acetate (PMA) and ionomycin was analyzed with intracellular staining.

Results: The proportions of T_{PH} cells as well as activated T_{PH} cells were increased in SLE patients than healthy controls. The frequency of T_{PH} cells positively correlated with SLEDAI and anti-DNA antibody titers, and negatively correlated with serum complement levels. Activated T_{PH} cells were also associated with SLEDAI, anti-DNA antibody titers, serum complement levels, and lymphocyte counts. We did not observe differences in relative frequencies of T_{PH} cells in SLE patients regardless of treatment. As previously reported, the frequency of plasmablasts was increased in SLE patients and correlated with disease activity. The frequency of activated T_{PH} cells were correlated with that of plasmablasts and activated switched memory B cells. Lupus T_{PH} cells had the capacity to produce IL-21, a pivotal cytokine for B cell and plasma cell differentiation.

Conclusion: Our data demonstrate that the increased frequency and activated status of T_{PH} cells are associated with the disease activity as well as enhanced B cell responses in SLE. CD4⁺ICOS⁺PD-1⁺ cells and plasma cells were reported to be present in the nephritic kidneys and associated with active disease in SLE. Because T_{PH} cells also express ICOS and PD-1, the interaction of T_{PH} cells with B cells may occur in the lupus kidneys and contribute to the autoantibody production in the peripheral tissue in SLE.

Disclosure: A. Makiyama, None; A. Chiba, Chugai Pharmaceutical Co. Ltd., 8; G. Murayama, None; K. Yamaji, None; N. Tamura, Chugai Pharmaceutical Co. Ltd., 2, Astellas Pharma Inc., 2, ASAHI KASEI MEDICAL, 2, Sanofi K.K., 8, Bristol-Myers Squibb, 8; S. Miyake, TAIHO PHARMACEUTICAL CO., LTD., 5, Astellas Pharma Inc., 8, Bristol-Myers Squibb, 8, Sanofi K.K., 8, Chugai Pharmaceutical Co. Ltd., 8, Pfizer Japan Inc., 8, AYUMI Pharmaceutical Corporation, 8.

Abstract Number: 2948

Deconstructing the in Situ Myeloid Cell Microenvironment in Human Lupus Nephritis Tissue

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis II

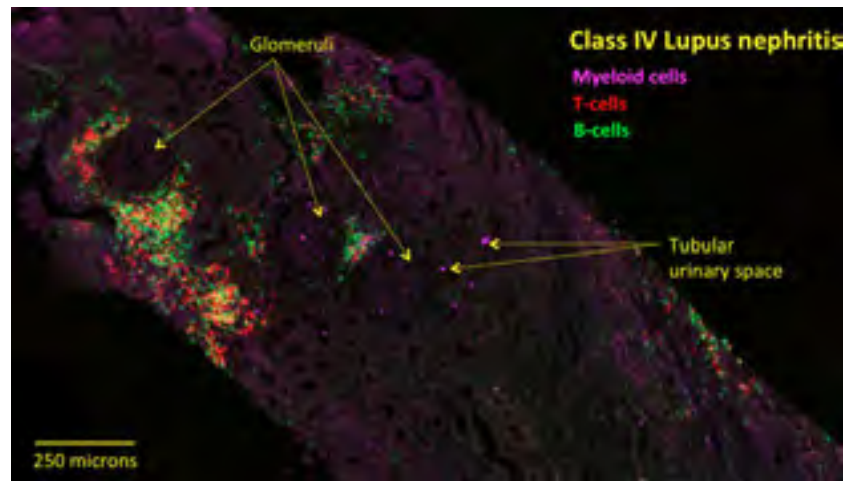
Session Type: ACR Concurrent Abstract Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: The cell-types and pathways driving lupus nephritis (LN) are incompletely understood. The Accelerating Medicine Partnership lupus network Pathway Exploration and Analysis in Renal disease (AMP-PEARL) consortium sequenced RNA from ~2,900 single cells from LN kidney biopsies from 24 patients and discovered 21 immune cell types, including 5 myeloid subsets. This study provided unprecedented molecular information, but lacked *in situ* immune cell spatial context and was underpowered for associations with clinical outcomes. We investigated the *in situ* organization of the immune landscape to determine whether it drives clinical outcomes. Because myeloid cells link innate and adaptive immunity, we hypothesized that their *in situ* organization reflects the physical configuration of larger immune cell networks that promote kidney remodeling and clinical outcomes.

Methods: We assembled a new cohort of 30 LN patients presenting with Class III or IV disease of varying severity who had their 1st kidney biopsies (naïve to potent immune-modulators). To dissect the *in situ* organization of the 5 new myeloid subsets (3 monocyte phenotypes, 1 dendritic cell, and 1 resident macrophage), we converted single cell RNA-sequencing signatures into molecular stains based on highly expressed myeloid subset-specific discriminatory genes with known biological functions. We then stained clinical samples from our cohort for multiplex fluorescent imaging and quantification across tissue sections.

Results: We validated the 5 new myeloid subsets and find they are similarly organized across class III and IV tissue: one monocyte subset (alternatively activated) is excluded from glomeruli but present in the interstitial space; two other monocyte subsets (inflammatory and phagocytic) are present in glomerular and interstitial space and enriched inside tubular urinary space. We also find that DCs are enriched in interstitial over glomerular space.



Conclusion: By converting single cell RNA sequencing information into molecular stains, we developed a novel approach to validate *in situ* the 5 newly identified myeloid subsets and mapped each to anatomic niches in class III and IV tissue, suggesting molecular organizing principles drive *in situ* cellular configurations. We are also mapping myeloid subsets in class V LN, histopathological lesions, and examining their connectivity to larger immune cell networks by quantifying the composition of neighboring immune cells (T, B, NK cells) to identify the rules of *in situ* immune cell organization. We will examine our findings with clinical outcomes, possibly laying the groundwork for disease re-classification based on the immune response and highlighting cell-types and intercellular connections for follow up studies. We anticipate that this approach can be applied to other cell and tissue types.

Disclosure: P. Hoover, None; T. Jones, None; C. Leatherwood, None; S. Waikar, None; K. Costenbader, None; N. Hacohen, None.

Abstract Number: 2949

African American and European American SLE Patients with Variable Disease Activity Reveal Distinct Differences in B Cells and TLR7/8 Pathways

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis II

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disorder with a heterogeneous clinical presentation and periods of waxing and waning disease. Heterogeneity in SLE is influenced by genetic and non-genetic susceptibility found in different ethnicities that drive disease expression and severity. The immune pathways that contribute to heightened disease activity in lupus and immune variation by race are critical to understanding SLE disease mechanisms and outcomes.

Methods: Peripheral whole blood samples of European or African American healthy controls (n=18) and SLE patients with either high (SLEDAI \geq 4) (n=20) or low (SLEDAI<4) (n=20) disease activity were stimulated for 4 minutes with either interferon- α (IFN α), PMA and ionomycin, or Toll-like receptor (TLR) ligands for either TLR4, TLR7/8 or TLR9 for phospho-protein analysis. Phenotype and phospho-protein analysis was assessed by CyTOF and cell heterogeneity was analyzed using t-SNE and manual gating. All SLE patients met ACR classification criteria.

Results: European American SLE patients with high disease activity were differentiated from patients with low disease activity by reduced frequencies of peripheral B cells, specifically naïve B cells (CD27-IgD+CD24^{lo}) (p=0.0101) and double negative B cells (CD27-IgD-) (p=0.0220), while African American patients with high disease activity had elevated frequencies of memory B cells (CD27+IgD-CD38+) (p<0.05) compared to patients with low disease activity. Several cell

subsets had increased expression of activation markers during high disease activity including B cells ($p=0.0350$) and plasmacytoid dendritic cells (pDCs) ($p=0.0435$) in European Americans (Figure 1A), and neutrophils ($p<0.05$), pDCs ($p=0.005$), CD8+ T Cells ($p=0.0003$) and NKT cells ($p=0.0033$) in African Americans (Figure 1B). Following whole blood stimulation with IFN α , African American high disease activity patients were distinguished by reduced ability to activate pSTAT5 in almost all major cell populations ($p<0.05$), and pSTAT3 in monocytes ($p=0.0157$), granulocytes ($p=0.01$) and B cells ($p=0.0409$) compared to low disease activity patients and controls, possibly due to higher basal levels of activation. Further, granulocytes and all antigen presenting cells had reduced activation or unchanged levels of pCREB, p-p38, pCREB and Syk following TLR7/8 stimulation in African American high versus low disease activity patients ($p<0.05$). European American high disease activity SLE patients were distinguished by increased signaling in B cells and dendritic cells following TLR4 and TLR7/8 stimulation, specifically in p-p38, pERK1/2, and pCREB ($p<0.05$).

Conclusion: Our results support a model where race influences heightened SLE disease activity mechanisms with dysregulation in B cell signaling and other antigen presenting cells following TLR7/8 and Type I IFN pathway activation.

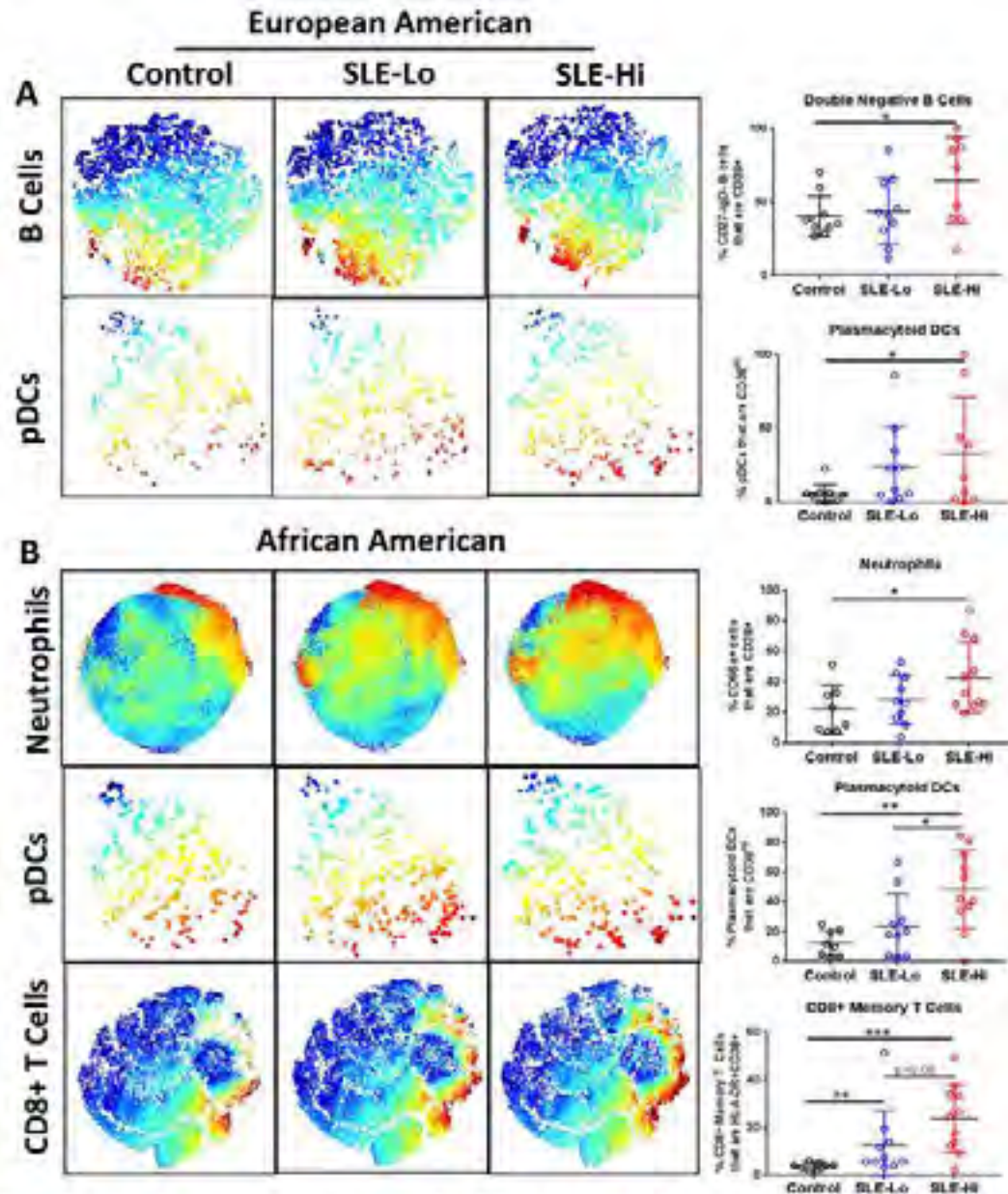


Figure 1. Cell activation markers are increased in SLE patients with high disease activity. All cell subsets as determined by gating in visNE were assessed for frequencies of activation, inhibitory and chemokine receptors. Concatenated files of controls and SLE patients were used to create visNE dot plots individually colored by channel using ArcSinh-5 transformed expression values. visNE of visNE plots was used for representation of specific populations showing CD38 expression in European Americans (A) B cells and pDCs, and African Americans (B) neutrophils, pDCs and CD8+ T Cells. Significant differences in cell surface marker expression are also shown using bar graphs. Median \pm interquartile range shown * $p<0.05$, ** $p<0.01$, and *** $p<0.001$.

Disclosure: S. Slight-Webb, None; M. C. Smith, None; H. T. Maecker, None; P. J. Utz, None; J. M. Guthridge, None; J. A. James, None.

Abstract Number: 2950

10X Genomics-Based Single-Cell RNA-Seq Analysis Identifies a Transcriptional Landscape of Inflammation and Fibrosis in Lupus Nephritis

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis II

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: Renal histology remains a primary tool for classification and treatment decisions in lupus nephritis (LN). Single-cell RNA-seq (scRNA-seq) analysis may provide mechanistic insights into the genesis; more precisely categorize different pathologic subtypes; and better inform treatment decisions and prognosis. Here we characterized single-cell transcriptome profiles of the renal cellular landscape using scRNA-seq.

Methods: ScRNA-seq was performed on ~2 mg cryostored kidney tissue collected from clinically indicated renal biopsies in 9 SLE patients and 2 healthy transplant donors. A droplet-based 10X Chromium platform (10X Genomics) was used to capture single cells in emulsion followed by cDNA synthesis. The cDNA library was sequenced on Illumina HiSeq 2500. Cell-barcode and unique molecular identifiers (UMIs) were tagged in read1, an adapter was trimmed from 5' of read2 and poly(A) sequences of length 6 or more were removed. The resulting reads were aligned to the human (hg38) reference genome and a single cell gene expression matrix was generated. Using a graph-based method embedded in the Seurat package, cell clustering analysis was performed. Cells with > 25% mitochondrial content were considered poor quality and filtered out as were any cells with < 100 genes detected.

Results: We obtained 16,192 and 3,104 high-quality scRNA-seq profiles from 9 LN patients (class I, II, IV/V and IV) and 2 donor controls respectively. Graph-based clustering analysis revealed several cell clusters as visualized by *t-distributed stochastic neighbor embedding (t-SNE)*. Differential gene expression analysis along with expression of established lineage markers revealed these clusters as loop of Henle (LH), proximal convoluted tubule (PCT), distal convoluted tubule (DCT), intercalated cells (IC), mesangial cells (MC), podocytes (PC), T cells (TC), macrophages (MAC), B cells (B cell), plasmablasts (PB), endothelial cells (EC) and fibroblasts (FB). Differential gene expression analysis revealed elevated levels of interferon response genes such as *IFI6*, *IFITM1*, *IFITM3* and *ISG15* in CD, DCT and EC of LN samples. In addition, *WFDC2*, recently described as an LN biomarker, was upregulated in CD and DCT of LN samples. PCT in the LN samples revealed increased expression of *COL4A1*, *COL4A2* and *COL18A1* genes whose proteins form the structural component of the basement membrane. FB detected in the LN samples expressed *COL1A1*, *COL1A2*, and *COL3A1* as the most abundant collagen genes.

Conclusion: ScRNA-seq derived from excess and limited cryostored renal biopsy tissue in LN can be used to generate a cellular atlas invaluable to the study of heterogeneity in disease. These data provide important insights into potential pathogenic mechanisms, particularly with regard to tissue fibrosis so highly relevant to the ultimate renal prognosis.

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Ustekinumab Treatment Response in SLE Is Associated with Changes in Type II but Not Type I Interferons

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Systemic Lupus Erythematosus – Etiology and Pathogenesis II

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: We previously reported that treatment with ustekinumab (UST), an anti-IL-12/23 p40 neutralizing monoclonal antibody, improved global and organ-specific measures of disease activity in a randomized, placebo (PBO)-controlled study of patients with active SLE (NCT02349061)¹. Type I interferon (IFN-I) and type II IFN (IFN-g) are elevated in a subset of SLE patients. The comparative effects of IFN-I and IFN-g in SLE remain uncertain, although targeting IFN-I (anifrolumab) has demonstrated clinical efficacy, whereas a preliminary study with anti-IFN-g mAb (AMG811) failed to establish benefit^{2,3}. Given the potential importance of the IFN-I and IFN-g pathways in SLE pathogenesis, we studied the effects of UST treatment on both IFN-I and IFN-g in patients with active SLE.

Methods: We conducted a phase 2, PBO-controlled study in 102 adults with seropositive SLE by SLICC criteria and active disease (baseline SLEDAI score ≥ 6 and ≥ 1 BILAG A and/or ≥ 2 BILAG B scores) despite standard-of-care therapy¹. Gene expression analysis using a previously published 21 gene IFN-I gene signature (IGS)⁴ was performed by microarray analysis using whole blood PAXgene RNA samples. Analysis of serum protein levels of IFN-g and IFN- α was performed using MSD (IFN-g) and Quanterix (IFN- α) platforms.

Results: Serum levels of IFN-g and IFN- α and the IGS were significantly elevated at baseline versus healthy controls ($p < 0.0001$). Approximately 67% of the SLE patients were IGS high at baseline. At 4 weeks, patients who received UST, but not PBO, exhibited decreased IFN-g protein levels ($p = 0.0032$). Despite non-significant differences at baseline, there was a trend toward greater reduction in IFN-g levels in UST-treated patients who achieved an SRI-4 response at wk24 compared to non-responders. There was no decrease in IFN- α protein levels or the IGS after treatment with either UST or PBO. Whereas the proportion of patients achieving an SRI-4 response at wk24 was numerically greater in the IGS low patients (81.8% UST vs. 54.5% PBO) versus the IGS high (48.6% UST vs. 20% PBO) population, the magnitude of the treatment effect (UST vs. PBO) was similar in both subsets (IGS low effect size = 27.3% vs. IGS high effect size = 28.6%).

Conclusion: In this SLE trial population which had significant upregulation of IFN-I protein and IGS at baseline, clinical response to UST was not associated with IFN-I reduction. In contrast, a significant decrease in IFN-g protein levels was associated with UST treatment. These findings suggest that a broad population of SLE patients may respond to UST regardless of baseline IFN status. Moreover, an effect of UST treatment on TH1 responses manifested by IFN-g levels in SLE patients was suggested, a finding that will be tested in a phase 3 trial.

¹ACR 2017 Abstract # 6L

²Furie, R., et al., *Arthritis Rheumatol*, 2017. 69(2): p. 376-386.1.

³Boedigheimer, M.J., et al., *Lupus Sci Med*, 2017. 4(1): p. e000226. ⁴Yao, Y., et al., *HGP*, 2009.

Disclosure: J. Jordan, Janssen Research Development, LLC, 3; K. Sweet, Janssen Research and Development, LLC, 3; M. Cesaroni, Janssen Research and Development, LLC, 3; K. Ma, Janssen Research and Development, LLC, 3; C. Franks, Janssen Research and Development, LLC, 3; L. Seridi, Janssen Research and Development, LLC, 3; J. Schreiter, Janssen Research and Development, LLC, 3; R. Gordon, Janssen Research & Development, LLC, 3; P. E. Lipsky, Janssen Research and Development, LLC, 2; S. Rose, Janssen Research & Development, LLC, 3; F. Baribaud, Janssen Research and Development, LLC, 3; M. Loza, Janssen Research and Development, LLC, 3; K. Campbell, Janssen Research and Development, LLC, 3.

Major NSAID Toxicity: Derivation and Internal Validation of a Simple Clinical Risk Score

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Session Information

Session Date: Wednesday, October 24, 2018

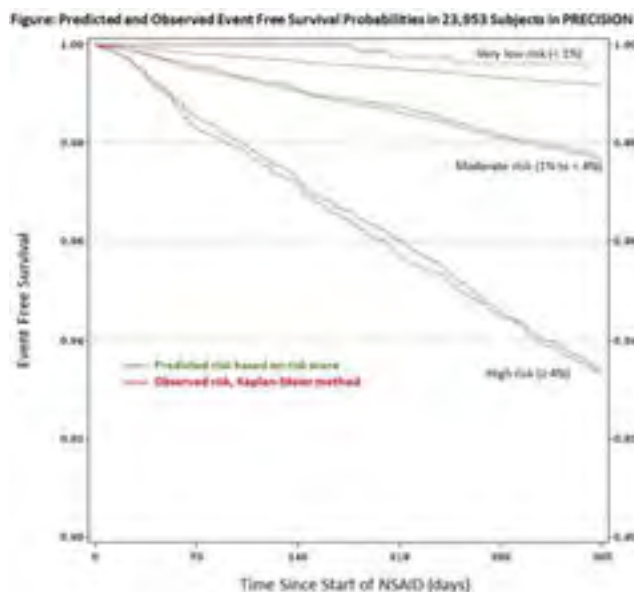
Session Title: Epidemiology and Public Health IV: Determinants and Consequences of Treatment

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: NSAIDs and Coxibs represent one of the most commonly prescribed drugs by rheumatologists and are used regularly by >10 million Americans. While most patients enjoy analgesic benefits with these medications, some experience major toxicities. Improving the risk-benefit ratio requires a more precise understanding of the risks for an individual patient. The goal of this research was to derive and validate a risk score for major NSAID toxicity.

Methods: The TRIPOD recommendations were followed for conducting this research, such that patients recruited during the first 4 years (n = 15,196) of enrollment in the PRECISION trial were used to derive a risk score and patients enrolled in last 5 years (n= 8,757) were used for validation. Participants were censored at 1 year, patient termination of study NSAID or time of first major toxicity. The major NSAID toxicity outcomes included cardiovascular (CV) event, clinically significant gastrointestinal event, significant renal events, or death. Variables significantly associated (p<0.1) with major toxicity after adjustment for baseline age and gender were candidates for inclusion in the final Cox proportional hazards regression model. Discrimination of the model was assessed with the c-index and calibration was assessed by examining the slope from the observed to expected risk plots. After derived models were found to have similar model fit statistics in the validation set, the cohorts were combined, allowing calculation of a risk score for the 1-year probability of major NSAID toxicity. Three risk categories were created: very low (<1%), moderate (1 to <4%) and high (4+%); agreement was assessed between predicted and observed risk.



Results: In the derivation cohort, statistically significant variables included age (HR1.03 per year), male sex (HR 1.51), history of CVD (HR 1.94), history of hypertension (HR1.29), history of diabetes (HR 1.42), aspirin use (HR 1.37), tobacco use (HR 1.55), statin use (HR 1.43), elevated serum creatinine (HR 2.83), hematocrit \geq 43% (HR 1.05), and RA (vs OA; HR 1.79). Harrell's c-index was 0.66 in the validation cohort and the model was well calibrated for the risk of major NSAID toxicity (calibration slope 0.75 for observed to predicted probabilities of outcomes). In the total population (n = 23,953), 1,389 (5.8%) had predicted 1 year risk <1%, 15,979 (66.7%) had predicted 1 year risk 1-4%, and 6,367(26.6%) had predicted 1 year risk >4%. Calibration in the combined cohort is demonstrated in the survival probability plot (see Figure).

Conclusion: We have derived and internally validated a risk score using data from the PRECISION trial to predict the 1 year risk of major NSAID toxicity for patients with osteoarthritis or rheumatoid arthritis on chronic NSAIDs. Elements of the score are easy to obtain and, if found to be externally valid, could help clinicians and patients determine risk-benefits of chronic NSAID use.

Disclosure: D. Solomon, None; M. Shao, None; K. E. Wolski, None; S. E. Nissen, None; M. E. Husni, None; N. Paynter, None.

Abstract Number: 2953

Disappearance of Autoantibodies in RA: Does It Occur with Current Treatment Strategies? a Long-Term Follow-up Study in Patients That Achieved DMARD-Free Sustained Remission

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Session Information

Session Date: Wednesday, October 24, 2018

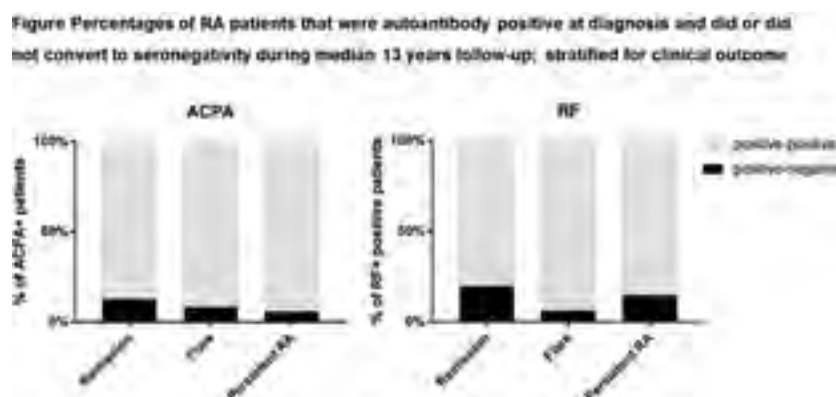
Session Title: Epidemiology and Public Health IV: Determinants and Consequences of Treatment

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Disease modifying antirheumatic drug (DMARD)-free sustained remission, the sustained absence of arthritis after cessation of all DMARD-therapy, is increasingly achievable with current treatment strategies. It is a proxy of cure of RA and also signifies normalisation of functional status. Absence of ACPA is an important predictor. Nonetheless, $\leq 10\%$ of ACPA positive patients currently achieves this outcome. It has recently been suggested that immunological remission, defined as disappearance of ACPA and RF, is a proxy of cure. (Schett G, *ARD*, 2016) We performed a long-term observational study in ACPA and/or RF positive patients to determine if these autoantibodies disappear in patients who achieve DMARD-free sustained remission, thus after having developed the best possible clinical outcome.

Methods: Of 1587 RA patients (970 RF and/or ACPA positive) included in the Leiden Early Arthritis Clinic, 339 (21%) achieved DMARD-free sustained remission. Of these, 117(35%) were ACPA and/or RF positive at diagnosis and were studied. In addition 22 autoantibody positive RA patients who experienced a late flare after having been in DMARD-free remission for 2.4 years were studied. As control, 50 autoantibody positive RA patients who were unable to stop DMARD therapy, were evaluated. DMARD-free sustained remission was achieved after a median follow-up of 4.5 years. Median total follow-up was 13 years. ACPA and RF levels were determined in serial samples, at least at baseline and at and/or after achieving DMARD-free remission.



Results: 12.8% of ACPA positive RA patients who achieved DMARD-free sustained remission, had converted to ACPA-negativity at achieving remission (Figure). However within RA patients with a late flare or with persistent disease and similar follow-up duration this occurred in 8.3% and 5.7%, respectively ($p=0.56$). For RF similar results were observed. RF positive RA patients who achieved DMARD-free sustained remission had seroconversion to RF-negativity in 19.7%, whereas this also occurred in 14.6% of RF positive RA patients with persistent disease. Evaluating the estimated slope of serially measured levels revealed that the RF levels decreased significantly more in patients that achieved DMARD-free

sustained remission compared to those that did not ($p<0.001$). Within ACPA-positive patients however, there was no enhanced decrease in ACPA levels ($p=0.66$).

Conclusion: DMARD-free sustained remission is achieved in 12% of RA patients that were autoantibody positive at diagnosis. Only a minority had converted to seronegativity when DMARD-free sustained remission was achieved; this proportion was not different from that in patients with persistent disease. The finding that ACPA remains present in RA patients with sustained absence of arthritis and normalized function after DMARD-cessation suggests that immunological remission, defined as disappearance of ACPA, probably should not be a treatment target.

Disclosure: D. M. Boeters, None; L. E. Burgers, None; R. E. M. Toes, None; A. H. M. van der Helm-van Mil, None.

Abstract Number: 2954

Factors Related to Initiation of TNF Inhibitor Versus Triple Therapy in Rheumatoid Arthritis Patients

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Table. Selected baseline characteristics and multivariable OR* (95% CI) of initiating TNFi plus MTX versus triple therapy

Characteristics	TNFi combination therapy	Triple therapy (reference group)	Multivariable OR (95% CI)
N	45,305	1,388	
Demographics			
Age, years	53.3 (±12.5)	53.7 (±12.8)	1.00 (0.99, 1.00)
Female	75.8	71.8	1.17 (1.04, 1.33)
Region			(Ref)
Midwest	25.0	33.3	
Northeast	14.3	9.4	1.96 (1.60, 2.39)
South	41.4	34.2	1.41 (1.23, 1.61)
West	17.9	21.9	1.08 (0.93, 1.26)
Comorbidities			
Coronary artery disease	4.9	4.4	1.60 (0.22, 11.65)
Myocardial infarction or angina	4.8	4.3	0.68 (0.05, 5.02)
Ischemic stroke	1.5	1.9	0.69 (0.46, 1.04)
Obesity	3.6	4.9	0.58 (0.45, 0.75)
Psoriasis	6.3	1.3	4.88 (3.05, 7.80)
Inflammatory bowel disease	1.0	0.2	3.57 (1.14, 11.14)
Medication use			
Proton pump inhibitor	24.7	16.8	1.30 (1.11, 1.52)
Bisphosphonate	9.4	5.9	1.59 (1.25, 2.02)
Insulin	4.3	3.7	1.00 (0.73, 1.36)
Other anti-diabetics	8.3	8.0	0.86 (0.66, 1.14)
Non-steroidal anti-inflammatory drugs	47.2	41.3	1.09 (0.97, 1.23)
Oral corticosteroid	57.8	52.3	0.88 (0.75, 1.03)
Recent oral corticosteroid (in 30 days)	27.6	23.9	1.05 (0.89, 1.24)
Antibiotics	42.8	38.3	0.93 (0.81, 1.06)
Antivirals	2.5	2.0	0.99 (0.64, 1.54)
Antifungals	8.3	5.7	1.28 (0.96, 1.70)
Number of generics	9.0 (±5.0)	7.8 (±4.7)	1.06 (1.04, 1.09)
Vaccination			
Flu vaccine	12.8	11.1	1.03 (0.87, 1.23)
Pneumonia vaccine	5.1	4.1	1.14 (0.86, 1.50)
Herpes vaccine	0.8	0.3	2.62 (0.97, 7.08)
Healthcare utilization			
Number of outpatient visit	6.2 (±4.0)	5.3 (±3.9)	1.01 (0.99, 1.03)
Number of rheumatologist visit	2.0 (±2.3)	1.3 (±1.8)	1.15 (1.11, 1.19)
Inpatient visit	6.2	4.7	1.38 (1.04, 1.83)
Emergency department	12.9	12.2	0.85 (0.71, 1.01)

*Adjusted for demographics, comorbidities, medication use, vaccination, and healthcare utilization; some variables are not shown here.

Figure. Geographic distribution of proportion of triple therapy in the US from 2003 to 2014



Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Epidemiology and Public Health IV: Determinants and Consequences of Treatment

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: While efficacy of triple therapy [methotrexate (MTX), sulfasalazine(HCO), and sulfasalazine(SSZ)] and TNF inhibitor (TNFi) plus MTX was similar in a previous clinical trial, use of triple therapy is infrequent in the US. We aimed to examine geographical and clinical factors associated with the two treatment strategies for RA.

Methods: We used Truven Market Scan data (2003-2014) to conduct a cohort study among RA patients ≥ 18 years old with MTX prescription. Triple therapy was defined as adding on both HCO and SSZ, and TNFi therapy was defined as adding a TNFi to MTX. Index date was the first dispensing date of the last drug to complete triple therapy, or TNFi. Exclusion criteria included malignancy, renal dialysis, HIV, nursing home stay, or hospitalized infection, and any prior use of study drugs except MTX 180 days before the index date. We assessed geographic patterns and baseline covariate including demographics, comorbidities, medications, and health care utilizations associated with starting TNFi or triple therapy using multivariable logistic regression.

Results: We identified a total of 46,693 patients (45,305 (97.0%) TNFi plus MTX and 1,388 (3.0%) triple therapy initiators). Females were more likely to receive TNFi therapy (OR, 95% CI = 1.17, 1.04-1.33, Table). We noted a significant geographical pattern with regard to initiation of triple therapy (Figure). Patients were most likely to receive triple therapy in Midwest (Table, Figure). Specifically, Nebraska had the highest rate of receiving triple therapy, followed by its adjacent states. We did not find any association between underlying cardiovascular diseases and either of two treatment groups. However, obese patients were 42% more likely to be started on triple therapy. Baseline psoriasis and inflammatory bowel disease increased odds of receiving TNFi (OR, 95% CI = 4.88, 3.05-7.80 and 3.57, 1.14-11.14). Generally, TNFi initiators used more medications and had rheumatologist or inpatient visit more frequently than those on triple therapy.

Conclusion: In this large nationwide cohort of RA patients, triple therapy use was infrequent. Geographical and certain clinical factors such as coexisting psoriasis or inflammatory bowel disease, use of bisphosphonates, proton pump inhibitors, frequency of rheumatologists visit, and inpatient visit were associated with choosing TNFi versus triple therapy.

Disclosure: Y. Jin, None; E. H. Kang, None; A. Tong, None; R. J. Desai, None; S. C. Kim, Roche, Pfizer, and Bristol-Myers Squibb, 2.

Risk of Neurological Adverse Events during Tumour Necrosis Factor Inhibitor Treatment for Arthritis: A Population-Based Cohort Study from Danbio and the Danish National Patient Registry

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Session Information

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Session Title: Epidemiology and Public Health IV: Determinants and Consequences of Treatment

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: Tumor necrosis factor alpha inhibitors (TNFi) have successfully been used for the treatment of immune-mediated inflammatory disorders including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) since 1998. However, several case reports and series have indicated that different neurological disorders including multiple sclerosis (MS), inflammatory neuropathies, demyelinating diseases and optic neuritis may be a serious, although rare, adverse event following TNFi treatment. A field of complexity as some studies show that RA is protective of MS and vice versa. We investigate the association between new-onset neurological events following TNFi-treatment in arthritis patients compared to non-TNFi-treated arthritis patients.

Methods: 41,026 patients registered in DANBIO between January 1, 2000 and January 20, 2017 were identified with a diagnosis of either RA, AS or PsA. Complete follow-up on mortality, emigration and newly diagnosed neurological diseases suspected to be associated with use of TNFi until May 10, 2017 was obtained by linkage to the Danish National Patient Registry and the Civil Registration System. A cox proportional hazard model was used to examine the association between use of TNFi and risk of a neurological event.

Results: The DANBIO arthritis cohort experienced 223,861 person-years of observation. 98 patients were diagnosed with demyelinating disease or inflammatory neuropathy during follow-up, with 49 contacts among ever TNFi-treated patients and 49 contacts among non-TNFi-treated patients corresponding to a Hazard Ratio (HR) of 1.52 (95% Confidence Interval (CI): 0.96-2.42) adjusted (adj) for age, gender and year of inclusion. TNFi treatment among RA patients was not associated with an increased risk of a neurological event ($HR_{adj}=1.19$, 95% CI: 0.65-2.18), whereas PsA and AS patients had an increased risk of having a neurological event following TNFi treatment ($HR_{adj}=2.61$, 95% CI: 1.11-6.13). In on-drug models the HR_{adj} for neurologic events in RA was 0.95 (95% CI: 0.49-1.83) and 2.43 (95% CI: 1.01-5.83) in PsA/AS.

Conclusion: The use of TNFi for the treatment of arthritis may be associated with increased risk of having a demyelinating disease or inflammatory neuropathy among patients with PsA or AS. Since these events are rare, larger multicenter studies are warranted to further characterize the risk.

Disclosure: L. Dreyer, Eli Lilly and Co., 8; T. Iskov Kopp, None; R. Kart Jacobsen, None; M. Magyari, None; E. H. Ibfelt, None; H. Locht, None; F. T. Sellebjerg, None; D. V. Jensen, None; R. Cordtz, None.

Changing Trends and Prescribing Patterns in Opioid-Treated Primary Care Patients with Non-Cancer Pain over a 10-Year Period

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Session Information

Session Date: Wednesday, October 24, 2018

Background/Purpose: The opioid epidemic in the U.S. has led to similar concerns about prescribed opioids in the U.K. In new users, the rate of escalation to more potent opioids is likely to contribute to long-term prescriptions, which in turn may be associated with opioid dependency, addiction and overdose. The scale of such escalation however is unclear in the U.K. We sought to: (i) describe trends of prescribed opioids for non-cancer pain in the UK primary care setting over a 10-year period (ii) assess the sequential transition of opioid strength from index date over a 2-year period. **Methods:** We conducted a retrospective observational study from 1/1/2006 to 31/12/2015 using Clinical Practice Research Datalink (CPRD). New users of opioids, >18 years without cancer in the 2 years prior to index date were identified. The number of prescriptions for each drug were calculated by each calendar year accounting for the number of eligible patients registered in CPRD for that year. Sunburst plots were created to evaluate the sequential transition of opioids over time. A 4-state hidden Markov model was used to estimate the transition probability for individuals escalating to more potent opioids over a 2 year period. States were defined as (i) no drug (ii) weak opioid (codeine, dihydrocodeine) (iii) moderate opioid (tramadol) (iii) strong opioid (all others).

Results: 968,797 opioid users were included: mean age (SD) was 55(18) years; 59% being female. New users of opioids were most commonly prescribed codeine (n=685,823; 71.0%), followed by dihydrocodeine(n=166,906; 17.2%), tramadol (n=85,840, 8.8%) with 194,373 (20.1%) strong opioid prescriptions. The rate of prescribing strong opioids/10,000 population increased 12 fold from 2006-2013 (Figure 1). Transitions between opioid strength are demonstrated in Figure 2. Of new users prescribed weak opioids as their first prescription, 5.2% transitioned to moderate opioids, 4.1% to strong opioids over 2 years. Transition probability of moving from weak to strong opioid at a given time point over 2 years was 0.001, whilst staying on a strong opioid (if first prescription) was 0.97.

Conclusion: Strong opioid prescribing increased till 2013-14 gradually decreasing following UK initiatives to improve monitoring and use of controlled drugs. Although less potent codeine prescriptions made up the majority of first prescriptions, the transition probability of staying on a strong opioid at 2 years remained high if prescribed first as a new user.

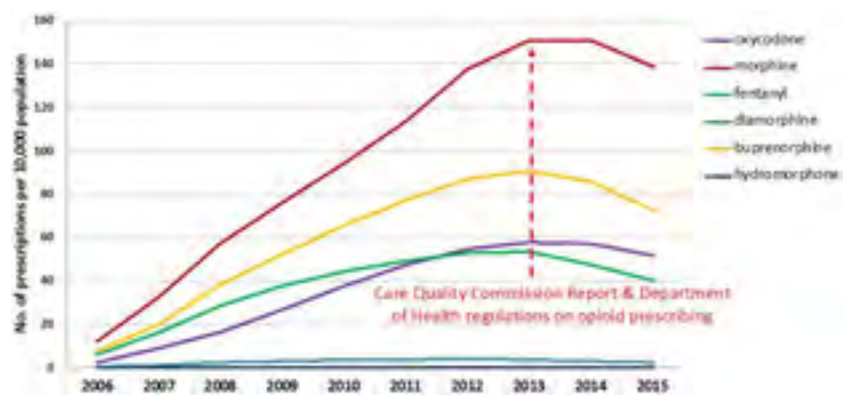


Figure 1:Trends in strong opioid utilisation in CPRD by individual opioids

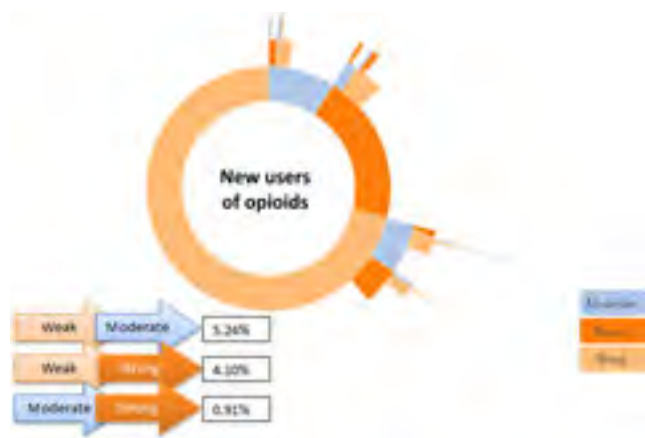


Figure 2: Opioid pathway over 2-year period from index date (excluding repeated prescriptions)

Socioeconomic Differences in Opioid Use By People with Inflammatory Arthritis

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Session Information

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Session Time: 11:00AM-12:30PM

Background/Purpose: Internationally, prescription opioid use is often higher among patients of lower socioeconomic status (SES). In addition, despite improved treatments for inflammatory arthritis, opioid use remains high among patients with inflammatory rheumatic diseases. The aim of this study was to determine the effect of lower SES on opioid use in people with inflammatory arthritis.

Methods: The Australian Rheumatology Association Database (ARAD) is an observational database that collects outcome data for people with rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and juvenile idiopathic arthritis (JIA). Participants complete semi-annual then annual questionnaires, which includes demographic and social details, self-reported medical history and medication use, and quality of life scales. We used the baseline questionnaire to examine opioid use between 2006 and 2016. Opioids classified were aspirin/codeine, paracetamol/codeine, dextropropoxyphene, oxycodone, oxycontin, morphine and tramadol. As a measure of SES, participants were assigned an Australian Bureau of Statistics (ABS) Socio-Economic Indexes for Areas (SEIFA) score (Index of Advantage/Disadvantage) based on their postcode (SEIFA 1= lowest quintile, SEIFA 5= highest quintile).

Results: 34.0% of 4,429 ARAD participants were taking opioids at baseline. Use was significantly more prevalent in lower SES participants (SEIFA 1: 47.4%, SEIFA 5: 36.6% (OR 1.56; 95%CI 1.22-2.00)). When other significant factors were considered in a multivariable model (including HAQ score (OR 1.85; 95%CI 1.64-2.09), currently smoking (OR 1.35; 95%CI 1.08-1.68) and being permanently unable to work (OR 1.66; 95%CI 1.26-2.19)), lower SES was still more prevalent but not significantly (OR 1.08; 95%CI 0.83-1.42). The prevalence of baseline opioid use between 2006 and 2016 did not change significantly. The prevalence of use in the SEIFA 1 participants remained higher than SEIFA 5 throughout this time period ($p < 0.05$). Although the most commonly used opioid was paracetamol/codeine, the more potent opioids (oxycodone and morphine) were associated with higher use in lower SES.

Conclusion: Although opioid use was more prevalent in the lower SES group, the strongest predictor of use was a high HAQ score, indicating more disability. Current smokers and those permanently unable to work were also more likely to take opioids. Higher use in lower SES groups has been evident over time and has not altered. Future research into the reasons for this difference may include further exploration of factors predictive of cessation and prescriber characteristics.

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Multi-Site Study Evaluating Performance on Lupus Nephritis Quality Measures

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Measures and Measurement of Healthcare Quality II: Quality Improvement in SLE, Gout and JIA

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Lupus nephritis (LN), seen in up to 60% of individuals with SLE, progresses to end stage renal failure in 10-30% of patients within 15 years of diagnosis. Few studies have evaluated performance on LN quality measures. Using measures from the SLE quality indicators project and 2012 ACR guidelines for monitoring and treating LN, we evaluated quality of care for LN across multiple clinical sites for patients enrolled in the multi-ethnic, population-based cohort of the California Lupus Epidemiology Study (CLUES).

Table 1: Description of quality measures and pass rates for each measure			
Quality Measure	Description	Eligible, n	Pass, n (%)
Screening measures (denominator population: prevalent SLE, no history of nephritis)			
1) Lupus nephritis labs	Urinalysis, urine protein/creatinine ratio, creatinine every 6 months in year prior to CLUES visit	129	53 (41.1)
2) SLE activity serologies	C3 or C4, and anti-DNA levels every 6 months in year prior to CLUES visit	129	48 (37.2)
3) Blood pressure	Blood pressure recorded every 6 months in year prior to CLUES visit	129	109 (84.5)
Diagnosis of lupus nephritis (denominator population: suspected LN defined by ACR criteria: i.e. increasing creatinine without alternative cause, proteinuria more than 1gm/24 hours, or proteinuria more than 0.5gm/24 hours plus hematuria, or proteinuria more than 0.5gm/24 hours with cellular casts)			
4) Renal Biopsy	Within 1 year of suspected LN unless contraindicated	89	58 (65.2)
Timely and appropriate treatment (denominator population: incident or relapsed LN)			
5) Initiation of immunosuppressant (mycophenolate, cyclophosphamide, azathioprine, cyclosporine, tacrolimus, rituximab)	Within 30 days of LN diagnosis	94	80 (85.1)
6) Initiation of anti-malarial treatment	Within 1 year of LN diagnosis	91	81 (89.0)
7) Initiation of ACE inhibitor or ARB	Within 1 year of LN diagnosis	93	75 (80.7)
8) Blood pressure target	≥140/90 within 1 year of diagnosis	94	71 (75.5)

Notes on eligibility:

4) Renal biopsy: 5 patients excluded from denominator because 3 patients had APLS on anticoagulation, 1 patient had ITP with intracerebral hemorrhage, 1 patient had prolonged coagulation studies.

6) Anti-malarial: 3 patients excluded from denominator because of allergy or intolerance to anti-malarial agent (1 patient with alopecia).

7) ACE inhibitor or ARB: 1 patient excluded from denominator because of renal failure presentation

Methods: Participants were recruited from 2015 to 2017. Data were collected during in-person clinical study visits and from a comprehensive medical record review. The primary outcome was performance on LN screening measures in those without prevalent LN, and for diagnosis and treatment measures in those with LN (Table 1). Covariates were

	No Lupus Nephritis (n = 129)		Lupus Nephritis (n = 94)	
	Unadjusted Pass Rates (95% CI)	Adjusted Pass Rates (95% CI)	Unadjusted Pass Rates (95% CI)	Adjusted Pass Rates (95% CI)
Characteristics				
Overall pass rate	54.3 (49.3, 59.2)		78.3 (74.3, 82.8)	
Demographics				
Gender			*	
Male	33.3 (13.3, 53.4)	29.0 (11.1, 47.0)	77.3 (68.3, 86.2)	71.4 (60.8, 82.1)
Female	55.6 (49.4, 61.8)	56.1 (50.8, 61.4)	78.6 (73.7, 83.5)	79.7 (75.8, 83.5)
Race/Ethnicity				
White	52.1 (42.8, 61.3)	57.2 (48.6, 65.8)	75.4 (63.9, 86.9)	79.8 (70.5, 89.0)
Hispanic	65.2 (50.3, 80.0)	62.4 (49.0, 75.9)	82.2 (74.7, 89.7)	80.3 (73.3, 87.3)
African American	44.4 (29.0, 59.8)	42.9 (29.8, 56.0)	80.0 (70.7, 89.3)	83.3 (76.1, 90.5)
Asian	55.3 (44.3, 66.3)	51.2 (41.6, 60.7)	75.8 (69.3, 82.3)	75.4 (68.8, 82.0)
Education			*	*
>High school graduate	57.3 (45.6, 69.0)	56.3 (45.7, 66.9)	86.4 (79.8, 93.0)	85.9 (79.4, 92.4)
<High school	53.3 (46.3, 60.3)	53.6 (47.2, 60.0)	74.6 (69.6, 80.1)	75.3 (70.0, 80.3)
Clinical and Practice Characteristics				
Lupus severity index	*	*		
1st quartile (score=4-9)	49.5 (43.0, 56.1)	49.2 (43.0, 55.5)	78.5 (73.9, 83.1)	78.1 (73.9, 82.2)
Median (score=5-1)	53.9 (47.9, 59.9)	53.8 (48.6, 59.0)	78.3 (73.9, 82.6)	78.4 (74.7, 82.0)
3rd quartile (score=0-3)	58.4 (51.3, 65.5)	58.6 (52.6, 64.5)	78.0 (73.3, 82.9)	78.7 (74.7, 82.6)
Provider Practice Setting	*	*	*	*
Academic	64.8 (56.6, 73.1)	64.1 (56.6, 71.5)	83.1 (79.0, 87.2)	83.1 (79.2, 86.9)
Community, staff model HMO	42.6 (28.2, 57.0)	41.1 (27.8, 54.4)	55.2 (38.2, 72.3)	61.9 (44.5, 79.4)
HMO Community, non-staff model	39.5 (31.1, 47.9)	41.4 (32.4, 50.4)	60.0 (47.5, 72.5)	54.4 (41.1, 67.7)
Based on GEE with an observation for each patient for each eligible quality measure.				
Models adjusted for all models shown, plus age, disease duration, and years with current provider, which were not associated with overall pass rates in any model.				
*p<0.05				

sociodemographics (age, gender, race/ethnicity, education, household income), clinical measures (disease duration and lupus severity index), and practice characteristics (provider setting and number of years with current provider). An overall pass rate was calculated, defined as the percentage of measures passed for which a patient was eligible; that is, among those eligible for a specific intervention, what percentage received it. Generalized estimating equations (GEE) with a logit function were used to estimate the probability of passing any one measure, with and without adjustment for covariates.

Results: Patients were followed in 25 clinical sites (2 academic, 1 staff model HMO with 6 practices and 17 community rheumatology practices). Performance on quality measures for 223 patients was evaluated, 94 of whom had LN. Overall pass rates were 54.4% for patients without LN and 78.3% for those with LN (Table 2). After adjustment in patients without LN, women and those with a higher lupus severity index had significantly higher pass rates, as did patients seen in academic settings. In patients with LN, patients with less educational attainment and those cared for in academic settings had significantly higher performance.

Conclusion: Across 25 diverse health settings, the largest gaps in care were for LN screening measures, with lower performance in community settings (vs academic) and for men. Across settings, performance was higher and more consistent for LN treatment quality measures, suggesting that once patients develop kidney disease, care is more standardized. Identification of these gaps in care can be used to target LN quality improvement initiatives.

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Abstract Number: 2959

Development of a Set of Potentially Preventable Adverse Conditions Specific to Lupus: A Delphi Consensus Study

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Session Information

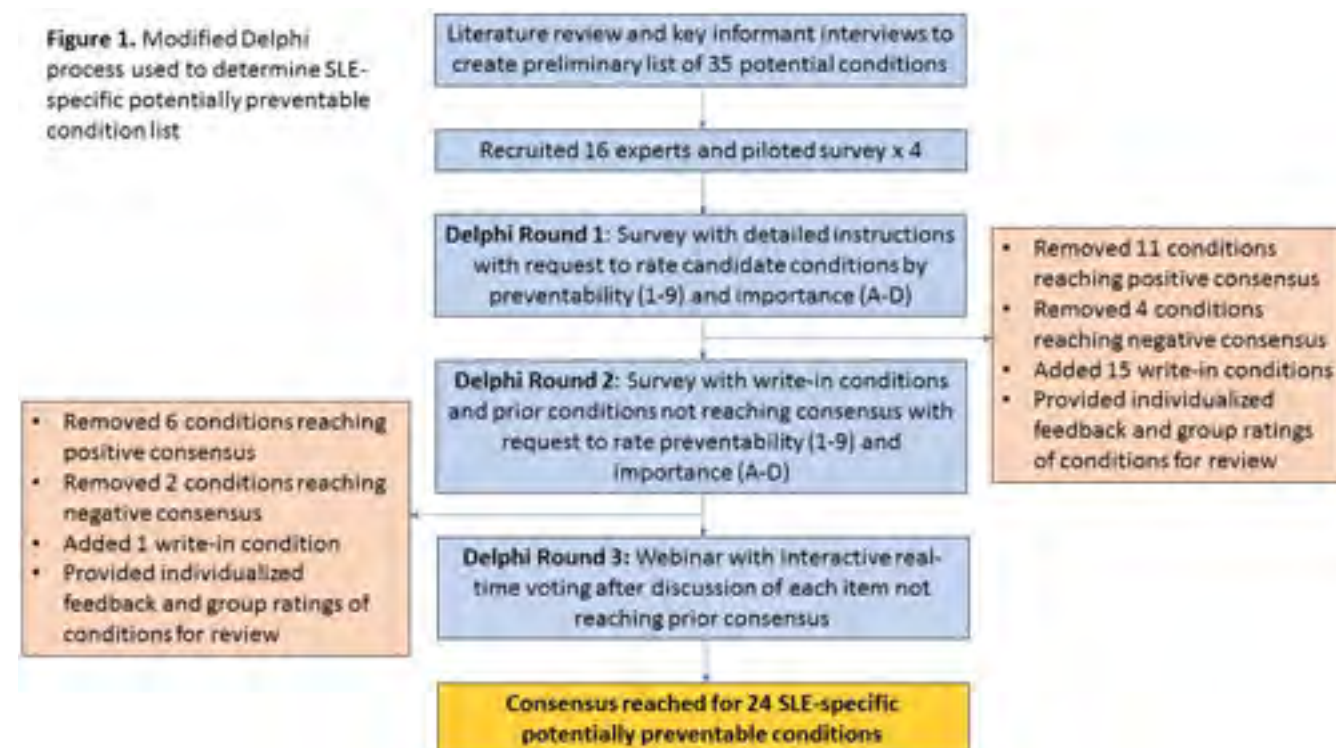
Session Date: Wednesday, October 24, 2018

Session Title: Measures and Measurement of Healthcare Quality II: Quality Improvement in SLE, Gout and JIA

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: The U.S. Agency for Healthcare Research and Quality developed a set of general ambulatory care-sensitive conditions that may result acute care use (hospitalizations and emergency department visits), potentially preventable if high quality, timely ambulatory care was provided. We aimed to update and extend this work to develop a list of conditions specific to patients with SLE that may result in acute care use and could be potentially prevented, or their complications minimized, if timely, effective ambulatory rheumatology care had been received.



Methods: We performed a literature review and conducted key informant interviews to inform the selection of SLE-specific potentially preventable conditions. We then used a modified Delphi method to further refine the list. We assembled a panel of 16 nationally-recognized experts across the U.S. including adult (7) and pediatric (2) rheumatologists/researchers, a neurologist, an obstetrician/gynecologist, a cardiologist, two nephrologists, an infectious disease specialist and a dermatologist/rheumatologist with expertise in the SLE patient care and research. Panelists independently completed two web-based survey rounds in which they were asked to rate both the preventability (1(preventable)-9 (not preventable)) and importance on a population scale (A(extremely important)-D (not important)) of each condition, and to provide comments and additional conditions for consideration. Analysis was guided by the RAND-UCLA Appropriateness Method. Consensus was determined by median scores ≤ 3 , < 3 extreme responses in the contrary direction, and $\geq 65\%$ with high [A or B] importance ratings. A final webinar was used to adjudicate conditions that did not reach prior consensus.

Results: Thirty-five potential conditions were initially considered (Figure 1). The response rate was 100% for both survey rounds and 14/16 panelists participated in the webinar process. 11 conditions met consensus criteria from round one, 6 from round two and 7 from the final round. Included conditions fell into 3 broad categories: medication-related toxicities (12 conditions), vaccine-preventable illnesses (5), or SLE-related complications (7) (Table).

Conclusion: SLE-specific potentially preventable adverse conditions include a diverse set of infectious, medication-related and SLE disease-related complications. This set of conditions will allow for identification of high risk SLE patients and facilitate targeted interventions with the goal of reducing preventable acute care use and adverse outcomes.

Table. Final set of SLE-specific potentially preventable conditions meeting consensus criteria as potentially preventable and important on a population level among patients with known SLE+

SLE-Specific Potentially Preventable Conditions	Preventability Rating 1 (definitely preventable) - 9 (not preventable)	Importance Rating*N (%)			
		A (very important) - D (not important on a population level)			
	Median (range)	A	B	C	D
Medication-related toxicities/complications					
Vision loss from hydroxychloroquine toxicity (N=15)	1 (1-3)	13 (87)	1 (7)	--	1 (7)
Teratogenesis while on teratogenic medications (N=16)	1.5 (1-8)	16 (100)	--	--	--
Opioid overdose (N=13)	2 (1-4)	9 (69)	4 (31)	--	--
Pneumocystis pneumonia while on moderate/high dose corticosteroids (N=15)	2 (1-4)	8 (53)	4 (27)	2 (13)	1 (7)
Chronic opioid use (N=13)	2 (1-4)	7 (54)	6 (46)	--	--
Vascular thrombosis in the setting of estrogen-based contraception and +APLAs (N=14)	2.5 (1-4)	9 (64)	5 (36)	--	--
Gastrointestinal bleed while on corticosteroids, NSAIDs or anticoagulation (N=12)	2.5 (2-4)	3 (25)	9 (75)	--	--
Uncontrolled steroid-induced diabetes (N=15)	3 (1-6)	10 (67)	4 (27)	1 (7)	--
Osteoporotic fracture while on corticosteroids (N=15)	3 (2-6)	9 (60)	6 (40)	--	--
Premature ovarian failure/infertility following standard dose cyclophosphamide without ovarian preservation therapy (N=13)	3 (1-5)	8 (62)	5 (38)	--	--
Spontaneous abortion while on teratogenic medications (N=15)#	3 (1-9)	8 (53)	5 (33)	1 (7)	--
Avascular necrosis while on prolonged corticosteroids (N=10)	3 (3-6)	3 (30)	6 (60)	1 (10)	--
Vaccine-preventable illnesses					
High-grade cervical dysplasia/cervical cancer (N=14)	2 (1-8)	12 (86)	2 (14)	--	--
Influenza (N=15)	2 (2-3)	9 (60)	5 (33)	1 (7)	--
Herpes zoster (N=11)	2 (2-5)	6 (55)	5 (45)	--	--
Bacterial meningitis (N=11)	2 (2-6)	4 (36)	4 (36)	3 (27)	--
Pneumococcal pneumonia (N=14)	3 (2-5)	9 (64)	4 (29)	1 (7)	--
SLE-related complications					
Vascular thrombosis in patients with APS (N=15)	2 (1-4)	12 (80)	3 (20)	--	--
Embolic stroke in patients with APS (N=15)	2.5 (2-5)	10 (67)	5 (33)	--	--
Lupus flare in the absence of UV protection (N=12)	2.5 (1-6)	5 (42)	7 (58)	--	--
Acute renal failure among patients with lupus nephritis (N=15)	3 (2-8)	12 (75)	3 (25)	--	--
Recurrent myocardial infarction (N=11)	3 (2-7)	9 (82)	2 (18)	--	--
Obstetrical complications in patients with APS (N=12)	3 (1-4)	8 (67)	4 (33)	--	--
Neonatal lupus/congenital heart block with a mother with +anti-Ro or anti-La antibodies (N=11)	3 (2-5)	7 (64)	4 (36)	--	--

+ Panelists with specific expertise could opt-out of rating conditions outside of their area; results presented for the final round for which consensus for inclusion was reached

* Importance was defined on the population level, including consideration of the prevalence of the outcome in the SLE population

One response of "not applicable" for the importance rating

APLAs= antiphospholipid antibodies, APS=antiphospholipid syndrome

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Evaluation of Performance Measures Reveals Delays and Sub-Optimal Access to Rheumatology Care and Treatment

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Measures and Measurement of Healthcare Quality II: Quality Improvement in SLE, Gout and JIA

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Early diagnosis, treatment and ongoing care are critical to optimize RA outcomes. The purpose of the study was to evaluate key elements of RA quality of care using 4 Arthritis Alliance of Canada performance measures (PMs) in Alberta, Canada: PM1) Waiting times for rheumatologist consultation for RA; PM2) Percentage of RA patients with at least one visit to a rheumatologist in the first year of diagnosis; PM3)Percentage of RA patients dispensed a disease modifying anti-rheumatic drug(DMARD); PM4) Time to DMARD initiation.

Methods: All prevalent RA cases 16 years and older between 2002/03 and 2016/17 in AB were defined using 2 or more physician billing codes at least 8 weeks apart and within a 2-year period, or 1 or more hospitalization codes for RA in health administrative data. PMs were estimated through linked datasets for fiscal years 2012-2015. PM1: The wait time in days (d) between referral and first appointment were calculated through linkage with central rheumatology triage databases in two sites. PM2: The percentage of incident RA cases with at least one visit to a rheumatologist within one year of their first RA code. PM3: The percentage of prevalent RA patients dispensed a DMARD (including conventional DMARDs, biologic agents and small molecule inhibitors) was calculated through linkage to a pharmacy database. PM4: Time from RA referral to DMARD dispensation was reported in the calendar year of RA incidence.

Fiscal Year	PM1: Waiting time for rheumatology consultation (Site 1) ¹			PM1: Waiting time for rheumatology consultation (Site 2) ²			PM2: % of RA patients with at least 1 visit to a rheumatologist ³ within the first year of diagnosis in Alberta		PM3: % of RA patients dispensed a DMARD (includes biologic and small molecule inhibitors)		PM4: Time in DMARD therapy from referral in new onset RA at or after rheumatologist appointment (Site 1)		PM4: Time in DMARD therapy from referral in new onset RA at or after rheumatologist appointment (Site 2)	
	Total incident RA	Median Waiting time (d) (Q1, Q3)	% meeting 28d benchmark	Total incident RA cases	Median Waiting time (d) (Q1, Q3)	% meeting 28d benchmark	Total incident RA cases	% meeting PM2	Total prevalent RA cases	% meeting PM3	Total incident RA cases	Median (Q1, Q3) days to DMARD	Total incident RA cases	Median (Q1, Q3) days to DMARD
2012	224	217.5 (119.5, 275.5)	0%	147	50 (28, 83)	25%	2730	55%	35113	41%	42	126.3 (49, 305)	42	73.3 (45, 135)
2013	306	89.5 (30, 221)	34%	137	53 (35, 91)	21%	2800	57%	37016	41%	216	30 (13, 268)	77	106 (52, 145)
2014	421	79 (23, 204)	20%	153	62 (27, 88)	20%	2977	60%	38806	41%	247	75 (26, 197)	67	84 (44, 230)
2015	335	128 (49, 245)	17%	154	42 (20, 88)	37%	2710	63%	40541	42%	138	165 (59, 354)	167	90 (76, 125)

RA case definition from the Public Health Agency of Canada's National Chronic Disease Surveillance System: RA cases aged more than 16 years old from linked hospitalization (Discharge Abstract Database (DAD)) and physician billing (administrative) databases using a validated case definition: 1. Hospitalization of 2 weeks (at least 6 weeks apart) within 2 years, with ICD-9-CM codes of 71.4A, or ICD-10-CA codes of M05.X, M06.X. Exclusion: applied subsequent to qualifying for other types of inflammatory arthritis.

¹Central triage waiting times in Site 1 includes waiting times to 20 rheumatologists

²Central triage in Site 2 includes waiting times to 12 rheumatologists

³As there is no rheumatologist identifier that is consistently used in the administrative database, interviews with some 10% of claims for RA were conducted to this PM and this was extrapolated for the entire province of Alberta (includes physicians not participating in central intake either Site 1 or Site 2)

Results: The PMs are reported in Table 1 by year and by site where appropriate based on available data sources needed to calculate some measures. Median wait times for rheumatology consultation (PM1) were longer in Site 1 than in Site 2 with between 9-28% meeting the 28-day benchmark in Site 1 and 21-37% in Site 2. Between 2012-2015 the percentage of RA incident cases seen by a rheumatologist within 1 year of onset (PM2) increased from 55 to 63%; however, during this time period the percentage of patients dispensed DMARD therapy (PM3) remained sub-optimal at approximately 40%. Median time to DMARD from referral also suboptimal (PM4).

Conclusion: RA patients in Alberta continue to experience long waiting times to care and treatment with up to 37% of suspected RA cases not seeing a rheumatologist within 1 year of onset. Furthermore, only 40% of RA patients are on DMARD therapy. Further research is warranted to evaluate predictors of adherence to the PMs and to determine the impact on patient outcomes.

Table 1. Performance on 4 AAC System-Level Performance Measures for RA in Alberta, Canada

Disclosure: C. Barber, None; D. Lacaille, None; P. Faris, None; D. P. Mosher, None; S. J. Katz, None; J. Homik, None; J. Patel, None; S. Zhang, None; C. Barnabe, None; G. Hazlewood, None; V. Ahluwalia, None; N. J. Shiff, None; V. P. Bykerk, None; M. Twilt, None; S. Benseler, Novartis, SOBI, AbbVie, 5; J. Burt, None; D. A. Marshall, None.

Abstract Number: 2961

Differences in Healthcare Transition Views, Practices, and Barriers Among North American Pediatric Rheumatology Providers from 2010 to 2018

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Session Information

Session Date: Wednesday, October 24, 2018

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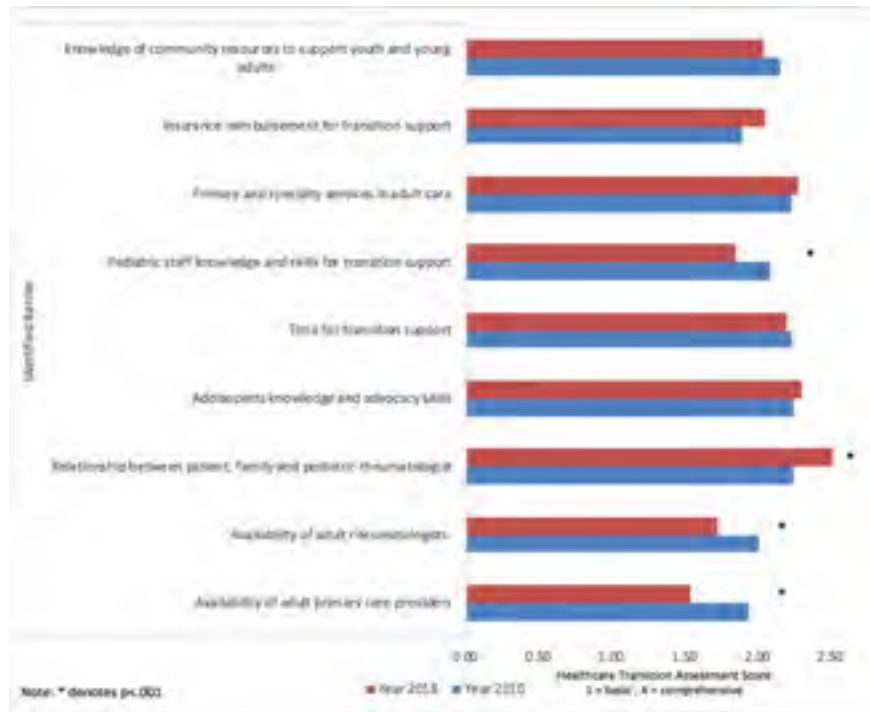
Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Healthcare transition is the “purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health care systems.” The American College of Physicians has partnered with national organizations, including the ACR, to develop guidelines and tools to promote a smooth transition to adult care. We aim to assess current transition practices and beliefs among North American pediatric rheumatology providers and to identify differences from a 2010 provider survey published by Chira et al.

Methods: In April 2018, Childhood Arthritis and Rheumatology Research Alliance (CARRA) members received a 25-item online survey about healthcare transition. *Got Transition's* Current Assessment of Health Care Transition Activities for Transitioning Youth to Adult Health Care Providers was used to measure clinical transition processes on a scale of 1 (basic) to 4 (comprehensive). Bivariate data analysis was used to compare 2010 and 2018 survey findings.

Results: Over half of CARRA members completed the 2018 survey. Participants included pediatric rheumatologists (74%), adult- and pediatric-trained rheumatologists (4%), pediatric rheumatology fellows (18%), and other (4%), including emeritus faculty and mid-level providers. Most belonged to university-affiliated practices (87%) in the U.S. (91%). Providers aim to transfer patients at age 18 (23%) or 21 (33%), but the actual age of transfer is often 21 or older (56%). The most common target age to begin transition planning was 15-17 (49%). Few providers use the ACR transition tools (31%) or have a dedicated transition clinic (23%). Only 17% have a transition policy in place; 63% do not consistently address healthcare transition. Transition outcomes of interest included an adult rheumatology visit within 6 months of the last pediatric visit (80%), adherence to medications and plan of care (78%), continuous insurance coverage (78%), and



patient-reported gaps in access to care (76%). When compared to the 2010 survey, improvement was noted in 3 of 12 transition barriers: availability of adult primary care providers, availability of adult rheumatologists, and transition knowledge and skills of pediatric staff ($p < 0.001$). However, more providers cited the close bond among adolescents, parents and pediatric providers as a barrier (Figure 1).

Conclusion: This survey of pediatric rheumatology providers demonstrates some improvement in transition barriers since 2010, though most practices still maintain minimal support for patients and providers around healthcare transition. Further research is needed to understand how to effectively facilitate transition to adult care for young adults with childhood-onset rheumatic diseases.

Figure 1. Barriers to Healthcare Transition Reported by Pediatric Rheumatology Providers, 2010 and 2018

Disclosure: K. Johnson, None; C. Edens, None; P. Chira, None; A. O. Hersh, None; Y. I. Goh, None; J. Hui-Yuen, None; R. E. Sadun, RRF CSE Grant; internal Duke grant for translational research, 2; N. G. Singer, None; L. R. Spiegel, None; J. N. Stinson, None; P. H. White, None; E. Lawson, None.

Abstract Number: 2962

Diagnostic Accuracy of Gout in Electronic Health Records and the Role of Rheumatology Electronic Consults

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Measures and Measurement of Healthcare Quality II: Quality Improvement in SLE, Gout and JIA

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Gout is the most prevalent inflammatory arthritis globally. Despite treatment advances, it still has a significant effect on quality of life and healthcare costs. Studies using administrative coding as a marker of accurate diagnoses have shown inconsistencies due to diagnostic criteria differences or gout misdiagnosis. Although gout can be solely managed by primary care physicians (PCPs), complex cases often require rheumatology consultation. The wait time for an initial rheumatology clinic visit ranges from 38 days to 47 weeks. However, electronic consults (e-consults) allow for swift two-way communication between PCPs and rheumatologists (pre-consult exchange) to facilitate coordination of care among providers.

Objectives: To determine the accuracy of gout diagnosis based on the International Classification of Diseases, ninth (ICD 9) and tenth (ICD 10) revision and the differences in gout outcomes depending on PCP management, e-consult or rheumatology clinic visits at the VA Medical Center in Long Beach, CA.

Methods: A retrospective cohort study of 81 e-consult patients was created with a control group of 176 patients from 2009-2014. In the e-consult group, 58 patients were ICD 9 or 10 coded for gout and 23 were not; in the control group, 116 were ICD 9 or 10 coded for gout and 60 were not. A blinded abstractor determined the accuracy of gout coding based on chart review and EULAR criteria.

Additionally, a second sample of 163 gout patients from 2009-2014 was identified and stratified to 3 modes of management: PCP only (48), e-consult (48), and rheumatology clinic visit (67). Data was reviewed for 24 months following initial gout diagnosis or e-consult. Management was evaluated based on frequency of flares and related ED visits, creatinine clearance, and serum uric acid levels (sUA).

Results: The sensitivity and specificity of ICD coding for accurate diagnosis of gout was 94% and 79% in the control (positive PPV and negative predictive values NPV were 88% and 90%). For e-consult patients, the sensitivity and specificity of accurate diagnosis coding was 100% and 70% (PPV 83%, NPV 100%). E-consult patients were more accurately diagnosed with gout by PCPs than in the control group ($p=0.03$).

Of e-consults, 77% were resolved electronically and 23% were converted to rheumatology clinic visits. The mean wait time for e-consult recommendations was 2.1 days. The mean clinic visit wait after pre-consult exchange was 22.9 days compared to an average of 43.1 days for direct rheumatology clinic consults. Both e-consult and rheumatology clinic patients had more gout flares and related ED visits at baseline; however, at 12 months, both groups had significantly fewer gout-related ED visits, decreased sUA, and improved creatinine clearance.

Conclusion: VA databases are an accurate source of gout patients based on ICD 9 and 10 coding. When viewing e-consults, rheumatologists can rely on accurate PCP gout diagnoses, confidently answer clinical questions, and triage to clinic more quickly. E-consult serves as an effective alternative in managing gout with shorter wait times for recommendations and appointments. Therefore, complex gout management can be enhanced by e-consults to decrease gaps in care and optimize healthcare resources.

Disclosure: J. Chang, None; M. Wong, None.

Abstract Number: 2963

Improving Clinically Inactive Disease in Patients with Juvenile Idiopathic Arthritis- a Quaternary Center Experience

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Measures and Measurement of Healthcare Quality II: Quality Improvement in SLE, Gout and JIA

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: Juvenile idiopathic arthritis (JIA), the most common pediatric rheumatologic diagnosis, influences many aspects of a child's life. Although there is no known cure, disease control is often achievable. Early recognition and treatment leads to better disease control that is crucial to prevent chronic pain, irreversible joint damage, and future disability. Clinically Inactive Disease (CID) has been defined and is the accepted outcome measure. In our large pediatric quaternary referral hospital, the number of JIA patients achieving CID was 11% whereas it is reported up to 40% in other centers nationally. Here, we report improvement from 11% to 37% CID within two years by implementing a quality improvement project.

Methods: A key driver diagram (KDD) was used to identify barriers to achieving CID and to develop optimal disease management strategies. The most effective interventions were initially centered around educating parents and patients on disease management, pre-visit planning and provider data entry of disease activity criteria. The physician global assessment

(PGA), a subjective score with interprovider variability, was identified as one of the top barriers to inactive disease. In efforts to standardization, PGA scoring exercises were conducted. In addition, providers reviewed currently active patient cases in population management to provide inputs to optimize therapy. These exercises helped standardize disease activity level scoring by allowing providers to challenge each other regarding optimal care of patients. Transparency in provider level feedback surrounding PGA scores and the percentage of patients with inactive disease was shared quarterly with providers. We had multiple other interventions as summarized in KDD (Figure 1).

Results: During the baseline period (Jan 2015-May 2016), only 11% of patients at our center met criteria for CID. After initial interventions, 20% of patients were considered inactive as of June 2016 (p-value <0.001). As population management and PGA exercises took effect, another shift in data occurred in January 2017, resulting in 25% of patients having no disease activity (p-value<0.001). The team has five data point reaching goal, ready for another shift in data (Figure2).

Conclusion: A dedicated QI project, focusing on multiple interventions, improved the disease activity level of patients with JIA. It is expected that as the team continues with these exercises and proceeds with next steps, the percentage of patients with inactive disease will continue to rise.

Disclosure: C. Yildirim-Toruner, None; O. AlAhmed, None; F. Barbar-Smiley, None; K. Jones, None; M. Kohlheim, None; S. Lemle, None; D. MacDonald, None; E. Mulvihill, None; E. Oberle, None; A. Sarkissian, None; V. Sivaraman, None; B. Thomas, None; K. Wise, None; S. P. Ardoin, None.

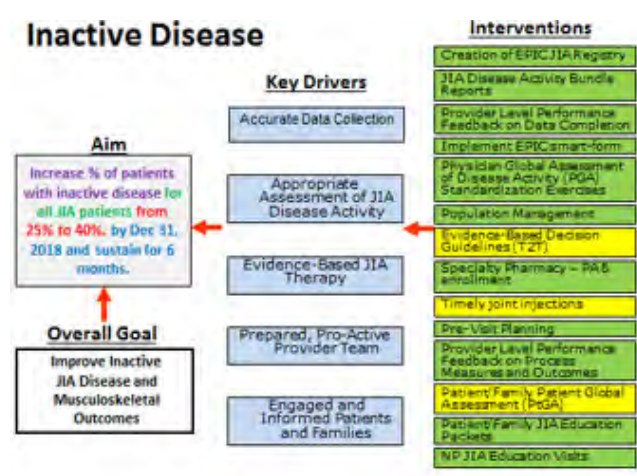


Figure 1. Key Driver Diagram for achieving Clinically Inactive Disease in JIA

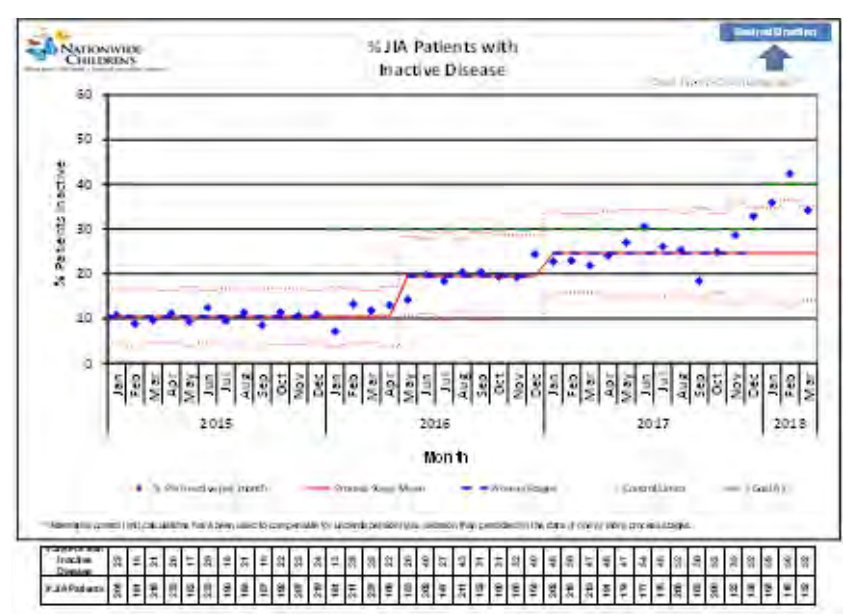


Figure 2. Runchart for percent of patients with CID per month

Detection of Uric Acid Crystals in the Vasculature of Patients with Gout Using Dual-Energy Computed Tomography

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic Science and Imaging

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: Many recent studies have shown an association between gout and increased cardiovascular risk, however the mechanism by which this occurs is unclear. Dual-Energy Computed Tomography (DECT) is a new technology that has been used to detect subclinical monosodium urate (MSU) deposition in the joints of patients with gout. In this study, we investigated whether DECT could also detect MSU deposition in the vasculature of patients with gout.

Methods: Fourteen tophaceous gout patients and ten non-tophaceous patients were recruited from a single-center urban academic hospital. All patients underwent DECT scans of the neck and chest using a Siemens Somatom Force CT scanner, and images were processed with SyngoVia imaging software to identify MSU deposits. An automated volume assessment program was used to calculate the volume of urate deposits in the vasculature of patients.

Results: The range of uric acid deposition within patients' vasculature varied widely, from 0 mm³ to over 450 mm³, but the majority of study participants (88%) were found to have evidence of MSU deposition in their vasculature. Due to the large volume of these deposits, we did not feel that this was consistent with artifact. The average MSU deposition volumes were 109.4 mm³ for the tophaceous patients and 116.5 mm³ for the non-tophaceous patients, but this difference was not statistically significant ($p = 0.84$).

Conclusion: DECT is able to detect the presence of MSU deposition in the vasculature of patients with both tophaceous and non-tophaceous gout. Whether or not this results in cardiovascular inflammation remain to be determined. Future directions include using PET/MRI to evaluate for local inflammation at the site of MSU deposits in the vasculature.

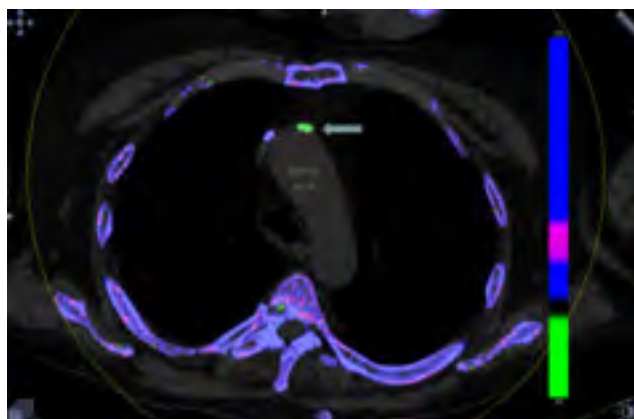


Figure1: This patient's aortic arch has about 20 mm² of uric acid in this slide alone, seen in green.

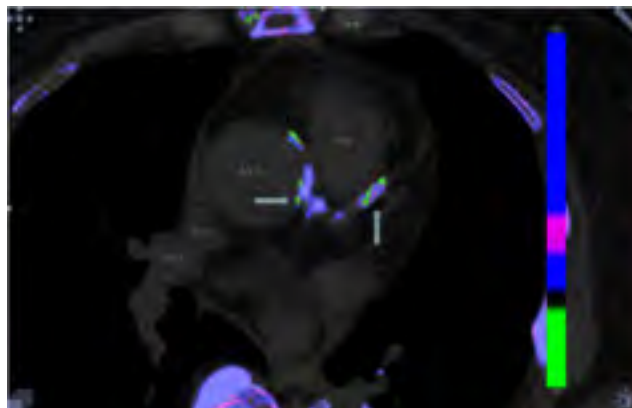


Figure 2: This patient has multiple discrete spots of MSU crystallization (green), lining his ascending thoracic aorta and in the interior of his coronary artery.

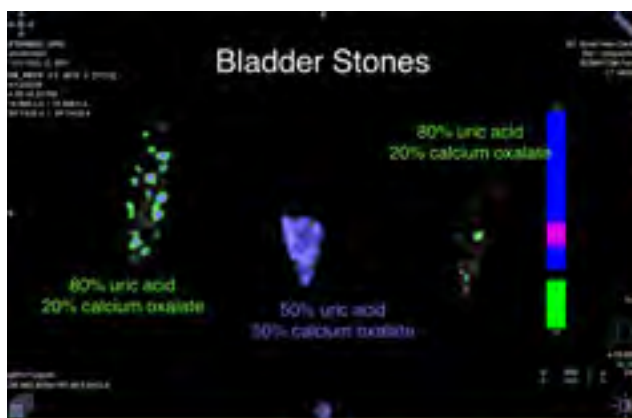


Figure 3: To confirm the calibration of the DECT scanner, we tested three bladder stone samples whose UA composition ranged from 50-80%; the remainder being calcium oxalate. Scans and analysis confirmed that the scanner is able to pick up MSU (green) and differentiate it from calcium derivatives (purple).

Disclosure: S. Barazani, None; W. Chi, None; R. Pyzik, None; A. Jacobi, None; T. O'Donnell, None; Z. Fayad, None; V. Mani, None; Y. Ali, None.

Abstract Number: 2965

Targeting Glucose Metabolism in the Murine Air Pouch Model of Acute Gouty Inflammation

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic Science and Imaging

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: Emerging evidence indicates that macrophage activation is critically supported by glucose metabolic shifts. Although macrophages are key contributors to inflammation, little is known about the role of glucose metabolism in the pathogenesis of inflammatory gouty arthritis. Thus, we evaluated glucose metabolism in the murine air-pouch model of acute gouty inflammation.

Methods: Mice (N=6 in each group) were injected with PBS or 3-bromopyruvate (BrPa; 7.5 mg/kg) 1 hour before MSU injection to assess the effect of glycolysis inhibition *in vivo*. After 6 hours injection of monosodium urate (MSU) crystals (3 mg/ml) in the air pouch, both the air pouch lavage and peripheral blood were collected. The infiltrating leukocytes obtained from the lavage after centrifugation and peripheral blood mononuclear cells (PBMCs) isolated from the blood were subjected to quantitative RT-PCR for expression of glycolysis-related genes Glut1 and LDHa, and NLRP3 inflammasome-related genes IL-1 β and NLRP3. Production of IL-1 β , CXCL1 and IL-6 were quantified from supernatant of the lavage by ELISA analysis. The air-pouch tissues were also collected and fixed, and subsequently H&E staining was performed. For *ex vivo* studies, thioglycolate-elicited peritoneal macrophages were collected and stimulated with LPS (100 ng/ml for four hours) and MSU (0.2 mg/ml overnight) with and without pretreatment of 2-deoxy-glucose (2DG, 10mM), another glycolysis inhibitor, for one hour. Expression of glycolysis-related genes and cytokine production were assessed from the cells and conditioned media, respectively, using the methods mentioned above.

Results: MSU crystals promoted glycolysis in both infiltrating leukocytes and PBMCs, evidenced by increased expression of Glut1 and LDHa. This was associated with upregulation of gene expression of IL-1 β and NLRP3 in both PBMC and air-pouch elicited cells. BrPa significantly lowered numbers of infiltrating leukocytes ($3.26 \pm 0.79 \times 10^6$ vs $0.74 \pm 0.1 \times 10^6$, $p < 0.01$, in the MSU group after PBS or BrPa respectively) and the amount of proinflammatory cytokines CXCL1 (2379 ± 620 vs 992 ± 255 pg/ml, $p < 0.05$), IL-1 β (429.6 ± 140.7 vs 103.3 ± 12 pg/ml, $p = 0.02$), and IL-6 (2111 ± 418 vs 865 ± 236 pg/ml) in the air pouch. It also markedly reduced leukocyte infiltration in the air pouch lining in response to MSU crystals (3 ± 0.66 vs 1 ± 0.57 , $p = 0.012$ in PBS or BrPa-treated mice respectively). Treatment with 2-DG in peritoneal macrophages significantly inhibited gene expression of Glut 1, hexokinase 2 (HK2), and LDHa, and production of CXCL1, IL-1 β , IL-6, and TNF after LPS and/or MSU stimulation.

Conclusion: Glycolytic inhibition could attenuate MSU crystal-induced inflammatory response. Targeting metabolic dysfunction could be a novel treatment strategy for acute gouty arthritis.

Disclosure: A. Cheng, None; R. Coras, None; R. Terkeltaub, None; R. Liu-Bryan, None; M. Guma, None.

Abstract Number: 2966

Ultrasound Shows Rapid Reduction of Uric Load during Treat-to-Target Approach in Gout Patients: Results from a Longitudinal Study

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic Science and Imaging

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Uric monosodium urate (MSU) depositions are detected by ultrasound (US), and US is included in the ACR/EULAR classification criteria for gout. OMERACT definitions for US elementary lesions in gout include the double contour sign (DC) (deposits of crystals on the surface of cartilage), tophus (larger hypo-echoic aggregation of crystals, usually well delineated), aggregates (small hyper-echoic deposits) and erosions. MSU depositions have some predilection sites, but only a few small studies have explored the decrease of depositions during treatment. The present purpose was to explore by US the longitudinal development of MSU depositions during a treat-to-target approach with urate lowering therapy (ULT) in patients with gout.

Methods: In a prospective observational study, patients with crystal-proven gout were included after a recent gout flare and if increased serum urate levels (>360 $\mu\text{mol/L}$ / >6 mg/dl). In a treat-to-target approach using ULT and increasing drug doses with monthly follow-up until treatment target was met (<360 $\mu\text{mol/L}$, or <300 $\mu\text{mol/L}$ if clinical tophi). An extensive US assessment was performed (GE E9 machine, grey scale 15MHz) at baseline and after 3, 6 and 12 months to detect MSU depositions (DC, tophi and aggregates) with bilateral assessment of radiocarpal joint, MCP 2, insertion of triceps and quadriceps, proximal and distal patellar and the Achilles tendon, cartilage of distal femur (maximal flexed knee) and the talar cartilage and MTP 1 joint. The degree of elementary lesions was semi quantitatively scored 0-3 (0=none, 1=possible, 2=certain, 3=major deposits). Total sum scores of DC, tophi and aggregates separately as well as all lesions were calculated for each visit. Changes from baseline were explored by paired samples T-test.

Results: 161 patients were included at baseline (93.3% men, mean (SD) age 57.0 (14.1) years, disease duration 8.0 (7.7) years). The mean (SD) serum urate level decreased from 487 (82) $\mu\text{mol/L}$ at baseline to 312 (52) $\mu\text{mol/L}$ at 12 months ($p<0.001$). Sum scores of deposits decreased over 12 months (table, $*=p<0.05$, $**=p<0.001$), and the numeric decrease was largest for DC (figure). In addition, the percentage of patients with no detected lesion increased most for DC (baseline to 12 months; DC: 8 to 53%, tophi: 8 to 16% and aggregates 1 to 3%).



Conclusion: During a treat-to-target approach with ULT all forms of deposits decreased, and most extensively for DC. This study shows that reduction of the uric load in gout during treat-to-target ULT may be visualised by US, and that DC may be the lesion most sensitive to change.

	Baseline (n=161) Mean (SD)	3 months (n=124) Mean (SD)	6 months (n=115) Mean (SD)	12 months (n=88) Mean (SD)
Double Contour sum score	4.2 (3.4)	3.1 (2.8)**	2.3 (2.7)**	1.2 (1.9)**
Tophi sum score	6.5 (6.6)	6.3 (5.7)	5.4 (6.1)**	4.2 (5.3)**
Aggregates sum score	9.1 (5.3)	8.8 (4.9)*	7.9 (5.2)**	6.7 (4.9)**
Double Contour, tophi and aggregates sum score	19.8 (13.6)	18.1 (12.0)**	15.6 (12.8)**	12.1 (10.9)**

Disclosure: H. B. Hammer, AbbVie Inc., Novartis, 8; L. F. Karoliussen, None; L. Terslev, Novartis, AbbVie, Pfizer, UCB, Roche and MSD, 8; E. A. Haavardsholm, None; T. Kvien, AbbVie, BMS, Boehringer Ingelheim, Celgene, Celltrion, Eli Lilly, Hospira, Merck-Serono, MSD, Novartis, Orion Pharma, Pfizer, Roche, Sandoz and UCB, 8; T. Uhlig, None.

Abstract Number: 2967

Potent Bifunctional Inhibitors of Xanthine Oxidase and URAT1 Block Fructose-Induced Inflammation Via Increase in AMP Kinase Activity

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Session Information

Session Date: Wednesday, October 24, 2018

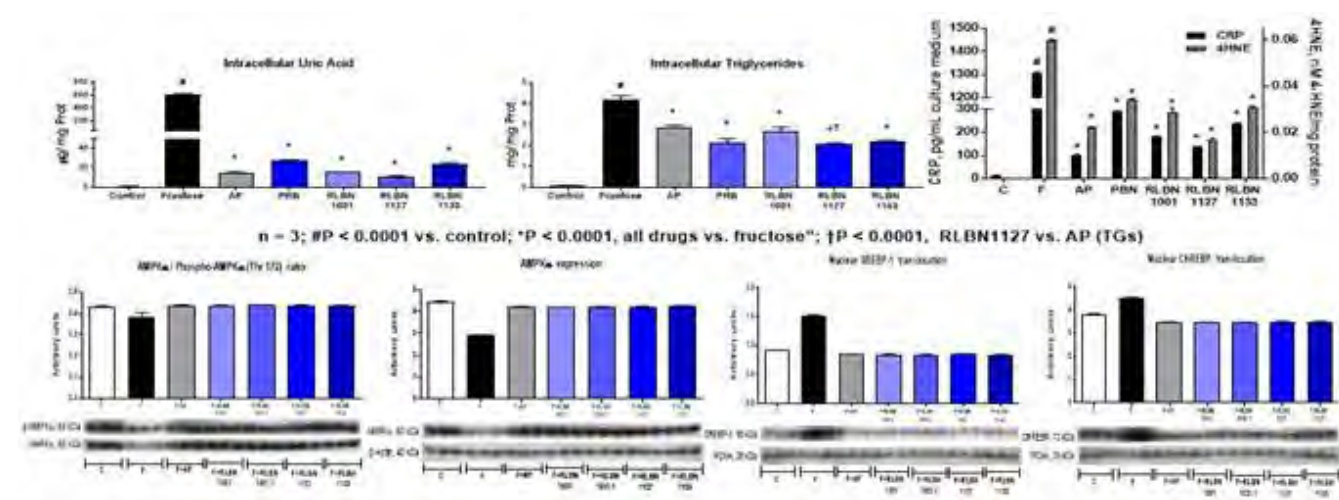
Session Title: Metabolic and Crystal Arthropathies – Basic Science and Imaging

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Dietary fructose promotes an increase in uric acid (UA) that may lead to gout. UA itself promotes lipogenesis and inflammation in both gout as well as other diseases, such as atherosclerosis, metabolic syndrome and NASH. *In vivo*, these effects can be blocked by hypouricemic drugs, but only in models with elevated UA. *In vitro* incubation with fructose also models lipogenic and inflammatory activities in hepatocytes. We discovered a prototype drug that markedly reduced serum UA in human subjects (frequently to $< 1.0 \text{ mg/dL}$), and we developed potent bifunctional derivatives that inhibit xanthine oxidase (XO) and URAT1 (and uricase). We evaluated fructose-induced increases in intracellular (IC) UA and triglycerides in HepG2 cells, explored mechanisms and metabolic consequences, and their modulation by both mono- and bi-functional hypouricemic drugs.

Methods: Control HepG2 cells were cultured in DMEM w/low glucose w/o phenol red for 48-72 h and changed every 24 h. Test cells were cultured with added fructose (25mM), plus new or standard drugs (RLBN1001, RLBN11127, RLBN1133, allopurinol [AP], and probenecid [PBN]) (100mM). IC and extracellular (EC) UA and triglycerides (TGs) were measured by enzymatic kits (Sekisui). Lipid content was confirmed by Oil Red O and colorimetry (Cayman). Micro-CRP and 4-hydroxynonenal (4HNE) were assessed by ELISA and colorimetry, respectively (Cayman). Experiments were conducted three times, each in triplicate. Expression of prolipogenic enzymes and inflammatory mediators were evaluated by WB.



Results: Fructose sharply increased IC UA, which was significantly suppressed by AP and RLBN1127 (95% and > 98%, respectively; see figure). Increased UA was accompanied by an increase in IC TGs with confirmed steatosis at 48 hours. While all hypouricemic drugs reduced IC TGs, RLBN1127 was significantly superior to AP in blocking TG production ($P < 0.0001$). All drugs reduced over-expression of fatty acid synthase, acetyl CoA carboxylase and ATP citrate lyase (data not shown). All drugs normalized fructose-related increases in nuclear translocation of SREBP-1 and ChREBP, and significantly reduced increases in 4HNE and CRP (graphic). Lastly, these drugs significantly increased and restored fructose-induced reductions in total expression and activity of AMP Kinase.

Conclusion: Suppression of fructose-induced increases in UA with hypouricemic drugs significantly reduced TGs and markers of lipid peroxidation and inflammation in hepatocytes. These agents acted via AMPK activation, a constitutive *in vivo* suppressor of lipogenesis and inflammation, which limits urate crystal-induced NF- κ B activation and IL-1 β release. These results suggest that bifunctional activity may confer advantages over monofunctional drugs. RLBN1127 is a clinical candidate for treatment of biomarker-targeted patients with inflammatory disease, particularly gout and NASH.

Disclosure: L. G. Sánchez Lozada, None; F. E. García-Arroyo, None; J. G. Juárez-Rojas, None; G. Gonzaga, None; R. P. Warrell Jr., Relburn-Metabolomics, Inc., 1.

Abstract Number: 2968

Role of Choline in Gouty Inflammation

Elsa Sanchez-Lopez¹, Zhenyu Zhong¹, Alex Stubelius², Shannon R Sweeney³, Ru Liu-Bryan^{4,5}, Juan Carlos Lacal⁶, Stefano Tiziani^{3,7,8}, Robert Terkeltaub^{4,9}, Monica Guma⁹ and Michael Karin¹, ¹Department of Pharmacology, School of Medicine. UCSD., La Jolla, CA, ²Division of Rheumatology, Allergy and Immunology. UCSD., La Jolla, CA, ³Department of Nutritional Sciences. The University of Texas at Austin., Austin, TX, ⁴VA San Diego Healthcare System, San Diego, CA, ⁵Medicine-Rheumatology, Division of Rheumatology, Allergy and Immunology. UCSD., La Jolla, CA, ⁶Translational Oncology. Department of Oncology, Hospital Universitario Fuenlabrada, Madrid, Spain, ⁷Department of Molecular Biosciences, College of Natural Sciences. The University of Texas at Austin., Austin, TX, ⁸Department of Pediatrics, Dell Medical School. The University of Texas at Austin., Austin, TX, ⁹Medicine, Division of Rheumatology, Allergy and Immunology. UCSD., La Jolla, CA

Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic Science and Imaging

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Gout is characterized by deposition of monosodium urate (MSU) crystals in articular joints, where they activate macrophages inducing NLRP3 inflammasome activation and bioactive IL-1 β release. However, it is not fully understood how the initiation of gouty inflammation takes place. Intake of meat and seafood is associated with frequency and intensity of gout flares. Choline is a vitamin-like essential nutrient, mainly found in meat and seafood. Choline transporter CTL1, and Choline Kinase (ChoK α), enzyme that converts choline into phosphocholine, are highly expressed in macrophages and fibroblast like synoviocytes in inflamed joints. Here we study whether choline uptake and phosphorylation contribute to NLRP3 inflammasome activation and gouty inflammation.

Methods: Wild type or AMPK α 1 knockout primary bone marrow derived macrophages (BMDM) were cultured in L929 media for 7 days. shCtrl, shCTL1 and shChoK α were generated by lentiviral infection. Choline and phosphocholine were measured by ¹HMRs. Choline deficiency was studied using media without or with 3.54 μ M choline. ChoK α inhibitor RSM932A was used at 5 μ M and colchicine at 10nM. BMDM were treated with 100ng/ml LPS for 4h and 400mg/ml MSU for 3h. IL-1 β was measured by ELISA. Protein levels were examined by immunoblot, and mRNA expression by QPCR. Mitophagy was defined by p62, LC3 or DRP1 recruitment to mitochondria by confocal microscopy (CM). MSU crystals-induced peritonitis was induced by 3mg/ml MSU crystals i.p. injection (n=4 mice/group). For synovium-like air pouch model, 2.5mg/Kg ChoK α inhibitor MN58b or PBS was injected 24h before adding 3mg/ml MSU crystals into the air pouch (n=6 mice/group). Cells from pouch fluids were counted; pouch tissue stained for F4/80, CTL1 and ChoK α and visualized by CM.

Results: LPS increased 6 fold CTL1 expression, and boosted intracellular choline by 238% (p<0.01) and phosphocholine by 559% (p<0.001). Choline deficiency reduced MSU-induced IL-1 β release by 60% (p<0.001), shCTL1 by 57% (p<0.05), and shChoK α by 89% (p<0.05) and ChoK α inhibition via RSM932A by 71% (p<0.005). Impaired choline uptake or ChoK α activity promoted AMPK activation and DRP1, LC3 and p62 recruitment to mitochondria. AMPK deletion blocked choline deficiency effect on IL-1 β release. Of note, treatment with colchicine, previously defined to inhibit NLRP3 inflammasome activity and activate AMPK, also reduced CTL1 (90%) and ChoK α levels (85%). *In vivo*, after MSU crystal injection, cells collected from peritoneal cavity strongly expressed both CTL1 (p<0.05) and ChoK α (p<0.01). F4/80 positive myeloid cells recruited into the air pouch also expressed ChoK α and CTL1. Last, treatment with ChoK α inhibitor MN58b reduced MSU crystal-induced leukocyte recruitment by 47% (p<0.05) and IL-1 β release by 66% (p<0.01).

Conclusion: Our results show that Choline, which is mainly sourced from diet, contributes to gouty inflammation. MSU crystal-induced activation of myeloid cells causes overexpression of genes involved in choline uptake and metabolism, and this is prevented by Colchicine treatment. Targeting choline transporter CTL1 or ChoK α , and limiting dietary choline, could be novel therapeutic anti-inflammatory approaches for gouty arthritis.

Disclosure: E. Sanchez-Lopez, None; Z. Zhong, None; A. Stubelius, None; S. R. Sweeney, None; R. Liu-Bryan, None; J. C. Lacal, None; S. Tiziani, None; R. Terkeltaub, Ironwood/Ardea-Astra-Zenec, 2, Selecta, Kowa, SOBI, RELBURN, Horizon, 5; M. Guma, None; M. Karin, None.

Abstract Number: 2969

Allopurinol Dose Escalation Slows Progression of CT Bone Erosion in People with Gout: Imaging Sub-Study of a Randomized Control Trial

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Metabolic and Crystal Arthropathies – Basic Science and Imaging

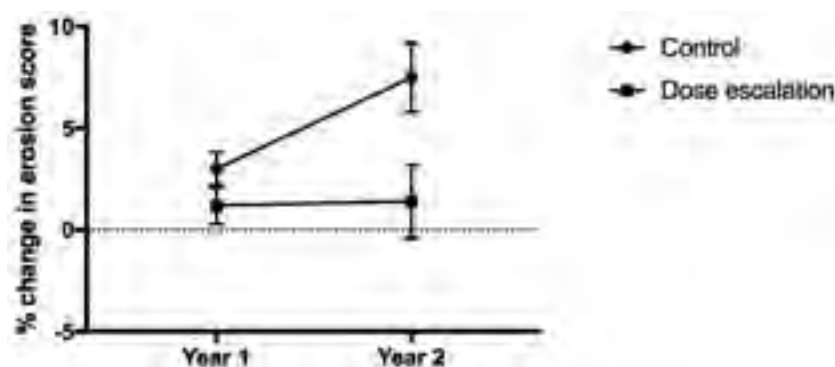
Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Bone erosion is a frequent complication of severe gout. Computed tomography (CT) is considered the gold standard for measurement of bone erosion. CT studies have demonstrated a close relationship between monosodium urate (MSU) crystals and bone erosion, suggesting that dissolution of MSU crystals with urate-lowering therapy may influence the progression of bone erosion in gout. The aim of this study was to examine whether serum urate lowering can prevent progression of bone erosion detected by CT in people with gout.

Methods: We conducted an imaging sub-study of a two-year randomized clinical trial of intensive vs. conventional allopurinol dosing in people with gout on allopurinol with serum urate (SU) \geq 6mg/dL. The intensive treatment group had

immediate escalation of allopurinol dose to achieve SU <6mg/dL. The control group had no change in their allopurinol dose in Year 1, and then had allopurinol dose escalation to achieve SU <6mg/dL. Participants at one of the two study sites were invited into an imaging sub-study, which included CT scans of both feet, and plain radiographs (XR) of the hands and feet at the baseline, Year 1 and Year 2 visits. CT scans were scored by two radiologists using a validated CT bone erosion scoring system for gout (erosion at seven bones/foot according to the RAMRIS method). XR were scored for erosion and joint space narrowing by a radiologist and rheumatologist using a gout-modified Sharp van der Heijde score. All scorers were blinded to treatment allocation, serum urate, and each other's scores. The pre-specified primary endpoint was change from baseline in CT erosion score, measure at Years 1 and 2. Data were log_e transformed and analyzed using ANCOVA with baseline score as a covariate.



Results: Data were available for 88 participants (46 control, 42 dose escalation) at Year 1 and 82 (44 control, 38 dose escalation) at Year 2. No difference between groups was observed for CT bone erosion scores from baseline to Year 1 (P=0.16). However, differences between randomization groups were observed from baseline to Year 2 (P=0.015). Over the two year study period, the rate of progression in CT erosion score was higher in the control group compared with the dose escalation group (percentage change (SEM) 7.5 (1.7) for the control group and 1.4 (1.8) for the dose escalation group) (Figure). No differences between groups were observed in XR erosion scores or joint space narrowing scores over the observation period.

Conclusion: This is the first randomized controlled trial to demonstrate that progression of bone erosion can be prevented using a treat to serum urate target strategy. These findings support the concept that reduction of serum urate to sub-saturation levels can influence structural damage in gout.

Figure. Change in CT erosion scores according to randomization group. Data are shown as percentage change in CT erosion scores (SEM).

Disclosure: N. Dalbeth, Horizon, 5, Kowa, 5, Amgen Inc., 2, AstraZeneca/Ironwood, 2, AbbVie Inc., 8, Pfizer, Inc., 8, Janssen, 8; K. Billington, None; A. Doyle, None; C. Frampton, None; P. Tan, None; J. Allan, None; J. Drake, None; A. Horne, None; L. K. Stamp, Amgen Inc., 8.

Abstract Number: 2970

In Idiopathic Retroperitoneal Fibrosis, Persistent FDG PET Uptake Helps Identifying Patients at Risk for Relapse

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases II

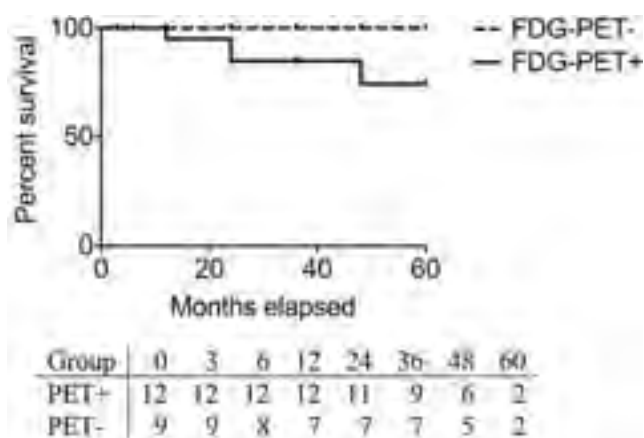
Session Type: ACR Concurrent Abstract Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: Idiopathic retroperitoneal fibrosis (IRF) is a rare disease characterized by abdominal periaortic fibro-inflammatory tissue. The aim of this study was to evaluate the prognostic value of fibrosis FDG uptake using FDG/PET CT in patients with IRF

Methods: In this monocentric retrospective cohort study, all patients admitted for IRF from January 2009 to December 2017 underwent a FDG/PET CT at diagnosis and during follow up. Metabolic activity assessed by fibrosis FDG uptake was measured by generating a volume of interest to calculate the maximal standardized uptake value (SUVmax). Complete remission was defined by the disappearance of initial symptoms associated with normal CRP, increased/stabilization of eGFR and decreased/stabilization of the retroperitoneal mass on CT-scan. The primary outcome was IRF relapse rate during follow-up

Results: FDG/PETCT was performed at diagnosis, 3.1 [1-8.7] months (i.e. 1st evaluation) and 10.4 [4.9-17.5] months (i.e. 2nd evaluation) after IRF diagnosis in 23 patients (54.7 [36.9-89] years, 73.9% of men). FDG fibrosis uptake was seen in 23 (100%; SUVmax 6.5 [3.8-11.9]), 16 (69.6%; SUVmax 3.65 [2.1-5.4]) and 12 (52.2%; SUVmax 3.75 [2.7-7.8]) patients at diagnosis, 1st and 2nd evaluation, respectively. All but one patient had received steroids at IRF diagnosis and 21 (91.3%) were incomplete remission at both 1st and 2nd evaluation. During a median follow-up period of 38.7 [3-107] months, 6 (26.1%) patients suffered IRF relapse that occurred 15.7 [9.2-42.8] months after diagnosis. Univariate analysis showed that CRP level at diagnosis, complete remission at 1st and 2nd evaluation and fibrosis FDG uptake at 2nd evaluation were associated with IRF relapse. In the multivariable analysis, only fibrosis FDG uptake at 2nd evaluation (p=0.046) was associated with IRF relapse. Sensitivity, specificity, negative predictive value and positive predictive value of fibrosis FDG uptake at 2nd evaluation to predict IRF relapse were respectively 100%, 60%, 100% and 50%. Eventually, patients with fibrosis FDG uptake at 2nd evaluation had a higher recurrence rate during followup (p=0.047)



Conclusion: In IRF, fibrosis FDG uptake during follow up is associated with clinical outcome. FDG/PET CT may help to better stratify the risk of relapse in IRF and target immunosuppressive therapy

Characteristic of patients

	Relapse (n=6)	No Relapse (n=17)	p
Age, years	53.3 [41.2-61.3]	57.1 [34.4-89]	ns
Men, n (%)	4 (66.7)	13 (76.5)	ns
Biopsy proven, n (%)	3 (50)	7 (41.2)	ns
IgG4, n (%)	1 (16.7)	2 (11.8)	ns
Abdominal pain at diagnosis, n (%)	6 (100)	14 (82.4)	ns
Constitutional symptoms at diagnosis, n (%)	4 (66.7)	9 (52.9)	ns
CRP at diagnosis, mg/L	40 [10-221]	17 [3-40]	0.0251
High CRP level at diagnosis, n (%)	5 (83.3)	7 (41.2)	ns
Serum creatinine at diagnosis, umol/L	143.5 [90-2254]	79 [54-560]	ns
High creatinine level at diagnosis, n (%)	3 (50)	7 (41.2)	ns
FDG-PET fibrosis uptake at diagnosis, n (%)	6 (100)	17 (100)	1
SUVmax at diagnosis	10.1 [5.5-11.9]	5.4 [3.2-10.7]	ns
Steroids at diagnosis, n (%)	6 (100)	16 (94.1)	1
Complete remission at 1st evaluation	4 (66.7)	17 (100)	0.0593
FDG-PET fibrosis uptake at 1st evaluation n (%)	6 (100)	10 (58.8)	ns
SUVmax at 1st evaluation	3.4 [3.1-3.7]	4.1 [2.1-5.4]	ns
Complete remission at 2nd evaluation	4 (66.7)	17 (100)	0.0593
FDG-PET fibrosis uptake at 2nd evaluation n (%)	6 (100)	6 (35.3)	0.0137
SUVmax at 2nd evaluation	5.3 [2.7-7.8]	3.4 [3.2-4.5]	0.08364
Follow up			
Length, months	47.9 [26.9-106.9]	33.8 [2.8-71.5]	ns
Cumulative months of steroids	45.5 [26.9-106.9]	23.4 [2.8-56.6]	ns
Steroids withdrawal, n (%)	2 (33.3)	8 (50)	ns
Immunosuppressive drugs at any time, n (%)	4 (66.7)	0	0.0017
Death	0	2 (11.8)	ns

Patients with FDG-PET fibrosis uptake (FDG-PET+) during follow up had higher rates of relapse than patients without FDG-PET fibrosis uptake (FDG-PET-)

Disclosure: G. Morin, None; A. Mageau, None; K. Benali, None; E. Piekarski, None; R. Bertinchamp, None; Q. Raimbourg, None; J. F. Alexandra, None; A. Dossier, None; T. Goulenok, None; D. van Gysel, None; T. Papo, None; K. Sacre, None.

Abstract Number: 2971

Rituximab Associated Hypogammaglobulinemia in Autoimmune Disease: Long Term Outcomes

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases II

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: Despite a low incidence of hypogammaglobulinemia (HG) in clinical trials using rituximab (RTX), HG occurs in follow-up of patients with autoimmune disease.

Immunoglobulin replacement therapy (IRT) has been used to reduce infection rates but there is a paucity of data on its efficacy and impact on longer-term outcomes.

We examined the characteristics of patients with RTX associated HG in autoimmune disease, and their long-term outcomes with and without IRT.

Methods: Patients attending a Vasculitis and Lupus clinic, who received RTX for autoimmune disease between 2004 and 2012, with an immunoglobulin G (IgG) <7 g/L on at least 2 occasions were included in this retrospective case note review. Patients were categorized into nadir IgG subgroups of <3 g/L, 3 to <5 g/L and 5 to <7 g/L. Categorical variables are summarised as proportions, and continuous variables as mean \pm standard deviation or median [interquartile range (IQR)]. Differences between nadir IgG subgroups were assessed by Chi squared tests and trends across subgroups confirmed by Somer's D tests. Continuous variables were compared using analysis of variance (ANOVA), Kruskal-Wallis and Wilcoxon sign ranked tests as appropriate. Analyses were performed in SPSS.

Results: Of 142 patients, 101 (71.1%) had ANCA associated vasculitis, 18 (12.7%) systemic lupus erythematosus and 23 (16.2%) other diagnoses. Most received RTX for relapsing (69.3%) or refractory (25.0%) disease. Mean follow-up was 97.2 months from first RTX.

Progressive HG was observed. Median time to IgG <5 g/L was 22.5 months [IQR 3.0 to 61.5] and to IgG <3 g/L was 24.5 months [IQR 4.0 to 80.75].

Mycophenolate use prior to RTX and prednisolone use following RTX were associated with a lower nadir of IgG (Table 1). These associations were confirmed by Somer's D tests.

IRT was commenced in 29 patients, the majority (65.5%) with IgG <3 g/L. It was well tolerated, with 2 discontinuing due to adverse effects. IRT was withdrawn without excess recurrent infections in 5 patients.

IRT was associated with a reduction in annual infection rates (Table 2). Severe infections (requiring intravenous antibiotics or hospital admission) were uncommon, with no change with the use of IRT.

Conclusion: RTX associated HG is progressively identified with longer term follow-up. Although annual infection rates were low, in patients with recurrent infection, use of IRT was associated with a reduction in infection burden.

Table 1

	All (n = 142)	nadir IgG 5 – 7 g/L (n = 40)	nadir IgG 3 – 5 g/L (n = 66)	nadir IgG < 3 g/L (n = 36)	p
Pre-RTX immunosuppression					
Cyclophosphamide	107/142 (75.4)	29/40 (75.0)	49/66 (74.2)	28/36 (77.8)	0.92
cum CYC	12.0 [6.0 – 26.0]	12.0 [5.8 – 27.8]	11.5 [6.0 – 17.3]	11.0 [5.7 – 27.0]	0.91
Azathioprine	88/141 (62.4)	27/40 (67.5)	39/65 (60.0)	22/36 (61.1)	0.73
Mycophenolate	94/141 (66.7)	25/40 (62.5)	39/65 (60.0)	30/36 (83.3)	0.05*
Methotrexate	36/141 (25.5)	10/40 (25.0)	20/65 (30.8)	6/36 (16.7)	0.30

Table . (Cont'd)

	All (n = 142)	nadir IgG 5 – 7 g/L (n = 40)	nadir IgG 3 – 5 g/L (n = 66)	nadir IgG < 3 g/L (n = 36)	p
PLEX	16/141 (11.3)	4/40 (10.0)	5/65 (7.7)	7/36 (19.4)	0.19
Number of prior IS medications	2.9 ± 1.7	2.9 ± 1.3	2.8 ± 1.8	3.2 ± 1.7	0.57
Cumulative RTX	9.0 ± 5.1	8.5 ± 4.7	9.8 ± 5.6	8.1 ± 4.4	0.23
Glucocorticoid use (prednisolone)					
Baseline	115/121 (95.0)	36/38 (94.7)	53/55 (96.4)	26/28 (92.9)	0.78
6 months	120/133 (90.2)	31/39 (79.5)	61/63 (96.8)	28/31 (90.3)	0.02
12 months	113/137 (82.5)	27/39 (69.2)	56/64 (87.5)	30/34 (88.2)	0.04*
24 months	98/133 (73.7)	22/37 (59.5)	48/62 (77.4)	28/34 (82.4)	0.06*

CYC: cyclophosphamide, PLEX: plasma exchange, IS: immunosuppressive

mean ± standard deviation, median [IQR], proportion (%)

Chi squared test p-values presented for proportions; *Somer's D test p-value ≤0.05

Table 2

	All (n = 142)	nadir IgG 5 – 7 g/L (n = 40)	nadir IgG 3 – 5 g/L (n = 66)	nadir IgG < 3 g/L (n = 36)	p
No IRT	113/142 (79.6)	39/40 (97.5)	57/66 (86.4)	17/36 (47.2)	<0.001*
Infections/yr	0.44 [0.15 – 0.99]	0.38 [0.14 – 0.94]	0.48 [0.15 – 1.04]	0.50 [0.00 – 1.12]	0.34
Severe inf/yr	0.00 [0.00 – 0.24]	0.12 [0.00 – 0.24]	0.00 [0.00 – 0.26]	0.00 [0.00 – 0.09]	0.39
IRT	29/142 (20.4)	1/40 (2.5)	9/66 (13.6)	19/36 (52.8)	<0.001*
Infections/yr (no IRT)	1.02 [0.54 – 1.88]	2.49	1.02 [0.57 – 1.98]	0.89 [0.44 – 1.85]	-
Infections/yr (IRT)	0.13 [0.00 – 0.35]				<0.001 ^α
Severe inf/yr (no IRT)	0.19 [0.00 – 0.45]	1.17	0.28 [0.00 – 0.66]	0.07 [0.00 – 0.41]	-
Severe inf/yr (IRT)	0.00 [0.00 – 0.89]				0.97 ^α

median [IQR], proportion (%)

^α IRT vs no IRT; Wilcoxon sign ranked tests

Chi squared test p-values presented for proportions; *Somer's D test p-value ≤0.05

Disclosure: J. Tieu, Roche, 2; S. Gopaluni, None; R. Smith, None; D. Jayne, Chemocentryx, GlaxoSmithKline, Sanofi, Roche, 2,Boehringer-Ingelheim, Astra-Zeneca, AbbVie, CSL, InflaRx, Bristol-Myers Squibb, Takeda, 5,Aurinia, 6.

Abstract Number: 2972

Multicentric Reticulohistiocytosis (1980-2017): A Rare Disease, Commonly Associated with Malignancy and Autoimmunity

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases II

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Multicentric reticulohistiocytosis (MRH) is a systemic disease characterized by papulo-nodular skin eruptions and progressive, deforming arthritis. We aimed to examine the clinical correlates and outcomes of MRH seen at our center, and study the association with malignancy and autoimmunity.

Methods: A retrospective cohort of MRH patients treated at our institution from 01/01/1980 to 04/30/2017 was assembled. Demographics, clinical features, laboratory tests, imaging findings, histopathology (HP), treatments and outcomes were abstracted. Auto immune (AI) disorders and malignancies before and after MRH diagnosis were collected.

Results: We identified 24 patients with MRH (58% female, 75% Caucasian, mean age at diagnosis 52y) with median follow up of 2.3 y. All patients had confirmed diagnosis by HP (23 skin, 7 synovial) and had cutaneous & articular involvement. Nodular skin lesions were noted in 96% patients (periungual area & dorsal hand in 87%, periarticular 61%, face 54%, arms 42%, back 29%, neck 21%, legs 21%, ears 12%, scalp 12%) and mucosal nodules in 30% patients. 92% patients had arthralgia, 88% had joint swelling, and 54% had synovitis. Frequency of joint involvement was upper extremity (UE) PIP(29%)> UE DIPs, MCPs, wrist>MTPs, Toes>Knees>Elbows. Radiographic erosions were noted in 67% patients. Constitutional symptoms included fatigue(15),unintentional weight loss(10),lymphadenopathy(4) and pruritis (11).Systemic features included dysphagia(5),photosensitivity(4), dry eyes(3), and serositis(3). Several patients had positive serologies: ANA(8),RF(5), CCP(3), SSA(3), SSB(2), dsDNA(1). A third of patients had concomitant AI disorders(RA[3],

SS[1], chronic focal granulomatous nephritis[1], JIA[1], psoriasis[1], myasthenia gravis and ITP[1]) and 1/3rd had malignancy (melanoma{3}, basal cell carcinoma[2], and 1 each with ovarian carcinoma, squamous cell carcinoma lung, peritoneal adenocarcinoma, and endometrial carcinoma). Most patients were treated with systemic CS(15) and DMARDs (13): MTX(8), CYC(10), chlorambucil(2) and CSA(1). Biologics (infliximab, etanercept, adalimumab) were used in 4 patients. 2 patients had complete resolution of symptoms, while majority showed only partial improvement. 10 patients developed joint deformities involving: wrist(4), MCP(4), PIP(7), DIP(4), MTP(3), and knee(2). None had arthritis mutilans. 75% were alive at last follow up.



Conclusion: To our knowledge, this is the largest series of MRH patients from a single institution, highlighting the rarity of the condition, and an unmet need for treatment options that can allow sustained disease remission. We emphasize the need for HP to distinguish it from mimicking rheumatic conditions and initiating early aggressive treatment to potentially prevent deforming arthritis. A high vigilance for malignancy and other AI diseases is necessary.

Disclosure: A. S. Sandhu, None; C. S. Crowson, None; D. Wetter, None; G. McKenzie, None; A. Makol, None.

Abstract Number: 2973

Clinical Features and Pulmonary Function Test Findings Associated with Large Airway Disease in Relapsing Polychondritis

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases II

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Session Time: 11:00 AM-12:30 PM

Clinical Features and Pulmonary Function Test Findings Associated with Large Airway Disease in Relapsing Polychondritis

Background/Purpose: Relapsing polychondritis (RP) is a systemic disease that can lead to fatal end-organ damage, including subglottic stenosis (SGS) and tracheobronchomalacia (TBM). The study objective was to evaluate the clinical disease features and pulmonary function test (PFT) findings associated with SGS and TBM.

Methods: Patients 18 years and older were selected from a prospective observational cohort of RP. All patients met McAdams or Damiani's diagnostic criteria and underwent dynamic expiratory phase CT imaging of the thorax, direct laryngoscopy, and PFTs. SGS was defined by pathological narrowing of the subglottis visualized by direct laryngoscopy. TBM was defined as antero-posterior and/or lateral flattening of the tracheal wall during expiration on dynamic CT. Percentage of tracheal collapse during mid-expiration was measured by a single radiologist. Airtrapping was defined as an area of low attenuation compared to the remainder of the lung parenchyma on expiratory CT images. Lung volumes and diffusion capacity were assessed for all patients. Differences were assessed by Fisher's exact test or Kruskal-Wallis test. Median values are presented.

Results: A total of 46 patients were included. 9 patients (20%) had SGS, 19 patients (41%) had TBM, and 4 patients (8%) had both (Table). Patients with SGS were predominantly female (100% vs 83, $p=0.07$) and younger at symptom onset (33 vs 40 years, $p=0.04$). There was no gender or age differences in patients with TBM compared to those without (84% vs 89% female, $p=0.68$; 43 vs 44 years, $p=0.94$). No clinical symptoms were significantly associated with SGS. Patients with TBM had significantly more wheezing (68% vs 23%, $p<0.01$), a prior diagnosis of asthma (79% vs 22%, $p<0.01$), and hearing loss (47% vs 19%, $p=0.05$). Patients with TBM had more respiratory symptoms such as choking sensation (84% vs 66%, $p=0.37$) and pleuritic chest pain (32% vs 15%, $p=0.27$) but these differences were not statistically significant. The median tracheal collapse in patients with TBM as compared with patients without was 71% vs 19% ($p<0.001$). Patients with air trapping on dynamic CT scan had significantly worse tracheal collapse (58% vs 24%, $p<0.01$). There were no significant associations between PFT results and SGS status. Total lung capacity was significantly higher in patients with TBM (102% vs 92%, $p=0.03$), but no other PFT parameters were associated with TBM.

Conclusion: SGS and TBM are relatively common in RP, and specific clinical features and PFT findings are associated with airway damage. Female gender and younger age at symptom onset are associated with SGS. Wheezing, hearing loss, air trapping, and increased total lung capacity are associated with TBM. These findings may help identify subsets of patients with RP who are likely to have large-airway involvement.

	With SGS (n = 9)	Without SGS (n = 36)	P-value	With TBM (n = 19)	Without TBM (n = 25)	P-value
Sex (Female, %)	9 (100%)	30 (83%)	0.07	16 (84%)	24 (89%)	0.68
Age at symptom onset (Years \pm SD)	33 (17-36)	40 (30-46)	0.04	43 (36-57)	44 (36-50)	0.94
Clinical Symptoms						
Constitutional symptoms	1 (11%)	7 (19%)	1	3 (16%)	5 (19%)	1
Inflammatory eye disease	2 (22%)	8 (22%)	1	4 (21%)	6 (14%)	1
Audiovestibular Symptoms						
Vertigo	6 (66%)	23 (62%)	1	12 (63%)	17 (63%)	1
Hearing loss	2 (22%)	12 (32%)	0.7	9 (47%)	5 (19%)	0.05
Tinnitus	5 (55%)	25 (68%)	0.69	12 (63%)	18 (67%)	1
ENT Symptoms						
Auricular chondritis	9 (100%)	35 (94%)	1	18 (95%)	26 (93%)	1
Saddle nose	1 (11%)	5 (14%)	1	4 (21%)	6 (13%)	1
Nasal chondritis	9 (100%)	35 (94%)	1	17 (89%)	23 (85%)	1
Sinonasal symptoms	5 (56%)	27 (73%)	0.4	13 (68%)	19 (70%)	1
Respiratory Symptoms						
Voice changes	31 (89%)	8 (84%)	1	17 (89%)	22 (81%)	0.68
Choking sensation	7 (78%)	27 (72%)	1	16 (84%)	18 (66%)	0.37
Dry cough	8 (89%)	33 (89%)	1	18 (95%)	23 (85%)	0.38
Shortness of breath	8 (89%)	30 (81%)	1	16 (84%)	22 (81%)	1
Pleuritic chest pain	2 (22%)	8 (22%)	1	6 (32%)	4 (15%)	0.27
Stridor	2 (22%)	6 (16%)	0.64	4 (21%)	4 (14%)	0.7
Wheezing	3 (33%)	17 (46%)	0.71	13 (68%)	7 (26%)	<0.01
Musculoskeletal Symptoms						
Tenosynovitis	4 (44%)	21 (57%)	0.71	12 (63%)	13 (48%)	0.37
Arthralgia	8 (89%)	33 (89%)	1	16 (84%)	24 (89%)	0.67
Costochondritis	8 (89%)	32 (86%)	1	17 (89%)	23 (85%)	1

Subglottic stenosis (SGS); Tracheobronchomalacia (TBM); Standard deviation (SD)

Disclosure: M. A. Ferrada, None; A. Sirajuddin, None; E. L. Goh, None; K. Quinn, None; K. B. Gribbons, None; J. Hansen-Falschen, None; N. Seam, None; R. Colbert, None; K. A. Sikora, None; W. Goodspeed, None; A. Thomas, None; H. J. Kim, None; A. Clint, None; M. Chen, None; J. D. Katz, None; P. C. Grayson, None.

Long-Term Survival in Lung Transplantation for Interstitial Lung Disease Due to Rheumatic Systemic Diseases. Study of 26 Cases of a Single Center

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Session Information

Session Date: Wednesday, October 24, 2018

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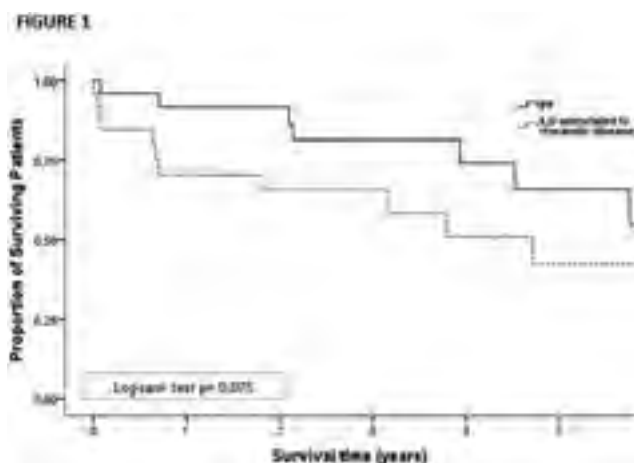
Session Time: 11:00AM-12:30PM

Background/Purpose: Interstitial lung disease (ILD) is one of the most serious complications associated with rheumatic systemic diseases. Patients with ILD have increased mortality and limited treatment options. Lung transplant has been recognized as an option for patients with end-stage ILD associated with rheumatic systemic diseases (RSD-ILD). However, rheumatic diseases are still sometimes considered a contraindication for lung transplant because of concerns for worse outcomes.

Our aims were to: a) assess long-term post-transplant survival in patients with RSD-ILD and b) compare post post-transplantsurvival of patients with RSD-ILD to patients with idiopathic pulmonary fibrosis (IPF).

Methods: Single center study in a referral center for lung transplant of all patients who underwent lung transplantation for RSD-ILD between 1998 and 2017. This cohort was compared with patients with IPF (group-matched for age, transplant year and basiliximab induction). Cumulative survival rates after transplantation were estimated by the Kaplan-Meier method and compared between groups using the log-rank test.

Results: We studied 26 patients with RSD-ILD matched to 26 patients with IPF. The underlying diseases of patients with RSD-ILD were: Rheumatoid arthritis (n=8), Scleroderma (n=6), Sjögren syndrome (n=4), ANCA-vasculitis (n=3), Anti synthetase syndrome (n=2), Takayasu arteritis (n=1), Dermatomyositis (n=1), Systemic lupus erythematosus (n=1). The comparative study of baseline characteristics between both groups is shown in the TABLE. Cumulative survival rates at 5 years post-transplant did no differ significantly between RSD-ILD and IPF [42.4% vs 65.8% (p=0.075)] (FIGURE 1).



Conclusion: Patients undergoing lung transplantation for RSD-ILD had similar long term post-transplant survival as those with IPF. These data support that lung transplantation should be considered in patients with end-stage ILD associated with rheumatic diseases.

Disclosure: D. Prieto Peña, None; A. Martinez Meñaca, None; M. Calderón Goercke, None; J. L. Martín-Varillas, None; B. Atienza-Mateo, None; V. M. Mora Cuesta, None; S. Fernandez Rozas, None; D. Iturbe Fernandez, None; C. González-Vela, None; J. M. Cifrian Martinez, None; M. A. González-Gay, None; R. Blanco, None.

Abstract Number: 2975

Anti-IL-1 Therapies in Patients with Familial Mediterranean Fever Related AA-Amyloidosis

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases II

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: The most devastating complication of Familial Mediterranean Fever is secondary AA amyloidosis and is still a problem in many cases. Efforts have been paid to prevent AA amyloidosis or to control an already formed Amyloidosis in order to prevent organ function loss, particularly renal insufficiency. There are emerging therapies in FMF related amyloidosis. Here is aimed to evaluate the role of anti-IL-1 regimens, Anakinra and Canakinumab regarding their efficacy and safety in FMF related amyloidosis.

Table 1-a: The parameters of renal functions and acute phase reactants in patients with initial Creatinine level below 1.5 mg/dL (Group 1)

	Anakinra(n= 19)			Canakinumab (n=10)		
	Before treatment	After treatment	p	Before treatment	After treatment	p
Creatinine (mg/dl)	0,9 ± 0,28	0,9 ± 0,44	<0,01	1,35 ± 1,57	1,78 ± 1,93	=0,01
GFR (ml/min)	90,3 ± 27,72	96,15 ± 38,58	<0,01	85,7 ± 40,6	80,8 ± 51,61	<0,01
Proteinuria (mg/day)	2686 ± 3257	2328 ± 4458	<0,01	6000 ± 5550	3730 ± 5030	<0,01
CRP (0-5 mg/L)	16 ± 14	4,47 ± 7,19	<0,01	8,1 ± 10,52	3,7 ± 4,3	=0,02
Sedimentation	43,5 ± 31,3	19,3 ± 26,4	<0,01	51,22 ± 33,54	17,1 ± 31,2	<0,01

Table 1-b: The parameters of renal functions and acute phase reactants in patients with initial Creatinine level above 1.5 mg/dL (Group 2)

	Anakinra(n= 13)			Canakinumab (n=9)		
	Before treatment	After treatment	p	Before treatment	After treatment	p
Creatinine (mg/dl)	3,3 ± 2,4	3,4 ± 2,4	<0,01	3,1 ± 2,4	3,2 ± 2,5	<0,01
GFR (ml/min)	30 ± 24,1	24,4 ± 21,4	<0,01	30 ± 22	27,5 ± 20,7	<0,01
Proteinuria (mg/day)	5482 ± 8040	3651 ± 4635	=0,01	7670 ± 7600	7585 ± 6830	=0,01
CRP (0-5 mg/L)	24,3 ± 13,9	6,4 ± 10	<0,01	23,44 ± 40,52	20,52 ± 29,31	=0,05
Sedimentation	56,8 ± 35,1	31,3 ± 17,8	<0,01	51,22 ± 33,54	34,55 ± 27,19	<0,01

Methods: In this single center study, 44 patients diagnosed with FMF and had a histologically proven diagnosis of amyloidosis, were exposed to anakinra or canakinumab. Patients who used anakinra less than one month and canakinumab less than 2 injections were not included in this review. For all patients recruited in this review, the indication for anti-IL-1 therapies was FMF-related amyloidosis and ongoing inflammation despite adequate colchicine treatment. Patients were questioned with regards to FMF related characteristics, comorbidities. MEFV gene status, laboratory measures, side events and therapy outcomes were tested and followed.

Results: Among 44 patients, 40 were initially treated with anakinra and 4 with canakinumab. Among 40 patients treated with anakinra initially, anakinra was switched to canakinumab due to allergic reactions or insufficient response in 15 patients. There are 16 patients still being treated with anakinra and 10 with canakinumab. In order to evaluate the efficacy of anti-IL-1 agents, the patients were divided into two groups with regards to their initial renal function. Patients with initial Creatinine level below 1.5 mg/dL when an anti-IL-1 drug was initiated were reviewed as Group 1 and the patients who initially had chronic renal insufficiency and Creatinine level above 1.5 mg/dL were defined as Group 2. The analysis of clinical outcome was then performed as summarized in Table 1-a and Table 1-b. The decrease in proteinuria is more modest ($p=0.01$) in Group 2 in comparison with Group 1 ($p<0.01$). At the time of this review 8 patients were still on hemodialysis. Three patients had renal transplantation.

Conclusion: In cases with FMF related AA amyloidosis, there is a need for sufficient inflammatory control. We suggest that anti-IL-1 therapies are effective and tolerable in amyloidosis. These agents are particularly effective when administered in initial stages of renal disease and the effect is less pronounced in case of an already formed renal insufficiency. The anti-IL-1 agents are generally well tolerated and the related side effects were mostly reversible.

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Abstract Number: 2976

Immune Checkpoint Inhibitor-Associated Myositis: A Characteristic Phenotype with a Poor Outcome Related to Concomitant Myocarditis

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Muscle Biology, Myositis and Myopathies II: Clinical and Miscellaneous Topics

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: Immune checkpoint inhibitors (ICI) are a major breakthrough in cancer treatment providing frequent durable responses and improving overall survival. Blocking immune checkpoints (Programmed cell Death 1 (PD-1)/PD-ligand 1 or Cytotoxic T Lymphocyte-Associated Protein 4 (CTLA-4)) to restore antitumor immune response may also induce immune-related adverse events (irAEs) targeting a large spectrum of organs including cardiac and skeletal muscle tissue. The overall mortality related to irAE is less than 2% with myocarditis being fatal in ~40-50% of cases. Myocarditis is associated with myositis in at least 25% of cases.

To date, only few cases of myositis have been reported. With the increased rate of ICI use, improvement in recognition, description, and management of muscular irAEs are required.

Methods: Data were collected from the VigiBase (<http://www.vigiaccess.org/>), the World Health Organization database of individual safety case reports (Uppsala, Sweden). Cases were identified using the High Level Term “Muscle infections and inflammations” of the Medical Dictionary for Regulatory Activities terms and at least one of seven following ICIs (Nivolumab, Pembrolizumab, Ipilimumab, Tremelimumab, Avelumab, Durvalumab, and Atezolizumab).

Results: Through March 2018, 180 myositis patients were identified (71 years [29-90]). They had most often been treated for melanoma (31.1%) or pulmonary cancer (30.6%) and 85% had received monotherapy, usually anti-PD1. The median time of myositis onset was 26 days [18-39] after the initial exposure to ICIs (data available in 61 patients). Amongst all myositis patients, 16.1% (n=29) also presented with myocarditis, 15.6% (n=28) with myasthenia gravis-like symptoms (oculomotor disorders and/or ptosis), 3.3% (n=6) with both and 13.9% with other concurrent irAEs including hepatitis (n=14), colitis (n=3), thyroiditis (n=3), nephritis (n=3), and hypophysitis (n=2). ICI-associated myositis caused significant morbidity and mortality, with fatalities occurring in 21.2% of patients. Moreover, 49.4% of patients with myositis had severe complications such as prolonged hospitalization, a life-threatening event, or a disabling effect. The mortality rate was significantly associated with combination therapy compared to monotherapy (38.5% vs. 18.1% p=0.02) and was higher in patients with concomitant myocarditis (51.7%) compared to those without myocarditis (14.9%, p<0.0001).

Conclusion: ICI-associated myositis occurs early during therapy and is most often reported with combination regimens. ICI-associated myositis has a unique clinical presentation including ocular signs and concomitant myocarditis. Systematic screening for myocarditis might be crucial in patients with ICI-associated myositis, due to the frequent overlap between these conditions and the high mortality of ICI-myocarditis.

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Abstract Number: 2977

Lenabasum, a Cannabinoid Type 2 Receptor Agonist, Reduces T-Cell Population and Downregulates Type 1 and 2 Interferon Activities in Lesional Dermatomyositis Skin

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Muscle Biology, Myositis and Myopathies II: Clinical and Miscellaneous Topics

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00 AM-12:30 PM

Background/Purpose: Lenabasum is a synthetic, non-immunosuppressive, selective cannabinoid receptor type 2 (CB2) agonist that activates resolution of innate immune responses. CB2 is a G-protein coupled receptor found primarily on activated immune cells. Lenabasum has improved skin inflammation and fibrosis in systemic sclerosis patients. In-vitro, it has shown to affect T-cell activity, alter Th1 and Th2 cytokine production, and decrease type I interferon activity. We sought to characterize the in vivo effect of lenabasum on inflammatory cells and cytokines thought to be involved in the disease pathogenesis of dermatomyositis (DM).

Methods: 22 adult patients with refractory, skin-predominant DM on stable standard-of-care treatments were recruited for a double-blind, placebo-controlled, randomized trial. 86% percent of subjects were on stable immunosuppressive medications. Lenabasum was initially administered orally at a dose of 20 mg a day for 4 weeks, which was subsequently raised to 20 mg twice a day for an additional 8 weeks. In a subset of subjects, lesional skin biopsies were collected at baseline and at Week 12. Immunohistochemical staining of CD4, IFN-beta, IFN-gamma, IL-4, IL-31 and IL-31 RA and QRT-PCR for Type I IFN, IFN-gamma, and IL-4 were performed on RNA extracted from the tissue samples. Sections were analyzed using the Nikon Eclipse 80i microscope. The percentage of the dermis with positive staining was quantified using NIS Elements Software. Comparisons of percent area of protein staining in the dermis and mRNA levels of various cytokines between lenabasum and placebo groups were performed using the Wilcoxon signed-rank test.

Results: There was strong co-localization of CB2 with Th1 CD4+ T cells in baseline biopsies. CD4+ area in the skin biopsies from lenabasum-treated subjects were significantly decreased at Week 12 compared to the placebo group (p<0.05). There were significant reductions in type I IFN signature, IFN-beta protein staining, and IFN-gamma mRNA and protein staining at Week 12 in subjects on lenabasum compared to those on placebo (p<0.05 for all). IL-31 protein (p<0.01) was reduced at Week 12 in subjects who received lenabasum compared to those taking placebo, but IL-31 mRNA expression and IL-31RA+ protein staining did not change. There were no changes in IL-4 protein or mRNA expression.

Conclusion: Lenabasum reduces Type 1 and 2 interferon levels as well as T cell inflammation in dermatomyositis. These effects have the potential to inhibit underlying disease pathways in DM and thus contribute to any clinical benefit of lenabasum in DM.

Disclosure: N. Reddy, None; M. Zeidi, None; B. White, Corbus Pharmaceuticals, Inc., 3; V. P. Werth, Corbus Pharmaceuticals, Inc., 5, 9.

Abstract Number: 2978

Performance of the 2017 European League Against Rheumatism / American College of Rheumatology (EULAR/ACR) Classification Criteria for Adult Idiopathic Inflammatory Myopathies (IIM) in an Australian Cohort

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Session Information

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Session Time: 11:00AM-12:30PM

Background/Purpose: EULAR/ACR recently approved classification criteria for idiopathic inflammatory myopathies (IIM) with 93% sensitivity and 88% specificity. An acknowledged limitation of the study is the absence of controls/comparators in the external validation cohort, prompting the authors to call for further validation studies in different populations. We sought to 1) evaluate the performance of the criteria in an Australian cohort of adult patients with suspected IIM; 2) determine the level of agreement between the EULAR/ACR criteria and traditional criteria (Bohan and Peter, and Targoff); 3) determine the optimal cut-point for Australian patients; 4) assess the effect of including MRI of the musculature or an extended panel of antibodies, as additional ‘risk factors’; 5) assess the effect of extending “endomysial infiltration of mononuclear cells surrounding but not invading myofibres” to include invasion of myofibres.

Methods: Data were collected retrospectively on all consecutive patients referred for muscle biopsy to two large tertiary teaching hospitals. Area under the receiver operator curve (AUC) was calculated to assess the overall performance of the EULAR/ACR criteria. The Youden method was used to determine the optimal cut point. Patients were scored for ‘risk of IMM’ according to the EULAR/ACR criteria and dichotomized into probable/definite and negative/possible groups. The predictive accuracy of the EULAR/ACR criteria was assessed by evaluating the sensitivity and specificity.

Results: Eighty seven of 204 patients had IIM. Overall, the EULAR/ACR criteria had an outstanding level of discrimination (AUC=0.90). Application of the criteria in this cohort however, showed lower sensitivity (71% vs. 93%) but comparable specificity (89% vs. 88%). The optimal cut point of 5.23 (sensitivity 91%, specificity 75%) for this sample was lower than the EULAR/ACR cut point of 6.7. The EULAR/ACR criteria had a moderate agreement with Bohan and Peter (kappa=0.45, 95%CI=0.28, 0.62, p<0.001) and Targoff (kappa=0.40, 95%CI=0.23, 0.57, p<0.001). Inclusion of MRI of the musculature (AUC=0.86, 95%CI=0.79, 0.93), or non-Jo1 myositis specific antibodies (AUC=0.84, 95%CI=0.77, 0.91) improved the ability of the model to identify IIM compared with the EULAR/ACR criteria alone (AUC=0.80, 95% CI=0.75, 0.86). Furthermore, extending the criteria so that endomysial infiltration of mononuclear cells included invasion of myofibres, resulted in a model with a comparable level of accuracy to the original criteria (both AUCs=0.90). However, the sensitivity was slightly improved (75% vs. 71%) while the specificity remained the same (89% vs. 89%).

Conclusion: The EULAR/ACR criteria had an outstanding discrimination between IIM and non-IIM. Application of the criteria to an Australian cohort has shown comparable specificity but lower sensitivity, and lower optimal cut-point than reported. There is moderate agreement with traditional criteria. Addition of MRI of the musculature, or non-Jo1 myositis specific antibodies, improved the ability of the model to identify IIM. Extending the criteria so that endomysial infiltration of mononuclear cells included invasion of myofibres may improve sensitivity.

Disclosure: Q. Luu, None; J. Day, None; A. Hall, None; V. Limaye, None; G. Major, None.

Innovative Approaches for the Assessment of Interstitial Lung Disease in Idiopathic Inflammatory Myopathies: Ultrasound Evaluation of Pleural Irregularities and Semiquantitative and Quantitative Analysis of Lung CT

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Background/Purpose: Interstitial Lung Disease (ILD) in patients with Idiopathic Inflammatory Myopathies (IIM) is associated to high mortality and morbidity. The study of pleural irregularities (PI) with lung ultrasound (US) and quantitative automated scoring of high resolution computed tomography (HRCT) have been recently proposed as a method for assessing the ILD. Purpose of our study is to compare the US assessment of PI and HRCT semi-quantitative and quantitative analysis of ILD.

Methods: Forty-five IIM patients (30 F, 15M, mean age 64 ± 12), 44 diagnosed according to Bohan and Peter (23 PM, 22 DM) and 1 IBM according to Griggs criteria, with a disease duration of 54 ± 86 months, were enrolled. Lung US was performed in 53 anterior and posterior intercostal spaces with 8-18 MHz linear probe, assigning a PI score ranging from 0 to 2 (0 (no PI), 1 (mild PI - 3-5mm), 2 (severe PI > 5 mm) and calculating the total PI score (PIS). In a subset of patients to assess reliability and reproducibility of the PIS, the lung ultrasounds were also repeated by the same operator after two days and by a second operator.

HRCTs were assessed by an expert radiologist to obtain a semiquantitative score - Warrick score (WS) and 26 HRCTs were also evaluated with a quantitative analysis by a volumetric texture and local volumetric histogram feature-based analysis software (CALIPER). With CALIPER were quantified lung involvement as a percent of interstitial lung abnormalities (ILD%): a combination of percent of areas of ground glass, reticulation and honeycombing. Analysis of the vascular involvement was obtained as percent of pulmonary vessel volume (PVRV %).

Results: PI were present in all patients with a mean PIS of 25 ± 14 . At HRCT, the semiquantitative analysis of CT data, identified ILD in 32 patients with a mean WS of 7.2 ± 7.0 . CALIPER software quantified a mean ILD% of 2.90 ± 5.72 and a mean PVRV% of 2.56 ± 1.29 .

A good correlation was identified between PIS and WS ($r=0.716$ $p<0.001$) and with PIS and ILD% and PVRV% ($r=0.559$ $p=0.003$ and $r=0.615$ $p<0.001$ respectively). Additionally, a good correlation was identified among WS and ILD% and PVRV% ($r=0.693$ $p<0.001$ and $r=0.651$ $p<0.001$ respectively).

The PIS score was repeatable (inter-reader reliability: $\alpha=0.916$) and reproducible (intra-reader reliability: $\alpha=0.945$).

Conclusion: The evaluation of ILD with innovative techniques may allow a more precise grading of ILD in IIM patients. Our study suggests a possible role for both PI and CALIPER in the evaluation of ILD in clinical practice and for RCTs, as PI US may be useful for the initial screening of ILD and the automatic software CALIPER could make ILD assessment easier and more reproducible.

Disclosure: S. Barsotti, None; C. Romei, None; E. Cioffi, None; C. Roncella, None; E. Perrone, None; A. Tripoli, None; M. Mosca, None; F. Falaschi, None; R. Neri, None.

Calcineurin Inhibitor for the Treatment of Myositis-Associated Interstitial Lung Disease: Comparison between Cyclosporine and Tacrolimus

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Session Information

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Background/Purpose: Treatment options for myositis-associated interstitial lung disease (ILD) include corticosteroids (CS) in combination with or without cyclophosphamide (CY), calcineurin inhibitors (CNIs) such as cyclosporine (CyA) and tacrolimus (TAC), mycophenolate mofetil, and/or rituximab. However, efficacy of individual treatment regimens has never been compared in randomized clinical trials, and treatment decision is made based on expertise of physicians. We have recently launched the multicenter retrospective cohort of Japanese Patients with Myositis-associated ILD (JAMI), which involved 497 incident cases of adult myositis-associated ILD from 44 institutions across Japan. By taking advantage of our large-scale cohort database, we investigated the efficacy of CNIs in myositis-associated ILD.

Methods: A total of 491 patients with adult-onset PM/DM were selected from the JAMI database. Clinical characteristics and survival rates were compared between the patient groups, followed by additional comparisons using propensity score matching method. Survival rates were calculated by the Kaplan-Meier method.

Results: The mean age at disease onset was 56, 67% were female, and median disease duration was 2 months. In a crude analysis, cumulative survival rate was significantly lower in 402 patients treated with regimens including CNI than in 89 patients treated with regimens without CNI ($P = 0.03$; Figure 1A). Clinical characteristics associated with CNI use included positive anti-MDA5, shorter disease duration, higher levels of CRP and ferritin, lower oxygen saturation, and more intensive immunosuppressive regimens. After matching patients for background using propensity score, there was a trend toward a better survival rate in patients treated with CNI than in those without (Figure 1B). When we further examined efficacy between 201 patients treated with CyA and 187 patients with TAC, treatment with TAC was associated with a better survival rate, compared with CyA treatment, in a crude analysis ($P = 0.02$). After matching patients for background using propensity score, the survival rates were similar between patients treated with CyA and TAC. The patients treated with CNIs were further divided into 4 subgroups according to main components contributing to the propensity score, including anti-MDA5, CRP, ferritin, and disease duration at diagnosis, there was no difference of survival rates between CyA-treated and TAC-treated patients in each subgroup (Figure 2).

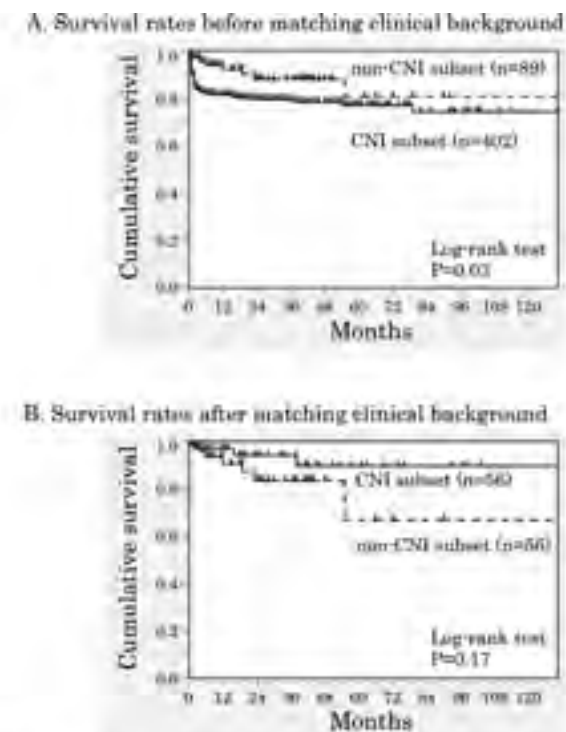


Figure 1. Overall survival rates between CNI subset and non-CNI subset

Conclusion: Our results suggest potential efficacy of CNI, either CyA or TAC, in combination with CS-based regimens for broad spectrum of myositis-associated ILD.

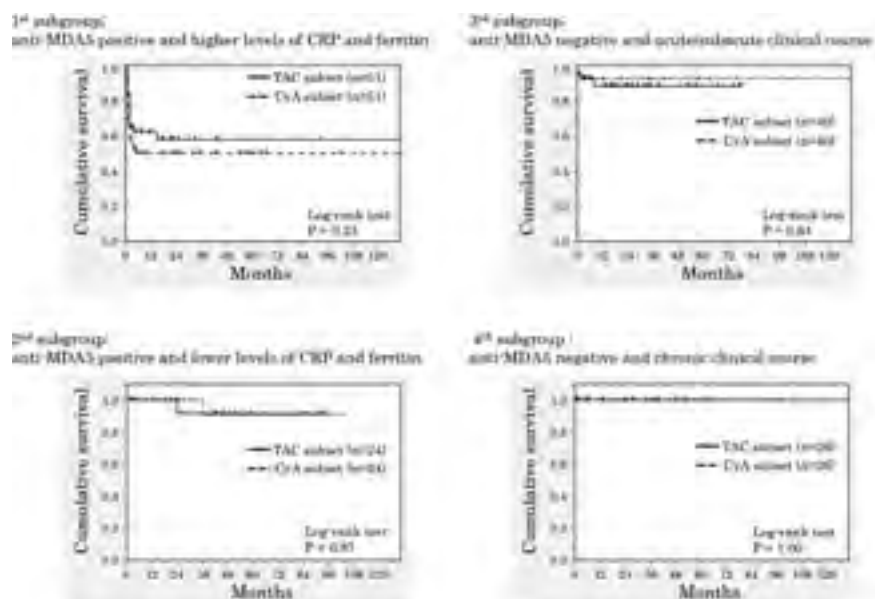


Figure 2. Overall survival rates of each subgroup after matching clinical background between CyA subset and TAC subset.

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Abstract Number: 2981

Mitochondrial Extrusion and Autoimmunity in Juvenile Dermatomyositis

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Muscle Biology, Myositis and Myopathies II: Clinical and Miscellaneous Topics

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: We recently made the fundamental observation that mitochondrial extrusion is instrumental in mediating inflammation, autoimmunity and organ damage in lupus. Mitochondrial stress and mitochondrial autoantibodies have been reported in adult dermatomyositis (DM). However, the role of mitochondrial extrusion in juvenile DM is not known. One debilitating manifestation of chronic JDM is calcinosis, the formation of calcium deposits in soft tissue. Calcification may occur intracellularly in organelles, including mitochondria, but the role of mitochondrial calcification in JDM has not been investigated. In the current study, we investigated the role of mitochondrial calcification and extrusion in JDM pathogenesis, as well as the clinical utility of mitochondrial biomarkers.

Methods: Anti-mitochondrial autoantibodies, as well as cell-free mtDNA levels were analyzed in healthy children (HC, n=20), pediatric lupus (n=10), polymyositis (n=7), JDM patients (n=66), and RNP+ myositis (9), by a state-of-the-art flow cytometry technique as well as an in-house qPCR assay. In the Juvenile Myositis (JM) population, 74% were female, with a mean age of 11.3 years. The association of mitochondrial markers with clinical parameters was tested, including disease activity scores (DAS) for skin, muscle and total, the presence of calcinosis as well as Myositis Specific Antibodies (MSA). Electron microscopy of muscle surrounding calcifications was performed.

Results: As determined by electron microscopy, JDM children had evidence of mitochondrial calcification in affected muscle biopsies. Though phagocytosed by tissue-resident macrophages, the engulfed calcified mitochondria were not

degraded, but remained in intracellular vesicles. Consistent with an important role of calcinosis in impaired mitochondrial extrusion and clearance, JM children with calcinosis had increased levels of cell-free mtDNA as compared to JM children without calcinosis and healthy children ($p<0.05$). Unexpectedly, levels of mtDNA were inversely correlated with DAS ($r=-0.32$, $p=0.007$) and the macrophage-derived inflammatory marker neopterin ($r=-0.44$, $p=0.0003$). Further, mitochondrial autoantibodies were elevated in JDM patients as compared to healthy individuals (40% vs 6%, $p<0.001$), with the highest frequency found in JDM children with p155/p140 (57%) and MDA5 (75%) MSA. For RNP+ myositis, the frequency was 42%. In JDM patients with no Myositis Associated Antibodies, only 18% of the children had anti-mitochondrial antibodies. Levels of anti-mitochondrial antibodies were associated with calcinosis ($p<0.05$), C4 levels ($r=-0.63$, $p=0.002$) and a bioassay for immune complexes ($r=0.38$, $p=0.002$). Children with SLE had increased anti-mitochondrial antibodies (90%, $p<0.0001$) as well as mtDNA ($p<0.05$).

Conclusion: Our results demonstrate a clear contribution of mitochondria in JDM pathogenesis and suggest mitochondrial calcification and subsequent extrusion and autoimmunity a novel, and potentially therapeutically targetable pathway. Further, mitochondrial biomarkers may offer clinical utility in monitoring disease activity and severity in Juvenile Myositis.

Disclosure: C. Lood, None; B. Duvvuri, None; R. Moore, None; G. A. Morgan, None; M. Klein-Gitelman, None; M. L. Curran, None; L. M. Pachman, None.

Abstract Number: 2982

Normal Mortality of the Cobra Early Rheumatoid Arthritis Trial Cohort after 23 Years Follow up

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes VI: Outcomes Reports

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

ACR abstract

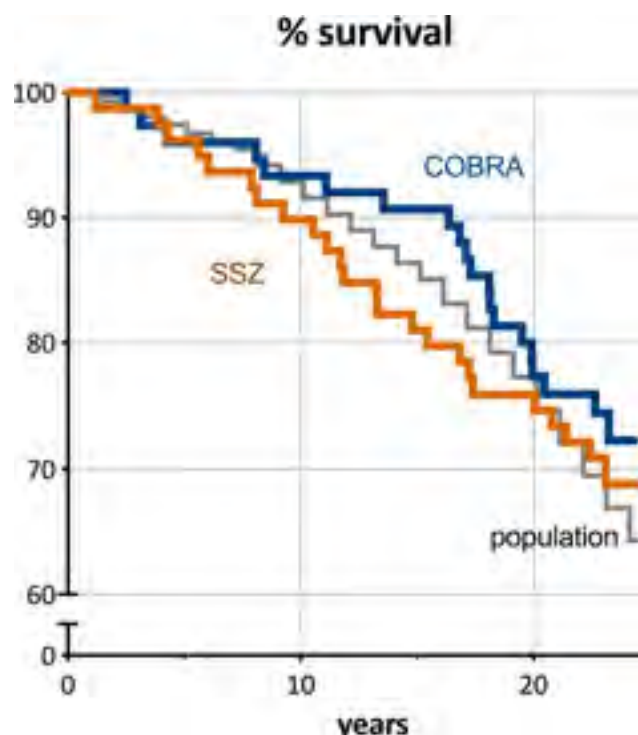
Background/Purpose: Mortality in patients with rheumatoid arthritis (RA) is higher than in the general population. In most studies this becomes apparent only after more than a decade of follow up. The COBRA (COmbinatie therapie Bij Reumatoïde Artritis) trial showed long-term effectiveness of combination therapy of early RA without undue harm [1]. After 11 years of follow up, patients with COBRA treatment had numerically lower mortality compared to patients with sulphasalazine (SSZ) monotherapy [2]. We now present mortality in the COBRA trial cohort after 23 years compared to the general population and explore early predictive factors.

Methods: In the COBRA trial, patients with early RA (median disease duration, 4 months) were treated with SSZ monotherapy ($n=79$) or a combination of SSZ, low-dose methotrexate and initially high, step-down prednisolone (COBRA, $n=76$). We investigated mortality in the COBRA cohort through the Dutch state registry for mortality (Centrum van Familiegeschiedenis). We compared the mortality in this cohort to a reference sample of the general population in the Netherlands matched for age and gender (Statistics Netherlands). The Standardized Mortality Ratio (SMR) compared the trial groups with the general population. We explored the following early predictive factors for mortality through forward stepwise Cox regression: smoking, treatment, disease duration (according to 3 definitions), disease activity score (DAS-44) and 16-week change; Health assessment questionnaire; rheumatoid factor (ACPA not available at that time); Sharp van der Heijde damage score and change at 28 and 56 weeks; HLA-DR1-4.

Results: Follow up was nearly complete (154/155 patients). Duration of follow up was mean 23 (inpatients alive, range 22-24) years. In total 44 patients died (28%, SMR = 0.80[95%CI: 0.59-1.06]); 20 of 75 COBRA patients (27%, SMR 0.75; [0.47-1.14]) and 24 of 79 SSZ patients (30%, SMR 0.85 [0.56-1.25]); the difference in mortality was not significant ($p=0.61$). In the general population reference sample ($n=154$) 55 people (36%) died. The positive trend for COBRA over SSZ decreased over time(Figure). 5 factors were significantly associated with increased mortality hazard: damage progression at 28 weeks; high HAQ score; and absence of HLA-DR 2 or 3. Disease duration from start of complaints showed a nonlinear pattern.

Conclusion: This is the first early RA (trial) cohort to show mortality similar to the general population after 23 years of follow up. In fact, mortality was numerically lower than expected. Some (but not all) predictive factors for disease severity

were apparent. Our study confirms that early, intensive treatment of RA (that can include glucocorticoids) has long-term benefits, and strongly suggests these benefits include normalization of mortality.



References: 1. Boers M. *Lancet* 1997;350:309-18.
2. van Tuyl LH. *Ann Rheum Dis* 2010;69:807-12.

Disclosure: P. Poppelaars, None; L. van Tuyl, None; M. Boers, None.

Abstract Number: 2983

The Changing Faces of Rheumatoid Arthritis Patients at Presentation: A 20-Year Study

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes VI: Outcomes Reports

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Session Time: 11:00AM-12:30PM

Background/Purpose: To analyze the evolution of baseline demographic, clinical, serological and genetic characteristics of patients with incident RA over 20 years.

Methods: Since July 1998, the Early Undifferentiated Poly Arthritis (EUPA) cohort recruits consecutive adults with recent-onset immune-mediated synovitis affecting at least 3 joints. Baseline characteristics were compared in three subgroups of patients fulfilling RA criteria according to date of inclusion (1998-2004;2005-2010; 2011-2017). Anti-cyclic citrullinated

peptide (CCP2) antibodies and RF were measured using commercial assays, while anti-Sa were measured with an in-house assay or a commercial assay calibrated with it (ArthritisRheum;2009;60:698-707). Human Leucocyte Antigen (HLA)-DR alleles were determined using sequence-specific primer PCR. False discovery rate correction was used to adjust p-values for multiple comparisons.

Results: 739 patients were included: 247 in 1998-2004; 263 in 2005-2010; 229 in 2011-2017. We observed a decrease in current smokers over time: 22.4, 18.6, 12.3%, respectively ($p=0.04$). Symptom duration increased (2.8, 3.5, 4.1 months; $p<0.001$). Markers of inflammation decreased (ESR (mm/h): 36, 26, 24, $p=0.01$; CRP (mg/L): 15.0, 11, 8.9, $p=0.002$), as did disease activity (DAS28-CRP: 5.5, 5.1, 5.0, $p=0.01$), and patient overall assessment of disease activity (PGA) (59.0, 56.5, 49.0 mm, $p=0.02$); without a parallel decrease in joint counts (SJC: 11, 11, 12 NS) or an increase in corticosteroid or DMARD use before inclusion (33.6, 50.2, 36.7%, $p=0.002$, 26.7, 39.5, 28.8%, $p=0.01$, respectively).

RF positivity decreased (47.8, 36.9, 36.7%, $p=0.03$), but positivity remained stable for anti-Sa (22.9, 18.0, 22.5% NS) and anti-CCP2 (40.8, 35, 35.4% NS), although the mean titers of anti-CCP2 significantly decreased (3.5, 3.2 and 1.0 IU/ml, $p<0.001$). The proportion of Shared epitope (SE) positive patients decreased significantly (51.0, 42, 35.2%; $p=0.04$), while the DERA epitope remained stable.

Relative to anti-CCP negatives, the proportion of SE (62.2 vs 33.8%, $RR=2.01$, $p<0.001$) and current smokers (21.8 vs 15.5%, $RR=1.28$, $p=0.04$) were higher among anti-CCP2+ patients, and remained stable in anti-CCP2+ patients over time (64.9, 61.8, 54.3%, NS; 25.3, 20.9, 18.8% NS respectively). SE positivity and current smoking decreased in anti-CCP2-

Table		1998-2004 (n=247)	2005-2010 (n=263)	2011-2017 (n=229)	Adjusted p-value
Age (years)	mean \pm standard deviation	247 59.0 \pm 15.8	263 60.1 \pm 14.7	229 61.2 \pm 14.4	0.4433
Women	frequency	247 146 (59.1)	263 166 (63.1)	229 132 (57.6)	0.5306
Body mass index (kg/m ²)	interquartile range: 25 th -75 th percentiles	209 26.0 (23.8-29.4)	261 26.7 (23.1-30.1)	228 26.6 (23.7-29.7)	0.8141
Smoker (current)		252 52 (24.4)	263 49 (18.6)	219 27 (12.3)	0.0355
Symptom duration (months)		247 2.8 (1.6-5.5)	263 3.5 (1.0-5.7)	229 4.1 (1.5-7.1)	0.0009
HLA-DR Shared epitope (SE)		243 124 (51)	243 107 (42)	88 31 (35.2)	0.0355
HLA-DR DERA epitope		243 59 (28.4)	243 64 (26.3)	88 21 (23.9)	0.7217
Anti-Cyclic Citrullinated Peptide second generation (CCP2) (IU/ml)		245 3.5 (3.0-235.6)	260 3.2 (2.8-52.5)	229 1.0 (0.6-45.5)	0.0009
Anti-CCP2 \geq 5 IU/ml		245 100 (40.8)	260 91 (35)	229 81 (35.4)	0.4433
Rheumatoid Factor (RF) (IU/ml)		247 20.0 (0.0-320.0)	263 0.0 (0.0-160.0)	229 0.0 (0.0-160.0)	0.0304
RF \geq 10 IU/ml		247 118 (47.8)	263 97 (36.9)	229 84 (36.7)	0.0339
Anti-Sa positive		245 56 (22.9)	261 47 (18)	222 50 (22.5)	0.4433
Anti-CCP2 and RF and Anti-Sa		244 45 (18.4)	260 40 (15.4)	222 41 (18.5)	0.6240
Anti-CCP2 or RF or Anti-Sa		244 132 (54.1)	260 111 (42.7)	222 101 (45.5)	0.0503
Erythrocyte Sedimentation Rate (ESR) (mm/h)		247 36.0 (21.0-46.0)	263 26.0 (16.0-49.0)	227 24.0 (13.0-42.0)	0.0117
ESR $>$ 20 mm/h		247 186 (75.3)	263 161 (61.2)	227 127 (55.9)	0.0009
C-reactive protein (CRP) (mg/L)		247 15.0 (6.0-37.0)	263 11.0 (4.0-31.6)	229 8.9 (3.3-21.9)	0.0016
CRP $>$ 8 mg/L, n (%)		247 166 (67.2)	263 146 (55.5)	229 118 (51.5)	0.0063
Modified Health Assessment Questionnaire (M-HAQ)		246 0.8 (0.4-1.4)	253 0.8 (0.4-1.4)	194 0.6 (0.3-1.3)	0.3409
Swollen joint count (SJC6)		247 11.0 (7.0-16.0)	263 11.0 (7.0-19.0)	229 12.0 (7.0-19.0)	0.5306
Tender joint count (TJC6)		247 10.0 (5.0-15.0)	263 9.0 (6.0-16.0)	229 10.0 (6.0-16.0)	0.5306
Evaluator/physician global assessment (PGA) (0-10 cm)		247 4.5 (3.1-6.2)	263 4.3 (2.8-6.6)	229 4.7 (2.9-7.1)	0.3485
Patient global assessment of disease activity (PGA) (0-100 mm)		245 59.0 (36.0-80.0)	260 56.5 (36.0-78.5)	203 49.0 (27.0-71.0)	0.0149
Disease activity score for 28 joints and CRP (DAS28-CRP)		245 5.5 (4.3-6.3)	258 5.1 (4.1-6.1)	202 5.0 (4.1-6.0)	0.0122
Treatment before inclusion					
DMARD		247 66 (26.7)	263 104 (39.5)	229 66 (28.8)	0.0117
Prednisone		247 83 (33.5)	263 104 (39.5)	229 81 (35.4)	0.0108
Corticosteroid		247 83 (33.6)	263 112 (50.2)	229 84 (36.7)	0.0016

patients (41.7, 30.3, 22.6%, $p=0.02$; 20.6, 17.2, 8.6%, $p=0.02$).

Conclusion: In this cohort of recent onset RA recruited over 20 years, we observed a constant drift towards less inflammatory RF-negative arthritis at baseline. Decreasing smoking rates paralleled lower levels but not lower incidence of positive CCP. The increasing proportion of SE negative patients in this RA cohort with a relatively stable incidence over 20 years suggest the implication of as yet unidentified environmental arthritis-inducing factors acting on this aging population.

Disclosure: N. Carrier, None; S. Roux, None; A. Masetto, None; A. J. D. Fernandes, None; P. Liang, None; M. Maoui, Bristol-Myers Squibb, 3; G. Boire, Bristol-Myers Squibb, 2.

Abstract Number: 2984

Lifestyle and MTX Use Are the Strongest Predictors of Not Achieving Remission in the First Year of Rheumatoid Arthritis: Results from the Canadian Early Arthritis Cohort (CATCH)

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes VI: Outcomes Reports

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Implementation of RA guidelines have improved remission outcomes in RA; nevertheless 45% of early RA participants do not achieve remission in the first year. Moreover, fewer women reached remission than men. Our goal was to identify and compare predictors of persistent disease activity (LDA/MDA/HAD) in the first year of RA treatment in men and women.

Methods: Sample included adults in CATCH (Canadian Early Arthritis Cohort) from 2007-16 with active disease at baseline and ≥ 12 m F/U. Standardized visits included clinical assessments, questionnaires, and lab tests. Logistic regression with backwards election was used to identify predictors of failing to achieve remission (DAS28 <2.6) by 12 months among baseline sociodemographic and RA characteristics and patient reported outcomes.

Results: The sample included 1628 adults with 2010 or 1987 ACR/EULAR criteria for RA, who were mostly female (72%) with a mean (SD) age of 55 (15), with 2 (2) comorbidities, and symptom duration of 6 (3) months. At enrollment, all had active disease (DAS28MDA (42%); HDA (53%)), almost all most were initially treated with csDMARDs and 75% with MTX. 44% of women and 36% of men did not reach remission by 12 months. Among women, multivariable results showed obesity more than doubled the likelihood of not achieving remission; other key predictors were minority status, lower education, and higher TJC and fatigue scores at baseline (Table). In men, current smoking was associated with a 3.5 greater odds of not achieving remission in the first year; other predictors included older age, and higher pain. Not using MTX increased the likelihood of not achieving remission in women by 28% and men by 45%. Longer symptom duration and higher ESR were associated with not achieving remission in all. Factors not related to persistent disease activity included family history of RA, RF/ACPA status, erosions, SJC, HAQ and depressive symptoms at baseline.

Conclusion: In this large pan-Canadian cohort of early RA patients receiving guideline-based arthritis care, obesity in women and current smoking in men were the strongest predictors of not achieving remission in the first 12 months followed by non-use of MTX, higher baseline inflammation and longer symptom duration. Additional poor prognostic indicators in women included minority status, lower education, and higher fatigue, whereas older age and greater pain were associated with persistent disease activity in men. Smoking cessation in men and weight reduction in women, and optimizing MTX use may facilitate rapid reduction of inflammation, an essential goal of treatment in early RA.

	Women	Men
N	1179	449
Sociodemographics		
Age (each 10 years)	1.04 (0.95, 1.14)	1.48 (1.22, 1.79)
Minority race	1.46 (1.07, 2.00)	Not selected
Education \leq high school	1.41 (1.09, 1.82)	Not selected

Table . (Cont'd)

	Women	Men
Comorbidities	1.12 (1.05, 1.21)	Not selected
Obese (BMI \geq 30 kg/m ²)	2.06 (1.49, 2.83)	1.65 (0.95, 2.85)
Current smoking	Not selected	3.45 (2.06, 5.77)
RA Characteristics		
Symptom duration (month)	1.10 (1.05, 1.14)	1.15 (1.07, 1.24)
Family history of RA	Not selected	1.62 (0.95, 2.77)
RF+ or ACPA+	1.23 (0.87, 1.75)	Not selected
Erosions	Not selected	Not selected
MTX Use	0.72 (0.54, 0.95)	0.55 (0.33, 0.90)
Oral Steroids (Y vs N)	0.80 (0.60, 1.07)	1.45 (0.92, 2.27)
Parenteral Steroids (Y vs N)	Not selected	Not selected
ESR (mm/h)	1.01 (1.01, 1.02)	1.02 (1.01, 1.03)
Swollen Joint Count (28)	Not selected	Not selected
Tender Joint Count (28)	1.03 (1.01, 1.06)	Not selected
Patient Reported Outcomes		
High depressive symptoms	Not selected	Not selected
Pain (0-10)	Not selected	1.11 (1.03, 1.20)
HAQ-DI (0-3)	Not selected	Not selected
Fatigue (0-10)	1.05 (1.00, 1.09)	Not selected
Fit Statistics		
AIC	1519	535
BIC	1601	581
Area under the curve	0.69	0.74

Disclosure: S. J. Bartlett, UCB, Inc., 5, Lilly, 5, Pfizer, Inc., 5, Novartis, 5; O. Schieir, Other, 2; M. F. Valois, Other, 2; C. Hitchon, Pfizer, Inc., 2; L. Bessette, Amgen Inc., 2, 5, 8, Bristol-Myers Squibb, 2, 5, 8, Janssen, 2, 5, 8, Roche, 2, 5, 8, UCB, Inc., 2, 5, 8, AbbVie Inc., 2, 5, 8, Pfizer, Inc., 2, 5, 8, Merck & Co., 2, 5, 8, Celgene Corporation, 2, 5, 8, Sanofi, 2, 5, 8, Eli Lilly and Co., 2, 5, 8, Novartis, 2, 5, 8; G. Boire, Merck & Co., 8, 9, BMS, 8, 9, Pfizer, Inc., 8, 9, Amgen Inc., 9, AbbVie Inc., 9, Novartis, 9, Eli Lilly and Co., 9, Janssen, 9; C. Thorne, Amgen Inc., 2, 5, 9, Pfizer, Inc., 2, 5, 9, UCB, Inc., 9, AbbVie Inc., 2, 5, 9, Medexus/Medac, 2, 5, 8, Eli Lilly and Co., 9, Merck & Co., 9, Hospira, 5, 9, Janssen, 9, Sanofi Genzyme, 5, 9, Celgene Corporation, 9, CaREBiodam, 9, Centocor, 5, Novartis, 9; J. E. Pope, Amgen Inc., 5, 9, Pfizer, Inc., 5, 9, UCB, Inc., 5, 9, AbbVie Inc., 5, Bristol-Myers Squibb, 5, 9, Actelion, 5, Eli Lilly and Co., 5, Merck & Co., 5, 9, Bayer, 5, 9, Roche, 5, 9, Novartis, 5, Sanofi, 5, Celtrion, 5, Seagen, 9, Genzyme, 5; V. P. Bykerk, Amgen Inc., 5, Pfizer, Inc., 5, UCB, Inc., 5, Bristol-Myers Squibb, 5, Sanofi-Genzyme/Regeneron, 5; E. C. Keystone, Amgen Inc., 2, 5, 8, Bristol-Myers Squibb, 2, F. Hoffmann-La Roche Inc, 2, Janssen, 2, Lilly Pharmaceuticals, 2, Pfizer Pharmaceuticals, 2, Sanofi-Aventis, 2, AstraZeneca, 5, Biotest, 5, Bristol-Myers Squibb, 5, Crescendo Bioscience, 5, F. Hoffmann-La Roche Inc, 5, Genentech Inc, 5, Janssen Inc, 5, Lilly Pharmaceuticals, 5, Merck & Co., 5, 8, Pfizer Pharmaceuticals, 5, UCB, Inc., 5, Bristol-Myers Squibb, 8, F. Hoffmann-La Roche Inc, 8, Janssen Inc, 8, Pfizer Pharmaceuticals, 8, Sanofi Genzyme, 8, UCB, Inc., 8; D. Tin, None; G. Hazlewood, None.

Abstract Number: 2985

Achievement of Remission in Two Early Rheumatoid Arthritis Inception Cohorts Implementing Different Treat-to-Target Strategies

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Session Information

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Session Title: Rheumatoid Arthritis – Diagnosis, Manifestations, and Outcomes VI: Outcomes Reports

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Session Time: 11:00AM-12:30PM

Background/Purpose: Treat-to-target (T2T) has become a key element in the management of rheumatoid arthritis (RA). Several different measures exist to define the preferred treatment target of remission. The objective of the present study was to compare treatment response and achievement of remission during the first 6 months after initiating first disease modifying anti-rheumatic drug (DMARD) therapy in two early RA-cohorts applying different T2T strategies.

Methods: We included 231 patients from the ARCTIC trial (inclusion period 2010-2013) and 434 patients from the observational NOR-VEAC study (inclusion period 2010-2016). Both studies applied a T2T strategy. In ARCTIC the treatment target was deep remission defined as Disease Activity Score (DAS) <1.6 with no swollen joints (44 joints), and

in half the patients, in addition no power-Doppler ultrasound activity. Patients were followed with visits at 1, 2, 3, 4 and 6 months and a fixed T2T escalation protocol. In NOR-VEAC the treatment target was sustained DAS28 remission (<2.6) and treatment was guided by current EULAR treatment recommendations for RA. All patients attended visits at 3 and 6 months, and extra monthly visits could be scheduled if needed. In the present study, included patients fulfilled the 2010 ACR/EULAR criteria for RA, were DMARD-naïve and started treatment with methotrexate (MTX). We used the Simplified Disease Activity Index (SDAI) 50/70/85% response criteria to assess improvement in disease activity from baseline to 3 months. Pearson's chi-squared test was used to compare achievement of SDAI response at 3 months and proportions in remission according to the ACR/EULAR Boolean-criteria, SDAI (≤ 3.3) and DAS28 at 6 months.

Results: At inclusion patients in ARCTIC were significantly younger, had higher disease activity and more were ACPA positive than in NOR-VEAC (age (SD) 51.5 (13.7) vs. 54.4 (13.7) years, $p=0.01$; SDAI 24.9 (13.1) vs. 21.0 (14.2), $p<0.001$; ACPA positivity 82% vs. 69%, $p<0.001$). The median baseline dose of MTX was similar in the two cohorts (15 mg), however at 3 and 6 months the median dose was higher in ARCTIC. More patients in NOR-VEAC had changed DMARD regimen at 3 months (9.2% vs. 0.9%, $p<0.001$) and 6 months (21.3% vs. 19.2%, $p=0.04$). At 3 months, SDAI improvement levels were significantly higher in ARCTIC than in NOR-VEAC (table). Median (25-75% percentile) time to first SDAI remission was 3.0 (1.2-8.1) months in ARCTIC and 6.4 (3.4-12.1) in NOR-VEAC ($p<0.001$). At 6 months, 38% of patients in ARCTIC vs. 30% in NOR-VEAC had reached ACR/EULAR Boolean-based remission, whereas 45% vs. 34% had reached SDAI remission.

Conclusion: In a tight control T2T cohort aiming for deep remission we observed greater improvement in disease activity the first 3 months, shorter time to first remission and a higher proportion of patients in remission according to the ACR/EULAR Boolean-criteria or SDAI at 6 months than in a real-life T2T cohort targeting DAS28 remission.

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Abstract Number: 2986

The Impact of Exercise and Clinical Factors on Perceived Cognitive Function in Patients with Rheumatoid Arthritis: Results from a Prospective Cohort Study

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Table Response levels at 3 months and achievement of remission at 6 months

	ARCTIC n=231	NOR-VEAC n=434	p-value*
3 months			
SDAI 50% response, n (%)	174 (78.4)	159 (60.7)	<0.001
SDAI 70% response, n (%)	127 (57.2)	109 (41.6)	0.001
SDAI 85% response, n (%)	80 (36.0)	67 (24.1)	0.004
6 months			
ACR/EULAR Boolean remission, n (%)	81 (37.9)	121 (30.1)	0.05
SDAI remission, n (%)	94 (43.9)	133 (34.1)	0.02
DAS28 remission, n (%)	140 (64.5)	206 (49.3)	<0.001

*Pearson's chi-squared test

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Background/Purpose: Modifiable lifestyle factors such as inactivity and obesity contribute to cognitive decline in the general population, but little is known about how these factors may contribute in the setting of a chronic inflammatory condition such as Rheumatoid Arthritis(RA). We studied the clinical and functional risk factors related to a decrease in perceived cognition function in patients with longstanding RA.

Methods: We collected data on joint exams, serologies and detailed clinical, psychological, exercise and functional outcomes over 10 years in a prospective academic RA cohort. Self-reported memory, concentration and word-finding difficulties were assessed yearly by questionnaire and graded from “never” to “often”. A repeated measures logistic regression model using pairs of years examined the role of exercise (defined as those meeting the Dept. of HHS physical activity guidelines of 75 minutes of vigorous or 115 minutes of moderate aerobic activity per week), Body Mass Index (BMI), sleep and depression (MHI-5) in the first year (T0) to the progression of cognitive complaints described as “often” 1 year later (T1). Regression models also adjusted for other clinical and demographic variables including DAS-CRP3 score, DMARD and corticosteroid use.

Results: Of 1219 RA subjects, 127 (10.4%) described either poor memory, poor concentration or word finding difficulties as affecting them “often” at the first study visit. Only the perception of memory difficulties increased over time ($R^2=0.64$, test for trend, $p=0.006$). RA patients, (mean age. 56.5 years, 82% female, 58% with a college education) were less likely to develop word finding difficulties and impaired concentration if they met the Dept. of HHS physical activity recommendations ($p<0.0001$; $p=0.0002$, respectively). Concentration worsened among those RA patients who were female ($p=0.03$), had a higher DAS28-CRP3 score ($p=0.04$), and higher MHI-5 depression scores ($p=0.05$); RA patients taking an anti-TNF therapy were less likely to develop worsened memory complaints ($p=0.0004$). Sleep, BMI, fatigue and medication use, such as methotrexate or corticosteroids, were not independently associated with a worsening of any of the cognitive complaints, adjusting for other covariates.

Conclusion: Clinical factors such as lower disease activity and anti-TNF use reduced the likelihood of worsened memory and concentration over time. However, meeting the Dept. of HHS guidelines for physical activity was protective against an increase in concentration and word retrieval difficulties. Our study suggests potential modifiable risk factors for the prevention of cognitive dysfunction in RA.

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RAPID Remission during the First Year in EARLY ACTIVE Rheumatoid Arthritis Is Associated with Better 5 YEARS Structural Damage Outcomes

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Background/Purpose: Remission is arguably the best and ultimate therapeutic goal in early rheumatoid arthritis (ERA). ERA patients (pts) who reach rapid and sustained remission are likely to retain good radiographic outcomes. The aim of this study was to evaluate the radiographic progression and the newly pathological joints in a Belgian ERA cohort during a

Table. Multivariable models of Demographic and Clinical Factors Associated with Worsened Cognitive Dysfunction (N = 1092)*

Variable	Worse Memory			Worse Word Finding			Worse Concentration		
	beta	SE	p value	beta	SE	p value	beta	SE	p value
Dept. HHS Physical Activity Guidelines**	-0.06	0.1	0.57	-0.47	0.1	0.0001	-0.19	0.05	0.0002
TNF Use	-0.4	0.31	0.0004	0.13	0.23	0.57	-0.28	0.35	0.06
DAS28	0.07	0.04	0.07	0.03	0.05	0.58	0.07	0.03	0.04
Gender (female)	1.09	0.61	0.08	0.15	0.49	0.76	1.6	0.74	0.03
Depression (FSMH15) (0-15)	0.01	0.01	0.07	0.01	0.01	0.41	0.01	0.01	0.05
Methotrexate Use	-0.15	0.10	0.42	-0.16	0.22	0.47	0.06	0.17	0.71
Steroid Use	-0.15	0.19	0.42	0.03	0.21	0.9	0.17	0.1	0.1
BMI	-0.001	0.02	0.95	0.004	0.02	0.8	-0.02	0.02	0.44
Education (College degree or more)	-0.14	0.33	0.67	-0.34	0.35	0.33	-0.17	0.37	0.64
Sleep Difficulties (MDHAQ) (0-3)	0.00	0.12	0.51	0.03	0.11	0.8	0.08	0.06	0.22
Fatigue (MDHAQ) (0-100)	-0.001	0.003	0.73	0.0004	0.003	0.88	-0.007	0.002	0.2
Age, years	0.003	0.01	0.82	-0.01	0.01	0.39	-0.01	0.01	0.37

*days between questionnaires adjusted

**meeting the Dept. HHS recommendation for physical activity

5 years follow-up and to correlate the Sharp score index with different indices of clinical remission observed during the first year.

Methods: This was a retrospective analysis of mean (95% CI) change from baseline (BL) to 5 years Sharp/Van der Heijde (SVdH) scoring according to DAS28, SDAI, CDAI and ACR/EULAR Boolean remission scores for pts at Month 3, 6 and 12. Newly pathological joint defined by a SVdH score of 0 at BL and a score greater than or equal to 1 at follow up were analyzed as a secondary objective. 133 ERA pts naïve to DMARDs therapies were analyzed (100 women and 33 men) with a mean age (49.9 +/- 13.3), mean DAS 28-CRP (4.89 +/- 1.3), mean HAQ (1.25 +/- 0.67), mean SDAI (28.4 +/- 15.5), mean CDAI (25.8 +/- 14.8) and mean SVdH (6 +/- 14). Differences were statistically tested using t tests.

Results: ERA ps were divided in 2 groups : “Xrays Stable” if the delta of SVdH score was ≤10 (n=90) or “Xrays Progressive” if the delta of SVdH score was >10 (n=43). As expected, number of pts with ACPA and BL erosion was higher in the Xrays Progressive group. No significant BL characteristics differences were observed for DAS28CRP, CDAI, SDAI, HAQ, smoking status, swollen joint count or CRP. % of pts reaching DAS28CRP, SDAI, CDAI and Boolean remission rates observed at 6 months were statistically significant different between groups (fig). Boolean remission was the most stringent test with a statistical difference observed also at month 3 (specificity 90.5%, sensitivity 32.2%). There was no significant difference in clinical responses between subgroups of pts who developed new pathological joints and those who did not.

Conclusion: These results demonstrate that remission is an important therapeutic goal to protect joint damage in ERA. All remission criteria were able to predict the radiological prevention. The identification of a new pathologic joint is not associated with lack of response.

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Abstract Number: 2988

Characteristics and Outcomes in a Prospective Cohort of Patients with Aortitis Diagnosed Following Surgical Resection

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Session Information

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Session Title: Vasculitis III: Clinical Subtypes and Outcomes

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Background/Purpose: Aortitis, characterized by inflammation of the aorta, is broadly divided into infectious and non-infectious aortitis (NIA); the latter group consists of a number of inflammatory conditions (most commonly giant cell arteritis [GCA] and rheumatoid arthritis [RA]) and idiopathic aortitis (IA), when an underlying inflammatory cause cannot be identified. Retrospective data depicts a high rate of development of subsequent vascular complications in NIA, but corresponding prospective studies are lacking.

Methods: We analyzed patients enrolled in a prospective observational cohort of patients with histologic aortitis, who were diagnosed at The Ottawa Hospital between 2013-2017 following surgical repair of thoracic aortic aneurysms or dissections. Upon referral, triggered by a positive histopathologic specimen, patients were assessed for evidence of inflammatory or infectious disease and presence of additional vascular lesions. Consenting patients with NIA were followed prospectively with periodic clinical assessments and laboratory and radiographic studies. Aortic outcomes during follow-up included 'significant events', defined as new thoracic or abdominal aortic aneurysms, dissection/rupture, or need for further surgery, as well as aortic branch ectasias, aneurysms, and stenosis. Fisher's exact and the Mann-Whitney tests were used for significance calculations.

Results: Sixteen patients were included; 9 had IA and 7 had secondary aortitis (SA), specifically GCA (5) and RA (2). IA patients were more likely to have smoked (100% vs. 43%, $p=0.02$), and had more associated arch or descending aortic aneurysms on pre-operative baseline imaging compared to SA (6 vs. 0, $p=0.01$). At median 3.6-years of follow-up, 8 patients had 13 significant aortic events (9 and 4 events in 5 IA and 3 SA patients, respectively) (Table 1). The incidence of aortic dissection or second intervention, and the average annual rate of growth of descending aortic aneurysms, was higher in the first year post-surgery, compared to subsequent years. Immunosuppressive therapy did not seem to affect the outcomes, while elevated inflammatory markers during follow-up seemed to correlate with accumulation of severe aortic damage. No IA patients were diagnosed with a defined inflammatory condition at follow-up.

Conclusion: This is the first reported prospective study in patients with surgically diagnosed aortitis. Within the statistical limitations of a small cohort, we report a high incidence of aortic complications, especially in the early post-surgical period, and unaltered by immunosuppression. Studies of larger sample size and longer follow-up will be needed to corroborate these findings.

Table 1 Cumulative number of patients with (and total number of) aortic events over entire duration of follow-up.

Event	IA (N=9)	SA (N=7)	Total (N=16)	Events By Year (1 st /2 nd /subsequent)
Median follow-up, years	4.1	3.2	3.6	
New thoracic aortic aneurysm	3 (3)	2 (2)	5 (5)	1/2/2002
New abdominal aortic aneurysm	1 (1)	0	1 (1)	0 / 0 / 1
New branch ectasia/aneurysm	2 (2)	2 (2)	4 (4)	2/1/2001
New stenosis or occlusion	3 (3)	0	3 (3)	3 / 0 / 0
Aortic dissection/rupture	2 (2)	1 (1)	3 (3)	3 / 0 / 0
Further surgical aortic intervention	2 (3)	1 (1)	3 (4)	3/1/2000
Significant aortic events*	5 (9)	3 (4)	8 (13)	8/3/2002

* 'Significant aortic events' is a composite outcome that includes new aneurysms, dissection/rupture, or further interventions.

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Cardiac Involvement in Systemic Vasculitis: A Retrospective Pathological Study

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Background/Purpose: Even though clinically significant heart involvement is rare, cardiovascular complications are leading causes of death in systemic vasculitis (SV). The comprehensive analysis of histopathologic findings is needed to elucidate the driving mechanisms of increased cardiovascular risk in SV. The purpose of this study was to investigate the variation of cardiac pathological findings in autopsy cases of Takayasu arteritis (TAK), polyarteritis nodosa (PAN) and granulomatosis with polyangiitis (GPA).

Methods: Microscopic examinations of the heart were performed in 108 autopsy cases of SV over a period of 15 years, of which 37 were PAN, 60 – TA and 11 – GPA.

Results: The destructive-productive vasculitis affecting myocardial, epicardial medium and small-sized arteries was observed in 81.1% cases of PAN. The most common acute change was panarteritis with intramural, and perivascular lymphocytes, and macrophages infiltrates. The most remarkable lesions in coronary arteries were nodules visible to the naked eye along coronary arteries (30%). In cases of chronic course of PAN, intimal hyperplasia due to proliferation of endothelial cells has been identified. In 5 (16.7%) cases, luminal occlusion due to intimal proliferation, fibrosis and thrombus formation led to the myocardial infarction. The pathological manifestation of cardiac involvement in PAN included the left ventricular hypertrophy due to renovascular arterial hypertension in 26 cases (70.3%). Interstitial myocarditis was observed in 4 cases (10.8%).

The pathological changes in coronary vessels have been found in all cases of GPA. The destructive-productive vasculitis affecting intramyocardial small arteries, arterioles, and capillaries was the most common. The acute stage has been characterized by abnormalities of the vessel wall from mucoid swelling to fibrinoid necrosis. The chronic lesions were characterized by intimal hyperplasia, fibrosis, hyalinosis of the vessels with their luminal narrowing. The most common lesion of myocardial interstitial matrix was extravascular granulomatous inflammation.

Our data show high frequency (76.7%) of pathological changes of coronary arteries in TAK such as intimal hyperplasia, granulomatous arteritis, and coronary atherosclerosis. Intimal hyperplasia consists of areas of musculo-fibrous proliferation or multi-layer scleral hyaline plaques. This pillow-like thickening of the intima around of the coronary orifices leads to their luminal narrowing. The coronary orifices were the site most commonly affected by TAK. Luminal narrowing of coronary arteries with coronary flow reduction led to subsequent fatal myocardial infarction in 15 cases (25%). Coronary atherosclerosis of varying severity was observed in 35 cases (58, 3%). The most common location of atherosclerotic deposits was regions of the pillow-like thickening of the intima around of the coronary orifices.

Conclusion: Our data suggest that cardiac involvement is common in SV with a wide range of acute and chronic changes and can be potentially life-threatening.

Disclosure: O. Zimba, None; M. Bahrii, None.

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Do Polymyalgia Rheumatica Patients Have an Increased Risk of Cardiovascular Events?: A Matched-Control Study

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Background/Purpose: Cardiovascular (CV) risk in chronic inflammatory diseases is increased. Polymyalgia Rheumatica (PMR) is an inflammatory condition that might have a prolonged course. Our objective was to compare incidence rates of cardiovascular events (CVE) in patients with PMR with matched controls from a university hospital-based health management organization (HMO).

Methods: PMR patients (fulfilling ACR 2012 criteria) diagnosed after the year 2000 from the HMO were identified and matched (1:2) by date of birth and sex with controls from the same HMO. Those PMR patients with CVE before PMR diagnosis were excluded. Controls with CVE before its correspondent case date of diagnosis were also excluded. Patients were followed until they voluntarily left the HMO, a CVE occurred, the end of study (May 1st 2018), or death. Electronic

medical records were manually reviewed and demographic, clinical and treatment data were collected. Incidence rates per 1000 person-years (PY) of each CVE were calculated and compared between groups. A multivariate cox regression analysis was performed to identify factors associated with CVE.

Results: 868 PMR patients and 1736 controls were included and contributed 10865.2 and 12654.6 PY of follow up respectively. Patients' characteristics are shown in table 1. PMR patients were 682 females (78.7, 95% CI 75.8-81.3) with a mean age at diagnosis of 75.2 years (SD 7.9). Overall CVE incidence rate was lower in PMR patients than controls: 10.3 per 1000 PY (95% CI 8.6-12.2) versus 14.8 per 1000 PY (95% CI 12.8-16.8) respectively, $p = 0.001$. Cardiovascular death was also less frequent in PMR patients than in controls: 0.6 per 1000 PY (95% CI 0.2-1.2) versus 1.9 per 1000 PY (95% CI 1.2-2.8) respectively, $p=0.02$. When analyzing each CVE, stroke and abdominal aneurism incidence rates were higher in controls than PMR (table 1) while other CVE were similar across groups. In the multivariate cox regression analysis, men (OR 2.2, 95% CI 1.7-2.8, $p < 0.001$) and arterial hypertension (OR 1.5, 95% CI 1.1-1.9, $p 0.003$) were associated with an increased CV risk, while a PMR diagnosis was protective (OR 0.4, 95% CI 0.3-0.5).

Conclusion: Despite having more traditional cardiovascular risk factors and having been followed longer than controls, CVE were more frequent in the control group than in PMR patients. This may be due to a closer medical follow-up.

	PMR patients(n= 868)	PMR controls(n= 1736)	p
Female, n (% , 95% CI)	682 (78.7, 75.8-81.3)	10391 (80.1, 78.2-81.9)	0.38
Arterial hypertension, n (% , 95% CI)	598 (68.1, 65.8-71.9)	10149 (66.2, 63.9-68.4)	0.15
Diabetes, n (% , 95% CI)	64 (7.4, 5.8-9.3)	92 (5.3, 4.3-6.4)	0.04
Ever Smoker, n (% , 95% CI)	194 (22.3, 19.7-25.2)	281 (16.2, 14.5-18)	<0.001
Dyslipidemia, n (% , 95% CI)	418 (48.3, 44.9-51.6)	532 (30.6, 28.5-32.8)	<0.001
Obesity, n (% , 95% CI)	135 (15.6, 13.3-18.1)	113 (8.2, 7-9.6)	<0.001
Aspirin user, n (% , 95% CI)	126 (14.5, 12.3-17)	149 (8.6, 7.3-9.9)	<0.001
Thoracic aneurism, n (% , 95% CI)	44 (5.1, 3.8-6.7)	52 (3.0, 2.3-3.9)	0.01
Thoracic aneurism, incidence rate, per 1000 patient-years (95% CI)	4.1 (3-5.4)	4.2 (3.2-5.4)	0.47
Abdominal aneurism, n (% , 95% CI)	1 (0.1, 0.02-0.8)	10 (0.6, 0.3-1.1)	0.09
Abdominal aneurism, incidence rate, per 1000 patient-years (95% CI)	0.1 (0.01-0.74)	0.8 (0.4-1.5)	0.01
Stroke, n (% , 95% CI)	29 (3.3, 2.3-4.8)	76 (4.4, 3.5-5.4)	0.21
Stroke, incidence rate, per 1000 patient-years (95% CI)	2.7 (1.9-3.9)	6.1 (4.8-7.5)	<0.001
Coronary event, n (% , 95% CI)	30 (3.5, 2.4-4.9)	40 (2.3, 1.7-3.1)	0.09
Coronary event, incidence rate, per 1000 patients-years (95% CI)	2.8 (1.9-3.9)	3.2 (2.4-4.3)	0.28
Peripheral arteriopathy, n (% , 95% CI)	19 (2.2, 1.4-3.4)	17 (0.9, 0.6-1.6)	0.01
Peripheral arteriopathy, incidence rate, per 1000 patients-years (95% CI)	1.7 (1.1-2.7)	1.3 (0.9-2.4)	0.21
Any Cardiovascular Event, n (% , 95% CI)	112 (12.9, 10.8-15.3)	187 (10.8, 9.4-12.3)	0.11
Any Cardiovascular Event, incidence rate, per 1000 patient-years (95% CI)	10.3 (8.6-12.2)	14.8 (12.8-16.8)	0.001
Cardiovascular death, n (% , 95% CI)	6 (0.7, 0.3-1.5)	24 (1.4, 0.9-2.1)	0.12
Cardiovascular death incidence rate per 1000 patient-years, (95% CI)	0.6 (0.2-1.2)	1.9 (1.2-2.8)	0.02

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Malignancies In Giant Cell Arteritis- A Population-Based Cohort Study

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Vasculitis III: Clinical Subtypes and Outcomes

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Session Time: 11:00 AM-12:30 PM

Background/Purpose: To investigate the cancer risk in patients with biopsy-proven giant cell arteritis (GCA).

Methods: The study population consisted of 830 patients (74 % women) with biopsy-proven GCA diagnosed between 1997 and 2010. The mean age at diagnosis of GCA was 76.3 years, 77.2 years for men and 75.8 for women. The cohort was cross-linked with data from the Swedish Cancer Registry. The patients were followed from GCA diagnosis until death or

December 31, 2013. All malignancies that occurred throughout the observation time were identified. Malignancies were divided into two groups; those preceding the date of the GCA diagnosis and those subsequently diagnosed. As a measure of relative risk, the age- and sex standardized incidence ratios (SIR) were calculated compared to the background population, i.e. the ratio of the incidence of observed cancer cases after the diagnosis of GCA to that of the expected number, based on cancer rates in the background population. SIRs were calculated for all types of cancer combined and for site-specific cancers.

Results: 107 patients (13%) were diagnosed with a total of 133 malignancies after the onset of GCA. Malignancies in the same organ/system were excluded, and thus 118 malignancies were included in SIR calculation. The overall risk for cancer after the GCA diagnosis was not increased with a SIR 0.98 (95% CI 0.81 – 1.17). However, there was an increased risk for myeloid leukemia SIR 2.31 (95% CI 1.06 – 4.39) and a reduced risk for breast cancer SIR 0.33 (95% CI 0.12 – 0.72) and upper gastrointestinal (GI) tract cancer SIR 0.16 (95% 0.004- 0.91). Rates of other site-specific cancers, e.g. cancer of the skin, lower GI tract, prostate or respiratory system, were not different from the expected (Table 1).

Conclusion: The overall risk for cancer in GCA patients was not increased compared to the background population. However, we found an increased risk for leukemia and a decreased risk for breast and upper gastrointestinal tract cancer. Possible explanations for these findings include effects of inflammation on tumor genesis and differences in other exposures that contribute to cancer risk. For example, some traditional risk factors for breast cancer, such as obesity, diabetes and late menopause, have been reported to be reduced in patients with GCA.

Table 1 Site-specific and total standardized incidence ratio of cancer in 830 patients with biopsy-proven GCA

Malignancy type	Observed, n	Expected, n	SIR	95% CI
Upper GI tract	1	6.1	0.16	0.00-0.91
Lower GI tract	18	18.1	0.99	0.59-1.57
Liver, Gallbladder, Pancreas, Peritoneum	0	4		
Respiratory	8	10.4	0.76	0.33-1.51
Breast	6	18.1	0.33	0.12-0.72
Female Reproductive system	8	7.3	1.10	0.47-2.16
Prostate	15	11.5	1.30	0.73-2.15
Male Reproductive system	0	0.2		
Kidneys	2	2.1	0.96	0.12-3.50
Urinary tract without kidneys	6	7.1	0.80	0.31-1.85
Skin	34	24.9	1.36	0.94-1.91
Eyes	0	0.2		
CNS	1	1.3	0.76	0.02-4.30
Endocrine system	0	1.7		
Sarcomas	0	0.8		
Unspecified	4	5	0.80	0.22-2.07
Lymphoma	3	4.3	0.69	0.14-2.03
Multiple Myeloma	2	1.7	1.17	0.14-4.25
Leukemia	9	3.9	2.31	1.06-4.39
Myelofibrosis	1	0.5	2.12	0.05-11.85
Total	118	120.8	0.98	0.81-1.17

Disclosure: P. Stamatis, None; C. Turesson, None; M. Willim, None; J. A. Nilsson, None; M. Englund, None; A. Mohammad, None.

Abstract Number: 2992

Are Specific Vascular Symptoms in Takayasu's Arteritis Reflective of Vascular Inflammation, Vascular Damage, or Both?

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Background/Purpose: Patients with Takayasu's arteritis (TAK) can experience symptoms due to vascular inflammation or vascular damage. The study objective was to investigate whether specific vascular symptoms are more closely associated with vascular disease activity measured by ^{18}F -fluorodeoxyglucosepositron emission tomography (FDG-PET) or vascular damage assessed by magnetic resonance angiography (MRA).

Methods: Patients with TAK were recruited into a prospective observational cohort. Participants underwent clinical assessment and standardized imaging assessment (FDG-PET and MRA) within a 24-hour period, blinded to each other. Vascular disease activity was defined as arterial FDG uptake > liver by visual assessment. Vascular damage was defined as either stenosis, occlusion, or aneurysm in specific arterial territories on MRA. Clinical symptoms present on the day of evaluation (carotidynia; frontal headache; arm claudication) were compared to imaging findings in corresponding arterial territories. Generalized symptoms (headache; dizziness; history of CNS event defined as TIA/stroke or syncope) were studied in association with the number of affected neck vessels by MRA. Performance characteristics were calculated and the association between clinical symptoms and imaging features was assessed by Fisher's exact test.

Results: 51 participants contributed data from 92 study visits. For FDG-PET, the sensitivity (SN) of specific clinical symptoms ranged from 16% to 33% and specificity (SP) from 74% to 98%. For MRA the SN of the same symptoms ranged from 6% to 71% and SP from 79% to 100%. Details of specific associations are shown in the Table. Carotidynia was significantly associated with carotid activity by FDG-PET ($p<0.01$) but not carotid damage by MRA($p=0.18$). Frontal headache was significantly associated with both carotid activity by FDG-PET ($p<0.01$) and carotid damage by MRA ($p=0.04$). Arm claudication was significantly associated with subclavian damage by MRA($p<0.01$) but not subclavian activity by FDG-PET ($p=0.47$). Headache ($p=0.02$) and history of CNS events ($p<0.01$) was significantly associated with damage to ≥ 2 neck arteries, and dizziness ($p<0.01$) was associated with damage to ≥ 3 neck arteries.

Conclusion: Absence of clinical symptoms does not rule out vascular abnormalities by FDG-PET or MRA, but presence of symptoms is often associated with imaging abnormalities. Certain features are more closely associated with FDG-PET activity while others are more closely linked to vascular damage. Complaints of headache, dizziness, and CNS events are associated with the burden of vascular pathology in the neck arteries. These findings have direct clinical implications and may inform the development of disease activity indices in TAK.

Table. Association of Clinical Symptoms with Imaging Findings in Takayasu's Arteritis

Symptom	Arterial territory	Image Study	TN	TP	FN	FP	P value	Sensitivity (95% CI)	Specificity (95% CI)
Carotidynia	L carotid artery	FDG-PET	122	8	17	5	<0.01	32% (15-54%)	96% (91-99%)
	R carotid artery	MRA	66	12	82	4	0.18	13% (7-21%)	94% (86-98%)
Frontal headache	L carotid artery	FDG-PET	125	4	21	2	<0.01	16% (5-36%)	98% (94-100%)
	R carotid artery	MRA	70	6	88	0	0.04	6% (2-13%)	100% (95-100%)
Arm claudication	L subclavian artery	FDG-PET	95	8	16	34	0.47	33% (16-55%)	74% (65-81%)
	R subclavian artery	MRA	67	38	49	8	<0.01	44% (33-55%)	89% (80-95%)
Any headache	≥ 2 vs <2 affected neck arteries (carotids, vertebrals)	MRA	45	12	12	12	0.02	50% (29-71%)	79% (66-89%)
History of CNS event (TIA, stroke, or syncope)	≥ 2 vs <2 affected neck arteries (carotids, vertebrals)	MRA	45	17	7	12	<0.01	71% (49-87%)	79% (66-89%)
Dizziness	≥ 3 vs <3 affected neck arteries (carotids, vertebrals)	MRA	61	7	11	2	<0.01	39% (17-64%)	97% (89-100%)

TN = True Negative; TP = True Position; FN = False Negative; FP = False Position; CNS = Central Nervous System; TIA = Transient Ischemic Attack

Disclosure: D. Michailidou, None; J. S. Rosenblum, None; M. A. Ahlman, None; J. Marco, None; P. C. Grayson, None.

Abstract Number: 2993

Vascular Involvement in Behcet's Syndrome May be Associated with Subclinical Atherosclerosis

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Background/Purpose: Behcet's Syndrome (BS) is a vasculitic process which is characterized by recurrent oral and genital aphthous ulcerations, ocular, vascular, neurological, and gastrointestinal involvement. Although the exact pathogenic mechanism for vascular lesions in BS patients is still unclear, endothelial dysfunction may be important in the development of these lesions. Endothelial dysfunction is accepted as the initial lesion in atherogenesis and recent studies have shown that the increase in carotid intima media thickness (cIMT) is significantly associated with endothelial dysfunction. In this study, it was aimed to determine the frequency of subclinical atherosclerosis (ATS) according to vascular involvement in BS patients.

Methods: A hundred patients with BS and 30 healthy controls (HC) were included in this study. Participants with a history of cardiovascular (CV) events, type 1 or 2 diabetes mellitus, chronic kidney disease, and malignancy were excluded. Bilateral cIMTs were evaluated by using B-mode ultrasonography (US) in BS patients and compared with those in controls. Subclinical atherosclerosis was defined by CIMENT \geq 0.9 mm or \geq 1 carotid plaque which accepted as US positive group.

Results: The demographic characteristics, cardiovascular risk factors and US findings of patients with BS and HC are listed in table1. cIMT in BS patients was higher compared to HC (0.78 ± 0.21 mm versus 0.69 ± 0.13 mm; $p=0.006$). Thirty two (32%) BS patients, and two (6,7%) HC had subclinical atherosclerosis (BS versus HC: $p=0.006$). cIMT in BS patients with vascular involvement was higher than nonvascular group (0.83 ± 0.21 versus 0.75 ± 0.21 ; $p=0.072$). Comparison of disease characteristics and traditional CV risk factors of US positive and US negative BS patients are shown in Table 2. In regression analysis, older age and having vascular disease were independently associated with subclinical ATS (Table 3).

Conclusion: This study showed that cIMT measurements were higher in BS patients than HC and also significantly higher in BS patients with vascular group than nonvascular group. Vascular involvement in BS patients is an independent risk factor for the development of ATS. Therefore, BS patients with vascular involvement should be carefully monitored for the development of CV disease.

Table 1 The demographic characteristics, CV risk factors, and carotid US findings of patients with Behcet's syndrome and healthy controls

	BS (n=100)	HC (n=30)	p value
Age, years	45.9 \pm 12.0	41.8 \pm 12.2	0.097
Female, n. (%)	62 (62)	18 (60)	0.834
Hypertension, n. (%)	17 (17)	7 (23.3)	0.433
Ever smoked, n. (%)	42 (42)	10 (33.3)	0.395
ESR, mm/hour	14.45 \pm 12.74	10.93 \pm 7.33	0.152
CRP, mg/liter	7.03 \pm 14.39	3.40 \pm 4.63	0.031
LDL cholesterol*, mg/dl	120.7 \pm 34.1	116.0 \pm 22.6	0.433
Low HDL cholesterol*, n. (%)	39 (52.7)	11 (47.8)	0.683
Total cholesterol*, mg/dl	195.4 \pm 42.1	184.9 \pm 23.8	0.137
Total cholesterol/HDL cholesterol*	4.29 \pm 1.02	3.97 \pm 0.88	0.176
Triglycerides >150 mg/dl*, n. (%)	25 (33.8)	4 (16)	0.091
Right CIMENT	0.79 \pm 0.25	0.70 \pm 0.14	0.011
Left CIMENT	0.77 \pm 0.21	0.68 \pm 0.14	0.029
Mean CIMENT	0.78 \pm 0.21	0.69 \pm 0.13	0.006
CIMENT \geq 0.90 mm, no. (%)	29 (29)	1 (3.3)	0.003
CIMENT \geq 0.90 mm and/or carotid plaque, n. (%)	32 (32)	2 (6.7)	0.006
Carotid plaques, no. (%)	8 (8)	1 (3.3)	0.684

* Lipid profile was available for 99 patientsTable 2 Characteristics of US positive and US negative BS patients

	US positive (n=32)	US negative (n=68)	p value
Age, years	53.2 \pm 9.6	42.5 \pm 11.5	< 0.001
Female, no. (%)	18 (56.3)	44 (64.7)	0.416
Disease duration, years	14.9 \pm 10.9	12.9 \pm 9.5	0.367
BSAS	14.8 \pm 9.8	14.3 \pm 9.2	0.792
Vascular Behcet disease, no. (%)	15 (46.9)	18 (26.5)	0.043
Posterior uveitis and retinal vasculitis ever, no. (%)	6 (18.8)	13 (19.1)	0.965
Major organ involvement, no. (%)	20 (62.5)	28 (41.2)	0.046
Glucocorticoid usage ever, no. (%)	10 (34.5)	28 (39.4)	0.643

Table . (Cont'd)

	US positive (n=32)	US negative (n=68)	p value
Immunosuppressive therapy, no. (%)	14 (43.8)	25 (36.8)	0.504
Hypertension, no. (%)	8 (25)	9 (13.2)	0.144
Ever smoked, no. (%)	10 (31.3)	32 (47.1)	0.135
ESR, mm/hour	17.6 ± 18.2	13.0 ± 8.9	0.177
CRP, mg/liter	7.27 ± 12.84	6.92 ± 15.15	0.912
LDL cholesterol*, mg/dl	121.2 ± 34.8	120.5 ± 34.1	0.934
Low HDL cholesterol*, no. (%)	15 (57.7)	24 (50)	0.527
Total cholesterol*, mg/dl	196.8 ± 36.7	194.7 ± 43.7	0.836
Total cholesterol/HDL cholesterol*	4.5 ± 1.0	4.2 ± 1.0	0.174
Triglycerides >150 mg/dl*, no. (%)	10 (38.5)	15 (31.3)	0.531

* Lipid profile was available for 99 patients Table 3 Multiple logistic regression analysis for the co-factors that affect subclinical atherosclerosis

	Univariate			Multivariate				
	p	OR	95% CI	B	SE	p	OR	95 % CI
Hypertension	0.150	2.185	0.754-6.333					
Triglyceride	0.057	1.008	1.000-1.016					
Total cholesterol/HDL	0.174	1.405	0.860-2.295					
Major organ involvement	0.014	3.367	1.285-8.827					
ESR	0.107	1.028	0.994-1.063	0.032	0.019	0.100	2.708	0.994-1.072
Age	< 0.001	1.096	1.045-1.149	0.096	0.030	0.001	1.101	1.038-1.167
Vascular Behcet disease	0.046	2.451	1.018-5.902	1.125	0.610	0.040	3.491	1.056-11.537

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Abstract Number: 2994

Costs Associated with Non-Medical Switching from Originator to Biosimilar Etanercept in Patients with Rheumatoid Arthritis in the UK

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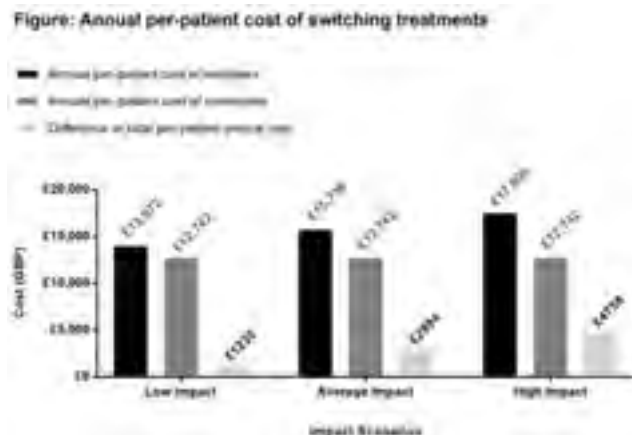
Session Time: 11:00AM-12:30PM

Background/Purpose: To estimate the cost impact of non-medical switching from originator etanercept (ETN) to biosimilar ETN in patients with rheumatoid arthritis (RA) in the UK.

Methods: A cohort-based decision tree model was developed with a 1-year time horizon. The model population included patients with stable RA who responded to originator ETN treatment and had no change in treatment in the prior 6 months. Patients could undergo a non-medical switch to an ETN biosimilar (first switch) and then switch again if required (second switch) after 3-6 months. Data on the proportion of patients switching therapies, baseline healthcare resource use (including visits to rheumatologists, nurses, medical imaging, blood tests, hospitalization and emergency room visits), and impact of switching on resource use was sourced from a survey of 150 rheumatologists from EU5 markets. The average impact of switching (based on mean values for change in resource utilization due to switching) was calculated as per-patient costs, with low- and high-impact scenarios (based on lower and upper values of the 95% confidence intervals for change in resource utilization due to switching) also modelled as sensitivity analyses. Cost data were sourced from published UK sources.

Results: The model assumed that 5000 patients were treated with originator ETN, with 1259 (25.2%) switching to a biosimilar. Of those, 875 (69.5%) switched to SB4 and 384 (30.5%) to GP2015. After 3 months, 26.3% of patients who switched treatments did so again: 8.3% back to originator ETN, 3.8% to the other ETN biosimilar, and 14.2% to another biologic (abatacept [ABA], adalimumab or tocilizumab). Annual per-patient cost of continuous originator ETN treatment (drug and other healthcare costs) was £12,742. Originator ETN was more expensive than SB4 or GP2015 (annual per-patient costs of £9295 vs £8528 and £8365, respectively). Across all 3 impact scenarios, switching was more costly than continuous originator ETN (Figure). All switching treatment chains had higher overall annual per-patient costs than continuous originator ETN treatment. Switching from originator ETN to GP2015 or SB4 resulted in the lowest impact of

switching vs. continuous originator ETN (mean [low scenario, high scenario] values of £1120 [£110, £2131] and £1283 [£272, £2293], respectively). The highest impact of switching occurred following a second switch to ABA. Cost impact of the ETN→GP2015→ABA treatment chain vs. continuous originator ETN was £10,189 [£6244, £14,134], and for the ETN→SB4→ABA treatment chain was £10,230 [£6285, £14,174].



Conclusion: Non-medical switching can result in increased costs to the healthcare payer because of increased healthcare resource use following switching.

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Healthcare Cost of Potential Glucocorticoid-Associated Adverse Events in Patients with Giant Cell Arteritis

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Background/Purpose: To quantify the healthcare expenditures associated with oral glucocorticoids-related-adverse events (OGCs-AEs), among patients in the US with giant cell arteritis (GCA) using claims data from MarketScan[®] Commercial and Medicare Supplemental Databases.

Methods: Patients age ≥50 years with GCA and at least one OGC prescription fill, during 1/1/2009-6/30/2014 (first OGC claim after GCA diagnosis date = index date) were selected. Cumulative dose of OGCs was measured during the 1-year post-index period. Patients were stratified in four cohorts (>0 to ≤2,607 mg, >2,607 to ≤4,800 mg, >4,800 to ≤7,200 mg, >7,200 mg) based on the distribution of OGC exposure. Incidence of potential AEs and AE-related direct healthcare costs (2016 USD) were also assessed during the 1-year post-index period. A generalized linear model with log link and gamma distribution was used to evaluate the association between the log of cumulative dose of OGCs and AE-related direct healthcare costs, adjusting for baseline characteristics.

Results: The 1,602 GCA patients (mean age 73, 69% females) had mean cumulative OGC dose post-index of 5,806 mg (median=4,800 mg), with most exposure occurring in the first 6 months. The proportion of patients with any potential OGCs-AEs was 36.5% overall (n=584) and increased as cumulative dose increased (30.7%-45.3% across quartiles). Unadjusted mean AE costs for patients with an AE was \$12,818 (median=\$1,844). In the multivariable model, increasing OGC dose was associated with increasing AE-related healthcare costs (cost ratio=1.38 [95% CI 1.16-1.64] per 1 unit

increase in log (cumulative OGC dose), $p < 0.001$). Mean (median) predicted AE costs for the dosing quartiles were: \$4,389 (\$2,749) for >0 to $\leq 2,607$ mg, \$5,176 (\$3,009) for $>2,607$ to $\leq 4,800$ mg, \$5,576 (\$3,633) for $>4,800$ to $\leq 7,200$ mg, \$6,609 (\$4,447) for $>7,200$ mg.

Conclusion: Rates of OGCs-AEs tended to increase with an increase in cumulative OGC dose, which resulted in increased healthcare costs. These results highlight the need for efficacious therapies that reduce the exposure and potential risks associated with OGCs.

Disclosure: J. H. Best, Genentech, Inc., 3; A. Kong, IBM Watson Health, 3; D. Smith, IBM Watson Health, 3; I. Abbass, Genentech, Inc., 3; M. Michalska, Genentech, Inc., 3.

Abstract Number: 2996

The Economic Burden of Systemic Lupus Erythematosus (SLE) within a Medicaid Cohort Stratified By Disease Severity

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Background/Purpose: Estimates of the economic burden of SLE within economically disadvantaged populations in the US are limited. The purpose of this study is to provide an assessment of the economic burden of SLE in a Medicaid cohort, with an emphasis on disease severity as measured by treatment indicative of moderate-to-severe SLE.



Figure 1: Mean unadjusted total costs, total and by type of service, and multivariable-adjusted total costs during 12-month follow-up period compared between Medicaid-insured moderate-to-severe and mild SLE patients. Generalized linear modeling with log link and gamma error distribution estimated total healthcare costs adjusting for differences in age, sex, race, health plan type, and mean Charlson Comorbidity Index (CCI). *p-value < 0.05 **p-value < 0.001.

Methods: SLE patients ages 18-64 years treated with antimalarials, immunosuppressants, biologics (belimumab, abatacept, or rituximab), or systemic glucocorticoids from 1/1/2010 through 12/31/2014 were identified from administrative claims in

the MarketScan[®] Medicaid Multi-state database. The first prescription fill date was the index date. Patients were required to have at ≥ 1 inpatient claim or 2 non-diagnostic outpatient claims >30 days apart for SLE during the 12 months prior to the index. If the patient had only outpatient claims, ≥ 1 SLE diagnoses must have been made by a rheumatologist or nephrologist. Patients were categorized according to their SLE treatment during a 6-month exposure period starting on the index as follows: 1) mild SLE: either antimalarial monotherapy or low-dose oral glucocorticoid (≤ 5 mg/day) monotherapy or 2) moderate-to-severe SLE: any immunosuppressive or combinations of SLE medications other than either antimalarial or low-dose oral glucocorticoid monotherapy. All-cause healthcare utilization and costs were evaluated during the 12 months following the initial exposure period (in 2016US dollars). Generalized linear modeling with log link and gamma error distribution estimated total costs and total costs excluding outpatient pharmacy costs during follow-up, adjusting for demographic and clinical characteristics.

Results: 802 treated SLE patients were identified (91.3% female; 56.1% black). Based on patients' SLE treatment, 74.8% were classified as having moderate-to-severe SLE. Patients with moderate-to-severe disease were significantly younger than those with mild disease (mean age [SD]: 41.4 years[12.4] vs. 46.5 years [9.9]; $p<0.001$) and were more likely to have lupus nephritis (34.2% vs. 18.1%; $p<0.001$). Mean unadjusted total costs and by type of service, and multivariable-adjusted total costs are shown in Figure 1. Over half of the total costs were derived from the inpatient setting. The mean multivariable-adjusted total costs incurred over 12 months of follow-up were \$66,935 among moderate-to-severe patients and \$53,329 among mild patients ($p=0.04$); mean multivariable-adjusted total costs excluding pharmacy costs were \$56,050 among moderate-to-severe patients and \$44,932 among mild patients ($p=0.06$).

Conclusion: Approximately $\frac{3}{4}$ of SLE patients within this Medicaid cohort received treatment indicative of moderate-to-severe SLE indicating a substantial burden of disease. Healthcare costs were high for all patients, and the greatest proportion of cost was due to inpatient admissions.

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Abstract Number: 2997

Association between Payments By Pharmaceutical Manufacturers and Prescribing Behavior in Rheumatology

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Session Type: ACR/ARHP Combined Abstract Session

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Background/Purpose: Prescription drugs are the third largest category of healthcare spending in the US. Four of the top five costliest drugs are biologics used for the treatment of RA. Financial relationships between physicians and pharmaceutical companies may affect prescribing. We examined the costs of drugs prescribed by rheumatologists to U.S. Medicare beneficiaries and assessed the relationship between pharmaceutical industry payments to physicians and prescribing behavior.

Methods: Three databases, Medicare part B, Medicare part D, and Open Payments were queried for non-research payments to rheumatologists between 2013-2015. Prescription drugs responsible for 80% of the total expenditure were identified for analysis (table). Prednisone was included for comparison. We calculated the mean annual drug cost per beneficiary per year; the percentage of rheumatologists who received any payments; and the median annual payment per physician per drug per year. Payments were categorized as Type 1 (intended for “key opinion leadership”) and Type 2 (intended for physicians who receive information from these experts including food and beverages, or educational materials). The relationship between industry payments and prescription drug expenditure was examined using Spearman rank correlation methods.

Medication	Number of Rheumatologist Prescribers	Average Annual Medication Cost (\$)	Average Annual Cost per Beneficiary ¹ (\$)	% MD with any Sunshine payment	% with payments type 1 ²	Per-Physician Median (IQR) Annual Payments, \$	Correlation Total Payments, Rho	Type 1 Payments, ⁴ Rho
rACTH	156	\$1,519,864	\$29,955	96.2	32.7	138 (\$7 - 2,367)	0.43	0.52
Adalimumab	3875	\$19,979,396	\$21,491	56.5	10.7	114 (\$2 - 266)	0.23	0.16
Etanercept	4071	\$40,776,562	\$20,728	46.5	3.6	73 (\$7 - 149)	0.23	0.08
Infliximab	1346	\$59,054,316	\$15,940	62.9	7.1	91 (\$2 - 70)	0.21	0.14
Golimumab	1123	\$6,215,740	\$15,476	88.4	0.1	86 (\$9 - 185)	0.19	0.17
Rituximab	490	\$108,285,620	\$15,172	72.9	5.9	99 (\$5 - 180)	0.19	0.14
Certolizumab	1037	\$11,309,336	\$13,941	70.0	11.6	79 (\$6 - 176)	0.26	0.14
Absorcept	1948	\$24,619,321	\$13,445	19.2	3.6	57 (\$1 - 123)	0.27	0.11
Toriparatide	1596	\$5,124,564	\$8,378	50.3	2.6	18 (\$9 - 46)	0.33	0.19
Denosumab	1675	\$9,064,445	\$1,297	62.1	1.0	86 (\$4 - 168)	0.18	0.09
HCQ ³	4672	\$2,381,281	\$62	-	-	-	-	-
Methotrexate ³	4735	\$13,695,960	\$358	22.4	1.3	9 (\$3 - 20)	0.22	0.06
Prednisone ³	4785	\$5,777,821	\$43	37.0	0.9	10 (\$3 - 29)	0.25	0.09

rACTH, repository corticotropin; HCQ, Hydroxychloroquine
¹ Defined as total drug cost divided by number of beneficiaries for the subset with available beneficiary costs (i.e., physicians with ≥10 beneficiaries per year)
² There were no payments associated with hydroxychloroquine
³ Brand versions associated with payments (Ravot, Ocremap, and Ravotop). No payments were associated with generics
⁴ Type payments—Speaker fees, consulting fees, honorariums, travel costs and non-research grants

Results: We identified 4,932 rheumatologists who prescribed any drug(s) to Medicare beneficiaries. Etanercept and adalimumab were the most commonly prescribed non-generic drugs while repository corticotropin (rACTH) was the least prescribed. Based on the mean annual medication costs, etanercept (\$741 million), adalimumab (\$620 million) and infliximab (\$539 million) had the highest expenditures. The annual cost of rACTH was \$82 million, or \$230,000 per beneficiary per year. Prednisone, the most commonly prescribed drug overall, had yearly mean annual cost of \$16 million. In general, biologic costs ranged between \$14,000 and \$21,000 per beneficiary per year, with the exception of denosumab which was much less costly. Drugs with the lowest annual cost per beneficiary were prednisone (\$42), methotrexate (\$358) and hydroxychloroquine (\$362). The correlation between total payments and total prescription costs per physician were low (rho<0.3), except for rACTH (rho=0.45; 95% confidence interval [CI]: 0.31, 0.57). The correlations between type 1 payments and total prescription costs were generally weaker (rho<0.2), except for rACTH (rho=0.52; 95% CI: 0.39, 0.62).

Conclusion: Payments by the pharmaceutical industry to rheumatologists are weakly associated with Medicare prescription costs. However, rACTH has a disproportionate cost relative to the number of prescribers and there was strong association between pharmaceutical payments and prescription costs related to rACTH. This finding is particularly important given the paucity of evidence and lack of clear indications for the use of rACTH.

Disclosure: A. Duarte-Garcia, None; C. S. Crowson, None; R. McCoy, None; J. Ross, None; E. L. Matteson, Amgen Inc., 2, Ardea biosciences, 2, Janssen, 2, Genentech, Inc., 2, Novartis, 2, Pfizer, Inc., 2, Mesoblast, 2, NIH, 2, Sun pharmaceutical, 2, UCB, Inc., 2, Celgene Corporation, 2, UpToDate, 7; N. Shah, None.

Abstract Number: 2998

Opioid Use Among SLE Patients and Controls in the Population-Based Michigan Lupus Epidemiology & Surveillance (MILES) Cohort

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Health Services Research – ACR/ARHP II: Economic and Clinical Implications of Rheumatic Disease

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: SLE patients frequently experience pain. Opioid use for the management of chronic pain has been associated with increased morbidity, mortality, and healthcare resource utilization. We investigated the prevalence and factors associated with opioid use among MILES Cohort participants to identify opportunities to improve quality of care in SLE.

Methods: Data were derived from structured interviews at baseline visit of MILES, a longitudinal, population-based cohort of 462 SLE participants and 192 controls matched across sex, age, race and geography in southeastern Michigan. Detailed information on opioid use including prescribed frequency (scheduled or as needed) and duration were obtained. For the 30 SLE participants who reported more than one opioid use, opioid with longest duration was included in the analyses. We used multivariable logistic regression to evaluate factors associated with opioid use among SLE participants. Variables determined *a priori* to be important, or with p-values <0.1 in univariate analysis, were included in multivariable models (see Table).

Figure: Duration of opioid use for the 8% of controls and 31% of SLE participants on opioids

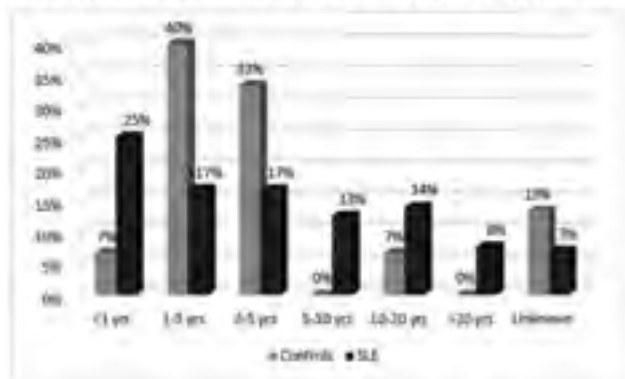


Table: Factors associated with opioid use among SLE participants

Variables	OR (95% CI)	p-value
Age	1.00 (0.98-1.03)	0.643
Female	1.04 (0.34-3.25)	0.940
Race		
Black	Reference	
White	1.31 (0.65-2.23)	0.542
Other	0.37 (0.04-3.84)	0.410
Insurance		
Medicaid	Reference	
Medicare	0.92 (0.40-2.09)	0.835
Private	0.66 (0.29-1.51)	0.327
Income	0.91 (0.61-1.38)	0.669
Access to Healthcare		
Transportation difficulty to access healthcare	0.71 (0.32-1.61)	0.436
Mental healthcare within 12 months	1.36 (0.65-2.82)	0.400
At least one ED visit in preceding 12 months	2.44 (1.25-4.76)	0.009†
At least one admissions in preceding 12 months	1.32 (0.65-2.68)	0.438
Duration of SLE	1.02 (0.98-1.05)	0.349
Pain		
Visual analog scale pain score	1.50 (1.28-1.75)	<0.01†
Pain catastrophizing score	1.00 (0.96-1.04)	0.861

†statistically significant p-value<0.05

Results: All 654 participants completed the MILES Cohort baseline visit; average age 53.4 (SD 12.8), 584 (89%) female, 288 (44%) black and 159 (24%) with Medicaid insurance. Only 15 controls (8%) reported opioid use compared to 143 among SLE participants (31%) ($p<0.001$). One in three controls were prescribed scheduled opioids, whereas half of the SLE participants on opioids were given scheduled prescriptions. SLE participants on average reported 6 years of opioid use (SD 7 years) compared to 3 years among controls (SD 2 years) ($p=0.140$). Moreover, 34% of SLE participants on opioids reported opioid usage ≥ 5 years, whereas only 7% of controls on opioids had usage ≥ 5 years ($p=0.037$) (see Figure). In multivariable analysis, among SLE participants, those with higher pain score [OR 1.50(95% CI 1.28-1.75)] and at least one ED visit in the preceding 12 months [2.43 (1.25-4.74)] were more likely to be on opioids (see Table).

Conclusion: One in three SLE participants reported opioid use, and a third of those have opioid usage ≥ 5 years. Higher pain score and having at least one ED visit were significantly associated with opioid use. Studies have shown patients who frequent the ED are more likely to be prescribed opioids for pain. Moreover, opioid prescription in the ED has been found to increase the risk of long-term opioid therapy and associated morbidity and mortality. Further study is warranted to improve pain management and reduce opioid use in SLE participants, particularly for those who frequent the ED, to improve quality of care.

Disclosure: J. Lee, None; A. Padda, None; W. Marder, None; S. Harlow, None; A. L. Hassett, AbbVie Inc., 5, 9; S. Zick, None; C. G. Helmick, None; K. E. Barbour, None; C. Gordon, None; D. Minhas, None; W. J. McCune, None; E. C. Somers, None.

Abstract Number: 2999

Does the Incremental Cost of ACPA-Positive Rheumatoid Arthritis Patients Vary By the Care Pathway They Follow?

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Session Information

Session Date: Wednesday, October 24, 2018

Session Title: Health Services Research – ACR/ARHP II: Economic and Clinical Implications of Rheumatic Disease

Session Type: ACR/ARHP Combined Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Rheumatoid Arthritis (RA) patients who are anti-citrullinated peptide antibody (ACPA) positive are prone to more severe structural damage, radiographic progression and inferior response to therapy. It's known that ACPA positive patients are associated with additional cost as compared to ACPA negative. It's unclear however if the incremental cost associated with ACPA-positive RA varies by the care pathway they follow. The study objective was to evaluate the incremental costs associated with ACPA-positivity in different groups of RA management pathways.

Methods: A retrospective cohort study was conducted in RA patients identified using electronic medical records from the Kaiser Permanente Southern California health plan. Between 01/01/2007 and 12/31/2015, we identified patients aged ≥ 18 years who had ≥ 2 RA diagnoses within a 12-month period, a disease-modifying antirheumatic drug (DMARD) prescription and laboratory test for ACPA. Patients were followed for two years post diagnosis. Latent class analysis (LCA) method was applied to identify ≥ 2 heterogeneous RA management patterns. RA-specific healthcare utilization during the first-year follow-up was used to identify the latent classes. During the second year of follow-up, we estimated total RA-specific expenditures associated with hospital stays; outpatient visits; office visits; pharmacy; laboratory and radiology utilization. A generalized linear model, evaluating the difference in expenditure between ACPA positive vs negative patients was specified with an effect modification term for latent class and adjusting for socio-demographics and comorbidities.

Results: We identified 2842 incident RA patients, mean age 56 years and majority female 76%. LCA indicated five latent classes representing mutually exclusive pathways of patient management and care (Table 1). Adjusted total RA-specific expenditure ranged from \$1167 in class one to \$21008 in class five for ACPA-positive patients (Table 2). The difference between ACPA positive and negative patients in the least severe class (Class 1) was statistically non-significant difference of \$214. However, in class two and above, this difference was statistically significant and progressively increasing. In patients characterized by high disease activity and high progression (Class 5) the expenditure difference was 27-fold higher (\$5708) as compared to Class 1 (Table 2).

Conclusion: Across the 5 distinct care pathways identified by LCA, based on the management and care of RA patients, the magnitude of the incremental cost associated with ACPA-positivity varied.

Table 1 Distribution of Markers of Latent Classes

	Class 1: Low Disease Activity Low Progression	Class 2: Low Disease Activity Moderate Progression	Class 3: Moderate Disease A ctivity with Pain	Class 4: High Disease Activity with Moderate Progression	Class 5: High Disease Activity with High Progression
	N = 367	N = 1105	N = 516	N = 616	N = 239
RA Office Visits (Mean)	3.2	4.9	6.9	8.2	9.3
RA ED Visits (Mean)	<0.01	0.01	0.01	0.04	0.02
Tradition DMARDs (Mean refills)	2.9	4.0	5.7	5.5	5.4
Biologic DMARDs (Mean refills)	<0.01	0.01	0.02	0.04	6.47
NSAIDs (Mean refills)	0.7	0.7	4.0	0.4	1.7
Corticosteroids (Mean refills)	0.7	0.5	1.8	3.8	2.6
RA Hospitalization	<0.01%	0.5%	0.9%	1.5%	2.6%
RA Surgery	<0.01%	0.2%	0.2%	0.2%	0.4%
CT Scans	9.4%	13.0%	19.3%	27.6%	16.8%
MRI	5.1%	7.8%	14.8%	13.2%	16.0%
Ultrasound	17.7%	15.2%	13.0%	23.9%	15.8%
X-Ray	64.2%	80.3%	84.5%	86.3%	88.9%
Rheumatoid Factor Lab	2.0%	21.9%	16.5%	18.7%	15.3%
ESR Lab	28.8%	97.9%	87.5%	92.5%	96.7%
CRP Lab	7.4%	73.8%	65.6%	64.8%	75.1%

Utilization during the one-year follow-up after first RA diagnosis

Table 2 RA-Specific Total Expenditure During Second Year (in 2016 US Dollars)

Latent Class	Adjusted Mean		Incremental Difference of ACPA Positive to ACPA Negative patients		
	ACPA Negative	ACPA Positive	Difference in Means	L-95% CI	H-95% CI
1	\$957	\$1,167	\$214	-\$305	\$733
2	\$1,368	\$2,162	\$790	\$320	\$1,259
3	\$2,404	\$3,581	\$1,178	\$230	\$2,126
4	\$2,925	\$4,143	\$1,191	\$233	\$2,148
5	\$15,567	\$21,008	\$5,708	\$1,255	\$10,160

Bold font indicates statistically significant estimates

Disclosure: A. Kawatkar, Bristol-Myers Squibb, 2; J. An, Bristol-Myers Squibb/Pfizer, 2; T. Cheetham, Bristol-Myers Squibb, 2; K. Gupta, Bristol-Myers Squibb, 1, 3; A. Marshall, Bristol-Myers Squibb, 3; E. Haupt, Bristol-Myers Squibb, 2; G. Okano, Bristol-Myers Squibb, 1, 3; T. Curtice, Bristol-Myers Squibb, 1, 3.

New Cardiovascular Events in Patients with Gout Treated with Xanthine-Oxidase Inhibitors: An Inception Cohort Analysis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: ACR Late-breaking Abstract Session

Session Type: Late-Breaking Abstract Poster Session

Session Time: 09:00AM-11:00AM

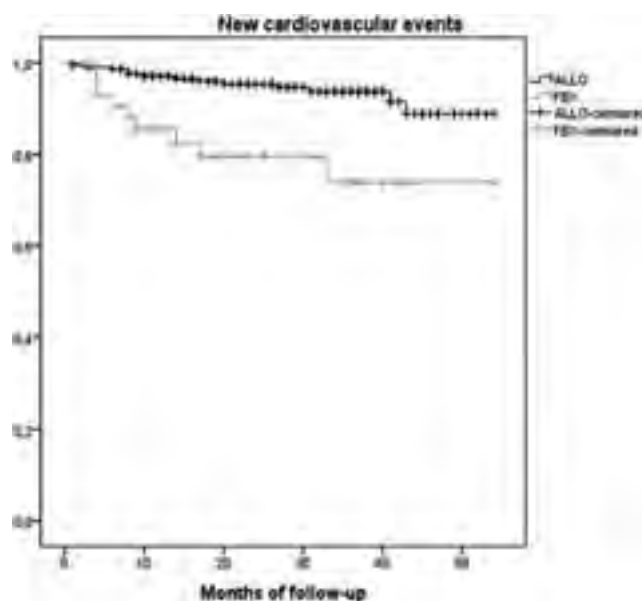
Background/Purpose: The recent CARES trial findings have contributed to the controversy around the development of cardiovascular (CV) events in gouty patients using febuxostat (FBX). In those with prior CV disease, FBX showed an increased CV mortality risk over allopurinol (ALLO), leading to the issue of an FDA warning. Whether this also applies to individuals without prior established CV disease is unknown. We aimed to assess the risk of new CV events in gout patients after the prescription of xanthine-oxidase inhibitors (XOI) in clinical practice.

Methods: Inception cohort (Jan'14-Dec'17), enrolling patients with crystal-proven gout in whom XOI (ALLO or FBX) were initiated and had at least 6 months of follow-up. The primary outcome were new CV events [CV death; coronary heart disease (CHD); congestive heart failure (CHF); stroke; peripheral artery disease (PAP)] after XOI initiation. Comparison between ALLO and FBX was performed using Kaplan-Meier plots and log-rank test. To adjust for confounders, Cox regression models were built, for the whole sample and stratified by the pre-existence CV disease. Covariates were selected if associated with the outcome or if they showed a different distribution between XOI groups.

Results: 256 patients were analyzed, 213 treated with ALLO and 43 with FBX. 69 cases (27.0%) had established CV disease. 22 new CV events occurred in a median of 9.5 months (IQR 4.5-19.3): 13 CHF cases, 5 CHD, 2 strokes, and 2 PAP, leading to 7 CV deaths. 16 events occurred in patients with a prior CV (23.2%), six in those with no prior CV events (3.2%). Regarding XOI treatment, 13 events happened with ALLO (6.1%) and 9 with FBX (20.9%). Use of colchicine at the time of the event was comparable. A higher incidence of new CV events in those treated with FBX was seen ($p < 0.001$, Kaplan-Meier plot). The simple Cox regression model confirmed a higher risk with FBX compared to ALLO (table), which persisted after adjustment. After stratification by prior CV disease, a significant CV risk with FBX was only detected in those with prior CV disease.

Conclusion: After adjustment for confounders, an excess risk of CV events is confirmed in patients with gout and prior CV disease treated with FBX. Whether this phenomenon relates to FBX itself needs further clarification.

*covariates: age, gender, hypertension, diabetes, dyslipidemia, smoking, established CV disease, baseline GFR, overweight, baseline SU, tophi, oligo/polyarthritis at presentation.



			HR	95%CI	P-value
Whole sample	Simple	ALLO	1.0	-	Ref
		FBX	4.4	1.3-15.3	0.021
	Multiple [†]	ALLO	1.0	-	Ref
		FBX	3.9	1.1-4.2	0.039
No prior CV disease	Simple	ALLO	1.0	-	Ref
		FBX	1.9	0.2-17.0	0.547
	Multiple [†]	ALLO	1.0	-	Ref
		FBX	1.1	0.1-21.6	0.974
Prior CV disease	Simple	ALLO	1.0	-	Ref
		FBX	2.9	1.4-7.7	0.035
	Multiple [†]	ALLO	1.0	-	Ref
		FBX	20.8	2.2-190.0	0.007

[†]covariates: age, gender, hypertension, diabetes, dyslipidemia, smoking, baseline GFR, overweight, baseline SU, tophi, oligo/polyarthritis at presentation.

Disclosure: N. Quilis, None; L. Ranieri, None; J. Sanchez-Paya, None; M. Andrés, Menarini, Grunenthal, Horizon, 5.

Quilis, N, Ranieri, L, Sanchez-Paya, J, Andrés, M
Allopurinol, cardiovascular disease, febuxostat and gout

Abstract Number: L02

Study of Tofacitinib in Refractory Dermatomyositis (STIR): An Open Label Pilot Study in Refractory Dermatomyositis

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: ACR Late-breaking Abstract Session

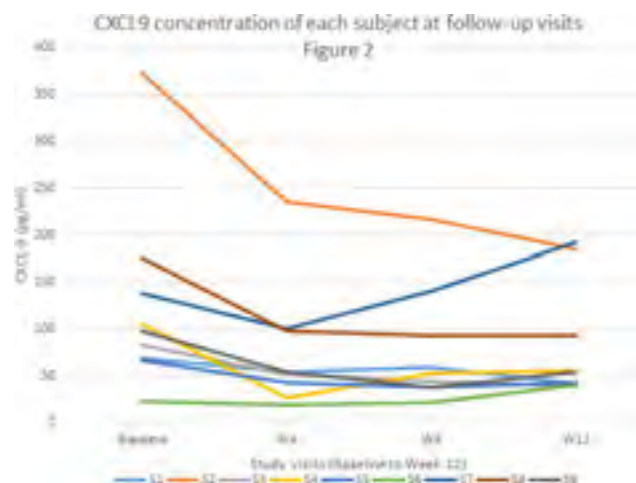
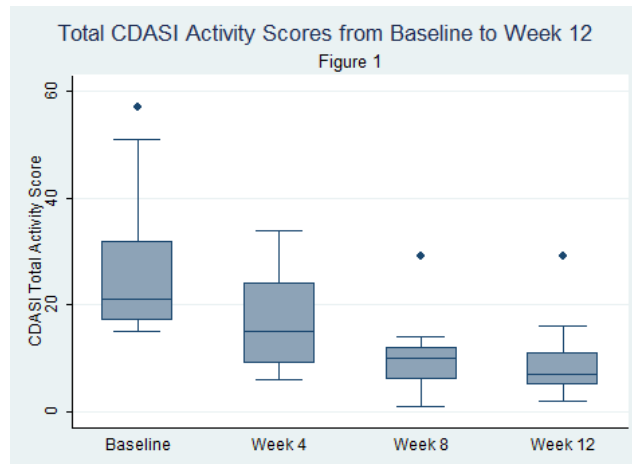
Session Type: Late-Breaking Abstract Poster Session

Session Time: 09:00AM-11:00AM

Background/Purpose: Dermatomyositis (DM) is an idiopathic inflammatory myopathy that primarily affects the muscle and skin. In refractory disease, it is common to fail 2 or more steroid sparing agents or high dose steroids. This open-label, 12-week proof-of-concept study was conducted to evaluate the efficacy and safety of tofacitinib, a JAK inhibitor, in active, treatment refractory DM.

Methods: 10 subjects were enrolled at one center. Tofacitinib was given as 11mg XR daily. Subjects were washed out of any steroid sparing agent and not allowed more than 20 mg of prednisone daily prior to study entry. The primary outcome was the proportion of subjects meeting the definition of improvement (DOI) at 12 weeks, defined by the International Myositis Assessment and Clinical Studies (IMACS) as improvement of $\geq 20\%$ in 3 of 6 core set measures (CSM) with no more than 2 worsening by $\geq 25\%$ [which cannot include the manual muscle testing (MMT)]. The secondary outcome measures were the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), steroid-sparing effect of tofacitinib, safety, and tolerability.

Results: 9 subjects were analyzed because the last subject has not yet completed the study. All subjects failed at least 2 steroid sparing agents or high dose steroids. All 9 subjects met the primary outcome DOI at 12 weeks, with 5 of 9 (56%) demonstrating moderate improvement and 4 of 9 (44.4%) having minimal improvement based on the Total Improvement Score (TIS) of the Myositis Response Criteria. The median TIS was 40 [IQR 32.5, 47.5] indicative of at least moderate improvement. The secondary outcome of the mean change in CDASI activity score from baseline to 12 weeks was statistically significant (28 ± 15.4 (baseline) vs. 9.5 ± 8.5 (12 weeks), $p=0.0005$) with clear trend in improvement (Figure 1). Chemokine data on CXCL-9/10 also showed a trend toward improvement with treatment but did not show a



statistically significant change from baseline (CXCL9, $p=0.09$; CXCL10, $p=0.06$) (Figure 2). Myositis autoantibody titers did not show any change in titer after treatment. Six subjects were positive for anti-TIF-1 gamma and 5 of 6 (83%) were moderate responders. Four of 9 (44.4%) were on prednisone 20mg/daily at entry and 3 of 4 (75%) were able to completely taper off all steroids. Tofacitinib was well tolerated without any serious adverse events.

Conclusion: Tofacitinib demonstrated evidence of strong clinical efficacy as measured by a validated myositis response criteria with a corresponding decrease in chemokine levels. A randomized controlled trial should be considered to further assess efficacy in dermatomyositis.

Disclosure: J. J. Paik, None; J. Albayda, None; E. Tiniakou, None; A. Koenig, Pfizer Inc, 1, Pfizer Inc, 3; L. Christopher-Stine, Inova Diagnostics, 7.

Paik, JJ, Albayda, J, Tiniakou, E, Koenig, A, Christopher-Stine, L
Clinical trials and dermatomyositis

Abstract Number: L03

Efficacy and Safety from a Phase 2b Trial of SM04690, a Novel, Intra-Articular, Wnt Pathway Inhibitor for the Treatment of Osteoarthritis of the Knee

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

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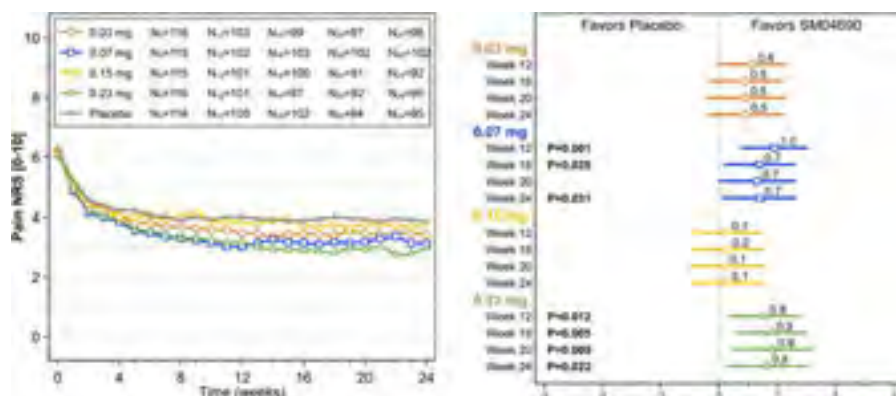
Background/Purpose: A previous Phase 2a study of SM04690, a small molecule, intra-articular (IA), Wnt pathway inhibitor, demonstrated positive effects on knee OA pain, physical function, and medial joint space width (mJSW) at 52 weeks in key subgroups compared to placebo¹. A 24 week Phase 2b study was performed to refine patient reported outcome (PRO) measures, target population, dose, and further evaluate safety. PRO results for weeks 12 and 24 are presented here.

Methods: Subjects had ACR-defined knee OA, Kellgren-Lawrence (KL) grades 2-3, Pain NRS ≥ 4 and ≤ 8 in target knee and < 4 in contralateral knee. A single IA injection of 2 mL SM04690 (0.03, 0.07, 0.15 or 0.23 mg), vehicle placebo (PBO), or sham (dry needle only) was given in the target knee at baseline. PRO endpoints included change from baseline compared with PBO in weekly average of daily OA target knee pain by numerical rating scale diary (NRS, [0-10]), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain [0-100], WOMAC Physical Function [0-100], and Patient Global Assessment (PTGA) (VAS [0-100]). This study was not formally powered, and sample size was based upon accepted dose-finding convention.

Results: 695 subjects (mean age 59.0 [± 8.5] years, BMI 29.0 [± 4.0] kg/m², female 58.4%, KL3 57.3%) were enrolled and dosed; 635 (91.4%) completed the study. No meaningful differences in incidence of adverse events were seen among treatment groups or between treatment and control groups.

In the full analysis set population (randomized, dosed subjects), significant improvements from baseline were observed in pain NRS for 0.07 mg (Week 12 [$P=0.001$], Week 24 [$P=0.031$]) and 0.23 mg (Week 12 [$P=0.012$], Week 24 [$P=0.022$]) SM04690 dose groups (**Figure**). Similar improvements were observed in WOMAC Pain for 0.07 mg (Week 12 [$P=0.04$]) and 0.23 mg (Week 12 [$P=0.003$], Week 24 [$P=0.031$]) dose groups. For WOMAC Physical Function, improvements were observed for 0.07 mg (Week 12 [$p=0.021$]) and 0.23 mg (Week 12 [$p=0.006$], Week 24 [$P=0.017$]) dose groups. PTGA improvements were observed for 0.07 mg (Week 12 [$P=0.031$]), and 0.23 mg (Week 12 [$P=0.010$], Week 24 [$P=0.033$]) dose groups.

Conclusion: SM04690, in development as a potential disease modifying OA drug, showed in this Phase 2b study statistically significant improvements from baseline in 0.07 mg and 0.23 mg SM04690 dose groups compared with PBO for Pain NRS, WOMAC Pain, WOMAC Physical Function and PTGA. These data further define outcome measures, target population, and dose for SM04690 as a potential treatment for knee OA. Ref: Yazici Y, et al. *Arthritis Rheumatol.* 2017; 69 (suppl 10). Actual observations over time and ladder plots depicting mean improvement ($\pm 95\%$ CI) of SM04690 compared with placebo adjusted for baseline for Pain NRS



Disclosure: Y. Yazici, Samumed, LLC, 1, 3; T. E. McAlindon, None; A. Gibofsky, Pfizer, Inc., 1, 5, 8, AbbVie Inc., 1, 5, 8, Celgene Corporation, 5, 8, Samumed, 5, Relburn Pharmaceuticals, 5, Fkexion Therapeutics, 5, Sandoz, 5, Merck & Co., 5, 8; N. Lane, None; C. Lattermann, Samumed, LLC, 5, Cartiheal, 5, Vericel, 5; N. Skrepnik, Samumed, LLC, 2, Sanofi, 5, Orthofix, 5; C. Swearingen, Samumed, LLC, 1, 3; A. DiFrancesco, Samumed, LLC, 1, 3; J. Tambiah, Samumed, LLC, 1, 3; M. Hochberg, Samumed, LLC, 5, EMD Serono, 5, Bioberica, 5, Novartis, 5, Plexicon, 5, Pfizer, Inc., 5, Regeneron, 5, Theralogix, LLC, 5.

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DMOAD, Knee, WNT Signaling, clinical trials and osteoarthritis

Pediatric Open-Label Clinical Study of Rituximab for the Treatment of Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA)

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SESSION INFORMATION

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Background/Purpose: PePRS is a Phase IIa international, multicenter, open-label single arm study of rituximab in pediatric patients with newly diagnosed or relapsing GPA or MPA. We report safety and exploratory efficacy data for the initial 6-month remission induction phase and for the long-term follow-up of all patients through ≥ 18 months.

Methods: Patients aged ≥ 2 to ≤ 18 years with recurrence or new onset of potentially organ- or life-threatening disease were included. Patients with severe disease requiring mechanical ventilation due to alveolar hemorrhage, requirement for plasmapheresis, or hemodialysis at screening were excluded. Three doses of pulsed intravenous (IV) methylprednisolone were administered during the screening period followed by four weekly IV rituximab infusions of 375 mg/m^2 body surface area and concomitant oral glucocorticoid taper. After the 6-month remission induction phase, patients received standard of care treatment (including additional rituximab infusions if required) for disease control. Visits occurred at 1, 2, 4 and 6 months during the remission-induction phase and every 3 months thereafter for a minimum of 18 months. The pediatric vasculitis activity score (PVAS) was used for exploratory efficacy assessments. Remission was defined as a PVAS of 0 and oral prednisone or prednisolone equivalent dose of $\leq 0.2 \text{ mg/kg/day}$ (max 10 mg/day).

Results: Of the 25 patients enrolled from 11 centers, 19 (76%) had GPA and 6 (24%) had MPA. The majority were female (20 patients [80%]), white (17 patients [68%]) and the median age was 14 years (range: 6-17 years). Most patients (18/25) had new-onset disease. Median baseline PVAS was 8 (IQR 5-15). The median duration of follow-up was 24 months (range: 16-54 months). All 25 patients completed the first 4 rituximab infusions and the 6-month remission induction phase; 24 of 25 completed ≥ 18 months of follow-up. All patients experienced ≥ 1 adverse event (AE) during the first 6 months, with infusion-related reactions (IRRs) being the most common AE (Table). IRRs occurred in 32% of patients with the first infusion and were less frequent thereafter. Overall, infections occurred in 68% of patients (with upper respiratory tract infection being the most frequent [16% of patients]). Ten serious AEs (SAEs) occurred in 7 patients during the 6-month remission induction phase, including 1 IRR. Over the entire study, 27 SAEs occurred in 12 patients, and no deaths were reported. Exploratory efficacy assessment showed that 56% of patients achieved remission by month 6; 100% of patients achieved remission by month 18. The median duration of remission during the study was 56 (IQR, 38-83) weeks.

Table. Common Adverse Events Reported in $\geq 10\%$ of Patients During Remission Induction Phase	
Adverse event	Number of patients (% of patients with ≥ 1 AE)
Infusion-related reaction	15 (60%)
Headache	4 (16%)
Nausea	4 (16%)
Upper respiratory tract infection	4 (16%)
Abdominal pain (upper)	3 (12%)
Constipation	3 (12%)
Arthralgia	3 (12%)
Back pain	3 (12%)
Cough	3 (12%)
Epistaxis	3 (12%)

AE, adverse event.

Conclusion: In this first global clinical trial of rituximab in pediatric patients with GPA/MPA, rituximab was well tolerated with an overall safety profile comparable to rituximab-treated adults with GPA/MPA. No new safety signals were observed. PVAS remission was achieved in 100% of patients by 18 months.

Disclosure: P. Brogan, Roche, 2, 5, SOBI, 2, 5, 8, Novartis, 2, 8, Chemocentryx, 2, UCB, Inc., 5; G. Cleary, AbbVie Inc., 8; A. O. Hersh, None; O. Kasapcopur, None; S. Rangaraj, None; R. S. M. Yeung, Novartis, 5, Eli Lilly and Co., 5; A. Zeff, None; S. Melega, Roche, 3; P. Brunetta, Genentech, Inc., 3; J. Cooper, Genentech, Inc., 3, 5; P. Pordeli, F. Hoffmann-La Roche Ltd., 3; P. B. Lehane, Roche Products, Ltd., 3.

Brogan, P, Cleary, G, Hersh, AO, Kasapcopur, O, Rangaraj, S, Yeung, RSM, Zeff, A, Melega, S, Brunetta, P, Cooper, J, Pordeli, P, Lehane, PB

ANCA, Wegener's granulomatosis, pediatric rheumatology and rituximab

Abstract Number: L05

Treatment-Naïve, Early Rheumatoid Arthritis Patients Demonstrate Reversible Abnormalities of Vascular Function on Cardiac MRI with RA Therapy with Preliminary Suggestion of Greater Improvement with Anti-TNF Compared to MTX/Conventional Therapy – a First, RCT Derived Longitudinal Study

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Background/Purpose: We previously reported abnormal cardiac MRI (CMR)-determined aortic stiffness in patients with early, treatment-naïve RA^{1,2}. We now report on whether this vascular stiffness is modifiable with RA DMARD therapy, and explore whether TNFi confers additional advantage over MTX csDMARD +/- subsequent escalation to TNFi.

Methods: A sub-grp of patients without CVD from an early (symptoms<1 yr), DMARD-naïve, RA (ACR/EULAR criteria) RCT³ with DAS28_{ESR}≥3.2 were recruited for 3.0T CMR to determine aortic distensibility (AD) at baseline, yrs 1 and 2 at a dedicated cardiology-CMR unit. Patients were randomised to first-line etanercept (ETN)+MTX (grp 1) or MTX/treat-to-target escalation to triple csDMARD, and switch to ETN+MTX at week 24 if failed to achieve clinical remission (grp 2; non-escalated subgroup 2a). At week 48, ETN was stopped, standard of care treatment maintained with observation up to week 96. AD values were natural log (ln) transformed prior to analysis; results are expressed as ratios between groups. Patients with DAS28_{ESR}≥2.6 at wk 48 defined non-responders. Change in AD value from baseline was evaluated in combined grps 1 and 2; between group, and within group (response states) change in AD at 1 and 2 years was compared adjusting for baseline DAS28_{ESR}.

Results: Eighty early RA patients of mean(SD) age 49.4(13.08) and systolic BP 123(16) were recruited. Median(IQR) ESR, CRP and mean(SD) DAS28 were 31(31)mm/hr, 8(23)mg/L and 5.6(1.5) respectively. 66(85%) and 59(76%) patients were ACPA and RF positive respectively. 17(21%) were current smokers.

Table 1 details the analyses, confirming significant reduction in mean AD from baseline to year 1 [3.59 (3.14,4.11) vs 2.99 (2.66,3.36) respectively; p<0.01]. This was maintained at year 2 [3.55(33.09,4.09) vs 2.99(2.66,3.36); p=0.04]. There appeared to be no numerical difference in change at years 1 (and 2, data not shown) when comparing grp 1 vs grp 2, all responders vs non-responders and grp 1 responders vs non-responders (all adjusted for baseline AD, age, sex). To clarify this apparent absence of effect of disease activity as represented by response status, correlation analyses between AUC disease activity and AD at year 1 in the combined grps 1&2, and between grps 1 & 2 also did not identify an association.

Table 1

Comparison		Ratio (95% CI), <i>P</i> value				
		Geometric mean AD (unadjusted)		Unadjusted	Adjusted for baseline AD	Adjusted for baseline AD, age, sex (\pm baseline DAS28ESR as applicable)
Combined Group 1 & 2 Baseline		2.99 (2.66,3.36)		1.20 (1.08,1.33), <i>p</i> <0.01	na	na
1 year		3.59 (3.14,4.11)				
Group 1 (all n=40)	Group 2 (all n=41)	3.74	3.44	0.91 (0.70,1.21), <i>p</i> =0.54	0.92 (0.76, 1.14) <i>p</i> =0.48	0.92 (0.76, 1.14) <i>p</i> =0.49
Group 1 & 2 non-responders (n=46)	Group 1 & 2 responders (n=35)	3.60	3.58	0.99 (0.76,1.30), <i>p</i> =0.97	0.97 (0.79,1.20) <i>p</i> =0.81	0.97 (0.78, 1.21) <i>p</i> =0.79
Group 1 non-responders (n=20)	Group 1 responders (n=20)	3.66	3.83	1.04 (0.71,1.53), <i>p</i> =0.82	1.00 (0.75, 1.34) <i>p</i> =0.98	1.00 (0.75, 1.36) <i>p</i> =0.96
Group 1 responders (n=20)	Group 2a responders (n=10)	3.83	2.75	0.72 (0.44,1.16), <i>p</i> =0.17	0.82 (0.60, 1.13), <i>p</i> =0.21	0.84 (0.60, 1.18) <i>p</i> =0.30
AUC DAS28						
Group 1 & 2 ^				1.07(0.79,1.44), <i>p</i> =0.65	1.03(0.82,1.3) <i>p</i> =0.78	1.05(0.83,1.33) <i>p</i> =0.69*
Group 1 (all n=40)	Group 2 (all n=41)	3.75	3.44	0.92(0.7,1.21), <i>p</i> =0.53	0.93(0.75,1.15) <i>p</i> =0.48	0.92(0.73,1.14) <i>p</i> =0.42*

^ Coefficients presented per 100 unit increase in AUC

* Adjusted for baseline AD, age, sex and AUC disease activity

Planned exploratory comparison of grp 1 ETN responders and grp 2a responders (no ETN exposure) suggested a 16% difference (0.84 (0.60, 1.18), *p*=0.30).

Conclusion: This first longitudinal CMR treatment-naïve ERA RCT cohort demonstrates vascular function abnormalities are modifiable (reduced) upon introduction of RA DMARD therapy. Treatment strategy rather than disease activity appeared to influence AD change; if confirmed in a larger trial this would suggest ETN+MTX confers a greater benefit over standard initial MTX/csDMARD.

References:

1. Erhayiem B, *et al.* Trials 2014
2. Erhayiem B, *et al.* Arthritis & Rheumatology 2015
3. Dumitru et al. BMC Musculoskeletal Disorders 2016

Disclosure: M. H. Buch, Pfizer, Inc., 2, Roche, 2, UCB, Inc., 2, AbbVie Inc., 5, Sanofi, 5, Eli Lilly and Co., 5, Sandoz, 5; B. Erhayiem, None; G. Fent, None; P. Baxter, None; E. M. A. Hensor, None; A. McDiarmid, None; P. Swoboda, None; A. Kidambi, None; D. Ripley, None; P. Garg, None; S. Horton, None; R. B. Dumitru, None; K. Naraghi, None; J. Greenwood, None; P. Emery, Bristol-Myers Squibb, AbbVie, Pfizer, MSD, Novartis, Roche and UCB, 5, AbbVie, Bristol-Myers Squibb, Pfizer, MSD and Roche, 2; S. Pavitt, None; S. Plein, None.

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Anti-TNF therapy, cardiovascular disease, magnetic resonance imaging (MRI), methotrexate (MTX) and rheumatoid arthritis (RA)

Abstract Number: L06

Safety and Efficacy of Filgotinib in a Phase 3 Trial of Patients with Active Rheumatoid Arthritis and Inadequate Response or Intolerance to Biologic Dmards

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SESSION INFORMATION

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Background/Purpose: Filgotinib (FIL), an oral, selective, Janus Kinase 1 (JAK1) inhibitor was effective in phase 2 studies of active RA in patients (pts) with insufficient response to MTX, warranting further evaluation in phase 3.

Methods: In this global, phase 3 study (ClinicalTrials.gov Identifier: NCT02873936), pts with moderately-to-severely active RA and an inadequate response or intolerance to 1 or more prior biologic DMARDs (bDMARDs), were randomized 1:1:1 to once daily FIL 200 mg, 100 mg, or placebo (PBO) for 24 weeks; pts were required to continue stable conventional synthetic DMARDs. The primary endpoint was the proportion of subjects who achieved an ACR20 response at Week (Wk) 12.

Results: Baseline characteristics of the 448 pts randomized and treated with the study drug (FIL 200 mg, n=147; FIL 100 mg, n=153; and PBO, n=148) included: 80.4% female; 23.4% ≥ 3 prior bDMARDs; 56 yrs mean age; 12.4 yrs RA disease duration; 27 of 68 tender joint count; 17 of 66 swollen joint count; and 5.9 DAS28(CRP). At Wk 12, an ACR20 response was achieved by more pts receiving FIL 200 mg or 100 mg than PBO (66.0, 57.5 and 31.1%, respectively; both $p < 0.001$) (Table 1). The reduction from baseline in HAQ-Disability Index (HAQ-DI) at Wk 12 was greater in the FIL 200 mg and 100 mg groups compared to the PBO group (-0.55 and -0.48 vs -0.23, respectively; both $p < 0.001$). Other key secondary endpoints, including SF-36 and FACIT-Fatigue, were also met at both FIL doses (Table 1). Adverse event (AE) rates were similar for FIL 200 mg, FIL 100 mg and PBO groups (69.4% and 63.4% vs 67.6%, respectively) as were rates of serious AEs (4.1%, 5.2% and 3.4%, respectively) (Table 2). There were 4 cases of uncomplicated herpes zoster (2 in each FIL group). There was one non-serious AE of retinal vein occlusion in the FIL 200 mg group; no other venous thrombotic events were reported. Two adjudicated MACE were reported: subarachnoid hemorrhage in the PBO group and myocardial ischemia in the FIL 100 mg group. There were no cases of opportunistic infection/active TB, malignancy, GI perforation or death.

	Week 12			Week 24		
	PBO N=148	FIL 200 mg N=147	FIL 100 mg N=153	PBO N=148	FIL 200 mg N=147	FIL 100 mg N=153
ACR20, (%)	31.1	66.0***	57.5***	34.5	60.4***	54.9***
ACR50/70, (%)	14.9/6.8	42.9***/21.8***	32.0***/14.4*	18.9/8.1	45.6***/32.0***	35.3***/20.3**
ACR20 in Pts with ≥ 3 prior bDMARDs, n (%)	17.6	70.3	58.8	32.4	67.6	50.0
DAS28(CRP) ≤ 3.2 , n (%)	15.5	40.8***	37.3***	20.9	48.3***	37.9**
DAS28(CRP) < 2.6 , n (%)	8.1	22.4***	25.5***	12.2	30.6***	26.1**
HAQ-DI, mean (SD)	1.40 (0.71)	1.15 (0.74)	1.15 (0.71)	1.22 (0.68)	0.95 (0.71)	1.04 (0.71)
HAQ-DI, mean CFB (SD)	-0.23 (0.55)	-0.55 (0.59)***	-0.48 (0.60)***	-0.42 (0.60)	-0.75 (0.62)***	-0.60 (0.66)**
SF-36 PCS, mean CFB (SD)	3.6 (8.16)	7.6 (7.68)**	6.8 (8.22)**	6.6 (7.95)	9.4 (8.23)***	9.0 (8.44)**
FACIT-Fatigue, mean CFB (SD)	4.5 (10.37)	9.6 (11.24)**	8.3 (10.80)**	7.0 (10.23)	11.6 (11.67)***	9.8 (10.39)

* $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ compared to placebo.

^aPatients lacking sufficient measurements to assess ACR response or DAS28(CRP) at Wk 12 were considered non-responders; p-value was provided from the mixed-effects model for repeated measures (MMRM) for HAQ-DI, SF-36 PCS and FACIT-Fatigue.

CFB, change from baseline; DAS28(CRP), Disease Activity Score 28-joint count with C-reactive protein; FACIT, Functional Assessment of Chronic Illness; HAQ-DI, Health Assessment Questionnaire Disability Index; SF-36 PCS, 36-Item Short Form Health Survey physical component score.

Conclusion: In this phase 3 study of pts with highly active RA and prior inadequate response/intolerance to bDMARDs, treatment with FIL over a 24-week period was associated with significant improvement in the signs and symptoms of RA, with a safety profile consistent with Phase 2 data. FIL may provide a novel treatment option for pts who continue to have active RA despite prior biologic therapies.

This study was sponsored by Gilead Sciences, Inc.

Table 2. Summary of Treatment-Emergent Adverse Events Over 24 Wks			
n, (%)	PBO N=148	FIL 200 mg N=147	FIL 100 mg N=153
AEs	100 (67.6%)	102 (69.4%)	97 (63.4%)
AEs leading to study drug discontinuation	3 (2.0%)	5 (3.4%)	6 (3.9%)
Serious AEs	5 (3.4%)	6 (4.1%)	8 (5.2%)
Death (any cause)	0	0	0
AEs of Interest			
Infection	38 (25.7%)	53 (36.1%)	52 (34.0%)
Serious infection	2 (1.4%)	1 (0.7%)	3 (2.0%)
Opportunistic infection	0	0	0
Herpes zoster (uncomplicated)	0	2 (1.4%)	2 (1.3%)
Active TB	0	0	0
DVT/PE ^a	0	1 (0.7%)	0
MACE (adjudicated)	1 (0.7%)	0	1 (0.7%)
GI perforation	0	0	0
Malignancy (excluding NMSC)	0	0	0
NMSC	0	0	0

^aretinal vein occlusion.

TB, tuberculosis; DVT/PE, deep vein thrombosis/pulmonary embolism; MACE, major adverse cardiovascular events; GI, gastrointestinal; NMSC, nonmelanoma skin cancer.

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Genovese, MC, Kalunian, KC, Walker, D, Gottenberg, JE, de Vlam, K, Mozaffarian, N, Bartok, B, Matzkies, F, Gao, J, Guo, Y, Tasset, C, Sundy, JS, Takeuchi, T
DMARDs, Janus kinase (JAK), methotrexate (MTX), rheumatoid arthritis (RA) and rheumatoid arthritis, treatment

Abstract Number: L07

VIB4920, a Novel, Engineered CD40L Antagonist Decreased Disease Activity and Improved Biomarkers of Immune Activation in Patients with Active Rheumatoid Arthritis in a Phase 1b, Multiple-Ascending Dose Proof-of-Concept Study

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SESSION INFORMATION

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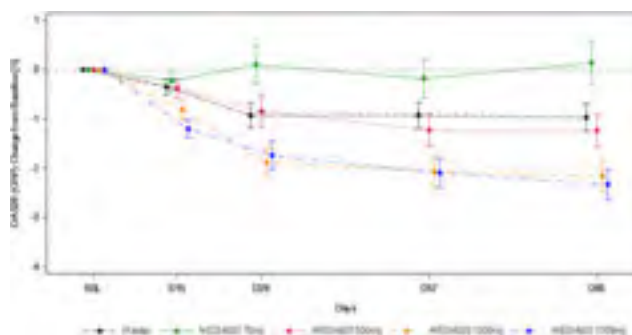
Background/Purpose: The CD40L/CD40 co-stimulatory pathway is important for T-cell-dependent antibody production and plays a central role in RA and other autoimmune diseases. VIB4920 (formerly MEDI4920) is an Fc-deficient CD40L antagonist which demonstrated acceptable safety and dose-dependent inhibition of TDAR in a Phase 1a study.

Methods: This Phase 1b, randomized, double-blind, placebo-controlled, multiple-ascending dose study enrolled 57 pts with active RA, defined as 28-joint Disease Activity Score–C-reactive protein [DAS28CRP] ≥ 3.2 ; and ≥ 4 tender and swollen

joints. Pts were positive for RF and/or anti-citrullinated peptide antibodies and previously had inadequate response to ≥ 1 DMARDs and/or anti-TNF therapy. Pts were treated with IV VIB4920 (75, 500, 1000 or 1,500 mg) or PBO every other week for 12 weeks. Key endpoints were safety, tolerability, pharmacokinetic parameters, anti-drug antibodies (ADAs), change in DAS28–CRP and biomarkers of disease activity (RF, CRP, Vectra-DA) at Day 85.

Results: Table 1 summarizes the main baseline demographic and clinical characteristics. Treatment emergent AEs were equally distributed among groups; no thrombotic events or coagulation abnormalities were noted. One grade 4 SAE of encephalitis was reported in the 1500mg VIB4920 dose group. This was considered unrelated to VIB4920. The patient subsequently was diagnosed with metastatic melanoma of the brain after recurrence of similar symptoms. ADAs were observed in over 30% of pts with the lower doses, but no ADAs were observed in the 1000 and 1500 mg dose groups. A significant dose response was demonstrated for the change from baseline in DAS28CRP at Day 85 ($P < 0.001$). A clinically important difference in DAS28CRP improvement versus placebo was observed in the 1000 and 1500 mg VIB4920 groups using mixed model for repeated measures (Figure and Table 1). Low disease activity or DAS28 remission was achieved in 50% of the 1,000 mg and 75% of the 1,500 mg dose groups compared to 13.4% in the PBO group at Day 85. There was a dose dependent decrease from baseline in RF and CRP levels and in Vectra-DA scores (Table) with the greatest effect in the two highest doses.

Baseline characteristics	PBO N=15	VIB 4920			
		75 mg N=8	500 mg N=10	1,000 mg N=12	1,500 mg N=12
Age, yrs, mean (SD)	58.3 (8.0)	57.9 (7.4)	53.7 (9.8)	52.1 (11.5)	50.9 (8.6)
Years since diagnosis, mean (min, max)	11.1 (1.1, 39.8)	12.8 (1.6, 28.5)	9.3 (2.2, 19.9)	12.6 (0.5, 44.0)	8.5 (1.2, 23.2)
DAS-28-CRP, mean (SD)	5.7 (1.18)	5.4 (0.85)	5.0 (0.98)	5.5 (0.56)	5.0 (0.58)
Swollen Joint counts, mean (SD)	10.0 (4.2)	9.5 (5.3)	7.1 (2.5)	8.8 (2.7)	6.6 (1.0)
Tender joint count, mean (SD)	16.9 (7.1)	19.3 (7.4)	11.5 (4.9)	16.2 (5.2)	11.5 (5.7)
RF/ACPA positive (%)	86.7/100	87.5/75	70.0/100	83.3/100	91.7/100
Key efficacy endpoints at Day 85					
DAS-28 adjusted mean change from BL (SE) (n)	-1.0 (0.3) (14)	0.1 (0.4) (6)	-1.2 (0.3) (10)	-2.2 (0.3) (12)	-2.3 (0.3) (12)
Low disease activity: (DAS28-CRP 2.6 to < 3.2) (%)	1 (6.7%)	0	1 (10.0)	2 (16.7)	4 (33.3)
Remission (DAS28-CRP < 2.6); (%)	1 (6.7)	0	2 (20.0)	4 (33.3)	5 (41.7)
Patient global assessment, adjusted mean change from BL (SE) (n)	-4.7 (5.8) (14)	1.8 (8.6) (6)	-11.8 (6.9) (10)	-24.0 (6.3) (12)	-25.6 (6.3) (12)
RF adjusted geometric mean reduction from BL; % (n)	6.5 (14)	0.1 (6)	39.1 (10)	48.2 (12)	51.3 (12)
Vectra-DA score adjusted mean change from BL (SE) (n)	2.1 (2.9) (14)	-0.3 (4.3) (6)	-0.1 (3.4) (10)	-8.2 (3.1) (12)	-12.2 (3.1) (12)
CRP adjusted geometric mean reduction from BL; % (n)	-14.6 (14)	15.2 (6)	-17.6 (10)	49.4 (12)	62.9 (12)



Conclusion: In this proof of concept study VIB4920 significantly decreased disease activity at Day85 achieving at least low level of disease activity in 50%-70% of patients in the two higher doses. Dose dependent decrease in RF levels and the Vectra DA score provides supportive evidence that VIB4920 effectively blocks the CD40/CD40L pathway. Combined with an acceptable safety profile these data support further development of VIB4920 for autoimmune diseases.

Disclosure: M. Albuлесcu, AstraZeneca, 1, 3; U. Müller-Ladner, None; R. Moate, AstraZeneca, 3; K. Middleton, AstraZeneca, 5; L. Wang, Viela Bio, 1, 3, AstraZeneca, 1; J. Drappa, Viela Bio, 1, 3, AstraZeneca, 1; G. Illei, Viela Bio, 1, 3, AstraZeneca, 1.

Albuлесcu, M, Müller-Ladner, U, Moate, R, Middleton, K, Wang, L, Drappa, J, Illei, G
B cell targeting, auto-immunity, clinical research, co-stimulation and rheumatoid arthritis (RA)

Abstract Number: L08

High Baseline Serum IL-6 Identifies a Subgroup of Rheumatoid Arthritis Patients with Rapid Joint Damage and Clinical Progression and Predicts Increased Sarilumab Treatment Response

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SESSION INFORMATION

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Session Title: ACR Late-breaking Abstract Session

Session Type: Late-Breaking Abstract Poster Session

Session Time: 09:00AM-11:00AM

Background/Purpose: Clinical application of biomarkers to predict response to therapy is the next frontier in RA. Despite the key role of IL-6 in RA, the utility of IL-6 to predict prognosis or treatment response in RA is limited. Post-hoc analyses of MOBILITY (NCT01061736) and MONARCH (NCT02332590) studies investigated if serum baseline IL-6 level was associated with radiographic and clinical responses to sarilumab versus comparator treatment.

Methods: Baseline IL-6 levels were measured using a validated assay in 1193 patients (pts) randomized to sarilumab (SC 150 or 200 mg q2w) +MTX or placebo (PBO) +MTX, and 300 randomized to sarilumab 200 mg or adalimumab 40 mg q2w. Efficacy was compared between and within treatment groups according to baseline IL-6 tertile using linear and logistic regression.

Results: All low tertile pts had normal IL-6 levels (<12.5 pg/mL) and >85% of high tertile pts had IL-6 levels $\geq 3 \times$ ULN. At baseline, pts in the high tertile had more joint damage, greater disease activity, and elevated levels of CRP vs the low tertile pts (nominal $P < 0.05$; Tables). In the MOBILITY PBO+MTX group, pts in the high tertile developed more joint damage than pts in the low tertile (mean \pm SD mTSS progression 4.67 ± 9.80 vs 1.51 ± 5.25 [Figure]; odds ratio 3.3; 95% CI 1.9, 5.6). Clinical and radiographic efficacy (sarilumab+MTX vs PBO+MTX) in MOBILITY improved with increasing baseline IL-6 tertile (Table 1). In MONARCH, sarilumab efficacy vs adalimumab was greater in the high vs low tertile (Table 2) – ACR20/70 for sarilumab vs adalimumab: 89%/30% vs 52%/4% [high tertile] and 64%/18% vs 58%/18% [low tertile]. Data show that high IL-6 is better than high CRP at predicting efficacy outcomes. The incidence of treatment emergent adverse events was similar across IL-6 tertiles.

Conclusion: Across clinical and radiographic endpoints, pts with elevated baseline IL-6 levels had greater response to sarilumab compared with MTX or adalimumab than pts with normal IL-6 levels. Prospective validation is warranted to confirm these data.

Acknowledgements: Study funding and medical writing support (Matt Lewis, Adelphi) provided by Sanofi and Regeneron Pharmaceuticals, Inc.

Table 1 – MOBILITY (pts with an inadequate response to MTX)

	High IL-6 (N=398)	Medium IL-6 (N=398)	Low IL-6 (N=397)	P value
Sarilumab 150 mg q2w/200 mg q2w/PBO q2w (all +MTX), n	146/121/131	129/147/122	126/128/143	
IL-6 level (pg/mL), median [range]	61.0 [31.2–648.7]	17.3 [9.8–30.7]	5.0 [1.6–9.6]	
Baseline disease characteristics, mean (SD)				
CRP (mg/L)	36.4 (30.1)	18.4 (15.5)	10.5 (11.6)	*
HAQ-DI	1.8 (0.7)	1.6 (0.6)	1.6 (0.6)	*
DAS28-CRP	6.3 (0.8)	5.9 (0.8)	5.6 (0.8)	*
mTSS	56.7 (65.7)	49.8 (62.1)	40.8 (56.5)	*

Table . (Cont'd)

	High IL-6 (N=398)	Medium IL-6 (N=398)	Low IL-6 (N=397)	P value
Sarilumab 150 mg q2w/200 mg q2w/PBO q2w (all +MTX), n	146/121/131	129/147/122	126/128/143	
CDAI	43.0 (12.4)	40.1 (12.3)	38.3 (11.6)	*
Mantel-Haenszel odds ratio (95% CI)\$ sarilumab 200 mg q2w +MTX versus PBO q2w + MTX (Week 52)				
mTSS progression	0.3 (0.1, 0.4)	0.6 (0.4, 1.0)	0.7 (0.4, 1.1)	**
ACR20	4.9 (2.8, 8.3)	3.3 (1.9, 5.7)	2.0 (1.2, 3.2)	**
ACR50	6.4 (3.5, 11.8)	3.4 (1.9, 6.2)	2.0 (1.2, 3.4)	**
ACR70	7.3 (3.3, 16.3)	3.5 (1.7, 7.4)	1.9 (1.0, 3.8)	**
DAS28-CRP <2.6	39.3 (9.4, 163.9)	4.4 (2.2, 8.9)	2.5 (1.4, 4.7)	**
CDAI ≤2.8	42.4 (4.7, 383.4)	3.9 (1.6, 9.5)	1.8 (0.8, 4.0)	**
HAQ-DI improvement ≥0.3 (Wk 16)	3.1 (1.8, 5.2)	2.2 (1.3, 3.7)	1.1 (0.7, 1.8)	**

Top *Kruskal-Wallis test $P < 0.05$ and bottom **nominal $P < 0.05$ for (high vs low) tertile IL-6-by-treatment interaction (logistic regression with treatment, study randomization stratification factors [prior biological use and region], tertile IL-6 at baseline, and tertile IL-6 at baseline-by-treatment interaction as fixed effects)

\$ Stratified by study randomization stratification factors

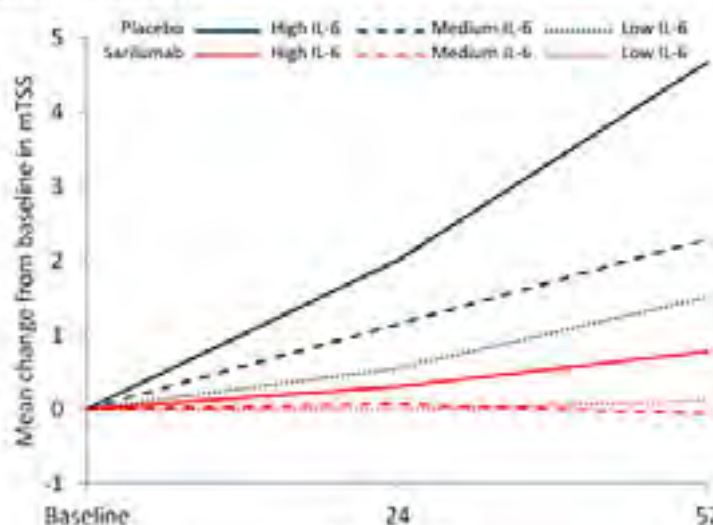
Table – MONARCH (pts with an intolerance or inadequate response to MTX)

	High IL-6 (N=100)	Medium IL-6 (N=100)	Low IL-6 (N=100)	P value
Sarilumab/adalimumab, n	46/54	47/53	55/45	
IL-6 level (pg/mL), median [range]	64.7 [39.6–692.3]	16.2 [7.2–39.5]	2.4 [1.6–7.1]	
Baseline disease characteristics, mean (SD)				
CRP (mg/L)	41.5 (34.1)	15.2 (17.1)	5.6 (9.2)	*
HAQ-DI	1.8 (0.6)	1.6 (0.6)	1.5 (0.6)	*
DAS28-CRP	6.5 (0.8)	6.0 (0.7)	5.5 (0.8)	*
CDAI	46.0 (12.2)	42.9 (11.4)	40.6 (11.7)	*
Mantel-Haenszel odds ratio (95% CI)\$ sarilumab versus adalimumab (Week 24)				
ACR20	6.6 (2.3, 18.6)	1.2 (0.5, 3.0)	1.4 (0.6, 3.1)	**
ACR50	5.5 (2.3, 13.2)	1.5 (0.6, 3.5)	1.6 (0.7, 3.7)	**
ACR70	10.5 (2.3, 48.4)	1.7 (0.6, 4.6)	1.1 (0.4, 3.2)	**
DAS28-ESR <2.6	33.9 (3.5, 328.7)	5.6 (1.6, 19.4)	1.5 (0.5, 4.4)	**
DAS28-ESR <3.2	10.5 (3.5, 31.4)	5.1 (1.8, 14.1)	2.6 (1.0, 6.7)	
DAS28-CRP <2.6	18.4 (3.8, 90.0)	4.0 (1.5, 10.9)	2.0 (0.8, 5.3)	**
DAS28-CRP <3.2	9.2 (3.4, 24.8)	2.2 (1.0, 5.1)	3.2 (1.3, 7.6)	
CDAI ≤10	3.6 (1.4, 9.0)	1.6 (0.7, 3.7)	3.1 (1.2, 7.7)	
HAQ-DI improvement ≥0.3	4.5 (1.8, 10.9)	1.4 (0.6, 3.2)	1.4 (0.6, 3.2)	

Top *Kruskal-Wallis test $P < 0.05$ and bottom **nominal $P < 0.05$ for (high vs low) tertile IL-6-by-treatment interaction (logistic regression with treatment, study randomization stratification factors [region], tertile IL-6 at baseline, and tertile IL-6 at baseline-by-treatment interaction as fixed effects)

\$ Stratified by study randomization stratification factor

Figure: Mean change from baseline in mTSS with sarilumab 200 mg q2w +MTX and placebo+MTX in MOBILITY



Disclosure: A. Boyapati, Regeneron Pharmaceuticals, Inc, 1, 3; J. Msihid, Sanofi, 1, 3; S. Schwartzman, Abbott/AbbVie, Hospira, Pfizer, Genentech, Xian Janssen Pharmaceuticals, Ltd., Novartis, Crescendo Myriad, Regeneron Pharmaceuticals, Ltd, 5, Abbott/AbbVie, Pfizer, Genentech, UCB Pharmaceuticals, Xian Janssen Pharmaceuticals, Ltd., 8, Crescendo Myriad, 5; E. Choy, Amgen, Bio-Cancer, Chugai Pharma, Ferring Pharmaceuticals, Novimmune, Pfizer, Roche, and UCB,

2, Abbvie, Amgen, AstraZeneca, Biogen, BMS, Boehringer Ingelheim, Celgene, Chelsea Therapeutics, Chugai Pharma, Daiichi Sankyo, Eli Lilly, Ferring Pharmaceutical, GSK, Hospita, ISIS, Jazz Pharmaceuticals, Janssen, MedImmune, Merrimack Pharmaceutical, MSD, Na, 6, Amgen, BMS, Boehringer Ingelheim, Chugai Pharma, Eli Lilly, Hospira, MSD, Novartis, Pfizer, Regeneron, Roche, Sanofi-Aventis, and UCB, 8; **M. C. Genovese**, Sanofi/Genzyme, Genentech/Roche, RPharm, 2, Sanofi/Genzyme, Genentech/Roche, RPharm, 5; **G. R. Burmester**, AbbVie, Pfizer, UCB, Roche, 2, AbbVie, Lilly, MSD, Pfizer, Sanofi, Roche, UCB, 5, AbbVie, Lilly, MSD, Pfizer, Sanofi, Roche, UCB, 8; **G. Lam**, Sanofi Genzyme, Regeneron, Bristol Myers Squibb, Janssen, Abbvie, UCB, 5, Regeneron, Bristol Myers Squibb, Janssen, Abbvie, UCB, 8; **T. Kimura**, Regeneron Pharmaceuticals Inc., 1, 3; **J. Sadeh**, Sanofi, 1, 3; **N. M. H. Graham**, Regeneron Pharmaceuticals, Ltd, 1, 3.

Boyapati, A, Msihid, J, Schwartzman, S, Choy, E, Genovese, MC, Burmester, GR, Lam, G, Kimura, T, Sadeh, J, Graham, NMH

IL-6, Personalized Medicine, biologic drugs and rheumatoid arthritis (RA)

Abstract Number: L09

Comparative Risk of Venous Thromboembolism with Tofacitinib Versus Tumor Necrosis Factor Inhibitors: A Cohort Study of Rheumatoid Arthritis Patients

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SESSION INFORMATION

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Background/Purpose: A potentially increased risk of venous thromboembolism (VTE) was noted in pre-marketing trials of baricitinib, which is a Janus kinase inhibitor (JAK-I). This led the FDA to restrict approval of baricitinib to only the low dose (2mg) for treatment of rheumatoid arthritis (RA). It remains unknown whether the risk of VTE is attributable to JAK-inhibition and extends to tofacitinib, which is increasingly used in RA since its approval in 2012.

Methods: We conducted a new-user cohort study using administrative claims data from the Truven Marketscan (2012-2016) and Medicare (parts A, B, and D, 2012-2015) databases to evaluate the risk of VTE with tofacitinib versus tumor necrosis factor (TNF)-inhibitors in RA patients. RA patients ≥ 18 years were identified during a 180-day baseline period of continuous insurance enrollment prior to a cohort entry date marked by treatment initiation with tofacitinib or a TNF inhibitor (adalimumab, certolizumab, etanercept, golimumab, or infliximab) without use of any biologics or tofacitinib any time prior. Patients were followed for the outcome of VTE, defined as a composite of pulmonary embolism or deep vein thrombosis diagnosis in inpatient claims, on as treated basis. A propensity score (PS) based fine-stratification weighting approach was used to account for 60 confounding variables. A weighted Cox proportional hazards model provided hazard ratio (HR) and 95% confidence intervals (CI). HRs were pooled across databases with inverse variance meta-analytic methods.

Results: A total of 34,074 and 17,086 RA patients were identified with a mean age of 50 and 71 years from Truven and Medicare, respectively; of whom 5.6% and 5.8% were tofacitinib initiators. A greater proportion of tofacitinib initiators had used ≥ 3 non-biologic disease modifying agents and glucocorticoids at baseline, indicating more active or longer duration RA in this group. PS-adjustment provided excellent balance on all 60 covariates. The incidence rates (IRs)/100 person-years were 0.60 and 0.34 in Truven and 1.12 and 0.92 in Medicare for tofacitinib and TNF-Is, respectively (**Table 1**). PS-adjusted HRs showed no significant differences in the risk of VTE between tofacitinib and TNF-Is in either database. The pooled HR was 1.33 with 95% CI ranging from 0.78 to 2.24.

Conclusion: We observed a numerically higher, but statistically non-significant, risk of VTE for tofacitinib versus TNF-Is in RA patients. The absolute rates of VTE in routine care RA patients were low and comparable to those observed in pre-marketing trials of baricitinib and tofacitinib. Although residual confounding is possible and the precision of estimates was limited due to a small event count, these results are helpful in ruling out the possibility of a large increase in the risk of VTE with tofacitinib and provide preliminary evidence regarding the safety of this JAK inhibitor agent with respect to VTE risk.

Table: Absolute and relative risk of venous thromboembolism incidence in rheumatoid arthritis patients initiating tofacitinib or tumor necrosis factor inhibitors (TNF-Is)

Data source	Exposure group	Sample size	Events	Total person years of follow-up	Incidence rates/100 person years (95% CI)	Unadjusted hazard ratio (95% CI)	PS-adjusted hazard ratio (95% CI)
Truven	TNF-I initiators	32,164	98	28,951	0.34 (0.27-0.41)	Ref.	Ref.
	Tofacitinib initiators	1,910	8	1,326	0.60 (0.26-1.19)	1.70 (0.82-3.49)	1.55 (0.75-3.18)
MarketScan	TNF-I initiators	16,091	117	12,660	0.92 (0.76-1.11)	Ref.	Ref.
	Tofacitinib initiators	995	<11*	625	1.12 (0.45-2.31)	1.16 (0.54-2.49)	1.12 (0.52-2.40)
Medicare	TNF-I initiators	48,255	215	41,611	0.52 (0.45-0.59)	Ref.	Ref.
	Tofacitinib initiators	2,905	15	1,951	0.77 (0.43-1.27)	1.42 (0.84-2.40)	1.33 (0.78-2.24)

Abbreviations: CI- Confidence interval, PS- Propensity score

* Actual number suppressed, as required by data-use agreement with the Centers for Medicare and Medicaid Services for counts below 11.

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Desai, RJ, Pawar, A, Weinblatt, ME, Kim, SC
Tofacitinib

Abstract Number: L10

Clinical Efficacy of Leflunomide/Hydroxychloroquine Combination Therapy in Patients with Primary Sjogren's Syndrome: Results of a Placebo-Controlled Double-Blind Randomized Clinical Trial

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SESSION INFORMATION

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Background/Purpose: Primary Sjogren's syndrome (pSS) is a systemic, progressive autoimmune disease characterized by secretory gland dysfunction which lacks effective therapy. Clinical trials in patients with pSS using leflunomide (LEF) or hydroxychloroquine (HCQ) previously effectively inhibited B cell hyperactivity, but induced only modest insignificant effects on clinical parameters. LEF and HCQ have complementary inhibitory properties on different immune cells, including B cells, T cells and pDCs. In vitro LEF and HCQ additively inhibit T and B cell activation as well as CXCL13 production. To study the potentially additive clinical effects of these drugs we conducted a randomized, double-blind, placebo-controlled, mono-center proof of concept study to evaluate the efficacy, safety and tolerability of LEF/HCQ therapy in patients with pSS (REPURpSS-I study).

Methods: Clinically active (ESSDAI \geq 5) pSS patients (n=29) were randomized to receive LEF 20mg daily and HCQ 400 mg twice daily or placebo/placebo (2:1) for 24 weeks. Primary and secondary endpoints were changes in ESSDAI and stimulated whole saliva (SWS) flow at 24 weeks, respectively. Other outcomes assessed were Patient Reported Indexes (ESSPRI), Multi-dimensional Fatigue Inventory (MFI), Physician's and Patient's Global Assessments, SF-36, and various circulating mediators. Outcomes also included safety assessments.

Results: Twenty-nine patients were enrolled: 8 patients received placebo and 21 received LEF/HCQ combination therapy (mean baseline ESSDAI scores of 11.5 and 11.8, respectively). Overall, LEF/HCQ was safe and well-tolerated. There was a single serious AE requiring de-blinding (pancreatitis at week 16 in the placebo cohort). The ESSDAI score at 24 weeks

significantly improved in the LEF/HCQ group ($p=0.044$, $n=9$ responders with ESSDAI decrease ≥ 3) compared to baseline, in contrast to those receiving placebo ($p=0.818$, 1 responder). As anticipated, lymphopenia and elevated CK levels were significantly higher in the LEF/HCQ group. When calculating ESSDAI scores without these, stronger decreases in the LEF/HCQ group ($p=0.000$) compared to placebo ($p=0.940$) were observed. In this case eleven patients in the LEF/HCQ group displayed a decline in ESSDAI of ≥ 3 (average decrease 6.64 points), whereas this was not observed in the placebo group. Oral dryness showed significant improvement (SWS from 823 to 1366 $\mu\text{l}/5$ minutes, $p=0.04$) in the LEF/HCQ treated group as compared to decline in the placebo group (SWS from 1125 to 815 $\mu\text{l}/5\text{min}$, $p=0.169$). Significant improvements in other measures such as ESSPRI, ESSPRI pain, ESSPRI fatigue, Physician's Global Assessment, and Patient's Global Assessment were also observed in the LEF/HCQ group (all at least $p<0.05$) but not in those receiving placebo. Serum IgG, IgM rheumatoid factor ($p<0.0001$ and 0.001 resp.) and CXCL13 decreased, whereas C3 and C4 increased ($p=0.016$ and $p=0.003$) in the LEF/HCQ group, but not in the placebo-treated patients.

Conclusion: This pilot RCT suggests clinical efficacy for LEF/HCQ combination therapy in almost half of the patients with primary Sjögren's syndrome. Larger RCT's are needed to confirm the observed effects and to identify potential biomarkers for response.

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Radstake, TRDJ, van der Heijden, EHM, Moret, FM, Hillen, MR, Lopes, AP, Rosenberg, T, Janssen, N, Kruize, AA, van Roon, JAG
DMARDs, RCT, Sjögren's syndrome and hydroxychloroquine

Abstract Number: L11

Etanercept and Methotrexate As Monotherapy or in Combination in Patients with Psoriatic Arthritis: A Phase 3, Double-Blind, Randomized Controlled Study

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Background/Purpose: Methotrexate (MTX) and tumor necrosis factor inhibitors (TNFi) such as etanercept (ETN) are often prescribed for psoriatic arthritis (PsA) either alone or in combination, but fundamental gaps in knowledge about their optimal use remain. This study examined the efficacy of MTX monotherapy relative to ETN monotherapy and the value of adding MTX to ETN in key clinical domains of PsA, including progressive joint damage.

Methods: This phase 3, randomized controlled, double-blind international study enrolled patients with active PsA based on Classification Criteria for Psoriatic Arthritis (CASPAR). They were naïve to biologic drugs with no prior MTX for PsA. A total of 851 patients were randomized to 3 groups for 48 weeks: ETN 50 mg plus MTX 20 mg weekly (Combo; $N = 283$); ETN 50 mg plus oral placebo weekly (ETN-mono; $N = 284$); or MTX 20 mg plus injectable placebo weekly (MTX-mono; $N = 284$). The primary endpoint was the American College of Rheumatology (ACR)20 response at week 24. The key secondary endpoint was Minimal Disease Activity (MDA) response at week 24. The study was powered to detect a treatment difference in ACR20 and MDA at week 24 between the Combo and the MTX-mono arms and between the ETN-mono and MTX-mono arms, tested in a Bonferroni-based gatekeeping chain procedure. Additional endpoints included other measures of inflammatory arthritis, radiographic progression, severity of non-articular disease manifestations, and patient-reported outcomes.

Results: Baseline characteristics were well balanced in the 3 study arms. Mean (SD) age was 48.4 (13.1) years, most patients were white, and median PsA duration was 0.6 years (mean [SD] 3.2 [6.3] years). From weeks 4 to 24, the MTX-containing arms maintained a mean MTX dose >18.8 mg. ACR20 and MDA response rates at week 24 were significantly greater for ETN-mono vs MTX-mono (ACR20: 60.9% vs 50.7% [$P=0.029$]; MDA: 35.9% vs 22.9% [$P=0.005$]) and for Combo vs MTX-mono (ACR20: 65.0% vs 50.7% [$P=0.005$]; MDA: 35.7% vs 22.9% [$P=0.005$]). At week 48, the Combo and ETN-mono arms showed less radiographic progression compared with the MTX-mono arm (Table). Other secondary outcomes are

shown in the Table. Overall, the Combo and ETN-mono arms had similar results, with some differences in skin outcomes. Aside from GI events, adverse event rates were similar in the 3 study arms. No new safety signals were seen.

Conclusion: This is the first head-to-head comparison of MTX and a TNFi to address fundamental questions in the treatment of PsA. ETN monotherapy or ETN in combination with MTX showed greater efficacy compared with MTX monotherapy. Addition of MTX to ETN did not appear to improve efficacy compared with ETN alone. These results support the use of ETN as monotherapy for PsA.

Acknowledgment: Linda Rice at Amgen Inc. and Julia Gage (on behalf of Amgen Inc.) assisted in abstract drafting. The study sponsor was Amgen Inc.

Table. Primary outcome and other measures of disease activity at week 24^a

	MTX Monotherapy N = 284	ETN Monotherapy ^b N = 284	Combination ^b N = 283
ACR 20 response, %	50.7	60.9; P=0.029	65.0; P=0.005
ACR 50 response, %	30.6	44.4; <i>P=0.006</i>	45.7; <i>P<0.001</i>
ACR 70 response, %	13.8	29.2; <i>P<0.001</i>	27.7; <i>P<0.001</i>
MDA response, %	22.9	35.9; P=0.005	35.7; P=0.005
VLDA response, %	4.8	15.2; <i>P<0.001</i>	14.3; <i>P<0.001</i>
PASDAS			
Mean (SE) at BL	6.1 (0.1)	6.0 (0.1)	6.0 (0.1)
Change from BL, mean (SE)	−2.0 (0.1)	−2.6 (0.1); <i>P<0.001</i>	−2.6 (0.1); <i>P<0.001</i>
DAPSA			
Mean (SE) at BL	46.5 (1.4)	43.4 (1.4)	43.8 (1.4)
Change from BL, mean (SE)	−22.6 (1.4)	−25.0 (1.3); <i>P=0.24</i>	−24.9 (1.4); <i>P=0.23</i>
LDI			
> 0 at BL, %	34.5	33.8	31.8
Change from BL, mean (SE)	−128.8 (26.8)	−119.1 (20.7); <i>P=0.85</i>	−110.2 (22.7); <i>P=0.68</i>
Patients with resolution, %	65.2	76.4; <i>P=0.12</i>	79.3; <i>P=0.057</i>
SPARCC Enthesitis			
> 0 at BL, %	67.3	66.5	69.3
Change from BL, mean (SE)	−3.1 (0.3)	−3.0 (0.3); <i>P=0.93</i>	−2.9 (0.3); <i>P=0.70</i>
Patients with resolution, %	43.1	52.6; <i>P=0.11</i>	47.5; <i>P=0.55</i>
BSA			
% improvement from BL in patients with ≥ 3% BSA at BL, mean (SE) [n] ^c	66.1 (2.8) [179]	69.8 (2.7) [166]; <i>P=0.49</i>	75.5 (3.7) [163]; <i>P=0.031</i>
% improvement from BL in patients with ≥ 10% BSA at BL, mean (SE) [n] ^c	65.7 (3.7) [92]	74.2 (3.3) [91]; <i>P=0.12</i>	81.6 (2.6) [86]; <i>P<0.001</i>
sPGA^d			
Clear or almost clear (0/1) status for patients with ≥ 3% BSA at BL, %	66.3	72.3; <i>P=0.40</i>	77.6; <i>P=0.019</i>
Clear or almost clear (0/1) status for patients with ≥ 10% BSA at BL, %	59.3	79.1; <i>P=0.012</i>	78.8; <i>P=0.004</i>
mNAPSI			
> 0 at BL, %	65.1	72.5	69.6
Change from BL, mean (SE)	−1.1 (0.2)	−1.5 (0.2); <i>P=0.10</i>	−1.7 (0.2); <i>P=0.020</i>
Patients achieving a score of 1, %	38.8	43.5; <i>P=0.44</i>	48.8; <i>P=0.14</i>
HAQ-DI			
Mean at BL (SE)	1.27 (0.04)	1.15 (0.04)	1.15 (0.04)
Change from BL, mean (SE)	−0.41 (0.04)	−0.44 (0.04); <i>P=0.67</i>	−0.47 (0.04); <i>P=0.34</i>
SF-36			
Overall mean (SE) at BL	80.8 (0.9)	82.9 (0.9)	83.6 (0.9)
Total change from BL, mean (SE)	9.2 (0.8)	10.6 (0.8); <i>P=0.31</i>	11.3 (0.9); <i>P=0.11</i>
PCS change from BL, mean (SE)	6.0 (0.6)	7.8 (0.6); <i>P=0.033</i>	8.0 (0.6); <i>P=0.015</i>
MCS change from BL, mean (SE)	3.3 (0.6)	2.8 (0.6); <i>P=0.56</i>	3.3 (0.6); <i>P=0.97</i>
Radiographic Progression			
Erosion score of > 0 at baseline, %	82.9	80.6	81.8
mTSS change from BL at week 48, mean (SE)	0.08 (0.03)	−0.04 (0.04); <i>P=0.014</i>	−0.01 (0.03); <i>P=0.041</i>
Non-progression at week 48 (mTSS change ≤ 0 from baseline), %	89.4	94.7; <i>P=0.088</i>	94.7; <i>P=0.033</i>

American College of Rheumatology; BL, baseline; BSA, (psoriasis-affected) body surface area; DAPSA, Disease Activity Index For Psoriatic Arthritis; ETN, etanercept; HAQ-DI, Health Assessment Questionnaire Disability Index; LDI, Leeds Dactylitis Index; MCS, mental component summary; MDA, minimal disease activity; mNAPSI, modified Nail Psoriasis Severity Index; mTSS, van der Heijde modified Total Sharp Score (scoring system for X-rays of the hands and feet taken at baseline and at weeks 24 and 48); MTX, methotrexate; PASDAS, Psoriatic Arthritis Disease Activity Score; PCS, physical component summary; SE, standard error; SF-36, Short Form (36) health survey; SPARCC, Spondyloarthritis Research Consortium of Canada; sPGA, static Physician Global Assessment; VLDA, Very Low Disease Activity. ^aExcept for the radiographic progression endpoints, which are shown for week 48. ^bP-values are for the comparison with MTX monotherapy. Only the P-values in bold for the ACR 20 primary endpoint and MDA key secondary endpoint measured statistical significance. All other P-values are descriptive and are italicized. ^c[n] refers to the number of patents analyzed. ^dThe sPGA scale ranges from 0 (clear) to 5 (severe).

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Combination therapies, etanercept, methotrexate (MTX), psoriatic arthritis and randomized trials

Abstract Number: L12

Efficacy and Safety of Ixekizumab in the Treatment of Radiographic Axial Spondyloarthritis: 16 Week Results of a Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial in Patients with Prior Inadequate Response or Intolerance to 1 or 2 Tumor Necrosis Factor Inhibitors

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: ACR Late-breaking Abstract Session

Session Type: Late-Breaking Abstract Poster Session

Session Time: 09:00AM-11:00AM

Background/Purpose: TNF inhibitors (TNFi) are recommended for patients with axial SpA (axSpA) who do not respond to or tolerate NSAIDs. Some patients are inadequate responders or intolerant to TNFi and this axSpA population has not been exclusively studied in a clinical trial. In COAST-W (NCT02696798), we investigated the efficacy and safety of ixekizumab, a high-affinity monoclonal antibody that selectively targets IL-17A, in patients with active radiographic axSpA (r-axSpA) with prior inadequate response (IR) or intolerance to 1 or 2 TNFi.

Methods: In this randomized, double-blind, placebo-controlled, Phase 3 trial, adult patients with IR/intolerance to 1 or 2 TNFi and an established diagnosis of r-axSpA (patients fulfilling ASAS classification criteria for axSpA, with radiographic sacroiliitis centrally defined by modified New York criteria) were recruited and randomized 1:1:1 to placebo (PBO) or 80-mg subcutaneous ixekizumab every 2 (IXEQ2W) or 4 (IXEQ4W) weeks, with either 80-mg or 160-mg starting dose (assigned 1:1). The primary endpoint was ASAS40 response rate at Week 16. Secondary outcomes and safety were also assessed. Categorical outcomes were analyzed by logistic regression with non-responder imputation. Continuous outcomes were analyzed by mixed-effects model of repeated measures except MRI SPARCC scores (analysis of covariance using observed case without imputation).

Results: In total, 316 patients were randomized to PBO (N=104), IXEQ2W (N=98), or IXEQ4W (N=114). All patients possessed very active (mean BASDAI: 7.4±1.3) and longstanding disease (median duration of symptoms = 16.7 years); 90% had a prior IR and 10% were intolerant to TNFi. At Week 16, significantly higher proportions of IXEQ2W (N=30 [30.6%]; p=0.003) or IXEQ4W (N=29 [25.4%]; p=0.017) patients achieved ASAS40 versus PBO (N=13 [12.5%]), with statistically significant differences as early as Week 1 for both treatment regimens. Significant improvements were observed for disease activity, function, quality of life, spinal MRI inflammation, and high sensitivity CRP (Table 1). The majority of treatment emergent adverse events (AE) were mild/moderate (Table 2). Serious AEs were consistent across arms. One death was reported (IXEQ2W) due to suicide, which was not attributable to study drug per the blinded principal investigator.

Conclusion: Both ixekizumab treatment regimens yielded rapid and significant improvements in the signs and symptoms of r-axSpA at Week 16 in patients with previous IR or intolerance to 1 or 2 TNFi, compared to PBO.

Table 1. COAST-W primary and secondary efficacy outcomes at Week 16 for the intent-to-treat population (N=315).^a Baseline (Week 0) results included for continuous outcomes.

	PBO N=104		IXEQ2W N=98		IXEQ4W N=114	
Binary Outcomes, Wk 16	n (%)		n (%)		n (%)	
ASAS40	13 (12.5)		30 (30.6) [†]		29 (25.4) [†]	
ASAS20	31 (29.8)		46 (46.9) [†]		55 (48.2) [†]	
ASDAS <2.1	5 (4.8)		16 (16.3) [†]		20 (17.5) [†]	
Continuous Outcomes	Wk 0 Mean±SD	Wk 16 LSM CFB±SE	Wk 0 Mean±SD	Wk 16 LSM CFB±SE	Wk 0 Mean±SD	Wk 16 LSM CFB±SE
ASDAS	4.1±0.6	-0.1±0.1	4.2±0.6	-1.1±0.1 [‡]	4.2±0.9	-1.2±0.1 [‡]
BASDAI	7.3±1.3	-0.9±0.2	7.5±1.3	-2.1±0.2 [‡]	7.5±1.3	-2.2±0.2 [‡]
BASFI	7.0±1.7	-0.6±0.2	7.4±1.4	-1.9±0.2 [‡]	7.4±1.8	-1.7±0.2 [‡]
SF-36 PCS	30.6±7.8	1.4±0.8	27.0±7.3	6.1±0.8 [‡]	27.5±8.3	6.8±0.8 [‡]
ASAS Health Index	9.0±3.5	-0.9±0.3	10.1±3.6	-1.6±0.4	10.0±3.7	-1.9±0.3 [†]
MRJ SPARCC	6.4±10.2	3.0±1.4	11.1±20.0	-4.0±1.0 [‡]	6.3±10	-3.0±1.4 [†]
High-Sensitivity CRP (mg/L)	16.0±22.3	9.7±2.7	16.9±19.8	-9.1±2.9 [‡]	20.2±34.3	-11.1±2.6 [‡]

CRP=315 patients with prior TNFi experience, 205 (65.1%) had an inadequate response to 1 TNFi, 78 (24.8%) had an inadequate response to 2 TNFi, and 32 (10.2%) were intolerant. One patient was inadvertently enrolled without prior TNFi experience.

^aNumber of patients observed at Week 16: PBO: N₁ = 48; IXEQ2W: N₂ = 45; IXEQ4W: N₃ = 49.

[†]p<0.05, [‡]p<0.01, ^{‡‡}p<0.001, all vs placebo.

ASAS = Assessment of Spondyloarthritis International Society criteria; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CFB = change from baseline; CRP = C-reactive protein; IXEQ2W = ixekizumab every 2 weeks; IXEQ4W = ixekizumab every 4 weeks; LSM = least squares mean; MRJ = magnetic resonance imaging; n = number of patients in analysis category; N = number of patients in analysis population; PBO = placebo; SD = standard deviation; SE = standard error; SF-36 PCS = Medical Outcomes Study 36-Item Short-Form Health Survey Physical Component Score; SPARCC = Spondyloarthritis Research Consortium of Canada; Wk = Week.

Table 2. Adverse events (AE) and treatment-emergent adverse events (TEAE) during the 16-week blinded treatment dosing period of COAST-W. Values presented as n (%).

	PBO N=104	IXEQ2W N=98	IXEQ4W N=114
TEAE (patients reporting ≥1 event)	51 (49.0)	59 (60.2)	73 (64.0)
Mild	18 (17.3)	23 (23.5)	34 (29.8)
Moderate	26 (25.0)	32 (32.7)	35 (30.7)
Severe	7 (6.7)	4 (4.1)	4 (3.5)
Discontinuation due to AE	2 (1.9)	3 (3.1)	10 (8.8)
Serious AE	5 (4.8)	3 (3.1)	4 (3.5)
Death	0	1 (1.0) ^a	0

^aCause of death was suicide which was determined to be unrelated to study drug by the blinded principal investigator. The patient had prior history of depression of about 1 year (reported as mild at study entry).

IXEQ2W = ixekizumab every 2 weeks; IXEQ4W = ixekizumab every 4 weeks; PBO = placebo; n = number of patients in analysis category; N = number of patients in analysis population.

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Biologics, ankylosing spondylitis (AS) and axial spondyloarthritis

Methods: Pts were initially randomized to receive intravenous (IV) SEC 10 mg/kg at baseline, Weeks (Wks) 2 and 4, followed by subcutaneous (SC) SEC 150 mg (IV→150 mg) or 75 mg (IV→75 mg) every 4 wks thereafter or matched placebo (PBO). Based on ASAS20 response at Wk 16, PBO pts were re-randomized to secukinumab 150 or 75 mg SC at Wk 16 (non-responders) or Wk 24 (responders). After the 2-year core trial, 274 pts entered the 3-year extension study. Detailed study design has been reported previously¹. Dose escalation from SEC 75 mg to 150 mg was allowed following a protocol amendment. Assessments at Wk 260 included ASAS20, ASAS40, ASAS5/6 and other efficacy outcomes (reported as observed). Clinical efficacy including dose escalation results are reported for all pts who entered the extension trial (i.e.

Efficacy endpoints	SEC Groups Including PBO Switchers		Dose Escalated Group
	SEC IV-150 mg and PBO-SEC 150 mg (N = 128)	SEC IV-75 mg and PBO-SEC 75 mg (N = 148)	SEC IV-75 mg and PBO-SEC 75 mg to 150 mg (N=52)
ASAS20 ≥40 n (%)	88 (78.0) / 73 (55.2)	93 (74.4) / 68 (54.4)	56 (75.6) / 42 (53.8)
BASDAI50 n (%)	71 (63.4)	71 (56.3)	45 (57.0)
BASDAI change from BL, mean±SD	-3.5 (2.08)	-3.2 (2.19)	-3.3 (2.33)
BASDAI, mean±SD	2.81 (1.76)	3.03 (1.93)	3.14 (2.03)
ASDAS-CRP/active Disease, n (%)	30 (27.3)	31 (24.5)	18 (23.1)
BAF1 change from BL, mean±SD	-3.1 (2.26)	-2.4 (2.18)	-2.1 (2.21)
BAF1, mean±SD	2.4 (3.77)	3.19 (2.31)	3.4 (2.51)
BASMI change from BL, mean±SD	-0.7 (1.12)	-0.41 (1.02)	-0.23 (0.91)
BASMI, mean±SD	3.23 (1.46)	3.78 (1.79)	3.89 (1.89)
ASAS Partial Remission, n (%)	39 (34.8)	26 (20.8)	14 (17.9)
ASAS PR, n (%)	73 (65.2)	75 (59.5)	47 (59.5)
SF-36 PCS change from BL, mean±SD	0.0 (8.02)	1.4 (8.74)	1.7 (7.38)
SF-36 PCS, mean±SD	46.3 (8.66)	44.8 (7.45)	44.7 (7.57)

Responses before and after dose escalation (based on patients with data up to 72 weeks after the escalation)

Variables	Pre-escalation (75mg) N = 52	Responses post-escalation (SEC 75 mg to 150 mg, N = 92)				
		12 to 20 wks N = 30	24 to 32 wks N = 75	36 to 44 wks N = 90/97	48 to 60 wks N = 51	54 to 72 wks N = 24
ASAS20, %	74.8	75.0	76.0	72.1 ^a	74.5	62.4
ASAS40, %	51.2	62.5	62.7	59.4 ^a	54.9	61.8
ASAS PR, %	15.9	20.0	18.7	22.1 ^a	19.6	17.6
ASAS50, %	56.1	60.0	60.7	58.2 ^a	62.7	73.5
BASDAI50, %	51.2	56.3	62.7	59.1 ^a	58.0	54.8

N for ASAS20 and ASAS40 was 112, 126 and 75 for SEC 150 mg, SEC 75 mg, and dose escalated group, respectively (all including PBO switchers). N for ASAS PR and BASDAI50 was 132, 128 and 75 for SEC 150 mg, SEC 75 mg, and dose escalated group, respectively (all including PBO switchers).

N, total number of randomized patients; M, number of evaluable patients; n, number of responders; ASDAS, Assessment of Spondyleritis Disease Activity Index; SF-36, Short-Form 36; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BAF1, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Mobility Index; CRP, C-reactive protein; PBO, placebo; SD, standard deviation; SEC, secukinumab; SF-36 PCS, short-form 36 physical component summary.

Re-escalation is defined as the last assessment done on or before the patient administered the escalated dose.

All values are confidence intervals unless noted with both one and a two-sided confidence intervals. Data available are included in this analysis.

including placebo-switchers); former is based on randomized dose whereas latter is based on treatment dose. Safety is reported as exposure adjusted incidence rate (EAIR)/100 pt-years for all pts (n = 360) who received ≥ 1 dose of study treatment.

Results: A total of 84.4% (108/128) and 83.6% (122/146) of all the pts (i.e. including PBO switchers) who received SEC 150 mg and 75 mg, respectively, completed 260 wks of treatment. Improvements in ASAS20, ASAS40, BASDAI50, and other efficacy outcomes were sustained through Wk 260 (Table). A total of 82 pts on SEC 75 mg (56.2% of total 75 mg population) had dose escalated to 150 mg after Week 168; ASAS40, ASAS PR, ASAS 5/6, and BASDAI50 responses were improved in pts whose dose was escalated from SEC 75 mg to 150 mg (Table). Across the entire treatment period (SEC exposure [mean \pm SD]: 206.6 \pm 90.17 weeks), SEC was well tolerated with a safety profile consistent over the course of the study. EAIRs of selected adverse events of interest were 0.1, 0.6, 1.8 and 0.5 per 100 pt-years for ulcerative colitis, Crohn's disease, uveitis and malignant/unspecified tumors, respectively.

Conclusion: Secukinumab provided sustained efficacy across multiple domains of AS including signs and symptoms, physical function, and objective markers of inflammation through 5 years. Efficacy improved in pts who had dose escalation from 75 mg to 150 mg. Secukinumab was well tolerated over long-term use with no new safety signals identified and a safety profile consistent with previous reports.¹

Reference:

1. Braun J, *et al. Ann Rheum Dis.* 2017;76:1070-1077

Disclosure: X. Baraliakos, AbbVie, Bristol-Myers Squibb, Celgene, Chugai, Janssen, MSD, Novartis, Pfizer and UCB Pharma, 2, 5, 8; J. Braun, AbbVie (Abbott), Amgen, BMS, Boehringer, Celgene, Celltrion, Centocor, Chugai, EBEWE Pharma, Medac, MSD (Schering-Plough), Mundipharma, Novartis, Pfizer (Wyeth), Roche, Sanofi-Aventis and UCB, 2, 5, AbbVie (Abbott), Amgen, BMS, Boehringer, Celgene, Celltrion, Centocor, Chugai, EBEWE Pharma, Medac, MSD (Schering-Plough), Mundipharma, Novartis, Pfizer (Wyeth), Roche, Sanofi-Aventis and UCB, 8; A. A. Deodhar, AbbVie Inc., 2, Eli Lilly and Co., 2, 5, Janssen, 2, 5, Novartis, 2, 5, Pfizer, Inc., 2, 5, UCB, Inc., 2, 5, Sun pharma, 2; D. Poddubnyy, AbbVie, Janssen, MSD, Novartis, Pfizer, BMS, Boehringer, UCB and Roche, 2, 5, 8; A. J. Kivitz, AbbVie, Pfizer, Genentech, UCB, Sanofi/Regeneron and Celgene, 5, : Celgene, Pfizer, Sanofi/Regeneron, Horizon and Merck, 8; H. Tahir, Novartis, Eli Lilly, and AbbVie, 8; F. van Den Bosch, AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly and Co., Janssen, Merck, Novartis, Pfizer, Sanofi, UCB, 2, 5, 8; E. M. Delicha, Novartis, 3; Z. Tallozy, Novartis, 1, 3; A. Fierlinger, Novartis, 1, 3.

Baraliakos, X, Braun, J, Deodhar, AA, Poddubnyy, D, Kivitz, AJ, Tahir, H, van Den Bosch, F, Delicha, EM, Tallozy, Z, Fierlinger, A
Ankylosing spondylitis (AS)

Abstract Number: L14

Top-Line Results of a Phase 2, Double-Blind, Randomized, Placebo-Controlled Study of a Reversible B Cell Inhibitor, XmAb[®] 5871, in Systemic Lupus Erythematosus (SLE)

Joan T. Merrill¹, Joshua June², Fotios Koumpouras³, Wambui Machua⁴, Mohammad Faisal Khan⁵, Anca Askanase⁶, Arezou Khosroshahi⁷, Saira Sheikh⁸, Paul A. Foster⁹ and Debra J. Zack⁹, ¹Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, ²Joshua June, DO, Lansing, MI, ³Internal Medicine, Rheumatology, Yale University School of Medicine, New Haven, CT, ⁴Internal Medicine, Piedmont Atlanta Hospital, Atlanta, GA, ⁵Arthritis & Rheumatology Center of Oklahoma, PLLC, Oklahoma City, OK, ⁶Director, Columbia University Lupus Center, Columbia University Medical Center, Bronx, NY, ⁷Department of Medicine, Division of Rheumatology, Emory University School of Medicine, Atlanta, GA, ⁸Medicine, University of North Carolina, Chapel Hill, NC, ⁹Xencor, Inc., San Diego, CA

SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: ACR Late-breaking Abstract Session

Session Type: Late-Breaking Abstract Poster Session

Session Time: 09:00AM-11:00AM

Background/Purpose: XmAb5871 is a humanized anti-CD19 antibody Fc-engineered for increased affinity to FcγRIIb. Co-ligation of CD19 and FcγRIIb inhibits B lineage cells key to SLE pathogenesis. This Phase 2 study was designed to

minimize background medications and placebo responses to improve interpretation of a small trial in a complex, heterogenous disease.

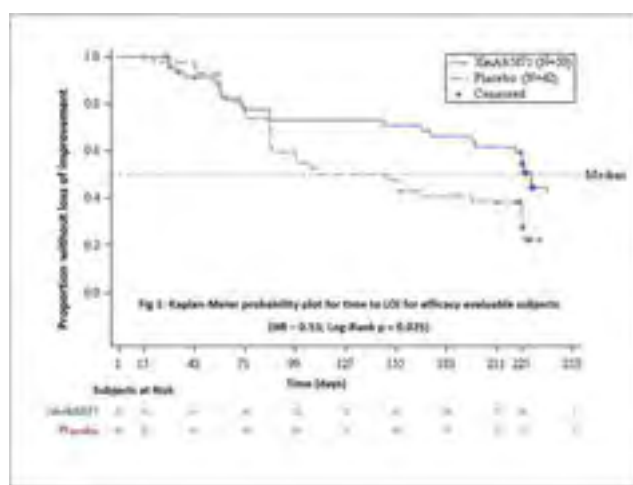
Methods: SLE patients were enrolled with moderate to severe, non-organ threatening disease, which was ameliorated during screening with ≥ 160 mg of IM Depo-Medrol. Improvement was required before randomization, defined by SLEDAI decrease ≥ 4 points or ≥ 1 grade decrease in ≥ 1 BILAG A or B score. All immunosuppressive drugs were withdrawn except antimalarials or up to 10 mg/day prednisone or equivalent. Subjects were randomized to IV XmAb5871 (5 mg/kg) or placebo and given Depo-Medrol 80 mg IM on Days 1 and 15. Study treatments were every 14 days for up to 16 doses until Day 225 or loss of improvement (LOI), defined as SLEDAI increase of ≥ 4 points OR new BILAG A or B, with investigator agreement of significance. At LOI, patients could receive standard of care and withdraw. The primary endpoint was the proportion of subjects with no LOI by Day 225 in the efficacy evaluable group, defined as those who completed Day 225, had LOI, or discontinued due to a drug-related adverse event. Those who dropped out for other reasons were excluded from this analysis.

Results: 104 patients (99 female) were randomized. Median age was 44.5 years (20-65). XmAb5871-treated subjects stayed in the study longer receiving more infusions than the placebo group – 6.9 months vs 3.6 months and 15 vs 8.5, respectively. Six XmAb-treated patients were withdrawn for infusion-related events. 10 patients terminated from the placebo arm vs 2 from the XmAb5871-treated arm with exclusion from the efficacy evaluable population. These exclusions led to higher placebo response rates compared to the ITT population.

Table 1: Primary and Secondary Endpoints: Maintenance of Improvement

	Efficacy Evaluable Population			Intent to Treat Population		
	XmAb5871	Placebo	p value	XmAb5871	Placebo	p value
% Response at Day 225	42	28.6	0.181	40.4	23.1	0.06
% Response at Day 169	58	40.5	0.11	57.7	34.6	0.02

¹ Primary Endpoint



The most common AEs in XmAb5871-treated patients were transient, infusion-related gastrointestinal side effects during the 1st or 2nd infusion. There were 8 SAEs in 7 XmAb-treated subjects, 5 in 4 placebo patients, no opportunistic infections, and no deaths. Major organ flares: Placebo: 2 nephritis, 1 enteritis, 1 systemic flare; XmAb5871: 1 pneumonitis. All were treated and stabilized. Infection rate was low compared to other SLE trials; one pneumonia occurred in an XmAb5871-treated patient.

Conclusion: XmAb5871 was well-tolerated, infection rate was low, flares were similar to other lupus trials. Preliminary data from this small trial supports further evaluation of XmAb5871 in SLE.

Disclosure: J. T. Merrill, Consulting: GSK, EMD Serono, Celgene, BMS, Astra Zeneca, Lilly, Immunopharma, Amgen, Janssen, Sanofi, Neovacs, Anthera. Remegen, Astellas, Incyte, Oncomed, ILTOO, Idorsia, Glenmark Grants and Contracts: Xencor, BMS, GSK, 2, 5; J. June, None; F. Koumpouras, None; W. Machua, None; M. F. Khan, None; A. Askanase, None; A. Khosroshahi, None; S. Sheikh, None; P. A. Foster, Xencor Inc, 1, 3; D. J. Zack, Xencor Inc, 1, 3.

Merrill, JT, June, J, Koumpouras, F, Machua, W, Khan, MF, Askanase, A, Khosroshahi, A, Sheikh, S, Foster, PA, Zack, DJ B cell targeting, Fc receptors, clinical trials and systemic lupus erythematosus (SLE)

The Diagnostic Accuracy of PET/CT Scan of the Head, Neck and Thorax Compared with Temporal Artery Biopsy in Patients Newly Suspected of Having GCA

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: ACR Late-breaking Abstract Session

Session Type: Late-Breaking Abstract Session

Session Time: 16:00PM-18:00PM

Background/Purpose: The diagnostic accuracy of PET/CT against temporal artery biopsy (TAB) in patients suspected of having GCA has not been well studied. PET/CT has traditionally been used to image the aorta and primary branches, but newer generation scanners can also detect inflammation in the smaller temporal (TA), occipital (OA), maxillary (MA) and vertebral arteries (VA). We assessed the accuracy of a newer generation PET/CT time-of-flight scanner for GCA.

Methods: 64 newly suspected GCA patients were enrolled over 20 months. All underwent PET/CT from the vertex to diaphragm within 72 hours of starting corticosteroids and before TAB. Two PET experienced nuclear medicine physicians

Figure: Axial PET/CT head from a biopsy positive GCA patient showing increased FDG tracer uptake in the maxillary and right superficial temporal arteries consistent with active arteritis



Table: PET/CT compared with a) temporal artery biopsy and b) clinical diagnosis for GCA

a) PET/CT compared with temporal artery biopsy (TAB) for GCA			
Patients			Performance
	TAB +	TAB -	Total
PET/CT +	11	7	18
PET/CT -	1	39	40
Total	12	46	58
			Sensitivity: 92% Specificity: 85% PPV: 61% NPV: 98%
b) PET/CT compared with clinical diagnosis for GCA			
Patients			Performance
	Clinical +	Clinical -	Total
PET/CT +	15	4	19
PET/CT -	8	39	45
Total	21	43	64
			Sensitivity: 71% Specificity: 91% PPV: 79% NPV: 87%

PPV: Positive predictive value. NPV: Negative predictive value

blinded to clinical and biopsy data independently reported scans as globally positive or negative for GCA. They also rated the grade that tracer (FDG) uptake exceeded background blood pool for 18 artery segments and the maximum grade per patient (0 = none, 1 = minimal/equivocal, 2 = moderate, 3 = very marked). Discordant results were resolved by consensus. The clinical diagnosis was made at the six-month mark by consensus between the PET/CT blinded treating clinician and blinded external reviewers.

Results: 58/64 (91%) patients underwent TAB and 12/58 (21%) biopsies were positive for GCA. 21/64 (33%) had a clinical diagnosis of GCA and 42 (66%) met the 1990 ACR criteria for GCA. Compared with TAB, global GCA assessment by PET/CT had sensitivity (Sn) 92%, specificity (Sp) 85%, positive predictive value (PPV) 61% and negative predictive value (NPV) 98%. Interobserver reliability was good ($\kappa = 0.65$). Compared with clinical diagnosis, PET/CT had Sn 71% and Sp 91%. 2/7 PET/CT 'false positive' cases had GCA consistent disease flares when corticosteroids were weaned. Defining an uptake grade cut-off 1+ in any vessel as a positive scan gave Sn 100% and Sp 46% against TAB while a cut-off 2+ gave Sn 83% and Sp 83%. Four (33%) TAB positive patients had grade 2+ uptake localized to the TA, OA, MA or VA arteries and may have been missed on older generation scans.

Conclusion: This PET/CT protocol had good diagnostic accuracy. The high NPV of 98% indicates that it could be used as a first-line test to rule out GCA.

Disclosure: A. Sammel, Arthritis Australia, 2; E. Hsiao, None; G. Schembri, None; K. Nguyen, None; J. Brewer, None; L. Schrieber, None; B. Janssen, None; P. Youssef, None; C. Fraser, None; E. Bailey, None; D. Bailey, None; P. Roach, None; R. Laurent, None.

Sammel, A, Hsiao, E, Schembri, G, Nguyen, K, Brewer, J, Schrieber, L, Janssen, B, Youssef, P, Fraser, C, Bailey, E, Bailey, D, Roach, P, Laurent, R

Diagnostic imaging, giant cell arteritis and positron emission tomography (PET)

Abstract Number: L16

Intra-Articular TPX-100 in Knee Osteoarthritis: Robust Functional Response at 6 and 12 Months Is Associated with Increased Tibiofemoral Cartilage Thickness

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SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: ACR Late-breaking Abstract Session

Session Type: Late-Breaking Abstract Session

Session Time: 16:00PM-18:00PM

Background/Purpose: TPX-100, a peptide derived from Matrix Extracellular Phosphoglycoprotein (MEPE), has been shown to induce articular cartilage regeneration after cartilage injury in animal models. A previously-reported Phase 2 double-blind, randomized, 12-month clinical trial in subjects with bilateral mild-to-moderate patellofemoral (PF) OA showed knees treated with TPX-100 (one IA injection/week for 4 weeks) had statistically significant and clinically meaningful improvements in knee function at 6 and 12 months compared with placebo-exposed knees. No between-knee differences in patellar cartilage morphology were seen; however, only 14% of knees had PF cartilage changes within limits of detection on follow-up MRIs, limiting comparative power. We now report a post-hoc clinical “responder” analysis, using pre-specified criteria for functional improvement (Roos 2003). Because nearly $\frac{3}{4}$ of subjects had bilateral tibiofemoral (TF) OA as well as PF OA, we analyzed TF cartilage thickness/volume changes in responders versus non-responders.

Methods: Adult men and women with MRI-confirmed bilateral (ICRS 2-3) PF OA were enrolled at 18 U.S. sites. Among subjects enrolled (n=118), one knee was randomly assigned to receive IA TPX-100 via 4 weekly injections (20-200 mg/injection), while the contralateral knee received identical placebo injections. The use of the contralateral knee as an internal control was designed to lessen bias due to inter-subject variation (e.g. age, sex, BMI, genetic factors, and activity levels). Knee-specific patient-reported outcomes (PROs) included the Knee Osteoarthritis Outcome Scores (KOOS) and WOMAC scores for each knee. Baseline, 6- and 12-month MRIs were read centrally, blind to treatment assignment. This analysis, while post hoc, was conducted based on pre-defined criteria for clinically-important differences derived from the literature. The database was locked prior to the present analysis.

Results: As reported previously, TPX-100 was safe and well tolerated. Overall analgesic use, including NSAIDs, declined by 68%. Efficacy analyses were based, per protocol, on subjects who received 4 weekly IA injections of 200 mg TPX-100 or placebo in each knee and who had at least one MRI after baseline (n=93 subjects/186 knees). Among TPX-100-treated knees, 61/93 (66%) met pre-defined responder criteria, with significantly more TPX-100-treated knees than placebo-exposed knees showing functional improvement at 6 or 12 months or both ($p \leq 0.02$). Among these subjects, 68 (73%) also had MRI-confirmed bilateral TF OA (ICRS 2-4), and 44/68 (65%) of TPX-100-treated knees met responder criteria at 6 or 12 months or both. TPX-100 responder knees also had significant increases in TF cartilage thickness compared with baseline ($p \leq 0.003$).

Conclusion: In clinical trials of disease-modifying OA drug (DMOAD) candidates, a frustrating discordance has been noted between structural (cartilage) change and measures of patient benefit, reflected in the FDA's new draft guidance document (August 2018). The present analysis represents, to our knowledge, the first time that clinically meaningful functional benefit has been linked with MRI-confirmed knee cartilage thickness increases.

Disclosure: D. McGuire, OrthoTrophix, Inc, 1, 3; N. Segal, Orthotrophix, Inc, 9; S. Metyas, OrthoTrophix, Inc, 9; H. R. Barthel, OrthoTrophix, Inc, 9; M. Miller, OrthoTrophix, Inc, 1, 3; D. Rosen, OrthoTrophix, Inc, 1, 3; Y. Kumagai, OrthoTrophix, Inc, 1, 3.

McGuire, D, Segal, N, Metyas, S, Barthel, HR, Miller, M, Rosen, D, Kumagai, Y
DMOAD and osteoarthritis

Abstract Number: L17

Dual Neutralization of IL-17A and IL-17F with Bimekizumab in Patients with Active Psoriasis: Results from a 48-Week Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study

Christopher T. Ritchlin¹, Arthur Kavanaugh², Joseph F. Merola³, Georg Schett⁴, Jose U. Scher⁵, Richard B. Warren⁶, Deepak Assudani⁷, Thomas Kumke⁸, Barbara Ink⁷ and Iain B. McInnes⁹, ¹University of Rochester Medical Centre, Rochester, NY, ²UC San Diego School of Medicine, La Jolla, CA, ³Brigham and Women's Hospital Harvard Medical School, Boston, MA, ⁴Friedrich Alexander University Erlangen-Nurnberg, Erlangen, Germany, ⁵Department of Medicine, NYU Langone Medical Center, New York, NY, ⁶The Dermatology Centre, Salford Royal NHS Foundation Trust, The University of Manchester, Manchester, United Kingdom, ⁷UCB Pharma, Slough, United Kingdom, ⁸UCB Pharma, Monheim am Rhein, Germany, ⁹University of Glasgow, Glasgow, United Kingdom

SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: ACR Late-breaking Abstract Session

Session Type: Late-Breaking Abstract Session

Session Time: 16:00PM-18:00PM

Background/Purpose: IL-17F shares structural homology and overlapping biologic function with IL-17A. *In vitro* studies demonstrate that IL-17F has biologic effector function that can modulate inflammation. Early clinical data support dual neutralization of IL-17A and IL-17F as a novel targeting approach in psoriasis, PsA and AS. We report interim results from a Phase 2b study (NCT02969525) assessing the dose response, long-term efficacy and safety of bimekizumab (BKZ), a mAb that potently and selectively neutralizes both IL-17A and IL-17F, over 48 weeks in patients with active PsA.

	Week 12 [†]						
n (%) of patients	Placebo n=42	BKZ 16 mg n=41	BKZ 160 mg n=41	BKZ 160 mg (LD) n=41	BKZ 320 mg n=41		
ACR20	8 (19.0)	22 (53.7)**	29 (70.7)***	25 (61.0)***	21 (51.2)**		
ACR50	3 (7.1)	11 (26.8)*	17 (41.5)**	19 (46.3)***	10 (24.4)		
ACR70	2 (4.8)	5 (12.2)	8 (19.5)	13 (31.7)**	6 (14.6)		
MDA	6 (14.3)	13 (31.7)	19 (46.3)	17 (41.5)	12 (29.3)		
	n=28	n=29	n=28	n=26	n=26		
PASI75 [‡]	2 (7.1)	13 (44.8)**	18 (64.3)***	20 (76.9)***	19 (73.1)***		
PASI90 [‡]	2 (7.1)	8 (20.7)	13 (46.4)**	14 (53.8)***	14 (53.8)**		
	n=21	n=19	n=22	n=22	n=23		
Resolution of enthesitis [§]	6 (28.6)	5 (26.3)	13 (59.1)	13 (59.1)	8 (34.8)		
	Week 24 [‡]						
	Placebo → BKZ 160 mg n=20	Placebo → BKZ 320 mg n=20	BKZ 16 mg → BKZ 160 mg n=22	BKZ 16 mg → BKZ 320 mg n=19	BKZ 160 mg → BKZ 160 mg n=40	BKZ 160 mg (LD) → BKZ 160 mg n=40	BKZ 320 mg → BKZ 320 mg n=41
ACR20	13 (65.0)	15 (75.0)	20 (90.9)	16 (84.2)	27 (67.5)	29 (72.4)	33 (80.5)
ACR50	9 (45.0)	10 (50.0)	13 (59.1)	12 (63.2)	24 (60.0)	23 (62.2)	22 (53.7)
ACR70	5 (25.0)	6 (30.0)	8 (36.4)	7 (36.8)	13 (32.5)	15 (40.5)	11 (26.8)
MDA	6 (30.0)	11 (55.0)	11 (50.0)	12 (63.2)	20 (50.0)	22 (59.5)	15 (36.6)
	n=11	n=15	n=14	n=15	n=27	n=23	n=26
PASI75 [‡]	10 (90.9)	13 (86.7)	12 (85.7)	14 (83.3)	22 (81.5)	19 (82.6)	21 (80.8)
PASI90 [‡]	5 (45.5)	11 (73.3)	11 (78.6)	11 (73.3)	18 (66.7)	16 (78.3)	20 (76.9)
	n=10	n=10	n=10	n=9	n=22	n=20	n=23
Resolution of enthesitis [§]	4 (40.0)	7 (70.0)	5 (50.0)	2 (22.2)	12 (54.5)	14 (70.0)	10 (43.5)
	Week 48 [‡]						
	Placebo → BKZ 160 mg n=20	Placebo → BKZ 320 mg n=20	BKZ 16 mg → BKZ 160 mg n=22	BKZ 16 mg → BKZ 320 mg n=19	BKZ 160 mg → BKZ 160 mg n=40	BKZ 160 mg (LD) → BKZ 160 mg n=37	BKZ 320 mg → BKZ 320 mg n=41
ACR20	13 (65.0)	14 (70.0)	19 (86.4)	17 (89.5)	28 (70.0)	27 (73.0)	31 (75.6)
ACR50	8 (40.0)	14 (70.0)	11 (50.0)	16 (84.2)	22 (55.0)	21 (56.8)	26 (63.4)
ACR70	8 (40.0)	8 (40.0)	6 (27.3)	10 (52.6)	17 (42.5)	17 (45.9)	16 (39.0)
MDA	8 (40.0)	11 (55.0)	9 (40.9)	15 (78.9)	24 (60.0)	20 (54.1)	19 (46.3)
	n=11	n=15	n=14	n=15	n=27	n=23	n=26
PASI75 [‡]	11 (100)	12 (80.0)	12 (85.7)	12 (80.0)	21 (77.8)	21 (91.3)	22 (84.6)
PASI90 [‡]	11 (100)	11 (73.3)	10 (71.4)	12 (80.0)	19 (70.4)	16 (69.6)	22 (84.6)
	n=10	n=10	n=10	n=9	n=22	n=20	n=23
Resolution of enthesitis [§]	4 (40.0)	7 (70.0)	4 (40.0)	4 (44.4)	15 (68.2)	14 (70.0)	13 (56.5)

Interim results were presented at the meeting. Values at Week 12, 24 and 48. *Indicates significant difference versus placebo (performed using Fisher's exact test or chi-square test, as appropriate). **Indicates significant difference versus placebo (performed using Fisher's exact test or chi-square test, as appropriate). ***Indicates significant difference versus placebo (performed using Fisher's exact test or chi-square test, as appropriate). †Indicates significant difference versus placebo (performed using Fisher's exact test or chi-square test, as appropriate). ‡Indicates significant difference versus placebo (performed using Fisher's exact test or chi-square test, as appropriate). §Indicates significant difference versus placebo (performed using Fisher's exact test or chi-square test, as appropriate). LD, loading dose; MDA, mean disease activity; PASI, Psoriasis Area and Severity Index.

Methods: 206 patients with active PsA, $\geq 3/76$ swollen joint count and $\geq 3/78$ tender joint count and fulfilling the CASPAR (score ≥ 3) criteria, were randomized (1:1:1:1) to receive subcutaneous BKZ 16 mg, 160 mg, 160 mg with 320 mg loading dose (160 mg [LD]), 320 mg, or placebo (PBO) Q4W, for 12 weeks (double-blind period). After Week 12, patients receiving PBO or BKZ 16 mg were re-randomized (1:1) to receive BKZ 160 mg or 320 mg; all other patients continued on their previous dose (dose-blind period). The primary endpoint was ACR50 response at Week 12.

Results: 203/206 and 189/206 patients completed the double- and dose-blind periods, respectively. Overall, demographics and baseline disease characteristics were balanced across groups. 19% of patients had prior exposure to TNF inhibitors. There was a statistically significant ($p < 0.05$) dose-response at Week 12 for ACR50 response rates. At Week 12, significantly more patients receiving BKZ versus PBO achieved ACR50 (primary endpoint: 16–160 mg [LD] doses), ACR20 and PASI90 (in those patients with baseline BSA $\geq 3\%$; 160–320 mg doses) (table). ACR20/50/70, PASI75/90, MDA and resolution of enthesitis response rates increased up to Week 24 in those continuing on their initial BKZ dose; responses were maintained through the study and were similar across the three highest dose groups at Week 48. In addition, rapid improvements were observed across all response criteria in patients re-allocated to BKZ 160 or 320 mg (table). There was no apparent relationship between dose and TEAEs. Serious AEs were reported by 9/206 (4.4%) patients up to Week 48 (8/206 [3.9%] receiving BKZ). The most common TEAE up to Week 48 was nasopharyngitis 25/206 [12.1%]. Oral candidiasis was reported at Week 48 by 10/206 (4.9%) patients (all cases during BKZ treatment). No deaths, or cases of IBD or MACE were reported.

Conclusion: BKZ provided substantial improvements in both musculoskeletal and skin outcomes; response rates continued to increase after Week 12 (primary analysis) and were sustained from Week 24 to 48, with a safety profile consistent with previous BKZ studies. These data provide further support that neutralizing IL-17F in addition to IL-17A with BKZ is a promising therapeutic approach in patients with active PsA.

Disclosure: C. T. Ritchlin, UCB, Amgen, Abbvie, 2, UCB, Amgen, AbbVie, Pfizer, Novartis, Lilly, 5; A. Kavanaugh, UCB, 2; J. F. Merola, Merck, AbbVie, Eli Lilly, Novartis, Janssen, UCB, Samumed, Celgene, Sanofi Regeneron, GSK, 5, AbbVie, 8, Biogen, Pfizer, Sanofi, Incyte, Actaris, Novartis, 2; G. Schett, None; J. U. Scher, UCB, Janssen, Novartis, BMS, 5; R. B. Warren, AbbVie, Almirall, Amgen, Celgene, Janssen, Lilly, Leo, Novartis, Pfizer, UCB, 2, AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Janssen, Leo, Lilly, Novartis, Pfizer, Sanofi, XenoPort, UCB, 5; D. Assudani, UCB Pharma, 1, 3; T. Kumke, None; B. Ink, None; I. B. McInnes, AstraZeneca, Celgene, Compugen, Novartis, Roche, UCB, 2, AbbVie, Galvani, Lilly, Pfizer, UCB, Novartis, Celgene, 5.

Ritchlin, CT, Kavanaugh, A, Merola, JF, Schett, G, Scher, JU, Warren, RB, Assudani, D, Kumke, T, Ink, B, McInnes, IB Immunoglobulin (IG), inflammation, interleukins (IL), monoclonal antibodies and psoriatic arthritis

Abstract Number: L18

A Randomized Controlled 24-Week Trial Evaluating the Safety and Efficacy of Blinded Tapering Versus Continuation of Long-Term Prednisone (5 mg/day) in Patients with Rheumatoid Arthritis Who Achieved Low Disease Activity or Remission on Tocilizumab

Gerd R. Burmester¹, Frank Buttgereit¹, Corrado Bernasconi², Jose Maria Alvaro-Gracia³, Nidia Castro², Maxime Dougados⁴, Cem Gabay⁵, Jacob van Laar⁶, J. Michael Nebesky², Attila Pethö-Schramm², Carlo Salvarani⁷, Marc Y. Donath⁸ and Markus R. John², ¹Charité-Universitätsmedizin Berlin, Free University and Humboldt University of Berlin, Berlin, Germany, ²F. Hoffmann-La Roche, Basel, Switzerland, ³Hospital Universitario de La Princesa IIS-IP, Madrid, Spain, ⁴Université Paris-Descartes, Paris, France, ⁵University Hospitals of Geneva, Geneva, Switzerland, ⁶University Medical Centre Utrecht, Utrecht, Netherlands, ⁷Università de Modena e Reggio Emilia, Modena, Italy, ⁸University Hospital Basel, Basel, Switzerland

SESSION INFORMATION

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Session Title: ACR Late-breaking Abstract Session

Session Type: Late-Breaking Abstract Session

Session Time: 16:00PM-18:00PM

Background/Purpose: Guidelines recommend low-dose, short-duration glucocorticoid (GC) treatment for RA,^{1,2} but long-term use, especially at prednisone-equivalent doses >5 mg/d, should be avoided.² Many patients (pts) with early and established RA receive long-term GCs, often ≥ 5 mg/d.³ SEMIRA (Steroid ELiMination In RA) compared GC tapering vs continuation for maintaining disease control in RA pts with chronic GC exposure who were receiving tocilizumab (TCZ).

Methods: Before randomization pts had to receive TCZ +/- conventional synthetic (cs)DMARDs and GC (prednisone-equivalent dose 5-15 mg/d) for ≥ 24 weeks (wks). At randomization pts had to be in at least stable low disease activity (LDA: DAS28-ESR ≤ 3.2) and stable concomitant therapy (prednisone 5 mg/d [GC5mg]) and TCZ +/- csDMARDs) for ≥ 4 wks. Pts were randomized either to continue blinded GC5mg for 24 wks or to undergo blinded taper (G Ctaper, starting at 4 mg/d with 1-mg reduction every 4 wks to 0 mg/d at wks 16-24) while receiving stable TCZ and csDMARD doses. Pts who experienced RA flare received open-label prednisone 5 mg/d rescue therapy for 2 wks and continued blinded treatment. The primary outcome was mean change in DAS28-ESR at wk 24. The key secondary outcome was "treatment

Table. Key efficacy results (intent-to-treat population)		
	TCZ+GC5mg N = 128	TCZ+GCtaper N = 131
Change in DAS28-ESR from baseline to week 24		
Primary end point		
Change from baseline to week 24, LSM (95% CI)	-0.075 (-0.271, 0.121)	0.538 (0.346, 0.729)
Difference between treatment groups: estimate (95% CI), <i>p</i> value for treatment group difference ^a	0.613 (0.346, 0.879) <i>p</i> < 0.001	
Subgroup analyses by baseline stratification factors		
	Difference between treatment groups, LSM (95% CI)	<i>p</i> value for difference between subgroups
TCZ use		
Monotherapy	0.47 (-0.05, 0.99)	<i>p</i> = 0.493
Combination with csDMARD	0.68 (0.36, 1.00)	
Baseline DAS28		
<2	0.57 (0.20, 0.95)	<i>p</i> = 0.862
≥2	0.63 (0.23, 1.02)	
Secondary end points		
Treatment success, n (%)	99 (77.3)	85 (64.9)
Treatment success effect (GCtaper vs GC5mg)		
Odds ratio ^b (95% CI)	0.50 (0.285, 0.889); <i>p</i> = 0.018	
Relative risk ^c (95% CI)	0.833 (0.714, 0.972); <i>p</i> = 0.021	
Patients who experienced ≥1 flare, ^d n (%)	14 (10.9)	34 (26.0)
Time from randomization to first flare, ^d weeks, mean (SD)	12.11 (7.93)	15.64 (7.13)
Patients who discontinued blinded treatment due to insufficient flare control, n	1	0
DAS28-ESR value at time of study treatment withdrawal was imputed for patients who withdrew from treatment prematurely, and DAS28-ESR value at initiation of rescue therapy was imputed for patients who received rescue therapy from week 20 or later.		
^a Least-squares mean from an ANCOVA model including treatment, baseline DAS28-ESR, and baseline stratification factors (weight, region, DMARD use at randomization) as covariates. ^b Logistic regression analysis with treatment and adjusted for the randomization stratification factors. ^c Cochran Mantel-Haenszel test with treatment and randomization stratification factors. ^d Flare defined as DAS28-ESR >3.2 and increase >0.6 units vs baseline		
ANCOVA, analysis of covariance; CI, confidence interval; GC5mg, stable 5-mg glucocorticoid; GCtaper, glucocorticoid taper; LSM, least-squares mean; SD, standard deviation; TCZ, tocilizumab.		

success”— DAS28-ESR ≤ 3.2 at wk 24 **and** no RA flare during 24 wks **and** no adrenal insufficiency requiring replacement therapy.

Results: 259 pts were randomized to GCtaper (n = 131) or GC5mg (n = 128); 114 and 112, respectively, completed 24 wks. Mean baseline DAS28-ESR was 1.9. Mean RA duration was 9.2 years. For the primary end point, the between-arm difference was 0.6 DAS28-ESR units (95% confidence interval: 0.346, 0.879) favoring GC5mg. Results were consistent across key subgroups (Table). The majority of pts in both arms achieved treatment success (65% GCtaper vs 77% GC5mg, with a significant difference; Table). No pts discontinued from the GCtaper arm due to insufficient flare control. Serious adverse events were reported for 5% of GC5mg vs 3% of GCtaper pts with no deaths. There were no cases of symptomatic adrenal insufficiency.

Conclusion: Continued GC 5 mg/d provided better DAS28-ESR control than GC taper in RA pts in LDA or remission. The 0.6 DAS28-ESR unit between-arm difference should be interpreted in the context of approximately two-thirds of tapered pts experiencing treatment success and no tapered pts discontinuing due to lack of flare control. The taper schedule was safe regarding adrenal insufficiency. Together these results suggest that all pts achieving LDA or remission with TCZ who are receiving long-term low-dose GC should be considered for GC tapering, ideally targeting discontinuation.

Reference:

1. Singh JA et al. *Arthritis Rheum*. 2016;68:1. 2. Smolen JS et al. *Ann Rheum Dis*. 2017;76:960. 3. Buttgereit F, Bijlsma JW. *Ann Rheum Dis*. 2017;76:1785.

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Burmester, GR, Buttgereit, F, Bernasconi, C, Alvaro-Gracia, JM, Castro, N, Dougados, M, Gabay, C, van Laar, J, Nebesky, JM, Pethö-Schramm, A, Salvarani, C, Donath, MY, John, MR
Glucocorticoids, rheumatoid arthritis (RA) and tocilizumab

Abstract Number: L19

Transcutaneous Electrical Nerve Stimulation (TENS) Reduces Pain and Fatigue and Improves Disease Impact in Women with Fibromyalgia: A Randomized Controlled Trial

Leslie Crofford¹, Dana Daily², Carol Vance³, Ruth Chimenti², Ericka Merriwether⁴, Miriam Bridget Zimmerman⁵, Jonathan Williams⁶, Meena Golchha⁶, Li Alemo Munters⁷, Katharine Geasland³, Barbara Rakel⁸ and Kathleen Sluka²,
¹Division of Rheumatology and Immunology, Vanderbilt University Medical Center, Nashville, TN, ²Physical Therapy, University of Iowa, Iowa City, IA, ³University of Iowa, Iowa City, IA, ⁴Physical Therapy, New York University, New York, NY, ⁵Public Health, University of Iowa, Iowa City, IA, ⁶Vanderbilt University Medical Center, Nashville, TN, ⁷Karolinska Institutet, Stockholm, Sweden, ⁸Nursing, University of Iowa, Iowa City, IA

SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: ACR Late-breaking Abstract Session

Session Type: Late-Breaking Abstract Session

Session Time: 16:00PM-18:00PM

Background/Purpose: Fibromyalgia (FM) is a chronic pain condition associated with pain and fatigue, especially during physical activity. Treatments designed to modulate central pain pathways to reduce activity-induced pain could improve function and quality of life in this population. TENS activates endogenous central inhibitory pathways and decreases central excitability thus we tested if using TENS during physical activity would improve activity-induced and resting pain and fatigue and lessen disease impact.

Methods: Women aged 18-70, meeting ACR 1990 FM criteria with reported pain ≥ 4 of 10 at two pre-randomization visits were randomly assigned to active TENS (n=103), placebo TENS (n=99) and no TENS treatment (n=99). Active TENS was applied on the upper and lower back at a mixed frequency, strong but comfortable intensity, 200µsec pulse duration. Placebo TENS was applied in the same manner as active TENS but delivered electrical current for 45s with a ramp to 0 in the last 15s. The no TENS group wore a non-active TENS unit during testing to blind the outcome assessor. Participants were instructed to use TENS during activity for at least 2h per day. Pain and fatigue during activity (6-minute walk test) and at rest were reported before and during application of TENS on the day of randomization and after one month of home use. Patient-reported outcomes were assessed with the brief pain inventory (BPI), multidimensional assessment of fatigue (MAF), revised FM impact questionnaire (FIQR), and a global rating of change. Using mixed model analyses, we examined the effect of TENS using an intention to treat analysis.

Results: After 1 month of active TENS, the primary outcome of activity-induced pain showed a mean reduction of 1.82 (95% CI: 2.39-1.25) that was significantly greater than placebo TENS (0.85, 95% CI: 1.43-0.27; $p=0.01$) and no TENS (0, 0.56 - +0.41; $p<0.01$). Similarly, activity-induced fatigue showed a mean reduction of 1.53 (2.23-0.83) that was significantly greater than placebo TENS (0.08, 0.79-0.63; $p<0.01$) and no TENS (+0.35, 0.34 - +1.04; $p<0.01$). With active TENS there were also significant improvements in resting pain, BPI interference, and MAF compared to placebo TENS and no TENS (all $p<0.05$). Active TENS improved the FIQR by a mean of 8.48 (12.92-4.04), which was significantly different from no TENS (1.39, 4.40- +1.62; $p<0.001$) but not placebo TENS (3.42, 6.54-0.30; $p=0.07$). The global rating of change indicated that 70% of those in the active TENS group improved compared to 31% in the placebo TENS group and 9% in the no TENS group ($p<0.001$).

Conclusion: Active TENS produced significant improvement in pain, fatigue, and disease impact compared to placebo TENS or no TENS. Most women who received active TENS reported global improvement in their condition. As a safe, inexpensive, home based-treatment, TENS may be included as part of the management strategy for women with FM.

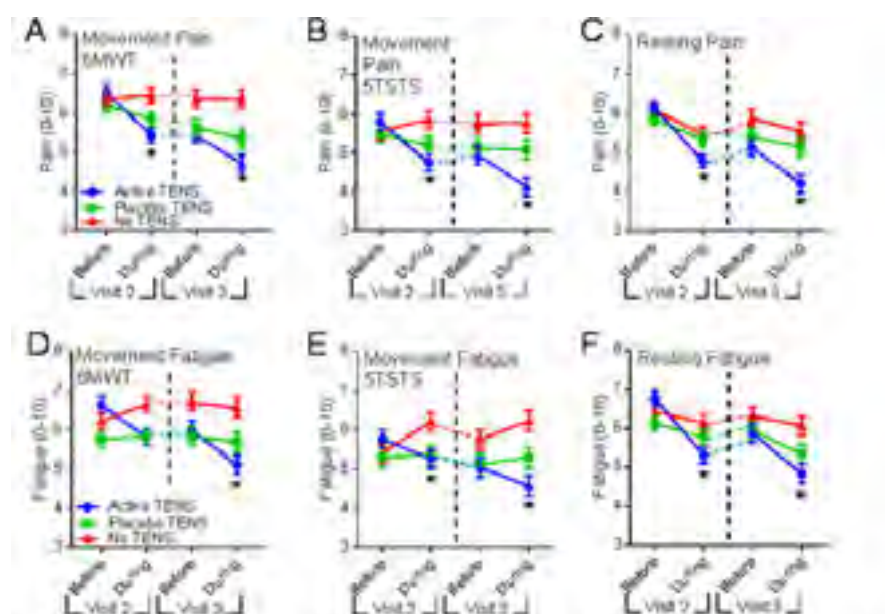


Figure 1: TENS Improves Pain and Fatigue in Women with FM. Compared with placebo TENS and no/mock TENS, active TENS significantly ($*p<0.05$) improved pain and fatigue before (resting) and during (movement) activity when applied acutely in the clinic during V2 and V3 (solid lines). There was evidence of a chronic effect after 1 month (hashed lines) of home use between the two visits and no tolerance to TENS was observed. GMWT=6-minute walk test; STSTS=5 times sit-to-stand.

Disclosure: L. Crofford, None; D. Daily, None; C. Vance, None; R. Chimenti, None; E. Merriwether, None; M. B. Zimmerman, None; J. Williams, None; M. Golchha, None; L. Alemo Munters, None; K. Geasland, None; B. Rakel, None; K. Sluka, Novartis, 5, American Pain Society, 2, IASP Press, 7.

Crofford, L, Daily, D, Vance, C, Chimenti, R, Merriwether, E, Zimmerman, MB, Williams, J, Golchha, M, Alemo Munters, L, Geasland, K, Rakel, B, Sluka, K
TENS, fatigue, fibromyalgia, pain management and physical therapy

Efficacy and Safety of Subcutaneous Tanezumab for the Treatment of Osteoarthritis of the Hip or Knee

Thomas J. Schnitzer¹, Richard Easton², Shirley Pang³, Dennis Levinson⁴, Glenn Pixton⁵, Lars Viktrup⁶, Isabelle Davignon⁷, Mark T. Brown⁷, Kenneth M. Verburg⁷ and Christine R. West⁷, ¹Northwestern University, Chicago, IL, ²Michigan Orthopaedic & Spine Surgeons, Rochester Hills, MI, ³St. Jude Medical Center, Fullerton, CA, ⁴Chicago Clinical Research Institute, Chicago, IL, ⁵Pfizer, Inc., Morrisville, NC, ⁶Eli Lilly and Company, Indianapolis, IN, ⁷Pfizer, Inc., Groton, CT

SESSION INFORMATION

Session Date: Tuesday, October 23, 2018

Session Title: ACR Late-breaking Abstract Session

Session Type: Late-Breaking Abstract Session

Session Time: 16:00PM-18:00PM

Background/Purpose: Tanezumab is a humanized mAb that blocks nerve growth factor (NGF) and is in clinical development for chronic pain treatment. Tanezumab administered intravenously has proven efficacy in previous studies of osteoarthritis (OA) pain.

Methods: A randomized, double-blind, placebo-controlled, multicenter, parallel-group, 40-week study (16-week treatment period; 24-week safety follow-up) was conducted to examine the efficacy and safety of subcutaneous (SC) tanezumab administered in two treatment regimens over 16 weeks: fixed-dosing (2.5 mg administered at Baseline and Week 8) and step-up dosing (2.5 mg administered at Baseline and 5 mg at Week 8). This study enrolled OA patients who had not responded to or could not tolerate standard pain treatments. Patients (N = 696) had: OA of the hip or knee based on clinical and radiographic ACR criteria, baseline WOMAC Pain and Physical Function scores of ≥ 5 (11-point numerical rating scale), baseline Patient's Global Assessment of OA (PGA-OA) of "fair," "poor," or "very poor", and a history of insufficient pain relief or intolerance to acetaminophen, NSAIDs, and either tramadol or opioids (or were unwilling to take opioids). Co-primary endpoints were change from Baseline to Week 16 in WOMAC Pain subscale, WOMAC Physical Function subscale, and PGA-OA. Safety assessments included adverse event (AE) reporting, physical and neurological examinations, joint x-rays, electrocardiogram, and laboratory tests.

Results: At Week 16, patients treated with tanezumab 2.5 mg or 2.5/5 mg experienced statistically significant improvement in WOMAC Pain, WOMAC Physical Function, and PGA-OA compared with patients receiving placebo (Table 1). Both tanezumab dosing regimens met the study co-primary endpoints. The most common AEs ($\geq 3\%$ in any treatment group and more frequent in each tanezumab treatment group than in the placebo treatment group) were nasopharyngitis, pain in extremity, and paresthesia. The incidence of serious AEs or withdrawals due to AEs was similar between treatment groups (Table 2). Adjudicated rapidly progressive OA occurred in 1.3% of tanezumab-treated subjects during the 40-week study.

Conclusion: Tanezumab 2.5 mg SC provided significant pain relief and improved both function and PGA-OA versus placebo in OA patients. Increasing the dose to 5 mg at Week 8 was associated with modest additional benefit versus continuation on tanezumab 2.5 mg. This study demonstrates that SC tanezumab may be an effective option for patients who have demonstrated intolerance or incomplete response to standard treatments for OA.

Table 1. Change in Baseline to Week 16 in WOMAC Pain subscale, WOMAC Physical Function subscale, and Patient's Global Assessment of OA.

	placebo N = 232	tanezumab 2.5 mg N = 231	tanezumab 2.5/5 mg N = 233
WOMAC Pain^a			
Mean (Range) Baseline Pain Score	7.30 (4.2, 10.0)	7.08 (4.8, 10.0)	7.33 (5.0, 10.0)
LS Mean (SE) Change from Baseline	-2.64 (0.23)	-3.23 (0.23)	-3.37 (0.22)
Diff of LS Means (SE)		-0.60 (0.24)	-0.73 (0.24)
p-value		0.0129	0.0023
WOMAC Physical Function^b			
Mean (Range) Baseline Physical Function Score	7.38 (4.4, 10.0)	7.18 (5.1, 9.9)	7.39 (3.2, 9.9)
LS Mean (SE) Change from Baseline	-2.56 (0.22)	-3.22 (0.22)	-3.45 (0.22)
Diff of LS Means (SE)		-0.66 (0.24)	-0.89 (0.24)
p-value		0.0065	0.0002
PGA-OA^c			
Mean (Range) Baseline Score	3.46 (3, 5)	3.42 (2, 5)	3.53 (3, 5)
LS Mean (SE) Change from Baseline	-0.65 (0.08)	-0.87 (0.08)	-0.90 (0.08)
Diff of LS Means (SE)		-0.22 (0.09)	-0.25 (0.09)
p-value		0.0109	0.0038

^a WOMAC Pain subscale on an 11-point numerical rating scale; higher score indicates higher pain levels

^b WOMAC Physical Function subscale on an 11-point numerical rating scale; higher score indicates worse function

^c PGA-OA scale ranges from 1 = "very good" to 5 = "very poor"

Table 2. Summary of adverse events and those reported in $\geq 3\%$ of patients in any treatment group during the Treatment Period.

	placebo N = 232	tanezumab 2.5 mg N = 231	tanezumab 2.5/5 mg N = 233
Adverse events			
Any adverse event, n (%)	115 (49.6)	128 (55.4)	109 (46.8)
Any treatment-related adverse event, n (%)	24 (10.3)	29 (12.6)	22 (9.4)
Any treatment discontinuation due to adverse events, n (%) ^a	2 (0.9)	0	1 (0.4)
Any study withdrawal due to adverse events, n (%)	2 (0.9)	1 (0.4)	2 (0.9)
Any serious adverse event, n (%)	4 (1.7)	4 (1.7)	4 (1.7)
Adverse event, n (%)			
Arthralgia	29 (12.5)	19 (8.2)	22 (9.4)
Nasopharyngitis	8 (3.4)	12 (5.2)	11 (4.7)
Musculoskeletal pain	8 (3.4)	7 (3.0)	2 (0.9)
Back pain	7 (3.0)	10 (4.3)	6 (2.6)
Headache	7 (3.0)	6 (2.6)	7 (3.0)
Fall	6 (2.6)	11 (4.8)	5 (2.1)
Upper respiratory tract infection	6 (2.6)	7 (3.0)	3 (1.3)
Joint swelling	4 (1.7)	8 (3.5)	4 (1.7)
Pain in extremity	2 (0.9)	4 (1.7)	7 (3.0)
Paresthesia	1 (0.4)	8 (3.5)	3 (1.3)

^a Patients with adverse events leading to treatment discontinuation, but not study withdrawal during the treatment period

Disclosure: T. J. Schnitzer, AbbVie Inc., 5, 9, Aptinyx, 5, Genzyme, 5, Eli Lilly and Co., 5, 9, Pfizer, Inc., 5, 9, Regeneron, 5, 9, Vertex, 5, Grunenthal, 9, Radius, 9; R. Easton, Pfizer, Inc., 2; S. Pang, Pfizer, Inc., 5; D. Levinson, None; G. Pixton, Pfizer, Inc., 1, 3; L. Viktrup, Eli Lilly and Company, 1, 3; I. Davignon, Pfizer, Inc., 1, 3; M. T. Brown, Pfizer, Inc., 1, 3; K. M. Verburg, Pfizer, Inc., 1, 3; C. R. West, Pfizer, Inc., 1, 3.

Schnitzer, TJ, Easton, R, Pang, S, Levinson, D, Pixton, G, Viktrup, L, Davignon, I, Brown, MT, Verburg, KM, West, CR
OA, monoclonal antibodies, osteoarthritis and pain management

Abstract Number: PP01

Physician, Patient, Person. Success in Balancing Multiple Roles Takes Support

Brandi Stevens¹ and Katharine Moore², ¹Pediatrics, Riley Hospital for Children at Indiana University, Indianapolis, IN, ²Pediatric Rheumatology, Children's Hospital Colorado, Aurora, CO

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Patient Perspectives Poster Session

Session Type: Patient Perspectives Poster Session

Session Time: 12:00PM-2:00PM

Background/Diagnosis: It was the most important conference of the year, and I could barely walk. With a slow limping gait, there is no hiding it in the midst of nearly 16,000 attendees at the world's largest gathering of rheumatologic experts. How embarrassing, I thought. I'm supposed to be the doctor here, not the patient. Little did I know how much this new eruption of arthritis would define my coming months.

At the same conference, a colleague is making excuses to others for her need to stop and catch her breath so frequently while walking between talks. She's become skilled at hiding that she's in the midst of a flare of hemolytic anemia secondary to systemic lupus erythematosus (SLE).

We are just two of a subset of rheumatology providers living with rheumatologic conditions. This adds a layer of complexity in caring for patients, interacting with colleagues, and providing self-care. Of the 6,400 rheumatology providers identified in the 2015 ACR Workforce report, 1 in 12 women and 1 in 20 men will develop an inflammatory autoimmune rheumatic disease in their lifetime.

As rheumatologists with rheumatic illnesses, life is an uninvited in-depth study on empathy and the reality of living with the illnesses we treat every day. Through failed and escalating treatments, we struggle not only with our daily function and disease, but also with loss of identity, temptation to self-treat, and the fear of loss of privacy and academic reputation. This can lead to feelings of isolation, and of being neither fully patient nor physician. Studies have documented that physicians are hesitant to approach colleagues for treatment of chronic illnesses and struggle to adapt to the patient role compromising their own well-being.

Treatment: My colleague with SLE connected me with other physicians with rheumatic disease through a private Facebook group. In this unique group, our role as providers does not limit our vulnerability to disease. It is a safe space to share worries, frustrations, and occasionally humorous perspectives on having these fickle, chronic diseases.

Maintenance: With support and the opportunity to share, we became less concerned with a loss of identity as physicians. Apprehension about symptoms or medications did not represent a deficiency in our knowledge, but the human experience of living in a changing and problematic body. We experienced as much diversity in our group with acceptance, anger, denial, and coping as when giving a new diagnosis to our own patients. Hearing the experiences of other physicians struggling with rheumatic illness is validating. Gaining the patient role in no way diminishes the ability to be excellent rheumatologists, and being a doctor does not make us less human.

Quality of Life: While autoimmune diseases are unpredictable, we have comfort in knowing that no matter what our illnesses and professional demands require, we have supportive and encouraging peers. Being a part of a group of women who are striving daily to be empowered patient physicians helps to alleviate stress and worries about the future, while also providing confidence in our ability to be successful rheumatologists, despite the struggles we face as patients.

Disclosure:

B. Stevens, None; K. Moore, None. :

Abstract Number: PP02

Sustained Weight Loss Managed by Multiple Medical Specialists

Lawrence Phillips, Arthritis Foundation, Atlanta, GA

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Patient Perspectives Poster Session

Session Type: Patient Perspectives Poster Session

Session Time: 12:00PM-2:00PM

Background/Diagnosis: A patient who was diagnosed in 1974 with type 1 diabetes and in 2000 with rheumatoid arthritis weighed 366 pounds in 2014. He found he was gasping for breath while doing even simple tasks like walking across the room. He contacted his rheumatologist believing he might be suffering from lung issues related to RA. His rheumatologist referred him to his heart specialist who after performing an examination ultimately referred him to a pulmonologist.

Treatment: The pulmonologist performed diagnostic tests and a complete examination and found no RA related lung issues. However, he did find that the patient was suffering from a fractured sternum emulating from open heart surgery in 2005. With that finding the pulmonologist referred the patient to a thoracic surgeon for repair. The surgeon performed an examination acknowledging the patient's sternum was fractured along the lines of the open-heart surgery. The thoracic surgeon declined to operate unless patient lost at least 100 pounds.

The patient decided to consult his endocrinologist who suggested a routine of prescribed food consumption and education. The patient was also selected for a bariatric surgery program. The patient elected to pursue the strict dietary program offered by his endocrinologist, and over the course of 14 months, he lost 93 pounds. The thoracic surgeon acknowledged the patient's commitment to weight loss and performed the sternum repair in 2015.

Following thoracic surgery, the patient gained 14 pounds, and his rheumatologist suggested he pursue a sustained weight management program. With the oversight of his endocrinologist and rheumatologist, the patient selected a long-term weight management program, and to date, the patient has lost an additional 43 pounds. He now weighs 222 pounds or 9 pounds more than his high school graduation weight. Patient and his rheumatologist have set a weight goal of 200 pounds.

Maintenance: Patient regularly attends meetings tracks his food intake and loves riding his bicycle. He consults with his rheumatologist and endocrinologist about his progress.

Quality of Life: Patient has found his quality of life has been greatly improved. He is using his 5th biologic treatment for RA which has been maintained for the past 4 years thus halting a rapid succession of treatments that failed. Patient has decreased average insulin usage by 63 units per day and has steadily maintained an A1C of less than 6.0 for the past 4 years. The patient reports his quality of life has significantly improved. Patient photographed in 2012 before the start of the weight loss journey. Patient photographed in April 2018.





Disclosure: L. Phillips, Eli Lilly and Co., 5, Janssen, 5, UCB, Inc., 5

Abstract Number: PP03

Managing OsteoArthritis Pain with Daily Meditation

Raquel Masco, Patient/Volunteer, Arthritis Foundation, Atlanta, GA

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Patient Perspectives Poster Session

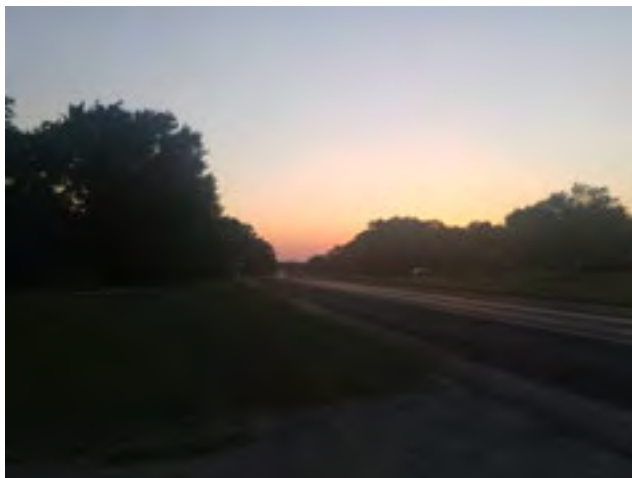
Session Type: Patient Perspectives Poster Session

Session Time: 12:00PM-2:00PM

Background/Diagnosis: Original diagnosis of OsteoArthritis in 2016 by family doctor(family medicine/general practitioner). There had been ongoing pain and symptoms for years. Original medications prescribed were Indomethacin and Ibuprofen (prescription). Subsequent diagnosis of -Inflammatory Polyarthritis -as of 2017. Cymbalta started in Spring 2018. Ibuprofen is still being taken.

Treatment: Began meditation in early 2017. It started as focusing on breathing when pain was really bad and progressed to a daily routine of focused meditation (including real-time and video guided meditation) - not just when pain set in - a regular time set aside to reduce stress, relieve stress and become centered. Physical activity in the form of a daily walk that is also meditative has also helped with the mental aspect of pain relief as well as physical.

Maintenance: Being mindful and deliberate about meditation makes a world of difference. I am able to meditate naturally and on purpose. Taking rest days from the daily walk is important as well. Giving my body time to bounce back and not overdoing is just as important maintaining the daily physical/mental activity.

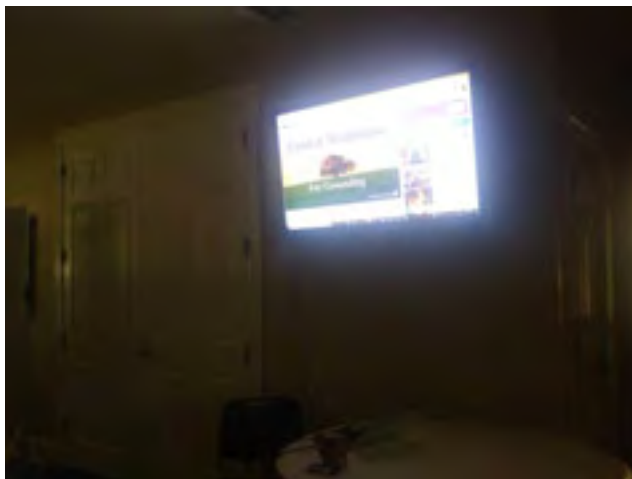


Quality of Life: The stiffness and decreased mobility was beginning to a toll on my emotional state as normal way of life. Running the nonprofit I began in 2011 was becoming difficult. There were many days of lateness and difficulty walking and providing services for clients. Daily meditation has made it easier to move around early in the morning before work. Being focused helps in better decision-making. This led to changing operations hours to make serving clients feasible and effective. Personal relationships have grown deeper as a result of a clearer mind and the ability to participate in socialization.

My daily walks that are in the evening are great setting for meditation

Meditation in the office is a part of daily meditation. Turning the lights down low and having a guided meditation video and/or music helps set the tone and the atmosphere.

A photo of me participating in a 7-day meditation challenge. We had to get grounded – no shoes– reflect on how we felt taking off barriers in nature.



Disclosure: R. Masco, None.

Abstract Number: PP04

Improved Quality of Life with Patient Engagement in Research

Kelly English¹ and Graham Macdonald², ¹Arthritis Patient Advisory Board, Arthritis Research Canada, Richmond, BC, Canada, ²Occupational Science and Occupational Therapy, University of British Columbia, Vancouver, BC, Canada

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Patient Perspectives Poster Session

Session Type: Patient Perspectives Poster Session

Session Time: 12:00PM-2:00PM

Background/Diagnosis: I am a woman, 60 years old who has lived with difficult-to-treat Rheumatoid Arthritis for 23 years. When first diagnosed with RA, there were constant tests, doctor's appointments, stress management classes, education classes, pain and illness to deal with as well as 2 young boys who needed their mother to be there to enjoy life with them. My best was saved for my boys but could not do the everyday things we had done in the past. We had to sell our house as it was not disability-friendly and there were financial needs relating to my disease. It took a year to diagnose and I had trouble with every med that was given to me; there was little efficacy as well. When biologics came into play, things were a little better for a couple of years, although I experienced constant infections. Then a severe reaction to a TNF receptor left me with neuropathic damage to my right leg that was not able to be reversed. The result is permanent pain on that side. It has affected my balance, gait and concentration.

Treatment: I am a patient fully engaged in several research teams from the point of hearing about a research idea and guiding the direction of research, to lay summaries and dissemination, and every phase of research in between. My 5 years since joining the Arthritis Patient Advisory Board has seen participation in quality of life research projects testing activity monitors, health journals and medicine adherence focus groups. I hoped this would give me a way to improve my life and give me new ideas about my RA. The environment at Arthritis Research Canada is an amazing one. Everyone from the scientific director to the secretaries to the trainees understand my disease and are flexible as well as encouraging. Patient engagement on research is a given here – not an exception to the rule.

Maintenance: See table 1

Table 1

Research Study	Goals	Difference to Me
Health Ethics	Focus group on social media & ethics	Start to my journey. Made me realize how much of new technology I was not using. I.e.: fitness trackers, wellness apps
Answer 2	To help people with decision making around Biologics	Great teaching tool about decision making – helped with video and with testing product. - became aware of other's concerns with meds. -could also check to see some of the available meds before talking to my rd.
Health Journal	To test a health journal testing joint count, depression screening, reporting to rheumatologist.	Since using this I have been more aware of symptoms and have gone back to record my past meds and reactions/side effects.
Fitbit/Fitvizz/ OPERA	Using a fitness tracker, combined with a physio consultation & now being tested as a complete program with Health Journal	This has been a game changer in my health. -Aware of how many active minutes of exercise, how closely or how apart they are, activity every hour. - invested in as I have been in the program throughout the testing/research period, from testing the product to critiquing the almost finished software changes.
Medicine Adherence focus group	Focus group on how people both remember to take and why they don't take medications for RA	Despite reading about this; I had no idea that people had so many reasons not to take and fears around medication - have been extra vigilant about my own meds especially compliant with vitamins
Framework for Patient Engagement in Research	To develop a framework for Patient Engagement in Research that will work not just in the Arthritis field but in any health field	- involved in from the beginning to dissemination. It has been true Patient Engagement in Research and is the project I am most proud to be in - have co-presented the poster at ACR 2017 - have assisted in developing the statements for the framework, wording of research paper, disseminated the information - have seen the process from start to finish which has been most important
<i>PRECISION: Preventing Complications from Inflammatory Skin, Joint and Bowel Conditions</i>	<i>Sit on the consumer core of the panel</i>	-Through PRECISION I have expanded my medical vocabulary. This has enabled me to understand better the posters at ACR and at the Canadian Rheumatology conferences - As part of the consumer core have heard of new discoveries as the team has researched them. -alerted on health problems such as potential COPD in the future - it has given me great hope as research by Dr. Diane Lacaille has shown that the lifespan of people with RA has actually improved over time. These are simply 2 discoveries out of many that have come out of this group

Quality of Life: It has been a long journey getting to where I am now. Results of Being a Patient in Research are:

- a team member on research projects
- an improvement in my fitness level,
- vitamin use isoptimal
- self esteem is higher than ever
- improved communication with my doctors by knowing medical terminology and treatments ahead of my appointments, and by having knowledge of new research findings to share with my rheumatologist and general practitioner from conferences and the research teams
- very supportive community in Arthritis Research Canada's Arthritis Patient Advisory Board
- attended ACR conferences and Canadian Rheumatology Conferences since I have been on the advisory board
- have a vested interest in the health research and pay very close attention to stretching my health knowledge and adherence. I know my quality of life has improved and my doctors acknowledge this.
- Depression has decreased.

My quality of life and the contributions I have made to others' lives is a result of being a Patient Engaged in Research.

Disclosure: K. English, None; G. Macdonald, None.

Abstract Number: PP05

Integrative Approach to Treatment of an Adult with Juvenile Rheumatoid Arthritis

Shannan O'Hara-Levi, Patient, Staten Island, NY

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Patient Perspectives Poster Session

Session Type: Patient Perspectives Poster Session

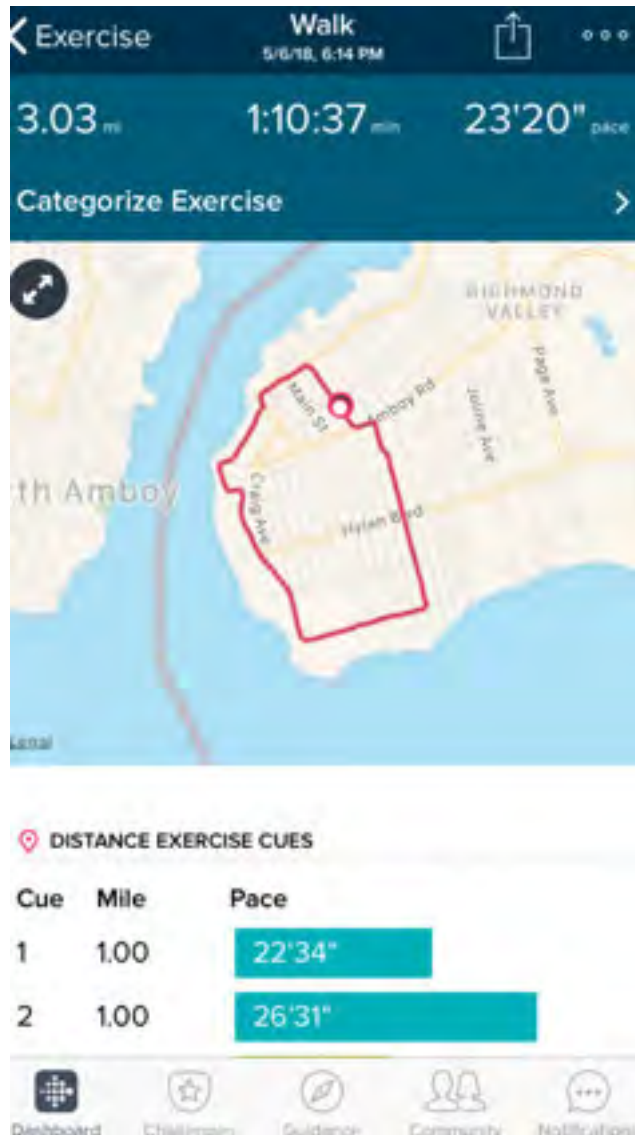
Session Time: 12:00PM-2:00PM

Background/Diagnosis: I was diagnosed in 1987 at age 3 with Polyarticular Juvenile Rheumatoid Arthritis which effected every joint in my body. At time of diagnosis I was expected to be in a wheelchair by age 6. With the help of NSAIDs, prednisone and Gold Injections, this was not the case. Eventually, I began trials of various drug cocktails that included those previously listed with the addition of DMARDs, namely Methotrexate and Plaquenil, and a rotation of various supplements including shark cartilage and vitamins. The ever changing trials of these cocktails continued until my mid-teenage years when biologic medication was introduced. After trying many different biologic medications and having varying results, I was taken off those medications and maintained on prednisone and Methotrexate for the time being. However, disease progression continues resulting in bilateral shoulder replacements in 2018.

Treatment: I have adapted an integrative approach to my treatment plan along with my medical team. This approach includes incorporating vitamin supplements and dietary restrictions under the supervision and recommendation of my rheumatologist and regular walking.

Maintenance: Prior to adding an integrative approach to my treatment, I was trying and most often failing drugs and drug cocktails regularly, which become stressful and disappointing. By adding specific supplements picked out by my doctor, I have guidance as to what is working for my body. In addition, dietary restrictions have improved my health and given me a sense of control over my illness. I use this sense of control to ensure that not only do I take my supplements and eat well; I move my body in one of the few ways it can regularly by walking daily. By ensuring that these integrative approaches are a regular part of my lifestyle, I am able to work better with my medical team as I am able to have some control of these treatments which will hopefully lead to decreased disease progression.





Quality of Life: Due to recent changes in my disease progression, the addition of these integrative approaches has ultimately led me to having a better quality of life. I am able to see these additions of supplements and dietary changes as a privilege instead of an additional burden of this disease because I do have some sort of control here. Walking has given me a boost of self-confidence as I “compete” with friends and family thru an app that tracks my walking. This added bonus is not only fun but keeps me accountable in a positive way. Prior to these changes, I was disappointed in my health and disease progression. Now, I am more confident in having a fun, healthy way of taking control over my health.

Disclosure: S. O’Hara-Levi, None;

Abstract Number: PP06

Learning to Self-Advocate in the Transition from Pediatric to Adult Lupus Care

Denita Perry¹ and Diane Gross², ¹Unaffiliated, Joliet, IL, ²Lupus Research Alliance, New York, NY

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Patient Perspectives Poster Session

Session Type: Patient Perspectives Poster Session

Session Time: 12:00PM-2:00PM

Background/Diagnosis: I was diagnosed with lupus at age 15. I was starting my sophomore year of high school and noticed a rash that the doctor said was eczema, but I knew it was not. I wasn't feeling well, I had pain and my hair was falling out. My mom took me to the hospital and I was diagnosed with lupus. I was hospitalized for a month, I couldn't take care of myself, I needed help to get dressed and eat, I was sore to the touch and I lost 20 pounds. It was information overload. I was 15, I didn't really understand what was going on, I was a dancer and on the track team with 2 college scholarship opportunities. Lupus took that all away from me.

Treatment: After the hospital, I started treatment at a children's health center, began getting better and went into remission.

The problem came when I turned 20 and had to transition to adult care. My new doctor started changing my medications, and I ended up hospitalized several times in one year. I was on methotrexate and folic acid and started having stomach issues. One day I was in so much pain that my doctor said to come to the office. After laying on her office floor she sent me to the emergency room without seeing me.

I never went back to that doctor. A friend of my mother suggested a hospital with a lupus center. I looked online and have been going there ever since.

I learned how to advocate for myself. I had to learn to be an adult. I used to keep things to myself and not share with doctor but learned to speak up.

I now have a good relationship with my doctor. I can call her at any time, it's like she's a second mom. It's worth the 1-2 hours it can take to get downtown.

Maintenance: I have done both physical and occupational therapy for my joints. I have changed how I eat, cutting out junk food. While I can't run like I did before lupus, I do exercise.

I know the signs that a flare is coming on and I get to the doctor sooner.

I learned to explain what I need. Now if I end up in the ER I can advocate for myself.

Quality of Life: I was diagnosed when I was young and very active. At first, I didn't always take my meds. I was embarrassed. My peers didn't understand. Whenever I tried to explain lupus, it was a pity party that I didn't want.

For the 5 years in pediatric care I saw the doctor regularly and had lupus under control. Then in the initial transition to adult care, for about 4 years, I got worse. Now I have a doctor who I can be honest with.

I am in school now and will finish my program this year. I take classes and am able to do easy temp work so I can call in day to day and not go in if I'm not feeling well. I am on disability and work part time to pay for school and my car.

I have potential jobs after graduation that are willing to work with me to accommodate my health issues. The disability office at school has been very helpful.

I was always angry, feeling sad, I didn't know how to feel, had so many emotions at once, I felt confused and lost.

That one fateful trip to the emergency room made me realize I had to take control. I learned to accept the situation, manage it, and make the best of it. I now know how to take care of myself and how to work with my healthcare team.

Disclosure: D. Perry, None; D. Gross, None.

Abstract Number: PP07

Strengthening My Resiliency: How My Interprofessional Healthcare Team and I Improved My Management of Lupus

Cecilia Amoakohene¹, Jorge Sanchez-Guerrero², Murray Urowitz², Dafna D Gladman², Zahi Touma² and Laura Wakani²,

¹Unaffiliated, Toronto, ON, Canada, ²University of Toronto Lupus Research Program, Toronto Western Hospital, Toronto, ON, Canada

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

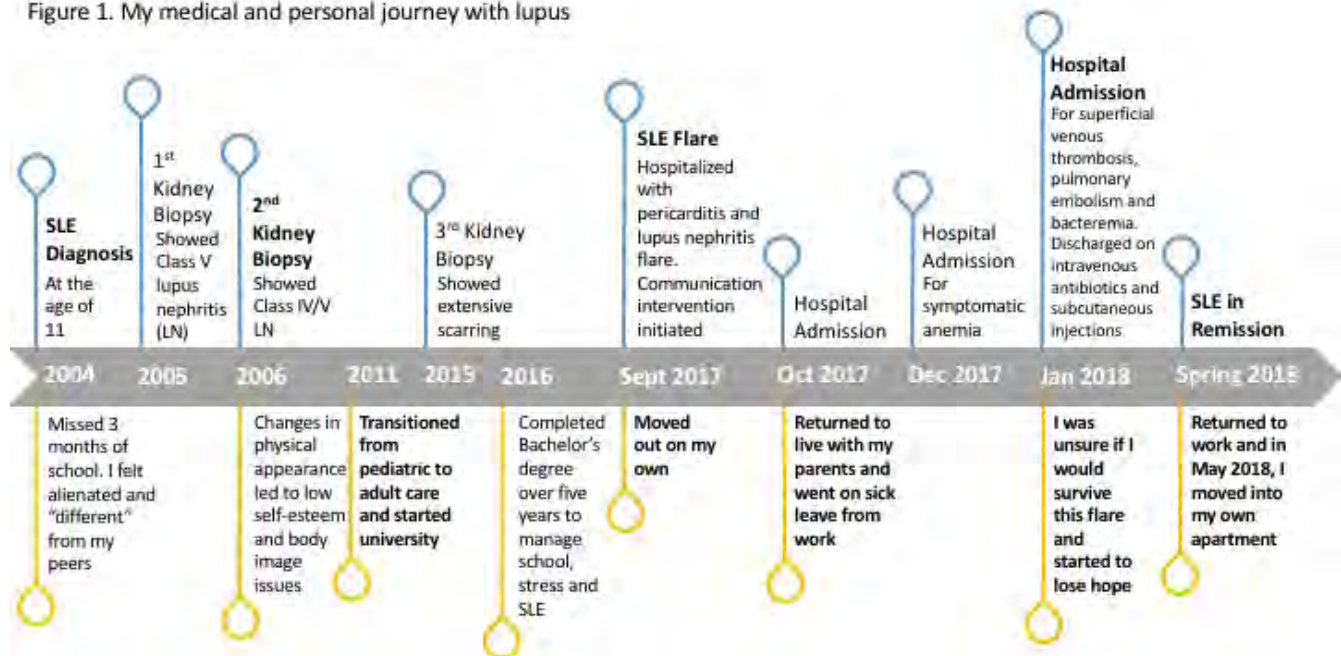
Session Title: Patient Perspectives Poster Session

Session Type: Patient Perspectives Poster Session

Session Time: 12:00PM-2:00PM

Background/Diagnosis: I was diagnosed with systemic lupus erythematosus (SLE) at the age of eleven and have experienced multiple SLE flares, hospitalizations, invasive procedures and complex treatment plans. My journey with SLE has at times made me feel isolated, affected my body image and self-esteem. While living with these challenges, I completed a Bachelor's degree and began a career. In 2017, a severe SLE flare left me on sick leave and often unable to perform basic daily tasks due to pain, fatigue and weakness, forcing me to return to live with my parents. My journey with lupus is outlined in Figure 1.

Figure 1. My medical and personal journey with lupus



Treatment: Cecilia's care team recognized the challenges she faced managing her latest SLE flare. As an interprofessional team, a care plan was developed and strategies implemented to promote patient-centered communication and improve disease management. As part of the care plan, regular communications with Cecilia were prompted by her healthcare team after each admission and change in treatment. Communication was predominantly nurse-led, via email, and covered symptoms, medications and side effects, and coping. Open-ended questions engaged Cecilia in identifying and prioritizing symptoms or concerns. Frequency of contact varied according to severity of symptoms or complexity of treatments, and often was weekly. Regular contact provided opportunities to improve symptom management, assistance and encouragement in managing treatments, and facilitated timely access to her rheumatology/nephrology team.

Maintenance: The interventions improved my self-management of SLE, engagement with my healthcare team and my resiliency during a stressful period of my life. Transitioning from pediatric to adult care, I felt I was a patient file, an "interesting case." By recognizing and responding to the challenges I was facing, I felt my healthcare team was invested in my care and thought of me as a person. Prompting me to check-in with myself increased my capacity to alert my team to symptoms or complications, seek urgent medical attention when needed, and manage intravenous antibiotics and subcutaneous injections at home. Increased self-awareness, paired with a receptive team, encouraged my involvement in clinic appointments and treatment decisions, and to seek additional supports, such as online support groups. My symptoms have significantly improved, I am tapering my prednisone dose and have returned to work. This resiliency helped me persevere and led me to where I am today—healthier and happier than I was before this flare began.

Quality of Life: My quality of life has greatly improved since the intervention and recovery from my SLE flare. I am able to perform basic daily tasks again, live on my own, and participate in activities I love, such as exercising. I am more confident about the future knowing I have the support of my healthcare team and the resiliency to live well with lupus.

Disclosure: C. Amoakohene, None; J. Sanchez-Guerrero, None; M. Urowitz, None; D. D. Gladman, None; Z. Touma, None; L. Wakani, None.

Abstract Number: PP08

Communication, Support, and Advocacy Lead to Improved Health and Quality of Life

Christele Felix, AstraZeneca, Gaithersburg, MD

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Patient Perspectives Poster Session

Session Type: Patient Perspectives Poster Session

Session Time: 12:00PM-2:00PM

Background/Diagnosis: In 2007 I was diagnosed with Lupus which has since then wreaked havoc on my kidneys, lungs, GI tract, peripheral nervous system, to name a few. Additionally, as is usually the case with Lupus, chronic fatigue and joint pain had a devastating effect on my everyday life. The overall goal for my rheumatologist and I was to prevent further organ damage, and tackle the 2 recurrent symptoms that threatened to affect my quality of life: Fatigue and joint pain. Pinpointing the ways these affected the goals I had for my life took time and communication. It is undeniable that patient's relationship with this/her doctor/health team may positively influence the patient's health and life under the right conditions.

Treatment: My 11 years as a chronic patient have seen many mid-to-long-terms interactions with doctors. My partnership with my rheumatologist continues to positively impact my life every day. Through our visits and communications, my rheumatologist made it a practice to ask about my life outside of Lupus. Aside from my care, she took an active interest in me as a whole person, strongly encouraged my advocacy, and prompted me to join support groups. Her support of my career goals and interests in research fostered a relationship of trust, inspiring me to take a more active participation in my care. She also validated my vision that my patient/advocacy experience would inform the work I would do.



Maintenance: The outcome of this new perspective is that I've taken charge of my health with a new approach, from consistency with my treatment plan to paying greater attention to my diet and exercise; This more comprehensive approach also included better managing my energy and stress levels. The culture among my support group peers is one of encouragement and of accountability. Support from my doctor and the support she encouraged me to receive from my peers push me to pursue my goals, and to speak up for people like us, to fight for better quality of life for people with Lupus. At patient education events, I spend time talking with doctors about doctor-patient relationships and adherence and how doctors can help.

Quality of Life: Chronic patients will greatly benefit from such support and encouragement from their doctors. Patients whose life goals/interests are taken into consideration develop a rapport of trust with their doctor which in turns increases treatment and lifestyle compliance. My doctor's active pursuit of a collaborative team with her patient led to a transformation in the way I do my part. I encourage doctors to consider establishing a personal connection with their patients (common interest, hobby, etc) and asking patients about what is important to them. Additionally, doctors should encourage support groups and self advocacy. This all leads to better treatment compliance, and a more engaged, healthier, and happier patient.

Disclosure: C. Felix, None;

Abstract Number: PP09

Improved Quality of Life and Decreased Symptoms of Lupus with Diet, Exercise, and Functional Medicine

Marisa Zeppieri-Caruana, Lupus Chick, New York, NY

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Patient Perspectives Poster Session

Session Type: Patient Perspectives Poster Session

Session Time: 12:00PM-2:00PM

Background/Diagnosis: Like most people who live with a chronic illness and/or autoimmune disease, my story started long before I realized. Symptoms came and went throughout my life without any answers. I headed to nursing school during college and things really went south after I was hit by a truck as a pedestrian, run over while I was crossing a street. I believe if I could survive that, there isn't much else life can throw at me that could get me down!

At the age of 23, I was diagnosed with Lupus after I suffered a small stroke and had a variety of classic symptoms come out at once. When you are in your twenties, receiving a diagnosis of a disease that has no cure and can be life-threatening is frightening and leaves you with a sense of uncertainty. I had never met anyone else with Lupus and most people were unfamiliar with it.

Over the years, the disease has taught me so much about how strong I truly am. It has also shaped my character and personality. Today I am even more motivated to accomplish my dreams because I know how quickly life can be taken away. I am dedicated, even more, compassionate towards others, and have a deeper focus on the important things in life.

Treatment: Through dietary changes and exercise and complementary therapies, I have been able to decrease certain lupus symptoms, increase energy, and improve my overall quality of life. Working with an allergist and nutritionist helped me determine what I was allergic to, and also how to add anti-inflammatory foods into my diet. Eating cleaner, preparing my own meals, and juicing increase my energy and even improved some of my vitamin and mineral levels in my blood work over the past few years. Adding restorative yoga when I am feeling well has helped me with anxiety and the overall stress of living with a chronic illness. It has also made my body feel stronger and in more control. Last, adding functional medicine supplements and working with a functional medicine doctor as part of my healthcare team, I have been able to increase energy and decrease some inflammation thanks to different herbal compounds and supplements.

Maintenance: Above and beyond my regular treatments for lupus, I am also the founder and editor in chief of "LupusChick", an online nonprofit that has been a tremendous source of hope and support for me and those in our community. Being surrounded by and having contact with a half a million people per month who are living with lupus and other chronic illnesses, who "get it", help me get through the difficult moments, flare-ups, and daily struggles that my medical team sometimes doesn't personally understand.

Quality of Life: All of this in combination with my regular medication, rest, and a positive attitude has made quite a difference in my life.

*AstraZeneca has provided sponsorship to cover the cost of the submission of this poster to the ACR, as well as travel and subsistence for the presenting author. AstraZeneca has had no involvement or input into the content or development of the poster, with the exception of support for layout and design.

Disclosure: M. Zeppieri-Caruana, None;

Abstract Number: PP10

Using a Mobile App to Facilitate Patient-Doctor Discussions to Make Informed Decisions Regarding 'Painsomnia'

Shelley Fritz¹, Kristine Carandang² and Dawn Gibson³, ¹ArthritisPower Patient Partner: CreakyJoints/Global Healthy Living Foundation, Tampa, FL, ²Chan Division of Occupational Science & Occupational Therapy, University of Southern California, Los Angeles, CA, ³Founder #SpoonieChat; CreakyJoints/Global Healthy Living Foundation Patient Partner, Upper Nyack, NY

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Patient Perspectives Poster Session

Session Type: Patient Perspectives Poster Session

Session Time: 12:00PM-2:00PM

Background/Diagnosis: As a patient with AS, Dawn founded #SpoonieChat to provide a space on twitter for people living with chronic diseases to support each other. One common theme in #SpoonieChat is the relationship between pain and sleep. 'Painsomnia' is a patient-generated term that addresses this cycle of pain and insomnia.

A follower of #SpoonieChat who experiences painsomnia is Shelley. Shelley was diagnosed with RA in 2012, following symptoms of symmetrical joint pain in hands and toes; fatigue, and malaise. After treatments including methotrexate, Plaquenil, and 5+ biologics, Shelley has made significant lifestyle changes and is currently on Rituximab. In addition to monthly blood work and physician exams, changes in Shelley's treatment are based on her own data gathered by weekly symptom tracking.

To understand patients' adaptations to manage painsomnia we used collective knowledge generated from #SpoonieChat with Shelley's unique experiences as an individual patient recorded through patient reported outcomes measures via ArthritisPower.



Treatment: ArthritisPower is a patient-led, patient-generated, app-based research registry for arthritis, bone and inflammatory skin conditions and is free to use for patients like Shelley to track symptoms, to record subtle changes, to see how they are doing over a period of time whether on a new medication and/or in connection to sleep, physical function and other measures.

By tracking pain interference, Shelley has found pain to be interrelated with levels of fatigue, sleep quality, and cognitive issues, thereby negatively impacting her quality of life. Figure 1 shows Shelley's pain interference scores over a six-month period. Shelley identifies the causes of fluctuations by also tracking dates of flares, steroid usage, periods of illness, and restful vacations.

Maintenance: Through this approach, Shelley worked with her rheumatologist to lessen the symptoms and progression of RA. Shelley continues to track these elements through ArthritisPower to look for patterns influenced by medication and maintenance strategies including diet, exercise, decreasing stress, and increasing sleep. This provides the doctor with information beyond blood work, lab tests and swollen joint counts to work with Shelley in managing her condition and treating the things that matter to her to help her live a better quality of life.

Quality of Life: Doctor and patient conversations can be more meaningful when patient experienced data is systematically collected and discussed. Data gathered through ArthritisPower gives patients like Shelley, an organized way to talk with their doctor on each of the indicators of pain and sleep which affect cognitive function, physical function, depression.

Disclosure: S. Fritz, None; K. Carandang, None; D. Gibson, None.

Abstract Number: PP11

The Road Less Traveled– Nontraditional Approaches to Increased Patient Adherence and Positive Outcomes

Carlene Harrison, AstraZeneca, Gaithersburg, MD

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Patient Perspectives Poster Session

Session Type: Patient Perspectives Poster Session

Session Time: 12:00PM-2:00PM

Background/Diagnosis: African-American female diagnosed with SLE, Lupus Nephritis, Discoid Lupus, and Raynaud's Phenomenon in 2011. Symptoms included joint pain, edema in the ankles, malar rash, flank pain, frothy urine, and fatigue.

Treatment: Patient was treated with corticosteroids, immunosuppressants, anti-malarials, and topical steroidal ointments. The patient disclosed she wasn't taking her medicine due to external pressure and stress. Remembering discussions about the patient's interest in research and career goals, the doctor brought copies of recent medical journal articles on SLE to a consult. Emphasizing the importance of treatment adherence, the doctor did something that was unheard of, she asked about her school and research focus. Patient opened up, her scientific curiosity and passion shining through. They discussed the effects of each medicine. She continued this approach throughout her time leading the patient's care. Incorporating the patient into the medical decision-making process, she continued printing materials relevant to the patient's care and was a model for collaborative care. This was evident in allowing the patient to choose a medicine to stop when data showed the regimen she was on, was making no meaningful change.

Maintenance: While there is mounting emphasis placed on quality healthcare outcomes, what is often omitted from the conversation is how these results come about. These interactions with this physician were different from many others she had encountered. Asking about the patient's research interests, showed the patient she wasn't viewed as a set of illnesses. She showed she cared; whether she truly cared or instead used this as a means to an end, it helped change the patient's behavior. The additional step of seeking feedback from the patient on the very medical decisions that impacted her life was paramount. It was no longer merely a physician-patient relationship. Although on different academic and career levels, the patient felt the physician viewed her as a colleague of sorts, even if one that required mentoring.

Quality of Life: The change in the doctor's approach to care led to a change in the patient's attitude toward her health and she became more open about her illness and joined local and online support groups. The patient currently mentors newly diagnosed patients, is an advocate for Lupus patients (often meeting with legislators to enact change), and co-manages a patient led healthcare community. The patient is still undergoing treatment for her Lupus and is receiving infusions of a biologic approved for Lupus treatment along with her other medications. She attributes the change in her attitude and lifestyle to the change in her physician's approach. She recently relocated back to the town where that physician is stationed. The physician now leads her medical team. The patient has full trust in the capabilities of the team because of the leadership. The most important take away from this patient's experience is to meet your patients where they are. Take an active interest in their whole lives and not just the symptoms you treat. Patient experience proves in overwhelming numbers, this will lead to better adherence and healthcare outcomes.

Disclosure: C. Harrison, None;

Abstract Number: PP12

Living a Full Life with A.S. Through Adaptations

Gail Wright, Spondylitis Association of America, Buffalo Grove, IL

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Patient Perspectives Poster Session

Session Type: Patient Perspectives Poster Session

Session Time: 12:00PM-2:00PM

Background/Diagnosis: After running a half marathon and 2 5'ks, I had unexplained back/ hip pain that wouldn't resolve. I returned to my PT. After 3 months of low back, hip work I woke up on a Saturday morning with the most intense chest pain I'd ever felt in my life. Moving my arms sent electric shocks throughout my body. I crawled into my PT. He sent me to the emergency clinic. After a chest x-ray and EKG to confirm that I didn't have breast cancer or a heart issue, my primary doc threw a whack of meds at me to get me at least out of the chair. I was very lucky. I was able to see a Rheumatologist within 2 weeks and was quickly diagnosed. Because of what I now know was Costochondritis, I was led to receive my diagnosis.

Treatment: My Rheumatologist quickly started me on a biologic and other supporting medications. I have been through a few different medications to find what works for me. I exercise on a regular basis. I have learned HOW to communicate with my docs. Short, factual sentences. I can stand for 7 minutes. I don't grocery shop anymore because it's too painful. Then, I'm quiet. I trust in my team. I show them that I trust and will follow their direction for care.

Maintenance: I continue to combine medications, exercise and support from friends and family to keep myself living a full life.





Quality of Life: Currently I live an extremely full life. I am able to hike, vacation, exercise, garden, work full time and lead a full social life. I maintain the attitude that there is nothing that I can't do. I to figure out HOW to do it. I love gardening. When I blew L4-L5 into pieces, my husband accepted my pinterest challenge to build a vertical garden. He built a staircase attached to my fence. My vegetable garden went vertical! The vertical garden has changed over time- and more planters have been added to the fence!

When I wanted to continue hiking and enjoying my love of the outdoors, we found a tool called a flip stick. With the flip stick, my husband and I enjoyed an incredible hike through Arches National Park

After my shoulder surgery and carpal tunnel surgeries- every day was leg day. After my lumbar fusions! 2D; you got it- every day was arm day.

As difficult as it is- at one point I was not able to walk more than about 2,000 steps in a day. This did not stop me from enjoying a trip to Las Vegas. Instead, I rented a scooter!

Disclosure: G. Wright, None;

Abstract Number: PP13

Support Groups and Patient Centred Care; Making a Difference in the Lives of People with Autoimmune and Rheumatic Conditions in Ghana

Paulina Padiki Narh¹, Abdul Aziz A. Adodo Can-Tamakloe¹ and Ida Dzifa Dey², ¹The Rheumatology Initiative tRi, Accra, Ghana, ²Department of Medicine, Rheumatology Unit, School of Medicine and Dentistry, University of Ghana, Accra, Ghana

SESSION INFORMATION

Session Date: Sunday, October 21, 2018

Session Title: Patient Perspectives Poster Session

Session Type: Patient Perspectives Poster Session

Session Time: 12:00PM-2:00PM

Background/Diagnosis: I felt relieved when my diagnosis was confirmed, but upon hearing Lupus and Nephritis and no cure, I felt shattered. I was referred to the only Rheumatology clinic in the country.

The Rheumatology Initiative tRi founded in 2012, is a non-profit organization dedicated to providing education, advocacy and research into the autoimmune rheumatic conditions.

Much has been achieved in reducing mortality of patients with autoimmune conditions worldwide. Unfortunately, for a significant proportion of patients in developing countries like Ghana, poverty limits access to these lifesaving medications and other supportive services that improve survival.



Treatment: tRi established a Patient Assistance Program which provides emergency medical assistance to those with a life altering diagnosis of an autoimmune disease, but are financially challenged and also life skills training as a long-term, empowering solution. Over the past five years, tRi has helped over 158 patients with treatment support. On average these can cost between 100 to 500 dollars a patient.

As a direct beneficiary when I had lupus nephritis in 2014, it was a huge source of relief to not have to worry about what would happen to my kidneys if I delayed treatment, due to challenges funding my induction therapy. I complete the whole course of treatment successfully and have been in remission for the past 2 years.

tRi support group, Rheusolute, focused on young and adolescent persons currently has over 180 members and doubles as source of information and healing interaction outside the consulting room.

Maintenance: As part of ensuring remission, I get daily reminders from tRi to take my maintenance medications, which reduces my tendency for non-compliance.

Knowing there were young people like me in the support group with similar conditions chasing their dreams and aspirations gave me so much comfort and strength, it's like a second home, always ready to listen and advice.

I have graduated from a beneficiary to an administrator who coordinates access to life saving medications for other patients who have an emergency.

It's with a sense of satisfaction that I end each day knowing that I was involved in potentially saving a life just as mine was.

Quality of Life: tRi is currently the only support group and advocate for autoimmune conditions in Ghana. Life with lupus can be very traumatic with high medical costs, flares and several other negatives. Taking daily medications hasn't been easy.

Living with Lupus means life style changes; always having a backup plan since plans can change at any time. Learning to know myself better, engage in less stressful activities, eat healthy and being positive. But, not even the previous fear of death I had persists.

I can now face the future with much hope and I would continue to tame the 'wolf' and take control of my life because lupus does not determine who I am.

Disclosure: P. P. Narh, None; A. A. A. A. Can-Tamakloe, None; I. D. Dey, None.

Author Index

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